TITLE: Randomized, Double Blinded Placebo-Controlled Study of Glutamine in Patients with Oral Mucositis on an mTOR Inhibitor-based Regimen or Esophagitis on a Regimen Receiving Radiation to the Esophagus

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1.0 Objectives and Endpoints

1.1 Primary Objectives:

- To determine whether glutamine decreases the severity of mucositis in patients on an mTOR inhibitor-based regimen or esophagitis in patients receiving radiation to the esophagus.

1.2 Secondary Objectives:

- To assess whether glutamine regimen improves quality of life (QOL) in patients during mTOR inhibitor containing regimen and esophagitis during radiation to esophagus.
- To assess whether glutamine improves other measures of mucositis/esophagitis including incidence of any mucositis/esophagitis, incidence of grade 3 or higher mucositis/esophagitis, duration of mucositis/esophagitis, delay in onset of mucositis/esophagitis, and interruption of cancer treatment due to mucositis/esophagitis.
- To assess whether glutamine affects weight loss after six months of treatment for mTOR inhibitor patients and after completion of radiation therapy for esophagus radiation patients.
- To assess toxicity profile of glutamine.
- To assess whether glutamine affects muscle breakdown.

2.0 Background

2.1 Introduction

2.1.1 mTOR Inhibitors and Mucositis

Temsirolimus (Torisel; Wyeth Pharmaceuticals, PA) is a mammalian target of rapamycin (mTOR) inhibitor that gained FDA approval in 2007 for the treatment of advanced renal cell carcinoma.[1] Another mTOR inhibitor, everolimus, has been approved for renal cell carcinoma, breast cancer, and neuroendocrine tumors.[2] In addition, mTOR inhibitors have demonstrated encouraging efficacy results in patients with a range of advanced malignancies, alone or in combination with other chemotherapy agents or targeted therapies in trials for multiple forms of malignancies.[3-6] As a central regulator of key pathways important in the proliferation of cancers, the mTOR inhibitor blocks the aberrant activation of phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, resulting in growth arrest of cancer cells halting in the G1 phase of the cell cycle. [7]

In general, mucositis is among the most common side effects reported from mTOR inhibitor-based treatment, which seems to be dose-related and occurs mostly in earlier cycles.[7-9] It has been identified repeatedly as one of the most common dose-limiting toxicities.[10] The mucositis incidence related to temsirolimus treatment as a single

agent was 41% in patients with solid tumors with 3% of grade 3 or above.[1,11] However, 2 recent reviews of temsirolimus-based treatment demonstrated that the mucositis incidence rate ranged from 60-65% with 5-10% of patients developing Grade 3.[9,12] The treatment that Investigational Cancer Therapeutics generally uses for the management of mucositis uses the following: xyloxylin (1:1:1 ratio of diphenhydramine, Maalox, lidocaine; 10 milliliters (mL) swish/ swallow every 6 hours as needed).[13] This treatment is not used prophylactically, but used when patient develops mucositis. There is no standard mucositis treatment; therefore, it is important to improve mucositis treatment for patients on therapy with mTOR inhibitors.

2.1.2 Radiation and Esophagitis

More than 1.5 million new cases of cancer are expected to occur in the United States in 2010, including more than 200,000 new cases of lung cancer and 16,000 new cases of esophageal cancer.[14,15] The primary aim of thoracic radiotherapy (TRT) in both NSCLC and esophageal cancer is to maximize the therapeutic ratio in order to deliver an effective dose to the tumor while maintaining an acceptable dose to the neighboring normal tissues. However, complications such as acute radiation-induced esophagitis (ARIE) may cause significant morbidity, unplanned treatment delays, and a decreased chance to escalate the dose to more effective levels. These issues may reduce tumor control and survival rates, as well as the patients' quality of life (QOL).

ARIE is often the dose-limiting complication that is reported in 5–100% of patients treated with TRT.[16-18] Clinical and dosimetric factors that may be related to the incidence and severity of ARIE include: age, tumor and nodal stage, concurrent chemoirradiation, mean esophageal dose and maximal dose point, and esophageal volume receiving >35 Gray (Gy) (V35), V45, V50, V60, percent length of esophagus receiving >40 Gy, and >66 Gy full circumferences.[19-24] Most of these factors are closely associated with the total radiation dose received by a certain volume of esophagus. Thus, to prevent ARIE, the dose to the esophagus must be kept under the organ tolerance level, which can possibly be achieved by complete exclusion of the esophagus from the RT field by using novel RT techniques, such as intensity modulated RT (IMRT). However, often this approach is not feasible due to the organ's central position in the mediastinum, and the proximity of involved lymph nodes relative to the esophagus. Therefore, the primary strategies in controlling ARIE currently revolve around identifying an effective radioprotective agent. Based on the significant prior data, review below (section 2.2 and 3.0) we believe that glutamine will prove to be a safe and effective radioprotector of the esophagus.

The rate of grade three esophagitis ranges between 15-30% in modern studies. The rate seen in most recent NSCLC trial using concurrent chemo/radiation at MD Anderson was 16%. This compares favorable compared to the historic rates of other institutions such as the CALGB 9781 which has a 27% rate.[25] For patients developing Grade 3 esophagitis, radiotherapy can be continued with pain management and IV support, or radiotherapy can be held for </= 5 days until symptoms are < Grade 3.

2.2 Rationale

2.2.1 Rationale in mTOR Treatment Patients

Anti-cancer agents damage cells in the intestine and oropharynx, which leads to mucositis. Mucositis induced by anti-cancer treatment may be the result of multiple factors. Anti-cancer agents inhibit the DNA synthesis of rapidly proliferating cells in the mucosa, and it hinders the renewal capacity of basal epithelium. Subsequently, that results in mucosal atrophy and collagen breakdown thus leading to ulceration.[26-29]

Mucositis is a notable side effect and dose-limiting toxicity for patients in mTOR-based regimens.[9] Mucositis is further associated with dehydration and weight loss among patients undergoing temsirolimus-based trials. In a recent study, mucositis was noted to be the most frequent adverse event overall (73.4%) among 2,822 patients who received a temsirolimus-based, everolimus-based, or ridaforolimus-based regimens.[9] In a study of single-agent temsirolimus treatment in patients with advanced renal cell carcinoma, mucositis was 41.3%.[11]

In a recent data review, we assessed the incidence and severity of mucositis in 87 patients who received one of 3 temsirolimus-based combination trials. Overall, the incidence of any grade of mucositis in our temsirolimus-based combination trials was 64.4%. The incidence rate of mucositis greater than grade 2 was higher at 9.2%.[12] We also examined the effectiveness of our mucositis management, which included one or more of the following: xyloxylin (1:1:1 ratio of diphenhydramine, Maalox, lidocaine; 10 milliliters (mL) swish/ swallow every 6 hours as needed), Caphosol (sodium phosphate; 15 mL swish/spit every 4 hours as needed), valacyclovir (500 mg *per os* 3 times daily), Biotene mouth wash (every 4 hours as needed), and Carafate (1 gram (gm)/ 10 mL; 10 mL swish/swallow or spit every 6 hours as needed) as previously described by Naing *et al*., 2011.[13] However, there was no standard protocol to treat mucositis. Based on physician discretion, there were some patients who received one or more of our mucositis regimens.[12]

A better regimen for mucositis is indeed warranted. Although not utilized in our 3 trials, oral glutamine may be a promising regimen for mucositis treatment. Use of oral glutamine during and after the anti-cancer treatment has been shown to reduce the duration and severity of mucositis.[30,31]

In mTOR based combination therapy, mucositis is a major obstacle. By optimizing treatment for mucositis through the use of glutamine, it will enable patients to continue to have an effective treatment while maintaining good quality of life. Hence, it is of great importance to devise an optimal regimen in both prophylactic and treatment settings. The primary objective of the current study is to prospectively demonstrate that oral glutamine use decreases the severity of mucositis in patients receiving mTOR-based therapy.

2.2.2 Rationale in Radiation Treatment Patients

An agent with potential radioprotective properties is glutamine, which is the primary oxidative fuel of the gut epithelium and is necessary for maintenance of the integrity of the gut structure during normal and stress conditions.[32-35] Significant amounts of glutamine are provided by skeletal muscles during hypercatabolic states such as cancer, however marked glutamine depletion develops over time, which cannot be compensated for by increased synthesis. Glutamine depletion under conditions of stress compromises the acid–base balance, immune functions, epithelial integrity, and facilitated bacterial translocation in the gut.[35] Furthermore, because of its protective functions against oxidative injury in normal tissues, depletion of glutathione (GSH), a byproduct of glutamine metabolism, may increase the extent of tissue damage caused by RT and/or chemotherapy (Ctx).[36-38] In this setting, glutamine supplementation not only normalizes the levels in the body, but also selectively increases normal tissue GSH levels, which may explain its selective radioprotective actions on normal tissues.[36,39]

In cancer patients, there is a tendency for progressive depletion of glutamine from muscle, which is a key factor in cancer-induced cachexia. As muscle depots are the immediate source of glutamine for gut epithelium, glutamine depletion in such conditions may lead to reduced radiation tolerance.[32,40] Additionally, ARIE and related complications such as nausea, vomiting, pain, dysphagia, or odynophagia may further worsen the tolerance of normal tissues to radiation. Therefore, it is reasonable to assume that glutamine supplementation may be beneficial in prevention of ARIE and related complications in patients undergoing TRT. This evidence suggests a selective radioprotective role for glutamine, and in the radiology department, we use glutamine in all patients with NSCLC in whom mediastinal irradiation is indicated. The primary objective of the current study is to prospectively demonstrate that oral glutamine use in the prevention of ARIE and weight loss in thoracic cancer patients during TRT.

3.0 Background Drug Information

Drug Name: Glutamine + disaccharide suspension (Healios)

Classification: Amino Acid, carbohydrates; Generally Recognized As Safe (GRAS) enteral nutrition and flavoring supplement

Description: Glutamine, a precursor for glutathione, plays a pivotal role in regulating the intracellular redox potential, and clinical investigations indicate that glutamine inhibits other mediators of mucosal barrier injury by reducing the production of proinflammatory cytokines and cytokine-related apoptosis. Other experimental evidence suggests that glutamine may improve mucosal barrier wound healing by increasing fibroblasts and collagen synthesis. Glutamine is also critically important to meet demands for tissue repair during times of high cellular replication. In these times of increased glutamine demand caused by physiologic stress (e.g., during and after cytotoxic chemotherapy), the requirements for glutamine may

exceed the body's ability to produce sufficient concentrations and exogenous glutamine may be needed.[41]

Glutamine suspension in combination with the disaccharide sucrose has vastly improved uptake by mucosal cells (Figure 1). It takes <10 seconds for this effect to be completed.

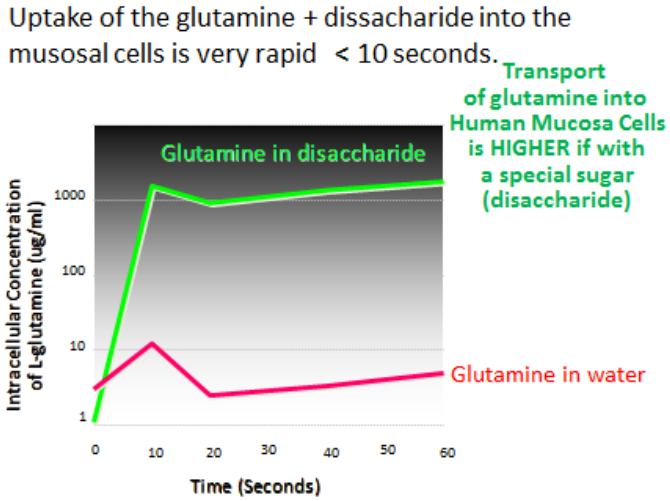

Figure 1. Glutamine transport into cells is facilitated by disaccharides. (from Peterson et al, ASCO plenary session 2008)

Until recently trehalose, a glucose-glucose disaccharide with cell membrane and protein stabilizing properties was expensive. It is now made from starch for mass production and is available as a good tasting sweetener (Treha, Cargill). Figure 2 shows the similar structures of sucrose and trehalose.

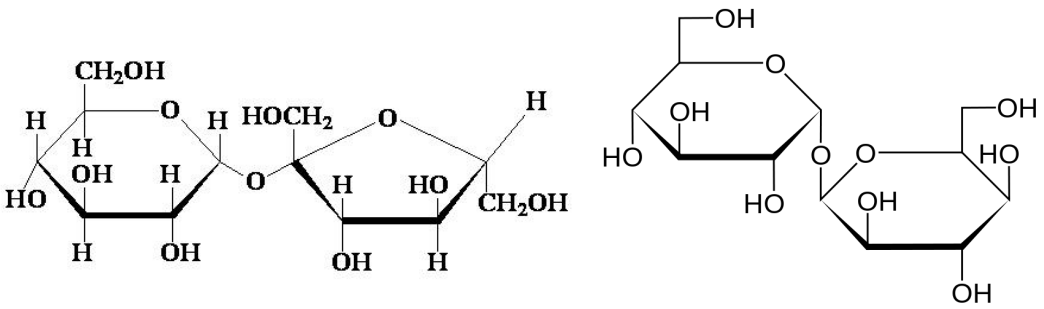

Figure 2. Sucrose is Glucose + fructose; trehalose is Glucose+Glucose (source: Google images)

Use of a glutamine + disaccharide suspension has been safe and effective in reducing mucositis pain and oral discomfort in 1 pilot study and 3 randomized, placebo double blind clinical trials.[30,31,42,43] Since trehalose is now commercially available, an improved orange-flavored formulation with all three generally recognized as safe components (glutamine, sucrose, trehalose) has been developed by Labrada Nutrition in Houston and given the brand name Healios.

3.1 Preparation:

The drug and placebo will be provided by Healios Oncology Nutrition.

Glutamine (Active): supplied as a powder. 1 scoop provides the individual serving of 4 grams glutamine (other components include 5 grams (gms) sucrose, 1.3 gm trehalose, 130 mg suspending agent to prevent quick settling, and 0.7 gm flavoring). One scoop is suspended with 25-100 milliliters (mL) water.

Glycine (Placebo): supplied as a powder. 1 scoop provides the individual serving of 4 grams glycine (other components include 5 grams (gms) sucrose, 1.3 gm trehalose, 130 mg suspending agent to prevent quick settling, and 0.7 gm flavoring). One scoop is suspended with 25-100 milliliters (mL) water

3.2 Method/Route of Administration:

Oral Administration

- **mTOR-based Therapy Cohort:** The suspension is swished for 10 seconds, then swallowed.
- **Espophageal Radiation Patients:** The suspension is swallowed in several small boluses.

4.0 Patient Eligibility

4.1 Inclusion Criteria

1) Patients who will be initiating therapy with any investigator-initiated mTOR inhibitor based therapy in the Department of Investigational Cancer Therapeutics (Phase I Program) or initiating radiation therapy to the esophagus.
2) For the esophagitis arm, any patient with thoracic malignancies, which will receive radiation alone or concurrent chemo/radiation. Radiation dose must be ≥ 45 Gy. For the esophagitis arm, induction chemotherapy is allowed.
3) Ability to understand and the willingness to sign a written informed consent. A signed informed consent must be obtained prior to any study specific procedures.
4) Patients must be >/= 17 years of age.
5) Women of child-bearing potential MUST have a negative serum or urine pregnancy test unless prior hysterectomy or menopause (defined as 12 consecutive months without menstrual activity). Patients should not become pregnant or breastfeed while on this study. Sexually active patients must agree to use contraception prior to study entry, for the duration of study participation, and for 30 days after the last dose.

4.2 Exclusion Criteria

1) Patients currently receiving therapy for mucositis.

5.0 Treatment Plan

There will be a total of 180 patients in this study. There will be a cohort of 100 patients on mTOR-based regimens (Phase I or Phase II) which will be enrolled in the Department of Investigational Cancer Therapeutics. There will be a cohort of 80 patients on radiation regimen which will be enrolled in the Department of Radiation Oncology.

5.1 Drug Administration and Treatment Schedule

This is randomized, double blinded, placebo-controlled trial examining Glutamine in patients receiving therapy with either mTOR inhibitor based therapy or radiation to the esophagus. Patients will be randomly assigned to receive Glutamine or Placebo. The study will be conducted in the Department of Investigational Cancer Therapeutics and the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Patients will take 1 scoop (4 grams) of glutamine or placebo mixed with water twice each day.

Caution: New Drug-Limited by Federal Law to Investigational Use.

Patients will be randomized to glutamine or placebo by the MDACC Investigational Pharmacy (Section 12.5). Patients will be dispensed the study drug (glutamine or placebo) in a plastic bottle. Each bottle will contain 30 doses (scoops), which will be enough study drug for 15 days. A monthly supply (2 bottles) will be dispensed to patients.

Per MDACC policy, any unused or expired drug will be disposed of by the Investigational Pharmacy.

5.1.1 mTOR Inhibitor Therapy

Four weeks of treatment constitute 1 cycle for patients on mTOR inhibitor therapy. Glutamine will start on day 1 of mTOR inhibitor treatment. Patients may be allowed to continue the treatment if there is clinical response (to include prevention or resolution) of any mucositis. Patients will be treated on the double, blinded placebo-controlled trial for as long as they are on mTOR inhibitor therapy. If the patient stops the mTOR inhibitor based therapy, mucositis treatment should continue for 4 weeks after the last dose of mTOR-inhibitor-based regimen to prevent further mucositis complications.

5.1.2 Radiation to the Esophagus

Radiation must be ≥45 Gy delivered alone or with concurrent chemotherapy. The type of concurrent chemo will be determined by the treating physician. For the esophagitis arm, induction chemotherapy is allowed. XRT must be given using

conventional daily fraction dose from 180-240 cGy per day. Radiation technique may include: 3D conformal, IMRT, and or protons. Glutamine will start on the first day of radiation, or within 10 days of the start of radiation and will be continued for 4 weeks after the last day of radiation. Radiation will be given daily (Monday through Friday) for 5 days per week. The number of weeks of radiation therapy will be determined by the treating physician. The end of treatment week will vary based on the number of weeks of radiation that the patient receives.

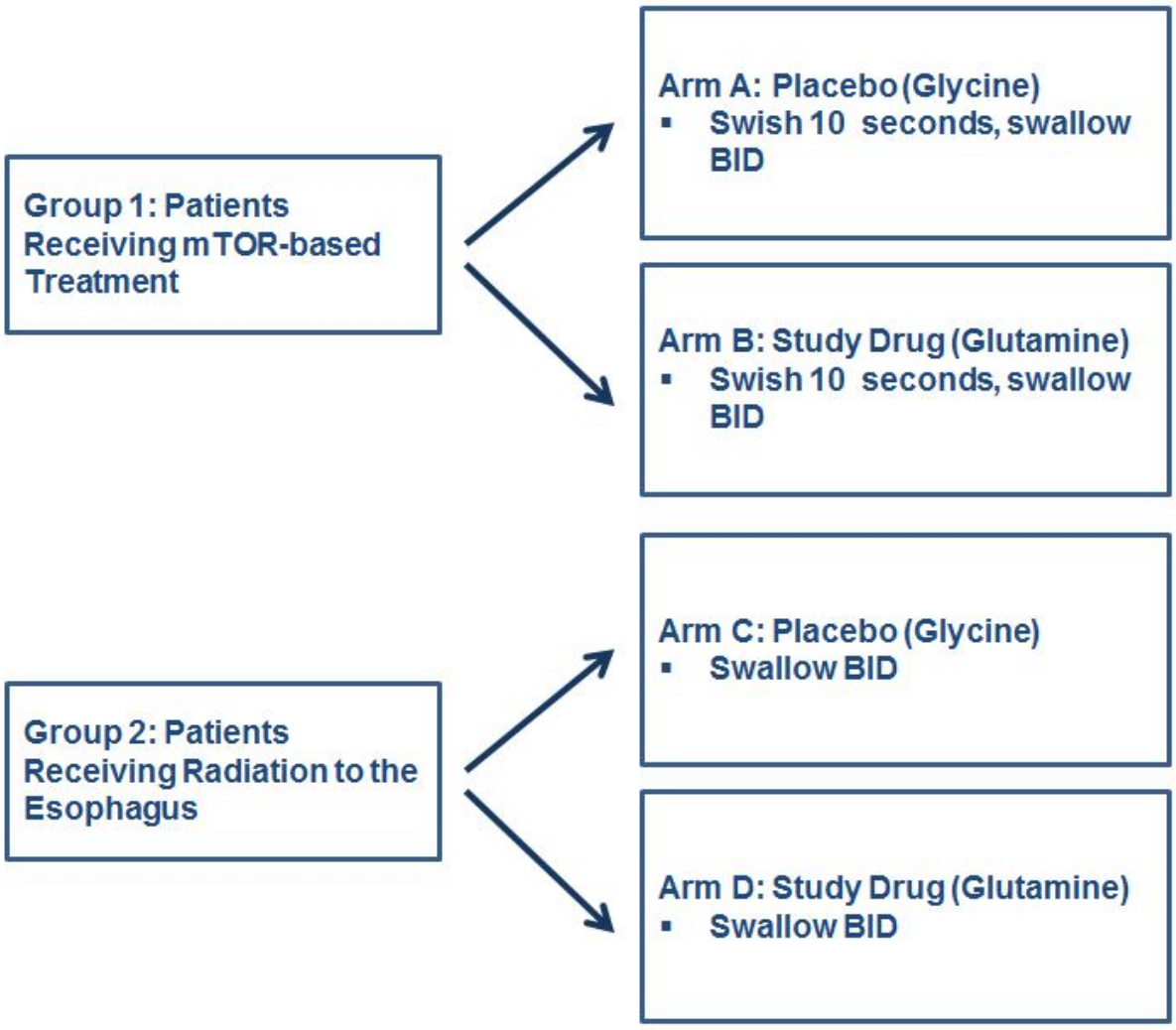

Figure 3. Treatment Regimen (Schema)

For patients who will receive mTOR inhibitor based therapy: the patients will be randomized to receive either placebo or Glutamine beginning on Day 1 of an mTOR inhibitor based therapy.

For patients who will receive radiation to the esophagus: the patients will be randomized to receive either placebo or Glutamine beginning on Day 1 of radiation treatment, or within 10 days of the start of radiation.

5.2 Evaluation of Response

For patients receiving mTOR inhibitor-based therapy, the patients will be evaluated weekly during the first 4 weeks of treatment for signs and symptoms of mucositis in the clinic using the CTCAE version 4.03 (Section 9.0). After four weeks of therapy, mucositis symptoms may be assessed by in person interview or phone call to the patient. If mucositis symptoms are ≥ grade 2, the patient will be asked to visit clinic for oral examination.

For patients receiving radiation therapy, the patients will be evaluated weekly based on the number of weeks of radiation therapy as determined by the treating physician, at end of treatment (or final week of radiation treatment based on number of weeks of radiation), 1 month, and 6 month post radiation therapy for signs and symptoms of esophagitis using the CTCAE version 4.03 (Section 9.0). Esophagitis symptoms may be assessed by in person interview or phone call to the patient.

5.3 Study Assessments and Procedures

Evaluation will take place as per protocol schedule unless patient/logistical/medical reasons intervene.

5.3.1 Assessment of Improvement in Quality of Life

MD Anderson Symptom Inventory (MDASI-HN)

MDASI was designed to assist in the assessment of 13 symptoms common in cancer patients (dry mouth, fatigue, pain, disturbed sleep, drowsiness, feeling of being distressed, anorexia, sadness, numbness/tingling, dyspnea, difficulty remembering, nausea, and vomiting) during the previous 24 hours. In addition, 9 head and neck cancer specific items are included in MDASI-HN which are mouth sores, taste, constipation, teeth/gum problems, skin pain, difficulty with voice, choking/coughing, difficulty swallowing, and problem with mucus. The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that symptom is absent and 10 meaning that it is of the worst possible severity. The instruments and techniques are both valid and reliable in the assessment of the intensity of symptoms in cancer populations.[12]

For patients receiving mTOR inhibitor-based therapy, the MDASI-HN will be administered at baseline, Day 15, Day 1 of Cycle 2 and beyond, end of study visit and 3 months (+/-14 days) and 6 months (+/-21 days) post end of mTOR inhibitor-based therapy. These questionnaires may be administered over the phone.

For patient receiving radiation, the MDASI-HN will be given at baseline, Week 3, Week 5, Week 7, end of treatment (or final week of radiation treatment based on number of weeks of radiation), at 1 month (+/-7 days), 3 months (+/-14 days), and 6 months (+/-21days) after radiation. These questionnaires may be administered over the phone.

Measure of Patient Satisfaction with Study Medication Satisfaction Scale
The Study Medication Satisfaction Scale is a short, 7-item scale, that asks patients about several areas of satisfaction. The scale includes questions about ease or difficulty of taking the medication in general and in its current form, convenience of taking the study medications as instructed and patient confidence that the study medication is of benefit.
For the patients receiving mTOR inhibitor-based therapy, the patient satisfaction scale will be given on Day 1 of Cycle 2 and beyond.
For the patients receiving radiation, the patient satisfaction scale will be given at Week 3, Week 5, Week 7, end of treatment (or final week of radiation treatment based on number of weeks of radiation), and 1 month post radiation therapy.

These surveys may be administered over the phone.

5.3.2 Pretreatment Evaluations:

To be completed within 4 weeks prior to initiation of therapy:
- Medical history including list of current concomitant medications and history of mucositis and esophagitis with prior therapy (mucositis and esophagitis history may be obtained by retrospective medical record review).
- Examination of oral mucosa.
- Informed consent
- Weight
- ALC (absolute lymphocyte count)
- Quality of life Questionnaire: MDASI-HN for all patients.
- Medical photograph of oral mucosa for patients receiving therapy with an mTOR inhibitor containing regimen. Attempts to perform medical photographs will be made at this timepoint, but if unsuccessful, will not be considered a deviation to the protocol since it is not a safety assessment.
- Women of childbearing potential will have a pregnancy test using urine and/or blood, and periodically as clinically indicated

5.3.3 Evaluation during Study:

- Examination of oral mucosa and grading of oral mucositis weekly during cycle 1 and monthly in subsequent cycles for patients receiving mTOR inhibitor therapy. For patients receiving radiation to the esophagus signs and symptoms of esophagitis (ie: dysphagia, weight loss) are to be evaluated in the routine monitoring weekly visits during therapy, as per the study calendar below.
- Weights to be obtained weekly during cycle 1 and monthly in subsequent cycles for patients receiving mTOR inhibitor therapy. For patients receiving radiation to the esophagus weights are to be obtained weekly during XRT.
- Concomitant medications to be reviewed weekly during cycle 1 and monthly in subsequent cycles for patients receiving mTOR inhibitor therapy and weekly, 4

weeks post last radiation and at 6 months post last radiation for patients receiving radiation to the esophagus .

- Quality of life questionnaire. MDASI-HN for patients receiving mTOR inhibitor therapy on day 15 and day 1 of Cycle 2 and beyond, end of study visit, and 3 months (+/-14 days) and 6 months (+/-21 days) post end of mTOR inhibitor-based therapy. Patients receiving radiation to the esophagus should complete the questionnaires at the Week 3, Week 5 and Week 7, end of treatment (or final week of radiation treatment based on number of weeks of radiation), as well as 1 month (+/-7 days) and 3 months (+/-14 days), and 6 months (+/-21days) after treatment.
- Patient Satisfaction Survey will be given on Day 1 of Cycle 2 and beyond for patients receiving mTOR inhibitor therapy and given at Week 3,Week 5, Week 7, end of treatment (or final week of radiation treatment based on number of weeks of radiation), and 1 month post treatment for patients receiving radiation to the esophagus.
- For patients on mTOR inhibitor-based therapy, ALC may be obtained at screening and Day 1 of Cycles 2 and beyond. Attempts to perform ALC labs will be made at this timepoint, but if unsuccessful, will not be considered a deviation to the protocol since it is not a safety assessment.
- For patients on radiation therapy, ALC may be weekly during radiation. Attempts to perform ALC labs will be made at these timepoints, but if unsuccessful, will not be considered deviations to the protocol since these are not safety assessments.
- Medical Photograph of oral mucosa at the worst grade of mucositis and at cycle 1 day 29 (prior to cycle 2) for patients receiving therapy with an mTOR inhibitor containing regimen. Attempts to obtain medical photographs will be made at this timepoint, but if unsuccessful, will not be considered a deviation to the protocol since it is not a safety assessment.

5.3.4 End of Study Visit

End of study for patients receiving mTOR inhibitor therapy will be within 4 weeks after the last dose of the mTOR inhibitor that they received. End of study for patients receiving radiation to the esophagus will be 6 months (+/- 21 days) after the last day of radiation. The following procedures will be completed at this time:

- Examination of oral mucosa and grading of oral mucositis for patients who received mTOR inhibitor therapy. For patients who received radiation to the esophagus signs and symptoms of esophagitis are to be evaluated.
- Weight
- Concomitant Medications
- ALC may be obtained. Attempts to perform ALC labs will be made at this timepoint, but if unsuccessful, will not be considered a deviation to the protocol since it is not a safety assessment.
- Quality of life questionnaires: MDASI-HN

6.0 Study Calendar

- Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy.
- Study Assessments will take place as per protocol schedule unless patient/logistical/medical reasons intervene.

6.1 Study Assessment for Patients Receiving mTOR Inhibitor Therapy

All evaluations will have a +/- 2 day window. Cycle 1 Day 1 of the study drug will be Day 1 of the mTOR treatment.

Study Assessment	Screening	Cycle 1				Cycle 2 and Beyond	End of Study[h]	3 months Post EOT[h] (+/- 14 days)[f]	6 months Post EOT[h] (+/- 21 days)[f]
	Within 28 Days of Cycle 1 Day 1 (+1 Day Prior to Dosing)	Day 1	Day 8	Day 15	Day 22	Day 1			
Informed Consent	X								
Medical History Review	X								
Mucositis History	X								
Oral Mucosa Exam[a]	X	X	X	X	X	X[i.]	X[i.]		
Mucositis Grading[a]	X	X	X	X	X	X[i.]	X[i.]		
Weight & Weight Loss[b]	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X		
ALC[g]	X					X	X		
Pregnancy Test	X								
Quality of Life Questionnaire[c]	X			X		X	X	X	X
Patient Satisfaction with Study Medication						X			
Medical Photography[e]	X					X			

[a] Mucositis grading according to CTCAE v4.03 to be documented with the oral mucosa exam for patients receiving mTOR inhibitor therapy.
[b] Weight loss to be calculated at each study assessment visit.

[c] QOL questionnaires will be performed at 3 months and 6 months if patients are still on mTOR inhibitor-based regimen
[d] To be done only on Cycle 1 day 29 (prior to receiving Cycle 2 Day 1)
[e] Medical Photography of the patient's oral mucosa at screening, worst grade of mucositis experienced, and cycle 1 day 29 (prior to beginning cycle 2). Attempts to obtain photographs will be made at these timepoints, but if unsuccessful, will not be considered deviations to the protocol since these are not safety assessments.
[f] This visit is for patients who remain on mTOR inhibitor containing therapy up to 3 or 6 months.
[g]. The ALC may be obtained. Attempts to perform ALC labs will be made at these timepoints, but if unsuccessful, will not be considered deviations to the protocol since these are not safety assessments.
[h.] The End of Study visit will be within 4 weeks after last dose of mTOR inhibitor therapy. The 3-month and 6-month follow-up visit will occur post end of treatment (EOT).
[i.] After 4 weeks of therapy, mucositis symptoms, weight (weight loss), concomitant medications, and questionnaires may be assessed by phone call to the patient.

The investigators are aware that the combination of mTOR inhibitors and glutamine, including sucrose and trehalose, may further increase mTOR inhibitor-induced hyperglycemia. The investigators will work closely with the endocrine collaborator.

6.2 Study Assessment for Patients Receiving Radiation to the Esophagus

All evaluations will have a +/- 2 day window.

Study Assessment	Screening	Weeks of Radiation[d]							End of Radiation Treatment[e]	Post Radiation Therapy		End of Study
	Within 28 Days of Day 1 of Protocol Therapy	1	2	3	4	5	6	7		1 month (+/- 7 days) [f.]	3 Months (+/- 14 days) [f.]	6 Months (+/- 21 days) [f.]
Informed Consent	X											
Medical History Review	X											
Esophagitis History[a]	X											
Esophagitis Grade[a]	X	X	X	X	X	X	X	X		X		X
ALC[b]	X	X	X	X	X	X	X	X		X		X [b]
Weight & Weight Loss[c]	X	X	X	X	X	X	X	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X		X		X
Pregnancy Test	X											
Quality of Life Questionnaire	X			X		X		X	X	X	X	X
Patient Satisfaction with Study Medication				X		X		X	X	X		

[a] Esophagitis grading will be according to CTCAE v4.03.

[b.] The ALC may be obtained. Attempts to perform ALC labs will be made at these timepoints, but if unsuccessful, will not be considered deviations to the protocol since these are not safety assessments. If the patient does not return to clinic at 6 month post treatment visit, ALC can be done at the first visit after 6 month post radiation treatment.

[c] Weight loss to be calculated at each study assessment visit.

d. Number of weeks is based on number of weeks of therapy that patient receives as determined by the treating physician. Radiation will be given daily (Monday through Friday) for 5 days per week.

e. End of Treatment visit will occur at the appropriate timepoint based on the number of weeks of radiation therapy that the patient receives as determined by the physician.

f. For the 1-month, 3-month, and/or 6-month visits, the assessments of esophagitis grading, weight (weight loss), concomitant medications, and questionnaires may be assessed by phone call to the patient if patient is not returning to clinic.

7.0 Concomitant medications

Concomitant medications that are being used to treat mucositis will be recorded at each visit.

8.0 Criteria for Removal from the Study

Patients may be removed from the study for the following reasons:

1. Patient withdraws consent for continued participation or refuses further treatment with the study medication.
2. If the patient develops grade 4 mucositis.
3. Completion of study medication: 4 weeks post the last dose of the mTOR inhibitor (or after completion of 6 Cycles) or post 6 months after completion of radiation.

9.0 Criteria for Evaluation

CTCAE version 4.03 will be used to assess the grade of mucositis and esophagitis.[44] The principal investigator will train physicians and mid-level providers on the interpretation and grading of mucositis and esophagitis to ensure uniformity and appropriate grading of oral exams.

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Mucositis Oral	**Asymptomatic or mild symptoms; intervention not indicated**	**Moderate pain; not interfering with oral intake; modified diet indicated**	**Severe pain; interfering with oral intake**	**Life-threatening consequences; urgent intervention indicated**	**Death**
Definition: A disorder characterized by inflammation of the oral mucosal.					

For oral mucositis, Grade 3 includes the use of opiates for severe mouth pain, IV fluids needed for decreased oral intake, or hold of mTOR inhibitor-based therapy due to severe mouth pain.

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Esophagitis	**Asymptomatic; clinical or diagnostic observations only; intervention not indicated**	**Symptomatic; altered eating/swallowing; oral supplements indicated**	**Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated**	**Life-threatening consequences; urgent intervention indicated**	**Death**
Definition: A disorder characterized by inflammation of the esophageal wall.					

For esophagitis, Grade 2 will be when patients start xyloxylin. Grade 3 is when they start lortab or other narcotics. Grade 3 is defined as feeding tube required secondary to swallowing difficulty rather than uncontrolled nausea.

If patients develop mucositis or esophagitis of grade 1 for more than 5 days or grade 2 or above, the attending physician may have the option to initiate the patient on a best supportive therapy (See Appendix A). The study coordinator or research nurse will record the type and time of treatment of any additional supportive therapy that patients may be given while on the study which will be included in the data analysis.

10.0 Reporting Requirements

Safety Monitoring
The principal investigator is responsible for monitoring the safety of patients who enroll in the study. All adverse events (AEs) occurring after any administration of the study drug will be followed until resolution, stabilization, death, loss to follow up, or commencement of new therapy.

10.1 Serious Adverse Event (SAE) Reporting

Adverse Event Definition
The CTEP active version of NCI Toxicity Criteria may be used by the Investigator as a guide in determining the severity of adverse events.
Clinically significant adverse events (AEs) and Serious Adverse Events (SAEs) occurring during the study that are thought to be related to Glutamine or Best Supportive Care should be documented in the medical record.

Toxicities of all grades that are felt to be related to Glutamine or Best Supportive Care, and all grades of mucositis, esophagitis, and weight loss will be documented in the patient electronic medical record. Unless otherwise documented in the electronic medical record as clinically significant and study drug related, all lab abnormalities will be assumed to be related to the patient's other co-morbid conditions, prior therapies, other concomitant therapies/medications, or underlying cancer. In this study, only adverse events related to the study drug, not related to mTOR inhibitor therapy or radiation therapy will be recorded.

Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the

adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

10.2 Data Collection

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD Anderson Cancer Center at Houston. Data will be collected and stored in the MD Anderson Protocol Data Management System (PDMS). Only adverse events related to the study drug will be captured in PDMS. Data from the MDASI and patient satisfaction survey will be stored in a Microsoft Access database that will be created and managed by Dr. Akhila Reddy's group.

Data Protection and Confidentiality

All patients who meet eligibility criteria and are enrolled in this trial will be registered in CORe at the University of Texas MD Anderson Cancer Center at Houston. All protocol participants must be registered in the CORE. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

10.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present.

11.0 Study Monitoring

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board, and the Data Safety and Monitoring Board (DSMB).

12.0 Statistical Considerations

Dr. Kenneth Hess (Professor, Department of Biostatistics) will perform all statistical analyses.

12.1 Study Objectives

Primary Objectives:

- To determine whether glutamine decreases the severity of mucositis in patients on an mTOR inhibitor-based regimen or esophagitis in patients receiving radiation to the esophagus.

Secondary Objectives:

- To assess whether glutamine regimen improves quality of life (QOL) in patients during mTOR inhibitor containing regimen and esophagitis during radiation to esophagus.
- To assess whether glutamine improves other measures of mucositis/esophagitis including incidence of any mucositis/esophagitis, incidence of grade 3 or higher mucositis/esophagitis, duration of mucositis/esophagitis, delay in onset of mucositis/esophagitis, and interruption of cancer treatment due to mucositis/esophagitis.

- To assess whether glutamine affects weight loss after six months of treatment for mTOR inhibitor patients and after completion of radiation therapy for esophagus radiation patients.
- To assess toxicity profile of glutamine.
- To assess whether glutamine affects muscle breakdown.

12.2 Study Endpoints

Primary Endpoints

- For mTOR inhibitor patients, the severity of oral mucositis will be taken as the maximum grade observed during the 6-month study period. For esophagus radiation patients, the severity of esophagitis will be taken as the highest grade observed by week six.

Secondary Endpoints

- For mTOR inhibitor patients, oral mucositis grade will be assessed at the following times: baseline, weekly during Cycle 1, and Day 1 of Cycle 2 and beyond, and end of study. For esophagus radiation patients, esophagitis grade will be assessed at the following times: baseline, weekly during radiation, end of treatment (or final week of radiation treatment based on number of weeks of radiation), and 1 month and 6 months post radiation therapy.
- For mTOR inhibitor patients, QOL will be assessed by MDASI-HN at the following times: baseline, Day 15 of Cycle 1, Day 1 of Cycles 2 and beyond, end of study, and 3 months and 6 months post end of treatment. For esophagus radiation patients, QOL will be assessed by MDASI-HN at the following times: baseline, Weeks 3, 5, and 7 of radiation, end of treatment (or final week of radiation treatment based on number of weeks of radiation), 1 month, 3 months, and 6 months post radiation therapy. For mTOR inhibitor patients, Patient Satisfaction with Study Medication will be assessed at Day 1 of Cycles 2 and beyond. For esophagus radiation patients, Patient Satisfaction with Study Medication will be assessed at Weeks 3, 5, and 7, end of treatment (or final week of radiation treatment based on number of weeks of radiation), and 1 month post radiation therapy.
- For mTOR inhibitor patients, body weight will be assessed at the following times baseline, weekly during Cycle 1, and Day 1 of Cycle 2 and beyond, and end of study. For esophagus radiation patients, body weight will be assessed at the following times: baseline, weekly during radiation, 1 month and 6 months post radiation therapy.
- For esophagus radiation patients, muscle breakdown will be assessed at baseline, weekly during radiation, 1 month and 6 months post radiation therapy.

12.3 Sample Size

There will be a total of 180 patients in this study. The cohort of patients on mTOR-based regimens will be 100, and the cohort of patients on radiation regimen will be 80.

For esophagus radiation, published data indicate that the distribution of patients by esophagitis grade is 0-1: 26%, 2: 37%, 3: 37% for patients not given glutamine[45]. If we target a modest treatment effect (0-1: 50%, 2: 38%, 3: 12%) then 40 patients per treatment arm would give us 81% power (assuming a two-sided 5% alpha and use of the Wilcoxon rank sum test for analysis).

For mTOR inhibitor patients, we have unpublished data from 87 patients indicating that the distribution of patients by oral mucositis grade is 0-1: 69%, 2: 22%, 3: 9% for patients not given glutamine. If we target (0-1: 95%, 2: 5%, 3: 0%) as the results in the glutamine arm, then 50 patients per arm would give us 94% power (assuming a two-sided 5% alpha, and use of the Wilcoxon rank sum test for analysis).

These calculations were made using nQuery Advisor 7.0.

12.4 Statistical Analysis Plan

Note: Analyses will be performed separately for patients treated with mTOR inhibitors and patients with esophagus radiation.

For the primary objective, we will use the Wilcoxon rank sum test to compare the ordered categories of mucositis/esophagitis severity between treatment arms. A patient must complete at least 60% of the planned doses of placebo or glutamine to be considered evaluable in the statistical analysis. As a sensitivity analysis for the appropriateness of 60% dosing cut-off, we will analyze the outcome according to the proportion of drug taken. The proportional of drug taken will be computed as the ratio of number of doses taken to the total number of doses prescribed. For the mTOR inhibitor group, the denominator will reflect the total time that each patient is on the study. For the esophagus radiation group, the denominator will reflect the total number of doses that are prescribed during the delivery of radiation.

For the secondary objectives/endpoints, we will compare between treatment arms (1) the trajectories of the mucositis/esophagitis scores over time using linear mixed effects; (2) the proportion of patients developing mucositis/esophagitis using a Pearson chi-squared test; (3) the proportion of patients developing grade 3 or higher mucositis/esophagitis using a Pearson chi-squared test; (4) the duration of mucositis/esophagitis using the Wilcoxon rank sum test; (5) the time to develop mucositis/esophagitis using Kaplan-Meier estimates and the log rank test (due to right censoring in patients not developing mucositis/esophagitis); (6) the proportion of patients having treatment interruptions using a Pearson chi-squared test; (7) the

weight change using the Wilcoxon rank sum test; and (8) the QOL survey scores using the Wilcoxon rank sum test.

For the secondary objective of describing the toxicity profile, descriptive statistics will be provided on the grade and type of toxicity by treatment arm.

For the secondary objective of assessing the muscle breakdown in the esophagus radiation group, we will compare the muscle breakdown between the patients that received glutamine versus placebo. Muscle breakdown will be assessed by reviewing patient CTs pre-treatment, during weeks of radiation, 1 month post treatment, and 6 months post treatment. The CT image at the level of the third lumbar vertebra will be auto-segmented using Pinnacle software. One cross section will highlight the skeletal muscle mass while the other cross section will highlight the adipose tissue surrounding the vertebra. LBM (lean body mass) and FM (fat mass) will be estimated from skeletal muscle and adipose cross-sectional area (cm^2) at the third lumbar vertebra using the formulae described by Chamchod et al.[47]

LBM_{CT} (kg) = 0.3 x [skeletal muscle at L3 (cm^2)] + 6.06

FM_{CT} (kg) = 0.042 x [total adipose tissue at L3 (cm^2)] +11.2

Stopping Rules

We will perform semi-annual futility analyses using Bayesian predictive probability methods.[46] These analyses would be timed to occur at the time of our annual DSMB review as well as mid-way in between the meetings. The more frequent interim futility analysis will allow us to determine in a more timely fashion when and if there is sufficient evidence that it is unlikely that we would conclude that one treatment was better than the other if we completed planned enrollment. Consideration should be given to stopping the trial early for futility if the predicted probability that a significant difference between glutamine and placebo would be observed in the trial if it were continued to completion is < 5%.

Separate analyses will be performed for the mTOR inhibitor patients and for the esophagus radiation patients.
The study statisticians will conduct the analyses and send the results to the DSMB for consideration. The PI will not be notified of the results of these analyses unless the DSMB determines to recommend that study enrollment be stopped.

12.5 Randomization and Blinding

Patients will be equally randomized between treatment arms using permuted blocks within strata separately for the two groups of patients. For patients who will receive mTOR inhibitor based therapy**,** randomization will be stratified by: prior mucositis (Y/N), and prior radiation therapy to the head and neck (Y/N). For patients who will

receive radiation to the esophagus**,** randomization will be stratified based on the volume of esophagus receiving 40 Gy: (1) 20-40%; (2) 41-60%; (3) 61-80%.

CORe will set up a Randomization website and the Investigational Pharmacy personnel will perform the randomization assignment.

Both patients and the research staff conducting the assessment will be blinded to the treatment assignment. Placebo powder identical to glutamine powder in appearance and taste will be compounded by Healios Nutrition Oncology, and both will be dispensed by Investigational Pharmacy at MD Anderson. At the end of the blinded phase, we will assess blinding by asking patients which study arm they believe they have been randomized to.

Unblinding Procedure:

1. The Statistician and the investigational pharmacist will have access to the codes/assignments.
2. The codes will be revealed only if there is a safety issue and the treating physician needs to be aware of the treatment assignment.
3. The PI should be contacted regarding the patient's circumstances.
4. Prior to unblinding a patient, the investigator or research team will inform the IND Office Medical Monitor.
5. The Investigator will then give permission for the unblinding to the statistician and the investigational pharmacist.
6. The investigator or research team will notify the DSMB and IRB of the unblinding.

Appendix A: Guidelines for Best Supportive Therapy

If patients develop mucositis or esophagitis of grade 1 for more than 5 days or grade 2 or above, the attending physician may have the option to initiate the patient on a best supportive therapy. The treatment that the Department of Investigational Cancer Therapeutics generally uses for the management of mucositis is the following[13]:

- Xyloxylin- 1:1:1 ratio of diphenhydramine, Maalox, lidocaine; 10 milliliters (mL) swish/ swallow every 6 hours as needed)
- Caphasol (sodium phosphate; 15 mL swish/spit every 4 hours as needed)
- Valacyclovir (500 mg po TID for treatment)
- Biotene (MW every 4 hours as needed)
- Carafate (1 gm/10 mL; 10 mL swish/swallow or spit QID as needed)

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