A PHASE II RANDOMIZED STUDY OF SHORT-TERM DEXAMETHASONE VERSUS PLACEBO FOR FATIGUE IN PATIENTS RECEIVING RADIATION ALONE OR RADIATION AND CHEMOTHERAPY FOR THE TREATMENT OF HEAD AND NECK AND NON-SMALL CELL LUNG CANCERS

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Investigational Product Supplier	**University of Arizona Research Pharmacy** **1501 N. Campbell Avenue** **Tucson, Arizona 85724**

Investigator Agreement

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

Signature

11/03/17
Date (MM/DD/YY)

Sun K. Yi, M.D.
Name of Principal Investigator

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1. INTRODUCTION

1.1 Phase:
This is a phase II, single center, randomized, double-blind, placebo-controlled study assessing the effects of dexamethasone versus placebo on radiation fatigue, quality of life (QoL), and treatment interruption in patients receiving definitive treatment for head and neck and non-small cell lung cancers. Subjects will be stratified by treatment (radiation alone vs. radiation plus systemic therapy) and randomized within strata to one of two treatment arms with equal probability.

1.2 Indication:
Dexamethasone for the treatment of radiation related fatigue, QoL, and treatment interruption in patients receiving radiation therapy (RT) for head and neck (HN) and non-small cell lung cancer

1.3 Endpoints:

Primary
- Fatigue score assessed via the Functional Assessment of Chronic Illness-Fatigue (FACIT-F) 13-item fatigue subscale

Secondary
- QoL score assessed via the FACIT-F 40-item total score (27+13)
- Total days and cause of treatment interruption

1.4 Patient population:
Eligible subjects must be able to understand and sign the study specific subject consent form. They must be $\geq$18 years of age, have a KPS of $\geq$60 with confirmed histologic or cytologic diagnosis of HN cancer (stage I-IV) or non-small cell lung cancer (stage II & III) for which they are receiving definitive treatment with either RT alone or in combination with systemic therapy. Subjects may not be diabetic and must have recent labs as defined in the inclusion and exclusion criteria found in Section 6.

2. STUDY DESIGN

2.1 Phase: This is a phase II, single center, randomized, double-blind, placebo-controlled study.

2.2 Number of centers: One
This study will be performed by The University of Arizona Medical Center (UAMC) Radiation Oncology Department at both the University Campus Hospital and Orange Grove Clinic.

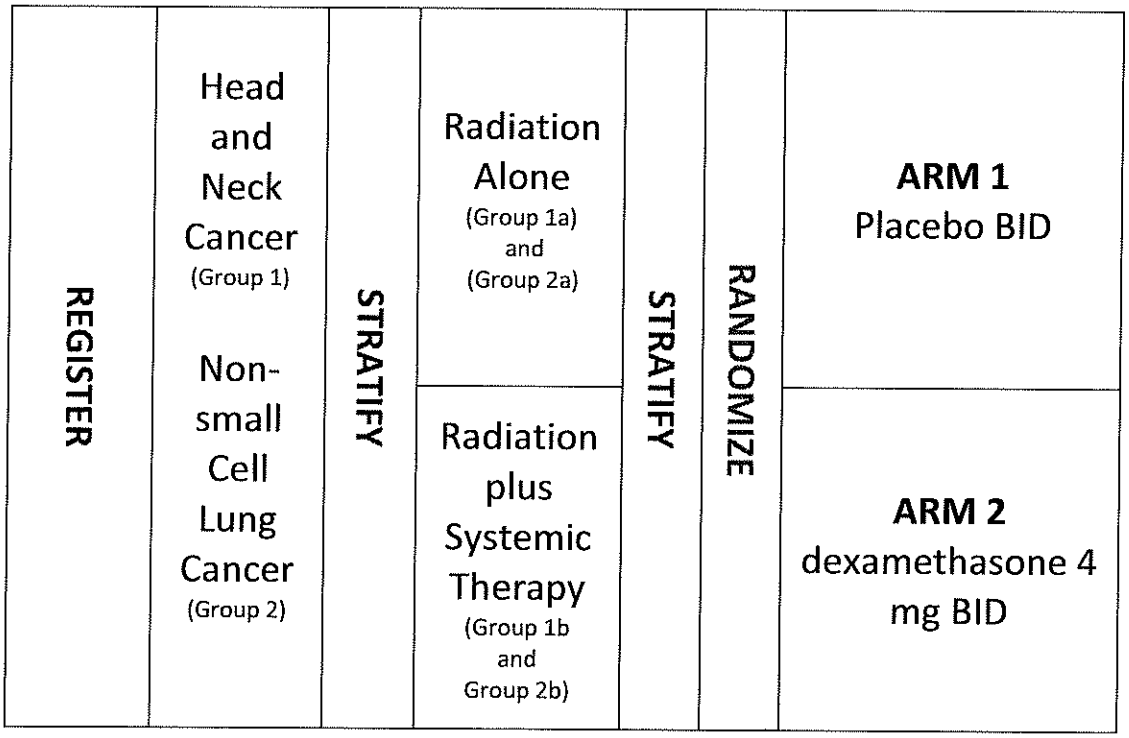
2.3 Number of subjects: Approximately 80

2.4 Subject participation time period:

Subjects will be enrolled in the study for approximately four months, including screening time, treatment time, and follow-up at 30 and 60 days post radiation therapy.

Subjects enrolled in this study are undergoing treatment at UAMC Main Campus or Orange Grove Clinic as part of standard of care for the treatment of HN or non-small cell lung cancer. Study subjects will be treated with either dexamethasone or placebo for 14 consecutive days during RT. Typical RT schedule is six to seven weeks in length with treatments administered Monday through Friday. Subjects will begin the taking the investigational product (dexamethasone or placebo) on RT day 16. Fatigue and QoL will be measured with validated FACIT-F patient surveys that will be completed during RT visits and 30 and 60day post RT follow-up evaluation. The number of days and cause of RT treatment interruption will also be tracked.

SCHEMA



3. OBJECTIVES

3.1 Primary:
To compare the effects of dexamethasone and placebo on radiation fatigue using validated measures

3.2 Secondary:
To determine the effect of dexamethasone on QoL and RT treatment interruption

4. BACKGROUND and RATIONALE

4.1 Disease

Among symptoms experienced by cancer patients, fatigue has been reported as being the most common and distressing.[1,2] Cancer related fatigue (CRF) is multi-factorial with comorbidities, tumor burden and treatment (i.e. surgery, chemotherapy, radiotherapy) all contributing. Survey studies have shown CRF to impact activities of daily living and quality of life (QoL) greater than pain, nausea, depression, and/or sexual dysfunction.[1] One may postulate that both cancer and treatment related fatigue may influence a patient's ability to successfully complete therapy uninterrupted, potentially impacting disease outcomes. It has been clearly demonstrated that interruption and/or delay in completion of radiotherapy (RT) in Head and Neck (HN) and lung cancer is a strong negative predictor for loco-regional control (LRC) and overall survival (OS).[3,4,5]

The relationship between RT and fatigue has been well described. Patients undergoing treatment for brain, HN, breast, lung, pelvis and lymphatic system cancers are best documented.[6] In a study by Hickok et al., 372 patients receiving RT for various cancers were followed prospectively and given weekly symptom inventory surveys for a minimum of five weeks to assess fatigue. Of 160 patients who reported no fatigue at baseline, 70% were found to experience fatigue related symptoms at some point during treatment. In contrast, only 13% of patients remained fatigue free.[7] In another study looking specifically at 117 patients receiving RT for HN cancer, Jereczek-Fossa et al. showed that all patients experienced some level of fatigue during RT with peak levels occurring at week six of treatment (see Figure 1 below).[8]

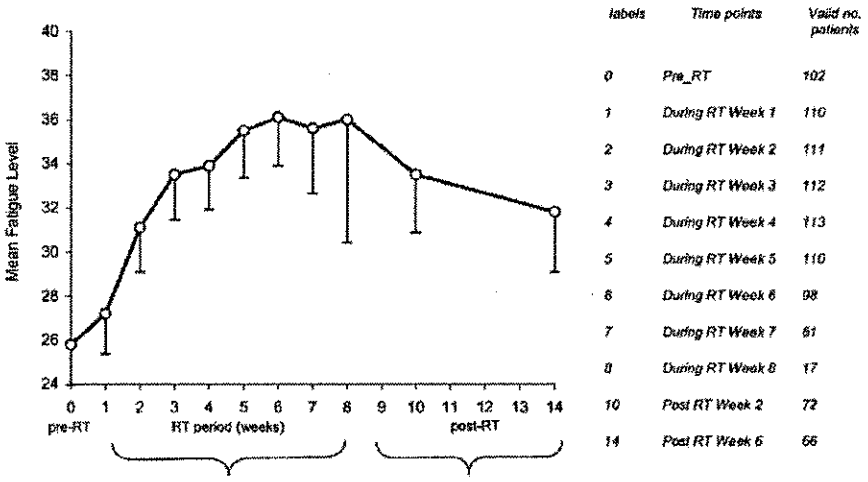


Fig. 1. Fatigue evolution during radiotherapy (RT) for head and neck tumor. Fatigue scores assessed before, during, and after RT with use of the Multidimensional Fatigue Inventory (MFI-20) questionnaire are shown. Data are mean ± standard deviation.

The use of corticosteroids for treatment of CRF has largely been anecdotal.[9,10] Corticosteroids not only improve fatigue but also pain, nausea, and anorexia, making this an attractive option in cancer management. A prospective randomized clinical trial conducted by Moertel el al., studied the impact of dexamethasone on performance

status (PS) in patients with unresectable gastrointestinal adenocarcinoma who were deemed unsuitable for chemotherapy. Patients were randomized to receive placebo, dexamethasone 0.75 mg four times a day, or dexamethasone 1.5 mg four times a day until death or intolerability of the medication. Both choice of corticosteroid and dose were based on clinical experience at the time of study design. A total of 116 patients were included and no difference in PS or OS was detected.[11] Some weaknesses of this study include the absence of a validated tool for measuring patient PS and low dose of corticosteroid.

Additional prospective studies for pharmacologic intervention in the management of CRF are highlighted in a 2013 review article by de Raaf and van der Rijt, where 10 trials investigating 7 medications (paroxetine, donepezil, adenosine triphosphate, L-carnitine, methylphenidate, dexamphetamine, and dexamethasone) were included. Among these studies, a significant improvement in CRF was present only in studies utilizing methylphenidate (1 of 4 studies) and dexamethasone (1 of 1 study).[12] Corticosteroids have the potential benefit over psycho-stimulants for patients receiving RT through their anti-inflammatory properties which likely reduce treatment related edema and potential late fibrotic related complications.

A double blind, randomized, placebo-controlled trial by Yennurajalingam et al., assessed the efficacy of dexamethasone in the management of CRF. Eighty four patients were randomized to placebo or dexamethasone 4 mg twice daily for 14 days. The previously validated Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) was used to measure change in mean fatigue from baseline to day 15. Patients were included if they had advanced cancer, Edmonton Symptom Assessment Scale (ESAS) score ≥4, and ≥3 of the following symptoms within 24 hours prior to enrollment: pain, fatigue, chronic nausea, anorexia/cachexia, sleep disturbances, and/or depression. Patients receiving RT were included in this study, although exact numbers were not reported. Results showed that dexamethasone significantly improved both FACIT-F subscale scores (9.0 vs. 3.1, P=0.008) and FACIT-F total quality of life scores (18.16 vs. 7.87, P=0.030) when compared to placebo. Adverse events were assessed with the National Cancer Institute Common Toxicity Criteria, and no significant differences were found.[13]

Few high quality prospective randomized clinical trials have been conducted for corticosteroid use in the management of CRF.[12,13,14] Of studies published thus far, all were non-selective for disease sites and cancer directed therapy offered, and most included patients deemed incurable and in the palliative setting. Nearly all patients undergoing chemoradiation for the definitive management of HN and lung cancers experience cancer and treatment related fatigue toward the end of their therapy, which often leads to unplanned treatment interruptions and potentially worse outcomes. We hypothesize that a short course steroid intervention midway through RT will impact fatigue related measures, QoL, treatment interruption, and potentially disease related outcomes.

4.2 Investigational Product: Decadron (dexamethasone)

Corticosteroids are structurally similar to endogenous cortisol and act on target cells by regulating the transcription of target genes.[15] Arguably their most clinically relevant side

effects involve the endocrine system, in particular adrenal suppression and hyperglycemia.[16,17]

Adrenal suppression occurs in a dose and duration dependent manner, and may cause an inadequate stress response if major illness concurrently occurs. Patients receiving any corticosteroid dose for less than three weeks duration are considered unlikely to develop suppression and may stop treatment without a taper.[18] This study will attempt to treat radiation fatigue with a 14 day non-tapered course of dexamethasone as previously published.[13]

Hyperglycemia with corticosteroids occurs because of decreased insulin sensitivity, increased gluconeogenesis, and inhibition of insulin secretion.[16] A typical 10-20% increase in blood glucose has been reported with up to one fifth developing steroid diabetes.[19] No official recommendation exists on monitoring blood glucose during acute treatment.[17] The only available guide is in the setting of chronic post-transplant therapy, which recommends screening fasting plasma glucose (FPG) levels once a week during the first four weeks.[20]

Some have argued that FPG levels may actually be a poor marker during corticosteroid treatment because these drugs influence post-prandial levels most significantly and often do not affect fasting levels. Trence recommends checking weekly random plasma glucose (RPG) levels during corticosteroid treatment with a goal below 180 mg/dL.[16] Similarly, Lansang and Hustak endorse RPG with a level of ≥200 and classic symptoms of diabetes for detecting glucocorticoid-induced diabetes.[17] This cutoff is taken directly from diabetes guidelines and is an official criterion for the diagnosis of diabetes.[21]

As an added safety measure this study will monitor RPG levels during dexamethasone treatment since they are influenced more than FPG and we wish to avoid fasting in our patient population. Encouraging fasting in patients who commonly experience anorexia and weight loss from both disease and RT would promote suboptimal care.

4.3 Pre-clinical Experience

A1988 review article by Ettinger and Portenoy highlighted the utilization of corticosteroids in cancer symptom management. Use was described as widely accepted in practice despite a lack of well-controlled studies. Dose selection has been derived empirically from pain dosages and the regimen of dexamethasone 4 mg every 6 hours has been suggested.[9] More recently, a 2009 National Comprehensive Cancer Network survey of 1,000 oncologists reported that 23% to 33% frequently prescribe corticosteroids for CRF at the end of life.[13]

4.4 Clinical Experience

Preliminary clinical data from one prior phase II study performed at MD Anderson support that dexamethasone 4 mg by mouth twice daily is more effective than placebo in improving CRF and QoL in patients with advanced cancer. No significant difference in adverse effects was observed between groups.[13]

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product (IP)
Dexamethasone 4 mg taken orally twice daily for 14 days or placebo taken orally twice daily for 14 days

5.2 Investigational Product Supply
The IP is an FDA approved drug which will be supplied from the UMC investigational pharmacy. The dexamethasone will either be cut in half or crushed and placed in a capsule. A placebo that is made from Equal sugar substitute will be placed in the same type of capsule as the dexamethasone and only the pharmacist will know if the medication given to the patient is dexamethasone or placebo.

5.3 Investigational Product Accountability
Because the IP will be ordered directly by the UMC Investigational pharmacist, the receipt of shipment, dispensing and return or destruction records will be tracked using the Investigational Agent Accountability Record or other applicable and similar record. Once a signed order for IP is received by pharmacy, the IP will be given to the research staff to dispense to the study participant. Participants will be asked to keep a pill diary. All containers will be returned by the patient and then taken to pharmacy by the research staff. The number of pills taken will be documented, and any pills not taken will be destroyed in accordance to the UAMC Pharmacy policy.

5.4 Storage
The IP will be stored in a temperature controlled room in the UAMC Research Pharmacy with limited access to personnel.

5.5 Preparation
The IP will be prepared by the investigational research pharmacists or technician in the investigation research section of the UMC pharmacy. Once an order is written by the treating doctor and received by pharmacy, the pharmacist will dispense the blinded study drug. A member of the research staff will pick up the prescription bottle and will give the bottle directly to the subject.

5.6 Handling
There is no special handling required for the IP

6. SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log in the UACC OnCore system of all potential (i.e. consented) study subjects, which will include as applicable (demographics, informed consent, eligibility, treatment assignment, on treatment, off treatment, follow up and off study dates).

6.1 Inclusion Criteria
1. ≥18 years of age

2. Histologic or cytologic confirmation of head & neck cancer (stage I-IV) or non-small cell lung cancer (stage II & III)
3. Undergoing definitive treatment with either radiation alone or in combination with systemic therapy
4. KPS≥60
5. Willing to consent to participate
6. Normal cognition and willingness to complete fatigue and quality of life forms at each designated time point along with a patient observation form and pill diary
7. Life expectancy ≥ 3 months
8. Able to tolerate oral medication
9. Adequate organ function: laboratory values to be obtained within 90 days prior to registration or if not already performed, after subject consenting
    a. Hematology: Absolute neutrophil count (ANC) ≥1500/μL, Hemoglobin (Hgb) ≥9.0

6.2 Exclusion Criteria

1. Hypersensitivity to dexamethasone or corticosteroids or Equal sugar substitute
2. Corticosteroid within the past 30 days prior to registration on this study for greater than one week duration
3. Planned Stereotactic Body Radiation Therapy (SBRT)
4. Active psychosis
5. Current pregnancy
6. Active peptic ulcer disease or evidence of gastrointestinal bleed
7. Current active tuberculosis or systemic fungal infection
8. Previous diagnosis of diabetes mellitus
9. Acute febrile illness
10. Human immunodeficiency virus or acquired immunodeficiency syndrome
11. Major surgery within two weeks of study registration of which the patient has not recovered
12. Psychostimulant use in the past 30 days prior to registration
13. History of phenylketonuria (PKU)
14. Allergy to sugar substitute.

6.3 Enrollment

The source of subjects is the patient population at the University of Arizona Health Network/Arizona Cancer Center. Patients who are scheduled as part of their routine care to consult with the radiation oncologist for definitive treatment of HN cancer (stage I-IV) or non-small cell lung cancer (stage II & III) will be provided with information regarding this study. See attached list for our website, newsletter and Front Desk Poster.

Subjects will be consented at an already scheduled appointment with the radiation oncologist. This could be either at their initial consult visit or during their CT simulation appointment. Subjects will have the opportunity to take their time in making a decision, and will be encouraged to take the Informed Consent Form

home and discuss it with whomever they would like. The treating physician will explain to the subjects the risks and benefits. They will be informed that their participation is voluntary, and lack of participation will not affect the subject's relationship with the treating staff or our facility. Subjects will be consented by either the PI, or the Research Staff of the Radiation Oncology department. Subjects will also be made aware that should they consent, they can withdraw their consent at any time. When new information becomes available, it will be given to the patient as soon as possible, either at their next visit, or if that is more than 30 days away, by phone call. Once an approved revised consent form is submitted and approved by the IRB, the subject will be asked to sign the new consent and the subject will be notified of the change to the consent form. The AZCC Verification of Consent form will be completed at the time the subject is consented. This form includes information pertaining to who is present at consenting, that the consent form was reviewed with the subject, the subject understood the consent form, and the date and the time of the consent. Also documented will be the version of the Subject Consent form and the HIPAA form. Only English speaking patients will be enrolled.

Subjects will be registered by the University of Arizona Research Pharmacy. Once subjects complete the screening process for this study and are deemed eligible, required information will be given to the pharmacy staff to register the subject in a stratification/randomization system designed by biostatistician Denise Roe, DrPH.. Each subject will be identified by a unique number and their initials. Only the pharmacy will know which arm the subject is randomized to.

7. STUDY PLAN

7.1 Treatment Regimen

Subjects will be stratified by type of disease and whether or not they will be receiving chemotherapy and then randomly assigned to receive either dexamethasone 4 mg twice daily or placebo twice daily for 14 days via the oral route. Assignment of IP will be done in a double-blinded fashion. Both active drug and placebo will be compounded to look identical in appearance. Treatment with IP will start on day 16 of RT and subjects will complete a pill diary in order to track their medication adherence. Subjects will be advised to take the IP with food at approximately 8 a.m. and 2 p.m. ±2 hours. Subjects will also be advised that if they are experiencing difficulty swallowing as a result of treatment and are unable to swallow a pill, they can mix the contents of the capsule with either applesauce or any liquid. They will also be asked to complete an observation form, beginning with their first day of IP and continuing until 60 days post RT, describing any side effects or problems they experience while on the study medication.

Subject's RPG levels will be monitored prior to starting IP via glucometer on RT days 15 [±2 days],20 [±2 days] and 25 [±2 days], with optional testing per physician discretion on the final day of RT and 30 and 60 day RT follow-up visits. If subjects have had blood drawn within the +/- 2 day window that includes glucose testing, they will not be required to have a fingerstick blood glucose test. Subjects who meet a modified Common Terminology Criteria Version 4.0 for adverse events Grade 3 hyperglycemia criteria, RPG level greater than or equal

to 250 mg/dL, will be told to discontinue IP immediately and have a repeat RPG level performed in 3 RT days.

Subjects will be seen once per week per standard of care for on-treatment visits. Weight, BP and evaluation of side effects (including mucositis evaluation) will be performed. FACIT-F 13-item fatigue subscale and FACIT-F 27-item total questionnaires will be completed by subjects during screening and on RT days 5 [±2 days], 10 [±2 days], 15 (day prior to IP start) [±2 days], 20 [±2 days], 25 [±2 days], 26 [±2 days] and 30 (or last day of RT if course extended) [±2 days] along with 30 day post RT follow-up [±7 days] and 60 day post RT follow-up [±7 days] to assess fatigue and QoL. If a subject discontinues IP early for any reason they will still complete FACIT surveys on RT day 26 [±2 days] so they can be included in an intention to treat analysis. Furthermore, if a patient has their RT extended, they will complete FACIT surveys on their last RT day rather than RT day 30.

7.2 Pre-medications: not applicable

7.3 Rescue medications: not applicable

7.4 Excluded medications:
Excluded medications include all psychostimulants (amphetamine salts, methylphenidate, modafinil, etc.) and are not to be used within 30 days prior to registration, during RT, or before the one month follow-up visit after the completion of RT [±5 days].

Corticosteroid usage greater than 1 week duration in the 30 days prior to registration is not permitted. Additionally, no new courses of corticosteroids should be initiated during RT or before the one month follow-up visit after the completion of RT [±5 days]. Subjects may continue pre-chemotherapy steroids during the study.

8. REQUIREMENTS FOR TREATMENT

8.1 Standard dose/treatment
The standard dose of dexamethasone varies by indication with a recommended initial dosage range of 0.75 mg to 9 mg daily. Daily dosages of up to 30 mg may be used in certain clinical settings.[22] The use of dexamethasone for CRF is off-label. The dosage and regimen selected for this study are identical to a previously performed study that treated CRF with dexamethasone 4 mg twice daily.[13]

8.2 Dose/treatment modification
Subjects experiencing bothersome side effects (insomnia or irritability) may reduce dose by 1/2 (by not taking the afternoon dose), if deemed necessary by the physician. If Subjects have a long RT treatment break (greater than one week) ithin the first 5 days of their study drug, they may be asked to discontinue the study drug and re-start once radiation therapy has re-started. This determination will be made by the PI of the study or the treating physician.

If a subject is taken off the IP due to elevated RPG, they will continue to complete weekly FACIT questionnaires during RT and FACIT questionnaires at a 30 and 60 day post RT follow-up evaluation [±7 days].

8.3 Investigational Product Dose Delay

Subjects will start taking IP on RT day 16. The IP will be taken twice per day continuously for 14 days. If there are RT interruptions prior to the IP start date, subjects will still begin IP treatment on RT day 16. If RT interruptions occur while taking the IP, subjects should continue IP per protocol. All subjects will take a full 14 day continuous course of IP unless instructed by the principal investigator to discontinue because of elevated RPG or unacceptable toxicity as deemed appropriate by the Principal Investigator. Subjects will be advised to take the IP with food at 8 a.m. and 2 p.m ± 2 hours. Subjects unable to swallow the IP capsule whole may open the capsule and sprinkle the contents into applesauce for assistance with administration.

If a subject misses a scheduled dose of IP within the recommended window, they should skip the missed dose and resume treatment at the next scheduled time. They should never double-up doses. Treatment course will not be extended beyond 14 days to compensate for missed doses. Subjects will stop treatment after 14 total days have passed and return any missed doses or unused drug as described in Section 5.

8.4 Definition of a Dose Limiting Toxicity (DLT)

Subjects will continue on IP twice daily for 14 days unless instructed to stop IP as described elsewhere. If the subject meets the criteria listed above to be taken off the study, they will discontinue IP, but all assessment will still be done.

9. STUDY PROCEDURES See Study Schedule, Section 26

9.1 Screening

Potential subjects will enter the screening period of the study after completely executing a study specific informed consent form.

9.2 Registration/Randomization

Once this study is approved by all internal regulatory agencies to enroll subjects, study enrollment will begin.

The stratification/randomization procedure utilized will be created by biostatistician Denise Roe, DrPH and will employ a system of prepared envelopes and blocks of random numbers.

Patients will be identified by their initials (First, Middle if available, Last) and a study number. Study numbers will begin with Yi-C-001and continue sequentially.

9.3 On IP treatment

Registered subjects will be treated with either dexamethasone 4 mg or placebo, both taken orally twice per day for 14 days. Once starting the IP subjects will be asked to complete a pill diary with the time of day each dose is taken. They will

also be asked to complete a patient observation form listing any side effects they may encounter.

9.4 End of IP Treatment
Subjects will complete IP after a 14 day course.

9.5 Follow up
Subjects will be seen for one 30 day [±15 days] follow-up visit after the end of RT and then again at 60 days post RT [±15 days] for a final follow-up visit. During these visits, routine vitals will be taken and review of systems, physical examination and adverse event documentation will be performed. See treatment plan calendar.

9.6 Early treatment termination
Subjects that terminate IP prior to the completion of the 14 day course will still be seen as per the study schedule and will complete FACIT surveys on RT day 25, 30 and the last day of RT if they receive more than 30 treatments [±2 RT days] so they can be included in an intention to treat analysis. For patients that have difficulty with transportation or keeping scheduled appointments, one of these follow-ups may be done over the phone. No vitals will be obtained, however, they will be asked the questions from the FACIT survey, as well as asked about any adverse events they may be experiencing.

9.7 Off study
Subjects will be considered off study after completing their 60 day post RT follow-up visit. All subjects, even those who did not complete the 14 day course of study treatment will be seen for an end of study visit, which will be done at the 60 day post RT follow-up. Subjects will also be considered off treatment if they chose to voluntarily withdraw from the study.

10. PHARMACOKINETIC STUDIES

Not applicable

11. DATA AND SAFETY MONITORING PLAN

Protocol Data and Safety Monitoring Plan (Medium Risk)

Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are not designated as high risk per NCI, do not meet the above criteria of medium plus IND risk, and do not require an the IND (i.e. IND exempt).

11.1 Data and Safety Monitoring Plan:
Identification of the DSMB obligated for oversight responsibilities:
The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

11.2 Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

11.3 Monitoring progress and data review process:
Routine monitoring of subject data will be conducted at least every six months. The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility - 50% of cases, up to two subjects;
- Data review - 50% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. A query/finding form or an electronic record will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form, or will be notified of the electronic record for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit. Electronic records will be available in the institution database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.
Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms, and subject questionnaires should be completed via the institution database or other acceptable data formats. Trials using paper CRFs will have the data entered with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

11.4 Process to implement study closure when significant risks or benefits are identified:
If a Common Terminology Criteria for Adverse Events (CTCAE Version 4) grade 5 toxicity occurs that is directly related to the dexamethasone or placebo, the study will be discontinued.

11.5 Description of adverse events and reporting procedures:

ADVERSE EVENTS
An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator. Adverse events will be documented for 30 days after the completion of radiation therapy [±5 days].

All adverse events will be classified using either the MedDRA term or NCI CTCAE version 4.0 and will address:

- Grade
- Relationship to study drug(not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, current illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS
A serious adverse event (SAE) is any untoward medical occurrence that at any dose:
1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the DSMB Coordinator. All serious adverse events, regardless of attribution, and any deaths will be reported within 5 days of notification of the event to the University of Arizona Human Subjects Protection Program.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

11.6 Plan for assuring data accuracy and protocol compliance:
Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;

11.7 Identification of the sponsor or funding agency
Not applicable

12. ADDITIONAL SAFETY REPORTING

Serious adverse events will be reported to the Data Safety Monitoring Board as well as the institutional IRB within 24 hours of notification of the event to the PI. Serious adverse events will be reported using the FDA MedWatch form to inform the DSMB, and using the F224 (Reportable Local New Information that is Potentially Problematic) form to inform the IRB.

13. QUALITY ASSURANCE MEASURES

Per the UACC DSMB Charter, Internal *Ad Hoc* audits may be performed on any UACC clinical trial if identified for audit, the audit will be conducted by an identified audit team per the UACC DSMB Charter. A QA/QC representative will coordinate the audit team functions and a written audit report will be provided to the principal investigator and the DSMB.

14. RECIST CRITERIA

Not applicable

15. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational product.

Subjects that wish to discontinue active IP treatment may elect to continue with the other protocol required assessments. The investigator should discuss with

the subject the options for continuation of the study schedule of assessments (i.e. blood work, scans, physical exams, diaries) and collection of data, including endpoints and adverse events.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, phone contact, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

16. STASTISITICAL CONSIDERATIONS

Statistical analysis will be performed in collaboration with Dr. Denise Roe, the Director of the University of Arizona Cancer Center Biometry Shared Service. The primary outcome is the change in the fatigue score between radiation days 15 (day prior to IP initiation) and 26 (day after IP completion) in the dexamethasone versus placebo patients as measured by the Functional Assessment of Chronic Illness-Fatigue (FACIT-F) 13-item fatigue subscale. Secondary endpoints include the QoL score as measured by the FACIT-F 40-item total score, and the total days and cause of treatment interruption. Randomization will be stratified by tumor location and treatment type (radiation alone versus radiation plus systemic therapy). Analysis of the continuous endpoints (change in FACIT-F fatigue subscale and change in FACIT-F total score) will be performed using a two-sample independent t test comparing the dexamethasone versus placebo patients. Analysis of the total days of treatment interruption will be performed using a Wilcoxon Rank Sum Test, since the number of days may not be normally distributed. Alternatively, the proportion of patients with any treatment interruptions will be compared using a Fisher's Exact Test.

The sample size of 40 patients per group was chosen based on the previous study of Yennurajalingam et al. in advanced cancer patients with at least three cancer-related fatigue symptoms.[13] They observed a mean improvement in the FACIT-F fatigue score of 9.0 (standard deviation = 10.30) in the dexamethasone treated group versus a mean improvement of 3.1 (standard deviation = 9.59) in the placebo group. We chose a one-sided statistical test (at the alpha = 0.05 level) as dexamethasone will only be recommended in our patient population if it improves cancer-related fatigue. Based on these considerations, 36 patients per group will provide 80% statistical power. We rounded the necessary sample size up to 40 patients to allow for the possibility of up to a 10% drop-out of patients from their radiation therapy between days 16 and 26.

Exploratory analyses will profile the change in the FACIT-F fatigue subscale and FACIT-F total score across the entire radiation therapy course (measured at baseline screening, on RT days 5, 10, 15, 20, 25, 26, and 30, and 60 day follow-

up) separately for the dexamethasone versus placebo treated patients. Descriptive statistics (mean, medians, standard deviations) will be computed separately for each treatment group at each time point.

The primary safety endpoint is random plasma glucose levels measured on radiation therapy day 15, 20 and 25. Treatment will be terminated in patients if the RPG ≥ 250 mg/dL. The FACIT-F questionnaire will continue to be administered per study protocol even if dexamethasone or placebo treatment is terminated. The proportion of patients with treatment terminations will be compared between the two groups using a Fisher's Exact Test. Adverse events will be summarized using CTCAE criteria for each treatment group separately.

17. ANALYSIS

17.1 Safety Analysis

The first safety analysis will be conducted when 20 subjects have completed study treatment. Additional analysis will be done every 20 patients. A brief report will be generated describing any adverse events experienced and number of subjects that were unable to complete IP treatment.

17.2 Efficacy Analysis

Efficacy analysis will be conducted at the completion of the study.

17.3 Interim Analysis

An interim analysis for futility will be performed when 18 patients per group have completed their radiation therapy treatment. A conditional power analysis will be performed based on the data accumulated to date. Briefly, the observed results will be used to generate predicted results for future patients (assuming a normal distribution) with the observed mean and standard deviation observed in each group. One thousand bootstrap samples with a sample size of 36 patients per group (target sample size) will be generated to estimate conditional power. The study will continue if the conditional power is > 80%. Note that this analysis is for futility only, so will not affect the overall alpha level.

18. REGULATORY OBLIGATIONS

18.1 Informed consent

Before a subject's participation in the clinical study, the investigator or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures, investigational product, intervention or device are administered or initiated.

18.2 Institutional Review Board

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

19. ADMINISTRATIVE PROCEDURES

19.1 Investigator responsibilities
The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

19.2 Data and Safety Monitoring Board protocol review
Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

19.3 Multicenter Trials
Not applicable

19.3.1 UACC DSMB and QA/QC Monitoring

The UACC QA/QC Program will be responsible for routine monitoring of local study data for the coordinating center.

19.3.2 Alternate DSMB Oversight
Not Applicable

20. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

21. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he has delegated study duties. All persons authorized to make entries and/or corrections on case report forms (CRF) will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

22. DATA

Applicable data as specified as required in the protocol will be reported/submitted in the CRF. Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. CRFs will be completed via the paper and OnCore. In addition, data will be entered into RedCap which is currently being used by many UMC departments for their study data bases.

Additional procedures and assessments may be performed as the institution's standard of care; however these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product.

23. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

Approvals or waivers for protocol deviations will be obtained from the investigator prior to occurring, except changes to eliminate an immediate hazard to study subjects. If immediate verbal approval is obtained, it will be documented by the

research staff obtaining the approval and followed by a written protocol deviation form per the site standard operating procedures. The investigator will sign the Protocol Deviation (Waiver) Approval Form or other similar document. The original will be filed in the regulatory binder and a copy will be placed in the subject's research file.

24. KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

25. COMMON TOXICITY CRITERIA

CTCAE version 4.0

26. STUDY SCHEDULE

		Baseline screening	RTD1	Weekly During RT (+/- 2 RT Days	RTD15	RTD16	RTD20	RTD25	RTD26	RTD30 **	Last Day of RT	30 & 60 day F/U
	Informed Consent/Enrollment	X										
Eligibility Assessment	Medical history (1)	X										
	Physical exam and KPS (2)	X								X **	X	X
	Assess recent/concurrent meds (3)	X										
	Hematology (4)	X										
	Tumor info and treatment (5)	X										
	Registration	X										
	Randomization	X										
	FACIT-F total QoL (6)	X		X	X[9]		X	X		X	X	X
	Dispense Medication				X							
	Investigational Product (7)					X			X12			
	Pill Diary				X				X12			
	Observation Form (11)				X				X		X	X
	RPG fingerstick (8)				X		X	X			X[10]	X[10]
	Adverse event evaluation		X	X	X		X	X		X	X	X
	RT treatment interruptions										X	

1 = Medical history will include demographics (this can be done within the last 60 days prior to registration as part of standard of care)
2 = All physical exams to include vitals (BP, pulse, temperature, weight) (this can be done within the last 60 days prior to registration as part of standard of care)
3 = Review current medications including corticosteroid, psychostimulant, and systemic cancer treatments in past 30 days
4 = Hematology to include Hgb and ANC within the last 90 days as part of standard of care, or after consenting, but prior to first treatment
5 = Confirmation of cytologic or histologic evidence of HN or non-small cell lung cancer
6 = QoL survey, 27 questions (completed ± 2 RT days from scheduled time point)
7 = Start IP and take for 14 consecutive days, unless IP stopped due to elevated RPG
8 = RPG fingerstick (completed ± 2 days from scheduled time point). IP will be stopped if RPG≥250
9 = Survey to be completed the day before IP initiation
10 = RPG per physician discretion

27. GLOSSARY: Not applicable

28. DEFINITIONS: Not applicable

29. REFERENCES

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30. APPENDIX

30.1 Treatment Plan Calendar
30.2 FACIT-F 13 item fatigue subscale
30.3 FACIT-F 40 item total score
30.4 Patient Observation Form
30.5 Patient Pill Diary
30.6 Pharmacy Information Form
30.7 Pharmacy Order Form