Early-Phase, Open-label Study of Tolinapant and Radiation in Cisplatin-Ineligible Patients with Previously Untreated, Locally Advanced Head and Neck Cancer

WINSHIP PROTOCOL #: WINSHIP5380-21

COORDINATING CENTER: Emory University

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EXTERNAL (NON-EMORY) COLLABORATORS

Dr. Carter Van Waes, Clinical Director of the National Institute on Deafness and Other Communication Disorders, will be an external collaborator on this project. Dr. Van Waes has expertise on the use of IAP antagonists for head and neck cancer, and his involvement will be limited to consultation and review of de-identified data. Given his expertise in the topic, Dr. Van Waes will assist with data interpretation. Dr. Van Waes has completed the required training in clinical research methodology and patient confidentiality at the NIH.

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☐ **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	8/15/21	Revised based on recommendations from PRMC, PAT, Office of Compliance, and Astex Pharmaceuticals
2	10/8/21	Revised based on comments from FDA
3	10/13/21	Second revision based on comments from FDA
4	10/28/21	Labs revised slightly with clarification from the study supporter
5	11/04/21	Error in lab schedule edits resolved
6	10/5/22	Clarifications made to eligibility checklist and renal function for eligibility; expanded eligibility to the adjuvant setting including oral cavity cancer
7	2/17/23	Increased consent/screening limit to 15 in order to meet enrollment goal of 10, based on 37% screen failures to date
8	11/30/23	Increased consent/screening limit to 20 in order to meet enrollment goal of 10, based on 50% screen failures to date
9	12/5/23	Protocol edited to fix discrepancies in upper limit of correct QT interval allowed for eligibility
10	9/6/24	Updating references of Astex to Taiho Oncology

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1. Study Summary

1.1 Synopsis

Title:	Early-Phase Open-label Study of Tolinapant and Radiation in Cisplatin-Ineligible Patients with Previously Untreated, Locally Advanced Head and Neck Cancer
Study Description:	This research study is an open label, single arm study, designed to evaluate the safety, tolerability, and efficacy of tolinapant combined with radiation in subjects with previously untreated head and neck squamous cell carcinoma (HNSCC) who are ineligible for treatment with cisplatin chemotherapy.
Objectives:	**Primary Objective**: To evaluate the safety and tolerability of the recommended phase 2 (RP2D) of tolinapant when given in combination with radiation. **Secondary Objectives:** To assess preliminary efficacy of the combination of tolinapant and radiation in cisplatin-ineligible patients with head and neck cancer as determined by locoregional control, two-year progression-free survival (PFS), and two-year overall survival (OS). **Exploratory Objective:** To compare immune cell infiltrates following the first cycle of tolinapant + radiation, compared with baseline biopsy tissue and peripheral blood.
Endpoints:	**Primary Endpoint:** The primary endpoint is safety of tolinapant when given with radiation. Safety measures include adverse events monitoring, vital sign measurements, physical examinations, and clinical laboratory tests. **Secondary Endpoint:** • The secondary endpoint is efficacy, as determined by two-year locoregional control, progression-free and overall survival. **Tertiary Endpoint:** • The exploratory endpoint is the anti-tumor immune response before and after the first cycle of tolinapant + radiation.
Study Population:	**Inclusion criteria** 1. Male or Female 2. Age ≥18 years. 3. ECOG performance status ≤1 (see Appendix A). 4. Patients with histologically or cytologically confirmed diagnosis of HNSCC, previously untreated and locally advanced, for whom definitive or adjuvant (post-surgical) radiation is planned but cisplatin chemotherapy is contraindicated. For the purposes of trial eligibility, anatomic subsites of HNSCC may include the oral cavity,

larynx, oropharynx, hypopharynx, nasopharynx, or unknown primary site presenting with neck lymph nodal disease.

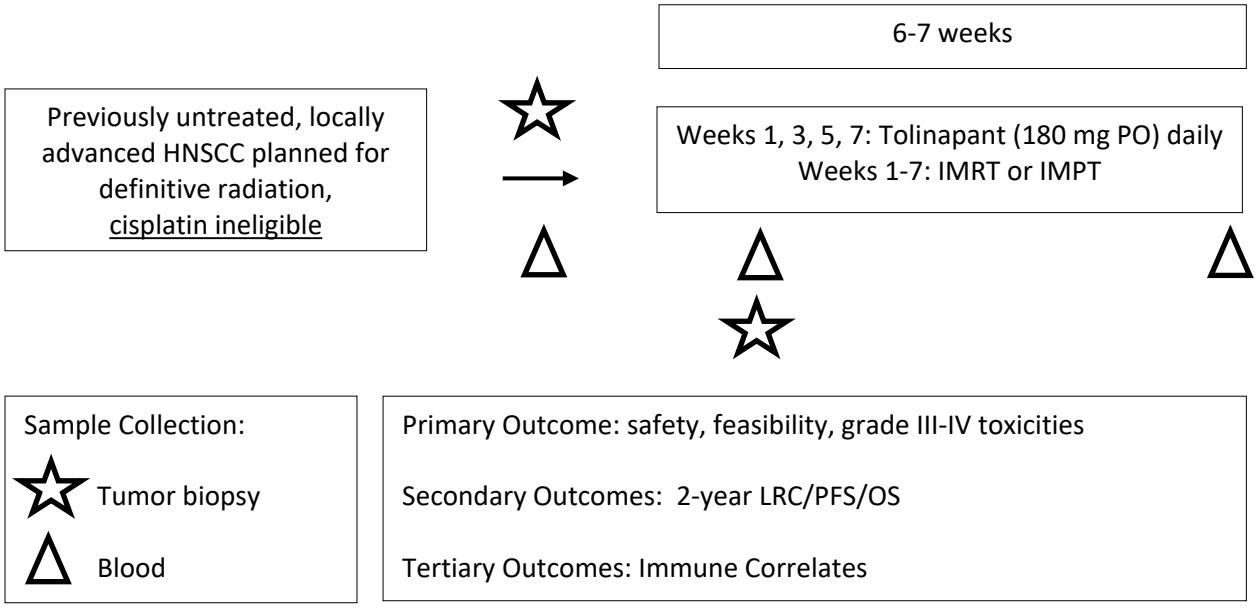
5. Acceptable organ function, as evidenced by the following laboratory data:
6. Absolute neutrophil count [ANC] ≥ 1,500 cells/μl; hemoglobin ≥ 9 g/dl, platelets ≥ 100,000/μl.
7. Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 50 ml/min.
8. Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.
9. Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN.
10. Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN.
11. Amylase and lipase ≤ ULN.
12. The effects of tolinapant on the developing human fetus are unknown. For this reason and because tolinapant as well as other therapeutic agents used in this trial are known to be teratogenic, females of child-bearing potential (FCBP) must have a negative serum pregnancy test prior to starting therapy.
13. Female patients of childbearing potential and men must agree to use adequate contraception (at least one highly effective method and one additional method of birth control at the same time or complete abstinence) prior to study entry, for the duration of study participation and for at least 6 months following study drug discontinuation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (if age > 55 years); if the female subject is < 55 years and she has been naturally postmenopausal for > 1 year her reproductive status has to be verified by additional lab tests (< 20 estradiol OR estradiol < 40 with FSH > 40 in women not on estrogen replacement therapy).
14. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.
15. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria:

1. Patients who have had prior radiotherapy to the head and neck region.
2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drug.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to tolinapant.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance

	with study requirements. 5. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure (or ejection fraction <50%); or Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy. 6. Contraindications to radiotherapy (e.g., uncontrolled connective tissue disorder). 7. Women who are pregnant or breast feeding. 8. Vulnerable populations including prisoners and adults who are unable to consent. 9. Known history of human immunodeficiency virus (HIV) infection, or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. 10. Grade 3 or greater neuropathy. 11. Known distant metastases (i.e., outside of the neck). 12. Known significant mental illness or other conditions such as active alcohol or other substance abuse that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol treatment or assessments. 13. Concurrent second malignancy requiring active therapy. 14. Patients with a history of allogenic transplant must not have ≥Grade 3 graft-versus-host disease (GVHD) or any clinically significant GVHD requiring systemic immunosuppression. 15. Systemic corticosteroids >20 mg daily prednisone equivalent (unless patient has been taking a continuous dose for >3 weeks prior to study entry). 16. Drugs known to cause QT prolongation, unless such drugs cannot be avoided.
Phase:	Early phase
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Patients will receive 3-4 cycles of tolinapant (180 mg PO daily for 7 days) during weeks 1, 3, 5, and 7 (where applicable) of radiation therapy.
Statistical Methods	The study is an early phase safety study; no formal hypotheses or sample size estimates will be generated. The study will enroll 10 subjects evaluable for efficacy; this number of subjects is sufficient to assess preliminary safety and activity to guide design of subsequent clinical studies. Descriptive statistics of response will be summarized: mean, standard deviation, minimum, maximum, median and interquartiles for duration of treatment response. Kaplan-Meier plots for LRC, OS and PFS will be provided.
Study Duration:	Each subject is treated for 7 weeks and followed for two years to estimate 2-year LRC,PFS, and OS. Based on the patient population, it is estimated that the study will require 12 months for accrual and 36 months to complete.

1.2 Schema


6-7 weeks
Previously untreated, locally advanced HNSCC planned for definitive radiation, cisplatin ineligible
Weeks 1, 3, 5, 7: Tolinapant (180 mg PO) daily
Weeks 1-7: IMRT or IMPT
Sample Collection:
Tumor biopsy
Blood
Primary Outcome: safety, feasibility, grade III-IV toxicities
Secondary Outcomes: 2-year LRC/PFS/OS
Tertiary Outcomes: Immune Correlates

1.3 Schedule of Events/Assessments

Procedures		Treatment Period							Follow up				
	Screening/ Enrollment	Wk. 1	Wk. 2	Wk. 3	Wk. 4	Wk. 5	Wk. 6	Wk. 7[a]	1 mo.	3 mos.	6 mos.	12 mos.	24 mos.
Informed consent	X												
Demographics	X												
Medical history	X												
Tolinapant daily x 7 days		X		X		X		X					
Collect dosing compliance information			X		X		X		X				
IMRT or proton therapy		X----------						----------X					
Physical exam	X			X			X		X	X	X	X	X
Vital signs	X			X			X		X	X	X	X	X
Height	X								X	X	X	X	X
Weight	X		X		X		X		X	X	X	X	X
Performance status	X		X		X		X		X	X	X	X	X
Concomitant medication evaluation	X	X	X	X	X	X	X	X	X				
Hematology	X	X		X		X		X	X	X			
serum chemistry [b]	X	X		X		X		X	X	X			
Pregnancy test [b]	X												
EKG	X[d]	X		X		X		X					
Echocardiogram or MUGA	X												
Radiologic/Imaging assessment	X									X		X	X
AEs review and evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for immune correlates	X		X					X					
Tumor biopsy for immune correlates (if feasible)	X		X										
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Week 7 of radiation + tolinapant will be omitted in the adjuvant setting.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, creatinine clearance, glucose, potassium, AST, ALT, sodium, amylase and lipase; PT/PTT/INR at screening; hepatitis serologies at screening if clinical concerns.
b: Serum pregnancy test (women of childbearing potential).
d: Triplicate EKG done at enrollment if QTc >470; QTc must be <470 for study entry.

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the safety and tolerability of tolinapant in combination with radiation in patients with head and neck squamous cell carcinoma (HNSCC).	• Safety: adverse events, grade 3/4 toxicities, delay in radiation therapy or missed radiation doses. • Feasibility: completion of treatment
Secondary	
• To evaluate the anti-tumor activity of the combination of tolinapant + radiation by assessing locoregional control (LRC) and overall survival (OS)	• Locoregional control (LRC) • Overall Survival (OS) • Progression-free survival (PFS) • Duration of treatment response
Tertiary/Exploratory	
• To assess the effects of the combination of tolinapant + radiation on immune cells in blood and tumor. • To assess the association between immune responses and FADD expression in tumors.	• Changes in immune system biomarkers after treatment with tolinapant + radiation and their relationship with efficacy. • Baseline tumoral FADD overexpression and its relationship with the anti-tumor immune response.

3. Background

3.1 Locally Advanced Head and Neck Cancer

Locally advanced head and neck squamous cell carcinoma (HNSCC) that is not amenable to surgery is treated with definitive radiation with concomitant systemic therapy when feasible. The standard radiosensitizing drug for HNSCC is cisplatin, which is associated with nephrotoxicity, myelosuppression, sensorineural hearing loss, and other adverse effects. As a result, many HNSCC patients may not be eligible for treatment with cisplatin due to advanced age and/or comorbid medical conditions. Further, cisplatin at high doses can be severely impair T cell proliferation; a recent randomized trial of high-dose cisplatin chemoradiation for HNSCC showed no benefit from adding the anti-PD-L1 antibody avelumab (Cohen et al., 2020).

Cetuximab has been given with radiation as an alternative, but recent trials in HNSCC driven by human papillomavirus (HPV) showed cetuximab to be less efficacious than cisplatin (Gillison et al., 2019; Mehanna et al., 2019). A combination of carboplatin and paclitaxel has also been used, but there are no large trials demonstrating comparative efficacy of this combination. Thus, there is an unmet clinical

need for a radiosensitizing agent that is less toxic, less immunosuppressive, and more effective versus cisplatin for locally advanced HNSCC.

3.2 Description of Tolinapant

Tolinapant (formerly ASTX660) is a synthetic small molecule dual antagonist of cellular inhibitor of apoptosis protein (cIAP) 1/2 and X-linked inhibitor of apoptosis protein (XIAP) that has been shown to have potent proapoptotic and tumor growth inhibitory activity in cell lines and preclinical mouse models.

Evasion of apoptosis is one of the hallmarks of cancer (Hanahan and Weinberg 2000) and can be achieved by overexpression of antiapoptotic proteins. Inhibitor of apoptosis proteins (IAPs), such as cIAP1, cIAP2, and XIAP, are key regulators of antiapoptotic and prosurvival signaling pathways; XIAP directly inhibits caspases, while cIAPs prevent the formation of proapoptotic signaling complexes. This leads to suppression of apoptosis through both the extrinsic and intrinsic apoptosis pathways (Fulda and Vucic 2012; Dubrez et al 2013; Bai et al 2014). Deregulation of IAPs through amplification, overexpression, or loss of endogenous antagonists occurs in various cancers and is associated with tumor growth and poor prognosis, making them attractive targets for anticancer therapy (Hunter et al 2007). In addition, IAPs have been shown to play a role in resistance to treatment; XIAP is upregulated in response to ionizing radiation (Holcik et al 2000), suggesting a role for IAP antagonists in combination therapy.

In response to tumor necrosis factor alpha (TNF-α), cIAPs ubiquitinate receptor interacting protein kinase 1 (RIP1), thereby promoting the formation of complexes (e.g., complex I) which activate survival signaling through the canonical NF-κB pathway. Simultaneously, formation of the death-inducing signaling complex (DISC), which drives apoptosis, is prevented. Antagonism and subsequent degradation of the cIAPs leads to the stabilization of NF-κB-inducing kinase (NIK), which activates the noncanonical NF-κB pathway, resulting in the production of multiple cytokines including TNF-α. Removal of the cIAPs also allows the DISC to form, leading overall to a switch in TNF-α signaling from pro-survival to pro-apoptotic (Mahoney et al 2008; Bertrand et al 2008; Micheau and Tschopp 2003; Varfolomeev et al 2007; Flygare and Fairbrother 2010).

This loss of cIAP, combined with the release of the XIAP-mediated block on caspases, which is essential for full activation of apoptosis, leads to a sustained proapoptotic effect in the presence of TNF-α via the extrinsic apoptosis pathway. In addition, the antagonism of XIAP-mediated caspase inhibition promotes apoptosis induced by stimulation of the intrinsic apoptosis pathway by agents such as chemotherapeutics or DNA damaging agents (Obexer and Ausserlechner 2014). This suggests that dual cIAP/XIAP antagonists can be used to promote apoptosis through both extrinsic and intrinsic pathways.

Potential adverse effects of IAP antagonists may arise from the increase in plasma TNF-α and inflammatory cytokines associated with their mechanism of action. Cytokine release syndrome (CRS) was reported as the dose-limiting toxicity in a Phase 1 dose-escalation study of LCL161 (Infante et al 2014); such effects have also been described in detail in nonclinical toxicity studies with another cIAP antagonist GDC-0152 (Erickson et al 2013). An antagonist with increased XIAP potency, such as tolinapant, may lead to improved efficacy due to the more effective activation of apoptosis provided by releasing the XIAP-block on caspases (Fulda 2014), and thereby increase the therapeutic window between efficacious dose and onset of cytokine-induced toxicity.

In a recent phase 1 study (Mita et al., 2020), tolinapant was administered orally once daily on a 7-day-on/7-day-off schedule in a 28-day cycle. Dose-limiting toxicities included elevations in amylase and lipase. The maximum tolerated dose (MTD) was determined to be 210 mg/day, and the recommended

phase 2 dose (RP2D) was determined to be 180 mg/day. Clinical activity with tolinapant monotherapy was not seen in cases of recurrent/metastatic HNSCC but was noted in one case of cutaneous T cell lymphoma. The phase 2 study is ongoing.

3.3 Rationale for the Study: Results with Tolinapant + Radiation in Preclinical Models of HNSCC

Several preclinical studies support a rationale for pairing tolinapant with radiation for HNSCC. Analysis of data from The Cancer Genome Atlas shows that a high proportion of HNSCC tumors have genomic alterations in pathways affected by IAP activity, including overexpression of FADD and mutations of caspase 8 (Eytan et al., 2016). When combined with TNF-α, tolinapant enhances killing of both HPV-positive and HPV-negative HNSCC cell lines (Xiao et al., 2019).

In murine models of HNSCC, tolinapant monotherapy shows very little activity, as noted in the phase 1 first-in-human study. However, synergistic anti-tumor activity has been noted when tolinapant or other IAP antagonists are paired with radiation. In a mouse xenograft model of HNSCC with FADD overexpression, the addition of birinapant, another IAP antagonist, to radiation resulted in synergistic activity with cure of a subset of tumors (Eytan et al., 2016). In an immunocompetent, syngeneic mouse model of oral cancer, the combination of tolinapant + radiation also resulted in synergistic anti-tumor activity, especially when anti-PD-1 immunotherapy was added (Xiao et al., 2018). Further, tolinapant + radiation was found to promote multiple aspects of anti-tumor immunity, including dendritic cell activation, immunogenic cell death, and antigen-specific T-cell killing of tumor cells (Xiao et al., 2018; Ye et al., 2020). Unlike cisplatin, tolinapant did not inhibit the *ex vivo* proliferation of T cells, even at very high, supraphysiologic doses.

3.4 Purpose of the Study

The purpose of this study is to determine the safety of tolinapant at the RP2D in combination with definitive radiation in HNSCC. In a recent phase 1/2 study, the IAP antagonist Debio 1143 was safely added to cisplatin chemoradiation for high-risk HNSCC and significantly improved 3-year PFS versus chemoradiation alone, though toxicities were higher with the addition of Debio 1143 (Le Tourneau et al., 2020). If tolinapant is safely combined with radiation in this study, then larger, future studies could investigate the efficacy of tolinapant when used *instead* of cisplatin chemotherapy as a radiosensitizer for HNSCC, with reduced toxicity. Immune correlative studies will also be performed based on preclinical evidence of enhanced anti-tumor immunity with the combination of tolinapant and radiation.

4. Study Intervention/Investigational Agent

4.1 Description

Tolinapant is a synthetic small molecule:
• Molecular formula: C30H42FN5O3.C3H6O3

Capsule Dosage Form: Each capsule contains tolinapant suitable for oral administration. Available dose strengths and bottle packaging details are provided in the pharmacy manual. The bottles are labeled as IP, in accordance with applicable regulations.

The formulation excipients for each dose strength are of compendial grade and are generally recognized as safe (GRAS) and are described in the IB.

4.2 Drug Handling

4.2.1 Tolinapant Storage

Store tolinapant refrigerated at 2°C to 8°C. In the Winship investigational pharmacy, storage must be in a secure, locked facility accessible only to authorized study personnel.

4.2.2 Tolinapant Dispensing

Capsule dosage form:
Capsules are provided in bottles containing 14 capsules each. A sufficient quantity of bottles will be dispensed to the subject by Emory Investigational Drug Services to permit oral self-administration at the required dose level, for the required number of days.

Records of the receipt and dispensing of drug will be kept by IDS and reconciled at the end of the study to provide a complete accounting of all used and unused drug.

4.2.3 Tolinapant Administration

Subjects will receive instructions for the storage and oral self-administration of tolinapant at home. When subjects self-administer the drug at home, they are expected to record the date and time of ingestion in their dosing diary, along with any pertinent notes (e.g., vomiting after ingestion of the dose). Capsules can be swallowed with water. For patients with dysphagia, the capsules may be dissolved in water and given by feeding tube.

An attempt should be made to administer study treatment at approximately the same time of day on each dosing day, not to exceed 6 hours after the established normal dosing time. If, on occasion, the dosing time is more than 6 hours after the normal dosing time, the dose for that day should be skipped. In either case, study treatment should be administered at the normal time the following day.

At any point in the study, the dose of tolinapant may be reduced, withheld, or discontinued for individual subjects in the event of unacceptable treatment-related toxicity. No placebo or active comparator is planned for this study.

Study treatment compliance will be assessed periodically throughout the treatment period. Subjects will be required to return all unused study treatment capsules (as applicable) to the study center, and to share their dosing diary with study staff.

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). Dr. Nicole Schmitt, Principal Investigator and IND Sponsor, will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

4.3 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log must record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages and dates prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP.
Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix C) will be returned to clinic staff at the end of each week of treatment with tolinapant.
Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This clinical trial is an open-label, single-arm, early-phase study of the safety, immunogenicity, and antitumor activity of the combination of tolinapant and external-beam radiotherapy for head and neck squamous cell carcinoma.

The study is divided into a Screening period, Treatment period, and Follow-up period.

During the Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period**. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

Treatment will consist of standard-of-care intensity-modulated photon-based radiation therapy (IMRT) or proton therapy (IMPT) in 35 fractions over 7 weeks with concomitant tolinapant daily for 7 days during weeks 1, 3, 5, and 7. Treatment will continue until unacceptable toxicity, death, Investigator's decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial.

Subjects will be assessed for safety weekly during the treatment period. During the study, subjects will be monitored for adverse events including signs of infection, tumor recurrence, and changes in hematological or chemistry parameters (see Schedule of Study Events/Assessments).

5.2 Dosing and Administration

Dosing will start at the RP2D of tolinapant (180 mg/day) and will not be escalated.

5.3 Definition of Dose-Limiting Toxicity and Stopping Rules

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as definitely treatment related that occurs within the 7 weeks of treatment and meets any of the criteria included below. National Cancer Institute Common Terminology Criteria for Adverse events version 5.0 (NCI CTCAE v. 5.0) will be used for all grading.

Criteria for defining dose-limiting toxicities

Dose-limiting toxicities are AEs judged to be related to tolinapant that occur during the first cycle of treatment and represent any 1 of the following, unless there is a clear alternative cause of the event:

- Thrombocytopenia of grade 4 (any duration) or grade 3 or higher with clinically significant bleeding.
- Febrile neutropenia or grade 4 neutropenia of duration more than 7 days.
- Cytokine release syndrome (CRS) of grade 3 or higher.
- Liver-associated abnormalities as listed below:
    - Any grade 3 or higher ALT or AST elevation excepting ALT or AST elevation >5X ULN and <8X ULN for less than 7 days.
    - ALT or AST > 3X ULN AND either total bilirubin > 2X ULN OR INR > 1.5.
    - ALT or AST > 3X ULN with clinical indications of liver toxicity (signs, symptoms, or other diagnostic findings).
- Excepting the AEs mentioned above, any other Grade 3 or higher nonhematologic or Grade 4 hematologic toxicity, except Grade 3 nausea, vomiting, or diarrhea lasting longer than 48 hours.

Management and dose modifications associated with the above adverse events are outlined in Section 5.4. Dose-limiting toxicity (DLT) is defined above.

All study agent administration will stop if any of the following events occur during the study:

- Death attributed to study drug;
- Serious systemic anaphylactic reaction

The FDA, IRB and DSMC will be notified immediately if one of these adverse events occurs and a comprehensive review of the safety data will be conducted prior to resumption of dosing.

Stopping Rules

1. If two of the first four subjects experience DLTs requiring dose modification, then the trial may continue with a reduced starting dose of tolinapant.
2. If two of the first four subjects are unable to complete radiation/proton therapy due to toxicity, the trial may continue with a reduced starting dose. If two of the subsequent four subjects are also unable to complete radiation/proton therapy due to toxicity despite the reduced starting dose of tolinapant, then the trial will be stopped. If >30% of patients at any time are not able to complete radiation/proton therapy despite the reduced starting dose due to toxicity, the trial will be stopped.

5.4 Dose Modification

If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk: benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level, or at a dose level intermediate to previously tested lower dose levels.

The PI or designee must provide the DSMC a report outlining the overall enrollment and path to decision for the reduced dose(s) selected.

A subset of specific grade 3-4 AEs are more likely to be related to radiotherapy versus tolinapant, including grade 3 dermatitis and dysphagia requiring placement of a feeding tube. If it is determined that these AEs or others are worse than expected with radiotherapy alone, dose modification or discontinuation of tolinapant may be instituted at the discretion of the investigator with guidance from the treating radiation oncologist.

Tolinapant dosing should be withheld in the case of a DLT in Cycle 1 (first 7-day cycle of tolinapant during week 1 of RT) or a toxicity in subsequent cycles that would have qualified as a DLT if it had occurred in Cycle 1. Dosing may resume, at the investigator's discretion, if and when study treatment-related toxicity has:
o completely resolved or returned to baseline (all AEs), or

o partially recovered to Grade 2 or less (anemia, fatigue, malaise, alopecia), or

o partially recovered to Grade 1 or less (all other toxicities)

If toxicity has not resolved as described above within 21 days, the investigator should consider withdrawing the subject from the study.

If and when dosing is resumed, the individual's dose should be adjusted to the next lower dose. All dose modifications should be discussed and approved by the Taiho Oncology Medical Monitor. A maximum of 2 dose reductions are permitted for any single subject. In the event of further unacceptable toxicity, the investigator should consider discontinuation of study treatment for that subject.

Table: Dose Reduction Guidelines

Dose Level	**Dose (mg)**	**Schedule**
1 (RP2D)	180 mg/day	Daily dosing on Days 1-7 and 15-21 of each 28-day cycle
-1 Dose level	120 mg/day	Daily dosing on Days 1-7 and 15-21 of each 28-day cycle
-2 Dose level	90 mg/day	Daily dosing on Days 1-7 and 15-21 of each 28-day cycle
RP2D=Recommended Phase 2 dose		

The investigator will decide whether any AE that occurs is related to tolinapant and determine whether dose modification or discontinuation is required per the guidance below.

Table: Dose Modification for Adverse Events Associated with Tolinapant

Adverse Event	**Dose Modification**
Liver toxicity: ALT or AST >5xULN or total bilirubin level >2xULN	Withhold tolinapant, then resume treatment at a lower dose when toxicities have recovered to Grade ≤1.
Liver injury: ALT or AST>8xULN; ALT or AST>5xULN for ≥7 days; ALT or AST >3xULN and either total bilirubin >2xULN or INR >1.5; or ALT or AST >3xULN with clinical symptoms indicating liver toxicity	Permanent discontinuation of tolinapant
Grade 2 pneumonitis	Interrupt study treatment until recovery to Grade ≤1. • Study treatment may restart at -1 dose level lower if subject can still benefit. • If not recovery to Grade ≤1 within 3 weeks, permanently discontinue study treatment. • Permanently discontinue for recurrent Grade 2 pneumonitis after lowering the dose.
Grade 3 or 4 pneumonitis	Permanently discontinue tolinapant.
Grade 2 maculopapular rash	Tolinapant may be continued at a lower dose with close monitoring if subject can still benefit. • If no recovery to Grade ≤1 within 2 weeks despite best supportive and symptomatic treatment, interrupt tolinapant. • Restart tolinapant when rash Grade ≤1 at a lower dose level.
Grade 3 maculopapular rash	Photograph the rash. • Interrupt tolinapant until recovery to Grade ≤1. • Restart tolinapant when rash Grade ≤1 at a lower dose • If no recovery to Grade ≤1 within 2 weeks, consider to permanently discontinue tolinapant. • Permanently discontinue tolinapant for recurrent Grade ≥3 rash after lowering the dose.
Grade 3 amylase/lipase increase:	Consider CT scan.

lipase: >2.0-5.0 × ULN or >5.0x and asymptomatic amylase: >2.0-5.0 × ULN or >5.0x and asymptomatic	• Tolinapant may be continued at a lower dose level and monitor for change in severity at least twice a week. • No tolinapant treatment until recovery to Grade ≤1 and restart with tolinapant reduced by 1 dose level • After dose interruption, if no recovery to ≤Grade 1 within 3 weeks, consider to permanently discontinue tolinapant
Grade 4 amylase/lipase increase: lipase: >5.0 × ULN and with signs or symptoms amylase: >5.0 × ULN and with signs or symptoms	Consider CT scan. • Interrupt tolinapant until recovery to Grade ≤1 and monitor for change in severity. • Restart with tolinapant reduced by 1 dose level. • If no recovery to Grade ≤1 within 3 weeks, consider to permanently discontinue study tolinapant.
Grade 2 facial nerve weakness:	Interrupt tolinapant until recovery to Grade ≤1 • Resume tolinapant at the same dose or at a lower dose with close monitoring if subject can still benefit • If no recovery to Grade ≤1 within 3 weeks despite best supportive and symptomatic treatment, consider to permanently discontinue tolinapant
Grade 3 facial nerve weakness:	Permanently discontinue study tolinapant

5.4.1 **Cytokine release syndrome**

Cytokine release syndrome (CRS) is a disorder resulting from immune system activation, specifically the release of cytokines from cells of the immune system (NCI CTCAE v. 4.03, Immune system disorders; Lee et al 2014). CRS appears to result from activation of large numbers of lymphocytes and/or myeloid cells, with subsequent release of inflammatory cytokines (e.g., IL-2, TNF-α, GM-CSF, IL-10, and IL-6); emerging evidence implicates IL-6 as a central mediator (Lee et al 2014). However, a consistent pattern of cytokine release that applies across groups of patients has not been found, and efforts to identify predictive biomarkers have not been successful to date.

CRS is typically characterized by fever, nausea, headache, tachycardia, hypotension, rash, and shortness of breath (summarized below)). However, individual signs and symptoms may have alternate causes, and a diagnosis of CRS does not require that all signs and symptoms are present. While fever is a hallmark, symptomatology and severity can vary or be complicated due to concurrent medical conditions; for example, isolated changes in hepatic transaminases may be due to exposure to an IMP, but a fever may be due to infection. Thus, an initial diagnosis of CRS may be found to have alternate causes, and conversely a diagnosis of CRS may be made retrospectively based on the totality of clinical and laboratory data.

Table: Clinical Signs and Symptoms Associated with Cytokine Release Syndrome

Constitutional	Fever (>101.5º F) ± rigors; malaise, fatigue, anorexia, myalgias, arthralgias, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure (from baseline), hypotension, increased cardiac output (early), decreased cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia

Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word-finding difficulty/aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

In general, if there is clinical suspicion that a subject may have CRS, that subject should immediately receive supportive care as appropriate, and a more detailed assessment of possibly affected organ systems should be performed. These activities should be undertaken in a clinical setting where aggressive medical support can be rapidly obtained if necessary (typically emergency departments or ambulatory care units with hospital facilities in reasonable proximity). Treatment of CRS should consider the individual subject's underlying medical condition and the severity of the signs and symptoms. In general, the approach is supportive, with the potential of adding anti-inflammatory or immunosuppressive agents if indicated; if institutional guidelines exist, these should be followed. Examples of the clinical management of CRS symptoms by severity grade are provided in the table below:

Table: Severity Grades of Cytokine Release Syndrome and Clinical Management of Symptoms

CTCAE Grade	**Toxicity (Examples)**	**Potential Management**	**Tolinapant Action**
1 Intervention not required	Mild reaction (e.g., low-grade fever, headache)	May require diagnostic work up (e.g., to assess for infection).	Depending on dose schedule, consider re-challenge, dose delay, or dose reduction.
2 Non-life-threatening symptoms but intervention required	Symptoms (e.g., rash, higher fever, dehydration, myalgias) require treatment (e.g., antihistamines, NSAIDS, IV fluids, etc.) and respond within 24 hours.	May require diagnostic workup and short-term (<24 hours) observation.	Hold tolinapant treatment and reduce next dose by 1 dose level for the next administration period.
3 Prolonged episode >24 hours, with hospitalization indicated	Clinical sequelae (e.g., renal impairment, pulmonary infiltrates, need for oxygen supplementation) requiring hospitalization; Grade 3 organ toxicity.	Supportive care (e.g., IV fluids, oxygen, work-up and treatment for infection); consider immunosuppressive agents (e.g., systemic corticosteroids, tocilizumab)	Hold tolinapant treatment during the diagnostic work-up. • In the absence of clear antitumor effect, permanently discontinue tolinapant. • In the presence of a clear antitumor effect, consider tolinapant dose reduction, pretreatment with corticosteroids and antihistamines, and possible close observation for additional treatment cycles.
4 Life-threatening symptoms	ICU supportive measures required (e.g., prolonged vasopressor support for grade 4 organ toxicity; mechanical ventilation for ARDS)	Discontinue tolinapant permanently.	
5	Death	N/A	N/A

5.5 Concomitant medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. Specifically, vaccinations against SARS-CoV-2 virus within two weeks of cycle 1 day 1 are not recommended due to the potential of overlapping AEs and potential impact on vaccine efficacy.

Other anticancer treatments, including other investigational drugs or therapies (including photopheresis and phototherapy), unless specified in the protocol, are prohibited. Any other medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator(s). Caution should be used when co-administering CYP3A4 inhibitors or inducers, QT-prolonging agents, or statins, as detailed below.

Tolinapant is metabolized mainly by CYP3A4, hence is sensitive to CYP3A4 induction and inhibition. Therefore, concomitant administration of drugs known to be potent CYP3A4 inhibitors or inducers has the potential to result in drug-drug interactions (DDIs) with tolinapant. Careful consideration should be given to balancing the medical needs of the subject and the potential effect on tolinapant before co-administering a drug that is known to be a potent CYP3A4 inhibitor or inducer, particularly if the drug has a narrow therapeutic window.

Examples of CYP3A4 inhibitors and inducers may be found on the following websites; note that the published lists are not comprehensive. Refer to the specific product information for an intended concomitant drug for its effect on CYP3A4.

- Pharmacytimes.com: http://www.pharmacytimes.com/publications/issue/2015/december2015/drug-interactions-with-cyp3a4-an-update
- FDA.gov: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Tolinapant is a weak-to-moderate inhibitor of CYP3A4 with an R value of 1.1 to 1.4 (depending on substrate), estimated using Cmax from preclinical models. Caution should be exercised when coadministering drugs with tolinapant that are sensitive CYP3A substrates with narrow therapeutic windows until the potential for DDI associated with tolinapant is fully understood. Tolinapant is not a potent inhibitor of the other major human CYP enzymes CYP1A2, 2D6, 2C9, 2C19 and is therefore not likely to cause DDIs when administered with other drugs that are sensitive substrates of these CYPs.

Tolinapant is a substrate for the MDR1 efflux transporter. An in vitro study indicated that tolinapant is also a potent inhibitor of MDR1, and as a result, caution should be exercised when coadministering tolinapant with P-gp substrate drugs with narrow therapeutic window (e.g., digoxin) and inhibitors or inducers of P-gp. Tolinapant is also a strong inhibitor of MATE1 transporter based on in vitro studies. While the full extent of the potential for drug-drug interactions via inhibition of MATE1 is yet to be understood, investigators should be aware of potential effects on the action of MATE1 substrate drugs (e.g., metformin) when coadministered with tolinapant.

Medications known to increase the risk of torsades de pointes were prohibited in Phase 1 and should be used with caution in the present study. In Phase 1 there was no evidence of QTc prolongation by tolinapant at dose levels below 270 mg. Posttreatment QTc prolongation at 270 mg (above the MTD) was mild (9, 21, and 39 msecs in 3 subjects, respectively). Phase 2 cardiac safety is protected by a 470 msec QTc eligibility limit and QTc testing in each cycle of therapy.

A list of QTc prolonging medications is provided at https://www.crediblemeds.org/ and discussed in Drew et al (2010).

Any medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator(s). For any questions or concerns, investigators should consult with the medical monitor on a case-by-case basis about potential concomitant use of QTc prolonging agents in individual subjects.
Due to the risk of potential cIAP-related liver injury, statins and other medications that can affect liver function should be used with caution.

Subjects on a stable dose of systemic corticosteroids >20 mg prednisone equivalent for at least 3 weeks prior to study entry may continue use at the same dose. Subjects on a stable dose of medium or low potency topical corticosteroids for at least 3 weeks prior to study entry may continue use at the same dose. However, investigators should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with systemic corticosteroids >20 mg prednisone equivalent or an increase in dose while on study is not permitted except to treat adverse events. Subjects may receive intra-articular corticosteroid injections, intraocular or otic corticosteroids drops, inhalation or nasal corticosteroids, and replacement doses of systemic corticosteroids as needed.

5.6 Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to 28 days prior to initiation of radiation/proton therapy as applicable. All subjects must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (triplicate if QTc >470)
- Echocardiogram
- Tumor biopsy (if feasible to perform on an outpatient basis)
- Review of prior/concomitant medications
- Review of CT/MRI

- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - Coagulation (PT, PTT, INR)
  - Creatinine Clearance
  - Serum pregnancy test (for women of childbearing potential)
  - Hepatitis serologies if any clinical concerns for hepatitis
  - Liver function tests, amylase and lipase

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3).

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - Creatinine Clearance
  - Liver function tests, amylase and lipase
- IMRT or proton therapy

End of Treatment

- End of treatment is defined as the last planned dosing visit within the 7-week dosing period. For subjects who discontinue treatment with both radiation and tolinapant, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 30 days of the end of treatment visit.
- Assessments for subjects who have completed treatment and achieved disease control or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Events/Assessments.
- All subjects will be followed for survival until the end of the study regardless of further treatments, or until the Sponsor-Investigator ends the study.

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events/Assessments. Full physical examinations should be conducted at screening/baseline and one month follow up visits (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
At Screening, a single ECG will be obtained on which QTcF must be <470 ms.
In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

Echocardiogram or MUGA Scan

Subjects will have an echocardiogram or multiple gated acquisition (MUGA) scan assessments performed at screening.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry including liver function tests, amylase, lipase, and creatinine clearance
- Coagulation studies (PT, PTT, INR)
- TSH
- Pregnancy test (female subjects of childbearing potential only)

Blood Collection for Immune Correlative Studies

Blood will be collected at enrollment and during weeks 2 and 7 of treatment for immune correlative studies.

Tumor Biopsy

For subjects with primary tumors in a location amenable to biopsy in the outpatient otolaryngology clinic setting, a tumor biopsy will be collected at the enrollment visit and during week 2 of treatment. Biopsies will be used to examine immune cell infiltrates before and after the first week of tolinapant + radiation. Local anesthesia will be injected as need into the peritumoral area, and then cup forceps will be used to remove a small portion of the tumor. Silver nitrate or sutures will be used as needed for hemostasis.

Radiotherapy

All subjects will be treated with standard-of-care IMRT or IMPT in 30-35 fractions during the 6-7-week treatment period with one fraction per day treatment. Radiation planning, initiation, delay or withholding of fractions will be done at the discretion of the co-Investigator Radiation Oncologist. Missed treatments due to holidays or logistical reasons can be compensated by delivering fractions given twice in one day, with a minimum inter-fraction interval of 6 hours, or by treating on weekends at the discretion of the treating physician.

Patients will either be treated with intensity modulated photon radiotherapy (IMRT) or with pencil beam scanning proton therapy (IMPT).

For patients treated in the definitive setting with IMRT, the PTV_7000 will receive a dose of 70 Gy in 2.0 Gy fractions. The PTV_5390, encompassing at-risk nodal regions, will receive a dose of 53.9 Gy in 1.54 Gy fractions. Patients will be treated with a simultaneous integrated boost technique.

For patients treated in the definitive setting with proton therapy, the CTV_7000 will receive a dose of 70 Gy(RBE) in 2.0 Gy(RBE) fractions. The CTV_5390, encompassing at-risk nodal regions, will receive a dose of 53.9 Gy(RBE) in 1.54 Gy(RBE) fractions. Patients will be treated with a simultaneous integrated boost technique.

For patients treated in the adjuvant (post-surgery) setting with IMRT, the PTV_6000 will receive a dose of 60 Gy in 2.0 Gy fractions. The PTV_5400, encompassing at-risk nodal regions, will receive a dose of 54 Gy in 1.8 Gy fractions. If used, the PTV_6300 will receive a dose of 63 Gy in 2.1 Gy fractions. Patients will be treated with a simultaneous integrated boost technique.

For patients treated in the adjuvant (post-surgery) setting with proton therapy, the CTV_6000 will receive a dose of 60 Gy(RBE) in 2.0 Gy(RBE) fractions. The CTV_5400, encompassing at-risk nodal regions, will receive a dose of 54 Gy(RBE) in 1.8 Gy(RBE) fractions. If used, the CTV_6300 will receive a dose of 63 GyE(RBE) in 2.1 Gy(RBE) fractions. Patients will be treated with a simultaneous integrated boost technique.

CT Simulation: CT simulation will be required in all patients. A thermoplastic mask shall be used for patient immobilization (shoulders along with head) for both CT-simulation and for each daily treatment. A bite block is permitted per the treating Radiation Oncologist. IV contrast is not required in patients if appropriate pre-operative CT scans and/or MRI or PET are available for nodal site delineation. Slice thickness of ≤ 3mm is required. The patient should be simulated and immobilized with the neck in a neutral position as best tolerated by the patient that will be reproducible daily. The scan should at a minimum extend from the top of the orbits to the carina.

Image Fusion: Additional imaging studies of the patient such as with MRI and 18- fluorodeoxyglucose PET will be permitted to facilitate the treatment planning process. However, the primary image set for the treatment planning will be the CT image set.

Target Volumes Delineation and Definitions: The definition of volumes will be in accordance with ICRU Reports #50 and #62.

In the definitive setting, target volume nomenclature shall include the following:

- Gross Tumor Volume (GTV) is defined as all known areas of pre-operative gross disease determined from CT, MRI, PET, clinical information, and endoscopic findings. Grossly involved lymph nodes are defined as any lymph node ≥1cm or nodes with a necrotic center or that have abnormal FDG uptake on PET. Whenever possible, it is recommended that diagnostic images be fused to the planning CT scan image dataset to more accurately determine the GTV. Smaller nodes located in close proximity to either the primary site and/or other grossly involved nodes, or those demonstrating significant PET uptake may be considered involved. The gross tumor at the primary site will designated as **GTVp**, and clinically involved gross lymph nodes are designated **GTVn**.
- Clinical Treatment Volumes (CTV)
    - **CTV_7000** represents a 5mm isotropic expansion of the GTVp and GTVn. CTVs should be edited along natural barriers to spread such as air cavities, bone, fascial planes, and the external body contour.
    - **CTV_5390** represents elective volumes for coverage of regions deemed by the treating radiation oncologist to be at risk for microscopic tumor spread, such as the structures at the skull base for a nasopharyngeal primary, the ipsilateral node-positive hemineck, and the uninvolved contralateral hemineck. A single elective nodal volume and dose level will be used.
- Planning Treatment Volumes (PTV) (for patients being treated with IMRT)
    - **PTV_7000** and **PTV_5390** consist of a minimum of 3mm isotropic expansion from their respective CTVs that is edited so as to not extend beyond skin.

In the adjuvant (post-surgery) **setting**, target volume nomenclature shall include the following:

- Clinical Treatment Volumes (CTV)
    - **CTV_6000** represents the regions of the surgical field with pathologic evidence of tumor involvement, including the resection bed of the primary tumor and dissected lymph node regions with lymph nodes found to be involved by tumor. This may be expanded at the discretion of the treating radiation oncologist to include areas adjacent to involved regions (*e.g.* level III may be included if level II is found to have involved lymph nodes) or otherwise thought to be at risk for microscopic tumor involvement based on patterns of tumor spread. CTVs should be edited along natural barriers to spread such as air cavities, bone, fascial planes, flap margins, and the external body contour.
    - **CTV_5400** represents both the regions of the surgical field at lower risk for microscopic disease and elective (undissected) volumes for coverage of regions deemed by the treating radiation oncologist to be at risk for microscopic tumor spread, such as the dissected node-negative hemineck, the uninvolved contralateral hemineck, and course of an at-risk cranial nerve without radiographic or pathologic perineural tumor spread.
    - At the discretion of the treating radiation oncologist, an optional **CTV_6300** may be used to treat a particular area of concern (*e.g.* close surgical margin)
- Planning Treatment Volumes (PTV) (for patients being treated with IMRT)
    - **PTV_6000** and **PTV_5400** (and **PTV_6300**, if applicable) consist of a minimum of 3mm isotropic expansion from their respective CTVs that is edited so as to not extend beyond skin.

Unilateral Treatment: Unilateral neck treatment is allowed on the study if it is in the institution's established practice at the discretion of the treating radiation oncologist.

Planning Parameters: The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the CTVs, PTVs and critical normal structures. For patients being treated with photon therapy, an "inverse" treatment plan using computerized optimization shall be used. The treatment aim will be the delivery of radiation to the PTVs and minimizing dose to critical structures and non-involved tissue. All plans shall be normalized such that at least 95% of the volume of the PTV is covered by the prescribed isodose surface.

For patients treated with proton therapy, robust optimization shall be used and the worst cast CTV dose distribution corresponding to a setup error of at least 3 mm and range uncertainty of at least 2% will be used for dose optimization, evaluation, and dose reporting, in place of the conventional PTV used in photon-based treatment planning.

Organs at Risk (OARs): The following critical structures should be carefully delineated and attempts made to minimize doses to these structures: SpinalCord, SpinalCord_05, BrainStem, BrainStem_03, OpticNerve_L, OpticNerve_R, OpticChiasm, Parotid_L, Parotid_R, Cavity_Oral, Mandible, PharyngealConstrictors, Esophagus, Larynx, Submandibular_L, Submandibular_R. These will be delineated and doses limited according to the Institution's practice patterns.

Radiotherapy Compliance: All treatment plans are to be normalized so that 95% of the PTV_7000 volume is covered by 70 Gy. Plan evaluation criteria are given in the table below. For patients being treated with IMPT, the PTVs will be replaced with the worst case CTVs in the table below. For patients receiving IMPT, dose will be reported in Gy(RBE), the radiobiologically equivalent dose.

Definitive

Structure	Parameter	Per Protocol	Variation Acceptable
PTV_7000	D95%	>= 70Gy	>= 69Gy
	V95%	>99%	>=90%
	D0.03cc	<=77Gy	<=82Gy
PTV_5390	D95%	>= 53.9Gy	>= 53Gy

	Per Protocol	Variation Acceptable
Overall Treatment Time	<50 days	50-54 days
Interruptions	0-2	2-4

Adjuvant

Structure	Parameter	Per Protocol	Variation Acceptable
PTV_6000	D95%	>= 60Gy	>= 59Gy
	V95%	>99%	>=90%
	D0.03cc	<=66Gy	<=69Gy
PTV_5400	D95%	>= 54Gy	>= 51Gy
PTV_6300	D95%	>=63Gy	>=62Gy

	Per Protocol	Variation Acceptable
Overall Treatment Time	<43 days	43-47 days
Interruptions	0-2	2-4

Quality-Assurance CT scans and replanning for factors such as weight loss, tumor shrinkage, or persistent difficulties in patient setup will be permitted at the discretion of the treating Radiation Oncologist.

6. Data and Specimen Banking

Blood and tumor samples will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study head and neck cancer. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in the subject's medical record. For this study, those items include: research blood and tumor biopsy collection.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (e.g., trial outcome results or results from studies of the subject's blood or tumor samples). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), patients will be treated for 7 weeks. Reasons that may lead to discontinuation of treatment sooner than 7 weeks include the following:

- Tumor progression while on treatment
- Death
- Unacceptable toxicity
- Symptomatic deterioration

• Investigator's decision to discontinue treatment
• Patient decision to discontinue treatment
• Patient withdraws consent
• Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the Follow Up procedures specified in the Schedule of Events/Assessments.

8.2 Duration of follow-up

Patients will be followed for approximately 30 days (Safety Follow-up) after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from the study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:
The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
• All patients will be contacted for survival every 4 weeks following the End of Treatment (EOT) visit.

Patients who have not initiated a new antineoplastic regimen will have the following assessments:
• Radiologic tumor assessments at 12 and 24 months post-treatment (± 30 days)
• In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to the study drug. If the patient discontinues the study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

9. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or Female.
2. Age ≥18 years.
3. ECOG performance status ≤1 (see Appendix A).
4. Patients with histologically or cytologically confirmed diagnosis of HNSCC, previously untreated and locally advanced, for whom definitive or adjuvant (post-surgical) radiation is planned but cisplatin chemotherapy is contraindicated. For the purposes of trial eligibility, anatomic subsites of HNSCC may

include the oral cavity, larynx, oropharynx, hypopharynx, nasopharynx, or unknown primary site presenting with neck lymph nodal disease.

Patients must have a contraindication to cisplatin as defined below. The scores must be recorded on a CRF.

Age ≥ 70 with moderate to severe comorbidity, defined as having **one or more** of the following conditions within 30 days prior to registration (can use comogram.org to calculate):

- Modified Charlson Comorbidity Index ≥ 1
- ACE-27 Index ≥ 1
- G-8 score ≤ 14
- CARG Toxicity Score ≥ 30%
- CIRS-G Score ≥ 4

—OR—

Age ≥ 18 with an absolute or relative contraindication to cisplatin, defined as **one or more** of the following criterion within 30 days prior to registration:

- o Pre-existing peripheral neuropathy grade ≥ 1;
- History of hearing loss, defined as either an existing need of a hearing aid OR moderate hearing loss as defined by the American Speech and Hearing Association (pretreatment audiogram showing 40-55 db HL hearing loss)
- Creatinine clearance (CrCl) must be > 30 and < 50 mL/min. For this calculation, use the Cockroft-Gault formula: CrCl = 0.85 (if female)* ((140–Age) / (Serum Creatinine)) * (Weight in kg / 72).

5. Acceptable organ function, as evidenced by the following laboratory data:
    - Absolute neutrophil count [ANC] ≥ 1,500 cells/µl; hemoglobin ≥ 9 g/dl, platelets ≥ 100,000/µl.
    - Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 60 ml/min (unless qualified for trial on the basis of creatinine clearance as listed above).
    - Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.
    - Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN.
    - Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN.
    - Amylase and lipase ≤ ULN.
6. The effects of tolinapant on the developing human fetus are unknown. For this reason and because tolinapant as well as other therapeutic agents used in this trial are known to be teratogenic, females of child-bearing potential (FCBP) must have a negative serum pregnancy test prior to starting therapy.
7. Female patients of childbearing potential and men must agree to use adequate contraception (at least one highly effective method and one additional method of birth control at the same time or complete abstinence) prior to study entry, for the duration of study participation and for at least 6 months following study drug discontinuation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (if age > 55 years); if the female subject is < 55 years and she has been naturally postmenopausal for > 1 year her reproductive status has to be verified by additional lab tests (< 20 estradiol OR estradiol < 40 with FSH > 40 in women not on estrogen replacement therapy).
8. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.

9. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have had prior radiotherapy to the head and neck region
2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to tolinapant.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
5. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure (or ejection fraction <50%); or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
6. Contraindications to radiotherapy (e.g. uncontrolled connective tissue disorder).
7. Women who are pregnant or breast feeding.
8. Vulnerable populations including prisoners and adults who are unable to consent.
9. Known history of human immunodeficiency virus (HIV) infection, or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.
10. Grade 3 or greater neuropathy.
11. Known distant metastases (i.e., outside of the neck).
12. Known significant mental illness or other conditions such as active alcohol or other substance abuse that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol treatment or assessments.
13. Concurrent second malignancy requiring active therapy.
14. Patients with a history of allogenic transplant must not have ≥Grade 3 graft-versus-host disease (GVHD) or any clinically significant GVHD requiring systemic immunosuppression.
15. Systemic corticosteroids >20 mg daily prednisone equivalent (unless patient has been taking a continuous dose for >3 weeks prior to study entry).
16. Medications known to cause QT prolongation including some antipsychotics ((chlorpromazine, haloperidol, droperidol, quetiapine, olanzapine, amisulpride, thioridazine), antiarrhythmics (quinidine, procainamide, disopyramide, flecanide, encainide, sotalol, amiodarone), antidipressants (amitriptyline, doxepin, imipramine, nortriptyline, desipramine), mianserin, citalopram, escitalopram, venlafaxine, bupropion, moclobemide), and antihistamines (diphenhydramine, astemizole, loratadine, terfenadine), macrolide antibiotics (erythromycin, clarithromycin), and antimalarials (chloroquine, hydroxychloroquine, quinine), unless the use of these drugs cannot be avoided.

10. Local Number of Participants

We will be recruiting 10 participants at Winship and will not be recruiting from other sites. We are expecting to have to screen and consent 20 participants to reach our recruitment goal of 10 at Winship. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

11. Recruitment Methods

Investigators, nurses (CRNs), research coordinators (CRCs) and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The CRN/CRC/data manager reviews accessible medical records to screen further for eligibility. The CRN/CRC reviews the eligibility with the physician.

Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options.
Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.
When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. OnCore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 20 business days. Issues that would cause treatment delays must be discussed with the Principal Investigator.

12.Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive tolinapant and/or radiation for >2 weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced. Subjects who discontinue treatment will be encouraged to remain on the study for follow up visits and safety monitoring.

13. Risks to Participants

a. Tolinapant:

Tolinapant has not yet been used with radiotherapy in a clinical setting. However, in a phase 2 study of tolinapant monotherapy,

the most common study treatment-related AEs were lipase increased/hyperlipasemia (N=43; 29.6%), rash/rash maculo-papular (N=42; 28.9%), amylase increased (N=38; 26.2%), alanine aminotransferase increased (N=25; 17.2%), and fatigue (N=25; 17.2%). The most common Grade ≥3 AE related to study treatment were lipase increased/hyperlipasemia (N=19; 13.1%), rash /rash maculo-papular (N=19; 13.1%), and amylase increased (N=11; 7.6%). A total of 70 subjects experienced SAEs in Phase 2; the most common events regardless of relationship were pneumonitis (N=5 [3.4%]), and pneumonia, pyrexia, and tumor pain (N=4; 2.8% for all 3 event terms). The most common SARs were pneumonitis (N=5; 3.4%), rash maculo-papular (N=3; 2.1%), and pancreatitis (N=2; 1.4%); all other SARs were observed in 1 subject (0.7%) each.

It is possible that as a radiosensitizer, tolinapant may increase the incidence and/or severity of common adverse effects of IMRT or proton therapy (described below).

b. Radiotherapy (IMRT or IMPT)

Acute (during treatment and through 90 days post-radiotherapy): Common radiotherapy-related adverse events occurring over this time period include pain, skin redness and breakdown, changes in taste and smell, dry mouth, fatigue, nausea, changes to swallowing, changes to speech.

Chronic (occurring more than 90 days post-radiotherapy): Common radiotherapy-related adverse events occurring over this time period include pain, fibrosis (scar tissue) affecting muscle and skin, decreased saliva, decreased taste, dental complications, changes in swallowing potentially requiring a feeding tube, decreased thyroid function.

c. Additional blood draws:

The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.

d. Data security:

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

14. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

15.Data Management and Confidentiality

15.1 Statistical considerations

15.1.1 Sample Size

This study is an early-phase study evaluating the safety of tolinapant given with IMRT or proton therapy in subjects with head and neck cancer and who are not eligible for treatment with standard cisplatin chemotherapy. No formal sample size estimation will be conducted. Approximately 20 subjects will be enrolled and screened in order to have 10 subjects deemed eligible for treatment; this number of subjects is sufficient to assess preliminary safety and activity to guide design of subsequent clinical studies.

15.1.2 Primary endpoints

The primary endpoints of the study are safety and feasibility. Safety will be assessed on clinical examination and measurement of laboratory parameters. All safety assessments including adverse events, clinical laboratory evaluations, and vital signs will be summarized with descriptive statistics, where appropriate, and listed in the data listings using MedDRA terms. Feasibility is defined as completion of treatment, which will be reported as a percentage, with a 95% exact confidence interval using the Clopper-Pearson method.

15.1.2.1 Adverse Events

All adverse events will be coded by system, organ, class and preferred term using the most current version of MedDRA.

Summary tables for treatment emergent adverse events will include number of occurrences of events by system, organ, class, and numbers and percentages of subjects experiencing adverse events by system, organ, class, and preferred term. If a subject has more than one AE which codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a system, organ, class category, the subject will be counted only once in that system, organ, class category. Summary tables to be generated include: summary of AEs, relationship of AEs to study drug, severity of AEs, AEs leading to study drug discontinuation and serious AEs. Data listings will be provided for AEs, AEs leading to study drug discontinuation, and serious AEs.

15.1.2.2 Clinical Laboratory Results

Results of laboratory tests from hematology and chemistry evaluations that are outside of the reference range will be flagged and displayed in the summary tables. Descriptive statistics (e.g., number of subjects, mean, standard deviation, minimum, maximum, median and interquartile) for hematology and serum chemistry measurements will be calculated for each time point. The same descriptive statistics will be generated for these changes from baseline for each measurement. A spaghetti plot will visually track each measurement over time for each patient. Baseline is defined as the last measurable value prior to dosing on Day 1. All clinical laboratory data will be provided in the data listing.

15.1.2.3 Vital Signs and Physical Examination

Descriptive statistics (e.g., number of subjects, mean standard deviation, minimum, maximum, and median) of vital sign measurements for systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature will be calculated for each measurement. Baseline is defined as the last measurable value prior to dosing on Day 1. All vital signs will be provided in the data listing.

Physical examination of individual subjects will be presented in the data listings. No summary tables will be provided.

15.1.3 Secondary endpoints

Although the study is designed primarily to evaluate safety, the anti-tumor effect of tolinapant + radiotherapy will also be assessed.

Efficacy assessments include:

- Overall survival (OS), defined as time from first treatment to date of death from any cause or last follow-up, where those alive are censored at date of last follow-up. OS will be estimated using the Kaplan-Meier method. Median OS will be reported with a confidence interval.

- Progression free survival (PFS), defined as time from first treatment to date of progression or to death, whichever occurs first, or last follow-up, where those alive without progression are censored at date of last follow-up. PFS will be estimated using the Kaplan-Meier method. Median PFS will be reported with a confidence interval.
- Duration of treatment response, defined as time from first documentation of CR or PR until first occurrence of disease progression or death. Response is determined on post-treatment PET-CT, using the Neck Imaging and Reporting and Data System (NI-RADS; Hsu and Juliano, 2020). For equivocal NI-RADS scores, response will be determined according to repeat scan or by salvage surgery, as indicated. Median, mean, and range will be reported.
- Locoregional control (LRC) is defined as time from first treatment to date of local or regional failure, or last follow-up, where those without local or regional failure are censored at date of last follow-up. LRC will be estimated using the Kaplan-Meier method.

15.1.4 Study populations

Safety population: All subjects enrolled in the study who receive tolinapant with IMRT or proton therapy.

Efficacy population: All subjects enrolled in the study who receive tolinapant with IMRT or proton therapy.

15.1.5 Safety stopping rules

Dose limiting toxicities (DLTs) and stopping rules are detailed in Section 5.3.

15.2 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files,

and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study head and neck cancer. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

16.Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An adverse event is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. For this study, only abnormal laboratory findings with clinical significance are considered adverse events.

A treatment emergent adverse event is defined as an adverse event with onset occurring at any time point after the first administration of tolinapant. A treatment emergent adverse event also may be a continuing adverse event reported prior to the date of the first dose of study drug, which worsens in severity after the first administration of tolinapant.

Disease progression is not an adverse event (non-serious or serious), although signs and symptoms thereof may be reportable as adverse events.

Definition of Serious Adverse Events (SAE)

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

- Death

- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant 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).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition. These should be considered serious.

Any pregnancy which occurs during this clinical trial must be treated as a serious adverse event with regard to the reporting timeline. Any pregnancy must be followed until conclusion of the pregnancy (delivery or termination). Administration of study drug will be discontinued in a subject who becomes pregnant. The subject will be asked to complete follow up evaluations. If a male subject reports a pregnancy of his spouse or significant other within Day 60 of last study treatment, every effort will be made to obtain data regarding the outcome of this pregnancy.

Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention

(dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Sponsor-Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment initiation through 30 days following cessation of treatment, all adverse events, that begin or worsen after informed consent, must be recorded by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or

between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase 1 studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes) should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning at treatment start through 30 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related

to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to IRB, DSMC, FDA, supporter or IND Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IND sponsor and should be provided as soon as possible. The IND sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Reporting to study supporter/IRB and or FDA:
All subjects with serious adverse events must be followed up for outcome.
Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported to the sponsor, IRB, and FDA as follow-up to the original episode.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAEs for drug studies must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following:

Reporting to Taiho Oncology:

All SAEs (regardless of causality assessment) that occur after the patient signs informed consent, during treatment, or within 30 days of the last dose of treatment must be reported to Taiho Oncology Clinical Safety and Risk Management (CSRM) at taihoctsafetyreporting@taihooncology.com
(preferred), or fax at (609) 750-7371, within 24 hours of learning of the occurrence. Any SAE that occur past the reporting timelines and which the investigator assessed as related to study drugs, should be reported as to Taiho Oncology CSRM.

Taiho Oncology Drug Safety will send quarterly listings of all SAEs received from the investigator. Any missing SAE(s) will be provided to Taiho Oncology Drug Safety. Taiho Oncology Clin Ops/Drug Safety or designee will send IND Safety Reports for SUSARs generated from our Taiho Oncology supported studies to the IST sites.

SAE due diligence queries will be performed by the IST site; however, Taiho Oncology CSRM can request for additional queries if deemed necessary based on medical judgement.

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor will also assess whether the event constitutes an unanticipated problem (UP) posing risks to subjects or others. This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRBs and investigators in accordance with all applicable global laws and regulations.

Coordinating center reporting to the Food and drug administration (FDA)

The Sponsor Investigator, as holder of the IND (as applicable), will be responsible for all communication with the FDA. The Sponsor Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.
All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

The Investigator must provide the Supporter (Taiho Oncology) and monitoring team appropriate information concerning any findings suggesting significant hazards, contraindications, side effects or precautions pertinent to the safety of the study drug. The Investigator will instruct subjects prior to administration of study drug to report any physical changes or new symptoms that they notice during the course of the study.

The institution shall address all regulatory correspondence, including Adverse Event, Serious Adverse Events and Unexpected Adverse correspondence to Taiho as provided in the Adverse Event and Serious Adverse Event Reporting Section of the Protocol and as follows:

Email (Preferred): taihoctsafetyreporting@taihooncology.com
Fax: (609) 750-7371

In the event of a serious adverse event, the Investigator must report:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

The Principal Investigator should report any follow-up information as it becomes available.

Adverse events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB within 10 working days of investigator determination event meets reporting requirements, or according to IRB Policies & Procedures.

Adverse events deemed serious and related to study drug or study procedures (regardless of expectedness) will be reported to the Emory IRB within 5 working days of knowledge of event.

Adverse events deemed serious, unexpected (i.e., not described in the protocol, Investigator's Brochure or informed consent documents) and related to study drug must be reported to Taiho Oncology using the FDA MedWatch form 3500a within 24 hours of knowledge of event at contact information listed above. The Sponsor-Investigator is responsible for reporting any event meeting IND Safety Reporting criteria to FDA.

Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through Oncore**.**
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Expectedness

Sponsor-Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the data coordinating center (DCC)/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will assess whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to

the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

17. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the

investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to Emory OneDrive and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

17.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the Emory/Winship IRB and Winship Cancer Institute Head and Neck Working Group. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

The Investigator will ensure that all necessary approvals are obtained from the hospital or other institution at which he or she will conduct the clinical study. A copy of the original IRB approval for the protocol and the Informed Consent form must be forwarded to the IND Sponsor or their representative before subject enrollment can begin. The Investigator will retain copies of any and all correspondence with the IRB, and the Institution will make them available for review by the IND Sponsor's representative or the FDA upon request. The Investigator must inform the IRB of all protocol amendments and of serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or conduct of the study. The Investigator must transmit in writing IRB approval to the IND Sponsor or representative.

The Investigator or designee will notify the IRB when the study is placed on "hold," completed, or closed to further subject enrollment.

17.2 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers for all reports. Subject names will not be supplied in the IND Sponsor data. Study findings stored on a computer will be maintained in accordance with local data protection laws.

In compliance with regulatory guidelines regarding the monitoring of clinical studies and in fulfillment of the Investigator's obligations to the IND Sponsor, it is required that data generated as a result of the study be available for inspection, on request, by personnel from the IND Sponsor and regulatory agencies. These will include all study-relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital

admissions occurring while the subject is on-study, and autopsy reports (if available) for deaths occurring during or in temporal proximity to the study.

As part of the required content of the informed consent, participants must be informed that their records will be reviewed by the monitoring team, IND Sponsor, and regulatory agencies. Should access to medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

17.3 Adherence to Reporting Requirements

Within a reasonable time following completion of the study, a final study report will be written, reviewed by the IND Sponsor or designee, and submitted to FDA.

17.4 Records

The Food and Drug Administration requires that an Investigator retains records for a period of two (2) years following the date a New Drug Application or Product License Application is approved for the drug for the indication for which it is being investigated; or, if no application or license is to be filed or, if the application or license is not approved for such indication, until two (2) years after the investigation is discontinued (21CFR 312.62).

The Investigator should ensure that the following records are maintained:

- Signed informed consent documents for all subjects
- Patient identification code list and enrollment log
- Record of all communications between the Investigator and the IRB
- Record of all communication between the Investigator, monitoring team, and the Sponsor
- List of subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all subjects
- Pharmacy files containing copies of the record of use for the study drug, instructions for completion of these records, and the Investigator's Brochure
- All other source documents (subject medical records, laboratory records, etc.)
- Investigator files containing copies of the documents required for the initiation of the study (executed form FDA 1572, signed Investigator's Agreement, Curricula Vitae for the Investigator, copy of the IRB approval of the protocol and Informed Consent forms).
  Note: Scanned documents are acceptable as source materials.

17.5 Protocol Approval and Amendments

Before the start of the study, the Investigator will submit the clinical study protocol, informed consent document, and any other appropriate documents to the IRB with a cover letter listing the documents submitted, the dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. The IND Sponsor will submit the protocol and appropriate documents to the FDA in accordance with legal requirements.

The Investigator will notify the IRB of all protocol amendments and administrative changes, in accordance with the site's requirements. The Sponsor or designee will notify the FDA of all protocol amendments and

administrative changes in accordance with legal requirements. Amendments must be evaluated to determine whether the informed consent document should be revised.

The Investigator must keep a record of all communication with the IRB and, if applicable, between the coordinating investigator and the IRB. This also applies to any communication between the Investigator (or coordinating investigator, if applicable) and the IND Sponsor or its designee.

17.6 Closure of the Study

The study must be closed at the site upon completion. Furthermore, the IND Sponsor or the Investigator has the right to close a study site at any time. As far as possible, premature closure should occur after mutual consultation. The IRB should be notified when the study is completed or terminated. The IND Sponsor will notify FDA when the study is completed or terminated including the reason for premature termination.

At the end of the study, all study drug must be returned, disposed of, or retained as directed by the Sponsor.

18. Economic Burden to Participants

The study supporter will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

19. Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record and research file. This signed consent form present in the medical record shall be considered documentation that the GCP informed consent process has been completed.

The Investigator will be responsible for obtaining from every subject prior to his/her participation in the study a written Informed Consent signed and dated in accordance with U.S. federal regulations (21CFR 50 and 21CFR 312.60) and HIPAA authorization to use and disclose PHI. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The IRB must approve the Informed Consent. The written Informed Consent and HIPAA Authorization will be obtained after the Investigator has provided to the subjects a full explanation, both verbally and in writing, of the purpose, risks and discomforts involved. The original signed and dated copy of the Informed Consent and HIPAA Authorization must be maintained in the institution's records. The names of subjects enrolled during the study will be considered confidential.

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.

At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time. Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future care. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.

Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:" Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers)

Not applicable.

Cognitively Impaired Adults

Not applicable.

Adults Unable to Consent

Not applicable.

20. Setting

The research will be conducted at Emory University.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board at Emory University.

21. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through

research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

22. References

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX B: Participant Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator and treating physician must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the Electronic Medical Record progress note.

Protocol Title:	**Early-Phase, Open-label Study of Tolinapant and Radiation in Cisplatin-Ineligible Patients with Previously Untreated, Locally Advanced Head and Neck Cancer**
Protocol Number:	**WINSHIP5380-21**
Principal Investigator:	**Nicole Schmitt, MD**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Provided Informed Consent	☐	☐	
2. Age ≥ 18 years	☐	☐	
3. ECOG performance status ≤1	☐	☐	
4. Patients with histologically or cytologically confirmed diagnosis of HNSCC, previously untreated and locally advanced, for whom definitive radiation is planned but cisplatin chemotherapy is contraindicated. For the purposes of trial eligibility, anatomic subsites of HNSCC may include the larynx, oropharynx, hypopharynx, nasopharynx, or unknown primary site presenting with neck lymph nodal disease. For cisplatin ineligibility: Age ≥ 70 with moderate to severe comorbidity, defined as having **one or more** of the following conditions within 30 days prior to registration (can use comogram.org to calculate): • Modified Charlson Comorbidity Index ≥ 1	☐ ☐	☐ ☐	

• ACE-27 Index ≥ 1 • G-8 score ≤ 14 • CARG Toxicity Score ≥ 30% • CIRS-G Score ≥ 4 —OR— Age ≥ 18 with an absolute or relative contraindication to cisplatin, defined as **one or more** of the following criterion within 30 days prior to registration: • o Pre-existing peripheral neuropathy grade ≥ 1; • History of hearing loss, defined as either an existing need of a hearing aid OR moderate hearing loss as defined by the American Speech and Hearing Association (pretreatment audiogram showing 40-55 db HL hearing loss) • Creatinine clearance (CrCl) must be > 30 and < 50 mL/min. For this calculation, use the Cockroft-Gault formula: CrCl = 0.85 (if female)* ((140–Age) / (Serum Creatinine)) * (Weight in kg / 72).			
5. Acceptable organ function, as evidenced by the following laboratory data: • Absolute neutrophil count [ANC] ≥ 1,500 cells/μl; hemoglobin ≥ 9 g/dl, platelets ≥ 100,000/μl. • Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 60 ml/min. • Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN. • Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN. • Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN. • Platelet count ≥ 100,000 cells/mm^3. • Amylase and lipase ≤ ULN.	☐	☐	
6. Females of child-bearing potential (FCBP) must have a negative serum pregnancy test prior to starting therapy.	☐	☐	
7. FCBP and men treated or enrolled on this protocol must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry for the duration of study participation, and 6 months after completion of tolinapant administration.	☐	☐	
8. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-	☐	☐	

specified laboratory tests, other study procedures, and study restrictions.			
Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Patients who have had prior radiotherapy to the head and neck region.	☐	☐	
2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs.	☐	☐	
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to tolinapant.	☐	☐	
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐	
5. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure (or ejection fraction <50%); or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.	☐	☐	
6. Contraindications to radiotherapy (e.g., uncontrolled connective tissue disorder).	☐	☐	
7. Women who are pregnant or breast feeding.	☐	☐	
8. Vulnerable populations including prisoners and adults who are unable to consent.	☐	☐	
9. Known history of human immunodeficiency virus (HIV) infection, or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.	☐	☐	
10. Grade 3 or greater neuropathy.	☐	☐	
11. Known distant metastases (i.e., outside of the neck).	☐	☐	
12. Known significant mental illness or other conditions such as active alcohol or other substance abuse that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol treatment or assessments.	☐	☐	
13. Concurrent second malignancy requiring active therapy.	☐	☐	
14. Patients with a history of allogenic transplant must not have ≥Grade 3 graft-versus-host disease (GVHD) or any clinically significant GVHD requiring systemic immunosuppression.	☐	☐	
15. Systemic corticosteroids >20 mg prednisone equivalent (unless patient has been taking a continuous dose for >3 weeks prior to study entry).			

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

APPENDIX C Drug Diary

Study ID:

Tolinapant Pill Diary

Subject Initials:___ Subject ID: _____ Treatment Week: _____

Instructions: Take your tolinapant at the same time every day with water. You can take it with or without food. Record the timing of each daily dose below. Between doses, store your tolinapant in the refrigerator. If you have a feeding tube and cannot swallow the tolinapant capsule, please refer to the instructions on the next page.

Planned Daily Dose: **__mg**

REMINDERS:

1. Avoid consuming grapefruit or grapefruit juice.
2. Check the bottle of tolinapant each day to make sure capsules are intact.

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Name of Medication	**Why did you take the medication?**	**Date Medication Started**	**Date Medication Stopped**

If you have any questions, please call: _____

APPENDIX D Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACE-27	Adult Comorbidity Evaluation-27
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
C_{max}	Maximum plasma concentration
CARG	Cancer and Aging Research Group
CIRS-G	Cumulative Illness Rating Scale – Geriatric
CR	Complete response
CRF	Case report form
CSA	Clinical study agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DCC	Data coordinating center
DDI	Drug-drug interaction
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
G-8	Geriatric-8
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF IMPT IMRT	Informed consent form Intensity-modulated proton therapy Intensity-modulated radiotherapy
IP	Investigational product
IRB	Institutional Review Board

IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
OAE OAR	Other significant adverse event Organ at-risk
OHRP	Office of Human Research Protection
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal