A Phase I/II Study of Metformin in Combination with Cisplatin and Radiation in Head and Neck Squamous Cell Carcinoma

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title: A phase I/II study of metformin in combination with cisplatin and radiation in head and neck squamous cell carcinoma.

Study Concept: The purpose of this study is to investigate the safety and efficacy of metformin when used in combination with standard of care cisplatin and external beam radiotherapy (EBRT) for patients with stage III/IV squamous cell carcinoma of the oropharynx, larynx, hypopharynx and oral cavity. Metformin is an anti-diabetic medication which has been widely utilized for nearly 2 decades, with a proven safety profile. Utilization of metformin during treatment of head and neck squamous cell carcinoma (HNSCC) has been shown to be associated with improved disease response, disease free survival and overall survival in retrospective studies. In combination with extensive pre-clinical studies, these data support the hypothesis that metformin can improve chemo-EBRT effectiveness in a prospective clinical trial. The proposed study is designed to determine whether metformin utilization in combination with standard of care cisplatin and EBRT demonstrates increased toxicity (phase I) and whether metformin utilization can improve the primary outcome of disease response (phase II) compared to historical controls treated with chemo-EBRT.

Study Design: This is a prospective study involving stage III/IV patients with squamous cell carcinoma of the oropharynx, larynx, hypopharynx and oral cavity. The phase I portion of the study will test 2 doses of metformin which are within the standard range used for management of diabetes mellitus. The goal of this phase I component is to determine whether metformin use is associated with increased systemic and locoregional treatment toxicity. The phase II portion will use the maximum tolerated dose (MTD) from the phase I to evaluate metformin efficacy in a prospective cohort of 20 patients using disease response as the primary outcome measure.

Number of Patients: 45

Primary Endpoint: The primary endpoint for the phase I component will be toxicity. The primary endpoint for the phase II component will be disease response ascertained via imaging following completion of treatment.

Secondary Endpoints: Secondary endpoints for the phase II component will include: progression free survival and overall survival.

2.0 OBJECTIVES

2.1 Primary Objectives

The primary objective for the phase I component is to define the maximum tolerated dose (MTD) of metformin and to document the safety of this compound when used in combination with cisplatin and external beam radiotherapy (EBRT).

The primary objective for the phase II component is to measure the effect of metformin in combination with standard of care cisplatin and EBRT on disease response when compared to historical controls treated with standard of care cisplatin and EBRT.

2.2 Secondary Objectives

Secondary endpoints for the phase II component will include: progression free survival and overall survival.

3.0 BACKGROUND AND RATIONALE

3.1 Study Disease

Every year, over 500,000 patients are diagnosed with a squamous cell carcinoma of the oral cavity, oropharynx, larynx and hypopharynx of which over 100,000 will be diagnosed in the US alone.[1] Non-operative management of these cancers has become the preferred approach over the last decade (NCCN guidelines). Advances in combinations of systemic therapy (cisplatin) and external beam radiotherapy (EBRT) technology has succeeded in decreasing treatment related toxicity, but survival rates for patients with advanced, stage III-IV disease remain low. This is particularly true for patients with stage III-IV SCC of the oropharynx, larynx, hypopharynx and oral cavity which do not exhibit evidence of infection with the human papilloma virus (HPV).[2-6] In contrast to HPV+ patients, HPV- patients continue to demonstrate low rates of disease control, disease free and overall survival. The overall goal of this study is to test the potential of metformin as an adjunct to standard of care non-operative management consisting of cisplatin and EBRT for patients with stage III/IV, HPV- SCC.

3.2 Agent/Drug Information

Metformin is a well-tolerated anti-hyperglycemic agent used by more than 120 million patients worldwide. Metformin has a demonstrated safety and efficacy profile in preventing diabetes and improving metabolic and hormonal parameters in non-diabetic patients with insulin resistance and polycystic ovary syndrome (PCOS).[7] Metformin safety has also been demonstrated in patients with non-alcoholic fatty liver disease.[8]

3.2.1 Antitumor Activity

Metformin has been shown by multiple investigators (including the principal investigator) to possess antitumor activity in preclinical models of squamous cell

carcinoma of the oral cavity, lung carcinoma, prostate carcinoma and breast carcinoma.[9-11] Retrospective data series have also shown improved clinical outcomes in patients taking metformin during treatment with standard of care regimens.[11-14]

3.2.2 Summary of Preclinical Studies

Over the last few years, multiple investigators have demonstrated an important relationship between radiation effects on tumor cells and tumor cell metabolism. This relationship is dictated to a large degree by the master metabolic regulators AMPK and mTOR.[9, 10, 15-17] We and others have shown that AMPK acts not only as a metabolic but also a genomic stress sensor that mediates cell cycle checkpoints and activates signaling events leading to radio-sensitization and cell death.[15, 16, 18] Metformin can exhibit profound effects on cellular metabolism, activate AMPK signaling and radiosensitize tumors in a variety of pre-clinical models.[9, 10, 19] In addition, metformin can potentiate the effectiveness of conventional chemotherapeutic agents in the pre-clinical setting.[20, 21] Importantly, metformin effects occur at doses that can be safely achieved in the serum of patients treated with standard oral doses of metformin.[22]

3.2.3 Summary of Clinical Studies

Clinical evidence to date indicates that utilization of metformin during cancer treatment can improve clinical outcomes in tumors of the upper aero-digestive tract.[10, 13, 23] To date, we have not detected evidence of increased treatment (chemotherapy + EBRT) toxicity in diabetic patients treated with metformin who received standard of care chemotherapy and EBRT.

3.3 Rationale for Development

Patients with stage III/IV HPV- SCC of the oral cavity, oropharynx, larynx and hypopharynx continue to demonstrate low rates of disease response and survival when treated with current standard of care chemotherapy and EBRT.[2-4, 6] There is a need to identify novel agents which can be added to standard of care regimens in order to improve disease outcomes. Because the toxicity of conventional chemotherapy and radiation is often additive and can prevent treatment escalation, there is a need to identify agents whose toxicity profile does not overlap with that of conventional treatment regimens. Metformin has an excellent safety record to date despite nearly 2 decades of widespread utilization in the Unites States. Phase I and II studies have demonstrated safe metformin use in non-diabetic patients.[24-27] Metformin does not cause hypoglycemia, has favorable metabolic effects on insulin resistance and obesity, and is not associated with lactic acidosis at standard therapeutic doses.[28,29]

Although metformin is currently being investigated in multiple other disease sites, there are no active clinical trials investigating the efficacy of metformin in combination with cisplatin and EBRT in the treatment of SCC of the oral cavity, oropharynx, larynx and hypopharynx. A single phase I trial is currently underway at the University of Cincinnati using dose of metformin higher than those proposed here and higher than those utilized in standard treatment of diabetes

mellitus. A phase I component was included in the current trial in order to evaluate any potential increase in toxicity associated with the combination of metformin, cisplatin and EBRT. The phase II component of this trial is the first of its kind in this disease site, and will provide the first prospective data regarding the potential efficacy of metformin in improving clinical outcomes for patients with stage III/IV HPV- SCC of the oral cavity, oropharynx, hypopharynx and larynx.

3.4 Correlative Studies Background

The preclinical data summarized above suggests that metformin can improve the cytotoxicity of chemotherapy and radiation, in part through perturbation of tumor metabolic pathways.[9, 10] We and others have shown that tumor cells which exhibit a less flexible metabolic phenotype are more susceptible to metformin effects.[9, 10] As a result, it is important to evaluate the metabolic phenotype of the patient tumors included in this study, in order to identify potential metabolic signatures of those tumors which are most responsive to metformin. To that end, tumors from patients enrolled in this study will be subjected to a multi-platform (mass spectroscopy / liquid chromatography) metabolomics analysis.[30]

Our preliminary studies indicate that metformin preferentially radiosensitizes tumor cells which express mutant TP53.[9, 10] Since metformin effectiveness can be impacted by the presence or absence of this and potentially other oncogenic events, we will evaluate the mutational landscape of tumors evaluated in this study using targeted sequencing.

Metformin has recently been shown to regulate the immune response associated with tumor development by regulating T cell survival and apoptosis.[31] Since the immune response can play an important role in regulation of tumor growth and treatment response, we will perform correlative studies for the following: 1) changes in circulating immune cells (i.e. effector T cells, myeloid derived suppressor cells, regulatory T cell) levels in patients before and after treatment completion; 2) changes of other cellular and humoral immune response related parameters before and after treatment completion. The correlative studies performed as part of this clinical trial will not impact treatment selection and will not be available to the treatment team. All correlative studies will be performed following completion of the prospective therapeutic trial.

4.0 PATIENT ELIGIBILITY: PATIENT INITIALS (FML):_____

_____a. Diagnosis: Patients must have histologically or cytologically confirmed squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx or larynx. Patients eligible for inclusion must have stage III-IV SCC of the above sites based on current AJCC clinical and imaging based staging (see **Appendix A** for staging criteria). For the phase II component, patients should present with: 1) HPV- SCC or 2) HPV+ SCC and a concomitant ≥10pack-year smoking history documented in the clinical record; HPV status will be ascertained using the currently utilized clinical standard of p16 overexpression via immunohistochemistry for all patients. Immunohistochemistry to determine p16 overexpression is only a requirement for oropharyngeal disease.[2, 4]

_____b. Disease Status: Patients must have active, measurable disease to be included in the study.

_____c. Prior Therapy: Patients must have fully recovered (ECOG 0-1) from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

_____d. Myelosuppressive chemotherapy: Must not have received within 4 weeks of registration onto this study (6 weeks if prior nitrosourea).

_____e. Hematopoietic growth factors: Patients must be at least 7 days since the completion of therapy with a growth factor prior to registration.

_____f. Biologic (anti-neoplastic agent): Patients must be at least 7 days since the completion of therapy prior to registration.

_____g. Monoclonal Antibody: At least 6 weeks must have elapsed since prior therapy that includes a monoclonal antibody prior to registration.

_____h. XRT: Prior to registration, patients must be ≥ 14days for local palliative XRT (small port); ≥ 90days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; ≥ 45days must have elapsed if other substantial bone marrow radiation.

_____i. Stem Cell Transplant or Rescue: No evidence of active graft vs. host disease and ≥ 2 months must have elapsed since transplant prior to registration.

_____j. Age: Patients must be ≥18 years of age.

_____k. Performance Status: ECOG performance status less than or equal to 3.

_____l. Organ Function: Patients must have normal organ and marrow function as defined below, within 14 days of registration:

i.	leukocytes	≥3,000/mcL
ii.	absolute neutrophil count	≥1,500/mcL
iii.	platelets	≥100,000/mcL
iv.	total bilirubin	within normal institutional limits
v.	AST(SGOT)	≤2.5X institutional upper limit of normal
vi.	ALT /(SGPT)	≤2.5X institutional upper limit of normal
vii.	creatinine < 1.5mg/dL OR creatinine clearance≥60 mL/min/1.73 m^2 for patients with creatinine levels > institutional normal	

_____m. Patients must be candidates for standard of care treatment consisting of chemotherapy (cisplatin) and radiation.

_____n. Willingness to Use Contraception: The effects of metformin on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence), 30 days prior to study drug initiation and 30days post completion of study drug administration. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

_____o. Informed Consent: Patients must have the ability to understand and the willingness to sign a written informed consent document.

_____p. Patients may not be receiving any other investigational agents.

_____q. Brain metastases: Patients may not have diagnosed brain metastases.

_____r. Prior Allergies: Patients may not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to metformin.

_____s. Patients must not have a diagnosis of diabetes mellitus (DM) or be receiving active treatment for DM. If patient does not have known DM diagnosis, the patient must have either fasting glucose or hemoglobin A1C test within 30 days of registration. Patient is not eligible if glucose level ≥ 126mg/dl or hemoglobin A1c ≥ 6.0%. (Either test is sufficient for eligibility; both tests are not needed.)

_____t. Patients may not have an 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.

_____x. Patients may not be pregnant or breastfeeding.

_____y Patients may not have diagnosed HIV.

_____z. Patients may not be taking metformin for a reason other than study participation.

_____aa. Patients may not have been treated for another SCC of the oral cavity, oropharynx, hypopharynx or larynx in the past.

Both men and women and members of all races and ethnic groups are eligible for this trial. Approximately 40% of the patient population in Harris County is Hispanic and many are primarily Spanish speaking, thus we will provide a fully translated and IRB approved Spanish consent to these subjects.

5.0 REGISTRATION PROCEDURES

5.1 General Guidelines

5.1.1 Eligible patients will be entered on study centrally at the Clinical Trials Support Unit in the Dan L. Duncan Comprehensive Cancer Center at the Baylor College of Medicine by the Study Coordinator. Coordinators at each facility will discuss eligibility with the study PI. Patient eligibility checklist must be completed prior to enrollment. Study consent must be obtained prior to performing any study related procedures.

5.1.2 Following Registration, patient should begin treatment within 30 days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

5.2 Registration Process

5.2.1 Eligibility will be determined as per CTSU policy, according to the criteria in Section 4.

5.2.2 Eligible subjects will be registered into OnCore, and assigned a study ID number.

5.2.3 Issues that would cause treatment delays should be discussed with the Principal Investigator.

5.2.4 Filing of the signed consent form will be done per CTSU policy.

6.0 TREATMENT/INTERVENTION PLAN

6.1 Agent Administration

All patients will receive immediate release metformin in a pill form that allows for it to be crushed and administered via gastrostomy tube if necessary.

Metformin should be taken 60-90 minutes prior to a meal. The first dose of the day should be taken prior to administration of the daily radiation fraction. On days on

which the patient will undergo cisplatin infusion, metformin should be taken at least 90 minutes prior to cisplatin infusion.

The drug will be dispensed to the patient from the institutional pharmacy with appropriate self-administration instructions. The patients will be provided with a drug log and will be asked to provide the drug log on a weekly basis to the treating team in order to ascertain compliance with administration schedule and instructions.

Dose Level	Drug
DL -1	500 mg, PO, BID
DL 1	850 mg, PO, BID
DL 2	1500 mg, PO, BID

Phase I component:

All patients will undergo a 2 week "lead in" period in order to decrease the gastrointestinal toxicity associated with metformin. During this "lead-in" period, all patients will start metformin at the dose of 500mg PO BID. Dose increases to the targeted Dose levels are delineated in detail below. The start of radiation is Day 1.

The following modification is planned for the Phase I component. We will forgo escalation to Dose level 2 and proceed to the Phase II component using Dose level 1. The previous Dose level 2 information has been left in the protocol for the purpose of documentation (12/19/2018).

Dose level 1: 850mg per os (PO) twice daily (BID). All patients will start metformin 14 days (Day -14) (+/-24hr) prior to initiation of radiation at the starting dose of 500mg PO BID (administered prior to breakfast and prior to dinner), 7 days/week. On day -7 (+/-24hr), the dose will be escalated to 850mg PO BID for the first 3 patients enrolled in the phase I component. The dose of 850mg PO BID will then be continued for the entire duration of chemoradiation, administered 7 days/week. If the timing of radiation start is altered following metformin initiation patient may continue on the study as follows.

- If the timing of radiation is moved up (i.e. sooner than planned), the patient may continue the "lead in" phase as described above, and initiate the target Dose level once the "lead in" phase has been completed.
- If the timing of radiation start is delayed following the "lead in" phase, the patient will initiate the target Dose level once the "lead in" phase has been completed and continue taking metformin while waiting for radiation start.

Dose level 2: 1500mg per os (PO) twice daily (BID). All patients will start metformin 14 days (Day -14) (+/-24hr) prior to initiation of radiation at the starting dose of 500mg PO BID (administered prior to breakfast and prior to dinner), 7 days/week. On day -7 (+/-24hr), the dose will be escalated to 850mg PO BID. On day -4 (+/-24hr) the dose will again be escalated to 1500mg PO BID. Patients will then continue the 1500mg PO BID regimen for the entire duration of chemoradiation, administered 7days/week. If the timing of radiation start is altered following metformin initiation patient may continue on the study as follows.

- If the timing of radiation is moved up (i.e. sooner than planned), the patient may continue the "lead in" phase as described above, and initiate the target Dose level once the "lead in" phase has been completed.
- If the timing of radiation start is delayed following the "lead in" phase, the patient will initiate the target Dose level once the "lead in" phase has been completed and continue taking metformin while waiting for radiation start.

Dose level -1: 500 mg per os (PO) twice daily (BID). Although the 850mg PO BID dose is well within the current clinical range for metformin, the phase I component will also include a Dose level -1. If patients experience metformin related toxicity (see below) on the 850mg dose, we will de-escalate to a dose of 500mg PO BID. Patients will start metformin 14 days (Day -14) (+/-24hr) prior to initiation of radiation at the starting dose of 500mgPO BID (administered prior to breakfast and prior to dinner), 7days/week and continue at this dose for the entire treatment course. This dose will then be utilized for the entire phase I component of the trial. All patients will receive immediate release metformin in a pill form that allows for it to be crushed and administered via gastrostomy tube if necessary. If the timing of radiation start is altered following metformin initiation patient may continue on the study as follows.

- If the timing of radiation is moved up (i.e. sooner than planned), the patient may continue the "lead in" phase as described above, and initiate the target Dose level once the "lead in" phase has been completed.
- If the timing of radiation start is delayed following the "lead in" phase, the patient will initiate the target Dose level once the "lead in" phase has been completed and continue taking metformin while waiting for radiation start.

Determination regarding maximum tolerated dose (MTD) for the phase I component will be performed as described. See section 7.2 specific metformin evaluable toxicities and dose limiting toxicities (DLTs). All patients who are enrolled and receive the study drug will be evaluated for toxicity, but only patients which complete ≥70% of the total planned study drug dose to be administered during the standard of care radiation treatment period will be used to ascertain absence of DLT as part of the Phase I component and planned escalation strategy detailed in the table in section 13.2.

Assignment of patients to a Dose levels will be performed by the PI or one of the co-investigators listed on the protocol if the PI is not immediately available. Study coordinators will not be expected to assign patients to Dose levels. All decisions regarding dose escalation or dose reduction will be made by the PI or one of the co-investigators listed on the protocol if the PI is not immediately available, using the general schema listed above and the toxicity driven modifications listed in Section 7. Modifications to the standard of care treatment consisting of chemotherapy and radiation will be made by the treating physicians, per standard clinical practice.

Phase II component:
All patients used for evaluation of the phase II component will be treated using one of the Dose levels determined by the process described in section 13.2.To be evaluable for response patients must have taken ≥70% of the total metformin dose to be administered during the standard of care radiation treatment period
Regardless of the determined MTD, all patients will start with a 1 week "lead-in" period of 500mg PO BID. If the timing of radiation start is altered following metformin initiation patient may continue on the study as follows. If the timing of radiation is moved up, the patient may continue the "lead in" phase as described above, and initiate the target Dose level once the "lead in" phase has been completed. If the timing of radiation start is delayed following the "lead in" phase, the patient will initiate the target Dose level once the "lead in" phase has been completed and continue taking metformin while waiting for radiation start.

6.2 Other Modality(ies) or Procedures

Chemotherapy: Weekly cisplatin will be administered at the discretion of the treating physicians. Below is a suggested regimen for administration that is recommended in order to standardize administration and treatment of side effects. Deviations from this regimen are allowed, but should be documented by the treating physician. It is recommended that cisplatin be infused over 60 minutes intravenously at 40 mg/m2 weekly, starting on week 1 day 1 of radiation, for a maximum of 7 weeks. Cisplatin can be given either before or after the radiation therapy fraction that is given on the same day. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes. The administration of cisplatin should follow the standard anti-emetic premedication and hydration as follows: Ondansetron 16mg + Dexamethasone 8 mg should be infused 30 minutes prior to cisplatin infusion. Normal saline 1000 mL + KCl 20 mEq / L + 1 gm MgSO4 will be infused over 2 hours prior to administration of cisplatin. Normal saline 500ml should be infused after completion of cisplatin. Any pre-existing dehydration should be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for additional management. Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy

administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone. Potential delayed nausea regimens include:
1. The NK-1 antagonist, aprepitant (125 mg p.o.), may be added for prevention of delayed emesis on the day of cisplatin administration and for two consecutive days thereafter (80, 80), with a corticosteroid, such as dexamethasone on days 1-4. Fosaprepitant 115 mg iv may be substituted for the aprepitant 125 mg on day 1. Dexamethasone should be reduced on day 1 to 12 mg and delivered at up to 8 mg total daily for the 3 days following cisplatin administration. A 5HT3 antagonist (e.g. granisetron, ondansetron) may be also given for the 3 days following cisplatin administration, only if palonosetron was not given prior to chemotherapy.
2. Delayed emesis also may be managed by the addition of dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days, beginning on the day after chemotherapy; and oral metoclopramide 0.5 mg/kg (usually 20-40 mg) qid x 2-4 days. A 5HT3 antagonist (e.g. granisetron, ondansetron) may also be given for up to 3 days after cisplatin.

External beam radiotherapy (EBRT): EBRT will be administered at the discretion of the treating physician as deemed appropriate for the individual patient and tumor characteristics. Below is a suggested regimen for administration that is recommended in order to standardize administration and treatment of side effects. Deviations from this regimen are allowed, but should be documented by the treating physician. For oral cavity and oropharynx primary tumors, the prescribed radiotherapy dose will be 69.96 Gy in 2.12 Gy once-daily fraction size (total of 33 fractions). For larynx and hypopharynx tumors primary tumors, the prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size (total of 35 fractions). The daily dose of 2.12 Gy will be prescribed such that 95% of the PTV69.96 volume receives 69.96 Gy. Radiotherapy should begin on a Monday, Tuesday or Wednesday. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for inter-current illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation. Missed treatments due to holidays or for logistic reasons can be compensated for by delivering an additional treatment (BID, two fractions in one day at least 6 hours apart) during the week, or treating on the Saturday or Sunday of that week, or adding to the end of treatment. IMRT will be utilized for treatment planning, and planning will consist of a single plan utilizing a simultaneous integrated boost (SIB) technique as outlined below. Daily image-guidance in the form of cone-beam CT is required to ensure accurate daily set-up and reproducibility.

Target and Normal Tissue Volume Definitions For Oral Cavity and Oropharynx
CTV69.96: This volume will receive 2.12 Gy per day in 33 fractions over 6.5 weeks. CTV69.96 consists of the primary tumor and grossly involved

lymphadenopathy with a 0.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion. A 0.3 cm expansion to CTV69.96 will be utilized to create PTV69.96. CTV63 will receive 1.91 Gy in 33 fractions and consists of intermediate-risk disease sites and is defined as a 1 cm expansion on the GTVs along with the remainder of neck levels with grossly involved disease (i.e. left level II with a grossly involved left level II node). Additionally, it includes anatomical patterns of microscopic spread defined at the discretion of the treating radiation oncologist. A 0.3 cm expansion to CTV63 will be utilized to create PTV63. CTV57 will receive 1.73 Gy per day in 33 fractions and consists of low-risk sub-clinical disease sites, including the uninvolved contralateral neck, and uninvolved ipsilateral low neck. A 0.3 cm expansion to CTV57 will be utilized to create PTV57.

Target and Normal Tissue Volume Definitions For Larynx and Hypopharynx
CTV70: This volume will receive 2.0 Gy per day in 35 fractions over 7 weeks. CTV70 consists of the primary tumor and grossly involved lymphadenopathy with a 0.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion. A 0.3 cm expansion to CTV70 will be utilized to create PTV70. CTV63 will receive 1.8 Gy in 35 fractions and consists of intermediate-risk disease sites and is defined as a 1 cm expansion on the GTVs along with the remainder of neck levels with grossly involved disease (i.e. left level II with a grossly involved left level II node). Additionally, it includes anatomical patterns of microscopic spread defined at the discretion of the treating radiation oncologist. A 0.3 cm expansion to CTV63 will be utilized to create PTV63. CTV57 will receive 1.63 Gy per day in 35 fractions and consists of low-risk sub-clinical disease sites, including the uninvolved contralateral neck, and uninvolved ipsilateral low neck. A 0.3 cm expansion to CTV57 will be utilized to create PTV57.

Radiation Treatment Related Toxicity
Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third to two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is recommended. Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields. These side effects vary in intensity and are typically managed during the weekly visit with the treating radiation oncologist. Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (<5% incidence with proper pre-therapy dental evaluation), and cervical myelopathy (<1% with restriction of spinal cord dose to ≤45 Gy).

6.3 Concomitant Medication and Supportive Care Guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

6.4 Duration of Treatment

Patients will be on metformin treatment for approximately 14 days prior to initiation of concurrent chemo-radiation in order to complete a metformin dose- escalation phase designed to decrease metformin toxicity. Patients will then complete a 6-7 week course of metformin + concurrent chemoradiation. Patients will continued to be monitored for toxicity (phase I) for 30 days following completion of radiation treatment prior to proceeding to the next dose level in the phase I component.

6.5 Criteria for Removal from Study

Criteria for removal from the study include: intercurrent illness that prevents further treatment administration, patient's decision to withdraw from the study, progression of disease, development of a 2nd primary tumor (lung, esophagus, oral cavity, oropharynx, larynx or hypopharynx) and delay in protocol initiation and/or completion. If the protocol is discontinued, all patient follow up will continue in accordance with institutional standard of care protocols.

6.6 Duration of Follow-Up

All patients will be followed for 2 years following radiation treatment completion. In the first year, patients will be evaluated every 3 months, in the second year every 4 months which is consistent with institutional practice and clinical guidelines for the management of patients with head and neck cancer

7.0 DOSING DELAYS/DOSE MODIFICATION

7.1 Cisplatin dose modifications. A suggested dose modification protocol is offered below; however, treating physicians may utilize other protocols which are consistent with current standard of care for this agent.

7.1.1 Leukopenia: hold cisplatin infusion if absolute neutrophil counts (ANC) falls below 1500/ml, and proceed with radiotherapy only. Check CBC in one week, resume cisplatin at 40mg/m2 if ANC ≥1500/ml; continue to hold cisplatin infusion and proceed with radiation only if ANC less than 1500/ml.

7.1.2 Thrombocytopenia: hold cisplatin infusion if platelet counts falls below 100,000/ml, and proceed with radiotherapy only. Check CBC every week, resume cisplatin at 40mg/m2 only if platelet count is over 100,000/ml, but continue radiation as scheduled.

7.1.3 Neurotoxicity: If grade 2 neurotoxicity developed, hold cisplatin (but continue RT) until toxicity improves to < grade 1, then resume cisplatin. If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin, but continue RT.

7.1.4 Renal Adverse Events: If creatinine > 1.5 mg / dL, hydrate the patient over a 24hr period using normal saline 2000 mL + KCl 20 mEq / L + 1 gm MgSO4 and administer the 100% dose if creatinine <1.5 mg / dL, reduce to 50% if creatinine> 1.5 mg / dL and <1.9 mg / dL. Hold cisplatin if creatinine increase to more than 1.9mg/dl, but continue on radiation as scheduled.

7.1.5 Nausea and Vomiting: Maximum supportive therapy will be given, and cisplatin will be continued at full dose for ≤ grade 2 nausea and vomiting. For grade 3 nausea and vomiting refractory to supportive therapy, cisplatin will be held until recovery to < grade 2. No dose reductions will be made.

7.1.6 Mucositis: Significant mucositis (grade 3-4, CTCAE, v. 4) is expected from radiation and cisplatin and should not be a reason for a treatment break, unless it significantly interferes with fluid intake or nutrition. Aggressive supportive care is encouraged.

7.1.8 For any other grade 3-4 non-hematologic adverse events possibly related to cisplatin, hold cisplatin until toxicities have recovered to grade 1 or less.

7.2 Metformin dose modifications. All metformin dose modifications refer to the BID dosing. For example, “decreased by 350mg” refers to a reduction from 500mg PO BID to 250mg PO BID or from 850mg PO BID to 500mg PO BID.

7.2.1 Hypoglycemia: Although the risk of hypoglycemia in euglycemic patients receiving metformin is very low, patients in this trial might have a low caloric intake due to complications of treatment, and will undergo weekly blood glucose monitoring.

If based on these lab values or associated symptoms, the treating physician diagnoses hypoglycemia (Grade 1 or greater), study drug treatment will be halted, while concurrent chemoradiation will continue. Once blood glucose normalizes, metformin will be restarted and the dose should be decreased to the next available lower dose (see table below) with daily monitoring of blood glucose. Patients will

be provided equipment and supplies for twice daily blood glucose checks, along with a form used to record values.

Instructions for Metformin Dose Reductions due to Adverse Events		
Starting Dose (mg PO BID)		Reduced Dose (mg PO BID)
1500 mg	→	1350 mg
1350 mg	→	1000 mg
1000 mg	→	850 mg
850 mg	→	500 mg
500 mg	→	0 (off treatment)

If hypoglycemia resolves to < Grade 1 after 7 days, daily monitoring will be discontinued and the patient will resume the previous dose. All dose de-escalation and re-escalation will be recorded in source documentation. If **hypoglycemia** symptoms persist **for more than 7 days**, the study drug will be stopped and this will be considered a DLT.

7.2.2 Gastrointestinal toxicity: In the event of grade 2-4 gastrointestinal toxicity (typically involving flatulence or diarrhea), patients will be supported with loperamide, at dosing schedules recommended in the package insert. Gastrointestinal side effects typically subside within 4-6 weeks of initiating metformin treatment.

Efforts should be made to maintain the dose as close to the planned total daily treatment dose as much as possible. Before dose-reducing, alterations to the daily intake schedule of metformin should be taken to reduce gastrointestinal symptoms, including taking metformin with food rather than before meals.

If alterations in intake schedule are insufficient in reducing gastrointestinal toxicity to ≤ grade 1, the metformin dose should be decreased to the next available lower dose for 1 week with loperamide support until symptoms subside.

If GI toxicity has not resolved to ≤ grade 1 after 1 week of dose reduction, then decrease the dose again to the next available lower dose; do this weekly until GI toxicity resolves. **If toxicity does not resolve despite de-escalation, metformin will be stopped and this will be considered a DLT.**

For patients in the Phase I component who experience toxicity, efforts should be made to re-escalate the dose of metformin back to the planned Dose level 2 weeks after the patients remain free of grade 2 toxicity.

For patients in the Phase II component who experience toxicity, efforts should be made to re-escalate the dose of metformin back to the MTD identified in Phase I 2 weeks after patients remain free of grade 2 toxicity. At least 2 attempts should be made to re-escalate the dose to the MTD identified in Phase I after each dose de-escalation takes place. In the event that re-escalation to a higher dose cannot be achieved without grade 2 toxicity, patients will be maintained at the highest tolerable dose for the remainder of the metformin treatment period.

All dose de-escalation and re-escalation will be recorded in source documentation.

Metformin treatment interruption will be permitted according to institutional guidelines at the time of routine CT scans with contrast infusion.

7.2.3 Criteria for discontinuation of metformin treatment include: toxicity (see 7.2.2) which cannot be improved with the measures listed above; progression of disease; development of a 2nd primary tumor (lung, esophagus, oral cavity, oropharynx, larynx or hypopharynx); or delay in protocol initiation and/or completion. If radiation is terminated prior to completion of the prescribed standard of care dose, metformin will be stopped.

7.2.4 If creatinine > 1.5 mg / dL, hydrate the patient over a 24hr period using normal saline 2000 mL + KCl 20 mEq / L + 1 gm MgSO4 and administer 100% of the planned metformin dose if creatinine <1.5 mg / dL. If Cr remains >1.5mg/dL hold metformin for 1 week and repeat creatinine. If creatinine <1.5mg/dL resume metformin at the previous dose; if not, continue to hold metformin unto Cr <1.5mg/dL.

7.2.5 Lactic acidosis is a historical concern in patients with normal renal function. There is no evidence of increased lactic acidosis risk in patients taking metformin. As such, screening for lactic acidosis will not be incorporated into this trial.[29]

7.2.6 If cisplatin regimen is discontinued or de-escalated to a lower dose of cisplatin or changed to a different cytotoxic or non-cytotoxic agent, metformin will be continued unless metformin related toxicity is observed and the data from that patient will be recorded as part of the study as long as the patient can continued to receive the prescribed dose of radiation.

7.2.5 If radiation is terminated prior to completion of the prescribed standard of care dose, metformin will be stopped.

7.3 Radiation dose modification

Consistent with current institutional and national standards, de-escalation of the radiation component will not be allowed during the protocol. Adjustments to specific components of the radiation field will be allowed at the discretion of the treating radiation oncologist based on tumor response, consistent with current institutional practice protocols. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for inter-current illness and not for social or logistical reasons. Missed treatments due to holidays or for logistic reasons can be compensated for by delivering an additional treatment (BID, two fractions in one day at least 6 hours apart) during the week, or treating on the Saturday or Sunday of that week, or adding to the end of treatment.

8 CORRELATIVE STUDIES (Optional For Patients)

NOTE: Optional correlative studies have been removed from the protocol with R10 due to insufficient evaluable data being available to draw meaningful conclusions.

9 TREATMENT EVALUATION

9.1 Pre-treatment evaluation

9.1.1 A complete history and physical examination by a medical, radiation or surgical (ENT or Head and Neck Surgery) oncologist, and baseline laboratory studies, including complete blood count (CBC), complete metabolic panel (CMP) and fasting glucose or non-fasting HgbA1c will be performed within 30 days of starting metformin escalation. Negative pregnancy test is required 10-14 days before registration for women of child bearing age who maintain reproductive potential (i.e. have not undergone hysterectomy).

9.1.2 Sample collection for baseline correlative studies will be performed before initiation of metformin escalation as outlined in the study calendar.

9.1.3 One of the following combinations of imaging is required within 8-12 weeks prior to registration:

a) A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast), or
b) A CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast). **Note**: A CT scan of neck and/or PET/CT performed for radiation planning and read by a radiologist may serve as both staging and planning tools.

Staging (T, N, M) will be performed by the treatment team following diagnosis and discussion at multi-disciplinary tumor conference, per standard of care practice. For the purpose of the study, the clinical TNM staging for each patient will be obtained by the PI or clinical coordinator from the medical record and entered into the study prior to treatment initiation.

9.1.4 Evaluation by a nutritionist and/or swallowing therapist is highly recommended within 2-4 weeks prior to the start of chemo-radiation treatment and should include evaluation for placement of prophylactic gastrostomy or other type of feeding tube. The decision to place a feeding tube should be individualized and may consider a number of factors including: prior weight loss, current nutritional status, size and location of the primary tumor (impacting high dose target volume), availability of feeding tube placement services, availability of speech and swallowing specialists, and social support. Feeding tubes may be placed after start of treatment at the discretion of the clinical team. If a tube is placed, documentation will be provided in the patient's protocol file if the tube was placed prophylactically (as a preventative measure) or therapeutically (because of nutritional compromise or other clinical indications).

9.2 Evaluation during treatment

9.2.1 Patients will be evaluated weekly by the treating team during the escalation phase of metformin administration. Patients will be evaluated weekly by the radiation oncology team during concurrent chemoradiation as per current institutional protocol. The drug log will be reviewed on a weekly basis. Study staff may contact patients via telephone to discuss investigational drug compliance and/or any other study related questions or tasks. Additional visits will be obtained as clinically indicated. History and physical exams, along with appropriate laboratory studies (CBC, BMP) will be performed at each additional visit.

9.1.2 Sample collection for baseline correlative studies will be performed during treatment as outlined in the study calendar.

9.3 Evaluation following treatment

9.3.1 A brief history and physical examination by a medical, radiation or surgical (ENT or Head and Neck Surgery) oncologist, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), should be done at 10 weeks following completion of radiation then every 3 months through year 1 and every 4 months through year 2. A 30 day visit or telephone interview is required for evaluation of Adverse Events. Radiographic imaging (CT, MRI, or PET as appropriate) at these time points is highly recommended if disease progression is suspected by the treating physician. If performed, radiographic imaging to evaluate the patient for both local-regional recurrence and distant metastases is highly recommended.

9.3.2 Chest imaging: A chest CT or a PET/CT of chest is recommended once per year.

9.3.3 Biopsy of any lesion(s) suspicious for tumor recurrence is recommended as clinically indicated.

9.3.4 The initial post-radiation imaging evaluation (CT at 8-10weeks or PET-CT at 10-12weeks) after the completion of chemoradiation is recommended to assess disease response. The imaging can be contrast enhanced CT (neck and chest) or PET-CT of the head and neck or "whole body" PET/CT (minimum neck and chest) based on the preference of the treating clinician, but must be consistent with the pre-treatment imaging modality.

9.2 Study Calendar

	Pre-study	wk -2 (d3+/-2d)	wk 1 (d3+/-2d)	wk 2 (d3+/-2d)	wk 3 (d3+/-2d)	wk 4 (d3+/-2d)	wk 5 (d3+/-2d)	wk 6 (d3+/-2d)	wk 7 (d3+/-2d)	30 days post radiation completion	Post-study (wk17+/-2wk)	Post-study (yr1 Q3mos)	Post-study (yr2 Q4mos)
Metformin tx		<----------BID metformin ---------->											
Chemo-radiation tx			<-------XRT (Daily); chemotherapy (weekly) --------->										
Collected information (ONCORE)													
Metformin pill diary/ compliance form		X	X	X	X	X	X	X	X				
Eligibility checklist	X												
Informed consent	X												
T, N, M staging	X												
Demographics	X												
Physical Exam	X	X	X	X	X	X	X	X	X		X	X	X
Medical history	X												
Vital signs	X										X	X	X
Weight	X	X	X	X	X	X	X	X	X		X	X	X
Performance status	X	X	X	X	X	X	X	X	X		X	X	X
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X		
CMP	X												
CBC, BMP	X	X	X	X	X	X	X	X	X		X	X	X
Glucose monitoring (if applicable) (A)		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*				
Disease response/ radiologic evaluation											X	X	X
Pregnancy test	X (B)												
Imaging (C)	X										X	X	X
Laryngopharyngoscopy											X	X	X

pre-study items to be collected within 30 days of initiation of metformin treatment
Pill diary/compliant may be discussed or completed via telephone.

A: patients wih hypoglycemia(<=60mg/dl) will receive instructions and supplies for BID glucose monitoring and recording

B: Serum or urine pregnancy test (women of childbearing potential).

C: Required within 8-12 weeks prior to registration, at end of radiation treatment, and at regular intervals following treatment completion.

D= day, Wk= week, Mos= months, Yr= year; d3+/-2d= to be completed on day 3 of any given week, +/- 2days

10 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 11.0.

10.1 Metformin. Metformin hydrochloride is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N-dimethl-limidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C4H,,N5.1-lCI and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK, of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Mechanism of Action: Metformin is an anti-hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Absorption and Bioavailability: The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak concentration and 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution: The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 + 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours

and are generally c 1 pg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 ug/mL, even at maximum doses.

Metabolism and Elimination: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients with Type 2 Diabetes. In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency. In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency. No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.

Geriatrics. Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C max is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin treatment should not be initiated in patients >80 years of age unless measurement of creatinine clearance demonstrates normal renal function.

Availability. Metformin is a commercially available anti-diabetic drug which will be purchased by the institutional pharmacy and dispensed to the study patients.

10.2 Agent Ordering

Metformin will be purchased by the study PI from the institutional pharmacy. Metformin will be dispensed from the institutional pharmacy to the patient along with appropriate self-administration instructions. The study PI will not dispense the medication. Metformin will be provided to research subjects for the duration of their participation in this trial at no charge to them or to their insurance provides. Only enough metformin for completion of the treatment protocol will be supplied to each patient.

10.3 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents utilizing the electronic medical record and pill diary.

10.4 Commercial Agent(s)

Cisplatin. Cisplatin is a commercially available chemotherapeutic agent. Cisplatin Injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively. The active ingredient, cisplatin, is a yellow to orange crystalline powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207° C. Plasma concentrations of the parent compound, cisplatin, decay monoexponentially with a half-life of about 20 to 30 minutes following bolus administrations of 50 or 100 mg/m^2 doses. Monoexponential decay and plasma half-lives of about 0.5 hour are also seen following 2-hour or 7-hour infusions of 100 mg/m^2. After the latter, the total-body clearances and volumes of distribution at steady-state for cisplatin are about 15 to 16 L/h/m^2 and 11 to 12 L/m^2.

Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl, the predominant molecular species are cisplatin and monohydroxymonochloro *cis*-diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultrafilterable) platinum in the plasma vary considerably between patients and range from 0.5 to 1.1 after a dose of 100 mg/m^2.

Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins, including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Following cisplatin doses of 20 to 120 mg/m^2, the concentrations of platinum are highest in liver, prostate, and kidney; somewhat lower in bladder, muscle, testicle, pancreas, and spleen; and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum.

Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/m^2 dose of cisplatin and decline in a biphasic manner with a terminal half-life of 36 to 47 days. Over a dose range of 40 to 140 mg cisplatin/m^2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over five days following administration of 40 to 100 mg/m^2 doses given as rapid, 2-to 3-hour, or 6-to 8-hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following five daily administrations of 20, 30, or 40 mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum-containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine from healthy subjects, except that the proportions are different.

The parent compound, cisplatin, is excreted in the urine and accounts for 13% to 17% of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal clearance of cisplatin exceeds creatinine clearance and is 62 and 50 mL/min/m^2 following administration of 100 mg/m^2 as 2-hour or 6-to 7-hour infusions, respectively. The renal clearance of free (ultrafilterable) platinum also exceeds the glomerular filtration rate indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption. There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent basis. No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance. Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

Contraindications. Cisplatin is contraindicated in patients with preexisting renal impairment. Cisplatin should not be employed in myelosuppressed patients, or in patients with hearing impairment. Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum-containing compounds.

Teratogenicity. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant. The carcinogenic effect of cisplatin was studied in BD IX rats. Cisplatin was administered intraperitoneally (i.p.) to 50 BD IX rats for 3 weeks, 3 X 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma. The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents. Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Drug interactions. Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

Pregnancy. Pregnancy Category D

Nursing Mothers. Cisplatin has been reported to be found in human milk; patients receiving cisplatin should not breast-feed.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established. All children should have audiometric monitoring performed prior to initiation of therapy prior to each subsequent dose, and for several years post therapy. Advanced testing methods may allow for earlier detection of hearing loss in an attempt to facilitate the rapid initiation of interventions that can limit the potential adverse impact of hearing impairment on a child's cognitive and social development.

Geriatric Use. Insufficient data are available from clinical trials of cisplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly patients respond differently than younger patients. In four clinical trials of combination chemotherapy for advanced ovarian carcinoma, 1484 patients received cisplatin either in combination with cyclophosphamide or paclitaxel. Of these, 426 (29%) were older than 65 years. In these trials, age was not found to be a prognostic factor for survival. However, in a later secondary analysis for one of these trials, elderly patients were found to have shorter survival compared with younger patients. In all four trials, elderly patients experienced more severe neutropenia than younger patients. Higher incidences of severe thrombocytopenia and leukopenia were also seen in elderly compared with younger patients, although not in all cisplatin-containing treatment arms. In the two trials where nonhematologic toxicity was evaluated according to age, elderly patients had a numerically higher incidence of peripheral neuropathy than younger patients. Other

reported clinical experience suggests that elderly patients may be more susceptible to myelosuppression, infectious complications, and nephrotoxicity than younger patients. Cisplatin is known to be substantially excreted by the kidney and is contraindicated in patients with preexisting renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

Adverse reactions

Nephrotoxicity. Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6-to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity. Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). The prevelance of hearing loss in children is particularly high and is estimated to be 40-60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy. The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and may be more severe in patients less than 5 years of age, patients being treated with other ototoxic drugs (e.g. aminoglycosides and vancomycin), and in patients with renal impairment. Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

Hematologic. Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the

same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal. Marked nausea and vomiting occur in almost all patients treated with cisplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

Other toxicities. Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances. Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia. Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity. Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7

months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity. Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions. Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity. Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other events. Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported. Local soft tissue toxicity has been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

Overdosage. Caution should be exercised to prevent inadvertent overdosage with cisplatin. Acute overdosage with this drug may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea and vomiting and/or neuritis. In addition, death can occur following overdosage. No proven antidotes have been established

for cisplatin overdosage. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of cisplatin's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

Dosage and administration. Cisplatin Injection is administered by slow intravenous infusion. CISPLATIN INJECTION SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION. Patients will undergo prehydration with a 1 liter of D_5NS over 2-4 hours and mannitol, 12.5g iv bolus immediately prior to cisplatin. Cisplatin, in 500-1000 ml NS is administered over 1-2 hours followed by an additional 1 to 1.5 liters of fluid. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for additional management.

Preparation of intravenous solutions

Preparation Precautions. Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water. More information is available in the references listed below.

Instructions for Preparation. The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6-to 8-hour period. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. NOTE TO PHARMACIST: Exercise caution to prevent inadvertent cisplatin overdosage. Please call prescriber if dose is greater than 100 mg/m^2 per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement: CALL DR. IF DOSE>100 MG/M^2/CYCLE.

Stability. Cisplatin Injection is a sterile, multidose vial without preservatives. Store at 15° C to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

11 TOXICITIES/SIDE EFFECTS

The most frequently reported side effect for the study drug metformin is gastrointestinal toxicity, more specifically flatulence and/or diarrhea. These side effects generally subside within several weeks of initiation of treatment and the risk of these side effects can be decreased through a dose-escalation phase such as the one built into the proposed trial. Gastrointestinal toxicity will be measured for all patients following initiation of metformin

treatment, and will be used as the primary measure for the Phase I component of the proposed trial.

Due to its mechanism of action (see above), the risk of hypoglycemia with metformin treatment is very low. However, since patients in this trial may experience a low caloric intake due to the side effects of the conventional treatment component (cisplatin- nausea, mucositis; radiation- xerostomia, altered taste) patients will undergo weekly blood glucose monitoring. If based on these lab values or associated symptoms, the treating physician diagnoses hypoglycemia, study drug treatment will be halted, while concurrent chemoradiation will continue. Once blood glucose normalizes, metformin will be restarted and the dose should be decreased by 250mg with daily monitoring of blood glucose. If there are no symptoms or signs of hypoglycemia in 1 week, daily monitoring will be discontinued. All dose de-escalation and re-escalation will be recorded in source documentation. Hypoglycemia will be measured for all patients following initiation of metformin treatment, and will be used as a secondary measure for the Phase I component of the proposed trial.

Toxicity recording will commence once patients start taking metformin and will be completed at 30days following completion of treatment.

12.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST1.1) Committee [Eur J Cancer. 2009 Jan; 45(2):228-47]. Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response following completion of treatment as per current institutional protocol for this disease site: 1) spiral contrast enhanced computed tomography (CECT) at 8-10 weeks following completion of treatment or 2) positron emission tomography (PET) at 10-12 weeks following completion of treatment. No additional imaging or tests will be performed as part of the current protocol. Following the first post treatment scan, patients will continue routine surveillance using CECT or PET per institutional protocols.

12.1.1. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with metformin until 30 days following treatment completion.

Evaluable for objective response. All patients included in the study must be assessed for response to treatment, even if there are major protocol

treatment deviations. These patients will have their response classified according to the definitions stated below.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CECT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using spiral CECT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Spiral contrast enhanced CT. Spiral CT should be performed using the approved institutional head and neck protocol.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial

lesions usually assessed by clinical examination.
Endoscopy. The utilization of this technique for objective tumor evaluation has not yet been fully and widely validated. Its use in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such a technique for objective tumor response should be restricted to validation purposes. However, such a technique may be useful to confirm complete pathological response when biopsies are obtained.
Tumor markers. Tumor markers alone cannot be used to assess response.
Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions
Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Overall Response: overall response will be ascertained via clinical exam and imaging at 8-12 weeks post treatment completion according to the table below.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response (measured at 8-12wk post treatment)
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

12.1.5 Duration of Response
Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

12.1.6 Progression-Free Survival: Defined as the duration of time from the date of study registration to the date of documented radiographic progression.

12.1.7 Overall survival: Defined as the duration of time from the date of study registration to the date of the patient's death due to any cause.

12.1.7 Response Review

All imaging will be reviewed by a trained head and neck clinical radiologist blinded to study participation, at the completion of the study.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single arm combination Phase I/II trial of Metformin to determine the maximum tolerated dose (MTD) of metformin among 2 dose levels (850mg, 1500mg administered orally, twice daily) and to evaluate the disease response rate at the MTD. Standard of care conventional chemotherapy (cisplatin) will be administered using current clinical protocols. Dose-limiting toxicity will be ascertained using the Common Terminology Criteria for Adverse Events v4.0. The dose-limiting toxicities ascertained for the phase I component will be gastrointestinal toxicity and hypoglycemia requiring dose reduction. The primary outcome for the phase II component will be disease response rate (RECIST criteria) at 8-12 weeks post treatment completion.

The secondary outcomes will be disease free and overall survival. All analysis of secondary studies will be performed post hoc and will not be used to influence clinical decision making during the therapeutic trial.

This study began as a Phase I "3+3"/ Phase II "Simon" design, but was converted into Bayesian Optimal Interval (BOIN) design before completion of the Phase I to provide monitoring of toxicity beyond the Phase I cohort. BOIN design has algorithmic escalation/de-escalation rules easy to implement like a traditional 3+3 design but allows for specification of the target DLT rate, different size cohorts, is more likely to correctly select the MTD and allocate more patients to the MTD and expands consistent toxicity monitoring to the entire cohort. BOIN design with a target DLT rate of 0.3 and cohort size of 3 begins exactly in the same fashion as the "3+3" allowing for the implemented design change in early stages. Calculations were done using R package BOIN.[32]

13.2 Sample Size/Accrual Rate

Phase I component considerations.

The study is designed to escalate the dose if the observed toxicity rate at the current dose is <= 0.2365, and de-escalate the dose if the observed toxicity rate at the current dose is >= 0.3585. If the observed toxicity rate is between 0.2365 and 0.3585, additional patients will be treated at the current dose. For cohorts of size 3, the decision boundaries are shown in table below. Two doses levels of Metformin (850 mg and 1500 mg) are evaluated, beginning with the lower dose.

DLT Regulation of Dose Escalation and De-Escalation									
Number of patients treated	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27+1**
Escalate* if number of DLT <=**	**0**	**1**	**2**	**2**	**3**	**4**	**4**	**5**	**6**
Treat additional 3 pts on current dose if number of DLT=	**1**	**2**	**3**	**3,4**	**4,5**	**5,6**	**5,6,7**	**6,7,8**	**7,8,9**
Deescalate* if number of DLT >=	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Eliminate if number of DLT >=**	**3**	**4**	**5**	**7**	**8**	**9**	**10**	**11**	**12**

*** At the lowest dose level, if the recommendation is to de-escalate AND the dose level has not been eliminated from consideration, 3 additional pts will be accrued at the same dose level; otherwise the trial will stop. Last cohort has 4 patients to reach the required sample size of 28.**

**** Eliminate dose level and all higher doses from further use.**

***** At the time of the design change the study escalated to the highest dose and will continue enrolling additional patients at this dose unless de-escalation is recommended.**

Phase II component considerations.

A response rate ≥60% would be considered effective for patients undergoing metformin plus standard of care, while a response rate ≤40% is not considered as effective. The phase II portion of the trial would require at least 28 evaluable patients treated at the MTD. For the purposes of this study, a response will be defined as overall complete response (CR) or overall partial response (PR) (see Table in section 12.1.4.3). Stable disease or progressive disease will be defined as a non-response. The criterion for significance (alpha) has been set at 0.10. The test is 1-tailed, which means that an effect in one direction (improvement) is expected and will be interpreted. Calculation are based on the assumptions of uniform accrual over time. With the proposed sample size of 28 patients the study will have power of 80% to yield a statistically significant result. The treatment strategy (metformin plus standard of care) is considered effective if 17 or more responses are observed among the 28 patients.

Total study sample size.

This study will enroll at least 3 patients at each dose level and at least 28 patients at the MTD level. Participants will continue to be enrolled and monitored for toxicity according to the rules specified above until 28 efficacy evaluable participants have been enrolled to any single dose level. For the purposes of this analysis, a subject is considered evaluable for the primary endpoint after completing at least one dose of Metformin. It is expected that all dose levels will be safe and assuming that even the highest dose level has a DLT rate substantially lower than the target (i.e. <10%), which is what we expect, we will have more than 99% chance of selecting the top dose level at the end of the trial. In this case the total number of patients enrolled would be 31 (3+28). Retrospective clinical studies have not demonstrated an increase in treatment toxicity for patients undergoing cisplatin for HNSCC while taking metformin. It is anticipated that 1-2 patients per month

will be accrued to the study. Depending on the toxicity, this will allow for completion of study within 33-39 months of study initiation.

13.3 Stratification Factors

No additional stratification will be utilized in this trial.

13.4 Analysis of Secondary Endpoints

Secondary endpoints including disease free and overall survival will be analyzed by Kaplan-Meier method. All of the analyses will be considered exploratory in nature.

13.5 Reporting and Exclusions

13.5.1 Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with metformin.

13.5.2 Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.] All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95%

confidence intervals should also be provided.

14.0 DATA MANAGEMENT

Subjects will be assigned a 4-digit study number (study ID) by the OnCore system which is the Clinical Trials Monitoring system utilized by the DLDCCC. The study number will not contain any identifiers. Study numbers will be assigned sequentially starting at "0001". The study number list will be stored electronically and only accessible to authorized study personnel. Physical research data (including patient records and consent forms) will be secured in a confidential manner in a locked room at the appropriate clinic/hospital, and in secure manner in the DLDCCC offices (Suite 450A Cullen at BCM). Electronic research data will be stored at BCM on BCM servers which are password-protected. Electronic research data will be kept on a DLDCC-specific shared drive on BCM servers; access is limited to authorized study personnel. Electronic research data will also be kept in the OnCore database on BCM secure server with limited user-specific, password-protected access. Data are entered into the web application by authorized research personnel via secure HTTPS connections. BCM Research staff are authenticated securely with BCM's LDAP/Active Directory. BCM IT maintains a firewall, intrusion protection service, and F5 Big IP servers for further protecting data within OnCore. All hardware systems are housed in HIPAA-compliant facilities that have 24-hour guards and access restricted by proximity cards and keys.

12.1 Study Documentation

Flow sheets documenting dates and doses of therapy as well as clinical chemistries, hematological parameters, the clinical status and occurrence of any adverse events and subsequent interventions are to be kept on all patients.

- Imaging reports
- Clinic notes
- Laboratory reports
- Surgical summaries
- Autopsy summaries, where appropriate
- Informed consent documents

12.2 Clinical Data Management and Analysis

All required clinical evaluation records are the responsibility of the study Principal Investigator, Dr. Vlad Sandulache, who will also be responsible for analysis of the clinical outcome and toxicity.

15.0 QUALITY ASSURANCE

This study will be monitored by the DLDCC Quality Assurance program for study conduct and quality of data, according to CTSU policy. Protocol compliance, eligibility verification, informed consent procedure verification and data accuracy will be monitored.

16.0 DATA AND SAFETY MONITORING

This study will be reviewed regularly by the Data Review Committee of the Dan L. Duncan Comprehensive Cancer Center, in accordance with the DLDCCC Data and Safety Monitoring Plan. The Data Review Committee will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data.

The frequency of data review by the DRC is determined by the Protocol Review and Monitoring Committee at the time of initial review and is based on the level of risk to the study subjects. Information reviewed by the committee includes:

a. Overall protocol accrual and expected number of patients to be treated
b. Patient registrations with regard to eligibility and evaluability
c. All adverse events and their relationship to the protocol therapy (e.g., by dose level, treatment arm, etc.), in order to determine if participants are being exposed to unanticipated or excessive toxicity
d. All serious adverse events or unanticipated problems requiring expedited reporting as defined in the protocol
e. Results of any planned interim analyses
f. Response evaluations, if relevant
g. Any issues with protocol conduct or compliance
h. Status of participation rate in correlative biology and/or imaging studies, if applicable
i. Study amendments or modifications that may have occurred since last review
j. Date of next planned review

17.0 PROTECTION OF HUMAN SUBJECTS

This is a voluntary study and all patients will undergo informed consent prior to participation. Patients will be allowed to withdraw from the study at any time; all patient data and samples will be destroyed at patient request upon withdrawal from the study. Patients will not be offered financial or other inducements to participate in the study. All patients who wish to receive standard of care in lieu of study participation will be offered standard of care treatment consistent with national guidelines and institutional standards.

Retrospective studies have demonstrated that patients taking metformin during chemo-radiation demonstrate improved response to conventional treatment and improved survival. No prospective studies to date have confirmed this effect, hence the current proposal. It is possible that patients enrolled in this study will in fact demonstrate improvement in clinical outcomes as detailed in the study. However, we would not expect that every individual patient in this trial will experience a clinical benefit from the proposed study.

This is the first and only (to date) proposed, prospective clinical trial testing the hypothesis that metformin can improve clinical outcomes in patients undergoing chemo-radiation for head and neck cancer. If our hypothesis is proven to be correct, it is possible that metformin will be incorporated into future clinical practice following additional prospective validation

of our results. Introduction of a cheap, readily available drug, with proven clinical effectiveness, would greatly impact large numbers of patients with head and neck cancer.

The risks associated with this clinical trial are relatively small. Although metformin, the investigational drug, can generate some systemic toxicity (i.e. gastrointestinal disturbances), the expected toxicity from current standard of care regimens consisting of chemo-radiation (i.e. xerostomia, mucositis, nausea, vomiting) greatly exceeds that of the investigational agent. Furthermore, clinical outcomes for the patient subset included in this study remain poor. As such, the potential to identify an effective potentiator of chemo-radiation effectiveness, with relatively low expected toxicity should outweigh the risks associated with conducting the trial.

18.0 ADVERSE EVENTS

18.1 Adverse Event Characteristics

18.1.1 The AE collection/reporting period will begin with the first day of treatment with metformin and will be completed at 30days following treatment completion. AEs after study registration but prior to the first day of study treatment will be captured as ongoing concurrent secondary diagnoses and symptoms present at the start of study. AEs will be graded in accordance with the NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) http://ctep.cancer.gov/ reporting/ctc.html. If not described in the NCI-CTCAE, AEs will be graded according to their severity using the following criteria: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life threatening).

18.1.2 This is the attribution scale which will be utilized to attribute relatedness of toxicity to the study:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

18.1.3 A definition of expected adverse event and unexpected adverse event:

18.1.3.1 Expected adverse events are those that have been previously identified as resulting from administration of the agent. For purposes of this study, an adverse event is considered expected when it appears in the current adverse event list in the Investigator's Brochure, the package insert, or is included in the informed consent document as a potential risk.

18.1.3.2 An adverse event is considered unexpected when it varies in nature, intensity, or frequency from information provided in

the current adverse event list in the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

18.2 Adverse Event Reporting

18.2.1 All adverse events (all grades), regardless of perceived relationship to study treatment, will be reported and recorded on the appropriate CRFs. New AEs and SAEs that are ongoing at the end of the study will be followed for 30 days from the patient's receipt of the last dose of protocol therapy, unless they have resolved earlier. SAEs and drug related AEs ongoing at the end of study will be followed until resolution.

18.2.2 The AE description will include the nature of the experience, the date of onset, the resolution date, the severity of each sign or symptom reported using the NCI-CTCAE (version 4.0), the seriousness of the event, the potential relationship to study treatment, the course of action taken, and the outcome of the experience.

18.2.3 Serious adverse events are to be reported to the institutional review board (IRB) according to each board's reporting requirements and required time frame.

18.2.4 The Study Chair/Principal Investigator will be responsible for reporting all adverse events to the FDA as per their reporting requirements and time frame.

18.2.5 Any event that is reportable to the BCM IRB must also be reported to the DLDCCC Data Review Committee (DRC), via the Patient Safety Officer at dldcc-pso@bcm.edu.

18.3 Safety Reporting Requirements for IND Holders

NA

18.4 Multicenter Guidelines

NA

19.0 Pregnancy

This study will exclude pregnant women. A subject who has a positive βhCG pregnancy test result at any time after the first dose of investigational therapy will be immediately withdrawn from participation in the study. All study conclusion/withdrawal assessments will be collected at the time of discontinuation as described in Section 9.0. Pregnancy information is to be recorded in the Case Report Forms. Pregnancy information will be collected from the first dose of investigational product to 30 days after the last dose. While pregnancy itself is not considered to be an SAE, it may result in an SAE. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE and will be reported as such.

A spontaneous abortion is always considered an SAE and will be reported as such.

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21.0 APPENDICES

APPENDIX A:

Staging criteria (AJCC Cancer Staging Manual 6th edition, 2002)

Oral Cavity

TX	Primary tumor cannot be assessed.
T0	There is no evidence of primary tumor.
Tis	Carcinoma is in situ.
T1	Tumor is 2 cm or less in greatest dimension.
T2	Tumor is more than 2 cm but not greater than 4 cm in greatest dimension.
T3	Tumor is more than 4 cm in greatest dimension.
T4 (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face—i.e., chin or nose.
T4a (oral cavity)	Tumor invades adjacent structures (e.g., through cavity) cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hypoglossus, palataglossus, and styloglossus], maxillary sinus, skin of face).
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery.

Oropharynx

T1	Tumor is 2 cm or less in greatest dimension.
T2	Tumor is more than 2 cm but not more than 4 cm in greatest dimension.
T3	Tumor is more than 4 cm in greatest dimension.
T4a	Tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible.
T4b	Tumor invades the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery.

Larynx

Primary Tumor (T)

TX	Primary tumor cannot be assessed.
T0	There is no evidence of primary tumor.
Tis	Carcinoma is in situ.

Supraglottis

T1	Tumor is limited to one subsite of the supraglottis, with normal vocal cord mobility.
T2	Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus), without fixation of the larynx.

T3	Tumor is limited to the larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Tumor invades prevertebral space, encases the carotid artery, or invades mediastinal structures.
Glottis	
T1	Tumor is limited to the vocal cords(s) (may involve anterior or posterior commissure), with normal mobility.
T1a	Tumor is limited to one vocal cord.
T1b	Tumor involves both vocal cords.
T2	Tumor extends to the supraglottis and/or subglottis, and/or with impaired vocal cord mobility.
T3	Tumor is limited to the larynx with vocal cord fixation and/or invades paraglottic space, and or minor thyroid cartilage erosion (e.g., inner cortex).
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Tumor invades prevertebral space, encases the carotid artery, or invades mediastinal structures.
Subglottis	
T1	Tumor is limited to the subglottis.
T2	Tumor extends to the vocal cord(s), with normal or impaired mobility.
T3	Tumor is limited to the larynx, with vocal cord fixation.
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b	Tumor invades prevertebral space, encases the carotid artery, or invades mediastinal structures.
Hypopharynx	
T1	Tumor is limited to one subsite of the hypopharynx and 2 cm or less in greatest dimension.
T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of the hemilarynx.

T3	Tumor is more than 4 cm in greatest dimension or with fixation of the hemilarynx.
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue.
T4b	Tumor invades prevertebral fascia, encases the carotid artery, or involves mediastinal structures.

Neck Staging Under the TNM Staging System for Head and Neck Tumors (excluding nasopharynx and thyroid)

NX	Regional lymph nodes cannot be assessed.
N0	There is no regional nodes metastasis.
N1	Metastasis is in a single ipsilateral lymph node, 3 cm or less in greatest dimension.
N2	Metastasis is in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or metastasis is in multiple ipsilateral lymph nodes, none more than 6 cm ingreatest dimension; or metastasis is in bilateral or contralateral lymph nodes, none greater than 6 cm in greatest dimension.
N2a	Metastasis is in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.
N2b	Metastasis is in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.
N2c	Metastasis is in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
N3	Metastasis is in a lymph node more than 6 cm in greatest dimension.

TNM Staging for the Larynx, Oropharynx, Hypopharynx, Oral Cavity, Salivary Glands, and Paranasal Sinuses

Stage Grouping

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 T1 N1 M0 T2 N1 M0 T3 N1 M0
Stage IVA	T4a N0 M0 T4a N1 M0 T1 N2 M0 T2 N2 M0 T3 N2 M0 T4a N2 M0

Stage IVB	T4b Any N M0
	Any T N3 M0
Stage IVC	Any T Amy N M1

Clinical Stage Grouping by T and N Status

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVa	IVb
N1	III	III	III	IVa	IVb
N2	IVa	IVa	IVa	IVa	IVb
N3	IVb	IVb	IVb	IVb	IVb

APPENDIX B

Pregnancy testing guidelines and acceptable birth control methods

The safety of metformin in pregnant females has not been definitively established. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of metformin

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use a reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting metformin; 2) throughout the entire duration of metformin treatment; 3) during dose interruptions; and 4) for at least 28 days after metformin discontinuation. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

Highly effective methods:

- oral contraceptive pills
- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone. Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting metformin

Female Patients:

FCBP must have one pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting metformin.

During study participation and for 28 days following metformin discontinuation

Female Patients:

At each visit, the Investigator must confirm with the FCBP that she is continuing to use a reliable method of birth control at each visit during the time that birth control is required. If pregnancy or a positive pregnancy test does occur in a study patient, metformin must be immediately discontinued. Pregnancy testing and counseling must be

performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Metformin treatment must be temporarily discontinued during this evaluation.

APPENDIX C

H-39773 Head and Neck Cancer Study
Medicine Intake Calendar

Patient Name: _____

Instructions to Participant:
Use this calendar as a reminder to take your study medication every day. Record the number of pills/tablets that you take each day. Take the pills at about the same time every day.
Bring this calendar and your pills/tablets with you to each study visit.

Month: _____ Year: _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

APPENDIX B

Blood glucose monitoring form

Patient Name: _____

Instructions to Participant:
If your blood glucose is high, your doctor will ask you to monitor your glucose at home each day. Your doctor will give you the test you will need to do this.

You will do this for one week, two times a day.
Each day, write the date, and write your blood glucose value from each test on the form below. Bring this form back to your doctor or the research staff at your next visit.

DATE COLLECTED:_____ (MM/DD/YYYY)

Day of the week, Date	AM value	PM value
Monday, _____	**value (mg/dl)**	**value (mg/dl)**
Tuesday, _____	**value (mg/dl)**	**value (mg/dl)**
Wednesday, _____	**value (mg/dl)**	**value (mg/dl)**
Thursday, _____	**value (mg/dl)**	**value (mg/dl)**
Friday, _____	**value (mg/dl)**	**value (mg/dl)**
Saturday, _____	**value (mg/dl)**	**value (mg/dl)**
Sunday, _____	**value (mg/dl)**	**value (mg/dl)**