Protocol #: *UCCI-HN-14-01*

TITLE: A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation in patients with locally advanced head and neck squamous cell carcinoma.

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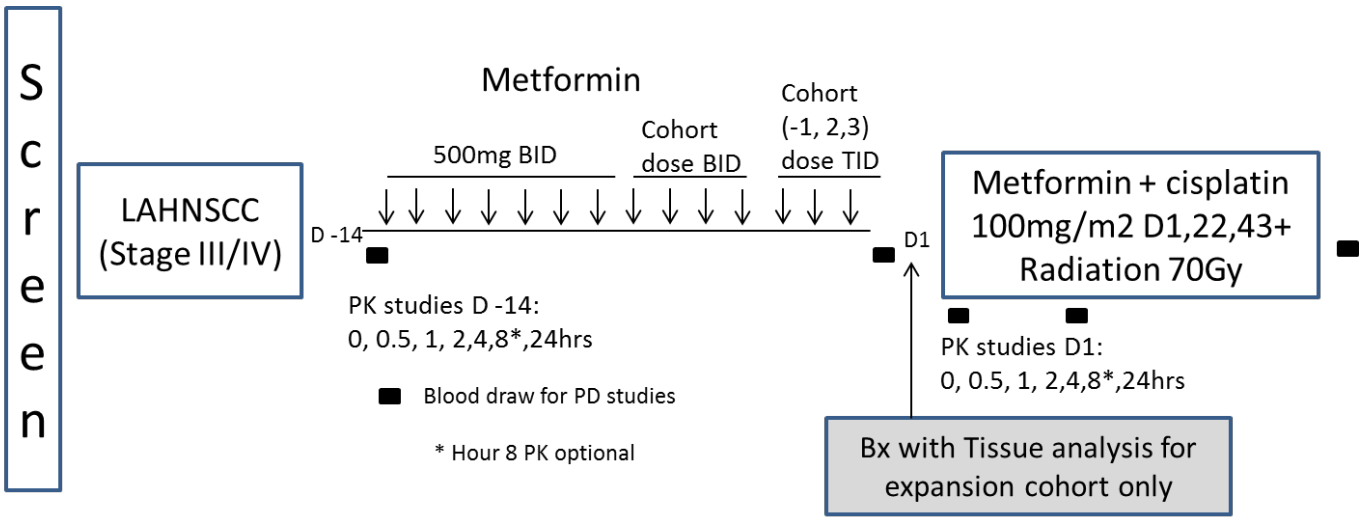
SCHEMA



Dose Escalation Schedule	
Dose Level	**Dose**
	Metformin Daily (in divided doses)
Level -1	1500mg
Level 1	2000mg
Level 2	2550mg
Level 3	3000mg
Expansion	MTD

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1. OBJECTIVES

1.1. Primary Objective

Determine the maximum tolerated dose of metformin in combination with concurrent cisplatin and radiation (CRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC).

1.2. Secondary Objectives

- Assess the anti-tumor effect of the addition of metformin to CRT in LAHNSCC.
- Define toxicities associated with the addition of metformin to CRT in LAHNSCC.
- Explore the change in critical effectors in the mTOR pathway including pS6, $pAKT^{S473}$, and AMPK in tumor biopsies in response to metformin treatment.
- Evaluate the change in metformin clearance and AUC when combined with cisplatin.
- Estimate the distribution of levels of inflammatory cytokines (IL-6, IL-8, Gro-a), angiogenesis molecules (HGF, VEGF-A, VEGF-C), and glucose/insulin/c-peptide levels in the blood before and after administration of metformin and CRT.
- Determine the change in immune cell subsets (CD3, CD4, CD8 and PD1) in response to metformin treatment.
- PFS and OS at 2 years

2. BACKGROUND

2.1 Metformin

2.1.1 Background:

Metformin is a biguanide and an oral antihyperglycemic agent, which is currently FDA approved for the treatment of type II diabetes. Metformin is widely used in many diabetic patients and overall very well tolerated. Unlike other antihyperglycemic agents such as the sulfonylureas, metformin does not usually cause hypoglycemia. Adverse effects are relatively minimal with diarrhea being the most common cause of discontinuation. However, lactic acidosis, although rare (estimated incidence of 4.3 cases per 100,000 person-years in metformin users), is a serious adverse event resulting in up to 50% mortality when it occurs[1,2]. Lactic acidosis has been associated with high plasma concentrations of metformin (>10mg/ml) which can occur in the presence of renal dysfunction. Therefore, careful monitoring of renal function of patients on metformin is imperative to reduce the incidence of this rare side effect. However, a recent retrospective study from the United Kingdom, demonstrated that there was no increase in lactic acidosis in patients taking metformin even in patients with severe kidney dysfunction (eGFR <30ml/hr)[3]. The latter study did not measure serum metformin levels. Therefore, further investigation of the safety of metformin, dosing, and the association with lactic acidosis is warranted.

2.2 Head and neck squamous cell carcinoma

HNSCC continues to be a major public health concern resulting in 650,000 new cases and 350,000 deaths worldwide each year. Etiologic factors include tobacco and alcohol use, and more recently, infection with human papillomavirus (HPV). Early stage tumors are often cured with single modality treatment, but unfortunately, up to 60% of HNSCCs present as locally advanced disease (LAHNSCC). Based on a pivotal phase III trial in 2003, concurrent chemotherapy and radiation (CRT) using cisplatin has become the standard of care for patients with unresectable locally advanced disease. In the latter study, three year overall survival was 23% in the radiation alone arm compared to 37% in the CRT arm (p value 0.014)[4]. Since this original study, retrospective studies have demonstrated improved survival and progression free survival, likely due to better supportive care, and radiation technique[5,6]. Another factor is the increasing rates of HPV related cancers, which have been shown to have improved prognosis[7]. However, despite current definitive therapy, many of these patients are still faced with frequent relapse rates. Upon recurrence or metastasis, the prognosis is dismal at only 10-15% with median overall survival of 10-12 months[8] necessitating the development of improved upfront regimens with increased complete response rates.

2.3 Rationale for metformin as treatment for HNSCC

Recently, activation of the PI3K, Akt and the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway was identified as being a prevalent molecular signature in many HNSCCs[9,10], resulting in potential strategies to target this pathway. In fact, activating mutations of the mTOR pathway are now recognized as drivers of some HNSCCs. However, targeting the mTOR pathway with rapamycin analogues, such as everolimus, results in undesirable side effects including mucositis, thrombocytopenia, and increased infection risk making combinatorial treatment with chemotherapy and radiation difficult. Interestingly, metformin, which is overall very well tolerated in diabetic patients, has been shown to inhibit the mTOR pathway. Specifically, metformin inhibits mTORC1 activity, through activation of the AMPK pathway resulting in decreased proliferation, metabolic synthesis and metastases in breast and colon cancer[11,12]. Additionally, metformin inhibits HNSCC cell growth *in vitro* and prevents development and progression of oral cavity tumors in a HNSCC mouse tumor model supporting a role for metformin as a cancer preventative[13]. The latter study demonstrated that metformin may also inhibit mTORC1 activity independent of AMPK activation. In line with these animal studies, retrospective population case-control cohort studies have demonstrated a decreased HNSCC risk in diabetic patients treated with metformin[14]. In addition, metformin use resulted in a better overall survival in diabetic patients diagnosed with laryngeal squamous cell carcinoma[15]. The potential impact of metformin use in non-diabetic HNSCC patients is unknown. In addition to prevention of HNSCC, several preclinical studies, in which metformin is used as an anticancer therapeutic, are promising.

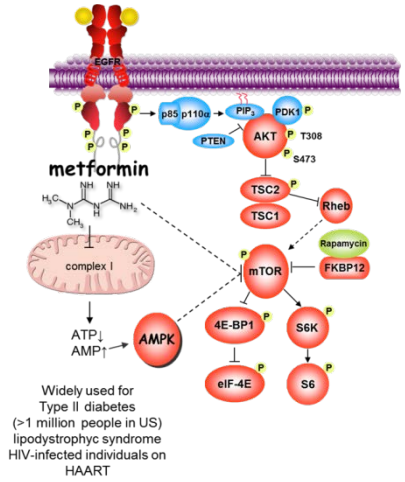

Figure 1. Effect of metformin on mTOR pathway.

Metformin was shown to overcome cisplatin resistance by inhibition of STAT3 phosphorylation in non-small-cell lung cancer cell lines and metformin potentiated cisplatin cytotoxicity and prevented metastases in an ovarian cancer mouse model[16,17]. Additionally, metformin may act as a radiosensitizer in patients with HNSCC and mutant p53 preventing locoregional recurrence[18]. These data suggest that metformin may be highly active in HNSCC and therefore may be a novel addition to current therapeutic options leading to our hypothesis that *daily metformin in combination with CRT in LAHNSCC is safe and will result in enhanced tumor response through the inhibition of the mTOR pathway*. This protocol will investigate patients with LAHNSCC and combine standard CRT with metformin to determine the safety and tolerability of this combination as well as examine the molecular pathways involved in responses to metformin.

2.4 Rationale for Metformin starting dose

The recommended starting dose of metformin in diabetic patients is 500mg orally twice a day which can be escalated by 500mg increments weekly as tolerated with the maximum recommended daily dose of 2550mg. However, the dose of metformin required in cancer for clinical efficacy is unknown. Phase I dose finding studies in adults have not yet been performed. There are several trials listed on clinicaltrials.gov currently accruing that are evaluating a fixed dose of metformin in combination with other anti-cancer therapies ranging from 1000-2000mg daily. This dose range is known to be safe and tolerable in diabetic patients with normal renal function. Here we propose to start at a dose of 2000mg daily in combination with cisplatin and radiation. Like in diabetics, patients on protocol will be given 500mg twice a day for the first several days, to allow for patient tolerance, and then escalated to assigned cohort dose. We propose to exceed the current recommended dose as in pre-clinical animal studies, metformin doses were given at 50mg/kg/day or the equivalent of 3000mg/day in a 60kg man when using weight based measurements. Therefore, we will attempt to escalate to this dose while monitoring for safety and tolerability and change in kidney function.

2.5 Correlative Studies Background

2.5.1 Pharmacodynamic Studies

As described in section 2.3, metformin has been shown both *in vitro* and *in vivo* to inhibit mTORC1 both dependently and independently of AMPK activation. Inhibition of the mTOR pathway results in decreased proliferation as well as cytotoxic effects in HNSCC cells. A trial to evaluate the pharmacodynamic effects of another mTOR inhibitor, temsirolimus, in newly diagnosed patients with HNSCC was published in 2010. [19] The investigators found a significant reduction in the levels of pS6 in the tumor biopsies, which was also reflected in reduced pS6 in peripheral blook monocyte cells (PBMCs), supporting that temsirolimus caused the inhibition of mTOR in its complex mTORC1 in the tumor tissues and in blood cells, with the latter serving as a surrogate marker of biochemical efficacy. Elevated activity of Akt was not observed as judged by Western blotting of total tumor samples, suggesting that in HNSCC tissues the inhibition of mTOR does not lead to a secondary increase in Akt activity. Instead, a reduction in $pAkt^{S473}$ was observed, albeit it did not reach statistical significance. As pAktS473 is a direct target of

mTORC2[20], these data suggest that mTOR in its complex mTORC2 may also be inhibited in HNSCC patients. Therefore, we propose to evaluate pre- and post-treatment biopsies for the effect of metformin on mTOR pathway mediators above as well as proliferation with Ki-67 and apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. We will also determine the levels of pS6 in PBMCs pre- and post-metformin treatment.

Although metformin has been shown to inhibit effectors of the mTOR pathway directly, other mechanisms in which metformin exerts an anti-cancer effect, have also been proposed, which may or may not be independent of mTOR inhibition. Lowering of insulin levels resulting in decreased tumor growth[21], reduction of inflammatory cytokines such as IL-6, resulting in decreased epithelial-mesenchymal transition[22], and inhibition of angiogenesis molecules have all been proposed as potential mechanisms. Therefore we will measure the distribution of levels of inflammatory cytokines (IL-6, IL-8, Gro-a), angiogenesis molecules (HGF, VEGF-A, VEGF-C), and glucose/insulin/c-peptide levels in the blood before and after administration of metformin and CRT.

2.5.2 **Pharmacokinetic and Pharmacogenetic Studies**

Metformin is primarily excreted in unchanged form by the kidney with the mean renal clearance (CL_R) of 500 mL/ min. This indicates that CL_R of metformin is higher than glomerular filtration rate (GFR), and active tubular secretion is the principal mechanism of metformin elimination[23]. Reported as a substrate of renal transporters such as organic cation transporter 1 and 2 (OCT1 and OCT2) which are expressed in proximal tubule epithelial cells in the kidney, recent studies suggested that significant differences in CL_R of metformin is a result of genetic polymorphisms of OCT1 and OCT2[24,25]. In particular, an increase in CL_R of metformin was observed in individuals carrying two reduced-function alleles of the p.420del and the p465G>R variants of OCT1, whereas the p.270A>S (c.808G>T) variant of OCT2 reduced CL_R in healthy volunteers. Cisplatin is well known to cause nephroxtoxicity [26]. In fact, its adverse effect on kidney function is one of its primary dose-limiting toxicities. Cisplatin accumulation in kidneys is considerably higher relative to other tissues. Thus, in the proposed combination study the systemic exposure (plasma levels and the overall Area Under the Curve) of metformin may be considerably impacted by the co-administration of cisplatin and/or OCT1 and OCT2 genotypic variability. The nephrotoxic effects of cisplatin may reduce metformin CL_R resulting in an increase in the systemic exposure. Likewise metformin levels may be higher in individuals expressing the 270A>S (c.808G>T) variant of OCT2. Both these scenarios are likely to result in adverse effects of metformin such as lactic acidosis [27]. The genetic variability in OCT1 (p.420del and the p465G>R) on the other hand may reduce metformin plasma levels. Thus, we propose to assess the pharmacokinetics and pharmacogenomics of metformin in this study.

3. PATIENT SELECTION

3.1 **Phase I Dose Escalation Eligibility Criteria**

3.1.1 Histologically or cytologically confirmed LAHNSCC defined as stage III or IV disease (T1-2, N2a-3 or T3-4). All sites except nasopharyngeal allowable.

3.1.2 No prior chemotherapy or radiation for HNSCC.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status 0 or 1 (Karnofsky ≥70%, see Appendix A).

3.1.5 Life expectancy of greater than 3 months.

3.1.6 CBC/differential obtained within 28 days prior to registration on study, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3;
- Platelets ≥ 100,000 cells/mm3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable).

3.1.7 Adequate hepatic function, defined as follows:

- Total bilirubin < 2 x institutional ULN within 14 days prior to registration;
- AST or ALT < 3 x institutional ULN within 14 days prior to registration.

3.1.8 Adequate renal function, defined as follows: Serum creatinine ≤ institutional ULN within 14 days prior to registration. Creatinine clearance (CC) ≥ 60 ml/min within 14 days prior to registration determined by 24- hour collection or estimated by Cockcroft-Gault formula:CCr male = [(140 – age) x (wt in kg)] [(Serum Cr mg/dl) x (72)]; CCr female = 0.85 x (CrCl male)

3.1.9 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential.

3.1.10 Documented p16 status on biopsy tissue (oropharyngeal only). Tissue must be available for staining but status does not need to be confirmed before enrollment.

3.1.11 Imaging prior to treatment including either:

1) CT with contrast of neck and PET/CT (preferred),
2) CT with contrast of neck and chest,
3) MRI of neck and CT of chest or
4) MRI of neck and PET/CT.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Phase I Dose Escalation Exclusion Criteria

3.2.1 Patients with known metastatic disease.

3.2.2 Patients with nasopharyngeal carcinoma are excluded.

3.2.4 Patients may not be receiving any other investigational agents.

3.2.4 History of allergic reactions attributed to metformin or other agents used in study.

3.2.5 Patients with known diagnosis of diabetes requiring insulin for control.

3.2.6 Administration of metformin within last 4 weeks.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing significant or serious active cardiovascular disease (CHF exacerbation, unstable angina or MI in last 6 months), infection including the diagnosis of AIDS or active hepatitis B or C infection, psychiatric illness or situations that would limit the patient's ability to participate.

3.2.8 Patients attempting to conceive, and pregnant or nursing women are excluded from this study.

3.2.9 Patients may not receive any medication or substance that is known to be strongly associated with lactic acidosis (ex. NRTIs) within 14 days of study.

3.3 Dose Expansion Eligibility Criteria

All criteria are the same as dose escalation except for the additional requirement of a 2nd biopsy prior to CRT.

3.4 Dose Expansion Exclusion Criteria

All criteria are the same as dose escalation (see 3.2)

3.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

Patients are registered by contacting the University of Cincinnati Clinical Trials Office at 513-584-7698. Patients must be registered and consent obtained prior to initiation of any protocol therapy.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for metformin and cisplatin and radiation are described in Section 7. Appropriate dose modifications for metformin, cisplatin and radiation are described in Section 6.

Patients must have screening labs performed within 2 weeks of start of treatment including a complete blood count, liver function tests, metabolic renal panel including magnesium, vitamin B12 level, lactate, and C-peptide. Renal panel must be verified within 24 hours of cisplatin administration. They must fulfill inclusion criteria as stated in 3.1.

Highly Recommended Evaluations/Management

- Evaluation for prophylactic gastrostomy tube placement (especially if the patient is > 10% below ideal body weight)
- EKG within 8 weeks prior to the start of treatment
- Audiogram before cisplatin treatment
- Banking of tumor tissue and blood in the UCCI Head and Neck Tumor Bank is highly encouraged but not required for protocol enrollment.

Protocol treatment must begin within 3 weeks after registration.

5.1.1 Metformin Dose Escalation

Dose-Escalation Schedule		
Dose Level	**Dose**	
	Metformin Daily (in divided doses)	**Cisplatin Days 1, 22, 43**
Level -1	1500mg	100mg/m2
Level 1	2000mg	100mg/m2
Level 2	2550mg	100mg/m2
Level 3	3000mg	100mg/m2
Expansion	MTD	100mg/m2

Cohort	Dose per Study Days		
	Day -14 to -8	**Day -7 to -4**	**Day -3 to end of study**
Level -1	500mg BID	500mg BID	500mg TID
Level 1	500mg BID	500mg TID	1000mg BID
Level 2	500mg BID	850mg BID	850mg TID
Level 3	500mg BID	1000mg BID	1000mg TID

Treatment:
Patients will receive metformin starting on day -14 at the starting dose of 500mg BID. Treatment must start ideally on a Monday or Tuesday but Wednesday will also be acceptable. On day -7, patients will increase or keep the same dose depending on their assigned dose cohort (See above). For cohort, or dose level 1, patients will ultimately take 1000mg BID for a total dose of 2000mg daily. For Cohort 2, patients will ultimately take 850mg in the morning, 850mg at lunch and 850mg at bedtime (850mg TID). For cohort 3, patients will ultimately take 1000mg TID and for cohort -1, patients will take 500mg TID. Metformin will be continued until the last day of chemotherapy or radiation (which ever comes last). Patients will also receive cisplatin at 100mg/m2 on days 1, 22 and 43 along with concurrent radiation (2Gy per day, 5 days per week for a total of 70 Gy). Total treatment time assuming no delays will be 8 weeks. Patients will undergo weekly exams the first 4 weeks, prior to the 2nd and 3rd cisplatin dose, followed by 4 weeks (+/-2) after completion of treatment. DLTs will continue to be assessed until 2 weeks after completion of radiation treatment.

Metformin should continue throughout treatment and even through delays unless patient is experiencing adverse effects attributed to metformin. Metformin should be taken with food. Patients will be provided with glucometers to monitor their blood glucose levels. They will be instructed to check their blood sugar every morning prior to eating and logging on calendar.They will also be instructed to check their blood sugar if they have any symptoms of hypoglycemia including but not limited to chills/shakiness, cold feeling, lightheadedness, dizziness, etc.

NOTE: Temporarily discontinue metformin in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized. It is generally recommended that metformin be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Continue to withhold metformin for 48 hours after the radiologic study.

5.1.2 Cisplatin Guidelines

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.

(Note: cisplatin given within 24 hours of days 1 and 22 and 43 due to holidays, for example, is acceptable). Weekends count as days. Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Patients must be vigorously hydrated along with adequate diuresis. Patients must receive pre-hydration with 1L 1/2NS with 1g magnesium sulfate over 2-4 hours given 1/2 hour prior to chemotherapy. Then cisplatin, 100 mg/m2 in 500-1000 ml NS plus 12.5 grams of mannitol is administered over 1-2 hours followed by an additional 1 to 1.5 liters of fluid. If a patient does not have central venous access, mannitol may be held from treatment at investigator discretion. Any pre-existing dehydration must be corrected prior to cisplatin administration. Additional i.v. hydration (500mls-1L) and BUN/creatinine check should be performed the following two days and also should be considered, if necessary, later in the week after cisplatin administration, in order to address any dehydration or severe fluid/electrolyte imbalance.

5.1.2.1 Supportive Care for Cisplatin

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. The following guidelines will be followed:

1) For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron 1 mg iv; ondansetron, up to 16 mg iv; or palonosetron, 0.25 mg iv; plus a corticosteroid, such as dexamethasone, up to 20 mg iv. Fosaprepitant may also be included as premedication.

2) Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist.

3) 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.

5.1.3 **Radiation Therapy**

5.1.3.1 Dose Specifications

The prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size (total of 35 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV volume receives at least 95% of prescribed dose. The spinal cord dose may not exceed 45 Gy to any volume larger than 0.03 cc.

5.1.3.2 Technical Factors

Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. IMRT treatment planning with simultaneous integrated boost (SIB) will be used, and treatment verification films must be taken daily (kv films or cone beam CT).

5.1.3.3 Localization, Simulation, and Immobilization

- Patients must have an immobilization device (e.g., aquaplast mask) made prior to treatment planning CT scan.
- All patients will undergo CT simulation for treatment planning. The treatment planning CT scan may be completed with or without IV contrast. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or less.

5.1.3.4 Target and Normal Tissue Volume Restrictions

Definition of Target Volumes

GTV70: This volume includes all gross tumor volume (primary tumor and nodal disease) based on clinical exam, PETCT scan and/or planning CT.

CTV70: This volume will receive 2 Gy per fraction. CTV70 will include the primary tumor plus up to a 1.5cm margin added for microscopic spread.

CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV70. For example, this would apply to ipsilateral or bilateral necks irradiated electively. This volume will receive 1.6 Gy per fraction.

CTV63 **Optional:** This may be defined at the discretion of the treating radiation oncologist. This would include a region or regions felt to be at especially high risk for recurrence (e.g., first echelon nodal regions that are clinically negative). This area will be receiving a daily fraction size of 1.8 Gy.

Planning Target Volumes (PTVs)

In general, the PTV should be pulled 3mm off of skin unless the skin is clinically involved with tumor.

PTV Expansion The CTV-to- PTV expansion is 3 mm as daily image guidance will be employed.

Definition of Normal Tissues/Organs at Risk (OARs)

Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk

Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self explanatory. The oral cavity will be defined as a composite structure consisting of the anterior 1⁄2 to $^{2/3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan.

OARpharynx: This will be defined as the posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (GSL): This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

5.1.3.5 Treatment Planning and Delivery

Dose Prescription to PTVs

As described in Section 5.1.3.1, prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size. For inverse planning IMRT, the goal is for 95% of the PTV70 to receive 95% of 2 Gy with a minimum dose (cold spot) of no less than 63 Gy.

For IMRT prioritization, PTV70 will be the highest priority target structure. PTV63 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV70 although higher priority than normal structures other than spinal cord and brain stem.

Dose Constraints to Normal Structures

Spinal Cord: The PRVcord (as defined in Section 6.4.2.1) should not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem (as defined in Section 6.4.2.2) should not exceed 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.

Lips: Reduce the dose as much as possible unless lips involved with primary tumor. The mean dose should be < 20 Gy. The maximum dose will be < 30 Gy.

Oral Cavity: Reduce the dose as much as possible. The mean dose should be < 30 Gy.

Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 Gy.

OARpharynx: Reduce the dose as much as possible to uninvolved regions. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.

Cervical Esophagus: Reduce the dose as much as possible to uninvolved regions. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended doses (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the esophagus exceeds 60 Gy.

Glottic and Supraglottic larynx (GSL): Mean < 35Gy to uninvolved regions.

Mandible: Reduce the dose as much as possible, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy. For tumors that were not clinically or pathologically involving the mandible, the CTV should be contoured off the mandible.

Unspecified Tissue Outside the Targets: For the typical case in which there is no CTV66, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

5.1.3.6 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed five

treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons.

5.1.3.7 Radiation Therapy Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 will be utilized for grading all adverse events. Placement of a feeding tube should be recorded as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, and skin erythema and desquamation within the treatment fields. Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and skin/soft tissue fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis, and cervical myelopathy (< 1% with restriction of spinal cord dose to max dose of 45 Gy).

5.2 **Definition of Dose-Limiting Toxicity**

5.2.1 Dose Limiting Toxicity

Dose limiting toxicity (DLT) is defined as the appearance of side effects during treatment that are severe enough to prevent further increase in dosage or strength of the treatment agent (metformin in this study), or to prevent continuation of treatment at any dosage level. Dose limiting toxicity is defined as grade 3 or 4 non-hematologic toxicities other than alopecia, nausea or vomiting. In addition, the following adverse effects are considered to be attributed to cisplatin or radiation and not to metformin:

- Grade 3 or 4 renal impairment
- Grade 2-4 neurotoxicity including ototoxicity
- Grade 3 or 4 mucositis
- Grade 3 or 4 myelosuppression
- Any other Grade 3 or 4 toxicity that clinician feels is attributed to chemotherapy rather than metformin

Although the above should result in dose modifications or delays as stated in section 6, they will NOT be considered DLTs for metformin on this study, and will NOT result in a dose cohort change in metformin. If a patient is taken off study due to the above and has not yet reached evaluation for toxicity attributed to metformin, they will be replaced with another patient on study.

Lactic acidosis is automatically considered a DLT due to its high mortality.

A patient is considered evaluable for toxicity if they complete ≥3 days of metformin.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.2.2 Dose Escalation for Phase I

Dose escalation and the MTD will be defined through the modified toxicity probability interval design (mTPI)[28]. A schematic of the dose escalation is below. It is expected that the de-escalation cohort (level -1) will unlikely be necessary based on prior metformin experience. Based on a traditional 3+3 design, for the remaining 3 cohorts, a total of 9-18 patients would be expected to be enrolled based on severity of toxicities. Therefore, the sample size for this study will include 18 total patients in phase I based on expected toxicities. Three patients can be enrolled into any cohort but only 1 cohort should be activated and only 3 patients may be under treatment at any one time. DLTs will be measured up and until 2 weeks after the completion of radiation. Dose-limiting toxicity (DLT) is defined above. The number of DLTs will determine which cohort the following patients will be enrolled based on the chart below. Subsequent cohorts are not to begin until assessments of DLTs (28 days after starting metformin) are completed for at least the first enrolled patient in the prior cohort but patients may be enrolled on rolling basis as long as no more than 3 patients are enrolled in any cohort at a time. If no DLTs are identified in the cohort, then up to three patients may be enrolled at the next cohort level. However, if two total DLTs are experienced in any cohort level at any time during the process, the following patients will only be enrolled one at a time (cohorts of one patient each) until DLTs are assessed for the rest of the enrolled 18 patients.

# of patients with at least 1 DLT at current dose	# of patients treated at current dose																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	E	E
4				DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10		E: Escalate to next higher dose								DU	DU	DU	DU	DU	DU	DU	DU	DU
11		S: Stay at current dose									DU	DU	DU	DU	DU	DU	DU	DU
12		D: De-escalate to next lower dose										DU	DU	DU	DU	DU	DU	DU
13		U: Current dose unacceptably toxic											DU	DU	DU	DU	DU	DU
14		MTD= 30%												DU	DU	DU	DU	DU
15		Sample size = 18													DU	DU	DU	DU
16																DU	DU	DU
17																	DU	DU
18																		DU

Schematic for patient dose assignment based on mTPI design. The x-axis represents the total number of patients in each cohort where the y-axis represents the total number of patients with ≥ 1 DLT that have been recorded at that dose level. The shaded area represents the first 3 patients in the first cohort. If no patients experience a DLT in the first cohort, then the next 3 patients are escalated (E) to the next cohort. If 1 patient out of 3 has a DLT, then the next 3 are enrolled at the same dose level. If 2 patients experience a DLT, then only 1 patient will be enrolled at a time for the rest of the study and the next patient will de-escalate (D) to the next lower dose level. If all 3 patients experience a DLT, the dose level is considered to have unacceptable toxicity (DU) and therefore, no patients can be escalated back to this dose for the remaining of the study. However, the next patient can be de-escalated to the next lower dose until no further cohorts are available.

The phase I portion will not be considered complete until all 18 patients have been enrolled or the number of observed DLTs have resulted in an unacceptable dose at the lowest dose level (level -1). The MTD will be the dose that is assigned most often to patients in the study and is usually the dose assigned to the last patient. Furthermore, if the first 9 patients are enrolled and none experience a DLT, the next 9 patients (who are likely to all receive the highest dose) will be enrolled into the study and will also be consented for biopsy as part of the expansion cohort (see below).

5.2.3 Expansion Cohort

An expansion cohort of 12 patients will be added after completion of dose escalation at the MTD (If dose expansion is ended early, the following nine patients that are enrolled as part of expansion [see previous section] will count towards the total of 12). These patients will undergo the same treatment with the MTD found in the phase I dose escalation portion. They will also be consented for a biopsy, for research purposes only, after 1 week of metformin and prior to starting CRT.

5.3 General Concomitant Medication Guidelines

Metformin is not affected by p450 enzymes and therefore p450 inhibitors are allowed.

Concomitant use of furosemide results in increased levels of metformin and therefore should be avoided if possible. However, furosemide may be used if needed for further diuresis.

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Therefore, these medications are to be avoided if possible while patient is on study but are allowable if felt to be necessary by patient's physician. However, it must be documented that patient was on these medications.

Nifedipine results in enhanced absorption of metformin. It must be documented if a patient is on nifedipine during the study but is allowable.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment will continue until completion of CRT or until one of the following criteria applies:

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

5.5 Treatment and Duration of Follow-up

5.5.1 General Follow-up:

Patients will be followed during treatment as above in section 5.1.1. Patients will then be evaluated at conclusion of treatment and then monthly for first 3 months, and then every 3 months for the first year followed by every 6 months for the following 2 years. DLTs will be

assessed until 2 weeks after completion of radiation. Patients will undergo a PET/CT at 12 weeks to assess for response.

5.5.2 Early Removal from study:

If patients did not complete CRT, patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients who do not complete DLT period (28 days after metformin initiation) will be replaced for assessment of MTD but will still be used for safety analysis.

5.6 **Criteria for Removal from Study**

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1. Cisplatin

6.1.1. Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1000/mm3, hold chemotherapy treatment but not the radiation until ANC ≥ 1000/mm3, then treat at 100% dose. Neutropenic fever (i.e. any fever > 38.5°C with an ANC <1000/mm3) will require a 25% dose reduction of the next cisplatin dose. If neutropenic fever occurs with both the first and second dose, cisplatin should be discontinued.

6.1.2 Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000/mm3, hold chemotherapy treatment but not the radiation until platelets are ≥ 75,000/mm3, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction of the following cisplatin dose.

6.1.3 Neurotoxicity: If grade 2 neurotoxicity develops, hold cisplatin (but continue RT) until toxicity improves to < grade 1, then reduce the following cisplatin dose to 80 mg/m2. If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin, but continue RT.

6.1.4 Renal Adverse Events: Cisplatin dose should be based on the serum creatinine or creatinine clearance immediately prior to the second and third cisplatin dose using the following guidelines:

> Note: If creatinine is > 1.5 mg/dl, creatinine clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. If the calculated clearance is 50 mL/min or above, a 24-hour urine collection is not needed, but if the calculation is less than 50 mL/min, a 24-hour urine collection is mandated, and the cisplatin dose will be determined as follows:

Serum Creatinine Creatinine Clearance Cisplatin Dose
≤ 1.5 mg/dl or > 50 ml/min then administer 100 mg/m2
> 1.5 mg/dl and 40-50 ml/min then administer 50 mg/m2
> 1.5 mg/dl and < 40 ml/min Hold drug*

*Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until it is < 1.5 mg/dl or the creatinine clearance is > 50 ml/min, and it is recommended that the next and following doses of cisplatin should be given at the reduced dose of 50 mg/m2 but the latter will be left to investigator discretion.

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6.1.5 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.

6.1.6 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 as well as consideration of a PEG tube if not already done.

6.1.7 Ototoxicity: For clinical hearing loss not requiring a hearing aid, reduce cisplatin to 50 mg/m2. For hearing loss requiring a hearing aid, discontinue cisplatin. For grade 2-3 tinnitus (CTCAE, v. 4) at the time of retreatment, hold cisplatin until improvement to grade 1 or less and then reduce the following doses of cisplatin to 50 mg/m2. If tinnitus does not improve to grade 1 or less by the last day of radiation therapy, discontinue cisplatin. An audiogram is recommended when there is any report of significant change in hearing and/or an increase in tinnitus.

6.1.8 Other Toxicities: For any other grade 3-4 adverse events, hold cisplatin until toxicities have recovered to grade 1 or less.

If the second or third dose of cisplatin is delayed more than 21 days because of hematologic, neurologic, renal, or other adverse events, that dose will be omitted. If a weight change of ≥10% occurs, the following cisplatin doses should be adjusted.

6.2 Metformin hydrochloride

6.2.1 Diarrhea: For grade 1 and 2 diarrhea, loperamide can be used without dose reduction or discontinuation. However, if diarrhea is grade 3 or 4, metformin should be held until ≤ grade 1. Metformin may be restarted at full dose using dose escalation chart in 5.1.1.

6.2.2 Dehydration: Although metformin itself does not cause dehydration, in patients with dehydration grade 2 or above should have metformin doses held until dehydration corrected

either by oral or IV hydration.

6.2.3 Lactic acidosis: In a very small proportion of patients, lactic acidosis defined as lactate levels >5 can occur with metformin especially those with renal impairment. Due to the seriousness of this event, metformin should be permanently discontinued.

6.2.4 Renal dysfunction: Although metformin does not cause renal dysfunction, the clearance of metformin and therefore risk of lactic acidosis increases. Therefore, metformin should be decreased by 50% if eGFR is 30 to 45ml/min and held if creatinine is above 1.5mg/dl (1.4mg/dl in women) or eGFR is <30ml/min. Metformin may be restarted at full dose (using dose escalation as provided) once kidney function improves above these parameters.

6.2.5 Hypoglycemia: Metformin should be held in the event of hypoglycemia until it resolves. If grade 1 or 2, metformin may be started at full dose using dose escalation. If grade 3 or 4, metformin can be restarted at recovery to normal but should be dose reduced as follows:

For grade 3 or 4 hypoglycemia		
Cohort	**Current Cohort Daily Dose**	**Dose reduction**
-1	1500mg	850mg
1	2000mg	1500mg
2	2550mg	2000mg
3	3000mg	2500mg

6.2.6 Vitamin B12 deficiency: Metformin does not need to be held for this indication as long as B12 is replaced.

6.2.7 Other Toxicities: For any other grade 3-4 adverse events (besides those mentioned in 5.2.1), hold metformin until toxicities have recovered to grade 1 or less.

6.2.8 Dose Reduction for Intolerability: If patients have side effects that are considered intolerable to patient but are less than grade 3, support patients with supportive medications (loperamide, omeprazole, anti-emetics, etc) and try alteration of their dosing schedule by reducing by 1 tablet (500mg or 850mg depending on cohort) at a time until toxicity is ≤ grade 1 for 1 week. Then attempt to re-escalate per chart in 5.1.1 or by adding 500mg/day every 3-5 days if unable to escalate at rate in chart. Every attempt should be made to keep metformin dose at assigned cohort but if unable to achieve the assigned dose, then metformin should be maintained at highest dose tolerated for remainder of treatment.

NOTE: Temporarily discontinue metformin in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized. It is generally recommended that metformin be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute

alteration in renal function). Continue to withhold metformin for 48 hours after the radiologic study.

NOTE: If metformin is held at any time for any reason, upon restarting the drug, it must be dose escalated again in reference to chart in 5.1.1.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

Adverse Event Characteristics

AE description and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas will have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A**ttribution** of the AE:

- 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.

7.1 Expedited Adverse Event Reporting

Expedited AE reporting for this study will be submitted to the PI, the FDA and the IRB.

To FDA:

Serious and unexpected adverse events that are likely to be related to metformin must be

reported quickly in the form of an IND Safety Report.

The time frame for reporting an IND Safety Report is:

- 7 calendar days for a fatal or life-threatening adverse drug experience
- 15 calendar days for a serious and unexpected adverse drug experience

Follow-up reports will be submitted as relevant information is available.

Reports will use FDA Form 3500A and be submitted to the attention of the person identified by the FDA in the initial IND notification letter. Reports for drug INDs are sent to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 5901-B Ammendale Road, Beltsville, MD 20705-1266

Phase 1 Trials

	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[1]**
	Unexpected and Expected	**Unex-pected**	**Expected**	**Unexpected with Hospitalization**	**Unexpected without Hospitalization**	**Expected with Hospitalization**	**Expected without Hospitalization**	**Unexpected and Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under an IND require reporting as follows:

FDA Form 3500A 24-hour notification followed by complete report within 5 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[1] Although FDA Form 3500A 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of

causality. Attribution to treatment or other cause must be provided.

Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via the University of Cincinnati within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via Form 3500A if the event occurs following treatment with an agent under an IND.
- Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

To UC IRB:

An adverse event or injury that is serious, and unexpected, and definitely, probably or possibly related to the study requires prompt reporting to the UC IRB within 10 business days of the research staff being notified of the event. A fatal or life threatening adverse drug experience requires prompt reporting within 24 hours. Reports will be submitted by completion of the New Reportable Event Form in ePAS.

Follow-up reports will be submitted as relevant information is available.

7.2 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through FDA Form 3500A must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

8.1 Metformin hydrochloride

Formulation: Metformin tablets come in 500mg, 850mg, and 1000mg tablets. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500 mg and 850 mg tablets contains hypromellose and the coating for the 1000 mg tablet contains hypromellose and polyethylene glycol. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin is soluble in water.

Mechanism of Action: 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 normally produce hypoglycemia in either patients with type 2 diabetes or normal subjects 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.

Administration: Metformin will be given orally in either BID or TID dosing dependent on assigned cohort.

Pharmacokinetics: The bioavailability of metformin when administered orally in a fasting state is around 50-60%[23]. Food does decrease absorption reflected in a decrease in Cmax of 40% and 25% decrease in area under the curve (AUC). Metformin is negligibly bound to plasma proteins and steady state plasma concentrations of metformin are reached within 24 to 48 hours. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. Renal clearance is approximately 3.5 times greater than creatinine clearance indicating that tubular secretion is the major route for metformin elimination. Following oral administration, approximately 90% of the absorbed drug eliminated via the renal route within 24 hours. Plasma elimination half-life is approximately 6.2 hours but 17.6 hours in blood indicating possible accumulation in erythrocytes.

Storage and Stability: Metformin should be stored at 20°–25° C (68°–77° F). It should be dispensed in light resistant containers. Metformin is stable at room temp for up to 2 years.

Adverse events: The most common human toxicities include diarrhea, abdominal pain, nausea and vomiting, and flatulence. In a small proportion of patients, especially those with renal impairment are at risk for lactic acidosis.

Supply: Metformin is commercially available for use in diabetes. Our pharmacy will supply the medication to patients on trial.

8.2 Cisplatin

Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

Mechanism of Action: The dominant mode of action of cisplatin is inhibition of the

incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although cisplatin is thought to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and other standard alkylating agents.

Administration: Cisplatin will be given as a bolus, infused over 1-2 hours along with appropriate hydration and anti-emetics.

Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Adverse Events: Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected as well.

Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 Immunohistochemistry Methods on Paraffin embedded tissue

For IHC, the fixed tissues will be dehydrated and embedded in paraffin following standard procedures. Hematoxylin-eosin stained 5 µm sections will be used for diagnosis. Unstained sections will be deparaffinized and processed for IHC, which will be performed using highly specific monoclonal or polyclonal antibodies. The antibodies to be used and the procedures to be carried out, which involve overnight incubation with the primary antibody, biotinylated secondary antibodies, and the ABC method to detect the presence of reactive antibodies recognizing each protein, have been previously described [9,29-31].

Two pathologists who will be blinded to any clinical information will independently analyze the biopsy slides. For every case, the whole tumor area will be quantified. The number of positive cells will be visually evaluated for each tissue and the results will re-expressed as a percentage of stained cells/total number of cells[32]. The intensity of immunoreactivity will also be evaluated (1 weak, 2 moderate, 3 strong). A score will be calculated by multiplying both parameters.

Collection, Handling and shipping of Biopsies

Pre-treatment biopsies will be obtained from the department of pathology at UC or the UCCI tumor bank. 2nd biopsy specimens from the expansion cohort will be performed as an outpatient procedure in the ENT office under standard procedures. The subject will be consented as per standard of care and hospital policy using the standard consent form for procedures. The tissue collection from these biopsies will be for research purposes only and will not be reviewed by a pathologist for clinical care purposes.

The tissue from the biopsy will be divided into two similar size aliquots. One will be immediately snap frozen on dry ice and transferred to a labeled cryovial and placed into dry ice in a Styrofoam bucket. The other will be placed in a standard pathology container for tissue fixation in Z-fix solution and labeled. Labels will contain unique accession numbers, but not subject ID numbers. Personal identifiers will not be included on sample labels. The tissues are then transported to the lab and shipped to Dr. Gutkind's laboratory at University of San Diego.

9.1.2 **Flow Cytometry methods**

Whole blood will be collected in EDTA tubes during screening before treatment begins and on days 1 and 22 and week 11 (see study calendar) and transferred at room temperature to UC pathology department or the Vontz Translational Laboratory for flow cytometry. Routine flow cytometry will be performed using antibodies directed at CD3, CD4, CD8, FoxP3, CD25 and PD1 to determine T cell subsets.

9.1.3 **Measurements of Serum Cytokines in Blood and Tissues**

Serum from subjects obtained before treatment and on Days 1, and 22, and week 11 (see Study Calendar for visit windows) will be analyzed using the Luminex 100 instrument with individual bead kits for multiple inflammatory and angiogenic cytokines detectable in patients with HNSCC, including but not limited to interleukin (IL)-6, IL-8, growth-related oncogene-1 (GRO-1), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) (Biosource, Invitrogen), as described [65].

Collection, Handling and shipping of Blood/Serum

Before venipuncture, the phlebotomist will prepare lavender top (EDTA) plastic 10 ml tubes and a red top plastic 5 ml blood collection tube and affix a label to each blood collection tube. Information to be encoded on labels for tubes being sent to Dr. Gutkind's laboratory will include a unique accession number, not a subject ID number. Personal identifiers will not be included on sample labels. The tubes will be placed in a test tube rack, in order of collection (lavender tops, then red tops). The phlebotomist will use standard venipuncture techniques. Following the collection of blood, lavender top tubes will be inverted 5 times to prevent clotting and platelet clumping. Approximate blood volume to be collected in each tube is 10 mls in lavender top, 5 ml in red top tube. The red top tube will be used for the separation of serum, as described in the following:

- Allow blood to clot for 15-30 minutes at room temperature

- Centrifuge blood at 3000 rpm for 10-15 minutes to separate out the serum
- Transfer the serum from the red top vacutainer into appropriately labeled new vial
- Immediately store serum in a -70°C or colder freezer, in liquid nitrogen, or in a Styrofoam container surrounded by excess dry ice
- Ship by courier on dry ice to Dr. Gutkind's laboratory at the University of San Diego

The lavender top (EDTA) tube collected at UC will be transported at room temperature (RT) from the clinical collection site to the sample processing laboratory at UC and Dr. Wise-Draper's laboratory at the Vontz. It will be used for the separation of peripheral blood mononuclear cells (PBMCs) using Ficoll gradients. PBMCs will be washed 2x with PBS and frozen at -80C in aliquots for future analysis.

9.2 **Pharmacokinetics/Pharmacogenetics**

For pharmacokinetic analysis, serial blood samples (5 mL per time point) will be collected at baseline (pre-dose), 0.5, 1, 2, 4, 8 (optional) and 24 hours after metformin administration on Days -14 and 1. If patients are undergoing routine blood draws at additional timepoints, a PK sample may be obtained at that time as well to increase PK data. Blood will be collected into BD vacutainer tubes containing EDTA mixed and centrifuged at approximately 1500 x g for approximately 10 minutes at 4°C. Plasma will be transferred into a storage tube and maintained on dry ice until stored in a -20°C freezer. A validated LC/MS method will be employed for metformin bioanalysis. Samples will be delivered on ice to Dr. Pankaj Desai in pharmacology at the University of Cincinnati. DNA will be also be extracted from whole blood for genotyping of OCT 1 and 2 in Dr. Desai's laboratory.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans must be done ≤4 weeks prior to the start of therapy. (If scans were done prior to this timepoint, then it is acceptable to use radiation oncology simulation scans prior to starting treatment as long as original scans meet inclusion criteria). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk -2	Wk -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk[g] 11	Wk 19[h]	Off Study[c]
Metformin (daily)		A	A	A	A	A	A	A	A	A						
Cisplatin (days 1,22,43)				B			B			B						
Radiation				C	C	C	C	C	C	C						
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X	X----------X														
Physical exam[e]	X		x	X	X	X	X			X				X		X
ENT exam	X														X	
Audiogram[f]	X															
Vital signs	X			X			X			X				X		X
Height	X															
Weight	X			X			X			X				X		X
Performance status	X			X			X			X				X		X
CBC w/diff, plts	X			X	X	X	X			X				X	X	X
Serum chemistry[a]	X			X	X	X	X			X				X	X	X
Adverse event evaluation		X----------X														X
Radiologic evaluation	X														X	
B-HCG	X[b]															
Vitamin B12, Lactate, C-peptide	X			X			X			X				X		X
PD blood draws	X			X			X							X		
PK blood draws		X		x												
2nd biopsy (expansion only)				X[d]												

A: Metformin: Dose as assigned
B: Cisplatin: Dose as assigned
C: Radiation: Dose as assigned
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.
d: prior to cisplatin and radiation

		e: Must occur within 48hrs of planned cisplatin days f: if felt to be clinically indicated, not required g: Can be done at week 9-11 h: +/- 2 weeks Follow-up after completion every 3 months for 1st year, then every 6 months for the following year

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed to determine the rate of complete response (CR). For the purposes of this study, patients should be re-evaluated at approximately 12 weeks post-completion of radiation and then as indicated after during follow-up period.

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study by assessing for the disappearance of tumors/lesions and PET FDG avidity.

11.1.1 Definitions

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline (using RECIST 1.1), have completed CRT, and have had their disease re-evaluated by PET/CT 12 weeks after radiation completion will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 Response Criteria

Complete Response (CR): Disappearance of all measurable disease and FDG avidity

Incomplete/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; or the continued presence of FDG avidity. In patients with this category, suspicious areas should be re-imaged or biopsied to verify persistent disease or CR.

Persistent Disease (PD): Biopsy proven disease after CRT

11.1.3 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.

11.1.4 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression. PFS will be evaluated for 2 years.

11.1.5 **Overall Survival**
OS is defined as the duration of time a patient is alive from start of treatment until time of death. OS will be evaluated for 2 years.

12 Data Storage

Data collection and storage will be managed by the University of Cincinnati Cancer Institute, Clinical Trials Office (UCCI CTO). The UCCI CTO will maintain storage of all clinical data in accordinace with federal guidelines and GCP. Data will be entered in a secure, password protected storage database, OnCore. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team.

13. Data and Safety Monitoring

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. A dictionary will be created to record variables and their definitions, followed by a data file template created by the statistician that includes all variables used in the study. The master template may be partitioned into several sub data files (such as blood, urine, tissue, and imaging files) for convenience of entry from different investigators. All sub files will be connected by study id as a link and later compiled into a synchronized file for analyses at interims and the final stage. Each patient, once being enrolled, will be provided a unique id from the study and their personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever necessary to the researchers.

Data entry will be monitored regularly **by the "Data Safety Monitoring Board"** which is an independent group of experts who will advise the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. Membership consists of persons independent of the investigators and any conflict of interest with the trial. Written documentation attesting to absence of conflict of interest is required. The DSMB includes experts in or representatives of the fields of relevant clinical expertise, and biostatistics. The DSMB will be provided feedback on a regular basis, including findings from adverse-event reports, and recommendations derived from data and safety monitoring, and members of the DSMB will have no personal or financial stake in the study. Interim reports will be prepared at least twice each year by the PI with the help of the study coordinator 1 month

prior to DSMB meeting for DSMB review. These reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events. All serious adverse events will be reported by the PI to the DSMB and IRB within 24 hours of knowledge of the occurrence.

HIPAA confidentiality will be maintained during the phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety. The DSMB will function in an advisory capacity and recommendations that emanate from monitoring activities will be reviewed by the responsible official (the principal investigator) and addressed.

The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval and at periodic intervals during the course of the trial, the **DSMB responsibilities are** to:

- •Periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and when appropriate, efficacy
- •Make recommendations to the study investigators and regulatory agencies (IRB, IBC, FDA, etc.) concerning the continuation, modification, or termination of the trial.

UCCI Site Visit by DSMB

Prior to enrollment of the first subject on this trial, the DSMB will meet, preferably via a site visit, the principal investigator, study investigators, data coordinators and review the study protocol and consent, data collection/capture format, and formalize the process for data presentation/study reports to the DSMB. A teleconference or web conference may substitute for an onsite visit.

It is the responsibility of the study sponsor to ensure that the DSMB is apprised of all new safety information relevant to the study IND and the study. This includes providing the DSMB with a copy of the study protocol in advance as well as providing all IRB/Regulatory Protocol revisions and all safety data reports.

Serious Adverse Events:

All serious and related adverse events will be reported immediately to the Chair and other members of the DSMB by the study sponsor or designee. The decision to meet by teleconference or on site to discuss the adverse event will be left to the discretion of the members of the DSMB. If the DSMB determines that the study procedures present a greater risk than expected, the board may recommend to the P.I. and the IRB that the study enrollment be suspended pending further evaluation.

Written reports:

Written reports should be sent to DSMB members prior to the meeting and should allow sufficient time for review. Written reports may consist of 2 separate parts:

Open Session Report:

This report provides information on study conduct, such as accrual, appropriate demographic representation, baseline characteristics, protocol compliance, site performance, quality control, currency of follow-up. General (ungrouped) adverse events and toxicity issues will be included in the open report.
Open Session reports will be distributed at least a week prior to a scheduled meeting to DSMB members, study investigators and other appropriate persons as directed by the DSMB.

Closed Session Report:

This report may contain data on study outcomes, including safety data and efficacy data. Closed session reports are distributed on the same schedule, but only to DSMB members, the chairman of the IRB, and others as designated by the DSMB Chair. This report is confidential and marked accordingly.

Verbal Report:

At the conclusion of the DSMB meeting, the DSMB should discuss its findings and recommendations with the study investigator and sponsor (or sponsor designee). The DSMB will issue a written summary report that identifies topics discussed by the DSMB and describes their individual findings, overall safety assessment and recommendations. The report should conclude with a recommendation to continue or terminate the study. The DSMB Chair or designee is responsible for drafting, circulating and obtaining approval from other DSMB members within 2 weeks of the meeting.

A final summary report: will be forwarded to the Study Sponsor and PI. The UCCI Regulatory Coordinator will forward the summary report to regulatory authorities as a part of the annual report unless immediate action is required.

Closed Session Report (optional: The DSMB may also prepare confidential minutes that include details of closed session discussions. These meeting minutes are to be held in strict confidence and only accessible to DSMB members until such a time when the study is closed or the DSMB recommends early termination or in the event the minutes are requested by the FDA for participant safety reasons or for regulatory purposes.

Immediate Action Report: The DSMB Chair will notify the Study Sponsor (or sponsor designee) directly of any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial. The report will be submitted to UCCI Regulatory Coordinator for appropriate dissemination to regulatory authorities. This will be done in order to identify significant adverse event trends, missing and incorrect inputs, and other outliers. A log file will be created and record any change/modification of data inputs for purpose of future inspection. Data files will be safely stored in the server of the cancer clinical trials office, with authorized

access to researchers and staffs only; and protected by double firewalls from both UC Health and the University of Cincinnati Information Technology (UCIT). All active study patients are reviewed at the weekly study team meeting. Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the Food and Drug Administration (FDA) or other authorized user, only under guidelines established by the Federal Privacy Act.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Primary Endpoint: Presence or absence of DLT, which is defined as any grade 3-4 toxicity outlined in NCI CTCAE v4.03.

The MTD will be defined through the mTPI design (see schematic in section 5.2.2). Three patients will be enrolled into the initial cohort and DLTs will be measured at four weeks after the completion of radiation. The number of DLTs will determine the dose assignments of future patients. If no DLTs are identified in the first three-patient cohort, then another three patients will be enrolled at the next highest dose. However, if a total of two DLTs are experienced at any dose level during the study, accrual will be slowed and future patients will only be enrolled one at a time until the previously enrolled patient has been completely followed for DLT.

14.2 Sample Size/Accrual Rate

The dose-finding portion of this study will enroll a maximum of 18 patients. This sample size was chosen based on the maximum number of patients that could have been enrolled on a traditional 3+3 design studying three doses (dose -1 is not part of the sample size calculation, as it is only a "fall-back" dose should dose 1 be unacceptably toxic). An expansion cohort of 12 patients will be added at MTD in order to show a 50% response rate measured as a decrease in mTOR pathway markers. With an observed response rate of 50%, 12 patients will be sufficient to produce a 95% confidence interval with a lower bound of 20%, which we view as an acceptable margin of error.

We see about 150 new HNSCC patients per year and of those, approximately 90 have LAHNSCC. About 25 patients will undergo concurrent CRT and we expect to enroll about 9 of these per year on this study. Therefore, we expect to complete the study within 3 years including the expansion cohort.

Due to the inclusion criteria requiring a second biopsy for the dose expansion cohort, it may be difficult to accrue quickly. If at least 6 patients are not accrued

within one year in the expansion phase, then the study will be terminated and an analysis will be performed with samples available.

14.3 **Analysis of Secondary Endpoints**

Secondary Endpoint(s):

- Complete response defined by RECIST criteria.
- All grade 1-5 toxicities outlined in CTCAE v4.1.
- Measurement of downstream effectors in the mTOR pathway by IHC using %+ staining and intensity of staining (0-4+) analyzed by a certified pathologist in the extension cohort; a decrease in the multiplication of the intensity of staining and percentage of at least 25% will be considered a response for that patient.
- Measurement of angiogenic and inflammatory cytokines by ELISA.
- Measurement of T cell subsets in peripheral blood by flow cytometry.
- Measurement of AUC, Cmax, and clearance of metformin and cisplatin in combination.

All secondary measures will be summarized with descriptive statistics, i.e, percentages for categorical outcomes and means/medians for continuous outcomes, with corresponding standard errors and 95% confidence intervals. Responses will be tabulated by determined response and toxicities will be tabulated by type and grade. For IHC, the percentage of positive cells per area will be multiplied by the staining intensity for each tumor to determine quantitative expression pre- and post-treatment; a 25% change in expression will be considered a positive response. We will use descriptive statistics and graphical displays to evaluate change in serum markers between pre- and post-treatment. Pharmacokinetic parameters will be graphically displayed using boxplots and summary statistics.

14.4 **Funding, Regulatory, and Feasibility Issues:**

The proposed chemotherapy and radiotherapy in this trial are currently FDA approved for this indication of LAHNSCC. Therefore they are both billable to insurance. Metformin is not FDA approved for this indication in LAHNSCC. The Department of Internal Medicine Grant awarded to Trisha Wise-Draper for $20,000 (grant period 8/1/14-7/31/15) will fund the metformin costs, some of the coordinator/personnel costs, and handling of specimens. Silvio Gutkind from the NIH will support the PD studies. We will also be applying for additional funding including the Cancer Conquer foundation to help support the PK studies. According to UCCI Cancer Institute administration, cost of the clinical trials office will be absorbed by the UCCI Cancer Institute.

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APPENDIX A

Performance Status Criteria

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