Clinical Study Protocol

Title:	A Randomized Phase 2 Trial of Neoadjuvant and Adjuvant Therapy with the IRX-2 Regimen in Patients with Newly Diagnosed Stage II, III or IVA Squamous Cell Carcinoma of the Oral Cavity. Protocol: IRX-2 2015A-Amendment 5
EudraCT #:	2016-000373-21
US BB IND #:	11,137
Investigational Medicinal Product (IMP)	IRX-2 (Leukocyte Derived Cytokine Mixture, Human)
Indication	Neoadjuvant and adjuvant therapy of head and neck cancer
Date:	**October 15, 2018**
Sponsor:	IRX Therapeutics, Inc. 140-A 58th Street, Suite 2100 Brooklyn, New York 11220 Phone: +1 (929) 281-2485 Fax: +1 (212) 582-3659
Investigators:	Details of participating investigators, clinical study sites and other study personnel is contained in the Clinical Trial Master File and may be obtained from the Sponsor

Investigator Agreement

I have read and approved this protocol. My signature confirms my agreement that **the clinical study will be conducted in full compliance with the protocol and all applicable laws, regulations and regulatory requirements including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP)**, the Code of Federal Regulations (CFR), the European clinical trial regulations, the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

I agree to monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority(ies) as required.

I understand that there is nothing in this document which is intended to limit my authority as a physician to provide emergency medical care under applicable regulations.

I understand the confidential nature of this document and that the information contained therein is proprietary to IRX Therapeutics, Inc.. Before any disclosure of such information, authorization in writing by the sponsor will be obtained. This document will be used solely for the purpose of reviewing or performing this study. At least 60 days prior to submitting or presenting a manuscript or other materials relating to this study to a publisher, reviewer, or other outside persons, I shall provide to IRX Therapeutics Inc. a copy of all such materials and manuscripts, and allow them 60 days to review and provide comment.

Investigator: _____ **Date:** _____

Institution: _____

Sponsor Agreement

The signatures of the Sponsor's representatives below constitute the Sponsor's agreement:

a) to all provisions of the protocol;

b) to comply with ICH GCP Guidelines and all applicable country-specific and local laws, regulations and guidelines.

Sponsor Approval: _____ **Date:** 19 October 2018

Ronald Guido MS, MS Phar. Med.
VP Regulatory and Quality
IRX Therapeutics, Inc.

_____ **Date:** 19 Oct 2018

Diane Hershock, MD
Medical Monitor
IRX Therapeutics, Inc.

†Important Note:

As of Protocol Amendment 4 all adjuvant, booster administration of study regimen has been discontinued. Randomized subjects will receive neoadjuvant treatment and will then be discontinued from further study drug. After discontinuation from study drug, all subjects will be followed for progression and survival as described in the protocol.

Protocol Synopsis IRX-2 2015A

Study Title	**A Randomized Phase 2 Trial of Neoadjuvant and Adjuvant Therapy with the IRX-2 regimen in Patients with Newly Diagnosed Stage II, III or IVA Squamous Cell Carcinoma of the Oral Cavity**
Study Phase	2b
Rationale for Study	The IRX-2 regimen has been studied in patients with head and neck squamous cell carcinoma (HNSCC) in two open-label, multi-center studies. A Phase 1 trial evaluated the IRX-2 regimen as therapy for advanced disease and a Phase 2a trial evaluated the IRX-2 regimen as neoadjuvant therapy prior to surgery. These trials established that the IRX-2 regimen has an acceptable safety profile and produced changes in lymphocyte infiltrate in surgically resected tumors compared to baseline tumor biopsies. In addition, the only subject to undergo PET imaging had significantly reduced metabolic activity after treatment with the IRX-2 regimen. Overall survival (OS) appeared favorable compared to historical controls and was greater in subjects who had higher tumor lymphocyte infiltration in the surgical specimen and in those with the greatest increase in tumor lymphocyte infiltration after treatment with the IRX-2 regimen. The present study is intended to further evaluate neoadjuvant therapy with the IRX-2 regimen in a randomized trial. In addition, the immunotherapy regimen will be enhanced by adding four adjuvant booster courses of a shorter IRX-2 regimen during the first postoperative year.†
Study Design	This is an open label, randomized, multi-center, multi-national Phase 2b clinical trial intended for patients with Stage II, III or IVA untreated SCC of the oral cavity who are candidates for resection with curative intent. Subjects will be randomized 2:1 to either Regimen 1 or Regimen 2 and treated for 21 days prior to surgery and then postoperatively with a booster regimen given every 3 months for 1 year (a total of 4 times.)† • **Regimen 1**: IRX-2 Regimen with cyclophosphamide, indomethacin, zinc-containing multivitamins, omeprazole and **IRX-2** as neoadjuvant and adjuvant† therapy as in the Tables below. • **Regimen 2**: Regimen 1 with cyclophosphamide, indomethacin, zinc-containing multivitamins, omeprazole but **without IRX-2** as neoadjuvant and adjuvant† therapy. Randomization will be 2:1 in favor of Regimen 1. Treatments will be allocated to study subjects using minimization with a stochastic algorithm based on the range method. Minimization will account for the major prognostic factors for SCC of the oral cavity (T and N stage) and study center to avoid imbalances in treatment allocation within centers. Postoperatively, subjects will first receive standard adjuvant radiation or chemoradiation therapy as determined by the investigators per protocol guidelines

<table>
<tr><td></td><td>and then will also receive Booster Regimen 1 or 2 as determined in the prior randomization.†

Subjects will be followed for the Primary, Secondary and Exploratory endpoints as discussed below and detailed in the Schedule of Study Events (Protocol Section 5.1). Protocol mandated follow-up will end 4 years after randomization of the last patient.</td></tr>
<tr><td>IRX-2 Regimen (Regimen 1)</td><td>IRX-2 is a primary cell-derived biologic with multiple active cytokine components, produced under pharmaceutical standards from phytohemagglutinin (PHA) and ciprofloxacin stimulated donor mononuclear cells.

The Neoadjuvant IRX-2 Regimen is a 21-day pre-operative regimen of cyclophosphamide on Day 1, indomethacin, zinc-containing multivitamins and omeprazole on Days 1-21, and subcutaneous IRX-2 injections in bilateral mastoid insertion regions for 10 days between Days 4 and 21†, as shown in the table below:

IRX-2 Neoadjuvant Regimen:
<table>
<tr><th>Agent</th><th>Dose</th><th>Route of Administration</th><th>Treatment Days</th></tr>
<tr><td>Cyclophosphamide</td><td>300 mg/m^2</td><td>IV</td><td>1</td></tr>
<tr><td>IRX-2</td><td>230 units daily (Bilateral injections of 115 units)</td><td>Subcutaneous at or near the mastoid insertion of both sternocleidomastoid muscles</td><td>Any 10 days between Days 4 and 21</td></tr>
<tr><td>Indomethacin</td><td>25 mg TID</td><td>Oral</td><td>1-21</td></tr>
<tr><td>Zinc-containing multivitamins</td><td>1 tablet containing 15-30 mg of zinc</td><td>Oral</td><td>1-21</td></tr>
<tr><td>Omeprazole</td><td>20 mg</td><td>Oral</td><td>1-21</td></tr>
</table>
The Booster IRX-2 Regimen is given at 3, 6, 9 and 12 months (-14 to +28 days) after surgical resection as detailed in Protocol Section 5.2.8.† It is a 10-day post-operative regimen of cyclophosphamide on Day 1, indomethacin, zinc-containing multivitamins and omeprazole on Days 1-10 and subcutaneous IRX-2 injections in bilateral deltoid regions for 5 days between Days 4 and 10 as shown in the table below:

IRX-2 Booster Regimen†:
<table>
<tr><th>Agent</th><th>Dose</th><th>Route of Administration</th><th>Treatment Days</th></tr>
<tr><td>Cyclophosphamide</td><td>300 mg/m^2</td><td>IV</td><td>1 dose every 3 months for 1 year</td></tr>
<tr><td>IRX-2</td><td>230 units daily (Bilateral injections of 115 units)</td><td>Subcutaneous into bilateral deltoid regions</td><td>Every 3 months Any 5 days between Days 4 and 10</td></tr>
<tr><td>Indomethacin</td><td>25 mg TID</td><td>Oral</td><td>Every 3 months Days 1-10</td></tr>
</table>
</td></tr>
</table>

	Zinc-containing multivitamins	1 tablet containing 15-30 mg of zinc	Oral	Every 3 months Days 1-10
	Omeprazole	20 mg daily	Oral	Every 3 months Days 1-10
Control Arm Regimen **(Regimen 2)**	The control arm will be dosed following the same regimen as Regimen 1 except that subjects will **not** receive IRX-2.			
Objectives	**Primary Objective:** To determine if the event-free survival (EFS) of subjects treated with Regimen 1 is longer than for subjects treated with Regimen 2. **Secondary Objectives:** 1) to determine if OS of subjects treated with Regimen 1 is longer than for subjects treated with Regimen 2. 2) to compare the safety of each Regimen. 3) to compare the feasibility of each Booster Regimen†. **Key Exploratory Objectives:** To determine and compare between the Regimens: 1) changes in tumor size from baseline to surgery measured by CT scans (MRI also acceptable, so long as the same modality is used for baseline and pre-surgery scans). 2) changes from baseline to surgery in functional imaging as estimated by PET scan. 3) lymphocyte infiltrates in the pre-treatment tumor biopsy, the surgical specimen and changes between these two samples. These data will be analyzed to seek any baseline characteristics that are correlated with differences in outcome between the Regimens. **Additional Exploratory Objectives:** To determine and compare between the Regimens: 1) surgical pathology, including tumor characteristics (depth of invasion, perineural invasion, pattern of invasion, extent of necrosis), tumor margins and lymph node involvement. 2) prognostic and predictive factors and clinical-pathologic-immunologic correlates, including, for example, nutritional status (body mass index, albumin), absolute lymphocyte count, lymphocyte subsets and histological differences in the surgical specimen and gene expression profiles with disease-free survival, recurrence, second primary tumors, and patterns of disease recurrence. 3) Human papilloma virus (HPV) status (p16 protein expression) and any relationship between tumor p16 protein expression and differences in outcome between the Regimens. 4) the peripheral T cell receptor profile prior to and post treatment during the first year of the trial. 5) RNA expression profiling of immune-inflammatory markers.			

Methods	**Primary Endpoint:** EFS will be assessed by physical examination at routine follow-up visits every 3 months after surgery for the first two years and by chest CT scans performed yearly x 4 years. During years 3-4 subjects will be contacted by phone to determine survival status, and will be assessed in person (eg, physical exam, laboratory evaluations, etc.) according to standard of care at their enrolling institution. Any indication of recurrence occurring at these SOC visits should be followed up with a confirmatory imaging and reported in the Recurrence CRF folder. Progression prior to surgical resection will not be considered an Event, but failure to resect tumor that was apparent at randomization for any reason will be considered an Event. Progression after resection should be confirmed by biopsy, and scans (CT, MRI or PET) should be performed to restage disease and establish patterns of relapse. The date of progression will be the date on which the decision not to resect tumor that was apparent at randomization is made or on which the Investigator first observes recurrent locoregional or metastatic disease by physical or radiologic examination. Death from any cause will also be considered an Event. Diagnosis of a second malignancy will not be considered an Event, but date of diagnosis, site and histology will be collected. **Secondary Endpoints:** Survival data will be collected in all subjects (phone contact after progression will be sufficient). Safety of each Regimen and feasibility of the Booster Regimens[†] will be assessed by the incidence and severity of adverse events, serious adverse events and subject discontinuations (as defined in the Protocol). **Exploratory Endpoints:** • Change in tumor size will be determined by a comparison of the imaging studies (CT or MRI) obtained pre-treatment and just prior to surgery. Percent changes in tumor size will be determined by central radiology review by radiologists blinded to the treatment Regimen. • Change in functional imaging will be determined by a comparison of the PET scans obtained pre-treatment and just prior to surgery. Percent changes in glycolytic activity will be estimated by central radiology review by radiologists blinded to the treatment Regimen. • Lymphocyte infiltrates in the pre-treatment tumor biopsies and the surgical specimens will be determined and compared. Subsets of lymphocytes will be evaluated including total T cells and naïve, cytotoxic and regulatory T cells. The analyses may include quantifications of cellular infiltrates and degree of activation by immunohistochemistry including (but not limited to): CD3, CD8, CD45RO, CD68 (myeloid derived suppressor cells) and Fox P3 on lymphocytes and MHC class I and II and PDL1 on tumor cells. Other immune subsets and activation markers may be evaluated. Tumor gene expression signatures may also be performed. Lymphocyte infiltrates and changes after treatment will also be evaluated using T cell receptor (TCR) repertoire analyses performed on extracted RNA. These studies will be performed by one or more external contract research organizations without knowledge of the treatment Regimen received.

	• Surgical pathology specimens will be centrally reviewed to explore the impact of the features described above on clinical outcome. HPV status will be assessed by p16 expression and its relationship to clinical outcome will be explored. Body mass index, serum albumin, peripheral blood absolute lymphocyte count and possibly other hematological, chemical or clinical data, including the peripheral T cell receptor profile prior to and post treatment during the first year of the trial, will be used to explore relationships to clinical outcome. RNA expression profiling of immuno-inflammatory markers will also be performed. *Analyses of exploratory endpoints will be conducted. The Sponsor may at any time alter or discontinue some or all of these evaluations so long as additional clinic visits, radiology studies or blood draws are not initiated.* *Analyses of some or all of the exploratory endpoints will be conducted by the Sponsor or designated representatives at intervals depending on the availability of sufficient data.*
Study Population	Subjects with Stage II, III or IVA squamous cell cancer of the oral cavity who have resectable primary tumors and are without medical contraindications to curative surgery.
Number of Subjects	A total of approximately 100 subjects will be randomized.
Number of Centers	Approximately 50.
Inclusion Criteria	1. Pathologically confirmed clinical Stage II, III or IVA squamous cell cancer of the oral cavity (excluding lip).Subjects must be staged using AJCC Cancer Staging Manual Edition 7.0 (Appendices 1 and 2). 2. Disease surgically resectable with curative intent 3. Hematological function: hemoglobin >9 g/dL; lymphocyte count >0.50 x 10^9/L; neutrophil count >1.5 x 10^9/L; platelet count >100 x 10^9/L 4. Hepatic function: serum albumin >3.0 g/dL; aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) <3x the upper limits of normal (ULN); alkaline phosphatase <2x the ULN 5. Prothrombin time (PT) and partial thromboplastin time (PTT) < 1.4x the ULN 6. Calculated creatinine clearance > 50 mL/minute (Appendix 4) 7. At least 18 years of age 8. Willing and able to give informed consent and adhere to protocol therapy 9. Karnofsky performance status (KPS) ≥70% 10. Females of childbearing potential (not surgically sterile or less than 12 months post-menopausal) must be able and willing to use a highly effective form of pregnancy prevention from the time of screening, during the study and 1 year after last dose of study regimen. Males with a partner of childbearing potential must use condoms with spermicide from the date of screening to 1 year after their last dose of study regimen (See Section 3.2.1 for details) 11. Negative urine/serum pregnancy test, if applicable

Exclusion Criteria	1. Prior surgery, radiation therapy, or chemotherapy other than biopsy or emergency procedure required for supportive care of this oral cavity cancer. 2. Any medical contraindications or previous therapy that would preclude treatment with either IRX-2 Regimen 1 or 2 or the surgery, reconstruction or adjuvant therapy required to treat the oral tumor appropriately. o Live vaccines should ideally not be administered to any patients undergoing treatment with chemotherapy or immunotherapy, but if need be, they should be administered >4 months prior to the initiation of treatment or >4 months after the completion of all treatment. o Inactivated vaccines should precede the initiation of any study regimen and/or standard adjuvant therapy by at least 2 weeks, but preferably 4 weeks or longer. 3. Clinical status of either subject or tumor such that administration of 21 day neoadjuvant IRX-2 Regimen 1 or 2 before surgery would be medically inappropriate. 4. Tumor of the oropharynx. 5. Tumor involvement of the following sites or any of these signs or symptoms likely to be associated with T4b cancer: o involvement of pterygopalatine fossa, maxillary sinus, or facial skin;. o gross extension of tumor to the skull base; o pterygoid plate erosion; o sphenoid bone or foramen ovale involvement; o direct extension to involve prevertebral fascia; o extension to superior nasopharynx or Eustachian tube; o direct extension into the neck with involvement of the deep neck musculature (neck node fixation); o suspected invasion (encasement) of the common or internal carotid arteries. Encasement will be assessed radiographically and will be defined as tumor surrounding the carotid artery 270º or greater; o direct extension of neck disease to involve the external skin; o direct extension to mediastinal structures; o regional metastases to the supraclavicular neck (low level IVB or VB) 6. Any investigational agent within the previous 30 days. 7. Daily administration of systemic immunosuppressive therapy or corticosteroids (except in physiological doses for hormone deficiency) during the previous 30 days. 8. Chronic anticoagulation, not including aspirin, but including heparins, warfarin, oral anticoagulation or other platelet function inhibitors, that can not, in the documented opinion of the investigator, safely be interrupted from at least 2 days prior to the initiation of the study regimen until after surgical resection of the tumor. 9. Symptomatic cardiopulmonary disease (including congestive heart failure and hypertension), coronary artery disease, serious arrhythmia or chronic lung disease. Patients with these conditions who are stable with relatively minor symptoms and who are appropriate candidates for surgical treatment of their tumor need not be excluded

	10. Myocardial infarction within the last 3 months 11. Distant metastases (M1 disease). 12. Known infection with hepatitis B, hepatitis C, or HIV. 13. Signs or symptoms of systemic infection (use of antibiotics to treat superficial infection or contamination of tumor shall not, by itself, be considered evidence of infection). 14. Clinically significant gastritis or peptic ulcer disease that would contraindicate the use of indomethacin. 15. Stroke or other symptoms of cerebral vascular insufficiency within the last 3 months. 16. Allergy to ciprofloxacin (or other quinolones), acetylsalicylic acid, or indomethacin. 17. Previous diagnosis of invasive cancer from which the individual is NOT disease-free AND that has required treatment within the past 5 years, except for superficial skin, cervical cancer in-situ, well-differentiated thyroid or early stage prostate or bladder cancer (i.e., treatment with curative intent and long term disease-free expectations). 18. Prior axillary dissection. 19. Breastfeeding women.
Study Monitoring **(Data Safety Monitoring Board)**	A Data and Safety Monitoring Board (DSMB) will be established to monitor the conduct of the study as well as safety data. The DSMB will consist of physicians and a statistician who are not otherwise involved in the trial. The DSMB will meet via teleconference or in person over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise. The DSMB will monitor the study for delay in definitive surgery as described in Section 8.4. Detailed information regarding standard of care adjuvant therapy for subjects in each arm will be reviewed. Additional details of DSMB procedures and communication with Investigators and the Sponsor will be described in a separate Charter.
Statistical Considerations	Assuming that the EFS at 24 months will be 50% for subjects receiving Regimen 2, this trial will have 61% power (one-sided $\alpha = 0.1$) to detect an increase in EFS of 15% (i.e. to 65%) at 24 months (hazard ratio [HR] = 0.62) for the subjects receiving Regimen 1. The required number of EFS events for the primary endpoint is 51 progressions or deaths. The primary analysis will be of the entire population as randomized (intent-to-treat). Assuming an average accrual of 2 patients per month during the first year, and 7 patients per month during the second year, the trial will have accrued 100 subjects in 24 months. Assuming that the OS at 36 months will be 55% for subjects receiving Regimen 2, this trial will have 66% power (one-sided $\alpha = 0.1$) to detect an increase in OS of 15% (i.e. to 70%) at 36 months (HR = 0.60) for the subjects receiving Regimen 1. The required number of OS events for the assessment of the OS endpoint is 51 deaths. An Interim Analysis (IA) will be performed as specified in Protocol Section 9.5.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

List of Definitions and Abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
Akt	protein kinase B
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANC	absolute neutrophil count
AST/SGOT	aspartate aminotransferase/ serum glutamic oxaloacetic transaminase
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
DFS	disease-free survival
DSMB	Data and Safety Monitoring Board
EFS	event-free survival
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
Fox P3	Fox P3 protein is involved in immune system responses
GM-CSF	granulocyte-macrophage colony stimulating factor
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IFN-α	interferon alpha
IFN-γ	interferon gamma
IL-1β	interleukin 1 beta
IL-2	interleukin 2
IL-7	interleukin 7

IL-10	interleukin 10
IL-12	interleukin 12
IL-15	interleukin 15
IRB	Institutional Review Board
IRX-2	primary cell-derived biologic with multiple active cytokine components
IRX-2 regimen	Twenty subcutaneous injections of 115 U of IRX-2 (over 10 days) preceded by cyclophosphamide with a 21 day course of indomethacin and zinc containing multivitamins
ITT	Intention-To-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
IxRS	Interactive Recognition System
KPS	Karnofsky performance status
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MHC class I	major histocompatibility complex class 1
MHC class II	major histocompatibility complex class 2
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK or NKT	natural killer T cells
OS	overall survival
PET	positron emission tomography
PDL1	programmed death ligand 1
PHA	Phytohemagglutinin
PI	Principal Investigator
PI3K	phosphoinositide 3 kinase
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

SCC	squamous cell carcinoma
T cells	cellular immune lymphocytes; derivation – thymus lymphocytes
T-bet	T box transcription factor
TCR	T cell receptor
T_{eff}	T effector cell
TGF-β	Transforming growth factor beta
T_{reg}	T regulatory cell; suppressor T cell
TID	three times a day
TNF-α	tumor necrosis factor alpha
TNM	tumor grading system (T-primary lesion; N-nodes; M-metastases)
U	unit(s)
ULN	upper limit of normal
US	United States

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Squamous Cell Carcinoma of the Oral Cavity

Squamous cell carcinoma (SCC) is the most frequently occurring malignant tumor in the head and neck. More than 90% of head and neck squamous cell carcinomas (HNSCC) originate from the mucosal linings of the oral cavity, pharynx, or larynx. The estimated worldwide incidence of HNSCC in 2000 was more than 551,000 with greater than 217,000 deaths [Parkin, 2001]. The epidemiology of HNSSC is discussed in more detail in the Investigator's Brochure (IB).

Oral cavity cancer can affect any part of the oral cavity, including the lip, tongue or mouth. Although five-year survival rates are around 50%, patients successfully treated may still have to cope with consequences of their treatment that affect appearance, function and quality of life.

This study will evaluate the effects of the IRX-2 Regimen in patients with Stage II to Stage IVA untreated SCC of the oral cavity compared to a control arm where no IRX-2 will be given.

1.1.2 Staging, Treatment, and Prognosis

Classification and staging of SCC of the oral cavity is performed according to the TNM tumor grading system, which describes the anatomical extent of the primary tumor (T stage), the regional lymph nodes (N stage), and the presence or absence of distant metastases (M stage) (American Joint Committee on Cancer [AJCC], Appendix 1 and Appendix 2).

The focus of this protocol is on cancer of the oral cavity, selected for study in part because of the limitations of currently available therapies. In addition, there is evidence that the impact of the immune system upon HNSCC differs by tumor site [Rapidis, 2009]. Thus, in order to maximize the ability to detect benefit conferred by immune modulation, i.e. the IRX-2 Regimen, a homogenous patient population with respect to site and standard treatment modality is required. In addition, relatively few new therapeutic approaches directed to cancer of oral cavity are being investigated.

1.1.3 Rationale for Inclusion of Stage II Patients

One-third to more than 50% of patients with clinical Stage II disease (i.e. node negative) are found upon pathological examination of resected lymph nodes to have nodal involvement and thus will be "upstaged" to Stage III [Ross, 2002; Sparano, 2004; O-Charoenrat, 2003]. Nodal size alone is an inaccurate predictor of nodal metastases, confirming the challenge of identifying pathological Stage III patients based on clinical staging [Alkureishi, 2007]. Seventy-two of 243 patients (30%) with clinical T1 or T2 N0 (Stages I or II) oral cancer were found to have pathological involvement of electively resected nodes, i.e. were upstaged to pathological Stage III [D'Cruz, 2015 and Supplemental Appendix, Table S4]. Patients with Stage III oral cavity cancer clearly have a worse prognosis for both recurrence and survival when compared to Stage I patients (Hazard Ratio for survival = 2.1-2.2), but it is clear that Stage II patients also have a poorer prognosis than do Stage I patients (Hazard Ratio for survival = 1.3) [Leoncini, 2015; Kreppel, 2011; Groome, 2001]. It is important to emphasize, however, that the above data are based on the pathological staging of patients, not on their pre-operative, clinical stage. Thus the Stage II Hazard Ratios for survival would be even greater if the above data were based on clinical, rather than pathological stage.

Subjects entered on this trial will be entered on study and randomized based upon their clinical stage, not their pathological stage. The randomization methodology will account for the major prognostic factors for HNSCC of the oral cavity, including T and N stage (and also study center; see Section 5.2.2 and Section 9). The prior Phase 1 and 2a trials of the IRX-2 Regimen (summarized in Section 1.3 below and in the Investigator's Brochure) did not reveal significant safety concerns that would make it inappropriate to include earlier stage patients. Finally, as with other immune therapies, it may be that patients with relatively smaller tumor burdens are more likely to benefit from the IRX-2 Regimen, an observation that may be missed if such patients are not included in the trial. Thus patients with clinical Stage II oral cavity cancer will be included in this trial.

1.1.4 Immune Deficiency and Immunotherapy in HNSCC Patients

The rationale for the pursuit of immunotherapy of HNSCC with the IRX-2 regimen stems from a considerable body of evidence, which indicates that immunologically competent cells are important host defense mechanisms. Many human cancers, however, including HNSCC, are associated with cellular immunodeficiency. Immunotherapies now in development for the treatment of HNSCC include nonspecific, systemic cell-mediated approaches, cytokine based immunotherapy (including delivery of granulocyte-macrophage colony stimulating factor [GM-CSF], interleukin-2 [IL-2], interferon alpha [IFN-α], interferon gamma [IFN-γ], interleukin-12 [IL-12], and IRX-2), tumor-associated antigens as therapeutic targets, monoclonal antibodies and cancer vaccines, either peptide/protein based, dendritic-cell based or nucleic acid based, and immune checkpoint inhibitors. Discussion of these many approaches is beyond the scope of this protocol Introduction but is presented in more detail in the Investigator's Brochure (IB) and in several reviews [Rapidis, 2009; Freiser, 2013; Gildener-Leapman, 2013].

1.1.5 The IRX-2 Regimen

Dose/Regimen Rationale: In the 1980s, investigators had shown that local administration of the cytokine interleukin-2 (IL-2) triggered lymphocytes from tumor-bearing mice to inhibit tumor growth [Forni, 1985] and that recurrent HNSCC could be treated with low doses of IL-2 injected perilymphatically [Cortesina, 1988]. Shortly thereafter, as discussed in Section 4.1.1 of the Investigator's Brochure, cytokine mixtures now designated as IRX-2 were shown to result in stimulation of T cells in several animal models [Hadden, 1989]. One of the major T cell stimulating constituents found in IRX-2 is IL-2; however, in these model systems recombinant IL-2 (rIL-2) alone was unable to reproduce completely the proliferative effects seen with IRX-2. IRX-2 was also able to induce proliferation in murine T cell precursors from the spleens of athymic nude mice to a greater degree than rIL-2 [Hadden, 1989]. IRX-2 administered *in vivo* augmented proliferation of T cells in nude mice and in a murine model of immunodeficiency using hydrocortisone-treated aged mice, IRX-2 was able to restore thymic function and T cell numbers. IRX-2 treatment increased the recovery of spleen and thymus weights and cellularity with a corresponding augmentation of proliferation and function of T lymphocytes [Hadden, 1992; Hadden, 1995b]. Recombinant IL2 was not able to duplicate this effect. These data suggested that cytokine components of IRX-2, in addition to IL-2, acted on T cell function and promoted T cell development and proliferation. These functional effects of IRX-2 on T cells led the scientific founder of IRX Therapeutics, Dr. Hadden, to hypothesize that IRX-2 might be therapeutically relevant for immune restoration in immune deficient subjects [Hadden, 1995a].

The IRX-2 biologic differs from other types of cytokine therapy in the following:

- physiologic rather than pharmacologic doses of the cytokines are administered;
- administration is by subcutaneous injection in the perilymphatic areas rather than intratumoral or intravenous injection; and
- product manufacture uses activated lymphocytes rather than recombinant DNA technology in order to simulate endogenous cytokine levels from native activated cells

The route of administration takes advantage of the normal afferent and efferent pathways of lymph node activation. Normally, lymphatics drain from an area of interest, such as a tumor bed, and antigens and other factors associated with disease migrate through the lymphatics to the regional nodes. At the regional nodes, antigen presenting (dendritic) cells are responsible for securing and processing these disease-related antigens and presenting them to T cells, with resultant proliferation of activated, antigen-specific T cells. By administering IRX-2 locally, rather than systemically, DCs and T cells are activated directly to proliferate and become cytotoxic lymphocytes. Additionally, by localized rather than intravenous administration, lower systemic drug levels are likely, leading to less systemic toxicity.

The major component of the IRX-2 Regimen is the cytokine mixture IRX-2 administered as above, but in a series of empiric studies, Dr. Hadden and colleagues added additional components, cyclophosphamide, indomethacin and multivitamins with zinc, for reasons summarized in Section 1.1.8 below and in several publications [Hadden, 1994; Verastegui, 1997; Barrera, 2000]. Omeprazole was subsequently added as a supportive medication to decrease the incidence and severity of gastritis induced by the indomethacin. After the manufacturing of IRX-2 was standardized per a US IND (# 11,137); (see Section 1.1.6 below and the Investigator's Brochure), a Phase 1 trial was performed in the United States and is summarized below in Section 1.3.1 and in more detail in the Investigator's Brochure. This study was followed by a Phase 2a neoadjuvant trial of the same IRX-2 regimen in 27 subjects with resectable HNSCC as summarized below in Section 1.3.2 and in more detail in the Investigator's Brochure. Thus, the doses and components of the IRX-2 Regimen to be studied in the current trial are based in part on preclinical data of IL-2 and IRX-2 in preclinical models, ancillary data that led to the addition of the non-cytokine components of the IRX-2 Regimen, the early clinical experience with the IRX-2 Regimen in the 1990s and finally, the current experience with this regimen in the Phase 1 and 2a trials performed in the United States indicating encouraging safety, immunological and survival results.

The concept that subjects with HNSCC might benefit from immune stimulation led to the development of the IRX-2 regimen, consisting of the cell-derived biologic IRX-2 that contains multiple cytokines, cyclophosphamide, indomethacin, and zinc (administered as a multivitamin preparation containing zinc). These four components are administered as a regimen consisting of an intravenous (IV) infusion of low-dose cyclophosphamide on Day 1, followed by oral indomethacin and oral zinc- containing multivitamins daily for 21 days, and IRX-2 administered as two subcutaneous injections per day for ten days, as outlined in the Synopsis and below in Table 1, Section 4.2. Omeprazole, a proton pump inhibitor, is given concurrently in accordance with its licensed dose and administration, to improve tolerance of the indomethacin. This IRX-2 Regimen has been previously studied in Phase 1 and 2a studies that are described below in Section 1.3

Booster Regimen†: This study will also investigate the benefit of an IRX-2 Booster. It is a 10-day post-operative regimen of cyclophosphamide on Day 1, indomethacin, zinc-containing multivitamins and omeprazole on Days 1-10 and subcutaneous IRX-2 injections in bilateral deltoid regions for 5 days between Days 4 and 10. The rationale for the Booster Regimen is to continue to provide a cytokine environment that will further stimulate T cells. We speculate that immune activation will be promoted in nodal tissue and this will further expand T cells that have already been primed to antigens found in the tumor. It is well established that immune responses, including cellular immune responses, are enhanced by continued stimulation. An abbreviated IRX-2 regimen is to be utilized for the Booster Regimen, since a shorter course of therapy every 3 months will be less burdensome to patients and thus likely will result in greater compliance. In addition, pre-clinical data suggest that a 5-day course of IRX-2 is comparable to a 10-day course for enhancement of cellular responses to tumor-associated antigens [Naylor, 2010].

1.1.6 Manufacture and Composition of IRX-2

IRX-2 is a primary cell-derived biologic with multiple active cytokine components produced under pharmaceutical standards as discussed in more detail in the IB. Briefly, human leukocytes ("buffy coats") pooled from multiple donors are stimulated with phytohemagglutinin and ciprofloxacin. Subsequently, the phytohemagglutinin, ciprofloxacin and all cellular elements are removed or significantly reduced, and the cell-free supernatant is filter sterilized, nanofiltered to clear viral particles, vialed, and frozen as IRX-2.

IL-2 is the major cytokine in IRX-2, followed by IFN-γ, TNF-α, and interleukin 1 beta (IL-1β). These cytokines when studied individually enhance cell-mediated immunity via several different mechanisms discussed below and in the IB.

1.1.7 Mechanism of Action of IRX-2

Recent in vitro studies have elucidated several potential mechanisms of action of IRX-2, and these various mechanisms of action need not be exclusive. IRX-2 treatment of human monocyte-derived dendritic cells results in changes consistent with the development of mature activated dendritic cells. Specifically, IRX-2 increased the percentage of cells expressing CD83 and CCR7, markers for dendritic cell maturation and migration and increased the expression of multiple markers that are critical mediators of T cell activation [Egan, 2007]. Similar results were obtained in a later study in cells obtained from patients with HNSCC [Schilling, 2013]. Also, in an in vitro study of peripheral blood mononuclear cells obtained from patients with HNSSC, IRX-2 up-regulated cytotoxicity of NK cells and did so more effectively than IL-2 [Schilling, 2012].

IRX-2 can also protect T cells from activation induced cell death by reversing microvesicle induced inhibition of the PI3K/Akt pathway and correcting the imbalance of pro- versus anti-apoptotic proteins induced by tumor-derived microvesicles [Czystowska, 2009; Czystowska 2011]. IRX-2 was superior to recombinant IL-7 and IL-15 in protecting T cells from tumor-induced apoptosis. The presence of IRX-2 in a tumor microenvironment model promoted the induction and expansion of IFN-γ^+T-bet$^+$ T_{eff} and significantly decreased the induction of inducible IL-10$^+$TGF-β^+ T_{reg}. The responsible mechanism involved IFN-γ^+-driven T cell polarization towards T_{eff} and suppression of T_{reg} differentiation [Schilling 2012]. In the Phase 2a study in patients with HNSSC (described below in Section 1.3.1), IRX-2 mediated reductions in circulating B and NKT cell numbers, suggesting redistribution of these cells to tissues [Whiteside 2012]. A decrease in naïve

T cells was also noted, suggesting their upregulation to memory T cells, while unchanged numbers of T_{regs} (suppressor T cells) after IRX-2 therapy indicated that IRX-2 does not expand this compartment, potentially benefiting anti-tumor immune responses [Whiteside, 2012].

Finally, IRX-2 has been shown to induce enhanced T cell responses when administered with tumor antigen vaccines, raising the possibility that IRX-2 treatment in patients with HNSCC enhances endogenous antigen-specific T cell responses to the tumor [Naylor, 2010].

1.1.8 Rationale for the Components of the IRX-2 Regimen

The rationale for the components of the IRX-2 regimen is outlined below.

Cyclophosphamide: One mechanism for reversal of anergy and reversal of suppression of immune responses in subjects with malignancy by adoptive immunotherapy may be related to inhibition of regulatory T cell function [North, 1982; North, 1984]. Evidence indicates that cyclophosphamide inhibits T_{reg} number and/or function [Emens, 2005]. Thus many clinical trials that involve immunotherapy or attempt to stimulate immune response to tumor antigens have employed low dose cyclophosphamide (300 mg/m^2) as a component of the treatment regimen. This immunomodulatory dose is less than one-third of a typical anti-cancer dose and is intended to enhance the development of cell-mediated immunity by providing contrasuppression of tumor-associated immune suppression (to reduce the number and function of regulatory T cells, i.e. T_{reg}) [Berd, 1982; Machiels, 2001].

Pathways of local immune tolerance, escape mechanisms active within the tumor microenvironment and superimposed potent systemic mechanisms of immune tolerance have been reviewed [Emens, 2005] and are discussed in more detail in the Investigator's Brochure (Section 3.5.1). The use of cytotoxic chemotherapy in doses and schedules designed to abrogate specific mechanisms of immune tolerance in order to release the full potential of an antitumor immune response is discussed. Specifically, cyclophosphamide may be used to prime the immune system by promoting the differentiation of CD4+ T helper cells and by abrogating the suppressive influence of CD4+CD25+ T regulatory (T_{reg}) cells. In the absence of T_{reg} influence, high-avidity CD8+ T cells are recruited to an antigen-specific immune response. Cyclophosphamide also facilitates the establishment of memory CD8+ T cells. Thus inclusion of cyclophosphamide in combination trials with other immune-modulatory agents is supported by both pre-clinical and clinical data as reviewed in more detail by Emens (2005) and in the Investigator's Brochure.

Indomethacin: Indomethacin, a nonselective COX-1/COX-2 inhibitor, is a potent inhibitor of prostaglandin synthesis and may reverse the immunosuppression induced by prostaglandin [Lapointe, 1992; Hadden, 1994]. Numerous experimental, epidemiologic, and clinical studies suggest that non-steroidal anti-inflammatory drugs, including indomethacin, suppress cyclooxygenase and have promise as anticancer agents, particularly for chemoprevention of and as adjuvant therapy in patients with cancer [Thun, 2002; Investigator's Brochure].

Zinc with multivitamins: Subclinical zinc deficiency is common in subjects with HNSCC, perhaps related to a history of alcohol consumption [Brookes, 1981]. The importance of zinc in cellular immunity has been described and several reviews are available [Good, 1979; Keen, 1990; Blewett, 2012; Haase, 2014]. Alcohol consumption is frequently associated with nutritional deficiency, which can also result in impaired immune response [Słotwińska, 2014; Bianchini, 2012; Wintergerst, 2007]. Thus, based on these observations and the lack of any contraindication to their use, zinc-containing multivitamins have been added to the IRX-2 regimen.

Omeprazole: Omeprazole, a proton pump inhibitor, is active at preventing indomethacin-induced gastritis. It is administered with the IRX-2 regimen to decrease the likelihood of indomethacin-induced gastritis. (An alternative, therapeutically equivalent proton pump inhibitor may be substituted for omeprazole.)

1.1.9 Delivery of IRX-2

The route of administration of IRX-2 takes advantage of the normal afferent and efferent pathways of lymph node activation. Normally, lymphatics drain from an area of disease, such as a tumor bed, and antigens and other factors associated with disease migrate in the lymphatics to the regional nodes. By presenting the cytokine-containing biologic in the area of the tumor-draining lymph nodes rather than systemically, there is an opportunity to mobilize antigen presenting cells and enhance dendritic cell function as well as directly activate T cells to proliferate and become cytotoxic lymphocytes. Additionally, subcutaneous administration may be less toxic since the systemic cytokine drug concentration is much lower.

The Booster Regimen† is also designed to take advantage of the normal afferent and efferent pathways of lymph node activation discussed above. Given that the most common recurrences of oral cancer are local or in the thorax, the IRX-2 injections in the Booster Regimen† will be given by subcutaneous injection in bilateral deltoid regions, thereby being administered regionally but avoiding those areas most likely to be affected by surgery or post-operative radiation.

1.2 Nonclinical Studies with the IRX-2 Regimen

Nonclinical studies have demonstrated an effect of IRX-2 on T cells in animal models as well as in cellular assays. Details of these studies are provided in the IB.

1.3 Clinical Experience with the IRX-2 Regimen in Subjects with HNSCC

1.3.1 Phase 1 Trial

IRX 2 2004-B was a multicenter, Phase 1 trial in subjects with HNSCC designed to evaluate the clinical and laboratory safety and tolerability of the IRX-2 regimen. Results of the study are presented in the IB and have been published [Freeman, 2010]. The results indicate that the IRX-2 regimen was well tolerated in subjects with advanced stage HSNCC who had progressed after surgery and/or radiation therapy. The reported toxicities were acceptable overall and did not preclude proceeding to additional trials.

1.3.2 Phase 2 Trial

1.3.2.1 Study Design and Patient Demographics

IRX-2 2005-A was a multi-center trial entitled “A Phase 2, Open-label Trial of the Safety and Biological Effect of Pre-operative Subcutaneous IRX-2 (with Cyclophosphamide, Indomethacin, and Zinc) in Subjects with Resectable Cancer of the Head and Neck.” Results of the study are presented in the IB and have been published [Wolf, 2011; Berinstein, 2012; Whiteside, 2012] and are also summarized here.

The study objectives were to determine the safety of the IRX-2 regimen when used as neoadjuvant (preoperative) therapy in a multi-center trial and to evaluate clinical, pathological, and radiographic tumor response and disease-free survival (DFS) and overall survival (OS). Of the 27

subjects, 15 had oral cavity cancer, 8 had oropharyngeal cancer, 1 had hypopharyngeal cancer, and 3 had laryngeal cancer.

1.3.2.2 Clinical Results

1.3.2.2.1 Radiographic changes:

Changes in tumor size between baseline and immediately pre-operative, i.e. after the IRX-2 regimen, measurements were evaluable in 23 subjects. Based on measurement of the longest single tumor diameter, tumor growth or shrinkage was as follows: 4 subjects had -20% to <-10% change, 7 subjects had -10% to <0% change, 9 subjects had 0% to <10% change, 1 subject had 10% to <20% change and 2 subjects had ≥30% change in the target lesions [Wolf, 2011]. Review of the radiologic findings in relation to the pathology finding in the resection specimens, established that lymph node enlargement due to reactive hyperplasia could not be distinguished from enlargement related to tumor growth based on computed tomography (CT) or magnetic resonance imaging (MRI) scans [Wolf, 2011].

One subject underwent a fluorodeoxyglucose positron emission tomography (FDG-PET) CT scan at baseline and at completion of the IRX-2 regimen. Elevated glycolytic activity was observed in 2 lymph nodes and in the primary tumor on the baseline PET scan. At the completion of the IRX-2 regimen, there was a 75% decrease in glycolytic activity in these lesions [Wolf, 2011].

1.3.2.2.2 Disease-free and Overall Survival:

After 5 years of follow-up, 7 of the 27 subjects enrolled in this study relapsed, 3 at the primary site, 2 in the neck and 2 with distant metastases. Five subjects died of other causes. DFS at 1, 2 and 3 years respectively was 72%, 64% and 62%; median DFS has not been reached. OS at 1, 2 and 3 years respectively was 92%, 73%, and 69%; median OS has not been reached. These results for both DFS and OS appeared to be slightly superior to those observed in a comparable group of 81 historical controls, treated at the University of Michigan and matched for baseline characteristics [G. Wolf, personal data].

1.3.2.3 Safety Results

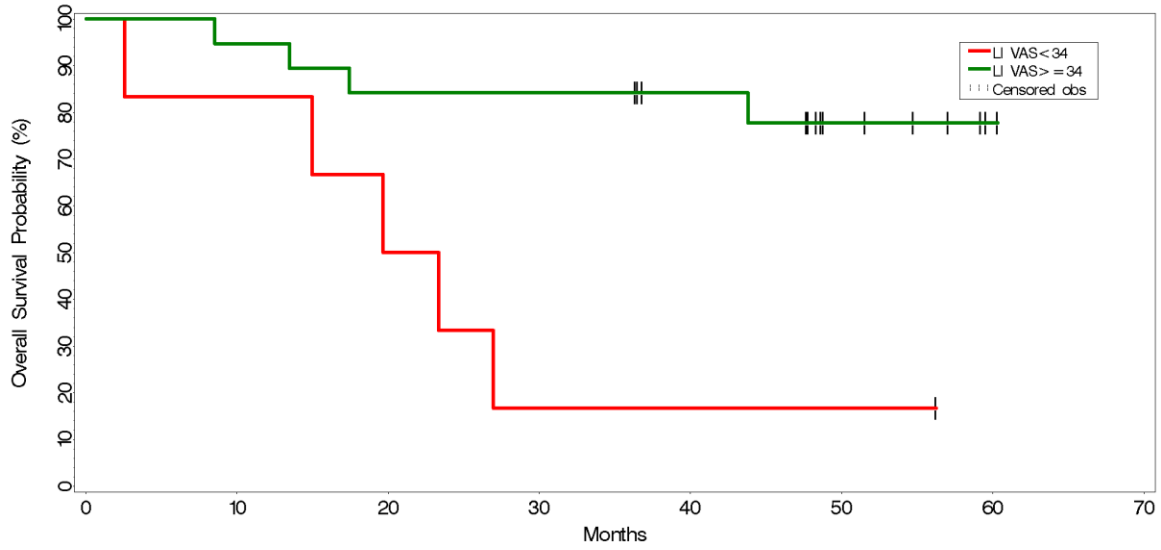
The IRX-2 regimen was tolerated with minimal toxicity. Compliance was excellent; all subjects completed the regimen and there were no unplanned delays in surgery as a result of the immunotherapy regimen. There were no reports from investigators of any unanticipated or unusual delays or difficulties in performing the planned resections or reconstructions or during the postoperative recovery. Twenty-six subjects underwent surgical resection, 9 patients received post-operative radiation therapy and 10 subjects received post-operative chemoradiation.

The most common adverse events (AEs) were headache (30%), injection site pain (22%), nausea 22%), constipation (15%), dizziness (15%), fatigue (11%), aspiration pneumonia (11%), anemia (11%) and myalgia (7%). All were grade 1-2 except for the aspiration pneumonias (one Grade 3, one Grade 4) and all resolved without sequelae. There were only minor (grade 1) alterations in post-treatment laboratory values. Eight serious adverse events (SAEs) in 7 subjects were reported during treatment and the 30-day post-operative period: aspiration pneumonia (n = 3), respiratory tract infection, asthma exacerbation, wound infection, neck abscess and alcohol withdrawal (n = 1 each); only the postoperative wound infection was considered related to the study treatment [Wolf, 2011]. During treatment, several subjects noted decreased pain or improved swallowing and no significant progressive symptoms were noted.

1.3.2.4 Immunologic Results

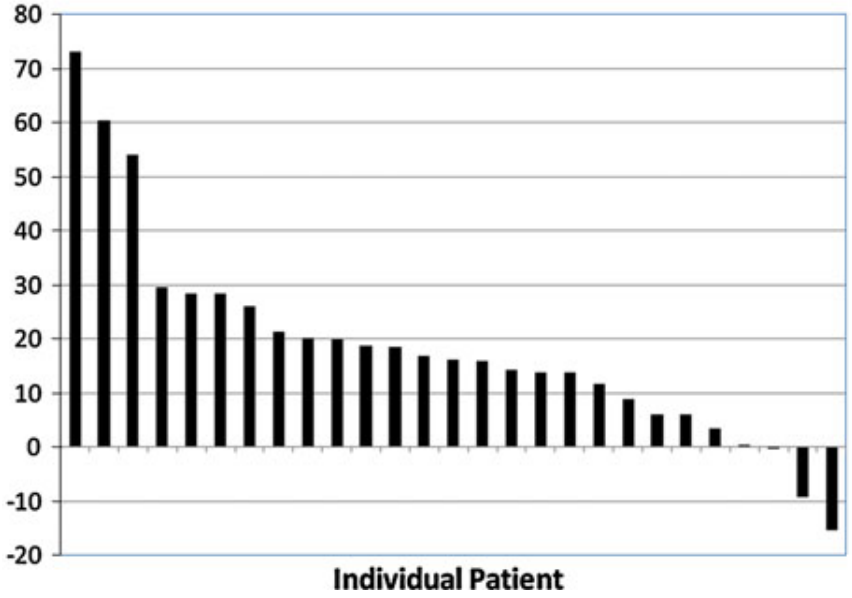
Pretreatment tumor biopsies and the tumor surgical specimens from 25 patients were characterized by three pathologists for lymphocyte infiltration, necrosis and fibrosis using both hematoxylin and eosin stains and immunohistochemistry [Berinstein, 2012]. Kaplan-Meier estimates of overall survival are displayed in Figure 1 as a function of high and low lymphocyte infiltration in the surgical specimens after the IRX-2 immunotherapy. Eighteen subjects were in the better survival group and 7 were in the inferior survival group; the survival curves are significantly different ($p < 0.05$) [Berinstein, 2012].

Figure 1 Overall Survival by High and Low Lymphocyte Infiltration in the Surgical Resection Specimen (Study IRX-2 2005-A)



When lymphocyte infiltration in the pretreatment biopsies was compared to that in the resected surgical specimen, increases in lymphocyte infiltration were seen as shown in Figure 2 (change in mean lymphocyte infiltration from the biopsy to the surgical specimen is shown on the y-axis) [Berinstein, 2012].

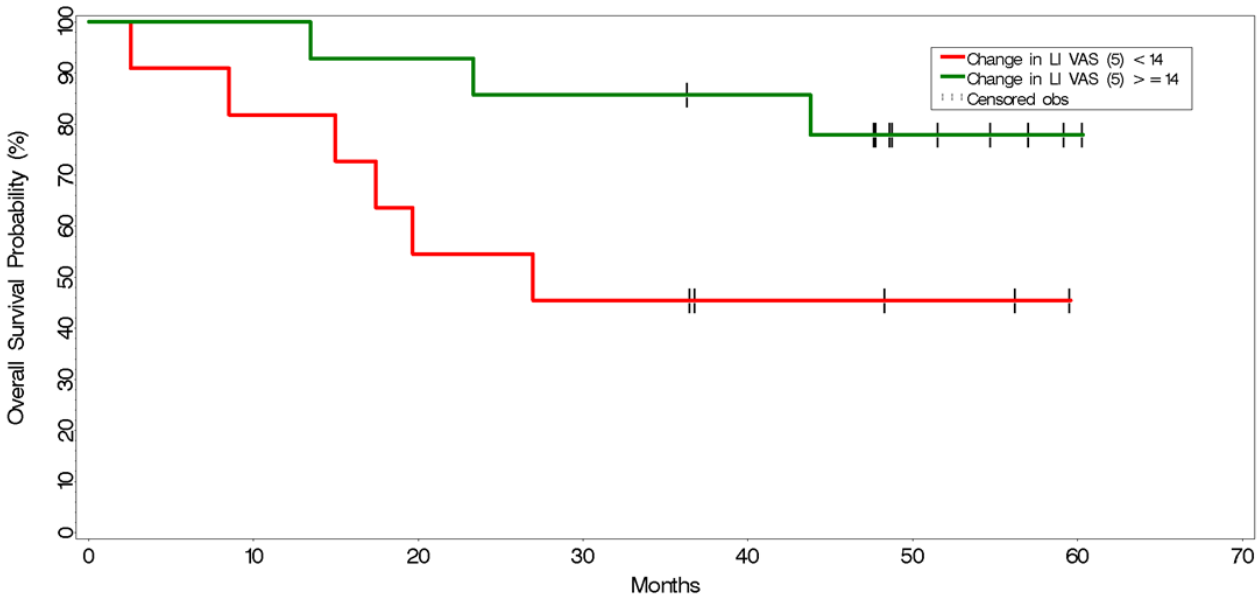
Figure 2 Lymphocyte Infiltration (Study IRX-2 2005-A)



In addition, subjects in whom the greatest increase in tumor lymphocyte infiltration from biopsy to surgery (n=14) was observed had a trend toward superior survival compared to subjects in whom no or more limited change was observed (n=11) as shown in

Figure 3 (p = 0.10) (IRX Therapeutics, unpublished observations).

Figure 3 Overall Survival by Change in Lymphocyte Infiltration from Biopsy to Resection Specimen (Study IRX-2 2005-A)



Peripheral blood lymphocyte subsets also were monitored pre- and post-treatment with the IRX-2 regimen to evaluate changes induced by the IRX-2 regimen (summarized in Section 1.1.7 above and in the IB). The IRX-2 regimen-mediated reductions in B and NKT cell numbers in the blood suggested a redistribution of these cells to tissues while the unchanged numbers of T_{regs} after IRX-2 therapy indicated that IRX-2 does not expand this compartment, potentially benefiting anti-tumor immune responses [Whiteside, 2012].

1.3.2.5 Time to Surgery

Among the 27 subjects in this trial, the mean time from diagnostic biopsy to surgical resection was 37 (range 22-63) days. Only one subject (4%) was operated upon >60 days from the date of

diagnostic biopsy. In 81 contemporary control patients treated at the University of Michigan matched to the 27 Phase 2 study patients, controlling for age, sex, tumor site and tumor stage (3:1 match), the mean time from diagnostic biopsy to surgical resection was 24 (range 5-115) days and 5 control patients (6%) underwent surgery >60 days from date of diagnosis (G. Wolf, unpublished data). Thus the 21 day neoadjuvant IRX-2 Regimen resulted in a prolongation of the time from biopsy to surgery of only approximately 13 days when compared to University of Michigan controls and the percent of patients with a time of >60 days was comparable. The IRX Medical Advisory Board considered such delay to be acceptable.

Among the 27 subjects in this Phase 2 trial, the mean time from the date of informed consent to cyclophosphamide dose was 6.6 $\pm$5.3 (range 1-23, median 4.0) days. The mean time from the cyclophosphamide dose to surgery was 24 $\pm$3 days (range 19-31, median 25 days). Overall, the mean time from informed consent to surgery in this study was 31 (range 22-47, median 32) days (IRX Therapeutics, unpublished observations). Also, there were no unplanned delays in surgery as a result of the immunotherapy regimen. Thus, the requirement of proceeding to surgery within 35 days following randomization is consistent with our prior experience.

2 STUDY OBJECTIVES

The purpose of the study is to evaluate neoadjuvant and adjuvant† IRX-2 therapy (Regimen 1) in a randomized setting compared to a regimen which does not include IRX-2 (Regimen 2).

2.1 Primary Objective

The primary objective is to determine if the event-free survival (EFS, defined in Section 6.1.1) of subjects treated with Regimen 1 is longer than for subjects treated with Regimen 2.

2.2 Secondary Objectives

Secondary objectives are:

1. to determine if OS of subjects treated with Regimen 1 is longer than for subjects treated with Regimen 2
2. to compare the safety of each Regimen
3. to compare the feasibility of each Booster Regimen†

2.3 Exploratory Objectives

To determine and compare between the Regimens:

1. changes in tumor size from baseline to surgery measured by CT scans (MRI also acceptable, so long as the same modality is used for baseline and pre-surgery scans)
2. changes from baseline to surgery in functional imaging as estimated by PET scan
3. lymphocyte infiltrates in the pre-treatment tumor biopsy, the surgical specimen and changes between these two samples. These data will be analyzed to seek any baseline characteristics that are correlated with differences in outcome between the Regimens
4. surgical pathology, including tumor characteristics (depth of invasion, perineural invasion, pattern of invasion, extent of necrosis), tumor margins and lymph node involvement
5. prognostic and predictive factors and clinical-pathologic-immunologic correlates, including, for example, nutritional status (body mass index, albumin), absolute lymphocyte count, lymphocyte subsets and histological differences in the surgical specimen, gene expression profiles with EFS, recurrence, second primary tumors, and patterns of disease recurrence
6. HPV status (p16 protein expression) and any relationship between tumor baseline p16 protein expression and differences in outcome between the Regimens
7. the peripheral T cell receptor profile prior to and post treatment during the first year of the trial
8. RNA expression profiling of immune-inflammatory markers

3 INVESTIGATIONAL PLAN

3.1 Study Design

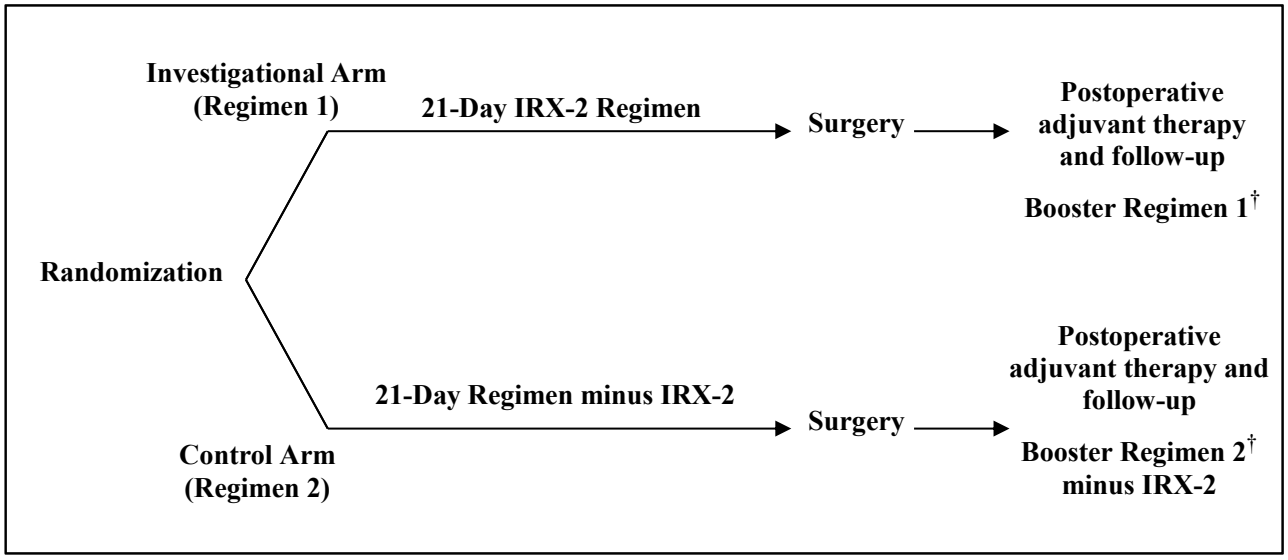
This is a prospectively randomized, open-label, multi-center, multi-national, Phase 2b clinical trial intended for patients with Stage II, III or IVA untreated SCC of the oral cavity who are candidates for resection with curative intent. Subjects will be randomized 2:1 in favor of Regimen 1 as described in Section 5.2.2.

The interventions to be used for the subjects randomized to these arms are:

- **Regimen 1:** Subjects will receive the neoadjuvant IRX-2 regimen prior to surgery, and then IRX-2 Booster Regimens† as clinically feasible every 3, 6, 9 and months 12 (-14 to +28 days) after surgical resection as detailed in Section 5.2.8 below.
- **Regimen 2:** Subjects will receive the IRX-2 regimen **minus the IRX-2 biologic** prior to surgery, and the IRX-2 Booster Regimen† **minus the IRX-2 biologic** as clinically feasible every 3, 6, 9, and 12 months 12 (-14 to +28 days) after surgical resection as detailed in Section 5.2.8 below.
- All randomized subjects are to receive standard of care surgery and postoperative adjuvant radiation or chemoradiation therapy, as appropriate. These non-investigational, standard of care therapies and related evaluations and supportive care are reasonable and medically necessary for the clinical management of the subject.

The flow chart presented in Figure 4 illustrates the study design of both arms.

Figure 4 Flow Chart of Study Design



3.1.1 Rationale for Study Design

The rationale for the study drug, IRX-2, has been discussed above in Sections 1.1.4-1.1.7, for the Booster Regimen† in Section 1.1.5 and for the other components of the IRX-2 regimen, cyclophosphamide, indomethacin, zinc with multivitamins and omeprazole, in Section 1.1.8.

In this randomized open label Phase 2 study, one study arm will receive the complete IRX-2 neoadjuvant and adjuvant booster regimens†. Many options for the therapy to be received by the control group were considered, ranging all the way from no therapy at all (go directly to surgery, the current standard of care in most institutions) to a double-blind study with placebo instead of IRX-2 injections. It was considered, however, that offering all patients the potential benefits of the components of the IRX-2 Regimen other than the IRX-2 injections would make the study more acceptable to both potential subjects and investigators. In addition, this design alleviates the difficulty of analysis of a study in which the time of the most important therapeutic intervention, i.e. surgical resection of the tumor, differs between the two study arms. The 2:1 randomization scheme was adopted to make the study more acceptable to both potential subjects and investigators. There was concern among potential study investigators that placebo injections would not be acceptable to many investigators or potential subjects. Thus a "middle ground" study design was chosen, i.e. the control arm is to receive all components of the IRX-2 regimen but no injections of study drug IRX-2, so the final analysis will focus primarily on the contribution of the investigational drug, IRX-2 to efficacy and safety.

This design, with awareness of both subject and investigator of the treatment arm, does introduce some possibility of bias. This will be minimized by close monitoring of the study as discussed in the following Section. Also, OS an important secondary endpoint will be less subject to bias than the primary endpoint, EFS.

3.1.2 Rationale for Endpoints

EFS and OS: Overall survival is generally the preferred endpoint for the evaluation of anticancer medicinal products in humans. In HNSCC, however, recurrence is in itself a clinically devastating event, requiring additional therapy, which unfortunately is likely to be associated with significant adverse events and only limited clinical benefit. Recurrence and death are closely correlated since treatment of recurrent disease is usually not curative, i.e., while recurrent HNSCCs are often responsive to chemotherapy, only a modest effect on survival has been demonstrated. Thus, median survival after recurrence is only 3 to 9 months, emphasizing the need for improvements in the initial therapy of HNSCC. Data from several meta-analyses have revealed that in this disease, EFS should be considered an acceptable surrogate endpoint for OS [Michiels, 2009]. This approach is also consistent with European Medicines Agency (EMA) standards, i.e. "prolonged progression-free or disease-free survival (PFS/DFS) are relevant measures of patient benefit, but the magnitude of the treatment effect should be sufficiently large to outbalance toxicity and tolerability problems" (EMA/CHMP/205/95/Rev.4). Using EFS as the primary study endpoint, and OS as an important secondary endpoint, will also enable an early decision to be made regarding the design and initiation of a larger, Phase 3 registration trial.

Safety of IRX-2: No significant safety concerns have been recognized in prior Phase 1 and Phase 2a clinical trials of the IRX-2 regimen. Nevertheless, both trials were relatively small trials without a comparator arm. Therefore, in this trial the safety of IRX-2 will be determined by comparison of AEs, surgical results, study discontinuation, etc., between the two study arms.

Feasibility of Booster Regimen†: The IRX-2 Booster Regimen has not been previously studied in clinical trials. Since both Booster Regimens are of shorter duration than the neoadjuvant regimen no safety concerns are anticipated. Nevertheless, subjects receiving the Booster Regimens will be post-operative and many will also have received adjuvant radiation or chemoradiation. Thus, their ability to receive and tolerate even a shorter IRX-2 regimen will be specifically evaluated in this study (See Section 5.2.8).

3.1.3 Benefit/Risk Assessment and Study Monitoring

Patients with Stage II-IVa SCC of the oral cavity face significant risks associated with their tumor, surgery, reconstruction, adjuvant radiation and chemotherapy as well as with frequently associated co-morbidities including smoking, alcohol, nutritional deficiency and immune suppression. This was seen in the prior study of the IRX-2 Regimen (see Section 1.3.2.3) and the IB), i.e. only one of eight SAEs, a post-operative wound infection, was considered possibly related to the study regimen. At this stage of development, the benefit of the IRX-2 regimen remains to be established, but given the rationale for the regimen and the prior experience, the potential benefit seems likely to exceed the associated risks, especially compared to the risks already faced by eligible patients, or, at the least, not to increase the risks already faced by eligible patients.

One risk specifically considered in the design of this study, however, was whether trial participants would be exposed to any risk by delay in time to surgery. The results of the multicenter Phase 2a study that preceded and led to this trial are reassuring in this regard, i.e. 26 of the 27 patients received the surgery originally intended and there were no unplanned delays in surgery (see Section 1.3.2.5).

Other subject safety issues (risks) will be assessed and, in so far as possible, mitigated by monitoring of the ongoing study by the Principal Investigator (see Sections 3.4 and 3.7.2), the Medical Monitors of the CRO and Sponsor (Section 3.7.1) and a DSMB (Section 3.8). The DSMB will consist of physicians and a statistician who are not otherwise involved in the trial and will specifically monitor the study for delay in definitive surgery (as described in Section 8.5 below), for adherence to protocol and international guidelines for adjuvant radiation and chemoradiation in each protocol arm and for the safety and feasibility of the Booster Regimens† in this study. At the discretion of the Sponsor an Interim Analysis (IA) may be preformed as specified in Protocol Section 9.5.

3.1.4 Estimated Duration of Study

As discussed in more detail in Section 9, the number of EFS events required for the assessment of the primary endpoint is 51. The required number of deaths for the assessment of the OS endpoint is also 51.

Protocol mandated follow-up will end 4 years after randomization of the last subject, i.e. in Q1 2022. Subjects should be on site for all Year 1 and Year 2 follow up visits (i.e., Y1M3, Y1M6, Y1M9, Y1M12, Y2M3, Y2M6, Y2M9 and Y2M12). Lab samples will be collected in Year 1 only (see Table 5 for required assessments). All follow up visits during Y3 and Y4 post-surgery will be performed via telephone calls to collect survival information. Subjects should receive yearly tumor imaging and be followed in the office per standard practice at each facility for physical examinations, etc. Any indication of progression or recurrence which is noted at a standard of care visit should be reported in the Recurrence case report form for this study.

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

To be enrolled in the study, subjects must meet the following inclusion criteria.

1. Pathologically confirmed clinical Stage II, III or IVA squamous cell cancer of the oral cavity (excluding lip). Subjects must be staged using AJCC Cancer Staging Manual Edition 7.0 (Appendix 1 and Appendix 2).
2. Disease is surgically resectable with curative intent
3. Hematological function: hemoglobin >9 g/dL; lymphocyte count >0.50 × 10^9/L; neutrophil count >1.50 × 10^9/L; platelet count >100 × 10^9/L
4. Hepatic function: serum albumin >3.0 g/dL; aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) <3× the upper limits of normal (ULN); alkaline phosphatase <2× ULN
5. Prothrombin time (PT) and partial thromboplastin time (PTT) <1.4× ULN
6. Calculated creatinine clearance >50 mL/min (Appendix 4)
7. At least 18 years of age
8. Willing and able to give informed consent and adhere to protocol therapy
9. Karnofsky performance status (KPS) is ≥70%
10. From the date of screening until 1 year after the last dose of study regimen, females of childbearing potential (not surgically sterile or less than 12 months post-menopausal) must be able and willing to use:
    - One highly effective form of pregnancy prevention defined as:
        - male condoms with spermicide,
        - intrauterine device (IUD) (hormonal or nonhormonal),
        - intrauterine hormone-releasing system (IUS),
        - oral contraception
        - or complete abstinence (defined as complete avoidance of heterosexual intercourse). Subjects who choose complete abstinence must continue to have pregnancy tests throughout the study. Alternate methods of contraception must be discussed in the event the subject chooses to forego complete abstinence.
    - Or two less effective methods of pregnancy prevention defined as:
        - male condoms without spermicide,
        - diaphragm with spermicide,
        - cervical cap with spermicide,
        - vaginal sponge,
        - female condom [not to be used with a male condom]

Males with a partner of childbearing potential must use condoms with spermicide from the date of screening to 1 year after their last dose of study regimen.

11. Negative urine/serum pregnancy test (females only), if applicable

3.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Prior surgery, radiation therapy, or chemotherapy other than biopsy or emergency procedure required for supportive care of this oral cavity cancer.
2. Any medical contraindications or previous therapy that would preclude treatment with either IRX-2 Regimen 1 or 2 or the surgery, reconstruction or adjuvant therapy required to treat the oral tumor appropriately.
    a. Live vaccines should ideally not be administered to any patients undergoing treatment with chemotherapy or immunotherapy, but if need be, they should be administered >4 months prior to the initiation of treatment or >4 months after the completion of all treatment.
    b. Inactivated vaccines should precede the initiation of any study regimen and/or standard adjuvant therapy by at least 2 weeks, but preferably 4 weeks or longer.
3. Clinical status of either subject or tumor such that administration of 21 day neoadjuvant IRX-2 Regimen 1 or 2 before surgery would be medically inappropriate.
4. Tumor of the oropharynx
5. Tumor involvement of the following sites or any of these signs or symptoms likely to be associated with T4b cancer:
    a. involvement of pterygopalatine fossa, maxillary sinus, or facial skin;
    b. gross extension of tumor to the skull base;
    c. pterygoid plate erosion;
    d. sphenoid bone or foramen ovale involvement;
    e. direct extension to involve prevertebral fascia;
    f. extension to superior nasopharynx or Eustachian tube;
    g. direct extension into the neck with involvement of the deep neck musculature (neck node fixation);
    h. suspected invasion (encasement) of the common or internal carotid arteries. Encasement will be assessed radiographically and will be defined as tumor surrounding the carotid artery 270^{o} or greater;
    i. direct extension of neck disease to involve the external skin;
    j. direct extension to mediastinal structures;
    k. regional metastases to the supraclavicular neck (low level VB and IVB)
6. Any investigational agent within the previous 30 days.
7. Daily administration of systemic immunosuppressive therapy or corticosteroids (except in physiological doses for hormone deficiency) during the previous 30 days.
8. Chronic anticoagulation, not including aspirin, but including heparins, warfarin, oral anticoagulation or other platelet function inhibitors, that can not, in the documented opinion of the investigator, safely be interrupted from at least 2 days prior to the initiation of the study regimen until after surgical resection of the tumor.

9. Symptomatic cardiopulmonary disease (including congestive heart failure and hypertension), coronary artery disease, serious arrhythmia or chronic lung disease. Patients with these conditions who are stable with relatively minor symptoms and who are appropriate candidates for surgical treatment of their tumor need not be excluded.
10. Myocardial infarction within the last 3 months.
11. Evidence of distant metastases (M1 disease) or other concurrent primary malignancy.
12. Known infection with hepatitis B, hepatitis C, or HIV.
13. Signs or symptoms of systemic infection (use of antibiotics to treat superficial infection or contamination of tumor shall not, by itself, be considered evidence of infection).
14. Clinically significant gastritis or peptic ulcer disease that would contraindicate the use of indomethacin.
15. Stroke or other symptoms of cerebral vascular insufficiency within the last 3 months.
16. Allergy to ciprofloxacin (or other quinolones), acetylsalicylic acid, or indomethacin.
17. Previous diagnosis of invasive cancer from which the individual is NOT disease-free AND that has required treatment within the past 5 years, except for superficial skin, cervical cancer in-situ, well-differentiated thyroid or early stage prostate or bladder cancer (i.e., treatment with curative intent and long term disease-free expectations).
18. Prior axillary dissection.
19. Breastfeeding women.

3.3 Tumor Staging

Initial tumor staging will be performed using National Comprehensive Cancer Network (NCCN) Surgical Guidelines prior to randomization and will be based on clinical and endoscopic criteria supplemented by thin section, high resolution CT or MRI of the neck and chest (inclusive of the adrenals). The TNM staging and stage grouping is based on American Joint Committee on Cancer (AJCC) clinical staging criteria Edition 7.0 (Appendix 1 and Appendix 2).

All subjects must have pre-treatment imaging with thin-slice CT or MRI of the neck and chest with contrast as necessary to include assessment of lymph nodes, deep neck muscles, nasopharynx, retropharyngeal space, mandible, and skull base. Supplemental information obtained through CT or MRI imaging for staging of the neck will be based on axial scans using ≤5 mm slices. Contrast enhancement will be used unless there are contraindications to its use. Nodes identified will be considered positive for staging purposes if any of the following criteria are met:

1. Size is >1.5 cm for one or more jugular digastric nodes;
2. Evidence of central necrosis in a node; or
3. Multiple nodes identified that each separately measure >1.0 cm.

The clinical level of lymph nodes (Level I-VI) identified by CT or MRI imaging will be documented. Subjects with a N0 neck by clinical examination that have CT or MRI imaging evidence of regional lymphadenopathy will be considered N+ for the purposes of staging and inclusion in the study.

All subjects will undergo pre-treatment endoscopic evaluation of tumor extent that must include direct, indirect, or fiber-optic laryngoscopy, bidirectional tumor measurements and adequate tumor biopsy.

PET scans will be obtained per institutional practice and for all those subjects to be assessed for Key Exploratory Endpoint #2, (changes from baseline to surgery in functional imaging).

3.4 Assessment of Surgical Resectability

The head and neck surgeon must consider the disease to be resectable for cure in order for the subject to be eligible for the study. Clinical and radiographic assessments will be used to determine whether the tumor is unresectable at either the primary site or in the neck. **Any uncertainty should be discussed via phone or email with the Study PI, Dr. Wolf.**

Ineligible subjects are those subjects for whom surgical excision is unlikely to result in negative margins including subjects with:

1. involvement of pterygopalatine fossa, maxillary sinus, or facial skin;
2. gross extension of tumor to the skull base (ie, T4b);
3. pterygoid plate erosion;
4. sphenoid bone or foramen ovale involvement;
5. direct extension to involve prevertebral fascia;
6. extension to superior nasopharynx or Eustachian tube;
7. direct extension into the neck with involvement of the deep neck musculature (neck node fixation);
8. suspected invasion (encasement) of the common or internal carotid arteries (T4b). Encasement will be assessed radiographically and will be defined as tumor surrounding the carotid artery 270° or greater;
9. direct extension of disease to involve the external skin;
10. direct extension to mediastinal structures; or
11. regional metastases to the supraclavicular neck (low level VB and IV B).

3.5 Termination of Study Treatment

The investigator can stop the study treatment Regimen due to an allergic or hypersensitivity reaction to the study drug, an SAE or clinically significant AE or laboratory abnormality, withdrawal of consent or for protocol noncompliance. If a subject is discontinued from the study due to an AE or SAE, the investigator should notify the designated CRO within 24 hours of the event. Any clinically significant AEs or SAEs leading to premature termination of a study treatment regimen are to be followed until stability or resolution.

Regardless of the reason for study termination, the investigator must complete the Study Disposition and Treatment Termination in the Case Report Form (CRF), specifying the reason. Subjects who discontinue study treatment should continue follow-up visits and be monitored for recurrence and survival, unless the subject specifically withdraws consent for follow-up.

NOTE: Subjects may experience changes in primary tumor or regional lymph nodes during treatment with the IRX-2 regimen, including inflammation, necrosis, or change in consistency. These changes should not be mistaken for tumor progression prior to surgery.

All treatment of all subjects will end after the last planned Booster Regimen†, approximately 12 months after surgery. Subjects will be followed for protocol-specified follow-up for 4 years after randomization but in-person follow up visits only need to be performed during Year 1 and Year 2 post-surgery (Y1M3, Y1M6, Y1M9, Y1M12, Y2M3, Y2M6, Y2M9, and Y2M12). Year 3-4 follow-up visits should be performed via telephone calls to collect survival information (see also Section 5.2.9). During years 3-4, subjects should receive yearly tumor imaging and be followed in the office per standard practice at each facility for physical examinations, etc. Any indication of progression or recurrence which is noted at a standard of care visit should be reported in the Recurrence case report form for this study. Subjects who withdraw prematurely from study-related treatment will be encouraged to continue protocol specified follow-up. Subjects who refuse protocol-specified follow-up will be encouraged to permit continued follow-up for survival. All randomized subjects will be analyzed and no subjects will be replaced.

3.6 Withdrawal of Consent

Any subject may terminate participation in the study at any time but every effort should be made to continue with study evaluations for tumor recurrence and survival, even if a subject declines further study treatment. If a subject elects to discontinue study participation at any time for safety, medical or personal reasons, the investigator should make a reasonable effort to determine the reason for the subject's withdrawal and document the reason on the CRFs.

3.7 Medical Monitoring

3.7.1 Medical Monitors

Medical Monitors are physicians trained in the conduct of clinical trials who are available to the clinical investigators for discussion of questions regarding the inclusion/exclusion criteria and any other medical issues that may arise. Medical Monitors will be designated by the Sponsor, IRX Therapeutics.

3.7.2 Principal Investigator(s)

The Study Principal Investigator or his designee should be contacted to discuss questions related to surgical resectability or operative details.

Principal Investigator:

Gregory T. Wolf, MD
University of Michigan
Otolaryngology Head and Neck Surgery
1500 E. Medical Center Drive
Ann Arbor, MI 48109
Phone: (734) 936-9178
Facsimile: (734) 936-9625
Email: gregwolf@med.umich.edu

3.8 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to monitor the conduct of the study as well as safety data. The DSMB will consist of physicians and a statistician who are not otherwise involved in the trial. The DSMB will meet via teleconference or in person over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise. The DSMB will monitor the study for delay in definitive surgery as described in Section 8.5. Detailed information regarding standard of care adjuvant therapy for subjects in each arm will be reviewed. Additional details of DSMB procedures and communication with Investigators and the Sponsor will be described in a separate Charter.

4 STUDY TREATMENTS

4.1 Study Design and Randomization

Subjects who meet all eligibility criteria will be randomized 2:1 to either Regimen 1 or Regimen 2 and treated for 21 days prior to surgery and then postoperatively with a Booster Regimen† given every 3 months for 1 year (a total of 4 times as detailed in Section 5.2.8 below).

- **Regimen 1**: IRX-2 Regimen with cyclophosphamide, indomethacin, zinc-containing multivitamins, omeprazole and IRX-2 as neoadjuvant and adjuvant† therapy as shown in Section 4.2.
- **Regimen 2**: Regimen 1 with cyclophosphamide, indomethacin, zinc-containing multivitamins, omeprazole but **without IRX-2** as neoadjuvant and adjuvant† therapy as shown in Section 4.3.

4.2 Regimen 1

The Neoadjuvant IRX-2 Regimen is a 21-day pre-operative regimen of IV cyclophosphamide on Day 1, oral indomethacin, zinc-containing multivitamins and omeprazole on Days 1-21, and subcutaneous IRX-2 injections in bilateral mastoid insertion regions for 10 days, between Days 4 and Day 21. **The last injection must be at least 48 hours prior to surgery.**

In jurisdictions where approved, subjects may have a visiting nurse or other qualified medical personnel come to their homes to administer study drug injections. Other properly trained individuals may administer study drug for study subjects at mutually acceptable locations if approved by the Medical Monitor and the investigation site. If the nurse or other qualified medical personnel receives information about an AE, she/he will document the event and notify Study site personnel.

4.2.1 IRX-2 Booster Regimen†

The IRX-2 Booster Regimen is a 10-day regimen, consisting of IV cyclophosphamide on Day 1, oral indomethacin, zinc-containing multivitamins and omeprazole on Days 1-10, and subcutaneous IRX-2 injections in bilateral deltoid regions for 5 days, between Days 4 and Day 10. Booster Regimens are to be administered as clinically feasible 3, 6, 9 and 12 months (-14 days to +28 days) after surgical resection as detailed in Section 5.2.8 below. Any Booster injection which cannot be given during the specified timeframe should be omitted and the next scheduled Booster Regimen should be administered subsequently at the appropriate designated interval after surgical resection. Missed Booster regimens must not be given at a later date.

The quarterly Booster Regimens must not be initiated until after completion and recovery from adjuvant radiation or chemoradiation as determined by the investigator. The investigator's determination of adequate recovery should be based review of any ongoing adverse events, and the overall clinical status of the subject as determined by the Investigator. Any uncertainty should be discussed with the Medical Monitor.

In jurisdictions where approved, subjects may have a visiting nurse or other qualified medical personnel come to their homes to administer any or all Booster study drug injections as described

above. Other properly trained individuals may administer study drug for study subjects at mutually acceptable locations if approved by the Medical Monitors and the investigation site PI.

The Neoadjuvant and Booster Regimens† are shown in Table 1 and Table 2: respectively:

Table 1: IRX-2 Neoadjuvant Regimen

Agent	Dose	Route of Administration	Treatment Days
Cyclophosphamide	300 mg/m^2	IV	1
IRX-2	230 units daily (Bilateral injections of 115 units)	Subcutaneous at or near the mastoid insertion of right and left sternocleidomastoid muscles	Any 10 days between Days 4 and 21*
*Indomethacin	25 mg TID	Oral	1-21
**Zinc-containing multivitamins	1 tablet containing 15-30 mg of zinc	Oral	1-21
**Omeprazole	20 mg daily	Oral	1-21

*** The last IRX-2 injection and oral indomethacin must be at least 48 hours prior to surgery.**

****Subjects should not make up the missed doses of these medications. See Section 4.4.4 for guidance on administration of all oral medications.**

Table 2 IRX-2 Booster Regimen†

Agent	Dose	Route of Administration	Treatment Days
Cyclophosphamide	300 mg/m^2	IV	1 dose on Day 1 every 3 months for 1 year
IRX-2	230 units daily (Bilateral injections of 115 units)	Subcutaneous into bilateral deltoid areas	Every 3 months Any 5 days between Days 4 and 10
*Indomethacin	25 mg TID	Oral	Every 3 months Days 1-10
*Zinc-containing multivitamins	1 tablet containing 15-30 mg of zinc	Oral	Every 3 months Days 1-10
*Omeprazole	20 mg daily	Oral	Every 3 months Days 1-10

***Subjects should not make up the missed doses of these medications. See Section 4.4.4 for guidance on administration of all oral medications.**

4.3 Regimen 2

4.3.1 Description of Regimen 2

The Neoadjuvant Control Regimen is a 21-day pre-operative regimen of IV cyclophosphamide on Day 1 and oral indomethacin, zinc-containing multivitamins and omeprazole on Days 1-21 as shown in Table 3:

The Control Booster Regimen† is a 10-day regimen consisting of IV cyclophosphamide on Day 1, oral indomethacin, zinc-containing multivitamins and omeprazole on Days 1-10, administered as clinically feasible every 3, 6, 9 and 12 months (-14 days to + 28 days), after surgical resection as detailed in Table 4 below.

Table 3 IRX-2 Neoadjuvant Control Regimen

Agent	Dose	Route of Administration	Treatment Days
Cyclophosphamide	300 mg/m^2	IV	1
*Indomethacin	25 mg TID	Oral	1-21
*Zinc-containing multivitamins	1 tablet containing 15-30 mg of zinc	Oral	1-21
*Omeprazole	20 mg daily	Oral	1-21

*** Subjects should not make up the missed doses of these medications. See Section 4.4.4 for guidance on administration of all oral medications.**

Table 4 IRX-2 Booster Control Regimen†

Agent	Dose	Route of Administration	Treatment Days
Cyclophosphamide	300 mg/m^2	IV	1 dose on Day 1 every 3 months for 1 year
*Indomethacin	25 mg TID	Oral	Every 3 months Days 1-10
*Zinc-containing multivitamins	1 tablet containing 15-30 mg of zinc	Oral	Every 3 months Days 1-10
*Omeprazole	20 mg daily	Oral	Every 3 months Days 1-10

*** Subjects should not make up the missed doses of these medications. See Section 4.4.4 for guidance on administration of all oral medications.**

4.4 Regimen Medications

4.4.1 IRX-2

IRX-2 is supplied as a pale yellow, sterile liquid for subcutaneous injection in 2.0 mL single-dose vials. All immediate study supply containers will be appropriately labeled to identify study number, kit numbers, lot number, and product identity. Kit and lot numbers of IRX-2 will be recorded in the CRF. Study syringes for subcutaneous IRX-2 administration will be disposed of in accordance with biosafety procedures. IRX-2 injections must be discontinued at least 48 hours prior to surgery.

4.4.2 IRX-2 Storage

IRX-2 must be stored in a secure area and maintained under labeled storage conditions at a range of −15ºC to –50º C.

4.4.3 Supply of Other Medications

Cyclophosphamide will be either purchased by the pharmacy of the study site and reimbursed by the Sponsor or directly supplied by the Sponsor. The Sponsor will supply indomethacin, zinc (with multivitamins) and omeprazole to study institutions. (An alternative, therapeutically equivalent proton pump inhibitor may be substituted by the subject or investigator for omeprazole.)

4.4.4 Administration of Other Medications

Intravenous administration of cyclophosphamide preferably should be administered into the tubing of an open i.v. infusion. Care should be taken that extravasation does not take place, however, should it occur, treat per manufacturer instructions.

A suggested antiemetic regimen would include a serotonin (5-HT3) antagonist and lorazepam. Corticosteroids are not needed because this dose of cyclophosphamide is associated with minimal nausea. Corticosteroid administration also may inhibit the intended stimulation of an anti-tumor immune response.

Administration of all oral medications (indomethacin, zinc containing multivitamins and omeprazole) should be limited to 21 days in the Neoadjuvant Regimen and 10 days in the Booster regimens[†], i.e. medication days should not be added to make up for missed days of medications, although omeprazole may be continued as clinically indicated.

Indomethacin and IRX-2 injections must be discontinued at least 48 hours prior to surgery.

For further guidance on the administration of all other drugs see the appropriate SmPC/Package Inserts.

4.5 Method of Assigning Subject Numbers

After a subject has signed the informed consent form, the investigator will use an integrated web and telephone interactive recognition system (IxRS) to have a subject number assigned to that subject. Subjects who withdraw from the study after being assigned a subject number will retain that number.

4.6 Treatment Compliance

The investigator, study personnel or other trained individuals will administer IRX-2 injections to ensure treatment compliance. Subjects should be asked each day that they are seen about compliance with oral medications and compliance (or lack thereof) documented in the clinical record.

4.7 Prohibited, Prior and Concomitant Treatments

Subjects in both Regimen 1 and Regimen 2, from randomization to surgery and during Booster Regimens[†], should **not** take aspirin (except for low-dose aspirin, e.g. 81 mg), corticosteroids or other non-prescribed, non-steroidal anti-inflammatory agents. Use of corticosteroids or other immunosuppressive medications after surgery is discouraged and should be minimized.

Information on all other concomitant prescribed medications, recognized over-the-counter medications, or any changes in medications during the study from randomization to surgery will be collected. Thereafter, only information on medications given to treat a reported AE or SAE, or as anti-tumor therapy, will be collected.

5 STUDY PROCEDURES AND SCHEDULE

5.1 Study Schedule

The Schedule of Study Procedures for both Regimen 1 and Regimen 2 is outlined in Table 5. All protocol deviations will be captured and reported.

Table 5 Schedule of Events

Study Procedure	Screening[a]	Treatment Period Assessments				Booster Regimens[†] and Follow-up Assessments[d,e]				
						Year 1[c]	Year 2	Year 3 (Phone calls)	Year 4 (Phone calls)	Recurrence[e], new tumor[e], or early termination
Study Day	**-21 to -1**	**DAY 1**	**Day 15-18 (+ 3 days;or last IRX-2 dose)**	**Days 1-5 Prior to Surgery**	**Day[b] 25-30**	**3, 6, 9, and 12 months post-surgery**	**Q 3 month**	**Q 6 month**	**Q 6 month**	
Informed consent	X									
Demographics	X									
Inclusion/Exclusion	X									
Medical history	X									
Alcohol and Tobacco history	X									
Endoscopy/Tumor staging	X									X
Assessment of Surgical Resect ability Tumor Stage	X									
Randomization	X After Screening, Within 7 days prior to Day 1									
Surgical Resection[b]					X[b]					
Weight	X	X		X		X	X			X
Height	X									
Vital Signs	X	X								
Physical examination	X									X
Head/Neck Exam[d]	X	X	X	X		X	X			X
Brief physical Exam		X		X		X	X			

Study Procedure	Screening[a]	Treatment Period Assessments				Booster Regimens[†] and Follow-up Assessments[d,e]				
						Year 1[c]	Year 2	Year 3 (Phone calls)	Year 4 (Phone calls)	Recurrence[e], new tumor[e], or early termination
Study Day	**-21 to -1**	**DAY 1**	**Day 15-18 (+ 3 days;or last IRX-2 dose)**	**Days 1-5 Prior to Surgery**	**Day[b] 25-30**	**3, 6, 9, and 12 months post-surgery**	**Q 3 month**	**Q 6 month**	**Q 6 month**	
KPS	X	X	X	X		X	X			X
CT (or MRI) of primary tumor and nodal areas	X			X						X
PET scan (optional)	X			X						X
CT scan of chest (annually post Randomization)	X[a]					X	X	X	X	X
Chemistry panel, PT/PTT, Hematology	X	X[j]	X	X		X				X
Pregnancy test, if applicable	X					X[k]				X
Immunogenicity testing[p]	X			X		X				X
Tumor Biopsy	X									X[e]
Tissue samples for Exploratory Analysis per Laboratory Manual	X				X					
Blood, serum and/or tissue samples per Laboratory Manual	X			X		X				X
HPV Typing[q]					X					
Concomitant meds[l]	X	X	X	X						X
Regimen Compliance			X	X		X				X
Adverse events[m]		X	X	X	X	X				X
SAEs [n]		X	X	X	X	X				X
Survival status[o]						X	X	X	X	

	Study Drug Administration Regimen 1 and 2								
Study Day	Regimen 1 and Regimen 2			Regimen 1 Only		Booster Regimens† 3, 6, 9, and 12 months post-surgery (-14 to +28 days)			
						Booster Regimen 1 and Regimen 2		Booster Regimen 1 Only	
	-21 to -1	Day 1	Days 2-21	Any 10 Days between Days 4-21	3 Days After Last IRX-2 Dose	Day 1	Days 2-10	Any 5 Days between Days 4 and 10	Days 2-4 After Last Dose of IRX-2
Cyclophosphamide		X				X			
Indomethacin [f,g], omeprazole, zinc with multivitamins		X	X			X	X		
IRX-2 (Regimen 1 only)[i]				X				X	
	Injection Site Checks – Regimen 1 only								
Clinic or Visiting nurse				X[h]				X[h]	
Phone					X[m]				X[m]

Footnotes for Schedule of Events Table:

a. Subjects will be screened for eligibility up to 21 days prior to randomization. CT of chest at screening acceptable if performed within 30 days of randomization. CT of chest need not be sent for central radiology review. PET, if performed, will satisfy this requirement.
b. Surgery and subsequent assessments and interventions are to be performed on all subjects randomized (independent of arm). Surgery should be scheduled 25-30 days after randomization and **must** take place no later than 35 days after randomization. In the event that Surgery is performed on Day 21 or 22, then evaluations required on Day-15 -18 and Days 1-5 Pre-op maybe combined.
c. Booster regimens are to begin 3 months post-surgery and be given every 3 months for a total of 4 Booster treatments, i.e. at 3 , 6, 9, and 12 (-14 days to +28 days) months after surgical resection. † Any Booster injection which cannot be given during the specified timeframe should be omitted and the next scheduled booster regimen should be administered at the appropriated designated interval after surgical resection. Missed Booster injections must not be administered at a later date. The quarterly Booster Regimens must not be initiated until after completion and recovery from adjuvant radiation or chemoradiation as determined by the investigator. The investigator's determination of adequate recovery should be based on review of any ongoing adverse events and the overall clinical status of the subject. Any uncertainty should be discussed with the Medical Monitor.
d. All subjects must be assessed clinically with particular attention to primary tumor and regional nodes every 3 months during Years 1 & 2 and according to SOC at their local facility in Years 3 & 4. Protocol mandated follow-up will terminate 4 years after randomization.
e. Suspicious lesions should be biopsied. If relapse confirmed, subjects should be restaged by CT, MRI and/or PET scans to restage disease and establish patterns of relapse. Possible second malignancies should be biopsied. In the event of disease recurrence, CT or MRI and/or PET scans of primary and recurrent disease, chest and any other clinically suspected disease sites should be done to document extent and pattern of recurrent, metastatic or second primary disease.
f. Indomethacin and IRX-2 injections must be discontinued at least 48 hours prior to surgery. Administration of oral medications should be limited to 21 days, i.e. medication days should not be added to make up for missed days of medications.
g. Missed days of oral medications should not taken later by the patient. i.e. medication days should not be added to make up for missed days of medications.
h. Visiting Nurses may be used to administer IRX-2 in jurisdictions where approved. Any or all Booster injections† can be administered by Visiting Nurses in approved jurisdictions.
i. **The first and last days of IRX-2 for the Neoadjuvant Regimen must be administered at the study site**.
j. If CBC and chemistry panels are collected more than 7 days prior to Day 1, then these tests need to be repeated at Day 1. PT/PTT determinations are required at screening and pre-op only. Blood samples must be sent to the designated Central Laboratory. If more immediate results are required for eligibility or during the study required, institutional laboratories may be used for treatment decisions, but duplicate specimens must be submitted to the Central Laboratory.
k. Pregnancy tests can be done by Local laboratory prior to Booster Regimen†
l. All concomitant medications should be documented at baseline. Thereafter, only medications given to treat a reported AE or SAE, or anti-tumor therapy (adjuvant as well as treatment for recurrence or a new primary) or considered immunosupressive or anti-proliferative should be documented. All updates to baseline medications should be documented.
m. Adverse events will be collected from day of randomization until 30 days after the last dose of study regimen in the Treatment Period. Additionally AEs will be captured from the first day of each study regimen administration through 30 days after the last dose of the study regimen dosing in each of the Booster Regimens†. Any Adverse Event that the Investigator feels is related to study medication should be reported regardless of the timing of that event. All AEs

will be monitored until stability or resolution (See Section 8.0). Follow-up phone calls to assess toxicity will be made to each subject on Day 21 (or 3 days after the last dose of IRX-2 for Regimen 1). If the date of the follow-up call occurs on a weekend or holiday the call should be made on the next available business day.

n. All Serious adverse events (regardless of relatedness to study regimen) will be collected continuously from day of randomization until 30 days after the last dose of study regimen. Any Serious Adverse Event that the Investigator feels is related to study medication should be reported regardless of the timing of that event. All SAEs and will be monitored until resolution or stability. (See Section 8.0).

o. Telephone calls for survival after progression to occur every 3 months if subject is not seen in follow-up.

p. 5 mL of blood will be collected, ≥2 mL of serum will be sent to Central Laboratory and stored for immunogenicity testing against the active components of IRX-2. Samples will be collected at screening, after neoadjuvant therapy, prior to initiation of each of the Booster Regimens† and finally at 3 months after the last Booster Regimen†.

q. HPV typing can be conducted at biospy, screening or on primary tumor removal.

5.2 Study Procedures

5.2.1 Screening

The purpose and procedures of the study will be fully explained to participants. Those wishing to enroll in the study will sign a written informed consent prior to initiating any protocol specific evaluations or procedures.

The following screening evaluations are to be performed within 21 days (unless otherwise noted) prior to randomization:

- Medical history, including assessment of all entry and exclusionary criteria, demographics (age, sex, race, menstrual status, weight, height), history of present illness, history of hypersensitivity (drug allergies), general medical history, and assessment of all current symptoms including severity.
- Determination of Karnofsky performance status (Appendix 3).
- History and current use of tobacco and/or alcohol.
- Concomitant medication review.
- Detailed head and neck exam, physical exam, including vital signs (blood pressure and pulse) and detailed description of the tumor and regional lymph node areas.
- Endoscopic evaluation of tumor extent, including direct, indirect, or fiber-optic laryngoscopy.
- Clinical laboratory assessments:
    - Hematology: complete blood count (CBC), differential, platelet count, PT and PTT.
    - Serum chemistry: serum albumin, total protein, serum bilirubin, lactate dehydrogenase (LDH), ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, blood urea nitrogen (BUN), glucose, and electrolytes.
    - Calculated creatinine clearance (Appendix 4)
- Pregnancy test (serum or urine, females only) if appropriate.
- CT or MRI imaging of primary site and neck and CT scan of chest with contrast for assessment of tumor (performed within 30 days of randomization). PET, if performed, may be substituted for CT scan of chest.
- PET imaging (optional).
- Tumor biopsy (within 3 months of randomization) for confirmation of diagnosis and research specimen. The standard of care when patients are evaluated for radical tumor resection is a full thickness tissue biopsy of the primary tumor. A rebiopsy of the primary tumor should be performed if the diagnosis has been by needle biopsy, but an adequate formalin fixed, paraffin embedded biopsy from a referring institution is sufficient.
- Assessment of surgical resectability and tumor stage.
- Collect blood samples for correlative studies.

All of the above evaluations, except for the collection of blood samples for correlative studies, are reasonable and medically necessary for the direct clinical management of the patient, and thus should be accepted for reimbursement under standard of care [Martin, 2014]. All surgical procedures and evaluations during and after surgery, other than administration of the Booster Regimens†, including all assessments for relapse or second tumors are also reasonable and medically necessary for the direct clinical management of the patient.

5.2.2 Randomization

Subjects will be randomized to either Regimen 1 or Regimen 2. Randomization will be 2:1 in favor of Regimen 1. Treatments will be allocated to study subjects using minimization with a stochastic algorithm based on the range method will account for the major prognostic factors for HNSCC of the oral cavity (T and N stage) and study center to avoid imbalances in treatment allocation [Pocock, 1975. Full details of the treatment algorithm are specified in the Interactive Response Technologies (IRT) requirements document prepared by PPD (the CRO responsible for study subject randomization), but in order to avoid selection bias that might result from any foreknowledge, randomization algorithms for treatment assignment will not be disclosed to the Sponsor or Investigators. For all subjects, treatment with their assigned Regimen should begin within 7 days of randomization and surgery should be scheduled 25-30 days after randomization and **must** take place no later than 35 days after randomization.

5.2.3 Day 1

The following procedures will be completed at this visit:

- Interval history and assessment of all current symptoms (AEs) including severity.
- Karnofsky performance status.
- Record concomitant medications.
- Brief general physical examination including weight and vital signs (blood pressure and pulse).
- Head and neck examination.
- Repeat laboratory assessments if more than 7 days since screening values obtained.
    - Hematology: CBC, differential, platelet count.
    - Serum chemistry: serum albumin, total protein, serum bilirubin, LDH, ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, BUN, glucose, and electrolytes.
- Administer the following medications:
    - Infusion of cyclophosphamide, 300 mg/m^2. Steroids must not be administered as antiemetic agents since these might interfere with immunomodulation by IRX-2. Antiemetic regimen should include a serotonin (5-HT3) antagonist and lorazepam or equivalent medications.
    - Begin indomethacin (25 mg, TID) to be taken orally from Day 1 through Day 21.
    - Begin zinc with multivitamins, once daily, to be taken orally from Day 1 through Day 21.
    - Begin omeprazole, 20 mg, once daily, to be taken orally from Day 1 through Day 21.

5.2.4 Days 4 to 21 (REGIMEN 1 Dosing)

IRX-2 should be administered by subcutaneous injection over any ten days between Days 4 and 21. **The last IRX-2 injection should be at least 48 hours prior to surgery.**

- IRX-2 should be administered by subcutaneous injection at two sites:
  - At or near the mastoid insertion of the sternocleidomastoid muscle (approximately 2 cm below the mastoid process) on the RIGHT side of the neck.
  - At or near the mastoid insertion of the sternocleidomastoid muscle (approximately 2 cm below the mastoid process) on the LEFT side of the neck.
  - In the event that tumor is present in one of the designated injection sites, the IRX-2 should not be injected into or immediately adjacent to tumor, but rather submandibularly approximately 2 cm posterior to the midline inferior aspect of the mandible.
- Each subcutaneous injection will be approximately 1.0 mL of IRX-2 (corresponding to 115 units of IRX-2 per injection or 2300 units during the total regimen).
- On the first day of IRX-2 injections, subjects will be monitored for 15 minutes after the IRX-2 injections for signs or symptoms of any reaction.

For subjects receiving Regimen 1, in the event of Grade 3 or higher toxicity, please see Section 5.2.10.

5.2.5 Clinical Assessments on Days 15-18

All subjects (Regimens 1 and 2) must return to the study site , on Days 15-18 (+3 days; or on the day of the last IRX-2 injection for subjects receiving Regimen 1) and the following evaluations must be performed (in the event that surgery is performed on Day 21 or 22, then evaluations required on Days-15 -18 and Days 1-5 Pre-op may be combined):

- Interval history and assessment of all current symptoms including severity (AEs).
- Head and neck examination.
- Karnofsky performance status.
- Clinical laboratory assessments:
  - Hematology: CBC, differential, platelet count.
  - Serum chemistry: serum albumin, total protein, serum bilirubin, LDH, ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, BUN, glucose, and electrolytes.

5.2.6 One to Five Days Prior to Surgery

The following procedures will be performed at this visit:

- Interval history and assessment of all current symptoms including severity (AEs).
- Record concomitant medications.
- Karnofsky performance status.

- Brief physical exam including weight.
- Head and neck exam and tumor assessment (documentation of change in tumor).
- Indomethacin and IRX-2 injections must be stopped at least 48 hours before surgery. Subjects are scheduled to take indomethacin through Day 21. If surgery is to be performed on Day 21 or 22, then the subject should discontinue IRX-2 and indomethacin on Day 19 or 20, respectively.
- Repeat CT (or MRI) scan as at screening and, at participating centers, PET scan
- Clinical laboratory assessments:
  - Hematology: CBC, differential, platelet count, PT and PTT.
  - Serum chemistry: serum albumin, total protein, serum bilirubin, LDH, ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, BUN, glucose, and electrolytes.
- Collect blood samples for correlative studies, including immunogenicity testing.
- Data on compliance with protocol medications will be collected.

5.2.7 Surgery

All subjects will undergo surgical resection of their tumor, reconstruction, and postoperative adjuvant therapy per usual standards of care according to the guidelines presented in Section 7.1. Surgery should take place 25-30 days after randomization and **must** take place no later than 35 days after randomization.

- All subjects will proceed to surgery, regardless of response to the IRX-2 regimen.
- For all subjects, if the tumor progresses by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria (>20% in longest unilateral measurement), the investigator has the option of stopping investigational therapy and taking the subject immediately to surgery.
- For all subjects, surgical and pathological data must be reported as described in this Protocol and the CRFs.
- For all subjects, postoperative standard of care adjuvant radiation or chemoradiation therapy administered must be recorded.

5.2.8 IRX-2 Booster Regimen vs. Control Booster Regimen†

Booster Regimens will not be given to subjects who had gross residual disease at surgery, recurrent or metastatic tumor or developed a second primary tumor.

The quarterly Booster Regimens must not be initiated until after completion and recovery from adjuvant radiation or chemoradiation as determined by the investigator. The investigator's determination of adequate recovery should be based on the review of any ongoing adverse events and the overall clinical status of the subject. Any uncertainty should be discussed with the Medical Monitor

Patients who are receiving chronic anticoagulation in addition to aspirin, including heparins, warfarin, oral anticoagulation or other platelet function inhibitors, may also initiate the Booster

Regimens. If more than Grade 1 injection-related ecchymoses are observed, however, the IRX-2 injections should be discontinued or alternately the chronic anticoagulation and/or aspirin should be held until completion of the IRX-2 injections.

The following procedures will be completed prior to the initiation of each Booster Regimen:

- Interval history and assessment of all current symptoms including severity (AEs).
- Record concomitant medications.
- Karnofsky performance status.
- Brief physical examination including weight.
- Head and neck examination.
- Laboratory assessments.
  - Hematology: CBC, differential, platelet count.
  - Serum chemistry: serum albumin, total protein, serum bilirubin, LDH, ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, BUN, glucose, and electrolytes.
  - Pregnancy test (serum or urine, females only) if appropriate.
  - Local laboratories may be used for treatment decisions, but duplicate specimens must be submitted to the Central Laboratory.
- Collect blood samples for correlative studies, including immunogenicity testing.
- Administer the following medications:
  - Infusion of cyclophosphamide, 300 mg/m^2. Steroids must not be administered as antiemetic agents since these might interfere with immunomodulation by IRX-2. Antiemetic regimen should include a serotonin (5-HT3) antagonist and lorazepam or equivalent medications
  - Begin indomethacin (25 mg, TID) to be taken orally from Day 1 through Day 10.
  - Begin zinc with multivitamins to be taken orally once daily from Day 1 through Day 10.
  - Begin omeprazole, 20 mg, to be taken orally once daily from Day 1 through Day 10.
  - After each Booster Regimen, data on compliance with protocol medications will be collected.

REGIMEN 1 ONLY

- IRX-2 should be administered by subcutaneous injection into bilateral **deltoid** regions.
- Each subcutaneous injection will be approximately 1.0 mL of IRX-2 (corresponding to 115 units of IRX-2 per injection or 1150 units during the total regimen).
- On the first day of IRX-2 injections, subjects will be monitored for 15 minutes after the IRX-2 injections for signs or symptoms of any reaction.

Subcutaneous IRX-2 injections are given in bilateral deltoid regions for 5 days, between Days 4 and Day 10, administered every 3, 6, 9 and 12 months (-14 days to +28 days) after surgical resection. Any Booster injection which cannot be given during the specified timeframe should be omitted and the next scheduled Booster Regimen should be administered subsequently at the designated interval after surgical resection. Missed Boosters must not be administered at a later date.

5.2.9 Follow-up Schedule

5.2.9.1 Protocol-Required Follow-up Monitoring

Subjects will be assessed clinically by physical examination of the oral cavity and regional nodes every 3 months for Years 1 and 2 (-14 days to +28 days). All follow-up visits from Year 3 through Year 4 (i.e., Y3M6, Y3M12, Y4M6, Y4M12) should be performed via telephone to collect survival information. However, CT scans of the chest should still be obtained at 1, 2, 3 and 4 years after randomization and in the event of disease recurrence. Protocol mandated follow-up will end 4 years after randomization.

The following procedures will be performed at the Years 1 and 2 post-surgery follow-up visits:

- Interval history and assessment of all current symptoms including severity (AEs).
- Record concomitant medications.
- Karnofsky performance status.
- Brief physical exam including weight.
- Head and neck exam.
- Pregnancy test (serum or urine, females only) if appropriate every 3 months for Year 1 only.
- Clinical laboratory assessments (every 3 months for Year 1 post-surgery; not done in Year 2):
    - Hematology: CBC, differential, platelet count.
    - Serum chemistry: serum albumin, total protein, serum bilirubin, LDH, ALT/SGPT, AST/SGOT, alkaline phosphatase, creatinine, BUN, glucose, and electrolytes.
    - Serum for immunogenicity testing.

Assessment should focus on physical exam, symptoms or signs relevant to the primary tumor site, regional disease (including lymph nodes), metastatic spread, second malignancy, and treatment complications.

CT scans of the chest should be performed yearly x 4 and as clinically indicated or in the event of a second primary tumor. Suspected disease recurrence must also be confirmed by needle aspiration or other biopsy procedure and should be documented by physical exam (if possible) and additional radiology studies to confirm the extent of disease.

5.2.9.2 Survival

Telephone calls for survival after progression to occur every 3 months if subject is not seen in follow-up.

5.2.9.3 Additional Follow-up Testing

Each investigator may obtain additional radiologic or other tests as recommended by applicable guidelines or according to his/her usual standard of practice, so long as consistency is maintained in obtaining them for all subjects, regardless of study arm. The Medical Monitor as well as the Data Safety Monitoring Board will assess adherence to this requirement at each study site.

5.2.10 Regimen 1 and 2 Dose Modification

For subjects receiving Regimen 1, in the event of Grade 3 or higher toxicity, no further IRX-2 should be injected and indomethacin should be discontinued for that course. Subsequent booster courses† can be attempted but should be permanently discontinued if the same Grade 3 toxicity reoccurs. In the event of Grade 2 toxicity, treatment should be delayed until stable and then resumed per protocol. Treatment should be discontinued in a subject if the treatment is delayed for more than 7 days, except that treatment with IRX-2 and zinc may be continued per protocol in a subject intolerant of indomethacin.

For subjects receiving Regimen 2, in the event of Grade 3 or higher toxicity, indomethacin should be discontinued for that course. Subsequent booster courses† can be attempted but should be permanently discontinued if the same Grade 3 toxicity reoccurs. In the event of Grade 2 toxicity, treatment should be delayed until stable and then resumed per protocol. Treatment should be discontinued in a subject if the treatment is delayed for more than 7 days, except that treatment zinc-containing multivitamins may be continued per protocol in a subject intolerant of indomethacin.

6 STUDY ASSESSMENTS

6.1 Endpoint Assessments

6.1.1 Primary Endpoint - EFS

EFS will be assessed by physical examination at routine follow-up visits every 3 months after surgery for the first 2 years and every 6 months during years 3 and 4 and by chest CT scans performed yearly x 4 years. During years 3-4 subjects will be contacted by phone to determine survival status, and will be assessed in person (eg, physical exam, laboratory evaluations, etc.) according to standard of care at their enrolling institution. Any indication of recurrence occurring at these SOC visits should be followed up with a confirmatory imaging and reported in the Recurrence CRF folder. Progression prior to surgical resection will not be considered an Event, but failure to resect tumor that was apparent at randomization for any reason or the presence of gross residual disease at surgery will be considered an Event. (The rationale for this definition of EFS is that increased cellular infiltration into tumor induced by the IRX-2 Regimen might result in increase in tumor size but not represent tumor progression. A secondary exploratory analysis, however, will be performed in which EFS will be assessed starting from randomization by RECIST).

Progression after resection should be confirmed by biopsy, but in the absence of biopsy confirmation, unequivocal clinical evidence of progression in the primary or nodal sites or distant metastatic disease using RECIST v1.1 criteria will be accepted as progression. Scans (CT, MRI or PET) should be performed to restage disease and establish patterns of relapse. The date of progression will be the date on which the decision not to resect tumor that was apparent at randomization is made or the date upon which the Investigator first observes recurrent locoregional or metastatic disease by physical or radiologic examination.

Death for any cause will also be considered an Event.

Diagnosis of a second malignancy will not be considered an Event, but date of diagnosis, site and histology will be collected.

6.1.2 Secondary Endpoints

6.1.2.1 Overall Survival

Survival data will be collected in all subjects (phone contact after progression will be sufficient). When the subject comes to clinic and/or is contacted by phone, the date of that contact is to be reported as an update of the subject's survival.

6.1.2.2 Safety and Feasibility

Safety of each Regimen and feasibility of the Booster Regimens† will be assessed by the incidence and severity of AEs, SAEs, and subject discontinuations. All subjects will be assessed for AEs as detailed on the Study Schedules (Section 5.1) and in Section 5.2 and evaluated for AEs as noted in Section 8.0.

6.1.3 Exploratory Endpoints

Exploratory endpoints will be determined in subjects enrolled at selected clinical sites. The Sponsor may at any time alter or discontinue some or all of these endpoints so long as additional clinic visits, radiology studies or blood draws are not initiated.

Analyses of some or all of the Exploratory Endpoints will be conducted by the Sponsor or designated representatives at intervals depending on the availability of sufficient data.

6.1.3.1 Key Exploratory Endpoints

6.1.3.1.1 Tumor Size

Change in tumor size will be determined by a comparison of the imaging studies (CT or MRI) obtained pre-treatment and just prior to surgery. Percent changes in tumor size will be determined by central radiology review by radiologists blinded to the treatment Regimen.

6.1.3.1.2 Functional Imaging

At selected institutions, change in functional imaging will be determined by a comparison of the FDP-PET scans obtained pre-treatment and just prior to surgery. Percent changes in glycolytic activity will be estimated by central radiology review by radiologists blinded to the treatment Regimen.

6.1.3.1.3 Lymphocyte Infiltrates

Lymphocyte infiltrates in the pre-treatment tumor biopsies and the surgical specimens will be determined and compared. Subsets of lymphocytes will be evaluated including total T cells and naïve, cytotoxic and regulatory T cells. The analyses may include quantifications of cellular infiltrates and degree of activation by immunohistochemistry including (but not limited to): CD3, CD8, CD68 (myeloid derived suppressor cells), CD45RO and Fox P3 on lymphocytes and MHC class I and II and PDL1 on tumor cells. Other immune subsets and activation markers may be evaluated. Tumor gene expression signatures may also be performed. Lymphocyte infiltrates and changes after treatment will also be evaluated using T cell receptor (TCR) repertoire analyses performed on extracted RNA. These studies will be performed by one or more external contract research organizations without knowledge of the treatment regimen received.

6.1.3.2 Additional Exploratory Endpoints

6.1.3.2.1 Pathology

Each surgical specimen must undergo complete pathological assessment of the resected specimen with particular attention to size and extent of tumor (pathological T stage), tumor differentiation (well, moderately, or poorly), number and location of involved lymph nodes (pathological N stage), extracapsular extension of tumor, closeness of tumor to resection margins (described in mm), perineural involvement, and vascular invasion (blood or lymphatic).

6.1.3.2.2 Prognostic Factors

Prognostic and predictive factors and clinical-pathologic-immunologic correlates, including, for example, nutritional status (body mass index, albumin), absolute lymphocyte count, lymphocyte subsets and histological differences in the surgical specimen and gene expression profiles will be evaluated for correlation with disease-free survival, recurrence, second primary tumors, and patterns of disease recurrence.

6.1.3.2.3 HPV Status

Although the impact of HPV status is greater in patients with oropharyngeal cancer than in patients with non-oropharyngeal HNSCC, it still impacts outcomes in the latter group of patients [Chung,

2014]. Therefore, HPV status will be assessed by p16 expression and its relationship to clinical outcome and benefit from the IRX-2 Regimen will be explored.

6.1.3.2.4 T cell Receptor Profile

The peripheral T cell receptor profile prior to and post treatment during the first year of the trial will be used to explore relationships to clinical outcome.

6.1.3.2.5 RNA Expression

RNA expression profiling of immune-inflammatory markers will be examined.

7 DISCIPLINE STANDARDS OF CARE

7.1 Surgery

Surgery and subsequent assessments and interventions are to be performed on all subjects randomized (independent of arm). For subjects randomized to either Arm, surgery is to be scheduled 25-30 days after randomization and **must** take place no later than 35 days after randomization.

Within one to five days before surgery, all subjects are to be re-evaluated by interval history, performance status, brief physical examination, and CBC with differential and serum chemistry tests to assess clinically significant changes between study entry and surgery.

For all subjects, the surgical procedure and reconstruction should be designed to resect all gross tumor achieving tumor-free surgical margins. The surgery should be planned and performed to resect the tumor and the surgical plan is to be defined and described prior to surgery.

For all subjects, if tumor progression by RECIST v1.1 criteria (>20% in longest unilateral measurement) is documented by radiographic study, the Investigator may, but is not required to, discontinue immunotherapy and take the subject immediately to surgery.

7.2 Radiation Therapy

Postoperative radiation therapy is to be given per protocol and NCCN guidelines (http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf) regardless of treatment arm unless medically contraindicated, as soon as adequate recovery from surgery has occurred but no later than 8 weeks after surgery. Protocol guidelines, consistent with NCCN Guidelines, are that subjects should receive radiation (unless medically contraindicated) if there is evidence of any of the following:

1. Extracapsular nodal spread
2. Multiple positive nodes (N2 or N3 disease)
3. Nodal disease in levels IV or V
4. Positive margins (ink at margin or margin of 5 mm or less)
5. pT3 or pT4 primary
6. Perineural invasion
7. Vascular invasion (blood or lymph vessel)

Standard dose and fractionation of radiation therapy are recommended, i.e., 60–66 Gy in 30–33 fractions of 2 Gy each over 6 to 7 weeks. Use of alternative radiation approaches, e.g. intensity modulated radiation therapy, concomitant or subsequent radiation boost, or hyperfractionated radiation, is permissible. Detailed information regarding standard of care adjuvant radiation therapy will be collected.

Aggressive nutritional support, including a feeding tube, is strongly recommended in all subjects who are to receive postoperative radiation therapy.

7.3 Chemotherapy with Radiation

Postoperative chemotherapy should be given concurrent with radiation therapy to subjects who meet the protocol and NCCN specified guidelines, regardless of treatment arm. Concurrent chemotherapy should be given (unless medically contraindicated) to subjects with:

1. Microscopic positive margin (surgical margin of 5 mm or less), or
2. Extracapsular nodal extension.

Chemoradiation should also be considered for subjects with other adverse risk factors as indicated in Section 7.2 and the NCCN Guidelines Version 2.2014. It is important that these criteria be followed independent of the treatment arm to which the subject was randomized. Detailed information regarding standard of care adjuvant chemoradiation therapy will be collected.

The preferred regimen for subjects who receive postoperative chemotherapy is cisplatin every 3 weeks at 100 mg/m^2 for three doses [Bernier, 2004; Cooper, 2004; Bernier, 2006]. If a subject is not medically able to receive cisplatin on the preferred dose and schedule, cisplatin may be administered at 50 mg or 40 mg/m2 intravenously weekly during radiation therapy [Bachaud, 1996]. Alternatively, if a subject is unable to receive cisplatin because of inadequate renal function, hearing impairment or neuropathy, carboplatin, AUC = 2, given weekly for the duration of radiation therapy, or AUC = 5, given every 3 weeks x three doses, may be substituted. The reason a subject is not able to receive cisplatin must be documented. If a subject is unable to continue adjuvant cis- or carboplatin, the subject should not receive alternative chemotherapy but should complete the planned course of radiation therapy. Administration of chemotherapy and supportive care for chemoradiation therapy should be given according to institutional standard practice, but must include adequate hydration and antiemetics.

Suggested guidelines for cisplatin dose modification are as follows:

On the day that treatment is due, absolute neutrophil count (ANC) must be ≥1000 and platelets >100,000/mm^3 for administration of cisplatin. If these parameters are not met, hold chemotherapy and reinstitute as indicated below:

1. Neutropenia: If ANC <1000, withhold treatment until >1000, and then give 100% of dose.
2. Thrombocytopenia: If platelets are <100,000/mm3, withhold dose until ≥100,000/mm3, and then give 100% dose.
3. Neurological motor or sensory neuropathy that impairs function – discontinue cisplatin, there will be no substitution of other platinum drugs.
4. Renal:

Creatinine		Creatinine Clearance	Dose
≤1.2 mg/dL	or	>50 mL/min	100 mg/m^2
>1.2 mg/dL	and	40-50 mL/min	60 mg/m^2
>1.2 mg/dL	and	<40 mL/min	Discontinue

8 ADVERSE EVENTS, REPORTING REQUIREMENTS, AND STOPPING RULES

8.1 Adverse Event Definitions

Definitions of AEs will follow the International Conference on Harmonization E6: Good Clinical Practice Step 5, Consolidated Guideline 1.5.96, April 1998 edition, and are summarized below. For this study, the investigational product is the IRX-2 regimen, including IRX-2, cyclophosphamide, indomethacin, and zinc-containing multivitamins.

An adverse drug experience (event) is any new undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs from the day of randomization until 30 days after the last dose of study regimen, whether or not considered to be drug related. Therefore, AEs are treatment-emergent signs and symptoms. This includes those events occurring from drug overdose, whether accidental or intentional, from drug abuse or from drug withdrawal. In general, abnormal laboratory findings without clinical significance based on the investigator's judgment are part of the database and should not be recorded as AEs.

Adverse events reported by the subject or observed by the investigator will be individually listed on an AE CRF page. The signs and symptoms, date of onset, duration, action taken, severity, outcome to date, and relationship to the study drug will be recorded. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 toxicity criteria. Severity will be classified as described in Section 8.1.4.

Adverse events will be collected from day of randomization until 30 days after the last dose of study regimen in the Treatment Period. Additionally, AEs will be captured from the first day of each study regimen administration through 30 days after the last dose of the study regimen dosing in each of the Booster Regimens[†]. Any Adverse Event that the Investigator feels that is related to study medication should be reported regardless of the timing of that event. All AEs will be monitored until stability or resolution. Follow-up phone calls to assess toxicity will be made to each subject on Day 21 (or 3 days after the last dose of IRX-2 for Regimen 1). If the date of the follow-up call occurs on a weekend or holiday, the call should be made on the next available business day.

All Serious Adverse Events regardless of relatedness to study regimen, will be collected continuously from day of randomization until 30 days after the last dose of study regimen. Any Serious Adverse Event that the Investigator feels is related to study medication should be reported regardless of the timing of that event. All SAEs will be monitored until resolution or stability.

Adverse events of Grade 3-4 will be reviewed by the Medical Monitor, who may assess with the Site Principal Investigator whether to modify or discontinue study treatment.

At each visit, the investigator will be prompted to report AEs and SAEs as "not", "possibly," or "definitely" related to the assigned study regimen.

Any pregnancy occurring during the clinical study should be reported immediately using the pregnancy report form.

8.1.1 Definition of Serious and Life Threatening Adverse Events

A serious adverse drug experience (event) is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
  - A life-threatening adverse drug experience is any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include a reaction that, had it occurred in a more severe form, might have caused death.
- A persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of existing hospitalization, except that planned hospitalization during days in clinic and surgery or hospitalization for the social reasons or the convenience of the subject or physician shall not be considered an SAE
- A congenital anomaly/birth defect
- Important medical event
  - Important medical events that may not result in death, be life-threatening, or require hospitalization but may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above

8.1.2 Protocol Defined Adverse Events for SAE Reporting

- For purposes of this protocol, **the following are considered important medical events and thus are to be reported as SAEs (even if they are not life-threatening or do not require hospitalization): fistula formation, wound dehiscence or other clinically significant complications of surgical or other treatment of advanced oral cavity cancer and any immune related adverse events.**

8.1.3 Definition of Relationship to Study Regimen and Drug

Association or relatedness to the study regimen will be graded as either “not”, “possibly,” or “definitely” related to the study regimen. Determination of relatedness is to the entire study Regimen as a whole, i.e. not to the individual components of the Regimen, and is defined as follows:

- **Definitely**, characterized as an AE that
  - Follows direct temporal sequence from regimen administration.
  - Abates upon discontinuation of the regimen.
  - Cannot be explained by the known characteristics of the subject’s clinical state or by other modes of therapy administered to the subject.
- **Possibly**, characterized as an AE that
  - Follows a reasonable temporal sequence from regimen administration.
  - Abates upon discontinuation of the regimen.
  - Could have been produced by the subject’s clinical state or by other modes of therapy administered to the subject.

- **Not Related**, characterized as an AE that
  - Does not follow any temporal sequence from regimen administration.
  - Is explained by the subject's clinical state or by other modes of therapy administered to the subject.

Association or relatedness of observed AEs to the study drug, IRX-2, will be determined by comparison of AEs between Regimens 1 and 2 as described below in Section 9.6 and in the SAP.

8.1.4 Definition of Severity

The severity of adverse changes in physical signs or symptoms will be graded according to the NCI-CTCAE v4.03. For AEs not listed in the table, the severity of adverse changes in physical signs or symptoms will be classified as follows:

Grade 1: **Mild** (transient or mild discomfort; no limitation in activity; no medical intervention/therapy required)

Grade 2: **Moderate** (mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required)

Grade 3: **Severe** (marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible)

Grade 4: **Life-threatening** (extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable)

Grade 5: **Death**

8.1.5 Definition of Action Taken

None: No action taken with regard to the study regimen

Interrupted: The study regimen was stopped but restarted after the subject's symptom abated. The subject was rechallenged with the study regimen.

Discontinued: The study regimen was permanently stopped

8.1.6 Definition of Outcome to Date

Resolved with sequelae: The subject has recovered from the AE with observable residual effects

Resolved without sequelae: The subject has fully recovered from the AE with no observable residual effects

Unresolved: The AE is present and observable

Death: The subject died as a result of the AE

Lost to Follow-up:	Source documentation confirms that repeated attempts to contact subject have failed

8.2 Notification of Serious or Unexpected Adverse Events

In case of any SAE, regardless of the relationship to study treatment or expectedness, the investigator must complete the SAE information in the CRF which will be submitted to the PPD Safety Surveillance Unit. In the event that the CRF is not available to the investigator, he/she should complete the SAE Form and fax a copy to the appropriate number below.

All SAE phone and fax lines are toll-free and in operation 24 hours a day, 7 days a week.

SAE Reporting (US and Canada): 1-888-483-7729 (phone): 1-888-529-3580 (fax)

SAE Reporting (Europe): +44 1223 374 240 (phone): +44 1223 374 102 (fax)

SAE Reporting (Mexico, Central and South America): +55 11 4504 4801 (phone)

+55 11 3958 0983 (fax)

Within 24 hours from the time that the investigator is aware of an SAE, copies of the medication logs and any other required documentation will be faxed to PPD using the appropriate numbers.

Contact information will be provided to the site along with other study information. The Safety Surveillance Unit will report the SAE to the Sponsor's Medical Monitor within 1 working day of the event.

For SAE reports, the Sponsor is required by US regulation (21 Code of Federal Regulations [CFR] Part 312.32) to:

- Notify the FDA by telephone or fax of any unexpected fatal or life-threatening event associated with use of the drug as soon as possible but in no event later than 7 calendar days after initial receipt of the information. A written safety report will be submitted to the FDA no later than 15 calendar days after initial notification of the information. Determination of expectedness to the IRX-2 Regimen should be made with consideration of the Reference Safety Information in the most current version of the IRX-2 Investigator's Brochure or more current published reference safety information;
- Notify all participating investigators of any SAE that is serious, assessed as definitely or possibly related to the study medication, and unexpected; and notify the FDA and investigators of any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made in writing as soon as possible but in no event later than 15 calendar days after receiving the initial information;
- Monitor the nature, frequency, and severity of SAEs known to be associated with the drug to identify an unexpected change in the nature, or increase in the rate of occurrence or severity of these events. If a change in the nature or an increased frequency or severity is identified, FDA must be notified in writing within 15 calendar days of the determination; and
- Submit to FDA any follow-up information in a safety report as soon as possible, but in no event later than 15 calendar days, as well as information amendments and annual progress reports. If

an AE initially not determined to be reportable, is reportable, the information shall be submitted in a safety report as soon as possible, but in no event later than 15 calendar days after determining that the event is reportable.

All safety issues should be communicated with the Sponsor who will forward them to the FDA or give instructions for PPD or the designated CRO to do so.

In the EU, applicable SAEs will be reported to the national Ministry of Health (or National Competent Authority) as required by 2001/20/EC: http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm#ct6. When the new clinical trial regulation EU No536/2014 becomes applicable, safety reporting will follow these and any future applicable requirements.

It is the responsibility of the Sponsor and the designated CRO to ensure that Ethics Committee, competent authorities and participating investigators are informed of applicable SAEs in accordance with local requirements.

8.3 Pregnancies

Subjects should be instructed to immediately inform the Investigator if they or a partner become pregnant during the study or within 1 year after the last study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor. Study treatment must be discontinued and monitoring of the patient should continue until conclusion of the pregnancy. Any abortion or congenital anomaly/birth defect in a child born to a female patient or partner exposed to study treatment should be classified as a Serious Adverse Event.

8.4 Reporting of Deaths

Any death occurring in the study population that is not preceded by the diagnosis of recurrent or progressive cancer must be reported within 24 hours using the SAE report form. The Safety Surveillance Unit will immediately report the death to the Sponsor and to the Medical Monitor.

8.5 Stopping Rules for Excessive Toxicity Leading to Delay in Definitive Surgery

In the current trial, 35 days has been set as the limit of the acceptable interval from the date of randomization to the date of surgery. Taking into consideration time from diagnostic biopsy to referral to a study center or Investigator, time to obtain Informed Consent, time for screening procedures prior to randomization and time from randomization to beginning of the assigned study Regimen, this limit is consistent with the data obtained in the prior Phase 2 study and with current clinical experience is an academic medical center (see Section 1.3.2.5).

Subjects in whom surgical resection takes place >35 days after randomization will be reviewed in order to establish whether toxicity from either neoadjuvant Regimen 1 or Regimen 2 is associated with unacceptable delays in definitive surgery. If either the Investigator or the DSMB Chair designates that the delay in surgical resection is definitely or possibly related to Study Regimen (per Section 8.1.2), the delay will be considered "definitely or possibly related to Study Regimen." This review will initially be undertaken by the Chair of the DSMB after every cohort of 20 patients has had surgery (hence after 20, 40, 60, etc. patients).

1. **Overall toxicity**: the incidence of overall delay (both Regimens combined) will be estimated and will be considered too high if the lower limit of "surgery later than 35 days considered definitely or possibly related to Study Regimen" of the 95% confidence interval excludes 15%.

This would be the case based on the normal approximation, for instance, if 8 out of 20 patients had delayed surgery, or 12 out of 40, etc. as shown in the following table:

# of subjects evaluated	# needed with surgery after day 35 to trigger "Stopping Rule"
20	8
40	12
60	16
80	20
100	24

2. **Toxicity to experimental treatment**: the difference in delay between Regimen 1 and Regimen 2 will be estimated, and Regimen 1 will be considered to have excessive delay if the lower limit of the the 95% confidence interval for the difference excludes 15%. This would be the case, for instance, if 5 out of 10 patients had delayed surgery in Regimen 1 vs. none out of 10 in Regimen 2, or 8 out of 20 vs. none out of 20, etc.

Note that no adjustment has been made for multiplicity (which is appropriate for a toxicity assessment) and that two-sided confidence intervals have been used in determination of the above numbers.

If either of these stopping rules were met and confirmed by a meeting of the entire DSMB, the Sponsor would be notified and the study would be placed on clinical hold until the Sponsor and relevant regulatory authorities agree that the study should proceed.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Considerations

Randomization will be 2:1 in favor of Regimen 1. Treatments will be allocated to study subjects using minimization with a stochastic algorithm based on the range method. Minimization will account for the major prognostic factors for HNSCC of the oral cavity (T and N stage) and study center to avoid imbalances in treatment allocation [Pocock, 1975].

The proposed clinical study is a randomized, Phase 2b clinical trial with a relaxed p-value [Rubinstein, 2005; Ratain, 2007; Buyse, 2006]. A total of approximately 100 subjects will be randomized. The study will have a power of 61% to detect an increase in EFS of 15% in subjects who receive Regimen 1 compared to those who receive Regimen 2, using a one-sided p-value of 0.10. The results of this trial, in conjunction with supportive data that may be obtained from analyses of co-primary exploratory and additional exploratory studies, will be adequate for use by the Company to make a decision on required size, optimal endpoints and chance of success of a potential randomized, double-blind Phase 3 clinical trial.

Assuming that the EFS at 24 months will be 50% for subjects receiving Regimen 2, this trial will have 61% power (one-sided $\alpha = 0.1$) to detect an increase in EFS of 15% (i.e. to 65%) at 24 months (hazard ratio [HR] = 0.62) for the subjects receiving Regimen 1. The required number of EFS events for the assessment of the primary endpoint is 51. The primary analysis will be of the entire population as randomized (intent-to-treat).

Assuming that the OS at 36 months will be 55% for subjects receiving Regimen 2, this trial will have 66% power (one-sided $\alpha = 0.1$) to detect an increase in OS of 15% (i.e. to 70%) at 36 months (HR = 0.60) for the subjects receiving Regimen 1. The required number of deaths for the assessment of the OS endpoint is 51.

9.2 Subject Populations

Intention-To-Treat (ITT) Population: The ITT population consists of all randomized subjects, whether or not they receive the Regimen to which they were randomized as intended. This is the primary population for the primary and secondary efficacy analyses.

Per-protocol Population: The PP population consists of subjects who did not have a major protocol deviation, received one dose of cyclophosphamide as neo-adjuvant therapy, and received at least 80% of the intended IRX-2 biologic as neo-adjuvant therapy in Regimen 1. For Regimen 2, the PP population consists of subjects who did not have a major protocol deviation and received one dose of cyclophosphamide as neo-adjuvant therapy. This population will be used with a descriptive intent to assess the effect of therapy when given in optimal conditions.

Safety Population: The Safety population includes all subjects who received at least one dose of a study Regimen. Subjects will be analyzed according to the treatment that they actually received. This is the primary population for the safety analysis.

9.3 Methods to be Used for Handling Missing or Spurious Data

No imputation of missing data will be applied. Spurious data will be ignored.

9.4 Efficacy

Efficacy analyses will be carried out on all randomized subjects (ITT population).

The primary evaluation will be based on event-free survival (EFS), which is defined as the time from randomization to progression after surgery, or at surgery, if failure to resect gross disease, or at time of death from any cause after randomization. Progression will be defined by RECIST v 1.1.

The Kaplan-Meier estimates of the proportion of subjects event-free at 3 months, 6 months, 12 months, 24 months, 36 months and 48 months as well as median EFS, 25th percentile and 75th percentile along with their 95% log-log transformed confidence intervals will be computed.

The primary analysis will be based on the inferential comparison between the 2 treatments by using a stratified log-rank test at the 0.1 significance level (one-sided). The test will be stratified on major prognostic factors for HNSCC of the oral cavity (T and N stage). A randomization test will be used, and will be complemented by the usual asymptotic log-rank test to assess the sensitivity of the analysis to the method used to allocate treatments to patients.

A stratified Cox proportional-hazards model, with the same stratification variables as used in the stratified log-rank test, will be applied to estimate the hazard ratio (HR) and corresponding two-sided 95% confidence interval.

A sensitivity exploratory analysis of event-free survival accounting for disease progression occurring prior to surgery will be conducted. The same methods applied for the primary analysis of EFS will be used.

A second sensitivity exploratory analysis of event-free survival defined as the time from surgery to first recurrence or death from any cause will be conducted. Subjects who do not undergo surgery or in whom surgery does not result in resection of all disease will have their DFS assigned as an event at time 0. Subjects who undergo surgery and who do not have an event will be censored at the last event assessment date. The same methods applied for the primary analysis of EFS will be used.

The secondary evaluation will be based on overall survival (OS), which is defined as the time from randomization to death for any cause. The same methods applied for the primary analysis of EFS will be used.

Further details on statistical analyses to be performed on the aggregate collected data for the primary and secondary endpoints will be described in the Statistical Analysis Plan (SAP).

Analyses of exploratory endpoints will be conducted. Analyses of some or all the exploratory endpoints will be conducted by the Sponsor or designated representatives throughout the study. These results from these exploratory analyses will be handled in a manner so as not to affect the analysis of the primary and secondary endpoints.

9.5 Interim Analysis

An interim analysis is foreseen for EFS in approximately Q1 2019. This analysis will use a conservative O'Brien-Fleming-like Lan-DeMets spending function to assess efficacy.

The spending function provides full flexibility as to when this interim analysis will be conducted, with the exact significance level to be used being determined by the number of events available at

the interim analysis time. Assuming the interim analysis is carried out at 70% information fraction, the significance level to be used for the interim analysis will be equal to 0.05, and the significance level to be used for the final analysis will be equal to 0.0857.

It is estimated that approximately 36 EFS events (about 70% of the required number) will have occurred by Q1 2019, and that the 51 EFS events required for the final analysis of EFS will have occurred by Q1 2020. There will be no assessment for futility as part of the Interim Analysis.

It is estimated that approximately 34 deaths (about 66% of the required number) will have occurred by Q1 2020, and that the approximately 51 deaths required for the final analysis of OS will have occurred by Q1 2022.

9.6 Safety

Safety analyses will be carried out from the date of randomization on all randomized subjects who receive any treatment (Safety population). Exposure to protocol defined study regimen will be summarized and adverse events will be summarized by system organ class and preferred term coded in accordance with MedDRA version 17.1. Regimen 1 will be compared to Regimen 2 in terms of:

- each type of AE at worst grade of severity
- any AE at worst grade of severity
- SAEs
- withdrawals (and reasons for them)
- dose modifications (and reasons for them)
- treatment interruptions (and reasons for them)
- abnormal laboratory findings that are considered clinically significant by the investigator
- early deaths, defined as deaths due to any cause occurring within 75 days after the date of randomization

Grade at baseline and worst grade during study will be summarized for laboratory parameters that can be graded with NCI CTCAE version 4.03. Abnormality grade (normal, abnormal) at baseline and worst abnormality grade during study will be summarized for all other laboratory parameters.

Change from baseline values for weight, pulse rate, systolic and diastolic blood pressure as well as Karnofsky Performance Score will be summarized at scheduled visits. Physical and head and neck abnormal examination at baseline and worst abnormality during study will be summarized.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Protection of Human Subjects

This study has been designed and will be conducted in accordance with the principles outlined in the Declaration of Helsinki.

10.2 Informed Consent

Once a patient is referred for consideration in the study, that individual's history and current status will be completely evaluated, and treatment recommendations will then be discussed thoroughly with the patient. The investigator will discuss with the patient any other treatments that may be available and their relative value compared to the possible use of IRX-2 therapy. The risks and hazards of the procedures will be explained to the patient. The investigator shall seek consent only under circumstances that provide the individual sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the individual shall be in understandable language. No informed consent may include any exculpatory language through which the individual is made to waive or appear to waive any of their legal rights, or releases or appears to release the investigator, IRX Therapeutics, the institution, or its agents from liability for negligence. The patient, or legal guardian, must be able to comprehend the informed consent form and sign prior to enrollment. The subject will then receive a signed copy of the consent form.

10.3 Institutional Review Board or Independent Ethics Committee

The investigator must obtain approval for the study from the institutional review board (IRB) or independent ethics committee (IEC). Prior to initiation of the study, the Sponsor or its designee must receive a copy of the written communication from the IRB/IEC indicating approval of the protocol and consent form. All changes to the protocol must be reviewed and approved prior to implementation, except where purely administrative or necessary to eliminate apparent immediate hazards to subjects. The investigator is responsible for obtaining annual IRB/IEC renewal through the duration of the study. Copies of the investigator's report and the IRB/IEC's continuance of approval must be submitted as directed. The Sponsor or its designee must be notified within 5 working days of any withdrawal of approval by the reviewing IRB/IEC.

11 STUDY ADMINISTRATION

11.1 Monitoring Plan

11.1.1 Pre-study Site Evaluation

The Sponsor or designated personnel will visit each study center to confirm the site's qualifications for implementing this protocol. The protocol and study procedures will be reviewed with the investigator and study personnel. This visit may be combined with the study initiation visit.

11.1.2 Site Initiation

The Sponsor or designated personnel will visit the site to train personnel on all protocol elements, study procedures, and safety, and to confirm site readiness prior to enrollment. There should be visits to clinical (surgery, radiation therapy, medical oncology), diagnostic radiology, and pathology study participants.

11.1.3 Interim Monitoring

Interim monitoring visits will be scheduled at regular intervals throughout the study, with the timing being dependent on subject enrollment. Generally, the study monitor will compare the data entered on the CRFs with the hospital or clinic records (primary source documents) and check for protocol compliance, including verification of informed consent, all subject visit dates, all AEs, all concomitant medications, and all key efficacy observations. In addition, the investigator site file containing essential documents, study drug accountability, and supporting records will be reviewed. Findings from this review will be summarized in writing and presented to the investigator, and the dates of the visits will be recorded by the study monitor in a sign-in log to be kept at the study site. During monitoring visits, the study coordinator and investigator should be available, all subject records and regulatory documents must be available, and a suitable environment must be provided for review of study-related documents.

11.1.4 Study Close-out

At the study's conclusion, there will be a monitoring close-out visit at which time a final review and reconciliation of all study and regulatory documents and study drug will be performed.

11.1.5 Site Responsibility

The procedures defined in the protocol and in the CRFs will be carefully reviewed by the investigator and his/her staff, prior to the time of study initiation, to ensure appropriate interpretation and implementation. No deviations from the protocol should be made. Minor exceptions may be approved on a case-by-case basis and must be authorized by the Medical Monitor or his designee and documented in writing, and the Sponsor informed. Significant deviations that may impact patient safety or study integrity will be reported to the institutional Ethics Committee and may result in termination of study participation. Any changes to the protocol will originate from the Sponsor in the form of an amendment.

11.2 Compliance Statement

This study will be conducted in accordance with the US CFR, Title 21, Parts 11, 50, 54, 56 and 312; the Good Clinical Practices: Consolidated Guideline (E6), International Conference on Harmonization, the Food and Drug Administration Guidance for Industry: Computerized Systems Used in Clinical Trials, the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

11.3 Investigational Product Accountability

The principal investigator is responsible for investigational product accountability. The investigator or his/her designee must maintain a current record of the receipt and disposition of investigational product, including dates, quantity, kit, lot, and subject numbers. The investigator or responsible designee will record the receipt, dispensation by subject number, kit number, lot number, and disposition of the product onto the drug accountability forms provided by sponsor or its designee. A copy of these will be collected and returned to sponsor or its designee on an ongoing basis. The investigator will maintain a copy for the institutional records. Drug dispensing records must also be maintained.

In addition, a quality assurance release form and a shipping form (if applicable) will be included with each shipment stating lot number and quantity of product shipped. The investigator or responsible designee will sign the forms in the designated area, which certifies the receipt of supplies, and retain a copy for the institutional records. At sites that are dispensing drug, the investigator, or designee, will also maintain a dispensing record of IRX-2.

Used and unused drug vials will be destroyed by the responsible pharmacist at each clinical site after study monitor reconciliation procedures. Specific instructions will be provided in the Investigational Product Guidelines. Each site will be requested to use the procedures that are locally approved for destruction of biological products, and the details of such destruction will be captured on a form provided in the guidelines. These forms will be retained and available for inspection at the study site.

11.4 Study Documents and Access to Records

It is the responsibility of the investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable and accessible for inspection/review at any time by the study monitor, the Sponsor or its designee, IRB/ IEC, and regulatory authorities. Elements should include, but are not limited to:

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- Study Files, containing the curriculum vitae of all investigators and his/her designees, FDA Form 1572, Financial Disclosure Forms, the protocol with all amendments, the IB, copies of all pre-study documentation, local lab certifications and lab normal ranges, and all correspondence to and from local Regulatory Authorities to the Sponsor or its designee.

- Subject Files, containing the completed original supporting source documentation and the signed informed consent form(s).
- Completed Electronic Case Report Forms
- Dispensing records of test agents.

The sponsor shall ensure that the important documents of the clinical trial, including the protocol, are kept for at least ten years after the end or termination of the trial.

11.5 Study Closure/Study Termination

The study will end when all treated subjects have either been followed for 4 years after the date of randomization, have expired or have withdrawn consent for survival follow-up.

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason, including but not limited to the following:

- Successful completion of the study
- Failure of the investigator to comply with the protocol or Good Clinical Practice/ International Conference on Harmonization guidelines
- Safety concerns
- Inadequate recruitment of subjects at a clinical site
- Decision to close the study for any reason

Disclosure of study termination will be made immediately to the IRB/IEC by the investigator.

11.6 Quality Assurance

The Sponsor and all designees will ensure the integrity of all data collected and calculations made during the conduct of the study according to their quality assurance standards of operations. Edit checks will be run on the data and queries issued. All data will undergo 100% review.

11.7 Confidentiality and Publication Policy

This trial will be listed in clinical trial databases as appropriate, e.g., www.clintrials.gov.

No written or oral reports or information about the trial, its progress, or results obtained for the duration of the trial will be provided by any investigator or anyone associated with this study, to anyone not involved in the trial other than to the Sponsor or its designees, or in confidence to the IRB/IEC, without the express, written permission of the Sponsor.

Following the completion of the study, the data will be reported at a scientific meeting and by publication in a scientific journal at the discretion of the participating investigators, voting in proportion to the number of subjects each has entered on the study. Since this research effort is a multi-center investigation, each investigator acknowledges that participation in the protocol involves a commitment to present and/or publish the data from this study in a cooperative manner prior to doing so on an individual basis.

Any abstract or publication presenting results of this trial shall be given to the Sponsor for review and approval at least 30 days prior to intended submission to a scientific journal for publication or

to a scientific meeting for oral or poster presentation. The Sponsor will not arbitrarily withhold or delay agreement to present the results of this study in appropriate scientific settings.

The Sponsor endorses published guidelines for the publication and presentation of clinical study results. The Sponsor and the investigators acknowledge their intent to resolve in good faith any differences of opinion regarding presentation or publication of study results.

12 REFERENCES

Alkureishi LW, Ross GL, MacDonald DG, et. al. Sentinel node in head and neck cancer: use of size criterion to upstage the no neck in head and neck squamous cell carcinoma. Head Neck. 2007;29(2):95-103.

Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys. 1996;36:999-1004.

Barrera J, Verastegui E, Meneses A, et al. Combination immunotherapy of squamous cell carcinoma of the head and neck: A phase II study. Arch Otolaryngol Head Neck Surg. 2000;126:345.

Berd D, Mastrangelo MJ, Engstrom PF, et al. Augmentation of the human immune response by cyclophosphamide. Cancer Res 1982;42:4862-4866.

Berinstein NL, Wolf GT, Naylor PH, et al. Increased lymphocyte infiltration in patients with head and neck cancer treated with the IRX-2 immunotherapy regimen. Cancer Immunol Immunother 2012;61:771-782.

Bernier J. Cetuximab in the treatment of head and neck cancer. Expert Rev Anticancer Ther 2006;11:1539-52.

Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without conconmitant chemotherapy for locally advanced head and neck cancer. NEJM 2004;19:1945-52.

Bianchini C, Ciorba A, Stomeo F, et al. Immunonutrition in head and neck cancer: have a look before surgery! Eur Arch Otorhinolaryngol. 2012;Jan;269(1):5-8

Blewett HJ, Taylor CG. Dietary zinc deficiency in rodents: effects on T-cell development, maturation and phenotypes. Nutrients 2012;4:449-66

Brookes GB, Clifford P. Nutritional status and general immune competence in patients with head and neck cancer. J Royal Soc Med 1981;74:132-139.

Buyse, ME. Role of stratification and randomization in early trials of targeted agents, Education Booklet, American Society of Clinical Oncology, 2006.

Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol. 2014;32:3930-8.

Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. NEJM 2004;19:1937-44.

Cortesina, G., DeStefani, A., Giovarelli, M., Barioglio, et al. Treatment of recorrent squamous cell carcinoma of the head and neck with low doses of intcrleukin-2 injected pcrilymphatically. Cancer 1988;62, 2482-2485.

Czystowska M, Han J, Szczepanski MJ, et al. IRX-2, a novel immunotherapeutic, protects human T cells from tumor-induced cell death. Cell Death Differ. 2009;16:708-718.

Czystowska M, Szczepanski MJ, Szajnik M, et al. Mechanisms of T-cell protection from death by IRX-2: a new immunotherapeutic. Cancer Immunol Immunother. 2011;60:495-506.

D'Cruz AK, Vaish R, Kapre N, et. al for the Head and Neck Disease Management Group. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 2015;373:521-9 and Supplementary Appendix http://www.nejm.org.offcampus.lib.washington.edu/doi/suppl/10.1056/NEJMoa1506007/suppl_file/nejmoa1506007_appendix.pdf

Egan JE, Quadrini KJ, Santiago-Schwarz F, et al. IRX-2, a novel in vivo immunotherapeutic, induces maturation and activation of human dendritic cells in vitro. J Immunother 2007;30:624-633.

Emens LA, Jaffee EM. Leveraging the activity of tumor vaccines with cytotoxic chemotherapy. Cancer Res 2005;65:8059-8064.

Forni G, Giovarelli M, Santoni A. Lymphokine-activated tumor inhibition in vivo. I. The local administration of interleukin 2 triggers nonreactive lymphocytes from tumor-bearing mice to inhibit tumor growth. J Immunol. 1985;134(2):1305-11.

Freeman SM, Franco JLB, Kenady DE, Baltzer L, Roth Z, Brandwein HJ, Hadden JW. A Phase 1 safety study of an IRX-2 regimen in patients with squamous cell carcinoma of the head and neck. Am J Clin Oncol 2010;34:173-8.

Freiser ME, Serafini P, Weed DT. The immune system and head and neck squamous cell carcinoma: from carcinogenesis to new therapeutic opportunities. Immunol Res. 2013;57:52-59.

Gildener-Leapman N, Ferris RL, Bauman JE. Promising systemic immunotherapies in head and neck squamous cell carcinoma. Oral Oncol. 2013;49:1089-1096.

Good RA, Fernandes G. Nutrition, immunity, and cancer-a review. Part I: Influence of protein or protein-calorie malnutrition and zinc deficiency on immunity. Clin Bull 1979;1:3-12.

Groome PA, Schulze K, Boysen M, et al. A comparison of published head and neck stage groupings in carcinomas of the oral cavity. Head Neck. 2001;23(8):613-24.

Haase H, Rink L. Zinc signals and immune function. Biofactors 2014;40:27-40.

Hadden EM, Malec P, Sosa M, et al. Mixed interleukins and thymosin fraction V synergistically induce T lymphocyte development in hydrocortisone-treated aged mice. Cellular Immunology 1992;144:228-36.

Hadden JW. The immunology and immunotherapy of head and neck cancer: prospects for immunotherapy. Clin Immunother 1995a;3:362-85.

Hadden, JW, Chen, H, Wang, Y and Hadden, EM. Strategies of immune reconstitution : Effects of lymphokincs on murinc T cell development in vivo and in vitro. Life Sci. AIDS Comm. 1989;44, 5-12.

Hadden JW, Endicott J, Baekey P, et al. Interleukins and contrasuppression induce immune regression of head and neck cancer. Arch Otolaryngol Head Neck Surg. 1994;120:395-403.

Hadden JW, Saha A, Sosa M, et al. Immunotherapy with natural interleukins and/or thymosin [alpha]1 potently augments T-lymphocyte responses of hydrocortisone-treated aged mice. Int Immunopharmacol 1995b;17: 821-8.

Keen CL, Gershwin ME. Zinc deficiency and immune function. Ann Rev Nutr 1990;10:413-415.

Kreppel M, Drebber U, Rothamel D, et al. Prognostic impact of different TNM-based stage groupings for oral squamous cell carcinoma. Head Neck. 2011;33(10):1467-75.

Lapointe H, Lampe H, Banerjee D. Head and neck squamous cell carcinoma cell line-induced suppression of in vitro lymphocyte proliferative responses. Otolaryngol Head Neck Surg 1992;106:149-158.

Leoncini E, Vukovic V, Cadoni G, et al. Clinical features and prognostic factors in patients with head and neck cancer: Results from a multicentric study. Cancer Epidemiology 2015;39:367-374.

Machiels J-PH, Reilly RT, Emens LA, et al. Cyclophosphamide, doxorubicin, and paclitaxel enhance the antitumor immune response of granulocyte/macrophage-colony stimulating factor-secreting whole-cell vaccines in HER-2/neu tolerized mice. Cancer Research 2001;61:3689-3697.

Martin PJ, Davenport-Ennis N, Petrelli NJ, et al. Responsibility for costs associated with clinical trials. J Clin Oncol. 2014;32:3357-9.

Michiels S, Le Maître A, Buyse M, et al. on behalf of the MARCH and MACH-NC Collaborative Groups. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. Lancet Oncol. 2009;10:341-350

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, May 28, 2009.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers, V.2.2014.

Naylor PH, Hernandez KE, Nixon AE, et al. IRX-2 increases the T cell-specific immune response to protein/peptide vaccines. Vaccine 2010;28:7054-7062.

North RJ. Cyclophosphamide-facilitated adoptive immunotherapy of an established tumor depends on elimination of tumor-induced suppressor T cells. J Exp Med 1982;55:1063-1074.

North RJ. The murine antitumor immune response and its therapeutic manipulation. Adv Immunol 1984;35:89-155.

O-Charoenrat P, Pillai G, Patel S, et. al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. Oral Oncol. 2003;39:386-90

Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globacan 2000. Int J Cancer 2001;94:153-156.

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31(1):103-15.

Rapidis AD, Wolf GT. Immunotherapy of head and neck cancer: current and future considerations. J Oncol 2009; 2009:346-345.

Ratain MJ, Karrison TG. Testing the wrong hypothesis in phase II oncology trials: there is a better alternative. Clin Cancer Res. 2007;13(3):781-2.

Ross G, Shoaib T, Soutar DS, et al. The Use of Sentinel Node Biopsy to Upstage the Clinically N0 Neck in Head and Neck Cancer. Arch Otolaryngol Head Neck Surg. 2002;128(11):1287-1291.

Rubinstein LV, Korn EL, Freidlin B, et. al. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 2005;23(28):7199-206.

Schilling B, Harasymczuk M, Schuler P, et al. IRX-2, a novel biologic, favors the expansion of T effector over T regulatory cells in a human tumor microenvironment model. J Mol Med (Berl) 2012;90:139-147.

Schilling B, Harasymczuk M, Schuler P, et al. IRX-2, a novel immunotherapeutic, enhances functions of human dendritic cells. PLoS One 2013;8:e47234.

Słotwińska SM, Słotwiński R. Host response, malnutrition and oral diseases. Part 1. Cent Eur J Immunol. 2014;39(4):518-21

Sparano A, Weinstein G, Chalian A, et. al., Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg. 2004;131:472-6.

Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst. 2002;94:252-66.

Verastegui E, Barrera J, Zinser J, et al. A natural cytokine mixture (IRX-2) and interference with immune suppression induce immune mobilization and regression of head and neck cancer. Int. J. Immunopharmac. 1997;19:619.

Whiteside TL, Butterfield LH, Naylor PH, et al. A short course of neoadjuvant IRX-2 induces changes in peripheral blood lymphocyte subsets of patients with head and neck squamous cell carcinoma. Cancer Immunol Immunother 2012;61:783-788.

Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab. 2007;51(4):301-23.

Wolf GT, Fee WE, Dolan RW, et al. Novel neoadjuvant immunotherapy regimen safety and survival in head and neck squamous cell cancer. Head Neck 2011;33:1666-1674.

†Important Note:

As of Protocol Amendment 4 all adjuvant, booster administration of study regimen has been discontinued. Randomized subjects will receive neoadjuvant treatment and will then be discontinued from further study drug. After discontinuation from study drug, all subjects will be followed for progression and survival as described in the protocol.

Appendix 1: American Joint Committee on Cancer: Staging of Head and Neck Cancer-Lip and Oral Cavity – TNM Staging

AJCC Staging Manual, 7th Edition

Definitions of TNM			
Primary Tumor (T)	Oral Cavity	T1	Tumor 2 cm or less in greatest dimension
		T2	Tumor >2 cm but not more than 4 cm in greatest dimension
		T3	Tumor >4 cm in greatest dimension
		T4a	Tumor invades adjacent structures (eg, through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, styloglossus], maxillary sinus, skin of face
		T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Regional lymph nodes (N)		N0	No regional lymph node metastasis
		N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension
		N2a	Metastasis in a single ipsilateral lymph node >3 cm but ≤ 6 cm in greatest dimension
		N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
		N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
		N3	Metastasis in a lymph node >6 cm in greatest dimension
Distant Metastasis		MX	Distant metastasis cannot be assessed
		M0	No distant metastasis
		M1	Distant metastasis

From AJCC Staging Manual, 7th Edition

Appendix 2: American Joint Committee on Cancer: Staging of Head and Neck Cancer-Lip and Oral Cavity – Stage Grouping AJCC Staging Manual, 7th Edition

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*	Any T	N3	M0
	T4b	Any N	M0
Stage IVC*	Any T	Any N	M1

* Stages 0, I, IVB and IVC are not eligible for the study.

From AJCC Staging Manual, 7th Edition

Appendix 3: Karnofsky Performance Status

Score	Performance
100	Normal: no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or do active work.
60	Requires occasional assistance from others; but able to care for most needs.
50	Requires considerable assistance from others, frequent medical care.
40	Disabled: requires special care and assistance.
30	Severely disabled: hospitalization indicated, death not imminent.
20	Very sick, hospitalization necessary, active supportive treatment necessary.
10	Moribund: fatal processes are progressing rapidly.
0	Dead

Source: Karnofsky D, Abelman W, Craver L, Burchenal J. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer 1948;1:634-56.

Appendix 4: Calculation of Creatinine Clearance by Cockcroft-Gault Equation

Formula: Creatinine Clearance = Sex (Male = 1.0, Female = 0.85) * ((140 - Age) / (Serum Creatinine)) * (Weight / 72)

Online calculator may be found at

http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault