A Window of Opportunity Trial of Cetuximab in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC)

NIDCR Protocol Numbers: 17-033-E; 17-034-E

NIDCR Grant Number: P50 DE026787

Principal Investigators: Justine Yang Bruce, MD
Randall J. Kimple, MD, PhD

NIDCR Program Official: Chiayeng Wang, PhD

NIDCR Medical Monitor: Kevin McBryde, MD

IND/IDE Sponsor: *Not applicable*

NCT03769311

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigators or Clinical Site Investigators: Justine Yang Bruce, MD and Randall J. Kimple, MD, PhD

Signed: _____ Date: _____

Name: Justine Yang Bruce, MD

Title: Associate Professor, Department of Medicine, University of Wisconsin School of Medicine and Public Health

Signed: _____ Date: _____

Name: Randall J. Kimple, MD, PhD

Title: Associate Professor, Department of Human Oncology, University of Wisconsin School of Medicine and Public Health

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse Event/Adverse Experience
ANC	absolute neutrophil count
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBC	complete blood cell count
CCND-1	cyclin D1
CFR	Code of Federal Regulations
CI	confidence interval
cm	Centimeter
CNS	Central nervous system
CRC	Clinical Research Committee (CRC)
CRF	case report form
CT	computed tomography
CTC	Common Toxicity Criteria
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTX	cetuximab
CTXR	cetuximab resistant
CTXS	cetuximab sensitive
CVA	cerebrovascular accident
dL	Deciliter
DLT	dose limiting toxicity
DOT	Disease Oriented Team
DSMC	Data Safety Monitoring Committee
DSMS	Data and Safety Monitoring System
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration

FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
HCl	hydrochloric acid
HER	human epidermal growth factor receptor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
hr	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intra uterine device
IV	Intravenous
kg	Kilogram
lb	Pound
mg	Milligram
min	Minute
mL	Milliliter
mm^3	cubic millimeters
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
NCI	National Cancer Institute
NDC	National Drug Code
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NS	Normal saline
OHRP	Office for Human Research Protections
OS	overall survival
PDX	patient-derived xenograft
PI	Principal Investigator
PHI	Protected Health Information

PI3K	phosphatidylinositol 3-kinase
PSR	Protocol Summary Report
PTEN	phosphatase and tensin homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RTK	receptor tyrosine kinase
SAE	Serious Adverse Event/Serious Adverse Experience
SCC	squamous cell carcinoma
SFK	Src Family Kinase
SOC	standard of care
SOP	Standard Operating Procedure
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risk to subjects or others
US	United States
USP	United States Pharmacopeia
UW	University of Wisconsin
UWCCC	University of Wisconsin Carbone Cancer Center
WHO	World Health Organization
WOCP	women of childbearing potential
wt	Weight

PROTOCOL SUMMARY

Title: A window of opportunity trial of cetuximab in patients with head and neck squamous cell carcinoma (HNSCC): examining the role of receptor tyrosine kinase AXL in HNSCC therapy resistance

Précis: This is a window of opportunity trial evaluating the hypothesis that AXL levels correlate with clinical response to cetuximab in head and neck patients. Patients with head and neck squamous cell carcinoma who are scheduled to undergo surgical resection of their tumor and are candidates for cetuximab chemotherapy are eligible to participate.

Objectives:

Primary:

1. To test the hypothesis that low AXL correlates with clinical response to cetuximab in head and neck cancer patients

Secondary:

1. To further describe the safety of pre-operative administration of cetuximab

Correlative:

1. To correlate AXL expression with change in Ki67 following cetuximab in HNC patients
2. To examine other putative markers of cetuximab sensitivity such as HER3 and change in circulating tumor cells
3. To establish the first panel of patient-derived xenografts from patients with known sensitivity or resistance to cetuximab

Population: 36 adult patients (≥ 18 years) of either sex and of any race or ethnicity, who have a biopsy proven, squamous cell carcinoma of the head and neck, are candidates for pre-operative therapy with cetuximab, and are scheduled for resection of the tumor.

Patients with advanced cutaneous head and neck squamous cell carcinoma are excluded.

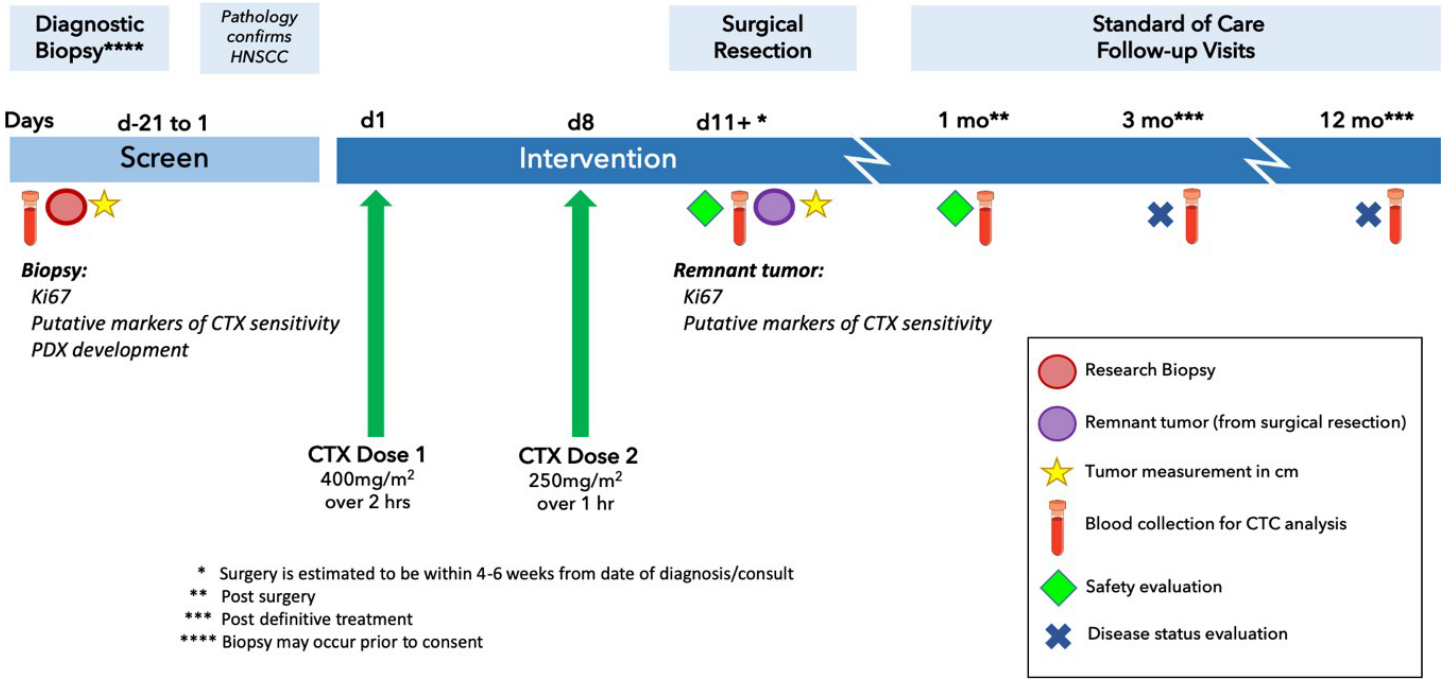
Phase: Window of Opportunity Study

Number of Sites: 1

Description of Intervention:	Following informed consent, tumor tissue from the research biopsy and a blood draw for circulating tumor cells will be obtained. The patient will then receive two weekly doses of pre-operative cetuximab during the interval between diagnostic biopsy and surgery ensuring that no delay in standard of care (SOC) will occur. For dose #1, patients will receive cetuximab 400 mg/m2 via intravenous infusion over 2 hours (maximum infusion rate 10 mg/min) as per the standard of care loading regimen for cetuximab monotherapy.[1] For dose #2, patients will receive cetuximab 250 mg/m2 via intravenous infusion over 1 hour (maximum infusion rate 10 mg/min) as per the standard of care dosing regimen for cetuximab monotherapy.[1] At the time of surgery, another blood draw will be obtained for analysis of circulating tumor cells, and a portion of the resected tumor will be obtained for study analysis. Correlative studies will include the measurement of proteins hypothesized to be involved in cetuximab resistance such as AXL, Ki67, EGFR, and HER3 expression from both the biopsy and the surgical specimen. Blood will be analyzed for correlative analysis of circulating tumor cells. Tissue from the research biopsy will be utilized for patient-derived xenograft (PDX) development.
Study Duration:	30 months
Subject Participation Duration:	13-16 months
Estimated Time to Complete Enrollment:	18 months

Schematic of Study Design:

The primary objective of this window of opportunity study is to test the hypothesis that low AXL expression correlates with clinical response to cetuximab in head and neck cancer patients. The secondary objective of this study is to further describe the safety of pre-operative administration of cetuximab. It is estimated that from the time of diagnosis/consult to resection of tumor is approximately 4-6 weeks. There is no absolute timeframe for study procedures to occur, although all protocol activities must be completed prior to resection.



This is a window of opportunity trial to study AXL and CTX in HNSCC patients. HNSCC patients who will undergo surgery will be identified. The tumor will be measured by the treating physician. A research biopsy will be taken and scored for Ki67 and proteins hypothesized to be involved in CTX resistance, such as AXL, EGFR and HER3. A section of the biopsy will be used for PDX development. A blood draw will be taken for circulating tumor cell analysis. Patients will receive two doses of cetuximab. Safety will be evaluated and blood will be collected for quantification of circulating tumor cells prior to resection. Remnant tissue from the resected tumor will be stained for Ki67 and compared to pre-treatment tumors. It will also be analyzed for proteins hypothesized to be involved in CTX resistance, such as AXL, EGFR and HER3. Patients will have blood draws for circulating tumor cells at 3 follow up timepoints: one month post-surgery, 3 months post definitive care and 12 months post definitive care. Patients will then continue on to standard of care.

1 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Justine Yang Bruce, MD University of Wisconsin Carbone Cancer Center WIMR Room 3019 1111 Highland Avenue Madison, WI 53705 Phone: (608) 262-4961 jybruce@medicine.wisc.edu Randall J. Kimple, MD, PhD University of Wisconsin Carbone Cancer Center WIMR Room 3107 1111 Highland Avenue Madison, WI 53705 Phone: (608) 265-9156 rkimple@humonc.wisc.edu
NIDCR Medical Monitor:	Kevin McBryde, MD
NIDCR Program Official:	Chiayeng Wang, PhD
Clinical Site Investigators:	Justine Yang Bruce, MD University of Wisconsin Carbone Cancer Center WIMR Room 3019 1111 Highland Avenue Madison, WI 53705 Phone: (608) 262-4961 jybruce@medicine.wisc.edu Randall J. Kimple, MD, PhD University of Wisconsin Carbone Cancer Center WIMR Room 3107 1111 Highland Avenue Madison, WI 53705 Phone: (608) 265-9156 rkimple@humonc.wisc.edu
Institutions:	*University of Wisconsin-Madison* Contact Person/Local Investigator: Justine Yang Bruce, MD University of Wisconsin Carbone Cancer Center 1111 Highland Avenue, WIMR 3109 Madison, WI 53705 Phone: (608) 262-4961 jybruce@medicine.wisc.edu

Other Key Personnel:

Co-Investigators

Clinical

Greg Hartig, MD
Department of Surgery
Division of Otolaryngology-Head & Neck Surgery
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue, MC 7375
Madison, WI 53792
Phone: (608) 265-8207
hartig@surgery.wisc.edu

Timothy M. McCulloch, MD
Department of Surgery
Division of Otolaryngology-Head & Neck Surgery
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue, MC 7375
Madison, WI 53792
Phone: (608) 263-0192
mccull@surgery.wisc.edu

Tiffany Glazer, MD
Department of Surgery
Division of Otolaryngology-Head & Neck Surgery
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue, MC 7375
Madison, WI 53792
Phone: (608) 265-8504
glazer@surgery.wisc.edu

Aaron Wieland, MD
Department of Surgery
Division of Otolaryngology-Head & Neck Surgery
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue, MC 7375
Madison, WI 53792
Phone: (608) 262-2876
wieland@surgery.wisc.edu

Seth Dailey, MD
Department of Surgery
Division of Otolaryngology-Head & Neck Surgery
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue, MC 7375
Madison, WI 53792-3284
Phone: (608) 265-8207
dailey@surgery.wisc.edu

Paul Harari, MD
Department of Human Oncology
University of Wisconsin School of Medicine and Public Health
K4/336, Clinical Science Center
600 Highland Avenue, MC 3674
Madison, WI 53792
Phone: (608) 263-5009
harari@humonc.wisc.edu

Scientific

Deric Wheeler, PhD
Department of Human Oncology
University of Wisconsin School of Medicine and Public Health
WIMR Room 3159
1111 Highland Avenue
Madison, WI 53705
Phone: (608) 263-3611
dlwheeler@wisc.edu

Seungpyo Hong, PhD
Pharmaceutical Sciences Division
University of Wisconsin School of Pharmacy
Rennebohm Hall
777 Highland Avenue
Madison, WI 53705
Seungpyo.hong@wisc.edu

Biostatisticians

Menggang Yu, PhD
University of Wisconsin
Department of Biostatistics and Medical Informatics
K6/436 Clinical Science Center
600 Highland Avenue
Madison, WI 53792
Phone: (608) 261-1988
meyu@biostat.wisc.edu

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Head and neck squamous cell carcinoma, and identification of potentially actionable mutations

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide with over 600,000 new cases diagnosed annually.[2] In the United States alone, in 2017, there were approximately 63,000 newly diagnosed HNSCC, with roughly 13,300 deaths.[3]

Head and neck cancer is a complex heterogeneous disease that arises from various sites including the oral cavity, tongue, pharynx, larynx and salivary glands. Over 90% of tumors that originate in the oropharyngolaryngeal axis are squamous cell carcinoma (SCC). Treatment for HNSCC patients includes surgery, radiation and chemotherapy in various combinations. Cure rates have improved only marginally over the last 30 years.[4] Typically, local or regional disease recurs in 30% of patients, and distant metastases appear in 25% of patients. The 5-year overall survival rate is 40%.[5] Despite the ability to cure localized and locally advanced disease, there is a significant unmet need for treatment of patients who undergo surgical resection of their head and neck cancer.

To identify molecular driver mutations in head and neck squamous cell carcinoma, the Cancer Genome Atlas Research Network profiled 279 HNSCC tumors and identified a series of mutations and amplifications. However, only a handful of identified oncogenes in head and neck squamous cell carcinoma are immediately targetable with agents in clinical development, namely epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), MET, cyclin D1 (CCND1) and phosphatidylinositol 3-kinase (PI3K) CA13.[6] The identification of these novel mutations and their ability to be effectively targeted expands the potential future treatment armamentarium for patients with head and neck squamous cell carcinoma, but the role they play in cetuximab resistance is unknown.

Cetuximab

In 2006, the FDA approved cetuximab, a monoclonal antibody against the EGFR, in the treatment of HNSCC. The addition of cetuximab to standard radiation improves absolute survival rates for newly diagnosed head and neck squamous cell carcinoma patients by approximately 10%[7,8] and is also valuable in the metastatic/recurrent setting where approximately 36% of patients experience response to cetuximab based combination therapy (vs. 20% to standard therapy).[9]

Although cetuximab offers a significant advance for many patients with head and neck squamous cell carcinoma, nearly two-thirds of EGFR expressing patients do not respond to cetuximab-based therapy. The response rate to cetuximab alone for patients with metastatic head and neck squamous cell carcinoma is only 10-20%, highlighting the need for improved treatments.[10,11] Virtually all patients who initially respond eventually become refractory to cetuximab. Intrinsic and acquired resistance to cetuximab is therefore a significant clinical problem in the treatment of HNSCC.[12]

Enhancing the effectiveness and survival impact of cetuximab would be highly valuable for the head and neck squamous cell cancer patient population.

Primary head and neck tumor sites and cetuximab usage

FDA approval has been issued for cetuximab (CTX) in the following settings:

i) locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy,
ii) recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-fluorouracil (5-FU), and
iii) recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Cetuximab is approved for squamous cell carcinomas of all head and neck sites. This approval includes usage in the adjuvant, recurrent or metastatic settings. In the landmark study of cetuximab in combination with concurrent radiotherapy for treatment in the locoregional setting, 424 patients were randomized. Sites of primary tumor represented by those 424 patients included oropharynx, hypopharynx, and larynx. A predominance of oropharyngeal primaries was enrolled with 56% of patients randomized to the concurrent cetuximab plus radiotherapy arm having oropharyngeal primaries. Sixty three percent (63%) of patients within the radiotherapy monotherapy arm had oropharyngeal primaries.[8]

In the EXTREME trial that led to approval of cetuximab in combination with 5-FU and platinum chemotherapy, 442 patients were enrolled with primary tumor sites including the oral cavity, oropharynx, hypopharynx, larynx, and a category of “other” unspecified squamous cell carcinomas of the head and neck. Again, the predominant primary tumor site was the oropharynx with 36% of patients randomized to chemotherapy plus cetuximab having primary oropharyngeal cancer. Thirty one percent (31%) of patients randomized to chemotherapy without cetuximab had an oropharyngeal primary. Squamous cell carcinomas originating from “other” head and neck sites accounted for 4 and 10% of primary tumors within the chemotherapy plus cetuximab and chemotherapy alone arms respectively.[9]

In the single-arm phase II study leading to approval of cetuximab monotherapy after platinum failure in the recurrent or metastatic setting, 103 patients were enrolled. Of those patients, pharyngeal primaries were again the most commonly enrolled, accounting for 38% of enrolled patients. Laryngeal primaries accounted for 20%. Primary paranasal sinus cancers accounted for 3%, while “other” and “unclassifiable” sites accounted for the remaining 39% of enrollment.[10] Other trials studying 1-3 weeks of anti-EGFR therapy demonstrated a significant decrease in tumor size in operable head and neck squamous cell carcinoma.[13,14]

Evidence for the usage of cetuximab in advanced cutaneous squamous cell carcinomas is lacking overall. As such, treatment of advanced cutaneous carcinomas will be excluded from this study.

Mechanisms of resistance

As the only molecular targeting agent approved in head and neck cancer therapy, detailed understanding of how head and neck squamous cell cancers become refractory to cetuximab therapy is central to further refining the impact of this promising molecular agent and its clinical efficacy. Furthermore, development of biomarkers leading to the identification of patients who will be responsive to cetuximab therapy is of high significance.

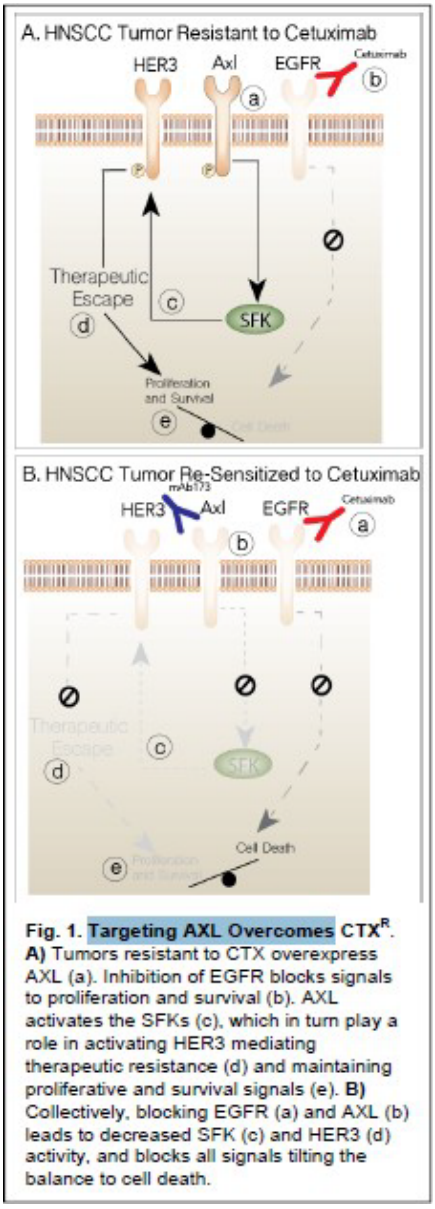


Fig. 1. Targeting AXL Overcomes CTX^R. **A)** Tumors resistant to CTX overexpress AXL (a). Inhibition of EGFR blocks signals to proliferation and survival (b). AXL activates the SFKs (c), which in turn play a role in activating HER3 mediating therapeutic resistance (d) and maintaining proliferative and survival signals (e). **B)** Collectively, blocking EGFR (a) and AXL (b) leads to decreased SFK (c) and HER3 (d) activity, and blocks all signals tilting the balance to cell death.

Resistance to cetuximab has been explored, and several mechanisms of resistance have been reported including: altered angiogenesis,[15-17] increased EGFR activity,[18] increased expression of human epidermal growth factor receptor (HER) family ligands,[19,20] decreased EGFR degradation,[18,21] epithelial to mesenchymal shift,[22] phosphatase and tensin homolog (PTEN) degradation,[23] a role for the nuclear EGFR signaling network[20] and activation of HER3.[18,24-29] Some tumors are intrinsically resistant to CTX and demonstrate no response to even the first dose of drug.[10] The mechanism of resistance is not known. Treatment of two doses of CTX has not been shown to lead to clinical resistance to therapy. HER3 is a member of the EGFR family of receptor tyrosine kinases (RTKs) and is unique in the absence of intrinsic kinase activity. Despite this lack of kinase activity, HER3 is phosphorylated by hetero-dimerization with other family members.[30] HER3 has multiple binding sites in the cytoplasmic tail for the regulatory subunit of phosphatidylinositol 3-kinase (PI3K) to be recruited and thus transmit signals to the PI3K/Akt/ mechanistic target of rapamycin (mTOR) survival pathway.[31,32] Recent work by several laboratories, has found a strong role for HER3 activity in therapeutic resistance.[24-30,33] (Figure 1)

To identify drivers of CTX resistance in HNSCC, University of Wisconsin (UW) investigators have utilized HNSCC human tumor specimens, patient-derived xenografts (PDXs) and a series of acquired and intrinsically resistant *in vitro* and *in vivo* model

systems.[18,33-37] Investigation of these models to isolate molecular mechanisms of cetuximab resistance has generated several significant findings.

Tissue analysis of a head and neck squamous cell carcinoma patient cohort (n=63) identified that the receptor tyrosine kinase AXL was overexpressed in both human papillomavirus (HPV) positive and HPV-negative head and neck squamous cell carcinoma tumors and was significantly associated with higher pathologic grade, distant metastases, and shorter relapse free survival.[37] Cetuximab-resistant head and neck squamous cell carcinoma patient-derived xenografts, relative to cetuximab-sensitive (CTXS) tumors, expressed significantly elevated levels of total and activated AXL.[35,37] HPV status does not predict CTX response.[38]

Models (*in vitro* and *de novo (in vivo))* of acquired resistance showed increased expression and activity of AXL.[35,37,39] Models of intrinsically resistant HNSCC lines showed increased AXL expression and activity.[35,37] Genetic ablation or therapeutic inhibition (antibody or small molecule inhibitors) of AXL led to increased sensitivity to cetuximab, both *in vitro* and *in vivo.*[35,37] Overexpression of AXL in cetuximab sensitive HNSCC lines rendered them resistant, whereas a kinase dead AXL retained sensitivity.[35] Proteomic analysis within cetuximab resistant models indicated a strong linkage between AXL, Src Family Kinase (SFK) and HER3 activity; a novel pathway leading to therapeutic escape from cetuximab therapy driven by AXL in HNSCC (data not shown).

To correlate AXL expression with clinical response to CTX, we will use both change in tumor dimensions as measured by treating physician and change in Ki67 expression (% cells with Ki67 staining). Ki67 staining has been used successfully in HNSCC (and other tumor types) window trials as a surrogate marker of response to cetuximab and to assess the pharmacodynamic effects of novel targeting agents and can serve as a surrogate for clinical response.[14,40-50]

Circulating Tumor Cells as a predictive biomarker for HNSCC

Circulating tumor cells are tumor cells that detach from the primary tumor or metastasis and circulate in the bloodstream of a cancer patient. Circulating tumor cells are extremely rare and are heterogeneous,[51] presenting a tremendous challenge for efficient, clinically significant detection of circulating tumor cells.

Advances in biomedical engineering have led to the development of capture devices for circulating tumor cells. Some of the most promising devices generally combine immunocytochemical capture with microfluidic devices to capture circulating tumor cells. CellSearch is the only FDA-approved system for clinical use (metastatic breast, prostate, and colorectal cancer). In these diseases, the presence and the number of circulating tumor cells have been shown to be prognostic for development of metastatic disease.[52]

However, the clinical use of circulating tumor cells has been limited due to low sensitivity of current circulating tumor cell capture technology. For example, the only reports of circulating tumor cells in HNSCC involved CellSearch, and they were only able to detect circulating tumor cells in 1 out of 3 patients.[53] Hence, there has been strong interest in the development of more sensitive devices to capture and evaluate circulating tumor cells as predictive biomarkers for cancer treatment.

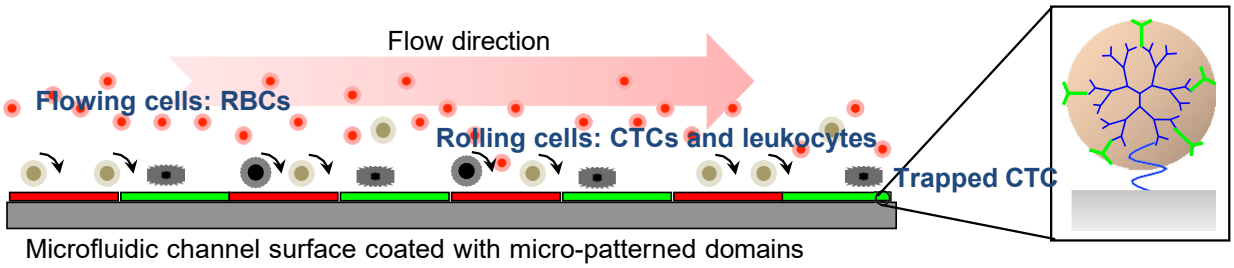
Highly Sensitive CTC Capture Assay

Utilizing several biomimetic technologies at the University of Wisconsin (UW), we have developed a novel and highly sensitive assay to capture circulating tumor cells, as illustrated in Fig. 2. First, it has a biomimetic surface that induces cell rolling. The biofunctional surface is engineered by immobilizing selectins which can engage cell surface receptors to induce cell rolling.[54] The cell rolling effect slows down the velocity of tumor cells and in turn improves capture specificity.[54]

Another unique feature of this device is application of nanotechnology to cell capturing. By utilizing a flexible dendrimer nanoparticle, the device enables multivalent binding between antibody-functionalized dendrimers and tumor cells.[55] Multivalent binding can improve binding affinity by as much as 106 times, thus improving sensitivity to capture circulating tumor cells.[56]

Lastly, the circulating tumor cells assay can incorporate multiple antibody ligands for tumor cell capture.[56] This enables the capture of circulating tumor cells with different surface biomarkers, such as cells that have undergone epithelial-mesenchymal transition.

In prior work at the University of Wisconsin, the surfaces of the highly sensitive assay captured a high number of circulating tumor cells (221 circulating tumor cells per mL of blood, ranging from 36 to 1,135) from all 27 patients recruited[57], which is significant considering that CellSearch could only detect circulating tumor cells from 1 of every three HNSCC patients.[53] Importantly, when the UW results were compared to the previously reported clinical data from similar groups of cancer patients with comparable or worse cancer stages using CellSearch,[53,58-60] the UW surfaces apparently achieved three orders of magnitude higher counts of circulating tumor cells than CellSearch (1,613 vs. 4.7 circulating tumor cells in 7.5 mL of blood). One can argue that the cells we captured could be non-circulating tumor cells; however, the UW device captured only 2.1 circulating tumor cells (could be epithelial cells) per mL from healthy donors' blood (n=8), mitigating the concern of potential false-positive detection.



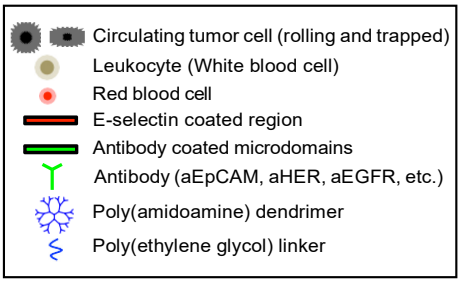


Fig 2. A schematic diagram of CTC capture on a micropatterned surface using iterative cell rolling (E-selectin: red) and multivalent stationary adhesion (antibody: green). The inset diagram represents immobilized antibody molecules (e.g. aEpCAM, aPD-L1, and aEGFR) through a flexible polymer nanolinker (dendrimer and PEG: blue) by which the multivalent effect can be achieved through locally concentrated antibodies.

Overall Goal and Importance of the Study

This clinical trial seeks to obtain baseline tissue from a research biopsy and circulating tumor cells to determine whether AXL expression pre- treatment correlates to clinical outcomes after two doses of cetuximab. The importance of this study is to describe if AXL expression can be used as a biomarker to predict clinical response to cetuximab treatment.

2.1 Rationale

Despite the broad advancement of molecularly targeted therapies across the oncology spectrum, cetuximab remains the only approved molecular targeted drug for the treatment of patients with head and neck squamous cell carcinoma. Cetuximab improves 5-year overall survival when combined with radiation in the curative treatment setting from 36.4% with radiation therapy alone to 45.6% with the combination.[7,8] When combined with chemotherapy in the metastatic/recurrent setting, cetuximab improves overall survival by 2.7 months.[9] This survival impact is modest, however, and the response rate to cetuximab alone for patients with metastatic head and neck squamous cell carcinoma is only about 10-20%, highlighting the need for improved treatments.[10,11] Enhancing the effectiveness and survival impact of cetuximab would be highly valuable for the head and neck squamous cell carcinoma patient population.

Preliminary data[35,37] suggest a role for AXL in cetuximab resistance in HNSCC, and the potential for AXL to serve as a functional biomarker for cetuximab response in humans. Targeting AXL has the potential to re-sensitize tumors to cetuximab therapy.

In this study, we propose a window of opportunity trial to evaluate levels of AXL in tumors pre- CTX treatment and compare that to the clinical response and changes in the size of the primary tumor mass or lymph nodes. Study participants will be treated with two doses of cetuximab given intravenously as per the standard of care regimen, except that the cetuximab will be administered during the interval between diagnostic biopsy and surgery instead of post-surgery. For dose #1, patients will receive a loading dose of cetuximab 400 mg/m2 via intravenous infusion over 2 hours as per the standard of care loading dose regimen for cetuximab monotherapy. For dose #2, patients will receive cetuximab 250 mg/m2 via intravenous infusion over 1 hour as per the standard of care regimen for cetuximab monotherapy.

We plan to use a portion of the pre-cetuximab treatment tumor samples to study correlative objectives of the role of AXL in cetuximab resistance and to create the first cohort of patient derived xenografts with known sensitivity or resistance to cetuximab treatment. These will be used to evaluate if targeting AXL in cetuximab resistant patient-derived xenografts will re-sensitize the tumor to cetuximab. In addition, blood samples will be collected to evaluate whether circulating tumor cells, among other biomarkers, correlate with response to treatment.

We hypothesize that low AXL correlates with clinical response to CTX in HNSCC. Furthermore, we hypothesize that circulating tumor cells correlate with response to treatment and that the AXL/HER3 circuit can be used as a biomarker to predict cetuximab resistance in HNSCC.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

Cetuximab-related risks include infusion reactions, acneiform rash, and in rare cases cardiopulmonary arrest and or interstitial lung disease (see details in section 6.2.1.) Other risks include those related to the research biopsy (bleeding and infection at the site where the needle is inserted, brief pain during the procedure) and blood draws (bruising, swelling at the injection site, dizziness and lightheadedness), as well as loss of confidentiality. Other study-related procedures that may introduce “risks” to study participants include:

1) Urine/serum pregnancy tests;
2) Premedication with diphenhydramine/acetaminophen prior to Cetuximab infusions;
3) Potential medications used to treat Cetuximab-related rashes (Hydrocortisone, Doxycycline, Clindamycin);
4) Risks of developing and/or correction of electrolyte disturbances due to Cetuximab infusion

2.2.2 Potential Benefits

There may be clinical benefit to the two administrations of cetuximab prior to surgery. Preliminary preclinical data[35,37] suggest a role for AXL in cetuximab resistance in head and neck squamous cell carcinoma. AXL may potentially serve as a functional biomarker for cetuximab response in humans. Targeting AXL has the potential to resensitize tumors to cetuximab therapy. Treatment with two doses of cetuximab may offer clinical benefit including decreasing the tumor volume of the cancer to allow for easier resection at the time of surgery. Other benefits may include a predictive response that may determine sensitivity of a patient's cancer to systemic treatment.

3 OBJECTIVES

3.1 Study Objectives

Primary: To evaluate the hypothesis that low AXL correlates with clinical response to cetuximab in head and neck cancer patients

Secondary: To further describe the safety of pre-operative administration of cetuximab

Correlative:

1. To correlate AXL expression with change in Ki67 following cetuximab in HNC patients
2. To examine other putative markers of cetuximab sensitivity such as HER3 and change in circulating tumor cells and other biomarkers
3. To establish the first panel of patient-derived xenografts from patients with known sensitivity or resistance to cetuximab

3.2 Study Outcome Measures

3.2.1 Primary Endpoint

The objective response rate (ORR) measured by clinical examination and clinical measurements at the time of diagnosis and within 48 hours prior to surgery

This objective is to compare levels of AXL prior to CTX treatment to the clinical response and changes in the size of the primary tumor mass or lymph nodes. Patients will have their squamous cell carcinoma (either primary site or nodal metastases) measured in centimeters by the clinical

team via clinical measurement at two timepoints: 1) the time of diagnosis (pre- CTX) and 2) after treatment with 2 doses of cetuximab and within 48 hours prior to surgery (post-CTX).

3.2.2 Secondary Endpoint

The rate of hospital re-admissions for wound care or surgical complications attributed to cetuximab (such as fistula or deep cellulitis) within 28 days after surgery

Although the use of cetuximab pre-operatively has been studied in a pre-operative trial[14], this clinical trial will expand upon this information to further evaluate any other complications during surgery due to pre-operative cetuximab. We will also plan a descriptive analysis of all AEs and SAEs associated with pre-operative cetuximab.

3.2.3 Exploratory Endpoints

3.2.3.1 Change in Ki67 from pre- versus post-cetuximab treated tumors and its correlation with levels of AXL expression pre-cetuximab treatment

3.2.3.2 Correlation of measures of putative markers of cetuximab sensitivity, including protein, RNA, circulating tumor cells with cetuximab response, measured by Ki67

3.2.3.3 Establishment of patient-derived xenografts with known sensitivity/resistance to cetuximab

4 STUDY DESIGN

This clinical trial is a single-site, single arm, open label, window of opportunity study for patients with squamous cell carcinoma of the head and neck. Subjects (targeted N=36) are patients who have biopsy-proven, squamous cell carcinoma of the head and neck, excluding advanced cutaneous head and neck squamous cell carcinoma, who are anticipated to undergo surgical resection of the tumor, and who are candidates for cetuximab pre-operative therapy. Patients with newly diagnosed cancer or those who present with recurrent disease are eligible for this trial. All patients will undergo a research biopsy (in clinic or at the time of panendoscopy—not standard of care) and a staging workup with cross-sectional imaging of the neck (standard of care).

<u>Research-related Biopsies and Blood Draws</u>

Research-related procedures include a separate research biopsy of the tumor at the time of the diagnostic biopsy for analysis of Ki67, putative markers of CTX sensitivity, and research-related blood draws for collection of circulating tumor cells at five timepoints: screening visit, within 24 hours prior to surgery, and at follow-up visits: approximately 1 month post-surgery, as well as approximately 3 and 12 months post definitive care. The tissue obtained for research biopsy will be placed in culture media or saline and provided to the biologic correlate study team. If pathology confirms a diagnosis other than HNSCC, the patient will be removed from the study, and the research biopsy tissue will be released to the University of Wisconsin Translational Science BioCore (TSB) Biobank. If the clinical biopsy is inconclusive, the research tissue will be released back to University of Wisconsin Surgical Pathology department to aid in a clinical diagnosis. The research-related blood draws will be given directly to the biologic correlate study team for quantification of circulating tumor cells and/or other biomarkers.

Cetuximab Administration in the Pre-operative Setting

Cetuximab is an FDA approved chemotherapy agent for the treatment of (a) locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy, (b) recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU, and (c) recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. Treatment with cetuximab prior to surgical resection is considered the investigational portion of this study, as neoadjuvant cetuximab is not considered standard of care. However, treatment with cetuximab as a monotherapy may offer a benefit to patients as cetuximab is a known and approved chemotherapy agent for the treatment of head and neck cancer. In patients with recurrent and/or metastatic HNSCC with progression on platinum-based chemotherapy, those patients who were treated with cetuximab monotherapy had overall response rates from 10-13% and disease control rates from 46-56%.[61] Although surgical resection will offer definitive treatment for local HNSCC, use of neoadjuvant cetuximab may offer disease response such as shrinkage of the tumor that may offer improved surgical resection.

Cetuximab will be given twice via IV infusions at pre-specified doses within a 14-day period between the time of their biopsy confirming their cancer and their scheduled surgery. Given that the standard of care time interval between diagnosis/consult and curative surgical resection is approximately 4-6 weeks at the University of Wisconsin, treatment with pre-operative cetuximab is not anticipated to delay curative surgical resection. No dose reductions of cetuximab are allowed although the rate of infusion of the drug can be reduced at the discretion of the investigator as per the standard of care infusion rate modifications noted in the FDA prescribing information of cetuximab.

Surgical Resection

The surgical resection is considered standard of care therapy for this study population. Patients will undergo definitive standard of care surgery within 4 weeks of the first protocol dose of cetuximab.

Specimens from the tumor resection will be transferred to pathology in culture media or saline per standard operating procedures. The biologic correlate study team will wait for the pathology team to access the specimen in the gross room and then will be given a portion of tissue that will not be required for diagnosis (i.e., remnant). The study team will then process and embed that fresh tissue to an FFPE block for downstream studies. Alternatively, the biologic correlate study team will request 20 x 5 µm unstained FFPE slides from the diagnostic tissue after surgical pathology clinical review is complete.

Post-Surgical Assessment

Patients will be assessed for post-surgical complications (readmission, wound healing, infection) at 1 month +/- 2 weeks post-surgery. Complications will be categorized as related, probably related, possibility related, unlikely related, or unrelated to cetuximab.

Post-surgical adjuvant therapy will be delivered based on standard of care therapy as per recommendations of the University of Wisconsin Multidisciplinary Head and Neck Oncology Tumor Board. Receiving the two doses of cetuximab in the pre-operative setting will not be grounds for exclusion of cetuximab use at a later point. Such usages would include concurrent chemoradiotherapy,[8] palliative combination chemotherapy[9] and/or palliative monotherapy with cetuximab.[10]

Distant metastatic disease and/or unresectable recurrent locoregional disease will be managed as per the institutional standard of care.

Expected duration of subject participation is approximately 13 to 16 months. The time to complete study enrollment is estimated to be 18 months. The time to complete the study analysis is estimated to be 30 months (from time of first patient enrolled to the time of last patient completed treatment).

4.1 Substudies (if applicable)

Not applicable.

5 STUDY ENROLLMENT AND WITHDRAWAL

This study is anticipated to enroll a target sample size of 36 subjects. We estimate approximately 100 subjects will be screened to reach the target enrollment.

5.1 Subject Inclusion Criteria

Adult men and women and members of all races and ethnic groups are eligible for this trial. Persons with impaired decision-making capacities will not be eligible for enrollment in this study. Eligibility criteria will be assessed via clinical labs, review of medical records as well as self-reporting. Subjects will be recruited from the University of Wisconsin Hospital and Clinics.

Step 1 registration will occur when subject has signed consent and consent has been registered (added) to ONCORE.:

- Age ≥ 18 years
- Informed consent: patients must be informed of the investigational nature of the study and must be able to sign a written informed consent.
- Inclusion criteria for research biopsy (screen)
  - Patients must have suspected or known clinical presentation of head and neck squamous cell carcinoma or a recurrence of head and neck squamous cell carcinoma after initial therapy. For newly suspected head and neck cancer, the procedure will obtain tissue for both standard of care biopsy and additional tissue for research.
  - Participants must have sufficient tumor volume (approximately 10 cc) to accommodate at minimum 2-3 core samples for the research biopsy. This will be approximated based on clinical evidence, such as physician visualization or palpitation.
  - Patients are required to consent to the TSB Biobank protocol (2016-0934) as part of this study.
  - Surgical management must be the chosen modality for management of the head and neck squamous cell cancer.
    - Other therapeutic modalities may follow, but surgery must be the choice for first therapy rendered.

For Step 2 enrollment on this study an individual must meet all criteria for Step 1 and the following criteria:

- Inclusion criteria for cetuximab treatment:
  - Patients must have a biopsy proven, squamous cell carcinoma of the head and neck, excluding advanced cutaneous head and neck squamous cell carcinoma.
  - ECOG performance status £ 1
  - Women of childbearing potential (WOCP) must not be pregnant (confirmed by a negative urine/serum pregnancy test within 7 days of cetuximab treatment). In addition, a medically acceptable method of birth control must be used such as an oral, implantable, injectable, or transdermal hormonal contraceptive, an intrauterine device (IUD), use of a double barrier method (condoms, sponge, diaphragm, or vaginal ring

with spermicidal jellies or cream), or total abstinence during the study participation and for 6 months after last dose of study drug. Women who are postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) are not considered to be WOCP.

- Men who are not surgically or medically sterile must agree to use an acceptable method of contraception. Male patients with female sexual partners who are pregnant, possibly pregnant, or who could become pregnant must agree to use condoms during the study and for 6 months post study drug. Total abstinence for the same study period is an acceptable alternative.
- Patients with other concomitant malignancies are allowed to participate on the clinical trial as long as the surgical resection of the head and neck squamous cell carcinoma is clinically indicated.
- Patients with metastatic disease are allowed to participate on the clinical trial as long as the surgical resection of the head and neck squamous cell carcinoma is clinically indicated.
-

5.2 Subject Exclusion Criteria

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

- Diagnosis of nasopharyngeal carcinoma, advanced cutaneous squamous cell carcinoma of the head & neck, and salivary gland tumors
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol
- Prior chemotherapy, radiotherapy, or major surgery within 8 weeks of study enrollment or those who have not recovered (to grade ≤ 1 or baseline) from clinically significant adverse events due to agents administered more than 8 weeks earlier (alopecia and fatigue excluded). Clinical significance to be determined by the study investigator
- Prior cetuximab therapy is allowed so long as administered ³ 8 weeks ago.
- History of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab
- Pregnancy, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of trial treatment
- Ongoing or active infection, including active tuberculosis or known infection with the human immunodeficiency virus (HIV). Patients with chronic, stable infections such as hepatitis C with an undetectable viral load, or HIV

infection on highly active antiretroviral therapy with undetectable viral load are allowed on the clinical trial.
- Ongoing treatment with other investigational agents.
- Any of the following cardiac conditions:
  - uncontrolled or poorly-controlled arrhythmia or uncontrolled cardiac insufficiency
  - uncontrolled or poorly-controlled hypertension (>180 mmHg systolic or > 130 mmHg diastolic)
- Any of the following conditions:
  - serious or non-healing wound, ulcer, or bone fracture
  - history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of study enrollment
  - history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study enrollment
  - history of myocardial infarction, ventricular arrhythmia, stable/unstable angina, symptomatic congestive heart failure, coronary/peripheral artery bypass graft or stenting or other significant cardiac disease within 6 months prior to study enrollment
  - history of arterial or venous thrombosis/thromboembolic event, including pulmonary embolism within 6 months of study enrollment
  - any condition requiring the use of immunosuppression, excluding rheumatologic conditions treated with stable doses of corticosteroids
  - Use of herbal supplements (St. John's Wort, gingko biloba, etc.) within one week of cetuximab treatment

For patients who do not meet eligibility criteria for Step 2 of the study, the tissue from the research biopsy will be released to the TSB Biobank or back to surgical pathology if needed for a clinical diagnosis.

5.3 Strategies for Recruitment and Retention

The most common method that will be used to recruit subjects is through pre-screening of medical records for patients of a study physician. Members of the study team will preview the schedules of the study physicians to determine the gross eligibility of upcoming patients. When a patient may meet gross eligibility, study team members will notify the physician. At the patient's next clinic visit, the physician may then include a discussion about study participation with the patient.

5.3.1 Subject Remuneration

Subjects are eligible to receive up to $200 for participating in this study to offset the barriers of the extra research procedures and visits. Participants will be provided remuneration in the amount of $100 after the research biopsy, and $50 after each CTX administration.

5.4 Treatment Assignment Procedures

Not applicable. This is a single arm Window of Opportunity study.

5.5 Subject Withdrawal

Subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation.

5.5.1 Reasons for Withdrawal

In addition to discontinuation from therapy related to toxicities as outlined in the Halting Rules of Section 9.5, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject.
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons.
  - If a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the electronic case report form (eCRF).
- A female subject becomes pregnant.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The study team should contact the subject or a responsible relative by telephone to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject’s study withdrawal should be made with an explanation of why the

subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

If a subject is unevaluable for safety and efficacy endpoints (i.e., lacks molecular/correlative studies, and creation of PDXs, subject has not received both cetuximab doses in their entirety and/or has not had surgical resection of the tumor), then the subject will be replaced at the discretion of the principal investigator.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to NIDCR and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

6 STUDY INTERVENTION

6.1 Study Product Description

Cetuximab (Erbitux®) is a Monoclonal Antibody/Epidermal Growth Factor Receptor (EGFR) Inhibitor. It is indicated for the treatment of:

- locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation therapy;
- recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU; and
- recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

See Package Insert for further information.

6.1.1 Acquisition

Commercial Cetuximab will be utilized in this study. Cetuximab will be prepared and administered per UWHC pharmacy and hospital guidelines.

See Package Insert for further information.

6.1.2 Formulation, Packaging, and Labeling

Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a solution with no preservatives, which contains 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

Cetuximab is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.

Cetuximab can be supplied to two dosage forms:

- A 100 mg/50 mL, single-use vial, individually packaged in a carton (NDC 66733-948-23)
- A 200 mg/100 mL, single-use vial, individually packaged in a carton (NDC 66733-958-23)

6.1.3 Product Storage and Stability

Product vials will be stored under refrigeration at 2º C to 8º C (36º F to 46º F). Product will not be frozen. Increased particulate formation may occur at temperatures at or below 0º C. This product contains no preservatives. Preparations of Erbitux in infusion containers are chemically and physically stable for up to 12 hours at 2º C to 8º C (36º F to 46º F) and up to 8 hours at controlled room temperature (20º C to 25º C; 68º F to 77º F). Any remaining solution will be discarded in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2º to 8º C. Any unused portion of the vial will be discarded.

6.2 Dosage, Preparation and Administration of Study Product

Cetuximab Preparation

Cetuximab will not be administered as an intravenous push or bolus. It will only be administered via infusion pump or syringe pump. The infusion rate will not exceed 10 mg/min.

Cetuximab will be administered through a low protein binding 0.22-micrometer in-line filter.

Parenteral drug products will be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. The solution is not to be shaken or diluted.

Cetuximab Administration Guidelines
Treatment with cetuximab will occur during the period between initial diagnosis and surgical resection. The standard of care (SOC) commonly utilizes approximately 4 weeks after diagnosis for preoperative scheduling and medical optimization. As such, this clinical trial does not delay standard of care curative treatment for head and neck cancer.

Prior to administration of cetuximab, subjects will be premedicated with diphenhydramine and acetaminophen as described in Section 6.6.

For Dose #1, subjects will be treated with cetuximab 400 mg/m^2 via intravenous infusion over 2 hours (maximum infusion rate 10 mg/min) as per the standard of care loading regimen for cetuximab monotherapy.[1]

For Dose #2, subjects will be treated with cetuximab 250 mg/m^2 via intravenous infusion over 1 hour (maximum infusion rate 10 mg/min) as per the standard of care dosing regimen for cetuximab monotherapy.[1]

See section 6.6 for concomitant medication as cetuximab pretreatment.

<u>Cetuximab Administration Monitoring</u>

- Vitals signs will be monitored every 15 minutes for the first hour, and then every 30 minutes until cetuximab infusion is complete for the first infusion as per the University of Wisconsin Hospital and Clinic guidelines. The nurse should remain with the patient for the first 15 minutes of drug administration for the first and second dose of cetuximab administration as per the University of Wisconsin Hospital and Clinics guidelines
- Hypersensitivity reaction to cetuximab can occur. For first and second dose, patient should be treated in a location to optimize emergency care.
- For the first dose of cetuximab, the subject must remain in the treatment area for 60 minutes following the completion of the cetuximab as per the University of Wisconsin Hospital and Clinics guidelines.

<u>Supportive Care</u>

Optimal patient care is to be given to all patients.

6.2.1 Potential adverse events and precautions

Infusion Reactions
Serious infusion reactions can occur during cetuximab administration. Serious infusion reactions include rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2–5% of patients in prior clinical studies with a fatal outcome in 1 patient [Cetuximab FDA prescribing information].[8,10,62,63]

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Thus, patients must be monitored for at least 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). For any subjects who experience an infusion reaction, longer monitoring may be necessary and is appropriate to confirm resolution of the event.

In the event of an infusion reaction,

- For NCI CTC grade 1, grade 2, and non-serious grade 3 infusion reaction, cetuximab will be temporarily held with administration of emergency medications as appropriate by the treating physician. Upon resolution of the infusion reaction, subjects may be rechallenged with cetuximab at a reduced infusion rate.
- For serious grade 3 and all grade 4 infusion reactions, cetuximab will be permanently discontinued.
- All subjects should receive appropriate medical intervention as appropriate by the treating physician
- Emergency medications to be available in the event of an infusion reaction include:
  - Diphenhydramine 25-50 mg IV
  - Dexamethasone 4-10 mg IV
  - Albuterol nebulization solution 2.5 mg/3ml

Cardiopulmonary Arrest
Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone.[8] Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last

dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. In Study 2, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 215 patients treated with chemotherapy alone.[9] Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin. Cardiopulmonary arrest and/or sudden death has been observed in a small percentage of patients during the trials that have led to approval of cetuximab, resulting in the issuance of an FDA black box warning.[1]

During cetuximab treatment and after completion of cetuximab treatment, subjects will have close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium.

Development of cardiopulmonary arrest will result in permanent discontinuation of cetuximab.

Pulmonary Toxicity
Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in colorectal cancer and head and neck cancer.[8,10,63]

- Subjects who develop acute onset pulmonary symptoms should have the cetuximab withheld and be evaluated by the treating physician.
- Subjects who have confirmed interstitial lung disease after treatment with cetuximab will be permanently discontinued from cetuximab treatment.

Dermatologic Toxicity
Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving cetuximab therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving cetuximab.[8,10,62,63] Severe acneiform rash occurred in 1–17% of patients. Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days.

- Study subjects will be monitored for dermatologic toxicities and infectious sequelae.
- Subjects will be instructed to limit sun exposure during cetuximab treatment
- Severe (NCI CTC Grade 3 or 4) acneiform rash will result in discontinuation of cetuximab therapy.[1]

- Intolerable grade 2 rash, despite maximum supportive care, will result in discontinuation.
- NCI CTC Grade 1 or 2 rash is to be treated with one or more of the following medications at the treating physician's discretion, based upon supportive care evidence.[64] Potential medications that can be used for the treatment of cetuximab-related rash may include, but are not limited to, the following:
    - Hydrocortisone 1 to 2.5% lotion
    - Doxycycline 100 mg bid
    - Clindamycin 1% lotion

Hypomagnesemia and Electrolyte Abnormalities

- Periodic monitoring for hypomagnesemia, hypocalcemia, and hypokalemia will be performed during and after completion of cetuximab. All abnormalities will be noted in the patient's medical record. The treating clinician will determine if the abnormality is clinically significant. Repletion of electrolyte deficits will be performed as per discretion of the treating physician.

Assessment of Research Biopsy Site

- Assessment of the research biopsy site will be monitored by treating physician until resolution.

6.3 Modification of Study Product Administration for a Subject

Dose Delays/Dose Modifications

- No dose modifications will be planned. Please refer to section 6.2.1 (subsection, Infusion Reactions) for more information regarding infusion rate decreases in the setting of infusion reaction.
- Dose delays secondary to intolerance (such as infusion reactions) are permitted. Subjects can be rechallenged with cetuximab within 3 days but will otherwise be discontinued from the study.
- Expected adverse events that would delay cetuximab infusion:
    - Grade 3 or higher nausea, vomiting, diarrhea, stomatitis, or rash uncontrolled despite maximal medical management due to a toxicity that is considered at least PROBABLY related to study treatment
    - Any other Grade 3 or higher non-hematologic toxicity, except grade 3 fatigue lasting >7 days, due to a toxicity that is considered at least PROBABLY related to study treatment
    - Grade 3 or 4 electrolyte abnormalities that are corrected within 48 hours will not be considered a serious adverse event.

6.4 Accountability Procedures for the Study Product

Cetuximab will be obtained and purchased as a commercial supply. The investigator or an approved representative (e.g. pharmacist) must maintain accurate records of dates and quantities of CTX dispensed under this study, and to whom study drug is dispensed.

Cetuximab should be stored in a secure area according to local regulations. Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations.

Drug Destruction

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place.

6.5 Assessment of Subject Compliance with Study Product Administration

Not applicable.

6.6 Concomitant Medications/Treatments

Prior to cetuximab (CTX) administration, participants will be premedicated with two medications, taking place 30-60 minutes prior to treatment:

- an H1 antagonist (50 mg of diphenhydramine) intravenously administered over 1 minute, taking place 30–60 minutes prior to the first dose; premedication will be administered for the subsequent cetuximab dose based upon clinical judgment and presence/severity of prior infusion reactions.[1]

- Acetaminophen (650 mg orally) will be administered 30-60 minutes prior to chemotherapy as per University of Wisconsin Hospital and Clinics guidelines.

7 STUDY SCHEDULE

See table in Appendix A. When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

COVID-19 testing: Literature reports suggest that SARS-CoV-2 can be detected in the saliva of patients known to be infected with the virus. Therefore COVID-19 testing may be required per UWHC recommendations for aerosolizing procedures (research biopsy for correlative study).

7.1 Screening / Baseline Visit (Day -21 to 1)

Study Visit 1 and 2

- Informed consent/HIPAA authorization obtained prior to any research procedures. Subjects will also be required to sign biobanking consent for banking of residual study samples. (research-related)
- Demographics (recorded for the study from medical records maintained as part of standard clinical care)
- Medical history including prior therapies and pathology (recorded for the study from medical records maintained as part of standard clinical care)
- Concomitant medications (recorded for the study from medical records maintained as part of standard clinical care)
- Physical exam, height (screening only), weight (recorded for the study from medical records maintained as part of standard clinical care)
- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care)
- ECOG performance status (recorded for the study from medical records maintained as part of standard clinical care)
- CBC with differential (recorded for the study from medical records maintained as part of standard clinical care)
- Blood chemistries (sodium, potassium, chloride, bicarbonate, BUN creatinine, glucose, AST, ALT, Alk Phos, T. bili, calcium, magnesium,
- T. protein and albumin (recorded for the study from medical records maintained as part of standard clinical care)
- Within 7 days prior to initiation of cetuximab: Urine pregnancy test for women of childbearing potential (WOCP). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. (standard clinical care for CTX administration)
- Adverse event evaluation (standard clinical care for CTX administration)
- Research biopsy for biological correlative studies
- Research blood draw for analysis of circulating tumor cells/biomarkers
- Measurement of tumor size via clinical assessement (research-related)

7.2 Intermediate Visits

Study Visit 3, Cetuximab Dose 1

- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Weight (recorded for the study from medical records maintained as part of standard clinical care for CTX administration) Only required if screening/baseline visit > 7 days prior to treatment.
- CBC with differential (recorded for the study from medical records maintained as part of standard clinical care for CTX administration) Only required if screening labs > 7 days prior to treatment.
- Blood chemistries (sodium, potassium, chloride, bicarbonate, BUN creatinine, glucose, AST, ALT, Alk Phos, T. bili, calcium, magnesium, T. protein and albumin) (recorded for the study from medical records maintained as part of standard clinical care for CTX administration). Only required if screening labs > 7 days prior to treatment.
- Adverse event evaluation (standard clinical care for CTX administration)
- Administration of cetuximab (research-related)

Study Visit 4, Cetuximab Dose 2 (7 days +/- 3 days from Study Visit 3)

- Vital signs (blood pressure only) (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Blood Chemistry: Potassium, calcium and magnesium (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Adverse event evaluation (standard clinical care for CTX administration)
- Administration of cetuximab (research-related)

Study Visit 5, Safety Evaluation (within 7 days prior to surgery)

- Concomitant medications (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Physical exam (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Weight (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)

- ECOG performance status (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- CBC with differential (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Blood chemistries (chloride, bicarbonate, BUN creatinine, glucose, AST, ALT, Alk Phos, T. bili, calcium, magnesium, T. protein and albumin) (recorded for the study from medical records maintained as part of standard clinical care for CTX administration)
- Adverse event evaluation (standard clinical care for CTX administration)
- Measurement of tumor size via clinical assessment (research-related)

SOC Surgery

- Blood draw for pre-surgical measurement of circulating tumor cells/biomarkers in serum should be done within 1 day prior to surgery (Research procedure)
- During surgery, a portion of the resected tumor which pathology will not need for diagnosis (remnant tissue) will be obtained for study analysis

SOC Follow Up Visit 1, 1 month post-surgery (+/- 2 wk)

- Blood draw for post-surgical measurement of circulating tumor cells/biomarkers in serum (Research procedure)
- Concomitant medications (recorded for the study from medical records maintained as part of standard clinical care)
- Physical exam (recorded for the study from medical records maintained as part of standard clinical care)
- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care)
- Weight (recorded for the study from medical records maintained as part of standard clinical care)
- ECOG performance status (recorded for the study from medical records maintained as part of standard clinical care)
- Serious adverse event evaluation (pertains to both research-related (section 9.1) AND standard clinical care)

SOC Follow Up Visit 2, 3 months post-definitive treatment* (+/- 4 wk)

- Physical exam (recorded for the study from medical records maintained as part of standard clinical care)

- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care)
- ECOG performance status (recorded for the study from medical records maintained as part of standard clinical care)
- Neck Imaging (findings recorded for the study from medical records maintained as part of standard clinical care)
- Blood draw for post-surgical measurement of circulating tumor cells/biomarkers in serum (research-related procedure)

7.3 Final Study Visit

SOC Follow Up Visit 3, 12 months post-definitive treatment* (+/- 4 wk)

- Physical exam (recorded for the study from medical records maintained as part of standard clinical care)
- Vital signs (blood pressure, heart rate, temperature) (recorded for the study from medical records maintained as part of standard clinical care)
- Weight (recorded for the study from medical records maintained as part of standard clinical care)
- ECOG performance status (recorded for the study from medical records maintained as part of standard clinical care)
- Neck Imaging (findings recorded for the study from medical records maintained as part of standard clinical care)
- Blood draw for post-surgical measurement of circulating tumor cells/biomarkers in serum (research-related procedure)

* Definitive therapy is defined as surgery alone, surgery + XRT or Surgery + chemoXRT

7.4 Withdrawal Visit

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The treating investigator should contact the subject or a responsible relative by telephone to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7.5 Unscheduled Visit

If a study subject should need an unscheduled visit, the treating physician should document the reason for the unscheduled visit (preferably in a clinic

note in the patient's chart). A complete description of the subject's symptoms and appropriate physical examination should be performed. In addition, the treating physician should document any recommendations and treatment plan for the subject at the time of the clinic visit. This information will be recorded on the eCRF.

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

Criteria for Disease Assessment

Assessment of Clinical Benefit Rate
Response assessment of cetuximab on clinical lesions will be determined by quantitative measurement performed by the treating physician pre-treatment and at the time of surgery. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Committee[65] criteria will be used to define clinical response prior to surgery.

Assessment of Disease Recurrence
Participants will be evaluated for evidence of recurrence on 2 occasions: 3 and 12 months post-definitive treatment (recorded for the study from medical records maintained as part of standard clinical care).

Given that all known disease will be surgically resected at the time of surgery, the only measure of relevance for this study will be recurrence of disease. Recurrence will be evaluated in this study using the new international criteria proposed by the RECIST 1.1 Committee.[65] Note: Lesions are either measurable or non-measurable using the criteria provided below.

Measurable Disease
At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows (per RECIST 1.1).[65]

Tumor lesions:
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm measurement by clinical exam (lesions which cannot be accurately measured or are <10mm should be recorded as non-measurable)
- 20 mm by chest X-ray.as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements

must be recorded in millimeters (or decimal fractions of centimeters). To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.

Malignant lymph nodes:
To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. The measurements will be recorded for the study from medical records maintained as part of standard clinical care.

Non-measurable disease
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

All clinical labs and evaluations done in this study are performed as standard medical care.

8.2.2 Special Assays or Procedures

Research Biopsy
Collection of specimen: In order to participate in this study, the tumor must be large enough to allow for the correlative study endpoints to be achieved. The minimum amount of tissue to achieve this is 2-3 core samples from the research biopsy with a strong preference for a cut-forceps biopsy (minimum recommended size: 2 x 2 x 2mm).

Remnant Tumor Tissue
Collection of surgical specimen: All specimens will go directly to the UWHC pathology department for diagnosis and processing. The biologic correlate study team will wait for the pathology team to access the specimen in the gross room and then will be given a portion of tissue that will not be required for diagnosis (i.e., remnant).

Circulating Tumor Cells/Biomarkers

Collection of specimen: We will collect blood for circulating tumor cell/or other biomarker identification at five timepoints: baseline, prior to surgical resection, one month post surgery, 3 and 12 months post definitive treatment. Approximately 10mL of blood will be collected in heparinized vaccutainers (green top) at each time point.

Establishment of Patient-Derived Xenografts
Collection of specimen: The research biopsy will also be used to establish patient-derived xenografts.

Determination of putative biomarkers of CTX sensitivity
Collection of specimen: the research biopsy will also be used for correlative analysis of putative biomarkers of CTX sensitivity.

8.2.3 Specimen Preparation, Handling, and Storage

Research Biopsy
Processing of specimen: The tissue obtained for research biopsy will be placed in culture media or saline, stored at room temperature and provided to the biologic correlate study team within 3 hours post-surgery. The samples will be identified with the research study number and “research biopsy”. The label will be stripped of all patient identifiers, such as MR number or dates. If squamous cell carcinoma is NOT confirmed, the tissue from the research biopsy will be relinquished to the TSB Biobank or surgical pathology based on clinical need.

Approximately 1/3 of the research biopsy will be formalin fixed and paraffin embedded. The remaining tissue will be used directly in mice to establish the first panel of PDX from patients with known sensitivity or resistance to cetuximab.

Tumor Tissue
Processing of specimen: The study team will process and embed the fresh tissue obtained from the pathology department to an FFPE block for downstream studies. Alternatively, the biologic correlate study team will request 20 x 5 µm unstained FFPE slides from the diagnostic tissue after surgical pathology clinical review is complete. The specimens will be labeled with the research study number, “surgical resection,” and section number, if applicable. The label will be stripped of all patient identifiers, such as the medical record number or dates.

Research Tissue samples and PDXs within the context of this protocol will be maintained under the supervision of Dr. Randy Kimple located at:
University of Wisconsin
3107 WIMR

1111 Highland Avenue
Madison WI 53705

Circulating Tumor Cells/Biomarkers
Processing of specimen: The samples will be picked up by a member of the biologic correlative study team and transported to Dr. Hong's lab. Upon arrival at the lab, PHI patient identifiers will be stripped from the sample and relabeled. The samples will be labeled with the subject's study ID number and coded time point (1- baseline, 2- pre-surgical resection, 3- one month post surgery, 4- three months post definitive-treatment, 5- twelve months post definitive treatment). Processing and storage of the circulating tumor cell samples within the context of this protocol will occur under the supervison of Dr. Seungpyo Hong's lab located at:

Pharmaceutical Sciences Division
University of Wisconsin School of Pharmacy
7234 Rennebohm Hall
777 Highland Avenue
Madison WI 53705

Determination of putative biomarkers of CTX sensitivity
The biologic correlate study team will formalin fix and paraffin embed (FFPE) approximately one third of the research biopsy tissue to be used to assess putative biomarkers of CTX sensitivity (e.g. total and phosphorylated AXL, EGFR and HER3 expression using immunohistochemistry assays). The FFPE research and surgical specimens will be used to establish the change in Ki67 (ΔKi67).

Correlations between the change in Ki67 index (ΔKi67) and AXL expression and HER3 expression in the research biopsy will be performed. Further correlation between other biomarkers and AXL expression will be performed.

Determination of circulating tumor cells
We hypothesize that changes in circulating tumor cells detected using the described head and neck cancer optimized capture approach (section 2) will correlate with response as determined by change in Ki67. Circulating tumor cells will be quantified at each time point. In addition, we plan to utilize captured circulating tumor cells to establish the first reported circulating tumor cell-derived head and neck cancer patient derived xenografts and to compare these PDXs to those established using standard techniques.

8.2.4 Specimen Shipment

Not applicable.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The first step is to identify the event using the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE document provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Adverse events, Serious adverse events and unanticipated problems will be recorded on the study eCRF's and reported per section 9.4. Certain toxicities are known and can be expected.

Cetuximab:
Common: Change in nails, rash, itching, dry skin, acne, dehydration, weight loss, loss of appetite, sores in mouth which may cause difficulty swallowing, constipation, diarrhea, vomiting, nausea, difficulty sleeping, headache, tiredness, pain, fever, infection, especially when white blood cell count is low, cough, shortness of breath, hypomagnesemia, hypokalemia and hypocalcemia

Occasional: Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat, confusion, depression, worry, fainting, severe blood infection, blood clot which may cause swelling, pain, shortness of breath

Rare: Scarring of the lungs, kidney damage which may require dialysis, cardiac arrest

Additional risks from study procedures
Biopsy
Possible risks from a tissue biopsy include bleeding and infection. There can also be some degree of pain associated with the biopsy.

Blood draw
Possible risks include: pain, bleeding and/or bruising, feeling faint, infection with redness, irritation, and, more rarely, a blood clot in the vein at the site where the blood is drawn.

In addition to physical risks there is also the risk of “breach of confidentiality”. If this occurs, it will be reported as an unanticipated problem.

9.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)

- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the duration of the study.

All AE's will be recorded from the time of informed consent until 28 days past last dose of study drug or day of surgery, whichever is first. SAE's will be recorded from the time of informed consent through 28 days past last dose of study drug or 28 days post-surgery, whichever is later. Serious adverse events that occur more than 28 days after surgery and have an attribution of possibly, probably, or definitely related to cetuximab (or other research procedures such as biopsy or blood draws) require reporting per table 1.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

Any adverse event, inclusive of all related study procedures, will be examined (section 9.1).

9.3.1 Relationship to Study Intervention

The causality, or attribution, of AEs refers to the relationship of the AE to the experimental intervention (drug/biologic). The investigator, using the following points, makes the assessment of whether there is a reasonable possibility of a causal relationship:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.

c. The event abates when the intervention is discontinued.

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

Based on the aforementioned points, the PI assigns attribution of the adverse event to the study treatment. Attribution categories are as follows:

- Definite: The AE is clearly related to the study treatment
- Probably: The AE is likely related to the study treatment
- Possible: The AE may be related to the study treatment
- Unlikely: The AE is doubtfully related to the study treatment
- Unrelated: The AE is clearly NOT related to the study treatment

9.3.2 Expectedness of SAEs

Expected events are those that have been previously identified as resulting from administration of the intervention. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in:

- Current known adverse events listed in this protocol
- Drug package insert (for commercially available agent)

9.3.3 Severity of Event

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the NCI website at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

9.4 Reporting Procedures

Procedures for Recording Adverse Events

- AEs will be recorded from time of informed consent until 28 days post discontinuation of study drug or day of surgery, whichever is first.
- AEs will be recorded regardless of whether or not they are considered related to the study intervention.
- AEs will be recorded in the subject's medical record and in the research study records.

- All AEs considered related to study drug(s) or procedure will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- At the 3 month and 12 month follow up visits, any AEs deemed by treating physician or study PI to be probably related to the research blood draw procedure will be recorded at time of visit and followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant.

Procedures for Recording and Reporting Serious Adverse Events

- SAEs will be reported from time of informed consent until 28 days after discontinuation of cetuximab or definitive surgery, whichever is later.
- Any SAEs experienced after this 28-day period will only be reported if the investigator suspects a causal relationship (possibly, probably or definitely related) to the study treatment.
- SAEs will be reported on the SAE Submission Form and entered in SAE tab in OnCore within 1 business day of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs, regardless of relation to study drug, will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 1 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table.

Table 1. Expedited Reporting Requirements for Adverse Events that Occur in Non-IND/IDE Studies Within 28 Days Post Surgical Intervention,

Reporting Requirements for Serious Adverse Events

NOTE: Investigators MUST immediately report to the *UWCCC DSMC, NIDCR (via Rho) and the IRB (if applicable)* ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention. See below.
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

<u> Hospitalization for planned surgical resection does not require reporting*</u>*

<u>Expedited AE reporting timelines are defined as:</u>

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]

[1] Serious adverse events that occur more than 28 days after the surgery and have an attribution of possibly, probably, or definitely related to cetuximab (or other research procedures such as biopsy or blood draws) require reporting as follows:

Expedited 24-hour notification followed by complete report within 10 calendar days for:

- All Grade 4, and 5 SAEs

SAE Requiring [24] Hour Reporting Occurs at UWCCC

Report to the UWCCC DSMC:
Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports**. A follow-up report is required to be submitted within 5 days of the initial [24] hour report.**
For this protocol, the following UWCCC entities are required to be notified:

a. saenotify@uwcarbone.wisc.edu
b. UWCCC PIs: Justine Yang Bruce, MD and Randall Kimple, MD, PhD
c. UWCCC PM: Diana Trask
d. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Report to the IRB
Please refer to the document "Unanticipated Problems/Adverse Event Reporting Decision Guide" found on the UW Health Science IRB website: *https://kb.wisc.edu/hsirbs/*. SAEs must be reported to the IRB Chair/director within 10 calendar days.

SAE Requiring [10] Calendar Day Reporting Occurs at UWCCC

Report to the UWCCC DSMC:
Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (*http://kb.wisc.edu/uwccc*) for specific instructions on how and what to report to the UWCCC for [10] calendar day reports.
For this protocol, the following entities are required to be notified:

a. saenotify@uwcarbone.wisc.edu
b. UWCCC PIs: Justine Yang Bruce, MD and Randall Kimple, MD, PhD
c. UWCCC PM: Diana Trask
d. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Other Reportable Events
Reporting timeframes begin when PI learns of the occurrence of the event. Refer to Table 2.

Table 2. Other Reportable Events Timeframe		
Event	**Definition**	**Reporting**
Breach of confidentiality	The exposure of any study information or communications directly related to a study subject to anyone not named as study staff or the release of a study subject's identifiable information to study staff who were not specified to receive such information in the protocol or IRB application.	Within 14 business days of knowledge of event
Protocol deviation	A deviation is an incident involving a departure from the IRB-approved protocol in the actual conduct of the study. Deviations may result from the action of the participant, investigator, or staff.	See details below
Major deviations	Deviations are considered major when the unapproved change(s) in previously approved research activities, implemented without IRB approval, may potentially adversely affect subjects' rights, safety, welfare, or willingness to continue participation, or affect the scientific design of the study and/or the integrity of the resultant data.	Within 14 business days of knowledge of event
Minor deviations	Deviations are considered minor when the unapproved change(s) in previously approved research activities, implemented without IRB approval, do not adversely affect subjects or the integrity of the study data.	Cumulative minor deviations are reported at the time of continuing review.

Table 2. Other Reportable Events Timeframe		
Event	**Definition**	**Reporting**
Protocol violation	An incident involving an intentional deviation from the IRB-approved protocol that was not implemented in response to an emergency situation and that may impact a subject's rights, safety, and/or welfare, makes a substantial alteration to risks to subjects, or affects the scientific design of the study and/or the integrity of the resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing non-compliance with the federal regulations and guidelines for ethical conduct of human subject research.	Within 14 business days of knowledge of event
Protocol Exceptions	A protocol exception is an IRB-approved deviation for a single subject or a small group of subjects but is not a permanent revision to the research protocol.	Protocol exceptions must be approved by local IRB prior to implementation.

9.4.1 Unanticipated Problem Reporting to IRB and NIDCR

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 10 calendar days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 10 calendar days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

9.4.2 Serious Adverse Event Reporting to NIDCR

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 10 calendar days of site awareness.

All SAEs will be followed until resolution or stabilization.

9.4.3 Reporting of SAEs and AEs to FDA

Not applicable.

9.4.4 Events of Special Interest (if applicable)

Not applicable.

9.4.5 Reporting of Pregnancy

- Pregnancy will be reported from time of first study drug until 6 months after discontinuation of either study drug.
- Pregnancy will be reported to UW via an unanticipated problem submission and the NIDCR medical monitor within 1 business day of discovery of the event.

To ensure subject safety, each pregnancy in a subject on study treatment will be reported to UW and the NIDCR medical monitor within 1 business day of learning of its occurrence. The pregnancy will be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

9.5 Halting Rules

During the conduct of this study, subjects with adverse events and serious adverse events that are probably attributed to cetuximab will be evaluated and

analyzed weekly by the principal investigators. If >25% of subjects have serious adverse events that are probably related to pre-operative cetuximab treatment, then enrollment for the study will be suspended for further analysis. Subsequent review of serious, unexpected, and related AEs will be evaluated by the DSMC, IRB, and the NIDCR. The NIDCR and local regulatory authorities retain the authority to suspend additional enrollment and administration of cetuximab for the entire study, as applicable.

10 STUDY OVERSIGHT

A summary of DSMC activities is as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews Adverse Events recorded by study team as described in section 9.4.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol PI of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the Clinical Research Committee (CRC) of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

Monitoring and Reporting Guidelines
UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCCC monitoring requirements for trials without an acceptable external DSMB are as follows:

- **Intermediate Monitoring**
  Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's

treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a bi-annual basis by the study team for review by the DSMC.

Review and Oversight Requirements

- Study Progress Review
  - Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.
  - Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.
  - In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

11 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The primary objective of this window of opportunity trial is to test the hypotheses that elevated AXL and HER3 can predict cetuximab resistance (CTXR) in head and neck cancer patients. Following informed consent, tumor tissue from the pre-treatment/research biopsy will be obtained for further analysis. The participant will then receive two weekly doses of cetuximab during the interval between research biopsy and surgery, ensuring that no delay in standard of care (SOC) will occur. At the time of surgery, additional tumor tissue will be obtained for study analysis.

Correlative studies will include the measurement of AXL and HER3 expression from the pre-treatment/research biopsy as well as collection of circulating tumor cells. Tissue from the pre-treatment/research biopsy will be utilized for patient-derived xenograft (PDX) development.

12.2 Sample Size Considerations

We plan to enroll 36 HNSCC patients, powered on the basis of the primary study endpoint: the clinical response rate to cetuximab according to RECIST criteria in low AXL vs. high AXL patients (measured using VECTRA/inForm software). Previous data show that 1 in 3 patients respond to cetuximab, and about one-third (21/57 or 37%) of HNSCC patients have high AXL expression.[37] This sample size is based on 90% power to detect a difference between a response rate of 20% in the high AXL (2+ or 3+) group vs. 65% in the low AXL (0 or 1) group, with an expected ratio of 2:1 low vs. high AXL expression participants. One-sided type I error was fixed at 5%.

For evaluation of safety endpoints, any participant that undergoes a research biopsy will be included. For evaluation of efficacy, molecular/correlative studies, and creation of PDXs, participants must receive both cetuximab doses in their

entirety and have surgical resection of the tumor. If a participant is unevaluable for these endpoints, then the patient will be replaced at the discretion of the principal investigator.

12.3 Planned Interim Analyses (if applicable)

Not applicable.

12.4 Final Analysis Plan

Analysis of Primary Endpoints

The relationship between AXL expression as a continuous variable with clinical response will be analyzed using the Wilcoxon rank sum test.

Analysis of Secondary Endpoints

The safety of pre-operative cetuximab, as evaluated by hospital re-admissions for wound care or surgical complications attributed to cetuximab within 28 days after surgery, will be reported as a proportion including an exact 95% confidence interval.

Analysis of Correlative Endpoints

Summary statistics of the change in Ki67 (ΔKi67), as established by the surgical specimen, will be reported for the response to cetuximab endpoint. Correlation between ΔKi67 and putative biomarkers will be analyzed as a continuous variable and will be tested using Pearson's correlation coefficient. Correlation between two biomarkers such as AXL and HER3 expression as continuous variables will be investigated using Pearson's correlation coefficient.

Summary statistics will be used to report circulating tumor cells at each time point and the changes between time points. The association of change in circulating tumor cells with ΔKi67 (early response) will be explored graphically and with Pearson's correlation coefficient.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Source documents will include all records within the HealthLink Electronic Medical Records system such as hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate and complete, photographs or digital photo files, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. In addition, protocol specific forms will be designed which require treating physician signature to serve as source documents. This may include forms such as toxicity forms with grading and attribution and tumor measurement forms.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring, Auditing, and Data Quality Control and Assurance Measures by Study Team.

All personnel involved in FDA regulated clinical trial activities are required to complete the Human Subjects Training and Good Clinical Practice (GCP) via CITI every 3 years. Training is monitored at each IRB continuing review and with the submission of protocol amendments.

At the protocol level, the Principal Investigators will assign and document protocol responsibilities based on study roles. Training on all IRB approved protocols (initial version and subsequent amendments) are documented for each person listed as key personnel on the University of Wisconsin Health Sciences IRB application. These documents are retained with the study regulatory files, and collection is coordinated by Human Oncology regulatory staff.

Eligibility checklists are signed by the study coordinator and the treating physician prior to enrollment. Adverse event grading and attributions are assigned by physicians at clinic visits and will be signed by the physician at that time.

A data report will be run quarterly to ensure study data is entered into the study database in a timely manner. After the report is run, the Research Program Manager will review and audit at least 25% of accrued cases since the last report was run. Auditing assistance will be provided by a study coordinator not involved in the cases being audited. Audits will include case review (Informed consent, eligibility, response, toxicity) and source document review.

Other relevant UWCCC SOPs that would be followed include:

- Adverse Event Assessment and Documentation_SOP
- CTRP and ClinicalTrials.gov Reporting_SOP
- Delegation of Authority Log_SOP

- DSMS Reporting Guidelines_SOP
- Informed Consent Process_SOP
- Maintaining a Regulatory File_SOP
- OnCore Data Quality Assurance_SOP
- Protocol Deviation_Guidance
- Reportable Events_SOP
- Reporting of Serious Adverse Events (SAEs) at UWCCC, 1SP, JC, And Affiliate Sites_SOP
- Source Documentation_SOP
- Study Close Out_SOP

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Persons who are not fluent in English and persons with impaired decision-making capacities will not be eligible for enrollment in this study.

Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator

or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children are excluded from this study because insufficient data are available in adults to judge potential risks in children.

Individuals of any gender or racial/ethnic group may participate in this study.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

All members of the study team will be listed on the IRB application and are required to undergo annual HIPAA training to ensure responsible conduct regarding protected health information (PHI) in research. In addition, Human Subjects Training and Good Clinical Practice trainings are required every three years for members of the study team.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. All PHI is stored securely on password protected servers.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all

researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (https://humansubjects.nih.gov/coc/index). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Residual samples will be relinquished to the TSB Biobank (2016-0934) for future exploratory analyses at the termination of this study. All subjects will have already signed a consent for the TSB Biobank protocol as part of the inclusion criteria.

Any use of specimens outside the context of this protocol, including genetic testing, will only occur after IRB approval.

16 DATA HANDLING AND RECORD KEEPING

This study will report clinical data using the UWCCC data management system utilizing study specific case report forms. Key study personnel are trained on the use of case report forms and will comply with protocol specific instructions for data collection.

Patient demographics, patient specific study treatment calendars, adverse events and other information will be maintained with the UWCCC data management system.

Participant data will be collected using protocol specific case report forms (CRFs). The CRFs will be approved by the study's Principal Investigator and the study biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into the UWCCC data management system at time of study entry, completing CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

UWCCC Radiotherapy will serve as the Clinical Research Office for this trial.

16.2 Data Capture Methods

Data will be collected through the web-based clinical research platform, OnCore (Forte Research), a system compliant with Good Clinical Practices and Federal Rules and Regulations. UWCCC personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel.

16.3 Types of Data

Patient demographics, patient medical history, patient specific study treatment calendars, adverse events, laboratory/pathology reports obtained during the course of treatment and afterwards, e.g., blood tests, biopsy results), findings from physical exams, and imaging scan reports/outcomes will be maintained with the UWCCC data management system.

16.4 Schedule and Content of Reports

The UWCCC Protocol Review and Monitoring Committee (PRMC) determines the level of risk, thus the appropriate timelines for review of study documents, conduct and accrual. Protocol Safety Reports are run, reviewed and signed off by the study PI per the determined schedule. PSRs are then sent for review to the Data Safety Monitoring Committee (DSMC). A summary of the DSMC decisions for this study will be provided to the medical monitor at NIDCR according to the determined DSMC meeting schedule.

Protocol Safety Reports include information such as accrual, adverse events, serious adverse events, and unanticipated problems. Annual review by the UW Health Sciences IRB will review accrual, reportable events, and study progress. A copy of the continuing review and supporting documents will be submitted to NIDCR at time of submission to the IRB.

16.5 Study Records Retention

Shadow research charts with original consent forms and documents specifically created for this study will be maintained in the Department of Human Oncology

until the study is terminated. The records will then be sent to Wisconsin State Records Archiving facility for long term storage (10 years) and re-archived as needed. Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

16.6 Protocol Deviations

Except in the case of a medical emergency, no protocol deviation is authorized. Changes to the protocol will be established by amendments by the Principal Investigator approved by the UW HS IRB. Protocol deviations may affect the conduct of the study from legal and ethical points of view and may influence the statistical analysis and pertinence of the study. Medical emergencies have to be handled in the patients' best interest. The investigator has to contact the Sponsor to clarify if a patient may continue in the study when a protocol violation out of medical reasons has occurred. Protocol deviations that are not identifiable from the eCRF have to be recorded in a protocol deviation form. Protocol deviations will be evaluated at the data review meeting before database lock and will be described in the statistical analysis plan.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to NIDCR and to the UW HS IRB per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

17 PUBLICATION/DATA SHARING POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The clinical trial will be registered on *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine.

The study investigators will have sole right to determine the content of the presented and published data. As PIs, Drs. Bruce and Kimple will retain a spot as both first and last author on all manuscripts, unless either elects to forgo this. Co-Is will have input into all remaining authorship spots.

18 LITERATURE REFERENCES

1. Erbitux(R) [package insert] IL, Branchburg, NJ; October 2016. (Accessed May 15, 2017, at *http://uspl.lilly.com/erbitux/erbitux.html*.).
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians 2011;61:69-90.
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians 2017;67:7-30.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians 2015;65:5-29.
5. Laramore GE, Scott CB, al-Sarraf M, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. International journal of radiation oncology, biology, physics 1992;23:705-13.
6. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517:576-82.
7. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-8.
8. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. The New England journal of medicine 2006;354:567-78.
9. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. The New England journal of medicine 2008;359:1116-27.
10. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171-7.
11. Gilbert J, Schell MJ, Zhao X, et al. A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma. Oral Oncol 2015;51:376-82.
12. Brand TM, Iida M, Wheeler DL. Molecular mechanisms of resistance to the EGFR monoclonal antibody cetuximab. Cancer Biol Ther 2011;11:777-92.
13. Bauman JE, Duvvuri U, Gooding WE, et al. Randomized, placebo-controlled window trial of EGFR, Src, or combined blockade in head and neck cancer. JCI insight 2017;2:e90449.
14. Schmitz S, Hamoir M, Reychler H, et al. Tumour response and safety of cetuximab in a window pre-operative study in patients with squamous cell

carcinoma of the head and neck. Annals of oncology : official journal of the European Society for Medical Oncology 2013;24:2261-6.
15. Viloria-Petit A, Crombet T, Jothy S, et al. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. Cancer research 2001;61:5090-101.
16. Ciardiello F, Bianco R, Caputo R, et al. Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. Clinical cancer research : an official journal of the American Association for Cancer Research 2004;10:784-93.
17. Bianco R, Rosa R, Damiano V, et al. Vascular endothelial growth factor receptor-1 contributes to resistance to anti-epidermal growth factor receptor drugs in human cancer cells. Clinical cancer research : an official journal of the American Association for Cancer Research 2008;14:5069-80.
18. Wheeler DL, Huang S, Kruser TJ, et al. Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. Oncogene 2008;27:3944-56.
19. Hatakeyama H, Cheng H, Wirth P, et al. Regulation of heparin-binding EGF-like growth factor by miR-212 and acquired cetuximab-resistance in head and neck squamous cell carcinoma. PloS one 2010;5:e12702.
20. Li C, Iida M, Dunn EF, Ghia AJ, Wheeler DL. Nuclear EGFR contributes to acquired resistance to cetuximab. Oncogene 2009;28:3801-13.
21. Lu Y, Li X, Liang K, et al. Epidermal growth factor receptor (EGFR) ubiquitination as a mechanism of acquired resistance escaping treatment by the anti-EGFR monoclonal antibody cetuximab. Cancer research 2007;67:8240-7.
22. Fuchs BC, Fujii T, Dorfman JD, et al. Epithelial-to-mesenchymal transition and integrin-linked kinase mediate sensitivity to epidermal growth factor receptor inhibition in human hepatoma cells. Cancer research 2008;68:2391-9.
23. Kim SM, Kim JS, Kim JH, et al. Acquired resistance to cetuximab is mediated by increased PTEN instability and leads cross-resistance to gefitinib in HCC827 NSCLC cells. Cancer Lett 2010;296:150-9.
24. Chakrabarty A, Sanchez V, Kuba MG, Rinehart C, Arteaga CL. Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors. Proc Natl Acad Sci U S A 2012;109:2718-23.
25. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43.
26. Garrett JT, Olivares MG, Rinehart C, et al. Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase. Proc Natl Acad Sci U S A 2011;108:5021-6.
27. Montero-Conde C, Ruiz-Llorente S, Dominguez JM, et al. Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF-mutant thyroid carcinomas. Cancer Discov 2013;3:520-33.
28. Schoeberl B, Faber AC, Li D, et al. An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. Cancer research 2010;70:2485-94.

29. Sergina NV, Rausch M, Wang D, et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 2007;445:437-41.
30. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127-37.
31. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov 2014;13:140-56.
32. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 2011;12:21-35.
33. Benavente S, Huang S, Armstrong EA, et al. Establishment and characterization of a model of acquired resistance to epidermal growth factor receptor targeting agents in human cancer cells. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:1585-92.
34. Wheeler DL, Iida M, Kruser TJ, et al. Epidermal growth factor receptor cooperates with Src family kinases in acquired resistance to cetuximab. Cancer Biol Ther 2009;8:696-703.
35. Brand TM, Iida M, Stein AP, et al. AXL mediates resistance to cetuximab therapy. Cancer research 2014;74:5152-64.
36. Iida M, Brand TM, Starr MM, et al. Overcoming acquired resistance to cetuximab by dual targeting HER family receptors with antibody-based therapy. Mol Cancer 2014;13:242.
37. Brand TM, Iida M, Stein AP, et al. AXL Is a Logical Molecular Target in Head and Neck Squamous Cell Carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2015;21:2601-12.
38. Swick AD, Prabakaran PJ, Miller MC, et al. Cotargeting mTORC and EGFR Signaling as a Therapeutic Strategy in HNSCC. Molecular cancer therapeutics 2017;16:1257-68.
39. Iida M, Brand TM, Starr MM, et al. Sym004, a novel EGFR antibody mixture, can overcome acquired resistance to cetuximab. Neoplasia 2013;15:1196-206.
40. Gross ND, Bauman JE, Gooding WE, et al. Erlotinib, erlotinib-sulindac versus placebo: a randomized, double-blind, placebo-controlled window trial in operable head and neck cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20:3289-98.
41. Klintman M, Dowsett M. Early Surrogate Markers of Treatment Activity: Where Are We Now? J Natl Cancer Inst Monogr 2015;2015:24-8.
42. Berruti A, Generali D, Bertaglia V, et al. Intermediate endpoints of primary systemic therapy in breast cancer patients. J Natl Cancer Inst Monogr 2011;2011:142-6.
43. Dowsett M, Smith I, Robertson J, et al. Endocrine therapy, new biologicals, and new study designs for presurgical studies in breast cancer. J Natl Cancer Inst Monogr 2011;2011:120-3.
44. Bjarnadottir O, Romero Q, Bendahl PO, et al. Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. Breast Cancer Res Treat 2013;138:499-508.

45. Foroni C, Milan M, Strina C, et al. Pure anti-tumor effect of zoledronic acid in naive bone-only metastatic and locally advanced breast cancer: proof from the "biological window therapy". Breast Cancer Res Treat 2014;144:113-21.
46. Hadad SM, Coates P, Jordan LB, et al. Evidence for biological effects of metformin in operable breast cancer: biomarker analysis in a pre-operative window of opportunity randomized trial. Breast Cancer Res Treat 2015;150:149-55.
47. Joshua AM, Zannella VE, Downes MR, et al. A pilot 'window of opportunity' neoadjuvant study of metformin in localised prostate cancer. Prostate Cancer Prostatic Dis 2014;17:252-8.
48. Niraula S, Dowling RJ, Ennis M, et al. Metformin in early breast cancer: a prospective window of opportunity neoadjuvant study. Breast Cancer Res Treat 2012;135:821-30.
49. Romero Q, Bendahl PO, Klintman M, et al. Ki67 proliferation in core biopsies versus surgical samples - a model for neo-adjuvant breast cancer studies. BMC Cancer 2011;11:341.
50. Hadad S, Iwamoto T, Jordan L, et al. Evidence for biological effects of metformin in operable breast cancer: a pre-operative, window-of-opportunity, randomized trial. Breast Cancer Res Treat 2011;128:783-94.
51. Plaks V, Koopman CD, Werb Z. Cancer. Circulating tumor cells. Science 2013;341:1186-8.
52. Lin H, Balic M, Zheng S, Datar R, Cote RJ. Disseminated and circulating tumor cells: Role in effective cancer management. Crit Rev Oncol Hematol 2011;77:1-11.
53. Grisanti S, Almici C, Consoli F, et al. Circulating tumor cells in patients with recurrent or metastatic head and neck carcinoma: prognostic and predictive significance. PloS one 2014;9:e103918.
54. Myung JH, Launiere CA, Eddington DT, Hong S. Enhanced tumor cell isolation by a biomimetic combination of E-selectin and anti-EpCAM: implications for the effective separation of circulating tumor cells (CTCs). Langmuir 2010;26:8589-96.
55. Myung JH, Gajjar KA, Saric J, Eddington DT, Hong S. Dendrimer-mediated multivalent binding for the enhanced capture of tumor cells. Angew Chem Int Ed Engl 2011;50:11769-72.
56. Myung JH, Gajjar KA, Chen J, Molokie RE, Hong S. Differential detection of tumor cells using a combination of cell rolling, multivalent binding, and multiple antibodies. Anal Chem 2014;86:6088-94.
57. Myung JH, Eblan MJ, Caster JM, et al. Multivalent Binding and Biomimetic Cell Rolling Improves the Sensitivity and Specificity of Circulating Tumor Cell Capture. Clinical cancer research : an official journal of the American Association for Cancer Research 2018;24:2539-47.
58. Bozec A, Ilie M, Dassonville O, et al. Significance of circulating tumor cell detection using the CellSearch system in patients with locally advanced head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2013;270:2745-9.

59. Grobe A, Blessmann M, Hanken H, et al. Prognostic relevance of circulating tumor cells in blood and disseminated tumor cells in bone marrow of patients with squamous cell carcinoma of the oral cavity. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20:425-33.
60. Nichols AC, Lowes LE, Szeto CC, et al. Detection of circulating tumor cells in advanced head and neck cancer using the CellSearch system. Head & neck 2012;34:1440-4.
61. Vermorken JB, Herbst RS, Leon X, Amellal N, Baselga J. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. Cancer 2008;112:2710-9.
62. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. The New England journal of medicine 2007;357:2040-8.
63. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. The New England journal of medicine 2004;351:337-45.
64. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079-95.
65. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

APPENDICES

A: SCHEDULE OF EVENTS

APPENDIX A: SCHEDULE OF EVENTS

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

	Study Visit 1 and 2	Study Visit 3	Study Visit 4	Study Visit 5	SOC	SOC Follow up 1	SOC Follow up 2	SOC Follow up 3
	Screening/ Baseline[1]	**Dose 1**	**Dose 2[2,]**	**Safety Eval[11]**	**Surgery**	**1 mo post-op +/- 2 wk**	**3 mo post-definitive care[10] +/- 4 wk**	**12 mo post-definitive care[10] +/- 4 wk**
REQUIRED ASSESSMENTS								
Informed consent	X[3]							
Demographics	X							
Medical History	X							
Concurrent meds review	X			X				
Physical exam	X			X		X	X	X
Vitals signs	X	X	X[13]	X		X	X	X
Height	X							
Weight	X	X[4]		X		X	X	X
ECOG Performance status	X			X		X	X	X
CBC with diff	X	X[4]		X				
Serum chemistry[5]	X	X[4]	X[9]	X				
Pregnancy test for WOCP		X[6]						
Adverse event evaluation[7]	X	X	X	X				
DISEASE ASSESSMENT								
Tumor measurements by clinical assessment	X			X				
Neck Imaging[12]							X	X
TREATMENT								
Cetuximab		X	X					
CORRELATIVE STUDIES								
Tumor tissue from surgery					X			
Blood collection for circulating tumor cells	X				X[8]	X	X	X
Research biopsy for biologic correlative studies	X							

FOOTNOTES

1. Pre-study tests to be done within 21 days of dose 1 cetuximab therapy.

2. Time between doses: 7 days (+/-3 days)
3. Informed consent to be obtained within 28 days of starting treatment.
4. If screening/baseline procedures are within 7 days prior to cetuximab dose 1, they don't need to be repeated on day of dose 1.
5. Serum chemistry should include: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, calcium, magnesium, protein, albumin.
6. A negative serum/urine pregnancy test is required within 7 days prior to cetuximab dose 1.
7. For subjects with unresolved treatment-related toxicity, follow as medically appropriate until resolution or stabilization.
8. Pre-surgical blood draw for circulating tumor cells in serum should be done within 1 day prior to surgery.
9. Prior to dose 2, required labs: magnesium, calcium and potassium
10. Definitive therapy is defined as surgery alone, surgery + XRT or Surgery + chemoXRT
11. Within 7 days prior to surgery, but as close as possible to surgery.
12. May include any of the SOC imaging such as PET/CT, PET/MRI, CT or MRI
13. Blood Pressure only