Title: A Randomized, Phase II Study of Ficlatuzumab with or without Cetuximab in Patients with Cetuximab-Resistant, Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

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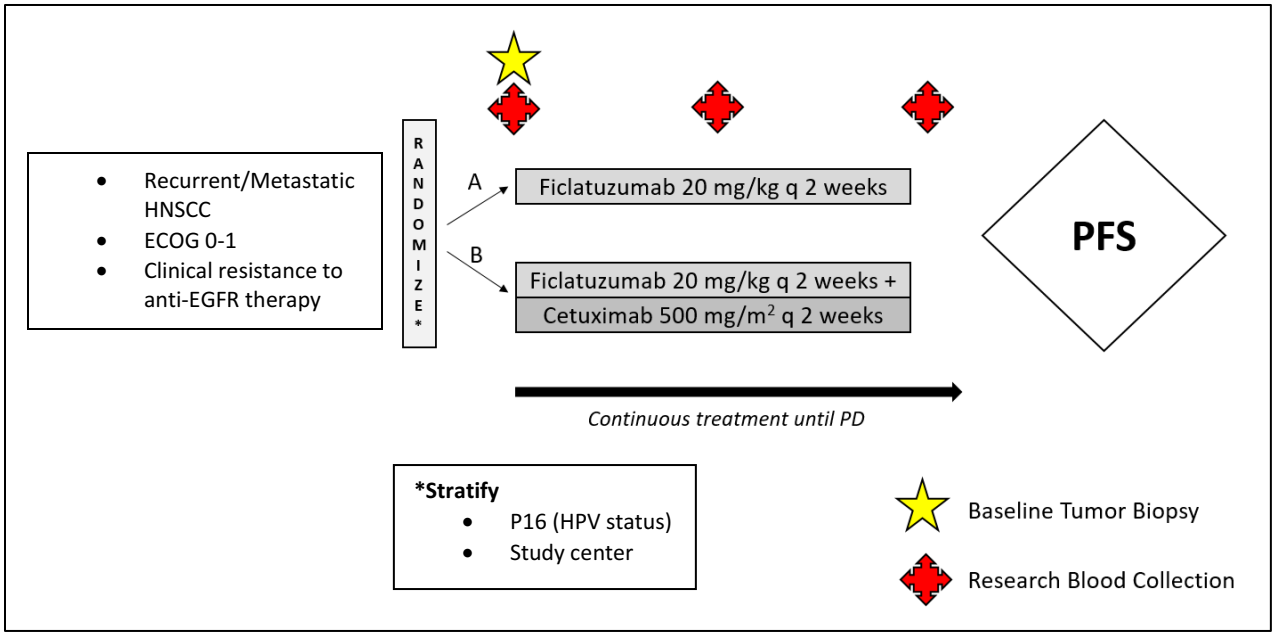
TRIAL SCHEMA



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1. BACKGROUND & RATIONALE

1.1 Background

Head and neck squamous cell carcinoma (HNSCC) is the most common cancer arising in the upper aerodigestive tract. HNSCC is the sixth leading incident cancer worldwide with 600,000 cases anticipated in 2012.[1] Despite advances in multimodality therapy, 5-year overall survival (OS) is 40-50%, and has increased only incrementally in the past two decades.[2] Patients with recurrent or metastatic (R/M) HNSCC have particularly poor prognosis, with median overall survival of 6-10 months. Options for palliative management are limited. For nearly three decades, the cornerstone of first line chemotherapy has been cisplatin,[3] frequently combined with fluorouracil or a taxane derivative due to increased response rate (RR) albeit no conclusive evidence of superior survival compared to cisplatin monotherapy.[4]

Ubiquitous expression of EGFR compelled the development of EGFR inhibitors for HNSCC treatment [5, 6]. The EGFR-directed monoclonal antibody, cetuximab, is the only targeted therapy to date FDA-approved for the treatment of HNSCC, and improves survival when added to front line platinum [7]. Despite aberrant EGFR signaling in the majority of HNSCC cases, the modest clinical activity of cetuximab has been disappointing; either primary or acquired resistance is inevitable. Co-targeting EGFR and a parallel or compensatory oncogenic pathway may overcome cetuximab resistance.

While immunotherapeutic antibodies inhibiting programmed death receptor 1 (PD-1) recently gained FDA approval in patients with platinum-refractory HNSCC, the OS benefit appears to be limited to approximately 20% [8, 9]. Currently, there is no standard therapy for patients after failure of platinum, cetuximab, and anti-PD1 therapy; all such patients will succumb with a median survival of less than 6 months. The lack of therapeutic options for patients with pan-refractory, recurrent/metastatic HNSCC represents a major unmet clinical need.

1.2 Epidermal Growth Factor Receptor in HNSCC

EGFR is a member of the ErbB/HER family of transmembrane glycoprotein receptor tyrosine kinases (RTK). Activated EGFR initiates a pleiotropic network of downstream signaling cascades including Ras/Raf/MAPK, PI3K/Akt, STAT, and Src Kinase effecting cellular proliferation, invasion, angiogenesis and metastasis.[10] *In vitro*, forced overexpression of EGFR causes malignant transformation of oral epithelial cells, suggesting its role as an oncogene in HNSCC. EGFR overexpression as measured by immunohistochemistry (IHC) and increased EGFR gene copy number as measured by fluorescence in situ hybridization occur in the majority of HNSCC, and associate with increased stage as well as reduced relapse-free and overall survival (OS).[6, 11-13] Thus, EGFR is both oncogene and prognostic biomarker in HNSCC.

EGFR's functional importance in HNSCC resulted in successful development of the first molecularly targeted strategy, the murine anti-EGFR monoclonal antibody cetuximab. Despite

clear clinical importance, intrinsic or acquired resistance to EGFR inhibition is the rule rather than the exception. Currently, there is no predictive molecular marker for resistance or sensitivity to anti-EGFR therapy in HNSCC, including EGFR gene copy number as assessed in the EXTREME study.[14] Given the poor prognosis and desperate lack of therapeutic options for patients with recurrent/metastatic HNSCC after failure of cetuximab, there is heightened interest in understanding resistance mechanisms in order to drive novel therapies for this population.

1.3 HGF/c-Met in Head and Neck Squamous Cell Carcinoma

An established intrinsic or acquired resistance mechanism to anti-EGFR therapy in HNSCC is primary or compensatory activation of alternate RTKs including c-Met. The *MET* oncogene encodes c-Met, an RTK bound exclusively by the ligand, hepatocyte growth factor (HGF). HGF is also known as "scatter factor;" this designation arose from early observations that HGF stimulates cellular decoupling and motogenesis. Overexpression of c-Met is transformative for normal cells and enhances motility, invasion/metastasis and angiogenesis.[15] *MET* is an established driver of epithelial-to-mesenchymal transition, a phenotype associated with cetuximab resistance in HNSCC.[16, 17]

c-Met and/or HGF are overexpressed in ~80% of HNSCC,[18] and *MET* amplification has been reported in 13% of HNSCC tumors.[19] Moreover, several mutations have been identified in the *MET* oncogene in HNSCC, including alterations in the semaphorin ligand-binding, juxtamembrane, and RTK domains.[19] An activating point mutation (Y1253D) was described in 14% of patients in a Swiss chemoradiotherapy trial for locally advanced disease and predicted decreased metastasis-free survival, although the presence of this mutation in HNSCC was not confirmed in two whole-exome sequencing projects.[20-22] Although validation and functional characterization of *MET* mutations in HNSCC is ongoing, the presence of *MET* overexpression, amplification, and mutation events suggests strong biologic relevance of this pathway. Furthermore, the current feasibility of measuring these events holds the promise that the clinical development of c-Met targeting in HNSCC may be accompanied by rational development of a predictive biomarker.

Of unique interest to the proposed study, the HGF/c-Met signaling pathway converges with the EGFR network at both the PI3K/Akt and MAPK nodes, suggesting the ability for reciprocal compensation. Several lines of evidence developed in our laboratories indicate that c-Met has an important role in resistance to EGFR based therapies. *In vitro*, the EGFR ligand TGF-α stimulated activation of c-Met in HNSCC cell lines, through prolonged tyrosine phosphorylation and increased c-Met protein expression. Moreover, dual inhibition of EGFR (gefitinib) and c-Met (crizotinib) maximally inhibited phosphorylation of MAPK and Akt compared to single inhibition of either RTK, effectively abrogating crosstalk. Similarly, dual inhibition significantly reduced cell proliferation, invasion and wound healing, compared to mono- inhibition of either

RTK. *In vivo*, dual inhibition of EGFR and c-Met retarded tumor growth, decreased the proliferative index, and enhanced apoptosis compared to either single agent.[23] A second laboratory found that dual blockade of c-Met (SU11274) and EGFR (erlotinib) in erlotinib-sensitive HNSCC cell lines decreased viability significantly more than exposure to either single agent, and isobologram indicated synergism.[19] Finally, growth factors have recognized potential to drive resistance to anticancer kinase inhibitors; in kinase addicted cell line models, the HGF ligand had broad potential to rescue kinase-addicted cancer cells dependent upon HER2 amplification, NRG1 autocrine stimulation, EGFR mutation, and BRAF mutation.[24] Finally, serum levels of HGF have been associated with resistance to EGFR inhibitors in *KRAS* wild-type metastatic colorectal cancer [25] and lung cancer [25-27].

Above, convergent data suggest that HGF/c-Met pathway inhibition may overcome resistance to anti-EGFR therapy in R/M HNSCC, such as in patients with clinical cetuximab resistance. In theory, targeting HGF/cMet may have independent activity when administered as monotherapy in this setting, although this hypothesis has not been clinically tested. However, the cross talk and mutual compensation between c-Met and EGFR suggest that optimal benefit may be achieved by continuing cetuximab concurrent with HGF/c-Met pathway inhibition, in spite of established clinical resistance.

Ficlatuzumab (AV-299) is a humanized HGF-inhibitory immunoglobulin G1 (IgG1) monoclonal antibody that exhibits anti-tumor effects *in vitro* and in animal tumor models by 1) binding and neutralization of free HGF, 2) inhibition of c-Met phosphorylation, 3) inhibition of proliferation, 4) induction of apoptosis, and 5) inhibition of invasion and motility. Ficlatuzumab in combination with cetuximab resulted in prolonged tumor stasis/regression in 3 HNSCC xenograft models tested with increased activity compared to cetuximab alone in two of the three models tested. The recommended phase II dose (RP2D) for ficlatuzumab monotherapy has been established as 20 mg/kg IV every 2 weeks.

1.4 Phase Ib Study of the Combination of Ficlatuzumab and Cetuximab

We recently completed a phase Ib study of the combination of ficlatuzumab and cetuximab in patients with cetuximab-resistant, recurrent/metastatic HNSCC (NCT XXXXXXXX; Bauman JE et al, ASCO 2017). In this Narayana k-in-a-row phase I design, fixed-dose cetuximab was administered at 500 mg/m^2 IV every 2 weeks. Ficlatuzumab dose tiers were 10 mg/kg (starting dose) or 20 mg/kg IV every 2 weeks (tier 2), with inter-patient escalation or de-escalation based on cumulative dose-limiting toxicities (DLT). The RP2D was set at dose tier 2 if no DLTs were observed after 8 enrolled patients, with expansion planned to n=12. Key eligibility criteria included: R/M HNSCC, cetuximab resistance (recurrence within 6 months of cetuximab-radiation or progression during/within 6 months of palliative cetuximab); ECOG performance

status 0-1; mandatory baseline research biopsy. Candidate biomarkers included serum Veristrat classification and tumor expression of pMet and HGF/cMet dimers.

From Sept 2015-June 2016, 12 pts were enrolled and treated. Primary site: 1 oral cavity; 3 oropharynx (1 p16+); 2 hypopharynx; 5 larynx; 1 external auditory canal. Platinum-refractory: 11/12. Veristrat: 8 poor; 4 good. Three were treated at tier 1 and 9 at tier 2. No DLTs were observed. Grade 3 adverse events included: edema (1), hypoalbuminemia (1), infection (2), and thromboembolic event (2). Median PFS and OS at RP2D were 6.0 mos (90% CI = 2 mos – not reached) and 8.2 mos (90% CI = 2.7 mos – not reached), respectively. Response rate was 17% (90% CI = 0-28%): 2/12 partial response (PR); 1/3 at 10 mg/kg; 1/9 at 20mg/kg. Clinical benefit rate (PR + stable disease) was 67%. Veristrat was not associated with PFS.

1.5 Study Rationale

Above, convergent data suggest that HGF/c-Met pathway inhibition may overcome resistance to anti-EGFR therapy in recurrent/metastatic HNSCC. The promising clinical activity observed in patients with cetuximab-resistant, recurrent/metastatic HNSCC during phase Ib compels further study in the same poor prognosis population. In theory, targeting HGF/cMet may have independent activity when administered as monotherapy in this setting, although this hypothesis has not been clinically tested. We also hypothesize that the cross talk and mutual compensation between c-Met and EGFR may necessitate the continuation of cetuximab with HGF/c-Met pathway inhibition, to optimize benefit. Thus we proposed a randomized, phase II study evaluating the efficacy of ficlatuzumab, with or without cetuximab, in patients with cetuximab-resistant, recurrent/metastatic HNSCC.

1.6 Ficlatuzumab (AV-299)

1.6.1 Introduction

Ficlatuzumab (AV-299) is a humanized HGF inhibitory immunoglobulin G1 (IgG1) monoclonal antibody that exhibits anti-tumor effects in vitro and in animal tumor models by 1) binding and neutralization of free HGF, 2) inhibition of c-Met phosphorylation, 3) inhibition of proliferation, 4) induction of apoptosis, and 5) inhibition of invasion and motility.

Hepatocyte growth factor is the soluble ligand for the c-Met tyrosine kinase receptor. Hepatocyte growth factor/c-Met pathway dysregulation by over-expression or genetic alteration is frequently observed in many types of cancer. Ficlatuzumab exhibited potent in vivo inhibitory activity in autocrine and paracrine xenograft models as single agents in GBM, multiple myeloma and RCC. Ficlatuzumab demonstrated enhanced antitumor activity when combined with targeted therapy or chemotherapy, such as erlotinib, cetuximab, tivozanib or temozolomide in a panel of xenograft models, suggesting ficlatuzumab may have anti-tumor activity in multiple tumor indications. Ficlatuzumab in combination with cetuximab resulted in prolonged tumor stasis/regression in all 3 HNSCC xenograft models tested with increased activity compared to cetuximab alone in two

of the three models tested

A summary of ficlatuzumab's pertinent efficacy results and safety data follow. Please refer to the ficlatuzumab Investigator Brochure (IB) for descriptions of all available data.

1.6.2 Ficlatuzumab clinical experience

An overview of the clinical data available for ficlatuzumab clinical studies; protocols P05538 (phase I), P05670 (pharmacodynamic study) and P06162 (phase Ib/II in NSCLC) is provided below. Final data for Protocols P05538 (with the exception of the 1 ongoing subject) and P05670 and preliminary data for Protocol P06162 are included in the Ficlatuzumab Investigator Brochure.

Protocol P05538 includes data for 41 subjects diagnosed with relapsed or refractory solid tumors that were metastatic or unresectable, or symptomatic relapsed or refractory multiple myeloma. There were 7 cohorts in total. The dose-escalation cohorts included subjects diagnosed with relapsed or refractory solid tumors that were metastatic or unresectable that were treated at the following dose levels: Cohort 1 (2 mg/kg), Cohort 2 (5 mg/kg), Cohort 3 (10 mg/kg), and Cohort 4 (20 mg/kg); safety expansion Cohort 5 (20 mg/kg, which was the RP2D). The additional cohorts were the Erlotinib Combination Cohort (ficlatuzumab 20 mg/kg and erlotinib 150 mg) and Multiple Myeloma Cohort (ficlatuzumab 20 mg/kg). There were 24 subjects enrolled in the dose escalation/safety expansion cohorts, 13 subjects enrolled in the Erlotinib Combination Cohort, and 4 subjects enrolled in the Multiple Myeloma Cohort. After an interim review of the data, there was no signal of clinical benefit to subjects with multiple myeloma; therefore, enrollment into this cohort was terminated.

Protocol P05670 was a pharmacodynamic study including data for 19 subjects with advanced solid tumors and liver metastases. There were 3 dose cohorts of ficlatuzumab (2, 10, and 20 mg/kg). Six subjects were enrolled in the Dose Level 1 Cohort (2 mg/kg), 7 subjects were enrolled in the Dose Level 2 Cohort (10 mg/kg), and 6 subjects were enrolled in the Dose Level 3 Cohort (20 mg/kg). The best responses in the study were stable disease seen 5/18 patients and the median duration of treatment was 6 weeks. The Pk of ficlatuzumab was characterized by low clearance and a half-life of 7-10 days. Ficlatuzumab treatment at 20 mg/kg, but not at 2 and 10 mg/kg, demonstrated pharmacodynamic modulation in the tumor by inhibiting HGF/c-Met pathway and downstream signaling for cell proliferation, survival, and angiogenesis in majority of the patients treated.

Protocol P06162 is a Phase 1b/2 study including preliminary data for 199 subjects. Phase 1b enrolled Asian subjects with NSCLC or other advanced solid tumors. Phase 2 enrolled Asian subjects (nonsmokers or light ex-smokers) with previously untreated lung adenocarcinoma. Subjects in Phase 1b are treated with a dose of ficlatuzumab 10 mg/kg or 20 mg/kg in

combination with gefitinib 250 mg. Subjects in Phase 2 are treated with a combination of ficlatuzumab 20 mg/kg and gefitinib 250 mg or gefitinib 250 mg monotherapy. Upon progression in the gefitinib monotherapy arm, subjects who initially demonstrated disease control with single agent gefitinib were offered to receive the combination of ficlatuzumab 20 mg/kg and gefitinib 250 mg, provided that safety was maintained and the subject continued to meet eligibility criteria. There were 15 subjects enrolled in Phase 1b (3 subjects enrolled in the 10 mg/kg cohort and 12 subjects enrolled in the 20 mg/kg) and 184 subjects enrolled in Phase 2 (90 subjects enrolled in the Combination Cohort and 94 subjects enrolled in the Gefitinib Monotherapy Cohort). Of the subjects enrolled in the Phase 2 Gefitinib Monotherapy Cohort, 20 were crossed over to receive the combination of ficlatuzumab 20 mg/kg and gefitinib 250 mg.

The addition of ficlatuzumab to gefitinib did not result in a significant improvement in ORR (primary endpoint) or PFS in the intent to treat population. The ficlatuzumab/gefitinib combination demonstrated a trend for increased ORR and OS in a subset of patients without EGFR sensitizing mutations and increased PFS, OS and ORR in a subset of patients with high stromal HGF. Overall survival data continues to mature and are being analyzed in the intent to treat group as well as other biomarker subsets. The combination of ficlatuzumab and gefitinib was well tolerated in this patient population.

1.6.3 Ficlatuzumab Safety Experience

Data from the first-in-human dose-escalation study (Study P05538) in 41 subjects diagnosed with relapsed or refractory solid tumors or lymphoma that was metastatic or unresectable, or symptomatic relapsed or refractory multiple myeloma showed ficlatuzumab to be well-tolerated as monotherapy at the 4 dose levels tested (2, 5, 10 or 20 mg/kg) and in combination with erlotinib (20 mg/kg ficlatuzumab and 150 mg/day erlotinib). The maximum administered dose of 20 mg/kg intravenous (IV) ficlatuzumab every 2 weeks as monotherapy and in combination with erlotinib (150 mg/day) was determined to be the RP2D.

There were no DLTs observed with single-agent ficlatuzumab. One subject in the ficlatuzumab plus erlotinib combination cohort experienced a Grade 3 mucositis which the investigator determined was possibly related to ficlatuzumab and related to erlotinib. The most common treatment-emergent adverse events (TEAEs) were fatigue (18 subjects, 44%), peripheral edema (13 subjects, 32%), hypokalemia (11 subjects, 27%), and nausea (10 subjects, 24%). The most frequently reported related TEAEs were fatigue (12 subjects [29%]; 9 subjects monotherapy [22%], 3 subjects erlotinib combination [7%]); peripheral edema (6 subjects [15%]; 5 subjects monotherapy [12%], 1 subjects erlotinib combination [2%])); headache (5 subjects [12%]; 4 subjects monotherapy [10%], 1 subjects erlotinib combination [2%]), pruritus (5 subjects [12%]; 3 subjects monotherapy [7%], 2 subjects erlotinib combination [5%]), and rash maculo-papular (5 subjects [12%]; 5 subjects erlotinib combination [12%]).

Serious adverse events (SAEs) considered at least possibly related to ficlatuzumab included Grade 1 blindness transient, Grade 4 hyperkalemia, and Grade 1 hypokalemia, one case each.

Data from a Phase 1 pharmacodynamic study (Study P05670) in 19 subjects with advanced solid tumors and liver metastases showed ficlatuzumab to be well-tolerated as monotherapy at the 2 to 20 mg/kg dose range tested. There were no DLTs in this study. The most frequently reported TEAEs were asthenia, peripheral edema, and hepatic pain (each reported by 6 subjects [32%]), and cough (5 subjects [26%]). The only related adverse event (AE) was pyrexia, which occurred in 1 subject in the 2 mg/kg treatment group (5%). There were no SAEs considered at least possibly related to ficlatuzumab.

The safety profile of ficlatuzumab was acceptable and similar to the drugs in its class. Serum albumin decreased to below the lower limit of normal at end of study for all exposed subjects. Serum albumin levels began to recover at the follow up visit.

Data from the Phase 1b portion of the Study P06162 in 15 subjects with non-small cell lung cancer (NSCLC) showed ficlatuzumab to be well-tolerated in combination with gefitinib. Ficlatuzumab at 20 mg/kg plus gefitinib at 250 mg/day was determined to be the RP2D.

Of the 12 Phase 1b subjects who received the RP2D, 2 subjects (17%) had DLTs: an SAE of diffuse alveolar damage in 1 subject that resulted in death, and Grade 3 acneiform dermatitis in 1 subject. Both of these events were assessed by the investigator as probably related to gefitinib and/or ficlatuzumab.

The most common TEAEs were dermatitis acneiform (in 10 subjects [67%]), decreased appetite (7 subjects [47%]), diarrhea (6 subjects [40%]), and cough, fatigue, and paronychia (each in 5 subjects [33%]). The most frequently reported study drug-related TEAEs were dermatitis acneiform (10 subjects [67%]), paronychia (5 subjects [33%]), and diarrhea (4 subjects [27%]).

Ficlatuzumab monotherapy has been generally well tolerated. Table 1 lists the TEAEs that, based upon preliminary monotherapy safety data, could be reasonably assumed to be associated with ficlatuzumab.

Data from the Phase 2 portion of the Study P06162 in 184 subjects with non-small cell lung cancer (NSCLC) showed ficlatuzumab to be well tolerated in combination with gefitinib. Table 2 lists the preliminary data on TEAEs with a ≥ 10% difference between the two treatment groups (ficlatuzumab+ gefitinib vs gefitinib monotherapy).

Table 1: Adverse Events Expected to Occur with Ficlatuzumab Monotherapy

MedDRA Preferred Term
Decreased appetite
Diarrhea
Dry skin
Edema peripheral
Fatigue
Headache
Hypoalbuminemia
Hypokalemia
Hypomagnesemia
Myalgia
Nausea
Pruritus
Rash

MedDRA = Medical Dictionary for Regulatory Activities

Table 2: TEAEs w/ ≥ 10% Difference between Treatment Groups (Study P06162)

TEAE, n (%)	Ficlatuzumab plus gefitinib n=90		Gefitinib alone n=94	
	All grades	Grade 3	All grades	Grade 3
Paronychia	42 (47)	-	23 (25)	1 (1)
Acne	24 (27)	1 (1)	15 (16)	-
Peripheral edema	34 (38)	2 (2)	4 (4)	1 (1)
Dizziness	17 (19)	-	8 (9)	-
Eczema	15 (17)	2 (2)	7 (7)	-
Hypoalbuminemia	18 (20)	2 (2)	3 (3)	-
Gingival bleeding	11 (12)	-	1 (1)	-

TEAE=treatment-emergent adverse event.

Ficlatuzumab has not been found to be immunogenic in any patients treated to date; no post-treatment anti-drug antibodies have developed.

1.7 Cetuximab

1.7.1 FDA Indications in HNSCC

Cetuximab is an IgG1, chimeric murine-human antibody against EGFR that was first approved by the U.S. Food and Drug Administration for the treatment of patients with recurrent/metastatic HNSCC in 2006. As cetuximab is a common and accepted standard of care, commercial cetuximab will be used in this study. Please see the cetuximab package insert for complete prescribing information (http://pi.lilly.com/us/erbitux-uspi.pdf).

The most common adverse events (≥25%) associated with cetuximab in clinical trials include:

cutaneous adverse reactions (acneiform rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions associated with cetuximab are: infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

1.7.2 Rationale for Every Two Week Dosing Schedule of Cetuximab

The early studies that established weekly dosing of cetuximab did not establish an MTD.[28, 29] Subsequent pharmacokinetic studies were conducted in patients with advanced colorectal cancer, exploring other doses and schedules. In studies of q2week dosing, cetuximab doses of 400 to 700 mg/m2 q2w were well tolerated and the MTD was not reached.[30] Pharmacokinetic analysis showed that trough cetuximab levels for the 500 mg/m^2 q2w, 600 mg/ m^2 q2w, and 250 mg/m^2 weekly regimens were comparable.[30, 31] Pharmacodynamic studies, in which subjects underwent skin biopsies at baseline and at week 4 showed that all cetuximab dose levels yielded comparable changes in the expression of pEGFR, pMAPK, Ki67, p27, and pSTAT3 as detected with immunohistochemistry.[32] Cetuximab at 500 mg/m^2 q2weeks was identified as a convenient and feasible dose.

In recurrent/metastatic HNSCC, a randomized phase II study compared two q2week cetuximab doses and found that the dose of 500 mg/m^2/q2weeks resulted in similar efficacy to weekly dosing at 250 mg/m^2/week, with no therapeutic advantage for 750 mg/m^2/q2weeks. Due to convenience and comparable efficacy, clinical trials in HNSCC are now integrating the q2week dosing schedule.[33]

1.8 Correlative Studies Background

1.8.1 Tumoral Activation of HGF/cMet Pathway

We have published a report of a cohort of 56 HNSCC patients with tumor protein levels of HGF and cMet calculated by the H score (intensity weighted by percent tumor).[18] We found that HNSCC tumors overexpress both HGF and c-Met as compared to adjacent tissue, as demonstrated below in Figure 1. Ongoing work indicates a bidirectional positive feedback loop between tumor-associated fibroblasts (TAF) which secrete HGF, and HNSCC tumor cells whose conditioned media stimulate HGF secretion from TAFs.[34] In a preclinical HNSCC-TAF co-culture model, ficlatuzumab inhibited HNSCC progression via reduced cMet and mitogen-activated protein kinase (MAPK) signaling.[35]

During the phase Ib trial evaluating the combination of ficlatuzumab and cetuximab in patients with cetuximab-resistant, recurrent/metastatic HNSCC, we evaluated three candidate baseline biomarkers for feasibility and relationship to response: Veristrat; tumoral expression of pMet; and tumoral expression of HGF/cMet dimers. There was no relationship between Veristrat status

and PFS. pMet and HGF/cMet dimer analyses are pending.

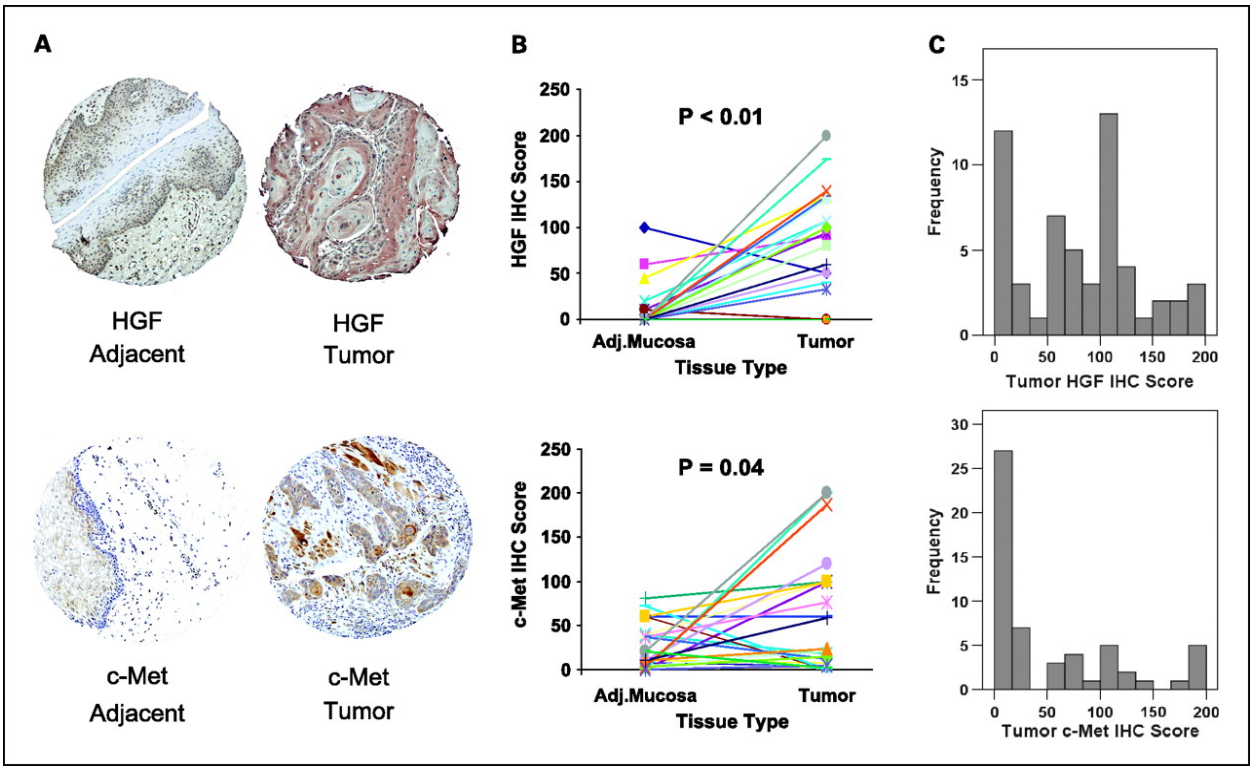

Figure 1: HGF and c-Met are overexpressed in head and neck cancer. HGF and c-Met protein levels were assessed by immunohistochemistry in HNSCC tumors and paired adjacent mucosa (n = 26). Intensity (integer scale 0 to +3) and percent of tumor stained were evaluated. A weighted score of intensity times percent of tumor stained was calculated. A, tumor tissues showed increased HGF and c-Met staining compared with paired adjacent mucosal tissues. B, two-tailed Wilcoxon signed-rank test for paired samples indicated significant differences in weighted HGF and c-Met intensity in tumor versus paired adjacent mucosa (HGF; $P < 0.001$; c-Met; $P = 0.04$). C, HGF and c-Met immunohistochemistry score frequency distributions indicate that higher levels of HGF are more frequently present in HNSCC tumors than c-Met.[18]

In this clinical trial, patients will undergo mandatory research biopsy at baseline. We will investigate the relationship between candidate biomarkers and clinical outcomes on each arm, including the following:

- Dimers (Monogram assay): HGF/cMet, EGFR/EGFR, EGFR/HER2
- Signaling proteins: pMet, bFGF, pMAPK, pAkt

We will also analyze HGF and cMet in archived diagnostic biopsies which took place before clinical cetuximab resistance, as available.

1.8.2 Peripheral Biomarkers of HGF/cMet Pathway Activation

We will also assess candidate peripheral biomarkers for relationship to clinical outcomes. As conducted during phase I, we will assess serum VeriStrat at baseline as well as longitudinally.

VeriStrat is a serum proteomic classifier that assigns patients to two groups: VeriStrat "good" or VeriStrat "poor." Patients who are classified as "good" have improved response to both platinum chemotherapy doublets and EGFR inhibitors in EGFR-wild type non-small cell lung cancer. Patients who are classified as "poor" have a poor overall prognosis, and experience minimal to no clinical benefit from EGFR inhibition.[36] Preliminary evidence indicates that ficlatuzumab may overcome resistance to EGFR inhibitors in the VeriStrat "poor" setting. The absence of association of VeriStrat with response or PFS in the phase Ib trial is intriguing, albeit the cohort was small and the study was underpowered to detect such an association. In the present study, we will evaluate candidate peripheral biomarkers related to HGF/c-Met pathway activation, including:

- Veristrat
- HGF
- Soluble HGF
- IL6

1.8.3 Genomic Alterations: *PIK3CA*, *PTEN*, and *HRAS*

The mutational landscape of HNSCC was assessed by whole exome sequencing of 74 tumor-normal pairs.[37] Several mutations in HNSCC interact with the EGFR and HGF/c-Met signaling pathways and may modulate the impact of pathway antagonism. These include *PIK3CA* (8%), *PTEN* (8%), and *HRAS* (4%) mutations. As we did not confirm the presence of activating *MET* mutations or amplification described by others, and the TCGA has demonstrated less than 1% prevalence in >300 case of *MET* mutation or *MET* amplification, we will not assess *MET* mutation or amplification status.[19].[38]

1.8.4 Immune Biomarkers

HNSCC is an immunosuppressive disease. Patients demonstrate lower absolute lymphocyte counts than healthy subjects [39], impaired natural killer (NK) cell activity [40, 41], and poor antigen-presenting function [42, 43]. Mechanistically, HGF inhibits dendritic cell activation by blocking IκB kinase activity and subsequent nuclear factor-κB activation. Inhibition of IκB kinase is mediated by HGF-induced activation of c-Src.[44] Bruton's tyrosine kinase is also necessary for the association of c-Src with c-Met.[45]

We will evaluate and describe the immune infiltrate in both archived biopsies (prior to cetuximab resistance) and the baseline research biopsies (after cetuximab resistance) from patients enrolled in this study. We will relate immunoscores to clinical outcomes.

1.8.5 Patient-Reported Outcomes

Quality of Life. The Functional Assessment of Cancer Treatment-Head and Neck Version 4

(FACT-H&N) will be used to measure global quality of life (QOL) and functional decline from the patient's perspective. The FACT-H&N is an internationally validated QOL tool. It is a multidimensional, patient-self report QOL instrument that has been specifically designed and validated for this patient population.[46] The questionnaire consists of 27 core items that assess patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by 12 site specific items to assess for head and neck related symptoms. Each item is rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QOL score; higher scores represent better QOL. The FACT-H&N can be completed by the patient in 5-10 minutes, is available in 26 languages, and will be completed at baseline and at the end of cycle 2. See Appendix A for FACT-H&N link.

2. STUDY OBJECTIVES

2.1 Primary

To assess the efficacy of ficlatuzumab, with or without concurrent cetuximab, in patients with cetuximab-resistant, recurrent/metastatic HNSCC as measured by Progression-Free Survival (PFS).

2.2 Secondary

- To describe toxicity and patient-reported quality of life.
- To evaluate response rate and overall survival in both treatment arms.
- To evaluate the relationship between clinical outcomes (PFS, RR) and candidate tumoral, genomic, peripheral, and immune biomarkers, including: HGF/cMet, EGFR/EGFR, and EGFR/HER2 dimers; mutations in PIK3CA, PTEN, and HRAS; peripheral serum biomarkers including VeriStrat, HGF, soluble HGF, and IL6; peripheral lymphocyte populations; archived and baseline immune infiltrate.

3. PATIENT SELECTION

3.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patients must have histologically confirmed HNSCC from any primary site. Basaloid, poorly differentiated, and undifferentiated carcinoma histologies will be accepted. Nasopharyngeal carcinoma, WHO Type I and II (keratinizing, non-EBV positive), will be included. Paranasal sinus, lip and external auditory canal sites will be included. Squamous cell carcinoma of unknown primary, clearly related to the head and neck, will be included.
- Recurrent/metastatic disease, fulfilling at least one of the criteria defined below:
    - Incurable disease as assessed by surgical or radiation oncology
    - Metastatic (M1) disease

- Persistent or progressive disease following curative-intent radiation, and not a candidate for surgical salvage due to incurability or morbidity. Patients who decline radical surgery are eligible.

- For patients with oropharyngeal primary site or unknown primary site only: tumoral HPV status must be known, as established by the local site. Acceptable standards include p16 immunohistochemistry (where a tumor is classified as p16-positive when showing diffuse nuclear and cytoplasmic staining in at least 70% of tumor cells) and/or assessment of HPV DNA.
- Patients must be cetuximab-resistant by fulfilling at least one of the criteria defined below:
  - Disease persistence or recurrence within 6 months of completing definitive radiotherapy for locally advanced disease. Radiation must have included concurrent cetuximab. Induction chemotherapy, if given, may or may not have included cetuximab.
  - Disease progression during, or within 6 months, of cetuximab treatment in the recurrent/metastatic setting.
  - Prior cetuximab exposure may have occurred in any line of therapy (first line, second line, etc.) and cetuximab is not required to be the most recent therapy received.
- Patients must be platinum-resistant or platinum-ineligible by fulfilling at least one of the criteria defined below:
  - Disease persistence or recurrence within 6 months of completing definitive radiotherapy for locally advanced disease, where platinum chemotherapy was administered as a component of induction and/or concurrent systemic treatment.
  - Disease progression during, or within 6 months, of treatment with platinum chemotherapy (eg. carboplatin or cisplatin) in the recurrent/metastatic setting.
  - The patient is not an acceptable candidate for platinum chemotherapy due to medical comorbidities, in the judgment of the local investigator.
  - Prior platinum exposure may have occurred in any line of therapy (first line, second line, etc.) and is not required to be the most recent therapy received.
- Patients must have prior exposure to an anti-PD1 or anti-PDL1 mAb, if eligible for immunotherapy in the judgment of the local investigator.
- Prior exposure to investigational immunotherapies, including anti-CTLA4, anti-OX40, anti-CD40, anti-CD27, anti-TNFR antibodies or other investigational immunotherapies, is acceptable. Eastern Cooperative Oncology Group Performance Status 0-1 at time of informed consent (see Appendix B).
- Age $\geq$ 18 years.

- Patients must consent to a research biopsy of tumor tissue at baseline, for conduct of correlative studies. In cases where a fresh biopsy is not feasible (i.e., if an accessible site cannot be biopsied with acceptable clinical risk), archival tissue may be submitted instead, after discussion with and approval by the principal investigator.
- Measurable disease per RECIST criteria, version 1.1 (see section 6)
- Patients must have the following laboratory values measured within 28 days of registration:
    - Absolute neutrophil count (ANC) $\geq 1500/mm^3$
    - Platelet count (PLT) $\geq 75{,}000/mm^3$
    - Creatinine clearance $\geq$ 40 ml/min as determined by 24-hour collection or estimated by the Cockraft-Gault formula:

      Calculated Creatinine Clearance = [(140-age) X (actual body weight in kg) X (0.85 if female)]/(72 X serum creatinine)
    - Serum bilirubin $\leq$ 1.5 times upper-limit of normal (ULN)
    - AST (aspartate aminotransferase) and ALT (alanine aminotransferase) $\leq$ 3 times ULN
- No prior severe infusion reaction to cetuximab or a monoclonal antibody
- Written informed consent must be obtained from all patients prior to beginning therapy. Patients should have the ability to understand and the willingness to sign a written informed consent document.
- If a woman of childbearing potential, documentation of negative pregnancy within 14 days prior to registration. A negative pregnancy test must also be confirmed within 3 days of the first dose of ficlatuzumab. Sexually active women of childbearing potential must agree to use adequate contraceptive measures, while on study and for 30 days after the last dose of study drug. All fertile female subjects (and their partners) must agree to use a highly effective method of contraception. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; or (b) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm).

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- Nasopharyngeal primary site, if WHO Type III (non-keratinizing and EBV-positive as established at the local site)
- History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational agent.
- Prior treatment with an HGF/cMet inhibitor such as rilotumumab, crizotinib, MetMAb, or ARQ197.

- Uncontrolled central nervous system (CNS) metastases, including leptomeningeal metastases, are not allowed. Subjects with previously treated brain metastases will be allowed if the brain metastases have been stable without steroid treatment for at least 2 weeks (radiotherapy or surgery).
- Failure to recover to Grade 1 or baseline from all toxic effects of previous chemotherapy, radiation therapy, biologic therapy, immunotherapy, and/or experimental therapy, with the exception of: alopecia, Grade ≤ 2 peripheral neuropathy, Grade ≤ 2 cetuximab-related rash or other skin changes, hypomagnesemia (acceptable values detailed below), hypokalemia (acceptable values detailed below), and the acceptable hematologic values summarized above. A washout period of 2 weeks from prior cetuximab is required; a washout period of 3 weeks from any prior cytotoxic chemotherapy, targeted therapy, immunotherapy or investigational drug is required.
- Significant pulmonary disease, including pulmonary hypertension or interstitial pneumonitis.
- Decreased serum albumin < 30 g/L (< 3 g/dL)
- Peripheral edema ≥ Grade 2 per NCI-CTCAE version 4.0.
- Significant electrolyte imbalance prior to enrollment (note that patients may be supplemented to achieve acceptable electrolyte values):
    - Hypomagnesemia <1.2 mg/dL or 0.5 mmol/L.
    - Hypocalcemia < 8.0 mg/dL or 2.0 mmol/L.
    - Hypokalemia < 3.0 mmol/L.
- Significant cardiovascular disease, including:
    - Cardiac failure New York Heart Association (NYHA) class III or IV.
    - Myocardial infarction, severe or unstable angina within 6 months prior to Study Day 1.
    - History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation).
    - Cardiac arrhythmia requiring anti-arrhythmic medication(s). Note that beta-blockers, calcium channel blockers, and digoxin administered for the purpose rate control of supraventricular tachycardia, including atrial fibrillation and atrial flutter, are not classified as anti-arrythmic medications for purposes of trial eligibility.
- Significant thrombotic or embolic events within 4 weeks prior to Study Day 1. Significant thrombotic or embolic events include but are not limited to stroke or transient ischemic attack (TIA). Catheter-related thrombosis is not a cause for exclusion. Diagnosis of deep vein thrombosis or pulmonary embolism is allowed if it occurred > 4 weeks prior to Study Day 1 and the patient is asymptomatic and stable on anti-coagulation therapy.

- Any other medical condition (eg, alcohol abuse) or psychiatric condition that, in the opinion of the Investigator, might interfere with the subject's participation in the trial or interfere with the interpretation of trial results.
- History of second malignancy within 2 years prior to Study Day 1 (except for excised and cured non-melanoma skin cancer, carcinoma in situ of breast or cervix, superficial bladder cancer, Stage I differentiated thyroid cancer that is resected or observed, or pT1a /pT1b prostate cancer comprising < 5% of resected tissue with normal prostate specific antigen (PSA) since resection, or cT1a/cT1b prostate cancer treated with brachytherapy or external beam radiation therapy with normal PSA since radiation).
- Major surgery within 6 weeks prior to Study Day 1 (subjects must have completely recovered from any previous surgery prior to Study Day 1).
- Active infection requiring systemic antibiotics or antifungals within 7 days prior to first dose of study drug. Exception: tetracycline family antibiotics (tetracycline, doxycycline, minocycline) administered for the management of cetuximab-related rash may be continued per the Investigator's judgment.
- HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible drug interactions with study drugs. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated. Note: HIV testing is not required for entry into this protocol.
- Women must not be pregnant or breastfeeding because ficlatuzumab and/or cetuximab may be harmful to the fetus or the nursing infant. Pregnant women are excluded from this study because ficlatuzumab and/or cetuximab have the potential for teratogenic or abortifacient effects.

4. PATIENT REGISTRATION AND RANDOMIZATION

4.1 Registration

For questions regarding the eligibility of subjects, Julie E. Bauman, M.D., M.P.H. should be contacted at 520-626-4101 or jebauman@email.arizona.edu.

Registration will be submitted to the University of Arizona Cancer Center Clinical Trials Office and will require the following information: 1) the coordinator's name and contact information; 2) protocol name and number; 3) date treatment is planned to begin; 4) subject initials; 5) subject date of birth, sex, and race/ethnicity; 6) site Principal Investigator's name and contact information; 7) treating Investigator's name and contact information; 8) primary treatment institution; 9) confirmation of eligibility checklist; 10) copies of the informed consent signature page; 11) verification that the informed consent was signed.

Following registration, institutions are requested to submit prior diagnostic tumor blocks for biomarker correlatives. A representative paraffin block of the original diagnosis and/or all repeat

biopsies, if available, will be submitted. In particular, a representative block from prior to cetuximab exposure is requested. All efforts must be made to obtain paraffin blocks. If paraffin blocks are not available and the pathology department will not release blocks, please contact the study coordinator prior to requesting tissue. A 3 mm core, punched from the tissue block with a punch tool, and 5-10 unstained slides of 5 micron thickness mounted on positively-charged glass slides may be acceptable. See Section 9.1 for shipping instructions.

Following registration and prior to study treatment, patients are required to undergo research biopsy. Archived tumor tissue may be substituted if an accessible site cannot be biopsied with acceptable clinical risk and the PI has approved omission of the baseline biopsy. Please see section 9.2 for biopsy, processing and shipping details.

4.2 Randomization

Randomization to ficlatuzumab vs. the combination of ficlatuzumab and cetuximab will occur at the UACC Biostatistics Shared Resource. Patients will be stratified by HPV status, a known prognostic factor in recurrent/metastatic HNSCC, and study center.

- HPV-positive vs. HPV-negative. For purposes of stratification, HPV-positive HNSCC will be assessed by p16 status performed per standard of care at the local site. To be classified as HPV-positive, patients must meet BOTH of the following criteria: 1) either oropharynx or unknown primary site; AND 2) p16+ by immunohistochemistry, where ≥ 70% of tumor cells demonstrate diffuse nuclear and cytoplasmic staining with p16 antibody. For purposes of stratification, the remainder of patients will be classified as HPV-negative.
- Study Center

5. TREATMENT PLAN

- Note: One cycle consists of 4 weeks, or two doses, of ficlatuzumab and cetuximab.
- For both agents: Recalculate the doses of both ficlatuzumab and cetuximab at the beginning of each cycle only if there is a ≥ 10% change in weight.

5.1 Ficlatuzumab

5.1.1 Route of Administration

The ficlatuzumab Pharmacy Manual should be referenced for drug preparation and administration information.

Ficlatuzumab will be administered as an IV infusion.

5.1.2 Dose and Schedule

Ficlatuzumab will be administered at the dose of 20 mg/kg IV every 2 weeks (+/- 3 days), beginning on the same day as the first dose of cetuximab. Ficlatuzumab will be administered over 30-60 minutes. Protocol-specified dose modifications are permitted. See Table 3 below for dose reduction levels.

5.1.3 Order of Administration

Cetuximab will be administered first. Ficlatuzumab will be administered 30-60 minutes after the completion of the cetuximab infusion.

5.2 Cetuximab

5.2.1 Route of Administration

Cetuximab will be administered as an IV infusion.

5.2.2 Dose and Schedule

Cetuximab will be administered at the dose of 500 mg/m^2 IV every 2 weeks (+/- 3 days), beginning on the same day as the first dose of ficlatuzumab. The first dose will be administered over 120 minutes (+/- 15 minutes) and subsequent doses may be infused at a rate no faster than 10 mg/min. Protocol-specified dose modifications are permitted. See Table 3 below for dose reduction levels.

5.2.3 Order of Administration

Cetuximab will be administered at the dose of 500 mg/m2 IV every 2 weeks (+/- 3 days), beginning on the same day as the first dose of ficlatuzumab. The first dose will be administered over 120 minutes (+/- 15 minutes) and subsequent doses may be infused over 60 minutes (+/- 15 minutes). Protocol-specified dose modifications are permitted. See Table 3 below for dose reduction levels.

5.2.4 Premedications

Prior to the first dose of cetuximab, 50 mg of diphenhydramine will be administered PO or IV. If the patient shows no evidence of hypersensitivity, the dose of diphenhydramine may be reduced to 25 mg PO or IV, or eliminated, per investigator judgment. In patients intolerant of diphenhydramine, a non-sedating antihistamine (eg. cetirizine 10 mg) may be substituted per local preference. Alternately or in addition, a dose of IV steroids (eg. dexamethasone 10 mg; hydrocortisone 50 mg) may be substituted per local preference.

5.3 General Concomitant Medication and Supportive Care Guidelines

Colony-Stimulating Factors: Colony stimulating factors, including G-CSF, pegylated G-CSF, and erythropoietin analogs may be used in accordance with local and national practice guidelines.

5.4 Duration of Treatment and Follow-up

In the absence of treatment delays due to adverse event(s), treatment will continue until disease progression or until one of the following criteria applies:

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

Patients will be followed for survival every 3 months for two years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Dose Delays and Modifications

5.5.1 Dose Reduction Levels

The following table summarizes dose levels available for protocol-specified dose reductions of ficlatuzumab and/or cetuximab (Table 3).

Table 3: Dose Reduction Levels

Dose Level	Ficlatuzumab	Cetuximab
-2	10 mg/kg/q2weeks	300 mg/m^2/q2weeks
-1	15 mg/kg/q2weeks	400 mg/m^2/q2weeks

5.5.2 Dose Modification for Hematologic Toxicity

While serious (Grade 3-4) myelosuppression has not been observed with ficlatuzumab monotherapy or the combination of ficlatuzumab with EGFR-inhibitors during phase I development, dose modifications are specified in Table 4A for neutropenia or thrombocytopenia, should either be observed during the course of this phase II study. As cetuximab does not cause myelosuppression, the cetuximab dose will not be affected by observed neutropenia or thrombocytopenia.

Table 4A. Ficlatuzumab and Cetuximab Dose Modifications for Hematologic Toxicity

NCI CTCAE Toxicity Grade (CTCAE v. 4)	Ficlatuzumab Dose	Cetuximab Dose
Neutropenia		
Grade 1-2 1 (1500-1999/mm^3) 2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level
Grade ≥3: 3 (500-999/mm^3) 4 (<500/mm^3)	Hold dose. When recovered to Grade 2 or better, decrease by 1 dose level.	Maintain dose level

Thrombocytopenia		
Grade 1 (75,000/mm^{3}-LLN)	Maintain dose level	Maintain dose level
Grade ≥ 2: 2 (50,000- 74,999/mm^{3}) 3 (25,000- 49,999/mm^{3}) 4 <25,000/mm^{3})	Hold dose. Re-assess prior to next scheduled dose. When recovered to Grade 1 or better, decrease by 1 dose level.	Maintain dose level

5.5.3 Dose Modification for Non-Hematologic Toxicity

Adverse events observed and deemed to be at least possibly related to study drug(s) will be managed according to the guidelines for dose interruption, delay, or reduction.

If the toxicity can be clearly and solely attributed to ficlatuzumab, the ficlatuzumab should be withheld or reduced as described below in Table 4B. If the toxicity is at least possibly related to both ficlatuzumab and cetuximab, then both study drugs should be modified as described below.

Table 4A. Ficlatuzumab and Cetuximab Dose Reductions for Non-Hematologic Toxicity

NCI CTCAE Toxicity Grade (CTCAE v. 4)	Ficlatuzumab Dose	Cetuximab Dose
Metabolic[a] **Hypomagnesemia, Hypokalemia, Hypophosphatemia, or Hyponatremia**		
Grade ≥ 3, Asymptomatic	Hold drug. Administer PO or IV replacement and reassess. When Grade ≤2, continue drug at same dose level. Same day re-assessment and dosing is permissible.	Hold drug. Administer PO or IV replacement and re-assess. When Grade ≤2, continue drug at same dose level. Same day re-assessment and dosing is permissible.
Grade ≥ 3, Symptomatic	Hold drug. Administer PO or IV replacement until ≤ Grade 2 and asymptomatic, then reduce by one dose level. Same day re-assessment and dosing is permissible.	Hold drug. Administer PO or IV replacement until ≤ Grade 2 and asymptomatic, then reduce by one dose level. Same day re-asseessment and dosing is permissible.
Hepatic Function **AST and/or ALT Elevation**		
Grade 2	Reduce by one dose level	Reduce by one dose level
Grade ≥ 3	Hold drug until ≤ grade 2 then reduce by one dose level	Hold drug until ≤ grade 2 then reduce by one dose level
AST or ALT elevation >3x ULN and concomitant elevation of bilirubin >2x ULN	Discontinue ficlatuzumab	Discontinue ficlatuzumab
Low Albumin		
Grade 3 Grade 4	No dose reduction Reduce by one dose level	No dose reduction No dose reduction

Edema[b] **Facial/Neck Edema** Grade 2 (intolerable) or Grade ≥ 3 **Peripheral Edema** Grade 2 Grade ≥ 3	 Hold drug. Administer steroids and/or PO or IV diuretics as clinically indicated. Resume drug when ≤ grade 2 and reduce by one dose level No dose reduction. Treat with PO diuretics as clinically indicated. Hold drug and administer PO or IV diuretics as clinically indicated. Resume drug when ≤ grade 2 and reduce by one dose level.	 No dose reduction
Fatigue Grade ≥ 3, lasting more than 7 days	Hold drug until ≤ grade 2 then reduce by one dose level	Hold drug until ≤ grade 2 then reduce by one dose level
Nausea/Vomiting ≥ Grade 3 with maximal medical management	Hold drug until ≤ grade 2 then reduce by one dose level	Hold drug until ≤ grade 2 then reduce by one dose level
Rash, Acneiform ≥ Grade 3	Maintain dose level	First Occurrence: Hold drug for two weeks. If improved to ≤ grade 2 then restart cetuximab at same dose level. If rash remains ≥ Grade 3 then discontinue cetuximab. Second Occurrence: Hold drug for two weeks. If improved to ≤ grade 2 then restart cetuximab at dose level -1. If rash remains ≥ Grade 3 then discontinue cetuximab. Third Occurrence: Hold drug for two weeks. If improved to ≤ grade 2 then restart cetuximab at dose level -2. If rash remains ≥ Grade 3 then discontinue cetuximab. Fourth occurrence: discontinue cetuximab.
Other, Grade ≥ 3	Hold drug until ≤ grade 1 or baseline, then reduce by one dose level.	Hold drug until ≤ grade 1 or baseline, then reduce by one dose level.

a. Cetuximab and ficlatuzumab can be associated with electrolyte abnormalities including hypomagnesemia and hypokalemia. Supplemental oral or IV electrolytes should be administered as indicated by the treating investigator. Sustained repletion may require both chronic oral and IV replacement. An EKG is strongly recommended in the event of: 1) symptomatic Grade ≥ 3 hypomagnesemia or hypokalemia or 2) asymptomatic Grade 4

hypomagnesemia or hypokalemia. Interventions, including hospitalization as necessary for correction of electrolyte derangement, should occur in accordance with clinical severity and investigator judgment.

b. Ficlatuzumab can be associated with edema. In patients with HNSCC, therapeutics that cause peripheral edema can also be associated with facial/neck edema. In the case of intolerable grade 2 or grade ≥ 3 facial/neck edema, hold ficlatuzumab. A brief steroid pulse (eg. Prednisone 40 mg/daily for 5 days) may also be considered. In the case of intolerable grade 2 or grade ≥ 3 peripheral edema, hold ficlatuzumab and administer PO or IV diuretics as indicated.

Subjects may have up to two dose reductions. Subjects at the lowest ficlatuzumab dose level (10mg/kg) who experience an attributable Grade 3 or 4 toxicity will be discontinued from ficlatuzumab. However, if in the investigator's opinion there is evidence of clinical benefit, a subject may resume treatment at 10 mg/kg after the AE has resolved or ameliorated to ≤ Grade 2 or baseline.

If any observed toxicity at least possibly related to ficlatuzumab and/or cetuximab prevents dosing within the scheduled study visit window, the dose for that study visit will be skipped and the next study drug administration will occur at the next scheduled dose. If a ficlatuzumab-related toxicity results in 2 consecutive missed doses, the ficlatuzumab will be discontinued permanently. However, if in the investigator's opinion there is evidence of clinical benefit, a subject with 2 consecutive missed doses may resume treatment after the AE has resolved to the minimum specifications in Table 4.

5.5.4 Dermatologic Toxicity

Cetuximab-related dermatologic toxicity should be graded according to the criteria outlined in Table 5 below. According to physician judgment, if a patient experiences ≥ grade 3 rash, cetuximab treatment adjustments should be made according to Table 4 above. In patients with mild and moderate skin adverse events, cetuximab should continue without adjustment.

Table 5: Grading of Cetuximab-Related Skin Changes

	1	2	3	4
Pruritus*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or

		instrumental ADLI; Responds promptly to symptomatic treatment	local superinfection with oral antibiotics indicated; Prolonged.	tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

*Onset of grade 3 will require dose modification for cetuximab. See Table 4 above.

Cetuximab-Related Rash Management

Skin rash, ranging from dry skin and erythema to a pustular eruption is extremely common during cetuximab therapy. Biopsy of the papulopustular rash demonstrates histopathologic suppurative inflammation and not acne vulgaris. Although the initial rash is sterile, superinfection may occur.

Patients developing dermatologic AEs while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash, adapted from the NCCN Task Force for the Management of Dermatologic Toxicities Associated with EGFR Inhibition in Patients with Cancer.[47] In the event of severe rash not responsive to topical treatments or oral antibiotics, dose modification per Table 4 is indicated.

- **Moisturizers:** Use of topical emollients to prevent and alleviate skin dryness is strongly advised. Examples include Aquaphor Ointment, Cetaphil Cream, Neutrogena Norwegian Formula Hand Cream, and Vaseline Intensive Care Advanced Healing Lotion.
- **Soap:** A mild, neutral pH soap is recommended.
- **Antibiotics**: Topical clindamycin or erythromycin, or an oral tetracycline family antibiotic (eg. tetracycline, minocycline, doxycycline) should be considered in the case of superinfection or suspected superinfection. Oral minocycline, tetracycline or doxycycline may be given prophylactically to patients with a history of severe acneiform eruption during prior cetuximab therapy.
- **Antihistamines**: Diphenhydramine or hydroxyzine may be helpful to control itching.

- **Topical Steroids**: Topical therapy with a low potency steroid to the face (eg. hydrocortisone valerate 0.2%) or a mid-potency steroid to the body (eg. triamcinolone acetonide 0.1%) may be used for management of cetuximab rash.
- **Sunlight**: It is recommended that patients wear sunscreen (at least SPF 40) and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (eg. benzoyl peroxide) are not advised.
- **Retinoids**: Use is not advised.

5.5.5 Cetuximab Infusion Reaction

Table 6: Management of Cetuximab Infusion Reaction

Grade	Management[a]
Grade 1: Transient flushing or rash; drug fever < 38º C (< 100º.4 F)	For mild infusion reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose but slow the infusion rate by 50%. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.
Grade 2 : Rash; flushing; urticaria; dyspnea; drug fever ≥ 38º C (≥ 100º.4 F)	For moderate infusion reactions manifesting only as delayed drug fever, slow the infusion rate for cetuximab by 50%, and consider administration of antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.
Grade 3: Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Severe infusion reactions **requires immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.
Grade 4: Anaphylaxis	**NO FURTHER CETUXIMAB** Life-threatening infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

[a] Study Therapy Retreatment Following Infusion Reactions: Once a cetuximab infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction with the slower infusion rate, the infusion should be stopped, and the subject should receive no further

cetuximab treatment. If a subject experiences a Grade 3 or 4 infusion reaction at any time, the subject should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 1-4, Dr. Julie Bauman should be contacted immediately to discuss and grade the reaction.

5.5.6 Interstitial Lung Disease

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, both cetuximab and ficlatuzumab should be interrupted and a prompt investigation of these symptoms should occur. Neither ficlatuzumab nor cetuximab retreatment should occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, both cetuximab and ficlatuzumab should be discontinued permanently and the patient should be treated appropriately.

6. RESPONSE ASSESSMENT

For the purposes of this study, patients should be re-evaluated for response every 8 weeks.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[48] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used.

6.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

The term unevaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, the primary tumor and pathologic neck lymph nodes will be characterized as either measurable or non-measurable.

6.1.1 Measurable Disease

Primary Tumor:
Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (2.0 cm) with conventional techniques or as ≥ 10 mm (1.0 cm) with spiral CT scan.

Neck Lymph Nodes:
Neck lymph nodes are considered pathologic and measurable if short axis ≥ 15 mm.

Neck lymph nodes are considered pathologic but non-measurable if short axis ≥ 10 mm but < 15 mm.

Neck lymph nodes are considered non-pathologic and non-measurable if short axis < 10 mm.

6.1.2 Non-measurable disease

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with spiral CT scan] are truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

6.1.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

The sum of the longest diameter of the primary tumor, and the short axis diameter of target pathologic lymph nodes, will be calculated at baseline and reported as the *baseline sum diameter*.

6.1.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.2 Response Criteria

6.2.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target)

must have reduction in short axis to <10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of target lesion diameters (longest diameter of non-nodal lesions; short axis diameter of the target lymph nodes), taking as reference the *baseline sum diameter*.

Progressive Disease (PD)

At least a 20% increase in the sum of target lesion diameters (longest diameter of non-nodal lesions; short axis diameter of the target lymph nodes), taking as reference the *smallest sum diameter* recorded since the baseline sum diameter measurements. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progressions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.2.2 Evaluation of Nontarget Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Complete Response (CR)

The disappearance of all nontarget lesions.

Partial Response/Stable Disease (SD)

The persistence of one or more nontarget lesion(s).

Progressive Disease (PD)

The appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

6.2.3 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having *symptomatic deterioration.*

6.2.4 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. Table 7 below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.

Table 7: Evaluation for Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Duration of Response

Duration of overall response - the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

Duration of Overall Complete Response

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

Survival

Survival will be measured from the date of entry on study.

Time to Progression and Progression-free survival

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

Progression-free survival (PFS) will be calculated from treatment initiation to disease progression or death from any cause.

6.3 Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at

baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

7. DRUG INFORMATION

7.1 Ficlatuzumab

7.1.1 Study Drug Materials

The Pharmacy Manual should be referenced for drug preparation and administration information.

Ficlatuzumab Concentrate for Injection, 50 mg/mL, is formulated in 10 mM histidine buffer pH 5.8. The formulation also includes 142 mM arginine (for isotonicity) and 0.01% polysorbate-80. The product is sterile filtered and aseptically filled into washed and depyrogenated 4-mL and 20 mL glass vials. An excess fill is provided in the vial to ensure that the label fill of 4.0 mL can be withdrawn. The product is a clear to slightly opalescent, colorless to slightly yellow, solution.

Ficlatuzumab Concentrate for Injection is to be administered by IV infusion as an admixture with normal saline solution. The admixture solution in an IV bag is connected to an infusion set containing a 0.22 μm low protein-binding in-line filter. The IV bag and the infusion set containing the in-line filter have been shown to be compatible with the admixture. The filtered admixture solution is clear to slightly opalescent.

7.1.2 Ficlatuzumab Study Drug Storage

Ficlatuzumab is to be stored under refrigerated conditions (2º C– 8ºC) and in a secure location.

Note: No other use of ficlatuzumab study drug intended for use in this trial is authorized by the sponsor. The investigator (or designee) will be responsible for the appropriate handling and

disposition of residual study drug in partially used vials.

Vial Labels: Ficlatuzumab vial labels will bear the appropriate label text for investigational agents, as required by governing regulatory agencies.

Complete study drug information (including packaging, labeling, storage and disposition) is provided in the Ficlatuzumab Investigator's Brochure (IB).

7.2 Cetuximab

Refer to the package insert for additional information.

Formulation: Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant.

Safety Precautions: Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

Preparation and Administration: Cetuximab must not be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administration must be through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:
Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).

1. Place the syringe into the syringe driver of a syringe pump and set the rate.
2. Administration must be through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
3. Connect up the infusion line and start the infusion after priming the line with cetuximab.
4. Repeat procedure until the calculated volume has been infused.
5. Use a new needle and filter for each vial.
6. Maximum infusion rate should not exceed 5 mL/min (10 mg/min).
7. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a one-hour observation period is recommended.

Storage Requirements/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.
Supply

Cetuximab is commercially available in the U.S.

8. CLINICAL AND LABORATORY EVALUATIONS

Schedule of Assessments. See Appendix C for Study Calendar.

8.1 Pre-treatment evaluations

NOTE: Evaluations should be performed within 4 weeks of registration unless otherwise indicated.

- History and physical examination, including vital signs, weight, height and performance status determination
- Complete blood count, including platelets and differential
- Blood chemistry studies, including BUN, creatinine, electrolytes (K^+, Na^+, Cl^-, CO_2), glucose, calcium, ionized calcium, Mg^{++} and liver function tests (total protein, albumin, total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase)
- For women of child bearing potential: Pregnancy test within 2 weeks (14 days) of registration to rule out pregnancy. (Note, negative pregnancy test must be confirmed again within 3 days of first study treatment.)
- Request archived tumor specimens for correlative research as outlined in section 9.1.

- Baseline tumor measurements within 4 weeks prior to registration.
- For oropharyngeal cases: p16 status must be known or established and recorded at baseline
- Tobacco history assessment form (See Appendix D)
- Quality of life assessment (complete FACT-H&N in Appendix A) (may be performed at screening or prior to study treatment on day 1)
- Blood samples for research purposes (may be performed at screening or prior to study treatment on day 1)
- Research biopsy of tumor tissue (See Section 9.2 for biopsy procedure, processing and shipping.)

8.2 Evaluations during treatment

EVERY TWO WEEKS (+/- 3 days, to coincide with study treatment)

Note: The following may be performed on the day of or the day prior to cetuximab/ficlatuzumab administration.

- History and physical examination, including vital signs, weight and performance status
- Toxicity assessment with attribution
- Update of concomitant medications
- Complete blood count, including platelets and differential
- Blood chemistries, including BUN, creatinine, electrolytes (K+, Na+, CI-, CO2), glucose, calcium, ionized calcium, Mg++ and liver function tests (total protein, albumin, total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase)

EVERY 8 WEEKS (the end of even cycles)

- Quality of life assessment (FACT-H&N) – end of cycle 2 only (may be done cycle 3, day 1)
- Tumor measurements according to RECIST 1.1 may be done during the last week of an even cycle or on day 1 of the following odd cycle, by CT scan or MRI.
- Toxicity assessment with attribution
- Blood samples for research purposes (note these may be performed concurrent with day 1 treatment labs for the following odd cycle)

8.3 Post-treatment evaluations

Patients who discontinue treatment for any reason will have an evaluation with the following tests, if possible (unless performed within the previous 2 weeks):

- History and physical examination, including vital signs, weight and performance status
- Toxicity assessment with attribution
- Update of concomitant medications
- Complete blood count, including platelets and differential
- Blood chemistries, including BUN, creatinine, electrolytes (K+, Na+, CI-, CO2), glucose, calcium, ionized calcium, Mg++ and liver function tests (total protein, albumin, total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase)
- Blood correlatives
- Tumor measurements according to RECIST 1.1 (unless performed within the previous 4 weeks)

If a patient discontinues treatment without progressive disease, he/she will be followed every 2 months until progression of disease with above tests. If such a patient initiates a new line of therapy, he/she will be censored for progression at that time point.

After a patient progresses, he/she will be followed for survival every 3 months for 2 years.

9. BIOMARKER, CORRELATIVE, OR SPECIAL STUDIES

9.1 Submission of archived diagnostic tissue

Submission of primary tumor tissue for biomarker correlatives, prior to clinical cetuximab resistance, is strongly encouraged. A representative paraffin block of the original diagnosis and/or any repeat diagnostic biopsies, if available, will be submitted. All efforts must be made to obtain paraffin blocks. If paraffin blocks are not available and the pathology department will only release slides, please contact the study coordinator prior to requesting slides. A 3 mm core, punched from the tissue block with a punch tool, and 5-10 unstained slides of 5 micron thickness mounted on positively-charged glass slides may be acceptable.

Specimens should be labeled with the study number, patient's unique study identifier, date of specimen collection, and anatomic site. Specimens may be batched.

Formalin-fixed specimens may be shipped at room temperature, and will be shipped overnight to the University of Arizona (See Lab Manual for shipping information). DO NOT SHIP ON FRIDAY OR BEFORE A HOLIDAY.

Note: Should fresh frozen tissue from the patient's diagnostic procedures be available, a representative sample should be submitted (quantity: minimum 40 mg). Frozen specimens may be batched and shipped on dry ice overnight. DO NOT SHIP ON FRIDAY OR BEFORE A HOLIDAY.

9.2 Research biopsies

Prior to initiation of protocol treatment, patients will undergo a research biopsy. Biopsies of primary tumor or accessible lymph node will occur in the outpatient office of the head and neck surgeon, with local anesthetic per standard of care. Biopsies of lymph nodes requiring imaging guidance or distant metastases will occur under the care of an interventional radiologist, with ultrasound or CT guidance and local anesthetic per standard of care.

9.2.1 Research Biopsy Methodology

All patients will be evaluated for a research biopsy at the time of enrollment. Research biopsies will consist of a cup forceps biopsy or a core needle biopsy that can be safely performed in the outpatient setting with only local anesthesia. (NOTE: Archived tumor tissue may be substituted if an accessible site cannot be biopsied with acceptable clinical risk and the PI has approved omission of the baseline biopsy.) During the biopsy procedure, at least two 1-cm cores of tissue should be obtained with a core biopsy needle (18-gauge or greater is preferred; 20-gauge is acceptable) – or the equivalent with cup forceps biopsy.

9.2.2 Sample Preparation and Shipment Instructions

For the research biopsies, the tissue samples will be processed as follows:

University of Arizona: The specimen will be divided into two parts. If biopsy material is limited then tissue is to be prioritized in the listed order:

1) The first part will be placed in a formalin-filled plastic container, at room temperature.

2) The second part will be immediately flash frozen in liquid nitrogen (or alternatively in a dry ice/ethanol bath).

Specimens should be labeled with the study number, patient's unique study identifier, date of specimen collection, and anatomic site. Both biopsies will be delivered to the University of Arizona (See Lab Manual for shipping information). Frozen samples should be delivered on dry ice.

Non-Arizona sites:

Biopsies will be performed as above.

Both samples should be shipped to University of Arizona, Monday through Thursday (See Lab Manual for shipping information). DO NOT SHIP ON FRIDAY OR BEFORE A HOLIDAY. Frozen samples should be shipped on dry ice. Samples can be batched. Specimens should be labeled with the study number, patient's unique study identifier, date of specimen collection, and anatomic site.

9.3 Research Blood

Blood will be collected at the following time points on study:

- baseline
- end of cycle 2 (may be drawn with cycle 3, day 1 treatment labs)
- end of every even cycle during study treatment (may be drawn with day 1 treatment labs for the following odd cycle)
- at progression if not collected within the prior 2 weeks

Peripheral blood obtained by venipuncture will serve as the source for laboratory testing. Up to 70 mL of blood may be obtained at each draw (See Lab Manual for collection information).

10. STATISTICAL METHODS

10.1 Study Design

This is an open-label phase II trial with a randomized, non-comparative, two-arm design (Arm A: ficlatuzumab vs. Arm B: ficlatuzumab + cetuximab) in patients with recurrent/metastatic head and neck squamous cell carcinoma after failure of anti-EGFR therapy.

10.2 Primary Objective

The primary objective is to estimate the efficacy of ficlatuzumab, with or without cetuximab, as measured by the endpoint of PFS. PFS will be measured from the date of randomization until the date of progression or death. Patients without progression will be censored at the date of last follow up.

10.3 Sample Size Determination

The primary objective of this study is to estimate PFS in both arms. The sample size calculation thus is based on the primary endpoint of PFS. Given no data are available for single-agent ficlatuzumab in patients with recurrent/metastatic HNSCC refractory to platinum, cetuximab, and PD-1 inhibition, the historical control will be represented by dealer's choice chemotherapy in the phase III trial of nivolumab in platinum-refractory HNSCC: 2 months. This median PFS is very similar to single-agent data in the refractory, recurrent/metastatic setting for cetuximab, afatinib, and methotrexate [49, 50]. We would like to investigate whether the new regimen in either arm can improve the median PFS from 2 months 3.33 months (i.e. 60% improvement in median PFS). To detect such an improvement, the study design requires 66 eligible patients (33 eligible patients on each arm) over 24 months with an additional follow-up of 6 months (making the study duration of approximately 2.5 years in total), using a log-rank test with 90% power while assuming a 0.10 one-sided type 1 error rate. Full information for the primary endpoint of PFS will occur at 33 events per arm. ***To account for an assumed 10% ineligibility/drop-out rate, 74 patients in total will be accrued to obtain the necessary 66 eligible randomized patients.*** If one arm achieves the hypothesized median PFS, that arm will be advanced to phase III testing. If both arms achieve the hypothesized PFS, the numerically superior arm will be advanced to phase III testing.

10.4 Secondary Objectives

The secondary objectives of this trial are to describe toxicity and patient-reported quality of life, to obtain additional measures of efficacy including response rate and overall survival, and to evaluate whether specific candidate biomarkers are prognostic in the context of treatment with ficlatuzumab.

10.4.1 Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with ficlatuzumab. The proportion of DLTs in each dosing cohort will be reported, as will the proportion of AEs in accordance with NCI CTCAE v.4 grading criteria.

10.4.2 Patient-Reported Outcomes

Quality of life will be described according to FACT-H&N scores obtained at baseline and after two cycles of study treatment.

10.4.3 Other Efficacy Endpoints

Response rate will be assessed by modified RECIST criteria, version 1.1. Overall survival will be measured from the date of randomization until the date of death.

10.4.4 Biomarker endpoints

We will evaluate the relationship between clinical outcomes (PFS, RR) and candidate tumoral, genomic, peripheral, and immune biomarkers, including: HGF/cMet, EGFR/EGFR, and EGFR/HER2 dimers; mutations in *PIK3CA*, *PTEN*, and *HRAS*; peripheral serum biomarkers including VeriStrat, HGF, soluble HGF, and IL6; peripheral lymphocyte populations; archived and baseline immune infiltrate.

Three candidate mechanistic biomarkers will be prioritized for specialized alpha spending: 1) baseline Veristrat; 2) baseline HGF/cMet dimers; 3) baseline pMet. Testing three biomarkers each at $\alpha = .05$ guarantees a maximum 15% false discovery rate for this secondary objective.

Other candidate biomarkers in tumor and blood described above will be quantitatively measured and will be evaluated as predictors of PFS and/or tumor response in appropriate generalized linear models. Calculated p values for testing the significance of the prediction models will be adjusted for false discovery by the method of Benjamini and Hochberg.[51]

10.5 Statistical Analysis Plan

Progression-free and overall survival will be estimated for each arm using a Kaplan-Meier curve. Toxicities and the response rate will be tabulated and reported with 95% exact confidence intervals. The relationship between progression-free survival and the candidate biomarkers will be assessed using Cox proportional hazards models. The relationship with clinical response will be assessed using logistic regression models.

10.6 Continuous Monitoring Rule for Futility

The study will include a continuous Bayesian monitoring rule for futility. We will accrue and observe the first 8 patients on each arm, then continuously observe the proportion of patients who are without progression at 16-weeks. Based on the hypothesized increase in median progression-free survival from the historical rate of 2 months to 3.33 months in either the ficlatuzumab arm or the ficlatuzumab plus cetuximab arm, the expected proportion progression-free at 16 weeks would be 0.46 under the alternative hypothesis. A Bayesian predictive probability design was used to estimate the rejection regions to stop an arm for futility.[52] The rejection regions to stop an arm for futility are: 0/8, 1/9, 2/13, 3/16, 4/19, 5/21, 6/24, 7/26, 8/28, 9/29, 10/31, 11/32, 12/33. Thus, if none of the first 8 patients is progression-free at 16 weeks, that arm will be stopped, or if only 1 of the first 9 patients is progression-free, that arm will be stopped, etc. This design has 80% power at $\alpha = 0.10$ with an expected sample size of 21.3 under the null hypothesis and 31.4 under the alternative hypothesis. The probability of early termination under the null hypothesis is 0.86. The rejection regions were derived to maximize power under the alternative hypothesis. There was no Bayesian predictive probability design with 90% statistical power given the proposed median survival times and sample size with $\alpha = 0.10$.

11. DATA SAFETY MONITORING PLAN

11.1 Identification of the DSMB obligated for oversight responsibilities

The University of Arizona Cancer Center (UACC) will assume the role of the Sponsor. The UACC Data and Safety Monitoring Board (DSMB) will assume overarching responsibility for Data and Safety Monitoring of this trial. Based on the UACC DSMB Charter this is a high risk study. Affiliate sites that participate in this trial will choose, through a reciprocal agreement with UACC, either to:

1) Accept the UACC deferral for local data and safety monitoring to institutions who have a fully approved NCI Data and Safety Monitoring Charter.
2) Allow UACC to conduct remote and on-site monitoring for this trial in accordance with the UACC approved NCI Data and Safety Monitoring Charter for trial and IND oversight.
3) Work with UACC to develop an appropriate DSM oversight plan for institutions who do not have a fully approved NCI Data and Safety Monitoring Charter. This plan must be compliant to the UACC DSMB Charter. The UACC DSMB will act as the oversight regulatory body for data and safety monitoring.

Monitoring reports for all sites will be submitted to the UACC DSMB regardless of local oversight for documentation of active oversight management activities.

11.2 Identification of the entity obligated for routine monitoring duties

Routine monitoring will be provided at the local institution under the provisions determined in 11.1. All serious adverse events (SAEs) will be submitted to the local PI or DSMB as well as the UACC DSMB. All monitoring reports should be completed and submitted within seven days to ensure that the investigation is conducted according to protocol design and regulatory requirements.

11.3 Monitoring progress and data review process

Routine monitoring of subject data will be in accordance with an NCI approved DSM Charter. Frequency and methodology may vary slightly from institution to institution. If a site opts to assume monitoring activities, these institutions will be responsible for developing a site specific DSM plan in accordance with the appropriate institutions NCI approved DSM Charter. Each of these site specific DSM plans will be submitted to the UACC DSMB for review and approval. If UACC is designated the responsibilities to conduct the on-site or remote monitoring, UACC will develop a DSM plan for that site.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues. There will be a (weekly or bi-weekly) teleconference among all site investigators to review all ongoing safety issues. Minutes of these teleconference meetings will be submitted to and reviewed by the UACC DSMB. In addition to review of site specific monitoring, the UACC DSMB will review all monitoring reports and findings every 6 months.

At each site, the Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms, serious adverse event forms, and protocol or patient deviations should be completed via the UACC OnCore CRMdatabase.

11.4 Requirements for site specific DSM plans

Prior to opening the trial for accrual at an affiliate site, the institution identified to be responsible for site monitoring will be develop a site specific DSM plan that is compliant with an NCI approved DSM charter and approved by the UACC DSMB. Elements that will be required to be included within each site specific DSM plan are:

- A process to verify eligibility by the local monitoring team.
- Documented timelines in which serious adverse events are reported to the sponsor.
- Frequency and extent of monitoring activities for this trial at the site

11.5 Process to implement study closure when significant risks or benefits are identified

This study may be prematurely terminated, if in the opinion of the investigator or Aveo, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Aveo by the terminating party.
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Aveo.

11.6 Description of Adverse Event Reporting Procedures

Adverse events will be recorded on the UACC adverse events record form in the UACC OnCore CRM and reviewed by the Principal Investigator. Only AEs meeting one of the following criteria will be entered into the OnCore CRM study database:

- Any AE that is Grade 3 or higher, regardless of relationship to the study drug
- Any intolerable Grade 2 AE
- Any Grade AE resulting in a dose reduction of ficlatuzumab or cetuximab
- Any Grade 2 laboratory or vital sign values that are deemed clinically significant by the treating investigator
- Any Grade AE in the following categories of interest:
    - Rash
    - Diarrhea
    - Edema, peripheral
    - Edema, head, face and neck

- Hypoalbuminemia

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the UACC DSMB and to the appropriate IRB of record and in accordance with the appropriate NCI DSM Charter.

All submitted serious adverse events will be processed by the UACC DSMB Coordinator monthly for trend analysis and then reviewed by the DSMB Chair. All SAE trends will be made available for review at the investigator teleconferences.

11.7 Plan for assuring data accuracy and protocol compliance

Each site will have a site specific DSM plan that describes monitoring activities. This DSM plan is required to be in compliance with an NCI approved DSM Charter. Routine study activity and safety information will be reported to the appropriate DSMB as described in the site DSM plan. These reports should include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events);
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Attachments (AE data reviewed by the site PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

In addition to site specific monitoring, the principal PI will complete a period report with summation of all sites associated data on a every 6 months. Routine study activity and safety information will be reported to the UACC DSMB. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;

- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;

11.7 Identification of the sponsor or funding agency, as applicable

The PI will immediately notify, in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the UACC DSMB, the SRC and all affiliate site study teams.

12. ADVERSE EVENT REPORTING

12.1 Definitions

The following definitions of terms apply to this section:

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the

adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.2 Review of Safety Information: Sponsor Responsibilities [1]

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

12.3 IND safety reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 12.3.1 to 12.3.4 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

12.3.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

12.3.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 12.3.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

12.3.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

12.3.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

12.3.5 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80 of this chapter).

Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

12.3.6 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under Section 12.3 of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

12.3.7 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

12.4 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Arizona Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

13. DATA HANDLING AND RECORD-KEEPING

The Sponsor-Investigator will maintain records in accordance with Good Clinical Practice guidelines.

The Sponsor-Investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

14. ETHICS

14.1 Institutional Review Board (IRB) approval

The Sponsor-Investigator will obtain, from the University of Arizona Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Sponsor-Investigator will promptly notify the University of Arizona IRB of the deviation. The University of Arizona IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Arizona IRB requires, as a condition of approval, substantial

changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Sponsor-Investigator's decision to modify the previously accepted clinical protocol:

- for a Phase 1 clinical study: The Sponsor-Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol may be addressed in the Annual Report to the IND.
- for Phase 2 and 3 clinical studies: The Sponsor-Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 or Phase 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 and 3 clinical protocol changes requiring the submission of a Protocol Amendment include:
    - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
    - Any significant change in the design of the protocol (such as the addition or deletion of a control group).
    - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

14.2 Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; ICH GCP Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the University of Arizona IRB and applicable federal agencies.

14.3 Subject informed consent

The Sponsor-Investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Sponsor-Investigator, or a sub-investigator(s) designated by the Sponsor-Investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Sponsor-Investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The Sponsor-Investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their

decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Sponsor-Investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

15. Protocol Signature Page

Investigator Agreement

STUDY TITLE: A Randomized, Phase II Study of Ficlatuzumab with or without Cetuximab in Patients with Cetuximab-Resistant, Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

By signing below I agree:

1) That my staff and I have read, understand and will adhere to the protocol as written, and that any changes to the protocol will be agreed to and approved by the Principal Investigator and the Institutional Review Board (IRB)

2) To abide by all obligations stated on the FDA Form 1572 and other documents required by regulation;

3) To conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practices (GCP) guidance, the Declaration of Helsinki, US FDA regulations and local IRB and legal requirements;

4) To obtain IRB approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events as required by their guidelines report the status of the study to them;

5) To ensure that each individual enrolled into the trial, or legally authorized representative, has read, understands, and has signed the Informed Consent form;

6) To ensure that I and all persons assisting me with the study are adequately informed and trained about the study and the possible adverse events associated with the study required medication

7) To make prompt reports of SAEs and deaths to the FDA according to the regulations;

8) To prepare and maintain adequate and accurate case histories to document all observations and other data pertinent to the study for each individual enrolled in the clinical trial.

_____ _____

Investigator Signature Date

Investigator Name (Print)

_____

APPENDICES

APPENDIX A: FACT-H&N

http://www.rtog.org/LinkClick.aspx?fileticket=Y09V2CIMEjU%3D&tabid=118

APPENDIX B: PERFORMANCE STATUS CRITERIA

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

APPENDIX C: STUDY CALENDAR

	Pre-study[a]	Study Treatment, 4 week cycles				End of study[m]	Long term follow-up
		Week of Cycle, on Study Treatment					
		1	3	Week 4, cycle 2	Week 4, even cycles starting cycle 4		
Medical History, PE, Vital Signs	x	x	x			x	
Height	x						
Weight	x	x	x			x	
ECOG Performance Status	x	x	x			x	
CBC with Differential [b]	x	x	x			x	
Serum chemistry[c]	x	x	x			x	
Liver function[d]	x	x	x			x	
Pregnancy test[e]	x						
Research biopsy[f]	x						
Tobacco Assessment	x						
Archived diagnostic specimens	x						
Oropharyngeal cases, p16[n]	x						
Tumor measurements, RECIST 1.1 (CT or MRI)[g]	x			x	x	x	x
Cetuximab[h]		x	x				
Ficlatuzumab[h]		x	x				
Concomitant medication review		x	x			x	
Adverse event evaluation[i]		x	x	x	x	x	x
Correlatives: blood[j]	x			x	x	x	
FACT-H&N[k]	x			x			
Survival assessment[l]							x

a. Pre-treatment evaluations will be performed within 4 weeks prior to registration, unless otherwise specified. The exception required within 2 weeks of study treatment is pregnancy test in WOCBP.
b. Complete blood count with differential (CBCD) should include WBC, ANC, PLT, Hb, Hct. CBCDs may be performed on the day of, or the day prior to, study treatment.
c. Serum chemistry should include Na, K, Cl, CO_2, BUN, Cr, Glucose, Calcium, ionized Calcium, and Magnesium. Chemistries may be performed on the day of, or the day prior to, study treatment.
d. Liver function tests should include SGOT (AST), SGPT (ALT), total bilirubin, total protein, albumin, alkaline phosphatase. LFTs may be performed on the day of, or the day prior to, study treatment.

e. A negative pregnancy test is required in women of child-bearing potential within 2 weeks prior to 1st study treatment.
f. A research biopsy at baseline is an eligibility requirement. NOTE: Archived tumor tissue may be substituted if an accessible site cannot be biopsied with acceptable clinical risk and the PI has approved omission of the baseline biopsy. See section 9.2.
g. Tumor measurements will occur in accordance with RECIST 1.1 at baseline and at the end of every even cycle while on treatment. Diagnostic CT scan is the preferred modality. MRI may be substituted per investigator judgment (eg. MRI of the neck with contrast, in cases where patient has an iodinated contrast allergy despite premedication). PET/CT may only be used for tumor measurements if the CT component is of diagnostic quality. PET/CT where CT is performed only for attenuation correction is not of sufficient quality for RECIST measurements. For scheduling convenience, tumor measurements may also occur on day 1 of the following odd cycle, prior to study treatment. If a patient comes off study for a non-progression reason, and has not undergone tumor measurements within the prior 4 weeks, then tumor measurements should be conducted. If a patient comes off study for a non-progression reason, tumor measurements should occur every 8 weeks (+/- 1 week) until documentation of progression. If a patient initiates another line of antineoplastic therapy, tumor measurements for the current study will be discontinued and the patient will be censored for progression at that time point.
h. Cetuximab and ficlatuzumab are administered every other week (day 1, 15 of a 28-day cycle). To accommodate scheduling issues, transportation and holidays, treatment may be administered +/- 3 days. Note that labs required pre-dosing are required on the day of or the day prior to study treatment.
i. AEs will be followed until resolution/ baseline or for 30 days after last dose of ficlatuzumab, whichever is later.
j. Blood for correlative studies will be taken at baseline, and at the end of every even cycle. For convenience, blood may be drawn simultaneous with pre-treatment labs on day 1 of the next odd cycle.
k. FACT-H&N will be performed at baseline and at the end of cycle 2. For scheduling convenience, FACT-H&N may occur on day 1 of the following odd cycle.
l. After a patient demonstrates disease progression, he/she will be followed for survival every 3 months for 2 years.
m. The end of study visit: If not performed in the previous 2 weeks, these tests should be performed (including blood correlatives). Note, however, that tumor measurements should only occur if not performed in the previous 4 weeks. If a patient discontinues treatment without progressive disease, he/she will be followed every 2 months until progression of disease with all of these tests. If such a patient initiates a new line of therapy, he/she will be censored for progression at that time point.
n. For oropharyngeal cases, p16 status must be established, if not previously known, before study treatment begins.

APPENDIX D: TOBACCO USE ASSESSMENT FORM

1. Have you ever smoked a total of 100 cigarettes (approximately 5 packs) or more over your life-time?

   ○ Yes ○ No

2. Have you ever smoked cigarettes regularly, that is, at least one cigarette per day for six months or longer?

   ○ Yes ○ No

3. How old were you when you first started smoking at least one cigarette per day?

   _____ years old

4. Do you currently smoke cigarettes?

   ○ Yes ○ No

   If no, how old were you when you last smoked a cigarette?

   _____ years old

5. Thinking about all the years that you have smoked, how many cigarettes do you (or did you) usually smoke in a day?

   ○ 1-9 cigarettes per day

   ○ 10 to 19 cigarettes per day

   ○ 20 to 29 cigarettes per day

   ○ 30 to 39 cigarettes per day

   ○ 40 to 49 cigarettes per day

6. Have you ever smoked cigars regularly, that is, at least one cigar per day for six months or longer?

   ○ Yes ○ No

7. How old were you when you first started smoking at least one cigar per day?

   _____ years old

8. Do you currently smoke cigars?

   ○ Yes ○ No

   If no, how old were you when you last smoked a cigar?

   _____ years old

9. How many cigars did you usually smoke in a day?

   _____ cigars per day

10. Have you ever smoked a pipe regularly, that is, at least one pipe per day for six months or longer?

    ○ Yes ○ No

11. How old were you when you first started smoking at least one pipe per day?

    _____ years old

12. Do you currently smoke a pipe?

    ○ Yes ○ No

    If no, how old were you when you last smoked a pipe?

    _____ years old

13. Thinking about all the years that you have smoked, how many pipes do you (or did you) usually smoke in a day?

    _____ pipes per day

APPENDIX E: CTCAE V.4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX F: MEDWATCH FORM 3500A

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

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