Study title: An exploratory study to assess the modulation of biomarkers in patients with squamous cell carcinomas of the head and neck randomized to receive preoperative treatment with cetuximab and/or IMC-A12, an anti-insulin-like growth factor-1 receptor monoclonal antibody

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Synopsis

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Study Center(s): The University of Texas M. D. Anderson Cancer Center, Houston, TX.

Concept and Rationale: Cetuximab, a monoclonal antibody directed to the epidermal growth factor receptor (EGFR), has been recently approved for the treatment of locally advanced (concurrent with radiation) or recurrent (as single agent) cisplatin-refractory squamous cell carcinoma of the head and neck (HNSCC). However, in the setting of recurrent disease, response rates to this agent are in the range of 13%. The reason why the majority of patients do not respond to EGFR-targeted drugs is poorly understood. The majority of HNSCC present overexpression and overstimulation of the insulin-like growth factor-1 receptor (IGF-1R) in cancer cells as compared to the adjacent normal mucosa. The IGF-1R shares common intracellular signaling pathways with EGFR (e.g., phosphatidil-inositol 3-kinase/Akt/mammalian target of rapamycin [mTOR]) and might function as an EGFR-independent activator of these pathways, driving cell proliferation and survival. IGF-1R signaling has been shown to mediate resistance to EGFR or HER-2 targeted drugs in breast, colon, prostate, and non-small cell lung cancer cell lines. In HNSCC, IGF-1R blockade leads to an increase in apoptosis *in vitro*, and the combination of IGF-1R and EGFR tyrosine kinase inhibitors results in an enhanced anti-neoplastic effect as compared to either drug alone. This effect has been shown to occur through down-regulation of phospho-Akt, ultimately leading to enhanced apoptosis, in part through inhibition of m-TOR mediated survivin synthesis. Taken together, these results indicate that signaling through the IGF-1R is an important stimulus for cancer growth and might be responsible for the *de novo* and / or acquired resistance of HNSCC to EGFR-targeted drugs. Therefore, therapeutic strategies directed to the inhibition of both IGF-1R and EGFR could potentially exhibit additive or synergistic anti-neoplastic effects.

IMC-A12 is a monoclonal antibody against the IGF-1R produced by ImClone, Inc. Phase I studies of this drug demonstrated a favorable toxicity profile, with hyperglycemia consisting of the most prevalent and clinically significant adverse event (4/21 patients).

As described above, there is a strong biological rationale to clinically develop the antibody in combination with EGFR-targeted drugs (e.g., cetuximab), which are now established treatment options for patients with HNSCC. The characterization of the molecular effects of cetuximab +/- IMC-A12 on HNSCC biomarkers will provide important information, so as to further elucidate the mechanism of resistance to EGFR- targeted drugs in these tumors and to define better treatment strategies in the palliative- or curative-intent setting of this disease.

Although the combination of cetuximab and IMC-A12 has not been extensively studied in humans, the non-overlapping toxicity profile of both drugs and their routes of elimination do not suggest a potential for enhanced side effects of this doublet. Initial

experience with the combination in patients with colorectal cancer revealed no unexpected toxicity and good tolerance. A phase II study is ongoing at M. D. Anderson Cancer Center to investigate the efficacy and safety of this regimen in patients with recurrent cisplatin-refractory HNSCC.

The present study will evaluate the effects of a 2- to 3-week treatment period of cetuximab +/- IMC-A12 on the modulation of biomarkers of patients with HNSCC for whom surgical treatment is planned. This is a window of opportunity study targeting patients that typically do not receive any anti-neoplastic pre-operative treatment as part of their standard care. Cetuximab will be given at the FDA-approved dose (loading dose of 400 mg/m^2, followed by 250 mg/m^2 on week 2, intravenously). IMC-A12 will be given at the recommended dose derived from the phase I study (6 mg/kg/week for 2 weeks, intravenously). A third dose of the study agent(s) might be given in case surgery is delayed. Although the phase I study was terminated before the maximal tolerated dose had been reached, IMC-A12 6 mg/kg/week maintained the serum levels of the drug above the therapeutic threshold (determined from animal xenograft models) for at least 7 days.

Objectives: The objective of this study is to assess modulation of biomarkers resulting from a short, pre-operative course of treatment of cetuximab and/or IMC-A12 in patients with HNSCC. Safety of the combination and its effects on glucose metabolism (with an emphasis on the pathophysiology of hyperglycemia) will also be evaluated. Objective response to, and histopathological changes after the short course of treatment will be determined as well.

Study Design: This is a randomized, biomarker driven study with a pharmacodynamic primary endpoint. Patients with a histologically confirmed diagnosis of HNSCC for whom surgical treatment is planned will be stratified according to the primary site (i.e., mucosal or cutaneous primary site) and need for any anti-hyperglycemic pharmacological treatment, and randomized into three different treatment groups: cetuximab alone, IMC-A12 alone, or cetuximab + IMC-A12. Two weekly doses of the investigational agent(s) will be administered, followed by surgical resection. A third dose of the study agent(s) might be given in case surgery is delayed. Baseline and post-treatment imaging studies will be obtained. Optional biopsies of skeletal muscle and adipose tissue will be performed at the time of surgery. Biomarkers on the surgical specimen and at baseline will be assessed for the evaluation of the primary and secondary pharmacodynamic endpoints. Toxicity, effects on intermediary metabolism, post-treatment molecular changes in the skeletal muscle and adipose tissue, objective response to treatment and post-treatment histopathological changes will also be determined.

Number of Patients: We plan to enroll 60 patients (20 per group). The sample size will provide us 90% power to detect the modulation between two groups with a 5% two-sided type I error rate. The sample size calculation is based on the following assumptions: (1) Wilcoxon rank sum test is applied to compare the modulation between any two of the three groups. (2) The effect size is assumed to be 1.5. Specifically, we assume that the difference between the phospho-AKT means of any two groups is 1.5 standard deviations. Consequently, the probability of phospho-AKT reduction in one group being

greater than in the other group is 0.856. (3) 10% inevaluable rate.

Main Criteria for Inclusion/Exclusion:

Inclusion criteria:

1. The patient has a histologically or cytologically-confirmed diagnosis of squamous cell carcinoma of the head and neck (excluding carcinomas of the nasopharynx types II and III according to the World Health Organization criteria), for whom surgical resection of the tumor is planned as part of the treatment. Patients with skin squamous cell carcinomas of the head and neck region will also be included in this study.
2. There is availability of a baseline, paraffin-embedded, tumor specimen for biomarker evaluation. No anti-neoplastic treatment is allowed between the time from obtaining the baseline tumor specimen and randomization. If a baseline tumor specimen is not available, a biopsy of the tumor will be performed prior to randomization.
3. Prior treatment with biological agents targeted to the epidermal growth factor receptor is allowed, provided the time from last exposure to this treatment was $\geq$ 6 months.
4. The patient has a fasting serum glucose < 130 mg/dL and HbA1C < 7.0%. Patients with a history of diabetes mellitus are allowed to participate, provided that they are on a stable dietary or therapeutic regimen for this condition.
5. The patient has adequate renal function, defined by serum creatinine $\leq$ 1.5 x the institutional upper limit of normal (ULN), or creatinine clearance $\geq$60 mL/min for patients with creatinine levels above the ULN
6. Because the teratogenicity of cetuximab and IMC-A12 is not known, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.
7. The patient is age $\geq$ 18 years.
8. The patient or the patient's legally authorized representative has the ability to understand and the willingness to sign a written informed consent document.
9. ECOG performance status of 0-2

Exclusion criteria

1. Patients receiving any other agent (investigational or not) with potential anti-neoplastic activity within 3 weeks prior to obtaining the baseline tumor specimen for biomarker evaluation.
2. Patients receiving concomitant radiation
3. Prior treatment with an agent targeted at the insulin-like growth factor-1 receptor
4. History of allergic reactions attributed to compounds of chemical and biological composition similar to those of cetuximab or IMC-A12
5. Pregnant patients, or patients who are breast feeding (patients who have a positive pregnancy test within the first 30 days before the first dose of treatment are excluded)
6. Patients with uncontrolled illnesses which, in the opinion of the investigator,

could be aggravated by the administration of the study drug(s)
Intervention and Mode of Delivery: Following randomization, the patients will receive weekly cetuximab, weekly IMC-A12, or weekly cetuximab followed by IMC-A12 at the following doses: Cetuximab: 400 mg/m^2 i.v. on week 1, and 250 mg/m^2 i.v. on week 2 and 3 (if applicable) IMC-A12: 6 mg/kg/week i.v. on weeks 1, 2 and 3 (if applicable)
Duration of Intervention and Evaluation: Patients will receive the investigational treatment(s) for 2 doses pre-operatively, followed by surgical resection. A third dose may be given in case surgery is delayed. Only patients who had surgery within 10 days of the last treatment will be evaluable for the primary endpoint. A 30 day post-operative follow-up visit or telephone call is planned for assessment of toxicity, in addition to the regular follow-up visits in the surgical clinic. Objective response to treatment will be determined by comparing baseline imaging studies to scans obtained between the last dose of treatment and surgery.
Primary Endpoints/Criteria for Evaluation: The primary endpoint of this study consists of the modulation of phospho-Akt in the post-treatment, surgical tumor specimen as compared to the baseline tumor specimen in the different treatment groups. An IHC scoring system will be used to quantify phospho-Akt levels based on staining intensity x extension. Staining intensity will be graded as undetectable (0), weak (1), medium (2), or strong (3). Staining extension will be graded as percentage of positive cells per high power field at x20 magnification. The final score will therefore range from 0 to 300.
Secondary Endpoints: Secondary endpoints will include evaluation of pre- (if applicable) and post-treatment blood-based biomarkers, tumor specimens biomarkers, biomarkers in the skeletal muscle and adipose tissue, toxicity, objective response to treatment and histopathological changes after treatment. Blood-based biomarkers will be evaluated in Dr. Hai Tran's laboratory. Tumor tissue-based biomarkers will be evaluated in the laboratories of Drs. Adel K. El-Naggar, Ho-Young Lee and Jeffrey Meyers. Tumor-tissue based biomarkers will include (but are not restricted to): IGF-1R, phospho-IGF-1R, IGF-2R, IGF-1, IGF-2, IGFBP-3, EGFR, phospho-EGFR, survivin, Ki-67, caspase-3, HIF-1 alpha, CD31, MMP-2, MMP-9, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important related to the use of EGFR and/or IGF-1R-targeted therapy. Skeletal muscle and adipose tissue-based biomarkers will include (but are not restricted to): insulin receptor, phosphorylated insulin receptor (phospho-tyrosine and phospho-serine) and its downstream effectors, insulin receptor substrate-1 (phospho-tyrosine and

phospho-serine), glucose transporter-1, glucose transporter-4, hexokinase, PPAR-alpha, PPAR-gamma, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for anti-IGF-1R therapy-induced toxicity.

Blood-based biomarkers will include (but are not restricted to): free and total IGF-1 and IGF-2, IGFBP-3, insulin, peptide C, free fatty acids, triglycerides, fructosamine, a panel of 59 cytokine and angiogenic factors measured by available luminex multiplex beads kits (Bio-Plex 27-Plex & 23-Plex Kits [Bio-Rad, Hercules, CA] and Human CVD Biomarker Panel 1 kit [Linco Research, Inc., St, Charles, MO]), VEGF, solubleVEGFR-1, soluble VEGFR-2, osteopontin, high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for characterization of cetuximab and/or IMC-A12 activity and/or toxicity.

Toxicity: evaluated by the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0.

Objective response to treatment: evaluated by RECIST guidelines and waterfall plots.

Histopathological changes after treatment: tumor tissue changes (necrosis, dyskeratosis, keratinization, and apoptosis) and host tissue changes (fibrosis, immune response, granulomatous inflammation, dystrophic features, and angiogenesis)

Correlative Studies: Correlative studies are described in the secondary endpoints section. They are assumed to represent pharmacodynamic indicatives of efficacy or toxicity of the investigational drug(s), or might predict response to treatment at the molecular level.

Statistical Methods: Modulation of phospho-Akt (difference in IHC score between the surgical specimen and the baseline biopsy) and other biomarkers will be compared between any two of the three treatment arms with the use of the Wilcoxon rank sum test. Type I error of alpha=0.05 (two-sided test) will be used. The correlation between biomarkers and molecular response or toxicity will be performed in an exploratory fashion.

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1 Introduction

Head and neck cancer is the sixth most common form of cancer,[1] with a worldwide incidence of half a million or more.[2] In 2008, cancers of the oral cavity and pharynx were estimated to account for more than 30,000 new diagnoses in the United States (US); the vast majority of cases are squamous cell carcinoma of the head and neck (HNSCC),[3] which collectively account for 3%-4% of all US cancers.[4]

A variety of therapeutic avenues are available to patients with HNSCC, including surgery, radiotherapy, combined chemo- and radiotherapy, and, more recently, targeted agents. The availability of multimodal and novel approaches has allowed for gradual improvement in the management of HNSCC; 5-year survival of patients with oral cavity and pharyngeal carcinomas has increased from 54% during the period 1974-1976 to 59% in the period 1995-2000.[5] However, a substantial percentage of patients will still develop incurable disease, despite aggressive, multimodality, upfront treatment; in turn, recurrent / metastatic disease responds only poorly to the available treatment options, including biologic agents (i.e., cetuximab). Therefore, understanding of the mechanisms of resistance to the current available treatments is clearly needed, as well as the development of strategies to overcome this resistance, leading to improved systemic management of HNSCC in both the curative and palliative settings.

1.1 Background: cetuximab

Cetuximab (Erbitux®, C-225) is a chimerized monoclonal antibody of the IgG_1 subclass. It was created by chimerization of the murine monoclonal antibody (M225) developed at the University of California, San Diego.[6] Cetuximab was genetically engineered by cloning the heavy and light chains of M225 and adapting them for expression together with constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization process resulted in an antibody with binding affinity to the epidermal growth factor receptor (EGFR) greater than the natural ligand epidermal growth factor (EGF); cetuximab blocks binding of EGF and transforming growth factor alpha (TGF-α) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor.[7]

Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with the ligand.[8]

1.1.1 Cetuximab in HNSCC

A number of clinical studies have demonstrated the utility and safety of cetuximab in the treatment of HNSCC. Trigo, et al,[9] administered cetuximab (at 400 mg/m^2 initial dose and 250 mg/m^2 weekly thereafter) to 103 patients with stage III/IV, platinum-refractory, recurrent or metastatic HNSCC; the objective response rate (ORR) in this population was 13%, with a median time to progression of 2.3 months and median overall survival (OS) of 5.9 months. Adverse events were considered manageable.

On the basis of this and other phase II studies,[9-11] a pair of pivotal phase III studies were initiated, both examining cetuximab in this setting. In the first, 117 patients with metastatic or recurrent HNSCC were randomized to either cetuximab (as described above) plus cisplatin (100 mg/m^2 every 28 days) or cisplatin plus placebo. The addition of cetuximab to cisplatin improved ORR (26% vs. 10%, p=0.03), median PFS (4.2 months vs. 2.7 months, hazard ratio for progression 0.78, 95% CI 0.54-1.12)), and median OS (9.2 months vs. 8.0 months, p=0.21). Although the study did not achieve its statistical endpoint of improving PFS, the increased response rate and trends to improved PFS and OS suggest benefit of combined therapy.[2] Cetuximab therapy was associated with increases in the risk of neutropenia, acneiform rash, and dyspnea, but the treatment was generally well tolerated. The second phase III trial enrolled 424 patients with locoregionally advanced stages III-IV HNSCC; subjects were randomized to cetuximab + radiotherapy (RT) or RT alone. Median PFS rates in the cetuximab/RT group and the RT alone group were 17.1 months and 12.4 months, respectively, with combination therapy yielding an OS of 49 months versus 29.3 months on RT alone. The primary observed adverse event in this trial was acneiform rash, encountered at a rate of 17% in the cetuximab/RT group and only 1% in the control group.[12]

Based on this data, cetuximab is currently Food and Drug Administration (FDA)-approved for use in combination with radiotherapy in the treatment of locally or regionally advanced HNSCC, and as a single agent in the treatment of patients with recurrent or metastatic HNSCC for whom prior platinum-based therapy has failed.
In June 2007, preliminary results from the phase III EXTREME trial, which compared cetuximab in combination with either cisplatin plus 5-fluorouracil (5-FU) or carboplatin plus 5-FU with combinations of cisplatin/5-FU or carboplatin/5-FU alone, were reported in abstract form, indicating a statistically significant survival benefit associated with adding cetuximab to these regimens.[13]

1.2 Background: the insulin-like growth factor axis

The insulin-like growth factor axis is composed of multiple receptors (insulin-like growth factor receptors 1 and 2, insulin receptors A and B, and the orphan insulin-receptor-related receptor), three ligands (insulin-like growth factors-1 and -2, and insulin), and six binding proteins (insulin-like growth factor binding proteins 1-6).[14]
The insulin-like growth factor-1 receptor (IGF-1R) is a transmembrane tyrosine kinase. It binds and is activated by two high affinity binding ligands, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2).[15] Unlike many cell surface receptors, the IGF-1R exists in the cell membrane as a disulfide-linked dimer composed of two extracellular α-chains and two membrane-spanning β-chains in a disulfide-linked β-α-α-β configuration.[16] Both polypeptides are encoded by a single gene product that is proteolytically processed following translation. Because the IGF-1R exists as a preformed dimer, it requires domain rearrangements rather than receptor oligomerization for cell signaling. Upon ligand binding, the IGF-1R undergoes a conformational change, thereby activating its tyrosine kinase activity and enabling autophosphorylation of a series of tyrosine residues within its cytoplasmic domain as well as on one or more adaptor proteins, such as insulin receptor substrate-1 (IRS-1), that initiate signal transduction from the IGF-1R.[16] The principal pathways for transduction of the IGF signal are the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt pathways.[15] The MAPK pathway is primarily responsible for the

mitogenic signal elicited following insulin-like growth factor (IGF) stimulation, but may also play a role in cell survival. IGF-dependent signaling through PI3K elicits survival processes including the phosphorylation and activation of the anti-apoptotic protein Akt and, as a result, has been shown to protect cells from damage-induced apoptosis.
The insulin-like growth factor-2 receptor (IGF-2R) binds IGF-2, among other proteins, but lacks tyrosine kinase activity and does not transduce signals. It seems to serve as a sink for IGF-2 and it has been hypothesized that loss of functional IGF-2R allows for enhanced interaction of IGF-2 with IGF-1R.[17]

The insulin receptor (IR) shares a high degree of homology to IGF-1R. It occurs in two isoforms (IR-A, more common in fetal tissues, and IR-B, more common in adult tissues). IGF-2 binds IR-A with high affinity, whereas IGF-1 does not[18]. Evidence from gene deletion studies suggest that the functions of IR and IGF-1R, although physiologically distinct, are still partially overlapping, with IR capable of stimulating growth and IGF-1R able to regulate a metabolic response.[19,20]

Many cells and tissues have hybrid receptors assembled with one chain of the IGF-1R and one of the IR. IGF-1R/IR-B hybrids have higher affinity for IGF-1, whereas IGF-1R/IR-A hybrids have equal affinity for IGF-2 and insulin.[21]

IGF-1 and IGF-2 are abundant in the serum of adults.[22] IGF-1 is secreted primarily by the liver as a result of stimulation by human growth hormone (GH), but can also be produced locally in tissues including muscle and bone. IGF-2 is not dependent upon GH and is expressed in a variety of tissues.

Six well-characterized insulin-like growth factor binding proteins (IGFBP-1 through -6) associate with IGF ligands in serum to stabilize these growth factors and modulate their ability to associate with IGF-1R. As a result of their association with the IGFBPs, only about 2% of IGF ligands exist in free form in serum.[22]

The IGF-1R is ubiquitously expressed in normal tissues at low levels. Functional aspects of IGF-1R signaling include the regulation of cellular metabolism, cell proliferation, cell size, and cellular differentiation.[15,16,22] Knockout and transgene overexpression studies have identified tissues in which alterations in IGF-1R signaling can influence normal cell growth and development. Specific ablation of IGF-1R results in perinatal death,[23] which is believed to occur from a failure to inflate the lungs due to poor development of the diaphragm and intercostal muscles. IGF-1 or IGF-2 knockout mice are also growth retarded (approximately 60% of normal), but IGF-$1^{-/-}$ mice exhibit a low degree of postnatal viability, whereas IGF-$2^{-/-}$ mice are viable at birth and survive to maturation. This suggests that these ligands play different roles in embryonic development.[24] Overexpression of either IGF-1 or IGF-2 in transgenic mice has demonstrated a growth-promoting effect on most tissues.[25] Notably, ligand overexpression increased the organ weights of the brain, heart, kidney, spleen, thymus, and uterus.

1.2.1 Insulin-like growth factor-1 receptor and human cancer

A large number of preclinical and clinical studies have implicated the IGF-1R and its ligands, IGF-1 and IGF-2, in the development, maintenance, and progression of cancer.[15,22,26] Immunohistochemical analysis of human tumor samples has indicated that a majority of tumor sections across many tissue types stained positive for IGF-1R.[27] In tumor cells, upregulation or overexpression of the receptor, often in concert with overexpression of IGF ligands, leads to potentiation of receptor signaling and, as a result, enhances cell proliferation and survival. A critical role of the IGF-1R in cell proliferation and transformation was demonstrated in experiments of IGF-1R knockout-derived mouse embryo fibroblasts. These primary cells grow at significantly reduced rates in culture medium containing 10% serum and fail to transform in the presence of several oncogenes including SV-40 Large T antigen gene. Upon reintroduction of IGF-1R into these cells by transfection with IGF-1R complementary deoxyribonucleic acid, it was determined that a surface receptor density of <15,000 receptors/cell was insufficient to elicit an IGF-1-dependent mitogenic signal.[16,28] However, an increase in receptor density to 22,000 receptors/cell or greater was sufficient to elicit a ligand-dependent mitogenic

signal and confer anchorage-independent growth in soft agar, suggesting that small increments in IGF-1R density could affect the mitogenic and transformation potential of cells in culture. Importantly, upregulation of expression and not amplification of IGF-1R is considered to be the primary mechanism for receptor activation in cancer development and progression.[26]

IGFs have been shown to be strong mitogens for a variety of solid tumors,[15,24,26,28] including melanoma, osteosarcoma, brain (such as gliomas and medulloblastomas), breast, colon, prostate, ovarian, pancreatic, esophageal, liver, and lung cancers; this effect is mediated through the IGF-1R. IGFs are also mitogens for hematologic malignancies, including multiple myeloma.[26,28] Results from multiple studies suggest that the risk of various cancers, including prostate, colon, and breast cancer, is increased in individuals who possess higher circulating levels of IGF-1.[26] Overexpression of IGF-2 in cell lines and tumors occurs with high frequency and may result from loss of genomic imprinting of the IGF-2 gene.[15,26,28] Loss of heterozygosity of the IGF-2R, a nonsignaling IGF-2 binding receptor that has been proposed to act as a sink for free IGF-2, has also been shown to correlate with increased IGF-2-dependent tumor cell proliferation.[26] In some instances, highly metastatic cancer cells have been shown to display higher expression of IGF-2 and IGF-1R than tumor cells that are less likely to metastasize.[29] IGF signaling through IGF-1R has also been shown to protect tumor cells from the cytotoxic effects of chemotherapy and radiation and may be an important factor in tumor cell drug resistance.[30,31] Additional recent evidence suggests that resistance to the anti-HER2 antibody trastuzumab (Herceptin®) in some forms of breast cancer may be due to activation of IGF-1R signaling.[24,32] IGF-1 and IGF-2 may also contribute to tumor angiogenesis; these factors are capable of inducing VEGF synthesis in tumor cells.[33,34]

1.2.2 Insulin-like growth factor axis and HNSCC

The role of the insulin-like growth factor axis in HNSCChas been evaluated in observational studies in humans and pre-clinical investigations with cell lines.

Wu et al. conducted a nested case-control study within a chemoprevention trial of retinoids for prevention of head and neck second primary tumors.[35] The results indicated that baseline higher levels of IGF-1 and lower and higher levels of IGFBP-3 were associated with an increased risk of second primary tumor development. A second study from the same group demonstrated a joint-effect of mutagen sensitivity (an indication of higher intrinsic carcinogen sensitivity) and circulating IGF-1 (an indication of proliferation potential) in raising the risk of second primary head and neck cancers.[36] These results indicate that, by enhancing cell proliferation, IGF-1 might increase the likelihood of propagation of genetic errors in cells with deficient DNA repair mechanisms, thus contributing for carcinogenesis.

In patients with oral cancer or oral pre-malignant lesions, reduced expression of IGFBP-3 evaluated by immunohistochemistry is associated with shorter disease-specific survival and adverse prognosis, respectively.[37]

In eight HNSCC established cell lines, IGF-1R expression was detected in all samples. IGF-1 stimulated a significant increase in S-phase entry in 5 of these cell lines, associated with an enhancement of Akt and Erk activity. Treatment of one of these cell lines (SCC-9) with IGFBP-3 reduced the IGF-1 stimulated S-phase entry. This effect was more pronounced when cells were treated with both IGFBP-3 and an IGF-1R tyrosine kinase inhibitor (NVP-AEW541), indicating a role for IGF-1R receptor signaling-mediated cell proliferation. Co-targeting the IGF-1R and EGFR (with IGFBP-3 and the EGFR tyrosine kinase inhibitor AG1478) resulted in a synergistic inhibitory effect on S-phase entry in these cells.[38]

Taken together, the clinical and pre-clinical data indicate that IGF-1R might represent a novel and valid target for the treatment of HNSCC.

1.2.3 Targeting the insulin-like growth factor-1 receptor in the treatment of cancer

A variety of strategies have been developed to inhibit the IGF-1R signaling pathway in tumor cells. Approaches utilizing antisense oligonucleotides, inhibitory peptide, soluble

receptor, and dominant-negative receptor mutants that target IGF-1R have been effective at inhibiting the proliferation of tumor cell lines in vitro and in experimental cancer models in vivo.[15,26] Murine antibodies directed against the human IGF-1R have also been shown to inhibit the proliferation in vitro and in vivo of a variety of human tumor cell types.

These studies have established targeting IGF-1R as an attractive anticancer therapeutic strategy and validated an antibody approach as an effective mechanism to inhibit IGF-1R signaling. However, murine antibodies are not ideal human therapeutics, due to their propensity to induce specific immune or allergic reactions. Fully human antibodies offer the greatest potential for success as human therapeutics since they are less likely to elicit an immune response and in general possess a longer half-life in vivo.

1.3 Human anti-insulin-like growth factor-1 receptor, IMC-A12

ImClone Systems has developed a fully human IgG1 monoclonal antibody, IMC-A12, which specifically targets the human IGF-1R.[39,40] IMC-A12 possesses high affinity for IGF-1R and acts as an antagonist of IGF-1 and IGF-2 ligand binding and signaling. IMC-A12 does not bind to or recognize the human insulin receptor. In addition to blockade of ligand binding, mechanistically, this antibody inhibits the IGF-1R pathway by effecting the internalization and degradation of IGF-1R, leading to a reduction in surface receptor density on treated cells. Hybrid receptors containing IGF-1R have also been shown to be downregulated by IMC-A12. IMC-A12 inhibits the proliferation and growth of a variety of human tumor cell lines, both in vitro and in vivo.[39] Based on this antitumor cell activity in tumor cell models, IMC-A12 has been advanced into human clinical studies.

1.3.1 Pre-clinical studies with IMC-A12

The toxicity and pharmacokinetics of intravenously administered IMC-A12 has been evaluated in three studies in cynomolgus monkeys that received one, four, or 13 weekly doses of IMC-A12; In addition, mice have been treated in numerous xenograft studies exploring the activity of IMC-A12. These results are briefly summarized below.

A single-dose pilot PK study was conducted in cynomolgus monkeys. Animals were administered 2 and 10 mg/kg and observed for 42 days. No adverse effects were noted other than vomiting in one monkey after dosing. PK analysis indicated that the area under the serum concentration versus time curve from time zero extrapolated to infinity (AUC_{inf}) and maximum serum concentration (C_{max}) increased in a greater than dose-proportional manner. In the 5-week (4-dose) monkey toxicology study, animals were dosed on days 1, 15, 22, and 29 with 6, 22, or 80 mg/kg. The 2-week gap after the first dose allowed detailed PK characterization. Data from the 5-week study indicate that the main toxicities in cynomolgus monkeys were mild weight loss and thymic atrophy. The thymic atrophy was completely reversible at 6 mg/kg, partially reversible at 22 mg/kg, and not reversible within the 7-week recovery period at 80 mg/kg. There were decreasing trends in erythrocytic parameters, but this effect also occurred in the control group and was likely due to the frequent blood sampling. Only one of 24 evaluable monkeys exhibited an immune response to IMC-A12. Pharmacokinetics were nonlinear and the low dose produced serum levels for 2 days that exceeded the minimum trough level associated with activity (60-158 µg/mL) in murine colorectal (Colo205) and pancreatic (BxPC-3) xenograft models.

Final data from the 13-week monkey toxicology study indicated that the weight loss and thymic atrophy became more pronounced and appeared at lower doses when the same doses were administered over a longer duration. The decreased thymus weight was associated with minimal to marked atrophy, depletion of cortical thymocytes, and loss of a distinct corticomedullary junction. Thymic tissue was replaced by adipose tissue and consisted of a loose fibro-adipose capsular tissue with abundant white and brown fat that often formed variably thick anastomosing fibrovascular trabeculae separating less densely populated cortical lobules. Despite the effects on the thymus, no effects were seen on the distribution of lymphocyte subsets in blood as assessed by flow cytometry. The toxicologic consequences of thymic atrophy are uncertain, but this target organ toxicity does not appear to pose a significant concern for adult patients with advanced cancers. In addition to the effects on thymus, IMC-A12 caused decreasing trends in red blood cells, hematocrit, and hemoglobin in both sexes (statistically significant in high-

dose females) as well as decreased mean platelet volume in all treated female groups. Decreased absolute and relative uterine weights associated with diffuse hypoplasia were noted. Ovarian immaturity consisting of a relative increase in the ovarian cortex with a less developed medulla and decreased follicles in different stages of development was seen in the 22- and 80-mg/kg groups. The ovarian immaturity and corresponding effects on the uterus may have been an adaptive response of the animals to nutritional stress and weight loss, but a direct effect of the test article cannot be ruled out. An increasing trend was observed in relative heart to body weights in all males and mid-dose females. This finding may be a result of the effects of IMC-A12 on body weight, since the heart to brain weight ratios were not statistically significantly different from the control animals and there was no electrocardiographic, heart rate, blood pressure, or histopathologic correlates. No serious toxicity affecting any vital organ has been observed following IMC-A12 administration for up to 13 doses.

Mice studies demonstrated that IMC-A12 cross-reacts with the mouse IGF-1R and binds with kinetics similar to the human IGF-1R (ImClone Systems, Inc., Investigator's Brochure). In a variety of wild-type and immunodeficient mice treated with intraperitoneal IMC-A12, decreased weight gain and weight loss were occasionally seen. The effects on body weight were reversible upon cessation of treatment. A cross-reactivity study in a panel of human and monkey tissues indicated that IMC-A12 cross-reactivity was consistent with the immunohistochemical distribution of IGF-1R in human tissues, as reported in the literature. The same human tissue types that expressed IGF-1R were stained in the cynomolgus monkey tissues. However, in some cases staining was observed in tissues of the cynomolgus monkey (granulosa and luteal cells, cytoplasmic staining of oocytes, thyroid C-cells, and lymphocytes in bronchial-associated lymphoid tissues) that were not observed in the human tissues. No unanticipated cross-reactivities were observed. The similarities in tissue profiles IMC-A12 cross-reactivity suggested that the cynomolgus monkey provides an appropriate animal model for nonclinical toxicity testing of the antibody.

1.3.2 Phase I studies of IMC-A12

As of 30 April 2011, data were available from 14 ImClone/Lilly-sponsored clinical studies. Study design and enrollment information are summarized in Table 6.1; data obtained from these studies in the table below, as well as in the DCSI.

Table 6.1. Summary of ImClone/Lilly-Sponsored Clinical Studies

Study No. Study Title	Design	Treatment Regimen	Patients[a,b] Enrolled/Treated On/Off Tx
CP13-0501 Phase I Study of Weekly Anti-Insulin-Like Growth Factor-I Receptor (IGF-IR) Monoclonal Antibody IMC-A12 in Patients With Advanced Solid Tumors Who No Longer Respond to Standard Therapy or for Whom No Standard Therapy Is Available	Phase 1, single-agent, dose-escalation study (weekly dosing)	Cixutumumab at 3 mg/kg per week (Cohort 1) with planned escalation in subsequent cohorts to 6 mg/kg, 10 mg/kg, 15 mg/kg, 21 mg/kg, and 27 mg/kg per week. See also Section 6.2.1.1.1	24/24 0/24 **Closed to Enrollment** *All patients off treatment*
CP13-0502 Phase I Study of Anti-Insulin-Like Growth Factor-I Receptor (IGF-IR) Monoclonal Antibody IMC-A12 Administered Every Other Week in Patients with Advanced Solid Tumors Who No Longer Respond to Standard Therapy or for Whom No Standard Therapy is Available	Phase 1, single-agent, dose-escalation study (every-2-week dosing)	Cixutumumab at 6 mg/kg every 2 weeks (Cohort 1) with planned escalation in subsequent cohorts to 10 mg/kg, 15 mg/kg, 21mg/kg, and 27 mg/kg every 2 weeks. See also Section 6.2.1.1.1	16/16 0/16 **Closed to Enrollment** *All patients off treatment*
CP13-0813 A Phase 1 Study Evaluating the Safety and Pharmacokinetic Profiles of IMC-A12 Administered Every 2 Weeks or Every 3 Weeks to Japanese Patients with Advanced Solid Tumors	Phase 1, single-agent, dose-escalation study (every-2-week or every-3-week dosing)	Four cohort study, with a cixutumumab dose of 6 mg/kg every 2 weeks in Cohort 1, 10 mg/kg every 2 weeks in Cohort 2, 15 mg/kg every 3 weeks in Cohort 3, and 20 mg/kg every 3 weeks in Cohort 4. After enrollment in Cohorts 1-4 completed, additional patients were to be enrolled in Cohorts 2 and 4 to a total of at least seven completed patients each. See also Section 6.2.1.1.1	20/20 5/15 **Enrolling**
CP13-0603 Phase 2 Single Arm, Open-Label Study of IMC-A12 in Asymptomatic, Chemotherapy-Naïve Patients with Metastatic Androgen-Independent Prostate Cancer	Phase 2, single-arm, single-agent, open-label study	**First 31 Patients:** Cixutumumab 10 mg/kg every 2 weeks **Additional 10-Patient Cohort** Cixutumumab 20 mg/kg every 3 weeks See also Section 6.2.1.1.2	41/41 1/40 **Closed to Enrollment**
CP13-0604 A Phase 2 Randomized, Multicenter Study of IMC-A12	Phase 2, open-label, randomized study (Pts. randomized [2:1] to	**Arm A** • Cixutumumab 10 mg/kg every 2 weeks	93/93 1/92

Table 6.1. Summary of ImClone/Lilly-Sponsored Clinical Studies

Study No. Study Title	Design	Treatment Regimen	Patients[a,b] Enrolled/Treated On/Off Tx
as a Single Agent or in Combination With Antiestrogens in Postmenopausal Women With Hormone Receptor-Positive Advanced or Metastatic Breast Cancer After Progression on Antiestrogen Therapy	Arm A or Arm B)	• Antiestrogen therapy (same dose and schedule to which disease became refractory) **Arm B** • Cixutumumab 10 mg/kg every 2 weeks See also Section 6.2.1.2.1	**Closed to Enrollment**
CP13-0605 A Randomized Phase 2 Clinical Trial of IMC-A12, as a Single Agent or in Combination with Cetuximab, in Patients with Metastatic Colorectal Cancer (mCRC) with Disease Progression on Prior Anti-EGFR Therapy	Phase 2, open-label study (Pts. randomized [1:1] to Arm A or Arm B, or assigned directly to Arm C (patients with KRAS wild-type patients only)); please see also Section 6.2.1.2.2	**Arm A** • Cixutumumab 10 mg/kg every 2 weeks **Arms B & C** • Cixutumumab 10 mg/kg every 2 weeks • Cetuximab 500 mg/m^2 every 2 weeks See also Section 6.2.1.2.2	65/64 0/64 **Closed to Enrollment** *All patients off treatment*
CP13-0706 A Randomized Phase 2 Open-Label Study of IMC-A12, as a Single Agent or in Combination With Cetuximab, in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) and Disease Progression on Prior Platinum-Based Chemotherapy	Phase 2, randomized, open-label study (Pts. randomized [1:1] to Arm A or Arm B)	**Arm A** • Cixutumumab 10 mg/kg every 2 weeks **Arm B** • Cixutumumab 10 mg/kg every 2 weeks • Cetuximab 500 mg/m^2 every 2 weeks See also Section 6.2.1.2.2	97/91 2/89 **Closed to Enrollment**
CP13-0707 A Five-Tier, Phase 2 Open-Label Study of IMC-A12 Administered as a Single Agent Every 2 Weeks in Patients With Previously-Treated, Advanced or Metastatic Soft Tissue and Ewing's Sarcoma/PNET	Phase 2, open-label single-agent, two-stage, five-tier study. Subjects are categorized into five tiers by diagnosis; a two-stage design allows interim analysis of efficacy for each of the study's five tiers.	**All Patients** • Cixutumumab 10 mg/kg every 2 weeks See also Section 6.2.1.1.2	113/111 1/110 **Closed to Enrollment**
CP13-0708 A Randomized Phase 2 Clinical Trial Investigating Irinotecan Plus Cetuximab With or Without Anti-Insulin-Like Growth Factor-I Receptor Monoclonal Antibody (IMC-A12) for the Treatment of Patients With Metastatic K-RAS Wild-Type Carcinoma of the Colon or Rectum That Has Progressed on Oxaliplatin and Bevacizumab Given as First-Line Therapy	Phase 2, open-label, randomized study (Pts randomized [1:1] to Group 1 or Group 2)	**Group 1** • Cetuximab 500 mg/m^2 every 2 weeks • Irinotecan 180 mg/m^2 every 2 weeks **Group 2** • Cetuximab 500 mg/m^2 every 2 weeks • Irinotecan 180 mg/m^2 every 2 weeks • Cixutumumab 10 mg/kg every 2 weeks See also Section 6.2.1.2.3	4/4 0/4 **Closed to Enrollment** *All patients off treatment*

Table 6.1. Summary of ImClone/Lilly-Sponsored Clinical Studies

Study No. Study Title	Design	Treatment Regimen	Patients[a,b] Enrolled/Treated On/Off Tx
CP13-0710 A Phase 2, Multicenter, Two-Tier Study of IMC-A12 in Combination With Depot Octreotide in Patients With Metastatic, Well- or Moderately-Differentiated Carcinoid or Islet Cell Carcinoma	Phase 2, open-label, nonrandomized, two-tier study (Tier 1 – patients with carcinoid tumors; Tier 2 – patients with islet cell tumors)	**All Patients** • Cixutumumab 10 mg/kg every 2 weeks • Same dose and schedule of the patient's last regimen of depot octreotide (usually Sandostatin LAR 30 mg every 28 days). See also Section 6.2.1.2.4	43/43 6/37 **Closed to Enrollment**
CP13-0811 Randomized, Open-Label, Stratified Phase 2 Trial of Gemcitabine, Carboplatin, and Cetuximab With Vs. Without IMC-A12 in Chemotherapy-Naïve Patients With Advanced/Metastatic Non-Small Cell Lung Cancer	Phase 2, randomized, open-label study. Patients are randomized (1:1 basis) to one of two treatment groups Initially, patients were randomized to receive gemcitabine, carboplatin, and cetuximab (GCC) in combination with cixutumumab, or GCC alone. Patients enrolled under Protocol Version 3.0 now receive gemcitabine, cisplatin, and cetuximab (GCiC) in combination with cixutumumab or GCiC alone. See Section 6.2.1.2.5 for additional study details	**GCiC Group** • Gemcitabine 1000 mg/m^2 on Days 1 and 8 of each (3-week) cycle • Cisplatin 75 mg/m^2 on Day 1 of each cycle (replacing carboplatin AUC = 5, Day 1 of each cycle) • Cetuximab 400 mg/m^2 on Day 1 of Cycle 1; 250 mg/m^2 once per week thereafter. **GCiC + Cixutumumab Group** • Gemcitabine 1000 mg/m^2 on Days 1 and 8 of each (3-week) cycle • Cisplatin 75 mg/m^2 on Day 1 of each cycle (replacing carboplatin AUC = 5, Day 1 of each cycle) • Cetuximab 400 mg/m^2 on Day 1 of Cycle 1; 250 mg/m^2 once per week thereafter. • Cixutumumab 6 mg/kg once per week See also Section 6.2.1.2.5	54/54 11/43 **Enrolling**
CP13-0812 A Multicenter, Single-Arm, Phase 2 Study Evaluating IMC-A12 in Combination With Sorafenib as First-Line Systemic Therapy for Patients with Advanced Hepatocellular Carcinoma (HCC)	Phase 2, single-arm, two-cohort, open-label study	**All Patients** • Cixutumumab 10 mg/kg every 3 weeks or 20 mg/kg every 3 weeks • Sorafenib twice daily (total of 800 mg/day) See also Section 6.2.1.2.7	26/26 2/24 **Enrolling**
CP13-0915/ I5A-MC-JAEM An Open-Label, Multicenter, Randomized Phase 2 Study Evaluating the Safety and Efficacy of Cisplatin and Pemetrexed with or without Cixutumumab as First-Line Therapy in Patients with	Phase 2, open-label, randomized study (patients are randomized [1:1] to either Arm A or Arm B)	**Arm A** • Cisplatin 75 mg/m^2 administered every 21 days • Pemetrexed 500 mg/m^2 administered every 21 days **Arm B**	2/2 2/0 **Planned (US)** **Enrolling (Ex-US)**

Table 6.1. Summary of ImClone/Lilly-Sponsored Clinical Studies

Study No. Study Title	Design	Treatment Regimen	Patients[a,b] Enroled/Treated Or/Off Tx
Advanced Nonsquamous Non-Small Cell Lung Carcinoma		• Cisplatin 75 mg/m^2 administered every 21 days • Pemetrexed 500 mg/m^2 administered every 21 days • Cirutumumab 20 mg/kg administered every 21 days After discontinuation of cisplatin treatment (maximum of 4 cycles), maintenance therapy may continue as follows: • Arm A: pemetrexed 500 mg/m^2 administered every 21 days • Arm B: pemetrexed 500 mg/m^2 plus cixutumumab 20 mg/kg administered every 21 days See also Section 6.2.1.28	
CP18-0601 A Phase 2, Multicenter, Randomized Study of IMC-A12 or IMC-1121B Plus Mitoxantrone and Prednisone in Metastatic Androgen-Independent Prostate Cancer (AIPC) Following Disease Progression on Docetaxel-Based Chemotherapy	Phase 2, open-label, randomized study (patients are randomized [1:1] to Arm A or Arm B)	**Arm A** • Cirutumumab 6 mg/kg administered weekly • Mitoxantrone 12 mg/m^2 on Day 1 of every 3-week cycle • Prednisone 5 mg twice daily **Arm B** • Ramucirumab (IMC-1121B) 6 mg/kg administered weekly • Mitoxantrone 12 mg/m^2 on Day 1 of every 3-week cycle • Prednisone 5 mg twice daily See also Section 6.2.1.26	138/132 2/130 **Closed to Enrollment**

[a] As of 30 April 2011
[b] Please see the following sections for more detail on patient disposition.

Cixutumumab is subject to a co-development agreement with the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). Based on this agreement a total of 23 clinical trials are conducted, as of December 2010 and 572 patients have been treated in these trials. For these trials CTEP reports all serious and/or unexpected adverse events to the FDA in accordance with the reporting obligations of 21 CFR 312.32 and forwards all such reports to ImClone/Lilly within 24 to 48 hours. In addition annual reports and other pertinent investigational new drug (IND) data are provided to ImClone/Lilly as they become available. For non-ImClone/Lilly -sponsored trials, further safety information is provided

to ImClone/Lilly at the discretion of CTEP. Since ImClone/Lilly does not own this data, the quantity is beyond the control of ImClone/Lilly and the quality cannot be validated.

Thus information pertaining to serious adverse reactions presented in IB is based on the total number of patients enrolled in ImClone/Lilly-sponsored trials and patients treated in CTEP sponsored trials combined, whereas information from the clinical database (adverse events, adverse reactions) is based on the number of patients enrolled in ImClone/Lilly-sponsored trials only.

1.3.2.1 Hyperglycemia

Hyperglycemia was the most common adverse event in the CP13-0501 trial (4 patients) and the only grade ≥ 3 toxicity (2 patients) observed. Three patients had a better characterization of hyperglycemia. Although known diabetes was an exclusion criteria for participation in the trial, all 3 patients with hyperglycemia had evidence of pre-existing glucose intolerance prior to initiation of the study on retrospective chart review. Increases in blood glucose levels occurred soon after the first dose (in 2 patients), were in the range of 350 mg/dL, and responded to oral hypoglycemic agents (glipizide or glyburide, and/or metformin).[41]

In a phase II trial of another anti-IGF1-R antibody (CP-751,871) given in combination with carboplatin and paclitaxel to 48 patients with lung cancer, grades 3-4 hyperglycemia occurred in 20% of patients (10% grade 3, 10% grade 4). However, there is no published data on further characterization of these hyperglycemic episodes, nor a detailed study of the pathophysiologic processes involved in this adverse event.[42]

Anti-IGF-1R-induced hyperglycemia might occur due to peripheral impaired glucose metabolism or decreased insulin secretion. IGF-1 has hypoglycemic effects *in vivo* in humans, which are thought to be mediated by the IGF-1R in adipose tissue and skeletal muscle and by the IR in the liver (since adults do not express IGF-1R in hepatocytes). In adipose tissue, IGF-1 induces pre-adipocyte differentiation into adipocytes by a mechanism involving PPAR-gamma, whereas in skeletal muscle, IGF-1R activation leads to increased GLUT-4 mediated glucose uptake. In the liver, IGF-1 has been shown to

decrease hepatic glucose production.[43] The role of IGF-1R signaling in insulin production by pancreatic beta-cells has also been recently characterized: both the presence of IR and IGF-1R (and their hybrid receptors) in these cells seems to be necessary for adequate insulin secretion.[44] IGF-1R also seems to play a major role in pancreatic beta-cells survival in the long term.[45]

Due to the complexity of the interactions of the insulin and insulin-like growth factor axis, the pathophysiologic mechanisms of anti-IGF-1R mediated hyperglycemia cannot be readily inferred. *In vivo*, impaired glucose uptake by skeletal muscle and adipose tissue might contribute to hyperglycemia. A compensatory raise in insulin release would be expected, in turn. However, it is unknown whether anti-IGF-1R also decreases insulin secretion due to downregulation of IGF-1R and IGF-1R/IR hybrids in pancreatic beta-cells. Furthermore, the compensatory increase of IGF-1 levels following anti-IGF-1R therapy[41] might counteract some of the hyperglycemic effects by reducing hepatic glucose production. On the other hand, growth hormone also seems to be up-regulated following anti-IGF-1R antibody treatment[42], which by itself produces hyperglycemic effects. Therefore, a better characterization of the hormonal and metabolic changes following anti-IGF-1R antibody administration to humans is needed.

1.4 Rationale

This trial is a "window of opportunity" study to establish the pharmacodynamic activity of a short, pre-operative course of treatment of cetuximab and/or IMC-A12 in patients with HNSCC. Safety of the combination and its effects on glucose metabolism (with an emphasis on the pathophysiology of hyperglycemia) will also be evaluated.

1.4.1 Rationale: cetuximab

Cetuximab has a well-established and documented history of efficacy and safety in the treatment of HNSCC, both in combination with radiotherapy (for patients with locally advanced disease) and as a single-agent in the treatment of patients with recurrent HNSCC that has progressed on prior platinum-based therapy; the product has been approved by the US FDA for use in these settings. A detailed description of the clinical

findings leading to this approval may be found in Section 1.1. These previous studies support the importance of EGFR-inhibition as a key strategy to improve clinical outcomes in patients with HNSCC.

1.4.2 Rationale: IMC-A12

1.4.2.1 Molecular rationale

IMC-A12 is a fully human monoclonal antibody of the IgG_1 subclass that possesses high affinity for IGF-1R receptor and acts as an antagonist of IGF-1 and IGF-2 ligand binding and signaling. IMC-A12 does not bind to or recognize the human insulin receptor.[16] In addition to blockade of ligand binding, mechanistically, this antibody inhibits the IGF-1R pathway by effecting the internalization and degradation of IGF-1R (through a lysosomal pathway), leading to a reduction in surface IGF-1 receptor density on treated or target cells.[15] As a result, IMC-A12 inhibits the proliferation and growth of a variety of human tumor cell lines both in vitro and in vivo. In preclinical study, IMC-A12 inhibited proliferation in the SCC1483 and SCC6 head and neck cancer cell lines (30%-50% of control); minimal (<20% of control) antiproliferative effects were also observed in the SCC1 and SCC22B cell lines.[46] Because IMC-A12 is a fully human IgG_1 antibody, it is also capable of inducing antibody dependent cell-mediated cytotoxicity that may inhibit the growth of tumor cells in vivo.

1.4.2.2 Clinical rationale

IMC-A12 has been studied in the clinical setting in two phase 1 trials, one of which has been presented in abstract form (please refer to section 1.3.2).[41] The antibody has been found to be well tolerated, with possible clinical activity against breast cancer, hepatocellular carcinoma, pheochromocytoma, pancreatic carcinoma and lymphangiomatosis (stable disease $\geq$ 4-6 months).

Three other anti-IGF-1R antibodies (AMG-479, CP-751,871, and R1507) have also been studied in humans so far. AMG-479 has shown activity against neuroendocrine

carcinomas (1 partial response and 1 minor response) and Ewing sarcoma (1 complete response) in a phase I study. The agent was also well tolerated, with thrombocytopenia considered dose limiting in one patient.[47] CP-751,871 has been given in combination with carboplatin and paclitaxel in a randomized phase 2 study of patients with non-small cell lung cancer. Response rates were higher in the experimental arm as compared to the chemotherapy-only arm (46 versus 32%, respectively), with 71% of patients with squamous cell carcinoma presenting an objective response. The drug was also well tolerated (dehydration and hyperglycemia were the most common grades 3-4 adverse events and easily manageable).[42] R1507 has been studied in two phase I studies given in different schedules, and has shown activity in Ewing sarcoma (2 partial responses) and disease stabilization in a number of tumor types (including soft tissue sarcomas, non-colorectal gastrointestinal cancer, colorectal cancer, melanoma, prostate cancer, mesothelioma, cervical cancer, and HNSCC). [48,49]. A trend toward increase glucose in serial oral glucose tolerance tests was detected in both studies of R1507. [48,49]
The safety of the antibodies against the IGF-1R receptor, and the early efficacy signals, especially in patients with squamous cell carcinomas, provide clinical rationale for testing IMC-A12 in the treatment of HNSCC.

1.4.2.3 Pharmacokinetics data and dose rationale

Pharmacokinetics data from the CP13-0501 phase I trial of weekly IMC-A12 indicate that there is a dose-dependant elimination of the drug and non-linear exposure, consistent with a saturable clearance mechanism. After the first administration, minimum serum concentrations of IMC-A12 given at 6 or 10 mg/kg were above 58 mcg/mL 7 days after the initial infusion. At steady-state, the 6 and 10 mg/kg cohorts exhibited a half-life of 209 and 202 hours. The minimum serum concentrations two weeks post- infusion of the drug were 146 and 259 mcg/mL for the 6 and 10 mg/kg doses, respectively.[41]
The target serum concentration for IMC-A12 is hypothesized to be one that maintains IMC-A12 trough concentrations at approximately 58 mcg/mL, which is the threshold level of IMC-A12 that demonstrated inhibition of growth in human tumor xenograft

models in mice. Therefore, the recommended dose for future studies, derived from the CP13-0501 phase I trial, was 6 mg/kg/week, and will be used in this trial as well.

1.4.3 Rationale for combination of cetuximab and IMC-A12 in HNSCC

The IGF-1R interacts with a variety of structurally distinct receptor families, including the HER family. Crosstalk between the IGF-1R and the EGFR was first identified in murine 3T3 fibroblasts, in which functional IFG-1R signaling is essential for EGF-induced mitogenesis.[50] This effect has been linked to prolonged activation of ERK2.[51] In mammary epithelial organ cultures, IGF-1 stimulated cell cycle progression weakly in the absence of EGF and, by upregulating cyclin E, was found to be essential for EGF-induced progression past the G1-S checkpoint.[52] An EGFR tyrosine kinase inhibitor, gefitinib, was found to block IGF-1-induced ERK1 and ERK2 signaling in the mammary epithelial cell line, HB4A. IGF-1 was found to promote tyrosine phosphorylation of both IGF-1R and EGFR in these cells and increased existing levels of a complex containing both receptors.[53] However, in breast cancer cell lines that all express IGF-1R, an EGFR TKI had no effect on MAPK signaling and IGF-1-induced proliferation was unimpeded in MCF-7 cells, which have a high level of IGF-1R expression.[53] These findings suggest that there is no requirement for a co-receptor to transduce signaling in these fully transformed cells, and therefore that cancer cells could circumvent blockade of EGFR-mediated signaling by increased utilization of the IGF-1R pathway; in such a case, targeting both pathways would be a useful strategy.

Preclinical research has demonstrated a synergistic antitumor effect associated with the combination of cetuximab and agents targeting the IGF-1R in BxPC-3 pancreatic carcinoma xenograft line,[54] HCT-8 colorectal cancer xenografts,[55] GEO xenografts,[56] H226 lung cancer lines,[46] and other cancer cell lines, with no observable side effects versus monotherapy. In many of these cell lines, exposure to EGFR or HER2 inhibitors increases levels of IGF-1R and EGFR or HER2 hetero-oligomers in a protein complex, the nature of which remains to be elucidated. It has also been shown that m-TOR mediated survivin synthesis could rescue lung cancer cells from the effects of erlotinib,

an EGFR TKI, suggesting that signaling through PI3K/AKT is involved in mediating resistance to EGFR inhibitors in this model.[57] As reported in other types of cancer cells, inhibition of IGF-1R restored sensitivity to erlotinib in these cells.

M.D. Anderson investigators have specifically studied the effects of the IGF-1R TKI OSI868, alone and in combination with an EGFR TKI (erlotinib), on HNSCC cell lines. Their data indicate that single agent treatment with OSI868 or erlotinib reduced the viable number of SqCC/Y1 cells with lower levels of pIGF-1R, IGF-1R, and EGFR expression compared to other cell lines. Cells with higher levels of pIGF-1R or EGFR expression showed very mild response to single agent treatment; the antiproliferative effect of combined erlotinib and OSI868 was significantly enhanced in such cells. Ultimately, the combination of erlotinib and OSI868 exhibited significantly enhanced growth inhibition compared to single agent treatment under both hypoxic and normoxic conditions (personal communication, Dr. HY Lee, Houston, TX). These observations in preclinical models provide rationale for simultaneous targeting of IGF-1R and EGFR in the clinic.

Currently, a phase II clinical trial of IMC-A12 alone or with cetuximab in patients with platinum-refractory recurrent and/or metastatic HNSCC is accruing at M. D. Anderson Cancer Center. Amendments to this protocol will be submitted should data from that study show any concerns as regards safety of the combination.

1.4.4 Rationale: selection of phospho-Akt modulation as primary endpoint

Three major intracellular signaling pathways downstream the EGFR are believed to mediate its neoplastic effects: Ras/Raf/MAP-kinase, PI3-kinase/Akt/mTOR and STAT3. The Ras/Raf/MAP-kinase pathway has been implicated in cell proliferation, whereas the PI3-kinase/Akt/mTOR pathway has been implicated in cell survival.[58] Similarly, the two major IGF-1R downstream signaling pathways have been shown to involve Ras/Raf/MAP-kinase and PI3-kinase/Akt/mTOR.[14]

Phosphorylated Akt has been demonstrated to be associated with failure of local disease control by radiation therapy in patients with HNSCC.[59] Moreover, patients with oral cancer harboring high levels of expression of phospho-Akt have a statistically significant inferior disease-free survival, independently of stage and nodal status.[60]

In non-small cell lung cancer, high basal levels of phospho-Akt (but not phospho-MAP-kinase) have been identified as a predictive marker of response in patients treated with the EGFR TKIs.[61,62] Interestingly, gefitinib-treated patients whose tumors were EGFR positive (independently of the method of EGFR assessment), had a better response rate, disease control rate, time to progression and survival if they had concomitant higher levels of phospho-Akt, as compared to EGFR positive/phospho-Akt negative tumors. The double positive EGFR/phospho-Akt group also had better outcome when compared to the group negative for EGFR and positive for phopsho-Akt, indicating that aberrant and not EGFR-dependant phospho-Akt activation may lead to gefitinib resistance.[63] Indeed, Lee et. al demonstrated that IGF-1R dependant Akt phosphorylation is associated with EGFR inhibitor's resistance in lung cancer cell lines, and when phospho-Akt is reduced by IGF-1R blocking, sensitivity to EGFR-targeted drugs is restored.[64] This effect is mediated by mTOR and survivin, both of which are downstream of phospho-Akt. Decreased phospho-Akt levels have also been demonstrated following IGF-1R signaling blockade in HNSCC cell lines, and combining EGFR and IGF-1R inhibitors led to an enhanced decrease in the number of viable cells in vitro, as compared to either drug alone (personal communication, Dr. HY Lee, Houston, TX).

Given the fact that phospho-Akt represents a crosstalk point between EGFR and IGF-1R intracellular signaling pathways, is inhibited by drugs targeted to both receptors, and has been implicated in mediating resistance to EGFR-targeted agents in non-small cell lung cancer in vitro, it has been selected as the primary endpoint for this biomarker-driven trial. Nonetheless, there is currently no standard method for assessing molecular response to either cetuximab or IMC-A12 in HNSCC and it is possible that phospho-Akt might not reflect molecular activity of these agents. To overcome this potential problem, modulation of several other biomarkers will be evaluated as secondary endpoints in this study as well.

Of note, biomarker modulation in tumors cells has been observed minutes to days after exposure to the investigational agents in pre-clinical models.[39,57]

1.4.5 Rationale: selection of biomarkers for secondary endpoints

Biomarkers chosen as secondary endpoints will be assessed in the following tissues: tumor, skeletal muscle , adipose tissue, and blood.

In the tumor tissue, markers of activation of the EGFR pathway (i.e. EGFR, phospho-EGFR) will be analyzed, so as to determine the activity of cetuximab +/- IMC-A12 upstream of phospho-Akt. Morgillo et al. have demonstrated that IGF-1R transphosphorylates EGFR in an in vitro models[64]. However, the magnitude of this novel mechanism of EGFR activation in vivo, and the ability of IMC-A12 to inhibit this transactivation and, accordingly, the activation of downstream signaling molecules is unknown. Similarly, markers of IGF-1R activation upstream of phospho-Akt (IGF-1R and phospho-IGF-1R) will also be evaluated. Local synthesis of IGF-1 and IGF-2 by cancer cells in response to IGF-1R and/or EGFR inhibition will also de determined, as well as the synthesis of a carrier protein responsible for regulating the bioavailability of IGF to its receptor (i.e., IGFBP-3)[14], and IGF-2R, a nonsignaling IGF-2 binding receptor that has been proposed to act as a sink for free IGF-2[26]. Modulation of these molecules could account for differences in the efficacy of IMC-A12 in regulating Akt phosphorylation in the tumors studied. Expression of survivin and HIF-1 alpha will be determined as a marker of activity downstream of phospho-Akt[64]. The degree of apoptosis (through caspase-3 staining) and proliferation (through Ki-67 staining) after treatment will also be evaluated, as markers of the effects of the targeted agents at the cellular level. Markers of invasiveness and angiogenesis (i.e., CD31, MMP-2, and MMP-9) will also be assessed. Additionally, the phosphorylation status of multiple kinases will be assessed using antibody arrays, as well as micro-RNA and messenger-RNA expression levels using high-throughput microarray chips, and proteomics (using high throughput methods), in an attempt to identify predictive markers of response.

In the blood, the levels of free (i.e., not bound to IGF binding proteins) and total IGF-1, IGF-2 and IGFBP-3 will be evaluated and will be correlated with both toxicity and levels

of apoptosis and proliferation. IGF-1 levels have been previously demonstrated to rise in response to IGF-1R inhibition, but the significance of this phenomenon is yet unknown and could potentially represent a mechanism of resistance to IGF-1R-targeted therapy[41]. Similarly, modulation of circulating IGF-2 and IGFBP-3, as well as modulation of the levels of a panel of 59 cytokines and angiogenic factors measured by available luminex multiplex beads kits (Bio-Plex 27-Plex & 23-Plex Kits [Bio-Rad, Hercules, CA] and Human CVD Biomarker Panel 1 kit [Linco Research, Inc., St, Charles, MO]), VEGF, soluble VEGFR-1, soluble VEGFR-2, osteopontin, and other proteins measured by high-throughput proteomic analysis could also be related with both efficacy and toxicity of cetuximab and/or IMC-A12.

With respect to intermediary metabolism markers, the levels of glucose, insulin, peptide C (which is secreted in equimolar levels to insulin), triglycerides and free fatty acids (which reflect the levels of lypolysis), and fructosamine (a marker of sustained hyperglycemia) will be determined, so as to evaluate the response of insulin secretion and the degree of insulin resistance following IGF-1R inhibition. The mechanisms of potential insulin resistance will also be evaluated, by determining the levels of the insulin receptor, its substrates (i.e. insulin receptor substrate-1) and downstream effectors, and their phosphorylated forms in adipose and skeletal muscle tissues. These sites represent, together with the liver, the main targets of insulin-mediated metabolic regulation[65]. Of note, phosphorylation of the insulin receptor and the insulin receptor substrate-1 in serine sites has been shown to be associated with impaired insulin action in these cells[66]. Glucose transporter-1 and 4 expression, which is up-regulated by insulin and plays a key role in clearing glucose from the blood[65], will also be determined in skeletal muscle and adipose tissues, as well as the phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis

Since this study represents in essence a biomarker-driven, discovery trial, evaluation of other biomarkers will be performed in the samples obtained, as new knowledge becomes available on the potential mechanisms of action, resistance and toxicity of cetuximab and IMC-A12.

2 Study objectives

2.1 Primary objective

The primary objective of this study is to assess the degree of modulation of phospho-AKT in HNSCC after a short, pre-operative course of treatment with cetuximab and/or IMC-A12.

2.2 Secondary objectives

The secondary objectives of this study are to assess:

1. Safety of cetuximab and/or IMC-A12 (particularly in the pre-operative setting),

2. Effects of IMC-A12 on glucose metabolism (with an emphasis on the pathophysiology of hyperglycemia).

3. Modulation of a panel of biomarkers in HNSCC after treatment with cetuximab and/or IMC-A12 and attempt correlation with clinical outcomes.

4. Objective response to, and histopathological changes after the short course of treatment.

3 Patient selection

3.1 Study population

Patients will be recruited from a population of HNSCC patients treated at the MDACC, for whom surgical resection of the tumor is indicated as part of the standard treatment plan.

It is anticipated that 60 patients (4/month) will be accrued over a period of 15 months.

3.2 Inclusion criteria

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

1. The patient has a histologically or cytologically-confirmed diagnosis of squamous cell carcinoma of the head and neck (excluding carcinomas of the nasopharynx types II and III according to the World Health Organization criteria), for whom surgical resection of the tumor is planned as part of the treatment. Patients with skin squamous cell carcinomas of the head and neck region will also be included in this study.

2. There is availability of a baseline, paraffin-embedded, tumor specimen for biomarker evaluation. No anti-neoplastic treatment is allowed between the time from obtaining the baseline tumor specimen and randomization. If a baseline tumor specimen is not available, a biopsy of the tumor will be performed prior to randomization.

3. Prior treatment with biological agents targeted to the epidermal growth factor receptor is allowed, provided the time from last exposure to this treatment was ≥ 6 months.

4. The patient has a fasting serum glucose < 130 mg/dL and HbA1C ≤ 7.0%. Patients with a history of diabetes mellitus are allowed to participate, provided that they are on a stable dietary or therapeutic regimen for this condition.

5. The patient has adequate renal function, defined by serum creatinine ≤ 1.5 x the institutional upper limit of normal (ULN), or creatinine clearance ≥60 mL/min for patients with creatinine levels above the ULN

6. Because the teratogenicity of cetuximab and IMC-A12 is not known, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

7. The patient is age ≥ 18 years.

8. The patient or the patient's legally authorized representative has the ability to understand and the willingness to sign a written informed consent document.

9. ECOG performance status of 0-2

3.3 Exclusion criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Patients receiving any other agent (investigational or not) with potential anti-neoplastic activity within 3 weeks prior to obtaining the baseline tumor specimen for biomarker evaluation.

2. Patients receiving concomitant radiation

3. Prior treatment with an agent targeted at the insulin-like growth factor-1 receptor

4. History of allergic reactions attributed to compounds of chemical and biological composition similar to those of cetuximab or IMC-A12

5. Pregnant patients, or patients who are breast feeding (patients who have a positive pregnancy test within the first 30 days before the first dose of treatment are excluded)

6. Patients with uncontrolled illnesses which, in the opinion of the investigator, could be aggravated by the administration of the study drug(s)

3.4 Patient enrollment

All patients meeting the eligibility requirements will be considered for enrollment regardless of sex, race, or religion. Discussions regarding protocol enrollment and patient eligibility will begin with any of the investigators named on the protocol. Patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. Each patient or patient's legally acceptable representative will be required to read, agree to, and sign a current Institutional Review Board (IRB)-approved informed consent form prior to being enrolled and/or any study-related procedure is performed. There will be no financial compensation for patients enrolling on this protocol. Baseline evaluations will be performed as described in section 7.1.

3.4.1 Screening

Patients will be referred from the head and neck surgical or medical oncology clinics for consideration for participation in this study. The trial has the full support of the chairs of the departments of Thoracic/Head and Neck Medical Oncology and Head and Neck Surgery. As part of this collaboration, we have added this clinical protocol to an interactive database managed by the department of Head and Neck Surgery. This database will alert research personnel of patients with certain characteristics, such as potentially resectable head and neck cancer, that have been evaluated for the first time in the Head and Neck Surgery clinic. Through this mechanism, these patients may be identified and, after obtaining permission from the primary attending physician, the patients will be contacted to discuss possible participation in this clinical trial. Also, eligible patients will be identified during the weekly Head and Neck planning conference, during which cases are discussed with the multidisciplinary team to define the treatment plan. These patients will also be contacted for possible study participation after obtaining permission from the primary attending physician.

3.5 Methods for assigning patients to treatment groups

Patients will be stratified according to the primary site of the head and neck cancer (i.e., non-skin primary or skin primary), and the current use of any anti-hyperglycemic pharmacologic agent and will be then randomly assigned 1:1:1 to one of the three treatment groups:

Arm A: cetuximab alone

Arm B: IMC-A12 alone

Arm C: cetuximab + IMC-A12

Patients will be assigned to each treatment arm by M. D. Anderson's computer-based CORE system. The randomization code will be generated by the study biostatistician and stored in the CORE database prior to initiation of the trial. The investigators will be

blinded to the code. Since we have two stratification factors, four sets of codes (one for each strata) will be produced. Random permuted block design with a block size of 3 or 6 will be used within each one on of the four strata.

Since there is limited data on the use of IMC-A12 in diabetic patients, as added precautions, if toxicity data on this study and on the randomized phase II conducted at M. D. Anderson in the setting of platin-refractory recurrent HNSCC raise concern about including diabetic patients, additional considerations will be made to include diabetes as an exclusion criteria and, as a result, stratification of patients according to the use of anti-hyperglycemic pharmacologic agent will no longer be performed.

After enrollment, patients will be assigned a unique study identification number and cohort. The study identification number and the patient's initials will be recorded on PDMS and/or CORE databases and correspondence regarding the patient.

4 Investigational plan

4.1 Overall study design and plan

This randomized, open-label study will enroll approximately 60 patients (20 in Arm A, 20 in Arm B, 20 in Arm C) with HNSCC for whom surgical resection of the tumor is planned as part of the standard treatment.

After obtaining informed consent, patients will undergo baseline screening to determine eligibility. These will include clinical laboratory tests (as described in section 6.5), imaging scans (as described in section 6.7), and assessment of the baseline biopsy for confirmation of diagnosis and adequacy for biomarker evaluation. If necessary, a baseline tissue specimen will be obtained (as described in section 6.6). The tentative date of tumor surgical resection (herein defined as day 0) will be recorded. Patients will be randomized to one of the treatment arms and will receive the study drug(s), before surgery, on day -9 (+/- 3 days) and day -2 (+/- 3 days). A third dose of the study treatment(s) may be administered 7 days (+/- 3 days) after the second dose, in case surgery is delayed. Repeated imaging studies will be performed after the last treatment and before surgery.

Surgery will be performed on day 0. However, surgery may be moved up or postponed if judged necessary by the attending physician. In this event, the reason for modifying the surgical date should be recorded. Optional biopsies of skeletal muscle and adipose tissue will be obtained at the time of surgery (as described in section 6.10). A post-operative follow-up visit or telephone call is planned for assessment of toxicity (Fig. 1), in addition to the regular follow-up visits in the surgery clinic. The complete study events table is outlined in section 7.5.

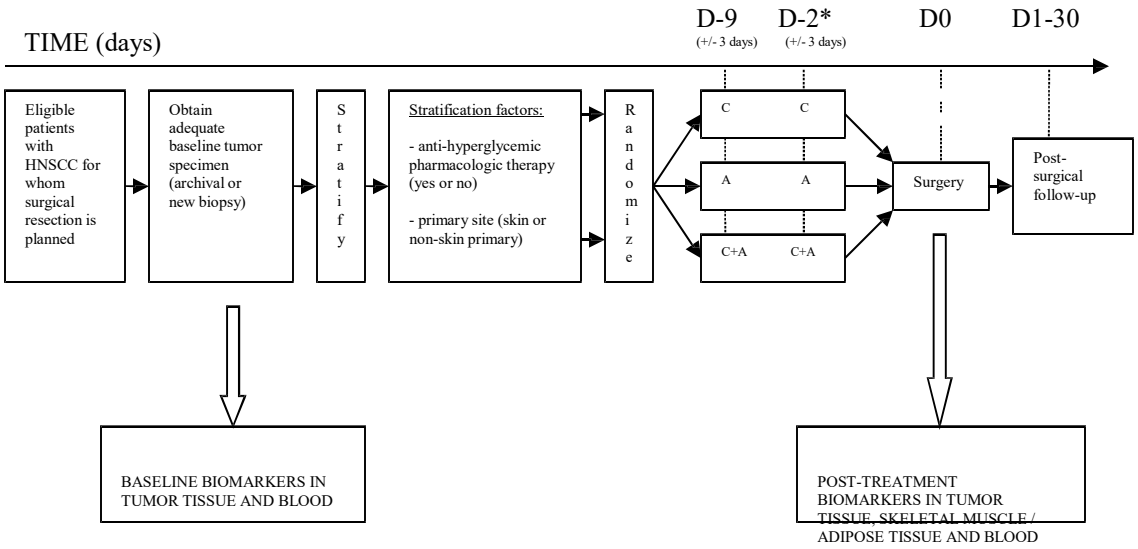

Figure 1: Time-line of events during the study. C = cetuximab; A = IMC-A12.

* A third dose of the study treatment(s) may be administered 7 days (+/- 3 days) after the second dose, in case surgery is delayed.

5 Study treatments

5.1 Treatments safe handling and administration

5.1.1 IMC-A12

Patients will receive IMC-A12 6 mg/kg i.v. via infusion over 1 hour in arms B and C. In arm C, IMC-A12 will be given 1 hour after the end of the cetuximab infusion. Patients do not need to be premedicated prior to administration of IMC-A12. The dose of IMC-A12 will be dependent upon the patient's baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. The dose of IMC-A12 will be aseptically withdrawn from the vial and transferred to a sterile ethylene vinyl acetate i.v. bag or an evacuated USP Type II glass i.v. container. For dose volumes < 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution will be added to the container to make the total volume 250 mL.

The container will be gently inverted to ensure adequate mixing. Different drug product lots should not be mixed in a single infusion. An infusion set with an in-line, 0.22-μm, protein-sparing filter will be required for administration of IMC-A12. Use 0.9% normal saline to flush the line at the end of the infusion. Please see Section 5.4.1 for storage requirements for IMC-A12.

Cixutumumab is an anti-IGF-IR recombinant human monoclonal antibody of the IgG1 class. Cixutumumab drug product (DP) is a sterile, preservative-free solution for infusion of cixutumumab formulated in an aqueous solution at a concentration of 5 mg/mL (250 mg/50 mL) or 10 mg/mL (500 mg/50 mL vial) or 15 mg/mL (750 mg/50 mL). The buffer contains 10mM sodium citrate, 100mM sodium chloride, 100mM glycine, and 0.01% polysorbate 80.

Cixutumumab DP is a clear or slightly opalescent and colorless or pale yellow liquid without visible particles. The pH is 6.5. The osmolality is 310 mmol/kg.

All excipients used for the manufacture of cixutumumab DP are of pharmacopoeial grade. No animal-derived components are used in the manufacture of cixutumumab DP excipients.

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Administration:

a)To administer using pre-filled IV infusion containers:

Calculate the respective dose and remove the corresponding volume of 0.9% normal saline from the prefilled 250 mL container of the correct composition. Aseptically transfer the calculated dose of cixutumumab DP to the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix.

b)To administer using empty IV infusion containers:

Aseptically transfer the calculated dose of cixutumumab DP into an empty I.V. container of the correct composition and add a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to bring the total volume to 250 mL. Gently invert the container to mix.

Only 0.9% normal saline should be used for dilution and post-infusion flushing of infusion line.

The infusion rate must never exceed 25 mg/minute. Different lot numbers of cixutumumab must not be mixed in a single infusion.

The infusion set must be flushed post-infusion with sterile normal saline equal to or exceeding the infusion line hold-up volume to ensure delivery of the calculated dose.

CAUTION: Infusion reactions may occur during or following IMC-A12 administration (see Section 9.2.1 for definitions of grade 3 or 4 infusion reactions).

5.1.2 Cetuximab

Cetuximab is prepared by ImClone Systems under appropriate manufacturing conditions as an injectable solution, in single-use 50-mL vials containing 2 mg/mL of product. Cetuximab requires no dilution. Different cetuximab lot numbers must not be mixed in a single infusion. Cetuximab will be administered as indicated on the package insert. All patients will be premedicated with diphenhydramine hydrochloride, 50 mg oral or i.v. (or a similar agent), prior to the first dose of cetuximab in an effort to prevent an infusion reaction. Premedication is recommended prior to subsequent doses; however, the dose of diphenhydramine hydrochloride (or a similar agent) may be reduced or eliminated at the investigator's discretion.

Patients will receive cetuximab intravenous infusions via infusion pump or gravity drip, through a non-PVC tubing. In arms A and C, the initial dose of cetuximab is 400 mg/m^2 and is administered over 120 minutes. The second and third (if applicable) dose of cetuximab is 250 mg/m^2 administered over 60 minutes, in arms A and C. The dose of cetuximab is dependent upon the patient's baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. The infusion rate must never exceed 10 mg/minute (5 mL/minute). Patients should be observed closely during each infusion of cetuximab. Infusion times may be increased for patients who experience grade 1 through 3 allergic reactions.

Prior to infusion, the appropriate volume of cetuximab will be drawn from the vial with a sterile syringe. Cetuximab will be transferred from the syringe into a sterile evacuated container. Cetuximab will then be filtered through a 0.22-µm protein-sparing or low-protein binding in-line filter. At the end of the infusion, 0.9% normal saline will be used to flush the line.

CAUTION: Infusion reactions, including severe reactions, may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses. The infusion reaction may occur during the infusion or may be delayed until any time after the infusion. A nurse must be present in the immediate treatment area throughout the infusion period. A physician must be in close proximity to the patient treatment area. In the event of an infusion reaction, the patient should be treated as described in Section 9.1.1. Patients should be instructed to report any delayed reactions to the investigator immediately.

5.2 Treatment compliance

Trained medical personnel will administer IMC-A12 and cetuximab. Treatment compliance will be monitored by drug accountability (Section 5.5); IMC-A12 and cetuximab administration will also be recorded in the patient's medical record.

5.3 Packaging and labeling

5.3.1 IMC-A12

Cixutumumab is an anti-IGF-IR recombinant human monoclonal antibody of the IgG1 class. Cixutumumab drug product (DP) is a sterile, preservative-free solution for infusion of cixutumumab formulated in an aqueous solution at a concentration of 5 mg/mL (250 mg/50 mL) or 10 mg/mL (500 mg/50 mL vial) or 15 mg/mL (750 mg/50 mL). The buffer contains 10mM sodium citrate, 100mM sodium chloride, 100mM glycine, and 0.01% polysorbate 80.

Cixutumumab DP is a clear or slightly opalescent and colorless or pale yellow liquid without visible particles. The pH is 6.5. The osmolality is 310 mmol/kg.

All excipients used for the manufacture of cixutumumab DP are of pharmacopoeial grade. No animal-derived components are used in the manufacture of cixutumumab DP excipients.

Cixutumumab DP is compatible with infusion containers composed of polyolefin, polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and evacuated glass (USP Type II or local equivalent). An infusion bag composed of polyolefin, polypropylene, and polyethylene prefilled with 0.9% Sodium Chloride Injection, such as AVIVA, may also be used. The following have been found to be compatible for cixutumumab DP infusion:

- A polyethylene-lined PVC infusion set with a 0.22 μm downstream high-pressure, protein-sparing in-line filter made of polyethersulfone of 10 cm2 surface area
- A PVC infusion set with a 0.2 μm protein-sparing filter made of polyethersulfone of 4.2 cm2 surface area
- A polyethylene-lined PVC infusion set with a 0.2 μm protein-sparing in-line filter made of polyethersulfone of 10 cm2 surface area
- A polyurethane infusion set with a 0.2 μm protein-sparing in-line filter made of polyethersulfone of 10 cm2 surface area
- A polybutadiene tubing with a 0.2μm protein-sparing in-line filter made of polysulfone of 9 cm2 surface area

5.3.2 Cetuximab

Cetuximab for injection is supplied by ImClone Systems in single-use, 50 mL vials containing 2 mg/mL of product.

5.4 Storage and Preparation

5.4.1 IMC-A12

Storage: Storage conditions of the drug product are located in section 4.2.1 of the Investigator's Brochure for Cixutumumab.
PREPARED CIXUTUMUMAB DOSING SOLUTION FOR INFUSION: Chemical and physical in-use stability for the prepared cixutumumab dosing solution has been demonstrated for up to 24 hours below 25°C (77°F). However, it is recommended that the prepared dosing solution be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared cixutumumab dosing solution must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for a duration not to exceed 24 hours. If the prepared solution is held at room temperature (below 25°C (77°F)) it must be used within 4 hours. DO NOT FREEZE AND/OR SHAKE PREPARED CIXUTUMUMAB DOSING SOLUTION FOR INFUSION.

5.4.2 Cetuximab

Cetuximab must be stored under refrigeration at 2˚C to 8˚C (36˚F to 46˚F). DO NOT FREEZE CETUXIMAB. Drug supplies must be kept in a secure, limited-access storage area under the recommended storage conditions. Once cetuximab is removed from the vial, the recommended maximum time at room temperature is 8 hours.

5.5 Accountability

It is the responsibility of the investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational products are inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- the amount received and placed in the storage area
- the amount currently in the storage area
- the label identification number or batch number
- the dates and initials of the person responsible for each investigational product inventory entry/movement
- the amount dispensed to each patient, including unique patient identifiers
- the amount transferred to another area for dispensing or storage
- non-study disposition (eg, lost, wasted, broken)
- the amount returned to ImClone Systems or a designee
- the amount destroyed at the study site, if applicable
- retained samples sent to a third party for bioavailability/bioequivalence, if applicable

5.6 Return of investigational product

Upon completion or termination of the study, all unused and/or partially used investigational products must be returned to ImClone Systems or a designee, if not authorized by ImClone Systems or a designee to be destroyed at the site.

5.7 Investigational product retention at study site

Opened vials may be disposed of at the investigation center as chemotherapy or biohazardous waste.

6 Study procedures

6.1 Informed consent

Written informed consent will be given by each patient prior to undergoing protocol-specific evaluations and prior to receiving treatment.

6.2 Medical history

Medical history will be documented at baseline. Medical history of follow-up visits may only include interim changes from last evaluation.

Concurrent medications will be documented in the patient's medical records but will not be recorded in the case report form (CRF).

6.3 Physical examination

Evaluation by pertinent body system, height (pretreatment only), weight, and body surface area (BSA), as well as ECOG performance status (pretreatment only) should be documented.

6.4 Vital signs

Vital signs will be recorded and should include temperature, pulse rate, and blood pressure.

6.5 Clinical laboratory tests

The blood-based clinical laboratory tests will include:

- Hematology profile: complete blood count with differential and platelet count
- Chemistry profile: fasting glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, sodium, potassium, carbon dioxide, magnesium, and amylase
- Pregnancy test: serum or urine pregnancy test

- Additional tests: 26 mL of blood will be collected and stored for additional studies of interest, including (but not restricted to) fasting insulin, fasting peptide C, triglycerides, fasting free-fatty acids and evaluation of blood-based biomarkers (refer to section 6.9.3). Briefly, blood will be collected using one EDTA (10 mL) tube and two 9-mL CPT tubes for blood cells separation and storage. Samples will be forwarded to the core laboratory to be processed within one hour of collection. Blood will be centrifuged in a standard clinical centrifuge at 2500 RPM at 4 ^{o}C for 10 minutes. Aliquots of 2.0-2.5 mL of serum should then be transferred into 2 (two) cryovials, labeled with the protocol number and the patient's unique study identification number. Cryovials will be stored at -80 ^{o}C. Peripheral blood cells will also be stored at -80 ^{o}C.

6.6 Baseline tissue specimens

Baseline tumor tissue specimens will be obtained before initiation of the investigational treatment and will be used for confirmation of diagnosis and adequacy for evaluation of biomarkers. Archival paraffin-embedded tissue may be used as the baseline specimen, provided no anti-neoplastic therapy has been administered to the patient from the time of the biopsy to study entry, in which case a new biopsy should be obtained. In the event the baseline tissue has been considered inappropriate for biomarker evaluation, a new baseline biopsy should also be obtained. Additional baseline biopsies may be performed if considered necessary by the investigator. For the purpose of this study, these additional baseline tumor biopsies will consist of an outpatient core biopsy, or a punch-biopsy performed under local anesthesia with a minimum of 4-5 mm diameter (which allows for the preparation of at least 30 slides). These specimens should be fixed in 10% formalin, preferably immediately and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. A portion of the specimen obtained may also be embedded in optimal cutting temperature compound immediately after received and not more than 1 (one) hour after excision, frozen, and stored at -80 ^{o}C for future biomarker analysis. All samples

stored at -80 ^{o}C should be placed in appropriate containers, labeled with the protocol number and the patient's unique study identification number.

6.7 Imaging studies

Computerized tomography scans or magnetic resonance imaging of the head and neck will be obtained within 30 days before treatment initiation and will be repeated in the period between the last dose of the study drug(s) and the surgical procedure to assess objective response to treatment.

6.8 Audiometry

Patients randomized to receive treatment with IMC-A12 (i.e. Arm B and Arm C) are required to have an audiometric evaluation within 90 days before starting treatment with the study drug(s). For all patients who received at least 1 dose of IMC-A12, a repeat audiometric evaluation will be performed within 90 days after surgery.

6.9 Surgical procedure and post-treatment tissue specimens

The extent of surgical resection of the tumor should be performed as originally planned by the attending physician and should not take into account response to the investigational treatment. The type of surgery will be recorded in the Operative Note (OP) and/or Procedure Note (PR) of the patient's medical record..

The surgically resected tumor specimen will be evaluated for efficacy endpoints as described in section 6.10. During surgery, an optional specimen of adipose tissue and skeletal muscle tissue from the surgical field will also be collected for post-treatment biomarker evaluation, if the patient has previously given consent and if the collection of these additional tissues is considered feasible (i.e., not associated with unreasonable risks) by the surgeon during the operative procedure. Surgery should not be extended for collection of skeletal muscle and adipose tissue. The recommended procedure for obtaining the tissue specimens is as follows: the primary tumor should be identified on

exam under anesthesia and at least 2 (two) large-cup forceps biopsies obtained prior to ligation of the tumor vessels, to avoid ischemia-induced activation of phosphatases. A portion of the tissue will be fixed in 10% formalin immediately after received and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. Another portion of the tumor specimen (preferably one sample $\geq$ 2 mm^3 or 100 mg) will be embedded in optimal cutting temperature compound immediately after received and not more than 1 (one) hour after excision, frozen and stored at -80 ^oC for future biomarker analysis. Skeletal muscle and adipose tissue (preferably two or more samples $\geq$ 2 mm^3 or 100 mg) may be obtained at the time of surgery (preferably prior to vessel ligation) or separated from the en block resected specimen containing the tumor in the pathology laboratory. A portion will be formalin-fixed (not more than 1 (one) hour after excision) and processed for paraffin-embedding according to the Institutional Standard Operating Procedures, while another portion will be embedded in optimal cutting temperature compound (not more than 1 (one) hour after excision), frozen and stored at -80 ^oC for future biomarker analysis. The remaining specimens resected during surgery (including the tumor, skeletal muscle and adipose tissue) and not used for routine histopathological diagnosis will also be stored for future biomarker studies.

6.10 Pharmacodynamic assessments

6.10.1 Biomarker evaluation in tumor specimens

Both baseline and post-treatment tumor specimens will be evaluated for modulation of biomarkers which could potentially indicate the molecular activity of the investigational treatments, or which could represent predictive markers of activity of such treatments. These will include:

phospho-Akt: modulation of phospho-Akt constitutes the primary endpoint of the trial. Phospho-Akt levels should be determined in paraffin-embedded tissues by immunohistochemistry both at baseline and in the post-treatment surgical specimens. A

scoring system based on staining intensity x extension will be used to quantify the phospho-Akt levels. Staining intensity will be graded as undetectable (0), weak (1), medium (2), or strong (3). Staining extension will be graded as percentage of positive cells per square at x20 magnification. The final score will therefore range from 0 to 300.

additional biomarkers: additional biomarkers in paraffin-embedded tumor specimens at baseline and after treatment will be evaluated depending on the availability of adequate amounts of tissues for such studies. The modulation of these biomarkers by the investigational treatments and their correlation with activity of the drugs will be analyzed in an exploratory fashion. The biomarkers proposed to be studied include (but are not restricted to): IGF-1R, phospho-IGF-1R, IGF-2R, IGF-1, IGF-2, IGFBP-3, EGFR, phospho-EGFR, survivin, Ki-67, caspase-3, HIF-1 alpha, CD31, MMP-2, MMP-9, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important related to the use of EGFR and/or IGF-1R-targeted therapy. Investigators evaluating the endpoints involving pharmacodynamic markers (e.g., phospho-Akt) will be blinded to the clinical data of the patients, as well as treatment received.

6.10.2 Biomarker evaluation in adipose tissue and skeletal muscle

Because the most common and clinically relevant toxicity of IGF-1R inhibitors identified so far is hyperglycemia, the characterization of the molecular effects of IMC-A12 in key organs of intermediary metabolism may help elucidate the pathophysiology of impaired glucose handling in these patients, leading to the development of the most appropriate strategies for treatment of this adverse effect. Therefore, skeletal muscle and adipose tissue specimens obtained during resection of the HNSCC (i.e., after exposure to the investigational treatments) will be evaluated for the following biomarkers related to glucose metabolism (depending on the availability of adequate amounts of tissues for

such studies): insulin receptor, phosphorylated insulin receptor (phospho-tyrosine and phospho-serine) and its downstream effectors, insulin receptor substrate-1 (phospho-tyrosine and phospho-serine), glucose transporter-1, glucose transporter-4, hexokinase, PPAR-alpha, PPAR-gamma, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for anti-IGF-1R therapy-induced toxicity. Correlation of these biomarkers with activity and toxicity of the study drugs will be analyzed in an exploratory fashion.

6.10.3 Blood-based biomarkers

Blood will be obtained at baseline, before the second treatment with the study drug(s), before surgical resection, and within 30 days after surgery, preferably in the morning, after at least 12 hours of fasting. The blood samples will be stored for the evaluation of biomarkers indicative of, or predictive of activity and / or toxicity of the investigational agents. These may include (but are not restricted to): free and total IGF-1 and IGF-2, IGFBP-3, insulin, peptide C, free fatty acids, triglycerides, fructosamine, a panel of 59 cytokine and angiogenic factors measured by available luminex multiplex beads kits (Bio-Plex 27-Plex & 23-Plex Kits [Bio-Rad, Hercules, CA] and Human CVD Biomarker Panel 1 kit [Linco Research, Inc., St, Charles, MOsa]), VEGF, solubleVEGFR-1, soluble VEGFR-2, osteopontin, high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for characterization of cetuximab and/or IMC-A12 activity and/or toxicity. Correlation of these biomarkers with efficacy and toxicity outcomes will be analyzed in an exploratory fashion.

7 Required evaluations

7.1 Pre-treatment evaluations

Pre-treatment evaluation will include screening (to determine patient eligibility), medical history, physical examination, vital signs, clinical laboratory tests, imaging studies as described in sections 6.2, 6.3, 6.4, 6.5 and 6.7, audiometric evaluation (as described in

section 6.8), as well as adverse events assessment (as described in section 8). These should be completed no later than 30 days prior to administration of the first dose of treatment. Additionally, a baseline tumor tissue specimen should be obtained as described in section 6.6.

Results of pre-treatment evaluations must be reviewed by the principal investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to patient randomization. Written informed consent must be obtained prior to any study-specific screening evaluations and prior to receiving treatment.

7.2 Treatment period

Medical history, physical examination, vital signs, clinical laboratory tests, and imaging studies (as described in sections 6.2, 6.3, 6.4, 6.5, and 6.7), as well as adverse events assessment (as described in section 8) will be obtained within 5 days prior to the second treatment.

7.3 End of therapy

Vital signs and clinical laboratory tests (as described in sections 6.4 and 6.5) should be obtained preferably on the day of surgery, or within 2 days before surgery.

7.4 Follow-up

One post-operative evaluation should be completed within 30 days after surgery. At this time, a medical history, physical examinational, vital signs (as described in sections 6.2, 6.3, 6.4), adverse events assessment (as described in section 8), and optional blood-based biomarkers (as described in section 6.5) should be obtained. Alternatively, a telephone call to assess adverse events may substitute for a medical history, physical examination, and vital signs in the event the patient is not evaluated by the investigator or his/her designee within 30 days after surgery. Audiometric evaluation should be obtained within 90 days after surgery in all patients who received at least one dose of IMC-A12 (as described in section 6.8). If toxicities related to the investigational drugs have not been resolved at the time of the post-operative evaluation, regular follow-ups are strongly

enforced with frequency to be determined by the investigator. After the end of therapy, patients should continue to be assessed by their primary physicians for long-term follow-up. Data on progression-free survival, and possible long-term toxicities will be retrospectively obtained through chart reviews. Patients (or their family members) might also be contacted (during clinic visits, by telephone, in writing, or electronic mail) to confirm or provide information on long-term follow-up.

7.5 Study events table

Procedure	Pre-Treatment Evaluations (within 30 days before first dose of treatment)	Treatment Period (within 5 days before second and third dose of treatment)	End of Therapy (day of surgery, preferably, or within 2 days before surgery)	Follow-Up (within 30 days after surgery)
Eligibility Assessments				
Informed Consent	X[1]			
Inclusion/Exclusion Criteria	X			
Medical History and Physical Examination	X			
Pregnancy Test	X			
Safety Assessments				
Medical History and Physical Examination[2]		X		X[8]
Vital Signs (blood pressure, heart rate, temperature)	X	X	X	X[8]
Toxicity Assessments/Adverse Events	X	X		X[2]
Laboratory Tests				
Hematology Profile	X	X	X	
Serum Chemistry Profile	X	X	X	
Imaging studies				
CT Scan or MRI of the H&N	X		X[4]	
Audiometry	X[9]			X[9]
Pharmacodynamic Assessments				
Tumor specimen biomarkers	X[5]		X	
Skeletal muscle/adipose tissue biomarkers[6]			X	
Blood-based biomarkers[3]	X	X[7]	X	X

[1] Informed consent should be obtained prior to registering for trial, undergoing protocol-specific evaluations, or receiving treatment.

[2] Initial medical history should include past or current medical conditions, current medications, date of diagnosis, stage (using the American Joint Committee on Cancer Staging Manual, Sixth Edition or higher), pathological confirmation of HNSCC and tentative date of surgery (if available). Any pre-existing toxicity should be documented and recorded as well. The physical examination will include an evaluation by pertinent body system, height (pretreatment only), weight, and body surface area (BSA), as well as ECOG performance status (pretreatment only) should be documented.

[3] 26 mL of blood (optional) will be collected and stored for additional studies of interest
[4] May be obtained at any time-point between the last dose of the study drug(s) and the surgical procedure. However, preferably, scans will be performed the day before surgery.
[5] Baseline tumor tissue may be obtained more than 30 days prior to treatment initiation.
[6] Collection of skeletal muscle / adipose tissue is optional and will only be obtained if the patient has previously given consent and if the collection of these additional tissues is considered feasible (i.e., not associated with unreasonable risks) by the surgeon during the operative procedure.
[7] Blood-based biomarkers will be obtained only before the second dose of treatment.
[8] A telephone call to assess adverse events may substitute for a medical history, physical examination, and vital signs in the event the patient is not evaluated by the investigator or his/her designee within 30 days after surgery
[9] Patients randomized to receive treatment with IMC-A12 (i.e. Arm B and Arm C) are required to have an audiometric evaluation within 90 days before starting treatment with the study drug(s). For all patients who received at least 1 dose of IMC-A12, a repeat audiometric evaluation will be performed within 90 days after surgery.

8 Adverse events assessment

8.1 Performing adverse events assessments

The assessment of reported adverse events will be performed at least within 5 days before the second and, if applicable, third treatment course, and within 30 days after surgery. Adverse events will be classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

8.2 Importance of adverse event reporting

Timely and complete reporting of safety information assists in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study patients; (2) a greater understanding of the overall safety profile of the investigational products; (3) recognition of dose-related investigational product toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

8.3 Adverse events definition

8.3.1 Adverse event

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory

finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product. Planned medical interventions (e.g., planned surgical resection) will not be considered an adverse event. For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported.

8.3.2 Serious adverse event

Serious Adverse Event Reporting (SAE) Language for M. D. Anderson-sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Deat
h
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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 (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events except events that in the opinion of the treating physician are related to planned surgical procedure occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IND Office.

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

SAE Investigator Communication of with Supporting Companies:
Adverse events classified as "serious" must be recorded on the MDACC Internal Adverse Event Reporting Form and reported to the Sponsor (Safety Project Manager ORE&RM) and to Eli Lilly & Co. to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All SAEs must be reported using the MDACC Internal Adverse Event Reporting Form. To the extent possible, the descriptive terminology and other SAE attributes entered on the MDACC Internal Adverse Event Reporting Form should approximate similar information in the patient's medical record. Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific MDACC Internal Adverse Event Reporting Form. The completed MDACC Internal Adverse Event Reporting Form must be faxed to **Lilly's Global Product Safety Fax Number for all SAEs at 866-644-1697 or 317-453-3402** within 24 hours of the study site personnel's initial notification/awareness of the event. Duly authorized study site personnel may sign completed forms; however, it is recommended that the investigator sign each final SAE report.

8.4 Assessment of causality

The following categories and definitions for assessing the causal relationship of an event to the investigational product(s) are provided as a guide to be used for every event reported in Eli Lilly & Co. clinical trials:

- Definite/Certain: there is a reasonable causal relationship between the investigational product(s) and the AE; the event responds to withdrawal of the

investigational product(s) (de-challenge) and recurs with re-challenge when clinically feasible.

- Probable: there is a reasonable causal relationship between the investigational product(s) and the AE; the event responds to de-challenge; re-challenge is not required.

- Possible: there is reasonable causal relationship between the investigational product(s) and the AE; de-challenge information is lacking or unclear.

- Not Likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.

- Unrelated: there is not a temporal relationship to the investigational product(s) administration (too early, late, or the investigational product was not taken) or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

8.5 Collection of safety information

Pre-existing toxicities will be collected and noted on patient's medical record.

Additionally, collection of AE information will be performed from the time the patient receives the initial infusion of the study drug(s), and must continue throughout the study until 30 days after the last dose, unless specified otherwise in the protocol. This includes pre-existing conditions or symptoms that worsened during the study, or whose relationship to the investigational product changed, but does not include pre-planned hospitalizations or procedures for pre-existing conditions. In addition, the investigator should notify Eli Lilly & Co. of any SAE or outcome that may occur after this time period that he/she believes to be related to IMC-A12 and/or cetuximab. An AE report must contain the following four basic elements: (1) an identifiable patient; (2) a suspect medicinal product; (3) an identifiable reporting source; and (4) an identifiable event or outcome. All identified AEs must be recorded and described in patient's medical record If known, the diagnosis of the underlying illness or disorder should be recorded in

addition to the presenting symptoms. The following information should be captured for all AEs: the date of the onset and resolution; the severity of the event as determined by PI or study collaborator (see definitions in NCI-CTCAE, Version 3.0); the investigator's opinion of the relationship of the event to the investigational drug/s (certainly/definitely, probably, possibly, unlikely, or not related); the treatment required for the AE; information regarding resolution/outcome; and if the AE is serious, a clear identification of the seriousness outcome.

8.6 Reporting Product Complaints

ImClone collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.
The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific product complaint form provided by ImClone for this purpose
- E-mailing the completed product complaint form within 24 hours to ImClone or its designee as listed on the product complaint form

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

8.7 Expectedness

The IMC-A12 Investigator's Brochure will be updated periodically to include new and relevant safety information. Until such time that an AE becomes identified in the Investigator's Brochure, it should be considered unexpected, regardless of whether the AE has been reported in a previous IND Safety Report.

8.8 Clinical significance

8.8.1 Pregnancy

Women of childbearing potential (WOCBP) and fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level ≥35 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (e.g., diaphragm, condoms, spermicides), to prevent pregnancy, are practicing abstinence, or whose partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test at baseline.
Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that the risk of failure is minimized.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. This discussion will be documented on the informed consent form required for study participation.

In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the investigator immediately if they suspect they or their partner

might be pregnant (eg, missed or late menstrual period) at any time during study participation.

If following initiation of study treatment, it is subsequently discovered that a trial patient is pregnant or may have been pregnant at the time of exposure to IMC-A12 and/or cetuximab, including during at least 6 half-lives after product administration, IMC-A12 and cetuximab will be permanently discontinued in an appropriate manner.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to Eli Lilly & Co. follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

8.9 Clinical laboratory adverse event

All laboratory test values captured as part of the study should be recorded on the appropriate source documents.

Abnormal laboratory tests will be considered clinically significant and will be documented in the adverse event record only if any of the following are true:

- Results in patient withdrawal from study participation
- Requires treatment and/or medical intervention (such as a treatment hold or dose reduction)
- Has clinical manifestations which are considered by the investigator as medically important

It is expected that wherever possible, the **clinical, rather than the laboratory term**, will be used by the reporting investigator (e.g., “anemia” is preferable to “a low hemoglobin value”), unless otherwise specified in this protocol.

8.10 Handling of serious adverse events

In addition to the information provided above, adverse events classified as "serious" must be recorded on the MDACC Internal Adverse Event Reporting Form and reported to the Sponsor (Safety Project Manager ORE&RM) and to Eli Lilly & Co. to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All SAEs must be reported using the MDACC Internal Adverse Event Reporting Form. To the extent possible, the descriptive terminology and other SAE attributes entered on the MDACC Internal Adverse Event Reporting Form should approximate similar information in the patient's medical record. Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific MDACC Internal Adverse Event Reporting Form. The completed MDACC Internal Adverse Event Reporting Form must be faxed to Lilly's Global Product Safety Fax Number for all SAEs for Cetuximab and IMC-A12 at 866-644-1697 or 317-453-3402 within 24 hours of the study site personnel's initial notification/awareness of the event. Duly authorized study site personnel may sign completed forms; however, it is recommended that the investigator sign each final SAE report.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries, additional lab and test results, autopsy reports, etc), should be collected subsequently, if not available at the time of the initial report, and immediately sent to Eli Lilly & Co. using the same procedure as the initial SAE report.

For ease of analysis, worldwide standardization, and regulatory reporting, Eli Lilly & Co. will code each reported adverse event or symptom to its corresponding preferred term and body system/organ class in the Medical Dictionary for Regulatory Activities version

adopted for the study. The NCI-CTCAE, Version 3.0, will serve as the reference document for determining/grading the severity or toxicity grade of all adverse events and other symptoms, with the exception of grade 4 infusion reaction (see Section 9.1.1 and 9.2.1). For AEs whose toxicity grading is not contained within the NCI-CTCAE Version 3.0 toxicity criteria, the principal investigator will be responsible for assessing severity based on the intensity of the event as it presented. Severity will be graded as mild (grade 1), moderate (grade 2), severe (grade 3), or very severe (life threatening – grade 4). Eli Lilly & Co. recommends that investigators and study site personnel enter the adverse event term on the patient's medical record and MDACC Internal Adverse Event Reporting Form as accurately as possible, regardless of the NCI-CTCAE Version 3.0 terminology for the event. The NCI-CTCAE Version 3.0 should only be used to assign the intensity/severity of the event as described above.

9 Treatment emergent adverse events

Patients will be closely monitored for treatment-related adverse events, especially infusion reactions. Adverse event monitoring will occur on a continuous basis for the duration that patients are on study therapy. In addition to the planned evaluations during follow-up visits, patients will be instructed to call their physician to report any adverse events between visits.

9.1 Cetuximab

The two significant adverse events occurring most commonly in cetuximab-treated patients are infusion reactions and acneiform rash. Other adverse events associated with cetuximab include asthenia, nausea, vomiting, diarrhea, hypomagnesemia, and fever.

9.1.1 Cetuximab infusion reactions

Infusion reactions may occur during a cetuximab infusion or may be delayed until any time after the infusion. Infusion reactions will be defined according to the NCI-CTCAE, Version 3.0, definition of allergic reaction/hypersensitivity, as follows:

- NCI-CTCAE Grade 1: transient flushing or rash, drug fever <38^{o}C

  - ✓ Treatment: decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.

- NCI-CTCAE Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38^{o}C

  - ✓ Treatment: stop the cetuximab infusion, administer appropriate therapy, and then restart the cetuximab infusion with a decrease in the infusion rate of 50% and monitor closely for any worsening.

- NCI-CTCAE Grade 1 or 2 Infusion Reaction manifesting only as a delayed drug fever (starting after the end of cetuximab infusion)

  - ✓ Treatment: maintain the cetuximab dose and infusion rate and consider administering acetaminophen or cyclooxygenase-2 inhibitors (at the dose and schedule of the investigator's discretion) prior to the subsequent cetuximab infusion, if not otherwise contraindicated in the patient.

- NCI-CTCAE Grade 3 or 4 Infusion Reaction

  - ✓ A grade 3 reaction consists of: symptomatic bronchospasm with or without urticaria, requiring parenteral medication(s); allergy-related edema/angioedema; hypotension.

  - ✓ A grade 4 reaction (anaphylaxis) is a life-threatening event characterized by rapid onset (often within minutes) of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension.

<u>Treatment of a Grade 3 or 4 Infusion Reaction:</u>

- Stop the cetuximab infusion immediately and disconnect infusion tubing from the patient.

- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Following a grade 3 or 4 infusion reaction, the patient is to receive no further cetuximab or IMC-A12 treatment. In the event of a grade 1 or 2 infusion reaction, the cetuximab infusion rate should be permanently reduced by 50%.
If there is any question as to whether an observed reaction is an infusion reaction of grades 1 to 4, the Eli Lilly & Co. Medical Monitor should be contacted immediately to discuss and grade the reaction.

9.1.2 Acneiform rash

The severity of acneiform rash is graded according to the NCI-CTCAE, Version 3.0, definition of rash/desquamation.

Based on emerging data, there appears to be a correlation between acneiform rash and various efficacy outcomes.[67-71] Therefore, if a patient experiences a grade 1 - 3 acneiform rash, cetuximab therapy may continue without dose modification or delay. The investigator could consider concomitant treatment with topical and/or oral antibiotics.

9.1.3 Hematologic toxicities

Hematologic toxicity is not an expected toxicity associated with cetuximab.

9.1.4 Nonhematologic toxicities

Guidelines for cetuximab dose modification related to nonhematologic toxicity may be found in Section 10.1.

9.1.5 Electrolyte monitoring

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTCAE Version 3.0 grades 3 and 4), was increased in patients receiving cetuximab alone or in combination with

chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving cetuximab experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of cetuximab. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known.

9.2 IMC-A12

Adverse events of concern, which may or may not be associated with IMC-A12 therapy, include infusion reactions, hyperglycemia, and peri-operative complications.

9.2.1 IMC-A12 infusion reactions

IMC-A12 infusion reactions will be defined according to the NCI-CTCAE Version 3.0 definition of allergic reaction/hypersensitivity, as detailed below. Consistent with usual medical practice, selected parenteral medications may be utilized for grade 2 allergic/hypersensitivity reaction as detailed below. The Eli Lilly & Co. Medical Monitor should be contacted immediately if questions arise concerning the grade of the reaction.

- Grade 1: transient flushing or rash, drug fever <38°C

✓ Treatment: Slow infusion rate by 50% and monitor patient for worsening of condition.

- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38°C

✓ Treatment: Stop the infusion, administer diphenhydramine hydrochloride 50 mg i.v., acetaminophen 650 mg orally for fever, and oxygen. Resume infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to grade 1; infusion duration should not exceed 2 hours. Monitor patient for worsening condition, and premedicate with diphenhydramine hydrochloride 50 mg i.v. for subsequent infusions.

✓ For a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg i.v.; for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg i.v., acetaminophen 650 mg orally, and dexamethasone 10 mg i.v. (or equivalent).

- Grade 3: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema, hypotension

✓ Treatment: Stop the infusion and disconnect infusion tubing from the patient. Administer diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v. (or equivalent), bronchodilators for bronchospasms, and other medications/treatment as medically indicated. Patients who have a grade 3 infusion reaction will not receive further IMC-A12 or cetuximab treatment, but will continue to be followed on the protocol.

- Grade 4: anaphylaxis (a life-threatening event characterized by the rapid onset [often within minutes] of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension)

✓ Treatment: stop the infusion and disconnect the infusion tubing from the patient. Administer diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v. (or equivalent), and other medications/treatment as medically indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. Patients who have a grade 4 infusion reaction will not receive further IMC-A12 or cetuximab treatment, but will continue to be followed on the protocol.

9.2.2 Hyperglycemia (Diabetes)

For the assessment of hyperglycemia (diabetes), both the NCI-CTCAE Version 3.0 Endocrine (pancreatic endocrine: glucose intolerance / diabetes) and Metabolic / Laboratory (glucose, serum-high / hyperglycemia) terms should be used.
If hyperglycemia/diabetes occurs during treatment with IMC-A12, treatment is dependent upon symptom severity. For grade 1 or 2 hyperglycemia (fasting glucose < 250 mg/dL),

IMC-A12 treatment should continue; oral agents or insulin may be used as clinically indicated.

For grade 3 hyperglycemia (fasting glucose 250-500 mg/dL), IMC-A12 treatment may continue if the patient is asymptomatic and glucose < 300mg/dL; insulin may be initiated. IMC-A12 and cetuximab should be discontinued for grade 3 hyperglycemia if there are symptoms interfering with ADL or if glucose is ≥ 300mg/dL
For grade 4 hyperglycemia (fasting glucose >500 mg/dL), IMC-A12 and cetuximab therapy should be discontinued.

9.2.3 Peri-operative complications

Cetuximab has not been studied pre-operatively in patients with HNSCC. However, preliminary reports of two studies of cetuximab in combination with chemotherapy prior to liver resection in patients with metastatic colorectal cancer did not raise post-operative toxicity concerns.[72,73] IMC-A12 has never been studied in the pre-operative setting. Although there is no pre-clinical data that suggests an increased incidence of peri-operative complications with IMC-A12, patients will be closely monitored for these adverse events. In case a higher than expected incidence of peri-operative complications is seen, considerations will be given to terminating the study, or modifying the protocol, so as to increase the interval between the last dose of the study drug(s) and the surgical procedure.

10 Dose modifications and study completion

10.1 Dose modifications

Dose reductions of either cetuximab or IMC-A12 are not permitted. However, treatment with both drugs may be delayed according to the following guidelines:

- For grade 1, no dose delay is required.

- Patients with any grade 2 adverse event may, at the investigator's discretion, continue to receive study drugs(s) per protocol provided that the event does not pose a serious health risk or is easily treated.

- For a grade 3 clinically significant toxicity (excluding fatigue, skin rash and hyperglycemia/diabetes) not adequately controlled with appropriate supportive care, discontinue treatment. For grade 3 toxicity not considered to be clinically significant by the investigator, withhold dose until toxicity is ≤ grade 1 or has returned to pretreatment baseline, then resume treatment with the protocol-planned dose.

- For a grade 4 possible, probable or definite treatment-related toxicity, discontinue treatment.

The above are considered general guidelines. The investigator should use his or her best judgment when determining treatment interruptions. For example, some grade 2 non-hematologic toxicities may require treatment delays, and some grade 3 or 4 organ toxicities (e.g., hepatic, renal, cardiac, central nervous system) may require a permanent discontinuation from the investigational treatment.

If cetuximab administration is interrupted, no re-bolus dose should be administered at the time of treatment resumption (i.e., subsequent dose of cetuximab will be 250 mg/m^2).
In arm C, if cetuximab treatment needs to be delayed or discontinued due to toxicity, so will treatment with A-12. Similarly, in arm C, if IMC-A12 treatment needs to be delayed or discontinued due to toxicity, so will treatment with cetuximab.

10.2 Removal of patients from therapy

A patient should be withdrawn from therapy if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If the patient does not return for a scheduled visit, every effort should be made to contact the patient; in any circumstance, patient outcome should be documented whenever possible.

A patient should be removed from therapy if:

- Tumor progression occurs, and is confirmed by radiographic progression (not solely based on clinical and/or tumor marker suggestions of progression, unless global deterioration of health status (symptomatic deterioration) requiring discontinuation occurs);

- A grade 4 possible, probable or definite treatment-related toxicity occurs;

- There is toxicity requiring more than 7 days delay of the second treatment dose;

- Other unacceptable toxicity necessitates cessation of treatment;

- The physician feels it is in the best interest of the patient to stop the treatment;

- The patient requests to be removed from the study;

- The patient is lost to follow-up;

- The patient becomes pregnant, or

- The sponsor (MDACC), supporting drug companies (Eli Lilly & Co. and ImClone Systems) or investigator terminates the study.

10.3 Study completion

This study will be considered complete when one or more of the following conditions is met:

- All patients have completed all required study visits.

- All patients have discontinued from the study.

- The IRB, Eli Lilly & Co., or ImClone Systems discontinues the study because of safety considerations.

Long-term efficacy and toxicity data may continue to be collected after the study has been completed.

11 Criteria for tumor response evaluation

11.1 Clinical response

Patients will be evaluated for response according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[74] Additionally, waterfall plots will be used to depict changes in post-treatment tumor size from baseline. There will be no confirmatory scans after a response has been documented, since patients are expected to have the tumor resected shortly after the imaging studies.

11.1.1 Baseline tumor assessment

The baseline tumor burden (unidimensionally-measurable and nonmeasurable disease) will be assessed as closely as possible to the beginning of treatment. The investigator will prospectively identify the lesions to be followed to evaluate the patient's response to therapy (see Section 11.1.4, Definitions of Response).

11.1.2 Method of tumor response assessment

All measurements should be taken and recorded in metric notation, using a ruler or calipers according to RECIST guidelines and documented on patient's medical record. Tumor measurements will be done by PI or collaborator.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at reassessment during treatment. Imaging-based evaluation will be preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. Lesions evaluated clinically will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). CT and MRI will be considered the best currently available and reproducible methods to measure target lesions (as defined in Section 11.1.4).

11.1.3 Definitions

Measurable lesions:
Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 2 cm with conventional techniques or as > 1 cm with spiral CT scan.
A lesion located in a previously irradiated area will be considered measurable only if there has been a documented increase in its size subsequent to irradiation but prior to study entry.

Non-measurable lesions:
All other lesions including small lesions (longest diameter < 2 cm with conventional techniques or < 1 cm with spiral CT scan) and truly non-measurable lesions.
Lesions considered to be truly non-measurable include the following: bone lesions; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions..

11.1.4 Definitions of response

Overall tumor response, as defined in the Criteria for Overall Response Table, will be based on an integration of the evaluation of target, non-target, and new lesions, as described below:

Target lesions:
Target lesions are all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the baseline sum longest diameter (LD). This baseline sum LD will be used

as the reference by which to characterize the objective tumor response. For lesions measurable in two or three dimensions, always report the longest diameter at the time of each assessment.

Complete Response (CR): The disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify progressive disease, taking as reference the smallest sum LD since the treatment started.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesion(s).

Non-target lesions
All lesions (or sites of disease) not characterized as target lesions, both measurable and nonmeasurable, will be identified as non-target lesions and will be recorded at baseline. Measurements will not be required, and these lesions will be followed as “present” or “absent.”

Complete Response (CR): The disappearance of all non-target lesions and the normalization of the tumor marker level (if tumor markers are measured and are initially above the upper limit of normal, those must normalize for a patient to be considered in complete clinical response).

Stable Disease (SD): The persistence of one or more non-target lesions and/or the maintenance of the tumor marker level above normal limits.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Because the clear isolated progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail.

11.1.5 Determination of overall clinical response

Each response parameter (target, non-target, and new lesions) will be reported independently at each radiologic read. The investigator will make a determination of overall response based on the evaluation of target, non-target, and new lesions, as shown in the Criteria for Overall Response Table below.

Criteria for Overall Response Table

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

11.2 Histopathological changes

Changes in histologic parameters in the post-treatment surgical specimen will be evaluated both in the tumor and in the host tissue, using a scoring system of 0, 1, 2, and 3 (0, 0-25%, 26-50%, more than 50% of the tissue showing the feature, respectively), or a binary system (positive or negative).

11.2.1 Tumor tissue

The features to be evaluated in the tumor tissue include: necrosis, dyskeratosis, keratinization, and apoptosis (all using the 0-3 scoring system).

11.2.2 Host tissue

The features to be evaluated in the host tissue include: fibrosis (using the 0-3 scoring system), immune response (binary system, accompanied by a description of the types of inflammatory cells involved), granulomatous inflammation (binary system), dystrophic features (binary system), and angiogenesis (binary system classifying as high or low).

12 Planned statistical method

12.1 Primary endpoint

The primary endpoint of this trial is the modulation of phospho-Akt in the post-treatment, surgical tumor specimen as compared to the baseline tumor specimen in the different treatment groups. Levels of phospho-Akt will be determined by IHC as described in section 6.9.1.

12.2 Secondary endpoints

12.2.1 Tissue- and blood-based biomarkers

Since there is no standard for determination of molecular activity of either cetuximab or IMC-A12, biomarkers in tumor tissue specimens and blood will be evaluated in an exploratory fashion so as to identify changes from baseline and differences between the two study arms and correlate them with other efficacy and toxicity outcomes. Biomarkers involved in intermediary metabolism will be evaluated in the blood and in the post-treatment specimens of skeletal muscle and adipose tissue in an exploratory fashion so as to identify differences between the two study arms and correlate them with toxicity outcomes.

Blood-based biomarkers will be evaluated in Dr. Hai Tran's laboratory. Tumor tissue-based biomarkers will be evaluated in the laboratories of Drs. Adel K. El-Naggar , Ho-Young Lee and Jeffrey Myers.

Tumor-tissue based biomarkers will include (but are not restricted to): IGF-1R, phospho-IGF-1R, IGF-2R, IGF-1, IGF-2, IGFBP-3, EGFR, phospho-EGFR, survivin, Ki-67, caspase-3, HIF-1 alpha, CD31, MMP-2, MMP-9, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important related to the use of EGFR and/or IGF-1R-targeted therapy.

Skeletal muscle and adipose tissue-based biomarkers will include (but are not restricted to): insulin receptor, phosphorylated insulin receptor (phospho-tyrosine and phospho-serine), insulin receptor substrate-1 (phospho-tyrosine and phospho-serine) and its downstream effectors, glucose transporter-1, glucose transporter-4, hexokinase, PPAR-alpha, PPAR-gamma, phosphorylation status of multiple kinases (using antibody arrays), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for anti-IGF-1R therapy-induced toxicity.

Blood-based biomarkers will include (but are not restricted to): free and total IGF-1 and IGF-2, IGFBP-3, insulin, peptide C, free fatty acids, triglycerides, fructosamine, a panel of 59 cytokine and angiogenic factors measured by available luminex multiplex beads kits (Bio-Plex 27-Plex & 23-Plex Kits [Bio-Rad, Hercules, CA] and Human CVD Biomarker Panel 1 kit [Linco Research, Inc., St, Charles, MO]), VEGF, solubleVEGFR-1, soluble VEGFR-2, osteopontin, high-throughput proteomic analysis, genomic analysis and other biomarkers that may emerge to be important for characterization of cetuximab and/or IMC-A12 activity and/or toxicity.

12.2.2 Objective response to treatment

RECIST guidelines and waterfall plots will be used to describe the objective response to treatment in each arm.

12.2.3 Histopathological changes after treatment

Tumor tissue changes: necrosis, dyskeratosis, keratinization, and apoptosis
Host tissue changes: fibrosis, immune response, granulomatous inflammation, dystrophic features, and angiogenesis.

12.2.4 Safety

The toxicity associated with each treatment arm will be observed and characterized; toxicity will be reported by type, frequency, and severity, as determined in section 8.

12.3 Analysis population

Analysis of the primary endpoint will be performed only in the evaluable population.
Toxicity endpoints will be analyzed in the safety population.
Populations:

- Evaluable population: will comprise all randomized patients who receive at least one dose of the study drug(s) in this trial, based on the arm to which they were randomized. Additionally, the last treatment dose should have been administered within 10 days of the surgical resection. The evaluable population will only include patients whose both baseline and post-treatment tumor tissue samples are successfully analyzed for phospho-Akt levels. The reasons for non-evaluability in each arm will be assessed, at the time of the final analysis.

- Safety population: will include all patients who received any dose of an investigational product. The patients will be analyzed for product safety as part of the treatment actually received, regardless of which treatment they were randomized to receive.

For the studies involving assessment of intermediary metabolism parameters, arms B and C may be combined and compared / contrasted to arm A.

12.4 Sample size

The number of patients planned to be enrolled in this study is 60 (20 per arm). The sample size will provide 90% power to detect the modulation between phospho-Akt levels between any two of the three groups with a 5% two-sided type I error rate (applying Bonferroni's correction for multiple comparisons). After the samples have been analyzed for the primary endpoint, additional subjects may be enrolled to the study so that at least 18 evaluable patients (based on the aforementioned definition of evaluable population) are treated in each arm.

The sample size calculation is based on the following assumptions: (1) the standard deviation (SD) of phospho-Akt levels will be 68 arbitrary units in both arms (this value is derived from the standard deviation of phospho-Akt observed in 106 samples of squamous cell carcinomas of the lung using the same IHC assay, personal communication, Dr. I. I. Wistuba, Houston, Texas). (2) The difference in means between arms will be equal to 1.5 SD. Since this trial is the first of its kind, the estimated treatment effect is somewhat arbitrary. However, in 106 squamous cell carcinomas of the lung, the median phospho-Akt score was 200 arbitrary units (personal communication, Dr. I. I. Wistuba, Houston, Texas), which would theoretically allow for detection of a possible 1.5 SD treatment-induced modulation; and (3) the distribution of phospho-Akt levels is approximately normal. Under these assumptions, the probability of a single reduction in one arm being greater than a single reduction in one of the other two arms is 0.856, and consequently the Wilcoxon test has 90% power with 18 evaluable subjects per arm. Allowing for a small fraction of inevaluable patients yields an N of 20 per arm.

12.5 Statistical analysis

Modulation of phospho-Akt (difference in IHC score between the surgical specimen and the baseline biopsy) and other biomarkers will be compared between any two of the three treatment arms with the use of Wilcoxon rank sum test. Further evaluations will adjust

comparisons of follow-up marker values for baseline values, when available, using analysis of covariance. Prior to analysis by parametric methods (such as analysis of covariance), we will assess the data for the need for transformation to normality, transforming where appropriate. We will use repeated measures analysis of variance to analyze endpoints that are observed at multiple time points (e.g. serum glucose). Spearman's rank correlation test will be used to investigate the relationship between different biomarkers and between biomarkers and toxicity. Correlations of categorical variables will be assessed by Fisher's exact test. A type I error rate of 0.05 (two-sided test) will be used for all comparisons.

12.6 Interim analysis

12.6.1 Interim efficacy analysis

No formal interim analysis of efficacy is planned.

12.6.2 Interim safety analysis

The combination of cetuximab and IMC-A12 has not been extensively assessed in human subjects. Because of the different anticancer mechanisms and non-overlapping clinical toxicities of these agents, it is not anticipated that the toxicity of this combination therapy will significantly exceed that observed with IMC-A12 or cetuximab monotherapy or present an undue risk to patients. Additionally, the combination of cetuximab and IMC-A12 was not associated with enhanced toxicity in preclinical in vivo studies. Nonetheless, the potential for unforeseen or additional toxicity exists with any novel combination. Hence, as added precautions, in the event that new safety signals are detected, or the incidence of serious adverse events exceeds that expected of the component drugs within the combination therapy, consideration will be given to protocol modification, termination, or additional safety review at specified time-points before accrual is completed.

A Bayesian toxicity monitoring rule will be applied in each arm separately to ensure patient safety. However, all toxicities across all arms will be examined together as well for identifying the patterns of toxicity to provide further protection of patient safety. It is defined that an acceptable target toxicity level is no more than 30% of the patients experiencing dose limiting toxicity (DLT, defined as grade 3–4 toxicities, except for hypersensitivity reactions and grade 3 skin toxicity and fatigue). If at any given time, the probability that the DLT rate exceeds the 30% target is high (probability > 0.8), consideration will be given to modifying the protocol accordingly. Assuming that the probability of DLT has a vague prior of beta (0.3, 0.7), the posterior distribution of the DLT rate is also a beta. The "stopping boundaries" (i.e., holding for new patients randomization) are 3/6, 4/8, 5/11, 6/14, 7/17, and 8/20 where "a"/"b" indicates "a" patients experiencing a DLT among the first "b" patients. In other words, in each given arm we will hold randomization for new patients if the number of DLTs given the number of patients treated is **greater than or equal to** the boundaries indicated above.

13 Administrative considerations

13.1 Institutional review board approval

The IRB must operate in accordance with 21 Code of Federal Regulations Part 56 and other appropriate governmental regulations. Before study initiation, the investigator must have specified written and dated approval from the IRB/aEC for the protocol, consent form, and patient recruitment materials/process (e.g., advertisements).
The investigator should provide the IRB/aEC with reports, updates, and other information (e.g., safety updates, amendments, and administrative letters) according to regulatory requirements or institution procedures.

13.2 Ethical conduct of the study

This study will be conducted under a United States (US) IND, and the findings of this study are expected to significantly contribute to subsequent regulatory submissions. Therefore, US FDA regulations (21 Code of Federal Regulations [CFR] Part 56 and Part

312), International Conference on Harmonization (ICH) guidelines, Eli Lilly & Co. and ImClone Systems policies require the investigator to be aware of his/her obligations in the conduct of this study.

This study will also be conducted in accordance with the ethical principles included in the "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects" adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; the 48th General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd World Medical Assembly, Edinburgh, Scotland, October 2000 and will conform to any more current revisions to these principles.

13.3 Compliance with the protocol and protocol revisions

The investigator must comply with all requirements of the protocol. When a situation occurs that requires a temporary departure from the protocol, the investigator will describe the departure from the protocol and the circumstances requiring it on the patient's medical record and will notify the IRB/aEC as appropriate.
Patients may not be enrolled in an amended protocol until that amendment has been IRB/aEC approved.

13.4 Patient information and consent

Written informed consent will be given by each patient before entering the study, in accordance with US Title 21 CFR Parts 50.20 through 50.27 and the current edition of the Declaration of Helsinki, as well as Good Clinical Practices (GCPs).
Investigators must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

13.4.1 Informed consent procedures

Preparation of the consent form is the responsibility of the investigator and must include all elements required by the ICH, GCP, and applicable regulatory requirements and must adhere to GCP and the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator must have the IRB/aEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients.

The investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be nontechnical and easily understood. The investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent form and any other written information provided to study patients prior to the patient's participation in the trial.

13.4.2 Update of the informed consent

The informed consent and any other information provided to patients or the patient's legally acceptable representative should be revised whenever important new information becomes available that is relevant to the patient's consent and should receive IRB/aEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator, should fully inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

If a protocol amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB/aEC for review and approval, (2) the revised consent form must be used to obtain consent from patients currently enrolled in the study, and (3) the new consent form must be used to obtain consent from new patients prior to enrollment.

13.5 Study monitoring

Representatives of Eli Lilly & Co and ImClone Systems must be allowed to visit all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

13.6 Case report forms and study records

An investigator will be required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with IMC-A12 and/or cetuximab. All data reported on the PDMS and/or CORE databases must be derived from source documents and be consistent with the source documents, or the discrepancies must be explained.

The confidentiality of records and information that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

The investigator will maintain, in confidence, all information furnished by Eli Lilly & Co. and/or ImClone Systems and all data generated in the study, except as provided or required by law, and will divulge such information to the IRB/aEC with the understanding that confidentiality will be maintained by the committee.

13.7 Access to source documentation

The study may be evaluated by auditors designated by Eli Lilly & Co. and/or ImClone Systems and by government inspectors who must be allowed access to source documents, and all other study files. Eli Lilly & Co. and/or ImClone Systems audit reports will be kept confidential.

13.8 Retention of data

The investigator must retain cetuximab and IMC-A12 disposition records, copies of PDMS and/or CORE databases (or electronic files), and source documents (including scans) for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer. Eli Lilly & Co. and ImClone Systems will notify the investigator when the trial records are no longer needed. If the investigator withdraws from the study (e.g., relocation, retirement), all records will be transferred to a designee (e.g., another investigator, IRB) who will assume responsibility for the study and its' conduct.

13.9 Publication and disclosure policy

The results of the study may be published as an original article in an appropriate medical journal and/or presented in a medical meeting. The choice of the journal will be made by the co-authors.

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