BATTLE-FL: A Biomarker-Integrated Study in Patients with Advanced Non-Small Cell Lung Cancer Treated in the Front-Line (FL) Setting

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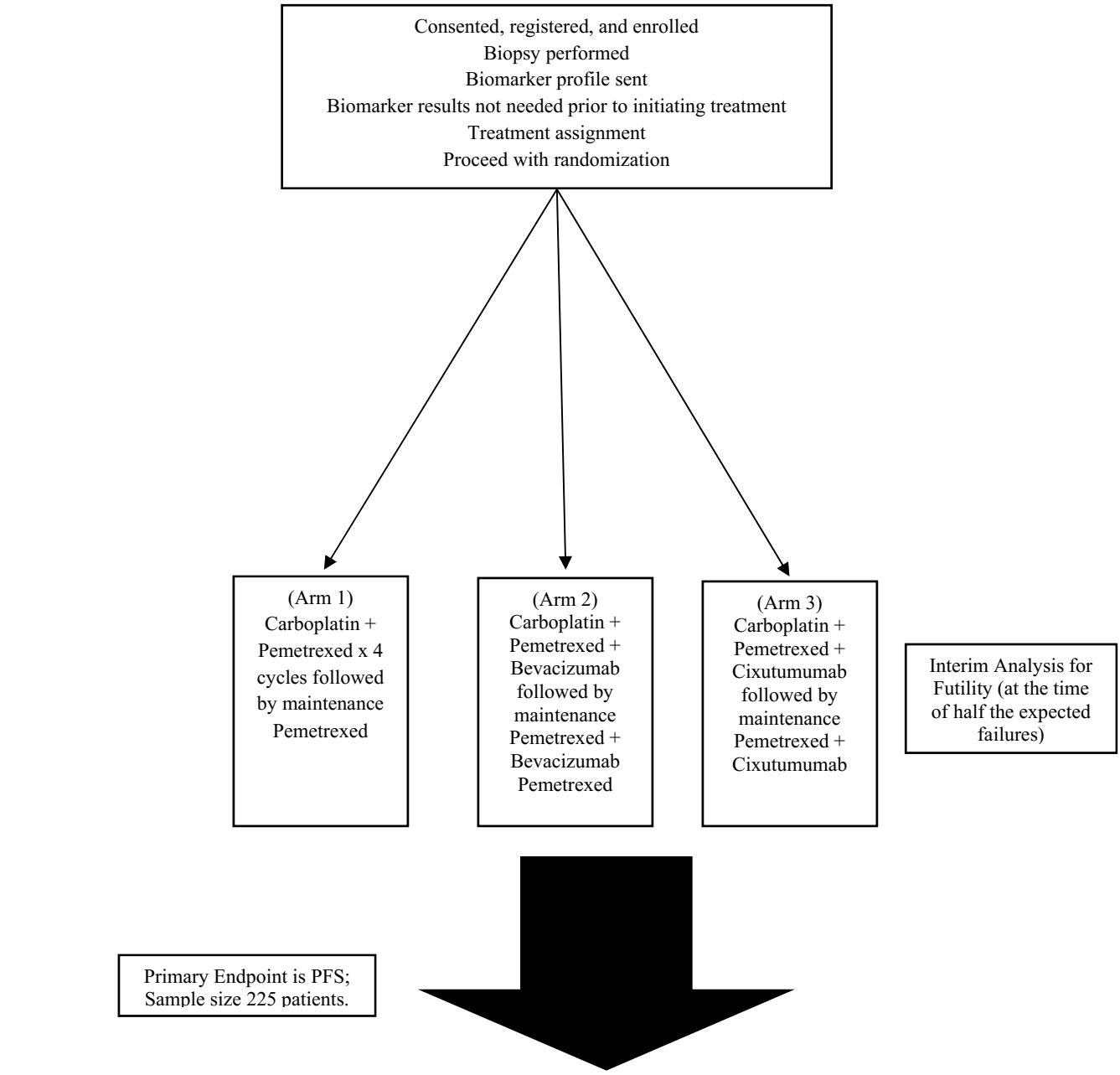
Study Schema



Restaging after 2 cycles of therapy
Optional biopsy of tumor for biomarkers after 2 cycles
Continue on study if stable or response.
Up to 4 cycles of Pemetrexed/Carboplatin +/- biologic, then biologic treatment with Pemetrexed
If progression, then off-study

The trials with their respective drugs will be compared to one another. They will be analyzed individually based on their biomarker profiles and the likelihood of enhancing PFS based on the biomarkers.

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1 OBJECTIVES

1.1 Primary Objectives

The primary objective of this study will be to:

- Determine the progression-free survival in patients with NSCLC who are being treated with front-line therapy for metastatic disease

1.2 Secondary Objectives

The secondary objectives of this study will be to:

- Determine the best individual treatment based on the biomarker profile of the patients cancer
- Determine the overall response rate
- Determine the overall survival
- Determine the time to disease progression
- Assess the safety/toxicity of the combinations
- Assess biomarker modulation in the tumor tissue from the treatment
- Assess biomarker modulation in the serum/blood from the treatment

1.3 Study Design

This is a single-center, Phase II open-label study in patients treated as front-line NSCLC. The study will consist of three arms, including two arms with combination targeted therapies. Patients will be administered carboplatin + pemetrexed (Arm 1), carboplatin + pemetrexed in combination with VEGF monoclonal antibody (Bevacizumab) (Arm 2), or carboplatin + pemetrexed in combination with a IGF-1R monoclonal antibody (Cixutumumab) (Arm 3).

The study is designed to develop individualized targeted therapy based on the identification and validation of specific molecular pathways of NSCLC. To address these new targeted therapeutic approaches, we propose to implement a translational lung cancer research program entitled, BATTLE-FL: Biomarker-integrated Approaches of Targeted Therapy of Lung Cancer Elimination-Front-Line, and provide a strong rationale-based targeted treatment strategy. The study is applying the same principles as our prior BATTLE-1 Program. The BATTLE-1 Program required that all eligible patients with advanced NSCLC undergo a core

biopsy of their tumors and applied biomarkers in the selection of individualized targeted therapy.

2 BACKGROUND AND RATIONALE

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States and worldwide. An estimated 215,020 new cases of lung cancer were diagnosed in the US in the year 2008 leading to approximately 161,840 deaths in the United States alone (Jemal 2008). Non-small cell lung cancer (NSCLC) accounts for almost 80% of newly diagnosed cases. Lung cancer deaths in the US surpass those resulting from breast, prostate, and colon cancers, and its incidence continues to rise. Only 16% of these patients in whom lung cancer develops live 5 years or more after the diagnosis is made. Despite substantial effort in developing methods for early diagnosis and treatment of lung cancer in the last two decades, currently at the time of diagnosis, more than 80% of patients present with locally advanced unresectable or metastatic disease and their chance to be cured by current oncology practice is low.

At presentation, the median survival for patients with advanced disease defined as inoperable Stage 3 or 4 non-small-cell lung cancer (NSCLC) is 8 to 10 months, with a one-year survival of 35 to 45% (Reck 2004). Most patients with inoperable NSCLC are candidates for palliative chemotherapy consisting of standard induction therapy with 4 to 6 cycles of a platinum-based chemotherapy doublet, per American Society of Clinical Oncology ASCO (Pfister 2004) and European Society for Medical Oncology guidelines (ESMO) (D Addario 2008). Recent reviews and meta-analyses of randomized trials in advanced NSCLC have suggested that 4 cycles is the optimal duration of platinum-based first-line treatment, regardless of response to initial therapy; platinum-based chemotherapy beyond 4 cycles was found to improve progression-free survival (PFS) but not overall survival (OS), and led to increased toxicity (Larsen 1995; Smith 2001; Socinski 2002; Lustberg 2007; Park 2007; Socinski 2007; Soon 2007).

In 2006, bevacizumab received FDA approval as an initial therapy for advanced NSCLC on the basis of Study ECOG 4599 (Sandler et al. 2006). Approval was based on improvement in OS for bevacizumab when combined with carboplatin and paclitaxel, as compared with the platinum doublet alone. This triplet regimen is now recommended by the National

Comprehensive Cancer Network (NCCN 2008) for patients with advanced, nonsquamous NSCLC and has become one of the standards of care in that setting.

Maintenance therapy for advanced NSCLC has also been explored in a large number of studies, although most were powered only for assessment of the entire regimen, and not just the maintenance phase of therapy (Prior et al. 1999; Socinski et al. 2002; Belani et al. 2008; Herbst et al. 2004; Herbst et al. 2005; Brodowicz et al. 2006; Davies et al. 2006; Sandler et al. 2006; Manegold et al. 2007). Despite methodological problems, studies with docetaxel (Sekine et al. 2006; Fidias et al. 2009), paclitaxel (Belani et al. 2008), gemcitabine (Brodowicz et al. 2006), and bevacizumab (Sandler et al. 2006) have suggested possible benefit of single-agent treatment beyond the recommended 4 to 6 cycles of platinum-based chemotherapy.

2.2 Molecularly Targeted Therapy in NCSLC

Advances in molecular biology, particularly the completion of the Human Genome Project, have led to substantial knowledge about the molecular basis of lung cancer, which provides a unique opportunity to develop novel strategies to target key pathways crucial for lung cancer development. This has led to emerging targeted therapy to attack lung cancer. However, to answer the question of how to develop smarter clinical trials using informative molecular biomarkers, these biomarkers must first be identified and then targeted with specific molecular inhibitors. Several large, randomized trials using targeted agents either alone or combined with chemotherapy failed to demonstrate the contribution of the targeted agent in the treatment of lung cancer (Gatzemeier 2004, Herbst 2004). Even when positive, such as the recent bevacizumab or cetuximab trials with chemotherapy, the magnitude of benefit has been small, suggesting the need for optimization of patient selection and more active agents (Pirker 2008, Reck 2009, Sandler 2006).

As described above, bevacizumab, a VEGF mononclonal antibody, is currently approved in combination with chemotherapy for patients with nonsquamous NSCLC. Other pathways of interest have completed studies or will shortly. These include the FLEX study and BMS 099 studies, chemotherapy with the addition of cetuximab, an *EGFR* monoclonal antibody, which demonstrated modest survival benefit in patients with NSCLC. IGFR has also been studied and Figitumumab (CP-751,871), a fully human, IgG_2 monoclonal antibody against the insulin-like growth factor type I receptor (IGF-IR), is currently in Phase III studies in combination with

chemotherapy in both squamous and nonsquamous NSCLC (Karp 2009). However, no validated biomarkers have been discovered with regards to treatment of monoclonal antibodies.

Promising biomarkers have been identified with regards to therapy with oral *EGFR* tyrosine kinase inhibitors. Several studies, however, have demonstrated that the proportion of *EGFR* mutation-positive patients is higher among gefitinib responders than nonresponders (Capuzzo 2005, Lynch 2004, Paez 2004, Sequist 2007) and showed that ORR and time to progression were significantly improved in gefitinib-treated *EGFR* mutation-positive patients than in those with wild-type *EGFR*, with a nonsignificant trend for longer overall survival. In placebo-controlled studies, there were either too few *EGFR* mutation-positive patients to evaluate survival (Hirsch 2006) or no evidence that *EGFR* mutation predicts for a greater survival advantage over placebo (Tsao 2005).

The discovery that somatic mutations in the *EGFR* kinase domain correlate and predict responses to the *EGFR* kinase inhibitors (gefitinib or erlotinib) underscores the importance of tailored individualized therapy based on the tumors underlying molecular biological profiles (Lynch 2004, Ding 2008, Kobayashi 2005). Indeed, the scientific advisory committee of the European Medicines Agency (EMEA), has issued a positive opinion supporting approval of the targeted oral anti-cancer drug, gefitinib, for adults with locally advanced or metastatic NSCLC with activating mutations of *EGFR*-TK in all lines of therapy based on findings from the IPASS study demonstrating significantly longer progression-free survival for patients with *EGFR* mutation-positive tumors treated with gefitinib than with doublet chemotherapy (Mok 2009) and the INTEREST study demonstrating similarly significant improvement in PFS and OS with gefitinib in patients with *EGFR* mutation positive tumors(Kim 2008).Resistance to *EGFR* inhibitors has emerged through development of acquired resistance (Bean 2008) or de novo resistance through other signaling pathways. (Marks 2008, Massarelli 2007, Pratilas 2008)

2.3 Biomarker Driven Targeted Therapy Clinical Trials Program (BATTLE-1)

The BATTLE-1 program (Kim 2009) was developed to establish individualized targeted therapy for NSCLC patients in whom standard therapy had failed by prospectively examining patients tumor biomarker profiles, obtained from a mandated fresh core tumor biopsy and assigning them to corresponding targeted therapies with the expectation to yield a better clinical outcome. Several unique aspects of this Department of Defense (DoD)-sponsored program

included: a) the unprecedented mandate for fresh tumor biopsies in an NCSLC clinical trial; b) using molecular classifications to guide selection of targeted therapies; and c) the use of a novel hierarchical Bayesian modeling approach to associate biomarkers with treatment outcome and, subsequently, apply adaptive randomization to guide treatment assignments towards the therapy arms most likely to benefit patients according their biomarker profiles and, conversely, away from arms that demonstrate lack of efficacy. Adaptive randomization under a Bayesian paradigm continues to learn by incorporating updated biomarker/outcome data over the course of the trial to guide treatment assignments (Zhou 2008). BATTLE-1 is composed of four Phase II clinical trials, including therapy with erlotinib, sorafenib, vandetanib, and bexarotene + erlotinib. Once patients are enrolled, consented and undergo a core biopsy of their tumor for biomarker analysis, each tumor is then profiled for prespecified biomarkers and biomarker groups. As of September 1, 2009, 327 patients have been enrolled into the program with acquisition of 290 biopsies. Biomarkers were successfully yielded in 82% of the patient population. The remaining 18% of the patient samples yielded no viable tumor tissue due to necrotic tissue and dense fibrosis.

Our ability to study efficacy in the Phase II setting as well as to correlate clinical data reliably with real-time biomarker analysis, and the knowledge gained through these programs regarding key regulatory mechanisms in NSCLC, has significant potential to lead to the identification of new therapeutic targets and strategies to be tested in future Phase III studies. The BATTLE-FL program capitalizes on our increased understanding of lung cancer biology, our capacity for timely development and analysis of biomarkers, our experience with clinical trial implementation and the enrollment of large numbers of patients with advanced NSCLC, and the availability of several promising agents of great interest to this group. This undertaking in front-line NSCLC is an area of unmet need: to move a step towards identifying biomarkers in these unselected patients.

2.4 RATIONALE

Vascular Endothelial Growth Factor (VEGF)

Angiogenesis plays a central role in non-small cell lung cancer (NSCLC) carcinogenesis, through one of its key mediators, the vascular endothelial growth factor (VEGF). Merrick et al. demonstrated that VEGF expression levels in bronchial epithelial cells of smokers progressively

increase in low to high grade dysplasia (Merrick 2005). In patients with established lung tumors, there is an association between high circulating levels or intratumoral overexpression of VEGF and poor prognosis (Yuan 2001, Shimanuki 2005, Kaya 2004, Han 2001, Fontanini 2006). VEGF may also facilitate pleural dissemination of lung cancers (Ishii 2004). In pre-clinical models of NSCLC, VEGF blockade has been shown to inhibit angiogenesis (Savai 2009) decrease tumor growth (Takayama 2000) stimulate apoptosis of cancer cells and enhance anti-neoplastic chemotherapy effects (Kabbinavar 2005). Taken together, these data support the evaluation of anti-VEGF therapies in patients with NSCLC.

Insulin-like Growth Factor Receptor (IGFR)

The type I insulin-like growth factor receptor (IGF-IR) is a member of a family of transmembrane tyrosine kinases that includes the insulin receptor and the orphan insulin receptor-related receptor (Adams 2000). The IGF-IR binds and is activated by two high affinity binding ligands, insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II) (Wang 2002).

A variety of strategies have been developed to inhibit the IGF-IR signaling pathway in tumor cells. Approaches utilizing antisense oligonucleotides, inhibitory peptide, soluble receptor, and dominant-negative receptor mutants that target IGF-IR have been effective at inhibiting the proliferation of tumor cell lines in vitro and in experimental cancer models in vivo (Wang 2002, Pollak 2004). Murine antibodies directed against the human IGF-IR have also been shown to inhibit the proliferation of a variety of human tumor cell types in vitro and in vivo. Notably, anti-IGF-IR antibodies, IGF-IR kinase inhibitors, and antisense oligonucleotides to the IGF-IR have been shown to inhibit the growth of prostate cancer both in vitro and in vivo (Blum 2003, Burfeind 1996, Pandini 2005)

These studies have established targeting the IGF-IR as an attractive anticancer therapeutic strategy and validated an antibody approach as an effective mechanism to inhibit IGF-IR signaling. As murine antibodies may induce specific immune or allergic reactions, 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.

3 STUDY AGENTS

3.1 Pemetrexed Background

Pemetrexed, a novel, multitargeted, antifolate antineoplastic agent approved for the first-line treatment of malignant pleural mesothelioma and the second-line treatment of NSCLC, is the chemotherapy agent most recently demonstrated to have activity in the first-line (Scagliotti 2008) and maintenance treatment (Ciuleanu 2008) of NSCLC.

The antitumor activity of pemetrexed likely derives from inhibition of several key folate-requiring enzymes, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih 1997). This diversity of enzyme targets and the potential to overcome inherent resistance suggest that pemetrexed could have a greater degree and broader scope of antitumor activity than other antifolate therapies, such as methotrexate and 5-fluorouracil. The mechanisms of action and molecular pharmacology of pemetrexed are well characterized (Shih 1998). This allows for correlative research of biomarkers in blood samples that may be predictive for high clinical benefit from pemetrexed-containing treatment.

The observed side effects of pemetrexed are similar to those of other antifolate therapies. These side effects include myelosuppression (mainly transient neutropenia), oral mucositis, diarrhea, and skin rash. Supplementation with folic acid and vitamin B12 reduces the severity and frequency of hematologic and non-hematologic toxicities. Pemetrexed has been investigated in a number of tumor types as a single agent and in combination with other cytotoxic agents. More detailed information about the known benefits and risks of pemetrexed may be found in the investigator's brochure (Lilly 2008).

3.2 Pemetrexed in Second-Line NSCLC Therapy

Global regulatory approvals of pemetrexed for the second-line treatment of patients with NSCLC were granted on the basis of the pivotal, randomized, open-label, Phase III study, H3E-MC-JMEI (JMEI). Patients with recurrent NSCLC received pemetrexed 500 mg/m2 or docetaxel 75 mg/m2 on Day 1 of each 21-day cycle until disease progression. In this study of 571 patients, pemetrexed resulted in clinically similar efficacy outcomes with significantly fewer side effects compared with docetaxel, the established standard of care (Hanna 2004). The RR was 9.1% and 8.8% for pemetrexed and docetaxel respectively, median PFS was 2.9 months in each arm,

median OS was 8.3 and 7.9 months for pemetrexed and docetaxel respectively, and the 1-year survival was 29.7% in each arm.

Subsequently, a retrospective subgroup analysis of Study JMEI revealed statistically significant treatment-by-histology interactions for OS (p = 0.001) and PFS (p = 0.004) (Peterson 2007). In the nonsquamous population, improved survival was demonstrated for patients who received pemetrexed compared with patients who received docetaxel, consistent with the statistically significant treatment-by-histology interaction (adjusted hazard ratio [HR] 0.778; 95% confidence interval [CI]: 0.607 to 0.997; p = 0.047; 9.3 months versus 8.0 months). Patients with predominantly squamous cell histology had shorter OS time with pemetrexed compared with docetaxel (adjusted HR 1.563; 95% CI: 1.079 to 2.264; p = 0.018; 6.2 months versus 7.4 months). No clinically relevant differences were observed for the safety profile of pemetrexed between the histologic subgroups. Because this was a retrospective analysis, the potential for different treatment results based on NSCLC histology was further evaluated in planned analyses for Studies H3E-MC-JMDB (JMDB) and H3E-MC-JMEN (JMEN).

3.3 Pemetrexed in First-Line NSCLC Therapy

Data from the multicenter, randomized, open-label, Phase III study, JMDB, formed the basis for global applications to regulatory authorities for the initial treatment of patients with locally advanced or metastatic NSCLC (first-line NSCLC). Study JMDB, which compared pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 on Day 1 of a 21-day cycle (PC) versus gemcitabine 1250 mg/m2 on Day 1 and Day 8 plus cisplatin 75 mg/m2 on Day 1 of a 21-day cycle (GC), met its primary endpoint and demonstrated that OS with PC was non-inferior to GC, with significantly fewer side effects (Scagliotti 2008).

In the intent-to-treat (ITT) population (all histologies), the 2 arms of the study were equivalent in terms of OS (unadjusted HR 0.93; 95% CI: 0.83 to 1.04; median 10.3 months for both arms), PFS (unadjusted HR 1.04; 95% CI: 0.95 to 1.15; median 4.8 and 5.1 months for the pemetrexed and gemcitabine arms, respectively), and RR (30.6% versus 28.2% for the pemetrexed versus the gemcitabine arm).

Preplanned analyses evaluating the differences in OS with respect to baseline patient and disease characteristics identified a differential effect on survival according to NSCLC histologic

subgroups. Overall survival time with PC was statistically superior to GC in patients with nonsquamous histology (adjusted HR 0.844; 95% CI: 0.74 to 0.96; p = 0.01 [data on file]). For patients with squamous histology, OS time with PC was shorter than with GC (adjusted HR 1.229; 95% CI: 1.00 to 1.51; p = 0.050).

In April 2008, the European Medicines Agency issued an approval for use of pemetrexed with cisplatin in the initial treatment of NSCLC other than predominantly squamous histology. The previously approved indication for use in second-line NSCLC was amended to include NSCLC with other than predominantly squamous histology only. In September 2008, the FDA approved pemetrexed in combination with cisplatin for the initial treatment of advanced nonsquamous NSCLC. The previously approved indication for use in second-line NSCLC was amended to include nonsquamous NSCLC only.

3.4 Pemetrexed with Carboplatin in First-Line NSCLC Therapy

The combination of pemetrexed and carboplatin was first tested in Study H3E-MCJMAU, a Phase I mesothelioma study that tested and verified the safety of this combination. A 32% response rate (RR) was noted with acceptable toxicity. Doses for the combination of pemetrexed and carboplatin were established at 500 mg/m2 and area under the curve (AUC) 6, respectively (Hughes 2002).

Two Phase II trials demonstrated that the regimen of pemetrexed with carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice.

In Study H3E-MC-JMEK, 83 chemotherapy-naïve patients with Stage IIIB or IV NSCLC were randomized to receive pemetrexed 500 mg/m2 plus either carboplatin AUC 6 (41 patients) or oxaliplatin 120 mg/m2 (42 patients) on Day 1 of a 21-day cycle, for up to 6 cycles of therapy (Scagliotti et al. 2005). In the pemetrexed-carboplatin arm, 12 of the 38 evaluable patients (31.6%) had best overall responses of partial response (PR) and 17 (44.7%) had best overall responses of stable disease (SD). Median PFS was 4.5 months, the 1-year survival rate was 43.9%, and median OS was 10.5 months. Grade 3/4 neutropenia was observed in 10 (25.6%) of 39 patients evaluable for safety. In Study H3E-US-JMEZ, 50 chemotherapy-naïve patients with Stage IIIB (with effusion) or IV NSCLC received pemetrexed 500 mg/m2 and carboplatin AUC 6 on Day 1 every 3 weeks for 6 cycles (Zinner et al. 2005). Twelve patients (24%) had PRs, and

25 (50%) had SD. Median TTPD was 5.4 months, the 1-year survival rate was 56%, and median OS was 13.5 months. Grade 3/4 neutropenia was observed in 13 (26%) patients. One (2%) patient had Grade 3 thrombocytopenia, and 1 (2%) patient had Grade 4 anemia. Three (6%) patients experienced Grade 3 non-hematologic side effects (nausea, fatigue, diarrhea, and vomiting).

Based on the data from these Phase II studies, the toxicity with the pemetrexed and carboplatin combination appears to be less than that seen with other standard regimens.

3.5 Pemetrexed Maintenance Therapy in NSCLC

Pemetrexed was then tested in the maintenance setting in the randomized, double-blind, placebo-controlled, Phase III study, JMEN. In this trial, patients received 4 cycles of induction therapy with 1 of 6 standard regimens (gemcitabine, paclitaxel, or docetaxel, with either carboplatin or cisplatin); regimen selection was at the discretion of the investigator. Patients who achieved complete response (CR), partial response (PR), or stable disease (SD) were randomized to maintenance with pemetrexed plus best supportive care (BSC) or placebo plus BSC until progression (Ciuleanu 2008).

Study JMEN demonstrated a significant improvement in PFS following induction chemotherapy for patients receiving pemetrexed maintenance therapy compared with placebo (unadjusted HR 0.60; 95% CI: 0.49 to 0.73; $p < 0.00001$; 4.04 versus 1.97 months) (data on file). In patients with nonsquamous histology, median PFS for patients receiving pemetrexed versus placebo was 4.4 months versus 1.8 months (unadjusted HR 0.47; 95% CI: 0.37 to 0.60; $p < 0.00001$). With 55% censoring, preliminary OS following induction chemotherapy in the overall study population was 13.0 months with pemetrexed and 10.6 months with placebo (unadjusted HR 0.798; 95% CI: 0.63 to 1.01; $p = 0.06$). In the nonsquamous population median OS was 14.4 months for pemetrexed-treated patients and 9.4 months for patients on placebo (unadjusted HR 0.66; 95% CI: 0.49 to 0.88; $p = 0.005$). In the squamous group, median OS was 9.6 and 11.9 months for pemetrexed and placebo treatment, respectively (unadjusted HR 1.28; 95% CI: 0.85 to 1.93; $p = 0.231$).

Response to maintenance therapy, analyzed according to Response Criteria in Solid Tumors (RECIST) version 1.0 guidelines (Therasse 2000), was significantly higher for the pemetrexed arm (3.4%; 95% CI: 2% to 6%) compared with the placebo arm (0.5%; 95% CI: 0%

to 3%; p = 0.042). Results of the analysis of disease control rate (DCR; CR+PR+SD) also demonstrated a significant improvement for patients receiving pemetrexed (49.1%; 95% CI: 44% to 54%) compared with patients receiving placebo (28.9%; 95% CI: 23% to 36%; p < 0.001).

3.6 Bevacizumab Background

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. By blocking the endothelial interaction of VEGF and its receptors, bevacizumab serves as an antiangiogenic agent.

Bevacizumab has been studied in more than 5000 patients and in multiple tumor types in Phase I, II, and III clinical trials. In addition, data are available from 3863 patients enrolled in 2 post-marketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials.

3.7 Bevacizumab in NSCLC

In the Genentech-sponsored, randomized, Phase II study AVF0757g, bevacizumab was added to the ECOG reference regimen established in Study ECOG 1594 (Schiller 2002). This Phase II study identified a relationship between fatal hemoptysis and central lesions with squamous histology in lung cancer patients treated with bevacizumab (Johnson et al. 2004). Based on these safety data, the subsequent Phase III study excluded patients with predominantly squamous cell carcinoma, hemoptysis, or both.

The Phase III study (ECOG 4599) randomized patients to either carboplatin-paclitaxel-bevacizumab or carboplatin-paclitaxel (Sandler et al. 2006). Patients who received 6 cycles of bevacizumab plus chemotherapy without progression continued on single-agent bevacizumab until progression. Median OS was 12.3 months for patients on the bevacizumab plus chemotherapy arm compared with 10.3 months for patients receiving carboplatin plus paclitaxel (HR 0.79; 95% CI: 0.67 to 0.92; p = 0.003). One-and 2-year survival rates were 51% and 23% for the Sandler regimen, compared with 44% and 15% for the chemotherapy-only regimen. The

RR was 35% (133/381) for patients on bevacizumab and 15% (59/392) for patients on chemotherapy only ($p < 0.001$).

The addition of bevacizumab resulted in modest changes to the expected toxicity profiles of chemotherapy alone (Genentech 2007). A number of safety signals, similar to those found in other bevacizumab studies, such as epistaxis, hypertension, and proteinuria, were identified, the majority of which were of low grade and did not require discontinuation of bevacizumab. Study ECOG 4599 suggested that the addition of a third noncytotoxic agent and/or maintenance therapy with an agent of low toxicity could result in improved outcomes in patients with advanced NSCLC. This study demonstrated that the treatment paradigm for patients with nonsquamous NSCLC (*bevacizumab eligible*) is different than the treatment paradigm for patients with squamous histology NSCLC based on a difference in safety (NCCN 2008).

In addition to ECOG 4599, the results of other trials exploring the incorporation of bevacizumab to first-line platinum-based doublets have been presented, including the randomized phase III AVAiL trial (cisplatin and gemcitabine +/- bevacizumab) (Reck 2009), as well as the single-arm phase II studies of bevacizumab combined with carboplatin plus docetaxel (William 2009), carboplatin plus pemetrexed (Patel 2009), oxaliplatin plus pemetrexed (Waples 2008), and carboplatin plus nanoparticle albumin-bound paclitaxel. (Reynolds 2007)**.**

3.8 Cixutumumab (IMC-A12) Background

ImClone LLC has developed a recombinant human immunoglobulin G, subclass 1 (IgG_1) monoclonal antibody, cixutumumab (IMC-A12), which specifically targets the human IGF-IR (Burtrum 2003, Wu 2005) cixutumumab possesses high affinity for IGF-IR and acts as an antagonist of IGF-I and IGF-II ligand binding and signaling. Cixutumumab does not bind to or recognize the human insulin receptor. In addition to blockade of ligand binding, this antibody inhibits the IGF-IR pathway by effecting the internalization and degradation of IGF-IR, leading to a reduction in surface receptor density on treated cells. As a result of the blockade of ligand signaling, the mitogenic and proliferative effects of IGF-I and IGF-II are significantly reduced. IGF signaling is also one mechanism by which cancer cells can become resistant to chemotherapy. By acting as an antagonist of IGF-IR signaling, cixutumumab can sensitize tumor cells to the damaging effects of chemotherapy. In xenograft tumor models in vivo, IGF-IR blockade by cixutumumab significantly inhibits the growth of a variety of tumor types,

(Burtrum 2003) including breast (estrogen receptor-positive and -negative), renal, colon, lung, prostate (androgen-dependent and independent), head and neck, and pancreatic tumors. Histological analysis of tumor sections demonstrated a marked increase in apoptotic tumor cells in antibody-treated animals.

Preclinical studies also demonstrated potential antitumor activity of cixutumumab when used in combination with conventional chemotherapy, including cisplatin, docetaxel, 5-fluorouracil/leucovorin, and irinotecan. Studies in models of lung cancer have also demonstrated increased benefit of cixutumumab in combination with radiation therapy. In models of prostate cancer, cixutumumab has also been shown to provide increased benefit when used in combination with hormone-ablation therapy. Furthermore, preliminary investigations with tamoxifen or trastuzumab resistant breast cancer cell lines demonstrated increased sensitivity to cixutumumab treatment.

Importantly, cixutumumab has been shown to inhibit the growth of both androgen-dependent and androgen-independent prostate cancer cell lines, enhance docetaxel-mediated growth inhibition in prostate cancer xenograft models, and delay the time to recurrence of androgen-independent prostate cancer when combined with hormone ablation therapy (Wu 2005, Wu 2006). Using a cixutumumab-responsive androgen-independent prostate model, it was determined that the addition of cixutumumab to weekly doses of docetaxel could increase the antitumor effects of cytotoxic therapy, leading to complete tumor arrest and some cases tumor regression. Notably, antitumor activity persisted after discontinuation of therapy in tumors treated with cixutumumab plus docetaxel; detectable levels of antibody present three weeks after discontinuation of therapy suggests that this continuation of antitumor activity is partially attributable to the persistence of cixutumumab. Cell cycle and differential gene expression analysis of tumors in each group indicated that combination therapy affected a sharp increase in apoptotic cells and reduction in proliferating tumor cells, accompanied by marked change in the expression of genes controlling apoptosis and cell cycle progression. Since androgen-independent prostate cancer frequently progresses to the development of bone metastases, the effects of combined cixutumumab and docetaxel on established osteoblastic prostate cancer bone metastases were also studied. Although docetaxel alone and docetaxel plus cixutumumab were shown to be effective in controlling osseous prostate cancer xenografts, the antitumor effects of combined therapy persisted after cessation of drug treatment.

3.8.1 Nonclinical Studies with Cixutumumab

The toxicity of intravenously-administered cixutumumab has been evaluated in three studies in cynomolgus monkeys that received one, four, or 13 weekly doses of cixutumumab; the results of this research are summarized in Table 1. In addition, mice have been treated in numerous xenograft studies exploring the activity of cixutumumab. Body weight and general health status are available from many of these mouse studies. A tissue cross-reactivity study has been conducted with a full panel of monkey and human tissues to support the overall safety assessment. Detailed descriptions of all studies are provided in the cixutumumab Investigator s Brochure; results are also briefly summarized below.

Cixutumumab cross-reacts with the mouse IGF-IR and binds with kinetics similar to the human IGF-IR. In a variety of wild-type and immunodeficient mice treated with intraperitoneal cixutumumab, 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 cixutumumab cross-reactivity was consistent with the immunohistochemical distribution of IGF-IR in human tissues, as reported in the literature. The same human tissue types that expressed IGF-IR 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 of cixutumumab cross-reactivity suggested that the cynomolgus monkey provides an appropriate animal model for nonclinical toxicity testing of cixutumumab.

3.8.2 Cixutumumab Preclinical Toxicology and Pharmacokinetics

A single-dose pilot pharmacokinetic (PK) study was conducted in cynomolgus monkeys. Animals were administered cixutumumab at 2 or 10 mg/kg and observed for 42 days. No adverse effects were noted other than vomiting in one monkey after dosing that was attributed to the stress of procedures. 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 a 5-week

(four-dose) monkey toxicology study, animals were dosed on days 1, 15, 22, and 29 with 0, 6, 22, or 80 mg/kg of cixutumumab. 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 cixutumumab. Pharmacokinetics were nonlinear and the lowest dose produced serum levels that exceeded the minimum trough level associated with activity (60-158 μg/mL) in murine colorectal (Colo205) and pancreatic (BxPC-3) xenograft models for 2 days.

Final data from the 13-week monkey toxicology study indicated that 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 fibroadipose 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 the thymus, cixutumumab 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 cixutumumab 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 cixutumumab 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 cixutumumab administration for up to 13 doses.

Table 1: Repeated-Dose Toxicology/Pharmacokinetic Studies

Species/ Group Size	Route and Schedule	Doses (mg/kg)	Major Findings
Single-dose cynomolgus monkey/ 3 females	I.V. slow bolus single dose	2 or 10	• One animal at 10 mg/kg vomited a foamy clear substance and displayed lethargy 23 minutes after dosing; believed to be due to stress from dose administration and blood sampling. • C_{max} and AUC_{inf} increased in a greater-than-dose-proportional manner. • Mean Values: C_{max} = 40 and 368 µg/mL, AUC_{inf} = 2783 and 27572 h µg/mL.
Four-dose cynomolgus monkey/ 3/sex in main study and 3 males per recovery groups examined 7 weeks after last dose	I.V. slow bolus once per week with 2-week gap after the first dose	0, 6, 22, 80	• No treatment-related effects on survival, clinical signs, food consumption, clinical chemistry, hematology (other than procedure-related anemia and reticulocytosis), urinalysis, ophthalmology, or blood pressure. • Dose-dependent slight body weight losses. • Decreasing trends in absolute and relative thymus and spleen weights. • Dose-dependent thymic atrophy. After 7-week recovery period thymic atrophy was reversible at low-dose, partly recovered at mid-dose, and not recovered at high-dose. • Anti-cixutumumab antibody incidence was 0 of 6, 0 of 8, 1 of 8, and 0 of 8 evaluable for the 0-, 6-, 22-, and 80-mg/kg groups, respectively. • Mean Values: C_{max} = 153, 528, and 2182 µg/mL; AUC_{inf} = 14032, 60620, and 253726 h●µg/mL; half-life = 5.0, 7.0, and 7.7 days; clearance = 0.436, 0.371, and 0.330 mL/h/kg.
13-dose cynomolgus monkey/ 3/sex in main study 4 to 6 per sex distributed in recovery groups that were examined 8 and 12 weeks after last dose	10-min I.V. infusion once per week	0, 6, 22, 80	• No treatment-related effects on survival, clinical signs, urinalysis, immunophenotyping, ophthalmology, or cardiovascular endpoints. • Body weight losses were 0%-14%, 4%-16%, and 4%-21% for the 6-, 22-, and 80-mg/kg groups, respectively. Weight was regained in recovery. • Decreasing trends in RBCs, HCT, and hemoglobin in both sexes (statistically significant in high-dose females) on Day 86; decreased RBCs and HCT in high-dose females on Day 28. • Decreased mean platelet volume in all female groups. • Decreased absolute and relative thymus weights associated with minimal to marked atrophy, depletion of cortical thymocytes, loss of corticomedullary junction, and fat replacement. • Decreased absolute and relative uterine weights associated with diffuse hypoplasia. • Ovarian immaturity consisting of a relative increase in the ovarian cortex with a less developed medulla and decreased follicles in different stages of development. • Increasing trend in relative heart:body weights in males and mid-dose females, but not relative heart:brain weights. • Anti-cixutumumab antibody incidence was 1 of 12, 4 of 8, 0 of 8, and 1 of 12 evaluable for the 0-, 6-, 22-, and 80-mg/kg groups, respectively. • Mean Values: C_{max} = 186, 748, and 2434 µg/mL; AUC_{inf} = 16276, 67659, and 267733 h µg/mL; half-life = 3.6, 4.6, and 4.4 days; clearance = 0.413, 0.377, and 0.332 mL/h/kg.

AUC_{inf} = area under the serum concentration vs. time curve from time zero extrapolated to infinity; C_{max} = maximum serum concentration; HCT = hematocrit; I.V. = intravenous; RBCs = red blood cells.

3.8.3 Cixutumumab Clinical Studies

The clinical information in this section represents data available as of the finalization of this protocol. Please refer to the most recent version of the cixutumumab Investigator s Brochure, including any Safety Updates (Investigator Notifications), for updated clinical information on safety and efficacy.

3.8.4 Phase I

Two Phase I studies, evaluating the safety and antitumor effects of cixutumumab administered either weekly (CP13-0501) or every other week (CP13-0502) at doses beginning at 3 mg/kg, have been conducted. Clinical data from these studies available to date are described in the sections below.

CP13-0501

A total of 24 patients were enrolled and treated in CP13-0501 (cixutumumab administered weekly to patients with advanced solid tumors), including seven at the 3-mg/kg dose level, nine at the 6-mg/kg dose level, six at the 10-mg/kg dose level, and two at the 15-mg/kg dose level. This patient population included 14 males and 10 females. The median patient age was 57.2 years, and patients ranged in age from 25 to 70 years.

All patients experienced at least one adverse event (AE) regardless of relationship to cixutumumab; the most frequently reported adverse events overall were fatigue (41.7%), nausea (33.3%), and vomiting (33.3%). Fifteen patients (62.5%) experienced at least one adverse event of Grade ≥ 3, including four in the 3-mg/kg cohort (57.1%), six in the 6-mg/kg cohort (66.7%), four in the 10 mg/kg cohort (66.7%), and one in the 15-mg/kg cohort (50%).

A total of 17 patients (70.8%) experienced adverse events possibly, probably, or definitely related (related) to treatment with cixutumumab. Hyperglycemia was the most common, affecting a total of four patients (16.7%) and considered a dose-limiting toxicity (Grade 3) in two. Section 9.11 details proposed management for potential therapy-related hyperglycemia.

The only possibly-, probably-, or definitely-related Grade ≥ 3 events reported during this study have been the two cases of Grade 3 hyperglycemia described above (one at the 3-mg/kg

dose level and one at the 10-mg/kg dose level), both of which resulted in treatment discontinuation, and one case of Grade 3 fatigue at the 6-mg/kg dose level.

A small increase in body fat percentage was noted in five of six patients for whom DEXA scan results were available both pretreatment and following 6 weeks of initial cixutumumab therapy (median 1% absolute increase). Mild weight loss was noted in seven of nine patients over this initial study period (median decrease 1 kg; 1% of body weight). The contribution of cixutumumab to these modest changes in body fat/weight is not easily discernible in these patients with advanced cancer.

Final efficacy data are not yet available. To date, 11 patients have experienced a best overall response of stable disease (SD), including two patients at the 3-mg/kg dose, five patients at the 6-mg/kg dose, two patients at the 10-mg/kg dose, and two patients at the 15 mg/kg dose. Among these eleven patients were four patients with SD greater than 8 months (male breast cancer [3 mg/kg], hepatocellular cancer [3 mg/kg], pheochromocytoma [10 mg/kg], and lymphangiomatosis [15 mg/kg]).

CP13-0502

A total of 16 patients were enrolled in study CP13-0502, a Phase I dose-escalation trial of cixutumumab administered every other week in advanced solid tumors: five patients at 6 mg/kg, nine patients at 10 mg/kg, and two patients at 15 mg/kg. The median age of these patients was 55.4 years (range: 19 - 79 years); the group includes six male patients and 10 female patients.

This regimen has been well-tolerated at all dose levels. The most frequently reported adverse events overall were fatigue (43.8%) and nausea (37.5%). Nine patients (56.3%) experienced at least one adverse event of Grade ≥ 3, including three patients (18.8%) with dyspnea (all in the 10-mg/kg cohort). Other reported AEs Grade ≥ 3 included fatigue, pain, cellulitis, dehydration, mental status changes, nausea, and vomiting.

Cixutumumab-related adverse events affected nine patients (56.3%). The most common related AEs were fatigue (three cases) and nausea (two cases). Two patients experienced AEs of Grade ≥ 3 that were considered at least possibly related to cixutumumab, both in the 10-mg/kg cohort: one patient with fatigue and one patient with Grade 3 QT_C prolongation (the latter resulting in study discontinuation).

PK data obtained during the course of this study suggest that cixutumumab should be present at sufficient concentrations to have therapeutic benefit when dosed at 10 mg/kg every 14 days. This dose has been established as the recommended dose for Phase II studies utilizing an every-other-week dosing schedule; study CP13-0502 was accordingly closed to enrollment. Four patients experienced stable disease lasting at least 3.5 months, including one patient with stable disease > 7 months and another with stable disease > 9 months.

Lymphocyte Counts

Absolute lymphocyte counts are available from Phase I cixutumumab studies for 15 patients, including both pretreatment values and levels following at least one cycle (four weekly doses over 6 weeks) of therapy. T-lymphocyte counts are available for seven patients, including both pretreatment values and levels following at least one cycle (four weekly doses over 6 weeks) of therapy. Across four dose levels (3 mg/kg 15 mg/kg per week), absolute lymphocyte counts increased in eight of 15 patients, remained unchanged in two of 15 patients, and decreased in five of 15 patients (range -39% to +49% change from pretreatment baseline; median: 2% increase [30/μL]). Across three dose levels (3 mg/kg 10 mg/kg per week), T-lymphocyte counts increased in four of seven and decreased in three of seven patients (range -42% to +45% change from pretreatment baseline; median: 10% increase [82/μL]). Increases and decreases were noted in patients treated both at 3 mg/kg and 10 mg/kg. Alterations in absolute lymphocyte count correlated highly with alterations in T-lymphocyte count ($r = 0.99$; Spearman coefficient). There was also a high level of correlation between absolute lymphocyte and T-lymphocyte counts both prior to and following cixutumumab therapy.

Long-term data regarding lymphocyte counts are available from two patients who experienced disease stabilization for at least 9 months while receiving cixutumumab therapy. In these patients (a 69-year-old man with metastatic breast cancer and extensive thoracic disease and a 54-year-old man with hepatocellular carcinoma, hepatitis C infection, and extensive hepatic tumor), absolute lymphocyte and T-lymphocyte counts remained largely stable and in the range of pretreatment baseline during the initial 6 to 8 months of therapy. In one patient (male breast cancer), reduced levels of lymphocytes and T-lymphocytes were noted only after 9 months of therapy, at the time of disease progression. Lymphocytes and T-lymphocytes remained at pretreatment levels in the other patient (hepatocellular carcinoma) over 6 months of initial

therapy, with a modest reduction (17% - 19% below pretreatment levels) noted during the subsequent months prior to disease progression.

No infectious adverse events have been noted during Phase I studies of cixutumumab. Preliminary investigations of another anti-IGF-1R antibody (CP-751,871) have also indicated an acceptable safety profile without significant infectious complications (Lacy 2006). Phase II studies of cixutumumab in combination with chemotherapy are underway.

4 EXPERIMENTAL PLAN

4.1 Overview of Study Design

The main objective of this phase II study is to determine the progression free survival in patients with advanced NSCLC. We plan to enroll 225 evaluable patients.

This study will be an open-label randomized Phase II design. Upon enrollment, each patient will be assigned a study ID number. A biomarker analyses will be performed on the available tumor tissue. If adequate tumor tissue is not available for molecular analyses a tumor biopsy will be performed at MDACC. Once the patient meets eligibility criteria the patient will be randomized into one of three treatment arms based on their clinical eligibility. The patient may be initiated on therapy while the biomarker analysis is pending. If biomarker results reveal an actionable molecular avberration, then the treating Physicians and/or Principal Investigator will discuss continued protocol participation versus off study standard of care treatment options. If the patient is removed from study, then the patient will be replaced to ensure that 225 eligible patients are enrolled on the study. The primary endpoint will be PFS for each of the individual arms (analyzed separately). Patients will be consented by the treating physician. Patients may request information and decide to enroll at a later date. Follow-up will occur through the research nurse.

The chemotherapy will be carboplatin (AUC 6) and pemetrexed (500 mg/m2) every 3 weeks for 4 cycles. Then maintenance pemetrexed (500 mg/m2 every 3 weeks) will be administered until disease progression or excessive toxicity. If patients are randomized into one of the arms with a biologic therapy, patients will take the chemotherapy prescribed above, but will also receive the biologic therapy during the same time period [bevacizumab 15 mg/kg every 3 weeks (Arm 2) or cixutumumab (IMC-A12) 20 mg/kg every 3 weeks (Arm 3)].

A second optional biopsy will be performed after 2 cycles while on study. This biopsy will be performed only for biomarker modulation purposes and not diagnostic information. There are three treatment arms planned at this time with up to 75 patients to be enrolled into each arm. In the BATTLE-FL Trial, patients with advanced NSCLC who are eligible to be treated with a front-line chemotherapy regimen will be enrolled. Progression-free survival will be evaluated after every two cycles of therapy. Responses will be confirmed 2 cycles after its initial assessment. Patients without progression (either complete or partial response or stable disease) will continue on therapy.

As an exploratory endpoint, we will assess the biomarkers (to be determined) to determine the role in relation to treatments. The selection of these biomarkers will be based on the current available literature as well as our preclinical testing. The combined information with these biomarker sets will allow us to hypothesize which biomarker(s) may predict best benefit in patients treated with chemotherapy alone or in combination with a targeted agent. These biomarkers will be subject to a Bayesian variable selection algorithm (see Section 12: Statistical Design and Data Analysis Considerations) with a goal to identify the important prognostic or predictive biomarkers.

Patients with progressive disease may be evaluated for other studies or treatments per their primary physician. There are no limits to the number of cycles of therapy a patient may receive while on protocol. If a patient, in the absence of progressive disease, experiences intolerable toxicities, the investigator may request of the Principal Investigator that the offending drug be discontinued or the patient be withdrawn from study. Optional serum samples will be performed at baseline, cycle 1, cycle 2, every 2 cycles thereafter and at disease progression. Patients will be seen and enrolled in the Thoracic/Head and Neck Medical Oncology clinics. Patients may be referred from outside referring physicians.

4.2 Patient Assignment in the Biomarker-Integrated Clinical Trials

Patients enrolled in the BATTLE-FL study will then be randomized into a specific treatment arm. If the patient s eligibility does not allow participation in a specific arm, the patient's randomization will exclude that arm(s).

4.3 Patient Eligibility

4.3.1 Inclusion Criteria

The following inclusion criteria must be met for entry into the study. Patients will also be clinically eligible for their specific treatment arm:

1) The patient has a diagnosis of pathologically confirmed nonsquamous (nonpredominant squamous) NSCLC by tumor biopsy and/or fine-needle aspiration. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the patient is ineligible.
2) The patient has a diagnosis of either stage IIIB or stage IV NSCLC or has recurrent NSCLC and is not a candidate for curative treatment. Patients may not have had chemotherapy for the advanced setting.
3) The patient has measurable NSCLC.
4) The patient s ECOG performance status is ≤ 2 at study entry.
5) The patient should have tumor available for EGFR mutations, ALK fusions and other molecular analyses (Appendix C). If there is no tissue then the patient should have biopsy accessible tumor.
6) The patient has adequate hematologic function as defined by an absolute neutrophil count (ANC) >/= 1,500/mm^3, platelet count >/= 100,000/mm^3, WBC >/= 3,000/ mm^3, and hemoglobin >/= 9 g/dL.
7) The patient has adequate hepatic function as defined by a total bilirubin level </= 1.5 X the upper limit of normal (Serum bilirubin >/= 1.5x Upper Limit of Normal in the setting of known Gilbert s disease is allowed), and alkaline phosphatase, AST and ALT </= 2.5 X the upper limit of normal or </= 5.0 x ULN if liver metastases are present.
8) The patient has adequate renal function as defined as CrCl of at least 45ml/min.
9) If patient has brain metastasis, they must have been stable (treated and/or asymptomatic) and off steroids for at least 2 weeks.
10) The patient is >/= 18 years of age.
11) The patient has signed informed consent.
12) Pregnancy Test. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for six (6) months after discontinuation of the study drugs.

Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation, hysterectomy or bilateral oophorectomy. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately. The patient, if a man, agrees to use effective contraception or abstinence for the duration of study participation and for six (6) months after discontinuation of the study drugs.

13) The ability to interrupt NSAIDS 2 days before (5 days for long-acting NSAIDs), the day of, and 2 days following administration of Pemetrexed.

4.3.2 Exclusion Criteria

A patient meeting any of the following criteria is not eligible to participate in this study:

1) The patient has received prior definitive therapy (chemotherapy, surgery, or radiotherapy) within 3 months of initiating study drug or within, 2 weeks of localized palliative radiotherapy. Patients treated with initial biologic therapy that progresses are eligible (no drug within 4 weeks). Patients must have recovered (≤ Grade 1 or baseline) from the acute toxic effects prior to Day 1 of Cycle 1.
2) Patients may not have had prior chemotherapy for first line treatment for NSCLC Stage IIIB/IV. Patient with activating EGFR mutations could have been treated with an EGFR tyrosine kinase inhibitor. Similarly patient with ALK or ROS1 fusions could have had treatment with crizotinib or other ALK inhibitors. Patients may not have had prior biologic therapy with antibodies targeting VEGF, or IGFR.
3) The patient has undergone prior thoracic or abdominal surgery within 30 days of study entry, excluding prior diagnostic biopsy.
4) The patient has a history of uncontrolled angina, arrhythmias, or congestive heart failure.
5) The patient has inadequately controlled hypertension (defined as systolic blood pressure > 140 and/or diastolic > 90 mm Hg on antihypertensive medications).
6) The patient has a history of stroke or transient ischemic attack within 6 months prior to Day 1 of Cycle 1.
7) The patient is unable or unwilling to take folic acid, vitamin B12 supplementation or dexamethasone according to protocol.
8) The patient has neuropathy >/= grade 2.

9) The patient has a history of gastrointestinal fistula, perforation, or abscess, inflammatory bowel disease, or diverticulitis.
10) The patient is currently receiving ongoing treatment with full-dose warfarin or equivalent (that is, unfractionated and/or low molecular weight heparin).
11) The patient is pregnant
12) The patient is breastfeeding.
13) Presence of significant third space fluid which cannot be controlled by drainage.
14) The patient s tumor harbors the EML4-ALK fusion gene.
15) Drug Specific Eligibility for Treatment Arms. Patients are excluded from the Bevacizumab arm if they have a history of hemoptysis (≥ teaspoon of bright red blood per episode) within 3 months prior to randomization.
16) Drug Specific Eligibility for Treatment Arms. Patients are excluded from Bevacizumab arm if the Urine Protein Creatinine (UPC) ratio is not within the institutional normal limits.
17) Drug Specific Eligibility for Treatment Arms. Patients are excluded from the IMC-A12 containing arm if they have poorly controlled diabetes: HBA1C>8% or if the patient has abnormally elevated fasting serum glucose (defined >110% ULN).
18) Drug Specific Eligibility for Treatment Arms. Patients are excluded if they have known hypersensitivity to any of the drugs.

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4.4 Study Withdrawal

Patients will be removed from the study for any of the following reasons:

1. Patient requests to withdraw
2. Unwilling or unable to comply with study requirements
3. Identification of recurrent or new cancer
4. Unrelated intercurrent illness that will affect assessment of clinical status to a significant degree as determined by the principal investigator or the treating physician.

The treating physician or investigator must discontinue the patient s study treatment if he/she thinks that the patient s health or well-being is threatened by continuation on study treatment.

Appropriate safety monitoring will continue until the patient is discharged from the study. Patients withdrawn from the study will be followed for survival. The reason for withdrawal and date of the discontinuation will be obtained. If a patient is non-compliant or lost to follow-up, the research nurse or his/her designee will make three attempts to call the patient over the period of one month. Attempts to contact will be documented. If the research nurse or his/her designee is unable to make contact with either the patient or a family member after three phone calls, then a letter will be sent to the patient s last known address.

4.5 Treatment Plan

Patients who meet the general eligibility criteria will be enrolled into the BATTLE-FL trial. Patients will be equally randomized into one of the three treatment arms based on the individuals clinical eligibility.

5 CARBOPLATIN

Carboplatin is a standard treatment for NSCLC. Commercially available supplies will be used for this study. Preparation instructions can be found in the FDA approved package insert. Carboplatin will be administered per institutional guidelines. Carboplatin will be provided by the institutional pharmacy. Carboplatin is administered after pemetrexed by intravenous infusion with standard antiemetics per local practice guidelines.

6 PEMETREXED

6.1 Investigational Product Description

Pemetrexed for injection will be provided by Eli Lilly and Company. Pemetrexed is FDA approved in combination with cisplatin therapy for the initial treatment of patients with locally

advanced or metastatic nonsquamous non-small cell lung cancer. Pemetrexed is also approved for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

6.2 Drug Accountability

All pemetrexed required for completion of the study will be provided by Eli Lilly and Company. The investigator will be responsible for drug accountability. Upon completion or termination of the study, all clinical supplies including partial and empty containers will be destroyed per institutional policy.

6.3 Packaging and Storage

Pemetrexed is supplied as a sterile, lyophilized powder for intravenous infusion packaged in a single-use glass vial. Each vial contains pemetrexed disodium equivalent to 500 mg of pemetrexed. The freeze-dried drug product is pemetrexed disodium and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may have been added during processing to adjust the pH. Each vial contains an excess of pemetrexed to facilitate the withdrawal of the label amount. The drug product is stable when stored at controlled room temperature and normal lighting conditions. For further details, see the Pemetrexed Investigator Brochure.

6.4 Preparation and Administration

Each vial must be reconstituted with sodium chloride (0.9%) solution for injection, without preservative, resulting in a solution containing 10 mg/mL to 50 mg/mL. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.8 and 7.8. Further dilution is required. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or a dark green color is observed, do not administer. The appropriate volume of reconstituted pemetrexed solution should be further diluted to 75 to 125 mL with sodium chloride (0.9%) solution for injection, without preservative. Pemetrexed infusion solutions prepared in this manner are compatible with polyvinyl chloride (PVC) and

polyolefin line administration sets and infusion bags. When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives. Chemical and physical stability of reconstituted and infusion solutions were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or room temperatures. From a microbiological point of view, the product should be used immediately or within 24 hours following initial reconstitution. Discard any unused portion. Reconstitution and further dilution prior to intravenous infusion is recommended with sodium chloride (0.9%) solution for injection, without preservative, only. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's injection and Ringer s Injection. Co administration of pemetrexed with other drugs and diluents has not been studied, and therefore, is not recommended. Clinical trial materials will be labeled according to local regulatory requirements.

6.5 Pretreatment Medications

Premedications for pemetrexed include:

- Folic acid 350-1000 micrograms po QD beginning day one of the first infusion of pemetrexed and continuing until the 3 weeks after discontinuation of pemetrexed.
- Vitamin B12 1000 microgram IM Q9weeks day one of the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed.
- Dexamethasone dosing will be administered by the attending physician using the standard of care dosing recommendations.

6.6 Treatment Schema

Pemetrexed will be administered 500 mg/m^2 IV on Day 1 (– 5 days) of a 21-day cycle per institutional guidelines. The pharmacy s standard method of preparing pemetrexed for infusion will be used following the manufacturer s instructions provided in the package insert. Patients will receive pretreatment medications as described in Section 6.5.

Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) must not take the NSAIDs 2 days before, the day of, and 2 days after receiving pemetrexed. If a patient is taking an NSAID with a long half-life (e.g., naproxen, piroxicam, diflunisal, or nabumetone), it should not be taken 5 days before, the day of, and 2 days after receiving pemetrexed.

Investigators should refer to the package insert for additional information such as safety issues, adverse reactions, and storage information.

6.7 Treatment Duration

Patients will take a maximum of 4 cycles of combination carboplatin and pemetrexed. If the patient has stable disease after 4 cycles, the patient will take maintenance pemetrexed every 21 days (– 5 days) until disease progression or excessive toxicity.

Patients will continue receiving pemetrexed maintenance 500 mg/m^2 IV q3weeks until they refuse further therapy, develop evidence of progressive disease, unacceptable toxicity, or any condition, which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or would pose undue risk to the patient through continuation. Should drug toxicity develop, dose delays and/or dose reductions will be carried out according to prespecified criteria.

For the purposes of this study, patients will undergo repeat radiographic evaluation via chest x-ray and CT or MRI after cycle 2 (6 weeks of therapy) and every two cycles of therapy thereafter. See Appendix B for methods of response assessment and classification.

6.8 Concomitant Medications and Therapy

Information on concomitant medications will be collected on this study. Medications for supportive care will be allowed as needed to treat nausea, pain, fever, rash, diarrhea, etc. Granulocyte growth factors (GCSF or GMCSF) will not be given routinely. Commercial suppliers of growth factors will be utilized. The use of growth factors will be according to ASCO guidelines. According to NCCN guidelines (Rodgers et al. 2008), erythropoiesis-stimulating agents (ESAs) are not indicated for treatment of cancer-related anemia in patients with solid tumors. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia for a hemoglobin < 10 g/dL after the patient has been counseled about the risks and benefits of ESA use. Because recommendations on the use of ESAs are rapidly evolving, investigators should frequently refer to the NCCN, ASCO, and/or Centers for Medicare and Medicaid Services web sites for the latest guidelines. The use of bisphosphanates for the purposes of treating bone metastases can be administered at the discretion of the treating physician. Other chemotherapeutic agents or investigational medications will not be allowed.

Other medication, which is considered necessary for the patient s safety and well being, may be given at the discretion of the investigator(s).

Leucovorin is allowed: (1) for treatment of CTCAE Grade 4 leukopenia or Grade 4 neutropenia lasting more than 3 days, beginning on the third day of Grade 4 myelosuppression; or (2) immediately, for treatment of Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis associated with pemetrexed. Appropriate doses of the oral formulation may also be used at the investigator s discretion.

Patients taking NSAIDs or salicylates will not take the NSAID or salicylate for 2 days before, the day of, and 2 days after receiving pemetrexed. Patients taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

6.9 Treatment of Pemetrexed Toxicity and Dose Modification:

All toxicities will be graded according to the CTCAE Version 4 guidelines. Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction must be discontinued from all study treatment. Discontinuation of study drug typically requires withdrawal from the study.

All patients will be evaluable for toxicity if they have received any study drug. Safety parameters will include description of toxic deaths, premature withdrawals from treatment for toxicity reasons, description of adverse events, serious adverse events (SAE), and evaluation of toxicity.

6.10 Hematologic Toxicity

At the start of each cycle, ANC must be $\geq 1.5 \times 10^9$/L and platelet count must be $\geq 100 \times 10^9$/L. Treatment should be delayed for up to 42 days to allow sufficient time for recovery. Dose adjustments will be based on neutrophil values at the start of the subsequent cycle of therapy.

6.11 Creatinine Clearance

Creatinine clearance will be estimated using the original, weight-based Cockcroft and Gault formula or measured using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA)

to determine glomerular filtration rate (GFR). The method of CrCl assessment used at baseline should be used throughout the study. Enrollment and dosing decisions based on CrCl may be made using locally determined clinical laboratory results (calculated using the original, weight-based Cockcroft and Gault formula). The serum creatinine must be assayed at the same local lab each time for that patient. If a local lab is being used to monitor a patient s renal function, the central laboratory sample still must be drawn for safety analysis.

At the start of each cycle, creatinine clearance should be ≥ 45 mL/min. The cycle may be delayed for up to 42 days to allow the patient time to recover from the toxicity. If a patient has not recovered on the CrCl and has not experienced disease progression within the 42 day window, the Principal Investigator and the treating physician may decide to allow the patient to remain on trial and continue with protocol treatment provided the patient meets the minimum creatinine clearance ≥ 45 mL/min.

6.12 Non-hematologic Toxicity

For Grade 3 or 4 non-hematologic toxicities, treatment should be delayed until resolution to less than or equal to the patient s baseline value. Dose reductions at the start of the subsequent cycle will be based on non-hematologic toxicities from the dose administered in the current cycle.

6.13 Dose Reductions

Any patient who requires a pemetrexed dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with two prior dose reductions who experiences a toxicity that would cause a third dose reduction must be discontinued from pemetrexed therapy and followed for survival. Patients who require a delay of more than 42 days in starting a new cycle of chemotherapy must be withdrawn from the study.

Hematologic Toxicity

Dose adjustments will be based on platelet and neutrophil nadir (lowest value) counts at the start of a subsequent cycle of therapy. The ANC must be ≥1.5 x 10^9/L and the platelet count must be ≥100 x 10^9/L prior to treatment of the subsequent cycle. Treatment should be delayed to allow time for recovery. Upon recovery, if treatment is resumed, it must be according to the guidelines in Table 6.1 below.

Table 6.1: Dose Adjustments for Pemetrexed Based on Nadir Blood Counts

Platelet (x 10^9/L) Nadir	ANC (x 10^9/L) Nadir	% of Previous Dose
≥50	and ≥0.5	100%
≥50	and <0.5	75%
<50	and any	50%

For patients who develop neutropenic fever, treatment should be delayed for up to 2 weeks until recovery of the ANC ≥1.5 x 10^9/L, resolution of fever, and treatment of documented infections are complete. Treatment should be resumed at 75% of the previous pemetrexed dose.

Diarrhea, Mucositis, or Other Non-Hematologic Toxicity

In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment will be delayed until diarrhea has resolved. Treatment should be resumed at 75% of the previous pemetrexed dose.

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals. If diarrhea is severe (requiring intravenous rehydration) and associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Hospitalization should be considered for patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting for intravenous hydration and correction of electrolyte imbalance.

For other nonhematologic toxicities greater than or equal to Grade 3 (with the exception of alopecia, Grade 3 transaminase elevations, nausea, or vomiting), treatment must be delayed until resolution to less than or equal to the patient s original baseline grade before proceeding. Treatment should resume at 75% of the previous dose if deemed appropriate by the investigator.

Table 6.2: Dose Modifications for Pemetrexed for Mucositis

CTCAE Toxicity Grade	% of Previous Dose
Grade 0 to 2	100%
Grade 3 to 4	50%

For patients who develop clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) during therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator s opinion the effusion represents progression of disease, the patient should be discontinued from all study medication and followed for survival.

Within 2 weeks following a dose interruption or reduction, study drug related toxicity must improve by at least one grade, or further dose reduction by one level will be required. Dosing may be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication. No more than two dose reductions will be allowed. If study drug related toxicity has not improved within 14 days of dose reduction or interruption, patients will be discontinued from the study.

7 BEVACIZUMAB

7.1 Investigational Product Description

Bevacizumab is FDA approved in combination with carboplatin and paclitaxel for treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer.

7.2 Product Descriptions

Commercially available supplies will be used for this study. Preparation instructions can be found in the FDA approved package insert. Bevacizumab will be administered per institutional guidelines.

7.3 Pretreatment Medications and Testing

Patients must have adequately controlled hypertension at time of screening (defined as systolic blood pressure > 140 and/or diastolic 90 mm Hg on antihypertensive medications).

Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1,000 mg for patient enrollment onto the Bevacizumab arm. The urine protein used to calculate the UPC ratio must be obtained within 4 weeks prior to randomization

7.4 Warnings and Precautions

Infusion Reactions

Monoclonal antibodies have caused infusion reactions. In some cases, these reactions are severe and rarely have fatal outcome. Severe reactions are characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension or angioedema and may require immediate interruption of infusion. Hypersensitivity reactions (non-IgE mediated reactions) have also been observed upon treatment with monoclonal antibodies and may respond to adjustments in the infusion rate and medical management.

7.5 Treatment of Infusion Reactions due to Bevacizumab

Guidelines for patients who experience an infusion reaction or hypersensitivity reaction during or after infusion with bevacizumab are shown in the Table 7.1. A two hour observation period is suggested after the first dose of bevacizumab infusion. For subsequent doses, a one hour observation period may be sufficient if the patient does not experience severe infusion reaction. Patients should be carefully observed until complete resolution of all signs and symptoms.

7.6 Treatment Schema

Patients will receive combination pemetrexed/carboplatin/bevacizumab after the initial biomarker assessment and randomization has occurred. This protocol defines the duration of one cycle of treatment as 3 weeks or 21 days (– 5 days). Starting Day 1 (– 5 days) of each 21-day cycle patients will be given 500 mg/m2 of pemetrexed IV, AUC 6 of carboplatin IV, and 15 mg/kg of bevacizumab IV. After the completion of 4 cycles of combination therapy, if the disease has not progressed, patients will receive maintenance pemetrexed maintenance 500 mg/m^2 IV q3wks in combination with bevacizumab 15 mg/kg of bevacizumab IV q3wks until progression of disease. Bevacizumab will be infused over 90 – 15 minutes for the initial dose, 60 – 10 minutes for the second dose and 30 – 10 minutes for the subsequent doses if the infusion rate is well tolerated.

7.7 Treatment Duration

Treatment will continue until there is objective evidence (radiological progression as per the RECIST criteria) of tumor progression, or until evidence of toxicities that are unacceptable and

thought to be related to study drug, which requires discontinuation of drug, withdrawal of patient consent or at the investigator s discretion.

Table 7.1: Guidance on Infusion and Hypersensitivity Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 is defined as: Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 is defined as: Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal inflammatory drugs (NSAIDS), narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: • IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. **If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100mL/hr to 50mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose.**	Patient may be premedicated 1.5h (+/- 30 minutes) prior to infusion with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grade 3/4 Grade 3 is defined as: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4 is defined as: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion** **Additional appropriate medical therapy may include but is not limited to**: IV fluids, Antihistamines, NSAIDS. Acetaminophen, Narcotics, Oxygen, Pressors, Corticosteroids, Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE). ***Note: NSAIDS should not be used in patients who have received pemetrexed in the previous 2 days.**		

7.8 Treatment of Toxicity and Dose Modification

Guidelines for Dose Modification

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in the Table 7.2. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 42 days.

Table 7.2: Bevacizumab Dose Management Due to Adverse Events – CTCAE Version 4	
Event	**Action to be Taken**
Hypertension:	No dose modifications for grade 1/2 events
Grade 3	If not controlled with medication, discontinue the patient from the study.
Grade 4	Discontinue the patient from the study.
Hemorrhage	Hemoptysis of any grade Discontinue the patient from study. No dose modifications for grade 1/2 events.
Grade 3	Patients who are also receiving full-dose anticoagulation will be discontinued from the study. All other patients will have study treatment held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from treatment.
Grade 4	Discontinue the patient from the study.
Venous Thrombosis	Note: Patients with lung cancer placed on anticoagulant therapy for a thrombotic event should be discontinued from study. No dose modifications for grade 1/2 events.
Grade 3 or Asymptomatic Grade 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting study drug treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan.
Symptomatic Grade 4	Discontinue the patient from the study.
Arterial Thromboembolic event Any grade	(Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event). Discontinue the patient from the study.
Proteinuria:	No dose modifications for grade 1
Grade 2 (2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs) Grade 3 (urinary protein >=3.5 g/24 hrs)	Proteinuria and/or nephrotic syndrome have been associated with use; risks may be increased in patients with history of hypertension. Thrombotic microangiopathy has been associated with bevacizumab-induced proteinuria. Withhold treatment for ≥2 g proteinuria/24 hours and resume when proteinuria is <2 g/24 hours;
Grade 4 (nephrotic syndrome)	Discontinue the patient from the study
GI Perforation requiring medical or surgical therapy	Discontinue the patient from the study.
Wound dehiscence requiring medical or surgical therapy	Discontinue the patient from the study.

7.9 Other Toxicities

Major adverse effects of bevacizumab include hypertension, proteinuria, and spontaneous hemorrhage including hemoptysis, epistaxis, and venous and arterial thromboses. Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome (RPLS) has also been reported. Infusion related reactions commonly manifest as fever and/or chills. Emergency equipment in case of anaphylactic or severe reactions should be available, including intubation equipment, oxygen, epinephrine, antihistamines and corticosteroids.

8 CITUXUMUMAB

8 Cixutumumab8.1 Investigational Product Description

Cixutumumab (IMC-A12) will be provided to participating patients free of charge by ImClone, LLC. Cixutumumab (IMC-A12) is a recombinant human immunoglobulin G, subclass 1 (IgG_1) monoclonal antibody which specifically targets the human IGF-IR. Cixutumumab possesses high affinity for IGF-IR and acts as an antagonist of IGF-I and IGF-II ligand binding and signaling. Cixutumumab does not bind to or recognize the human insulin receptor.

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.

8.2 Drug Accountability

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.

8.3 Package and Storage

Cixutumumab DP is supplied in single-use, 50-mL nominal volume, United States Pharmacopeia (USP) Type I glass vials. Each vial contains 250 mg of cixutumumab at a concentration of 5 mg/mL or 500 mg of cixutumumab at a concentration of 10 mg/mL or 750 mg of cixutumumab at a concentration of 15 mg/mL in a sterile, preservative-free solution. Each vial has a coated butyl rubber latex-free plug stopper and is sealed with an aluminum seal and a flip-off cap.

Cixutumumab must be stored under refrigeration at 2°C to 8°C (36°F-46°F) with protection from direct light. DO NOT FREEZE AND/OR SHAKE CIXUTUMUMAB DP. Stability studies have demonstrated that the drug product can withstand transient excursions to room temperature without adverse effect; however, storage at this temperature is not recommended.

8.4 Cixutumumab Dosage and Administration

Patients will receive cixutumumab 20 mg/kg intravenously via infusion. The dose of cixutumumab 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. Cixutumumab may be administered in an appropriate outpatient setting, but physicians should remain vigilant for signs and symptoms of hypersensitivity reactions.

8.4.1 Preparation for Administration

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.

Different drug product lots or formulations must not be mixed in a single infusion; additionally, on the same day of treatment there should be no mixing of lot numbers irrespective of whether they are from the same formulation.

All excipients used for the manufacture of cixutumumab drug product are of pharmacopeial grade. No animal-derived components are used in the manufacture of cixutumumab drug product excipients. For dose volumes < 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution will be added (or removed as in the case of prefilled AVIVA bags) to the container to make the total volume 250 mL. The container will be gently inverted to ensure adequate mixing. In the event that the total dose volume exceeds 250 mL, the infusion rate should not exceed 25 mg/minute. Cixutumumab is compatible with commonly used infusion containers. Refer to the investigator s brochure for detailed information about study drug information.

8.4.2 Administration

The dose of cixutumumab should be aseptically withdrawn from the vial and transferred to a sterile I.V. container composed of AVIVA, EVA, polyolefin, PVC, or an evacuated glass container. For dose volumes other than 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution should be added (or removed) to the container to make the total volume 250 mL. In the event that the total dose volume exceeds 250 mL, the infusion rate should not exceed 25 mg/minute (equal to 5 mL/minute of native solution for infusion).

Safe Handling and Administration

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

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.

8.5 Pretreatment Medications

Patients should not be routinely premedicated prior to administration of cixutumumab, except in the context of an infusion reaction (See Section 9.9 for infusion reaction guidelines)

8.6 Treatment Schema

Patients will receive cixutumumab/carboplatin/pemetrexed after the initial biomarker assessment and randomization has occurred. This protocol defines the duration of one cycle of treatment as 3 weeks or 21 days (– 5 days). Starting Day 1 (– 5 days) of each 21-day cycle patients will be given 20 mg/kg cixutumumab every 3 weeks, AUC 6 of carboplatin IV every 3 weeks, and 500 mg/m2 of pemetrexed IV every 3 weeks. After the completion of 4 cycles of combination therapy, if the disease has not progressed, patients will receive maintenance pemetrexed (500 mg/m2 of pemetrexed IV every 3 weeks) in combination with cixutumumab 20 mg/kg cixutumumab every 3 weeks until disease progression, intolerable toxicity, or withdrawal of consent.

8.7 Maintenance Period dose of Cixutumumab

The maintenance dose will be 20 mg/kg once every three weeks (– 5 days). Cycles repeat every 3 weeks until there is disease progression, intolerable toxicity, or withdrawal of consent.

8.8 Treatment of Toxicity and Dose Modification

Adverse events of concern, which may or may not be associated with cixutumumab therapy, include infusion reactions, hyperglycemia, and weight loss. If treatment with cixutumumab is held due to cixutumumab-related toxicity, chemotherapy may be continued without adjustment.

8.9 Cixutumumab Infusion Reactions

Cixutumumab infusion reactions will be graded based on the NCI-CTCAE Version 4.0 definition of infusion-related reactions (detailed below).

Symptoms occurring during or following infusion of investigational therapy may also be defined according to adverse event categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the adverse event term Infusion-Related Reaction and any additional terms (including those not listed here) that best describe the event. Those described above should be graded as follows:

Table 9.1: NCI-CTCAE Version 4.0 Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

In general, if a patient experiences a Grade 1 or 2 infusion reaction, the infusion rate should be decreased for the duration of the infusion and all subsequent infusions, as directed in the protocol. In addition, patients with Grade 1 and 2 infusion reactions should be treated according to standard medical practices. After a Grade 1 or 2 infusion reaction, patients should be premedicated with antihistamines, steroids, acetaminophen, etc, as appropriate for subsequent infusions.

A Grade 3 or 4 infusion reaction will require immediate treatment, including the use of epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm, I.V. fluids and/or pressors for hypotension, and immediate and permanent discontinuation of cixutumumab with appropriate supportive care. The ImClone liaison should be contacted immediately if questions arise concerning the grade of the reaction.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 infusion-related reaction as detailed below. The ImClone liaison should be contacted immediately if questions arise concerning the grade of the reaction. The following are general treatment guidelines for cixutumumab infusion-related reactions.

Grade 1

Slow the infusion rate by 50%

Monitor the patient for worsening of condition

For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator s discretion

Grade 2

Stop the infusion

Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen

Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours

Monitor for worsening of condition

For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator s discretion

- For a second Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine
- hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone
- 10 mg I.V. (or equivalent).

Grade 3

Stop the infusion and disconnect the infusion tubing from the patient
Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated
Patients who have a Grade 3 infusion reaction will not receive further cixutumumab treatment, but will continue to be followed on the protocol

Grade 4

Stop the infusion and disconnect the infusion tubing from the patient
Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), and other medications/treatment as medically indicated
Give epinephrine or bronchodilators as indicated
Hospital admission for observation may be indicated
Patients who have a Grade 4 infusion reaction will not receive further cixutumumab treatment, but will continue to be followed on the protocol

8.11 Hyperglycemia

Hyperglycemia that was at least possibly related to cixutumumab therapy has been observed in multiple studies of cixutumumab. Guidelines presented below are intended to enable cixutumumab administration in the context of clinical studies while minimizing the potential to develop AE-related symptoms or more severe AEs.

For the assessment of hyperglycemia (diabetes), Metabolism/Nutrition Terms (Version 4.0) should be used preferentially over Laboratory terms. If hyperglycemia/diabetes occurs during treatment with cixutumumab, treatment is dependent upon symptom severity. For Grade 1 or 2, cixutumumab treatment should continue; oral agents for hyperglycemia/diabetes may be used as clinically indicated.

For Grade 3 (symptoms interfering with activities of daily living [ADL] or insulin indicated), cixutumumab treatment may continue if the patient is asymptomatic and glucose < 300 mg/dL; the investigator should consider initiating insulin therapy if the patient is not controlled using oral agents. Cixutumumab should be held for Grade 3 hyperglycemia if there are symptoms interfering with ADL or if glucose is ≥ 300 mg/dL; cixutumumab may be restarted when the patient is asymptomatic, glucose is consistently (in the opinion of the investigator) below 300 mg/dL, and the patient is on a stable insulin regimen (if necessary).

Reintroduction of cixutumumab following stabilization of a Grade 3 hyperglycemic event may occur with no dose reduction if glucose is ≤ 200 mg/dL after stabilization. If glucose is between 200 mg/dL and 300 mg/dL, a 20% reduction to the dose of cixutumumab may be warranted.

For Grade 4, cixutumumab therapy should be withheld until the patient is asymptomatic, glucose is consistently (in the opinion of the investigator) below 300 mg/dL, and the patient is on a stable insulin regimen. When treatment resumes, the cixutumumab dose should be reduced by 20%.

8.12 Dose Reductions

Patients will undergo dose reduction, if necessary, according to the following guidelines.

Table 9.2: Cixutumumab Dose Reduction Guidelines

Starting Dose	Level -1	Level -2
20 mg/kg q 3 weeks	Decrease starting dose by 20%	Decrease Level -1 by an additional 20%

Hematologic Toxicity

For Grades 1-2 hematologic toxicity, no dose modification is required. For Grade 3 toxicity not adequately controlled with appropriate supportive care (including hematopoietic growth factors, if indicated), withhold dose until toxicity ≤ Grade 2, or has returned to pretreatment baseline; at this time, dose should be reduced by 20% and treatment resumed. In the case of Grade 4 hematologic toxicity associated with cixutumumab, withhold dose until toxicity is ≤ Grade 2, then reduce dose by two levels and resume treatment.

Non-Hematologic Toxicity

PLEASE NOTE: Specific guidelines for dose reduction in patients who experience infusion reactions or hyperglycemia while receiving treatment with cixutumumab may be found in Section 8.10 and 8.11.

General guidelines for dose modification for other non-hematologic toxicities related to cixutumumab are as follows:

- For Grade 1, no dose modification is required.
- Patients with any Grade 2 cixutumumab-related clinical adverse event may, at the investigator s discretion, continue to receive cixutumumab per protocol provided that the event does not pose a serious health risk or is easily treated; if necessary, the patients may be dose reduced up to two times during the study.
- For a Grade 3 clinical toxicity not adequately controlled with appropriate supportive care, withhold dose until toxicity is ≤ Grade 1 or has returned to pretreatment baseline, and then resume treatment with a dose reduction of one level. If toxicity recurs after therapy resumes, a second dose reduction is permitted; if more than two toxicity-related cixutumumab dose reductions are required, treatment with this agent will be permanently discontinued.
- For Grade 4 clinical toxicity, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment with dose reduced by two levels. If toxicity recurs after therapy resumes, cixutumumab treatment will be discontinued.
- If treatment with cixutumumab is withheld for more than 3 continuous weeks from the next scheduled dose due to a treatment-related toxicity that does not resolve, the patient will be withdrawn from the study, unless the Investigator feels that the patient should

remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study therapy.

- Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE Version 4.0 Grade 1-2 adverse events should not have dose reductions related to the persistence or mild worsening of these symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator. Asymptomatic Grade 3-4 laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined to be clinically significant by the investigator.

9 STUDY CONDUCT

9.1 Patient Accrual and Patient Identification

Patients will be enrolled at MD Anderson Cancer Center only. A total of 225 patients will be equally randomized into one of the three treatment arms. An accrual of rate of 5 patients per month is expected. The projected trial duration is 4 years with 30 months of accrual and an additional 18 months of follow up period. A 3-digit accession number will be assigned to each patient as the master ID. A password protected secured file will be created to store the cross reference list between the master ID and confidential patient information such as name, birth date, hospital number, and social security number (if available), etc. Master ID will be used throughout the trial and in database for patient identification purpose. Confidential patient information will be used only when it is necessary such as in patient care setting.

Note: Patients must be enrolled and have protocol assessments completed at the MD Anderson Cancer Center main institution. Labs can be completed at the RCCs if appropriate.

9.2 Patient Enrollment

Patients must be consented prior to any study-related procedures being performed. Once patients are consented for the BATTLE-FL protocol and appropriate procedures are completed, they will be assigned into one of the treatment arms.

9.3 Replacement of Patients

Participants who withdraw from the study prior to completion of the study treatments for reasons other than serious adverse events, unacceptable toxicity or progressive disease will be defined as dropouts and will be replaced. Replacement participants will be assigned the next sequential number.

9.4 Screening Procedures

All patients must undergo pre-treatment evaluations within 4 weeks (unless otherwise specified) prior to initiating therapy. Pre-treatment evaluations will be used to determine the patient s study eligibility. Patients must sign an informed consent form prior to undergoing protocol-specific evaluations and prior to receiving treatment.

1. Signed informed consent
2. Medical history including smoking history (duration and intensity)
3. Full physical exam: including height, weight, and ECOG performance status assessment. Vital signs including pulse, blood pressure, temperature
4. Serum chemistry and electrolytes to include: total protein, uric acid, blood urea nitrogen (BUN), creatinine, LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium chloride, magnesium, calcium, albumin, glucose, CO_2, and HbA1c done within 4 weeks prior to treatment.
5. Hematology to include: CBC with automated differential and platelet count
6. Brain MRI/CT
7. Chest x-ray within 4 weeks of starting treatment
8. CT or MRI scans of chest within 4 weeks of starting treatment.
9. Biopsy of tumor for biomarker evaluation to include diagnostic fine needle aspiration (FNA) and core needle biopsies (CNB) (See Appendix C) Please Note: In some instances (i.e. local irradiation for the management of tumor-related symptoms, surgical procedure,

etc.), the length of time from the baseline biopsy and the initiation of study treatment may exceed the 28 day window stated above to allow adequate recovery of study participants prior to study therapy.

10. Serum biomarker evaluation (optional)
11. Pregnancy Test to be performed within 72 hours of dosing for women of childbearing potential. Serum and/or urine may be used in the event a 2nd pregnancy test is required due to slightly elevated HCG levels above normal. If a 3rd pregnancy test is required, a Gynecological consult will be required to satisfy inclusion criteria.
12. Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1,000 mg for patient enrollment onto the Bevacizumab arm. The urine protein used to calculate the UPC ratio must be obtained within 4 weeks prior to randomization.
13. Electrocardiogram
14. Diagnostic archival tumor sample (optional)
15. Audiometry assessment (cixutumumab arm only)
16. PT/INR within 4 weeks of starting treatment
17. AE Assessment
18. Concomitant Medication Assessment

9.4.1 Tumor Tissue Biopsy

Tissue biopsies (FNA and CNB) will be performed at prior to randomization and at the end of 2 cycles of treatment (optional) while participating in the study. In addition, archival diagnostic tissue samples (optional) will also be collected for biomarker analysis. Tissue may be obtained via Image-guided core biopsy or other core biopsy methods to available tissue (i.e. subcutaneous or cutaneous or lymph node disease).

Image-guided core biopsy: Study patients will undergo an image-guided core biopsy after being NPO in regard to solid food for a minimum of six hours and NPO for oral medications and small amounts of liquids for two hours prior to the procedure. The participant will be monitored with continuous electro-cardiographic, respiratory, and oximetric monitoring, with intermittent blood pressure monitoring. At least 2 core biopsies of the tumor will be

performed (more if can be safely performed). Specimens will be used to analyze biomarkers, genomic, proteomic, and other biomarker studies.

9.4.1.1 Exploratory tumor biomarkers

Pre-treatment tumor tissue will be analyzed for potential markers associated with clinical outcome or therapeutic response to the different treatment arms as described below. In addition, optional biopsies taken after two cycles of treatment will be compared to baseline tumor biopsies to assess biomarker modulation and its relationship to treatment response. These markers will include multiplex profiling of DNA mutations; DNA copy number variations; gene expression profiling; protein markers; and other potential molecular markers that may be relevant. These markers are detailed in Appendix G.

9.4.2 Serologies

Optional blood samples will be collected at baseline, end of Cycle 2 and end of study while participating in the study. Blood will be collected and either immediately analyzed or stored frozen until ready for analysis. Cells from blood, including circulating tumor cells (CTCs) will be quantitated and isolated by antibody-based capture methods using tumor antigens including Ep-CAM. Isolated cells will be assessed for markers from relevant pathways through analysis of DNA (mutations, copy number variations, and single nucleotide polymorphisms (SNPs)), gene expression, and protein. Proteomic studies of circulating proteins including cytokines and angiogenic factors (CAFs) will also be conducted. Additional details of these analyses are provided in Appendix G.

9.5 Study Treatment Procedures

All study evaluations and/or clinic visits may be conducted within – 5 days of the date specified in the protocol.

1. A full physical exam including weight, ECOG performance status assessment, vital signs including pulse, blood pressure, and temperature will be conducted Day 1 of each cycle.
2. Tumor tissue biopsy after cycle 2 (optional).
3. Serum chemistry and electrolytes to include: total protein, uric acid, blood urea nitrogen (BUN), creatinine, LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin,

sodium, potassium chloride, magnesium, calcium, albumin, glucose, and CO_2 each cycle. (HbA1c on Day 1 of each cycle for Cixutumumab arm only; and Cetuximab arm only weekly (– 1 day) labs (Days 8 and 15 of each cycle) include only magnesium).

4. Hematology to include: CBC with automated differential and platelet count each cycle.
5. Serum samples for biomarkers will be collected at end of cycle 2 (optional).
6. Brain MRI/CT (if clinically indicated).
7. Chest X-ray at the completion of cycle 2 and then every 2 cycles.
8. CT/MRI of the chest (and abdomen if indicated) at the completion of cycle 2 and then every 2 cycles.
9. Adverse event assessment.
10. Concomitant medication assessment.
11. PT/INR (within 4 weeks of starting treatment and per standard of care if patient is on warfarin or other anticoagulant).
12. Urinalysis and UPC ratio. Patients on the Bevacizumab arm will undergo a urine analysis and a UPC ratio prior to treatment of every cycle.

** Patients who have been previously randomized to the cetuximab arm will have magnesium levels drawn weekly (Day 8 and 15 of each cycle) prior to cetuximab infusion.

9.6 End of Therapy Procedures

End of therapy evaluations will be determined as:

- Progression of disease, or symptomatic deterioration,
- Unacceptable toxicity,
- Treatment delay greater than 42 days,
- The patient may withdraw from the study at any time for any reason,
- Treating physician and/or Principal Investigator discretion.

End of therapy evaluations will include a physical examination, hematology, and serum chemistry profiles, PT/INR (if indicated), urinalysis and UPC (if clinically indicated), imaging

studies (if indicated), audiometry assessment (cixutumumab arm only) and electrocardiogram. An optional serum sample will be collected at end of study visit.

9.7 Follow-up Procedures

Subjects withdrawn from the study will be followed for survival. The reason for withdrawal and date of the discontinuation will be obtained. If a subject is non-compliant or is lost to follow-up, the research nurse or his/her designee will make three attempts to call the subject over a period of one month. Attempts to contact will be documented. If the research nurse or his/her designee is unable to make contact with either the subject or a family member after three phone calls, then a letter will be sent to the subject s last known address.

Patients will have a follow-up evaluation performed 4 weeks (– 5 days) from the date of discontinuation to assess for resolution of any toxicities. This evaluation may be a visit or phone contact by the research personnel. Patients will be followed every three months after study discontinuation for up to 3 years.

9.8 Evaluation Criteria

Tumor Response

The initial tumor response (unidimensionally measured disease) will be assessed by a Radiology collaborator at the completion of two cycles of therapy and will be compared to pre-treatment values. Subsequent tumor response for patients receiving therapy will be assessed following the completion of every two cycles of therapy. Responses will be based on a comparison to the pre-treatment tumor evaluation. All patients who have received treatment with at least one cycle of treatment will be considered evaluable for response. Imaging and diagnostic studies of measurable and evaluable tumors should be repeated following every two cycles of therapy. (See Appendix B) The tumor measurements will be documented on study specific source documents and in the electronic database.

NOTE: The pre-treatment and all subsequent imaging and diagnostic studies should be obtained from the same source, for example, CT scan or MRI. Each response parameter will be reported independently. Responses are to be scored based on measurable and nonmeasurable criteria and overall response to therapy.

10 SAFETY DATA COLLECTION, RECORDING AND REPORTING

Safety assessments will consist of monitoring and recording adverse events following Table 10, the Recommended Adverse Event Recording Guidelines for Phase II. These safety assessments should be performed within – 5 days of the scheduled day of cycle visit. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 grading system.

10.1 Adverse events

Information about adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded. Documentation of the adverse events includes: grade, start/stop dates, attribution, action taken, no action taken, possible interruption, discontinuation (temporarily or permanently), concomitant medications, non-drug therapy, hospitalization/prolonged hospitalization), and whether it constitutes a serious adverse event (SAE). Adverse events will be documented in the patient s medical record. Based upon best clinical judgment, the Principal Investigator will assign attribution of adverse events to each study agent separately.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results will be documented. Based upon best clinical judgment, the investigator will determine if the value is clinically significant.

Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators Brochure or will be communicated between IB updates in the form

of Investigator Notifications. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

10.2 Serious Adverse Event Reporting (SAE)

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:

- Death
- 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
- Persistent or significant disability/incapacity a substantial disruption of a person s ability to conduct normal life functions
- 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 patient 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 MDACC IND Office.

10.3 Reporting Procedures for Adverse Events

All events 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 IND Office, regardless of attribution (within 5 working days of knowledge of the event). Adverse event recording will follow Phase II recording guidelines from the IND Office.

Table 10. Recommended Adverse Event Recording Guidelines for Phase II					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	N/A	N/A	Yes	Yes	Yes
Unlikely	N/A	N/A	Yes	Yes	Yes
Possible	Yes	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	Yes	Yes
Definitive	Yes	Yes	Yes	Yes	Yes

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 IND Office. The MDACC Internal SAE Report Form for Prompt Reporting will be used for reporting to IND Office. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test 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 IND Office. This may include the development of a secondary malignancy.

10.3.1 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 that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the MDACC IND Office guidelines, and Institutional Review Board policy.

10.3.2 Investigator Communication with Eli Lilly and Company

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.

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.

10.3.3 Investigator Communication regarding Cixutumumab Serious Adverse Events

All serious adverse events related to Cixutumumab must be reported, by FAX to Global Product Safety for Eli Lilly. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must also be reported. Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the ImClone study drug (or therapy) is suspected.

This unified organization supports the entire oncology portfolio, inclusive of Lilly and ImClone development projects and marketed products, and allows us to implement a single quality system and procedures to ensure compliance in the collection, processing, analysis, and reporting of adverse event data, and effective characterization and communication of the safety profiles of our developmental and marketed compound.

10.3.4 Exclusions to SAE Reporting Requirements

The following are not considered SAEs:

- Pre-planned or elective hospitalization including social and/or convenience situations (e.g., respite care).
- SAEs that occur within the 30-day post study treatment window but related to subsequent therapies.
- Patients who have completed study treatment or who terminate from study and then undergo subsequent alternate therapies (such as chemotherapy, RT, biotherapy, immunotherapy, etc) during the 30-day safety period and experience an SAE specifically related to the administration of the alternate therapy will not have those events reported as AEs. This exclusion will include elective hospitalizations necessary for the administration of such therapies, as well as any specific adverse effect known to be due to the alternate therapy.

10.3.5 Reporting of Patient Death to MDACC IRB

Any unexpected, and possibly, probably, or definitely related to study intervention death that occurs during and within 30 days after last day of active study intervention must be reported to the IRB within 24 hours by telephone. A full written report must follow as soon as possible.

10.4 Adverse event reporting on Case Report Form

All adverse events, regardless of severity or causality, will be documented in the medical record and entered into the electronic case report form (PDMS/CORe) Adverse event onset and resolution dates, severity/grade, outcome, any action taken due to an AE, and the relationship to the investigational study agent(s) will be documented in the medical record. Known adverse events relating to the underlying clinical condition will be reported in the electronic case report form (PDMS/CORe).

10.5 Reproductive Risks and Reporting of Pregnancy

Investigational drugs should not be used during pregnancy or lactation. Pre-menopausal women of childbearing potential will follow an approved, medically accepted birth control regimen (e.g., abstinence, birth control pills, intrauterine device, condoms, and implants) or agree to abstain from heterosexual intercourse while participating in the study and for six (6) months following the last dose of the investigational agents. Men who are not surgically sterile must agree to practice a medically acceptable contraceptive regimen including barrier methods from study treatment initiation until at least six (6) months after the last administration of the investigational agents.

All women of childbearing potential MUST have a negative pregnancy test within 72 hours prior to receiving the investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study. It is not known whether the investigational drugs can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of these agents in pregnant women. Results of animal studies indicate that investigational agents may cross the placenta and is found in fetal plasma. During the course of the trial, all patients of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the

treating physician. If a female patient or the treating physician suspects that the female patient may be pregnant prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study. Throughout the entire pregnancy, additional contact should be made with the patient and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 4 weeks. If a male patient is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of eight weeks. Upon live-birth delivery, the minimum information that should be collected includes date of birth, length of pregnancy, sex of infant, major and minor anomalies identified at birth. Outcomes can be obtained via mailed questionnaires, maternal interviews, medical record abstraction, or a combination of these methods. All serious adverse event reports relating to the pregnancy, including spontaneous abortion, elective abortion and congenital anomalies, should be forwarded to the FDA & supporting companies. It is not known whether the investigational agents are excreted in human milk. All of these agents can have serious risks to infants including mutagencity and carcinogenicity, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Any pregnancy that occurs during study participation should be reported to IND Office. To ensure patient safety each pregnancy must also be reported to Eli Lilly Global Product Safety. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications

11 STATISTICAL DESIGN AND DATA ANALYSIS CONSIDERATIONS

11.1 Sample Size and Design

This study is a randomized phase II trial. Randomization is used to achieve patient comparability across the arms. Patients will be equally randomized into one of the three treatment arms with equal number of patients within each arm by using the block randomization with a block size of multiples of 3. To achieve the statistical objective of this trial, our goal is to enroll 225 eligible and evaluable patients. For the interim and final analysis, we will use the information accrued to the trial per protocol. For patients who have actionable molecular aberration and are removed from the study, the data acquired prior to the removal of study will be used for analysis as planned. Additional information acquired outside the trial can also be used to supplement the secondary analysis.

The primary endpoint of the study is progression free survival (PFS), which is defined as time from randomization to disease progression or death or last follow-up whichever occurred first. Disease progression and death are events.

The projected trial duration is 5 years with 48 months of accrual (accrual rate ~5/per month) and an additional 12 months of follow up. The expected censoring rate at the end of trial is 10%, which includes patients who are lost-to-follow-up. An interim analysis is planned when half of the expected events, i.e., 101 progression deaths are observed.

We assume that, after the initial screening procedure, there will be 10 biomarkers in the full model. Some of the biomarkers could be constructed by forming composite scores of several biomarkers. We further assume that there are 3 important biomarkers in the true model, with biomarker 1 being prognostic and biomarkers 2, and 3 being predictive for experimental arms 2, and 3, respectively. For each biomarker, we assume the percentage of patients with positive biomarker is 50%. Based on our preliminary data, PFS is assumed to be exponentially distributed with a median of 4 months under the null hypothesis. The true PFS by treatment and biomarker status under the null and the alternative hypotheses are shown in Table 11.1.

Table 11.1. Median progression free survival in month by treatment and biomarker status under the null and the alternative hypotheses given the assumption in the first 4 rows.

Biomarker Status	Null Hypothesis				Alternative Hypothesis			
(M1, M2, M3)	Trt 1	Trt 2	Trt 3		Trt 1	Trt 2	Trt 3	
(0,0,0)	4	4	4		4	4	4	
(1,0,0)	4	4	4		6	6	6	
(0,1,0)	4	4	4		4	12	4	
(0,0,1)	4	4	4		4	4	12	
(0, 1, 1)	4	4	4		4	12	12	
(1,1,0)	4	4	4		6	18	6	
(1,0,1)	4	4	4		6	6	18	
(1,1,1)	4	4	4		6	18	18	

Based on the assumptions given in Table 11.1, simulated survival times were generated from an exponential distribution with following hazard rate for Treatment *j*:

$$\lambda_j = \lambda_0 \exp\left[\beta_j T_j + \sum_{k=1}^{K} \gamma_k M_k + \sum_{k=1}^{K} \eta_{jk} T_j M_k \right], \qquad (1)$$

where T_j is the treatment indicator for Arm *j*, *j*=2, 3 (with Arm 1 as the reference/control group), and M_k is the marker positive indicator for Marker *k*, *k*=1, 2, *K*.

11.2 Toxicity Monitoring

Unacceptable toxicities are defined as grade III or higher non-hematologic toxicities, grade IV hematologic toxicities or treatment related death. With respect to the stopping boundaries, the time period in which toxicity events will be counted is one (1) cycle of treatment. We will monitor toxicity for each arm separately. Denote the probability of unacceptable toxicity as P_tox E for each arm. The intolerable level of toxicities is defined as Probability (P_tox_E > 0.2) > 0.9, i.e., the probability of unacceptable toxicity is high as compared to historical data. We will start to monitor the toxicity in each arm after a total of 10 patients (per arm) are treated. With a prior of beta (200, 800) for historical toxicity rate which has a mean toxicity rate of 20% with very small variance, and a non-informative beta (0.5, 0.5) prior for P_tox_E, the stopping boundaries for toxicity on or after the 10^{th} patients treated are to have toxicities greater than or equal to a/b where a is the number of unacceptable toxicities and b is

the total number of patients treated. Using Multc_Lean version 2, the stopping conditions are as follows:

# Patients	Stop the trial if there are this many toxicities total:
5	Never stop with this many patients
10	4-10
15	6-15
20	7-20
25	8-25
30	9-30
35	11-35
40	12-40
45	13-45
50	14-50
55	15-55
60	17-60
65	18-65
70	19-70
75	Always stop with this many patients

The operating characteristics are shown in the following table. If the true toxicity rate is 30% for a particular arm, the probability of early stop that arm is 86%, and the averaged patients treated is 31.

True Prob(Toxicity)	Probability of Early Stopping	Average patients treated
0.05	0.001	75
0.10	0.021	74
0.20	0.285	60
0.30	0.857	31

11.3 Interim Futility Analysis

At interim analysis, the following reduced model

$$\lambda_j = \lambda_0 \exp\left[\beta_j T_j\right] \quad (2)$$

will be used to make inference on the marginal treatment effects for both experimental treatments, j=2, 3, where λ_0 is the baseline hazard rate of the control arm (note the actual value of λ_0 is the same as the λ_0 in equation (1)), and T_2, and T_3 are indicators for the 2 experimental treatments respectively. If the standardized coefficients z of T2 or T3 (β_1, or β_2 divided by their corresponding standard deviation) is less than a cutoff value of -1.05, we will declare the corresponding treatment is not promising and suspend randomizing patients into that arm. If only one experimental arm is suspended, the remaining patients will be equally randomized between the remaining 2 arms. If none of the experimental treatments are promising, then the whole trial will be stopped. The early stopping probabilities and the mean sample sizes under the null and alternative hypotheses are shown in Table 11.2.

Table 11.2. Early stopping probabilities of each experimental arm and all arms at interim analysis when half of the expected death events 101 are observed.

z=-1.05	Trt 2	Trt 3	Both Experimental Arms are Stopped	Mean Sample Size
Null hypothesis	0.834	0.849	0.75	152
Alternative hypothesis	0.078	0.079	0.022	223

Naïve Frequentist power calculation for prognostic and predictive biomarkers using nQuery

We assume that the trial duration is 5 years with 48 months of accrual (accrual rate ~5/per month) and an additional 12 months of follow up period, and 10% of dropout rate. We further assume that the percentage of patients with positive biomarker is 50%. Given the parameters in

table 11.1, we can compute the median PFS for any combination of the true markers and treatments under the alternative hypothesis (Table 11.3).

Table 11.3. Marginal median PFS for the treatment by marker status according to table 1, assuming each of the 4 top cells of each column accounts for 25% of the patients under the alternative hypothesis.

M1	(M2,/M3)	Median PFS for the experimental arms (arm 2 or 3)	Median PFS for the control arm (arm 1)	Note
0	**0**	4	4	
1	**0**	6	6	
0	**1**	12	4	
1	**1**	18	6	
0/1	**0**	5	5	Trt * Predictive marker (-) marginal
0/1	**1**	15	5	Trt *Predictive marker (+) marginal
0	**0/1**	8	4	Trt *Prognostic marker (-) marginal
1	**0/1**	12	6	Trt * Prognostic marker (+) marginal
0/1	**0/1**	10	5	Treat marginal

Note: Overall prognostic marker (-): (8+8+4)/3=6.67 months; Overall prognostic marker (+): (12+12+6)/3=10.5 months.

Assuming that there is a prognostic marker and a predictive marker for each experimental arm (under the alternative hypothesis), a sample size of 75 patients (approximate 37 predictive marker positive vs. 37 maker negative) will achieve 91% power to detect the improvement of median PFS from 5 months (50% prognostic positive) to 15 months in biomarker positive subgroups with a one-sided 5% type I error rate based on a two group test of equal exponential survival with accrual rate and dropout rate using nQuery 7 (Table 11.4).

Table 11.4. Power for comparing marker positive vs. marker negative within each experimental treatment arm.

	Scenario 1 (15 vs. 5 mon)	Scenario 2 (15 vs. 5 mon)	Scenario 3 (15 vs. 5 mon)
Test significance level, α	0.100	0.050	0.050
1 or 2 sided test?	1	1	1
Length of accrual period	48.00	48.00	48.00
Maximum length of followup	60.00	60.00	60.00
Common exponential dropout rate, d	0.1	0.1	0.15
Group 1 exponential parameter, λ1	0.1386	0.1386	0.1386
Group 2 exponential parameter, λ2	0.0462	0.0462	0.0462
Hazard ratio, h=λ1/ λ2	3	3	3
Power (%)	95	91	84
n per group	37	37	37
Total number of events required, E	30	30	23

Note: Lambda.0= ln(2)/5 = 0.1386294; Lambda.1 ln(2)/15 = 0.04620981; Lambda.1 ln(2)/10 = 0.0693; Lambda.1 ln(2)/6.67 = 0.1039

Similarly, with a sample size of 75 patients per arm, we will have 89% power to detect the improvement of median PFS from 5 months to 10 months in each of the experimental arm as compared to the control arm with a one-sided 5% type I error rate (11.5).

Table 11.5. Power for comparing the experimental arms (median PFS=10 months) to the control arm (median PFS=5month).

	Scenario 1 (10 vs. 5 mon)	Scenario 2 (10 vs. 5 mon)
Test significance level, α	0.100	0.050
1 or 2 sided test?	1	1
Length of accrual period	48.00	48.00
Maximum length of followup	60.00	60.00
Common exponential dropout rate, d	0.1	0.1
Group 1 exponential parameter, λ1	0.1386	0.1386
Group 2 exponential parameter, λ2	0.0693	0.0693
Hazard ratio, h=λ1/ λ2	2	2
Power (%)	94	89
n per group	75	75
Total number of events required, E	71	71

Note: Lambda.0= ln(2)/5 = 0.1386294; Lambda.1 ln(2)/15 = 0.04620981; Lambda.1 ln(2)/10 = 0.0693; Lambda.1 ln(2)/6.67 = 0.1039

With an overall sample size of 225 patients (approximate 112 prognostic marker positive as 112 prognostic marker negative), we will have 77% power to detect the improvement of

median PFS from 6.67 months to 10 months in the prognostic marker positive subgroup compared to the marker negative subgroup with a one-sided 10% type I error rate (11.6).

Table 11.6. Power for comparing overall prognostic marker positive vs. negative for all patients.

	Scenario 1 (10 month vs. 6.67 month)	Scenario 2 (10 month vs. 6.67 month)
Test significance level, α	0.100	0.100
1 or 2 sided test?	1	1
Length of accrual period	48.00	48.00
Maximum length of followup	60.00	60.00
Common exponential dropout rate, d	0.1000	0.0500
Group 1 exponential parameter, $\lambda 1$	0.0693	0.0693
Group 2 exponential parameter, $\lambda 2$	0.1039	0.1039
Hazard ratio, h=$\lambda 1$ /$\lambda 2$	0.667	0.667
Power (%)	77	85
n per group	112	112
Total number of events required, E	100	135

Note: Lambda.0= ln(2)/5 = 0.1386294; Lambda.1 ln(2)/15 = 0.04620981; Lambda.1 ln(2)/10 = 0.0693; Lambda.1 ln(2)/6.67 = 0.1039

Power calculation based on simulations and using Cox proportional hazards model

We simulated survival data based on the parameters in Table 11.1. We conservatively estimate power based on 90% of the total accrual (i.e. up front exclude the 10% of lost-to-follow up patients assuming that they contain no information). We would declare that an experimental arm is positive if the standardized coefficients of T2 or T3 of ($\beta 1$, or $\beta 2$ divided by their standard deviation is less than a cutoff value z of -1.64, the power of comparing the experimental arms to the control based on the reduced model (Model (2)) is shown in Table 11.7. With the sample size we proposed, we will achieve 93-94% of power to declare positive of the experimental arms with 4-6% of type I error rate.

Table 11.7. Power for comparing the experimental arms to the control arm at the end of the trial based on simulations and Cox proportional hazards model.

z=-1.64	Trt 2	Trt 3
Null hypothesis	0.055	0.045
Alternative hypothesis	0.93	0.94

11.4 Final Analysis

At the end of the trial, all existing data will be subjected to a variable selection procedure to identify potentially important biomarkers. We assume that, after screening, there will be pool of 10 biomarkers, including 3 truly important biomarkers and 7 unimportant biomarkers. Based on our model parameterization, the prognostic effect will be characterized by a large biomarker main effect (γ_k), and predictive effect will be characterized by a large biomarker-treatment interaction term (η_{jk}). A biomarker will be deemed as being important if it has either a prognostic effect or a predictive effect. To facilitate the identification of prognostic and predictive effects, we apply the least absolute shrinkage and selection operator (Lasso) method and implement the biomarker selection procedure through a Bayesian Lasso strategy. Laplace prior is used in Bayesian Lasso for covariates effects. Laplace prior can shrink covariates estimation towards zero, and smaller covariate effects will be penalized more. Therefore, Bayesian Lasso can result with good estimation and variable selection simultaneously (Park and Casella 2008). In order to obtain more consistent estimates for the model parameters, we use a Bayesian version of the adaptive Lasso (Zou 2006) to provide variable selection.

Let S be the set of biomarkers, the prior of $\{\theta_k : k \in S\}$ in the adaptive Lasso of variable selection is $\pi(\theta_k \mid \lambda) \propto \exp\left(-\lambda \frac{|\theta_k|}{|\tilde{\theta}_k^{LS}|}\right)$, where θ_k is a generic representation of either the biomarker main effect or the biomarker-treatment interaction and $\tilde{\theta}_k^{LS}$ is the least square estimation of the parameter without regularization. A variable will be selected if empirical

posterior probability of the coefficient being less than 0 is greater than 0.9. The selections of cut off value can be adjusted to achieve desirable type I error rate and power. The results for variable selection are shown in Table 11.8. The predictive biomarker can be correctly identified with >95% power under the alternative hypothesis, while the selection probability of the unimportant biomarkers are controlled at about 7%. The prognostic biomarker can be correctly identified with 72% power under the alternative hypothesis.

Table 11.8. Variable selection probabilities of under different scenarios. The mean selection probability of null case is controlled at 7%. Nonzero parameters are highlighted. A variable is selected if Prob (beta <0|data) >0.9.

		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Null Hypothesis	Biomarker Main Effect	0.069	0.07	0.079	0.071	0.06	0.068	0.084	0.075	0.075	0.051
	Biomarker:Trt2	0.065	0.071	0.067	0.083	0.084	0.072	0.069	0.079	0.075	0.063
	Biomarker:Trt3	0.081	0.07	0.079	0.083	0.063	0.075	0.093	0.075	0.071	0.068
Alternative Hypothesis	Biomarker Main Effect	**0.724**	0.114	0.101	0.082	0.068	0.076	0.085	0.075	0.088	0.065
	Biomarker:Trt2	0.116	**0.966**	0.072	0.083	0.093	0.081	0.086	0.094	0.081	0.077
	Biomarker:Trt3	0.132	0.072	**0.975**	0.091	0.072	0.072	0.085	0.077	0.084	0.074

12 PUBLICATION STATEMENT

Data will be reviewed by the collaborating biostatistician prior to publication. Participating sponsors will have 30 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 10-15 days to review all abstracts.

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Appendix A: ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

We will also report response as a continuous variable, as % change in tumor size from baseline.

Definitions

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable if they have increased in size since completion of radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be

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

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

Methods for Evaluation of Measurable Disease

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

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

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

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

Tumor biomarkers Tumor biomarkers will not be used to assess response.

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor biomarker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor biomarkers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor biomarker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

Progression-free survival will be defined as the duration of time from initiation of study drug until death, progression of tumor by RECIST 1.1 criteria, or for worsening of tumor that did not meet RECIST 1.1 criteria but that did require discontinuation of therapy, whichever occurs first.

Appendix C: Pathology Tissue Processing

Tissue Collection and Processing

For patient with existing tumor tissue, the sample will be deemed adequate if the sample is a Core Needle Biopsy (CNB) or a surgical specimen (Fresh or FFPE). For patients without adequate tissue may undergo a biopsy as part of the study. The types of tumor tissue that will be collected from the patients are:

1) fresh tumor CNB samples; or
2) resection from the original biopsy site or surgical resection will be obtained as part of the standard of care diagnostic workup; or
3) archival diagnostic biopsy samples for patients with tumor diagnostic workout that may have taken place before initiation of any systemic treatment will be obtained.

In addition to the fresh CNB, FNA samples may be obtained for assessing the quality of the CNB specimens. Archival tissue will be used to test for biomarker evaluations for EGFR Mutation and ALK fusions. Additional available tissue may be used for testing for other molecular aberrations, IHC analyses, expression profiling, FISH analyses for DNA copy number information and whole exome or whole genome deep sequencing.

Tumor core biopsies before (baseline) and after (optional, two months) targeted therapy will be obtained by Interventional Radiologists. The fresh CNB samples will be collected by interventional radiologists, who will take 4 or 5 cores that should specimens 1 mm in diameter and 1.2 1.8 cm long (1.5 cm on average). The fresh CNB tissue will be collected from the IR suite or operating room. The specimens will be divided in the collection site in 2 types: 1) molecular diagnostic, at least one tissue core; and, 2) research the remaining tissue cores. The molecular diagnostic tissue sample will be kept always in the chain of custody of the MDACC Pathology Department and the MMDL, while the research specimen will be handled by Dr. Wistuba s lab research personnel. The FNA obtained at the time of the CNB collection, and the archival diagnostic biopsies will be collected from the file of the MDACC Pathology Department or outside institutions by Dr. Wistuba s lab personnel.

Appendix D: Clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A

Substrates (competitive inhibition)

Antibiotics:
clarithromycin*
erythromycin
telithromycin*

Anti-arrhythmics:
quinidine

Benzodiazepines:
alprazolam
diazepam
midazolam
triazolam

Immune Modulators:
cyclosporine
tacrolimus (FK506)

HIV Protease Inhibitors:
indinavir*
ritonavir*
saquinavir*

Prokinetic:
cisapride

Antihistamines:
astemizole
chlorpheniramine

Calcium Channel Blockers:
amlodipine
diltiazem
felodipine
nifedipine
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors:
cerivastatin
lovastatin
simvastatin

Miscellaneous:
aprepitant
aripiprazole
buspirone
gleevac*
haloperidol
methadone
pimozide
quinine
sildenafil
tamoxifen
trazodone
vincristine

Inducers

Carbamazepine
Phenobarbital
Phenytoin*
Rifabutin*
Rifampin*
St John s wort
Troglitazone

Inhibitors

Amiodarone
Cimetidine
Clarithromycin
Delaviridine
Diltiazem
Erythromycin
Fluvoxamine*
Grapefruit juice
Sevilla Orange
Indinavir
Itraconazole*
Ketoconazole*
Voriconazole
Posaconazole
Mibefradil
Nefazodone*
Nelfinavir*
Troleandomycin
Verapamil

*asterisk denotes strong inhibition/induction
Strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates
Moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.
Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotherapy with a macrolide is desirable in a patient being treated with RAD001
Statins: Atorvastatin and pravastatin may be administered concomitantly with RAD001, since a PK interaction study has shown that there is no relevant PK interaction.
Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104 and[http://www.medicine.iupui.edu/flockhart/clinlist.htm as of February 15, 2007]

Appendix E: New York Heart Association (NYHA) Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix F: Study Procedures

Study Procedures	Screening [L] - 28 to 0	Cycle [a] 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Maintenance Cycles	End of Therapy	Follow-Up 30 day (+/- 5 days)	Long Term Follow-Up Every 3 months (up to 3 years)
Informed Consent	X										
Eligibility Criteria	X										
Physical Examination [b]	X	X			X	X	X	X	X		
Tumor Biopsy	X					X [OP]					
Diagnostic Archival Tumor Sample (Optional)	X										
Disease Assessment [c] (CT or MRI and Chest X-ray)	X					X		X	X		
Hematology (CBC with Diff, Platelets) [d]	X	X [i]			X	X	X	X	X		
Chemistry [d, e, k]	X	X [i]	X[k]	X[k]	X	X	X	X	X		
Urinalysis and UPC [f]	X	X			X	X	X	X	X		
Brain MRI/CT	X					X [m]		X [m]	X [m]		
Electrocardiogram	X								X		
Pregnancy Test [g]	X										
Serum for Biomarker Analysis and Storage (Optional) [h]	X					X			X		
AE/Toxicity Assessment	X	X			X	X	X	X	X	X	
Concomitant Medication(s)	X	X			X	X	X	X	X		
Study Drug Administration		X	X[k]	X[k]	X	X	X	X			
Drug Accountability					X	X	X	X	X		
Subsequent Anticancer Therapy										X	X
Survival Status										X	X
Audiometry Assessment [j]	X								X		

a Cycle = 21 days ± 5 days

b Full physical exam includes height (screening only), weight, blood pressure, pulse, temperature, smoking history (screening only) and ECOG Performance Status.

c After every 2 cycles ± 5 days

d Prior to infusion each cycle

e Including total protein, uric acid, BUN, creatinine, PT/INR (screening: PT/INR within 4 weeks of starting treatment , and if clinically indicated thereafter for preceding cycles), LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium, magnesium, chloride, calcium, albumin, CO^2, glucose and HbA1c (HbA1c on Day 1 of each cycle for Cixutumumab arm only)

f Including routine dipstick measurements, microscopic analysis, and urine protein. Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1,000 mg for patient enrollment onto the Bevacizumab arm. The urine protein used to calculate the UPC ratio must be obtained within 4 weeks prior to randomization. Patients on the Bevacizumab arm will undergo a urine analysis and a UPC ratio prior to treatment of every cycle.

g b-HCG Test and/or urine test to be performed within 72 hours of dosing for women of childbearing potential

h Optional serum samples will be collected at screening, end of Cycle 2 and end of therapy.

i Only performed if previous pre-treatment evaluations are not conducted within 28 days prior to initiating study therapy

j Cixutumumab arm only

k Patients who have been previously randomized to treatment arm Arm 3 carboplatin + pemetrexed in combination with an *EGFR* monoclonal antibody (Cetuximab) will continue with their assigned treatment arm. Cetuximab only is given on a weekly (± 1 day) basis– Weekly labs (Days 8 and 15 of each cycle) include magnesium only.l Please Note: In some instances (i.e. local irradiation for the management of tumor-related symptoms, surgical procedure, etc.), the length of time from the baseline biopsy and the initiation of study treatment may exceed the 28 day window stated above to allow adequate recovery of study participants prior to study therapy.

m After 2 cycles ± 5 days of treatment and every 2 cycles ± 5 days thereafter, if clinically indicated.

APPENDIX G: Biomarker Analyses

Circulating Tumor Cells (CTCs)

Isolation of CTCs and molecular analysis of these CTCs including mutational profiling.

We will be isolating CTCs using methods such as the CTC microfluidic chip previously described (N Engl J Med 2008; 359:366-377). Other methodologies that are not dependent on antibody are also being tested and will be used if their utility and technical performance has been established. The captured cells of interest can be subsequently interrogated through immunohistochemistry (e.g. fluorescent in situ hybridization or FISH) somatic mutation profiling (e.g. Sequenome profiling), SNP profiling, and gene expression analysis with a focus on pathways relevant to NSCLC and drugs under investigation (e.g. EGFR, MEK, PI3K pathways).

Previously we have established that rare circulating cells can be quantitated using frozen peripheral blood mononuclear cells (PBMCs) (Clin Canc Res 2007; 13(9): 2643-50). This permits batched analysis of stored samples. Therefore, we will isolate and freeze PBMCs using methods we have previously described. From each sample, blood will be subjected to gradient separation of mononuclear cells, placed in DMSO-containing freeze media, cooled using a controlled freeze protocol, and stored at -80C until analysis as described above.

Cytokines and Angiogenic Factors (CAFs)

CAF profiling using serum or plasma to detect biomarkers and signatures of response

The availability of multiplexing technologies permits the simultaneous assessment of large numbers of biologically relevant proteins, such as cytokines, angiogenic factors, and receptors, and soluble markers of hypoxia and endothelial damage, using small amounts (i.e., less than one milliliter) of plasma. We refer to the broad assessment of these multiple markers as the CAF (cytokine and angiogenic factor) profile. We and other investigators have studied a number of these circulating biomarkers in peripheral blood and observed that baseline levels , or changes in these factors, may be markers of drug response or the emergence of therapeutic resistance [1-5].

Circulating CAFs will be assessed using established methods as we have previously described [1-5]. A CAF profile (typically 60-70 analytes) of plasma biomarkers will be assessed using a combination of multiplex technology (e.g. Luminex and Searchlight platforms) and enzyme-linked immunosorbent assays (ELISA). Multiplex magnetic bead-based technology enables the simultaneous quantitation of up to 100 analytes. These Luminex based assays contain dyed beads conjugated with monoclonal antibodies specific for a target protein. The antibody-conjugated beads are allowed to react with sample and a secondary, or detection, antibody in a microplate well to form a capture sandwich immunoassay. Multiplex assays can be created by mixing bead sets with different conjugated antibodies to simultaneously test for many analytes in a single sample. The use of this technique has been well documented in the literature and results are comparable to that of ELISA (8-10). Currently up to 50 human cytokines can be analyzed from 3 separate kits using a total volume of less than 1 milliliter. The remainder of analytes will be determined using by validated, enzyme-linked immunosorbent assays (ELISA) assays such as Human Osteopontin (OPN), CA-

9, Collagen IV, sVEGFR2, NGAL; and using the Searchlite multiplex platform. Other analytical platforms will be considered if they are established to have advantages (e.g. lower volume requirements or greater sensitivity). For each plate, the standard curves will be assessed to ensure that the expected assay range was achieved. For each individual sample, the mean concentration is calculated for duplicate samples, and the coefficient of variance % (CV%) is calculated for each of the analytes. If the median CV% is greater than 25%, analysis of the sample was repeated. In our experience, less than 10% of samples require repeat analysis.

Single Nucleotide Polymorphism Analysis. Prior studies have established that germline SNPs in cancer related pathways (e.g. VEGF, VEGFR2) may be markers for therapeutic response [6]. To identify new markers for the treatments in this study we will investigate germline SNPs relevant to the treatment regimens in this study. SNPs will be selected based on several criteria including: previous report of an association with an inflammatory disorder, angiogenesis, lung cancer, or another cancer; minor allele frequency (prioritizing those with frequency of at least 5%); location in the promoter, untranslated region (UTR), or coding region of the gene. The SNPs will be genotyped using standard methods such as SNPlex, a technology developed by Applied Biosystems that enables simultaneous genotyping of up to 48 SNPs in a single tube using an oligonucleotide ligation assay. The assay principle and procedures are detailed in the manufacturer s user guide (PN4360858). As methods for assessing SNPs are rapidly improving we will evaluate and potentially incorporate other available methods for SNP assessment at the time of analysis.

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6. Schneider BP, Wang M, Radovich M, et al: Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. J Clin Oncol 26:4672-8, 2008

APPENDIX H: Blood biomarkers -Collection, processing, and storage of plasma, serum, and peripheral blood mononuclear cells (PMBCs).

Blood sample collection and processing

Collect a total of 56 mL of blood:

Whole Blood --- 2 x 10 mL tubes
1) Collect blood for Circulating Tumor Cells using established laboratory procedures.

Plasma Processing --- 2 x 10 mL "EDTA Vacutainer"
1) Place blood into "EDTA Vacutainer"
2) Mix gently
3) Centrifuge tubes at 1500 RPM x 20 minutes
4) Into each cryovial, place 500 microliters of plasma aliquot and screw cap the vial
5) Appropriately label each vial
6) Place labeled-vials into freezer and note exact location in THNMORDB
7) All samples information will be logged into Tissue Station.

Peripheral Blood Monomuclear Cells (PBMC) Collection and Processing
1) Using two (2) BD Vacutainer sodium citrate "CPT" blood collection tube,
a) The Vacutainer CPT Tube with Sodium Citrate should be at room temperature (18-25° C) and properly labeled for patient identification.
2) Collect blood into the Tube using the standard technique for Vacutainer Brand Blood Collection Tubes
3) After collection, store Tube upright at room temperature until centrifugation. Blood samples should be centrifuged within two hours of blood collection for best results.
4) Centrifuge Tube/blood sample at room temperature (18-25° C) in a horizontal rotor (swing-out head) for a minimum of 20 minutes at 1500 to 1800 RCF (Relative Centrifugal Force).
5) From upper layer, place 500 microliters of plasma aliquots and screw-cap the vial
6) PBMC band, collect cells into cryovial and screw cap the vial (approximately 500 uL)
7) Add equal volume (approximately 500 uL) of freezing media (RPMI-1640+20% DMSO) to sample vial
8) Appropriately label each vial (no patient identifier no specific information will be used)
9) Place labeled-vials into freezer (-80*C) (into specific protocol sample BOX) and note exact location of sample in THNMORDB
10) All sample information will be logged into Tissue Station.