Local Protocol #: TBD

ClinicalTrials.gov Identifier: TBD

TITLE: A Feasibility and Biomarker Study to Evaluate Necitumumab in the Neoadjuvant Setting with Gemcitabine and Cisplatin in Surgically Resectable Squamous Lung Cancer

Coordinating Center: Montefiore Medical Center, Albert Einstein College of Medicine

Co-Principal Investigators:
Missak Haigentz, Jr., M.D.
Morristown Medical Center/Atlantic Health System
Carol G. Simon Cancer Center
100 Madison Avenue, Second Floor
Morristown, NJ 07960
973-971-7960
Fax: 973-397-2901
missak.haigentz@atlantichealth.org

Balazs Halmos, M.D.
Montefiore Medical Center, Albert Einstein College of Medicine
1695 Eastchester Road, 2nd Floor
Bronx, NY 10461
718-405-8404
Fax: 718-405-8433
bahalmos@montefiore.org

Statistician:
Dr. Xiaonan (Nan) Xue
1300 Morris Park Avenue
Belfer Room 1303C
Bronx, NY 10461
(718) 430-2431
Fax: (718) 430-8780
xiaonan.xue@einstein.yu.edu

NCI-Supplied Agent(s): N/A
Other Agent(s): Necitumumab, Eli Lilly; Gemcitabine, commercial; Cisplatin, commercial

Protocol Type / Version # / Version Date: Original / Version #7 / April 21, 2017

SCHEMA

Study Schema

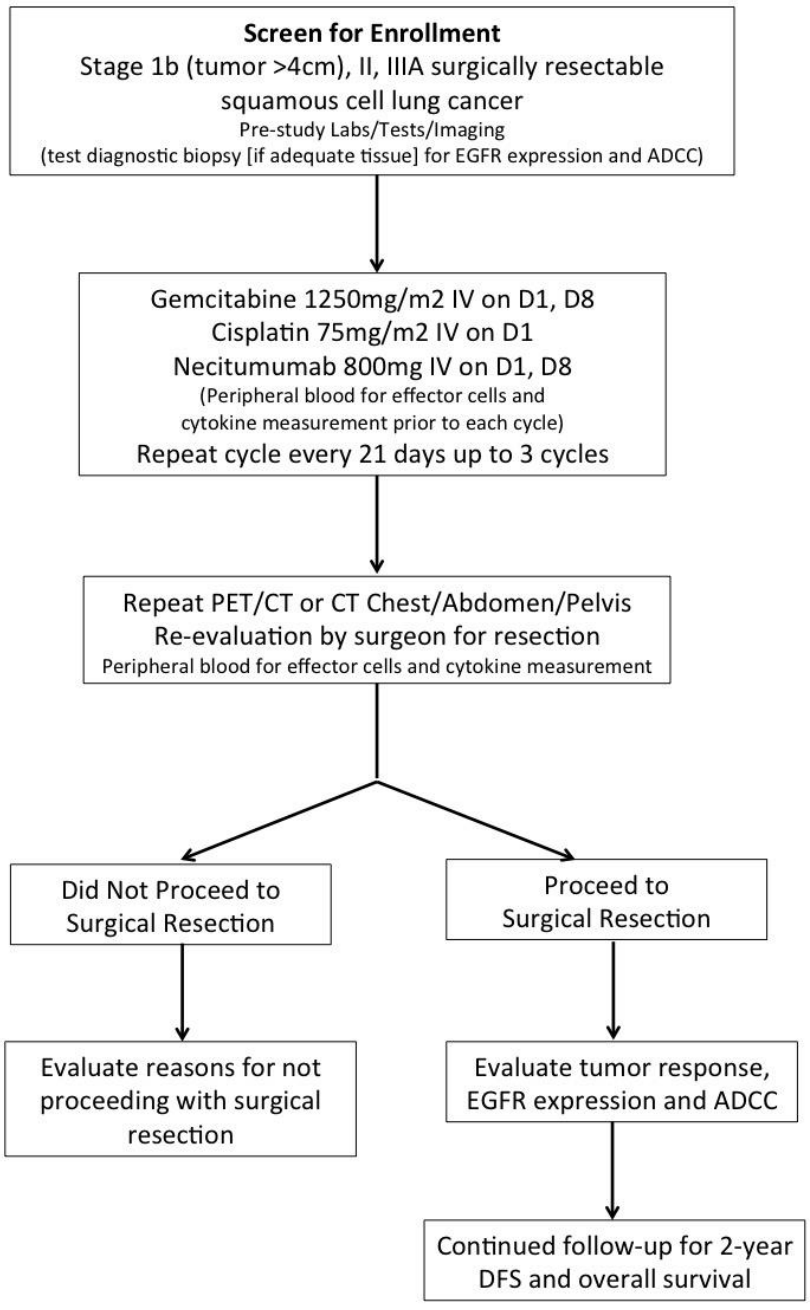


TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To assess the proportion of patients able to proceed to surgery after administering necitumumab in the neoadjuvant setting with gemcitabine and cisplatin in surgically resectable patients with stage IB with tumor size >4cm, II and potentially resectable IIIA squamous cell lung cancer.

1.2 Secondary Objectives

1.2.1 To evaluate the response rate of neoadjuvant chemotherapy with necitumumab, gemcitabine, and cisplatin.

1.2.2 To evaluate the frequency and severity of toxicities in patients while receiving neoadjuvant chemotherapy with necitumumab, gemcitabine and cisplatin.

1.2.3 To evaluate the pathologic complete response (pCR) rate in patients receiving neoadjuvant chemotherapy with necitumumab, gemcitabine, and cisplatin followed by surgical resection.

1.2.4 To determine the 2-year disease-free survival (DFS) in patients receiving neoadjuvant chemotherapy with necitumumab, gemcitabine, and cisplatin followed by surgical resection.

1.2.5 To determine the overall survival at 2 years in patients receiving neoadjuvant chemotherapy with necitumumab, gemcitabine, and cisplatin followed by surgical resection.

1.3 Exploratory Objectives

1.3.1 To evaluate EGFR expression on pre-chemotherapy diagnostic tissue biopsy (if adequate tissue is available) and tissue specimens obtained from post-chemotherapy surgical resection.

1.3.2 To evaluate EGFR gene amplification copy number on pre-chemotherapy diagnostic tissue biopsy (if adequate tissue is available) and tissue specimens obtained from post-chemotherapy surgical resection.

1.3.3 To evaluate markers of antibody-dependent cellular-mediated cytotoxicity (ADCC) on peripheral blood specimens prior to neoadjuvant chemotherapy, during neoadjuvant chemotherapy and following neoadjuvant chemotherapy.

1.3.4 To evaluate markers of ADCC on pre-chemotherapy diagnostic tissue biopsy and tissue specimens obtained from post-chemotherapy surgical resection.

1.3.5 To evaluate tumor infiltrating lymphocytes on resected surgical specimens and compare with historical controls obtained from the Montefiore lung cancer biorepository.

1.3.6 To evaluate necitumumab-binding on tissue specimens obtained from post-chemotherapy surgical resection.

2. BACKGROUND

2.1 Squamous Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung cancer (NSCLC) can be divided into two histological classes: non-squamous and squamous cell carcinoma (SCC). SCC accounts for approximately 25-30% of lung cancer cases.[1] While the treatment of non-squamous cell carcinomas has greatly benefited from the identification of targetable somatic mutations such as EGFR and ALK mutations, the treatment of SCC, until the recent incorporation of immunotherapy, has remained mostly restricted to conventional chemotherapy.

2.2 Neoadjuvant Chemotherapy for NSCLC

Standard treatment for SCC includes platinum-based therapy combined with gemcitabine, vinorelbine or a taxane. The use of neoadjuvant chemotherapy for all histologic classes of NSCLC can also be considered for selected patients based on a meta-analysis including 13 randomized control trials showing that overall survival (OS) was significantly improved in patients receiving neoadjuvant chemotherapy compared to surgery alone (HR = 0.84, 95% CI 0.77-0.92, p=0.0001).[2]

The use of the gemcitabine and cisplatin neoadjuvant chemotherapy regimen in patients with stages IB to IIIA NSCLC was reported by Scagliotti et al. In this study, patients were randomized to receive either three preoperative cycles of gemcitabine and cisplatin every 3 weeks followed by surgery, or surgery alone. In this study, 129 patients were randomly assigned to the chemotherapy plus surgery group, and 127 patients received at least one dose of chemotherapy. Of the 127 patients who received at least one dose of chemotherapy, 110 (87%) of patients proceeded to surgical resection. We use this data as our benchmark to evaluate feasibility of this study regimen. Of the 17 patients who did not proceed to surgical resection, the reasons were: patient decision (3), progression of disease (4), lost to follow-up (2), other causes (7) or no information was available (3). In the surgery alone group, after randomization, 96% (136 of 141) of patients received surgery. Of note, the pathologic complete response rate was reported as 4% in the chemotherapy plus surgery group.[3]

The use of neoadjuvant chemotherapy has several advantages as opposed to administering adjuvant chemotherapy such as increased therapeutic compliance and

ability to treat micrometastatic disease. In addition, neoadjuvant chemotherapy allows for analysis of the post-treatment effects on the primary tumor.

2.3 Squamous Cell Lung Cancer and EGFR Antagonists

In SCC, EGFR activating mutations are rare, however EGFR overexpression has been reported in about 85-95% of cases.[4,5] Cetuximab is an anti-EGFR monoclonal antibody (mAb) composed of a murine anti-EGFR antibody joined to the human IgG1 heavy and light chain regions, which binds to the extracellular domain of the EGF receptor. Competitive inhibition with cetuximab leads to decreased signaling of downstream pathways, EGFR internalization and degradation. In addition, antibody-dependent cellular-mediated cytotoxicity (ADCC), complement-mediated cytotoxicity and adaptive immunity-mediated by CD8+ cytotoxic T lymphocytes have also been described.[6-8]

Several studies have studied the use of cetuximab in NSCLC. The FLEX trial reported on the use of cetuximab with cisplatin and vinorelbine in patients with advanced NSCLC. They found that the addition of cetuximab improved OS at 11.3 months compared to cisplatin and vinorelbine alone at 10.1 months (HR 0.871, 95% CI 0.762-0.996, p=0.04). There was also an improvement in response rates at 36% with cetuximab compared to 29% with cisplatin and vinorelbine alone (p=0.01).[9] However, no difference in progression-free survival was observed. Subgroup analysis of EGFR expression from FLEX study patients was conducted using immunohistochemistry. High EGFR expression was found in 31% of the patients, and low EGFR expression was found in 69% of the patients. Patients in the high EGFR expression group had an increased overall survival in the cetuximab and chemotherapy group compared to the chemotherapy alone group (median OS: 12 months vs. 9.6 months, HR 0.73, 95% CI 0.58-0.93, p=0.011). No survival benefit was found in the low EGFR expression group. A treatment interaction test suggested a predictive value for EGFR expression (p=0.044).[4]

2.4 Necitumumab

Necitumumab is a recombinant human IgG1 monoclonal antibody that binds to the extracellular domain of EGFR. Results from the SQUIRE study recently led to the FDA approval of necitumumab in combination with gemcitabine and cisplatin in advanced SCC. In this study, 1093 patients were randomly assigned to either necitumumab with gemcitabine and cisplatin or gemcitabine and cisplatin alone. Although a median overall survival benefit of 1.6 months was observed with the necitumumab containing regimen (median OS: 11.5 vs. 9.9 months, stratified HR 0.84, 95% CI 0.74-0.96), the improvement in median progression free survival appeared more modest (median PFS: 5.7 vs. 5.5 months, stratified HR 0.85, 95%CI 0.74-0.98) and no improvement in overall response was observed (ORR 31% for the combination with necitumumab vs. 29% with chemotherapy alone, p=0.40).[10]

2.5 Gemcitabine/Cisplatin

Several chemotherapy regimens have been used in adjuvant chemotherapy trials with

positive results. As a result, these regimens have also been used in the neoadjuvant setting.[2,3] Because gemcitabine and cisplatin in combination with necitumumab were used in the SQUIRE trial in the metastatic setting, we propose to use these agents in this trial. In addition, gemcitabine and cisplatin were used in the neoadjuvant setting by Scagliotti et al. This regimen has shown to have reduced neuropathy, alopecia and hypersensitivity reactions compared to taxane regimens.

2.6 Rationale

SCC is a challenging and difficult subtype of lung cancer to treat due to the lack of targetable mutations. The results of the SQUIRE trial led to the FDA approval of necitumumab for metastatic SCC with an overall survival benefit of 1.6 months, however there was a lack of effect of necitumumab on ORR and had a modest effect on PFS. The mechanism of action of necitumumab, similar to cetuximab, likely involves both inhibition of EGFR leading to the targeting of downstream pathways affecting cell growth and proliferation, and ADCC. As a result, a class effect of anti-EGFR therapies may be present as suggested by the SQUIRE trial for necitumumab and the FLEX trial for cetuximab where a survival benefit was seen, but either a modest effect or no effect on PFS. We propose that pathological response is a more reliable measure of anti-cancer activity than is observed in a radiographic evaluation of response. The use of necitumumab in the neoadjuvant setting would also allow for assessment of treatment-related responses in the tumor, as well as providing better understanding and perhaps identification of predictive biomarkers to necitumumab. In addition, the benefits of preoperative chemotherapy including improved therapeutic compliance, and the potential to treat micrometastatic disease may also be an advantage.

As necitumumab has not yet been used in the neoadjuvant or adjuvant settings, we propose this study to assess the feasibility of administering necitumumab in combination with cisplatin and gemcitabine neoadjuvant chemotherapy and the ability to proceed with surgical resection. Additional information regarding response rate and possible biomarkers will also be obtained. Results of this study may serve as a platform for the development of future studies in using necitumumab in the neoadjuvant setting. Further understanding of the immunological mechanisms of necitumumab may also identify potential advantages of its use in combination with immunotherapy.

2.7 Correlative Studies Background

2.7.1 EGFR Expression by Immunohistochemistry

A recent subpopulation analysis of EGFR protein expression was recently reported. In this study, 982 patients from the SQUIRE trial had evaluable immunohistochemistry results which represented approximately 90% of the SQUIRE study participants. They found that 95% of tumor samples expressed EGFR protein. The EGFR >0 patients demonstrated a significantly longer median overall survival in the necitumumab with gemcitabine and cisplatin group of 11.7 months compared to gemcitabine and cisplatin alone of 10.0 months (stratified HR 0.79, 95% CI 0.69-0.92, p=0.002). The patients with

EGFR = 0 did not appear to show a benefit from the addition of necitumumab with gemcitabine and cisplatin with an overall survival hazard ratio of 1.52. Despite this, the number of patients with EGFR = 0 was small and the lack of benefit of necitumumab in this population is not yet conclusive.[5] This study will evaluate EGFR expression on pre-chemotherapy diagnostic tissue biopsies and post-chemotherapy tissue specimens and correlate it with necitumumab-treatment response.

2.7.2 EGFR Gene Copy Number by FISH

The SWOG S0819 trial was conducted to determine if cetuximab improved outcome in combination with chemotherapy in patients with stage IV NSCLC. A subgroup analysis of this trial on was recently presented reporting on the use of EGFR gene amplification positivity in squamous NSCLC and found an improved median overall survival of 11.8 months in the cetuximab and chemotherapy group, compared to 6.4 months who received chemotherapy alone (HR 0.56, p=0.006). EGFR gene amplification was measured by fluorescence in situ hybridization (FISH) testing and determined by the Colorado Scoring System, defined as EGFR FISH-positive if >40% of cells displaying >4 copies of the EGFR signal, or EGFR to CEP7 ratio >2 over all scored nuclei, or gene clusters (>4 spots) or >15 copies of the EGFR signals in >10% of tumor cells.[11]

EGFR FISH analysis was also done on patient samples from the SWOG0342 trial. This study compared sequential versus concurrent cetuximab and paclitaxel-carboplatin chemotherapy. In a subgroup analysis, they reported 59.2% of patients with available tumor tissue to be EGFR FISH-positive. Disease control rate, median PFS, and median OS were all found to have statistically significant improvements over EGFR FISH-negative patients.[12] This study will evaluate EGFR gene copy number on pre-chemotherapy diagnostic tissue biopsies and post-chemotherapy tissue specimens and correlate it with necitumumab-treatment response.

2.7.3 Antibody-Dependent Cellular-Mediated Cytotoxicity (ADCC)

ADCC is an immunologic mechanism triggered by the binding of a monoclonal antibody to the surface of tumor cells. This mechanism has been well described with trastuzumab for breast cancer and rituximab for B-cell lymphoma.[13] Preclinical studies have compared the level of ADCC activity in necitumumab, cetuximab and panitumumab. Necitumumab and cetuximab both belong to the IgG1 class allowing them to activate ADCC, whereas panitumumab of the IgG2 class could not.[14] The Fc fragment of the mAb interacts with the Fc-gamma receptors (FcγR) of immune cells such as macrophages and NK cells, leading to the activation of these immune cells and resulting in lysis of the antibody-coated tumor cells. Various cytokines have been shown to enhance cetuximab-mediated ADCC reactions, such as IL-12 and IL-2. Interestingly, various genotypes of the FcγRs have been described, some of which may be relevant to ADCC. For example, in colorectal cancer, the FcγRIIIa VV or FF genotypes have shown improved clinical response to cetuximab.[15]

Kurai et al. evaluated the relationship of EGFR expression and cetuximab-mediated

ADCC activity in *in vitro* lung cancer cell lines. To test for induction of ADCC activity by cetuximab, they used a 4-hour ^{51}Cr release assay against various lung cancer cell lines with various EGFR expression levels using healthy human peripheral blood mononuclear cells (PBMC). They found that cetuximab-mediated ADCC activity was capable even at low levels of EGFR, but had no linear correlation with the EGFR expression. They further evaluated cetuximab-mediated ADCC activity by collecting PBMCs and determined that the cell type likely responsible for ADCC activity were $CD3^{-}CD56^{+}$ NK cells. Because cytotoxic drug have been previously reported to deplete NK cell function, this study also investigated whether ADCC activity was affected by chemotherapy and found that cetuximab-mediated ADCC activity was less susceptible to immunosuppression than NK activity by cytotoxic drugs.[13]

Tregs are increased in the tumor microenvironment and increased Tregs often correlated with a poor prognosis in epithelial cancer types such as lung cancer. Pircher et al. investigated the correlation of regulatory T cells (Treg $CD4^{+}CD25^{high+}FoxP3^{+}$) on NK-mediated cetuximab-mediated ADCC. In an *in vitro* setting, they showed that human Tregs potently inhibited cetuximab-mediated and NK-cell mediated ADCC against EGFR-expression target cells. The study also evaluated the impact of neoadjuvant chemotherapy and cetuximab on the immune cells. They showed that after neoadjuvant chemotherapy, decreasing Treg counts in the peripheral blood correlated significantly with clinical response. Using immunohistochemistry on tumor tissue, the study also compared the Treg levels in peripheral blood to levels in the tumor tissue, but found there was no correlation between the two. Due to insufficient tissue from pre-chemotherapy specimens, they were unable to compare the Treg levels before and after therapy.[16] This study will compare the levels of Treg levels prior to each administration of necitumumab therapy and evaluate for any changes between doses.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed squamous cell non-small cell lung cancer with any of the following stage groupings: IB with tumor size >4cm, II or potentially resectable IIIA.

3.1.2 Patients who have been evaluated by thoracic surgery and eligible for resection.

3.1.3 Patients must have adequate fresh frozen paraffin embedded (FFPE) tumor tissue available to perform pre-treatment biomarker testing.

3.1.4 No prior systemic treatment for squamous cell non-small cell lung cancer.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status 0-1 (Karnofsky ≥70%, see Appendix A).

3.1.7 Patients must have hematologic function as defined by:

- absolute neutrophil count ≥1.5 x 10^9/L
- hemoglobin ≥9.0 g/dL
- platelets ≥100 x 10^9/L

3.1.8 Patients must have organ function as defined below:

- bilirubin ≤1.5 × the upper limit of normal (ULN), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and asparate transaminase (AST) ≤3.0 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤5.0 times ULN are acceptable.
- If a patient experiences elevated ALT >5 × ULN and elevated total bilirubin >2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3 × ULN, monitoring should be triggered at ALT >2 × baseline.
- calculated creatinine clearance >50mL/min (per the Cockcroft-Gault formula).
- serum albumin ≥2.5 g/dL

3.1.9 Patients may be on a stable regimen of therapeutic anticoagulation or may be receiving prophylactic anticoagulation of venous access devices.

3.1.10 The patient is a woman of child-bearing potential who tests negative for pregnancy within 14 days prior to receiving first dose of study medication based on serum pregnancy test and agrees to use 2 methods of birth control or abstain from heterosexual activity during the study and for 6 months following the last dose of the study drug(s) or country requirements, whichever is longer or be of non-child bearing potential.

Non-childbearing potential is defined as (by other than medical reasons):

- ≥45 years of age and has not had menses for greater than 2 years,
- amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pretrial (screening) evaluation, or
- post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 6 months after the last dose of study therapy.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.1.12 The patient is willing to comply with protocol schedules and testing.

3.2 Exclusion Criteria

3.2.1 Patients with histologically or cytologically confirmed non-squamous cell, small cell or mixed histology lung carcinoma.

3.2.2 Patients with stage IIIB or stage IV disease.

3.2.3 Prior history of other malignancy, provided that he/she has been free of disease for ≥3 years, with the exception of in-situ carcinoma of the cervix or completely resected basal cell carcinoma of the skin.

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 The patient has a known allergy / history of hypersensitivity reaction to any of the treatment components, including any ingredient used in the formulation of necitumumab, or any other contraindication to one of the administered treatments.

3.2.6 History or evidence of current clinically relevant coronary artery disease ≥ Grade III by the Canadian Cardiovascular Society Angina Grading Scale or uncontrolled congestive heart failure of current > Class III as defined by the New York Heart Association.

3.2.7 The patient has experienced myocardial infarction within 6 months prior to study enrollment.

3.2.8 The patient has any ongoing or active infection, including active tuberculosis or known infection with the human immunodeficiency virus.

3.2.9 Recent (within 30 days before enrollment) or concurrent yellow fever vaccination.

3.2.10 The patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of trial treatment.

3.2.11 History of arterial or venous thromboembolism within 3 months prior to study enrollment. Patients with a history of venous thromboembolism beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin.

3.2.12 The patient has any NCI-CTCAE Version 4.0 Grade ≥2 peripheral neuropathy.

3.2.13 The patient has any other serious uncontrolled medical disorders or psychological conditions that would, in the opinion of the investigator, limit the patient's ability to complete the study or sign an informed consent document.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Patient Registration

To register a patient, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Study Coordinator at the Montefiore-Einstein Cancer Center Clinical Trials Office, Tianfeng He, phone 718-405-8344, fax, or email: the@montefiore.org:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form

The research nurse or data manager at the participating site will then contact the CPDMU registration office at the Montefiore-Einstein Cancer Clinical Trials Office, phone 718-379-6866 or email: cpdmu-registration@montefiore.org to verify eligibility. To complete the registration process, the Coordinator will:

- assign a patient study number
- register the patient on the study
- fax or e-mail the patient study number to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration.

Once patients are found eligible for the study, they will be registered with the Montefiore-Einstein Cancer Center Coordinating Center.

4.2 General Guidelines

The **coordinating center** is:

Montefiore-Einstein Cancer Center
Clinical Trials Office Department of Oncology
1695 Eastchester Road, 2nd Floor
Bronx, New York 10461
Phone 718-405-8344
Fax 718-405-8433
Coordinator: Tianfeng He
Email: the@montefiore.org

The eligible patients will be entered on study centrally at the Montefiore-Einstein Cancer Center Clinical Trials Office by the Study Coordinator. All sites should call the Study Coordinator Tianfeng He, phone 718-405-8344 to verify availabilities.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a

patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

Following written informed consent, all subjects will undergo screening to determine eligibility for study interventions. All baseline procedures with the exception of translational studies are standard of care for subjects with stage Ib, II, and IIIA squamous cell lung cancer that are surgically resectable. Postoperative cancer management will be at the discretion of the multidisciplinary treatment team. Patients with N2 disease will have a recommendation for postoperative radiotherapy.

Patients will be evaluated by a thoracic surgeon and medical and/or radiation oncologist and be determined to have potentially resectable disease.

Patients, who are eligible for the study, will be treated with preoperative/neoadjuvant necitumumab, gemcitabine and cisplatin every 21 days for 3 cycles as outlined in section 7.1.

Patients will be evaluated with repeat imaging studies (PET/CT or CT Chest, Abdomen, Pelvis) and will be re-evaluated for surgical resection. Patients who had progressive disease or are NOT a surgical candidate will come off the study and will be treated according to standard therapies. All patients will be followed up for 2-year disease-free survival and overall survival.

To be completed within 14 days prior to first dose of study drug administration:

1. Complete history and physical exam, including blood pressure, weight
2. ECOG Performance Status
3. CBC with differential and platelet count
4. Serum chemistry profile to include: comprehensive panel: serum bilirubin, alkaline phosphatase, AST, ALT, serum creatinine, serum electrolytes, serum calcium, serum albumin, serum magnesium
5. Beta HCG in women capable of becoming pregnant (defined as a sexually mature female), has not undergone hysterectomy (surgical removal of the uterus) or bilateral oophorectomy (surgical removal of both ovaries), has not been naturally postmenopausal for at least 24 consecutive months.
6. PET/CT from Base of Skull to Upper Thigh if not already done
7. MRI Brain (for patients with Stage IIIA disease only)

Complete history and physical exam, including blood pressure, weight will be repeated every 3 weeks.

Repeat CBC with differential and platelet count and serum chemistry profile as included above will be completed prior to each dose of chemotherapy. Additional tube of peripheral blood will be collected for NK cell measurement and ADCC activity analysis.

CT Chest, Abdomen and Pelvis will be obtained following completion of cycle 3 of chemotherapy and necitumumab. If a PET/CT from Base of Skull to Upper Thigh is able to be obtained instead, this is permissible (preferred).

5.1 Chemotherapy and Necitumumab Administration Schedule

Treatment will be administered on an outpatient basis. All chemotherapy doses will be based on the patient's actual weight. The actual weight at screening will be used for calculating body surface area (BSA). The BSA should only be recalculated if a patient's weight changes by >10%. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Prior to each administration of study therapy, hematology, liver, and renal function must be adequate (see below) and all other toxicities must be resolved to Grade ≤2 (except for alopecia and skin toxicity) or baseline.

Criteria for Treatment

Neutrophils:	$\geq 1.5 \times 10^9$ / L
Platelets:	$\geq 100 \times 10^9$ / L
Calculated creatinine clearance:	≥ 50 mL/min
Bilirubin	≤ 1.5 x ULN
AST:	≤ 5 x ULN in the presence of liver metastasis; ≤ 3 x ULN in the absence of liver metastasis
ALT:	≤ 5 x ULN in the presence of liver metastasis; ≤ 3 x ULN in the absence of liver metastasis

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Necitumumab	Previous Grade 1 or 2 infusion-related reaction (IRR), pre-medicate with diphenhydramine hydrochloride prior to all subsequent infusions. For patients who have experienced a second Grade 1	800mg in 250 cc NS	IV over 60 minutes **before** gemcitabine	Days 1, 8, of 3 week cycle	21 days (3 weeks)

	or 2 occurrence of IRR, pre-medicate for all subsequent infusions with diphenhydramine hydrochloride, acetaminophen, and dexamethasone prior to each infusion. (or equivalent of each of above)				
Gemcitabine	Dexamethasone 10mg IV on Day 1, 8	1250mg/m^2 in 250 cc NS	IV given 60 minutes after necitumumab, given over 30 minutes	Days 1, 8, week 1-3	
Cisplatin	Pre- and post-hydration	75mg/m^2 in 500 cc NS	IV following gemcitabine over 120 minutes	Day 1, week 1-3	

5.1.1 Chemotherapy Regimen

Gemcitabine 1250mg/m^2 IV over 30 minutes, days 1 and 8 following necitumumab

Cisplatin 75mg/m^2 IV over 60 minutes, day 1, immediately following gemcitabine

Each cycle is 3 weeks (21 days).

The regimen will be given for a total of 3 cycles.

5.1.1.1 Antiemetics

It is strongly recommended that all patients receive adequate anti-emetics with cisplatin- based chemotherapy. The specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral dexamethasone and a high dose of oral or IV 5HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional anti-emetics consisting of 4 days of oral dexamethasone (8 mg PO bid for 2 days (days 2, 3) then 4 mg PO bid for 2 days (days 4, 5) and scheduled metoclopramide or 5HT3 antagonist for days 2-5 for delayed emesis (see supportive care Section 5.2.7).
NOTE: Dexamethasone dose should be reduced by 50% when

administered with aprepitant.

5.1.1.2 Hydration Requirements

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

5.1.2 Necitumumab

Necitumumab 800mg absolute dose IV over a minimum of 60 minutes, days 1 and 8 prior to chemotherapy regimen

Each cycle is 3 weeks (21 days).

The regimen will be given for a total of 3 cycles.

5.1.2.1 Premedication

- For patients who have experienced a previous Grade 1 or 2 infusion-related reaction (IRR), pre-medicate with diphenhydramine hydrochloride (or equivalent) prior to all subsequent necitumumab infusions.
- For patients who have experienced a second Grade 1 or 2 occurrence of IRR, pre-medicate for all subsequent infusions, with diphenhydramine hydrochloride (or equivalent), acetaminophen (or equivalent), and dexamethasone (or equivalent) prior to each necitumumab infusion.

5.2 Surgical Resection

Patients who had significant clinical down staging and deemed medically fit to tolerate surgery will have surgical resection within 4 weeks after last staging imaging studies.

Patients with non-progressive disease who are not going for surgery should have mediastinal restaging done by either EUS/EBUS or mediastinoscopy.

5.2.1 Mediastinoscopy

A mediastinoscopy is highly recommended for all patients prior to neoadjuvant

therapy for confirmation of mediastinal disease.

5.2.2 Pulmonary resection

Thoracotomy or video-assisted thoracoscopic surgery (VATS) may be performed 4-6 weeks after neoadjuvant therapy. Surgery is performed if post neoadjuvant induction CT scan shows no significant progression of disease. Patients must be medically fit to tolerate surgery as deemed by the operative surgeon (post operative predicted FEV1> 40% predicted, no severe active comorbidity-see section 3). Complete surgical resection is the goal. This may entail pneumonectomy, bilobectomy, or lobectomy. Any procedure less than lobectomy is not recommended. Intraoperative frozen sections are performed at the discretion of the surgeon (bronchial resection margin is recommended). Reasons for incomplete resection will be documented. Bronchial stump coverage with local vascularized tissue is recommended.

5.2.3 Handling of mediastinal lymph nodes at thoracotomy

At the time of thoracotomy or VATS, mediastinal lymph node dissection is performed at the nodal station biopsied positive on prior mediastinoscopy. Either a full mediastinal lymph node dissection or mediastinal lymph node sampling is performed at all other lymph node stations at the discretion of the surgeon. For right-sided lesions, this will include lymph node station 2, 4, 7, 8, 9, 10, and 11. Station 12 and 13 will be submitted along with the lung specimen. For left sided lesions, this will include lymph node station 5, 6, 7, 8, 9, 10, and 11. Station 12 and 13 will be submitted along with the lung specimen. On the left side, dissection or sampling of station 2 and 4 are at the discretion of the surgeon.

Proper documentation of mediastinal lymph node sampling in operative report is mandatory for the study. If the specific stations are not sampled, the reason should be documented in operative report. Failure to document mediastinal node sampling will be considered major protocol violation.

5.2.4 Operative complications

In hospital and 30 day morbidity and mortality will be prospectively monitored.

5.3 Supportive Care Guidelines

5.3.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.3.2 The clinical tolerance of the patients, the overall clinical tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression, until the initiation of any new systemic therapy.

5.3.3 Suggested supportive care medications may be substituted at the discretion of the investigator based on drug availability.

5.3.4 Concomitant aminoglycoside antibiotic use should be avoided during cisplatin therapy until patient has fully recovered (i.e., at least 4 weeks from last dose of cisplatin).

5.3.5 Pegylated G-CSF or G-CSF may be used at the discretion of the investigator after neutropenia is documented, or prophylactically to reduce the chance of febrile neutropenia. Growth factor use or dose reduction is only mandated, however, in the setting of prior febrile neutropenia. If used, it would be given on day 9, 24 hours following the last administration of necitumumab and gemcitabine.

5.3.6 Diarrhea may occur. Appropriate supportive measures including Imodium and/or Lomotil should be implemented immediately to prevent dehydration.

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre- and post- cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consistent of NS at 500cc/hr x 1 liter and post-cisplatin hydration consist of ½ NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

5.3.7 Antiemetic therapy is critical for proper administration of cisplatin. The specific anti-emetic regimen is at the discretion of the treating physician, provided adequate control is achieved. However, on the day of cisplatin therapy, the investigator should consider use of a steroid medication and a 5HT3 antagonist. One such regimen consists of 20mg of dexamethasone and a high dose of a 5HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron or 32 mg ondansetron or equivalent) and continuing with 4 days of dexamethasone or equivalent steroid and 4 days of scheduled anti-emetic such as metoclopramide or a 5HT3 antagonist. If this regimen is ineffective, consideration of the long-acting 5HT3 antagonist palonosetron and the agent aprepitant should be considered at the discretion of the investigator.

NOTE: Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater

than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

NOTE: Dexamethasone dose should be reduced by 50% when administered with aprepitant.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 3 cycles, given 3 weeks apart, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) including but not limited to:
  - Immediately and permanently discontinue necitumumab for severe (grade 3 or 4) IRRs
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
  - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Cases of pregnancy that occur during maternal or paternal exposures to study treatment should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.5 Duration of Follow Up

Patients will be followed for at least 2 years after the last patient has been enrolled after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Monitoring of magnesium level for at least 8 weeks post-necitumumab completion will be performed.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Gemcitabine/Cisplatin

6.1.1 Hematologic Toxicity (Gemcitabine)

6.1.1.1 Intra-cycle adjustments (e.g. day 8)

Day 8 dose adjustment for neutropenia and/or platelets is not a permanent dose reduction.

Absolute Neutrophil Count (x 10^6/L)		**Platelets (x 10^6/L)**	**% full dose Gemcitabine**
≥ 1000	AND	≥ 75,000	100
500-999	OR	50,000-74,999	75
<500	OR	<50,000	0

Omitted day 8 doses of gemcitabine will not be made up.

6.1.1.2 Day 1 cycle dose adjustments (hematologic toxicity):

Dose reductions are not required for neutropenia, unless febrile neutropenia occurs. If a platelet nadir of <25,000 is reached, future cycles require dose reduction. Day 1 dosing may only resume for platelet count ≥100,000 and ANC ≥1500. Please see table below:

Dose Reductions for Hematologic Toxicity

	Cisplatin	**Gemcitabine**
1st episode*	No adjustment	Dose reduce by 1 level**
2nd episode*	No adjustment	Dose reduce by 1 level**
3rd episode	Discontinue protocol chemotherapy – may continue necitumumab alone	Discontinue protocol therapy – may continue necitumumab alone
Anemia	No adjustment	No adjustment

* Episodes = Febrile Neutropenia or Platelet Nadir <25,000
** Alternatively, if current episode is febrile neutropenia, growth factor support (G-CSF or pegylated G-CSF) may be used with all subsequent cycles instead of dose reduction. If growth factor support has already been instituted, than dose reduction is required for the next episode of febrile neutropenia. **ANC must be at least 1,5000/mm^2 and platelet count must be at least 100,000/µl on day 1 of each cycle**.

Dose Reduction Levels

	Original Dose	**Reduced Dose**
Gemcitabine	1250 mg/m^2	950 mg/m^2
	950 mg/m^2	625 mg/m^2

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1500/mm^3 and the platelet count is at least 100,000/mm^3. However, if the counts have not recovered in 3 weeks, the patient's protocol chemotherapy treatment will be

discontinued. The patient will still be followed for toxicity and response. Patient and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

If chemotherapy must be delayed due to hematologic toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits for treatment. The treatment schedule will then proceed in the usual schedule.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's discretion. The use of blood transfusions for anemia will be allowed as indicated.

Dose reductions, once initiated, are permanent for all future cycles. If both febrile neutropenia and thrombocytopenia of <25,000 occur, the dose reduction will be to the lower dose specified.

6.1.2 Gastrointestinal Toxicities (Cisplatin)

Nausea and/or vomiting should be controlled with antiemetics. If grade 3 nausea/vomiting occurs in spite of maximum antiemetics (steroid pre-medication for 4 days after administration, 5HT3 antagonist, and aprepitant or similar agent if available), the dose of cisplatin should be reduced by 25% for the next course. If tolerated, increase back to 100% as soon as possible.

NOTE: Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

Oral Mucositis
If, on day 1 of any treatment cycle, the patient has >grade 1 oral mucositis, the treatment should be delayed until the oral mucositis has resolved to grade 1 or less. If the oral mucositis has not cleared in 3 weeks, the patient's protocol chemotherapy treatment will be discontinued. (For grade 1 oral mucositis not related to treatment, treatment may be given on schedule.) If acute grade 3 oral mucositis occurs at any time, the dose of cisplatin should be given at 75% dose when the oral mucositis is completely cleared. This is a permanent dose reduction.

6.1.3 Renal (Cisplatin)

Creatinine	Cisplatin	Gemcitabine
≤ 1.5 x ULN	100%	100%
> 1.5 but ≤2.0 x ULN	50%	100%

Creatinine	Cisplatin	Gemcitabine
>2.0 x ULN	0%	0%

If serum creatinine is elevated such that treatment is not administered as scheduled (i.e. > 2.0 X ULN), repeat the abnormal tests at weekly intervals. If the serum creatinine returns to ≤ 2.0 x ULN within 3 weeks, cisplatin may be reinstituted at 75% of the full dose during the next cycle (permanent dose reduction). A more aggressive hydration regimen must be instituted as well with all subsequent doses of cisplatin. If the cisplatin is held, the gemcitabine will be held as well so that both drugs are kept on the same schedule. If creatinine is still ≥ 2.0 x ULN after 3 weeks, either discuss with study chair, substitute with carboplatin AUC 5 as per standard protocol in the setting of cisplatin-induced nephrotoxicity, or discontinue protocol chemotherapy.

6.1.4 Sensory or Motor Neuropathy (Cisplatin)

Cisplatin doses should be modified as follows for sensory or motor neuropathy. Day 1 value should be used in determining dose.

Grade of Toxicity	Dose
0	100%
1	100%
2	Delay treatment until patient recovers to grade 1 toxicity, then resume cisplatin treatment at 75% dose
≥3	Delay treatment until patient recovers to grade 1; then resume cisplatin treatment at 50% dose

Delay cisplatin and gemcitabine until patient recovers to grade 1 toxicity. Reduce cisplatin dose once therapy is re-initiated. If within 3 weeks the sensory or motor neuropathy has not recovered to grade 1, discontinue protocol treatment. Dose reductions for sensory or motor neuropathy are permanent.

6.1.5 Ear and Labyrinth Disorders: Hearing Impairment (Cisplatin)

Cisplatin is well known to cause high-frequency hearing loss. Continued use of the drug does not always result in hearing loss, although it may do so. If grade 2 or worse hearing loss is noted, the patient should be presented with a discussion of the relative risks of hearing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin. Severe hearing loss (grades 3 and 4) is an indication to discontinue the drug.

6.1.6 Other Toxicities

For any clinically significant grade 3 or 4 toxicity felt to be related to chemotherapy treatment, not mentioned above, the treatment should be delayed until the patient recovers completely or to grade 1 or better. The treatment should then be resumed with at least a 25% dose reduction in the agent felt most likely to have caused the toxicity

(permanent dose reduction). At the discretion of the investigator, both drugs may be reduced and the reduction may be more significant if warranted. If, within 3 weeks, the toxicity has not resolved to grade 1 or completely recovered, discontinue protocol chemotherapy treatment. For grade 1 and 2 toxicities, no dose reductions are necessary per protocol.

6.2 Necitumumab

In the case of necitumumab-related toxicity, such as grade 3 or 4 electrolyte abnormalities, administration of necitumumab will be interrupted, but chemotherapy will continue according to the planned schedule. Subsequent cycles of necitumumab may be administered in these patients once hypomagnesemia and related electrolyte abnormalities have improved to grade ≤2.

In the case of chemotherapy-related toxicity, the start of the next cycle of chemotherapy will be delayed until recovery but necitumumab will be administered as planned. However, in the case of grade 3 or 4 electrolyte abnormalities, necitumumab therapy will also be delayed. When chemotherapy-related toxicity has resolved, chemotherapy and necitumumab will resume on the regular schedule.

Dose modifications are permitted for necitumumab following non-life threatening reversible CTCAE Grade ≥3 AEs that require delay of necitumumab treatment for up to 6 weeks following Day 1 of the most recent treatment cycle. In this setting, necitumumab may be re-administered at a reduced dose (600mg) if necessary only if AE is resolved to grade ≤2. A second dose reduction (to 400mg) is permitted for this level of event (Grade ≥3.)

If a patient experiences CTCAE Grade ≥3 hematologic toxicity possibly related to necitumumab, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of necitumumab must be reduced by 1 dose level (see above).

If a patient experiences CTCAE Grade ≥3 non-hematologic toxicity possibly related to necitumumab, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of necitumumab must be reduced by 1 dose level (see above).

Events that necessitate more than 2 dose reductions warrant discontinuation from necitumumab treatment.

6.2.1 Infusion-Related Reactions (IRR)

Hypersensitivity/infusion-related reactions were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Monitor patients during and following the infusion for signs of hypersensitivity and infusion-related reactions with resuscitation equipment readily available. For mild or

moderate (grade 1 or 2) IRRs, adjust dose per table below:

Toxicity Grade[a]	**Management Recommendations (Any Occurrence)**
Grade 1	• Decrease infusion rate by 50% for the duration of infusion.[b] • Monitor patient for worsening of condition.
Grade 2	• Stop the infusion; when the reaction has resolved to ≤ Grade 1, resume infusion at a 50% decreased infusion rate.[b] • Monitor patient for worsening of condition.
Grade 3-4	• Stop the infusion. • Permanently discontinue treatment with necitumumab.

a – Grade per NCI-CTCAE, Version 3.0
b – Once the infusion rate has been reduced for a Grade 1 or 2 hypersensitivity/infusion related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

6.2.2 Dermatologic Toxicity

Dose delays and or modifications for necitumumab are to be considered in case of skin reactions of Grade 3 or that are considered intolerable. If a patient experiences Grade 4 skin reactions, treatment with necitumumab should be permanently discontinued.

Management Recommendations for Skin Reactions

Toxicity Grade[a]	**Management Recommendations (Any Occurrence)**
Grade 3	• Temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade ≤ 2. • Following improvement to Grade ≤ 2, re-administer with a dose reduction of 50% (400 mg). This dose may be increased to 75% of the original dose (600 mg) after a minimum of one treatment cycle (3 weeks), if symptoms do not recur. • If symptoms do not recur for another treatment cycle, the dose may be re-escalated to the full recommended dose (800 mg). • Permanently discontinue if reactions do not resolve to Grade ≤ 2 after 6 weeks (i.e., after withholding two consecutive doses), or if reactions recur or become

	intolerable at 50% of the original dose. • Immediately and permanently discontinue for patients who experience Grade 3 skin induration / fibrosis.
Grade 4	• Immediately and permanently discontinue treatment with necitumumab.

a – Grade per NCI-CTCAE, Version 3.0

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events

7.1.1 Adverse Event List for Necitumumab

For a comprehensive list, please see the package insert.

7.1.1.1 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 3.0% of patients treated with necitumumab in combination with gemcitabine and cisplatin. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, with aggressive replacement when warranted during and after necitumumab administration.

In cases of sudden death, investigators are requested to record on the SAE report form as much information as possible regarding the symptoms and signs immediately preceding death and any postmortem results so that an accurate cause of death may be established (specifically so that thromboembolism may be confirmed or denied).

7.1.1.2 Hypomagnesemia

Hypomagnesemia occurred very commonly (83%) in patients receiving necitumumab in combination with gemcitabine and cisplatin, and was severe in 20% of patients. Monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia prior to each dose of necitumumab during treatment and for at least 8 weeks following completion of necitumumab. Withhold necitumumab for Grade 3 or 4 electrolyte abnormalities. Replete electrolytes as medically appropriate.

7.1.1.3 Venous and Arterial Thromboembolic Events

Venous and arterial thromboembolic events (VTE and ATE), some fatal, were observed with necitumumab in combination with gemcitabine and cisplatin. The incidence of VTE was 9% in patients receiving necitumumab plus gemcitabine and

cisplatin versus 5% in patients receiving gemcitabine and cisplatin alone and the incidence of Grade 3 or higher VTE was 5% versus 3%, respectively. The incidence of fatal VTEs was similar between arms (0.2% versus 0.2%). The most common VTEs were pulmonary embolism (5%) and deep-vein thrombosis (2%).

The incidence of ATEs of any grade was 5% versus 4% and the incidence of Grade 3 or higher ATE was 4% versus 2% in the necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone, respectively. The most common ATEs were cerebral stroke and ischemia (2%) and myocardial infarction (1%).

Treatment of any thromboembolic events occurring under necitumumab treatment should be as clinically indicated according to local standards, and the continuation of necitumumab therapy in these cases should be decided by the investigator after thorough risk-benefit assessment for the individual patient.

Discontinue necitumumab for patients with serious or life threatening VTE or ATE.

7.1.1.4 Dermatologic Toxicities

Dermatologic toxicities, including rash, dermatitis acneiform, acne, dry skin, pruritus, generalized rash, skin fissures, maculo-papular rash and erythema, occurred in 79% of patients receiving necitumumab. Skin toxicity was severe in 8% of patients. Skin toxicity usually developed within the first 2 weeks of therapy and resolved within 17 weeks after onset. For Grade 3 skin reactions, modify the dose of necitumumab. Limit sun exposure. Discontinue necitumumab for severe (Grade 4) skin reactions, or for Grade 3 skin induration/fibrosis.

7.1.1.5 Infusion-Related Reactions

In a study of necitumumab plus gemcitabine and cisplatin, 1.5% of necitumumab treated patients experienced IRRs of any severity with 0.4% Grade 3 IRR. No patients received premedication for IRR for the first dose of necitumumab in that study. Most IRRs occurred after the first or second administration of necitumumab. Monitor patients during and following necitumumab infusion for signs and symptoms of IRR. Discontinue necitumumab for serious or life-threatening IRR.

7.1.2 Adverse Event List for Gemcitabine

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. For a comprehensive list, please see the package insert.

7.1.3 Adverse Event List for Cisplatin

The most common adverse reactions for cisplatin are nausea/vomiting, peripheral neuropathy, nephrotoxicity, ototoxicity, anemia, neutropenia, thrombocytopenia, and

hepatic transaminitis and thromboembolic events. For a comprehensive list, please see the package insert.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).
- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

An adverse event can occur on any clinical trial; it is the responsibility of the Principal Investigator and his/her research team to identify, review and report all necessary adverse events to the institutional IRB, the sponsor and governmental agencies (i.e., NCI and/or FDA) as appropriate. Adverse events should be identified through standard, routine protocol review and clinical assessment of each subject participating in the clinical trial. This review should be timely in order to meet the requirements for adverse event reporting defined below.

Definitions:

1. Adverse Event (AE):
Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse Events encompass both physical and/or psychological harms.

In the context of multicenter clinical trials, Adverse Events can be characterized as either *internal adverse events* or *external adverse events*. From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all Adverse Events would be considered *internal adverse events.*

2. Unanticipated Problem:
Any event, deviation, or problem, that meets ALL of the following criteria:

- *unexpected;* AND
- *possibly, probably or definitely related to study participation;* AND
- serious.

a. Unexpected: An event can be categorized as unexpected if it occurs in one or more subjects participating in a research protocol; and the nature, severity, or frequency of which is **not** consistent with either:

i. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in protocol-related documents such as: the IRB-approved research protocol; any applicable investigator brochure: the current IRB-approved informed consent document; or other relevant sources of information, such as product labeling and package inserts; or
ii. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

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

i. death,
ii. a life-threatening adverse reaction,
iii. inpatient hospitalization or prolongation of existing hospitalization,
iv. persistent or significant disability/incapacity,
v. a congenital anomaly/birth defect,
vi. or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.3 Reporting requirements

In addition to the IRB reporting guidelines described below, all serious adverse events (SAE) will be reported to Lilly Global Patient Safety via fax within 24 hours with a causality assessment. The Lilly Global Patient Safety Fax Number for all SAEs is 866-644-1697 or 317-453-3402.

7.3.1 Determination of reporting requirements

Unanticipated Problems must be reported to the IRB using the Reportable Events Form within **5 business days** of the identification of the event by the research staff. Only the Principal Investigator may sign off on reportable event submissions, although any member of the research team may initiate the report. Exceptions (e.g. when the PI is unavailable for an extended period of time) will be considered by the IRB on a case-by-case basis.

[N.B. Internal Adverse Events that have been anticipated in the risks outlined in the protocol and informed consent document, or that are clearly unrelated to the research protocol, or that are not serious, do not have to be reported individually to the IRB. However they must be recorded in the adverse events log. Anticipated non-serious adverse events need not be reported to the IRB or logged.]

External Adverse Events that are serious, unexpected, and related or possibly related to the research must be reviewed by the PI. They should be submitted to the IRB **only** if they result in an amendment to the protocol or informed consent document. These AEs are then reported to the IRB as the basis for the proposed amendment (using the Amendment Form, not the Reportable Event Form).

Other events that must be reported to the IRB include:

- The death of a participant in a "greater-than-minimal-risk" protocol being conducted at a site under the jurisdiction of the Einstein IRB, even if "anticipated", if it occurs within 30 days of a study-related procedure or the administration of a study drug.
- A Protocol Deviation that may place the participant or others at greater medical, physiological, social risk or economic risk than was previously known or recognized.
- Deviation from the IRB Informed Consent Policy.
- Any deviation from IRB or Institutional Policy or Procedure which has the potential to adversely impact one or more subjects or the overall integrity of data collected.
- Systematic data collection error that has the potential to adversely impact the overall integrity of the data collected.
- Breach of confidentiality.
- Any incident, experience, or outcome that indicates that the participant or others were placed at greater medical, physiological, social risk or economic risk than was previously known or recognized.
- Any action taken to eliminate an apparent immediate hazard to a research subject.
- Incarceration of a research subject.
- Sponsor or regulatory audit that requires corrective action.
- Any reporting the PI is required to report directly to the FDA (e.g. the PI is the sponsor-Investigator, a protocol involving the use of an HUD).
- Complaint from a participant or other individual when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Disqualification or suspension of the Investigator by the FDA, NIH or other agency.
- Suspension or restriction of an Investigator's clinical professional license.

- Any reporting that the IRB cites as a condition of approval of the protocol.

Reporting requirements may include the following considerations: 1) whether the patient has received necitumumab, gemcitabine or cisplatin; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; and 3) whether or not hospitalization or prolongation of hospitalization was associated with the event.

7.3.2 Expedited Reporting Guidelines

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0*. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCl has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in section 7.1.1, 7.1.2, and 7.1.3.

Step 5: Review the ”Additional instructions, requirements, and exceptions for this protocol specific requirements” for expedited reporting of specific adverse events that require special monitoring.

Step 6: Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.

7.3.3 Reporting methods

Any event that meets the definition of an Unanticipated Problem must be reported to the Montefiore-Einstein IRB within 5 business days. The Unanticipated Problem Report Form can be found on the Einstein IRB website: http://einstein.yu.edu/administration/institutional-review-board/forms.aspx. All Reportable Events must be submitted to the IRB within 5 business days of the

identification of the event by the research staff. Only the Principal Investigator may sign off on reportable event submissions, although any member of the research team may initiate the report. A record of non-reportable events and deviations must be maintained by the PI in a log and for greater than minimal risk studies must be submitted to the IRB as part of the annual review of the protocol.

For events that are deemed reportable at participating sites, a copy of the reportable event must be submitted to Montefiore Medical Center within 2 business days. You may send to the Principal Investigator and the Study Coordinator. All contact information is located at the cover page of this document. If not reportable, Adverse Events should be logged in the CRF page, and any non-reportable serious and/or unanticipated adverse events should be logged on the Adverse Event Log provided by Montefiore for review at the Montefiore Data Safety Monitoring Committee meetings and during IRB annual review.

An internal log(s) of all* AE, UP and PD events that come to the attention of the staff responsible for the research must be maintained. The log(s) will be examined by the IRB during the course of a routine or for-cause audit of the protocol. For studies that are greater than minimal risk, this log must be submitted to the IRB as part of the continuing review of the protocol. *NOTE: Anticipated non-serious AEs need not be logged.

8. PHARMACEUTICAL INFORMATION

8.1 Necitumumab

8.1.1 Other Names

Portrazza

8.1.2 Classification

Epidermal Growth Factor Receptor (EGFR) Antagonist

8.1.3 Mode of Action

Necitumumab is a recombinant human lgG1 monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) and blocks the binding of EGFR to its ligands. Expression and activation of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis. Binding of necitumumab induces EGFR internalization and degradation in vitro. In vitro, binding of necitumumab also led to antibody-dependent cellular cytotoxicity (ADCC) in EGFR-expressing cells.

8.1.4 Storage and Stability

Store vials in a refrigerator at 2° to 8°C (36° to 46°F) until time of use. Keep the vial in

the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

8.1.5 Dose Specifics

Necitumumab will be given at a dose of 800 mg administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle prior to gemcitabine and cisplatin infusion. Each cycle is to be repeated every 3 weeks for 3 cycles.

8.1.6 Preparation

Inspect vial contents for particulate matter and discoloration prior to dilution. Discard the vial if particulate matter or discoloration is identified. Store vials in a refrigerator at 2° to 8°C (36˚ to 46˚F) until time of use. Keep the vial in the outer carton in order to protect from light.

- Dilute the required volume of necitumumab with 0.9% Sodium Chloride Injection, USP in an intravenous infusion container to a final volume of 250 mL. Do not use solutions containing dextrose.
- Gently invert the container to ensure adequate mixing.
- DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medication.
- Store diluted infusion solution for no more than 24 hours at 2° to 8°C (36° to 46°F), or no more than 4 hours at room temperature (up to 25°C [77°F]).
- Discard vial with any unused portion of necitumumab.

8.1.7 Administration

Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discoloration is identified, discard the solution.

Administer diluted necitumumab infusion via infusion pump over 60 minutes through a separate infusion line. Flush the line with 0.9% Sodium Chloride Injection, USP at the end of the infusion.

8.1.8 Incompatibilities

No information available.

8.1.9 Availability

Necitumumab is supplied in single-dose vials as a sterile, preservative-free solution: 800 mg/50 mL (16 mg/mL).

8.2 Gemcitabine

8.2.1 Other Names

2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

8.2.2 Classification

Antimetabolite (nucleoside pyrimidine analogue)

8.2.3 Mode of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly initially by deoxycitidine kinase to monophosphate nucleoside and subsequently to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

8.2.4 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

8.2.5 Dose Specifics

Gemcitabine will be given by IV at a dose of 1250 mg/m2 over 30 minutes on days 1 and 8 of each cycle (immediately prior to cisplatin administration on Day 1). Each cycle is to be repeated every 3 weeks for 3 cycles.

8.2.6 Preparation

Reconstitute the 200 mg vial with 5 mL and the 1 g vial with 25 mL preservative free normal saline to make a solution containing 38 mg/mL. Shake to dissolve.

8.2.7 Administration

The drug may be administered as prepared above or further diluted with normal saline to a minimum concentration of 0.1 mg/mL. Gemcitabine is commonly diluted in 100 mL or 250 mL of saline. Reconstitution at greater than 40 mg/mL may result in incomplete dissolution of drug. The drug is typically administered over 30 minutes.

8.2.8 Incompatibilities

No information available.

8.2.9 Availability

Gemcitabine is commercially available in 200 mg and 1 g vials.

8.3 Cisplatin

8.3.1 Other Names

Cis-diaminedichloroplatinum, Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875.

8.3.2 Classification

Alkylating agent.

8.3.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.3.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Solutions diluted with sodium chloride or dextrose are stable for up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

8.3.5 Dose Specifics

Cisplatin will be given by IV at a dose of 75 mg/m^2 over 60 minutes on day 1 of each cycle (each cycle to be repeated every 3 weeks for 3 cycles), immediately following gemcitabine.

8.3.6 Preparation

The desired dose of cisplatin is diluted with 250-1000 mL of saline and/or dextrose solution. Varying concentrations of 0.225-5% sodium chloride and 5% dextrose may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

8.3.7 Route of Administration

Cisplatin is usually administered as an intravenous infusion over 30 minutes to 24 hours; multiday continuous infusions are occasionally used. The drug may also be administered intra-arterially, intraperitoneally and intravesicularly.

8.3.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

8.3.9 Compatibilities

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.

Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations.

8.3.10 Availability

Commercially available as a mg/mL solution in 50 and 100 mg vials.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Exploratory Correlative Studies

9.1.1 EGFR Expression by Immunohistochemistry on Paraffin-Embedded Tissue

To evaluate whether EGFR expression by immunohistochemistry (IHC) is correlated with response rate to necitumumab. Pre-chemotherapy diagnostic tissue biopsy (if

adequate tissue available) and tissue specimens obtained from post-chemotherapy surgical resection will be evaluated for EGFR expression by IHC. EGFR expression by immunohistochemistry will be scored based on the H-score. Based on the H-score, samples from pre- and post-surgery will be classified as either "EGFR expressors" or "EGFR non-expressors."

9.1.1.1 Collection of Specimen(s)

We will put all effort to obtain the diagnostic tissue blocks from the diagnostic biopsy for the pre-chemotherapy EGFR expression analysis. Post-treatment EGFR expression analysis will be obtained from the surgical resection. Pre- and post-treatment tumor specimens will be obtained in available patients.

9.1.1.2 Handling of Specimens(s)

Baseline levels of EGFR expression (if pre-treatment tissue available) and post-treatment EGFR expression will be evaluated in paraffin embedded tissue and fresh frozen tissue (if available) by immunochemistry.

9.1.1.3 Site(s) Performing Correlative Study

Immunohistochemistry for EGFR expression will be performed at Montefiore Medical Center.

9.1.2 EGFR Gene Copy Number by FISH

To determine if EGFR positivity by EGFR copy number on pre-chemotherapy diagnostic tissue biopsy (if adequate tissue available) and tissue specimens obtained from post-chemotherapy surgical resection is correlated with response rate to necitumumab. EGFR positive by FISH is defined by the Colorado Scoring Criteria by >40% of cells displaying >4 copies of the EGFR signal, or EGFR to CEP7 ratio >2 over all scored nuclear, or gene clusters (>4 spots) or >15 copies of the EGFR signals in >10% of tumor cells.

9.1.2.1 Collection of Specimen(s)

We will put all effort to obtain the diagnostic tissue blocks from the diagnostic biopsy for the pre-chemotherapy EGFR gene copy number by FISH analysis. Post-treatment EGFR gene copy number analysis will be obtained from the surgical resection. Pre- and post-treatment tumor specimens will be obtained in available patients.

9.1.2.2 Handling of Specimens(s)

Baseline levels of EGFR gene copy number (if pre-treatment tissue available) and post-treatment EGFR gene copy number will be evaluated in paraffin embedded tissue and fresh frozen tissue (if available) by FISH.

9.1.2.3 Site(s) Performing Correlative Study

Fluorescence in-situ hybridization will be performed by Montefiore Medical Center.

9.1.3 Antibody-Dependent Cellular-Mediated Cytotoxicity (ADCC) Testing on Peripheral Blood Mononuclear Cells (PBMCs) and on Paraffin Embedded Tissue by Immunohistochemistry

To compare markers of antibody-dependent cellular-mediated cytotoxicity (ADCC) pre-necitumumab and post-completion of necitumumab administration by peripheral blood collection and conducting flow cytometry of effector cells (T-cell subsets, NK-cells), measuring IL-2 and IL-12 cytokine levels and evaluation of regulatory T-cells (anti-CD4, anti-CD8, anti-CD20 and anti-$FoxP3^{+}$) from tumor tissue by immunohistochemistry.

9.1.3.1 Collection of Specimen(s)

We will collect 5 ml of peripheral blood prior to initiation of neoadjuvant therapy, prior to cycle 2 and cycle 3 of neoadjuvant therapy and following completion of neoadjuvant therapy.

We will put all effort to obtain the diagnostic tissue blocks from the diagnostic biopsy for the pre-chemotherapy presence of regulatory T-cells (Treg). Post-treatment Treg presence or absence will be obtained from the surgical resection. Pre- and post-treatment tumor specimens will be obtained in available patients.

9.1.3.2 Handling of Specimen(s)

Flow cytometry of peripheral blood mononuclear cells will be analyzed for $CD3^{-}$ $CD56^{+}$ NK cells and T-cell subsets. Measurement of IL-2 and IL-12 will also be conducted.

Baseline levels of regulatory T-cells (Treg $CD4^{+}CD25^{high+}FoxP3^{+}$) (if pre-treatment tissue available) and post-treatment Tregs will be evaluated in paraffin embedded tissue and fresh frozen tissue (if available) by immunochemistry.

9.1.3.3 Site(s) Performing Correlative Study

Flow cytometry, cytokine level measurement and immunochemistry will be performed by Montefiore Medical Center.

9.2 Priority of Exploratory Correlative Studies

In the event that inadequate amount of tissue is available for all 3 correlative studies (EGFR expression testing by IHC, EGFR gene copy number by FISH and ADCC testing on paraffin embedded tissue by IHC), the studies should be conducted in this order of priority:

1. EGFR expression testing by IHC
2. ADCC testing on paraffin embedded tissue by IHC
3. EGFR gene copy number by FISH

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Day 1 of Cycles 2 and 3 (during Weeks 4 and 7) may be started ±3 days of scheduled date.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10-12	Wk 13-15	Wk 16-20	Off Study[e]
Necitumumab		A	A		A	A		A	A					
Gemcitabine		B	B		B	B		B	B					
Cisplatin		C			C			C						
Surgical Resection												X		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											X	
Physical exam	X	X			X			X			X		X	X
Vital signs	X	X			X			X			X		X	X
Height	X													
Weight	X	X	X		X	X		X	X		X		X	X
Performance status	X	X			X			X			X		X	X
CBC w/diff, plts	X	X	X		X	X		X	X		X			X
Serum chemistry[a, b]	X	X	X		X	X		X	X	X	X	X	X	X
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	
Radiologic evaluation[d]	X										X			
B-HCG	X[c]													
EGFR Expression by IHC	X[e]												X	
EGFR Copy Number by FISH	X[e]												X	
PBMC for ADCC activity		X			X			X			X			
FoxP3$^+$ by IHC	X[d]												X	

A: Necitumumab: Dose as assigned; *administration schedule*
B: Gemcitabine: Dose as assigned*; administration schedule*
C: Cisplatin: Dose as assigned; *administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum magnesium should be followed for at least 8 weeks following the completion of necitumumab.
c: Serum pregnancy test (women of childbearing potential).
d: PET/CT at diagnosis; follow-up imaging at week 10-12 may be CT Chest/Abdomen/Pelvis or PET/CT if able to obtain
e: If adequate tissue sample is available.
f: Off-study evaluation.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 3 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 2-4 weeks prior to surgical resection.

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.

11.1.1 Definitions

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

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.

11.1.2 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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.

11.1.3 Methods for Evaluation of Measurable Disease

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.

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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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.

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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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 (0.5 cm). (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.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers 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 marker 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).

11.1.4.3 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.

11.1.5 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.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.2 Other Response Parameters

Pathologic complete response (pCR) will be evaluated separately at the lung primary tumor and nodal sites. It will be defined as the absence of residual invasive disease following neoadjuvant treatment.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

This trial will be monitored by the Albert Einstein Cancer Center Data Safety Monitoring Committee (AECC DSMC). A copy of the monitoring plan is maintained at the CPDMU**.** The DSMC as part of its function performs quarterly reviews of Clinical Trials Compliance Audits, monthly reviews Adverse Events Reports, and monthly reviews of internally monitored Phase I/Phase II trials for accrual and response. Other monitoring activities are established as necessary in a protocol specific manner**.**

This trial will be part of the monthly Quality Assurance Audits. Each patient will be evaluated within 8 weeks of registration. This permits evaluation of consent, eligibility, and treatment/dose modification/Adverse Event (AE) reporting, and data quality for the

first cycle (or month) of treatment.

This trial may also be eligible for quarterly Quality Enhancement Audit. Each audit consists of a review of regulatory documents, pharmacy drug accountability (if applicable) and patient case review, confirming eligibility, protocol compliance and source documentation

The results of the audit will be presented at the following month's DSMC meeting. The DSMC has the authority to close trial to patient accrual should the risk to patients be excessive or results require a corrective plan from the Principal Investigator. All study suspensions and closures will be forwarded to the IRB and study sponsor. All audit reports are forwarded to the DSMC and presented to the DSMC by the Audit Committee Coordinator.

12.2 Data Management

This trial will be monitored by the Albert Einstein Cancer Center Data Safety Monitoring Committee (AECC DSMC). A copy of the monitoring plan is maintained at the CPDMU**.** The DSMC as part of its function performs quarterly reviews of Clinical Trials Compliance Audits, monthly reviews Adverse Events Reports, and monthly reviews of internally monitored Phase I/Phase II trials for accrual and response. Other monitoring activities are established as necessary in a protocol specific manner**.**

12.3 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This will be a single-arm study to primarily evaluate the feasibility of administering necitumumab added to gemcitabine and cisplatin as neoadjuvant treatment in treatment-naïve patients with stage IB (tumor size >4cm), II or IIIA squamous NSCLC. Feasibility will be assessed by the proportion of patients able to proceed to surgery after administering necitumumab in the neoadjuvant setting. These patients would otherwise be offered standard adjuvant chemotherapy (without necitumumab) for squamous cell lung cancer. Determination of surgical resectability will be reviewed at a multidisciplinary thoracic tumor board, attended by surgical oncology, medical oncology, radiation oncology, radiology, and pathology.

13.2 Primary Endpoint

The primary endpoint is a binary outcome: whether the patient is eligible to proceed to surgery following neoadjuvant chemotherapy with at least 1 cycle of necitumumab, gemcitabine and cisplatin. If the proportion of patients proceeding to surgery is greater

than 90%, the regimen is considered to be acceptable; if less than 70% of patients eligible to proceed to surgery, the regimen is deemed unacceptable and not feasible. A Simon's optimal two-stage design will be used with 80% power and a two-sided type I error rate less than 10%. Specifically, after testing necitumumab on 6 patients in the first stage, the trial will be terminated if 4 or fewer are eligible for surgery. If the trial goes on to the second stage, a total of 20 patients will be studied. If the total number of patients eligible for surgery is less than or equal to 16, the drug is rejected and the regimen is deemed not feasible. The proportion of eligibility for surgery will be reported as well as its 95% CI.

13.3 Secondary Endpoints

Secondary endpoints include:

- Response (CR or PR) by RECISTv1.1
- Pathologic complete response rate (pCR)
- Disease-free survival/Progression-free survival defined as the duration from date of study enrollment to date of first documentation of progression assessed by central review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.
- Overall survival
- Safety assessment and toxicity evaluation as defined by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 with neoadjuvant chemotherapy and necitumumab.

The pathologic complete response rate (pCR) will be evaluated using a one-stage design on these 20 patients. If the total number of patients with pCR is less than or equal to 2, the study will fail to conclude an adequate increase in pCR. This sample size has 80% power to detect an increase of pCR from the historical control of 4% to a target of 20%, with a type I error rate not more than 10%.

The clinical response rate, frequency and severity of toxicities, and estimated 2-year disease-free survival of these patients will be estimated by proportions and presented with associated 95% confidence intervals. With 20 patients, proportions can be estimated with standard error not more than 6%. Any toxicity with at least 10% prevalence has at least an 88% chance of being observed. A Kaplan-Meier survival curve will also be generated to report the overall survival.

13.4 Sample Size/Accrual Rate

In this study, we plan to accrue 22 patients in order to obtain a preliminary estimate of the proportion of patients able to proceed to surgery and assess the feasibility of the regimen and account for a 10% attrition rate. The finding of the study will be used to design future more definitive studies to evaluate the efficacy of this regimen defined as clinical

response and/or pathological response in comparison with standard therapy.

This study will be conducted within the major oncology practice sites of the Montefiore Health System, the largest provider of healthcare and particularly oncological care in the Bronx and Lower Westchester region of New York. The study will be primarily conducted at Montefiore Medical Center, which sees approximately 400 lung cancer patients each year, and its new affiliate site, White Plains Hospital, which sees approximately 200 lung cancer patients each year. Of the approximately 600 lung cancer patients, we estimate approximately 30 patients per year across the health system will present with resectable squamous NSCLC. In addition to these Centers, the trial will be performed at up to 2 additional Centers in the NY/NJ region. We estimate that the proposed study can be fully accrued within 18-24 months of study activation, and should take approximately 30 months to complete the study. We expect an accrual rate of 1-2 patients per month for a total duration of 12-18 months of study activation.

13.5 Correlative Studies

EGFR expression by immunohistochemistry will be scored based on the H-score. Based on the H-score, samples from pre- and post-surgery will be classified as either “EGFR expressors” or “EGFR non-expressors.” EGFR gene copy number by FISH will be either positive or negative based on Colorado Scoring Criteria and correlated with response rate of necitumumab. The EGFR expression will be correlated with response rate of necitumumab using a two-sample t-test by comparing the EGFR levels between responders and non-responders.

In addition, presence of markers for antibody-dependent cellular-mediated cytotoxicity (ADCC) will be investigated on pre-necitumumab and post-completion of necitumumab doses by peripheral blood collection and subsequent flow cytometry of effector cells (T-cell subsets, NK-cells) and cytokines (IL-2, IL-12) and correlated with response rate of necitumumab. $FoxP3^{+}$ for regulatory T-cell expression by immunochemistry on pre-necitumumab (if adequate tissue available) and post-necitumumab treatment on surgical resection will be conducted and correlated with response rate of necitumumab. Analysis of within person change from pre- to post-necitumumab will be compared using a paired t-test. Further, the change between pre- and post-necitumumab will be correlated with response rate of necitumumab.

REFERENCES

1. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3:819-31.
2. Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. J Thorac Oncol 2010;5:510-6.
3. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012;30:172-8.
4. Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol 2012;13:33-42.
5. Paz-Ares L, Socinski MA, Shahidi J, et al. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol 2016.
6. Bleeker WK, Lammerts van Bueren JJ, van Ojik HH, et al. Dual mode of action of a human anti-epidermal growth factor receptor monoclonal antibody for cancer therapy. J Immunol 2004;173:4699-707.
7. Dechant M, Weisner W, Berger S, et al. Complement-dependent tumor cell lysis triggered by combinations of epidermal growth factor receptor antibodies. Cancer Res 2008;68:4998-5003.
8. Srivastava RM, Lee SC, Andrade Filho PA, et al. Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer patients. Clin Cancer Res 2013;19:1858-72.
9. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-31.
10. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763-74.
11. Herbst R, Redman MW, Kim ES, et al. A randomized, phase III study comparing carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced non-small cell lung cancer (NSCLC): SWOG S0819. World Conference on Lung Cancer. Denver, CO.2015.
12. Hirsch FR, Herbst RS, Olsen C, et al. Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. J Clin Oncol 2008;26:3351-7.
13. Kurai J, Chikumi H, Hashimoto K, et al. Antibody-dependent cellular cytotoxicity mediated by cetuximab against lung cancer cell lines. Clin Cancer Res 2007;13:1552-61.
14. Genova C, Hirsch FR. Clinical potential of necitumumab in non-small cell lung carcinoma. Onco Targets Ther 2016;9:5427-37.
15. Trivedi S, Concha-Benavente F, Srivastava RM, et al. Immune biomarkers of anti-

EGFR monoclonal antibody therapy. Ann Oncol 2015;26:40-7.
16. Pircher A, Gamerith G, Amann A, et al. Neoadjuvant chemo-immunotherapy modifies CD4(+)CD25(+) regulatory T cells (Treg) in non-small cell lung cancer (NSCLC) patients. Lung Cancer 2014;85:81-7.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B INFORMED CONSENT

ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

A Feasibility and Biomarker Study to Evaluate Necitumumab in the Neoadjuvant Setting with Gemcitabine and Cisplatin in Surgically Resectable Squamous Cell Lung Cancer

OR

Study Title for Participants:
Testing the Addition of Necitumumab to Standard Chemotherapy with Gemcitabine and Cisplatin Before Surgery in Squamous Cell Lung Cancer

Introduction

You are being asked to participate in a research study called **A Feasibility and Biomarker Study to Evaluate Necitumumab in the Neoadjuvant Setting with Gemcitabine and Cisplatin in Surgically Resectable Squamous Cell Lung Cancer.** Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

The researchers in charge of this project are called the "Principal Investigators." His name is Dr. Balazs Halmos. You can reach Dr. Halmos at:
Office Address:
1695 Eastchester Road, 2nd Floor
Bronx, NY 10461
Telephone #: 718-405-8404
For questions about the research study, or if you believe you have an injury, contact the Principal Investigator or the IRB.

The Institutional Review Board (IRB) of the Albert Einstein College of Medicine and Montefiore Medical Center has approved this research study. The IRB # is in the stamp in the upper right hand corner. If you have questions regarding your rights as a research subject you may contact the IRB office at 718-430-2253, by e-mail at irb@einstein.yu.edu, or by mail:

Einstein IRB
Albert Einstein College of Medicine
1300 Morris Park Ave., Belfer Bldg #1002
Bronx, New York 10461

Support for this research study is provided by **Eli Lilly.**

Why is this study being done?

The goal of this study is to explore whether it is possible to add another drug called necitumumab to standard treatment for patients with squamous cell lung cancer that

can be surgically removed. This study is important because we want to determine whether there is added benefit to giving necitumumab with chemotherapy before surgery. It is currently already known that chemotherapy given before or after surgery has better outcomes compared to only receiving surgery. Results from this study would help to develop more effective treatments for patients with squamous cell lung cancer like you.

The U.S. Food and Drug Administration (FDA) has approved necitumumab in combination with chemotherapy drugs called gemcitabine and cisplatin to treat stage IV or metastatic squamous cell lung cancer, but the FDA has not approved necitumumab to treat squamous cell lung cancer that can be surgically removed.

Analyzing the tumor cells from many cases of squamous cell lung cancer has shown that this cancer often expresses a special protein called EGFR on the tumor cell. Necitumumab is a type of treatment called a monoclonal antibody that specifically targets EGFR on cancer cells.

Results from a published medical study showed that patients with stage IV or metastatic squamous cell lung cancer who received necitumumab with gemcitabine and cisplatin showed a small, but significant, improvement in survival. We believe trying to gather more information about the way necitumumab interacts with cancer cells will help us to learn how to use necitumumab more effectively.

This study will allow us to see the effects of treating an earlier stage of squamous cell lung cancer using necitumumab with gemcitabine and cisplatin. It will also allow us to better analyze tumor cells after they have been treated with necitumumab and chemotherapy that are obtained after surgical resection. Although it is not guaranteed, some people who receive chemotherapy before surgery have tumor shrinkage. Other blood samples that will be drawn during the treatment will also allow us to see the effect of necitumumab on both the body and the tumor cells. We also want to observe any side effects that may result from this treatment.

Why am I being asked to participate?

You are being asked to participate in this study because you have been diagnosed with a type of lung cancer called Squamous Cell Lung Cancer. Your physicians have determined that you have stage IB (with tumor size >4cm), stage II, or IIIA disease and may benefit from chemotherapy prior to surgical resection.

At this point, there may be other standard treatment options for patients with your condition. Standard of care treatment includes the option of chemotherapy prior to surgical resection or receiving chemotherapy after surgical resection. You are being offered this study because your physician thinks that a drug called necitumumab in addition to the standard of care of gemcitabine and cisplatin prior to surgical resection might have added benefit.

How many people will take part in the research study?

You will be one of about **22** people who will be participating in this study.

How long will I take part in this research?

It will take you about **6 months** to complete this research study. During this time, we will ask you to make **7** study visits to Montefiore Medical Center.

What will happen if I participate in the study?

The Screening Visit will take about **30 minutes**. During this visit, we will do some tests and procedures to see if you are eligible to take part in this research study. The study doctor will review the results of these tests and procedures. If you aren't eligible, the study doctor will tell you why. At this visit we will:

- Ask you about your medical history
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample of about two (2) tablespoons of blood to be drawn from one of your veins to conduct laboratory tests of blood cell counts (number of each type of blood cell), chemistries (elements and minerals in your blood).
- Ask you for a urine sample
- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- You will have a PET/CT scan, if not already done as part of your standard work up, to determine the extent of your disease and stage
- If you have stage IIIA disease, we will obtain a MRI Brain to complete staging.

It is possible that after these tests and procedures are reviewed, you will not be able to take part in the study. There may also be other reasons why you cannot participate which will be discussed with you by your doctor.

If you are eligible for the medical study, you will begin treatment within 2 weeks.

This will be a single arm medical study and all the patients in the medical study will receive the same kind of treatment.

Treatment will be given in cycles.

- You will be asked to return to the clinic once every three weeks for a visit with your physician during the treatment with necitumumab, gemcitabine and cisplatin. You will be receiving the chemotherapy over a period of about 9 weeks then be evaluated for surgery.
- One cycle is three weeks (21 days). You will need to come to the clinic to receive the treatment.

- You will have two (2) tubes of blood drawn prior to each chemotherapy session, about 2 tablespoons, to check your blood cell counts (number of each type of blood cell) and chemistries (elements and minerals in the blood). This blood draw would have been done even if you were not in this study and receiving standard of care chemotherapy.
- You will have one (1) additional tube of blood drawn on day 1 of each cycle for research purposes to check the possible effect of necitumumab on your blood cells.
- You will receive necitumumab and gemcitabine once a week during week 1 and week 2, and cisplatin once a week during week 1. During week 3 you will receive no treatment.
- We will continue the same treatment regimen for three cycles (9 weeks).
- Necitumumab, gemcitabine and cisplatin will be given by intravenous infusion through your veins. Treatment during week 1 with necitumumab, gemcitabine and cisplatin will last between 4-5 hours. Treatment during week 2 with necitumumab and gemcitabine will last between 2-3 hours.
- After three (3) cycles of chemotherapy treatment, you will have a CT or PET/CT scan to determine whether you are responding to treatment (i.e. whether or not the tumor became smaller in size or remains stable) or not. You will then be evaluated by a surgeon who will recommend if you should have surgical removal of the remaining tumor.
- Your treatment after the surgery will be determined by your treating physician and it will be influenced by your response to the treatment with necitumumab, gemcitabine and cisplatin.

It is important to understand that taking part in this study requires a commitment from you to visit the clinic for the regular appointments. You may withdraw from the study at any time.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Laboratory Research Studies

If you participate in this study, your tumor tissue collected from a previous biopsy or surgery will be sent to researcher to determine several molecular and cellular biomarkers in the tumor. Researchers hope this research will help them understand how your disease responds to the treatment.

The results of the laboratory research studies will not be sent to you or your doctor, will not be placed in your medical records, and will not affect your care. These tests are for research purposes only.

Genetic Testing

Genes are made up of DNA, and have the information needed to build and operate the human body. Your tumor tissue will be tested for genetic changes that may reveal genetic information about your tumor. The meaning of the results of this genetic research is not known; therefore we will not give you the results of these studies. You should be aware that insurance companies sometimes use information from genetic testing to deny life insurance or disability coverage to applicants. If you decide to participate in this research study, if your insurance company asks, you should state that although you have had a genetic test performed as part of a research study, the test is investigational and has no clinical meaning, and you will not be provided with the results.

Specimen Banking (Future Use and Storage)

We will store your specimens and information about you in a "biobank," which is a library of information and specimens (tissue and blood) from many studies. These specimens and information cannot be linked to you. In the future, researchers can apply for permission to use the specimens and information for new studies to prevent, diagnose, or treat disease, including genetic research. Your specimens and information may be kept for a long time, perhaps longer than 50 years. If you agree to the future use, some of your de-identified genetic and health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government.

You can choose not to participate in the biobank and still be part of the main study and this will not affect your treatment at this facility.

INITIAL ONE (1) OF THE FOLLOWING OPTIONS

_____ I consent to have my specimens and information about me used for future research studies.

_____ I do NOT consent to have my specimens and information about me used for future research studies. Information about me will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Will I be paid for being in this research study?

You will not receive any payment or other compensation for taking part in this study.

Some researchers may develop tests, treatments or products that are worth money. You will not receive payment of any kind for your specimens and information or for any tests, treatments, products or other things of value that may result from the research.

Will it cost me anything to participate in this study?

- Taking part in this study may lead to added costs to you or your insurance company There may be extra costs that may or may not be covered.
- There is no cost to you for necitumumab. However, you or your insurance company will be paying for the costs of other necessary medications for your disease, routine blood tests, scans, other laboratory tests, surgical procedures and your routine medical care.
- If your insurance company does not cover the cost of routine care, then you will have to pay these costs. You have the right to ask what it will cost you to take part in this study or to have other treatments.
- You will not be charged for any research related studies like the laboratory and future research done on your blood or tumor tissue, if you agree.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What will happen if I am injured because I took part in this study?

If you are injured as a result of this research, only immediate, essential, short term medical treatment, as determined by the participating hospital or sponsoring company will be available for the injury without charge to you personally.

- No monetary compensation will be offered.
- You are not waiving any of your legal rights by signing this informed consent document

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to **Dr. Balazs Halmos at (718) 405-8404**.

What else do I have to do?

- *You must tell the research study doctor about any past and present diseases or allergies you are aware of and about all medications you are taking including "over-the-counter" remedies and nutritional supplements or herbs.*
- *If you do not feel well at any time, call your doctor or the research study doctor immediately.*
- ***Drugs may cause a reaction that, if not treated promptly, could be life-threatening. It is important that you report all symptoms, reactions and other complaints to the research study doctor.***
- *If you think you have become pregnant, contact your research study doctor immediately.*

- *If any other doctor recommends that you take any medicine, please inform him/her that you are taking part in a research study. You should give the other doctor the research study doctor's name and phone number.*
- *You may carry out all your normal daily activities.*

Confidentiality

We will keep your information confidential. Your research records will be kept confidential and your name will not be used in any written or verbal reports. Your information will be given a code number and separated from your name or any other information that could identify you. The form that links your name to the code number will be kept in a secure manner and only the investigator and study staff will have access to the file. All information will be kept in a secure manner and computer records will be password protected. Your study information and specimens will be kept as long as they are useful for this research.

Medical information collected during the research, such as test results, may be entered into your Montefiore electronic medical record and will be available to clinicians and other staff at Montefiore who provide care to you.

The only people who can see your research records are:

- the research team and staff who work with them
- the organization that funded the research
- organizations and institutions involved in this research: Eli Lilly
- groups that review research (the Einstein IRB, and the Office for Human Research Protections, and the US Food and Drug Administration)

These people who receive your health information, may not be required by privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them. All of these groups have been asked to keep your information confidential.

Are there any risks to me?

Blood Draw

Rarely, the vein where we inserted the needle will become sore or red. Sometimes, a temporary harmless "black and blue" may develop. Very rarely, fainting may occur.

Risks of Taking Necitumumab

Common side effects (in 100 patients receiving necitumumab, 20 or more patients might experience):

- Skin rash
- Vomiting
- Diarrhea
- Low magnesium

Less common side effects (in 100 patients receiving necitumumab, 6 to 20 patients might experience):

- Loss of weight
- Headache
- Inflammation of the mouth or lips
- Coughing up of blood
- Blood clot

Uncommon side effects (in 100 patients receiving necitumumab, 5 or less patients might experience):

- Reaction while the drug is being infused through your vein
- Cardiac arrest
- Blood clot in the lung
- Breakdown in the skin

There may be other risks of **necitumumab** that are currently unknown.

Risks of Taking Gemcitabine and Cisplatin (These drugs are part of standard treatment.)

Common side effects (in 100 patients receiving gemcitabine and cisplatin, 20 or more patients might experience):

- Nausea
- Vomiting
- Infection, especially when white blood cell count is low
- Anemia which may require blood transfusions
- Bruising, bleeding
- Kidney damage, which may cause swelling, may require dialysis
- Hearing loss including ringing in ears
- Flu-like symptoms of muscle pain, fever, headache, chills and fatigue
- Rash
- Hair loss
- Muscle weakness
- Blood in urine
- Feeling of “pins and needles” in arms and legs
- Numbness and tingling of the arms and legs
- Tiredness
- Difficulty sleeping
- Swelling of arms, legs

Less common side effects (in 100 patients receiving gemcitabine and cisplatin, 6 to 20 patients might experience):

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Confusion
- Difficulty with balance

- Diarrhea, constipation
- Sores in mouth which may cause difficulty swallowing
- Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles
- Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

Uncommon side effects (in 100 patients receiving necitumumab, 5 or less patients might experience):

- Cancer of bone marrow (leukemia) caused by chemotherapy later in life
- Seizure
- Abnormal heartbeat
- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, and tiredness
- Blisters on the skin
- Sores on the skin
- Blood clot
- Liver damage which may cause yellowing of eyes and skin, swelling
- Damage to organs which may cause shortness of breath
- Scarring of the lungs
- Fluid around lungs
- Blockage of the airway which may cause cough

Risks to Women Who Are or May Become Pregnant

The effect of necitumumab on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding or sharing breast milk

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control for 3 months after completing necitumumab.

Acceptable birth control methods for use in this study are:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants

- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug.

For your safety during this study, call your study doctor BEFORE you take any:

- New medications prescribed by your doctor
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

Allergic Reaction to Study Drug

Any drug can cause an allergic reaction which could be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you are having trouble breathing, call 911 immediately.

New Findings

If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them. We will discuss the new findings with you and whether you want to continue in the study. If you decide to withdraw, your study doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to remove you from the study. He/she will explain the reasons and arrange for your care to continue.

Unknown Risks

We have described all the risks we know. However, because this is research, there a possibility that you will have a reaction that we do not know about yet and is not expected. If we learn about other risks, we will let you know what they are so that you can decide whether or not you want to continue to be in the study.

Are there possible benefits to me?

You may or may not receive personal, direct benefit from taking part in this study. Although it is not possible to predict or guarantee whether any person benefit will result from your participation in this study, one possible benefit is decreasing the size of your tumor with necitumumab followed by complete surgical resection. Although this does not guarantee cure, it may increase your chances of being cured or living longer. In addition, the information learned from this study will benefit other patients with squamous cell lung cancer in the future.

What choices do I have other than participating in this study?

You can refuse to participate in the study. If you decide not to participate, the medical care providers at this facility will still give you all of the standard care and treatment that is appropriate for you.

Your other choices are:

- You may choose not to participate in this medical study and/or take part in another medical study.
- You may receive chemotherapy followed by surgery.
- You may receive surgical resection followed by either chemotherapy alone or chemotherapy and radiation.
- You may receive other investigational protocols with chemotherapy that may be available for your disease.
- You may choose no treatment.

Please ask any questions you may have and take as much time as you need to make your decision.

Are there any consequences to me if I decide to stop participating in this study?

No. If you decide to take part, you are free to stop participating at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility. However, some of the information may have already been entered into the study and that will not be removed. The researchers and the sponsor may continue to use and share the information they have already collected.

To revoke (take back) your consent and authorization, you must contact the Principal Investigator in writing at the address on page 1 of this form. However, you may first call or speak to the Principal Investigator and he will stop collecting new information about you. If you take back your consent and authorization, you will not be allowed to continue to participate in this research study.

Can the study end my participation early?

We will not let you participate in the study any more if:

- Your disease becomes worse.
- Your medical condition changes during treatment and continuing in the study does not appear to be in your best interest, you will be told, the treatment will be stopped, and other options for your medical care will be discussed with you.
- Any severe or life-threatening side effects develop. The drugs will be stopped if such side effects develop and appropriate medical care will be provided.
- Any safety issues or regulatory requirements arise that would cause the end of your participation in the study or that would end the study altogether.
- You are a woman, and you become pregnant.

In addition, your participation will end if the investigator or study sponsor stops the study earlier than expected.

You may stop participating at any time. However, if you decide to stop participating in this medical study we encourage you to talk to the study doctor first.

Who can answer my questions about the study?

Researcher's Name: Dr. Balazs Halmos
Office Address: 1695 Eastchester Road, Bronx, NY 10461
Office Phone: 718-405-8404

- If any questions arise related to this medical study, or you believe you have any injury related to this study, you can call the researchers above.
- You may also call [RESEARCH NURSE].
- If you have questions regarding your rights as a research participant, you may also call the Manager of Einstein IRB at (718) 430-2253, Monday through Friday between 9 AM and 5 PM.

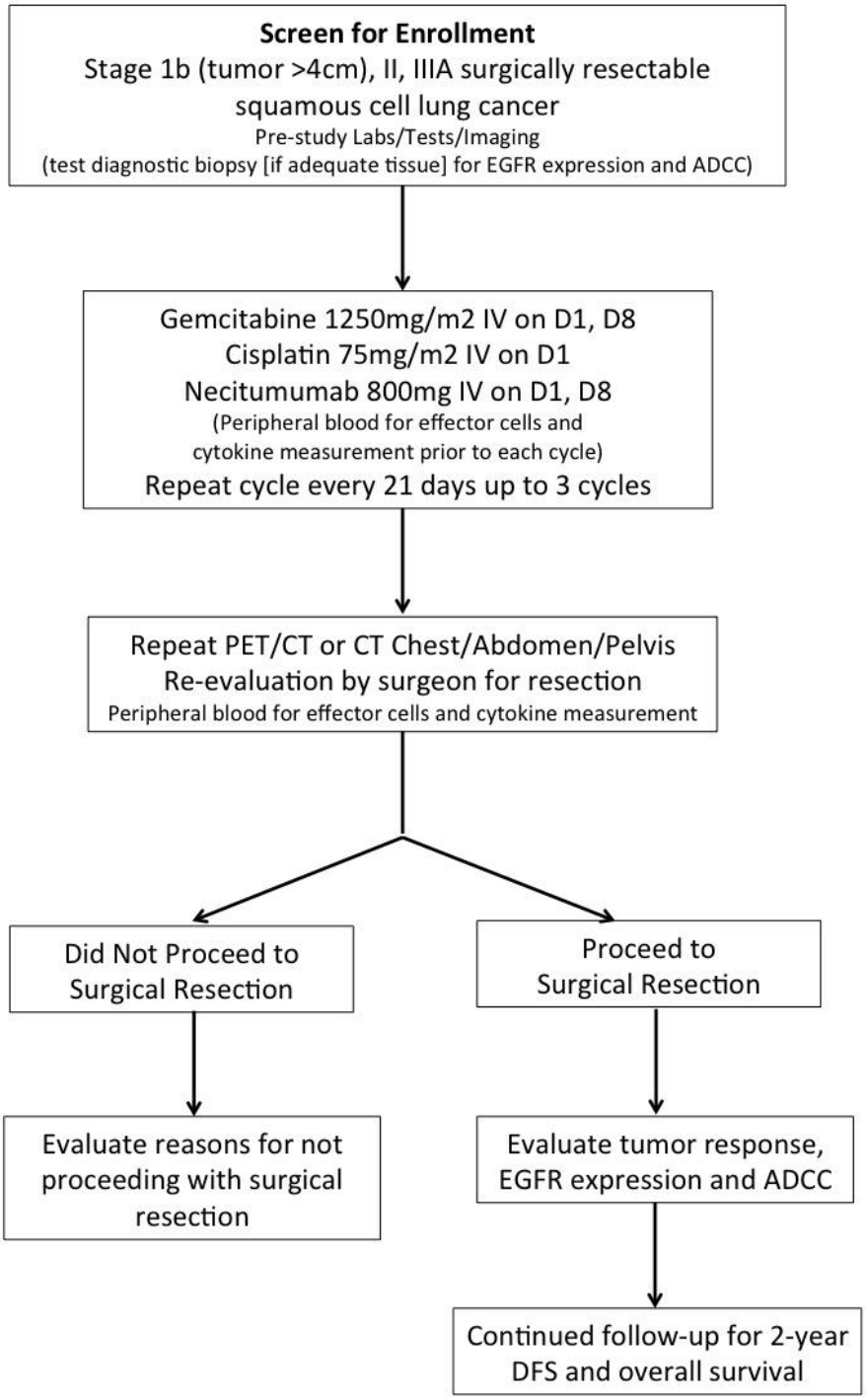
CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant	Date	Time
Printed name of the person conducting the consent process	Signature	Date	Time

APPENDIX C STUDY SCHEMA FOR PARTICIPANT

Study Schema



APPENDIX D STUDY CALENDAR FOR THE PARTICIPANT

Of note, treatment can sometimes be delayed for abnormal blood tests, side effects or other events and this schedule may need to be changed if necessary.

Time	Schedule of Treatment/Tests/Imaging/Procedure
Pre-Study	• Clinic visit to obtain medical history, medication list, physical exam, vital signs, level of activity • Baseline blood tests • Baseline EKG • PET/CT scan if not already completed • MRI Brain for stage IIIA patients only
Week 1	• Clinic visit for history and physical exam • Pre-chemotherapy blood tests and research blood test • Cycle 1 Day 1 of Necitumumab, Gemcitabine and Cisplatin
Week 2	• Pre-chemotherapy blood tests • Cycle 1 Day 8 of Necitumumab and Gemcitabine
Week 3	Week Off of Treatment
Week 4	• Clinic visit for history and physical exam • Pre-chemotherapy blood tests and research blood test • Cycle 2 Day 1 of Necitumumab, Gemcitabine and Cisplatin
Week 5	• Pre-chemotherapy blood tests • Cycle 2 Day 8 of Necitumumab and Gemcitabine
Week 6	Week Off of Treatment
Week 7	• Clinic visit for history and physical exam • Pre-chemotherapy blood tests and research blood test Cycle 3 Day 1 of Necitumumab, Gemcitabine and Cisplatin
Week 8	• Pre-chemotherapy blood tests • Cycle 3 Day 8 of Necitumumab and Gemcitabine
Week 9	Week Off of Treatment
Week 10-12	• Clinic visit for history and physical exam • Post-chemotherapy blood tests including magnesium and research blood test • Repeat PET/CT or CT Chest/Abdomen/Pelvis to evaluate for response • Re-evaluation by surgeon
4-6 weeks after completing chemotherapy	If the tumor has decreased in size or remained stable and you are medically fit, you will undergo surgical resection.
4 weeks after surgery	• Clinic visit for history and physical exam • Routine blood tests including magnesium levels for at least 8 weeks following completion of necitumumab. • Continued routine followup of your disease.