GI 201

A Phase II Study of Nab-paclitaxel plus Ramucirumab for the Second-line Treatment of Patients with Metastatic Gastroesophageal Cancer

SCRI INNOVATIONS STUDY NUMBER:	GI 201
STUDY DRUG(S):	Nab-paclitaxel
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Johanna Bendell, MD Director, GI Oncology Research Associate Director, Drug Development Unit Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI jbendell@tnonc.com
DATE FINAL:	18 November 2014

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Statement of Compliance

A Phase II Study of Nab-paclitaxel plus Ramucirumab for the Second-line Treatment of Patients with Metastatic Gastroesophageal Cancer

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from SCRI Innovations, shall be defined as a deviation from the protocol, and shall be formally documented as such.

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Signature Approval Page

A Phase II Study of Nab-paclitaxel plus Ramucirumab for the Second-line Treatment of Patients with Metastatic Gastroesophageal Cancer

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Johanna Bendell, MD		
Study Chair	**Study Chair Signature**	**Date**

Sheetal Khedkar		
SCRI Development Innovations, LLC	**SCRI Development Innovations, LLC Representative Signature**	**Date**

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Principal Investigator Signature Form

A Phase II Study of Nab-paclitaxel plus Ramucirumab for the Second-line Treatment of Patients with Metastatic Gastroesophageal Cancer

SCRI INNOVATIONS STUDY NUMBER:	GI 201
DATE FINAL:	18 November 2014

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations, LLC
3322 West End Avenue, Suite 900
Attn: GI 201 Study Team
Nashville, TN 37203

GI 201 PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study of Nab-paclitaxel plus Ramucirumab for the Second-line Treatment of Patients with Metastatic Gastroesophageal Cancer	
SCRI Innovations Study Number:	GI 201	
Sponsor:	SCRI Development Innovations, LLC – Nashville - TN	
Study Duration:	The total duration of the study is planned to be 27 months	**Phase of Study:** II
Study Centers:	This study will be conducted at multiple sites.	
Number of Patients:	Up to 65 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objective** The primary objective of this study is to: • Determine the progression free survival (PFS) of patients receiving nab-paclitaxel in combination with ramucirumab as second-line therapy for metastatic gastroesophageal (GE) cancer. **Secondary Objectives** The secondary objectives of this study are to: • Evaluate other efficacy measurements of this regimen (response rate [RR], time to progression [TTP], and overall survival [OS]) of nab -paclitaxel plus ramucirumab as second-line therapy for metastatic gastroesophageal cancer • Further evaluate toxicities associated with this regimen in patients with metastatic GE cancer.	
Study Design:	This is a Phase II, open-label, non-randomized study. Patients will be given nab-paclitaxel by IV at a dose of 125 mg/m^2 on Days 1, 8, and 15 of a 28 day cycle (weekly for 3 weeks with 1 week of rest) in combination with ramucirumab 8 mg/kg IV on Days 1 and 15. Restaging will occur every 2 cycles (8 weeks), and patients with an objective response or stable disease will remain on study until evidence of progressive disease or unacceptable toxicity.	
Study Drugs, Doses, and Modes of Administration:	Nab-paclitaxel 125 mg/m^2 IV Ramucirumab 8 mg/kg IV	

GI 201 PROTOCOL SYNOPSIS

Inclusion Criteria:	Patients must meet all the following criteria in order to be included in the research study: 1. Histologically confirmed metastatic adenocarcinoma of the esophagus, GE junction, or stomach that is not responsive to standard therapies. 2. Measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria Version 1.1 (Appendix E). 3. Patients must have progressed on one prior line of chemotherapy in the metastatic setting • Patients will be allowed to have had previous neoadjuvant and/or adjuvant chemotherapy or chemoradiation therapy as long as treatment was completed > 6 months prior to diagnosis of metastatic disease. The neoadjuvant or adjuvant therapy in this setting will not be counted as a line of therapy in the metastatic or advanced setting. • Patients who develop metastatic disease or worsening of localized disease within 6 months of the completion of neoadjuvant or adjuvant therapy will have the neoadjuvant or adjuvant therapy count as one line of therapy in the advanced setting. • Previous radiation therapy alone or in combination with single agent fluoropyrimidine (5-FU, capecitabine) in the localized or palliative setting will not count as a line of therapy. 4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A). 5. Adequate hematologic function defined as: – Absolute neutrophil count (ANC) ≥1500/mm^3 – Hemoglobin (Hgb) >9 g/dL – Platelets >100,000/mm^3 6. Adequate liver function defined as: – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) – Alkaline phosphatase ≤ 2.5 X upper limit of normal, unless bone metastasis is present in the absence of liver metastasis – Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin) 7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance >40 mL/min as calculated by Cockcroft and Gault Formula. 8. Patients must have < Grade 2 pre-existing peripheral neuropathy (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.03) 9. Women of childbearing potential must have a negative serum or urine pregnancy test performed ≤7 days prior to start of treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately. 10. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 6 months following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study (Appendix C). 11. Life expectancy > 3 months.

GI 201 PROTOCOL SYNOPSIS

Inclusion Criteria, continued	12. Age ≥18 years. 13. Willingness and ability to comply with study and follow-up procedures. 14. Ability to understand the nature of this study and give written informed consent.
Exclusion Criteria:	1. Patients who have received any other investigational agents, chemotherapy, biologic therapy, or radiation therapy within the 28 days prior to Day 1 of the study. For investigational, chemotherapy, or biologic therapy, patients will be allowed on study if 5 half- lives or greater have elapsed since last dose of drug or 28 days, whichever is shorter. 2. History of other carcinomas (in situ and invasive) within the last five years that, in the investigator's opinion, may affect interpretation of the endpoints of this study. 3. Patients with other concurrent severe and/or uncontrolled medical disease which could compromise safety of treatment as so judged by treating physician (i.e., severely impaired lung function, severe infection, ventricular arrhythmias active ischemic heart disease, known active vasculitis of any cause, chronic liver or renal disease). 4. Patients with prior taxane chemotherapy. 5. A known history of HIV seropositivity, hepatitis C virus, acute or chronic active hepatitis B infection, or other serious chronic infection requiring ongoing IV treatment. 6. Women who are pregnant or breast-feeding 7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit safety or compliance with study requirements or may interfere with the interpretation of the results.. 8. Inadequately controlled hypertension (blood pressure [BP]>150 systolic and/or diastolic >100 mmHg) (patients with values above these levels must have their BP controlled with medication prior to starting treatment). 9. Any of the following cardiac diseases currently or within the last 6 months: − Left Ventricular Ejection Fraction (LVEF) <45% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO) − QTc interval >480 ms on screening electrocardiogram (ECG) per institutional standard − Unstable angina pectoris − Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B]) − Acute myocardial infarction − Clinically significant conduction abnormality not controlled with pacemaker or medication − Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible) − Valvular disease with significant compromise in cardiac function 10. History of hypertensive crisis or hypertensive encephalopathy. 11. History of stroke or transient ischemic attack (TIA) within the past 6 months. 12. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of therapy. 13. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months. 14. Patients may not have received other agents, either investigational or marketed, which act by primary anti-angiogenic mechanisms.

GI 201 PROTOCOL SYNOPSIS

Exclusion Criteria, continued	15. Major surgical procedure, open biopsy; or significant traumatic injury within 28 days prior to study initiation, or anticipation of need for major surgical procedure during the course of the study. 16. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to initiation of therapy. 17. Patients with proteinuria, as demonstrated by a Urine Protein on dipstick of 2+ or greater at screening. 18. Any non-healing wound, ulcer, or bone fracture. 19. Any clinical evidence or history of a bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation). 20. Therapeutic anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Anticoagulation with low molecular weight heparin or anti-Factor Xa agents will be allowed. 21. History of hemoptysis (≥ ½ teaspoon of bright red blood per episode) within 1 month prior to initiation of therapy.
Statistical Methodology:	This is a Phase II, open-label, non-randomized study. The study is designed to determine the PFS of nab-paclitaxel in combination with ramucirumab for patients as second-line therapy for metastatic gastroesophageal cancer. The historical median PFS is 2.8 months; we hypothesize that nab-paclitaxel plus ramucirumab will increase median PFS to 5 months. With a 2-sided alpha of 5% and 80% power, a total of 52 events (progressions or deaths) will need to be observed. With an 18-month recruitment and 6 months follow-up, assuming 20% of patients recruited will be free from progression or death at the end of the study, 65 patients will need to be recruited into the study in order to observe 52 events.

GI 201 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CEA	Carcinoembryonic antigen
CI	Confidence interval
CMP	Comprehensive metabolic profile
CO_2	Carbon dioxide
CR	Complete response/remission
CT	Computerized tomography
DCR	Disease control rate
DHEA	Dehydroepiandrosterone
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GE	Gastroesophageal
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator study file
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition

LIST OF ABBREVIATIONS (continued)

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDx	Pharmacodynamic
PHI	Protected health information
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response/remission
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality assurance
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SCRI Innovations SD	SCRI Innovations Safety Department
SD	Stable disease
SPARC	Secreted protein acidic and rich in cysteine
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
TTP	Time to progression
UAE	Unexpected Adverse Event
ULN	Upper limit of normal
USPI	US package insert
VEGF-2	Vascular endothelial growth factor receptor-2

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1. INTRODUCTION

1.1 Background

Adenocarcinoma of the esophagus and the gastroesophageal junction (GE junction) is the ninth most common cancer worldwide. Late mortality rate is high with only 8% of patients surviving more than five years with a median survival of nine months. Esophageal carcinoma affects adult patients in all ages with no difference in survival according to sex, racial background, or histological type. Over the past two decades, a shift in the incident and lethality of the gastric cancer has been noted in the Western countries. While incidents of distal gastric cancers have decreased, the incidence of adenocarcinomas of the proximal stomach and distal esophagus has increased (Blot et al. 1991; Pera et al. 1993; Devesa et al. 1998). In addition, the unique behavior of these proximal tumors makes them challenging to treat. These tumors are often located at the crossroads of two major body cavities; therefore, the lymphatic spread of the disease may occur in two directions—proximally into the mediastinum and distally to the celiac lymph nodes (Lerut et al. 2004). As a result, these tumors remain undiagnosed at an early stage and patients often present with a relatively advanced stage disease (Ajani et al. 2004).

1.2 Treatment for Metastatic Gastroesophageal Tumors

A multitude of trials in the metastatic setting exist for both esophageal and gastric adenocarcinoma, the preponderance including GE junctional tumors. Despite this abundance, there is no regimen in either disease that can achieve more than marginal success or superiority. As with most chemotherapy, combination regimens seem to be better for initial response, but this does not necessarily translate into survival.

Currently, multiple regimens are used in the treatment of metastatic esophagogastric cancers. These include: cisplatin and fluorouracil (5-FU) or CF, epirubicin, cisplatin, and 5-FU (ECF), epirubicin, oxaliplatin, and 5-FU (EOX), cisplatin and irinotecan, docetaxel, cisplatin, and 5-FU (DCF). The current United States Food and Drug Administration (FDA) standard comparator regimen is a combination of 5-FU and cisplatin. Until recently, there was no FDA standard comparator except best supportive care in the second line setting. There is data on the efficacy of taxane-based therapy in the second-line setting after progression on a prior platinum-based regimen. Studies have shown response rates of second line paclitaxel or docetaxel to range from 20% to 30%. Trials evaluating docetaxel or paclitaxel in this setting have shown time to treatment failure rates in the range of 2-5 months. The COUGAR trial was a randomized Phase III study that randomized second-line gastric cancer patients to docetaxel every three weeks or best supportive care. Patients who received docetaxel had an improved overall survival (OS) of 5.2 months compared to 3.6 months (hazard ration [HR] 0.67). Response rate (RR) to docetaxel was 7% (Ford et al. 2012). A recent randomized Phase III study of the anti-vascular endothelial growth factor receptor-2 (VEGFR2) antibody ramucirumab versus best supportive care for second-line treatment of gastric cancers showed an improved OS akin to docetaxel (5.2 vs. 2.6 months) and improved progression-free survival (PFS) (2.1 vs. 1.3 months) (Fuchs et al. 2012). Given the utilization of taxanes as second-line therapy, the RAINBOW study evaluated weekly paclitaxel plus or minus ramucirumab. This study showed an improvement in PFS (4.40 vs. 2.86

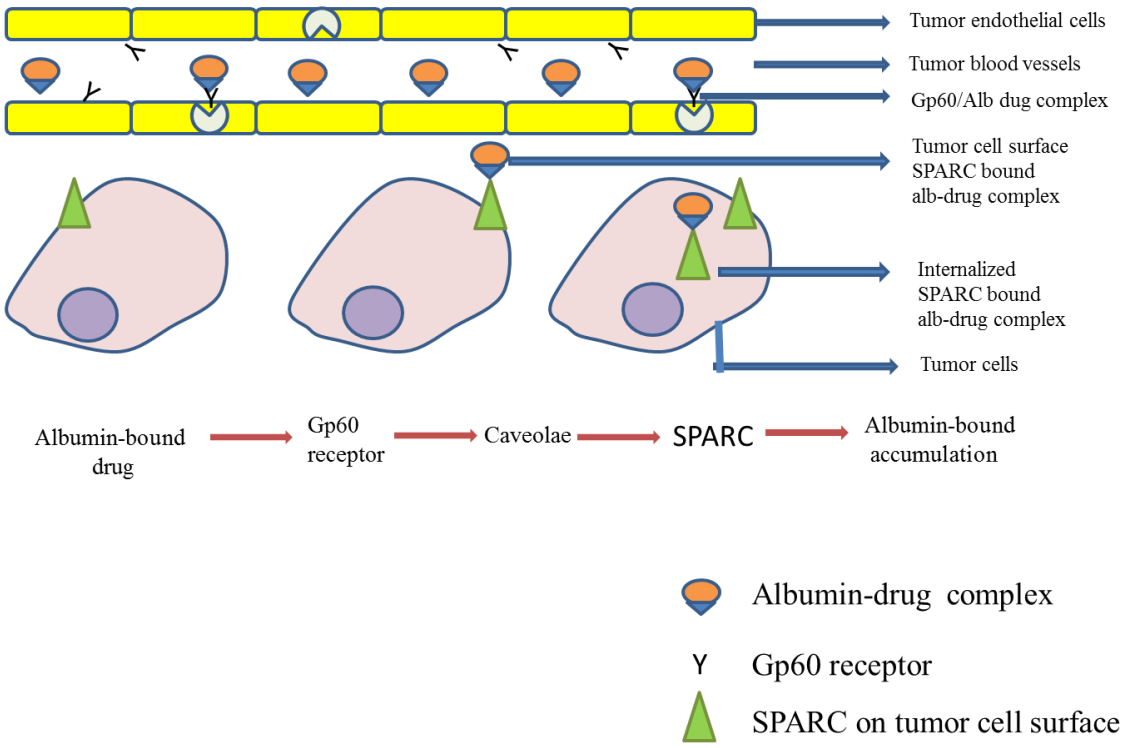
months, HR 0.635) and OS (9.63 vs. 7.63 months, HR 0.807) for patients who received the combination of paclitaxel and ramucirumab (Wilke et al. 2014). The FDA approved ramucirumab for treatment of patients in the second-line setting in April 2014.

1.3 Nab-paclitaxel

Nab-paclitaxel (Abraxane® [ABI-007]) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel, which also contains human albumin in a noncrystalline amorphous state, with a mean particle size of approximately 130 nanometers. Paclitaxel enhances the polymerization of tubulin to stable microtubules and also interacts directly with microtubules, stabilizing them against depolymerisation. The highly stable tubulin complexes lead to the formation of discordant and dysfunctional microtubule arrays, visible as "bundles" during mitotic cell division and results in apoptosis and cell death. Nab-paclitaxel has a similar mode of action and was developed to improve the therapeutic index and reduce toxicity, and can be administered via the intravenous (IV) route.

Nab-paclitaxel uses a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. This albumin-specific receptor mediated process involves the binding of a specific receptor (gp60) on the endothelial cell wall, resulting in the activation caveolin-1, which initiates an opening in the endothelial wall with formation of a little caves or caveolae, with transport of the albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium. A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane. Nab-paclitaxel is the first biologically interactive nanoparticle that exploits the gp-60/caveolin-1/SPARC pathway to enhance intra-tumoral concentration of the drug thereby significantly reducing normal tissue toxicity. Clinical studies have demonstrated less toxicity with nab-paclitaxel compared to solvent-based paclitaxel.

Figure 1 Mechanism of transport and accumulation of nab-paclitaxel in tumor cells



As of October 2013, nab-paclitaxel has been approved in over 40 countries/regions, for the treatment of patients with metastatic breast cancer, as well as for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) and metastatic adenocarcinoma of the pancreas.

1.4 Ramucirumab

Angiogenesis is required for cancer progression and establishment of metastatic lesions in distant organs. Vascular endothelial growth factor receptor-2 (VEGFR-2) is considered a key factor in cancer-associated angiogenesis, and is substantially expressed and associated with negative prognostic features in gastroesophageal and other cancers. Anti-VEGFR-2 antibodies have been shown to inhibit VEGF-stimulated receptor activation and proliferation of human leukemia cells (Lu et al. 2002; Lu et al. 2003). Therefore, these antibodies hold promise for further therapeutic application in other types of cancers including solid tumors and hematologic tumors, such as leukemia and lymphomas.

Ramucirumab (IMC-1121B [LY3009806]) is a recombinant human monoclonal antibody that specifically binds to the extracellular domain of the VEGFR-2. The binding of ramucirumab to VEGFR-2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D) and blocks activation of VEGFR-2 and its downstream intracellular signaling components,

including p44/p42 mitogen-activated protein kinases, inhibiting ligand-induced proliferation and migration of human endothelial cells.

1.5 Rationale for the Study

The REGARD trial (Fuchs et al. 2012) showed that ramucirumab was beneficial in patients with cancers of the esophagus and stomach. The RAINBOW trial (Wilke et al. 2014) demonstrated a beneficial effect on the OS when ramucirumab plus paclitaxel was used, compared to paclitaxel alone. However, neutropenia was more frequently reported in the combination arm.

The Phase II study we propose uses an albumin-based formulation of paclitaxel, which may potentially increase the tumor uptake of the drug, improving efficacy and minimizing the side effects. The biological rationale of using this combination is that ramucirumab will inhibit tumor angiogenesis and nab-paclitaxel will induce apoptosis of the rapidly dividing tumor cell.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Determine the progression-free survival (PFS) of patients receiving nab-paclitaxel in combination with ramucirumab as second-line therapy for metastatic gastroesophageal cancer.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate other efficacy measurements of this regimen (response rate [RR], time to progression [TTP], and overall survival [OS]) of nab -paclitaxel plus ramucirumab as second-line therapy for metastatic gastroesophageal cancer.
- Further evaluate toxicities associated with this regimen in patients with metastatic gastroesophageal cancer.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Histologically confirmed metastatic adenocarcinoma of the esophagus, GE junction, or stomach that is not responsive to standard therapies.
2. Measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria Version 1.1 (Appendix E).
3. Patients must have progressed on one prior line of chemotherapy in the metastatic setting

- Patients will be allowed to have had previous neoadjuvant and/or adjuvant chemotherapy or chemoradiation therapy as long as treatment was completed > 6 months prior to diagnosis of metastatic disease. The neoadjuvant or adjuvant therapy in this setting will not be counted as a line of therapy in the metastatic or advanced setting.
- Patients who develop metastatic disease or worsening of localized disease within 6 months of the completion of neoadjuvant or adjuvant therapy will have the neoadjuvant or adjuvant therapy count as one line of therapy in the advanced setting.
- Previous radiation therapy alone or in combination with single agent fluoropyrimidine (5-FU, capecitabine) in the localized or palliative setting will not count as a line of therapy.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
5. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) $\geq 1500/mm^3$
   - Hemoglobin (Hgb) >9 g/dL
   - Platelets $>100,000/mm^3$
6. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN)
   - Alkaline phosphatase ≤ 2.5 X upper limit of normal, unless bone metastasis is present in the absence of liver metastasis
   - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance >40 mL/min as calculated by Cockcroft and Gault Formula.
8. Patients must have < Grade 2 pre-existing peripheral neuropathy (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.03)
9. Women of childbearing potential must have a negative serum or urine pregnancy test performed ≤7 days prior to start of treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately.
10. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 6 months

following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study (Appendix C).

11. Life expectancy >3 months.
12. Age ≥18 years.
13. Willingness and ability to comply with study and follow-up procedures.
14. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients who have received any other investigational agents, chemotherapy, biologic therapy, or radiation therapy within the 28 days prior to day 1 of the study. For investigational, chemotherapy, or biologic therapy, patients will be allowed on study if 5 half- lives or greater have elapsed since last dose of drug or 28 days, whichever is shorter.
2. History of other carcinomas (in situ and invasive) within the last five years that, in the investigator's opinion, may affect interpretation of the endpoints of this study.
3. Patients with other concurrent severe and/or uncontrolled medical disease which could compromise safety of treatment as so judged by treating physician (i.e., severely impaired lung function, severe infection, ventricular arrhythmias active ischemic heart disease, known active vasculitis of any cause, chronic liver or renal disease).
4. Patients with prior taxane chemotherapy.
5. A known history of HIV seropositivity, hepatitis C virus, acute or chronic active hepatitis B infection, or other serious chronic infection requiring ongoing intravenous treatment.
6. Women who are pregnant or breast-feeding
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit safety or compliance with study requirements or may interfere with the interpretation of the results.
8. Inadequately controlled hypertension (blood pressure>150 systolic and/or diastolic >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).
9. Any of the following cardiac diseases currently or within the last 6 months:
    - Left Ventricular Ejection Fraction (LVEF) <45% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc interval >480 ms on screening electrocardiogram (ECG) per institutional standard
    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B])

- Acute myocardial infarction
- Clinically significant conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
- Valvular disease with significant compromise in cardiac function

10. History of hypertensive crisis or hypertensive encephalopathy.
11. History of stroke or transient ischemic attack (TIA) within the past 6 months.
12. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of therapy.
13. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.
14. Patients may not have received other agents, either investigational or marketed, which act by primary anti-angiogenic mechanisms.
15. Major surgical procedure, open biopsy; or significant traumatic injury within 28 days prior to study initiation, or anticipation of need for major surgical procedure during the course of the study.
16. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to initiation of therapy.
17. Patients with proteinuria, as demonstrated by a Urine Protein on dipstick of 2+ or greater at screening.
18. Any non-healing wound, ulcer, or bone fracture.
19. Any clinical evidence or history of a bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
20. Therapeutic anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Anticoagulation with low molecular weight heparin or anti-Factor Xa agents will be allowed.
21. History of hemoptysis (≥ ½ teaspoon of bright red blood per episode) within 1 month prior to initiation of therapy.

3.3 Discontinuation from Study Treatment

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

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol

- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per NCI CTCAE v 4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

4. STUDY REGISTRATION

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Innovations Central Enrollment Desk. Patient registration will be confirmed via email within 24 hours, or by the next business day.

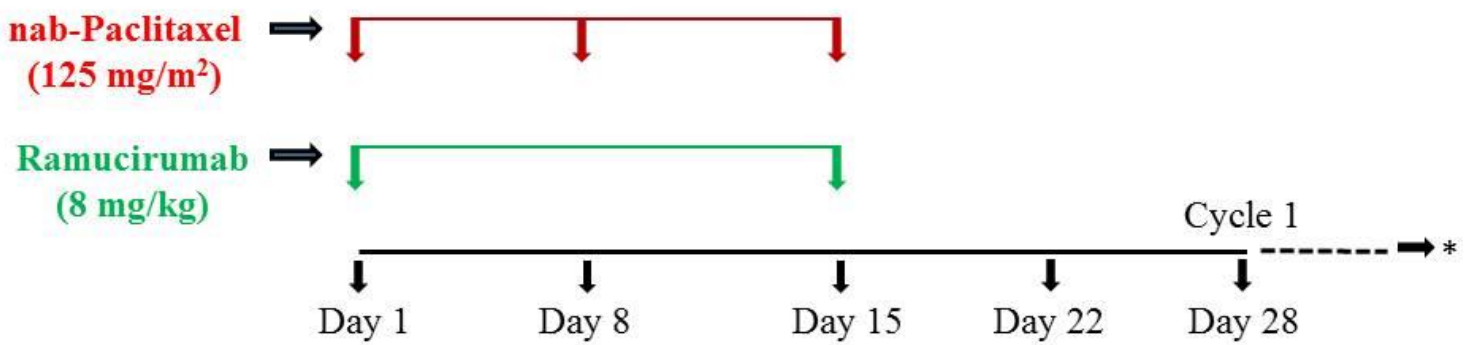
5. STUDY DESIGN

This is a Phase II, open-label, non-randomized study. Patients will be given nab-paclitaxel by IV at a dose of 125 mg/m^2 on Days 1, 8, and 15 of a 28 day cycle (weekly for 3 weeks with 1 week of rest) in combination with ramucirumab 8 mg/kg IV on Days 1 and 15. Restaging will occur every 2 cycles (8 weeks), and patients with an objective response or stable disease (SD) will remain on study until evidence of progressive disease, unacceptable toxicity, or study termination.

The planned enrollment for this study is 65 patients.

The study schema is presented in Figure 2.

Figure 2 Study Schema



*Patients with an objective response or stable disease will remain on study until evidence of progressive disease or unacceptable toxicity. Restaging will occur every 2 cycles (8 weeks).

5.1 Treatment Plan

5.1.1 Nab-paclitaxel

Nab-paclitaxel IV on D1, D8, and D15

All patients entering this study will receive 125 mg/m^2 of nab-paclitaxel by IV per institutional standard on Days 1, 8, and 15 of each 28-day cycle. Nab-paclitaxel will be given prior to ramucirumab infusion.

5.1.2 Ramucirumab

All patients entering this study will receive 8 mg/kg of ramucirumab by IV per institutional standard on Days 1 and 15 of each 28-day cycle.

Premedication is recommended prior to infusion of ramucirumab. The recommended premedication agents include H1 antagonists such as diphenhydramine hydrochloride (or equivalent) 25-50 mg PO or IV given 15-30 minutes prior to start of infusion. Additional premedication may be provided at investigator discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 6.2.2.1. All premedication administered must be adequately documented in the eCRF.

5.2 Treatment Duration

Patients will be evaluated for toxicity at the start of each cycle. Every 2 cycles, restaging will occur with imaging and laboratory chemistries as defined in Appendix D. Patients will continue on treatment until progression as defined in Appendix E or intolerance to side effects.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrolment or for a new condition that develops while on study, including but not limited to the following:

- Therapeutic anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Should a thrombotic event occur while the patient is receiving treatment, the patient may continue on protocol treatment, but low molecular weight heparin will be the preferred treatment
- The use of granulocyte colony-stimulating factor (G-CSF) is permitted during investigational therapy at the discretion of the investigator, in accordance with ASCO guidelines (Smith et al. 2006). G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC <1.0 x 10^3/μL [1.0 x 10^9/L] with a single temperature ≥38.3°C or a sustained temperature of ≥38.0°C for more than 1 hour).

- The use of erythroid-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator consistent with institutional guidelines.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

6. DOSE MODIFICATIONS

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. If dose modification below dose level -1 is required in a patient receiving benefit, the schedule of one or both drugs may be modified with approval of the Study Chair.

If the investigator believes the toxicity to be due to only one of the study agents, that agent may be held and/or dose reduced and treatment with the other agent may continue.

All dose reductions will be made from the planned dosages, with a maximum allowable treatment delay of 3 weeks during chemotherapy. If toxicity remains unresolved, the patient will discontinue the offending study agent and treatment with the other agent may continue. Patients should be evaluated weekly (at a minimum), if therapy is on hold.

The dose level reductions to be used in this study are shown in Table 1. No dose re-escalation is allowed.

Table 1 Dose Level Modifications

Dose Level	Nab-paclitaxel	Ramucirumab
Starting Dose	125 mg/m^2	8 mg/kg
Dose Level -1	100 mg/m^2	6 mg/kg
Dose Level -2	75 mg/m^2	5 mg/kg

6.1 Dose Modifications Due to Hematologic Toxicity

6.1.1 Administration of Nab-Paclitaxel to Patients with Abnormal Hematologic Function

Nab-paclitaxel dosing should not be administered at the start of each cycle until the ANC returns to ≥1.5 x 10^9 cells/L and the platelet count returns to ≥100 x 10^9 cells/L. For patients receiving weekly nab-paclitaxel, for each subsequent dose of nab-paclitaxel within a cycle (Days 8 and 15), patients must have an ANC ≥1.0 x 10^9 cells/L and platelets >75 x 10^9 cells/L. If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be omitted, but the total cycle length will remain the same.

6.1.2 Dose Reductions and Guidelines for Optional use of Growth Factors for Hematologic Toxicity

Prophylactic G-CSF use is not permitted during Cycle 1. Table 2 provides a guideline for implementing dose reductions and optional use of growth factor treatment for hematologic toxicity.

Table 2 Use of G-CSF and Nab-paclitaxel Dose Reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC <0.5 x 10^9 cells/L (nadir count) with neutropenic fever >100.4°F OR Delay of next cycle due to persistent neutropenia (ANC <1.5 x 10^9 cells/L) OR For patients on weekly treatment whose next treatment within the cycle (Day 8 or Day 15) is omitted due to persistent neutropenia (ANC <1.0 x 10^9 cells/L) OR Neutropenia <0.5 x 10^9 cells/L for >1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level for every protocol treatment will be required for subsequent cycles once ANC is ≥1.5 x 10^9 cells/L If G-CSF is given concurrently with weekly nab-paclitaxel, administration may begin the day after nab-paclitaxel is given and should stop at least 48 hours prior to when nab-paclitaxel is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level**

*See the National Cancer Institute Toxicity Criteria Scale for the definitions of Grade 3 and Grade 4 events.

**If dose modification below dose level -1 is required in a patient receiving benefit, the schedule of one or both drugs may be modified with approval of the Study Chair.

G-CSF Administration

For weekly nab-paclitaxel administration, administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose.

6.2 Dose Modifications Due to Non-Hematologic Toxicity

Dose modifications for non-hematologic toxicities for nab-paclitaxel and ramucirumab are addressed in this section.

6.2.1 Nab-Paclitaxel Non-Hematologic Dose Modifications

6.2.1.1 Administration of Nab-Paclitaxel to Patients with Abnormal Hepatic Function

Nab-paclitaxel should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur, but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

6.2.1.2 Sensory Neuropathy

Nab-paclitaxel should be withheld in patients who experience ≥ Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 1) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to ≤ Grade 1 should be the AE duration used for AE reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 1) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. Note: the investigator may elect to dose modify for Grade 3 sensory neuropathy.

6.2.1.3 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur with nab-paclitaxel. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. Patients with mild or moderate reactions may be premedicated per institutional standard and may continue treatment. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of nab-paclitaxel administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged. It is not recommended to administer nab-paclitaxel to patients with prior hypersensitivity to a taxane.

6.2.2 Ramucirumab Non-Hematologic Toxicity

6.2.2.1 Infusion Related Reactions

As with other monoclonal antibodies, infusion-related reactions may occur during or following ramucirumab administration. Patients should be closely monitored for signs and symptoms indicative of an infusion-related reaction starting with the initiation of the infusion until at least 1 hour after the end of the infusion in an area where resuscitation equipment and other agents (e.g., epinephrine, corticosteroids) are readily available.

The following are treatment guidelines for infusion-related reactions:

Grade 1

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- After symptoms resolve, medication may resume at previous rate per investigator's discretion.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen

- Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8 to 10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg IV (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Patients who have a Grade 3 infusion-related reaction will not receive further ramucirumab, but will continue on nab-paclitaxel.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 4 infusion-related reaction will not receive further ramucirumab, but will continue to be followed on on nab-paclitaxel.

6.2.2.2 Hypertension

The following are treatment guidelines for hypertension that develops during the study:

Grade <3

- If the hypertension is not associated with symptoms, continue ramucirumab and initiate antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.
- If ramucirumab is held for hypertension (that is, symptomatic hypertension, markedly elevated blood pressure unresponsive to antihypertensive therapy), the dose of ramucirumab should be reduced upon re-treatment (resolution to Grade 1) to 6 mg/kg

every 2 weeks. A second dose reduction to 5 mg/kg every 2 weeks should be undertaken if an additional postponement of ramucirumab is required.

Grade 3 (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated).

- For Grade 3 hypertension not associated with symptoms, continue ramucirumab with more intensive antihypertensive therapy. If systolic BP remains ≥160 mm Hg or diastolic BP ≥100 mm Hg >2 weeks after initiation of additional antihypertensive therapy, hold ramucirumab while continuing appropriate antihypertensive therapy (resolution to Grade 1).
- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.
- If ramucirumab is held for hypertension (that is, symptomatic hypertension, markedly elevated blood pressure unresponsive to antihypertensive therapy), the dose of ramucirumab should be reduced upon re-treatment to 6 mg/kg every 2 weeks. A second dose reduction to 5 mg/kg every 2 weeks should be undertaken if an additional postponement of ramucirumab is required.

Grade 4 or refractory

- Patients with Grade 4 hypertension (life-threatening consequences; for example, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (>160 mm Hg systolic or >100 mm Hg diastolic for >4 weeks) despite appropriate oral medication (>2 oral agents at maximum tolerated dose) will be discontinued from ramucirumab.

6.2.2.3 Proteinuria

If, while on ramucirumab therapy, a patient has proteinuria ≥2+ per a dipstick or routine urinalysis, ramucirumab therapy will continue as scheduled, and a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment cycle. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab therapy at the same dose without interruption. If the protein level is ≥2 g/24 hours, hold ramucirumab therapy for that treatment and a 24-hour urine collection will be repeated. Ramucirumab treatment will resume at 6 mg/kg once the protein level returns to <2 g/24 hours. A second dose reduction of ramucirumab to 5 mg/kg is permitted if proteinuria ≥2 g/24 hours recurs. The patient will be discontinued from ramucirumab treatment if the protein level is >3 g/24 hours, if there is a third occurrence of proteinuria ≥2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 3 weeks.

6.2.2.4 Thromboembolic Events

Ramucirumab therapy should be discontinued in the event of any Grade 3/4 ATE or any Grade 3/4 venous thromboembolism that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. Ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary

embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

6.2.2.5 Other Ramucirumab Non-Hematological Toxicities

The events in Table 3 are associated with ramucirumab or other antiangiogenic therapeutic agents.

Table 3 Other Ramucirumab Non-Hematological Toxicities

Event	Action to be taken
Bleeding (hemorrhagic) event Grade 3 or 4	Discontinue ramucirumab
Gastrointestinal perforation Any grade	Discontinue ramucirumab
Fistula formation Any grade	Discontinue ramucirumab
Wound dehiscence (Requiring medical or surgical therapy)	Discontinue ramucirumab
Congestive heart failure (CHF) Grade 3 or 4	Discontinue ramucirumab
Reversible Posterior Leukoencephalopathy Syndrome (RPLS) Any grade (confirmed by MRI)	Discontinue ramucirumab

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D. The baseline physical examination, medical history, ECOG performance status, complete blood counts (CBC), differential and platelets, complete metabolic profile (CMP) plus magnesium and phosphorous, urinalysis, prothrombin time (PT)/International Normalization Ratio (INR) and partial thromboplastin time (PTT) and ECG should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not

have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤8 weeks prior to initiation of treatment, as should the tumor marker, carcinoembryonic antigen (CEA).

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
- Physical examination, measurements of height (first visit) and weight
- Vital signs (resting heart rate, BP, respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A)
- 12-lead ECG
- Concomitant medication review
- CBC (complete blood count) including Hgb, hematocrit, white blood cell count with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin plus magnesium and phosphorous.
- Coagulation analysis: PT/PTT/INR (at baseline and then as clinically indicated)
- Urine dipstick
- Serum or urine pregnancy test (must be performed within 72 hours of Cycle 1 Day 1)
- CEA tumor marker ≤ 8 weeks prior to initiation of study treatment
- CT scans of the chest, abdomen/pelvis ≤ 8 weeks prior to initiation of study treatment. CT scans of abdomen/pelvis are preferred but CT scans of the abdomen will be accepted.

7.3 Study Treatment Assessments

7.3.1 Day 1 of each cycle (+/- 72 hours)

- Update of medical history
- Physical examination, including measurement of weight
- Vital signs
- ECOG performance status
- Adverse event (AE) assessment
- Concomitant medication review

- CBC, including 3-part differential and platelets
- CMP plus magnesium and phosphorous
- Urine dipstick

7.3.2 Day 8 and 15 of each cycle

- AE assessment
- CBC, including 3-part differential and platelets
- Urine dipstick (Day 15 only)

7.4 Response Assessment Every 2 Cycles

Patients will be evaluated for response to treatment after every 2 cycles of treatment, at the End of Treatment Visit and in follow-up prior to disease progression. The following assessments will be performed:

- CT scans of chest, abdomen and pelvis
- CEA tumor marker

Patients with progressive disease or unacceptable toxicity should be discontinued from the study unless the patient is receiving clinical benefit and the Study Chair has approved patient to stay on study; patients with SD or response to therapy will continue treatment.

7.5 End-of-Study Treatment

The follow-up evaluations required after treatment ends due to disease progression or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix D.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days (+3) after the last dose of study drug. The following assessments will be performed:

- Update of medical history
- Physical examination, including measurement of weight
- Vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP plus magnesium and phosphorous
- Urine dipstick
- CT scans of chest, abdomen and pelvis (if not done in the previous 8 weeks)

- CEA tumor marker

7.6 Follow-up

7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients discontinuing treatment for any reason other than progressive disease (PD) will be monitored for evidence of disease progression. Patients will be followed every 3 months for up to 12 months after the last patient has been enrolled on study. Assessments at these visits will be performed as described in Appendix D.

7.6.2 Survival Follow-Up

Survival will be assessed in all patients at 6 and 12 months after the last patient has been enrolled on the study. Patients may be contacted during outpatient visits or by telephone. After 12 months no additional follow-up will be required.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 Nab-Paclitaxel

Investigational Product	Dosage Form and Strength	Manufacturer
Nab-paclitaxel	100 mg	Celgene Corporation

8.1.1 Labeling, Packaging, and Supply

Nab-paclitaxel will be supplied by Celgene.

The immediate packaging will contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for nab-paclitaxel are included on the investigational product label.

The SCRI Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of Nab-paclitaxel

Nab-paclitaxel is prepared and administered as an IV infusion per institutional standard.

No premedication to prevent hypersensitivity reactions is required prior to administration of nab-paclitaxel. However, if a mild or moderate hypersensitivity reaction occurs, the patient may be premedicated per institutional standard.

Additional information can be found in the prescribing information for nab-paclitaxel.

8.1.3 Precautions and Risks Associated with Nab-paclitaxel

Precautions and risks are located in the IB.

8.2 Ramucirumab

Ramucirumab is to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. Please refer to the US Package Insert (USPI) for detailed information on how to prepare and administer ramucirumab.

8.2.1 Labeling, Packaging, and Supply

Each site will procure a supply of ramucirumab, which is commercially available.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for ramucirumab can be found in the USPI.

SCRI Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration of Ramucirumab

Ramucirumab is to be prepared and administered over 60 minutes and in accordance with institutional standard.

8.2.3 Precautions and Risks Associated with Ramucirumab

Please refer to the USPI for detailed information on the risks associated with the use of ramucirumab.

8.3 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by SCRI Innovations or its representatives and regulatory agency inspectors upon request.

At the end of the study, all SCRI Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the SCRI Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by SCRI Innovations or its representative. Please contact SCRI Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. The term “evaluable” in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a Phase II, open-label, non-randomized study. The study is designed to determine the PFS of nab-paclitaxel in combination with ramucirumab for patients as second-line therapy for metastatic gastroesophageal cancer.

10.2 Sample Size Considerations

This study seeks to improve median PFS in this patient population. The historical median PFS is 2.8 months; we hypothesize that nab-paclitaxel plus ramucirumab will increase median PFS to 5 months. With a 2-sided alpha of 5% and 80% power, a total of 52 events (progressions or deaths) will need to be observed. With an 18-month recruitment and 6 months follow-up, assuming 20% of patients recruited will be free from progression or death at the end of the study, 65 patients will need to be recruited into the study in order to observe 52 events.

10.3 Analysis Populations

The following analysis populations will be used:

- Full Analysis Set is defined as all patients who are enrolled in the study.
- Safety Analysis Set is defined as patients in the Full Analysis Set who have received at least one dose of study treatment.
- Efficacy Analysis Set is defined as patients in the Full Analysis Set who have received at least one dose of study treatment and have a baseline tumor assessment.
- Per Protocol Set is defined as patients in the Efficacy Analysis Set who received at least 75% of their intended starting doses of both nab-paclitaxel and ramucirumab study treatment during Cycles 1 and 2, and who either have at least one post-baseline tumor assessment, or who discontinued the study prior to their first post-baseline tumor assessment due to death or objective disease progression.

10.4 Data Analysis

Data will be summarized by using counts and percentages for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. Baseline data to be tabulated will include demographic features such as gender, age, and race, as well as disease specific characteristics. The number and percentage of patients who complete the study or who withdraw for any reason will be presented.

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CI) for median time to event.

All analyses will be performed using SAS version 9.3 or later.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, randomized, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented.

10.4.2 Efficacy Analysis

Response evaluation will be based on RECIST v1.1 criteria (Appendix E).

Analyses of PFS, TTP, OS, ORR and Disease Control Rate (DCR) will be performed using the Efficacy Analysis Set.

- PFS is defined as the time from the first day of study drug administration (Day 1) to objective disease progression as defined by the RECIST v1.1 criteria, or death on study from any cause. Patients who are alive and free from disease progression will be censored at the date of last adequate tumor assessment. If no adequate post-treatment tumor assessments were obtained for a patient, PFS will censored at Day 1. PFS is the primary endpoint variable in this study.

- TTP is defined as the time from the first day of study drug administration (Day 1) to objective disease progression as defined by the RECIST v1.1 criteria. Patients who are alive and free from disease progression will be censored at the date of last adequate tumor assessment. If no adequate post-treatment tumor assessments were obtained for a patient, TTP will censored at Day 1.

- OS is defined as the time from the first day of study drug administration (Day 1) to death from any cause. Patients who are alive will be censored at the date of last known alive.

- ORR is defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR), i.e., two CRs and/or PRs at least 4 weeks apart, according to the RECIST v1.1 criteria.

- DCR is defined as the proportion of patients with best response of confirmed CR, confirmed PR, or SD, according to the RECIST v1.1 criteria.

    - For ORR and DCR, patients without a post-baseline tumor assessment will be classified as not evaluable (NE) and considered as non-responders in the efficacy analyses.

For PFS, TTP and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI be provided.

For ORR and DCR, the estimates and the associated 95% CI (based on the Wald normal approximation method) will be calculated.

Efficacy analyses will be repeated on each of the efficacy endpoint variables (PFS, TTP, OS, ORR, and DCR) using the Per Protocol Set.

10.4.3 Safety Analysis

Safety analyses will be performed for all patients in the Safety Analysis Set.

Safety (discussed in Section 11) will be assessed through the analysis of the reported incidence of adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), AEs leading to treatment discontinuation, events of at least CTCAE Version 4.03 Grade 3 in severity, and AEs related to study treatment. Laboratory data and other safety data will be summarized as appropriate. A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term. In addition, summaries of TEAEs, SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Laboratory results (observed values and changed from baseline) will be listed and summarized by visit. CTCAE grades will be applied to laboratory parameters where applicable. Summaries of NCI CTCAE Version 4.03 grading and shifts from baseline will be tabulated as appropriate.

Vital signs parameters (observed values and change from baseline) will be listed and summarized by visit.

ECG and ECOG performance status findings will be listed and summarized by visit.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur when a total of at least 52 PFS events have been observed.

10.5.2 Safety Review

There are no scheduled interim safety reviews planned for this study.

10.5.3 Efficacy Review

There are no scheduled interim efficacy analyses planned for this study.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the SCRI Innovations Safety Department (SD) (see Section 11.1.5). It is SCRI Innovations responsibility

to report relevant SAEs to the applicable local or national regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and

seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.03, and changes will be documented.

If the AE is serious, it should be reported immediately to SCRI Innovations SD. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to nab-paclitxel and ramucirumab treatment (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to SCRI Innovations SD in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of the study Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 days after their last dose of study drug follow-up period after the last study treatment. **The SCRI Innovations SD must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to SCRI Innovations SD via fax or e-mail using the using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report, and a copy of the confirmation should be retained with the patient's records.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations SD as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen and should not be reported as an SAE. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations SD.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of ≥24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study and properly documented in the eCRF), does not require reporting as an SAE to the SCRI Innovations SD.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the SCRI Innovations SD. SCRI Innovations SD should be notified immediately, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations SD.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the SCRI Innovations SD immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy. All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4 SCRI Innovations Safety Department Serious Adverse Event Reporting Requirements

SCRI Innovations SD will forward SAE information to Celgene Corporation within 1 business day of SCRI Innovations Safety Department personnel becoming aware of the SAE.

SCRI Innovations SD will forward Pregnancy information to Celgene Corporation within 1 business day on a Pregnancy Form and Follow-Up Pregnancy Form with more information when the outcome of pregnancy is known.

SCRI Innovations SD is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

Safety Reporting to Celgene Corporation:

Safety reporting will be communicated to Celgene Corporation using the contact information below:

Celgene Corporation

Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Celgene Corporation Study number: AX-CL-OTHER-PI-004374
SCRI Study number: GI 201

The Celgene Corporation study number and SCRI study number referenced above should appear on the fax cover page.

11.4.1 SCRI Innovations Safety Department Assessment of Unexpected

SCRI Innovations is responsible for assessing an AE or SAR as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current USPI)
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected AE may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure [IB] or USPI), and are serious (as defined by the protocol) and require

expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

11.4.2 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the SCRI Innovations SD must also be faxed to pharmaceutical company that is supporting the study:

Celgene Corporation

Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

E-mail: drugsafety@celgene.com

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by SCRI Innovations or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At SCRI Innovations discretion, Source Document may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, SCRI Innovations or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by SCRI Innovations or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for nab-paclitaxel, will be prepared by SCRI Innovations or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, SCRI Innovations will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, SCRI Innovations will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH Good Clinical Practice guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of SCRI Innovations, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to SCRI Innovations. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the SCRI Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by SCRI Innovations. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by SCRI Innovations, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by SCRI Innovations as applicable, and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Regulatory Department
3322 West End Avenue, Suite 900
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of SCRI Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from SCRI Innovations and/or applicable regulatory authorities. The ISF must

consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

SCRI Innovations shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from SCRI Innovations or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). SCRI Innovations will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both SCRI Innovations and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to SCRI Innovations. The investigator must obtain SCRI Innovations written permission before disposing of any records, even if retention requirements have been met. All study files will be SCRI Innovations throughout the study, and will be held by SCRI Innovations at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable SCRI Innovations to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. SCRI Innovations reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per SCRI Innovations publication process.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the funding partner as appropriate. Investigator shall provide the funding partner thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the funding partner requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the funding partner to seek patent protection and to remove any funding partner Confidential Information from all publications.

15. REFERENCES

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16. APPENDICES

Appendix A: ECOG 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 no 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: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 3 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of child-bearing potential must use condoms plus spermicidal agent during the study treatment period and for 6 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the SCRI Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to **SCRI Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: Schedule of Assessments

ASSESSMENTS	Pre-Treatment	STUDY TREATMENT (*Cycles repeated every 28 days*)					FOLLOW-UP	
	Baseline[a]	Day 1	Day 8	Day 15	Every 2 Cycles	End of Study Treatment[h]	Disease-Free Survival[l]	Survival[m]
Tests and Observations								
Informed consent	X							
Medical history	X	X				X	X	
Physical exam[b]	X	X				X[b]	X[b]	
Vital Signs[c]	X	X				X		
ECOG PS	X	X				X		
12-lead ECG	X							
Adverse event evaluation		X	X	X		X		
Concomitant medication review	X	X				X		
Survival status								X
Laboratory Observations								
CBC, 3-part differential, and platelets	X	X	X	X		X	X	
CMP plus magnesium and phosphorous[d]	X	X				X	X	
PT, PTT, INR[e]	X							
Urine dipstick[f]	X	X		X		X		
Serum or Urine Pregnancy Test[g]	X							
CEA[i]	X				X	X	X	
Staging								
CT Scan Chest[j]	X				X	X	X	
CT Scan abdomen /pelvis[k]	X				X	X	X	

Appendix D: Schedule of Assessments (continued)

a Baseline procedures including medical history, physical examination, 12-lead ECG, ECOG PS, CBC, CMP plus magnesium and phosphorous, PT/PTT/INR, ECG, , and urine dipstick should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A serum or urine pregnancy test must be performed within 72 hours of Cycle 1 Day 1.

b Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs.

c Vital signs will include resting heart rate, blood pressure, respiratory rate, and temperature.

d CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin plus magnesium and phosphorous. CMP may be done up to 72 hours prior to treatment.

e If PT/PTT or INR are normal at baseline, they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

f Urine dipstick (pH, protein, glucose, blood, ketones, and leukocytes)

g Serum or urine pregnancy tests are to be conducted in women of childbearing potential.

h Patients should visit the study center 30 days(+ 3) for end-of-treatment assessments. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

i CEA tumor marker will be collected≤8 weeks prior to initiation of treatment, every 2 cycles, and at the End of Study visit.

j CT scans of the chest ≤8 weeks prior to initiation of treatment, every 2 cycles, and at the End of Study visit if scans were not taken in the previous 8 weeks.

k CT scans of the abdomen/pelvis ≤8 weeks prior to initiation of treatment, every 2 cycles, and at the End of Study visit if scans were not taken in the previous 8 weeks. CT Scans of the abdomen/pelvis is preferred, but CT scans of the abdomen will be accepted for CT scans of the abdomen/pelvis.

l Patients discontinuing treatment for any reason other than PD will be monitored for evidence of disease progression. Patients will be followed every 3 months for up to 12 months after the last patient has been enrolled on study for disease progression.

m Survival will be assessed in all patients at 6 and 12 months after the last patient has been enrolled on the study. Patients may be contacted during outpatient visits or by telephone. After 12 months no additional follow-up will be required.

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

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible 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), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. 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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

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

Stable Disease (SD): Persistence of one or more non-target lesions and/or persistence 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. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.