SCRI DEVELOPMENT℠ INNOVATIONS

GU 124

A Phase II Study of Nanoparticle Albumin-bound Paclitaxel plus Gemcitabine as First-line Therapy for the Treatment of Cisplatin-ineligible or Cisplatin-incurable Advanced Urothelial Carcinoma

SCRI INNOVATIONS STUDY NUMBER:	GU 124
STUDY DRUGS:	Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) Gemcitabine
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
STUDY CO-CHAIRS:	John Hainsworth, MD Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 615-329-7274 Guru Sonpavde, MD University of Alabama at Birmingham 1720 2nd Ave South, NP 2540 Birmingham, AL 35294-3500 205-975-2914
DATE FINAL:	02 May 2016

SCRI DEVELOPMENT℠
INNOVATIONS

Clinical Study Statement of Compliance

A Phase II Study for using Nanoparticle Albumin-bound Paclitaxel plus Gemcitabine as First-line Therapy for Cisplatin-ineligible or Cisplatin-incurable Advanced Urothelial Carcinoma

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 the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Clinical Study Signature Approval Page

A Phase II Study for using Nanoparticle Albumin-bound Paclitaxel plus Gemcitabine as First-line Therapy for Cisplatin-ineligible or Cisplatin-incurable Advanced Urothelial Carcinoma

SCRI INNOVATIONS STUDY NUMBER:	GU 124
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John Hainsworth, MD.

Study Co-Chair	**Study Co-Chair Signature**	**Date**

Guru Sonpavde, MD

Study Co-Chair	**Study Co-Chair Signature**	**Date**

Sheetal Khedkar, MD.

Sponsor Representative SCRI Development Innovations, LLC	**Sponsor Representative Signature**	**Date**

SCRI DEVELOPMENT℠ INNOVATIONS

Clinical Study Principal Investigator Signature Form

A Phase II Study for using Nanoparticle Albumin-bound Paclitaxel plus Gemcitabine as First-line Therapy for Cisplatin-ineligible or Cisplatin-incurable Advanced Urothelial Carcinoma

SCRI INNOVATIONS STUDY NUMBER:	GU 124
DATE FINAL:	02 May 2016

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

John Hainsworth, MD

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

Guru Sonpavde, MD

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: GU 124 Study Team
Nashville, TN 37203

GU 124 PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study for using Nanoparticle Albumin-bound Paclitaxel plus Gemcitabine as First-line Therapy for Cisplatin-ineligible or Cisplatin-incurable Advanced Urothelial Carcinoma	
SCRI Innovations Study Number:	GU 124	
Sponsor:	SCRI Development Innovations, LLC – Nashville - TN	
Study Duration:	The total duration of the study is planned to be 36 months	**Phase of Study:** II
Study Centers:	This study will be conducted in twelve sites.	
Number of Patients:	Up to 55 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objective** The primary objective of this study is to evaluate the efficacy of first-line treatment with nab-paclitaxel-gemcitabine in patients with advanced urothelial carcinoma who are either poor candidates for cisplatin-containing chemotherapy or have visceral metastases and are cisplatin-incurable. The primary endpoint is the progression-free survival (PFS) rate at 6 months after the start of treatment. **Secondary Objectives** The secondary objectives of this study are to evaluate the safety, objective response rate (ORR), complete response (CR) rate, and overall survival (OS) with the nab-paclitaxel-gemcitabine combination. **Exploratory objectives** The exploratory objectives are to evaluate archival tumor tissue by immunohistochemistry (IHC) for SPARC and gene expression and sequencing of a panel of genes to examine their association with PFS, ORR and OS	
Study Design:	This is an open-label non-randomized Phase II study to determine the benefit of the combination of nab-paclitaxel and gemcitabine given for 6 cycles, followed by maintenance nab-paclitaxel alone, in patients with cisplatin-ineligible or cisplatin-incurable advanced urothelial carcinoma (UC).	
Study Drugs, Doses, and Modes of Administration:	**Induction phase**: All patients in this study will receive nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) by IV infusion on Day 1 and Day 8 of each 21-day cycle. Responding or stable patients will be treated with a minimum of 3 cycles and up to 6 cycles before starting the single agent maintenance therapy. Doses of gemcitabine and nab-paclitaxel should be recalculated if there is a $\geq$ 10% change in the patient's body weight since the previous calculation. **Maintenance phase**: Patients who have objective response (CR or PR) or SD after completing 3-6 cycles of induction therapy with nab-paclitaxel-gemcitabine will continue treatment with single agent nab-paclitaxel (260 mg/m^2 IV every 21 days) until disease progression, intolerable toxicity or patient decision to discontinue treatment. Patients who have SD or respond to nab-paclitaxel-gemcitabine but cannot complete 6 cycles due to poor tolerance may switch to maintenance treatment with single-agent nab-paclitaxel after completing a minimum of 3 cycles of combination therapy.	

GU 124 PROTOCOL SYNOPSIS

Inclusion Criteria:	1. Histologically confirmed diagnosis of UC that is either metastatic (any N+ M1) or locally advanced and unresectable (T4bN0). A component of urothelial (transitional cell) carcinoma is required. 2. Two groups of patients are eligible: a. Poor candidates for cisplatin-based chemotherapy, based on the presence of ≥ 1 the following: • Glomerular filtration rate of 30-60 ml/min (Cockcroft-Gault formula) • ECOG performance status score of 2 (Appendix A) • Hearing loss (trouble communicating with hearing aids or hearing loss at ≤ 3 KHz) • Grade ≥3 heart failure (NYHA Appendix B) • Age ≥80 years • Other concurrent illness which may make the patient a poor candidate for receiving cisplatin. Note: Enrollment of patients with 2 or more of these criteria should occur only after careful consideration by the treating physician regarding the patient's ability to tolerate combination chemotherapy. OR b. Poor prognosis and defined as cisplatin-incurable due to the presence of metastasis to at least one visceral site (these patients are not required to have any of the cisplatin-ineligibility criteria). • ECOG performance status score of 0, 1, or 2 (Appendix A). 3. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix E). 4. Patients with previously treated brain metastases are eligible if c. Treatment was completed ≥ 4 weeks prior to study treatment, d. Neurologic symptoms are minimal and stable during the preceding 4 weeks, and e. Maintenance dexamethasone is not required. 5. Any pre-existing peripheral neuropathy must be < Grade 2. 6. Adequate hematologic function at baseline, defined as: – Absolute neutrophil count (ANC) ≥1500/μL – Hemoglobin (Hgb) ≥ 9 g/dL (use of growth factor or red blood cell transfusion to achieve this level is allowed) – Platelets >100,000/μL 7. Adequate liver function at baseline, defined as: – Bilirubin ≤1.5 mg/dL – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal [ULN] (unless bone marrow metastases are present in the absence of liver metastasis), ≤5 x ULN if liver metastases are present 8. Calculated creatinine clearance ≥30 mL/minute (Cockcroft-Gault formula)

Inclusion Criteria:	9. 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 3 months following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study (Appendix C). 10. Women of childbearing potential (WoCBP) must have a negative serum or urine β-hCG pregnancy test performed within 72 hours prior to start of treatment and must use two forms of acceptable contraception, including one barrier method, contraceptive method during treatment and for 3 months after completing 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. 11. Age ≥18 years. 12. Willingness and ability to comply with study and follow-up procedures. 13. Ability to understand the nature of this study and give written informed consent.
Exclusion Criteria:	1. Previous systemic chemotherapy for UC, with the exception of perioperative (neoadjuvant or adjuvant) treatment or treatment with concurrent chemo-radiation for locally advanced disease. All of these treatments must have been completed > 1 year previously. 2. Presence of small-cell or sarcomatoid component in tumor histology 3. Women who are pregnant or breast-feeding 4. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 5. Any of the following cardiac diseases currently or within the last 6 months: • QTc interval >480 ms (per institutional standard) on screening electrocardiogram (ECG) • Unstable angina pectoris • Acute myocardial infarction • 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 6. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] ≥180 mmHg or diastolic blood pressure [DBP] ≥100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment). 7. Currently receiving treatment with therapeutic doses of warfarin sodium. However, a maximum daily dose of 1 mg will be permitted for port line patency. Low molecular weight heparin is allowed. 8. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 9. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C (screening for these diseases is not required). 10. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years previously. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 11. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

GU 124 PROTOCOL SYNOPSIS

Correlative Testing:	If available, tumor tissue from archival biopsies will be collected to be centrally studied in the future with separate funding. Potential IHC studies performed centrally will include but are not limited to secreted protein acidic and rich in cysteine (SPARC) expression. Gene expressing profiling of tumor tissue using Nanostring or other similar technology may also be performed.
Statistical Methodology:	The purpose of this open-label non-randomized Phase II trial is to study the efficacy and toxicity of the gemcitabine/nab-paclitaxel combination followed by maintenance single-agent nab-paclitaxel as the first-line treatment of patients with advanced UC. Two groups of patients will be eligible for this study: 1) patients who are considered poor candidates for treatment with cisplatin, and 2) patients with visceral metastases, who are incurable and unlikely to derive long-term benefit from treatment with cisplatin-based regimens.

GU 124 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CBC	Complete blood count
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response/remission
Cr Cl	Creatinine clearance
CT	Computerized tomography
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GC	Gemcitabine plus cisplatin
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
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
PFS6	6-month progression-free survival

LIST OF ABBREVIATIONS (continued)

PFS	Progression-free survival
PHI	Protected health information
PR	Partial response/remission
PT	Prothrombin time
RR	Response rate
SAE	Serious adverse event
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SPARC	Secreted protein acidic and rich in cysteine
SUSAR	Suspected Unexpected Serious Adverse Reactions
UC	Urothelial carcinoma
ULN	Upper limit of normal
USPI	US Package Insert
WoCBP	Women of childbearing potential

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1. INTRODUCTION

1.1 Background

According to the American Cancer Society report in year 2015, urothelial carcinoma (UC) is the fourth most common cancer (~74,000 new cases a year), and is the eighth most common cause of death in men in the USA (Siegel et al. 2015). Approximately 25% of new cases have muscle-invasive disease with or without metastases. Approximately 50% of patients with localized muscle invasive UC will develop metastatic disease despite optimal surgical and perioperative chemotherapy (Stein et al. 2006, Grossman et al. 2003, International Collaboration of Trialist 2011, Advanced Bladder Cancer Collaboration 2005, Shariat et al. 2006a, Shariat et al. 2006b, International Bladder Cancer Nomogram Consortium et al. 2006). Locally advanced or metastatic UC is initially responsive to first-line therapy (overall response rate [ORR], 50-70%; complete response [CR] rate, 10-20%). In addition, a minority of patients (approximately 5-15%) have long-term disease-free survival following treatment with conventional cisplatin-based regimens (Logothetis et al. 1990, von der Maase et al. 2000, Saxman et al. 1997, Loehrer et al. 1992, Sternberg et al. 2006).

Although some patients with advanced UC derive substantial benefit from treatment, the median progression-free survival (PFS) and overall survival (OS) for the entire group are only 8 and 15 months, respectively (Logothetis et al. 1990, von der Maase et al. 2000, Saxman et al. 1997, Loehrer et al. 1992, Sternberg et al. 2006, Galsky et al. 2012). Two major prognostic factors, Karnofsky performance status (KPS) <80 and visceral metastasis, can be used to define patient groups with markedly different survival (Bajorin et al. 1999). Median OS for patients with zero, one, or two risk factors are 33, 13.4, and 9.3 months, respectively. Patients with complete remission and long-term survival following cisplatin-based therapy are almost always in the most favorable group (i.e. good KPS, no visceral metastases). Conversely, patients with visceral metastases rarely have complete responses or long-term survival after standard cisplatin-based chemotherapy, and have been defined as cisplatin-incurable and included in trials accruing cisplatin-ineligible patients (Balar et al. 2013).

At present, the combination of gemcitabine and cisplatin (GC) is the preferred first-line regimen for the treatment of patients with advanced urothelial cancer. In a Phase III study, GC had similar efficacy outcomes but better tolerability compared to a combination of methotrexate, vinblastine, doxorubicin, cisplatin (MVAC), the previous standard of care (von der Maase et al. 2000, von der Maase et al. 2005).

One of the major problems in managing patients with advanced UC is that many of these patients are unable to tolerate conventional cisplatin-based chemotherapy. Patients with advanced UC have a median age of 65-70 years, and frequently have associated comorbidities and poor performance status (PS). Addition, approximately 50% of patients with advanced UC have age-dependent diminished renal function (Galsky et al. 2011a, Dash et al. 2006, Sonpavde et al. 2014). Clinical features universally associated with poor tolerance of cisplatin include renal dysfunction (estimated creatinine clearance [Cr Cl] <60 ml/min) and poor performance status (Eastern Cooperative Oncology Group [ECOG] PS≥2). In addition, frailty associated with advanced age and several other comorbidities (e.g. Grade ≥ 2 hearing loss, Grade ≥ 2

neuropathy, New York Heart Association Class [NYHA] III heart failure) may also render patients cisplatin-ineligible (Galsky et al. 2011a, Galsky et al. 2011b).

The difficulties involved in treating patients with advanced bladder cancer are reflected in the practice patterns documented in recent studies. In a retrospective analysis, only 107 of 299 patients (36%) with stage IV UC who were managed in a community-based cancer center system received cisplatin-based chemotherapy; the remainder received carboplatin-based treatment (27%), nonplatinum-based chemotherapy (8.4%), or no chemotherapy (24%) (Dash et al. 2006). In another retrospective study of 1031 patients with advanced UC and aged ≥66 years, 48% received no chemotherapy; only 20% received cisplatin-based therapy (Sonpavde et al. 2012). Although the reasons for non-administration of cisplatin were not available in either of these studies, various combinations of renal dysfunction, poor performance status, elderly age and comorbidities are likely.

1.2 Treatment for advanced urothelial carcinoma in cisplatin-ineligible patients

Carboplatin is often substituted for cisplatin in cisplatin-ineligible patients, but is associated with inferior response rates, especially CR (Galsky et al. 2012). In a meta-analysis of randomized Phase II trials, cisplatin-based chemotherapy was associated with a significantly higher likelihood of achieving a CR (relative risk [RR] = 3.54 and 95% confidence interval [CI] 1.48-8.49; P = 0.005) and ORR (RR = 1.34; 95% CI 1.04-1.71; P = 0.02 (Galsky et al. 2012). A Phase III trial comparing gemcitabine-carboplatin with MCAVI (methotrexate, carboplatin, vinblastine) in patients who were cisplatin-ineligible due to poor performance status (ECOG PS 2) and/or renal dysfunction (Cr Cl >30 to <60 ml/min) demonstrated better tolerance of gemcitabine-carboplatin, but with median survivals of only 8-9 months with both regimens (De Santis et al. 2012). This outcome is considerably poorer than expected for gemcitabine-cisplatin. It is not clear whether these poor outcomes are related to host factors, tumor or therapy-related factors, or a combination of both. However, the component(s) attributable to suboptimal therapy may be modified by improving systemic chemotherapy.

1.3 Nab-paclitaxel

Nab-paclitaxel (Abraxane® [ABI-007]) is an injectable 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.

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 binding to a specific receptor gp60, an endothelial cell membrane 60-kDa albumin-binding protein. Binding to gp60 activates caveolin-1, which initiates the opening of caveolae in the endothelial wall. The albumin-bound chemotherapeutic complex is then transported via these caveolae to the underlying tumor interstitium. A protein specifically secreted by the tumor (secreted protein acidic and rich in cysteine or 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 which exploits the gp-60/caveolin-1/SPARC pathway to enhance intra-tumoral concentration of the drug, creating the potential for increased efficacy and decreased toxicity.

Nab-paclitaxel is currently approved for the treatment of several advanced cancers. In metastatic breast cancer, first-line treatment with weekly nab-paclitaxel resulted in prolonged PFS and decreased toxicity when compared to standard dose docetaxel (Gradishar et al. 2009). In advanced pancreatic cancer, the addition of nab-paclitaxel to gemcitabine improved OS and was generally well tolerated (Von Hoff et al. 2011, Von Hoff et al. 2013). In the first-line therapy of advanced non-small cell lung carcinoma (NSCLC), weekly nab-paclitaxel in combination with carboplatin resulted in modestly improved efficacy and substantially reduced toxicity when compared to standard paclitaxel-carboplatin (Socinski et al. 2012). Efficacy and tolerability differences were particularly evident in the subgroup of patients ≥70 years old. Therefore, the augmentation of efficacy coupled with reduced toxicity as predicted by the formulation and mechanism of action of nab-paclitaxel has been demonstrated clinically in the treatment of several cancers.

1.3.1 Nab-paclitaxel in the Treatment of Urothelial Carcinoma

Nab-paclitaxel has been evaluated as a single agent in patients with advanced UC who progressed within 1 year of platinum-based therapy (Ko et al. 2013). In a Phase II trial, 48 patients received intravenous (IV) nab-paclitaxel (260 mg/m^2) every 3 weeks. Forty seven patients were evaluable: one (2%) had a complete response and 12 (26%) had partial responses, resulting in an overall response of 28% (95% CI 17-44). The most frequently recorded adverse events (AEs) of any grade were fatigue (79%), pain (77%), alopecia (71%), and neuropathy (77%). The most frequently recorded AEs of Grade 3 or higher were pain (23%), fatigue (23%), hypertension (6%), neuropathy (6%), and joint stiffness (4%). Median actuarial OS in all patients was 10.8 months (95% CI 5.8–16.9) and median PFS was 6.0 months (95% CI 3.9–8.5), both comparing favorably with historical regimens (Sonpavde et al. 2013). An ongoing randomized Phase II trial is comparing nab-paclitaxel vs. paclitaxel in the second-line setting.

1.4 Gemcitabine

Gemcitabine is a cytotoxic anticancer drug and currently approved for treating patients with pancreatic cancer, breast cancer, ovarian cancer, and lung cancer. Cytotoxic ability of gemcitabine depends on disruption of specific phases of the cell cycle. Gemcitabine is an antimetabolite that inhibits DNA-synthesis (S-phase) and also blocks progression from G1 to S phase. Gemcitabine is typically administered intravenously at a dose of 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.

Although gemcitabine is not specifically approved for use in metastatic bladder cancer, the combination of gemcitabine-cisplatin is currently considered the standard first-line therapy (von der Maase et al. 2000, von der Maase et al. 2005). In addition, the combination of gemcitabine with carboplatin is widely used, and is an active, less toxic regimen for patients who are predicted to have difficulties tolerating a cisplatin-containing regimen.

1.5 Rationale for the Study

Given the single-agent activity of nab-paclitaxel and the role of gemcitabine as a standard component of first-line therapy, the investigation of the nab-paclitaxel-gemcitabine combination

is appropriate. The addition of paclitaxel to a gemcitabine-carboplatin combination has been previously explored and resulted in a numerically improved OS (median 15. 8 months vs. 12.7 months with gemcitabine-carboplatin; p=0.075) (Bellmunt et al. 2012). In addition to efficacy, the combination of nab-paclitaxel-gemcitabine is likely to be well tolerated by patients with advanced bladder cancer who are poor candidates for cisplatin-containing chemotherapy. The combination of nab-paclitaxel-gemcitabine has been well tolerated by patients with advanced pancreatic cancer, including those who were elderly or had poor performance status (Von Hoff et al. 2013).

An additional potential advantage of nab-paclitaxel is the ability to continue administration as maintenance therapy following combination therapy. This study aims to determine whether a combination of nab-paclitaxel and gemcitabine given for 6 cycles, followed by maintenance with nab-paclitaxel alone, may provide an extension of treatment benefit in patients with cisplatin-ineligible locally advanced or metastatic UC.

In this Phase II study, the combination of nab-paclitaxel-gemcitabine will be administered as first-line treatment for patients with advanced bladder cancer who are poor candidates for cisplatin-based chemotherapy (see definition below). In addition, patients who are considered very unlikely to have a CR or long-term remission with cisplatin who are termed cisplatin-incurable (i.e. patients with metastases at visceral sites, regardless of performance status) will be candidates for this study.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of first-line treatment with nab-paclitaxel-gemcitabine in patients with advanced urothelial carcinoma who are either poor candidates for cisplatin-containing chemotherapy or have visceral metastases and are cisplatin-incurable. The primary endpoint is the PFS rate at 6 months after the start of treatment. .

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the safety, ORR, CR rate, and OS with the nab-paclitaxel-gemcitabine combination.

2.3 Exploratory objectives

The exploratory objectives are to evaluate archival tumor tissue by immunohistochemistry (IHC) for SPARC and gene expression and sequencing of a panel of genes to examine their association with PFS, ORR and OS.

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 diagnosis of UC that is either metastatic (any N+ M1) or locally advanced and unresectable (T4bN0). A component of urothelial (transitional cell) carcinoma is required.
2. Two groups of patients are eligible:
    a. Poor candidates for cisplatin-based chemotherapy, based on the presence of ≥ 1 the following:
        - Glomerular filtration rate of 30-60 ml/min (Cockcroft-Gault formula)
        - ECOG performance status score of 2 (Appendix A)
        - Hearing loss (trouble communicating with hearing aids or hearing loss at ≤ 3 KHz)
        - Grade ≥3 heart failure (NYHA Appendix B)
        - Age ≥80 years
        - Other concurrent illness which may make the patient a poor candidate for receiving cisplatin.

        Note: Enrollment of patients with 2 or more of these criteria should occur only after careful consideration by the treating physician regarding the patient's ability to tolerate combination chemotherapy.

    OR

    b. Poor prognosis and defined as cisplatin-incurable due to the presence of metastasis to at least one visceral site (these patients are not required to have any of the cisplatin-ineligibility criteria).
        - ECOG performance status score of 0, 1, or 2 (Appendix A).
3. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix E).
4. Patients with previously treated brain metastases are eligible if
    a. Treatment was completed ≥ 4 weeks prior to study treatment,
    b. Neurologic symptoms are minimal and stable during the preceding 4 weeks, and
    c. Maintenance dexamethasone is not required.
5. Any pre-existing peripheral neuropathy must be < Grade 2.
6. Adequate hematologic function at baseline, defined as:
    - Absolute neutrophil count (ANC) ≥1500/μL
    - Hemoglobin (Hgb) ≥ 9 g/dL (use of growth factor or red blood cell transfusion to achieve this level is allowed)
    - Platelets >100,000/μL
7. Adequate liver function at baseline, defined as:

- Bilirubin ≤1.5 mg/dL
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal [ULN] (unless bone marrow metastases are present in the absence of liver metastasis), ≤5 x ULN if liver metastases are present

8. Calculated creatinine clearance ≥30 mL/minute (Cockcroft-Gault formula)
9. 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 3 months following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study (Appendix C).
10. Women of childbearing potential (WoCBP) must have a negative serum or urine β-hCG pregnancy test performed within 72 hours prior to start of treatment and must use two forms of acceptable contraception, including one barrier method, contraceptive method during treatment and for 3 months after completing 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.
11. Age ≥18 years
12. Willingness and ability to comply with study and follow-up procedures.
13. 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. Previous systemic chemotherapy for UC, with the exception of perioperative (neoadjuvant or adjuvant) treatment or treatment with concurrent chemo-radiation for locally advanced disease. All of these treatments must have been completed > 1 year previously.
2. Presence of small-cell or sarcomatoid component in tumor histology
3. Women who are pregnant or breast-feeding
4. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
5. Any of the following cardiac diseases currently or within the last 6 months:
   - QTc interval >480 ms (per institutional standard) on screening electrocardiogram (ECG)
   - Unstable angina pectoris
   - Acute myocardial infarction
   - 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

6. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] ≥180 mmHg or diastolic blood pressure (DBP) ≥100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).
7. Currently receiving treatment with therapeutic doses of warfarin sodium. However, a maximum daily dose of 1 mg will be permitted for port line patency. Low molecular weight heparin is allowed.
8. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
9. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C (screening for these diseases is not required).
10. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years previously. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
11. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

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 AEs for 30 calendar days after their last dose of study drugs.

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 investigator must record his or her reasoning for this decision in the patient's medical record and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [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 patient's medical record and as a comment in the eCRF.

4. PATIENT REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board [IRB/]) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

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. The enrollment desk may be reached by calling (877) MY-1-SCRI. Registration may be done via fax (866) 699 0258 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This open-label non-randomized Phase II trial evaluates the efficacy and toxicity of first-line treatment with a combination of gemcitabine and nab-paclitaxel, followed by maintenance nab-paclitaxel in patients with metastatic or locally advanced unresectable UC. Two groups of patients will be eligible for this study:

1) Patients who are poor candidates for treatment with cisplatin-containing chemotherapy regimens, as defined in Section 3.1 and Figure 1.

2) Patients with visceral metastases who are incurable and unlikely to derive long-term benefit from treatment with cisplatin-based regimens.

All eligible patients will receive gemcitabine (1000 mg/m^2) and nab-paclitaxel (**125 mg/m^2**) via IV infusion on days 1 and 8 of a 21-day cycle. Patients will be seen by the treating investigator every cycle (3 weeks) and assessed for treatment response after every 3 cycles (9 weeks) of treatment. After up to 6 cycles of treatment are delivered, patients with objective response (OR), i.e., CR or PR, or stable disease (SD) will continue treatment with maintenance single agent nab-paclitaxel (**260 mg/m^2** every 3 weeks) until progression or toxicities or patient decision.

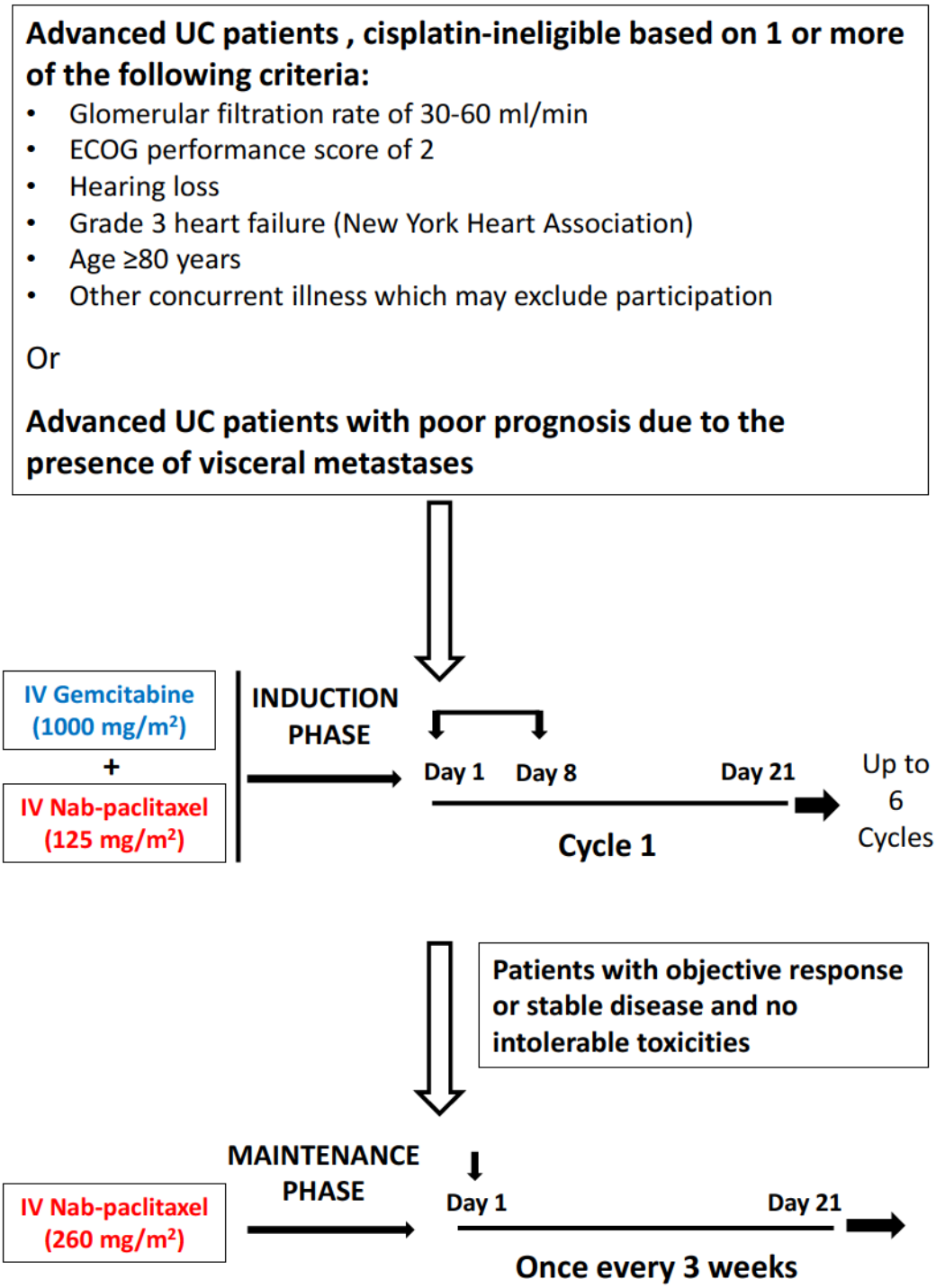
Response to therapy will be assigned using RECIST v1.1.

The planned enrollment for this study is up to 55 patients.

The study schema is presented in Figure 1.

Archival FFPE tumor samples will be collected from all patients (if available) for exploratory genomic and immunohistochemistry (IHC) biomarker evaluations. If archival tissue is not available or the patient is not allowing that to be used for this study, repeat biopsy is not required, and the patient is eligible to participate in this study.

Figure 1 **Study Schema**



5.1 Treatment Plan

5.1.1 Gemcitabine and nab-paclitaxel

Induction phase: All patients in this study will receive nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) by IV infusion on Day 1 and Day 8 of each 21-day cycle. Responding or stable patients will be treated with a minimum of 3 cycles and up to 6 cycles before starting the single agent maintenance therapy. Doses of gemcitabine and nab-paclitaxel should be recalculated if there is a $\geq$ 10% change in the patient's body weight since the previous calculation.

Maintenance phase: Patients who have objective response (CR or PR) or stable disease (SD) after completing 3-6 cycles of induction therapy with nab-paclitaxel-gemcitabine will continue treatment with single agent nab-paclitaxel (260 mg/m^2 IV every 21 days) until disease progression, intolerable toxicity or patient decision to discontinue treatment. Patients who have SD or respond to nab-paclitaxel-gemcitabine but cannot complete 6 cycles due to poor tolerance may switch to maintenance treatment with single-agent nab-paclitaxel after completing a minimum of 3 cycles of combination therapy.

5.2 Treatment Duration

Patients who tolerate treatment well and do not have tumor progression will receive 6 cycles of nab-paclitaxel/gemcitabine, followed by nab-paclitaxel alone every 3 weeks until progression, intolerable toxicities or patient decision. Radiographic evaluation will be performed at baseline and response to treatment will be assessed every 3 cycles (RECIST v1.1), and earlier if clinically warranted.

Patients who discontinued treatment prior to disease progression will continue to have reevaluations performed every 6 weeks until progression is documented. After disease progression, all patients will be followed for survival; further management will be at the discretion of the treating physician.

Patients will be evaluated for toxicity at the start of each cycle.

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 enrollment or for new conditions that develop while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines.

- Anticoagulation with coumadin-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 study treatment but low molecular weight heparin (LMWH) 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. 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.
- 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.

5.3.2 Prohibited Concomitant Medications and Treatments

The following treatments are prohibited while in this study:

- No anticancer agents other than the study medications should be given to patients. If such agents are required, then the patient must first be withdrawn from the study.
- No radiation therapy to areas of new metastases or worsening symptoms from known metastases should be given. These patients should be considered to have disease progression and removed from study. Palliative radiation to limited areas of bone metastases is allowed if lesions were present at baseline and pain has not worsened substantially.
- Treatment with other investigational agents is not permitted.
- Herbal preparations/medications that are not allowed during the study include: 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. Other herbal medicines should be discussed with and approved by the treating physician.

5.4 Correlative Studies

If available, tumor tissue from archival biopsies will be collected to be centrally studied in the future with separate funding. Potential IHC studies performed centrally will include but are not limited to SPARC expression. Gene expressing profiling of tumor tissue using Nanostring or other similar technology may also be performed.

5.4.1 Tumor Tissue Samples

Archival FFPE tumor samples (15 unstained slides of 5 μM thick sections each) will be collected during the study. Correlative tests of protein, RNA and DNA expression on these samples will be performed. Patients who do not have tumor samples available from previous biopsies do not require repeat biopsy and are still eligible for the study. Genomic DNA is isolated using Phenol:Chloroform extraction by standard molecular biology techniques. dsDNA is quantified using the Qubit Broad Range dsDNA kit (Invitrogen, Carlsbad, CA) and DNA quality

assessment is performed by gel electrophoresis. RNA is harvested using the Qiagen RNAeasy kit and quality of RNA is confirmed via the 260/280 ratio using nanodrop. Future protein assays include immunohistochemistry (IHC) for SPARC expression. DNA and RNA evaluations include Next Generation Sequencing and Nanostring gene expression to evaluate genes in the PanCan panel of 770 essential cancer pathway and driver genes . The IHC for SPARC and gene expression and sequencing data will be examined for their association with PFS, ORR and OS.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of nab-paclitaxel and gemcitabine will be modified based on hematologic and non-hematologic toxicity. A maximum of 2 dose reductions of nab-paclitaxel and gemcitabine are allowed during both the induction and maintenance treatment (Table 1). If toxicity recurs after 2 dose reductions, the responsible drug or drugs should be discontinued. If only 1 drug is discontinued, the patient may continue on the other drug. Dose reductions of gemcitabine and nab-paclitaxel are permanent for the remainder of study treatment.

Treatment during the induction and the maintenance phases may be delayed up to 3 weeks to allow recovery from treatment-related toxicity. Patients should be re-evaluated weekly while treatment is being held. If toxicity has not improved to Grade ≤1 after 3 weeks, the responsible drug(s) should be discontinued.

Table 1 Dose Level Modifications

Induction phase:

Dose Level	Nab-paclitaxel	Gemcitabine
Starting Dose	125 mg/m^2	1000 mg/m^2
Dose Level -1	100mg/m^2	800 mg/m^2
Dose Level -2	80 mg/m^2	600 mg/m^2

Maintenance phase:

Dose Level	Nab-paclitaxel
Starting Dose	260 mg/m^2
Dose Level -1	220 mg/m^2
Dose Level -2	180 mg/m^2

6.1 Dose Modifications Due to Hematologic Toxicity

Hematologic toxicity is a common and expected toxicity caused by nab-paclitaxel and gemcitabine. Management and dose modifications for neutropenia and thrombocytopenia are outlined in Table 2, Table 3, and Table 4. Generally, dose reductions (without prophylactic G-CSF) are considered based on hematologic toxicities, but prophylactic G-CSF may be considered from cycle 1 day 8-9 per ASCO guidelines or later if the patient is benefiting from therapy and it is deemed in the best interest of the patient to maintain dose.

6.1.1 Induction Treatment (Nab-paclitaxel and Gemcitabine)-Day 1

Nab-paclitaxel and gemcitabine dosing should not be administered at the start of each cycle until the ANC returns to $\geq 1.5 \times 10^9$ cells/L and the platelet count returns to $\geq 100 \times 10^9$ cells/L. Table 2 summarizes the required interventions and dose reductions based on blood counts determined on Day 1 of each treatment cycle.

Table 2 Dose Reductions of Nab-paclitaxel and Gemcitabine Based on Day 1 Blood Counts During Induction Therapy

Event	Management	Dose Modification	
Neutropenia (ANC)		**Nab-paclitaxel**	**Gemcitabine**
ANC >1500/μL	Administer dose	No dose reduction	No dose reduction
ANC 500-1500/μL	Delay dose 1 week or until ANC >1500/μL	No dose reduction	1 dose level reduction
ANC <500/μL or Day 8 omitted during previous cycle due to neutropenia or Febrile neutropenia during previous cycle	Delay dose 1 week or until ANC > 1500/μL	1 dose level reduction	1 dose level reduction
Thrombocytopenia			
Platelets >100,000/μL	Administer dose	No dose reduction	No dose reduction
Platelets 75,000-100,000/μL	Delay dose 1 week or until platelet count > 100,000/μL	No dose reduction	1 dose level reduction
Platelets <75,000/μL or Platelet transfusion required during previous cycle or Day 8 dose omitted during previous cycle due to thrombocytopenia or Bleeding associated with thrombocytopenia during previous cycle	Delay dose 1 week or until platelet count > 100,000/μL	1 dose level reduction	1 dose level reduction

6.1.2 Induction Treatment (Nab-paclitaxel and Gemcitabine)-Day 8

Day 8 dosing of nab-paclitaxel and gemcitabine will be administered if the ANC ≥1000/μL and platelets ≥75,000/μL. If either count is lower than these levels, the Day 8 dose will be omitted. Total cycle length will remain at 21 days. Table 3 summarizes the required interventions and subsequent dose reductions based on blood counts determined on Day 8 of each treatment cycle.

Table 3 Dose Reductions of Nab-paclitaxel and Gemcitabine Based on Day 8 Blood Counts During Induction Therapy

Event	Management	Dose Modification	
		Nab-paclitaxel	Gemcitabine
ANC ≥1000/μL and platelets ≥75,000/μL	Administer dose	No dose reduction	No dose reduction
ANC <1000/μL OR Platelets <75,000/μL First episode	Omit Day 8 dose	No dose reduction beginning Day 1 of next cycle	Reduce by 1 dose level beginning Day 1 of next cycle
Second episode	Omit Day 8 dose	Reduce by 1 dose level beginning Day 1 of next cycle	Reduce by 1 dose level beginning Day 1 of next cycle
Platelets <75,000/μL AND ANC <1,000/μL	Omit Day 8 dose	Reduce by 1 dose level beginning Day 1 of next cycle	Reduce by 1 dose level beginning Day 1 of next cycle

6.1.3 Maintenance Treatment (Single-agent Nab-paclitaxel)-Day 1

If dose reductions of nab-paclitaxel were required during induction therapy, the matching nab-paclitaxel dose reduction (i.e. same level of dose reduction) should be used to should be used to start maintenance therapy (See Table 1).

Table 4 summarizes the required interventions and dose reductions based on blood counts determined on Day 1 of each maintenance treatment cycle.

Table 4 Dose Reductions of Maintenance Nab-paclitaxel based on Day 1 Blood Counts

Event	Management	Dose Modification
Neutropenia		**Nab-paclitaxel**
ANC ≥1500/μL	Administer dose	No dose reduction
<1500/μL	Delay dose till ANC > 1500/μL	1 dose level reduction
Thrombocytopenia		
Platelets ≥100,000/μL	Administer dose	No dose reduction
Platelets <100,000/μL	Delay dose 1 week or until platelets > 100,000/μL	1 dose level reduction

6.2 Dose Modifications Due to Non-Hematologic Toxicity

Dose modifications for non-hematologic toxicity during the induction and maintenance phases are summarized in Table 5. During the induction phase, if the toxicity is clearly related to 1 of the study drugs, modification will be made only in the dose of that drug. However, doses of both drugs will be decreased if the toxicity cannot be confidently attributed to just 1 of the study drugs.

If toxicity has not improved to Grade ≤1 after 3 weeks treatment delay, the drug responsible for the toxicity will be discontinued. During the induction phase, if the patient is judged to be benefiting from treatment, study treatment may continue with the remaining study drug.

If toxicity recurs after 2 dose reductions have already been made, the drug will be discontinued.

Table 5 Dose Reductions for Grade 3 or 4 Non-Hematologic Toxicities

Toxicity Grade	Nab-paclitaxel[a]	Gemcitabine[a]
Grade 0, 1, or 2	None	None
Grade 3 or 4[b]	Hold[a]	Hold[a]
Toxicity resolves to Grade ≤1	Reduce the dose of the offending agent or agents by 1 dose level (Table 1)	
Second incidence of Grade 3 or 4 toxicity[b]	Hold[a]	Hold[a]
Toxicity resolves to Grade ≤1	Reduce the dose of the offending agent or agents by 1 additional dose level (Table 1)[c]	

[a] Both drugs should be held and the patient should be seen weekly until toxicity resolves to ≤ Grade 1. Patients who develop irreversible Grade 3/4 non-hematologic toxicity, or toxicity that does not resolve to ≤ Grade 1 within 3 weeks, should have the offending agent(s) discontinued.

[b] Dose modification for Grade 3/4 nausea, vomiting, or diarrhea will be made only if these toxicities occur in spite of maximal medical prophylaxis/management

[c] No more than 2 dose reductions of nab-paclitaxel and gemcitabine are allowed.

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.

7.2 Baseline Study Assessments

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

Within 30-Days prior to initiation of treatment

- Written informed consent prior to any other study-related procedures
- Medical history
- Physical examination and measurements of height (first visit) and weight)
- Vital signs (resting heart rate, blood pressure [BP], respiratory rate, and temperature
- ECOG performance status
- Single 12-lead ECG
- Smoking history
- Review of all medications
- CT scans of the chest, abdomen and pelvis
- Bone Scan or PET scan (only in patients with signs/symptoms suggestive of bone metastases)
- Archived tumor tissue or 15 unstained slides of 5 µM thickness sections may be obtained preferably prior to end of Cycle 1, if available and if the patient gives consent

Within14-Days prior to initiation of treatment

- Complete blood count (CBC) with 3-part differential and platelets (must be performed within 72 hours prior to treatment)
- Fasting comprehensive metabolic profile (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
- Prothrombin time (PT) or international normalized ratio (INR)
- Urine dipstick for pH, protein, glucose, blood, ketones, leucocytes
- For WoCBP, serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)

7.3 Study Treatment Assessments

7.3.1 Induction Therapy with Nab-paclitaxel/Gemcitabine

Day 1 of each cycle

- Update of medical history
- Physical examination (including weight)
- Vital signs
- ECOG performance status
- CBC, including 3-part differential and platelets (must be performed within 72 hours prior to treatment)
- Clinical chemistry (CMP) (must be performed within 72 hours prior to treatment)
- For WoCBP, serum or urine pregnancy test (must be performed within 72 hours prior to treatment)
- AE assessment
- Concomitant medication review
- Study drugs infusion

Day 8 of each cycle

- CBC, including 3-part differential and platelets
- Study drug infusion

7.3.2 Maintenance Therapy with Single-Agent Nab-paclitaxel

Day 1 of each cycle

- Update of medical history
- Physical examination (including weight)
- Vital signs

- ECOG performance status
- CBC, including 3-part differential and platelets (must be performed within 72 hours prior to treatment)
- CMP (must be performed within 72 hours prior to treatment)
- For WoCBP, serum or urine pregnancy test (must be performed within 72 hours prior to treatment)
- Concomitant medication review
- AE assessment

7.3.3 Response Assessment Every 3 Cycles (± 7 days)

Patients will be evaluated for response to treatment after every 3 cycles of treatment. The following assessments will be performed:

- CT scans of chest, abdomen and pelvis (at restaging, only scans that were abnormal at baseline need to be repeated unless additional areas are clinically indicated)
- Bone Scan or PET (if positive at baseline, repeat every 6 cycles of therapy)

Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from study treatment; patients with SD or response to therapy will continue treatment.

7.4 End of Study Evaluation (to be completed within 30 days of treatment discontinuation)

All patients must be seen and evaluated within 30 days after stopping study treatment. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfil the End-of-Treatment Visit. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

- Update of medical history
- Physical examination
- Vital signs
- ECOG performance status
- CBC, including 3-part differential and platelets
- CMP
- For WoCBP, serum or urine pregnancy test
- Concomitant medication review
- AE assessment

7.5 Follow-up

7.5.1 Follow-up prior to disease progression every 6 weeks (± 7 days):

Patients who discontinue study treatment without evidence of disease progression should be followed if possible to determine the date of progression. The following assessments will take place:

- Update of medical history
- Physical examination
- Vital signs
- ECOG performance status
- CT scans of chest, abdomen and pelvis (only scans that are abnormal at baseline need to be repeated, unless additional areas are clinically indicated)
- Bone Scan or PET scan (only if abnormal at baseline)

7.5.2 Follow-up after disease progression (survival follow up)

After disease progression is documented, patients will be followed every 3 months for survival (i.e., date and cause of death) for the first year, and then every 6 months thereafter up to 5 years or death whichever comes first. Patients may be contacted during outpatient visits or by telephone.

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

Study Drug	Dosage Form and Strength	Manufacturer
Nab-paclitaxel (Abraxane or ABI-007)	Each vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin	Celgene
Gemcitabine (Gemzar)	Each vial contains 200 mg/ 1 gm	Eli Lilly and Company

8.1 Nab-paclitaxel

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.

8.1.2 Preparation and Administration

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.

8.1.3 Precautions and Risks

Precautions and risks are located in the IB.

8.2 Gemcitabine

Gemcitabine 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) (http://pi.lilly.com/us/gemzar.pdf) for detailed information on how to prepare and administer gemcitabine.

8.2.1 Labeling, Packaging, and Supply

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

All study medications must be kept in a secure place under appropriate storage conditions. Storage conditions for gemcitabine can be found in the relevant USPI. The expiration date on the label must not be exceeded.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration

Please refer to the USPI for detailed information on how to prepare and administer gemcitabine

8.2.3 Precautions and Risks

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

8.3 Accountability for Nab-paclitaxel provided for the Study

The Principal Investigator (or designee) is responsible for accountability of all used and unused nab-paclitaxel provided for this study.

All inventories of nab-paclitaxel provided for this study must be made available for inspection by the Sponsor 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. Supplies of nab-paclitaxel provided for this study must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact SCRI Innovations regarding disposal of any nab-paclitaxel provided for this study.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. All patients participating in this study will have measurable lesions per RECIST Version 1.1.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

The purpose of this open-label non-randomized phase II trial is to study the efficacy and toxicity of the gemcitabine/nab-paclitaxel combination followed by maintenance single-agent nab-paclitaxel as the first-line treatment of patients with advanced UC. Two groups of patients will be eligible for this study: 1) patients who are considered poor candidates for treatment with cisplatin (Figure 1), and 2) patients with visceral metastases, who are incurable and unlikely to derive long-term benefit from treatment with cisplatin-based regimens.

10.2 Sample Size Considerations

This will be an open-label single-stage non-randomized Phase II trial to evaluate the efficacy and toxicity of the gemcitabine/nab-paclitaxel combination followed by maintenance dose of nab-paclitaxel regimen. We expect approximately 80% of patients to contribute a progression event to the analysis. The primary endpoint is 6-month PFS (PFS6).

We have evidence from a Phase III trial that gemcitabine/carboplatin (a regimen frequently administered to patients considered poor candidates for cisplatin) produces a 6-month PFS of ~45% (Sonpavde et al. 2012, Podhajcer et al. 2008), De Santis et al. 2012). It is assumed therefore that a PFS6 of ≥65% is an optimal estimate for a meaningful improvement using the gemcitabine/nab-paclitaxel combination followed by maintenance single-agent nab-paclitaxel. An improvement in PFS6 from a historical 45% to 65% translates to an approximated hazard ratio of 0.54. A sample size of 55 patients will provide at least 80% power for a 2-sided test for the PFS6 assuming a significance level of 0.05 and a drop-out/non-evaluable rate of no more than 10% of patients (i.e. 5 patients). Sample size was determined using ARTSURV in the statistical package STATA (v12). Power assessments were not conducted for secondary endpoints.

10.3 Data Analysis

The database, randomization and safety monitoring will be managed centrally by Sarah Cannon Research Institute (SCRI).

10.3.1 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 reason will be presented.

10.3.2 Efficacy Analysis

All primary efficacy analyses will be performed using the population of patients who receive study treatment, and minimum follow-up period of 6 months after starting therapy or progression, whichever comes first for each patient. The recruitment period will be ~18 months.

Primary efficacy endpoint: PFS Event Free Rate at Month 6

6-month PFS event free rate is defined as the number of patients with PFS >6 months (or 26 weeks to accommodate the tumor assessment schedule) divided by number of patients with baseline tumor assessment.

The primary endpoint, 6-month PFS event free rate, will be presented as the point estimate with its associated 95% Clopper-Pearson confidence interval (CI).

Secondary Efficacy Endpoints:

Efficacy analyses will also be performed on the 2 patient subgroups eligible for this trial (i.e. patients who are cisplatin-ineligible and patients with poor prognosis due to visceral metastases).

- Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) according to RECIST v1.1.
- Clinical Benefit Rate (CBR) is defined as the proportion of patients with CR, PR or SD according to RECIST v1.1.
    - For ORR and CBR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responders.
- Progression Free Survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the RECIST v1.1 criteria, or death on study, whichever comes first. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.
- Overall Survival (OS) is defined as the time from the first day of study drug administration (Day 1) or death on study. Patients who are alive will be censored at last known date alive.

For ORR and CBR, the estimates and the associated 95% CI (based on the Clopper-Pearson method) for the entire treatment group will be calculated. The ORR and CBR will also be calculated for the 2 patient subgroups.

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI be provided. Curves will be generated for the entire treatment population, and for the 2 eligible subgroups of patients.

10.3.3 Safety Analysis

All patients who receive at least 1 dose of study treatment will be included in the safety population. Safety will be assessed through the analysis of the reported incidence of treatment-

emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v4.03. 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 for all patients in the Safety Population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented for all patients in the Safety Population.

Other safety endpoints, including laboratory results, will be summarized for all patients in the Safety Population.

10.3.4 Correlative Studies

Tumor tissue from archival biopsies will be collected to be centrally studied in the future. Genomic DNA will be isolated using Phenol:Chloroform extraction by standard molecular biology techniques. dsDNA will be quantified and DNA quality assessment will be performed by gel electrophoresis. RNA will be harvested using the Qiagen RNAeasy kit and quality of RNA will be confirmed by measuring the 260/280 ratio using nanodrop. Protein assays planned for this study will include immunohistochemistry (IHC) for SPARC expression. DNA and RNA evaluations for this study will include Next Generation Sequencing and Nanostring gene expression to evaluate genes in the PanCan panel of 770 essential cancer pathway and driver genes. For analysis of gene sequencing, raw sequence data in Fastq format will be aligned to human reference genome and quantified and compared. Digital raw counts of RNA abundance by Nanostring will be normalized using internal controls and housekeeping genes. Pathway analysis will be performed using Ingenuity Pathway Analysis (IPA) software. The IHC for SPARC and gene expression and sequencing data will be examined for their association with PFS, ORR and OS. The association of IHC and genomic studies with PFS, OS and response will be examined using Cox regression.

10.4 Analysis Time Points

10.4.1 Final Analysis

The final analysis of the study will occur after 55 patients are enrolled and at least 40 have experienced disease progression.

10.4.2 Planned Interim Analysis

There will be no planned interim analysis.

10.4.3 Safety Review

There will be no planned interim safety reviews.

10.4.4 Efficacy Review

There will be no planned interim analyses of treatment efficacy.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and Serious Adverse Events (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 (see Section 11.1.5). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB/EC according to the policies of that IRB/EC.

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 judgment 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" AE, 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 means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions (SARs) where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction 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 suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, 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 Safety Department. 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-paclitaxel/gemcitabine 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 Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 day follow-up period after the last study treatment. **The SCRI Innovations Safety Department 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 Safety Department 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. Phone #: 1-615-329-7358
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.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form.

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 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. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations Safety Department.

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), does not require reporting as an SAE to the SCRI Innovations Safety Department.

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 11.2). 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, or within 3 months of the last dose of nab-paclitaxel or gemcitabine, a Pregnancy Form should be completed and faxed to the SCRI Innovations Safety Department. SCRI Innovations Safety Department (SCRI Innovations SD) should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

Nab-paclitaxel and gemcitabine are to be discontinued immediately if a patient becomes pregnant while on study. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to SCRI Innovations SD immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE 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.

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 study drugs 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.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, during treatment or for 6 months after stopping treatment, the male subject taking study drugs should notify the study doctor. This pregnancy must be reported to the SCRI Innovations Safety Department and they will inform Celgene immediately. The pregnant female

partner should be advised to call their healthcare provider 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.

11.3.9 Overdose of Nab-paclitaxel of Gemcitabine

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with either nab-paclitaxel or gemcitabine that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of nab-paclitaxel or gemcitabine, see the appropriate (nab-paclitaxel) Investigator's Brochure or follow standard guidelines.

11.4 Sponsor Serious Adverse Event Reporting Requirements

SCRI Innovations Safety Department will forward SAE information (using SCRI SD SAE form) to Celgene within 1 business day of SCRI Innovations Safety Department personnel becoming aware of the SAE. The written report must be completed and supplied to Celgene by facsimile within 1 business day. 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. The Celgene Corporation study number and the SCRI study number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

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-BLD-PI-004993
SCRI Study number: GU 124

SCRI Innovations 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.

11.4.1 Sponsor Assessment of Unexpected

The SCRI Innovations is responsible for assessing an AE or suspected adverse event as "unexpected."

An AE or suspected adverse reaction (SAR) is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the Investigator's Brochure (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 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 Package Insert 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 Safety Department must also be faxed to Celgene:

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

12. 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).

12.1 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 the Sponsor 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 the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

12.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor 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.

12.3 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.

12.3.1 Confidentiality

12.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). 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 GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB/EC 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 the Sponsor. 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/PIS.

12.3.1.2 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.

12.4 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.

13. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

13.1 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 the Sponsor. 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 the Sponsor, 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 the Sponsor as applicable and IRB/EC 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.

13.2 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:

SCRI Innovations

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/EC approval of the study and the IRB/EC 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 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)

13.3 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 the Sponsor 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, 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.

The Sponsor 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 the Sponsor 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). Sponsor 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 the Sponsor 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 the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor throughout the study, and will be transferred to the Sponsor at the conclusion of the study.

13.4 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 the Sponsor 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.

13.5 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC 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 the Sponsor's discretion, Source Document Verification (SDV) 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, the Sponsor or its representative(s).

13.6 Quality Assurance and Quality Control

Each study site shall be required to have Standard Operating Procedures to define and ensure quality assurance/control processes for study conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7 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. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

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 Sponsor as appropriate. Investigator shall provide the Sponsor 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 Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any SCRI Innovations Confidential Information from all publications.

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15. 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.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, during treatment or for 6 months after stopping treatment, the male subject taking study drugs should notify the study doctor, and the pregnant female partner should be advised to call their healthcare provider immediately.

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	BASELINE[a]		TREATMENT				End of Study Evaluation for patients with PD or intolerable toxicities (within 30 days of treatment discontinuation)	FOLLOW-UP	
			Induction Phase (*Cycles repeat every 21 days*) x *maximum 6 cycles*		Maintenance Phase (*Cycles repeat every 21 days*)- Until PD or intolerable toxicities	Response assessment		For patients discontinued prior to disease progression[m] (every 6 weeks [± 7 Days])	After disease progression[n]
	-30 Days	-14 Days	Cycle 1 Day 1	Cycle 1 Day 8	Every 21 Days	Every 3 Cycles (± 7 Days)			
Tests and Observations									
Informed consent	X								
Medical history	X		X		X		X	X	
Smoking history	X								
Physical exam[b] (Height only at first visit)	X		X		X		X	X	
Vital Signs[c]	X		X		X		X	X	
ECOG PS	X		X		X		X	X	
12-lead ECG	X								
Adverse event evaluation			X		X		X		
Concomitant medication review	X		X		X		X		
Laboratory Observations									
CBC, 3-part differential, and platelets		X	X[a]	X	X		X		
Chemistry (CMP)[d]		X	X[a]		X		X		
PT or INR[e]		X							
Urine dipstick[f]		X							
Serum or Urine Pregnancy Test[g]		X	X[a]		X		X		
Staging and follow up									
CT Scan Chest, abdomen and pelvis	X					X[h]	X[h,i]	X[h]	
Bone Scan or PET scan[j] (only if bone metastases are suspected)	X					X[k]	X[k,i]	X[k]	
Follow up for survival									X
Correlative studies									
Archived Tumor Tissue Samples (15 FFPE slides of 5 µM thickness sections)[l]	X								
Treatment									
Nab-paclitaxel infusion			X	X	X				
Gemcitabine infusion			X	X					

Appendix D: Schedule of Assessments (continued)

a Baseline blood counts, chemistries and pregnancy test do not have to be repeated on Cycle 1 Day 1 if obtained within 72 hours.

b Physical examination will include measurements of height (pre-treatment visit only), weight. Measurement of weight is not required for visits occurring after completion of treatment.

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, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

e If PT 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 (within 72 hours of study treatment start).

h Only CT scans that were abnormal at baseline need to be repeated at restaging, unless additional areas are clinically indicated.

i Only if PD not previously diagnosed and most recent scans were done > 9 weeks prior

j Bone scans or PET scans will be done 30 days prior to start of treatment in patients with signs/symptoms suspicious for bone metastases.

k If baseline bone scan (or PET scan) is abnormal, repeat every 6 cycles (18 weeks)..

l Archival tumor tissue samples from patients (who have and consented to provide it)should be obtained by study site personnel for correlative studies, preferably prior to the end of Cycle 1.

m If possible, patients who discontinue study treatment prior to disease progression should be seen every 6 weeks (± 7 Days), with re-evaluations as indicated, until disease progression is documented.

n After disease progression, patients will be followed every 3 months for survival status (i.e. death date and cause of death) for the first year, and then every 6 months thereafter up to 5 years. Patients may be contacted during visits or by telephone.

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) version 1.1 (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.