A Single-arm Feasibility Study of Gemcitabine, Cisplatin, and Nab-Paclitaxel as Neoadjuvant Therapy for Resectable Oncologically High-Risk Intrahepatic Cholangiocarcinoma

Protocol #: EU4339-18

NCT#:

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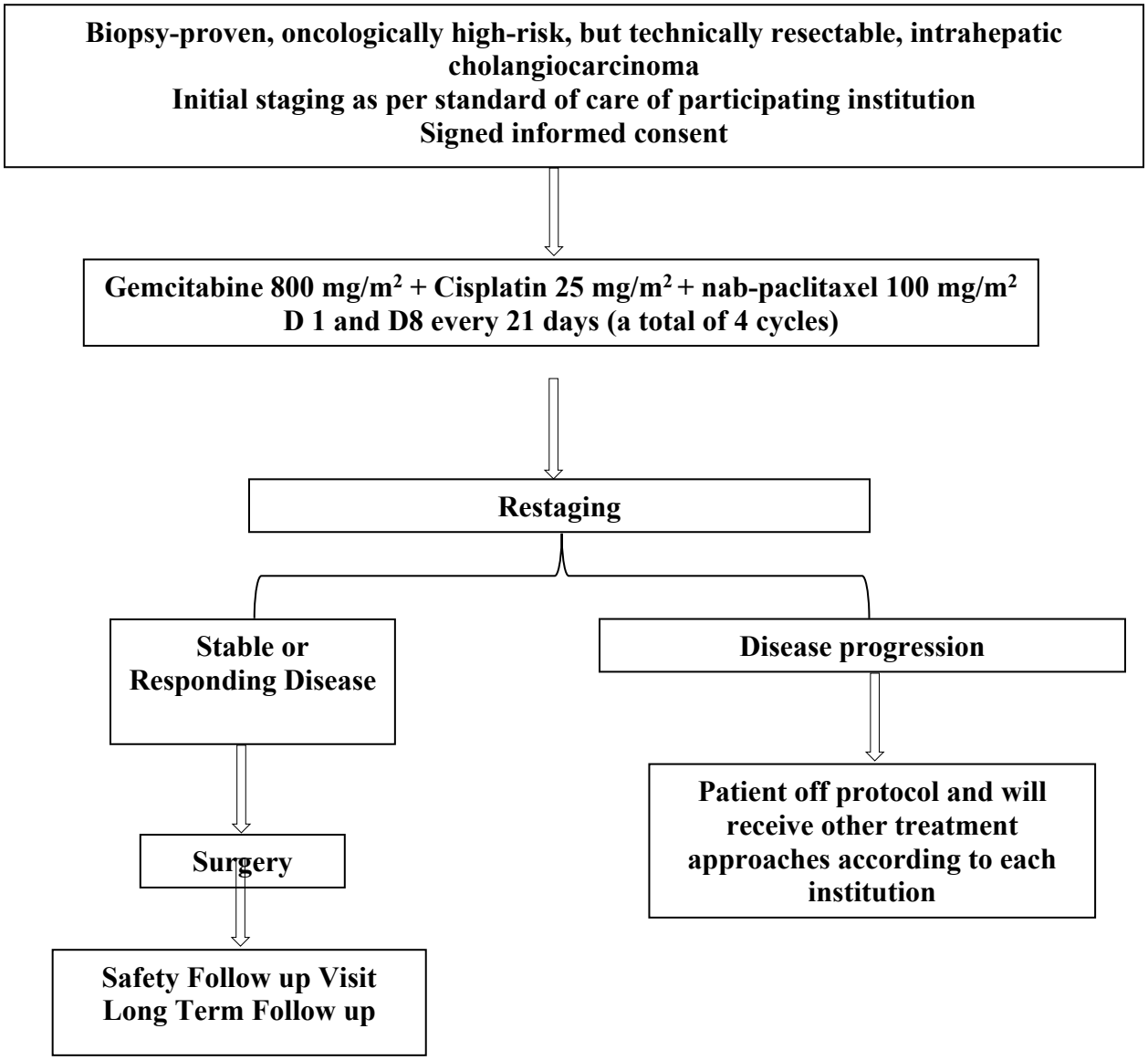
1. SYNOPSIS

Institution/Affiliation:	Department of Surgery, Division of Surgical Oncology, Emory University School of Medicine
Protocol Title:	A Single-arm Feasibility Study of Gemcitabine, Cisplatin, and Nab-Paclitaxel as Neoadjuvant Therapy for Resectable Oncologically High-Risk Intrahepatic Cholangiocarcinoma
Phase of Development:	II
Trial Locations:	1) MD Anderson Cancer Center 2) Mayo Clinic Rochester 3) Virginia Mason Hospital 4) Emory University
Number of sites:	4
Patient Population:	Resectable Oncologically High-Risk Intrahepatic Cholangiocarcinoma
Estimated Number of Patients:	37 patients
Primary Objective:	To assess the feasibility of neoadjuvant chemotherapy including gemcitabine, cisplatin, and nab-paclitaxel for resectable oncologically high-risk intrahepatic cholangiocarcinoma that is treated with surgical resection. Thus, the primary aim will be completion of all treatment including neoadjuvant therapy and resection, while assessing safety and tolerability of the preoperative chemotherapy regimen prior to surgery.
Secondary Objectives:	1) To assess the radiological response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) 2) To determine the R0 resection rate 3) To determine recurrence-free survival (RFS) 4) To identify patients' overall survival (OS) rate.
Study Design:	1) Phase II 2) 37 patients
Select Inclusion Criteria:	1) Diagnosis of intrahepatic cholangiocarcinoma 2) Oncologic high-risk disease at the time of enrollment defined as(must meet at least one of the criteria below) ❖ T-stage ≥ Ib (Ib – IV) ❖ Solitary lesion > 5 cm ❖ Multifocal tumors or satellite lesions present confined to the same lobe of the liver as the dominant lesion but still technically resectable

	❖ Presence of major vascular invasion but still technically resectable ❖ Suspicious or involved regional lymph nodes (N1) 3) High-quality cross-sectional imaging (CT or MRI) performed within 6 weeks prior to enrollment 4) No distant extrahepatic disease (M0) 5) Adults >18 years of age 6) Able to give informed consent 7) Able to adhere to study visit schedule and other protocol requirements 8) ECOG performance status of 0-1 9) Absolute neutrophil count ≥ 1500/mm3 10) Platelet count ≥ 100,000/mm3 11) Albumin ≥3 g/dl
Select Exclusion Criteria	1) Serum creatinine > 1.5x upper limit of normal 2) Serum total bilirubin > 1.5x upper limit of normal 3) Presence of active infection 4) Pregnant and/or breastfeeding 5) Active other primary malignancy 6) Concurrent severe and/or uncontrolled medication conditions which could compromise participation in study such as unstable angina, MI within 6 months, unstable symptomatic arrhythmia, symptomatic CHF, serious active or uncontrolled infection after inadequate biliary drainage if tumor obstructing bile duct.
Length of Study:	Our plan is to enroll 37 resectable oncologically high-risk intrahepatic cholangiocarcinoma patients over an 18 month period starting from May 1st 2018 in order to have 30 evaluable patients. Last study participant will be enrolled 6 months prior to study completion. All patients will be followed for recurrence free survival and overall survival as part of routine care.
Additional Therapies	1) Gemcitabine 2) Cisplatin 3) nab-paclitaxel

Scheme


Biopsy-proven, oncologically high-risk, but technically resectable, intrahepatic cholangiocarcinoma
Initial staging as per standard of care of participating institution
Signed informed consent
Gemcitabine 800 mg/m2 + Cisplatin 25 mg/m2 + nab-paclitaxel 100 mg/m2
D 1 and D8 every 21 days (a total of 4 cycles)
Restaging
Stable or Responding Disease
Disease progression
Surgery
Patient off protocol and will receive other treatment approaches according to each institution
Safety Follow up Visit
Long Term Follow up

2. BACKGROUND

Intrahepatic cholangiocarcinoma (IHCCA) is the second most common primary liver cancer, with a rising incidence but without parallel advances in treatment or patient outcome. Surgical resection is the only potentially curative treatment for IHCCA and is associated with 5-year survival rates between 15% and 40%. Up to two-thirds of patients are not resectable at presentation and of those who undergo curative-intent resection, two-thirds suffer postoperative disease recurrence, most commonly in the remnant liver, followed by the peritoneum and abdominal lymph nodes. Risk factors for disease recurrence include vascular invasion, multiple tumors, lymph node metastases, increased tumor size, and periductal infiltrating tumor morphology.[1,2]

Neoadjuvant chemotherapy for intrahepatic cholangiocarcinoma

The potential benefits of neoadjuvant therapy in IHCCA are early treatment of micrometastases, downsizing of tumors to increase margin-negative resection rates, eradication of disease from regional lymph nodes, and improved selection of patients for complex liver resection. To date, a prospective study on neoadjuvant therapy for resectable IHCCA has not been conducted.

A retrospective study by Le Roy et al investigated the efficacy of neoadjuvant chemotherapy in locally advanced IHCCA. They enrolled 170 IHCCA including 74 locally advanced and 96 resectable tumors. Out of 74 patients, 51 were treated with gemcitabine based regimens and 19 received 5-fluorouracil, oxaliplatin and irinotecan. In their study, 39 (53%) out of 74 locally advanced IHCCA patients became resectable after receiving 6 months of systemic chemotherapy. There was no statistically significant difference in the median overall survival (OS) of locally advanced IHCCA patients' who received neoadjuvant chemotherapy as compared to patients who had surgery alone for resectable disease. These data suggested that the survival of patients with locally advanced disease treated with neoadjuvant therapy may be similar to those who received primary resection.[3]

Stromal interactions in biliary cancers and the role of Nab-Paclitaxel

Tumor progression and growth has been previously linked to dynamic interactions between tumor cells and the surrounding stromal tissue. Cancers with a "reactive" stroma are associated with a high density of alpha-smooth muscle actin (α-SMA)-positive fibroblasts, hypovascularity, and activated stellate cells.[4-7] The presence of α-SMA-positive fibroblasts within the cholangiocarcinoma stroma has been associated with a poor prognosis.[6-8]

IHCCA is characterized by fibroinflammatory desmoplasia and hypoperfused stroma. In preclinical studies of pancreatic cancer, which incites a similarly dense desmoplastic reaction, nab-paclitaxel, an FDA-approved chemotherapy for treatment of metastatic pancreatic cancer, induced stromal collapse and increased intratumoral delivery of gemcitabine.[9] In a study of potentially resectable pancreatic cancer patients treated with Nab-Paclitaxel and gemcitabine, surgical specimens of patients with a marked pathologic

response demonstrated stromal disruption, characterized by collagen disorganization, and a lower density of α-SMA-positive fibroblasts suggesting a role for this combination in other stromal-rich malignancies like biliary tracts cancers (BTC).[10] Therefore, both preclinical and clinical data support the use of neoadjuvant nab-paclitaxel, gemcitabine, and cisplatin for IHCCA.

Currently, the standard of care regimen for unresectable IHCCA is gemcitabine and cisplatin, which is associated with a median progression-free survival (PFS) of 8 months and overall survival (OS) of 11.7 months.[11]

Safety of combining gemcitabine, cisplatin, and Nab-Paclitaxel

The safety of combining gemcitabine and cisplatin and gemcitabine and Nab-Paclitaxel has been previously described in BTC and pancreatic cancers, respectively.[11,12] A recent phase II study of 51 patients was completed at MD Anderson Cancer Center with unresectable BTC treated with gemcitabine, cisplatin, and nab-paclitaxel (GAP). Patients treated initially with cisplatin 25mg/m^2, nab-paclitaxel 125mg/m^2 and gemcitabine 1000mg/m^2 experienced grade 3/4 hematological toxicity including neutropenia, febrile neutropenia, anemia, and thrombocytopenia leading to treatment discontinuation in 6 out of 30 patients. Nab-paclitaxel was reduced to 100mg/m^2 and gemcitabine to 800mg/m^2. After dose reduction, treatment was better tolerated and only 3 patients experienced grade 4 hematological toxicity. Moreover, grade 3 non-hematological toxicities developed in 19 patients including nausea, vomiting, diarrhea, thromboembolic event, cardiovascular arrhythmia, hypokalemia, constipation, cystitis, and elevations of liver transaminases. The median PFS = 11.4 mos (95% CI: 6.1, 16.1) with median OS = 19.2 (95%CI: 13.6, NA) and 1-year survival rate 67.6%. The disease control rate was demonstrated in 84.3% of patients and 12 initially unresectable cases were operated on post treatment with 1 patient having had a complete pathologic response.[13]

3. DRUG INFORMATION

3.1 Nab-Paclitaxel

3.1.1 The Product

NAB-PACLITAXEL for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. NAB-PACLITAXEL is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. NAB-PACLITAXEL is free of solvents. The active agent in NAB-PACLITAXEL is paclitaxel.

3.1.2 Indication

In the United States, NAB-PACLITAXEL for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

3.1.3 Introduction

NAB-PACLITAXEL is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intraluminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium.[14] Other postulated mechanisms of action for the combination of gemcitabine with nab-paclitaxel include downregulation of cytidine deaminase by paclitaxel resulting in higher/sustained concentrations of gemcitabine, macropinocytosis of proteins such as albumin by Ras-transformed cells which would allow for enhanced uptake of paclitaxel loaded albumin nanoparticles into pancreatic cancer tumor cells.[15,16]

3.1.4 Preclinical Studies with NAB-PACLITAXEL

Preclinical studies comparing NAB-PACLITAXEL to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for NAB-PACLITAXEL compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, NAB-PACLITAXEL treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for NAB-PACLITAXEL versus solvent based paclitaxel, indicating more effective intratumoral accumulation of NAB-PACLITAXEL.[14]

3.1.6 Clinical Studies with NAB-PACLITAXEL

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing NAB-PACLITAXEL plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the NAB-PACLITAXEL/gemcitabine arm (N=431) or to the gemcitabine arm (N=430). Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to NAB-PACLITAXEL/gemcitabine received NAB-PACLITAXEL 125 mg/m2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m2 on Days 1, 8 and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

In the intent to treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

The median overall survival of the NAB-PACLITAXEL/gemcitabine group was 8.5 months compared to 6.7 months in the gemcitabine alone group (HR 0.72, $p<0.0001$). PFS was similarly improved in the combination arm (5.5 vs. 3.7 months, HR 0.69, $p<0.0001$). Overall response rate by central review was 23% with NAB-PACLITAXEL/gemcitabine and 7% with gemcitabine alone ($p<0.0001$).

3.1.6 Potential Risks of NAB-PACLITAXEL Toxicities

As of 06 Oct 2014, approximately 11,867 subjects have been treated with nab-paclitaxel in clinical studies, with 3,905 in the Celgene development program worldwide and an estimated 7,962 in non-Celgene-sponsored studies globally. It is estimated that cumulative exposure to nab-paclitaxel during marketing experience is approximately 296,427 patients. Therefore, overall estimated cumulative exposure to nab-paclitaxel during clinical trials and commercial experience is approximately 308,294 patients. Clinically significant adverse drug reactions identified during clinical trials or post-marketing surveillance, considered by Celgene to be at least possibly associated with nab-paclitaxel, are provided below.

Very common (≥ 10%):

- anemia, red blood cell count decreased
- febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia
- constipation
- diarrhea

• nausea
• vomiting
• abdominal pain, abdominal pain upper
• stomatitis, mucosal inflammation
• SMQ peripheral neuropathy
• dizziness
• headache
• asthenia, fatigue
• arthralgia, back pain, bone pain, chest pain, musculoskeletal pain, myalgia, pain in extremity
• edema, edema peripheral
• pyrexia
• chills
• decreased appetite
• dysgeusia
• weight decreased
• insomnia
• depression
• cough
• dyspnea
• alopecia
• rash, generalized rash, maculopapular rash
• pruritus
• nail disorder, nail discoloration, onycholysis
• alanine aminotransferase increased, aspartate aminotransferase increased
• dehydration
• epistaxis
• hypokalemia

Common (≥ 1% to < 10%):

• bone marrow depression (failure), pancytopenia
• candidiasis, cholangiitis,folliculitis, lower respiratory infection, nail infection, oral candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
• neutropenic sepsis, sepsis
• bronchitis
• pneumonitis
• colitis, intestinal obstruction, small intestinal obstruction
• dysphagia
• dyspepsia
• hyperbilirubinaemia, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased
• acute renal failure
• hematuria
• ataxia

• muscle weakness
• anxiety
• nasal congestion
• oropharyngeal pain
• dry mouth, dry throat, nasal dryness
• hemoptysis
• pulmonary embolism, deep vein thrombosis
• pleural effusion
• flushing, erythema
• dry skin
• palmar-plantar erythrodysaethesia syndrome
• hypertension
• hypotension
• tachycardia, cardiac failure congestive, palpitations
• increased lacrimation
• visual disturbance, visual Impairment vision blurred
• infusion site extravasation, infusion site inflammation, infusion site rash, infusion site reaction, injection site reactions, injection site infection, extravasation
• lymphedema

Uncommon (0.1% < 1.0%):

• arrhythmia, sinus bradycardia, atrioventricular block, supraventricular tachycardia
• cardiac arrest
• drug hypersensitivity, hypersensitivity, dermatitis allergic
• thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
• cystoid macular edema, maculopathy
• conjunctivitis
• keratitis
• fluid retention
• malaise
• lethargy
• skin exfoliation
• urticaria
• erythema multiforme
• facial palsy, VIIth nerve paralysis

Elderly

In subjects ≥ 65 years old with metastatic breast cancer who received nab-paclitaxel monotherapy, a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema has been reported.

<u>nab-Paclitaxel in combination with gemcitabine</u>

In subjects with metastatic pancreatic cancer, who received the combination of nab-paclitaxel and gemcitabine, there may be an increase of sepsis. Pneumonitis appears to occur more often (4%) when the two drugs are given together. This requires early detection and treatment as it may be life-threatening or even fatal. In addition, acute renal or kidney failure and hemolytic uremic syndrome have been reported commonly and uncommonly, respectively, in combination of nab-paclitaxel with gemcitabine.

A very rare condition known as Posterior Reversible Encephalopathy Syndrome has occurred when gemcitabine is given alone or in combination with other chemotherapy medications.

A very rare condition known as Capillary Leak Syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications.

Additional side effects observed during post-marketing surveillance of gemcitabine, not otherwise noted above include:
- vasculitis
- gangrene

Additional side effects observed during post-marketing surveillance of nab-paclitaxel, not otherwise noted above include:
- cranial nerve palsies and vocal cord paresis
- palmar-plantar erythrodysethesia syndrome
- photosensitivity reaction
- Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme radiation pneumonitis, radiation recall phenomenon

Elderly

In subjects ≥ 65 years old, who received nab-paclitaxel and gemcitabine, a higher incidence of diarrhea, decreased appetite, dehydration, and epistaxis has been reported compared to subjects < 65 years old. In subjects ≥ 75 years old, a higher incidence of serious adverse reactions and adverse reactions leading to treatment discontinuation has been reported.

Adverse drug reactions reported from post-marketing experience, even though their frequency is unknown, have been similar in type and severity to those reported in nab-paclitaxel clinical trials.

nab-Paclitaxel in combination with carboplatin

Concomitant use of yellow fever vaccine is contraindicated and concomitant use of live attenuated vaccines (except yellow fever) is not recommended in subjects receiving

carboplatin due to the risk of potentially life-threatening, systemic complications. Although uncommon, subjects receiving carboplatin have an increased risk of bleeding in their cancer tumor(s).
Additional clinically important side effects for carboplatin, not already stated above for nabpaclitaxel and /or stated with a different frequency or severity include:

Very common (≥ 10%):

- Myelosuppression
- Decreased levels of certain minerals in the blood (sodium, potassium, calcium, and magnesium)
- Decreased hearing

- Pediatric patients: clinically significant hearing loss has been reported to occur in pediatric patients administered at higher than recommended doses in combination with other ototoxic agents. Cases of hearing loss with a delayed onset have been reported in pediatric patients. A long-term audiometric follow-up in this population is recommended.
- Elderly patients: Ototoxicity is more likely seen in patients older than 65 years old and/or previously treated with other platinum treatments and other ototoxic agents.

Common (≥ 1% to < 10%):

- Ringing sensation in the ear
- Abnormal kidney function (defined as a decrease in creatinine clearance below 60 ml/min)

Uncommon (0.1% < 1.0%):
- Taste changes

Elderly
In subjects ≥ 65 years old, who received nab-paclitaxel and carboplatin, a higher frequency of bone marrow depression, SMQ peripheral neuropathy, and arthralgia have been reported compared to patients < 65 years old.

3.1.7 Further Information

See Appendix 2, Nab paclitaxel (Nab-PaclitaxelTM) Prescribing Information (Updated 7/2015) – Accessed via Nab-Paclitaxel Website: http://www.Nab-Paclitaxel.com/docs/Nab- Paclitaxel_PrescribingInformation.pdf

3.2 Gemcitabine

3.2.1 The Product

Gemcitabine for injection, USP (GEMZAR®) is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white, lyophilized

powder in a 10-mL size sterile single-use vial – NDC 0002-7501-01 (No.7501) or 1g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial – NDC 0002-7502-01 (No. 7502). Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F). Do not refrigerate as crystallization can occur.

3.2.2 Potential Risks of Gemcitabine Toxicities

The most common toxicities reported for gemcitabine include myelosuppression, transient elevations in serum transaminases (approximately 70%), nausea and vomiting (69%), fever (41%), rash (30%), diarrhea (19%), flu syndrome, (19%), infection (16%), alopecia (15%), edema (13%), stomatitis (11%),) neurotoxicity (mild 10%, severe <1%), mild proteinuria and hematuria; Hemolytic Uremia Syndrome (HUS) reported rarely (0.25%), dyspnea (0.2%) and serious pulmonary toxicity (0.06%). Also reported include constipation and pruritus.

Myelosuppression with Gemcitabine

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent gemcitabine. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving gemcitabine in combination with another drug.

Pulmonary Toxicity and Respiratory Failure with Gemcitabine

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine. Discontinue gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity.

Hemolytic Uremic Syndrome with Gemcitabine

Hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis, can occur in patients treated with gemcitabine. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS Assess renal function prior to initiation of gemcitabine and periodically during treatment. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN) Permanently discontinue gemcitabine in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.

Hepatic Toxicity with Gemcitabine

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Transient elevation in serum transaminases occurs in approximately 70% of patients. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine and periodically during treatment. Discontinue gemcitabine in patients that develop severe liver injury.

Embryo and Fetal Toxicity with Gemcitabine

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking gemcitabine, the patient should be apprised of the potential hazard to a fetus.

Capillary Leak Syndrome with Gemcitabine

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents. Immediate discontinuation of Gemcitabine should be done if CLS develops during therapy.

Posterior Reversible Encephalopathy Syndrome with Gemcitabine

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with MRI and discontinue Gemcitabine immediately if PRES develops during therapy.

3.2.3 Further Information

Gemcitabine (GemzarTM) Prescribing Information (Updated 2/2011) – Accessed via Gemzar Website: http://pi.lilly.com/us/gemzar.pdf

3.3 Cisplatin

3.3.1 The Product

Cisplatin for injection, USP (CISPLATIN®) is available in a sterile, multiple dose vial without preservatives. Cisplatin Injection (1 mg/mL) is supplied as follows: NDC No. Fill Volume 16729-288-11 for 50 mL and 16729-288-38 for 100 mL. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. HOW SUPPLIED: Store at 20° to 25°C (68° to 77°F). This container closure is not made with natural rubber latex. Needles or intravenous sets containing aluminum parts that

may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin, causing precipitate formation and a loss of potency.

3.3.2 Potential Risks of Cisplatin Toxicities

The most common toxicities of cisplatin include nephrotoxicity (28-36%; acute renal failure and chronic renal insufficiency), peripheral neuropathy (dose and duration dependent), nausea and vomiting (76% to 100%), myelosuppression (25% to 30%; nadir: day 18-23; recovery: by day 39; mild with moderate doses, mild-to-moderate with high-dose therapy), liver enzymes increased (especially SGOT and bilirubin), ototoxicity (10% to 30%; manifested as high frequency hearing loss; ototoxicity is especially pronounced in children), tissue irritation (extravasation).
Other toxicities (<1%) include alopecia (mild), anaphylactic reaction, arrhythmias, arterial vasospasm (acute), blurred vision, bradycardia, diarrhea, heart block, heart failure, hemolytic anemia (acute), hemolytic uremic syndrome, hypercholesterolemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, limb ischemia (acute), mesenteric ischemia (acute), myocardial infarction, myocardial ischemia, mouth sores, neutropenic typhlitis, optic neuritis, orthostatic hypotension, pancreatitis, papilledema, phlebitis, reversible posterior leukoencephalopathy syndrome (RPLS), SIADH, stroke, thrombophlebitis, thrombotic thrombocytopenic purpura.

Nephrotoxicity with Cisplatin

Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity with Cisplatin

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy. The risk of ototoxicity may be increased by prior or

simultaneous cranial irradiation, and may be more severe in patients being treated with other ototoxic drugs (e.g., aminoglycosides and vancomycin), and in patients with renal impairment.

Hematological toxicity with Cisplatin

Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal toxicity with Cisplatin

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

Serum Electrolytes disturbance with Cisplatin

Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia with Cisplatin

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity with Cisplatin

Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported. Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity with Cisplatin

Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions with Cisplatin

Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity with Cisplatin

Transient elevations of liver enzymes, especially AST, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

3.3.3 Further Information

Cisplatin Prescribing Information (updated 2012) – Accessed via Daily Med (National Library of Medicine) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a440f077-46f6-4688-a209- 65bce38d1c92

4. OBJECTIVES

4.1 Primary endpoint

To assess the feasibility of therapeutic approach that includes neoadjuvant chemotherapy including gemcitabine, cisplatin, and nab-paclitaxel for high-risk but technically resectable intrahepatic cholangiocarcinoma and is completed with surgical resection. Thus, the primary aim will assess completion of all treatment including neoadjuvant therapy and resection, while assessing safety and tolerability of the preoperative chemotherapy regimen as well.

4.2 Secondary endpoints

1. To assess the radiological response rate to neoadjuvant systemic chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST)
2. To determine the R0 resection rate
3. To determine patients' recurrence-free survival (RFS)
4. To identify patients' overall survival (OS) rate.

5. PATIENT ELIGIBILITY

Patients will be included in the study based on the following inclusion and exclusion criteria.

5.1 INCLUSION CRITERIA

- Diagnosis of intrahepatic cholangiocarcinoma

- High-quality cross-sectional imaging by computerized tomography (CT) or magnetic resonant imaging (MRI) performed within 6 weeks prior to enrollment and showed a resectable, but high-risk, IHCCA confined to the liver, bile duct, and /or regional lymph nodes. Tumors will be considered high-risk if the high-quality, contrast-enhanced CT and/or MRI +/- positron emission tomography (PET) scan showed: (must meet at least one of the criteria below)

  1. T-stage ≥ Ib (Ib – IV)
  2. Solitary lesion > 5 cm
  3. Multifocal tumors or satellite lesions present confined to the same lobe of the liver as the dominant lesion but still technically resectable
  4. Presence of major vascular invasion but still technically resectable
  5. Suspicious or involved regional lymph nodes (N1)

- No distant extrahepatic disease (M0)
- Adults >18 years of age
- Able to give informed consent
- Able to adhere to study visit schedule and other protocol requirements

- ECOG performance status of 0-1
- Adequate bone marrow reserves as evidenced by:
  a) ANC ≥1,500 cells/µl; and
  b) Platelet count ≥100,000 cells/µl; and
  c) Hemoglobin ≥9 g/dL
- Adequate hepatic function as evidenced by:
  a) Serum total bilirubin ≤1.5 x ULN; and
  b) AST and ALT ≤2.5 x ULN; and
  c) Albumin ≥3 g/dl
- Adequate renal function as evidenced by creatinine ≤1.5 x ULN.
- Male, or a non-pregnant and non-lactating female.
- Women of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must commit to true abstinence from heterosexual contact, or agree to use, and be able to comply with, effective contraception without interruption for 28 days prior to starting gemcitabine/cisplatin/nab- paclitaxel (including dose interruptions) until treatment with gemcitabine/cisplatin/nab-paclitaxel is complete.
- Male subjects must practice true abstinence or agree to use a condom during sexual contact with a female of childbearing potential or a pregnant female while on treatment (including during dose interruptions) with gemcitabine/cisplatin/nab-paclitaxel and for 6 months following gemcitabine/cisplatin/nab- paclitaxel discontinuation, even if he has undergone a successful vasectomy.

5.2 EXCLUSION CRITERIA

- Peripheral neuropathy of grade 2 or greater by Common Terminology Criteria for Adverse Events (CTCAE) 4.0. In CTCAE version 4.0 grade 2 sensory neuropathy is defined as “moderate symptoms; limiting instrumental activities of daily living (ADLs)”.
- Concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study such as unstable angina, myocardial infarction within 6 months, unstable symptomatic arrhythmia, symptomatic congestive heart failure, uncontrolled diabetes, serious active, uncontrolled infection after inadequate biliary drainage if tumor obstructing bile duct, or psychiatric illness/social situations.
- Pregnancy (positive pregnancy test) or lactation.

- Known CNS disease, except for treated brain metastasis. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable dose) are allowed. Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.
- Previous (within the past 5 years) or concurrent presence of other cancer, except non-melanoma skin cancer and in situ carcinomas.
- History of allergy or hypersensitivity to any of the study drugs.
- Current abuse of alcohol or illicit drugs.
- Inability or unwillingness to sign the informed consent form.

6. TREATMENT PLAN

This is a multi-institution, open label phase II study designed to investigate the feasibility of gemcitabine/cisplatin/nab-paclitaxel as a neoadjuvant systemic chemotherapy for patients with reseactable oncologically high-risk IHCCA. This study will enroll up to 37 patients from all participating institutions with an accrual rate of 2 patients per month in order to have 30 evaluable patients.

This will be an open-label, single arm study with each cycle equal to 21 days. All three drugs will be administered intravenously on day 1 and day 8 of each cycle. Dosing will be calculated using body surface area (BSA) based on the actual weight of the patient at each visit. Nab-Paclitaxel will be given at 100 mg/m^2, followed by cisplatin at 25 mg/m^2 and then gemcitabine at 800 mg/m^2 for 2 weeks in a row followed by a week of rest. Patients will receive 4 cycles of neoadjuvant systemic chemotherapy. Restaging will be done after 4 cycles (+/- 1 week) by radiological imaging. If radiological scans demonstrate stable disease or partial or complete tumor response and the tumor remains resectable, surgery will be performed. For patients with radiological scans that document disease progression during the study, treatment will be discontinued off the protocol and will not be evaluable for other secondary endpoints. Resection will be performed per standard of care and will include a portal lymphadenectomy for all cases. Objective evidence of recurrent disease after resection will be recorded at the time of recurrence. Patients will be followed for overall survival endpoint as well.

Table 1: Starting Dose Level

Drug	Dose	Infusion Time	Schedule (in 21-day cycle)
IV Nab-Paclitaxel	100 mg/m^2	30 min (+/- 5 min)	Day 1 and 8
IV Cisplatin	25 mg/m^2	60 min (+/- 5 min)	Day 1 and 8

IV Gemcitabine	800 mg/m^2	30 min (+/- 5 min)	Day 1 and 8

Dosing and Administration

The study drugs will be stored according to package inserts. Local institutional guidelines and administration protocols for anti-emetics, pre-hydration, and supportive care will be utilized for administration of the chemotherapy medications. Suggested guidelines include the following specified pre-medications and hydration:

- Pre-cisplatin hydration: 0.9% Sodium Chloride Injection 1000 mL with Mannitol 18.5 grams and Magnesium Sulfate 2 grams IV infusion over 2 hours on days 1 and 8 repeated every 21 days.
- Aloxi (palonosetron) 0.25 mg IV, Emend (fosaprepitant) 150 mg IV and dexamethasone 12 mg IV within 30 minutes prior to treatment on days 1 and 8, repeated every 21 days. Patients will continue oral antiemetic prophylaxis at home with dexamethasone 4 mg bid for 2 days after chemotherapy.
- Nab-paclitaxel 100mg/m^2 in NS dilute to a total concentration of 5 mg/mL (DO NOT FILTER) over 30 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
- Cisplatin 25mg/m^2 in 500 mL of NS over 60 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
- Gemcitabine 800 mg/m^2 in 500ml over 30 minute IV infusion on days 1 and 8 repeated every 21 days
- Post-cisplatin hydration: 0.9% Sodium Chloride Injection 1000 mL IV infusion over 3 hours on days 1 and 8 repeated every 21 days. May start at the same time as the gemcitabine infusion.

Dose Modifications and Toxicity Management

Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described below. Any toxicity associated or possibly associated with gemcitabine, cisplatin, and Nab-Paclitaxel treatment should be managed according to standard medical practice.

A cycle of therapy may be delayed up to 3 weeks to allow for weather events, patient's personal emergencies, observation of holidays, or other unforeseen delays that the Investigator deems to be in the best interest of the patient. For any dose interruptions, re-initiation of therapy may be delayed for a maximum of 21 days to allow recovery from any toxicity. In exceptional cases where subjects are responding, re-initiation of therapy after missing > 21 consecutive days of treatment may be done on a case-by-case basis after confirmation with the Primary Investigator. Day 8 of cycle can be delayed up to 2 weeks or a treating physician's discretion.

Toxicity will be graded according to the NCI CTCAE, Version 4.0 (which is available at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm). For any

event which is apparent at baseline, the dose modification will apply according to the corresponding shift in toxicity grade if the investigator feels this is appropriate, (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes).

Dose modifications of gemcitabine and Nab-Paclitaxel will be done based on the specific toxicity. Once a dose of any study drug has been reduced, it should not be increased at a later time. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in progress notes. Growth factors may be used to treat hematologic toxicity and will not constitute a dose reduction. A maximum of a 3-week treatment delay is permitted to allow recovery of toxicities.

Table 2: Dose Levels

Dose Level	Nab-Paclitaxel (mg/m2)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
0 – baseline	100	25	800
-1	75	25	600
-2	50	25	600
-3	50	20	600

Hematologic Toxicity

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of nab-paclitaxel, cisplatin, and gemcitabine may be adjusted as detailed below. In the event that patients must have treatment delayed within a treatment cycle due to hematologic toxicities, those doses held during a cycle will not be made up.

Table 3: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1,500 cells/mm^3	AND	≥ 100,000/uL	Treat on time
< 1,500 cells/mm^3	OR	< 100,000/uL	Delay by 1 week intervals until recovery

Table 4: Dose Modifications for Day 8 of Each Cycle (Hematologic Toxicity)*

Day 8 Laboratory Results	Day 8 Nab-Paclitaxel	Day 8 Cisplatin	Day 8 Gemcitabine
ANC > 1000 and Platelets ≥ 100,000	100%	100%	100%

ANC 500-1000[a] or Platelets 50,000-99,000	Decrease dose by 1 level (treat on time)	100%	Decrease dose by 1 level (treat on time)
ANC < 500 or Platelets < 50,000	HOLD	HOLD	HOLD
Febrile Neutropenia (Grade 3 or 4)[b]	HOLD. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	HOLD	HOLD. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)	Decrease 2 dose levels (to 75 mg/m^2) and do not re-escalate throughout the rest of treatment.	HOLD	Decrease 2 dose levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.

* See Table 3 for dose reductions guidelines.

[a] If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

[b] Febrile neutropenic should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to non-neutropenic levels before resuming chemotherapy treatment.

Special Instructions Regarding Treatment of Chemotherapy-related Toxicity

Dose modification or delay may occur in the setting of lower Grade toxicity if the treating physician believes that it is in the interest of a subject's safety. Alopecia and nausea and/or vomiting that can be controlled by antiemetics do not require dose modification or interruption. No dose reduction or interruption will be required for anemia as it can be satisfactorily managed by transfusions. Dose reductions for non-hematologic toxicity should be as below. Nab-Paclitaxel and Gemcitabine and specific exceptions are listed separately below Tables 6 and 7.

Table 5: Dose Modifications for Nab-Paclitaxel and Gemcitabine on Day 1 of Each Cycle (Non-Hematologic Toxicity)*

Toxicity/Dose Held	Nab-Paclitaxel+Gemcitabine dose this cycle
Grade 0-2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of nab-paclitaxel and gemcitabine should be reduced to next lower dose level – see below)
Grade 3 toxicity[a,c]	Decrease Nab-Paclitaxel and gemcitabine to next lower dose level[a]

Grade 4 toxicity[b]	Off protocol treatment[b]
Dose held in 2 previous consecutive cycles	Decrease Nab-Paclitaxel and gemcitabine to next lower dose level and continue throughout the rest of treatment

*Except peripheral neuropathy and nephrotoxicity (see below)
[a]If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced (see below).
[b]Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (see below).
[c]Excluding electrolyte abnormalities per judgment of the physician/investigator.

Table 6: Dose Modifications for Nab-Paclitaxel and Gemcitabine on Day 8 of Each Cycle (Non-Hematologic Toxicity)

CTC Grade	% of Day 1 Nab-Paclitaxel+Gemcitabine Dose
0-2	100%[a]
3+	Hold treatment until resolution to ≤ Grade 1[b,c]

[a]Except for cutaneous toxicity (see below).
[b]Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.
[c]Excluding electrolyte abnormalities per judgment of the physician/investigator.

6.1 G-CSF Administration

The exact dosage amount and schedule for G-CSF support will be left to the treating physician's discretion. A recommended approach would be to administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator's standard of care) 24 hours after chemotherapy until recovery to the predetermined neutrophil count.

6.2 Sensory Neuropathy

Cisplatin and nab-paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Cisplatin may be resumed at the same dose and nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 2. Patients experiencing peripheral neuropathy that requires a delay in scheduled cisplatin and nab-paclitaxel dosing for ≥ 21 days will discontinue study treatment. The time to resolution to Grade ≤ 2 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, both drugs should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 2. Note: the investigator may elect to dose modify for Grade 2 sensory neuropathy.

6.3 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin

should not be given unless adequate renal function is confirmed with a calculated creatinine clearance of $\geq$ 45 mL/min.

6.4 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level as per Table 3. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

6.5 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, all 3 study drugs should be withheld until resolution to $\leq$ Grade 1, then reinstituted at the next lower dose level as per Table 3. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

6.6 Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

6.7 Interstitial Pneumonitis

Pulmonary toxicity has been reported for both gemcitabine and paclitaxel. Epidemiology reports show that gemcitabine monotherapy is weakly associated with lung toxicity. A retrospective review of pooled clinical trial data of 4,448 patients with mixed cancer indications reported an incidence of dyspnea of 0.2% and serious pulmonary toxicity of 0.06%.

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Prevention, Surveillance and Management of Interstitial Pneumonitis

- During study treatment, episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and CT scans (normal or high resolution) may be indicated to look for infiltrates, ground-glass opacities or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
- Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.
- Study drug administration should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further study drug

treatment. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy and secondary pathogen coverage should be instituted without delay. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

6.8 Sepsis

Sepsis has been reported in less than 1% during Nab-Paclitaxel monotherapy and fatalities attributed to these events have been rare. However, the risk was appreciably higher in patients with advanced or metastatic pancreatic cancer receiving Nab-Paclitaxel in combination with gemcitabine with a rate of 5% in patients in patients with or without neutropenia receiving Nab-Paclitaxel/gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. The increased risk of sepsis in the setting of advanced or metastatic cancer in combination with gemcitabine could be managed with prophylactic antibiotic treatment in febrile patients (regardless of neutrophil count) and dose reduction, and with G-CSF treatment in neutropenic patients. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Nab-Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels.

Prophylaxis Against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5°C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily) or amoxicillin/clavulanate (500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts and to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. If hospitalization is required, this should be reported as a Serious Adverse Event (SAE).

6.9 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to Nab-Paclitaxel should not be re-challenged. It is not recommended to administer Nab-Paclitaxel to patients with prior hypersensitivity to a taxane. If mild to moderate cisplatin hypersensitivity develops (per NCI CTCAE), the patient may be desensitized using the

standard desensitization protocol of the institution. In the setting of a severe hypersensitivity reaction, cisplatin should be discontinued.

Nab-Paclitaxel Premedication

Patients do not require premedication prior to Nab-Paclitaxel administration, as hypersensitivity reactions are rare. Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release (Ten Tije et al, 2003), the administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out.

In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue Nab-Paclitaxel.

Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

7. EVALUATION DURING STUDY

Patients must begin Cycle 1 within 30 days of signing the informed consent document and after the screening assessments. Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other out-patient setting appropriate for chemotherapeutic infusions. All assessments should be performed within 48 hours of each specified time parameter, with the exception of Cycle 1 in which physical and laboratory assessments must be conducted within 7 days and radiological assessment within 6 weeks.

Day 1 of each cycle (except where noted)

- Inclusion/exclusion review (Cycle 1 only)
- Directed physical exam with neuropathy assessment
- Vital Signs
- Measurement of weight (kg) and BSA calculation prior to dosing
- ECOG Performance Status (see Appendix 1)
- Hematology: CBC with differential and platelet count
- Serum chemistries: BUN, creatinine, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), total protein, albumin, serum glucose, lactic dehydrogenase (LDH), and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance.
- Tumor markers: CA 19-9 and CEA
- Serum Pregnancy (at Screening only)
- AEs using the NCI CTCAE (http://ctep.info.nih.gov)
- Concomitant medication notation

Day 8 of each cycle

- Directed physical exam with neuropathy assessment
- Vital Signs
- Measurement of weight (kg)
- ECOG Performance Status (see Appendix 1)
- Hematology: CBC with differential and platelet count
- Serum chemistries
- AEs using the NCI CTCAE (http://ctep.info.nih.gov)
- Concomitant medication notation

After Cycles 4

- Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements.
- In order to more precisely determine the tumor response, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.

Table 7: Study Assessments

Procedure	Screening Visit (within 7 days unless otherwise noted)[b]	Gemcitabine/Cisplatin/Nab- paclitaxel cycles (21 day cycle, x 4cycles)[a]								Surgical resection evaluation 4 weeks (± 1 week) following last dose	End of Treatment Visit 4 weeks (± 1 week) following last dose or post-surgery	Long Term Survival Follow-up (every 4 months for 3 years)
		Cycle 1		Cycle 2		Cycle 3		Cycle 4				
		Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8			
Informed consent	x											
Medical history & Demographics	x											
Concomitant meds	x	x	x	x	x	x	x	x	x	x	x	
Examination												
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	
Vital signs	x	x	x	x	x	x	x	x	x	x	x	
Height	x											
Weight	x	x	x	x	x	x	x	x	x			
ECOG PS	x	x	x	x	x	x	x	x	x	x	x	
Laboratory												
CBC total/differential	x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[c]	x	x	x	x	x	x	x	x	x	x	x	
Tumor markers[d]	x	x		x		x		x		x	x	x
Pregnancy test[e]	x											
Radiology												
CT chest, abdomen, and pelvis[f]	x									x	x	x
Toxicity assessment		x	x	x	x	x	x	x	x	x	x	
Recurrence, and overall survival reporting												x

[a]Each cycle of therapy may be delayed up to 3 weeks to allow for weather events, patient's personal emergencies, observation of holidays, or other unforeseen delays that the Investigator deems to be in the best interest of the patient. For any dose interruptions, re-initiation of therapy may be delayed for a maximum of 21 days to allow recovery from any toxicity. In exceptional cases where subjects are responding, re-initiation of therapy after missing > 21 consecutive days of treatment may be done on a case-by-case basis after confirmation with the Primary Investigator. Day 8 of cycle can be delayed up to 2 weeks or a treating physician's discretion.

[b]All screening procedures must be done within 7 days from treatment start date except patient height can be done at any time during the screening window and baseline diagnostic imaging must be done within 6 weeks prior to first day of study treatment.

[c]Serum chemistry includes urea, creatinine, total bilirubin, AST, ALT, total protein, albumin, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium), glucose, and LDH

[d]Tumor markers include carcinoembryonic antigen (CEA) and Cancer antigen 19-9 (CA19-9)

[e]For females of childbearing potential only. May be repeated any time during the study at investigator discretion.

[f]Radiological imaging will be performed during the screening window, approximately within 6 weeks before starting chemotherapy to identify patients' eligibility for study enrollment, then within 2 weeks (+/- 1 week) after administration and completion of 4 cycles of chemotherapy (12 weeks) to assess response to therapy according to RECIST criteria 1.1. If radiological scans demonstrates a stable, partial or complete tumor response and tumor still resectable, surgery will be performed. Surveillance imaging after surgery will be performed every 4 months. If radiological scans demonstrated disease progression, treatment will be discontinued off the protocol and will not be evaluable for other secondary endpoints.

1. Informed consent must be obtained before any evaluations are initiated. Diagnostic imaging studies must be completed within 6 weeks prior to first day of study treatment. All other baseline evaluations, except for height (which can be obtained at any time prior to enrollment), must be completed within 7 days prior to first dose of study drug.
2. For Cycle 1, baseline evaluations will be sufficient if they are performed within 7 days prior to first dose of study drug (except for imaging studies which are performed within 6 weeks prior).
3. For all other chemotherapy cycles except for Cycle 1, baseline physical and laboratory assessment must be done within 48 hours prior to start of day 1 and day 8.
4. Imaging should be obtained within 2 weeks (+/- 1 week) after completion of 4 cycles of chemotherapy. If radiological scans demonstrates stable disease or partial or complete tumor response and the tumor remains resectable, surgery will be performed. Patients with radiologically documented disease progression at any point during the study treatment with study drugs under this protocol will be discontinue. Objective evidence of recurrent disease after resection will be recorded at the time of recurrence. Earlier radiological evaluations are allowed if, in the investigator's opinion, this evaluation is in the patient's best interest.
5. Surgical resection will be performed per standard of care and will include a portal lymphadenectomy for all cases.
6. CT of the chest, abdomen, and pelvis with contrast will be used. MRI may be used in cases where it is felt to be unsafe to perform CT secondary to patient's history of dye allergy, or if the tumor is not adequately seen on CT for the purposes of this study. Positron emission tomography (PET) scan may be done to exclude the presence of any suspicious metastatic lesion.
7. Treatment-related adverse events occurring during study treatment or within 30 days (window of 28-35 days allowed) after the last administration of study drug(s) will be followed until resolution or stabilization. If the patient is unable or unwilling to return to the participating treating center for this assessment, the patient will be contacted by phone for this assessment.

7.1 End of treatment evaluations

The investigator will evaluate the results of the following clinical and laboratory assessments to be conducted at the time the patient discontinues study treatment. This will be done within 4 weeks post-surgery or after the last dose of systemic therapy in patient who have disease progression and will not undergo surgery.

- Physical examination with neuropathy assessment
- ECOG Performance Status
- Weight
- Vital signs (blood pressure)
- Hematology: CBC with differential and platelet count
- Serum chemistries: BUN, creatinine, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), total protein, albumin, serum glucose, lactic dehydrogenase (LDH), and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance.
- Tumor markers: CA 19-9 and CEA
- Concomitant medication notation

- Toxicity (adverse events) assessment (including neurologic toxicities) using NCTCTCAE Version 4.0
- Tumor evaluations including CT scan or MRI of the chest, abdomen, and pelvis

7.2 Long-term follow-up

All patients will be followed for survival and/or recurrence status. All study enrolled patients who will undergo tumor resection will be followed every 4 months (+/- 1 month) post-surgery for up to 3 years to assess recurrence free survival. Survival status may be obtained by checking the electronic medical record or by telephone call. If radiological scans demonstrated disease progression after neoadjuvant chemotherapy that prohibits surgery, treatment will be discontinued off the protocol but the patient will be still be followed for the secondary endpoint of overall survival. After a patient completes all intended therapy, including neoadjuvant chemotherapy and surgery, the patient will be followed for secondary endpoints of recurrence and overall survival. If a patient recurs during postoperative surveillance, they will still be followed for overall survival. During long term follow-up, there is no specific requirement for labs or toxicity recording as the patient will not be receiving any therapy on protocol.

8. CRITERIA FOR REMOVAL FROM THE STUDY

Subjects who meet the following criteria should be discontinued from the study:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) as determined by the treating physician
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

9. RESPONSE EVALUATION

9.1 Measurement of effect

Response, progression, and recurrence will be evaluated in this study using the new international RECIST criteria (version 1.1, 2009) proposed by the RECIST committee.[17] All patients who have measurable disease according to the RECIST criteria and who have their disease re-evaluated will be evaluable for response. For the purposes of this study, patients should be reevaluated for response after 4 cycles of neoadjuvant chemotherapy. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.2 Definitions

All sites of disease should be followed as either target or non-target lesions, as categorized at baseline. All measurable lesions up to a maximum of 2 lesions per organ or 5 lesions in total, representative of all involved organs should be identified as target lesions, while all other lesions (either additional measurable lesions or non-measurable lesions) should be classified as non-target lesions. In cases where a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. To ensure comparability, the

baseline radiology/scans and subsequent radiology/scans to assess response should be performed using identical techniques (eg, scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent, and preferably the same scanner). The same method, radiological or physical, should be employed and assessed by the same individual on each occasion, when possible.

9.3 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan (with minimum slice thickness no greater than 5mm, or 10mm caliper measurement by clinical exam, or 20mm by chest X-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Pathological lymph nodes may also be considered as target or non-target lesions. To be considered pathologically enlarged and measurable (target lesion), a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes with a short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathologic and should not be recorded. The short axis measurement of any lymph node that is considered a target lesion should continue to be recorded regardless if the node progresses to below 10 mm. This may prevent the sum of lesions from being zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In rare circumstances, when a target lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

9.4 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI). For bone and cystic lesions, please refer to the RECIST criteria (version 1.1, 2009).

9.5 Target lesions

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters for all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum diameters (LD). The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

9.6 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. It is possible

to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.7 Guidelines for evaluation of measurable disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor 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). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Conventional CT and Magnetic Resonance Imaging. Conventional CT and MRI should be performed to obtain images of 5 mm or less slice thickness.
Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.8 Response Criteria

9.8.1 Evaluation of target lesions

- **Complete Response (CR):** Disappearance of all target and non-target lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis). Complete response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which CR was observed.
- **Partial Response (PR)**: At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
- **Progressive Disease (PD)**: At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- **Non-CR/Non-PD:** Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

9.8.2 Evaluation of non-target lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level
- **Incomplete Response/ Stable Disease (SD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
- Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the study PI (Maithel).
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.9 Time point evaluation

At each protocol specified time point, a response assessment occurs. Table 8 provides a summary of this for patients who have measurable disease at baseline. Table 9 provides a summary of this for patients with non-measurable (therefore non-target) disease.

Table 8: Response for Measurable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	≥ 4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 6 weeks from baseline
Not All Evaluated	Non-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. NE = inevaluable Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 9: Response for Non-measurable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

9.10 Evaluation of Best Overall Response

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

Table 10: Response Assignment

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

NE = inevaluable. If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact, the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having

"symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.11 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessment at a minimum follow-up interval of 6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

9.12 Duration of overall response

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

9.13 Duration of stable disease

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

10. STATISTICAL METHODS

This is a phase II open-label, non-randomized, multicenter clinical trial. Our primary objective is to assess the feasibility of therapeutic strategy that begins with neoadjuvant therapy with gemcitabine, cisplatin, and nab-paclitaxel for resectable oncologically high-risk IHCCA patients prior to complete surgical resection. Anticipating maximum 20% dropout rate due to screen failures or withdrawals, our planned sample size for this trial will be 37 subjects to have 30 evaluable patients. The primary endpoint will be completion of all preoperative and operative therapy. Secondary endpoints will include radiological response according to Response Evaluation Criteria in Solid Tumor (RECIST), RFS, and OS.
The analysis will be performed for all patients registered to the trial who receive at least one dose of study drug. Patients who are registered to the study but do not receive study treatment will be summarized separately. The method of Thall, Simon and Estey will be used for futility and toxicity monitoring in this study. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson Cancer Center (MDACC) was used to generate the stopping boundaries and the operating characteristics table for futility and toxicity monitoring. This is free software accessible through https://biostatistics.mdanderson.org/softwaredownload/.

10.1 Power estimation

The primary endpoint is completion of all therapy. We hypothesize that the new treatment will improve this rate to 70%. A sample size of 30 evaluable patients will provide approximately 73% power for detecting an increase from 50% to 70% in this study at 1-sided type I error of 0.05. The

power estimation is based on the exact binomial test. To account for up to 20% dropout rate due to screen failures or withdrawals, the maximum study accrual will be 37 participants to have 30 evaluable patients.

10.2 Futility monitoring

We assume a target rate of 70% and a rate of 50% or lower will be considered not desirable. The study will be stopped early if the data suggest that:

$$Pr(P_E > P_H + 0.20 \mid data) < 0.025$$

where P_E and P_H are the rates for this combination and historical treatment, respectively. That is, if at any time during the study we determine that there is less than 2.5% chance that the rate improves over historical rate by more than 20%, the trial will be stopped due to futility. P_E and P_H are assumed to follow a prior of Beta (1, 1) and Beta (50, 50), respectively. We will apply these stopping boundaries in cohort sizes of 5. The stopping boundaries for futility based on these assumptions and monitoring conditions are provided in Table 11.

Table 11. Stopping boundaries for futility monitoring

# of evaluable patients	Stop the trial if # of patients completing therapy is:
5	0-1
10	0-3
15	0-6
20	0-9
25	0-12
30	0-15

10.3 Toxicity monitoring

Unacceptable toxicities are defined as any Grade 3 or higher toxicities by CTCAE criteria or a treatment delay of >4weeks. Denote the probability of toxicity by P_T. We assume as a priori, $P_T \sim$ beta (1, 1). Our stopping rule is given by the following probability statement:

$$Pr(P_T > 0.50 \mid data) > 0.90.$$

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 90% chance that the unacceptable toxicity rate is more than 50%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then in cohort size of 5. Stopping boundaries corresponding to this stopping rule are listed in Table 12. The operating characteristics for futility and toxicity monitoring are summarized in Table 13.

Table 12. Early stopping boundaries for toxicity monitoring

# of evaluable patients (in cohort size of 5, starting from the 5th patient)	Stop the trial if there are this many patients with unacceptable toxicities:
5	5
10	8-10
15	11-15

20	13-20
25	16-25
30	19-30

Table 13. Operating characteristics for futility and toxicity monitoring

True resectability rate	True toxicity rate	Prob(stop the trial early)	Average number of patients treated
0.6	0.40	0.2701	25.5
	0.50	0.3841	23.8
	0.60	0.6345	19.9
0.7	0.40	0.0931	28.3
	0.50	0.2347	26.3
	0.60	0.5458	21.7
0.8	0.40	0.0470	29.2
	0.50	0.1958	27.1
	0.60	0.5227	22.3

10.4 Statistical analysis plan

For the primary analysis, all enrolled patients who received at least one dose of study treatment will be included in the statistical analysis. We will record the completion of all therapy rate, along with the 95% credible interval. Safety and tolerability will be assessed in terms of adverse events (AEs), and serious adverse events (SAEs). Summary of these events will be tabulated by the maximum reported Common Terminology Criteria for Adverse Events (CTCAE) grade and by it is relation to study treatment. Both AEs and SAEs will be tabulated using frequencies and percentages. For secondary endpoint of radiological response rate it will be defined as the percentage of patients who will have complete response (CR), partial response (PR) or stable disease (SD) after the neoadjuvant therapy. We will estimate the radiological response rate, along with the 95% confidence interval.

RFS (Recurrence-free survival) is defined as the time between the date of surgery and the date of disease recurrence or death, whichever occurred first. If a patient did not have an event (i.e. disease recurrence or death) by the time of final analysis, patient will be censored at the last disease evaluation time. Overall survival (OS) is defined as the time from date of neoadjuvant treatment start to the date of death from any cause or to the date of last follow-up if patients are alive. If a patient is alive by the time of final analysis, the patient will be censored at the last follow-up date. The Kaplan-Meier method will be used to estimate RFS or OS. The two-sided log-rank tests will be used to assess the differences of RFS or OS between groups.

11. REGISTRATION PROCESS

Please see Appendix 3 for a detailed description of the registration process for all sites.

12. DATA AND PROTOCOL MANAGEMENT

Designated research personnel must enter the information required by the protocol onto electronic Case Report Forms (CRFs). The Emory University Clinical Oncology Research (OnCore) system will be used for this study. The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and assigned dose cohort. All data must be entered no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The MSC will provide OnCore training and request access to the appropriate staff at the participating site. OnCore is a clinical research information management system. The OnCore CRF is an electronic document designed to record all the protocol-required information to be reported on each trial subject.
OnCore provides data entry templates as defined in the protocol. Users must have clearance through the Emory University Information Services Security Department in order to access OnCore. OnCore login is password protected. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

For details regarding the process for data collection among all participating centers involved in the study, please see Appendix 4.

13. SAFETY REPORTING OF ADVERSE EVENTS

13.1 Adverse Event Reporting and Definitions

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. Adverse events will be collected from the signing of the informed consent until 30 days after the last dose of study drug, or any time after that if the PI determines the event is related to the study drug.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (mild, moderate, severe or grade 1-5)
- Its relationship to the study drug(s) (suspected/not suspected)
- Its duration (start and end dates or if continuing at final exam)
- Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

- Whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
Information about common side effects already known about drug can be found in the Investigators' Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

13.2 Adverse event attribution

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Adverse events for this protocol will be recorded using the Recommended Adverse Event Recording Guidelines for phase II protocols.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated			Phase II	Phase II	Phase II
Unlikely			Phase II	Phase II	Phase II
Possible	Phase II	Phase II	Phase II	Phase II	Phase II
Probable	Phase II	Phase II	Phase II	Phase II	Phase II
Definitive	Phase II	Phase II	Phase II	Phase II	Phase II

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

13.3 Serious adverse event (SAE) reporting

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]

- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety 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 OTHERAPPROPRIATE 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 IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

Overdose

Overdose, as defined for this protocol, refers to nab-paclitaxel, gemcitabine, and cisplatin dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of nab-paclitaxel, gemcitabine, and cisplatin assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Summit, New Jersey 07901
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

Expedited reporting by investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to ABRAXANE® based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product. Information not available at the time of the initial report (e.g., an end date for the adverse event 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 tracking number (AX-CL-CHOL-PI-13255) and the institutional protocol 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. Participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to Emory University, the primary study site within 48 hours of awareness.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the

criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse event updates/IND safety reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

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Data and Safety Monitoring Language Guidelines for Investigator-Initiated Studies

A sensible data safety monitoring plan (DSMP) for a particular clinical trial must be based on the medical or health-related context of the particular study and in particular the degree of risk to which participants in the trial are exposed. (NCI Data and Safety Monitoring Guidelines, 2005)

I. Standard language for Investigator-Initiated studies under purview of Winship DSMC:

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report

responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

The data safety monitoring plan will be implemented by Dr Maithel, the Principal Investigator (P.I.) of this study. The plan is based on weekly-monitoring by the GI Working Group, and monitoring via Winship Cancer Institute Data Safety Monitoring Committee (DSMC) as per Winship DSMP. Dr. Maithel and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain one spread sheet which will summarize all the patient data for patients actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual patient. During weekly meetings of the GI Oncology Working Group, the group will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, case report form completion and roadmap for each patient on the trial. Decisions to continue treating subjects and/or if the trial accrual should continue, along with the recruitment methods and the insurance of confidentiality are also discussed during these meetings. Documentation of the discussions during these meetings are completed and filed. The P.I. and the study investigators will discuss any required modifications to this study at the weekly meetings. No modifications to this study are implemented until they are submitted for review and approved by the Emory University IRB. The comments from the Winship Cancer Institute DSMC are forwarded to the IRB at the time of the annual renewal of this study or sooner if warranted and requested by the Winship Cancer Institute DSMC.

The Winship Cancer Institute DMSC does not tolerate protocol deviations, but does recognize that they occur unintentionally. Any protocol violations are reviewed and reported to the Winship Cancer Institute DSMC, IRB, and all other designated regulatory agencies as required by the study protocol, IRB policy or regulations.

Appendix 1 – Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Appendix 2 - Nab-Paclitaxel – Additional Information

Contacts:

For Celgene International Sàrl
Investors:
+41 32 729 8303 ir@celgene.com

Media:
+41 32 729 8304 media@celgene.com

NAB-PACLITAXEL® DEMONSTRATES STATISTICALLY SIGNIFICANT IMPROVEMENT IN OVERALL SURVIVAL FOR PATIENTS WITH ADVANCED PANCREATIC CANCER IN PHASE III STUDY

BOUDRY, Switzerland – (November 9, 2012) – Celgene International Sàrl, a subsidiary of Celgene Corporation (NASDAQ: CELG) today announced that its phase III study of NAB-PACLITAXEL® (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) in combination with gemcitabine in treatment-naïve patients with advanced pancreatic cancer met its primary endpoint of overall survival. In the study, NAB-PACLITAXEL in combination with gemcitabine demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine alone.

In the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study, a Celgene-sponsored, open-label, randomized, international study 861 metastatic pancreatic cancer patients were randomized to receive either NAB-PACLITAXEL plus gemcitabine (125 mg/m^2 followed by 1000 mg/m^2 gemcitabine for 3 weeks followed by a week of rest) or gemcitabine alone (1000 mg/m^2 administered weekly for 7 weeks followed by a week of rest followed by cycles of weekly administration for 3 weeks followed by one week of rest).

The primary endpoint for the study is improvement in overall survival. Secondary endpoints include evaluation of progression-free survival, objective tumor response and the safety and tolerability of this combination in this patient population.

The safety profile of NAB-PACLITAXEL in combination with gemcitabine observed in the study is comparable with other NAB-PACLITAXEL clinical trials in pancreatic cancer. A late-breaker placeholder abstract for this study has been submitted to the American Society of Clinical Oncology's (ASCO) 2013 Gastrointestinal Cancers Symposium being held in San Francisco on January 24-26, 2013.

Based on the results of the MPACT study, the company plans to submit dossiers for registration in the US, Europe and other markets.
Abraxane is now indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

About Advanced Pancreatic Cancer
Advanced pancreatic cancer is a difficult-to-treat cancer with the lowest survival rates among all cancer types. Across all patients with pancreatic cancer, relative 5-year survival is 5.5%. There are two main types of pancreatic cancer - adenocarcinomas, which accounts for approximately 95% of all pancreatic cancer, and neuroendocrine tumors. Pancreatic cancer is relatively uncommon with new cases accounting for only 2.1% of all newly diagnosed cancers. However, pancreatic cancer is the fourth most common cause of cancer death in the United States and throughout the world.

About NAB-PACLITAXEL®
NAB-PACLITAXEL is an albumin-bound form of paclitaxel that is manufactured using patented *nab*® technology. NAB-PACLITAXEL is formulated with albumin, a human protein, and is free of solvents.

In the United States, NAB-PACLITAXEL was first approved in January 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. NAB-PACLITAXEL is also available in Europe, Canada, Russia, Australia, New Zealand, India, Japan, South Korea, Bhutan, Nepal, United Arab Emirates and China for the treatment of metastatic breast cancer.

In October 2012, NAB-PACLITAXEL was approved by the U.S. Food and Drug Administration for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

For the full prescribing information for NAB-PACLITAXEL please visit http://www.Nab-Paclitaxel.com.

NAB-PACLITAXEL is currently in various stages of investigation for the treatment of the following cancers: pancreatic, metastatic melanoma, bladder, ovarian, and expanded applications for breast cancer.

NAB-PACLITAXEL® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin bound) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

NAB-PACLITAXEL is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are

not candidates for curative surgery or radiation therapy. Other indications include metastatic breast cancer and pancreas adenocarcinoma.

Important Safety Information

WARNING - NEUTROPENIA

- **Do not administer NAB-PACLITAXEL therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NAB-PACLITAXEL**

- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS**

CONTRAINDICATIONS

Neutrophil Counts

- NAB-PACLITAXEL should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3

Hypersensitivity

- Patients who experience a severe hypersensitivity reaction to NAB-PACLITAXEL should not be rechallenged with the drug

WARNINGS AND PRECAUTIONS

Hematologic Effects

- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of NAB-PACLITAXEL
- Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 for metastatic breast cancer (MBC) and Days 1, 8, and 15 for non-small cell lung cancer (NSCLC)
- Do not administer NAB-PACLITAXEL to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3
- In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of NAB-PACLITAXEL therapy, reduce the dose of NAB-PACLITAXEL in subsequent courses in patients with either MBC or NSCLC
- In patients with MBC, resume treatment with every-3-week cycles of NAB-PACLITAXEL after ANC recovers to a level >1,500 cells/mm^3 and platelets recover to >100,000 cells/mm^3
- In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly NAB-PACLITAXEL and every-3-week carboplatin after ANC recovers to at least 1,500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle

Nervous System

- Sensory neuropathy is dose- and schedule-dependent
- The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification
- If ≥ Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 for MBC or until resolution to ≤ Grade1 for NSCLC followed by a dose reduction for all subsequent courses of NAB-PACLITAXEL

Hypersensitivity
- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Patients who experience a severe hypersensitivity reaction to NAB-PACLITAXEL should not be re-challenged with this drug

Hepatic Impairment
- Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of NAB-PACLITAXEL in patients with hepatic impairment should be performed with caution
- The starting dose should be reduced for patients with moderate or severe hepatic impairment

Albumin (Human)
- NAB-PACLITAXEL contains albumin (human), a derivative of human blood

Use in Pregnancy: Pregnancy Category D
- NAB-PACLITAXEL can cause fetal harm when administered to a pregnant woman
- If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus
- Women of childbearing potential should be advised to avoid becoming pregnant while receiving NAB-PACLITAXEL

Use in Men
- Men should be advised not to father a child while receiving NAB-PACLITAXEL

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study
- The most common adverse reactions (≥20%) with single-agent use of NAB-PACLITAXEL in the MBC study were alopecia (90%), neutropenia (all cases 80%; severe 9%), sensory neuropathy (any symptoms 71%; severe 10%), abnormal ECG (all patients 60%; patients with normal baseline 35%), fatigue/asthenia (any 47%; severe 8%), myalgia/arthralgia (any 44%; severe 8%), AST elevation (any 39%), alkaline phosphatase elevation (any 36%), anemia (all cases 33%; severe 1%), nausea (any 30%; severe 3%), diarrhea (any 27%; severe <1%) and infections (24%)
- Sensory neuropathy was the cause of NAB-PACLITAXEL discontinuation in 7/229 (3%) patients
- Other adverse reactions of note included vomiting (any 18%; severe 4%), renal dysfunction (any 11%; severe 1%), fluid retention (any 10%; severe 0%); mucositis (any 7%; severe

<1%), hepatic dysfunction (elevations in bilirubin 7%), hypersensitivity reactions (any 4%; severe 0%), thrombocytopenia (any 2%; severe <1%), and injection site reactions (<1%). In all NAB-PACLITAXEL treated patients (n=366) ocular/visual disturbances were reported (any 13%; severe 1%). Dehydration and pyrexia were also reported

- Severe cardiovascular events possibly related to single-agent NAB-PACLITAXEL occurred in approximately 3% of patients and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension
- Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported

Non-Small Cell Lung (NSCLC) Cancer Study

- Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of NAB-PACLITAXEL and carboplatin in NSCLC were: anemia (28%); neutropenia (47%); thrombocytopenia (18%), and peripheral neuropathy (3%)
- The most common adverse reactions (≥ 20%) of NAB-PACLITAXEL in combination with carboplatin for NSCLC were anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue
- The most common serious adverse reactions of NAB-PACLITAXEL in combination with carboplatin for NSCLC were anemia (4%) and pneumonia (3%)
- The most common adverse reactions resulting in permanent discontinuation of NAB-PACLITAXEL were neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)
- The most common adverse reactions resulting in dose reduction of NAB-PACLITAXEL were neutropenia (24%), thrombocytopenia (13%), and anemia (6%)
- The most common adverse reactions leading to withholding or delay in NAB-PACLITAXEL dosing were neutropenia (41%), thrombocytopenia (30%), and anemia (16%)
- The following common (≥10% incidence) adverse reactions were observed at a similar incidence in NAB-PACLITAXEL plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the NAB-PACLITAXEL plus carboplatin treatment group)

Post-Marketing Experience with NAB-PACLITAXEL and other Paclitaxel Formulations

- Severe and sometimes fatal hypersensitivity reactions have been reported with NAB-PACLITAXEL. The use of NAB-PACLITAXEL in patients previously exhibiting hypersensitivity to paclitaxel injection or to human albumin has not been studied
- There have been reports of congestive heart failure and left ventricular dysfunction with NAB-PACLITAXEL, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs
- There have been reports of extravasation of NAB-PACLITAXEL. Given the possibility of extravasation, it is advisable to monitor closely the NAB-PACLITAXEL infusion site for possible infiltration during drug administration

DRUG INTERACTIONS

- Caution should be exercised when administering NAB-PACLITAXEL concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4

USE IN SPECIFIC POPULATIONS

Nursing Mothers

- It is not known whether paclitaxel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric

- The safety and efficacy of NAB-PACLITAXEL in pediatric patients have not been evaluated

Geriatric

- No toxicities occurred notably more frequently among patients ≥ 65 years of age who received NAB-PACLITAXEL for MBC
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with NAB-PACLITAXEL and carboplatin in NSCLC

Renal Impairment

- The use of NAB-PACLITAXEL has not been studied in patients with renal impairment

DOSAGE AND ADMINISTRATION

- Dose adjustment is recommended for patients with moderate and severe hepatic impairment and patients who experience severe neutropenia or severe sensory neuropathy during treatment with NAB-PACLITAXEL
- Withhold NAB-PACLITAXEL if AST >10 x ULN or bilirubin > 5 x ULN
- Dose reductions or discontinuation may be needed based on severe hematologic or neurologic toxicities
- Monitor patients closely

Please see full Prescribing Information, including Boxed WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

About Celgene International Sàrl

Celgene International Sàrl, located in Boudry, in the Canton of Neuchâtel, Switzerland, is a wholly owned subsidiary and international headquarters of Celgene Corporation. Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through gene and protein regulation. For more information, please visit the Company's website at www.celgene.com.

Forward-Looking Statements

This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," “outlook” and similar

expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in our Annual Report on Form 10-K and our other reports filed with the Securities and Exchange Commission.

Appendix 3 - Registration Process for Participating Sites

Centralized Registrations

A centralized registration procedure will be used. Subjects who are considered candidates for the study will be evaluated for eligibility by the participating investigators. There will be a 2-part registration procedure:

1) Participating Institutions Registration
Subjects at participating institutions should be registered with their institutional central registration following each institution's established policies.

2) Emory University Registration
Participating institutions must register subjects with Emory University in accordance with project specific procedures. After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail. All participating institution subjects must be registered with Emory University before protocol treatment is initiated. **Late registrations will not be accepted.**

Registrations will be completed by Emory University within 1 business day after the date the registration is received from the participating site.

Subject ID Number
At the time of registration, the participating institution's subject will be assigned an Emory University subject number. This number is unique to the subject and must be used for registrations onto subsequent protocols and written on all data and correspondence for that subject prior to submission to Emory University.

Emory University subjects will be registered using their Emory University subject number.

Registration Verification Letter
A Registration Verification Letter will be created by Emory University and then faxed or emailed to the participating institutions after the registration is completed.

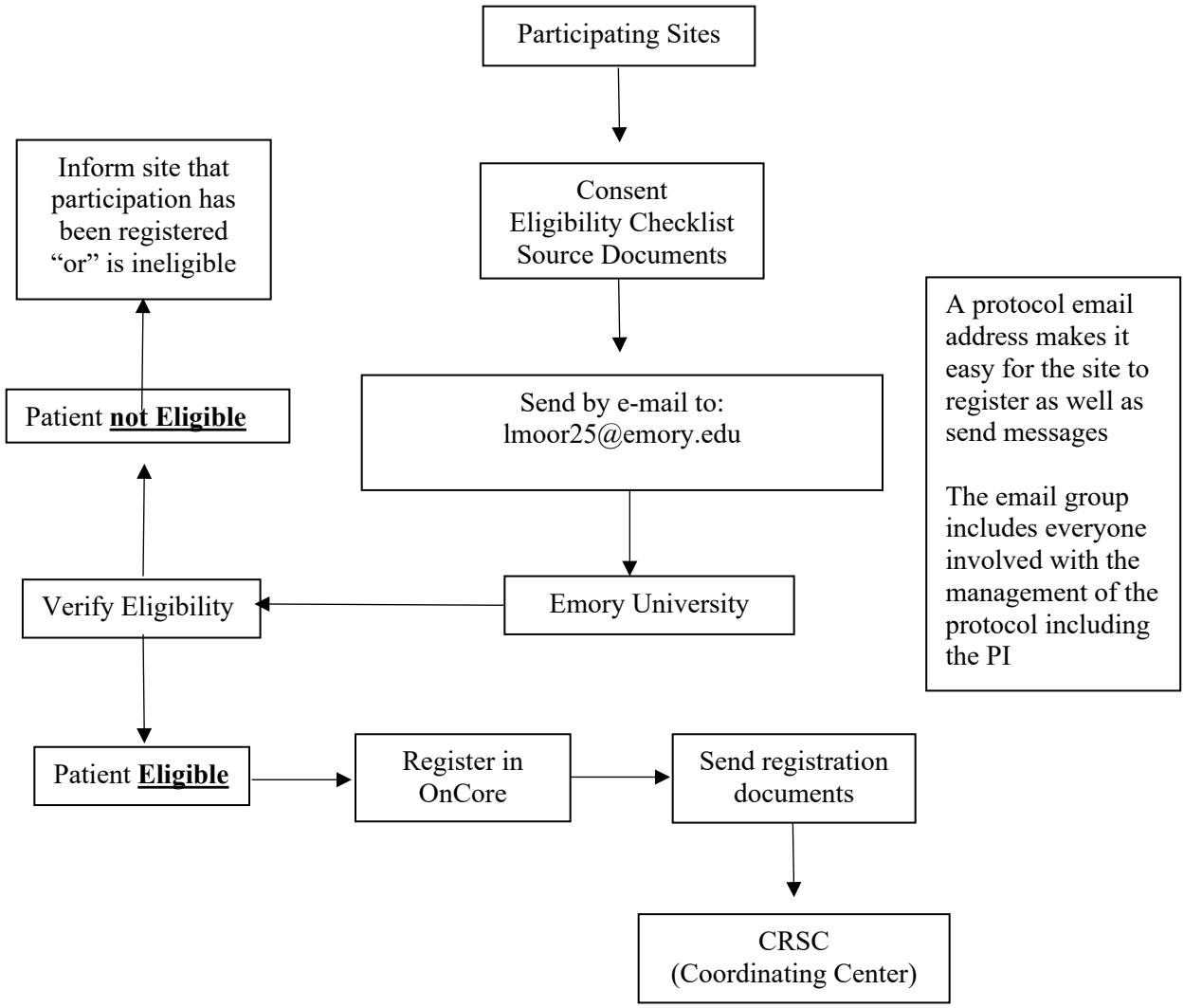
Initiation of Therapy
Subjects must be registered with Emory University before receiving study treatment. Treatment may not be initiated until the participating institutions receive the subject's Registration Verification Letter from Emory University.

Confidentiality
All documents, investigative reports, or information relating to the subject are strictly confidential. Any subject specific data or reports (i.e. Pathology Reports, MRI Reports,

Operative Reports, etc.) that the site submits to Emory University will adhere to a policy of strict confidentiality.

Patient registration process flowchart below.

Patient Registration Process Flowchart



APPENDIX 4

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Multicenter Project

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1. INTRODUCTION

The purpose of the Data Quality Management Plan (DQMP) is to establish standards which will ensure that the conduct of an Emory University multicenter protocol complies with institutional guidelines, Federal regulations (21 CFR Part 11), Good Clinical Practice (GCP) Guidelines, and Health Insurance Portability and Accountability Act (HIPAA) requirements.

The DQMP outlines the procedures required for participating institutions in the conduct of an Emory University multicenter protocol.

2. GENERAL ROLES AND RESPONSIBILITIES

Each participating site is responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments. Each site-PI will assume the same responsibility at their own respective site.

The Emory University Protocol Principal Investigator, Coordinating Center, and the Participating Institution Principal Investigator will all agree to the general responsibilities as follows:

2.1 Protocol Principal Investigator (Protocol PI)

Being charged with the administrative responsibilities of the Emory University multicenter protocol, the Protocol PI will accept the following:

- Obtain initial approval of the protocol and approval of any subsequent amendments from the Emory University IRB, and/or sponsor or supporting entity (if applicable).
- Identify participating institutions and investigators, and obtain accrual commitments.
- Include the list of participating institutions and responsible investigators in the abstract or protocol appendix.
- Coordinate contractual agreements with sponsor or supporters (when applicable), and with each participating institution.
- Assure that all participating institutions are using the correct version of the protocol.
- Assure that all participating institutions obtain IRB (or equivalent) approval of the protocol prior to performing any study related activities with potential subjects.
- Participating sites will promptly provide the coordinating investigator/site with copies of adverse event reports that require expedited reporting to their local IRBs
- Coordinating investigator/site will forward adverse events reports requiring expedited reporting to participating sites
- Coordinating/Lead investigator will review data summary reports of adverse events on a regular basis, at least annually
- Coordinating/ Lead investigator will submit data summary reports to the Data Safety Monitoring Committee for review as per their guidelines.

- Ensure timely submission of protocol data from all participating institutions.
- Review and assess protocol data from all participating institutions for study analysis in a timely fashion.
- Submit all required reports to Emory University, IRB, Sponsor or Supporter, and any other relevant regulatory agencies.
- Monitor the overall conduct and progress of the study at all participating institutions.

2.2 Coordinating Center

To assist the Protocol PI in fulfilling these responsibilities, the study teams in the Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine and the Multi-site coordinator / regulatory specialist at Emory University, will provide the administrative support and assume the following responsibilities to ensure data quality and protocol compliance at all participating institutions.

- Act as liaison between Emory University and the participating institutions.
- Implement quality assurance and quality control systems to ensure quality data and protocol compliance.
- Distribute Emory University IRB approved protocol and its amendments to all participating institutions.
- Collect and maintain documentation of IRB approval for all participating institutions.
- Collaborate with the Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine in providing protocol and database trainings to ensure that all investigators and staff are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs/eCRFs.
- Review, process, and maintain records of Adverse Events/Serious Adverse Events from all participating institutions on a timely basis to assure participant safety.
- Review, process, and maintain records of Deviations or Unanticipated problems that are reported from all participating institutions on a timely basis to assure participant safety and protocol integrity.
- Distribute Safety Reports (External Adverse Events), if applicable, to all participating institutions.
- Ensure timely submission and accuracy of protocol data from all participating institutions.
- Assist in the submission of all required reports to the Protocol PI, Emory University IRB and any other relevant regulatory agencies.

2.3 Participating Institution Principal Investigator (Participating PI)

- Commit to accrual to the Emory University protocol.
- Submit the Emory University IRB approved protocol and its amendments to the institution's local or central IRB (or equivalent) for approval prior to performing any study related activities with potential subjects.
- Assume overall responsibility for the trial at his/her institution.

- Oversee the conduct of the clinical trial at his/her institution.
- Identify study collaborators from that institution who agree to participate.
- Assure that all involved research personnel are aware of the effort required to oversee and conduct the trial.
- Balance the trial needs with other commitments.
- Assure adequate staff with adequate research and protocol training.
- Assure adequate facilities to conduct the trial.
- Provide, and update as needed, a list of contact information of involved staff and Delegation Authority Log for the protocol to the Coordinating Center.
- Ensure that the multicenter trial procedures are performed at his/her institution in compliance with the protocol and the DQMP.

3. COORDINATING CENTER

3.1 Correspondence Information

Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine

(Patient Registrations to be performed by the Central Subject Registrar

- Phone: 404-778-5471
  Fax: 404-778-5071
  Email: winshipcsr@emory.edu

- **Mailing address: for all U.S. Mail excluding express mail:**
  Winship Cancer Institute, Emory University
  Clinical Trials Office
  1365-C Clifton Road NE, Suite C3012
  Atlanta, GA 30322

- **Mailing address for Federal Express, Airborne, and UPS:**
  Winship Cancer Institute, Emory University
  Clinical Trials Office
  1365-C Clifton Road NE, Suite C3012
  Atlanta, GA 30322

Clinical Research Support Center at Emory University

(Regulatory oversight, study monitoring and auditing, and general correspondence)

Mailing address: for all U.S. Mail excluding express mail:
1784 North Decatur Rd., Ste 402
Atlanta, GA 30322

Mailing address for Federal Express, Airborne, and UPS:
Winship Cancer Institute, Emory University
Clinical Trials Office
1365-C Clifton Road NE, Suite C3012
Atlanta, GA 30322
Email: lmoor25@emory.edu

3.2 Hours of Operation

The staff at both the Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine and Clinical research Support Center (Coordinating Center) at Emory University are available between the hours of 8:00 a.m. and 5:00 p.m. Eastern Standard Time, Monday through Friday, excluding holidays. On designated Emory University holidays, the office will be closed.

Transactions (i.e. participant registration, correspondences) will not take place on holidays. Occasionally, the Coordinating Center may close due to hurricanes or other inclement weather conditions. Each participating institution will be notified of office closures by phone, fax, or e-mail.

Night, Weekend, and Holiday Emergencies:
If participant-related emergencies or questions arise when the Coordinating Center is closed, please email the Protocol PI and confirm receipt by contacting the PI the next business day at the telephone number listed in the protocol.

4. PROTOCOL MANAGEMENT

The Coordinating Center will maintain copies of all IRB approvals from each participating institution.

4.1 Protocol Distribution

The Coordinating Center will distribute the final Emory University IRB approved protocol and any subsequent amended protocols to all participating institutions within thirty (30) days of approval.

4.2 Protocol Revisions and Closures

The Participating Institutions will receive fax or e-mail notification of protocol revisions from the Coordinating Center. Protocol revisions will be submitted in pdf format to participating institutions. It is the responsibility of each participating institution to notify its IRB of these revisions within the timeline set forth below.

Major Amendment: A substantive change in the study which may increase or decrease the risk to study subjects. Major revisions require full IRB approval.
Participating institutions shall provide its IRB approval of the revision within 90 days after notice. If more than 90 days, participant enrollment shall be temporarily suspended at participating institution until its IRB approval is submitted to the Coordinating Center.

The following are examples of major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention

- Change of device
- Change in primary objective evaluation process

Non-life-threatening Revisions: Participating institutions will receive written (faxed or emailed) notification of revisions regarding non-life-threatening events from the Coordinating Center. Non-life-threatening revisions must be submitted to the participating institution's IRB within fourteen (14) days from the date of notification.

Revisions for Life-threatening Causes: Participating institutions will receive a phone notification followed by the written (faxed or emailed) notification from the Coordinating Center concerning protocol revisions required to protect lives. Life-threatening protocol revisions must be submitted to the local IRB within one business day from date of notification. Immediate closure of the protocol will be required until the protocol amendment is approved.

Once the participating institution's IRB has approved the amendment, notification of IRB approval should be sent to the Coordinating Center within fourteen (14) business days of approval.

Protocol Closures and Temporary Holds: Participating institutions will receive written (fax or e-mail) notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

4.3 Informed Consent Requirements

The Protocol PI or designee will ensure review and approval of the participating institution's Informed Consent Document (ICD) prior to its submission to the institution's IRB.

The Participating PI will identify members of the study team who will be obtaining participants' signed ICD for protocols, as per the delegation of authority log and the institution's Informed Consent Policy.

4.4 Regulatory Documents

The following must be on file with the Coordinating Center prior to participant registration:

Participating Institution

- Participating institution's IRB approval memo/letter of the protocol and ICD
- IRB approval for all amendments within the predetermined timelines
- CLIA, CAP, and Normal Lab Values (if applicable)

Participating Institution Research Personnel

- Certification of Human Subjects Protection Training
- Current Medical License (Participating PI and co-investigators)
- Curriculum Vitae
- Delegation of Authority Log

4.5 Participating Institution Site Initiation

Before an institution begins participating in an Emory University multicenter protocol, the following steps must be completed:

- Submit all required regulatory documents to the Coordinating Center
- Participate in a site initiation visit, webcast, or conference call
- Receive training regarding study specific CRFs/eCRFs
- Execute all required contractual agreements

After these requirements have been fulfilled, the participating institution will receive a written Site Activation Notification by fax or e-mail. Once the Site Activation Notification has been received, the participating institution may begin to register patients to the protocol.

4.6 IRB Annual Review

Continuing IRB approval from the participating institution is required in order to register participants onto a protocol. There is no grace period for annual reviews.

Protocol registrations will be suspended if an annual review letter is not received by the Coordinating Center from the participating institutions within thirty (30) days of the anniversary of the previous approval date.

4.7 Participant Confidentiality and Authorization Statement

In order for covered entities to use or disclose protected health information during the course of this trial, the participant in the trial must sign an authorization. This authorization may or may not be separate from the Informed Consent.

Emory University will attempt to limit its use of protected health information in its Multicenter Project trials. However, portions of a participant's protected health information may be collected. In order for Emory University to collect this information on any participant enrolled, the participant must have signed an informed consent document, which includes an authorization for the release of protected personal health information (IC/A). The authorization that each institution obtains to use and disclose protected health information must include Emory University as an entity with whom they will share data. Each institution should also list study sponsor or supporter in their authorization form.

All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology Reports, MRI Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number de-identified and the assigned Emory University participant ID number , accession number and protocol number written in. Participant initials need to be included or retained for cross verification of identification.

The de-identification process can be waived only when the following criteria are met:

1) The participating institution provides the Coordinating Center an IRB policy or a written statement that the de-identification process is not required on all documents submitted to Emory University.

2) The study participants give their authorization to Emory University for the use and disclosure of their Protected Health Information in either the protocol specific Informed Consent or HIPAA Authorization Form.

4.8 Patient Registration

The Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine is responsible for central patient registration and randomization.

All participants must be registered centrally before a protocol treatment is initiated. Late registrations will not be accepted.

Fax: 404-778-5071
Phone: 404-778-5471
Email: winshipcsr@emory.edu

Registration hours are 8:00 a.m. to 5:00 p.m. Eastern Standard Time, Monday through Friday, except holidays.

4.8.1 Registration Information

The following are required for registration. All subject related information sent via fax or email must be encrypted.

- Copy of the signed ICD and HIPAA authorization
- Completed and signed Eligibility Checklist
- Source documents supporting each eligibility requirement

4.8.2 Multicenter Project Participant Number

Once eligibility has been established, non Emory University patients will be assigned a ten character patient number. This number is unique to the patient and must be written on all correspondence related to the patient.

4.8.3 Eligibility Exceptions: There will be no eligibility exceptions.

All documents submitted to Emory University must be identified with:

1. Emory University protocol number
2. Assigned multicenter protocol participant ID number
3. Participant initials

All participants must be registered in the OnCore system at Emory University with the correct corresponding institution and investigator.

4.9 Schedule of Data Entry and Source Document Submission

All documents, except for those sent at the time of registration, are to be forwarded to the Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine via OnCore. Case Report Form/s (CRF), will be used for data collection for this protocol. The schedule for data submission (CRF) and submission of source documents into OnCore as agreed is specified in this document.

COMMON FORMS & DOCUMENTS

- Signed Informed Consent/Patient Authorization for the Release of Personal Health Information
- Eligibility Checklist
- Baseline Medical History
- Treatment Data (Chemotherapy documentation - Medication Administration Record, Laboratory Results, administration of any blood products)
- Evaluation Data (Protocol Response)
- Adverse Events
- Off-Treatment Update
- Follow-Up Update Off Study Update
- Source Documents (e.g. Pathology, Radiology, Operative, Laboratory Reports; History and Physical, Progress Notes)

PROTOCOL [EU4339-18] DATA AND SOURCE SUBMISSION SCHEDULE (See table below)

	DATA	CASE REPORT FORM	SOURCE DOCUMENT	EVENT INTERVAL	SUBMISSION SCHEDULE
1.	Informed Consent with HIPAA Authorization	N/A	Copy of signed/initialled **Informed Consent w/HIPAA Authorization**	Baseline	On or before registration date.
2.	Demographics	Pre-registration Form	Baseline History & Physical Note or Demographic Form	Baseline	On or before registration date.
3.	Eligibility Checklist	Inclusion-Exclusion Form	History and Physical Progress Note that includes prior treatment history (medical/surgical/ and other treatments such us chemotherapy, radiotherapy), pathology report, and laboratory report (to include tumor markers).	Baseline	On or before registration date.

4.	Baseline History and Evaluation Data	Medical History Form, Physical Exam Form, Vital Signs Form, Concomitant Medication Form, Laboratory Results Form, Other Data Submission Form, Research Specimen Status Form	History and Physical Progress Note that includes prior treatment history (medical/surgical/ and other treatments such us chemotherapy, radiotherapy), pathology report, and laboratory report (to include tumor markers).	Baseline	On or before registration date.
5.	Disease Evaluation Data	Disease Evaluation Form (Target and Non Target Tumor Measurements), Other Data Submission Form	CT (or MRI) Scan Report of the chest, abdomen and pelvis.	Baseline	On or before registration date.
6.	Treatment Data	Treatment Form, Physical Exam Form, Vital Signs Form, Concomitant Medication Form, Laboratory Results Form, Adverse Event Form, Multicenter SAE Form (if applicable).	Serious Adverse Event source (if applicable), physician treatment orders, and chemotherapy MAR/infusion records.	Treatment Phase	Within 14 days after end of each of cycle.
7.	Disease Evaluation Data	Disease Evaluation Form (Target and Non Target Tumor Measurements), Other Data Submission Form	To include clinical evaluations to determine response (CT or MRI reports of the chest, abdomen and pelvis after cycle 4 and 6). *Continue to submit report until **first** Progressive Disease (PD) event.*	Treatment Phase	Within 14 days after event date.
8.	End of Treatment Summary Data	End of Treatment Form, Physical Exam Form, Vital	N/A	Off-treatment Phase	Within 4 weeks after the end of

		Signs Form, Concomitant Medication Form, Laboratory Results Form, Adverse Event Form, Disease Evaluation/Target and Non Target Tumor Measurements Form, Other Data Submission Form, Research Specimen Status Form.			last dose or post-surgery.
9.	Disease Evaluation Data	N/A	CT scan or MRI report of the chest, abdomen and pelvis (off treatment patients who met first PD at this interval)	Off Treatment Phase	Within 14 days after event date.
10.	Follow-Up ▪ Off Treatment Data ▪ Survival Status Data (Long term follow-up)	Survival Follow-up Form, Adverse Event Form	N/A	Follow-up Phase	Within 59 days after end of treatment protocol date.
11.	Off Study Data	Off Study Form	Off Study Note	Off Study Phase	Within 14 days after off study date.

4.10 Data Form and Source Document Review

The data entered in the CRFs and source document submitted via OnCore as agreed are reviewed by the Coordinating Center for:

- **Timeliness:** Did the form arrive on time as specified in the protocol?
- **Completeness:** Is all the information provided as required per protocol?
- **Patient Eligibility:** Does the patient meet the eligibility requirements for the study?
- **Treatment Compliance:** Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.
- **Adverse Events:** Did the patient experience adverse events attributed to protocol treatment? Was the treatment delayed due to an adverse event? What were the maximum grade, duration, and attribution of the event? Notations concerning adverse events will contain grade, start and stop date, and attribution.

- **Response:** Response will be assessed using the RECIST Criteria (version 1.1, 2009). Responses must be verified, documented, and signed in the local medical record by the local PI.

4.11 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If data entered in the CRFs is incomplete, or if there is a conflict between data entered and source documents reviewed, queries will be generated. Responses to any queries generated are due within 14 days. Source documents are also expected to be available within 14 days of occurrence.

Missing Source Documents

If source documents are not submitted or available for viewing on schedule, the participating institution will receive a "Missing and Deficient Report" from the coordinating center noting the missing source document (s). These reports are distributed on a monthly basis. If source documents are 30 or more days late, the site will be contacted by telephone for assistance in obtaining delinquent forms. If forms are $\geq$ 60 days late, the Protocol PI (Maithel) will contact the participating institution's Principal Investigator for assistance.

Missing Query Responses:

If replies to Queries are not received on schedule, the institution will receive a "Missing and Deficient Query Report" from the coordinating center noting the missing Query. These reports are compiled and distributed on a monthly basis. If responses are 30 or more days late, the coordinating center will communicate with the participating institution's Research staff for assistance in obtaining the forms. If responses are 60 or more days late, the Protocol PI and the Participating PI will be notified via email. All delinquencies will also be discussed in the monthly consortia meetings.

5. STUDY DRUG REQUISITION

Gemcitabine and Cisplatin are FDA approved and commercially available drugs for the treatment of biliary cancer. The study will not provide these 2 study agents and the patient and/or insurance will be charged for the drugs.

Nab-Paclitaxel is provided by Celgene. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with nab-paclitaxel upon identification and screening of a potential trial subject.

Upon identification of a potential subject and for re-supply of drug, sites must email a completed Drug Request Form to Celgene Corporation (NonIMIDUSOrders@celgene.com). Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. To order study supplied drugs contact:
Ralph F. Petruzzi

6. SAFETY ASSESSMENTS AND TOXICITY MONITORING

6.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or 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 participant or 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 in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse (21 CFR 312.32).

6.2 Oversight for Safety Assessments and Toxicity Monitoring

6.2.1 Participating Institution

The Emory University multicenter protocol which outlines the methods to be used for data safety monitoring will be submitted by the participating institution to its own IRB. The participating institution IRB will be responsible for reviewing and approving the protocol, as well as, monitoring the conduct of the study at its institution. Data and safety monitoring at the participating institution must be consistent with the data and safety monitoring guidelines delineated in the Emory University protocol. The participating institution will ensure that all safety information related to their study site has been forwarded to the Coordinating Center.

6.2.2 Coordinating Center

All patients receiving study drugs will be evaluated for safety. The safety parameters include all laboratory and hematologic abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Clinical Toxicity Criteria Scale (0-5) using the NCI's CTCAE Criteria Version 4.0 and recorded prior to each course of therapy. A copy of the CTCAE Criteria can be downloaded from the CTEP home page http://ctep.cancer.gov/reporting/ctc.html

Life- threatening toxicities should be reported immediately to the Protocol PI, site PI, and the respective site IRB where the toxicity occurred.

6.3 Reporting Serious Adverse Events

The Division of Surgical Oncology, Department of Surgery, at Emory University School of Medicine will report SAEs in accordance with Emory University IRB policies and procedures and this protocol.

Participating Multicenter Institution SAE reporting requirements will be as follows:

- Any Serious Adverse Event (SAE) will be reported to the local institution's IRB and the Coordinating Center as specified below. The circulation of unexpected and related SAEs to the participating institutions will be performed by the coordinating center.
- Any adverse event falling under the definition of serious will be reported immediately to the Protocol PI.
- Symptoms related to progressive disease will not be reported as toxicity or as Serious Adverse Events.
- Participating institutions will notify the Coordinating Center of all life-threatening serious adverse events or Deaths within 24 hours of knowledge of the event.
- SAEs that do not result in death but are serious and **unexpected** and **related**, are to be reported within 5 working days from the time the research team becomes aware of the event.
- SAEs that do not result in death and **unrelated**, are to be reported within 5 working days from the time the research team becomes aware of the event.
- The Coordinating Center will notify the Protocol PI or his designee of the SAE.
- The initial SAE report from the participating institution will be forwarded to the Protocol PI or his designee for review and signature.
- The Emory University Multicenter Serious Adverse Event Report form will be used for the study by all participating institutions, and the Coordinating Center will maintain documentation of all Adverse Event Reporting.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized or there has been acceptable resolution of the event.

Follow up Information:
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original Multicenter SAE report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original Multicenter SAE form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

6.4 Additional Adverse Event Reporting by the Coordinating Center (CRSC)

Emory University and the participating centers will ensure that investigators will comply with all safety reporting regulations as set forth in the Code of Federal Regulations and the protocol. The Coordinating Center at Emory University and each participating center will notify Celgene of the occurrence of;

- Serious Adverse Events (SAE) within twenty four (24) hours of becoming aware of a confirmed adverse event.
- Any correspondence to the FDA regarding adverse events or other safety issues **will be simultaneously submitted to Celgene**.
- The MedWatch 3500A form should be utilized to report serious adverse events to the FDA.
- Non-serious adverse drug reactions are to be reported as required in the protocol and in accordance with the procedures outlined in the protocol (Adverse Event [AE] data capture via AE CRF) and this DQMP.

Celgene's contact information for submitting SAEs:
Facsimile: 908-673-9115

7. PROTOCOL DEVIATIONS AND UNANTICIPATED PROBLEMS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." The definition is often left to the lead institution IRB. Accordingly, since Emory University is the lead institution and the Protocol PI must adhere to those policies set by the Emory University IRB, the definitions for protocol deviation as described by the Emory University IRB will be applied for reporting purposes for all institutions participating in the Emory University Multicenter Project.

7.1 Definitions

Minor Protocol Deviation / Protocol Non-Compliance: Noncompliance with the required elements of the protocol that does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data. Deviations may be caused by the action of, or the omission of, the subject, the investigator, the research team, or natural events. Continuing non-compliance of the protocol may meet reporting requirements.

Protocol Deviation / Non-Compliance:

The PI shall review any instance of a deviation from a research protocol that has not been approved in advance by the IRB or non-compliance with a research protocol to determine if the protocol deviation/protocol non-compliance meets any of the following criteria:
(a) Adversely affects the rights, welfare or safety of subjects.
(b) Adversely affects the integrity of the research data.
(c) Adversely affects the subject's willingness to continue participation in the research.
(d) Concerns study documentation associated with an FDA-regulated study.
(e) Was a protocol deviation undertaken to prevent immediate hazard to a human subject.

Examples include but are not limited to:

Informed Consent Document

- ICD not signed and dated by the participant
- Protocol specific procedures conducted prior to obtaining informed consent
- ICD used was not current IRB-approved version at the time of participant registration
- Participant not re-consented within timelines

Eligibility
- Enrollment of ineligible participant

Treatment and Procedures
- Incorrect agent/treatment/procedure used
- Additional agent/treatment/procedure used which is excluded by protocol
- Errors in dosing (error greater than +/- 10%)
- Dose modifications not followed per protocol or unjustified
- Unjustified continuation of treatment

Disease Outcome and Response
- Tumor measurements/evaluation of status or disease not performed or documented adequately to assess baseline or interpret response
- Documented response status cannot be verified

Adverse Events
- Serious or Unexpected Adverse Events not reported as required by protocol and IRB policy

Evaluations
- Protocol- specified laboratory, diagnostic tests, or evaluations to assess participant eligibility, safety, or response not completed

Unanticipated Problems (UAPs):

Unanticipated Problem Involving Risks to Participants or Others (referred to herein as UAP): Any unexpected problem related to the Research, including any Unexpected Adverse Experience, whether Serious or not, that affects the rights, safety or welfare of subject or others or that significantly impacts the integrity of the Research data. The problem may be physical, or it could involve social harm or risk (i.e., breach of confidentiality or harm to a subject's reputation) or psychological or legal harm or risk thereof in the future. The problem may or may not involve drugs or devices. Examples: (a) breach of confidentiality stemming from theft of lap top computer containing identifiable data; (b) protocol violations; (c) complaints about research procedures or treatment by research study personnel.

(Please note: it is important to bear in mind that a UP as defined here is not the opposite of an Anticipated Problem (defined above). The key distinction lies in the qualifying phrase "involving risk to participants or others." By contrast, the true opposite of an Anticipated

Problem would be an Adverse Experience or event (including an experience or event associated with a drug or device) that negatively affects the rights, safety or welfare of subjects and that is not described as such in the materials describing risks associated with the study.)

Examples include but are not limited to:

- Participant complaints
- Breach of confidentiality of research data
- Lost, stolen or destruction of confidential information
- Disqualification or suspension of investigators
- Change in FDA labeling or withdrawal from marketing of a drug, device or biologic agent
- Injury to research staff or others while conducting study-related procedures
- Expected events not reported in a timely manner as required by the protocol or IRB policy
- New information becomes available that may affect the participant's willingness to participate
- Issues with preparation, storage or handling of a study drug or device
- Unaccounted for study drug
- Drug stability issues
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm

7.2 Reporting Procedures

The Protocol Principal Investigator: The Protocol PI will be responsible for ensuring that all protocol deviations/UAPs involving subjects at an Emory site are promptly reported to the IRB per Emory University institutional guidelines.

Participating Institutions: Protocol deviations/UAPs occurring at a participating institution will be promptly reported to the coordinating center at Emory University even if they do not meet local IRB reporting requirements. Participating institutions should also report to their IRB according to their local policies and procedures. A copy of the participating institution's deviation report and the local IRB response will be included in the site's protocol regulatory file. The local IRB response to the report will be forwarded to the Coordinating Center upon receipt.

Coordinating Center: Upon receipt of the deviation report from the participating institution, the Coordinating Center will submit the report to the Protocol PI for review before the submission to the Winship DSMC.

8. QUALITY ASSURANCE

The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. Emory University provides quality assurance oversight for the protocol with three basic mechanisms:

1) Ongoing monitoring of protocol compliance
2) Verification of study data
3) On-Site Audit

8.1 Ongoing Monitoring of Protocol Compliance

The Coordinating Center will perform the ongoing protocol compliance monitoring based on the data provided in the CRF and source documents submitted via OnCore as agreed with the support of the Protocol PI, Participating PI and research staff. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

Monitoring plan of Subsite(s):

At the time of study initiation at a non-Emory site, the Protocol PI, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spread sheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spread sheet will be shared with the Emory PI via e-mail. Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The PI at Emory will communicate with participating sites via email as needed. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site. Chart reviews will be performed on selected cases by the participating site staff to confirm that the data collection is accurate.

Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (annually once onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

8.2 Verification of Study Data

All data submitted to the Coordinating Center will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. If study documents/data are submitted with missing pages, inaccurate or illegible data, the site will be notified and is required to resubmit the corrected document/data within 14 calendar days.

If study documents/data are not submitted on schedule, the Coordinating Center will notify the participating institution regarding the delinquency and describe a corrective action that includes deadline for bringing the data current.

Failure to comply with the delinquency notification will be communicated to the Protocol PI for further decision regarding the participating institution's study participation.

8.2 On-Site Audit

As part of the quality assurance process, the Clinical Research Support Center (CRSC) will conduct on-site audits/inspections on multicenter human subject research projects for which Emory University is the lead institution.

The CRSC auditing staff will notify the site PI immediately of any findings that may suggest intentional misrepresentation of data or disregard for regulatory safeguards for any component of the audit. Documentation of all findings will be included in the final audit report submitted to the PI.

9. EVALUATION OF PARTICIPATING INSTITUTION PERFORMANCE

The Emory University Coordinating Center and Clinical Research Support Center are bound by institutional and federal regulations in the conduct of cancer research trials. Protocol performance concerns are reported to the Protocol PI.

9.1 Sub-Standard Performance

The Protocol Principal Investigator is charged with considering the totality of an institution's performance when evaluating each institution.

9.2 Corrective Actions:

Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, and adherence to protocol requirements may be recommended for a probationary period. Such institutions must respond with a corrective action plan and must demonstrate during the probationary period that deficiencies have been corrected, as evidenced by improved performance. Institutions that fail to demonstrate significant improvement may be subject to reduced funding (if applicable) or revocation of participation as determined by the Protocol Principal Investigator.