THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
DIVISION OF CANCER MEDICINE

Protocol 2014-0524: A Phase II Study of Gemcitabine, Cisplatin, and Nab-Paclitaxel in Advanced Biliary Cancers

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Dose level

TABLE OF CONTENTS

APPENDICES

1. **STUDY RATIONALE**

Biliary cancers are a heterogeneous group of malignancies with a limited number of chemotherapeutic options in advanced disease. The current standard of care for palliative treatment of biliary cancers is the combination of gemcitabine and cisplatin[1]. Nab-Paclitaxel is FDA-approved for treatment of metastatic pancreatic cancer, and is presumed to enhance delivery of chemotherapy by modifying the dense stromal barrier that is thought to surround pancreatic cancer cells[2]. Given the presence of a strong desmoplastic response in biliary cancers as well, we hypothesize that the combination of gemcitabine, cisplatin, and Nab-Paclitaxel in advanced biliary cancers will improve drug delivery and enhance response and progression-free survival in these deadly malignancies.

2. BACKGROUND

2.1 Biliary Cancers

Biliary cancers are comprised of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma. They are an aggressive group of malignancies but heterogeneous in their presentations and clinical pictures. The majority of patients present at an advanced stage, and median survival of locally-advanced or metastatic biliary tract cancers is less than one year. These malignancies are characterized by lymph node involvement and distant metastases[3].

Gallbladder cancer (GBC) is the most common form of biliary tract cancers. Internationally, Israel has the highest incidence worldwide, with 7.5 cases per 100,000 men and 13.8 cases per 100,000 women. Other countries with significant incidence rates include Mexico, Bolivia, Chile, and northern Japan[4]. In the US, about five thousand new cases are reported every year. The incidence has been on the decline owing to the increase in the number of cholecystectomies for other reasons like acute or chronic symptomatic cholecystitis. Less than 10 percent of patients with GBC live more than five years after diagnosis. The mortality is very high and is attributed to the late diagnosis and an advanced stage of the disease[5].

At the same time, cholangiocarcinoma is a highly fatal cancer of the biliary tree. In the United States, approximately 5,000 new cases of cholangiocarcinoma are diagnosed annually; these cases are equally distributed between intra-hepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC)[6]. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) indicate that the incidence of ICC is increasing[7]. The incidence of ICC in the US almost tripled between 1975 and 1999[8]. The reasons behind this increase are not clear.

Chemotherapy for biliary cancers

Biliary cancers are often treated similarly to pancreatic cancers given their equally strong desmoplastic response creating dense stromal barriers that play a role in the chemoresistance seen in these malignancies[9]. Furthermore, like pancreatic cancers, gemcitabine has been the mainstay of chemotherapy in these diseases. The ABC-01 study was a phase II trial that examined the combination of gemcitabine and cisplatin in advanced biliary cancers. 86 patients were randomized to gemcitabine alone versus the doublet regimen. The primary endpoint of 6-month progression-free survival was 45.5% vs. 57.1% in the two arms with median time to progression being 8 months with the gemcitabine and cisplatin combination[10]. The benefit of the addition of cisplatin to gemcitabine was verified with the ABC-02 study, a randomized phase III trial of 410 patients with overall survival as the primary endpoint. The authors found that the combination of gemcitabine and cisplatin significantly improved median overall survival (11.7 months vs. 8.1 months) and progression-free survival (8.0 months vs. 5.0 months) compared to gemcitabine alone[1].

Taxanes in biliary cancers

The efficacy of taxanes in biliary cancers has been reported in the literature. A phase II study of single-agent docetaxel in twenty-five untreated, advanced biliary cancer patients demonstrated a response rate of 20% and a median overall survival of 8.0 months[11]. The combination of erlotinib and docetaxel was investigated in refractory hepatobiliary cancers. 64% of the patients with biliary cancers achieved the primary endpoint of 16-week progression-free survival[12]. In another study, 43 patients were treated with the combination of gemcitabine and docetaxel with a disease control rate of 67.4% and a median survival of 11 months[13]. Reports of the efficacy of paclitaxel have also been published[14,15].

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[16-19]. The presence of α-SMA-positive fibroblasts within the cholangiocarcinoma stroma has been associated with a poor prognosis[18,20].

Preclinical studies in pancreatic cancer have demonstrated that Nab-Paclitaxel enhances delivery of gemcitabine to pancreatic tumors by depleting the desmoplastic stroma that surrounds them and by enhancing the microvasculature[21]. 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 cancers[22].

A Phase IB/II study was conducted with gemcitabine/Nab-Paclitaxel in metastatic pancreatic cancer and significant efficacy (RECIST response rate of 48%, PFS of 7.9 months and overall survival of 12.2 months at the MTD) was observed[23]. These findings led to a phase III study involving 861 patients with metastatic pancreatic cancer who were randomized to gemcitabine alone versus gemcitabine and Nab-Paclitaxel. The combination arm demonstrated a significant improvement in overall survival from 6.7 months to 8.5 months ($p<0.001$). Median progression-free survival was 5.5 months with gemcitabine and Nab-Paclitaxel compared to 3.7 months with gemcitabine alone ($p<0.001$). Response rates, similarly, were higher with the combination (23% versus 7%, $p<0.001$)[2]. The most common adverse events included neutropenia, fatigue, and neuropathy, however, overall the combination was relatively well-tolerated with no difference in serious adverse events between the two arms.

The combination of gemcitabine and Nab-Paclitaxel is currently being investigated with the PrECOG study, a phase II trial as first-line therapy in cholangiocarcinoma. This multi-institutional trial will be looking at progression-free survival as the primary endpoint with a maximum of 70 patients enrolled (http://clinicaltrials.gov/show/NCT02181634).

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 biliary cancers and pancreatic cancers, respectively[1,2]. The tolerability of the combination of gemcitabine, cisplatin, and Nab-Paclitaxel is currently being investigated by the Pancreatic Cancer Research Team in a phase IB/II pilot study of previously untreated, metastatic pancreatic cancer patients. 3 patients were enrolled with gemcitabine at 1000 mg/m^2, Nab-Paclitaxel at 125 mg/m^2, and cisplatin at 25 mg/m^2 on days 1 and 8 of a 21-day cycle with no dose-limiting toxicities. The first patient enrolled on the cohort of cisplatin at 50 mg/m^2 was hospitalized with febrile neutropenia, and thus the first cohort of cisplatin at 25 mg/m^2 has now been expanded. 2 additional patients have been treated to date in this expanded cohort of cisplatin at 25 mg/m^2 with toxicities being manageable and no dose-limiting toxicities seen (personal communication with research team).

3. DRUG INFORMATION

3.1 NAB-PACLITAXEL

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.

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. 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[24]. 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[25,26].

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[27].

5. 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 ($p<0.0001$).

6. Potential Risks of NAB-PACLITAXEL Toxicities

The most common toxicities reported with NAB-PACLITAXEL when given with gemcitabine in the pancreatic cancer studies include myelosuppression (neutropenia: 73%, thrombocytopenia: 38%), fatigue (59%), peripheral edema (46%), pyrexia (41%), nausea (54%) vomiting (36%), diarrhea (44%), sensory neuropathy (54%), alopecia (50%), arthralgia (11%), myalgia (10%). During post marketing

surveillance, rare cases of severe hypersensitivity reactions have occurred.

7. Further Information
   See Appendix 2
   Nab paclitaxel (Nab-PaclitaxelTM) Prescribing Information (Updated 1/2012) – Accessed via Nab-Paclitaxel Website: http://www.Nab-Paclitaxel.com/docs/Nab-Paclitaxel_PrescribingInformation.pdf

3.2 GEMCITABINE

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.

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

3.3 CISPLATIN

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.

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

PRIMARY

Determine the progression-free survival (PFS) of gemcitabine, cisplatin, and Nab-Paclitaxel in advanced, untreated biliary cancers (intrahepatic cholangiocarcinomas, extrahepatic cholangiocarcinomas, and gallbladder cancers).

SECONDARY

- Determine the response rate (RR) and disease control rate (partial response + complete response + stable disease) of gemcitabine, cisplatin, and Nab-Paclitaxel in advanced biliary cancers
- Determine overall survival (OS) of gemcitabine, cisplatin, and Nab-Paclitaxel in advanced biliary cancers
- Evaluate the toxicity of gemcitabine, cisplatin, and Nab-Paclitaxel in advanced biliary cancers

EXPLORATORY

- Correlate the carbohydrate antigen (CA) 19-9 response (defined as >50% decrease from baseline) with tumor response, PFS and OS
- Assess RRMI, ERCC1 pre-treatment status and correlate with tumor response, PFS and OS on an exploratory basis
- Collect optional *blood and tissue at the start of treatment and at progression to explore mechanisms of resistance.
    - *Blood collection is mandatory at screening/baseline, however, it is optional at progression/end of treatment.

5. PATIENT ELIGIBILITY

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

INCLUSION CRITERIA

1. Patient must have histologically or cytologically confirmed intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer or may undergo a repeat biopsy for histologic confirmation if pre-existing biopsy is not sufficient for diagnosis.

2. Metastatic or unresectable disease documented on diagnostic imaging studies.

3. May not have received prior chemotherapy. If patient has received prior adjuvant therapy, must be > 6 months from treatment.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 1).

5. Adequate organ function including:

Absolute neutrophil count (ANC)	≥1,500 cells/mm^3
Platelets	≥100,000/ul
Hemoglobin	>9.0 g/dL
Total bilirubin [1]	≤1.5mg/dL
AST and ALT	≤5 x ULN
Creatinine	≤1.5 gm/dL

[1] In patients with known Gilbert's syndrome direct bilirubin ≤1.5 x ULN will be used as organ function criteria, instead of total bilirubin

6. Negative serum or urine pregnancy test in women with childbearing potential (WOCBP) defined as not post-menopausal for 12 months or no previous surgical sterilization, within one week prior to initiation of treatment. WOCBP must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 12 weeks after the last dose of study drug to minimize the risk of pregnancy.

7. A male subject of fathering potential must use an adequate method of contraception to avoid conception throughout the study and for up to 12 weeks after the last dose of study drug to minimize the risk of pregnancy. If the partner is pregnant or breastfeeding, the subject must use a condom.

8. Patients must sign an Informed Consent and Authorization indicating that they are aware of the investigational nature of this study and the known risks involved.

9. Patient is ≥ 18 years of age on the day of consenting to the study.

EXCLUSION CRITERIA

1. 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)"

2. 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, uncontrolled diabetes, serious active or uncontrolled infection.
3. Pregnancy (positive pregnancy test) or lactation.
4. 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

6. TREATMENT PLAN

This is a multi-center, open-label phase II study. Patients with advanced biliary cancers will be enrolled. All patients must be registered on the M. D. Anderson Cancer Center Clinical Oncology Research (CORe) system prior to initiation of treatment and patients from Mayo Clinic will have their information sent to MD Anderson for registration into the system.

This study will enroll up to 50 patients to at MD Anderson Cancer Center and the Mayo Clinic hospitals. Accrual is projected to be 2 to 2.5 subjects per month.

This will be an open-label, single arm study with each cycle being 21 days. All three drugs will be administered intravenously on day 1 and day 8 of the cycle. Dosing will be calculated using body surface area (BSA) based on the actual weight of the patient. 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. Restaging will be done every 3 cycles (+/- 1week). Treatment will be continued until progression unless other reasons for study discontinuation occur as listed in section 8 “Criteria for Removal from the Study.” Additionally, patients who have therapy interrupted for consolidative therapies (including, but not limited to radiation therapy, radioembolization, and chemoembolization) or at the physician’s discretion, will remain on study for survival analyses.

Table 2: 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. They will be administered in the following order with the 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 3: 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 4: 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 5: 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	100%	100%	100%

and Platelets ≥ 100,000			
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 6: 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 7: 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, willbe 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 ≥ 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 ≤ 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 24 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 7 days or if medical or scheduling conditions require a delay. Request of 20 unstained tumor slides of 5 to 10 microns thick will be sent at enrollment.

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: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, 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.
- CA 19-9, CA 125, and CEA
- Urinalysis (at Screening only)
- 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

Prior to Cycles 4, 7, 10, etc.

- In order to more precisely determine time to progression, 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.
- Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements.

Table 8: Study Assessments (treatment cycle is 21 days)

Evaluation or Procedure	Screening[1]	Study Treatment	End of Treatment Evaluation[11]	30-day Post-Treatment Evaluation[12]/Long Term Follow-up
		On or before Day 1 and day 8 of each cycle		
Informed consent	X			
Medical History	X			
Physical Examination	X	X[3,4]	X	
Inclusion/Exclusion criteria	X			
Height	X			
Weight	X	X[3,4]	X	
Vital Signs (Blood Pressure)	X	X[3,4]	X	
ECOG Performance Status	X	X [3,4]	X	
Hematology[10]	X	X[3,4]	X	
Biochemistry[10]	X	X[3,4]	X	
Urinalysis	X			
Serum or urine pregnancy test (for females of child-bearing potential)	X			
Tumor Tissue Collection	X[2]		X[2]	
Blood Collection for exploratory analysis	X[13]		X	
Toxicity assessment	X	X[3,4]	X	X[8]
Diagnostic Imaging for Tumor Assessment[7]	X	Every 3 cycles[5]	X[6]	X[6]
Survival				X[9]

1. Informed consent must be obtained before any evaluations are initiated. Diagnostic imaging studies must be completed within 28 days 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. Archival tissue will be collected for correlative studies. Patients may initiate study treatment prior to the receipt of the archival tissue. The collection of archival tumor tissue is not an absolute requirement for study enrollment and if no prior tissue is available than patients may still be enrolled and undergo study treatment. Additional tumor and unaffected liver tissue may be collected at the time of standard of care biopsy for diagnostic confirmation if a clear histologic diagnosis is unable to be made

with archival tissue. At time of disease progression, if a biopsy for routine clinical molecular profiling (using commercial assays such as Foundation One or Caris) is done, again, additional tumor and liver tissue may be obtained. For both time points (at time of standard of care diagnostic confirmation and at time of progression when performing routine clinical molecular profiling), additional preferably fresh frozen 2-3 cores of tumor tissue using an 18 gauge needle should be collected. Tissue will be flash frozen and stored in a -80 degree freezer or shipped on dry ice to the Borad laboratory. If fresh frozen tissue is not available, archival tissue may be used. Preferably tissue should be sent as 3 scrolls of 50 micron thickness. If not available in this format, up to 20 unstained, standard 5 to 10 micron slides can be sent. Collection of additional tissue at time of standard of care biopsies at screening and progression likewise is optional.

3. For Cycle 1, baseline evaluations will suffice as they are performed within 7 days prior to first dose of study drug (except for imaging studies which are performed within 28 days prior).
4. Within 48 hours prior to start of day 1 and day 8 of each cycle (except for Cycle 1 as noted above).
5. Imaging should be obtained every 3 cycles (+/- 1week). After a tumor demonstrates a tumor response (partial or complete), confirmation of the response will be obtained by a second evaluation to be performed 3 cycles later (+/- 1week). Evaluations earlier than every 3 cycles are allowed if, in the investigator's opinion, this evaluation is in the patient's best interest.
6. The end of treatment imaging does not have to be repeated if recent imaging has been completed within 4 weeks. For patients discontinued from the study for reasons other than progression, it is recommend to perform every 12 weeks (+/- 5 week) after the End of Treatment Evaluation visit until documentation of progression or for 12 months after their first dose of study drug, whichever comes first, if no other anti-cancer treatment is given.
7. CT of the chest, abdomen, and pelvis. 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.
8. 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 M. D. Anderson or Mayo Clinic for this assessment, the patient will be contacted by phone for this assessment.
9. Every 3 months (+/- 5 weeks) from Post-Treatment Evaluation.
10. Hematology: complete blood count with differential. Chemistry: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase, albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). Tumor markers (CEA, CA19-9, and CA-125) as indicated. Tumor markers are performed every 3 cycles. If starting a new cycle is delayed, no need to repeat tumor markers. In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin.
11. Within 10 days of decision to discontinue study treatment.

12. At 28-45 days from last dose of study medication.
13. 10 cc of blood will be collected at the same time as standard of care labs in an EDTA tube. Buffy coat will be separated after centrifugation and sample will be shipped over dry ice or stored at -80 degrees Celsius.

7.1 End of treatment evaluations

Within 10 days of decision to discontinue treatment

- The investigator will evaluate the results of the following clinical and laboratory assessments to be conducted at the time the patient discontinues study treatment:
- Physical examination with neuropathy assessment
- ECOG Performance Status
- Weight
- Vital signs (blood pressure)
- Hematology: complete blood count with differential
- Biochemistry: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). Tumor markers (CEA, CA19-9, and CA-125) as indicated. In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin.

- 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 (if recent imaging within 4 weeks, tumor evaluation does not need to be repeated)

7.2 Follow-up (off-treatment)

Follow-up/observation for all treatment related adverse events will be through Day 30 (Day 28 to Day 45 allowed) following the last dose of study drug or until resolution or stabilization of the toxicity or start of another treatment regimen. If it is not feasible for the patient to return to M. D. Anderson or Mayo Clinic for the Day 30 toxicity assessment, the patient will be contacted by phone for this assessment.

Patients with documented (radiological) disease progression at any point during the study will discontinue treatment with study drugs under this protocol. Objective evidence of progressive disease will be recorded at the time of progression. Patients without evidence of progression while on study, regardless of the number of treatment cycles received, will be followed for progression until it is documented. If a patient is off treatment with no documented disease progression and no subsequent anti-cancer treatment is received, he/she should be followed every 12 weeks (+/- 5 weeks) after the End of Treatment Evaluation visit with tumor evaluations until

disease progression is documented or for 12 months after their first dose of study drug, whichever comes first.

7.3 Long-term follow-up

All patients will be followed for survival status approximately every 3 months 30-day post-treatment evaluation. Survival status may be obtained by checking the electronic medical record or by telephone call.

8. CRITERIA FOR REMOVAL FROM THE STUDY

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

- 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 and progression will be evaluated in this study using the new international RECIST criteria (version 1.1, 2009) proposed by the RECIST committee[28]. 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 approximately every 3 cycles. 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 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination 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

<u>Evaluation of target lesions</u>

- **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. Partial response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which PR was observed.
- **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.

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 chair.
- 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 9 provides a summary of this for patients who have measurable disease at baseline. Table 10 provides a summary of this for patients with non-measurable (therefore non-target) disease.

Table 9: 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 10: 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 11: 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

10.1 STUDY DESIGN AND SAMPLE SIZE

This is a single arm, open label, phase II trial to assess the efficacy and toxicity of Nab-Paclitaxel when added to gemcitabine and cisplatin in patients with advanced bile duct cancer. The primary objective is to evaluate the efficacy of the combination therapy. The primary endpoint is the progression-free survival (PFS). A maximum of 50 patients will be enrolled in the study at an estimated accrual rate of 2-3 patients per month. The study will monitor for futility and safety.

10.2 Futility monitoring:

The Bayes factor single arm time-to-event model by Johnson & Cook will be used to monitor the PFS time[29]. Based on historical data, the median PFS time for the standard of care (gemcitabine and cisplatin) is 8 months (mean PFS = 11.54 months), and we expect that the combination treatment proposed in this study would prolong the median PFS time to 10 months (mean PFS = 14.43 months). Thus, using this Bayesian hypothesis test-based design, we assume the median PFS time is 8 months under the null hypothesis (H0), and the median PFS time is 10 months under the alternative hypothesis (H1).
We assume that the sample distribution of PFS time follows an exponential distribution, and use an inverse moment prior for mean PFS time under the alternative hypothesis.

10.3 Futility Stopping Rules:

We implement the following futility stopping rule during the trial, that is, we will stop the trial for futility if the posterior probability of the alternative hypothesis is less than 0.15, i.e. $Pr(H1|Data) < 0.15$.

10.4 Operating Characteristics:

The operating characteristics of the design were produced using the M.D. Anderson Cancer Center Department of Biostatistics software **Bayes Factor TTE**, version1.1.0.

Table 12: Operating characteristics for Futility monitoring

Scenario	True median (mean) PFS in months	Pr(Stopping for H0)	Average # patients treated (10%, 25%, 50%, 75%, 90%)

1	6 (8.66)	0.842	36.18 (23, 28, 36, 45, 50)
2	8 (11.54)	0.36	45.39 (33, 43, 50, 50, 50)
3	10 (14.43)	0.082	49.04 (50, 50, 50, 50, 50)
4	12 (17.31)	0.019	49.71 (50, 50, 50, 50, 50)

Based on simulations, if the true median PFS time is 6.0 months (Scenario 1), the trial will stop with a probability of 84.2% in favor of the null hypotheses. The average number of patients (10%, 90%) treated is 36.18 (23, 50). if the true median PFS time is 8.0 months (Scenario 2, the null hypothesis), the trial will stop with a probability of 36% in favor of the null hypotheses. The average number of patients (10%, 90%) treated is 45.39 (33, 50). If the true median PFS time is 10 months (Scenario 3, the alternative hypothesis), the trial will stop with a probability of 8.2% in favor of the null hypotheses. The average number of patients (10%, 90%) treated is 49.71 (50, 50).

10.5 Futility Stopping Boundaries:

The entire simulation output from Bayes Factor TTE is attached as Appendix 3, including boundaries of stopping for futility.

10.6 Safety monitoring:

Toxicity will be monitored closely using the method of Thall et al[30]. Denote the probability of toxicity by P_E, where toxicity is defined as any Grade 4 or higher hematologic and Grade 3 or higher non-hematologic toxicities related to the treatment. We assume $P_E \sim$ beta (0.6, 1.4). We will stop the trail if at any point $Pr(P_E > 0.30 \mid \text{data}) > 0.90$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the toxicity rate is more than 30%. The trial will be stopped if (the number of patients with toxicities /number of patients) ≥6/10, 7/13, 8/15, 9/18, 10/21, 11/23, 12/26, 13/29, 14/32, 15/35, 16/38, 17/41, 18/43, 19/46 and 20/49. We will implement this monitoring rule continuously during the trial, starting from the 10th patient. The operating characteristics are listed in table 13 below.

Table 13: The operating characteristics for toxicity monitoring are summarized in the following table

True toxicity probability	Probability of early stop	Sample size percentiles (10, 25, 50, 75, 90)
0.2	0.033	50 50 50 50 50
0.3	0.265	12 40 50 50 50

0.4	0.739	10 12 22 50 50
0.5	0.974	10 10 11 19 31

The stopping probabilities shown in Table 12 and Table 13 are based on marginal probabilities. The early termination of the study can be caused by either lack of efficacy or excessive toxicity. If the efficacy and toxicity are considered jointly, the stopping probabilities will be higher than the probabilities shown in Table 12 and Table 13.
Table 14 shows several scenarios of the joint stopping probabilities assuming the efficacy and toxicity is independent.

Table 14: Operating characteristics considering efficacy and toxicity jointly

True Median PFS (Months)	True probability of toxicity	Stop Probability
6	0.2	0.847
8	0.2	0.381
8	0.3	0.53
10	0.2	0.112
10	0.3	0.325
12	0.4	0.975

All calculations were performed using Bayes Factor TTE v1.1 and Multc99 v2.1.

10.7 Futility monitoring in CTC website

The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) to monitor futility for patients enrolled on this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

10.8 Statistical analysis:

SAS software V9.3 (SAS Institute Inc., Cary, NC) will be used for statistical analysis.

Patients demographic, clinical and adverse events observe during the trial will summarized using descriptive statistics, including means, frequencies and graphs. All

patients who receive one cycle of therapy will be reported for final toxicity analysis, while efficacy will be reported for both an intent to treat population (all patients who received one dose of study drug) and for the efficacy evaluable population (all patients who received 3 cycles of therapy).

For the primary analysis, we will calculate the Bayes factor, which represents the odds in favor of the alternative hypothesis. We will also use the Kaplan-Meier method to estimate the PFS probability, OS probability, and duration of response. In addition, we will tabulate toxicities and adverse events by frequency and percentage, and estimate response rate and its 95% confidence interval. For exploratory purpose, we will use Fisher's exact test and logistic regression analysis to evaluate the association between biomarkers and response, and use log rank test and Cox proportional hazards regression analysis to evaluate the association between biomarkers and OS or PFS. Paired t test and McNemar's test will be used to compare marker expressions at baseline and at the time of disease progression in blood and tissue (if available).

11. REGISTRATION PROCESS

Please see Appendix 4 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 University of Texas MD Anderson Cancer Center's Clinical Oncology Research (CORE) system, and the University of Texas MD Anderson Cancer Center's Protocol Data Management System ©(PDMS) CRF system will be used for this study. PDMS is a clinical research information management system. The PDMS CRF is an electronic document designed to record all the protocol-required information to be reported on each trial subject.

PDMS provides data entry templates as defined in the protocol. Laboratory results are automatically transferred from MD Anderson Cancer Center Laboratory Medicine's server to PDMS each morning. Users must have clearance through the MD Anderson Cancer Center Information Services Security Department in order to access PDMS. PDMS 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 centers involved in the study (MD Anderson and Mayo Clinic), please see Appendix 5.

13. CORRELATIVE STUDIES

All patients who sign consent for this study will provide consent for the collection of previously collected paraffin embedded tissue. Up to 20 unstained slides of 5 to 10 microns thick will be requested from the outside institution or prepared from the patient's tumor block, if applicable. Any residual tumor tissue above what is specified here will be returned to the sending institution. Collected paraffin embedded tissue will be handled by GI Medical Oncology research personnel. Only the PI and her authorized research staff will have access to the identifiable information from this study. All the samples extracted from the paraffin tissue used in this study will be coded and identifiers (name, medical record number) will not be present on any material that is undergoing analysis. Patient information and relevant data will be stored on password –protected institution computers behind the institution firewall. At the closure of this study all unused material will be either returned to the sending institution or destroyed.

When patients are enrolled, we will collect their pre-existing tissue biopsies, if available, for testing for protein expression using IHC for RRM1 and ERCC1. If a clear pathologic diagnosis is not able to be made with pre-existing biopsies, a repeat biopsy will be performed for histologic confirmation. From this additional tissue, as an optional part of the study, 2-3 cores using an 18 gauge needle and 1 core of unaffected liver tissue, will be flash frozen and stored in a -80 degree freezer or shipped over dry ice, to the address below. About 10% of each biopsy should be cut at the time of sampling and submitted for routine pathological evaluation.

Similarly, an optional biopsy will be done at the time of disease progression in the context of routine clinical molecular profiling (e.g. Foundation One or Caris) for consideration of further lines of therapy, including clinical trials with targeted inhibitors. Tissue will be obtained from tumor using 2-3 cores of 18-gauge needle and tissue will be obtained from normal liver using 1 core of 18-gauge needle. Samples will preferably be flash frozen and stored in -80 degree freezer or shipped to the address below. About 10% of each biopsy end should be cut at the time of sampling and submitted for routine pathological evaluation.

If fresh frozen samples are not available in the instances described above, FFPE tissue may be utilized. Preferably this would be in the form of up to 3, 50-micron scrolls or more standard 5 micron slides (up to 20).

We will also collect blood samples at the start of therapy (mandatory) and at progression (optional). Genomic analyses would include RNASeq, flow sorting enabled whole exome sequencing and whole methylome analysis at both timepoints. These analyses would be performed in the laboratory of Dr. Mitesh Borad at Mayo Clinic Phoenix. Samples should be shipped to:

Mayo Clinic PRC/Biobank
ATTN: Leslie Dixon
13400 E. Shea Blvd.
SCJ 3-308
Scottsdale, AZ 85259
Telephone: (480) 301-6867
Lab Telephone: (480) 301-6379
Fax: (480) 301- 9241
Email: Dixon.Leslie@mayo.edu

Baseline and at progression blood samples will be collected in the following vacutainers:

- One-10ml Lavender Top EDTA vacutainer tube

Buffy coat should be separated from sample and blood samples should be shipped over dry ice (or stored in -80 degree freezer if stored for later shipment) to the address listed above and should be obtained at the same time standard of care labs are being drawn.

14. SAFETY REPORTING OF ADVERSE EVENTS

14.1 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.

14.2 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.

14.3 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 occurring while the subject (or female partner of a male subject) is on study or within 30 days after the subject's last dose of Nab-Paclitaxel are considered expedited reportable events. If the subject is on Nab-Paclitaxel, it is to be discontinued immediately. The pregnancy must be reported to Celgene Drug Safety immediately on a Pregnancy Reporting Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene Drug Safety of the outcome on a Pregnancy Follow-Up Reporting Form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to Celgene (i.e., report the event to Celgene Drug Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to Nab-Paclitaxel must be reported to Celgene within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to Nab-Paclitaxel should also be reported.

In the case of a live "normal" birth, Celgene Drug Safety should be advised as soon as the information is available.

Celgene Drug Safety Contact Information:

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

Investigator Reporting Responsibilities

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

IND Annual Reports - (If Applicable)
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

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

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

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-OTHER-PI-003908) 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 MD Anderson Cancer Center, the primary study site.

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.

15. REFERENCES

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Appendix 1 – Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

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.
These results are from an investigational phase III study. NAB-PACLITAXEL is not currently approved for the treatment of advanced pancreatic cancer.

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.

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 – Statistical Simulation

The software BayesFactorTTE V1.1 for single arm TTE trial monitoring with Bayes factors was used for simulation of futility monitoring. This software implements the clinical trial monitoring method proposed by Valen Johnson and John Cook in "Bayesian Design of Single-Arm Phase II Clinical Trials with Continuous Monitoring," Clinical Trials 2009; 6(3):217-26. The software was downloaded from the software download site in the department of Biostatistics MDACC https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware.aspx?Software_Id=89

Output Report
BayesFactorTTE (version 1.1.0)
Bayes Factor One-arm Time-to-event Outcome
Random seed for simulation: 12345

Design input parameters:

Parameter	Value
Maximum number of patients	50
Null hypothesis of median (mean) TTE in month	8 (11.54)
Alternative hypothesis of median (mean) TTE in month	10 (14.43)
Cutoff to stop for futility if Pr(H1|Data) <	0.15
Cutoff to stop for superiority if Pr(H1|Data) >	1
Accrual rate per month	3
Number of repetitions for the simulation	1000
Do you need to print out the stopping boundaries	Yes

Note: H1 = alternative hypothesis

Simulation Results

Scenario	True median (mean) TTE	Pr(Stopping for H0)	Average # patients treated (10%, 25%, 50%, 75%, 90%)
1	6 (8.66)	0.842	36.18 (23, 28, 36, 45, 50)
2	8 (11.54)	0.36	45.39 (33, 43, 50, 50, 50)

3	10 (14.43)	0.082	49.04 (50, 50, 50, 50, 50)
4	12 (17.31)	0.019	49.71 (50, 50, 50, 50, 50)

Note:H0 = null hypothesis; H1 = alternative hypothesis

Stopping Boundaries

Number Events	Max total time-on-test in days (months) to claim futility
0	0 (0)
1	0 (0)
2	0 (0)
3	0 (0)
4	0 (0)
5	0 (0)
6	98 (3.2)
7	502 (16.5)
8	905 (29.7)
9	1309 (43)
10	1711 (56.2)
11	2114 (69.5)
12	2516 (82.7)
13	2917 (95.8)
14	3319 (109)
15	3720 (122.2)
16	4120 (135.4)
17	4521 (148.5)
18	4921 (161.7)
19	5320 (174.8)

20	5720 (187.9)
21	6119 (201)
22	6518 (214.1)
23	6917 (227.3)
24	7316 (240.4)
25	7714 (253.4)
26	8112 (266.5)
27	8510 (279.6)
28	8908 (292.7)
29	9305 (305.7)
30	9703 (318.8)
31	10100 (331.8)
32	10497 (344.9)
33	10894 (357.9)
34	11290 (370.9)
35	11687 (384)
36	12083 (397)
37	12479 (410)
38	12875 (423)
39	13271 (436)
40	13667 (449)
41	14062 (462)
42	14458 (475)
43	14853 (488)
44	15248 (501)
45	15643 (513.9)

46	16038 (526.9)
47	16433 (539.9)
48	16828 (552.9)
49	17222 (565.8)

Appendix 4 - Registration Process for Mayo Clinic 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 investigator. There will be a 2-part registration procedure:

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

2) MD Anderson GI Medical Oncology Registration
Participating institutions must register subjects with GI Medical Oncology in accordance with project specific procedures. All participating institution subjects must be registered with GI Medical Oncology before protocol treatment is initiated. **Late registrations will not be accepted.**

Registrations will be completed by GI Medical Oncology 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 MD Anderson 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 GI Medical Oncology.

MD Anderson Cancer Center subjects will be registered using their MD Anderson subject number.

Registration Verification Letter
A Registration Verification Letter will be created by GI Medical Oncology and then faxed or emailed to the participating institution after the registration is completed.

Initiation of Therapy
Subjects must be registered with GI Medical Oncology before receiving study treatment. Treatment may not be initiated until the participating institution receives the subject's Registration Verification Letter from GI Medical Oncology. GI Medical Oncology must be notified of any exceptions to this policy**.**

Eligibility Exceptions
The MD Anderson Cancer Center policy regarding exceptions to eligibility will be applied unless eligibility exceptions (also known as PI Overrides) are specifically prohibited by the project or protocol. The Clinical Research Support Center (CRSC)

policy on Multicenter Eligibility Exceptions describes the inclusion of subjects from participating sites in this process.

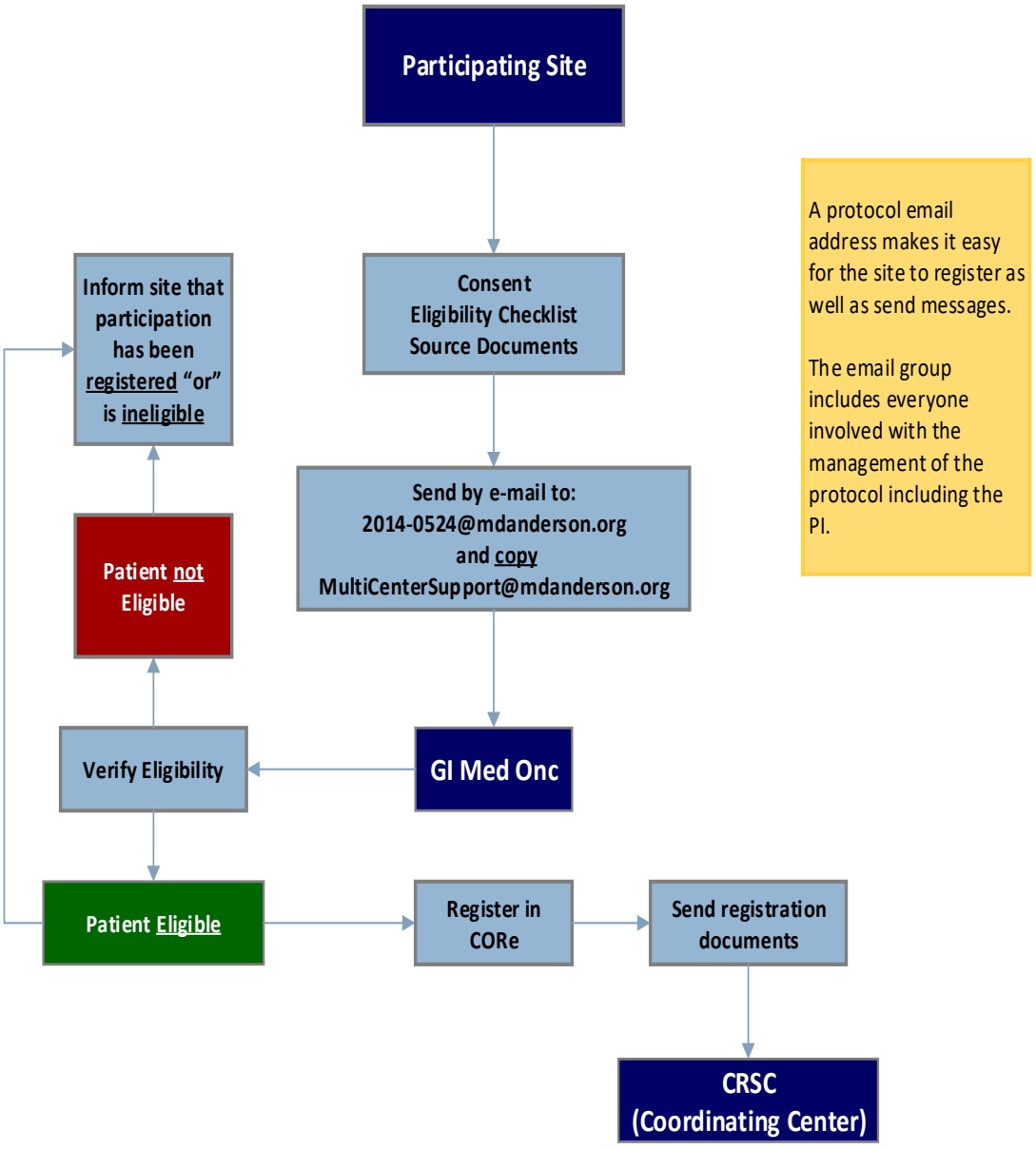
Eligibility Exceptions will be processed within 1 business day from the time the Lead Principal Investigator's written approval and the rationale for allowing the exemption is received in GI Medical Oncology.

The subject registration will not be completed until after the Exception has been approved by all parties.

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 GI Medical Oncology will adhere to the CRSC's Multicenter Subject Confidentiality Policy.

Patient registration process flowchart below (next page).

Patient Registration Process Flowchart



APPENDIX 5

PROTOCOL 2014-0524
DATA QUALITY MANAGEMENT PLAN
Multicenter Project

TABLE OF CONTENTS

1.0 INTRODUCTION

The purpose of the Data Quality Management Plan (DQMP) is to establish standards which will ensure that the conduct of an MD Anderson Cancer Center (MD Anderson) 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 a MD Anderson multicenter protocol.

2.0 GENERAL ROLES AND RESPONSIBILITIES

Being the lead institution, MD Anderson and its Institutional Review Board (IRB) are responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments.

The MD Anderson 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 MD Anderson multicenter protocol, the Protocol PI will accept the following:

- Obtain initial approval of the protocol and approval of any subsequent amendments from the MD Anderson 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.
- Review Adverse Events/Serious Adverse Events from all participating institutions on a timely basis to assure participant safety.

- Review deviations, violations or unanticipated problems that are reported from all participating institutions on a timely basis to assure participant safety and protocol integrity.
- 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 the MD Anderson 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 Department of Gastrointestinal Medical Oncology and the Clinical Research Support Center (CRSC) at MD Anderson, 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 MD Anderson and the participating institutions.
- Implement quality assurance and quality control systems to ensure quality data and protocol compliance.
- Distribute MD Anderson IRB approved protocol and its amendments to all participating institutions.
- Collect and maintain regulatory documents for all participating institutions.
- Collaborate with the Department of Gastrointestinal Medical Oncology 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, Violations 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, MD Anderson IRB and any other relevant regulatory agencies.

2.3 Participating Institution Principal Investigator (Participating PI)

- Commit to accrual to the MD Anderson protocol.
- Submit the MD Anderson 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.

3.0 COORDINATING CENTER

3.1 Correspondence Information

Department of Gastrointestinal Medical Oncology at MD Anderson
(Patient Registrations to be performed by the GI Medical Oncology team)

- Phone: 713/794-4869
  Fax: 713/745-3662
  Email: **2014-0524@mdanderson.org**

- **Mailing address: for all U.S. Mail excluding express mail:**
  The University of Texas
  MD Anderson Cancer Center, Unit 426
  Department of Gastrointestinal Medical Oncology
  1515 Holcombe Blvd.
  Houston, Texas 77030-4009
- **Mailing address for Federal Express, Airborne, and UPS:**
  The University of Texas
  MD Anderson Cancer Center
  Department of Gastrointestinal Medical Oncology
  1515 Holcombe Blvd, Unit 426
  Houston, Texas 77030

Clinical Research Support Center at MD Anderson

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

- **Mailing address for all U.S. Mail excluding express mail**:
  The University of Texas
  MD Anderson Cancer Center
  Clinical Research Support Center, Unit 1635P.O. Box 301407
  7007 Bertner Avenue
  Houston, Texas 77230-1407

- **Mailing address for Federal Express, Airborne, and UPS:**
  The University of Texas
  MDAnderson Cancer Center
  Clinical Research Support Center
  7007 Bertner, Suite 12.2152
  Houston, Texas 77030
- **Email:** **MultiCenterSupport@mdanderson.org**
  Facsimile: 713-563-5468

3.2 Hours of Operation

The staff at both the Department of Gastrointestinal Medical Oncology and Clinical research Support Center (Coordinating Center) at MD Anderson are available between the hours of 8:00 a.m. and 5:00 p.m. Central Standard Time, Monday through Friday, excluding holidays. On designated University of Texas 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.

4.0 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each participating institution has the appropriate assurance on file with the Office of Human

Research Protection (OHRP). Additionally, 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 M.D. Anderson 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

- Federal Wide Assurance
- 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
- FDA 1572
- Current Medical License (Participating PI and co-investigators)
- Curriculum Vitae
- Delegation of Authority Log
- Application Access Authorization Request Form (AAAR Form)

4.5 Participating Institution Site Initiation

Before an institution begins participating in a MD Anderson 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

Annual IRB review 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.

MD Anderson 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 MD Anderson 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 MD Anderson 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 MD Anderson 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 MD Anderson.
2) The study participants give their authorization to MD Anderson 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 Department of Gastrointestinal Medical Oncology at MD Anderson 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: 713-745-3662
Phone: 713-794-4869
Email: 2014-0524@mdanderson.org

Registration hours are 8:00 a.m. to 5:00 p.m. Central 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 should be encrypted or password protected.

- 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 MD Anderson 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 MD Anderson must be identified with:

1. MD Anderson protocol number
2. Assigned multicenter protocol participant ID number
3. Participant initials

All participants must be registered in the Clinical Oncology Research (CORe) system at MD Anderson 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 Department of Gastrointestinal Medical Oncology via EDMS or other systems as agreed. Case Report Form/s (CRF), will be used for data collection for this protocolThe schedule for data submission (CRF) and submission of source documents into the EDMS or other systems 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 2014-0524 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	Baseline	On or before registration date.

		includes prior treatment history (medical/surgical/ and other treatments such us chemotherapy, radiotherapy), pathology report, and laboratory report (to include tumor markers).		
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 every 3 cycles). *Continue to submit report until **first***	Treatment Phase	Within 14 days after event date.

		Progressive Disease (PD) event.		
8. End of Treatment Summary Data	End of Treatment Form, Physical Exam Form, Vital 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.	N/A	Off-treatment Phase	Within 14 days after the end of treatment date.
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 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 EDMS or other systems 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 Chair 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.

5.0 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. To order study supplied drugs contact:

Ralph F. Petruzzi
Contractor - US Medical Affairs IIT Management
Celgene Corporation
86 Morris Avenue
L2-804E
Summit, NJ 07901
(908) 219-0978 (O)
(908) 673-2779 (F)
rpetruzzi@celgene.com

6.0 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 <u>Participating Institution</u>

The MD Anderson 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 MD Anderson 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).

Life- threatening toxicities should be reported immediately to the Protocol PI and MD Anderson IRB.

6.3 Reporting Serious Adverse Events

The MD Anderson Department of Gastrointestinal Medical Oncology will report SAEs in accordance with MD Anderson 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 in accordance with the study agreement.
- Any adverse event falling under the definition of serious will be reported immediately to the Protocol PI who, in turn, must notify MD Anderson IRB per IRB policy.

- 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 per MD Anderson policy for reporting serious adverse events.
- The initial SAE report from the participating institution will be forwarded to the Protocol PI or his designee for review and signature.
- The MD Anderson 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.

Multicenter SAE forms are to be submitted via EDMS:

Clinical Research Support Center Multicenter Support
EDMS: https://iview.mdanderson.org
E-mail: multicentersupport@mdanderson.org

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)

MDACC 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 MD Anderson 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

7.0 PROTOCOL VIOLATIONS, 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 MD Anderson is the lead institution and the Protocol PI must adhere to those policies set by the MD Anderson IRB, the definitions for protocol violation and deviation as described by the MD Anderson IRB will be applied for reporting purposes for all institutions participating in the MD Anderson Multicenter Project.

7.1 Definitions

Protocol Deviation: 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 be considered a violation.

Protocol Violation: Changes to protocol procedures without prior approval of the IRB/Sponsor. These changes may have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data, and may cause an unanticipated problem to the subject or others. Violations may significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity and adversely affect patient's safety and rights.

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 described in IRB policy

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): An incident, experience or outcome, that is unexpected, related or possibly related to participation in the research and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized. These incidents do not meet the definition of an adverse event. Unanticipated problems are not limited to study participants, and may also include others such as family members and research staff.

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 violation**s**/deviations/UAPs are promptly reported to the IRB per MD Anderson institutional guidelines.

Participating Institutions: Protocol violations/deviations/UAPs occurring at a participating institution will be promptly reported to the coordinating center at MD Anderson 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 violation/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 violation/deviation report from the participating institution, the Coordinating Center will submit the report to the Protocol PI for review before the submission to the MD Anderson IRB.

8.0 QUALITY ASSURANCE

The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. MD Anderson 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 EDMS or other systems 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.

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 and/or MD Anderson IRB for further decision regarding the participating institution's study participation.

8.3 On-Site Audit

As part of the quality assurance process, the Clinical Research Support Center (CRSC) is authorized by the M.D. Anderson IRB to conduct on-site audits/inspections on multicenter human subject research projects for which MD Anderson is the lead institution.

The CRSC auditing staff will notify the IRB 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 IRB.

9.0 EVALUATION OF PARTICIPATING INSTITUTION PERFORMANCE

The MD Anderson 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 and/or the MD Anderson IRB.