Protocol #: PCRT 12-001

A PHASE IB/II PILOT TRIAL OF NAB-PACLITAXEL PLUS CISPLATIN PLUS GEMCITABINE (NABPLAGEM) IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA

IND Exempt

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SOURCE OF SUPPORT

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VERSION DATE

Original Version (February 8, 2013)

INVESTIGATOR'S PROTOCOL AGREEMENT

Protocol No.: **PCRT 12-001**

Study Title: A Phase Ib/II Pilot Trial of Nab-Paclitaxel plus Cisplatin plus Gemcitabine (NaBPlaGem) in Patients with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma

Version Date: Original Version (February 8, 2013)

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the study specified herein. In particular, I/we have agreed to:

- abide by all obligations stated on Form FDA 1572 and on other document(s) required by local regulatory authority.
- retain records and documents related to this trial for at least 7 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational products.
- comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- maintain confidentiality and assure security of PCRT confidential documents.
- obtain Institutional Review Board (IRB) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events and periodically report the status of the study to them.
- not implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the subjects or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- assure that each patient enrolled into the trial has read, understands, and has signed the Informed Consent.
- ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol.
- make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning of the death and 2 business days of learning of the SAE) to PCRT/TD2.
- assure access by PCRT/TD2 monitors, and/or FDA to original source documents.
- prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- cooperate fully with any study-related GCP audit as performed by PCRT/TD2 quality assurance group specified by the sponsor.
- abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

Investigator's Printed Name: _____

Investigator's Signature: _____ Date: _____

SAE REPORTING

All SAEs must be reported promptly to PCRT/TD2 after the Investigator recognizes/classifies the event as a SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE **within 1 business day** of becoming aware of the event, preferably by fax or alternatively by phone or email.

SAE Reporting:

Phone: 602-358-8385 (M-F, 8 am-5 pm PST)

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1 BACKGROUND

Pancreatic cancer continues to be a highly lethal disease with an overall 5 year survival of only 6%. Since 2004, the incidence of pancreatic cancer has been increasing by 1.5% per year and it is estimated that there will be 43,920 new cases diagnosed in the United States in 2012, with 37,390 expected deaths. Pancreatic cancer is the fourth most common cause of cancer-related deaths in both men and women, and the incidence is about equal in both sexes (ACS 2012). Of all types of pancreatic cancers, pancreatic ductal adenocarcinoma (PDA) is by far the most common, representing 80% of cases (Dragovich 2012).

Due to lack of adequate screening techniques, greater than 80% of patients at the time of diagnosis present with unresectable, advanced disease. Standard treatment options for inoperable patients with locally advanced and metastatic PDA have been quite limited. Gemcitabine monotherapy, approved by the FDA in 1996, demonstrated a median survival of 5.7 months (Burris 1997), and has been the mainstay in treating patients with PDA. The first combination regimen to demonstrate any survival benefit compared with gemcitabine alone was gemcitabine plus erlotinib, with median survival of 6.24 months versus 5.91 months for single agent gemcitabine (Moore 2007).

A meta-analysis of randomized trials by Heinemann and colleagues showed that patients with advanced pancreatic cancer and a good performance status may benefit from combination chemotherapy with gemcitabine plus a platinum agent or a fluoropyrimidine (Heinemann 2008). Multiple combination regimens are being utilized.

Recently, the regimen of 5-fluorouracil/leucovorin/irinotecan/oxaliplatin (FOLFIRINOX) compared with gemcitabine demonstrated improvement in both progression-free survival (6.4 vs. 3.3 months) and overall survival (11.1 vs. 6.8 months) for patients with a good performance status. FOLFIRINOX, however, is associated with substantial grade 3 and 4 toxicities, including diarrhea, nausea, vomiting, fatigue, neutropenia and febrile neutropenia, and cannot be given to patients >76 years of age or in some cases patients with head of the pancreas tumors (Conroy 2011, Assaf 2011).

Current treatment regimens for advanced PDA although offering modest improvements in progression-free survival (PFS) and overall survival (OS), are clearly inadequate in achieving long term survival in these patients. Additional treatment strategies are desperately needed.

Von Hoff and colleagues recently presented data supporting the use of nab-paclitaxel and gemcitabine in a phase I/II trial in patients with previously untreated advanced PDA. All patients at the recommended phase II dose (n=44) had a decrease in CA 19-9. This regimen also demonstrated an objective response rate of 48% with median survival of 12.2 months and 48% 1-year survival and 25% 2-year survival. It is speculated that reducing the dense tumor stroma, using an albumin-coated nanoparticle (nab-paclitaxel) homing to the protein SPARC (secreted protein acidic and rich in cysteine), may allow the chemotherapy to reach the tumor tissue more efficiently (Von Hoff 2011). An international phase III trial comparing this combination to gemcitabine single agent has completed accrual and results demonstrated a statistically significant improvement in overall survival for advanced pancreatic cancer patients using the gemcitabine and nab-paclitaxel over gemcitabine alone (see Appendix G).

Building on the design and mechanisms of action of the nab-paclitaxel and gemcitabine combination, this protocol introduces a third cytotoxic agent, cisplatin, to be added to this dublet. The rationale for adding cisplatin to nab-paclitaxel and gemcitabine is that in a study of 1,029 patients whose pancreatic cancer tumors were sent for molecular profiling, 57% of these tumors were negative for ERCC1, indicating sensitivity to a platinum anti-tumor agent (Von Hoff 2012. In addition to the above, in our whole genome/transcriptome sequencing analysis, we found that abnormal repair pathways were a feature of all of the pancreatic cancers that were sequenced (Liang 2012). Cisplatin prevents cellular DNA repair by binding to and causing crosslinking of

DNA, triggering apoptosis. Cisplatin has been used in other combination regimens to treat patients with PDA. For example, the cisplatin, epirubicin, 5-fluorouracil and gemcitabine (PEFG) regimen had an acceptable toxicity profile and was associated with a 24% partial response rate, 5 month progression-free survival (PFS) and 8.3 month overall survival as second line therapy (Reni 2008).

There are no documented reports of the combination of cisplatin with nab-paclitaxel and gemcitabine in the treatment of any human cancer. However, cisplatin has been combined with paclitaxel and gemcitabine in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) patients and has shown substantial antitumor activity with an acceptable safety profile. In this phase I-II study of 65 patients with advanced NSCLC, the overall response rate was 57% (Frasci 1999).

1.1 Potential Risks of nab-Paclitaxel

The most common toxicities reported for nab-paclitaxel include myelosuppression, predominantly neutropenia, infections (24%), dyspnea (12%), peripheral neuropathy and nausea and vomiting, myalgias and arthralgias, mucositis, alopecia, transaminitis, serum creatinine elevation. Other reported infrequent toxicities include; allergic reaction, loss of appetite, diarrhea, constipation, cough, edema, fever, pruritis, hypotension, nail changes, vision changes, rash, pulmonary edema, irregular heartbeat (see Appendix E).

1.2 Potential risks of 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 (see Appendix E).

1.3 Potential Risks of 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 (see Appendix E).

1.4 Potential risks of nab-Paclitaxel plus Gemcitabine

The safety of nab-paclitaxel plus gemcitabine was initially reported by Von Hoff and colleagues (Von Hoff 2011). The most common toxicities seen at the recommended phase 2 dose were anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, alopecia, sensory neuropathy and nausea (Von Hoff 2011).

1.5 Potential risks of nab-Paclitaxel, plus Cisplatin, plus Gemcitabine

The combination of nab-paclitaxel, cisplatin, and gemcitabine has not been reported. However, a similar combination of paclitaxel, cisplatin, and gemcitabine given on days 1 and 8 every 21 days studied by Frasci, et al, (see section 1.0), showed anticipated toxicities to include myelosuppression, neutropenia, neuropathy, nephrotoxicity diarrhea, vomiting, fatigue, musculoskeletal pain and rhinorrhagia. In that study, grade 2 neurotoxicity was seen in 8 patients (10.6%), grade 3 sensory and motor neuropathy was seen in one patient (1.3%). Mild or moderate nephrotoxicity occurred in a total of 7 patients (9.3%) (Frasci 1999).

1.6 Study and Dose Rationale

This is a phase Ib/II open-label, pilot study evaluating the preliminary efficacy and safety of nab-paclitaxel 125mg/m^2, cisplatin 25 mg/m^2 or 50 mg/m^2, and gemcitabine 1000 mg/m^2, all administered intravenously (IV) on Days 1 and 8 every 21 days until development of toxicity that is unacceptable in the opinion of the patient or the Investigator or upon disease progression. The doses of the nab-paclitaxel and gemcitabine are taken from the phase I/II trial (Von Hoff 2011). The dose of cisplatin will be 25mg/m^2 for the first 3 patients to assess tolerability of the combination. If the first 3 patients treated at the 25mg/m^2 dose tolerate well without any grade 3 toxicities during the first cycle, (excluding hematologic and sub-optimally treated nausea, vomiting and diarrhea), then the dose of cisplatin will be escalated to 50mg/m^2 for the remainder of the patients treated. However, if the above stated toxicities are noted in 1 of 3 patients treated at 25mg/m^2 dose level during the first cycle, then up to an additional 3 patients will be added to this cohort. If ≥ 2 of 6 patients experience the above stated toxicities during the first cycle, then the study will be terminated.

If the first 3 patients treated at the 50mg/m^2 dose tolerate well without any grade 3 toxicities during the first cycle, (excluding hematologic and sub-optimally treated nausea, vomiting and diarrhea), then the dose of cisplatin will be continued at 50mg/m^2 for the remainder of the patients treated. However, if the above stated toxicities are noted in 1 of 3 patients treated at the 50mg/m^2 dose level during the first cycle, then an additional 3 patients will be added to this cohort. If ≥ 2 of 6 patients experience the above stated toxicities during the first cycle, then an intermediary dose will be considered by the Principal Investigator. The dosing schedule of the 3 drug combination is taken from the aforementioned lung cancer study (Liang 2012).

1.7 Sequence of Drug Administration and Rationale

The sequence of drug administration is nab-paclitaxel, then cisplatin, then gemcitabine. Nab-paclitaxel is given first, targets SPARC (secreted protein acidic and rich in cysteine) in tumor cells and may be taken up by the process of macropinocytosis. Then after adequate hydration (see Section 4.1), the cisplatin is given. Gemcitabine is given last because nab-paclitaxel decreases cytidine deaminase which potentiates gemcitabine activity (less degradation of gemcitabine by the enzyme).

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the efficacy of nab-paclitaxel plus cisplatin plus gemcitabine for patients with metastatic PDA.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety of cisplatin plus nab-paclitaxel plus gemcitabine

2.3 Overview

This is a phase Ib/II open-label pilot study evaluating the preliminary efficacy and safety of nab-paclitaxel cisplatin, and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma.

An individual cycle of therapy will be defined as Days 1 and 8 every 21 days. Multiple cycles may be administered until the patient is withdrawn from therapy.

Overall response rates as well as individual categories of response (CR, PR, SD, and PD) will be determined using RECIST 1.1 (Frese 2012). Time-to-event endpoints, including PFS and OS will be assessed using the Kaplan-Meier method (Kaplan 1958). Evaluation of stable disease at 9 weeks will also be assessed. Toxicity (adverse events) will be recorded using the NCI CTCAE, version 4.0 (published 28 May 2009) (see Appendix D).

2.4 Primary Endpoints

- To evaluate the complete response rate as defined by CT scan using RECIST 1.1 criteria and CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9) down to normal limits (from at least > 2X ULN). We expect to accomplish this in ≥ 5% of patients. When a CR is documented, a confirmatory PET scan will be obtained.
- If 1 or more of 10 patients demonstrate a complete response, will continue to enroll to a total of 25 patients.
- If intolerable adverse events or no clinical benefit are noted in the first 6 patients, will discontinue study enrollment.

2.5 Secondary Endpoints

- To evaluate the disease control rate (CR, PR and SD at 9 weeks) in patients with metastatic PDA.
- To evaluate the treatment-related toxicities in this patient population.
- To evaluate the change in CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9) in this patient population.

3 STUDY POPULATION

3.1 Patient Selection and Study Duration

Up to 25 patients will be recruited from up to 5 study centers in the United States. The expected duration of this study is 24 months. Enrollment into the screening or treatment phase of the study will be stopped when the anticipated or actual patient numbers have been achieved across all study sites.

3.2 Inclusion Criteria

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

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma.
3. Capable of providing informed consent and complying with trial procedures.
4. Karnofsky Performance Status (KPS) of ≥ 70%.
5. Life expectancy ≥ 12 weeks.
6. Measurable tumor lesions according to RECIST 1.1 criteria.
7. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating. Both male and female patients of reproductive potential must agree to use a reliable method of birth control during the study.

3.3 Exclusion Criteria

Patients meeting the following criteria will not be enrolled:

1. Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatments in the adjuvant setting with gemcitabine and/or 5-FU or gemcitabine administered as a radiation sensitizer are allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present.
2. Palliative surgery and/or radiation treatment less than 4 weeks prior to initiation of study treatment.
3. Exposure to any investigational agent within 4 weeks prior to initiation of study treatment.
4. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit).
5. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥5 years.
6. Laboratory values: Screening serum creatinine > upper limit of normal (ULN); total bilirubin > (ULN); alanine aminotransferase (ALT) and AST ≥ 2.5 ULN or ≥ 5.0×ULN if liver metastases are present; absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <27% for females or <30% for males, or coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5×ULN unless on therapeutic doses of warfarin.

7. Current, serious, clinically significant cardiac arrhythmias as determined by the investigator.
8. History of HIV infection.
9. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
10. Major surgery within 4 weeks prior to initiation of study treatment.
11. Any condition that might interfere with the patient's participation in the study or in the evaluation of the study results.
12. Any condition that is unstable and could jeopardize the patient's participation in the study.

3.4 Patient Enrollment

This is an open-label study. A patient ID number will be assigned by the site when the patient signs the Informed Consent Form. A copy of the signed informed consent will be required for study entry.

The exact date and time of each administration of medications will be recorded in the case report form (CRF). Cisplatin, nab-paclitaxel and gemcitabine will be administered according to the clinical study protocol only to patients who have given written informed consent. Patients withdrawn from the study will retain their patient ID number. New patients must always be allotted a new patient ID number.

3.5 Patient Discontinuation

Patients will be discontinued from the treatment under the following circumstances:

1. Disease progression.
2. Patient's physician considers a change of therapy would be in the best interest of the patient.
3. Patient requests discontinuation.
4. Continued unacceptable toxicities despite optimal treatment or dose reduction.
5. Patient becomes pregnant or fails to use adequate birth control (for those patients who are fertile).
6. Need for any treatment not allowed by the protocol.
7. Non-compliance.

3.6 Study Discontinuation

PCRT/TD2 has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating the study include, but are not limited to, the following:

1. Incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
2. Patient enrollment is unsatisfactory.
3. Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

4 STUDY TREATMENT

4.1 Administration and Dosing

Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's malignancy.

The names, titles, and addresses of the Investigators and study personnel who administer the study medication will be listed in the Site Contacts list for Protocol PCRT 12-001 and will be available from PCRT/TD2 or its representative.

The solution for infusion will be prepared at each investigational site. Detailed guidelines for the preparation and administration of nab-paclitaxel, cisplatin and gemcitabine are provided in Appendix E. The order of infusion with premedication is as follows:

- 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) 0.25mg IV, Emend (fosaprepitant) 150 mg IV and dexamethasone 20mg 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 ondansetron 8mg bid and dexamethasone 4mg bid for 2 days after chemotherapy.
- Nab-paclitaxel 125mg/m^2 over 30 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
- Cisplatin 25mg/m^2 or 50mg/m^2 (see section 1.6), in 500 mL of NS over 60 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
- Gemcitabine 1000mg/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.

In the event of extravasation during the infusion of nab-paclitaxel, cisplatin and gemcitabine, the infusion should be immediately terminated and patients treated according to local site protocols. The infusion should then be restarted in another vein.

4.2 Body Surface Area Calculation

The calculation of the dose of cisplatin, gemcitabine, and nab-paclitaxel will be based on the patient's body surface area (BSA) using the Mosteller formula (Verbraeken 2006). The BSA will be calculated before each cycle, based on the actual height and weight of the patient. If there has been a > 10% weight change from Cycle 1 Day 1, the calculated dose will be adjusted downward to the nearest whole milligram.

4.3 Dose Modification for Toxicity

Toxicities will be graded using the NCI CTCAE v4.0 (see Appendix D). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment may be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

Doses of nab-paclitaxel and gemcitabine may be reduced in individual patients in accordance with the schedule in Table 1. In general, doses that have been reduced for toxicity will not be escalated back to the starting level. 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 1. Dose Reduction Schema

Dose Level	nab-Paclitaxel (mg/m2)	Cisplatin Dose 1	Gemcitabine (mg/m2)
Level - 0 (baseline)	125mg/m2	No change	1000mg/m2
Level -1	100mg/m2	No change	800mg/m2
Level -2	75mg/m2	No change	600mg/m2

4.3.1 Hematological 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 in Table 2 and Table 3.

Dose Modifications at Day 1

Table 2. Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1.5 x 10^9/L	And	≥ 100 x 10^9/L	Treat on time
< 1.5 x 10^9/L	Or	< 100 x 10^9/L	Delay by 1 week intervals until recovery

Dose Adjustments within a Treatment Cycle

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. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 3.

Table 3. Dose Modification for Day 8 of Each Cycle (Hematologic Toxicity)*

Day 8 Laboratory Results	Day 8 Nab-paclitaxel	Day 8 Cisplatin	Day 8 Gemcitabine
ANC > 1000 and Platelets ≥ 75,000	100%	100%	100%
ANC 500-1000[a] or Platelets 50,000-74,999	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/m2) and do not re-escalate throughout the rest of treatment	Hold	Decrease 2 dose levels (to 600 mg/m2) and do not re-escalate throughout the rest of treatment.

* see Table 1 for dose reduction schedule

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

[b] Febrile patients (regardless of neutrophil count) 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. Febrile neutropenic 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 baseline levels before resuming chemotherapy treatment.

4.3.2 Non-hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken in accordance with Table 4. Cisplatin is addressed in sections 4.3.2.1, 4.3.2.2, and 4.3.2.7.

Table 4. Nab-paclitaxel and gemcitabine Dose Modifications for Day 1 of Each Cycle (Non-hematologic Toxicity)*

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	***nab*-paclitaxel + gemcitabine dose this cycle**
Grade 0, 1 or 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: please refer to Section 4.3.2.3**)**
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

* Excluding peripheral neuropathy (section 4.3.2.1) and nephrotoxicity (section 4.3.2.2).

[a] If the toxicity only affects neuropathy, then only *nab*-paclitaxel should be reduced (please see Section 4.3.2.1).

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.5).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

Table 5. *Nab*-paclitaxel and gemcitabine Dose Modifications Day 8 Each Cycle (Non-hematological Toxicity)

CTC Grade	Percent 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: please refer to Section 4.3.2.3.
[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.5).
[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

4.3.2.1 Peripheral 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 1. 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 ≤ 1 should be the adverse event duration used for adverse event reporting.

4.3.2.2 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics (see Appendix E). 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 serum creatinine is WNL and BUN is < 25 mg/dL.

4.3.2.3 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 1. 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.

4.3.2.4 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 1. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

4.3.2.5 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.

4.3.2.6 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 (Meadors 2006) 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%.

Paclitaxel monotherapy is weakly associated with lung toxicity (Rowinsky 1995). Dyspnea with bronchospasm has been reported in 0.3 to 0.9%, with 30% of type 1 hypersensitivity reactions. Combination chemotherapy of gemcitabine and paclitaxel shows a higher incidence of this complication compared to either drug alone.

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.

4.3.2.7 Hypersensitivity Reactions

Hypersensitivity reactions are not usually expected with cisplatin, *nab*-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, 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 the offending agent and aggressive symptomatic therapy. Patients who develop a severe hypersensitivity reaction should not be re-challenged.

4.3.2.8 Colony Stimulating Factors

Based on the ASCO guidelines (Smith 2006) for use of granulocyte colony stimulating factors, (G-CSF) for regimens with at least a 20% risk of febrile neutropenia, pegfilgrastim will be administered subcutaneously on day 9 of each treatment cycle. G-CSF may also be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC < 500 cells/μL (see Appendix E). Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

4.3.2.9 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 (Augmentin®, 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, please refer to Section 7.7 of this protocol to report the event as a Serious Adverse Event (SAE).

4.4 Intended Dose Delays

Intended cycles may be delayed for non-toxicity reasons for up to 7 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF.

4.5 Concomitant Therapy

Necessary supportive measures for optimal medical care may be given throughout the study, including IV antibiotics to treat infections, blood components, and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the appropriate CRF.

Radiotherapy is not allowed while the patient is enrolled in this study.

Routine **prophylactic use** of a colony-stimulating factor (G-CSF) should be used according to the American Society of Clinical Oncology guidelines (Appendix F).

Erythropoietin is permitted if clinically indicated.

4.6 Concomitant Therapies Requiring Caution

Cisplatin nephrotoxicity may be exacerbated by treatment with other nephrotoxic drugs (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs). Caution with use of other nephrotoxic drugs.

If anticoagulation with warfarin is necessary, frequent monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended.

5 STUDY ASSESSMENTS

5.1 Laboratory Assessments

All hematology, blood chemistries, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local laboratory for each investigational site.

Prior to study enrollment, each patient will have the following assessments (see Appendix A).

5.2 Screening (Within 21 Days Prior to First Dose)

1. Written informed consent and Medical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix D), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy)
2. Complete physical examination including height (cm) and weight (kg)
3. Karnofsky Performance Status (KPS) (see Appendix B).
4. Vital signs (blood pressure, pulse, respiratory rate, and temperature)
5. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only.). If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 5 days prior to starting chemotherapy (see RECIST 1.1 criteria in Section 6)
6. Electrocardiogram (ECG)
7. Complete blood count (CBC) with differential and platelet count
8. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
9. CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
10. Urinalysis (lab): protein, specific gravity, glucose, and blood
11. Serum pregnancy test (if applicable)
12. Concomitant medication notation (to include all medications taken within 30 days prior to study enrollment)

Once eligibility is confirmed, site personnel should assign a patient ID number.

5.3 On-Study Assessments

Patients must begin Cycle 1 within 21 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 72 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 24 hours (except those noted), or if medical or scheduling conditions require a delay.

The analysis of CGH (comparative genomic hybridization) from archived paraffin blocks will be used to look for gene aberrations. This will be optional.

Day 1 of each cycle (except where noted)

- Inclusion/exclusion review (Cycle 1 only)
- Directed physical exam
- Vital Signs (see Section 5.2)
- Measurement of weight (kg) and BSA calculation prior to dosing (After Cycle 1, the BSA only needs to be changed if there has been a change >10% in body weight from Cycle 1-Day 1 (See Section 4.2)).
- Karnofsky Performance Status (KPS) (see Appendix B)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Urinalysis (see Section 5.2)
- Serum Pregnancy
- AEs using the NCI CTCAE (see Appendix D)
- Concomitant medication notation

Day 8 of each cycle

- Directed physical exam
- Vital Signs (see Section 5.2)
- Measurement of weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- AEs using the NCI CTCAE (see Appendix D)

Concomitant medication notation*Day 15 of each cycle*

- Directed physical exam
- Vital Signs (see Section 5.2)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- AEs using the NCI CTCAE (see Appendix D)
- 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. When a CR is documented, a confirmatory ^{18}F-FDG PET scan will be obtained.

5.4 End of Treatment

When the patient completes all cycles of study medication, or withdraws from treatment prior to completing all cycles, the following assessments will be performed 14-28 (+/- 2) days after completing the last dose of study medication:

- Directed physical exam, if deemed necessary
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (see Section 5.2)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Urinalysis (see Section 5.2)
- Concomitant medication notation
- CT/MRI scan to evaluate disease status (using same imaging method as Baseline)
- AEs using the NCI CTCAE Version 4.0 (see Appendix D)

5.5 Follow-Up Assessments after End of Study or Early Termination

Follow-up assessments by telephone will be conducted for all patients or their families every 12 weeks to determine the date of death.

5.6 Statistical Considerations

The sample size of this pilot study will be up to 25 patients. This is based on a test of a null hypothesis of a 5% complete response or less, versus an alternative hypothesis of a 25% complete response rate or greater. We will treat an initial cohort of 10 patients, and if there are no complete responders the trial will be closed. One or more complete responders in 10 will be required in order to proceed to the total enrollment of 25 patients. Four or more complete responders out of 25 patients will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. This design has a power of 87% at a one-sided Type I error rate of 3%.

Time-to-event endpoints, including PFS and OS will be assessed using the Kaplan-Meier method (Kaplan 1958).

Objective response rates, clinical benefit response, and CA 19-9, will be summarized descriptively.

5.7 Treatment Assignment

This is a phase 1b/2 open-label pilot trial, with the identity of the treatment known to the patients, Investigators, and Sponsor.

5.8 Patient Disposition

A detailed description of patient disposition will include:

- A summary of data on patient discontinuation from treatment.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol deviations.

All patients enrolled in the study will be included in the summation. An evaluable patient is any patient who has received even one dose of drug. The number of patients who do not qualify for analysis, who die or discontinue before treatment begins, will be specified.

5.9 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate.

5.10 Efficacy Analysis

The efficacy analysis will include the following parameters: objective response rate (CR + PR), disease control rate (CR + PR + SD at 9 weeks), progression-free survival (PFS), stable disease rate at 9 weeks (SD), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of cisplatin, nab-paclitaxel and gemcitabine and have at least one post baseline tumor assessment.

Objective responses will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD), will be estimated by the percentage of patients achieving these criteria. The disease control rate will consist of the sum of CR + PR + SD for 9 weeks. When a CR is documented, a confirmatory PET scan will be obtained.

Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed.

Overall survival will be measured from the date of registration (i.e. assignment of patient number) to the date of death due to any cause, or the date of last contact (censored observations).

5.11 Safety Analysis

All patients who receive any amount of cisplatin, nab-paclitaxel and gemcitabine will be included in the safety analyses, which will include the following:

- The incidence, severity, duration, causality, seriousness, and type of AEs and changes in the patient's physical examination, vital signs, and clinical laboratory results.
- In addition, deaths and other SAEs will be tabulated.
- Use of concomitant medications.

5.12 Replacement of Patients

Patients who are enrolled into the study, but fail to receive nab-paclitaxel, cisplatin, and gemcitabine may be replaced.

5.13 Quality Assurance

The study will be initiated and conducted under PCRT/TD2. CRFs will be supplied by PCRT/TD2 or its representative. Representatives of PCRT/TD2 will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCP guidelines as well as other applicable regulations and guidelines.

6 EVALUATION OF RESPONSE

6.1 Best Overall Response

Best overall response is defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for tumor progression, 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.

6.2 Overall Tumor Response

The overall tumor response rate is defined as the total proportion of patients who have an objective tumor response (CR + PR). Rates for the individual categories of response (CR, PR, SD, and PD) will also be determined.

6.3 Not Evaluable

Patients will be defined as being not evaluable for response if a radiological assessment cannot be made. These patients will be counted as treatment failures in the analysis of tumor response data.

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

6.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from enrollment (i.e. assignment of patient ID number) to first documentation of objective tumor progression or to death due to any cause in the absence of previous documentation of objective tumor progression will be censored at the last date the patient was known to be progression-free in patients who do not have objective tumor progression and who are: 1) still on study at the time of an analysis; 2) are given anti-tumor treatment other than the study treatment; or 3) are removed from study follow-up prior to documentation of objective tumor progression.

6.5 Survival

Survival is defined as the time from enrollment (i.e. assignment of patient ID number) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

6.6 Analysis Plan

Continuous variables will be summarized using the mean (SD) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics on response and toxicity rates. The distribution of time-to-event endpoints (e.g. response duration, progression-free survival, overall survival) will be estimated using the Kaplan and Meier method. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

6.7 Guidelines for Measuring Disease

Antitumor activity will be evaluated by RECIST 1.1 criteria (Eisenhauer 2009). These response criteria are widely recognized and accepted as the standard criteria for determining response in patients with solid tumors.

6.8 Disease Definitions

Measurable disease is defined as the presence of ≥1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

At Baseline, tumor lesions will be categorized as:

Measurable Lesions: lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

Malignant lymph nodes: to be considered pathologically enlarged and measureable, 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). At Baseline and follow-up, only the *short* axis will be measured and followed.

or

Non-measurable Lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines in the Study Manual.

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 beginning of 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.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is to be done.

6.9 Methods of Measurement

Tumor measurements should be performed using the same method as well as the same staff member per patient, if possible, throughout the study. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of ≤5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen, and pelvis.

As a rule, the minimum size of the lesion should be no less than double the slice thickness.

Lesions on chest x-rays are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary.

Tumor markers *alone* cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors) if required by protocol.

6.10 Baseline Documentation of “Target” and “Non-target” Lesions

Target Lesions: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]), be representative of all involved organs, and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum of the LD will be used as reference to further characterize the objective tumor response.

Non-target Lesions: all other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and will also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.11 Response Criteria

Table 6. RECIST Target Lesion Response Criteria

Target Response Criteria	Definition
Complete Response (CR)	The disappearance of all target lesions and no new sites or disease-related symptoms confirmed at least 4 weeks after initial documentation. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. All sites must be assessed, including non-measurable sites, such as effusions, or markers.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference the baseline sum of the diameters confirmed at least 4 weeks after initial documentation. PR is also recorded when all measurable disease has completely disappeared, but a non-measurable component (i.e., ascites) is still present but not progressing.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters recorded since on study (this includes the baseline sum if that is the smallest on study), which must also demonstrate an absolute increase of at least 5 mm; or the appearance of one or more new lesions;

Non-target lesion response will be classified according to the RECIST Non-Target Lesion Response Criteria in the following table.

Table 7. RECIST Non-target Lesion Response Criteria

Non-Target Response Criteria	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level confirmed at least 4 weeks after initial documentation. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD)	Persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more non-target lesions and/or unequivocal progression of existing non-target lesions (“unequivocal progression” is defined as an overall level of substantial worsening in non-target disease that is of magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy).

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 PD the smallest measurements recorded since the treatment started). In general, the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be classified as having “symptomatic deterioration.” Every effort will be made to document the objective evidence of disease 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) to confirm the complete response status.

Table 8. RECIST Overall Response Criteria

Target Response	Non-Target Response	New Lesions	Overall Response
CR	CR	No	CR
CR	non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE = inevaluable

6.12 Duration of Overall Response

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

6.13 Duration of Stable Disease

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

For the purposes of this trial, the minimal time interval required between 2 measurements for determination of SD is 6 weeks (at least 2 consecutive assessments 6 weeks apart revealing SD). This time interval takes into account the expected clinical benefit that such a status may bring to the population under study.

7 SAFETY

The investigator is responsible for monitoring the safety of patients who have enrolled in the study. All adverse events (AEs) occurring after any administration of the study medication will be followed until the event resolves, until the patient begins alternative treatment, or until the end of the study. Investigators will grade AEs using the NCI CTCAE, version 4.0 (published 28 May 2009) (see Appendix D).

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first dose of study medication and including the protocol-defined post-treatment follow-up period (21 CFR §312.64[b]) on designated CRF pages. AEs occurring following the signature of the informed consent, but prior to the first dose of study drug, will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to PCRT/TD2 or its representative within 24 hours of knowledge of their occurrence.

7.1 Adverse Events

An AE is any unfavorable medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the CRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs.

Patients should be instructed to report any AE that they experience to the Investigator, starting from the time of their first dose. Investigators should assess AEs at each visit. AEs occurring during the clinical trial, starting at the time of the initial study drug infusion, and the follow-up period should be recorded on the appropriate AE page of the CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

7.2 Serious Adverse Events

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Life-threatening is defined as an event with immediate risk of death from the event as it occurred. It does not include an event that might have caused death if it occurred with a greater severity.
- In-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- 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 listed outcomes above.

7.3 Adverse Event Severity

AE will be graded according to the NCI CTCAE, Version 4.0 (see Appendix D)

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

7.4 Causality Assessment

The relationship of an AE to the study drug must be classified as one of the following:

- **Unrelated:** The AE is clearly not related to the study medication
- **Possibly Related:** The AE may be related to the study medication
- **Definitely Related:** The AE is clearly related to the study medication

7.5 Safety and Tolerance Analysis

The incidence of all AEs (regardless of causality) and all treatment-related AEs (those AEs thought to be possibly, probably, or definitely related to study drug) will be summarized by NCI CTCAE Version 4.0 term and maximum grade. The incidence of SAEs and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented. Narratives will be provided for patients who experience an SAE.

7.5.1 Laboratory Assessments

7.5.1.1 Hematology Parameters

To investigate the maximal degree of myelosuppression, the NCI CTCAE Version 4.0 grade for WBC, ANC, platelet count, and hemoglobin concentration will be summarized by the most severe grade in the first treatment cycle and by the most severe grade during the therapy for each treatment group; testing of treatment group differences will be performed using a CMH test. The incidence of patients with NCI CTCAE Version 4.0 hematology values of Grade 3 or 4 that occurred after the first dose of study drug will be presented. Data for patients with Grade 3 or 4 hematology values will be listed.

7.5.1.2 Clinical Chemistry

Liver and renal function will be summarized using the NCI CTCAE Version 4.0 for alkaline phosphatase, ALT, AST, total bilirubin, BUN and creatinine. The number and percentage of patients who have more than one NCI CTCAE Version 4.0 grade will be summarized using the most severe Grade for the first cycle of therapy and for anytime during therapy for each treatment group; testing of treatment group differences will be performed using a Cochran-Mantel-Hanzel test. The incidence of patients with NCI CTCAE Version 4.0 chemistry values of Grade 3 or 4 that occurred after the first dose of study drug will be presented. Data for patients with Grade 3 or 4 chemistry values will be listed.

7.5.1.3 Peripheral Neuropathy

Peripheral neuropathy events will be captured according to protocol and reported by Investigators and investigative staff in accordance with adverse event and SAE reporting standards.

7.6 Patient Reporting of AEs and SAEs

Patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between office visits. These events should be considered in the same fashion as if they had been reported at a scheduled office visit. At each scheduled office visit, after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the following standard questions

- Have you had any (other) medical problems since your last clinic visit?
- Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you in this study, since your last visit/assessment?
- Have any new procedures been performed since your last study visit?

7.7 Investigator Reporting Serious Adverse Events

The Investigator is responsible for recording, reporting and following all Grade 3 or 4 AEs, regardless of causality, observed during the study period, starting with initial dose of study drug and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later. The Investigator should follow AEs until the event is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms. The only exception to this is for an AE that occurs prior to the first dose of study drug but is due to a procedure associated with assessments carried out to determine eligibility or to permit participation in this protocol – this should be recorded as an AE (rather than a pre-treatment sign or symptom).

The Investigator or designee must completely and promptly record each AE in the source documentation, regardless of relationship to study drug as determined by the Investigator. Grade 3 and 4 AEs must be recorded in the CRF. **The Investigator must assess AE/SAE causality for any patients treated at his/her site and for any patients treated under the direct care of his/her sub-Investigators.** The Investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Clinically significant laboratory abnormalities present at the baseline visit will be recorded as pre-treatment signs and symptoms.

Grade 3 and 4 adverse events and SAEs should be reported on the appropriate case report forms. **In addition, all SAEs must be reported promptly to PCRT/TD2 after the Investigator recognizes/classifies the event as a SAE.** The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 24 hours/ 1 business day of becoming aware of the event, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. If an SAE is reported by phone or by e-mail, the Investigator must fax a completed SAE report form to PCRT/TD2 within 1 business days. For an event that is not life-threatening or fatal, the Investigator must fax a completed SAE report form within 2 business days after he/she recognizes/classifies the event as an SAE.

The Investigator should follow all AEs/SAEs observed during the study until they resolve or stabilize, the patient is lost to follow-up, or the events are otherwise explained.
For any additional questions regarding reporting requirements of a SAE, please contact the following individual:

SAE Coordinator: Jocelyn Harmon
13208 E. Shea Blvd, Suite 100
Scottsdale, AZ 85259
Phone: 602-358-8385
Fax: 480-452-1610
24-hour Phone: 253-568-6901
E-mail: jharmon@td2inc.com

7.7.1 Expedited Reporting by Investigator to PCRT/TD2

Serious adverse events (SAE) are defined above. The Investigator must inform PCRT/TD2 in writing of any SAE within 24 hours (for life threatening or fatal event) of being aware of the event. The date of awareness should be noted on the report. This must be documented on a PCRT/TD2 Reporting Form.
This form must be completed and supplied to PCRT/TD2 within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). 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 PCRT/TD2 Reporting Form. A final report to document resolution of the SAE is required. The Study protocol number (PCRT 12-001) and the institutional protocol number should be included on SAE reports to PCRT/TD2. A copy of the fax transmission confirmation of the SAE report (or on the fax cover letter) sent to PCRT/TD2 should be attached to the SAE and retained with the patient records.

7.7.2 IRB Notification of SAEs

The Investigator is responsible for promptly notifying the IRB of all SAEs, including any follow-up information, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from PCRT/TD2.

7.8 SAE Follow-Up

For all SAEs occurring after first dose of study medication or within 30 days of the last administration of study medication, the investigator must submit follow-up reports to PCRT/TD2 or its representative regarding the status of the SAE and the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

7.8.1 Sponsor Notification of Post-Study SAEs

The Investigator should notify PCRT/TD2 of any death or SAE occurring after a patient has withdrawn from the study, or after 30 days of the last study drug dose, whichever is later, when such death or SAE may reasonably be related to the medication used in the study. However, Investigators are not obligated to actively seek AEs in former study participants.

7.9 Pregnancy

While not considered a SAE unless a serious criterion is met, pregnancies occurring in patients enrolled on the study or in their partners must be reported. The investigator should complete the pregnancy report form and fax it to PCRT/TD2 within 24 hours of knowledge of the pregnancy.

8 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

8.1 Ethics

8.1.1 Institutional Review Board/Ethics Committee Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by PCRT/TD2prior to submission to the IRB. The Investigator will forward to PCRT/TD2 or Sponsor-nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CFR 56 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.

In addition, the Investigator will be responsible for forwarding to PCRT/TD2 or Sponsor-nominated designee a description of the IRB board members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB for informational purposes.

Clinical supplies will not be shipped to the clinical site until IRB approval is obtained for the protocol. Any existing amendments, informed consent, and photocopies of the approved documents must be received by PCRT/TD2 or other sponsor-nominated designee prior to drug shipment.

8.1.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

8.1.3 Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the Investigator in accordance with the FDA regulations set forth in 21 CFR 50 as well as the applicable regulatory bodies in all other participating countries outside the United States.

The Investigator must provide the patient with a copy of the informed consent form in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

Changes made by a participating site to the recommended informed consent must be must be forwarded to PCRT/TD2 for approval prior to submission to the corresponding IRB. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the Investigator's study records.

8.1.4 Data Safety and Monitoring

This treatment regimen combines 2 chemotherapeutic agents with known toxicity profiles, with a subsequent treatment of a combination of 3 chemotherapeutic agents with known toxicity profiles. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data reported to the sponsor will be received by the Lead Principal Investigator on a regular basis and not less than once a month. In addition, SAEs will be reported to the Sponsor immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the Lead Principal Investigator and the site Principal Investigators who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The statistical group (CRAB) will provide listings of toxicities on a regular basis.

8.2 Disclosure of Data

8.2.1 Study Data Monitoring Plan

Data monitoring procedures will be carried out by Cancer Research And Biostatistics (CRAB) for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff, drug accountability), and review of drug accountability will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the study will be provided with a copy of the written monitoring notes for resolution of the findings.

The CRAB site monitor will complete a written monitoring report and forward it to the site Principal Investigator and to the Pancreatic Cancer Research Team (PCRT) Administration. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to PCRT/TD2 Administration and the CRAB site monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's study file at Cancer Research And Biostatistics for follow-up at the next monitoring session.

8.2.2 Confidentiality

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of PCRT/TD2, and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and,
- information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.

If the study site is a 'covered site' under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by PCRT/TD2 and its designees for the purposes of regulatory submissions, study publications, and drug approval.

8.2.3 Publication

The Investigator(s) shall have the right, consistent with academic standards and with due regard to the protection of PCRT/TD2' confidential information and intellectual property, to publish or present the results of work performed in accordance with the study; provided that any proposed publication or presentation is first reviewed and approved in writing by PCRT/TD2. PCRT/TD2 shall complete its review within 60 days after receipt of the proposed publication or presentation. Upon PCRT/TD2' request, proposed publication or presentation will be delayed up to 60 additional days to enable PCRT/TD2 to secure adequate intellectual property protection of property of PCRT/TD2 that would be affected by such proposed publication or presentation. If PCRT/TD2 believes in good faith that any proposed publication or presentation contains any confidential information and/or intellectual property, PCRT/TD2 shall have the right to remove references to any such confidential information and/or intellectual property. Individual arm in this study may be published individually.

8.3 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from TD2/PCRT, in addition to written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to TD2/PCRT and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

8.4 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Cancer Research and Biostatistics may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

8.5 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the Lead Principal Investigator or PCRT/TD2, there is sufficient reasonable cause.

PCRT/TD2 has the right to discontinue the study under the conditions specified in the clinical trials agreement. Written notification documenting the reason for study termination will be provided to the site investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to PCRT/TD2.

8.6 Investigator Documentation

8.6.1 Form FDA 1572

The Investigator must provide PCRT/TD2 with a fully executed Form FDA 1572. Any updates must be provided via a new fully executed Form FDA 1572.

8.6.2 Curriculum Vitae

The Investigator must provide PCRT/TD2 with his/her current signed and dated curriculum vitae and a current signed and dated curriculum vitae for each sub-Investigator listed on Form FDA 1572. Current signed and dated curriculum vitae is defined as updated within 2 years of study start up.

8.6.3 Financial Disclosures

The Investigator and sub-Investigator(s) must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements that may be of concern to FDA per 21 CFR 54.

8.6.4 Laboratory Certification and Normal Ranges

The Investigator will indicate on the Form FDA 1572 the name and location of any local laboratories that will be used for laboratory assessments. The Investigator will provide a copy of all clinical laboratory certifications, certification numbers, dates of certifications, and a list of the normal ranges for all laboratory tests for all facilities listed. Updated versions of these documents must be provided to PCRT/TD2 as appropriate. In the event the clinical laboratory is changed during the study, PCRT/TD2 will be promptly notified, and the Form FDA 1572 will be updated. Appropriate documentation will be submitted to PCRT/TD2 to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by PCRT/TD2, and included on the Form FDA 1572.

8.7 Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location. PCRT/TD2 will inform the Investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

PCRT/TD2 reserves the right to terminate the study for refusal of the Investigator and/or investigational site to comply with any requirements stated in this study protocol.

8.8 Protocol Deviations

Deviations from the protocol must be addressed as protocol amendments with IRB approval required prior to implementation. Apart from the regulatory requirements, it is vital to the success of the study that the Investigator adheres to the details of the protocol and thus holds to a minimum the number of cases that may be later classified as “incomplete,” “unusable,” or “not evaluable.”

9 DATA MANAGEMENT

9.1 Patient Enrollment Instructions

Patients must be registered within 5 working days prior to initiation of protocol therapy. This study uses a web based patient enrollment system for data submission through the data management services of Cancer Research And Biostatistics (CRAB). Patient enrollment materials and instructions may be accessed online through the study website at www.pcrt.org (Members Only page). For questions or assistance using this site, please contact: PCRTHelp@crab.org

9.2 Data Submission Instructions

This study uses a web based electronic data capture system for data submission through the data management services of Cancer Research And Biostatistics (CRAB). All study case report forms may be accessed online through the study website at www.pcrt.org (Members Only page). This website is used to register patients and submit data using eCRFs. In addition, study resource information (SAE submission forms, protocol documents and other study guidelines) and be found on the website. For questions or assistance using this site, please contact: PCRTHelp@crab.org. The original reports, traces and films must be retained by the Investigators for future reference.

Screening Form: at time of screening

Enrollment Form: after eligibility confirmed.

All screening/baseline/treatment/off-treatment Forms: within 2 weeks of occurrence.

Adverse Event Form: within 2 weeks of each scheduled adverse events evaluation until adverse events have resolved following permanent discontinuation of treatment, documenting adverse event information, including toxicities indicated by lab testing. NOTE: all Serious Adverse Events must also be reported on the Adverse Event Form.

Serious Adverse Events (SAE) documentation: **submit directly to TD2/PCRT and the Lead Principal Investigator** within the time frame and per the guidelines specified in Section 7.7. NOTE: all SAEs must also be reported on the *Adverse Event Form.*

Notice of Death Form: within 2 weeks of knowledge of death.

10 TERMINATION OF STUDY

PCRT/TD2 reserves the right to discontinue this study at any time.

11 INVESTIGATOR'S PROTOCOL AGREEMENT

The Investigator must sign the Investigator's Protocol Agreement. The original must be kept on file at PCRT/TD2 and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued by PCRT/TD2.

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APPENDIX A SCHEDULE OF TREATMENT AND EVALUATIONS

Assessment	Screening Within 21 Days	Cycle 1			Cycle 2+			Prior to Cycles 4, 7, 10, etc.	Week 9	End of Study or Early Termination[10]	Follow-up
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15				
Signed informed consent	X										
Review inclusion/exclusion	X	X									
Medical history[1]	X	X	X	X	X	X					
Physical examination	X	X	X	X	X	X				X	
Height (cm)	X										
Weight (kg)	X	X	X		X	X				X	
BSA calculation		X			X[2]						
Vital signs	X	X	X	X	X	X				X	
Karnofsky PS	X	X	X	X	X	X				X	
CT/ MRI scan / tumor measurements[3]	X							X		X	
PET/CT[4]									X		
ECG	X										
CBC w/differential & PLTs	X	X	X	X	X	X	X			X	
Serum chemistries[6]	X	X	X	X	X	X	X			X	
CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)	X	X			X					X	
Urinalysis[6]	X	X			X					X	
Archived blocks of tumor specimen for CGH.[7]		X									
Serum/urine pregnancy	X	X			X					X	
Concomitant medications[8]	X	X	X	X	X	X	X			X	
Adverse events[9]		X	X	X	X	X	X			X	
Telephone follow-up[11]											X
TREATMENT											
Nab-pacilitaxel[12]		X	X		X	X					
Cisplatin[12]		X	X		X	X					
Gemcitabine[12]		X	X		X	X					

NOTE: All assessments must be performed within 72 hour of each specified time parameter, except Cycle 1 (see Section 5 for details).

Schedule of Events footnotes:

1. To include concurrent baseline conditions (using NCI CTCAE, version 4.0), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. BSA only needs to be changed if there has been a change >10% in body weight from Cycle 1-Day 1 (See Section 4.2).
3. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan required to exclude brain metastases). If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 5 days of starting chemotherapy. In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria in Section 7). Follow-up scans are due every 3 cycles (prior to cycle 4, 7, 10)
4. When a CR is documented, a confirmatory PET scan will be obtained.
5. To include BUN, phosphorus, magnesium, creatinine, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, and electrolytes (chloride, sodium, potassium, and bicarbonate) and CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9).
6. Lab urinalysis to include protein, specific gravity, glucose, and blood.
7. Archived paraffin block of tumor specimen, if collected, prior to treatment. Optional.
8. To include all medications taken within 30 days prior to study enrollment.
9. Patient will be followed until resolution of any drug-related AE or SAE occurring during the study, including, within 30 days of last administration of study medication, or when the patient begins alternative therapy; whichever is sooner.
10. End of Study or Early Termination assessments can be completed 14-28 (+/- 2) days from the last dose of study medication
11. Follow-up assessments by telephone will be conducted in all patients every 12 weeks to determine date of response, date of disease progression, and date of death.
12. The sequence of drug administration is nab-paclitaxel, then cisplatin, then gemcitabine.

APPENDIX B KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Status		
	Score	**Descriptions**
Able to carry on normal activity and to work; no special care needed.	100	Normal: no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activities or to do active work
	60	Requires occasional assistance, but is able to care for most of personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled: requires special care and assistance
	30	Severely disabled: hospital admission is indicated although death not imminent
	20	Very sick: hospital admission necessary; active supportive treatment needed
	10	Moribund: fatal processes are progressing rapidly
	0	Dead

APPENDIX C LIST OF ABBREVIATIONS

Term	Definition
Abraxis	Abraxis BioScience, Inc
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Curve
BCC	Basal Cell Carcinoma
β-hCG	Beta subunit of human chorionic gonadotrophin (hCG)
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
˚C	Degrees Celsius
CA 125	Carbohydrate Antigen 125
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CGH	Comparative Genomic Hybridization
CI	Confidence Interval
CIB	Clinical Investigator's Brochure
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CML	Chronic myelogenous leukemia
CrEL	Cremophor-EL
CRF	Case Report Form
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Term	Definition
EPR	Enhanced Permeability and Retention
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	Questionnaire to assess quality of life of patients with cancer
EORTC QLQ-BM22	EORTC QLQ Bone metastases module
EOS	End of Study
FAS	Full Analysis Set
˚F	Degrees Fahrenheit
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice(s)
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
GTX	Gemzar® plus Taxotere® plus Xeloda®
HA	Human Albumin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibody
Hgb	Hemoglobin
Hh	Hedgehog
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not Done
NIH	National Institutes of Health
non-DEHP	Non-(di(2-ethylhexyl) phthalate)
ORR	Overall Response Rate
PCRT	Pancreatic Cancer Research Team
PD	Progressive Disease

Term	Definition
PET	Positron-Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCLC	Small-cell lung cancer
SD	Stable Disease
S.D.	Standard Deviation
SGOT	Serum Glutamate Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SOP	Standard Operating Procedure
SPARC	Secreted Protein Acidic and Rich in Cysteine (a glycoprotein)
SUV	Standard Uptake Value
T_{max}	Time of Maximum Observed Plasma Concentration
TEAE	Treatment Emergent Adverse Event
TEAV	Treatment Emergent Abnormal Laboratory Value
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WCBP	Women of Child-Bearing Potential
WHO	World Health Organization
WHODD	WHO Drug Dictionary

APPENDIX D REVISED NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE), VERSION 4.0 (PUBLISHED 28 MAY 2009)

Revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (published 28 May 2009)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 can be viewed on-line at the following NCI web site:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX E DRUG STUDY DRUG PREPARATION, DOSING, ADMINISTRATION AND STORAGE

See links below to website access

Nab paclitaxel (Abraxane™) Prescribing Information (Updated 1/2012) – Accessed via Abraxane Website: http://www.abraxane.com/docs/Abraxane_PrescribingInformation.pdf

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

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

APPENDIX F 2006 UPDATE OF ASCO PRACTICE GUIDELINE RECOMMENDATIONS FOR THE USE OF WHITE BLOOD CELL GROWTH FACTORS: GUIDELINE SUMMARY

Setting/Indication	Recommendation
Primary prophylaxis	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose-dense” regimens, CSF is required and recommended. Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher.
Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
Secondary prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Therapeutic use: Afebrile neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
Therapeutic use: Febrile neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 109/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Dose intensity/density of chemotherapy	Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.

Setting/Indication	Recommendation
Adjuncts to progenitor-cell transplantation	Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
AML: Initial or repeat induction chemotherapy	CSF use following initial induction therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
AML: CSF for priming effects	Use of CSF for priming effects is not recommended.
AML: Consolidation chemotherapy	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical trials.
MDS	Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
ALL	CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
Acute leukemia in relapse	CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
Radiotherapy ± chemotherapy	CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
Older patients	Prophylactic CSF for patients aged ≥ 65 years with lymphoma treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.
Pediatric patients	As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should

Setting/Indication	Recommendation
	be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
Comparative clinical activity of G-CSF and GM-CSF	No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. Further trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of GCSF and GM-CSF.
Treatment for radiation injury	Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

Abbreviations: CSF, colony-stimulating factors; FN, febrile neutropenia; PBPC, peripheral-blood progenitor cell; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, filgrastim; GM-CSF, sargramostim; pegylated G-CSF, pegfilgrastim.

APPENDIX G ABRAXANE® DEMONSTRATES STATISTICALLY SIGNIFICANT IMPROVEMENT IN OVERALL SURVIVAL FOR PATIENTS WITH ADVANCED PANCREATIC CANCER IN PHASE III STUDY

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ABRAXANE® 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 ABRAXANE® (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, ABRAXANE 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 ABRAXANE 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 ABRAXANE in combination with gemcitabine observed in the study is comparable with other ABRAXANE 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. ABRAXANE 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 ABRAXANE®
ABRAXANE is an albumin-bound form of paclitaxel that is manufactured using patented *nab*® technology. ABRAXANE is formulated with albumin, a human protein, and is free of solvents.

In the United States, ABRAXANE 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. ABRAXANE 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, ABRAXANE 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 ABRAXANE please visit http://www.abraxane.com.

ABRAXANE 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.

ABRAXANE® 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.

ABRAXANE 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 ABRAXANE 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 ABRAXANE**

- **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
- ABRAXANE 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 ABRAXANE 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 ABRAXANE
- 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 ABRAXANE 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 ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC
- In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE 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 ABRAXANE 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 ABRAXANE

Hypersensitivity
- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Patients who experience a severe hypersensitivity reaction to ABRAXANE 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 ABRAXANE 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)
- ABRAXANE contains albumin (human), a derivative of human blood

Use in Pregnancy: Pregnancy Category D
- ABRAXANE 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 ABRAXANE

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

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study
- The most common adverse reactions (≥20%) with single-agent use of ABRAXANE 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 ABRAXANE 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 ABRAXANE 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 ABRAXANE 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 ABRAXANE and carboplatin in NSCLC were: anemia (28%); neutropenia (47%); thrombocytopenia (18%), and peripheral neuropathy (3%)
- The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for NSCLC were anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue
- The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC were anemia (4%) and pneumonia (3%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE were neutropenia (24%), thrombocytopenia (13%), and anemia (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing were neutropenia (41%), thrombocytopenia (30%), and anemia (16%)
- The following common (≥10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE 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 ABRAXANE plus carboplatin treatment group)

Post-Marketing Experience with ABRAXANE and other Paclitaxel Formulations

- Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE 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 ABRAXANE, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs
- There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration

DRUG INTERACTIONS

- Caution should be exercised when administering ABRAXANE 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 ABRAXANE in pediatric patients have not been evaluated

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

Renal Impairment
- The use of ABRAXANE 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 ABRAXANE
- Withhold ABRAXANE 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.

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