University of Iowa Hospitals and Clinics
Holden Comprehensive Cancer Center

Phase II Study of Nab-Paclitaxel with Gemcitabine for Relapsed Small Cell Cancer or Those with Progression on First Line Therapy

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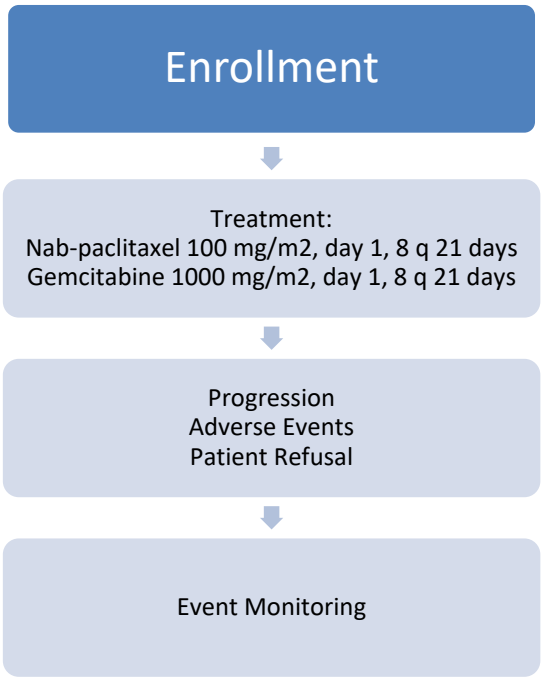
Schema



Generic names: albumin-bound paclitaxel; paclitaxel protein-bound particles for injectable suspension (albumin-bound); Nab-paclitaxel
Brand name: Abraxane ®
Availability: HCCC pharmacy

Generic name: gemcitabine
Brand name: Gemzar ®
Availability: HCCC Pharmacy

1.0 Background

1.1 Overview of Small Cell Lung Cancer

Small cell lung cancer (SCLC) comprises approximately 14% of bronchogenic carcinomas of the lungs. For all lung cancers overall in 2014, it is estimated that there will be 224,210 new cases and 159,260 deaths, accounting for highest age-adjusted cancer death rates in the United States[1]. The incidence of SCLC is mostly related to smoking. The incidence of small cell lung cancer has decreased in the past 20 years[2]. SCLC is a chemosensitive cancer; however, most patients develop relapse within 2 years after initial treatment and die of systemic metastases. Relapsed SCLC is relatively resistant to chemotherapy with only 10-25% response rate to subsequent therapy. Median survival of limited stage SCLC is 15-20 months and 9.4-12.8 months in extensive-stage disease[3]. National Comprehensive Cancer Network (NCCN) guidelines list single-agent topotecan, oral or intravenous, as the only category 1 treatment for sensitive relapsed SCLC[4]. Other agents including paclitaxel, docetaxel, irinotecan, vinorelbine, gemcitabine, ifosfamide, temozolomide, bendamustine, amrubicin and oral etoposide are also active in phase II trials. Only topotecan and etoposide are approved for this indication along with methotrexate and mechlorethamine[5].

Several combinations of chemotherapeutic agents and targeted therapies for second line treatment of SCLC have been investigated. Most of the studied combinations can be divided into platinum-based and irinotecan-based therapy..

Nab-paclitaxel and gemcitabine in combination have been well studied in patients with metastatic pancreatic cancer where the combination has an improved response rate and increased survival compared to gemcitabine alone[6] with an acceptable toxicity profile. Paclitaxel and gemcitabine, as single agents, were shown to have efficacy in SCLC[7-10]and a phase I study of the combination showed responses in 3 of 6 patients

1.2 Standard Treatment for Small Cell Lung Cancer

Patients who do not respond to initial therapy or who develop relapse within 90 days after completion of their initial therapy are considered to have resistant or refractory disease and are likely to respond poorly to subsequent chemotherapy (14.8% response rate). Patient who developed relapse after 90 days from the initial treatment have a better prognosis with a longer median overall survival (7.7 months vs. 5.4 months, p=0.0035)[11]. Patients who relapse after 6 months after initial treatment should be treated with the same regimen used for initial therapy.

Topotecan was first shown to be equivalent to a cyclophosphamide-doxorubicin-vincristine (CAV) regimen in a multi-centered phase III study[12] with response rate of 24.3% vs. 18.3% in topotecan and CAV arms, respectively in relapse sensitive disease. Median survival in the topotecan group was 25.0 weeks vs 24.7 weeks in CAV. No statistical difference was found in either response rate or median survival. However, topotecan had less grade 4 neutropenia (37.8% vs. 51.4%). Grade 4 thrombocytopenia and grade 3/4 anemia were more common in the topotecan group (9.8% and 17.7% vs. 1.4 and 7.2%). Other toxicities were similar. In this study topotecan 1.5 mg/m^2 was given intravenously as a 30-minute infusion daily for 5 days of 21-day cycle for 6 cycles or until disease

progression or unacceptable toxicity occurred. Since then topotecan has become standard of care for sensitive relapsed SCLC. Later, oral topotecan was demonstrated to have benefit over best supportive care[13] when it is given 2.3 mg/m^2/day in the same fashion as intravenous route. The response rate was 7% partial and 44% stable disease and median survival was 25.9 weeks (vs. 13.9 in best supportive care group). A subsequent trial suggested equivalency of oral and intravenous topotecan in this setting[14]. NCCN list oral or intravenous topotecan as the only category 1 treatment for sensitive relapsed SCLC. However, a more recent report from SWOG emphasized that other prognostic factors are more important than "platinum sensitivity" and that platinum sensitivity is not associated with PFS or overall survival[15].

There are several single-agents that have been shown efficacy in the treatment of relapsed SCLC. Etoposide[16] and irinotecan[17] were tested in randomized controlled studies while other agents including paclitaxel[9,10], docetaxel[18], gemcitabine[7,8], bendamustine[19], picoplatin[20] (not available in the United States), vinorelbine[21], oral etoposide[22], and temozolomide[23] were tested in non-comparative or phase II studies. We had previously reported trials of intravenous and subcutaneous IL-2 in relapsed small cell lung cancer. With intravenous therapy, 4 of 24 patients achieved a complete remission for a response rate of 21% The remission durations were 8, 9 and ongoing at 11 months. One patient had not relapsed at 8 months but had developed acute leukemia[24,25].

These agents (except bendamustine, IL2, and picoplatin) are currently in category 2A in the NCCN guideline.

1.3 Combination Treatment for Small Cell Lung Cancer

Combinations of two to four chemotherapeutic agents have been investigated in relapsed SCLC[3]. Most of the studies were platinum-based or irinotecan-based regimens. The observed response rates ranged from 10% (liposomal doxorubicin-cyclophosphamide-vincristine) to 88% (cisplatin-vincristine-doxorubicin-etoposide) and median survival time from 4.4 months (vincristine-ifosfamide-mesna-carboplatin) to 11.8 months (cisplatin-etoposide-irinotecan). However, these studies may have enrolled different study population and should not be compared directly.

The only combination therapy in the NCCN guideline (category 2A) is CAV regimen that was studied in the topotecan trial mentioned above.

An intensive regimen of irinotecan/etoposide for previously treated extensive small call had a 71% response rate. Growth factor support was used[26].

A phase II trial of irinotecan/paclitaxel in recurrent or refractory small cell enrolled 51 patients who had at least one dose of therapy. The overall response rate was 21% and there was substantial hematologic toxicity. A trial of paclitaxel and bevacizumab in chemosensitive relapsed small cell had an overall response rate of 18%[27].

1.4 Gemcitabine as Single Agent for Treatment of Small Cell Lung Cancer

Gemcitabine is a nucleoside (deoxycytidine) analog acting as a pyrimidine antimetabolite in its triphosphate form[28] by competing with natural deoxycytidine 5-triphosphate in DNA replication. Its diphosphate metabolite also inhibits ribonucleotide reductase (RNR)

needed for deoxyribonucleotides synthesis and DNA repair. Gemcitabine is used for treatment in variety of cancers such as non-small cell lung cancer, pancreatic cancer, bladder cancer, breast cancer.

The activity in SCLC was first evaluated by van der Lee *et al* in a single-center study in the Netherlands[8] in 41 patients with resistant disease (progression during or within 3 months of finishing the primary regimen). Gemcitabine 1000 mg/m^2 was given intravenously on day 1, 8, and 15 of four-week cycle for maximum of five cycles. Response rate was 13% (95% confidence interval (CI) 6-27%) with median survival of 17 weeks. Related toxicity included grade 3 thrombocytopenia (29%) and grade 3 leukopenia (18%) and it was otherwise well tolerated.

Subsequently, gemcitabine efficacy was investigated in a phase II study[7] that also included 26 patients with relapsed sensitive disease and 20 patients with primary resistant disease. Only one patient in primary resistant group had partial response; however, 4 patients (16.7%) in the sensitive relapse group had partial response. Median survival was 7.3 months in relapsed sensitive disease group. There were 47.7% of patients who experienced worst toxicity as grade 3. 18.2% had worst toxicity as grade 4 including thrombocytopenia (9.1%), neutropenia (6.8%), leukopenia (2.3%), anemia (2.3%), vomiting (2.3%) and liver toxicity (2.3%). The author concluded that gemcitabine was well-tolerated with an observed response rate and survival similar to a previous study of CAV.

Another trial was published in the2003 by Hoang *et al*[29] in the same setting as the previous study and recruited 27 patients (15 patients were sensitive disease.) Three patients achieved stable disease after six cycles but none achieved response. Median time to progression was 6 weeks in sensitive group and 5.6 weeks in resistant group and the median survival was 8.8 months in sensitive group and 4.2 months in resistant group. Hematologic adverse effects included grade 3/4 neutropenia and grade 3 thrombocytopenia, both of which occurred in 5 patients (30%).

According to 2 phase-II trials[7,8] mentioned above, NCCN guideline has adopted gemcitabine as a subsequent chemotherapy in both relapsed resistant and sensitive SCLC.

1.5 Nab-Paclitaxel as Single Agent for Treatment of Small Cell Lung Cancer

Taxanes work through the inhibition of microtubule depolymerization, resulting in a stagnation of cells in G2 and M phases and leading to cell death. Paclitaxel and docetaxel are known to have high insolubility in water. The current formulation used Kolliphor EL (also called Cremophor EL, a polyethoxylated castor oil) and dehydrated ethanol to stabilize the emulsion of non-polar paclitaxel in aqueous system to allow intravenous administration. This solvent-based paclitaxel is associated with varieties of adverse reactions, for example, hypersensitivity reactions, peripheral neuropathy, and neutropenia. Nab-paclitaxel (Abraxane®) was developed to avoid these toxicities which are potentially related to the non-ionic surfactant used in the formulation[30]. When nab-paclitaxel enters the blood stream, the non-covalently bound albumin-paclitaxel complex is dissolved and some paclitaxel molecules are released and bound with albumin or other biomolecules in the blood stream. The albumin molecule was found to help nab-paclitaxel reach the tumor by receptor-mediated transcytosis (via albumin-specific

receptors: glycoprotein 60 and caveolae) and by enhanced permeation and retention effect (via secreted protein acidic and rich in cysteine, SPARC). Kolliphor EL was also found to be inhibitory in paclitaxel transcytosis through endothelial cells[31].

As noted above, paclitaxel has been incorporated in the NCCN guideline for treatment of SCLC based on the results of two following phase-II studies:

Smit et al.[9] conducted a phase II study of paclitaxel in previously treated primary resistant SCLC patients (last cytotoxic treatment less than 3 months). Intravenous paclitaxel 175 mg/m^2 was administered every 21 days. 7 of 24 patients (29%) had a partial response with median time to progression of 65 days and median survival of 100 days. Toxicities included grade 3/4 leukopenia in 10 out of 63 evaluable cycles and grade 3/4 thrombocytopenia in 5 of 63 evaluable cycles.

After reports of activity and tolerability of weekly paclitaxel compared to every 3 weeks, Yamamoto et al[10] conducted a study of weekly paclitaxel in SCLC. Paclitaxel 80 mg/m^2 was administered weekly for 6 weeks of the 8-week cycle; 21 patients were included (11 patients with sensitive disease). Three out of 11 (27.3%) with sensitive disease patients and 2 out of 10 (20.0%) with resistant disease achieved a partial response and the median survival was 5.8 months. The most frequent toxicity was neutropenia and 6 patients (28.6%) developed grade 4 neutropenia.

A clinical study of nab-paclitaxel in SCLC was done as part of a phase I trial in which nab-paclitaxel was combined with gemcitabine and will be discussed in the next section.

There is a case report published on a patient with complete remission of SCLC after administration of nab-paclitaxel 100 mg/m^2 for 2 cycles[32]. Unfortunately, the patient developed severe interstitial pneumonitis and died of respiratory failure after a week of diagnosis. The tumor was found to be positive for caveolin-1 but negative for SPARC by immunohistochemistry.

1.6 Combination of Nab-Paclitaxel and Gemcitabine for Treatment of Malignancy: Efficacy and Toxicity

Both paclitaxel and gemcitabine have demonstrated activity in SCLC. Both agents have different mechanisms of action and also non-overlapping toxicities. Nab-paclitaxel has been designed to improve its pharmacokinetics and has fewer adverse events compared to its solvent-based formula. Nab-paclitaxel and gemcitabine in combination is a very attractive option for investigation for activity and safety in clinical trial. There was a trial of gemcitabine and paclitaxel as second line therapy for small cell with a response rate of 22% but the dose of paclitaxel weekly x 2 was 135 mg/m2 and there was unacceptable toxicity[33].

There is only one clinical trial of the combination of nab-paclitaxel and gemcitabine in treatment of SCLC to date, a phase-I trial of nab-paclitaxel combined with gemcitabine in patients with thoracic malignancy[34], which included 6 patients with SCLC. Three out of 5 evaluable SCLC patients achieved partial response. The chemotherapeutic agents administered were nab-paclitaxel at 3 different doses (260 mg/m^2, 300 mg/m^2, and 340

mg/m^2) on day 1 and gemcitabine 1000 mg/m^2 on day 1 and day 8 of 21-day cycle. This regimen was relatively well-tolerated with only one episode of grade 4 neutropenia and one grade 3 febrile neutropenia. Efficacy of this combination in SCLC is obviously limited by its phase-I design and small sample size.

A phase-II study sponsored by National Cancer Center, Korea has investigated the efficacy and toxicity of combination of weekly paclitaxel plus gemcitabine as second-line in SCLC. The study was completed in March 2010 but there is no result available through clinicaltrials.gov (NCT00453167)[35] or searchable publication.

A recent phase III study[6] of combination of nab-paclitaxel and gemcitabine showed an increase in survival in advanced pancreatic adenocarcinoma compared to gemcitabine alone. The most common non-hematologic adverse reaction was fatigue (54%), alopecia (50%), and nausea (49%). Nab-paclitaxel-gemcitabine group had more grade 3/4 hematologic adverse events than in the gemcitabine-alone group (neutropenia 38% vs. 27%, thrombocytopenia 13% vs. 9%, febrile neutropenia 3% vs. 1% in nab-paclitaxel-gemcitabine and gemcitabine-alone groups, respectively. The result of this study has put nab-paclitaxel in combination with gemcitabine into category 1 treatment of metastatic pancreatic adenocarcinoma.

Comparing the toxicity of Topotecan as second line therapy for small cell lung cancer and the toxicity of nab/paclitaxel in pancreatic cancer, the combination appears to be associated with less neutropenic fever and less transfusion requirement.

2.0 Goal

2.1 Primary Endpoint

To evaluate the response rate per RECIST 1.1 of nab-paclitaxel plus gemcitabine (with clinically meaningful response rate defined as 35% of patients responding)

2.2 Secondary Endpoints

2.2.1 To estimate the time to progression
(defined as the first day of treatment to the date that disease progression is reported)

2.2.2 To estimate the overall survival
(defined as the first day of treatment to the date of death)

2.2.3 To examine the toxicity related to the therapy
(defined as predefined toxicity occurred from the first day of treatment to 28 days after administration of the last dose of the studied drugs)

3.0 Patient Eligibility

3.1 Eligibility criteria

3.11 Age ≥18 years old, both male and female

3.12 Histologically or cytologically confirmed SCLC or small cell cancer from other organs or poorly differentiated neuroendocrine tumors that are treated like small cell cancer. This study is for patients with metastatic or recurrent disease.

3.13 ECOG performance status 0-2

3.14 Patients must have at least one measurable lesion as defined per RECIST 1.1

3.15 Progression during or after first-line chemotherapy. . Prior maintenance therapy, targeted therapy, and immunotherapy are allowed. Prior use of Rovalpituzumab or other ADC agent is allowed. Immunotherapy or targeted therapy if used as 2nd line therapy will not be considered as second line therapy as these are not true chemotherapeutic agents. Patients treated with definitive chemo-radiation will be eligible if they progressed within a year of definitive therapy (as definitive therapy will be considered 1st line therapy for these patients).

3.16 Before study therapy, a minimum of 21 days must have elapsed since any prior chemotherapy and 2 weeks from the last dose of prior targeted or immunotherapy.

3.17 Prior definitive XRT is allowed if it has been 2 weeks since the end of definitive XRT. For palliative XRT, protocol-specified treatment can begin at minimum 48 hours after completion of radiation. . Lesions within the XRT field can only be used as target lesions if definite progression has been demonstrated since the completion of radiation.

3.18 Adequate major organ function including the following:
Hematologic function: Absolute neutrophil count (ANC) ≥ 1800 /mm3, platelet count ≥ 100,000/mm3, and Hgb ≥ 9.0 gm/dl

Hepatic function: bilirubin ≤ 1.5 x ULN, AST and ALT levels ≤ 2.5 x ULN. If liver metastases are present, then AST and ALT ≤ 5 x ULN.

Renal function: serum creatinine ≤ 1.5 x ULN.

3.19 Patients must be willing and able to sign informed consent for themselves

3.19a If female: childbearing potential either terminated by surgery, radiation, or menopause, or attenuated by use of an approved contraceptive method (intrauterine device [IUD], birth control pills, or barrier device) during and for 6 months after trial. If male, use of an approved contraceptive method during the study and 6 months afterwards. Females with childbearing potential must have a urine negative hCG test within 7 days prior to the study therapy.

Females of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally

postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:

- Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP; and
- Have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, as per clinical judgement of the investigator, and after the end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

3.19b Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following IP discontinuation, even if he has undergone a successful vasectomy.

** True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].*

3.2 Exclusion criteria

3.21 Any of the following because this study involves an agent that has known genotoxic, mutagenic, and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential, who are unwilling to employ adequate contraception as determined by treating physician, while on this study and for 6 months after the end of treatment with the study drugs.

3.22 History of the following within the prior **6 months**: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or clinically significant ECG abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder.

3.23 Serious concurrent infection or nonmalignant illness that is uncontrolled or whose control may be jeopardized by complication of study therapy

3.24 History of other invasive malignancy that is currently active and/or has been treated within **12 months** prior to enrollment (notable exceptions include; basal cell carcinoma, squamous cell carcinoma of the skin, localized prostate cancer, in

situ carcinomas of the cervix and breast, and superficial bladder cancers [non-muscle invasive]).

3.25 Psychiatric disorder which, per treating physician discretion, may preclude compliance

3.26 Major surgery in the last two weeks of starting study therapy. This does not include procedures like biopsy (needle or excisional) or port placement as these are not considered as major surgery.

3.27 Individuals with the presence of symptomatic CNS metastasis requiring radiation, surgery, or ongoing use of corticosteroids. Untreated or brain metastasis causing any symptoms. Treated brain metastasis must be stable for **4 weeks** prior to first dose of study drug and not requiring steroids for at least 7 days prior to study treatment.

3.28 Pre-existing peripheral neuropathy > Grade 1 (using CTCAE v 4.3 criteria)

3.29a Received any prior treatment with any taxane (docetaxel or paclitaxel) for small cell lung cancer.

3.29b History of allergy or hypersensitivity to albumin-bound paclitaxel, or gemcitabine.

4.0 Test Schedule

Test and Procedures	Within 30 days prior to therapy	Within 15 days prior to study therapy (screening visit)	Within 3 days prior to or day of each subsequent cycle of treatment	Active monitoring Phase			Post treatment[8]
				Weekly for first two cycles	Every two cycles	End of treatment[7]	
History and physical examination (including weight, performance status, concurrent medications)		X	X			X	X
Height and weight[4]	X		X			X	
Pregnancy test (serum)		1					
Complete blood count with differential counts		X	X	X[9]		X	X
Complete metabolic profile[5]		X	X			X	X
Adverse Event Assessment		X	2			2	
Uric acid, LDH, CEA[6]		X					
Tumor measurement	3				3		X

1. For women of childbearing age only. Must be done within 7 days prior to therapy.
2. Adverse events form. Any grade 4 toxicity or unanticipated grade 3 or 4 toxicity must be reported within 24 hours (MON-FRI) to the data safety monitoring board, and Celgene, the sponsor of the study. Event must be reported to the IRB within 10 days.
3. Measure every other cycle if done by CT, CXR, or MRI depending on the study used for the initial tumor measurement (i.e. prior to cycles 1, 3, 5, …). 2-3 days window is allowed for the scans if needed.. Same method must be used for baseline and throughout study. Patients with stable disease or response after 6 cycles of treatment may have CT scans scheduled less frequently than every 2 cycles as clinically indicated.
4. Height only needs to be collected at baseline.
5. TESTS in the CMP to include Na, K, Cl, CO2, BUN, creatinine, AST, ALT, ALK Phos, albumin, calcium, TP, glucose.
6. LDH, CEA and uric acid are to be determined at baseline but will only need to be repeated as clinically indicated for care of the patient.
7. End of Treatment visit: Every effort will be made to follow the patient off study (regardless of the reason) at approximately 28 days (+/- 7 days to accommodate scheduling). Followup visit will include physical, vitals, weight, ECOG status, assessment of toxicities and labs including CBC and CMP. Other clinic visit can be utilized for this purpose if all of the assessments are made.

8. Every effort will be made to follow all patients after the completion of therapy every 2 months ± 3 weeks for progression, whether or not they ended the therapy as it was completed or if they came off study therapy for any other reason. Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subjects will be contacted by telephone every 12 ± 4 weeks to assess for survival status until death, withdrawal of consent, or 3 years from screening date or till the end of study, whichever occurs first.
9. Weekly CBC/diff may be obtained locally (Day 15 CBC is not required after 2 cycles).

5.0 Stratification Factors

There will not be stratification for platinum sensitivity or any other factors

6.0 Screening

6.1 Treatment cannot begin prior to screening and must begin within 14 days after screening, if patient is eligible and completed all required testing.

6.2 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.

6.3 All required baseline symptoms must be documented

6.4 Study drug availability checked.

6.5 Rescreening is allowed.

7.0 Protocol Treatment

7.1 Treatment Schedule

Actual weight will be used to calculate body surface area unless the subject has significant edema. In that case, ideal body weight will be used as far as it is less than actual body weight. Height needs to be recorded only once at screening (within 30 days of therapy). Weight needs to be monitored on Day 1 of each cycle. The body surface area and drug dose should be recalculated only if the subject's weight changes by $\geq$ 10% during the course of the study from Cycle 1 day 1.

Treatment may be given as inpatient or outpatient at discretion of treating physician.

Treatment visits and chemotherapy infusions may be performed +/- 3 days of the "scheduled day" for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. This needs to be documented in the subject's chart and/or research documents.

Drug will be assigned to subjects by the Investigational Drug Service (IDS) at University of Iowa Hospitals and Clinics per their SOPs. Drug accountability will also be the responsibility of the IDS.

Agent	Sequence	Dose Level 0 (mg/m^2)	Dose Level -1 (mg/m^2)	Dose level -2 (mg/m^2)	Route	Day	Cycle Frequency
Nab-Paclitaxel	First	100 mg/m^2	80	60	IV (30 min)	1, 8	q 21 days
Gemcitabine	Second	1,000 mg/m^2	800	600	IV (30 min)	1, 8	q 21 days

8.0 Dosage Modification Based on Adverse Events

Following tables serve as a guide for dose modifications of chemotherapy during study period.. If multiple adverse events are observed, the one with greatest dose reduction should be followed. Dose delay due to toxicities, febrile neutropenia and due to other illnesses (except hematologic toxicities) for up to 3 weeks is allowed. If period of more than 3 weeks is required, then approval of principal investigator is needed. Dose modifications or clinical situations not covered in the section below need to be discussed with PI.

8.1 Nab-paclitaxel/Gemcitabine based on day of treatment counts

8.11 **Dose Level modification Table**

Day of cycle	ANC (cell/µL)	Platelets (µL)	Dose level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Day 1	>1800	>100,000	0	100	1000
Day 1	>1500-1800	>100,000	-1	80	800
Day 1	≤1500	≤ 100,000		Hold treatment until counts improve *	Hold treatment until counts improve*
Day 8	> 1500	>100,000	0	100	1000
Day 8	> 1000-1500	> 75-100,000	-1	80	800
Day 8	500-1000	50,000-75,000	-2	60	600-
Day 8	≤ 499	≤49,999	Hold	Hold treatment until counts improve **	Hold treatment until counts improve**

ANC: Absolute neutrophil count
* Modification for day 1:

1. If patient had delay in chemotherapy in the previous cycle due to treatment related toxicities the next cycle will start at 1 dose level below the prior dosing level and dose will not be re-escalated. If dose reduction was required during the previous cycle, new cycle will start at the new reduced dose level. In the event that a patient was dose reduced directly from level 0 to level -2, the investigator may choose to re-challenge the patient at dose level -1 to assess the tolerability at this dose level.

2. New cycle will begin after a week of chemotherapy break (no chemotherapy in the prior week).

** Modifications for Day 8:

1. Follow dose levels as per table 8.11 and 8.2.

2. If ANC or Platelet counts are ≤ 499 or 49,999/ul respectively, hold chemotherapy by 1 week. Administer at 1 dose level below the previous dosing level on day 15 if counts recovered to or above that dose level.

3. If ANC or Platelet counts are ≤ 499 or 49,999/ul respectively on day 8 and day 15, then day 8 chemotherapy will not be administered and on day 21 patient will receive next cycle Day 1 at 1 dose level below the previous dosing level if counts recovered to or above that dose level for Day 1. I If Day 8 therapy can't be administered on day 8 or 15 while patient received Day 1 at dose level -2 for more than once then patient will be taken off the study and will be monitored for events.

8.12 Please note that there are two different dose adjustment schedules:

1) Adjustment at the beginning of the new course of therapy, based upon labs on the scheduled day of treatment and upon the worst adverse event encountered in the previous course;
2) Adjustment or actions based on adverse events observed since the start of the course or during the interval until the start of the next cycle.

8.13 Noted that all dose modification should be based on the worst preceding adverse event and are relative to the starting dose.
If several adverse events with different grades or severity occur at the same time, the dose reductions should be based on the greatest reduction applicable.

8.2 Dose modifications based on interval adverse events (other than day 1)

Please refer to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 unless otherwise specified.

CTCAE v.4.03 category	Adverse Events	Agents	Action
Blood and lymphatic system disorders	Hematologic	Nab-paclitaxel Gemcitabine	
	Any time during cycle or on Day 15: (when noticed during first 2 cycles or beyond) ANC < 100/ul and/***or*** PLT <-10,000/ul		Consider decrease to 1 dose level below the prior dosing level with the next scheduled dose. Consider growth factor support

	Thrombotic microangiopathy (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)	Gemcitabine	Discontinue patient from trial
Nervous System disorders	Neuropathy (paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy) ≥ grade 3	Nab-paclitaxel	Omit Nab-paclitaxel until ≤ grade 1. .
Respiratory, thoracic and mediastinal disorders	Pneumonitis ≥ grade 2	Gemcitabine Nab-paclitaxel	Discontinue therapy of both Gemcitabine and Abraxane and discontinue patient from trial. Initiate steroid therapy if due to drug therapy
Other non-hematologic adverse events	Intolerable Grade 3	Nab-paclitaxel Gemcitabine	Hold gemcitabine and Abraxane until resolution to ≤ grade 1. Then resume therapy at next lower dose as scheduled. If occurs recurrently while patient is at dose level -2 then consider taking patient off study and monitor for events.
	Grade 4 (except pulmonary embolism)	Nab-paclitaxel Gemcitabine	Discontinue appropriate drug(s). Patients must be followed on study until adverse event is resolved or stable.

8.3 Dose modifications at the time of re-treatment (start of new cycle)

Adjustment should be based on worst adverse event encountered during the previous cycle.

CTCAE v.4.03 category	Adverse Events	Agents	Action
Blood and lymphatic system disorders	ANC < 1500 ***or*** PLT < 100,000	Nab-paclitaxel Gemcitabine	Hold all study drugs until ANC and PLT above these values (reevaluate every week until recovery). See above 8.11
Renal dysfunction	Creatinine 1.5 -3.0 x ULN	Gemcitabine	Consider 1 dose level below the prior dosing level.
	Creatinine > 3 x ULN		Discontinue on study therapy
Hepatobiliary disorders	Bilirubin > 1.5 x ULN and/or AST or ALT > 5 x ULN	Nab-paclitaxel	Hold nab-paclitaxel until these chemistries get within parameters of administration. Perform appropriate work up. Continue Gemcitabine.
Nervous system disorders	Neuropathy (paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy) ≥ grade 3	Nab-paclitaxel	Omit Nab-paclitaxel until ≤ grade 1.. Continue with Gemcitabine
	Neuropathy grade 4		Patients with grade 4 toxicity should be removed from study
Respiratory, thoracic and mediastinal disorders	Pneumonitis ≥ grade 2	Gemcitabine Nab-paclitaxel	Discontinue study drugs and begin supportive care.
Other non-hematologic adverse events	Intolerable grade 3	Nab-paclitaxel Gemcitabine	Omit appropriate drug(s) until ≤ grade 1, and decrease 1 dose level below the prior dosing level. If recurrent grade 3 toxicity at dose level -2, then discontinue patient from study therapy
	Grade 4		Discontinue study therapy. Patients must be followed on study until adverse event is resolved or stable. (If all study drugs are discontinued, patient goes to Event Monitoring.)

8.4 Modification of regimen

If the doublet proves intolerable based on the AEs observed in the first 6 patients, the trial would continue using only single agent nab-paclitaxel. If greater than 3 patients experience grade 3-4 non-hematologic toxicities or grade 4 hematologic toxicities with the first 6 patients treated during the first 2 cycles, it will be concluded the doublet is not tolerable in this patient population and the study would continue with single agent nab-paclitaxel. The grade 4 toxicity of neutropenic fever would be grade 4 at any time in the cycle.

9.0 Ancillary Treatment

9.1 Patient should receive full supportive care while they are on the study including blood product transfusion support, antibiotics, and treatment of other new of underlying medical conditions.
All blood products and other supportive medications (antiemetics, antidiarrheals, analgesics, etc.) that the patient receives from the start of study drugs until 30 days after final dose are to be recorded in the medical record and on the treatment form.

9.2 Use of hematopoietic growth factors such as G-CSF, GM-CSF, are allowed at discretion of treating physician. Erythropoietin is not allowed on this study Oncologists are encouraged to follow ASCO or NCCN guidelines and to discontinue growth factor use 96 hours prior to initiation of the next cycle of chemotherapy. Any use of growth factors must be documented in the patient's record and on treatment form.

9.21 Use of colony-stimulating factors is allowed at physician discretion for patients with neutropenia necessitating dose reduction or delay as guided by dose modification table.

9.22 Therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at physician discretion.

9.3 Both nab-paclitaxel and gemcitabine have low emetic risk (10-30% frequency of emesis). Antiemetics must be given and may include ondansetron or granisetron or palonosetron with or without aprepitant or other agents as clinically indicated.

9.4 For management of myalgia and/or arthralgia from nab-paclitaxel, treating physician may consider non-steroidal anti-inflammatory drug (NSAID), anti-histamines, or for severe cases, a narcotic analgesic agent.

9.5 The use of bisphosphonates (i.e., pamidronate, zoledronic acid) or denosumab will be allowed for palliation of pain or lytic lesions from bone metastasis.

9.6 Patient will not be allowed to enroll in a different clinical study in which investigational therapies are administered while receiving treatment in this study. However, exception may be granted for trials related to symptom management (Cancer Control) which do not interfere with the study drugs. Treating physician must consult the Study Chair regarding specific trial participation.

10.0 Adverse Event (AE) Reporting and Monitoring

Toxicity will be scored using CTCAE Version 4.03 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

10.1 Monitoring, Recording and Reporting of Adverse Events

10.11 An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

10.12 Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

10.13 In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for ABRAXANE® overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

10.14 All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

10.15 All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made

known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2 Evaluation of Adverse Events

10.21 **Seriousness**

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing

condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

10.22 Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.23 Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- *Not suspected*: Means a causal relationship of the adverse event to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation

for the observed event.

- *Suspected*: Means there is a reasonable possibility that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.24 **Duration**

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.25 **Action Taken**

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.26 **Outcome**

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, not recovered or death (due to the SAE).

10.27 **Abnormal Laboratory Values**

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention;
- or is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event. If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

10.3 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 6 months are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

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

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., SPONTANEOUS OR THERAPEUTIC ABORTION), THE INVESTIGATOR SHOULD REPORT THE ABNORMAL OUTCOME AS AN AE. IF THE ABNORMAL OUTCOME MEETS ANY OF THE SERIOUS CRITERIA, IT MUST BE REPORTED AS AN SAE TO CELGENE DRUG SAFETY IMMEDIATELY BY FACSIMILE, OR OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT FORM.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

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

10.4 Overdose

10.41 Overdose, as defined for this protocol, refers to Abraxane or Gemcitabine dosing only.

10.42 On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of Abraxane or Gemcitabine assigned to a given patient, regardless of any associated adverse events or sequelae.

> 10% over the protocol-specified dose

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

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

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

10.5 Celgene Drug Safety Contact Information

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

10.6 Adverse events to be graded at each evaluation per CTCAE v.4.03

Category (CTCAE v 4.03)	**Adverse Events/Symptoms**	**Baseline**	**Each evaluation**
Blood and lymphatic	Anemia	x	x
	Febrile neutropenia (ANC < 1000/mcL and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature ≥ 38 degrees C (100.4 degrees F) for more than 1 hour		x
Cardiac	Chest pain (substernal discomfort due to insufficient myocardial oxygenation) or Acute coronary syndrome		x
Gastrointestinal	*Stool count/day*	x	
	Diarrhea		x
	Mucositis (oral)	x	x
	Nausea	x	x
	Vomiting	x	x
General disorder and administration site conditions	Edema (limbs)	x	x
	Fatigue/Malaise	x	x
	Fever (without neutropenia)		x
	Infusion related reaction/infusion site extravasation		x
	Pain	x	x
Immune system	Allergic reaction/serum sickness		x
Investigations	AST, ALT, alkaline phosphatase increased	x	x
	Blood bilirubin increased	x	x
	Neutrophil count decreased	x	x
	Platelet count decreased	x	x
Nervous system	Peripheral sensory neuropathy	x	x
Renal and urinary	Acute kidney injury	x	x
Respiratory, thoracic and mediastinal	Dyspnea	x	x
	Pharyngeal mucositis	x	x
Skin and subcutaneous tissue	Rash (acneiform/maculo-papular)	x	x

11.0 Treatment Evaluation Using RECIST 1.1 Criteria

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 6 weeks.

11.2 Definitions of Measurable and Non-measurable Disease

11.21 Measurable disease is defined as at least one lesion which can be measured accurately at least in on dimension with a minimum size of:
10 mm by CT Scan or MRI (slice thickness ≤ 5 mm)
10 mm by caliper measurement by clinical exam
20 mm by chest x-ray. However, CT is preferable.
If it is malignant lymph-node then it must be ≥15 mm in short axis

11.22 Non-measurable disease: that do not fit the above criteria or leptomeningeal disease, effusions, ascites, blastic lesions in bones, simple cysts or lesion that have received prior local therapies unless developed progression afterwards.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable imaging modalities for measurable disease: CT scan (conventional and spiral), MRI, chest x-ray, and physical examination.

- Conventional CT and MRI must be performed with slice thickness of ≤ 5 mm.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan will be obtained in 6 weeks (after 2 more chemotherapy cycles as scheduled) following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease will be considered if possible to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.4 Measurement of Effect

11.41 **Target Lesions**

All measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 5 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions. To meet study criteria, 1 lesion is enough.

For any one organ, no more than 2 lesions need to be measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions (short axis for lymph nodes) will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

11.42 **Non-Target Lesions**

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline as present or absent. Measurements are not required. .

11.43 **Response Criteria**

11.431 All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.

11.432 ***Evaluation of Target Lesions***

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a ≥30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD.
Progression of disease (PD)	At least a ≥20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and as defined by RECIST 1.1 guidelines.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

11.433 ***Evaluation of Non-Target Lesions***

Complete Response (CR)	Disappearance of all non-target lesions
Progression of disease (PD)	Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.
Stable disease (SD)	Persistence of one or more non-target lesions.

11.44 **Overall Objective Status**

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, non-target lesions, and new disease as defined in the following table.

Target lesions	**Non-target lesions**	**New lesions**	***Overall objective status***
CR	CR	None	**CR**
CR	SD	None	**PR**
PR	Non-PD	None	**PR**
SD	Non-PD	None	**SD**
PD	Non-PD	None	**SD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

11.45 **Residual Disease**: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.46 **Symptomatic Deterioration**: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease

progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration:

- Clear worsening of tumor-related symptoms convincing enough to call clinical progression of the tumor as determined by the treating physician or investigator.
- Significant decline in performance status due to increasing tumor burden as determined by the treating physician or investigator.

11.5 Formal statistical definitions of analysis variables involving response and disease progression are contained in Section 15.0.

12.0 Descriptive Factors

12.1 Prior chemotherapy: Cisplatin and etoposide, Carboplatin and etoposide or others.

13.0 Treatment and Follow-up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event monitoring phase per Section 16.0.

13.4 The criteria for discontinuation of study therapy are:

- Tumor progression
- Patient refusal
- Unacceptable adverse events
- Intercurrent illness which would affect assessments of clinical status to a significant degree or require discontinuation of study treatment
- Administration of non-protocol anti-tumor therapy
- Treatment delay >3 weeks, or need for recurrent dose modifications that clearly indicates intolerability of the regimen as judged by the treating physician or investigator.
- Pregnancy
- Loss to follow up
- Symptomatic deterioration as defined in Section 11.46

13.5 10. If a patient has discontinued study therapy for any reason, the patient enters the event monitoring phase of the trial, in which, every effort will be made to follow all patients every 2 months ± 3 weeks for progression. Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, they will be contacted by telephone every 12 ± 4 weeks to assess for survival status until death, withdrawal of consent, or 3 years from registration or the end of the study, whichever occurs first.

13.6 Once a patient enters the event-monitoring phase, the next treatment used for the patient's small cell lung cancer (chemotherapy, radiation, etc.) will be attempted to be be documented on the Event Monitoring Form.

13.7 A patient is deemed ***ineligible*** if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 16.0 of the protocol.
-

13.8 A patient is deemed a ***cancel*** if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Drug Information

14.1 nab-Paclitaxel

14.11 **Overview**

nab-Paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as "Celgene"], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with a mean particle size of approximately 130 nanometers. *nab*-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because *nab*-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur (Ibrahim, 2002; Sparreboom, 1999; ten Tije, 2003). *nab*-Paclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in *nab*-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m2 for *nab*-paclitaxel (Study DM97-123) versus 175 mg/m2 for Taxol (Nyman, 2004). The use of albumin-bound paclitaxel also enables *nab*-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, *nab*-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries / regions as a new product, rather than as a generic formulation of Taxol. *nab*-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent-related HSRs (Taxol US prescribing information). Cremophor EL has been shown to leach plasticizers, specifically di(2-ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing (Gelderblom, 2001; Venkataramanan, 1986; Pfeifer, 1993; Allwood, 1996; Song, 1996; Xu, 1998). Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (e.g., carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (e.g., those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel (Ibrahim, 2002; Nyman, 2004).

As of October 2014, *nab*-paclitaxel is approved under the trade name of ABRAXANE® in 51 countries worldwide for the treatment of patients with metastatic breast cancer. ABRAXANE® is also approved in 8 countries worldwide for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), and in 40 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and it is approved in Japan for treatment of advanced gastric cancer.

14.12 Indications and Usage

In the United States, ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin bound) is indicated for the treatment of metastatic 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.

It is also indicated for the first-line treatment of locally advanced or metastatic NSCLC (non-small cell lung cancer), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy, and is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

14.13 Adverse Events

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

<u>Very common (≥ 10%):</u>

- anemia, red blood cell count decreased
- febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia
- constipation
- diarrhea
- nausea
- vomiting
- abdominal pain, abdominal pain upper
- stomatitis, mucosal inflammation
- SMQ peripheral neuropathy
- dizziness
- headache
- asthenia, fatigue
- arthralgia, back pain, bone pain, chest pain, musculoskeletal pain, myalgia, pain in extremity
- edema, edema peripheral
- pyrexia
- chills
- decreased appetite
- dysgeusia
- weight decreased
- insomnia

- depression
- cough
- dyspnea
- alopecia
- rash, generalized rash, maculopapular rash
- pruritus
- nail disorder, nail discoloration, onycholysis
- alanine aminotransferase increased, aspartate aminotransferase increased
- dehydration
- epistaxis
- hypokalemia

Common (≥ 1% to < 10%):

- bone marrow depression (failure), pancytopenia
- candidiasis, cholangitis, folliculitis, lower respiratory infection, nail infection, oral candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
- neutropenic sepsis, sepsis
- bronchitis
- pneumonitis
- colitis, intestinal obstruction, small intestinal obstruction
- dysphagia
- dyspepsia
- hyperbilirubinemia, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased
- acute renal failure
- hematuria
- ataxia
- muscle weakness
- anxiety
- nasal congestion
- oropharyngeal pain
- dry mouth, dry throat, nasal dryness
- hemoptysis
- pulmonary embolism, deep vein thrombosis
- pleural effusion
- flushing, erythema
- dry skin
- palmar-plantar erythrodysesthesia syndrome
- hypertension
- hypotension
- tachycardia, cardiac failure congestive, palpitations
- increased lacrimation
- visual disturbance, visual Impairment vision blurred
- infusion site extravasation, infusion site inflammation, infusion site rash, infusion site reaction, injection site reactions, injection site infection, extravasation

- lymphedema

Uncommon (0.1% < 1.0%):

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

Elderly

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

nab-Paclitaxel in combination with gemcitabine

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

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

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

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

- vasculitis
- gangrene

Additional side effects observed during post-marketing surveillance of nab-paclitaxel, not otherwise noted above include:

- cranial nerve palsies and vocal cord paresis
- palmar-plantar erythrodysesthesia syndrome
- photosensitivity reaction
- Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme radiation pneumonitis, radiation recall phenomenon

Elderly

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

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

14.14 Clinical Pharmacology

Pharmacokinetics and Drug Metabolism

Absorption

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE® at dose levels of 80 to 375 mg/m2 were determined in clinical studies. Dose levels of mg/m2 refer to mg of paclitaxel in ABRAXANE®. Following intravenous administration of ABRAXANE®, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel for ABRAXANE® were independent of the duration of intravenous administration. The pharmacokinetic data of 260 mg/m2 ABRAXANE® administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for ABRAXANE® than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution

Following ABRAXANE® administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE® (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE® compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum

proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Metabolism

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Elimination

At the clinical dose range of 80 to 300 mg/m2, the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m2, and the mean terminal half-life ranges from 13 to 27 hours. After a 30-minute infusion of 260 mg/m2 doses of ABRAXANE®, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

Specific Populations

Pharmacokinetics in Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of paclitaxel following ABRAXANE® administration was studied in patients with advanced solid tumors. The results showed that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN, AST ≤10 x ULN, n=8) had no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤ 3 x ULN, AST ≤10 x ULN, n=7) or severe (total bilirubin >3 to ≤5 x ULN, n=5) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ULN, AST ≤ULN, n=130).

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for ABRAXANE® exposure. Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic

adenocarcinoma of the pancreas.

Pharmacokinetics in Renal Impairment
The effect of pre-existing mild (creatinine clearance ≥60 to <90 mL/min, n=61) or moderate (creatinine clearance ≥30 to <60 mL/min, n=23) renal impairment on the pharmacokinetics of paclitaxel following ABRAXANE® administration was studied in patients with advanced solid tumors. Mild to moderate renal impairment had no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Other Intrinsic Factors
Population pharmacokinetic analyses for ABRAXANE® show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m2), gender, race (Asian vs. White), age (24 to 85 years) and type of solid tumors do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Pharmacokinetic Interactions between ABRAXANE® and Carboplatin
Administration of carboplatin immediately after the completion of the ABRAXANE® infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUCinf of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

14.15 **Supplier(s)**

ABRAXANE® will be supplied by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the [protocol number (AG001), product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form as well as the Drug Accountability Log to Celgene Corporation at 908-673-2779.

14.16 **Dosage form**

Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

14.17 **Receipt of study drug**

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the

information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

14.18 **Storage and Stability**

Please see local prescribing information for ABRAXANE® for detailed instructions on the reconstitution, storage conditions and IV administration of ABRAXANE®.

14.19 **Study Medication Administration**

ABRAXANE® is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

14.19a **Reconstitution and use of ABRAXANE®**

Please see local prescribing information for ABRAXANE® for detailed instructions on the reconstitution and administration.

14.19b **Special Handling Instructions**

nab-Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling *nab*-paclitaxel. The use of gloves is recommended. If *nab*-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to *nab*-paclitaxel, events may include tingling, burning and redness. If *nab*-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

14.19c **Unused Study Drug Supplies**

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty vials or unused vials to the clinic site.

14.19d **Dose Reduction / Discontinuation Recommendations**

Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. Please refer to the Prescribing Information (section 2.5) and Section 8.0 of this protocol.

14.19e **Administration of Study Drug to Patients with Hepatic Impairment**

For patients with mild hepatic impairment (total bilirubin greater than ULN and less than or equal to 1.5 x ULN and aspartate aminotransferase [AST] less than or equal to 10 x ULN), no dose adjustments are required, regardless of indication.
Do not administer ABRAXANE® to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.
Do not administer ABRAXANE® to patients with total bilirubin greater than 5 x ULN or AST greater than 10 x ULN regardless of indication as these patients have not been studied.

14.19f **Warnings and Precautions**

All warnings and precautions can be found in Section 5 of the Prescribing information. Please note the following:

Sensory Neuropathy

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, withhold ABRAXANE® treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE®.

Hypersensitivity Reactions

Hypersensitivity reactions rarely occur, but severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to ABRAXANE® should not be re-challenged. The use of ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE® in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt ABRAXANE® and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels per Section 2.5 of Prescribing Information.

Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE® in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt ABRAXANE® and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE® and gemcitabine.

14.19g **Albumin (Human)**

ABRAXANE® contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.
For adverse event reporting, please see section 10.0.

14.19h **References**

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14.2 Gemcitabine (Gemzar®)

14.21 **Preparation and storage**

Gemcitabine is supplied as a lyophilized powder in 200 mg and 1000 mg vials. Store intact vials at room temperature, do not refrigerate. Reconstitute the 200 mg vials with 5 mL normal saline and the 1000 mg vials with 25 mL of normal saline (NS) to yield a concentration of 38 mg/mL. The reconstituted solution contains no preservatives and should be used within 24 hours. IV solutions in 250 mL NS are stable for 24 hours. IV infusion in 250 mL NS over 30 (up to 60) minutes. (The maximum final concentration should not exceed 40 mg/mL - may dilute up to 400 mL NS if needed). Do not use other diluents. The pH of the final solution is around 3. There may be some local irritation due to the low pH (pain at injection site). Gemcitabine is not a vesicant.

14.22 **Known potential adverse events**

- Hematologic: Myelosuppression (neutropenia, anemia, thrombocytopenia).
- Dermatologic: Alopecia, transient mild erythematous pruritic rash, desquamation, Stevens Johnson Syndrome.
- Gastrointestinal: Nausea, vomiting, anorexia, diarrhea.
- CNS: Somnolence, agitation, insomnia, dizziness, paresthesia, confusion, convulsion, coma.
- Renal: Renal dysfunction (increased BUN and creatinine values, proteinuria, hematuria, anuria), kidney damage.
- Other: Headache, shortness of breath, mild chills and fever, arthralgias, tachycardia, flu-like symptoms, asthenia, malaise, and fatigue, weakness with or without myalgia, cardiac insufficiency, irregular heartbeat, elevated bilirubin, capillary leak syndrome.

14.23 **Drug procurement**

HCCC Pharmacy

14.24 **Nursing guidelines**

- Monitor CBC, differential, PLT prior to each dose. Myelosuppression is the principal dose-limiting factor. Modification may be considered by physician when bone marrow suppression is suspected.
- Evaluate hepatic and renal function prior to initiation of therapy and periodically thereafter. Closely observe those patients with a history of preexisting mild renal impairment or hepatic insufficiency. Encourage hydration.
- Gemcitabine clearance is affected by age and gender. Grade ¾ thrombocytopenia has been more common in elderly women.
- Antiemetics may be required for probable mild to moderate nausea and vomiting.
- Instruct patient in management of possible mild diarrhea and stomatitis.
- Gemcitabine may cause fever in the absence of clinical infection. Fever can be accompanied by other flu-like symptoms. Instruct patient to report fever or flu-like symptoms to healthcare team. Treat symptoms as they occur.
- Macular or finely granular maculopapular eruptions were experienced by 30% of patients tested. Instruct patients to report any skin changes.
- Instruct patient to report any respiratory changes.

15.0 Statistical Considerations and Methodology

15.1 **Overview**

This protocol will assess the efficacy of nab-paclitaxel plus gemcitabine in patients with relapsed small cell lung cancer who progressed on first line therapy using a single stage phase II study design.

15.11 Primary Endpoint

The primary endpoint of this trial is the response rate, defined as the sum of complete response rate and partial response rate, of greater than or equal to 35% to be considered clinically meaningful.

15.2 **Statistical Design**

15.21 This study will assess the efficacy of nab-paclitaxel (Abraxane) plus gemcitabine in patients with relapsed small cell lung cancer whose cancer has progressed on first line therapy. This will confirm our pilot assessment and set hypotheses for a larger study. We've designed a single-stage phase II study in which the primary endpoint is the response rate to treatment. Response rate is defined as the sum of complete response rate and partial response rate. Current standard of care is topotecan which is estimated to have a response rate around 15%, In addition, topotecan has a higher rate of serious adverse events when compared with Abraxane/Gemcitabine — These include anemia (31%) for Topotecan vs 13% for Abraxane/gemcitabine), febrile neutropenia (10% for Topotecan vs 3% for Abraxane/gemcitabine, neutropenia (54% for Topotecan vs 38% for Abraxane/gemcitabine), thrombopenia (54% for Topotecan vs 13% Abraxane/gemcitabine) . Based on the phase I data, it is reasonable to expect a response rate closer to 35% for Abraxane plus Gemcitabine

Within two-and-half years, we expect approximately 35 patients seen in our institution will meet our treatment criteria.

A sample of size 28 achieves 82% power to detect a difference of 20% using a one-sided binomial exact test. The target significance level is 0.05 and the achieved level is 0.04. The results assume that the current standard of care has a response rate of 15%.

There will be 28 evaluable patients (for the primary endpoint of response) accrued onto this study unless undue adverse events are encountered. We anticipated accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Having set our attrition rate to 12.5%, a total of 32 patients will be accrued onto this study in order to reach 28 evaluable patients.

We will report the actual response rate among the evaluable subjects as well as an exact confidence interval around the observed response rate. In addition, the study will keep track of the proportion of adverse events (AE) and serious adverse events (SAE) so that SAE profiles can be compared between nab-paclitaxel plus gemcitabine and current standard of care Topotecan. This report of toxicity profile is necessary so that the full benefit of nab-paclitaxel and

gemcitabine can be documented.

***Sample size needed**:* 32 patients to reach 28 evaluable

15.22 **Accrual Time and Study Duration**

The number of patients anticipated to be accrued is 1.5 patients per month. Therefore, the accrual period for this Phase II study is expected to be 24 months. The final analysis can begin approximately 24 months after the trial begins, i.e. as soon as the last patient has been observed for 3 months.

15.23 **Other Considerations**

Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

15.3 **Analysis Plan**

The analysis for this trial will commence at planned time points (see 16.23) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accordance with availability of data for secondary endpoints (e.g., laboratory correlates) and the level of data maturity.

15.31 **Primary Endpoint**

- ***Response rate*** is defined to be either a CR or PR noted as the objective status on 2 consecutive evaluations at least 6 weeks apart. The confirmed response rate will be estimated by the number of confirmed responses in evaluable patients divided by the total number of evaluable patients. The appropriate confidence interval will be calculated based on the binomial distribution.

15.32 **Secondary Endpoints**

- ***Survival time*** is defined as the time from Screening to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).
- ***Time to progression:*** Defined as the time from screening until tumor progression. Time to progression does not include deaths. Death will be censored.
-
- ***Progression-free survival time*** is defined as the time from registration to the earliest date of documentation of disease progression. If a patient dies without a documentation of disease progression the patient will be considered to have had disease progression at the time of their death. If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression 1 day post-screening. The distribution of time to progression will be estimated using the method of Kaplan-Meier (1958).

- ***Adverse Events***: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Adverse event monitoring will be done until 30 days after the last dose of nab-paclitaxel or Gemcitabine

15.33 **Data & Safety Monitoring**

The principal investigator and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing.

Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. CTCAE v4.03 will be used to determine grading for these stopping rules.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- If 3 or more patients in the first 15 treated patients (or 10% after 20 patients have been accrued) experience a Grade 4 or higher non-hematologic adverse event.

We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

15.4 **Inclusion of Women and Minorities**

15.41 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

15.42 There is no information currently available regarding differential effects of this treatment regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

15.43 According to the Surveillance, Epidemiologic, and End Results (SEER) database[2], we expect 50% of patients will be women.

16.0 Records and Data Collection Procedures

All required clinical data will be entered into the Clinical Trials Management System, OnCore. Electronic case report forms (eCRF) will be designed and developed to capture study specific data. All corrections or revisions to the eCRFs must be made by authorized personnel and an audit trail will be maintained.

All finalized data will be reviewed by the Investigator. Data recorded in the eCRFs will be retained by the site in accordance with FDA regulations.

17.0 References

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Appendix I

HCCC Clinical Trial Data and Safety Monitoring Plan (DSMP)

Type of Clinical Trial:

- ☑ Investigator-initiated (UI/HCCC)
- ❑ Pilot study
- ❑ Phase I/II
- ❑ Phase III
- ☑ Interventional Treatment
- ❑ Non-Interventional
- ❑ Investigator-initiated, participating site
- ❑ Phase I
- ☑ Phase II
- ❑ Compassionate-use drug protocol
- ❑ Interventional Non-Treatment

Study risk-level:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ❑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ☑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ❑ Level 4—risk of death* >5% or grade 4 – 5 SAE >15%
- ❑ Drugs being used on a "compassionate" basis

* *Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Provide an annual progress report to the DSMC and PRMC
- Register subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations

Selected monitoring strategy based on risk-level:

Risk Level 3

Interventional treatment and non-treatment trials with a risk of death* (1% – 5% or grade 4 – 5 SAE 1% – 5%), e.g. moderate risk procedures Phase I or II clinical trials with available safety data in humans, studies treating subjects with placebo for a recognized disease, and trials with risk of radiation exposure.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least annually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements

- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum once per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. A minimum of 25% of subject records will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent,
  - determine compliance with protocol's study plan,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy of data in the research record with the primary source documents,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation must begin from the first day of study treatment and typically continue through 30 days after the last dose of IP.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Data Monitoring and Management

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Subject registration includes the following:

- Consent date and the IRB approved consent used
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

Subject Data

In addition to the subject registration and subject status data entered in OnCore for all HCCC trials, research staff also enters the subject study data into electronic case report forms (eCRFs) for HCCC investigator initiated studies. eCRFs are approved by the PI and statistician prior to study activation to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are generally maintained in the subject's file. eCRF data are expected to be entered into OnCore within 30 calendar days after a subject's study visit.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all mandatory fields are entered completely, accurately and within time requirements. The assigned DSMC monitor manages the logistics associated with the data monitoring review. Once the clinical trial is identified for

monitoring, the monitor arranges for a selection of cases to review from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries within the eCRF to resolve missing, incomplete and/or incorrect information. A member of the research team is expected to respond to monitoring queries within 14 business days.

This process can often identify a misunderstanding or deficiency in protocol requirements early in the study and can improve data quality.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.