A PHASE 3, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY OF *nab*®-PACLITAXEL PLUS GEMCITABINE VERSUS GEMCITABINE ALONE AS ADJUVANT THERAPY IN SUBJECTS WITH SURGICALLY RESECTED PANCREATIC ADENOCARCINOMA

INVESTIGATIONAL PRODUCT (IP):	***nab*-Paclitaxel**
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Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Open-label, Randomized Study of *nab*-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone as Adjuvant Therapy in Subjects With Surgically Resected Pancreatic Adenocarcinoma

Indication

nab-Paclitaxel, in combination with gemcitabine, is indicated as adjuvant treatment in subjects with pancreatic adenocarcinoma following complete macroscopic surgical resection with no prior radiotherapy or neo-adjuvant chemotherapy.

Objectives

Primary Objective

- To compare disease-free survival (DFS) between subjects randomized to *nab*-paclitaxel in combination with gemcitabine and subjects randomized to gemcitabine alone

Secondary Objectives

- To assess overall survival (OS) between subjects randomized to *nab*-paclitaxel in combination with gemcitabine and subjects randomized to gemcitabine alone
- To assess safety and tolerability of the 2 treatment regimens

Exploratory Objectives

- To assess tumor molecular heterogeneity and associate identified tumor molecular subtypes with clinical outcome
- To investigate whether circulating tumor nucleic acids are associated with disease recurrence
- To evaluate the effect of *nab*-paclitaxel in combination with gemcitabine and gemcitabine alone on subject's quality of life (QoL)

Study Design

This is a Phase 3, international, multicenter, randomized, open-label, controlled study to assess the efficacy of *nab*-paclitaxel in combination with gemcitabine (Arm A) compared with gemcitabine alone (Arm B) as adjuvant treatment for 6 cycles. Subjects will be assigned to treatments by a stratified randomization with 1:1 ratio.

The stratification factors will include:

- Resection Status: R0 (tumor-free margin) versus R1 (microscopically positive margin)
- Nodal Status: lymph node (LN)+ versus LN-
- Region (North America, Europe and Australia versus Asia Pacific)

Study Population

The study will enroll adult male and female subjects with confirmed resected pancreatic adenocarcinoma with macroscopic complete resection (R0 and R1) and no evidence of metastases. Subjects will consent for study participation postresection, however, subjects should be randomized to the study as early as adequately recovered from surgery, but no later than 12 weeks postsurgery. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening, ie, ≤ 14 days prior to randomization, and must have had no prior neo-adjuvant treatment or radiation therapy for pancreatic adenocarcinoma.

Length of Study

Enrollment is expected to take approximately 30 months and approximately 9 additional months of follow-up.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.

Study Treatments

Arm A will receive *nab*-paclitaxel 125 mg/m^2 administered IV followed by gemcitabine 1000 mg/m^2 given intravenously (IV) weekly on Days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles.

Arm B will receive gemcitabine 1000 mg/m^2 administered IV weekly on Days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles.

Dose interruptions, and up to 2 dose reductions to 100 mg/m^2 and 75 mg/m^2 for *nab*-paclitaxel and 800 mg/m^2 and 600 mg/m^2 for gemcitabine, are allowed.

Overview of Efficacy Assessments

Subjects will be assessed by computed tomography (CT) scan performed within 14 days prior to randomization (during the screening period), every 8 weeks for the first 24 weeks after randomization, then every 12 weeks for the next 2.5 years (130 weeks) until 3 years after randomization, and then every 24 weeks thereafter until disease recurrence for the next 2.5 years (130 weeks) up to 5.5 years after randomization. Magnetic resonance imaging (MRI) can be used based on the investigator's judgment or institution policy, as long as the same modality is used throughout the study. Subjects who are discontinued from treatment prior to completing the 6 cycles of treatment in the absence of disease recurrence (eg, subjects discontinued for unacceptable toxicity or subject/investigator discretion) should undergo repeat imaging until disease recurrence, death, or the start of new anticancer therapy is documented.

During the study, DFS will be determined by independent radiologist(s) who are blinded to the treatment assignment. The independent radiologic review will follow a separate imaging charter. Imaging assessments for disease recurrence will be stopped after the number of events for the primary endpoint have been achieved and after the final analysis of DFS by independent radiology. At this point, any ongoing subjects who have not had disease recurrence should follow local standard of care for any additional imaging assessments.

Subjects will be followed for survival every 12 weeks from end of treatment, or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

Overview of Safety Assessments

Safety and tolerability will be monitored through continuous reporting of adverse events (AEs), AEs of special interest (identified based on previous experience in a similar population, including such AEs as myelosuppression, pneumonitis, and sepsis), laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE. 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 serious adverse events (SAEs) made known to the investigator at any time thereafter that are suspected of being related to IP.

Physical examination (source documented only), vital signs, laboratory assessments (eg, serum chemistry, hematology), peripheral neuropathy and ECOG performance status will be monitored. All SAEs (regardless of relationship to IP) will be followed until resolution. Laboratory analysis will be performed as per study schedule.

Overview of Statistical Methods

This Phase 3 randomized study is designed to compare the DFS of *nab*-paclitaxel plus gemcitabine versus gemcitabine alone as adjuvant therapy in subjects with resected pancreatic adenocarcinoma. A permuted-block randomization method and an Interactive Randomization Technology (IRT) will be used to carry out a central randomization. One interim analysis for safety is planned after the first 100 subjects have completed 2 cycles of treatment, and 1 interim analysis on efficacy is planned after observing 163 DFS events to assess futility. A second interim analysis on efficacy had been planned for futility and superiority after observing 70% DFS events or enrollment of 800 subjects, whichever was later. However, at the time of Protocol Amendment 3, the interim analysis for futility at 163 DFS events has been performed and no subjects are receiving further investigational product (IP). To avoid premature interruption of the trial, and to ensure that the study has sufficient duration of follow-up to verify clinical benefit and assess benefit-risk in this setting, this second interim analysis has been removed from the study. An independent Data Monitoring Committee (DMC) will be established to review the interim safety and efficacy data.

Efficacy Analyses:

The primary efficacy endpoint is DFS, which is defined as the time from the date of randomization to the date of disease recurrence or death, whichever is earlier. Disease recurrence will be determined by the independent radiological review of CT (or MRI) scans. The survival distribution of DFS will be estimated using the Kaplan-Meier method; medians and two-sided 95% confidence intervals (CIs) will be provided by treatment arms. The comparison of DFS between the 2 arms will be conducted using a stratified log-rank test, with the stratification factors of resection status (R0 versus R1), nodal status (LN+ versus LN-) and region, and p-values will be provided. The associated hazard ratios (HRs) and two-sided 95% CIs will be provided using the stratified Cox proportional hazard model.

The secondary efficacy endpoint will be OS, which is defined as the time from the date of randomization to the date of death. Subjects who are alive will be censored on the last-known-to-be-alive date. The survival distribution of OS will be estimated using the Kaplan-Meier method; medians and two-sided 95% CIs will be provided by treatment arms. The survival rates at different time points will be provided. P-values based stratified log-rank test will be provided. The associated HRs and two-sided 95% CIs will be provided using the Cox proportional hazard model.

Safety Analyses:

The treated population, which includes all randomized subjects who received at least 1 dose of IP, will be the analysis population for all safety analyses. Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAE), defined as any event that begins or worsens in grade after the start of the IP through 28 days after the last dose of the IP. All events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be summarized per treatment arms by MedDRA system organ class and preferred terms. Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction, and dose interruption, and TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms. Additionally, adverse events of special interest of the *nab*-paclitaxel plus gemcitabine combination will be summarized in the same manner.

In order to investigate the maximal degree of myelosuppression, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade for absolute neutrophil count (ANC), white blood cell count (WBC), platelet count, and hemoglobin will be summarized for each treatment group by the most severe grade in each treatment cycle and by the most severe grade at any time during the treatment. Hepatic and renal function will be summarized for each treatment group using the most severe NCI CTCAE grade for alanine aminotransferase (ALT/SGPT), aspartate transaminase (AST/SGOT), total bilirubin, and creatinine by cycle during the study and at any time during the treatment.

Sample Size

The primary objective is to compare DFS in subjects who received *nab*-paclitaxel in combination with gemcitabine and subjects who received gemcitabine alone.

The hypotheses are the following:

H_0: $HR_{A+G/G} = 1$

versus

H_1: $HR_{A+G/G} \neq 1$

where $HR_{A+G/G}$ is the hazard ratio between the *nab*-paclitaxel in combination with gemcitabine arm and the gemcitabine alone arm.

With the assumption of the true median DFS of 13.5 months in the gemcitabine arm and 18.5 months in the *nab*-paclitaxel in combination with gemcitabine arm, which is equivalent to an $HR_{A+G/G}$ of 0.73, approximately 438 DFS events from 800 subjects are required to allow 90% power to detect a 27% reduction of risk in disease recurrence or death from the treatment arm at

a two-sided significance level of 0.05. One interim analysis on efficacy is planned at about 33% information time to assess the futility.

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1. INTRODUCTION

1.1. Pancreatic Cancer

Worldwide, pancreatic cancer is the thirteenth most common cancer, with 278,684 new cases diagnosed in 2008. The prognosis is poor, and as a result, pancreatic cancer is the eighth leading cause of cancer-related death worldwide, with an estimated 266,669 deaths in 2008 (CancerStats, 2011). Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (US), with an estimated 38,460 deaths from the disease and an estimated 45,220 new cases expected in 2013 (Siegel, 2013). The incidence of pancreatic cancer is higher in men than women and increases with age, with 90% of pancreatic cancer presenting in subjects over the age of 55 years and more than 70% presenting over the age of 65 years (Howlader, 2013). In Europe, pancreatic cancer is the fourth leading cause of cancer-related death with 80,266 deaths predicted in 2013 (Malvezzi, 2013). Forecasts from the United Nations, World Population Prospects, GLOBOCAN 2008 data for cancer incidence and mortality predicted that the incidence of new cases of pancreatic cancer in the European Union (EU) to be 77,241 cases by 2015 (Ferlay, 2010). As in the US, the pancreatic cancer incidence in the EU is higher in men than women (Seufferlein, 2012), and incidence also increases with age.

The pancreas is composed of two main cell types: exocrine (cells that produce digestive enzymes) and endocrine (cells of the islets of Langerhans, that produce among others the hormones insulin and glucagon). Exocrine tumors are by far the most common type of pancreatic cancer, with adenocarcinoma accounting for about 95% of cancers of the exocrine pancreas (ACS, 2013). The focus of the proposed indication is pancreatic adenocarcinoma.

Initial staging classifies pancreatic cancers as resectable, borderline resectable, locally advanced, and metastatic (NCCN, 2013). In the case of resectable disease, the entire tumor can be surgically removed with curative intent, whereas for both locally advanced and metastatic disease, surgery may not be an option because the tumor cannot be completely removed and surgery would only be conducted to relieve symptoms (Seufferlein, 2012). Most patients (80% to 85%) have unresectable disease at the time of diagnosis (Corbo, 2012). For all stages of pancreatic cancer combined, the 5-year OS rate is about 6%, which is the lowest 5-year OS rate of any cancer in the US (Siegel, 2013). At less than 10% survival at 5 years reported within Europe, pancreatic cancer is one of the most fatal cancers (Berrino, 2007).

1.2. Treatment for Resectable Pancreatic Cancer

Surgical resection, using procedures such as pancreaticoduodenectomy (Whipple procedure) or total pancreatectomy, offers patients an improved chance of long-term survival, especially with advances in perioperative and postoperative care. In patients able to undergo a successful curative resection, median OS ranges from 17 to 20 months, and the 5-year OS rate is 9% to 14% (Neoptolemos, 2009; Neuhaus, 2008; Oettle, 2007).

In general, results of meta-analyses suggest that adjuvant chemotherapy with either fluorouracil (5-FU) and folinic acid, or gemcitabine is efficacious (Boeck, 2007; Stocken, 2005). A formal comparison of gemcitabine and 5-FU plus folinic acid found no substantive difference in terms of DFS or OS. However, gemcitabine treatment was associated with less toxic side effects compared with bolus fluorouracil (Neoptolemos, 2010). Adjuvant chemotherapy with either gemcitabine or fluorouracil, using the Mayo Clinic bolus fluorouracil schedule improved the 5-

year survival rate from ~10% to ~20% in patients (Neoptolemos, 2004; Oettle, 2007; Seufferlein, 2012).

Meta-analyses and randomized controlled studies showed evidence that adjuvant chemotherapy after surgery improves both survival rates and DFS in patients with pancreatic cancer (Table 1 and Table 2) (Boeck, 2007; Neoptolemos, 2001a; Neoptolemos, 2004; Oettle, 2007; Stocken, 2005):

Table 1: Disease-free Survival and Overall Survival in Randomized Controlled Studies of Adjuvant Chemotherapy in Pancreatic Cancer

Parameter	Study	Chemotherapy	No Chemotherapy	Significance
Median DFS (months)	CONKO-001[a]	13.4 (95% CI = 11.4 - 15.3)	6.9 (95% CI = 6.1 - 7.8)	p < 0.001
	ESPAC -1[b]	15.3 (95% CI = 10.5 – 19.2)	9.4 (95% CI = 8.4 – 15.2)	p = 0.02
	JSAP -02[c]	11.4	5.0	p = 0.01, HR = 0.60 (95% CI = 0.40–0.89)
Median OS (months)	CONKO-001[d]	22.8	20.2	p = 0.005
	ESPAC -1[b]	20.1 (95% CI = 6.5-22.7)	15.5 (95% CI = 13.0 – 17.7)	p = 0.009, HR = 0.71
	JSAP -02[c]	22.3	18.4	p = 0.19, HR = 0.77 (95% CI = 0.51-1.14)
OS at 2 years	CONKO-001[a]	47%	42%	NA
	ESPAC -1[b]	40%	30%	NA
	JSAP -02[c]	48.3%	40%	NA

Abbreviations: CI = confidence interval; CONKO = Charité Onkologie; DFS = disease-free survival; ESPAC = European Study Group for Pancreatic Cancer; HR = hazard ratio; NA = not available; OS = overall survival; JSAP = Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer.

[a] Oettle, 2007 – treatment: 6 cycles of gemcitabine, primary endpoint: DFS.

[b] Neoptolemos, 2004 – treatment: 6 cycles of 5-FU/Leucovorin, primary endpoint: OS.

[c] Ueno 2009 – treatment: 3 cycles of gemcitabine, primary endpoint: OS.

[d] Neuhaus, 2008 – updated data for median OS; initial data from Oettle, 2007 indicated chemotherapy median OS of 22.1 months (95% CI, 18.4-25.8) and nonchemotherapy median OS of 20.2 months (95% CI, 17-23.4), p = 0.06.

A meta-analysis of 875 patients showed a 25% significant reduction in the risk of death with chemotherapy versus surgery alone, and the 5-year survival rate almost doubled with the use of adjuvant chemotherapy compared with no chemotherapy (Stocken, 2005). Another analysis of 951 patients enrolled in randomized studies showed a significant survival benefit for median survival after adjuvant chemotherapy, but not for the 5-year survival rate (Boeck, 2007). This analysis also provided evidence that adjuvant therapy substantially prolonged DFS along with improving OS (Boeck, 2007).

Although there is no European- or US-approved medicine for adjuvant treatment of pancreatic adenocarcinoma, standard pancreatic adenocarcinoma treatment guidelines provided by National Comprehensive Cancer Network (NCCN) are followed in the US and China (NCCN, 2013),

while in Europe, guidance on standard of care for treatment of subjects with pancreatic cancer is provided by the European Society for Medical Oncology (ESMO) (Seufferlein, 2012).

The NCCN guidelines recommend 6 treatment options for the postoperative adjuvant setting. Enrollment into a clinical study is the first recommended treatment option, followed by either gemcitabine or fluorouracil/leucovorin before or after chemoradiation, and then chemotherapy alone with gemcitabine or fluorouracil/leucovorin, and lastly, capecitabine (NCCN, 2013).

The ESMO guidelines (Seufferlein, 2012) recommend 6 months of gemcitabine or fluorouracil given postoperatively based on the results of three randomized studies (Neoptolemos, 2004; Neoptolemos, 2010; Oettle, 2007). Since there is no evidence of any advantage of adjuvant chemoradiation as compared to adjuvant chemotherapy alone, the ESMO guidelines recommend that chemoradiation in the adjuvant or additive setting should only be performed within randomized, controlled clinical studies.

In early 2013, data from a study conducted in Japan (JASPAC-01) revealed significant improvements in 2-year relapse-free survival (RFS) and OS rates with a new investigative product, S-1, a combination of tegafur (an oral fluoropyrimidine), gimeracil, and oteracil potassium, versus gemcitabine (Table 2; Uesaka, 2013). S-1 was originally developed as a gastric cancer treatment in Japan where it is used as a standard of care since its initial approval there in 1999. S-1 is not approved for use as adjuvant therapy in patients with surgically resected pancreatic adenocarcinoma, and the study was limited to only Japanese patients. The appropriate dose and efficacy is not established in non-Asian patients.

Table 2: Relapse-free Survival and Overall Survival in JASPAC-01[a]

Parameter	Gemcitabine	S-1[b]	Significance
Median RFS (months)	11.2 months (95% CI = 9.7-13.5)	23.2 months (95% CI = 17.5-32)	p < 0.0001, HR = 0.56 (95% CI = 0.43 to 0.71)
Median OS (months)	25.9 months	Not matured	p < 0.0001, HR = 0.56 (98.8% CI = 0.36 to 0.87)
OS at 2 years	53% (95% CI = 46-60)	70% (95% CI = 63-76)	NA

Abbreviations: CI = confidence interval; HR = hazard ratio; JASPAC = Japan Adjuvant Study Group of Pancreatic Cancer; NA = not available; OS = overall survival; RFS = relapse-free survival.
[a] Uesaka, 2013 – primary endpoint: OS.
[b] S-1: tegafur, gimeracil, and oteracil potassium.

At the interim analysis, moderate improvement in survival in resectable pancreatic cancer was achieved with adjuvant chemotherapy, with median OS of 20 to 24 months and 21% to 24% 5-year OS rates (Seufferlein, 2012). More efficacious treatment options are needed.

1.3. *nab*-Paclitaxel (ABRAXANE)

nab-Paclitaxel (interchangeable with ABRAXANE and ABI-007) is a unique protein formulation of a noncrystalline, amorphous form of paclitaxel in an insoluble particle state. *nab*-Paclitaxel was designed to improve the chemotherapeutic effects of paclitaxel by exploiting endogenous

transport pathways to deliver higher doses of paclitaxel to the tumor and to reduce the solvent-related hypersensitivity and other toxicities associated with Taxol® (paclitaxel) injections, the solvent Cremophor EL, and ethanol vehicle. *nab*-Paclitaxel provides more rapid tissue distribution and increased tumor accumulation compared to Cremophor-EL paclitaxel (Desai 2006, Gardner 2008, Chen 2014). Mechanistically, albumin receptor-mediated transport across the endothelium, binding to interstitial proteins, and macropinocytic or receptor-mediated uptake into tumor cells as well as sequestration of paclitaxel by Cremophor-EL may contribute to the observed differences. Furthermore, *nab*-paclitaxel synergizes with gemcitabine in preclinical models. The Cremophor-EL-free medium enables *nab*-paclitaxel to be given at a higher dose and in a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions (Desai, 2006).

As of March 2014, *nab*-paclitaxel is approved under the trade name of ABRAXANE in over 45 countries/regions, including the US, Canada, India, European Union/European Economic Area, South Korea, China, Australia, Bhutan, United Arab Emirates, Nepal, New Zealand, Japan, Russia, Sri Lanka, Argentina, Hong Kong, and Lebanon for the treatment of patients with metastatic breast cancer. ABRAXANE is also approved for the first-line treatment of locally advanced or metastatic non small cell lung cancer (NSCLC) in the US, Japan, Argentina, Australia, and New Zealand, for treatment of advanced gastric cancer in Japan, and for first-line treatment of metastatic adenocarcinoma of the pancreas in the US, EU/EEA, Australia, New Zealand and Argentina. *nab*-Paclitaxel alone and in combination is being evaluated as chemotherapeutic agent for the treatment of patients with various solid tumor malignancies.

Please refer to the Investigator's Brochure for more detail on and concerning the available preclinical, pharmacology, toxicology, drug metabolism, clinical study data, and AE profile of *nab*-paclitaxel.

1.3.1. Preclinical and Clinical Experience with *nab*-Paclitaxel Plus Gemcitabine in Pancreatic Cancer

Preclinical studies have demonstrated that *nab*-paclitaxel may play a role in sensitizing the tumor to chemotherapeutic agents and specifically increases the antitumor efficacy when combined with gemcitabine. While the mechanism of action for the synergy is unclear, preclinical studies have generated hypothetical models. One hypothesis is a remodeling and weakening of the stroma barrier, allowing the chemotherapeutic agents to have better access to the tumor cells. Weakening the tumor-stroma barrier is particularly important in cancer that is characterized by dense stroma, such as pancreatic cancer. In mice with primary patient derived pancreatic tumor xenografts, *nab*-paclitaxel plus gemcitabine versus gemcitabine alone resulted in increased tumor regression and depleted the desmoplastic stroma as observed by the less dense, disorganized, wisps of collagen type 1 fibers after 4 weeks of treatment (Von Hoff, 2011). In this study, the intratumoral concentration of gemcitabine was increased by 2.8-fold after 5 days of treatment when *nab*-paclitaxel was added to gemcitabine. It was hypothesized that *nab*-paclitaxel may play a role in reducing the dense stroma and may have contributed to the increased intratumoral gemcitabine uptake. Additional preclinical studies in a genetically engineered mouse model of pancreatic adenocarcinoma, coadministration of *nab*-paclitaxel and gemcitabine also demonstrated tumor regression and increased intratumoral gemcitabine levels after 8 days of treatment. Apoptosis of tumor epithelial cells were observed; however, there were no changes in stromal components or collagen density in this short term treatment model (Frese, 2012). The

increased intratumoral gemcitabine levels were attributed to a marked decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase, by *nab*-paclitaxel. Finally, a recent clinical study in subjects with resectable pancreatic cancer treated with neoadjuvant *nab*-paclitaxel plus gemcitabine showed reduction in fibrotic collagenous stroma, further supporting a stroma active mechanism for *nab*-paclitaxel (Alvarez, 2013).

In a clinical Phase 1/2 dose ranging study (CA040, NCT003980860), *nab*-paclitaxel plus gemcitabine antitumor activity and tolerability were established in patients who had no prior treatment for metastatic pancreatic cancer (Von Hoff, 2011). The maximum tolerated dose and recommended dose for further studies was determined to be 125 mg/m^2 *nab*-paclitaxel in combination with 1000 mg/m^2 gemcitabine.

In the subsequent randomized international Phase 3 study (MPACT, CA046, NCT00394251) that enrolled 861 patients with metastatic pancreatic cancer, *nab*-paclitaxel in combination with gemcitabine exhibited a clinically meaningful, statistically significant improvement in OS and progression-free survival (PFS). The median OS (primary endpoint) in the intent-to-treat population was 8.5 months (95% CI = 7.89-9.53) with *nab*-paclitaxel/gemcitabine compared with 6.7 months (95 % CI = 6.01-7.23) with gemcitabine, $p < 0.0001$, HR = 0.72 (95% CI = 0.617-0.835). Long-term survival was improved in the *nab*-paclitaxel/gemcitabine arm versus gemcitabine alone, with a 59% increase at 1 year (35% versus 22%) and doubling at 2 years (9% versus 4%). The secondary (PFS, overall response rate [ORR]) and all other efficacy endpoints showed consistent, statistically significant improvements with *nab*-paclitaxel/gemcitabine, supporting the results from the primary analysis of OS. Specifically, PFS (by independent review) was 5.5 months (95% CI = 4.47-5.95) versus 3.7 months (95% CI = 3.61-4.04) in the *nab*-paclitaxel/gemcitabine arm versus gemcitabine alone arms, respectively $p < 0.0001$; HR =0 .69; 95% CI = 0.581-0.821). The improvement in PFS corresponded to a 31% reduction in the risk of progression or death with *nab*-paclitaxel/gemcitabine. Furthermore, in this study of metastatic unresectable adenocarcinoma of the pancreas, subjects in the combination arm were on therapy longer than those receiving single agent gemcitabine, indicating disease improvement and tolerable treatment (Von Hoff, 2013). The suitability of the dosing regimen was confirmed by the observation that the majority of patients did not require a dose reduction, and that 71% of *nab*-paclitaxel doses were delivered at the starting dose of 125 mg/m^2. The safety profile for both regimens was consistent with previous reports. Serious life threatening toxicities were not increased; AEs were acceptable and manageable. The most notable differences in toxicity between the 2 treatment arms was peripheral neuropathy, which was cumulative and rapidly reversible with dose delay and reduction, and neutropenia, which was manageable with dose delays and dose reductions. The incremental risks of sepsis and pneumonitis were managed by protocol amendments to increase awareness, and for early diagnosis and treatment to reduce the risk of fatal outcomes.

Since the above described initial analysis of the MPACT study, the updated OS with a cutoff of May 2013 showed that the benefit continued to improve with *nab*-paclitaxel in combination with gemcitabine, with 8.7 versus 6.6 median months, respectively (Goldstein, ASCO GI 2014). The updated survival rates also significantly favored *nab*-paclitaxel plus gemcitabine at year 1 (35% versus 22%), year 2 (10% versus 5%), and year 3 (4% versus 0%) as compared with gemcitabine alone.

To date, the only other trial that resulted in clinically meaningful improvement in OS in pancreatic adenocarcinoma was the Phase 2/3 FOLFIRINOX versus gemcitabine study, which was conducted in 1 country (Conroy, 2011). While numerous promising Phase 2 studies have been conducted in advanced pancreatic cancer, most subsequent large Phase 3 studies have failed to show significant improved survival (Colucci, 2010; Cunningham, 2009; Kindler, 2010; Oettle, 2005; Philip, 2010; Poplin, 2009; Rocha Lima, 2004).

As a result of the clinically meaningful benefit observed in the MPACT trial, the 2013 NCCN guidelines were updated to include *nab*-paclitaxel plus gemcitabine under treatment option category 1 for patients with metastatic pancreatic adenocarcinoma (NCCN, 2013).

1.4. Study Rationale

Currently no adjuvant chemotherapy regimen for pancreatic adenocarcinoma can claim superiority and the approaches to treatment differ only slightly between the US and the EU (Herreros-Villanueva, 2012). Despite the noted improvements of chemotherapy following surgery, recurrence rates are still high and survival rates poor, and there remains a high unmet medical need for more effective adjuvant therapies.

The positive results from the global pivotal Phase 3 Study CA046 with *nab*-paclitaxel plus gemcitabine in the metastatic setting form the basis for the evaluation of this combination in the adjuvant therapy setting.

Gemcitabine is proposed as the active comparator in this study as it is considered a standard chemotherapy for the treatment of subjects with surgically resected pancreatic adenocarcinoma and is one of the recommended treatments in the NCCN guidelines and a recommended treatment of choice by ESMO guidelines (NCCN, 2013; Seufferlein, 2012).

The goal of adjuvant treatment is to cure or induce a longer disease-free period (versus a shorter disease-free period requiring early and possibly longer symptom control), thus the primary measurement of a disease-free state is clinically relevant. This was paramount when selecting the endpoint of the proposed adjuvant study. Selecting DFS as an endpoint is most appropriate in settings, as in pancreatic cancer, where it is predicted that disease recurrence represents a major component of morbidity and mortality in the treated population (Gill, 2006). Using OS as a primary endpoint in the adjuvant setting presents a major challenge, with confounding factors, such as the subsequent anticancer therapies after disease recurrence which would impact the OS results.

The evidence obtained from studies of other cancer types with established adjuvant therapy supports the use of DFS as a valid and reliable measure of clinical benefit. From both a patient's and physician's perspective, the prevention or delay of pancreatic cancer recurrence and associated improved survival is meaningful.

DFS and OS were highly correlated in more than 20,000 patients with resected high-risk colon cancer treated in Phase 3 adjuvant clinical studies, both within subjects and across studies (Sargent, 2005). A recent meta-analysis of more than 7,000 subjects from 25 clinical studies provided evidence that DFS is a valid surrogate endpoint for OS in operable NSCLC in the adjuvant chemotherapy setting (Michiels, 2011). In this meta-analysis, a high level of correlation was seen between DFS and improvement in OS.

As detailed in Section 1.3, in published studies of adjuvant chemotherapy in subjects with surgically resected pancreatic cancer, the results suggest that prolonged DFS was associated with survival benefit in these subjects.

Although there can be challenges with using DFS as the primary endpoint in a clinical study, these can be overcome as demonstrated by the studies that have supported registration of the medicinal products described above. This protocol proposes to address these known challenges with DFS in the proposed adjuvant study by implementing the following:

- Ensure the symmetrical disease evaluation and assessment between the two treatment arms
- Mitigate assessment bias from the investigator assessment through the use of an independent blinded radiology review
- Include clearly defined censoring rules in the statistical plan to address the impact of missing or unscheduled visits.

Based on the improvement in survival with *nab*-paclitaxel in combination with gemcitabine in subjects with metastatic pancreatic cancer (Von Hoff, 2013), *nab*-paclitaxel plus gemcitabine adjuvant therapy may extend DFS compared with gemcitabine alone and provide a meaningful clinical benefit in subjects with surgically resectable pancreatic adenocarcinoma.

1.4.1. Rationale for Stratification Factors

Subjects are proposed to be stratified at randomization based on:

- Resection Status: R0 versus R1
- Nodal Status: LN+ versus LN-
- Region (North America, Europe, and Australia versus Asia Pacific)

The resection status and nodal status are known prognostic factors in pancreatic cancer and have been selected based on their use in a previous successful Phase 3 study of adjuvant therapy in subjects with resected pancreatic cancer (Oettle, 2007), as well as previous reports describing the prognostic relationship between these factors and survival. In the CONKO-001 study, LN- versus LN+ categories were associated with longer survival (Oettle, 2007). Lymph node invasion also showed a statistically significant correlation with early relapse in a small retrospective analysis of patients with resected pancreatic cancer (Fischer, 2012). Because of the possible regional differences in this global study, randomization will be stratified by region as well.

One of the main pathologic predictors of survival after surgery is resection margin status. Resection of margin-positive (R1) pancreatic tumors have poorer prognosis than R0. Results from the ESPAC-1 study showed that both R1 and R0 patients benefit from both resection and adjuvant chemotherapy, but not chemoradiation; however, the magnitude of benefit for chemotherapy treatment was reduced for patients with R1 margins versus those with R0 margins (Neoptolemos, 2001b).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare DFS between subjects randomized to *nab*-paclitaxel in combination with gemcitabine and subjects randomized to gemcitabine alone.

2.2. Secondary Objectives

The secondary objectives of the study are to:

- Assess OS between subjects randomized to *nab*-paclitaxel in combination with gemcitabine and subjects randomized to gemcitabine alone
- Evaluate safety and tolerability

2.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Assess tumor molecular heterogeneity and associate identified tumor molecular subtypes with clinical outcome
- Investigate whether circulating nucleic acids are associated with disease recurrence
- Evaluate the effect of *nab*-paclitaxel in combination with gemcitabine and gemcitabine alone on subject quality of life (QoL)

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of the study is independently assessed DFS, determined by an independent radiologist(s) who is blinded to the treatment assignment, which is defined as the time from the date of randomization to the date of disease recurrence or death, whichever is earlier.

3.2. Secondary Endpoint(s)

The secondary endpoints of the study are:

- OS, which is defined as the time from the date of randomization to the date of death
- The incidence of TEAEs, SAEs, laboratory abnormalities and other safety parameters

3.3. Exploratory Endpoint(s)

The exploratory endpoints of the study are:

- Molecular profiling of tumor tissue
- Identification of tumor nucleic acids from blood
- Differences in outcomes between the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ), EORTC QLQ-C30 and QLQ-PAN26, during and after treatment versus at baseline

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 3, international, multicenter, randomized, open-label, controlled study assessing the efficacy of *nab*-paclitaxel in combination with gemcitabine versus gemcitabine alone as adjuvant therapy in adult subjects with surgically resected pancreatic adenocarcinoma. See Figure 1 for Overall Study Design.

Subjects will be screened and if eligible, randomized 1:1 to receive:

Arm A - *nab*-Paclitaxel 125 mg/m^2, IV infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 IV infusion over 30 to 40 minutes, given once weekly for 3 weeks (Days 1, 8 and 15) followed by a week of rest (28-day cycle) for 6 cycles

or

Arm B - Gemcitabine 1000 mg/m^2, IV infusion over 30 to 40 minutes, given weekly for 3 weeks (Days 1, 8 and 15) followed by a week of rest (28-day cycle) for 6 cycles.

Subjects will be administered 6 cycles of treatment, unless there is evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death. Subjects will be assessed by CT scan at screening (≤ 14 days prior to randomization), at the schedule specified in Section 6.3.3. Magnetic resonance imaging can be used based on the investigator's judgment or institution policy, as long as the same modality is used through-out the study. Imaging assessments for disease recurrence should be continued until after the final analysis of DFS, at which point, any ongoing subjects who have not had disease recurrence should follow local standard of care for any additional imaging assessments. All subjects will also be followed for survival. The initiation and the types of new anticancer therapies will be collected.

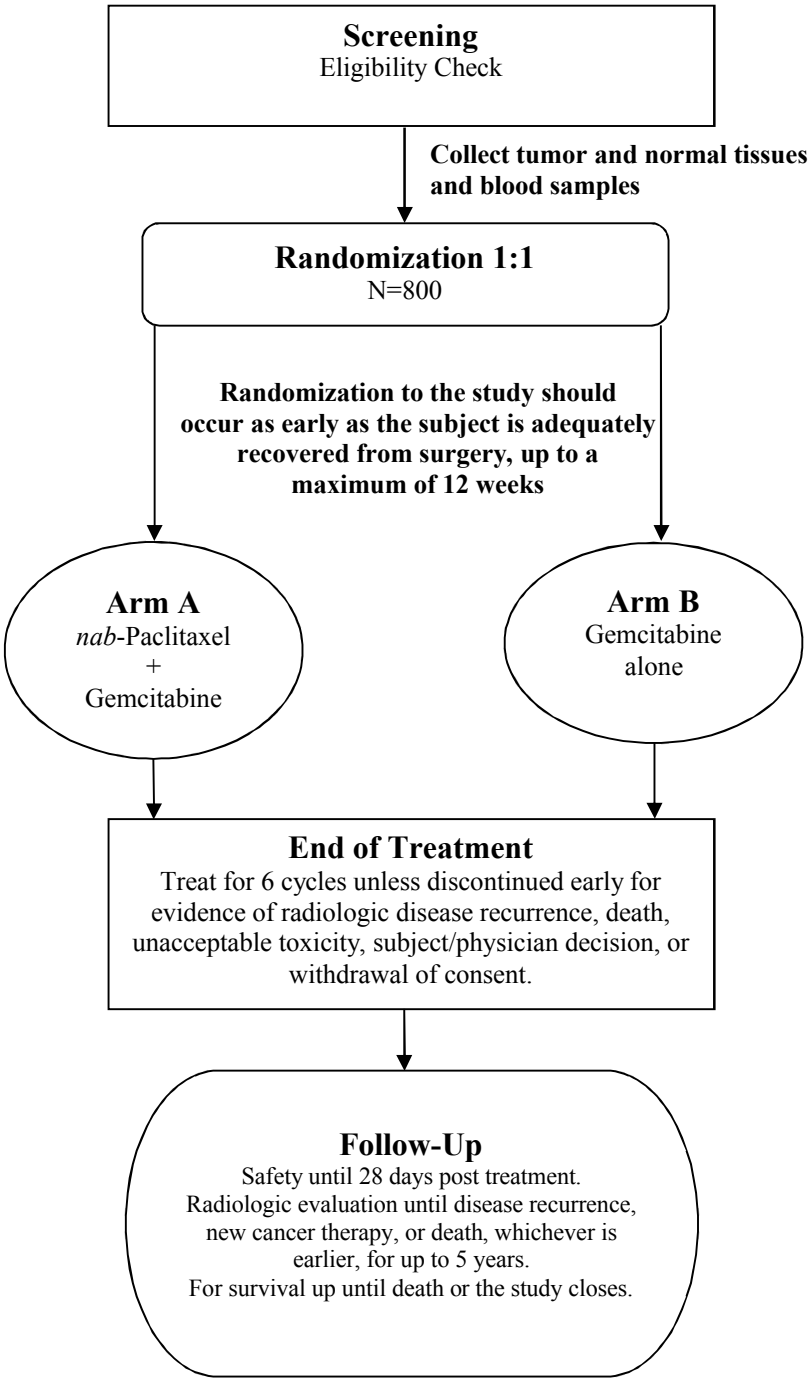
The study will enroll approximately 800 subjects. Randomization will be stratified between treatment arms by:

- Resection Status: R0 (tumor-free margin) versus R1 (microscopically positive margin)
- Nodal Status: LN+ versus LN-
- Region (North America, Europe, and Australia versus Asia Pacific)

A DMC (Section 10.9.1) and a Steering Committee (SC) (Section 10.9.2) will be assembled to assess the ongoing conduct of this study.

There will be 2 interim analyses conducted during the course of the study, as described in Section 10.8.

Figure 1: Overall Study Design



4.2. Study Duration

Eligible subjects should be randomized to the study as early as adequately recovered from surgery, but no later than 12 weeks postsurgery. Study treatment should start within 3 days of randomization. Enrollment is expected to take approximately 30 months, and approximately 9 months of follow-up is needed to observe the required number of DFS events.

4.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol.

5. TABLE OF EVENTS

Table 3: Table of Events

Assessment[a]	Screening[b]	Cycle 1 through Cycle 6 (Treatment Period)			End of Treatment (EOT) Visit[d]	Follow-up Period
		Day 1[c]	Day 8	Day 15		
Informed Consent	X					
Randomization	X[e]					
Demographics	X					
Medical History	X					
Physical Examination	X	X			X	
Height and Weight	X	X[f]			X[f]	
Urinalysis	X					
BSA Calculation[g]		X				
Prior/Concomitant Medication Evaluation	X	X	X	X	Until 28 days after the last dose of IP	
Prior/Concurrent Procedures Evaluation	X	X	X	X	Until 28 days after the last dose of IP	
Peripheral Neuropathy Evaluation	X	X			X	
Vital Signs[h]	X	X	X	X	X	
ECOG PS	X	X	X	X	X	
Pregnancy Test[i]	X				X	
ECG (12 lead)	X					
Clinical Chemistry Panel	X	X			X	

Table 3: Table of Events (Continued)

Assessment[a]	Screening[b]	Cycle 1 through Cycle 6 (Treatment Period)			End of Treatment (EOT) Visit[d]	Follow-up Period
		Day 1[c]	Day 8	Day 15		
CBC, Differential, Platelet Count	X	X	X	X	X	
PT, PTT, INR	X					
Collect mandatory surgical primary pancreatic tumor sample [j]	X					
Collect mandatory surgical normal (duodenum or other) sample	X					
Biomarker blood sample [n]	X	Upon disease recurrence at any time during treatment or follow-up period, until the number of events for the primary endpoint is achieved sample must be collected prior to the start of new therapy				
Collect tumor sample from biopsy [k, n]		Upon disease recurrence, if available, and until the number of events for the primary endpoint is achieved				
CT /MRI Scan [n]	X	• 8 weeks after randomization for the first 24 weeks • then every 12 weeks for the next 2.5 years (130 weeks) until 3 years after randomization • then every 24 weeks thereafter until disease recurrence for the next 2.5 years				
Serum CA19-9 [n]	X	Same schedule, or on the same week, as CT/MRI				
Quality of Life [n]	X	Cycle 4 day 1 only			X	X[l]
Treatment Arm A: *nab*-Paclitaxel/Gemcitabine Arm		X	X	X		
Treatment Arm B: Gemcitabine-only Arm		X	X	X		
Adverse Events	Continuous starting from signing of Informed Consent until 28 days after last dose of IP					
Follow-up for Survival and Anticancer Therapy[m]						X

Abbreviations: AE = adverse event; BSA = body surface area; β-hCG = beta-human chorionic gonadotropin; CA19-9 = carbohydrate antigen 19-9; CBC = complete blood count; CT = computed tomography; ECG – electrocardiogram; EOT = end of treatment; MRI = magnetic resonance imaging; ECOG PS= Eastern Cooperative Oncology Group performance status; INR= International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time.

[a] Unless otherwise specified, visits must occur within ± 2 days of the planned visit date.
[b] Screening evaluations to be obtained ≤ 14 days prior to randomization.
[c] Cycle 1 Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.
[d] For subjects who complete 6 cycles of treatment, the EOT visit should be performed as soon as possible after end of Cycle 6 (ie, after Cycle 6 Day 28), but no later than 14 days after Cycle 6 Day 28. For subjects who discontinue treatment prior to completing 6 cycles of treatment, the EOT visit should be performed as soon as possible after the decision is made to discontinue treatment.
[e] Randomization to occur within 72 hours of planned Cycle 1 Day 1.
[f] Weight only.
[g] Body Surface Area calculations to be performed Cycle 1 Day 1 and recalculated per the site's standard of care, or when body weight changes by more than 10%.
[h] Vital signs include temperature, systolic and diastolic blood pressure, and pulse.
[i] For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess subject eligibility at screening prior to first IP administration (negative results required for IP administration). Urine pregnancy test will be performed at EOT (can be done locally) and as clinically indicated as per institutional guidelines.
[j] Samples will be collected any time prior to first IP administration, but after informed consent is signed. It is mandatory for patients to provide surgical samples, if they are available and local regulations allow it. FFPE tumor blocks are preferred. Normal surgical sample (ie, duodenum, negative margin) will be collected for molecular marker analysis.
[k] Biopsy surgical sample: FFPE tumor tissue from biopsy will be collected (tumor blocks are preferred – refer to Laboratory Manual for details). Ensure the surgical pathology report is submitted with tumor tissue sample
[l] Quality of Life questionnaires (EORTC QLQ-C30 and QLQ-PAN26) will be collected prior to dosing. During the follow-up period, follow the same schedule, or on the same week, when a CT or MRI is performed until disease recurrence. The QLQ-PAN26 questionnaire will not be collected in Finland, Portugal and Singapore.
[m] Follow-up for survival and subsequent anticancer therapy can be performed by telephone contact every 3 months or more frequently if needed, from EOT.
[n] All the procedures during the follow-up period, except for the follow up for survival and anticancer therapy, will be terminated once the number of events for the primary endpoint is achieved.

6. PROCEDURES

6.1. Central Laboratory and Central Imaging

Central imaging and a Clinical Laboratory Improvement Amendments (CLIA) approved central laboratory will be used for laboratory testing.

Sites will be required to use the designated central lab(s) for the study. Central labs must be drawn for all eligibility assessments, but subjects may be randomized based on local lab results only if the central lab results are not readily available to permit randomization and dosing. The local lab results should be well within the range for eligibility as to likely yield central lab results that will confirm the eligibility criteria. Subject eligibility for the study will be defined by central lab results, except for coagulation tests which are acceptable locally. Specific instructions regarding specimen collection and handling may be found in the Laboratory Manual. Decisions with respect to IP dosing can be made based on a local lab draw if the central laboratory results have not been received. EOT pregnancy test may be done locally.

A central imaging reviewer(s) blinded to treatment will provide an independent review for disease recurrence for all subjects enrolled into the study. Prospective collection of all on-study scans for all subjects enrolled in the study will be included as part of the review.

Films or electronic copies should be collected by the investigative sites and sent to the central imaging reviewer(s) and a copy of the file will be kept on site. Complete details regarding image handling and submission can be found in the Radiology Manual. Additional details on when scans will be obtained on subjects are found in Sections 6.2, 6.3, 6.4, 6.5.

6.2. Screening Evaluations

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be obtained ≤ 14 days prior to randomization. Any questions regarding subject eligibility should be directed to Celgene or other sponsor-nominated representatives or designees for approval.

The following evaluations will be performed at screening after informed consent has been obtained:

- Demographics (if allowed by local regulations, collect initials, date of birth, sex, race, and ethnicity)
- Medical history (including cancer history and specific information regarding any prior therapy)
- Physical examination (source documented only)
- Height and weight assessment
- Urinalysis (a urine dipstick may be used)
- Prior/concomitant medication evaluation: all medications taken ≤ 28 days prior to screening

- Prior/concurrent procedures evaluation: all procedures done ≤ 28 days prior to screening
- Peripheral neuropathy evaluation
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test (for women of childbearing potential only) will be conducted prior to first IP administration (negative results required for IP administration)
- 12-lead ECG
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin and creatinine);
- Complete blood count (CBC), differential and platelet count
- Coagulation studies (eg, PT/PTT, local lab results allowed to confirm subject eligibility)
- Collect archival surgical primary pancreatic tumor sample for molecular and biomarker analysis (mandatory if available). Collect archival surgical normal sample (duodenum or other) for baseline analysis (mandatory, if available)
- Collect pathology report from surgical tumor sample
- Collect a biomarker blood sample (mandatory)
- CT or MRI scan
- Serum carbohydrate antigen 19-9 (CA19-9)
- QoL questionnaire completion: EORTC QLQ-C30 and QLQ-PAN26
- Adverse event assessment (refer to Section 11.1 for details)

6.3. Randomization and Treatment Phase Evaluations

The subject may be randomized once all inclusion/exclusion criteria are met during screening and is adequately recovered from surgery. Subjects should return within 3 days of randomization to begin Cycle 1 of IP dosing.

- Subjects should have Cycle 1 day 1 (C1D1) dosing planned for within 3 days of randomization. If the subject cannot be dosed within this time, it will need to be discussed with the sponsor

Unless otherwise specified, visits where disease recurrence assessments are not performed must occur within ±2 days of the planned visit date.

If the investigator suspects a drug-related toxicity, an unscheduled visit with additional laboratory tests may be performed.

nab-Paclitaxel and gemcitabine should be administered for 6 cycles as specified in Section 8.2.

6.3.1. Day 1 Assessments

The following assessments will be performed on Day 1 of each of the 6 treatment cycles:

- Physical examination (source documented only)
- Weight assessment
- BSA calculation
- Concomitant medication evaluation
- Concurrent procedures evaluation
- Peripheral neuropathy evaluation
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin and creatinine)
- CBC, differential and platelet count
- QoL questionnaire completion (only at Cycle 4 Day 1 prior to dosing)
- AE assessment

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

6.3.2. Per Cycle Evaluations

On Day 8 and Day 15 of each of the 6 treatment cycles, the following assessments will be performed:

- Concomitant medication evaluation
- Concurrent procedures evaluation
- Vital signs
- ECOG performance status
- CBC, differential and platelet count
- AE assessment

6.3.3. Assessment of Disease Recurrence

Disease recurrence will be assessed by CT; image preparation and evaluation for new lesions will follow the specifications provided in the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. RECIST will be used only as a guidance to identify new lesions: new lesions will not be followed. Magnetic resonance imaging can be used based on the

investigator's judgment or institution policy, as long as the same modality (CT or MRI) is used at screening and throughout the study.

CT/MRI scan of the chest and abdomen/pelvis is to be performed at the following frequency until disease recurrence irrespective of treatment status:

- ≤ 14 days prior to randomization (screening period)
- every 8 weeks after randomization for the first 24 weeks
- followed by every 12 weeks for the next 2.5 years (130 weeks) until 3 years after randomization
- followed by every 24 weeks thereafter until disease recurrence for the next 2.5 years (130 weeks) up to 5.5 years after randomization

Scans can be done +/- 7 days from the time of the planned assessment. An unscheduled scan for suspected disease recurrence may be performed at any time. However, adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments.

CA19-9 values will be obtained on the same week as the CT scans, but are not to be used alone as evidence of disease recurrence.

During the evaluation for disease recurrence, subjects may develop suspicious lesions or accumulate ascites, pleural or other fluids that may or may not be suspected to be recurrent disease. In such cases, it is recommended that a biopsy be obtained. Pathology reports from these biopsies should be submitted, and in the setting of a positive biopsy for disease recurrence, a tumor sample should be sent to the central laboratory, if available.

In all subjects who have had disease recurrence (regardless of whether a biopsy was obtained), a blood sample will also be collected prior to the start of any new therapy.

At the time of disease recurrence, if a biopsy is performed, a tumor sample will be collected and sent to the central laboratory, if available. Ensure that the surgical pathology report is submitted with the tumor tissue sample. Refer to the Laboratory Manual for processing and shipping details.

6.4. End of Treatment (EOT) Evaluations

An EOT evaluation should be performed for all subjects according to the following schedule:

- For subjects who complete 6 cycles of treatment, as soon as possible after end of Cycle 6 (ie, after Cycle 6 Day 28), but no later than 14 days after Cycle 6 Day 28
- For subjects who discontinue treatment prior to completing 6 cycles of treatment, as soon as possible after the decision is made to discontinue treatment

A completed subject is defined as a subject that has completed 6 cycles of treatment and received at least 2 doses during Cycle 6.

A discontinued subject is defined as not completing all 6 cycles of treatment, or only received 1 dose during Cycle 6.

The following procedures will be completed at the EOT Visit:

- Physical examination (source documented only)
- Weight assessment
- Concomitant medication evaluation and ≤ 28 days after the last dose of IP
- Concurrent procedures evaluation and ≤ 28 days after the last dose of IP
- Peripheral neuropathy evaluation
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status
- Urine pregnancy test for females of childbearing potential (can be done locally)
- Clinical chemistry panel (to include sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin and creatinine);
- CBC, differential and platelet count
- QoL questionnaire completion
- AE assessment

6.5. Follow-up Period (for Disease Recurrence)

Subjects who are discontinued from study treatment in the absence of disease recurrence (eg, subjects who completed 6 cycles of treatment or are removed for unacceptable toxicity or subject/investigator discretion) are followed for disease recurrence. Subjects should undergo repeat imaging until disease recurrence, death, or the start of new anticancer therapy is documented (except as noted below), whichever is earlier. CT/MRI scans should be performed until disease recurrence (as specified in Section 6.3.3) irrespective of treatment status. Adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments.

All subjects will be followed for survival and subsequent or new anticancer therapies (recorded on the respective electronic case report form [eCRF]) unless the subject withdraws consent from the entire study or dies.

Subsequent anticancer therapy (including radiation) should not be instituted until disease recurrence is documented. If a subject starts subsequent anticancer therapy prior to disease recurrence, then repeat imaging assessments should be discontinued, except as follows:

- Subjects randomized to *nab*-paclitaxel + gemcitabine → who receive subsequent therapy with *nab*-paclitaxel, or gemcitabine, or both (without any other agents)
- Subjects randomized to gemcitabine → who receive subsequent therapy with gemcitabine (without any other agents)

CA19-9 values will be obtained on the same week as the CT scans, but are not to be used alone as evidence of disease recurrence.

QoL questionnaire will also be completed on the same week as the CT or MRI scans.

Imaging assessments for disease recurrence, QoL, CA19-9, and biopsy collection will be stopped after the number of events for the primary endpoint have been achieved and after the final analysis of DFS by independent radiology. At this point, any ongoing subjects who have not had disease recurrence should follow local standard of care for any additional imaging assessments and laboratory testing.

6.6. Follow-up Period for Overall Survival and Anticancer Therapy

Post-treatment OS and any subsequent anticancer therapy information status will be monitored every 3 months or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is earliest. This evaluation may be by record review and/or telephone contact.

6.7. Biomarker and Pharmacogenomic Testing

The key objective of the tumor molecular profiling is to identify specific markers that are predictive of response or emerging resistance to the combination of *nab*-paclitaxel and gemcitabine or gemcitabine alone. The key objective of the biomarker blood sampling is to investigate whether blood sampling can serve as a "liquid biopsy" to monitor disease recurrence.

When surgical tumor tissue is available, the collection of formalin fixed paraffin embedded (FFPE) tumor blocks (preferred) or 15 unstained slides is mandatory for all subjects for biomarker and pharmacogenomic testing. Additionally, a surgical normal tissue sample, such as from the duodenum, is requested if available (FFPE tumor block or 15 unstained slides). A biomarker blood sample at screening is mandatory. A surgical pathology report will be collected for each tumor sample provided.

A blood sample will be collected at the time of disease recurrence prior to the start of new anti-cancer therapy. It is highly recommended that a biopsy is performed at the time of disease recurrence, when possible. A tumor sample should be collected at the time of biopsy and sent to the central laboratory along with the surgical pathology report. The suspected tumor recurrence biopsy should represent a core needle or greater sized sample that would be sufficient for molecular analysis. Data have been emerging on potential markers of treatment resistance, and will potentially lead to the development of new therapeutic interventions for these subsets of patients. Therefore, it is highly recommended that a biopsy be submitted for further analysis whenever clinically feasible.

Details on processing and shipping subject samples are described in the Laboratory Manual.

Overview of Biomarker and Pharmacogenomic Testing

- FFPE tumor and normal blocks:
    - Tumor tissue sample: In order to achieve the key objective of identifying a biomarker, it is essential that the tissue samples be as uniform as possible. Therefore, primary pancreatic tumor tissue from the surgical resection is requested. If necessary, resected lymph node tissue may be substituted.
    - Normal tissue sample: The normal duodenum or other normal tissue sample provides a baseline for biomarker analyses that is comparably processed.

- Tumor molecular profiling:
  - Tumor tissue RNA and DNA will be profiled and compared with normal tissue RNA and DNA to identify genomic markers that correlate with clinical outcome with a key objective to identify specific markers that are predictive of response to the combination of *nab*-paclitaxel and gemcitabine. Analyses of the profiles will be performed to characterize the range of molecular heterogeneity for the tumors and to look for evidence of molecular subtypes of tumors. If tumor molecular subtypes are identified, correlations between subtypes and clinical outcome will be explored. Specific assays will be prioritized after study completion, as informed by emerging data and methodologies.
  - It is preferred that a surgical specimen FFPE block representative of the diagnosis be sent so that sections from each specimen can be generated at the central testing laboratory. However, in cases where FFPE blocks may not be released from the custody of the site and additional FFPE blocks cannot be provided from the surgically resected tumor, the sections may be prepared at the site. At least 15 slides are requested for the molecular profiling work (refer to the Laboratory Manual for details). The surgical pathology report for the tumor should be sent with the tissue.
  - If a biopsy is performed upon recurrent disease, FFPE tumor block from the biopsy (or 15 slides, refer to the Laboratory Manual) should be provided, if available. The surgical pathology report should be sent with the tissue.
- Immunohistochemistry (IHC) analysis:
  - Human equilibrative nucleoside transporter 1 (hENT1) and secreted protein acidic and rich in cysteine (SPARC) are examples of proteins that may be analyzed by IHC. SPARC is associated with prognosis of pancreatic cancer in the adjuvant setting (Infante, 2007; Sinn, 1997). hENT1 may be a predictor of response to gemcitabine-based chemotherapy (Neoptolemos, 2013).

- Biomarker blood samples:
  - Cell-free DNA Blood Collection Tubes (BCT) collected at:
    - Screening
    - Upon disease recurrence (regardless if tissue was collected)

Nucleic acids extracted from blood will be used for normal genome (if needed) and circulating tumor nucleic acid profiling. The collection of a blood sample upon disease recurrence is highly recommended as it may provide important data on drug resistance mechanisms. Methodologies for circulating tumor nucleic acid identification may include but are not limited to DNA profiling or targeted gene sequencing, as informed by emerging data and methodologies.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 800 subjects will be enrolled at approximately 160 sites globally.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Histologically confirmed resected ductal pancreatic adenocarcinoma with macroscopic complete resection (R0 and R1). Subjects with neuroendocrine (and mixed type) tumors are excluded.
2. Pancreatic cancer staging: T 1-3, N0-1, M0.
3. Subject should be able to start treatment no later than 12 weeks postsurgery.
4. Male or non-pregnant, non-lactating females who are ≥ 18 years of age at the time of signing the informed consent form (ICF).
5. ECOG performance status of 0 or 1
6. Acceptable hematology parameters:
   - Absolute neutrophil count ≥ 1500 cell/mm^3
   - Platelet count ≥ 100,000/mm^3
   - Hemoglobin (Hgb) ≥ 9 g/dL
7. Acceptable blood chemistry levels:
   - AST/ SGOT and ALT/ SGPT ≤ 2.5 × upper limit of normal range (ULN)
   - Total bilirubin ≤ ULN (subjects with Gilbert's syndrome can have bilirubin of up to 1.5 x ULN)
   - Alkaline phosphatase ≤ 2.5 x ULN
   - Serum creatinine within upper limits of normal or calculated clearance ≥ 50 mL/min/1.73 m^2. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg, using the Cockroft-Gault formula). For subjects with a Body Mass Index (BMI) >30 kg/m^2, lean body weight should be used instead
8. CA19-9 < 100 U/mL assessed within 14 days of randomization
9. Acceptable coagulation studies (eg, PT or INR, and PTT within normal limits, ±15%)
10. 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 [ie, has had menses at any time during the preceding 24 consecutive months]) must:

- Agree to the use of two physician-approved contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study IP; and for 3 months following the last dose of IP; and
- Has negative serum pregnancy test (β -hCG) result at screening

11. Male subjects:
    a. 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.
12. Understand and voluntarily sign an ICF prior to any study related assessments or procedures being conducted.
13. Be able to adhere to the study visit schedule and other protocol requirements.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Prior neo-adjuvant treatment, radiation therapy, or systemic therapy for pancreatic adenocarcinoma
2. Presence of or history of metastatic or locally recurrent pancreatic adenocarcinoma
3. Any other malignancy within 5 years prior to randomization, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, or nonmelanomatous skin cancer (all treatment of which should have been completed 6 months prior to randomization)
4. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment
5. Known history of human immunodeficiency virus (HIV) infection, or known history of active hepatitis B or C and are currently serologically positive with evidence of prior or signs of active chronic hepatitis
6. History of allergy or hypersensitivity to *nab*-paclitaxel or gemcitabine or any of their excipients
7. Serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders, which could compromise the subject's safety or the study data integrity. These include, but are not limited to:
    a. History of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa)

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

b. History of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies

c. History of the following within 6 months prior to Cycle 1 Day 1: 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 ECG abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder

d. Peripheral neuropathy $\geq$ Grade 2

e. Concomitant use of immunosuppressive or myelosuppressive medications that would in the opinion of the investigator, increase the risk of serious neutropenic complications

8. Enrollment in any other clinical protocol or investigational study with an interventional agent or assessments that may interfere with study procedures
9. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
10. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
11. Any condition that confounds the ability to interpret data from the study
12. Unwillingness or inability to comply with study procedures

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

nab-Paclitaxel will be supplied by the sponsor and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number, EudraCT number (if applicable), 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.

Gemcitabine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines.

Additional information may be included on the label as needed or applicable. Label(s) for IP supplied to sites outside the US will contain information as required per local health authority.

IP supply will be managed by Interactive Randomization Technology (IRT). All IP must be stored in accordance with the product label in a secured area to prevent unauthorized access.

8.1.1. ABRAXANE (*nab*-Paclitaxel)

nab-Paclitaxel will be supplied by the sponsor, Celgene Corporation, in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Please see local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions and IV administration of *nab*-paclitaxel.

Temperature records for *nab*-paclitaxel must be made available to Celgene or other sponsor-nominated monitoring teams for verification of proper IP storage.

8.1.2. Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor.

Gemcitabine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines.

Please see gemcitabine prescribing information for more details on available formulations, preparation, storage conditions, the approved indications, known precautions, warnings, and adverse reactions of gemcitabine (see current version of Prescribing Information).

8.2. Treatment Administration and Schedule

Treatment cycles are 28 days in duration and subjects are to complete 6 cycles.

Investigational Product, Dose, and Mode of Administration

- **Arm A**
  - *nab*-Paclitaxel 125 mg/m^2 as a 30- to 40-minute infusion followed by gemcitabine 1000 mg/m^2 as a 30- to 40-minute infusion on Days 1, 8 and 15 of a 28-day cycle for 6 cycles. Following administration of *nab*-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.
- **Arm B**
  - Gemcitabine 1000 mg/m^2 as a 30- to 40-minute infusion administered on Days 1, 8 and 15 of a 28-day cycle for 6 cycles

Subjects do not require premedication prior to *nab*-paclitaxel administration, as hypersensitivity reactions are not expected. If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. If felt to be in the subject's best interest, at the investigator's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for solvent-based paclitaxel.

For gemcitabine, the prescribing information for recommended premedication strategies needs to be followed.

Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

8.2.1. Rules for Dose Omissions and Modified Schedules

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

Day 1 Dose Missed

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the subject (ie, 1-2-3-Rest, X-1-2-3-Rest, etc).

Day 8 Dose Is Missed

Cycle continues per protocol, with one dose not given (ie, 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc).

Day 15 Dose Missed

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the subject is considered to have had a x2q3 (21-day) cycle (ie, 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

The maximum delay between a missed scheduled dose, due to drug related toxicity, and the next one (whichever dose was missed) should not be longer than 21 days (except for peripheral neuropathy; see Table 6).

8.2.1.1. Dose Modification Tables

Doses will be reduced, one level at a time, for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0.

Two levels of dose modifications are permitted, for each drug, according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either IP, additional dose reductions are not permitted. However, further treatment should be discussed with the sponsor.

Table 4: Dose Modifications

Dose Level	*nab*-Paclitaxel Dose (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]
Study Dose	125	1000
-1	100	800
-2[b]	75	600

[a] Dose reductions may or may not be concomitant, refer to Table 5. If the dose is withheld due to hematologic toxicity on Day 15, with either a held dose, or no dose modification on Day 8, subjects should be considered for either treatment at the next lower dose level and/or addition of white blood cell (WBC) growth factor support when the subject has adequate absolute neutrophil count (ANC) and platelet counts to begin Day 1 of the next cycle. Refer to Table 5 for specific recommendations regarding dose modifications for Day 1.

The lowest dose level for each drug in a single dose administration is 75 mg/m^2 *nab*-paclitaxel or 600 mg/m^2 gemcitabine.

8.2.1.1.1. Dose Modifications

In the event dose modifications are required at the start of a cycle or within a cycle due to hematologic toxicities of neutropenia and/or thrombocytopenia, doses of *nab*-paclitaxel and gemcitabine may be adjusted as detailed in Table 5. In the combination arm, the investigator may hold one agent while continuing the other and remain on study. The combination may be restarted at the discretion of the treating physician.

WBC growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC < 500 cells/mm^3. Subjects not experiencing resolution of neutropenia within 21 days, despite uninterrupted WBC growth factor treatment, will discontinue study treatment. In addition, WBC growth factors may be administered as supportive therapy to recover ANC adequately such that dosing levels may be maintained. If a dose reduction was required due to neutropenia, a dose re-escalation may be considered with continued growth factor support. If a dose reduction is required for a reason other than neutropenia, a dose re-escalation could be permitted after discussion with the sponsor. If hematologic toxicity is restricted to platelet counts alone, dose modification of only gemcitabine could be considered after discussion with the sponsor.

Table 5: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	*nab*-Paclitaxel Dose	Gemcitabine Dose
Day 1	≥ 1500	AND	≥ 100,000	Treat on time at current dose levels	
	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Treat with same doses as Day 8; consider following with WBC growth factors for support*	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Option A: Maintain dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 1 dose levels from Day 1	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Option A: Reduce 1 dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 2 dose levels from Day 1	
	< 500	OR	< 50,000	Withhold doses	

Abbreviations: ANC = absolute neutrophil count; WBC = white blood cell.

* The use of WBC growth factors is only applicable if the dose limiting hematologic toxicity was limited to neutropenia or febrile neutropenia.

Dose modifications for other adverse drug reactions are provided in Table 6.

Table 6: Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	*nab*-paclitaxel Dose	Gemcitabine Dose
Febrile Neutropenia[a]: Grade 3 or 4	Withhold doses until fever resolves and ANC is ≥ 1500; resume at next lower dose level[b]	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improvement to ≤ Grade 1; resume at next lower dose level[b]	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce doses to next lower dose level[b]; discontinue treatment if ADR persists	
For all other nonhematologic toxicities (except nausea, vomiting, alopecia and pulmonary embolism[c]) of ≥ Grade 3	Withhold dose of either or both agent(s) until improvement to ≤ Grade 1; resume at next lower dose level[b]	

Abbreviations: ADR, adverse drug reaction; ANC = absolute neutrophil count.
[a] White blood cell growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC of < 500 cells/mm^3.
[b] See Table 4 for dose level reductions.
[c] See Section 8.2.1.1.3.

8.2.1.1.2. Administration of IP to Subjects with Abnormal Hepatic Function

Hepatic toxicity may occur, but it is uncommon. Therefore, hepatic dysfunction that occurs while the subject is on study should prompt an evaluation to determine the cause, including the possibility of metastatic disease and hepatotoxicity from concurrent medications, alcohol use, or other factors.

8.2.1.1.3. Pulmonary Embolism and Deep-vein Thrombosis

To resume IP administration in the event of a pulmonary embolism or deep-vein thrombosis, subjects must be started on low molecular weight heparin or similar anticoagulation therapy. Grade 4 events must be resolved to Grade ≤ 3 within 21 days to continue IP.

8.2.1.1.4. Interstitial Pneumonitis

While participating in this study, subjects should be carefully monitored to prevent or minimize the occurrence of interstitial pneumonitis. Careful prestudy screening with continuous on-study monitoring for signs and symptoms is required. Should a subject develop symptoms of pneumonitis during this study, the timely initiation of appropriate management is required. Recommended guidelines are as follows:

1. Before enrollment, evaluate candidate subjects for familial, environmental, or occupational exposure to opportunistic pathogens, and do not enroll those with a history of slowly progressive dyspnea and unproductive cough, or of conditions such as

sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies (controlled or uncontrolled) that in the opinion of the investigator may pose a risk to the subject or study.

2. During study treatment, provide close attention to episodes of transient or repeated dyspnea with unproductive persistent cough or fever. Radiographic evaluation with chest x-rays and CT scans (normal or high resolution) may be indicated to evaluate for infiltrates, ground-glass opacities, or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
3. Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.
4. Administration of IP should be interrupted upon diagnosis of interstitial pneumonitis and subjects permanently discontinued from further study drug treatment. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Subjects with an added immunological agent may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

8.2.1.1.5. Prophylaxis Against Sepsis

In the metastatic pancreatic cancer Phase 3 study (CA046), an increase in cases of non-neutropenic sepsis was observed with the combination of *nab*-paclitaxel and gemcitabine. An exploratory analysis suggested that the presence of biliary stents may have increased the risk of sepsis in that population. Investigators were to provide oral broad spectrum antibiotics to subjects who were then to initiate these antibiotics at the first occurrence of fever. Subjects enrolled in this clinical trial may not have the same risk of sepsis as metastatic pancreatic cancer patients. Subjects should be advised that there could be an increased risk of serious infection and they should contact their physician for evaluation when they develop a fever. Fever or similar symptoms should be fully evaluated as an early sign of a serious infection. Broad spectrum antibiotics such as fluoroquinolones may be provided to subjects to treat or as prophylaxis for infection at the discretion of the treating physician.

8.2.1.1.6. Hypersensitivity Reactions

Hypersensitivity reactions are infrequent with *nab*-paclitaxel. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of IP administration and aggressive symptomatic therapy.

Subjects who develop a severe hypersensitivity reaction to *nab*-paclitaxel should not be rechallenged.

8.2.2. Overdose

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of IP assigned to a given subject, regardless of any associated AEs or sequelae.

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about IP administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of AEs associated with overdose.

8.3. Method of Treatment Assignment

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will be randomized to receive either *nab*-paclitaxel in combination with gemcitabine or gemcitabine alone. The permuted block randomization method will be used to generate the randomization codes and the randomization will be performed by IRT to ensure a 1:1 treatment assignment ratio. The randomization schedule will be generated by the sponsor or its designee.

The randomization will be stratified by the factors described in Section 4.1.

8.4. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene (or its designee) will review with the investigator and relevant site personnel the process for IP return, disposal, and/or destruction, including the responsibilities for the site versus Celgene (or designee).

Investigational product containers that are not completely empty should be disposed of in accordance with institutional/regional requirements, unless otherwise agreed with Celgene. Completely used containers should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Drug Accountability Record Form.

The investigator, or designee, shall record the dispensing of IP to subjects in the IP accountability record form. The IP record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel, for the purpose of accounting for the IP supply. Inspections of the IP supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or its designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the investigator to another investigator or site. Under certain circumstances, and with sponsor permission, cooperative groups may manage IP between locations within their network as clinical study agreement and local guidelines permit.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's electronic case report form (eCRF) and source documents. The investigator or designee is responsible for accounting for all study-specific IP either administered or in their custody during the course of the study.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the eCRF.

9.1. Permitted Concomitant Medications and Procedures

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease recurrence. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the investigator.

WBC growth factors may be administered at the discretion of the investigator, consistent with institutional guidelines (refer to Section 8.2.1.1.1 for details) and with the Prescribing Information for such growth factors. WBC growth factors should be used only in patients who have demonstrated prior events of neutropenia; primary prophylaxis with WBC growth factors is not permitted.

Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines.

Subjects receiving warfarin should be closely followed for therapeutic levels of anticoagulation; low-molecular weight heparins (LMWH) may be used instead. As the chemotherapy regimens may result in thrombocytopenia, subjects receiving full dose aspirin, clopidogrel or other potential platelet depleting agents should be closely monitored.

The potential drug-drug interactions precautions contained in the *nab*-paclitaxel prescribing information will be applied to this study, unless otherwise specified in the protocol (refer to Prescribing Information). Specifically, the metabolism of paclitaxel is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4. Caution is recommended when administering *nab*-paclitaxel concomitantly with substrates or inhibitors of the cytochrome P450 isozymes CYP2C8 and CYP3A4.

For information regarding other drugs that may interact with either *nab*-paclitaxel or gemcitabine and affect their metabolism, pharmacokinetics, or excretion, please see the gemcitabine and *nab*-paclitaxel package inserts (refer to Prescribing Information).

9.2. Prohibited Concomitant Medications and Procedures

Radiation treatment is not allowed during the study. Administration of other chemotherapy, immunotherapy, or antitumor therapy during the study is not allowed until documented disease recurrence.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a Phase 3, international, multicenter, open-label, randomized, controlled study of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone as adjuvant therapy in subjects with surgically resected pancreatic adenocarcinoma. Subjects will be randomized in a 1:1 ratio to two treatment arms following permuted block randomization methods. The randomization will be stratified by the following factors:

- Resection Status: R0 (tumor-free margin) versus R1 (microscopically positive margin)
- Nodal Status: LN+ versus LN-
- Region (North America, Europe, and Australia versus Asia Pacific)

A DMC will be used to review the safety and efficacy results from the planned interim analyses. The sections below provide an overview of the proposed statistical considerations and analyses. The final statistical analysis methods will be documented in detail in the statistical analysis plan (SAP).

10.2. Study Population Definitions

10.2.1. Intent-to-treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether the subject received any IP or had any efficacy assessments collected.

10.2.2. Treated Population

The treated population will consist of all randomized subjects who received at least one dose of IP. The treatment groups for the safety analyses are based on the treatment as received if different from the assigned treatment by randomization.

10.2.3. Per-Protocol Population

The per-protocol population consists of all treated as randomized subjects who met all eligibility criteria and had no radiological evidence of pancreatic cancer prior to randomization by independent review.

10.3. Sample Size and Power Considerations

The primary objective is to compare the DFS in subjects who received *nab*-paclitaxel in combination with gemcitabine and subjects who received gemcitabine alone.

The hypotheses are the following:

H_0: $HR_{A+G/G} = 1$

versus

H_1: $HR_{A+G/G} \neq 1$

where $HR_{A+G/G}$ is the hazard ratio (HR) of DFS between the *nab*-paclitaxel in combination with gemcitabine arm and the gemcitabine alone arm.

Disease-free survival was reported with a median of 13.4 months and 14.3 months for patients with surgically resected pancreatic adenocarcinoma who received gemcitabine as adjuvant treatment in two separate randomized Phase 3 studies (Neoptolemos, 2010; Oettle, 2007). With the assumption of the true median DFS of 14 months in the gemcitabine arm and 19 months in the *nab*-paclitaxel in combination with gemcitabine arm which is equivalent to a $HR_{A+G/G}$ of 0.74, at least 489 DFS events from 800 subjects are required to allow 90% power to detect a 26% reduction of risk in disease recurrence or death from the treatment arm at a two-sided significance level of 0.05. One interim analysis of efficacy is planned at about 33% information time (ie, after 163 DFS events) to assess futility. The accrual rate is estimated to be approximately 26.7 subjects per month for a total estimated enrollment period of 30 months. The nonbinding stopping boundary will be based on the Gamma family spending function with parameter = -2 (Hwang, 1990) to control the Type 2 error rate at 10%. The HR boundary for futility at 33% information time is ≥ 0.98, however the actual boundary may vary depending on the number of DFS events at the time of analysis.

As of April 2016, a total of 866 subjects were enrolled in the study. After enrollment to this protocol was completed, more contemporaneous Phase III studies with gemcitabine in the targeted population of surgically resected pancreatic adenocarcinoma have shown consistently that DFS for patients may be lower than the median DFS of 14 months in the CONKO-001 study (Oettle, 2007), which provided the rationale for the timing and duration of the DFS assessments in the ABI-007-PANC-003 study. Results from the CONKO-005 (Sinn, 2017) and PRODIGE 24 (Conroy, 2018) studies showed a median DFS with adjuvant gemcitabine of 11.4 and 12.8 months, respectively. Based on these new data, Protocol Amendment 4 will revise the final DFS analysis to be earlier than originally planned (489 events).With the assumption of the true median DFS of 13.5 months in the gemcitabine arm and 18.5 months in the *nab*-paclitaxel in combination with gemcitabine arm, which is equivalent to an $HR_{A+G/G}$ of 0.73, approximately 438 DFS events are required to allow 90% power to detect a 27% reduction of risk in disease recurrence or death from the treatment arm at a two-sided significance level of 0.05. The data cutoff date for the revised final DFS analysis is projected to be December 2018, by which time 438 DFS events may be reached.

Overall survival data will be analyzed as supportive analyses. The reported median survival from 2 randomized Phase 3 studies in subjects with surgically resected pancreatic adenocarcinoma who received gemcitabine as adjuvant treatment (Neoptolemos, 2010; Oettle, 2007) ranged from 22 months to 24 months. Table 7 illustrates the probability that the nominal two-sided p-value would be less than 0.05 under different assumptions when approximately 630 events are observed. It is projected that between 410 and 440 deaths will have occurred at the time of the data cut-off for the final DFS analysis and all subjects remaining on study will have at least 32 months of survival follow-up.

Table 7: Power Calculation for Overall Survival with N = 800

Hazard Ratio of OS	Median OS (months)	Number of Deaths/N	Power
0.85	$M_G = 22$ $M_{A+G} = 26$	624/800	55%
0.80	$M_G = 22$ $M_{A+G} = 27.5$	633/800	82%
0.75	$M_G = 22$ $M_{A+G} = 29$	630/800	95%

Abbreviations: M_G = median for gemcitabine arm; M_{A+G} = median for *nab*-paclitaxel/gemcitabine arm; OS = overall survival.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentage for both treatment and follow-up phases.

10.6. Efficacy Analysis

All efficacy analysis will be conducted based on the ITT population. The primary and secondary efficacy analyses will also be conducted based on the treated population and per-protocol population. While key analyses are described in this section, additional analyses, including sensitivity analyses and subgroup analyses, will be specified in the SAP.

10.6.1. Primary Efficacy Analyses

The primary efficacy endpoint will be DFS which is defined as the time from the date of randomization to the date of disease recurrence or death, whichever is earlier. Disease recurrence will be determined by the independent radiological review of CT or MRI scans. Subjects who received new anti-cancer therapy or cancer-related surgery prior to disease recurrence or death will be censored. Detailed censoring rules will be documented in the SAP.

The survival distribution of DFS will be estimated using the Kaplan-Meier method: medians and two-sided 95% CIs will be provided by treatment arms. The comparison of DFS between the two arms will be conducted using stratified log-rank test, with the stratification factors: resection status (R0 versus R1), nodal status (LN+ versus LN-), and region (North America, Europe, and Australia versus Asia Pacific). The associated HR and two-sided 95% CIs will be provided using the Cox proportional hazard model.

10.6.2. Secondary Efficacy Analyses

The secondary efficacy endpoint will be OS which is defined as the time from the date of randomization to the date of death. Subjects who are alive will be censored on the last-known-to-be-alive date. The survival distribution of OS will be estimated using the Kaplan-Meier methods: medians and two-sided 95% CIs will be provided by treatment arms. The survival rates at different time points will be provided. P-values based on stratified log-rank test will be provided. The associated HRs and two-sided 95% CIs will be provided using the Cox proportional hazard model.

10.7. Safety Analysis

All safety analyses will be conducted based on the treated population.

10.7.1. Adverse Events

The safety population, which includes all randomized subjects who received at least 1 dose of IP, will be the analysis population for all safety analyses. Adverse events will be analyzed in terms of TEAE defined to be any event that begins or worsens in grade after the start of IP through 28 days after the last dose of IP. All events will be coded using MedDRA. AEs will be summarized by severity/grade based on the NCI CTCAE Version 4.0. If a subject experiences the same AE multiple times during the treatment, the event will be counted only once and by the greatest severity.

Treatment-emergent adverse events, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms. Adverse events of special interest of the *nab*-paclitaxel plus gemcitabine combination identified in previous trials in a similar population will be summarized in the same manner.

10.7.2. Laboratory Results

In order to investigate the maximal degree of myelosuppression, the NCI CTCAE Version 4 grade for ANC, WBC, platelet count, and hemoglobin will be summarized for each treatment group by the most severe grade in each treatment cycle and by the most severe grade at any time during the treatment.

Hepatic and renal function will be summarized for each treatment group using the most severe NCI CTCAE grade for ALT(SGPT), AST(SGOT), total bilirubin, and creatinine by cycle and at any time during the treatment.

10.8. Interim Analysis

One interim analysis on safety is planned after the first 100 subjects have completed 2 cycles of treatment. Additionally, one interim analysis on efficacy is planned at about 33% information time (ie, after 163 DFS events). A second interim analysis on efficacy had been planned for futility and superiority after observing 70% DFS events or enrollment of 800 subjects, whichever was later. However, at time of Protocol Amendment 3, the interim analysis for futility at 163 DFS events has been performed and no subjects are receiving investigational

product (IP). To avoid premature interruption of the trial, and to ensure that the study has sufficient duration of follow-up to verify clinical benefit and assess benefit-risk in this setting, this second interim analysis has been removed from the study. The analysis will be conducted by an independent third party statistician and the DMC will examine the interim results and provide recommendations to continue the study or terminate the study early. Additional details will be provided in the DMC charter and SAP.

10.9. Other Topics

10.9.1. Data Monitoring Committee

A DMC will be convened that will include medical oncologists with experience in treating subjects with pancreatic cancer and a statistician, all of whom are not otherwise involved in the study conduct. During the course of the study, the DMC will review the safety and efficacy data in accordance with the guidelines for the preplanned interim analyses. The committee will review safety data after the first 100 subjects have completed 2 cycles of the treatment. One interim analysis on efficacy is planned at about 33% information time (ie, after 163 DFS events). The DMC will review the interim efficacy results and provide the recommendation on whether the study should be discontinued due to lack of efficacy. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled meeting. Operational details for the DMC will be detailed in the DMC charter.

10.9.2. Steering Committee

The conduct of this trial will be overseen by a SC, presided over by the coordinating principal investigator and if possible the representative regional investigators from countries participating in this study. The SC will serve in an advisory capacity to the Sponsor. Operational details for the SC will be detailed in a separate SC charter.

Note: The SC is separate from the DMC.

10.10. Exploratory Analyses

10.10.1. Tumor Markers

Statistical analysis of the exploratory data collected from plasma and tissue samples will be described in an analysis plan separate from the SAP and reported in a stand-alone report separate from the CSR.

10.10.2. Quality of Life

Quality of life will be evaluated for both *nab*-paclitaxel in combination with gemcitabine and gemcitabine alone using the EORTC-QLQ-30 and EORTC QLQ- PAN26 questionnaires. The QLQ-PAN26 questionnaire will not be collected in Finland, Portugal and Singapore. The differences in quality of life outcomes between the two study arms will be statistically investigated cross-sectionally and longitudinally, sample size and data permitting. Changes from baseline in overall score and sub-scores will be analyzed using methodologies, such as ANOVA/ANCOVA.

11. ADVERSE EVENTS

11.1. Monitoring, Recording, and Reporting of Adverse Events

An 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 (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. Disease recurrence and death due to the progression of disease will not be recorded as an AE.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.2. for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. 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.

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 other appropriate tests and procedures.

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 SAEs will be recorded on the AE page of the eCRF 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.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all AEs as to:

11.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death
- Is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE)
- Requires in-patient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an in-patient 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 (eg, 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 (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment or elective procedure of a preexisting condition unrelated to the studied indication.
- Emergency out-patient 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 eCRF 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.

11.2.2. 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 NCI CTCAE Version 4.0.

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.

11.2.3. 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 AE 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 AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE

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.

11.2.4. Duration

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

11.2.5. Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation. Interruption, or reduction of IP, as appropriate), and report whether concomitant and/or additional treatments were given for the event.

11.2.6. 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, recovered with sequelae, not recovered, or death (due to the SAE).

11.3. 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
- is judged to be of significant clinical importance

Regardless of severity grade, only laboratory abnormality that fulfills a seriousness criterion needs to be documented as an SAE.

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 eCRF. 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 (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

11.4.1. Females of Childbearing Potential:

Pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product 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 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 (eg, spontaneous 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 by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety 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.

11.4.2. Male Subjects

If a female partner of a male subject taking the IP becomes pregnant, the male subject taking the IP should notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. 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. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time of signing of the informed consent form to 28 days after the last dose of IP), and those made known to the investigator at any time thereafter that are suspected of being related to IP.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to *nab*-paclitaxel based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32. For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner, to all Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, gemcitabine, based on the UK Summary of Product Characteristics (SmPC). For the purpose of regulatory reporting in the EEA, Celgene non-IMP gemcitabine SAEs and nonserious SAEs will be reported to the Regulatory Authorities, in accordance with Regulation (EC) No. 726/2004 and/or Directive 2001/83/EC as amended, and also in accordance with country-specific requirements for countries within the EEA.

Celgene or its authorized representative shall notify the investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR)
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information,)

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the SAE Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

12.1. Discontinuation from Investigational Product

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- AE(s) (that are intolerable)
- Disease recurrence
- Physician decision
- Withdrawal of consent (from treatment only)
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on the eCRF)

The reason for treatment discontinuation should be recorded in the eCRF and in the source documents.

12.2. Discontinuation from the Study

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

At the time of withdrawal, it should be determined whether the subject is withdrawing from treatment alone, or from treatment and collection of further data (eg, survival).

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after the title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after the title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/CRO Medical Monitor, who will then contact the investigator promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if the investigator is not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators, who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, and study treatments, as well as study-related duties and functions including obligations of confidentiality of Celgene information. The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries, and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of eCRFs and queries.

14.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be reconsented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and will be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title, and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations, and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a coordinating investigator and the IRB/EC. This statement also applies to any communication between the investigator (or coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study
- Deviations from the protocol or anything that may involve added risk to subjects

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment
- GCP noncompliance
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy; and the laboratories, as well as copies of eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICF for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the investigator, Celgene, and their authorized representative(s)
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures
- Copies of eCRFs and of documentation of corrections for all subjects
- IP accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Study)

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRF, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRF against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRF or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria, and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada), and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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