

# DISCLOSURE

## REDACTED STATISTICAL ANALYSIS PLAN

ABI-007-PANC-003

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

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## STATISTICAL ANALYSIS PLAN

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

**STUDY DRUG:** nab-Paclitaxel

**PROTOCOL NUMBER:** ABI-007-PANC-003

**DATE FINAL:** 15 Aug 2016

**AMENDMENT DATE:** 17 Jan 2019

Prepared by:

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**SIGNATURE PAGE**

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SAP AMENDMENT VERSION, DATE	Final 17 Jan 2019		
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INVESTIGATIONAL PRODUCT	nab-Paclitaxel		
PROTOCOL NUMBER	ABI-007-PANC-003		
PROTOCOL VERSION, DATE	Amendment 4, 12 Sep 2018		
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.		
<b>Statistical Therapeutic Area Head</b>			
Signature	<i>{See appended electronic signature page}</i>		
Printed Name	_____ Date _____		
<b>Lead Clinical Research Physician / Clinical Research Physician</b>			
Signature	<i>{See appended electronic signature page}</i>		
Printed Name	_____ Date _____		
<b>Lead Product Safety Physician</b>			
Signature	<i>{See appended electronic signature page}</i>		
Printed Name	_____ Date _____		

## 1. LIST OF ABBREVIATIONS

**Table 1: Abbreviations and Specialist Terms**

AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
BMI	Body mass index
BSA	Body surface area
CA19-9	Carbohydrate antigen 19-9
CI	Confidence interval
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
HR	Hazard ratio
LN	Lymph nodes
IP	Investigational product
IPMN	Intraductal papillary mucinous neoplasm
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable



NCI	National Cancer Institute
OS	Overall survival
PET	Positron emission tomography
PN	Peripheral neuropathy
PP	Per-protocol
PT	Preferred term
QLQ	Quality of life questionnaires
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SMQ	Standardised MedDRA Query
SOC	System organ class
STDEV	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limit

## 2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol ABI-007-PANC-003 "A Phase 3, Multicenter, Open-label, Randomized Study of *nab*<sup>®</sup>-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone as Adjuvant Therapy in Subjects With Surgically Resected Pancreatic Adenocarcinoma" which was originally issued on 06 Sep 2013 and subsequently amended on 23 Jun 2014 (Amendment No. 1) and on 03 Dec 2015 (Amendment No. 2). It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

Following finalization of the SAP on 15 Aug 2016, Protocol Amendment No. 3 and 4 were released on 21 Dec 2016 and 12 Sep 2018, respectively. This SAP amendment reflects all changes to the planned analysis. Other clarifications and incidental formatting changes were made throughout the document.

This study includes 2 protocol pre-planned interim analyses, one final analysis on disease-free survival (DFS) and one supportive analysis on overall survival (OS). Throughout this SAP, the treatment arms will be referred to as *nab*-paclitaxel in combination with gemcitabine (Arm A) and gemcitabine alone (Arm B). The name "*nab*-paclitaxel" is interchangeable with "ABRAXANE<sup>®</sup>". The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to any data analysis prior to database lock. This SAP amendment will be finalized and signed prior to the clinical database lock for the final analysis on DFS. All statistical analyses detailed in the SAP amendment will be conducted using SAS<sup>®</sup> Version 9.2 or higher. The clinical cutoff date will be determined based on the occurrence of DFS or OS events as specified in the SAP amendment.

### 3. STUDY OBJECTIVES

#### 3.1. 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.

#### 3.2. Secondary Objectives

The secondary objectives of the study are to:

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

#### 3.3. Exploratory Objectives

The exploratory objectives of the study are to:

- CCI [REDACTED]
- CCI [REDACTED]
- Evaluate the effect of *nab*-paclitaxel in combination with gemcitabine and gemcitabine alone on subject's quality of life (QoL)

## 4. INVESTIGATIONAL PLAN

### 4.1. Overall Study Design and Plan

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. The study will enroll approximately 800 subjects and 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)

The study will consist of the following visits:

**Screening Evaluations:** To be obtained  $\leq 14$  days prior to randomization.

**Randomization:** Eligible subjects should be randomized to the study as early as adequately recovered from surgery, but no later than 12 weeks postsurgery. Subjects should be dosed within 3 days of randomization. If the subject cannot be dosed within this time, it will need to be discussed with the sponsor.

**Treatment:** The treatment cycles are 28 days and the study drug (s) are administered for 6 cycles as specified in protocol Section 8.2. The dosing schedule for each treatment arm is as follows:

- Arm A
  - nab-Paclitaxel 125 mg/m<sup>2</sup> as a 30- to 40-minute infusion followed by gemcitabine 1000 mg/m<sup>2</sup> 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 (IV) 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<sup>2</sup> as a 30- to 40-minute infusion administered on Days 1, 8 and 15 of a 28-day cycle for 6 cycles

**Disease Recurrence Assessments:** Subjects will be evaluated for disease recurrence by computed tomography (CT) scans; image preparation and evaluation for new lesions will follow the specification provided in the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. RECIST ([Eisenhauer, 2009](#)) will be used only as a guidance to identify new lesions; new lesions will not be followed. Magnetic resonance imaging (MRI) 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 through the study. The CT/MRI scan of the chest and abdomen/pelvis is to be performed  $\leq 14$  days prior to randomization (screening period), every 8 weeks after randomization for the first 24 weeks, then every 12 weeks for the next 2.5 years until 3 years after randomization, and then every 24 weeks thereafter until disease recurrence for the next 2.5 years up to 5.5 years after randomization. Scans can be done  $\pm 7$  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.

Carbohydrate Antigen 19-9 (CA19-9) will be obtained at the same week as the CT scans, but are not to be used alone as evidence of disease recurrence.

**End-of-Treatment (EOT) Evaluation:** 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, the EOT visit should be performed as soon as possible after the decision is made.

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.

**Follow-up for Disease Recurrence:** Subjects who are discontinued from study treatment in the absence of disease recurrence (e.g., subjects 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.

Subsequent anticancer therapy (including radiation) should not be instituted until disease recurrence is documented. If a subject starts a subsequent anticancer therapy prior to disease recurrence, then repeat imaging and tumor response 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).

**Follow-up 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.

## 4.2. Study Endpoints

### 4.2.1. Primary Efficacy Endpoint

The primary endpoint of the study is independently assessed DFS, which is defined as the time from the date of randomization to the date of disease recurrence or death, whichever is earlier.

### 4.2.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint of the study is OS, which is defined as the time from the date of randomization to the date of death.

### 4.2.3. Exploratory Efficacy Endpoint(s)

Other efficacy endpoints of interest include:

- CCI [REDACTED]
- CCI [REDACTED]
- Difference 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.

Statistical analysis of the exploratory data collected from plasma and tissue samples will be described in an analysis plan separate from this SAP. Similarly, the QoL analyses will be addressed separately in a different analysis plan.

#### 4.2.4. Safety Endpoints

The safety/tolerability endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), grade 3 or higher TEAEs, TEAEs leading to dose reduction and dose interruption, TEAEs leading to treatment discontinuation and TEAEs with an outcome of death coded by Medical Dictionary for Regulatory Activities (MedDRA) and categorized and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE V4.0); incidence of adverse events of special interest of the *nab*-paclitaxel plus gemcitabine combination identified in previous trials in a similar population
- Centrally reviewed laboratory results (chemistries and blood counts) analyzed using NCI CTCAE V4.03
- Incidence of dose reductions, delays and omissions and reasons for dose reduction.

#### 4.3. Stratification and Randomization

Randomization will be performed by Interactive Randomization Technology (IRT) to ensure a 1:1 assignment ratio between two treatment arms. The permuted-block randomization will be used and the randomization will be stratified by the following factors:

- 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)

#### 4.4. Sample Size Determination

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:

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

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

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

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 two-sided significance level of 0.05. One interim analysis for efficacy is planned at about 33% information time (ie, after 163 DFS events) to assess futility.

As of April 2016, a total of 866 subjects were enrolled in the study. After enrollment to this study was completed, more contemporaneous Phase 3 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, 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.

OS data will be analyzed as supportive analysis. Table 2 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 2: Power Calculation for Overall Survival (OS) with N=800**

Hazard Ratio of OS	Median OS (months)	Number of Death/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

## 5. GENERAL STATISTICAL CONSIDERATIONS

### 5.1. Reporting Conventions

- For each dry-run prior to database lock, the treatment arm on the tables, listings, figures (TLFs) will be displayed in the blinded format using dummy codes;
- Data from all study centers will be combined for analysis;
- All stratified efficacy analyses will use the stratification factors including resection status (R0 versus R1) and nodal status (LN+ versus LN-), unless specified differently in specific analysis;
- All statistical tests of the treatment effect will be interpreted based on the stopping boundaries at each pre-specified interim analysis;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects (or cycles, if appropriate) in each category for discrete variables, and the sample size, mean, median, standard deviation (STDEV), minimum and maximum for continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to whole numbers. The number and percentage will be presented in the form XX (XX), where the percentage is in the parentheses. The percentages greater than 0 but rounded to 0 will be presented as <1 and the percentages less than 100 but rounded to 100 will be presented as >99 in the parentheses;
- All listings will be sorted for presentation in order of treatment arm, study site, subject identification number, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects) for each treatment group in the column heading;
- The day of the first dose of any investigational product (IP) will be defined as Day 1;
- Each cycle starts with the date of the first dose date of the cycle, and the end date of the cycle is the date before the first dose date of the subsequent cycle;
- For the last cycle, the end date of the cycle is the date the subject completed 6 cycles of treatment or the treatment discontinuation date recorded on the Treatment Disposition case report form (CRF). For subjects who are still on treatment at the time of the clinical cutoff, a nominal 28 days will be used as the last cycle duration. If the end date based on the planned duration is beyond the clinical cutoff date, the cutoff date will be used as the end date;
- In by cycle analyses, assessments taken pre-dose on Day 1 of a given cycle (e.g. laboratory measures) will be grouped with the previous cycle;



- Baseline value will be defined as the last non-missing value before the first dose of IP is administered; if multiple values are present for the same time point, the assessment with better result either by normal range or NCI CTCAE grade will be used; otherwise, the average of these values will be used as the baseline. For subjects who were not treated, the baseline will be the assessment value taken on the visit of Cycle 1 Day 1 if available; otherwise, the value on or prior to randomization date will be used;
- Partial dates will be imputed based on the rules specified in Section 16.2;
- All laboratory data will be reported using standard international (SI) units;
- Summaries of the most severe toxicity grade in clinical laboratory in each treatment cycle and most severe grade post-baseline overall and shifts from baseline to most severe toxicity grade post-baseline overall will include all scheduled and unscheduled assessments. The similar approach will be used for summaries in physician assessment of peripheral neuropathy (PN) grades;
- For safety parameters, the Final Evaluation will be defined as the last on-treatment value which is the last non-missing assessment on or prior to last dose date + 28 days or the treatment discontinuation date, whichever is later;
- SAS® Version 9.2 (or higher) will be the statistical software package used to produce all other data summaries, listings, graphs, and statistical analyses.

## 5.2. Analysis Populations

### 5.2.1. Intent-to-Treat Population

The Intent-to-treat (ITT) population includes all randomized subjects regardless of whether the subject received any IP or had any efficacy assessment collected.

### 5.2.2. Treated Population

The Treated population includes all randomized subjects who received at least one dose of IP. If a subject receives IP other than the subject's randomized treatment assignment, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study. Unless otherwise specified, the Treated population will be the analysis population for all safety analyses. Only subjects with clear documentation that no IP was administered will be excluded from the Treated population.

### 5.2.3. Per-Protocol Population

The Per-protocol (PP) population includes all treated as randomized subjects who met all eligibility criteria, and had no radiological evidence of pancreatic cancer prior to randomization by independent review.

## 6. SUBJECT DISPOSITION

The number of subjects screened, the number and percentage of subjects randomized and not randomized with screen failure, and the eligibility criteria failed will be summarized. The above percentages will be based on the number of subjects screened.

Analysis population allocation will be summarized. The number and percentage of subjects who were randomized and treated, completed, and discontinued the treatment period, and the number and percentage of subjects who discontinued the study will be presented for the ITT, Treated and PP populations by treatment arm and for all subjects combined. Each reason for treatment discontinuation and each reason for study discontinuation collected on the CRF will be summarized in the subject disposition table.

The randomization will be summarized by all strata and treatment arms. Enrollment will be summarized by treatment arm, and by region, country and study site. The number and percentage of subjects eligible or not eligible for the study and of subjects randomized under each protocol amendment will be summarized.

Subject disposition listing will include all subjects in the ITT population with reason for treatment discontinuation or reason for study discontinuation displayed for discontinued subjects. Listings of subject eligibility and subjects excluded from PP population will be provided. The listing for subjects randomized but not treated and the randomization scheme will also be provided.

## 7. PROTOCOL VIOLATIONS

The protocol violations will be identified and assessed by clinical research physician or designee following institution standard operational procedures. The protocol violations will be summarized by treatment arm for the ITT population.

A listing of subjects with protocol violations in the ITT population will be provided.

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## 8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT population by treatment arm and for all subjects combined. Individual subject listings will be provided to support the summary tables.

### 8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI) (weight [kg]/ height [m<sup>2</sup>]) at baseline, and body surface area (BSA) (m<sup>2</sup>) at baseline will be summarized by sample size, mean, median, STDEV, minimum, and maximum values. Age category (< 65 years and ≥ 65 years, < 75 years and ≥ 75 years), sex, race, ethnicity, region, country, ECOG performance status at baseline, PN at baseline and tobacco history (never smoked, passive smoker, past smoker, current smoker, and smokeless tobacco user) will be summarized by number and percentage of subjects in each category.

Age will be calculated as follows: Age = maximum integer ≤ ([Date of randomization – Date of Birth +1] / 365.25).

The summary for demographics will be provided for the ITT, Treated and PP populations.

### 8.2. Cancer History and Surgery

The number and percentage of subjects in each of the following categories will be presented:

- Type of surgery;
- Laparoscopic surgery;
- Pancreas position;
- Surgical staging;
- TNM classification;
- Nodal status;
- Resection status;
- Histology of primary diagnosis;
- Tumor grade;
- Presence of perineural invasion;
- Presence of lymphovascular invasion;
- Presence of local invasion;
- Intraductal papillary mucinous neoplasm (IPMN) being identified

Baseline value for CA19-9 from central lab data will also be summarized descriptively by treatment arm. The frequency summary of baseline CA 19-9 categories (within normal limit [WNL], upper limit of normal [ULN] - < 100 U/mL and ≥ 100 U/mL) will be provided.

Time from primary diagnosis to randomization, time from surgery to randomization, time from primary diagnosis to surgery, time from randomization to the first dose, tumor size, number of lymph nodes removed, and number of lymph nodes involved with cancer will be summarized descriptively by

treatment arm. For microscopic distance from tumor to the closest margin, the frequency summary of categories (< 1 mm and ≥ 1 mm) will be provided by treatment arm.

### **8.3. Baseline Disease Status**

Subjects will be summarized by disease status (either being disease free or having residual disease) prior to randomization, based on independent radiological assessment of scans. The subject who has no baseline scan by independent radiological assessment is presented as “Not Evaluable”.

### **8.4. Medical History**

A summary of medical history collected on CRF will be presented by MedDRA system organ class (SOC) and preferred term (PT).

### **8.5. Prior Therapy**

Any prior therapy will be collected at screening and only subjects who had no prior neo-adjuvant treatment or radiation therapy or systemic therapy for pancreatic adenocarcinoma will be eligible for this study. The prior therapies will be provided in listings.

#### **8.5.1. Prior Other Anti-cancer Therapy**

Prior other anti-cancer therapies will be coded to therapeutic drug classes and preferred drug names using the World Health Organization (WHO) Drug Dictionary. The incidence by therapeutic drug class and preferred drug name will be summarized.

#### **8.5.2. Prior Radiation Therapy for Other Diseases**

The number and percentage of subjects who had any prior radiation therapy for other diseases will be presented. For subjects with prior radiation therapy, the number and percentage of subjects with each type of radiation therapy will be presented.

#### **8.5.3. Prior Cancer Surgery for Other Diseases**

The number and percentage of subjects who had any prior cancer surgery for other diseases will be presented.

### **8.6. Prior and Concomitant Medications**

Medications reported on the Prior and Concomitant Medications CRF will be coded to therapeutic drug classes and preferred drug names using the WHO drug dictionary. All medication taken prior to screening and ≤ 28 days after the last dose of IP will be collected and included.

#### **8.6.1. Prior Medications**

A prior medication will be any medication stopped prior to the date of the first dose of IP. A summary will be presented showing the number and percentage of subjects who took prior medications by therapeutic drug class and preferred drug name, as well as the number and percentage of subjects that took any prior medication.

### 8.6.2. Concomitant Medications

Concomitant medication is defined as the medication that was either initiated before the first dose of IP and continued during the study treatment, or initiated on/after the date of the first dose of IP but on or before 28 days after the last dose of IP.

A summary will be presented showing the number and percentage of subjects who took concomitant medications by WHO therapeutic drug class and preferred drug name, as well as the number and percentage of subjects who took any concomitant medications.

Separate summary focusing on subjects receiving concomitant white blood cell (WBC) growth factors, transfusions with blood and blood-derived products, erythropoietin, narcotics, and systemic anti-infective (oral or IV, excluding topical medications and vaccines) will be provided.

Listing of prior and concomitant medications by subject will be provided.

### 8.7. Concomitant Procedures/Surgeries

Procedures/Surgeries reported on the Concomitant Procedures/Surgeries CRF will be coded using MedDRA SOC and PT, which including those done prior to the first dose of IP.

A concomitant procedure/surgery is defined in a manner similar to the concomitant medication (Section 8.6.2). A summary will be presented showing the number and percentage of subjects who had concomitant procedures/surgeries by SOC and preferred term, as well as the number and percentage of subjects who had any concomitant procedures/surgeries.

Listing of concomitant procedures/surgeries collected on Concomitant Procedures/Surgeries CRF by subject will be provided.

## 9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Treated population.

### 9.1. Treatment Duration

The treatment start date is the date of the first dose of IP. The treatment end date is the date the subject completed 6 cycles of treatment, or on which the decision was made by investigator to discontinue subject's treatment and record it on the treatment disposition page. Specifically, for the subjects who completed 6 cycles of treatment, the treatment end date will be the dosing date for Cycle 6 Day 15 + 13 days or the dosing date for Cycle 6 Day 8 + 20 days if the Cycle 6 Day 15 dosing date is missing. For subjects who are still on treatment at the time of study closure or clinical cutoff, the treatment end date will be the last date of the planned cycle (27 days after first dose of the last cycle). If the end date based on the planned duration is beyond the clinical cutoff date, the cutoff date will be used as the end date.

Treatment duration (in weeks) is calculated as (treatment end date – the date of the first dose of IP + 1) / 7 and rounded to one decimal place. Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (< 4 weeks, ≥ 4 to < 8 weeks, ≥ 8 to < 12 weeks, ≥ 12 to < 16 weeks, ≥ 16 to < 20 weeks, ≥ 20 to < 24 weeks, and ≥ 24 weeks) will be provided. The descriptive statistics and frequency summary for total number of treatment cycles subject received and number of subjects dosed at each cycle will be provided by treatment arm. The descriptive statistics for the number of doses administered separately for nab-paclitaxel and gemcitabine will be provided by treatment arm. The number of doses by treatment cycle will be summarized separately for nab-paclitaxel and gemcitabine by treatment arm.

### 9.2. Cumulative Dose

Cumulative dose is defined as the sum of all administered doses in mg/m<sup>2</sup>. The descriptive statistics for the cumulative dose (mg/m<sup>2</sup>) separately for nab-paclitaxel and gemcitabine will be provided.

### 9.3. Dose Intensity

Dose intensity will be calculated as the cumulative dose divided by the treatment duration in weeks which is defined in Section 9.1. The descriptive statistics for the dose intensity (mg/m<sup>2</sup>/week) for nab-paclitaxel and gemcitabine will be provided separately.

### 9.4. Percentage of Protocol Dose

Percentage of protocol dose will be calculated as the dose intensity divided by the protocol weekly dose x 100%.

- For nab-paclitaxel the protocol weekly dose is  $125 \times 3/4 = 93.75$  mg/m<sup>2</sup>/week;
- For gemcitabine: the protocol weekly dose is  $1000 \times 3/4 = 750$  mg/m<sup>2</sup>/week.

Summary statistics for percentage of protocol dose and as well as a frequency summary of subjects within each percentage of protocol dose categories (≥ 90%, < 90% to 80%, < 80% to 70%, and < 70%) will be provided separately for nab-paclitaxel and gemcitabine by treatment arm.

### 9.5. Dose Reduction/Delay/Omission

Dose reduction is defined as when the dose administered after Cycle 1 Day 1 dose is at the lower dose level than the one subject received from the previous dosing visit.

Dose delay is defined as when the actual dose is administered  $\geq 3$  days after the scheduled dosing date.

Dose omission is defined as when the scheduled dose was not given for the scheduled visit which does not include dose delay.

Dose reduction/delay/omission will be summarized by treatment arm as follows:

- Separately for *nab*-paclitaxel and gemcitabine, the number and percentage of subjects with at least 1 dose reduction, number of dose reductions, reasons for reduction, and dose reduction for each treatment cycle;
- Separately for *nab*-paclitaxel and gemcitabine, the number and percentage of subjects with at least 1 dose delay, number of dose delays, and dose delay for each treatment cycle;
- Separately for *nab*-paclitaxel and gemcitabine, the number and percentage of subjects with at least 1 dose omitted, number of dose omissions, and dose omission for each treatment cycle.



## 10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the ITT population. Supportive analysis of the primary and key secondary efficacy endpoints using the Treated and PP population will be conducted for the final analysis. Statistical comparisons will be made between nab-paclitaxel + gemcitabine and gemcitabine arm. Efficacy results that will be considered statistically significant after consideration of the strategy for controlling the family-wise Type 1 error rate are described in Section 13. All statistical tests will be two-sided at the significance levels which were pre-specified for each interim analyses and the final analysis, and the corresponding p-values and two-sided confidence intervals (CIs) for intended point estimates will be reported. Listings of lesion assessments by independent review and by investigator review will be provided.

### 10.1. Multiplicity

There is no multiplicity adjustment for the secondary endpoint OS.

### 10.2. Analysis of Primary Efficacy Endpoint

#### 10.2.1. Primary Efficacy Analysis on DFS

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 due to any cause, whichever is earlier. Disease recurrence will be determined by the independent radiological review of CT or MRI scans. Subjects who did not have disease recurrence or did not die will be censored at the last tumor assessment date with disease-free status or the randomization date if the last tumor assessment with disease-free status was missing. Disease-free status refers to a status that is neither being disease recurrent nor indeterminate or not evaluable. Subjects who received new anti-cancer therapy or cancer-related surgery prior to disease recurrence or death will be censored at the date of last tumor assessment with disease-free status prior to the start of new anti-cancer therapy or cancer-related surgery or the randomization date. The censoring rule is illustrated in Table 3:

**Table 3: Censoring Rules for DFS**

Value of Disease-free Survival Date (ADT)	Censored (Y,N)	Derivation
ADT = min(death date, disease recurrence date)	N	If a subject died or had disease recurrence and did not receive any new anti-cancer therapy or cancer-related surgery before death or disease recurrence.
ADT = the last tumor assessment date with disease – free status/randomization date	Y	If a subject did not die or had no disease recurrence, and did not receive any subsequent new anticancer therapy or cancer-related surgery.  If the last tumor assessment date with disease –free status is missing, ADT = the randomization date.
ADT = the last tumor assessment date with disease-free status prior to start of subsequent new anticancer therapy or cancer-related surgery/randomization date	Y	If a subject did not die or had no disease recurrence prior to the start of subsequent new anticancer therapy or cancer-related surgery  If the last tumor assessment date with disease-free status prior to the start of subsequent new anti-cancer therapy or cancer-related surgery is missing, ADT = the randomization date.
ADT = randomization date	Y	If there was residual or recurrent disease at baseline or no baseline scan assessment.
ADT =Analysis Date ; N = no; Y = yes.		

The null ( $H_0$ ) and alternative ( $H_1$ ) hypotheses for testing the primary efficacy endpoint of DFS are:

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

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

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

The survival distribution of DFS will be estimated using Kaplan-Meier method, the quartiles (25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentile) including two-sided 95% CIs for each treatment arm will be provided. The survival distributions for two treatment arms will be compared using the stratified log-rank test adjusting for stratification factors of resection status (R0 versus R1) and nodal status (LN+ versus LN-) based on IRT data, and p-value will be provided. The associated HR and two-sided 95% CI will be estimated by using stratified Cox proportional hazard model adjusting for the same stratification factors as for stratified log-rank test. Kaplan-Meier curves will be provided by treatment arm. The survival rates will be provided for different time points.

The DFS will be analyzed by the randomization stratification factors:

- Resection status (R0 versus R1);
- Nodal status (LN+ versus LN-);
- Region (North America, Europe and Australia versus Asia Pacific).

When using stratified Cox proportional hazard model or estimating stratified log-rank p-value, resection status or nodal status will not be included as a stratification factor for the DFS analysis by resection status or nodal status, respectively. Kaplan-Meier curves will be provided by treatment arm and by stratum within each stratification factor.

Medians with two-sided 95% CIs estimated through Kaplan-Meier methods, and the associated HRs with two-sided 95% CIs from Cox model will be provided for all randomization strata.

A multivariate analysis on DFS will be conducted by using Cox proportional hazard model to evaluate the treatment effect adjusted for the stratification factors. The associated HRs with two-sided 95% CIs, and p-values for treatment effect and stratification factors as covariates will be displayed.

#### 10.2.2. Sensitivity Analyses on DFS

The following sensitivity analyses will be conducted to evaluate the robustness of the DFS results:

1. To evaluate the robustness of the treatment effect based on different censoring time calculation, a sensitivity analysis will be performed by censoring the subjects who had no DFS event and no post-baseline scan with disease-free status at the last survival follow-up date, if available. If the censoring date is still missing, the randomization date (similar to the primary DFS analysis) will be used.
2. A sensitivity analysis will be performed where disease recurrence will be determined by the independent radiological review of CT or MRI scans or confirmed biopsy.
3. Missing assessment analysis: If a subject died or had disease recurrence by independent review, and the time interval between the death date/disease recurrence date and the previous tumor assessment date with disease-free status or the randomization date is more than two scheduled tumor assessment visits, the subject will be censored at the last tumor assessment date with disease-free status or the randomization date.
4. The DFS by independent review will also be compared between two treatment arms by using non-stratified log-rank test, p-value will be provided. The HR and two-sided 95% CI will be estimated using non-stratified Cox proportional hazard model.
5. A sensitivity analysis will be performed to evaluate the impact of surgery date. In this analysis, DFS is defined as the time from the date of surgery to the date of disease recurrence by the independent radiological review of CT or MRI scans or death due to any cause, whichever is earlier. Subjects who had residual or recurrent disease at baseline will be censored to the surgery date. For those subjects who were disease-free at baseline, had no DFS event and no post-baseline scans with disease-free status, they will be censored to the baseline scan date. The rest of censoring rules remain the same as the primary analysis of DFS by independent review.
6. An analysis of DFS based on disease recurrence assessed by investigator or determined by biopsy will be conducted. All censoring rules remain the same as the primary analysis of DFS by

independent review. The concordance in disease recurrence between by independent review and by investigator's review will be summarized and Kappa statistics will be presented.

For the sensitivity analyses, the analyses by randomization factors or by randomization strata or the multivariate analysis will not be conducted.

### 10.3. Analyses of Secondary Efficacy Endpoint

The secondary efficacy endpoint is OS, which is defined as the time from the date of randomization to the date of death due to any cause. Subjects who are alive at the end of study or clinical data cut will be censored on the last-known-to-be-alive date or the clinical cutoff date, whichever is earlier.

The survival distribution of OS will be estimated using Kaplan-Meier method, the quartiles (25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentile) including two-sided 95% CIs for each treatment arm will be provided. The survival distributions for two treatment arms will be compared using the stratified log-rank test adjusting for stratification factors of resection status (R0 versus R1) and nodal status (LN+ versus LN-) based on IRT data, and p-value will be provided. The associated HR and two-sided 95% confidence interval will be estimated by using stratified Cox proportional hazard model adjusting for the same stratification factors as for stratified log-rank test. Kaplan-Meier curves will be provided by treatment arm. The survival rates will be provided for different time points. A sensitivity analysis on OS will be conducted by censoring subjects on the start date of subsequent new anticancer therapy or cancer-related surgery.

A sensitivity analysis will also be performed to evaluate the impact of surgery date. In this analysis, OS is defined as the time from the date of surgery to the date of death due to any cause.

The OS will also be analyzed by the randomization stratification factors:

- Resection status (R0 versus R1);
- Nodal status (LN+ versus LN-);
- Region (North America, Europe and Australia versus Asia Pacific).

When using stratified Cox proportional hazard model or estimating stratified log-rank p-value, resection status or nodal status will not be included as a stratification factor for the OS analysis by resection status or nodal status, respectively. Kaplan-Meier curves will be provided by treatment arm and by stratum within each stratification factor.

Medians with two-sided 95% CIs estimated through Kaplan-Meier methods, and the associated HRs, with two-sided 95% CIs from Cox model will be provided for all randomization strata.

A multivariate analysis on OS will be conducted by using Cox proportional hazard model to evaluate the treatment effect adjusted for the stratification factors. The associated HRs with two-sided 95% CIs, and p-values for treatment effect and stratification factors as covariates will be displayed.

### 10.4. Subgroup Analysis

The primary analysis of DFS and OS will also be analyzed within the following subgroups, note that the geographic region, resection status (R0 versus R1), nodal status (LN+ versus LN-) will be based on the clinical data instead of IRT data:

1. Geographic Region (North America, Europe, Australia and Asia Pacific);
2. Age (< 65 years and  $\geq$  65 years);

3. Sex (male and female);
4. ECOG PS (0 and 1);
5. Pancreatic cancer location (head and other);
6. Surgical staging;
7. Tumor grade (well differentiated, moderately differentiated, poorly differentiated and undifferentiated);
8. Resection status (R0 versus R1);
9. Nodal status (LN+ versus LN-);
10. Level of CA19-9 at baseline if indicated by the data (WNL, ULN -  $< 100$  U/mL and  $\geq 100$  U/mL);
11. Microscopic distance from tumor to the closest margin ( $< 1$  mm and  $\geq 1$  mm).

If too few subjects fall in any of the above subgroups determined based on data review prior to database lock, the analysis within that subgroup may not be performed.

The methods described in Sections 10.2.1 and 10.3 for the endpoints of DFS and OS respectively, will be used for each subgroup. Resection status or nodal status will not be included as a stratification factor for the resection status or nodal status subgroup analysis, respectively, in the stratified Cox proportional hazard model or when estimating stratified log-rank p-value.

A forest plot will be provided based on the stratified HRs for each subgroup.

Additional subgroup analyses may be conducted if the overall treatment effect is significant and further understanding of the treatment effect within subgroups is of interest.

A multivariate analysis on DFS and OS will be conducted by using Cox proportional hazard model to identify potential prognostic factors by including treatment group, and all the subgroups mentioned above using stepwise method with selection level of 0.10.

A summary table of serum CA19-9 values and changes from baseline by cycle and treatment arm based on central lab data will be provided.

The subsequent anti-cancer therapies and clinically reviewed subsequent new anti-cancer therapies or cancer-related surgeries will be summarized by treatment arm. Listings will be provided.

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## 11. SAFETY ANALYSIS

All safety analyses will be conducted based on the Treated population. Safety analyses will be evaluated by the incidence of TEAEs, SAEs, grade 3 or higher TEAEs, TEAEs leading to dose reduction and dose interruption, TEAEs leading to treatment discontinuation, TEAEs with an outcome of death, AEs of special interest [based on risk definitions (search criteria) as outlined in the Abraxane Risk Management Plan], laboratory abnormalities, and other safety parameters during the treatment.

### 11.1. Adverse Events

Adverse events will be analyzed in terms of TEAEs which are defined as 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 the MedDRA

A treatment-related TEAE is defined as TEAE which was considered to be related to the IPs and reported as “Suspected” on the CRF. For the treatment Arm A, a treatment related TEAE is a TEAE with relationship reported as “Suspected” to either *nab*-paclitaxel or gemcitabine. AEs with a missing relationship will be treated as “treatment-related.”

The incidence of TEAE will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5). Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs;
- All TEAEs by maximum CTCAE grade as well as grade 1 or 2 vs.  $\geq$  grade 3, and  $\geq$  grade 3 vs. all grades;
- All TEAE with CTCAE grade  $\geq$  3;
- TEAEs reported as treatment-related;
- Treatment-related grade 3 or higher TEAEs;
- Treatment-related grade 3 or higher TEAEs by cycle;
- Serious TEAE;
- Serious TEAE by SAE criteria;
- Treatment-related serious TEAEs;
- Treatment-related serious TEAEs by SAE criteria;
- TEAEs with action of study drug withdrawn;
- Treatment-related TEAEs with action of study drug withdrawn;
- TEAEs with action of study drug dose reduced;
- Treatment-related TEAEs with action of study drug dose reduced;
- TEAEs with action of study drug interrupted;

- Treatment-related TEAEs with action of study drug interrupted;
- TEAEs with outcome of death;
- Treatment-related TEAEs with outcome of death;
- All death within 28 days of last dose by cause of death category as collected on Death CRF;
- Most frequent ( $\geq 5\%$  in either arm; no SOC) TEAEs;
- Most frequent treatment-related TEAEs ( $\geq 5\%$  in either arm; no SOC) TEAEs;
- TEAEs for the following baseline subgroups (provided the number of subjects are sufficient):
  - Sex (male and female);
  - Geographic Region (North America versus Europe versus Australia versus Asia Pacific).

For subgroup with age ( $< 65$  years and  $\geq 65$  years, and  $< 75$  years and  $\geq 75$  years), the following analyses will be provided:

- All TEAEs;
- Grade 3 or higher TEAEs;
- Serious TEAEs;
- TEAEs with action of study drug withdrawn;
- TEAE with action of study drug dose reduced;
- TEAE with action of study drug interrupted;
- TEAEs with outcome of death

If a subject experiences the same AE more than once with different toxicity grade, then the event with the maximum grade will be tabulated in “by grade” tables. If a subject experiences multiple AEs under the same SOC/PT, then the subject will be counted only once for that SOC/PT. If the severity of an AE is missing for one or more occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all occurrences of the AE, the subject will be counted only once in the ‘Missing’ category for severity.

The analysis of TEAE by cycle will be based on the onset date of AE to determine the cycle. AEs with a duration that overlaps multiple cycles will only be counted in the first overlapped cycle.

The TEAE tables will be sorted by the frequencies of SOC and PT within SOC in a descending order within nab-paclitaxel plus gemcitabine treatment arm.

The AE Listing will be provided that includes the verbatim term, PT, and SOC as well as full details of AEs for subjects in the ITT population. Non-TEAEs will be flagged on this listing.

Separate listings for subjects in Treated population will be prepared for grade 3 or higher TEAEs, serious TEAEs, TEAEs with action of study drug withdrawn, TEAEs with action of study drug dose reduced, TEAEs with action of study drug dose interrupted and TEAEs with outcome of death. The listing of inpatient hospitalizations will be provided. All deaths will be listed with the cause of death category from Death CRF form.

## 11.2. Adverse Events of Special Interest

### 11.2.1. AE of Special Interest

TEAEs of special interest based on risk definitions (search criteria) as outlined in the Abraxane Risk Management Plan or included based on inherent risks of the study design using MedDRA coding are as follows:

- Myelosuppression (anaemia, neutropenia, and thrombocytopenia);
- Peripheral neuropathy;
- Gastrointestinal events;
- Myalgia and arthralgia;
- Hypersensitivity reactions;
- Cranial nerve paralysis;
- Cardiotoxicity;
- Cardiotoxicity-Congestive Heart Failure/Left Ventricular Dysfunction;
- Stevens-Johnson Syndrome/Toxic epidermal necrolysis;
- Pneumonitis;
- Infusion site reactions/extravasation;
- Cystoid macular edema;
- Hepatic toxicity (Drug-induced liver injury);
- Acute renal failure and Hemolytic-uremic syndrome (including HUS in combination with gemcitabine);
- Clinically severe infections, sepsis;
- Drug-induced lupus erythematosus;
- Haemorrhage and bleeding (AESI specific for the study);
- Motility Disorders (Post-surgical complications specific for this study);
- Fistula/Leak (Post-surgical complications specific for this study);
- Haemorrhage (Post-surgical complications specific for this study);
- Hyperglycemia/Diabetes (Post-surgical complications specific for this study);
- Pancreatitis (Post-surgical complications specific for this study)

After review of data, there may be other AEs of special interest identified and summarized.

The following summaries will be provided for TEAEs included in the above-mentioned AEs of interest:

- All TEAEs;
- Grade 3 or higher TEAEs;



- Serious TEAEs;
- TEAEs with action of study drug withdrawn;
- TEAE with action of study drug dose reduced;
- TEAE with action of study drug interrupted;
- TEAEs with outcome of death.

The similar summaries will also be presented by age group (< 65 years and ≥ 65 years) and (< 75 years and ≥ 75 years).

In addition, sub-risks of AE of special interest as defined in subjects older than 75 years are to be analyzed by age group < 65 years, 65-74 years and ≥ 75 years for the TEAEs of special interest in this population as specified below:

- Myelosuppression (anemia, neutropenia, febrile neutropenia, thrombocytopenia);
- Peripheral neuropathy;
- Clinically severe infections – pneumonia;
- Clinically severe infections – sepsis;
- Clinically severe infections – pneumonia and sepsis;
- Dehydration;
- Decreased appetite;
- Diarrhea;
- Epistaxis;
- Fatigue;
- Peripheral edema.

TEAEs of special interest listings will be provided similarly as AE listings. TEAEs of special interest as defined for subjects older than 75 years old will be also provided.

#### 11.2.2. Pneumonitis and Sepsis

If warranted (i.e., substantial subjects have pneumonitis or sepsis), in the final analysis, pneumonitis (as defined by broad scope of Standardised MedDRA Query [SMQ] interstitial lung disease) and sepsis (as defined by ad-hoc preferred terms) will be examined through the following analyses:

1. Time to onset;
2. Duration of events in days for pneumonitis only.

The time to onset of pneumonitis and sepsis respectively and duration of pneumonitis events will be summarized descriptively.

#### 11.2.3. Peripheral Neuropathy

The physician will assess PN using the NCI CTCAE Version 4.0 of “Neuropathy – Sensory” and record grades on CRF. The frequency of each PN grade (0 – 5) by physician assessment at baseline, the most

severe PN grade in each treatment cycle and on Final Evaluation will be presented. The frequency of worst PN grade during treatment (i.e. any time after the first dose of IP) will also be presented. A shift table representing the shift from the baseline grade to the most severe grade during treatment will be provided.

Additionally, PN events will be reported as AEs of special interest and will be analyzed (as defined by broad scope of SMQ peripheral neuropathy) as outlined in Section 11.2.1.

If warranted (i.e., substantial subjects have grade 3 or higher PN as defined by SMQ), time to first occurrence of grade 3 or higher PN from the first dose date will be descriptively summarized. Time to improvement from grade 3 or higher PN by at least 1 grade and the time to improvement of grade 3 or higher PN to grade 1 or better will be analyzed using Kaplan-Meier methods based on PN SMQ. Subjects who are not experiencing improvement will be censored at the last time the subjects are evaluated for AEs.

### 11.3. Clinical Laboratory Evaluations

The central laboratory results will include laboratory assessments which were collected from screening to the date of last dose date + 28 days or the treatment discontinuation date, whichever is later. The central laboratory values will be graded using NCI CTCAE V4.03. For hematologic and chemistry laboratory values fall outside of the grade criteria of NCI CTCAE V4.03, the grade of 0 will be assigned. The collected local laboratory results will be listed.

#### 11.3.1. Hematology

In order to investigate the maximal degree of myelosuppression, the NCI CTCAE grade for absolute neutrophil counts (ANC), WBC, platelet counts, and hemoglobin will be summarized by the most severe grade in each treatment cycle and by the most severe grade during treatment. The number and percentage of subjects with each NCI CTCAE grade will be presented by treatment arm. A shift table representing the shift from the baseline grade to the most severe grade during treatment will be provided by treatment for these laboratory results.

#### 11.3.2. Clinical Chemistry

Hepatic and renal function will be summarized using the NCI CTCAE grade for alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, and creatinine. The number and percentage of subjects that have each NCI CTCAE grade will be summarized by treatment arm using the most severe grade for each treatment cycle and overall during treatment. A shift table representing the shift from the baseline grade to the most severe grade during treatment will be provided by treatment arm for each of these laboratory tests.

### 11.4. Vital Sign Measurements

For vital signs, listings will be provided.

### 11.5. ECOG Performance Status

For ECOG performance status, the shift from baseline to the worst during treatment will be displayed in cross-tabulations for each treatment arm.

**11.6. Physical Examination**

Any findings from physical examination before the start of IP are documented as medical history and any findings after the start of IP are documented as adverse events on CRF. Therefore, there will be no separate analysis for physical examination.

**11.7. Electrocardiograms**

The overall electrocardiogram (ECG) 12 lead interpretation is documented on screening. A listing will be provided.

**11.8. Pregnancy Test**

For pregnancy test, a listing will be provided.

CELGENE PROPRIETARY INFORMATION

## 12. QUALITY OF LIFE ANALYSIS

QOL will be analyzed using the EORTC-QLQ C-30 and QOL-PANC26 questionnaires which are collected at screening, at cycle 4 Day 1 prior to dosing, EOT, then on the same days when a CT or MRI is performed until disease recurrence. Details for the quality of life analysis will be provided in a separate document.

CELGENE PROPRIETARY INFORMATION

## 13. INTERIM ANALYSIS

### 13.1. General Information

There were 2 interim analyses conducted during the course of the study. The first interim analysis on safety was planned after the first 100 subjects have completed 2 cycles of treatment. Additionally, one interim analysis on efficacy was planned at about 33% information time (ie, after 163 DFS events) to assess futility. A second interim analysis on efficacy had been planned for futility and superiority at either 70% information time (ie, after 342 DFS events) or the completion of accrual of 800 subjects, whichever is later. However, at time of Protocol Amendment 3, the interim analysis for futility at about 163 DFS events has been performed and no subjects are receiving 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 DMC was convened which was composed of two medical oncologists with experience in treating subjects with pancreatic adenocarcinoma and a statistician, all of whom are not otherwise involved in the study as investigators. During the course of the study, the DMC will review the efficacy data in accordance with the guidelines for the pre-planned interim analysis. The committee will also review safety data. Operational details for the DMC and the algorithm and its validation by an expert panel will be detailed in the DMC charter.

### 13.2. Statistical Approaches for Control of Alpha and Beta

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  $\geq 0.98$ , however, the actual boundaries for the interim analyses may vary depending on the actual number of DFS events at the time of analysis.

#### **14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL**

The subgroup analysis was added in this SAP. The multivariate analysis through Cox proportional hazard model using stepwise selection method to identify potential prognostic factors for DFS and OS would be performed when overall treatment effect is significant and exploratory analysis is needed.

After randomization was completed but prior to database lock, stratification categories were examined for sparse data cells and it was decided to remove region from the stratified efficacy analyses due to the small number for Asia Pacific group in region. Therefore, in all the stratified analyses, only two stratification factors (resection status [R0 versus R1] and nodal status [LN+ versus LN-]) will be included.

## 15. REFERENCE

Conroy T, Hammel P, Hebbar M, et al. Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. *J Clin Oncol* 36, 2018 ASCO Annual Meeting Abstracts. 2018;36, (18 suppl): Abstract LBA4001.

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Hwang I, Weichung S, De Cani J. Group sequential designs using a family of type I error probability spending functions. *Stat Med* 1990;9:1439-1445.

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Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial. *J Clin Oncol*. 2017;35:3330-3337.

## 16. APPENDICES

### 16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

**Procedure Dates** are the dates on which given protocol-specified procedure are performed.

They include the dates of laboratory testing, physical examinations, tumor scans, etc.

They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database.

Procedure dates will not be imputed.

**Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.

**Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.

**Outcome Dates** are dates corresponding to study endpoints such as survival and disease recurrence. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the disease recurrence date is derived from the date of the tumor scan that was used to determine disease recurrence). They may be subject to endpoint-specific censoring rules if the outcome did not occur or disease recurrence or death following more than 1 missing tumor assessment, but are not otherwise subject to imputation.

**Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

### 16.2. Date Imputation Guideline

#### 16.2.1. Impute Missing Adverse Events/ Prior or Concomitant Medications/Procedures

##### Incomplete Start Date:

*Missing day and month*

If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.

If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.



If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

*Missing day only*

If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.

If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.

If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

If the stop date is not missing, and the imputed start date is after the **stop date**, the start date will be imputed by the stop date.

*Missing day, month, and year*

No imputation is needed, the corresponding AE will be included as TEAE.

**Incomplete Stop Date:** If the imputed stop date is before the **start date**, then the imputed stop date will be equal to the start date.

*Missing day and month*

If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.

If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.

If the year of the **incomplete** stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

*Missing day only*

If the **month** and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

### 16.2.2 Impute Missing Cancer History Dates

When necessary for analysis purposes, the diagnosis dates without a specific day of the month given (i.e., JAN2008) will be assigned the 15th day of the month and dates without a specific day or month (i.e., 2008) will be assigned the 30th day of June to complete the date. If the above imputation inappropriately results in a diagnosis date on or after surgical date or randomization date, then the incomplete date will be assigned to the day prior to surgical date or randomization date, whichever is earlier. The similar imputation rule will be used for the partial surgical date.

### 16.2.3 Impute Missing Subsequent Anti-cancer Therapy

When necessary for analysis purposes, the subsequent anti-cancer therapy dates without a specific day of the month given (i.e., JAN2008) will be assigned the 15th day of the month and dates without a specific day or month (i.e., 2008) will be assigned the 30th day of June to complete the date. If the above imputation inappropriately results in a date on or before the last dose date, then the incomplete date will be assigned to the day following the last dose date. If imputation results in an imputed start date after the corresponding stop date, then the start date will be set to the day prior to the stop date.



## Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink.  
This page is the manifestation of the electronic signature(s) used in compliance with  
the organizations electronic signature policies and procedures.

UserName: PPD [REDACTED]  
Title: PPD [REDACTED]  
Date: Thursday, 17 January 2019, 03:52 PM Eastern Daylight Time  
Meaning: Approved, no changes necessary.  
=====

UserName: PPD [REDACTED]  
Title: PPD [REDACTED]  
Date: Thursday, 17 January 2019, 04:58 PM Eastern Daylight Time  
Meaning: Approved, no changes necessary.  
=====

UserName: PPD [REDACTED]  
Title: PPD [REDACTED]  
Date: Thursday, 17 January 2019, 07:56 PM Eastern Daylight Time  
Meaning: Approved, no changes necessary.  
=====

CELGENE PROPRIETARY INFORMATION

## 1. JUSTIFICATION FOR AMENDMENT

Following finalization of the SAP on 15 Aug 2016, Protocol Amendment No. 3 and 4 were released on 21 Dec 2016 and 12 Sep 2018, respectively. This SAP amendment reflected all changes to the planned analysis. Other clarifications and incidental formatting changes were made throughout the document.

Significant changes included in this amendment are summarized below:

- Modification of Stratification by Region

Per Protocol Amendment 1 and 2, the subjects are to be stratified at randomization based on Region (North America versus Europe versus Australia versus Asia Pacific). To reflect the reality of the stratification applied to the randomization, which is based on original protocol, the wording is revised to Region (North America, Europe and Australia versus Asia Pacific).

Revised sections: SAP Section 4.1 Overall Study Design and Plan, Section 4.3 Stratification and Randomization, and Section 10.2 and 10.3 for analysis of disease-free survival (DFS) or overall survival (OS) by the randomization stratification factors, respectively

- Update the stratification factors for stratified efficacy analyses (stratified Cox proportional hazard model and stratified log-rank test for p-value) by exclusion of region due to the small number for Asia Pacific group in Region.

Revised sections: SAP Section 10.2.1 Primary Efficacy Analysis on Disease-free Survival (DFS), Section 10.3 Analysis of Secondary Efficacy Endpoints, and Section 10.4 Subgroup Analysis

- Added languages to clarify one more change to the Statistical Analyses Section of the Protocol about exclusion of region as the stratification factor for the stratified efficacy analyses

Revised section: SAP Section 14

- Removal of the second interim analysis of efficacy

Final SAP stated that two interim analyses of efficacy were planned: the first is to be conducted at about 33% information time (ie, after 163 DFS events) to assess futility and the second at either 70% information time (ie, after 342 DFS events) or the completion of accrual of 800 subjects, whichever is later, to assess both futility and superiority. At the time of Protocol Amendment 3, a total of 866 subjects have been randomized and completed or discontinued treatment. Based on health authority recommendation 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, the second interim analysis has been removed from the study.

Revised sections: SAP Section 4.4 Sample Size Determination, Section 13.1 General Information and Section 13.2 Statistical Approaches for Control of Alpha and Beta. Original Table 3 Stopping Boundaries for Interim Analysis and Final Analysis on Efficacy was removed from the SAP Section 13.2.

- Revised the final DFS analysis to be earlier than was originally planned (489 events)

As of April 2016, a total of 866 subjects were enrolled in the study. After enrollment to this protocol was completed, more contemporaneous Phase 3 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 follow-up 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, 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, at least 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.

For the OS, 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.

Revised sections: Section 4.4 Sample Size Determination and Section 15 Reference.

Other minor clarifications and updates are listed below:

- Updated the CTCAE version from 4.0 to 4.03 for centrally reviewed laboratory results grading

Revised sections: SAP Section 4.24 Safety Endpoints and Section 11.3 Clinical Laboratory Evaluations

- Clarify that the percentages greater than 0 but rounded to 0 will be presented as <1 and the percentages less than 100 but rounded to 100 will be presented as >99 in the parentheses

Revised section: SAP Section 5.1 Reporting Conversion

- Updated “prior and concurrent procedures/surgeries” into “concomitant procedure/surgeries” to be consistent with the corresponding Case Report Form name

Revised sections: SAP Section 8.7 Concomitant Procedures/Surgeries

- Added language to clarify the CA19-9 analysis is based on central lab

Revised sections: SAP Section 8.2 Cancer History and Surgery and Section 10.4 Subgroup Analysis

- Clarification on baseline definition

Further clarification are provided when there are multiple assessments on the same time point prior to first dose. In the case of multiple values with various levels (ie. normal range or CTCAE toxicity), the assessment with better result will be defined.

Revised section: SAP Section 5.1 Reporting Conversion

- Added language for the summary of time from primary diagnosis to surgery

Revised section: SAP Section 8.2 Cancer History and Surgery

- Added language to define the baseline disease status as “Not Evaluable” for the subject who has no baseline scan by independent radiological review

Revised section: SAP Section 8.3 Baseline Disease Status

- Added language to clarify the censoring rule for the subject who has no baseline scan by independent radiological review

Revised section: SAP Section 10.2.1 Primary Efficacy Analysis on DFS and Table 3 Censoring Rules for DFS within this section

- Shifted power calculation for OS from SAP Section 13.2 Statistical Approaches for Control of Alpha and Beta to SAP Section 4.4 Sample Size Determination
- As specified in Section 11.5 ECOG Performance Status, for ECOG performance status, the shift from baseline to the worst during treatment will be displayed in cross-tabulations for each treatment arm. ‘Eastern Cooperative Oncology Group (ECOG) performance status and’ was removed from Section 5.1 Reporting Conventions, to be consistent with Section 11.5.

Revised section: SAP Section 5.1 Reporting Conventions