DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ABI-007-PANC-007

NAB-PACLITAXEL (ABRAXANE®) PLUS GEMCITABINE IN SUBJECTS WITH LOCALLY ADVANCED PANCREATIC CANCER (LAPC): AN INTERNATIONAL, OPEN-LABEL, MULTI-CENTER, PHASE 2 STUDY (LAPACT)

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STATISTICAL ANALYSIS PLAN

nab-Paclitaxel (Abraxane®) plus Gemcitabine in Subjects with Locally Advanced Pancreatic Cancer (LAPC): An International, Open-label, Multi-center, Phase 2 Study (LAPACT)

STUDY DRUG: *nab*®[1]-PACLITAXEL

PROTOCOL NUMBER: ABI-007-PANC-007

DATE FINAL: 13 Nov 2017

Prepared by:

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On behalf of

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SIGNATURE PAGE

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SAP TITLE	Statistical Analysis Plan. Protocol ABI-007-PANC-007
SAP VERSION, DATE	Final Version, 13-Nov-2017
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PROTOCOL VERSION, DATE	Final, 27 Aug 2014
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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BMI	Body mass index
BSA	Body surface area
CA19-9	Carbohydrate antigen 19-9
CBC	Complete blood cell
CI	Confidence interval
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of trial
Hgb	Hemoglobin
IC	Investigator's choice
IP	Investigational product
IV	Intravenous
LAPC	Locally advanced pancreatic cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
ND	Not done
NQ	Not quantifiable
ORR	Overall Response Rate

OS	Overall survival
PFS	Progression-free survival
PT	Preferred term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNL	Ratio of lymphocytes to neutrophils
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SI	Standard international
SOC	System organ class
STDEV	Standard deviation
TEAE	Treatment-emergent adverse event
TTF	Time to treatment failure
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-007 "*nab*-Paclitaxel (Abraxane®) plus Gemcitabine in Subjects with Locally Advanced Pancreatic Cancer (LAPC): An International, Open-label, Multi-center, Phase 2 Study (LAPACT)" which was issued on 27 Aug 2014. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one interim analysis and one final analysis. Throughout this SAP, the treatment arm will be referred to as *nab*-paclitaxel and gemcitabine. 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 will be finalized and signed prior to the clinical database lock for the interim analysis. Significant changes after interim analysis and prior to final database lock will be documented in Final SAP Amendment. All statistical analyses detailed in this SAP will be conducted using SAS® version 9.2 or higher.

The SAP supersedes the analyses described in the protocol should there be differences between the two.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the time to treatment failure (TTF) in LAPC subjects treated with nab-paclitaxel plus gemcitabine as induction therapy followed by Investigator's Choice of treatment.

3.2. Secondary Objectives

The secondary objectives are:

- To evaluate the disease control rate (DCR) after the first 6 cycles of *nab*-paclitaxel and gemcitabine;
- To evaluate the overall response rate (ORR);
- To evaluate progression-free survival (PFS) and overall survival (OS);
- To evaluate the overall safety profile;
- To evaluate the subject's health-related QoL (will be described in an analysis plan separate from this SAP).

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4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is an international, non-randomized, open-label, multi-center, Phase 2 study in subjects with LAPC treated with nab-paclitaxel and gemcitabine for 6 cycles followed by an Investigator's Choice of continuation of treatment with nab-paclitaxel and gemcitabine, chemoradiation therapy, or surgery.

This study consists of 2 parts (see Figure 1):

1) A treatment induction phase that consists of a single arm where subjects receive *nab*-paclitaxel and gemcitabine on Days 1, 8, and 15 of each 28-day cycle for 6 cycles.

2) Investigator's Choice phase: once 6 cycles of study drug have been completed, subjects without disease progression or unacceptable toxicity may continue on to the Investigator's Choice of either: continuation of treatment with *nab*-paclitaxel and gemcitabine, chemoradiation therapy, or surgery. If tumor response allows for surgical intervention, the subject will be eligible for that treatment as deemed appropriate by the investigator. Surgical intervention may occur prior to completing the planned 6 cycles of nab-paclitaxel and gemcitabine if subjects demonstrate a major response to therapy.

Subjects who discontinue treatment with *nab*-paclitaxel and gemcitabine, chemoradiation, or surgery for any reason will have a safety follow-up visit 28 days after treatment discontinuation and will be followed for disease progression approximately every 56 days. All subjects will be followed for overall survival (OS) and post-study anticancer therapies approximately every 90 days by phone or review of medical records until death, withdrawal of consent, or lost to follow-up. At any time during the study, subjects with disease progression or unacceptable toxicity will be discontinued from the study treatment. During the study, subjects, including those who discontinue treatment without disease progression, will have CT/MRI scans every 56 days (-3/+7 days) until documented progression of disease, withdrawal of consent from active participation in the study, lost to follow-up, or death, whichever is earliest. Tumor evaluations will be assessed by the Investigators and response will be determined according to RECIST v1.1 guidelines.

The study will consist of the following visits:

Screening/re-screening Assessments: to be obtained ≤ 14 days prior to study drug administration.

Treatment: Treatment will commence on Day 1 for 6 cycles:

- *nab*-Paclitaxel 125 mg/m2 IV infusion over approximately 30 to 45 minutes on Days 1, 8, and 15, followed by gemcitabine 1000 mg/m2 IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

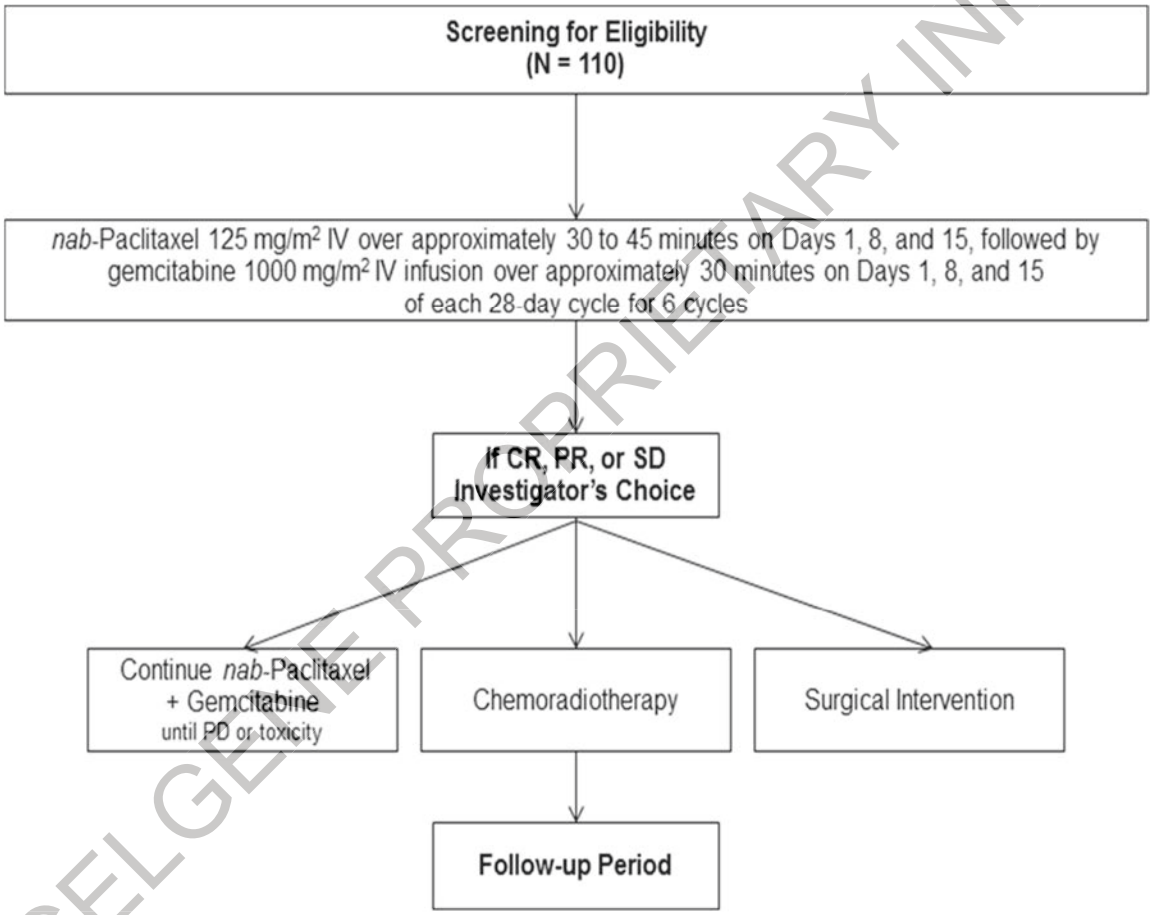
Once 6 cycles have been completed, subjects without disease progression or unacceptable toxicity will continue on to the Investigator's Choice treatment. See description in study parts (see Figure 1).

Safety Follow-up: Subjects who discontinue treatment with *nab*-paclitaxel and gemcitabine for any reason will have a safety follow-up visit 28 days after treatment discontinuation. Subjects who are planned to undergo chemoradiation or surgery will have a safety visit pretreatment (with chemoradiation or surgery), and at 28 days after discontinuation with chemoradiation, or 28 days post surgery.

Efficacy Follow-up: Subjects who discontinue treatment without disease progression will continue to have CT/MRI scans every 56 days (-3/+7 days) until documented disease progression, withdrawal of consent, lost to follow-up, or death (by any cause), whichever is earliest.

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 [CCI] analysis, whichever is the later date.

Figure 1: Overall Study Design



CR = complete response; IV = intravenously; PD = progressive disease; PR = partial response; SD = stable disease.

4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary endpoint of the study is TTF, measured as the time from the first dose of study therapy to treatment failure. Treatment failure is defined as discontinuation of study therapy due to disease progression, death (by any cause), or the start of a non-protocol-defined anticancer therapy.

4.2.2. Secondary Endpoints

4.2.2.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints included in this SAP are:

- The disease control rate (DCR) after 6 cycles of *nab*-paclitaxel and gemcitabine, defined as the combined incidence of complete response (CR), partial response (PR) and stable disease (SD);
- Overall response rate(ORR), defined as the combined incidence of CR and PR;
- Progression-free survival (PFS) defined as the time from the first dose of study therapy to disease progression or death (by any cause);
- Overall survival (OS) defined as the time from the first dose of study therapy to death (by any cause);
- Differences in outcomes from baseline, during treatment, and after treatment with *nab*-paclitaxel and gemcitabine for the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ), EORTC QLQC30 and QLQ-PAN26 (will be described in an analysis plan separate from this SAP).

4.2.2.2. Secondary Safety Endpoints

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs);
- Laboratory results (chemistries and blood counts) analyzed using NCI CTCAE V4.0;
- Other safety parameters including incidence of dose reductions, delays and omissions.

CCI [redacted]

4.3. Stratification, Randomization and Blinding

Not applicable for this study.

4.4. Sample Size Determination

The primary endpoint for this study is median TTF. The null (H_0) and alternative (H_a) hypotheses for this endpoint are as follows, where M is the median TTF and 5.1 months is the median TTF observed in the CA046 study:

H_0: $M \leq 5.1$

H_a: $M > 5.1$

A total sample size of 100 subjects will have 80% power to detect a 30% increase in the median TTF of 5.1 to 6.6 months (Table 2). The sample size is calculated assuming a one-sided alpha of 0.05, that subjects will be enrolling for 24 months and that each subject will be followed for a minimum of 1 year. One hundred ten subjects will be enrolled assuming a 10% drop out rate.

Table 2: Power Calculation for Median Time to Treatment Failure and Sample Size

Percent increase in median TTF	Median TTF for the Alternative-Hypothesis (Months)	Accrual Duration (Months)	N	Power
20%	6.1	24	100	0.54
		30	100	0.55
30%	**6.6**	**24**	**100**	**0.80**
		30	**100**	**0.81**
50%	7.7	24	100	0.99
		30	100	0.99

TTF = time to treatment failure.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- For the purposes of data analysis, two analysis phases for post-baseline data are defined: the induction chemotherapy phase and the Investigator's Choice phase.
- Data from all study sites will be combined for 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 90% 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), Q1 and Q3, 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;
- The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses;
- All listings will be sorted for presentation in order of study site, subject ID and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (i.e., number of subjects) in the column heading;
- The day of the first dose of any study drug will be defined as Day 1;
- Each cycle starts with the date of the first dose date of the cycle, and the last day of the cycle is the day before the first dose date of the subsequent cycle;
- For the last cycle, the last day of the cycle is the treatment completion or discontinuation date on the 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.
- 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 on or before the date that the first dose of study drug is administered; if multiple values are present for the same date, 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 first dose date will be used;

- Partial dates will be imputed based on the rules specified in Section 15.2;
- 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;
- SAS® Version 9.2 (or higher) will be the statistical software package used to produce all data summaries, listings, graphs, and statistical analyses.

5.2. Analysis Populations

The population for this study will consist of all subjects enrolled in the study who were diagnosed with LAPC.

All statistical analyses including but not limited to tables, listings and graphs will be based on the definitions of analysis populations in this SAP. If there are any discrepancies between SAP and protocol, the definitions in SAP overwrite those in the protocol.

5.2.1. Intent-to-treat (ITT) Population

The ITT population is defined as all subjects enrolled in the study.

5.2.2. Per Protocol (PP) Population

The PP population is defined as all subjects enrolled in the study who receive at least 1 dose of investigational product (*nab*-paclitaxel and gemcitabine) and fulfill the study enrollment criteria.

5.2.3. Treated Population

The Treated population consists of all subjects who receive at least 1 dose of *nab*-paclitaxel or gemcitabine. Treated population is used for all safety analyses.

A summary of analysis populations will be presented.

6. SUBJECT DISPOSITION

The number of subjects with screen failure will be summarized. The subjects with the violated eligibility criteria will be included in the summary. A summary of subject disposition will be presented for the ITT population. The number of subjects treated and reasons for treatment discontinuation for both induction phase and Investigator's choice phase will be presented.

Reasons for discontinuation of the study (i.e., no more follow up visit and no longer participating the study) will be summarized per CRF for all treated subjects.

The enrollment will also be summarized by study site.

Listings of subject eligibility and listings for subject disposition and study disposition will also be provided.

7. PROTOCOL VIOLATIONS

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

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

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized. No inferential statistics will be presented. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

The following characteristics will be summarized and listed:

- Age (years)
- Age category (<65 years , 65 - 75 years, and > 75 years)
- Sex
- Primary race
- Ethnicity
- Height (cm) and weight (kg)
- Body mass index
- Baseline ECOG performance status
- Physician assessment of peripheral neuropathy (PN) at baseline
- Time from primary diagnosis to first dose (days)

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

The demographics and baseline characteristics will be summarized for ITT population.

The baseline albumin, serum CA 19-9 level and specified categories for serum CA 19-9 level will be summarized descriptively for ITT population.

8.2. Baseline Lesion Status

For lesions identified at baseline, descriptive statistics will be provided for the following variables based on ITT population.

- Number of target lesions
- Sum of longest lesion diameters (mm) of target lesions

8.3. Medical History

A frequency summary of relevant medical history will be presented by system organ class (SOC) and preferred term for the ITT population according to Medical Dictionary for Regulatory Activities (MedDRA version 20.0).

8.4. Prior Therapy

Subjects who had prior anticancer therapy for pancreatic carcinoma will be excluded from this study. Prior anticancer surgeries will be coded using MedDRA version 20.0. The number and percentage of subjects who had any prior cancer surgery for this disease by system organ class and preferred term will be presented for the ITT population. The prior anticancer surgery data will be presented in a listing.

8.5. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant Medications CRF will be coded using WHO Drug Enhanced March, 2017 and will be summarized by Anatomical Therapeutic Chemical (ATC) classification level 1 and preferred drug name for the ITT population. Concomitant medications and procedures of special interest as listed in Protocol section 19.2 will be summarized separately.

8.5.1. Prior Medications

A prior medication will be any medication stopped prior to the date of the first dose of study drug. 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.

8.5.2. Concomitant Medications

Concomitant medication is defined as the medication that was either initiated 14 day before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug but continued on or before 28 days after the last dose of study drug.

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

Separate summaries of concomitant medication of interest focusing on subjects receiving concomitant white blood cell (WBC) growth factors, transfusions with blood and blood-derived products, erythropoietins, antiemetic medications and systemic anti-infective will be provided.

Separate summary of concomitant medications of special interest as listed in Protocol section 19.2 will be provided.

Listing of prior and concomitant medications by subject will be provided. Concomitant medications of special interest will be indicated in a flag column of the listing.

8.6. Concomitant Procedures/Surgeries

A concomitant procedure/surgery is defined in a manner similar to the concomitant medication (Section 8.5.2). Procedures/Surgeries will be coded using MedDRA version 20.0.

A frequency table will be presented showing the number and percentage of subjects who had concomitant procedures/surgeries by system organ class and preferred term, as well as the

number and percentage of subjects who had any concomitant procedures/surgeries. Separate summary of concomitant procedures/surgeries of special interest as listed in Protocol section 19.2 will be provided.

Listing of concomitant procedures/surgeries by subject will be provided. Concomitant procedures/surgeries of special interest will be indicated in a flag column of the listing.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment with *nab*-paclitaxel or gemcitabine and extent of exposure summaries will be provided based on the treated population. Summaries will be provided for subjects that have *nab*-paclitaxel or gemcitabine treatment during the induction phase. In addition, treatment exposure data will also be summarized for subjects continuing with treatment of any *nab*-paclitaxel or gemcitabine per Investigator's Choice after 6-cycles of study drug.

9.1. Treatment Duration

The treatment start date is the date of the first dose of study drug. For subjects who are discontinued early from study treatment, the treatment end date is the date of last dose recorded on the CRF treatment disposition page plus drug holidays. The number of drug holidays to be added is 6 days for Day 1 dose as the last dose administration, 6 days for Day 8 dose administration and 13 days for Day 15 dose administration. 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 treatment end date as defined is beyond the clinical cutoff date, the cutoff date is used as the treatment end date.

Treatment duration (in weeks) is calculated as (treatment end date – the date of the first dose of study drug + 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 (<2 weeks, ≥ 2 to < 4 weeks, ≥ 4 to < 8 weeks, ≥ 8 to < 12 weeks, and every 4 week intervals so forth) will be provided.

Descriptive statistics for the total number of treatment cycles subjects received and the number of doses administered for each study drug will be provided. A summary of the frequency of subjects dosed at each cycle and number of cycles administered per subject will also be provided.

9.2. Cumulative Dose

Cumulative dose is defined as the sum of all administered doses in mg/m^2. Descriptive statistics for the cumulative dose (mg/m^2) separately for *nab*-paclitaxel and gemcitabine by induction phase and Investigator's Choice phase will be provided.

9.3. Dose Intensity

Dose intensity (DI) will be calculated as the cumulative dose divided by the total treatment weeks. Descriptive statistics for the dose intensity (mg/m^2/week) for induction phase and Investigator's Choice phase will be provided.

9.4. Relative Dose Intensity

Relative Dose Intensity (RDI) will be defined as follows.

RDI = 100 x (cumulative dose through treatment completion/discontinuation) / (expected amount of dose given through treatment completion/discontinuation per schedule).

The expected amount of dose assumes no modification of dose or schedule. The cumulative dose as defined in Section 9.2 includes dose modification. Both of these measures are measured in mg/m^2 unit.

9.5. Dose Reduction/Delay/Omission

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered up to 2 days from the scheduled date. Study treatments must be 7 or more days apart from each other. A dose reduction is defined as the planned dose reduced to the next lower dose level compared to the planned previous dose due to toxicities. 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 (See Table 5 in section 8.2.1.2 of protocol).

Dose delay is defined as the scheduled dose administered >= 3 days after the scheduled dosing date.

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

Dose reduction/delay/omission will be summarized as follows:

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

A listing of investigational product administration will be provided.

9.6. Overdose

Overdose, as defined in this study, refers to dosing for nab-paclitaxel or gemcitabine only.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of nab-paclitaxel or gemcitabine to a given subject, regardless of any associated adverse events (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.

Drug overdose will be summarized as follows:

- Separately for nab-paclitaxel and gemcitabine for induction phase and Investigator's Choice phase, respectively, the number and percentage of subjects with at least 1 drug overdose, overdose frequency as defined by overdose definition for each category (on per dose basis, on schedule or frequency basis, and on infusion rate basis) and for each treatment cycle.

A listing of investigational drug overdose will be provided.

10. EFFICACY ANALYSIS

The primary analyses will be performed on the ITT and PP population. The secondary efficacy analysis will be performed on the ITT population.

Summaries of efficacy endpoints will be provided at the end of study. Disease control rate will be analyzed only for induction phase.

10.1. Multiplicity

There is no adjustment for multiplicity of endpoints because of the exploratory nature of this study and the lack of statistical testing.

10.2. Analysis of Primary Efficacy Endpoint

Time to treatment failure is defined as the time after the first dose of study therapy to discontinuation of study therapy due to disease progression, death (by any cause), or the start of a new non-protocol-defined anticancer therapy. If a subject does not progress, die or start a new non-protocol-defined anticancer therapy, then the subject will be censored on the last tumor assessment date. Therapies serving as maintenance or standard of care after surgery or chemoradiation are not considered as part of non-protocol-defined anticancer therapies. A listing of these subsequent anticancer therapies (section 10.3.5) is provided for clinical review to determine the nature of the anticancer therapy. The TTF will be summarized using standard Kaplan-Meier methods. Median TTF and a 2-sided 90% CI using the method of Brookmeyer and Crowley will be reported.

Summaries will be provided at the end of study for both ITT population and PP population.

A Kaplan-Meier plot will also be produced.

No formal statistical testing will be done with this endpoint.

10.3. Analysis of Secondary Efficacy Endpoints

10.3.1. Disease Control Rate

Disease control rate is defined as the percentage of responders, defined as subjects with CR, PR or SD. In order to qualify for DCR calculation, SD must last for >= 16 weeks from the date of first treatment. The tumor response is assessed by investigators according to RECIST 1.1 guidelines. Disease control rate after 6 cycles of nab-paclitaxel and gemcitabine and 90% CI using Wilson score method [1] will be provided during induction phase.

The summaries will be repeated for the following endpoints.

- DCR during induction phase with SD >=16 weeks excluding tumor assessments after non-protocol-defined anticancer therapy/surgery
- DCR during induction phase with SD >=24 weeks

- DCR during induction phase with SD >=24 weeks excluding tumor assessments after non-protocol-defined anticancer therapy/surgery
- DCR at month 6
- DCR at month 6 excluding tumor assessments after non-protocol-defined anticancer therapy/surgery

10.3.2. Overall Response Rate

Subjects with Investigator-determined CR or PR according to RECIST 1.1 guidelines will be considered as responders. The ORR will be presented with 2- sided 90% CI using Wilson score method. Summaries will be provided at the end of study.

10.3.3. Progression-free Survival

Progression-free survival is defined as the time from the first dose of study therapy to the start of disease progression or death (by any cause), whichever occurs first. Subjects who do not have disease progression or have not died will be censored to last tumor assessment date with progression-free.

The following sensitivity analysis of progression-free survival will also be conducted: if a subject had disease progression or died right after missing 2 or more consecutive scheduled tumor assessment, the subject will be censored on the previous tumor assessment date with progression-free; if a subject received a new non-protocol-defined anti-cancer therapy/surgery prior to documented disease progression or death, the subject will be censored on the last tumor assessment date with progression-free prior to the initiation of this new therapy/surgery.

The censoring rule is illustrated in Table 3.

Table 3: Censoring Rules for Progression-free Survival

Value of Progression-free Survival/Censor Date	Censored	Derivation
Analysis Date = minimum (death date, disease progression date)	No	If a subject died or had disease progression.
Analysis Date = the last progression-free assessment date/ first dose date	Yes*	If a subject had disease progression or died right after missing 2 or more consecutive scheduled tumor assessments (as defined by the time interval between the death date/progression date and the previous tumor assessment date with progression-free response or the first dose date is greater than 120 days).
Analysis Date = the last tumor assessment date/first dose date	Yes	If a subject did not die or have progression. If there was no post-baseline tumor assessment, then ADT = the first dose date.
Analysis Date = last tumor assessment date with progression-free prior to the initiation of this new therapy/surgery	Yes*	If a subject received a new non-protocol-defined anti-cancer therapy/surgery prior to documented disease progression or death.
Note: Progression-free response refers to a response that was neither progressive disease (PD) nor un-evaluable (UE). * This rule applies to sensitivity analysis.		

The survival distribution of PFS will be estimated using the Kaplan-Meier method, the median and associated 2-sided 90% CIs calculated using the method of Brookmeyer and Crowley will be provided. The PFS rates will be provided for different time points.

Summaries will be provided at the end of study.

A Kaplan-Meier plot will also be produced for both PFS and sensitivity PFS endpoints.

10.3.4. Overall Survival

The overall survival is defined as the time from the date of first dose of study therapy to the date of death (by any cause). Subjects who are alive at the end of study or clinical data cut will be censored on the last known time that the subject was alive or the clinical cutoff date, whichever is earlier.

The survival distribution of OS will be estimated using the Kaplan-Meier method, the median including 2-sided 90% CI calculated using the method of Brookmeyer and Crowley will be provided. The survival rates will be provided for different time points.

Summaries will be provided at the end of study.

A Kaplan-Meier plot will also be produced.

10.3.5. Tumor Response

Tumor evaluations are assessed by the Investigators and response (complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), unevaluable (UE)) is determined according to RECIST v1.1 guidelines.

Data listings for tumor response will be provided:

- Overall best response for subject
- Per subject visit:
    - Date of assessment
    - Assessment of target lesions
    - Assessment of non-target lesions
    - Presence of symptomatic deterioration
    - Overall tumor response assessment
    - Best overall response
- Per lesion at each subject visit:
    - Location
    - Method of assessment
    - Tumor length (target lesions only)

A waterfall plot will be provided for best percent change from baseline in sum of longest diameter (SLD) of target lesions.

10.3.6. Subsequent Anti-cancer Therapy

The subsequent anti-cancer therapies will be summarized. Listings will be provided.

10.3.7. Health-related Quality of Life

Differences in outcomes from baseline, during treatment, and after treatment for the EORTC QLQs, EORTC QLQ-C30 and QLQ-PAN26 will be described in an analysis plan separate from this SAP.

CCI [redacted]

10.5. Other Efficacy Analyses

For subjects with surgical intervention during the study per Investigator's Choice, the number and percentage of subjects will be summarized with respect to surgery type, pancreas position, nodal status, resection status, and histology details.

11. SAFETY ANALYSIS

All safety analyses will be conducted based on the treated population. Whenever possible, combine induction phase and investigator's choice phase into one summary table. Summaries will be provided for data collected during chemotherapy induction phase, chemotherapy including both phases, chemoradiation therapy for IC phase, and surgery for IC phase. The columns in the headers of summary tables are (1) Induction Phase *nab*-Paclitaxel/Gemcitabine, (2) Overall *nab*-Paclitaxel/Gemcitabine, (3) Chemoradiation, (4) Surgical Intervention.

11.1. Adverse Events

Adverse events (AEs) will be analyzed in terms of TEAEs of a study phase which are defined as any AEs that begin or worsen on or after the start of study drug or procedure of the phase. (1) TEAE in the induction phase is an AE onset on or after the first dose of chemotherapy up to cycle 7 day 1 if the subject enters IC with chemotherapy, or to 28 days after last dose of *nab*-Paclitaxel and Gemcitabine if the subject discontinues the study during induction phase, or to the date of chemoradiation or surgery. (2) TEAE in chemotherapy overall is an AE that has to start on or after the first dose of chemotherapy up to 28 days after last dose of chemotherapy. (3) TEAE in Chemoradiation is an AE onset on or after first chemoradiation up to 28 days after last dose of chemoradiation. (4) TEAE in Surgical Intervention is an AE onset on or after the surgery up to 28 days after the surgery. All AEs will be coded using the MedDRA Version 20.0.

A treatment-related TEAE is defined as TEAE which was considered to be related to one or both of the study drugs and reported as "Suspected" on the CRF. AEs with a missing relationship will be treated as "treatment-related" in summary and presented as missing in subject data listings.

The incidence of TEAE will be summarized by MedDRA system organ class (SOC) and preferred terms (PTs). 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;
- Treatment-related TEAEs;
- TEAEs by maximum grade;
- Treatment-related grade 3 or higher TEAEs;
- Serious TEAEs;
- Serious TEAEs by maximum grade;
- Treatment-related Serious TEAEs;
- Serious TEAEs by SAE criteria;
- TEAEs with action of study drug withdrawn;

- TEAEs with action of study drug dose reduced;
- TEAEs with action of study drug dose interrupted;
- TEAEs with outcome of death;
- All deaths within 28 days of last dose with cause of death.

If a subject experiences the same AE more than once with a 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 system organ class/preferred term, then the subject will be counted only once for that system organ class/preferred term In addition, AEs with a missing severity/intensity will be presented in the summary table as an intensity category of "Missing".

Listings will be prepared that include the verbatim term, PT, and SOC as well as full details of all AEs for subjects in the treated population.

Separate listings will also be prepared for grade 3 and higher TEAEs, serious TEAEs, TEAEs leading to death (either outcome of death or SAE due to death), and TEAEs resulting in discontinuation of IP. All deaths will be listed with the cause of death collected on the Death CRF page.

Treatment-related TEAE, TEAE (and treatment-related TEAE) with action of drug withdrawn, dose reduction or dose interruption will not be summarized for surgery group and chemoradiation group at investigator's choice phase.

11.2. Adverse Events of Special Interest

11.2.1. AE of Special Interest

Adverse events of special interest of *nab*-paclitaxel and gemcitabine combination identified in previous trials in a similar population will be summarized. TEAEs of special interest are as follows:

- Myelosuppression (to include Anaemia, Neutropenia, and Thrombocytopenia);
- Peripheral Neuropathy;
- Gastrointestinal events;
- Myalgia and arthralgia;
- Hypersensitivity;
- Cranial nerve paralysis;
- Cardiotoxicity including Congestive Heart Failure/Left Ventricular Dysfunction;
- Stevens-Johnson Syndrome/toxic epidermal necrolysis;
- Pneumonitis;
- Infusion site reactions/extravasation;

- Cystoid macular edema;
- Hepatotoxicity;
- Acute renal failure and Hemolytic uremic syndrome;
- Clinically severe infections; sepsis
- Posterior reversible encephalopathy syndrome (PRES);
- Capillary leak syndrome (CLS).

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 leading to death.

TEAE of special interest leading to action of drug withdrawn, dose reduction or dose interruption will not be summarized for surgery group and chemoradiation group at investigator's choice phase.

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.

11.2.2. Peripheral Neuropathy

Peripheral neuropathy (PN) will be assessed by physician using the NCI CTCAE Version 4.0 of "Neuropathy – Sensory". An overview of peripheral neuropathy will be summarized. The frequency of physician assessment of PN grade (0 – 5) will be presented by phase and cycle. The frequency of worst PN grade during treatment will also be presented. Additionally, PN events will be reported as part of the AEs and will be analyzed as outlined in Section 11.1.

11.3. Clinical Laboratory Evaluations

All scheduled laboratory samples will be performed locally. The laboratory values will be graded using NCI CTCAE V4.0. For hematologic and chemistry laboratory values that fall outside of the grade criteria of NCI CTCAE V4.0, the grade of 0 will be assigned. Listings will be provided for all clinical lab evaluations with normal ranges included.

11.3.1. Clinical Chemistry

The NCI CTCAE grade for chemistry panel tests will be summarized by the most severe grade during treatment of chemotherapy in induction phase, of chemotherapy overall, of chemoradiation, and of surgery.

11.3.2. Hematology

The NCI CTCAE grade for hematology panel tests will be summarized by the most severe grade during treatment of chemotherapy in induction phase, of chemotherapy overall, of chemoradiation, and of surgery.

11.3.3. Serum Carbohydrate Antigen 19-9 (CA19-9)

Serum CA19-9 levels will be collected at the time of every CT/MRI scan assessment. Absolute CA19-9 levels and change from baseline will be summarized by cycle during induction chemotherapy phase and Investigator's Choice phase. The maximum change of CA19-9 from baseline is defined as the percentage change at the nadir from the baseline value and will be summarized descriptively. For subjects with both baseline and post baseline assessments, the percent of subjects with a maximum drop in CA19-9 of at least 20%, 50%, 70% and 90% will be calculated. The maximum change in CA19-9 from baseline for each subject will be produced in a waterfall plot.

11.4. Vital Sign Measurements

For vital signs, results will not be collected in the eCRF, and if results are abnormal and clinically significant at screening, they will be recorded as medical history, and if results are abnormal and clinically significant after screening, they will be recorded as an AE or SAE. Therefore, there will be no separate analysis for vital sign.

11.5. Physical Examination

Any results from physical examination will not be collected in the eCRF, and if results are abnormal and clinically significant at screening, they will be recorded as medical history, and if results are abnormal and clinically significant after screening, they will be recorded as an AE or SAE. Therefore, there will be no separate analysis for physical examination.

11.6. ECOG Performance Score

The worst ECOG performance status during treatment will be summarized for the induction phase, chemoradiation therapy for IC phase and overall.

11.7. Other Safety Analysis

A descriptive summary table for the treated population will be provided with respect to neutrophils, lymphocytes and ratio of neutrophils to lymphocytes (NLR), as well as a frequency summary of NLR categories (NLR $\leq$ 5 vs. NLR > 5).

12. INTERIM ANALYSIS

12.1. Analysis Methods

An interim analysis will be conducted when all subjects completed 6 cycles of *nab*-paclitaxel and gemcitabine in the induction phase or discontinued early from the study. The DCR analysis proposed in this SAP and analyses listed below that are deemed necessary for the induction phase will be performed for the interim analysis. The same analysis methods will be used as full analysis described in previous sections of this SAP.

In addition to DCR, interim analysis also includes:

- Subjects who discontinued from study therapy in induction phase, subjects who completed induction phase and subjects who entered Investigator's Choice phase will be summarized. Reasons for discontinuation from induction phase will be summarized;
- The demographics, baseline characteristics, and medical history will be summarized in the same way as full analysis;
- Summary of concomitant medications, treatment exposure and dose modification for the induction phase;
- Overall summary of TEAE for the induction phase;
- Summary of treatment-related TEAE by system organ class and preferred term for the induction phase;
- Analysis of other efficacy endpoints including TTF, PFS and OS.

13. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

Section 10.3.3 of this SAP: progression-free survival analysis will be conducted by two approaches. The different censoring rules are used to examine the sensitivity of PFS analysis.

14. REFERENCES

[1] Robert G. Newcombe, Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. Statistics in Medicine 1998;17:857-872

[2] Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45 (2): 228-47.

15. APPENDICES

15.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY 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.

15.2. Date Imputation Guideline

15.2.1. 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 doing 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 doing 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.