STATISTICAL ANALYSIS PLAN

STUDY TITLE:	A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer
STUDY DRUG:	FG-3019
PROTOCOL NUMBER:	FGCL-3019-087
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
VERSION	Version 2.0
RELEASE DATE:	24 June 2024

CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

This document has been signed and dated using 21 CFR part 11 compliant electronic signatures (see appended final page). By signing, the signee is attesting that the content of the document is compliant with regulatory requirements and guidelines, complete and accurate.

CHANGES TO PROTOCOL

Description of Change	Rationale for Change	Section affected
Per Protocol (PP) Population is added in the Analysis Population section. Primary and secondary endpoints will also be conducted for PP population.	This will distinguish between ITT and PP Population	Section 4.1.1 , Section 4.1.2 and Section 5.1.2
Best Overall Objective response rate (ORR) is added as a secondary endpoint	Addition of standard endpoint for Oncology study	Section 4.1.3
QOL Endpoint has changed to Exploratory and will be analyzed by MMRM model	Switch to Exploratory Endpoint	Section 4.1.4
Added number of cycles as exploratory endpoint	To compare the number of cycles between treatment arms	Section 4.1.4

REVISION HISTORY

Version	Date	Description
1.0	Apr 15, 2022	
2.0	June 24, 2024	Global study (Cohort 1) is based on protocol Amendment 5.0. Added statistical analysis plan for combined China patients from Cohort 1 and Cohort 2 based on protocol Amendment 5.1 (China-Only). Clarified CA19-9 subgroup based on any change from baseline in Section 6.6.3.4 Updated ADA analysis section for clarification. Clarified PFS event and censoring rules in new Table 8. Clarified approximately 233 events are needed to achieve at least 80% power in Section 3.3. Removed Section 6.6.7.7 Response at EOT in SAP v 1.0 (based on protocol Amendment 4.0) due to an update to remove this exploratory endpoint in protocol Amendment 5.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BSA	Body Surface Area
BP	Blood Pressure
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CI	Confidence Interval
C_{min}	the minimum blood plasma concentration reached by a drug during the time interval between administration of two doses
C_{max}	the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose
CM	Concomitant Medications
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CS	Clinically Significant
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
CV	Coefficient of Variation
DMC	Data Monitoring Committee
EBL	Estimated Blood Loss
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EFS	Event-Free Survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of Treatment
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FDG-PET	[^{18}F]-Fluorodeoxyglucose-Positron Emission Tomography
FG-3019	Pamrevlumab
G/NP	Gemcitabine plus Nab-paclitaxel
HAHA	Human Anti-Human Antibodies
HR	Hazard Ratio
IAP	Interim Analysis Plan
IEC	Independent Ethics Committees
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
KM	Kaplan-Meier
LAPC	Locally Advanced unresectable Pancreatic Cancer
LLN	Lower Limit of Normal for a laboratory parameter
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
MRB	Multidisciplinary Review Board
MRI	Magnetic Resonance Imaging
MTV	Metabolic Tumor Volume
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	Not Clinically Significant
ORR	Best Overall Objective Response Rate
OS	Overall Survival
PCS	Potentially Clinically Significant

PD	Progressive Disease
PE	Physical Examination
PF	Physical Functioning
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PH	Proportional Hazards
PK	Pharmacokinetic(s)
PP	Per-Protocol
PR	Partial Response
PROs	Patient Reported Outcomes
PT	Preferred Term
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Study Data Tabulation Model
SE	Standard Error
SMA	Superior Mesenteric Artery
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
Std	Standard Deviation
SUVmax	Maximum Standardized Uptake Value
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Tables, Listings, Figures
TNM	Tumor Node Metastasis
ULN	Upper Limit of Normal
VS	Vital Sign
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) documents planned analyses for Study FGCL-3019-087 Amendment 5.0 (May 16, 2022) and Amendment 5.1 (China-Only, Aug 16, 2022) entitled "A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer". And it is an update from the previous SAP V1.0 based on Study FGCL-3019-087 Protocol Amendment 4.0 (Oct 25, 2021).

This SAP includes statistical analysis methods, statistical models, definitions, and data handling rules. It supersedes the statistical section in the protocol in case of any difference.

2. STUDY OBJECTIVES

The primary objective of this trial is:

- To evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab in combination with either gemcitabine plus nab-paclitaxel (G/NP) or FOLFIRINOX when compared to treatment with either G/NP or FOLFIRINOX alone in locally advanced, unresectable pancreatic cancer.

The secondary objective of this trial is:

- To evaluate the effect of neoadjuvant treatment with pamrevlumab in combination with either G/NP or FOLFIRINOX on Event-Free Survival.

3. STUDY DESIGN

3.1. Overview

This is a Phase 3, randomized, double-blind trial to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab or placebo in combination with either G/NP or FOLFIRINOX, in the treatment of locally advanced unresectable pancreatic cancer (LAPC) subjects. Approximately 280 subjects will be enrolled in this trial, across approximately 100 study centers in the following locations: North America, Europe, and Asia Pacific.

When completion of global study enrollment (approximately N=280, Cohort 1) is reached, China sites will continue enrollment in Cohort 2 until the planned number of subjects in China is achieved.

This trial has five periods:

- Screening Period (up to 30 days)
- Neoadjuvant Treatment Period (~24-30 weeks)
- Evaluation for Surgical Exploration (~ 4-5 weeks after last dose)
- Surgery (~4-8 weeks after last dose)
- Follow-up Period (Up to 6 years)

A schematic overview of the study, including study period timeframes, is provided in Figure 1 of the protocol.

3.2. Study Population

Patients with locally advanced unresectable pancreatic cancer.

3.3. Sample Size Determination

The study is planned to enroll approximately 280 subjects with 1:1 randomization ratio to the two treatment arms.

Sample size estimation was based on the assumption that the median Overall Survival (OS) duration for the pamrevlumab arm and the placebo arm are 24 and 16.3 months, respectively. This improvement represents a hazard ratio (HR) of 0.68. With this HR, approximately 233 deaths will provide at least 80% power with a two-sided significance level of 0.05. With the enrollment of approximately 280 subjects, 233 deaths will be estimated by the end of the Follow-up period.

Based on the treatment effect on EFS having an HR of 0.60, 161 events would be required to provide 75% power using a stratified log-rank test with a one-sided 0.005 false positive error rate.

3.4. Randomization and Treatment Assignment

Subjects will be randomized 1:1 to one of two treatment arms:

- **Arm A**: pamrevlumab + either G/NP or FOLFIRINOX
- **Arm B**: placebo + either G/NP or FOLFIRINOX

Subjects will be stratified at randomization according to the following factors:

- Chemotherapy treatment regimen (G/NP or FOLFIRINOX)
- SMA (Superior Mesenteric Artery) encasement (> or ≤ 180°)
- Unreconstructible disease (yes or no)
- Geographic region (North America/Europe or Asia Pacific)

Randomization will be conducted centrally across all sites using an Interactive Response System.

3.5. Dosing Schedule

Each treatment cycle is 28 days long and subjects may receive up to six cycles of treatment. Basically, investigators and their subjects will choose to be treated with either gemcitabine plus nab-paclitaxel or FOLFIRINOX as the backbone chemotherapy treatment regimen to be administered in combination with pamrevlumab or placebo as shown in Table 1.

Table 1: Dosing Schedule

Arm A	Arm B
Pamrevlumab, 35 mg/kg by IV infusion on Days 1 and 15 of each 28-day treatment cycle. An additional dose will be given on Day 8 of the first cycle.	**Placebo**, 35 mg/kg by IV infusion on Days 1 and 15 of each 28-day treatment cycle. An additional dose will be given on Day 8 of the first cycle.
AND	
• Gemcitabine, 1000 mg/m^2 by IV infusion on Days 1, 8, and 15 of each 28-day treatment cycle. • Nab-paclitaxel, 125 mg/m^2 by IV infusion on Days 1, 8, and 15 of each 28-day treatment cycle. OR FOLFIRINOX • (Oxaliplatin – 85 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle • Folinic Acid/Leucovorin – 400 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle • Irinotecan* – 180 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle • Fluorouracil* – 400 mg/m^2 by IV infusion (bolus infusion) on Days 1 and 15 of each 28-day treatment cycle • Fluorouracil – 2400 mg/m^2 by IV infusion (46-hour continuous infusion) on Days 1-3 and Days 15-17 of each 28-day treatment cycle)	

* Doses may be adjusted per local/institutional guidelines to support modified FOLFIRINOX dosing regimen (mFOLFIRINOX)

Arm A treatment consists of:

- **Pamrevlumab, 35 mg/kg by IV infusion on Days 1 and 15 of each 28-day treatment cycle. An additional dose will be given on Day 8 of the first cycle.**

AND

- Gemcitabine, 1000 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.
- Nab-paclitaxel, 125 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.

OR FOLFIRINOX

- (Oxaliplatin – 85 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Folinic Acid/Leucovorin – 400 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Irinotecan* – 180 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Fluorouracil* – 400 mg/m^2 by IV infusion (bolus infusion) on Days 1 and 15 of each 28-day treatment cycle

- Fluorouracil – 2400 mg/m^2 by IV infusion (46-hour continuous infusion) on Days 1-3 and Days 15-17 of each 28-day treatment cycle)

Arm B treatment consists of:

- **Placebo, 35 mg/kg by IV infusion on Days 1 and 15 of each 28-day treatment cycle. An additional dose will be given on Day 8 of the first cycle.**

AND

- Gemcitabine, 1000 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.
- Nab-paclitaxel, 125 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.

OR FOLFIRINOX

- (Oxaliplatin – 85 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Folinic Acid/Leucovorin – 400 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Irinotecan* – 180 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle
- Fluorouracil* – 400 mg/m^2 by IV infusion (bolus infusion) on Days 1 and 15 of each 28-day treatment cycle
- Fluorouracil – 2400 mg/m^2 by IV infusion (46-hour continuous infusion) on Days 1-3 and Days 15-17 of each 28-day treatment cycle)

*Doses may be adjusted per local/institutional guidelines to support modified FOLFIRINOX dosing regimen (mFOLFIRINOX)

3.6. Study Assessments

The schedule of assessment is provided in Appendix Section 9.1.

Eligibility for surgical exploration is evaluated for all subjects who complete 6 cycles of study treatment. Subjects who undergo surgical exploration within the protocol-specified window are followed for surgical complications and outcomes per protocol. Tissue samples are collected during resection and provided to central pathology. Subjects who do not undergo surgical exploration (e.g., subjects who did not complete 6 cycles of treatment or do not meet any of the protocol defined criteria or had a contraindication to surgery) continue in the Follow-up period to be followed for progression, survival and additional anticancer therapies. Subjects in the Follow-up period may receive treatment as per Standard of Care for each institution.

Vital Signs (VS): Vital signs are collected including heart rate, blood pressure, respirations, temperature, height and weight.

Physical Exam (PE): A full physical exam is required during screening and on Day 1 of each treatment cycle. All other physical exams may be abbreviated unless a full physical exam is warranted in the opinion of the investigator.

Electrocardiogram (ECG): ECGs are performed in accordance with institutional standards at screening, Day 1 of each cycle and EOT.

Laboratory Evaluations: Labs are evaluated by a central laboratory (lab). Central lab results obtained during the screening period are used to determine subject eligibility for participation in the trial. Central lab results are reviewed by the investigator for clinical significance and to determine appropriate reporting of adverse events. Central lab results for CA19-9 are used to determine eligibility for surgical exploration. Local lab results were not captured in the database. However local lab results were approved to be used during COVID-19 in case sites were restricted from central lab and /or when central lab kits were in shortage due to COVID-19. These local lab results will be captured in the clinical database.

Pharmacokinetics and Pharmacodynamics: Additional samples are collected to evaluate PK, HAHA, HAHA-NA and CTGF.

Pharmacokinetics: Plasma samples are collected in all subjects for evaluation of C_{max} and C_{min} trough levels of pamrevlumab (FG-3019). A central laboratory measures plasma pamrevlumab levels using a validated assay. For the analysis of C_{max} and C_{min} data, it is critical to accurately record the dosing time and date in addition to the sampling collection time and date.

HAHA and CTGF: Plasma samples are collected for evaluation of human anti-human antibodies (HAHA), also named as ADA, HAHA-NA and connective tissue growth factor (CTGF) in all subjects. Central laboratories measure HAHA and CTGF level using validated assays.

Pharmacodynamics and Biomarkers: Tumor tissue are collected from all resected subjects for histological analysis and examination of nucleic acids. Plasma samples are collected from all subjects to support the exploratory analysis of protein and nucleic acid markers.

Eastern Cooperative Oncology Group (ECOG): The ECOG performance scale is used to evaluate subject's performance status during screening and throughout the trial.

Karnofsky Performance Scale Index: The Karnofsky performance scale is used to evaluate subject's performance at EOT only. Karnofsky performance scores are evaluated by the central review team in determination of eligibility for surgical exploration per protocol.

Carbohydrate Antigen 19-9 (CA 19-9): CA 19-9 levels are measured at baseline and regularly throughout the study. CA 19-9 results are evaluated by the central laboratory.

Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Scan: An FDG-PET scan is performed at baseline and EOT to evaluate SUVmax and metabolic tumor volume (MTV) in the primary pancreatic tumor. Central imaging will evaluate all PET scans collected for the study.

Computer Tomography (CT) Scan: CT scans are performed using pancreatic protocols and in accordance with the central imaging charter until progression. Central imaging will conduct Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 reads on all CT scans collected during screening, the neoadjuvant treatment period and follow-up.

Baseline CT scans (collected during the screening period) are evaluated by the central radiological/surgical review team to confirm subjects have locally advanced, unresectable disease prior to enrollment.

All CT scans collected during the study are evaluated by the central review team for progression per RECIST 1.1 until progression is noted. EOT CTs, for subjects who complete all 6 cycles of treatment, are evaluated at EOT by the central review team in determination of eligibility for surgical exploration per protocol.

If a subject cannot tolerate a contrast CT, Magnetic Resonance Imaging (MRIs) may be performed. If MRIs are performed during screening or the neoadjuvant treatment period due to contrast intolerance, they will be sent to central imaging for review.

Patient Reported Outcomes (PROs): PROs data are collected in all subjects to evaluate the most important patient reported symptoms, treatment-related symptoms and functional impacts that may be responsive to treatment. EORTC QLQ-C30 and PRO-CTCAE™ questionnaires are administered as specified in Appendix 1 in protocol (prior to dosing in all applicable instances).

- **EORTC QLQ-C30:** EORTC QLQ-C30 Version 3.0 is the most recent version and is used for this study. This questionnaire is collected on Day 1 of each treatment cycle (prior to dosing), at EOT and the Safety Follow-up visit.
- **PRO-CTCAE™:** The following symptoms from the PRO-CTCAE™ library are included in a symptom-specific patient questionnaire: decreased appetite, nausea, vomiting, diarrhea, abdominal pain, and fatigue. This questionnaire is collected on Days 1, 8 and 15 in the first three treatment cycles (Cycles 1-3), on Days 1 and 15 in the last three treatment cycles (Cycles 4-6) and at the EOT and Safety Follow-up Visit.

Surgical Outcomes and Complications: All subjects that undergo surgery within the protocol-specified window (at least 4 weeks after the last dose and no longer than 8 weeks after the last dose) are followed for surgical outcomes and complications for 90 days after their discharge. Surgical safety is assessed by the collection of surgical outcomes measures and surgical complications that occur during this timeframe.

- **Surgical Complications:** All surgical complications that occur are collected and graded in severity according to the Clavien-Dindo Classification (Appendix 4 in protocol).
- **Surgical Outcomes:** The following surgical outcomes are measured:
  - Type of procedure/resection
  - Resection outcome
  - >10 lymph nodes
  - Operative time >10 hours
  - Length of hospital stay
  - Estimated blood loss (EBL) at time of surgery

- Transfusions; units of blood
- Return to operating room within 30 days

4. STUDY ENDPOINTS AND DEFINITIONS

4.1. Study Endpoints

4.1.1. Primary Endpoint

The primary endpoint of this trial is Overall Survival (OS), defined as the time from randomization to death due to any cause.

4.1.2. Event-Free Survival Endpoint for Accelerated Approval

The Event-Free Survival (EFS) Endpoint is a composite time-to-event endpoint, the event being 'treatment failure' defined as the earliest occurrence of:

- Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery)
- Local or distant recurrence, or
- Death

EFS is also a key secondary endpoint.

4.1.3. Secondary Endpoints

The secondary endpoints of this trial are:

- Event-Free Survival (as described above)
- Progression-Free survival (PFS), defined as the time from randomization until objective tumor progression or death (whichever occurs first).
- RECIST 1.1 – Best Overall Objective Response Rate (ORR), defined as the proportion of patients who achieve Complete Response (CR) or Partial Response (PR) during treatment period.

4.1.4. Exploratory Endpoints

- Exploratory endpoints for this trial are:
- Change in Patient Reported Outcomes (PROs) as measured by:
  - Mean change from baseline during the treatment period in physical function by EORTC QLQ-C30
  - Mean change from baseline during the treatment period in abdominal pain by
  - NCI-PRO-CTCAE

  - Mean change from baseline during the treatment period in fatigue by NCI-PRO-CTCAE
- Proportion of all randomized subjects in whom R0 or R1 resection is achieved
- Difference in OS between resected and non-resected subjects
- The proportion of subjects considered eligible for surgical exploration per protocol-defined criteria
- Mean change from baseline during the treatment period in CA19-9
- Change in FDG-PET SUVmax and MTV at EOT when compared to baseline
- Correlative analyses of baseline CTGF serum levels with clinical outcomes
- PK exposure-response analysis
- Histological analysis in tumor tissues collected during resection
- Evaluation of CTGF as prognostic or predictive biomarker
- Evaluation of other selected protein and nucleic acid markers in plasma samples
- Evaluation of number of chemotherapy cycles between the two arms

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Analysis Populations

5.1.1. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects regardless of whether or not study treatment is received. The primary analysis of efficacy will be based on the ITT population (based on treatment randomized).

5.1.2. Per-Protocol (PP) Population

The Per-Protocol (PP) Population is defined as all subjects who have completed the 6-cycle study treatment, had baseline and at least one post-baseline tumor assessments.

5.1.3. Safety Population

The Safety Population is defined as all randomized subjects who have received study medication. All analyses of safety will be based on the Safety population (based on treatment received).

5.1.4. PK Population

The Pharmacokinetic (PK) population is defined as all randomized subjects who have signed informed consent to participate in the study, received at least one dose of study medication, and have corresponding PK concentration data.

5.1.5. Immunogenicity Analysis Set (IGS)

The IGS will include all subjects who are in the Safety Population and have a baseline evaluable immunogenicity assessment and at least 1 post-baseline evaluable (i.e., positive, negative) immunogenicity assessment.

5.2. Multiple Endpoints Hypotheses and Decision Rules

By design, two-sided 0.01 alpha will be allocated to EFS, the primary endpoint for accelerated approval, while two-sided 0.04 will be allocated to OS, the primary endpoint for full approval.

The alpha designated to EFS will be spent at the time of 161 EFS events (or more depending on completion of accrual).

A hierarchical approach will be implemented. If the analysis of the effect of pamrevlumab on EFS is statistically significant at two-sided p=0.01 at the interim analysis, then that alpha will be carried forward to the final analysis of OS, which then would be conducted at the two-sided p=0.05 level. If the effect of pamrevlumab on EFS is not statistically significant at two-sided p=0.01 at the interim analysis, then the final analysis of pamrevlumab's effect on OS would be conducted at the two-sided p=0.04 level.

At the time of 161-event analysis of EFS (or more depending on completion of accrual), an interim look of OS will also be conducted at that time by the Data Monitoring Committee (DMC) for lack of benefit analysis. The final analysis of OS will occur when 233 OS events have occurred, estimated to be approximately 48-54 months into the trial.

Please refer to the Interim Analysis Plan (IAP Version 1.2, dated of 28 February 2022) for detailed description of the interim analysis.

5.3. Handling of Dropouts or Missing Data

All assessments collected will be considered for analyses regardless of whether such data were collected during treatment or after a subject discontinued treatment. All analyses assume the missing data are missing at random (MAR), unless stated otherwise. Except for the cases described in this section and Section 6.6, only observed data without imputation will be used in analyses.

5.3.1. Handling Missing/Incomplete AE Onset Date

Incomplete Start Date

The following imputation rules apply to the case where the start date is incomplete (i.e., partially missing) for adverse events.

Missing day and month

If the year is same as the year of first day on double-blind study medication, then the day and month of the start date of double-blind study medication will be assigned to the missing fields.

If the year is not the same as the year of first day on double-blind study medication, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year are same as the year and month of first day on double-blind study medication, then the start date of double-blind study medication will be assigned to the missing day.

If the month and year are not the same as the year and month of first day on double-blind study medication, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If needed, the following imputation rules apply to the case where the end date is incomplete (i.e., partially missing) for adverse events. Other partial end date will not be imputed.

Missing day and month, or Missing month only

December 31 will be assigned to the missing fields.

Missing day only

The last day of the month will be assigned to the missing day.

5.3.2. Handling Missing/Incomplete CM Start/Stop Dates

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

Incomplete Start Date

The following rules will be applied to impute the missing start date. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

If the year of the incomplete start date is the same as the year of the first dose date of double-blind study medication, then the day and month of the first dose date will be assigned to the missing fields.

If the year of the incomplete start date is not the same as the first dose date of double-blind study medication, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose date of double-blind study medication, then the day of the first dose date will be assigned to the missing day.

If the month and year of the incomplete start date are the same as the first dose date of double-blind study medication, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date

The following rules will be applied to impute the missing stop date, if needed. If the last dose date of double-blind study medication is missing, impute it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be replaced with the start date.

Missing day and month

If the year of the incomplete stop date is the same as the year of the last dose date of double-blind study medication, then the day and month of the last dose date will be assigned to the missing fields.

If the year of the incomplete stop date is not the same as the year of the last dose date of double-blind study medication, then December 31 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year of the incomplete stop date are the same as the month and year of the last dose date of double-blind study medication, then the day of the last dose date will be assigned to the missing day.

If the month and year of the incomplete stop date are not the same as the month and year of the last dose date of double-blind study medication, then the last day of the month will be assigned to the missing day.

5.4. Stratification Factors

Comparisons between treatment arms will be adjusted for the following factors.

- Chemotherapy treatment regimen (G/NP or FOLFIRINOX)
- SMA encasement (> or ≤ 180°)
- Unreconstructible disease (yes or no)
- Geographic region (North America/Europe or Asia Pacific)

5.5. Definition of Baseline

Unless otherwise specified, baseline is defined as the last evaluable observation collected prior to the first dose of study drug.

5.6. Study Day Calculation

The day when a subject receives the first dose of any study drugs (pamrevlumab/placebo, gemcitabine, nab-paclitaxel, or FOLFIRINOX) after randomization is designated as Day 1. For subjects who have not received any study drug in an ITT analysis, their randomization date will be used as Day 1.

Study day of an assessment/procedure is calculated as following:

- For assessments or procedures on Day 1 or later,

  Study day = assessment/procedure date – Day 1 date + 1.

- For assessments or procedures earlier than Day 1,

  Study day = assessment/procedure date – Day 1 date.

5.7. Efficacy Analysis Visit Window

Efficacy assessments will be summarized by analysis visit based on actual date of assessment. Visit windows will have the widths of the corresponding assessments centered at the scheduled day as shown in Table 2.

Table 2: Analysis Visit Window

Study Period	Assessment Interval	Target Assessment	Window
Cycle 1	Day 1	1st day of Cycle 1 (Day 1)	Days=1 ± 4
	Day 8	8-th day of Cycle 1 (Day 8)	Days=8 ± 4
	Day 15	15-th day of Cycle 1 (Day 15)	Days=15 ± 4
Cycles 2-6	Day 1	k-th day of Cycle x (Day (k + 28 * (x-1)))	Days= (k + 28 * (x-1)) ± 4
	Day 8	k-th day of Cycle x (Day (k + 28 * (x-1)))	Days=(k + 28 * (x-1)) ± 4
	Day 15	k-th day of Cycle x (Day (k + 28 * (x-1)))	Days=(k + 28 * (x-1)) ± 4
End of Treatment[a]	Last assessment between Day 2 and EOT visit day, match to the closest scheduled visit in protocol if patient had not been off drug for more than 14 days. EOT visit should occur within ±2 days of protocol-specified time point.		
Safety Follow-up Visit[a]	Around 28 days after the last dose. The Safety Follow-up visit should occur within ±3 days of the specified time point.		

[a]: Subjects who discontinue treatment early for any reason will complete End of Treatment (EOT) visit and continue in the Follow-up period.

All scheduled and unscheduled assessments are included in analyses. If two assessments are available in the same window, the later assessment will be used in analysis. Assessments that do not fall in any windows will not be included in analyses. Assessments in follow-up periods will be summarized by nominal clinic visit.

Safety data (lab tests, vital signs, ECG, physical exams) are summarized by nominal clinic visit. Data collected during the unscheduled visits are not included in the summary tables, but are included in data listings and in evaluations for clinically significant abnormal changes.

ADA assessment: select in the order of 1) last ADA+ assessment; 2) earlier ADA+ assessment; 3) last ADA- assessment.

5.8. Interim Analyses and Data Monitoring Committee

In addition to routine safety monitoring, an independent Data Monitoring Committee (DMC) (Ellenberg 2019; Fleming 2018) will be established to review safety data on an ongoing basis. A DMC charter will establish the procedures, meeting frequency, and scope of responsibilities of the committee.

The DMC will be comprised of individuals with relevant expertise who are external to the study and are not directly involved with the study conduct. The sponsor proposes to convene the DMC within 21 days after the first 10 subjects have received at least 3 cycles of investigational drug in combination with the FOLFIRINOX regimen to specifically evaluate the safety of this combination. After this initial DMC meeting and if no additional signal has been identified in addition to what is seen with FOLFIRINOX, the DMC will meet approximately every 6 months during the study, in accordance with the DMC Charter.

At the time of 161 EFS events (or more depending on completion of accrual), a hypothesis of equality of EFS between Pamrevlumab and Placebo will be tested at an alpha of 0.01 (two-sided), while these data will be available only to the DMC and the independent reporting statistician who is the liaison between the DMC and the database. At this time of EFS interim analysis, approximately 70 OS events would have occurred, an interim analysis of OS to test for lack of benefit will be conducted by the DMC.

At the interim, a recommendation for early termination of the study for lack of benefit would be based on an O'Brien-Fleming monitoring boundary ruling out the final OS hazard ratio being < 0.77 (the threshold for benefit at the final analysis of OS at the two-sided 0.05 level).

This O'Brien-Fleming monitoring boundary for 'lack of benefit' for OS will be applied at the time of the EFS analysis. At that time, if 70 of the 233 OS events have occurred at the interim, an early termination for lack of benefit would be achieved if the estimated HR is >1.84, while early termination would occur at 80 OS events if the estimated HR of OS is >1.65.

At the time of the Interim Analysis, the DMC will issue the recommendation that these results be discussed with the FDA regarding a potential application for Accelerated Approval, if all of the following conditions are met:

- Statistical significance for EFS is achieved at the one-sided $p < 0.005$;

- The O'Brien-Fleming monitoring boundary for 'lack of benefit' for OS has not been crossed, i.e., the trial has not met the criteria for early termination due to lack of benefit on OS (HR>1.84 if 70 OS, or HR>1.65 if 80 OS, etc.);
- There is no evidence of substantial safety concerns in DMC routine safety review and assessment.

If all of the above conditions are met, the recommendation to discuss this outcome with the FDA will be communicated with FibroGen Chief Medical Officer only and the interim data may be subsequently released to limited personnel of the sponsor in accordance with the Data Access Plan.

Under all circumstances when the study continues after the interim analysis, to protect the integrity of the OS data for the final analysis, confidentiality and blinding of data will be maintained (Fleming, et al. 2018).

For detailed description and computation please refer to the IAP.

All study sites are pooled in all analyses due to the small number of subjects enrolled at each site.

5.9. General Layout

All study parameters, including baseline characteristics, efficacy, safety, PK, and biomarkers, will be summarized descriptively or analytically. Descriptive statistics including the number of subjects (n), mean, standard deviation (Std) for baseline variables or standard error (SE) for efficacy parameters, median, Q1-Q3, minimum and maximum will be presented for continuous variables. For continuous PK parameters, coefficient of variation (CV) and geometric mean may also be presented. Number (n) and percentage (%) of subjects in each category will be summarized for categorical variables.

Detailed format requirement will be described in Appendix Section 9.2. Efficacy parameters will be summarized analytically. Analytical statistics include least squares (LS) mean and SE, 95% confidence interval (CI) for the mean or median, and p-value. Depending on the nature of the parameter and statistical model employed, treatment difference will be expressed in absolute or percent difference, odds ratio, or HR.

Summary of baseline tables like demographics will be presented by treatment group as well as a combined group (Arm A, Arm B, Overall). Nominal p-values will be presented on the baseline table comparing between the two treatment arms for reference only. All other efficacy and safety summaries except PK will be presented by treatment group, unless specified otherwise.

Raw data and derived parameters will be presented in data listings.

Figures, such as line-chart, bar-chart, boxplot, scatter plot, forest plot, or waterfall plot, are in general included to facilitate comparison between treatment arms and evaluation of trend. SE (instead of Std) will be used in all figures applicable.

There will be two sets of analyses, one set for Cohort 1 and the other set for combined China patients from both Cohort 1 and Cohort 2. The statistical analysis plan for Cohort 1 is summarized in Section 6. The statistical analysis plan for combined China patients is summarized in Appendix Section 9.8.

6. STATISTICAL ANALYSES

6.1. Subject Enrollment and Disposition

The number of subjects in each study population (ITT, PP, Safety and PK) will be summarized by treatment group. The number (%) of subjects who completed or discontinued the treatment and/or study and reasons for early discontinuation are summarized by treatment for subjects in the ITT population.

Subject who discontinued the treatment/study early and the reasons for discontinuation will be tabulated and listed.

The data will be summarized with respect to:

- number of subjects screened,
- number (%) of subjects screen-failed,
- number of subjects randomized (defined as subjects who signed informed consent form and received treatment randomization),
- number (%) of subjects randomized, not treated,
- number (%) of subjects randomized, treated,
- number (%) of subjects completed treatment,
- number of (%) subjects prematurely discontinued from treatment by specific reason
- number (%) of subjects completed study,
- number (%) of subjects prematurely discontinued from the study.

Percent of screen-failed will be based on the number of subjects screened. All other percentages for subjects will be based on the number of subjects in the ITT population.

The number of subjects enrolled at each study site will be summarized by treatment group in a separate table.

6.2. Protocol Deviations

Only important protocol deviations need to be reported for Clinical Study Report.

Important protocol deviations will be summarized by treatment (in columns) and by study site (in rows). COVID-19-related summary table and listing will be provided here. All recorded important protocol deviations will be listed by site. Reported items that are not considered as important protocol deviations will not be included in summary tables. Minor protocol deviations will be presented in listing only.

6.3. Demographics and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized descriptively for subjects in both ITT and safety populations. Each parameter will be presented in data listings.

6.3.1. Subject Demographics and Baseline Characteristics

Subject demographics and baseline characteristics include age, age group (18-64, 65-74, ≥ 75), sex, ethnicity, race, height, weight, body mass index (BMI), body surface area (BSA), smoking status, number of years that subject smoked, and smoking pack-years.

BSA and BMI are defined below:

$$\text{BSA in } m^2 = \text{Sqrt (weight in kg * height in cm} \div 3600)$$

$$\text{BMI} = \text{Weight (kg)} / (\text{Height (m)})^2$$

Smoking pack-years is defined as average packs per day * duration (years).

6.3.2. Baseline Disease Stage

Baseline disease and disease stage include the following variables:

- Time from diagnosis (days) defined as date of first dose ─ date of diagnosis + 1
- Disease stage (1, 2a, 2b, 3, or 4)
- Tumor Node Metastasis (TNM) stage
- Primary location of the tumor in the pancreas (Head, Body or Tail)
- ECOG performance status

6.3.3. Medical History

Medical conditions, including allergies and surgeries, are coded in system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0 or higher).

The medical conditions will be tabulated by SOC and PT. A subject with multiple medical conditions within an SOC is only counted once in this SOC. Similarly, a subject with multiple medical conditions within a PT is only counted once in this PT. The tabulation will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC in the ITT population.

6.4. Prior and Concomitant Medications

The World Health Organization Drug Dictionary (WHODrug Mar 2022) will be used to classify concomitant medications by therapeutic class and generic name.

Prior and concomitant medications, defined below, are summarized by Anatomic Therapeutic Class (ATC) Level 3 and PT.

1. Prior medications are those that are stopped prior to the first infusion.
2. Concomitant medications are those that are used concomitantly with the study drug, which are defined as medications that are not stopped before the first infusion, excluding medications started 60 days after the last dose of study drug.

Subjects reporting more than one use of the same medication will be counted only once in the summary tables.

Table 3 provides the classification guideline when medication starting or ending dates are missing.

Table 3: Classification of Prior and Concomitant Medications

Start Date \ End Date	Before start of study drug administration	On or after start of study drug administration	Missing
Before start of study drug administration	Prior	Concomitant	Concomitant
On or after start of study drug administration and before the last dose date +60 days.	N/A	Concomitant	Concomitant
Missing	Prior	Concomitant	Concomitant

Prior cancer therapies including systemic, surgical, and radiation will be summarized descriptively and presented in data listing.

Both prior and concomitant medication usage will be summarized by the number (%) of subjects receiving the drug within each therapeutic class and ATC code level 3 PT for Safety population. Multiple usage of the same drug by a patient will be counted only once.
Separate summaries may be provided for prior and concomitant medications of special interest.

All post neo-adjuvant anticancer medications/procedures/surgeries and non-drug therapies will be presented in data listings.

6.5. Study Drug Exposure and Treatment Compliance

6.5.1. Study Drug Exposure

Study drug exposure will be characterized by the following measures:

- Duration in days from first dose to last dose of any study drug
- Number of infusions
- Average dose amount in mg over the entire treatment period for individual subjects

Average dose (mg) will be derived using these formulas listed below:

- Pamrevlumab dose amount in mg = 35 * body weight in kg.
- Gemcitabine dose amount in mg = 1000 * BSA in m^2.
- Nab-paclitaxel dose amount in mg = 125 * BSA in m^2.

FOLFIRINOX

- Oxaliplatin dose amount in mg = 85 * BSA in m^2.
- Folinic Acid or Leucovorin dose amount in mg = 400 * BSA in m^2.
- Irinotecan* dose amount in mg = 135 * BSA in m^2.
- Fluorouracil* dose amount in mg = 400 * BSA in m^2.
- Fluorouracil dose amount in mg = 2400 * BSA in m^2.

NOTE: FOLFIRINOX may be administered at the investigator's discretion and per their institutional guidelines.

These measures will be summarized descriptively for the Safety population. Study drug administration log will be listed.

Number of treatment cycles will also be summarized.

6.5.2. Treatment Compliance

Compliance will be calculated as the number of doses the subject received divided by the number of doses the subject is scheduled to receive during the participation in treatment. The compliance of pamrevlumab, gemcitabine, nab-paclitaxel and FOLFIRINOX will be calculated separately.

Compliance = Actual doses received / Scheduled doses while actively in treatment * 100%

Scheduled doses of the study drugs are listed in Table 4.

Table 4: Scheduled Doses of Study Drugs

Day within a Cycle	Number of Pamrevlumab (or Placebo) Doses / Number of Gemcitabine/Nab-paclitaxel Doses/ Number of FOLFIRINOX					
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
1	1/1/1	4/4/3	6/7/5	8/10/7	10/13/9	12/16/11
8	2/2/1	4/5/3	6/8/5	8/11/7	10/14/9	12/17/11
15	3/3/2	5/6/4	7/9/6	9/12/8	11/15/10	13/18/12

Compliance of pamrevlumab, gemcitabine, nab-paclitaxel, and FOLFIRINOX will be summarized in the following categories: 100%, 90-99%, 80-89%, and less than 80%.

Early compliance (1-3 cycles) and late compliance (4-6 cycles) will also be summarized.

6.6. Efficacy Analyses

All efficacy analyses described in this section will be based on the ITT population.

6.6.1. Interim Analysis

Event-Free survival (EFS) will be used as a surrogate endpoint for OS at a pre-planned interim analysis. If the interim analysis of the effect of pamrevlumab on EFS is statistically significant at two-sided p=0.01, then that alpha will be carried forward to the final analysis of OS, which then would be conducted at the two-sided p=0.05 level. If the effect of pamrevlumab on EFS is not statistically significant at two-sided p=0.01, then the final analysis of pamrevlumab's effect on OS would be conducted at the two-sided p=0.04 level.

At the time of 161 EFS events occur in the trial (or more depending on completion of accrual), an assessment of OS will be performed by the DMC. Following the completion of the interim analysis for EFS/OS, procedures will be in place to avoid pre-judgment of OS data by properly maintaining its confidentiality until final OS analysis is complete or unless there is agreement with the Regulatory agency to do otherwise.

EFS is defined as the time from randomization to death, or objective tumor progression, or failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery), whichever occurs first. A more specific algorithm is presented in Table 6.

6.6.2. Multiple Comparison Adjustment

After approximately 233 deaths are reached, the final analysis for the primary endpoint and secondary endpoints will be conducted. A fixed sequence analysis approach is applied to preserve the study-wide error rate of 5%. Under the sequential analysis, the primary and secondary efficacy endpoints will be tested in a defined sequence according to the order listed in Table 5, each at the usual alpha= 0.05 level of statistical significance. The testing will cease when a failure occurs in the pre-determined sequential hypothesis testing and all p-values for the subsequent testing will be considered nominal.

Table 5: Fixed Sequence Testing Order of Primary and Secondary Endpoints

Fixed sequence testing order	Endpoints
1 (primary endpoint)	Overall Survival (OS), defined as the time from randomization to death due to any cause, as defined in Section 4.1.1.
2	Event-Free Survival (EFS), as defined in Section 4.1.2.
3	Progression-Free Survival (PFS), as defined in Section 4.1.3.
4	Best Overall Objective Response Rate (ORR), as defined in Section 4.1.3.

Following the rejection of the primary efficacy null hypothesis, each secondary hypothesis will be tested sequentially. Each treatment effect testing will be relevant only if the preceding tests have been rejected at the same 5% level of significance (two-sided) as for the primary endpoint.

6.6.3. Primary Endpoint - Overall Survival (OS)

6.6.3.1. Definition of Estimand for Overall Survival

Overall Survival (OS) is defined as the time from randomization until death from any cause. Date of death is recorded on the Death CRF. For subjects who are alive at data cut or at study closure, the recorded latest date of last known alive, last contact date, or the date of the last clinic visit is defined as the censoring date for OS.

Handling of intercurrent events:

Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by subject, Physician Decision, Protocol Deviations, etc.). Treatment policy strategy prescribed in ICH E9 Guidance and Addendum (R1) will be used: the occurrence of the intercurrent event is irrelevant here due to censoring at the last date. All observed values will be used regardless of whether the intercurrent event occurs. Missing data are assumed to be MAR.

6.6.3.2. Primary Analysis of Overall Survival

The null hypothesis of the primary endpoint is no treatment difference for OS between the two treatment groups.

Treatment comparison will be performed using the stratified log-rank test stratified by factors: chemotherapy treatment regimen (G/NP or FOLFIRINOX), SMA encasement (> or ≤ 180°), Unreconstructible disease (yes or no), and Geographic region (North America/Europe or Asia Pacific). The p-value from stratified log-rank test will be used for hypothesis testing for the primary analysis.

Sample SAS code:

```
PROC LIFETEST;

 TIME {time-to-event variable} * censor (1);

 STRATA stratification-factors / GROUP=arm;

RUN;
```

The 1-year, 2-year, 3-year, on-treatment, Kaplan-Meier (KM) estimates with 95% CI can be obtained and calculated from the KM curve with the corresponding cutoffs.

Hazard ratio and 95% Confidence Interval (CI) will be derived from Cox Proportional Hazard Model with the same stratification factors. Comparisons between the two treatment arms will be characterized using the following statistics:

- Hazard ratio (HR) and its 95% CI
- Median time-to-event and its 95% CI
- Proportions of subjects with 1-year, 2-year, and 3-year survival

Hazard ratio is based on the assumption that the ratio of the hazard rates at each time interval is approximately constant during the study. The null hypothesis that this ratio is 1 (event hazard rates are the same between treatment group and placebo).

The Cox proportional hazards model, with adjustment of the stratification factors: chemotherapy treatment regimen, SMA encasement, unreconstructible disease, and geographic region, will be used to compare the 2 treatment arms and to estimate the HR and the 95% CI. The key assumption of the Cox model is the proportional hazard function assumption. Specifically, the model assumes that each covariate has a multiplicative effect in the hazards function that is constant over time. If the proportional hazard assumption is rejected then the following stratified Cox Model will be used instead.

Sample SAS code:

```
PROC PHREG;
 MODEL {time-to-event variable} * censor (1) = arm /rl;
STRATA stratification-factors;
 HAZARDRATIO arm/CL = PL;
RUN;
```

6.6.3.3. Sensitivity Analyses of Primary Endpoint of Overall Survival - Difference in Restricted Mean Survival Time (RMST) Method and Per-Protocol Population

The RMST methodology is applicable free of the proportional hazards (PH) assumption and can be used as a sensitivity analysis to explore the robustness of the primary analysis results. In particular, as it pertains to the cutoff point (τ) to evaluate the RMST, it is noted that the cutoff point should not exceed the minimum of the largest observed time for both treatment arms so that the RMST of both treatment arms being evaluated can be adequately estimated and comparison between treatments is feasible; τ should be clinically meaningful and closer to the end of the study follow-up so that the majority of survival outcomes will be covered by the time interval.

- τ = minimum of (largest observed survival time for Arm A, largest observed survival time for Arm B).

The following statements use PROC LIFETEST to perform analyses of the RMST in addition to the standard analyses:

```
PROC LIFETEST DATA=xxxx TIMELIM= <τ>;
 TIME survtime * censor (1);
 STRATA stratification-factors/ GROUP= arm;
RUN;
```

The OS analysis will also be applied to PP Population.

6.6.3.4. Subgroup Analysis using the Primary Model

Subgroup analyses will be performed for the following subgroups in the Primary Analysis for the primary endpoint of OS by using Log-rank test for comparison:

- Sex: male, female;
- Race: White, Black, Asian, American Indian or Other
- Age: < 65, ≥ 65 years old;
- FOLFIRINOX, GEMICITABIN
- Unreconstructible disease: Yes, No
- SMA encasement: > 180 degrees, ≤ 180 degrees
- Geographic region: North America/Europe, Asia Pacific
- Patients with any change from baseline during the treatment period in CA19-9 is ≥ 50%, Patients with all change from baseline during the treatment period in CA19-9 is < 50%
- Patients with ≥ 30% reduction from baseline in FDG-PET SUVmax at EOT, Patients with < 30% reduction from baseline in FDG-PET SUVmax at EOT
- ADA status (positive, negative, or unknown; details in Section 6.8).

6.6.4. Event-Free Survival for Accelerated Approval

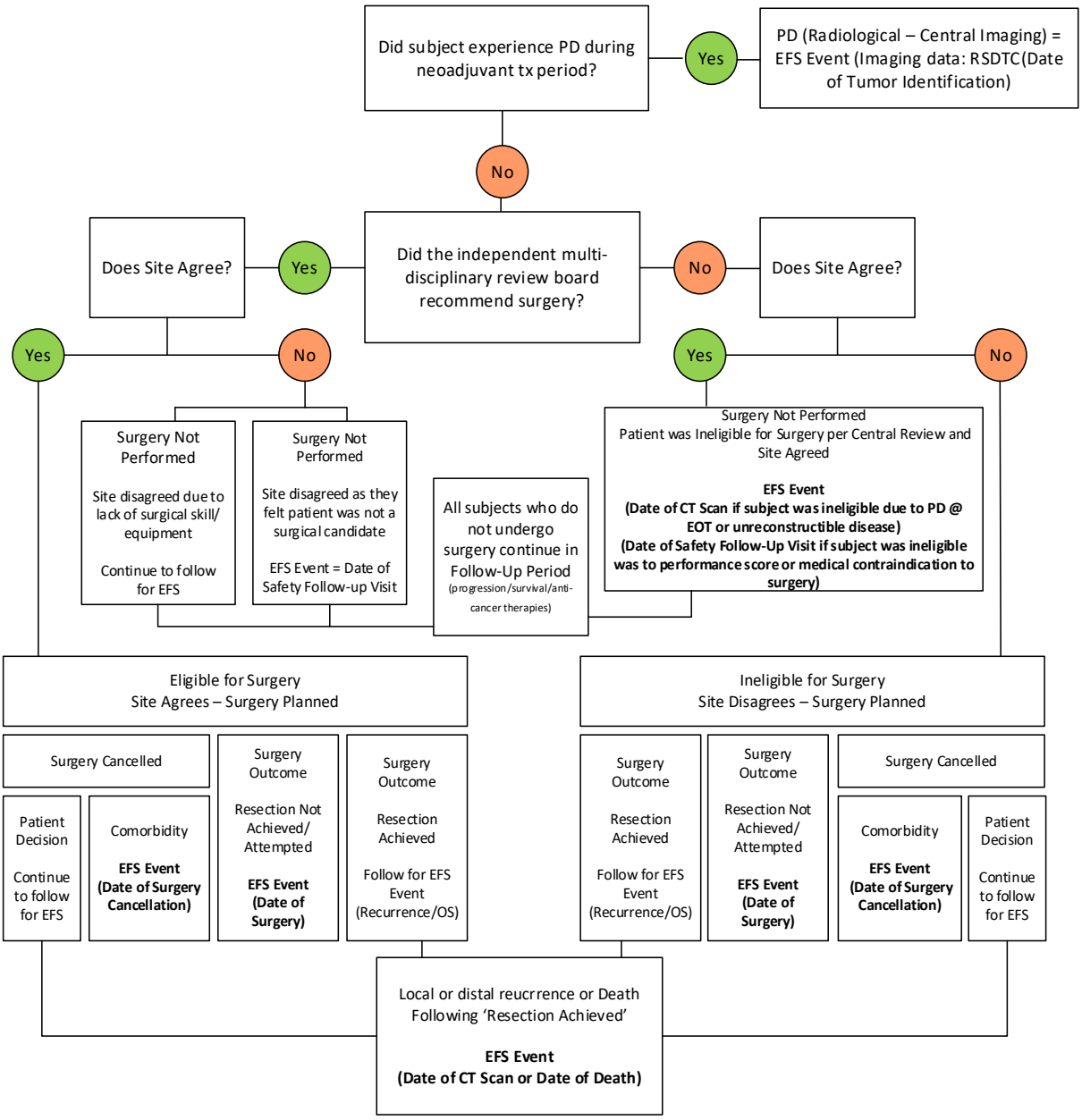
6.6.4.1. Definition of Estimand for Event-Free Survival

Subjects are considered to have an EFS event (shown in Figure 1) at the earliest time that any of the following occurs:

- Progression that precludes surgery
- Local or distant recurrence
- Death

For subjects who did not have the event at study closure or data cutoff for interim analysis, the latest date of the following events is defined as the censoring date: last post-baseline CT, last post-baseline PET scan, the last known record of 'Not progressed', surgical exploration, date of surgery cancellation, and date of safety follow-up visit (Details of censoring rules in Table 6).

Figure 1: EFS Event Determination Criteria Flowchart



Handling of Intercurrent Events:

- Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by subject, Physician Decision, Protocol Deviations, etc.). Treatment policy strategy is applied: the occurrence of the intercurrent event is irrelevant. All observed values will be used regardless of whether the inter-current event occurs.
- Death: Composite strategy: death is captured through the endpoint definition.

The null hypothesis for EFS is the equality of EFS between Arm A and Arm B.

Table 6: Censoring Rules for EFS Analysis (FDA Censoring Rules)

Situation	Event/Censor	Days to EFS or Censoring
Incomplete or no baseline tumor assessments	**Censored**	1
Progression documented between scheduled visits	Event	Earliest of: [Date of response assessment showing new lesion (if progression is based on new lesion); or Date of last response assessment] - Date of randomization + 1
No progression	**Censored**	Date of last response assessment with no documented progression - Date of randomization + 1
Treatment discontinuation for undocumented progression	**Censored**	
New anticancer treatment started	**Censored**	Date of last response assessment with documented non-progression before start of new treatment - Date of randomization + 1
Death before first PD assessment	Event	Death date - Date of randomization + 1
Death between adequate assessment visits	Event	
Death or progression after more than one missed assessment	**Censored**	Date of last response assessment prior to missing assessments with documented non-progression - Date of randomization + 1
Disease progressed or death before surgical evaluation	Event	Earliest date of CT scan date and death date - Date of randomization + 1
Surgery not performed (MRB recommend surgery, site not agree)	Event	Date of safety follow-up visit - Date of randomization + 1
Surgery planned (MRB recommend surgery, site agree), but cancelled.	Event	Date of surgery cancellation - Date of randomization + 1
Surgery not performed (MRB not recommend surgery, site agree)	Event	Date of CT scan (mets/unreconstructible) - Date of randomization + 1 If not above, Date of safety follow-up visit - Date of randomization + 1
Surgery planned (MRB not recommend surgery, site not agree), but cancelled.	Event	Date of surgery cancellation - Date of randomization + 1
Surgery performed but resection not achieved/attempted	Event	Date of surgery - Date of randomization + 1
Surgery planned (MRB not recommend surgery, site not agree), but resection Achieved and Local or distal recurrence or death following resection achieved	Event	Earliest date of CT scan date and death date - Date of randomization + 1

Situation	Event/Censor	Days to EFS or Censoring
No event at data cut or at study closure	Censored	Latest date of (last post-baseline CT date, last post-baseline PET scan date, the last known record of 'Not progressed' date, surgical exploration date, date of surgery cancellation) - Date of randomization + 1

MRB: Multidisciplinary Review Board.

6.6.4.2. Analysis of Event-Free Survival

Event-Free Survival will be summarized using the KM method. Median time-to-event and its 95% CI will be estimated by KM method using SAS PROC LIFETEST procedure.

Comparison of EFS between treatment and placebo will be performed using the stratified log-rank test stratified by factors: chemotherapy treatment regimen (G/NP or FOLFIRINOX), SMA encasement (> or ≤ 180°), Unreconstructible disease (yes or no) and Geographic region (North America/Europe or Asia Pacific). The p-value from stratified log-rank test will be used for hypothesis testing for treatment comparison.

Sample SAS code:

```
PROC LIFETEST;
  TIME {time-to-event variable} * censor (1);
  STRATA stratification-factors / GROUP=arm;
RUN;
```

The Cox proportional hazard model including treatment and stratification factors: chemotherapy treatment regimen, SMA encasement, unreconstructible disease and geographic region will be used to estimate the HR and corresponding 95% CI. The key assumption of the Cox model is the proportional hazard function assumption. Specifically, the model assumes that each covariate has a multiplicative effect in the hazards function that is constant over time.

If the proportional hazard assumption is rejected then the following stratified Cox Model will be used instead.

Sample SAS code:

```
PROC PHREG;
  MODEL {time-to-event variable} * censor (1) = arm /rl;
  STRATA stratification-factors;
  HAZARDRATIO arm /CL = PL;
RUN;
```

Initially, the stratification factors are included in the model one at the time. Finally, all the explored adjustment of multiple factors will be included in the model. Those factors with a significant p-value by using likelihood test (or Wald test) will be kept in the stratified Cox model.

6.6.4.3. Sensitivity Analyses of EFS

Sensitivity analysis will be conducted to evaluate the robustness of EFS analysis results. It will be carried out for EFS endpoint by implementing different censoring rule in the definition of EFS (Table 7). This sensitivity analysis will be conducted in the ITT Population.

More specifically this sensitivity analysis for EFS analysis will be based on European Medicines Agency (EMA) Censoring rule. Note that EMA uses similar rules as FDA (Table 6), except that EMA does not differentiate special situations such as new anticancer treatment or missing assessments (regardless of these situations) when considering censor/event.

The EFS (FDA censoring rule) will also be conducted for PP Population as another sensitivity analysis.

Table 7: Censoring Rule for EFS Analysis (EMA Censoring Rules)

Situation	Event/Censor	Days to EFS or Censoring
New anticancer treatment started	**Censored**	Date of last adequate response assessment - Date of randomization + 1, regardless of new anticancer treatment
New anticancer treatment started	Event	Date of documented progression - Date of randomization + 1, regardless of new anticancer treatment
Death or progression after more than one missed assessment	Event	Date of event - Date of randomization + 1, regardless of missing assessments

6.6.5. Secondary Endpoint - Progression-Free Survival (PFS)

6.6.5.1. Definition of Estimand for Progression-Free Survival

Progression-Free Survival is defined as the time from randomization until disease progression or death, whichever occurs first. Date of disease progression is defined as the date of radiological progression per RECIST 1.1 criteria recorded the Disease Progression CRF.

Handling of Intercurrent Events:

- Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by subject, Physician Decision, Protocol Deviations, etc.). Treatment policy strategy will be applied: the occurrence of the intercurrent event is irrelevant. All observed values will be used regardless of whether the intercurrent event occurs.
- Death. Composite strategy is applied: death is taken to be a component of the variable.

6.6.5.2. Analysis of Progression-Free Survival

Progression-Free Survival will be summarized using the KM method for the ITT Population and PP Population. Median time-to-event and its 95% CI will be estimated by KM method using SAS PROC LIFETEST procedure. Comparison of PFS between treatment and placebo will be performed using the stratified log-rank test stratified by factors: chemotherapy treatment regimen (G/NP or FOLFIRINOX), SMA encasement (> or ≤ 180°), Unreconstructible disease (yes or no) and Geographic region (North America/Europe or Asia Pacific). The p-value from stratified log-rank test will be used for hypothesis testing for treatment comparison.

Refer to Table 8 for details on PFS event and censoring definitions.

Table 8: PFS Event and Censoring Definitions

#	Situation	Date of event or censoring	Outcome
1	No baseline tumor assessment	Randomization	Censored
2	No adequate post-baseline tumor assessment and no death occurs prior to first scheduled post-baseline tumor assessment	Randomization	Censored
3	Centrally-determined progression	Date of progression	PFS Event
4	Death	Date of death	PFS Event
5	Two or more consecutively missed scheduled tumor assessments immediately followed by centrally-determined progression or death	Date of last adequate tumor assessment prior to the consecutively missed tumor assessments	Censored
6	Start of new anticancer therapy* without centrally-determined progression or death	Date of last adequate tumor assessment prior to the new anticancer therapy	Censored
7	No centrally-determined progression or death	Date of last adequate tumor assessment	Censored

*For calculating PFS, start of protocol-specified surgery after the neoadjuvant will not be considered as initiating a new anticancer therapy.

6.6.6. Secondary Endpoint – Best Overall Objective Response Rate (ORR)

Best overall objective response rate (ORR) is the secondary endpoint where Objective response is defined as a CR or PR according to RECIST 1.1. Objective response will be based on the best overall response recorded from Day 1 until centrally-assessed progressive disease (PD), death, or first administration of anti-tumor treatment (other than study medication), whichever occurs first. Patients who receive anti-tumor treatment other than the study medication prior to reaching a CR

or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

6.6.6.1. Analysis of Best Overall Objective Response Rate (ORR)

ORR will be summarized by using the analysis of the difference between two proportions for the ITT Population and PP Population. Normal approximation method will be used as the sample size is larger than 30. Estimation and 95% CI for the ORR for the two arms will be computed and difference of the two proportions and its 95% CI will be estimated by SAS PROC FREQ procedure. The p-value for testing the difference of the two proportions will be used for hypothesis testing for treatment comparison.

6.6.7. Exploratory Endpoints

6.6.7.1. Physical Functioning

Definition of Estimand for Physical Functioning by EORTC QLQ-C30

EORTC QLQ-C30 is a health-related quality of life questionnaire (HRQOL) developed to assess the quality of life of cancer patients. EORTC QLQ-C30 Version 3.0 is the most recent version and is used for this study. Physical functioning (PF) is assessed using the EORTC QLQ-C30 instrument on Day 1 of every cycle as well as EOT (2 weeks from the last dose), and at safety follow-up (4 weeks from last dose). PF scores will be derived as defined in the EORTC QLQ-C30 Manual.

Analysis of Physical Functioning by EORTC QLQ-C30

PF scores will be derived as defined in the EORTC QLQ-C30 Manual. For functional scale, the scoring is not affected if there are at least half of the items from the scale answered. All the items that are completed are used to calculate the raw score then through a linear transformation to a standardized score for the scale. The standardized score ranges from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. If there are more than half of the items from the scale that are missing, then the scale score at the visit is set to missing. Missing data will not be imputed.

Difference between treatment arms in mean change from baseline Physical Functional score at selected visits during the treatment period is assessed using a Mixed effect Model Repeat Measurement (MMRM) model, with adjustment for randomization stratification factors and baseline PF scores. The LS mean and the corresponding 95% confidence intervals for the differences between Arm A (pamrevlumab + either G/NP or FOLFIRINOX) and Arm B (placebo + either G/NP or FOLFIRINOX) will be presented along with the p-values for the treatment differences resulting from the model. The unstructured covariance is applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure is used. If this second model does not converge then the (homogeneous) Toeplitz structure is tried, and if all the covariance failed to converge then the compound symmetry is used. All assessments will be included in the model.

Sample SAS code – MMRM (PF Scores):

```
PROC MIXED DATA = xxx;
  CLASS arm subjid;
  MODEL Δscore = arm stratification-factors /SOLUTION COVB;
  REPEATED  /SUBJECT=subjid TYPE=UN;
  LSMEANS arm/ DIFF CL ALPHA=0.05;
  ODS OUTPUT lsmeans=mixlsmeans diffs=mixdiffs;
RUN;
```

6.6.7.2. Abdominal Pain and Fatigue Score

Definition of Estimand for Abdominal Pain and Fatigue Score by NCI-PRO-CTCAE

Abdominal pain and fatigue are assessed using the PRO-CTCAE™ Questionnaire. This questionnaire is collected on Days 1, 8 and 15 in the first three treatment cycles (Cycles 1-3), on Days 1 and 15 in the last three treatment cycles (Cycles 4-6) and at the EOT and Safety Follow-up Visit.

Analysis of Abdominal Pain and Fatigue Score by NCI-PRO-CTCAE

The abdominal pain and fatigue scales are scored according to the scoring manual.

The difference between treatment arms in mean change from baseline abdominal pain and fatigue score at selected visits during the treatment period is assessed using a MMRM model, with adjustment for randomization stratification factors and baseline Abdominal score and baseline fatigue scores. The stratification factors include chemotherapy treatment regimen, SMA encasement, unreconstructible disease, and geographic region. The LS mean and the corresponding 95% confidence intervals for the differences between Arm A (pamrevlumab + either G/NP or FOLFIRINOX) and Arm B (placebo + either G/NP or FOLFIRINOX) will be presented along with the p-values for the treatment differences resulting from the model. The unstructured covariance is applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure is used. If this second model does not converge then the (homogeneous) Toeplitz structure is tried, and if all of the covariance failed to converge then the compound symmetry is used. All assessments will be included in the model.

6.6.7.3. Difference in OS between Resected and Non-Resected Subjects

Resection rate is defined as proportion of all randomized subjects in whom R0 or R1 resection is achieved. Resection outcome (R0 or R1) is determined by pathological examination of the surgical specimen after resection and is recorded on Surgical Outcome CRF. An outcome of R0 or R1 will be considered a successful resection. An R2 resection or the inability to resect the tumor following surgical exploration (Resection Not Achieved) will be considered a resection failure.

Difference in OS will be tested by log-rank test between resected subjects and non-resected subjects.

6.6.7.4. Eligibility for Surgical Exploration

Subjects are considered eligible for surgical exploration if one or more of the following criteria are met and have no contraindications:

- Reduction in CA19-9 level ≥50% at EOT when compared to baseline.
- FDG-PET SUVmax decrease by ≥30% at EOT when compared to baseline.
- Partial Response (PR), Complete Response (CR) or Stable Disease (SD) per RECIST 1.1 at EOT.
- Resectable or borderline resectable per National Comprehensive Cancer Network (NCCN) Version 2.2018

Contraindications include:

- Development of distant metastases or local progression per RECIST 1.1
- Performance status of Karnofsky score ≤ 50
- Unreconstructible disease as determined by central radiological/surgical review
- Other conditions that are considered by the PI/surgeon to be contraindications to surgery

The central review board (to include radiologists, surgeons, and oncologists) review information provided by the site and determine whether a subject is eligible for surgical exploration per protocol. The PI/surgeon ultimately decide whether a subject will undergo surgery.

The proportion of subjects considered eligible for surgical exploration will be summarized by treatment group.

Exact 95% CIs for the point estimates as well as the treatment difference will be obtained from SAS PROC FREQ procedure with EXACT option. The two treatment arms will be compared using the Cochran-Mantel-Haenszel (CMH) test controlling for the stratification factors listed in Section 5.4.

6.6.7.5. Mean Change from Baseline during Treatment Period in CA19-9

The CA19-9 endpoint defined only in subjects with baseline CA19-9 value higher than the upper limit of normal (ULN). ULN is defined as 37 U/mL in this study (Ballehaninna and Chamberlain, 2012). The CA19-9 is performed at Day 1 of each cycle, End of Treatment (EOT), Safety Follow-up Visit and Surgical Follow-up Visit. Baseline CA19-9 is defined as the assessment on Day 1 prior to study drug dosing. If Day 1 assessment is missing, then the last assessment prior to dosing is used.

Mean change from baseline of CA19-9 values at Day 1 of each cycles, EOT, Safety Follow-up Visit and Surgical Follow-up Visit will be used for this endpoint. Comparison between the two arms will be evaluated using the two-sample Wilcoxon rank sum test.

6.6.7.6. Change in PET SUV_{max} at End of Treatment (EOT) when compared to Baseline

An FDG-PET scan is performed at baseline and EOT. Maximum standardized uptake value (SUVmax) is read by radiologists at each site. Change in FDG-PET SUVmax at EOT when compared to baseline is summarized.

Change from baseline in PET SUVmax is evaluated using the one-sample Wilcoxon signed rank test. Comparison between the two arms will be evaluated using the two-sample Wilcoxon rank sum test.

6.6.7.7. Correlative analyses of baseline CTGF serum levels with clinical outcomes

CTGF samples are collected on Day 1 pre-dose and at safety follow-up visit. CTGF data are summarized descriptively by scheduled time point.

The Cox model described in Section 6.6.3.2 will be used to evaluate the correlation of baseline CTGF serum levels with clinical outcomes of OS, , EFS and PFS.

6.6.7.8. Histological Analysis in Tumor Tissues Collected during Resection

Tumor tissue will be collected from all resected subjects for histological analysis. The histological analysis data will be listed and summarized descriptively by treatment group.

6.6.7.9. Evaluation of CTGF as Prognostic or Predictive Biomarker

The subjects were divided into two groups by the median of CTGF levels: lower CTGF levels (< median) and higher CTGF levels (≥ median). Proportion of patients with Partial Response (PR), Complete Response (CR), Stable Disease (SD) as well as Objective Response (PR+CR) at EOT will be summarized by CTGF levels. The two CTGF levels will be compared using the Chi-square test controlling for the stratification factors listed in Section 5.4 to evaluate the potential of CTGF as prognostic biomarker.

Additional analysis of relationship between clinical outcomes and CTGF, treatment, and CTGF by treatment interaction will be explored.

6.6.7.10. Evaluation of Other Selected Protein and Nucleic Acid Markers in Plasma Samples

Biomarker data will be presented in a separate report.

6.6.7.11. ECOG

Change from baseline in ECOG status will be summarized in a shift table of post-baseline versus baseline.

6.6.7.12. Disease Stage

Disease TNM stage and cancer staging will be summarized in a shift table of EOT versus Screening.

6.6.7.13. Number of Treatment Cycles

Number of cycles will be compared between treatment arms using ANOVA. The impact of number of cycles and treatment compliance on OS and EFS will be explored using Cox proportional hazard model.

6.7. Safety Analyses

Safety analyses will include summary of adverse events (AEs), surgical safety parameters, lab test results, vital signs, ECGs, and physical exams. In general, safety data will only be summarized descriptively and no formal inferential statistical test will be applied. All analyses described in this section will be based on the Safety population.

6.7.1. Adverse Events

The definitions of AEs, serious adverse events (SAEs), severity, and relationship to study medication are described in Section 8.2 of the protocol. Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0 or higher) for system organ class (SOC) and preferred term (PT) for summary.

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events (TEAEs) are defined as new or worsening AEs that occurred in the time window of first dose of study drug (Day 1) and within 60 days after the last dose of study drug. Detailed definitions are in Table 9.

Table 9: Definition of TEAE and Study Period When AE Occurred.

AE Onset Date Relative to Dosing*	AEPRIOR Flag on CRF	TEAE	Study Period (EPOCH)
AE onset date < Day 1	Any	No	Screening
AE onset date = Day 1	Yes	No	Screening
	No	Yes	Treatment
Day 1 < AE onset date ≤ date of last dose in treatment period	Any	Yes	Treatment
Date of last dose < AE onset date ≤ date of last dose + 60	Any	Yes	60-day follow-up
AE onset date > date of last dose + 60	Any	No	Additional follow-up beyond 60 days

*First dose refers to first of any study medication; last dose refers to last of any study medication.

AE Severity Rating

AEs are rated by the investigators as “mild”, “moderate”, “severe”, “life threatening”, or “fatal” based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system as described in Section 8.3.3 of the protocol. If a subject reports multiple occurrences of an AE within one SOC or PT, the most severe occurrence will be presented in the summary by severity rating. Missing severity rating will not be imputed.

AEs Related to Pamrevlumab/Placebo, or Gemcitabine, or Nab-paclitaxel, or FOLFIRINOX

Investigators determine the relationship of AEs with the study medications as described in Section 8.3.4 of the protocol. If related and unrelated occurrences of an AE within one SOC or PT are reported in a subject, the related occurrence will be presented in the summary by relationship. Missing relationship will be imputed as "Related". The pamrevlumab, gemcitabine, nab-paclitaxel and FOLFIRINOX-related AEs will be listed and summarized separately.

Analysis of Adverse Events

All reported AEs will be presented in listings. Treatment-emergent adverse events (TEAEs) will be summarized by treatment arm, SOC and PT. The summary tables will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC, based on the rate of both treatment arms combined. A subject with multiple AE within an SOC is only counted once in this SOC. Similarly, a subject with multiple AE within a PT is only counted once in this PT.

In addition to listing of all reported AEs and summary of incidence of all TEAEs, the following subgroups of AEs will be summarized:

- Treatment-emergent serious adverse events (TESAEs) (Table and Listing) and relationship to the study drugs (whether related or unrelated)
- Fatal SAEs
- TEAEs leading to treatment or study discontinuation
- TEAEs with incidence ≥ 5% in either arm
- TEAEs occurred in 2 or more subjects in either arm
- TEAEs with severity grade ≥ 3
- TEAEs with severity grade ≥3 that are at least possibly related to pamrevlumab/placebo (as assessed by investigators)
- Most frequent non-serious TEAEs with incidence ≥ 5% in either arm
- All cause deaths

All deaths captured on Death CRF will be included in the summary of deaths (within 60 days of last dose of study drug and beyond 60 days of last dose of study drug).

6.7.2. Laboratory Data

The lab tests in Table 10 are evaluated at every clinic visit to assess treatment tolerability.

Table 10: Laboratory Tests

CBC Panel:	**Chemistry Panel:**
Absolute neutrophil count (ANC)	Bicarbonate
Eosinophils	BUN
Erythrocyte count (RBC)	Calcium

CBC Panel:	Chemistry Panel:
Hematocrit	Creatinine
INR	Chloride
PTT/PT	Magnesium
Hemoglobin	Glucose
Leukocyte count (WBC)	Aspartate aminotransferase (AST)
Lymphocytes	Alanine aminotransferase (ALT)
Mean corpuscular volume	Alkaline phosphatase (ALP)
Monocytes	Bilirubin, total
Neutrophils	Albumin
Platelets	Phosphorous
CRP	Potassium
Basophils	Sodium

Investigators review and determine whether the lab results are normal or abnormal, and if abnormal, whether they are clinically significant (CS) or not clinically significant (NCS).

In addition to investigators' assessments, CTCAE grading is used to evaluate the lab results. CTCAE grade 3 or higher is considered potentially clinically significant (PCS). The CTCAE Version 5.0 grading for the study-specific tests is presented in Appendix Section 9.5.

Analysis of Laboratory Data

Laboratory test results and change from baseline are summarized descriptively by visit.

CTCAE grade 3 or higher lab test results will be considered PCS. These results will be presented in a data listing.

Shift tables for selected laboratory data will be used to summarize changes from baseline to each visit in CTCAE categories are tabulated. Shift from baseline to most severe CTCAE category during the study is also summarized. In addition, shift tables from baseline to most abnormal laboratory finding (low, normal, and high) will also be presented.

Lab data are summarized by nominal clinic visit. Data collected during the unscheduled visits outside of a visit window are not included in the summary tables, but are included in data listings and in evaluations for PCS abnormal changes.

Some lab data are collected using local labs (in lieu of the ICON central lab) due to central lab kit shortages caused by the COVID-19 pandemic. In these cases, local lab values and reference ranges collected from CRFs will be integrated with central lab data when appropriate and feasible. Local lab values will be flagged in datasets and data listings to be differentiated from central lab values. Sensitivity analyses may be performed for key analyses of lab parameters without local lab values (i.e., set to missing).

6.7.3. Vital Signs

Vital sign parameters include heart rate, systolic/diastolic blood pressures (BP), respiration, and temperature as well as weight and height (height is collected during screening only).

Potentially clinically significant vital sign changes are those which meet both criteria in the Table 11 below.

Table 11: Potentially Clinically Significant (PCS) Values in Vital Signs

Vital Sign Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic BP (mm Hg)	High	≥ 160 mmHg	Increase of ≥ 20 mmHg
	Low	≤ 95 mmHg	Decrease of ≥ 20 mmHg
Diastolic BP (mm Hg)	High	≥ 110 mmHg	Increase of ≥ 10 mmHg
	Low	≤ 45 mmHg	Decrease of ≥ 10 mmHg
Heart Rate (bpm)	High	≥ 100 bpm	Increase of ≥ 20 bpm
	Low	≤ 50 bpm	Decrease of ≥ 20 bpm
Body temperature (ºC)		37	>3

BP=blood pressure; bpm=beats per minute; ºC=Celsius
* A post-baseline value is considered as a PCS value if it meets both criteria for observed change from baseline.

Analysis of Vital Signs

Vital sign observed values and change from baseline will be summarized descriptively by Tables and Listings and by visit and by treatment arm.

In addition, incidence of PCS observed values or changes from baseline, which are defined in Table 7, will be tabulated for each visit.

All measurements and change from baseline will be presented in tables and data listings with PCS values or changes from baseline flagged.

6.7.4. Physical Examinations

At each clinic visit, investigators perform physical examination for the following body systems: general appearance, head, eyes, ears, nose, throat (HEENT), lungs, heart, chest, back, abdomen, extremities, neurologic, and skin. Investigators determine whether the body systems are normal or abnormal. For the abnormal cases, descriptions are provided and clinical significance is identified. Baseline is defined as the findings on Day 1 prior to first dose.

Findings from physical examinations will be summarized in shift tables that include cross-tabulation of 'Normal', 'Abnormal NCS', 'Abnormal CS' from baseline to worst post-treatment. The number and percent of subjects with "Normal", "Abnormal", "Not Done", and "Missing" physical examination results will be summarized by body system, treatment arm, and visit.

The data listing includes abnormal findings.

6.7.5. ECG Data

ECG is evaluated at baseline, Day 1 of each treatment cycle, and EOT.

ECG findings will be summarized in shift tables that include cross-tabulation of investigator assessments of 'Normal', 'Abnormal NCS', 'Abnormal CS' at Day 1 of each treatment cycle, and EOT versus baseline.

Detailed findings will be presented in the data listing.

6.7.6. Surgical Safety

Surgical safety assessed during surgery:

- Duration of the surgery
- Estimated blood loss (EBL) during surgery
- Any blood transfusion
- Amount of blood transfusion (cc)

Surgical complication during post-operative follow-up:

- Return to operating room within 30 days of surgery

Surgical safety measures described in Section 7.2.10 of the protocol will be summarized descriptively for subjects who have undergone a R0 or R1 resection.

6.8. Immunogenicity Analysis and PK

6.8.1. Terms and Definitions

6.8.1.1. Sample ADA Status

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment.
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment.
- **Treatment-emergent ADA-Positive**: Meets definition of treatment-induced or treatment-boosted ADA:
  - **Treatment-induced ADA-Positive**: A post-treatment positive ADA is detected in a subject for whom pre-treatment ADA assessment is either negative or not assessable
  - **Treatment-boosted ADA-Positive**: Pre-existing ADA was boosted to a higher level following study treatment, i.e. pre-treatment positive ADA titer was boosted by at least 2 dilution steps (4-fold) following study treatment.
- **ADA-negative sample**: After initiation of treatment, ADA is not treatment-emergent ADA-positive.

Next, using the sample ADA status, the subject's ADA status is defined.

6.8.1.2. Subject ADA Status

- Baseline ADA-positive subject: A subject with a baseline ADA-positive sample.
- Baseline ADA-negative subject: A subject with baseline ADA-negative sample.
- ADA-positive subject: An evaluable subject with at least one treatment-emergent ADA-positive sample at any time during the study.
- Neutralizing-positive: At least one treatment-emergent ADA-positive sample with neutralizing antibodies detected (if available).
- ADA-negative subject: An evaluable patient without a treatment-emergent ADA sample during the study.
- ADA-unknown: Patients without evaluable baseline and/or post-baseline ADA samples will be categorized as "ADA-unknown".

6.8.2. Statistical Analysis for Characterization of ADA Immune Response

6.8.2.1. Incidence of ADA

- Percentage of treatment-emergent ADA patients for the defined study period, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup.
- Number (%) of subjects will be reported for the following parameters based on evaluable subjects:
  - Baseline ADA-positive
  - Treatment-emergent ADA-positive (treatment-induced, or treatment-boosted)
  - Neutralizing-positive (if available)
  - ADA-negative
  - ADA-unknown
- **ADA prevalence**: Percentage of treatment-emergent ADA patients at any given time point, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup at that time point.
- A listing of all ADA assessments will be provided.
- Additionally, a separate listing of ADA assessments for all neutralizing antibody (NAb)-positive subjects will be provided (if available).

6.8.2.2. ADA Titer Kinetics

All ADA-positive subjects will be included in the analysis.

- Summary statistics of subject-level ADA titers using the maximum titer value post-baseline within an ADA-positive subject will be presented for baseline ADA-negative subjects and baseline ADA-positive subjects. The median, interquartile range, and

range of the maximum titers will be reported. For ADA-positive subjects with a baseline ADA-positive sample, the median and interquartile range of the fold increase from baseline in titer (ratio of maximum post-baseline titer to baseline titer) will also be reported. Graphical presentation of the summary data may be provided using boxplots, as appropriate.

- For sample-level ADA titers, boxplots of ADA titers at each assessment time point will be provided, as appropriate, to demonstrate whether the ADA levels tend to change over time during the treatment, along with ADA incidence at each assessment time point.
- Spider plots may be considered to show the trend of ADA titer over time.

6.8.3. Clinical Implication of ADA Immune Response

Clinical implication of ADA immune response will only be assessed if there are at least ~10 subjects with treatment-emergent ADA-positive samples. Otherwise, individual subject's safety profile will be examined and described based on listings.

6.8.3.1. PK and ADA Immune Response

- Effect of ADA response on drug exposure will be explored by examining the drug exposures using graphical plots of observed drug concentration levels by ADA status and sampling time. Corresponding numerical values of geometric mean, arithmetic mean, and standard deviation will be displayed under the figures. The observed concentration below LLOQ will be presented as zero.

A listing of drug concentrations will be provided. Time course of observed concentrations by study visit with identifiers for antibody response will be plotted for each subject separately.

6.8.3.2. Safety and Efficacy

Effect of ADA response on safety will be explored by examining the frequency and type of AEs of interest, including (1) Total TEAEs, (2) Standardized MedDRA Queries (SMQ) for Drug Hypersensitivity, (3) Events Associated with Anaphylaxis as defined by Sampson et al 2006, and (4) Infusion-related Reactions.

For each of the above category of AEs, summary tables for incidence will be provided for each of the preferred terms and overall, within a category by ADA status, if the number of ADA-positive subjects is of sufficient size (e.g., at least ≈10 subjects). Otherwise, individual subject's safety profile will be examined and described based on a listing. Preferred term will be determined prior to the database lock.

Listing of AEs will be provided. The listing will indicate study day and study period of the positive responses.

Primary endpoint will be summarized by ADA status. A listing for all positive subjects (relative to baseline) will be provided. The listing will also indicate study day and study period of the positive responses.

7. VALIDATION AND QUALITY ASSURANCE

Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM), tables, listings, figures (TLF) will be programmed by two programmers independently. The results must be 100% matched.

Both primary and validation programmers will develop programs independently based on the specifications and/or SAP. If the outputs are datasets, the final outputs will be compared electronically. If the outputs are TLFs, benchmark results will be generated and compared. The validation findings and resolutions are documented on a Validation Worksheet.

The detailed process for validation and quality assurance is documented in the Standard Operating Procedures of Q2, Inc.

8. REFERENCES

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9. APPENDICES

9.1. Appendix 1: Schedule of Assessments

Table 12: Schedule of Assessments

Assessments[a]	**Screening Period[b]**	**Cycle 1**			**Cycles 2-6**			**End of Treatment[c]**	**Safety Follow-up Visit**	**Final Safety Follow-up Contact**	**Surgical Resection[d]**	**Surgical Follow-up[e]**	**Follow-up[f]**
	30 days	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**~2 weeks post-last dose**	**~28 days post-last dose**	**~60 days post-last dose**	**4-8 weeks post-last dose**	**90 days post discharge**	**Up to 6 years**
Written Informed Consent	X												
Inclusion/Exclusion Criteria[b]	X												
Demographics/Medical History[g]	X												
Vital Signs/Weight[h] (include height at screening)	X	X	X	X	X	X	X	X	X				
Disease Stage (TNM)	X							X					
Performance status[i]	X	X			X			X	X				
Physical Exam[j]	X	X	X	X	X		X	X	X				
12-Lead EKG[k]	X	X			X			X					
CBC/Chemistry	X	X	X	X	X	X	X	X	X				
Specialty Labs (PK/PD)		See Appendix 2 of the protocol for details.											
Pregnancy Test[l]	X	X			X			X					

Table 12: Schedule of Assessments

Assessments[a]	**Screening Period[b]**	**Cycle 1**			**Cycles 2-6**			**End of Treatment[c]**	**Safety Follow-up Visit**	**Final Safety Follow-up Contact**	**Surgical Resection[d]**	**Surgical Follow-up[e]**	**Follow-up[f]**
	30 days	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**~2 weeks post-last dose**	**~28 days post-last dose**	**~60 days post-last dose**	**4-8 weeks post-last dose**	**90 days post discharge**	**Up to 6 years**
Chemotherapy Regimen (G/NP or FOLFIRINOX)		See Section 6.1.2 or 6.1.3 of the protocol for details			See Section 6.1.2 or 6.1.3 of the protocol for details								
FG-3019 or placebo[m]		X	X[m]	X	X		X						
CA19-9[n]		X			X			X	X			X	
FDG-PET	X							X[o]					
CT[p]	X	Q8W until PD is detected						X[p]					X[p]
EORTC QLQ-C30[q]		X			X			X	X				
PRO-CTCAE Questionnaire[q]		X	X	X	X	X[q]	X	X	X				
AEs/CMs[r]	X	X	X	X	X	X	X	X	X	X[r]			X[r]
Eligibility for Surgical Exploration[s]									X				
Surgery/Outcomes[t]											X		
Surgical Complications												X	
Progression/Survival/ Follow-on Treatment													X

CBC = complete blood count; CT = computer tomography; ECOG = Eastern Cooperative Oncology Group; EKG = electrocardiogram; EOT = end of treatment; FDG-PET = [^{18}F]-fluorodeoxyglucose-positron emission tomography.

a. All visits (including the EOT visit) should occur within ±2 days of protocol-specified time point during the neoadjuvant treatment period. The Safety Follow-up and the Surgical Follow-up visit should occur within ±3 days of the specified time point. Visit windows should be calculated based on the previous study visit date, NOT Cycle 1 Day 1.
b. All screening activities should be conducted within 30 days prior to Day 1 Cycle 1. A diagnostic biopsy, which may be performed per SOC, is required for histological or cytological confirmation of PDAC.
c. Subjects who complete 6 cycles of study treatment or discontinue early will undergo an End of Treatment visit approximately 2 weeks following their last dose. All final efficacy assessments will be performed. Subjects who complete 6 cycles of treatment will be evaluated by the central review team to determine eligibility for surgical exploration.
d. All surgeries will occur within 4-8 weeks from the subjects' last dose. Surgery will be performed in accordance with institutional standards and SOPs. Surgeons performing surgery for this study will be trained on the protocol. Tumor tissue will be collected during surgical resection and provided to central pathology for determination of surgical outcome.
e. All subjects who undergo surgical exploration will be followed for surgical safety for 90 days (± 3 days) post discharge, in accordance with the institutions' standard of care. A clinic visit should be scheduled to review surgical complications (if any) and collect CA19-9.
f. All subjects will be followed in Long-Term Follow-up for progression, survival and any additional anticancer therapy (follow-on treatment for pancreatic cancer) until the last subject to complete treatment has been followed for 18 months post-last dose. It is recommended that Long-Term Follow-up be conducted approximately every 3 months.
g. Medical history includes smoking history.
h. Height is collected during screening only.
i. ECOG to be evaluated at screening, Day 1 of each treatment Cycle, and EOT. Karnofsky scores will be evaluated at EOT only.
j. A full physical exam is required during screening and on Day 1 of each treatment cycle.
k. A 12-lead EKG will be performed during screening, on Day 1 of each cycle and EOT.
l. A serum pregnancy test is required for all females of childbearing potential during screening. The central lab will provide results for the screening serum pregnancy test. Additionally, any female of childbearing potential must have a negative serum or urine pregnancy test confirmed at the site on Day 1 of each cycle (prior to study drug administration) and at EOT.
m. Dosing for pamrevlumab (or placebo) will be based on the weight obtained on Day 1 of each dosing cycle (i.e., Cycle 1 Day 1, Cycle 2 Day 1). An additional dose of pamrevlumab or placebo to be administered on Day 8 of Cycle 1 only. Pamrevlumab (or placebo) to be infused over 1 hour (± 15 minutes) following infusion of chemotherapy agents.

n. CA 19-9 to be collected at baseline (Cycle 1 Day 1) prior to dosing, Day 1 of each treatment cycle, EOT and safety follow-up visit for all subjects. CA19-9 will also be collected at the surgical follow-up visit (approx. 90 days post-surgery discharge) for those subjects who undergo surgical exploration.

o. If a subject discontinues treatment early, an EOT PET scan is required unless the baseline PET was performed less than 8 weeks from EOT.

p. A baseline CT scan will be conducted during the screening period and approximately every 8 weeks thereafter until disease progression is detected by central imaging review:

- For subjects who complete 6 cycles of treatment, the EOT scan will be evaluated by the central review board in determination of surgical eligibility.
- If a subject completes 6 cycles of treatment without evidence of disease progression, but does not undergo surgical exploration, CT scans should continue to be collected approximately every 8 weeks and submitted for central review until progression is detected (per RECIST 1.1).
- If a subject undergoes surgical exploration and resection, CT scans should be conducted approximately every 4 months following for up to 2 years post-resection and approximately every 6 months from 2-5 years post-resection.
- If recurrence of disease is suspected clinically at any time during the post-resection follow-up, a CT scan may be performed "off schedule" and submitted to central imaging for review/confirmation of progression/recurrence.

q. All PROs to be collected prior to dosing where applicable. PRO-CTCAE™ questionnaire will be administered on Days 1, 8 and 15 of Cycles 1-3 and Days 1 and 15 of each treatment cycle thereafter and at the EOT and Safety follow-up visits.

r. Adverse events and concomitant medications are collected from Day 1 of the study through 60 days following a subject's last dose of study treatment. Serious adverse events should be collected/reported from the signing of Informed Consent through 60 days following the subject's last dose of study treatment. A Safety Follow-up visit must be conducted ~28 days post-last dose and a final safety follow-up contact (via phone) must be conducted ~60 days post-last dose. Additionally, pamrevlumab related SAEs (including deaths) that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

s. Eligibility for surgical exploration per protocol will be determined by a central review board. However, ultimately, the decision to operate on a subject lies with the site PI/surgeon. See Section 4 of the protocol for details.

t. Tumor tissue will only be collected during resection. Surgical outcomes of R0, R1 and R2 will be determined by central pathological review of tissue samples collected per the study-specific pathology protocol during surgical resection. Tissue collected during resection may also be evaluated for exploratory analysis (i.e., review of slides or digital images for purposes other than determining resection outcome).

9.2. Appendix 2: General Specifications for Tables, Listings and Figures

9.2.1. Software Used

All programming of tables, listings, and figures (TLFs) will be performed using the statistical software package SAS® version 9.3 or greater.

9.2.2. General

All TLFs are based on SDTM and/or ADaM datasets. By default, data listings reflect the actual values captured in SDTM and ADaM datasets, including date/time variables and missing values. Except for concatenation of some variables for compact display purpose, data are presented directly with minimum manipulation. In general, the character standard result variables, such as –STRESC, are presented in data listings. Date is presented in listings in format yyyy-mm-dd. For incomplete date, CDISC presentation convention is followed.

For continuous variables that are recorded as "<X" or ">X", the value of "X" will be used in the calculation of summary statistics. The value "X" is also captured in the numeric variable in the SDTM datasets as well as in the ADaM datasets for consistency, although SDTMIG recommends capturing missing values in the numeric variables.

In general, reported verbatim, such as terms of AE, medical history, medication names, specifications to the 'Other' fields, findings, etc., are presented in upper case. However, when reported fields are long, such as comments and protocol deviation descriptions, listing in lower case enhances readability.

9.2.3. Table/Listing/Figure Output File Type and Organization

In general, the final set of TLFs will include both PDF and RTF files. Outputs are combined in several large PDF files, e.g., all tables, all listings, and all figures. A table of content should be included with hyperlinking to individual outputs. True RTF files (in-text format) will be created for tables and listings. SAS outputs for statistical procedures used in analysis of primary, secondary, and exploratory efficacy endpoints will also be included.

9.2.4. Page Layout

All column headers (consisting of one or several words) will start with uppercase and thereafter only lowercase characters, except for acronyms and abbreviations. In case values from the database will be displayed in column headers, they may be displayed as in the database. Pages will be numbered as 'Page x of y', where 'y' is the total number of pages of the corresponding table or listing. The page specifications are presented in Table 13.

Table 13: Specifications for Page Layout

Paper Size	**Letter**
Orientation	Landscape
Alignment	Center
Font size	9
Font type	Courier New (default)
Margins	
Top	0.75”
Bottom	0.38”
Left	1.00”
Right	1.00”

The margin sizes and font size for listings may be flexible to provide sufficient information on a single page to facilitate review and comparison.

When created using SAS, tables and listings will be created using ODS, and output files will be produced in RTF. When RTF files are produced, titles and footnotes will appear as document headers/footers.

9.2.5. Titles and Footnotes

All tables and listings will have a header showing “FibroGen, Inc.”, the protocol number (A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer), database cutoff date, Date of data of Extraction or ‘Final Database (database lock date)’, and Page x of y. A footer will show the program file path/name, output file path/name, run date and time.

All titles are written in title format, with uppercase at the beginning of each notional word; articles, prepositions, and conjunctions, which are of three characters length or less will start with lowercase letters (Mixed Case). Footnotes are in regular text format.

Titles

In total there are up to 10 titles available, defined as following:

first title	“FibroGen, Inc.” (left aligned) and “Database extraction date: ddMMMyyy” or “Final Database (database lock date)” (right aligned)
second title	protocol number (A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer) + “Clinical Study Report” (left aligned) and “Page x of y” (right aligned)
third title	blank

fourth title:	table/listing/figure number
fifth title:	table/listing/figure title
sixth title:	population names if provided in SAP, or brief definition of specific analysis set

Footnotes

Up to 10 footnote lines are available for tables, listings, and figures. Footnotes 1, 9 and 10 are standard. Footnotes 2 to 8 (left aligned) might be used as needed. They are to be specified in the Shell.

first footnote	is a separating horizontal line.
second – eighth	are free text which can be used for explanations.
ninth footnote	left blank; in case needed may also be used as for explanations.
tenth footnote	the word "Confidential", the program name (left aligned); date of data cutoff, the date and time in the format ddMMMyyyyThh:mm when the output was created; reference Table(s) or Listing(s).

If footnotes take more than 30% of the space of a long listing, they may be presented only on a standalone first page.

For summary tables, the corresponding listings with the parameters being summarized should be footnoted as reference. For figures, the corresponding summary table should be footnoted as reference.

9.2.6. Table, Listing, Figure Metadata

The table, listing, and figure (TLF) metadata will include the TLF numbers, titles, analysis populations, program names, and input dataset names. For tables and figures, PARAMCD, PARAM, and other conditions will be specified. TLF numbers, titles, and footnotes will be imported from this master spreadsheet. In addition, this spreadsheet will record the names of the original programmer and the validator/reviewer and the date of validation approval.

9.2.7. Significant Digits of Summary Statistics

For variables of direct measurements, summary statistics are displayed with the following specifications of decimal places in Table 14.

Table 14: Significant Digits of Summary Statistics

Description	Characteristic	Number of decimal places
Count	N	0
Mean	Mean	As in source + 1
Standard deviation	Std	As in source + 1
Standard error of the mean	SEM	As in source + 2
Confidence Interval	CI	As in source + 1
Minimum	Min	As in source
Median	Median	As in source
Maximum	Max	As in source
Q1 / Q3	Q1/Q3	As in source
10% / 90%	10%/90%	As in source
Percentage	%	All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero
Coefficient of variation	CV (%)	1
p-value	p-value	p-values will be rounded to four decimal places and will be presented as '<.0001' if they are less than 0.0001 after rounding

N=number; Std=Standard deviation; CI=Confidence Interval; Min=minimum; Max=maximum; CV=Coefficient of variation

As a general guideline for derived parameters, 3 significant digits may be displayed for min and max; 4 significant digits for median, mean, Q1/Q3 and CI; and 5 significant digits for Std or SE. If a derived parameter is in the same scale as some related measured parameters, such as MAP, QTc, the same display format may be used as the measured parameters.

Summary Statistics are to be displayed in the following order: Count, Mean, Standard Deviation, <Coefficient of Variation, Standard Error of the Mean, Confidence Interval>, Minimum, <10%>, <Q1>, Median, <Q3>, <90%>, Maximum.

For categorical variables the categories will be displayed in the TLFs in the same order they appear in the CRF.

9.2.8. Figure Specifications

- In general, figures should include annotation of key summary statistics: n, mean, Std or SE, median for continuous variables; n and percent for categorical variables; number of subjects at risk and cumulative number of events as well as median and 95% CI for time-to-event data. Other statistics such as quartiles, ranges may be included depending on need and space.
- P-values should be presented if comparisons are of interest.

- For scatter plots, linear or non-linear trend lines should be included if the association of the two variables is of interest. Correlation coefficient or regression coefficients as well as corresponding p-values should be presented.
- For line-charts, if space allows, 1-sided or 2-sided standard error bars should be presented.
- For box plots, 'BOXSTYLE=SCHEMATIC' should be used. The whiskers are drawn to the most extreme points in the group that lie within the fences. The upper fence is defined as the third quartile (represented by the upper edge of the box) plus 1.5 times the interquartile range. The lower fence is defined as the first quartile (represented by the lower edge of the box) minus 1.5 times the interquartile range. Observations outside the fences are identified with a special symbol.

9.2.9. Unit Conversion

Units Presented in TLFs	Units Reported or Derived from CRF	Conversion Formula
Kilogram (kg)	Pound (lb)	kg = lb/2.2
Centimeter (cm)	Inch (in)	cm = 2.54 * in
Celsius (C°)	Fahrenheit (F°)	C° = (5/9) * (F° – 32)
Year	Day	1 year = 365.25 days
Months	Day	1 month = 30.4375 days

9.3. Appendix 3: RECIST (1.1) Criteria

Below Table 15 and Table 16 are an outline of the definition of RECIST response categories, extracted from Eisenhauera, et al. (2009).

Table 15: Time Point Response: Patients with Target and Non-Target Lesions

Assessment Category	Response Category	Response Criteria
Target lesions	Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
	Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
	Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
	Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Non-target Lesions	Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
	Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
	Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table 16: Overall Response: Patients with Target and Non-Target Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/no-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	In-evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

9.4. Appendix 4: TNM and AJCC Staging Definitions

The definitions below are extracted from AJCC Cancer Staging Manual, 7th Edition (2010).

TNM definitions

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor limited to the pancreas, ≤2 cm in greatest dimension

T2: Tumor limited to the pancreas, >2 cm in greatest dimension

T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

Distant metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

AJCC Pancreatic Cancer Staging

Stage	*TNM Category*
0	Tis, N0, M0
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T3, N0, M0
IIB	T1, N1, M0 T2, N1, M0 T3, N1, M0
III	T4, any N, M0
IV	Any T, any N, M1

9.5. Appendix 5: CTCAE Toxicity Grading for Laboratory Tests

The following Table 17 and Table 18 are extracted from NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Table 17: CTCAE Toxicity Grading for Chemistry

		Grade 1	Grade 2	Grade 3	Grade 4
Bicarbonate	Decreased	<LLN and no intervention initiated	None	None	None
Creatinine	Increased	ULN – 1.5 x ULN	>1.5 – 3.0 x baseline[2] >1.5 – 3.0 x ULN	>3.0 x baseline[2] >3.0 – 6.0 x ULN	>6.0 x ULN
Albumin	Decreased	3 g/dL – LLN	2 - <3 g/dL	<2 g/dL	
Alkaline phosphatase (ALP)	Increased	ULN – 2.5 x ULN[4]; 2.0 - 2.5 x baseline[5]	>2.5 – 5.0 x ULN[4]; >2.5 - 5.0 x baseline[5]	>5.0 – 20.0 x ULN[4]; >5.0 - 20.0 x baseline[5]	> 20.0 x ULN[4]; >20.0 x baseline[5]
ALT	Increased	ULN – 3.0 x ULN[4]; 1.5 - 3.0 x baseline[5]	>3.0 – 5.0 x ULN[4]; >3.0 - 5.0 x baseline[5]	>5.0 – 20.0 x ULN[4]; >5.0 - 20.0 x baseline[5]	>20.0 x ULN[4]; >20.0 x baseline[5]
AST	Increased	ULN – 3.0 x ULN[4]; 1.5 - 3.0 x baseline[5]	>3.0 – 5.0 x ULN[4]; >3.0 - 5.0 x baseline[5]	>5.0 – 20.0 x ULN[4]; >5.0 - 20.0 x baseline[5]	>20.0 x ULN[4]; >20.0 x baseline[5]
Total bilirubin	Increased	ULN – 1.5 x ULN[4]; > 1.0 - 1.5 x baseline[5]	>1.5 – 3.0 x ULN[4]; >1.5 - 3.0 x baseline[5]	>3.0 – 10.0 x ULN[4]; >3.0 - 10.0 x baseline[5]	>10.0 x ULN[4]; >10.0 x baseline[5]
Calcium (Corrected)	Decreased	8.0 mg/dL – LLN	7.0 - <8.0 mg/dL	6.0 - <7.0 mg/dL	<6.0 mg/dL
	Increased	ULN – 11.5 mg/dL	>11.5 – 12.5 mg/dL	>12.5 – 13.5 mg/dL	>13.5 mg/dL
Glucose (Random)	Decreased	55 mg/dL – LLN	40 - <55 mg/dL	30 - <40 mg/dL	<30 mg/dL
Potassium	Decreased	3.0 mmol/L – LLN	3.0 mmol/L – LLN[1]	2.5 - <3.0 mmol/L	<2.5 mmol/L
	Increased	ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L[3]	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Sodium	Decreased	130 mmol/L – LLN	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L
	Increased	ULN – 150 mmol/L	>150 – 155 mmol/L[3]	>155 – 160 mmol/L	>160 mmol/L

		Grade 1	Grade 2	Grade 3	Grade 4
Magnesium	Decreased	1.2 mg/dL – LLN	0.9 - <1.2 mg/dL	0.7 - <0.9 mg/dL	<0.7 mg/dL
	Increased	ULN – 3.0 mg/dL	None	>3.0 – 8.0 mg/dL	>8.0 mg/dL

Table 18: CTCAE Toxicity Grading for Serum Hematology

		Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	Decreased	10.0 g/dL – LLN	8.0 - <10.0 g/dL	<8.0 g/dL	
	Increase from baseline	>0 – 2 g/dL	>2 – 4 g/dL	>4 g/dL	
Platelet	Decreased	75,000 /mm^3 – LLN	50,000 – <75,000 /mm^3	25,000 - <50,000 /mm^3	<25,000 /mm^3
WBC	Decreased	3,000 /mm^3 – LLN	2,000 - <3,000 /mm^3	1,000 - <2,000 /mm^3	<1,000 /mm^3
	Increased	None	None	>100,000 /mm^3	
aPTT	Increased	ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN	
Lymphocytes	Decreased	800 /mm^3 – LLN	500 - <800 /mm^3	200 - <500 /mm^3	<200 /mm^3
	Increased	None	>4,000 – 20,000 /mm^3	>20,000 /mm^3	
Neutrophils	Decreased	1500 /mm^3 - LLN	1000 - <1500 /mm^3	500 - <1000/mm^3	<500/mm^3
Eosinophils	Increased	>ULN and >Baseline	None	Steroids initiated	None
Neutrophils	Decreased	1,500 /mm^3 – LLN	1,000 - <1,500 /mm^3	500 - <1,000 /mm^3	<500 /mm^3

Decreased: below LLN; Otherwise, above ULN;
[1] Symptomatic, Intervention indicated
[2] Baseline is used if it is above ULN
[3] Intervention indicated
[4] ULN is used if Baseline was normal
[5] Baseline is used if Baseline was abnormal

9.6. Appendix 6: Terminology Used in This Study

Tumor Grade

The grade of the cancer (how abnormal the cells look under the microscope) uses a scale from G1 to G3 (or sometimes G1 to G4), with G1 cancers looking the most like normal cells and having the best outlook.

The details of grading are a little different for pancreatic neuroendocrine tumors (NETs), where measures of how many of the cells are in the process of dividing is an important part of grading. This is determined by counting mitoses (cells that have started to split into two new cells) under

a microscope and with a Ki-67 test that recognizes cells that are almost ready to start splitting. Based on these tests, NETs are divided into 2 groups:

- **Well-differentiated NETs** (which includes low-grade [G1] and intermediate-grade [G2] tumors) have 20 or fewer mitoses and a Ki-67 index of 20% or lower.
- **Poorly differentiated tumors** (high-grade [G3] tumors) have more than 20 mitoses or a Ki-67 index of more than 20%. These are also called *neuroendocrine carcinomas*, and they often grow and spread quickly.

Extent of Resection

For patients who have surgery, another important factor is the *extent of the resection* — whether or not all of the tumor is removed:

- **R0:** All of the cancer is thought to have been removed. (There are no visible or microscopic signs suggesting that cancer was left behind.)
- **R1:** All visible tumor was removed, but lab tests of the removed specimen show that some small areas of cancer were probably left behind.
- **R2:** Some visible tumor could not be removed.

Resectable versus Unresectable Pancreatic Cancer

The AJCC staging system gives a detailed summary of how far the cancer has spread. But for treatment purposes, doctors use a simpler staging system, which divides cancers into groups based on whether or not they can be removed (resected) with surgery:

Resectable

If the cancer is only in the pancreas (or has spread just beyond it) and the surgeon believes the entire tumor can be removed, it is called *resectable* (In general, this would include most stage IA, IB, and IIA cancers in the TNM system).

It is important to note that some cancers might appear to be resectable based on imaging tests such as CT scans, but once surgery is started it might become clear that not all of the cancer can be removed. If this happens, only a sample of the cancer may be removed to confirm the diagnosis (if a biopsy has not been done already), and the rest of the planned operation will be stopped to help avoid the risk of major side effects.

Borderline Resectable

This term is used to describe some cancers that might have just reached nearby blood vessels, but which the doctors feel might still be removed completely with surgery. This would include some stage III cancers in the TNM system.

Unresectable

These cancers cannot be removed entirely by surgery.

Locally advanced: If the cancer has not yet spread to distant organs but it still cannot be removed completely with surgery, it is called *locally advanced.* Often the reason the cancer cannot be removed is because it has grown into or surrounded nearby major blood vessels. (In general, this would include stage IIB and most III cancers in the TNM system.)

Surgery to try to remove these tumors would be very unlikely to be helpful and could still have major side effects. Some type of surgery might still be done, but it would be a less extensive operation with the goal of preventing or relieving symptoms or problems like a blocked bile duct or intestinal tract, instead of trying to cure the cancer.

Metastatic: If the cancer has spread to distant organs, it is called *metastatic*. These cancers cannot be removed completely. Surgery might still be done, but the goal would be to prevent or relieve symptoms, not to try to cure the cancer.

9.7. Appendix 7: China CDE Requirements

Efficacy data, mainly including overseas key clinical trial data and clinical trial data conducted in China, should not only confirm the efficacy of the study drug as a whole, but also analyze the consistency between Chinese subgroups and the overall population.

Safety data, including all domestic and foreign data used for safety evaluation, should be analyzed not only for overall safety, but also for consistency between Chinese subgroup and overall population.

All TLF in China may be provided per China regulatory requirements if regulatory submission in China is pursued (NMPA guidance).

9.8. Appendix 8: Analyses of Data from China Patients

According to protocol Amendment 5.1 (China-Only, Aug 16, 2022), when completion of global study enrollment (approximately N=280, Cohort 1) is reached, China sites will continue enrollment in Cohort 2 until the planned number of subjects in China is achieved. It is expected that data analysis from Chinese patients will be used to support a submission in China, in addition to the global study Cohort 1 data analysis described in the main body of this SAP. An analysis including all patients recruited in China (Chinese patients from global Cohort 1 and China Cohort 2) will be provided.

Definition of China Analysis Sets

China patients are patients enrolled in sites located in China and declaring themselves as Chinese.

China-only Full Analysis Set

The China-only Full Analysis Set will include all China patients randomized in China. This included all patients randomized in China as part of the global study in Cohort 1 and all additional patients recruited in China Cohort 2.

The China-only Full Analysis Set will be used for all China-only efficacy analyses and treatment groups will be summarized on the basis of randomization, regardless of treatment actually received.

China-only safety analysis set

The China-only safety analysis set will consist of China-only Full Analysis Set patients who received at least one dose of study treatment. The China-only Safety Analysis Set will be based on the treatment actually received.

China-only pharmacokinetic analysis set

The China-only Pharmacokinetic Analysis Set is defined as patients in the China-only FAS who received at least one dose of study treatment, and have at least one evaluable PK concentration.

Analysis methods for China Patients

All efficacy, safety, PRO and PK variables will be derived in the same way as detailed for the global study analysis. The analyses described for main study will be repeated for the patients randomized in China using the China-only analysis sets defined in this Appendix. All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available and only descriptive statistics will be presented. Subgroup analysis will not be conducted. Statistical analysis will be based on unstratified analysis method due to small sample size.

The China patients' analyses will be performed using the same data cutoff date as the final OS analysis for global main study.