# STATISTICAL ANALYSIS PLAN

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|---|---|
| **STUDY TITLE:** | A Randomized, Open-Label, Phase 1/2 Trial of Gemcitabine plus Nab-paclitaxel with or without FG-3019 as Neoadjuvant Chemotherapy in Locally Advanced, Unresectable Pancreatic Cancer |
| **PROTOCOL NUMBER:** | FGCL-3019-069 |
| **SPONSOR:** | FibroGen, Inc.<br>409 Illinois Street<br>San Francisco, California 94158 USA |
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## CONFIDENTIALITY STATEMENT

## STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

### Approvals

I have reviewed and accepted the information in this document to be a true and accurate representation of the Statistical Analysis Plan, Version 1.0 for Study FGCL-3019-069.

**Initiator:**

**Signature:** [redacted] **Date:** 3/21/2018

**Reviewed by**

**Signature:** [redacted] **Date:** 3/22/2018

**Signature:** [redacted] **Date:** 3/21/2018

**Signature:** [redacted] **Date:** 3/21/2018

**Signature:** [redacted] **Date:** 3/22/2018

**Signature:** [redacted] **Date:** 3/22/2018

### Signature Significance

The following significance is lent to the signatures on the Approvals page of this document.

| Signatory | Significance |
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| **Initiator** | By signing, the author is attesting that the content of the document is complete and accurate. |

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|---|---|
| **Reviewer** | By signing, the reviewer is attesting that the document's approach and contents are compliant with the study protocol, all appropriate, regulatory requirements, and other significant guidelines. This individual(s) has reviewed the document for accuracy and completeness. |

## REVISION HISTORY

| Version | Date | Description |
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# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AJCC | American Joint Committee on Cancer |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| BP | Blood Pressure |
| CA | Carbohydrate Antigen |
| CBC | Complete Blood Count |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CR | Complete Response |
| CRF | Case Report Form |
| CS | Clinically Significant |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTGF | Connective Tissue Growth Factor |
| DBP | Diastolic Blood Pressure |
| EBL | Estimated Blood Loss |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eDISH | evaluation of Drug Induce Severe Hepatotoxicity |
| EFS | Event Free Survival |
| EOS | End of Study |
| EOT | End of Treatment |
| EUS | Endoscopic Ultrasound |
| FDG-PET | [18F]-fluorodeoxyglucose-positron emission tomography |
| HAHA | Human Anti-FG-3019 Antibody |
| HR | Heart Ratio |
| ICF | Informed Consent Form |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| LLN | Lower Limit of Normal for a laboratory parameter |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NCS | Not Clinically Significant |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PET | Positron Emission Tomography |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetic(s) |
| PR | Partial Response |
| PT | Preferred term |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RMST | Restricted mean survival time |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Stable Disease, Standard deviation |
| SE | Standard Error |
| SMQ | Standardized MedDRA queries |
| SOC | System Organ Class |
| SSI | Surgical Site Infection |
| SUVmax | Maximum standardized uptake value |
| TEAE | Treatment-emergent Adverse Event |
| TESAE | treatment-emergent serious adverse event |
| TNM | tumor/node/metastasis |
| TTP | Time to Progression |
| ULN | Upper Limit of Normal for a laboratory parameter |
| WHO-DD | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) documents planned analyses for Study FGCL-3019-069 Amendment 6 (September 29, 2016): A Randomized, Open-Label, Phase 1/2 Trial of Gemcitabine plus Nab-paclitaxel with or without FG-3019 as Neoadjuvant Chemotherapy in Locally Advanced, Unresectable Pancreatic Cancer.

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

# 2 STUDY OBJECTIVES

The objectives of this trial are:

- To investigate the safety, tolerability, and efficacy of FG-3019 administered with gemcitabine and nab-paclitaxel in the treatment of locally advanced, unresectable pancreatic cancer.
- To evaluate the pharmacokinetics of FG-3019 (concentration maximum [$C_{max}$] and concentration minimum [$C_{min}$]) and correlation with other study endpoints in this treatment setting.

The exploratory objectives of this trial are:

- To assess the effects of neoadjuvant treatments on a panel of tumor and plasma biomarkers.
- To evaluate the effects of neoadjuvant treatment on gene and protein expression profiling using freshly obtained tumor tissues or blood samples.

# 3 STUDY DESIGN

## 3.1 Overview

This is a Phase 1/2, randomized, open-label trial to evaluate safety, tolerability and efficacy of gemcitabine plus nab-paclitaxel with FG-3019 (Arm A) and gemcitabine plus nab-paclitaxel (Arm B) in subjects with locally advanced, unresectable pancreatic cancer. Up to 42 evaluable subjects will be included in this trial. Each treatment cycle is 28 days long and subjects may receive up to six cycles of treatment. Subjects will be evaluated for their surgical eligibility at end of treatment. Subjects will be followed for at least 28 weeks post End of Treatment for disease progression and survival.

Blood samples will be collected periodically for the assessment of PK and pharmacodynamics (PD). Study centers participating in this study have the option of participating in the collection of tumor core biopsies that will be used in an exploratory portion of this study evaluating tumor biomarkers including protein expression. At centers not participating, tumor samples obtained from resected specimens may be used in biomarker studies.

This trial has four periods:

- Screening and Disease Staging
- Treatment
- Surgery or Short-Term Follow Up
- Long-Term Follow Up

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

A total sample size of 42 evaluable subjects, 28 in Arm A and 14 in Arm B, is considered appropriate, based on clinical judgment, for initial exploration of safety, tolerability, and treatment effect.

## 3.4 Randomization and Treatment Assignment

Prior to Amendment 3, eligible subjects were randomized 1:1 to:

- **Arm A:** gemcitabine, nab-paclitaxel, and FG-3019

  or

- **Arm B:** gemcitabine and nab-paclitaxel

In Protocol Amendment 4, the randomization schedule was changed to 3:1 in order to achieve an overall 2:1 randomization (approximately 28 in Arm A and 14 in Arm B at study end).

## 3.5 Dosing Schedule

Each treatment cycle is 28 days long and subjects may receive up to six cycles of treatment.

- **Arm A treatment consists of:**
  - 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.
  - FG-3019, 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.
- **Arm B treatment consists of:**
  - 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

### 3.6 Study Assessments

The schedule of assessment is provided in the Appendix 1 of the protocol.

Subject's baseline characteristics, which include demographics, cancer TNM status and staging, medical history, smoking history, prior therapies for cancer including surgery, radiation, and systemic treatment, are collected at Screening.

Eligibility for surgical exploration is evaluated at EOT. For subjects who undergo surgery, surgical outcomes are collected. Post-surgical evaluation is performed 30 days after discharge.

CT scan and RECIST assessment are performed at Screening (within 2 weeks of Cycle 1 Day 1) and approximately every 8 weeks thereafter (prior to Cycle 3, 5 and at EOT) until disease progression or discontinuation of study treatment. Unscheduled scans may be performed at the discretion of the investigators.

PET scan is performed at Screening and at EOT.

CA 19.9 is assessed by local lab at each site at Screening, Day 1 of each cycle (Day 1, Weeks 5, 9, 13, 17, 21), and at EOT.

ECOG performance status is assessed at Screening, Day 1 of Cycle 1, 3, 5, and at EOT. Karnofsky score is additionally evaluated at EOT for the purpose of determining surgical eligibility.

Long-term follow-up for progression and survival is conducted approximately every month for the first 28 weeks following EOT and quarterly thereafter.

Adverse events, concomitant medications, procedures and non-drug therapies are collected from signing ICF through 28 days after the last dose.

Safety lab tests are evaluated at the local lab of each study site at every clinic visit.

Vital signs are measured at every clinic visit.

Physical examination is performed at every clinic visit.

ECG is performed at Screening and at EOT.

Plasma samples for evaluation of FG-3019 concentration level are collected from subjects in Arm A pre- and post-dose on Days 1, 8, 15 of Cycle 1, pre-dose on Day 15 of Cycle 2, pre-and post-dose on Day 1 of Cycles 3 and 6, pre-dose on Day 1 of Cycle 5 and at EOT, and 28 days after last dose.

CTGF and HAHA samples are collected on Day 1 prior to first dose and 28 days after last dose.

Plasma samples for protein expression profile and whole blood sample for PAX gene are collected on Day 1 of Cycles 1, 3, 5 prior to study drug dosing and at EOT.

Up to 4 core biopsies are collected while subjects are undergoing endoscopic ultrasound EUS procedure at Screening. Post-treatment tumor tissues are collected during surgery or during post-treatment EUS. Subjects who are not eligible for surgical exploration are to undergo EUS guided core tumor biopsies to obtain post-treatment tissue samples.

# 4 STUDY ENDPOINTS AND DEFINITIONS

## 4.1 Study Endpoints

### 4.1.1 Safety Endpoints

- Treatment-emergent adverse events (TEAEs), serious treatment-emergent adverse events (TESAEs), death, clinical laboratory tests, and discontinuation of treatment for treatment-related TEAEs.
- Surgical safety with respect to complication rates post resection.

### 4.1.2 Efficacy Endpoints

- The proportion of subjects who become eligible for surgery.
- The proportion of subjects in whom R0 resection is achieved.
- The proportion of subjects in R0 or R1 resection is achieved.
- Tumor response rates measured by:
  - Complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1),
  - At least 50% reduction from baseline in serum CA19-9, or
  - At least 30% reduction from baseline in SUV[max] assessed by FDG-PET
- Median overall survival and 1-year survival rate.
- Median progression free survival and 1-year progression free rate.

### 4.1.3 Exploratory Outcome Measures

The exploratory outcome measures are:

- FG-3019 plasma concentrations, including trough level ($C_{min}$) and maximum concentration ($C_{max}$).
- Tissue expression of biomarkers including CTGF, alpha-smooth muscle actin (alpha-SMA), Ki67, Cleaved Caspase-3, and SPARC assessed by immunohistochemistry or ribonucleic acid (RNA).
- Gene and protein expression profiling using freshly obtained tumor tissues, plasma samples or whole blood sample.
- Event free survival (EFS)

## 4.2 Detail Definitions of the Study Endpoints

### 4.2.1 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 by more than 50% at EOT when compared to baseline.
- FDG-PET $SUV_{max}$ decrease by $\geq$30% from baseline.

- Radiological tumor response (PR or CR) per RECIST 1.1.
- Meet the definition of resectable or borderline resectable per NCCN Guidelines

Contraindications include

- Development of distant metastases confirmed by CT scan
- Local progression confirmed by CT scan or progression precluding vascular reconstruction
- Local complication preventing surgery (e.g., PV/SVT thrombosis, pancreatitis)
- Performance status decline to Karnofsky score ≤50% or absolute contraindication to surgery
- Other contraindications as specified

### 4.2.2 Resection Outcome

Resection outcome (R0 or R1) is determined by pathological examination of the surgical specimen after resection and is recorded on Surgical Outcome CRF.

### 4.2.3 Overall Survival, Time to Progression, Progression-free Survival, and Event-free 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 date of last known alive recorded on the Long-Term Follow-up CRF or the date of last clinic visit is defined as the censoring date for OS.

Time to progression (TTP) is defined as the time from randomization until objective tumor progression. Date of disease progression is defined as the date of radiological progression per RECIST 1.1 criteria recorded the Disease Progression CRF. For subjects who have no documented record of radiologic progression at data cut or at study closure, the latest date of the following events is defined as the censoring date for TTP: last post-baseline CT, last post-baseline PET scan, the last record of 'Not Progressed' on the Long-Term Follow-up CRF, and last dose.

Progression free survival (PFS) is defined as the time from randomization until objective tumor progression or death. Specifically, PFS is equal to TTP if the progression event is observed, or equal to OS if the progression event is censored.

Event-free survival (EFS) is defined as the time from randomization to death, or objective tumor progression, or failure to achieve an R0 or R1 resection, or failure to meet surgical eligibility criteria, whichever occurs first.

| Event | EFS | Censor or Event |
|---|---|---|
| Disease progressed or death before surgical evaluation | EFS =PFS | Event |

| | | |
|---|---|---|
| Discontinued early and had no follow up progression record | EFS = latest date of (last post-baseline CT, last post-baseline PET scan, last dose) – Date of randomization + 1 | Censor |
| Ineligible for surgical exploration | EFS = 24 weeks (168 days) | Event |
| Eligible but R0/R1 resection not achieved | EFS = Date of surgical exploration or date of surgery cancelation – Date of randomization + 1 | Event |
| Disease progression or death after achieving R0 or R1 resection | EFS = PFS | Censor or event the same as PFS |

Alternatively, EFS may be defined as the time from randomization to death, or objective tumor progression, or failure to achieve an R0 or R1 resection, whichever occurs first. For subjects who did not progress at EOT and did not achieve an R0 or R1 resection (regardless of meeting the surgical eligibility criteria or not), EFS is defined as an event on day 168 (week 24). A more specific algorithm is presented in the table below.

| Event Timing | EFS | Censor or Event |
|---|---|---|
| Death or disease progression before Day 168 | EFS = PFS | Event |
| Discontinued early and had no follow up progression record | EFS = latest date of (last post-baseline CT, last post-baseline PET scan, last dose) – Date of randomization + 1 | Censor |
| Discontinued treatment early and disease progression occurred after Day 168 | EFS = 168 days | Event |
| Completed 6 treatment cycles and R0 or R1 resection not achieved | EFS = 168 days | Event |
| Death or disease progression after achieving R0 or R1 resection | EFS = PFS | Censor or event the same as PFS |

### 4.2.4 CT Tumor Measurement

Per RECIST 1.1 criteria, up to 10 measureable target lesions are selected at baseline. The longest diameter (LD) for each target lesion is measured. The sum of the LDs of the target lesions, as well as the percent change from the baseline sum LD and the percent change from the smallest sum LD are derived. In this study, only the lesion at the pancreas will be evaluated. The two types of percent changes are used to determine treatment response per RECIST (1.1) criteria.

% change from baseline = (LD of the lesion at the pancreas – Baseline)/Baseline * 100%

Partial response is defined as at least a 30% decrease from baseline.

% change from the smallest sum = (LD of the lesion at the pancreas – the smallest measure during the study)/the smallest measure during the study * 100%

Progressive disease is defined as an absolute increase of at least 5 mm and at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, or the appearance of one or more new lesions.

Non-target lesions are identified and recorded at baseline and are assessed as ‘improved’, ‘stable’, ‘worsened’, or ‘new’ at follow-up visits.

### 4.2.5 RECIST (1.1) Response and Best Overall Response

Radiological treatment response is determined by radiologists at each site using RECIST 1.1 criteria (Eisenhauera, et al. 2009). Appendix III presents an outline of the RECIST response criteria for target lesions, non-target lesions, and overall response.

Best overall response is the most favorable overall response recorded during the 24-week treatment period, determined by the following order: CR, PR, SD, and PD.

The best objective response is defined as the best response being CR or PR.

### 4.2.6 CA 19.9: Percent Change from Baseline, Response, and Normalization

CA 19.9 endpoints are defined only in subjects with baseline CA19-9 value higher than the upper limit normal (ULN). ULN is defined as 37 U/mL in this study (Ballehaninna and Chamberlain, 2012). 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.

Percent change from baseline is defined as:

% Change from Baseline = (Assessment at a given time point – Baseline) / Baseline * 100

The protocol defined CA 19.9 response is reduction from baseline ≥ 50%. Additional response criteria, such as reduction from baseline ≥ 70%, ≥ 90%, and ≥ 95% will be evaluated.

For each subject, best CA19-9 response is defined as the minimum percent change from baseline. (The largest reduction or smallest increase.)

CA 19.9 normalization is defined as CA 19.9 < ULN for those whose baseline value ≥ ULN.

### 4.2.7 PET SUVmax: Percent Change from Baseline, Response, and Normalization

Maximum standardized uptake value (SUVmax) is read by radiologists at each site. Metabolic response is defined as reduction from baseline in $SUV_{max}$ ≥ 30% for lesion at the pancreas only. A complete metabolic response is defined as SUVmax = 0.

### 4.2.8 Exceptional Treatment Response

Exceptional treatment response is defined:

- CA19.9 reduction from baseline ≥ 95% or normalization at any time point.
- PET SUV normalization, i.e., SUV = 0 at EOT

### 4.2.9 ECOG Performance Status

Assessment on Day 1 or the last assessment prior to first dose is defined as the baseline. The ECOG grading scale is shown below:

| GRADE | ECOG PERFORMANCE STATUS |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |
| 5 | Dead |

### 4.2.10 Adverse Events

The definitions of adverse events (AE), serious adverse events (SAE), severity, and relationship to study medication are described in Section 8.4 of the protocol. Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) for system organ class (SOC) and preferred term for summary.

*Treatment Emergent Adverse Event in the Study (TEAE)*

TEAEs are defined as new or worsening AEs that occurred in the window of first dose of any study drug (Day 1) and within 28 days of the last dose of study drug or the day before surgery, whichever occurs first.

**Definition of TEAE and Study Period When AE Occurred**

| AE Onset Date Relative to Dosing* | AEPRIOR | TEAE | Study Period (EPOCH) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| AE onset date < Day 1 | Any | No | screen |
| AE onset date = Day 1 | Yes | No | screen |
| | No | Yes | treatment |
| Day 1 < AE onset date ≤ date of last dose in randomized treatment period | Any | Yes | treatment |
| Date of last dose < AE onset date ≤ earlier date of {last dose + 28, date of surgery - 1} | Any | Yes | Within 28 days from last dose follow-up |
| AE onset date > date of last dose + 28 | Any | No | Additional Follow-up beyond 28 days |
| *First dose refers to first of any one of the study medications; last dose refers to last of any one of the study medications. | | | |

AEs may be recorded in multiple records due to changes of characteristics such as seriousness, severity, frequency, treatment, and other aspects. These records will be linked together for summary purposes. The most severe grade, seriousness, relatedness to study drug will be used in AE summary tables. Below are the rules:

(1) Multiple AE records are linked as one AE if they have the same SOC/preferred term and onset date of a later record is the same as stop date of the previous record.

(2) If the linked AE starts in the TEAE window, it is a TEAE.

(3) If the linked AE starts in screening, then the post dose record will be compared with the screening record. It is a TEAE if it is worsened comparing to the screening record. 'Worsened' is defined as increased grade in seriousness, severity, and frequency.

(4) Once an AE record is determined to be a TEAE, all subsequent records of the linked AE, including the records past 28 days after last dose, are considered TEAE. The highest grade of severity and seriousness of the linked TEAE will be included in the AE summary tables.

The hypothetic example below illustrates the algorithm. Of note, AE #1 occurred in Screening; AE #2 and #3 were not worse than AE #1; these 3 AEs are not TEAEs. AE#4 worsened during the TEAE window; the subsequent AE #5 is also a TEAE by the algorithm.

**Example of Definition of TEAE for Multiple Records of the Same AE**

| AE # | Onset | AE | Severity | Seriousness | Related to study drug? | TEAE |
|---|---|---|---|---|---|---|
| 1 | Screening | Headache | 2 | N | N | N |
| 2 | Day 2 | Headache | 1 | N | N | N |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | Last dose | Headache | 2 | N | Y | N |
| 4 | 10 days post last dose | Headache | 3 | Y | N | Y |
| 5 | 45 days post last dose | Headache | 5 | Y | N | Y |
| 6 | Day 10 | Headache | 2 | N | | |
| Consolidated for summary | | Headache | 5 | Y | Y | Y |

*AE Severity Rating*

AEs are rated by the investigators as “mild”, “moderate”, “severe”, “life threatening”, or “fatal” based on the CTCAE v4.0 grading system as described in Section 8.4.3 of the protocol. If a subject reports multiple occurrences of an AE within one system organ class or preferred term, the most severe occurrence will be presented in the summary by severity rating. Missing severity rating will not be imputed and it is ranked the lowest in summary by severity rating.

*AEs Related to FG-3019, or Gemcitabine, or Nab-paclitaxel*

Investigators determine the relationship of AEs with the study medications as described in Section 8.4.4 of the protocol. For summary purposes, ‘Possibly related’ AEs are grouped with the ‘Related’ AEs. If related and unrelated occurrences of an AE within one system organ class or preferred term are reported in a subject, the related occurrence will be presented in the summary by relationship. Missing relationship evaluation will not be imputed and it is ranked the lowest in summary by relationship.

*Anaphylactic Reactions and Hypersensitivities*

Anaphylactic reactions and hypersensitivities are defined as the TEAEs with matching preferred terms of the Standardized MedDRA Queries (SMQ) (Appendix IX).

The infusion reaction tick box completed by the sites on the AE CRF will not be included in the summary.

### 4.2.11 Surgical Safety Measures and Post-surgery Follow-up

Surgical safety assessed during surgery

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

Surgical complication during hospitalization

- Duration of hospitalization post-surgery (date of discharge – date of surgery + 1)

- Intra-abdominal abscess
- Postoperative leaks
- Surgical site wound infection (SSI)
- Other complication

Surgical complication during post-operative follow-up

- Re-admission to hospital within 30 days from discharge
- Return to operating room within 30 days from discharge
- Intra-abdominal abscess
- Postoperative leaks
- Surgical site delayed wound healing and or infection (SSI)
- Other complication

### 4.2.12 Laboratory Evaluations

The lab tests in the following table are evaluated at every clinic visit to assess treatment tolerability.

**Laboratory Tests**

| **Hematology Panel:** | **Chemistry Panel:** |
|---|---|
| Hemoglobin (Hb) | Sodium |
| Hematocrit (HCT) | Potassium |
| Erythrocytes | Blood urea nitrogen (BUN) |
| Mean corpuscular volume (MCV) | Bicarbonate |
| Leukocytes (WBCs) | Creatinine |
| Neutrophils | Glucose |
| Lymphocytes | Calcium |
| Monocytes | Phosphorus |
| Eosinophils | Aspartate aminotransferase (AST) |
| Platelets | Alanine aminotransferase (ALT) |
| Absolute neutrophil count (ANC) | Alkaline phosphatase (ALP) |
| | Total bilirubin |

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. The CTCAE 4.03 (June 14, 2010) grading for the study-specific tests is presented in Appendix VI.

Instead of using the reference ranges provided by individual local labs, a common set of reference ranges for chemistry and hematology presented in the New England Journal of Medicine 2004; 351: 1548-63, is used in this study. These reference range are presented in Appendix V.

Baseline for lab tests is defined as the last assessment prior to the first dose.

### 4.2.13 Vital Signs

Vital sign parameters include systolic/diastolic blood pressures, pulse rate, respiratory rate, and body temperature. Baseline for vital signs is defined as the average of the last Screening value and the Day 1 pre-infusion measurement.

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

**Potentially Clinically Significant Changes in Vital Signs**

| Parameter | Observed Values | Change from Baseline |
|---|---|---|
| Systolic BP (mm Hg) | <90 or>140 mm Hg | >20 mm Hg |
| Diastolic BP (mm Hg) | <50 or>90 mm Hg | >20 mm Hg |
| Pulse Rate (bpm) | <50 or>100 bpm | >20 bpm |
| Body temperature (ºC) | 37 | >3 |

BP=blood pressure; bpm=beats per minute; ºC = Celsius

### 4.2.14 Physical Examination

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

### 4.2.15 ECG

ECG is evaluated by investigator as:

Normal,

Abnormal, CS, or

Abnormal, NCS.

Abnormal findings are described.

### 4.2.16 PK

Plasma samples are collected from subjects assigned to treatment Arm A for evaluation of FG-3019 concentration level at the following time points. Post-dose samples are collected between 30 minutes to 2 hours from the end of infusion of FG-3019.

| CYCLE | DAY | TIME |
|---|---|---|
| 1 | 1 | Pre-dose |
| | | Post-dose |
| | 8 | Pre-dose |
| | | Post-dose |
| | 15 | Pre-dose |

| | | |
|---|---|---|
| | | Post-dose |
| 2 | 15 | Pre-dose |
| 3 | 1 | Pre-dose |
| | | Post-dose |
| 5 | 1 | Pre-dose |
| 6 | 1 | Pre-dose |
| | | Post-dose |
| | 28/EOT | |
| Safety FU | 28 days post last dose | |

### 4.2.17 CTGF

CTGF samples are collected on Day 1 predose and at safety follow-up visit (70 days after the last dose for subjects enrolled under the original protocol or 28 days after the last dose for subjects enrolled after Amendment 1). CTGF parameters include CTGF N+W and CTGF W.

### 4.2.18 Protein Expression Profile and PAX Gene

Plasma samples for protein expression profile and whole blood samples for PAX gene evaluation are collected on Day 1 predose of Cycles 1, 3, 5 and at EOT. Analysis of these data will be provided in separate reports.

### 4.2.19 Tumor Biopsy Evaluation

Analysis of the tumor biopsy samples will be provided in a separate report.

### 4.2.20 HAHA

Blood samples for human anti-human antibodies (HAHA) measurement are collected from subjects randomized to treatment Arm A in heparinized tubes at pre-dose on Day 1 of Cycle 1 and at the safety follow-up visit approximately 28 days after the last dose with study treatment. HAHA assay results are “Reactive” or “Non-Reactive”. For those with ‘Reactive’ results, further evaluation of “Specific” or “Not Specific”, and % Inhibition by HAHA are provided.

# 5 GENERAL STATISTICAL CONSIDERATIONS

## 5.1 Analysis Populations

The Randomized Population includes all subjects who have received a treatment arm assignment, regardless of whether they received study treatment.

In this study, the Intent-to-Treat (ITT) Population and the Safety Population are both defined as all randomized subjects who have taken any amount of study drugs including FG-3019, or gemcitabine, or nab-paclitaxel. The Per Protocol (PP) Population is defined as subjects who have completed the study treatment, as defined on the End-of-Treatment Disposition CRF. If actual treatment received differs from the randomized treatment arm, the actual treatment arm will be used in all data analysis.

The ITT Population will be used in baseline and efficacy summaries; the Safety population will be used for safety summaries. The PP Population will be used in selected efficacy parameters.

## 5.2 Hypotheses and Decision Rules

Data in this exploratory study will be examined in a hypothesis-generating manner via various statistical methods and models. Adjustment for Multiple Comparisons

No adjustments will be made for multiple tests.

## 5.3 Handling of Dropouts or Missing Data

Except for the cases described in this section, only observed data without imputation will be used in analyses.

### 5.3.1 Handling Missing Data in Responder Analyses

When performing a responder analysis, subjects with missing data will be considered non-responders. All subjects in the defined population will be included in the evaluation.

### 5.3.2 Handling Missing/Incomplete AE Onset Date

If the AE onset date is incomplete or missing, the following rules will be applied to obtain imputed AE onset date.

- If year and month are present, only day is missing,
  a) If AE onset Year/month = Day 1 Year/month, assign onset date = date of Day 1;
  b) If AE onset Year/month ≠ Day 1 Year/month, assign onset Day = 1;
- If year is present, month and day are missing,
  a) If onset year = year of Day 1, assign onset date = date of Day 1;
  b) If onset year ≠ year of Day 1, assign January 1$^{st}$ to onset month and day.
- If onset date is completely missing, assign onset date = date of Day 1.

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.

### 5.3.3 Handling Missing/Incomplete CM Start/Stop Dates

For the purpose of grouping medications in different study period, the following rules will be used to impute incomplete CM start and end date:

- Incomplete CM start date: assign 1 to missing Day, January to missing Month.
- Incomplete CM end date: assign 30 to missing Day, December to missing Month. Impute CM end date only if 'ONGOING' is not checked.

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.

No imputation will be performed for the following cases:

- CM end date will not be imputed if 'ONGOING' is checked.
- Year of CM start or end is missing. If CM end year is missing, the CM will be grouped in the 'Concomitant Medication' category.

## 5.4 Adjustment for Covariates

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

- Baseline TNM Stage (T3 vs.T4)
- Baseline TNM Stage (N0 vs. N1/NX)
- Baseline ECOG (0 vs. 1)
- Baseline CA 19.9 (below vs. above median)
- Baseline PET SUV (below vs. above median)
- Baseline tumor size (below vs. above median)
- Baseline SMA Involvement (> 180 degree vs. <180 degree)
- Baseline celiac Abutment Status (Yes vs. No)
- Baseline unreconstructible SMV/Portal Occlusion Status (Yes vs. No)
- Tumor anatomy (head vs. body/tail)

## 5.5 Definition of Baseline

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

## 5.6 Study Day Calculation

The day when a subject receives the first dose of any study drugs (FG-3019, gemcitabine, or nab-paclitaxel) after randomization is designated as Day 1.

Study day of an assessment/procedure is calculated as follows.

- 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 time, as shown in the table below, except for the upper bound of the Week 24 window, which is set on Week 30 (Day 210)

| Assessment Interval | Assessment | Target Assessment | Window |
|---|---|---|---|
| 4 weeks | CA19-9 | k-th Cycle Day 1 | Target day [4*(k-1)*7 + 1] +13/-14 days For EOT k = 7. |
| 8 weeks | CT, ECOG | k-th Cycle Day 1 | Target day [4*(k-1)*7 + 1] + 27/-28 days For EOT k = 7. |
| 24 weeks | PET | EOT | Day 85 - 210 |

All scheduled and unscheduled assessments are included. If two assessments are available in the same window, the one closer to the target day is used. If two assessments with equal distance to the target day, the later assessment will be used in analysis. Assessments that do not fall in any windows will not be included in analyses.

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.

## 5.8 Interim Analyses and Data Monitoring

In this open label study efficacy and safety data are monitored periodically throughout the study.

## 5.9 Pooling Data of Study Sites

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

## 5.10 General Layout

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

Efficacy parameters will be summarized analytically. Analytical statistics include LS mean and standard error, 95% CI for the mean or median, p-value. Depending on the nature of the parameter, treatment difference will be expressed in absolute or percent difference, odds ratio, or hazard ratio.

All summaries except PK will be presented by treatment group as well as a combined group (Arm A, Arm B, Overall), unless specified otherwise.

Raw data and derived parameters will be presented in data listings, which will be organized in the order by treatment arm followed by subject ID.

Figures, such as line-chart, bar-chart, box-plot, scatter plot, forest plot, or waterfall plot, are in general included to facilitate comparison between treatment arms and evaluation of trend.

### 5.11 Data Errata and Hard-Coding

Data errors identified after database lock are documented in an errata log. Under special circumstances, hard-coding in SAS programs is necessary to correct data errors in order to avoid obscure study results. Only limited cases deemed necessary and are approved by study team will be hard-coded. The changed values as well as approval from the study team will be documented.

# 6 STATISTICAL ANALYSES

## 6.1 Subject Enrollment and Disposition

The number of subjects enrolled in each study site will be summarized.

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

The number of subjects remaining in the study at each visit will be summarized.

Subject who discontinued the study early and the reasons will be listed.

## 6.2 Protocol Deviations

Protocol deviations will be categorized as follows:

- Entry Deviation: Subject entered study, but did not satisfy eligibility criteria.
- Withdrawal Deviation: Subject met withdrawal criteria during the study but was not withdrawn.
- Dosing Deviation: Subject received the wrong treatment or incorrect dose; including incorrect timing of a dose.
- Prohibited Medication Deviation: Subject received an excluded concomitant treatment.
- Operational Deviation: All other deviations; including, but not limited to: informed consent form-related deviations other than consent not obtained, IRB/IEC approval expired, study drug not stored under protocol-specified conditions, missing laboratory report, out-of window visit, etc.; includes missed visits, and subject refusal of a study procedure or procedures.

Deviations are summarized by subject count and by event count, by cohort and by study site. All recorded protocol deviations are listed. Reported items that are not considered as protocol deviations are not included in summary tables and data listings, but remain in the database for reference.

## 6.3 Demographics and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized descriptively for subjects in the ITT population. Each parameter will be presented in data listings.

### 6.3.1 Subject Demographics and General Characteristics

Demographic parameters and general characteristics include age, age group (< 18, 18-64, 65-74, ≥ 75), sex, ethnicity, race, height, weight, body-mass index (BMI), BSA, smoking status, and number of years that subject smoked.

Age is defined as the age on the day of signing inform consent:

age = INTCK( ‘YEAR’, Birth Date, Date of Informed Consent, ‘C’)

where INTCK is a SAS function.

BSA and BMI are defined below:

BSA in $m^2$ = Sqrt(weight in kg * height in cm ÷ 3600)

BMI = Weight (kg) / (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:

- Tumor name ("PDAC" or "Other")
- Time from diagnosis (days) defined as date of first dose - date of diagnosis + 1
- Disease stage (1, 2a, 2b, 3, or 4)
- TNM stage
- ECOG performance status

### 6.3.3 Baseline Tumor Unresectability per NCCN Criteria

The following unresectability characteristics are summarized:

- Does the tumor have greater than 180 degrees SMA encasement
- Does the tumor have any celiac abutment
- Does the tumor have inferior vena cava
- Does the tumor have the unreconstructible SMV/portal occlusion
- Does the tumor have aortic invasion or encasement

### 6.3.4 Baseline Tumor Burden

Baseline tumor burden will be characterized by the following variables:

- Size of target lesions
- Presence of non-target lesions
- FDG-PET $SUV_{max}$
- CA19-9

### 6.3.5 Medical History

Medical conditions, including allergies and surgeries, are coded in system organ class (SOC) and preferred term (PT) using MedDRA.

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 based on the ITT Population.

## 6.4 Prior and Concomitant Medications

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

Prior and concomitant medications, defined below, are summarized by ATC class and preferred term.

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.

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

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

All medications and non-drug therapies are 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 of any study drug to last dose of any study drug
- Number of infusions
- Average dose amount in mg over the entire study period for individual subjects

During the course of 22 weeks of treatment duration (6 treatment cycles, last dose on Day 15 of Cycle 6), subjects in Arm A will receive up to 13 FG-3019 infusions, with 3 infusions administered during the first cycle and 2 during each of the remaining 5 cycles. All subjects will receive up to 18 infusions of gemcitabine and up to 18 infusions of nab-paclitaxel.

FG-3019 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 $m^2$.

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

### 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 the study.

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

Scheduled doses of the study drugs are listed in the table below.

| Day within a Cycle | Number of FG-3019 Doses / Number of Gemcitabine/Nab-paclitaxel Doses | | | | | |
|---|---|---|---|---|---|---|
| | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 |
| 1 | 1/1 | 4/4 | 6/7 | 8/10 | 10/13 | 12/16 |
| 8 | 2/2 | 4/5 | 6/8 | 8/11 | 10/14 | 12/17 |
| 15 | 3/3 | 5/6 | 7/9 | 9/12 | 11/15 | 13/18 |

Compliance will be summarized in the following categories; 100%, 90-99%, 80-89%, and less than 80 percent.

## 6.6 Efficacy Analyses

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

### 6.6.1 Analysis of Eligibility for Surgical Exploration

Surgical eligibility is defined in Sections 4.2.1. Proportion of subjects in the following categories will be summarized by treatment group:

- met the protocol defined criteria with no contraindication,
- met the protocol defined criteria with contraindication,
- did not meet the protocol defined criteria

Exact 95% CIs for the point estimates as well as the treatment different 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 baseline factors listed in Section 5.5.

### 6.6.2 Analysis of Resection Outcome

The proportion of subjects achieving different resection outcomes will be summarized descriptively. The CMH test controlling for the baseline factors listed in Section 5.5 is used to compare the two treatment arms.

### 6.6.3 Analysis of Time-to-Event Parameters

Time-to-event endpoints include overall survival (OS), progression free survival (PFS), and event free survival (EFS). Comparisons between the two treatment arms will be characterized using the following statistics:

- Hazard ratio (HR) and it's 95% CI
- Median time-to-event and its 95% CI
- Proportions of subjects with 1-year, {2-year, and 3-year} event-free and the corresponding 95% CIs
- Restricted mean survival time (RMST) over time

The Cox regression model, with adjustment of the baseline factors listed in Section 5.5, will be used to compare the 2 treatment arms and to estimate the hazard ratio and the 95% CI.

```
proc phreg;
  model  {time-to-event variable} * censor (1) = ARM baseline-factor;
  hazardratio ARM /CL = PL;
run;
```

Baseline factors are included in the model one at the time. Adjustment of multiple factors may be explored.

Median time-to-event and its 95% CI will be estimated by Kaplan-Meier method using SAS PROC LIFETEST procedure. 95% CI for the event-free rates will be estimated using the Clopper-Pearson method by PROC FREQ with option BINOMIAL (EXACT).

```
proc lifetest;
  time  {time-to-event variable} * censor (1);
  strata  ARM;
run;
```

Comparison between resected versus non resected subjects, with resection status being used as time dependent covariate, will be performed.

Since the proportional hazards assumption may be violated in EFS, additional analysis using the accelerated failure time model will be performed.

### 6.6.4 Analysis of RECIST Response and Change in Tumor Measurements

The best RECIST response defined in Section 4.2.5 will be compared between the two arms using the exact procedures described in Section 6.6.1. RECIST response by visit will be summarized descriptively.

Absolute change and percent change from baseline in the sum of the longest diameters (LD) of the target lesions are summarized by visit and treatment arm. Percent change from baseline within each arm is evaluated using one-sample Wilcoxon signed-rank test. Comparison between the two treatment arms is based on two-sample Wilcoxon rank-sum test. Nonparametric methods are used due to the skewed distribution of the percent change data.

Tumor reduction ≥30% is also summarized by visit and treatment arm. Comparison between treatment arms will be based on Fisher's exact test.

Status of non-target lesions will be summarized by visit.

### 6.6.5 Analysis of Change in CA19-9 and CA19-9 Response

CA 19-9 responses defined in Section 4.2.6 will be summarized descriptive by visit. Comparison between the two arms in the dichotomous parameters will be based on the exact procedures described in Section 6.6.1. Ordered categories will be compared using chi-square test with ordinal outcome.

Change from baseline will be 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. Nonparametric methods are used due to the skewed distribution of the percent change data.

### 6.6.6 Summary of Change in FDG-PET SUVmax and PET Response

PET responses defined in Section 4.2.7 will be summarized descriptive. Comparison between the two arms in the dichotomous parameters will be based on the exact procedures described in Section 6.6.1.

Change from baseline will be 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. Nonparametric methods are used due to the skewed distribution of the percent change data.

### 6.6.7 ECOG

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

### 6.6.8 Disease Stage

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

### 6.6.9 NCCN Resectability

NCCN resectability condition will be summarized in shift tables of EOT versus Screening.

## 6.7 Exploratory Analyses

As an exploration, event free survival will be analyzed using Cox regression model with change from baseline in CA19.9 as time-dependent covariate. Further exploratory analyses will be documented in a separate analysis plan.

## 6.8 Safety Analyses

Safety analyses will include summary of adverse events, 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.

### 6.8.1 Adverse Events

All reported AEs will be presented in listings. Treatment emergent adverse events (TEAEs), as defined in Section 4.2.10, will be summarized by treatment arm, system organ class (SOC) and preferred term (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 adverse events within a SOC is only counted once in this SOC. Similarly, a subject with multiple adverse events within a PT is only counted once in this PT.

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

- SAEs (listing) for both arms and relationship to the IP (whether related or unrelated)
- TEAEs and fatal SAEs (tables)
- TEAEs and fatal SAEs
- TEAEs leading to study or treatment discontinuation
- TEAE with incidence >= 10% in the overall safety population
- TEAE occurred in 2 or more subjects in either arm
- AEs with severity grade >= 3
- AEs with severity grade >=3 that are possibly related to FG-3019 (as assessed by investigators)

### 6.8.2 Mortality

Deaths as an outcome of TESAEs will be summarized as a safety measure. Long-term all-cause mortality events are captured as an efficacy measure and will be summarized in the efficacy section.

### 6.8.3 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 potentially clinically significant. These results are presented in a data listing.

Shift tables 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 based on investigators' assessments are also presented.

An eDISH (evaluation of drug induce severe hepatotoxicity) analytical graph, which is a scatter plot of maximum observed total bilirubin versus maximum observed ALT or AST, will be generated to identify cases in Hy's law range.

Box-plots for selected lab tests by visit are presented to evaluate trend.

Lab data 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 potentially clinically significant abnormal changes.

### 6.8.4 Vital Signs

Vital sign observed values and change from baseline are summarized descriptively by visit and by treatment arm.

In addition, potentially clinically significant changes from baseline, which are defined in Section 4.2.13, are tabulated for each visit.

All measurements and change from baseline are presented in data listings. Potential clinically significant changes from baseline are flagged.

Box-plots of vital sign measurements by visit, pre- and post-infusion separately, are presented to evaluate trend.

### 6.8.5 Physical Examinations

Findings from physical examinations will be summarized in shift tables that include cross-tabulation of 'Normal', 'Abnormal NCS', 'Abnormal CS' at each visit versus baseline. The number and percent of subjects with "Normal", "Abnormal", "Not Done", and "Missing" physical examination results are summarized by body system, cohort, and visit. Shift table of changes from baseline will also be summarized by visit.

The data listing includes abnormal findings.

### 6.8.6 ECG Data

ECG findings will be summarized in shift tables that include cross-tabulation of investigator assessments of 'Normal', 'Abnormal NCS', 'Abnormal CS' at EOT versus Screening.

Detailed findings are presented in the data listing.

### 6.8.7 Surgical Safety

Surgical safety measures described in Section 4.2.11 will be summarized descriptively for subjects who have undergone a R0 or R1 resection. Subjects who have undergone surgical exploration but resection was not attempted will be summarized separately.

## 6.9 Analysis of PK, CTGF, and HAHA

### 6.9.1 Summary of PK Data

PK concentration level will be summarized descriptively by time point. It will be plotted over time for each subject.

### 6.9.2 Summary of CTGF Data

CTGF – N+W and CTGF – W are summarized descriptive by scheduled time point.

### 6.9.3 Summary of HAHA Data

Number of subjects with reactive and specific antibodies to FG-3019 is summarized. HAHA data are also presented in a data listing.

### 6.9.4 Summary of Biomarker Data

Biomarker data will be presented in a separate report.

# 7 VALIDATION AND QUALITY ASSURANCE

All datasets (SDTM, ADaM), tables, listings, figures are programmed by two programmers independently. The results must be 100% match.

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

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

# 8 REFERENCES

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Ballehaninna UK, Chamberlain RS, The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. Journal of Gastrointestinal Oncology, Vol 3, No 2 June 2012

NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010)

New England Journal of Medicine 2004; 351: 1548-63, for lab value reference range

# APPENDIX I GENERAL SPECIFICATIONS FOR SUBMISSION DATA

## 1. Study Data Tabulation Model (SDTM)

Raw datasets will be mapped to SDTM datasets following variable names and attributes specified in the SDTM Implementation Guide (version 3.2 and subsequent update). Data coding is also mapped to the SDTM controlled terminology. OpenCDISC module will be run to confirm compliance to the SDTM guidelines. Deviations from the guidelines will be documented. Variables that exist in different source datasets, such as lab data collection date, will be consolidated and included once in the SDTM datasets. Unscheduled 'Not Done' records are excluded from the SDTM datasets. Detailed mapping specifications are documented in Define.xml and annotation CRFs.

CRF variables that are not included in the SDTM datasets will be marked as 'Not Submitted', since the SDTM datasets will be submitted as the raw datasets and the raw datasets that match the CRFs will not be submitted to regulatory agencies.

The SDTM datasets are the basis to derive the analysis datasets. Summary tables and listings that do not require complex derived variables may be generated directly from SDTM datasets.

Table A contains a list of SDTM datasets to be created for the study. The corresponding supplemental datasets are not included. This set of SDTM datasets includes only data for the Randomized Treatment Period as described in Section 1.

**Table A. Study Data Tabulation Model Datasets (SDTM)**

| SDTM Domain | SDTM Domain Description | SDTM Domain Structure | General Observation Class | Source Data Used | Key Variables |
|---|---|---|---|---|---|
| AE | Adverse Events | One record per adverse event per subject | Events | AE | STUDYID, USUBJID, AESTDTC, AEENDTC, AEDECOD, AESPID |
| CM | Concomitant Medications | One record per recorded medication occurrence per subject | Interventions | CM | STUDYID, USUBJID, CMCAT, CMTRT, CMDECOD, CMSTDTC, CMENDTC, CMSPID |
| DD | Death Details | One record per subject | Findings | DTH | STUDYID, USUBJID, DDTESTCD, DDDTC |
| DM | Demographics | One record per subject | Special Purpose Domains | DM, EX, ICF, DTH, SITE_INV | STUDYID, USUBJID |
| DS | Disposition | One record per disposition status or protocol milestone per subject | Events | DS, ICF, DTH, EX | STUDYID, USUBJID, DSSTDTC, DSDECOD, DSSPID |

| | | | | | |
|---|---|---|---|---|---|
| EC | Exposure as Collected | One record per protocol-specified study treatment per collected-dosing interval per subject | Interventions | EX | STUDYID, USUBJID, VISITNUM, ECTRT, ECSCAT, ECSTDTC, ECENDTC |
| EG | ECG Test Results | One record per ECG observation per visit per subject | Findings | EG | STUDYID, USUBJID, EGTESTCD, VISITNUM, EGDTC |
| EX | Exposure | One record per constant dosing interval per subject | Interventions | EX | STUDYID, USUBJID, VISITNUM, EXTRT, EXSCAT, EXSTDTC, EXENDTC |
| FA | Findings About Events or Interventions | One record per finding, per object, per time point, per visit per subject | Findings | DISE | STUDYID, USUBJID, VISITNUM, FATESTCD, FAOBJ |
| IE | Inclusion/Exclusion Criteria Not Met | One record per inclusion/exclusion criterion not met per subject | Findings | IE | STUDYID, USUBJID, IETESTCD |
| LB | Laboratory Test Results | One record per lab test per visit per subject | Findings | LBC, LBH, LBPREG | STUDYID, USUBJID, VISITNUM, LBCAT, LBTESTCD, LBDTC, LBNAM |
| MH | Medical History | One record per medical history event per subject | Events | MH | STUDYID, USUBJID, MHSPID, MHTERM |
| PC | Pharmacokinetic Concentrations | One record per sample characteristic or time-point concentration per reference time point or per analyte per subject | Findings | CA, PKCTGF, PKFG, PKPAX, PKPRO | STUDYID, USUBJID, PCTESTCD, VISITNUM, PCTPTNUM |
| PE | Physical Examination | One record per body system or abnormality per visit per subject | Findings | PE | STUDYID, USUBJID, PETESTCD, VISITNUM |

| | | | | | |
|---|---|---|---|---|---|
| PP | Pharmacokinetic Parameters | One record per PK parameter per time-concentration profile per modeling method per subject | Findings | eDT | STUDYID, USUBJID, PPTESTCD, PPCAT, PPRFTDTC |
| PR | Procedures | One record per recorded procedure per occurrence per subject | Interventions | NDT, PCASUR, PCARAD, DISE | STUDYID, USUBJID, PRCAT, PRSPID, PRSTDTC, PRENDTC |
| QS | Questionnaires | One record per questionnaire per question per time point per visit per subject | Findings | ECOG, KARNOF | STUDYID, USUBJID, VISITNUM, QSCAT, QSTESTCD |
| RS | Disease Response | One record per response assessment per visit per subject per assessor | Findings | RECIST, DISPROG | STUDYID, USUBJID, RSGRPID, VISITNUM, RSTESTCD |
| SC | Subject Characteristics | One record per characteristic per subject | Findings | DM | STUDYID, USUBJID |
| SE | Subject Elements | One record per actual Element per subject | Special Purpose Domains | SDTM.DM, SDTM.SV, SDTM.DS, SDTM.EX, SDTM.SS | STUDYID, USUBJID, TAETORD, SESTDTC |
| SS | Subject Status | One record per finding per visit per subject | Findings | EOS, LTFU | STUDYID, USUBJID, SSTESTCD, VISITNUM, SSDTC |
| SU | Substance Use | One record per substance type per reported occurrence per subject | Intervention | SUTOB | STUDYID, USUBJID, SUTRT |
| SV | Subject Visits | One record per actual visit per subject | Special Purpose Domains | All datasets which include VISIT information | STUDYID, USUBJID, VISITNUM |
| TA | Trial Arms | One record per planned Element per Arm | Trial Design | N/A | STUDYID, ARMCD, TAETORD |
| TD | Trial Disease Assessments | One record per planned constant assessment period | Trial Design | N/A | STUDYID, TDORDER |
| TE | Trial Elements | One record per planned Element | Trial Design | N/A | STUDYID, ETCD |
| TI | Trial Inclusion/Exclusion Criteria | One record per I/E criterion | Trial Design | N/A | STUDYID, TIVERS, IETESTCD |

| | | | | | |
|---|---|---|---|---|---|
| TR | Tumor Results | One record per tumor measurement/assessment per visit per subject per assessor | Findings | TRNTL, TRTL, PETRES, PETRESUV | STUDYID, USUBJID, TRGRPID, VISITNUM, TRLNKGRP, TRTESTCD, TRLNKID |
| TS | Trial Summary | One record per trial summary parameter per value | Trial Design | N/A | STUDYID, TSPARMCD, TSSEQ |
| TU | Tumor Identification | One record per identified tumor per subject per assessor | Findings | TRNTL, TRTL, PETRES, PETRESUV | STUDYID, USUBJID, VISITNUM, TUTESTCD, TULNKID |
| TV | Trial Visits | One record per planned Visit per Arm | Trial Design | N/A | STUDYID, VISITNUM, ARMCD |
| VS | Vital Signs | One record per vital sign measurement per time point per visit per subject | Findings | VS | STUDYID, USUBJID, VISITNUM, VSTESTCD |
| YH | Human Anti-human Antibody Assessment | One record per test per visit per subject | Findings | HAHA, eDT HAHA external data | STUDYID, USUBJID, YHTESTCD, VISITNUM, YHDTC, YHGRPID |
| ZA | Surgical Eligibility Assessment | One record per test per subject | Findings | SA | STUDYID, USUBJID, ZATESTCD, VISITNUM, ZAORRES |
| ZC | Cancer Pathology | One record per test per visit per subject | Findings | CANPATH | STUDYID, USUBJID, ZCTESTCD, VISITNUM |
| ZF | Surgical (post-operative) Follow-up | One record per test per visit per subject | Findings | SURFU | STUDYID, USUBJID, ZFGRPID, ZFCAT, ZFTESTCD, VISITNUM |
| ZO | Surgery/Surgical Outcomes | One record per test per visit per subject | Findings | SURO | STUDYID, USUBJID, VISITNUM, ZOCAT, ZOTESTCD |

## 2 Analysis Data Model (ADaM)

The ADaM datasets are created based on the SDTM datasets following the ADaM Implementation Guide (version 1.0 and subsequent update). They include derived parameters and flags that are needed to generate tables/listings/figures. ADSL and ADAE are created using the specifications provided in the ADaMIG. Study endpoints are included in analysis files in ADaM Basic Data Structure (BDS). Horizontal analysis files are created for analyses on relationship of multiple endpoints. Variable names and labels of the horizontal files are from PARAMCD and PARAM of the corresponding BDS files. Detail derivations of each variable in the ADaM datasets are documented in the Metadata.

**Table B. Analysis Data Model (ADaM)**

| Dataset | Description | Structure | Keys |
|---|---|---|---|
| ADSL | Subject-Level Analysis Dataset | One record per subject | STUDYID, SUBJID |
| ADAE | Analysis Dataset Adverse Events | One record per subject per adverse event per start date | STUDYID, USUBJID, AESTDTC, AEENDTC, AEDECOD, AESPID |
| ADCM | Analysis Dataset Concomitant Medications | One record per subject per recorded medication occurrence | STUDYID, USUBJID, CMCAT, CMTRT, CMDECOD, CMSTDTC, CMENDTC, CMSPID |
| ADDD | Analysis Dataset Death | One record per subject per parameter | STUDYID, USUBJID, PARAMCD |
| ADDISE | Analysis Dataset Disease Stage | One record per subject per parameter per analysis visit | STUDYID, USUBJID, PARAMCD, AVISITN |
| ADEFF | Analysis Dataset Efficacy | One record per subject per parameter per analysis visit per Link ID | STUDYID, USUBJID, PARCAT1, PARAMCD, AVISITN, ADT, VISITNUM, TRLNKID |
| ADEG | Analysis Dataset for ECG Test Results | One record per subject per analysis visit | STUDYID, USUBJID, PARAMCD, AVISITN, ADT |
| ADEX | Analysis Dataset Exposure | One record per subject per parameter per analysis visit | STUDYID, USUBJID, PARAMCD, AVISITN |
| ADLB | Analysis Dataset Laboratory Test Results | One record per subject per category per parameter per analysis visit | STUDYID, USUBJID, PARCAT1, PARAMCD, AVISITN |
| ADMH | Analysis Dataset Medical History | One record per subject per medical history per time interval of medical history | STUDYID, USUBJID, MHSPID, MHTERM |
| ADPE | Analysis Dataset Physical Examination | One record per subject per parameter per analysis visit | STUDYID, USUBJID, AVISITN, PARAMCD |
| ADQS | Analysis Dataset for Questionnaire | One record per subject per category per parameter per analysis visit | STUDYID, USUBJID, PARCAT1, PARAMCD, AVISITN |

| | | | |
|---|---|---|---|
| ADRS | Analysis Dataset Disease Response | One record per subject per parameter per analysis visit | STUDYID, USUBJID, PARAMCD, AVISITN |
| ADSURG | Analysis Dataset Surgical Assessment | One record per subject per category per parameter per analysis visit per analysis value per group ID | STUDYID, USUBJID, PARCAT1, PARAMCD, AVISITN, AVALC, ZFGRPID |
| ADTR | Analysis Dataset Tumor Results | One record per subject per category per parameter per analysis visit per Link ID | STUDYID, USUBJID, PARCAT1, PARAMCD, AVISITN, TRLNKID |
| ADTTE | Analysis Dataset Time-to-Event | One record per subject per parameter | STUDYID, USUBJID, ASEQ, PARAMCD |
| ADVS | Analysis Dataset Vital Signs | One record per subject per parameter per analysis visit | STUDYID, USUBJID, PARAMCD, AVISITN |

# APPENDIX II GENERAL SPECIFICATIONS FOR TABLES, LISTINGS, FIGURES

## 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.

## 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 are presented in listings in format yyyy-mm-dd. For incomplete date, CDISC presentation convension 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.

## 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, eg, all tables, all listings, and all figures, in the order as in the planned TLF in Section 12. 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.

## 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 A.

**Table A. 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 | 0.75” |
| Right | 0.38” |

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.

## 5 Titles and Footnotes

All tables and listings will have a header showing “FibroGen, Inc.”, the protocol number, database cutoff date or ‘Final Database’, 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 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” (right aligned) |
| second title | protocol number + “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. Footnotes will be referenced using numbers in square brackets, starting with [1], followed by [2] etc. |
| ninth footnote | left blank; in case needed may also be used as for explanations. |
| tenth footnote | the program name (left aligned); the date and time in the format ddMMMyyyy hh:mm when the output was created; the version (e.g. draft or final); and the word “Confidential”. |

Footnotes are denoted by [1], [2], and so on.

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

TLF numbers and titles should be inputted from an external file that can be directly copy-and-pasted from the SAP planned TLFs, rather than including in the body of the program. This is to ensure consistency between the SAP and the actual outputs.

Footnotes may be inputted from an external file as well for ease of managing changes.

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.

## 6 Table, Listing, Figure Metadata

The table, listing, and figure (TLF) metadata will include the TLF numbers, titles, analysis populations, program names, 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.

## 7 Significant Digits of Summary Statistics

- All percentages will be rounded to one decimal place and aligned by the decimal place.
- If the count is zero, the percentage will be suppressed and only ‘0’ will be presented.
- Any p-values will be rounded to four decimal places and will be presented as ‘<.0001’ if they are less than 0.0001 after rounding.
- For variables of direct measurements, summary statistics are displayed with the following specifications of decimal places in Table B.

**Table B. 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 a parameter with an overall mean less than 100; otherwise, 1 decimal place may be used. 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.

## 8 Figure Specifications

- In general, figures should include annotation of key summary statistics: n, mean, SD 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 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 |

## APPENDIX III RECIST (1.1) CRITERIA

Below is an outline of the definition of RECIST response categories, extracted from Eisenhauera EA et al. (2009).

| 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 tumour 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). |

| 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 | inevaluable |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

## APPENDIX IV 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<br>T2, N1, M0<br>T3, N1, M0 |
| ***III*** | T4, any N, M0 |
| ***IV*** | Any T, any N, M1 |

## APPENDIX V NEW ENGLAND JOURNAL OF MEDICINE REFERENCE RANGES

The following chemistry and hematology reference ranges are from the New England Journal of Medicine 2004; 351: 1548-63

### Chemistry

| Lab Test | Units | Lower[1] | Upper[1] |
|---|---|---|---|
| Alanine Aminotransferase (ALT) | U/L | 0 | 35 |
| Alkaline Phosphatase (ALP) | U/L | 30 | 120 |
| Aspartate Aminotransferase (AST) | U/L | 0 | 35 |
| Bicarbonate | mmol/L | 21 | 28 |
| Total Bilirubin | µmol/L | 5.1 | 17 |
| Blood Urea Nitrogen | mmol/L | 3.6 | 7.1 |
| Calcium | mmol/L | 2.2 | 2.6 |
| Creatinine | µmol/L | 0 | 133 |
| Glucose | mmol/L | 4.2 | 6.4 |
| Phosphate | mmol/L | 1 | 1.4 |
| Potassium | mmol/L | 3.5 | 5 |
| Sodium | mmol/L | 136 | 145 |

[1] Reference ranges from New England Journal of Medicine 2004; 351: 1548-63

**Hematology**

| Lab Test | Units | Lower[1] | Upper[1] |
|---|---|---|---|
| Erythrocyte MCV | fL | 80 | 100 |
| Erythrocytes (Male) | $10^{12}$/L | 4.5 | 5.9 |
| Erythrocytes (Female) | $10^{12}$/L | 4.0 | 5.2 |
| Hematocrit (Male) | proportion of 1 | 0.41 | 0.53 |
| Hematocrit (Female) | proportion of 1 | 0.36 | 0.46 |
| Hemoglobin (Male) | g/dL | 13.5 | 17.5 |
| Hemoglobin (Female) | g/dL | 12 | 16 |
| Leukocytes | $10^{9}$/L | 4.5 | 11.0 |
| Neutrophils | proportion of 1 | 0.4 | 0.7 |
| Neutrophils | $10^{9}$/L | 1.8 | 7.7 |
| Lymphocytes | proportion of 1 | 0.22 | 0.44 |
| Lymphocytes | $10^{9}$/L | 0.99 | 4.84 |
| Eosinophils | proportion of 1 | 0 | 0.08 |
| Eosinophils | $10^{9}$/L | 0 | 0.88 |
| Platelets | $10^{9}$/L | 150 | 350 |
| ANC | $10^{9}$/L | 1.8 | 7.8 |

[1]Reference ranges from New England Journal of Medicine 2004; 351: 1548-63

## APPENDIX VI CTCAE TOXICITY GRADING FOR LABORATORY TESTS

The following table is extracted from NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010)

### Chemistry

| | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Albumin | Decreased | 3 g/dL – LLN | 2 - <3 g/dL | <2 g/dL | |
| Alkaline phosphatase (ALP) | | ULN – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 20.0 x ULN | > 20.0 x ULN |
| ALT | | ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| AST | | ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| Total bilirubin | | ULN – 1.5 x ULN | >1.5 – 3.0 x ULN | >3.0 – 10.0 x ULN | >10.0 x ULN |
| Calcium (Corrected) | Decreased | 8.0 mg/dL – LLN | 7.0 - <8.0 mg/dL | 6.0 - <7.0 mg/dL | <6.0 mg/dL |
| | | ULN – 11.5 mg/dL | >11.5 – 12.5 mg/dL | >12.5 – 13.5 mg/dL | >13.5 mg/dL |
| GGT | | ULN – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 20.0 x ULN | > 20.0 x ULN |
| Glucose (Random) | Decreased | 55 mg/dL – LLN | 40 - <55 mg/dL | 30 - <40 mg/dL | <30 mg/dL |
| Glucose (Fasting) | | ULN – 160 mg/dL | >160 – 250 mg/dL | >250 – 500 mg/dL | > 500 mg/dL |
| Phosphorous | Decreased | 2.5 -<LLN mg/dL | 2.0 -<2.5 mg/dL | 1.0 - <2.0 mg/dL | <1.0 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 |
| | | ULN – 5.5 mmol/L | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L | >7.0 mmol/L |
| Sodium | Decreased | 130 mmol/L – LLN | None | 120 - <130 mmol/L | <120 mmol/L |
| | | ULN – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L | >160 mmol/L |
| Magnesium | Decreased | 1.2 mg/dL – LLN | 0.9 - <1.2 mg/dL | 0.7 - <0.9 mg/dL | <0.7 mg/dL |
| | | ULN – 3.0 mg/dL | None | >3.0 – 8.0 mg/dL | >8.0 mg/dL |

Serum Hematology

| | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Uric acid | | ULN – 10 mg/dL[2] | None | ULN – 10 mg/dL[3] | >10 mg/dL |
| Creatinine<br>Enzymatic | | >1 – 1.5 x baseline[4]<br>ULN – 1.5 x ULN | >1.5 – 3.0 x baseline[4]<br>>1.5 – 3.0 x ULN | >3.0 x baseline[4]<br>>3.0 – 6.0 x ULN | >6.0 x ULN |
| Triglycerides | | 150 – 300 mg/dL | >300 – 500 mg/dL | >500 – 1,000 mg/dL | >1,000 mg/dL |
| Hgb | Decreased | 10.0 g/dL – LLN | 8.0 - <10.0 g/dL | <8.0 g/dL | |
| | | >0 – 2 g/dL<br>(+ ULN/Baseline)[5] | >2 – 4 g/dL<br>(+ ULN/Baseline)[5] | >4 g/dL<br>(+ ULN/Baseline)[5] | |
| 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$^3$ |
| | | None | None | >100,000 /mm$^3$ | |
| aPTT | | ULN – 1.5 x ULN | >1.5 – 2.5 x ULN | >2.5 x ULN | |
| Lymphocytes | Decreased | 800 /mm3 – LLN | 500 - <800 /mm$^3$ | 200 - <500 /mm$^3$ | <200 /mm$^3$ |
| | | None | >4,000 – 20,000 /mm$^3$ | >20,000 /mm$^3$ | |
| Neutrophils | Decreased | 1,500 /mm3 – 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] without physiologic consequences

[3] with physiologic consequences

[4] Baseline is used if it is above ULN

[5] Increase from ULN/baseline: if baseline is above ULN, the increase should be above the baseline; otherwise, the increase should be above ULN.

## APPENDIX VII NCCN VERSION 2. 2014 PANCREATIC CANCER RESECTABILITY CRITERIA

The following is extracted from 'NCCN Guidelines Version 2.2014, Pancreatic Adenocarcinoma', page 19.

Tumors considered to be unresectable demonstrate the following:

- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic or inferior vena cava (IVC) invasion or encasement
- BODY
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable

# APPENDIX VIII 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’s 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 hasn't 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 can't be removed entirely by surgery.

**Locally advanced:** If the cancer has not yet spread to distant organs but it still can't be removed completely with surgery, it is called *locally advanced.* Often the reason the cancer can't 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 can't 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.

# APPENDIX IX STANDARDIZED MEDDRA QUERIES (SMQ) FOR ANAPHYLACTIC REACTION AND HYPERSENSITIVITY

## SMQ for Anaphylactic Reaction

| Name | Code | Level |
|---|---|---|
| Anaphylactic reaction | 10002198 | PT |
| Anaphylactic shock | 10002199 | PT |
| Anaphylactic transfusion reaction | 10067113 | PT |
| Anaphylactoid reaction | 10002216 | PT |
| Anaphylactoid shock | 10063119 | PT |
| Circulatory collapse | 10009192 | PT |
| Dialysis membrane reaction | 10076665 | PT |
| Kounis syndrome | 10069167 | PT |
| Shock | 10040560 | PT |
| Shock symptom | 10040581 | PT |
| Type I hypersensitivity | 10045240 | PT |
| Acute respiratory failure | 10001053 | PT |
| Asthma | 10003553 | PT |
| Bronchial oedema | 10056695 | PT |
| Bronchospasm | 10006482 | PT |
| Cardio-respiratory distress | 10049874 | PT |
| Chest discomfort | 10008469 | PT |
| Choking | 10008589 | PT |
| Choking sensation | 10008590 | PT |
| Circumoral oedema | 10052250 | PT |
| Cough | 10011224 | PT |
| Cyanosis | 10011703 | PT |
| Dyspnoea | 10013968 | PT |
| Hyperventilation | 10020910 | PT |
| Irregular breathing | 10076213 | PT |
| Laryngeal dyspnoea | 10052390 | PT |
| Laryngeal oedema | 10023845 | PT |
| Laryngospasm | 10023891 | PT |
| Laryngotracheal oedema | 10023893 | PT |
| Mouth swelling | 10075203 | PT |
| Nasal obstruction | 10028748 | PT |
| Oedema mouth | 10030110 | PT |

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|---|---|---|
| Oropharyngeal oedema | 10078783 | PT |
| Oropharyngeal spasm | 10031111 | PT |
| Oropharyngeal swelling | 10031118 | PT |
| Pharyngeal oedema | 10034829 | PT |
| Respiratory arrest | 10038669 | PT |
| Respiratory distress | 10038687 | PT |
| Respiratory failure | 10038695 | PT |
| Reversible airways obstruction | 10062109 | PT |
| Sensation of foreign body | 10061549 | PT |
| Sneezing | 10041232 | PT |
| Stridor | 10042241 | PT |
| Swollen tongue | 10042727 | PT |
| Tachypnoea | 10043089 | PT |
| Throat tightness | 10043528 | PT |
| Tongue oedema | 10043967 | PT |
| Tracheal obstruction | 10044291 | PT |
| Tracheal oedema | 10044296 | PT |
| Upper airway obstruction | 10067775 | PT |
| Wheezing | 10047924 | PT |
| Allergic oedema | 10060934 | PT |
| Angioedema | 10002424 | PT |
| Erythema | 10015150 | PT |
| Eye oedema | 10052139 | PT |
| Eye pruritus | 10052140 | PT |
| Eye swelling | 10015967 | PT |
| Eyelid oedema | 10015993 | PT |
| Face oedema | 10016029 | PT |
| Flushing | 10016825 | PT |
| Generalised erythema | 10051576 | PT |
| Injection site urticaria | 10022107 | PT |
| Lip oedema | 10024558 | PT |
| Lip swelling | 10024570 | PT |
| Nodular rash | 10075807 | PT |
| Ocular hyperaemia | 10030041 | PT |
| Oedema | 10030095 | PT |

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|---|---|---|
| Periorbital oedema | 10034545 | PT |
| Pruritus | 10037087 | PT |
| Pruritus allergic | 10063438 | PT |
| Pruritus generalised | 10052576 | PT |
| Rash | 10037844 | PT |
| Rash erythematous | 10037855 | PT |
| Rash generalised | 10037858 | PT |
| Rash pruritic | 10037884 | PT |
| Skin swelling | 10053262 | PT |
| Swelling | 10042674 | PT |
| Swelling face | 10042682 | PT |
| Urticaria | 10046735 | PT |
| Urticaria papular | 10046750 | PT |
| Blood pressure decreased | 10005734 | PT |
| Blood pressure diastolic decreased | 10005737 | PT |
| Blood pressure systolic decreased | 10005758 | PT |
| Cardiac arrest | 10007515 | PT |
| Cardio-respiratory arrest | 10007617 | PT |
| Cardiovascular insufficiency | 10065929 | PT |
| Diastolic hypotension | 10066077 | PT |
| Hypotension | 10021097 | PT |

## SMQ for Hypersensitivity

| Name | Code | Level |
|---|---|---|
| Acute generalised exanthematous pustulosis | 10048799 | PT |
| Administration site dermatitis | 10075096 | PT |
| Administration site eczema | 10075099 | PT |
| Administration site hypersensitivity | 10075102 | PT |
| Administration site rash | 10071156 | PT |
| Administration site recall reaction | 10075964 | PT |
| Administration site urticaria | 10075109 | PT |
| Administration site vasculitis | 10075969 | PT |
| Allergic bronchitis | 10052613 | PT |
| Allergic colitis | 10059447 | PT |
| Allergic cough | 10053779 | PT |

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|---|---|---|
| Allergic cystitis | 10051394 | PT |
| Allergic eosinophilia | 10075185 | PT |
| Allergic gastroenteritis | 10075308 | PT |
| Allergic hepatitis | 10071198 | PT |
| Allergic keratitis | 10057380 | PT |
| Allergic myocarditis | 10001715 | PT |
| Allergic oedema | 10060934 | PT |
| Allergic otitis externa | 10075072 | PT |
| Allergic otitis media | 10061557 | PT |
| Allergic pharyngitis | 10050639 | PT |
| Allergic reaction to excipient | 10078853 | PT |
| Allergic respiratory disease | 10063532 | PT |
| Allergic respiratory symptom | 10063527 | PT |
| Allergic sinusitis | 10049153 | PT |
| Allergic transfusion reaction | 10066173 | PT |
| Allergy alert test positive | 10075479 | PT |
| Allergy test positive | 10056352 | PT |
| Allergy to immunoglobulin therapy | 10074079 | PT |
| Allergy to surgical sutures | 10077279 | PT |
| Allergy to vaccine | 10055048 | PT |
| Alveolitis allergic | 10001890 | PT |
| Anaphylactic reaction | 10002198 | PT |
| Anaphylactic shock | 10002199 | PT |
| Anaphylactic transfusion reaction | 10067113 | PT |
| Anaphylactoid reaction | 10002216 | PT |
| Anaphylactoid shock | 10063119 | PT |
| Anaphylaxis treatment | 10002222 | PT |
| Angioedema | 10002424 | PT |
| Antiallergic therapy | 10064059 | PT |
| Antiendomysial antibody positive | 10065514 | PT |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | 10050894 | PT |
| Application site dermatitis | 10003036 | PT |
| Application site eczema | 10050099 | PT |
| Application site hypersensitivity | 10063683 | PT |
| Application site rash | 10003054 | PT |

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|---|---|---|
| Application site recall reaction | 10076024 | PT |
| Application site urticaria | 10050104 | PT |
| Application site vasculitis | 10076027 | PT |
| Arthritis allergic | 10061430 | PT |
| Aspirin-exacerbated respiratory disease | 10075084 | PT |
| Atopy | 10003645 | PT |
| Blepharitis allergic | 10005149 | PT |
| Blood immunoglobulin E abnormal | 10005589 | PT |
| Blood immunoglobulin E increased | 10005591 | PT |
| Bromoderma | 10006404 | PT |
| Bronchospasm | 10006482 | PT |
| Catheter site dermatitis | 10073992 | PT |
| Catheter site eczema | 10073995 | PT |
| Catheter site hypersensitivity | 10073998 | PT |
| Catheter site rash | 10052271 | PT |
| Catheter site urticaria | 10052272 | PT |
| Catheter site vasculitis | 10074014 | PT |
| Chronic eosinophilic rhinosinusitis | 10071399 | PT |
| Chronic hyperplastic eosinophilic sinusitis | 10071380 | PT |
| Circulatory collapse | 10009192 | PT |
| Circumoral oedema | 10052250 | PT |
| Conjunctival oedema | 10010726 | PT |
| Conjunctivitis allergic | 10010744 | PT |
| Contact stomatitis | 10067510 | PT |
| Contrast media allergy | 10066973 | PT |
| Contrast media reaction | 10010836 | PT |
| Corneal oedema | 10011033 | PT |
| Cutaneous vasculitis | 10011686 | PT |
| Dennie-Morgan fold | 10062918 | PT |
| Dermatitis | 10012431 | PT |
| Dermatitis acneiform | 10012432 | PT |
| Dermatitis allergic | 10012434 | PT |
| Dermatitis atopic | 10012438 | PT |
| Dermatitis bullous | 10012441 | PT |
| Dermatitis contact | 10012442 | PT |

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|---|---|---|
| Dermatitis exfoliative | 10012455 | PT |
| Dermatitis exfoliative generalised | 10012456 | PT |
| Dermatitis herpetiformis | 10012468 | PT |
| Dermatitis infected | 10012470 | PT |
| Dermatitis psoriasiform | 10058675 | PT |
| Device allergy | 10072867 | PT |
| Dialysis membrane reaction | 10076665 | PT |
| Distributive shock | 10070559 | PT |
| Documented hypersensitivity to administered product | 10076470 | PT |
| Drug cross-reactivity | 10076743 | PT |
| Drug eruption | 10013687 | PT |
| Drug hypersensitivity | 10013700 | PT |
| Drug provocation test | 10074350 | PT |
| Drug reaction with eosinophilia and systemic symptoms | 10073508 | PT |
| Eczema | 10014184 | PT |
| Eczema infantile | 10014198 | PT |
| Eczema nummular | 10014201 | PT |
| Eczema vaccinatum | 10066042 | PT |
| Eczema vesicular | 10058681 | PT |
| Eczema weeping | 10055182 | PT |
| Encephalitis allergic | 10056387 | PT |
| Encephalopathy allergic | 10014627 | PT |
| Eosinophilic granulomatosis with polyangiitis | 10078117 | PT |
| Epidermal necrosis | 10059284 | PT |
| Epidermolysis | 10053177 | PT |
| Epidermolysis bullosa | 10014989 | PT |
| Epiglottic oedema | 10015029 | PT |
| Erythema multiforme | 10015218 | PT |
| Erythema nodosum | 10015226 | PT |
| Exfoliative rash | 10064579 | PT |
| Eye allergy | 10015907 | PT |
| Eye oedema | 10052139 | PT |
| Eye swelling | 10015967 | PT |
| Eyelid oedema | 10015993 | PT |
| Face oedema | 10016029 | PT |

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|---|---|---|
| Fixed eruption | 10016741 | PT |
| Giant papillary conjunctivitis | 10018258 | PT |
| Gingival oedema | 10049305 | PT |
| Gingival swelling | 10018291 | PT |
| Gleich's syndrome | 10066837 | PT |
| Haemorrhagic urticaria | 10059499 | PT |
| Hand dermatitis | 10058898 | PT |
| Henoch-Schonlein purpura | 10019617 | PT |
| Henoch-Schonlein purpura nephritis | 10069440 | PT |
| Heparin-induced thrombocytopenia | 10062506 | PT |
| Hereditary angioedema | 10019860 | PT |
| Hypersensitivity | 10020751 | PT |
| Hypersensitivity vasculitis | 10020764 | PT |
| Idiopathic urticaria | 10021247 | PT |
| Immediate post-injection reaction | 10067142 | PT |
| Immune thrombocytopenic purpura | 10074667 | PT |
| Immune tolerance induction | 10070581 | PT |
| Immune-mediated adverse reaction | 10077665 | PT |
| Implant site dermatitis | 10063855 | PT |
| Implant site hypersensitivity | 10063858 | PT |
| Implant site rash | 10063786 | PT |
| Implant site urticaria | 10063787 | PT |
| Incision site dermatitis | 10073168 | PT |
| Incision site rash | 10073411 | PT |
| Infusion site dermatitis | 10065458 | PT |
| Infusion site eczema | 10074850 | PT |
| Infusion site hypersensitivity | 10065471 | PT |
| Infusion site rash | 10059830 | PT |
| Infusion site recall reaction | 10076085 | PT |
| Infusion site urticaria | 10065490 | PT |
| Infusion site vasculitis | 10074851 | PT |
| Injection site dermatitis | 10022056 | PT |
| Injection site eczema | 10066221 | PT |
| Injection site hypersensitivity | 10022071 | PT |
| Injection site rash | 10022094 | PT |

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|---|---|---|
| Injection site recall reaction | 10066797 | PT |
| Injection site urticaria | 10022107 | PT |
| Injection site vasculitis | 10067995 | PT |
| Instillation site hypersensitivity | 10073612 | PT |
| Instillation site rash | 10073622 | PT |
| Instillation site urticaria | 10073627 | PT |
| Interstitial granulomatous dermatitis | 10067972 | PT |
| Intestinal angioedema | 10076229 | PT |
| Iodine allergy | 10052098 | PT |
| Kaposi's varicelliform eruption | 10051891 | PT |
| Kounis syndrome | 10069167 | PT |
| Laryngeal oedema | 10023845 | PT |
| Laryngitis allergic | 10064866 | PT |
| Laryngospasm | 10023891 | PT |
| Laryngotracheal oedema | 10023893 | PT |
| Limbal swelling | 10070492 | PT |
| Lip oedema | 10024558 | PT |
| Lip swelling | 10024570 | PT |
| Mast cell degranulation present | 10076606 | PT |
| Medical device site dermatitis | 10075572 | PT |
| Medical device site eczema | 10075575 | PT |
| Medical device site hypersensitivity | 10075579 | PT |
| Medical device site rash | 10075585 | PT |
| Medical device site recall reaction | 10076140 | PT |
| Medical device site urticaria | 10075588 | PT |
| Mouth swelling | 10075203 | PT |
| Mucocutaneous rash | 10056671 | PT |
| Multiple allergies | 10028164 | PT |
| Nephritis allergic | 10029120 | PT |
| Nikolsky's sign | 10029415 | PT |
| Nodular rash | 10075807 | PT |
| Oculomucocutaneous syndrome | 10030081 | PT |
| Oculorespiratory syndrome | 10067317 | PT |
| Oedema mouth | 10030110 | PT |
| Oral allergy syndrome | 10068355 | PT |

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|---|---|---|
| Oropharyngeal blistering | 10067950 | PT |
| Oropharyngeal oedema | 10078783 | PT |
| Oropharyngeal spasm | 10031111 | PT |
| Oropharyngeal swelling | 10031118 | PT |
| Palatal oedema | 10056998 | PT |
| Palatal swelling | 10074403 | PT |
| Palisaded neutrophilic granulomatous dermatitis | 10068809 | PT |
| Palpable purpura | 10056872 | PT |
| Pathergy reaction | 10074332 | PT |
| Periorbital oedema | 10034545 | PT |
| Pharyngeal oedema | 10034829 | PT |
| Pruritus allergic | 10063438 | PT |
| Radioallergosorbent test positive | 10037789 | PT |
| Rash | 10037844 | PT |
| Rash erythematous | 10037855 | PT |
| Rash follicular | 10037857 | PT |
| Rash generalised | 10037858 | PT |
| Rash macular | 10037867 | PT |
| Rash maculo-papular | 10037868 | PT |
| Rash maculovesicular | 10050004 | PT |
| Rash morbilliform | 10037870 | PT |
| Rash neonatal | 10037871 | PT |
| Rash papulosquamous | 10037879 | PT |
| Rash pruritic | 10037884 | PT |
| Rash pustular | 10037888 | PT |
| Rash rubelliform | 10057984 | PT |
| Rash scarlatiniform | 10037890 | PT |
| Rash vesicular | 10037898 | PT |
| Reaction to azo-dyes | 10037973 | PT |
| Reaction to colouring | 10037974 | PT |
| Reaction to drug excipients | 10064787 | PT |
| Reaction to preservatives | 10064788 | PT |
| Red man syndrome | 10038192 | PT |
| Rhinitis allergic | 10039085 | PT |
| Scleral oedema | 10057431 | PT |

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|---|---|---|
| Scleritis allergic | 10051126 | PT |
| Scrotal oedema | 10039755 | PT |
| Serum sickness | 10040400 | PT |
| Serum sickness-like reaction | 10040402 | PT |
| Shock | 10040560 | PT |
| Shock symptom | 10040581 | PT |
| Skin necrosis | 10040893 | PT |
| Skin reaction | 10040914 | PT |
| Skin test positive | 10040934 | PT |
| Solar urticaria | 10041307 | PT |
| Solvent sensitivity | 10041316 | PT |
| Stevens-Johnson syndrome | 10042033 | PT |
| Stoma site hypersensitivity | 10074509 | PT |
| Stoma site rash | 10059071 | PT |
| Swelling face | 10042682 | PT |
| Swollen tongue | 10042727 | PT |
| Symmetrical drug-related intertriginous and flexural exanthema | 10078325 | PT |
| Tongue oedema | 10043967 | PT |
| Toxic epidermal necrolysis | 10044223 | PT |
| Toxic skin eruption | 10057970 | PT |
| Tracheal oedema | 10044296 | PT |
| Type I hypersensitivity | 10045240 | PT |
| Type II hypersensitivity | 10054000 | PT |
| Type III immune complex mediated reaction | 10053614 | PT |
| Type IV hypersensitivity reaction | 10053613 | PT |
| Urticaria | 10046735 | PT |
| Urticaria cholinergic | 10046740 | PT |
| Urticaria chronic | 10052568 | PT |
| Urticaria contact | 10046742 | PT |
| Urticaria papular | 10046750 | PT |
| Urticaria physical | 10046751 | PT |
| Urticaria pigmentosa | 10046752 | PT |
| Urticaria vesiculosa | 10046755 | PT |
| Urticarial vasculitis | 10048820 | PT |
| Vaccination site dermatitis | 10069477 | PT |

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|---|---|---|
| Vaccination site eczema | 10076161 | PT |
| Vaccination site exfoliation | 10069489 | PT |
| Vaccination site hypersensitivity | 10068880 | PT |
| Vaccination site rash | 10069482 | PT |
| Vaccination site recall reaction | 10076188 | PT |
| Vaccination site urticaria | 10069622 | PT |
| Vaccination site vasculitis | 10076191 | PT |
| Vaccination site vesicles | 10069623 | PT |
| Vaginal exfoliation | 10064483 | PT |
| Vaginal ulceration | 10046943 | PT |
| Vasculitic rash | 10047111 | PT |
| Vessel puncture site rash | 10077117 | PT |
| Vessel puncture site vesicles | 10077813 | PT |
| Vulval ulceration | 10047768 | PT |
| Vulvovaginal rash | 10071588 | PT |
| Vulvovaginal ulceration | 10050181 | PT |
| Acute respiratory failure | 10001053 | PT |
| Administration site photosensitivity reaction | 10075961 | PT |
| Airway remodelling | 10075289 | PT |
| Allergy to chemicals | 10061626 | PT |
| Allergy to fermented products | 10054929 | PT |
| Alpha tumour necrosis factor increased | 10059982 | PT |
| Alveolitis | 10001889 | PT |
| Antibody test abnormal | 10061425 | PT |
| Antibody test positive | 10061427 | PT |
| Anti-insulin antibody increased | 10053815 | PT |
| Anti-insulin antibody positive | 10053814 | PT |
| Anti-insulin receptor antibody increased | 10068226 | PT |
| Anti-insulin receptor antibody positive | 10068225 | PT |
| Application site photosensitivity reaction | 10058730 | PT |
| Asthma | 10003553 | PT |
| Asthma late onset | 10003559 | PT |
| Asthma-chronic obstructive pulmonary disease overlap syndrome | 10077005 | PT |
| Asthmatic crisis | 10064823 | PT |
| Auricular swelling | 10003800 | PT |

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|---|---|---|
| Blister | 10005191 | PT |
| Blister rupture | 10073385 | PT |
| Blood immunoglobulin A abnormal | 10005584 | PT |
| Blood immunoglobulin A increased | 10005586 | PT |
| Blood immunoglobulin D increased | 10063244 | PT |
| Blood immunoglobulin G abnormal | 10005594 | PT |
| Blood immunoglobulin G increased | 10005596 | PT |
| Blood immunoglobulin M abnormal | 10005599 | PT |
| Blood immunoglobulin M increased | 10005601 | PT |
| Bronchial hyperreactivity | 10066091 | PT |
| Bronchial oedema | 10056695 | PT |
| Bullous impetigo | 10006563 | PT |
| Caffeine allergy | 10074895 | PT |
| Capillaritis | 10068406 | PT |
| Charcot-Leyden crystals | 10008413 | PT |
| Choking | 10008589 | PT |
| Choking sensation | 10008590 | PT |
| Conjunctivitis | 10010741 | PT |
| Corneal exfoliation | 10064489 | PT |
| Cytokine release syndrome | 10052015 | PT |
| Cytokine storm | 10050685 | PT |
| Ear swelling | 10014025 | PT |
| Eosinophil count abnormal | 10061125 | PT |
| Eosinophil count increased | 10014945 | PT |
| Eosinophil percentage abnormal | 10058133 | PT |
| Eosinophil percentage increased | 10052222 | PT |
| Eosinophilia | 10014950 | PT |
| Eosinophilia myalgia syndrome | 10014952 | PT |
| Eosinophilic bronchitis | 10065563 | PT |
| Eosinophilic oesophagitis | 10064212 | PT |
| Eosinophilic pneumonia | 10014962 | PT |
| Eosinophilic pneumonia acute | 10052832 | PT |
| Eosinophilic pneumonia chronic | 10052833 | PT |
| Erythema | 10015150 | PT |
| Flushing | 10016825 | PT |

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|---|---|---|
| Gastrointestinal oedema | 10058061 | PT |
| Generalised erythema | 10051576 | PT |
| Generalised oedema | 10018092 | PT |
| Genital rash | 10018175 | PT |
| Genital swelling | 10067639 | PT |
| Haemolytic transfusion reaction | 10067122 | PT |
| HLA marker study positive | 10067937 | PT |
| Immune complex level increased | 10064650 | PT |
| Immunoglobulins abnormal | 10021497 | PT |
| Immunoglobulins increased | 10021500 | PT |
| Immunology test abnormal | 10061214 | PT |
| Implant site photosensitivity | 10073415 | PT |
| Infantile asthma | 10049585 | PT |
| Infusion site photosensitivity reaction | 10065486 | PT |
| Injection site photosensitivity reaction | 10053396 | PT |
| Interstitial lung disease | 10022611 | PT |
| Laryngeal dyspnoea | 10052390 | PT |
| Laryngeal obstruction | 10059639 | PT |
| Leukotriene increased | 10064663 | PT |
| Lip exfoliation | 10064482 | PT |
| Localised oedema | 10048961 | PT |
| Mechanical urticaria | 10068773 | PT |
| Medical device site photosensitivity reaction | 10076137 | PT |
| Mesenteric panniculitis | 10063031 | PT |
| Mouth ulceration | 10028034 | PT |
| Mucocutaneous ulceration | 10028084 | PT |
| Mucosa vesicle | 10028103 | PT |
| Mucosal erosion | 10061297 | PT |
| Mucosal exfoliation | 10064486 | PT |
| Mucosal necrosis | 10067993 | PT |
| Mucosal ulceration | 10028124 | PT |
| Nasal crease | 10078581 | PT |
| Necrotising panniculitis | 10062579 | PT |
| Neurodermatitis | 10029263 | PT |
| Neutralising antibodies positive | 10064980 | PT |

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|---|---|---|
| Noninfective conjunctivitis | 10074701 | PT |
| Non-neutralising antibodies positive | 10064982 | PT |
| Occupational asthma | 10070836 | PT |
| Occupational dermatitis | 10030012 | PT |
| Oedema mucosal | 10030111 | PT |
| Oral mucosal exfoliation | 10064487 | PT |
| Orbital oedema | 10031051 | PT |
| Panniculitis | 10033675 | PT |
| Penile exfoliation | 10064485 | PT |
| Penile oedema | 10066774 | PT |
| Penile swelling | 10034319 | PT |
| Perineal rash | 10075364 | PT |
| Perivascular dermatitis | 10064986 | PT |
| Photosensitivity reaction | 10034972 | PT |
| Pneumonitis | 10035742 | PT |
| Prurigo | 10037083 | PT |
| Pruritus | 10037087 | PT |
| Pruritus generalised | 10052576 | PT |
| Pulmonary eosinophilia | 10037382 | PT |
| Reactive airways dysfunction syndrome | 10070832 | PT |
| Respiratory arrest | 10038669 | PT |
| Respiratory distress | 10038687 | PT |
| Respiratory failure | 10038695 | PT |
| Respiratory tract oedema | 10070774 | PT |
| Reversible airways obstruction | 10062109 | PT |
| Rhinitis perennial | 10039094 | PT |
| Scrotal swelling | 10039759 | PT |
| Seasonal allergy | 10048908 | PT |
| Septal panniculitis | 10056876 | PT |
| Skin erosion | 10040840 | PT |
| Skin exfoliation | 10040844 | PT |
| Skin oedema | 10058679 | PT |
| Skin swelling | 10053262 | PT |
| Sneezing | 10041232 | PT |
| Status asthmaticus | 10041961 | PT |

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|---|---|---|
| Stomatitis | 10042128 | PT |
| Streptokinase antibody increased | 10053797 | PT |
| Stridor | 10042241 | PT |
| Suffocation feeling | 10042444 | PT |
| Throat tightness | 10043528 | PT |
| Tongue exfoliation | 10064488 | PT |
| Tracheal obstruction | 10044291 | PT |
| Tracheostomy | 10044320 | PT |
| Transplantation associated food allergy | 10075008 | PT |
| Upper airway obstruction | 10067775 | PT |
| Vaccination site photosensitivity reaction | 10076186 | PT |
| Vaginal oedema | 10063818 | PT |
| Visceral oedema | 10065768 | PT |
| Vulval oedema | 10047763 | PT |
| Vulvovaginal swelling | 10071211 | PT |
| Wheezing | 10047924 | PT |