1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	011952
STUDY DRUG:	FG-3019
INDICATION:	Pancreatic Cancer
FIBROGEN MEDICAL MONITOR	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail: [redacted]
ORIGINAL PROTOCOL DATE	14 April 2014
PROTOCOL VERSION & DATE:	Amendment 1: 12 May 2014 Amendment 2: 24 September 2014 Amendment 3: 31 October 2015 Amendment 4: 13 November 2015 Amendment 5: 30 March 2016 Amendment 6: 29 September 2016

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

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

FGCL-3019-069

Original: 14 April 2014
Amendment 1: 12 May 2014
Amendment 2: 24 September 2014
Amendment 3: 31 October 2015
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Amendment 5: 30 March 2016
Amendment 6: 29 September 2016

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen at the address provided below. Please retain the original for your study files.

Attention: FGCL-3019-069 Clinical Operations
FibroGen, Inc.
409 Illinois Street
San Francisco, California 94158 USA

CONFIRMATION OF PROTOCOL APPROVAL

This protocol is approved by FibroGen.

Original Protocol Date: 14 April 2014

Amendment 1: 12 May 2014

Amendment 2: 24 September 2014

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Amendment 4: 13 November 2015

Amendment 5: 30 March 2016

Amendment 6: 29 September 2016

[redacted] 29, Sep- 16

Date

[redacted] FibroGen Inc.

AMENDMENT 6: KEY CHANGES FROM AMENDMENT 5

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, flow, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Description of Key Change	Rationale for Change	Section(s) Affected
Revision to Exclusion Criterion 7 to specify that any subject that has been exposed to another investigational drug within 42 days days prior to first dosing visit in study FGCL-3019-069 or 5 half-lives of the study product (whichever is longer) is not eligible for participation in the study.	Previous language did not specify that it was exposure to **investigational drug** in a clinical protocol or investigational trial within a specific time period that was prohibited.	Section 5.2
Addition to Exclusion Criteria to specify that subjects with solid tumor contact with superior mesenteric artery (SMA) >180° will be excluded.	Subjects with >180° SMA encasement are unlikely to achieve an R 0 resection	Section 5.2
Reduced safety follow-up period from 70 days (±1 week) to 28 days (±1 week).	Based on the half-life and known PK of FG-3019, and ICH/GCP guidelines, 28-day safety follow-up period following the last dose of study drug is sufficient.	Sections 4.1, 7.2.2, 8.4.1, and 8.4.2, Figure 1, Appendix 1, Appendix 2.
All subjects will be followed in the Long Term Follow-up Period until the last subject enrolled completes at least 28 weeks of follow-up following EOT. Subjects will be followed monthly for the first 28 weeks and quarterly thereafter.	To ensure that incidence of disease progression and survival are captured in a more timely and accurate manner within the first 28 weeks following completion of treatment. Duration of Long Term Follow-up decreased from 5 years to at least 28 weeks, allowing for all subjects to be assessed for at least 1 year progression free and overall survival.	Section 4.1, Appendix 1.
Clarification of language to ensure that all subjects are followed for both disease progression and survival during Long Term Follow-up.	Ensure clarity of protocol.	Synopsis, Section 4.1, Appendix 1.
Collection of follow-on treatment for pancreatic cancer in Long Term Follow-up.	Collection of follow-on treatments for pancreatic cancer received by subjects during Long Term Follow-up will allow for an assessment of impact to disease progression or overall survival.	Appendix 1.
Clarification of language regarding study objectives and safety and efficacy endpoints	Ensure clarity of protocol	Synopsis, Section 3.1, 3.2

Addition of language to specify that, for subjects enrolled in Arm A, the FG-3019 dosing should proceed per protocol even if chemotherapy dose is modified or withheld for 1 or 2 doses, as per standard of care. Additionally, if chemotherapy is withheld for more than 2 doses, the medical monitor should be contacted, and if chemotherapy is terminated, treatment with FG-3019 should be discontinued.	To clarify for sites that FG-3019 dosing should proceed when chemotherapy is modified or withheld as per standard of care, per the protocol defined dosing schedule.	Section 6.1, Appendix 1, Appendix 3.

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:	**Number of Subjects Planned:**	**Study Centers Planned:**
FGCL-3019-069	~ 42	Approximately 10

Key Objectives:

Objectives:

- 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 (PK) of FG-3019 (concentration maximum [C_{max}] and concentration minimum [C_{min}]) and correlation with other study endpoints in this treatment setting.

Endpoints

Safety Endpoint:

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

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 whom 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

Other Endpoints:

- FG-3019 plasma concentrations, including trough level (C_{min}) and maximum concentration (C_{max})

Study Design

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) with an A:B ratio of 2:1, 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.

Study Periods

This trial has four periods:

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

Key Eligibility Criteria

Inclusion Criteria:

- Have a histologically proven diagnosis of pancreatic ductal adenocarcinoma (PDAC).
- Have radiographic and pathologic staging (including staging laparoscopy) consistent with pancreatic cancer, locally advanced, unresectable as defined by NCCN Guidelines®.
- Have laparoscopic confirmation that the PDAC is locally advanced (non metastatic).
- Biliary stents are permitted.
- Have measurable disease as defined by Response Evaluation Criteria in Solid Tumors RECIST 1.1 criteria.

Exclusion Criteria:

- Prior chemotherapy or radiation for pancreatic cancer.
- Solid tumor contact with SMA > 180°

Study Treatment: Dose and Mode of Administration

FG-3019:	35 mg/kg, IV, Days 1 and 15 of each cycle; additional dose given on Day 8 of Cycle 1 only.
Gemcitabine:	1000 mg/m2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.
Nab-paclitaxel:	125 mg/m2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.

Key Statistical Methods

Efficacy Analyses: All efficacy endpoints will be summarized by treatment group using descriptive statistics. To compare the efficacy endpoints between the two treatment groups, Fisher's Exact test will be used in dichotomous variables; log-rank test will used in time-to-event variables; t-test or nonparametric test (depending on the data distribution) will be used in continuous variables.

Safety Analyses: Treatment-emergent adverse events (TEAEs) will be tabulated to examine their frequency, severity, organ systems affected, and relationship to study treatment. TESAEs and TEAEs leading to study or treatment discontinuation will be summarized separately. Surgical complications will be summarized by treatment arm, as well.

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2 BACKGROUND

2.1 FG-3019

FG-3019 is a fully human, recombinant DNA-derived IgG1 kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) in domain 2 of the N-terminal fragment of CTGF with high affinity (Kd = 0.1–0.2 nM).

See the Investigator's Brochure for information regarding the investigational product; summaries of non-clinical and clinical studies relevant to this trial; a summary of known potential risks and benefits to human subjects; and description and justification of route of administration, dosage, dosage regimen, and treatment period(s).

2.2 Connective Tissue Growth Factor

Connective tissue growth factor (CTGF) is a 36 kDa glycoprotein that was originally described as an immediate early gene induced by transforming growth factor beta (TGFβ). It is a matricellular protein of the CCN family (Cyr61, CTGF, and Nov, and other related proteins) with four modular domains that display homology to other protein motifs (Kindler, 2005, Perbal, 2004, Rachfal, 2005). CTGF interacts as a cofactor with molecules such as TGFβ and insulin-like growth factor-1 (IGF-1) to increase matrix production, and it appears that CTGF may mediate the profibrotic effects of TGFβ (Lam, 2003, Grotendorst, 1997).

Elevated CTGF expression is detected in many tumor types, in particular, pancreatic ductal adenocarcinoma (PDAC) and invasive breast carcinoma (Wenger, 1999, Xie, 2001). Among 19 samples of pancreatic tumors, 15 showed an average 59-fold enhancement of CTGF expression, compared with a 4.5-fold increase observed in chronic pancreatitis (Wenger, 1999). CTGF was identified as an invasion-specific gene in PDAC (Ryu, 2001) and is highly expressed within the neoplastic epithelium (Iacobuzio-Donahue, 2002). In any specific tumor, CTGF can be expressed by PDAC tumor cells, by stellate or stromal cells within the tumor, or by both cell types (Hidalgo, 2012, Wenger, 1999, Iacobuzio-Donahue, 2002, Frazier, 1997, Hartel, 2004).

FG-3019 has been tested in immunodeficient mice with induced pancreatic tumor and shown to dramatically reduce tumor growth in a heterotopic model (Dornhofer, 2006) and significantly reduce tumor growth, neovascularization, and tumor metastases in an orthotopic model (Aikawa, 2006). Studies in the LSL-KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre (KPC) transgenic mouse model of pancreatic cancer showed that treatment with FG-3019 in combination with gemcitabine prolonged survival and increased tumor cell apoptosis associated with the down-regulation of the anti-apoptotic protein xIAP (Neesse, 2013). This suggests that CTGF may promote chemoresistance, known to be a particular problem in pancreatic cancer, through induction of anti-apoptotic genes.

2.3 Rationale for Study

PDAC is the fourth leading cause of cancer death in the United States. Overall 5-year survival is only 6%, because of both the advanced stage at diagnosis and limited response to currently available therapies (Siegel, 2013), (Evans, 2001), and (Burris, III, 1997). In general, long-term survival is only achievable through successful (R0[(microscopically negative margins]) surgery, however only 10-20% of patients are candidates for this procedure (Sener, 1999).

More recently, the concept of "downstaging" patients with locally advanced pancreatic cancer (45% of all patients with pancreatic cancer) has been under investigation. Based on standard criteria (NCCN Guidelines®) about one third of patients with locally advanced disease are candidates for this approach. Although there is no universally accepted approach for downstaging at this time, the literature suggests an overall 25% successful downstaging rate in this population (Morganti, 2010); with single-institution rates as high as 40% (Katz, 2008). In general, subjects with locally advanced pancreatic cancer who are successfully downstaged have similar survival rates to those who are downstaged *de novo*.

In 2008, [redacted] (Rose, 2014), embarked on an approach to downstage borderline resectable pancreatic cancer. This approach was unique in that 1) all subjects were laparoscopically staged prior to therapy initiation and 2) initial downstaging therapy consisted of 24 weeks of gemcitabine and docetaxel. Currently, 70 subjects have been downstaged using this methodology. Of the 58 subjects who have been followed for over 6 months, 88% (51/58 subjects) successfully completed all 24 weeks of therapy; the R0 resection rate for this subject group was 50% (29/58 subjects).With median follow up of 16 months, 25/58 subjects (43%) remain progression free; 25/29 (88%) R0-resected subjects remain alive. Median overall survival for the 58 fully evaluable subjects is 27 months, which is superior to many clinical trials of subjects resected *de novo.* In light of these encouraging results, this approach is being extended to the approximately 30% of subjects with locally advanced, unresectable PDAC who are not considered surgical candidates (because of circumferential involvement of encasement of the superior mesenteric artery [SMA] or celiac axis) but with an anti-stromal agent added to the initial 24 weeks of downstaging therapy. Pancreatic ductal adenocarcinoma tumors often exhibit a high degree of desmoplasia, characterized by extensive connective tissue stromal, likely due to CTGF effects on extracellular matrix production (Wenger, 1999, Hartel, 2004). Desmoplasia (Kalluri, 2006) and associated high CTGF expression typically correlate with worsening prognosis. In this regard, the use of anti-stromal agents (such as FG-3019) is particularly appealing, both from the standpoint of antitumor effect and from the standpoint of changing the typically fibrotic character of pancreatic cancer to make it more amenable to surgical resection from proximate major blood vessels.

Nab-paclitaxel combined with gemcitabine, showed improved overall survival compared to gemcitabine alone in a Phase 3 trial (Von Hoff, 2013). The response rates to the gemcitabine-nab-paclitaxel combination may be higher in in subjects who were positive for secreted protein acid and rich in cysteine (SPARC; a protein expressed on both pancreatic cancer and pancreatic stromal cells) (Feig, 2012). In September 2013, the combination of nab-paclitaxel (Abraxane®) and gemcitabine was approved by the FDA for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. Since the FDA approved this combination, it has become the standard of care for many subjects with PDAC.

2.4 Rationale for Dose

In a dose-finding study (FGCL-MC3019-028), FG-3019 was tested in combination with gemcitabine and erlotinib in subjects with Stage 3 or 4 pancreatic adenocarcinoma. Treatment with FG-3019 was well tolerated. The majority of treatment-emergent adverse events were mild-to-moderate in severity and were consistent with those observed in patients treated with gemcitabine and erlotinib without FG-3019 (Van Cutsem, 2009).

Based on the data analysis as of March 2014, 75 subjects with advanced or metastatic pancreatic cancer treated per FibroGen protocol FGCL-MC3019-028, overall survival correlates inversely with baseline CTGF levels and directly with FG-3019 drug exposure (Picozzi, 2014). Day 15 C_{min} ≥150 mcg/mL was associated with improved median OS at 9.4 months and 1 year survival at 37% vs. 4.8 months (p=0.02) and 11% (p=0.01) at C_{min} < 150 mcg/mL. CA19-9 response evaluated by maximum reduction of ≥50% from baseline was 56% (C_{min} ≥150) and 27% (C_{min} <150 mcg/mL). Higher FG-3019 doses achieved C_{min} >150 mcg/mL that was associated with improved survival. In bivariate analysis, Day 15 C_{min} ≥150 mcg/mL and baseline CTGF < median were associated with better survival (p=0.04 and 0.02 respectively). Greatest survival was in subjects with Day 15 C_{min} >150 mcg/mL and baseline CTGF < median.

Preliminary analysis of the data from FGCL-MC3019-028 revealed that a FG-3019 dose of 35 mg/kg administered every 2 weeks to subjects with pancreatic cancer will achieve a Day 15 C_{min} >150 mcg/mL in 78% of subjects. The next dose level (45 mg/kg biweekly) did not increase the number of subjects who reached with C_{min} >150 mcg/mL. Therefore a dose of 35 mg/kg was established as the dose of FG-3019 to be used in this trial. Modeling further revealed that the target C_{min} >150 mcg/mL is achieved rapidly if FG-3019 is administered on Day 8 of the first treatment cycle, as is planned for this trial.

The dose of gemcitabine and nab-paclitaxel are identical to those used in the recently completed phase 3 trial that showed this regimen improved survival compared to treatment with gemcitabine alone (Von Hoff, 2013).

Given the above data, it is proposed to study the FG-3019, gemcitabine, and nab-paclitaxel combination using methodology analogous to that used by investigators at [redacted] to determine the safety of this combination in the neoadjuvant setting and to obtain a preliminary estimate of the efficacy of the combination for converting locally advanced, unresectable pancreatic cancer to resectable status in subjects currently considered “unresectable” by NCCN Guidelines®.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 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.

3.1.2 Exploratory Objectives

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.

3.2 Endpoints

3.2.1 Safety Endpoints

- Treatment-emergent adverse events (TEAEs), serious treatment-emergent adverse events (TESAEs), clinical laboratory tests, and discontinuation of treatment for treatment-related TEAEs. See Section 3.2.2 for additional endpoints related to safety and tolerability.
- Surgical safety with respect to complication rates post resection.

3.2.2 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.

3.2.3 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.

4 STUDY DESIGN

4.1 Description of the Study

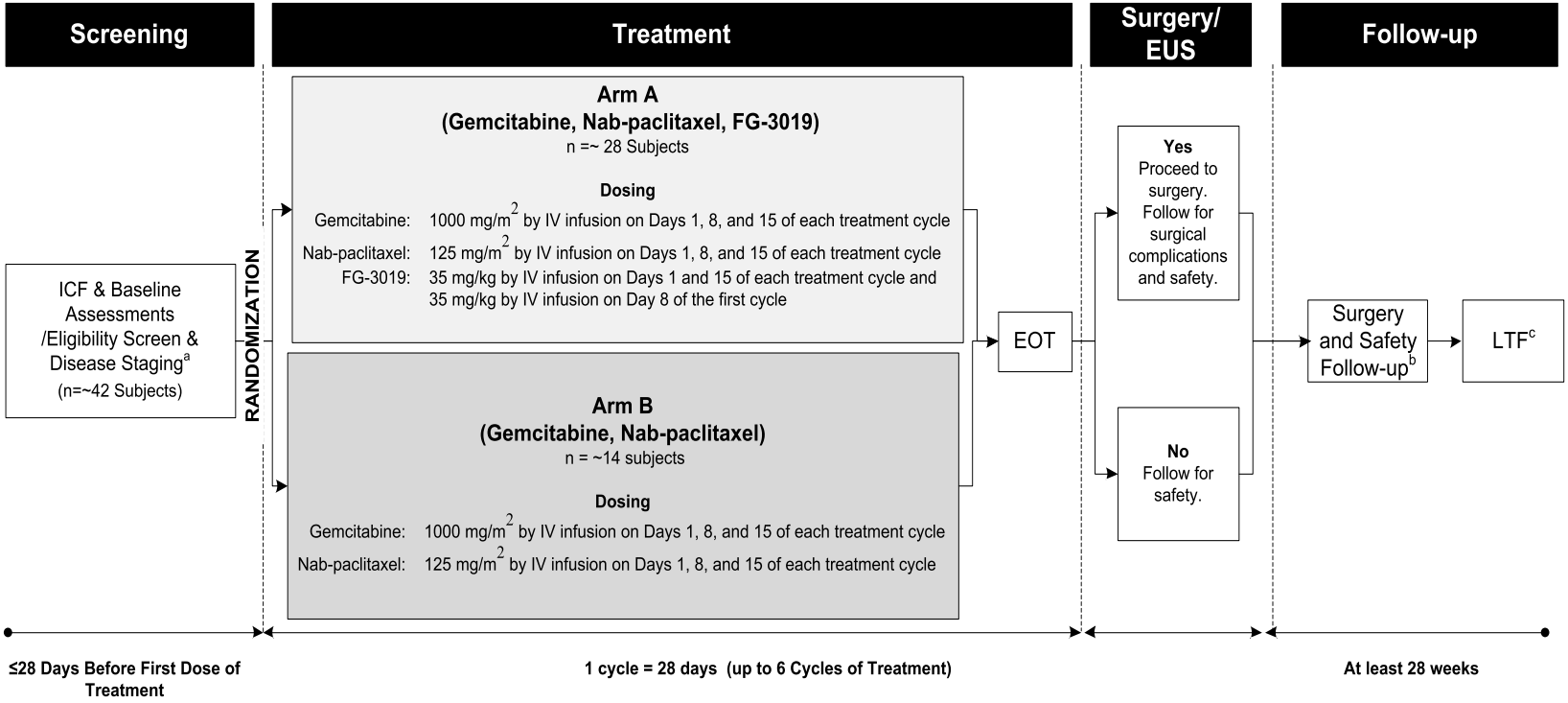
This is a Phase 1/2, randomized, open-label trial to evaluate safety and tolerability of gemcitabine plus nab-paclitaxel with FG-3019 (Arm A) and gemcitabine plus nab-paclitaxel (Arm B) with A:B ratio of 2:1, in subjects with locally advanced, unresectable pancreatic cancer. Up to 42 evaluable subjects (as defined in Section 9.3) will be included in this trial. Each treatment cycle is 28 days long and subjects may receive up to six cycles of treatment. All subjects will be followed in Long-Term Follow-up until the last subject enrolled completes at least 28 weeks of follow-up following EOT. In the Long-Term Follow-up period subjects will be followed approximately monthly for the first28 weeks and quarterly thereafter for disease progression and survival.

This trial has four periods:

- Screening and Disease Staging
- Treatment
- Surgery and Safety Follow Up
- Long-Term Follow Up

A schematic overview of the study, including study period timeframes, is provided in Figure 1. A detailed overview of assessments and the timing of assessments is provided in Appendix 1.

Figure 1 FGCL-3019-069 Study Schema



Abbreviations: EOT=end of treatment; EUS=endoscopic ultrasound; n=number of subjects; ICF=informed consent form; IV=intravenous; LTF=long-term follow-up.

NOTE: A treatment cycle is defined as a 28-day period of treatment.

a Including laparoscopic staging with peritoneal wash
b Surgical Follow-up: 30 days after hospital discharge; Safety followup:28 days ±7 days after last dose.
c Long term followup: EOT + at least 28 weeks. Disease progression and survival are assessed in LTFU.

Screening and eligibility criteria are outlined in Section 5 and in Appendix 1. Screening includes staging by laparoscopy with peritoneal washing to rule out occult metastatic disease that may not be detected by standard imaging procedures like CT scans.

Tumor status will be evaluated at intervals specified in Appendix 1. Upon completion of treatment, subject(s) will be evaluated for surgical exploration for possible R0 resection using criteria based on changes in CT scan, FDG-PET scan, CA19-9, and NCCN® guidelines as outlined in Section 7.1.1.

Subjects who are considered candidates for surgical exploration will undergo surgery in an effort to achieve R0 resection.

Subjects who have disease progression will be discontinued from study treatment. Subjects who discontinue early due to disease progression or other reasons should complete the Cycle 6, Day 28 End of Treatment (EOT) assessments and the follow-up period.

Safety is assessed routinely throughout the study by clinical and laboratory assessments (Section 8 and Appendix 1).

All subjects will be followed for 28 ± 7 days after last dose of study treatment for safety endpoints. In addition, subjects who undergo surgery will be followed for 30 days after discharge for assessment of post-operative complications.

Blood samples will be collected periodically for the assessment of pharmacokinetics (PK) and pharmacodynamics (PD). Details regarding the types of samples to be collected and the timing of these samples are available in Appendix 2.

All subjects, including those who discontinue from the study during the treatment period without evidence of disease progression, will be followed in Long-Term Follow-up until the last subject enrolled completes at least 28 weeks of follow-up following the EOT visit. In Long-Term Follow-up, subjects will be followed approximately monthly for the first 28 weeks and quarterly thereafter for disease progression and survival.

All study centers will have the option to participate in an exploratory portion of this study to evaluate tumor protein expression. For participating study centers, the collection of adequate tumor tissue for exploratory analyses is required at baseline and end of treatment for all subjects. Subjects who do not have adequate tumor tissue at baseline will be required to undergo endoscopic ultrasound (EUS) guided core tumor biopsy to collect up to 4 core biopsies. Post-treatment tumor tissue may be obtained during surgery for those subjects who are eligible for surgical exploration. If post-treatment tumor tissue cannot be safely obtained at the time of surgery or the subject is deemed ineligible for surgery, they will undergo a second EUS guided core tumor biopsy procedure to collect up to 4 core biopsies post treatment. EUS biopsies will be performed by a qualified gastroenterologist at each participating study center.

4.1.1 Control Groups

This is a randomized Phase 1/2 trial; Arm B serves as the control group.

4.1.2 Randomization and Treatment Assignment

4.1.2.1 Randomization

Randomization is based on a randomization schedule prepared by FibroGen. See Section 9.2 for additional information.

4.1.2.2 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).

4.1.3 Blinding

This is an open-label study.

4.2 Study 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

Additional information regarding FG-3019, gemcitabine, and nab-paclitaxel is located in Section 6.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

In order to be eligible for inclusion in this trial, a subject must:

1. Understand and sign the informed consent.
2. Be a male, or a non-pregnant and non-lactating female.
3. Be ≥18 years old.
4. Have a histologically proven diagnosis of pancreatic ductal adenocarcinoma (PDAC).
5. Have radiographic and pathologic staging (including staging laparoscopy) consistent with pancreatic cancer, locally advanced, unresectable as defined by NCCN® guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).
6. Have laparoscopic confirmation that the PDAC is locally advanced (non-metastatic). Biliary stents are permitted.
7. Have measurable disease as defined by RECIST 1.1.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Have adequate liver function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2.5 x upper limit of normal, alkaline phosphatase <2.5 x upper limit of normal, and bilirubin ≤1.5 x Upper Limit Normal (ULN).
10. Have adequate bone marrow function: platelets >100,000 cells/mm^3, hemoglobin >9.0 l/dL, and absolute neutrophil count (ANC) >1,500 cells/mm^3.
11. Have adequate renal function: creatinine <1.5 x ULN.
12. Agree to the conditions for contraception set forth in Section 6.3.3.
13. Have a negative serum β-hCG pregnancy test at screening (for female subjects of childbearing potential only).
14. Have < Grade 2 pre-existing peripheral neuropathy (per Common Terminology Criteria for Adverse Events [CTCAE]).

5.2 Exclusion Criteria

Subjects will be ineligible for this trial if any of the following apply:

1. Prior chemotherapy or radiation for pancreatic cancer.
2. Solid tumor contact with SMA > 180 °
3. Previous (within the past 5 years) or concurrent, malignancy diagnosis, except non-melanoma skin cancer and in situ carcinomas.
4. Major surgery within 4 weeks prior to Day 1 on study.
5. History of allergy or hypersensitivity to human, humanized or chimeric monoclonal antibodies.

6. Any medical or surgical condition that may place the subject at increased risk while on study.
7. Any condition potentially decreasing compliance to study procedures.
8. Exposure to another investigational drug within 42 days of first dosing visit, or 5 half-lives of the study product (whichever is longer).
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active systemic infection, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
10. Current abuse of alcohol or drugs.
11. Any medical condition that, in the opinion of the Investigator, may pose a safety risk to a subject in this trial, may confound the assessment of safety and efficacy, or may interfere with study participation.

5.3 Subject Withdrawal

Subjects may withdraw from study treatment at any time.

Reasons for discontinuing the subject from study treatment include the following:

- Progressive Disease
- Adverse Event
- Lost to Follow-Up
- Non-compliance with study drug (including gemcitabine and nab-paclitaxel)
- Physician decision
- Pregnancy
- Major protocol deviation that substantially affects subject safety or assessment of efficacy endpoints
- Withdrawal of Consent

Discontinued subjects should be evaluated in the clinic for the Cycle 6, Day 28/EOT visit and then followed for safety, disease progression (if not noted), and overall survival as presented in Figure 1 and Appendix 1.

5.4 Replacement of Subjects

Subjects may be replaced for this study. Replacement decision will be made by agreement between sponsor and investigator per each circumstance.

5.5 Study Termination by FibroGen

This trial can be terminated by the sponsor at any time for any reason.

6 TREATMENT OF SUBJECTS

Treatment is administered over a 28 day cycle, for up to six cycles. If dosing delays occur due to AEs or scheduling conflicts, for example, it is acceptable to extend the overall treatment period by up to 4 weeks to accommodate missed/delayed doses.

Information regarding storage and handling, and preparation of dose for administration is found in the FG-3019 Investigator's Brochure and the Study Manual. This information for gemcitabine and nab-paclitaxel can be found in the package inserts for these products.

6.1 FG-3019-For Subjects Randomized to Arm A Only

The dose, route, and schedule for the administration of FG-3019 is provided in Table 1. The dose of FG-3019 is calculated using the Day 1 or screening weight. If a subject has a weight change of more than 10%, the total FG-3019 dose will be adjusted based on the new weight. Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. Modification of the dose of FG-3019 is not permitted in this trial. FG-3019 is administered AFTER the administration of the chemotherapy agents has completed. In the event that chemotherapy administration is modified or withheld for 1 or 2 doses, as per standard of care, the dosing schedule for FG-3019 should be maintained, at the discretion of the Investigator. In the event that chemotherapy is withheld for more than 2 doses the medical monitor should be contacted. If chemotherapy is terminated, treatment with FG-3019 should also be discontinued. See the Investigator's Brochure or the Pharmacy Manual for additional details regarding administration of FG-3019.

Table 1 FG-3019 (Arm A Only): Dose, Route, and Administration

Agent	Dose	Route	Schedule	Cycle length
FG-3019	35 mg/kg	IV, over one hour following completion of chemotherapy infusions	Days 1, 8[a], 15	28 days (4 weeks)

Abbreviation: IV = intravenous.
a Day 8 dosing in Cycle 1 only.

Notes: DO NOT ADMINSITER FG-3019 AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.

6.2 Gemcitabine and Nab-paclitaxel for Subjects in Arm A and Arm B

The dose, route, and schedule for administration of gemcitabine and nab-paclitaxel used in Arm A and Arm B is provided in Table 2. The dose of gemcitabine and/or nab-paclitaxel may be modified as described in Appendix 3. However, doses of gemcitabine and/or nab-paclitaxel may be modified according to the investigator's discretion based on the subject's medical condition if it differs from package insert. Warnings and precautions for gemcitabine and nab-paclitaxel are also located in Appendix 3.

Table 2 Gemcitabine and Nab-paclitaxel (Arm A and B): Dose, Route, and Administration

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle length**
Gemcitabine	1000 mg/m^2	IV, following nab-paclitaxel	Days 1, 8, 15	28 days (4 weeks)
Nab-paclitaxel	125 mg/m^2	IV	Days 1, 8, 15	

Abbreviation: IV = intravenous.

6.2.1 Procedures for Assuring Treatment Compliance

All treatments are administered at the investigational site by qualified personnel and documented in the corresponding case report form (CRF).

6.3 Concomitant Medications

6.3.1 Permitted

Regular supportive care as clinically indicated is permitted during this trial.

6.3.2 Prohibited

FG-3019 should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

See the FG-3019 Investigator's Brochure and the package inserts for gemcitabine and nab-paclitaxel for additional prohibited medications.

6.3.3 Contraception

Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use double barrier contraception methods during the conduct of the study and for 3 months after the last dose of study drug.

7 ASSESSMENTS OF EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS

The primary objective of this study is the safety and tolerability of FG-3019 neoadjuvant chemotherapy (Section 8). As a secondary objective, this study will evaluate the efficacy of neoadjuvant chemotherapy treatments in enabling R0 resection. This study will also explore the effects of neoadjuvant treatment on tissue and blood biomarkers. These studies may identify biomarkers that identify subjects likely to respond to neoadjuvant treatment or provide insights into mechanisms of action. See Appendix 1 for additional information regarding the timing/frequency of assessments.

7.1 Efficacy

7.1.1 Evaluation for Surgery and Tumor Response

Subjects who finish study treatment will undergo evaluation to determine their eligibility for surgical exploration if one or more of the following criteria are met:

- Reduction in CA19-9 level by more than 50% at EOT when compared to baseline.
- FDG-PET SUV_{max} decrease by $\geq$30%.
- Radiological tumor response (partial response [PR] and/or complete response [CR]) per RECIST 1.1.
- Meet the definition of resectable or borderline resectable per NCCN® (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

A subject will be classified as ineligible or contraindicated for surgical exploration if any of the following occur:

- Development of distant metastases or local progression on CT scan
- Tumor involvement precluding vascular reconstruction
- Local complications preventing surgery (eg, PV/SVT thrombosis, pancreatitis)
- Performance status decline to Karnofsky score ≤50% or absolute contraindication to surgery (eg, recovery from myocardial infarction [MI])

The decision regarding whether or not a subject will undergo surgery is ultimately up to the treating physicians. However, any questions regarding surgical eligibility that cannot be resolved by the above may be referred to the lead study Investigators at [redacted] in making a final determination.

7.1.2 Clinical Laboratory Evaluations

Assessment of clinical laboratory parameters will be conducted as part of the assessment of efficacy and safety. A local laboratory will be used to analyze all labs collected per standard of care. Table 3 lists the parameters to be tested and evaluated.

Table 3 Laboratory Tests

CBC:	**Chemistry Panel:**
Absolute neutrophil count	Bicarbonate
Eosinophils	BUN
Erythrocyte count (RBC)	Calcium
Hct	Creatinine
Hb	Glucose
Leukocyte count (WBC)	*Liver Function Tests*
Lymphocytes	ALP
Mean corpuscular volume	ALT
Monocytes	AST
Neutrophils	Bilirubin, total
Platelets	Phosphorous
Special Laboratory Analytes:	Potassium
CA19-9	Sodium

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell; WBC = white blood cell.

7.2 FG-3019 Pharmacokinetics and Pharmacodynamics

7.2.1 Pharmacokinetics

Plasma samples will be collected from subjects assigned to treatment Arm A for evaluation of C_{max} (30 minutes to 2 hours post end-of -infusion) and C_{min} trough levels of FG-3019 according to the schedule in Appendix 2. Approximately 5 mL of blood will be collected in a K2-EDTA tube at each time point. Plasma prepared from the tube will be aliquoted by the investigator and stored frozen for subsequent measurement of plasma levels of FG-3019. A central laboratory will measure plasma FG-3019 levels using a validated assay. For the analysis of C_{max} and C_{min} data, it is critical to accurately record the dosing time and date in addition to the sampling collection time and date.

7.2.2 Human Anti-Human Antibodies

Blood samples for human anti-human antibodies (HAHA) measurement will be collected from subjects randomized to treatment Arm A in heparinized tubes at baseline, pre-dose Cycle 1, Day 1 and at the safety follow-up visit approximately 28 days after the last dose with study treatment according to the schedule in Appendix 2. Plasma prepared from the tube will be aliquoted by the investigator and stored frozen for subsequent measurement of plasma levels of FG-3019 HAHA. A central laboratory will measure HAHA using a validated assay.

7.2.3 Pharmacodynamics and Biomarkers (Blood and Tumor Tissue)

Tumor tissue, plasma and whole blood will be collected according to the schedule in Appendix 2. The following section describes the tentative analysis planned for these samples. Final decisions about the specific markers to be evaluated will be made at the time of analysis and will be based on review of the medical literature, additional data regarding FG-3019's mechanism of action, preliminary results and availability of material for assay. Tumor tissue will be collected before and after study treatment for all subjects at participating sites participating in the biopsy portion of the study. In addition, tumor tissue obtained during surgical resection of a tumor at any site may be analyzed for biomarkers in all subjects who undergo surgery.

7.2.3.1 Plasma and Whole Blood Samples

Plasma will be collected at the indicated times in Appendix 2 for protein, metabolite and/or nucleic acid assays. A FibroGen laboratory will measure CTGF levels using a proprietary ELISA. A FibroGen lab will optionally examine plasma samples for changes in RNAs. Central laboratories will optionally examine changes in plasma proteins and/or metabolites to identify biomarkers.

Whole blood will be collected for analysis of nucleic acids in PAXgene tubes. A FibroGen laboratory will isolate nucleic acids and examine them for gene expression changes that could serve as a biomarker.

7.2.3.2 Tumor Tissue Samples

Freshly collected tumor tissue from the pre and post-treatment core biopsies or tumor resections will be processed by formalin fixation and paraffin embedding. These tissues will be used for:

- Immunohistochemistry (IHC) of biomarkers of interest. Tentatively the following biomarkers have been selected:
    - Target antigen: CTGF
    - Proliferation: Ki67
    - Activated pancreatic stellate cells: alpha smooth muscle actin
    - Apoptosis: Cleaved caspase-3
    - Tumor stroma: SPARC
    - Invasiveness: Tumor margins
    - Immune cell infiltration: morphology
    - Stem cells: SOX2
    - Microvessel density: CD31
- Protein array multiplexing using laser captured tumor and stroma.

- Analysis of RNA levels by next generation sequencing. Tentatively, the following genes are of particular interest to examine:
    - Regulators of apoptosis: XIAP, cIAP, MCL-1, Bcl-XL
    - Stem cell Markers: SOX2, BMI-1, CD44, Cytokeratins, cKit
    - Regulators of immune cell response: CXCL12, TGFβ, IL6, IL13, TNFα, SMAD4, etc.
    - ECM deposition: Collagens, fibronectin, MMPs, TIMPs, CTGF, αSMA, LOX, etc.
    - Response to chemotherapy: hENT1 (SLC29a1), SPARC, Notch3

Detailed sample collection and processing instructions for all PK/PD and tumor tissue samples are provided in the laboratory manual.

8 ASSESSMENTS OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the study drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1. The investigator must immediately (within 24 hours of awareness) report to the sponsor all SAEs, regardless of whether the investigator believes they are related to the study drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AEs is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.4.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A ***serious adverse event*** is any AEs or suspected adverse reaction that results in any the following outcomes:

- Death,
- A life-threatening AEs (ie, if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (eg, infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

- Occurs during or within 1 hour after infusion; and
- Clinical manifestations consistent with:
  - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
  - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion related reaction is one that meets both of the following criteria:

- Occurs >1 hour after the infusion; and
- Clinical manifestations as described above.

Both acute and delayed infusion reactions will be captured as AEs and also reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, eg, name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated safety vendor within the same timeframe as SAEs on a Medication Error report form.

8.3 Safety Management/Monitoring Programs

Safety will be assessed throughout the study through adverse event monitoring, clinical laboratory testing, ECG, ECOG Performance Status, vital signs, and physical examinations. A medically complete, baseline profile of each subject will be established by Study Day 1. Any medically significant changes from baseline will be reported during the study (as per Section 8.4) and appropriate interventions will be taken accordingly. Subjects will be monitored for potential infusion reactions during each infusion and for 1 hour afterward. Blood samples will be collected for identification of HAHA to FG-3019 at Day 1 (predose) and at follow-up.

Safety signal monitoring will include monthly review of adverse events.

See Appendix 1 for additional information regarding the timing/frequency of assessments.

8.3.1 Clinical Laboratory Evaluations

See Section 7.1.2.

8.3.2 Surgical Complications Outcomes

All subjects that undergo surgery will be followed for 30 days after their discharge from the hospital. Subjects will undergo surgical safety assessment per standard of care (SOC). Surgical safety with respect to complication rates will be evaluated in both treatment arms. This includes but is not limited to:

- Rate of intra-abdominal abscess and perioperative leaks
- Rate R0 vs R1 resection
- Risk adjusted perioperative mortality
- % resections >10 lymph nodes sampled
- 30 day readmission rate
- Operative time >10 hours
- Length of hospital stay
- Estimated blood loss (EBL) at time of surgery
- Return to operating room within 30 days
- % Surgical Site Infection (SSI)

8.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.4.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 28 days after the last dose of study drug, except for pregnancy reporting (Section 8.4.7). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or lost to follow-up. If an AE is not resolved or stabilized at the subject's last visit, it is up to the discretion of the investigator and study medical monitor to determine if further monitoring of the event is warranted.

Adverse events collected prior to dosing of study drug will be considered "non-treatment emergent" while those reported after the first dose of study drug and up to 28 days after the last dose of study drug will be considered "treatment emergent" and be assessed for relationship to study drug.

8.4.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or

previous visit, but shall not be specifically solicited. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (ie, after informed consent is obtained until 28 days after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Abnormal, clinically significant laboratory results, physical examination findings, and ECG changes will be recorded as AEs if they are deemed the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to each study drug
- Relationship to study procedures
- Outcome
- Action taken regarding each study drug
- Other treatment required
- Determination of "seriousness"

8.4.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) guidelines (Version 4.0). For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; Likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.

- **Grade 4, Life-threatening:** The subject is at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.4.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the product safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as possibly related or related to study drug.

- **Related:**
    - Any event for which there is evidence to conclude that the study drug caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- **Possibly Related:**
    - A single occurrence of an event that is uncommon and *known to be strongly associated with drug exposure,* such as angioedema, anaphylaxis, rhabdomyolysis, Stevens-Johnson syndrome, etc.
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture.
- **Not Related:**
    - The event represents a pre-existing underlying disease which has not worsened on study.
    - The event has the same characteristics of a known side-effect associated with a co-medication received by the study subject.
    - The event is an anticipated medical condition of anticipated severity for the study population (eg, cardiovascular events in an elderly population).
    - The most plausible explanation fore the event is a factor that is independent of exposure to study drug.

8.4.5 Reporting Serious Adverse Events on the SAE Report Form

All SAEs must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the form to the Sponsor's designated safety management vendor. In case of emergency or doubt, the Investigator shall call Sponsor's Medical Monitor for guidance. Follow-up reports must be submitted in a timely manner as additional information becomes available:

U.S. Toll-Free Fax Number: [redacted]

E-mail: [redacted]

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age.
- The date of report.
- A description of the SAE (event, seriousness of the event).
- Causal relationship to the study drug.

Follow-up information for the event should be sent promptly as necessary.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

8.4.6 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide to the investigator a copy of expedited safety reports that it intends to submit to global regulatory authorites.

Deaths: If the death occurred within the SAE collection and reporting period (signed ICF to 28 days after last dose), the investigator must submit the SAE Report Form in the same manner as described above in Section 8.4.5. Additionally, the site must complete the appropriate CRF page. This includes death attributed to progression of the subject's underlying disease.

When reporting a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the primary event term.

8.4.7 Pregnancies: Reporting and Follow-up of Subjects

Pregnancy is not an AE. A pregnancy in a female subject must be confirmed by a positive serum β-hCG test. If a female subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to Sponsor or its designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. A pregnant subject is immediately withdrawn from receiving study treatment. The investigator must follow up with the pregnant subject to completion of the pregnancy to ascertain its outcome (eg, spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether

any AEs occur during pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety management vendor within 24 hours of the investigator becoming aware of the outcome.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome (and be handled on a case by case basis with IRB/IEC approval).

8.4.8 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether the abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (eg, abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Clinically significant laboratory abnormalities will be reported as AEs, however, if the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9 STATISTICS

9.1 Sample Size Determination

The total sample size of 42 evaluable subjects, is considered appropriate, based on clinical judgment, for initial exploration of safety, tolerability, and treatment effect.

9.2 Randomization or Treatment Assignment

Subjects will be randomized centrally in sequential order across all sites to either treatment Arm A or Arm B by FibroGen following a permuted-block randomization list.

Subjects were initially randomized in a 1:1 ratio. In Protocol Amendment 4, the randomization schedule was changed to achieve a final 2:1 randomization (approximately 28 subjects in Arm A and 14 subjects in Arm B).

9.3 Analysis Populations

The Intent-to-Treat (ITT) Population and the Safety Population are both defined as all subjects who took at least one dose of study medication.

The Per Protocol (PP) Population, which will be defined in detail in the Statistical Analysis Plan (SAP), may be used additionally to evaluate the key parameters and may be used in addition to the populations above to evaluate key efficacy parameters.

Additional analysis populations, which will be defined in the statistical analysis plan, may be used to evaluate key parameters.

9.4 Statistical Analysis

Baseline characteristics, safety, efficacy, and biomarker data will be summarized based on available data in the Safety Population, except for the parameters specifically indicated otherwise. The key efficacy and safety evaluations may be additionally summarized based on the PP population. All subjects in the Safety Population will be included in the data listings.

Analyses will include only observed data. Missing data will not be imputed. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Since this is an exploratory study, no adjustments will be made in the significance level for multiple tests.

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, or standard error, median, minimum, and maximum. Categorical variables will be presented by counts of subjects and percentage. Two-sided 95% confidence intervals will be included for the key efficacy parameters

9.4.1 Subject Enrollment and Disposition

The number (%) of subjects who completed or discontinued the study and reasons for early discontinuation will be summarized by treatment for subjects in the safety population.

9.4.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for subjects in the safety population.

9.4.3 Efficacy Analyses

All efficacy endpoints will be summarized by treatment group using descriptive statistics. To compare the efficacy endpoints between the two treatment groups, Fisher's Exact test will be used in dichotomous variables; log-rank test will used in time-to-event variables; t-test or nonparametric test (depending on the data distribution) will be used in continuous variables.

9.4.3.1 Summary of R0 Resection Rate

The proportion of subjects in whom R0 tumor resection is achieved will be summarized. R0 resection is determined by pathological examination of the surgical specimen after resection (Section 7.1.1).

9.4.3.2 Summary of Overall Survival, Time to Progression, and Progression Free Survival

Overall survival (OS) is defined as time from randomization to death of any cause. If a subject is still alive at the time of data analysis, including interim looks and the final analysis, OS is censored at the time of last contact.

Time to progression (TTP) is defined as time from randomization to date of disease progression. If a progression event is not observed, TTP is censored at the last disease evaluation. Progression free survival (PFS) is the same as TTP when a progression event is observed; otherwise, PFS is the same as OS if progression event is not observed.

Median OS/PFS will be estimated using the Kaplan-Meier method. One-year survival rate and 1-year non-progression rate will be tabulated.

9.4.3.3 Summary of Tumor Response

Radiological evaluation of tumor sizes and change from baseline will be summarized by treatment arm. Best RECIST response over the course of treatment period will be tabulated.

Proportion of CA 19-9 responders, which will be defined as CA19-9 decrease of ≥50% from baseline will be tabulated by treatment arm. Subjects with baseline CA19-9 value lower than 2 times upper limit normal are excluded from this analysis.

Proportion of PET responders, which will be defined as the SUV_{max} decrease >30% from baseline, will be tabulated by treatment arm

9.4.3.4 Pharmacokinetic and Pharmacodynamics Analyses

Plasma concentration C_{max} and C_{min}, which are defined below, will be summarized descriptively. Association of these PK parameters with efficacy parameters will be explored using appropriate models such as Cox regression model or logistic regression model, with adjustment for prognostic factors such as ECOG performance status, or other exploratory biomarkers at baseline.

- C_{max}: Maximum observed plasma concentration.
- C_{min}: Trough concentration prior to dose.

9.4.4 Safety Analyses

Safety analysis will include all subjects who receive at least one dose or any part thereof. Treatment-emergent adverse events (TEAEs) will be tabulated to examine their frequency, severity, organ systems affected, and relationship to study treatment. TESAEs and TEAEs

leading to study or treatment discontinuation will be summarized separately. Surgical complications will be summarized by treatment arm, as well.

Other safety data, such as observed and change from baseline lab values, physical examination, will be summarized descriptively at each assessment time point.

9.5 Interim Analysis

No formal interim analysis is planned for this open-label exploratory study. Safety will be monitored continuously and efficacy data will be evaluated periodically.

9.6 Statistical Analysis Plan

The Statistical Analysis Plan will include detailed analysis methods, statistical models, definitions, as well as data handling rules. The SAP will document additional exploratory endpoints that are not specified in the protocol. Any deviations from the SAP will be described in a protocol amendment and/or the clinical study report, as needed.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents.
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments.
- The reported data are reconciled across all data sources (eg, laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation.
- Routine study site monitoring.
- Documented study and system training.
- CRF and query review against source documents.
- Local laboratory normal ranges will be collected from each local laboratory at the onset of the study and throughout the study whenever there are changes to the normal ranges.

11.2 Database Audit

A database audit will be conducted to ensure data quality and integrity.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the ICH E6 Guideline for Good Clinical Practice, the Declaration of Helsinki, any other applicable regulatory requirements, and IRB or IEC requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent Form (ICF) from the subject or the subject's legally authorized representative. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (eg, MedDRA and World Health Organization Drug [WHODrug] Dictionary).

The investigator is responsible for reviewing, verifying, and approving all subject data, ie, CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

15 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

Aikawa T, Gunn J, Spong SM, Klaus SJ, Korc M (2006) Connective tissue growth factor-specific antibody attenuates tumor growth, metastasis, and angiogenesis in an orthotopic mouse model of pancreatic cancer. Molecular Cancer Therapeutics **5:** (5):1108-1116

Burris HA, III, Moore MJ, Andersen J, et al. (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology **15:** (6):2403-2413

Dornhofer N, Spong S, Bennewith K, et al. (2006) Connective tissue growth factor-specific monoclonal antibody therapy inhibits pancreatic tumor growth and metastasis. Cancer Research **66:** (11):5816-5827

Evans, D. B., Abbruzzese, J. L., and Willett, C. G. (2001) Cancer of the pancreas. DeVita, V. T., Hellman, S., and Rosenberg, S. A. *Cancer, Principles and Practice of Oncology*. 6. Philadelphia: 1126-1161.

Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA (2012) The pancreas cancer microenvironment. Clinical Cancer Research **18:** (16):4266-4276

Frazier KS, Grotendorst GR (1997) Expression of connective tissue growth factor mRNA in the fibrous stroma of mammary tumors. Int J Biochem Cell Biol **29:** (1):153-161

Grotendorst GR (1997) Connective tissue growth factor: a mediator of TGF-beta action on fibroblasts. Cytokine Growth Factor Rev **8:** (3):171-179

Hartel M, di Mola FF, Gardini A, et al. (2004) Desmoplastic reaction influences pancreatic cancer growth behavior. World Journal of Surgery **28:** (8):818-825

Hidalgo M, Von Hoff DD (2012) Translational therapeutic opportunities in ductal adenocarcinoma of the pancreas. Clinical Cancer Research **18:** (16):4249-4256

Iacobuzio-Donahue CA, Ryu B, Hruban RH, Kern SE (2002) Exploring the host desmoplastic response to pancreatic carcinoma: gene expression of stromal and neoplastic cells at the site of primary invasion. The American Journal of Pathology **160:** (1):91-99

Kalluri R, Zeisberg M (2006) Fibroblasts in cancer. Nat Rev Cancer **6:** (5):392-401

Katz MH, Fleming JB, Pisters PW, Lee JE, Evans DB (2008) Anatomy of the superior mesenteric vein with special reference to the surgical management of first-order branch involvement at pancreaticoduodenectomy. Ann Surg **248:** (6):1098-1102

Kindler HL, Friberg G, Singh DA, et al. (2005) Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology **23:** (31):8033-8040

Lam S, Van Der Geest RN, Verhagen NA, et al. (2003) Connective tissue growth factor and IGF-I are produced by human renal fibroblasts and cooperate in the induction of collagen production by high glucose. Diabetes **52:** (12):2975-2983

Morganti AG, Massaccesi M, La TG, et al. (2010) A systematic review of resectability and survival after concurrent chemoradiation in primarily unresectable pancreatic cancer. Ann Surg Oncol **17:** (1):194-205

Neesse A, Frese KK, Bapiro TE, et al. (2013) CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer. Proc Natl Acad Sci U S A **110:** (30):12325-12330

Perbal B (2004) CCN proteins: multifunctional signalling regulators. Lancet **363:** (9402):62-64

Picozzi, V. J., Pipas, J. M., Koong, A. C., Giaccia, A. J., Bahary, N., Krishnamurthi, S., Lopez, C., O'Dwyer, P. J., Modelska, K., Carney, M., Hernandez, H., Chou, J., Lee, T., Zhong, M., Porter, S., Neff, T. B., and Valone, F. (2014) FG-3019, a human monoclonal antibody to Connetive Tissue Growth Factor (CTGF), with gemcitabine/erlotinib (G/E) in patients with locally advanced or metastatic pancreatic ductal adenocarconoma (PDAC). Abstract: Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology

Rachfal AW, Brigstock DR (2005) Structural and functional properties of CCN proteins. Vitamins and Hormones **70:**69-103

Rose JB, Rocha FG, Alseidi A, et al. (2014) Extended Neoadjuvant Chemotherapy for Borderline Resectable Pancreatic Cancer Demonstrates Promising Postoperative Outcomes and Survival. Ann Surg Oncol **21:** (5):1530-1537

Ryu B, Jones J, Hollingsworth MA, Hruban RH, Kern SE (2001) Invasion-specific genes in malignancy: serial analysis of gene expression comparisons of primary and passaged cancers. Cancer Research **61:** (5):1833-1838

Sener SF, Fremgen A, Menck HR, Winchester DP (1999) Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg **189:** (1):1-7

Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin **63:** (1):11-30

Van Cutsem E, Vervenne WL, Bennouna J, et al. (2009) Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol **27:** (13):2231-2237

Von Hoff DD, Ervin TJ, Arena FP, et al. (2013) Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology **31:** (4_suppl):LBA148

Wenger C, Ellenrieder V, Alber B, et al. (1999) Expression and differential regulation of connective tissue growth factor in pancreatic cancer cells. Oncogene **18:** (4):1073-1080

Xie D, Nakachi K, Wang H, Elashoff R, Koeffler HP (2001) Elevated levels of connective tissue growth factor, WISP-1, and CYR61 in primary breast cancers associated with more advanced features. Cancer Research **61:** (24):8917-8923

17 APPENDICES

Appendix 1 Schedule of Assessments

Assessments	Screening Period [a]	Treatment Period (6 Cycles)			EOT/ Re-staging	Safety Follow-up	Surgery & Follow-up	Long-Term Follow-up [c]
	-28 to -1 days	Day 1 [d] (± 2 days)	Day 8 (± 2 days)	Day 15 (± 2 days)	Cycle 6 Day 28 (±2 days)	+28 days after last dose (±7 days)	Surgery (+30 days after discharge)	at least 28 weeks after EOT
Written Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographics/Medical History	X							
Vital Signs/Weight (include height at screening)	X	X	X	X	X	X		
Performance status [e]	X	X			X			
Physical Exam	X	X	X	X	X	X		
12-Lead EKG	X				X			
CBC (including; differential, platelets)	X	X	X	X	X	X		
Serum Chemistry (include phosphorous)	X	X	X	X	X	X		
Serum Pregnancy Test	X				X			
Nab-Paclitaxel		X	X	X				
Gemcitabine		X	X	X				
FG-3019		X	X [f]	X				
CA19-9	X	X			X			
CT Scan [g]	X				X			
Laparoscopic staging	X							
FDG-PET	X				X			
Tumor Tissue Collection [h]	X				X		X [i]	
Adverse Events [b]	X	X	X	X	X	X		
Concomitant Medications [b]	X	X	X	X	X	X		
Surgery/Post-surgical Evaluation							X	
Progression/Survival/Follow-on Treatment [c]								X

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

Footnotes on following page.

a. All screening activities should be conducted within 28 days prior to Day 1 Cycle 1 dosing except PET and Laparoscopy, in which the screening windows are extended up to 30 days and 42 days prior to Day 1 Cycle 1 dosing respectively.

b. Adverse events and concomitant medications are collected from the signing of the Informed Consent through 28 days following a subjects last dose of study treatment. Follow-on treatment for pancreatic cancer will also be collected through the Long Term Follow-up Period.

c. All subjects will be followed in Long Term Follow-up until the last subject enrolled completes 28 weeks of follow-up following EOT. It is recommended that Long Term Follow-up be conducted approximately every month for the first 28 weeks following EOT and quarterly thereafter.

d. Day 1 visit window applies to Day 1 of Cycle 2 through Cycle 6 only.

e. ECOG to be evaluated at baseline and every 8 weeks thereafter (including EOT). Karnofsky score will be evaluated at EOT only for the purposes of determining surgical eligibility.

f. For Cycle 1 only.

g. The baseline CT scan must be performed within 2 weeks of Day 1, Cycle 1 dosing. CT scans to be conducted approximately every 8 weeks thereafter, in accordance with SOC (prior to the start of Cycle 3, Cycle 5, and at EOT). CT scans will be performed per institutional protocols for pancreatic cancer.

h. For subjects enrolled at participating study centers only:

- At baseline, subjects will undergo an EUS collecting up to 4 core biopsies during screening unless adequate tissue is available from a previous biopsy.
- If post-treatment tumor tissue cannot be safely obtained during surgery or the subject is deemed ineligible for surgery, a post-treatment EUS collecting up to 4 core biopsies will be performed. EUS should be performed during the surgical follow-up period OR within a week of determining that a subject is ineligible for surgery.
- 19G needles are preferred for core biopsies. 22G needles are allowed if 19G needles are contraindicated per physician's discretion.

i. Post treatment tumor tissue may be obtained during surgery for any subject deemed eligible for surgical exploration, regardless of a site's participation in the optional tumor study. These samples may be included in biomarker studies.

Appendix 2 Pharmacokinetics and Pharmacodynamics Sampling Times

TIMEPOINT			FG-3019 (Plasma)	HAHA (Plasma)	CTGF (Plasma)	Protein Expression Profile (Plasma)	PAX Gene (Whole Blood)
CYCLE	DAY	TIME					
Screening							
1	1	Pre-dose [a]	X	X [b]	X	X	X
		Post-dose [c]	X				
	8	Pre-dose [a]	X				
		Post-dose [c]	X				
	15	Pre-dose [a]	X				
		Post-dose [c]	X				
2	15	Pre-dose [a]	X				
3	1	Pre-dose [a]	X			X	X
		Post-dose [c]	X				
5	1	Pre-dose [a]	X			X	X
6	1	Pre-dose [a]	X				
		Post-dose [c]	X				
	28/EOT		X			X	X
Safety FU	28 days post last dose		X	X	X		

Abbreviations: CTGF = connective tissue growth factor; EOT = end of treatment; EUS = endoscopic ultrasound; FU = follow up; HAHA = human anti-human antibody

a. Pre-dose is prior to the administration of chemotherapy.
b. Blood samples for HAHA may be collected during screening.
c. Post dose is during 30 minutes to 2 hours post-end of infusion of FG-3019.

Appendix 3 Dose Modification for Nab-paclitaxel/Gemcitabine

Dose modification will be followed according to package inserts across all treatment cycles throughout the study. However, doses of gemcitabine and/or nab-paclitaxel may be modified according to the investigator's discretion based on the subject's medical condition if it differs from package insert.

Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	Absolute Neutrophil Count ($cells/mm^3$)		Platelet count ($cells/mm^3$)	Nab-paclitaxel / Gemcitabine
Day 1	<1500	OR	<100,000	Delay doses until recovery
Day 8	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level
	<500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were reduced or given without modification:	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level from Day 8
	<500	OR	<50,000	Withhold doses
Day 15: IF Day 8 doses were withheld:	≥1000	OR	≥75,000	Reduce 1 dose level from Day 1
	500 to <1000	OR	50,000 to <75,000	Reduce 2 dose levels from Day 1
	<500	OR	<50,000	Withhold doses

Dose Modifications for Non-Hematologic Toxicity

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

IMPORTANT NOTE: Dose modifications of gemcitabine and nab-paclitaxel may follow the guidelines outlined in the package inserts, but may also be modified at the discretion of the Investigator. It is ultimately the Investigator's decison to reduce, withhold or discontinue treatment. In the event that chemotherapy is modified or withheld for 1 or 2 doses, as per standard of care, the dosing schedule of FG-3019 should be maintained, at the discretion of the Investigator. In the event that chemotherapy is withheld for more than 2 doses, the medical monitor should be contacted. If chemotherapy is terminated, treatment with FG-3019 should be discontinued.

Gemcitabine Warnings and Precautions

- Schedule-dependent toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly. Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression.
- Pulmonary Toxicity and Respiratory Failure: Discontinue gemcitabine immediately for unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity.
- Hemolytic-Uremic Syndrome (HUS): Monitor renal function prior to initiation and during therapy. Discontinue gemcitabine for HUS or severe renal impairment.
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during therapy. Discontinue gemcitabine for severe hepatic toxicity.
- Embryofetal Toxicity: Can cause fetal harm. Advise women of potential risk to the fetus.
- Exacerbation of Radiation Therapy Toxicity: May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy.
- Capillary Leak Syndrome: Discontinue gemcitabine.
- Posterior reversible encephalopathy syndrome (PRES): Discontinue gemcitabine.

Nab-paclitaxel Warnings and Precautions

- Causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed.
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption.
- Sepsis occurred in patients with or without neutropenia who received nab-paclitaxel in combination with gemcitabine; interrupt nab-paclitaxel and gemcitabine until sepsis resolves, and if neutropenic, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels.
- Pneumonitis occurred with the use of nab-paclitaxel in combination with gemcitabine; permanently discontinue treatment with nab-paclitaxel and gemcitabine.
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug.
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution.
- Nab-paclitaxel contains albumin derived from human blood, which has a theoretical risk of viral transmission.
- Fetal harm may occur when administered to a pregnant woman.
- Advise women of childbearing potential to avoid becoming pregnant while receiving nab-paclitaxel.
- Advise men not to father a child while on nab-paclitaxel.

Appendix 4 Performance Status Scales / Scores

Performance Status Criteria			
ECOG (Zubrod)		**Karnofsky**	
Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.

ECOG = Eastern Cooperative Oncology Group

Cancer Therapy Evaluation Program
Common Toxicity Criteria, Version 2.0
DCTD, NCI, NIH, DHHS March 1998

Revised March 23, 1998
Publish Date: April 30, 1999