Synopsis

Clinical Trial NCT04699539

Last approval data: The study protocol was approved on August 16, 2020.

Study title: Recurrence-pattern-based-volume versus conventional-volume stereotactic body radiation therapy in locally advanced pancreatic cancer: an open-label, randomized, phase 2 trial

Regimen:

Arm A: Stereotactic body radiation therapy (SBRT) with a conventional-volume. Gemcitabine (1000 mg/m^2) and nab-paclitaxel (125mg/m^2) administered intravenously on day 1 and 8 of each 21-day cycle for six cycles before SBRT.

Arm B: Stereotactic body radiation therapy (SBRT) with a recurrence-pattern-based-volume. Gemcitabine (1000 mg/m^2) and nab-paclitaxel (125mg/m^2) administered intravenously on day 1 and 8 of each 21-day cycle for six cycles before SBRT.

Study phase: phase 2

Research hypothesis: SBRT with a recurrence-pattern-based-volume will provide improved survival for patients with locally advanced pancreatic cancer compared with SBRT with a conventional-volume.

Objectives:

Primary objective:

- To assess one-year progression free survival rate of patients with locally advanced pancreatic cancer receiving SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine and nab-paclitaxel.

Secondary objective:

- To investigate overall survival.
- To investigate progression free survival
- To evaluate and compare overall safety and adverse effects of SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine and nab-paclitaxel, determined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Pre-specified exploratory analysis

- To evaluate the overall survival and progression free survival of subgroups.

Study design: This is an open-label, phase 2, randomized controlled trial, which attempts to compare outcomes of patients with locally advanced pancreatic cancer receiving SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine and nab-paclitaxel. Patients with cytologically or histologically verified pancreatic adenocarcinoma are eligible for this study. Patients were randomly allocated into SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine (1000 mg/m^2) and nab-paclitaxel (125mg/m^2) administered intravenously on day 1 and 8 of each 21-day cycle for six cycles. Prior treatment, assessment of eligibility and safety evaluations during the study are conducted by a committee composed of a group of study investigators who are experts in treating patients with pancreatic cancer. Any patient who meets criteria for discontinuation following treatment will proceed to follow-up. All patients who are discontinued from treatment will continue to be followed for safety, progression, and overall survival

after discontinuation of study medication based on the assessment schedules. This study will continue for about five years.

Study durations:

Enrollment is planned to take about three years.

Treatment continues until disease progression or unacceptable toxicities.

Follow-up is completed within approximately 3 years after the initiation of treatment.

Anticipated duration of the study is about 5 years.

Study center: single center

Patient eligibility criteria:

Key inclusion criteria:

- Cytologically or histologically verified pancreatic adenocarcinoma
- Imaging examinations confirmed locally advanced pancreatic cancer
- No previous radiotherapy, chemotherapy, immunotherapy or targeted therapy
- ECOG of 0 to 1
- Age of 18 years or older
- Adequate bone marrow function, defined as: Absolute neutrophil count (ANC) ≥ 1.5×10^9 cells/L, leukocyte count≥ 3.5×10^9 cells/L, platelets ≥ 70×10^9 cells/L, hemoglobin ≥ 8.0 g/dl
- Adequate liver and renal, defined as: Albumin > 2.5 g/dL, total bilirubin < 3 mg/dL, creatinine < 2.0 mg/dL, AST<2.5 × ULN (Upper Limit of Normal) (0-64U/L), ALT<2.5 × ULN (0-64U/L)
- Adequate blood clotting function, defined as: international normalized ratio (INR)

< 2 (0.9-1.1)

- Ability of the research subject or authorized legal representative to understand and the willingness to sign a written informed consent document

Key exclusion criteria:

- Previously receiving radiotherapy, immunotherapy or targeted therapy
- Evidences of metastatic disease confirmed by chest CT or PET-CT
- ECOG ≥2
- Age <18 years
- Secondary malignancy
- Abnormal results of blood routine examinations and liver and kidney and coagulation tests
- Patients with active inflammatory bowel diseases or peptic ulcer
- Gastrointestinal bleeding or perforation within 6 months
- Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals
- Medical history of symptomatic congestive heart failure: New York Heart Association Class III to IV
- Medical history of respiratory insufficiency
- Women who are pregnant or breastfeeding
- Participation in another clinical treatment trial
- Inability of the research subject or authorized legal representative to understand and the willingness to sign a written informed consent document

Statistical considerations:

Sample size: Previous studies have demonstrated that one-year progression free survival rate of SBRT with chemotherapy for pancreatic cancer ranged from 17%-60%. Hence, it was supposed that the one-year progression free survival rate of SBRT with a recurrence-pattern-based-volume and conventional-volume is 60% and 30% months, respectively. Therefore, we calculated that 80 patients were needed to be enrolled (40 per group) to give 80% power to detect a statistically significant difference between treatment groups with a type I error of 5% (two-sided).

Analyses:

Demographics and baseline characteristics: Demographic, disease and treatment characteristics were summarized with frequency and percentage for categorical variables, and median and interquartile range (IQR) for continuous variables. Categorical binary variables were compared with Fischer's exact test or χ^2 test (depending on number of observations). Student t-test or Mann-Whitney U test was used for analysis in the case of normally or non-normally distributed continuous covariates.

Efficacy analyses: The primary endpoint is one-year progression free survival rate, defined as the ratio of the number of patients without progression at one year to the total number of patients. While progression free survival is the time from the random assignment to treatment until documentation of any clinical or radiological disease progression or death, whichever occurred first.

The secondary endpoint is overall survival and progression free survival. Overall survival is defined as the time from the random assignment to treatment until death

irrespective of cause. The corresponding 95% CI will be estimated using the Kaplan-Meier product-limit method. OS and PFS curves will be plotted using the Kaplan-Meier method. Log-rank method will be used to compare OS and PFS of two groups.

Safety analyses: Safety analyses will be summarized in all treated patients. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All treatment-emergent adverse effects and severe adverse effects will be tabulated using worst grade per NCI CTCAE by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE criteria.

Exploratory analyses: Post-hoc subgroup analyses of OS and PFS will be performed. Patients will be categorized into different subgroups according to specified factors.

1. Introduction

1.1 Background

Pancreatic cancer is one of the most lethal malignancies and fourth leading cause of cancer death in both genders in US, where the mortality and incidence increase over the past decade with a lowest 5-year survival rate of 13% among all cancers [1]. Although surgical resection is deemed to provide long-term disease control, only 20% patients were candidates for upfront surgery. Therefore, SBRT as local therapy with chemotherapy is preferred.

For decades, a uniform 2-5 mm margin expansion of gross tumor volume (GTV) to form planning target volume (PTV) has been recommended. It is more likely that pancreatic cancer cells extend along vessels, nerves, and collagen structures [2], which may result in high rates of perineural (~62%) and lymphovascular (~54%) invasion [3, 4]. Therefore, 2-5 mm margin expansion of GTV may not sufficient to cover micro-lesions. As a result, the Alliance A021501 targeted gross tumor and full circumstance of involved vasculature with tight margins, which was consistent with ASTRO clinical practice guidelines from 2019 and which reflected caution towards large target volume in the setting of hypofractionated radiotherapy for pancreatic cancer [5]. Additionally, similar notion has also been proposed by Australasian Gastrointestinal Trials Group and Trans-Tasman Radiation Oncology Group that GTV should include fibrotic areas near vessels, which was defined as tumor vessel interface. In principle, any major vessel within 5 mm of the tumor should be contoured from 5 mm proximal to 5 mm distal of the GTV [6]. In our previous study,

it was demonstrated that areas closer to the celiac artery, superior mesenteric artery, and retroperitoneal space were at a high risk of local recurrences. Therefore, we postulated that nonuniform expansion of GTV covering enough volumes around the celiac artery, superior mesenteric artery, and retroperitoneal space was required [7]. As a result, the aim of our study was to evaluate outcomes of recurrence-pattern-based-volume versus conventional-volume SBRT for locally advanced pancreatic cancer.

1.2 Research hypothesis

SBRT with a recurrence-pattern-based-volume would provide improved survival for locally advanced pancreatic cancer compared with SBRT with a conventional-volume.

1.3 Objectives

1.3.1 Primary objective

- To assess one-year progression free survival rate of patients with locally advanced pancreatic cancer receiving SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine and nab-paclitaxel.

1.3.2 Secondary objective:

- To investigate overall survival.
- To investigate progression free survival.
- To evaluate and compare overall safety and adverse effects of SBRT with a recurrence-pattern-based-volume or conventional-volume after gemcitabine and

nab-paclitaxel, determined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

1.3.3 Exploratory analysis

- To evaluate the overall survival and progression free survival of subgroups.

2. Ethical considerations

2.1 Good clinical practice

This study will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee approval/favorable opinion prior to initiation of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

2.2 Institutional Review Board/Independent Ethics Committee

Before the study, investigators must have written and dated approval/favorable opinion

from the Institutional Review Board/Independent Ethics Committee for the protocol,

consent form, and any other written information to be provided to participants.

Investigators should also provide the Institutional Review Board/Independent Ethics Committee with a copy of the Investigator Brochure or product labeling information to be provided to participants and any updates.

Investigators should also provide the Institutional Review Board/Independent Ethics Committee with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

All potential serious breaches must be reported to Institutional Review Board/Independent Ethics Committee immediately. A serious breach is a breach of the conditions and principles of Good Clinical Practice in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

2.3 Informed consent

Participants must be clearly and fully informed of the purpose of procedures of the study, their potential benefits and risks, and other critical issues about the clinical trial by investigators. However, in situations where participants could not receive consent, their legally acceptable representatives should be informed of procedures of the study, their potential benefits and risks, and other critical issues about the clinical trial.

Investigators should prepare an appropriate informed consent, which include all elements required by International Conference on Harmonization, Good Clinical

Practice and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

(1) Provide the informed consent form and written information in the language where participants are most proficient. The purposes and procedures, potential benefits and risks and other issues of the study should be clarified clearly, and the language must be non-technical and easily understood.

(2) Provide enough time for participants or their leally acceptable representatives to have a comprehensive understanding about the details of the study.

(3) Obtain and keep an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.

(4) Obtain the Institutional Review Board/Independent Ethics Committee's written approval/favorable opinion of the written informed consent form and any other information to be provided to the participants before study initiation, and after any revisions are completed for new information.

(5) If informed consent is initially given by a participant's legally acceptable representative, and the participant later becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant. Meanwhile, the participant must also be informed about the details of the study to the extent compatible with his or her

understanding

(6) Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator or a person designated by the investigator should fully inform the participant or the participant's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements. The consent form must also include a statement that regulatory authorities have direct access to subject records.

The explicit wish of a participant who is unable to provide his or her written consent, but who is capable of giving an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

3. Investigational plan

3.1 Study design

This is an open-label, single center, phase 2, randomized controlled trial to compare outcomes of patients with locally advanced pancreatic cancer receiving SBRT of a recurrence-pattern-based-volume following chemotherapy with those of patients receiving SBRT of a conventional-volume after chemotherapy. Patients with

cytologically or histologically verified pancreatic adenocarcinoma are eligible for the study. Patients enrolled in the study will be randomly allocated into two groups: SBRT of a recurrence-pattern-based-volume and a conventional-volume following chemotherapy. Treatment continued until disease progression or unacceptable toxicity.

For patients with SBRT of a recurrence-pattern-based-volume following chemotherapy: gemcitabine (1000 mg/m^2) and nab-paclitaxel (125mg/m^2) administered intravenously on day 1 and 8 of each 21-day cycle for six cycles. SBRT would be performed two to three weeks after completion of chemotherapy. It would be delivered in five to six fractions, and prescription dose would be 30-50Gy/5-6f. The target volume delineations were as follows. Gross tumor volume (GTV) was defined as a radiographically evident gross disease. Planning target volume (PTV) should include GTV with a 3mm margin in the anterior and lateral directions, 10mm margin in the cranial and caudal directions that should cover the full circumstance of celiac artery and superior mesenteric artery, 15mm in the posterior direction that should cover the retroperitoneal space.

For patients with SBRT of a conventional-volume following chemotherapy: The same chemotherapy regimen and radiation dose would be given. The target volume delineations were as follows. Gross tumor volume (GTV) was defined as a radiographically evident gross disease. PTV should include GTV with a uniform 3mm margin in all directions.

3.2 Durations of the study

Enrolment is planned to occur approximately 2 to 3 years. Follow-up is projected to be continued for approximately 3 years after the initiation of treatment. Therefore, the anticipated duration of the study is about 5 years.

The screening period is about 2 to 3 weeks. Patients are required to receive 6 cycles of chemotherapy. Upon commencing study treatment, patients may continue receiving study drug until the occurrence of any of unacceptable toxicity. Regardless of reason for discontinuation from study treatment, all participants may be contacted every month until death or until follow-up data collection is no longer of scientific value or otherwise needed (at the investigator's discretion), to obtain information about subsequent treatment(s) and survival status.

3.3 Study population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion criteria

1. Signed written informed consent

1) Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal care.

2) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2. Target population

1) Cytologically or histologically verified pancreatic adenocarcinoma.

2) No history of radiotherapy, chemotherapy, immunotherapy or targeted therapy.

3) Contrast enhanced CT/MR and PET-CT are required to determine stage by multidisciplinary approach. These imaging examinations provided should be obtained one to two weeks before study initiation, when available, so that the imaging is representative of the baseline state prior to entry into the present study.

4) ECOG of 0 to1

5) Age of 18 years or older

6) Adequate bone marrow function, defined as:

- Absolute neutrophil count (ANC) $\geq 1.5\times10^9$ cells/L
- Leukocyte count$\geq 3.5\times10^9$ cells/L
- Platelets $\geq 75\times10^9$ /L
- Hemoglobin $\geq$ 8.0 g/dl

7) Adequate liver and renal function, defined as:

- Albumin > 2.5 g/dL
- Total bilirubin < 3 mg/Dl
- Creatinine <2.0 mg/Dl
- AST<2.5 × ULN (Upper Limit of Normal) (0-64U/L)
- ALT<2.5 × ULN (0-64U/L)

8) Adequate blood clotting function, defined as:

- International normalized ratio (INR) < 2

9) Women must not be breastfeeding nor pregnant.

10) Investigators shall counsel women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the use of highly effective methods of contraception. And they must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception including:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

——Oral

——Intravaginal

——Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:

——Oral

——Intravaginal

——Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Vasectomized partner
- Complete sexual abstinence

3.3.2 Exclusion criteria

1) Treatment prior to enrolment into the study including radiotherapy, chemotherapy, immunotherapy and targeted therapy.

2) Lack of sufficient imaging examinations to evaluate objective response during chemotherapy.

3) Age of 18 years or younger.

4) ECOG of 2 points or more.

5) Medical history of myocardial infarction within 6 months before registration, symptomatic congestive heart failure (New York Heart Association Class III to IV), troponin levels consistent with myocardial infarction as defined according to American College of Cardiologists (ACC) guidelines, unstable angina, or serious cardiac arrhythmia requiring treatment

6) Medical history of respiratory insufficiency

7) Significant gastrointestinal bleeding or perforation within the last 6 months of randomization/registration

8) History of active inflammatory bowel diseases or peptic ulcer

9) History of other malignancy(ies)

10) Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals

11) Inadequate bone marrow function, defined as:

- Absolute neutrophil count (ANC) < 1.5×10^9 cells/L
- Leukocyte count < 3.5×10^9 cells/L
- Platelets < 75×10^9 /L
- Hemoglobin < 8.0 g/dl

12) Inadequate liver and renal function, defined as:

- Albumin ≤ 2.5 g/dL
- Total bilirubin ≥ 3 mg/ dL
- Creatinine ≥ 2.0 mg/dL
- AST ≥ 2.5 × ULN (Upper Limit of Normal) (0-64U/L)
- ALT ≥ 2.5 × ULN (0-64U/L)

13) Inadequate blood clotting function, defined as:

- International normalized ratio (INR) ≥ 2

14) Social, familial, or geographical factors that would interfere with study participation or follow-up

15) Current participation in a therapeutic clinical study

16) Pregnant or breastfeeding, or planning to become pregnant

17) Inability of the research subject or authorized legal representative to understand and the willingness to sign a written informed consent document

3.4 Concomitant treatments or examinations

3.4.1 Prohibited and/or restricted treatments

Any immunosuppressive agents or systemic corticosteroids should be consulted via

multidisciplinary approaches.

3.4.2 Restrictions and precautions of contrast enhanced CT or MRI

Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to CT and MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. Contrast should not be given to this subject population. In addition, participants with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and principal investigator should determine the appropriate precautions or guidelines that should be instituted for subjects with tattoos, body piercings or other body art. The ultimate decision to perform CT and MRI in an individual patient in this study rests with the site radiologist, the investigator and the standard set by the Institutional Review Board/Independent Ethics Committee.

3.5 Discontinuation of participation following any treatment with study drugs or SBRT

Participants MUST discontinue chemotherapy drug or SBRT at the discretion of the investigator for any of the following reasons:

- Participant’s request to stop study treatment

- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation including the development of treatment-emergent, treatment-related unacceptable toxicity

In the case of pregnancy, the investigator must immediately notify the Institutional Review Board/Independent Ethics Committee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Institutional Review Board/Independent Ethics Committee must occur.

All participants who discontinue treatment should comply with protocol specified follow-up procedures. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If chemotherapy or SBRT is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form page.

The primary reason for the permanent discontinuation of study treatment must be documented in the subject's medical records and electronic case report form. Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated with study regimens.

If the subject voluntarily discontinues from treatment due to toxicity, adverse events will be recorded as the primary reason for permanent discontinuation in the electronic case report form.

All subjects who permanently discontinue all study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up.

All subjects who permanently discontinue all study treatment without disease progression will be followed for progression. In addition, all subjects who permanently discontinue all study treatment will be followed for survival and new anti-cancer therapy. Follow-up contact to assess survival and new anti-cancer therapy may be made via clinic visit, phone, or email.

3.6 Withdraw of consent

Participants who request to discontinue treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of

consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate case report form page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law. All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

4. Rationale

4.1 Rationale for the trial and selected population

Pancreatic cancer is one of the most lethal malignancies and fourth leading cause of cancer death in both genders in US, where the mortality and incidence increase over the past decade with a lowest 5-year survival rate of 13% among all cancers.1

Although surgical resection is deemed to provide long-term disease control, only 20% patients were candidates for upfront surgery. Therefore, regarding locally advanced pancreatic cancer, SBRT is given the first priority as the radical local therapy, which was recommended in NCCN guideline. Additionally, gemcitabine and nab-paclitaxel was also considered as the first-line chemotherapy regimen. Therefore, SBRT plus gemcitabine and nab-paclitaxel was a preferred in the case of locally advanced pancreatic cancer. Nevertheless, owing to that perineural and perivascular invasion are very common in pancreatic cancer, a uniform expansion of GTV to form PTV without taking potential micro-lesions around the tumor into account may result in early treatment failure. Previous studies have demonstrated that peri-celiac artery and superior mesenteric artery, retroperitoneal space, which may be noted as the "triangle"volume as demarcated by the celiac artery and superior mesenteric artery medially, the common hepatic artery superiorly and the portal vein/superior mesenteric vein laterally are areas at risk of recurrence. Hence, these areas should be also encompassed in GTV to be irradiated. As a result, the aim of the study was to compare outcomes of patients with locally advanced pancreatic cancer receiving SBRT of a recurrence-pattern-based-volume with those of patients receiving SBRT of a conventional-volume following chemotherapy.

4.2 Rationale for dose selection/regimen/modification

4.2.1 Gemcitabine and nab-paclitaxel

Gemcitabine (1000 mg/m^2) and nab-paclitaxel (125mg/m^2) is administered

intravenously on day 1 and 8 of each 21-day cycle for six cycles, which has been recommended in NCCN guideline. Doses calculated from body surface area are truncated in 10 mg/body and nab-paclitaxel is truncated in 10 mg/body. However, the acceptable range drug dose is ±10%. Calculation of body surface area and drug dosage is the responsibility of the institution, and the body surface area and drug dosage at the time of enrollment are for double-checking with the physician's calculation. Weight change after initiation of treatment should not be corrected for dosage if the weight is less than 5kg to that at enrollment. However, if weight loss exceeding 5kg is observed, the body surface area should be recalculated to determine the dosage again. After recalculation, if weight loss exceeds 5kg relative to body weight at recalculation, the body surface area should be recalculated to determine the dose. Details of dose modifications would be shown in following sections.

4.3 Rationale for endpoints

4.3.1 Efficacy endpoints

Primary endpoints:

The primary efficacy endpoint of the study is one-year progression free survival (PFS) rate. Given that it was a phase 2 trial, PFS or PFS rate could be considered as the primary outcome. PFS is an acceptable measure of clinical benefit for a randomized phase III trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for many clinical trials on

outcomes evaluations of immunotherapy or targeted therapy in different types of cancer. PFS will be assessed per RECIST 1.1 by a blinded independent central imaging vendor that will be blinded to the treatment assignment to minimize any bias in the response assessments. In addition, final determination of radiologic progressive disease will be based on the blinded independent central imaging vendor assessment of progression, rather than local site investigator/radiology assessment. Expedited assessment by the blinded independent central imaging vendor in instances of suspected radiological progression will be communicated to the study team. Hence, one-year PFS rate is the ratio of the number of patients without disease progression to the total number of patients.

Secondary endpoint:

The secondary endpoint of the study is overall survival (OS) and PFS. Although the study allows participants to select other subsequent anti-cancer treatment recommended by NCCN guideline upon progression, which may affect the assessment of OS, OS is still a standard endpoint to demonstrate superiority of anticancer therapy.

4.3.2 Safety endpoints

The safety objective is to characterize the safety and tolerability of SBRT with a recurrence-pattern-based volume and a convetional-volume following chemotherapy in patients with locally advanced pancreatic cancer. The following safety parameters will be analyzed: adverse effects and severe adverse effects graded per NCI CTCAE,

Version 4.0 criteria with time to onset/recovery, causality and outcome; changes in laboratory values, vital signs since baseline, treatment discontinuations and reason for discontinuation, death and cause of death, etc. Concomitant medications will be collected with time and reasons for use. These are routine safety parameters collected and analyzed in Phase II/III oncology trials.

5. Study treatments

5.1 Treatment assignment

5.1.1 Treatment group

Patients will be randomly assigned to two different treatment groups: SBRT of a recurrence-pattern-based volume and conventional volume following gemcitabine and nab-paclitaxel. Once assigned, participants will remain on study in their treatment group and will not change groups.

5.1.2 Method of treatment allocation

Patients are enrolled by the investigators and randomly assigned (1:1) to receive SBRT of a recurrence-pattern-based volume or conventional volume following gemcitabine and nab-paclitaxel with an interactive voice or web response system. A randomization list is produced by the response technology provider, which ensure random assignment of patients' ID to randomization numbers after they are eligible. Each number is linked to a treatment group.

5.1.3 Blinding

This study is an open-label study and no blinding will be performed.

5.2 Study drugs

Study drug includes both Investigational [Medicinal] Product and Non-investigational [Medicinal] Product and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication
- Other drugs administered as part of the study that are critical to claims of efficacy
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

5.2.1 Investigational agents

There are no investigational products in this study.

5.2.2 Non-investigational agents

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product is: gemcitabine and nab-paclitaxel.

5.3 Administration

Trial Treatment should begin within 3 days of randomization. The treatments to be used in this trial are outlined below in Table 1.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

Table 1. Trial treatment

Drug	Dose/Potency	Dose frequency	Route of Administration	Regimen/ Treatment Period	Use in Study
SBRT of a recurrence-pattern-based volume following gemcitabine and nab-paclitaxel					
Gemcitabine	1000 mg/m^2	Q3W	IV infusion	d1, 8, each 21-day cycle for 6 cycles	Experimental
Nab-paclitaxel	125 mg/m^2	Q3W	IV infusion	d1, 8, each 21-day cycle for 6 cycles	Experimental
SBRT of a conventional volume following gemcitabine and nab-paclitaxel					
Gemcitabine	1000 mg/m^2	Q3W	IV infusion	d1, 8, each 21-day cycle for 6 cycles	Comparator
Nab-paclitaxel	125 mg/m^2	Q3W	IV infusion	d1, 8, each 21-day cycle for 6 cycles	Comparator

Abbreviations: Q3W=every 3 weeks, PD=progressive disease

5.4 Handling and storage of study drugs

Gemcitabine and nab-paclitaxel must be stored in a secure area under the appropriate physical conditions for the products. Study treatments are to be stored at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required. Access to and administration of the study treatment will be limited to the investigator and authorized site staff. Gemcitabine and nab-paclitaxel must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol. Procedures for final disposition of unused study treatments will be provided in the Study Procedures Manual.

5.5 Treatment compliance

Compliance with study treatment will be assessed through querying the participant during the site visits and documented in the source documents and electronic case report form.

A record of the number of study drugs dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates of dose modifications and/or interruptions or dose reductions will also be recorded in the electronic case report form. The investigator will make every effort to bring non-compliant subjects in to compliance.

5.6 Procedures of SBRT

SBRT was performed via Cyberknife, an image-guided frameless stereotactic robotic radiosurgery system (Accuray Corporation, Sunnyvale CA). The protocol was similar to that in our previous studies.[5, 6] Gold fiducials within or adjacent to the pancreatic tumor were preferable. Gross tumor volume (GTV) was defined as a radiographically evident gross disease. In the case of the recurrence-pattern-based volume, PTV should include GTV with a 3mm margin in the anterior and lateral directions, 10mm margin in the cranial and caudal directions that should cover the full circumstance of celiac artery and superior mesenteric artery, 15mm in the posterior direction that should cover the retroperitoneal space. While in the conventional-volume group, PTV should include GTV with a uniform 3mm margin in all directions. Dose constraints of organs at risk were referred to the American Association of Physicists in Medicine guidelines in TG-101.[7] The initial contours were reviewed together by a radiation oncologist and a radiologist for accuracy. Ninety percent of PTV should be covered by the prescription dose. The prescription isodose line is limited to 70-75%, which would restrict the tumor Dmax. The prescribed dose of PTV varies from 30-50Gy/5-6f.

Table 2. Dose constraints

Serial tissues	**Max critical volume above threshold**	**Five fractions**	
		Threshold dose (Gy)	**Max point dose (Gy)**
Spinal cord	<0.35cc	23 (4.6Gy/f)	30 (6Gy/f)
Esophagus	<5cc	19.5 (3.9Gy/f)	35 (7Gy/f)
Stomach	<10cc	18 (3.6Gy/f)	32 (6.4Gy/f)
Duodenum	<5cc	18 (3.6Gy/f)	32 (6.4Gy/f)
	<10cc	12.5 (2.5Gy/f)	
Jejunum/ileum	<5cc	19.5 (3.9Gy/f)	35 (7Gy/f)
Colon	<20cc	25 (5Gy/f)	38 (7.6Gy/f)

Parallel tissues	Minimum critical volume below threshold	Threshold dose (Gy)	Max point dose (Gy)
Liver	700cc	21 (4.2Gy/f)	NA-Parallel tissue
Renal cortex (right and left)	200cc	17.5 (3.5Gy/f)	NA-Parallel tissue

5.7 Dose selection

Gemcitabine and nab-paclitaxel: the dose amount required to prepare the gemcitabine and nab-paclitaxel infusion solution will be based on 1000 mg/m^2 and 125 mg/m^2, on day 1 and 8, each 21-day for a cycle. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.8 Protocol treatment termination/completion criteria

5.8.1 Definition of protocol treatment completion

There is no definition of protocol treatment completion because both groups continue protocol treatment until they meet protocol discontinuation criteria.

5.8.2 Criteria for termination of protocol treatment

Protocol treatment is terminated in any of the following cases:

1) Judged as protocol treatment is ineffective (when progression of the underlying disease was observed after initiation of treatment).

*Even if it is judged to be PD in the response evaluation by the image, it is not considered to be the progression of the pathogenesis, when it is judged that the protocol treatment continuation is clinically appropriate, and the protocol treatment is continued.

2) Protocol treatment cannot be continued due to adverse events.

(a) Grade 4 non-hematologic toxic (except for the following adverse events) 'hypernatremia', 'hyponatremia', 'hyperkalemia', 'hypokalemia', 'hyperglycemia', 'hypoglycemia', 'increased alkaline phosphatase', 'alanine aminotransferase', 'increased aspartate aminotransferase', 'increased blood bilirubin', 'increased serum amylase', 'increased lipase', 'increased GGT'. (Non-hematological toxicity: Adverse events other than anemia, bone marrow hypocellular, lymphocyte count decreased, neutrophil count decreased, white blood cell decreased, platelet count decreased, and CD4 lymphocyte decreased in CTCAE v4.0)

(b) In the presence of Grade 1-3 pneumonitis (interstitial pneumonitis)

(c) When an allergic response to Grade 3 is observed

(d) When macular edema is confirmed

(e) If the next course cannot be initiated beyond 21 days due to adverse events related to the protocol treatment, determine as possible, probable, definite.

f) When the criteria for terminating protocol treatment in the treatment modification criteria (5.9) are met.

g) Adverse events other than the treatment modification criteria that the investigator/sub-investigator judges to require termination of protocol treatment

(3) If the patient offers termination of protocol treatment for reasons not denied to be associated with the adverse event

- This category should be used if an association with an adverse event cannot be ruled out.

(4) When the patient offers termination of protocol treatment because of reasons for denial of association with adverse events

- In case of patient refusal after enrollment and before initiation of protocol treatment
- If an adverse event is initially ruled out, such as a relocation of the person or family during protocol treatment

(5) Death during protocol treatment

- Death before deciding to terminate protocol treatment for other reasons

(6) Other

- Progression before initiation of post-enrollment treatment (protocol treatment could not be initiated due to rapid progression)
- When protocol violation is found
- When the treatment is changed due to ineligibility due to changes in the pathological diagnosis after enrollment, etc
- When it is judged difficult to continue protocol treatment due to social reasons or safety management problems

The protocol treatment discontinuation date is the date of death in case of 6.2.2.5, the date of ineligibility by the treating physician in case of ineligibility after enrollment, and the date of discontinuation of protocol treatment in other cases.

5.9 Treatment modification criteria

The following terms shall be used for the treatment modification.

- Termination: Discontinuation of a part of or all of the treatment without restarting.
- Deferral: Prolonged dosing interval, delayed dosing beyond regulation
- Suspending: temporary interruptions or withdrawals that may be resumed if conditions are met
- Skip: Do not administer one or more drugs and proceed to the next schedule.

"Infection" and "rash" in this chapter refer to the following.

Infection: Bronchial infection; Lung infection; Upper respiratory tract infection; Catheter-related infection; Biliary tract infection; Urinary tract infection; Peritoneal infection; Infectious small bowel colitis

Rash: Maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

5.9.1 Treatment modification criteria for gemcitabine and nab-paclitaxel

(1) Dose level

Dose level

	Gemcitabine	Nab-paclitaxel
Level 0 (starting dose)	1000mg/m^2	125mg/m^2
Level-1	800mg/m^2	100mg/m^2
Level-2	600mg/m^2	75mg/m^2

(2) Course initiation criteria after the second course

- After the second course, the course should be started on the day of or prior to the

course, after confirming that all the criteria for administration of the gemcitabine and nab-paclitaxel administration criteria are met (Table 3).

- Both gemcitabine and nab-paclitaxel will be administered if all of the gemcitabine and nab-paclitaxel administration criteria (Table 3) are met and if the nab-paclitaxel administration criteria are met (Table 4).
- If all the 6.3.1.a gemcitabine and nab-paclitaxel administration criteria (Table 3) are met but the nab-paclitaxel administration criteria are not met, only gemcitabine will be administered and nab-paclitaxel will be stopped (if the nab-paclitaxel Dosing Criteria (Table 4) are met after the next dose, nab-paclitaxel will be restarted).
- If any one of 6.3.1.a gemcitabine and nab-paclitaxel administration criteria (Table 3) are not met, postpone the initiation of the course. If the initiation of the course is deferred, day 1 is the date gemcitabine and nab-paclitaxel administration is started.
- If the next course cannot be initiated beyond 21 days of the expected course due to adverse events related to the protocol treatment (if the course cannot be initiated by day 1 of the expected course start date and by day 22), the protocol treatment should be discontinued.
- If the next course cannot be initiated beyond 14 days of the expected course due to adverse events related to the protocol treatment, the protocol treatment should be discontinued.
- If nab-paclitaxel cannot be restarted beyond 21 days after nab-paclitaxel pause

day due to peripheral sensory neuropathy/peripheral motor neuropathy, the protocol treatment is discontinued.

- Gemcitabine and nab-paclitaxel is temporarily paused and gemcitabine monotherapy is administered if all of the gemcitabine and nab-paclitaxel administration criteria (Table 3) are met and the nab-paclitaxel administration criteria (Table 4) are met but nab-paclitaxel cannot be administered due to discontinuation of nab-paclitaxel. Even if the dose is reduced or rescheduled during gemcitabine and nab-paclitaxel, gemcitabine monotherapy is initiated as one course at gemcitabine 1,000 mg/m2, day 1 and 8. If the treatment is changed to other than GEM monotherapy, the protocol treatment should be discontinued.
- Though gemcitabine and nab-paclitaxel is resumed in principle after nab-paclitaxel supply is resumed, gemcitabine monotherapy can be continued or gemcitabine and nab-paclitaxel can be used.
- After resuming nab-paclitaxel supply, when resuming gemcitabine and nab-paclitaxel, resume administration at the same dose level and on the same schedule as prior to gemcitabine and nab-paclitaxel cessation.
- If nab-paclitaxel can be resumed when gemcitabine monotherapy is considered ineffective, gemcitabine and nab-paclitaxel should not be discontinued as a protocol treatment.

Table 3. Gemcitabine and nab-paclitaxel administration criteria

Item	gemcitabine and nab-paclitaxel

	administration criteria
Neutrophil count	≥ 1.0×10^9 cells/L
Platelet count	≥ 75×10^9 /L
Total bilirubin	≤ 3.0 mg/dL
AST, ALT	≤ 150U/L
Anorexia, nausea/vomiting and diarrhea	Grade 0-1
Oral mucositis, rash	Grade 0-2
Infection	Grade 0-1
Symptomatic of suspected macular edema	None

Rash: Maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

Infection: Bronchial infection; lung infection; upper respiratory tract infection; catheter-related infection; biliary tract infection; urinary tract infection; peritoneal infection, enterocolitis infectious

Symptomatic of suspected macular edema: Decreased visual acuity, blurred vision, metamorphopsia (distorted vision), etc.

Table 4. Nab-paclitaxel administration criteria

Item	Nab-paclitaxel administration criteria
Peripheral sensory neuropathy Peripheral motor neuropathy	Grade 0-2

(3) Day 8 criteria for gemcitabine and nab-paclitaxel administration and schedule modification

- The day of administration of gemcitabine, nab-paclitaxel may be changed as long as 1 day before or after, depending on the patient's convenience, etc. However, when the change is made, the day of administration of both gemcitabine, nab-paclitaxel should be changed (gemcitabine, nab-paclitaxel should be administered on the same day).
- On or before the expected date of day 8 administration, the administration should be performed after confirming that all items of gemcitabine and nab-paclitaxel administration criteria (Table 3).
- Both gemcitabine and nab-paclitaxel will be administered if all of the gemcitabine and nab-paclitaxel administration criteria are met and if the nab-paclitaxel administration criteria are met.
- If all gemcitabine and nab-paclitaxel administration criteria are met but the nab-paclitaxel administration criteria are not met, only gemcitabine will be administered and nab-paclitaxel will be stopped (resume nab-paclitaxel if the nab-paclitaxel administration criteria will be met after the next dose).
- If any one of the gemcitabine and nab-paclitaxel administration criteria are not met, both drugs are skipped. If day 8 is skipped, day 15 will be the expected date of starting the next course.
- If two consecutive courses do not meet the gemcitabine and nab-paclitaxel administration criteria and day 8 administration is skipped, and during that time does not fall under the dose reduction criteria for gemcitabine and nab-paclitaxel, the subsequent administration will be 1 week on and 1 week off.

- After the schedule is changed, the original schedule is not restored.

(4) Dose reduction for gemcitabine and nab-paclitaxel

- If an event that is judged to be related to a drug corresponding to the following dose reduction criteria for gemcitabine and nab-paclitaxel are confirmed between the start of the previous drug administration and the day of the next drug administration, the dose of each drug will be reduced from the next drug administration according to the criteria.
- Re-escalation (increase level) of the drug once the dose has been reduced is not performed.
- If more than one “dose reduction criterion” is met, the lowest drug dose level should be used.
- Dose reduction only with gemcitabine during a pause of nab-paclitaxel due to peripheral sensory neuropathy/peripheral motor neuropathy.
- If further dose reductions from level-2 occur with either gemcitabine or nab-paclitaxel, the protocol treatment should be discontinued.

Table 5. Dose reduction for gemcitabine and nab-paclitaxel

Item	Dose reduction criteria	Nab-paclitaxel	Gemcitabine
Neutrophil count	$<0.5\times10^9$ cells/L	1-level reduction	1-level reduction
Platelet count	$<50\times10^9$ /L	1-level reduction	1-level reduction

Febrile neutropenia	Grade 3	1-level reduction	1-level reduction
Infection	Grade 3	1-level reduction	1-level reduction
Anorexia, nausea/vomiting and diarrhea	Grade 3	1-level reduction	1-level reduction
Oral mucositis, rash	Grade 3	1-level reduction	1-level reduction
Peripheral sensory neuropathy Peripheral motor neuropathy	Grade 3	Level 0, 1: 1-level reduction	1-level reduction
		Level 2: No dose reduction	No dose reduction

Infection: Bronchial infection; lung infection; upper respiratory tract infection; catheter-related infection; biliary tract infection; urinary tract infection; peritoneal infection, enterocolitis infectious

Rash: Maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

(5) Criteria for initiating gemcitabine monotherapy

Gemcitabine and nab-paclitaxel is temporarily paused and gemcitabine monotherapy is administered if all of the gemcitabine and nab-paclitaxel administration criteria are met and nab-paclitaxel administration criteria are met but nab-paclitaxel cannot be administered due to discontinuation of nab-paclitaxel supply. Gemcitabine monotherapy is initiated as one course of gemcitabine 1,000 mg/m^2, day1 and 8, even if the dose is reduced or rescheduled during gemcitabine and nab-paclitaxel.

On or before the start of the course, the course should be started after confirming that

all of the gemcitabine administration criteria are met (Table 6).

If any one of the gemcitabine administration criteria are not met, the course start is postponed. If course initiation is deferred, the date of gemcitabine initiation is day 1.

If the next course cannot be initiated beyond 14 days of the expected course due to adverse events related to the protocol treatment, the protocol treatment should be discontinued.

In principle, gemcitabine and nab-paclitaxel is resumed after nab-paclitaxel supply is resumed. However, gemcitabine monotherapy can be continued, or gemcitabine and nab-paclitaxel could be used.

If nab-paclitaxel can be resumed when gemcitabine monotherapy is considered ineffective, gemcitabine and nab-paclitaxel should not be discontinued as a protocol treatment.

Table 6. Gemcitabine administration criteria

Item	Gemcitabine administration criteria
Neutrophil count	$\geq 1.0\times10^9$ cells/L
Platelet count	$\geq 75\times10^9$ /L
Total bilirubin	≤ 3.0 mg/dL
AST, ALT	≤ 150U/L
Anorexia, nausea/vomiting and diarrhea	Grade 0-1
Oral mucositis, rash	Grade 0-2
Infection	Grade 0-1

Rash: Maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

Infection: Bronchial infection; lung infection; upper respiratory tract infection; catheter-related infection; biliary tract infection; urinary tract infection; peritoneal infection, enterocolitis infectious

(6) Day 8 criteria for gemcitabine administration and schedule modification

- The day of administration of gemcitabine may be changed as long as 1 day before or after, depending on the patient's convenience, etc.
- On or before the expected date of day 8 administration, the administration should be performed after confirming that all items of gemcitabine administration criteria are met.
- If any one of gemcitabine administration criteria are not met, the administration should be skipped. If day 8 is skipped, day 15 will be the expected date of starting the next course.
- If two consecutive courses do not meet the gemcitabine administration criteria and day 8 administration is skipped, and the patient does not meet the dose reduction criteria for gemcitabine during that time (Table 7), the subsequent administration will be 1 week on and 1 week off.
- It does not return to the original schedule after the schedule change during gemcitabine therapy (if gemcitabine and nab-paclitaxel is resumed, the same dose-level as prior to gemcitabine and nab-paclitaxel cessation and resume gemcitabine and nab-paclitaxel on the schedule).

- For gemcitabine and nab-paclitaxel, day1 received gemcitabine and nab-paclitaxel, but nab-paclitaxel was discontinued due to nab-paclitaxel supply, resulting in day 8 receiving gemcitabine, then gemcitabine of the course will be scheduled at the same dose-level as before gemcitabine and nab-paclitaxel was discontinued.

(7) Dose reduction criteria for GEM monotherapy

- If an adverse event is confirmed to be related to a drug that meets the following dose reduction criteria for gemcitabine during the period from the start of the previous administration to the day of the next administration of the drug, gemcitabine will be reduced from the next administration of the drug according to the criteria.
- Re-escalation (increase) of gemcitabine once it has been reduced is avoided.
- If further dose reduction from level-2 occurs, discontinue protocol treatment.

Table 7. Dose reduction criteria for gemcitabine

Item	Dose reduction criteria	Gemcitabine
Neutrophil count	$<0.5\times10^9$ cells/L	1-level reduction
Platelet count	$<50\times10^9$ /L	1-level reduction
Febrile neutropenia	Grade 3	1-level reduction
Infection	Grade 3	1-level reduction
Anorexia, nausea/vomiting and diarrhea	Grade 3	1-level reduction

Oral mucositis, rash	Grade 3	1-level reduction

Infection: Bronchial infection; lung infection; upper respiratory tract infection; catheter-related infection; biliary tract infection; urinary tract infection; peritoneal infection, enterocolitis infectious

Rash: Maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

5.10 Concomitant treatment and supportive care

5.10.1 Recommended/not recommended concomitant treatment/supportive care

The following concomitant treatment and supportive care are recommended. Even if it is not carried out, it is not regarded as protocol deviation.

(1) Addressing Fever During Neutropenia

(i) Assessment at onset of febrile neutropenia

(a) If the neutrophil count is less than 0.5×10^9 /L, or less than 1×10^9 /L and is predicted to decrease to less than 0.5×10^9 /L in less than 48 hours, and if the axillary temperature is 37.5°C (oral 38°C) or higher, then immediately assess the severity risks and start the supportive treatment as appropriate.

(b) Severity risk assessment is performed with reference to Multinational Association for Supportive Care in Cancer (MASCC) scoring system

(c) For initial evaluation, complete blood cell count including differential and platelet count, renal function, (BUN, creatinine), electrolytes, liver function (transaminases, total bilirubin, and alkaline phosphatase) tests, two or more sets of venous blood cultures before initiation of antimicrobials, one set of

cultures from the catheter lumen and one set from a peripheral vein if a central venous catheter is in place, culture of suspected infected areas, and plain chest x-ray if respiratory symptoms or signs are present.

(d) When febrile neutropenia develops in a patient with a central venous catheter, blood cultures from the catheter and peripheral blood are performed, and catheter-related infections are considered if there is a time difference of more than 120 minutes in the positivity of both. If appropriate antimicrobial therapy does not improve after more than 72 hours, catheter should be removed. For infections caused by Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus, fungi, and acid-fast bacilli, the catheter should be removed and appropriate antimicrobial therapy based on culture results should be performed.

(ii) Antibiotic use

(a) In high-risk patients, β-lactams with anti-Pseudomonas aeruginosa activity are administered intravenously as a single agent. However, other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to a single agent in the initial regimen in patients with unstable or complicated conditions or when drug-resistant organisms are strongly suspected. Low-risk patients may be treated with antibiotics orally or intravenously, hospitalized, or with adequate evaluation, if appropriate, as outpatients.

(b) The antimicrobial agent should be reassessed 3-4 days after initiation, and antimicrobial agents should be continued or changed. As a rule, antimicrobials

should be continued until the neutrophil count is at least 0.5×10^9 /L.

(c) Empiric antifungal therapy is recommended in high-risk patients who do not respond to 4-7 days of broad-spectrum antibiotics.

(d) Fluoroquinolone prophylaxis is recommended in high-risk patients with an expected neutrophil count $\leq0.1\times10^9$ /L lasting >7 days.

(iii) Therapeutic administration of G-CSF

Therapeutic administration of G-CSF during the development of FNs is referred to the following section.

Multinational Association for Supportive Care in Cancer (MASCC) scoring system.

Item	Score
Clinical manifestations (select one of the followings)	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No decrease in blood pressure	5
No chronic obstructive pulmonary disease	4
Solid tumors, or hematopoietic tumors without a history of fungal infection	4
No dehydration symptoms	3
Patients with fever during outpatient management	3
Age < 60	2

The total score is up to 26 points. Twenty-one points or more are considered low risk and 20 points or less are considered high risk.

(2) Influenza and pneumococcal vaccination

Evidence on the usefulness of immunization and timing of vaccination before or during chemotherapy is unclear. However, when the benefit of vaccination is expected and the safety is judged to be ensured, consideration should be given to the time of protocol treatment and vaccination.

(3) Nausea and vomiting

Aggressively administer the antiemetic including the prophylactic administration, referring to the antiemetic proper use guideline.

Gemcitabine and nab-paclitaxel is moderately emetogenic risky. Therefore, dual use of 5-HT3 receptor antagonists and steroids is recommended. However, the administration of steroids may lead to a hyperglycemic state, and the dose adjustment should be considered because special attention should be paid to patients with pancreatic cancer. Nevertheless, for those with no response to 5-HT3 receptor antagonists and steroids, triple combinations of NK1 receptor antagonists, 5-HT3 receptor antagonists, and steroids are recommended.

(4) Skin rash

For the rash, the use of external use moisturizer and steroid external use medicine is

carried out. Systemic therapy may include antihistamines (H1-blocker and H2-blocker) and corticosteroids.

(5) Palmar-plantar erythrodysesthesia syndrome

The use of external use moisturizer and steroid external use medicine for Palmar-plantar erythrodysesthesia syndrome is carried out. Oral administration of pyridoxine hydrochloride (vitamin B6) is also recommended.

(6) Mucositis-stomatitis

Mucosa protective agents such as analgesics, or surface anesthetics should be used as appropriate according to symptoms. Narcotics may be used when pain is severe.

(7) Allergic reaction

Severe symptoms such as dyspnea and hypotension accompanied by oxygen desaturation.

Intramuscular epinephrine, oxygenation, and fluid therapy are performed to ensure the stability of the general condition. If cardiac arrest or respiratory arrest occurs, CPR such as cardiac massage or mechanical ventilation should be performed.

Antihistamines (H1- blocker and H2-blocker) and corticosteroids are given to prevent further deterioration.

Symptoms such as hot flushes, rash, hives, pruritus, itching of the pharyngolarynx tightness, cold sweat, dyspnea without oxygen desaturation, and fever. If

chemotherapy is delivered, administration should be once stopped. Management is shown in the following Table.

Table 8. Management of allergic reactions

Allergic reaction	Response to the next course
Grade 1	If premedication for allergic reaction was not used in the previous course ● Premedication with antihistamines (H1-blocker and H2-blocker) or adequate corticosteroids ● Gemcitabine and nab-paclitaxel are not reduced, but the infusion time may be extended to 4 to 6 h.
	Premedication for allergic reactions in the previous course ● Gemcitabine and nab-paclitaxel are not reduced, but the infusion time may be extended to 4 to 6 h.
Grade 2	If premedication for allergic reaction was not used in the previous course ● Premedication with antihistamines (H1-blocker and H2-blocker) or adequate corticosteroids ● Gemcitabine and nab-paclitaxel are not reduced, but the infusion time may be extended to 4 to 6 h.
	Premedication for allergic reactions in the previous course: Discontinue protocol treatment
Grade 3	With or without premedication for allergic reactions in the previous course: Discontinue protocol treatment
Grade 4	With or without premedication for allergic reactions in the previous course: Discontinue protocol treatment

(8) Pneumonitis (interstitial pneumonitis)

If pneumonitis is suspected because of cough or fever, chest X-ray and blood gas analysis are performed immediately. When pneumonitis is diagnosed as a result, appropriate measures such as discontinuing treatment and starting the administration of steroids are taken.

(9) Macular edema

If symptoms such as decreased visual acuity, blurred vision, and metamorphopsia (distorted vision) appear, the possibility of macular edema is suspected and the ophthalmologist is consulted early. If needed, corrected visual acuity, fundus examination, optical coherence tomography, and fluorescein angiography are performed, and if macular edema is confirmed, chemotherapy is discontinued.

(10) Jaundice reduction treatment

If jaundice or hyperbilirubinemia is observed, appropriate jaundice reduction treatment should be taken.

5.10.2 Permitted medications and non-drug therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death. Any

concomitant medication(s), including dietary supplements, taken during the study will be recorded in the electronic case report form. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the electronic case report form.

Participants should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted provided that INR is monitored in accordance with local institutional practice. Therapeutic administration of G-CSF should be performed according to the approved dosage and administration shown in the table below.

Table 9. Therapeutic administration of G-CSF

Time of initiation	When neutrophil count are below 1×10^9 /L and fever (38°C or higher as a general rule) occurs When neutrophil count < 0.5×10^9 /L were observed
Dosage Dosing regimen	● Filgrastim: 50 μg/m^2 subcutaneously once daily or 100 μg/m2 intravenously once daily ● Naltograstim: 1 μg/kg subcutaneously once daily or 2μg/kg IV once daily ● Renograstim: 2 μg/kg subcutaneously once daily or 5μg/kg

	IV once daily
Timing of discontinuation	● If neutrophil count reaches a nadir level of at least 0.5×10^9 /L after the elapse, discontinue administration ● If the neutrophil count recover to $\geq2\times10^9$ /L, if there are no symptoms suspicious of infection, and if the patient's safety is determined to be ensured, discontinue or reduce the dose of the drug.

5.10.3 Prohibited medications and non-drug therapies

(1) Chemotherapy other than that included in the protocol treatment regimen.

(2) Radiotherapy, surgery, hormonal therapy, immunotherapy, antibody therapy, hyperthermia, and other anti-malignancy treatments

(3) G-CSF administration on the day of anticancer drug administration.

5.11 Treatment after discontinuation of study treatment or withdrawal from/completion of study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition and providing specific post-study treatment.

Post-study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non-protocol) anti-cancer therapy at the discretion of the treating physician. New anti-

cancer therapy should be documented in the electronic case report form. Every effort should be made to complete the required follow-up evaluations prior to initiating new anti-cancer therapy. Subjects will be followed for survival even if other assessments are not performed.

Refer to Section 3.5 for follow-up assessment of subjects who are to be followed for survival and/or disease progression after permanently discontinuing both study treatments.

Upon study closure, subjects who are still receiving study treatment will have the option to continue to receive study treatment.

6. Study assessment and procedures

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Procedures conducted as part of the subject's routine clinical management (e.g., imaging) and obtained prior to signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe specified in the protocol. Central laboratory results for coagulation, hematology, clinical chemistry, and serum pregnancy are required for eligibility.

Refer to the Time and Events Table (Table 10) for the timing of all assessments. Assessments must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Details on efficacy and

safety assessments are presented in Section 6.1 and Section 6.2, respectively. Details on health outcomes are presented in Section 6.3.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

Table 10. Study assessments and timing for patients with gemcitabine and nab-paclitaxel following SBRT

	Treatment cycles (3-week cycle)[1]																				
Study assessments[2]	**Screening**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5**	**5**	**5**	**6**	**6**	**6**	**SBRT**	**Treatment Discon**
Day in cycle		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**N/A**	
Visit window (Days)	**≤28 days except where noted[3,5]**	**±1 days**																			**±7 days**
Clinical and safety assessments																					
Informed consent[4]	X																				
Demographic data[5]	X																				
Past and current medical condition[6]	X																				
Family history	X																				
Disease characteristics[7]	X																				
Prior anti-cancer therapy[8]	X																				
Staging assessment[9]	X																				
Abdominal and pelvic CT/MRI[10]	X							X												X (Before SBRT)	X
PET-CT[11]	X																				
ECOG	X	X			X			X			X			X			X			X	X
Inclusion/exclusion criteria[12]	X																				

Randomization	X																				
Physical examination[13]	X complete	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief	X brief
Adverse event[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dermatologic skin assessment[15]	X				X			X			X			X			X			X	X
ECG[16]	X																				
Chest CT[17]	X							X												X (Before SBRT)	X
Concomitant medications[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatments																					
Dispensation of medication[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of compliance[20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments																					
Chemistry and hematology[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[22]	X				X			X			X			X			X			X	
Pregnancy test[23]	X serum (⩽7 days)																				
CA19-9[24]	X				X			X			X			X			X			X	X
Urinalysis[35]	X				X			X			X			X			X			X	X

1. Patients would not discontinue receiving gemcitabine and nab-paclitaxel until disease progression if no unacceptable adverse effects occur.

2. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. A post baseline study visit window of 1 days is allowed for visits during treatment.

3. Screening procedures may be performed up to 28 days prior to randomization, unless otherwise noted in the table. Screening visits with a different window are noted

in parentheses.

4. Informed consent may be given at any time prior to the performance of any study-related procedures.

5. Record demographic data.

6. Record past and current medical conditions, surgical procedures and cardiovascular family history.

7. Record date of diagnosis, primary tumor type, histology, stage, and other disease characteristics as indicated in the electronic case report form.

8. Details of treatment for pancreatic cancer before local recurrence should be recorded.

9. Staging before treatment initiation must be done to preclude distant metastases.

10. Diagnostic quality, contrast enhanced CT scan of the abdomen and pelvis must be performed at all visits indicated in the table. Intravenous contrast should be used, for the CT scans, and preferably with oral contrast as well. CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT scanning frequency is not permitted or ethics requirements or if CT contrast is contraindicated. If MRI scanning is not possible, and CT intravenous contrast is contraindicated, CT without contrast is allowed, but it is the least preferable option. Method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT must be done at all future time points). Abdominal and pelvic CT/MRI should be performed after the third cycle and before the initiation of SBRT.

11. PET-CT should be performed for eligibility to preclude distant metastases. Additionally, for patients with suspected disease progression during treatment and follow-up, PET-CT should be performed at the discretion of physicians.

12. Only subjects who meet all inclusion and exclusion criteria will be eligible to enter into the study.

13. All physical exams will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations. In addition, a complete physical exam including a thorough genitourinary (pelvic) examination, inspection of the head and

neck region, and digital rectal examination for both male and female subjects must be performed at Screening, or discontinuation if discontinuation occurs. For female subjects the genitourinary exam must include a PAP smear. If the subject has had a genitourinary and rectal exam within 6 months of randomization these do not need to be repeated at screening. Brief physical examinations will be performed at all other time points as indicated.

14. Adverse events will be recorded from the time the first dose of study treatment is administered until discontinuation of study treatment. Serious adverse events will be collected over the same time period as adverse events except serious adverse events assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, concomitant medication which must be recorded from the time a subject consent to participate in the study up to and including any follow-up contact.

15. A thorough dermatologic exam should be performed by the Investigator at Screening, or at discontinuation if discontinuation occurs. This may be referred to a dermatologist at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.

16. ECG must be performed at Screening. A single 12-lead ECG will be performed by qualified site personnel after the subject has rested in a semi-recumbent or supine position for at least 5 minutes. Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection if necessary. ECGs should be done in triplicate when the initial test is abnormal.

17. Chest CT is required for evaluations of pulmonary toxicity. For those with respiratory symptoms, chest CT must be performed to identify the causes of symptoms. Additionally, for patients with suspected disease progression, chest CT may be given if PET-CT is not permitted to confirm lung metastases. Chest CT should be performed after the third cycle and before the initiation of SBRT.

18. All medications taken by the subject during the study from the time of screening until 30 days after the last dose of study treatment will be recorded; any new anti-cancer therapy, if taken after study treatment discontinuation will be recorded.

19. Dosing instructions must be provided to the subject. Subjects should start treatment as soon as possible after randomization but no later than 72 hours post-randomization. Study treatment will be dispensed at randomization and monthly.

20. Compliance will be assessed at all visits after Day 1 (Randomization). To assess compliance subjects should be instructed to return study drug at each visit; compliance will be assessed by querying the subject. Dose reductions, dose interruptions/delays, and/or dose escalations must be recorded in the electronic case report form.

21. Analysis of clinical chemistry and hematology samples including those at screening will be performed by a central laboratory. Screening labs must be performed within 28 days prior to randomization. Comprehensive chemistry and hematology assessments should be performed at Day 1, 8 and 15 in each cycle.

22. Coagulation sample to be obtained at screening and before the initiation of each cycle and analyzed by a central laboratory.

23. For all women of childbearing potential a serum pregnancy test will be required within 7 days prior to randomization; preferably, as close to the first dose as possible. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable. A urine test must be performed to confirm the subject is not pregnant prior to restarting study treatment.

24. Sometimes, patients may present with elevations of CA19-9 but without any progressions in imaging, which may indicate micro-metastases. Therefore, CA19-9 should be performed every cycle, which is more frequently than imaging examinations.

25. Urinalysis should be performed at Day 1 in each cycle to identify whether proteinuria occurs.

Table 11.

	Follow-up[8]				**Study completion[10]**
	Before recurrence		**After recurrence**		**Conclusion**
Study assessments[1]	**Every 2-3 Months (M3-M36)**	**Every 3 Months After Month 36**	**Every 2-3 Months (M3-M36)**	**Every 3 Months After Month 36**	**Conclusion**
Visit windows (Days)	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**N/A**
Hematology and chemistry[2]	X	X	X	X	
ECOG	X	X	X	X	
Physical examination[3]	X (brief)	X (brief)	X (brief)	X (brief)	
Chest, abdomen and pelvic CT scans[4]	X	X	X	X	
Concomitant medication[5]	X	X	X	X	
Adverse events[6]	X	X	X	X	
Tumor biomarker (CA19-9)[7]	X (every month)	X (every month)	X (every month)	X (every month)	
Follow-up contact, anti-cancer therapies and best response[8]	X	X	X	X	X
PET-CT[9]		X (after recurrences confirmed)	If clinically indicated		
Subject completion					X
Death					X

1. All assessments mandated throughout the study must be performed on a calendar schedule. A study visit window of ±7 days is allowed for all follow-up visits.

2. Analysis of clinical chemistry and hematology samples will be performed by a central laboratory. Labs should be drawn at Month 18 then annually thereafter during follow-up prior to disease recurrence and at the time of disease recurrence.

3. All physical exams will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations. In addition, a complete physical exam including a thorough genitourinary (pelvic) examination, inspection of the head and neck

region, and digital rectal examination for both male and female subjects must be performed at Month 18. For female subjects the genitourinary exam must include a PAP smear. Brief physical examinations will be performed at all other time points as indicated.

4. Diagnostic quality, contrast enhanced CT scan of the chest, abdomen and pelvis must be performed at all visits indicated in the table. Intravenous contrast should be used, for the CT scans, and preferably with oral contrast as well. CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT scanning frequency is not permitted per country or ethics requirements or if CT contrast is contraindicated. If MRI scanning is not possible, and CT intravenous contrast is contraindicated, CT without contrast is allowed, but it is the least preferable option. Method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT must be done at all future time points). MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain should be performed as clinically indicated.

5. All medications taken by the subject during the study from the time of screening until 30 days after the last dose of study treatment will be recorded; any new anti-cancer therapy, if taken after study treatment discontinuation will be recorded.

6. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events will be collected over the same time period as adverse events except severe adverse events assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, concomitant medication which must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

7. Tumor biomarker (CA19-9) is required to assess recurrences and response to the treatment.

8. Follow-up will start once treatment is complete and continue through the end of the study even if disease recurs. Follow-up contact prior to disease recurrence will include clinic visits. Follow-up after disease recurrence should follow the schedule as noted in Table 17. However, the information collected will be limited to: quality of life information, any radiotherapy, surgical procedure or new anti-cancer therapy initiated until study completion, withdrawal or death, best response to any follow-up

treatment, method of assessment of best response, subsequent progression dates, and survival data.

9. PET-CT will be performed in the case of patients with suspected progression at the discretion of physicians.

10. To be completed if the subject permanently withdraws from the study (i.e. death, withdrawal of consent, lost to follow-up).

6.1 Efficacy

6.1.1 Primary endpoint

The primary endpoint of this study is one-year progression free survival (PFS) rate. PFS is defined as the time from randomization to disease recurrence or death from any cause. Recurrence of or death from the same cancer and all deaths from other causes are events. Therefore, one-year PFS rate is the ratio of the number of patients without disease progression at one year to the total number of patients. And lost to follow-up is censored.

- Types of recurrence to be considered as an event include loco-regional, distant metastases.
- Any death occurring without prior documentation of tumor recurrence will be considered as an event (and will not be censored in the statistical analysis).
- If no event has occurred by the time of the analysis, then the time to event will be censored as the date of the last adequate assessment of the patient in question.
- Any new primary cancer at another site will not be considered as a recurrence and should be reported as a severe adverse event. Tumor tissue sample should be obtained for histopathological examinations.

6.1.2 Secondary endpoints

The secondary endpoint of this study is overall survival (OS) and PFS. OS is defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive will be censored at the date of the last contact. The definition

of PFS is clarified above. And lost to-follow-up is censored.

Additionally, one-year OS will also be included in the secondary endpoints. One-year OS is defined as the proportion of patients alive at 1 year.

6.1.3 Efficacy assessments

See the Time and Events Tables (Table 10-11) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline efficacy assessments, a window of ±3 days is permitted to allow for flexible scheduling.

The following are required for efficacy assessment:

- Clinical examination
- Diagnostic quality, contrast-enhanced CT scan of the chest, abdomen and pelvis should be performed at baseline and subsequent time points as indicated in the Time and Events Tables (Table 10-11). Intravenous contrast should be used for the CT scans preferably with oral contrast as well. CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT frequency prescribed in the Time and Events Table is not permitted or ethics requirements or if CT contrast is contraindicated. The method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT will be done at all future time points). All CTs/MRIs will be collected.
- A baseline abdominal and pelvic CT and MRI of the recurrent lesion is required

for all subjects. Subsequent abdominal and pelvic CT and MRI should be performed according to the Time and Events Tables (Table 10). Additionally, the imaging examinations may be performed at any time as clinically indicated. Abdominal and pelvic CT and MRI will be collected.

6.1.4 Assessment guidelines

Please note the following:

- The same diagnostic method, including use of contrast, when applicable, must be used throughout the study. Contrast agents must be used in accordance with the Image Acquisition Guidelines presented in the Study Procedures Manual, where not contraindicated.
- Fluorodeoxyglucose positron emission tomography (FDG)-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI.
- If PET/CT is performed then the CT component can only be used for standard disease assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the case report form.

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. MRI is acceptable (refer to Section 6.1.3), but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type of disease. Whenever possible the same scanner should be used.

Scans of the recurrent lesion of pancreatic cancer: For the baseline scans of the recurrent lesion of pancreatic cancer and any post-baseline imaging examinations, contrast enhanced MRI and CT are both required.

6.1.5 Follow-up assessments for subjects permanently discontinued from study treatment prior to protocol treatment period

Refer to Section 3.5 Discontinuation of participation following any treatment with study drugs and the Time and Events Schedule (Table 18) for follow-up assessment of subjects for disease recurrence and survival after permanently discontinuing from study treatment.

6.1.6 Assessment of subject completion

If a subject withdraws from the study during Months 1 through Month 24, the last radiographic assessment was more than 3 months prior to withdrawal from study and disease recurrence has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

If a subject withdraws from the study after Month 24, the last radiographic assessment was more than 6 months prior to withdrawal from study and disease recurrence has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

6.2 Safety

6.2.1 Safety endpoints

The secondary endpoints of the study include characterizing the safety of SBRT of a recurrence-pattern-based volume and conventional-volume following gemcitabine and nab-paclitaxel. As a consequence, clinical assessments including vital signs and physical examinations, 12-lead ECG, chemistry and hematology laboratory values, and adverse events will be monitored and evaluated.

6.2.2 Adverse events

The investigators will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event or severe adverse event as outlined in Section 6.2.2.1 and Section 6.2.2.2, respectively.

6.2.2.1 Definition of an adverse event

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse.

Examples of events meeting the definition of an adverse event include:

- Exacerbation of a chronic or intermittent pre-existing condition including either

an increase in frequency and/or grade of the condition.

- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an adverse event/severe adverse event) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an adverse event or severe adverse event. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an adverse event or severe adverse event, if they fulfill the definition of an adverse event or severe adverse event.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an adverse event.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms

of the disease/disorder being studied, unless more severe than expected for the subject's condition.

6.2.2.2 Definition of a severe adverse event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to

conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-specific severe adverse events:

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN and INR>1.5, if INR measured) or termed ‘Hy’s Law’ events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is

unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ⩾2xULN, then the event is still reported as a severe adverse event. If INR is obtained, include values on the severe adverse event form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancers and treatment emergent malignancies.
- Laboratory abnormalities.
- Central serous retinopathy or retinal vein occlusion.
- Renal insufficiency, and/or severe rigors/chills in the absence of an obvious infectious cause.

6.2.2.3 Laboratory and other safety assessment abnormalities reported as adverse events and severe adverse events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an adverse event or severe adverse event, in accordance with the definitions provided. In addition, an associated adverse event or severe adverse event is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as adverse events or severe adverse events.

6.2.2.4 Disease-related outcomes not qualifying as severe adverse events

An event which is part of the natural course of the disease under study (i.e., disease recurrence or hospitalization due to disease recurrence) does not need to be reported as a severe adverse event. Death due to disease under study is to be recorded on the Death case report form. However, if the underlying disease (i.e., recurrence) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with gemcitabine and nab-paclitaxel or protocol design/procedures and the disease recurrence, then this must be reported as a severe adverse event. Local or distant relapse is the primary efficacy endpoint of the study and should not be reported as a severe adverse event.

6.2.2.5 Time period and frequency of detecting adverse events and severe adverse events

The investigator is responsible for detecting, documenting and reporting events that meet the definition of an adverse event or severe adverse event.

From the time a subject consent to participate in and completes the study, all severe adverse events assessed as related to study participation (e.g., protocol-mandated

procedures, invasive tests, or change in existing therapy), will be reported promptly to Institutional Review Board/Independent Ethics Committee. Severe adverse events will be collected over the same time period as stated above for adverse events. In addition, any new malignancy (defined in Section 6.2.2.2) or any severe adverse events assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or concomitant medication must be recorded from the time a subject consent to participate in the study up to and including any follow-up contact. All severe adverse events will be reported to Institutional Review Board/Independent Ethics Committee within 24 hours, as indicated in Section 6.2.2.6.

After discontinuation of study treatment, the investigator will monitor all adverse events/severe adverse events that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days from the last dose of study treatment, the investigator may report any adverse event that they believe is possibly related to study treatment. Treatment emergent malignancies should be reported regardless of the time from treatment discontinuation to occurrence of the event.

6.2.2.6 Prompt reporting of severe adverse events and other events to Institutional Review Board/Independent Ethics Committee

Severe adverse events, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to Institutional Review

Board/Independent Ethics Committee as described in the following table once the investigator determines the event meets the protocol definition for that event.

Table 12. Time frames for reporting severe adverse events and other events

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy notification form	2 Weeks	Pregnancy follow up form
Liver chemistry abnormalities:				
ALT≥3xULN PLUS Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[1]	24 hours[2]	SAE data collection tool. Liver Event CRF and liver imaging and/or biopsy CRFs if applicable[3]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[3]
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	Liver Event CRF[3]	24 hours	Updated Liver Event CRF[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	Liver event CRF does not need completing unless elevations persist for 2 weeks or	24 hours	

		subject cannot be monitored weekly for 2 weeks[3]		
ALT≥5xULN and bilirubin <2xULN that persists≥2 weeks	24 hours[2]	Liver event CRF[3]	24 hours	Updated liver event CRF[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]		

1. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

2. Institutional Review Board/Independent Ethics Committee to be notified at onset of liver chemistry elevations to discuss subject safety.

3. Liver Event Documents (i.e., "Liver Event Case Report Form" and "Liver Imaging Case Report Form" and/or "Liver Biopsy Case Report Form", as applicable) should be completed as soon as possible.

6.2.2.7 Regulatory reporting requirements for severe adverse events

Prompt notification of severe adverse events by the investigator to Institutional Review Board/Independent Ethics Committee is essential so that legal obligations and

ethical responsibilities towards the safety of subjects are met.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who completes an investigator safety report describing a severe adverse event(s) or other specific safety information (e.g., summary or listing of severe adverse events) will notify the Institutional Review Board/Independent Ethics Committee, if appropriate according to local requirements.

6.2.3 Laboratory assessments

All protocol required laboratory assessments, as defined in Table 10 should be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule in Table 11. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided by the central laboratory.

If any additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinical significant by the investigator (for example severe adverse events or adverse events or dose modifications) the results must be recorded in the subject's

electronic case report form.

Clinical chemistry and hematology parameters to be tested are listed in Table 13.

Female subjects will have a serum pregnancy test at screening.

Table 13. Clinical chemistry and hematology parameters

Clinical Chemistry Parameters
Albumin
Alkaline Phosphatase
Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT)
Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT)
Bicarbonate
Blood Urea Nitrogen (BUN) or urea
Calcium
Chloride
Creatinine[1]
Glucose (random)
Lactate Dehydrogenase (LDH)
Phosphate
Potassium
Sodium
Total Bilirubin[2]
Total Protein
Hematology Parameters
White Blood Cell (WBC) Count
Hemoglobin
International Normalized Ratio (INR; at screening only)[3]
Platelet Count
Prothrombin Time (PT; at screening only) [3]
Partial Thromboplastin Time (PTT; at screening only) [3]
Automated WBC Differential (expressed as %):
Basophils
Eosinophils
Lymphocytes
Monocytes

Neutrophils

1. If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula.

2. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal.

3. Coagulation panel to be done at Screening only.

6.2.4 Vital signs

Vital sign measurements will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at screening). Body temperature, weight and height measurements should be recorded in the metric scale. All blood pressure assessments should be performed under optimal conditions i.e. after (i) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (ii) subject is relaxed comfortably for at least 5 minutes, (ii) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the right cuff size have been ensured, (iii) the arm is supported so that the middle of the cuff is at the heart level, and (iv) the subject remains quiet during the measurement. In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. Only the averaged value should be entered in the electronic case report form.

6.2.5 Physical examinations

All physical exams will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations as well as assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Brief physical examinations will be performed at all other time points as indicated in the Time and Events Tables (Table 11).

6.2.6 Dermatologic examination

Exams may be performed by the investigator or may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.

6.2.7 Electrocardiograms

Twelve (12)-lead ECGs will be obtained using an electrocardiograms machine that automatically calculates heart rate and measures PR, QRS, QT, RR and QTcB intervals.

At each assessment, a single 12-lead ECG will be performed by qualified site personnel after the subject has rested in a semi-recumbent or supine position for at least 5 minutes. Two copies of the ECG tracing should be obtained at the time of the electrocardiograms; the first copy will be kept in the subject's medical chart and the

second copy will be kept in the study file for retrospective collection by the Sponsor if necessary.

7. Data management

For this study subject data will be entered into electronic case report forms, transmitted electronically to Institutional Review Board/Independent Ethics Committee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities and custom drug dictionary. The electronic case report form (including queries and audit trails) will be retained by investigators, and copies will be sent to the Institutional Review Board/Independent Ethics Committee to maintain for potential future review.

8. Data analysis and statistical considerations

8.1 Hypotheses

The primary objective of this two-arm study is to evaluate the efficacy of SBRT of a recurrence-pattern-based volume and conventional volume following gemcitabine plus nab-paclitaxel with respect to one-year progression free survival (PFS) rate for

subjects with locally advanced pancreatic cancer.

The study is designed to provide evidence regarding one-year PFS rate to either support the null hypothesis, H0: $\lambda = 1$ or reject it in favor of the alternative hypothesis, HA: $\lambda \neq 1$, where λ is the hazard ratio (HR) of combination therapy relative to recommended therapy.

8.2 Analysis of endpoints

8.2.1 Efficacy

The primary endpoint is one-year PFS rate. PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. Therefore, one-year PFS rate is the proportion of patients without disease progressions at one year.

The secondary endpoint is OS and PFS. OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow up. PFS is defined as above.

8.2.2 Safety endpoints

The secondary objectives of the study include characterizing the safety of SBRT of recurrence-pattern-based-volume and conventional-volume following gemcitabine plus nab-paclitaxel. As a consequence, clinical assessments including vital signs and physical examinations, 12-lead ECG, chemistry and hematology laboratory values, and adverse events will be monitored and evaluated.

The investigators will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event or severe adverse event as outlined in Section 6.2.2.1 and Section 6.2.2.2, respectively.

8.3 Analysis population

8.3.1 Efficacy analysis population

The Intention-to-Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.4.1 - Statistical Methods for Efficacy Analyses.

8.3.2 Safety analysis population

The All Subjects as Treated population will be used for the analysis of safety data in this study. The All Subjects as Treated population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the All Subjects as Treated population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct

treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.4 Statistical analysis methods

8.4.1 Statistical methods for efficacy analyses

This section describes the statistical methods that address the primary and secondary objectives. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.4.1.1 Overall survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves in each treatment group including the OS rates at one year (based on data adequacy). The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

8.4.1.2 Progression frees survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group including the PFS rates at one year (based on data adequacy). The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

Since disease progression is assessed periodically, progressive disease can occur any time in the time interval between the last assessment where progressive disease was not documented and the assessment when progressive disease is documented. The true date of disease progression will be approximated by the date of the first assessment at which progressive disease is objectively documented per RECIST 1.1. Death is always considered as a confirmed progressive disease event. Subjects who do not experience a PFS event will be censored at the last disease assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1, one primary and two sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if progressive disease or death events occur immediately after more than one missing disease assessment, the PFS data are censored at the last disease assessment prior to the missing visits. Also, data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer

therapy.

The first sensitivity analysis follows the intention-to-treat principle. That is, progressive diseases/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than complete response or initiation of new anti-cancer treatment (whichever occurs later) to be a progressive disease event for subjects without documented progressive disease or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 14.

Table 14. Censoring rules for primary and sensitivity analyses of progression free survival

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer	Progressed at date of documented PD or death	Progressed at date of documented PD or death

therapy, if any	therapy, if any		
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function vs. time for PFS will be plotted for the comparison between SBRT of a recurrence-pattern-based-volume and conventional-volume following gemcitabine and nab-paclitaxel. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect.

8.4.2 Statistical methods for safety analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory tests, and vital signs.

8.4.2.1 Adverse events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. Adverse events will be graded by the investigator according to the NCI-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all adverse events, drug-related adverse events, serious adverse events and adverse events leading to discontinuation of study treatment. If the adverse event is listed in the NCI CTCAE (version 4.0) table, the maximum grade will be summarized. The incidence of deaths and the primary cause of death will be summarized.

8.4.2.2 Clinical laboratory evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment.

8.4.2.3 Other safety measures

The results of scheduled assessments of vital signs, ECOG performance status and 12-lead ECG will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in 'worse case' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

8.4.3 Summaries of demographic and baseline characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (e.g., age), baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.5 Sample size and power calculations

The study will randomize subjects in a 1:1 ratio into the experimental arm of SBRT of a recurrence-pattern-based-volume after gemcitabine and nab-paclitaxel and the control arm of SBRT of a conventional-volume following gemcitabine and nab-paclitaxel. One-year PFS rate is primary endpoint for this study.

Therefore, for the one-year PFS rate endpoint, as per the protocol design, the

following assumptions were made in the estimation of the required sample size:

- We assumed that one-year PFS rate of the experimental and control group were about 60% and 30%, respectively.
- A 1:1 randomization scheme.
- An overall 5%, one-sided risk of erroneously claiming superiority of the combination therapy in the presence of no true underlying difference (i.e., overall Type I error).
- A 80% chance of successfully claiming superiority of the combination therapy in the presence of a true underlying difference (i.e., power or Type II error).

Therefore, an estimated total of 80 subjects (i.e., 40 subjects in each of the arms) would need to be enrolled. The final primary one-year PFS rate analysis will be performed at the pre-defined cut-off date, by which time it is expected that approximately 80 PFS events will have been accrued.

8.6 Subgroup analysis

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the dual primary endpoints will be estimated and plotted within each category of the following classification variables:

- Sex (Female vs. male)
- Age (<65 years vs. ≥65 years)
- ECOG (0 point vs. 1 point)

- CA19-9 level (<200U/ml vs. ≥200U/ml)
- History of smoking
- History of alcohol

9. Study conduct considerations

9.1 Posting of information on publicly available clinical trial registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2 Regulatory and ethical considerations, including the informed consent process

Prior to initiation of the study, the investigator will obtain favorable opinion/approval from the Institutional Review Board/Independent Ethics Committee to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice. The study will be conducted in accordance with all applicable regulatory requirements. The study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board/Independent Ethics Committee review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.

- Investigator reporting requirements.

Written informed consent must be obtained from each subject prior to participation in the study.

9.3 Quality monitoring

In accordance with applicable regulations and Good Clinical Practice, Institutional Review Board/Independent Ethics Committee will contact our center before the start of the study to review with the investigator the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the case report form will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the Institutional Review Board/Independent Ethics Committee direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

Data are authentic, accurate, and complete.

Safety and rights of subjects are being protected.

Study is conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonization Good Clinical Practice, and all applicable regulatory requirements.

9.4 Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, staff of Institutional Review Board/Independent Ethics Committee may conduct a quality assurance assessment and regulatory inspection at any time during or after completion of the study. In the event of an assessment, the investigator must agree to grant the advisor(s), auditor(s) and inspector(s) of Institutional Review Board/Independent Ethics Committee direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5 Source documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.6 Case report form

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the case report form must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. Case report forms may be requested for adverse events and/or laboratory abnormalities that are reported or identified during the course of the study.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on case report forms.

The completed case report form, including any paper or electronic severe adverse

event/pregnancy case report forms, must be promptly reviewed, signed, and dated by the investigator. The investigator must retain a copy of the case report forms including records of the changes and corrections.

9.7 Study closure

Upon completion or termination of the study, staff of Institutional Review Board/Independent Ethics Committee will conduct study closure activities with the investigator in accordance with applicable regulations and International Conference on Harmonization Good Clinical Practice.

Institutional Review Board/Independent Ethics Committee reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Institutional Review Board/Independent Ethics Committee determines that such action is required, Institutional Review Board/Independent Ethics Committee will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Institutional Review Board/Independent Ethics Committee will provide advance notice to the investigator of the impending action.

If a study is suspended or terminated for safety reasons, Institutional Review Board/Independent Ethics Committee will promptly inform all investigators conducting the study and provide the reason(s) for the suspension/termination.

9.8 Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

9.9 Independent data monitoring committee

An Independent Data Monitoring Committee will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

10. Reference

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J

Clin. 2025; 75: 10-45.

2. Kiemen AL, Braxton AM, Grahn MP, et al. CODA: quantitative 3D reconstruction of large tissues at cellular resolution. Nat Methods. 2022; 19: 1490-1499.

3. Javed AA, Mahmud O, Fatimi AS, et al, and the PANC-PALS Consortium. Predictors for long-term survival after resection of pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. Ann Surg Oncol 2024; 31: 4673-4687.

4. Stoop TF, Javed AA, Oba A, et al. Pancreatic cancer. Lancet. 2025; 405: 1182-1202.

5. Palta M, Godfrey D, Goodman KA, et al. Radiationtherapy for pancreatic cancer: executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol. 2019; 9: 322-332.

6. Oar A, Lee M, Le H, et al. Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT). Pract Radiat Oncol. 2020; 10: e136-e146.

7. Zhu X, Ju X, Cao Y, et al. Patterns of local failure after stereotactic body radiation therapy and sequential chemotherapy as initial treatment for pancreatic cancer: implications of target volume design. Int J Radiat Oncol Biol Phys. 2019; 104: 101-110.

11. Appendices

11.1 Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
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.

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6): 649-655.

11.2 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

NCI CTCAE version 4.0 will be utilized for adverse events reporting

(http://ctep.cancer.gov/reporting/ctc.html)

11.3 New York Heart Association (NYHA) Guidelines

The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure [The Criteria Committee of the New York Heart Association, 1994]. It places subjects in 1 of 4 categories based on the level of limitation experienced during physical activity:

Functional Capacity	Objective Assessment
Class I: Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.	**A:** No objective evidence of cardiovascular disease.
Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B:** Objective evidence of minimal cardiovascular disease.
Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C:** Objective evidence of moderately severe cardiovascular disease.
Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D:** Objective evidence of severe cardiovascular disease.

Reference:

The Criteria Committee of the New York Heart Association. Nomenclature and

criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown, & Co; 1994:253-256.