NANT PANCREATIC CANCER VACCINE: COMBINATION IMMUNOTHERAPY WITH HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.060**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
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Protocol Version	**Date**
Version 1	15 September 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
2. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen])
3. GI-4000 (RAS yeast vaccine)
4. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

5. Avelumab (BAVENCIO® injection, for IV use)
6. Bevacizumab (AVASTIN® solution for IV infusion)
7. Capecitabine (XELODA® tablets, for oral use)
8. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
9. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
10. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
11. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
12. Omega-3-acid ethyl esters (LOVAZA® Capsules, for oral use)
13. Oxaliplatin (ELOXATIN® injection for IV use)
14. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

1. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
2. Ad5 [E1-, E2b-]-CEA
3. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L); and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
4. NK92 [CD16.158V, ER IL2] cells

Approved Products:

5. Avelumab
6. Bevacizumab
7. Capecitabine
8. Cyclophosphamide (anhydrous)
9. Fluorouracil, USP
10. Leucovorin (calcium salt)
11. Paclitaxel, USP
12. Omega-3-acid ethyl esters
13. Oxaliplatin, USP
14. Radiation

Title of Study:

NANT Pancreatic Cancer Vaccine: combination immunotherapy with high-affinity natural killer (haNK) in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.060

Study Phase:
Phase 1b/2 (Simon's two-stage optimal design).

Study Objectives:

Phase 1b

- The primary objective is to evaluate the overall safety profile of the NANT pancreatic cancer regimen in subjects with pancreatic cancer who have progressed after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

Phase 2

- The primary objective is to determine the efficacy of the NANT pancreatic cancer regimen as assessed by ORR.
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA; and their correlations with subject outcomes.

Study Design:

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with pancreatic cancer who have progressed on or after previous SoC chemotherapy. Phase 2 will be based on Simon's two-stage optimal design.

Preliminary assessment of the safety of the treatment regimen will occur by an independent Data Safety Monitoring Committee (IDMC) and the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment will be administered in two phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be discontinued if the subject experiences progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The maximum time on study treatment, including both the induction and maintenance

phases, is 2 years.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, at the end of the initial induction phase (8 weeks after the start of treatment), and during potential prolonged induction and maintenance phases (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 4 weeks in the induction phase and every 8 weeks in the maintenance phase during routine blood draws for exploratory immunology and ctDNA/ctRNA analyses, as described in Section 6.4.2 and Section 6.4.3, respectively.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT of target and non-target lesions in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC).

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status and will be used to determine whether GI-4000 will be administered. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected at screening. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.6.8.1, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated RAS oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

Induction Phase:

The induction phase will consist of repeated 2-week cycles for a maximum treatment period of 1 year. The treatment regimen of ALT-803, avelumab, bevacizumab, cyclophosphamide, Ad5-based vaccine (ETBX-011), 5-FU/leucovorin, yeast-based vaccine (GI-4000), haNK, nab-paclitaxel, omega-3-acid ethyl esters, and oxaliplatin will be repeated every 2 weeks. Concurrent stereotactic body radiotherapy (SBRT) will be given during the first four 2-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

The induction phase of study treatment will be conducted in accordance with the following dosing regimen:

Daily:

- Omega-3-acid ethyl esters (by mouth [PO] twice a day [BID] [3 × 1 g capsules and 2 × 1 g capsules])

Day 1 every 2 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg BID)

Days 1, 3, 5, 8, 10 and 12, every 2 weeks:

- 5-FU (400 mg/m^2 continuous IV infusion over 16 hours)
- Leucovorin (20 mg/m^2 IV bolus)

Day 1 and 8, every 2 weeks:

- Nab-paclitaxel (125 mg IV)
- Oxaliplatin (40 mg/m^2 IV)

Day 5, 19, 33 (every 2 weeks for 3 doses then every 8 weeks thereafter):

- ETBX-011 (5×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])
- GI-4000 (40 yeast units [YU]/dose SC), 2 hours after administration of the Ad5-based vaccine

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above.

Day 8, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)

Day 8, 22, 36, 50 (every 2 weeks for 4 doses):

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist)

Day 9, every 2 weeks:

- ALT-803 (10 µg/kg SC 30 minutes prior to haNK infusion)

Day 9 and 11, every 2 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of ALT-803, avelumab, bevacizumab, cyclophosphamide, capecitabine, Ad5-based vaccine (ETBX-011), yeast-based vaccine (GI-4000), haNK, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 2 weeks.

The maintenance phase of study treatment will be conducted in accordance with the following dosing regimen:

Daily:

- Omega-3-acid ethyl esters (PO BID [3 × 1 g capsules and 2 × 1 g capsules])

Day 1, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (125 mg IV)

Days 1–5 and 8–12, every 2 weeks:

- Capecitabine (650 mg/m^2 PO BID)
- Cyclophosphamide (50 mg BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC, 30 minutes prior to haNK infusion)
- haNK (2 x 10^9 cells/dose IV)

Day 5, every 8 weeks thereafter:

- ETBX-011 (5×10^{11} VP/vaccine/dose SC)
- GI-4000 (40 YU/dose SC), 2 hours after administration of the Ad5-based vaccine

  Prospective molecular profiling will determine whether GI-4000 will be administered, as described above.

Phase 1b

Primary Endpoint:

- Incidence of treatment-emergent adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Secondary Endpoints:

- ORR by RECIST Version 1.1 and irRC.
- PFS by RECIST Version 1.1 and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months).
- QoL by PROs.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with subject outcomes.
- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1 and irRC.

Secondary Endpoints:

- PFS by RECIST Version 1.1 and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months).
- QoL by PROs.
- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with subject outcomes.
- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. In the phase 2 portion of the study, 23 subjects will be enrolled in the first stage of Simon's two-stage optimal design. If the study proceeds to the second stage of Simon's two-stage optimal design, an additional 33 subjects will be enrolled in the second stage, for a total of 56 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 80 subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed pancreatic cancer with progression on or after SoC therapy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.

2. Within 5 years prior to first dose of study treatment, any evidence of other active malignancies or brain metastasis except controlled basal cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, cervical); prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable prostate-specific antigen (PSA) (< 0.2 ng/mL); bulky (≥ 1.5 cm) disease with metastasis in the central hilar area of the chest and involving the pulmonary vasculature.
3. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
4. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
5. History of organ transplant requiring immunosuppression.
6. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
7. Requires whole blood transfusion to meet eligibility criteria.
8. Inadequate organ function, evidenced by the following laboratory results:
    a. White blood cell (WBC) count < 3,500 cells/mm^3
    b. Absolute neutrophil count < 1,500 cells/mm^3.
    c. Platelet count < 100,000 cells/mm^3.
    d. Hemoglobin < 9 g/dL.
    e. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    f. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    g. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    h. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
9. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
10. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
11. Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
12. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.

13. Known hypersensitivity to any component of the study medication(s).
14. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
15. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
16. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
17. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
18. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
19. Concurrent participation in any interventional clinical trial.
20. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK™ for Infusion	2×10^{9} cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2	PO BID
Cyclophosphamide	50 mg	PO BID
5-FU	400 mg/m^2	16-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg	IV
Omega-3-acid ethyl esters	5 g	PO
Oxaliplatin	40 mg/m^2	IV
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

- Induction phase: 8 weeks (minimum) to 1 year (maximum).
- Maintenance phase: Up to 1 year.

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase) or until they experience progressive disease, unacceptable toxicity (not corrected with dose reduction), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed every 90 days (± 14 days) for:

- Resolution of any SAEs attributed to treatment (see Section 7)
- CT, MRI, or PET-CT scan assessment (see Section 6.1.2)
- Vital status: subjects will be followed until either death or for a minimum of 18 months past administration of the first dose of chemotherapy to the last subject enrolled in the study, whichever comes first.

Subjects may continue to be followed by the investigational physician or a third party by phone or review of medical records approximately every 90 days until withdrawal of consent, lost to follow-up, or death (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 4.03.

Efficacy:

ORR and PFS will be assessed by CT, MRI, or PET-CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Hepatobiliary Cancer (FACT-Hep) instrument on study day 1, every 28 days thereafter, and at the end-of-treatment (EOT) visit.

Exploratory Analysis:

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the absolute amounts of specific proteins, to confirm expression of genes that are correlative of disease progression and/or response, and to determine the cutoff values for response.

Immunologic Analysis: Immune responses to the NANT pancreatic cancer regimen will be evaluated by flow cytometry and enzyme-linked immunospot (ELISpot) assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

ctDNA/ctRNA Analysis: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

Statistical Methods:

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

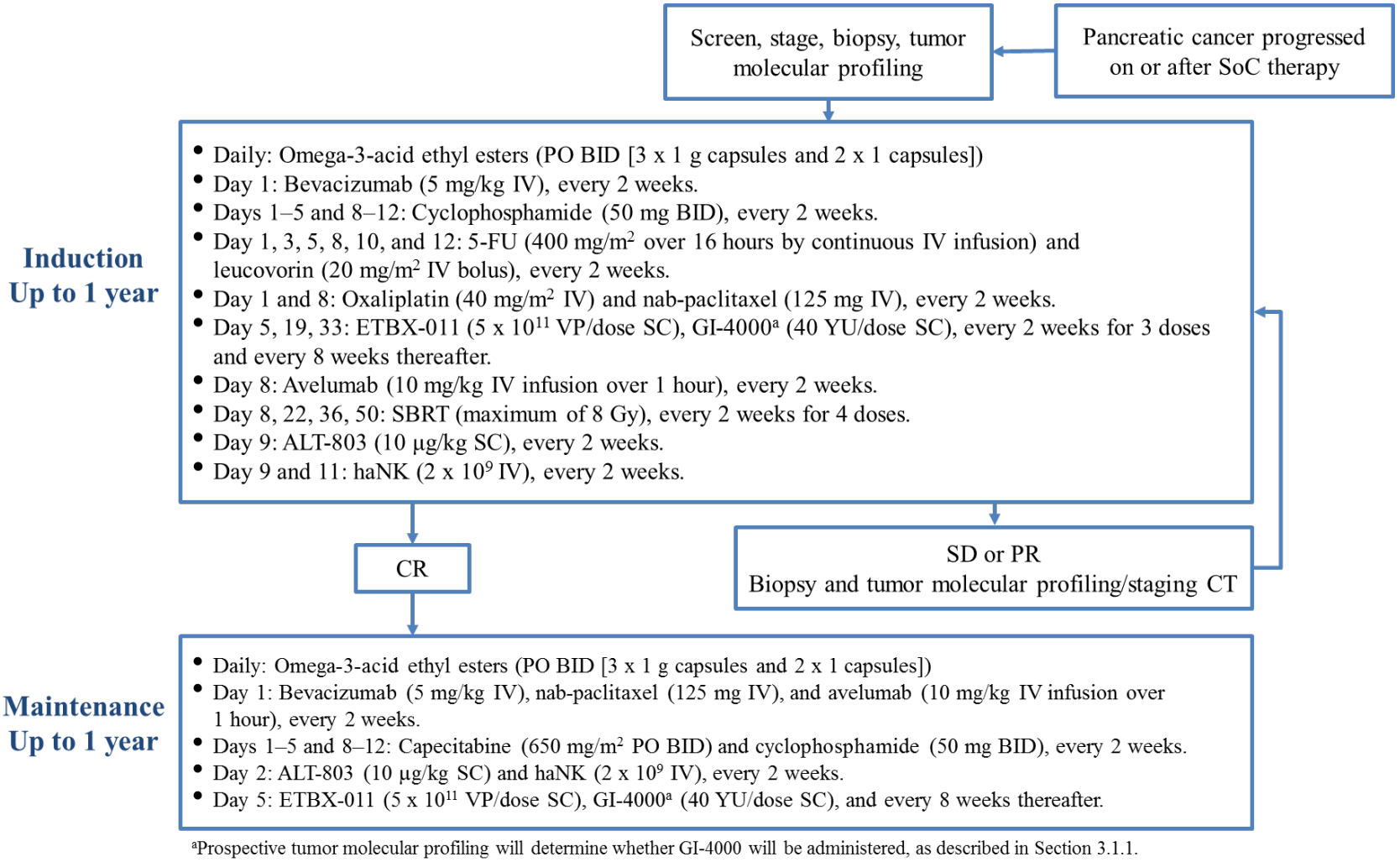
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will be evaluated similar to ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

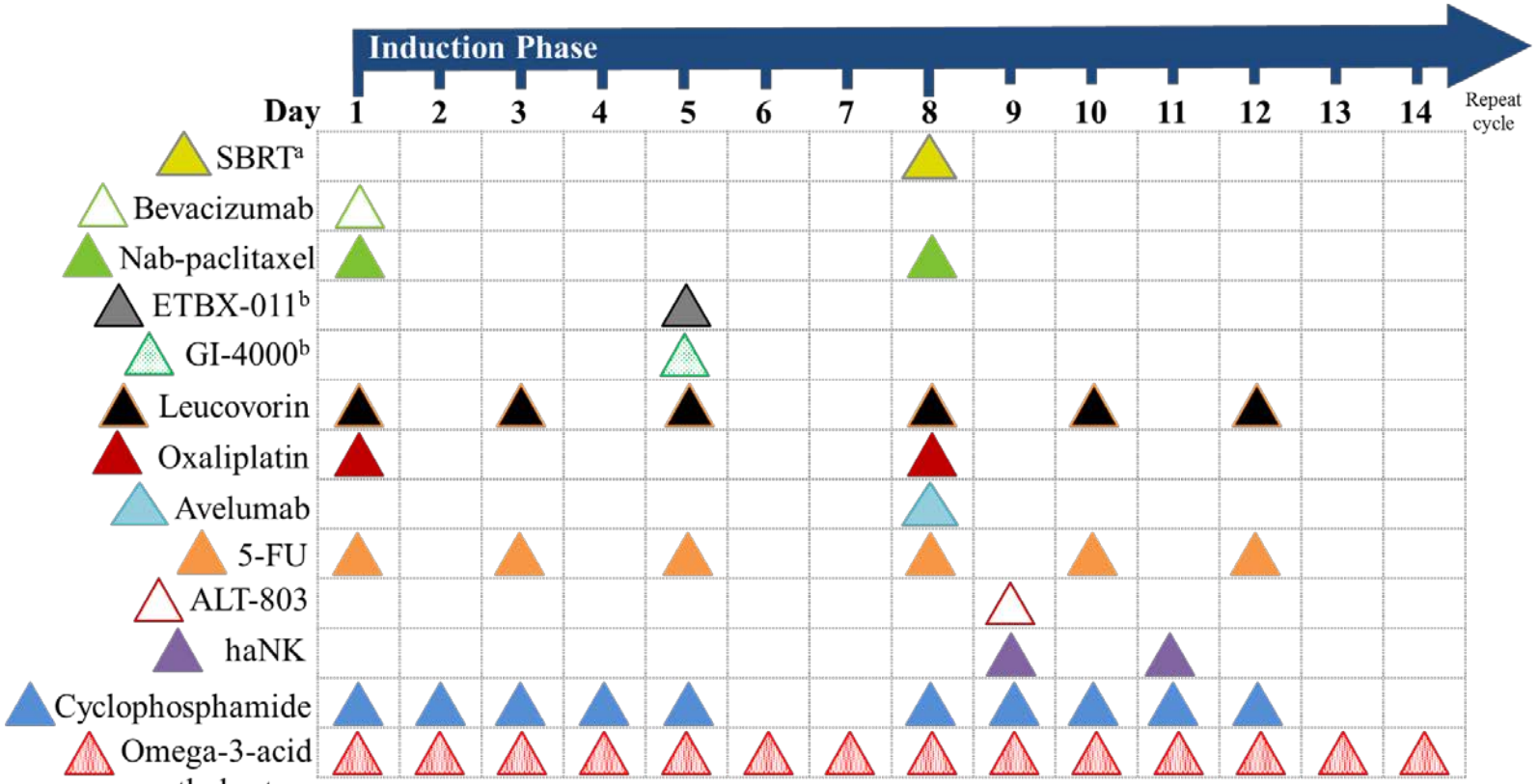
Correlations of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Figure 2: Induction Phase Treatment Schema

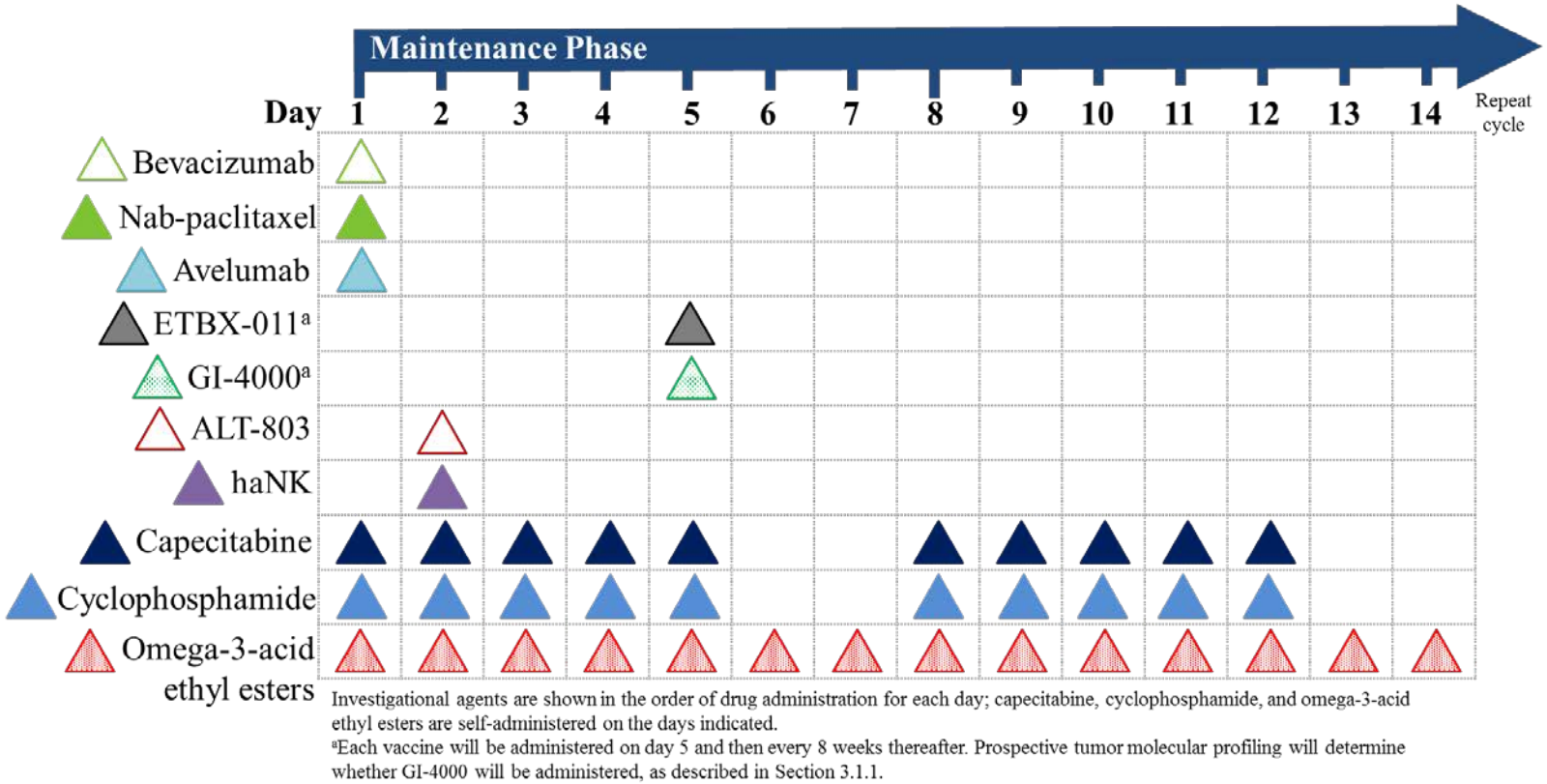


Investigational agents are shown in the order of drug administration for each day; cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.

[a]SBRT will be administered every 2 weeks for 4 doses.

[b]Each vaccine will be administered every 2 weeks for 3 doses and then every 8 weeks thereafter. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Figure 3: Maintenance Phase Treatment Schema



Investigational agents are shown in the order of drug administration for each day; capecitabine, cyclophosphamide, and omega-3-acid ethyl esters are self-administered on the days indicated.

[a]Each vaccine will be administered on day 5 and then every 8 weeks thereafter. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Table 19: Schedule of Events for Induction Phase of Study

	Screening	Induction Phase Treatment (repeats every 2 weeks, except where noted)[a]														EOT Visit[b]	Unscheduled Visit[c]
Study Week		1							2								
Study Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
General Assessments																	
Informed consent	X																
Inclusion/exclusion[d]	X																
Demographics	X																
Medical history[e]	X																
Confirm availability of FFPE tumor sample[f]	X																
Concomitant medications	X	X							X							X	X
Physical exam: height[g], weight	X	X							X							X	X
Vital signs[h]	X	X		X		X			X	X	X	X	X			X	X
ECOG performance status	X	X							X							X	X
12-lead ECG[i]	X	X	Every 4 weeks													X	
Confirm contraceptive measures	X																
FACT-Hep Questionnaire	X	X	Every 4 weeks													X	
Adverse event collection		X		X		X			X	X	X	X	X			X	X
Laboratory Assessments																	
Chemistry panel[j]	X	X[k]							X							X	
CA19-9	X	X[k]	Every 4 weeks													X	

	Screening	Induction Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week		**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Hematology[l]	X	X[k]							X							X	
Urinalysis	X	X[k]														X	
Pregnancy test[m]	X	X[k]	Every 4 weeks													X	
Serum virology (HIV, HBV, HCV)[n]	X																
Determine *RAS* mutational status[o]	X																
Collect whole blood for tumor molecular profiling[p]	X																
Collect whole blood for immunology analysis[q]	X	Every 4 weeks during routine blood draws														X	
Collect whole blood for ctDNA/ctRNA analysis[q]	X	Every 4 weeks during routine blood draws														X	
Collect historic tumor biopsy specimen for tumor molecular profiling[r]	X																
Tumor biopsy[r]	X	At the end of the initial induction phase (8 weeks after the start of treatment)															
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion.																
Tumor Imaging and Assessments																	
CT, MRI, or PET-CT[s]	X	Every 8 weeks														X	

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment.

[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
[g] Height required at screening visit only.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vitals signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes. For visits where a subject is receiving an infusion of any study compounds, vital signs will be recorded at 15 minutes and 30 minutes after the start of the infusion and, except for 5-FU, at 30-minute intervals thereafter through the post-infusion hydration period.
[i] 12-lead ECG to be performed in triplicate at screening.
[j] Chemistry panel to include laboratory assessments noted in Table 18.
[k] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[l] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
[m] Serum pregnancy test at screening; urine dipstick pregnancy test for all other visits (for females of child-bearing potential).
[n] Virology tests include HIV (as determined by ELISA and confirmed by western blot) and HBV/HCV (as determined by HBsAg and hepatitis C serology).
[o] Assessment of *RAS* mutational status to determine whether GI-4000 will be administered to the subject, as described in Section 3.1.1.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 4 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling will be collected only for subjects enrolled in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. A tumor biopsy is also required at the end of the initial induction phase (8 weeks after the start of treatment), if considered safe by the Investigator
[s] Tumor imaging by CT scan, MRI, or PET-CT will be performed at screening and every 8 weeks thereafter in the induction phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

Table 20: Schedule of Events for Maintenance Phase of Study

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Concomitant medications	X														X	X
Physical exam, weight	X														X	X
Vital signs[d]	X	X			X										X	X
ECOG performance status	X														X	X
12-lead ECG	X	Every 4 weeks													X	
Confirm contraceptive measures	X															
Adverse event collection	X	X			X										X	X
FACT-Hep	X	Every 4 weeks													X	
Laboratory Assessments																
Chemistry panel[e]	X														X	
CA19-9	X	Every 4 weeks													X	
Hematology[f]	X														X	
Urinalysis	X														X	
Pregnancy test[g]	X	Every 4 weeks													X	
Collect whole blood for immunology analysis[h]	X	Every 8 weeks during routine blood draws													X	
Collect whole blood for ctDNA/ctRNA analysis[h]	X	Every 8 weeks during routine blood draws													X	
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion															
CT, MRI, or PET-CT[i]	X	Every 12 weeks													X	

[a] Subjects will remain in the maintenance phase of the study for up to 1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

[b] EOT visit must be performed 30 (±5 days) after the last study treatment.

[c] Additional assessments performed during an unscheduled visit are at the discretion of the PI or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.

[d] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vitals signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes. For visits where a subject is receiving an infusion of any study compounds, vital signs will be recorded at 15 minutes and 30 minutes after the start of the infusion and, except for 5-FU, at 30-minute intervals thereafter through the post-infusion hydration period.

[e] Chemistry panel to include laboratory assessments noted in Table 18.

[f] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.

[g] Urine dipstick pregnancy test for females of child-bearing potential.

[h] Blood collection for exploratory immunology and ctDNA/ctRNA analyses will be performed every 8 weeks in the maintenance phase during routine blood draws, and at the end-of-treatment visit.

[i] Tumor imaging by CT scan, MRI, or PET-CT will be performed every 12 weeks in the maintenance phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Combination immunotherapy with high-affinity natural killer (haNK) cell therapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.060
Version Number:	1
Final Date:	15 September 2017

This clinical trial protocol was subject to critical review and has been approved by NantKwest. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 9-18-17

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NANT PANCREATIC CANCER VACCINE: COMBINATION IMMUNOTHERAPY WITH HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.060**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	15 September 2017
Version 2	15 February 2018

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
2. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen])
3. GI-4000 (RAS yeast vaccine)
4. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

5. Avelumab (BAVENCIO® injection, for IV use)
6. Bevacizumab (AVASTIN® solution for IV infusion)
7. Capecitabine (XELODA® tablets, for oral use)
8. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
9. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
10. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
11. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
12. Oxaliplatin (ELOXATIN® injection for IV use)
13. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

1. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
2. Ad5 [E1-, E2b-]-CEA
3. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L); and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
4. NK-92 [CD16.158V, ER IL2] cells

Approved Products:

5. Avelumab
6. Bevacizumab
7. Capecitabine
8. Cyclophosphamide (anhydrous)
9. Fluorouracil, USP
10. Leucovorin (calcium salt)
11. Paclitaxel, USP
12. Oxaliplatin, USP
13. Radiation

Title of Study:

NANT Pancreatic Cancer Vaccine: combination immunotherapy with high-affinity natural killer (haNK) in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.060

Study Phase:
Phase 1b/2 (Simon's two-stage optimal design).

Study Objectives:

Phase 1b

- The primary objective is to evaluate the overall safety profile of the NANT pancreatic cancer regimen in subjects with pancreatic cancer who have progressed after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

Phase 2

- The primary objective is to determine the efficacy of the NANT pancreatic cancer regimen as assessed by ORR.
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA; and their correlations with subject outcomes.

Study Design:

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with pancreatic cancer who have progressed on or after previous SoC chemotherapy. Phase 2 will be based on Simon's two-stage optimal design.

Preliminary assessment of the safety of the treatment regimen will occur by an Independent Data Safety Monitoring Committee (IDMC) and the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment will be administered in two phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be discontinued if the subject experiences progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The maximum time on study treatment, including both the induction and maintenance

phases, is 2 years.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, 8 weeks after the start of treatment, and during potential prolonged induction and maintenance phases (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 4 weeks in the induction phase and every 8 weeks in the maintenance phase during routine blood draws for exploratory immunology and ctDNA/ctRNA analyses, as described in Section 6.4.2 and Section 6.4.3, respectively.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT of target and non-target lesions in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC).

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status and will be used to determine whether GI-4000 will be administered. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected at screening. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.6.8.1, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated RAS oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

Induction Phase:

Treatment in the induction phase will consist of repeated 2-week cycles for a maximum treatment period of 1 year, as follows:

Day 1 every 2 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg by mouth [PO] twice a day [BID])

Days 1, 3, 5, 8, 10 and 12, every 2 weeks:

- 5-FU (400 mg/m^2 continuous IV infusion over 16–24 hours)
- Leucovorin (20 mg/m^2 IV bolus)

Day 1 and 8, every 2 weeks:

- Nab-paclitaxel (125 mg IV)
- Oxaliplatin (40 mg/m^2 IV)

Day 5, 19, 33 (every 2 weeks for 3 doses then every 8 weeks thereafter):

- ETBX-011 (5×10^{11} virus particles [VP]/dose subcutaneously [SC])
- GI-4000 (40 yeast units [YU]/dose SC), 2 hours after administration of the Ad5-based vaccine

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above.

Day 8, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)

Day 8, 22, 36, 50 (every 2 weeks for 4 doses):

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist)

Day 9, every 2 weeks:

- ALT-803 (10 µg/kg SC at least 30 minutes prior to haNK infusion)

Day 9 and 11, every 2 weeks:

- haNK (2 x 10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase, as follows:

Day 1, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (125 mg IV)

Days 1–5 and 8–12, every 2 weeks:

- Capecitabine (650 mg/m^2 PO BID)
- Cyclophosphamide (50 mg PO BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC, at least 30 minutes prior to haNK infusion)
- haNK (2 x 10^9 cells/dose IV)

Day 5, every 8 weeks thereafter:

- ETBX-011 (5×10^{11} VP/dose SC)
- GI-4000 (40 YU/dose SC), 2 hours after administration of the Ad5-based vaccine

  Prospective molecular profiling will determine whether GI-4000 will be administered, as described above.

Phase 1b

Primary Endpoint:

- Incidence of treatment-emergent adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Secondary Endpoints:

- ORR by RECIST Version 1.1 and irRC.
- PFS by RECIST Version 1.1 and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months).
- QoL by PROs.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with subject outcomes.
- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1 and irRC.

Secondary Endpoints:

- PFS by RECIST Version 1.1 and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months).
- QoL by PROs.
- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with subject outcomes.
- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. In the phase 2 portion of the study, 23 subjects will be enrolled in the first stage of Simon's two-stage optimal design. If the study proceeds to the second stage of Simon's two-stage optimal design, an additional 33 subjects will be enrolled in the second stage, for a total of 56 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 80 subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed pancreatic cancer with progression on or after SoC therapy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.

2. Within 5 years prior to first dose of study treatment, any evidence of other active malignancies or brain metastasis except controlled basal cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, cervical); prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable prostate-specific antigen (PSA) (< 0.2 ng/mL); bulky (≥ 1.5 cm) disease with metastasis in the central hilar area of the chest and involving the pulmonary vasculature.
3. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
4. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
5. History of organ transplant requiring immunosuppression.
6. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
7. Requires whole blood transfusion to meet eligibility criteria.
8. Inadequate organ function, evidenced by the following laboratory results:
    a. White blood cell (WBC) count < 3,500 cells/mm^3
    b. Absolute neutrophil count < 1,500 cells/mm^3.
    c. Platelet count < 100,000 cells/mm^3.
    d. Hemoglobin < 9 g/dL.
    e. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    f. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    g. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    h. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
9. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
10. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
11. Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
12. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.

13. Known hypersensitivity to any component of the study medication(s).
14. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
15. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
16. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
17. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
18. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
19. Concurrent participation in any interventional clinical trial.
20. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK™ for Infusion	2×10^{9} cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2 PO	BID
Cyclophosphamide	50 mg PO	BID
5-FU	400 mg/m^2	16–24 hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg	IV
Oxaliplatin	40 mg/m^2	IV
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

- Induction phase: 8 weeks (minimum) to 1 year (maximum).
- Maintenance phase: Up to 1 year.

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase) or until they experience progressive disease, unacceptable toxicity (not corrected with dose reduction), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed every 90 days (± 14 days) for:

- Resolution of any SAEs attributed to treatment (see Section 7)
- CT, MRI, or PET-CT scan assessment (see Section 6.1.2)
- Vital status: subjects will be followed until either death or for a minimum of 18 months past administration of the first dose of chemotherapy to the last subject enrolled in the study, whichever comes first.

Subjects may continue to be followed by the investigational physician or a third party by phone or review of medical records approximately every 90 days until withdrawal of consent, lost to follow-up, or death (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

Reference Therapy, Dosage, and Mode of Administration:
Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 4.03.

Efficacy:

ORR and PFS will be assessed by CT, MRI, or PET-CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Hepatobiliary Cancer (FACT-Hep) instrument on study day 1, every 28 days thereafter, and at the end-of-treatment (EOT) visit.

Exploratory Analysis:

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the absolute amounts of specific proteins, to confirm expression of genes that are correlative of disease progression and/or response, and to determine the cutoff values for response.

Immunologic Analysis: Immune responses will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

ctDNA/ctRNA Analysis: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

Statistical Methods:

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

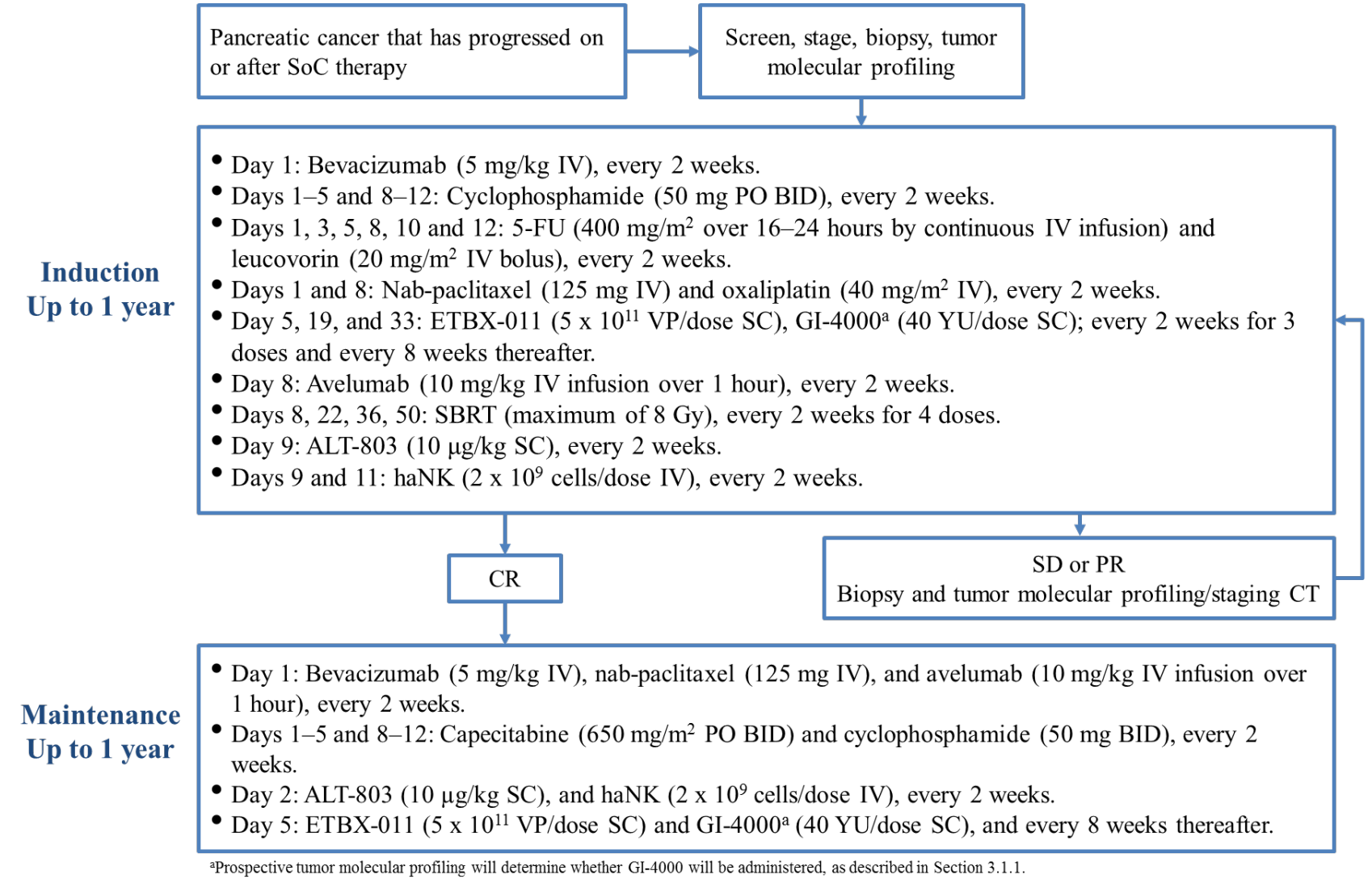
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will be evaluated similar to ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

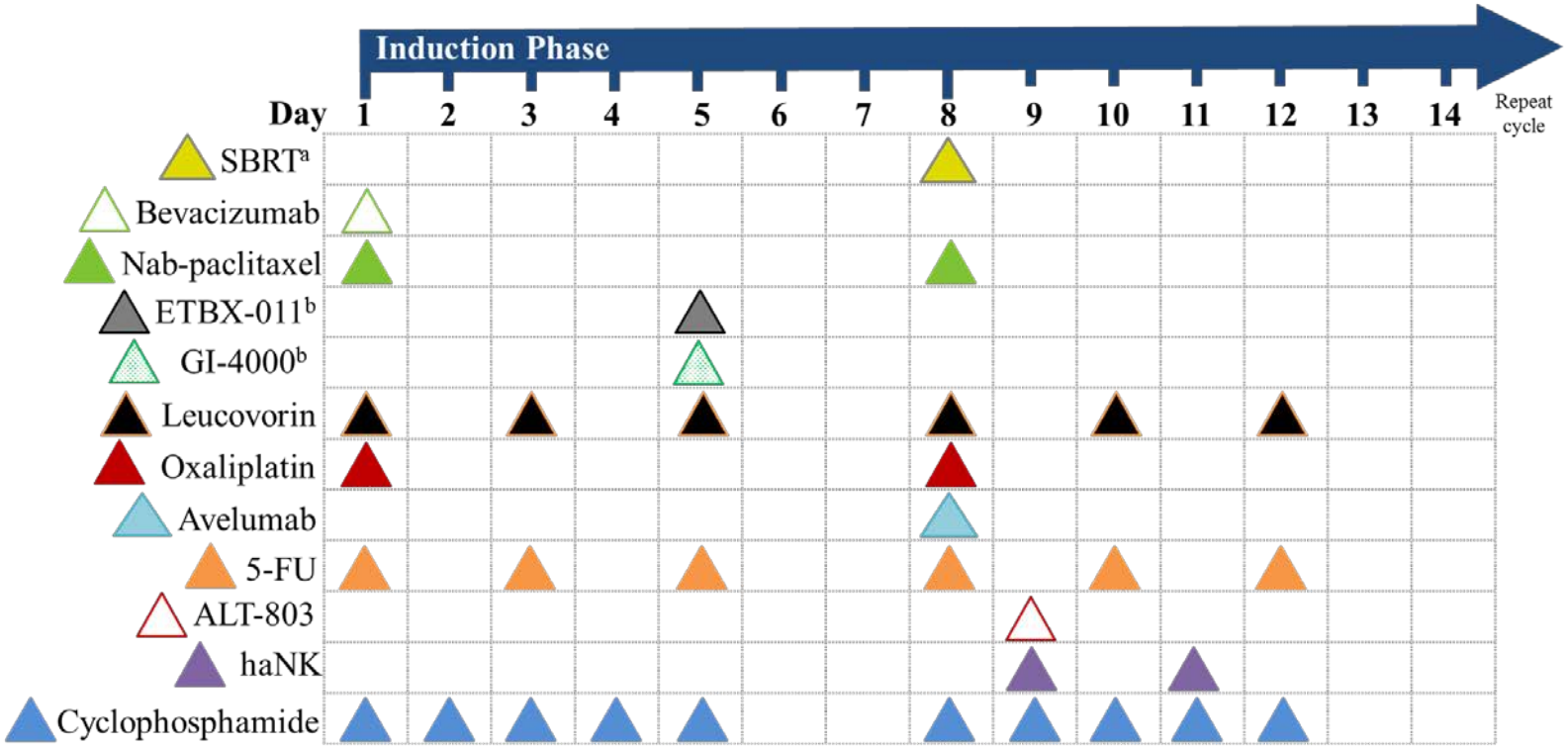
Correlations of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



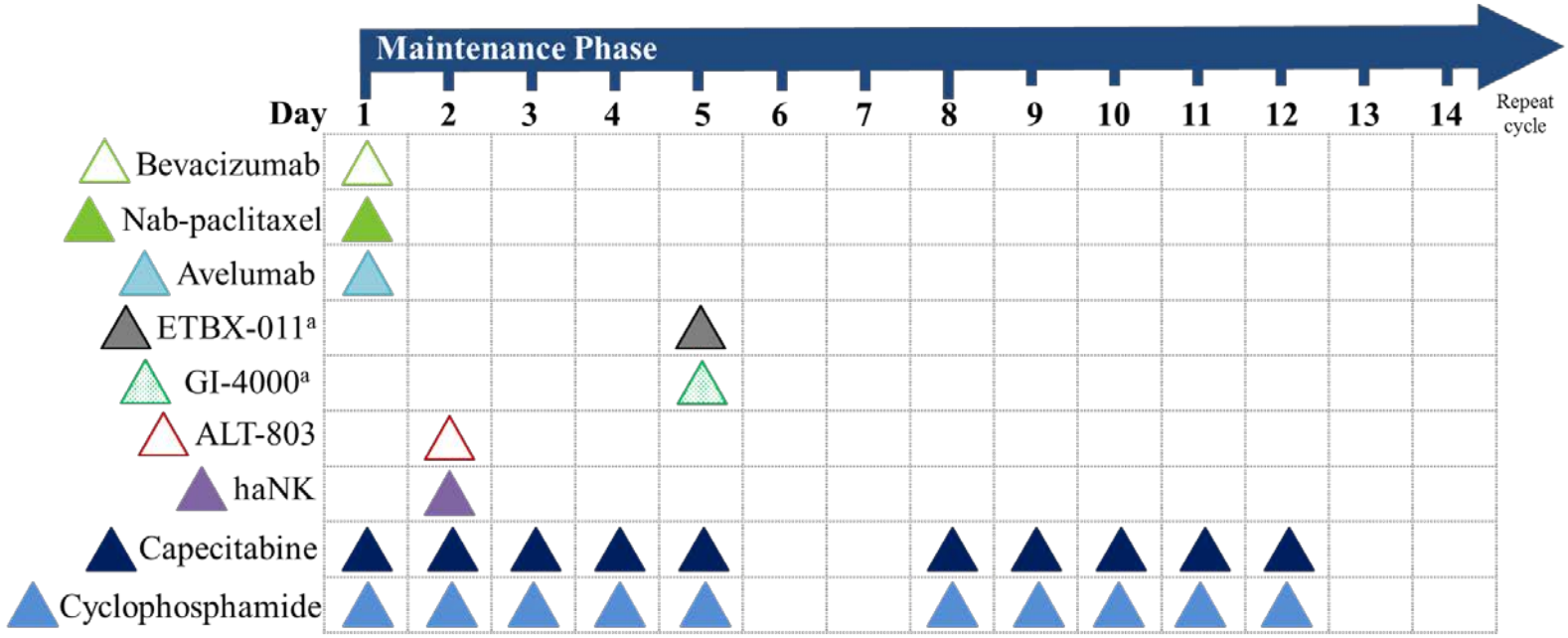
[a]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Figure 2: Induction Phase Treatment Schema



Investigational agents are shown in the order of drug administration for each day; cyclophosphamide is self-administered on the days indicated.
[a]SBRT will be administered every 2 weeks for 4 doses.
[b]Each vaccine will be administered every 2 weeks for 3 doses and then every 8 weeks thereafter. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Figure 3: Maintenance Phase Treatment Schema



Investigational agents are shown in the order of drug administration for each day; capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Each vaccine will be administered on day 5 and then every 8 weeks thereafter. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Table 19: Schedule of Events for Induction Phase of Study

	Screening	Induction Phase Treatment (repeats every 2 weeks, except where noted)[a]														EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
General Assessments																	
Informed consent	X																
Inclusion/exclusion[d]	X																
Demographics	X																
Medical history[e]	X																
Confirm availability of FFPE tumor sample[f]	X																
Concomitant medications	X	X							X							X	X
Physical exam: height[g], weight	X	X							X							X	X
Vital signs[h]	X	X		X		X			X	X	X	X	X			X	X
ECOG performance status	X	X							X							X	X
12-lead ECG[i]	X	X	Every 4 weeks													X	
Confirm contraceptive measures	X																
FACT-Hep Questionnaire	X	X	Every 4 weeks													X	
Adverse event collection		X		X		X			X	X	X	X	X			X	X
Laboratory Assessments																	
Chemistry panel[j]	X	X[k]							X							X	
CA19-9	X	X[k]	Every 4 weeks													X	

	Screening	Induction Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week		**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Hematology[l]	X	X[k]							X							X	
Urinalysis	X	X[k]														X	
Pregnancy test[m]	X	X[k]	Every 4 weeks													X	
Serum virology (HIV, HBV, HCV)[n]	X																
Determine *RAS* mutational status[o]	X																
Collect whole blood for tumor molecular profiling[p]	X																
Collect whole blood for immunology analysis[q]	X	Every 4 weeks during routine blood draws														X	
Collect whole blood for ctDNA/ctRNA analysis[q]	X	Every 4 weeks during routine blood draws														X	
Collect historic tumor biopsy specimen for tumor molecular profiling[r]	X																
Tumor biopsy[r]	X	At the end of the initial induction phase (8 weeks after the start of treatment)															
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion.																
Tumor Imaging and Assessments																	
CT, MRI, or PET-CT[s]	X	Every 8 weeks														X	

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. Any required blood draws and safety laboratory sample collections (including urinalysis) may be performed within a 3-day window of the time indicated.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment.

[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
[g] Height required at screening visit only.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes and within 30 minutes prior to the start of any infusional study treatment. For visits where a subject is receiving an infusion of any study compounds, vital signs will be collected at the following time points in relation to the start of first infusion of the day: prior to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.
[i] 12-lead ECG to be performed in triplicate at screening.
[j] Chemistry panel to include laboratory assessments noted in Table 18.
[k] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[l] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
[m] Serum pregnancy test for females of child-bearing potential.
[n] Virology tests include HIV (as determined by ELISA and confirmed) and HBV/HCV (as determined by HBsAg and hepatitis C serology).
[o] Assessment of *RAS* mutational status to determine whether GI-4000 will be administered to the subject, as described in Section 3.1.1.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 4 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling will be collected only for subjects enrolled in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator
[s] Tumor imaging by CT scan, MRI, or PET-CT will be performed at screening and every 8 weeks thereafter in the induction phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

Table 20: Schedule of Events for Maintenance Phase of Study

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Concomitant medications	X														X	X
Physical exam, weight	X														X	X
Vital signs[d]	X	X			X										X	X
ECOG performance status	X														X	X
12-lead ECG	X	Every 4 weeks													X	
Confirm contraceptive measures	X															
Adverse event collection	X	X			X										X	X
FACT-Hep	X	Every 4 weeks													X	
Laboratory Assessments																
Chemistry panel[e]	X														X	
CA19-9	X	Every 4 weeks													X	
Hematology[f]	X														X	
Urinalysis	X														X	
Pregnancy test[g]	X	Every 4 weeks													X	
Collect whole blood for immunology analysis[h]	X	Every 8 weeks during routine blood draws													X	
Collect whole blood for ctDNA/ctRNA analysis[h]	X	Every 8 weeks during routine blood draws													X	
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion															
CT, MRI, or PET-CT[i]	X	Every 12 weeks													X	

[a] Subjects will remain in the maintenance phase of the study for up to 1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required blood draws and safety laboratory sample collections (including urinalysis) may be performed within a 3-day window of the time indicated.±

[b] EOT visit must be performed 30 (±5 days) after the last study treatment.

[c] Additional assessments performed during an unscheduled visit are at the discretion of the PI or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.

[d] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes and within 30 minutes prior to the start of any infusional study treatment. For visits where a subject is receiving an infusion of any study compounds, vital signs will be collected at the following time points in relation to the start of first infusion of the day: prior to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.

[e] Chemistry panel to include laboratory assessments noted in Table 18.

[f] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.

[g] Serum pregnancy test for females of child-bearing potential.

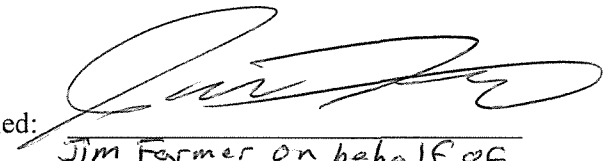
[h] Blood collection for exploratory immunology and ctDNA/ctRNA analyses will be performed every 8 weeks in the maintenance phase during routine blood draws, and at the end-of-treatment visit.

[i] Tumor imaging by CT scan, MRI, or PET-CT will be performed every 12 weeks in the maintenance phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Combination immunotherapy with high-affinity natural killer (haNK) cell therapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.060
Version Number:	2
Final Date:	15 February 2018

This clinical trial protocol was subject to critical review and has been approved by NantKwest. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 16 Feb 2018

Jim Farmer on behalf of

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