NANT PANCREATIC CANCER VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.070**
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	10 November 2017
Version 2	12 December 2017
Version 3	27 December 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. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. GI-4000 (RAS yeast vaccine)
5. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. 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)
5. NK92 [CD16.158V, ER IL2] cells

Approved Products:

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

Title of Study:

NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy

Study Number:
QUILT-3.070

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 vaccine regimen in subjects with pancreatic cancer who have progressed on or 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 vaccine regimen as assessed by ORR using RECIST Version 1.1.
- 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.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by 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.

In phase 2, subjects will be enrolled into 1 of 2 cohorts: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy. In phase 2, ORR will be evaluated separately for each cohort using Simon's two-stage optimal design.

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 who experience ongoing stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at

the Investigator's discretion. 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 6 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-computed 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. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. 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 prior to treatment on this study. Treatment with all study drugs except GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available. 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 1.6.9, 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 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, 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 3 weeks. Concurrent SBRT will be given during the first two 3-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 (2 g by mouth [PO] twice a day [BID])

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 15–19, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)

Days 1–5, 8–12, and 15–19 every 3 weeks:

- Cyclophosphamide (25 mg PO BID)

Days 1 and 8, every 3 weeks:

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

Days 1 and 15, every 3 weeks:

- Leucovorin (20 mg/m^2 IV bolus)

Day 5, every 3 weeks for 3 cycles then every 9 weeks thereafter:

- ETBX-011 (5×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Days 8 and 15, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV on day 8 and 30 mg/m^2 IV on day 15)

Days 8 and 15, every 3 weeks:

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

Days 9, 11, 16, and 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 11, every 3 weeks for 3 cycles and every 9 weeks thereafter:

- GI-4000 (40 yeast units [YU] /dose SC)

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

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 duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's discretion. The maintenance phase will consist of repeated

2-week cycles. The treatment regimen of aldoxorubicin HCl, 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 (2 g PO BID)

Day 1, every 2 weeks:

- Aldoxorubicin HCl (60 mg/m^2 IV)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC at least 30 minutes prior to haNK infusion)
- Avelumab (10 mg/kg IV over 1 hour)
- haNK (2×10^9 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 tumor 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.
- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months) by RECIST and irRC.
- 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.

Secondary Endpoints:

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- 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. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject.

In the phase 2 portion of the study, ORR will be evaluated separately using Simon's two-stage optimal design for cohorts that include: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy.

For cohort 1, 37 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 57 subjects will be enrolled in the second stage, for a total of 94 subjects in the phase 2 portion of the study for cohort 1.

For cohort 2, 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study for cohort 2.

The maximum total enrollment for the study is 173 subjects.

Eligibility Criteria:

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 adenocarcinoma 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. 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.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert’s syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
   h. Medically uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 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. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution’s lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring

continuous oxygen therapy.

9. Positive results of screening test for human immunodeficiency virus (HIV).
10. 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.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. 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.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 or 30 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK cells	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	25 mg	PO BID

5-FU	1500 mg/m^2	85-hour to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
Omega-3-acid ethyl esters	2 g	PO BID
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, electrocardiograms (ECGs), echocardiograms (ECHOs), 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 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 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc.) prior to treatment during induction phase, every 12 weeks during maintenance, 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 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 efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

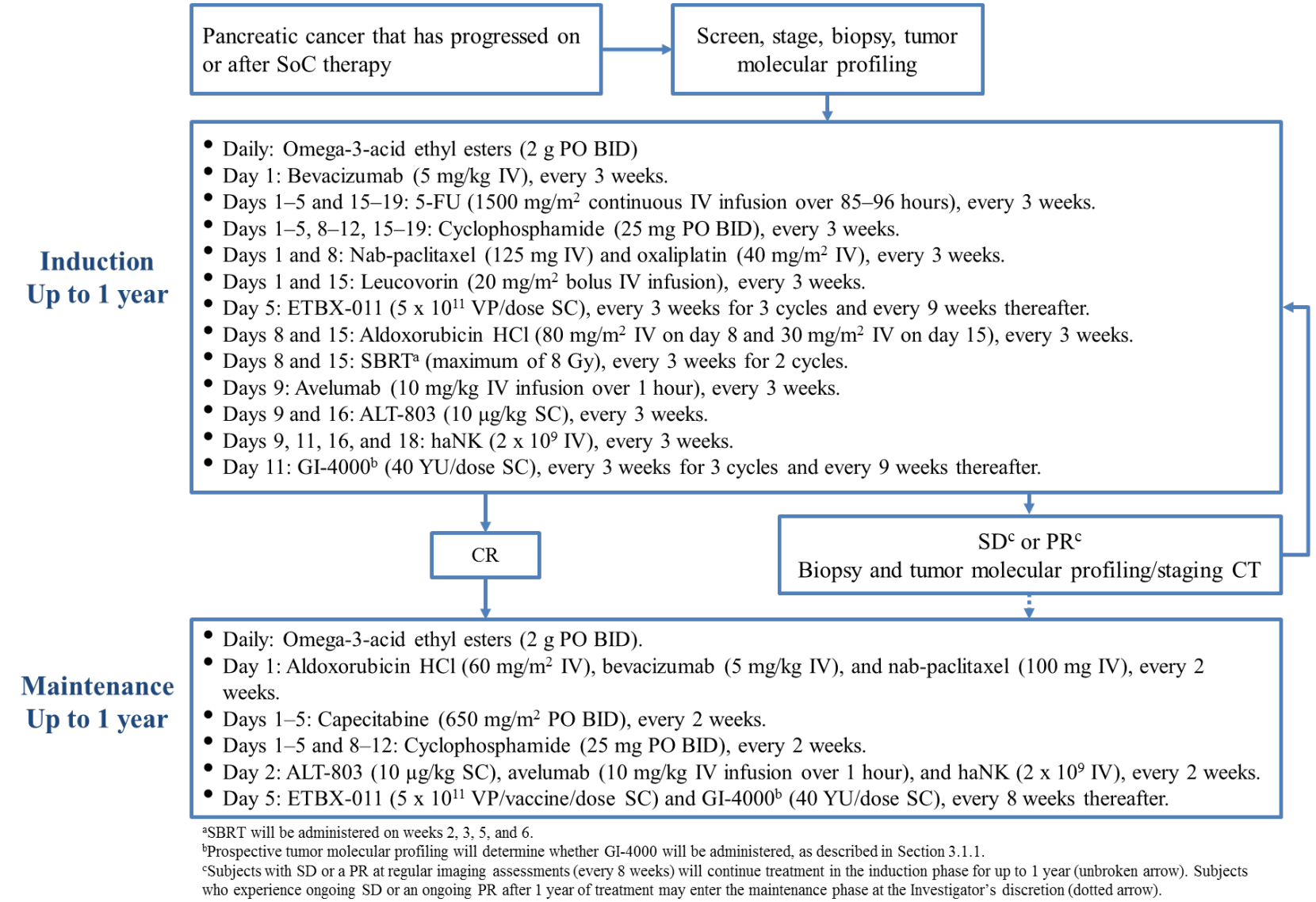
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2

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, ECHOs, 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]SBRT will be administered on weeks 2, 3, 5, and 6.
[b]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[c]Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).

Figure 2: Induction Phase Treatment Schema

	Day																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bevacizumab	●																				
Aldoxorubicin HCl								●							●						
Nab-paclitaxel	●							●													
Ad5-based vaccine[a]					●																
Leucovorin	●														●						
Oxaliplatin	●							●													
Avelumab									●												
SBRT[b]								●							●						
5-FU	●	●	●	●	●										●	●	●	●	●		
ALT-803									●							●					
haNK									●		●					●		●			
Yeast-based vaccine[c]											●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]The Ad5-based vaccine ETBX-011 will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]The yeast-based GI-4000 vaccine will be administered every 3 weeks for 3 cycles and then every 9 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

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bevacizumab	●													
Aldoxorubicin HCl	●													
Nab-paclitaxel	●													
Avelumab		●												
ALT-803		●												
haNK		●												
Ad5-based vaccine[a]					●									
Yeast-based vaccine[a]					●									
Capecitabine	●	●	●	●	●									
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●

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 every 8 weeks thereafter. The Ad5-based vaccine includes ETBX-011. The yeast-based vaccine includes GI-4000. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy
Study Number:	QUILT-3.070
Version Number:	3
Final Date:	27 December 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: 12-27-17

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

NANT PANCREATIC CANCER VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADAPTIVE T-CELL THERAPY (ADENOVIRUS, YEAST, FUSION PROTEIN VACCINE) IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.070**
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	10 November 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. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. GI-4000 (RAS yeast vaccine)
5. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. 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)
5. NK92 [CD16.158V, ER IL2] cells

Approved Products:

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

Title of Study:

NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy

Study Number:
QUILT-3.070

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 vaccine regimen in subjects with pancreatic cancer who have progressed on or 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 vaccine 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. In phase 2, subjects will be enrolled into 1 of 2 cohorts: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy. In phase 2, ORR will be evaluated separately for each cohort using Simon's two-stage optimal design.

Preliminary assessment of the safety of the treatment regimen will occur by 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 who experience ongoing stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at

the Investigator's discretion. 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 6 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) 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. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. 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 prior to treatment on this study. Treatment with all study drugs except GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available. 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 1.6.9, 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 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, 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 3 weeks. Concurrent stereotactic body radiotherapy (SBRT) will be given during the first two 3-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 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 15–19, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)

Days 1–5, 8–12, and 15–19 every 3 weeks:

- Cyclophosphamide (50 mg BID)

Days 1 and 8, every 3 weeks:

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

Days 1 and 15, every 3 weeks:

- Leucovorin (20 mg/m^2 IV bolus)

Day 5 (every 3 weeks for 3 cycles then every 8 weeks thereafter):

- ETBX-011 (5×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Days 8 and 15, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV on day 8 and 30 mg/m^2 IV on day 15)

Days 8 and 15 (every 3 weeks for 2 cycles):

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

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

Days 9, 11, 16, and 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 11, every 3 weeks for 3 cycles and every 8 weeks thereafter:

- GI-4000 (40 yeast units [YU] /dose SC)

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

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 duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's discretion. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of aldoxorubicin HCl, 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:

- Aldoxorubicin HCl (60 mg/m^2 IV)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC, 30 minutes prior to haNK infusion)
- Avelumab (10 mg/kg IV over 1 hour)
- 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 tumor 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, ORR will be evaluated separately using Simon's two-stage optimal design for cohorts that include: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy.

For cohort 1, 37 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 57 subjects will be enrolled in the second stage, for a total of 94 subjects in the phase 2 portion of the study for cohort 1.

For cohort 2, 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study for cohort 2.

The maximum total enrollment for the study is 173 subjects.

Eligibility Criteria:

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 adenocarcinoma 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. 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.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 900 cells/mm^3.
    b. Platelet count < 75,000 cells/mm^3.
    c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 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. To control hypertension, it is recommended to first start propranolol SR 80 mg daily prior to initiating other hypertensive medications.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. 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.

11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. 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.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 or 30 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK cells	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	1500 mg/m^2	85-hour to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	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, electrocardiograms (ECGs), echocardiograms (ECHOs), 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 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 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc.) prior to treatment during induction phase, every 12 weeks during maintenance, 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 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 efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

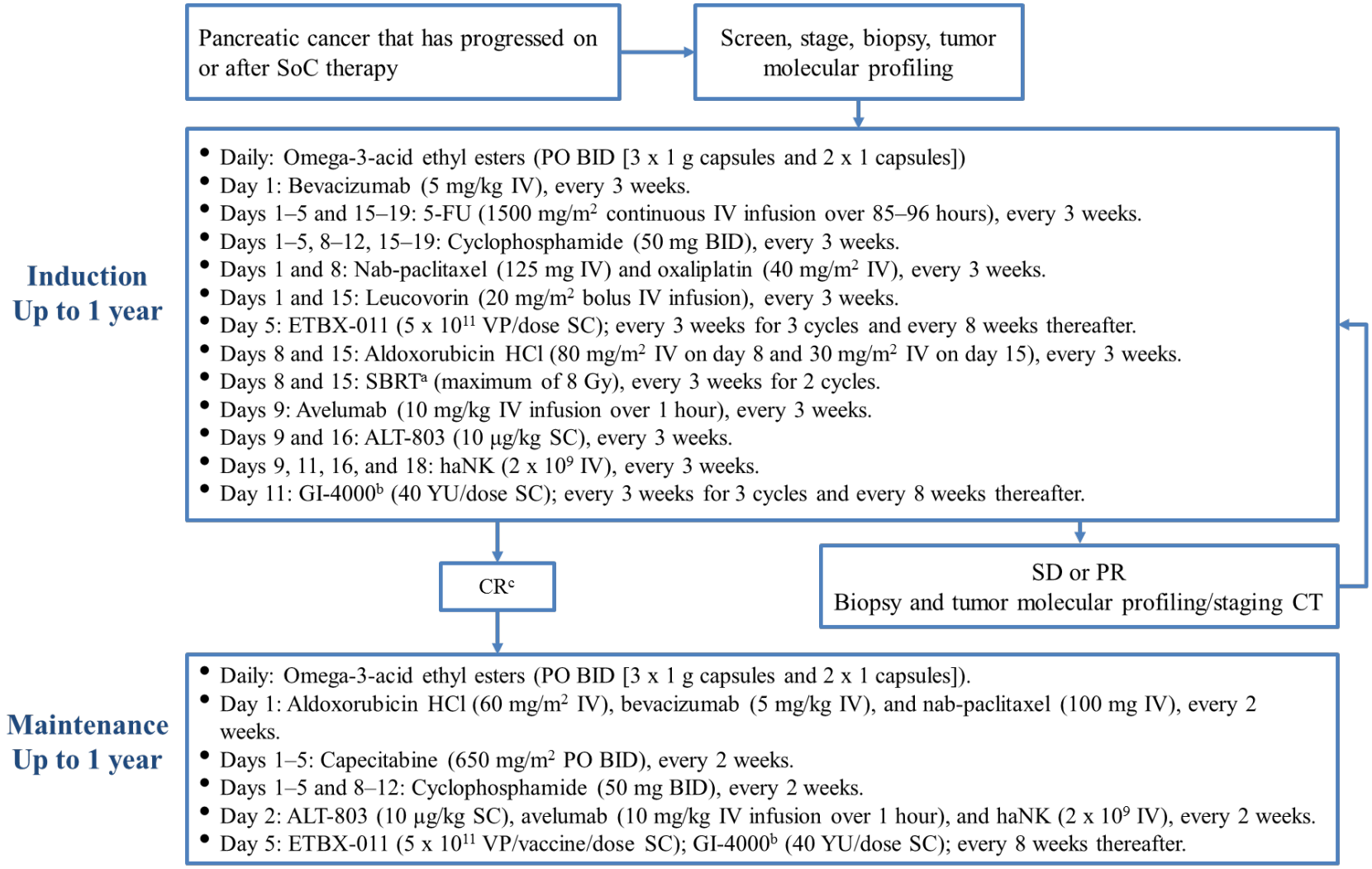
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2

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, ECHOs, 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]SBRT will be administered on weeks 2, 3, 5, and 6.
[b]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[c]Subjects who experience ongoing SD or an ongoing PR at 1 year may enter the maintenance phase at the Investigator's discretion.

Figure 2: Induction Phase Treatment Schema

	Day																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bevacizumab	●																				
Aldoxorubicin HCl								●							●						
Nab-paclitaxel	●							●													
Ad5-based vaccine[a]					●																
Leucovorin	●														●						
Oxaliplatin	●							●													
Avelumab									●												
SBRT[b]								●							●						
5-FU	●	●	●	●	●										●	●	●	●	●		
ALT-803									●							●					
haNK									●		●					●		●			
Yeast-based vaccine[c]											●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]The Ad5-based vaccine ETBX-011 will be administered every 3 weeks for 3 cycles and then every 8 weeks thereafter.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]The yeast-based GI-4000 vaccine will be administered every 3 weeks for 3 cycles 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

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bevacizumab	●													
Aldoxorubicin HCl	●													
Nab-paclitaxel	●													
Avelumab		●												
ALT-803		●												
haNK		●												
Ad5-based vaccine[a]					●									
Yeast-based vaccine[a]					●									
Capecitabine	●	●	●	●	●									
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●

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 every 8 weeks thereafter. The Ad5-based vaccine includes ETBX-011. The yeast-based vaccine includes GI-4000. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy
Study Number:	QUILT-3.070
Version Number:	1
Final Date:	10 November 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: Nov 13, 2017

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

NANT PANCREATIC CANCER VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.070**
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	10 November 2017
Version 2	12 December 2017
Version 3	20 December 2017
Version 4	23 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. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. GI-4000 (RAS yeast vaccine)
5. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. 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)
5. NK92 [CD16.158V, ER IL2] cells

Approved Products:

1. Avelumab
2. Bevacizumab
3. Capecitabine
4. Cyclophosphamide (anhydrous)
5. Fluorouracil, USP
6. Leucovorin (calcium salt)
7. Paclitaxel, USP
8. Oxaliplatin, USP
9. Radiation

Title of Study:

NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy

Study Number:
QUILT-3.070

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 vaccine regimen in subjects with pancreatic cancer who have progressed on or 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 cancer antigen 19-9 (CA 19-9), 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 vaccine regimen as assessed by ORR using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- 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 CA 19-9, 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.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by 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.

In phase 2, subjects will be enrolled into 1 of 2 cohorts: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy. In phase 2, ORR will be evaluated separately for each cohort using Simon's two-stage optimal design.

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 who experience ongoing

stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at the Investigator's discretion. 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 6 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-computed 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). In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. For responding subjects (PR or CR), a confirmatory response assessment should be done at 4 weeks after the initial response.

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. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. 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 prior to treatment on this study, as described in Section 3.1.1. 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.

Induction Phase:

Treatment in the induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year, as follows:

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)
- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Oxaliplatin (40 mg/m^2 IV)

Days 1–5, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)

- Cyclophosphamide (25 mg by mouth [PO] twice a day [BID])

Day 5 (±1 day), every 3 weeks for 3 cycles then every 9 weeks thereafter:

- ETBX-011 (5×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Day 8, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV over 30 minutes)
- Oxaliplatin (20 mg/m^2 IV)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- ALT-803 (10 µg/kg SC at least 30 minutes prior to haNK infusion)
- haNK (2×10^9 cells/dose IV)

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 11, every 3 weeks for 3 cycles and every 9 weeks thereafter:

- GI-4000 (40 yeast units [YU] /dose SC)

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

Day 15, every 3 weeks:

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Day 16, every 3 weeks:

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

Day 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

Treatment in the maintenance phase will last for up to 1 year following completion of the last treatment in the induction phase, as follows:

Day 1, every 2 weeks:

- Aldoxorubicin HCl (60 mg/m^2 IV)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC at least 30 minutes prior to haNK infusion)
- Avelumab (10 mg/kg IV over 1 hour)
- haNK (2×10^9 cells/dose IV)

Day 5 (±1 day), 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 tumor 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.
- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months) by RECIST and irRC.
- QoL by PROs.

Exploratory Endpoints:

- CA 19-9 level and correlations with subject outcomes.
- 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.

Secondary Endpoints:

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

- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

Exploratory Endpoints:

- CA 19-9 level and correlations with subject outcomes.
- 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.

In the phase 1b portion of the study response will be assessed by the Investigator; in the phase 2 portion of the study response will be assessed by BICR. A charter for the conduct of BICR will be prepared by the vendor selected to perform the independent review.

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject.

In the phase 2 portion of the study, ORR will be evaluated separately using Simon's two-stage optimal design for cohorts that include: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy.

For cohort 1, 37 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 57 subjects will be enrolled in the second stage, for a total of 94 subjects in the phase 2 portion of the study for cohort 1.

For cohort 2, 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study for cohort 2.

The maximum total enrollment for the study is 173 subjects.

Eligibility Criteria:

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 adenocarcinoma with progression on or after SoC therapy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 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. 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.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
   h. Medically uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 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. Subjects with uncontrolled hypertension should be

medically managed on a stable regimen to control hypertension prior to study entry.

7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. 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.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. 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.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV over 30 minutes
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK cells	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 BID	PO
Cyclophosphamide	25 mg BID (days 1–5, induction); 25 mg daily (days 8–12, induction); 25 mg BID (maintenance)	PO
5-FU	1500 mg/m^2	85-hour to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
Oxaliplatin	40 mg/m^2 (day 1, induction); 20 mg/m^2 (day 8, induction)	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, electrocardiograms (ECGs), echocardiograms (ECHOs), 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 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. In order to document PD, unscheduled tumor assessments may be done if the investigator observes any signs and symptoms of PD. For responding subjects (PR or CR), a confirmatory response assessment should be done at 4 weeks after the initial response.

OS, DOR, and DCR will also be assessed. In the phase 1b portion of the study, response will be assessed by the Investigator; in the phase 2 portion of the study, the primary assessment of response will be based on the BICR.

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 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc.) prior to treatment during induction phase, every 12 weeks during maintenance, 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 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 efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

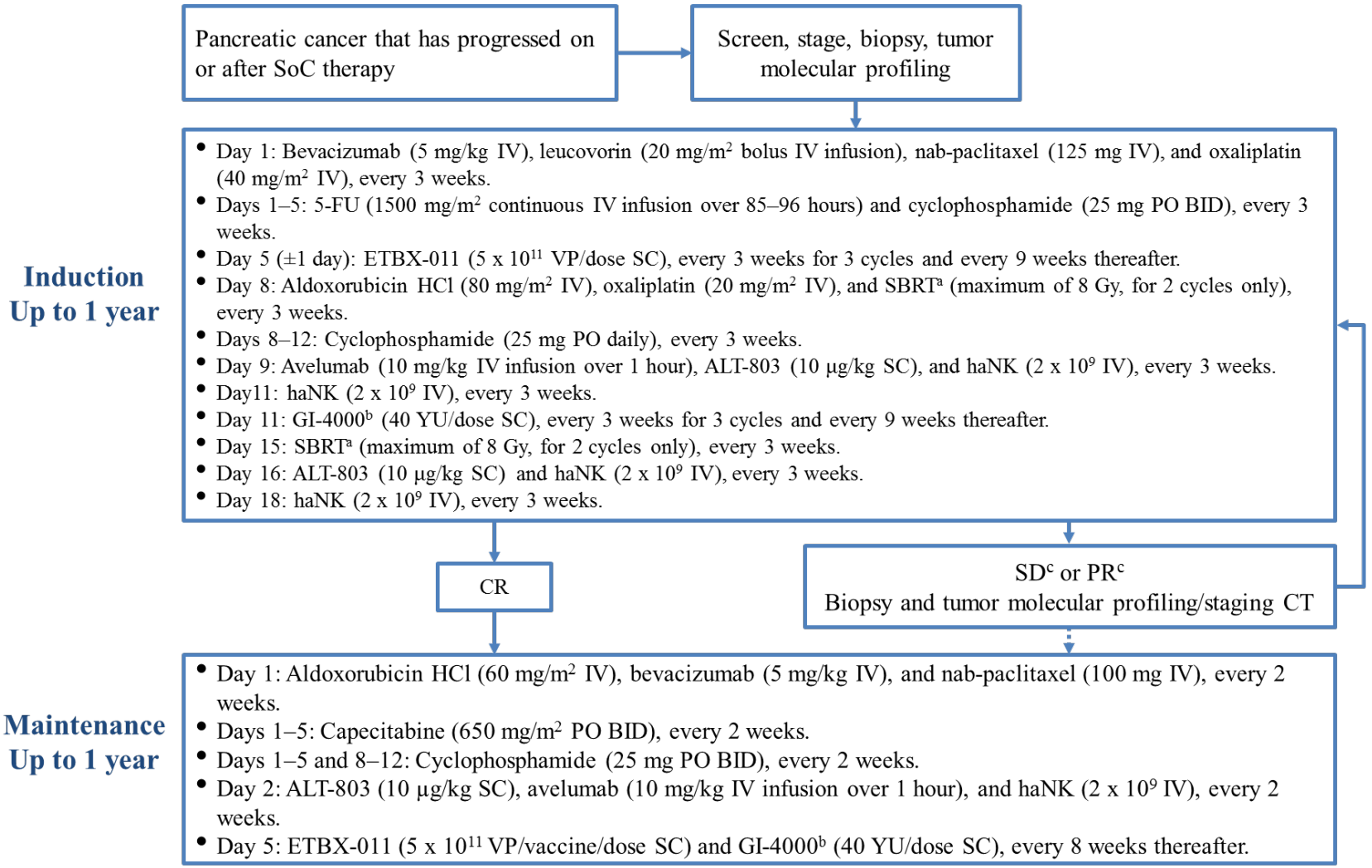
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2.

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, ECHOs, 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]SBRT will be administered on weeks 2, 3, 5, and 6.
[b]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[c]Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).

Figure 2: Induction Phase Treatment Schema

	Day																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bevacizumab	●																				
Leucovorin	●																				
Nab-paclitaxel	●																				
Oxaliplatin	●							●													
5-FU	●	●	●	●	●																
Ad5-based vaccine[a]					●																
Aldoxorubicin HCl								●													
SBRT[b]								●							●						
Avelumab									●												
ALT-803									●							●					
haNK									●		●					●		●			
Yeast-based vaccine[c]											●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●									

Cyclophosphamide and is self-administered on the days indicated.
[a]The Ad5-based vaccine ETBX-011 will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]The yeast-based GI-4000 vaccine will be administered every 3 weeks for 3 cycles and then every 9 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

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bevacizumab	●													
Aldoxorubicin HCl	●													
Nab-paclitaxel	●													
Avelumab		●												
ALT-803		●												
haNK		●												
Ad5-based vaccine[a]					●									
Yeast-based vaccine[a]					●									
Capecitabine	●	●	●	●	●									
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●		

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Each vaccine will be administered on day 5 and every 8 weeks thereafter. The Ad5-based vaccine includes ETBX-011. The yeast-based vaccine includes GI-4000. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy
Study Number:	QUILT-3.070
Version Number:	4
Final Date:	23 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: Feb 23 2018

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

NANT PANCREATIC CANCER VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.070**
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	10 November 2017
Version 2	12 December 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. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. GI-4000 (RAS yeast vaccine)
5. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. 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)
5. NK92 [CD16.158V, ER IL2] cells

Approved Products:

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

Title of Study:

NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy

Study Number:
QUILT-3.070

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 vaccine regimen in subjects with pancreatic cancer who have progressed on or 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 vaccine regimen as assessed by ORR using RECIST Version 1.1.
- 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.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by 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.

In phase 2, subjects will be enrolled into 1 of 2 cohorts: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy. In phase 2, ORR will be evaluated separately for each cohort using Simon's two-stage optimal design.

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 who experience ongoing stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at

the Investigator's discretion. 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 6 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-computed 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. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. 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 prior to treatment on this study. Treatment with all study drugs except GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available. 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 1.6.9, 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 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, 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 3 weeks. Concurrent SBRT will be given during the first two 3-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 (2 g by mouth [PO] twice a day [BID])

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 15–19, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)

Days 1–5, 8–12, and 15–19 every 3 weeks:

- Cyclophosphamide (25 mg PO BID)

Days 1 and 8, every 3 weeks:

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

Days 1 and 15, every 3 weeks:

- Leucovorin (20 mg/m^2 IV bolus)

Day 5, every 3 weeks for 3 cycles then every 9 weeks thereafter:

- ETBX-011 (5×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Days 8 and 15, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV on day 8 and 30 mg/m^2 IV on day 15)

Days 8 and 15, every 3 weeks:

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

Days 9, 11, 16, and 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 11, every 3 weeks for 3 cycles and every 9 weeks thereafter:

- GI-4000 (40 yeast units [YU] /dose SC)

  Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

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 duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's discretion. The maintenance phase will consist of repeated

2-week cycles. The treatment regimen of aldoxorubicin HCl, 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 (2 g PO BID)

Day 1, every 2 weeks:

- Aldoxorubicin HCl (60 mg/m^2 IV)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- ALT-803 (10 µg/kg SC at least 30 minutes prior to haNK infusion)
- Avelumab (10 mg/kg IV over 1 hour)
- haNK (2×10^9 cells/dose IV)

Day 5, every 9 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 tumor 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.
- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months) by RECIST and irRC.
- 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.

Secondary Endpoints:

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- 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. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject.

In the phase 2 portion of the study, ORR will be evaluated separately using Simon's two-stage optimal design for cohorts that include: (1) subjects who have failed first-line SoC therapy (first-line metastatic or progressed after adjuvant chemotherapy specifically including FOLFIRINOX, gemcitabine and nab-paclitaxel, gemcitabine and capecitabine, or gemcitabine alone), and (2) subjects who have been treated with more than one line of SoC therapy.

For cohort 1, 37 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 57 subjects will be enrolled in the second stage, for a total of 94 subjects in the phase 2 portion of the study for cohort 1.

For cohort 2, 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study for cohort 2.

The maximum total enrollment for the study is 173 subjects.

Eligibility Criteria:

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 adenocarcinoma 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. 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.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count < 900 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert’s syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
   h. Medically uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 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. To control hypertension, it is recommended to first start propranolol SR 80 mg daily prior to initiating other hypertensive medications.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution’s lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring

continuous oxygen therapy.

9. Positive results of screening test for human immunodeficiency virus (HIV).
10. 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.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. 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.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 or 30 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	5×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
haNK cells	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	25 mg	PO BID

5-FU	1500 mg/m^2	85-hour to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
Omega-3-acid ethyl esters	2 g	PO BID
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 treatement.

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, electrocardiograms (ECGs), echocardiograms (ECHOs), 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 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 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc.) prior to treatment during induction phase, every 12 weeks during maintenance, 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 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 efficacy of metronomic combination therapy in subjects with pancreatic cancer whose tumors have progressed on or after SoC treatment.

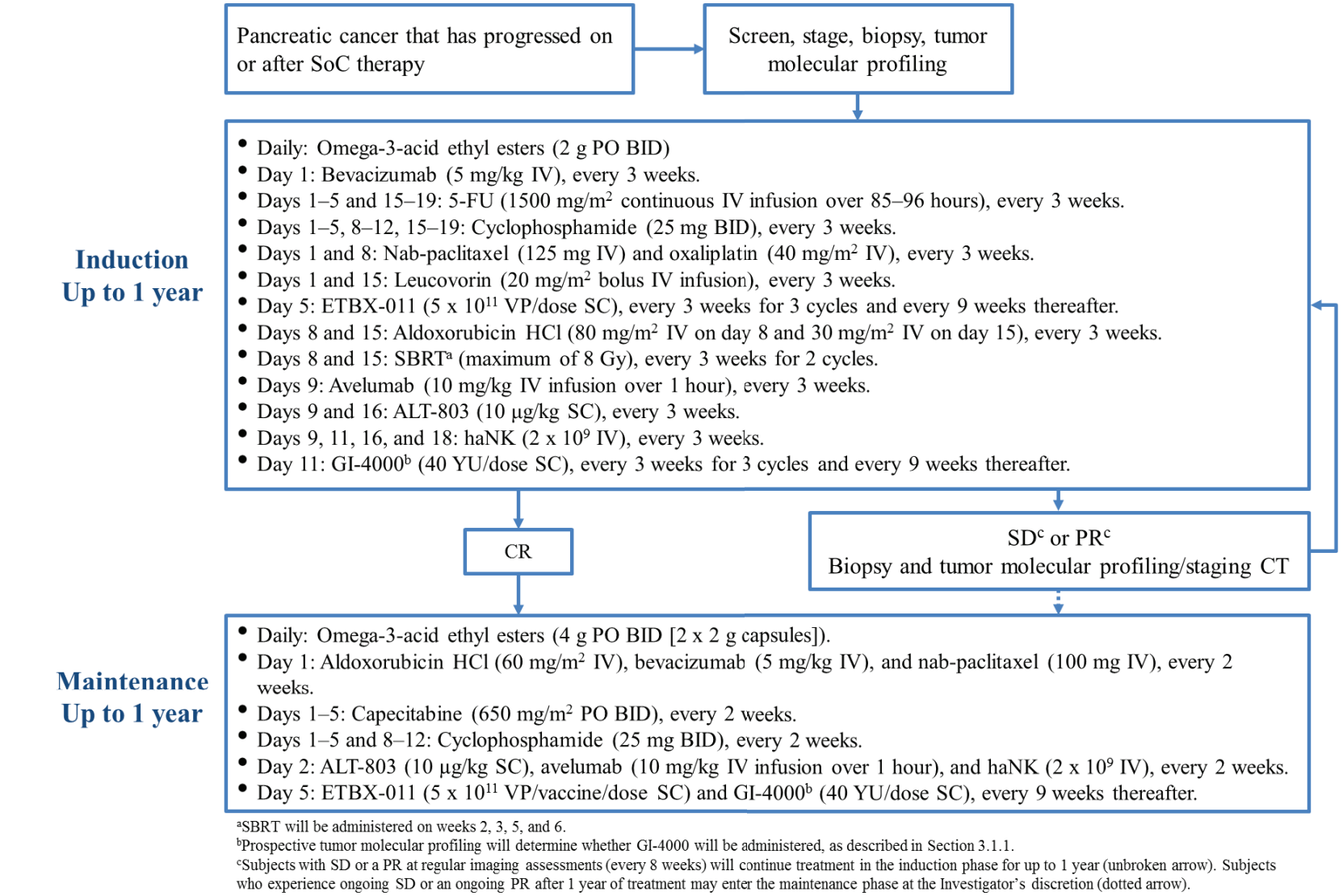
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2

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, ECHOs, 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]SBRT will be administered on weeks 2, 3, 5, and 6.
[b]Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[c]Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).

Figure 2: Induction Phase Treatment Schema

	Day																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bevacizumab	●																				
Aldoxorubicin HCl								●							●						
Nab-paclitaxel	●							●													
Ad5-based vaccine[a]					●																
Leucovorin	●														●						
Oxaliplatin	●							●													
Avelumab									●												
SBRT[b]								●							●						
5-FU	●	●	●	●	●										●	●	●	●	●		
ALT-803									●							●					
haNK									●		●					●		●			
Yeast-based vaccine[c]											●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]The Ad5-based vaccine ETBX-011 will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]The yeast-based GI-4000 vaccine will be administered every 3 weeks for 3 cycles and then every 9 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

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bevacizumab	●													
Aldoxorubicin HCl	●													
Nab-paclitaxel	●													
Avelumab		●												
ALT-803		●												
haNK		●												
Ad5-based vaccine[a]					●									
Yeast-based vaccine[a]					●									
Capecitabine	●	●	●	●	●									
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●		
Omega-3-acid ethyl esters	●	●	●	●	●	●	●	●	●	●	●	●	●	●

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 every 9 weeks thereafter. The Ad5-based vaccine includes ETBX-011. The yeast-based vaccine includes GI-4000. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Pancreatic Cancer Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy
Study Number:	QUILT-3.070
Version Number:	2
Final Date:	12 December 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: 12-12-17

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