PHASE 1B/2 TRIAL OF THE NANT PANCREATIC CANCER VACCINE AS TREATMENT FOR SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.080**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
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Protocol Version	**Date**
Version 1	28 June 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-carcinoembryonic antigen [CEA] vaccine)
4. ETBX-021 (Ad5 [E1-, E2b-]-human epidermal growth factor receptor 2 [HER2] vaccine)
5. ETBX-051 (Ad5 [E1-, E2b-]-Brachyury vaccine)
6. ETBX-061 (Ad5 [E1-, E2b-]-mucin 1 [MUC1] vaccine)
7. GI-4000 (RAS yeast vaccine)
8. GI-6207 (CEA yeast vaccine)
9. GI-6301 (Brachyury yeast vaccine)
10. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. ALT-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. 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)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

Approved Products:

11. Avelumab
12. Bevacizumab
13. Capecitabine
14. Cyclophosphamide (anhydrous)
15. Fluorouracil, USP
16. Leucovorin (calcium salt)
17. Paclitaxel, USP
18. Oxaliplatin, USP
19. Radiation

Title of Study:

Phase 1b/2 trial of the NANT Pancreatic Cancer Vaccine as treatment for subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.080

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 Response Evaluation Criteria in Solid Tumors (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.

Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee after the first 3 subjects have completed the dose-limiting toxicity (DLT) assessment period. Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggests 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 confirmed 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. Subjects with PD upon radiologic evaluation per RECIST Version 1.1 may, at the discretion of the treating physician, continue to receive study treatment for additional treatment cycles (ie, continue to receive treatment for up to 6 additional weeks following the conclusion of the subject's current treatment cycle) in case of pseudoprogression. If pseudoprogression is observed, subjects are allowed to continue treatment. The maximum time on study treatment is 2 years.

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 confirmed 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.

Subjects who withdraw from the trial for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

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) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with 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. When disease progression per RECIST Version 1.1 is initially observed, an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, subjects are allowed to continue treatment and response assessments will continue every 8 or 12 weeks and evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

Prospective Tumor Molecular Profiling

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.

RAS mutational status and HER-2 positivity will be used to determine which subjects will receive GI-4000 (RAS) and/or ETBX-021 (HER2), respectively. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. Subjects will receive ETBX-021 (HER2) if their tumor is HER2-positive (IHC 3+ or FISH positive), as determined by an FDA-approved test. Treatment with all study drugs except GI-4000 (RAS) and ETBX-021 (HER2) 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 *RAS* mutations targeted by GI-4000 (RAS) and/or positive for HER2 by ETBX-021 (HER2) will begin as soon as molecular profiling results are available. All other agents in the NANT Pancreatic Cancer Vaccine regimen will be administered regardless of tumor molecular profile.

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 for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- 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 (1,500 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:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

  Prospective tumor molecular profiling will determine whether ETBX-021 (HER2) will be administered, as described above.

Day 8, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV)
- 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:

- ALT-803 (15 µg/kg SC)
- Avelumab (10 mg/kg IV)
- 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:

- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 yeast units [YU]/vaccine/dose SC)

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

Day 15, every 3 weeks for 2 cycles:

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

Day 16, every 3 weeks:

- 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 consist of repeated 2-week cycles 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)
- Nab-paclitaxel (100 mg IV)

Day 1, every 12 weeks thereafter:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} VP/vaccine/dose SC)
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (40 YU/vaccine/dose SC)

  Prospective tumor molecular profiling will determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered, as described above.

Days 1–5, every 2 weeks:

- Capecitabine (650 mg/m^2 PO BID; up to a maximum of 1,000 mg per dose)
- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- ALT-803 (15 µg/kg SC)
- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)

Days 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO daily)

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 a local independent radiologist; 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.

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 receipt of testosterone-lowering therapy in men with prostate cancer, or treatment with any NANT Cancer Vaccine therapy.
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
ALT-803	15 µg/kg	SC
ETBX-011 (CEA)	1×10^{11} VP/dose	SC
ETBX-021 (HER2)	1×10^{11} VP/dose	SC
ETBX-051 (Brachyury)	1×10^{11} VP/dose	SC
ETBX-061 (MUC1)	1×10^{11} VP/dose	SC
GI-4000 (RAS)	40 YU/dose	SC

Products, Dosage, and Mode of Administration:		
Investigational Products	**Investigational Products**	**Investigational Products**
GI-6207 (CEA)	40 YU/dose	SC
GI-6301 (Brachyury)	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, up to a maximum of 1,000 mg per dose	PO
Cyclophosphamide	25 mg BID (days 1-5 of induction and maintenance); 25 mg daily (days 8-12 of induction and maintenance)	PO
5-FU	1,500 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 of induction); 20 mg/m^2 (day 8 of 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 confirmed 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 for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Assessment of serum CA19-9 level (co-incident with CT/MRI assessments)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

Following documented PD, subjects may continue to be followed by the investigational physician or a third party by phone or review of medical records until withdrawal of consent, lost to follow-up or death (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.

In the phase 1b portion of the study, response will be assessed by a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on 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.

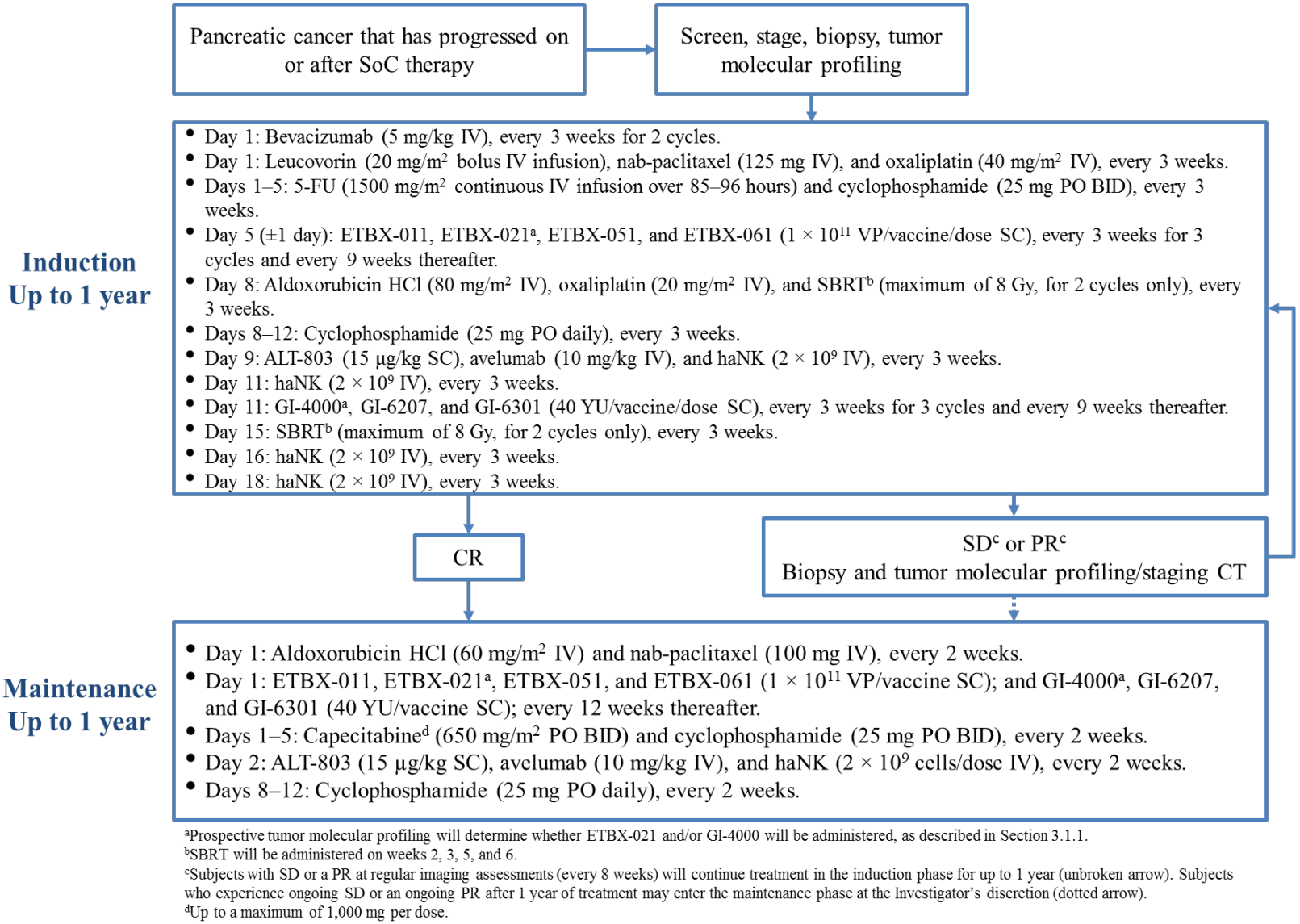
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2.

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 CA 19-9 level, tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Prospective tumor molecular profiling will determine whether ETBX-021 and/or GI-4000 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[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).
[d]Up to a maximum of 1,000 mg per dose.

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[a]	●																				
Leucovorin	●																				
Nab-paclitaxel	●																				
Oxaliplatin	●							●													
5-FU	●	●	●	●	●																
Ad5-based vaccines[b]					●																
Aldoxorubicin HCl								●													
SBRT[c]								●							●						
ALT-803									●												
Avelumab									●												
haNK									●		●					●		●			
Yeast-based vaccines[b]											●										
Cyclophosphamide[d]	●	●	●	●	●			●	●	●	●	●									

[a]Bevacizumab will be administered every 3 weeks for 2 cycles only.
[b]Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Ad5-based vaccines may be given within ±1 day of the scheduled day. Ad5-based vaccines include ETBX-011, ETBX-021, ETBX-051, and ETBX-061. Yeast-based vaccines include GI-4000, GI-6207, and GI-6301. Prospective tumor molecular profiling will determine whether GI-4000 and/or ETBX-021 will be administered, as described in Section 3.1.1.
[c]SBRT will be administered on weeks 2, 3, 5, and 6.
[d]Cyclophosphamide is self-administered on the days indicated.

Figure 3: Maintenance Phase Treatment Schema

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

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Each vaccine will be administered on day 1 and every 12 weeks thereafter. The Ad5-based vaccines are ETBX-011, ETBX-021, ETBX-051, and ETBX-061. The yeast-based vaccines are GI-4000, GI-6207, and GI-6301. Prospective tumor molecular profiling will determine whether ETBX-021 and/or GI-4000 will be administered, as described in Section 3.1.1.

Table 18: Schedule of Events for Induction Phase of Study

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																					EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
General Assessments																								
Informed consent	X																							
Inclusion/exclusion[d]	X																							
Demographics	X																							
Medical history[e]	X																							
Confirm availability of FFPE tumor sample[f]	X																							
Concomitant medications	X	X							X								X						X	X
Physical exam: height, weight[g]	X	X							X								X						X	X
Vital signs[h]	X	X				X			X	X		X					X		X				X	X
ECOG performance status	X	X							X								X						X	X
12-lead ECG[i]	X	X[j]	Every 6 weeks																				X	
ECHO (with ejection fraction)	X	X[j]	Every 12 weeks																				X	
Confirm contraceptive measures	X																							
FACT-Hep Questionnaire	X	X	Every 6 weeks																				X	
Adverse event collection		X				X			X	X		X					X		X				X	X
Laboratory Assessments																								
Chemistry panel[k]	X	X[j]							X								X						X	
CA19-9	X	X[j]	Every 3 weeks																				X	
Hematology[l]	X	X[j]							X								X						X	

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																				EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**							
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Urinalysis	X	X[j]							X								X						X	
Pregnancy test[m]	X	X[j]	Every 6 weeks																				X	
Serum virology (HIV)[n]	X																							
Determine HER2 positivity and *RAS* mutational status[o]	X																							
Collect whole blood for tumor molecular profiling[p]	X																							
Collect whole blood for immunology analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect whole blood for ctDNA/ctRNA analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect historic tumor biopsy specimen for tumor molecular profiling[r]	X																							
Tumor biopsy[r]	X	8 weeks after the start of treatment																						
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.																						
Tumor Imaging and Assessments																								
CT or MRI[s]	X	Every 8 weeks																					X	

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

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

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

[d] Inclusion/exclusion criteria will also be evaluated at enrollment.

[e] Medical history will also be evaluated at enrollment.

[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study 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 HER2 and specific *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available.

[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.

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

[i] 12-lead ECG to be performed in triplicate at screening.

[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.

[k] Chemistry panel to include laboratory assessments noted in Table 17. HbA1c to be assessed in screening blood draw only.

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

[m] Serum pregnancy tests for females of child-bearing potential.

[n] HIV status to be determined by an approved test.

[o] Assessment of HER2 positivity and *RAS* mutational status to determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered to the subject, as described in Section 3.1.1.

[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.

[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.

[r] Historic tumor biopsy specimen for tumor molecular profiling will be collected only for subjects enrolled in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator.

[s] Tumor imaging by CT or MRI will be performed at screening and every 8 weeks thereafter in the induction phase, as described in Section 6.1.2.

Table 19: Schedule of Events for Maintenance Phase of Study

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

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

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

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

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

[e] Chemistry panel to include laboratory assessments noted in Table 17.

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

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

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

[CT] or MRIi Tumor imaging by CT or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6.1.2.

PHASE 1B/2 TRIAL OF THE NANT PANCREATIC CANCER VACCINE AS TREATMENT FOR SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.080**
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	28 June 2018
Version 2	15 August 2018
Version 3	01 October 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-carcinoembryonic antigen [CEA] vaccine)
3. ETBX-021 (Ad5 [E1-, E2b-]-human epidermal growth factor receptor 2 [HER2] vaccine)
4. ETBX-051 (Ad5 [E1-, E2b-]-Brachyury vaccine)
5. ETBX-061 (Ad5 [E1-, E2b-]-mucin 1 [MUC1] vaccine)
6. GI-4000 (RAS yeast vaccine)
7. GI-6207 (CEA yeast vaccine)
8. GI-6301 (Brachyury yeast vaccine)
9. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
10. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. Ad5 [E1-, E2b-]-CEA
3. Ad5 [E1-, E2b-]-HER2
4. Ad5 [E1-, E2b-]-Brachyury
5. Ad5 [E1-, E2b-]-MUC1
6. 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)
7. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
8. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
9. NK-92 [CD16.158V, ER IL2] cells
10. N-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Approved Products:

11. Avelumab
12. Bevacizumab
13. Capecitabine
14. Cyclophosphamide (anhydrous)
15. Fluorouracil, USP
16. Leucovorin (calcium salt)
17. Paclitaxel, USP
18. Oxaliplatin, USP
19. Radiation

Title of Study:

Phase 1b/2 trial of the NANT Pancreatic Cancer Vaccine as treatment for subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.080

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 cell-free circulating DNA (cfDNA) and RNA (cfRNA); 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 Response Evaluation Criteria in Solid Tumors (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 cfDNA and cfRNA; 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.

Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee after the first 3 subjects have completed the dose-limiting toxicity (DLT) assessment period. Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggests 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 confirmed 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. Subjects with an initial assessment of PD per RECIST Version 1.1 may, at the discretion of the Investigator, continue to receive study treatment until PD is confirmed as detailed in Section 6.1.2. The maximum time on study treatment is 2 years.

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.

Subjects who withdraw from the trial for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

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 cfDNA/cfRNA 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) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST Version 1.1 and immune-related response criteria (irRC). Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST Version 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, subjects are allowed to continue treatment and response assessments will continue every 8 or 12 weeks and be evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

Prospective Tumor Molecular Profiling

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.

RAS mutational status will be used to determine which subjects will receive GI-4000 (RAS). Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. Treatment with all study drugs except GI-4000 (RAS) 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 *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available. All other agents in the NANT Pancreatic Cancer Vaccine regimen will be administered regardless of tumor molecular profile.

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 for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- 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 (1,500 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:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 yeast units [YU]/vaccine/dose SC)

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

Day 8, every 3 weeks:

- Aldoxorubicin HCl (100 mg/m^2 IV)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for ≤ 4 cycles only)

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)
- N-803 (15 μg/kg SC)

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 15, every 3 weeks:

- Nab-paclitaxel (100 mg IV)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for ≤ 4 cycles only)

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

Treatment in the maintenance phase will consist of repeated 2-week cycles 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)
- Nab-paclitaxel (100 mg IV)

Day 1, every 12 weeks thereafter:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} VP/vaccine/dose SC)
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 YU/vaccine/dose SC)

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

Days 1,3, and 5, every 2 weeks:

- Capecitabine (650 mg/m^2 PO BID; up to a maximum of 1,000 mg per dose)

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)
- N-803 (15 µg/kg SC)

Days 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO daily)

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 SD lasting for at least 2 months) by RECIST Version 1.1 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 cfDNA and cfRNA 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 and 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 cfDNA and cfRNA and correlations with subject outcomes.

In the phase 1b portion of the study response will be assessed by a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on 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.

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 receipt of testosterone-lowering therapy in men with prostate cancer, or treatment with any NANT Cancer Vaccine therapy.
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	100 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ETBX-011 (CEA)	1×10^{11} VP/dose	SC
ETBX-021 (HER2)	1×10^{11} VP/dose	SC
ETBX-051 (Brachyury)	1×10^{11} VP/dose	SC
ETBX-061 (MUC1)	1×10^{11} VP/dose	SC
GI-4000 (RAS)	40 YU/dose	SC
GI-6207 (CEA)	40 YU/dose	SC

GI-6301 (Brachyury)	40 YU/dose	SC
haNK cells	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2 BID, up to a maximum of 1000 mg per dose	PO
Cyclophosphamide	25 mg BID (days 1-5 of induction and maintenance); 25 mg daily (days 8-12 of induction and 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 (day 1 of induction); 100 mg (day 15 of induction and day 1 of maintenance)	IV
Oxaliplatin	40 mg/m^2 (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 confirmed progressive disease or 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 for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Assessment of serum CA 19-9 level (co-incident with CT/MRI assessments)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

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 or MRI 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.

In the phase 1b portion of the study, response will be assessed by a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on 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 Vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

cfDNA/cfRNA Analysis: cfDNA and cfRNA 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.

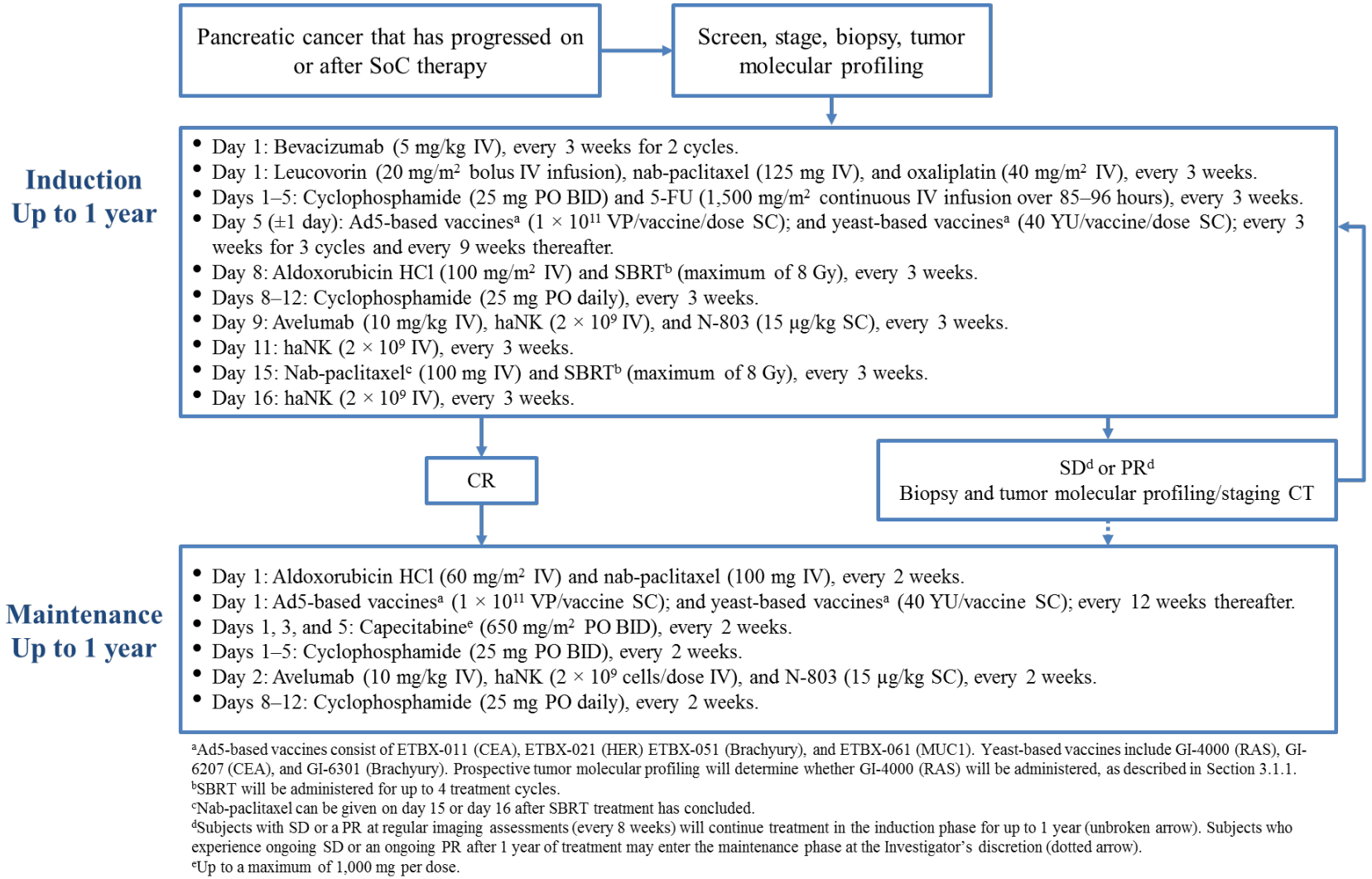
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2.

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 CA 19-9 level, tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in cfDNA and cfRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Ad5-based vaccines consist of ETBX-011 (CEA), ETBX-021 (HER) ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[b]SBRT will be administered for up to 4 treatment cycles.
[c]Nab-paclitaxel can be given on day 15 or day 16 after SBRT treatment has concluded.
[d]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).
[e]Up to a maximum of 1,000 mg per dose.

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[a]	●																				
Leucovorin	●																				
Oxaliplatin	●																				
5-FU	●	●	●	●	●																
Nab-paclitaxel[b]	●														●						
Ad5-based vaccines[c]					●																
Yeast-based vaccines[c]					●																
Aldoxorubicin HCl								●													
SBRT[d]								●							●						
Avelumab									●												
N-803									●												
haNK									●		●					●					
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●									

[a]Bevacizumab will be administered every 3 weeks for 2 cycles only.
[b]Nab-paclitaxel can be given on day 16 after SBRT treatment has concluded.
[c]Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines may be given within ±1 day of the scheduled day. Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[d]SBRT will be administered for up to 4 treatment cycles.

Figure 3: Maintenance Phase Treatment Schema

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

[a]Each vaccine will be administered on day 1 and every 12 weeks thereafter. The Ad5-based vaccines are ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). The yeast-based vaccines are GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Table 18: Schedule of Events for Induction Phase of Study

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																				EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
General Assessments																								
Informed consent	X																							
Inclusion/exclusion[d]	X																							
Demographics	X																							
Medical history[e]	X																							
Confirm availability of FFPE tumor sample[f]	X																							
Concomitant medications	X	X							X								X						X	X
Physical exam: height, weight[g]	X	X							X								X						X	X
Vital signs[h]	X	X				X			X	X		X				X	X						X	X
ECOG performance status	X	X							X								X						X	X
12-lead ECG[i]	X	X[j]	Every 6 weeks																				X	
ECHO (with ejection fraction)	X	X[j]	Every 12 weeks																				X	
Confirm contraceptive measures	X																							
FACT-Hep Questionnaire	X	X	Every 6 weeks																				X	
Adverse event collection		X				X			X	X		X				X	X						X	X
Laboratory Assessments																								
Chemistry panel[k]	X	X[j]							X								X						X	
CA 19-9	X	X[j]	Every 3 weeks																				X	

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																			EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**							
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
Hematology[l]	X	X[j]							X								X						X	
Urinalysis	X	X[j]							X								X						X	
Pregnancy test[m]	X	X[j]	Every 6 weeks																				X	
Serum virology (HIV)[n]	X																							
Determine HER2 positivity and *RAS* mutational status[o]	X																							
Collect whole blood for tumor molecular profiling[p]	X																							
Collect whole blood for immunology analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect whole blood for cfDNA/cfRNA analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect historic tumor biopsy specimen for tumor molecular profiling[r]	X																							
Tumor biopsy[r]	X	8 weeks after the start of treatment																						
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.																						
Tumor Imaging and Assessments																								
CT or MRI[s]	X	Every 8 weeks																					X	

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

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

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

[d] Inclusion/exclusion criteria will also be evaluated at enrollment.

[e] Medical history will also be evaluated at enrollment.

[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study 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 (RAS) will begin as soon as molecular profiling results are available.

[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.

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

[i] 12-lead ECG to be performed in triplicate at screening.

[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment. For ECG and ECHO assessments only, day 1 assessments can be skipped if the screening assessment was performed within 28 days prior to the start of treatment.

[k] Chemistry panel to include laboratory assessments noted in Table 17. HbA1c to be assessed in screening blood draw only.

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

[m] Serum pregnancy tests for females of child-bearing potential.

[n] HIV status to be determined by an approved test.

[o] Assessment of *RAS* mutational status to determine whether GI-4000 (RAS) will be administered to the subject, as described in Section 3.1.1. Assessment of HER2 positivity may be conducted as soon as tumor tissue is available, and results from this assessment will not affect the drug regimen administered to subjects in this study.

[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.

[q] Whole blood for immunology and cfDNA/cfRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.

[r] Historic tumor biopsy specimen for tumor molecular profiling will be collected only for subjects enrolled in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator.

[s] Tumor imaging by CT or MRI will be performed at screening and every 8 weeks in the induction phase, as described in Section 6.1.2.

Table 19: Schedule of Events for Maintenance Phase of Study

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Concomitant medications	X														X	X
Physical exam, weight	X														X	X
Vital signs[d]	X	X													X	X
ECOG performance status	X														X	
12-lead ECG	X	Every 12 weeks													X	
ECHO (with ejection fraction)	X	Every 12 weeks													X	
Confirm contraceptive measures	X															
Adverse event collection	X	X													X	X
FACT-Hep questionnaire	X	Every 12 weeks													X	
Laboratory Assessments																
Chemistry panel[e]	X														X	
CA 19-9	X	Every 4 weeks													X	
Hematology[f]	X														X	
Urinalysis	X														X	
Pregnancy test[g]	X	Every 12 weeks													X	
Collect whole blood for immunology analysis[h]	X	Every 8 weeks during routine blood draws													X	
Collect whole blood for cfDNA/cfRNA analysis[h]	X	Every 8 weeks during routine blood draws													X	
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion															
Tumor Imaging and Assessments																
CT or MRI[i]	X	Every 12 weeks													X	

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

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

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

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

[e] Chemistry panel to include laboratory assessments noted in Table 17.

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

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

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

[i] Tumor imaging by CT or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6.1.2.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1b/2 trial of the NANT Pancreatic Cancer Vaccine as treatment for subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.080
Version Number:	3
Final Date:	01 October 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: Oct 1 2018

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PHASE 1B/2 TRIAL OF THE NANT PANCREATIC CANCER VACCINE AS TREATMENT FOR SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

Study Number:	**QUILT-3.080**
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	28 June 2018
Version 2	15 August 2018
Version 3	01 October 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-carcinoembryonic antigen [CEA] vaccine)
3. ETBX-021 (Ad5 [E1-, E2b-]-human epidermal growth factor receptor 2 [HER2] vaccine)
4. ETBX-051 (Ad5 [E1-, E2b-]-Brachyury vaccine)
5. ETBX-061 (Ad5 [E1-, E2b-]-mucin 1 [MUC1] vaccine)
6. GI-4000 (RAS yeast vaccine)
7. GI-6207 (CEA yeast vaccine)
8. GI-6301 (Brachyury yeast vaccine)
9. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
10. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

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

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. Ad5 [E1-, E2b-]-CEA
3. Ad5 [E1-, E2b-]-HER2
4. Ad5 [E1-, E2b-]-Brachyury
5. Ad5 [E1-, E2b-]-MUC1
6. 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)
7. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
8. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
9. NK-92 [CD16.158V, ER IL2] cells
10. N-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Approved Products:

11. Avelumab
12. Bevacizumab
13. Capecitabine
14. Cyclophosphamide (anhydrous)
15. Fluorouracil, USP
16. Leucovorin (calcium salt)
17. Paclitaxel, USP
18. Oxaliplatin, USP
19. Radiation

Title of Study:

Phase 1b/2 trial of the NANT Pancreatic Cancer Vaccine as treatment for subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.080

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 cell-free circulating DNA (cfDNA) and RNA (cfRNA); 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 Response Evaluation Criteria in Solid Tumors (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 cfDNA and cfRNA; 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.

Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee after the first 3 subjects have completed the dose-limiting toxicity (DLT) assessment period. Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggests 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 confirmed 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. Subjects with an initial assessment of PD per RECIST Version 1.1 may, at the discretion of the Investigator, continue to receive study treatment until PD is confirmed as detailed in Section 6.1.2. The maximum time on study treatment is 2 years.

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.

Subjects who withdraw from the trial for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

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 cfDNA/cfRNA 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) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST Version 1.1 and immune-related response criteria (irRC). Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST Version 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, subjects are allowed to continue treatment and response assessments will continue every 8 or 12 weeks and be evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

Prospective Tumor Molecular Profiling

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.

RAS mutational status will be used to determine which subjects will receive GI-4000 (RAS). Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. Treatment with all study drugs except GI-4000 (RAS) 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 *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available. All other agents in the NANT Pancreatic Cancer Vaccine regimen will be administered regardless of tumor molecular profile.

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 for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- 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 (1,500 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:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 yeast units [YU]/vaccine/dose SC)

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

Day 8, every 3 weeks:

- Aldoxorubicin HCl (100 mg/m^2 IV)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for ≤ 4 cycles only)

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)
- N-803 (15 μg/kg SC)

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 15, every 3 weeks:

- Nab-paclitaxel (100 mg IV)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for ≤ 4 cycles only)

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

Treatment in the maintenance phase will consist of repeated 2-week cycles 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)
- Nab-paclitaxel (100 mg IV)

Day 1, every 12 weeks thereafter:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} VP/vaccine/dose SC)
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 YU/vaccine/dose SC)

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

Days 1,3, and 5, every 2 weeks:

- Capecitabine (650 mg/m^2 PO BID; up to a maximum of 1,000 mg per dose)

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)
- N-803 (15 µg/kg SC)

Days 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO daily)

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 SD lasting for at least 2 months) by RECIST Version 1.1 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 cfDNA and cfRNA 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 and 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 cfDNA and cfRNA and correlations with subject outcomes.

In the phase 1b portion of the study response will be assessed by a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on 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.

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 receipt of testosterone-lowering therapy in men with prostate cancer, or treatment with any NANT Cancer Vaccine therapy.
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	100 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ETBX-011 (CEA)	1×10^{11} VP/dose	SC
ETBX-021 (HER2)	1×10^{11} VP/dose	SC
ETBX-051 (Brachyury)	1×10^{11} VP/dose	SC
ETBX-061 (MUC1)	1×10^{11} VP/dose	SC
GI-4000 (RAS)	40 YU/dose	SC
GI-6207 (CEA)	40 YU/dose	SC

GI-6301 (Brachyury)	40 YU/dose	SC
haNK cells	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2 BID, up to a maximum of 1000 mg per dose	PO
Cyclophosphamide	25 mg BID (days 1-5 of induction and maintenance); 25 mg daily (days 8-12 of induction and 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 (day 1 of induction); 100 mg (day 15 of induction and day 1 of maintenance)	IV
Oxaliplatin	40 mg/m^2 (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 confirmed progressive disease or 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 for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Assessment of serum CA 19-9 level (co-incident with CT/MRI assessments)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

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 or MRI 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.

In the phase 1b portion of the study, response will be assessed by a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on 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 Vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

cfDNA/cfRNA Analysis: cfDNA and cfRNA 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.

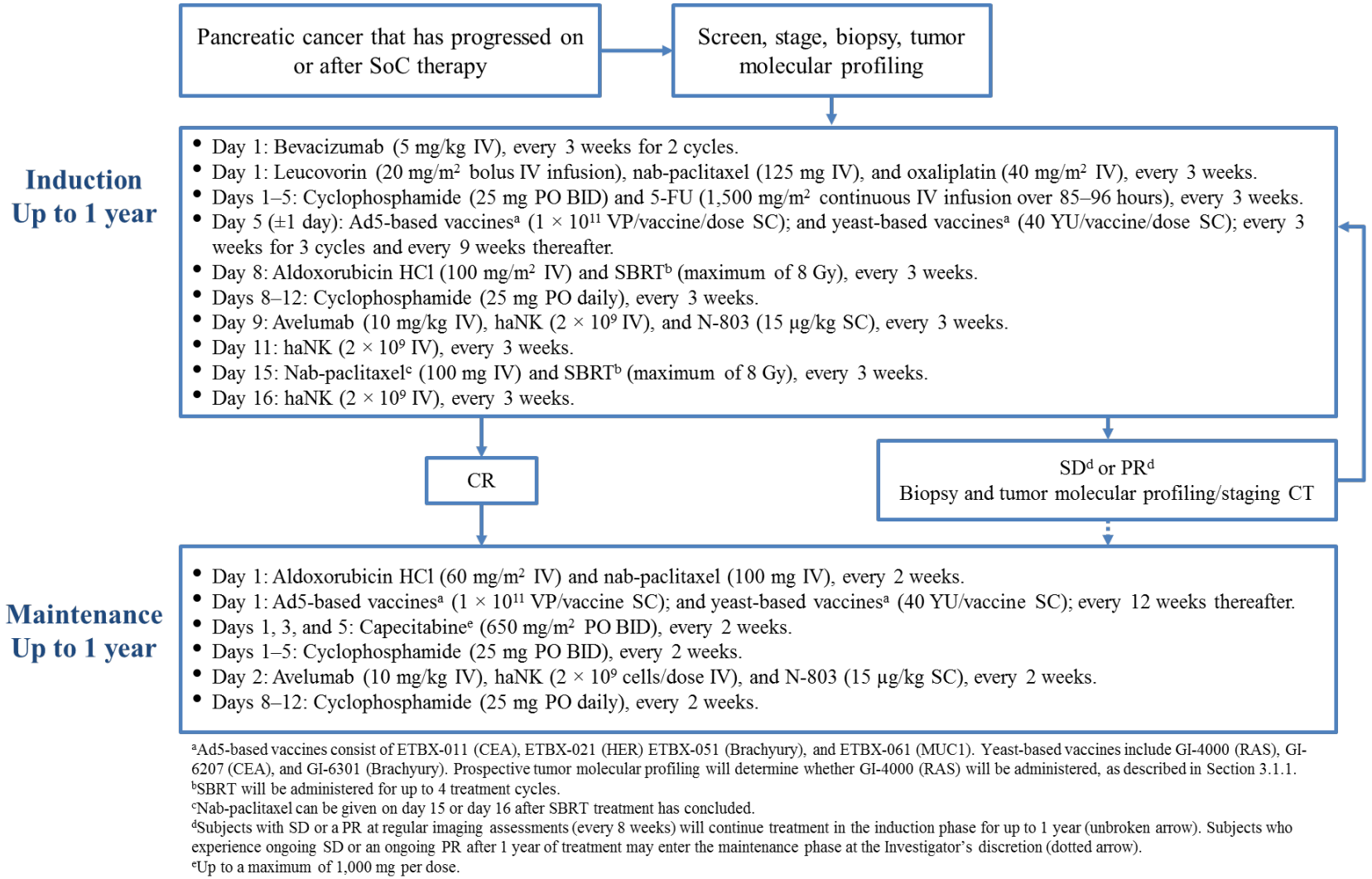
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen and presented separately for cohorts 1 and 2.

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 CA 19-9 level, tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in cfDNA and cfRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Ad5-based vaccines consist of ETBX-011 (CEA), ETBX-021 (HER) ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[b]SBRT will be administered for up to 4 treatment cycles.
[c]Nab-paclitaxel can be given on day 15 or day 16 after SBRT treatment has concluded.
[d]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).
[e]Up to a maximum of 1,000 mg per dose.

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[a]	●																				
Leucovorin	●																				
Oxaliplatin	●																				
5-FU	●	●	●	●	●																
Nab-paclitaxel[b]	●														●						
Ad5-based vaccines[c]					●																
Yeast-based vaccines[c]					●																
Aldoxorubicin HCl								●													
SBRT[d]								●							●						
Avelumab									●												
N-803									●												
haNK									●		●					●					
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●									

[a]Bevacizumab will be administered every 3 weeks for 2 cycles only.
[b]Nab-paclitaxel can be given on day 16 after SBRT treatment has concluded.
[c]Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines may be given within ±1 day of the scheduled day. Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[d]SBRT will be administered for up to 4 treatment cycles.

Figure 3: Maintenance Phase Treatment Schema

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

[a]Each vaccine will be administered on day 1 and every 12 weeks thereafter. The Ad5-based vaccines are ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). The yeast-based vaccines are GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.

Table 18: Schedule of Events for Induction Phase of Study

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																				EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
General Assessments																								
Informed consent	X																							
Inclusion/exclusion[d]	X																							
Demographics	X																							
Medical history[e]	X																							
Confirm availability of FFPE tumor sample[f]	X																							
Concomitant medications	X	X							X								X						X	X
Physical exam: height, weight[g]	X	X							X								X						X	X
Vital signs[h]	X	X				X			X	X		X				X	X						X	X
ECOG performance status	X	X							X								X						X	X
12-lead ECG[i]	X	X[j]	Every 6 weeks																				X	
ECHO (with ejection fraction)	X	X[j]	Every 12 weeks																				X	
Confirm contraceptive measures	X																							
FACT-Hep Questionnaire	X	X	Every 6 weeks																				X	
Adverse event collection		X				X			X	X		X				X	X						X	X
Laboratory Assessments																								
Chemistry panel[k]	X	X[j]							X								X						X	
CA 19-9	X	X[j]	Every 3 weeks																				X	

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																			EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**							
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
Hematology[l]	X	X[j]							X								X						X	
Urinalysis	X	X[j]							X								X						X	
Pregnancy test[m]	X	X[j]	Every 6 weeks																				X	
Serum virology (HIV)[n]	X																							
Determine HER2 positivity and *RAS* mutational status[o]	X																							
Collect whole blood for tumor molecular profiling[p]	X																							
Collect whole blood for immunology analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect whole blood for cfDNA/cfRNA analysis[q]	X	Every 6 weeks during routine blood draws																					X	
Collect historic tumor biopsy specimen for tumor molecular profiling[r]	X																							
Tumor biopsy[r]	X	8 weeks after the start of treatment																						
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.																						
Tumor Imaging and Assessments																								
CT or MRI[s]	X	Every 8 weeks																					X	

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

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

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

[d] Inclusion/exclusion criteria will also be evaluated at enrollment.

[e] Medical history will also be evaluated at enrollment.

[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study 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 (RAS) will begin as soon as molecular profiling results are available.

[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.

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

[i] 12-lead ECG to be performed in triplicate at screening.

[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment. For ECG and ECHO assessments only, day 1 assessments can be skipped if the screening assessment was performed within 28 days prior to the start of treatment.

[k] Chemistry panel to include laboratory assessments noted in Table 17. HbA1c to be assessed in screening blood draw only.

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

[m] Serum pregnancy tests for females of child-bearing potential.

[n] HIV status to be determined by an approved test.

[o] Assessment of *RAS* mutational status to determine whether GI-4000 (RAS) will be administered to the subject, as described in Section 3.1.1. Assessment of HER2 positivity may be conducted as soon as tumor tissue is available, and results from this assessment will not affect the drug regimen administered to subjects in this study.

[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.

[q] Whole blood for immunology and cfDNA/cfRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.

[r] Historic tumor biopsy specimen for tumor molecular profiling will be collected only for subjects enrolled in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator.

[s] Tumor imaging by CT or MRI will be performed at screening and every 8 weeks in the induction phase, as described in Section 6.1.2.

Table 19: Schedule of Events for Maintenance Phase of Study

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Concomitant medications	X														X	X
Physical exam, weight	X														X	X
Vital signs[d]	X	X													X	X
ECOG performance status	X														X	
12-lead ECG	X	Every 12 weeks													X	
ECHO (with ejection fraction)	X	Every 12 weeks													X	
Confirm contraceptive measures	X															
Adverse event collection	X	X													X	X
FACT-Hep questionnaire	X	Every 12 weeks													X	
Laboratory Assessments																
Chemistry panel[e]	X														X	
CA 19-9	X	Every 4 weeks													X	
Hematology[f]	X														X	
Urinalysis	X														X	
Pregnancy test[g]	X	Every 12 weeks													X	
Collect whole blood for immunology analysis[h]	X	Every 8 weeks during routine blood draws													X	
Collect whole blood for cfDNA/cfRNA analysis[h]	X	Every 8 weeks during routine blood draws													X	
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion															
Tumor Imaging and Assessments																
CT or MRI[i]	X	Every 12 weeks													X	

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

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

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

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

[e] Chemistry panel to include laboratory assessments noted in Table 17.

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

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

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

[i] Tumor imaging by CT or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6.1.2.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1b/2 trial of the NANT Pancreatic Cancer Vaccine as treatment for subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.080
Version Number:	3
Final Date:	01 October 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: Oct 1 2018

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