# NANT PANCREATIC CANCER VACCINE: COMBINATION IMMUNOTHERAPY IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.039** |
| **IND Sponsor:** | NantCell, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 16 March 2017 |

## STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

# PROTOCOL SYNOPSIS

**Name of Sponsor/Company:**
NantCell, Inc.

**Name of Investigational Products:**

**Approved**

1. CYCLOPHOSPHAMIDE tablets, for oral use
2. ELOXATIN® (oxaliplatin) injection for intravenous (IV) use
3. XELODA (capecitabine) tablets, for oral use
4. Fluorouracil Injection, for IV use
5. LEUCOVORIN Calcium for Injection, for IV or IM use
6. ABRAXANE® (Nab-paclitaxel) for injectable suspension
7. AVASTIN (Bevacizumab) solution for IV infusion

**Investigational**

1. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
2. aNK™, NK-92 ( activated natural killer cell line, aNK™ for Infusion)
3. ETBX-011: Ad5 [E1-, E2b-]-CEA (carcinoembryonic antigen)
4. Avelumab, a human anti-PD-L1 IgG1 monoclonal antibody
5. GI-4000, a vaccine derived from recombinant *Saccharomyces cerevisiae* yeast expressing mutant Ras proteins
6. Trabedersen (AP 12009), TGF-β2-Specific phosphorothioate antisense oligonucleotide

**Name of Active Ingredients:**

**Approved**

1. 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate (cyclophosphamide)
2. cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum (oxaliplatin)
3. 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine (capecitabine)
4. 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione (5-Fluorouracil)
5. L-Glutamic acid, N-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt (leucovorin)
6. Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-(2aR, 4S, 4aS, 6R, 9S, 11S, 12S, 12aR, 12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-y1ester,(αR,βS)-(9CI) bound to albumin (nab-paclitaxel)
7. Recombinant human anti-VEGF IgG1 monoclonal (bevacizumab)

**Investigational**

1. Recombinant human super agonist interleukin-15 (IL-15) complex (ALT-803)
2. NK-92 cells (aNK for Infusion)
3. Ad5 [E1-, E2b-]-CEA
4. Recombinant human anti-PD-L1 IgG1 monoclonal antibody (avelumab)
5. GI-4000 Ras vaccine
6. TGF-β2-specific phosphorothioate antisense oligonucleotide

**Title of Study:**

NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

**Study Number:**

QUILT-3.039

**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 regimen in subjects with pancreatic cancer who have progressed after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and patient-reported outcomes (PROs) of pancreatic cancer symptoms.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT regimen as assessed by ORR.
- The secondary objectives are to determine additional measures of efficacy (PFS, DOR, DCR, PROs of pancreatic cancer symptoms), and additional safety data.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**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 first line therapy and chemotherapy. Phase 2 will be based on 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 until they experience progressive disease (PD) or experience unacceptable toxicity (not correctable with dose reduction), withdraw consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue throughout the maintenance phase until the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment.

Tumor biopsies and tumor molecular profiling will be conducted at screening and at the end of the initial induction (8 weeks) and during a potential prolonged induction phase (depending on response). In addition, during routine weekly blood draws, a separate blood tube will be collected to analyse blood for changes in circulating RNA.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 3 months during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) of target and non-target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC).

**Induction Phase:**

The induction phase will consist of repeated 2 week cycles of low-dose radiation and metronomic chemotherapy. The treatment regimen of cyclophosphamide, oxaliplatin, 5-FU/leucovorin, nab-paclitaxel, trabedersen, bevacizumab, ALT-803, aNK, vaccines (Ad5 and GI-4000), and avelumab will be repeated every 2 weeks. Concurrent stereotactic body radiotherapy (SBRT) will be given during the first four 2-week cycles. Radiation will be administered to all feasible tumor sites using SBRT. Techniques allowed include linear-accelerator based therapies (3D and intensity-modulated radiation therapy [IMRT]) and gamma and cyber knife.

The induction treatment will continue until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Subjects that have a CR in the induction phase will enter the maintenance phase of the study. Response assessments using CT/MRI evaluated according to RECIST Version 1.1 and irRC will be performed every 8 weeks during the induction phase.

Days 1–4 every 2 weeks:

- Trabedersen (140 mg/m$^2$/day over 24 hours as a continuous infusion).

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg twice a day [BID]).

Day 1 and 8, every 2 weeks:

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

Day 1 every 2 weeks:

- Bevacizumab (5 mg/kg IV)

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

- 5-fluorouracil (400 mg/m$^2$ over 24 hours as a continuous infusion)
- Leucovorin (20 mg/m$^2$ IV bolus)

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

- SBRT (8 Gy)

Day 9, every 2 weeks:

- ALT-803 (10 µg/kg subcutaneously [SC] 30 minutes prior to aNK infusion)

Day 9 and 11, every 2 weeks:

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

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

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 yeast units [YU] SC; use dependent on genomic sequencing indicating required KRAS mutations)

Day 8, every 2 weeks:

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

**Maintenance Phase:**

The duration of the maintenance phase will be 1 year following completion of the last treatment in the induction phase. Treatment will continue throughout the maintenance phase unless the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Response assessments using CT/MRI evaluated according to RECIST Version 1.1 and irRC will be performed every 3 months during the maintenance phase.

Days 1–5 and 8–12, every 2 weeks:

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

Day 1, every 2 weeks:

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

Day 2, every 2 weeks:

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

Day 5, every 8 weeks thereafter:

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 YU SC)

**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 and irRC.
- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months).
- PROs of pancreatic cancer symptoms.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST and irRC.

**Secondary Endpoints:**

- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR .
- PROs of pancreatic cancer symptoms.
- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Enrollment (planned):**

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

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

- Age ≥ 18 years old.
- Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
- Histologically-confirmed pancreatic cancer with progression on or after SoC therapy.
- ECOG performance status of 0 to 2.
- Have at least 1 measurable lesion and/or non-measurable disease evaluable according to RECIST Version 1.1.
- Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anti-cancer treatment and be willing to release the specimen for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period.
- Must be willing to provide blood samples for exploratory analyses.
- Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
- Agreement to practice effective contraception for female subjects with child-bearing potential and non-sterile males.

**Exclusion Criteria:**

- History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
- History of other active malignancies or brain metastasis except: controlled basal cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, cervical); prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable prostate-specific antigen (PSA) (< 0.2 ng/mL); bulky (≥ 1.5 cm) disease with metastasis in the central hilar area of the chest and involving the pulmonary vasculature. Subjects with a history of another malignancy must have > 5 years without evidence of disease.
- 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.

- Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
- History of organ transplant requiring immunosuppression.
- History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
- Requires whole blood transfusion to meet eligibility criteria.
- Inadequate organ function, evidenced by the following laboratory results:
  - White blood cell (WBC) count < 3,500 cells/$mm^3$
  - Absolute neutrophil count < 1,500 cells/$mm^3$.
  - Platelet count < 100,000 cells/$mm^3$.
  - Hemoglobin < 9 g/dL.
  - Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
  - Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
  - Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
  - Serum creatinine > 2.0 mg/dL or 177 μmol/L.
  - International normalized ratio (INR) or activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).
- Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
- Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
- Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
- 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.
- Known hypersensitivity to any component of the study medication(s).
- Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications. See Excluded Medications list.

- Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
- Concurrent participation in any interventional clinical trial.
- Pregnant and nursing women.

**Investigational Product, Dosage, and Mode of Administration:**

- Cyclophosphamide 50 mg BID (induction and maintenance)
- Oxaliplatin 40 mg/$m^2$ IV (induction)
- Trabedersen 140 mg/$m^2$ IV (induction)
- Capecitabine 650 mg/$m^2$ PO BID (maintenance)
- 5-FU 400 mg/$m^2$ over 24 hours as a continuous infusion (induction)
- Leucovorin 20 mg/$m^2$ IV bolus (induction)
- Nab-paclitaxel 125 mg IV (induction and maintenance)
- Bevacizumab 5 mg/kg IV (induction and maintenance)
- Avelumab 10 mg/kg IV(induction and maintenance)
- SBRT 8 Gy (induction)
- ALT-803 10 µg/kg SC (induction and maintenance)
- aNK 2 x $10^9$ cells/dose IV (induction and maintenance)
- Ad5 [E1-, E2b-]-CEA 5 x $10^{11}$ VP/dose SC (induction and maintenance)
- GI-4000 RAS vaccine 40 YU (induction and maintenance)

**Duration of Treatment:**

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

Subjects will be treated until they experience progressive disease, unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

**Duration of Follow-up:**

After discontinuation or completion of the study, subjects will be followed every 3 months for 18 months to collect follow-up information, including survival status and any current cancer treatment regimen.

**Reference Therapy, Dosage, and Mode of Administration:**

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

ORR and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks and will be evaluated according to RECIST Version 1.1 and irRC. OS, DOR, and DCR will also be assessed.

An assessment of pancreatic cancer symptoms will be conducted via PROs using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) instrument on study day 1, every 28 days thereafter, and at the day 28 follow-up visit.

**Exploratory Analysis:**

***Molecular Profiling and Analysis:***

Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Plasma will be collected and circulating tumor RNA (ctRNA) will be isolated. A PCR-based assay (LiquidGenomicsDx) will be used to assess the level of PD-L1 circulating RNA. The levels of PD-L1 ctRNA will be correlated with efficacy outcomes.

**Statistical Methods:**

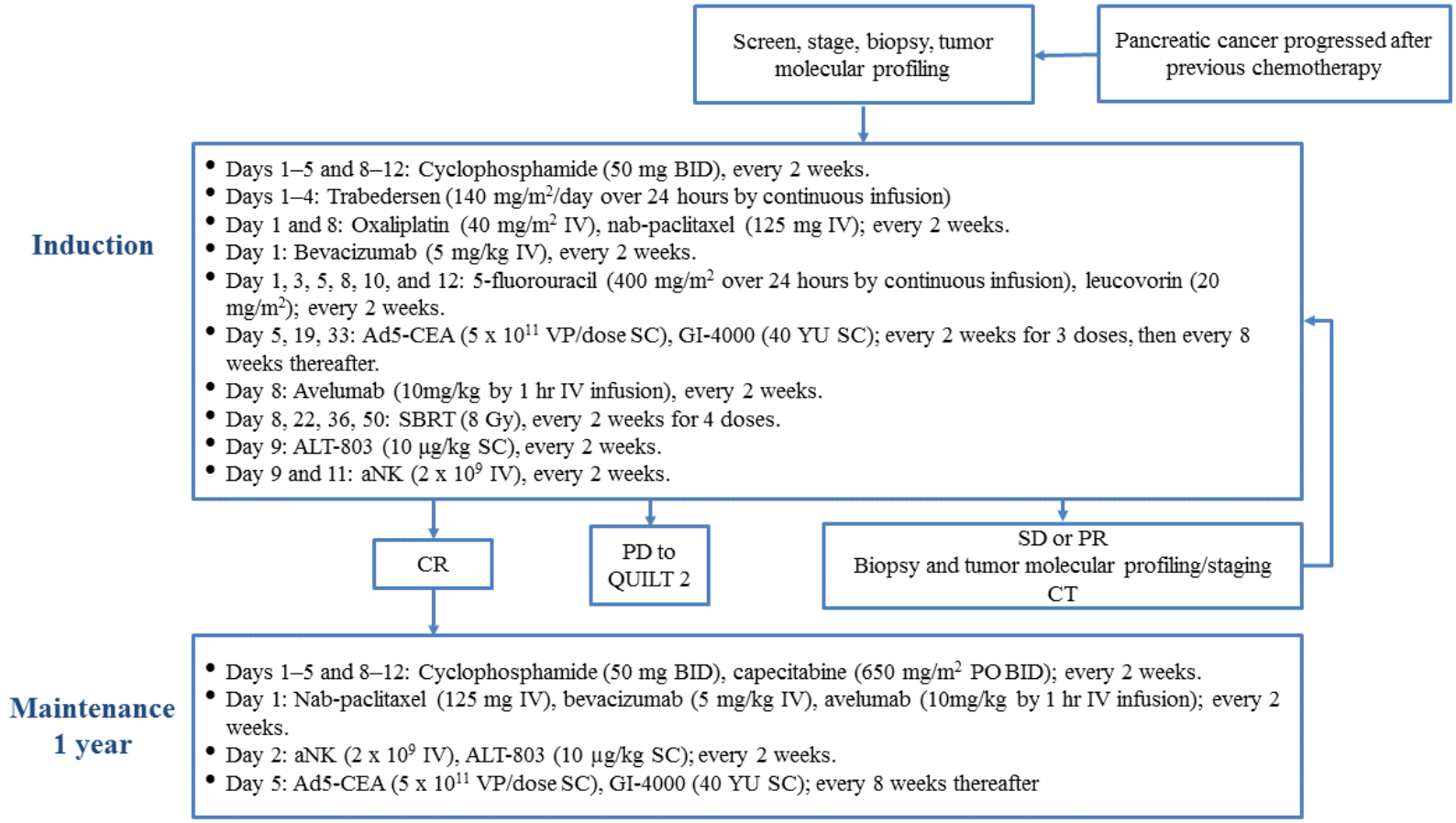
This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with pancreatic cancer patients whose tumors have progressed on or after SoC treatment.

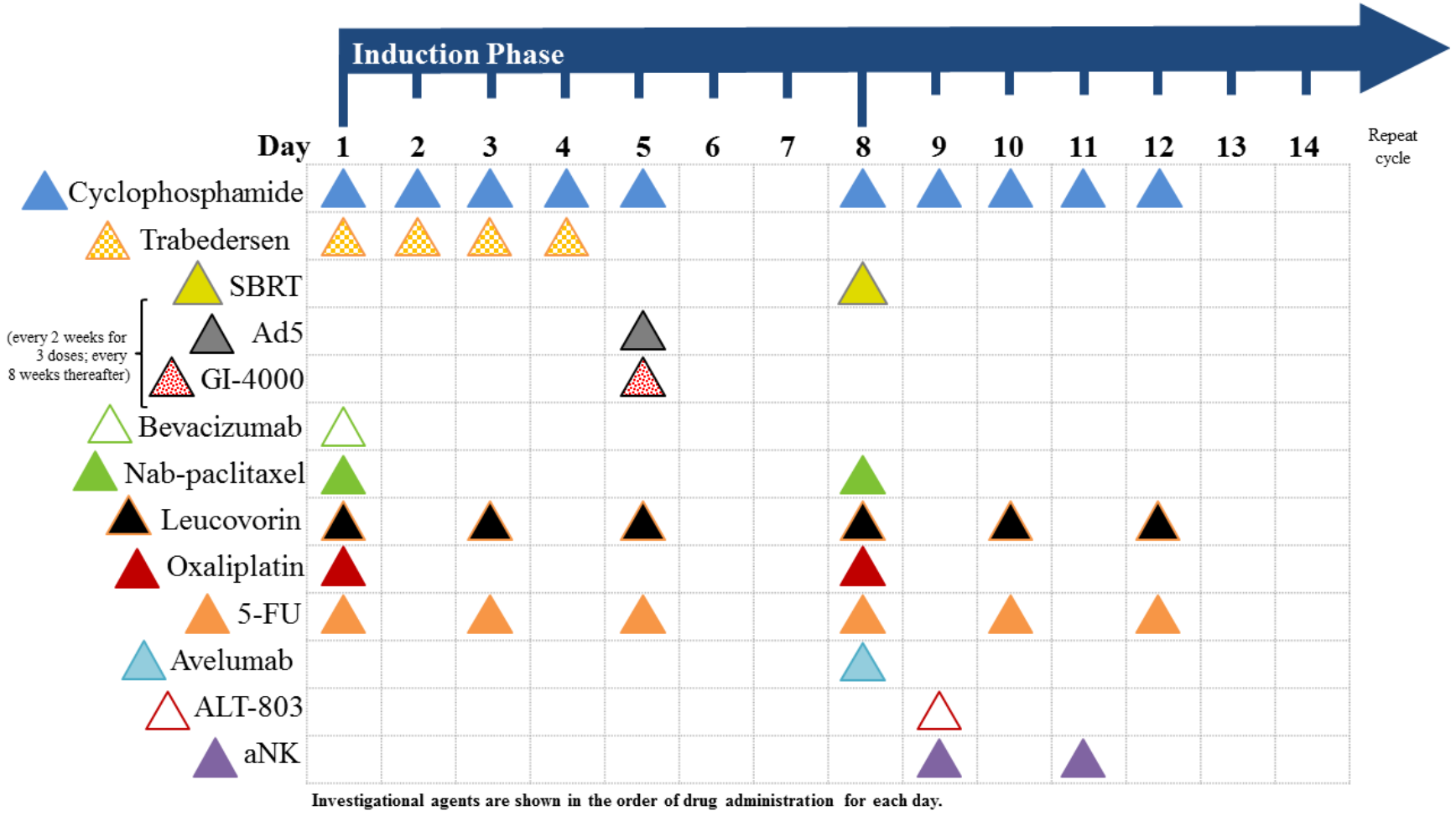
Results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

ORR will be evaluated according to 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.

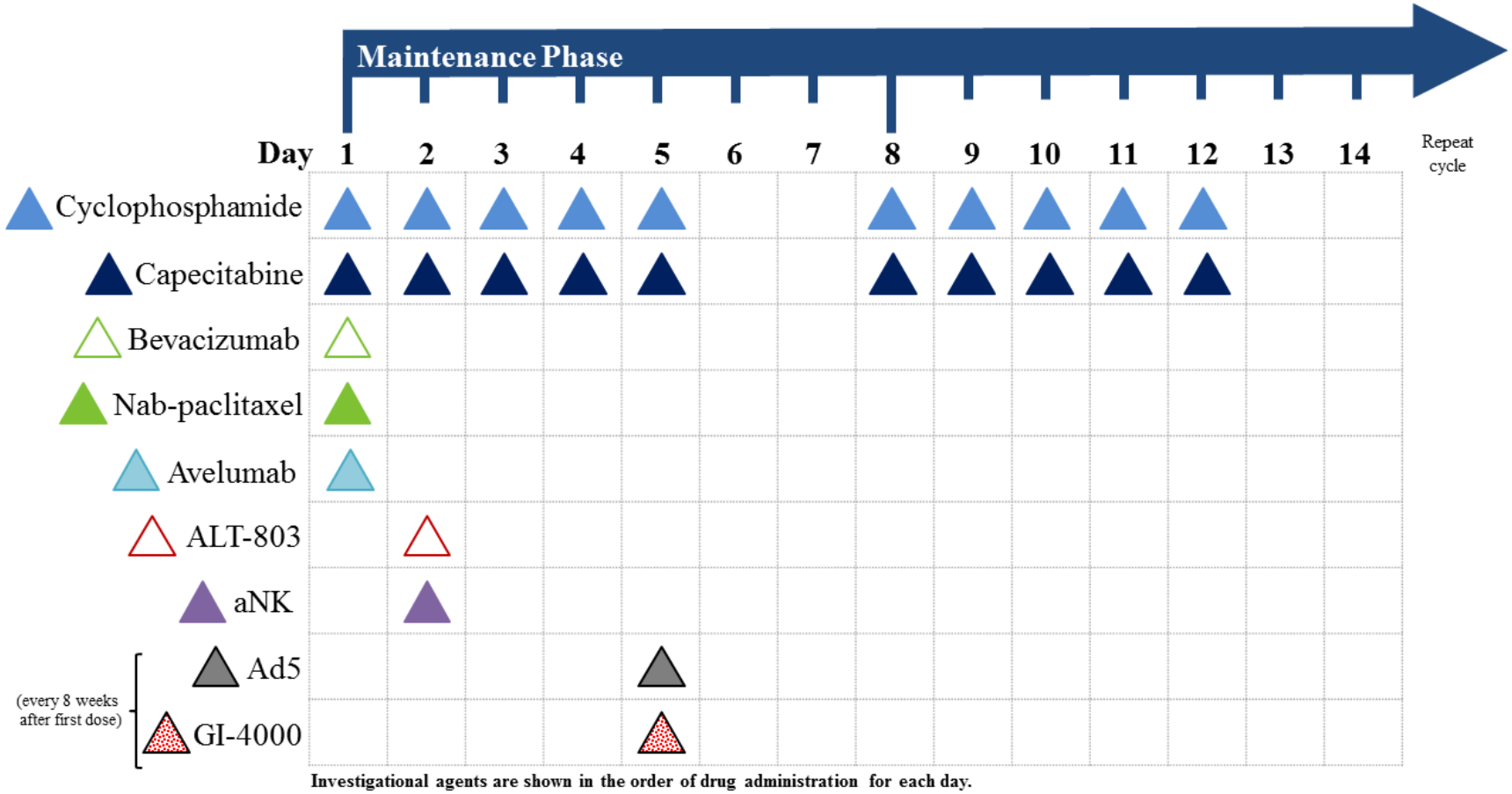
Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

**Figure 1: Study Treatment Schema**






**Investigational agents are shown in the order of drug administration for each day.**


Maintenance Phase
Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Repeat cycle
Cyclophosphamide
Capecitabine
Bevacizumab
Nab-paclitaxel
Avelumab
ALT-803
aNK
Ad5
GI-4000
(every 8 weeks after first dose)
Investigational agents are shown in the order of drug administration for each day.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy. |
| **Study Number:** | QUILT-3.039 |
| **Version Number:** | 1 |
| **Final Date:** | 16 March 2017 |

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

Signed: _____ Date: 3-16-17

John H. Lee, MD
Senior Vice President Adult Medical Affairs, NantKwest Inc.
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Culver City, CA 90232
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# NANT PANCREATIC CANCER VACCINE: COMBINATION IMMUNOTHERAPY IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

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

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 16 March 2017 |
| Version 2 | 06 April 2017 |

## STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

# PROTOCOL SYNOPSIS

**Name of Sponsor/Company:**
NantCell, Inc.

**Name of Investigational Products:**

**Approved**

1. CYCLOPHOSPHAMIDE tablets, for oral use
2. ELOXATIN® (oxaliplatin) injection for intravenous (IV) use
3. XELODA (capecitabine) tablets, for oral use
4. Fluorouracil Injection, for IV use
5. LEUCOVORIN Calcium for Injection, for IV or IM use
6. ABRAXANE® (Nab-paclitaxel) for injectable suspension
7. AVASTIN (Bevacizumab) solution for IV infusion

**Investigational**

1. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
2. aNK™, NK-92 ( activated natural killer cell line, aNK™ for Infusion)
3. ETBX-011: Ad5 [E1-, E2b-]-CEA (carcinoembryonic antigen)
4. Avelumab, a human anti-PD-L1 IgG1 monoclonal antibody
5. GI-4000, a vaccine derived from recombinant *Saccharomyces cerevisiae* yeast expressing mutant Ras proteins

**Name of Active Ingredients:**

**Approved**

1. 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate (cyclophosphamide)
2. cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum (oxaliplatin)
3. 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine (capecitabine)
4. 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione (5-Fluorouracil)
5. L-Glutamic acid, N-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt (leucovorin)
6. Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-(2aR, 4S, 4aS, 6R, 9S, 11S, 12S, 12aR, 12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-y1ester,(αR,βS)-(9CI) bound to albumin (nab-paclitaxel)
7. Recombinant human anti-VEGF IgG1 monoclonal (bevacizumab)

**Investigational**

1. Recombinant human super agonist interleukin-15 (IL-15) complex (ALT-803)
2. NK-92 cells (aNK for Infusion)
3. Ad5 [E1-, E2b-]-CEA
4. Recombinant human anti-PD-L1 IgG1 monoclonal antibody (avelumab)
5. GI-4000 Ras vaccine

**Title of Study:**

NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

**Study Number:**
QUILT-3.039

**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 regimen in subjects with pancreatic cancer who have progressed after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and patient-reported outcomes (PROs) of pancreatic cancer symptoms.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT regimen as assessed by ORR.
- The secondary objectives are to determine additional measures of efficacy (PFS, DOR, DCR, PROs of pancreatic cancer symptoms), and additional safety data.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**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 first line therapy and chemotherapy. Phase 2 will be based on 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 until they experience progressive disease (PD) or experience unacceptable toxicity (not correctable with dose reduction), withdraw consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue throughout the maintenance phase until the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment.

Tumor biopsies and tumor molecular profiling will be conducted at screening and at the end of the initial induction (8 weeks) and during a potential prolonged induction phase (depending on response). In addition, during routine weekly blood draws, a separate blood tube will be collected to analyse blood for changes in circulating RNA.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 3 months during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) of target and non-target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC).

**Induction Phase:**

The induction phase will consist of repeated 2 week cycles of low-dose radiation and metronomic chemotherapy. The treatment regimen of cyclophosphamide, oxaliplatin, 5-FU/leucovorin, nab-paclitaxel, bevacizumab, ALT-803, aNK, vaccines (Ad5 and GI-4000), and avelumab will be repeated every 2 weeks. Concurrent stereotactic body radiotherapy (SBRT) will be given during the first four 2-week cycles. Radiation will be administered to all feasible tumor sites using SBRT. Techniques allowed include linear-accelerator based therapies (3D and intensity-modulated radiation therapy [IMRT]) and gamma and cyber knife.

The induction treatment will continue until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Subjects that have a CR in the induction phase will enter the maintenance phase of the study. Response assessments using CT/MRI evaluated according to RECIST Version 1.1 and irRC will be performed every 8 weeks during the induction phase.

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg twice a day [BID]).

Day 1 and 8, every 2 weeks:

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

Day 1 every 2 weeks:

- Bevacizumab (5 mg/kg IV)

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

- 5-fluorouracil (400 mg/$m^2$ over 24 hours as a continuous infusion)
- Leucovorin (20 mg/$m^2$ IV bolus)

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

- SBRT (8 Gy)

Day 9, every 2 weeks:

- ALT-803 (10 µg/kg subcutaneously [SC] 30 minutes prior to aNK infusion)

Day 9 and 11, every 2 weeks:

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

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

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 yeast units [YU] SC; use dependent on genomic sequencing indicating required KRAS mutations)

Day 8, every 2 weeks:

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

**Maintenance Phase:**

The duration of the maintenance phase will be 1 year following completion of the last treatment in the induction phase. Treatment will continue throughout the maintenance phase unless the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Response assessments using CT/MRI evaluated according to RECIST Version 1.1 and irRC will be performed every 3 months during the maintenance phase.

Days 1–5 and 8–12, every 2 weeks:

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

Day 1, every 2 weeks:

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

Day 2, every 2 weeks:

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

Day 5, every 8 weeks thereafter:

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 YU SC)

**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 and irRC.
- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months).
- PROs of pancreatic cancer symptoms.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST and irRC.

**Secondary Endpoints:**

- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR .
- PROs of pancreatic cancer symptoms.
- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Enrollment (planned):**

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

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

- Age ≥ 18 years old.
- Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
- Histologically-confirmed pancreatic cancer with progression on or after SoC therapy.
- ECOG performance status of 0 to 2.
- Have at least 1 measurable lesion and/or non-measurable disease evaluable according to RECIST Version 1.1.
- Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anti-cancer treatment and be willing to release the specimen for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period.
- Must be willing to provide blood samples for exploratory analyses.
- Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
- Agreement to practice effective contraception for female subjects with child-bearing potential and non-sterile males.

**Exclusion Criteria:**

- History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
- History of other active malignancies or brain metastasis except: controlled basal cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, cervical); prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable prostate-specific antigen (PSA) (< 0.2 ng/mL); bulky (≥ 1.5 cm) disease with metastasis in the central hilar area of the chest and involving the pulmonary vasculature. Subjects with a history of another malignancy must have > 5 years without evidence of disease.
- 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.

- Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
- History of organ transplant requiring immunosuppression.
- History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
- Requires whole blood transfusion to meet eligibility criteria.
- Inadequate organ function, evidenced by the following laboratory results:
  - White blood cell (WBC) count < 3,500 cells/$mm^3$
  - Absolute neutrophil count < 1,500 cells/$mm^3$.
  - Platelet count < 100,000 cells/$mm^3$.
  - Hemoglobin < 9 g/dL.
  - Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
  - Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
  - Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
  - Serum creatinine > 2.0 mg/dL or 177 μmol/L.
  - International normalized ratio (INR) or activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).
- Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
- Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
- Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
- 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.
- Known hypersensitivity to any component of the study medication(s).
- Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications. See Excluded Medications list.

- Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
- Concurrent participation in any interventional clinical trial.
- Pregnant and nursing women.

**Investigational Product, Dosage, and Mode of Administration:**

- Cyclophosphamide 50 mg BID (induction and maintenance)
- Oxaliplatin 40 mg/$m^2$ IV (induction)
- Capecitabine 650 mg/$m^2$ PO BID (maintenance)
- 5-FU 400 mg/$m^2$ over 24 hours as a continuous infusion (induction)
- Leucovorin 20 mg/$m^2$ IV bolus (induction)
- Nab-paclitaxel 125 mg IV (induction and maintenance)
- Bevacizumab 5 mg/kg IV (induction and maintenance)
- Avelumab 10 mg/kg IV(induction and maintenance)
- SBRT 8 Gy (induction)
- ALT-803 10 µg/kg SC (induction and maintenance)
- aNK 2 x $10^9$ cells/dose IV (induction and maintenance)
- Ad5 [E1-, E2b-]-CEA 5 x $10^{11}$ VP/dose SC (induction and maintenance)
- GI-4000 RAS vaccine 40 YU (induction and maintenance)

**Duration of Treatment:**

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

Subjects will be treated until they experience progressive disease, unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

**Duration of Follow-up:**

After discontinuation or completion of the study, subjects will be followed every 3 months for 18 months to collect follow-up information, including survival status and any current cancer treatment regimen.

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

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

ORR and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks and will be evaluated according to RECIST Version 1.1 and irRC. OS, DOR, and DCR will also be assessed.

An assessment of pancreatic cancer symptoms will be conducted via PROs using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) instrument on study day 1, every 28 days thereafter, and at the day 28 follow-up visit.

**Exploratory Analysis:**

***Molecular Profiling and Analysis:***

Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Plasma will be collected and circulating tumor RNA (ctRNA) will be isolated. A PCR-based assay (LiquidGenomicsDx) will be used to assess the level of PD-L1 circulating RNA. The levels of PD-L1 ctRNA will be correlated with efficacy outcomes.

**Statistical Methods:**

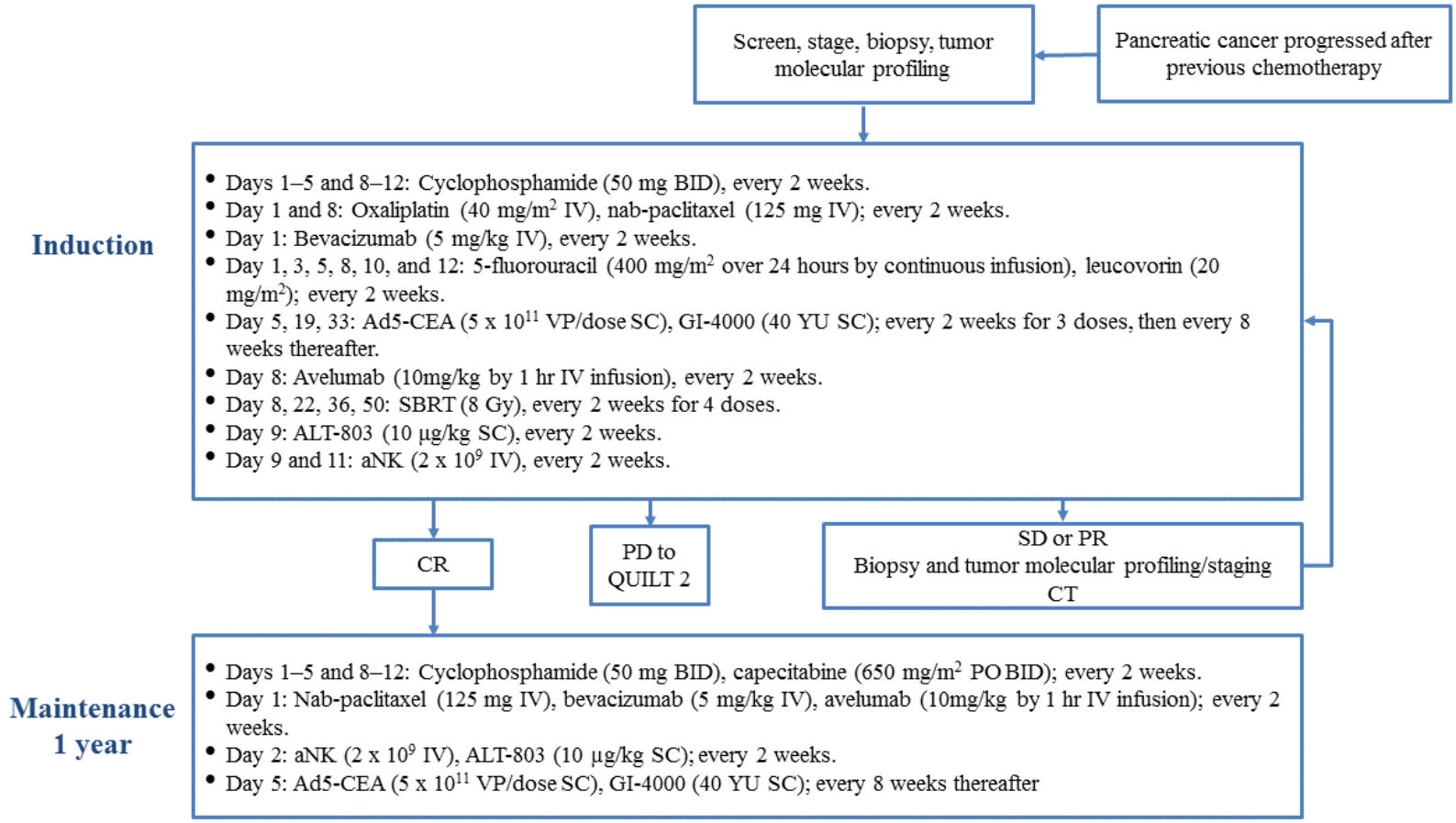
This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with pancreatic cancer patients whose tumors have progressed on or after SoC treatment.

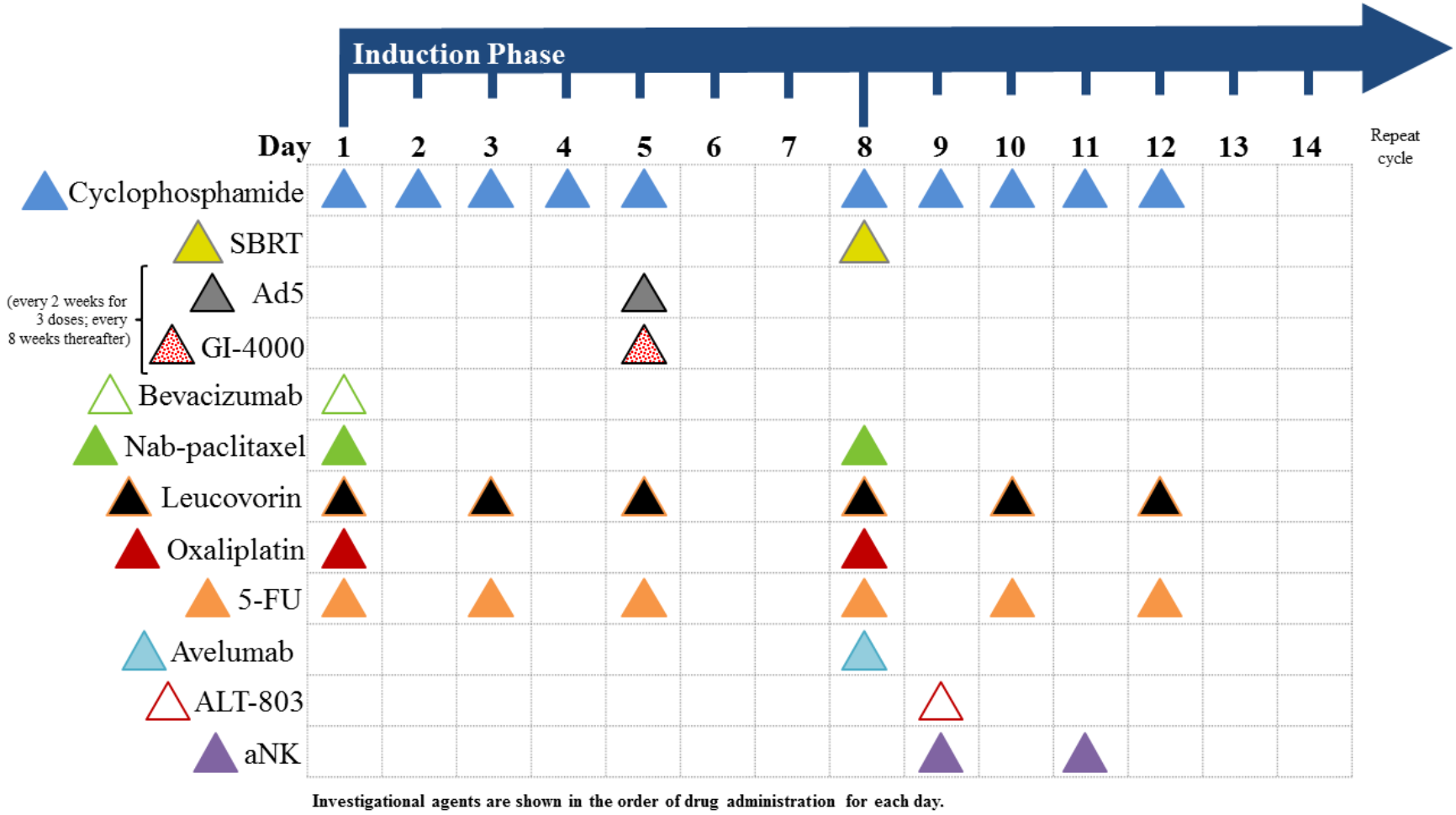
Results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

ORR will be evaluated according to 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.

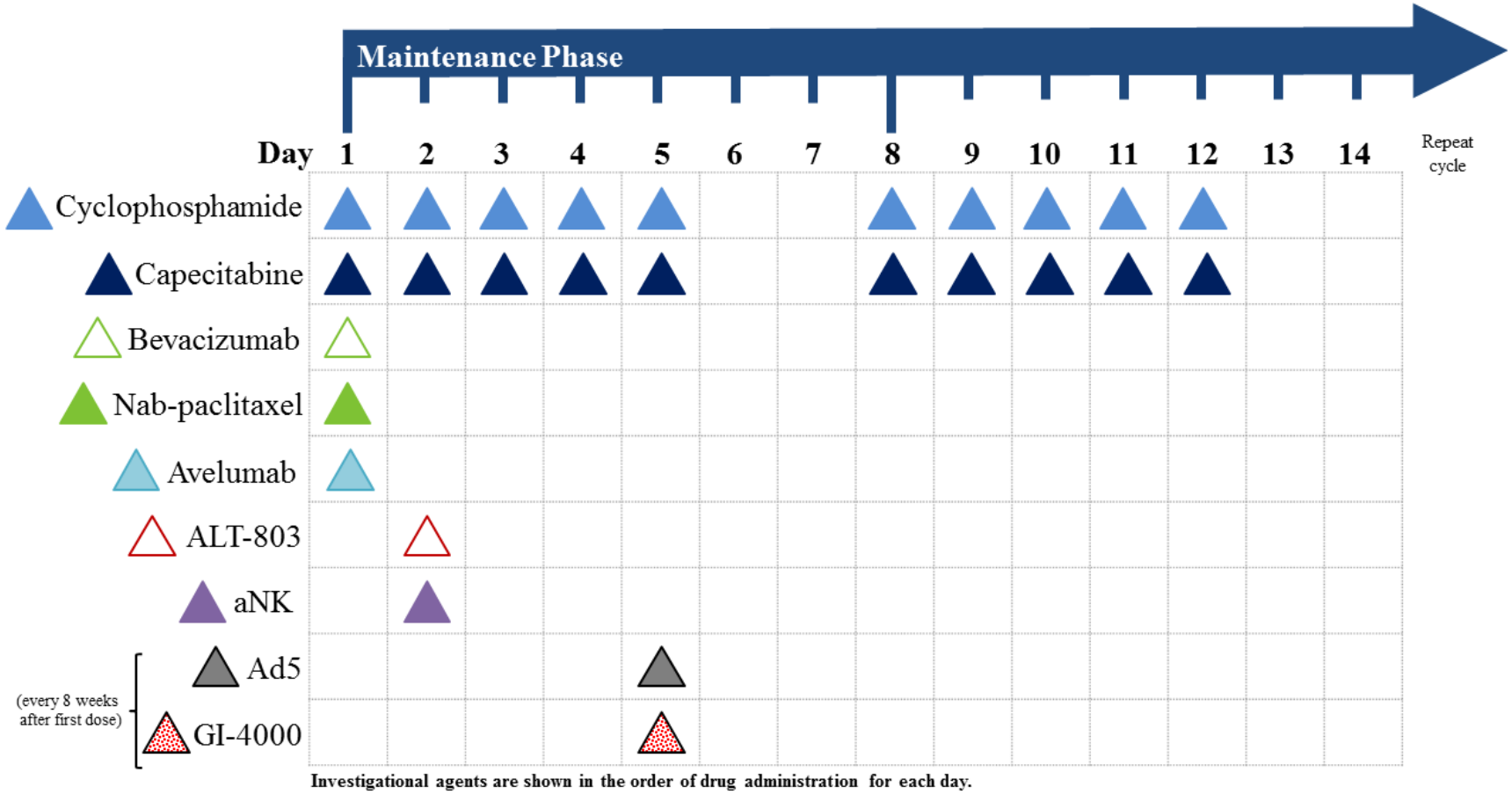
Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

**Figure 1: Study Treatment Schema**






**Investigational agents are shown in the order of drug administration for each day.**


Maintenance Phase
Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Repeat cycle
Cyclophosphamide
Capecitabine
Bevacizumab
Nab-paclitaxel
Avelumab
ALT-803
aNK
Ad5
GI-4000
(every 8 weeks after first dose)
Investigational agents are shown in the order of drug administration for each day.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy. |
| **Study Number:** | QUILT-3.039 |
| **Version Number:** | 2 |
| **Final Date:** | 06 April 2017 |

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

Signed: _____ Date: 4-6-17

John H. Lee, MD
Senior Vice President Adult Medical Affairs, NantKwest Inc.
9920 Jefferson Blvd
Culver City, CA 90232
Email: John.Lee@Nantkwest.com
Cell Phone: +1-605-610-6391

# NANT PANCREATIC CANCER VACCINE: COMBINATION IMMUNOTHERAPY IN SUBJECTS WITH PANCREATIC CANCER WHO HAVE PROGRESSED ON OR AFTER STANDARD-OF-CARE THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.039** |
| **IND Sponsor:** | NantCell, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 16 March 2017 |
| Version 2 | 06 April 2017 |
| Version 3 | 03 June 2017 |

## STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

# PROTOCOL SYNOPSIS

**Name of Sponsor/Company:**
NantCell, Inc.

**Name of Investigational Products:**

**Approved**

1. CYCLOPHOSPHAMIDE tablets, for oral use
2. ELOXATIN (oxaliplatin) injection for intravenous (IV) use
3. XELODA (capecitabine) tablets, for oral use
4. Fluorouracil Injection, for IV use
5. LEUCOVORIN Calcium for Injection, for IV or IM use
6. ABRAXANE (Nab-paclitaxel) for injectable suspension
7. AVASTIN (Bevacizumab) solution for IV infusion
8. BAVENCIO (avelumab) injection, for IV use

**Investigational**

1. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
2. aNK™, NK-92 ( activated natural killer cell line, aNK™ for Infusion)
3. ETBX-011: Ad5 [E1-, E2b-]-CEA (carcinoembryonic antigen)
4. GI-4000, a vaccine derived from recombinant *Saccharomyces cerevisiae* yeast expressing mutant Ras proteins

**Name of Active Ingredients:**

**Approved**

1. 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate (cyclophosphamide)
2. cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum (oxaliplatin)
3. 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine (capecitabine)
4. 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione (5-Fluorouracil)
5. L-Glutamic acid, N-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt (leucovorin)
6. Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-(2aR, 4S, 4aS, 6R, 9S, 11S, 12S, 12aR, 12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-y1ester,(αR,βS)-(9CI) bound to albumin (nab-paclitaxel)
7. Recombinant human anti-VEGF IgG1 monoclonal (bevacizumab)
8. Fully human anti-PD-L1 IgG1 lambda monoclonal antibody (avelumab)

**Investigational**

1. Recombinant human super agonist interleukin-15 (IL-15) complex (ALT-803)
2. NK-92 cells (aNK for Infusion)
3. Ad5 [E1-, E2b-]-CEA
4. GI-4000 Ras vaccine

**Title of Study:**

NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy.

**Study Number:**
QUILT-3.039

**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 regimen in subjects with pancreatic cancer who have progressed after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and patient-reported outcomes (PROs) of pancreatic cancer symptoms.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT regimen as assessed by ORR.
- The secondary objectives are to determine additional measures of efficacy (PFS, DOR, DCR, PROs of pancreatic cancer symptoms), and additional safety data.
- Exploratory objectives include determination of any correlations between tumor molecular profiles and efficacy, examination of cell phenotypes in tumors and whole blood, and assessment of circulating tumor RNA (ctRNA) for detection of PD-L1 expression.

**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 first line therapy and chemotherapy. Phase 2 will be based on Simon's two-stage optimal design.

The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities.

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, until they experience progressive disease (PD) or experience unacceptable toxicity (not correctable with dose reduction), withdraw consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue throughout the maintenance phase until the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment.

Tumor biopsies and tumor molecular profiling will be conducted at screening and at the end of the initial induction (8 weeks) and during a potential prolonged induction phase (depending on response).

In addition, circulating RNA and exploratory immune analyses will be carried out on blood collected every 4 weeks during the induction phase and every 8 weeks during the maintenance phase.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 3 months during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) of target and non-target lesions in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC).

**Induction Phase:**

The induction phase will consist of repeated 2 week cycles of low-dose radiation and metronomic chemotherapy. The treatment regimen of cyclophosphamide, oxaliplatin, 5-FU/leucovorin, nab-paclitaxel, bevacizumab, ALT-803, aNK, vaccines (Ad5 and GI-4000), and avelumab will be repeated every 2 weeks. Concurrent stereotactic body radiotherapy (SBRT) will be given during the first four 2-week cycles. Radiation will be administered to all feasible tumor sites using SBRT, as described in Section 5.1.5.1. Techniques allowed include linear-accelerator based therapies (3D and intensity-modulated radiation therapy [IMRT]) and gamma and cyber knife.

The induction treatment will continue for up to 1 year, until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Subjects that have a CR in the induction phase will enter the maintenance phase of the study. Response assessments using CT/MRI evaluated in accordance with RECIST Version 1.1 and irRC will be performed every 8 weeks during the induction phase.

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg twice a day [BID]).

Day 1 and 8, every 2 weeks:

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

Day 1 every 2 weeks:

- Bevacizumab (5 mg/kg IV)

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

- 5-fluorouracil (400 mg/$m^2$ over 24 hours as a continuous infusion)
- Leucovorin (20 mg/$m^2$ IV bolus)

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

- SBRT (8 Gy)

Day 9, every 2 weeks:

- ALT-803 (10 µg/kg subcutaneously [SC] 30 minutes prior to aNK infusion)

Day 9 and 11, every 2 weeks:

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

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

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 yeast units [YU] SC, 2 hours after administration of Ad5 [E1-, E2b-]-CEA; use dependent on genomic sequencing indicating required KRAS mutations)

Day 8, every 2 weeks:

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

**Maintenance Phase:**

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. Treatment will continue throughout the maintenance phase unless the subject experiences PD or unacceptable toxicity, withdraws consent, or the investigator feels it is no longer in the subject's best interest to continue treatment. Response assessments using CT/MRI evaluated in accordance with RECIST Version 1.1 and irRC will be performed every 3 months during the maintenance phase.

Days 1–5 and 8–12, every 2 weeks:

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

Day 1, every 2 weeks:

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

Day 2, every 2 weeks:

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

Day 5, every 8 weeks thereafter:

- Ad5 [E1-, E2b-]-CEA (5 x $10^{11}$ VP/dose SC)
- GI-4000 (40 YU SC, 2 hours administration of Ad5 [E1-, E2b-]-CEA)

**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 and irRC.
- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for at least 2 months).
- PROs of pancreatic cancer symptoms.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST and irRC.

**Secondary Endpoints:**

- PFS by RECIST and irRC.
- OS.
- DOR.
- DCR .
- PROs of pancreatic cancer symptoms.
- Incidence of treatment-emergent AEs, SAEs, graded using the NCI CTCAE Version 4.03.

**Exploratory Endpoints:**

- Determination of tumor genomic, transcriptomic, and proteomic profiles and correlations with subject outcomes.
- Determination of PD-L1 expression from ctRNA and correlation with subject outcomes.

**Enrollment (planned):**

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 23 subjects will be enrolled in the first stage of Simon's two-stage optimal design. If the study proceeds to the second stage of Simon's two-stage optimal design, an additional 33 subjects will be enrolled in the second stage, for a total of 56 subjects in the phase 2 portion of the study. The maximum total enrollment will the study is 80 subjects.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed pancreatic cancer with progression on or after SoC therapy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anti-cancer treatment and be willing to release the specimen for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period.
7. Must be willing to provide blood samples for exploratory analyses.
8. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
9. Agreement to practice effective contraception for female subjects with 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.

**Exclusion Criteria:**

1. History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
2. History of other active malignancies or brain metastasis except: controlled basal cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, cervical); prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable prostate-specific antigen (PSA) (< 0.2 ng/mL); bulky (≥ 1.5 cm) disease with metastasis in the central hilar area of the chest and involving the pulmonary vasculature. Subjects with a history of another malignancy must have > 5 years without evidence of disease.

3. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
4. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
5. History of organ transplant requiring immunosuppression.
6. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
7. Requires whole blood transfusion to meet eligibility criteria.
8. Inadequate organ function, evidenced by the following laboratory results:
    a. White blood cell (WBC) count < 3,500 cells/$mm^3$
    b. Absolute neutrophil count < 1,500 cells/$mm^3$.
    c. Platelet count < 100,000 cells/$mm^3$.
    d. Hemoglobin < 9 g/dL.
    e. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    f. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    g. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    h. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    i. International normalized ratio (INR) or activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).
9. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
10. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
11. Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
12. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
13. Known hypersensitivity to any component of the study medication(s).
14. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications. See Excluded Medications list.

15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
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.

**Investigational Product, Dosage, and Mode of Administration:**

- Cyclophosphamide 50 mg BID (induction and maintenance)
- Oxaliplatin 40 mg/$m^2$ IV (induction)
- Capecitabine 650 mg/$m^2$ PO BID (maintenance)
- 5-FU 400 mg/$m^2$ over 24 hours as a continuous infusion (induction)
- Leucovorin 20 mg/$m^2$ IV bolus (induction)
- Nab-paclitaxel 125 mg IV (induction and maintenance)
- Bevacizumab 5 mg/kg IV (induction and maintenance)
- Avelumab 10 mg/kg IV(induction and maintenance)
- SBRT 8 Gy (induction)
- ALT-803 10 µg/kg SC (induction and maintenance)
- aNK 2 x $10^9$ cells/dose IV (induction and maintenance)
- Ad5 [E1-, E2b-]-CEA 5 x $10^{11}$ VP/dose SC (induction and maintenance)
- GI-4000 RAS vaccine 40 YU (induction and maintenance)

**Duration of Treatment:**

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

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase), or until they experience progressive disease, unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

**Duration of Follow-up:**

After discontinuation or completion of the study, subjects will be followed every 3 months for 18 months to collect follow-up information, including survival status and any current cancer treatment regimen.

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

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

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

An assessment of pancreatic cancer symptoms will be conducted via PROs using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) instrument on study day 1, every 28 days thereafter, and at the day 28 follow-up visit.

**Exploratory Analysis:**

***Molecular Profiling and Analysis:***

Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Plasma will be collected and circulating tumor RNA (ctRNA) will be isolated. A PCR-based assay (LiquidGenomicsDx) will be used to assess the level of PD-L1 circulating RNA. The levels of PD-L1 ctRNA will be correlated with efficacy outcomes.

**Statistical Methods:**

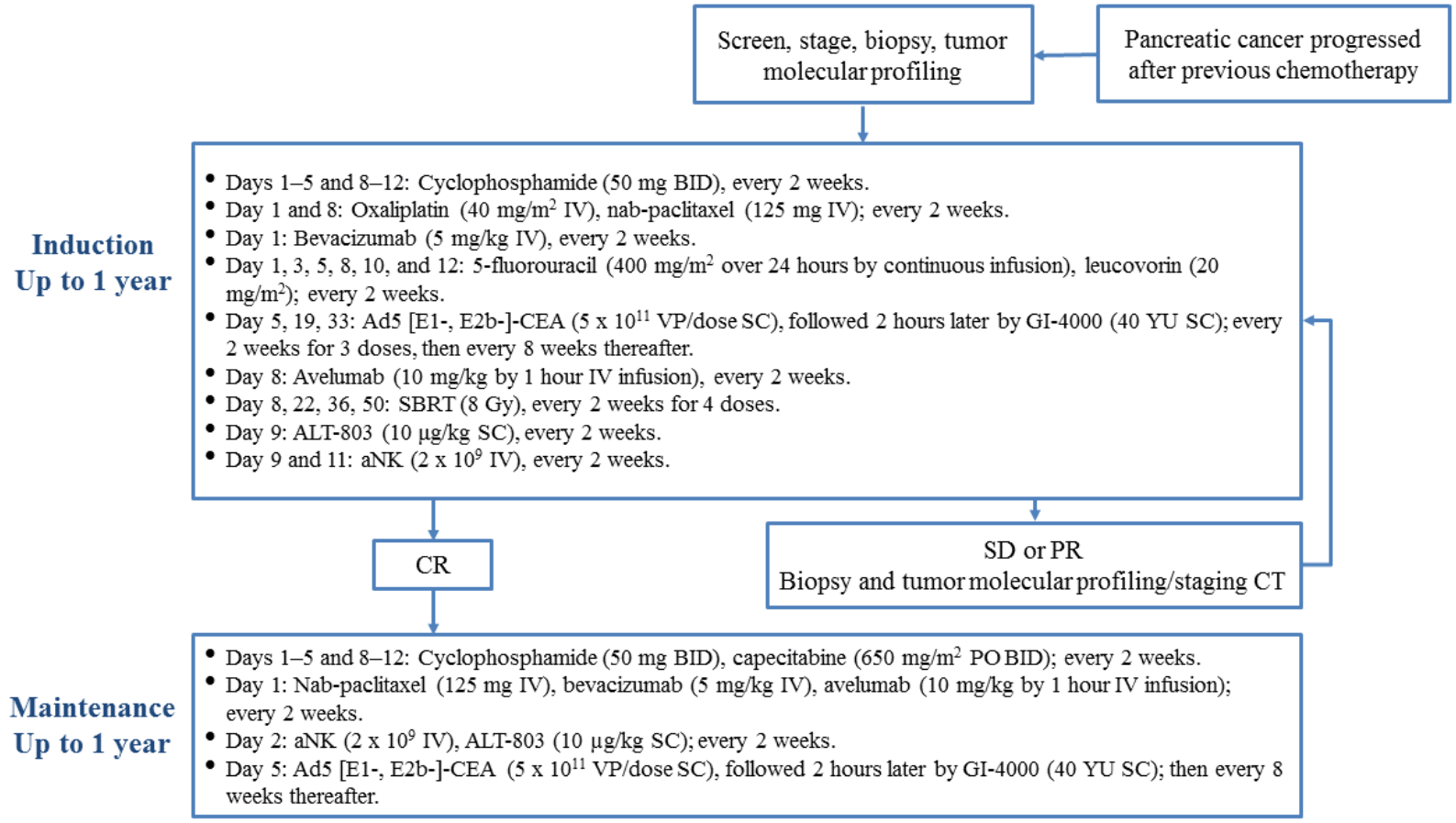
This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with pancreatic cancer patients whose tumors have progressed on or after SoC treatment.

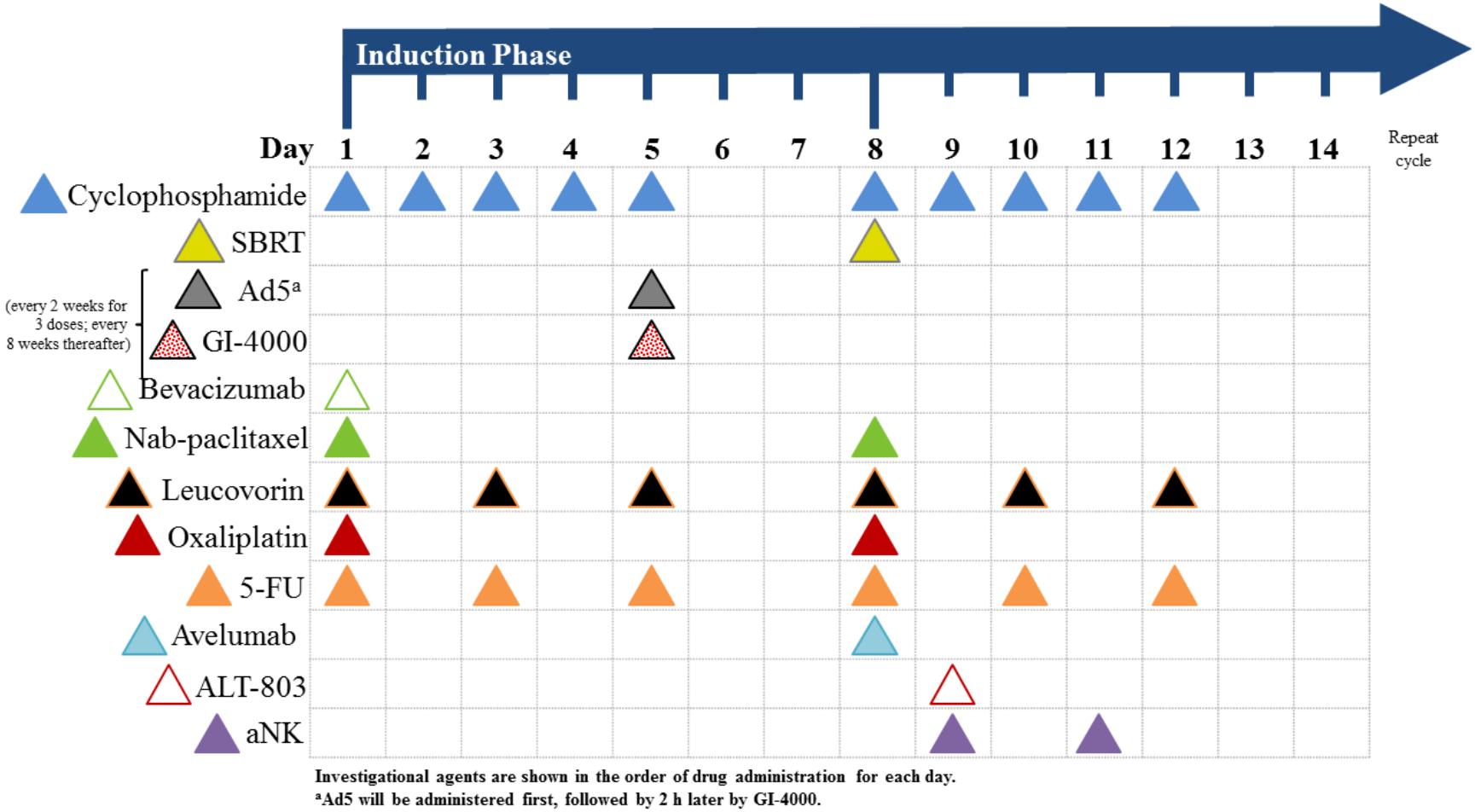
Results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

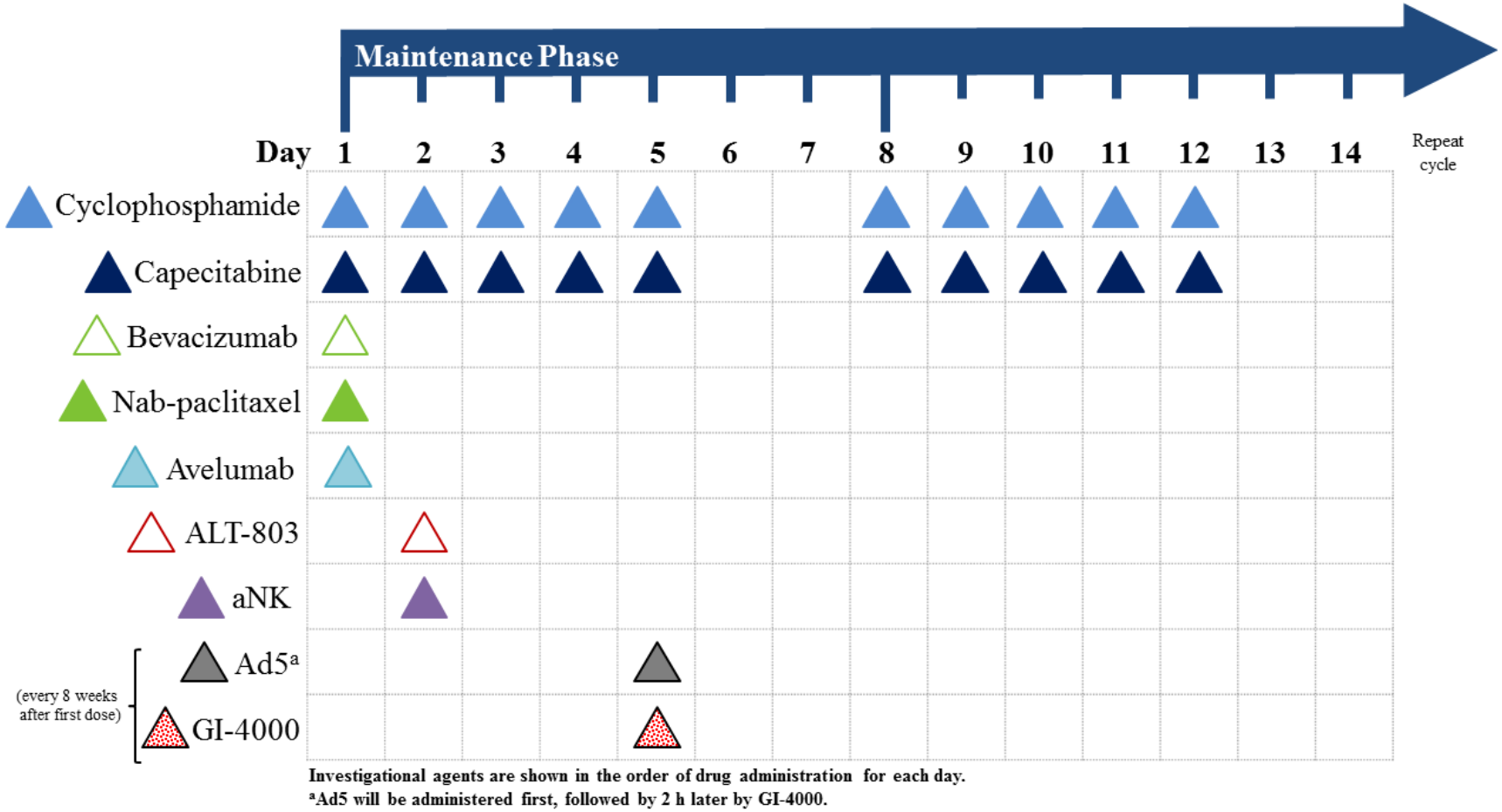
ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will be evaluated similar to ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods. Descriptive statistics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

Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

**Figure 1: Study Treatment Schema**




Induction Phase
Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Repeat cycle
Cyclophosphamide
SBRT
Ad5[a]
GI-4000
(every 2 weeks for 3 doses; every 8 weeks thereafter)
Bevacizumab
Nab-paclitaxel
Leucovorin
Oxaliplatin
5-FU
Avelumab
ALT-803
aNK
Investigational agents are shown in the order of drug administration for each day.
[a]Ad5 will be administered first, followed by 2 h later by GI-4000.




**Investigational agents are shown in the order of drug administration for each day.**
**[a]Ad5 will be administered first, followed by 2 h later by GI-4000.**

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Pancreatic Cancer Vaccine: combination immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy. |
| **Study Number:** | QUILT-3.039 |
| **Version Number:** | 3 |
| **Final Date:** | 03 June 2017 |

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

Signed: _____ Date: 6-3-17

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