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

Study Number:	**QUILT-3.067**
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	21 November 2017

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ad5	Adenovirus serotype-5
β-HCG	β-Human chorionic gonadotropin
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CAR	Chimeric antigen receptor
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CEP	Circulating endothelial progenitor cell
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete response
CRF	Case report form
CSC	Cancer stem cell
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAMP	Damage-associated molecular pattern
DCR	Disease control rate
DC	Dendritic cell
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Independent Drug Safety Monitoring Board
DTH	Delayed-type hypersensitivity
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram

Abbreviation or Specialist Term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ER	Estrogen receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast Cancer
FFPE	Formalin-fixed paraffin-embedded
FOLFIRINOX	Folinic acid (leucovorin), 5-FU, irinotecan, and oxaliplatin
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GTV	Gross tumor volume
GvHD	Graft versus host disease
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSA	Human serum albumin
HSCT	Hematopoietic stem cell transplant
HTD	Highest tested dose
ICD	Immunological cell death
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IMRT	Intensity-modulated radiation therapy
IP	Investigational product

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related response criteria
irSD	Immune-related stable disease
IV	Intravenous
KIR	Killer cell immunoglobulin-like receptor
LDH	Lactate dehydrogenase
LDMC	Low-dose, metronomic cytotoxic chemotherapy
LLD	Longest lesion diameter
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
M2 cells	M2 macrophages
MCB	Master cell bank
MCC	Merkel cell carcinoma
mCRC	Metastatic colorectal cancer
MDSC	Myeloid-derived suppressor cell
MedRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory protein
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUC1	Mucin 1
MV	Megavolt
NANT	Neoantigen, Adenovirus, NK Cell, T cell: delivery of combined immune oncology multi-modality treatment
NCI	National Cancer Institute
NK	Natural killer (cell)
NOD/SCID	Non-obese diabetic severe combined immunodeficiency
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer

Abbreviation or Specialist Term	Explanation
NSG	Non-obese diabetic scid gamma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial response
PRO	Patient-reported outcome
qPCR	Quantitative polymerase chain reaction
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SBRT	Stereotactic body radiotherapy
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCID	Severe combined immunodeficiency
SD	Stable disease
SoC	Standard of Care
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TAA	Tumor-associated antigen
TAM	Tumor-associated macrophage
TME	Tumor microenvironment
TNF	Tumor necrosis factor
Treg	Regulatory T cells
ULN	Upper limit of normal
US	United States

Abbreviation or Specialist Term	Explanation
VEGF	Vascular endothelial growth factor
VP	Viral particles
WBC	White blood cell
YU	Yeast unit

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. 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)

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for IV use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. Omega-3-acid ethyl esters (LOVAZA® Capsules, for oral use)
19. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

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

Approved Products:

10. Avelumab
11. Bevacizumab
12. Capecitabine
13. Cisplatin
14. Cyclophosphamide (anhydrous)
15. Fluorouracil, USP
16. Leucovorin (calcium salt)
17. Paclitaxel, USP
18. Omega-3-acid ethyl esters
19. Radiation

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.067

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

Phase 2

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

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

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

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

withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The maximum time on study treatment, including both the induction and maintenance phases, is 2 years.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, 8 weeks after the start of treatment, and during potential prolonged induction and maintenance phases (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 6 weeks in the induction phase and every 8 weeks in the maintenance phase during routine blood draws for exploratory immunology and ctDNA/ctRNA analyses, as described in Section 6.4.2 and Section 6.4.3, respectively.

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

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. Treatment with all study drugs except GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.5.12, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated RAS oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cisplatin, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-051, and ETBX-061), 5-FU/leucovorin, yeast-based vaccines (GI-4000, GI-6207, GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 3 weeks. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Daily:

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1 and 15, every 3 weeks:

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

Days 1–5 and 15–19, every 3 weeks:

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

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

- Cyclophosphamide (50 mg PO BID)

Days 1 and 8, every 3 weeks:

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

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

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Days 8 and 15 (every 3 weeks):

- Aldoxorubicin HCl (80 mg/m^2 IV on day 8; 30 mg/m^2 IV on day 15)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

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

- haNK (2×10^9 cells/dose IV)

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

- GI-4000, GI-6207, and GI-6301 (40 yeast units [YU]/vaccine/dose SC)

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

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cyclophosphamide, capecitabine, Ad5-based vaccines (ETBX-011, ETBX-051, and ETBX-061), yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 2 weeks.

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

Daily:

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

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg PO BID)

Day 2, every 2 weeks:

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

Day 5, every 8 weeks thereafter:

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} VP/vaccine/dose SC)
- GI-4000, GI-6207, GI-6301 (40 YU/vaccine/dose SC), 2 hours after administration of the Ad5-based vaccines

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

Phase 1b

Primary Endpoint:

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

Secondary Endpoints:

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

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1 and irRC.

Secondary Endpoints:

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

Exploratory Endpoints:

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

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. In the phase 2 portion of the study, 19 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 36 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy or subject has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 750 cells/mm^3.
    b. Platelet count < 75,000 cells/mm^3.
    c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. To control hypertension, it is recommended to first start propranolol SR 80 mg daily prior to initiating other hypertensive medications.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.

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

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 or 30 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	1×10^{11} VP/dose	SC
ETBX-051	1×10^{11} VP/dose	SC
ETBX-061	1×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
GI-6207	40 YU/dose	SC
GI-6301	40 YU/dose	SC
haNK cells	2×10^9 cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2	PO BID
Cisplatin	40 mg/m^2	IV
Cyclophosphamide	50 mg	PO BID
5-FU	1500 mg/m^2	85- to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus

Approved Products	Dosage	Mode of Administration
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
Omega-3-acid ethyl esters	5 g	PO
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

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

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

Duration of Follow-up:

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

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

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

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

Evaluation of Endpoints:

Safety:

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

Efficacy:

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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 TNBC vaccine 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 preliminary efficacy of metronomic combination therapy in subjects with TNBC whose tumors have progressed on or after SoC treatment.

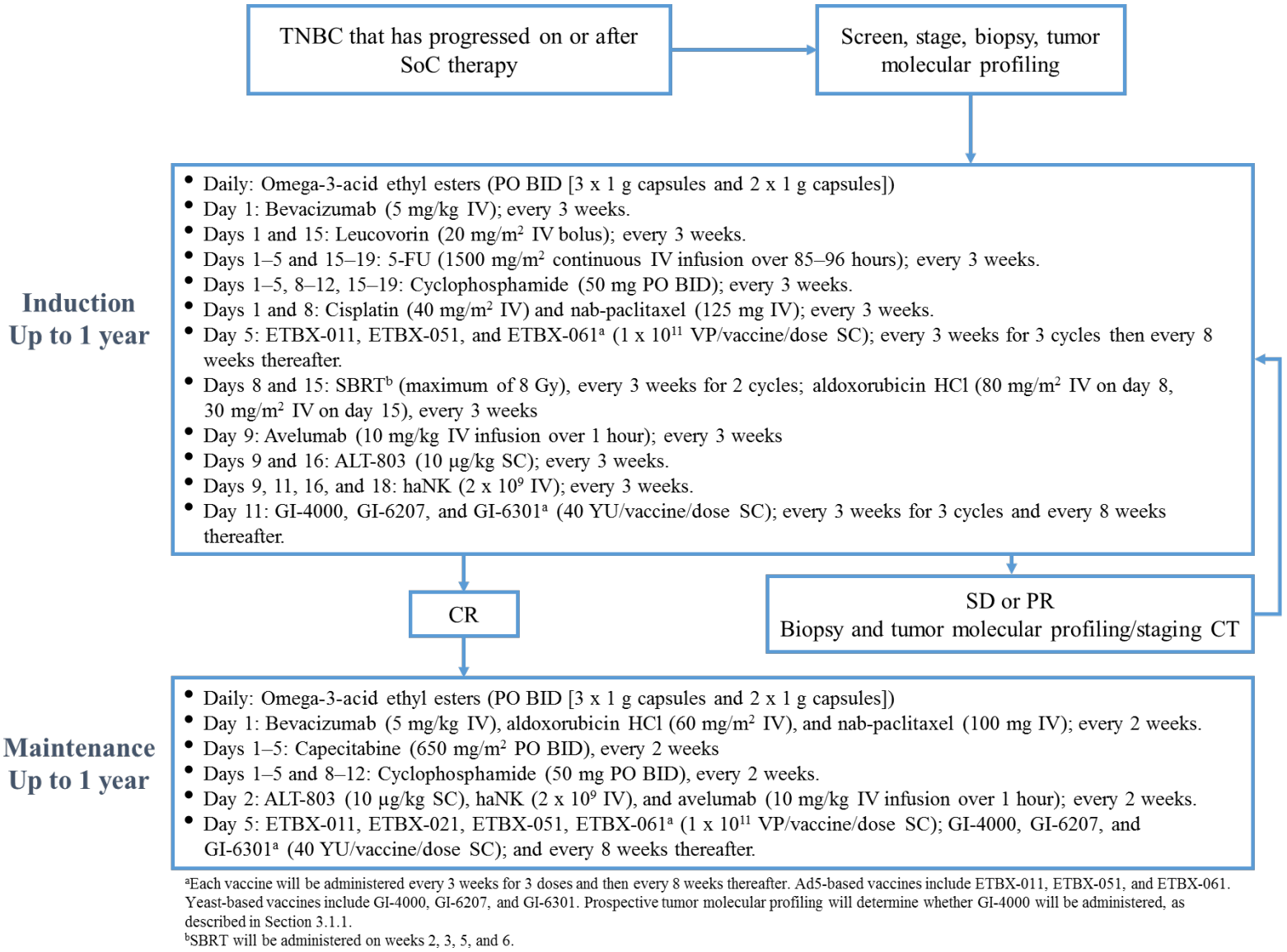
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

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

Figure 1: Study Treatment Schema



[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.

Figure 2: Induction Phase Treatment Schema

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

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.

Figure 3: Maintenance Phase Treatment Schema

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

Capecitabine, cyclophosphamide, and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered on Day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	1
Final Date:	21 November 2017

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

Signed: _____ Date: Nov 21 2017

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

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

Study Number:	**QUILT-3.067**
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	21 November 2017
Version 2	27 December 2017

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human super agonist interleukin-15 (IL-15) complex [also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-CEA [carcinoembryonic antigen] vaccine)
4. 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)

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. Omega-3-acid ethyl esters (LOVAZA® Capsules, for oral use)
19. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

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

Approved Products:

10. Avelumab
11. Bevacizumab
12. Capecitabine
13. Cisplatin
14. Cyclophosphamide (anhydrous)
15. Fluorouracil, USP
16. Leucovorin (calcium salt)
17. Paclitaxel, USP
18. Omega-3-acid ethyl esters
19. Radiation

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.067

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

Phase 2

- The primary objective is to determine the efficacy of the NANT TNBC vaccine regimen as assessed by ORR using RECIST Version 1.1.
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA; and their correlations with subject outcomes.

Study Design:
This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with TNBC who have progressed on or after previous SoC 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. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

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

stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at the Investigator's discretion. Subjects may remain on the maintenance phase of the study for up to 1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The maximum time on study treatment, including both the induction and maintenance phases, is 2 years.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, 8 weeks after the start of treatment, and during potential prolonged induction and maintenance phases (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 6 weeks in the induction phase and every 8 weeks in the maintenance phase during routine blood draws for exploratory immunology and ctDNA/ctRNA analyses, as described in Section 6.4.2 and Section 6.4.3, respectively.

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

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. Treatment with all study drugs except GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.5.12, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated RAS oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cisplatin, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-051, and ETBX-061), 5-FU/leucovorin, yeast-based vaccines (GI-4000, GI-6207, GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 3 weeks. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Daily:

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1 and 15, every 3 weeks:

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

Days 1–5 and 15–19, every 3 weeks:

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

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

- Cyclophosphamide (25 mg PO BID)

Days 1 and 8, every 3 weeks:

- Nab-paclitaxel (125 mg IV)
- Cisplatin (40 mg/m^2 IV over 1 hour)

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

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Days 8 and 15, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV on day 8; 30 mg/m^2 IV on day 15)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

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

- haNK (2×10^9 cells/dose IV)

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

- GI-4000, GI-6207, and GI-6301 (40 yeast units [YU]/vaccine/dose SC)

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

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cyclophosphamide, capecitabine, Ad5-based vaccines (ETBX-011, ETBX-051, and ETBX-061), yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 2 weeks.

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

Daily:

- Omega-3-acid ethyl esters (2 g PO BID)

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

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

Day 5, every 8 weeks thereafter:

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} VP/vaccine/dose SC)
- GI-4000, GI-6207, GI-6301 (40 YU/vaccine/dose SC), 2 hours after administration of the Ad5-based vaccines

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

Phase 1b

Primary Endpoint:

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

Secondary Endpoints:

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

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

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

Exploratory Endpoints:

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

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 19 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 36 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy or subject has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.

10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 1000 cells/mm^3.
    b. Platelet count < 75,000 cells/mm^3.
    c. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
    d. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    e. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    f. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. 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 30 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 or 30 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	1×10^{11} VP/dose	SC
ETBX-051	1×10^{11} VP/dose	SC
ETBX-061	1×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
GI-6207	40 YU/dose	SC
GI-6301	40 YU/dose	SC
haNK cells	2×10^9 cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2	PO BID
Cisplatin	40 mg/m^2	IV
Cyclophosphamide	25 mg	PO BID
5-FU	1500 mg/m^2	85- to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Approved Products	**Dosage**	**Mode of Administration**
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
Omega-3-acid ethyl esters	2 g	PO BID
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

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

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

Duration of Follow-up:

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

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

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

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

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

Efficacy:

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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 TNBC vaccine 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 preliminary efficacy of metronomic combination therapy in subjects with TNBC whose tumors have progressed on or after SoC treatment.

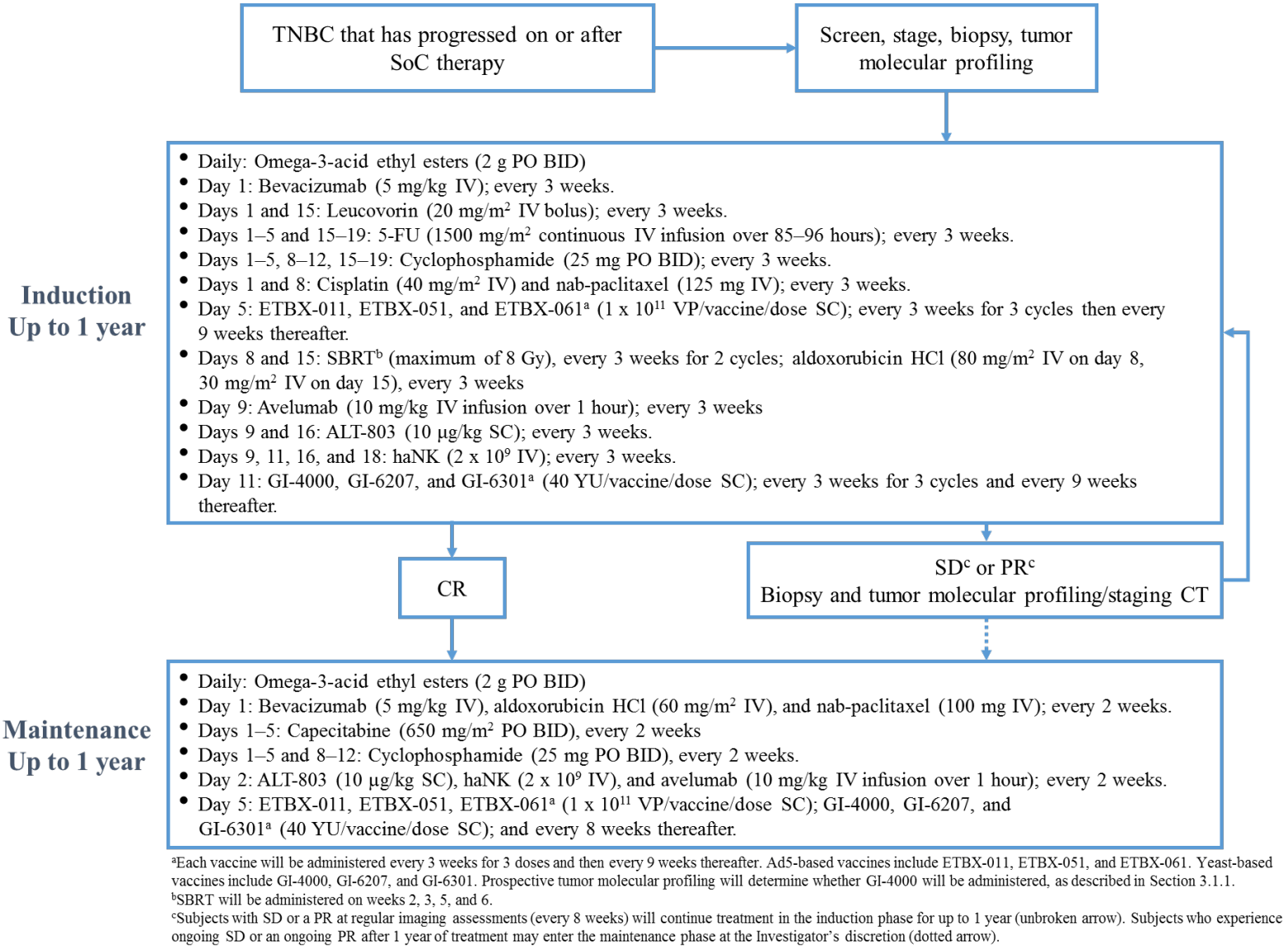
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

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

Figure 1: Study Treatment Schema



[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 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).

Figure 2: Induction Phase Treatment Schema

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

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.

Figure 3: Maintenance Phase Treatment Schema

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

Capecitabine, cyclophosphamide, and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered on Day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	2
Final Date:	27 December 2017

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

Signed: _____ Date: 12-27-17

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

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

Study Number:	**QUILT-3.067**
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	21 November 2017
Version 2	27 December 2017
Version 3	01 March 2018

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human 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-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)

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

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

Approved Products:

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

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:
QUILT-3.067

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

Phase 2

- The primary objective is to determine the efficacy of the NANT TNBC vaccine regimen as assessed by ORR using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of 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 TNBC who have progressed on or after previous SoC 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. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

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

1 year. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The maximum time on study treatment, including both the induction and maintenance phases, is 2 years.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, 8 weeks after the start of treatment, and during potential prolonged induction and maintenance phases (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 6 weeks in the induction phase and every 8 weeks in the maintenance phase during routine blood draws for exploratory immunology and ctDNA/ctRNA analyses, as described in Section 6.4.2 and Section 6.4.3, respectively.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT) of target and non-target lesions in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC). In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. For responding subjects (PR or CR), a confirmatory response assessment should be done at 4 weeks after the initial response.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on formalin-fixed, paraffin-embedded (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.

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)
- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (40 mg/m^2 IV over 1 hour)

Days 1–5, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)
- Cyclophosphamide (25 mg by mouth [PO] twice a day [BID])

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

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

Day 8, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV over 30 minutes)
- Cisplatin (20 mg/m^2 IV over 1 hour)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

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

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

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

- GI-4000, GI-6207, and GI-6301 (40 yeast units [YU]/vaccine/dose SC)

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

Day 15, every 3 weeks:

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

Day 16, every 3 weeks:

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

Day 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles.

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

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

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

Day 5 (± 1 day), every 8 weeks thereafter:

- ETBX-011, ETBX-051, ETBX-061 (1×10^{11} VP/vaccine/dose SC)
- GI-4000, GI-6207, GI-6301 (40 YU/vaccine/dose SC), 2 hours after administration of the Ad5-based vaccines

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

Phase 1b

Primary Endpoint:

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

Secondary Endpoints:

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

- QoL by PROs.

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

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

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

Enrollment (planned):

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 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. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy or subject has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent 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 (ANC) < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
   d. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   e. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   f. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. 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 30 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.

16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	10 µg/kg	SC
ETBX-011	1×10^{11} VP/dose	SC
ETBX-051	1×10^{11} VP/dose	SC
ETBX-061	1×10^{11} VP/dose	SC
GI-4000	40 YU/dose	SC
GI-6207	40 YU/dose	SC
GI-6301	40 YU/dose	SC
haNK cells	2×10^9 cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Bevacizumab	5 mg/kg	IV
Capecitabine	650 mg/m^2 BID	PO
Cisplatin	40 mg/m^2 (day 1); 20 mg/m^2 (day 8)	IV
Cyclophosphamide	25 mg BID (days 1–5, induction) 25 mg daily (days 8–12, induction) 25 mg BID (maintenance)	PO
5-FU	1500 mg/m^2	85- to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

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

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

Duration of Follow-up:

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

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

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

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

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

Efficacy:

ORR and PFS will be assessed by CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. For responding subjects (PR or CR), a confirmatory response assessment should be done at 4 weeks after the initial response. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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 TNBC vaccine 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 preliminary efficacy of metronomic combination therapy in subjects with TNBC whose tumors have progressed on or after SoC treatment.

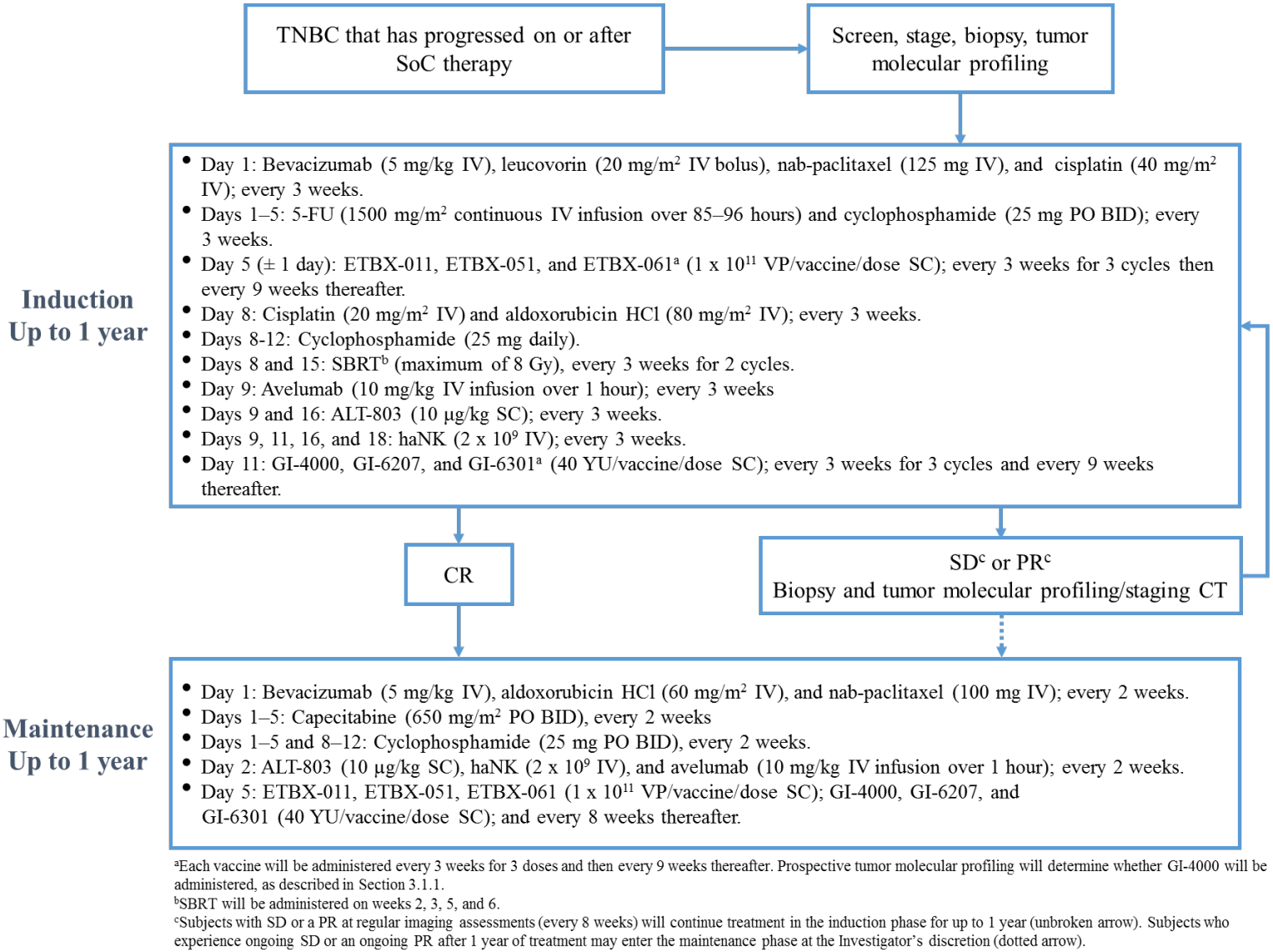
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

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

Figure 1: Study Treatment Schema



[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Prospective tumor molecular profiling will determine whether GI-4000 will be administered, as described in Section 3.1.1.
[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).

Figure 2: Induction Phase Treatment Schema

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

Cyclophosphamide is self-administered on the days indicated.
[a]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.

Figure 3: Maintenance Phase Treatment Schema

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

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Each vaccine will be administered on Day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, 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 will be administered, as described in Section 3.1.1.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	3
Final Date:	01 March 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: March 1 2018

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

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

Study Number:	**QUILT-3.067**
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	21 November 2017
Version 2	27 December 2017
Version 3	01 March 2018
Version 4	02 July 2018

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human 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-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)

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. 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-]-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

Approved Products:

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

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:

QUILT-3.067

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

Phase 2

- The primary objective is to determine the efficacy of the NANT TNBC vaccine regimen as assessed by ORR using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of 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 TNBC who have progressed on or after previous SoC 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. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment will be administered in two phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be discontinued if the subject experiences 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. 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.

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 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC). In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4–6 weeks after the initial response. Subjects who withdraw from the study for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on formalin-fixed, paraffin-embedded (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.

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV), for the first 2 cycles only
- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (40 mg/m^2 IV)

Days 1–5, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)
- Cyclophosphamide (25 mg by mouth [PO] twice a day [BID])

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

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

Day 8, every 3 weeks:

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

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- Avelumab (10 mg/kg IV)
- ALT-803 (15 µg/kg SC)
- 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 (MUC1) (40 yeast units [YU]/vaccine/dose SC)

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

Day 15, every 3 weeks:

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

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles.

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

Day 1, every 2 weeks:

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

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 over 1 hour)
- haNK (2×10^9 cells/dose IV)

Day 5 (± 1 day), every 8 weeks thereafter:

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-051 (Brachyury), ETBX-061 (MUC1) (1×10^{11} VP/vaccine/dose SC)
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), GI-6301 (Brachyury) (40 YU/vaccine/dose SC), 2 hours after administration of the Ad5-based vaccines

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

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 Version 1.1 and irRC.
- QoL by PROs.

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

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

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. 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy or subject has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent 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 (ANC) < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
   d. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   e. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   f. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. 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 30 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ALT-803	15 µg/kg	SC
ETBX-011 (CEA)	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
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
Cisplatin	40 mg/m^2 (day 1); 20 mg/m^2 (day 8)	IV

Cyclophosphamide	25 mg BID (days 1–5) 25 mg daily (days 8–12)	PO
5-FU	1500 mg/m^2	85- to 96-hour continuous IV infusion
Leucovorin	20 mg/m^2	IV bolus
Nab-paclitaxel	125 mg (induction); 100 mg (maintenance)	IV
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

- Induction phase: Up to 1 year.
- Maintenance phase: Up to 1 year.

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

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI scan assessment (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 24 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 (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

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

Efficacy:

ORR and PFS will be assessed by CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-6 weeks after the initial response. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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 TNBC vaccine 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 preliminary efficacy of metronomic combination therapy in subjects with TNBC whose tumors have progressed on or after SoC treatment.

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

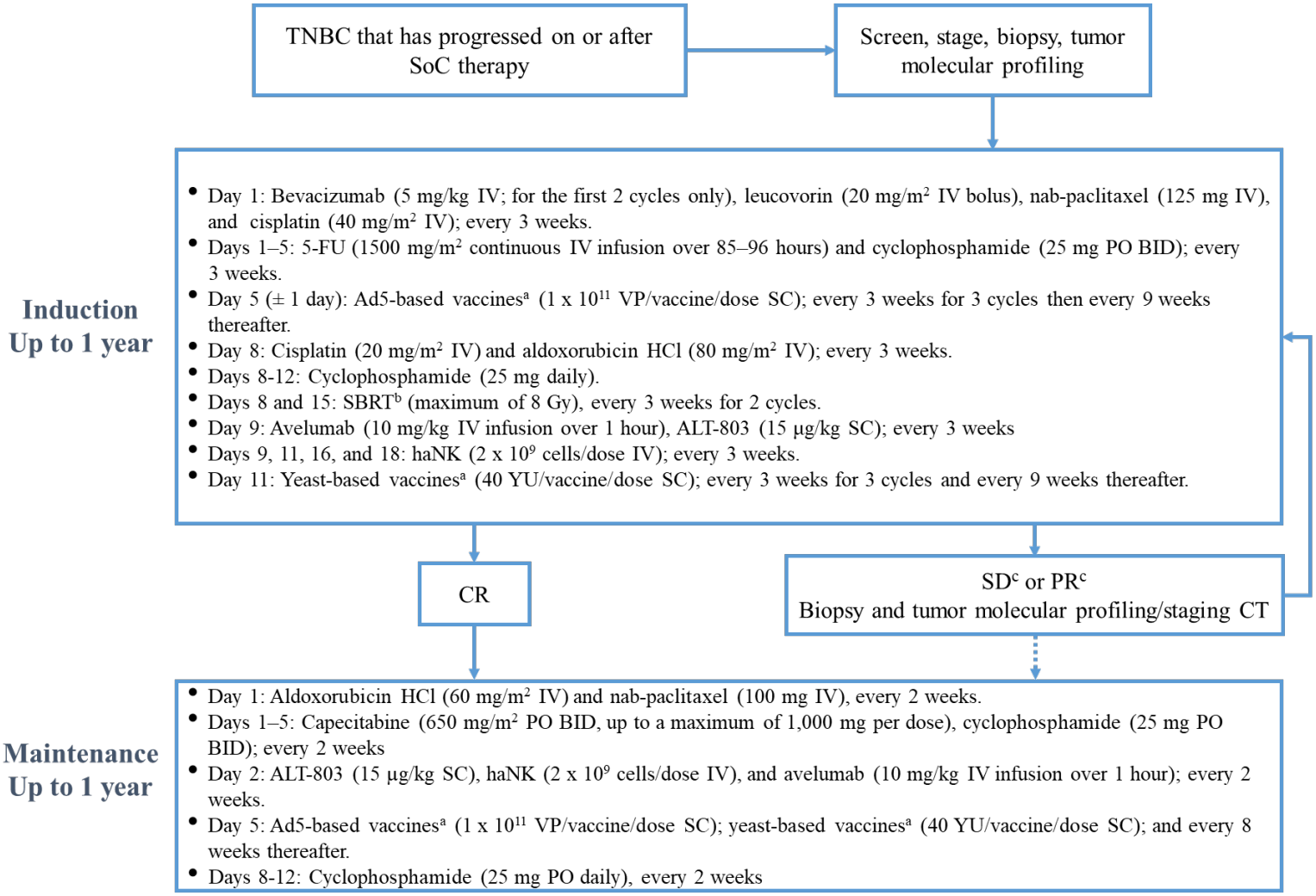
Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, ECHOs, and vital signs.

ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will

be evaluated similar to ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

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

Figure 1: Study Treatment Schema



[a]Ad5-based vaccines include ETBX-011 (CEA), 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 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).

Figure 2: Induction Phase Treatment Schema

	Cycle 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	●																				
5-FU	●	●	●	●	●																
Nab-paclitaxel	●																				
Cisplatin	●							●													
Ad5-based vaccines[b]					●																
Aldoxorubicin								●													
SBRT[c]								●							●						
Avelumab									●												
ALT-803									●												
haNK									●		●					●		●			
Yeast-based vaccines[a]											●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●									

Cyclophosphamide is self-administered on the days indicated.
[a]Bevacizumab will be administered for the first 2 cycles only.
[b]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.
[c]SBRT will be administered on weeks 2, 3, 5, and 6.

Figure 3: Maintenance Phase Treatment Schema

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

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Each vaccine will be administered on Day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	4
Final Date:	02 July 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: July 2, 2018

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

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

Study Number:	**QUILT-3.067**
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	21 November 2017
Version 2	27 December 2017
Version 3	01 March 2018
Version 4	02 July 2018
Version 5	01 August 2018

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human 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-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)

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. 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-]-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

Approved Products:

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

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:

QUILT-3.067

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

Phase 2

- The primary objective is to determine the efficacy of the NANT TNBC vaccine regimen as assessed by ORR using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of 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 TNBC who have progressed on or after previous SoC 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. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment will be administered in two phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be discontinued if the subject experiences 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. 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.

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 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC). In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4–6 weeks after the initial response. Subjects who withdraw from the study for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on formalin-fixed, paraffin-embedded (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.

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year.

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV), for the first 2 cycles only
- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (32 mg/m^2 IV)

Days 1–5, every 3 weeks:

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

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

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

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-051 (Brachyury), 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 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

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 up to 4 cycles)

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 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 up to 4 cycles)

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 2-week cycles.

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

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

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)

Day 2, every 2 weeks:

- ALT-803 (15 µg/kg SC)
- Avelumab (10 mg/kg IV over 1 hour)
- haNK (2×10^9 cells/dose IV)

Day 5 (± 1 day), every 8 weeks thereafter:

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

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

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 Version 1.1 and irRC.
- QoL by PROs.

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

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

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. 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy or subject has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent 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 (ANC) < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
   d. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has

documented Gilbert's syndrome).
   e. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   f. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. 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 30 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	100 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-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
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
Cisplatin	32 mg/m^2	IV
Cyclophosphamide	25 mg BID (days 1–5) 25 mg daily (days 8–12)	PO
5-FU	1500 mg/m^2	85- 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
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

- Induction phase: Up to 1 year.
- Maintenance phase: Up to 1 year.

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

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI scan assessment (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 24 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 (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

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

Efficacy:

ORR and PFS will be assessed by CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-6 weeks after the initial response. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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.

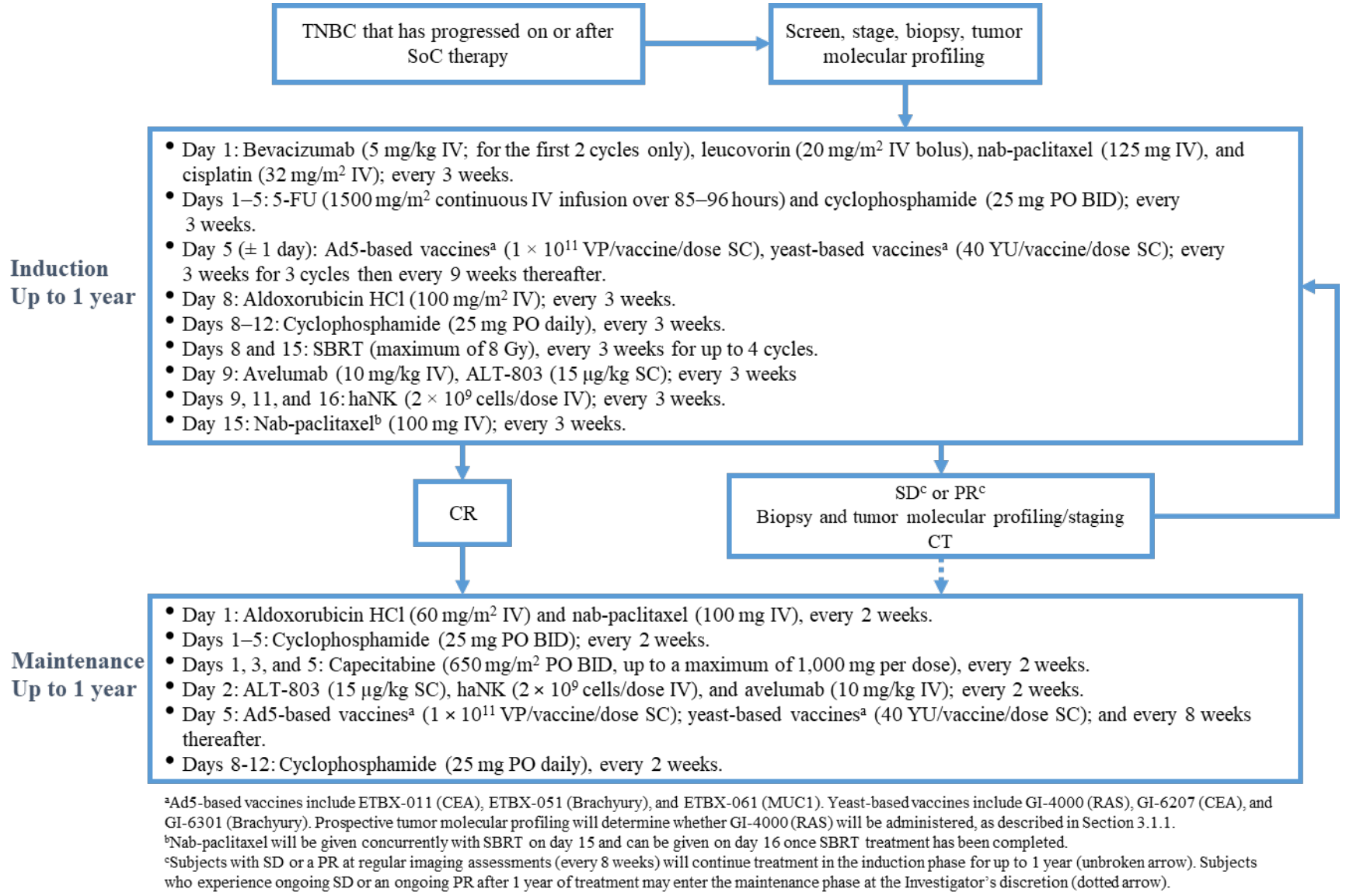
Exploratory Analysis:

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 TNBC vaccine 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 preliminary efficacy of metronomic combination therapy in subjects with TNBC whose tumors have progressed on or after SoC treatment. Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, ECHOs, and vital signs. ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will be evaluated similar to ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented. Correlations of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Ad5-based vaccines include ETBX-011 (CEA), 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]Nab-paclitaxel will be given concurrently with SBRT on day 15 and can be given on day 16 once SBRT treatment has been completed.
[c]Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).

Figure 2: Induction Phase Treatment Schema

	Cycle 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	●																				
5-FU	●	●	●	●	●																
Nab-paclitaxel	●														●						
Cisplatin	●																				
Ad5-based vaccines[b]					●																
Yeast-based vaccines[b]					●																
Aldoxorubicin HCl								●													
SBRT[c]								●							●						
Avelumab									●												
ALT-803									●												
haNK									●		●					●					
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●									

[a]Bevacizumab will be administered for the first 2 cycles only.
[b]Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.
[c]SBRT will be administered for up to 4 cycles.

Figure 3: Maintenance Phase Treatment Schema

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

[a]Each vaccine will be administered on day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	5
Final Date:	01 August 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: 8-1-2018

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

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

Study Number:	**QUILT-3.067**
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	21 November 2017
Version 2	27 December 2017
Version 3	01 March 2018
Version 4	02 July 2018
Version 5	01 August 2018
Version 6	25 March 2019

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(R2)) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

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

Name of Approved Products:

10. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
11. Bevacizumab (AVASTIN® solution for IV infusion)
12. Capecitabine (XELODA® tablets, for oral use)
13. Cisplatin (CISplatin injection)
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. Stereotactic Body Radiation Therapy (SBRT)

Name of Active Ingredients

Investigational Products:

1. Aldoxorubicin HCl
2. Ad5 [E1-, E2b-]-CEA
3. Ad5 [E1-, E2b-]-Brachyury
4. Ad5 [E1-, E2b-]-MUC1
5. 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)
6. Recombinant yeast-based vaccine expressing the full length human 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
7. Recombinant yeast-based vaccine expressing the human Brachyury oncoprotein
8. NK-92 [CD16.158V, ER IL2] cells
9. N-803, recombinant human superagonist IL-15 complex
   (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Approved Products:

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

Title of Study:

NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.

Study Number:

QUILT-3.067

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 TNBC vaccine regimen in subjects with TNBC who have progressed on or after standard-of-care (SoC) therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses; and their correlations with subject outcomes.

Phase 2

- The primary objective is to determine the efficacy of the NANT TNBC vaccine regimen as assessed by ORR using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to obtain additional measures of safety and efficacy (PFS, OS, DOR, DCR, and QoL by PROs).
- Exploratory objectives include the assessment of tumor molecular profiles, therapy-induced changes in immune responses; 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 TNBC who have progressed on or after previous SoC 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. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment will be administered in two phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be discontinued if the subject experiences 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. 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.

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 analyses, as described in Section 6.4.2.

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 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related response criteria (irRC). In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4–6 weeks after the initial response. Subjects who withdraw from the study for reasons other than progression are encouraged not to initiate another anticancer treatment unless/until progression has been documented at a follow-up visit.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status, and will be used to determine whether GI-4000 will be administered. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on formalin-fixed, paraffin-embedded (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.

Induction Phase:

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year.

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV), for the first 2 cycles only
- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (32 mg/m^2 IV)

Days 1–5, every 3 weeks:

- 5-FU (1500 mg/m^2 continuous IV infusion over 85–96 hours)
- Cyclophosphamide (25 mg by mouth [PO] twice a day [BID])

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

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-051 (Brachyury), 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 will be administered, as described above. GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available.

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 up to 4 cycles)

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- N-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 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 up to 4 cycles)

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Maintenance Phase:

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The maintenance phase will consist of repeated 4-week cycles consisting of 2 weeks of treatment followed by a 2-week rest period.

Each cycle will consist of the following dosing regimen:

Day 1, every 4 weeks:

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

Days 1–5, every 4 weeks:

- Cyclophosphamide (25 mg PO BID)

Days 1, 3, and 5, every 4 weeks:

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

Day 2, every 2 weeks:

- N-803 (15 µg/kg SC)
- Avelumab (10 mg/kg IV over 1 hour)
- haNK (2×10^9 cells/dose IV)

Day 5 (± 1 day), every 8 weeks thereafter:

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

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

Days 8–12, every 4 weeks:

- Cyclophosphamide (25 mg PO daily)

If a subject has had a dose reduction for any agent in the induction phase and that dose is lower than the maintenance phase starting dose for that agent, the subject may continue receiving the lower dose in the maintenance phase.

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 Version 1.1 and irRC.
- QoL by PROs.

Exploratory Endpoints:

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

Phase 2

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

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

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. 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 32 subjects will be enrolled in the second stage, for a total of 55 subjects in the phase 2 portion of the study. The maximum total enrollment for the study is 79 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 metastatic or unresectable TNBC that has either progressed on or after anthracycline-based chemotherapy (or other approved standard of care therapy) or subject

has refused anthracycline-based chemotherapy, or other taxane- and platinum-based therapies. TNBC is defined as breast cancer that lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent 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 (ANC) < 1,000 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
   d. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   e. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).

f. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. 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 30 days prior to initiation of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	100 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ETBX-011 (CEA)	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 1,000 mg per dose	PO
Cisplatin	32 mg/m^2	IV
Cyclophosphamide	25 mg BID (days 1–5) 25 mg daily (days 8–12)	PO
5-FU	1500 mg/m^2	85- 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
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

- Induction phase: Up to 1 year.
- Maintenance phase: Up to 1 year.

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

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI scan assessment (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)

Subjects should be followed until either death (any cause) or for a minimum of 24 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 (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

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

Efficacy:

ORR and PFS will be assessed by CT of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. In order to document PD, unscheduled tumor assessments may be done if the Investigator observes any signs and symptoms of PD. 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, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-6 weeks after the initial response. OS, DOR, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) 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 TNBC vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

Statistical Methods:

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

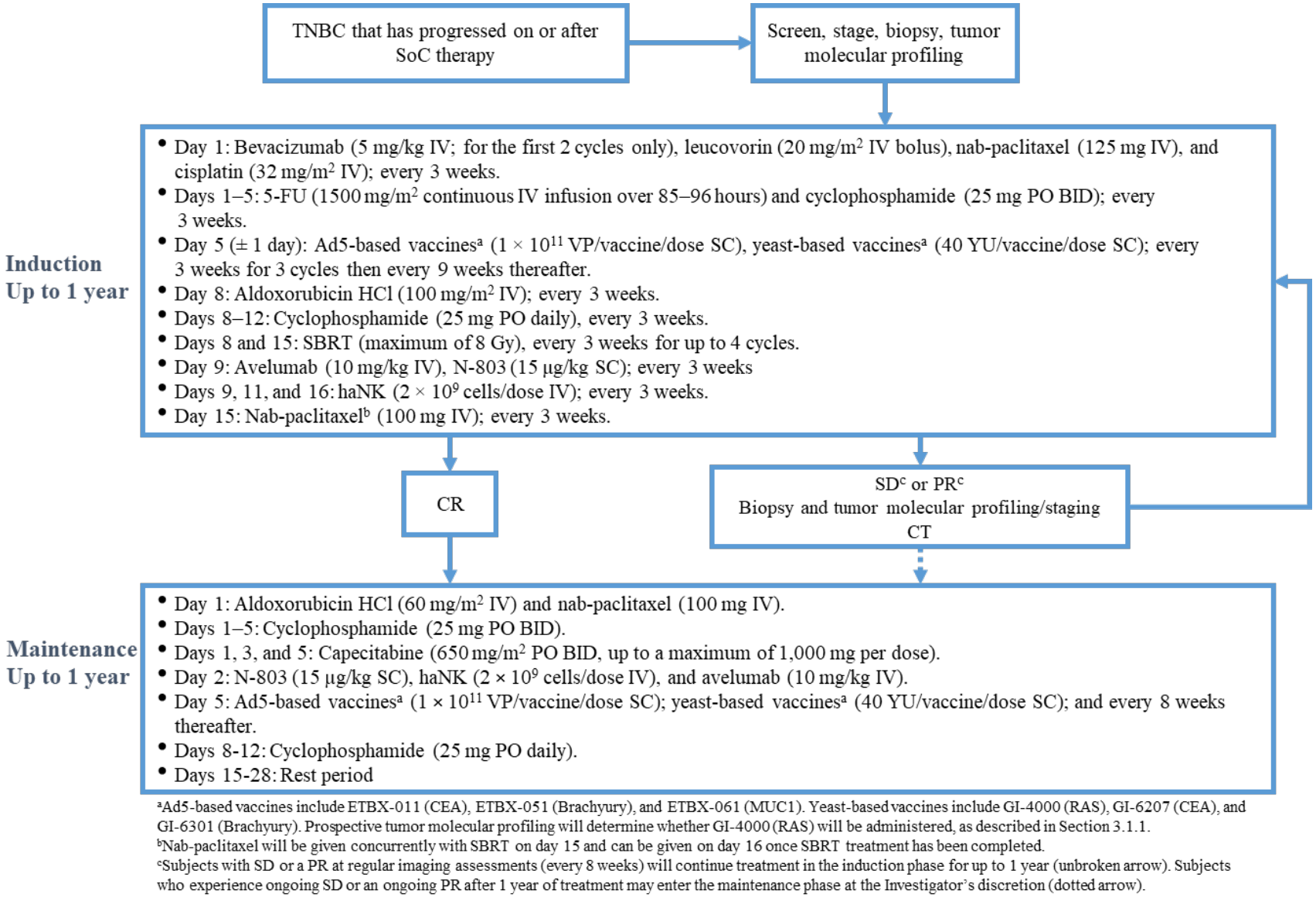
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

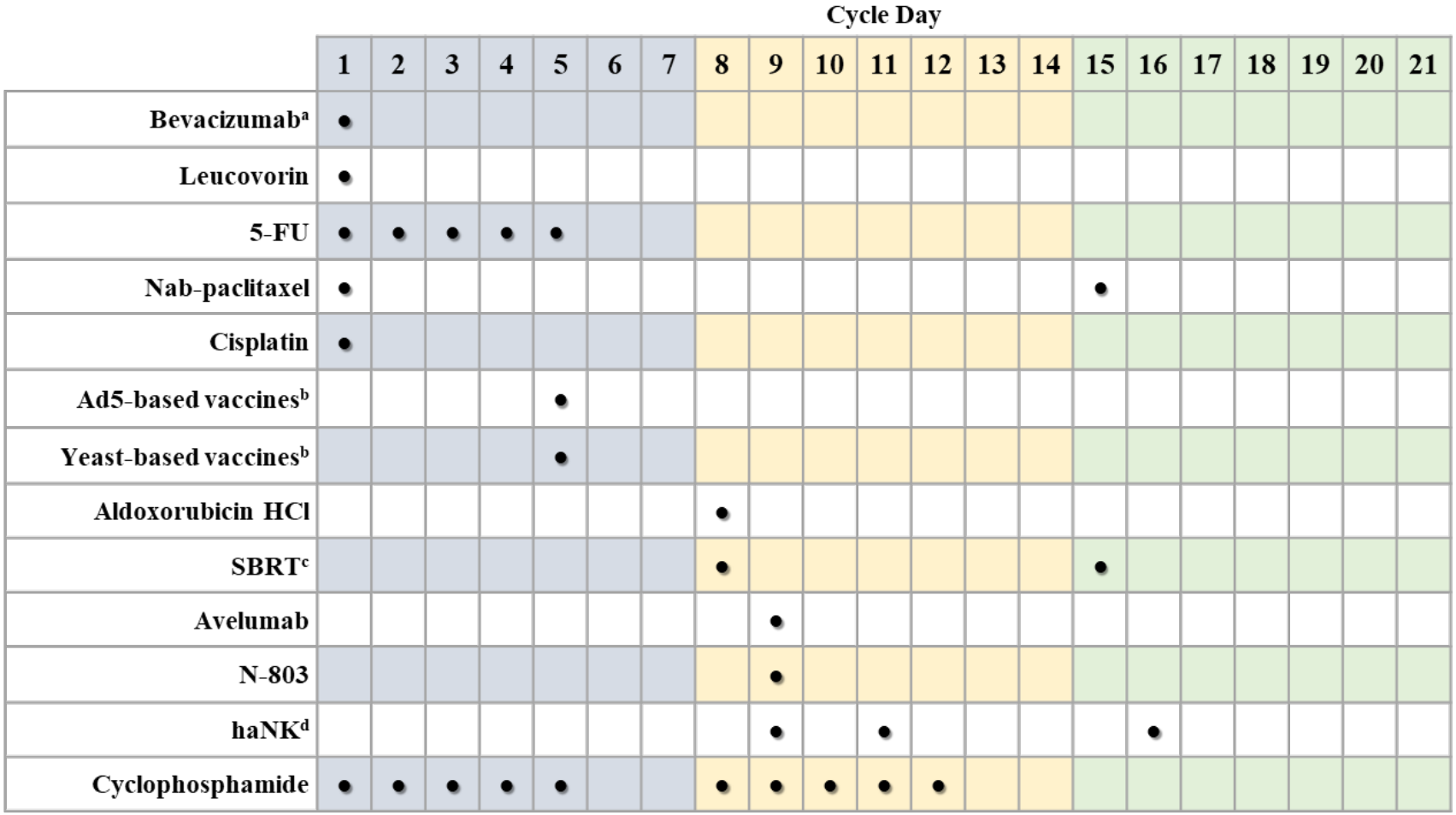
Correlations of tumor molecular profiles and therapy-induced changes in immune responses with subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]Ad5-based vaccines include ETBX-011 (CEA), 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]Nab-paclitaxel will be given concurrently with SBRT on day 15 and can be given on day 16 once SBRT treatment has been completed.
[c]Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).

Figure 2: Induction Phase Treatment Schema



[a] Bevacizumab will be administered for the first 2 cycles only.
[b] Each vaccine will be administered every 3 weeks for 3 doses and then every 9 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.
[c] SBRT will be administered for up to 4 cycles.
[d] A -1 day window is allowed for day 16 haNK administration.

Figure 3: Maintenance Phase Treatment Schema

	Cycle Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-28
Aldoxorubicin HCl	●														REST
Nab-paclitaxel	●														
Avelumab		●													
N-803		●													
haNK		●													
Ad5-based vaccines[a]					●										
Yeast-based vaccines[a]					●										
Capecitabine	●		●		●										
Cyclophosphamide	●	●	●	●	●			●	●	●	●	●			

[a]Each vaccine will be administered on day 5 and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), 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.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with TNBC who have progressed on or after standard-of-care therapy.
Study Number:	QUILT-3.067
Version Number:	6
Final Date:	25 March 2019

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: 3-25-2019

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