NANT COLORECTAL CANCER (CRC) VACCINE: A PHASE 1B/2 TRIAL OF THE NANT CRC VACCINE VS REGORAFENIB IN SUBJECTS WITH METASTATIC CRC WHO HAVE BEEN PREVIOUSLY TREATED WITH STANDARD-OF-CARE (SOC) THERAPY

Study Number:	**QUILT-3.071**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
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Protocol Version	**Date**
Version 1	24 April 2018

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

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

Name of Approved Products:

1. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
2. Capecitabine (XELODA® tablets, for oral use)
3. Cetuximab (ERBITUX® injection, for IV infusion)
4. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
5. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
6. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
7. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
8. Oxaliplatin (ELOXATIN® injection for IV use)
9. Regorafenib (STIVARGA® tablets, for oral use)
10. Stereotactic body radiation therapy (SBRT)
11. Trastuzumab (HERCEPTIN® injection, for IV use)

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-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human Brachyury oncoprotein
10. NK-92 [CD16.158V, ER IL2] cells

Approved Products

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

Title of Study:
NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy

Study Number:
QUILT-3.071

Study Phase:
Phase 1b/Phase 2 (randomized and single-arm [using Simon's two-stage optimal design])

Study Objectives:

Phase 1b

- The primary objective is to evaluate the overall safety profile of the NANT CRC vaccine regimen in subjects with recurrent or metastatic CRC who have been previously treated with SoC therapy that included fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF inhibitor, and an anti-EGFR therapy if *RAS* wild-type.
- 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

Randomized component – The randomized component of the phase 2 portion of the study will compare the NANT CRC Vaccine regimen to regorafenib monotherapy in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy that did not include regorafenib.

- The primary objective is to compare efficacy as assessed by PFS using RECIST Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to compare safety and additional measures of efficacy (PFS by irRC, ORR, 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.

Single-arm component – The single-arm component of the phase 2 portion of the study will evaluate the NANT CRC Vaccine regimen in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy and regorafenib.

- The primary objective is to evaluate the efficacy of the NANT CRC vaccine regimen as assessed by ORR using RECIST Version 1.1 based on BICR.
- Secondary objectives are to evaluate safety and additional measures of efficacy (ORR by irRC, 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 recurrent or metastatic CRC who have previously received SoC therapy. The phase 2 portion of the study will consist of both a single-arm component and a randomized component.

In phase 1b, the NANT CRC Vaccine will be assessed for safety. 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 NANT CRC Vaccine treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable. In total, 6 to 24 subjects will be enrolled in the phase 1b portion of the study.

In the randomized component of the phase 2 portion, subjects who have received SoC therapy that did not include regorafenib for recurrent or metastatic CRC will be randomized to receive either the NANT CRC Vaccine or regorafenib monotherapy. Randomization will be stratified by tumor sidedness (left vs right), performance status (ECOG 0 vs 1), and *RAS* mutational status (positive vs negative). For the regorafenib arm of the randomized portion, subjects who progress on or after discontinuing regorafenib may be enrolled in the single-arm component described below after a 14-day washout period.

The single-arm component of the phase 2 portion will enroll subjects who have progressed or experienced unacceptable toxicity on SoC and regorafenib, and subjects who have progressed on or after regorafenib treatment in the randomized phase 2 portion of this study.

The NANT CRC Vaccine regimen will be administered in 2 phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. 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 and Sponsor's discretion. Subjects may remain in the maintenance phase of the study for up to 1 year. The time on NANT CRC Vaccine treatment, including both the induction and maintenance phases, is up to 2 years.

In the randomized component of the phase 2 portion of the study, the regorafenib arm will self-administer regorafenib every day for the first 21 days of every 28-day treatment cycle.

At any time during the trial, treatment with the NANT CRC Vaccine or regorafenib will be discontinued if 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.

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

For all subjects, 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 treatment periods (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 4 or 8 weeks 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 for all subjects. Tumor response will be assessed every 8 or 12 weeks until progression occurs, regardless of the treatment administered, 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 performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. 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.

All subjects will be tested for *RAS* mutations. In the randomized component of the phase 2 study, *RAS* mutational status will be used in stratifying subjects during randomization.

For subjects treated with the NANT CRC Vaccine, *RAS* mutational status will be used to determine which subjects will receive GI-4000. Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing.

In addition, for subjects treated with the NANT CRC Vaccine, prospective tumor molecular profiling will be conducted to inform *HER2* expression and will be used to determine whether ETBX-021 and trastuzumab will be administered. Subjects will receive ETBX-021 and trastuzumab if their tumor is HER2-positive (IHC 3+ or FISH positive), as determined by FDA-approved diagnostic tests. All other agents in the NANT Cancer Vaccine regimen will be administered regardless of tumor molecular profile.

NANT CRC Vaccine: Induction Phase

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

Day 1, every 3 weeks:

- Leucovorin (20 mg/m^2 IV bolus)
- Nab-paclitaxel (125 mg IV)
- Oxaliplatin (40 mg/m^2 IV over 1 hour)

Days 1–5, every 3 weeks:

- 5-FU (1,500 mg/m^2 continuous IV infusion over 85–96 hours)
- Cyclophosphamide (25 mg by mouth [PO] twice a day [BID])

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

- ETBX-011, ETBX-021, ETBX-051, and ETBX-061
  (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])

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

Day 8, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m^2 IV over 30 minutes)
- Oxaliplatin (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)
- Trastuzumab (2 mg/kg IV infusion)

Prospective tumor molecular profiling will determine whether trastuzumab will be administered, as described above.

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)

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

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

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)
- Cetuximab (250 mg/m^2 IV)
- Trastuzumab (2 mg/kg IV infusion)

  Prospective tumor molecular profiling will determine whether trastuzumab will be administered, as described above.

Day 18, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

NANT CRC Vaccine: 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, as follows:

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)

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Cetuximab (250 mg/m^2 IV)
- Trastuzumab (2 mg/kg IV)
- ALT-803 (10 µg/kg SC) (at least 30 minutes prior to haNK infusion)
- haNK (2×10^9 cells/dose IV)

  Prospective tumor molecular profiling will determine whether trastuzumab will be administered, as described above.

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

- ETBX-011, ETBX-021, 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 Ad-5 based vaccines

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

Days 8-12, every 2 weeks

- Cyclophosphamide (25 mg PO daily)

Phase 1b

Primary Endpoints:

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

Secondary Endpoints:

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

irRC.

- QoL by PROs.

Exploratory Endpoints:

- 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

Randomized Component

Primary Endpoint:

- PFS by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

- 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.

Single-Arm Component

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.

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

Exploratory Endpoints:

- 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.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC vaccine regimen or regorafenib monotherapy. During the trial, 120 subjects are expected to accrue 96 PFS events. An interim analysis is planned once 50% of the PFS events have accrued (48 events). Based on the interim analysis, the study sample size may be increased to a maximum of 240 subjects.

In the phase 2 single-arm component of the study, 27 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 41 subjects will be enrolled in the second stage, for a total of 68 subjects in the phase 2 single-arm component of the study.

The maximum total enrollment for the study is 332 subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed recurrent or metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild-type, an anti-EGFR therapy; or subjects who are ineligible for these therapies.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available,

the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Phase 2 single-arm component only

11. Must have progressed on or after regorafenib treatment in the randomized phase 2 portion of the study OR progressed or experienced unacceptable toxicity on SoC and regorafenib prior to enrollment on the study.

Exclusion Criteria:

1. Microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient tumors eligible for, but not yet treated with, a PD-1 inhibitor.
2. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drugs used in this study or that would put the subject at high risk for treatment-related complications.
3. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
4. History of organ transplant requiring immunosuppression.
5. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
6. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3.
    b. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
    c. Platelet count < 75,000 cells/mm^3.
    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 (ALP) 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.

7. 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.
8. Serious myocardial dysfunction defined by echocardiogram (ECHO) as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
9. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
10. Positive results of screening test for human immunodeficiency virus (HIV).
11. 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.
12. Known hypersensitivity to any component of the study medication(s).
13. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
14. 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.
15. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
16. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
17. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
18. Concurrent participation in any interventional clinical trial.
19. Pregnant and nursing women.

Phase 2 randomized component only

20. Prior regorafenib treatment.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	80 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV over 30 minutes
ALT-803	10 μg/kg	SC
ETBX-011	1×10^{11} VP/dose	SC
ETBX-021	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	2×10^9 cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Capecitabine	650 mg/m^2 BID up to a maximum of 1,000 mg per dose	PO
Cetuximab	250 mg/m^2	IV
Cyclophosphamide	25 mg BID (days 1-5) 25 mg daily (days 8-12)	PO
5-FU	1,500 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
Oxaliplatin	40 mg/m^2 (day 1 of induction); 20 mg/m^2 (day 8 of induction)	IV
Regorafenib	160 mg	PO
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation
Trastuzumab	2 mg/kg	IV

Duration of Treatment:

NANT CRC Vaccine (Experimental Arm)

- 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 PD, unacceptable toxicity (not correctable with dose reduction), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Regorafenib (Control Arm)

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

Subjects that experience PD on or after treatment with regorafenib in the phase 2 randomized component of the study may be subsequently treated with the NANT CRC Vaccine in the phase 2 single-arm component of the study.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed until either death (any cause) or 24 months past administration of the first IP, whichever comes first, as follows:

- 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 24 months past administration of the first dose of chemotherapy to the last subject enrolled in the study, whichever comes first.

Following documented PD, 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 (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:

Regorafenib:
Regorafenib treatment will consist of repeated 4-week cycles for a maximum treatment period of 2 years, as follows:

Days 1-21, every 4 weeks:

- Regorafenib (160 mg PO)

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:

PFS and ORR will be assessed by CT, MRI, or PET-CT of target and non-target lesions every 8 or 12 weeks until progression occurs regardless of the treatment administered and will be evaluated in accordance with RECIST Version 1.1 and irRC. In order to document PD, unscheduled tumor assessments may be done if the investigator observes any signs and symptoms of PD. For responding subjects (PR or CR), a confirmatory response assessment should be done at 4 weeks after the initial response.

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C) instrument. Assessments will occur at screening and prior to treatment on day 1, every 4 or 12 weeks thereafter, and at the end-of-treatment (EOT) visit.

Exploratory Analyses:

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 CRC vaccine regimen and regorafenib monotherapy 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 evaluate the safety and efficacy of metronomic combination therapy in subjects with recurrent or metastatic CRC who have failed SoC therapy.

Six to 24 subjects will be enrolled in the phase 1b portion of the study.

In the phase 2 single-arm component of the study, ORR based on RECIST Version 1.1 will be evaluated using Simon's two-stage optimal design.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC vaccine regimen or regorafenib monotherapy. A total of 120 subjects are expected to accrue 96 PFS events during the trial with a 12-month enrollment period and 12 months of follow-up after the last subject is enrolled. Based on median PFS of 2 and 4 months for regorafenib and the NANT CRC Vaccine, respectively, a 20% lost-to-follow-up rate, and a 5% type 1 error, 120 subjects with 96 PFS events has a power of 90% to detect a hazard ratio (HR) of 0.50.

In the phase 2 randomized component of the study, an interim analysis is planned once 50% of the PFS events have accrued (48 events). The Lan DeMets/O'Brien Fleming spending function will be used for the interim analysis which allocates a 0.3% and 4.9% type 1 error rate to the interim and final PFS analyses, respectively. The trial may be stopped early for strong efficacy if the interim PFS analysis shows superiority (ie, $p < 0.003$). The trial may be stopped early for futility if the interim PFS analysis displays a conditional power < 15%. Based on the interim PFS analysis, the study sample size for the randomized phase 2 component may be increased to a maximum of 240 subjects using the "Promising Zone" methodology for an adaptive sample size increase.

The interim analysis will be performed by an independent statistician separate from the study team. The interim analysis results will not be shared with the study team during the conduct of the study. The interim analysis results will be presented to the Independent Data Monitoring Committee (IDMC) who will make recommendations to the study team whether to stop the study for efficacy or futility, or increase the study sample size. For the NANT CRC Vaccine regimen, safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. For the regorafenib treatment, safety results will be presented for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimens.

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.

PFS will be analyzed using Kaplan-Meier methods. The median PFS (and 95% confidence interval [CI]) will be summarized. PFS Kaplan-Meier curves will be presented. For the phase 2 randomized component, comparison of PFS between the NANT CRC Vaccine regimen and regorafenib monotherapy will be based on the stratified log-rank test, stratified by tumor sidedness, performance status, and *RAS* mutational status. PFS assessed by RECIST Version 1.1 will be the primary PFS analysis and PFS assessed by irRC will be a secondary analysis.

OS and DOR will be analyzed in the same manner as PFS.

ORR (and 95% CI) will be summarized. For the phase 2 randomized component, comparison of ORR between the NANT CRC Vaccine regimen and regorafenib monotherapy will be based on the stratified Fisher exact test, stratified by tumor sidedness, performance status, and *RAS* mutational status. ORR assessed by RECIST Version 1.1 will be the primary ORR analysis and ORR assessed by irRC will be a secondary analysis.

DCR will be analyzed in the same manner as ORR.

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

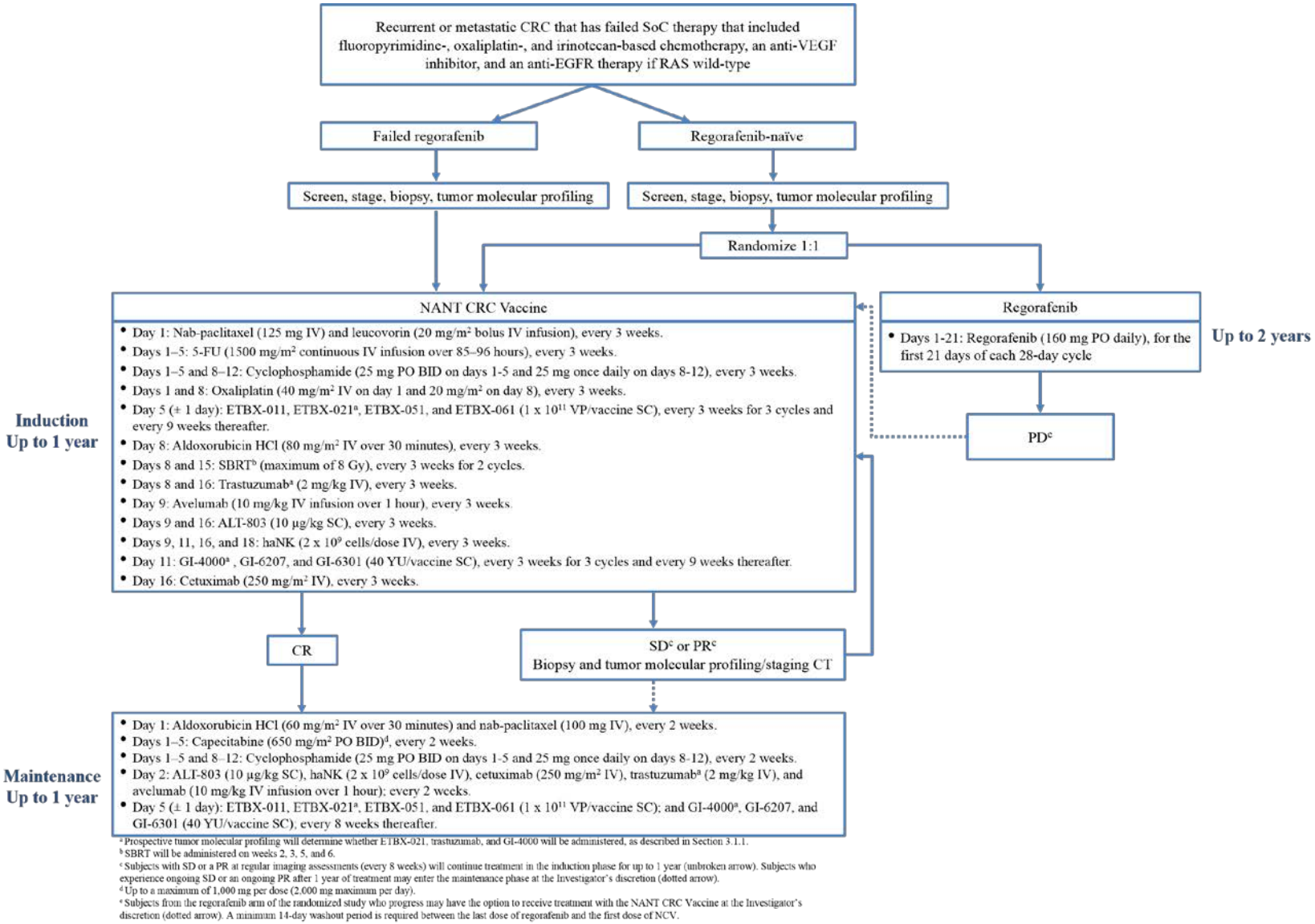

Figure 2: Induction Phase Treatment Schema for NANT CRC Vaccine

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

[a] Oxaliplatin will be administered at 40 mg/m^2 on day 1 and 20 mg/m^2 on day 8.
[b] Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Ad5-based vaccines will be administered on day 5 (±1 day). Yeast-based vaccines will be administered on day 11. Ad5-based vaccines include ETBX-011, ETBX-021, ETBX-051, and ETBX-061. Yeast-based vaccines include GI-4000, GI-6207 and GI-6301. Prospective tumor molecular profiling will determine whether ETBX-021 and GI-4000 will be administered, as described in Section 3.1.1.
[c] SBRT will be administered on weeks 2,3,5, and 6.
[d] Prospective tumor molecular profiling will determine whether trastuzumab will be administered, as described in Section 3.1.1.
[e] Cyclophosphamide is self-administered on the days indicated. On days 1-5, subjects take 25 mg PO BID. On days 8-12, subjects take 25 mg once daily.

Figure 3: Maintenance Phase Treatment Schema for NANT CRC Vaccine

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

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a] Prospective tumor molecular profiling will determine whether trastuzumab will be administered, as described in Section 3.1.1.
[b] Each vaccine will be administered on Day 5 (± 1 day) and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011, ETBX-021, ETBX-051, and ETBX-061. Yeast-based vaccines include GI-4000, GI-6207 and GI-6301. Prospective tumor molecular profiling will determine whether ETBX-021 and GI-4000 will be administered, as described in Section 3.1.1.
[c] On days 1-5, subjects take 25 mg PO BID. On days 8-12, subjects take 25 mg once daily.

Table 18: Schedule of Events for NANT CRC Vaccine Induction Phase of Study

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

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																					EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
Adverse event collection		X				X			X	X		X				X	X		X				X	X
Laboratory Assessments																								
Chemistry panel[k]	X	X[j]							X							X							X	
CEA	X	X[j]	Every 4 weeks																				X	
Hematology[l]	X	X[j]							X							X							X	
Urinalysis	X	X[j]							X							X							X	
Pregnancy test[m]	X	X[j]	Every 4 weeks																				X	
Serum virology (HIV)[n]	X																							
Determine HER2 expression and *RAS* mutational status[o]	X																							
Collect whole blood for tumor molecular profiling[p]	X																							
Collect whole blood for immunology analysis[q]	X	Every 4 weeks during routine blood draws																					X	
Collect whole blood for ctDNA/ctRNA analysis[q]	X	Every 4 weeks during routine blood draws																					X	
Collect historic tumor biopsy specimen for tumor	X																							

	Screening	Induction Phase Treatment (repeats every 3 weeks, except where noted)[a]																			EOT Visit[b]	Unscheduled Visit[c]
Study Week		**1**							**2**							**3**								
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
molecular profiling[r]																								
Tumor biopsy[r]	X	8 weeks after the start of treatment																						
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.																						
Tumor Imaging and Assessments																								
CT, MRI, or PET-CT[s]	X	Every 8 weeks																					X	

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. Subjects who experience ongoing SD or an ongoing PR at 1 year may enter the maintenance phase at the Investigator's and Sponsor's discretion. Any required laboratory sample collection (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study will have a minimum 14-day washout period between last regorafenib treatment and first NANT CRC Vaccine treatment. Patients who crossover will begin at day 1 of the above schedule, except that relevant new medical history will be collected. Tumor imaging does not need to be performed on day 1 for crossover patients if they have had an imaging assessment within the last 28 days.

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

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

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

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

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

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

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

to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.

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

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

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

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

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

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

[o] Assessment of HER2 expression to determine whether ETBX-021 and trastuzumab will be administered to the subject and assessment of *RAS* mutational status to determine whether GI-4000 will be administered to the subject, as described in Section 3.1.1. *RAS* status will also be used as a stratification factor in the Phase 2 randomized portion of the study.

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

[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 4 weeks in the induction phase during routine blood draws, and at the EOT visit.

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

[s] Tumor imaging by CT scan, MRI, or PET-CT will be performed at screening and every 8 weeks during the induction phase, as described in Section 6.1.2. All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

Table 19: Schedule of Events for NANT CRC Vaccine Maintenance Phase of Study

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Concomitant medications	X														X	X
Physical exam, weight	X														X	X
Vital signs[d]	X	X			X										X	X
ECOG performance status	X														X	
12-lead ECG	X	Every 12 weeks													X	
ECHO (with ejection fraction)	X	Every 12 weeks													X	
Confirm contraceptive measures	X															
Adverse event collection	X	X			X										X	X
FACT-C questionnaire	X	Every 12 weeks													X	
Laboratory Assessments																
Chemistry panel[e]	X														X	
CEA	X	Every 12 weeks													X	
Hematology[f]	X														X	
Urinalysis	X														X	
Pregnancy test[g]	X	Every 12 weeks													X	
Collect whole blood for immunology analysis[h]	X	Every 8 weeks during routine blood draws													X	
Collect whole blood for ctDNA/ctRNA analysis[h]	X	Every 8 weeks during routine blood draws													X	

	Maintenance Phase Treatment (repeats every 2 weeks, except where noted)[a]															
Study Week	**1**							**2**							**EOT Visit**[b]	**Unscheduled Visit**[c]
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Additional tumor biopsy	May be collected at any time point, as clinically indicated at the Investigator's discretion															
Tumor Imaging and Assessments																
CT, MRI, or PET-CT[i]	X	Every 12 weeks													X	

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

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

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

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

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

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

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

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

[i] Tumor imaging by CT scan, MRI, or PET-CT will continue to be performed every 12 weeks during the maintenance phase of treatment, as described in Section 6.1.2. RECIST and irRC documentation to be completed at each assessment period.

Table 20: Regorafenib Treatment Arm – Schedule of Events

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1 - 8	Weeks 12-52	Weeks 53 – 104		
		Frequency of Assessment				
General Assessments						
Informed consent	X					
Inclusion/exclusion[d]	X					
Demographics	X					
Medical history[d]	X					
Confirm availability of FFPE tumor sample[e]	X					
Confirm contraceptive measures	X					
Concomitant medications	X	Weekly	Every 4 weeks		X	X
Physical exam: height[f], weight	X	Weekly	Every 4 weeks		X	X
Vital signs[g]	X	Weekly	Every 4 weeks		X	X
Adverse event collection		Weekly	Every 4 weeks		X	X
ECOG performance status	X	Weekly	Every 4 weeks		X	
12-lead ECG[h]	X	Every 4 weeks[i]		Every 12 weeks	X	
FACT-C Questionnaire	X	Every 4 weeks		Every 12 weeks	X	
Laboratory Assessments						
Serum virology (HIV)[j]	X					
Determine *RAS* mutational status[k]	X					
Collect whole blood for tumor molecular profiling[l]	X					
Collect historic tumor biopsy specimen for tumor molecular profiling[m]	X					

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1 - 8	Weeks 12-52	Weeks 53 – 104		
Chemistry panel[n]	X	Weekly[i]	Every 4 weeks		X	
Hematology[o]	X	Weekly[i]	Every 4 weeks		X	
Urinalysis	X	Weekly[i]	Every 4 weeks		X	
Pregnancy test[p]	X	Every 4 weeks[i]		Every 12 weeks	X	
CEA	X	Every 4 weeks[i]		Every 12 weeks	X	
Collect whole blood for immunology analysis (during routine blood draws)	X	Every 4 weeks		Every 8 weeks	X	
Collect whole blood for ctDNA/ctRNA analysis (during routine blood draws)	X	Every 4 weeks		Every 8 weeks	X	
Tumor biopsy[m]	X	8 weeks after the start of treatment				
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.				
Tumor Imaging and Assessments						
CT, MRI, or PET-CT[q]	X	Every 8 weeks		Every 12 weeks	X	

[a] Treatment will continue until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those subjects who have a CR in the first year will move to the schedule of events for year 2. Any required laboratory sample collection listed below (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study do not need to have an EOT visit as long as they commence treatment with the NANT CRC Vaccine within 30 (± 5 days) of their last regorafenib treatment, at which time they will be assessed according to the schedule of events described in Table 18. Crossover patients do not need to undergo screening assessments described in Table 18, except for providing any relevant new medical history occurring after enrollment in the trial.

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

[d] Also evaluated at enrollment.

[e] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study

drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

[f] Height required at screening visit only.

[g] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes.

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

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

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

[k] Assessment of *RAS* mutational status to allow stratification of subjects during randomization.

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

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

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

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

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

[q] All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy
Study Number:	QUILT-3.071
Version Number:	1
Final Date:	24 April 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: 4-24-18

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NANT COLORECTAL CANCER (CRC) VACCINE: A PHASE 1b/2 TRIAL OF THE NANT CRC VACCINE VS REGORAFENIB IN SUBJECTS WITH METASTATIC CRC WHO HAVE BEEN PREVIOUSLY TREATED WITH STANDARD-OF-CARE (SOC) THERAPY

Study Number:	**QUILT-3.071**
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	24 April 2018
Version 2	10 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-021 (Ad5 [E1-, E2b-]-human epidermal growth factor receptor 2 [HER2] vaccine)
5. ETBX-051 (Ad5 [E1-, E2b-]-Brachyury vaccine)
6. ETBX-061 (Ad5 [E1-, E2b-]-mucin 1 [MUC1] vaccine)
7. GI-4000 (RAS yeast vaccine)
8. GI-6207 (CEA yeast vaccine)
9. GI-6301 (Brachyury yeast vaccine)
10. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Approved Products:

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

Name of Active Ingredients:

Investigational Products

1. Aldoxorubicin HCl
2. ALT-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human Brachyury oncoprotein
10. NK-92 [CD16.158V, ER IL2] cells

Approved Products

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

Title of Study:
NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC Vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy

Study Number:
QUILT-3.071

Study Phase:
Phase 1b/Phase 2 (randomized and single-arm [using Simon's two-stage optimal design])

Study Objectives:

Phase 1b

- The primary objective is to evaluate the overall safety profile of the NANT CRC Vaccine regimen in subjects with recurrent or metastatic CRC who have been previously treated with 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

Randomized component – The randomized component of the phase 2 portion of the study will compare the NANT CRC Vaccine regimen (experimental arm) to regorafenib monotherapy (control arm) in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy that did not include regorafenib.

- The primary objective is to compare efficacy as assessed by PFS using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to compare safety and additional measures of efficacy (PFS by immune-related response criteria (irRC), ORR, 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.

Single-arm component – The single-arm component of the phase 2 portion of the study will evaluate the NANT CRC Vaccine regimen in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy that included regorafenib.

- The primary objective is to evaluate the efficacy of the NANT CRC Vaccine regimen as assessed by ORR using RECIST Version 1.1 based on BICR.

- Secondary objectives are to evaluate safety and additional measures of efficacy (ORR by irRC, 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 recurrent or metastatic CRC who have previously received SoC therapy. The phase 2 portion of the study will consist of both a single-arm component and a randomized component.

In phase 1b, the NANT CRC Vaccine will be assessed for safety. 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 NANT CRC Vaccine treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable. In total, 6 to 24 subjects will be enrolled in the phase 1b portion of the study.

In the randomized component of the phase 2 portion, subjects who have received SoC therapy that did not include regorafenib for recurrent or metastatic CRC will be randomized to receive either the NANT CRC Vaccine (experimental arm) or regorafenib monotherapy (control arm). Randomization will be stratified by tumor sidedness (left vs right) and performance status (ECOG 0 vs 1). For the control arm of the randomized portion, subjects who progress on or after discontinuing regorafenib may be enrolled in the single-arm component described below after a 14-day washout period.

The single-arm component of the phase 2 portion will enroll subjects who have progressed or experienced unacceptable toxicity on SoC that included regorafenib, and subjects who have progressed on or after regorafenib treatment in the randomized phase 2 portion of this study.

The NANT CRC Vaccine regimen will be administered in 2 phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. 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 and Sponsor's discretion. Subjects may remain in the maintenance phase of the study for up to 1 year.

In the randomized component of the phase 2 portion of the study, the control arm will self-administer regorafenib every day for the first 21 days of every 28-day treatment cycle.

Treatment in the study will be discontinued if the subject experiences confirmed progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Subjects receiving treatment in the control arm may cross over to treatment in the induction phase of the experimental arm after experiencing PD. Subjects receiving treatment in the experimental arm with an initial assessment of PD per RECIST Version 1.1 may, at the discretion of the Investigator, continue to receive study treatment until PD is confirmed as detailed in Section 6.1.2. The maximum time on study treatment is 2 years.

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

For all subjects, 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 treatment periods (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 4 weeks (induction phase for experimental arm and year 1 or until CR for control arm) or 8 weeks (maintenance phase for experimental arm and year 2 or post-CR for control arm) 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 for all subjects. Tumor response will be assessed every 8 weeks (induction phase for experimental arm and year 1 or until CR for control arm) or 12 weeks (maintenance phase for experimental arm and year 2 or post-CR for control arm) until progression occurs, regardless of the treatment administered, by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST Version 1.1 and irRC. The same mode(s) of assessment used to identify/evaluate lesions at screening should be used throughout the course of the study unless subject safety necessitates a change (eg, allergic reaction to contrast media). Unscheduled tumor assessments should be carried out if the investigator observes any signs or symptoms of PD. When disease progression per RECIST Version 1.1 is initially observed for a subject in the experimental arm, 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 for a subject in the experimental arm, 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 subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted on tumor samples from all subjects receiving the NANT CRC Vaccine to inform HER2 expression and *RAS* mutational status, and will be used to determine whether the Ad5-based vaccine ETBX-021 (HER2), cetuximab, and the yeast-based vaccine GI-4000 (RAS) will be administered. Subjects will receive ETBX-021 (HER2) if their tumor is HER2-positive (IHC 3+ or FISH positive), as determined by FDA-approved diagnostic tests. Subjects will receive cetuximab if their tumor is *RAS* wild-type as determined by whole genome sequencing. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. ETBX-021 (HER2), cetuximab, and GI-4000 (RAS) administration will be initiated as soon as results from tumor molecular profiling are available. All other agents in the NANT CRC Vaccine regimen will be administered regardless of 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.

NANT CRC Vaccine: Induction Phase

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

Day 1, every 3 weeks:

- Leucovorin (20 mg/m^2 IV bolus)
- Oxaliplatin (40 mg/m^2 IV)
- Nab-paclitaxel (125 mg 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-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) (1×10^{11} virus particles [VP]/vaccine/dose subcutaneously [SC])
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury) (40 yeast units [YU]/vaccine/dose SC)

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

Day 8, every 3 weeks:

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

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

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

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 15, every 3 weeks:

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

Day 16, every 3 weeks:

- haNK (2×10^9 cells/dose IV)
- Cetuximab (250 mg/m^2 IV)

  Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described above.

NANT CRC Vaccine: 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, as follows:

Day 1, every 2 weeks:

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

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

- Capecitabine (650 mg/m^2 PO BID, up to a maximum of 1000 mg per dose)

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg BID)

Day 2, every 2 weeks:

- ALT-803 (15 µg/kg SC)
- haNK (2×10^9 cells/dose IV)
- Avelumab (10 mg/kg IV)
- Cetuximab (250 mg/m^2 IV)

  Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described above.

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

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

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

Days 8-12, every 2 weeks

- Cyclophosphamide (25 mg PO daily)

Study Endpoints

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.

Phase 1b

Primary Endpoint:

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

Secondary Endpoints:

- ORR by RECIST Version 1.1.
- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.

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

Exploratory Endpoints:

- 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

Randomized Component

Primary Endpoint:

- PFS by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

- 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.

Single-Arm Component

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

- 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.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC Vaccine regimen or regorafenib monotherapy. During the trial, 120 subjects are expected to accrue 96 PFS events. An interim analysis is planned once 50% of the PFS events have accrued (48 events). Based on the interim analysis, the study sample size may be increased to a maximum of 240 subjects.

In the phase 2 single-arm component of the study, 27 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 41 subjects will be enrolled in the second stage, for a total of 68 subjects in the phase 2 single-arm component of the study.

The maximum total enrollment for the study is 332 subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed recurrent or metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. These chemotherapy regimens may or may not have included an anti-VEGF biological therapy, and if *RAS* wild-type, an anti-EGFR therapy. Subjects who are ineligible or have declined these therapies may also be enrolled.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Phase 2 single-arm component only

11. Must have progressed on or after regorafenib treatment in the randomized phase 2 portion of the study OR progressed or experienced unacceptable toxicity on SoC and regorafenib prior to enrollment on the study.

Exclusion Criteria:

1. Microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient tumors eligible for, but not yet treated with, a PD-1 inhibitor.
2. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drugs used in this study or that would put the subject at high risk for treatment-related complications.
3. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
4. History of organ transplant requiring immunosuppression.
5. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
6. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3.
   b. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
   c. Platelet count < 75,000 cells/mm^3.

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 (ALP) 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.

7. 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.
8. Serious myocardial dysfunction defined by echocardiogram (ECHO) as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
9. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
10. Positive results of screening test for human immunodeficiency virus (HIV).
11. 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.
12. Known hypersensitivity to any component of the study medication(s).
13. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
14. 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.
15. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
16. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
17. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
18. Concurrent participation in any interventional clinical trial.
19. Pregnant and nursing women.

Phase 2 randomized component only 20. Prior regorafenib treatment.		
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-021 (HER2)	1 × 10^{11} VP/dose	SC
ETBX-051 (Brachyury)	1 × 10^{11} VP/dose	SC
ETBX-061 (MUC1)	1 × 10^{11} VP/dose	SC
GI-4000 (RAS)	40 YU/dose	SC
GI-6207 (CEA)	40 YU/dose	SC
GI-6301 (Brachyury)	40 YU/dose	SC
haNK	2 × 10^9 cells/dose	IV
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Capecitabine	650 mg/m^2 BID up to a maximum of 1000 mg per dose	PO
Cetuximab	250 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
Oxaliplatin	40 mg/m^2	IV
Regorafenib	160 mg	PO
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

NANT CRC Vaccine (Experimental Arm)

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

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

Regorafenib (Control Arm)

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

Subjects that experience PD on or after treatment with regorafenib in the phase 2 randomized component of the study may be subsequently treated with the NANT CRC Vaccine in the phase 2 single-arm component of the study.

Duration of Follow-up:

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

- CT or MRI imaging and response assessments (see Section 6.1.2).
- 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.

Reference Therapy, Dosage, and Mode of Administration:

Regorafenib:
Regorafenib treatment will consist of repeated 4-week cycles for a maximum treatment period of 2 years, as follows:

Days 1-21, every 4 weeks:

- Regorafenib (160 mg PO)

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:

PFS and ORR will be assessed by CT or MRI of target and non-target lesions every 8 or 12 weeks until progression occurs regardless of the treatment administered 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 4–6 weeks after the initial response.

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C) instrument. Assessments will occur at screening and prior to treatment on day 1, every 4 or 12 weeks thereafter, and at the end-of-treatment (EOT) visit.

Exploratory Analyses:

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 CRC Vaccine regimen and regorafenib monotherapy 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 evaluate the safety and efficacy of metronomic combination therapy in subjects with recurrent or metastatic CRC who have failed SoC therapy.

Six to 24 subjects will be enrolled in the phase 1b portion of the study.

In the phase 2 single-arm component of the study, ORR based on RECIST Version 1.1 will be evaluated using Simon's two-stage optimal design.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC vaccine regimen or regorafenib monotherapy. A total of 120 subjects are expected to accrue 96 PFS events during the trial with a 12-month enrollment period and 12 months of follow-up after the last subject is enrolled. Based on median PFS of 2 and 4 months for regorafenib and the NANT CRC Vaccine, respectively, a 20% lost-to-follow-up rate, and a 5% type 1 error, 120 subjects with 96 PFS events has a power of 90% to detect a hazard ratio (HR) of 0.50.

In the phase 2 randomized component of the study, an interim analysis is planned once 50% of the PFS events have accrued (48 events). The Lan DeMets/O'Brien Fleming spending function will be used for the interim analysis which allocates a 0.3% and 4.9% type 1 error rate to the interim and final PFS analyses, respectively. The trial may be stopped early for strong efficacy if the interim PFS analysis shows superiority (ie, $p < 0.003$). The trial may be stopped early for futility if the interim PFS analysis displays a conditional power < 15%. Based on the interim PFS analysis, the study sample size for the randomized phase 2 component may be increased to a maximum of 240 subjects using the "Promising Zone" methodology for an adaptive sample size increase.

The interim analysis will be performed by an independent statistician separate from the study team. The interim analysis results will not be shared with the study team during the conduct of the study. The interim analysis results will be presented to the Independent Data Monitoring Committee (IDMC) who will make recommendations to the study team whether to stop the study for efficacy or futility, or increase the study sample size. For the NANT CRC Vaccine regimen, safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. For the regorafenib treatment, safety results will be presented for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimens.

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.

PFS will be analyzed using Kaplan-Meier methods. The median PFS (and 95% confidence interval [CI]) will be summarized. PFS Kaplan-Meier curves will be presented. For the phase 2 randomized component, comparison of PFS between the NANT CRC Vaccine regimen and the control treatment will be based on the stratified log-rank test, stratified by tumor sidedness and performance status. PFS assessed by RECIST Version 1.1 will be the primary PFS analysis and PFS assessed by irRC will be a secondary analysis.

OS and DOR will be analyzed in the same manner as PFS.

ORR (and 95% CI) will be summarized. For the phase 2 randomized component, comparison of ORR between the NANT CRC Vaccine regimen and the control treatment will be based on the stratified Fisher exact test, stratified by tumor sidedness and performance status. ORR assessed by RECIST Version 1.1 will be the primary ORR analysis and ORR assessed by irRC will be a secondary analysis.

DCR will be analyzed in the same manner as ORR.

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

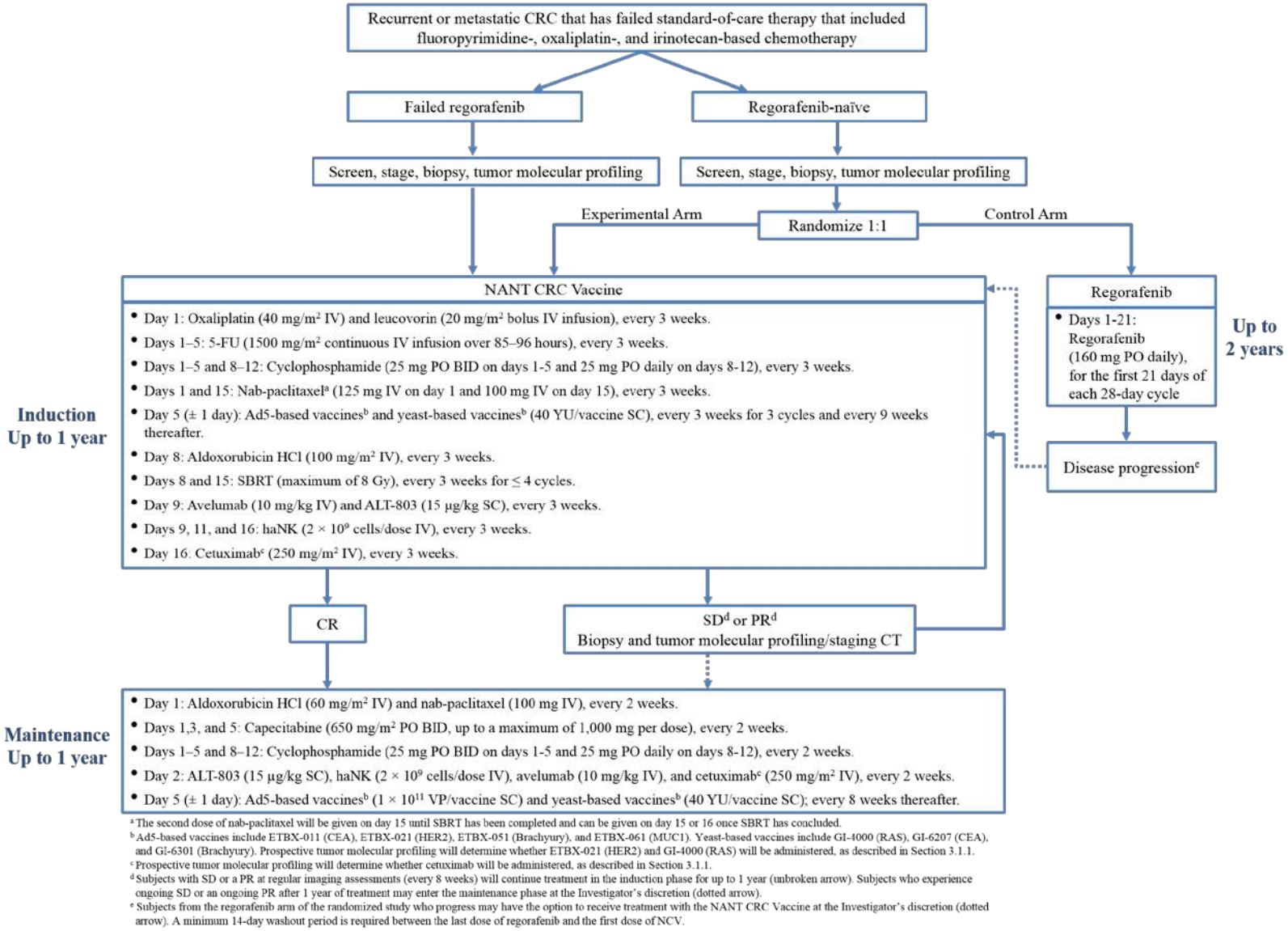

Figure 2: Induction Phase Treatment Schema for NANT CRC Vaccine

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

[a] The second dose of nab-paclitaxel will be given on day 15 until SBRT has been completed and can be given on day 15 or 16 once SBRT has concluded.
[b] Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines will be administered on day 5 (±1 day). Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[c] SBRT will be administered for up to 4 treatment cycles.
[d] Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described in Section 3.1.1.

Figure 3: Maintenance Phase Treatment Schema for NANT CRC Vaccine

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

[a] Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described in Section 3.1.1.
[b] Each vaccine will be administered on Day 5 (± 1 day) and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered, as described in Section 3.1.1.

Table 18: Schedule of Events for NANT CRC Vaccine Induction Phase of Study

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

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

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences confirmed PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. Subjects who experience ongoing SD or an ongoing PR at 1 year may enter the maintenance phase at the Investigator's and Sponsor's discretion. Any required laboratory sample collection (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study will have a minimum 14-day washout period between the last regorafenib treatment and the first NANT CRC Vaccine treatment. Patients who crossover will begin at day 1 of the above schedule, except that relevant new medical history will be collected. Tumor imaging does not need to be performed on day 1 for crossover patients if they have had an imaging assessment within the last 28 days.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 4 weeks in the induction phase during routine blood draws, and at the EOT visit.

[r] Historic tumor biopsy specimen for tumor molecular profiling is required to determine eligibility for participation in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be

scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator.

[s] Tumor imaging by CT or MRI will be performed at screening and every 8 weeks during the induction phase, as described in Section 6.1.2. All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

Table 19: Schedule of Events for NANT CRC Vaccine Maintenance Phase of Study

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

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

interest to continue treatment. Any required laboratory sample collection (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated.

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

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

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

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

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

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

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

[i] Tumor imaging by CT or MRI will continue to be performed every 12 weeks during the maintenance phase of treatment, as described in Section 6.1.2. RECIST and irRC documentation to be completed at each assessment period.

Table 20: Regorafenib Control Arm – Schedule of Events

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1-8	Weeks 13-52	Weeks 53-104		
		Frequency of Assessment				
General Assessments						
Informed consent	X					
Inclusion/exclusion[d]	X					
Demographics	X					
Medical history[d]	X					
Confirm availability of FFPE tumor sample[e]	X					
Confirm contraceptive measures	X					
Concomitant medications	X	Weekly	Every 4 weeks		X	X
Physical exam: height[f], weight	X	Weekly	Every 4 weeks		X	X
Vital signs[g]	X	Weekly	Every 4 weeks		X	X
Adverse event collection		Weekly	Every 4 weeks		X	X
ECOG performance status	X	Weekly	Every 4 weeks		X	
12-lead ECG[h]	X	Every 4 weeks[i]		Every 12 weeks	X	
FACT-C Questionnaire	X	Every 4 weeks		Every 12 weeks	X	
Laboratory Assessments						
Serum virology (HIV)[j]	X					
Collect whole blood for tumor molecular profiling[k]	X					
Collect historic tumor biopsy specimen for tumor molecular profiling[l]	X					
Chemistry panel[m]	X	Weekly[i]	Every 4 weeks		X	

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1-8	Weeks 13-52	Weeks 53-104		
Hematology[n]	X	Weekly[i]	Every 4 weeks		X	
Urinalysis	X	Weekly[i]	Every 4 weeks		X	
Pregnancy test[o]	X	Every 4 weeks[i]		Every 12 weeks	X	
CEA	X	Every 4 weeks[i]		Every 12 weeks	X	
Collect whole blood for immunology analysis[p]	X	Every 4 weeks		Every 8 weeks	X	
Collect whole blood for ctDNA/ctRNA analysis (during routine blood draws)[p]	X	Every 4 weeks		Every 8 weeks	X	
Tumor biopsy[l]	X	8 weeks after the start of treatment				
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.				
Tumor Imaging and Assessments						
CT or MRI[q]	X	Every 8 weeks		Every 12 weeks	X	

[a] Treatment will continue until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those subjects who have a CR in the first year will move to the schedule of events for year 2. Any required laboratory sample collection listed below (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study do not need to have an EOT visit as long as they commence treatment with the NANT CRC Vaccine within 30 (± 5 days) of their last regorafenib treatment, at which time they will be assessed according to the schedule of events described in Table 18. Crossover patients do not need to undergo screening assessments described in Table 18, except for providing any relevant new medical history occurring after enrollment in the trial.

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

[d] Also evaluated at enrollment.

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

[f] Height required at screening visit only.

[g] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes.

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

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

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

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

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

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

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

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

[p] Blood collection for exploratory immunology and ctDNA/ctRNA analyses will be performed every 4 weeks (year 1or prior to CR) or 8 (year 2 or after CR) weeks during routine blood draws and at the end-of-treatment visit.

[q] All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy
Study Number:	QUILT-3.071
Version Number:	2
Final Date:	10 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: 8-10-18

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NANT COLORECTAL CANCER (CRC) VACCINE: A PHASE 1b/2 TRIAL OF THE NANT CRC VACCINE VS REGORAFENIB IN SUBJECTS WITH METASTATIC CRC WHO HAVE BEEN PREVIOUSLY TREATED WITH STANDARD-OF-CARE (SOC) THERAPY

Study Number:	**QUILT-3.071**
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	24 April 2018
Version 2	10 August 2018
Version 3	28 September 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. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-carcinoembryonic antigen [CEA] vaccine)
3. ETBX-021 (Ad5 [E1-, E2b-]-human epidermal growth factor receptor 2 [HER2] vaccine)
4. ETBX-051 (Ad5 [E1-, E2b-]-Brachyury vaccine)
5. ETBX-061 (Ad5 [E1-, E2b-]-mucin 1 [MUC1] vaccine)
6. GI-4000 (RAS yeast vaccine)
7. GI-6207 (CEA yeast vaccine)
8. GI-6301 (Brachyury yeast vaccine)
9. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
10. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

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

Name of Active Ingredients:

Investigational Products

1. Aldoxorubicin HCl
2. Ad5 [E1-, E2b-]-CEA
3. Ad5 [E1-, E2b-]-HER2
4. Ad5 [E1-, E2b-]-Brachyury
5. Ad5 [E1-, E2b-]-MUC1
6. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
7. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
8. Recombinant yeast based vaccine expressing the human Brachyury oncoprotein
9. NK-92 [CD16.158V, ER IL2] cells
10. N-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)

Approved Products

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

Title of Study:
NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC Vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy

Study Number:
QUILT-3.071

Study Phase:
Phase 1b/Phase 2 (randomized and single-arm [using Simon's two-stage optimal design])

Study Objectives:

Phase 1b

- The primary objective is to evaluate the overall safety profile of the NANT CRC Vaccine regimen in subjects with recurrent or metastatic CRC who have been previously treated with 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

Randomized component – The randomized component of the phase 2 portion of the study will compare the NANT CRC Vaccine regimen (experimental arm) to regorafenib monotherapy (control arm) in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy that did not include regorafenib.

- The primary objective is to compare efficacy as assessed by PFS using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to compare safety and additional measures of efficacy (PFS by immune-related response criteria (irRC), ORR, 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.

Single-arm component – The single-arm component of the phase 2 portion of the study will evaluate the NANT CRC Vaccine regimen in subjects with recurrent or metastatic CRC who have previously been treated with SoC therapy that included regorafenib.

- The primary objective is to evaluate the efficacy of the NANT CRC Vaccine regimen as assessed by ORR using RECIST Version 1.1 based on BICR.

- Secondary objectives are to evaluate safety and additional measures of efficacy (ORR by irRC, 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 recurrent or metastatic CRC who have previously received SoC therapy. The phase 2 portion of the study will consist of both a single-arm component and a randomized component.

In phase 1b, the NANT CRC Vaccine will be assessed for safety. 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 NANT CRC Vaccine treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable. In total, 6 to 24 subjects will be enrolled in the phase 1b portion of the study.

In the randomized component of the phase 2 portion, subjects who have received SoC therapy that did not include regorafenib for recurrent or metastatic CRC will be randomized to receive either the NANT CRC Vaccine (experimental arm) or regorafenib monotherapy (control arm). Randomization will be stratified by tumor sidedness (left vs right) and performance status (Eastern Cooperative Oncology Group (ECOG) performance status of 0 vs 1). For the control arm of the randomized portion, subjects who progress on or after discontinuing regorafenib may be enrolled in the single-arm component described below after a 14-day washout period.

The single-arm component of the phase 2 portion will enroll subjects who have progressed or experienced unacceptable toxicity on SoC that included regorafenib, and subjects who have progressed on or after regorafenib treatment in the randomized phase 2 portion of this study.

The NANT CRC Vaccine regimen will be administered in 2 phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. 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 and Sponsor's discretion. Subjects may remain in the maintenance phase of the study for up to 1 year.

In the randomized component of the phase 2 portion of the study, the control arm will self-administer regorafenib every day for the first 21 days of every 28-day treatment cycle.

Treatment in the study will be discontinued if the subject experiences confirmed progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Subjects receiving treatment in the control arm may cross over to treatment in the induction phase of the experimental arm after experiencing PD. Subjects receiving treatment in the experimental arm with an initial assessment of PD per RECIST Version 1.1 may, at the discretion of the Investigator, continue to receive study treatment until PD is confirmed as detailed in Section 6.1.2. The maximum time on study treatment is 2 years.

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

For all subjects, 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 treatment periods (depending on response), as described in Section 6.4.1. Separate blood tubes will be collected every 4 weeks (induction phase for experimental arm and year 1 or until CR for control arm) or 8 weeks

(maintenance phase for experimental arm and year 2 or post-CR for control arm) 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 for all subjects. Tumor response will be assessed every 8 weeks (induction phase for experimental arm and year 1 or until CR for control arm) or 12 weeks (maintenance phase for experimental arm and year 2 or post-CR for control arm) until progression occurs, regardless of the treatment administered, by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST Version 1.1 and irRC. The same mode(s) of assessment used to identify/evaluate lesions at screening should be used throughout the course of the study unless subject safety necessitates a change (eg, allergic reaction to contrast media). Unscheduled tumor assessments should be carried out if the investigator observes any signs or symptoms of PD. When disease progression per RECIST Version 1.1 is initially observed for a subject in the experimental arm, 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 for a subject in the experimental arm, 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 subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

Prospective Tumor Molecular Profiling

Prospective tumor molecular profiling will be conducted on tumor samples from all subjects receiving the NANT CRC Vaccine to inform *RAS* mutational status, and will be used to determine whether cetuximab and the yeast-based vaccine GI-4000 (RAS) will be administered. Subjects will receive cetuximab if their tumor is *RAS* wild-type as determined by whole genome sequencing. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. Cetuximab and GI-4000 (RAS) administration will be initiated as soon as results from tumor molecular profiling are available. All other agents in the NANT CRC Vaccine regimen will be administered regardless of 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.

NANT CRC Vaccine: Induction Phase

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

Day 1, every 3 weeks:

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

Days 1–5, every 3 weeks:

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

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

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

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

Day 8, every 3 weeks:

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

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

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

Day 11, every 3 weeks:

- haNK (2×10^9 cells/dose IV)

Day 15, every 3 weeks:

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

Day 16, every 3 weeks:

- Cetuximab (250 mg/m^2 IV)

  Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described above.
- haNK (2×10^9 cells/dose IV)

NANT CRC Vaccine: 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, as follows:

Day 1, every 2 weeks:

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

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

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

Days 1–5, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV)
- Cetuximab (250 mg/m^2 IV)

  Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described above.
- haNK (2×10^9 cells/dose IV)
- N-803 (15 µg/kg SC)

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

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

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

Days 8-12, every 2 weeks

- Cyclophosphamide (25 mg PO daily)

Study Endpoints

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.

Phase 1b

Primary Endpoint:

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

Secondary Endpoints:

- ORR by RECIST Version 1.1.
- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.

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

Exploratory Endpoints:

- 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

Randomized Component

Primary Endpoint:

- PFS by RECIST Version 1.1.

Secondary Endpoints:

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

Exploratory Endpoints:

- 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.

Single-Arm Component

Primary Endpoint:

- ORR by RECIST Version 1.1.

Secondary Endpoints:

- ORR by irRC.

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

Exploratory Endpoints:

- 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.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC Vaccine regimen or regorafenib monotherapy. During the trial, 120 subjects are expected to accrue 96 PFS events. An interim analysis is planned once 50% of the PFS events have accrued (48 events). Based on the interim analysis, the study sample size may be increased to a maximum of 240 subjects.

In the phase 2 single-arm component of the study, 27 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 41 subjects will be enrolled in the second stage, for a total of 68 subjects in the phase 2 single-arm component of the study.

The maximum total enrollment for the study is 332 subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed recurrent or metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. These chemotherapy regimens may or may not have included an anti-VEGF biological therapy, and if *RAS* wild-type, an anti-EGFR therapy. Subjects who are ineligible or have declined these therapies may also be enrolled.
4. ECOG performance status of 0 or 1.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following

the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Phase 2 single-arm component only

11. Must have progressed on or after regorafenib treatment in the randomized phase 2 portion of the study OR progressed or experienced unacceptable toxicity on SoC and regorafenib prior to enrollment on the study.

Exclusion Criteria:

1. Microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient tumors eligible for, but not yet treated with, a PD-1 inhibitor.
2. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drugs used in this study or that would put the subject at high risk for treatment-related complications.
3. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
4. History of organ transplant requiring immunosuppression.
5. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
6. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3.
    b. Uncorrectable grade 3 anemia (hemoglobin < 8 g/dL).
    c. Platelet count < 75,000 cells/mm^3.
    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 (ALP) 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.

7. 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.
8. Serious myocardial dysfunction defined by echocardiogram (ECHO) as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
9. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
10. Positive results of screening test for human immunodeficiency virus (HIV).
11. 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.
12. Known hypersensitivity to any component of the study medication(s).
13. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
14. 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.
15. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
16. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
17. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
18. Concurrent participation in any interventional clinical trial.
19. Pregnant and nursing women.

Phase 2 randomized component only

20. Prior regorafenib treatment.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
Aldoxorubicin HCl	100 mg/m^2 (induction); 60 mg/m^2 (maintenance)	IV
ETBX-011 (CEA)	1 × 10^{11} VP/dose	SC
ETBX-021 (HER2)	1 × 10^{11} VP/dose	SC
ETBX-051 (Brachyury)	1 × 10^{11} VP/dose	SC
ETBX-061 (MUC1)	1 × 10^{11} VP/dose	SC
GI-4000 (RAS)	40 YU/dose	SC
GI-6207 (CEA)	40 YU/dose	SC
GI-6301 (Brachyury)	40 YU/dose	SC
haNK	2 × 10^9 cells/dose	IV
N-803	15 μg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV
Capecitabine	650 mg/m^2 BID up to a maximum of 1000 mg per dose	PO
Cetuximab	250 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
Oxaliplatin	40 mg/m^2	IV
Regorafenib	160 mg	PO
SBRT	8 Gy maximum (exact dose to be determined by the radiation oncologist)	External beam radiation

Duration of Treatment:

NANT CRC Vaccine (Experimental Arm)

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

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

Regorafenib (Control Arm)

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

Subjects that experience PD on or after treatment with regorafenib in the phase 2 randomized component of the study may be subsequently treated with the NANT CRC Vaccine in the phase 2 single-arm component of the study.

Duration of Follow-up:

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

- CT or MRI imaging and response assessments (see Section 6.1.2).
- 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.

Reference Therapy, Dosage, and Mode of Administration:

Regorafenib:
Regorafenib treatment will consist of repeated 4-week cycles for a maximum treatment period of 2 years, as follows:

Days 1-21, every 4 weeks:

- Regorafenib (160 mg PO)

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:

PFS and ORR will be assessed by CT or MRI of target and non-target lesions every 8 or 12 weeks until progression occurs regardless of the treatment administered 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 4–6 weeks after the initial response.

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C) instrument. Assessments will occur at screening and prior to treatment on day 1, every 4 or 12 weeks thereafter, and at the end-of-treatment (EOT) visit.

Exploratory Analyses:

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 CRC Vaccine regimen and regorafenib monotherapy 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 evaluate the safety and efficacy of metronomic combination therapy in subjects with recurrent or metastatic CRC who have failed SoC therapy.

Six to 24 subjects will be enrolled in the phase 1b portion of the study.

In the phase 2 single-arm component of the study, ORR based on RECIST Version 1.1 will be evaluated using Simon's two-stage optimal design.

The phase 2 randomized component of the study is initially planned for 120 subjects to be randomized 1:1 to the NANT CRC vaccine regimen or regorafenib monotherapy. A total of 120 subjects are expected to accrue 96 PFS events during the trial with a 12-month enrollment period and 12 months of follow-up after the last subject is enrolled. Based on median PFS of 2 and 4 months for regorafenib and the NANT CRC Vaccine, respectively, a 20% lost-to-follow-up rate, and a 5% type 1 error, 120 subjects with 96 PFS events has a power of 90% to detect a hazard ratio (HR) of 0.50.

In the phase 2 randomized component of the study, an interim analysis is planned once 50% of the PFS events have accrued (48 events). The Lan DeMets/O'Brien Fleming spending function will be used for the interim analysis which allocates a 0.3% and 4.9% type 1 error rate to the interim and final PFS analyses, respectively. The trial may be stopped early for strong efficacy if the interim PFS analysis shows superiority (ie, $p < 0.003$). The trial may be stopped early for futility if the interim PFS analysis displays a conditional power < 15%. Based on the interim PFS analysis, the study sample size for the randomized phase 2 component may be increased to a maximum of 240 subjects using the "Promising Zone" methodology for an adaptive sample size increase.

The interim analysis will be performed by an independent statistician separate from the study team. The interim analysis results will not be shared with the study team during the conduct of the study. The interim analysis results will be presented to the Independent Data Monitoring Committee (IDMC) who will make recommendations to the study team whether to stop the study for efficacy or futility, or increase the study sample size. For the NANT CRC Vaccine regimen, safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. For the regorafenib treatment, safety results will be presented for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimens.

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.

PFS will be analyzed using Kaplan-Meier methods. The median PFS (and 95% confidence interval [CI]) will be summarized. PFS Kaplan-Meier curves will be presented. For the phase 2 randomized component, comparison of PFS between the NANT CRC Vaccine regimen and the control treatment will be based on the stratified log-rank test, stratified by tumor sidedness and performance status. PFS assessed by RECIST Version 1.1 will be the primary PFS analysis and PFS assessed by irRC will be a secondary analysis.

OS and DOR will be analyzed in the same manner as PFS.

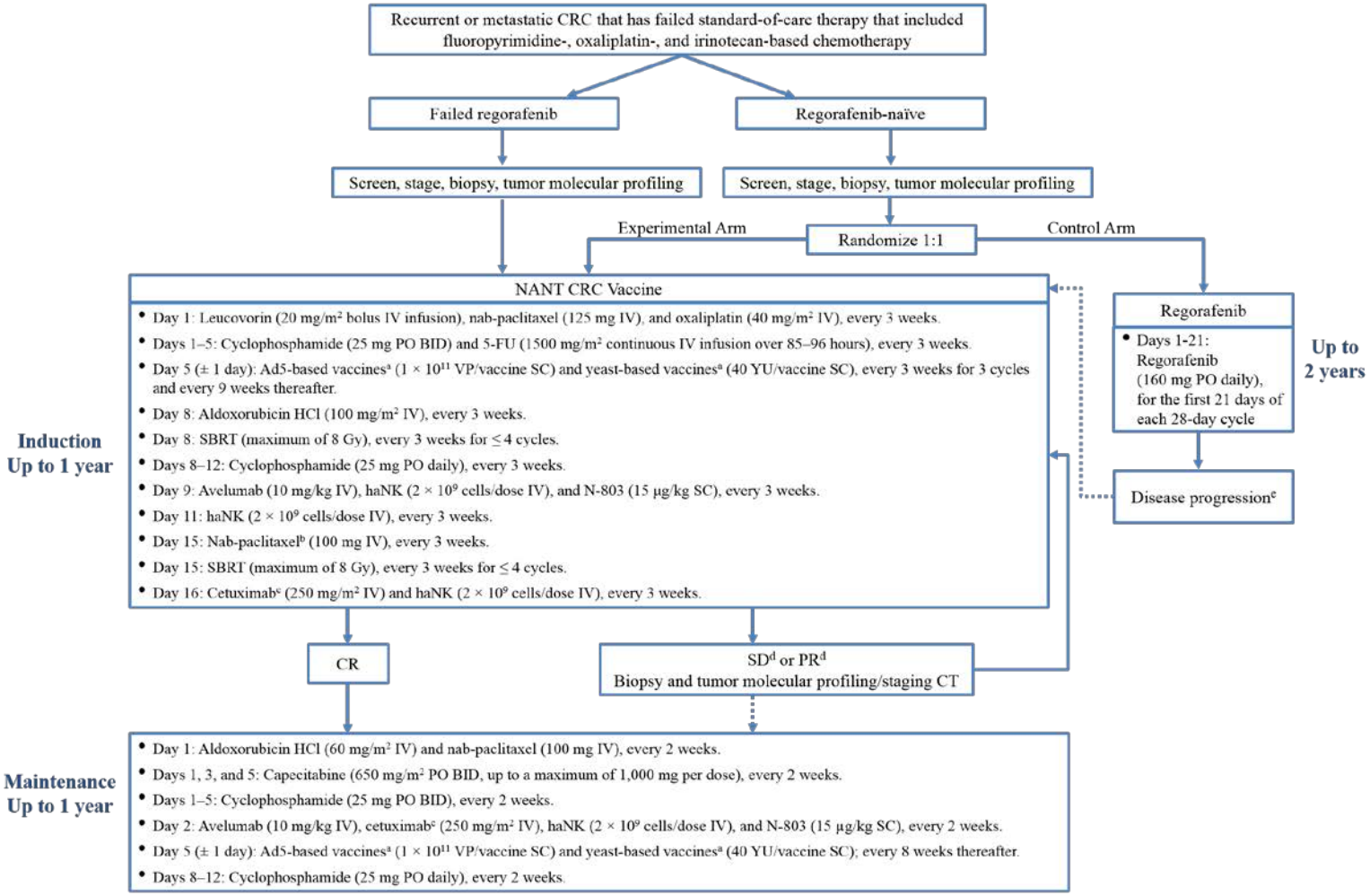
ORR (and 95% CI) will be summarized. For the phase 2 randomized component, comparison of ORR between the NANT CRC Vaccine regimen and the control treatment will be based on the stratified Fisher exact test, stratified by tumor sidedness and performance status. ORR assessed by RECIST Version 1.1 will be the primary ORR analysis and ORR assessed by irRC will be a secondary analysis.

DCR will be analyzed in the same manner as ORR.

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-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[b] The second dose of nab-paclitaxel will be given on day 15 until SBRT has been completed and can be given on day 15 or 16 once SBRT has concluded.
[c] Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described in Section 3.1.1.
[d] Subjects with SD or a PR at regular imaging assessments (every 8 weeks) will continue treatment in the induction phase for up to 1 year (unbroken arrow). Subjects who experience ongoing SD or an ongoing PR after 1 year of treatment may enter the maintenance phase at the Investigator's discretion (dotted arrow).
[e] Subjects from the regorafenib arm of the randomized study who progress may have the option to receive treatment with the NANT CRC Vaccine at the Investigator's discretion (dotted arrow). A minimum 14-day washout period is required between the last dose of regorafenib and the first dose of NCV.

Figure 2: Induction Phase Treatment Schema for NANT CRC Vaccine

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

[a] The second dose of nab-paclitaxel will be given on day 15 until SBRT has been completed and can be given on day 15 or 16 once SBRT has concluded.
[b] Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines will be administered on day 5 (±1 day). Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[c] SBRT will be administered for up to 4 treatment cycles.
[d] Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described in Section 3.1.1.

Figure 3: Maintenance Phase Treatment Schema for NANT CRC Vaccine

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

[a] Prospective tumor molecular profiling will determine whether cetuximab will be administered, as described in Section 3.1.1.
[b] Each vaccine will be administered on Day 5 (± 1 day) and every 8 weeks thereafter. Ad5-based vaccines include ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1). Yeast-based vaccines include GI-4000 (RAS), GI-6207 (CEA), and GI-6301 (Brachyury). Prospective tumor molecular profiling will determine whether GI-4000 (RAS) will be administered, as described in Section 3.1.1.

Table 18: Schedule of Events for NANT CRC Vaccine Induction Phase of Study

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

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

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences confirmed PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. Subjects who experience ongoing SD or an ongoing PR at 1 year may enter the maintenance phase at the Investigator's and Sponsor's discretion. Any required laboratory sample collection (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study will have a minimum 14-day washout period between the last regorafenib treatment and the first NANT CRC Vaccine treatment. Patients who crossover will begin at day 1 of the above schedule, except that relevant new medical history will be collected. Tumor imaging does not need to be performed on day 1 for crossover patients if they have had an imaging assessment within the last 28 days.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 4 weeks in the induction phase during routine blood draws, and at the EOT visit.

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

[s] Tumor imaging by CT or MRI will be performed at screening and every 8 weeks during the induction phase, as described in Section 6.1.2. All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

Table 19: Schedule of Events for NANT CRC Vaccine Maintenance Phase of Study

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

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

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

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

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

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

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

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

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

[i] Tumor imaging by CT or MRI will continue to be performed every 12 weeks during the maintenance phase of treatment, as described in Section 6.1.2. RECIST and irRC documentation to be completed at each assessment period.

Table 20: Regorafenib Control Arm – Schedule of Events

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1-8	Weeks 13-52	Weeks 53-104		
		Frequency of Assessment				
General Assessments						
Informed consent	X					
Inclusion/exclusion[d]	X					
Demographics	X					
Medical history[d]	X					
Confirm availability of FFPE tumor sample[e]	X					
Confirm contraceptive measures	X					
Concomitant medications	X	Weekly	Every 4 weeks		X	X
Physical exam: height[f], weight	X	Weekly	Every 4 weeks		X	X
Vital signs[g]	X	Weekly	Every 4 weeks		X	X
Adverse event collection		Weekly	Every 4 weeks		X	X
ECOG performance status	X	Weekly	Every 4 weeks		X	
12-lead ECG[h]	X	Every 4 weeks[i]		Every 12 weeks	X	
FACT-C Questionnaire	X	Every 4 weeks		Every 12 weeks	X	
Laboratory Assessments						
Serum virology (HIV)[j]	X					
Collect whole blood for tumor molecular profiling[k]	X					
Collect historic tumor biopsy specimen for tumor molecular profiling[l]	X					
Chemistry panel[m]	X	Weekly[i]	Every 4 weeks		X	

	Screening (days -28 to -1)	On day 1 of each week[a]			EOT Visit[b]	Unscheduled Visit[c]
		Weeks 1-8	Weeks 13-52	Weeks 53-104		
Hematology[n]	X	Weekly[i]	Every 4 weeks		X	
Urinalysis	X	Weekly[i]	Every 4 weeks		X	
Pregnancy test[o]	X	Every 4 weeks[i]		Every 12 weeks	X	
CEA	X	Every 4 weeks[i]		Every 12 weeks	X	
Collect whole blood for immunology analysis[p]	X	Every 4 weeks		Every 8 weeks	X	
Collect whole blood for ctDNA/ctRNA analysis (during routine blood draws)[p]	X	Every 4 weeks		Every 8 weeks	X	
Tumor biopsy[l]	X	8 weeks after the start of treatment				
Additional tumor biopsy		May be collected at any time point, as clinically indicated at the Investigator's discretion.				
Tumor Imaging and Assessments						
CT or MRI[q]	X	Every 8 weeks		Every 12 weeks	X	

[a] Treatment will continue until the subject experiences PD or unacceptable toxicity (not correctable with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those subjects who have a CR in the first year will move to the schedule of events for year 2. Any required laboratory sample collection listed below (eg, blood draws, urinalysis) may be performed within a 3-day window of the time indicated.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment. Subjects crossing over to treatment with the NANT CRC Vaccine in the single-arm phase 2 component of the study following disease progression on or after discontinuing regorafenib in the randomized phase 2 component of the study do not need to have an EOT visit as long as they commence treatment with the NANT CRC Vaccine within 30 (± 5 days) of their last regorafenib treatment, at which time they will be assessed according to the schedule of events described in Table 18. Crossover patients do not need to undergo screening assessments described in Table 18, except for providing any relevant new medical history occurring after enrollment in the trial.

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

[d] Also evaluated at enrollment.

[e] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
[f] Height required at screening visit only.
[g] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes.
[h] 12-lead ECG to be performed in triplicate at screening.
[i] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment. For ECG only, day 1 assessment can be skipped if the screening assessment was performed within 28 days prior to the start of treatment.
[j] HIV status to be determined by an approved test.
[k] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[l] Historic tumor biopsy specimen for tumor molecular profiling is required to determine eligibility for participation in the study. If an historic specimen is not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study medications. A tumor biopsy is also required 8 weeks after the start of treatment, if considered safe by the Investigator.
[m] Chemistry panel to include laboratory assessments noted in Table 17.
[n] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
[o] Serum pregnancy tests for females of child-bearing potential
[p] Blood collection for exploratory immunology and ctDNA/ctRNA analyses will be performed every 4 weeks (year 1or prior to CR) or 8 (year 2 or after CR) weeks during routine blood draws and at the end-of-treatment visit.
[q] All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation are to be completed at each assessment period.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	NANT Colorectal Cancer (CRC) Vaccine: A phase 1b/2 trial of the NANT CRC vaccine vs. regorafenib in subjects with metastatic CRC who have been previously treated with standard-of-care (SoC) therapy
Study Number:	QUILT-3.071
Version Number:	3
Final Date:	28 September 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: 9-28-18

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