# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADAPTIVE T-CELL THERAPY (ADENOVIRUS, YEAST, FUSION PROTEIN VACCINE) IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
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| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |

# 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:**

11. Avelumab (BAVENCIO® injection, for IV use)
12. Bevacizumab (AVASTIN® solution for IV infusion)
13. Capecitabine (XELODA® tablets, for oral use)
14. Cetuximab (ERBITUX® injection, for IV infusion)
15. Cisplatin (CISplatin injection)
16. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
17. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
18. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
19. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
20. Necitumumab (Portrazza® injection)
21. Omega-3-acid ethyl esters (LOVAZA® Capsules, for oral use)
22. Stereotactic body radiation therapy (SBRT)

**Name of Active Ingredients:**

**Investigational Products**

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

**Phase 2**

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

**Study Design:**

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

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

Treatment will be administered in 2 phases, an induction and a maintenance phase, as described below. Subjects will continue induction treatment for up to 1 year. Treatment in the study will be

discontinued if the subject experiences progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects who experience ongoing stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at the Investigator's and Sponsor's discretion. Subjects may remain in the maintenance phase of the study for up to 1 year. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The time on study treatment, including both the induction and maintenance phases, is up to 2 years. The duration of the study may exceed 2 years if the subject remains in the maintenance phase for more than 1 year, as described above.

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

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

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be conducted to inform HER2 expression and *RAS* mutational status and will be used to determine whether ETBX-021 and GI-4000 will be administered. ETBX-021 and GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. Treatment with all study drugs except ETBX-021 and GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations with ETBX-021 and GI-4000, respectively, will begin as soon as tumor molecular profiling results are available. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive ETBX-021 if their tumor overexpresses HER2 (≥ 750 attomole/µg of tumor tissue, as determined by quantitative proteomics with mass spectrometry). Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.5.14.1, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated Ras oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

**Induction Phase:**

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cetuximab or necitumumab, cisplatin, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-021, ETBX-051, and ETBX-061), 5-FU/leucovorin, yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 3 weeks. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Daily:

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 15–19, every 3 weeks:

- 5-FU (1,500 mg/m$^2$ continuous IV infusion over 85–96 hours)

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

- Cyclophosphamide (50 mg BID)

Days 1 and 8, every 3 weeks:

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

Days 1 and 15, every 3 weeks:

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

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

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

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

Days 8 and 15:

- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist), every 3 weeks for 2 cycles
- Aldoxorubicin HCl (80 mg/m$^2$ IV on day 8 and 30 mg/m$^2$ IV on day 15) , every 3 weeks

Days 8 and 16, every 3 weeks:

- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer.

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

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

- haNK ($2 \times 10^9$ cells/dose IV)

Day 11, every 3 weeks for 3 cycles and every 8 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.

**Maintenance Phase:**

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit from treatment, per the Investigator's and Sponsor's discretion. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, capecitabine, cetuximab or necitumumab, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-021, ETBX-051, and ETBX-061), yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 2 weeks.

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

Daily:

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

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (50 mg BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Cetuximab (250 mg/m$^2$ IV)

  **OR**
  necitumumab (400 mg IV)
- ALT-803 (10 µg/kg SC) (30 minutes prior to haNK infusion)
- haNK ($2 \times 10^9$ cells/dose IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

Day 5, every 8 weeks thereafter:

- ETBX-011, ETBX-021, ETBX-051, ETBX-061 ($1 \times 10^{11}$ 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.

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

**Exploratory Endpoints:**

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

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1 and irRC.

**Secondary Endpoints:**

- PFS by RECIST Version 1.1 and irRC.
- OS.
- DOR.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months).
- QoL by PROs.
- Incidence of treatment-emergent AEs 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. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.

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

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 900 cells/$mm^3$.
    b. Platelet count < 75,000 cells/$mm^3$.
    c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert’s syndrome).
    d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    e. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    f. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    g. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. To control hypertension it is recommended to first start propranolol SR 80 mg daily prior to initiating other hypertensive medications.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

| **Products, Dosage, and Mode of Administration:** | | |
|---|---|---|
| **Investigational Products** | **Dosage** | **Mode of Administration** |
| Aldoxorubicin HCl | 80 mg/m$^2$ or 30 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV |
| ALT-803 | 10 µg/kg | SC |
| ETBX-011 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-021 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-051 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-061 | $1 \times 10^{11}$ VP/dose | SC |
| GI-4000 | 40 YU/dose | SC |
| GI-6207 | 40 YU/dose | SC |
| GI-6301 | 40 YU/dose | SC |
| haNK | $2 \times 10^9$ cells/dose | IV |
| **Approved Products** | **Dosage** | **Mode of Administration** |
| Avelumab | 10 mg/kg | IV |
| Bevacizumab | 5 mg/kg | IV |
| Capecitabine | 650 mg/m$^2$ | PO BID |
| Cetuximab | 250 mg/m$^2$ | IV |
| Cisplatin | 40 mg/m$^2$ | IV |
| Cyclophosphamide | 50 mg | PO BID |
| 5-FU | 1500 mg/m$^2$ | 85- to 96-hour continuous IV infusion |
| Leucovorin | 20 mg/m$^2$ | IV bolus |
| Nab-paclitaxel | 125 mg (induction);<br>100 mg (maintenance) | IV |
| Necitumumab | 400 mg | IV |
| Omega-3-acid ethyl esters | 5 g | PO |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

- Induction phase: 8 weeks (minimum) to 1 year (maximum)
- Maintenance phase: Up to 1 year. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion.

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. The duration of the study can exceed 2 years if the subject continues to benefit and the maintenance phase is extended, per the Investigator's and Sponsor's discretion.

**Duration of Follow-up:**

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

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

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

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

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7,13,19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***ctDNA/ctRNA Analysis***: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

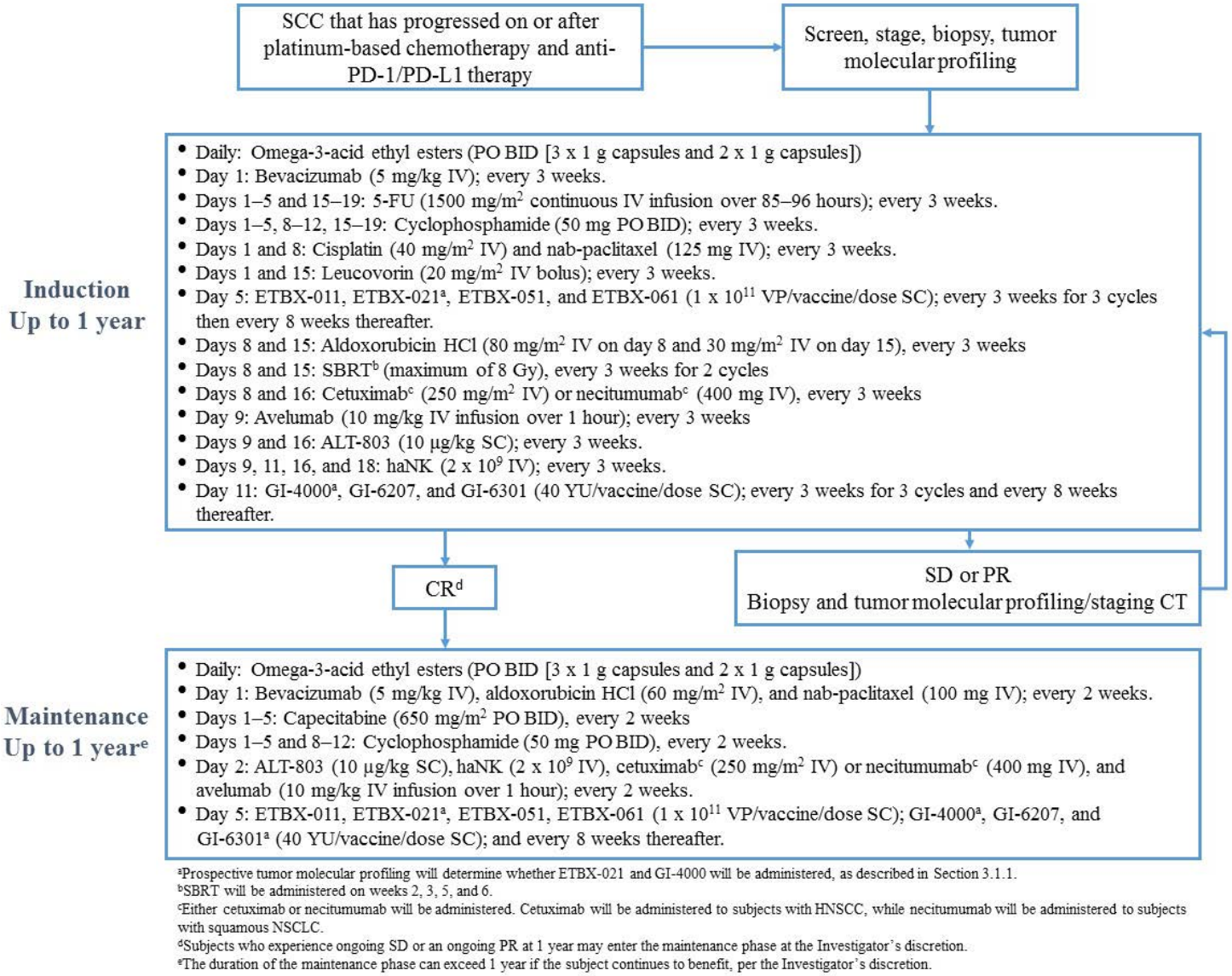
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

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

**Figure 1: Study Treatment Schema**



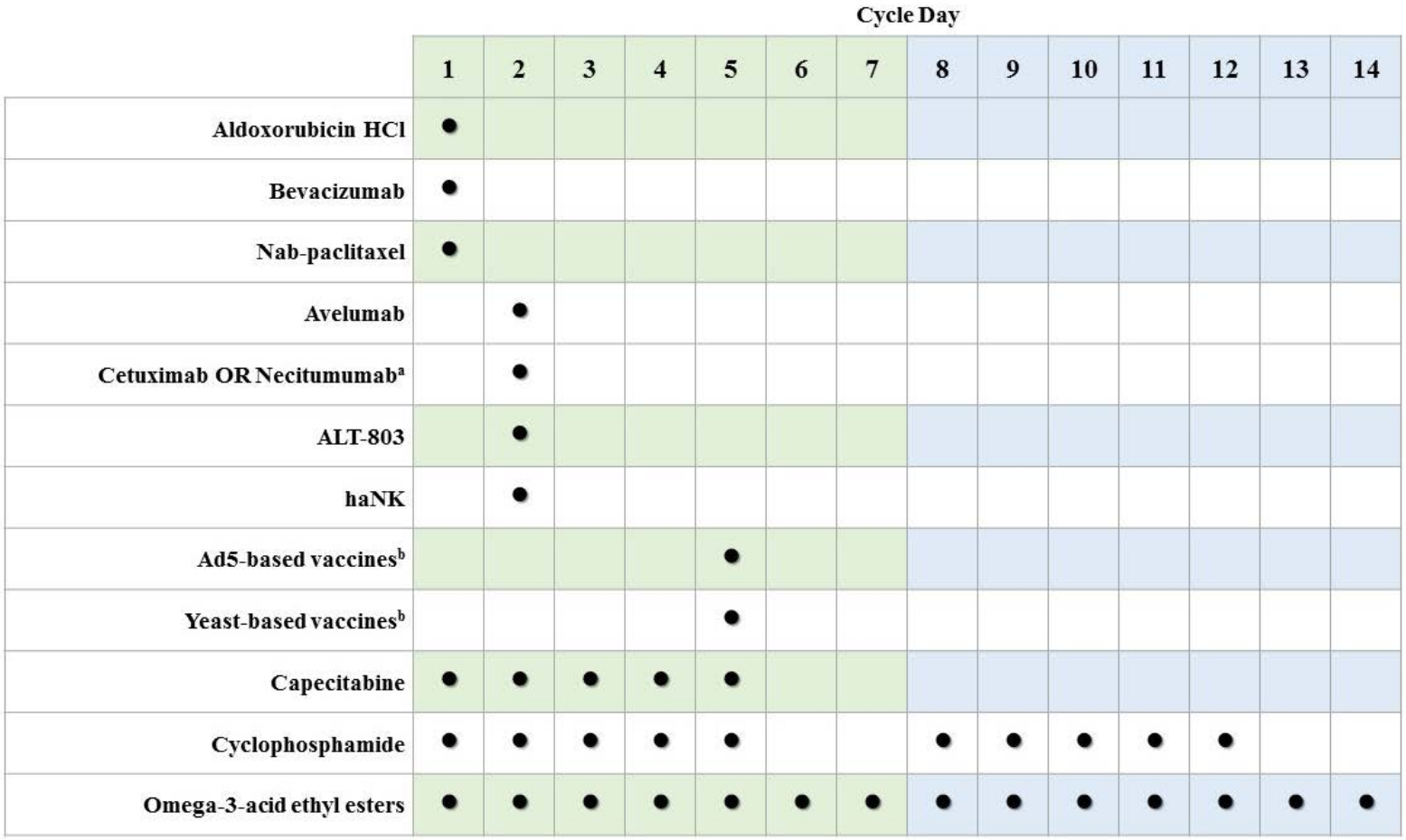

[a]Prospective tumor molecular profiling will determine whether ETBX-021 and GI-4000 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[d]Subjects who experience ongoing SD or an ongoing PR at 1 year may enter the maintenance phase at the Investigator's discretion.
[e]The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's discretion.

**Figure 2: Induction Phase Treatment Schema**

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

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered every 3 weeks for 3 cycles and then 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.
[b]SBRT will be administered on weeks 2,3,5, and 6.
[c]Aldoxorubicin will be dosed at 80 mg/m$^2$ IV on day 8 and 30 mg/m$^2$ IV on day 15
[d]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

**Figure 3: Maintenance Phase Treatment Schema**




Capecitabine, cyclophosphamide, and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[b]Each vaccine will be administered on Day 5 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.

**Table 18: Schedule of Events for Induction Phase of Study**

| | Screening | Induction Phase Treatment (repeats every 3 weeks, except where noted)[a] | | | | | | | | | | | | | | | | | | | | EOT Visit[b] | Unscheduled Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | | **1** | | | | | | | **2** | | | | | | | **3** | | | | | | | | |
| **Study Day** | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | | |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion[d] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history[e] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Confirm availability of FFPE tumor sample[f] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | | | | | | | X | | | | | | | X | | | | | | | X | X |
| Physical exam: height[g], weight | 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 | X |
| 12-lead ECG[i] | X | X | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X | Every 12 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Adverse event collection | | X | | | | 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[j] | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Hematology[l] | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Urinalysis | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Pregnancy test[m] | X | X[k] | Every 6 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for ctDNA/ctRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| CT, 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 corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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.

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

[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[g] Height required at screening visit only.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vitals 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, 1 hour post, 2 hours post, 3 hours post, 4 hours post, 5 hours post, 6 hours post, 7 hours post, and 8 hours post infusion. 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] Chemistry panel to include laboratory assessments noted in Table 17.
[k] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[l] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
[m] Serum pregnancy test at screening; urine dipstick pregnancy test for all other tests (for females of child-bearing potential).
[n] HIV status to be determined by ELISA and confirmed by western blot.
[o] Assessment of HER2 expression to determine whether ETBX-021 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. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling 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 thereafter in the induction phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). 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. The same mode of imaging is required to be carried through each subject's respective treatment period.

**Table 19: Schedule of Events for Maintenance Phase of Study**

| | **Maintenance Phase Treatment (repeats every 2 weeks, except where noted)**[a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | **1** | | | | | | | **2** | | | | | | | **EOT Visit**[b] | **Unscheduled Visit**[c] |
| **Study Day** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | | |
| Concomitant medications | X | | | | | | | | | | | | | | X | X |
| Physical exam, weight | X | | | | | | | | | | | | | | X | X |
| Vital signs[d] | X | X | | | X | | | | | | | | | | X | X |
| ECOG performance status | X | | | | | | | | | | | | | | 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | 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 | | | | | | | | | | | | | | | |
| 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. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

[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. Vitals 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, 1 hour post, 2 hours post, 3 hours post, 4 hours post, 5 hours post, 6 hours post, 7 hours post, and 8 hours post infusion. 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] Urine dipstick 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 be performed every 12 weeks in the maintenance phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adaptive T-Cell therapy (adenovirus, yeast, fusion protein vaccine) in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| **Study Number:** | QUILT-3.090 |
| **Version Number:** | 1.0 |
| **Final Date:** | 20 November 2017 |

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

Signed: _____ Date: Nov 21 2017

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# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |
| Version 2 | 27 December 2017 |

# 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:**

11. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
12. Bevacizumab (AVASTIN® solution for IV infusion)
13. Capecitabine (XELODA® tablets, for oral use)
14. Cetuximab (ERBITUX® injection, for IV infusion)
15. Cisplatin (CISplatin injection)
16. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
17. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
18. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
19. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
20. Necitumumab (Portrazza® injection)
21. Omega-3-acid ethyl esters (LOVAZA® Capsules, for oral use)
22. Stereotactic body radiation therapy (SBRT)

**Name of Active Ingredients:**

**Investigational Products**

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

**Phase 2**

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

**Study Design:**

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that the combination therapy is tolerable.

Treatment 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. Treatment in the study will be discontinued if the subject experiences progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a complete response (CR) in the induction phase will enter the maintenance phase of the study. Subjects who experience ongoing stable disease (SD) or an ongoing partial response (PR) at 1 year may enter the maintenance phase at the Investigator's and Sponsor's discretion. Subjects may remain in the maintenance phase of the study for up to 1 year. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. The time on study treatment, including both the induction and maintenance phases, is up to 2 years. The duration of the study may exceed 2 years if the subject remains in the maintenance phase for more than 1 year, as described above.

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

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

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be conducted to inform HER2 expression and *RAS* mutational status and will be used to determine whether ETBX-021 and GI-4000 will be administered. ETBX-021 and GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. Treatment with all study drugs except ETBX-021 and GI-4000 may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations with ETBX-021 and GI-4000, respectively, will begin as soon as tumor molecular profiling results are available. More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive ETBX-021 if their tumor overexpresses HER2 (≥ 750 attomole/µg of tumor tissue, as determined by quantitative proteomics with mass spectrometry). Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. As described in Section 1.5.14.1, GI-4000 is 4 separate products from the GI-4000 series (GI-4014, GI-4015, GI- 4016, and GI-4020); each of these expresses a combination of mutated Ras oncoproteins. The specific *RAS* mutation will determine which GI-4000 product will be used for

treatment (GI-4014 for G12V, GI-4015 for G12C, GI-4016 for G12D, GI-4020 for G12R or Q61H, and GI-4014, GI-4015, or GI-4016 for Q61L or Q61R).

**Induction Phase:**

The induction phase will consist of repeated 3-week cycles for a maximum treatment period of 1 year. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, cetuximab or necitumumab, cisplatin, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-021, ETBX-051, and ETBX-061), 5-FU/leucovorin, yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 3 weeks. Concurrent SBRT will be given during the first two 3-week cycles. Radiation will be administered to no more than 5 tumor sites using SBRT, as described in Section 5.1.5.1.

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

Daily:

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)

Days 1–5 and 15–19, every 3 weeks:

- 5-FU (1,500 mg/m$^2$ continuous IV infusion over 85–96 hours)

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

- Cyclophosphamide (25 mg BID)

Days 1 and 8, every 3 weeks:

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

Days 1 and 15, every 3 weeks:

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

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

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

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

Days 8 and 15, every 3 weeks:

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

Days 8 and 16, every 3 weeks:

- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).

Day 9, every 3 weeks:

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

Days 9 and 16, every 3 weeks:

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

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

- haNK ($2 \times 10^9$ 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.

**Maintenance Phase:**

The duration of the maintenance phase will be up to 1 year following completion of the last treatment in the induction phase. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit from treatment, per the Investigator's and Sponsor's discretion. The maintenance phase will consist of repeated 2-week cycles. The treatment regimen of aldoxorubicin HCl, ALT-803, avelumab, bevacizumab, capecitabine, cetuximab or necitumumab, cyclophosphamide, Ad5-based vaccines (ETBX-011, ETBX-021, ETBX-051, and ETBX-061), yeast-based vaccines (GI-4000, GI-6207, and GI-6301), haNK cells, nab-paclitaxel, and omega-3-acid ethyl esters will be repeated every 2 weeks.

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

Daily:

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

Day 1, every 2 weeks:

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

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Cetuximab (250 mg/m$^2$ IV)

  **OR**
  necitumumab (400 mg IV)
- ALT-803 (10 µg/kg SC) (at least 30 minutes prior to haNK infusion)
- haNK ($2 \times 10^9$ cells/dose IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

Day 5, every 8 weeks thereafter:

- ETBX-011, ETBX-021, ETBX-051, ETBX-061 ($1 \times 10^{11}$ 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.

**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 stable disease [SD] lasting for at least 2 months) by RECIST Version 1.1 and irRC.

- QoL by PROs.

**Exploratory Endpoints:**

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

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1.

**Secondary Endpoints:**

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- QoL by PROs.
- Incidence of treatment-emergent AEs 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. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.5 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 1,000 cells/$mm^3$.
    b. 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 levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
g. Serum creatinine > 2.0 mg/dL or 177 µmol/L.
h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

| **Products, Dosage, and Mode of Administration:** | | |
|---|---|---|
| **Investigational Products** | **Dosage** | **Mode of Administration** |
| Aldoxorubicin HCl | 80 mg/m$^2$ or 30 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV |
| 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 |
| Bevacizumab | 5 mg/kg | IV |
| Capecitabine | 650 mg/m$^2$ | PO BID |
| Cetuximab | 250 mg/m$^2$ | IV |
| Cisplatin | 40 mg/m$^2$ | IV |
| Cyclophosphamide | 25 mg | PO BID |
| 5-FU | 1500 mg/m$^2$ | 85- to 96-hour continuous IV infusion |
| Leucovorin | 20 mg/m$^2$ | IV bolus |
| Nab-paclitaxel | 125 mg (induction);<br>100 mg (maintenance) | IV |
| Necitumumab | 400 mg | IV |
| Omega-3-acid ethyl esters | 4 g | PO |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

- Induction phase: 8 weeks (minimum) to 1 year (maximum)
- Maintenance phase: Up to 1 year. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion.

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. The duration of the study can exceed 2 years if the subject continues to benefit and the maintenance phase is extended, per the Investigator's and Sponsor's discretion.

**Duration of Follow-up:**

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

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

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

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

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7,13,19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***ctDNA/ctRNA Analysis***: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

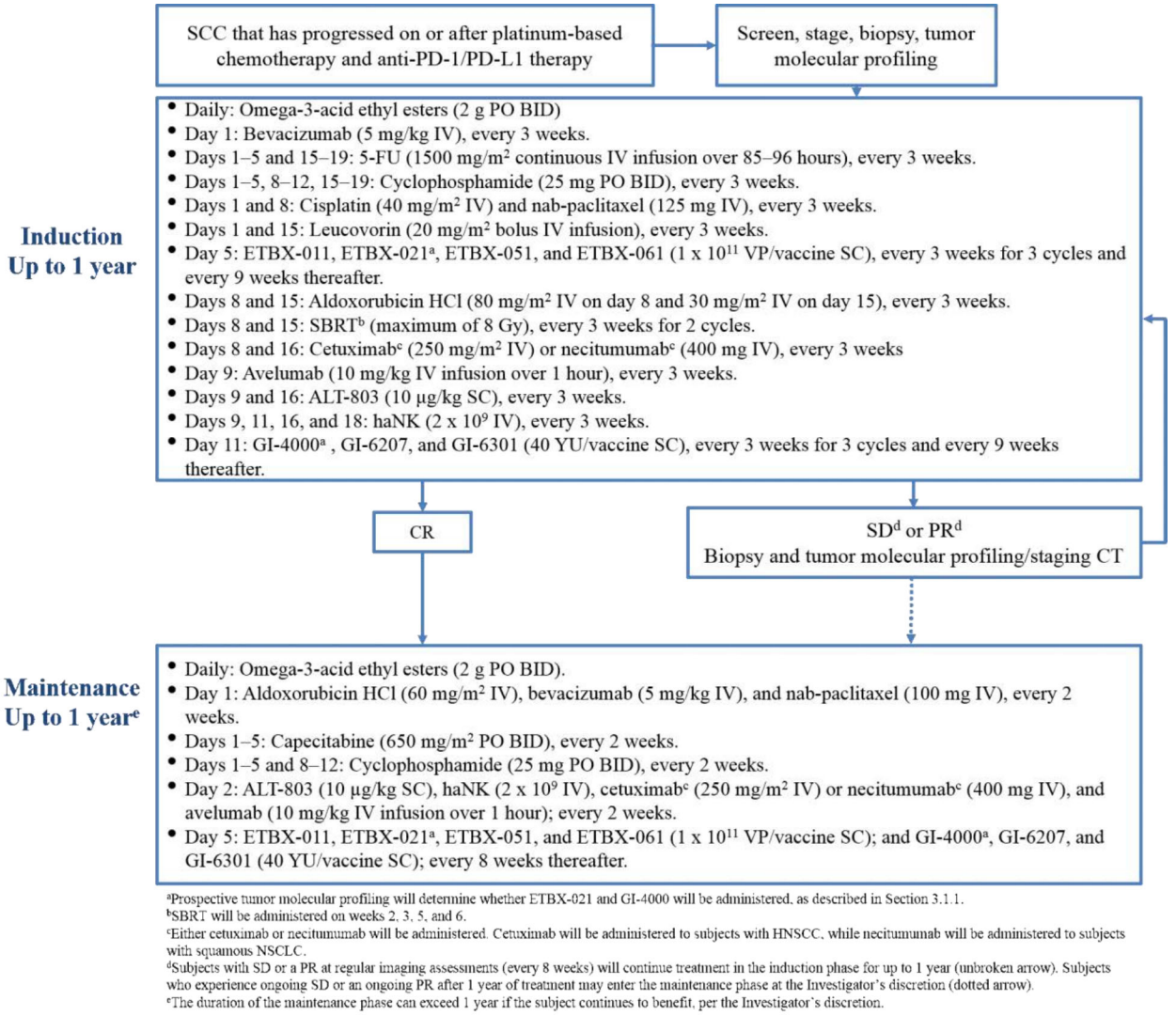
Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

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

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

**Figure 1: Study Treatment Schema**




[a]Prospective tumor molecular profiling will determine whether ETBX-021 and GI-4000 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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]The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's discretion.

**Figure 2: Induction Phase Treatment Schema**

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

Cyclophosphamide and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 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.
[b]SBRT will be administered on weeks 2,3,5, and 6.
[c]Aldoxorubicin will be dosed at 80 mg/m$^2$ IV on day 8 and 30 mg/m$^2$ IV on day 15
[d]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

**Figure 3: Maintenance Phase Treatment Schema**

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

Capecitabine, cyclophosphamide, and omega-3-acid ethyl esters are self-administered on the days indicated.
[a]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[b]Each vaccine will be administered on Day 5 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.

**Table 18: Schedule of Events for Induction Phase of Study**

| | Screening | Induction Phase Treatment (repeats every 3 weeks, except where noted)[a] | | | | | | | | | | | | | | | | | | | | EOT Visit[b] | Unscheduled Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | | **1** | | | | | | | **2** | | | | | | | **3** | | | | | | | | |
| **Study Day** | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | | |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion[d] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history[e] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Confirm availability of FFPE tumor sample[f] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | | | | | | | X | | | | | | | X | | | | | | | X | X |
| Physical exam: height[g], weight | 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 | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X | Every 12 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Adverse event collection | | X | | | | 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[j] | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Hematology[l] | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Urinalysis | X | X[k] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Pregnancy test[m] | X | X[k] | Every 6 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for ctDNA/ctRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| CT, 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 corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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. Any required blood draws may be performed within a 3-day window of the time indicated.

[b] End-of-treatment visit must be performed 30 (±5 days) after the last study treatment.
[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[g] Height required at screening visit only.
[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] Chemistry panel to include laboratory assessments noted in Table 17.
[k] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[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 ELISA.
[o] Assessment of HER2 expression to determine whether ETBX-021 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. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling 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 thereafter in the induction phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). 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. The same mode of imaging is required to be carried through each subject's respective treatment period.

**Table 19: Schedule of Events for Maintenance Phase of Study**

| | **Maintenance Phase Treatment (repeats every 2 weeks, except where noted)**[a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | **1** | | | | | | | **2** | | | | | | | **EOT Visit**[b] | **Unscheduled Visit**[c] |
| **Study Day** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | | |
| Concomitant medications | X | | | | | | | | | | | | | | X | X |
| Physical exam, weight | X | | | | | | | | | | | | | | X | X |
| Vital signs[d] | X | X | | | X | | | | | | | | | | X | 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | 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 | | | | | | | | | | | | | | | |

| | **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** | | |
| 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. The duration of the maintenance phase can exceed 1 year if the subject continues to benefit, per the Investigator's and Sponsor's discretion. Treatment will continue in the maintenance phase until the subject experiences PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required blood draws 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 be performed every 12 weeks in the maintenance phase. Evaluations may include CT, MRI, or PET-CT scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at screening), and brain (only as clinically warranted based on symptoms/findings). RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| **Study Number:** | QUILT-3.090 |
| **Version Number:** | 2 |
| **Final Date:** | 27 December 2017 |

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

Signed: _____ Date: 12-27-17

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# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |
| Version 2 | 27 December 2017 |
| Version 3 | 27 February 2018 |

# 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. Bevacizumab (AVASTIN® solution for IV infusion)
3. Capecitabine (XELODA® tablets, for oral use)
4. Cetuximab (ERBITUX® injection, for IV infusion)
5. Cisplatin (CISplatin injection)
6. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
7. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
8. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
9. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
10. Necitumumab (Portrazza® injection)
11. Stereotactic body radiation therapy (SBRT)

**Name of Active Ingredients:**

**Investigational Products**

1. Aldoxorubicin HCl
2. ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

**Phase 2**

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

**Study Design:**

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial

3 subjects suggest that the combination therapy is tolerable.

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

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

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

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be conducted to inform HER2 expression and *RAS* mutational status and will be used to determine whether ETBX-021 and GI-4000 will be administered. ETBX-021 and GI-4000 administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study, as described in Section 3.1.1). More information on the collection of tumor tissue and whole blood is described in Section 6.4.1.2 and is similar to the collection of samples for the exploratory tumor molecular profiling.

Subjects will receive ETBX-021 if their tumor overexpresses HER2 (≥ 750 attomole/µg of tumor tissue, as determined by quantitative proteomics with mass spectrometry). Subjects will receive GI-4000 if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing.

**Induction Phase:**

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

Day 1, every 3 weeks:

- Bevacizumab (5 mg/kg IV)
- Leucovorin (20 mg/m$^2$ IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (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 ($1 \times 10^{11}$ virus particles [VP]/vaccine/dose subcutaneously [SC])

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

Day 8

- Aldoxorubicin HCl (80 mg/m$^2$ IV over 30 minutes)
- Cisplatin (20 mg/m$^2$ IV over 1 hour)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)
- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily [QD])

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 ($2 \times 10^9$ cells/dose IV)

Day 11, every 3 weeks:

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

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).

Day 18, every 3 weeks:

- haNK ($2 \times 10^9$ cells/dose IV)

**Maintenance Phase:**

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

Day 1, every 2 weeks:

- Aldoxorubicin HCl (60 mg/m$^2$ IV over 30 minutes)
- Bevacizumab (5 mg/kg IV)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Days 1–5 and 8–12, every 2 weeks:

- Cyclophosphamide (25 mg PO BID)

Day 2, every 2 weeks:

- Avelumab (10 mg/kg IV over 1 hour)
- Cetuximab (250 mg/m$^2$ IV)

**OR**
necitumumab (400 mg IV)

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

Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

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

- ETBX-011, ETBX-021, ETBX-051, ETBX-061 ($1 \times 10^{11}$ 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.

**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 stable disease [SD] lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- QoL by PROs.

**Exploratory Endpoints:**

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

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1.

**Secondary Endpoints:**

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- QoL by PROs.
- Incidence of treatment-emergent AEs 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 assessed on BICR. A charter for the conduct of BICR will be prepared by the vendor selected to perform the independent review.

**Enrollment (planned):**

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count < 1,000 cells/$mm^3$.
   b. 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 levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
   g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
   h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

| **Products, Dosage, and Mode of Administration:** | | |
|---|---|---|
| **Investigational Products** | **Dosage** | **Mode of Administration** |
| Aldoxorubicin HCl | 80 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV |
| ALT-803 | 10 µg/kg | SC |
| ETBX-011 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-021 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-051 | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-061 | $1 \times 10^{11}$ VP/dose | SC |
| GI-4000 | 40 YU/dose | SC |
| GI-6207 | 40 YU/dose | SC |
| GI-6301 | 40 YU/dose | SC |
| haNK | $2 \times 10^9$ cells/dose | IV |
| **Approved Products** | **Dosage** | **Mode of Administration** |
| Avelumab | 10 mg/kg | IV |
| Bevacizumab | 5 mg/kg | IV |
| Capecitabine | 650 mg/m$^2$ BID | PO |
| Cetuximab | 250 mg/m$^2$ | IV |
| Cisplatin | 40 mg/m$^2$ (day 1) or 20 mg/m$^2$ (day 8) | IV |
| Cyclophosphamide | 25 mg BID (days 1-5 of induction);<br>25 mg once daily (days 8-12 of induction);<br>25 mg BID (maintenance) | PO |
| 5-FU | 1500 mg/m$^2$ | 85- to 96-hour continuous IV infusion |
| Leucovorin | 20 mg/m$^2$ | IV bolus |
| Nab-paclitaxel | 125 mg (induction);<br>100 mg (maintenance) | IV |
| Necitumumab | 400 mg | IV |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

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

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase), or until they experience 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.

**Duration of Follow-up:**

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

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

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

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

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

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

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

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7,13,19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***ctDNA/ctRNA Analysis***: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Safety results will be presented separately for the induction and maintenance phases of treatment as well as overall for the entire treatment regimen. Efficacy results will be summarized for the overall treatment regimen.

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

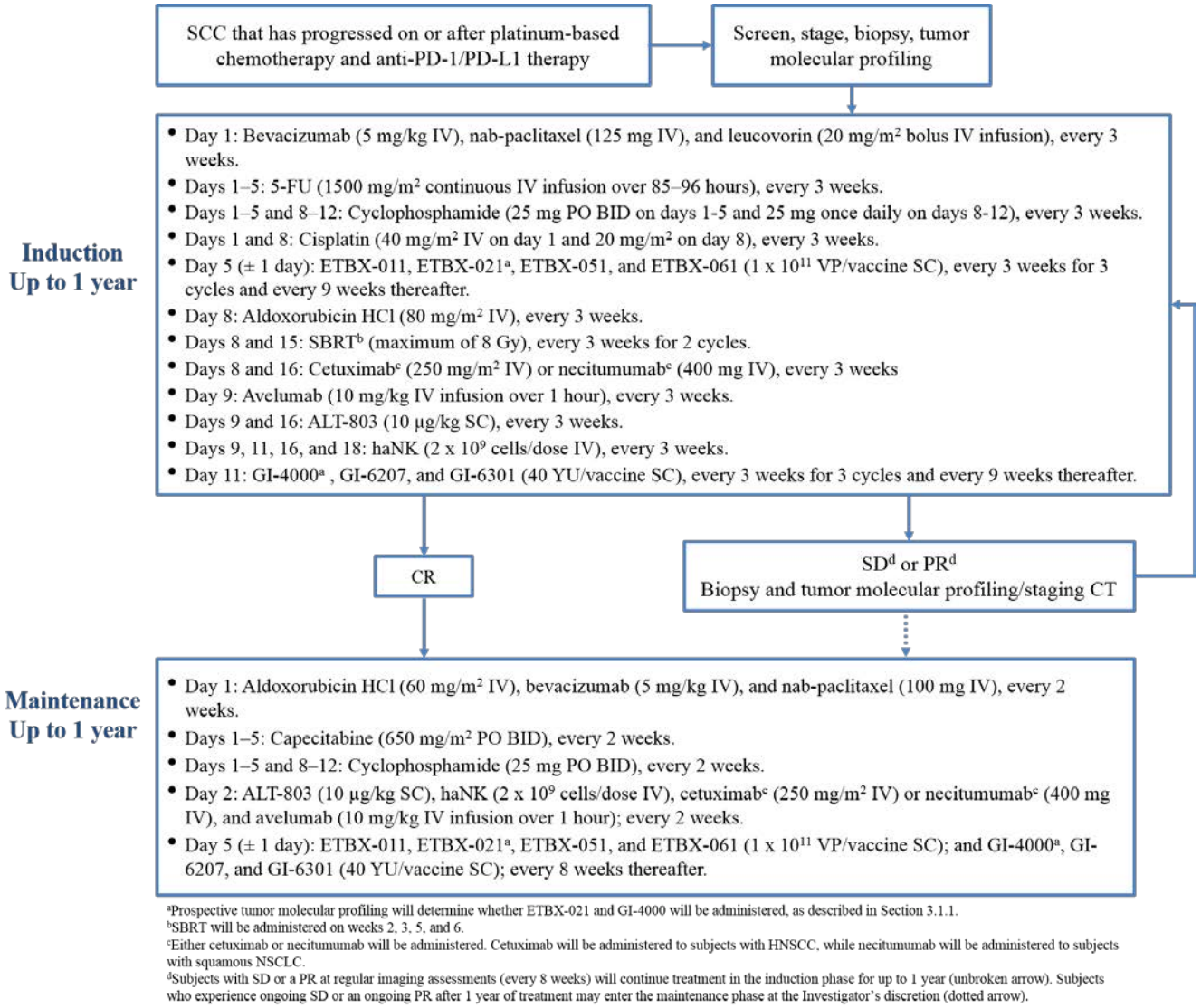
ORR will be evaluated in accordance with RECIST Version 1.1 and irRC. The percentage of subjects (and 95% confidence interval [CI]) who achieve a confirmed response will be summarized. DCR will be evaluated similar to ORR.

PFS, OS, and DOR will be analyzed using Kaplan-Meier methods.

Descriptive statistics of PROs will be presented.

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

**Figure 1: Study Treatment Schema**




[a]Prospective tumor molecular profiling will determine whether ETBX-021 and GI-4000 will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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).

**Figure 2: Induction Phase Treatment Schema**

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

[a]Cisplatin 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 may be given on days 4 or 6 instead if necessitated by scheduling issues. 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]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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**

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

Capecitabine and cyclophosphamide are self-administered on the days indicated.
[a]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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.

**Table 18: Schedule of Events for Induction Phase of Study**

| | Screening | Induction Phase Treatment (repeats every 3 weeks, except where noted)[a] | | | | | | | | | | | | | | | | | | | | EOT Visit[b] | Unscheduled Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | | **1** | | | | | | | **2** | | | | | | | **3** | | | | | | | | |
| **Study Day** | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | | |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion[d] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history[e] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Confirm availability of FFPE tumor sample[f] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | | | | | | | X | | | | | | | X | | | | | | | X | X |
| Physical exam: height, weight[g] | X | X | | | | | | | X | | | | | | | X | | | | | | | X | X |
| Vital signs[h] | X | X | | | | X | | | X | X | | X | | | | X | X | | X | | | | X | X |
| ECOG performance status | X | X | | | | | | | X | | | | | | | X | | | | | | | X | |
| 12-lead ECG[i] | X | X[j] | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X[j] | Every 12 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Adverse event collection | | X | | | | 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 | |
| Hematology[l] | X | X[j] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Urinalysis | X | X[j] | | | | | | | X | | | | | | | X | | | | | | | X | |
| Pregnancy test[m] | X | X[j] | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Serum virology (HIV)[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Determine HER2 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for ctDNA/ctRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| CT, 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 corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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. Any required laboratory sample collection (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.
[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes and within 30 minutes prior to the start of any infusional study treatment. For visits where a subject is receiving an infusion of any study compounds, vital signs will be collected at the following time points in relation to the start of first infusion of the day: prior to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.
[i] 12-lead ECG to be performed in triplicate at screening.
[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[k] Chemistry panel to include laboratory assessments noted in Table 17.
[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 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. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 will begin as soon as molecular profiling results are available.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling 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. 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 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | 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 | | | | | | | | | | | | | | | |

| | **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** | | |
| 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 corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required 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 be performed every 12 weeks in the maintenance phase, as described in Section 6. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| **Study Number:** | QUILT-3.090 |
| **Version Number:** | 3 |
| **Final Date:** | 27 February 2018 |

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

Signed: _____ Date: Feb 27 2018

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# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |
| Version 2 | 27 December 2017 |
| Version 3 | 01 March 2018 |
| Version 4 | 06 July 2018 |

## STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

# PROTOCOL SYNOPSIS

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

**Name of Investigational Products:**

1. Aldoxorubicin hydrochloride (HCl)
2. ALT-803 (recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])
3. ETBX-011 (adenovirus serotype-5 [Ad5] [E1-, E2b-]-carcinoembryonic antigen [CEA] vaccine)
4. ETBX-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. Bevacizumab (AVASTIN® solution for IV infusion)
3. Capecitabine (XELODA® tablets, for oral use)
4. Cetuximab (ERBITUX® injection, for IV infusion)
5. Cisplatin (CISplatin injection)
6. Cyclophosphamide (Cyclophosphamide Capsules, for oral use; or Cyclophosphamide Tablets, USP)
7. 5-Fluorouracil (5-FU; Fluorouracil Injection, for IV use only)
8. Leucovorin (LEUCOVORIN Calcium for Injection, for IV or intramuscular [IM] use)
9. Nab-paclitaxel (ABRAXANE® for Injectable Suspension [paclitaxel protein-bound particles for injectable suspension] [albumin-bound])
10. Necitumumab (Portrazza® injection)
11. Stereotactic body radiation therapy (SBRT)

**Name of Active Ingredients:**

**Investigational Products**

1. Aldoxorubicin HCl
2. ALT-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC Vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT SCC Vaccine regimen as assessed by ORR using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to determine additional measures of safety and efficacy (ORR by immune-related response criteria (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 SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial

3 subjects suggest that the combination therapy is tolerable.

Treatment 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.

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

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

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase until progression occurs 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, experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4-6 weeks after the initial response.

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. 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.

Prospective tumor molecular profiling will be conducted to inform HER2 expression and *RAS* mutational status and will be used to determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered. ETBX-021 (HER2) and GI-4000 (RAS) administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive all other agents regardless of their tumor molecular profile.

Subjects will receive ETBX-021 (HER2) if their tumor is HER2-positive (IHC 3+ or FISH positive), as determined by an FDA-approved test. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing.

**Induction Phase:**

Treatment in the induction phase will consist of repeated 3-week cycles for a maximum treatment

period of 1 year, as follows:

Day 1, every 3 weeks for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- Leucovorin (20 mg/m$^2$ IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (40 mg/m$^2$ IV over approximately 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:

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

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

Day 8, every 3 weeks:

- Aldoxorubicin HCl (80 mg/m$^2$ IV over approximately 30 minutes)
- Cisplatin (20 mg/m$^2$ IV over approximately 1 hour)
- SBRT (not to exceed 8 Gy, exact dose to be determined by the radiation oncologist; for the first 2 cycles only)
- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).

Days 8–12, every 3 weeks:

- Cyclophosphamide (25 mg PO daily)

Day 9, every 3 weeks:

- ALT-803 (15 µg/kg SC at least 30 minutes prior to haNK infusion)
- haNK ($2 \times 10^9$ cells/dose IV)
- Avelumab (10 mg/kg IV over approximately 1 hour)

Day 11, every 3 weeks:

- haNK ($2 \times 10^9$ cells/dose IV)

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

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

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

Day 15, every 3 weeks:

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

Day 16, every 3 weeks:

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

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

Day 18, every 3 weeks:

- haNK ($2 \times 10^9$ cells/dose IV)

**Maintenance Phase:**

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

Day 1, every 2 weeks:

- Aldoxorubicin HCl (60 mg/$m^2$ IV over approximately 30 minutes)
- Nab-paclitaxel (100 mg IV)

Days 1–5, every 2 weeks:

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

Day 2, every 2 weeks:

- ALT-803 (15 µg/kg SC) (at least 30 minutes prior to haNK infusion)
- haNK ($2 \times 10^9$ cells/dose IV)

- Avelumab (10 mg/kg IV over approximately 1 hour)
- Cetuximab (250 mg/$m^2$ IV)

  **OR**
  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

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

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), ETBX-061 (MUC1) ($1 \times 10^{11}$ VP/vaccine/dose SC)
- Yeast-based vaccines: GI-4000 (RAS), GI-6207 (CEA), GI-6301 (Brachyury) (40 YU/vaccine/dose SC), approximately 2 hours after administration of Ad-5 based vaccines

  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)

**Phase 1b**

**Primary Endpoint:**

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

**Secondary Endpoints:**

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

**Exploratory Endpoints:**

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

- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1.

**Secondary Endpoints:**

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- QoL by PROs.
- Incidence of treatment-emergent AEs 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 a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on BICR. A charter for the conduct of BICR will be prepared by the vendor selected to perform the independent review.

**Enrollment (planned):**

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Age $\geq$ 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for prospective tumor molecular profiling and exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 1,000 cells/$mm^3$.
    b. 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 levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases,

or >10 × ULN in subjects with bone metastases).
g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

| **Products, Dosage, and Mode of Administration:** | | |
|---|---|---|
| **Investigational Products** | **Dosage** | **Mode of Administration** |
| Aldoxorubicin HCl | 80 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV over approximately 30 minutes |
| ALT-803 | 15 µg/kg | SC |
| ETBX-011 (CEA) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-021 (HER2) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-051 (Brachyury) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-061 (MUC1) | $1 \times 10^{11}$ 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 | $2 \times 10^9$ cells/dose | IV |
| **Approved Products** | **Dosage** | **Mode of Administration** |
| Avelumab | 10 mg/kg | IV over approximately 1 hour |
| Bevacizumab | 5 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 |
| Cisplatin | 40 mg/m$^2$ (day 1 of induction) or 20 mg/m$^2$ (day 8 of induction) | IV over approximately 1 hour |
| Cyclophosphamide | 25 mg BID (days 1-5);<br>25 mg once daily (days 8-12) | PO |
| 5-FU | 1500 mg/m$^2$ | 85- to 96-hour continuous IV infusion |
| Leucovorin | 20 mg/m$^2$ | IV bolus |
| Nab-paclitaxel | 125 mg (induction);<br>100 mg (maintenance) | IV |
| Necitumumab | 400 mg | IV |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

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

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase), or until they experience confirmed 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.

**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 or MRI 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 IP.

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 (by any cause). Additional information from a subject's medical records relevant to this study may be provided to NantKwest as needed to understand the safety and efficacy of the regimen tested in this protocol.

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

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

ORR and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. 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-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7,13,19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC Vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***ctDNA/ctRNA Analysis***: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

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

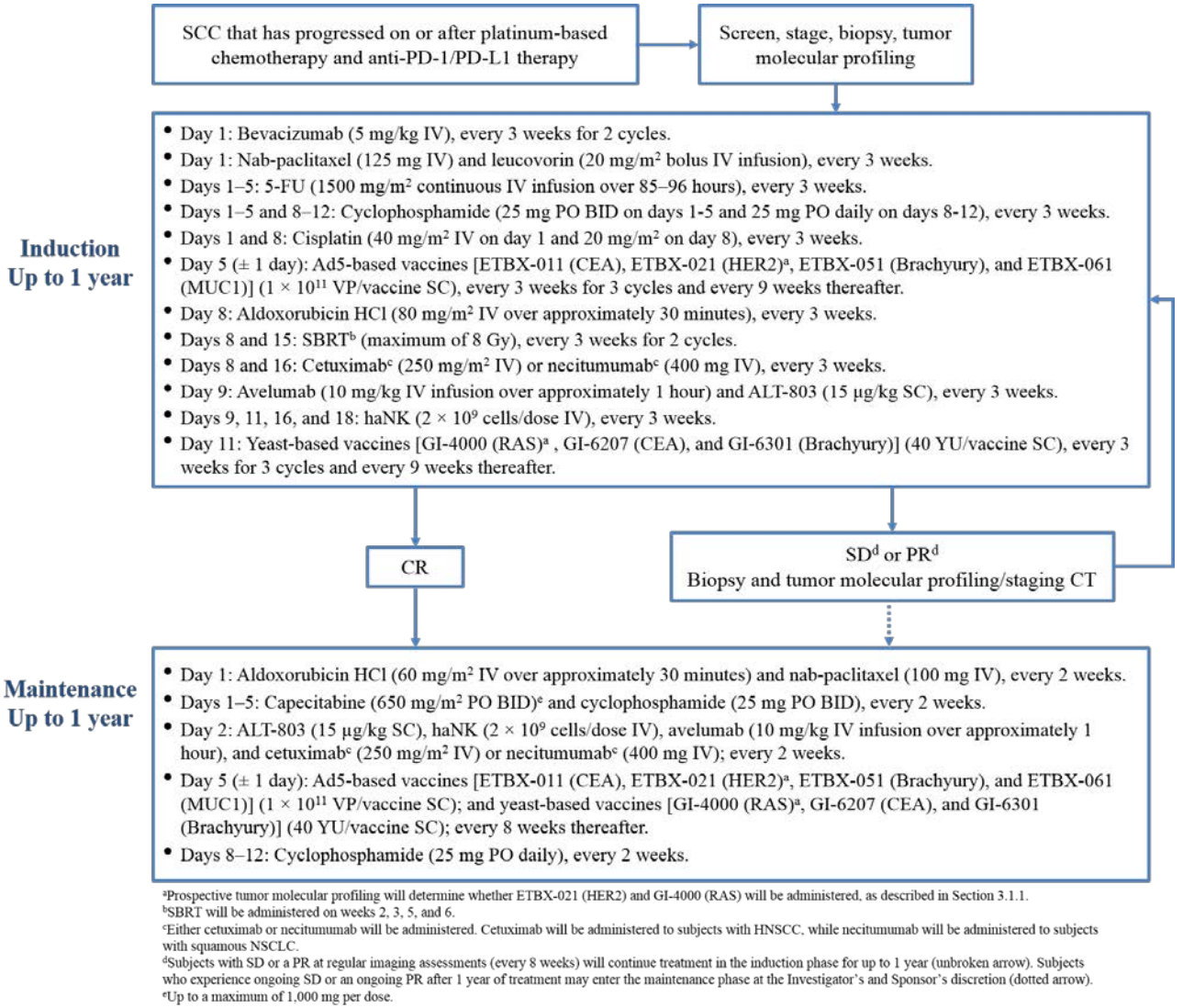
Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, ECHOs, and vital signs.

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

Descriptive statistics of PROs will be presented.

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

**Figure 1: Study Treatment Schema**




[a]Prospective tumor molecular profiling will determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered, as described in Section 3.1.1.
[b]SBRT will be administered on weeks 2, 3, 5, and 6.
[c]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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 and Sponsor's discretion (dotted arrow).
[e]Up to a maximum of 1,000 mg per dose.

**Figure 2: Induction Phase Treatment Schema**

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

[a]Administered for first 2 cycles only.
[b]Cisplatin will be administered at 40 mg/m$^2$ on day 1 and 20 mg/m$^2$ on day 8.
[c]Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Ad5-based vaccines will be given on day 5 (± 1 day) and yeast-based vaccines will be given on day 11. 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.
[d]SBRT will be administered on weeks 2,3,5, and 6.
[e]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[f]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**

| | Cycle Day | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| **Aldoxorubicin HCl** | ● | | | | | | | | | | | | | |
| **Nab-paclitaxel** | ● | | | | | | | | | | | | | |
| **Avelumab** | | ● | | | | | | | | | | | | |
| **Cetuximab[a] OR necitumumab[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]Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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.
[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 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 6 weeks | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X[j] | Every 12 weeks | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 weeks | | | | | | | | | | | | | | | | | | | X | |
| Adverse event collection | | X | | | | 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 | |
| Hematology[l] | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Urinalysis | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Pregnancy test[m] | X | X[j] | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Serum virology (HIV)[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Determine HER2 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for ctDNA/ctRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| CT or MRI[s] | X | Every 8 weeks | | | | | | | | | | | | | | | | | | | | | X | |

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences confirmed PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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. Any required laboratory sample collection (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.
[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available.
[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes and within 30 minutes prior to the start of any infusional study treatment. For visits where a subject is receiving an infusion of any study compounds, vital signs will be collected at the following time points in relation to the start of first infusion of the day: prior to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.
[i] 12-lead ECG to be performed in triplicate at screening.
[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment.
[k] Chemistry panel to include laboratory assessments noted in Table 17.
[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) will be administered to the subject, as described in Section 3.1.1. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and ctDNA/ctRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling 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 or MRI will be performed at screening and every 8 weeks during the induction phase, as described in Section 6. 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 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **<u>Laboratory Assessments</u>** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | 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 | | | | | | | | | | | | | | | |

| | **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** | | |
| 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 PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required 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 or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

## APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| **Study Number:** | QUILT-3.090 |
| **Version Number:** | 4 |
| **Final Date:** | 06 July 2018 |

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

Signed: _____ Date: July 10 2018

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# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |
| Version 2 | 27 December 2017 |
| Version 3 | 01 March 2018 |
| Version 4 | 06 July 2018 |
| Version 5 | 01 August 2018 |

# PROTOCOL SYNOPSIS

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

**Name of Investigational Products:**

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

**Name of Approved Products:**

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

**Name of Active Ingredients:**

**Investigational Products**

1. Aldoxorubicin HCl
2. ALT-803, recombinant human superagonist interleukin-15 (IL-15) complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
3. Ad5 [E1-, E2b-]-CEA
4. Ad5 [E1-, E2b-]-HER2
5. Ad5 [E1-, E2b-]-Brachyury
6. Ad5 [E1-, E2b-]-MUC1
7. GI-4014 expressing mutations in *RAS* at codon 12 (G12V), and codon 61 (Q61R and Q61L); GI-4015 expressing mutations in *RAS* at codon 12 (G12C), and codon 61 (Q61R and Q61L); GI-4016 expressing mutations in *RAS* at codon 12 (G12D) and codon 61 (Q61R and Q61L) and GI-4020 expressing mutations in *RAS* at codon 12 (G12R) and codon 61 (Q61L and Q61H)
8. Recombinant yeast based vaccine expressing the full length human carcinoembryonic antigen (CEA), with a modified gene coding sequence to code for a single amino acid substitution (asparagine to aspartic acid) at the native protein amino acid position 610
9. Recombinant yeast based vaccine expressing the human brachyury oncoprotein
10. NK92 [CD16.158V, ER IL2] cells

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC Vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
- Secondary objectives are to obtain preliminary estimates of efficacy by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).
- Exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in circulating tumor DNA (ctDNA) and RNA (ctRNA); and their correlations with subject outcomes.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT SCC Vaccine regimen as assessed by ORR using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to determine additional measures of safety and efficacy (ORR by immune-related response criteria (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 SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that

the combination therapy is tolerable.

Treatment 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.

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

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

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase until progression occurs 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, experimental treatment may continue and an imaging assessment should be done 4-6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. 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.

Prospective tumor molecular profiling will be conducted to inform HER2 expression and *RAS* mutational status and will be used to determine whether ETBX-021 (HER2) and GI-4000 (RAS) will be administered. ETBX-021 (HER2) and GI-4000 (RAS) administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive other agents regardless of their tumor molecular profile.

Subjects will receive ETBX-021 (HER2) if their tumor is HER2-positive (IHC 3+ or FISH positive), as determined by an FDA-approved test. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing.

**Induction Phase:**

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

Day 1, every 3 weeks for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- Leucovorin (20 mg/$m^2$ IV bolus)
- Nab-paclitaxel (125 mg IV)
- Cisplatin (32 mg/$m^2$ IV)

Days 1–5, every 3 weeks:

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

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

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) ($1 \times 10^{11}$ 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 ($2 \times 10^9$ cells/dose IV)
- Avelumab (10 mg/kg IV)

Day 11, every 3 weeks:

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

  **OR**

necitumumab (400 mg IV)

Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).

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 ($2 \times 10^9$ cells/dose IV)
- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

**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:

- Cyclophosphamide (25 mg PO BID)

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

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

Day 2, every 2 weeks:

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

  **OR**
  necitumumab (400 mg IV)

Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

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

- Ad5-based vaccines: ETBX-011 (CEA), ETBX-021 (HER2), ETBX-051 (Brachyury), and ETBX-061 (MUC1) ($1 \times 10^{11}$ 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)

**Phase 1b**

**Primary Endpoint:**

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

**Secondary Endpoints:**

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

**Exploratory Endpoints:**

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

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1.

**Secondary Endpoints:**

- ORR by irRC.
- PFS by RECIST Version 1.1.
- PFS by irRC.
- OS.
- DOR by RECIST Version 1.1 and irRC.
- DCR (confirmed CR, PR, or SD lasting for at least 2 months) by RECIST Version 1.1 and irRC.
- QoL by PROs.
- Incidence of treatment-emergent AEs 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 a local independent radiologist; in the phase 2 portion of the study, the primary assessment of response will be based on BICR. A charter for the conduct of BICR will be prepared by the vendor selected to perform the independent review.

**Enrollment (planned):**

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

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

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 1,000 cells/$mm^3$.
    b. 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 levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.

6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

| **Products, Dosage, and Mode of Administration:** | | |
|---|---|---|
| **Investigational Products** | **Dosage** | **Mode of Administration** |
| Aldoxorubicin HCl | 100 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV |
| ALT-803 | 15 µg/kg | SC |
| ETBX-011 (CEA) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-021 (HER2) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-051 (Brachyury) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-061 (MUC1) | $1 \times 10^{11}$ 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 | $2 \times 10^9$ cells/dose | IV |
| **Approved Products** | **Dosage** | **Mode of Administration** |
| Avelumab | 10 mg/kg | IV |
| Bevacizumab | 5 mg/kg | IV |
| Capecitabine | 650 mg/m$^2$ BID up to a maximum of 1,000 mg per dose | PO |
| Cetuximab | 250 mg/m$^2$ | IV |
| Cisplatin | 32 mg/m$^2$ | IV |
| Cyclophosphamide | 25 mg BID (days 1-5);<br>25 mg once 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 |
| Necitumumab | 400 mg | IV |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

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

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase), or until they experience confirmed 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.

**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:**

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

ORR and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. 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-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC Vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***ctDNA/ctRNA Analysis***: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

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

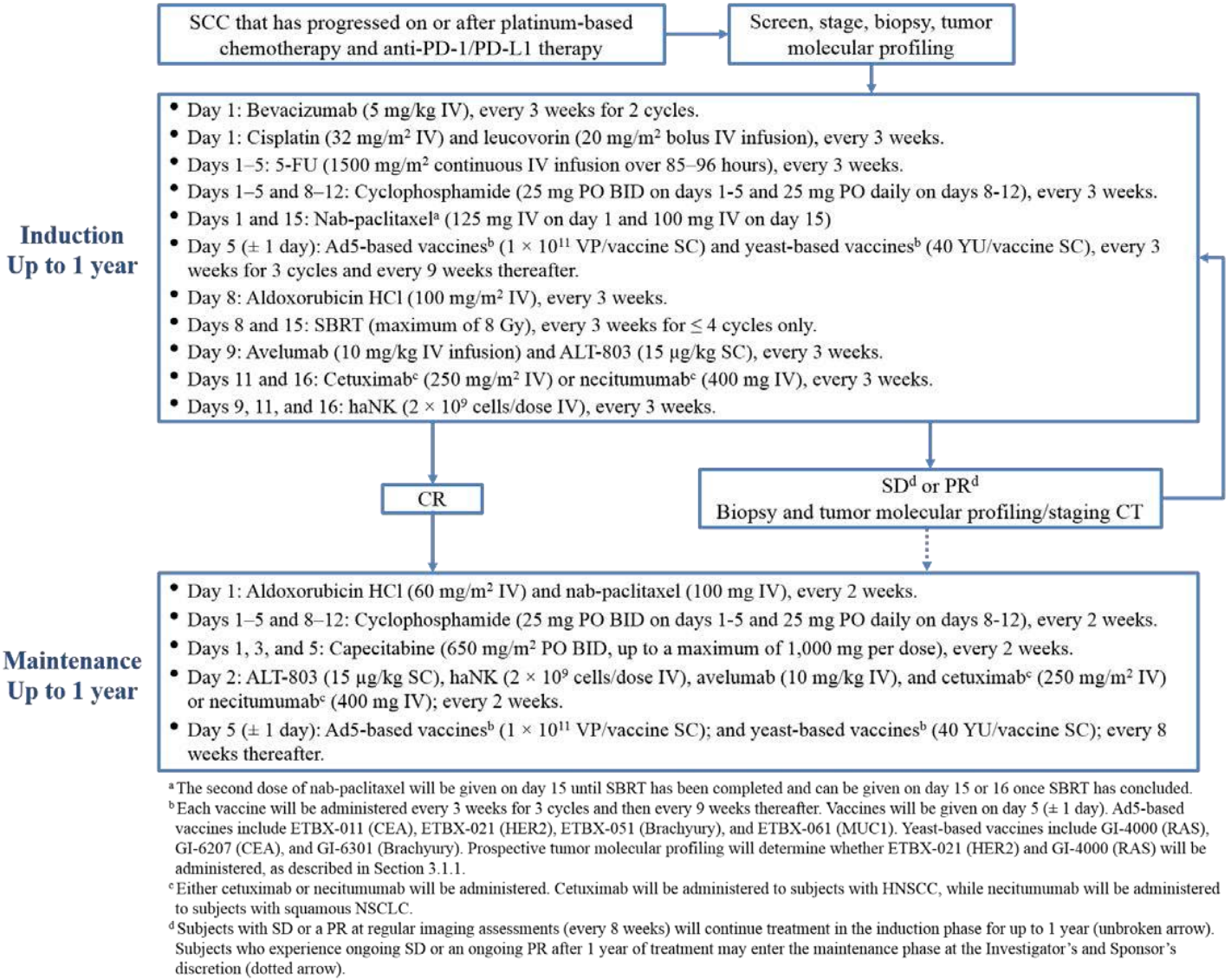
Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, ECHOs, and vital signs.

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

Descriptive statistics of PROs will be presented.

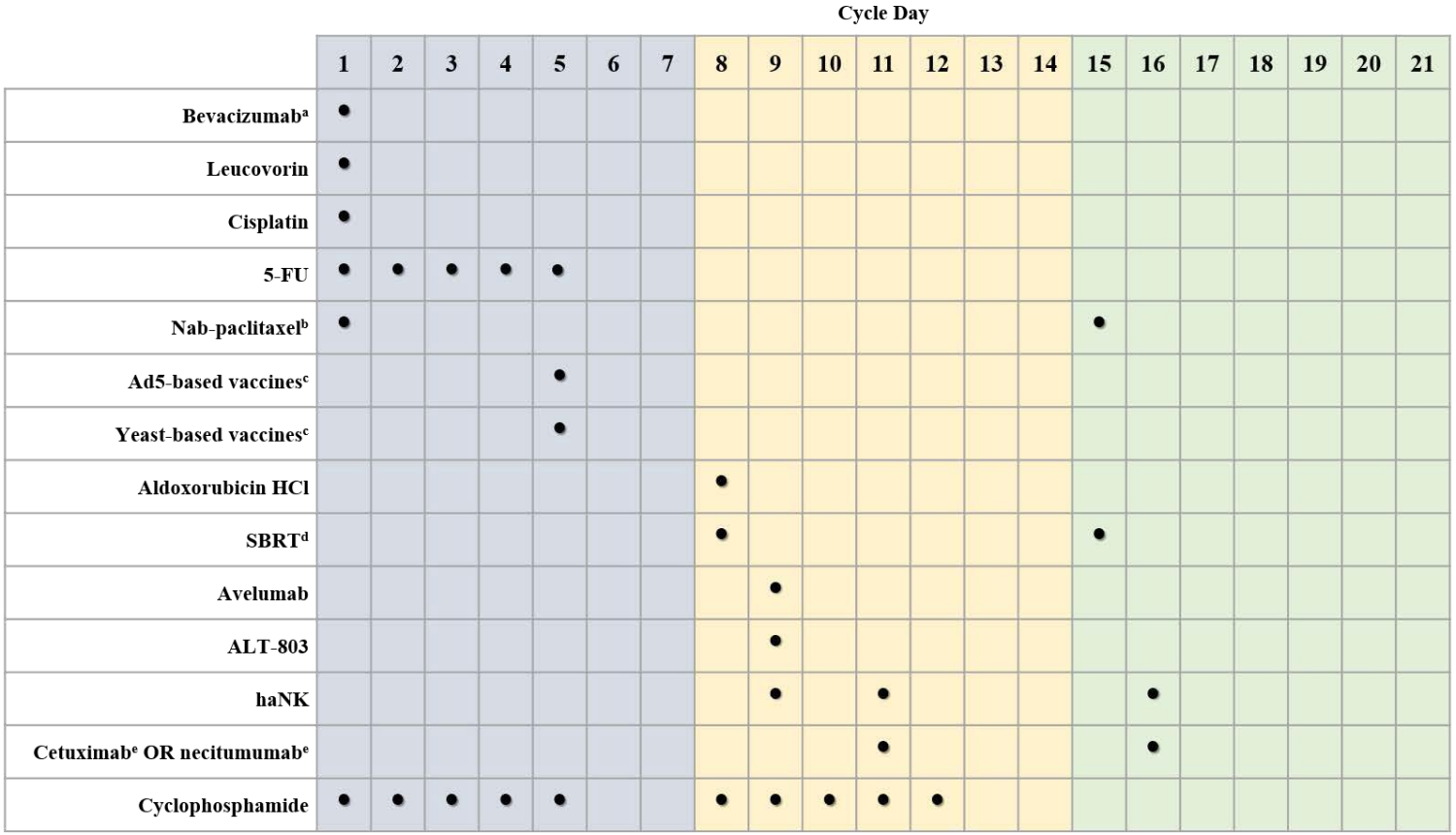
Correlations of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in ctDNA and ctRNA with subject outcomes will be explored.

**Figure 1: Study Treatment Schema**




[a] 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 given 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] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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 and Sponsor's discretion (dotted arrow).

**Figure 2: Induction Phase Treatment Schema**




[a] Administered for first 2 cycles only.
[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] Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines will be given 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.
[d] SBRT will be administered for up to 4 treatment cycles.
[e] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

**Figure 3: Maintenance Phase Treatment Schema**

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

[a] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

[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 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 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X[j] | Every 12 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 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 | |
| Hematology[l] | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Urinalysis | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Pregnancy test[m] | X | X[j] | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Serum virology (HIV)[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Determine HER2 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for ctDNA/ctRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| CT or MRI[s] | X | Every 8 weeks | | | | | | | | | | | | | | | | | | | | | X | |

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences confirmed PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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. Any required laboratory sample collection (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.

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

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

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

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

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

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

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

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

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

[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) will be administered to the subject, as described in Section 3.1.1. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors positive for HER2 expression or specific *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available.

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

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

[r] Historic tumor biopsy specimen for tumor molecular profiling 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 or MRI will be performed at screening and every 8 weeks during the induction phase, as described in Section 6. 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 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | 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 | | | | | | | | | | | | | | | |

| | **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** | | |
| 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 PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required 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 or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

# APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| Study Title: | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| Study Number: | QUILT-3.090 |
| Version Number: | 5 |
| Final Date: | 01 August 2018 |

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

Signed: Date 45 !-µ/b

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# NANT SQUAMOUS CELL CARCINOMA (SCC) VACCINE: MOLECULARLY INFORMED INTEGRATED IMMUNOTHERAPY COMBINING INNATE HIGH-AFFINITY NATURAL KILLER (haNK) CELL THERAPY WITH ADENOVIRAL AND YEAST-BASED VACCINES TO INDUCE T-CELL RESPONSES IN SUBJECTS WITH SCC WHO HAVE PROGRESSED ON OR AFTER PLATINUM-BASED CHEMOTHERAPY AND ANTI-PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)/PROGRAMMED DEATH-LIGAND 1 (PD-L1) THERAPY

| | |
|---|---|
| **Study Number:** | **QUILT-3.090** |
| **IND Sponsor:** | NantKwest, Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232 |
| **Sponsor Contact:**<br>**(For medical questions/emergencies)** | John H. Lee, MD<br>Senior Vice President Adult Medical Affairs,<br>NantKwest Inc.<br>9920 Jefferson Blvd<br>Culver City, CA 90232<br>Email: John.Lee@Nantkwest.com<br>Cell Phone: +1-605-610-6391 |

| **Protocol Version** | **Date** |
|---|---|
| Version 1 | 20 November 2017 |
| Version 2 | 27 December 2017 |
| Version 3 | 01 March 2018 |
| Version 4 | 06 July 2018 |
| Version 5 | 01 August 2018 |
| Version 6 | 03 October 2018 |

# PROTOCOL SYNOPSIS

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

**Name of Investigational Products:**

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

**Name of Approved Products:**

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

**Name of Active Ingredients:**

**Investigational Products**

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

**Approved Products**

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

**Title of Study:**

NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy.

**Study Number:**

QUILT-3.090

**Study Phase:**

Phase 1b/2 (Simon's two-stage optimal design)

**Study Objectives:**

**Phase 1b**

- The primary objective is to evaluate the overall safety profile of the NANT SCC Vaccine regimen in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 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 cell-free circulating DNA (cfDNA) and RNA (cfRNA); and their correlations with subject outcomes.

**Phase 2**

- The primary objective is to determine the efficacy of the NANT SCC Vaccine regimen as assessed by ORR using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on Blinded Independent Central Review (BICR).
- Secondary objectives are to determine additional measures of safety and efficacy (ORR by immune-related response criteria (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 cfDNA and cfRNA; and their correlations with subject outcomes.

**Study Design:**

This is a phase 1b/2 study to evaluate the safety and efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after previous platinum-based chemotherapy and anti-PD-1/PD-L1 therapy. Phase 2 will be based on Simon's two-stage optimal design.

In phase 1b, the initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC). Enrollment into the phase 1b portion will continue if data from the initial 3 subjects suggest that

the combination therapy is tolerable.

Treatment 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.

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

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

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks during the induction phase, and every 12 weeks during the maintenance phase until progression occurs 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, experimental treatment may continue and an imaging assessment should be done 4-6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRC. For subjects exhibiting a response (PR or CR), a confirmatory imaging assessment should be done 4–6 weeks after the initial response.

**Prospective Tumor Molecular Profiling**

Prospective tumor molecular profiling will be performed on FFPE tumor tissue and whole blood (subject-matched normal comparator against the tumor tissue) collected prior to treatment on this study. 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.

Prospective tumor molecular profiling will be conducted to inform *RAS* mutational status and will be used to determine whether GI-4000 (RAS) will be administered. Subjects will receive GI-4000 (RAS) if their tumor is positive for specific *RAS* mutations, as determined by whole genome sequencing. GI-4000 (RAS) administration will be initiated as soon as results from tumor molecular profiling are available. All subjects will receive other agents regardless of their tumor molecular profile.

**Induction Phase:**

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

Day 1, every 3 weeks for 2 cycles:

- Bevacizumab (5 mg/kg IV)

Day 1, every 3 weeks:

- Cisplatin (32 mg/m$^2$ IV)
- Leucovorin (20 mg/m$^2$ IV bolus)
- Nab-paclitaxel (125 mg 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) ($1 \times 10^{11}$ 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 ($2 \times 10^9$ cells/dose IV)
- N-803 (15 μg/kg SC)

Day 11, every 3 weeks:

- Cetuximab (250 mg/m$^2$ IV)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with head and neck squamous cell carcinoma (HNSCC), while necitumumab will be administered to subjects with squamous non-small cell lung cancer (NSCLC).
- haNK ($2 \times 10^9$ 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)

  **OR**

  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
- haNK ($2 \times 10^9$ cells/dose IV)

**Maintenance Phase:**

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

- Cyclophosphamide (25 mg PO BID)

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

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

Day 2, every 2 weeks:

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

  **OR**
  necitumumab (400 mg IV)

  Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

- haNK ($2 \times 10^9$ 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) ($1 \times 10^{11}$ 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)

**Phase 1b**

**Primary Endpoint:**

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

**Secondary Endpoints:**

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

**Exploratory Endpoints:**

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

**Phase 2**

**Primary Endpoint:**

- ORR by RECIST Version 1.1.

**Secondary Endpoints:**

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

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

**Exploratory Endpoints:**

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

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

**Enrollment (planned):**

In the phase 1b portion of the study, 6 to 24 subjects will be enrolled. The initial 3 subjects will be enrolled in a staggered fashion, with a 21-day interval between each subject. In the phase 2 portion of the study, 21 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 20 subjects will be enrolled in the second stage, for a total of 41 subjects in the phase 2 portion of the study. The maximum total enrollment in the study is 65 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 HNSCC or squamous NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for prospective and exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

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

**Exclusion Criteria**:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count < 1,000 cells/$mm^3$.
    b. 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 levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    g. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
    h. Serum anion gap > 16 mEq/L or arterial blood with pH < 7.3.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication. Subjects with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
7. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) 10% below the institution's lower limit of predicted normal.

8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
13. Concurrent or prior use of a strong cytochrome P450 (CYP)3A4 inhibitor (including ketoconazole, itraconazole, posaconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, and grapefruit products) or strong CYP3A4 inducers (including phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St John's Wort) within 14 days before study day 1.
14. Concurrent or prior use of a strong CYP2C8 inhibitor (gemfibrozil) or moderate CYP2C8 inducer (rifampin) within 14 days before study day 1.
15. Participation in an investigational drug study or history of receiving any investigational treatment within 30 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
16. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
17. Concurrent participation in any interventional clinical trial.
18. Pregnant and nursing women.

**Products, Dosage, and Mode of Administration:**

| **Investigational Products** | **Dosage** | **Mode of Administration** |
|---|---|---|
| Aldoxorubicin HCl | 100 mg/m$^2$ (induction);<br>60 mg/m$^2$ (maintenance) | IV |
| ETBX-011 (CEA) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-021 (HER2) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-051 (Brachyury) | $1 \times 10^{11}$ VP/dose | SC |
| ETBX-061 (MUC1) | $1 \times 10^{11}$ 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 | $2 \times 10^9$ cells/dose | IV |

| | | |
|---|---|---|
| N-803 | 15 µg/kg | SC |
| **Approved Products** | **Dosage** | **Mode of Administration** |
| Avelumab | 10 mg/kg | IV |
| Bevacizumab | 5 mg/kg | IV |
| Capecitabine | 650 mg/m$^2$ BID up to a maximum of 1,000 mg per dose | PO |
| Cetuximab | 250 mg/m$^2$ | IV |
| Cisplatin | 32 mg/m$^2$ | IV |
| Cyclophosphamide | 25 mg BID (days 1-5);<br>25 mg once 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 |
| Necitumumab | 400 mg | IV |
| SBRT | 8 Gy maximum (exact dose to be determined by the radiation oncologist) | External beam radiation |

**Duration of Treatment:**

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

Subjects will be treated for up to 2 years (up to 1 year in each treatment phase), or until they experience confirmed 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.

**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:**

Not applicable.

**Evaluation of Endpoints:**

**Safety:**

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

**Efficacy:**

ORR and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the induction phase and every 12 weeks during the maintenance phase and will be evaluated in accordance with RECIST Version 1.1 and irRC. 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-Head and Neck (FACT-H&N) or Functional Assessment of Cancer Therapy-Lung (FACT-L) instruments on study day 1, every 6 weeks thereafter (day 1 of weeks 7, 13, 19, etc) prior to treatment during induction phase, every 12 weeks during maintenance, and at the end-of-treatment (EOT) visit.

**Exploratory 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 SCC Vaccine regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

***cfDNA/cfRNA Analysis***: cfDNA and cfRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

**Statistical Methods:**

This phase 1b/2 study will examine the overall safety profile and preliminary efficacy of metronomic combination therapy in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

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

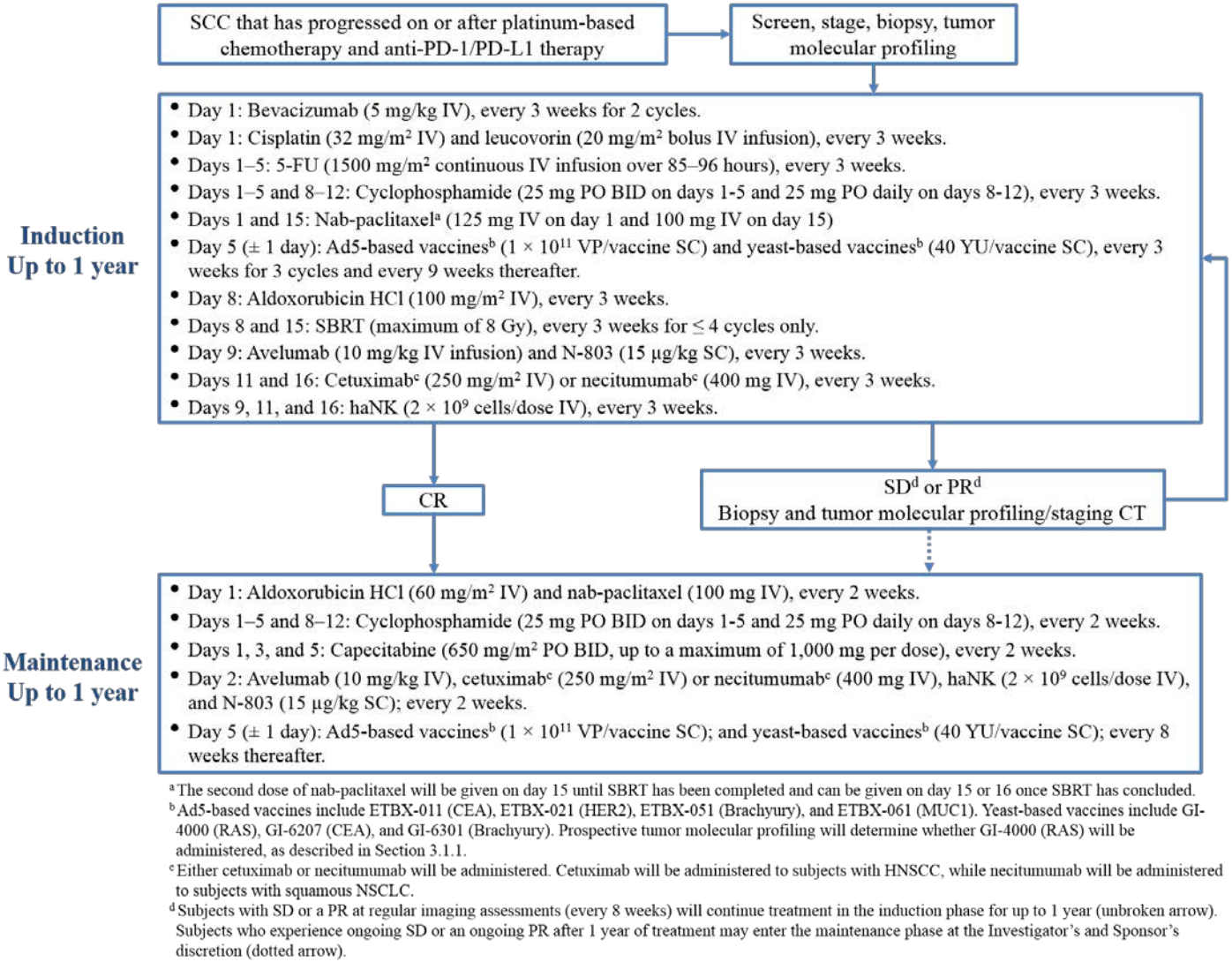
Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, ECHOs, and vital signs.

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

Descriptive statistics of PROs will be presented.

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

**Figure 1: Study Treatment Schema**




[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] 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] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.
[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 and Sponsor's discretion (dotted arrow).

**Figure 2: Induction Phase Treatment Schema**

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

[a] Administered for first 2 cycles only.
[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] Each vaccine will be administered every 3 weeks for 3 cycles and then every 9 weeks thereafter. Vaccines will be given 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.
[d] SBRT will be administered for up to 4 treatment cycles.
[e] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

**Figure 3: Maintenance Phase Treatment Schema**

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

[a] Either cetuximab or necitumumab will be administered. Cetuximab will be administered to subjects with HNSCC, while necitumumab will be administered to subjects with squamous NSCLC.

[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 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 6 weeks | | | | | | | | | | | | | | | | | | | X | |
| ECHO (with ejection fraction) | X | X[j] | Every 12 weeks | | | | | | | | | | | | | | | | | | | X | |
| Confirm contraceptive measures | X | | | | | | | | | | | | | | | | | | | | | | |
| FACT-H&N or FACT-L Questionnaire | X | X | Every 6 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 | |
| Hematology[l] | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Urinalysis | X | X[j] | | | | | | | X | | | | | | | | X | | | | | | X | |
| Pregnancy test[m] | X | X[j] | Every 6 weeks | | | | | | | | | | | | | | | | | | | | X | |
| Serum virology (HIV)[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Determine HER2 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 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect whole blood for cfDNA/cfRNA analysis[q] | X | Every 6 weeks during routine blood draws | | | | | | | | | | | | | | | | | | | | | X | |
| Collect historic tumor biopsy specimen for tumor molecular profiling[r] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor biopsy[r] | X | 8 weeks after the start of treatment | | | | | | | | | | | | | | | | | | | | | | |
| Additional tumor biopsy | | May be collected at any time point, as clinically indicated at the Investigator's discretion. | | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Imaging and Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| CT or MRI[s] | X | Every 8 weeks | | | | | | | | | | | | | | | | | | | | | X | |

[a] Subjects will remain in the induction phase of the study for up to 1 year. Treatment will continue in the induction phase until the subject experiences confirmed PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Those who have a CR in the induction phase will enter the maintenance phase of the study. 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. Any required laboratory sample collection (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.

[c] Additional assessments performed during an unscheduled visit are at the discretion of the Investigator or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
[d] Inclusion/exclusion criteria will also be evaluated at enrollment.
[e] Medical history will also be evaluated at enrollment.
[f] Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed, if considered safe by the Investigator. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used. Treatment on this study may be initiated before FFPE tumor tissue and/or results from prospective tumor molecular profiling are available; in the event that this occurs, treatment of subjects with tumors with specific *RAS* mutations targeted by GI-4000 (RAS) will begin as soon as molecular profiling results are available.
[g] Height required at screening visit only. Weight on day 1 of each treatment cycle should be used to calculate drug doses.
[h] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Assessment of vital signs and AEs on day 15 is required only if study treatment is administered on that day. Vital signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes and within 30 minutes prior to the start of any infusional study treatment. For visits where a subject is receiving an infusion of any study compounds, vital signs will be collected at the following time points in relation to the start of first infusion of the day: prior to infusion, 15 minutes post, 30 minutes post, and hourly until the subject is discharged. Temperature will be documented each visit at the first pre-infusion assessment of vital signs and subsequently if clinically indicated.
[i] 12-lead ECG to be performed in triplicate at screening.
[j] Day 1 assessments can be skipped if the screening assessment was performed within 1 week prior to the start of treatment. For ECG and ECHO assessments only, day 1 assessments can be skipped if the screening assessment was performed within 28 days prior to the start of treatment.
[k] Chemistry panel to include laboratory assessments noted in Table 17.
[l] Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
[m] Serum pregnancy tests for females of child-bearing potential.
[n] HIV status to be determined by an approved test.
[o] Assessment of *RAS* mutational status to determine whether GI-4000 (RAS) will be administered to the subject, as described in Section 3.1.1. Assessment of HER2 positivity may be conducted as soon as tumor tissue is available, and results from this assessment will not affect the drug regimen administered to subjects in this study.
[p] Whole blood for tumor molecular profiling will be collected during the screening period for subjects who have been enrolled in the study.
[q] Whole blood for immunology and cfDNA/cfRNA analyses will be collected during the screening period for subjects who have been enrolled in the study, every 6 weeks in the induction phase during routine blood draws, and at the EOT visit.
[r] Historic tumor biopsy specimen for tumor molecular profiling 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 or MRI will be performed at screening and every 8 weeks during the induction phase, as described in Section 6. 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 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-H&N or FACT-L questionnaire | X | Every 12 weeks | | | | | | | | | | | | | X | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Chemistry panel[e] | X | | | | | | | | | | | | | | X | |
| Hematology[f] | X | | | | | | | | | | | | | | X | |
| Urinalysis | X | | | | | | | | | | | | | | X | |
| Pregnancy test[g] | X | Every 12 weeks | | | | | | | | | | | | | X | |
| Collect whole blood for immunology analysis[h] | X | Every 8 weeks during routine blood draws | | | | | | | | | | | | | X | |
| Collect whole blood for cfDNA/cfRNA analysis[h] | X | Every 8 weeks during routine blood draws | | | | | | | | | | | | | X | |
| Additional tumor biopsy | May be collected at any time point, as clinically indicated at the Investigator's discretion | | | | | | | | | | | | | | | |

| | **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** | | |
| 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 PD or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment. Any required 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 cfDNA/cfRNA analyses will be performed every 8 weeks in the maintenance phase during routine blood draws, and at the end-of-treatment visit.

[i] Tumor imaging by CT scan or MRI will be performed every 12 weeks in the maintenance phase, as described in Section 6. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each subject's respective treatment period.

## APPENDIX 1. SPONSOR SIGNATURE

| | |
|---|---|
| **Study Title:** | NANT Squamous Cell Carcinoma (SCC) Vaccine: Molecularly informed integrated immunotherapy combining innate high-affinity natural killer (haNK) cell therapy with adenoviral and yeast-based vaccines to induce T-cell responses in subjects with SCC who have progressed on or after platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. |
| **Study Number:** | QUILT-3.090 |
| **Version Number:** | 6 |
| **Final Date:** | 03 October 2018 |

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

Signed: _____ Date: 10-5-18

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