Phase 1b/2 Study of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) Vaccine in Combination With ALT-803 (Super-agonist IL-15) in Subjects Having CEA-Expressing Cancer.

Protocol Number:	QUILT-3.03X
Principal Investigator:	**Michael Morse, MD** Duke University Medical Center 200 Trent Dr. Durham, NC 27710 Email: morse004@mc.duke.edu Office Phone: 919-681-3480
Principal Research Investigator	**Jeffrey Schlom, PhD** Center for Cancer Research National Cancer Institute Building 10, Room 8B09 Bethesda, MD 20892-1750 Email: js141@nih.gov Office Phone: 301-496-4343
IND Sponsor:	**Etubics Corporation** 410 West Harrison Suite 100 Seattle, WA 98119Office Phone: 206-838-5110
Funded by:	**Etubics Corporation** 410 West Harrison Suite 100 Email: frank@etubics.com Office Phone: 206-838-5110
Sponsor Contact: **(For medical questions/emergencies)**	**John Lee, MD** 9920 Jefferson Boulevard Culver City, CA 90232 Email: John.Lee@nantkwest.com Office Phone: 605-610-6391 Mobile Phone: 605-610-6391
Sponsor Contact: **(For study administration, operations, and execution questions)**	**Elizabeth S. Gabitzsch** Etubics Corporation 410 West Harrison Suite 100 Seattle, WA 98119Email: beth@etubics.com Office Phone: 206-838-5110 Ext 103 Email: beth@etubics.com **Amy Rock, PhD**. Altor BioScience 28 North Commerce Parkway

	Miramac, FL 33025 Office Phone: 954-443-8600 Email: AmyRock@altorbioscience.com

Protocol Version	Date
QUILT-3.03X	6 December, 2016

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 Etubics Corporation 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: Michael Morse, MD

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

Etubics Corporation

Name of Investigational Product:

A combination of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) vaccine and ALT-803 (Super-agonist IL-15)

Name of Active Ingredient:

ETBX-011: Ad5 [E1-, E2b-]-CEA(6D)

ALT-803: IL-15N72D:IL-15RαSu/IgG1 Fc complex (Superagonist IL-15)

Title of Study:

Phase 1b/2 Study of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) Vaccine in Combination with ALT-803 (Super-agonist IL-15) in Subjects Having CEA-Expressing Cancer

Study Number:

QUILT-3.03X

Study Phase:

Phase 1b/2

Study Objectives:

Primary Objectives

Phase 1b

- Determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of the ETBX-011 plus ALT-803 combination treatment in subjects with carcinoembryonic antigen (CEA)-expressing cancers whose tumor has recurred after standard-of-care treatment

Phase 2

- Determine the overall safety and tolerability profile for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in subjects with CEA expressing cancers whose tumor has recurred after standard-of-care treatment.
- Preliminary evaluation of the overall response rate (ORR) for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in the following indications known to express CEA:
  1. Histologically confirmed unresectable locally advanced or metastatic medullary thyroid cancer that expresses CEA and have progressed on at least cabozantinib or vandetanib.
  2. Histologically confirmed unresectable locally advanced or metastatic colon cancer that expresses CEA and have progressed on at least one prior standard-of-care treatment with a FOLFIRI- or FOLFOX-based combination therapy.
  3. Histologically confirmed unresectable locally advanced or metastatic ovarian cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
  4. Histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.

5. Histologically confirmed unresectable locally advanced or metastatic lung cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
6. Histologically confirmed unresectable locally advanced or metastatic pancreatic cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
7. Other histologically confirmed unresectable locally advanced or metastatic cancers that express CEA and have progressed on at least one prior standard-of-care–based combination therapy.

Secondary Objectives

- Preliminary evaluation of duration of response, progression-free survival (PFS), and overall survival (OS) for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in the indications outlined above.

Exploratory Objectives

- Evaluate the immunogenicity against CEA over the course of treatment with combined ETBX-011 plus ALT-803
- To determine the genomic, transcriptomic, and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic, transcriptomic, and proteomic profiles and efficacy outcome will be assessed.

Study Design:

This is a phase 1b/2, open-label, multicenter, dose-escalation study of ETBX-011 vaccine used in combination with ALT-803 in subjects with previously treated locally advanced or metastatic CEA-expressing cancer.

The trial will consist of a phase 1b study with of ETBX-011 as a fixed dose with a dose escalation of ALT-803 unless de-escalation is required. The proposed phase 2 expansion study will give additional safety data for the MTD as well as preliminary efficacy data in several indications known to express CEA.

The studies will be conducted in conformity with Good Clinical Practice.

The study will involve a previously determined safe dose of ETBX-011 (5×10^{11} virus particles [VP]/dose). In the phase 1b study, the ALT-803 dose will be escalated using the standard 3 + 3 design. The dose levels will be:

- Level 1: ETBX-011 (5×10^{11} VP/dose) and ALT-803 (10 µg/kg/dose).
- Level 2: ETBX-011 (5×10^{11} VP/dose) and ALT-803 (15 µg/kg/dose).
- If needed, dose de-escalation of ETBX-011 will be used (1×10^{11} VP/dose).
- If needed, dose de-escalation of ALT-803 will be used (6 µg/kg/dose).

In the phase 2 study, subjects from several indications known to express CEA will be treated at the MTD.

Primary Endpoints:

Phase 1b

- DLTs
- MTD

Phase 2

- Treatment-emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), and vital signs.
- ORR

Secondary Endpoints:

- Duration of response
- PFS
- OS

Exploratory Endpoints:

- Immunogenicity of ETBX-011 by flow cytometric and ELISpot analysis of T-cell frequency, activation status, cytokine profiles, and CEA antibody, adenovirus antibody levels, and potential antibody development against the IL-15N72D:IL-15RαSu/IgG1 Fc complex
- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy

Enrollment (planned):

It is expected that up to 12 subjects will be enrolled in the phase 1b study with 3 to 6 subjects sequentially enrolled starting at dose level 1. In the phase 2 study, up to 20 subjects for each indication will be enrolled and treated at the MTD determined in phase 1b. Subjects from the phase 1b study who were treated at the MTD will be included in the phase 2 enrollment targets.

Diagnosis and Main Criteria for Inclusion:

Subjects must be diagnosed with one of the following indications:

1. Histologically confirmed unresectable locally advanced or metastatic medullary thyroid cancer that expresses CEA and have progressed on at least cabozantinib or vandetanib.
2. Histologically confirmed unresectable locally advanced or metastatic colorectal cancer that expresses CEA and have progressed on at least one prior standard of care treatment with a FOLFIRI- or FOLFOX-based combination therapy.
3. Histologically confirmed unresectable locally advanced or metastatic ovarian cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
4. Histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
5. Histologically confirmed unresectable locally advanced or metastatic lung cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
6. Histologically confirmed unresectable locally advanced or metastatic pancreatic cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.

7. Other histologically confirmed unresectable locally advanced or metastatic cancers that express CEA and have progressed on at least one prior standard-of-care–based combination therapy.

The tumor must express CEA as defined by immunohistochemical staining (at least 50% of the tumor with at least moderate intensity of staining) or must be known to be universally CEA positive (ie, colon and rectal cancer).

Investigational Product, Dosage, and Mode of Administration:

ETBX-011 immunization (5×10^{11} VP/dose in 1.0 mL) will be administered by subcutaneous (SC) injection every 3 weeks for 3 injections.

ALT-803 will be administered by SC injection one week after the ETBX-011, and a second injection of ALT-803 will be administered one week after the first. ALT-803 will be administered at a separate location from the ETBX-011 immunization site.

Duration of Treatment:

Subjects will receive treatment during 3-week cycles for a planned 3 cycles (8 weeks total). Subjects will receive treatments unless they experience progressive disease, DLT, withdraw consent, or if the investigator determines it is no longer in their best medical interest to continue treatment.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of DLT and MTD, treatment-emergent AE, SAE, and clinically significant changes in safety laboratory tests, such as changes in ECG, physical examinations, and vital signs. Toxicities will be determined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response will be determined according to the Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Analyses:

Exploratory Immune Analysis: T-cell immune responses will be detected and quantified by flow cytometry and ELISpot. CEA, adenoviral antibody levels, and potential antibody development against the IL-15N72D:IL-15RαSu/IgG1 Fc complex will be determined by enzyme-linked immunosorbent assay (ELISA).

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

Statistical Methods:

Overall safety and tolerability will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Tumor response will be evaluated according to RECIST Version 1.1; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods.

Phase 1b data will be presented by dose level for all indications combined. Phase 2 data will be presented separately for each indication.

In the phase 2 study, up to 20 subjects for each indication will be enrolled and treated at the MTD determined in phase Ib. Assuming a 5% ORR, a sample size of 20 subjects will provide a 95% confidence interval of ORR from 0 to 15%.

Immune responses assessed in ELISpot, flow cytometry, and ELISA tests will be analyzed employing statistical methods as described in Section 8.1.3 .

Table 5: Time and Events Schedule

Assessment	**Screening**	**Treatment (Every 3-Week Vaccine Dosing)**									**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	
ETBX-011 Vaccine		X			X			X				
ALT-803			X	X		X	X		X	X		
CT scan Imaging	X									X		
Informed Consent	X											
Inclusion/Exclusion	X											
Demographics	X											
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]			X			X			X	
Medical History[c]	X	X										
Obtain biopsy for CEA Expression and genomic testing	X									X		
Confirm CEA Expression[d]	X											
Concomitant Medications	X	X			X			X			X	
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X				X			X			X	
Confirm Contraceptive Measures[g]	X											
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X	X	X	X	X	X	X	X	
Dispensation of Subject Diary Card[i]		X			X			X				
Review of Subject Diary Card[i]			X	X	X	X	X	X	X	X	X	
Telephone Contact 72 Hours Post Injection		X	X	X	X	X	X	X	X	X		
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X	X	
Urinalysis	X				X			X			X	
Chemistry Panel	X[b]	X[b]	X	X	X	X	X	X	X	X	X	

Assessment	Screening	Treatment (Every 3-Week Vaccine Dosing)									End of Study	Post Study Follow Up
Study Week	**Day -28 to -1**	**Baseline/0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X	X	X	X	X	X	
CEA level	X	X			X			X			X	
Coagulation	X				X			X			X	
Serum Virology (HIV, HBV, HCV)[l]	X										X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X			X			X		X		
Telephone Follow Up[m]												X

[a] Height will only be assessed at screening.
[b] If the assessment is performed within 24 hours prior to the first dosing, a second assessment at baseline/week 0 can be omitted.
[c] Complete medical history will be evaluated at screening and includes current and past cardiac and pulmonary history, documentation of diagnosis including history of current and prior cancers, prior treatment(s), and prior radiologic studies. Any new events in the medical history will be evaluated at baseline.
[d] Confirmation of CEA expression by IHC, derived from the most recent metastatic biopsy sample available. Genomic testing will also be performed.
[e] Vital signs include temperature, heart rate, blood pressure, and respiratory rate. Vital sign assessments are to be obtained after the subject has been in a seated resting position for at least 5 minutes. For the first injection, vital signs must be assessed 30 and 60 minutes after the injection. Vital signs must be assessed 30 minutes after the subsequent injections.
[g] Acceptable contraceptive measures are described in **Section 4.1.**
[h] Injection site reactions will be monitored, as described in **Section 6.6.1.**
[i] Subjects will be given a diary card for the self-evaluation and reporting of injection site reactions, as described in **-**
[j] All baseline tumor measurements should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. Tumor imaging and assessments will be performed as described in **Section 6.7.2.**
[k] Serum pregnancy test will be performed on females of childbearing-potential and women < 12 months since the onset of menopause. The pregnancy test will be performed at each dosing visit with the result confirmed as negative prior to dosing.
[l] Serum virology test for HIV (as determined by ELISA and confirmed by western blot), and HBV and HCV (as determined by HBsAg and hepatitis C serology).
[m] After the subject completes or withdraws from the study, the study team will contact the subject approximately every 3 months for 12 months and then approximately every 6 months thereafter for 12 months to collect follow-up information, including survival status (as described in **Section 6.7.1**.) and any current cancer treatment regimen.

PHASE 1B/2 STUDY OF ETBX-011 (AD5 [E1-, E2B-]-CEA(6D)) VACCINE IN COMBINATION WITH ALT-803 (SUPER-AGONIST IL-15) IN SUBJECTS HAVING CEA-EXPRESSING CANCER.

Protocol Number:	QUILT-3.040
Principal Investigator:	**Michael Morse, MD** Duke University Medical Center 200 Trent Dr. Durham, NC 27710 Email: morse004@mc.duke.edu Office Phone: 919-681-3480
Principal Research Investigator:	**Jeffrey Schlom, PhD** Center for Cancer Research National Cancer Institute Building 10, Room 8B09 Bethesda, MD 20892-1750 Email: js141@nih.gov Office Phone: 301-496-4343
IND Sponsor:	**Etubics Corporation, a Wholly-Owned Subsidiary of NantCell, Inc.** 410 West Harrison Suite 200 Seattle, WA 98119Office Phone: 206-838-5110
Sponsor Contact: **(For medical questions/emergencies)**	**John Lee, MD** 9920 Jefferson Boulevard Culver City, CA 90232 Email: John.Lee@nantkwest.com Office Phone: 605-610-6391 Mobile Phone: 605-610-6391
Sponsor Contact: **(For study administration, operations, and execution questions)**	**Elizabeth S. Gabitzsch** Etubics Corporation 410 West Harrison Suite 100 Seattle, WA 98119Email: beth@etubics.com Office Phone: 206-838-5110 Ext 103 Email: beth@etubics.com **Amy Rock, PhD** Altor BioScience 2810 North Commerce Parkway Miramar, FL 33025 Office Phone: 954-443-8600 Email: AmyRock@altorbioscience.com

Protocol Version	Date
QUILT-3.040	06 December 2016
QUILT-3.040 Amendment 1	13 April 2017

STATEMENT OF COMPLIANCE

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

Etubics Corporation, a wholly-owned subsidiary of NantCell, Inc.

Name of Investigational Product:

A combination of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) vaccine and ALT-803 (Super-agonist IL-15)

Name of Active Ingredient:

ETBX-011: Ad5 [E1-, E2b-]-CEA(6D)

ALT-803: IL-15N72D:IL-15RαSu/IgG1 Fc complex (Superagonist IL-15)

Title of Study:

Phase 1b/2 Study of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) Vaccine in Combination with ALT-803 (Super-agonist IL-15) in Subjects Having CEA-Expressing Cancer

Study Number:

QUILT-3.040

Study Phase:

Phase 1b/2

Study Objectives:

Primary Objectives

Phase 1b

- Determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of the ETBX-011 plus ALT-803 combination treatment in subjects with carcinoembryonic antigen (CEA)-expressing cancers whose tumor has recurred after standard-of-care treatment

Phase 2

- Determine the overall safety and tolerability profile for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in subjects with CEA expressing cancers whose tumor has recurred after standard-of-care treatment.
- Preliminary evaluation of the overall response rate (ORR) for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in the following indications known to express CEA:
  1. Histologically confirmed unresectable locally advanced or metastatic medullary thyroid cancer that expresses CEA and have progressed on at least cabozantinib or vandetanib.
  2. Histologically confirmed unresectable locally advanced or metastatic colon cancer that expresses CEA and have progressed on at least one prior standard-of-care treatment with a FOLFIRI- or FOLFOX-based combination therapy.
  3. Histologically confirmed unresectable locally advanced or metastatic ovarian cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
  4. Histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.

5. Histologically confirmed unresectable locally advanced or metastatic lung cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
6. Histologically confirmed unresectable locally advanced or metastatic pancreatic cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
7. Other histologically confirmed unresectable locally advanced or metastatic cancers that express CEA and have progressed on at least one prior standard-of-care–based combination therapy.

Secondary Objectives

- Preliminary evaluation of duration of response, progression-free survival (PFS), and overall survival (OS) for the MTD dose of the ETBX-011 plus ALT-803 combination treatment in the indications outlined above.

Exploratory Objectives

- Evaluate the immunogenicity against CEA over the course of treatment with combined ETBX-011 plus ALT-803
- Tumor molecular profiles and correlations with safety and efficacy.
- To assess changes in circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA) using a genomics panel.

Study Design:

This is a phase 1b/2, open-label, multicenter, dose-escalation study of ETBX-011 vaccine used in combination with ALT-803 in subjects with previously treated locally advanced or metastatic CEA-expressing cancer.

The trial will consist of a phase 1b study with of ETBX-011 as a fixed dose with a dose escalation of ALT-803 unless de-escalation is required. The proposed phase 2 expansion study will give additional safety data for the MTD as well as preliminary efficacy data in several indications known to express CEA.

The studies will be conducted in conformity with Good Clinical Practice.

The study will involve a previously determined safe dose of ETBX-011 (5×10^{11} virus particles [VP]/dose). In the phase 1b study, the ALT-803 dose will be escalated using the standard 3 + 3 design. The dose levels will be:

- Level 1: ETBX-011 (5×10^{11} VP/dose) and ALT-803 (10 µg/kg/dose).
- Level 2: ETBX-011 (5×10^{11} VP/dose) and ALT-803 (15 µg/kg/dose).
- If needed, dose de-escalation of ETBX-011 will be used (1×10^{11} VP/dose).
- If needed, dose de-escalation of ALT-803 will be used (6 µg/kg/dose).

In the phase 2 study, subjects from several indications known to express CEA will be treated at the MTD.

Primary Endpoints:

Phase 1b

- DLTs
- MTD

Phase 2

- Treatment-emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), and vital signs.
- ORR

Secondary Endpoints:

- Duration of response
- PFS
- OS

Exploratory Endpoints:

- Immunogenicity of ETBX-011 by flow cytometric and ELISpot analysis of T-cell frequency, activation status, cytokine profiles, and CEA antibody, adenovirus antibody levels, and potential antibody development against the IL-15N72D:IL-15RαSu/IgG1 Fc complex
- To assess tumor molecular profiles (genomics, transcriptomics, and proteomics) and correlations with safety and efficacy outcomes
- To assess changes in circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA) using a genomics panel.

Enrollment (planned):

It is expected that up to 12 subjects will be enrolled in the phase 1b study with 3 to 6 subjects sequentially enrolled starting at dose level 1. In the phase 2 study, up to 20 subjects for each indication will be enrolled and treated at the MTD determined in phase 1b. Subjects from the phase 1b study who were treated at the MTD will be included in the phase 2 enrollment targets.

Diagnosis and Main Criteria for Inclusion:

Subjects must be diagnosed with one of the following indications:

1. Histologically confirmed unresectable locally advanced or metastatic medullary thyroid cancer that expresses CEA and have progressed on at least cabozantinib or vandetanib.
2. Histologically confirmed unresectable locally advanced or metastatic colorectal cancer that expresses CEA and have progressed on at least one prior standard of care treatment with a FOLFIRI- or FOLFOX-based combination therapy.
3. Histologically confirmed unresectable locally advanced or metastatic ovarian cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
4. Histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
5. Histologically confirmed unresectable locally advanced or metastatic lung cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.

6. Histologically confirmed unresectable locally advanced or metastatic pancreatic cancer that expresses CEA and have progressed on at least one prior standard-of-care–based combination therapy.
7. Other histologically confirmed unresectable locally advanced or metastatic cancers that express CEA and have progressed on at least one prior standard-of-care–based combination therapy.

The tumor must express CEA as defined by immunohistochemical staining (at least 50% of the tumor with at least moderate intensity of staining) or must be known to be universally CEA positive (ie, colon and rectal cancer).

Investigational Product, Dosage, and Mode of Administration:

ETBX-011 immunization (5×10^{11} VP/dose in 1.0 mL) will be administered by subcutaneous (SC) injection every 3 weeks for 3 injections.

ALT-803 will be administered by SC injection one week after the ETBX-011, and a second injection of ALT-803 will be administered one week after the first. ALT-803 will be administered at a separate location from the ETBX-011 immunization site.

Duration of Treatment:

Subjects will receive treatment during 3-week cycles for a planned 3 cycles (8 weeks total). Subjects will receive treatments unless they experience progressive disease, DLT, withdraw consent, or if the investigator determines it is no longer in their best medical interest to continue treatment.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of DLT and MTD, treatment-emergent AE, SAE, and clinically significant changes in safety laboratory tests, such as changes in ECG, physical examinations, and vital signs. Toxicities will be determined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response will be determined according to the Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Analyses:

Exploratory Immune Analysis: T-cell immune responses will be detected and quantified by flow cytometry and ELISpot. CEA, adenoviral antibody levels, and potential antibody development against the IL-15N72D:IL-15RαSu/IgG1 Fc complex will be determined by enzyme-linked immunosorbent assay (ELISA).

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

Plasma will be collected and a PCR-based assay will be used to assess expression levels, and directly measure fusion genes and mutations in circulating DNA and RNA.

Statistical Methods:

Overall safety and tolerability will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Tumor response will be evaluated according to RECIST Version 1.1; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods.

Phase 1b data will be presented by dose level for all indications combined. Phase 2 data will be presented separately for each indication.

In the phase 2 study, up to 20 subjects for each indication will be enrolled and treated at the MTD determined in phase Ib. Assuming a 5% ORR, a sample size of 20 subjects will provide a 95% confidence interval of ORR from 0 to 15%.

Immune responses assessed in ELISpot, flow cytometry, and ELISA tests will be analyzed employing statistical methods as described in Section 8.1.3 .

6. STUDY PROCEDURES AND EVALUATIONS

All required study procedures and evaluations are to be conducted as outlined in this protocol. In the event of a deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must notify the Sponsor as soon as possible.

All laboratory assessments and evaluations will be performed as described below.

6.1. Time and Events Schedule

The schedule of study assessments is provided in Table 5.

Table 5: Time and Events Schedule

Assessment	**Screening**	**Treatment (Every 3-Week Vaccine Dosing)**									**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	
ETBX-011 Vaccine		X			X			X				
ALT-803			X	X		X	X		X	X		
CT scan Imaging	X									X		
Informed Consent	X											
Inclusion/Exclusion	X											
Demographics	X											
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]			X			X			X	
Medical History[c]	X	X										
Obtain biopsy for CEA Expression and genomic testing (optional for week 8 sample)	X									X		
Confirm CEA Expression[d]	X											
Concomitant Medications	X	X			X			X			X	
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X				X			X			X	
Confirm Contraceptive Measures[g]	X											

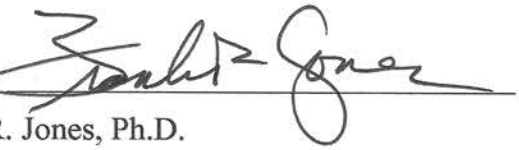
Assessment	**Screening**	**Treatment (Every 3-Week Vaccine Dosing)**									**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X	X	X	X	X	X	X	X	
Dispensation of Subject Diary Card[i]		X			X			X				
Review of Subject Diary Card[i]			X	X	X	X	X	X	X	X	X	
Telephone Contact 72 Hours Post Injection		X	X	X	X	X	X	X	X	X		
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X	X	
Urinalysis	X				X			X			X	
Chemistry Panel	X[b]	X[b]	X	X	X	X	X	X	X	X	X	
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X	X	X	X	X	X	
CEA level	X	X			X			X			X	
Coagulation	X				X			X			X	
Serum Virology (HIV, HBV, HCV)[l]	X										X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis and genomics		X			X			X		X		
Telephone Follow Up[m]												X

[a] Height will only be assessed at screening.
[b] If the assessment is performed within 24 hours prior to the first dosing, a second assessment at baseline/week 0 can be omitted.
[c] Complete medical history will be evaluated at screening and includes current and past cardiac and pulmonary history, documentation of diagnosis including history of current and prior cancers, prior treatment(s), and prior radiologic studies. Any new events in the medical history will be evaluated at baseline.
[d] Confirmation of CEA expression by IHC, derived from the most recent metastatic biopsy sample available. Genomic testing will also be performed.
[e] Vital signs include temperature, heart rate, blood pressure, and respiratory rate. Vital sign assessments are to be obtained after the subject has been in a seated resting position for at least 5 minutes. For the first injection, vital signs must be assessed 30 and 60 minutes after the injection. Vital signs must be assessed 30 minutes after the subsequent injections.
[g] Acceptable contraceptive measures are described in Section 4.1.
[h] Injection site reactions will be monitored, as described in Section 6.6.1.
[i] Subjects will be given a diary card for the self-evaluation and reporting of injection site reactions, as described in Appendix 2 and Appendix 3.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	Phase 1b/2 Study of ETBX-011 (Ad5 [E1-, E2b-]-CEA(6D)) Vaccine in Combination with ALT-803 (Super-agonist IL-15) in Subjects Having CEA-Expressing Cancer
Study Number:	QUILT-3.040 Amendment 1
IND Number:	IND14325
Final Date:	13 April 2017

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

Signed:  Date: April 13, 2017

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