8 STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess whether use of GI-6207 is able to result in reductions of the growth rates of tumors in patients with MTC. The changes in growth rates will be compared between two arms with either initial assignment to vaccine or surveillance, as well as secondarily determining if there is a significant change within the arm that initially receives surveillance followed by 6 months of vaccine.

Prior to randomization, patients will be stratified according to whether they were noted to have a calcitonin doubling time of <24 months vs. >24 months at baseline.

The primary endpoint will be the change from baseline to 6 months of the growth rate parameter. With 17 total patients per arm (34 total), with complete measurements of this main parameter at baseline and at 6 months after randomization, there would be 80% power to detect a difference between the two groups with respect to a change from baseline to 6 months equal to 1.0 standard deviations of the change (1.0 effect size) using a two-tailed 0.05 level two-sample t-test. In practice, if the differences from baseline to 6 months are not normally distributed on both arms (that is, if $p<0.05$ by a Shapiro Wilks test) then a Wilcoxon rank sum test will be performed instead.

As an important secondary objective, using the surveillance arm, two related secondary endpoints will be explored, both the actual magnitude of the change in the growth rate parameter as well as the fraction who exhibit a substantial, 50% decline in the growth rate as a result of treatment.

For the 17 patients will be enrolled on the surveillance arm, the growth rate determined at 12 months (after 6 months of vaccine) will be subtracted from that obtained at 6 months (after surveillance) to determine the actual change in the growth rate for receiving vaccine after 6 months of surveillance. With 17 patients, there is 82% power to detect a difference in the values at the two time points equal to ¾ of the SD of the change (.75 effect size) assuming that a two-tailed 0.05 alpha level paired t-test is used.

Also, as an additional secondary exploration, using all 17 patients on the surveillance arm, the fraction that experiences a 50% decline relative to the time of starting vaccine will be determined. Using an exact binomial test, 17 patients will have 83% power to test whether the fraction exceeds a null fraction of 20% and is consistent with 50% who have 50% declines, with a one-tailed 0.05 alpha level test. In practice, the fraction with a 50% decline will have a 95% confidence interval created about the result in order to describe what values it would be consistent with.

Exploratory analyses will also be performed to compare the growth rate changes at additional time points, such as 7, 10 and 12 months.

It is expected that the trial will accrue approximately 1-2 patients per month may be accrued; thus it is expected that this study may enroll 34 evaluable patients within 24-30 months. To allow for the possibility of a rare inevaluable patient, the accrual ceiling will be set at 37.

Abbreviated Title: GI-6207 in MTC
NantCell Study Number: QUILT-3.006
NCI Protocol #: 13-C-0095 OSP#: 1301-1199
Version Date: May 14, 2018 IBC#: RD-13-I-10
Amendment: G

Title: A phase 2 study of GI-6207 in patients with recurrent medullary thyroid cancer

NCI Principal Investigator:

Ravi A. Madan, M.D.
Genitourinary Malignancies Branch, CCR, NCI
10 Center Drive
Building 10, Room 13N240
Bethesda, MD 20892
Phone: 301-480-7168
Email: madanr@mail.nih.gov

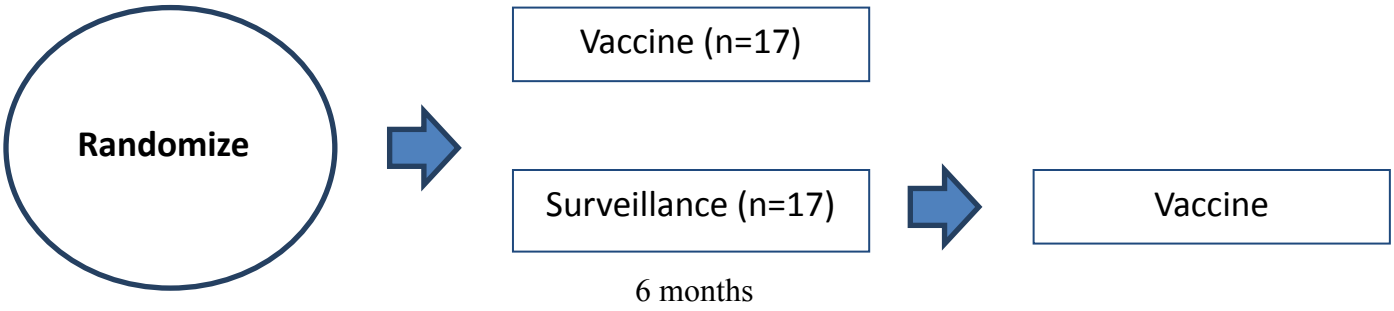
Sponsor Contact:

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

Investigational Agent:

Drug Name:	GI-6207 [Recombinant Saccharomyces cerevisiae-CEA (610D)]
IND Number:	15344
Sponsor:	NantCell, Inc.
Manufacturer/Supplier:	GlobeImmune

Schema



- All patients enrolled will have evaluable disease
- Consistent with phase 1 study dosing, all patients will be given GI-6207 every 2 weeks for 3 months and then monthly. Dose = 40/YU.
- Half of the patients will be on surveillance for 6 months to determine a growth rate for comparison to those who start GI-6207 immediately
- The primary endpoint will compare the calcitonin growth rate in the GI-6207 arm at 6 months, with patients on the surveillance arm at 6 months.
- A secondary endpoint will compare the surveillance arm growth rate after 6 months of GI-6207 to each patient's own baseline growth rate determined after 6 months of surveillance.
- Patients will be evaluated with radiographic imaging at enrollment and every 3 months while on study
- Patients will be removed from treatment if there is clinical progression or radiographic progression (based on the immune-related response criteria) while on GI-6207 treatment
- Patients will be stratified based on pre-treatment doubling time of less than or greater than 24 months.
- Once patients have completed one year of therapy with GI-6207, patients without radiographic progression will have the option to receive vaccine every 3 months for an additional 12 months. Patients who remain on vaccine will continue to be scanned every 3 months.

STATEMENT OF COMPLIANCE

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

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

Principal Investigator:

Signed: _____ Date: _____

PRÉCIS

Background:

- CEA is overexpressed in multiple malignancies, including medullary thyroid cancer where CEA is universally expressed on tumor cells.
- There is no standard treatment for patients with asymptomatic or minimally symptomatic, metastatic medullary thyroid cancer. The only effective FDA-approved therapy (vandetanib) comes with significant toxicity, so it is not used until patients have symptomatic or rapidly progressing disease.
- Preclinical studies have shown that GI-6207 can induce a strong immune response to CEA as well as therapeutic anti-tumor responses.
- A previous phase 1 GI-6207 study has demonstrated safety and enhanced immune response in some patients.
- Preliminary data suggests that tumor growth rates can be calculated in medullary thyroid cancer patients within 3 months.
- Retrospective data from prostate cancer studies suggest that vaccines can alter tumor growth rates within 3-4 months.

Objective:

Primary

- To determine the effect of GI-6207 on calcitonin growth rate kinetics after 6 months of therapy in patients with medullary thyroid cancer.

Eligibility:

- Patients will have evidence of metastatic medullary thyroid cancer including disease that is evaluable on bone or CT scan.
- Patients with minimal or no disease related-symptoms (minimal symptoms will include those that do not affect activities of daily living or pain that does not require regularly schedule narcotics).
- ECOG 0-1
- No previous chemotherapy
- No previous vandetanib
- Should have no autoimmune diseases; no evidence of being immunocompromised; no serious inter-current medical illness; no cardiac disease; no prior splenectomy. (History of previous thyroid autoimmune disease will be allowed as these patients will have had total thyroidectomy.)
- No brain metastasis, history of seizures, encephalitis, or multiple sclerosis
- No pericardial-based masses greater than 1 cm or thoracic lesions larger than 2 cm

Design:

- Randomized, phase 2 study to determine the effect of GI-6207 on calcitonin growth rate after 6 months of GI-6207
- Patients will be randomized to either initial GI-6207 therapy or 6 months of surveillance followed by GI-6207 therapy.
- GI-6207 will be administered subcutaneously at 4 sites at dose of 10 yeast units per site, biweekly for 7 visits (day 1, 15, 29, 43, 57, 71, 85), then monthly up to 1 year of treatment. (For patients randomized to surveillance and then GI-6207, they will get a full year of GI-6207 after a 6 month surveillance period.)
- Once patients have completed one year of therapy with GI-6207, patients without radiographic progression will have the option to receive vaccine every 3 months for an additional 12 months. Patients who remain on vaccine will continue to be scanned every 3 months.
- Immune monitoring via apheresis will be done prior to enrollment and at 6 months for all appropriate and consenting patients. Patients who are evaluable for immunologic response by the ELISPOT Assay (HLA 02, 03 and 24) will have apheresis at start of GI-6207 therapy and then every 3 months while on GI-6207 treatment when feasible.

SPONSOR SIGNATURE

Study Title:	A phase 2 study of GI-6207 in patients with recurrent medullary thyroid cancer
Study Number:	QUILT-3.006
Version Date:	14 May 2018

This clinical trial protocol was subject to critical review and has been approved by NantCell.

The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 5-16-18

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

Abbreviated Title: GI-6207 in MTC
Study number: QUILT-3.006
NCI Protocol #: 13-C-0095 OSP#: 1301-1199
Version Date: 30 01 2018 IBC#: RD-13-I-10
Amendment: F

Title: A Phase 2 study of GI-6207 in patients with recurrent medullary thyroid cancer

NCI Principal Investigator: Ravi A. Madan, M.D. [A, B, C, D, E, F]
Genitourinary Malignancies Branch, CCR, NCI
10 Center Drive
Building 10, Room 13N240
Bethesda, MD 20892
Phone: 301-480-7168
Email: madanr@mail.nih.gov

Statistician: *Seth Steinberg, Ph.D., OCD, CCR, NCI [E, F]

NIH Associate Investigators:
James L. Gulley, M.D., Ph.D., GMB, CCR, NCI [A, B, C, D, E, F]
Julius Strauss, M.D., OCD, CCR, NCI [A, B, C, D, E, F]
Marijo Bilusic, M.D., Ph.D., GMB, CCR, NCI [A, B, C, D, E, F]
Jaydira Del Rivero, M.D., OCD, CCR, NCI [A, B, C, D, E, F]
Myrna Rauckhorst, R.N., OCD, CCR, NCI [A, B, C, E, F]
Sheri McMahon, R.N., OCD, CCR, NCI [A, B, C, E, F]
Guinevere Chun, R.N., OCD, CCR, NCI [A, B, C, E, F]
Amy Hankin, P.A., GMB, CCR, NCI [A, B, C, D, E, F]
Lisa Cordes, PharmD, Pharmacy Department, CC [E, F]

Non-NIH Associate Investigator: Philip M. Arlen, M.D. [V], GMB, CCR, NCI [A, B, E, F]

Referral Contact/
Study Coordinator: Myrna Rauckhorst, R.N., OCD, CCR, NCI
10 Center Drive
Building 10, Room 13N210
Bethesda, MD 20892
Phone: 240-760-6069
Email: mrauckhorst@mail.nih.gov

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

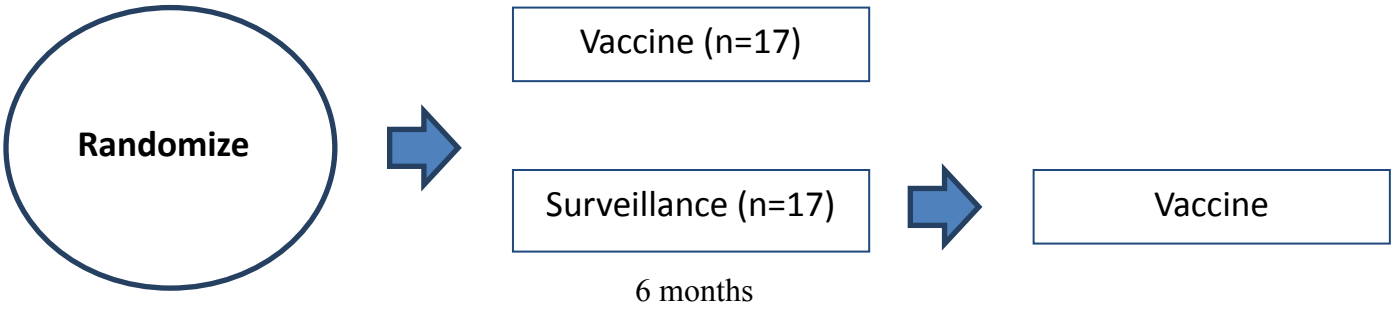
*Indicates Associate Investigators who will not be making protocol-related medical decisions.

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
F. *Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
G. *Some/all research activities performed outside NIH*

Investigational Agent:

Drug Name:	GI-6207 [Recombinant Saccharomyces cerevisiae-CEA (610D)]
IND Number:	15344
Sponsor:	NantCell, Inc.
Manufacturer/Supplier:	GlobeImmune

Schema



- All patients enrolled will have evaluable disease
- Consistent with phase I study dosing, all patients will be given GI-6207 every 2 weeks for 3 months and then monthly. Dose = 40/YU.
- Half of the patients will be on surveillance for 6 months to determine a growth rate for comparison to those who start GI-6207 immediately
- The primary endpoint will compare the calcitonin growth rate in the GI-6207 arm at 6 months, with patients on the surveillance arm at 6 months.
- A secondary endpoint will compare the surveillance arm growth rate after 6 months of GI-6207 to each patient's own baseline growth rate determined after 6 months of surveillance.
- Patients will be evaluated with radiographic imaging at enrollment and every 3 months while on study
- Patients will be removed from treatment if there is clinical progression or radiographic progression (based on the immune-related response criteria) while on GI-6207 treatment
- Patients will be stratified based on pre-treatment doubling time of less than or greater than 24 months.
- Once patients have completed one year of therapy with GI-6207, patients without radiographic progression will have the option to receive vaccine every 3 months for an additional 12 months. Patients who remain on vaccine will continue to be scanned every 3 months.

PRÉCIS

Background:

- CEA is overexpressed in multiple malignancies, including medullary thyroid cancer where CEA is universally expressed on tumor cells.
- There is no standard treatment for patients with asymptomatic or minimally symptomatic, metastatic medullary thyroid cancer. The only effective FDA-approved therapy (vandetanib) comes with significant toxicity, so it is not used until patients have symptomatic or rapidly progressing disease.
- Preclinical studies have shown that GI-6207 can induce a strong immune response to CEA as well as therapeutic anti-tumor responses.
- A previous Phase I GI-6207 study has demonstrated safety and enhanced immune response in some patients.
- Preliminary data suggests that tumor growth rates can be calculated in medullary thyroid cancer patients within 3 months.
- Retrospective data from prostate cancer studies suggest that vaccines can alter tumor growth rates within 3-4 months.

Objective:

Primary

- To determine the effect of GI-6207 on calcitonin growth rate kinetics after 6 months of therapy in patients with medullary thyroid cancer.

Eligibility:

- Patients will have evidence of metastatic medullary thyroid cancer including disease that is evaluable on bone or CT scan.
- Patients with minimal or no disease related-symptoms (minimal symptoms will include those that do not affect activities of daily living or pain that does not require regularly schedule narcotics.)
- ECOG 0-1
- No previous chemotherapy
- No previous vandetanib
- Should have no autoimmune diseases; no evidence of being immunocompromised; no serious inter-current medical illness; no cardiac disease; no prior splenectomy. (History of previous thyroid autoimmune disease will be allowed as these patients will have had total thyroidectomy.)
- No brain metastasis, history of seizures, encephalitis, or multiple sclerosis
- No pericardial-based masses greater than 1 cm or thoracic lesions larger than 2 cm

Design:

- Randomized, phase 2 study to determine the effect of GI-6207 on calcitonin growth rate after 6 months of GI-6207
- Patients will be randomized to either initial GI-6207 therapy or 6 months of surveillance followed by GI-6207 therapy.
- GI-6207 will be administered subcutaneously at 4 sites at dose of 10 yeast units per site, biweekly for 7 visits (day 1, 15, 29, 43, 57, 71, 85), then monthly up to 1 year of treatment. (For patients randomized to surveillance and then GI-6207, they will get a full year of GI-6207 after a 6 month surveillance period.)
- Once patients have completed one year of therapy with GI-6207, patients without radiographic progression will have the option to receive vaccine every 3 months for an additional 12 months. Patients who remain on vaccine will continue to be scanned every 3 months.
- Immune monitoring via apheresis will be done prior to enrollment and at 6 months for all appropriate and consenting patients. Patients who are evaluable for immunologic response by the ELISPOT Assay (HLA 02, 03 and 24) will have apheresis at start of GI-6207 therapy and then every 3 months while on GI-6207 treatment when feasible.