Abbreviated Title: Ph 2 Yeast-Brachyury Chordoma
Study number: QUILT-3.011
CC Protocol #: 15-C-0118 OSP#: 1407-1336
Version Date: 30 01 2018 IBC#: RD-15-III-13
Amendment: G
NCT Number: NCT02383498

Title: A Randomized, Double-Blind, Phase 2 Trial of GI-6301 (Yeast-Brachyury Vaccine) Versus Placebo in Combination with Standard of Care Definitive Radiotherapy in Locally Advanced, Unresectable, Chordoma

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Investigator Roles:

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 Agents:

Drug Name	GI-6301 Vaccine (Yeast-Brachyury)
IND Number	BB-IND # 14895
Sponsor	NantCell, Inc.
Manufacturer/Supplier	GlobeImmune

Commercial Device: wGT3X-BT manufactured by Actigraph. Associate Investigator in the Diabetes, Endocrinology, and Obesity Branch of NIDDK will provide the actigraphy equipment.

PRÉCIS

Background:

- Chordoma is a rare disease, affecting about 3,000 people in the United States, with about 300 new cases diagnosed per year.
- Brachyury is a member of the T-box family of transcription factors, characterized by a highly conserved DNA-binding domain designated as T-domain.
- Brachyury is expressed universally in chordoma cells.
- GI-6301 (Yeast-brachyury vaccine) has demonstrated immunogenicity with a tolerable and acceptable safety profile in a phase 1 trial.
- Brachyury specific T cells can lyse human cancer cells expressing brachyury in an MHC restricted manner.
- There have been indications of clinical benefit in patients with chordoma enrolled on the phase I trial of GI-6301.
    - 1 **Partial Response**
    - 1 **Mixed Response** in Chordoma patients who received Radiation
    - 6 of 9 patients with progressive disease at enrollment had Stable Disease at Day 85 restaging
- In vitro, chordoma cell lines are killed significantly better by brachyury-specific T cells after radiation exposure using either proton beam or gamma radiation.

Endpoints:

Primary Objective:

- To determine if there is a difference in overall response rate (ORR) defined as complete response (CR) or partial response (PR) by RECIST 1.1 in the irradiated tumor site after up to 24 months among patients with Chordoma who are treated with radiation plus vaccine vs. radiation plus placebo.

Eligibility:

- Patients at least 18 years old with advanced (unresectable, chordoma who are planning to be treated with definitive radiotherapy to at least one lesion.
- No history of autoimmune disease (with exceptions detailed in section **2.1**)
- Measurable disease as defined by RECIST 1.1
- Adequate organ function

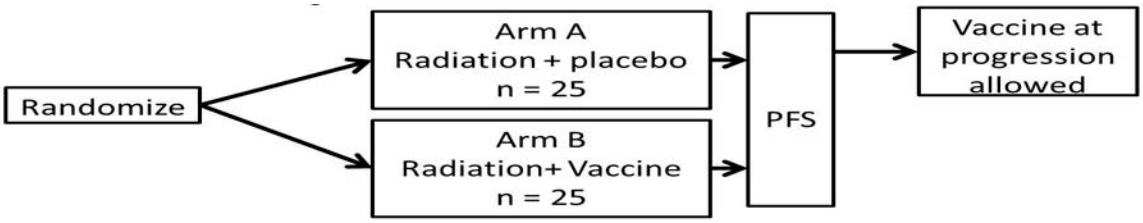
***Design*:**

- Randomized, double-blind, placebo controlled phase 2 clinical trial of radiation plus placebo vs. radiation plus yeast-brachyury vaccine in patients with chordoma.
- Participants will be randomized on a 1:1 basis to the two arms
- Participants assigned to the placebo arm will be allowed to cross-over at time of confirmed disease progression.
- Participants who have had a response in the irradiated target lesion and then have progression outside of the irradiated site will have the option to receive irradiation or other local intervention to the area of disease outside of the radiation field. Progression

will be determined only by the target lesion which had been irradiated. Other lesions will be monitored and intervened upon as clinically necessary. If alternative systemic therapy is required, patients would be taken off study at that point.

- Radiographic progression at the irradiated lesion will be unblinded. Those who did not receive the vaccine will have the option to receive it in combination with radiation to the lesion which is demonstrating disease progression.
- Participants will be evaluated for objective response, and time to progression of the irradiated tumor mass as well as overall survival
- Up to 55 participants will be accrued to the study

Randomization Schema



<u>Primary endpoint</u>: Overall response rate (RECIST 1.1) in the irradiated tumor site(s)

<u>Secondary endpoints</u>:

-Progression free survival (irradiated tumor), PFS (other sites), overall survival
-Patient Report Outcomes

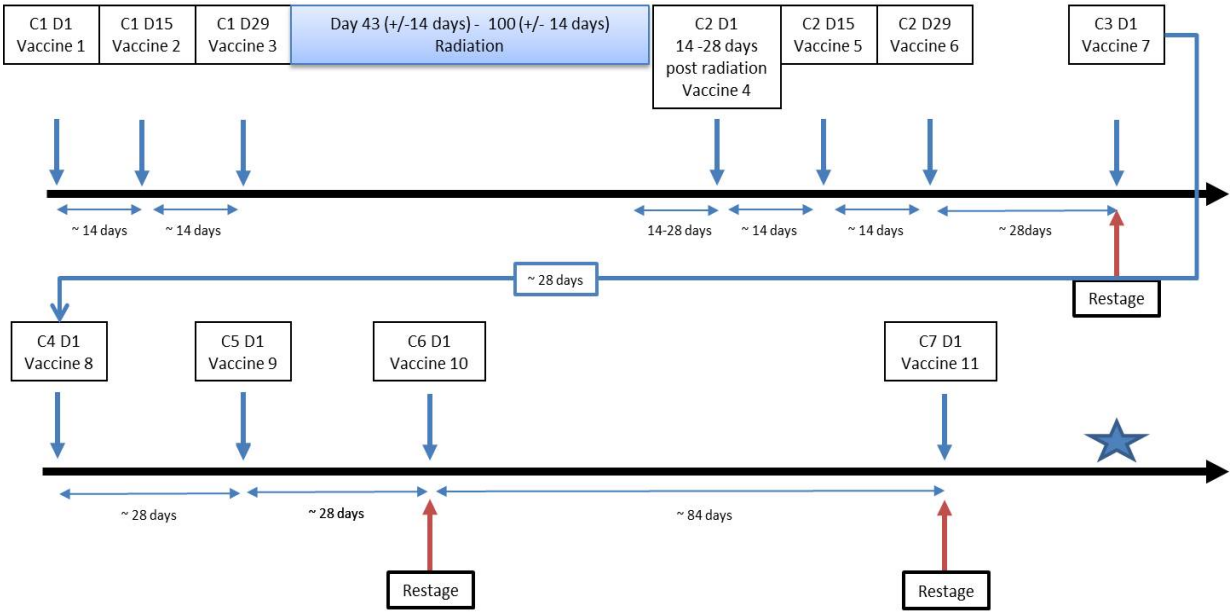
<u>Exploratory endpoints</u>:

- Evaluations of response rate and PFS using other criteria
  - (Volumetric, Growth rate kinetics, Choi)
- To evaluate brachyury-specific T cell response pre-, during, and post-treatment.
- To evaluate other parameters of general immune activation detailed in the protocol.
- To evaluate the quantity and quality of tumor infiltrating lymphocytes and other markers of local immune response and inflammation pre- and post-treatment in both groups.
- Daily Activity

<u>Statistical assumption</u>:

- Goal: improve ORR from 5% to 30%

Treatment Schema



After C7, study agent doses will be given every 3 months (85 days, -7 / +28 days). Restaging scans will be performed at fixed intervals from the time of completion of radiation: 3 months (-7 / +28 days, corresponds to C3D1), 6 months (+/- 4 weeks, corresponds to C6D1), 9 months (+/- 4 weeks, corresponds to C7D1), 12 months (+/- 4 weeks, corresponds to C8D1), 18 months (+/- 8 weeks, C10D1), 24 months (+/- 8 weeks, C12D1), 36 months (+/- 8 weeks, C16D1) and yearly thereafter (+/- 8 weeks). MDASI assessment will take place at baseline and at each restaging imaging timepoint.

8 STATISTICAL CONSIDERATIONS

The primary objective of the trial is to determine if there is a difference in overall response rate (ORR) defined as complete response (CR) or partial response (PR) by RECIST 1.1 in the irradiated tumor site after up to 24 months among patients with Chordoma who are treated with radiation plus placebo vs. radiation plus vaccine.

Based upon results in the literature[35], patients who would be eligible to be randomized on this trial would be expected to have an estimated 5% ORR after up to 24 months if treated in a standard manner with radiation alone. The goal of this study will be to determine if the use of radiation along with vaccine will result in patients having an increased response rate by 24 months which is consistent with 30%.

Following the principles of a phase 2.5 design, to compare these two groups and have 80% power to detect a difference between a 5% and 30% 24 month response rate with a 0.10 one-

tailed Fisher's exact test, a total of 25 evaluable subjects per arm (50 total) will need to be randomized over an expected 2 to 3 years, and followed for up to 2 years after randomization.

Patients will be stratified for:

1. Standard fractionation versus hypofractionation radiotherapy dosing
2. Proton versus photon radiation

The vaccine is likely to be very safe, and because the trial is a small randomized phase 2 study, the trial will not require a DSMB to evaluate the findings.

In addition to comparing responses, PFS and OS will be evaluated as secondary endpoints, with Kaplan-Meier curves and a two-tailed log-rank test as the analysis methods. Exploratory evaluations will include response evaluation by other methods, such as Choi and immune-related RECIST criteria (irRC).

It is expected that 20 patients can be accrued onto this trial per year. In order to allow for a very small number of inevaluable patients, the accrual ceiling will be set at 55 patients.

[redacted]

12.3 APPENDIX C: TREATMENT AND MONITORING SCHEDULE: PRE, DURING AND POST THERAPY

	Screening	**Baseline[1]**	**C1 D1**	**C1 D15**	**C1 D29**	**Days 43-100 (+/-14)**	**C2 D1**	**C2 D15**	**C2 D29**	**C3 D1 – C5 D1**	**C6 D1 → 2 years on study**	**Post-treatment follow-up visit**
History and Physical[1]	X	X										
Medical Assessments[2]		X	X		X		X		X	X	X	X[14]
Imaging[3]	X[3]									X[3]	X[3]	
Urinalysis	X	X		X	X		X		X	X	X	
Serum HIV antibody[4]	X	X										
Serum Hepatitis B & C[5]	X											
CBC with differential, platelet count	X	X		X	X		X	X	X	X	X	X[14]
Chemistry[6]	X	X		X	X		X	X	X	X	X	X[14]
EKG	X								X			
Immunology (blood)[7]		X		X	X		X	X	X	X	X	X [14]
ANA titer[8]		X			X						X	
CD3, 4, 8, 19 subsets, NK markers and CD4:CD8 ratio[8]		X			X						X	
HLA Typing	X											
Skin testing[9]	X											
Serum Beta-	X											

	Screening	Baseline[1]	C1 D1	C1 D15	C1 D29	Days 43-100 (+/-14)	C2 D1	C2 D15	C2 D29	C3 D1 – C5 D1	C6 D1 → 2 years on study	Post-treatment follow-up visit
HCG[10]												
Radiotherapy						X						
GI-6301 (Yeast-Brachyury Vaccine) or placebo[11]			X	X	X		X	X	X	X	X[11]	
Yeast allergy test[12]												
Adverse Events		X		X	X		X	X	X	X	X	
Tissue Samples[13]		X									X	
Concomitant Medications		X		X	X		X	X	X	X	X	
MDASI		X[3]								X[3]	X[3]	
Actigraphy		X	X	X	X	X	X	X	X			

[1] Baseline: H & P and laboratory studies should be completed within 16 days of initiating treatment. Baseline radiographic, ECOG performance status, EKG and immunologic studies should be obtained within 28 days of initiating treatment.

[2] Medical assessments: interim history (since last visit), vital signs, physical examination and ECOG performance status, must be performed within 3 days of each dose

[3] Radiologic studies consisting of CT chest/abdomen/pelvis and MRI will be performed within 28 days prior to enrollment, after completion of cycle 2 (on or around C3 D1, and every 3 months (-7 days / +28 days) thereafter. After 1 year of SD, PR, or CR, imaging may be performed approximately every 6 months during year 2, and then yearly thereafter. Imaging can be repeated early at the discretion of the investigator/physician. MDASI assessments will take place along with imaging studies.

[4] Serum HIV antibody should be completed within 12 weeks of initiating treatment. A positive screening test must be confirmed by detectable virus in the serum by PCR.

[5] Serum hepatitis B & C antibody should be completed within 12 weeks of initiating treatment. A positive screening test must be confirmed by detectable virus in the serum by PCR.

[6] Chemistry panel: Na+, K+, Cl-, CO_2, glucose, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, TSH, and LDH.

[7] Blood will be obtained for immunologic assays. Research blood will be drawn at baseline and prior to each dose. 2 SST tubes, 6 green top tubes are required.

[8] ANA and CD3, 4, 8, 19 subsets will be drawn at baseline and prior to C6 D1.

[9] For patients with questionable history of yeast allergy, this test is performed at the screening visit to detect if the subject has a hypersensitivity to *Saccharomyces cerevisiae*. **A negative response is required for entry into this trial.**

[10] In females of child-bearing age, beta-HCG to be done within 48 hours prior to day 1.

[11] Administered subcutaneously at 4 sites. Dosing will be given as follows: on C1 D1, C1 D15, C1 D29 (all +/-3 days). Dosing will be interrupted for the duration of radiation and will resume 14-28 days post radiation depending on patient schedule and any time required to recover. Treatment is then resumed on C2 D1, C2 D15, C2 D29 (all +/- 3 days). C3 D1 (28 days (+/- 7 days) after C2 D29) begins monthly (28 day +/- 7 days) dosing for 4 doses (cycles 3, 4, 5, and 6). C6 D1 begins every 3 month (85 days -7/+28 days) dosing, which goes on for at least 2 years. After 2 years on study, doses may be given less frequently (every 6-12 months) based on vaccine supply and patient preference

[13] Performed in subjects with a questionable history of allergy to yeast

[13] Baseline tissue sample is preferred. These may be fresh biopsy samples or archived tissue. If archived tissue, at least 10 unstained slides are required. On-study biopsy specimens will be analyzed by immunohistochemistry for evidence of immune response within the tumor. These samples may be obtained at 6 or 12 months or at evidence of tumor response or tumor progression. Biopsy is allowable for research purposes at other times at investigator discretion with patient consent to biopsy.

[14]Post-treatment follow-up labs are not required if the subject prefers to follow-up via phone contact.

Abbreviated Title: Ph 2 Yeast-Brachyury Chordoma
NantCell Study number: QUILT-3.011
CC Protocol #: 15-C-0118 OSP#: 1407-1336
Version Date: May 14, 2018 IBC#: RD-15-III-13
Amendment: H
NCT Number: NCT02383498

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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 Agents:

Drug Name	GI-6301 Vaccine (Yeast-Brachyury)
IND Number	BB-IND # 14895
Sponsor	NantCell, Inc.
Manufacturer/Supplier	GlobeImmune

Commercial Device: wGT3X-BT manufactured by Actigraph. Associate Investigator in the Diabetes, Endocrinology, and Obesity Branch of NIDDK will provide the actigraphy equipment.

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:

- Chordoma is a rare disease, affecting about 3,000 people in the United States, with about 300 new cases diagnosed per year.
- Brachyury is a member of the T-box family of transcription factors, characterized by a highly conserved DNA-binding domain designated as T-domain.
- Brachyury is expressed universally in chordoma cells.
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- Brachyury specific T cells can lyse human cancer cells expressing brachyury in an MHC restricted manner.
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Eligibility:

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***Design*:**

- Randomized, double-blind, placebo controlled phase 2 clinical trial of radiation plus placebo vs. radiation plus yeast-brachyury vaccine in patients with chordoma.
- Participants will be randomized on a 1:1 basis to the two arms
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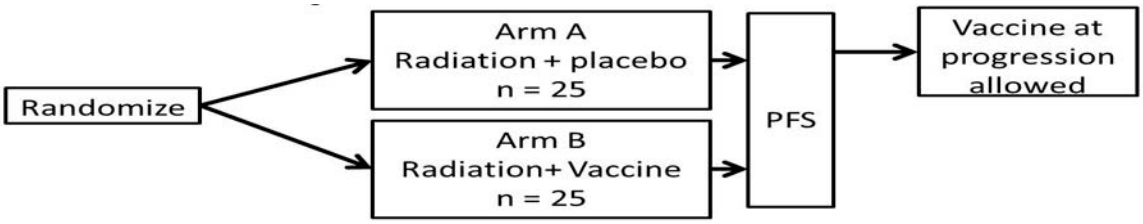

<u>Primary endpoint</u>: Overall response rate (RECIST 1.1) in the irradiated tumor site(s)

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<u>Statistical assumption</u>:

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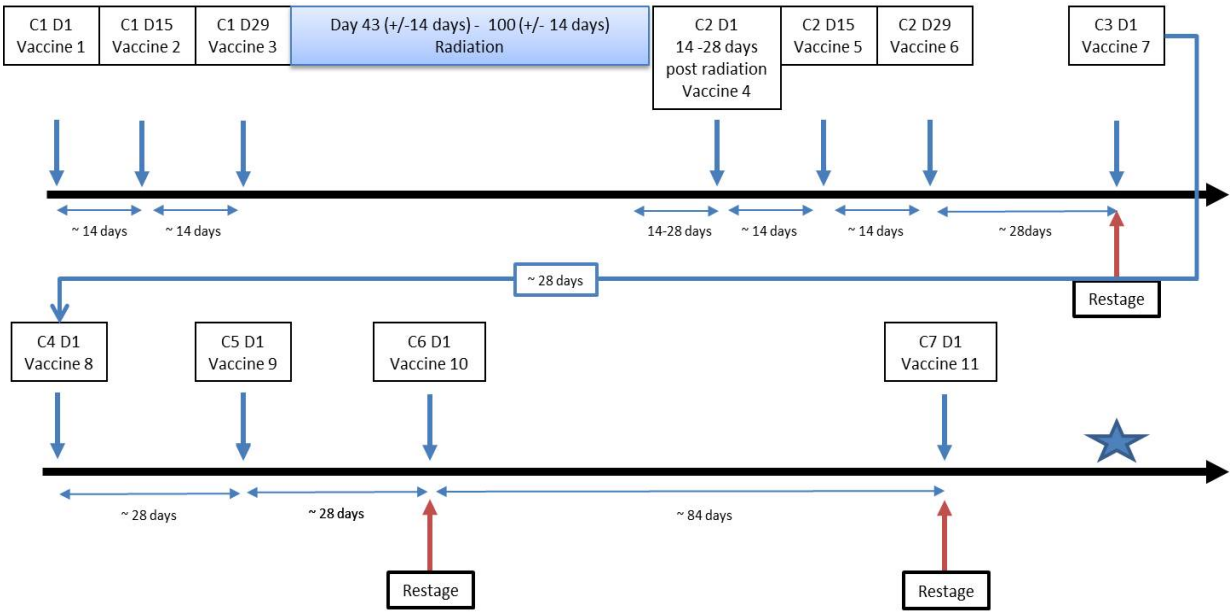

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12.3 APPENDIX C: TREATMENT AND MONITORING SCHEDULE: PRE, DURING AND POST THERAPY

	Screening	**Baseline[1]**	**C1 D1**	**C1 D15**	**C1 D29**	**Days 43-100 (+/- 14)**	**C2 D1**	**C2 D15**	**C2 D29**	**C3 D1 – C5 D1**	**C6 D1 → 2 years on study**	**Post-treatment follow-up visit**
History and Physical[1]	X	X										
Medical Assessments[2]		X	X		X		X		X	X	X	X[14]
Imaging[3]	X[3]									X[3]	X[3]	
Urinalysis	X	X		X	X		X		X	X	X	
Serum HIV antibody[4]	X	X										
Serum Hepatitis B & C[5]	X											
CBC with differential, platelet count	X	X		X	X		X	X	X	X	X	X[14]
Chemistry[6]	X	X		X	X		X	X	X	X	X	X[14]
EKG	X								X			
Immunology (blood)[7]		X		X	X		X	X	X	X	X	X [14]
ANA titer[8]		X			X						X	
CD3, 4, 8, 19 subsets, NK markers and CD4:CD8 ratio[8]		X			X						X	
HLA Typing	X											
Skin testing[9]	X											

	Screening	**Baseline[1]**	**C1 D1**	**C1 D15**	**C1 D29**	**Days 43-100 (+/-14)**	**C2 D1**	**C2 D15**	**C2 D29**	**C3 D1 – C5 D1**	**C6 D1 → 2 years on study**	**Post-treatment follow-up visit**
Serum Beta-HCG[10]	X											
Radiotherapy						X						
GI-6301 (Yeast-Brachyury Vaccine) or placebo[11]			X	X	X		X	X	X	X	X[11]	
Yeast allergy test[12]												
Adverse Events		X		X	X		X	X	X	X	X	
Tissue Samples[13]		X									X	
Concomitant Medications		X		X	X		X	X	X	X	X	
MDASI		X[3]								X[3]	X[3]	
Actigraphy		X	X	X	X	X	X	X	X			

[1] Baseline: H & P and laboratory studies should be completed within 16 days of initiating treatment. Baseline radiographic, ECOG performance status, EKG and immunologic studies should be obtained within 28 days of initiating treatment.

[2] Medical assessments: interim history (since last visit), vital signs, physical examination and ECOG performance status, must be performed within 3 days of each dose

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[6] Chemistry panel: Na+, K+, Cl-, CO_2, glucose, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, TSH, and LDH.

[7] Blood will be obtained for immunologic assays. Research blood will be drawn at baseline and prior to each dose. 2 SST tubes, 6 green top tubes are required.

[8] ANA and CD3, 4, 8, 19 subsets will be drawn at baseline and prior to C6 D1.

[9] For patients with questionable history of yeast allergy, this test is performed at the screening visit to detect if the subject has a hypersensitivity to *Saccharomyces cerevisiae*. **A negative response is required for entry into this trial.**

[10] In females of child-bearing age, beta-HCG to be done within 48 hours prior to day 1.

[11] Administered subcutaneously at 4 sites. Dosing will be given as follows: on C1 D1, C1 D15, C1 D29 (all +/-3 days). Dosing will be interrupted for the duration of radiation and will resume 14-28 days post radiation depending on patient schedule and any time required to recover. Treatment is then resumed on C2 D1, C2 D15, C2 D29 (all +/- 3 days). C3 D1 (28 days (+/- 7 days) after C2 D29) begins monthly (28 day +/- 7 days) dosing for 4 doses (cycles 3, 4, 5, and 6). C6 D1 begins every 3 month (85 days -7/+28 days) dosing, which goes on for at least 2 years. After 2 years on study, doses may be given less frequently (every 6-12 months) based on vaccine supply and patient preference

[13] Performed in subjects with a questionable history of allergy to yeast

[13] Baseline tissue sample is preferred. These may be fresh biopsy samples or archived tissue. If archived tissue, at least 10 unstained slides are required. On-study biopsy specimens will be analyzed by immunohistochemistry for evidence of immune response within the tumor. These samples may be obtained at 6 or 12 months or at evidence of tumor response or tumor progression. Biopsy is allowable for research purposes at other times at investigator discretion with patient consent to biopsy.

[14]Post-treatment follow-up labs are not required if the subject prefers to follow-up via phone contact.

SPONSOR SIGNATURE

Study Title:	A Randomized, Double-Blind, Phase 2 Trial of GI-6301 (Yeast-Brachyury Vaccine) Versus Placebo in Combination with Standard of Care Definitive Radiotherapy in Locally Advanced, Unresectable, Chordoma
Study Number:	QUILT-3.011
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

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Abbreviated Title: Ph 2 Yeast-Brachyury Chordoma
NantCell Study number: QUILT-3.011
CC Protocol #: 15-C-0118 OSP#: 1407-1336
Version Date: July 11, 2018 IBC#: RD-15-III-13
Amendment: I
NCT Number: NCT02383498

Title: A Randomized, Double-Blind, Phase 2 Trial of GI-6301 (Yeast-Brachyury Vaccine) Versus Placebo in Combination with Standard of Care Definitive Radiotherapy in Locally Advanced, Unresectable, Chordoma

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Investigational Agents:

Drug Name	GI-6301 Vaccine (Yeast-Brachyury)
IND Number	BB-IND # 14895
Sponsor	NantCell, Inc.
Manufacturer/Supplier	GlobeImmune

Commercial Device: wGT3X-BT manufactured by Actigraph. Associate Investigator in the Diabetes, Endocrinology, and Obesity Branch of NIDDK will provide the actigraphy equipment.

PRÉCIS

Background:

- Chordoma is a rare disease, affecting about 3,000 people in the United States, with about 300 new cases diagnosed per year.
- Brachyury is a member of the T-box family of transcription factors, characterized by a highly conserved DNA-binding domain designated as T-domain.
- Brachyury is expressed universally in chordoma cells.
- GI-6301 (Yeast-brachyury vaccine) has demonstrated immunogenicity with a tolerable and acceptable safety profile in a phase 1 trial.
- Brachyury specific T cells can lyse human cancer cells expressing brachyury in an MHC restricted manner.
- There have been indications of clinical benefit in patients with chordoma enrolled on the phase I trial of GI-6301.
    - 1 **Partial Response**
    - 1 **Mixed Response** in Chordoma patients who received Radiation
    - 6 of 9 patients with progressive disease at enrollment had Stable Disease at Day 85 restaging
- In vitro, chordoma cell lines are killed significantly better by brachyury-specific T cells after radiation exposure using either proton beam or gamma radiation.

Endpoints:

Primary Objective:

- To determine if there is a difference in overall response rate (ORR) defined as complete response (CR) or partial response (PR) by RECIST 1.1 in the irradiated tumor site after up to 24 months among patients with Chordoma who are treated with radiation plus vaccine vs. radiation plus placebo.

Eligibility:

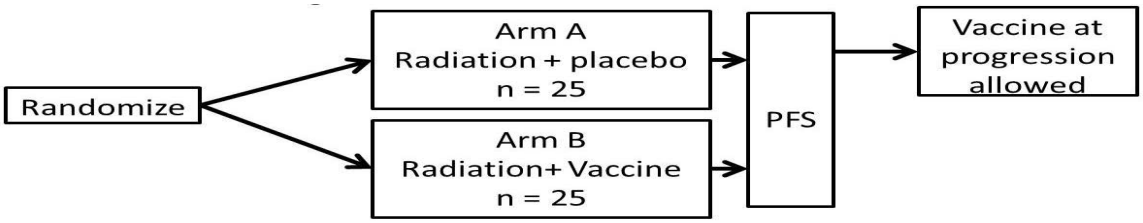
- Patients at least 18 years old with advanced unresectable, chordoma who are planning to be treated with definitive radiotherapy to at least one lesion.
- No history of autoimmune disease (with exceptions detailed in section **2.1**)
- Measurable disease as defined by RECIST 1.1
- Adequate organ function

***Design*:**

- Randomized, double-blind, placebo controlled phase 2 clinical trial of radiation plus placebo vs. radiation plus yeast-brachyury vaccine in patients with chordoma.
- Participants will be randomized on a 1:1 basis to the two arms
- Participants assigned to the placebo arm will be allowed to cross-over at time of confirmed disease progression.

- Participants who have had a response in the irradiated target lesion and then have progression outside of the irradiated site will have the option to receive irradiation or other local intervention to the area of disease outside of the radiation field. Progression will be determined only by the target lesion which had been irradiated. Other lesions will be monitored and intervened upon as clinically necessary. If alternative systemic therapy is required, patients would be taken off study at that point.
- Radiographic progression at the irradiated lesion will be unblinded. Those who did not receive the vaccine will have the option to receive it in combination with radiation to the lesion which is demonstrating disease progression.
- Participants will be evaluated for objective response, and time to progression of the irradiated tumor mass as well as overall survival
- Up to 55 participants will be accrued to the study

Randomization Schema



<u>Primary endpoint</u>: Overall response rate (RECIST 1.1) in the irradiated tumor site(s)

<u>Secondary endpoints</u>:

-Progression free survival (irradiated tumor), PFS (other sites), overall survival
-Patient Report Outcomes

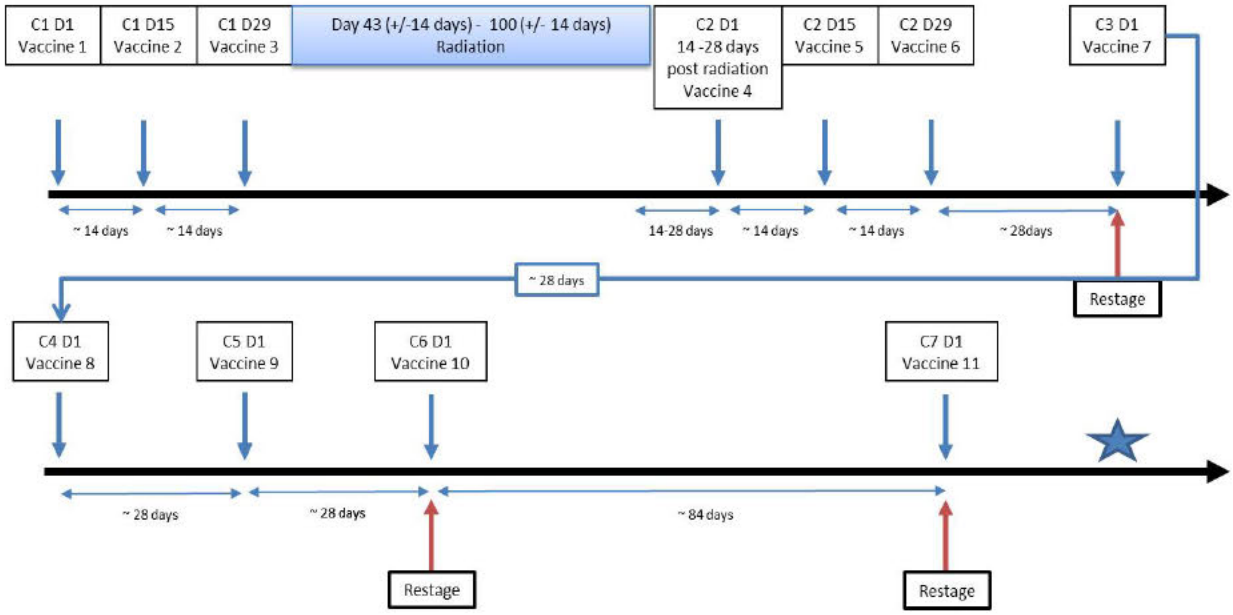
<u>Exploratory endpoints</u>:

- Evaluations of response rate and PFS using other criteria
  - (Volumetric, Growth rate kinetics, Choi)
- To evaluate brachyury-specific T cell response pre-, during, and post-treatment.
- To evaluate other parameters of general immune activation detailed in the protocol.
- To evaluate the quantity and quality of tumor infiltrating lymphocytes and other markers of local immune response and inflammation pre- and post-treatment in both groups.
- Daily Activity

<u>Statistical assumption</u>:

- **Goal: improve ORR from 5% to 30%**

Treatment Schema



After C7, study agent doses will be given every 3 months (85 days, -7 / +28 days). Restaging scans will be performed at fixed intervals from the time of completion of radiation: 3 months (-7 / +28 days, corresponds to C3D1), 6 months (+/- 4 weeks, corresponds to C6D1), 9 months (+/- 4 weeks, corresponds to C7D1), 12 months (+/- 4 weeks, corresponds to C8D1), 18 months (+/- 8 weeks, C10D1), 24 months (+/- 8 weeks, C12D1), 36 months (+/- 8 weeks, C16D1) and yearly thereafter (+/- 8 weeks). MDASI assessment will take place at baseline and at each restaging imaging timepoint.

8 STATISTICAL CONSIDERATIONS

The primary objective of the trial is to determine if there is a difference in overall response rate (ORR) defined as complete response (CR) or partial response (PR) by RECIST 1.1 in the irradiated tumor site after up to 24 months among patients with Chordoma who are treated with radiation plus placebo vs. radiation plus vaccine.

Based upon results in the literature[35], patients who would be eligible to be randomized on this trial would be expected to have an estimated 5% ORR after up to 24 months if treated in a standard manner with radiation alone. The goal of this study will be to determine if the use of radiation along with vaccine will result in patients having an increased response rate by 24 months which is consistent with 30%.

Following the principles of a phase 2.5 design, to compare these two groups and have 80% power to detect a difference between a 5% and 30% 24 month response rate with a 0.10 one-tailed Fisher's exact test, a total of 25 evaluable subjects per arm (50 total) will need to be randomized over an expected 2 to 3 years, and followed for up to 2 years after randomization.

Patients will be stratified for:

1. Standard fractionation versus hypofractionation radiotherapy dosing
2. Proton versus photon radiation

The vaccine is likely to be very safe, and because the trial is a small randomized phase 2 study, the trial will not require a DSMB to evaluate the findings.

In addition to comparing responses, PFS and OS will be evaluated as secondary endpoints, with Kaplan-Meier curves and a two-tailed log-rank test as the analysis methods. Exploratory evaluations will include response evaluation by other methods, such as Choi and immune-related RECIST criteria (irRC).

It is expected that 20 patients can be accrued onto this trial per year. In order to allow for a very small number of inevaluable patients, the accrual ceiling will be set at 55 patients.

12.3 APPENDIX C: TREATMENT AND MONITORING SCHEDULE: PRE, DURING AND POST THERAPY

	Screening	Baseline[1]	C1 D1	C1 D15	C1 D29	Days 43-100 (+/-14)	C2 D1	C2 D15	C2 D29	C3 D1 – C5 D1	C6 D1 → 2 years on study	Post-treatment follow-up visit
History and Physical [1]	X	X										
Medical Assessments[2]		X	X		X		X		X	X	X	X[14]
Imaging[3]	X[3]									X[3]	X[3]	
Urinalysis	X	X		X	X		X		X	X	X	
Serum HIV antibody [4]	X	X										
Serum Hepatitis B & C[5]	X											
CBC with differential, platelet count	X	X		X	X		X	X	X	X	X	X[14]
Chemistry[6]	X	X		X	X		X	X	X	X	X	X[14]
EKG	X								X			
Immunology (blood)[7]		X		X	X		X	X	X	X	X	X [14]
ANA titer[8]		X			X						X	
CD3, 4, 8, 19 subsets, NK markers and CD4:CD8 ratio[8]		X			X						X	

	Screening	Baseline[1]	C1 D1	C1 D15	C1 D29	Days 43-100 (+/-14)	C2 D1	C2 D15	C2 D29	C3 D1 – C5 D1	C6 D1 → 2 years on study	Post-treatment follow-up visit
HLA Typing	X											
Skin testing[9]	X											
Serum Beta-HCG[10]	X											
Radiotherapy						X						
GI-6301 (Yeast-Brachyury Vaccine) or placebo[11]			X	X	X		X	X	X	X	X[11]	
Yeast allergy test[12]												
Adverse Events		X		X	X		X	X	X	X	X	
Tissue Samples[13]		X									X	
Concomitant Medications		X		X	X		X	X	X	X	X	
MDASI		X[3]								X[3]	X[3]	
Actigraphy		X	X	X	X	X	X	X	X			

[1] Baseline: H & P and laboratory studies should be completed within 16 days of initiating treatment. Baseline radiographic, ECOG performance status, EKG and immunologic studies should be obtained within 28 days of initiating treatment.

[2] Medical assessments: interim history (since last visit), vital signs, physical examination and ECOG performance status, must be performed within 3 days of each dose

[3] Radiologic studies consisting of CT chest/abdomen/pelvis and MRI will be performed within 28 days prior to enrollment, after completion of cycle 2 (on or around C3 D1, and every 3 months (-7 days / +28 days) thereafter. After 1 year of SD, PR, or CR, imaging may be performed approximately every 6 months during year 2, and then yearly thereafter. Imaging can be repeated

early at the discretion of the investigator/physician. MDASI assessments will take place along with imaging studies.

[4] Serum HIV antibody should be completed within 12 weeks of initiating treatment. A positive screening test must be confirmed by detectable virus in the serum by PCR.

[5] Serum hepatitis B & C antibody should be completed within 12 weeks of initiating treatment. A positive screening test must be confirmed by detectable virus in the serum by PCR.

[6] Chemistry panel: Na+, K+, Cl-, CO_2, glucose, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, TSH, and LDH.

[7] Blood will be obtained for immunologic assays. Research blood will be drawn at baseline and prior to each dose. 2 SST tubes, 6 green top tubes are required.

[8] ANA and CD3, 4, 8, 19 subsets will be drawn at baseline and prior to C6 D1.

[9] For patients with questionable history of yeast allergy, this test is performed at the screening visit to detect if the subject has a hypersensitivity to *Saccharomyces cerevisiae*. **A negative response is required for entry into this trial.**

[10] In females of child-bearing age, beta-HCG to be done within 48 hours prior to day 1.

[11] Administered subcutaneously at 4 sites. Dosing will be given as follows: on C1 D1, C1 D15, C1 D29 (all +/-3 days). Dosing will be interrupted for the duration of radiation and will resume 14-28 days post radiation depending on patient schedule and any time required to recover. Treatment is then resumed on C2 D1, C2 D15, C2 D29 (all +/- 3 days). C3 D1 (28 days (+/- 7 days) after C2 D29) begins monthly (28 day +/- 7 days) dosing for 4 doses (cycles 3, 4, 5, and 6). C6 D1 begins every 3 month (85 days -7/+28 days) dosing, which goes on for at least 2 years. After 2 years on study, doses may be given less frequently (every 6-12 months) based on vaccine supply and patient preference

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[14]Post-treatment follow-up labs are not required if the subject prefers to follow-up via phone contact.

12.4 APPENDIX D: MODIFIED CHOI CRITERIA

The Choi Criteria was introduced for radiographic evaluation of gastrointestinal stromal tumors treated with imatinib mesylate[44,45] and has been evaluated in other soft tissue sarcomas [43] and renal cell carcinoma[46].

The differences between RECIST and Choi Criteria are defined in the table below:

SPONSOR SIGNATURE

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Study Number:	QUILT-3.011
Version Date:	11 July 2018

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

Signed: _____ Date: July 16 2018

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