# A Phase 2 study of a yeast-based therapeutic cancer vaccine targeting CEA, GI-6207, in patients with asymptomatic, metastatic medullary thyroid cancer (NCT01856920)

Ravi A. Madan[1,2], Nishith Singh[2], Ann Gramza[2,3], Joseph Kim[2], Christopher R. Heery[1,2], Tito Fojo[2], Myrna Rauckhorst[1], Sheri McMahon[1], Thomas H King[4], David Apelian[4], Jeffrey Schlom[1,2], James L. Gulley[1,2]

[1]Laboratory of Tumor Immunology & Biology, [2]Medical Oncology Branch, [3]Endocrine Oncology Branch, NCI, CCR, NIH, [4]GlobeImmune, Inc.

## ABSTRACT

**Background:** *Saccharomyces cerevisiae* (yeast) has been genetically modified to express CEA protein and employed as a heat-killed immune-stimulating, therapeutic cancer vaccine (GI-6207). A previous phase I study with GI-6207 demonstrated safety, bio-marker stabilization and enhanced immune response in some patients. CEA is over-expressed in multiple malignancies, including medullary thyroid cancer (MTC). The recently FDA-approved therapies for metastatic MTC (vandetanib, cabozantinib) come with significant toxicity and are reserved for symptomatic/progressive disease. There is a large population of asymptomatic MTC patients with small tumor burden and/or disease that remains indolent. The standard management of these patients is observation. Preliminary data suggest that tumor growth rate (as measured by CEA and calcitonin) is a quantifiable variable within a 3-6 month time-frame. Retrospective data from prostate cancer studies suggest that vaccines can alter growth rates within 3-4 months. We hypothesize that GI-6207 can alter tumor growth rate in this asymptomatic, indolent MTC patient population, and potentially impact long term outcome.

**Methods:** A phase 2 study at the NCI will evaluate the effect of GI-6207 on calcitonin growth rates in metastatic MTC. 34 patients with minimally symptomatic, radiographically-evaluable, metastatic MTC will be randomized 1:1. Arm A will receive vaccine for a year from the time of enrollment. Arm B will receive the same schedule vaccine after a period of 6 months of surveillance. GI-6207 will be administered subcutaneously at 4 sites at 10 yeast units/site, every 2 weeks for 7 visits (day 1, 15, 29, 43, 57, 71, 85), then monthly up to 1 year of treatment. The primary end point will compare the effect of GI-6207 on calcitonin growth rate kinetics between the vaccine and surveillance arms at 6 months. Secondary end points include immunologic responses (CEA-specific T cells, effector/regulatory T-cell ratio, natural killer cells, myeloid derived suppressor cells) objective responses, time to progression, and changes in CEA kinetics. If this trial can prospectively demonstrate that vaccines can alter tumor growth rate, and such changes are associated with clinical outcomes, then changes in tumor growth rate may become a clinical metric to evaluate vaccine efficacy in MTC and other populations.

## Yeast as a Recombinant Vector

- Easily engineered to express transgenes (such as the CEA antigen)
- Cultured rapidly in large quantities
- Can be administered multiple times
- Recruits and matures dendritic cells

.

## BACKGROUND: Preclinical Data

### Recombinant Yeast-CEA Results in Phenotypic Maturation of Immature Murine Dendritic Cells (DC)

DC+Yeast-CEA (1:1 ratio) → 48h → FACS (14 Markers)

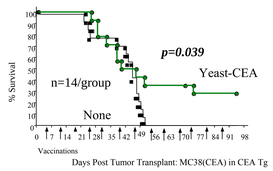
DC Panel [%positive cells (MFI)]

| Treatment | I-Ab | H-2Kb/Db | CD11b | CD11c | CD40 | B7-2 | B7-1 | ICAM-1 | LFA-3 | CD45 |
|---|---|---|---|---|---|---|---|---|---|---|
| None | 75 (1109) | 96 (923) | 24 (158) | 37 (209) | 47 (259) | 50 (794) | 60 (455) | 92 (870) | 84 (482) | 37 (105) |
| Yeast (1:1) | 89 (1846) | 97 (1274) | 22 (160) | 50 (303) | 68 (387) | 70 (1103) | 83 (708) | 99 (1524) | 95 (653) | 33 (135) |

DC+Yeast-CEA (1:1) → 8h → SuperArray (260 genes focused on DC activation)


Bernstein MB et al. Vaccine. 2008

### Yeast-CEA Improves Survival in a Pulmonary Metastasis Model




Wanlsey EK et al. Clin Cancer Res, 2008

### In Vitro Responses to Human Dendritic Cells from Healthy Donors

| Co-culture (ratio) | IL-2 (pg/ml) | IL-8 (pg/ml) | GM-CSF (pg/ml) | IFN- g (pg/ml) | IL-6 (pg/ml) | TNF- a (pg/ml) |
|---|---|---|---|---|---|---|
| CD4+: CD40L-treated DCs (5:1) | 11 | 5871 | 62 | 682 | 0 | 28 |
| CD4+: YEAST-treated DCs (5:1) | 154 | 7976 | 218 | 1583 | 76 | 139 |
| CD4+: CD40L-treated DCs (5:1) + CEA | 9 | 8990 | 81 | 1857 | 187 | 39 |
| CD4+: YEAST-treated DCs (5:1) + CEA | 79 | 10,106 | 322 | 4785 | 288 | 194 |

Cereda V et al. Vaccine. 2011

## BACKGROUND: Phase I Trial

### Yeast CEA Phase I Trial

- Enrolled 25 patients with advanced carcinoma (22 colorectal patients, 1 each with medullary thyroid cancer, pancreatic cancer and lung cancer)
- Patients were heavily pre-treated (median 4 previous chemotherapy regimens)
- There was no DLT (max dose of 40 Yeast Units (YU))

### Yeast CEA Vaccine is Well Tolerated

| Toxicity | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Abdominal pain | 0 | 1 (<0.1%) | 0 |
| Back pain | 0 | 1 (<0.1%) | 0 |
| Dyspnea | 0 | 1 (<0.1%) | 0 |
| Elevated AST | 1 (<0.1%) | 0 | 0 |
| Fever | 1 (<0.1%) | 1 (<0.1%) | 0 |
| Flu-like syndrome | 1 (<0.1%) | 0 | 0 |
| Headache | 1 (<0.1%) | 0 | 0 |
| Hypoxia | 0 | 1 (<0.1%) | 0 |
| Injection-site reaction | 1 (<0.1%) | 1 (<0.1%) | 0 |
| Myalgia | 1 (<0.1%) | 0 | 0 |
| Pain | 0 | 1 (<0.1%) | 0 |
| Pleural effusion | 1 (<0.1%) | 1 (<0.1%) | 0 |
| Rash | 1 (<0.1%) | 0 | 0 |
| Pneumonitis | 0 | 1 (<0.1%) | 0 |

All toxicities possibly, likely, or definitely attributable to vaccine, based on CTCAE 3.0/4.0. Percentages are based on total number of events from 135 vaccine administrations.

Madan RA et al. ASCO Annual Mtg. 2011

### Clinical and Immunologic Outcomes

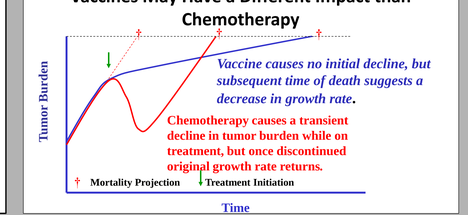
- Although these were heavily pre-treated patients with advanced disease, 5 patients had stable disease beyond 3 months and all 5 had stabilization of their serum CEA
- Some patients showed evidence of increases in antigen-specific CD8+ T cells, as well as CD4+ T lymphocytes, and decreases in regulatory T cells, post-vaccination

## Hypothesis: Vaccines Alter Tumor Growth Rate

- Two vaccines in prostate cancer have extended survival in randomized trials without changing short term progression
- Retrospective studies suggest that vaccines slow growth rate and thus impact long term outcomes

Kantoff PW et al, NEJM 2011; Gulley JL et al Cancer Immunol Immunotherapy 2010; Stein, WD Clin Cancer Res, 2011

### Vaccines May Have a Different Impact than Chemotherapy




### Medullary Thyroid Cancer May be Ideal for Vaccine Therapy

- CEA expressing tumors
- Indolent disease course
- No upfront chemotherapy to impair immune response
- Vaccines are less toxic than FDA approved therapies (vandetanib, cabozantonib)

## TRIAL DESIGN / SCHEMA

Open-Label, Randomized, Phase II

- Patients randomized to
  - Vaccine for 1 year
  - *or*
  - 6 months of surveillance followed by vaccine for 1 year

RANDOMIZE

- Yeast CEA Vaccine for 1 year (n=17)
- Surveillance for 6 months (n=17) → Yeast CEA Vaccine for 1 year

Patients are re-staged at 3 month intervals while on vaccine

## KEY ELIGIBILITY

- Metastatic medullary thyroid cancer
- No prior vandetanib, cabozantonib
- No history of autoimmune disease
- Minimal symptoms related to disease (i.e. no regularly scheduled narcotics)
- No pericardial-based lesions more ≥1cm or pleural based lesions ≥2 cm

## END-POINTS

**PRIMARY ENDPOINT**

- Change in growth rate as measured by calcitonin at 6 months relative to the surveillance arm

**SECONDARY ENDPOINTS**

- Immunologic changes after treatment
- Changes in CEA kinetics after vaccine

## CORRELATIVE STUDIES

- Antigen-specific T-cell responses
- Changes in regulatory T-cell number and function
- Other immune parameters will also be analyzed including NK cells, MDSCs, and cytokines

## ACCRUAL OF TRIAL TO DATE

Total Accrual = 34 patients

- 17 patients will get vaccine first
- 17 patients will get surveillance for 6 months followed by vaccine

CURRENT ENROLLMENT:

- 5 patients have been enrolled since study opened in March, 2013

***Note: All patients will be treated at the NCI but travel subsidy is provided***

## REFERRAL INFORMATION

Patients or providers can call Ms. Laura Otten (301-451-1228)

Questions about the study can be sent to madanr@mail.nih.gov