The Promise of Immunotherapy for Chordoma

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Tumor Immunology Overview

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Chen and Mellman, Immunity 2013
Tumor Immunology Overview

Tumor Immunology Overview

1. Priming and activation of T cells

2. IFN-γ-mediated upregulation of tumor PD-L1

3. PD-L1/PD-1-mediated inhibition of tumor cell killing

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Tumor Immunology Overview

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   - Anti-PD-1
   - IDO inhibitors
Immunogenic Cell Death and Modulation
Role of Natural Killer Cells in Tumor Immunity
PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 Yeast Unit (1 YU = $10^7$ yeast particles) per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until progression</td>
</tr>
<tr>
<td>2</td>
<td>4 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression</td>
</tr>
<tr>
<td>3</td>
<td>10 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression</td>
</tr>
<tr>
<td>4</td>
<td>20 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression</td>
</tr>
</tbody>
</table>
END POINTS

Primary: Safety
Secondary:
  a. CD8 and CD4 T-cell immune response specific for Brachyury
  b. Clinical benefit (describe PFS, tumor marker changes or rate of change)
  c. Other

Immune subsets
Cytokines

PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>All cancers (n = 34)</th>
<th>Chordoma (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (56)</td>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
<td>15 (54)</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Age - Median (range)</strong></td>
<td>58 (32-79)</td>
<td>Age - Median (range)</td>
</tr>
<tr>
<td><strong>Advanced cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>11 (32)</td>
<td>Clival</td>
</tr>
<tr>
<td>Chordoma</td>
<td>11 (32)</td>
<td>Sacral</td>
</tr>
<tr>
<td>Breast</td>
<td>5 (15)</td>
<td>Spinal</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (20)</td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># events (%) doses</td>
<td># pts (%) of pts</td>
</tr>
<tr>
<td><strong>Likely/Possibly related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>48 (18)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (0.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>1 (0.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (1.5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Joint effusion/joint swelling</td>
<td>1 (0.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Myalgias/body aches</td>
<td>1 (0.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.4)</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

Calculation based on 266 administered doses. No events greater than grade 2 attributed to IND.

IMMUNE RESPONSES

17 out of 31 (54%) patients evaluated to date showed a Brachyury-specific immune response post vaccine by ICS
Confirmed Partial Response – Case History

- 47 year old male
- Diagnosed in 2004 (12cm)

- Surgery → Radiation → recurrence in 1 year

- Radiation → no effect → surgery → radiation to tumor bed → recurrence 2 years later

- Surgery → recurrence 2 years later → experimental therapy 2012, no effect

- Hypofractionated radiation March 2013 → enrolled July 2013

- PR December 2013 (8 doses), confirmed January 2014 (9 doses), ongoing response (42% decrease) September 2014
• 61 year old male
• Diagnosed in 2008 (sacral chordoma)

• Gleevec, Rapamycin →
  Surgery → recurrence in 1 year to wrist, right iliac bone

• Radiation to iliac bone
  November 2013 →
  progression of disease
  January 2014 to pelvis, lumbar spine

• Gleevec February 2014 →
  discontinued due to side effects → enrolled April 2014
In this phase 1 study, GI-6301 has been well tolerated, immunogenic, and has evidence of clinical activity in both advanced epithelial cancers and chordomas.

- Well tolerated: most common AEs were injection site reactions
- Immunogenic: 17/31 patients demonstrated immune responses
- Clinical Activity:
  - 1 Partial Response
  - 1 Mixed Response in Chordoma patients who received Radiation
  - Favorable PFS compared with historical studies
  - 1 patient went on to receive anti-PD-L1 and had prolonged stable disease
    - Possible combination to study in the future
Subjects with locally advanced, unresectable chordoma, eligible for definitive radiation for disease control (>70 Gy)

• Primary endpoint: Overall response rate (RECIST 1.1)
• Secondary endpoints:
  - Progression free survival, overall survival
• Exploratory endpoints:
  - 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.
• Statistical assumption:
  - Goal: improve ORR from 5% to 30%;
  - stratification factors: primary vs recurrent tumor and clival vs. other location

Randomized, Double-Blind Phase II Study Design

-Opened for enrollment May 2015
-9 patients enrolled and treated
-5 patients have had restaging
  - 1 unconfirmed PR
  - 3 SD
  - 1 unconfirmed PD
Randomized, Double-Blind Phase II Study: Screening

1. Please Refer Any Potentially Eligible Patients

2. Eligibility
   a) Currently need to rule out metastatic disease (MRI of tumor site and CT CAP for other sites)
      • In the last month, this has prevented 2 otherwise good candidates from enrolling
      • Amendment currently under consideration
   b) Radiation plan in place (tentative) must meet minimal requirement
      • 50 Gy in standard fractionation
      • 50 Gy biologic equivalence in hypofractionation
      • Proton or photon radiation allowed (stratification factor to ensure balance between arms)
   c) ECOG Performance Status 0-2
   d) No significant laboratory abnormalities

3. Please call me directly or email me if you have any issues with referrals
   • heerycr@mail.nih.gov
   • 301-443-7767
Subjects with locally advanced (and/or clinically irrelevant metastatic disease), unresectable chordoma, eligible for definitive radiation for disease control (>70 Gy) 50Gy

- Primary endpoint: Overall response rate (RECIST 1.1) at site of irradiated mass
- Secondary endpoints:
  - Progression free survival (irradiated and non-irradiated masses separately), overall survival
- Exploratory endpoints:
  - 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.
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- Statistical assumption:
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  - stratification factors: primary vs recurrent tumor and clival vs. other location

Randomized, Double-Blind Phase II Study Design

Current proposed amendment = red
Additional change (if accepted): Will allow enrollment of ages 13 and older on study
MVA-BRACHYURY-TRICOM

**PHASE I**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 n = 3</td>
<td>1 site of injection at $2 \times 10^8$ IU given every 28 days for 3 doses. If no evidence of disease progression, 3 more monthly doses may be given.</td>
</tr>
<tr>
<td>2 n = 17</td>
<td>2 sites of injection at $2 \times 10^8$ IU given every 28 days for 3 doses. If no evidence of disease progression, 3 more monthly doses may be given.</td>
</tr>
<tr>
<td>3 n = 18</td>
<td>4 sites of injection at $2 \times 10^8$ IU given every 28 days for 3 doses. If no evidence of disease progression, 3 more monthly doses may be given.</td>
</tr>
</tbody>
</table>

**MVA (modified vaccinia ankara)**
- non-replicating pox virus
- Safe (current smallpox vaccine)
- Can be given repeatedly

**Brachyury**
- T-box transcription factor
- Master driver of EMT
- Expression correlates with invasion, migration, and treatment resistance
- Poor prognostic factor
- Significant expression in Chordoma, rare mesodermal remnant tumor

**TRICOM**
- 3 human costimulatory molecules
- Not amenable to murine studies

*An additional modality for sequential therapy*
Conclusions to Date with MVA-Brachuryy-TRICOM

1. Safety profile established and very good

2. Brachury-specific immune responses observed in early sample analysis

3. Other correlative studies pending (paired biopsy analysis, circulating tumor cell, 123-subset analysis)
these studies used exogenous IFN-γ
model system to recapitulate IFN-γ release from antigen-specific T-cells (from vaccine) into microenvironment and interrogate PD-L1 ADCC
### Other Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Enrolled with Chordoma</th>
</tr>
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<tbody>
<tr>
<td>Yeast-brachyury vaccine</td>
<td>11</td>
</tr>
<tr>
<td>MVA-brachyury-TRICOM vaccine</td>
<td>13</td>
</tr>
<tr>
<td>NHS-IL12</td>
<td>3</td>
</tr>
<tr>
<td>HuMax anti-IL8</td>
<td>7</td>
</tr>
<tr>
<td>Anti-PD-L1</td>
<td>1</td>
</tr>
<tr>
<td>Anti-PD-L1-TGF-beta-TRAP</td>
<td>1</td>
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ACKNOWLEDGEMENTS

Laboratory of Tumor Immunology and Biology, NCI
Jeffrey Schlom, PhD, Chief

Preclinical and Translational:
Claudia Palena, PhD
James Hodge, PhD
Rika Fujii, PhD
Al Tsang, PhD
John Greiner, PhD
Duane Hamilton, PhD
Romaine I. Fernando Ph.D.
Benedetto Farsaci, MD PhD
Renee Donahue, PhD
Sofia Gameiro Ph.D.
Italia Grenga M.D
Lauren Lepone Ph.D.

Clinical Trials group:
James L. Gulley, MD, PhD
Ravi A. Madan, MD
Julius Strauss, MD
Jenn Marte, MD
Sheri McMahon
Myrna Rauckhorst, RN
Chrisa Thomas
Israel Oyelakin, RN

Collaborators
GlobeImmune
Celgene
EMD-Serono
Bavarian Nordic
Cormorant Therapeutics

Chordoma Foundation

Thank you to the patients!