MGDO09, a B7-H3 x CD3 Bispecific Dual-Affinity Re-Targeting (DART®) Molecule Directing T Cells to Solid Tumors

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http://e.macrogenics.com/reviewes.cfm

Abstract

B7-H3 (CD276) is a member of the B7 family of immune regulators that is overexpressed on solid tumors, but displays limited expression on normal human tissues. Consistent with its described T-cell inhibitory role, B7-H3 tumor expression has been associated with reduced T-cell infiltration, progressive and metastatic disease, and correlates with poor prognosis and patient survival. To promote T-cell recruitment and targeting of B7-H3-expressing tumors, we have generated MGDO09, an Fc-bearing B7-H3 x CD3 bispecific DART protein capable of simultaneously binding to B7-H3 and CD3, thereby mediating redirected cytotoxic T-lymphocyte (CTL) activity against B7-H3-expressing cancer cells of various origin (including renal, breast, prostate, lung, pancreatic, pharyngeal cancer, melanoma, and glioblastoma). MGDO09 activity is accompanied by T-cell activation and expansion that is strictly dependent on co-engagement of T cells with B7-H3-positive targets. Treatment with MGDO09 of immune-deficient mice reconstituted with human blood mononuclear cells (PBMCs) and bearing established Detroit562 pharyngeal carcinoma showed recruitment of T cells to tumor site and dose-dependent antitumor activity with tumor regression. Evaluation of pharmacokinetics (PK) in cynomolgus monkeys, whose orthologs cross-react with MGDO09, revealed linear PK with a prolonged half-life supporting dosing at once weekly or longer intervals in humans. A phase 1 study of MGDO09 in patients with B7-H3-expressing solid tumors is currently enrolling.

B7-H3: Member of B7 Family of Immune Regulators

<table>
<thead>
<tr>
<th>Antigen-presenting T-cell</th>
<th>Acto / Inh.</th>
</tr>
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<tbody>
<tr>
<td>Fc-T1 or Fc-L2</td>
<td>PD-1</td>
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</table>

Background

- B7 family member mediating immunomodulatory activity
- Negative regulator of T-cell mediated responses
- Crystal structure resolved and T-cell inhibitor domain mapped

Expression Profile

- Limited expression on adult normal tissue or resting immune cells (Panels A-C)
- Expression on tumor cells across multiple solid tumor types, including expression on tumor neoantigual (Panels C-D)
- High expression correlates with advanced disease, metastases, decreased patient survival

Role in Tumor Biology & Immunology

- Mediation reduces tumor migration and invasion and increases sensitivity to chemothermoy
- Drives immune escape and invasiveness of glioblastoma
- Suppresses T-cell mediated antitumor immune response in lung cancer

Introduction

B7-H3 Displays Favorable Tumor/Normal Differential

A. Restricted Immune Cell Expression

<table>
<thead>
<tr>
<th>Tumor</th>
<th>CD3+ T Cells</th>
<th>CD8+ T Cells</th>
<th>CD4+ T Cells</th>
<th>NK Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>84%</td>
<td>52%</td>
<td>43%</td>
<td>7%</td>
</tr>
<tr>
<td>Breast</td>
<td>62%</td>
<td>45%</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Prostate</td>
<td>78%</td>
<td>52%</td>
<td>34%</td>
<td>5%</td>
</tr>
<tr>
<td>Lung</td>
<td>62%</td>
<td>45%</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Colon</td>
<td>84%</td>
<td>52%</td>
<td>43%</td>
<td>7%</td>
</tr>
</tbody>
</table>

B. Limited Normal Tissue Expression

C. Normal/Tumor Tissue Differential

Results

Enabling Effector Cells to Kill Tumors

- Co-engagement of T cells (CD3) with tumor-associated antigens (e.g., B7-H3 x CD3)
- Monovalent binding to CD3 to avoid target independent T-cell activation
- Strict dependence on co-engagement of both targets for T-cell activation
- T-cell receptor & MHC-independent tumor-cell recognition: virtually any T cell can kill cancer cells

Ongoing clinical trials with DART proteins that redirect T cells to tumors:
- CD133 x CD3 (MGDO06)
- gpA33 x CD3 (MGDO07)
- CD19 x CD3 (MGDO01)

MGDO09: B7-H3 x CD3 DART Protein Incorporates an Fc Domain for Enhanced PK

MGDO09 Binds Human and Cynomolgus Monkey CD3 and B7-H3

Equilibrium Dissociation Constants

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Kd (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>320 (nM)</td>
</tr>
<tr>
<td>CD3 (nM)</td>
<td>320</td>
</tr>
</tbody>
</table>

Flow Cytometry Analysis

- Human T Cells
- Cynomolgus T Cells
- MGDO09 binds to human and cynomolgus monkey CD3 and B7-H3

MGDO09 Mediates Redirected Killing of Multiple B7-H3-expressing Tumor Lines

- MGDO09 mediates redirected killing using purified human T cells against DH1 cells expressing human or cynomolgus monkey B7-H3

MGDO09 Mediates Antitumor Activity in Multiple In Vivo Models

- MGDO09 displays favorable tumor/normal differential
- Treatment with MGDO09 is associated with T-cell recruitment to Tumor Xenografts

MGDO09 Displays Prolonged PK in Cynomolgus Monkeys

- MGDO09 Pk were linear over 0.1 to 1 mg/kg dose range with Cmax and AUC increasing in proportion to dose
- Mean clearance was 0.9 ml/h/kg
- Mean beta half-life (t1/2) ranged from 114-136 hours
- Mean residence time (MRT) ranged from 144-160 hours

Conclusions

- MGDO09 mediates in vitro redirected T-cell killing of B7-H3-expressing human cancer cell lines originated from a wide range of tumor types
- MGDO09 mediated T-cell activation and proliferation is strictly dependent on co-engagement of B7-H3-expressing target cells with T cells
- MGDO09 demonstrated inhibition of growth and tumor regression of B7-H3-expressing tumor xenografts in human T cell or PBMC-reconstituted mice
- MGDO09 demonstrated prolonged half-life (5-6 days) in cynomolgus monkeys, supporting dosing at biweekly intervals in humans

These data support evaluation of MGDO09 in patients with B7-H3-positive tumors.

A Phase 1 study of unreactive or metastatic B7-H3-expressing tumors, including non-small cell lung cancer, bladder cancer, squamous cell carcinoma, head and neck, mesothelioma, and melanoma, is currently recruiting patients. (ClinicalTrials.gov Identifier: NCT02628535)

References