Interim Results of an Ongoing Phase 1, Dose Escalation Study of MGA271 (Enoblituzumab), an Fc-optimized Humanized Anti-B7-H3 Monoclonal Antibody, in Patients with Advanced Solid Cancer

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  – BMS
  – Merck

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B7-H3 (CD276): Member of B7 Family of Immune Regulators

Immunosuppressive Role

- Expression on lung cancer cells and macrophages suppresses T-cell mediated anti-tumor immune response (*Chen 2013*)
- B7-H3-positive myeloid-derived suppressor cells found in tumor microenvironment (*Zhang 2015*)
- Crystal structure resolved: T-cell inhibitory domain mapped (*Vigdorovich 2013*)

Tumor Invasion and Metastatic Role

- Silencing reduces migration and invasion of melanoma and breast cancer cell lines (*Chen 2008*)
- Enhances metastatic potential of melanoma cells (*Tekle 2012*)
B7-H3: Tissue Expression and Prognosis

**B7-H3 Tissue Expression**
- High level expression in a broad range of tumors
- Minimal expression on normal tissue
- Expressed on tumor neo-vasculature
- Correlation of high expression with advanced disease, presence of metastases and poor outcome

<table>
<thead>
<tr>
<th>Fixed Tumor MicroArray</th>
<th>IHC Summary of Samples Screened</th>
<th>B7-H3 Positive</th>
<th>2+ or Above</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead Potential Indications:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and Neck</td>
<td>19/19</td>
<td>100%</td>
<td>19/19 100%</td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td>77/78</td>
<td>99%</td>
<td>75/78 96%</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>226/272</td>
<td>83%</td>
<td>211/272 78%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>119/164</td>
<td>73%</td>
<td>115/164 70%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>88/99</td>
<td>89%</td>
<td>51/99 52%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>66/70</td>
<td>94%</td>
<td>32/70 46%</td>
</tr>
<tr>
<td>Bladder</td>
<td>14/20</td>
<td>70%</td>
<td>9/20 45%</td>
</tr>
<tr>
<td><strong>Other Potential Indications:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>65/66</td>
<td>98%</td>
<td>63/66 95%</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>34/35</td>
<td>97%</td>
<td>33/35 94%</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>41/44</td>
<td>93%</td>
<td>39/44 89%</td>
</tr>
<tr>
<td>Pancreas Cancer</td>
<td>69/78</td>
<td>88%</td>
<td>45/78 58%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>59/79</td>
<td>75%</td>
<td>36/79 46%</td>
</tr>
</tbody>
</table>

**Timeline of selected B7-H3 articles in peer-reviewed publications**

- 2015: Esophageal NSCLC, Colorectal Bladder, Breast, Liver, Gastric, Leukemia, Pancreatic
- 2014: Ovarian Bladder
- 2013: Langerhans Cell Sarcoma, Colorectal, Squamous NSCLC, Hepatocellular Carcinoma, Melanoma, Glioblastoma, Endometrial
- 2012: Prostate, Breast
- 2011: Gastric, Mesothelioma, Head and Neck, Ovarian
- 2010: Pancreatic
- 2009: Prostate
Enoblituzumab (MGA271, Anti-B7-H3 Antibody)

• Humanized IgG1 monoclonal antibody recognizing human B7-H3 with high affinity (KD $\approx 7$ nM)
• Terminal Half Life $\approx 3$ weeks
• Fc-optimized via mutation to enhance effector function (e.g., ADCC)
  – Increased affinity for activating Fcγ receptor (FcγRII, CD16A)
  – Decreased affinity for the inhibitory Fcγ receptor (FcγRIIB, CD32B)
• Once-weekly intravenous dosing
• Currently in clinical trials as monotherapy (described today) and in combination with checkpoint inhibitors including pembrolizumab and ipilimumab (see SITC Trials-In-Progress Poster Session)
Enoblituzumab
Potential Mechanisms of Action

Direct Killing of Tumor Cells

Control of Neovascularure

Presentation of Tumor Antigens via Fc-mediated Interactions

Enhancement of Adaptive Responses

NK Cells
Tumor Cells

enoblituzumab
T-cells

Macrophage

Tumor vasculature
Study Design: Ongoing Phase 1 Dose Escalation and Cohort Expansion

**Original Expansion Cohorts**
- Enrollment complete
- *(n=15 per cohort)*
- Melanoma
- Prostate
- Other Tumors

**New Expansion Cohorts**
- Initiated 4Q14, Ongoing
- *(n=16 per cohort)*
- Head & Neck – HPV +/-
- Triple-negative Breast
- Renal Cell
- Melanoma (all post-Anti CTLA-4 and or PD-1/L1)
- NSCLC or Bladder

**Original Study Design**
- Cycle 1: dosing weekly x 4, then off x 4 weeks
- Cycle 2: dosing weekly x3, then off 1 week
- Standard RECIST for eval. & management
- Premed 10 mg dexamethasone, dose #1 & #2

**New Trial Design**
- Continuous weekly dosing for all cycles
- Management according to IR principles
- Evaluation by RECIST and irRECIST
- Premed 50-100mg hydrocortisone, dose #1 & #2
Study Objectives

• **Primary Objective**
  – Describe safety profile of enoblituzumab in patients with advanced cancer that expresses B7-H3 in tumor and/or tumor-associated vasculature

• **Secondary Objectives**
  – Determine Maximum Tolerated Dose or Maximum Administered Dose of enoblituzumab
  – Evaluate preliminary anti-tumor activity of enoblituzumab
  – Determine enoblituzumab pharmacokinetics/pharmacodynamics

• **Exploratory Objectives**
  – Evaluate and assess IHC diagnostic test for B7-H3 expression on tumor cells and tumor vasculature
Key Inclusion/Exclusion Criteria

**Inclusion**

- B7-H3 expression on tumor cells or tumor vasculature
  - \( \geq 10\% \) of tumor cells with 2 or 3+ IHC* staining or \( \geq 25\% \) of tumor vasculature having 2 or 3+ IHC staining
- Progressive disease during or following last treatment regimen
  - Up to 4 to 5 prior treatments allowed depending on tumor type
- Prior checkpoint inhibitor therapy allowed (mandated for melanoma)
- ECOG Performance Status \( \leq 1 \)
- Measurable disease by RECIST 1.1
  - Prostate cancer required measurable disease in new trial design
- Completed systemic anticancer therapy \( \geq 28 \) days prior to enrollment

**Exclusion**

- \( \geq \) Grade 3 autoimmune toxicity with prior immune checkpoint inhibitor
- Concurrent systemic steroids \( >10 \) mg/day of oral prednisone/equivalent
- Active brain metastases

*IHC: Immunohistochemistry with B7-H3 cell surface staining*
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Escalation n=26</th>
<th>Original Expansion n= 48</th>
<th>Additional Expansion n= 42</th>
<th>Total n= 116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, (range), years</td>
<td>62 (42-77)</td>
<td>64 (26-88)</td>
<td>67 (24-83)</td>
<td>63 (24-88)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>17 (65)</td>
<td>33 (69)</td>
<td>28 (67)</td>
<td>78 (67)</td>
</tr>
<tr>
<td><strong>Prior Cancer Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median no. (range): Chemo and Immunotherapy</td>
<td>2 (1-5)</td>
<td>3 (0-8)</td>
<td>3 (0-5)</td>
<td>3 (0-8)</td>
</tr>
<tr>
<td>Prior Chemotherapy, no. (%)</td>
<td>21 (81)</td>
<td>34 (71)</td>
<td>37 (88)</td>
<td>92 (79)</td>
</tr>
<tr>
<td>Prior Immunotherapy, no. (%)</td>
<td>6 (23)</td>
<td>18 (38)</td>
<td>7 (17)</td>
<td>31 (27)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (62)</td>
<td>20 (42)</td>
<td>10 (24)</td>
<td>46 (40)</td>
</tr>
<tr>
<td>1</td>
<td>10 (38)</td>
<td>28 (58)</td>
<td>32 (76)</td>
<td>70 (60)</td>
</tr>
</tbody>
</table>

*Data as of September 21, 2015*
Enoblituzumab-Related Adverse Events

- Acceptable safety profile
- No drug-related treatment discontinuation
- Mild-moderate infusion reactions readily managed with conventional supportive care including corticosteroids, decreased infusion rate

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event ≥10% of Patients</th>
<th>No. (%) of Patients</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>86 (74)</td>
<td>42 (76)</td>
</tr>
<tr>
<td>Infusion related reaction/ cytokine release syndrome</td>
<td>39 (34)</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (32)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (19)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (13)</td>
<td>10 (18)</td>
</tr>
</tbody>
</table>

*New study design is continuous, uninterrupted weekly infusion of enoblituzumab with reduced steroid pre-med

Data as of September 21, 2015
Best Change in Target Lesion Size

All Response Evaluable Patients: Escalation and Expansion

- Tumor regression at multiple dose levels (0.15mg/kg – 15mg/kg)
- Enrollment continues under new trial design: ≈ half of planned patients enrolled

Data as of September 21, 2015
Best Change in Target Lesion Size

Response Evaluable, Tumor-Specific Expansion Cohorts: 15 mg/kg Cohorts: Melanoma, Prostate, TNBC, SCCHN, NSCLC, Bladder, RCC

- Tumor regression observed in each disease cohort

Data as of September 21, 2015
Change in Target Lesion Size Over Time

Response-Evaluable Tumor-Specific Expansion Cohorts: 15 mg/kg
Cohorts: Melanoma, Prostate, TNBC, SCCHN, NSCLC, Bladder, RCC

Data as of September 21, 2015
Best Change in Target Lesion Size: Melanoma

All patients are post-checkpoint inhibitor

N=18 Patients with response evaluable disease
#Progressive disease as best response on previous check point
+Most recent previous therapy not a checkpoint inhibitor
*Ongoing

All but one patient treated 15mg/kg enoblituzumab

Data as of September 21, 2015
Metastatic Melanoma

73-year-old man previously progressed on Anti-PD-L1 And Trametinib

<table>
<thead>
<tr>
<th>Pre-Treatment Baseline</th>
<th>Day 22 (3 Doses enoblituzumab - 15mg/kg)</th>
<th>Day 98 (11 Doses enoblituzumab - 15mg/kg)</th>
</tr>
</thead>
</table>

- Near complete regression of ulcerated 4 cm tumor in groin
- Regression of small pulmonary nodules on CT

Courtesy of Dr. Chmielowski at UCLA Jonsson Comprehensive Cancer Center

Data as of September 21, 2015
Metastatic Prostate Cancer
87-year-old man

<table>
<thead>
<tr>
<th>Pre-Treatment Baseline</th>
<th>Right Paratracheal Lymph Node</th>
<th>Left Paratracheal Lymph Node</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21x29 mm</td>
<td>17x23 mm</td>
</tr>
<tr>
<td>Day 287</td>
<td>11x19 mm</td>
<td>9x14 mm</td>
</tr>
</tbody>
</table>

Day 287
34 Doses enoblituzumab (15mg/kg)

Patient remains on therapy after 11 months of treatment

Courtesy of Dr. Chmielowski at UCLA Jonsson Comprehensive Cancer Center

Data as of September 21, 2015
Vitiligo in Melanoma Patient with Progression on Prior Therapy with Checkpoint Inhibitors

52-year-old woman previously progressed on anti-CTLA-4 and anti PD-1

Pre-Treatment Baseline

Left Ext Iliac Lymph Node #1

Day 58
8 Doses enoblituzumab (15mg/kg)

Development of Vitiligo (Post-enoblituzumab)

Data as of September 21, 2015

Courtesy of Dr. Chmielowski’s patient at UCLA Jonsson Comprehensive Cancer Center
Increase in T-Cell Receptor Repertoire Clonality Following Enoblituzumab

Evaluation of T-Cell Clonality in the Peripheral Blood

Population Clonality

Clonality: 2 Patients with Tumor Shrinkage

Baseline (Day 1) v D50 Post-treatment (42 patients)

Analyses performed in collaboration with Adaptive Biotechnologies
Conclusions from Ongoing Enoblituzumab CP-MGA271-01 Study

• Manageable and tolerable safety profile
  – No treatment related discontinuation
  – No severe immune mediated toxicity

• Preliminary anti-tumor activity in broad range of tumors
  – Post check-point inhibitor failure melanoma
  – New study design: management principles used in immune oncology

• Initial demonstration of T-cell modulation with enoblituzumab

• Interim results:
  – Support continued evaluation of enoblituzumab monotherapy
  – Support evaluation of enoblituzumab in combination with check-point inhibitors: anti PD-1 and anti CTLA-4
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  – University of Pennsylvania/Abramson Cancer Center, Philadelphia, PA
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