A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics (PK) of MGA012 (anti-PD-1 antibody) in Patients with Advanced Solid Tumors

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Background

MGA012: Anti-PD-1 Monoclonal Antibody (mAb) with Favorable Design Features

- Humanized proprietary anti-PD-1 mAb
  - Hinge stabilized humanized IgG4
  - Benchmarks favorably against approved anti-PD-1 mAbs
- Anti-PD-1 becoming mainstream of cancer immunotherapy
- Basis for combination immunotherapy

MGA012: Favorable Preclinical Profile

<table>
<thead>
<tr>
<th>Metric</th>
<th>MGA012 Compared to:</th>
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<tbody>
<tr>
<td>Nivolumab*</td>
<td>6x greater</td>
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<tr>
<td>Pembrolizumab*</td>
<td>6x greater</td>
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<tr>
<td>Affinity for human PD-1</td>
<td>&gt;4x greater</td>
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<tr>
<td>Off-rate for human PD-1</td>
<td>&lt;2x lower</td>
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<tr>
<td>Cell binding (MRI)</td>
<td>&gt; Equivalent</td>
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<tr>
<td>PD-1/PD-L2 binding blockade</td>
<td>&gt; Equivalent</td>
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<tr>
<td>T-cell activation of NPsy</td>
<td>&gt; Equivalent</td>
</tr>
<tr>
<td>PK in cynomolgus monkeys</td>
<td>&gt; Equivalent</td>
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</tbody>
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MGA012 Results

- Tissue cross-reactivity: No unanticipated findings
- Toxicology in cynomolgus monkeys: IV at 10, 40 or 150 mg/kg, QW x 4
- No unanticipated findings
- NOAEL = 150 mg/kg
- Predicted half-life in humans: ~18 days

Rationale for Targeting PD-1

- Checkpoint receptors are subverted by tumors or APCs to evade immune system
- Tumors induce state of immune suppression (TGF-β)
- PD-1 receptors are expressed on “exhausted” T cells
- Interactions with corresponding ligands negate anti-tumor T cell activity

MGA012 Enhances Activation of SEB-stimulated Human T Cells

- Human PBMCs were pre-stimulated with 0.5 mg/mL SEB for 48h and re-stimulated for 48h in presence or absence of indicated mAbs
- IFNγ in supernatant was measured by ELISA

Key Study Objectives

Primary Objective

- Characterize safety, tolerability, DLT, maximum tolerated dose (MTD) or maximum administered dose (MAD) of MGA012 when administered IV every two or four weeks to patients with relapsed/refractory locally-advanced or metastatic solid tumors

Secondary Objectives

- Characterize PK and immunogenicity of MGA012
- Investigate preliminary anti-tumor activity of MGA012 using both conventional RECIST 1.1 and immune-related RECIST (iRECIST)

Exploratory Objectives

- Explore relationships between PK, pharmacodynamics, patient safety, and anti-tumor activity of MGA012
- Investigate immune-regulatory activity of MGA012 in vivo, including various measures of T cell activation in peripheral blood and/or tumor biopsy specimens
- Determine PK/L1 expression via IHC staining of formalin-fixed, paraffin-embedded tumor biopsy specimens
- Determine relationships between membraneous expression of PD-L1 on tumor cells, immune cell infiltration within biopsy specimens (e.g., CD4+ and CD8+ T cells), PD-L1 expression on immune cell infiltrate, and clinical response via IHC
- Characterization of T cell repertoire using T-cell receptor sequencing of peripheral blood mononuclear cells

Entry Criteria

- No history of malignancy (other than eligible in Cohort Expansion)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Acceptable laboratory parameters
- Tumor type / stage / grade
- Determined PD-L1 expression via IHC staining of formalin-fixed, paraffin-embedded tumor

Patient Demographics — Dose Escalation

- Broad array of tumor types evaluated
- 24 female, 13 male
- Median age 63 years
- 7 of 37 (19%) have prior checkpoint exposure

Preliminary Pharmacokinetic Analysis

- For 3 mg/kg and 10 mg/kg dose levels:
  - Cmax and AUCt are dose proportional
  - T1/2 (β) approximately 17 days
  - Achievement of steady-state in approximately 85 days
- For 1 mg/kg dose level:
  - MGA012 showed faster elimination; however, only 3 patients evaluated

Preliminary Safety Results

- Treatment-related AEs in ≥2 Patients
- Most common treatment-related AEs include fatigue (n=15, 42.5%), nausea (n=15, 42.5%), and diarrhea (n=11, 30.6%)
- One patient reported a grade 3 fatigue event
- No treatment-related serious AEs or DLTs reported
- No evidence of target lesion growth

Conclusions

- MGA012 demonstrated acceptable tolerability with no DLTs at completion of Dose Escalation
- MAD – 10 mg/kg Q2W; no MTD exceeded or defined
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- Thirty-one response-evaluable patients at data cutoff (10 Oct 2017)
- Two confirmed partial responses (uterine papillary serous carcinoma and MSI-H colorectal carcinoma)
- Nine patients with stable disease as best response
- Others had radiographic progressive disease or clinical progression

Patient Vignette

- 64-yr-old female with uterine papillary serous carcinoma (3 mg/kg Q2W)
- Prior treatments: TAH-BSO with 6 cycles of adjuvant carboplatin + taxol
- Target lesions: 19 mm L axillary lymph node; 21 mm R Ext Iliac lymph node
- Scans demonstrated 40% and 40% decreases in tumor burden at end of Cycles 2 and 4, respectively
- Patient remains on study, currently on Cycle 6