A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of MGD013, a Bispecific DART® Molecule Binding PD-1 and LAG-3 in Patients with Unresectable or Metastatic Neoplasms


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Presenter Disclosure Information

Jason J. Luke, MD, FACP

- **Data and Safety Monitoring Board**: TTC Oncology
- **Scientific Advisory Board**: 7 Hills, Actym, Alphamab Oncology, Kanaph, Mavu (now part of AbbVie), Onc.AI, Pyxis, Springbank, Tempest
- **Consultancy**: Abbvie, Akrevia, Algios, Array, Astellas, Bayer, Bristol-Myers Squibb, Eisai, EMD Serono, Ideaya, Incyte, Janssen, Merck, Mersana, Novartis, PTx, RefleXion, Regeneron, Silicon, Tesaro, Vividion
- **Research Support**: (all to institution for clinical trials unless noted) AbbVie, Agios (IIT), Array (IIT), Astellas, Bristol-Myers Squibb, CheckMate (SRA), Compugen, Corvus, EMD Serono, Evelo (SRA), Five Prime, FLX Bio, Genentech, Immunocore, Incyte, Leap, MedImmune, MacroGenics, Necktar, Novartis, Palleon (SRA), Merck, Springbank, Tesaro, Tizona, Xencor
- **Travel**: Akrevia, Bayer, Bristol-Myers Squibb, EMD Serono, Incyte, Janssen, Merck, Mersana, Novartis, Pyxis, RefleXion
- **Patents** (both provisional): Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)
Rationale for Dual Targeting of PD-1 and LAG-3

- Checkpoint molecules are leveraged by tumors or APCs to evade the immune system
- PD-1 and LAG-3 receptors are expressed on “exhausted” T-cells
  - Interactions with corresponding ligands negates anti-tumor T cell activity
- Synergy of anti-PD-1 + anti-LAG-3 mAbs in animal tumor models
  - Combination trials of anti-PD-1 plus anti-LAG-3 are ongoing
- MGD013, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  - Greater synergistic T-cell activation (IFN-γ) with MGD013 compared with combination of individual constituents
- DART bispecific platform:
  - Stable diabody format
  - Multiple configurations & applications

MGD013

PD-1 × LAG-3

Tetravalent Bispecific DART Molecule
MGD013 Phase 1 Trial Design

**Primary objectives:**
- Safety, tolerability
- DLTs, MTD, MAD
- Alternate dose

**Secondary objectives:**
- Pharmacokinetics
- Immunogenicity
- Preliminary activity

**Exploratory PD objectives:**
- Receptor/ligand expression
- Serum biomarkers
- Gene expression profiling

**Dose Escalation in Previously Treated Advanced Solid Tumors**

DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose; IHC = immunohistochemistry; Q2W = every 2 weeks. ClinicalTrials.gov identifier: NCT03219268. ‡ Margetuximab is an investigational Fc-optimized mAb targeting HER2. a Monotherapy and combination expansion cohorts are ongoing. b Combination cohort involved a one-step dose escalation followed by expansion. c Separate hepatocellular carcinoma (HCC) 3+3 dose escalation initiated after corresponding dose levels cleared in primary Dose Escalation. d Other expansion cohorts enrolling patients with SCCHN, SCLC, HCC, cholangiocarcinoma, cervical cancer, gastric/gastroesophageal junction carcinoma, and DLBCL. Data cutoff: April 25, 2020.
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Dose Escalation 1 -1200 mg Q2W (n=53)</th>
<th>Monotherapy Cohort Expansion 600 mg Q2W (n=205)</th>
<th>Combination Cohort Expansion MGD013 + Margetuximab (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>64 (24, 84)</td>
<td>60 (27, 84)</td>
<td>62 (29, 83)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (60.4)</td>
<td>74 (36.1)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (39.6)</td>
<td>131 (63.9)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (41.5)</td>
<td>60 (29.3)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>1</td>
<td>31 (58.5)</td>
<td>145 (70.7)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td><strong>Median prior lines of therapy (range)</strong></td>
<td>2 (1, 9)</td>
<td>2 (1, 9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (1, 7)</td>
</tr>
<tr>
<td><strong>Prior Checkpoint Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (43.4)</td>
<td>55 (26.8)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>No</td>
<td>30 (56.6)</td>
<td>139 (67.8)</td>
<td>20 (95.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Monotherapy Cohort Expansion median prior lines of therapy derived from n=200 patients (5 patients without this information available). Data cutoff: April, 25, 2020.
Pharmacokinetics and Receptor Occupancy

Linear PK (400-1200 mg dose range) and sustained receptor occupancy (≥120 mg)

Estimates $t_{1/2} = 274$ hours (~11 days)

$pembro C_{trough} = $ published serum trough concentration of pembrolizumab at 2 mg/kg Q3W (23.6 μg/mL)

[CDER, KEYTRUDA (pembrolizumab) Clinical Pharmacology and Biopharmaceutics Review(s). 2014]
Confirmed Partial Responses (n=1, each):

- TNBC (10 mg)
- Mesothelioma (800 mg)
- Gastric Cancer (1200 mg) Refractory to anti-PD-1 treatment
- 18 patients with SD as best overall response (DCR = 48.8%)

- Well-tolerated with manageable irAEs
- Safety consistent with anti-PD-(L)1 toxicity profile
- MTD not exceeded or defined at up to 1200 mg Q2W
- Dose limiting toxicities:
  - Immune-mediated hepatitis (1200 mg – primary dose escalation); resolved without sequelae
  - Lipase increase with radiographic evidence of pancreatitis (600 mg – HCC escalation); dose level subsequently cleared

### Immune-Related Adverse Events of Special Interest (AESIs)

<table>
<thead>
<tr>
<th>All Grades (N=53)</th>
<th>&gt; Grade 3 (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Immune-mediated hepatitis</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

* Based on patients with baseline and post-treatment tumor measurements. Data cutoff: April, 25, 2020
### MGD013 Monotherapy Cohort Expansion: Safety

#### Overall AE Totals

<table>
<thead>
<tr>
<th>Category</th>
<th>All Grades (N=205)</th>
<th>≥ Grade 3 (N=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE (irrespective of causality)</td>
<td>178 (86.8)</td>
<td>86 (42.0)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>118 (57.6)</td>
<td>37 (18.0)</td>
</tr>
<tr>
<td>SAE (irrespective of causality)</td>
<td>63 (30.7)</td>
<td>47 (22.9)</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>18 (8.8)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>18 (8.8)</td>
<td>16 (7.8)</td>
</tr>
</tbody>
</table>

#### AESIs in ≥ 2 Patients

<table>
<thead>
<tr>
<th>AESI</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>IRR or CRS</td>
<td>13 (6.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (4.4)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>

* Includes MedDRA Preferred Terms of Rash and Maculopapular Rash.
** Includes MedDRA Preferred Terms of Pruritus and Generalized Pruritus.

* Grade 4 drug-related AEs include: lipase increased (n=3), neutrophil count decreased, and IRR (n=1, each). No Grade 5 TRAEs have been reported.

MGD013 Monotherapy Cohort Expansion: Activity

Anti-tumor activity observed in multiple tumor types

<table>
<thead>
<tr>
<th></th>
<th>TNBC</th>
<th>EOC</th>
<th>NSCLC, CPI-Naïve</th>
<th>NSCLC, post-PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable Patients</td>
<td>23</td>
<td>23</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>ORR (Confirmed)</td>
<td>4.3% (1/23)</td>
<td>8.7% (2/23)</td>
<td>14.3% (2/14)</td>
<td>0% (0/15)</td>
</tr>
<tr>
<td>ORR (Confirmed + Unconfirmed)</td>
<td>17.4% (4/23)</td>
<td>8.7% (2/23)</td>
<td>21.4% (3/14)</td>
<td>13.3% (2/15)</td>
</tr>
<tr>
<td>SD</td>
<td>34.8% (8/23)</td>
<td>43.5% (10/23)</td>
<td>50.0% (7/14)</td>
<td>53.3% (8/15)</td>
</tr>
<tr>
<td>DCR</td>
<td>39.1% (9/23)</td>
<td>52.2% (12/23)</td>
<td>64.3% (9/14)</td>
<td>53.3% (8/15)</td>
</tr>
</tbody>
</table>

Data cutoff: April, 25, 2020
Complete Response after Single MGD013 Administration

27-year-old male with DLBCL progressive disease after CAR-T cell therapy

- Relapsed subsequent to DA-R-EPOCH and JCAR017
- Pre-treatment biopsy: High levels of LAG-3 & PD-L1
- Received MGD013, 600 mg x 1
- Admitted on Day 11 for management of Grade 2 CRS
- CR on Day 24 (per Lugano classification)
- No evidence of CAR-T in circulation
- Allogeneic SCT performed
- Currently in remission:
  - 11 months post-MGD013
  - 9 months post-transplant

PD-1/LAG-3 Co-expression

PD-1 (magenta) and LAG-3 (green) co-localized staining
Objective Responses Associated with LAG-3 Expression

Inflammatory interferon-γ signature elevated in patients with clinical response

Archival biopsies from TNBC, EOC, and NSCLC expansion cohorts analyzed for LAG-3 (N=46) or PD-L1 (N = 45) by IHC. LAG-3 score was determined by calculating mean value of LAG-3+ cells per 40x field across 5 LAG-3+ hot spots (Chen et al., e15086 ASCO 2020). PD-L1 expression was determined per Agilent PD-L1 (22C3) pharmDx kit; TPS (NSCLC) was calculated as per interpretation manual and CPS (EOC, TNBC) calculated as follows: number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100. CPS <1 or TPS <1% was considered negative.

The NanoString PanCancer IO 360™ assay was used to interrogate gene expression, including the abundance of 14 immune cell types and 32 immuno-oncology signatures from archival biopsies from EOC (N= 14) NSCLC (N= 25) and TNBC (N=13 ) expansion cohorts.
Can Tumors Be Made More Responsive to PD-1 × LAG-3 Intervention?

Enhancing effector-cell activation via Fc-engineered mAb

**Margetuximab**
Investigational Fc-engineered anti-HER2 mAb

- Same anti-HER2 properties as trastuzumab
- Enhanced Fc-mediated effector function\(^a\)
- Superior PFS to trastuzumab in clinical study
  - SOPHIA: Head-to-head Phase 3 study in mBC\(^b\)
- Anti-tumor activity in advanced gastric cancer
  - In combination with anti-PD-1\(^c\)

\(^a\) Nordstrom, et al., 2011 Breast Cancer Research, 13: R123
\(^b\) Rugo, et al., ASCO 2019, Chicago, IL
\(^c\) Catenacci, et al., ASCO GI 2019, San Francisco, CA | Catenacci et al. 2020 Lancet Oncology, in press
**Fc-engineered mAb plus PD-1 x LAG-3 DART: Combinatorial Biology**

**Fc-engineered Margetuximab**
Up-regulates LAG-3/PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>NK</th>
<th>Monocyte</th>
<th>CD4 T</th>
<th>CD8 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAG-3</td>
<td>0.39</td>
<td>0.33</td>
<td>0.59</td>
<td>1.62</td>
</tr>
<tr>
<td>PD-1</td>
<td>0.099</td>
<td>0.14</td>
<td>3.92</td>
<td>6.93</td>
</tr>
<tr>
<td>PD-L1</td>
<td>0.49</td>
<td>0.038</td>
<td>0.69</td>
<td>9.41</td>
</tr>
</tbody>
</table>

**Upregulation of LAG-3 and PD-L1 on NK, monocytes and T cells**

Human PBMC (Donor # 731) + N87 (HER2+) gastric cancer cells; E:T = 15:1 +/- margetuximab (no supplementary IL-2)

**PD-1 x LAG-3 (MGD013) Enhances Lytic Activity of Immune Cells Primed by Fc-engineered mAb (Margetuximab)**

ADCC (target: margetuximab opsonized N87, E:T=10) and NK-cell killing (target: K562, E:T=10) mediated by immune cells activated for 6 days by margetuximab +/- MGD013 in the presence of N87 tumor cells.
Fc-engineered αHER2 plus PD-1 × LAG-3 DART (Margetuximab plus MGD013)

**Preliminary results in patients with relapsed/refractory HER2+ solid tumors**

- ORR = 42.9% (6/14 evaluable pts)
- Includes unconfirmed objective responses
- Well-tolerated
- Responding patients remain on therapy

**Baseline PD-L1 & LAG-3 in # of Responding Patients (N = 6)**

<table>
<thead>
<tr>
<th>PD-L1 CPS:</th>
<th>&lt; 1</th>
<th>1</th>
<th>TBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LAG-3 Score:</th>
<th>&lt; 5</th>
<th>5-15</th>
<th>TBD/NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

# GEJ pt with apparent pseudo-progression (PD per RECIST), now with 37.5% reduction in target lesions (iPR per iRECIST).
Durable Response in Patient Receiving MGD013 plus Margetuximab

Resolution of chest wall disease with confirmed PR of overall tumor burden

Metastatic HER2+ breast cancer in 67-year-old female

- Previously progressed on:
  - 1L pertuzumab/trastuzumab/anastrozole
  - 2L TDM1/anastrozole
  - 3L TDM1

Baseline tumor burden:

- Right breast, liver and lymph nodes
- PD-L1 CPS: <1; LAG-3 score: 0.8
- Patient remains on treatment in Cycle 15 with improved clinical status and ongoing partial response
  - 1st tumor assessment: -46%
  - 2nd tumor assessment: -61%
  - 3rd tumor assessment: -65%
  - 4th tumor assessment: -66%

Baseline

Baseline Day 15†

Baseline Day 28†

Baseline Day 70

Baseline Day 295

Note: Images correspond to the patient’s right chest wall
† Day 15 and Day 28 images obtained after one dose of the combination

Jason J. Luke, MD, FACP @jasonlukemd
MGD013 (PD-1 × LAG-3 DART Molecule): Conclusions

First-in-class bispecific checkpoint inhibitor
• Designed to independently or coordinately block PD-1 and LAG-3
• Well tolerated at doses up to 1200 mg Q2W
• RP2D: 600 mg Q2W or Q3W
• Safety profile consistent with anti-PD-1 monotherapy

Encouraging monotherapy activity in multiple tumor types
• Baseline LAG-3 expression & IFN-γ signature associated with objective response

Compelling preliminary combinatorial activity with margetuximab (Fc-engineered mAb)
• >40% ORR observed in low PD-L1-expressing, relapsed/refractory HER2+ tumors
  • Compares favorably to low historical response rates to anti-HER2 ± CPI

Evaluation of MGD013 as monotherapy and in combination with Fc-engineered mAbs (incl. margetuximab) is ongoing
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Girish Mallesara
Andrew Weickhardt

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Nadezhda Miteva
Krasimir Nikolov
Krasimir Oreshkov

Spain
Analia Azaro Pedrazzoli
Javier Cortes Castan
Maria Jose De Miguel Luken

Thailand
Chaiyut Charoentum
Arunee Dechapunkul
Virote Sriuranpong

Poland
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Lucjan Wyrwicz

Ukraine
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Yevhen Hotko
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Bartosz Chmielowski
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Lipika Goyal
Erika Hamilton
Hedy Kindler
Jason Luke
Robin Norris
Manish Patel
Cesar Santa-Maria
Susanna Ulahannan
Jie Wang

Investigators
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