A Phase 1, Open-Label Study of MGD013 (Tebotelimab), a Bispecific DART® Molecule Binding PD-1 and LAG-3, in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Wang J¹, Asch AS², Hamad N³, Weickhardt⁴, Tomaszewska-Kienca M⁵, Dlugosz-Danecka M⁶, Pylypenko H⁷, Bahadur S⁸, Ulahannan S², Koucheki J⁹, Sun J⁹, Li H⁹, Chen F⁹, Zhang X⁹, Muth J⁹, Kaminker P⁹, Moore PA⁹, Sumrow BJ⁹

¹Duke University Medical Center; Durham, NC. ²OUHSC Oklahoma City, OK/SCRI, Nashville, TN. ³St Vincent’s Health Network; Kinghorn Cancer Centre; Sydney, Australia. ⁴Austin Health, Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia. ⁵BioVirtus Research Site Sp. Z o.o.; Jozefow, Poland. ⁶Pratia MCM Krakow; Krakow, Poland. ⁷Cherkasy Regional Oncology; Cherkasy, Ukraine. ⁸Banner MD Anderson Cancer Center, Gilbert, AZ. ⁹MacroGenics, Inc., Rockville, MD
Disclosure Information

Speaker:
Jie Wang, MD
Duke Cancer Institute
Durham, NC

Industry Relationships:
Advisory Boards: Verastem, Kyowa Kirin
Background

• PD-1 and LAG-3 receptors are expressed on “exhausted” T cells
  – Interactions with corresponding ligands negate anti-tumor T-cell activity

• Unmet need remains for relapsed/refractory DLBCL patients
  – LAG-3 highly expressed in DLBCL¹, and has emerged as therapeutic target of interest in this population
  – PD-1-targeted therapy (e.g., nivolumab) has yielded modest efficacy ²

• Tebotelimab, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  – Tetravalent (bivalent for each target) structure with IgG4 Fc
  – Greater synergistic T-cell activation (IFN-γ) in vitro with tebotelimab compared with combination of individual constituents

• Ongoing phase 1 study demonstrated safety up to 1200 mg Q2W, with evidence of antitumor activity as monotherapy and in combination with margetuximab in various advanced solid tumor populations
  – Monotherapy objective responses associated with increased baseline LAG-3 expression (IHC) and IFN-γ gene signature³
  – Combination (margetuximab) antitumor activity associated with baseline mRNA expression of LAG-3 and PD-1⁴
  – RP2D defined as 600 mg

---

Tebotelimab 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**

- Flat Dosing Q2W: Single Patient Cohorts’ followed by 3+3 design
- 1 mg^†
- 3 mg^†
- 10 mg†
- 30 mg
- 120 mg
- 400 mg
- 800 mg
- 1200 mg

**Monotherapy Cohort Expansion (600 mg Q2W/Q3W)**
- Ovarian (EOC)
- TNBC
- NSCLC ‡
- SCCHN ‡
- Cervical
- SCLC
- Cholangio
- HCC
- GC/GEJ
- DLBCL

**Combination Cohort Expansion**
- HER2+ Solid Tumors
- Tebotelimab (300 or 600 mg) + Margetuximab^§ 15 mg/kg (both Q3W)

‡ separate CPI-naïve and post-PD-1 cohorts

**Trial Registration:** NCT03219268
Key Entry Criteria

- Relapsed or refractory (R/R) DLBCL treated with at least one chemo combination, including therapeutic anti-CD20 Ab and autologous SCT, if indicated
  - Patients ineligible for, or who decline SCT, are eligible
  - Patients with primary CNS lymphoma or uncontrolled brain metastasis are not eligible
  - Minimum of 10 patients must have previously received prior CD19-directed CAR T cell therapy
- Age ≥18 years
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks
- ≥1 Measurable lesion >1.5 cm as defined by Lugano classification
- Acceptable laboratory parameters

Baseline Demographics

<table>
<thead>
<tr>
<th>DLBCL Expansion (n=20)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>63 (27, 75)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (25)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (30)</td>
</tr>
<tr>
<td>1</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Median prior lines of therapy (range)</td>
<td>3 (1, 6)</td>
</tr>
<tr>
<td>Disease Subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>GCB</td>
<td>5 (25)</td>
</tr>
<tr>
<td>non-GCB (i.e. ABC)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Double-hit (MYC/BCL2)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Prior CAR T, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (50)</td>
</tr>
<tr>
<td>No</td>
<td>10 (50)</td>
</tr>
</tbody>
</table>
Preliminary Results*

### Safety Overview

<table>
<thead>
<tr>
<th>Overall AE Totals</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (N=20)</td>
</tr>
<tr>
<td>AE (irrespective of causality)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>13 (65)</td>
</tr>
<tr>
<td>SAE (irrespective of causality)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>3 (15)</td>
</tr>
<tr>
<td>AE leading to tx discontinuation</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

#### Treatment-Related Adverse Events in > 1 Patient

- Pyrexia: 3 (15) | 0 (0)
- IRR/CRS: 2 (10) | 0 (0)
- Fatigue: 2 (10) | 0 (0)
- Anemia: 2 (10) | 1 (5)
- Hyperthyroidism/thyroiditis: 2 (10) | 0 (0)

- Generally well-tolerated with safety profile consistent with anti-PD-(L)1 therapy
- Infusion-related reactions (n=2) have been Grade 2 and reversible with supportive treatment
- No evidence of tumor lysis syndrome observed

### End of Treatment Disposition

<table>
<thead>
<tr>
<th>DLBCL Expansion: Tebotelimab 600 mg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Treated</td>
</tr>
<tr>
<td>Response-Evaluable Patients, n (%)</td>
</tr>
<tr>
<td>Median duration of therapy, weeks (min, max)</td>
</tr>
<tr>
<td>Continuing treatment, n (%)</td>
</tr>
<tr>
<td>Treatment discontinuation, n (%)</td>
</tr>
</tbody>
</table>

#### Reasons for discontinuation, n (%)

- Disease Progression (Radiographic): 5 (25)
- Disease Progression (Clinical): 3 (15)
- Death: 2 (10)
- Complete Response (➔ allo-SCT): 1 (5)
- Adverse Event†: 1 (5)

†Grade 5 event of gastrointestinal hemorrhage related to underlying disease (not related to tebotelimab)

*Data cut: 23-October-2020
ENCOURAGING EVIDENCE OF ANTITUMOR ACTIVITY*

- Preliminary ORR of 53.8%
  - 71.4% (5/7) for CAR T naive patients
  - 33.3% (2/6) for CAR T experienced patients
- Responding patients (n=7) encompass activated B-cell (ABC), germinal center B-cell (GCB), and double-hit (MYC/BCL2) molecular subtypes
- Duration of Response ranges from 1 (2nd scan data pending) to 168 days, with 6 of 7 responders remaining in response

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Response-Evaluable Patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post CAR T (N=6)</td>
</tr>
<tr>
<td><strong>Best Overall Response‡</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>2 (33.3)</td>
</tr>
<tr>
<td><strong>DCR, n (%)</strong></td>
<td>2 (33.3)</td>
</tr>
</tbody>
</table>

† patients treated with at least one post-baseline tumor assessment, and excludes 3 patients who discontinued treatment prior to first scan due to death (n=2) and adverse event (n=1)
‡ tumor assessments per the Lugano classification

*Allogeneic stem cell transplant (allo-SCT) performed after CR and end of treatment. Patient remains in remission approx. 16 months post-allo-SCT.

*Data cut: 23-October-2020
Association of Objective Responses with Baseline LAG-3 Expression

Retrospective IHC Analyses Performed on Preliminary Set of Patients Treated with Tebotelimab

Pre-treatment biopsies available from the DLBCL expansion cohort for IHC analyses (N = 11) were analyzed for LAG-3 and PD-L1 expression, including patients with (▲ N= 6) or without (● N = 5) prior CAR T therapy. LAG-3 expression 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; CPS was calculated as follows: number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100.
Complete Response after Single Tebotelimab Administration

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

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Screening**

**Tebotelimab 600 mg x1**

**Study Day 24**

**Complete Response**

**Grade 2 CRS**

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- After Grade 2 CRS, early scan demonstrated Complete Response at Day 24
- JCAR017’s EGFR epitope not detected pre- or post-tebotelimab
- The patient remains in remission approximately 18 months post-tebotelimab and 16 months post-allo-SCT

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**CD3 (2GV6)**

**CD79a (SP18)**

**PD-1 (NAT105)**

**LAG-3 (EPR4392(2))**

**DAPI**

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)

**DA-R-EPOCH** → Relapse

**JCAR017** → Relapse

- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

**Serum Cytokine Kinetics**

- **Hrs Post Treatment**
- **pg/mL**
- **IFN-g**
- **IL-6**

**Pre-CAR T**

**Post-CAR T**

(Pre-tebotelimab)
Conclusions

• Tebotelimab monotherapy generally well-tolerated among heavily pre-treated R/R DLBCL patients
  – Infusion related reactions manageable and no evidence of tumor lysis syndrome

• Encouraging preliminary evidence of antitumor activity observed among CAR T-experienced and -naive R/R DLBCL patients, representing various molecular subtypes
  – Preliminary ORR: 53.8%
  – Baseline LAG-3 expression appears to associate with clinical response

• A complete response observed in a post-CAR T patient after single tebotelimab administration
  – Pre-tebotelimab tumor tissue demonstrated increased expression of LAG-3, PD-1, and respective ligands
  – Marked enhancement of circulating IFN-γ, with only modest IL-6
  – No evidence of CAR T or CAR T expansion by flow cytometry for EGFR marker
  – Remission ongoing 15 months after allo-SCT

• Further DLBCL enrollment and additional correlative translational analyses ongoing