A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of MGD019, an Investigational Bispecific PD-1 × CTLA-4 DART® Molecule in Patients with Advanced Solid Tumors

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- Syros
- TaiRx
- Tempest Therapeutics
- Tesaro
- Treadwell Therapeutics
• PD-1 and CTLA-4 are checkpoint molecules with complementary mechanisms of action
• Dual blockade has yielded enhanced efficacy with approved agents, albeit with increased toxicity
• MGD019, an investigational DART molecule:
  – Maintains uncompromised PD-1 blockade versus benchmark mAbs
  – Blocks both PD-1 and CTLA-4 pathways with potentially enhanced CTLA-4 blockade on dual-expressing cells prevalent in TME

MGD019: Bispecific Molecule Engineered for Co-Blockade of PD-1 & CTLA-4

10-100 fold enhanced activity by MGD019 relative to PD-1/CTLA-4 mAb combination
**MGD019 is Well Tolerated in Non-human Primates**

GLP Toxicology Results Compare Favorably to Ipilimumab + Nivolumab Preclinical Profile

<table>
<thead>
<tr>
<th>Finding</th>
<th>PD-1 × CTLA-4 bispecific (MGD019)</th>
<th>PD-1 mAb (Retifanlimab)</th>
<th>PD-1 + CTLA-4 two mAb combo&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse clinical signs</td>
<td>–</td>
<td>–</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Body weight loss</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Increased spleen weight</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Lymphoid hyperplasia/hypertrophy in spleen</td>
<td>–</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Gastrointestinal tract inflammation</td>
<td>–</td>
<td>–</td>
<td>+&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Cytokine induction</td>
<td>–</td>
<td>–</td>
<td>not reported</td>
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<tr>
<td>T cell expansion</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Ki67&lt;sup&gt;+&lt;/sup&gt; CD8&lt;sup&gt;+&lt;/sup&gt; T cell increase</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>ICOS&lt;sup&gt;+&lt;/sup&gt; CD4&lt;sup&gt;+&lt;/sup&gt; T cell increase</td>
<td>+</td>
<td>++</td>
<td>+++</td>
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</tbody>
</table>


<sup>b</sup> Dose-related diarrhea; decreased food consumption at high dose [50 mg/kg anti-PD-1 + 10 mg/kg anti-CTLA-4]

<sup>c</sup> Large intestine: diffuse lymphoplasmacytic inflammation in the lamina propria with concurrent enlargement of the colonic or pelvic lymph nodes.

“+” = observed, with quantification (e.g., +, ++, +++); “–” = not observed
**MGD019 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

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

- Weight-based dosing
- 3+3 Design

- **MTD/MAD/alternate dose**

**MGD019 Monotherapy Cohort Expansion**

- **NSCLC**
- **Cervical**
- **MSS CRC**
- **STS**
- **SCCHN**
- **RCC**
- **Other TBD**

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**Clinical Trial Design**

- DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose; STS = soft tissue sarcoma; MSS CRC = microsatellite stable colorectal cancer; Q3W/Q6W = every 3 or 6 weeks. ClinicalTrials.gov identifier: NCT03761017. 
  - Additional patients backfilled at dose levels of interest (3, 6, and 10 mg/kg) after completion of Dose Escalation.
  - Enrollment of select monotherapy expansion cohorts at recommended Phase 2 dose [RP2D] of 6.0 mg/kg are forthcoming.
  - Separate NSCLC cohorts for checkpoint-inhibitor (CPI) naïve and experienced patients.
  - SCCHN cohort of CPI-experienced patients.
  - RCC cohort of CPI-naïve patients.
  - Induction Period (Q3W) for 24 weeks followed by Maintenance Period (Q6W) until study completion. Data cutoff: July 21, 2020.
## Baseline Demographics

### Dose Escalation

<table>
<thead>
<tr>
<th>Dose Escalation 0.03 – 10 mg/kg (n=43)</th>
</tr>
</thead>
</table>

### Median age (range), years

- Median age: 62 (30, 85)

### Gender, n (%)

- Male: 21 (48.8)
- Female: 22 (51.2)

### ECOG PS, n (%)

- ECOG PS 0: 14 (32.6)
- ECOG PS 1: 29 (67.4)

### Median prior lines of therapy (range)

- Median prior lines of therapy: 3 (1, 10)

### Prior Checkpoint Inhibitor

- Yes: 17 (39.5)
- No: 26 (60.5)

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### Tumor Types Treated

- pancreatic, 7
- CRC, 6
- ovarian, 4
- SCLC, 2
- adrenal, 2
- NSCLC, 2
- thymic, 2
- penile, 2
- appendiceal, 2
- eccrine, 1
- leiomyosarcoma, 1
- prostate, 1
- endometrial, 1
- breast, 1
- vaginal, 1
- gastric, 1
- carcinoid, 1
- RCC, 1
- urethral, 1
- melanoma, 1
- fallopian, 1

Data cutoff: July 21, 2020
### End of Treatment Disposition

<table>
<thead>
<tr>
<th>Escalation Dose Levels</th>
<th>0.03 – 1.0 mg/kg</th>
<th>3.0 mg/kg</th>
<th>6.0 mg/kg</th>
<th>10.0 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Treated, n</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>Response-Evaluable Patients, n (%)</td>
<td>12 (80)</td>
<td>7 (100)</td>
<td>3 (37.5)</td>
<td>8 (61.5)</td>
<td>30 (69.8)</td>
</tr>
<tr>
<td>Median duration of therapy, weeks (min, max)</td>
<td>11.6 (1.3, 60.4)</td>
<td>14.1 (6.0, 34.9)</td>
<td>6.6 (4.3, 24.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.1 (3.1, 36.1)</td>
<td>12.0 (1.3, 60.4)</td>
</tr>
<tr>
<td>Active Patients, n (%)</td>
<td>0 (0)</td>
<td>2 (28.6)</td>
<td>5 (62.5)</td>
<td>1 (7.7)</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>Reasons for discontinuation, n (%)</td>
<td>14 (93.3)</td>
<td>3 (42.9)</td>
<td>3 (37.5)</td>
<td>5 (38.5)</td>
<td>25 (58.1)</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (38.5)</td>
<td></td>
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<tr>
<td>Adverse Event</td>
<td>-</td>
<td>1 (14.3)</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Patient/Physician decision/withdrawal</td>
<td>1 (6.7)</td>
<td>1 (14.3)</td>
<td>-</td>
<td>1 (7.7)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (7.7)</td>
<td>1 (2.3)</td>
</tr>
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</table>

<sup>a</sup> Ongoing patients in 6.0 mg/kg cohort (n=5) remain active early in their 1st cycle of treatment. Data cutoff: July 21, 2020.
Pharmacokinetics and Receptor Occupancy

Linear PK (1.0 – 10.0 mg/kg dose range) and Sustained Receptor Occupancy (≥ 1.0 mg/kg Q3W)

First Dose PK

Estimated $t_{1/2}$ = 298 hours (~12 days)

First-dose PK profiles of 0.03 to 10 mg/kg. Symbols and solid lines represent observed data and model fitted median curves, respectively. “Target” refers to 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]

Receptor (PD-1) Occupancy

MGD019 peripheral PD-1 receptor occupancy for CD4+ T cells collected 21 days after second infusion (green) compared to measured immediately after third infusion (blue).

PD-1 Blockade

MGD019 blocks binding of competing anti-PD-1 mAb (J105) to peripheral CD4+ T cells of patients. Connected symbols represent individual patients before and after (day 8) MGD019 administration.
• Generally well-tolerated at dose levels < 10 mg/kg
• Despite no DLTs, intolerance at 10 mg/kg evident with increased incidence of Grade 3 irAEs, including:
  – Myocarditis (1)
  – Enterocolitis (1)
  – Hepatitis (1)
  – Bullous dermatitis (1)
  – Maculopapular rash (3)
• irAEs recovered with immunosuppression and/or treatment interruption/discontinuation

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<th>Overall AE Totals</th>
<th>No. (%) of Patients</th>
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<tr>
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<td>All Grades (N=43)</td>
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<tr>
<td>AE (irrespective of causality)</td>
<td>42 (97.7)</td>
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<tr>
<td>Treatment-related AE (TRAE)</td>
<td>34 (79.1)</td>
</tr>
<tr>
<td>SAE (irrespective of causality)</td>
<td>18 (41.9)</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>8 (18.6)</td>
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</table>

a Includes one Grade 4 TRAE (IRR), occurring in setting of baseline pleural effusion. No Grade 5 TRAEs have been reported. Seven of 14 patients experiencing Grade ≥ 3 TRAEs (50%) occurred at 10 mg/kg dose level. b Treatment-related SAEs (n=6) include Gr3 myocarditis, Gr3 enteritis, Gr3 enterocolitis, Gr2 arthralgia, Gr2 pneumonitis, and Gr3 bullous dermatitis (n=1, each), four of which occurred at 10 mg/kg. Data cutoff: July 21, 2020.
MGD019 Dose Escalation: Preliminary Activity

Best % Reduction of Target Lesions
RECIST Evaluable Population (n=30)*

Objective Responses (n=4):
- Microsatellite stable CRC – cPR
- Metastatic type AB thymoma – cPR
- Serous fallopian tube carcinoma\(^b\) – uPR
- mCRPC – cCR
- 10 patients with SD as best response

Preliminary Results\(^d\):
- All Dose Levels: ORR 13.3%; DCR 43.3%
- Doses ≥ 3 mg/kg: ORR 22.2%; DCR 50.0%

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* Based on patients with baseline and post-treatment tumor measurements. \(^b\) Previously refractory to anti-PD-L1 therapy in combination with anti-CD47 mAb. \(^c\) PD-L1 expression determined per Agilent PD-L1 (22C3) pharmDx kit; CPS = number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100. \(^d\) Includes the unconfirmed PR. Data cutoff: July 21, 2020
Patient Vignettes

Anti-tumor Activity in Tumors Conventionally Unresponsive to Checkpoint Inhibition

33-year-old female with CRC (3.0 mg/kg)
- MSS disease, low TMB (5 mutations/mB), KRAS mutation
- Clinical course: worsening of celiac disease and Grade 3 enteritis
- Treatment Response: confirmed PR with complete resolution of rib mass and 3 cm subcarinal lymph node (images below); resolution of CEA: 23 (pre-MGD019) to <1 ng/mL
- Off-treatment due to enteritis, with persistent response

61-year-old male with mCRPC (3.0 mg/kg)
- Post 6 prior lines of systemic therapy; disease limited to LNs
- Clinical course: immune-mediated hypothyroidism and transaminitis
- Treatment Response: confirmed CR with complete resolution of disease; resolution of PSA (0.5 ng/mL)
- Remains on MGD019 treatment (35+ weeks)

Screening

Study Day 107

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<th>ΔPSA (ng/mL)</th>
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<tbody>
<tr>
<td>Provenge</td>
<td>abiraterone</td>
<td>cabazitaxel</td>
<td>enzalutamide</td>
<td>MGD019 C1D1</td>
<td>uCR</td>
<td>cCR</td>
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<tr>
<td>docetaxel</td>
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Pharmacodynamics of PD-1 and CTLA-4 Blockade

**T cell Proliferation (Ki67)**

- Day 1
- Day 22

**ICOS Upregulation by Dose Level and BoR**

- Dose-dependent ICOS upregulation on peripheral CD4 T-cells attributable to CTLA-4 arm based on cross-comparison with other MacroGenics’ PD-1 based molecules.

MGD019 increases fraction of Ki67+ T cells in patients’ PBMCs.
Purpose-designed bispecific checkpoint inhibitor

- Effects independent or coordinate blockade of PD-1 and CTLA-4
  - Enhanced CTLA-4 blockade on dual-expressing TILs vs. PD-1/CTLA-4 mAb combination
  - Maintains uncompromised PD-1 blockade vs. anti-PD1 mAb benchmarks
- GLP toxicology results compare favorably to that of ipilimumab + nivolumab preclinical profile

Encouraging activity in tumors traditionally unresponsive to checkpoint blockade

- Generally well tolerated at doses < 10 mg/kg
- Full peripheral PD-1 blockade evident at doses ≥ 1 mg/kg
- Dose-dependent ICOS upregulation evident in responding patients
- Responding patients with low PD-L1 expression at baseline

Enrollment in select monotherapy expansion cohorts at RP2D of 6.0 mg/kg forthcoming