A Single Dose of a Novel Anti-Human CD117-Amanitin Antibody Drug Conjugate (ADC) Engineered for a Short Half-Life Provides Dual Conditioning and Anti-Leukemia Activity and Extends Survival Compared to Standard of Care in Multiple Preclinical Models of Acute Myeloid Leukemia (AML)

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Financial Disclosure

Magenta Therapeutics

- Employment
- Salary
- Equity holder
Bone Marrow Transplant: The Patient Journey to a Cure

ADC-mediated conditioning

STEM CELL COLLECTION

GENE MODIFICATION

STEM CELL INFUSION & ENGRAFTMENT

PATIENT

POST-TRANSPLANT COMPLICATIONS
Acute toxicities can include:

- Neutrophil loss (infections)
- Platelet loss (bleeding)
- Anemia
- T-cell depletion (infection)
- Thymic damage (infection)
- Mucositis

Long-term toxicities can include:

- Secondary malignancies
- Organ damage
- Infertility
- Stunted growth
CD17 (c-KIT) - Is an Ideal Target for ADC-Mediated Conditioning

CD17 is overexpressed in >80% of AML and MDS patients
(Tsao et al., Leukemia Research 2004)
CD117-Targeted Conditioning for Stem Cell Gene Therapy and Hematologic Malignancies

Opportunity:
- Less toxic conditioning
- Potential for disease control
- Immune preservation
- Avoid secondary malignancy and infertility
- Broaden access for elderly patients

Applications in transplant:
- Gene therapy
- Hematologic malignancies

Target: CD117
selective depletion of HSCs

Payload:
Potent killing of quiescent and dividing cells

Engineering:
Fc silencing
Rapid clearance following target cell depletion
Effector Silencing and Epitope Selection to Avoid Mast Cell Degranulation

Fc Silencing Diminishes Effector Function

Anti-CD117-Mediated Mast Cell Degranulation is Diminished by Fc Engineering

Anti-CD117 EC50 = 23.7 pM

Concentration [M]

% Phagocytosis

β-hexosaminidase release (Abs at 405 nm)

hIgG1

Anti-CD117

Fc Silenced

Pos. control

Pos. control, Fc silenced

hIgG1

Anti-CD117

Anti-CD117, Fc silenced

Magenta Therapeutics
Engineered Half-Life for Appropriate Clearance Compatible with Transplant

Enhanced Clearance in NHP model

<table>
<thead>
<tr>
<th>Group</th>
<th>Half Life (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engineered half-life IgG</td>
<td>11</td>
</tr>
<tr>
<td>Wild-type IgG</td>
<td>60</td>
</tr>
</tbody>
</table>
# Amanitin Conjugation to Effectively Deplete Target Cells Prior to Transplant

<table>
<thead>
<tr>
<th>Amanitin</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DNA damaging inhibitor of RNA polymerase II</td>
<td>Avoid risks of secondary malignancy and infertility</td>
</tr>
<tr>
<td>Cytotoxic to quiescent and dividing cells</td>
<td>Deplete HSCs with anti-tumor activity</td>
</tr>
<tr>
<td>Potent cytotoxicity on low copy number cells</td>
<td>Allows for substantial elimination of CD117+ cells</td>
</tr>
<tr>
<td>Serum stable</td>
<td></td>
</tr>
<tr>
<td>Low membrane permeability</td>
<td>Low off-target toxicity</td>
</tr>
</tbody>
</table>

| Optimized Linker Payload                       | Broadened therapeutic index across species                             |

**MGTA-117**

**Target:** CD117 selective depletion of HSCs

**Payload:** Optimized Linker Amanitin
Potent killing of quiescent and dividing cells

**Engineering:**
- Fc silencing
- Rapid clearance following target cell depletion
MGTA-117 Demonstrates Potent Killing of AML and Human CD34+ Cells in vitro

AML Cell Line (Kasumi-1)

Primary Human CD34+CD90+

- MGTA-117 IC₅₀: 1 pM
- Isotype-AM

- MGTA-117 IC₅₀: 7 pM
- Isotype-AM

% of untreated control

Concentration (M)

% of untreated control

Concentration (M)
Single Dose of MGTA-117 Selectively Depletes Human CD34+ Cells in Humanized Mice

Humanized mouse bone marrow

- Human CD34+ Cell
- Human CD45+ Cell
- Mouse CD45+ Cell

Single injection of MGTA-117

Blood analysis at day 7, 14 and 21

Bone Marrow Analysis at Day 21

Graphs showing the effects of MGTA-117

- hCD34+: Cells/femur (day 21)
- hCD33+: % of baseline
- hCD3+: % of baseline
- hCD19+: % of baseline

MGTA-117

N =5 per group

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MGTA-117 Extends Median Survival a Cell Line Derived Xenograft AML Model

**Kasumi-1 AML Xenograft**

- **Time Post-Implant (Days)**: 0 to 240
- **Percent survival**

**Treatment Groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (Days Post Implant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>87</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>96</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>116±</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>&gt;237*±</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>&gt;237*±</td>
</tr>
<tr>
<td>3 mg/kg QODx2</td>
<td>&gt;237*±</td>
</tr>
<tr>
<td>ARA-C 30 mg/kg QDx5</td>
<td>98</td>
</tr>
</tbody>
</table>

Log-rank test p ≤ 0.01 compared to *PBS or Isotype-ADC; ± compared to ARA-C

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MGTA-117 Effectively Depletes Human Leukemic Cells in Two PDX AML Models

**Model**

**Type**

- AML, M4

**Previous treatment**

- No previous treatment

**Karyotype; Mutation**

- 46, XY, FLT3+, NPM1+

---

**AML PDX 1**

- **Treatment Begin:** Days Post Implant

**AML PDX 2**

- **Treatment Begin:** Days Post Implant

---

**Model**

**Type**

- AML recurrent/Relapse

**Previous treatment**

- AlloHSCT, Sorafenib, Hydroxyurea, Decitabine

**Karyotype; Mutation**

- Normal; FLT3+, NPM1+, DNMT3A+, IDH1+

---

**Model**

**Type**

- AML recurrent/Relapse

**Previous treatment**

- No previous treatment

**Karyotype; Mutation**

- 46, XY, FLT3+, NPM1+

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**Previous treatment**

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**Karyotype; Mutation**

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**Model**

**Type**

- AML recurrent/Relapse

**Previous treatment**

- No previous treatment

**Karyotype; Mutation**

- 46, XY, FLT3+, NPM1+
MGTA-117 Significantly Extends Survival in Two PDX AML Models

**Model**

Type/previous treatment:

- **AML PDX 1**
  - AML, M4; no previous treatment

- **AML PDX 2**
  - AML recurrent/Relapse; AlloHSCT, Sorafenib, hydroxyurea, Decitabine

**Graphs**

**AML PDX 1**

- Treatment Begin
- Percent survival vs. Days Post-Treatment
- Treatment Groups:
  - PBS
  - ARA-C 30 mg/kg QDx5
  - 3 mg/kg
  - 10 mg/kg MGTA-117
  - 10 mg/kg Isotype-AM

**AML PDX 2**

- Treatment Begin
- Percent survival vs. Days Post-Treatment
- Treatment Groups:
  - PBS
  - ARA-C 30 mg/kg QDx5
  - 3 mg/kg
  - 10 mg/kg MGTA-117
  - 10 mg/kg Isotype-AM

**Table**

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<th>Treatment Groups</th>
<th>Median Survival (Days Post Implant)</th>
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<tbody>
<tr>
<td>PBS</td>
<td>76±</td>
</tr>
<tr>
<td>ARA-C 30 mg/kg QDx5</td>
<td>97*</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>195±</td>
</tr>
<tr>
<td>10 mg/kg MGTA-117</td>
<td>251±</td>
</tr>
<tr>
<td>10 mg/kg Isotype-AM</td>
<td>84±</td>
</tr>
<tr>
<td>10 mg/kg ARA-C 30 mg/kg QDx5</td>
<td>60*</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>77±</td>
</tr>
<tr>
<td>10 mg/kg MGTA-117</td>
<td>83±</td>
</tr>
<tr>
<td>10 mg/kg Isotype-AM</td>
<td>49±</td>
</tr>
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Log-rank test p ≤ 0.01 compared to *PBS or Isotype-ADC; ± compared to ARA-C
Conclusions

• We have demonstrated that a single dose administration of MGTA-117 is well tolerated and capable of:
  
  – Reducing tumor burden by potently targeting leukemia cells in both treatment naïve and relapsed refractory patient derived high risk AML xenograft models.
  
  – Significantly extending median survival in established leukemia xenograft models (cell line and patient derived) compared to controls and clinically validated standard of care

• These results, combined with prior reports on MGTA-117’s robust conditioning ability, demonstrate the dual potential of this agent to be a potent targeted conditioning agent that could improve HSCT outcomes in AML by reducing leukemic burden prior to transplant
Acknowledgments

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