PHASE 1 FIRST-IN-HUMAN TRIAL OF AMV564, A BIVALENT BISPECIFIC (2×2) CD33/CD3 T-CELL ENGAGER, IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (AML)

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AMV564 Is a Bivalent, Bispecific CD33/CD3 T-cell Engager

**Potential Advantages**

- Intermediate half-life
  - Not renally cleared due to size (103 kDa)
  - Gradual drug accumulation for controlled T cell activation
  - Enables rapid hematologic recovery
  - Intermittent dosing possible

- High CD3 and CD33 affinity
  - Greater activity/avidity

- Minimal risk of off-target T-cell activation
  - No risk of FcRn and Fc-gamma mediated cytokine release

- CD33 targeted
  - Well characterized target and clinically validated for AML
Potent and Broadly Active in AML Patient Samples

Equipotent across the disease spectrum with single digit pM activity

Data: R. Walter Group, FHCRC (Note: Positive T cell selection)
Eliminates AML Patient-Derived Xenograft (PDX) Tumor in Stringent Mouse Model with Autologous T Cells

In NSG mice injected with leukemic cells alone >40% of spleen cells and >45% of BM cells were confirmed by FACS to be leukemic blasts by Day 38.

- Eliminated blasts from both bone marrow and spleen at low doses

Data: J. DiPersio, ASCO 2015
Phase 1 Clinical Study Design: AMV564 in R/R AML (NCT03144245)

**3+3 DESIGN**

- 0.5 mcg
- 1.5 mcg
- 5 mcg
- 15 mcg
- 50 mcg
- 100 mcg
- 150 mcg
- 200 mcg

**14 Day Continuous Infusion**

**Dose Escalation**

**PATIENTS**

- Age ≥ 18 years
- High-risk disease
  - 1-4 prior induction regimens
  - Post AlloHSCT relapse allowed
  - 2nd AML allowed
- Normal renal/hepatic function

**KEY OBJECTIVES**

- Define MTD/RP2D
- Evaluate preliminary efficacy
- Assess PK/BMx
# Phase 1 Study in AML: High Risk Patient Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median age (range), y</td>
<td></td>
<td>72 (24, 84)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td></td>
<td>9 (53)</td>
</tr>
<tr>
<td>ECOG score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>11 (65)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>5 (29)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1 (6)</td>
</tr>
<tr>
<td>Secondary AML, n (%)</td>
<td></td>
<td>9 (53)</td>
</tr>
<tr>
<td>≥ Second salvage, n (%)</td>
<td></td>
<td>13 (76)</td>
</tr>
<tr>
<td>Prior intensive chemotherapy, n (%)</td>
<td></td>
<td>9 (53)</td>
</tr>
<tr>
<td>MRC cytogenetic risk group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>7 (41)</td>
</tr>
<tr>
<td>Adverse</td>
<td></td>
<td>10 (59)</td>
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<tr>
<td>Enrollment BM, median (range)</td>
<td></td>
<td>30% (5%, 95%)</td>
</tr>
<tr>
<td>Baseline WBC, median (range), × 10^9/L</td>
<td></td>
<td>1.7 (0.4, 31.8)</td>
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</table>

0.5 – 50 mcg x 14 d (N = 17)

MRC, Medical Research Council; WBC, white blood cell

Data: 07Jun2018
AMV564 Clinical Pharmacokinetics

PK Attributes:
- Gradual accumulation to steady-state
- Terminal $t_{1/2}$ $\sim$ 2 d
- Lower clearance than monovalent BiTE®/DART

Preclinical Comparisons:
- Leukemic Blast Elimination
  - $EC_{95}$ $\sim$ 13 – 58 pM
- NHP HNSTD Exposure
  - $C_{ss}$ $\sim$ 100 pM

Continuous IV infusion of AMV564 for 14 days

0.01 0.1 1 10 100
AMV564 Concentration (pM)

0 3 6 9 12 15 18
Time Since First Dose (Days)

Continuous IV infusion of AMV564 for 14 days
Safety Summary: Only Mild Treatment-Emergent Adverse Events (AEs)

- No related Grade 3+ adverse events
- No cytokine release syndrome (CRS) ≤ 15 mcg; manageable Grade 2 CRS at 50 mcg (1 pt)
- 0% 30-day mortality
- Repeat cycles well tolerated

No Dose Limiting Toxicities through 50 mcg

Data: 07JUN2018
Activity Observed at Doses ≤ 50 mcg

**T-cell activation**
- Increased cytokine levels following administration of AMV564
- Increased antigen markers of T cell activation

**Modest bone marrow blast reductions**
- 13 – 38% reductions in bone marrow blasts 10 of 16 evaluable patients

**Extramedullary improvements**
- Reduction in spleen size
Patient 03-016 Treated at 50 mcg

Background

- Severe myelofibrosis
- Received 2 cycles of AMV564 at 50 mcg

<table>
<thead>
<tr>
<th>AGE/SEX</th>
<th>DIAGNOSIS</th>
<th>SALVAGE #</th>
<th>CG RISK</th>
<th>BLAST %</th>
<th>PRIOR IC</th>
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<tbody>
<tr>
<td>70/F</td>
<td>2nd AMLa</td>
<td>2nd</td>
<td>Intermediate</td>
<td>45%</td>
<td>No</td>
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</table>

T cell activation accompanied by manageable CRS

- Fever, mild hypotension onset ~6 hours of infusion
- Managed with tocilizumab, IVF’s, temporary cessation of infusion
- Subsequent resumption of infusion well-tolerated

Efficacy: Activity observed

- Spleen size reduction from 18 cm to 11 cm
- Decrease in BM cellularity from 30% to 10%
- Reduction in BM blasts from 45% to 23%
Cytokines Increased

- Continuous IV infusion of AMV564 for 14 days
- IL2, IL4, and IFN-gamma were below the LLOQ
AMV564 Phase 1 Study in AML: Summary

Unprecedented and Differentiated PK Profile

- ~2 day terminal half-life
- Gradual drug accumulation to steady-state concentrations

Well Tolerated

- No DLTs, manageable CRS observed
- 0% 30-day mortality rate in high-risk AML population

Activity Observed at Low Doses

- Reductions in bone marrow blasts at doses below EC95
- Evidence of significant T-cell activation at doses ≥ 15 mcg
- Evidence of response in extramedullary sites (Decrease in spleen size)