AMV564, A NOVEL BIVALENT, BISPECIFIC T-CELL ENGAGER, TARGETS MYELOID-DERIVED SUPPRESSOR CELLS

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Disclosures

• Amphivena: Employment
Myeloid Derived Suppressor Cells (MDSC): S100A9 and CD33 Signaling

- MDSC suppress T cell responses and promote immune suppression in solid tumors
  - Correlation with poor outcome, lack of response to therapy including checkpoint blockade
- Mice lacking S100A9 mount potent anti-tumor immune responses and reject implanted tumors: this effect is reversed by MDSC administration from wild-type mice (Cheng *et al.* J. Exp. Med. (2008) 205: 2235-2249)

**IL10, TGFβ, VEGF production after CD33 activation in U937 cells**
AMV564 Selectively Engages CD33+ Cell Subsets via Avid Binding

- AMV564 is a potent bivalent, bispecific T cell engager
  - EC$_{50}$ 4 - 8 pM for target-dependent killing of AML cell lines

AMV564 can distinguish cell types due to its bivalency
Preference for CD33 clusters

MDSC
Leukemic Blast

Neutrophil, monocyte, other normal myeloid cell

Monovalent T-cells engagers cannot distinguish cell types
**AMV564 Clinical Trials (Phase 1)**

<table>
<thead>
<tr>
<th>Study</th>
<th>AMV564-101</th>
<th>AMV564-201</th>
<th>AMV564-301*</th>
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</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Relapsed/refractory AML</td>
<td>Intermediate/high risk MDS</td>
<td>Advanced solid tumors</td>
</tr>
<tr>
<td>Cycle (days on/off)</td>
<td>14 /14 4-week cycle</td>
<td>14 /14 4-week cycle</td>
<td>5/2/5 3-week cycle</td>
</tr>
<tr>
<td>Administration</td>
<td>Continuous IV infusion</td>
<td>Continuous IV infusion</td>
<td>Daily subcutaneous injection</td>
</tr>
</tbody>
</table>

- AMV564 has been well tolerated and shown evidence of anti-leukemic blast activity in phase 1 first-in-human ascending dose studies
  - Intermediate half life (~ 2 days terminal half-life)
  - Manageable cytokine release syndrome (≤ grade 2)
- AMV564-301 (NCT04128423) initiated in October (*Poster P416, Saturday*)
AMV564 Depletes MDSC and Activates T Cells *ex vivo*

- AMV564 treatment of primary cells (PBMC, MDS bone marrow, tumor PBMC) *ex vivo*:
  - negates reactive oxygen species (ROS) produced in response to S100A9 stimulation of PBMC
  - results in selective depletion of MDSC
  - yields increase in CD4 and CD8 T cell numbers and activation state (IFNγ positive fraction)
Patient samples (AML) collected at baseline, days 2, 3 and 15 of dosing cycle, MDSC assessed using procedures described in Mandruzzato et al Can. Imm. Imm (2016) 65:161-169 and as developed at Moffitt Cancer Center (Wei lab)
• Substantial increases in different populations of MDSC are apparent in peripheral blood and bone marrow, in response to T cell activation.

• In this example (AML), this dosing regimen of AMV564 does not yield control of MDSC.
MDSC are Dynamic and Respond to T Cell Activation in Patients

- Increase in MDSC in response to T cell activation is observed in lead-in dosing (days 1-3) in some patients
  - T cell margination is apparent even in patients with low levels of baseline T cells or low CD8 T cells
- At target dose, MDSC are controlled
- Decreased MDSC in bone marrow (treatment day 15 vs screen)
- However, MDSC can rebound once AMV564 treatment is stopped
Translating the Activity of AMV564 to Solid Tumors

- **Bone marrow:** Mobilization of MDSCs
- **Tumor microenvironment:** TERNARY COMPLEX
  - T cell
  - AMV564
  - Target cell (MDSCs)
  - T eff cell
  - T cell
  - CD3
  - TCR
  - CD33
- **Restoration of antigen presentation:**
  - TCR re-engagement
  - APC
  - T eff-cell activation
- **Lymph node:**
  - Rest. of antigen presentation
  - CD3
  - TCR

- **Proliferation:**
- **MDSC destruction:**
  - Spares neutrophils and monocytes
- **T eff cell**
- **Mobilization of MDSCs**
- **T eff cell**

**Key Terms:**
- MDSCs (Myeloid-Derived Suppressor Cells)
- RBCs (Red Blood Cells)
- T cells
- T eff cell (T effector cell)
- APC (Antigen Presenting Cell)

MDSC Negatively Impact Anti-Tumor Immunity

Preexisting immunity
Excluded infiltrate
Immunologically ignorant

Respond favorably to checkpoint inhibition
Convert to inflamed phenotype with combinations

Conclusions and Next Steps

Conclusions

• AMV564 reduces MDSC in bone marrow and periphery in AML and MDS patients in a 14 day dosing regimen
• AMV564 demonstrates selectivity for MDSC and leukemic blasts vs neutrophils and monocytes
• AMV564 activates T cells
• MDSC populations are dynamic and can increase in response to T cell activation

Next Steps

• Transition to a continuous dosing regimen to control MDSC (and leukemic blasts)
• Solid tumor study initiated to evaluate the impact of AMV564 on MDSC and T cell activation
Acknowledgments

• AMV564-101 and AMV564-201 clinical trial investigators, sites and staff
• Patients