**BACKGROUND**

- Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are common hematologic malignancies characterized by clonal expansion of myeloid progenitors (blasts) in the bone marrow and peripheral blood.
- Removal of both leukemic blasts and leukemic stem cells (LSCs) is key to eradicate minimal residual disease (MRD) and prevent relapse, therefore novel therapies are required that target both of these cell types.
- The efficacy of allogeneic natural killer (NK) cell immunotherapies can be enhanced by tumor-targeting bispecific antibodies that redirect NK cells to tumors, and enhance NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC).
- Innate Cell Engager (ICE®) molecules bind both to CD16A on NK cells and a tumor cell-surface antigen, redirecting NK cells to target cells and stimulating ADCC.
- AFM28 (CD123/CD16A) is a novel ICE® designed to target CD123, an antigen universally expressed on both leukemic blasts and LSCs.
- Initial studies have shown effective anti-tumor activity of AFM28, and a favorable safety profile in cynomolgus toxicity models.
- Combination of AFM28 with allogeneic NK cells, as a pre-complexed product or co-administered, may represent a novel treatment modality by enhancing ADCC towards both leukemic blasts and LSCs expressing CD123.

**OBJECTIVE**

To investigate the anti-leukemic activity of AFM28 both when pre-complexed and co-administered with allogeneic NK cells.

**RESULTS**

AFM28 binds to both NK cells and tumor cells and stimulates induction of ADCC

AFM28 mediated NK cell activation is CD123+ target cell-dependent and does not induce NK cell fratricide

AFM28 can be pre-complexed or co-administered with NK cells

AFM28 induces ADCC at comparable levels both when pre-complexed or co-administered with NK cells

AFM28 can induce targeted tumor cell lysis (via ADCC) in combination with cryopreserved NK cells

**CONCLUSIONS**

- AFM28 is a novel ICE® specific to CD16A on NK cells, and CD123 on AML and MDS leukemic cells.
- AFM28-mediated activation of NK cells induces ADCC towards primary leukemic blasts from peripheral blood and bone marrow of patients with AML and requires the presence of CD123+ tumor target cells.
- AFM28 stimulates ADCC both when pre-complexed and when co-administered with NK cells.
- AFM28 binds with high affinity to NK cells, even in the presence of competing IgG, and exhibits greater cell surface retention than conventional monoclonal antibodies, including Fc-enhanced IgG1.
- Feasibility of cryopreserving AFM28 pre-complexed NK cells whilst maintaining anti-tumor activity suggests promise for an off-the-shelf therapy targeting leukemic blasts and LSCs in patients with AML and MDS.