Acute myeloid leukemia (AML) can be treated with curative intent using high-dose chemotherapy and hematopoietic stem cell transplant; however, substantial medical need remains as many patients are considered ineligible due to age and co-morbidities.

In treatment-naive patients, relapse is common due to failure to eradicate residual leukemic stem cells (LSCs), and ultimately prognosis is poor. Novel, alternative therapies are required to treat patients ineligible for standard of care therapy, as well as those who relapse or become refractory to frontline therapy due to persistent minimal residual disease (MRD).

Allogeneic natural killer (NK) cell therapy has shown promising clinical activity in patients with relapsed or refractory (R/R) AML, and the activity of these therapies may be enhanced in combination with Innate Cell Engagers (ICEs).

AFM28 is a CD123/CD16a bispecific ICE developed to redirect and enhance NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) towards CD123+ AML leukemic blasts and LSCs, which may eradicate MRD in patients with R/R AML.

**BACKGROUND**

- Acute myeloid leukemia (AML) can be treated with curative intent using high-dose chemotherapy and hematopoietic stem cell transplant; however, substantial medical need remains as many patients are considered ineligible due to age and co-morbidities.
- In treatment-naive patients, relapse is common due to failure to eradicate residual leukemic stem cells (LSCs), and ultimately prognosis is poor. Novel, alternative therapies are required to treat patients ineligible for standard of care therapy, as well as those who relapse or become refractory to frontline therapy due to persistent minimal residual disease (MRD).

**OBJECTIVE**

Evaluate the efficacy of AFM28 to enhance NK cell-mediated ADCC towards CD123+ AML leukemic blasts and LSCs.

**RESULTS**

AFM28 induces NK cell-mediated lysis of CD123+ target cells with high efficacy and potency, irrespective of the presence of high-risk driver mutations, as well as CD123 and CD4 expression levels.

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**CONCLUSIONS**

- AFM28 induces NK cell-mediated lysis of CD123+ tumor cells with high efficacy and potency.
- AFM28-mediated ADCC activity in vitro is not affected by high-risk mutational status or low CD123 expression and, in contrast to Fc-enhanced monomeric antibodies, activity is unaffected by D646 expression.
- AFM28 can inhibit tumor cell proliferation through blocking of IL-3-induced STAT3 phosphorylation downstream of CD123, thus inhibiting a secondary mechanism of action in addition to induction of NK cell-mediated ADCC.
- In ex vivo AML and MDS patient BMMC samples, AFM28 demonstrated efficient depletion of both CD123+ leukemic blasts and, importantly, LSCs.

Potent anti-tumor efficacy of AFM28 was exhibited in a murine AML model.

Leveraging the innate immune system by combining AFM28 with allogeneic NK cells may offer the potential to induce tumour regression in a broad patient population in R/R AML and HR-MDS.

**REFERENCES**