

852 **TRIFUNCTIONAL NKP46/CD16A-NK CELL ENGAGER TARGETING CD123 OVERCOMES ACUTE MYELOID LEUKEMIA RESISTANCE TO ADCC**

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Background There is a clear need for targeted therapies to treat acute myeloid leukemia (AML), the most common acute leukemia in adults. CD123 (IL-3 receptor alpha chain) is an attractive target for AML treatment.¹ However, cytotoxic antibody targeting CD123 proved insufficiently effective in a combination setting in phase II/III clinical trials.² T-cell engagers targeting CD123 displayed some clinical efficacy but were often associated with cytokine release syndrome and neurotoxicity.³ Interest in the use of NK cells for therapeutic interventions has increased in recent years, as a potential safer alternative to T cells. Several NK-cell activating receptors, such as CD16a, NKG2D, and the natural cytotoxicity receptors NKp30 and NKp46, can be targeted to induce antitumor immunity. We previously reported the development of trifunctional NK-cell engagers (NKCEs) targeting a tumor antigen on cancer cells and co-engaging NKp46 and CD16a on NK cells.⁴

Methods We report here the design, characterization and pre-clinical development of a novel trifunctional NK cell engager (NKCE) targeting CD123 on AML cells and engaging the activating receptors NKp46 and CD16a on NK cells. The CD123 NKCE therapeutic molecule was engineered with humanized antibodies targeting NKp46⁴ and CD123.⁵ We compared CD123-NKCE and a cytotoxic ADCC-enhanced antibody (Ab) targeting CD123, in terms of antitumor activity in vitro, ex vivo and in vivo. Pharmacokinetic, pharmacodynamic and safety profile of CD123-NKCE were evaluated in non-human primate (NHP) studies.

Results The expression of the high affinity Fc gamma receptor CD64 on patient-derived AML cells inhibited the ADCC of the Ab targeting CD123 in vitro and ex vivo, but not the antitumor activity of CD123-NKCE. CD123-NKCE had potent antitumor activity against primary AML blasts and AML cell lines, promoted strong NK-cell activation and induced cytokine secretion only in the presence of AML target cells. Its antitumor activity in mouse model was greater than that of the comparator antibody. Moreover, CD123-NKCE had strong and prolonged pharmacodynamic effects in NHP when used at very low doses, was well-tolerated up to high 3 mg/kg dose and triggered only minor cytokine release.

Conclusions The data for activity, safety, pharmacokinetics, and pharmacodynamics provided here demonstrate the superiority of CD123-NKCE over comparator cytotoxic antibody, in terms of antitumor activity in vitro, ex vivo, in vivo, and its favorable safety profile, as compared to T-cell therapies. These results constitute proof-of-principle for the efficacy of CD123-NKCE for controlling AML tumors in vivo, and provide consistent support for their clinical development.

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