# Preclinical Evaluation Of ISB 1442, A First-in-Class CD38 and CD47 Bispecific Antibody Innate Cell Modulator for the Treatment of AML and T-ALL

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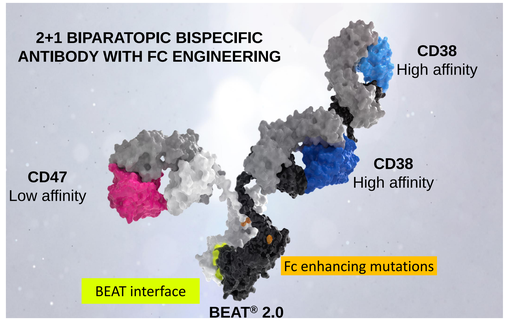
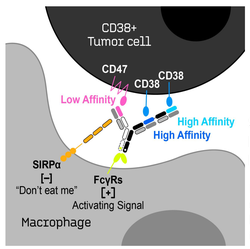
## INTRODUCTION




- ISB 1442 is a bispecific antibody (BsAb) using Ichnos' proprietary BEAT® platform that co-targets CD38 and CD47 with a 2+1 format
- ISB 1442 has dedicated Fc engineering that enhances Fc effector functions, including (Complement Dependent Cell Cytotoxicity), Antibody Dependent Cell Cytotoxicity (ADCC) and Antibody Dependent Cell Phagocytosis (ADCP)
- ISB 1442 has higher potency relative to daratumumab in CD38$^{high/low}$ multiple myeloma tumor models, as measured by several antibody-dependent mechanisms of action *in vitro* and *in vivo*
- ISB 1442 shows low on-target off-tumor binding and no RBC depletion compared to anti-CD47 mAb (5F9)
- ISB 1442 is currently in a Phase 1 clinical trial for relapsed refractory multiple myeloma (rrMM) (NCT05427812, see Abstract #4571)
- CD38 and CD47 are also expressed in other hematologic cancers, including acute myeloid leukemia (AML) and T cell acute lymphoblastic leukemia (T-ALL)
- Anti-CD47 magrolimab has shown activity in AML/MDS, including p53 mutated disease, when used in combination with demethylating agents and BCL-2 inhibitors
- T-ALL is characterized with high CD38 expression. Co-targeting CD38 and CD47 by combining monoclonal antibodies has demonstrated efficacy in multiple preclinical models of refractory T-ALL. Additionally, the combination of CD38-targeted daratumumab and chemotherapy is under investigation for this indication (NCT03384654)
- First-in-class biparatopic bispecific antibody ISB 1442, which targets both CD38 and CD47, has enhanced Fc effector functions and the potential to treat AML and T-ALL patients




**Schematic Mode of Action of ISB 1442 Mediated Induction of Phagocytosis of Tumor Cells**

ISB 1442 CD38 Fab arms preferentially drive binding to tumor cells and enable blocking of proximal CD47 receptors on the same cell via avidity-induced binding

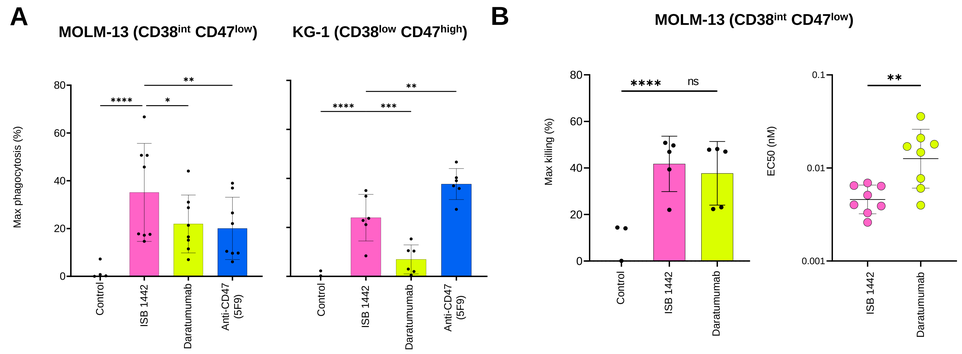
**References**

Majeti et al. Cell 2009; Naik et al. Haematologica 2019; Daver et al: ASH 2021, Sallman et al: ASH 2020; Muller K et al., Blood 2022; Sammicheli S et al. ASH 2021.

**Statistics:**

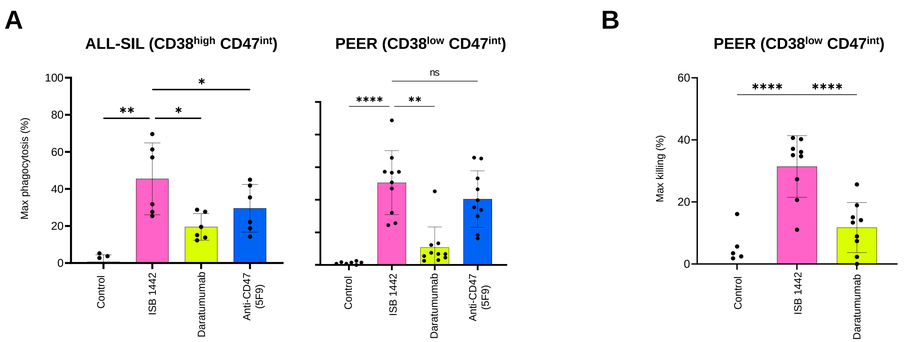
Not significant (NS), * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001

## ISB 1442 Killing of AML Cell Lines Compared to Anti-CD38 and Anti-CD47 Mono-Targeting Antibodies



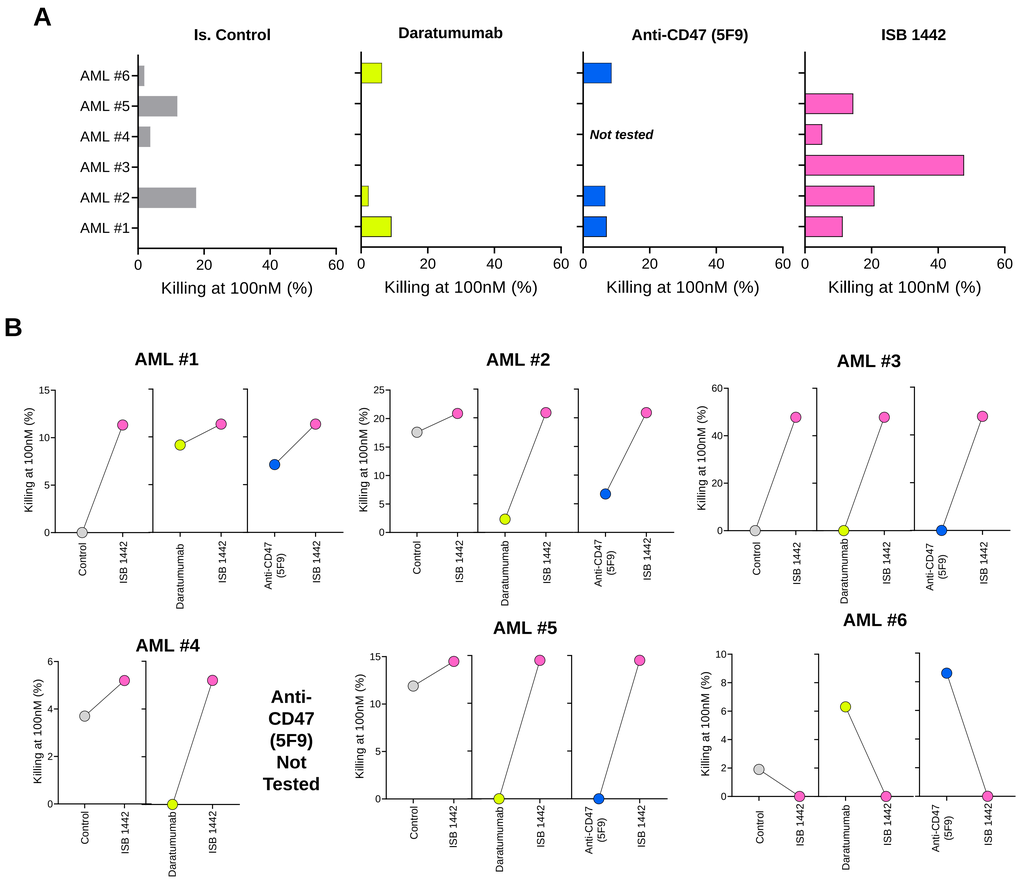

- ISB1442 induces higher phagocytosis of AML cell lines with intermediate or low CD38 expression as compared to isotype control (Is. Control) and daratumumab (A)
- ISB1442 shows higher potency than daratumumab in ADCC (B) and is superior at inducing killing of this AML cell line against both daratumumab and anti-CD47 (5F9) using an *in vitro* Multiple Mode of Action of Killing (MMoAK) assay (C, D)

## ISB 1442 Killing of T-ALL Cell Lines Compared to Anti-CD38 and Anti-CD47 Mono-Targeting




- ISB1442 induces higher phagocytosis (A) and more potent ADCC (B) of T-ALL cell lines with intermediate or low CD38 expression as compared to daratumumab and anti-CD47 (5F9)

## ISB 1442 Killing of AML blasts *Ex Vivo*




- ISB 1442 induces killing of AML blasts in a direct killing assay of patients' samples *ex vivo* with higher frequency as monospecific anti-CD38 daratumumab or anti-CD47 (A)
- A higher trend of killing was mediated by ISB 1442 in 5 out of the 6 samples where killing was detectable *ex vivo* as compared to isotype control and monospecific anti-CD38 daratumumab or anti-CD47 (5F9) (A-B)

## CONCLUSIONS

- ISB1442 induces killing of AML and T-ALL cell lines in multiple in vitro assays, including ADCP, ADCC and MMoAK as a function of CD38 and CD47 expression
- ISB 1442 show superior activity to daratumumab in AML and T-ALL cell lines having intermediate or low CD38 expression
- In AML bone marrow aspirates where direct killing was detectable, ISB 1442 showed more frequent killing of AML blasts and higher potency as compared to monospecific anti-CD38 daratumumab or anti-CD47 (5F9)

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