A PHASE 1/2, FIRST-IN-HUMAN, MULTICENTER, OPEN-LABEL, DOSE ESCALATION AND DOSE-EXPANSION STUDY OF SINGLE-AGENT ISB 1442 IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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PRESENTED AT THE 64TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING
NEW ORLEANS, LA | DECEMBER 12, 2022

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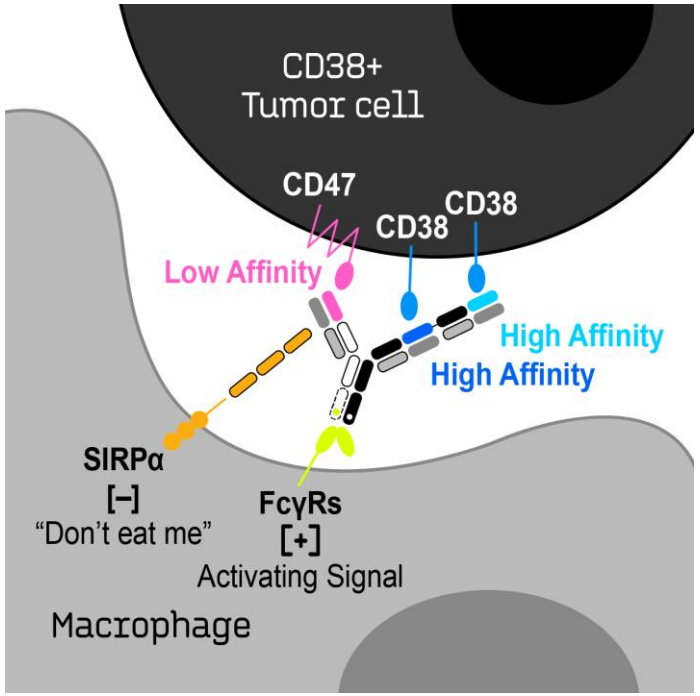
High Unmet Medical Need Remains in Patients with Relapsed / Refractory Multiple Myeloma, Despite Recent Advances in Treatment

- Incorporation of daratumumab into the treatment for multiple myeloma has improved outcomes, however relapse still occurs with development of resistance[1]
- BCMA targeted therapy, including CAR-T and T cell engagers, have demonstrated high overall response rates, however relapse continues to be observed[2]
- Several primary and acquired known tumor resistance mechanisms are implicated in relapse following treatment with CD38-targeted antibodies[3]
    + Decreased CD38 cell surface density
    + Resistance to Complement Dependent Cytotoxicity (increased complement regulatory protein expression)
    + Resistance to phagocytosis (CD47 “do not eat me” signal overexpression)
- New multispecific antibodies designed to overcome daratumumab resistance and activate other innate immune cells may offer additional benefits to patients with multiple myeloma

1. *Gandhi UH et al. Leukemia 2019; 33: 2266–75*
2. *Watson, et al. Expert Rev Hematol. 2022 Jun;15(6):503-517*
3. *Saltarella I. et al. CELLS 2020*

ISB 1442 Redirects Myeloid Cells To CD38+ Tumors Using Ichnos' Proprietary BEAT® Platform

ISB 1442 (CD38 X CD47) BISPECIFIC ANTIBODY	BEAT® 2.0



FIRST-IN-CLASS KEY ATTRIBUTES

- Two high-affinity Fab arms drive binding to distinct CD38 epitopes on tumor cells
  - + Neither epitope shows functional competition with daratumumab
- One Fab arm blocking CD47-SIRPa binding in cis on tumor cells to enhance ADCP
  - + Increased tumor phagocytosis
  - + Reduced potential for antigen sink with lower-affinity Fab binding to ubiquitously expressed CD47
- Potent ADCC and CDC based on
  - + Optimized affinity, epitope, architecture/avidity and Fc engineering
- Optimized tolerability
  - + Low potential for hemagglutination, platelet aggregation

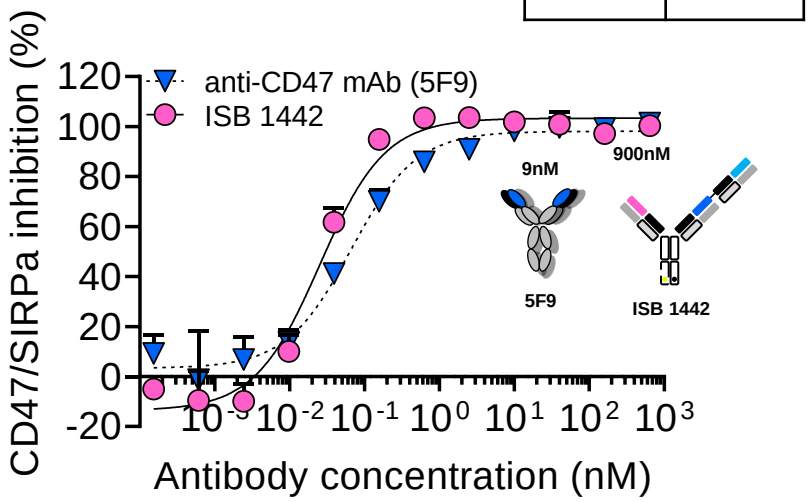
*BEAT®: **B**ispecific **E**ngagement of **A**ntibodies based on the **T**CR*
ADCP: Antibody-Dependent Cell Phagocytosis
ADCC: Antibody-Dependent Cell Cytotoxicity
CDC: Complement-Dependent Cytotoxicity

ISB 1442 Blocks CD47/SIRPα Interactions & Induces Enhanced Phagocytosis of CD38 Low-Expressing Tumor Cells vs. Daratumumab

Blocks CD47/Sirpα Interactions

CD38^{high} (Daudi)

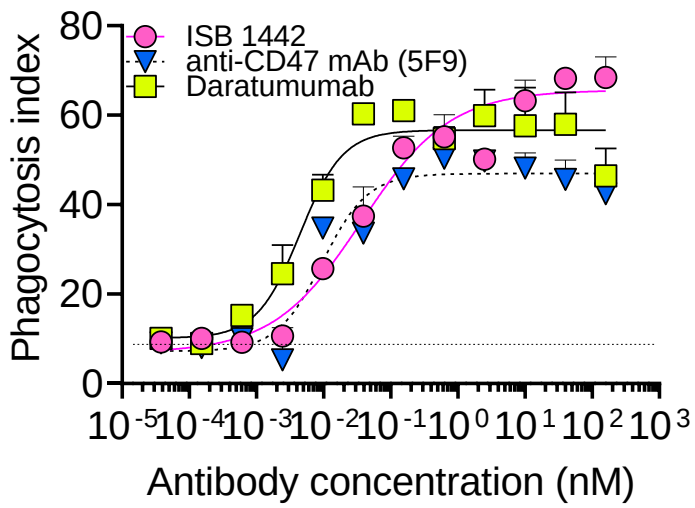
CD38	CD47
180,000	60,000



Higher Phagocytocis Relative to Daratumumab in CD38^{low}

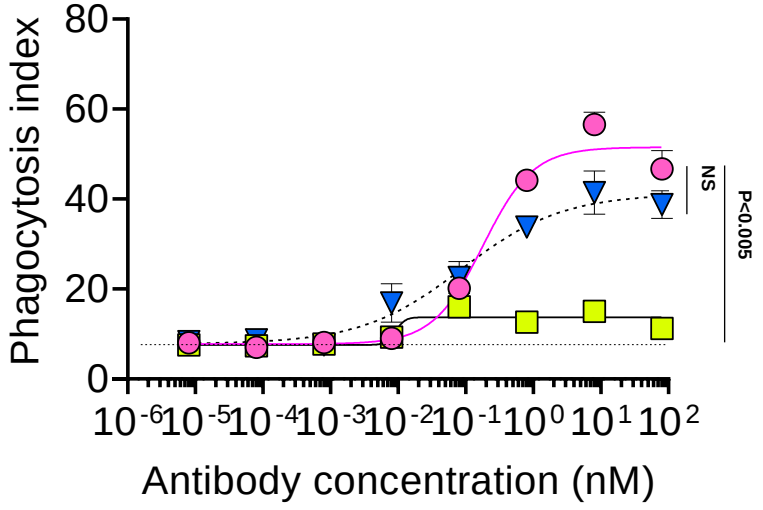
CD38^{high} (Daudi)

CD38	CD47
180,000	60,000



CD38^{low} (KMS-12-BM)

CD38	CD47
5,000	210,000



Statistics: Tukey's Multiple Comparison Test
Data Presented At American Society Of Hematology 2021 Annual Meeting. Author, Stefano Sammicheli, et. al.

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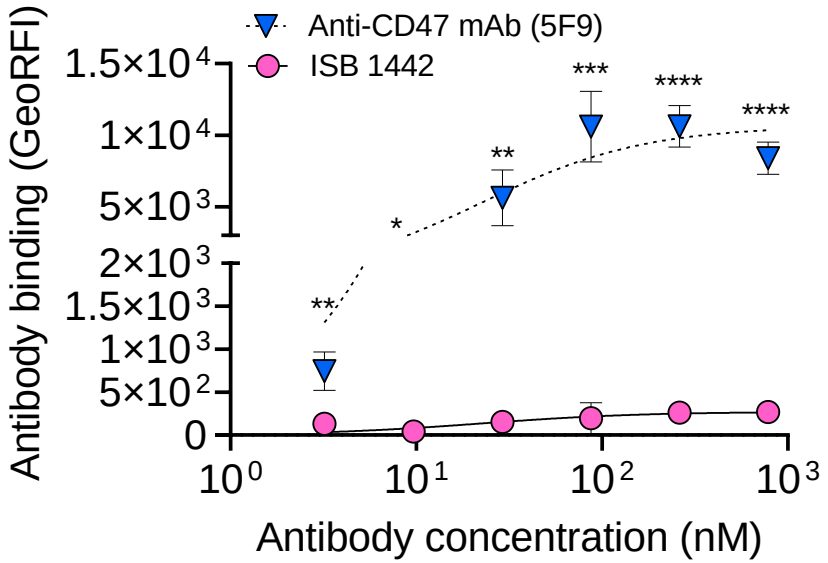
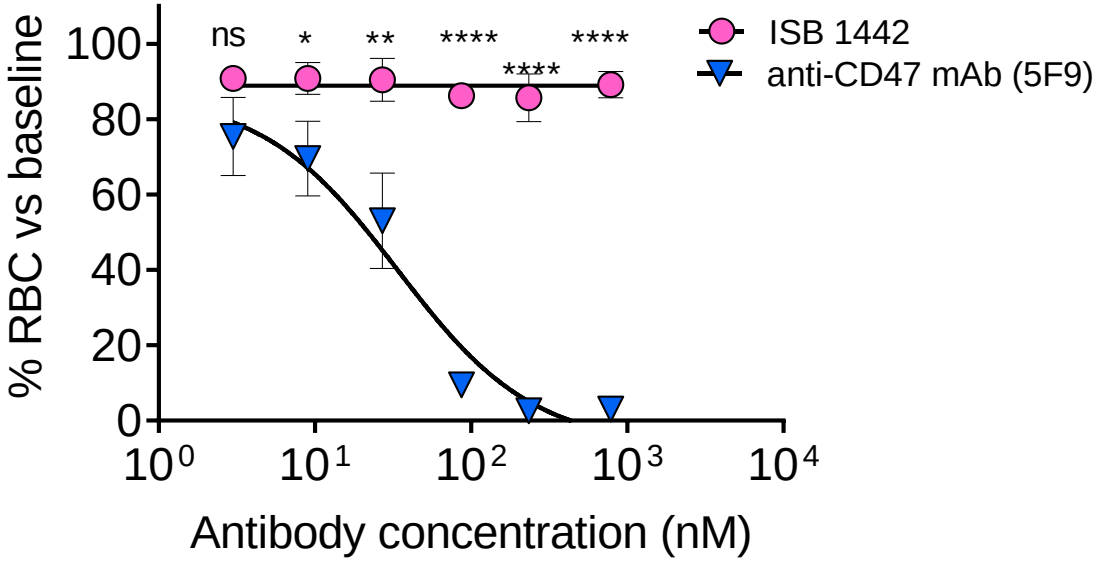
ISB 1442 Only Binds to CD47 After Engaging CD38, Reducing Potential For On-Target, Off-Tumor Depletion of Red Blood Cells

Reduced Binding To RBC



Statistics: 2-way ANOVA with multiple comparisons.

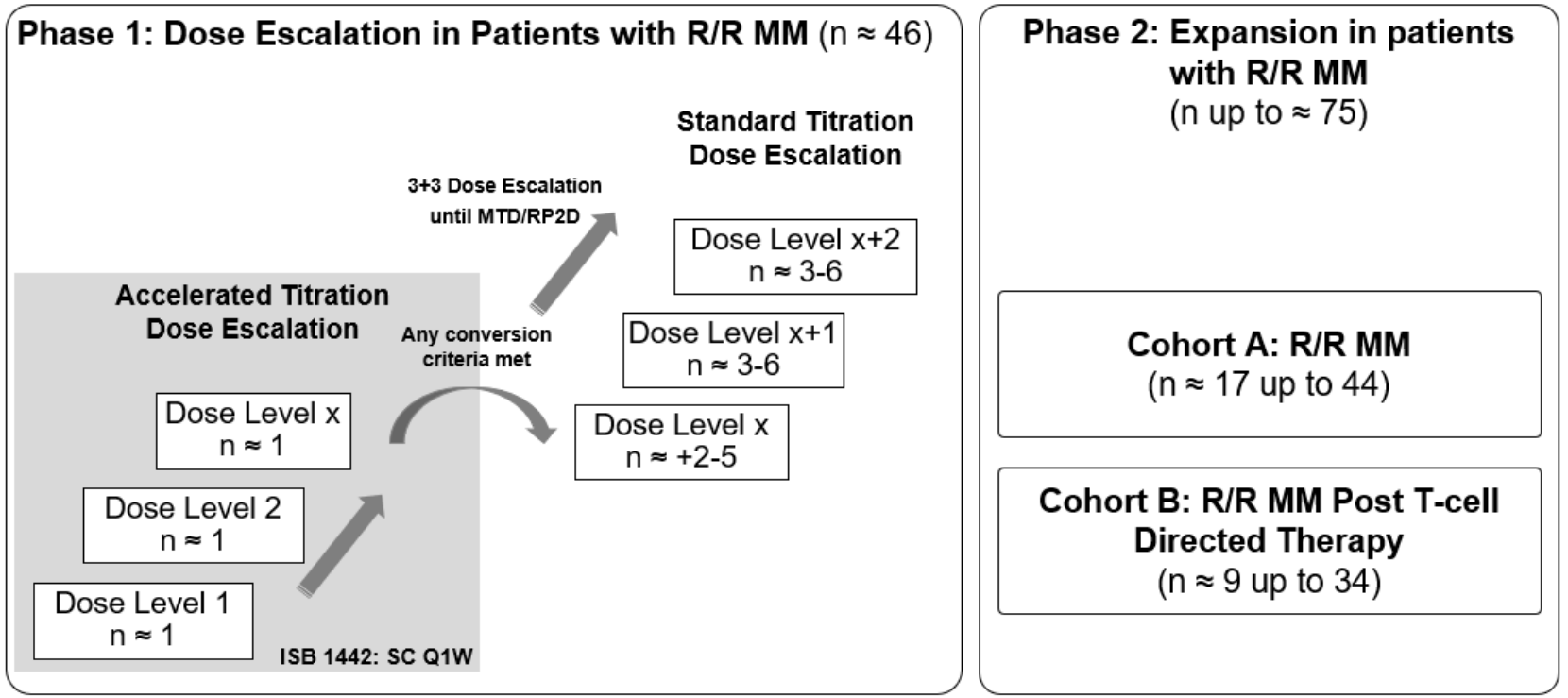
Minimal RBC Depletion



Statistics: 2-way ANOVA with multiple comparisons.

NS P≥ 0.05
P<0.05
** P<0.01
*** P<0.001
**** P<0.0001

ISB 1442-101 Study Design



Key Eligibility

- R/R MM patients with measurable disease after therapy with a CD38 antibody, IMiDs, PIs, and who must not be candidates for regimens known to provide clinical benefit
- Failed 3 or more prior lines of therapies (study requirements in US)

Primary Objectives

- Phase 1: Assess safety, tolerability and Determine MTD/RP2D
- Phase 2: Evaluate efficacy

Secondary Objectives

- PK, immunogenicity

Exploratory Objectives

- Biomarker, MRD

ClinicalTrials.gov Identifier: NCT05427812
ACTRN: ACTRN12622000856718

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ISB 1442-101 Study: Site Selection and Activation Status

- HREC accepted on 27-May-2022
- Pindara Private Hospital, Benowa, QLD, Australia
- One Clinical Research Pty Ltd, Nedlands, Western Australia, Australia
- 4 Additional sites to be opened

- FDA IND accepted on 29-Apr-2022
- Site activation in process

Conclusions

- ISB 1442 represents a novel approach for the treatment of CD38+ tumors by co-targeting CD38 and CD47 with a 2+1 biparatopic bispecific antibody
- ISB 1442 shows higher potency *in vitro* relative to daratumumab in CD38$^{high/low}$ tumor models as measured by multiple antibody-dependent mechanisms of action
- ISB 1442 shows low on-target off-tumor binding compared to anti-CD47 mAb (5F9), with a potential for a better therapeutic index than anti-CD47 bivalent mAbs
- Enrollment in the First-in-Human ISB 1442 trial is ongoing (ClinicalTrials.gov identifier: NCT05427812. ACTRN: ACTRN12622000856718)