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

Hanlon Sia[1], Peter Tan[2], Joshua Richter[3], P. Joy Ho[4], Tara Cochrane[5], Hang Quach[6], Binod Dhakal[7], Tony Jiang[8], Emaryn Mancino[8], Stefano Sammicheli[9], Girish Gudi[8], Andrew Garton[8], Eric Feldman[8], Andrew Spencer[10]

[1]. Pindara Private Hospital, Benowa, QLD, Australia; [2]. One Clinical Research Pty Ltd, Nedlands, Western Australia, Australia; [3]. Icahn School of Medicine, New York, NY, USA; [4]. Royal Prince Albert Hospital, Camperdown, NSW, Australia; [5]. Gold Coast University Hospital, Southport, QLD, Australia; [6]. St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [7]. Medical College of Wisconsin, Milwaukee, WI, USA; [8]. Ichnos Sciences, New York, NY, USA; [9]. Ichnos Sciences, La Chaux-de-Fonds, Switzerland; [10]. The Alfred Hospital-Melbourne, Melbourne, VIC, Australia

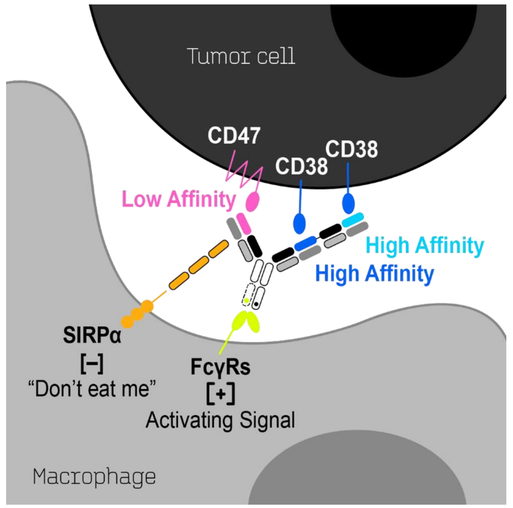
BACKGROUND

Addition of anti-CD38 monoclonal antibodies such as daratumumab into the standard of care for Multiple Myeloma (MM) has improved disease outcomes; however, resistance mechanisms remain. These include reduced:

- CD38 expression
- Antibody-dependent cell cytotoxicity (ADCC)
- Antibody-dependent cell phagocytosis (ADCP) due to overexpression of CD47
- Complement-dependent cytotoxicity (CDC)

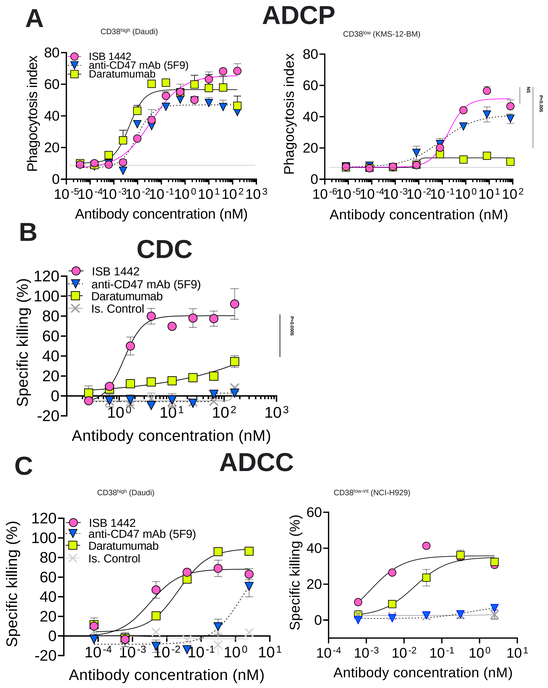
ISB 1442

- 2+1 biparatopic bispecific antibody
- CD38 and CD47 targeting domains
- Engineered Fc domain to enhance ADCP, CDC, and ADCC
- Two Fab regions binding to distinct CD38 epitopes than those of daratumumab



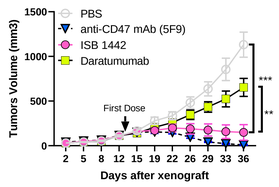
PRECLINICAL DATA

ISB 1442 Possesses Higher CDC and ADCC Activities Relative to Clinical Benchmark Daratumumab



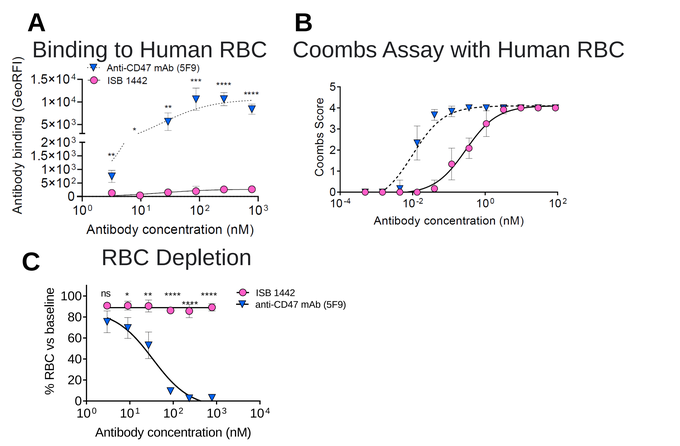
Representative curves of specific killing of (A) ADCP assay performed with CD38^{high} (Daudi) or CD38^{low} (KMS-12-BM); (B) CDC assay performed with CD38^{high} (Daudi) tumor cells; (C) ADCC assay performed with CD38^{high} (Raji) or CD38 $^{low\text{-}int}$ (NCI-H929) tumor cells. Statistical analysis conducted by 1-way ANOVA w. Tukey post hoc testing. ** - P<0.01 *** - P<0.001

ISB 1442 Shows Improved Tumor Growth Inhibition in Xenograft Model Compared to Daratumumab



Assay: 10 million Raji cells were implanted s.c. into CB17/SCID mice and animals were randomized into groups when tumor volume reached ~100 mm3. ISB 1442 and 5F9 (anti CD47) were dosed QW at 10 mg/kg, Daratumumab was dosed BIW at 16 mg/kg. PBS: Phosphate buffered saline (control). Graph shows mean +/- SEM of tumor volume for 5 mice. Statistical analysis conducted by 1-way ANOVA w. Tukey post hoc testing. ** - P<0.01 *** - P<0.001

ISB 1442 Shows a More Favorable On-Target Specificity, with Reduced Binding on RBC, Hemagglutination and RBC Depletion Compared to Anti-CD47 Monoclonal 5F9 Antibody



(A) Antibodies binding to human RBCs. Figures show binding curves of each antibody with standard deviation (n=6 per arm). (B) Indirect Coombs assay of human RBCs, developed in-house using Biorad kit. Figures show hemagglutination curves induced by each antibody with standard deviations (n=6 per arm). (C) RBCs recovery of human whole blood analyzed using a hemato-analyzer. Figure shows RBCs depletion induced by each antibody with standard deviations (n=6 per arm). Statistics: 2-way ANOVA with multiple comparisons. ns p≥ 0.05; * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001.

This open-label, first-in-human, multicenter Phase 1/2 study is assessing the safety, tolerability, efficacy, pharmacokinetics(PK), and pharmacodynamics of ISB 1442 in relapsed/refractory multiple myeloma (R/R MM) patients. The study is currently open for enrollment. ClinicalTrials.gov identifier: NCT05427812. ACTRN: ACTRN12622000856718.

Key Patient Eligibility Criteria:

- R/R MM with measurable disease after 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)

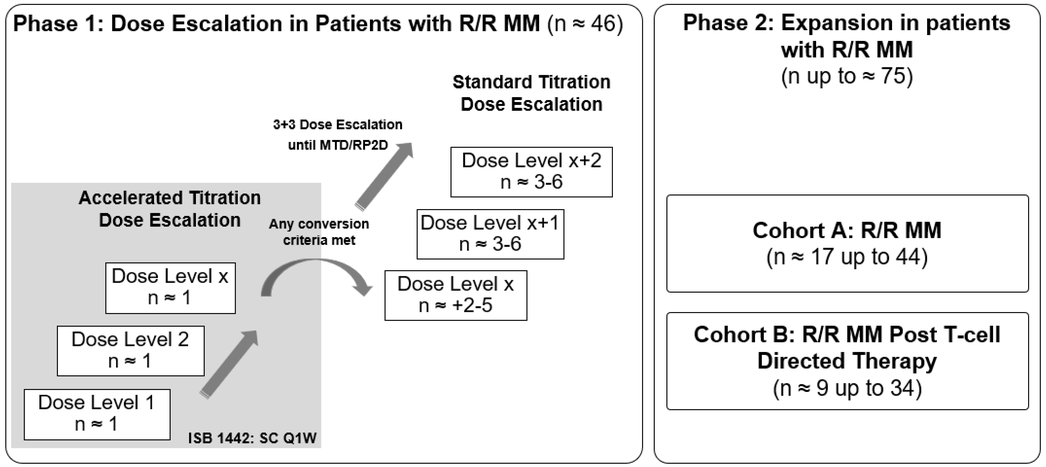
Primary Objectives:

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

Secondary Objectives:

- PK, immunogenicity

STUDY DESIGN



Presented at the 64th American Society of Hematology Annual Meeting
New Orleans, LA | December 11, 2022