

ISB 1442

Preclinical Data Summary: First-in-Class CD38 and
CD47 Bispecific Antibody Innate Cell Modulator for
Relapsed / Refractory Multiple Myeloma

Stefano Sammiceli, et al

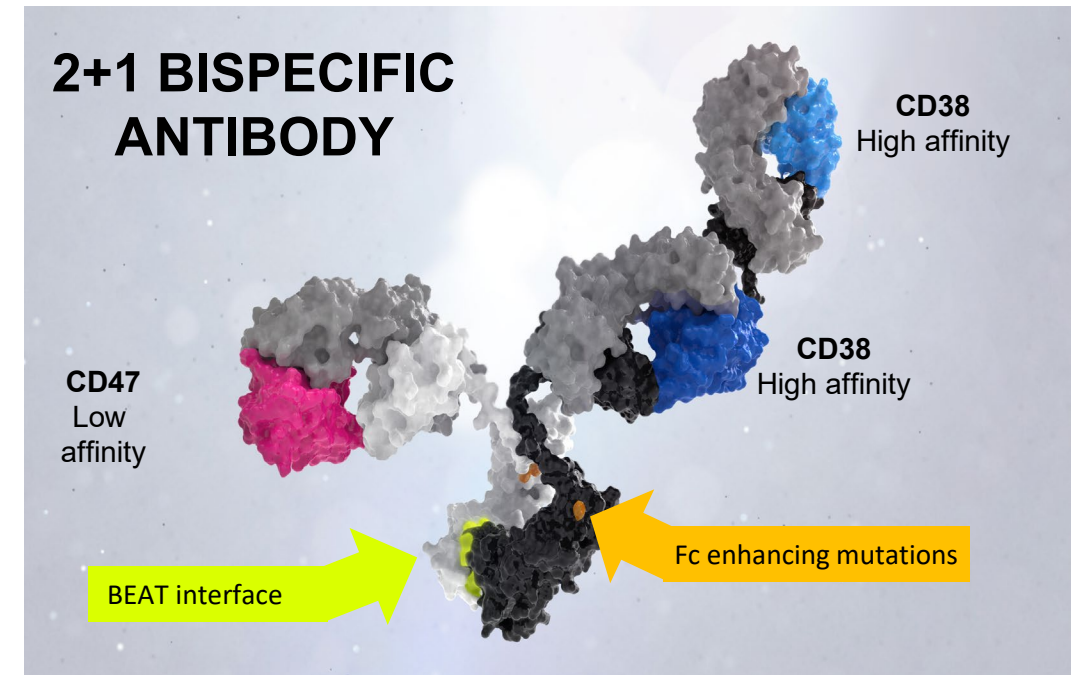
High Unmet Medical Need Remains in Patients with Relapsed / Refractory Multiple Myeloma, Despite Recent Advances in Treatment

- Significant unmet medical need exists in triple refractory patients that have progressed following treatment with proteasome inhibitors, IMiD and anti-CD38 monoclonal antibodies¹
 - ORR with subsequent therapies is 31%
 - Median OS is 9.3 months and median PFS is 3.4 months
- Several primary and acquired known tumor resistance mechanisms are implicated in relapse following treatment with CD38-targeted antibodies²
 - 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 therapies with more complete and durable responses are needed

¹ Gandhi UH et al. Leukemia 2019; 33: 2266–75.

² Saltarella I. et al. CELLS 2020

ISB 1442 Redirects Myeloid Cells to CD38+ Tumors Using Ichnos' Proprietary Beat[®] 2.0 Platform



BEAT[®] 2.0
(Bispecific Engagement by Antibodies based on the T-cell receptor)

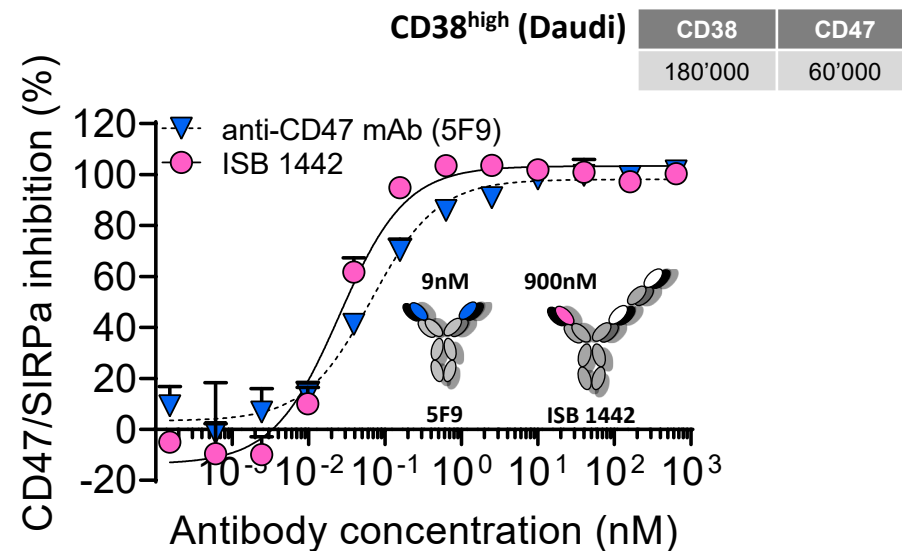
FIRST-IN-CLASS ISB 1442 KEY ATTRIBUTES

- Two high-affinity Fab arms drive binding to distinct CD38 epitopes on tumor cells
 - None of the epitopes show functional competition with daratumumab
- One Fab arm blocking CD47-SIRP α binding in cis on tumor cells to enhance ADCP
 - Increased tumor phagocytosis
 - Reduced potential for antigen sink with lower-affinity Fab binding to ubiquitous CD47
- Potent ADCC and CDC based on
 - Optimized affinity, epitope, architecture/avidity and Fc engineering
- Optimized tolerability
 - Low potential for hemagglutination, platelet aggregation

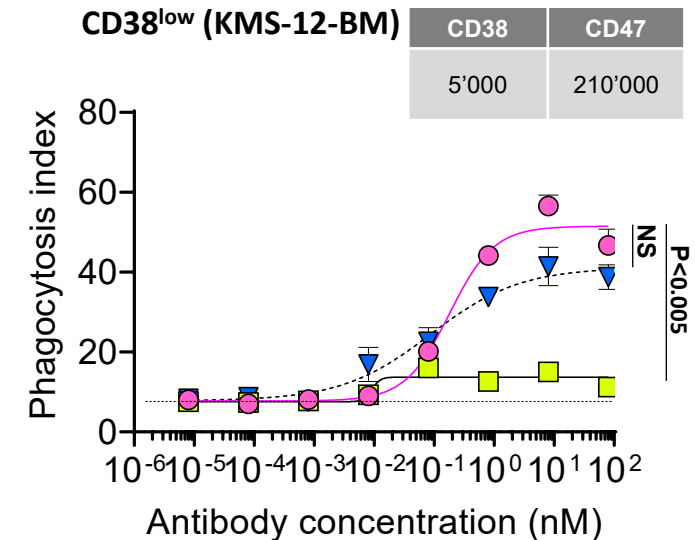
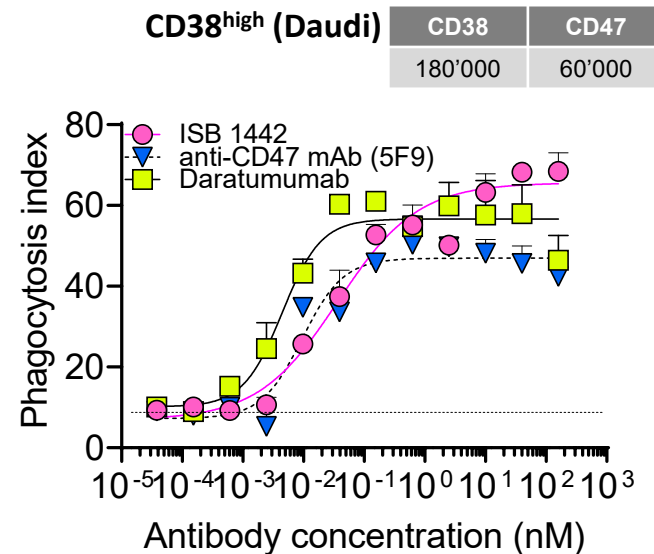
ADCP: Antibody-Dependent Cell Phagocytosis, ADCC: Antibody-Dependent Cell Cytotoxicity, CDC: Complement Dependent Cytotoxicity

ISB 1442 Efficiently Blocks CD47/SIRP α Interactions and Induces Enhanced Phagocytosis of CD38 Low-Expressing Tumor Cells Compared to Daratumumab

ISB 1442 induces comparable blockade of CD47/SIRP α interactions to that of clinical benchmark 5F9 (bivalent high affinity anti-CD47 fab arms equivalent to magrolimab).



While phagocytosis of CD38^{high} expressing tumor is comparable to that induced by benchmarks, ISB 1442 enables a significant increase in maximal phagocytosis of KMS-12-BM (CD38^{low}) tumor cells relative to that of daratumumab.

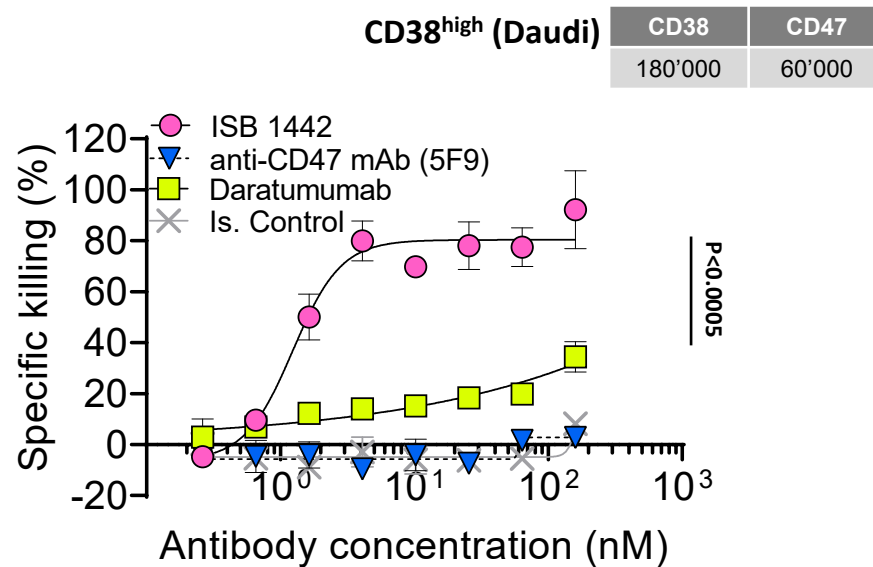


Statistics: Tukey's multiple comparison test.

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

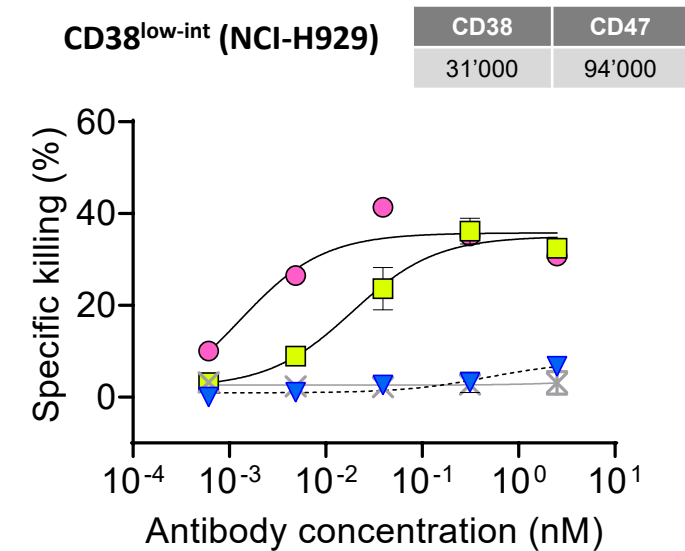
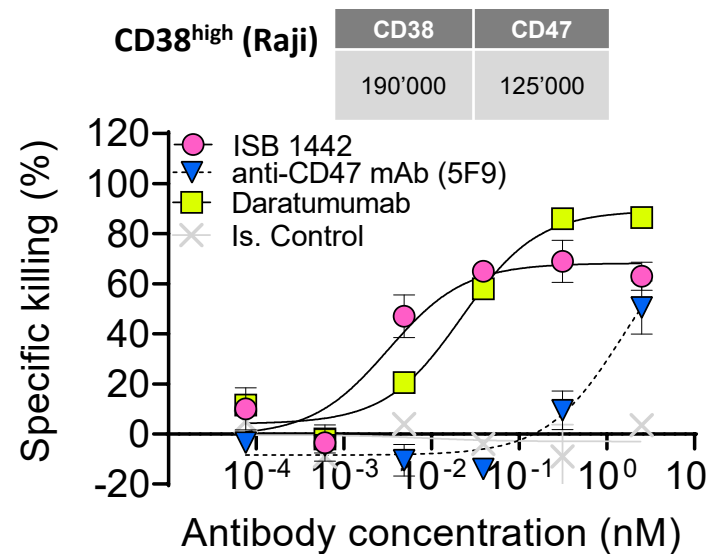
Complement Dependent Cell Cytotoxicity (CDC)

- ISB 1442 shows higher CDC of tumor cells compared to clinical benchmark daratumumab
- Results with CD38^{low} tumor cells are not shown because these cells express a high level of complement inhibitory proteins¹ and CD38 density is not sufficient to enable CDC



Antibody Dependent Cell Cytotoxicity (ADCC)

- ISB 1442 induces comparable killing of CD38^{high} expressing tumor cells to daratumumab
- In NCI-H929 tumor cells, ISB 1442 shows a lower EC50 compared to daratumumab, suggesting a higher potency in the context of CD38^{low} expression



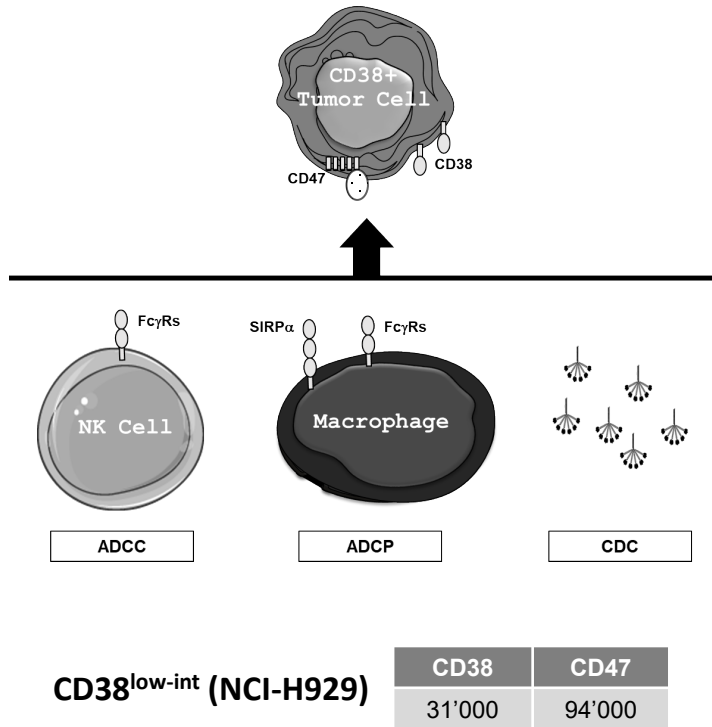
NCI-H929	EC50 (nM)	SD	P-value
ISB 1442	0.001	0.001	<0.05
Daratumumab	0.012	0.012	

¹ Nijhof I.S. et al. *Blood* 2016.

5F9 is expected to induce low/absent CDC given its IgG4 construct.
 Statistics: Tukey's multiple comparison test. EC50: Half Maximal Effective Concentration, SD: Standard deviations

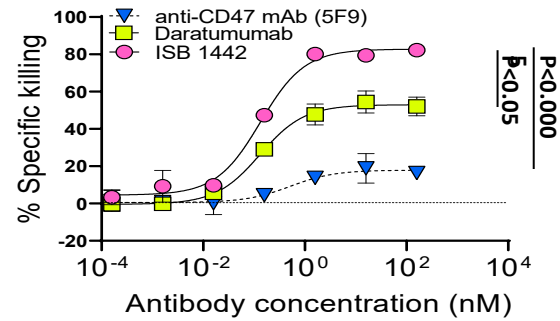
ISB 1442 Shows Superior Tumor Cell Killing In a MMoAK Assay Compared To Daratumumab and 5F9 Clinical Benchmarks and Their Combination, and Is Not Impacted by CD38 or CD47 Antigen Sink

Multiple Mode of Action of Killing (MMoAK)

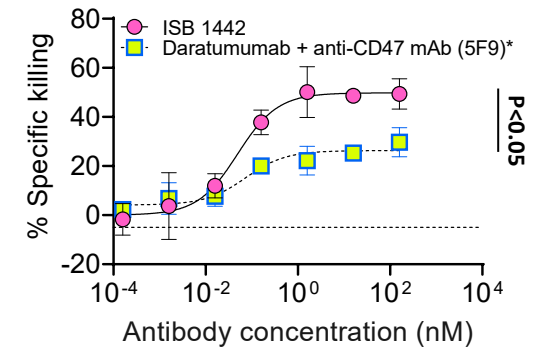


In Vitro Potency in MMoAK Assay

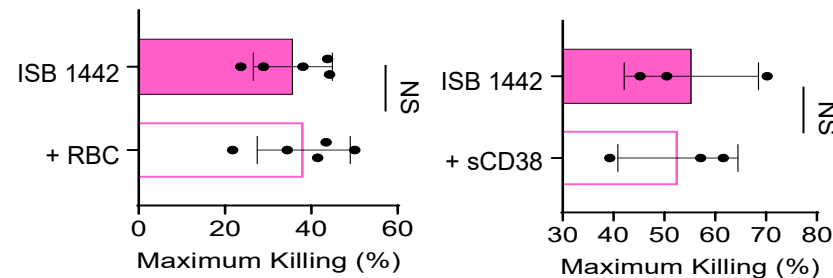
A ISB 1442 Against Benchmarks Anti-CD47 (5F9) and Daratumumab



C ISB 1442 Against Anti-CD47 (5F9) + Daratumumab Combination



B ISB 1442 Potency in the Presence of CD38 and CD47 Antigen Sink



- A. ISB 1442 induces higher killing of tumor cells in MMoAK compared to benchmarks daratumumab and anti-CD47 (5F9)
- B. ISB 1442 potency *in vitro* is not impacted by presence of CD38 and CD47 antigen sink
- C. ISB 1442 induces higher maximal killing of tumor cells compared to the combination of daratumumab and anti-CD47 (5F9)

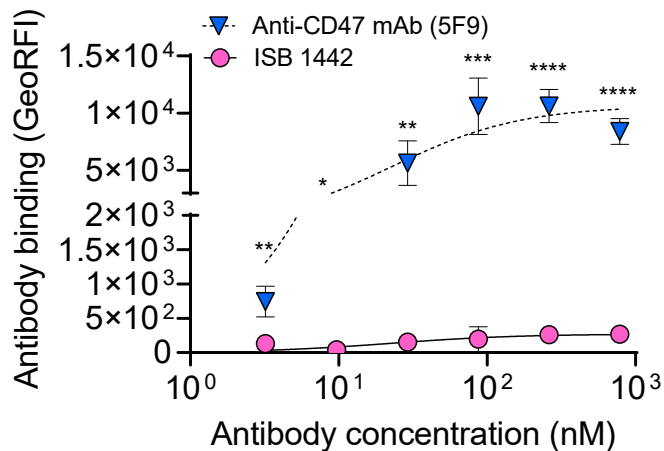
Statistics: Tukey's multiple comparison test.

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

ISB 1442 low affinity anti-CD47 Fab arm allows avidity induction binding to CD47 only upon CD38 targeting, thereby avoiding on target-off tumor binding to CD47 on RBC

Binding to Red Blood Cells (RBC)

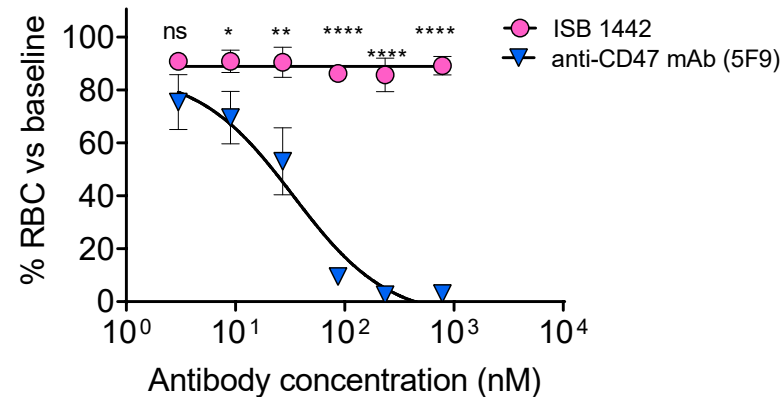
- ISB 1442 shows limited binding to RBC compared to anti-CD47 5F9 mAb



Statistics: 2-way ANOVA with multiple comparisons. P values: 0.1223 (ns), 0.0332(*), 0.0021(**), 0.0002(***), <0.0001(****).

RBC Depletion

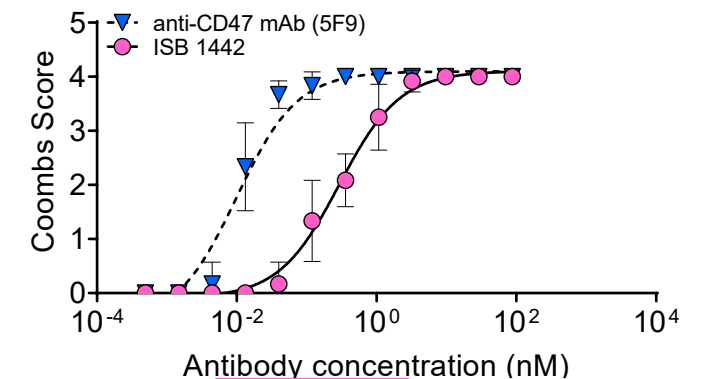
- ISB 1442 does not deplete RBC *in vitro*, unlike prominent depletion observed with anti-CD47 5F9 mAb



Statistics: 2-way ANOVA with multiple comparisons. P values: 0.00990 (ns), 0.0140 (*), 0.0022(**), <0.0001(****).

Hemagglutination (Coombs Assay)

- ISB 1442 shows higher EC50 of hemagglutination compared to that induced by anti-CD47 5F9 mAb

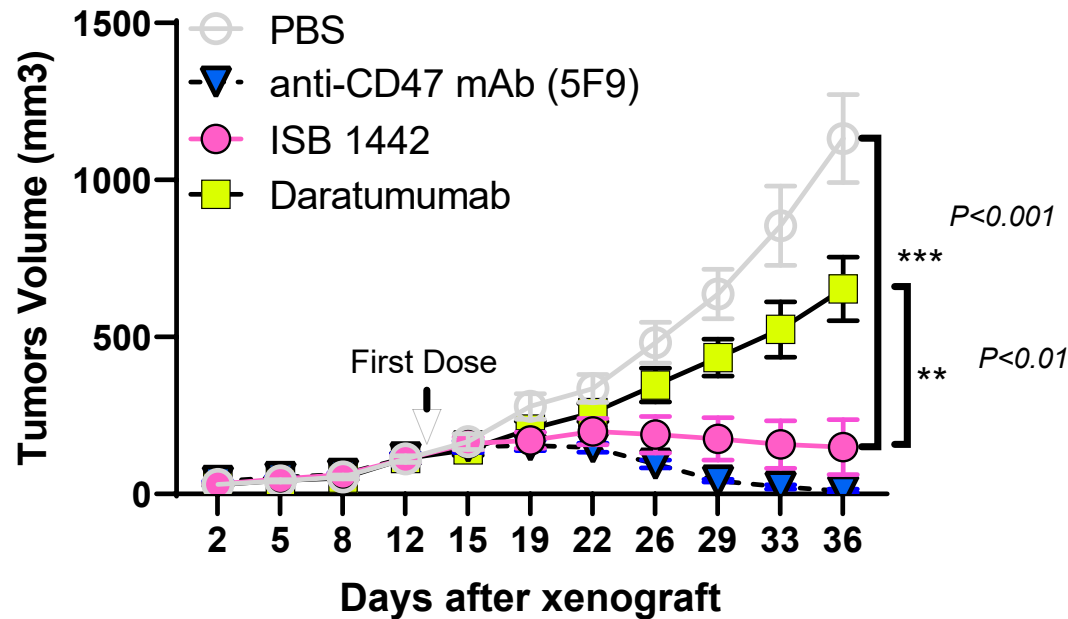


	EC50 (nM)	SD	P-value
ISB1442	0.34	0.169	<0.0001
5F9	0.01	0.004	

Statistics: Tukey's multiple comparison test
EC50: Half Maximal Effective Concentration, SD: Standard deviations

ISB 1442 Shows Improved Tumor Growth Inhibition In Preclinical Model Compared To Daratumumab

Raji model



- ISB 1442 shows higher tumor growth inhibition than daratumumab
- ISB 1442 shows comparable tumor control to that induced by high affinity anti-CD47 mAb (5F9)
- High efficacy with anti-CD47 bivalent 5F9 mAb is expected in this mouse model because anti-tumor immunity is driven by innate effectors with a strong bias to the CD47-SIRP α axis

- 10 million Raji cells were implanted subcutaneously into CB17/SCID mice.
- Animals were randomized when tumor volume reached ~100 mm³.

Doses: ISB 1442 and 5F9 (anti CD47) dosed IV QW at 10 mg/kg, Daratumumab dosed IV BIW at 16 mg/kg.

Statistics: 1-way ANOVA w. Tukey post hoc testing.

Conclusions

01

ISB 1442 represents a novel approach for the treatment of CD38+ tumors by co-targeting CD38 and CD47 in a 2+1 biparatopic bispecific antibody

04

ISB 1442 shows low on-target off-tumor binding compared to anti-CD47 mAb (5F9), potentially resulting in a better therapeutic index than anti-CD47 bivalent mAbs

02

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

05

Enrollment in the first-in-human ISB 1442 trial is expected to start in mid-2022

03

ISB 1442 shows higher tumor growth inhibition than daratumumab in CD38^{high} preclinical models

A black and white photograph of a scientist in a lab coat and gloves using a pipette in a laboratory setting. The scientist is a woman with dark hair, looking intently at the pipette tip. The background is a blurred laboratory with various pieces of equipment.

**THANK
YOU**