

ISB 1442

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

Stefano Sammicheli, et al

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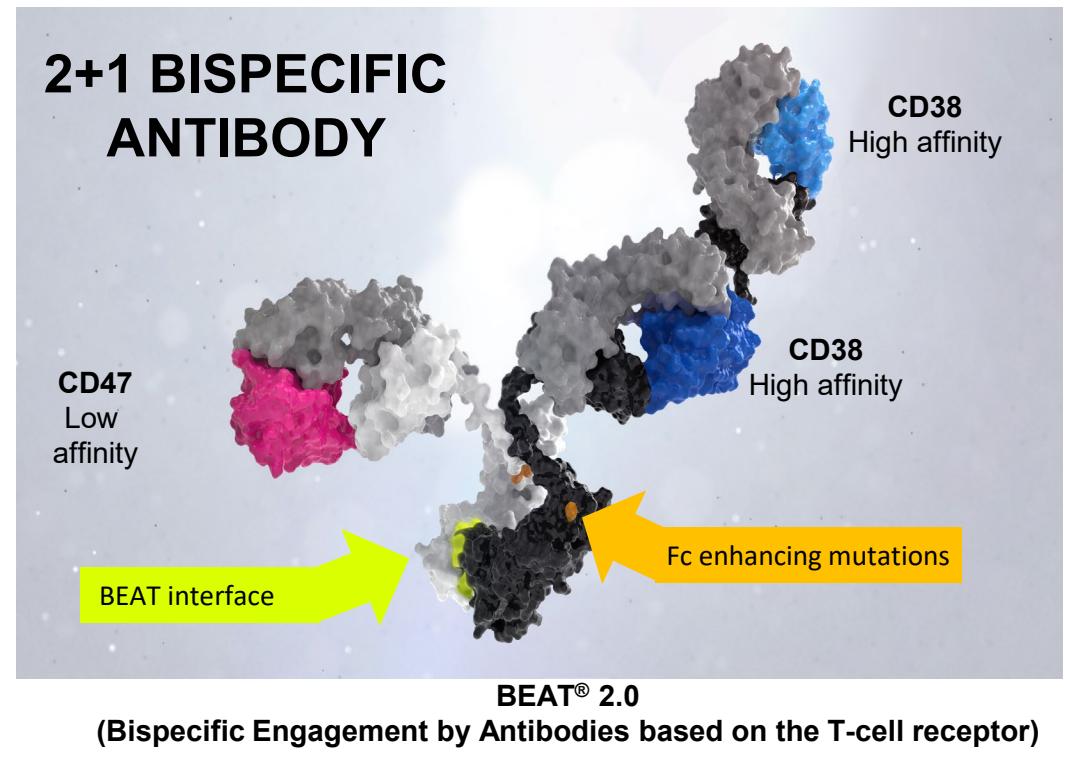
High Unmet Medical Need Remains in Patients with Relapsed / Refractory Multiple Myeloma, Despite Recent Advances in Treatment

- 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



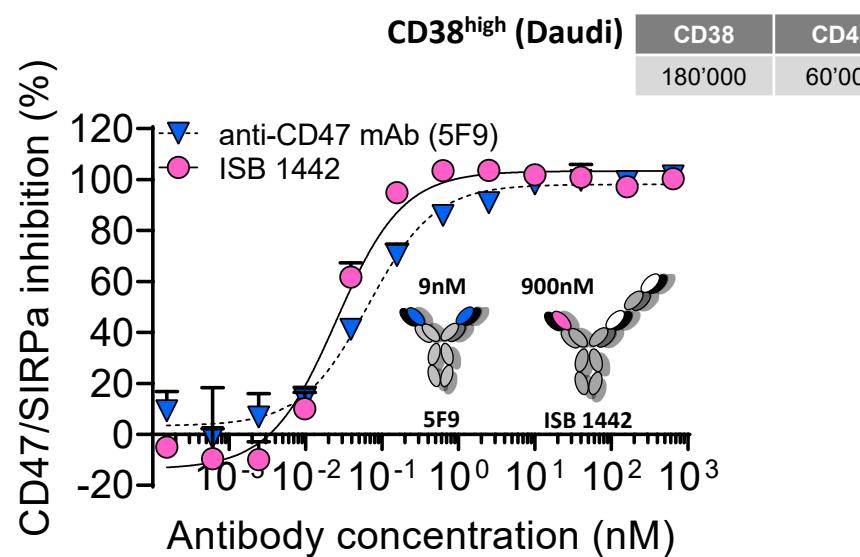
FIRST-IN-CLASS ISB 1442 KEY ATTRIBUTES

- 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

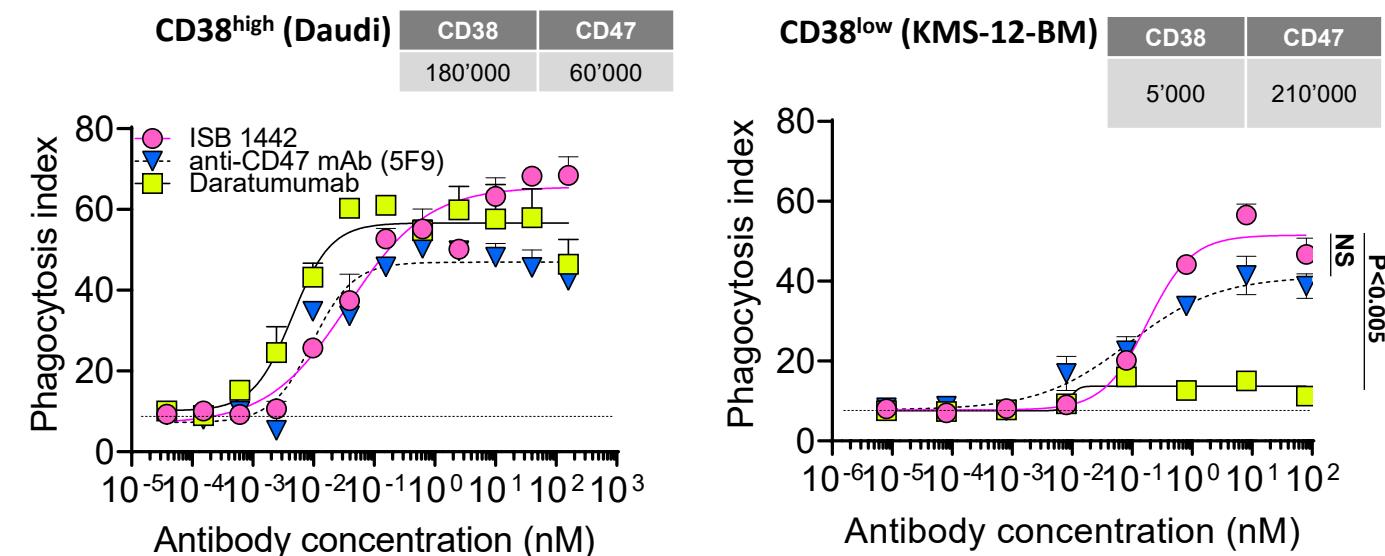
ADCP: Antibody-Dependent Cell Phagocytosis, ADCC: Antibody-Dependent Cell Cytotoxicity,
CDC: Complement Dependent Cytotoxicity

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.

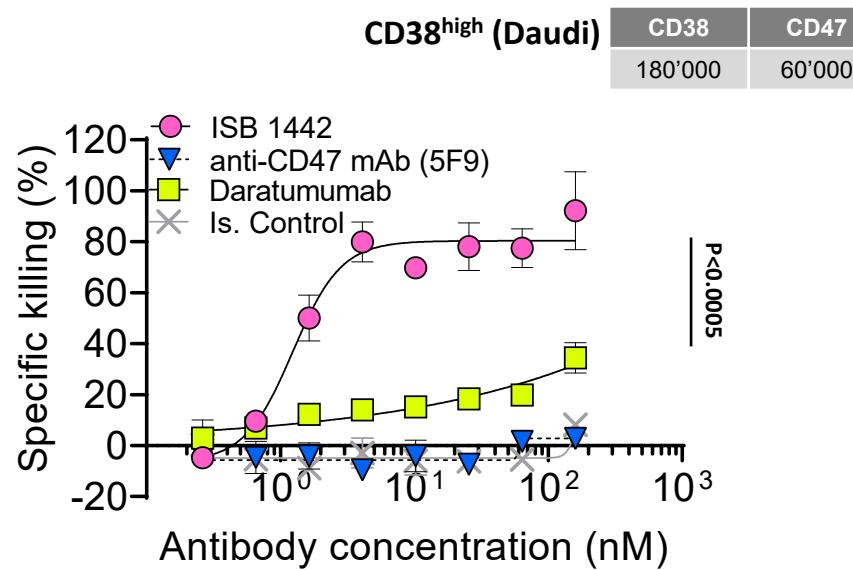


Statistics: Tukey's multiple comparison test.

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

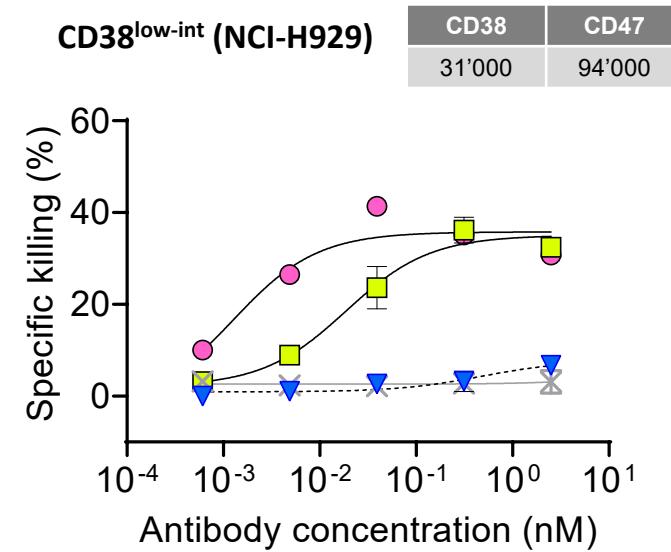
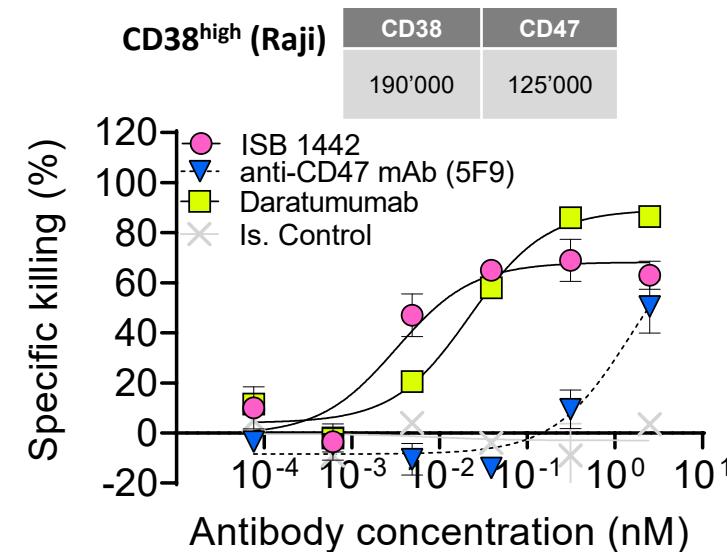
Complement Dependent Cell Cytotoxicity (CDC)

- 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

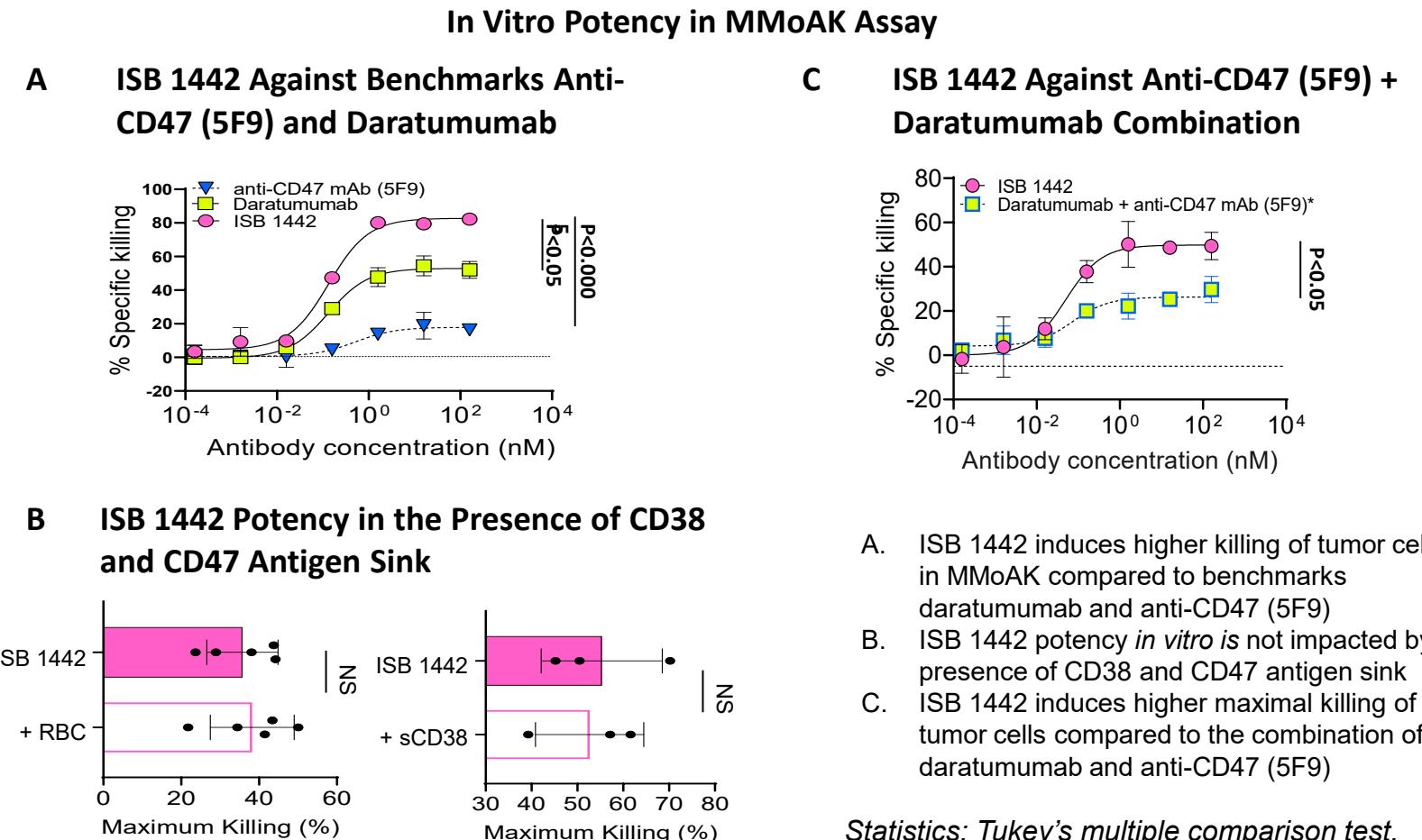
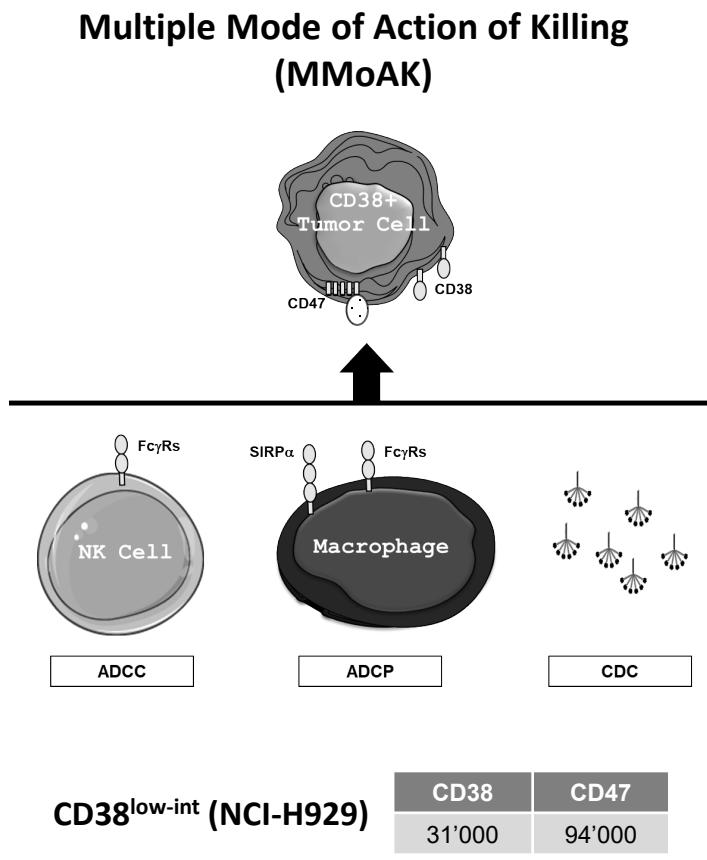


NCI-H929	EC50 (nM)	SD	P-value
ISB 1442	0.001	0.001	<0.05
Daratumumab	0.012	0.012	

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

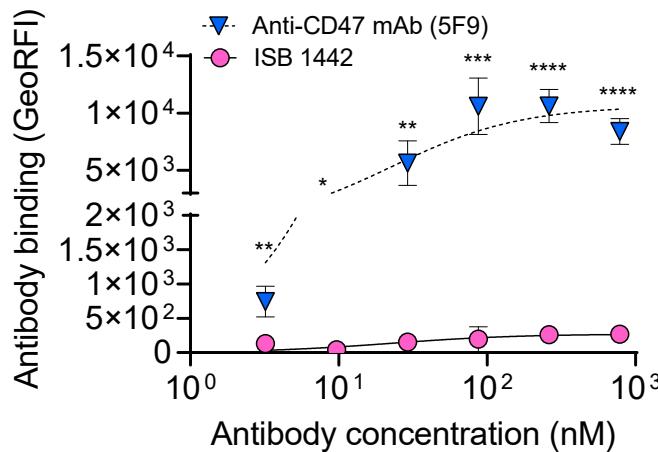


ISB 1442 Shows a More Favorable On-Target Specificity, with Reduced Binding on RBC, Hemagglutination and RBC Depletion Compared to Anti-CD47 Monoclonal 5F9 Antibody

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)

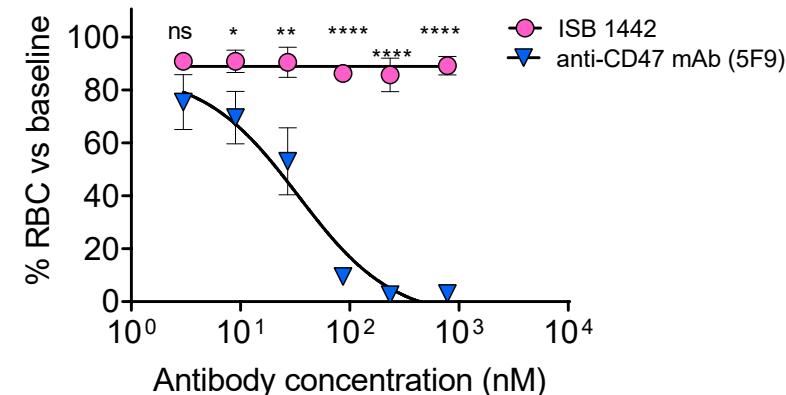
- ISB 1442 shows limited binding to RBC compared to anti-CD47 5F9 mAb



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

RBC Depletion

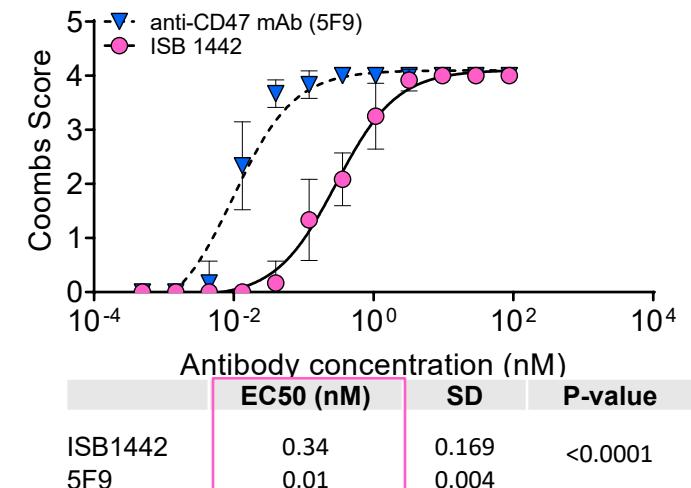
- ISB 1442 does not deplete RBC *in vitro*, unlike prominent depletion observed with anti-CD47 5F9 mAb



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

Hemagglutination (Coombs Assay)

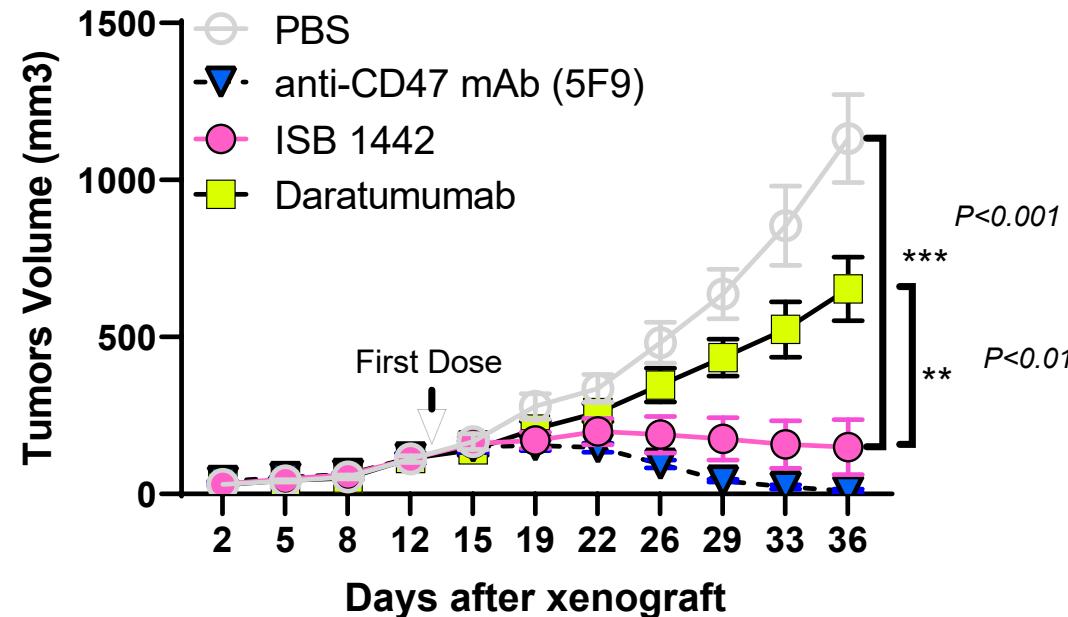
- ISB 1442 shows higher EC50 of hemagglutination compared to that induced by anti-CD47 5F9 mAb



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

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

03

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

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

05

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



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