ISB 2001, A FIRST-IN-CLASS TRISPECIFIC BCMA AND CD38 T CELL ENGAGER DESIGNED TO OVERCOME MECHANISMS OF ESCAPE FROM TREATMENTS FOR MULTIPLE MYELOMA BY TARGETING TWO ANTIGENS

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PRESENTED AT THE 64TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING
NEW ORLEANS, LA | DECEMBER 10, 2022

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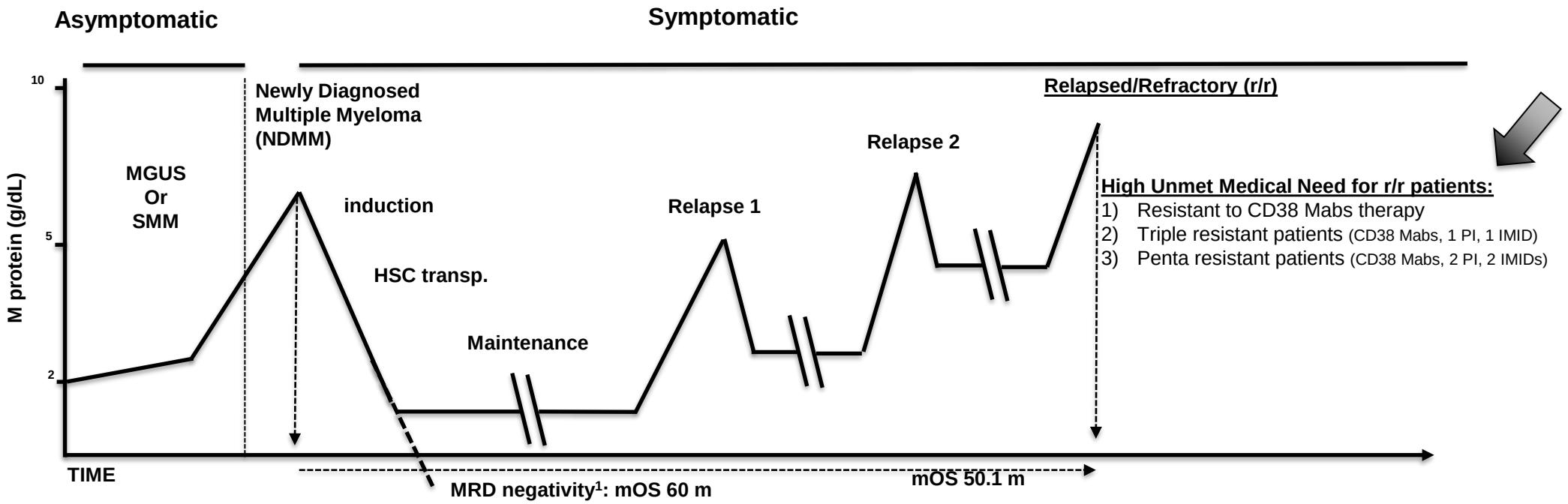
Treatment Paradigm: High Unmet Medical Need Remains in Patients with Relapsed/Refractory Multiple Myeloma (RR MM)



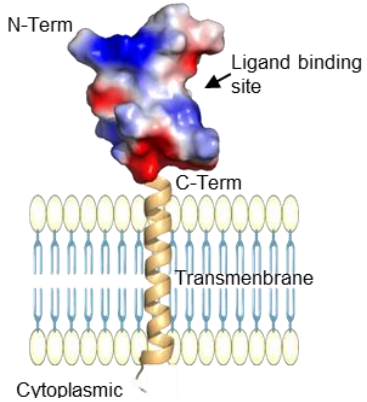
Treatment for Relapsed/Refractory Setting

Previous therapeutic treatment for r/r MM
Post CD38 MAbs therapy2: mOS 8.6 months
Recently approved immunotherapy treatment for r/r MM

Teclistamab (BCMAxCD3)3: mOS 18.3 months
Ide-cel (BCMA CAR-T)4: mOS 19.4 months

ISB 2001 (BCMA X CD38 X CD3): First TREAT™ Trispecific Antibody for R/R MM

BCMA



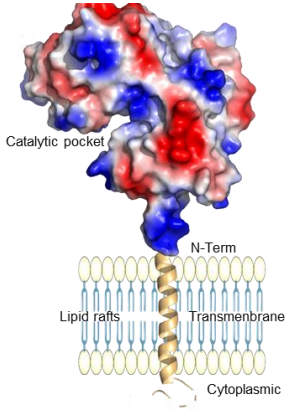
BCMA is a member of the TNFR superfamily

PROS[8]: Validated target, recently approved for BCMA-targeting CAR T (Ide-cel[9]) and TCE (teclistamab[10])

CONS: High concentration of shed BCMA in the blood may interfere with efficacy1[11], [12], [13]

RESISTANCE MECHANISMS:
1) Downregulated upon therapy[14,15,16,17]

CD38



CD38 is a receptor for CD31 and an ectoenzyme with NADase activity[5]

PROS: Validated target, high expression on MM cells

CONS: Also expressed at lower levels on healthy cells

RESISTANCE MECHANISMS
1) Downregulated upon therapy[6,7]

Targeting two antigens on MM cells may overcome mechanisms of antigen escape.

TNFR: tumor necrosis factor receptor
TCE: T cell engager
CAR-T: chimeric antigen receptor;
BCMA: B cell maturation antigen

[5]*Morandi F. et al. Front. Imm. 2018*
[6]*Saltarella I. et al. Cells 2020*
[7]*Nijhof, I. S. et al. Blood 2016*
[8]*Shah N et. al. Leukemia 2020*
[9]*Usmani SZ et. al. Lancet 2021*
[10]*Moreau P et. al. NEJM 2022*
[11]*Sanchez et. al. BMJ 2012*
[12] *Pillarisetti et. al. Blood 2020*
[13]*Chen H et. al. Leuk Res. 2019*
[14]*Cohen et. al. JCI 2019*
[15]*Brudno et. al. JCO 2018*
[16]*Ali et. al. Blood 2016*
[17]*Green et. al. Blood 2018*

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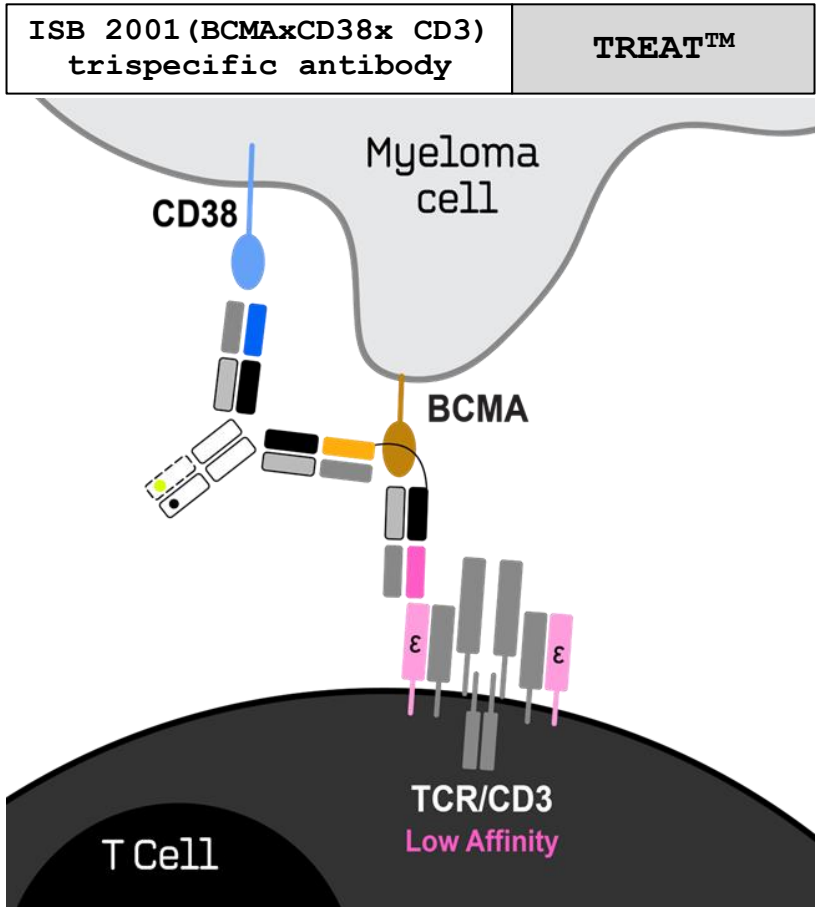
ISB 2001 (BCMA X CD38 X CD3): First TREAT™ Trispecific Antibody for R/R MM



KEY ATTRIBUTES

- Three proprietary fragment antigen-binding arms: CD3ε on T cells; BCMA and CD38 on MM cells
- Heterodimerisation based on the BEAT® platform in a TREAT™ format
- Binding arms derived from synthetic phage display library with common light chain (Vκ3-15 + IgκJ1)
- Increased binding specificity to MM cells due to enhanced avidity-based binding of the two TAA binders
- IND-enabling studies are ongoing, and a first-in-human study is expected to start in 2023

TREAT™: Trispecific Engagement by Antibodies based on the TCR
BEAT®: Bispecific Engagement by Antibodies based on the TCR

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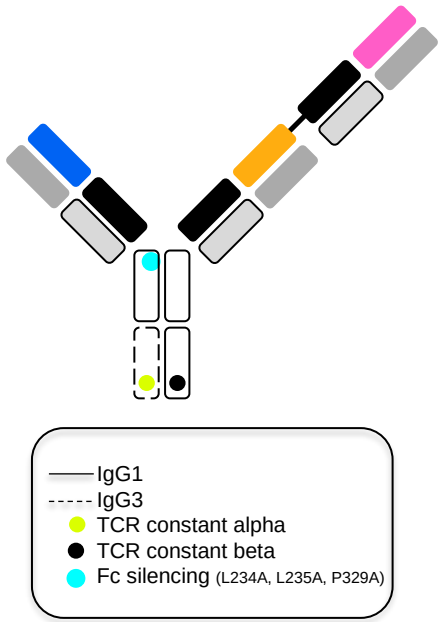
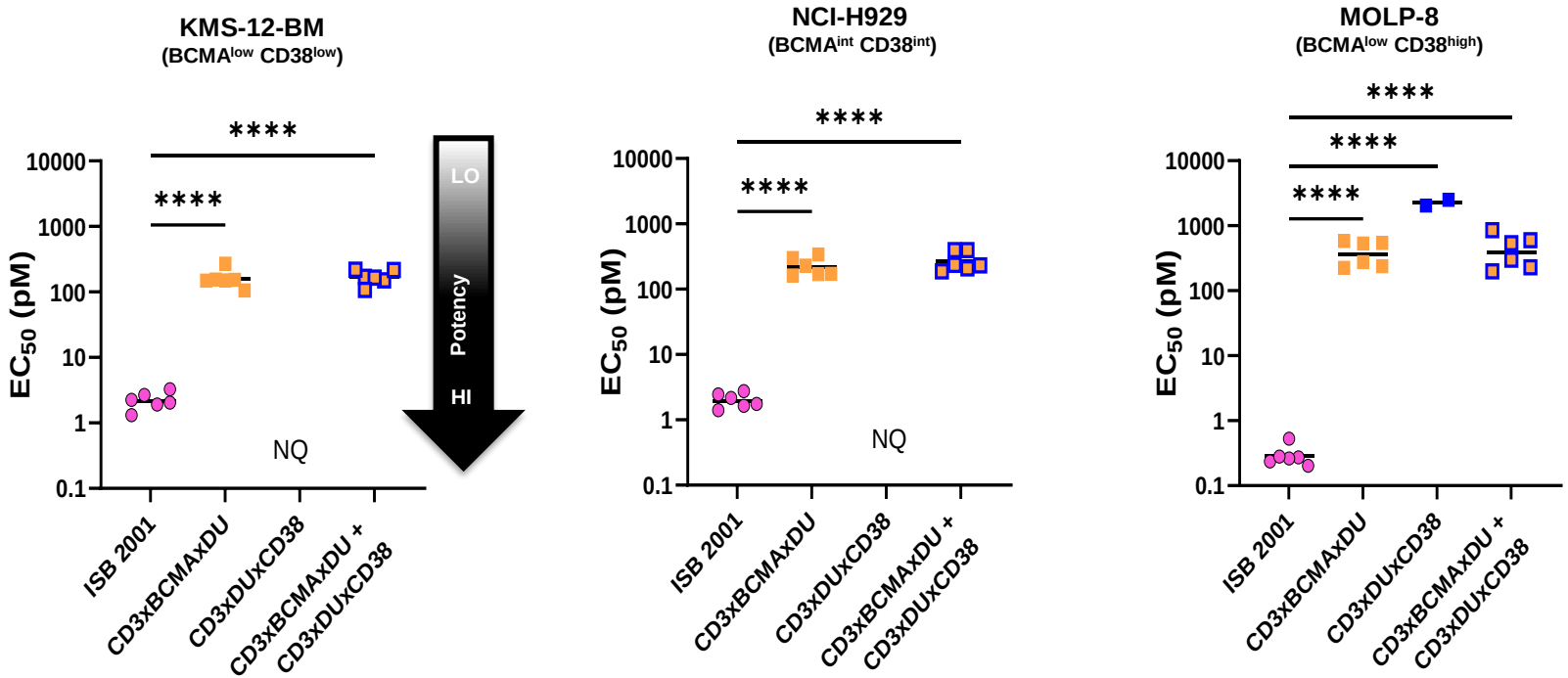
ISB 2001 Designed to Mediate Potent MM Cell Killing via Dual Targeting Avidity-Driven Tumor Binding





Expression sABC	CD38 mean	BCMA mean
KMS-12-BM	28 000	9 000
NCI-H929	85 000	52 000
MOLP-8	512 000	3 200

**=p <0.01
***= p <0.001
****= p <0.0001

NQ: Not Quantifiable
DU: Dummy (irrelevant binder)

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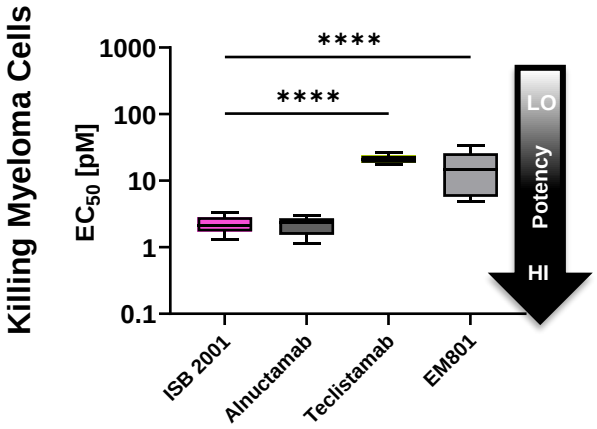
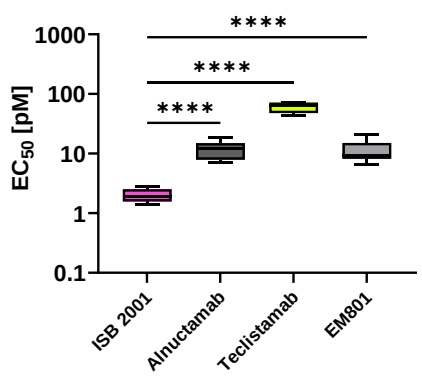
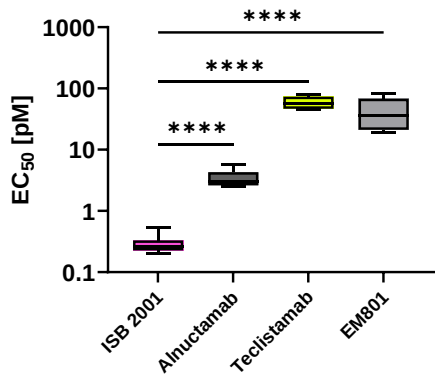
ISB 2001 Possesses the Highest Cytotoxic Potency on Myeloma Cell lines with Low to Intermediate Expression of BCMA Compared to Benchmarks

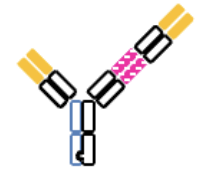




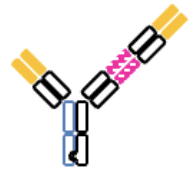


TECLISTAMAB
IgG4 LALA

ALNUCTAMAB
IgG1 PG-LALA



EM-801
IgG1 PG-LALA



ISB 2001
IgG1 PA-LALA

CD3 VH or VL

BCMA VH or VL

CD38 VH or VL

**=p <0.01
***= p <0.001
****= p <0.0001

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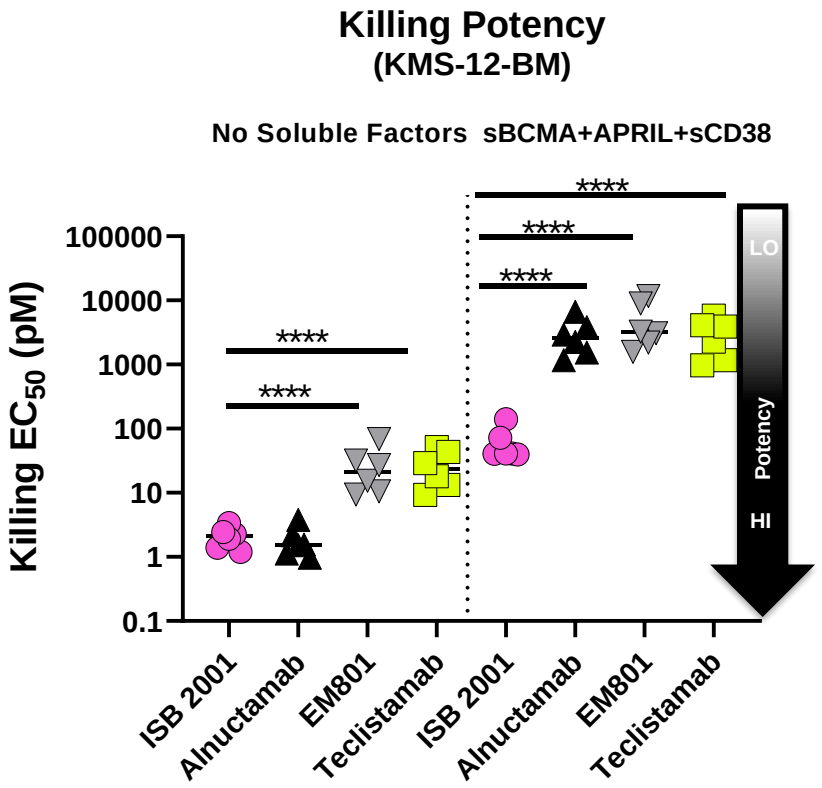
ISB 2001 Potency is Less Affected by the Presence of Soluble Factors Compared to BCMA-Specific T-Cell Engager Benchmarks



Tumor Killing EC_{50} (pM)	ISB 2001	Alnuctamab	EM801	Teclistamab
No Soluble Factors	2.1	1.9	27.1	27.4
sBCMA+APRIL+sCD38	62.5	3059.7	5144.1	3037.6
Fold Difference (sEC50/EC50)	**30**	**1647**	**190**	**111**

**=p <0.01
***= p <0.001
****= p <0.0001

Each dot represents a single donor.
Bar shows the mean of the data by samples.
Paired one-way ANOVA shows differences between the treatments and those were then compared using Tukey HSD post Hoc comparison.

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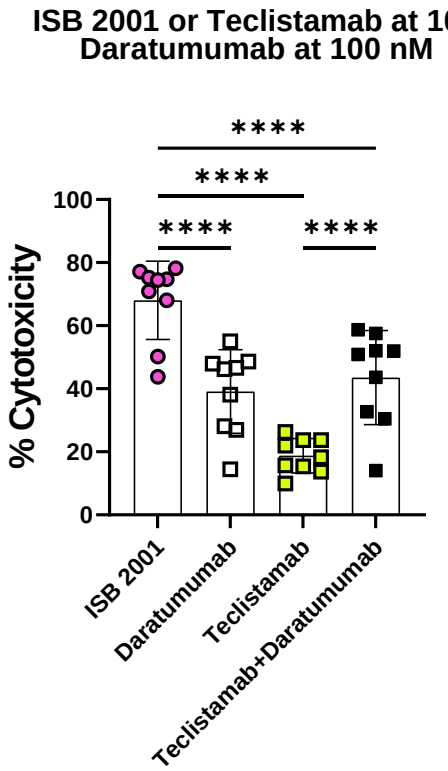
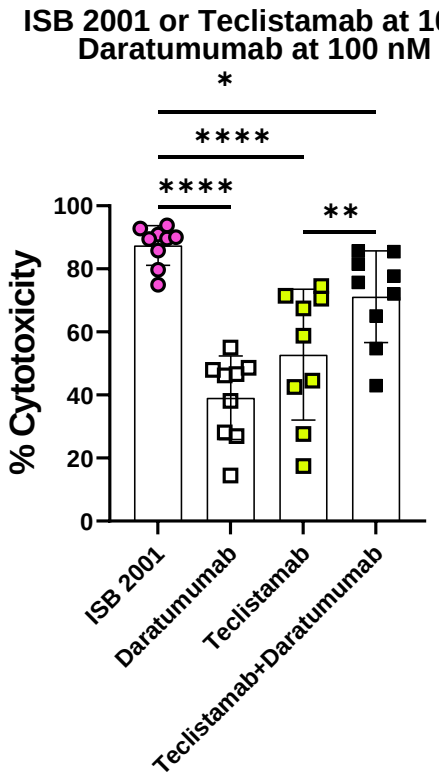
ISB 2001 Potency Is Superior to the Combo of Teclistamab + Daratumumab





MMoAK assay of tumor cell line KMS-12-BM. The tumor cells were incubated for 48 hours with human PBMCs from healthy donors at a 5:1 effector to target ratio. 10 pM or 100 pM of ISB2001, teclistamab in the presence of 100 nM of daratumumab were added to the culture. The percentage of cytotoxicity are displayed.

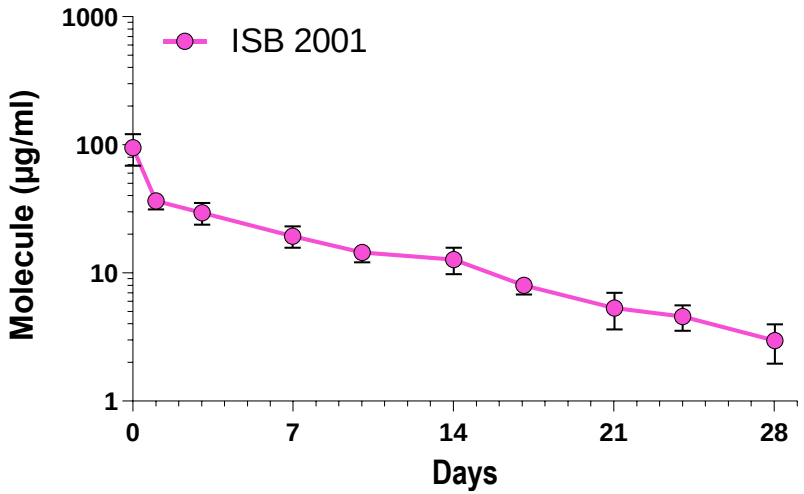
*=p <0.05
**=p <0.01
***= p <0.001
****= p <0.0001

Paired one-way ANOVA followed by Tukey's multiple comparisons test

ISB 2001 Exhibits Desirable PK and Enables 100% Complete Responses *in vivo* in a BCMA^{low} and CD38^{low} MM Model

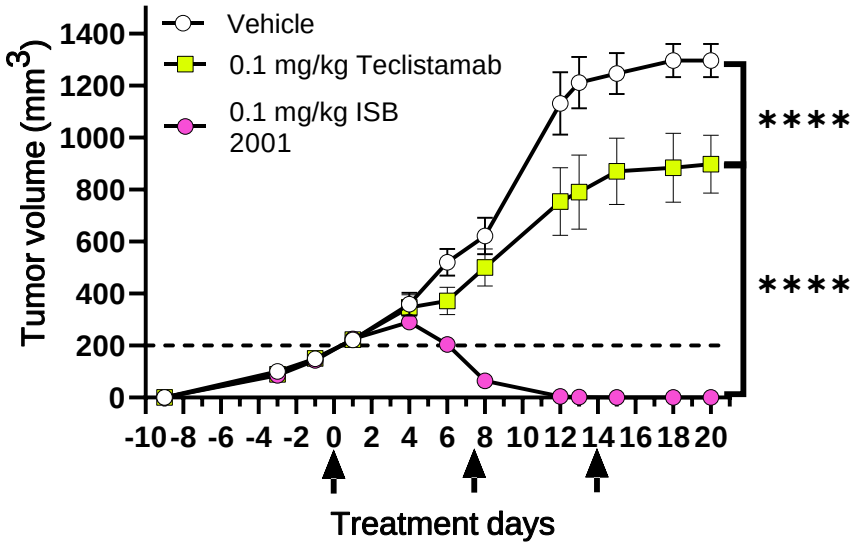
ISB 2001 Half-Life in Tg32 (huFcRn Tg) Mice

Pharmacokinetic 5 mg/kg single dose i.v.



Molecule	Half-Life (days)	Cmax (µg/ml)	AUC (µg.days/ml)
ISB 2001	**7.6** ± 0.9	**95** ± 26	**417** ± 75

Efficacy in NSG-PBMC transfer Mouse Model (KMS-12-BM)



Treatment	Complete Response
Teclistamab	**0%** (0/8 mice)
ISB 2001	**100%** (8/8 mice)

**=p <0.01
***= p <0.001
****= p <0.0001

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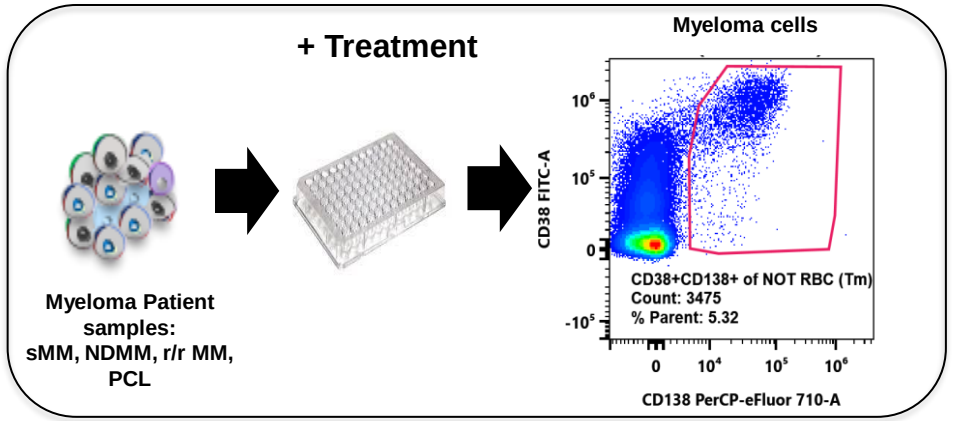
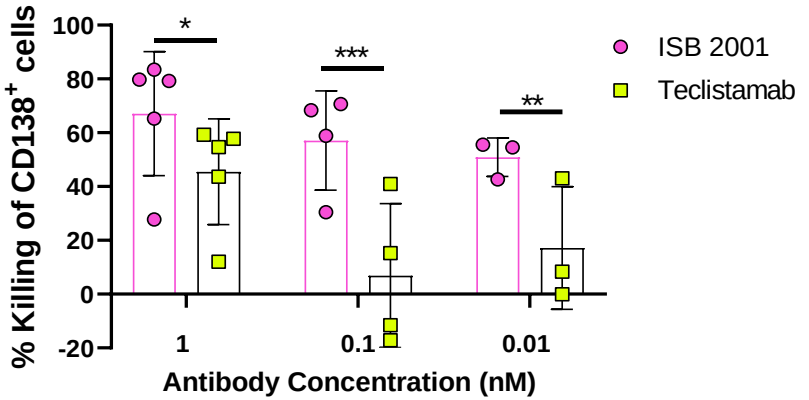
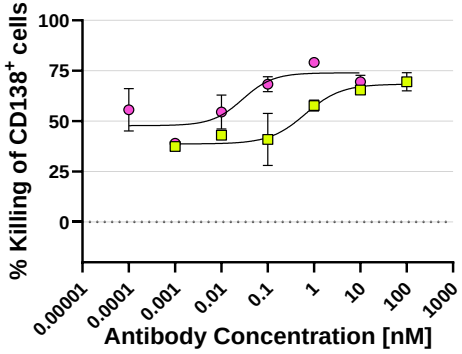
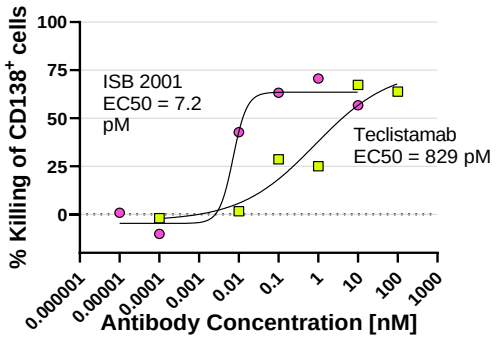
ISB 2001 Exhibits Higher Potency ex vivo Compared to Teclistamab on MM Patient Samples

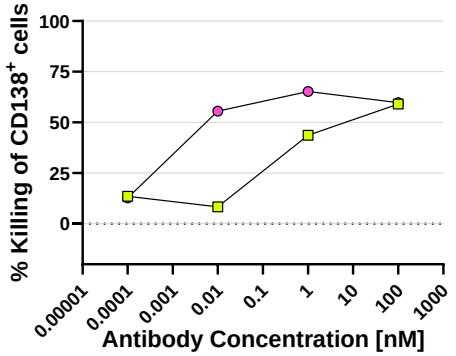


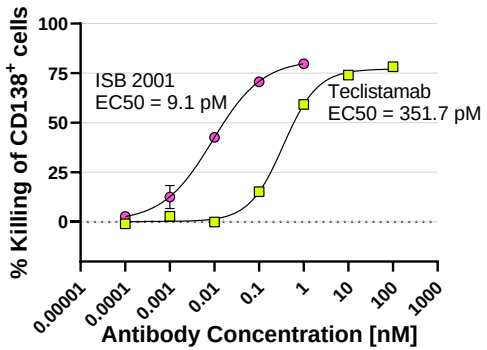


Smoldering MM → **Newly Diagnosed MM** → **r/r MM** → **Plasma Cell Leukemia**









*=p <0.05
**=p <0.01
***= p <0.001
****= p <0.0001

sMM: Smoldering Multiple Myeloma
NDMM: Newly Diagnosed Multiple Myeloma
r/r MM: Relapsed Refractory Multiple Myeloma
PCL: Plasma Cell Leukemia

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Conclusions: ISB 2001 Potential in Treatment of Multiple Myeloma

- Increased killing of tumor cells across variable levels of expression of both BCMA and CD38 compared to teclistamab, alnuctamab and EM-801
- Minimally affected by soluble factors (sCD38, sBCMA, APRIL) when compared to teclistamab, alnuctamab and EM-801, ensuring tumor killing potency is maintained
- Increased potency in vitro when compared to combination of daratumumab and teclistamab
- Demonstrates a half-life of more than 7 days in Tg32 mice, suggesting acceptable dosing regimen in clinic
- Superior potency relative to teclistamab, results in 100% complete remission in MM in vivo models
- Superior cytotoxicity over teclistamab in ex vivo assays in patient bone marrow aspirates
- The CTN and IND filing is planned for Q1 2023. Phase 1 is planned to initiate before mid-2023