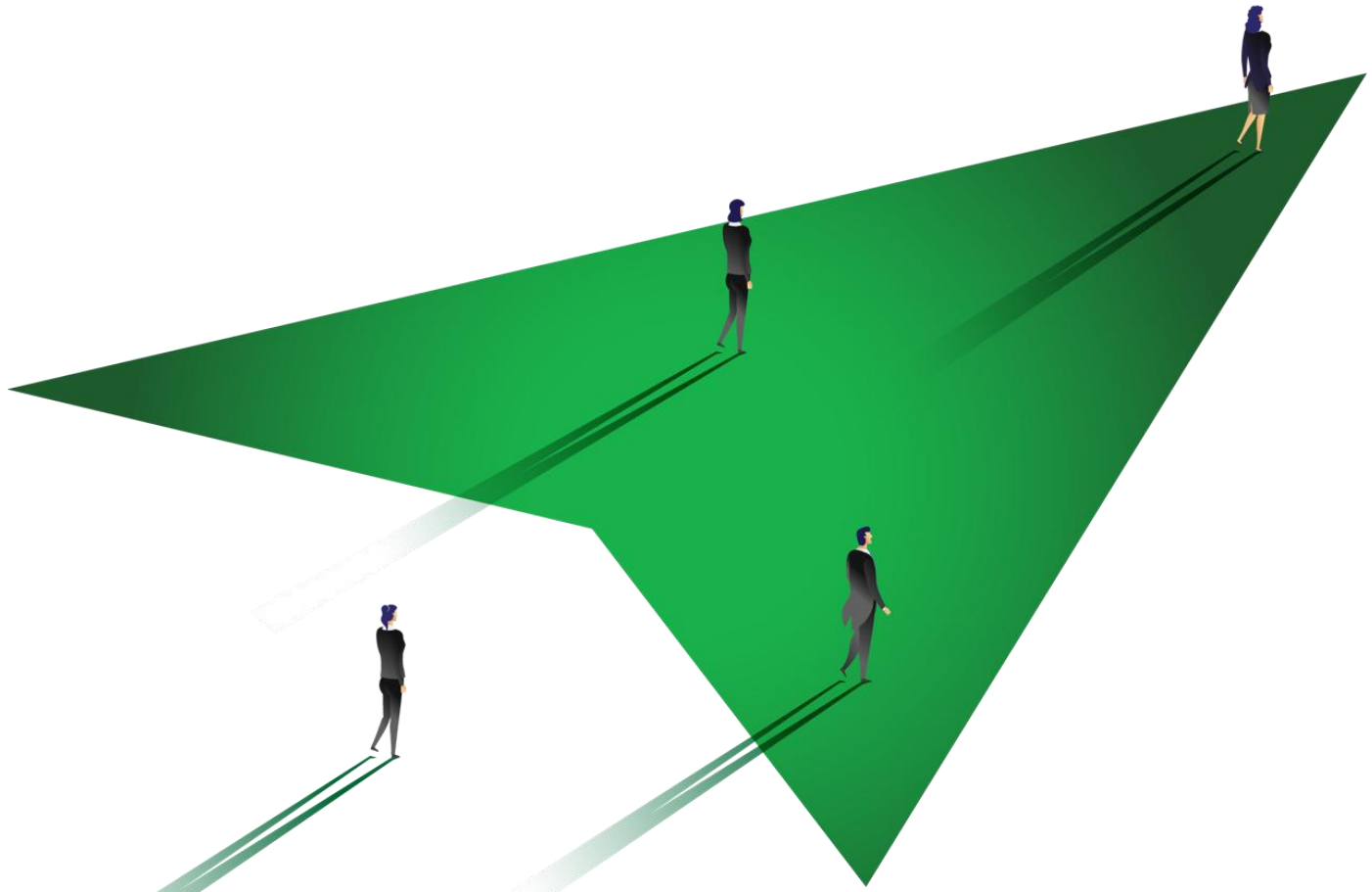
ISB 2001, a First-in-Class Trispecific BCMA and CD38 T Cell Engager Designed to Overcome Mechanisms of Escape from Multiple Myeloma Treatments

ICHNOS GLENMARK INNOVATION

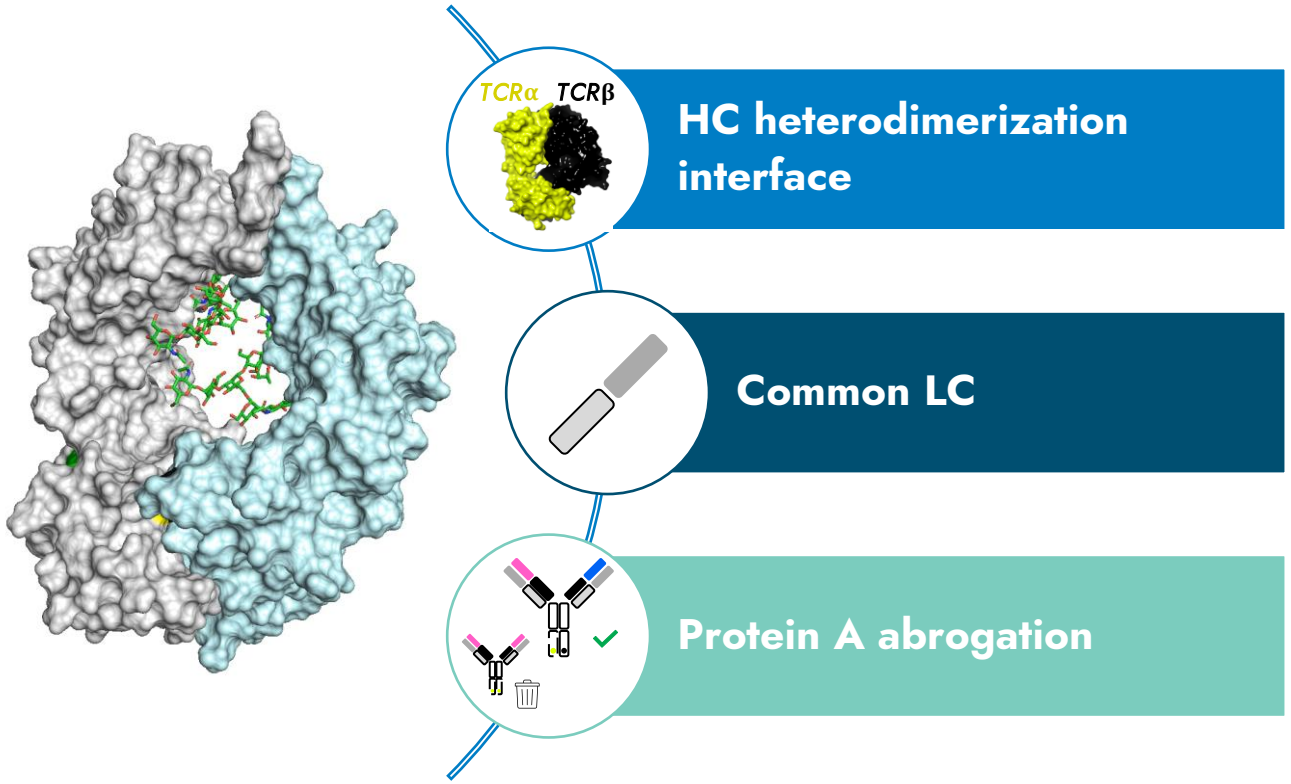


Mario Perro, PhD
Head of Biologics Research,
SVP

Antibody Engineering & therapeutic, Basel, 2025

IGI multi-specific platform: Combining TCR interface-based HC Pairing and cLC Technologies to simplify development of multispecific Antibodies

3 Pillars of the BEAT® platform

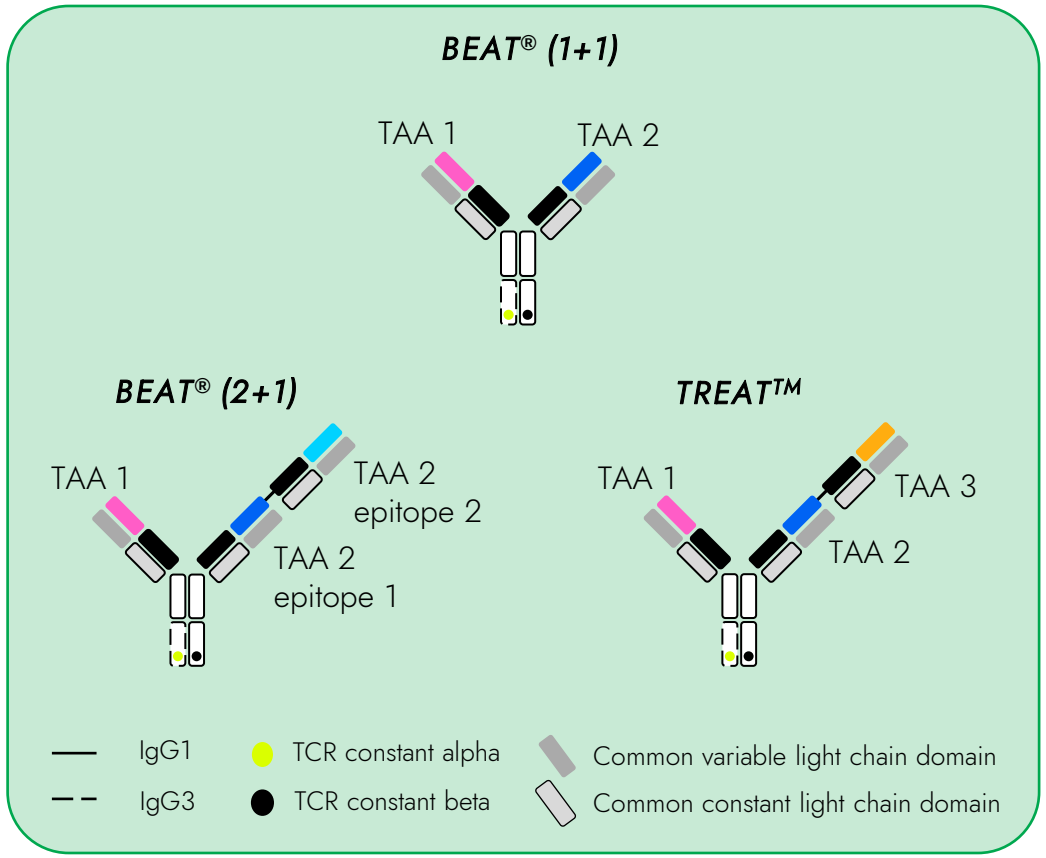


Model based on the PDB 4N0U and 1HZH
Residues shaded in grey: BEAT chain A
Residues shaded in blue: BEAT chain B
Residues shaded in green: protein A abrogation site in BEAT chain A

Residues shaded in yellow: TCR constant alpha
Residues shaded in black: TCR constant beta
Sticks represent glycans

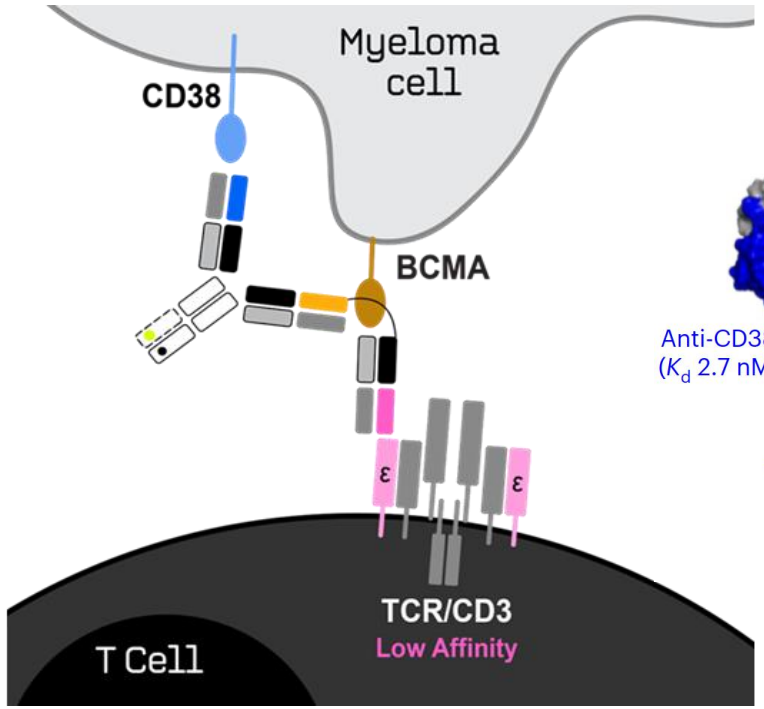
Proprietary ***plug-and-play modular platform***

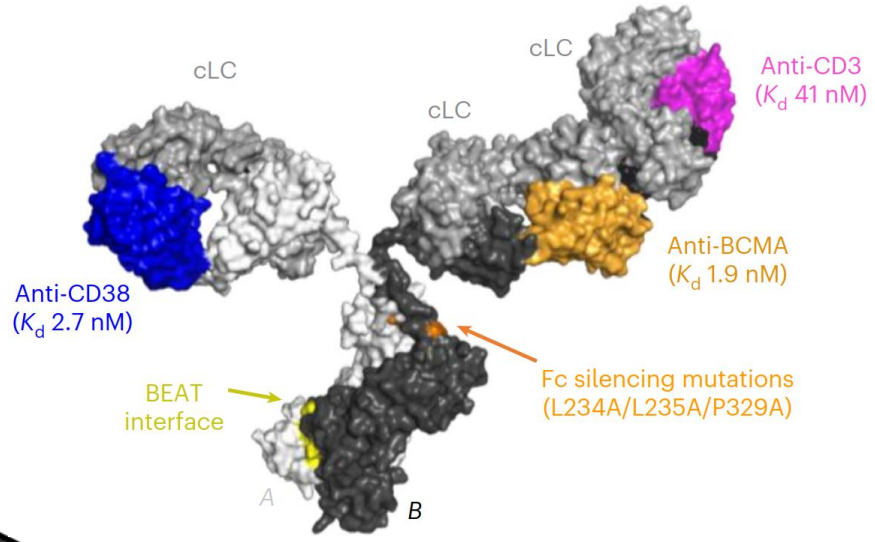
enables a plurality of multi specific configurations



Skegro D. et al. J Biol Chem 2017; 292(23):9745-59
Stutz C. and Blein S. J Biol Chem 2020; 295(28): 9392-9408

ISB 2001 (BCMAxCD38xCD3): First TREAT TM Trispecific Antibody for Relapsed/Refractory Multiple Myeloma





Key Attributes

Generated using IGI's proprietary BEAT® protein platform

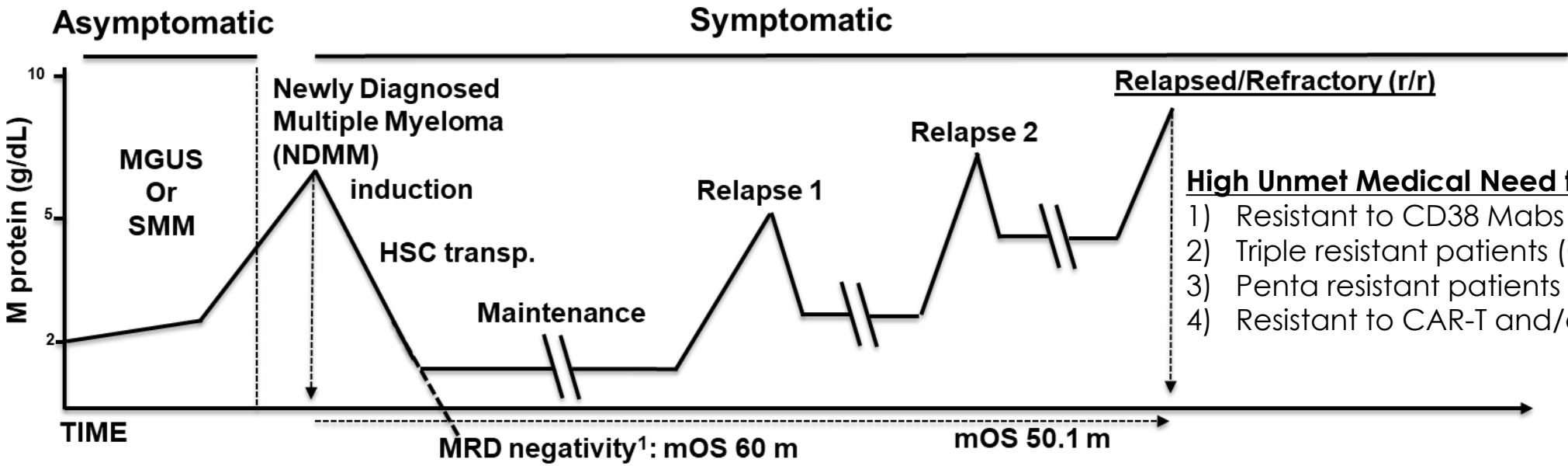
Enhanced avidity-based binding to myeloma cells with both BCMA and CD38 Fab domains

CD38 Fab domain targets non-overlapping epitopes with Daratumumab

Tuned BCMA>CD38>CD3 binding affinity and distal positioning of the CD38 vs CD3 binders drive potent tumor killing while minimizing CD38-related off-tumor adverse events

TREAT ™, Trispecific Engagement by Antibodies based on the TCR; BEAT®, Bispecific Engagement by Antibodies based on the TCR
Carretero-Iglesia L, et al. *Nat Cancer.* 2024 Oct;5(10):1494-1514. DOI

Treatment Paradigm: High Unmet Medical Need Remains In Patients With Relapsed/Refractory Multiple Myeloma (r/r MM)



High Unmet Medical Need for r/r patients:

1) Resistant to CD38 Mabs therapy
2) Triple resistant patients (CD38 Mabs, 1 PI, 1 IMID)
3) Penta resistant patients (CD38 Mabs, 2 PI, 2 IMIDs)
4) Resistant to CAR-T and/or TCE (NEW)

Previous therapeutic treatment for r/r MM

- Post CD38 MAbs therapy[2]: mOS 8.6 months

Approved immunotherapy treatment for r/r MM

- Ide-cel (BCMA CAR-T)[3]: mOS 19.4 months
- Teclistamab (BCMAxCD3)[4]: mOS 18.3 months
- Elranatamab (BCMAxCD3)[5]: ORR 61%, mOS not reached at 15 months
- Talquetamab (GPRC5DxCD3)[6]: ORR 70%, mOS not reached at 12 months

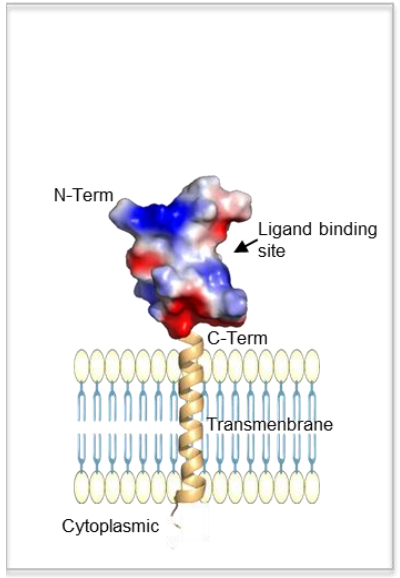
M protein: myeloma protein
MGUS: Monoclonal gammopathy of undetermined significance
sMM: smoldering multiple myeloma

HSC: hematopoietic stem cell transplantation
mOS: median overall survival
m: months

1) Munshi N. C. Et al Blood Adv 2020
2) Gandhi UH et al. Leukemia 2019
3) Munshi, N. C. et al. 384, 705–716 (2021)
4) Moreau, P. et al. NEJM (2022)
5) Lesokhin A.M. Et al. Nature medicine (2023
6) Schinke C et al. ASCO 2023

ISB 2001 Targets Validated Antigens For Immunotherapy: Pros, Cons, Resistance Mechanisms And Evaluated Models

BCMA

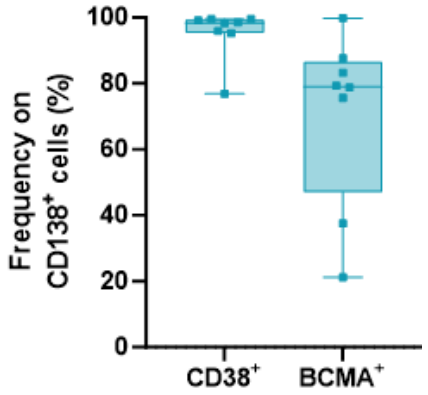


BCMA is a member of the TNFR superfamily

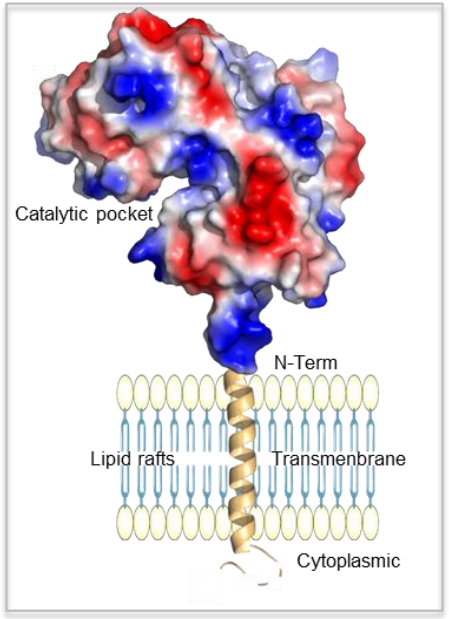
Pros[1]: Validated target, recently approved for BCMA-targeting CAR T (Ide-cel[2]) and TCE (teclistamab[3])

Cons: High concentration of shed BCMA in the blood may interfere with efficacy[4, 5, 6]

Resistance Mechanisms:
1) Downregulated upon therapy [7,8,9,10]
2) Heterogeneity of expression



CD38



CD38 is a receptor for CD31 and an ectoenzyme with NADase activity[11]

Pros: Validated target, high expression on MM cells

Cons: Also expressed at lower levels on healthy cells

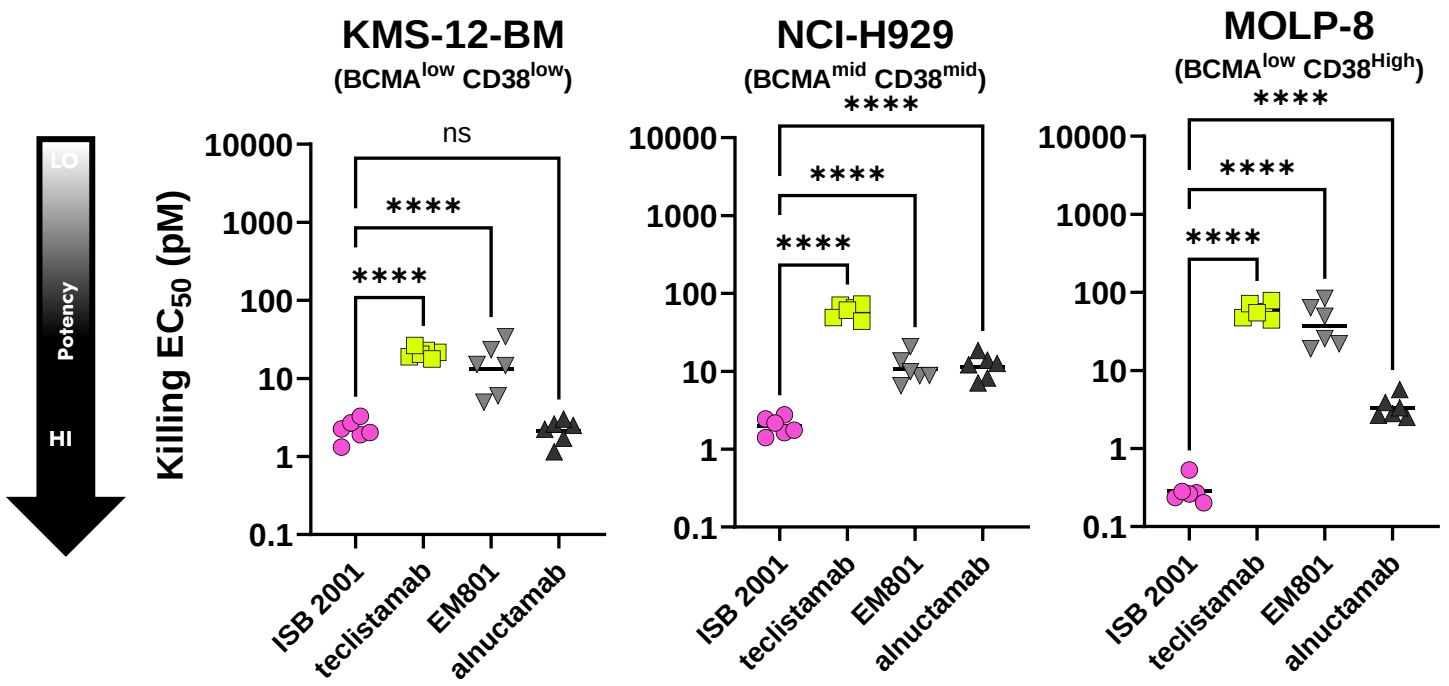
Resistance Mechanisms:
1) Downregulated upon therapy[12,13]

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

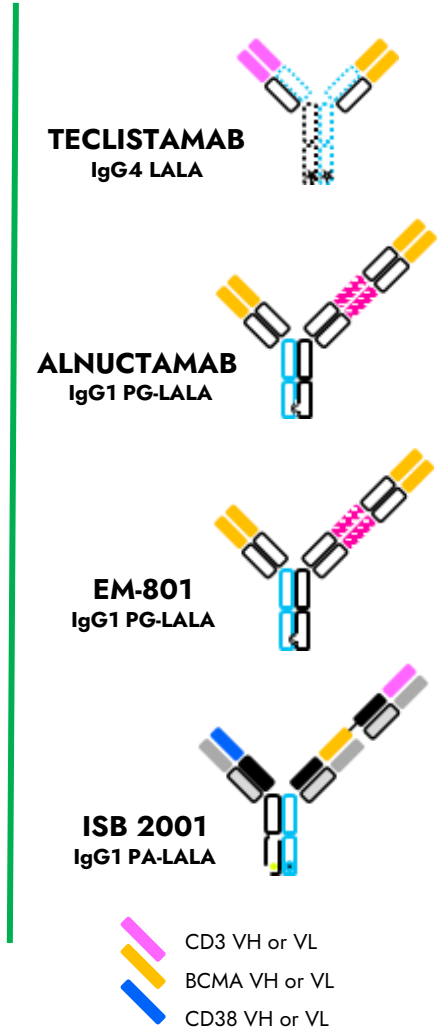
Mario Perro,
AE&T Basel 2025

1) Shah N et al Leukemia 2020
2) Usmani SZ et al. Lancet 2021
3) Moreau P et a. NEJM 2022
4) Sanchez et al. BMJ 2012;
5) Pillarisetti et al. Blood 2020
6) Chen H et al Leuk Res. 2019
7) Cohen et al. JCI 2019
8) Brudno et al. JCO 2018
9) Ali et al. Blood 2016
10) Green et al. Blood 2018
11) Morandi F. et al Front. Imm. 2018
12) Saltarella I. et al. Cells 2020
13) Nijhof, I. S. et al. Blood 2016

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



Expression sABC	CD38 expression (sABC)	BCMA expression (sABC)	Clinical case modelling
KMS-12-BM	**LOW** 28000	**LOW** 9000	Post treatment with daratumumab + teclistamab
NCI-H929	**MID** 85000	**MID** 52000	Newly Diagnosed or post IMIDs + PI
MOLP-8	**HIGH** 512000	**VERY LOW** 3200	Post BCMA targeted therapy



****= p <0.0001

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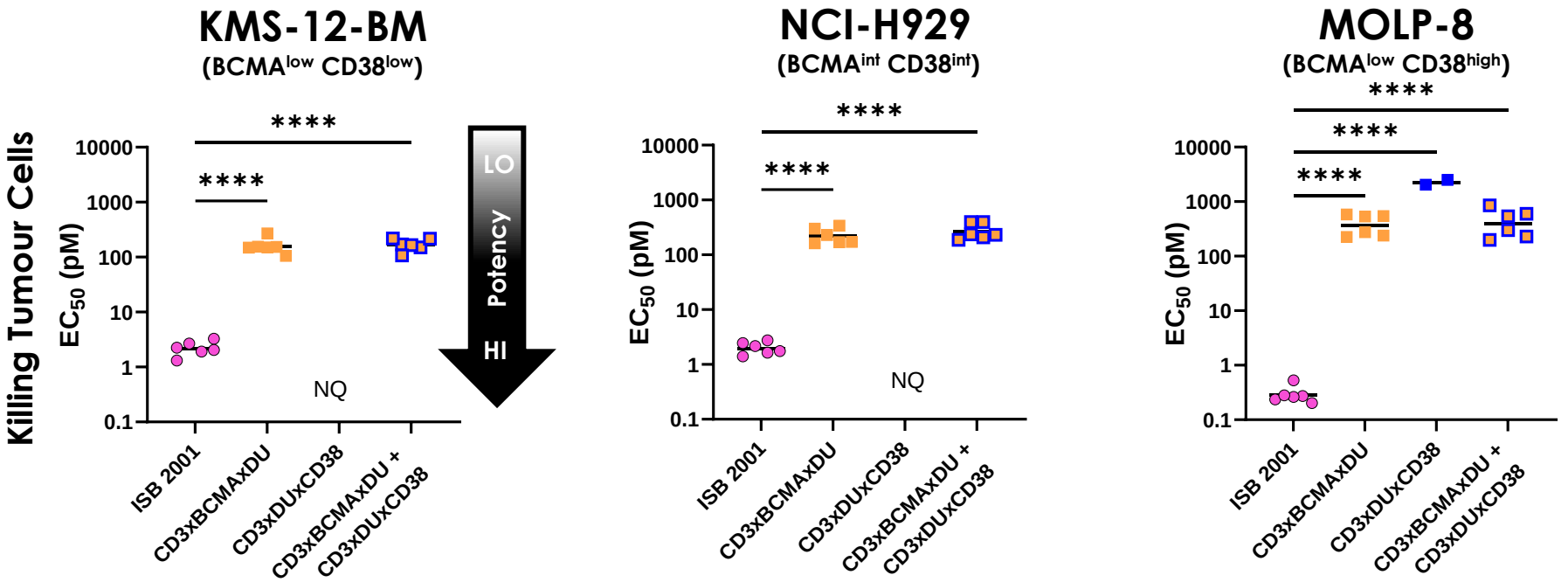
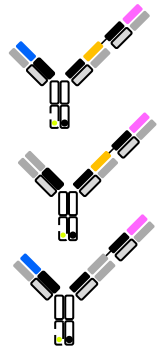
Carretero-Iglesia L. et al. Nature Cancer 2024

ISB 2001 Mediates Potent Killing of MM Tumor cells Expressing Different Levels of BCMA and CD38 via Dual Targeting Avidity-Driven Tumor Binding





ISB 2001

CD3xBCMAxDU

CD3xDUxCD38

Expression sABC	CD38 expression (sABC)	BCMA expression (sABC)	Clinical case modelling
KMS-12-BM	**LOW** 28,000	**LOW** 9,000	Post treatment with daratumumab + teclistamab
NCI-H929	**MID** 85,000	**MID** 52,000	Newly Diagnosed or post IMIDs + PI
MOLP-8	**HIGH** 512,000	**VERY LOW** 3,200	Post BCMA targeted therapy

sABC: Specific Antigen binding capacity .

Each dot represents one donor measurement of EC50

NQ: not quantifiable; DU: Dummy (irrelevant binder);

****= p <0.0001

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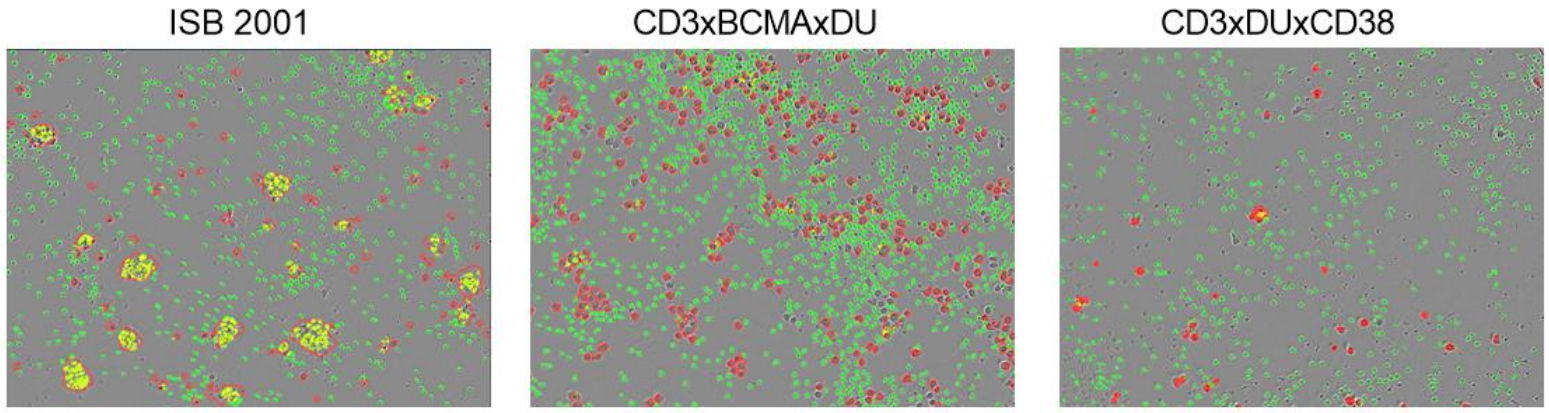
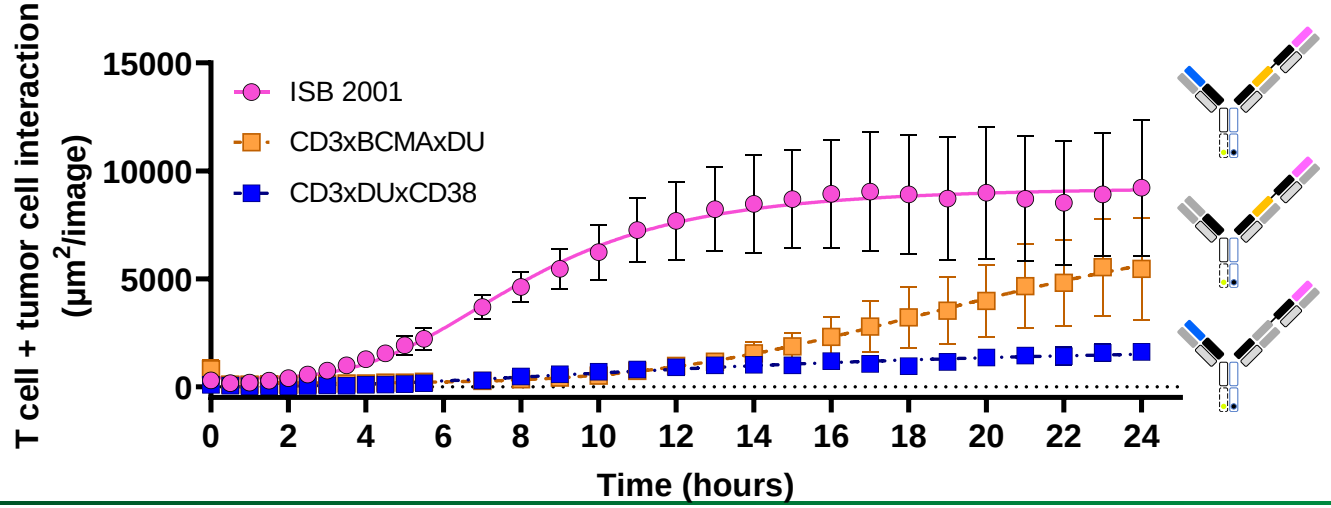
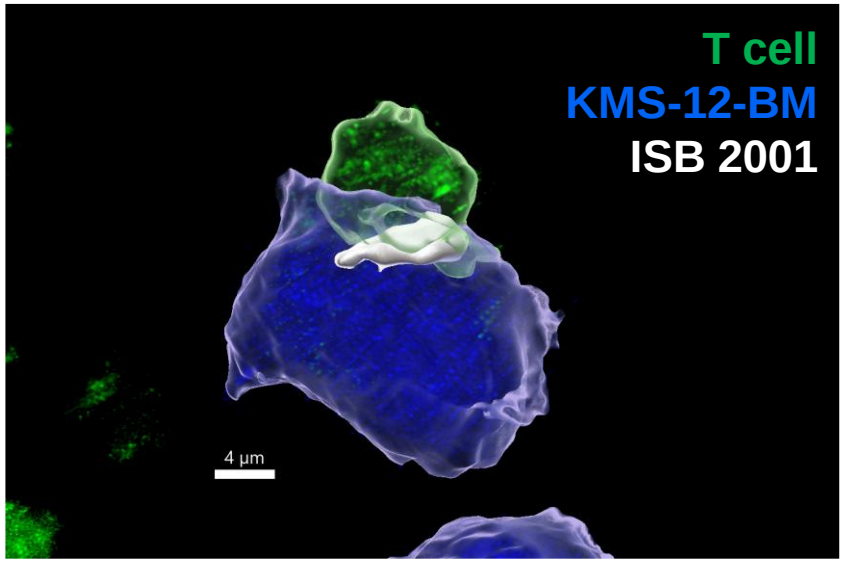
ISB 2001 induces strong and stable synapses



Incucyte live imaging, representative image at 18h with 2 nM of each molecule.



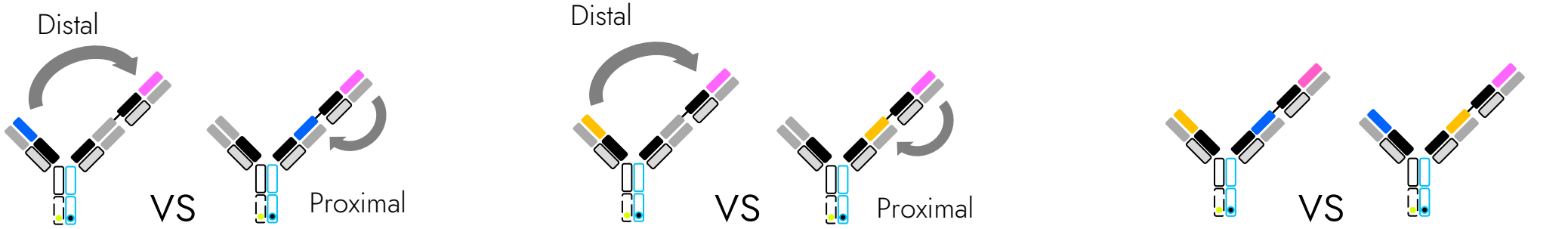
ISB 2001 is enriched in the synapse between T cells and MM cell line



Confocal microscopy representative image.

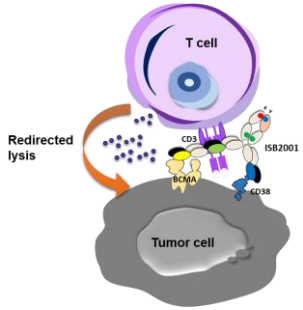
Carretero-Iglesia L. et al. Nature Cancer 2024

Generation of Control Molecules to Evaluate Relationship between Architecture and Functionality of the Trispecific Antibody ISB 2001

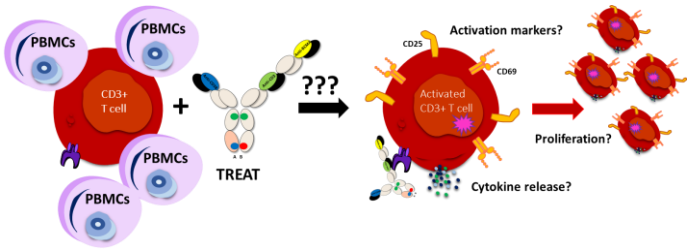


CD3xDUxCD38 CD3xCD38xDU CD3xDUxBCMA CD3xBCMAxDU CD3xCD38xBCMA ***ISB 2001*** CD3xBCMAxCD38

Tumor cytotoxic potency
Redirected lysis assay

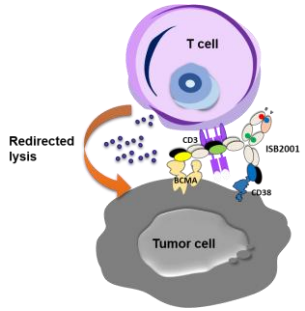


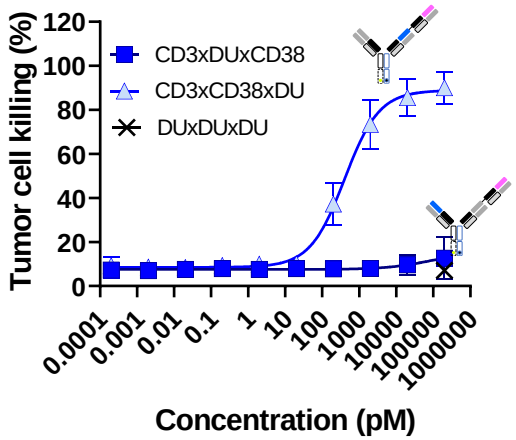
On-target off-tumor T-cell activation
HD-PBMC assay

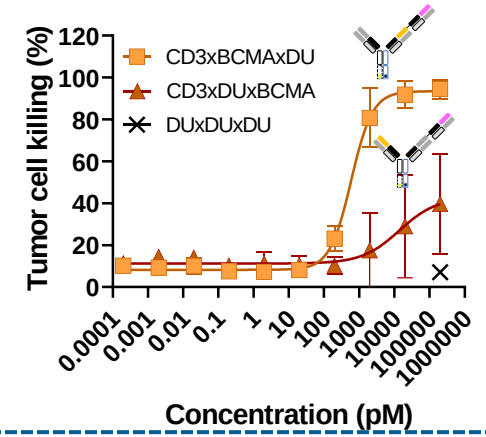


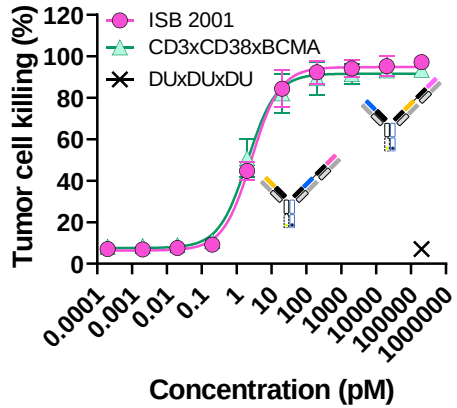
The Geometry of ISB 2001 Drives Strong Cytotoxicity while preserving a good on-target/off-tumour profile

Cytotoxic potency

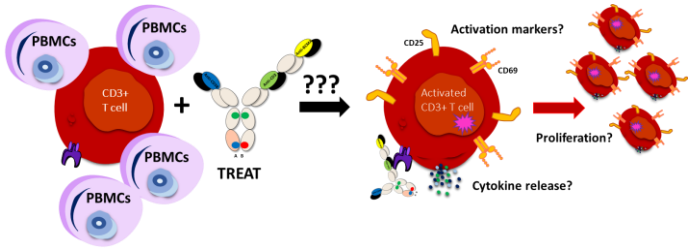


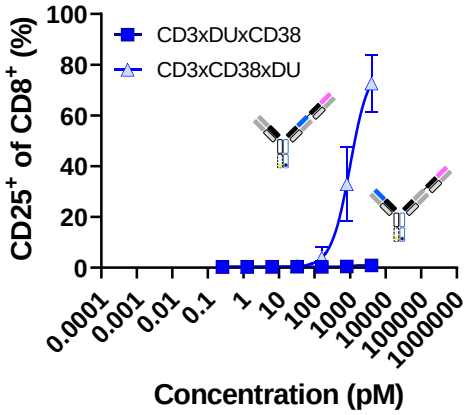


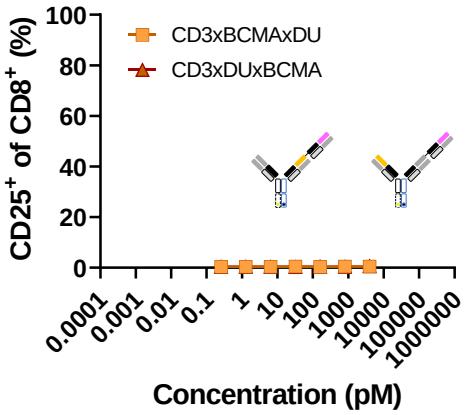


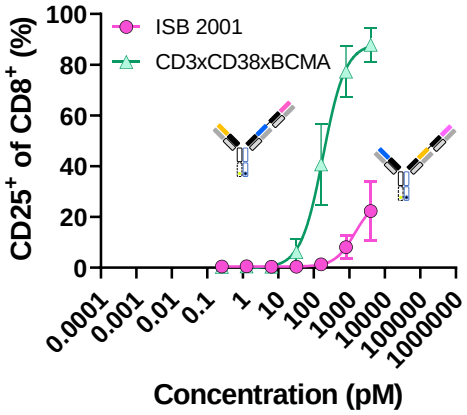


On-target off-tumor









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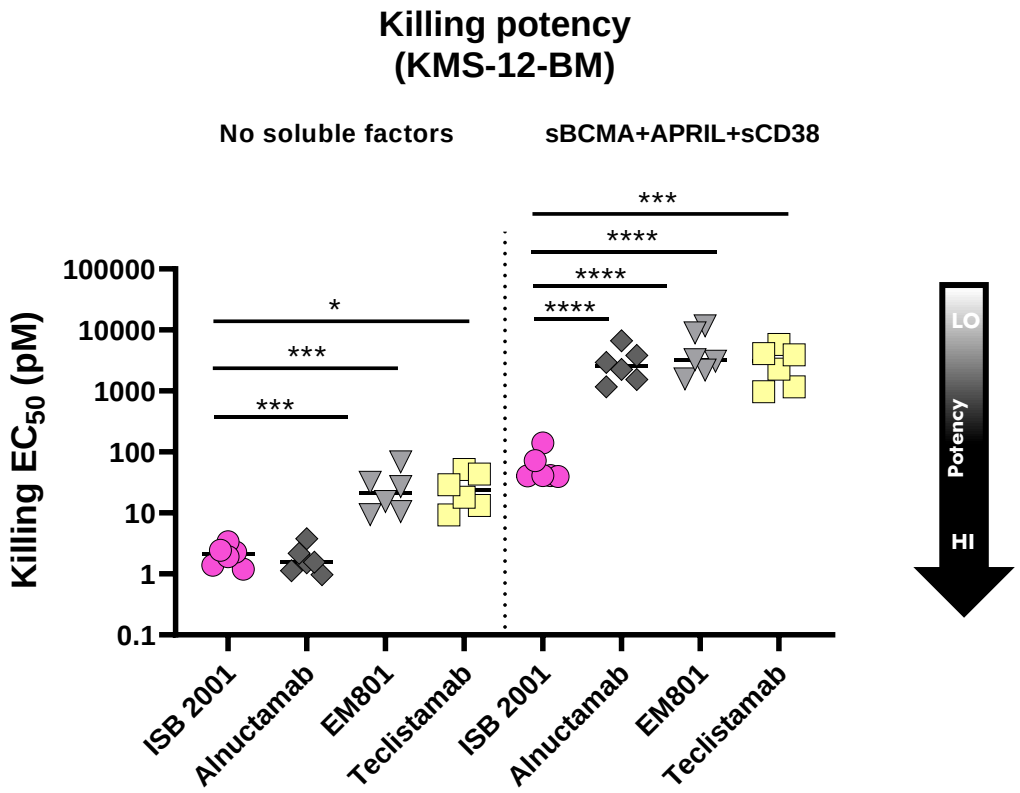
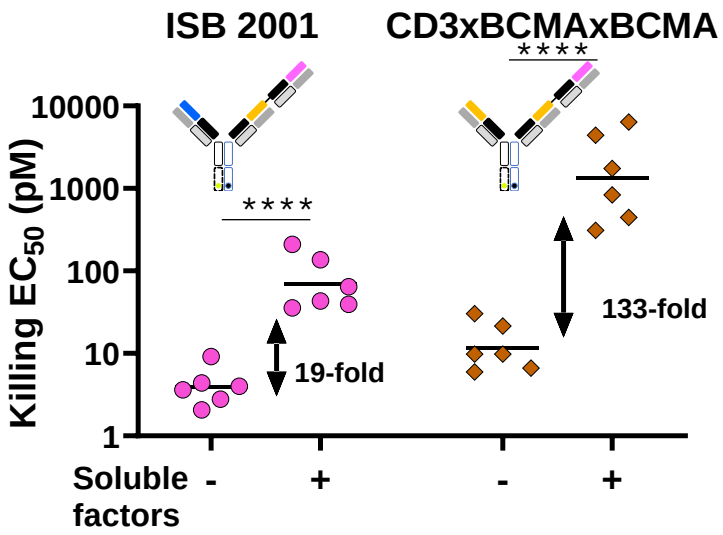
Adapted from Carretero-Iglesia L. et al. Nature Cancer 2024

ISB 2001 Potency is Less Affected by Soluble Factors relative to Teclistamab and Alnuctamab



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

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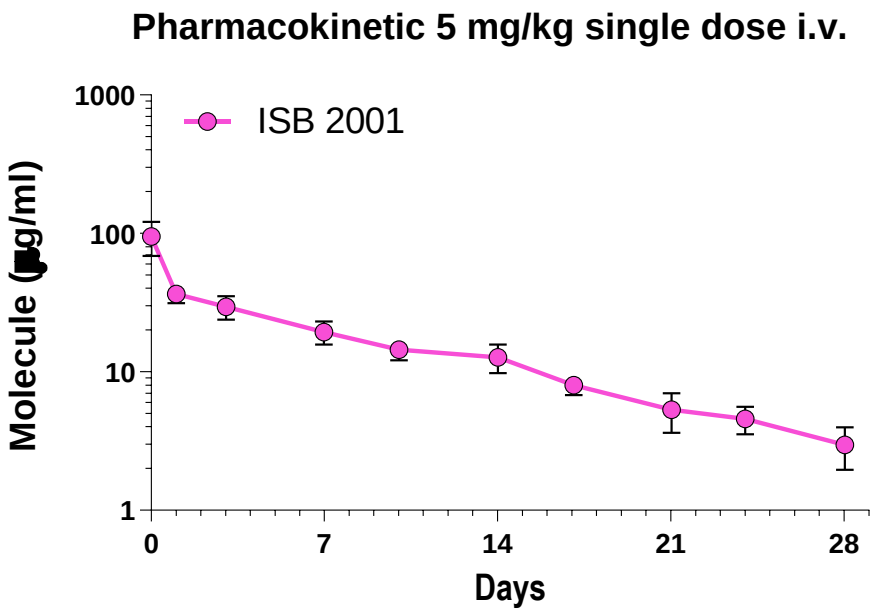
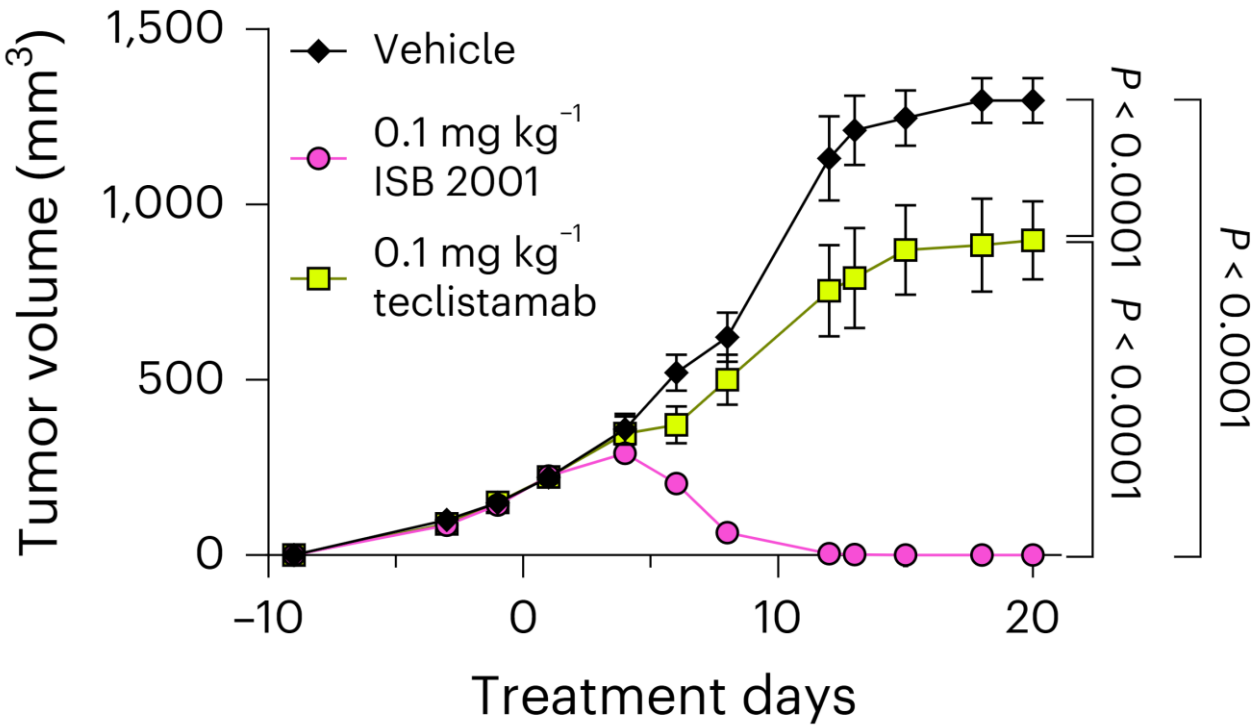
Carretero-Iglesia L. et al. Nature Cancer 2024

Potent In Vivo Efficacy of ISB 2001 in KMS-12-BM Myeloma Mouse Model with Low BCMA and CD38 Expression

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



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



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

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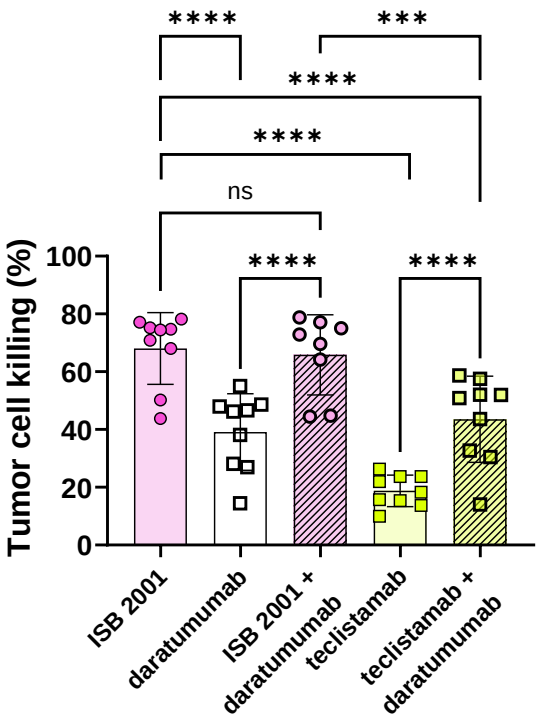
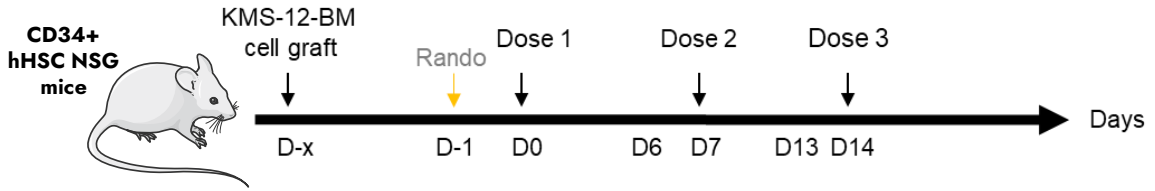
ISB 2001 Enhances Anti-Tumour Activity In Vitro and In Vivo Compared to BCMA and CD38 targeted therapies alone or in Combination

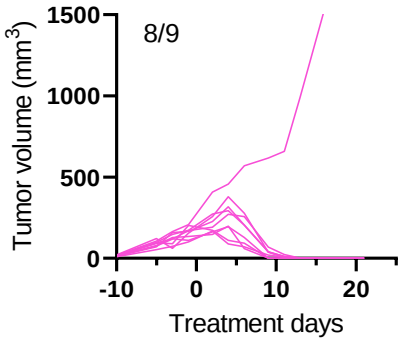
ISB 2001 is significantly more potent than Teclistamab + Daratumumab combination



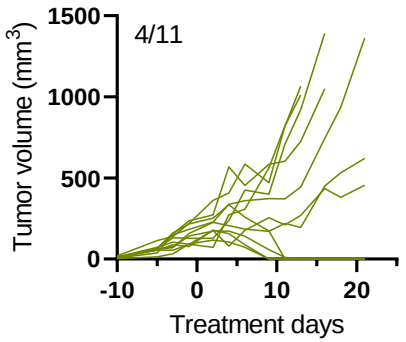
**=p <0.01
***= p <0.001
****= p <0.0001



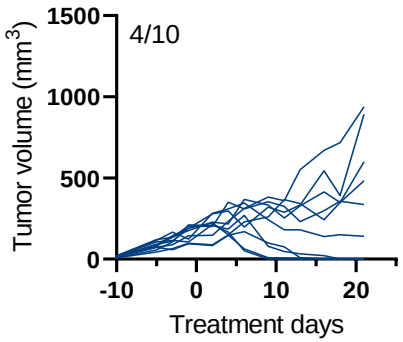
ISB 2001
1.5 mg/kg



Teclistamab
1.5 mg/kg



Teclistamab + Daratumumab



Treatment	Complete response	% of cured mice	2-way ANOVA vs ISB 2001
Vehicle	0/10	0 %	****
ISB2001	8/9	89 %	N.A.
Teclistamab	3/11	27 %	****
Daratumumab	0/9	0 %	****
Teclistamab + Daratumumab	3/10	30 %	****

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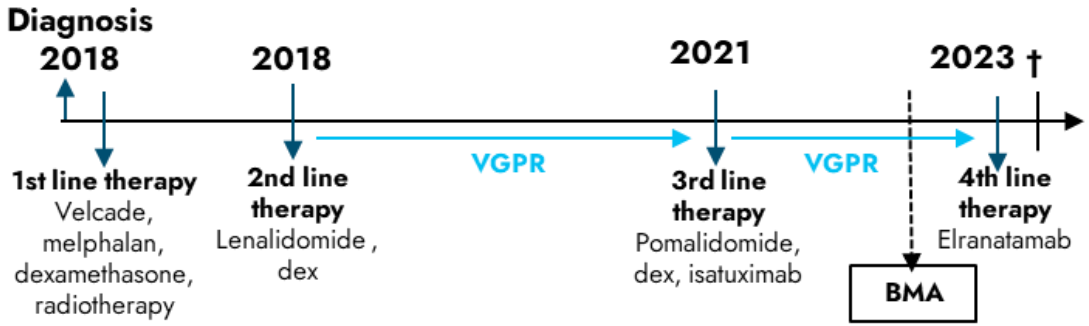
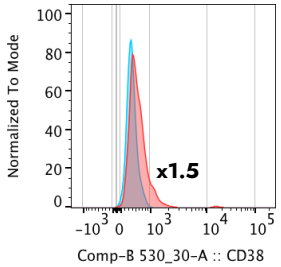
ISB2001 Overcome Escaping Mechanisms: ex vivo Evaluation of Patients Relapsing post CD38 or BCMA Targeted Therapies

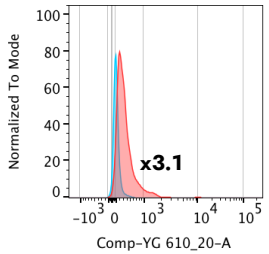
CD38-targeted therapy resistant patient



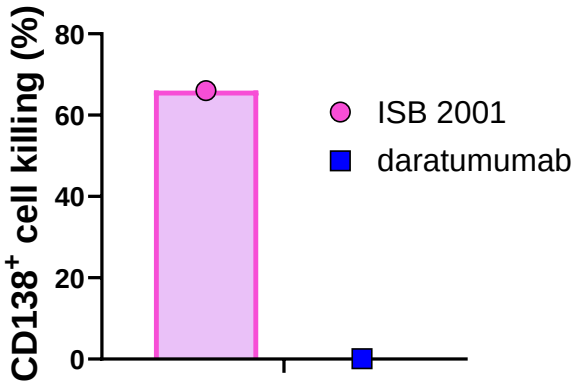
CD38



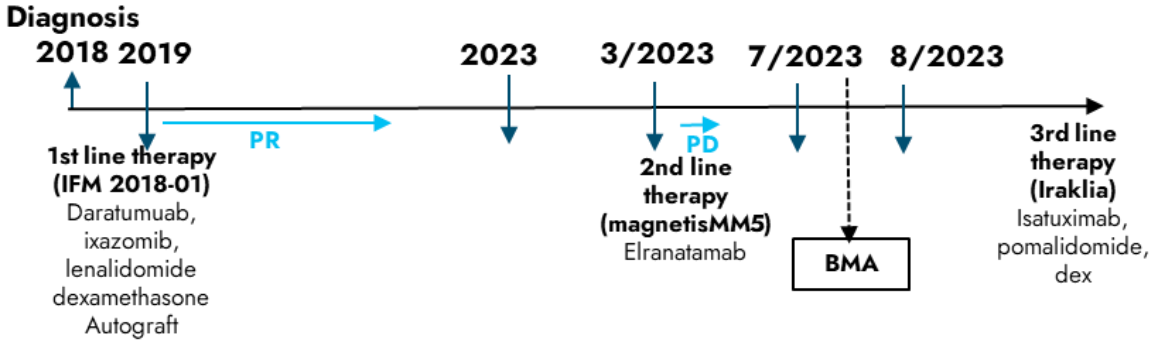
BCMA



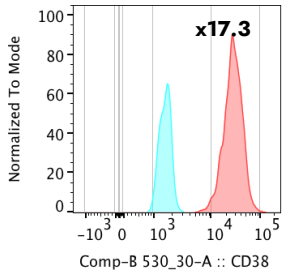
r/r MM post CD38 targeted therapy



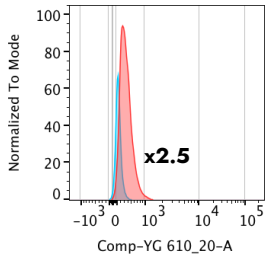
BCMA-targeted therapy resistant patient



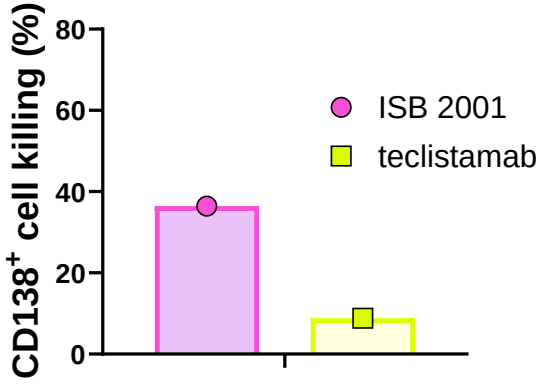
CD38



BCMA

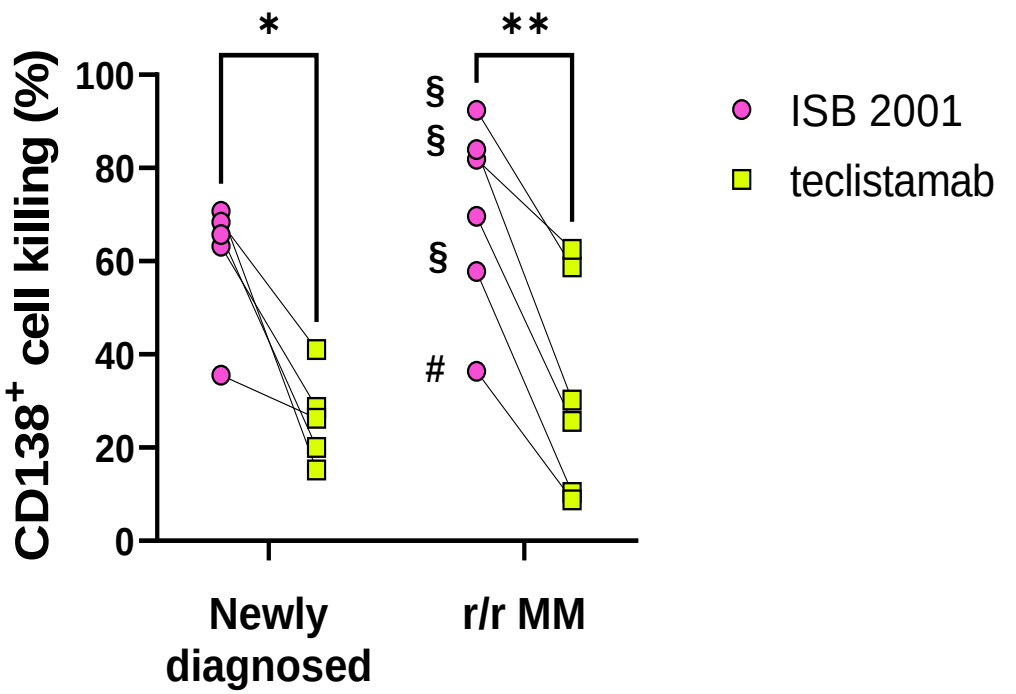


r/r MM post BCMA targeted therapy



ISB 2001 Exhibits Higher Potency ex vivo Compared To Teclistamab Across a Broad Range of Patient-Derived Bone Marrow Aspirates

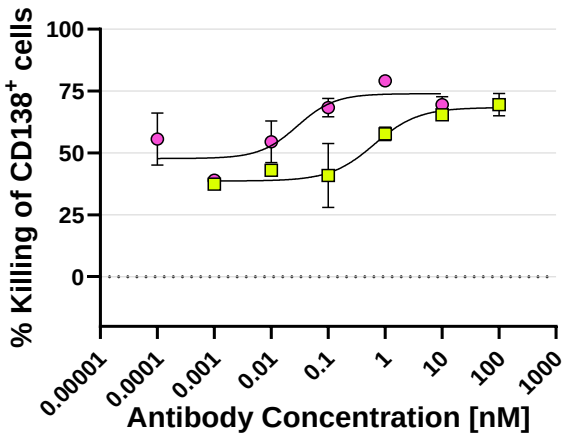
Newly Diagnosed MM & R/R MM



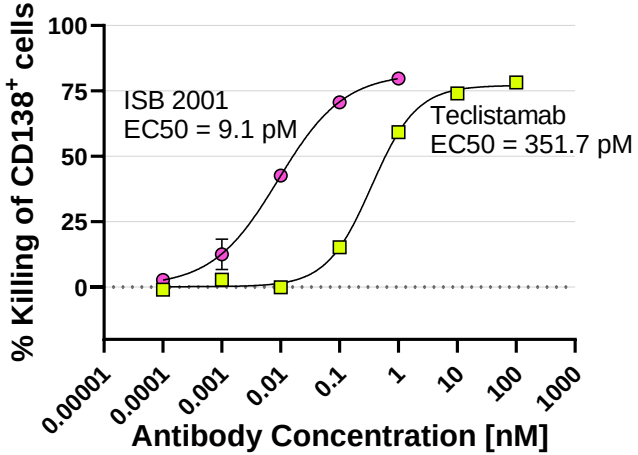
§ relapsing post anti-CD38 treatment
# relapsing post anti-BCMA treatment

*=p <0.05
**=p <0.01

Smoldering MM



Plasma Cell Leukemia



r/rMM: relapsed refractory multiple myeloma

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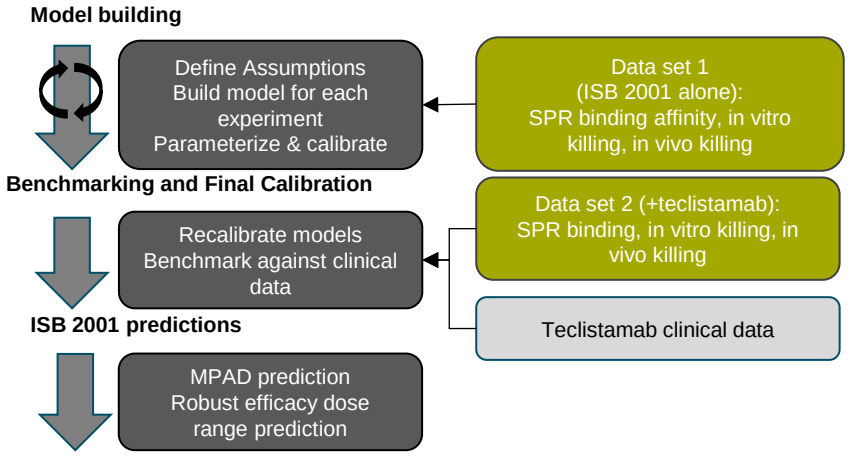
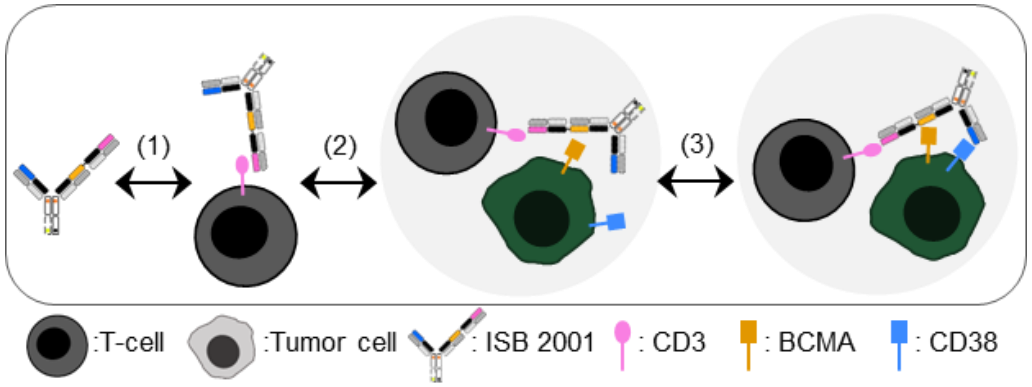
Carretero-Iglesia L. et al. Nature Cancer 2024

QSP modeling allows MPAD prediction of ISB 2001 starting dose

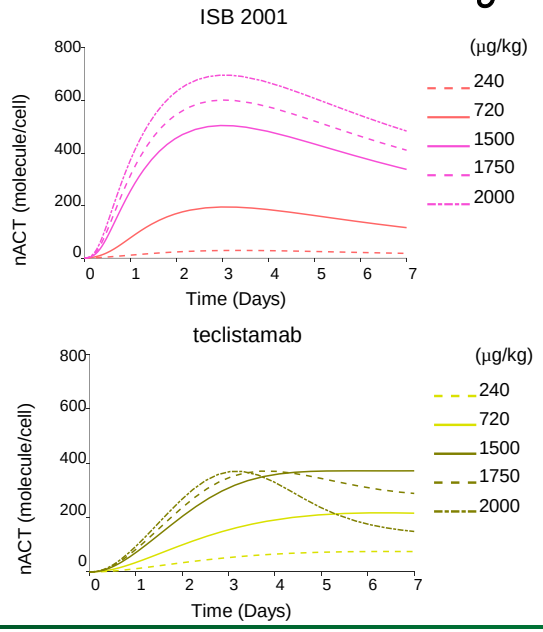
Workflow for developing QSP model



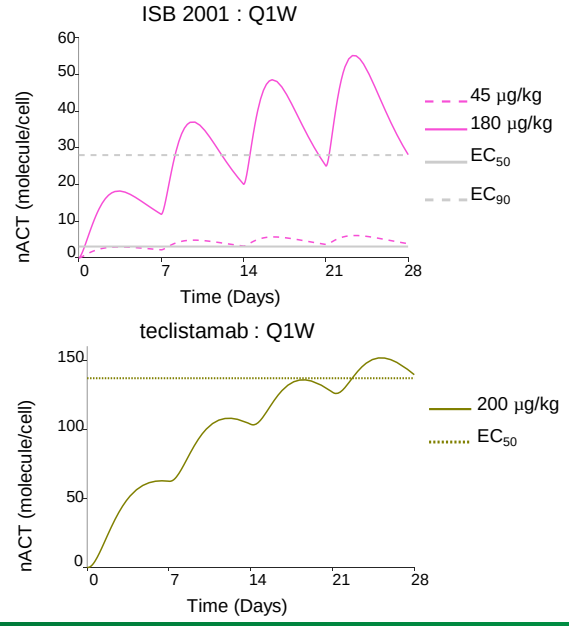
Simplified binding schematic



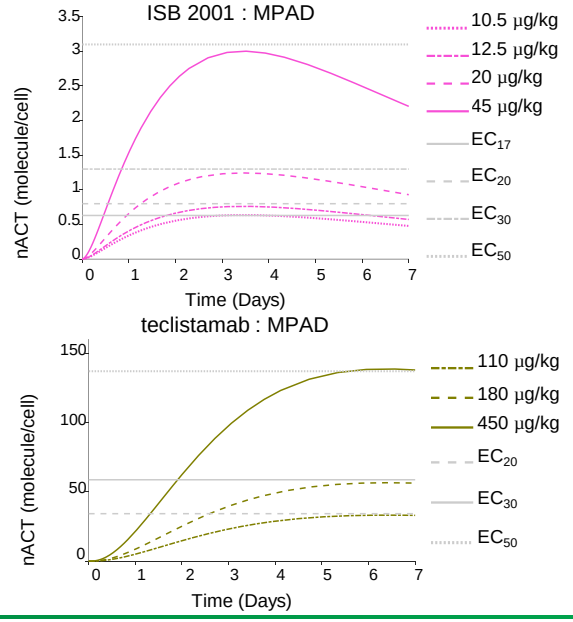
maximum nACT Dose-range



nACT levels upon repeated dose



MPAD predictions



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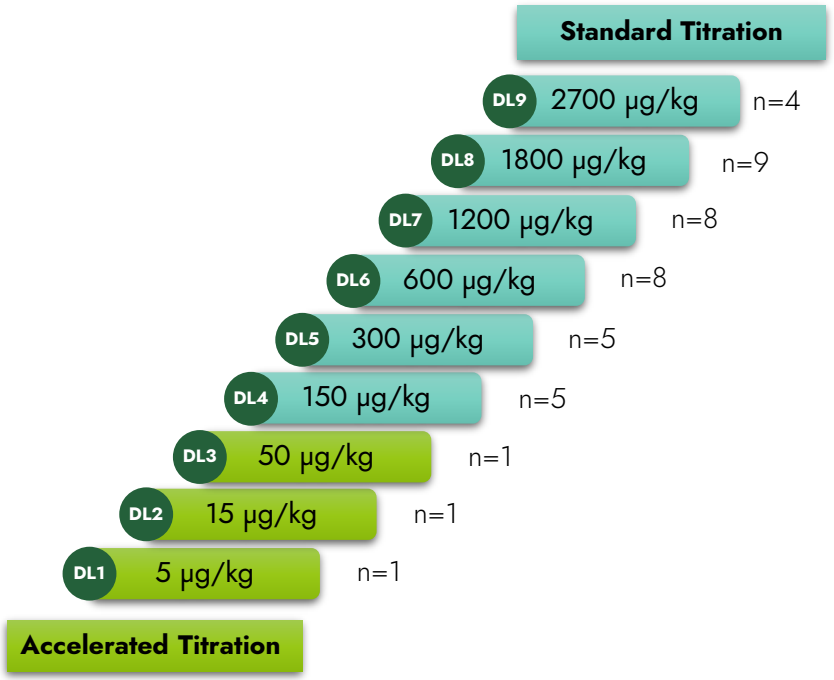
Carretero-Iglesia L. et al. Nature Cancer 2024

TRIgnite-1: Deep and Lasting Responses of ISB-2001 Observed at ≥ 50 µg/kg

Dose Escalation



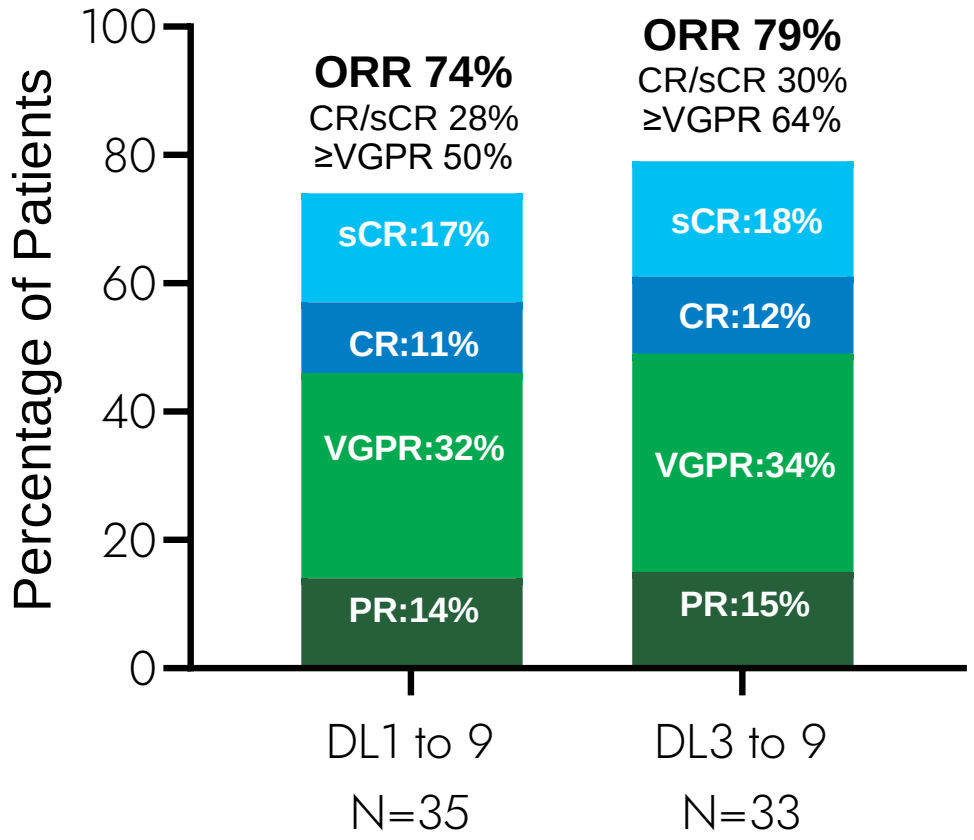
Key Eligibility :

- RRMM, after CD38 antibody, PIs, IMiDs
- Failed 3 or more prior lines
- Prior CARTs and/or bispecifics allowed

Dosing :

- ISB 2001 administered SC, weekly
- Preceded by 2 step-up doses on Day 1 and Day 4

Best Overall Response



➢ClinicalTrials.gov Identifier: NCT05862012

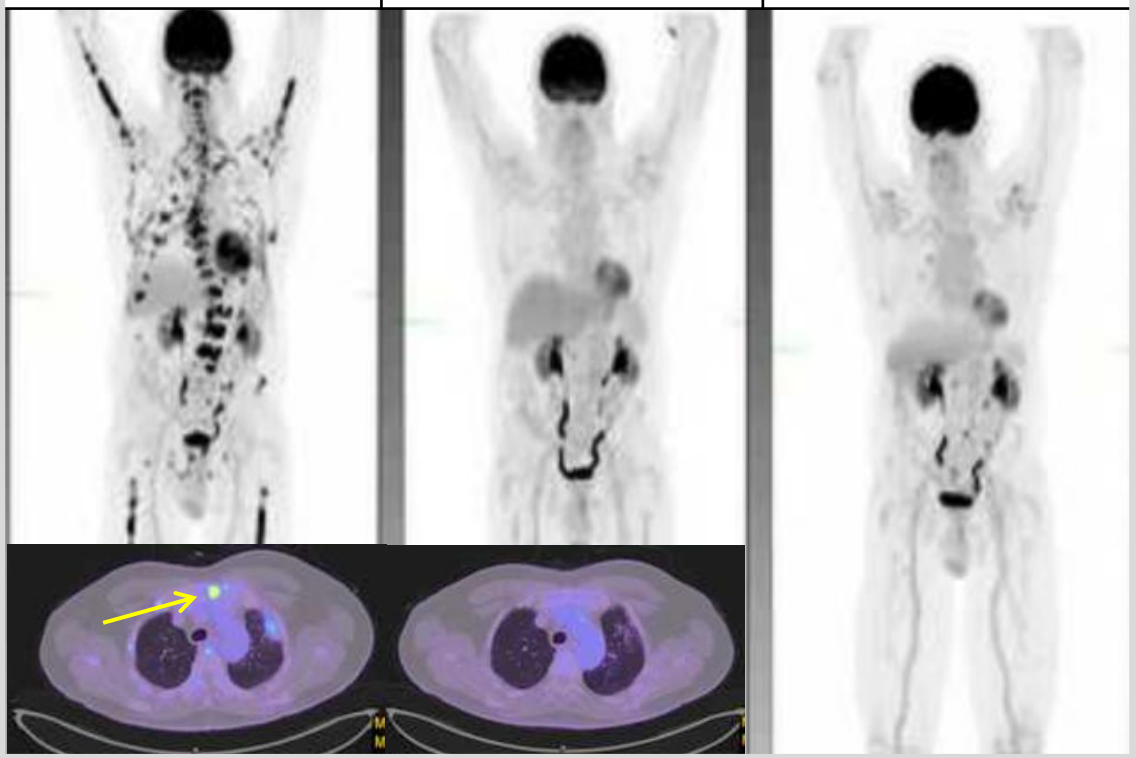
ORR: overall response rate
CR: complete response
sCR: stringent complete response
VGPR: very good partial response
PR: partial response

ASCO 2025: data cut-off 8th May 2024

ISB 2001: Rapid and Sustained Responses by PET-CT in Two Patients (TRIgnite-1)

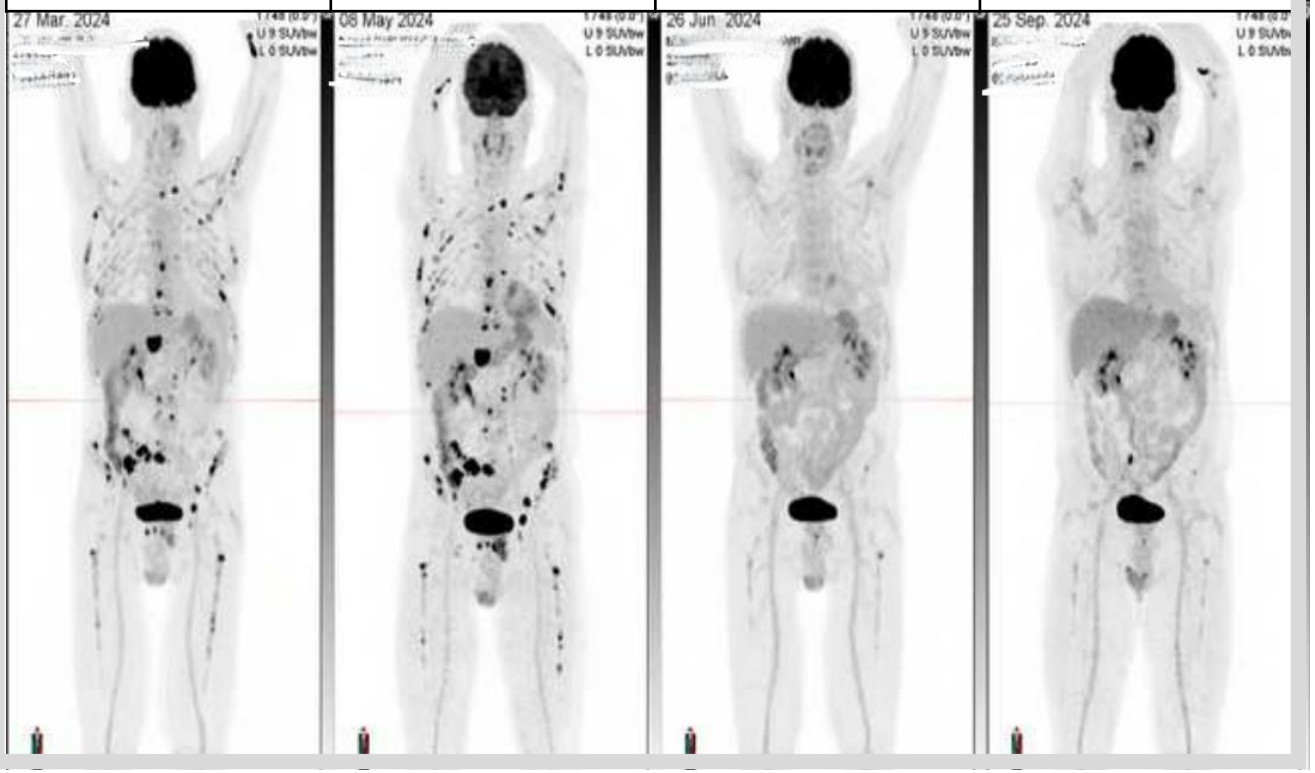
Patient 1 (DL5): 4 Prior lines

Baseline	After 1 Cycle (PR)	After 6 Cycles (VGPR)



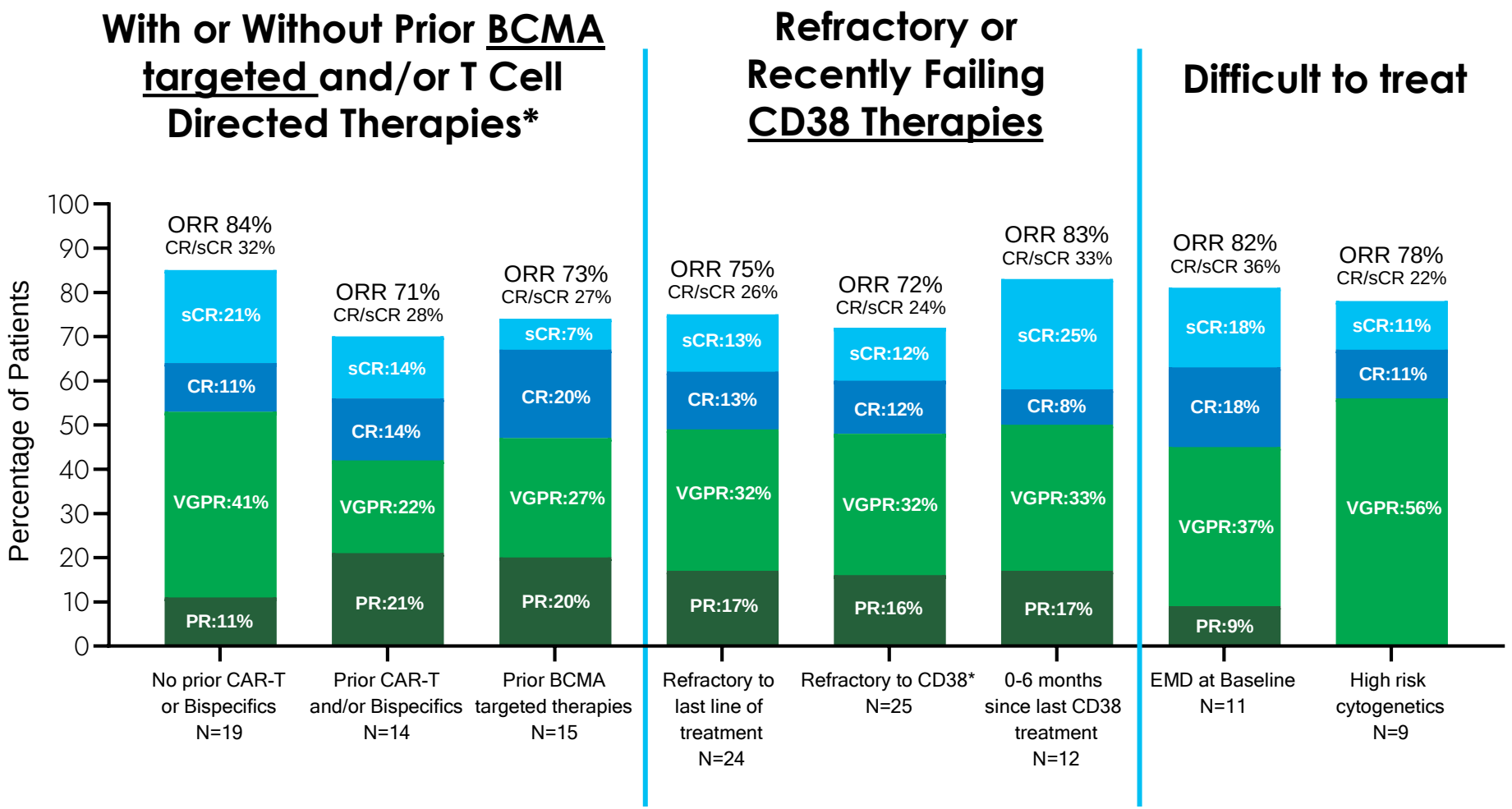
Patient 2 (DL5): 3 Prior Lines Including T Cell Directed Therapy (Forimtamig)

Baseline	After 1 Cycle (PR)	After 3 Cycles (VGPR)	After 5 Cycles (CR)



➢ClinicalTrials.gov Identifier: NCT05862012

ISB 2001 overcomes resistance mrntsechanismsin difficult to treat patients (TRIgnite-1)



➢ClinicalTrials.gov Identifier: NCT05862012

Responses in DL3 to DL9

* T cell directed therapies include CD3 bispecifics and CAR T cell therapies

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ORR: overall response rate
CR: complete response
sCR: stringent complete response
VGPR: very good partial response
PR: partial response

ASCO 2025: data cut-off 8th May 2024

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