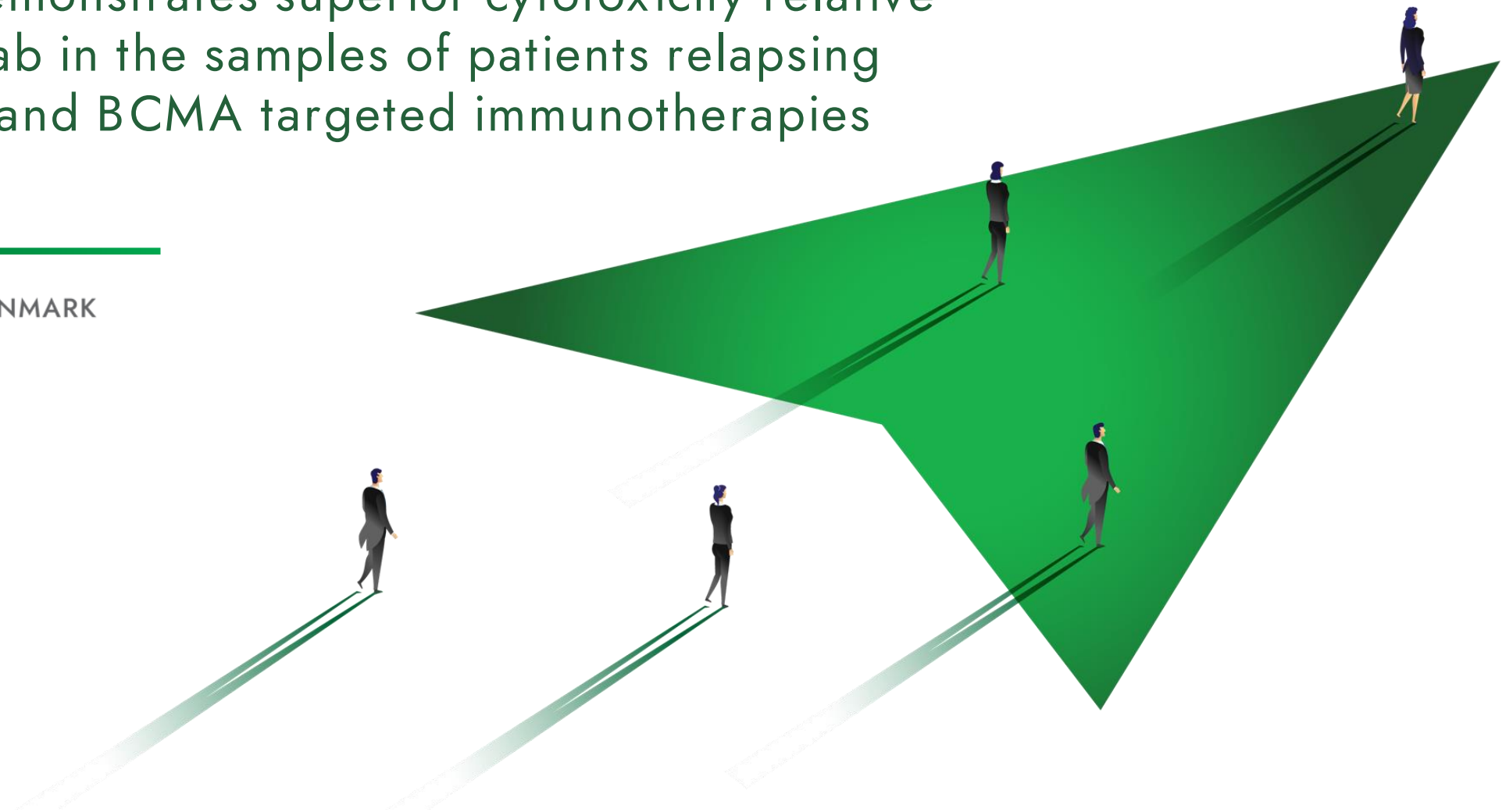
ISB 2001, a BCMA and CD38 dual targeting T cell engager, demonstrates superior cytotoxicity relative to teclistamab in the samples of patients relapsing from CD38 and BCMA targeted immunotherapies

ICHNOS GLENMARK INNOVATION



L. Carretero-Iglesia[1], M. Pihlgren[1], J. Berret[1], A. Drake[1], D. Pais[1], C. Dreyfus[1], V. Menon[2], T. Matthes[3], C. Edwards[4], J. Edwards[4], C. Pellat-Deceunynck[5], P. Moreau[6], C. Touzeau[6], T. Matsuura[7], P. van der Graaf[7], L. Pacaud[2], C. Konto[2], E. Zhukovsky[1], M. Perro[1];

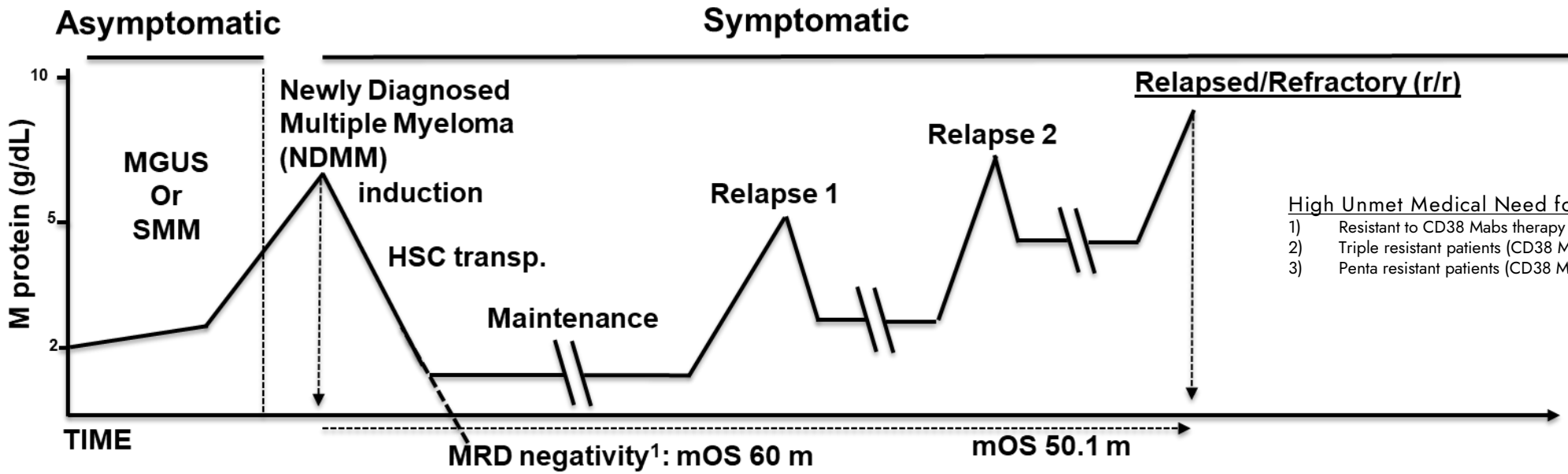
Disclosure Information

Mario Perro

I have the following relevant financial relationships to disclose:

Employee of: Ichnos Glenmark Innovation

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)

Treatment for Relapsed/Refractory Setting

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

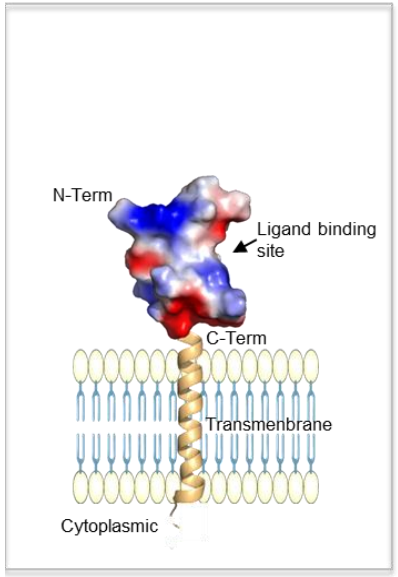
M protein: myeloma protein
MGUS: Monoclonal gammopathy of undetermined significance
sMM: smoldering multiple myeloma

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)

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

BCMA



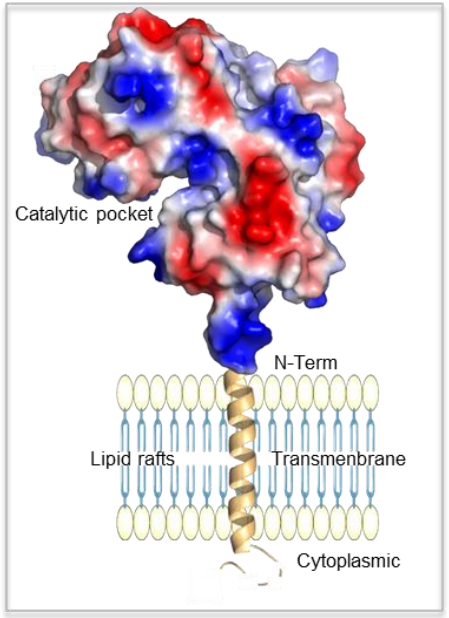
BCMA is a member of the TNFR superfamily

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]

CD38

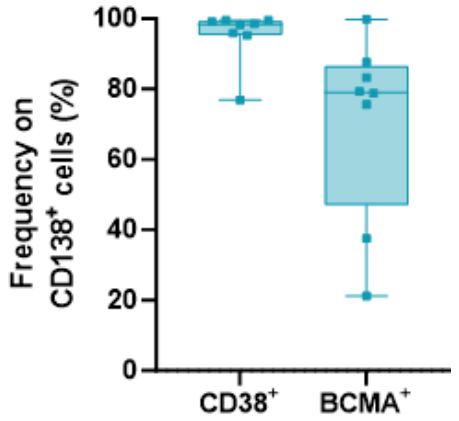


CD38 is a receptor for CD31 and an ectoenzyme with NADase activity[11]

Pros: Validated target, high expression on MM cells

Cons: Also expressed at lower levels on healthy cells

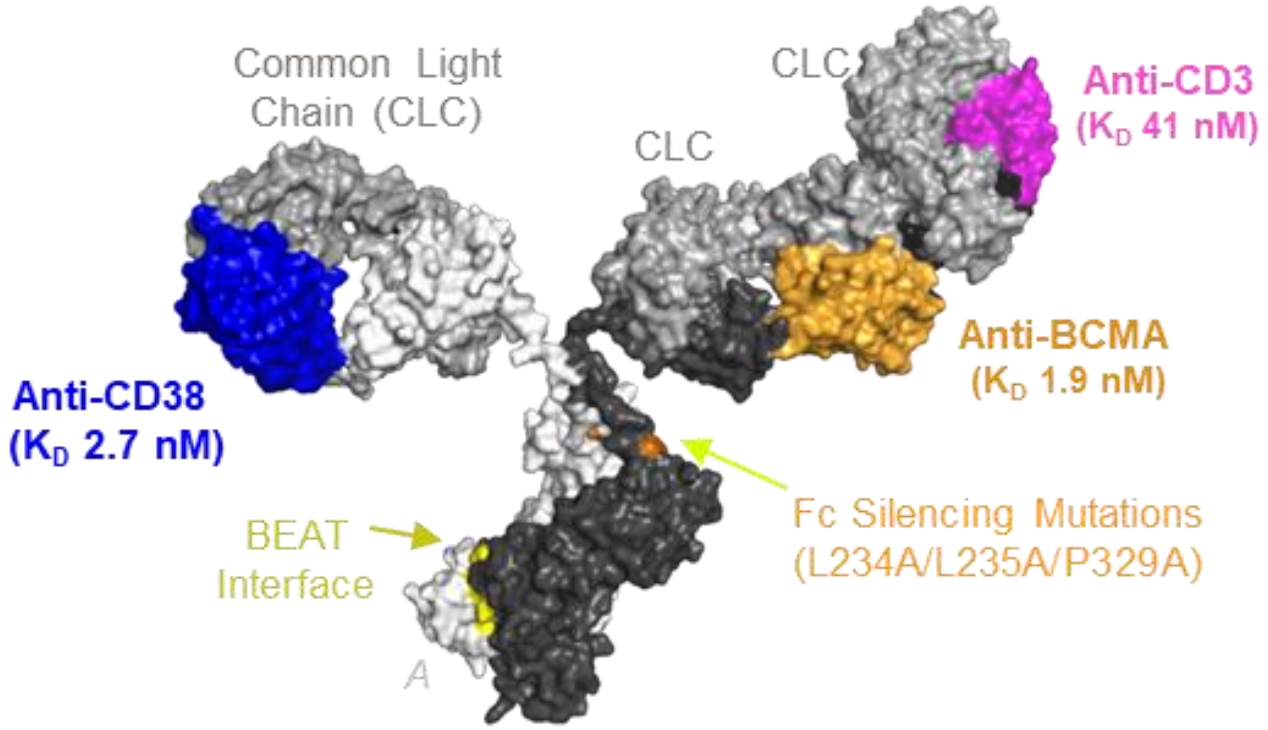
Resistance Mechanisms:
1) Downregulated upon therapy[12,13]
2) Heterogeneity of expression



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

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

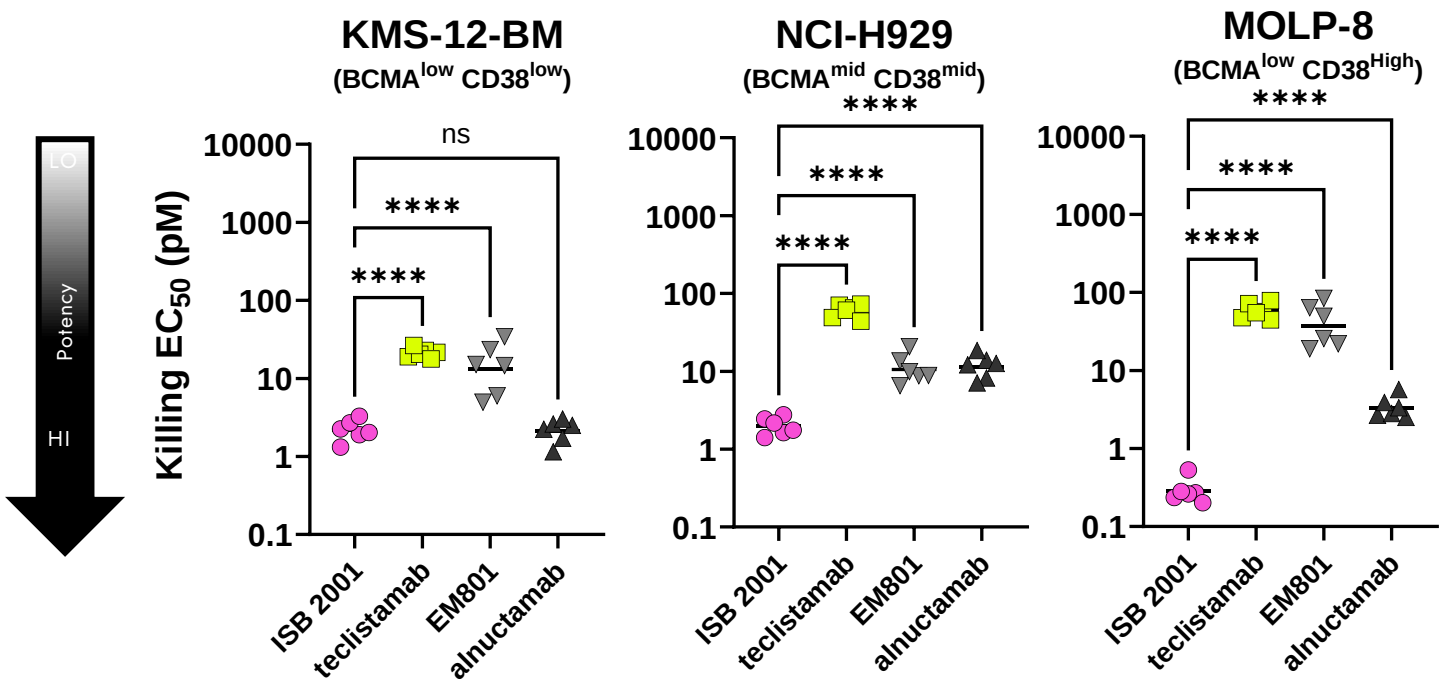
ISB 2001 (BCMA X CD38 X CD3): First TREAT™ Trispecific Antibody for r/r MM



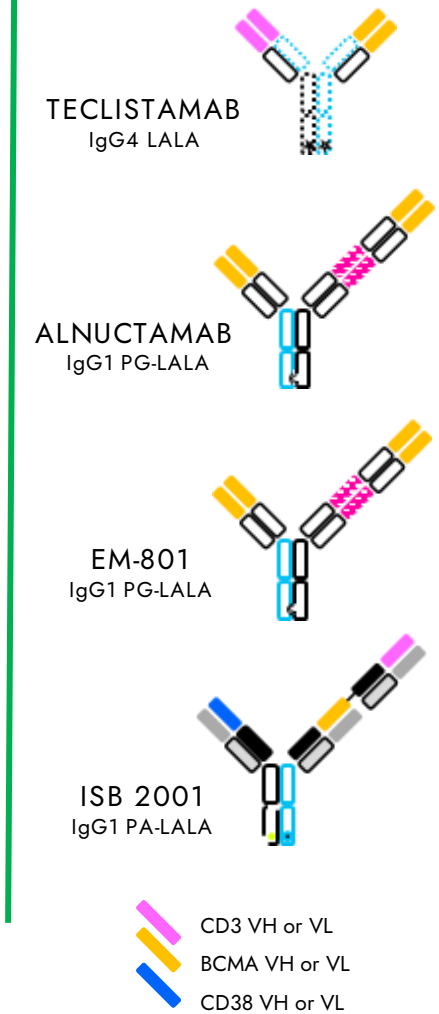
- Three proprietary fragment antigen-binding arms: CD3ε on T cells; BCMA and CD38 on MM cells
- Heterodimerisation based on the BEAT® platform in a TREAT™ format
- Fab domains derived from synthetic phage display library with common light chain (Vκ3-15 + IgκJ1)

TREAT: Trispecific Engagement by Antibodies based on the TCR

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



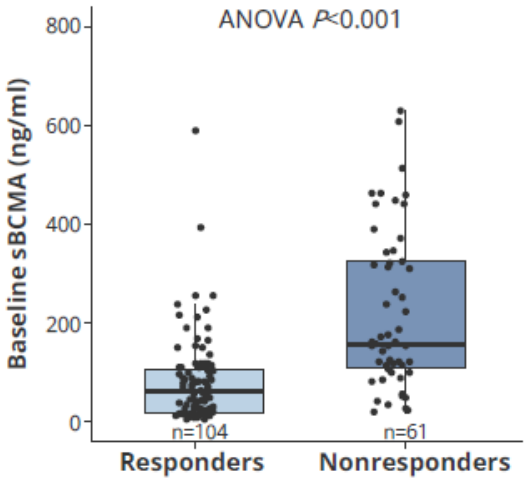
Expression sABC	CD38 expression (sABC)	BCMA expression (sABC)	Clinical case modelling
KMS-12-BM	LOW 28000	LOW 9000	Post treatment with daratumumab + teclistamab
NCI-H929	MID 85000	MID 52000	Newly Diagnosed or post IMIDs + PI
MOLP-8	HIGH 512000	VERY LOW 3200	Post BCMA targeted therapy



****= p <0.0001

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

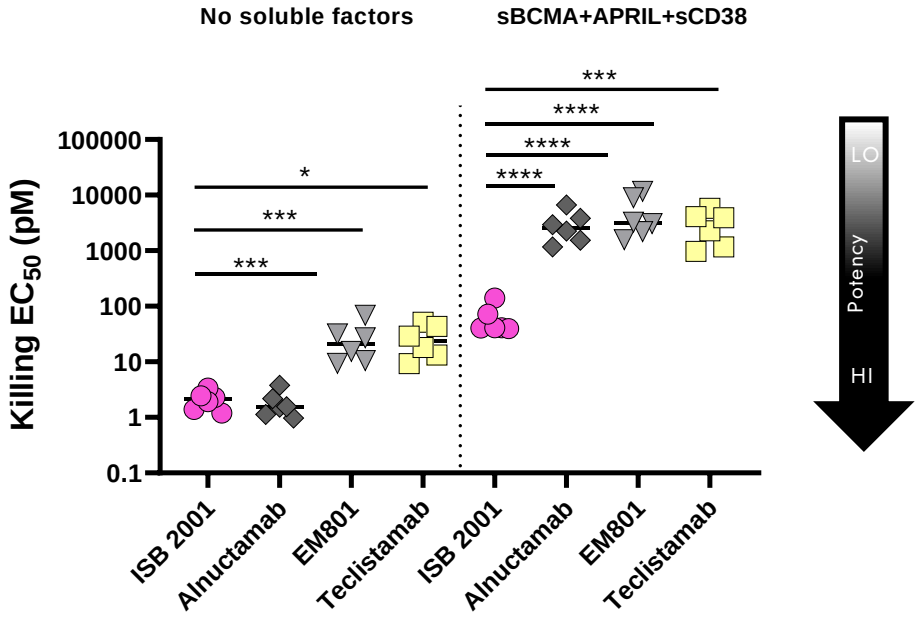
sBCMA Levels[1]



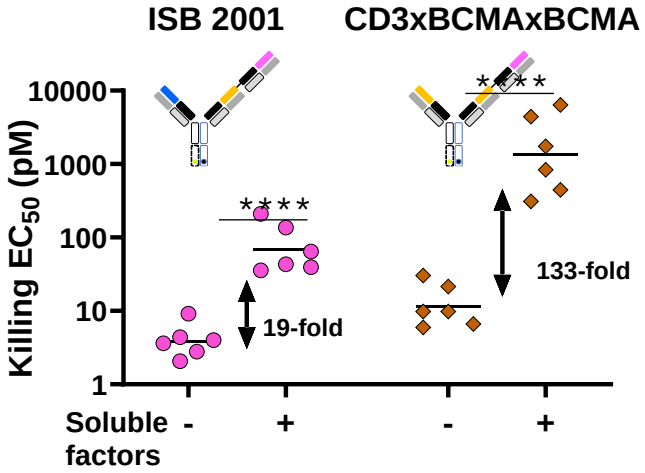
- Patients responding to teclistamab had significantly lower sBCMA levels at baseline

1. Girgis S, et al. Blood Adv 2022

Killing potency (KMS-12-BM)



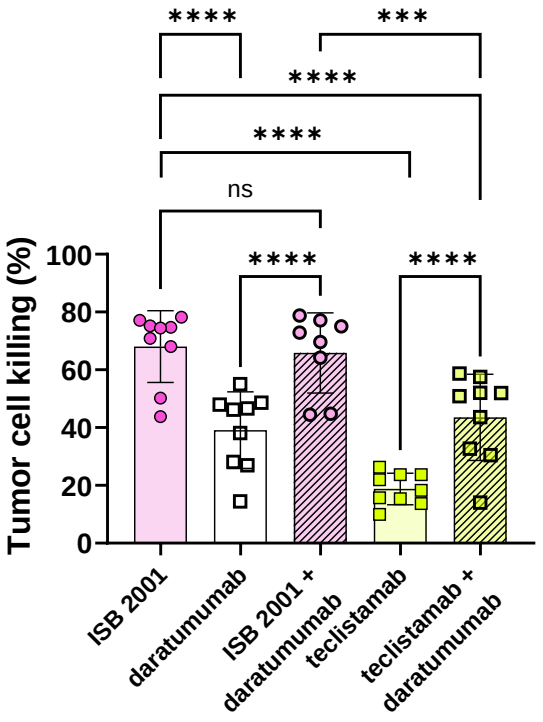
Tumor Killing EC_{50} (pM)	*ISB 2001*	*alnuctamab*	*EM801*	*teclistamab*
No Soluble Factors	2.1	1.9	27.1	27.4
sBCMA+APRIL+sCD38	62.5	3059.7	5144.1	3037.6
Fold Difference (sEC50/EC50)	***30***	***1647***	***190***	***111***



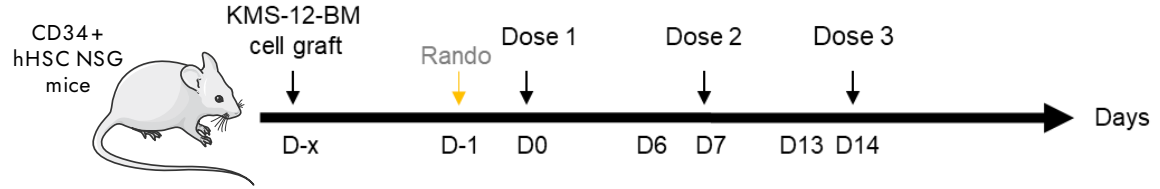
**=p <0.01
***= p <0.001
****= p <0.0001

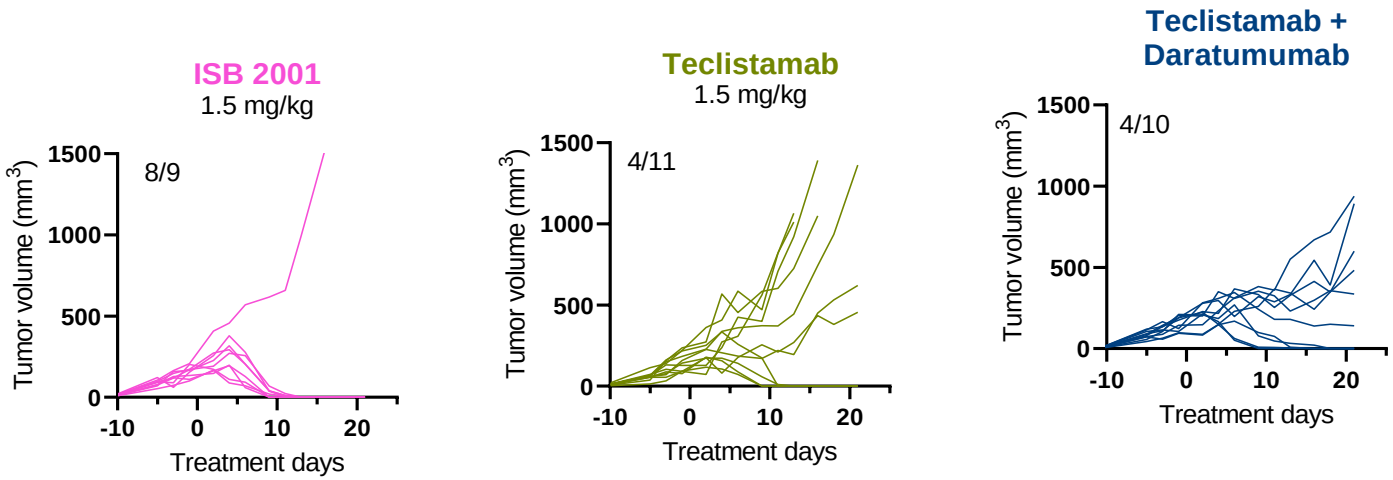
ISB 2001 Enhances Anti-Tumour Activity In Vitro and In Vivo Compared to BCMA and CD38 targeted therapies alone or in Combination

ISB 2001 is significantly more potent than Teclistamab + Daratumumab combination



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

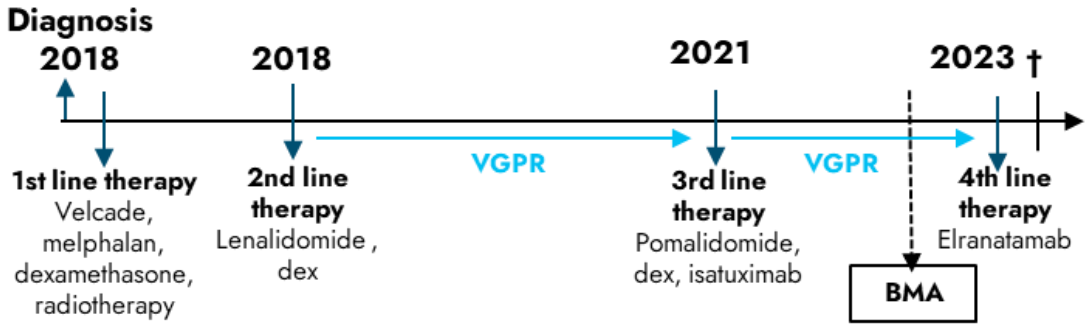




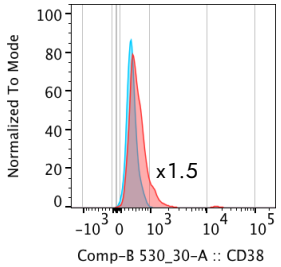
Treatment	Complete response	% of cured mice	2-way ANOVA vs ISB 2001
Vehicle	0/10	0 %	****
ISB2001	8/9	89 %	N.A.
Teclistamab	3/11	27 %	****
Daratumumab	0/9	0 %	****
Teclistamab + Daratumumab	3/10	30 %	****

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

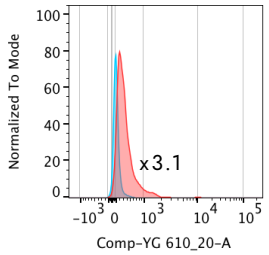
CD38-targeted therapy resistant patient



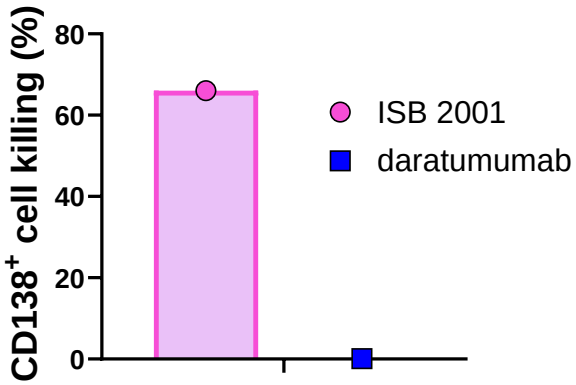
CD38



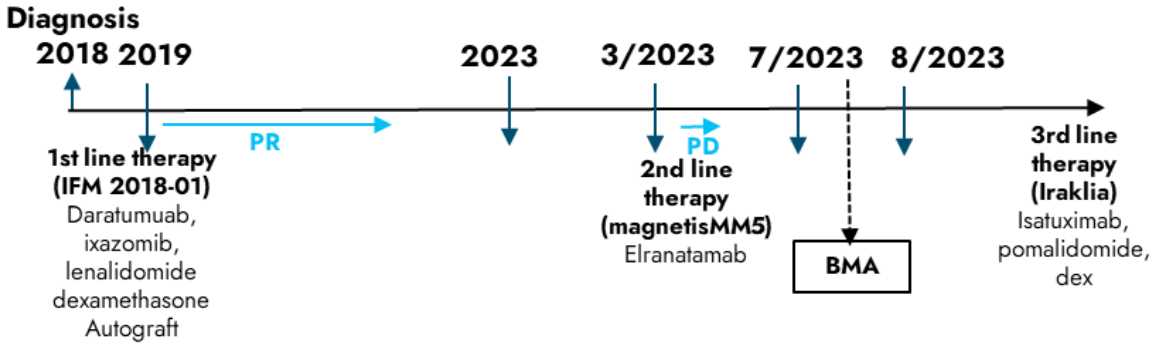
BCMA



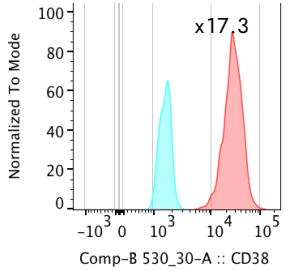
r/r MM post CD38 targeted therapy



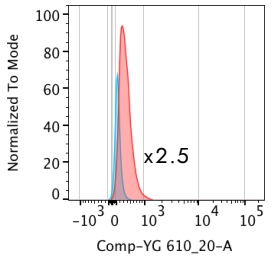
BCMA-targeted therapy resistant patient



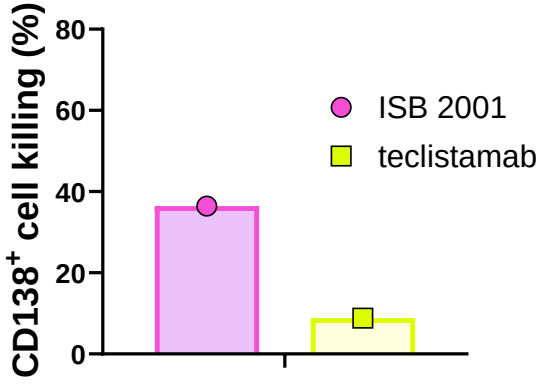
CD38



BCMA

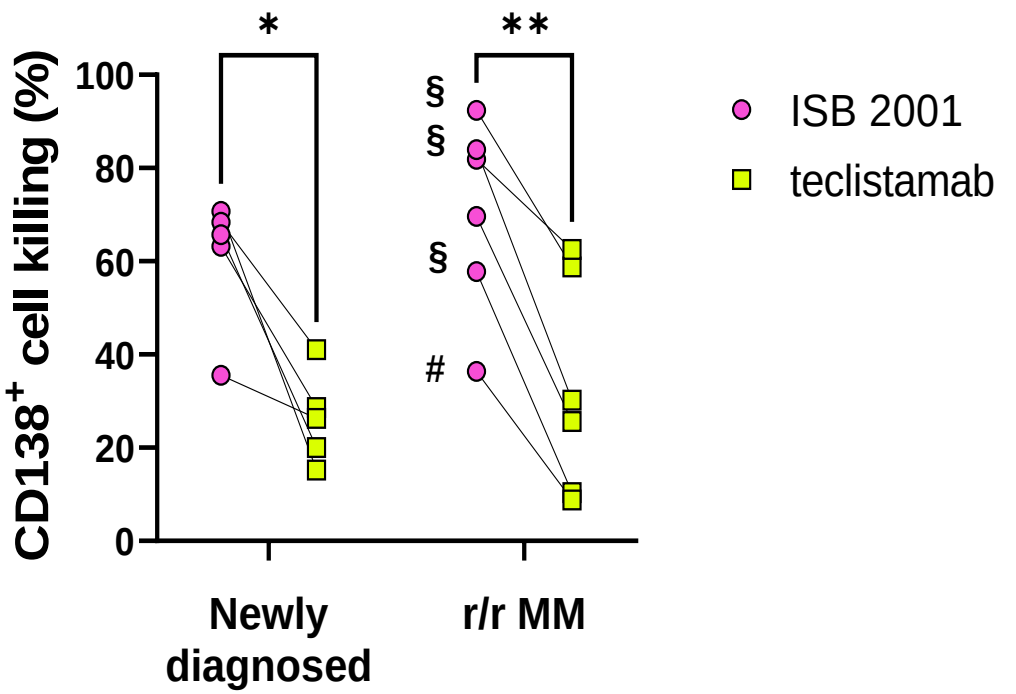


r/r MM post BCMA targeted therapy



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

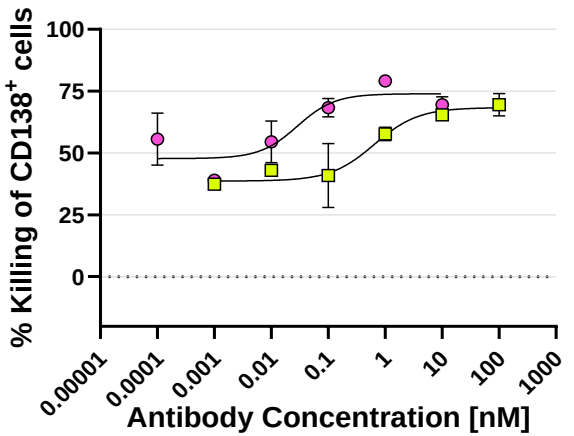
Newly Diagnosed MM & R/R MM



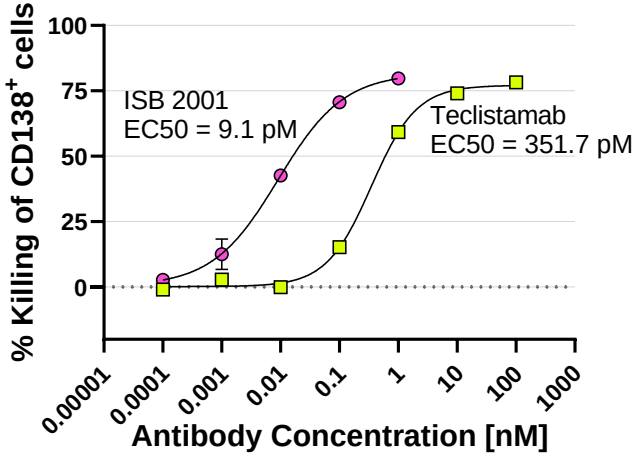
§ relapsing post anti-CD38 treatment
# relapsing post anti-BCMA treatment

*=p <0.05
**=p <0.01

Smoldering MM



Plasma Cell Leukemia



r/rMM: relapsed refractory multiple myeloma

A Phase 1, First-in-Human, Dose Escalation and Dose-Expansion Study of Single-Agent ISB 2001 in Subjects With r/r MM[1]

➢Enrolling Patients with R/R MM that have been treated with immunomodulatory drugs (IMiDs), proteasome inhibitors, and anti-CD38 therapies either in combination or as a single agent

➢Part 1: Dose Escalation to define Maximal Tolerated Dose
•ISB 2001 administered weekly on Days 1, 8, 15, and 22 of each 28-day cycle, with an additional double step-up dose in Cycle 1 on Day 4.
•Administration until 1) disease progression; 2) unacceptable toxicity

➢Part 2: 2 Dose Expansion cohorts
•Administration until disease 1) progression; 2) unacceptable toxicity;

➢Started on November 1st 2023.

➢ClinicalTrials.gov Identifier: NCT05862012

[1]Hanlon Sia at al, Blood Suppl. https://doi.org/10.1182/blood-2023-187106

Conclusions: ISB 2001 Displays a Promising Activity Profile for the Treatment of Patients with r/r MM

- Increased killing of MM cells compared to teclistamab, alnuctamab and EM-801 across variable levels of expression of both BCMA and CD38
- Minimally affected by soluble factors (sCD38, sBCMA, APRIL) compared to teclistamab, alnuctamab and EM-801
- Increased killing of MM cells in vitro relative to the combination of daratumumab and teclistamab
- Superior tumor growth inhibition in MM xenograft mouse models relative to teclistamab + daratumumab combination
- Maintained cytotoxicity on MM cell from patients relapsing from CD38 or BCMA targeted therapies
- Superior cytotoxicity of MM cells over teclistamab in ex vivo assays in patients' bone marrow aspirates
- Enrolling Phase 1 clinical study (ClinicalTrials.gov : NCT05862012)
- Ichnos is open for asset partnerships and BEAT® platform collaborations

Acknowledgement

Oncology Research

Maria Pihlgren
Laura Carretero
Jérémy Berret
Adam Drake
Daniela Pais
Olivia Hall
Myriam Chimen
Julie Macoin
Cynthia
Min Ma
Tania Thoos
Camille Aguesse
Stefano Sammicheli
Marica Anderle
Maria Panagopoulou
Valentina Labanca
Stefania De Angelis
Elie Dheilly

Antibody Engineering

Carole Estoppey
Jérémy Loyau
Thierry Monney
Aurore Delachat
Amelie Laurendon
Michael Dyson
Lydia N. Caro
Rebecca Croasdale-Wood
Cyrille Dreyfus
Ankita Srivastava

Development Team

Dominique Duchesne
Jeppe Koch Olsen
Vinu Menon
Andrew Garton
Elena Luganovski
Beata Holkova

INSERM- Nantes

Catherine Pellat-Deceunynck
Philippe Moreau
Nicoletta Libera Lilli
Cyril Tozeau

University of Geneva

Prof. Thomas Matthes

University of Oxford

Zeynep Kaya
Prof. Claire Edwards
Prof. James Edwards

Leadership

Cyril Konto
Eugene Zhukovsky
Lida Pacaud

Glenmark

Samitabh Chakraborti
Dipti Upadhye
Juilee Kadam