First Results of a Phase 1, First-in-Human, Dose-Escalation Study of ISB 2001, a BCMAxCD38xCD3 Targeting Trispecific Antibody in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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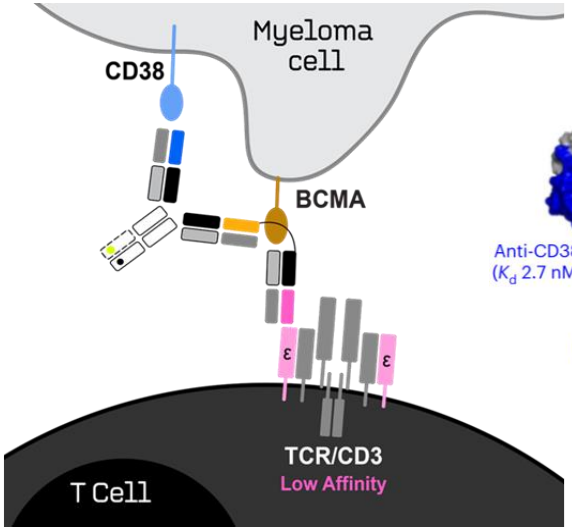
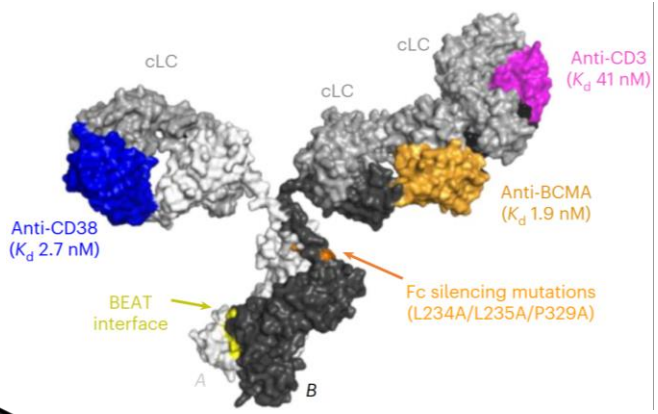
ISB 2001 (BCMAxCD38xCD3): First TREAT ™ Trispecific Antibody for Relapsed/Refractory Multiple Myeloma





Key Attributes

Generated using IGI's proprietary BEAT® protein platform

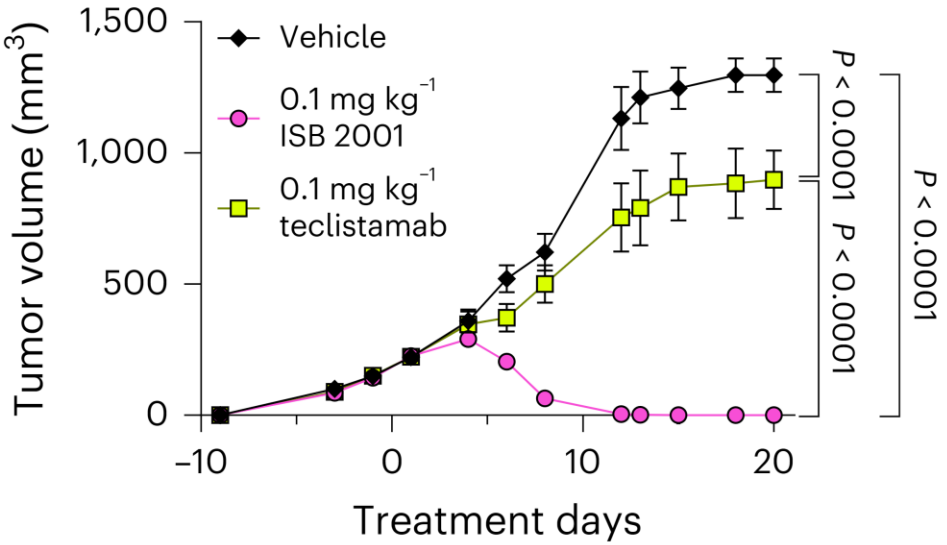
Enhanced avidity-based binding to myeloma cells with both BCMA and CD38 Fab domains

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

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

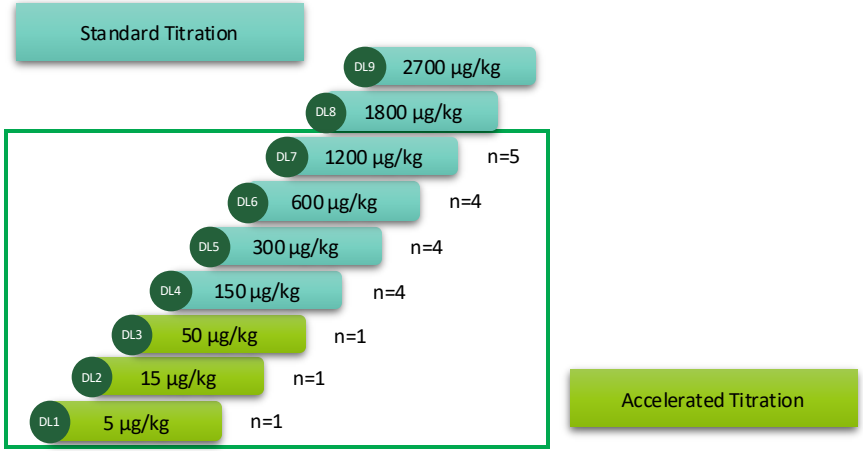


Treatment	Complete Response
Teclistamab	0% (0/8 mice)
ISB 2001	100% (8/8 mice)

Carretero-Iglesia L, et al. *Nat Cancer.* 2024 Oct;5(10):1494-1514. DOI

ISB 2001-101: Phase 1 Dose-Escalation/Expansion Study

On-going Part 1 : Dose Escalation (n ≈ 40)



In dose escalation, ISB 2001 is administered subcutaneously (SC) once weekly (q1w) in 28-day cycles, starting with 2 step-up doses on Days 1 and 4, followed by the full target dose from Day 8 onwards.
Backfill to each DL allowed.

Key Eligibility Criteria:

- R/R MM, after a CD38 antibody, IMiDs, PIs, not candidates for regimens known to provide benefit
- Failed 3 or more prior lines of therapies
- Prior CAR-Ts and/or bispecifics allowed, prior BCMA-targeted agents allowed

Primary Objectives:

- Assess safety and tolerability
- Determine MTD/RP2D

Secondary Objectives:

- PK, immunogenicity
- Preliminary clinical activity by IMWG

Status:

- As of 1-Oct-2024, 20 subjects dosed in Australia and US in DL1 to DL7
- Dose-expansion part 2 will test at least 2 putative Phase 2 doses and dosing schedule to establish Recommended Phase 2 Dose

BCMA, B-cell maturation antigen; CAR, Chimeric antigen receptor; MTD, Maximum tolerated dose; RP2D, recommended phase 2 dose; IMWG, International Myeloma Working Group; PK, pharmacokinetics; DL dose level. ClinicalTrials.gov identifier NCT05862012

ISB 2001-101: Demographics and Disease Characteristics

Characteristic	Total (N=20)
Gender	
Female, n (%)	8 (40)
Median Age, range (years)	66 (52; 80)
Race, n (%)	
Black or African American	1 (5)
White	16 (84)
Other	2 (11)
Ethnicity, n (%)	
Not Hispanic or Latino	19 (95)
ECOG performance status, n (%)	
0	15 (75)
1	5 (25)
Lytic Bone Disease, n (%)	15 (75)
Extramedullary Disease, n (%)	6 (30)
Revised ISS, n (%)	
I	11 (55)
II	5 (25)
III	1 (5)
Cytogenetics available, n (%)	12 (60)
High risk cytogenetics	5 (42)
Bone Marrow Myeloma/Plasma cells ≥ 30%, n (%)	5 (25)

Characteristic	Total (N=20)
Median number of lines of previous therapy (range)	6 (3; 11)
Previous therapy exposure, n (%)	
Triple-exposed	20 (100)
Triple-refractory	5 (25)
Penta-exposed	14 (70)
Penta-refractory	2 (10)
Refractory to last line of therapy	13 (65)
ASCT	19 (95)
Anti-BCMA CAR-T	2 (10)
Bispecifics	9 (45)
BCMA	1 (5)
FcRH5	6 (30)
GPRC5D	4 (20)
Anti-BCMA ADC	5 (25)

High risk cytogenetics defined as presence of del(17), del(1p), t(14:16), t(14:20), t(4:14) or 1q amp

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ASCT, Autologous stem cell transplantation; FcRH5, Fc receptor-like protein 5; GPRC5D, G-protein coupled receptor family C group 5 member D; ADC, antibody-drug conjugate

ISB 2001: Clinically Manageable Safety Profile

Summary of TEAEs (N=20)	
n (%)	**Total**
Any AE Drug-related	20 (100) 20 (100)
Serious AE Drug-related	14 (70) 7 (35)
Grade 3-4 AE Drug-related	18 (90) 12 (60)
Grade 5 AE	0
AE leading to treatment discontinuation	0
Dose Limiting Toxicity	0

n, Number of patients ; TEAE, Treatment Emergent Adverse Events

ISB 2001: Low Rate of Hematologic and Infection Drug-Related TEAEs

Drug-Related Hematologic TEAEs (N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Hematologic TEAEs	12 (60)	6 (30)	3 (15)
Anaemia	1 (5)	1 (5)	0
Lymphocyte count decreased	2 (10)	1 (5)	0
Neutropenia	7 (35)	3 (15)	3 (15)
Thrombocytopenia	8 (40)	2 (10)	0

Drug-Related Infections (N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Infections	9 (45)	3 (15)	0
Lower respiratory tract infection	3 (15)	2 (10)	0
COVID-19	2 (10)	0	0
Upper respiratory tract infection	2 (10)	0	0
Cytomegalovirus viraemia	1 (5)	0	0
Pneumonia	1 (5)	1 (5)	0
Sinusitis	1 (5)	0	0

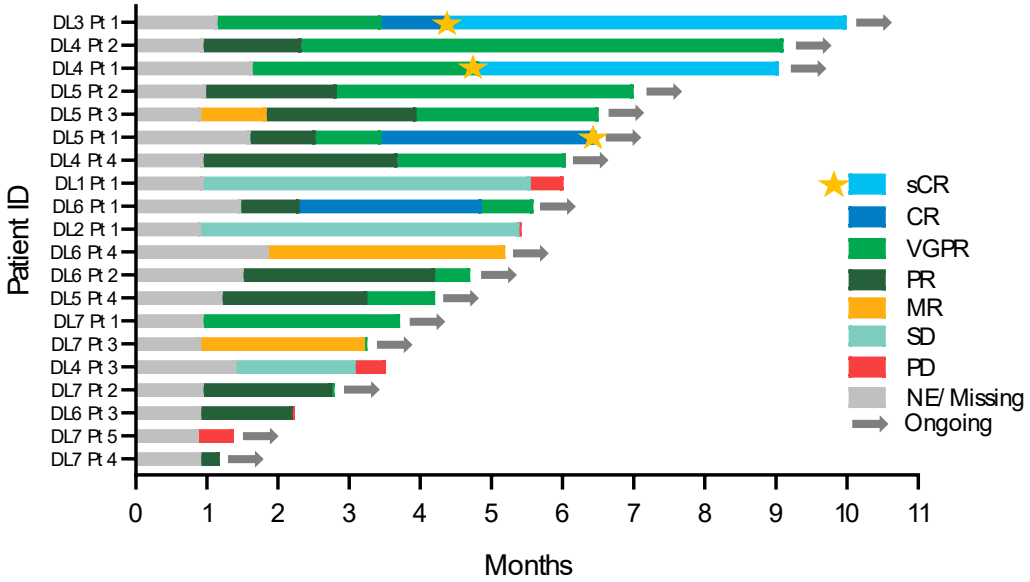
ISB 2001: Low Rates of Severe Non-Hematologic Drug-Related TEAEs

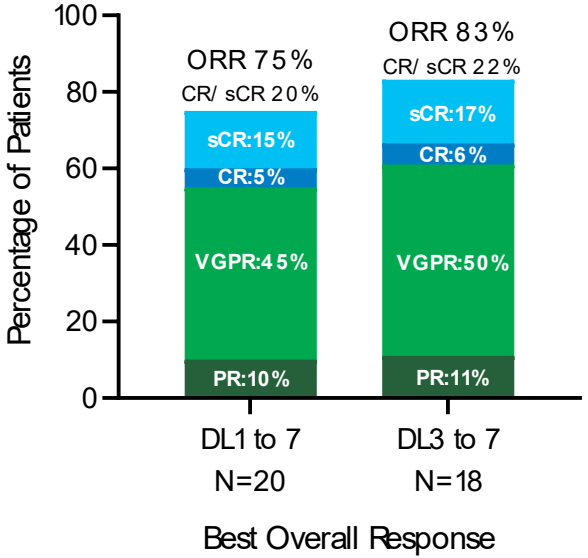
Non-Hematologic Drug-Related TEAEs (≥ 15%, N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Non-Hematologic TEAEs	20 (100)	3 (15)	0
Cytokine release syndrome	15 (75)	0	0
Injection site reaction	12 (60)	0	0
Alanine aminotransferase increased	5 (25)	0	0
Aspartate aminotransferase increased	4 (20)	1 (5)	0
Fatigue	3 (15)	0	0
Gamma-glutamyltransferase increased	3 (15)	0	0
Nausea	3 (15)	0	0

- No ICANS
- CRS events mostly G1 limited to first administration of ISB 2001
- All CRS reported were G1 except 2 cases reported as G2, one on Day 1 and second case on Day 118 (confounded by COVID-19)
- Median time to CRS: 3 (1;118) days
- Median Duration of CRS: 2 (1;8) days
- 2 subjects received Dexamethasone, and 7 subjects received Tocilizumab

ICANS, Immune effector cell-associated neurotoxicity syndrome; CRS, Cytokine Release Syndrome

ISB 2001: Deep and Lasting Responses Observed at ≥ 50 µg/kg



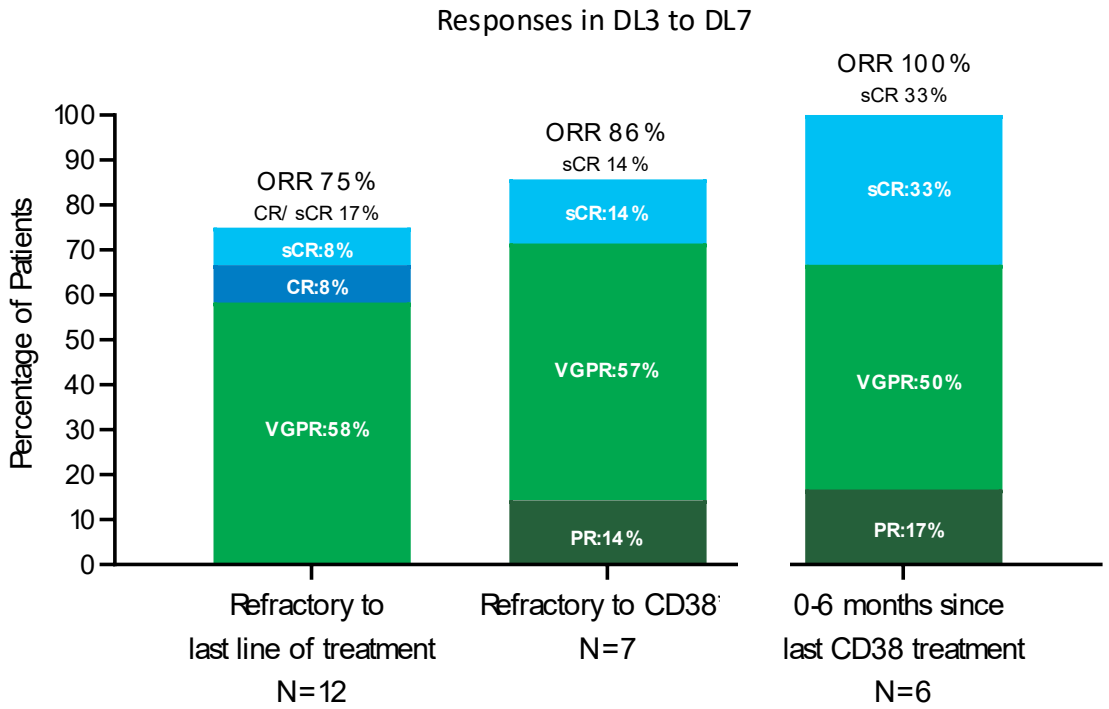


Median follow up 6 months (range: 2-10)

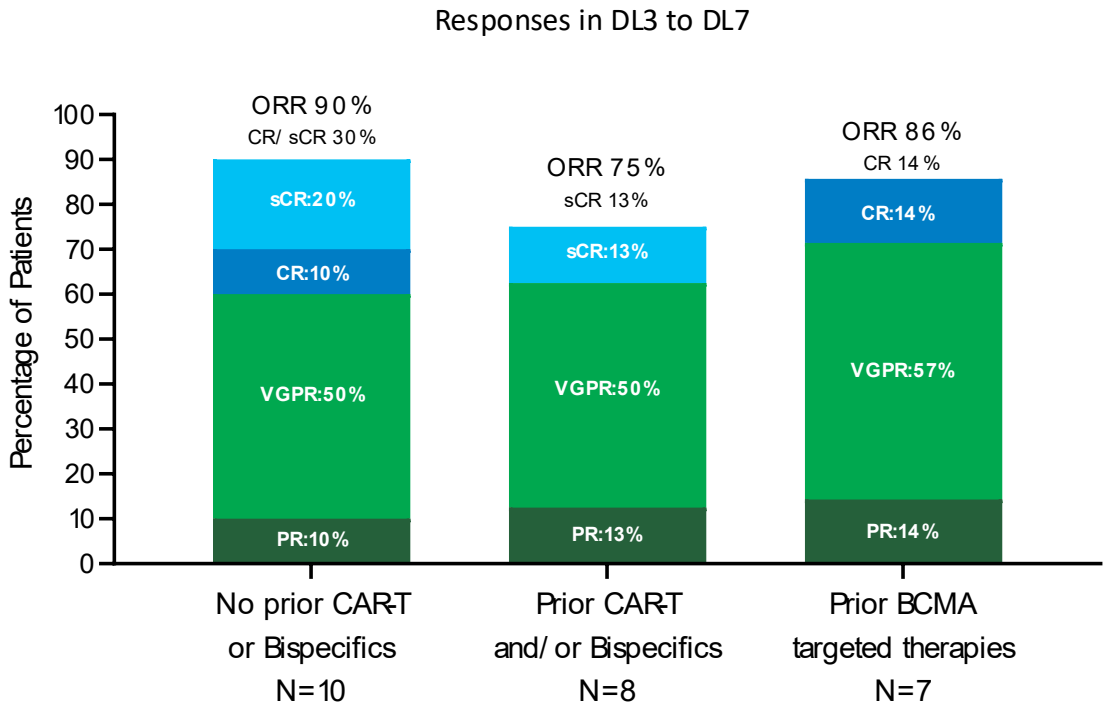
First objective response observed at DL3 (sCR, MRD negative at 10^{-5} level)

Median time to first response was 36 days (range: 29-57)

ISB 2001: High Response Rates In Patients Refractory to Last Line of Therapy, Refractory or Recently Failing CD38 Therapies



ISB 2001: High Response Rates in Patients With or Without Prior BCMA targeted and/or T Cell Directed Therapies*

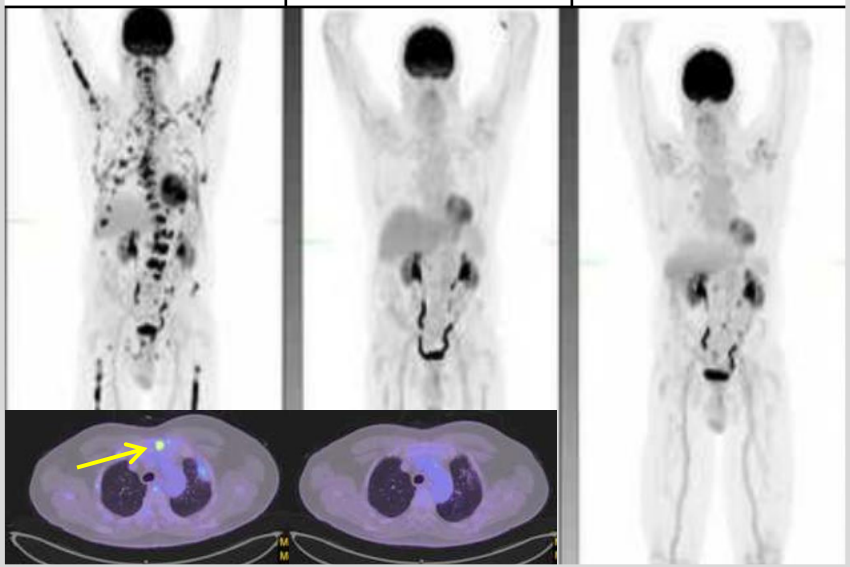


* T cell directed therapies include CD3 bispecifics and CAR T cell therapies

ISB 2001: Rapid and Sustained Responses by PET-CT in Two Patients

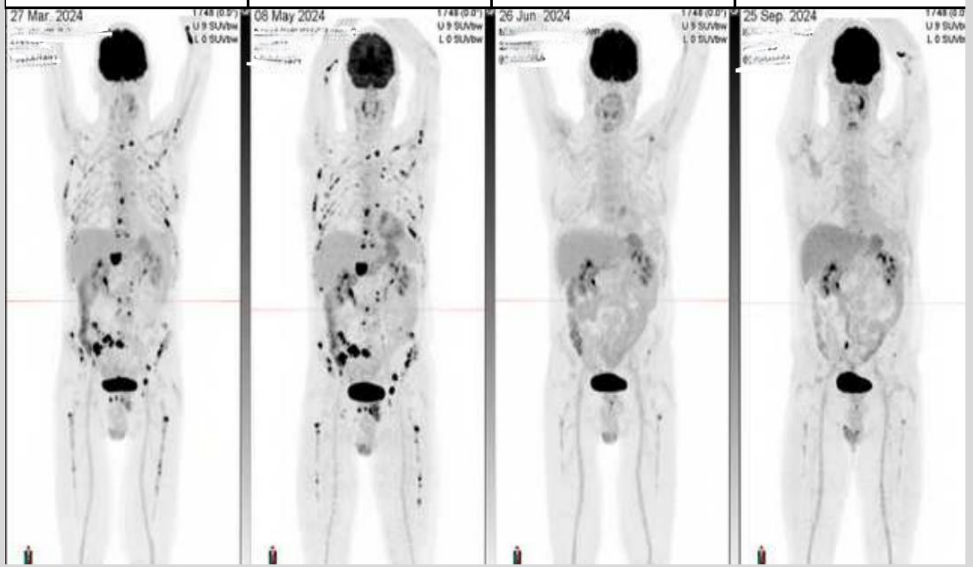
Patient 1 (DL5): 4 Prior lines

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

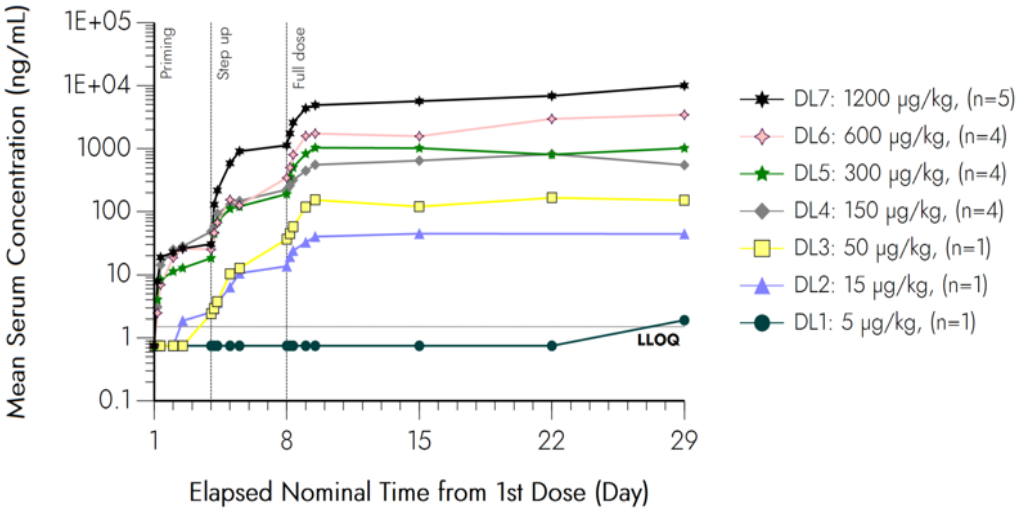


Patient 2 (DL5): 3 Prior Lines Including T Cell Directed Therapy (Forimtamig)

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



Dose-Proportional PK Profile and Long Half-Life Supporting Less-Frequent Dosing Schedule for ISB 2001



Slow absorption, consistent with expected PK profile of SC administration

Near dose proportional increase in serum exposures observed from DL2 to DL7

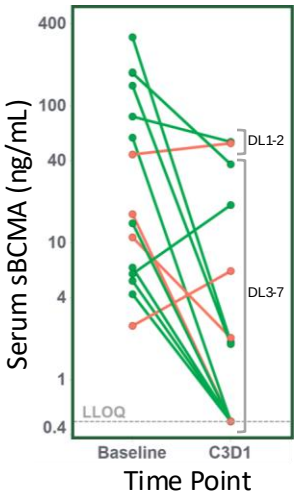
Preliminary half-life of over 10 days

In total 2 out of 20 evaluable patients (10%), one each in DL1 and DL4, showed positive ADA

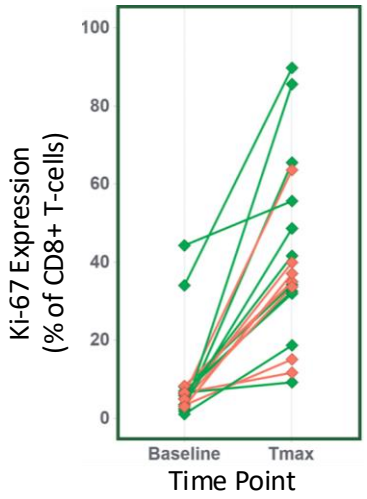
LLOQ: Lower Limit of Quantitation; SC: Subcutaneous; ADA: Anti-Drug Antibody

T-Cell Activation and Reduction of Soluble BCMA After ISB 2001

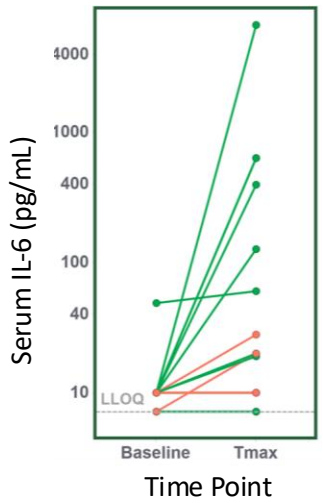
Reduced Serum sBCMA



Increased T Cell Proliferation (Ki-67)



Increased Serum IL-6



Prior CAR-T and/or Bispecifics

Yes
No

Reduction in serum soluble BCMA levels within 1-2 treatment cycles in responding subjects

ISB 2001 induced T cell proliferation and activation (Ki-67, PD-1) in CD4+ and CD8+ cells

Mild increases in serum cytokines observed in most subjects, constant with mild clinical CRS profile

Effects observed in patients previously treated with a CAR-T and/or bispecifics

Early Clinical Results of ISB 2001 a novel TREAT ™ Trispecific

Safety:

- No DLTs up to 1200 µg/kg weekly dosing.
- Mild CRS and injection site reactions, no ICANS.
- Low infection and hematological toxicity rates.

Early and sustained responses were observed across effective dose levels (DL3 to DL7):

- Anti-myeloma activity From 50 µg/kg (MRD-negative sCR) and higher
- 83% ORR overall (22% CR or better, 50% VGPR, 11% PR),
- 90% and 75% ORR in CAR-T/bispecific-naïve or pretreated patients, 86% with prior BCMA therapy, 86% in CD38-refractory patients.

PK and Translational:

- Dose-proportional PK with long half-life supports less-frequent dosing.
- T cell activation observed at effective doses.

Next Steps:

- Escalation continues to 2700 µg/kg, followed by dose-expansion to establish RP2D and best dosing schedule.

Acknowledgment

Participating patients and their families

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Ichnos Glenmark Innovation team

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