Initial Results of Dose Escalation of ISB 1342, a Novel CD38xCD3 Bispecific Antibody, in Patients with Relapsed / Refractory Multiple Myeloma (R/R MM)

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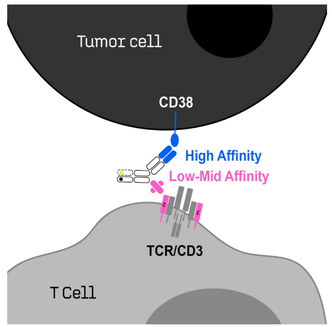
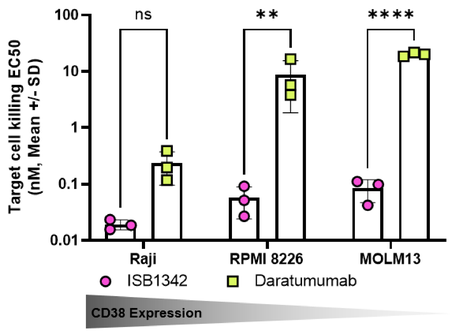
BACKGROUND

ISB 1342:

- A heterodimer based on the Ichnos proprietary BEAT® platform (Bispecific Engagement by Antibodies based on the TCR) .
- A humanized CD38xCD3 bispecific antibody
- Simultaneously engages CD38 antigens with high affinity on multiple myeloma (MM) cells and CD3 antigens with moderate affinity on T cells.
- Preclinically, ISB 1342 demonstrated potency in both CD38 high- and low-expressing cells.



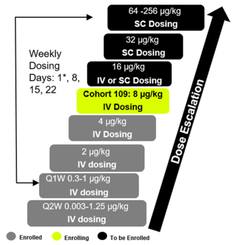
ISB 1342 Potency Maintained in Tumor Cells Across Levels of CD38 Expression



Reported here are findings from the Q1W dose-escalation portion of an ongoing, multi-center, open-label, single-agent international phase 1 study (NCT03309111) of ISB 1342 in patients with R/R MM.

DESIGN AND RESULTS

3 + 3 Design



Patients

- 29 patients were enrolled in bi-weekly dosing cohorts
- **30** patients have been enrolled in weekly dosing cohorts

Eligibility:
- Adults (>18 yo) with RRMM
- Triple class refractory
- Anti-CD38 Rx 2-month washout
- Measurable disease

Phase I Objectives

- **Primary:** Determine MTD and/or recommended Phase 2 dose
- **Secondary:** Assess safety and tolerability, PK &PD, immunogenicity, antimyeloma activity

*Priming dose administered on Cycle 1 Day 1 followed by maintenance dose onwards (as shown). Data cutoff as of Oct 25, 2022 (including 3 ongoing patients in cohort 109 who received 1, 3, and 3 doses of ISB 1342).

Baseline Characteristics	ISB 1342-101 Q1W cohort
Median age	68 (54-76)
ISS stage at BL (n=21)	
Stage 1	30%
Stage 2	30%
Stage 3	30%
Median prior regimens	6.0 (2-11)
Triple refractory	90%
Penta-refractory	73%
Median time from last CD38-directed therapy	16.6 months (3-50)
Prior anti-BCMA	30%
Prior T-cell-based treatment	10%

TEAE[#] (>10% Q1W cohort)	All Grade n (%)	Grade ≥3 n (%)
Any TEAE	30 (100.0)	25 (83.3)
Infusion related reaction	13 (43.3)	5 (16.7)
Anemia	10 (33.3)	7 (23.3)
Thrombocytopenia	9 (30.0)	3 (10.0)
Blood creatinine increased	6 (20.0)	1 (3.3)
Cytokine release syndrome*	6 (20.0)	0
Hypoalbuminemia	5 (16.7)	0
Hypokalemia	5 (16.7)	0
Hyponatremia	4 (13.3)	0
Leukopenia	4 (13.3)	1 (3.3)
Lymphopenia	4 (13.3)	2 (6.7)

[#] Data in this table include all treated patients in the Q1W IV cohort as of Oct 25, 2022. At the data cutoff, cohort 109 testing a priming dose of 2 µg/kg followed by a weekly dose of 8 µg/kg is open, and 3 patients have received 1, 3, and 3 doses of ISB 1342.
*Tocilizumab was given to 1 patient

A single DLT (Grade 3 delirium) was observed in a 73-year-old patient treated in cohort 104 (0.3/0.55 µg/kg) after the third dose of ISB 1342. This event was not a CRS event.

Q1W Cohort	Priming Dose (µg/kg)	Target Dose (µg/kg)	# of 1342 Doses[1]	IRR/CRS Occurrences[2] Grade 1	Grade 2	Grade 3
103	0.20	0.30	13	0	2	1
104	0.30	0.55	54	2	3	0
105	0.55	0.75	38	7	3	6
106	0.75	1.0	23	3	8	1
107	1.0	2.0	19	0	0	0
108	1.0	4.0	38	2	2	1
109	2.0	8.0	8	1	1	0

[1]. Number of ISB 1342 administrations given at the cohort
[2]. Number of IRR/CRS events encountered

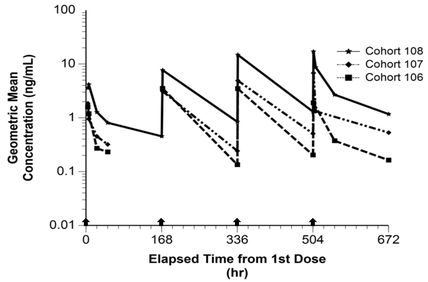
Increased Expression of CD69 in T-cells Following Treatment with ISB 1342

T-cell expression of CD69 was assessed by flow cytometry analysis of peripheral blood samples collected during treatment Cycle 1 from a patient enrolled in cohort 108. Comparison of CD69 expression frequencies generally indicate increased T-cell activation levels at 48h post-dose compared to the pre-dose samples.

T-Cell Activation and Serum Cytokine Level Changes Following Treatment with ISB 1342

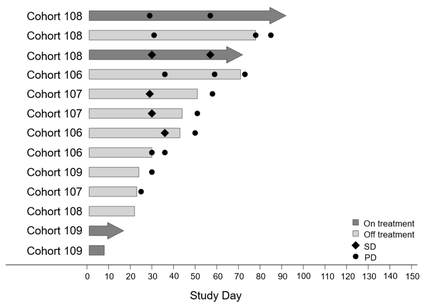
Expression of several potential markers of T-cell activation was monitored by flow cytometry analysis of peripheral blood samples collected during treatment cycle 1 from a patient enrolled in cohort 108 (left panel). Several activation markers exhibited transient increases in frequency of expression following ISB 1342 dosing. Arrows indicate the ISB 1342 dosing time points. Cytokine levels were measured in serum collected from the same patient, indicating transient increases in cytokine levels associated with T-cell activation (right panel).

Dose Related Increases in ISB 1342 Trough Serum Concentrations Observed



Geometric mean ISB 1342 serum concentration versus time profile from Cohort 106 (0.75 µg/kg -> 1 µg/kg), Cohort 107 (1 µg/kg -> 2 µg/kg) and Cohort 108 (1 µg/kg -> 4 µg/kg) are shown.

Clinical Responses To Date*



*Cohort 106 (0.75 µg/kg priming, 1.0 µg/kg targeted dose) is the lowest dose predicted to result in clinical response per QSP modeling (data not shown).

CONCLUSIONS

- Treatment with ISB 1342 was well tolerated at the evaluated Q1W dose levels.
- The observed CRS events were moderate and manageable with supportive care.
- Dose escalation continues with participants enrolling in additional cohorts.

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