4707 Initial Dose Escalation of ISB 1442, a Novel CD38 Biparatopic x CD47 Bispecific Antibody, in Patients with Relapsed / Refractory Multiple Myeloma (RRMM)

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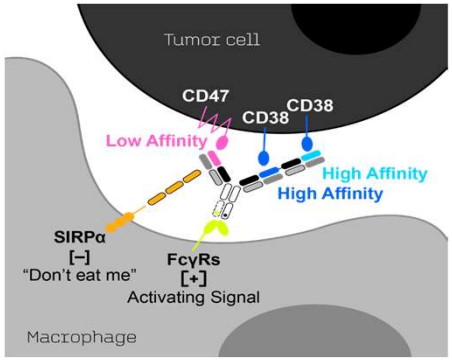
BACKGROUND

ISB 1442

- ISB 1442 is a biparatopic bispecific antibody which has dual binding to CD38 and CD47 epitopes, generated using Ichnos' Bispecific Engagement by Antibodies based on the T cell receptor (BEAT®) platform.
- Two Fab regions bind to two distinct CD38 epitopes which do not compete functionally with daratumumab.
- One arm blocks CD47-SIRPa binding on tumor cells to enhance ADCP.
- Engineered Fc domain to enhance ADCP, CDC, and ADCC.
- Expected to have optimized tolerability with low potential for adverse effects on red blood cells (RBC) such as hemagglutination, platelet aggregation and RBC depletion.

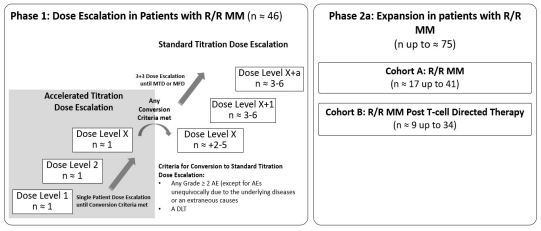


ISB 1442-101 Clinical Trial

Reported here are findings from dose-escalation of an ongoing, multi-center, open-label, single-agent international Phase 1/2a study (NCT05427812) of ISB 1442 in patients with R/R MM.

Data extraction: 10/20/23 (ongoing database)

DESIGN AND RESULTS



Part 1: Dose Escalation Ongoing

Dose Level	Dose (mg/patient)	
DL-1	3	Accelerated Titration is completed
DL1	6	
DL2	20	
DL3	60	
DL4	150	Standard Titration with n =3+3, and modified Fibonacci Dose Escalation is ongoing
*DL5	300	
DL6	450	
DL7	600	
DL8	750	
DL9	935	
DL10	1170	

- ISB 1442 is administered weekly subcutaneously (SC).
- No priming dose given in DL1 to DL4.
- Priming dose implemented starting from DL5 (60mg on day 1, followed by 300mg on day 8 and onwards).
  - Implementation of priming dose was pre-specified in the protocol if CRS would occur.
- Subjects ongoing in DL3 have been escalated to 300mg (intra-patient escalation, DL3-Esc cohort).

Demographics

Patient characteristics	Statistics	DL1(6mg) (N=2)	DL2(20mg) (N=1)	DL3(60mg) (N=3)	DL3 Esc (N=2)	DL4(150mg) (N=9)	DL5(300mg) (N=1)	Total (N=18)
Gender								
Female	n (%)	1 (50%)	1 (100%)	0	2 (100%)	4 (44%)	0	8 (44%)
Male	n (%)	1 (50%)	0	3 (100%)	0	5 (55%)	1 (100%)	10 (55%)
Age (years)								
	Median	63.0	48.0	70.0	77.5	65.0	68.0	68.0
Race								
Black or African American	n (%)	0	0	0	0	2 (22%)	0	2 (11%)
White	n (%)	2 (100%)	1 (100%)	3 (100%)	2 (100%)	7 (78%)	1 (100%)	16 (89%)
Cancer stage								
I	n (%)	1 (50%)	0	1 (33%)	0	0	0	2 (11%)
II	n (%)	0	0	0	0	5 (55%)	0	5 (27%)
III	n (%)	0	0	1 (33%)	0	0	0	1 (5.6%)
Unknown	n (%)	1 (50%)	1 (100%)	1 (33%)	2 (100%)	4 (44%)	0	9 (50%)
Extramedullary Disease								
Yes	n (%)	1 (50%)	0	1 (33%)	2 (100%)	4 (44%)	0	8 (44%)
No	n (%)	1 (50%)	1 (100%)	1 (33%)	0	3 (33%)	0	6 (33%)
Unknown	n (%)	0	0	1 (33%)	0	2 (22%)	0	3 (16%)
Lytic Bone Disease								
Yes	n (%)	2 (100%)	0	2 (67%)	1 (50%)	6 (67%)	0	11 (61%)
No	n (%)	0	1 (100%)	0	0	1 (11%)	0	2 (11%)
Unknown	n (%)	0	0	1 (33%)	1 (50%)	2 (22%)	0	4 (22%)
Number of prior lines of therapy								
	Median (Min;Max)	4.0 (3 ;5)	7.0 (7 ;7)	5.0 (2 ;8)	6.0 (5 ;7)	7.0 (5 ;13)	6.0 (6 ;6)	6.0 (2 ;13)
Prior Lines of Therapy								
IMIDs	n (%)	2 (100%)	1 (100%)	3 (100%)	2 (100%)	9 (100%)	1 (100%)	18 (100%)
PI's	n (%)	2 (100%)	1 (100%)	3 (100%)	2 (100%)	9 (100%)	1 (100%)	18 (100%)
CD38 antibody	n (%)	2 (100%)	1 (100%)	3 (100%)	2 (100%)	9 (100%)	1 (100%)	18 (100%)
ASCT	n (%)	2 (100%)	1 (100%)	2 (66.6%)	1 (50%)	6 (66.6%)	1 (100%)	13 (72.2%)
Prior CAR-T	n (%)	0	0	0	0	2 (22.2%)	0	2 (11.1%)

Drug Related Aes(Hematology)

	Total** (N=18) n (%)	Grade 1 (N=18) n (%)	Grade 2 (N=18) n (%)	Grade 3 (N=18) n (%)	Grade 4 (N=18) n (%)
Anemia*	2 (11.1)	0	0	2 (11.1)	0
Haemolysis	1 (5.6) **	1 (5.6)**	0	0	0
Neutropenia	1 (5.6)	0	0	1 (5.6)	0
Pancytopenia	1 (5.6)	0	1 (5.6)	0	0
Thrombocytopenia	1 (5.6)	0	0	0	1 (5.6)

* Anemias pre-existing and/or also related to underlying Multiple Myeloma in these 2 subject.
** Grade 1 hemolysis reported, however peripheral smear without signs of hemolysis, no bleeding, no transfusion, recovered

Overall, hemoglobin values were stable based on all treated subjects to date (data not shown).
No grade 5 drug related AEs observed

Adverse Events of Special Interest

	DL1(6mg) N=2 n (%)	DL2(20mg) N=1 n (%)	DL3(60mg) N=3 n (%)	DL3 Esc N=2 n (%)	DL4(150mg) N=9 n (%)	DL5(300mg) N=1 n (%)	Total N=18 n (%)
Any Adverse Events of Special Interest	1 (50.0)	0	1 (33.3)	1 (50.0)	8 (88.9)	1 (100.0)	12 (66.7)
Grade 1	1 (50.0)	0	1 (33.3)	0	3 (33.3)	1 (100.0)	6 (33.3)
Grade 2	0	0	0	1 (50.0)	4 (44.4)	0	5 (27.8)
Grade 3	0	0	0	0	1 (11.1)	0	1 (5.6)
Immune system disorders	0	0	0	1 (50.0)	8 (88.9)	1 (100.0)	10 (55.6)
Cytokine release syndrome	0	0	0	1 (50.0)	8 (88.9)	1 (100.0)	10 (55.6)
Grade 1	0	0	0	0	3 (33.3)	1 (100.0)	4 (22.2)
Grade 2	0	0	0	1 (50.0)	5 (55.6)	0	6 (33.3)
General disorders and administration site conditions	0	0	1 (33.3)	0	1 (11.1)	0	2 (11.1)
Injection site reaction	0	0	1 (33.3)	0	1 (11.1)	0	2 (11.1)
Grade 1	0	0	1 (33.3)	0	1 (11.1)	0	2 (11.1)
Blood and lymphatic system disorders	1 (50.0)	0	0	0	0	0	1 (5.6)
Haemolysis	1 (50.0)	0	0	0	0	0	1 (5.6)
Grade 1	1 (50.0)*	0	0	0	0	0	1 (5.6)
Renal and urinary disorders	0	0	0	0	1 (11.1)	0	1 (5.6)
Acute kidney injury	0	0	0	0	1 (11.1)**	0	1 (5.6)
Not Related	0	0	0	0	1 (11.1)	0	1 (5.6)
Grade 3	0	0	0	0	1 (11.1)	0	1 (5.6)

*Grade 1 hemolysis, peripheral smear without signs of hemolysis, no bleeding, no transfusion, recovered
** Grade 3 AKI with hypercalcemia due to progressive disease

Soluble Biomarker Changes Following ISB 1442 administration

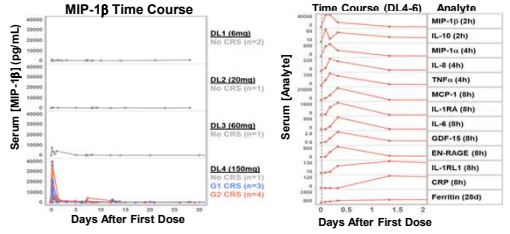
- A total of 65 analytes were quantified in serum samples from patients treated with ISB 1442, using Luminex or ELISA assays. The table shows the maximum fold-increase for a subset of these analytes, including all 14 biomarkers that demonstrated at least 3-fold increases post-treatment in at least 5 patients.
- Several macrophage activation-related biomarkers (MIP-1β, IMP-1α, MCP-1) were increased in multiple patients, suggesting macrophage-related mechanism of action.

< 3-Fold
3 to 10-Fold
> 10-Fold

Dose (mg)	Pt #	CRS Grade	MIP-1β	MIP-1α	MCP-1	IL-6	IL-8	IL-10	IL-1RA	TNFα	TNFR2	IL-1RL	EN-RAGE	GDF-15	CRP	Ferritin	IFN-γ
6	DL1-1	≠	2	2	2	4	1	1	1	1	1	1	3	3	16	1	1
	DL1-2	≠	2	2	4	1	1	3	1	1	3	1	1	3	4	2	1
20	DL2-1	≠	2	2	2	1	3	2	2	1	1	2	3	1	24	1	1
60	DL3-1	≠	23	4	2	2	3	31	3	2	2	9	14	1	3	3	1
150	DL4-1	≠	10	2	1	1	1	27	2	1	1	8	3	2	28	1	1
	DL4-2	1	50	19	49	155	19	8	39	6	3	15	21	3	74	3	1
	DL4-3	2	22	3	11	4	2	3	3	3	3	16	13	3	54	6	1
	DL4-4	1	70	8	57	51	33	31	55	12	3	17	7	2	196	5	2
	DL4-5	1	24	5	34	5	2	6	11	4	2	3	2	2	19	2	1
	DL4-6	2	52	12	50	121	31	4	22	10	4	6	7	3	21	3	1
	DL4-7	2	31	86	39	75	12	65	11	42	4	12	5	8	6	9	27
	DL4-8	2	10	2	2	12	3	5	2	4	4	3	2	2	22	2	1

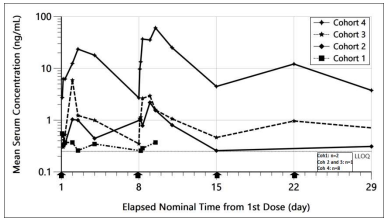
Dose-Dependence and Time Course of Soluble Biomarker Changes Following Treatment with ISB 1442

- Transient increases in soluble biomarkers were predominantly observed following the first dose of ISB 1442, with greater increases at dose level 4 (150 mg) compared to lower dose levels, and in patients exhibiting CRS-like symptoms (left panel).
- The time course of biomarker changes during the first 48h after dosing is shown for one patient (DL4-ptatient 6), demonstrating the different timing of peak levels for several serum biomarkers after dosing within this patient (right panel).



Pharmacokinetics

- Mean ISB 1442 serum concentration versus time profile from Cohort 1 (6 mg SC), Cohort 2 (20 mg SC), Cohort 3 (60 mg SC) and Cohort 4 (150 mg SC) are shown.
- Rich PK samples collected after C1D1 and C1D8 doses, followed by pre-dose samples for the remaining dose occasions.
- Super-Proportional Increases in ISB 1442 Serum exposures (C_{max} and AUC) most evident between cohorts 3 to 4.
- Slow absorption of ISB 1442 after SC injection with T_{max} achieved mostly on the 2nd day of dosing.



Clinical Responses To Date ^

Best Overall Response	DL1(6mg) N=2	DL2(20mg) N=1	DL3(60mg) N=5	DL4(150mg) N=9	DL5(300mg) N=1
Stable disease (SD)	0	0	1 (33%)	3 (33%)	0
Progressive Disease (PD)	1 (50%)	1 (100%)	1 (33%)	4 (44%)	0
Not Evaluable (NE)	1 (50%)	0	0	0	0
Missing	0	0	1 (33%)	2 (22%)	1 (100%)

^Data extract update from 6th December, 2023

Based on in-vitro modeling, current DL4 mean ISB 1442 concentration is in the EC50 range. EC90 range could potentially be achieved with DL 6 to 7 dose (450-600mg).

CONCLUSIONS

- Overall, treatment with ISB 1442 is well tolerated
- CRS events observed at DL4 (150mg) were of low grade (1 or 2) and mostly resolved within one day.
- No risk of neurotoxicity, hemolytic anemia or infections have been observed to date.
- Soluble biomarker changes, with increased macrophage-related markers are among the first changes observed.
- Dose escalation is ongoing with participants enrolling in DL5 (300
- mg).