3694. Clinical validation of a quantitative systems pharmacology (QSP) model of ISB 2001 used for deriving first in human (FIH) dose and efficient phase 1 dose escalation design in relapsed/refractory multiple myeloma (RRMM) patients

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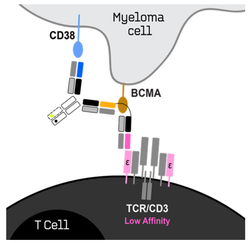
ISB 2001 MOLECULAR DESIGN

- Three proprietary antigen-binding arms: CD3ε on T cells; BCMA and CD38 on Multiple Myeloma cells
- 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
- ISB 2001 was not fully cross-reactive to any preclinical species
- No monkey toxicology or pharmacokinetic (PK) studies were done to support clinical translation as this can not fully recapitulate the safety or PK profiles

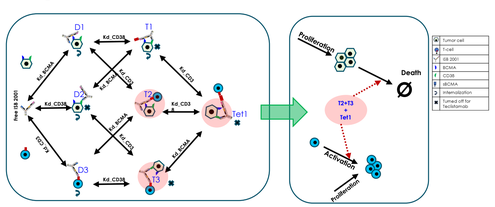


THE CHALLENGE

- No safety or PK data in monkey studies to support clinical translation and phase 1 study design in terms of First in Human (FIH) dose, and anticipated efficacy dose range.
- Literature search revealed very low FIH dose selection in T-cell engager (TCE) space through MABEL approach based on in vitro data, leading to FIH studies with multiple sub-therapeutic cohorts

METHOD: *IN VITRO* PHARMACOLOGY MODEL

Step 1: Target engagement model for ISB 2001 and teclistamab was developed using in-house data from *in vitro* functional and binding assays
Step 2: In vitro model for ISB 2001 and Teclistamab for T-cell activation and tumor cytotoxicity was developed and calibrated using experimental data

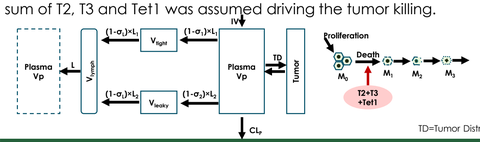


D1, D2, D3: Dimers, T1, T2, T3: Trimers, Tet1: Tetramer; Pink circle indicate pharmacologically active species (ACT) driving the tumor killing

- Binding constants (Kd, Kon & Koff), cell counts, receptor density/cell except for CD3[1] were data generated inhouse. Internalization rates for CD3[2], BCMA[3], CD38[4] bound drug were obtained from literature.
- Pharmacologically active species normalized to tumor cells (nACT) was the most important translational parameter across experiments, species driving the efficacy

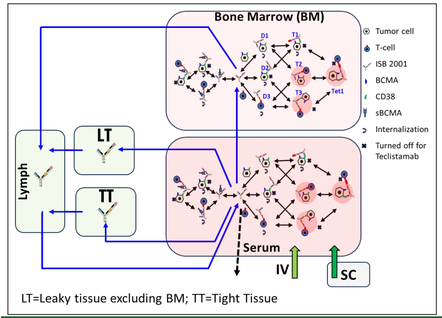
METHOD: *IN VIVO* PRECLINICAL EFFICACY MODEL

Step 3: Mouse PK data of ISB 2001 and teclistamab with and without tumor was fitted to a minimal physiologically-based pharmacokinetic (mPBPK) model[5]. The physiological parameters were fixed to the published IgG parameters except CL[5]. The CL was estimated from the mouse PK data.
Step 4: Mouse PKPD data of ISB 2001 and teclistamab was fitted to a mPBPK-PD model combining minimal PBPK[5], tumor compartment and target engagement model, tumor volume change was described by a transduction model[1]. The sum of T2, T3 and Tet1 was assumed driving the tumor killing.



METHOD: HUMAN QSP MODEL

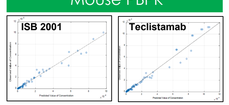
Step 5: A modified human PBPK model was developed from published mPBPK model[5]. The leaky tissue compartment was subdivided into bone marrow and other leaky tissues. All physiological parameters except CL were fixed to typical IgG parameters for both ISB 2001 and teclistamab[6,7]. ISB 2001 CL was allometrically scaled from mouse data, teclistamab CL was estimated from literature[8].
Step 6: Target engagement model was combined with the modified PBPK model to make an integrated QSP model for both ISB 2001 and teclistamab. For teclistamab model the CD38 interaction dynamics was turned off. CD4+T cells , CD8+ T-cells and plasma cells, other cell types which express CD38 (such as monocytes, neutrophils and natural killer (NK) cells were added to plasma compartment as source of target mediated drug disposition.



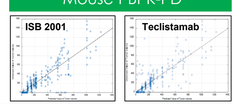
LT=Leaky tissue excluding BM; TT=Tight Tissue

GOODNESS OF FIT PLOTS

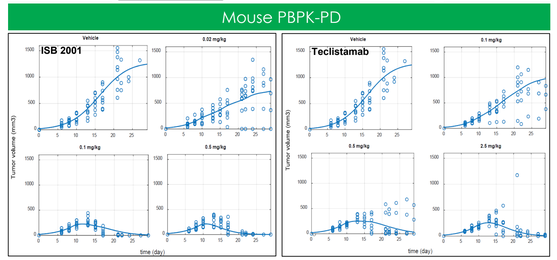
Mouse PBPK



Mouse PBPK-PD



Mouse PBPK-PD



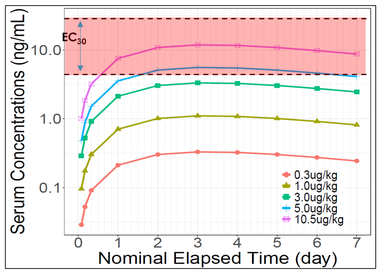
FIH DOSE AND EFFICACY DOSE RANGE PREDICTION

Teclistamab Benchmarking			ISB 2001 Clinical Dose Prediction	
Teclistamab Clinical Dose	Simulated BM nACT in Patient	Invivo mouse PKPD model ECx	Simulated BM nACT in patient	ISB 2001 Clinical Dose to predicted to achieve equivalent BM nACT
60 µg/kg SC*	24	EC_{13}	0.50	8.0 µg/kg SC
38.4 µg/kg IV	**27**	**EC_{17}**	**0.63**	**10.5 µg/kg SC**
300 µg/kg SC*	91	EC_{40}	2.1	32.0 µg/kg SC
450 µg/kg SC	137	EC_{50}	3.1	70.0 µg/kg SC
1500 µg/kg SC*	320	EC_{70}	7.0	130 µg/kg SC
NA	NA	EC_{90}	28.0	320 µg/kg SC

*: Teclistamab approved doses

- Teclistamab QSP simulations of BM nACT at 60, 300 and 1500 µg/kg SC enabled identifying critical ECx for ISB 2001 dose predictions
- Predicted minimal pharmacologically active dose (MPAD) of ISB 2001 was 10.5 µg/kg based on equivalent tumor cell normalized pharmacologically active species (nACT) based ECx after teclistamab benchmarking at 38.4 µg/kg IV, where the 1st response was observed during escalation phase[9].
- ISB 2001 anticipated efficacy dose ranged from 11 µg/kg to 300 µg/kg SC

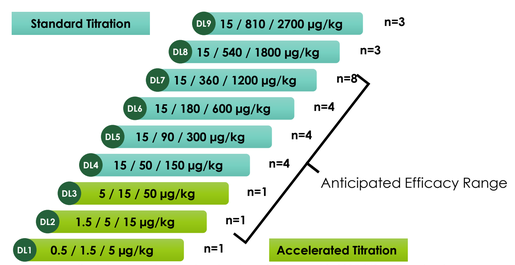
In vitro Cytokine Release EC_{30} vs Simulated C_{max}



- FIH dose of 5 µg/kg SC was selected to maintain serum C_{max} below the in vitro cytokine release EC_{30}
- Proposed dose schedule included Priming (0.5 µg/kg) and Step-up dose (1.5 µg/kg, preemptively

ISB 2001-101 STUDY DESIGN PART 1: DOSE ESCALATION

- ISB 2001 is administered subcutaneously (SC) once weekly (Q1W) in 28-day cycles
- Step-up doses are administered on Days 1 and 4, followed by the full target dose from Day 8 onwards
- Step-Up dose 1 was maintained at 15 µg/kg starting from Dose Level 4 to minimize severity of CRS events during initial treatments with ISB 2001



n: Total patients treated at each dose level as of February 10, 2025 (US, AUS regions)

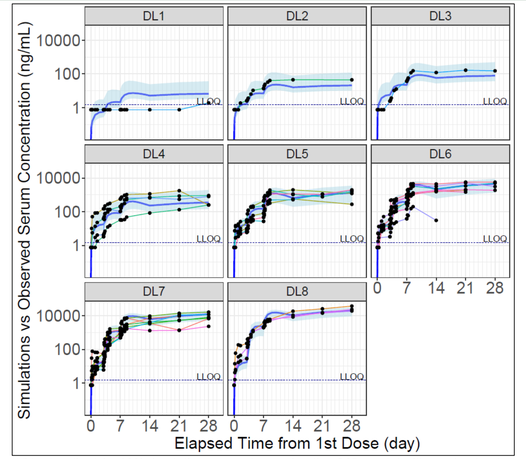
ISB 2001-101 PK Bioanalysis

Free ISB 2001 in human serum was quantified using a validated electrochemiluminescence (ECL) method developed using MSD platform.

CLINICAL VALIDATION OF THE ISB 2001 QSP MODEL

No CRS Incidence at DL1 (Starting Dose) or DL2									
Dose Occasion	DL1 N=1	DL2 N=1	DL3 N=1	DL4 N=4	DL5 N=5	DL6 N=7	DL7 N=5	DL8 N=3	Total N=30
C1D1	0/1	0/1	0/1	3/4	3/5	3/7	4/8	1/3	14/30
C1D4	0/1	0/1	0/1	1/4	0/5	1/7	4/8	0/3	6/30
C1D8	0/1	0/1	0/1	0/4	1/5	0/7	0/7	0/3	1/29

Observed Concentration-Time Profile Match with Simulation



Virtual patient (n=100) simulations were done using the QSP model with varying body weights and target density; Solid blue line is median of simulation, light blue shade indicate min and max simulations, solid lines with markers are individual patient profiles

Observed Anti-Tumor activity Dose Range Match with Model Predictions

	DL1 N=1	DL2 N=1	DL3 N=1	DL4 N=4	DL5 N=4	DL6 N=4	DL7 N=5	Total N=20
Responder (sCR/CR/VGPR/PR)	0	0	1	3	4	3	4	15
Non-Responder (SD/PD)	1	1	0	1	0	1	1	5

sCR: Stringent Complete Response, CR: Complete Response, VGPR: Very Good Partial Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease

CONCLUSION

- Despite the absence of monkey PK and toxicology data, this QSP-guided approach successfully predicted an optimal FIH dose, clinical PK, safety, and anti-myeloma activity, while minimizing patient exposure to sub-therapeutic doses.
- The QSP based FIH estimation, and efficacy dose range estimation offers an effective pathway for designing phase 1 studies for future TCEs

REFERENCES

1. Betts A, et al. AAPS J. 2019 May 22;21(4):66.
2. Press OW, et al. Cancer Res. 1988 Apr 15;48(8):2249-57
3. Ghose J, et al. Oncoimmunology. 2018 Jul 23;7(10)
4. Lee L, et al. Br J Haematol. 2016 Sep;174(6):911-22
5. Yuan D, et al. AAPS J. 2018 Mar 14;20(3):48.
6. Cao Y, et al. J Pharmacodyn. 2014 Aug;41(4):375-87
7. Cao Y, et al. J Pharmacokinet Pharmacodyn. 2013 Oct;40(5):597-607
8. Girgis S, et al. Target Oncol. 2022 Jul;17(4):433-439
9. Usmani SZ, et al. Lancet. 2021 Aug 21;398(10301):665-674