A multicentre Phase I clinical trial demonstrates manufacturing feasibility, safety and activity of novel humanized BCMA-directed CAR-T cell therapy.

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BACKGROUND

- hBCMA - a humanized anti-BCMA next-generation CAR-T design demonstrated strong target-binding affinity, potent anti-tumor activity, and an acceptable safety profile in preclinical studies (*Khan et al., ASH 2024*).

- The first-in-human Phase I/II clinical trials to evaluate hBCMA as a safe and effective therapeutic option for relapsed/refractory multiple myeloma (rrMM) were initiated (CTRI/2025/01/079364).
- Here, we report the manufacturing feasibility and safety in Phase I clinical study and early activity of hBCMA.

OBJECTIVES

- To evaluate the assess safety by determining the incidence of adverse events and dose-limiting toxicities (DLTs) was of hBCMA for rrMM.

- Determine persistence and quantification of hBCMA cells.
- To determine overall response rate and survival outcomes
- To assess the durability of response (DOR)

CONCLUSION

- hBCMA showed complete absence of neurotoxicity (any grade) and minimal incidence of Grade III/IV CRS in Phase I dose escalation study
- hBCMA CAR-T cells were successfully manufactured for all patients (100% MSR) with robust expansion and persistence *in vivo*.
- Low doses of hBCMA demonstrated significant anti-tumor activity with responses lasting beyond 6 months in heavily pretreated patients.

METHODS

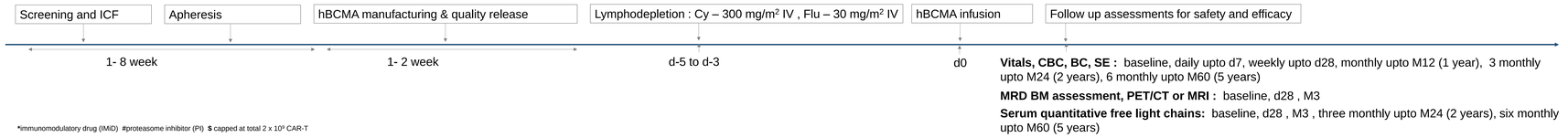
Multicenter , Non-randomized , single arm Phase I/II study

Key eligibility criteria:
- Relapsed/Refractory MM , ≥18 years
- Failed ≥ 2 lines or double refractory to IMiD* and PI#
- Measurable residual disease

Phase I objective (Safety):
- Maximum tolerated Dose (MTD) -RP2D
- Adverse events of interest
- Dose limiting toxicity (DLT) (3+3 design)

Dose levels$:
- DL 1 : 0.5 – 2 x 10^6 CAR-T cells/kg
- DL 2 : 2 – 5 x 10^6 CAR-T cells/kg
- DL 3 : 5 – 10 x 10^6 CAR-T cells/kg

Phase II objective (Efficacy):
- ORR at Month 3 , MRD assessment
- Progression free survival (PFS), Overall survival (OS)
- N =45



Vitals, CBC, BC, SE : baseline, daily upto d7, weekly upto d28, monthly upto M12 (1 year), 3 monthly upto M24 (2 years), 6 monthly upto M60 (5 years)

MRD BM assessment, PET/CT or MRI : baseline, d28 , M3

Serum quantitative free light chains: baseline, d28 , M3 , three monthly upto M24 (2 years), six monthly upto M60 (5 years)

*immunomodulatory drug (IMiD) #proteasome inhibitor (PI) $ capped at total 2 x 10^9 CAR-T

RESULTS

Patient baseline characteristics

Characteristics	DL 1 (n=3)	DL 2 (n=3)
Sex		
Male	1 (33%)	2 (67%)
Female	2 (67%)	1 (33%)
Age (in years)		
Median (range)	59 (54-65)	54 (53-64)
ECOG PS		
0-1	3 (100%)	3 (100%)
Extramedullary disease	0 (0%)	0 (0%)
Refractory status		
Triple refractory[a]	1 (33%)	0 (0%)
Penta refractory[b]	2 (67%)	3 (100%)
Prior therapy		
Lenalidomide	1 (33%)	3 (100%)
Pomalidomide	3 (100%)	3 (100%)
Thalidomide	3 (100%)	2 (67%)
Bortezomib	3 (100%)	3 (100%)
Carfilzomib	2 (67%)	1 (33%)
Daratumumab	2 (67%)	2 (67%)
Dexamethasone	3 (100%)	3 (100%)
Prior ASCT	1 (33%)	3 (100%)
Bridging therapy	2 (67%)	0 (0%)

[a] Triple refractory defined as refractory to ≥ 01 immuno-modulatory drug, ≥ 01 proteosome inhibitor, and ≥ 01 anti-CD38 monoclonal antibody

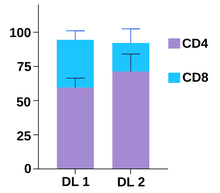
[b] Penta refractory defined as refractory to ≥ 02 immuno-modulatory drugs, ≥ 02 proteosome inhibitors, and ≥ 01 anti-CD38 monoclonal antibody

Manufacturing Feasibility

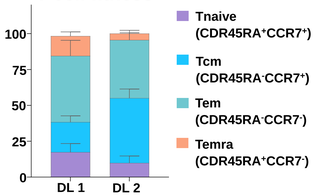
Characteristics	DL 1 (n=3)	DL 2 (n=3)
Manufacturing success rate (MSR)	3/3 (100%)	3/3 (100%)
Production cycle, days		
Median (range)	6 (6-8)	7 (6-7)
Fold expansion		
Median (range)	0.94 (0.78-1.81)	0.99 (0.85-2.08)
Transduction efficiency, %		
Median (range)	42 (19-45)	41 (40-52)
Vein to Vein time, days		
Median (range)	26 (19-36)	26 (25-32)

hBCMA product characteristics

CD4,CD8 distribution



T cell fitness



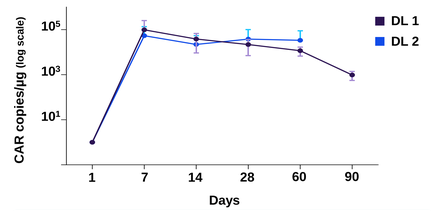
Safety profile

	All patients (n=6)	DL1 (n=3)	DL2 (n=3)
Toxicities, n(%)			
CRS			
Grade III/IV	1 (17%)	0 (0%)	1 (33%)
All Grades	5 (83%)	2 (67%)	3 (100%)
ICANS			
Grade III/IV	0 (0%)	0 (0%)	0(0%)
All Grades	0 (0%)	0 (0%)	0(0%)
Hypogammaglobulinemia			
All Grades	5 (83%)	3 (100%)	2 (67%)
IEC-HS			
Grade III/IV	0 (0%)	0 (0%)	0 (0%)
All Grades	4 (67%)	2 (67%)	2 (67%)
Anemia			
Grade III/IV	4 (67%)	2 (67%)	2 (67%)
All Grades	6 (100%)	3 (100%)	3 (100%)
Platelet count decreased			
Grade III/IV	4 (67%)	2 (67%)	2 (67%)
All Grades	5 (83%)	2 (67%)	3 (100%)
Neutrophil count decreased			
Grade III/IV	6 (100%)	3 (100%)	3 (100%)
All Grades	6 (100%)	3 (100%)	3 (100%)

HCRU for toxicity management

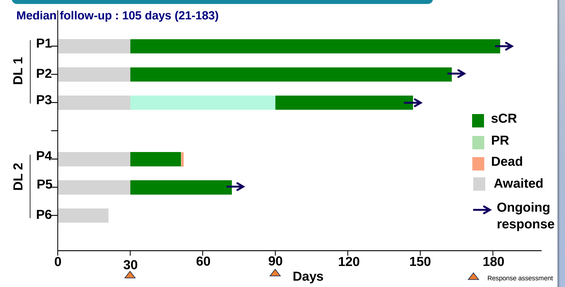
	All patients (n=6)	DL1 (n=3)	DL2 (n=3)
Hospitalization			
Median (range), days	9 (7-29)	8 (7-8)	13 (9-29)
ICU admissions	3 (50%)	2 (67%)	1 (33%)
ICU Median (range), days	4 (1-7)	4 (1-7)	4 (4)
Drugs for AEs management			
Tocilizumab	5 (83%)	2 (67%)	3 (100%)
Anakinra	3 (50%)	1 (33%)	2 (67%)
Ruxolitinib	2 (33%)	2 (67%)	0 (0%)
IVIG	6 (100%)	3 (100%)	3 (100%)

hBCMA *in vivo* expansion and persistence



hBCMA Efficacy

Median follow-up : 105 days (21-183)



All patients (n=6)	Day 28	Month 3
No. of pts evaluable	**5**	**4**
ORR	5/5 (100%)	3/4 (75%)
sCR	4/5 (80%)	3/4 (75%)
PR	1/5 (20%)	0 (0%)
Death	0 (0%)	1/4 (25%)

References:
- Khan, Aalia N., et al. Blood 144 (2024): 4809.
- IPA no. 202421019457, PCT/IB2025/052672.

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