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CAR T CELL THERAPY FOR MYELOMA

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Disclosures

- I do not have anything to disclose

CAR T cell targets in multiple myeloma (MM)

Targets	Rationale	Trials
CD19	• Not detectable by current methods but present on MM cells • Myeloma stem cells may express CD19	CD19 CAR given after 2nd auto BMT 2/10 patients – remission inversion[1]
Kappa	To target only malignant cells	4/7 patients – stable disease[2] (kappa not expressed on MM cells surface)
CD138	High expression on MM cells	4/5 patients – stable disease[3] (CD138 also expressed on variety of normal tissues)
BCMA	✓ B cell maturation/plasma cell survival via NF-KB pathway (via APRIL) ✓ High expression on MM cells	>8 trials
CS1 (SLAMF7)	▪ B cell proliferation (signaling lymphocyte activation molecule family) ▪ Very high expression on MM cells	City of Hope trial

1. Garfall AL, et al. N Engl J Med. 2015;373(11):1040–7
2. Ramos CA, et al. J Clin Invest. 2016;126(7): 2588–96
3. Guo B, et al. J Cell Immunother. 2016;2(1):28–35.
4. Matteo Giovanni Carrabba, et al. Blood 2018 132:5790
5. Eric L. Smith, et al. Blood 2018 132:589

Other pre-clinical stage CAR T:

- CD38 - also expressed on hematopoietic cells
- CD56 - also expressed on CNS cells
- CD44v6 – also on keratinocytes[4]
- GPRC5D - 95% on MM cells[5]

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ABSTRACT 957

JCARH125, Anti-BCMA CAR T-cell Therapy for Relapsed/Refractory Multiple Myeloma: Initial Proof of Concept Results From a Phase 1/2 Multicenter Study (EVOLVE)

Sham Mailankody, Myo Htut, et al. Oral Presentation Abstract 957 : ASH 2018

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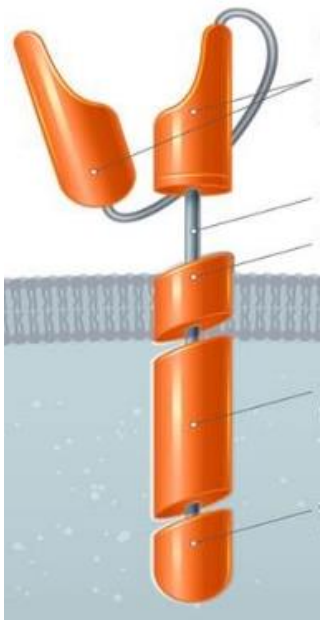
JCARH125—design and manufacturing features



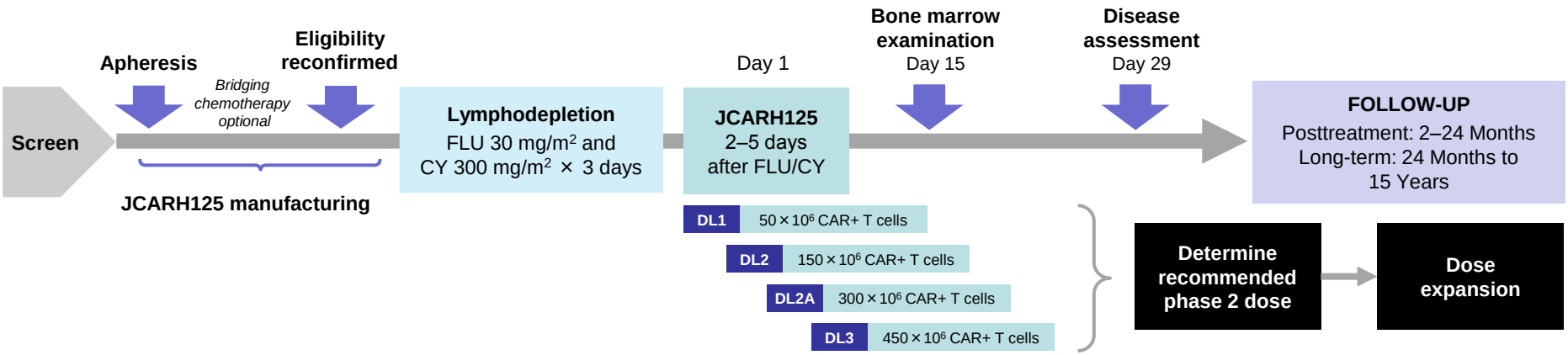
- **JCARH125 CAR construct**
  - Fully human binder with low affinity for sBCMA (MSKCC)[1]
  - Active on target cells that express low BCMA density
- **Manufacturing process**

  T cells enriched for central memory phenotype cells, potentially increasing persistence and durability

1. Smith et al. *Mol Ther*. 2018;26:1447-1456.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; sBCMA, soluble B-cell maturation antigen.

Sham Mailankody, Myo Htut, et al. Oral Abstract 957:ASH 2018

EVOLVE: Phase 1/2 Study (NCT03430011)



Key Eligibility

- **Relapsed/refractory multiple myeloma**
- **Failed at least 3 prior therapies**
  - **Autologous stem cell transplantation**
  - **IMiD, proteasome inhibitor**
  - **Anti-CD38 (combination or monotherapy)**
- **Refractory to last line of therapy**
- **ECOG performance status 0–1**
- **No selection based on BCMA expression**

Study Objectives (Phase 1)

Primary

- To evaluate safety and tolerability (DLTs, adverse events)
- To determine a recommended phase 2 dose

Secondary

- To determine JCARH125 pharmacokinetics (C_{max}, T_{max}, AUC)
- To evaluate preliminary antitumor activity
- To evaluate MRD

AUC, area under the curve; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; C_{max}, maximum concentration; CY, cyclophosphamide; DL, dose level; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FLU, fludarabine; IMiD, immunomodulatory drug; MRD, minimal residual disease; T_{max}, time to maximum concentration.

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Baseline characteristics

		CAR+ T Cell Dose		
	Total	50 × 10^6	150 × 10^6	450 × 10^6
	(N=44)	(N=14)	(N=28)	(N=2)
Median (range) age, y	**62 (36–79)**	56 (36–70)	63 (42–79)	67 (64–69)
Male, n (%)	**25 (57)**	9 (64)	15 (54)	1 (50)
High-risk cytogenetics, n (%)[a]	**34 (77)**	11 (79)	22 (79)	1 (50)
ECOG performance status 0 or 1, n (%)	**43 (98)**	14 (100)	27 (96)	2 (100)
Median (range) time since initial diagnosis, years	**6 (2–17)**	6 (2–15)	5 (2–17)	6 (5–7)
ISS stage III, n (%)	**11 (25)**	1(7)	9 (32)	1 (50)
Measurable serum M-protein spike, n (%)	**24 (55)**	4 (29)	19 (68)	1 (50)
Measurable urine M-protein spike, n (%)	**23 (55)**	8 (62)	14 (52)	1 (50)
Measurable by sFLC only, n (%)	**8 (18)**	4 (29)	3 (11)	1 (50)
Received bridging chemotherapy, n (%)	**34 (77)**	9 (64)	23 (82)	2 (100)
Progressed on bridging chemotherapy, n (%)	**19 (56)**	5 (56)	12 (52)	2 (100)

[a]High-risk cytogenetics is based on local testing and includes: del(17p), t(4;14), t(14;16), 1q21 amp.
CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; ISS, international staging system; sFLC, serum free light chain.

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Treatment history

	Total	CAR+ T Cell Dose		
		50×10^6	150×10^6	450×10^6
	(N=44)	(N=14)	(N=28)	(N=2)
Median (range) number of prior regimens	**7 (3–23)**	**8 (4–23)**	**7 (3–14)**	**7 (7–7)**
Prior autologous SCT, n (%)				
1	30 (68)	10 (71)	19 (68)	1 (50)
>1	12 (27)	4 (29)	7 (25)	1 (50)
Cumulative exposure, n (%)				
Prior PI, IMiD agent, and anti-CD38 agent	44 (100)	14 (100)	28 (100)	2 (100)
Prior 2 IMiD agents, 2 PIs, and anti-CD38 agent	38 (86)	12 (86)	24 (86)	2 (100)

IMiD, immunomodulatory drug, PI; proteasome inhibitor; SCT, stem cell transplant.

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Safety summary

	Total	CAR+ T Cell Dose		
		50×10^6	150×10^6	450×10^6
	(N=44)	(N=14)	(N=28)	(N=2)
Any SAE, n (%)	**12 (27)**	1 (7)	9 (32)	2 (100)
AEs of special interest grade ≥3/4, n (%)				
Neutropenia	**38 (86)**	11 (79)	25 (89)	2 (100)
Anemia	**22 (50)**	6 (43)	15 (54)	1 (50)
Thrombocytopenia	**19 (43)**	4 (29)	13 (46)	2 (100)
Febrile neutropenia	**8 (18)**	1 (7)	6 (21)	1 (50)
Infections[a]	**6 (14)**	0	4 (14)	2 (100)
CRS	**4 (9)**	1 (7)	2 (7)	1 (50)
Neurological events[b]	**3 (7)**	0	2 (7)	1 (50)
TLS	**1 (2)**	0	1 (4)	0
DLT, n	**1**	0	0	1

- A DLT of grade 4 CRS occurred at the dose level of 450×10^6 CAR+ T cells:
  The patient with a history of chronic kidney disease related to myeloma developed CRS grade 4 and a neurological event of confusion, as well as lack of pharyngeal reflex, acute kidney injury, and *Klebsiella pneumoniae* sepsis as a nosocomial infection. The patient died on Day 19 after JCARH125 infusion.

[a]Pneumonia, appendicitis, campylobacter infection, cellulitis, sepsis. [b]Confusional state, agitation, areflexia, lethargy, depressed level of consciousness.
AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; SAE, serious adverse event; TLS, tumor lysis syndrome.

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CRS and neurological events

	Total	CAR+ T Cell Dose		
		50×10^6	150×10^6	450×10^6
	(N=44)	(N=14)	(N=28)	(N=2)
Cytokine release syndrome, n (%)	**35 (80)**	**11 (79)**	**22 (79)**	**2 (100)**
Median time to onset, days (range)	3 (1–10)	7 (3–10)	3 (1–10)	1
Median duration, days (range)	5 (1–19)	3 (2–16)	5 (1–19)	8
Neurological events, n (%)	**11 (25)**	**1 (7)**	**8 (29)**	**2 (100)**
Median time to onset, days (range)	3 (1–12)	11	3 (1–12)	3 (2–3)
Median duration, days (range)	6 (1–58)	3	9 (1–58)	6
Treatment of CRS and/or neurological events, n (%)	**16 (36)**	3 (21)	11 (39)	2 (100)
Tocilizumab (IL-6R)	15 (34)	3 (21)	10 (36)	2 (100)
Siltuximab (IL-6)	3 (7)	0	2 (7)	1 (50)
Anakinra (IL-1R)	2 (5)	0	1 (4)	1 (50)
Steroids	9 (20)	1 (7)	6 (21)	2 (100)
Tocilizumab and steroids	8 (18)	1 (7)	5 (18)	2 (100)
Admitted to ICU, n (%)	3 (7)	0	1 (4)	2 (100)

- **CRS events—**one patient required high-dose vasopressor.

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICU, intensive care unit.

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PROLONGED CYTOPENIAS[a]

- **Grade 3/4 anemias and thrombocytopenias** before start of lymphodepleting chemotherapy occurred in 18% of patients
- **Grade 3/4 Cytopenias** lasting longer than 29 days occurred in 67% of patients
- **Cytopenias** resolved to grade ≤2 by month 3 in 71% of patients
- **Median time to resolution[b]**:
  - Neutropenia 2.1 months
  - Anemia 2.2 months
  - Thrombocytopenia 3.4 months

[a]Laboratory assessment.
[b]Recovery is defined as grade 2 or lower without transfusion within 1 week of lab assessment or without growth factor support within 1 week of lab assessment (2 weeks for pegfilgrastim).

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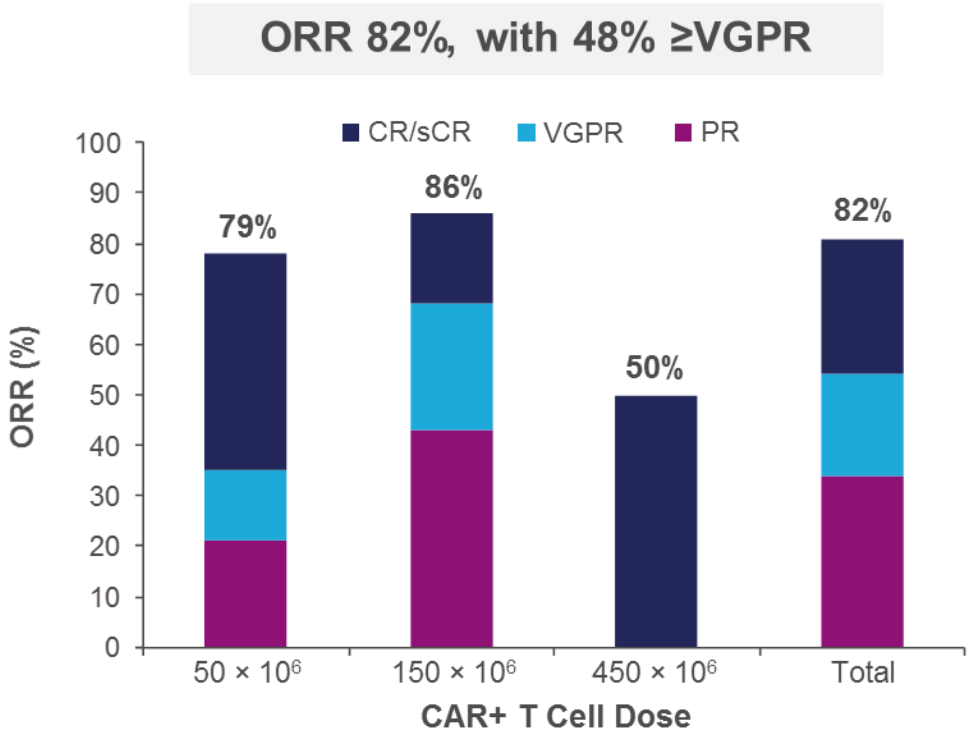
Best Overall response



Patients, n:	**14**	**28**	**2[a]**	**44**
Median follow-up, weeks:	**17**	**9**	**7**	**11**

[a]One patient was not evaluable for efficacy (no postbaseline response evaluation at Day 29).
CAR, chimeric antigen receptor; CR, complete response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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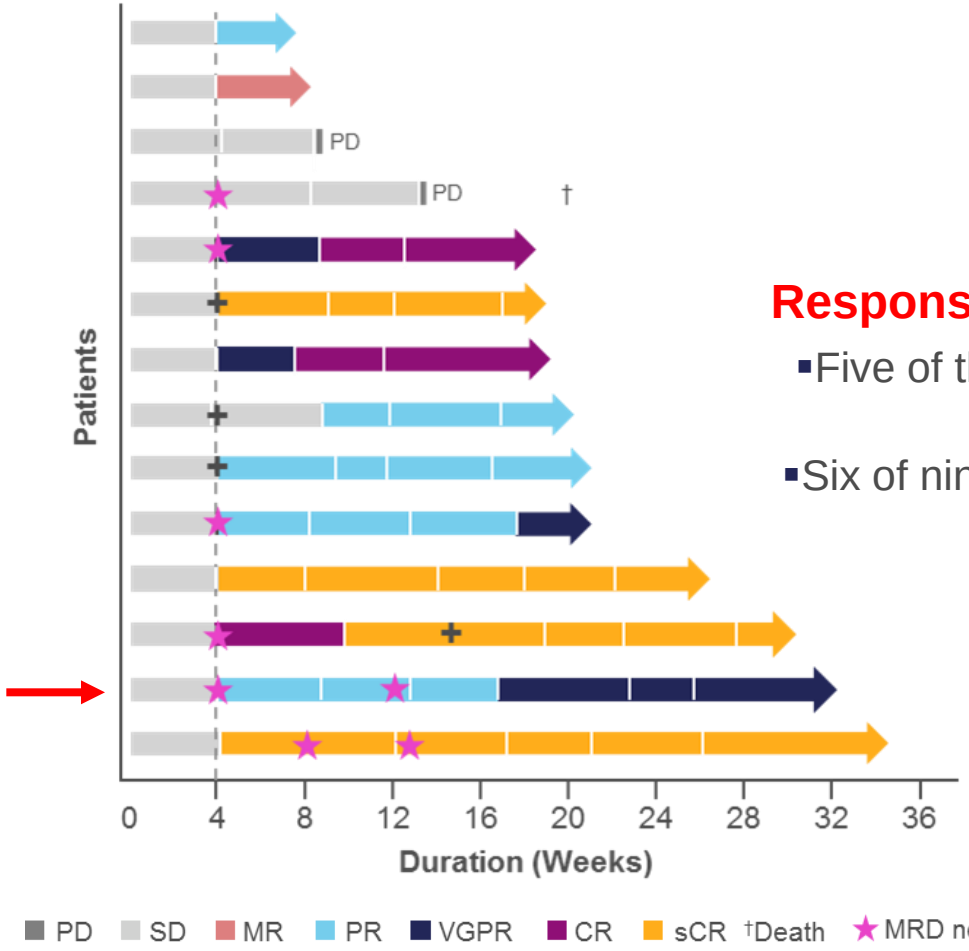
Response over time at dose of 50 × 10^6 CAR+ T cells (Longest Follow-up)



Responses continued to improve over time

- Five of the 14 patients (36%) showed deepening of response past Day 29
- Six of nine evaluable patients were MRD-negative by NGS at Day 29[a]

[a]One patient had MRD assessment at Month 2

CR, complete response; DL, dose level; MR, minimal response; MRD, minimal residual disease; NGS, next generation sequencing; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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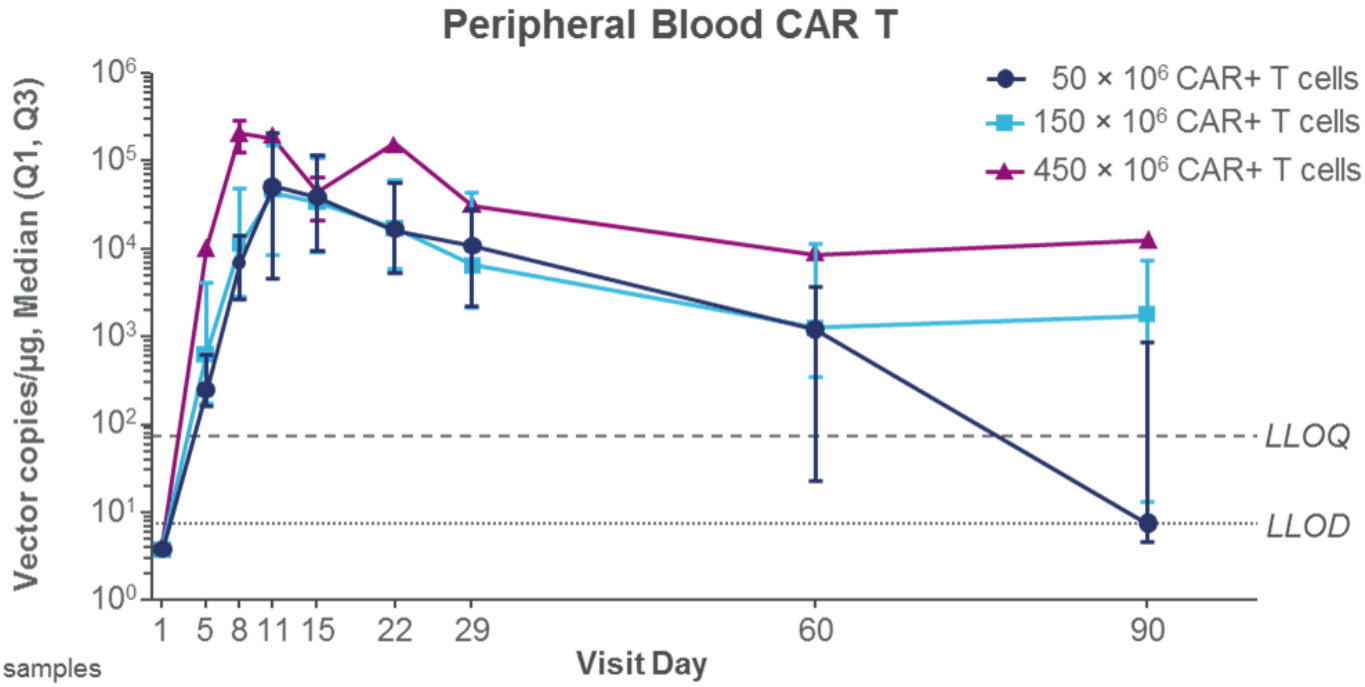
JCARH125 expansion and Long-term Persistence



Number of samples								
50 × 10^6 CAR+ T cells	14	12	14	14	13	14	14	12	11
150 × 10^6 CAR+ T cells	28	24	26	26	28	28	27	19	9
450 × 10^6 CAR+ T cells	2	1	2	1	2	1	1	1	1

- Robust expansion observed at all dose levels
- Trend for increased persistence past Month 2 at dose levels ≥150 × 10^6 CAR+ T cells

Vector copy number assessed by quantitative polymerase chain reaction, using genomic deoxyribonucleic acids extracted from whole blood.
CAR, chimeric antigen receptor; LLOQ, lower limit of quantification; LLOD, lower limit of detection.

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BCMA targeted CAR T cell clinical trials for relapsed MM

Institution/ Company	NCI[1]	Bluebird Multicenter[2]	Nanjing Legend[3]	UPenn[4]	MSK[5]	Juno therapeutics[6]	Poseida Therapeutics[7]
scFv source	Murine Hybridoma	Murine Hybridoma	Murine Hybridoma	Human Library	Human Library	Human Library	Human Library
Costimulatory molecule	CD28	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Gene transfer	Retrovirus	Lentivirus	Lentivirus	Lentivirus	Retrovirus	Lentivirus	PiggyBac DNA modification
BCMA expression required	>50%	>50%	"clear expression"	No	>1%	No	No
Median prior lines	9.5	7	3	7	6	7	3-9 prior lines
ORR (≥ PR)	81%	89%	88%	45%	64%	82%	83% (excluding 1st cohort)
Number of patients	16	18	57	21 (20 Evaluable)	11	44	12

NCI- National Cancer Institute, UPenn- University of Pennsylvania, MSK- Memorial Sloan Kettering, ORR- Overall response (≥ partial response)

1. Brudno JN, et al. J Clin Oncol. 2018;36(22):2267–80
2. Berdeja JG, et al. Blood. 2017;130:740
3. Zhao W-H, et al. 2018 ASH annual meeting. Abstract – 955
4. Cohen AD, et al. Blood. 2017;130:505
5. Mailankody S, et al. 2018 ASH Annual meeting. Abstract 959
6. Mailankody S, Htut M, et al. 2018 ASH annual meeting. Abstract: 957
7. Gregory T, et al. ASH; 2018. abstract 1012

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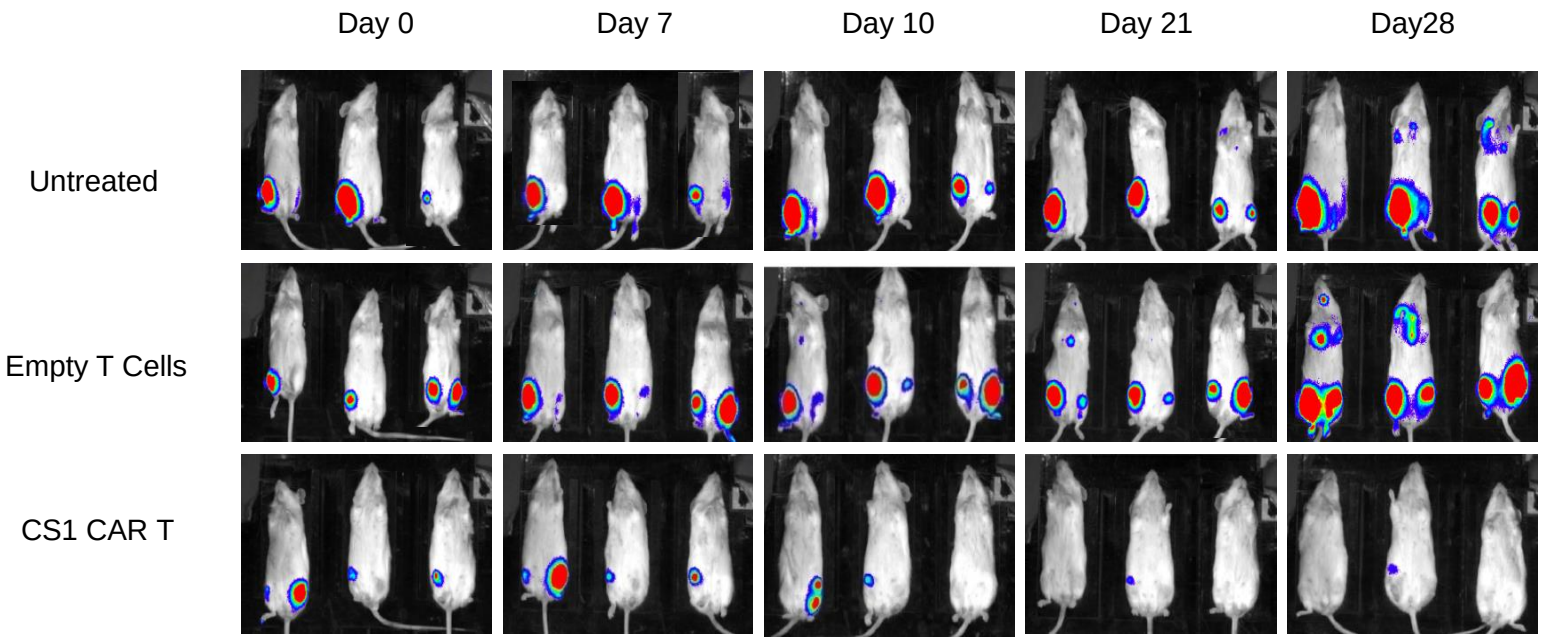
M Htut : Curr Hematol Malig Rep. 2019 Jan 21 doi: 10.1007/s11899-019-0492-z

CS1 CAR-T Cells exhibit efficient anti-Myeloma activity (City of Hope)



First-in-human trial – Enrolling patients at City of Hope (NCT03710421)

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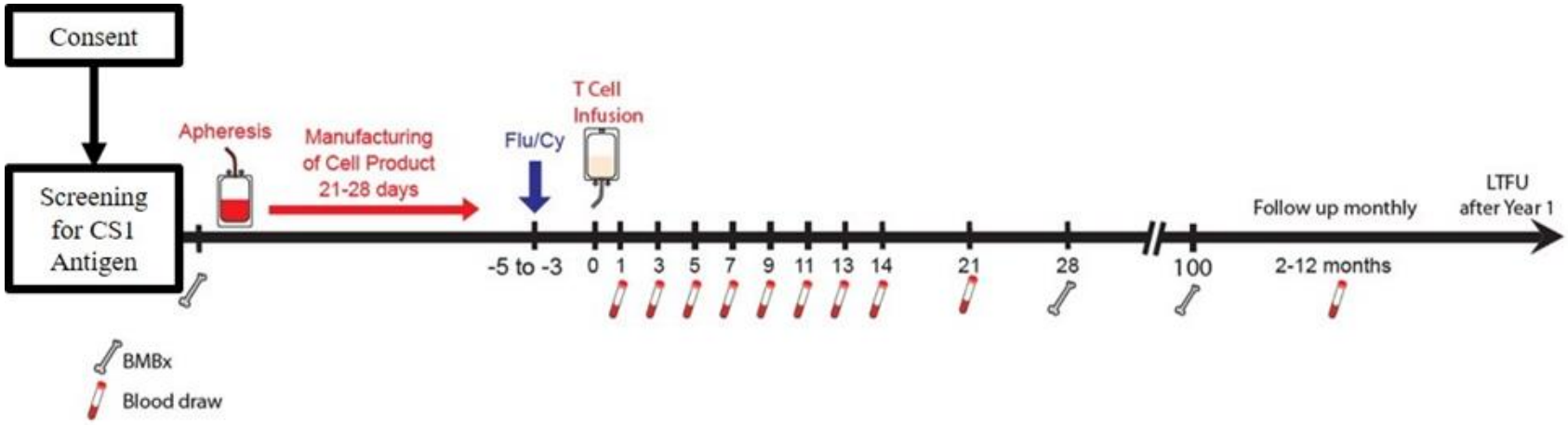
Wang X, Htut M, et al. Clin Cancer Res. 2018 Jan 1;24(1):106-119

Anti- CS1 CAR T cell trial (IRB-17403)



Key Eligibility

- Relapsed/refractory myeloma
- Progress after 3 prior therapies
- Refractory to last line of therapy

Total number – 18-24 patients

Primary Objective - safety and tolerability CS1-CAR T cells

Secondary Objectives - response rates, CS1 expression of MM cells, persistence and phenotyping of CAR T cells

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Anti- CS1 CAR T cell trial (IRB-17403)

CAR+ Cell Dose Schedule				
	Dose -1	Dose 0 (Starting Dose)	Dose 1	Dose 2
Dose Range	26-33M	80-100M	160-200M	320-400M
Modified Dose Range for subjects weighing <50kg	0.66M/kg	2M/kg	4M/kg	8M/kg

Future direction

- CAR T targeting dual antigens (BCMA and CS1)
- 4th Gen CAR secreting cytokines (Trucks/armored), scFv secreting CAR
- (bb21217) Addition of PI3 kinase inhibitor during ex vivo culture to enrich memory-like T cell phenotype[1]
- T cell enhancers – PD-1 inhibitors after CAR T therapy[2]

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1. Nina Shah, et al. Blood 2018 132:488
2. Luca Bernabei, et al. Blood 2018 132:1973