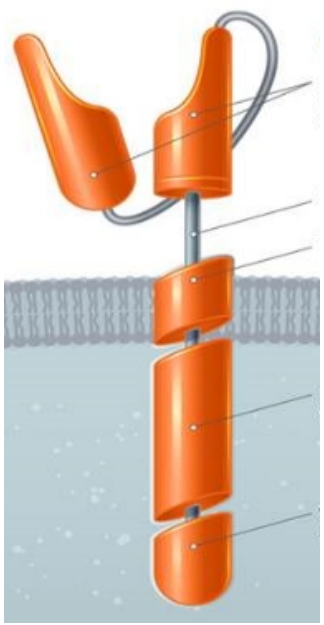
JCARH125—DESIGN AND MANUFACTURING FEATURES



- **JCARH125 CAR construct**
  - Fully human binder with low affinity for sBCMA[1]

To date, JCARH125 has been successfully manufactured for all patients

1. Smith et al. *Mol Ther*. 2018;26:1447-1456.
2. Long et al. *Nat Med*. 2015;21(6):581–590.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; sBCMA, soluble B-cell maturation antigen.

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)

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Modified spacer to enhance binding to BCMA on target cells

Minimized tonic signaling to reduce antigen-independent exhaustion[2]

Active on target cells that express low BCMA density

This study was funded by Juno Therapeutics, a Celgene Company

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.

TREATMENT HISTORY

		CAR+ T Cell Dose		
	Total	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.

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.

CRS AND NEUROLOGICAL EVENTS

		CAR+ T Cell Dose		
	Total	**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	15 (34)	3 (21)	10 (36)	2 (100)
Siltuximab	3 (7)	0	2 (7)	1 (50)
Anakinra	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.

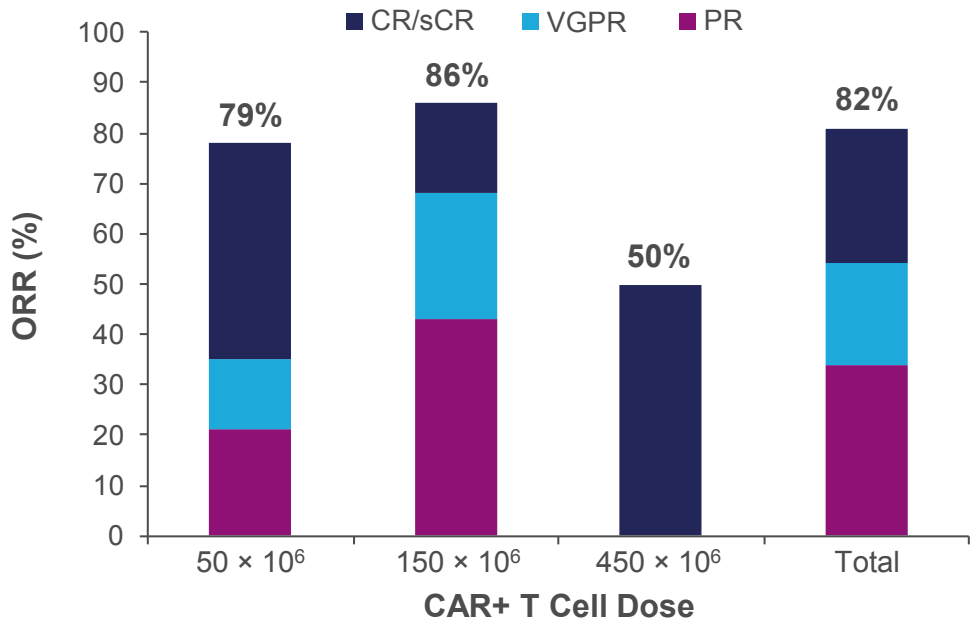
PROLONGED CYTOPENIAS[a]

- **Grade 3/4 anemias and thrombocytopenias** before start of lymphodepleting chemotherapy occurred in 18% of patients
- **Cytopenias grade 3 and 4** lasting longer than 29 days occurred in 28/42 patients (67%)
- **Cytopenias resolved to grade ≤2 by month 3 in 17/24 patients with 3 months follow-up (71%)**
- **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).

BEST OVERALL RESPONSE

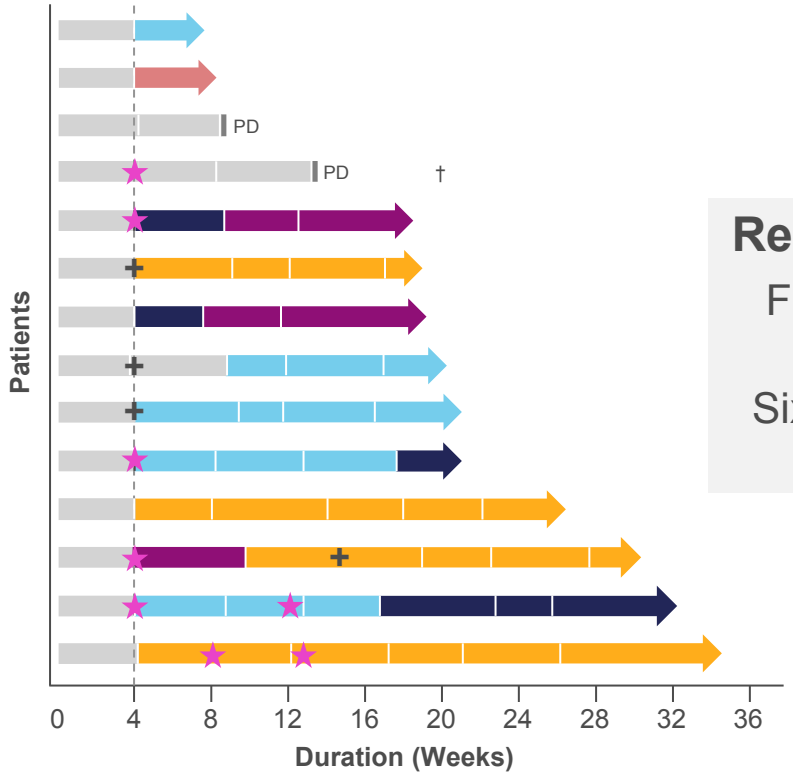
ORR 82%, with 48% ≥VGPR



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.

RESPONSE OVER TIME AT DOSE OF 50 × 10^6 CAR+ T CELLS (Longest Follow-up)



Responses continued to improve over time

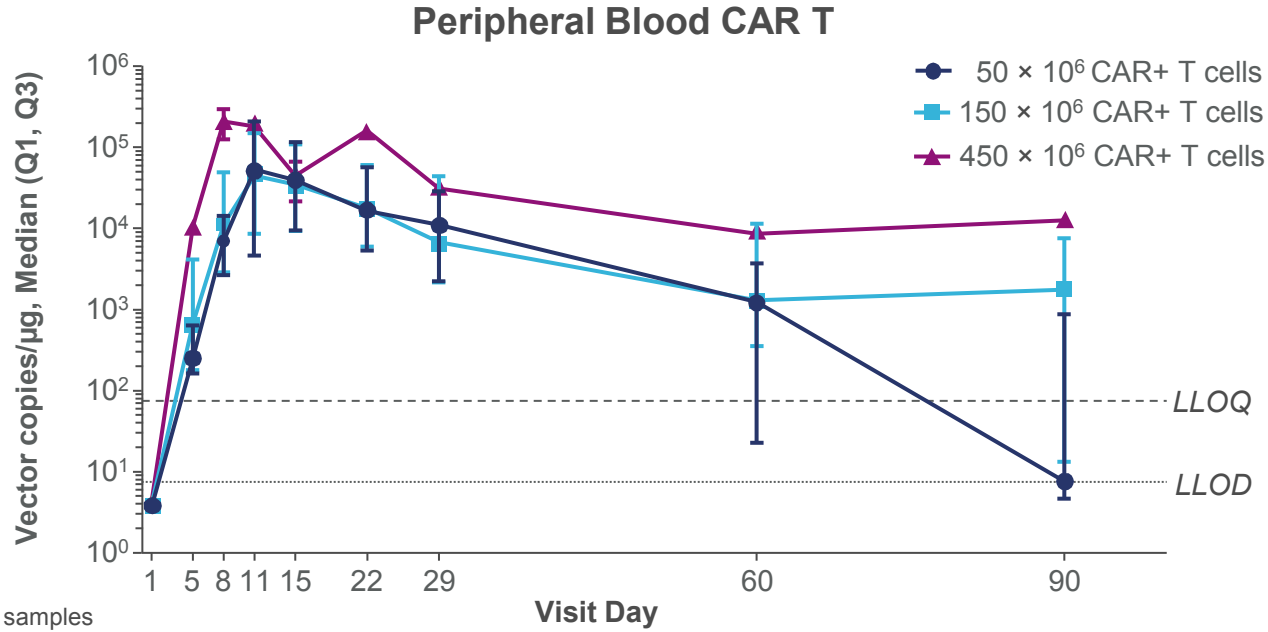
Five of the 14 patients (36%) showed deepening of response past Day 29

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.

JCARH125 EXPANSION AND LONG-TERM PERSISTENCE

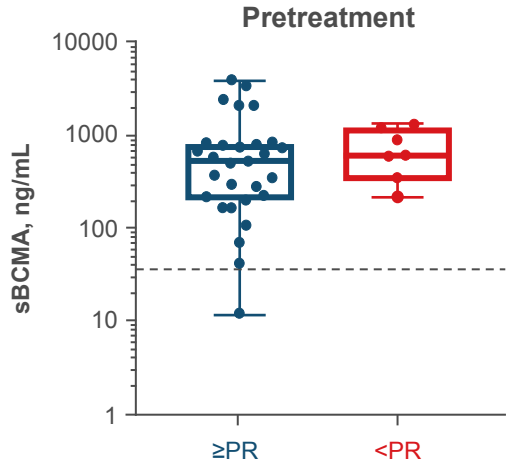


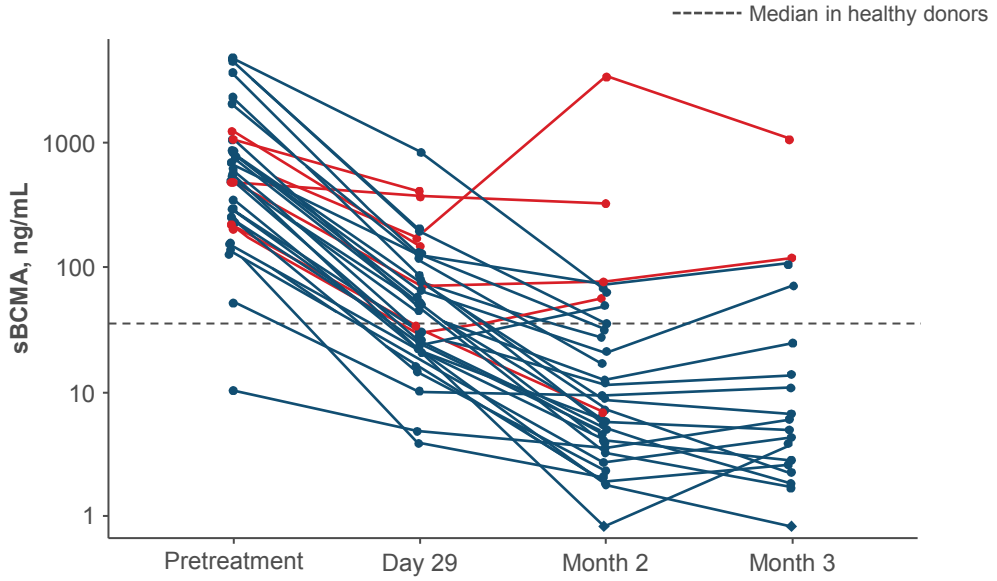
Number of samples									
50 × 10^6 CAR+ T cells	14	12	14	14	13	14	14	12	11
150 × 10^6 CAR+ T cells	28	24	26	26	28	28	27	19	9
450 × 10^6 CAR+ T cells	2	1	2	1	2	1	1	1	1

- 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.

SERUM sBCMA PRE- AND POST-JCARH125 TREATMENT





- Responses were observed across a broad range of baseline sBCMA levels
  - Response did not correlate with baseline sBCMA level
- Decline in sBCMA post-JCARH125 treatment is consistent with tumor cell killing activity
- Greater decline in patients with best overall response of PR or better vs nonresponders (MR or SD) at Day 29 and later

MR, minimal response; PR, partial response; sBCMA, soluble B-cell maturation antigen; SD, stable disease; Tx, treatment.

CONCLUSIONS

- JCARH125 is a BCMA CAR T cell product with a fully human binder and optimized manufacturing process that enriches for central memory T cell phenotype
- JCARH125 was **highly active (ORR 82%)** in heavily pretreated RRMM patient population
  - **Limited median follow-up** of 11 weeks so far
  - **Robust expansion in all dose levels**, with a trend for increased persistence at higher doses
- CR/sCR was achieved by 27% patients with trend of **deepening responses over time**
  - **CR/sCR (43%) observed at the lowest dose level** of 50 × 10^6 CAR T cells
- JCARH125 **toxicity was generally manageable**
  - CRS grade 1 or 2 occurred in 71% of patients, CRS grade ≥3 in 9% of patients
  - Neurological events grade 1 or 2 occurred in 18% of patients, grade ≥3 in 7% of patients
- JCARH125 was active in patients with **high baseline levels of sBCMA**
- Study continues to enroll patients to further define the recommended phase 2 dose

CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; ORR, overall response rate; RRMM, refractory resistant multiple myeloma; sBCMA, soluble B-cell maturation antigen, sCR, stringent complete response.

ACKNOWLEDGMENTS

Patients, Families, and Caregivers

Study staff and healthcare professionals at:

- Memorial Sloan-Kettering Cancer Center, New York, NY
- University of Chicago Medical Center, Chicago, IL
- City of Hope, Duarte, CA
- Roswell Park Cancer Institute, Buffalo, NY
- Swedish Cancer Institute, Seattle, WA
- University of California San Francisco, San Francisco, CA
- Hackensack University Medical Center, Hackensack, NJ
- Emory University, Atlanta, GA
- University of Alabama, Birmingham, AL

Funding and Support

- This study was funded by Juno Therapeutics, a Celgene Company
- Editorial and graphics support provided by Lockwood, with funding provided by Celgene Corporation