Phase 1 Study of CART-ddBCMA, a CAR-T therapy utilizing a novel synthetic binding domain for the treatment of subjects with relapsed and refractory Multiple Myeloma

Matthew J. Frigault, MD[1], Michael Bishop, MD[2], Elizabeth K O'Donnell, MD[1], Noopur Raje, MD[1], Allegra Mondillo[1], Daniella Cook[1], Jacalyn Rosenblatt, MD[4], Chelsey Gibson, RN[4], David E. Avigan, MD[4], Heather Daley[3], Kit Shaw, PhD[3], Diego Hernandez Rodriguez[3], Sarah Nikiforow, MD, PhD[3], Carissa Mangus[5], David W. LaFleur[6], Janine M. Buonato, PhD[6], Justin P. Edwards, PhD[6], Laura K. Richman, DVM, PhD[6], Maria T. Polianova, PhD[6], Marianna Sabatino, MD[6], Scott Currence[6], Travis Quigley, MS[6], Angela Shen, MD[6], Marcela V. Maus, MD, PhD[1]

[1]Massachusetts General Hospital Cancer Center, 55 Fruit St, Boston, MA 02114
[2]University of Chicago Comprehensive Cancer Center, 5758 S. Maryland Ave, Chicago, IL 60637
[3]Dana Farber Cancer Institute, Cell Manipulation Core Facility, 450 Brookline Avenue, Brookline, MA 02215
[4]Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02115
[5]CE3, Inc., 6 Post Office Square, Clinton, CT 06413
[6]Arcellx, Inc., 25 West Watkins Mill Road, Suite A, Gaithersburg, MD 20878

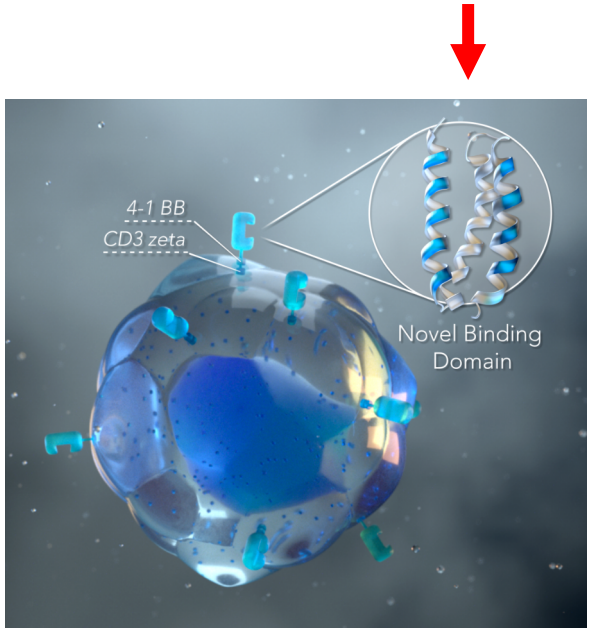
Data presented at the 62nd ASH Annual Virtual Meeting, December 5–8, 2020

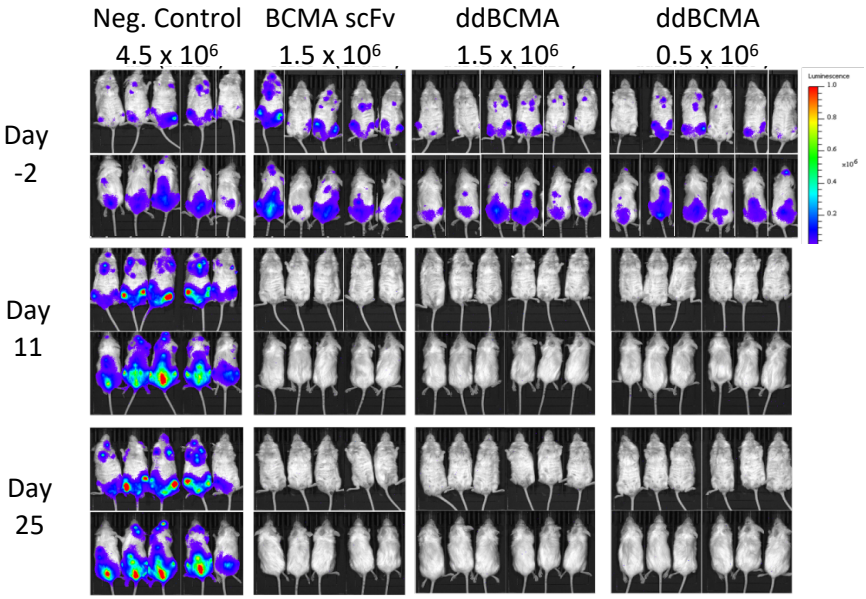
Background

- Conventional chimeric antigen receptors utilize an antibody-derived scFv as the binding domain
- In contrast, the CART-ddBCMA binding domain is based on a computationally designed synthetic protein[1] that:
  - Is not an scFv and not related to antibodies
  - Is a 73aa protein (~8kDa) not found in nature
  - Contains no disulfide bonds or native glycosylation
  - Is engineered for reduced immunogenicity
  - Rapidly folds and is highly stable
- CART-ddBCMA clears tumor in murine model of multiple myeloma
- CART-ddBCMA is manufactured with a simple process in a semi-automated, functionally enclosed system

Deimmunized Anti-BCMA binding D domain (ddBCMA)

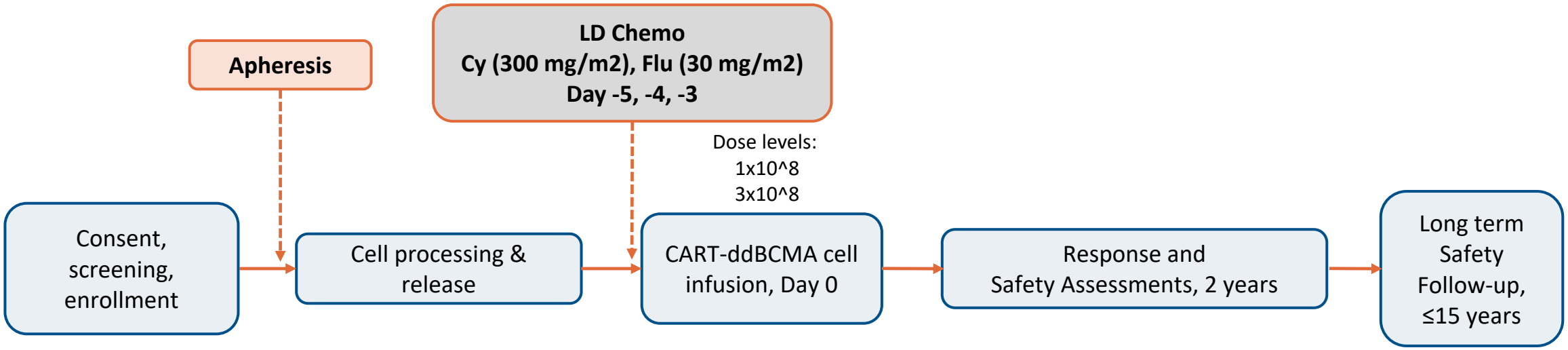
- Ex vivo T cell assays demonstrate no immunogenicity following removal of potential epitopes
- Low risk for clinical immunogenicity





[1]Qin, Haiying, et al. "Chimeric antigen receptors incorporating D domains targeting CD123 direct potent mono- and bi-specific antitumor activity of T cells." *Molecular Therapy* 27.7 (2019): 1262-1274

Study Design & Patient Disposition



- **9 subjects enrolled (as of 2 Nov 2020)**
  - All subjects were successfully manufactured
  - 7 subjects treated
    - 1 subject is pending first assessment
  - 1 subject pending treatment
  - 1 subject d/c prior to cell infusion due to AE

- **Relapsed and refractory multiple myeloma**
  - Prior IMiD, PI, and CD38-targeted therapy
  - Received ≥3 prior therapies or triple refractory
- **Key Endpoints:** Safety and disease response per IMWG criteria

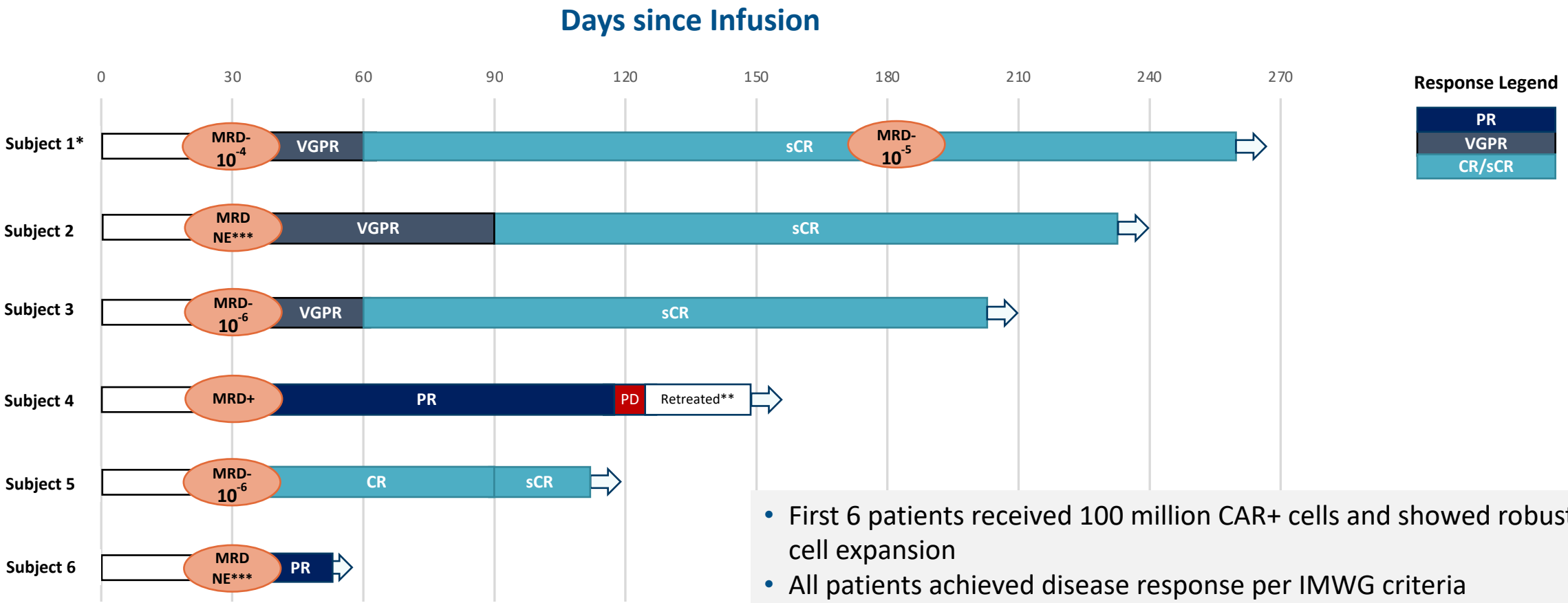
Patient Demographics and Characteristics (as of 29 Oct 2020)

Subject #	Age/Sex	Myeloma	Prior Lines / Prior ASCT	Prior Therapy Status	High Risk Cytogenetics	Bone Marrow Plasma Cells	Extra-Medullary Disease	Dose (+/- 20%) CAR+ T Cells
1	73/M	IgA	5 / No	penta-refractory	t(4;14), 1q+	95%	Yes	100 million
2	73/F	Light Chain	5 / No	penta-refractory + BRAFi	sample not evaluable	0%	Yes	100 million
3	75/M	IgA	7 / No	penta-refractory + anti-CS1 mAb	1q+	95%	Yes	100 million
4	74/F	IgG	5 / Yes	penta-refractory	del17p, 1q+	70%	No	100 million
5	66/F	Light Chain	5/ Yes	penta-refractory +BRAFi	1q+	10%	No	100 million
6	66/F	IgA	7 / Yes	penta-refractory + anti-CS1 mAb	1q+	< 5%	Yes	100 million

ASCT = Autologous stem cell transplant

Penta-refractory: refractory to ≥2 PIs, ≥2 IMiDs, and anti-CD38

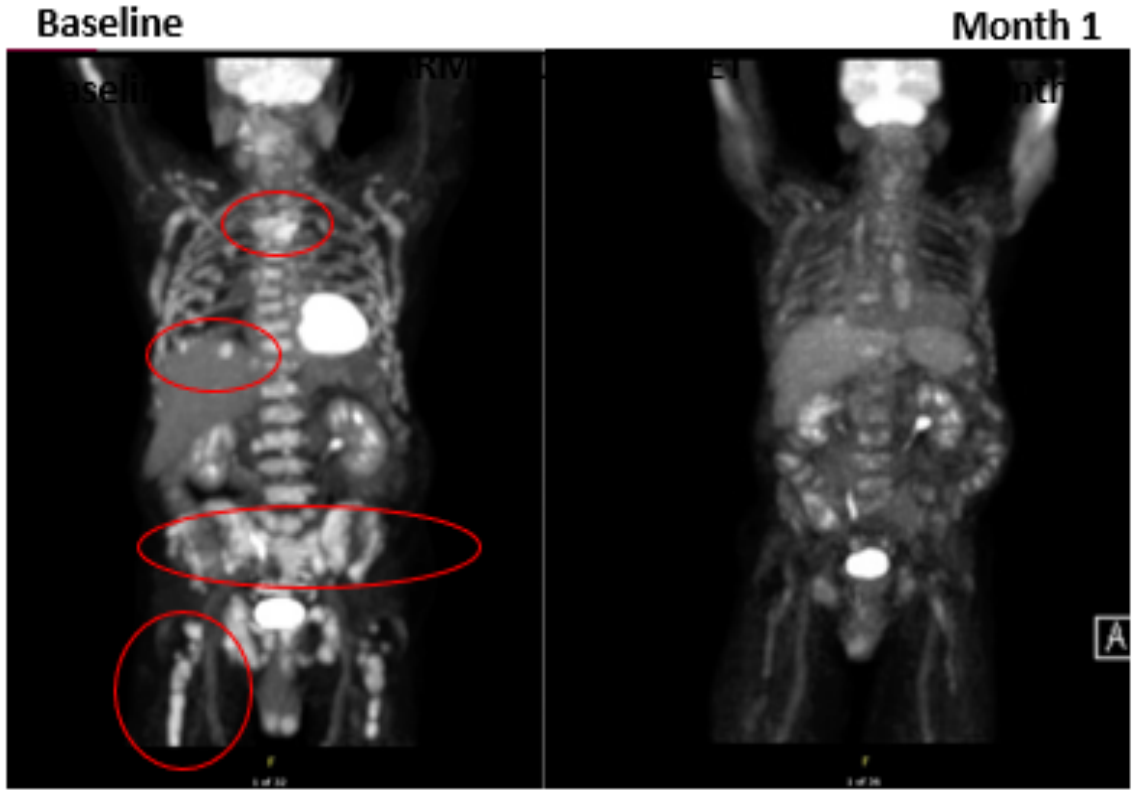
Time on Study from CART-ddBCMA Infusion (as of 29 Oct 2020)

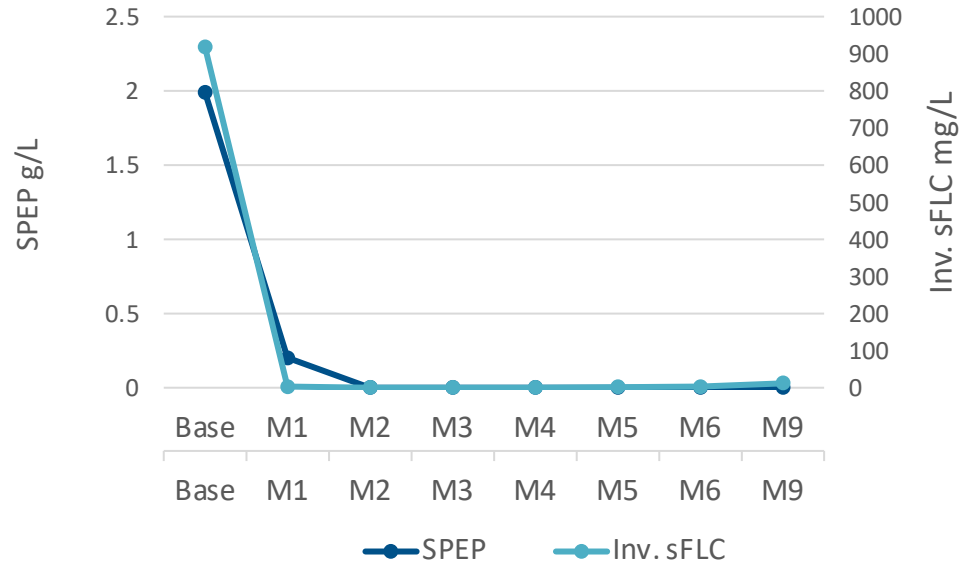


* *Unable to assess MRD status at 10^{-6}*
** *Pending*
*** *NE = not evaluable*

- First 6 patients received 100 million CAR+ cells and showed robust cell expansion
- All patients achieved disease response per IMWG criteria
- Median time to CR/sCR = 2 months
- 5/6 subjects experienced rapid clearance of sFLC and SPEP within 2 months

Subject #1: Rapid, Deep, and Durable Response (sCR) with expansion and persistence of CART-ddBCMA



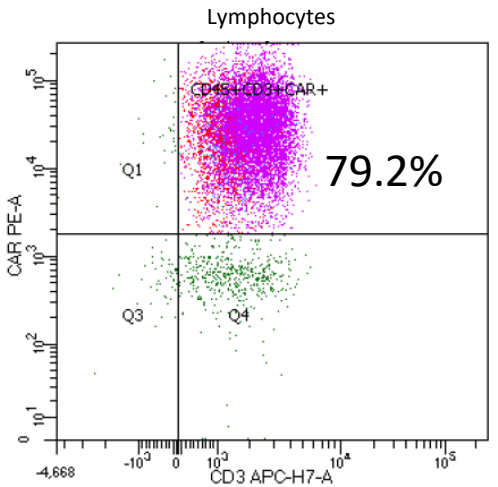


High disease burden (95% BMPC) at baseline with IgA myeloma, extra-medullary disease, and high-risk cytogenetics

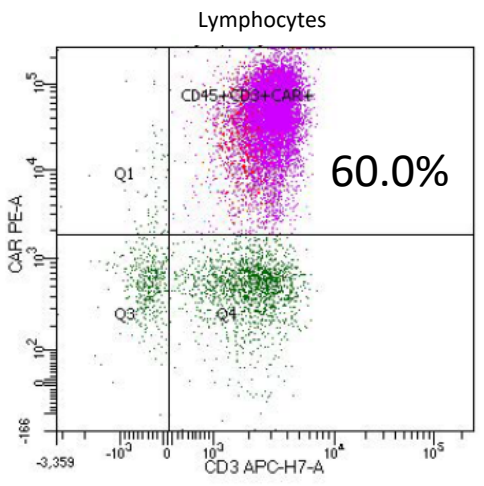
⇒ Negative bone marrow by Month 1

- MRD-negative to 10^{-4} at Month 1
- MRD-negative to 10^{-5} at Month 6
- Unable to assess MRD status at 10^{-6}

BMPC = bone marrow plasma cells
BM = bone marrow
MRD = minimal residual disease



Day 14



Day 28

Adverse Events (as of 29 Oct 2020, N=6)

- No SAEs related to CART-ddBCMA
- No treatment-emergent Grade 3/4 infections

All Grade 3/4 AEs after cell infusion Regardless of Relatedness, (N=6)	
Hematologic	
Neutropenia	6
Febrile Neutropenia	2
Lymphocytopenia	4
Decreased hemoglobin	4
Thrombocytopenia	2
Decreased WBC	3
Coagulopathy	1
Non-hematologic	
Abdominal pain	1
Muscle hematoma	1
Hypertension	2
Hyponatremia	1

CAR-T-associated AEs Per ASTCT criteria	Grade 1, 2 (N=6)	Grade 3, 4 (N=6)
CRS	**6**	None
Median onset	2.5 days (0-4)	
Median duration	5 days (3-7)	
Neurotoxicity (ICANs)	**1**	None
Median onset	2 days	
Median duration	2 days	
Toxicity Management	**4**	None
Tocilizumab administration	4	
Dexamethasone doses		
single-dose	2	
multi-dose	1	
Other anti-cytokine therapy	None	

CART-ddBCMA: Highly Consistent and Efficient CAR expression

CART-ddBCMA
Initial Drug Product Data

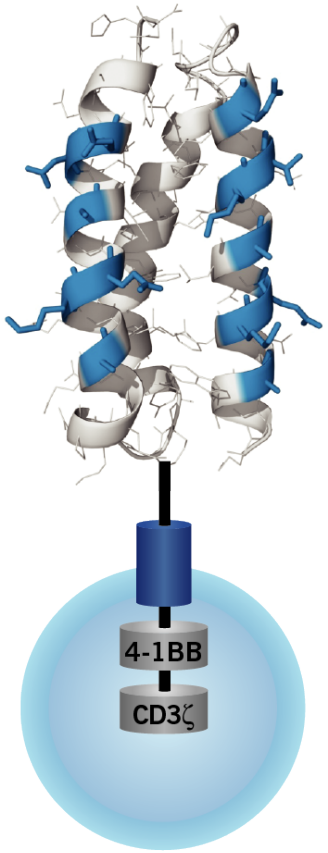
Subject	VCN	% CAR+
1	2.34	78
2	2.12	76
3	2.61	72
4	2.33	76
5	2.33	73
X	2.36	78
6	3.07	87
7	2.04	69
8	2.02	72

VCN = Vector copy number

- Highly consistent autologous drug products
- Efficient CAR expression
  - median 76% [min:max 69–87%]
- Manufactured in a semi-automated, functionally enclosed system
- Simple transduction and expansion process
- Consistency and efficiency of CAR expression may be related to high stability of novel binding domain

Conclusions

CART-ddBCMA



- CART-ddBCMA utilizes a novel, non-scFv binding domain, that is highly stable and engineered to reduce immunogenicity
- CRS and neurotoxicity have been limited to Grade 1/2 with rapid resolution
- Rapid, deep, and durable responses have been observed at the first dose level (100 million CAR+ cells) in patients with various poor prognostic factors:
  - Older median age (73 years old)
  - High risk cytogenetics
  - Extramedullary disease
  - Penta-refractory myeloma
- Simple manufacturing process in a semi-automated, functionally enclosed system has yielded consistent product with efficient CAR expression
- Currently exploring CART-ddBCMA activity in patients with prior BCMA-targeted therapy

Thank you to the patients and their families, the healthcare professionals who cared for the patients, and the study staff who supported this clinical trial