3832 Phase I study of CART-ddBCMA: a CART-Therapy Utilizing a Novel Synthetic Binding Domain for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma

Matthew J. Frigault, MD[1], Jacalyn Rosenblatt, MD[2], Noopur S. Raje, MD[3], Gabriel Depinho, B.S.[4], Daniella Cook, BS[5], Emma K. Logan[2], Christopher R. Heery, MD[6], Christine Cornwell[6], Melissa Sheppard[7], Marcela V. Maus, MD, PhD[1], David Avigan, MD[2], Andrzej Jakubowiak[8], and Michael R. Bishop, MD[9]

[1]HCTCT, Massachusetts General Hospital Cancer Center, Boston, MA; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Division of Hematology and Oncology, Mass General Hospital Cancer Center, Boston, MA; [4]Massachusetts General Hospital, Boston, MA; [5]Cancer Center, Massachusetts General Hospital, Boston, MA; [6]Arcellx, Inc., Gaithersburg, MD; [7]Department of Medicine, Section of Hematology and Oncology, University of Chicago Medical Center, Chicago, IL; [8]University of Chicago, Chicago, IL; [9]The David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL

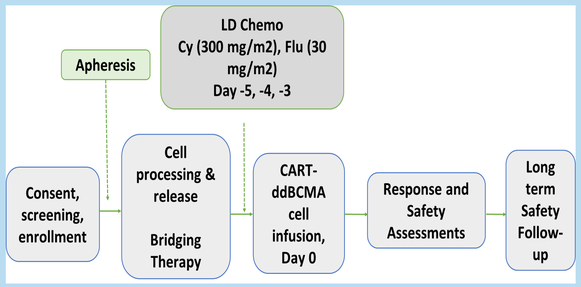
INTRODUCTION

Chimeric Antigen Receptor (CAR) T cell therapies directed against B-cell maturation antigen (BCMA) have demonstrated compelling clinical activity and manageable safety in subjects with relapsed and/or refractory Multiple Myeloma (RRMM). CART-ddBCMA is a unique anti-BCMA CAR T cell encoding a synthetic binding domain targeting BCMA, instead of the typical scFv approach, a 4-1BB costimulatory motif, and CD3-zeta activation domain. The binding domain is a small stable protein comprising 73 amino acids engineered to reduce the risk of immunogenicity. CART-ddBCMA is being studied in a first-in-human clinical study to assess the safety, pharmacokinetics, immunogenicity, efficacy, and duration of effect.

METHODS

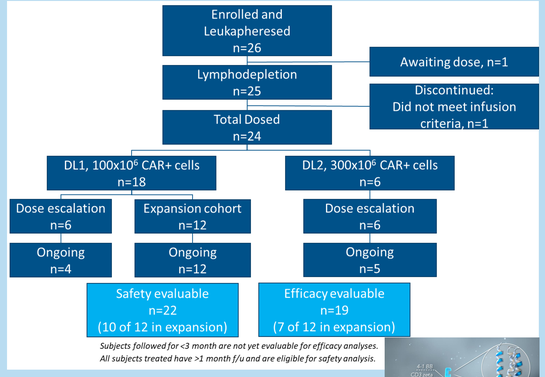
This Phase 1, multi-center, open label, dose escalation trial is enrolling approximately 40 subjects with RRMM who have received ≥ 3 prior regimens, including a proteasome inhibitor, an immuno-modulatory agent, and a CD38 antibody or are triple-refractory. There is no prescreening or requirement for BCMA expression on tumor cells. Peripheral blood mononuclear cells are collected via leukapheresis and sent to a central facility for selection, transduction, and expansion. The drug product is cryopreserved and undergoes release testing prior to being returned to the site for infusion. Subjects undergo lymphodepletion with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) daily for 3 days, then receive CART-ddBCMA as a single infusion. Dose escalation was performed at 100 (DL1) and 300 (DL2) x 10^6 (+/- 20%) CAR+ T cells and additional subjects were enrolled in DL1 to further assess safety, efficacy, and pharmaco-kinetics and -dynamics. The primary outcome measure is incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Additional outcome measures are quality and duration of clinical response assessed according to the IMWG Uniform Response Criteria for MM, evaluation of minimal residual disease (MRD), progression-free and overall survival, and quantification of CAR+ cells in blood. MRD negative results were obtained by next-generation sequencing (Adaptive clonoSEQ). Subjects were considered evaluable for safety if >1 month had occurred since Day 0 and evaluable for efficacy if >3 months since Day 0. The data presented were cut on November 4, 2021.

STUDY SCHEMA

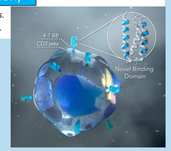


RESULTS

PATIENT DISPOSITION



Autologous drug products successfully and consistently manufactured for all subjects
- VCN median 2.33 (1.33–3.55)
- **CAR expression median 74% (61–87%)**



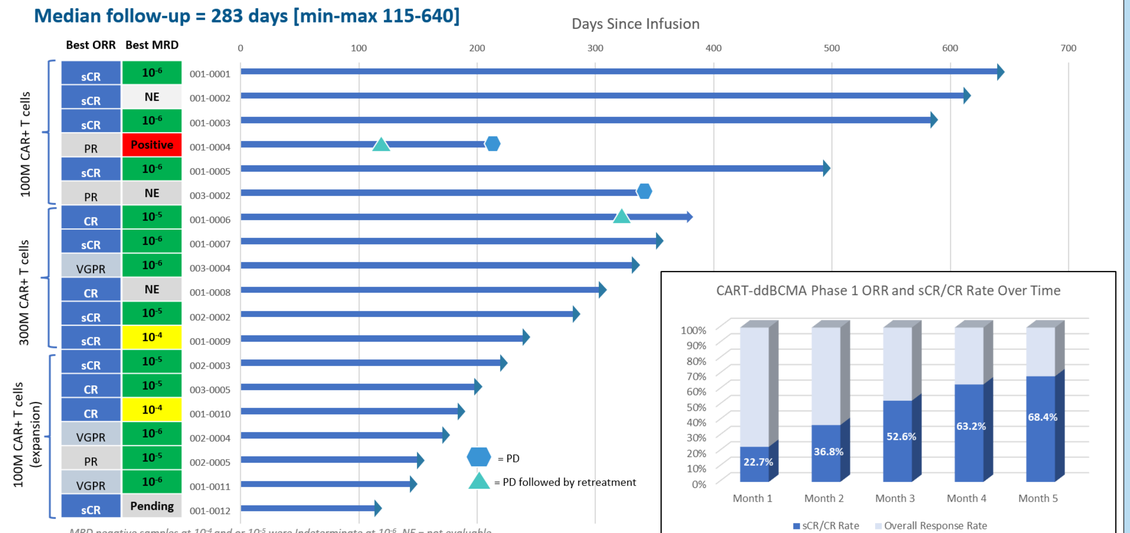
PATIENT CHARACTERISTICS

Characteristics	Dose Level 1 100 million CAR-T (n=18)	Dose Level 2 300 million CAR-T (n=6)	Total (n=24)
Age, median (min-max)	69 (44-76)	60 (52-65)	66 (44-76)
Gender	8 Male (44%) 10 Female 56%)	5 Male (83%) 1 Female (17%)	13 Male (54%) 11 Female (46%)
BMPC >50%	6/18 (33%)	4/6 (67%)	10/24 (42%)
Extra-medullary disease	6/18 (33%)	3/6 (50%)	9/24 (38%)
High-risk cytogenetics per IMWG	13/14 (93%)*	4/5 (80%)*	17/19 (89%)*
Prior Lines of Therapy, median (min-max)	5 (3-9)	4 (3-16)	5 (3-16)
Triple refractory	15/18 (83%)	5/6 (83%)	20/24 (83%)
Penta refractory	13/18 (72%)	4/6 (67%)	17/24 (71%)
IgG myeloma	10	5	15
IgA myeloma	3	0	3
Light ch: Median	4	1	5

Subjects followed for <3 month are not yet evaluable for efficacy analyses. All subjects treated have >1 month f/u and are eligible for safety analysis.

OVERALL RESPONSE & DISEASE STATUS FOLLOWING CART-ddBCMA TREATMENT

Median follow-up = 283 days [min-max 115-640]

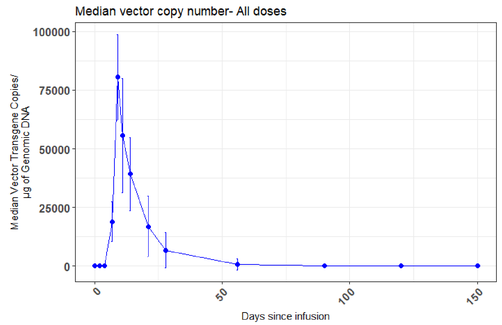


MRD negative samples at 10^{-4} and or 10^{-5} were Indeterminate at 10^{-6}. NE = not evaluable
Subjects followed for <3 months are not yet evaluable for efficacy analyses

Responses to CART-ddBCMA deepened over time, maximum depth typically occur at 3-6 months

RESULTS

CART-ddBCMA CELL EXPANSION & PERSISTANCE



Peak CART-ddBCMA peak expansion within two weeks of treatment

CART-ddBCMA ADVERSE EVENTS OF SPECIAL INTEREST

All Non-AESI Grade 3/4 AEs after cell infusion Regardless of Relatedness, (N=22)	
Hematologic	
Neutrophil count decreased	15 (68.2%)
Hemoglobin decreased	12 (54.5%)
Lymphocyte count decreased	10 (45.5%)
Platelet count decreased	9 (40.9%)
White blood cell count decreased	6 (27.3%)
Febrile neutropenia	5 (22.7%)
Activated partial thromboplastin time prolonged	1 (4.5%)
CD4 lymphocytes decreased	1 (4.5%)
Non-hematologic	
Hypertension	3 (13.6%)
Blood sodium decreased	2 (9.1%)
Aspartate aminotransferase increased	1 (4.5%)
Blood bilirubin increased	1 (4.5%)
Blood phosphorus decreased	1 (4.5%)
Blood potassium decreased	1 (4.5%)
Hypotension	1 (4.5%)
Acute myocardial infarction	1 (4.5%)
Abdominal pain	1 (4.5%)
Skin infection	1 (4.5%)
Hyperglycaemia	1 (4.5%)
Malnutrition	1 (4.5%)
Haematoma muscle	1 (4.5%)

CAR-T-associated AEs Per ASTCT criteria	100 million (N=16)		300 million (N=6)	
Cytokine Release Syndrome (CRS)	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
	16 (100%)	**0**	**5 (83%)**	**1 (17%)**
Median onset (min-max)	1 days (0-6 days)		1 day (0-3 day)	
Median duration (min-max)	6.5 days (2-8 days)		4.5 days (3-6 days)	
Neurotoxicity (ICANs)	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
	2 (13%)	**1 (6%)**	**0**	**1 (17%)**
Median onset (min-max)	3 days (2-4 days)		6 days	
Median duration (min-max)	8 days (4-9 days)		17 days	
Toxicity Management				
Tocilizumab	14		5	
Dexamethasone	9		3	
Anakinra	1		1	

CART-ddBCMA well tolerated at DL1 and DL2
Grade ≥3 CRS and/or ICANS events in ~6% subjects at DL1

CONCLUSIONS

- **CART-ddBCMA utilizes a novel, non-scFv binding domain, that is highly stable and engineered to reduce immunogenicity**
  2 dose levels studied (100 and 300 million CAR+ T-cells); MTD not reached
- **Toxicities including CRS and ICANS have been manageable at both dose levels**
  No off-target toxicities observed
  Only 1 grade 3 (or greater) CRS or ICANS event at DL1 , ~6% of evaluable cases.
- **Phase 1 expansion at 100 million CAR+ T cells; well-tolerated and 100% ORR**
- **100% ORR per IMWG across both dose levels; deep and durable responses observed in patients with poor prognostic factors**
  19/19 ORR: 13 CR/sCR (68%), 3 VGPR (16%), 3 PR (16%)
  16/19 (84%) responses are ongoing;
  Maximum depth of response occur after month 3 in most cases
  4 responses ongoing >15 months (66% of 6 treated > 1 year ago)
- **Pivotal phase 2 trial planned**