3313 Phase 1 Study of CART-ddBCMA for the Treatment of Subjects with Relapsed and/or Refractory Multiple Myeloma

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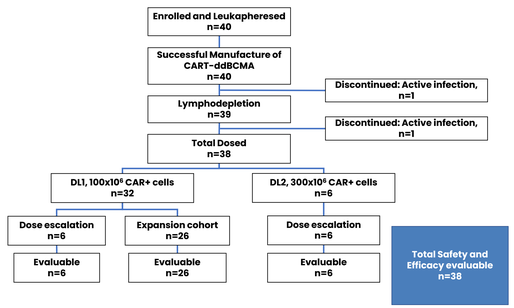
INTRODUCTION

B-cell maturation antigen (BCMA) targeting chimeric Antigen Receptor (CAR) T cell therapies have shown compelling clinical activity and manageable safety in subjects with relapsed and/or refractory Multiple Myeloma (RRMM). CART-ddBCMA is an autologous anti-BCMA CAR T cell therapy with a unique, 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, called a D-Domain, comprising 73 amino acids. CART-ddBCMA is being studied in a first-in-human clinical study.

METHODS

This Phase 1, multi-center, open label, dose escalation trial enrolling subjects with RRMM who have received ≥3 prior regimens, including a proteasome inhibitor, an Immune-modulatory agent, and a CD38 antibody, or are triple-refractory. Lymphodepletion is administered (fludarabine (30 mg/m2/day) and cyclophosphamide (300 mg/m2/day)) daily on days -5 to -3, then CART-ddBCMA is given as a single infusion on day 0. Dose escalation was performed at 100 (DL1) and 300 (DL2) x 10^6 (+/- 20%) CAR+T cells and enrollment was continued at 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).

PATIENT DISPOSITION



Drug products successfully and consistently manufactured for all subjects

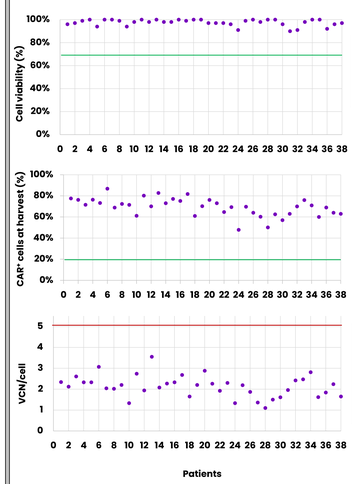
RESULTS

PATIENT CHARACTERISTICS

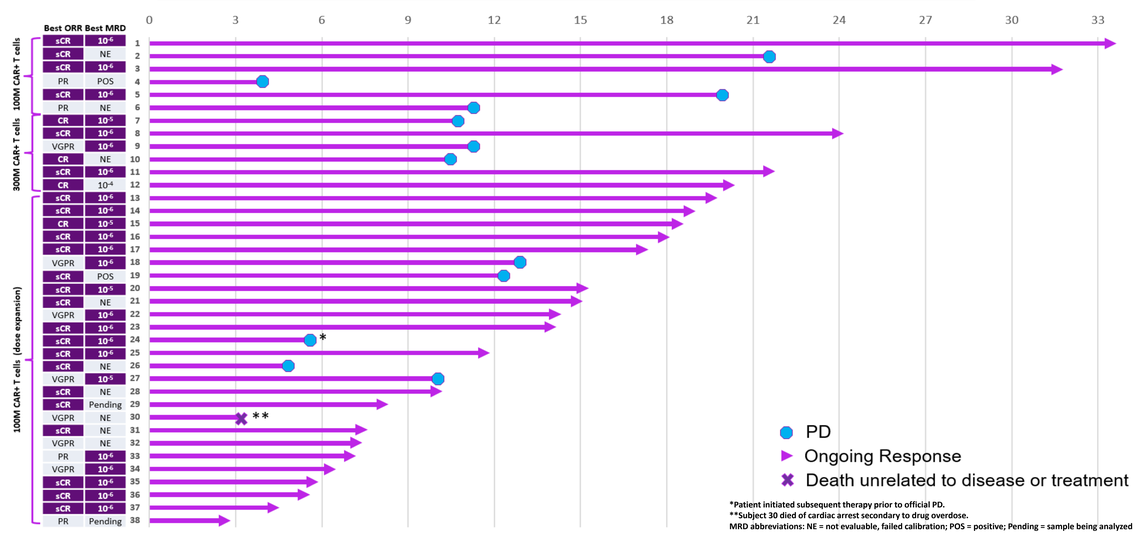
Characteristics	Dose Level 1 100 million CAR-T (n=32)	Dose Level 2 300 million CAR-T (n=6)	Total (n=38)
Age, median (min - max)	66 (44 - 76)	60 (52 - 65)	66(44 - 76)
Gender	18 Male (56%) 14 Female (44%)	5 Male (83%) 1 Female (17%)	23 Male (61%) 15 Female (39%)
ECOG PS* 0 1	 9/32 (28%) 23/32 (72%)	 3/6 (50%) 3/6 (50%)	 12/38(32%) 26/38 (68%)
High Risk Prognostic Feature	16/32 (50%)	6/6 (100%)	22/38 (58%)
BMPC ≥60%	6/32 (19%)	3/6 (50%)	9/38 (24%)
ISS Stage III (B2M ≥ 5.5)	3/32 (9%)	2/6 (33%)	5/38 (13%)
Extra-medullary disease	10/32 (31%)	3/6 (50%)	13/38 (34%)
High Risk Cytogenetics**	9/32 (28%)	2/6 (33%)	11/38 (29%)
Prior Lines of Therapy, Median (min - max)	5 (3 - 7)	4 (3 - 16)	4 (3 - 16)
Triple refractory***	32/32 (100%)	6/6 (100%)	38/38 (100%)
Penta refractory	21/32 (66%)	5/6 (83%)	26/38 (68%)
IgG myeloma IgA myeloma Light chain only	19 6 5	5 0 1	24 6 6

*Eastern Cooperative Oncology Group Performance Status Scale. **Defined as Del 17p, t(14;16), t(4;14); ***Note: modified from ASCO 2022 due to data cleaning efforts.

CART-ddBCMA PRODUCT SPECIFICATIONS



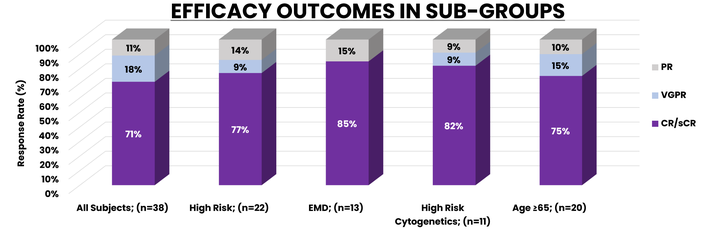
OVERALL RESPONSE & DISEASE STATUS FOLLOWING CART-ddBCMA TREATMENT



Deepening of response to CART-ddBCMA treatment with time

RESULTS

EFFICACY OUTCOMES IN SUB-GROUPS



	Patients n (%)	6-month PFS % (95% CI)	12-month PFS % (95% CI)	18-month PFS % (95% CI)
Overall	38 (100%)	91.8% (76.7%, 97.2%)	72.7% (52.2%, 85.5%)	64.6% (43.7%, 79.4%)
≥ 65 years	20 (52.6%)	95.0% (69.4%, 99.3%)	82.3% (54.3%, 94.0%)	75.4% (46.7%, 90.1%)
Complete Responders	27 (71.1%)	96.2% (75.7%, 99.4%)	86.0% (62.3%, 95.3%)	80.7% (55.6%, 92.4%)
High Risk Features*	22 (57.9%)	90.5% (67.0%, 97.5%)	69.2% (43.7%, 84.9%)	63.4% (38.0%, 80.7%)
Extramedullary disease	13 (34.2%)	91.7% (53.9%, 98.6%)	64.2% (30.2%, 84.6%)	64.2% (30.2%, 84.6%)
High Risk Cytogenetics	11 (28.9%)	90.8% (42.3%, 94.8%)	69.2% (31.1%, 89.1%)	69.2% (31.1%, 89.1%)

*High risk features defined as presence of EMD, BMPC ≥ 60, or B2M ≥ 5.5

Durable Response to CART-ddBCMA was seen in all sub-groups

CAR-T CELL ASSOCIATED AEs per ASTCT CRITERIA

CAR-T-associated AEs Per ASTCT criteria	100 million (N=32)		300 million (N=6)	
Cytokine Release Syndrome (CRS)	**Grade 1/2** **30 (94%)**	**Grade 3** **0**	**Grade 1/2** **5 (83%)**	**Grade 3** **1 (17%)**
Median onset (min-max)*	2 days (1-12 days)		2 day (1-2 days)	
Median duration (min-max)	8 days (2-14 days)		5 days (3-10 days)	
Neurotoxicity (ICANs)	**Grade 1/2** **5 (16%)**	**Grade 3** **1 (3%)**	**Grade 1/2** **0**	**Grade 3** **1 (17%)**
Median onset (min-max)*	4.5 days (3-6 days)		7 days	
Median duration (min-max)	7.5 days (4 - 11 days)		23 days	
Toxicity Management				
Tocilizumab	27 (84%)		5 (83%)	
Dexamethasone	20 (63%)		2 (33%)	

*Infusion Day 0 is considered as Study Day 1

No Grade≥3 CRS events at DL1

CONCLUSIONS

- **CART-ddBCMA utilizes a novel, synthetic highly stable binding domain**
  - 2 dose levels studied (100 and 300 million CAR+ T-cells); MTD not reached
  - High CAR-T cell viability, low inter-patient variability in CAR+ cells and high CAR-T cell yield
- **Adverse Event profile indicates relatively well-tolerated CAR T product**
  - No tissue-targeted toxicities observed; No cases grade 3 (or greater) CRS, 1 case (3%) Grade 3 ICANS event at RP2D (n=32)
  - No delayed neurotoxicity or parkinsonian-like events in entire population (n=38)
- **100% ORR per IMWG across both dose levels**
- **24 of 27 (89%) of MRD evaluable subjects achieved Negativity at ≥10^{-5}**
- **Median Duration of Response Not Reached for Overall Population**
  - PFS Rate: @6 months 92%, @12 months 73%, @ 18 months 65%
- **Deep and durable responses**
  - **All Patients: 38/38 (100%) ORR; 27/38 (71%) CR/sCR**, 7/38 (18%) VGPR, 4/38 (11%) PR; ≥VGPR = 34/38 (89%)
  - **Pts w/ 12 mo f/u: 25/25 (100%) ORR; 20/25 (80%) CR/sCR**, 3/25 (12%) VGPR, 2/25 (8%) PR; ≥VGPR = 23/25 (92%)
  - **Pts w/ 18 mo f/u: 16/16 (100%) ORR; 13/16 (81%) CR/sCR**, 1/16 (6%) VGPR, 2/16 (13%) PR; ≥VGPR = 14/16 (88%)
- **Durable responses in patients with high-risk features**
  - PFS rate 63% @18 months in population defined by EMD, BMPC ≥ 60%, and/or B2M ≥ 5.5
- **Pivotal phase 2 trial is now enrolling at RP2D, 115±10 million CAR+ T cells**