ELSEVIER

Blood 142 (2023) 1023–1025

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Phase 1 Study of CART-Ddbcma for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Results from at Least 1-Year Follow-up in All Patients

Matthew J. Frigault, MD MS[1], *Jacalyn Rosenblatt, MD*[2], *Binod Dhakal, MBBS*[3], *Noopur S. Raje, MD*[4], *Daniella Cook, BS*[5], *Mahmoud Gaballa, MD*[5], *Estelle Emmanuel-Alejandro*[6], *Danielle Nissen*[7], *Kamalika C Banerjee*[8], *Anand Rotte, PhD*[8], *Christopher R Heery, MD*[8], *David Avigan, MD*[2], *Andrzej J Jakubowiak, MDPhD*[9], *Michael R. Bishop, MD*[9]

[1] Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA
[2] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
[3] BMT and Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI
[4] Harvard Medical School, Boston, MA
[5] Massachusetts General Hospital Cancer Center, Boston, MA
[6] Beth Israel Deaconess Medical Center, Boston, MA
[7] Medical College of Wisconsin, Milwaukee, WI
[8] Arcellx Inc, Redwood City, CA
[9] University of Chicago, Chicago, IL

Introduction: CART-ddBCMA, an autologous anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapy with a unique, synthetic binding domain, is being studied in a first-in-human clinical trial in patients (pts.) with relapsed &/or refractory multiple myeloma (RRMM). One-year or more follow-up clinical data from all patients are presented in this report.

Methods: Details of study design have been previously reported (Frigault et al Blood Adv 2023). Briefly, pts with RRMM who have received ≥3 prior lines of therapy were enrolled & received a single infusion of CART-ddBCMA following lymphodepletion chemotherapy (fludarabine: 30 mg/m ^{2}/d & cyclophosphamide: 300 mg/m ^{2}/d daily for 3 days). Two dose levels (DL1 & DL2 respectively) of 100 & 300 (±20%) $\times 10^6$ CAR+ cells were evaluated. The primary endpoints included incidence of adverse events (AEs) & dose-limiting toxicities (DLTs). Additional endpoints included quality & duration of clinical response assessed according to the IMWG Uniform Response Criteria for MM, evaluation of minimal residual disease (MRD), progression-free (PFS) & overall survival (OS). Correlative analyses related to CART-ddBCMA expansion, characterization, patient & disease-related features were also evaluated.

Results: As of June 2, 2023, 40 pts; median age 66 years (range: 44-76) were enrolled; 38 received CART-ddBCMA (32, DL1; 6, DL2) & 38 were evaluable for initial safety & clinical response. Two pts who were not dosed had cell product manufactured but were not eligible for cell infusion due to medical complications. Pts had a median of 4 (range: 3-16) prior lines of therapy. All infused pts (100%) were triple-refractory, & 26 (68%) were penta-refractory; 34 pts (89%) were refractory to last-line of treatment; 9 pts (24%) had high tumor burden with ≥60% bone marrow plasma cells; 13 (34%) pts had extramedullary disease; & 11 (29%) pts had high-risk cytogenetics (Del 17p, t(14;16), t(4;14)) at baseline. Median follow-up after CART-ddBCMA infusion was 22 months (range: 9-40 months). CAR+ cells comprised a median 70% (range: 48-87%) of total CD3+ T cells; median vector copy number was 2.2 copies/cell (range: 1.1-3.5); median cell viability was 98% (range: 90-100%), & median cell manufacturing yield was 1174 $\times 10^6$ CAR $^+$ cells (range: 470-1626 $\times 10^6$). CART-ddBCMA product characteristics were consistent with the specifications in all the lots, & there were no manufacturing failures. CRS occurred in 36/38 (95%) pts but only 1 pt in DL2 had grade (Gr) 3 CRS & all other cases were Gr≤2. ICANS occurred in 7 pts (5, Gr≤2; 2, Gr3), with 1 Gr3 case in each DL. All cases of CRS & ICANS resolved without further sequalae with management. No cases of off-tumor cell mediated toxicity, delayed neurotoxicity events (i.e., occurring after day 28), or Parkinsonian-like symptoms were observed. All 38 evaluable pts demonstrated investigator-assessed clinical response per 2016 IMWG criteria (ORR, 100%) with 22 sCR, 7 CR (≥CR rate, 76%), 6 VGPR (≥VGPR rate, 92%), & 3 PR. Responses deepened over time & conversion to CR/sCR was observed with longer follow-up (as late as month 12). Of those evaluable for MRD testing to date (n=29), 25 (86%) were MRD-neg at 10^{-5}. Median duration of response, PFS, & OS were not reached at the time of data-cut because 25 of 38 evaluable pts (66%) had ongoing response. The Kaplan-Meier estimated PFS rates for 6, 12 & 18 months were 92%, 74%, & 67% respectively. Durable responses

were also observed in patients with high-risk features (EMD, BMPC ≥ 60%, or B2M ≥ 5.5 at baseline) & high-risk cytogenetics. PFS rates at 6-, 12-, & 18-months are shown in Table 1. Based on the results from the study, a dose of 115 ± 10 $\times 10^6$ cells, consistent with DL1, was recommended for the phase 2 study.

Conclusions: Adverse events with CART-ddBCMA, including CRS & ICANS, were manageable & no off-tumor tissue-targeted toxicity, delayed neurotoxicity, or Parkinsonian-like events were observed in the entire cohort at the time of data-cut. Ongoing efficacy results are encouraging, with 100% ORR, including 35 (92%) response of VGPR or better & 29 (76%) with CR/sCR. More importantly, clinical responses were durable with an overall estimated 18-mo PFS rate of 67% with comparable clinical responses seen in 'high-risk' patients known to have poor prognosis. Updated data with additional follow-up based on later data-cut will be presented.

Disclosures Frigault: *BMS:* Consultancy; *Kite:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Covance:* Consultancy; *Arcellx:* Research Funding. **Rosenblatt:** *Bristol Myers Squibb:* Research Funding; *Parexel:* Consultancy; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees, Other: Karyopharm; *Advare:* Consultancy; *Sanofi:* Research Funding; *Bioclinica:* Consultancy. **Dhakal:** *Janssen, Karyopharm, GSK, Arcellx, GSK, Sanofi, Genentech, Pfizer:* Consultancy, Honoraria, Speakers Bureau. **Raje:** *Immuneel:* Consultancy; *2seventy Bio:* Consultancy, Research Funding; *Roche:* Consultancy; *Caribou Bioscience:* Consultancy; *K36 Therapeutics:* Consultancy; *Sanofi:* Consultancy; *Pfizer:* Consultancy, Research Funding; *Amgen:* Consultancy; *Abbvie:* Consultancy; *GSK:* Consultancy; *Janssen:* Consultancy. **Banerjee:** *Arcellx:* Current Employment. **Rotte:** *Arcellx:* Current Employment. **Heery:** *Arcellx:* Current Employment. **Avigan:** *Celgene:* Consultancy, Other: Advisory role, Research Funding; *Paraxel:* Current Employment; *Bristol-Myers Squibb:* Consultancy, Other: Advisory board; *Partner Therapeutics:* Consultancy, Other: Advisory board; *Aviv Med Tech:* Consultancy, Other: Advisory board; *Kite/Gilead:* Consultancy, Other: Advisory role, Research Funding; *Legend Biotech:* Consultancy, Other: Advisory role; *Sanofi:* Consultancy, Other: Advisory board; *Karyopharm Therapeutics:* Consultancy, Other: Advisory role; *Chugai Pharma:* Consultancy, Other: Advisory role; *Juno Therapeutics:* Consultancy, Other: Advisory role; *Takeda:* Consultancy, Other: Advisory role; *Janssen:* Consultancy, Other: Advisory board; *Kowa Pharmaceutical:* Consultancy, Other: Advisory board; *Pharmacyclics:* Research Funding; *Kite, a Gilead Company:* Research Funding. **Jakubowiak:** *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi-Aventi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Bishop:** *Triumvira:* Research Funding; *Immatics:* Research Funding; *Autolus:* Consultancy, Research Funding; *Arcellx:* Consultancy, Research Funding; *WindMIL Therapeutics:* Consultancy; *Bluebird Bio:* Consultancy; *Iovance:* Consultancy; *CRISPR Therapeutics:* Consultancy, Research Funding; *Agios:* Consultancy, Honoraria, Other: Travel support, Speakers Bureau; *BMS:* Honoraria, Other: Travel support, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Other: Travel support, Research Funding; *Sanofi:* Honoraria, Speakers Bureau; *Celgene:* Honoraria; *Incyte:* Honoraria, Other: Travel support, Speakers Bureau; *Chimeric Therapeutics:* Consultancy; *Tmunity:* Research Funding; *Kite, a Gilead Company:* Consultancy, Honoraria, Other: Travel support, Research Funding, Speakers Bureau; *Sana Biotechnology:* Consultancy; *ADC Therapeutics:* Speakers Bureau; *Servier:* Speakers Bureau; *KITE/Gilead, Novartis, CRISPR Therapeutics, Autolus Therapeutics, BMS/JUNO Therapeutics, Incyte, Sana Biotechnology, Iovance Biotherapeutics, In8bio, Chimeric Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BMS, Kite/Gilead, Servier, AstraZeneca, ADC Therapeutics, Incyte:* Speakers Bureau.

OffLabel Disclosure: CART-ddBCMA is an autologous CAR-T cell therapy evaluated for the treatment of relapsed/refractory multiple myeloma

Table 1. Estimated PFS rate in CART-ddBCMA treated patients

	PFS Rates (%)		
	6-month	12-month	18-month
All dosed (n=38)	92.1	74.3	67.5
Age ≥65 years (n=20)	95.0	84.4	78.4
Complete responders (n=29)	96.4	88.8	84.6
High Risk Features* (n=24)	91.7	73.3	68.1
Extramedullary Disease (n=13)	92.3	64.6	64.6
High Risk Cytogenetics (n=11)	81.8	70.1	70.1

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

Figure 1

https://doi.org/10.1182/blood-2023-189761