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Phase 1 Study of CART-ddBCMA for the treatment of subjects with relapsed and refractory multiple myeloma

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Abstract:
Relapsed and refractory multiple myeloma (RRMM) is a plasma cell neoplasm defined by progressively refractory disease necessitating chronic and increasingly intensive therapy. Despite recent advances, limited treatment options exist for RRMM. This single-arm, open label phase 1 study (NCT04155749) aimed to evaluate the safety of novel BCMA-targeting CAR T construct that leverages a completely synthetic antigen binding domain (CART-ddBCMA), which was specifically engineered to reduce immunogenicity and improve CAR cell surface stability. Thirteen RRMM patients with age {greater than or equal to}18 years who received at least 3 prior regimens of systemic therapy were enrolled in the study. Patients received a single dose of $100x10^6$ CART-ddBCMA (DL1) or $300x10^6$ CART-ddBCMA (DL2) following standard lymphodepleting chemotherapy. The primary endpoints of the study were to evaluate the incidence of treatment emergent adverse events, including dose limiting toxicities, and establish a recommended phase 2 dose (RP2D). Results showed that CART-ddBCMA was well tolerated and demonstrated a favorable toxicity profile. Only 1 case of grade {greater than or equal to}3 CRS and ICANS were reported, which were both at DL2 and were manageable with standard treatment. No atypical neurological toxicities and Parkinson's disease-like movement disorders were observed. The maximum tolerated dose was not reached. All infused patients responded to CART-ddBCMA and 9/12 (75%) patients achieved CR/sCR. Responses deepened over time and at the time of last data-cut (median follow-up 56 weeks), 8/9 (89%) of evaluable patients achieved minimal residual disease negativity. In conclusion, the findings demonstrate the safety of CART-ddBCMA cells and document durable responses to CART-ddBCMA in RRMM patients.

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KEY POINTS

- CART-ddBCMA are safe for use in patients with relapsed or refractory multiple myeloma
- CART-ddBCMA produce deep and durable responses in patients with poor prognostic factors

ABSTRACT

Relapsed and refractory multiple myeloma (RRMM) is a plasma cell neoplasm defined by progressively refractory disease necessitating chronic and increasingly intensive therapy. Despite recent advances, limited treatment options exist for RRMM. This single-arm, open label phase 1 study (NCT04155749) aimed to evaluate the safety of novel BCMA-targeting CAR T construct that leverages a completely synthetic antigen binding domain (CART-ddBCMA), which was specifically engineered to reduce immunogenicity and improve CAR cell surface stability. Thirteen RRMM patients with age ≥18 years who received at least 3 prior regimens of systemic therapy were enrolled in the study. Patients received a single dose of $100x10^6$ CART-ddBCMA (DL1) or $300x10^6$ CART-ddBCMA (DL2) following standard lymphodepleting chemotherapy. The primary endpoints of the study were to evaluate the incidence of treatment emergent adverse events, including dose limiting toxicities, and establish a recommended phase 2 dose (RP2D). Results showed that CART-ddBCMA was well tolerated and demonstrated a favorable toxicity profile. Only 1 case of grade ≥3 CRS and ICANS were reported, which were both at DL2 and were manageable with standard treatment. No atypical neurological toxicities and Parkinson's disease-like movement disorders were observed. The maximum tolerated dose was not reached. All infused patients responded to CART-ddBCMA and 9/12 (75%) patients achieved CR/sCR. Responses deepened over time and at the time of last data-cut (median follow-up 56 weeks), 8/9 (89%) of evaluable patients achieved minimal residual disease negativity. In conclusion, the findings demonstrate the safety of CART-ddBCMA cells and document durable responses to CART-ddBCMA in RRMM patients.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm with treatment aimed at disease control rather than cure. Despite new therapeutic options, which include immunomodulatory agents (IMiDs), proteasome inhibitors, and anti-CD38 monoclonal antibodies (mAb), the natural disease course is characterized by relapse with progressively refractory disease, while patients accumulate disease- and treatment-related toxicities.[2] Historically, patients with triple- (proteasome inhibitors, IMiD, and anti-CD38 mAb) and penta-refractory (two IMiDs, two proteasome inhibitors, and anti-CD38 mAb) disease have demonstrated median progression free survival (PFS) of 3.5 and 2.3 months and median overall survival (OS) of 14.7 and 6.6 months, respectively.[3-5] Due to the poor survival in this highly refractory patient population, novel treatment strategies are critically needed to improve outcomes in MM patients.

Recently, MM therapies targeting the B-cell maturation antigen (BCMA) have emerged as promising options for highly refractory patients.[6,7] BCMA is highly expressed on MM cells, with limited expression outside of terminally differentiated B cells and normal plasma cells, and is involved in promoting MM cell survival and proliferation,[8-11]. Approaches to target BCMA, utilizing bispecific T-cell engagers and antibody-drug conjugates (ADCs), have shown overall (ORR) of 60–75% and complete response/stringent complete response rates (CR/sCR) of 30–40%, but require frequent repeated infusions.[12-16] In contrast, autologous chimeric antigen receptor (CAR) T cells engineered to target surface antigens in hematologic malignancies are typically given once and mediate prolonged remissions.[17-22] The KarMMA trial of idecabtagene vicleucel (ide-cel) demonstrated an ORR of 73% and led to FDA approval of the first CAR-T cell targeting BCMA in March 2021.[23,24] In the CARTITUDE-1 trial, ciltacabtagene autoleucel (cilta-cel), showed an ORR of 97% at the time of reporting,[25] and the respective BLA is currently under FDA evaluation. Additional therapeutics products targeting BCMA are currently in development.[26-32]

Although effective, the available CAR-T cell therapies are limited by durability of response, disease resistance as well as safety and production issues.[33-35] The typical antigen-binding domains of CARs are derived from animal antibodies and use combinations of either single chain variable fragments (scFv) that link variable light and heavy chains or single-domain heavy-chain (VHH) antibodies. Despite specific antigen binding, these molecules can have promiscuous oligomerization of the scFv fragments, leading to ineffective or tonic downstream signaling, which can be detrimental to CAR-T cell effector function and persistence.[36-38] These non-human derived proteins can also induce development of anti-CAR antibodies and prime T-cell responses that may to lead rejection and decreased persistence of otherwise autologous products.[39] To overcome these limitations, alternatives to scFVs such as ankyrin repeats,[40] adnectins,[41] thermo-stable DNA-binding proteins,[42] affibodies,[43] and D-domain proteins[44] have been proposed. D-domain proteins are synthetic proteins with unique advantages including small size (~8 kDa) lack disulfide bonds and N-linked glycosylation which allows for rapid protein folding, absence of tonic signaling and high cell surface stability.[44,45]

We developed anti-BCMA CAR-T cells with a CAR composed of a D-domain-based antigen binder fused to the CD8 hinge and transmembrane domain in tandem with the intracellular signaling domains of 4-1BB and CD3ζ and introduced into human T cells via lentiviral vector (CART-ddBCMA). Based on the encouraging efficacy seen in preclinical studies, we initiated a phase I clinical study of CART-ddBCMA patients with relapsed/refractory MM (NCT04155749).

METHODS

CART-ddBCMA

CART-ddBCMA drug product consists of autologous T cells genetically modified ex vivo to express a binding domain that specifically recognizes BCMA. The binding domain was identified in a library of randomized α3D sequences using standard phage-display technologies, and site-directed mutagenesis was used to enhance target affinity and minimize immunogenicity.[44] The resulting sequence encoding a 73 amino acid D domain with nanomolar affinity for human BCMA was cloned into a lentiviral vector along with CD8 hinge and transmembrane region, 4-1-BB and CD3ζ intracellular signaling domains. Pre-clinical studies of CAR T cells utilizing D-domains showed the absence of tonic signaling, consistently high levels of cell surface expression, and low immunogenicity based *on in silico* modeling.[46] CART-ddBCMA displayed reproducible BCMA-dependent NFAT signaling, cytokine (IL-2, IFN-γ) secretion, and induced BCMA-specific cytotoxicity in tumor cell lines. In the mouse-human xenograft models, CART-ddBCMA eradicated BCMA-expressing tumors within 2 weeks of single administration. Body weights of the mice were not impacted by CART-ddBCMA treatment and there were no histopathological findings in the in vivo studies that were attributable to ddBCMA exposure.[47-49]

Study design

This open-label, multi-center phase 1 trial enrolled adults with relapsed/refractory MM to evaluate the safety of intravenous administration of CART-ddBCMA (Supplementary Figure S1). The protocol was approved by the Institutional Review Board at each center, and the trial was performed in accordance with the principles of the Declaration of Helsinki. Eligible patients required treatment with at least 3 prior lines of systemic therapy including a proteasome inhibitor, an IMiD, and an anti-CD38 antibody. Alternatively, patients were eligible if deemed to have "triple-refractory" disease following treatment with proteasome inhibitor, IMiD, and anti-CD38 antibody as part of the same or different regimens. Eligibility criteria also included adequate organ function (creatine clearance (CrCl) ≥50 mL/min and left ventricular ejection fraction (LVEF) ≥45%) and an Eastern Cooperative Group Performance Status of 0-1.

Patients with plasma cell leukemia or active central nervous system (CNS) involvement were excluded but ongoing anticoagulation were allowed. Patients with prior BCMA-targeted therapy were eligible after medical monitor discussion.

After providing written informed consent, patients were enrolled and underwent leukapheresis. Bridging therapy was allowed, but a 2-week washout was required prior to lymphodepleting chemotherapy and cell infusion. Repeat baseline assessments were required prior to initiation of lymphodepleting chemotherapy (LDC). For LDC, patients received a regimen of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) daily on days -5, -4, and -3 prior to cell infusion. Cells were manufactured by the Connell and O'Reilly Families Cell Manipulation Core Facility of the Dana-Farber/ Harvard Cancer Center. Patients received a dose of $100x10^6$ CART-ddBCMA (dose level 1, DL1) or $300x10^6$ CART-ddBCMA (dose level 2, DL2) on day 0. Blood was collected at days 0, 1-4, 7, 9, 11, 14, 21, and 28 post CART-ddBCMA infusion and then months 2-6, 9, 12, 15, 18, 21, and 24 to monitor CAR-T cell expansion and persistence. Additional blood was drawn to evaluate correlative pharmacodynamic effects. Patients are also monitored for disease progression up to 24 months. At the time of disease progression, or at 24 months if progression did not occur, patients are transferred to long-term follow-up phase of the study. Re-treatment of the patients was possible with FDA and IRB approval, and patients were dosed from material remaining from initial manufacturing run.

End points

The primary end points of the study were to evaluate the incidence of treatment-emergent adverse events (TEAEs), including dose limiting toxicities (DLTs), and to establish the recommended phase 2 dose (RP2D). DLTs were defined as any investigational study drug-related grade 3+ toxicity occurring within the first 28 days, as well as any grade 4 life-threatening toxicity, grade ≥3 cytokine release syndrome

(CRS) that did not improve to ≤ grade 2 within 72 hours, any grade ≥3 neurotoxicity including any seizures, any grade ≥3 toxicity involving vital organs (e.g. cardiac, pulmonary) that resulted in significant and irreversible organ damage, any grade ≥3 non-hematologic toxicity that did not improve to ≤ grade 2 within 72 hours, and any death not attributed to underlying malignancy. Toxicity grading was performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. CRS and immune effector cell-associated neurotoxicity (ICANS) were graded according to the American Society for Transplant and Cellular Therapy consensus criteria.[50] Secondary endpoints included, but were not limited to, duration of response, PFS, OS as well as correlative and exploratory studies. Response assessments were performed per the International Myeloma Working Group (IMWG) consensus criteria.[51]

Statistical analysis

Sample size was based on a 3+3 dose escalation design.[52] A total of 6 evaluable subjects were enrolled in each dose level to ensure adequate evaluation for potential DLT incidence in selecting a RP2D. Data are presented as the median and range for continuous variables and frequency for categorical variables. Time-to-event analyses and the associated 95% confidence intervals were estimated using the Kaplan-Meier method. Subjects were censored at the date of last follow up. All patients who received CART-ddBCMA infused were included in this analysis as was planned per protocol.

RESULTS

Patient disposition and characteristics

Between November 19, 2019, and April 14, 2021, 13 subjects were enrolled and 12 were infused with CART-ddBCMA, 6 at DL1 and 6 at DL2 (**Figure 1**). One subject discontinued prior to cell infusion due to disease-related complications unrelated to the investigational product. As of the data cut for this

analysis, on November 4, 2021, the median follow-up was 56 weeks (range, 33–90). Drug products were successfully manufactured for all 13 patients with a median vein-to-vein time of 35 days (range 33–42 days) for infused patients. CAR expression in the final product was consistent for all patients and the variability in % CAR^+ cells in the final product was low between patients. The median CAR^+ cells in total $CD3^+$ cells was 74.5% (range, 61–87%). The median patient age was 69 years (range, 44–76) for patients treated with $100x10^6$ CART-ddBCMA and 60 (range, 52–65) for those treated with $300x10^6$ CART-ddBCMA (**Table 1**). The median time since diagnosis was 6.5 years (range 1.8–11.8 years), and patients had received a median of 5 (range 5–7), 4 (range 3–16), and 5 (3–16) prior lines of therapy in DL1, DL2, and overall, respectively. Nine of the 10 subjects with evaluable cytogenetics (90%) had high-risk features per IMWG, 7 of 12 subjects (58%) had extramedullary disease at time of treatment, and 10 of 12 (83%) were considered penta-refractory at time of enrollment. One patient had progressed following treatment with a BCMA ADC. All enrolled patients received bridging therapy following leukapheresis for progressive and/or symptomatic disease.

Safety

All patients experienced grade 3 or 4 TEAEs following CART-ddBCMA infusion, as shown in **Table 2**. The most common AEs were hematologic, including neutropenia (92%), anemia (83%), lymphocytopenia (67%), and decreased hemoglobin (75%). Most patients had cytopenias resolved to baseline or ≤grade 2 by 28 days. Of those that did not, all but one patient were resolved to baseline or ≤grade 2 with standard interventions by month 5. Lymphocytopenia in one patient was resolved to baseline levels by month 12. Investigator attribution of these events was related to lymphodepletion chemotherapy plus underlying bone marrow function. In all cases of CR or sCR, improvement in cytopenias occurred compared to a screening of baseline value. The most common non-hematologic grade 3 or 4 AEs were

hypertension (25%) and electrolyte imbalances (17%). There were no treatment-emergent grade 3 or 4 infections.

CAR-T cell-associated toxicities occurred in all subjects, but most were low grade and manageable. CRS occurred in all patients, with a median onset of 2.5 days (range 0–6 days) and duration of 7 days (range 3–8 days) in DL1 and 1 day (range 0–3 days) and 4.5 days (range 3–6 days), respectively, in DL2. No patient in DL1 experienced grade 3+ CRS, but one patient experienced grade 3 CRS in DL2 that was partly attributed to a delay in defined tocilizumab administration (**Table 3**). Four subjects in DL1 and 5 subjects in DL2 (9/12 overall) required tocilizumab for the management of CRS (median 1 dose, range 1–2 doses). Two subjects in DL1 and 3 subjects in DL2 received one dose of dexamethasone for CRS management. ICANS occurred in two subjects, one in DL1 and one in DL2. The subject in DL1 experienced grade 2 ICANS that began on D+2 and resolved by D+5 with administration of steroids. The subject in DL2 experienced ICANS on D+6 as decreased mental status and decreasing Immune Effector Cell-Associated Encephalopathy (ICE) score of 7 consistent with grade 1 characteristics. Severe CRS was not seen in this subject and the patient did not require tocilizumab. The severity of ICANS was grade 3 on D+9 based on clinical presentation and ICE score of 2 which was solely driven by global aphasia rather than decreased level of consciousness as the patient remained able to follow commands and intermittently respond. Following treatment with anakinra and steroids, the subject improved to grade 2 ICANS on D+19, to grade 1 on D+20 and the AE was completely resolved on D+22. No long-term deficits or sequela have been identified in both subjects. Also, at the time of last data-cut there were no cases of delayed onset progressive movement disorders with features of Parkinson's disease, as described in other investigational and commercially available BCMA-targeted CAR T cell products.[53,54] Given the low incidence of high-grade CAR-T cell-related AEs and only one observed DLT, a maximum tolerated dose of CART-ddBCMA was not reached.

Efficacy

At the time of data-cut, all subjects in the study had over 200 days of follow-up. The median duration of follow-up was 12.6 months in all patients (15.6 months in DL1 and 8.3 months in DL2). The objective response rate was 100% across both dose levels of CART-ddBCMA, with 9 patients (75.0%) having CR/sCR, 1 (8.3%) with a very good partial response (VGPR), and 2 (16.7%) with a partial response (PR; **Figure 2)**. The median time to response for all subjects was 28 days (range 28–87) with deepening of responses over time. Median time to response was 28.5 days (range 28–57) in DL1 and 28 days (range 28-87) in DL2. Median duration of response, PFS and OS were not reached at both DLs. As the ORR was comparable between DL1 and DL2, and the toxicities were lower at DL1, additional subjects were enrolled in DL1.

Minimal residual disease (MRD) was evaluated by next-generation sequencing at day +28 in 9/12 patients. One month following CART-ddBCMA infusion, 5/9 patients were MRD negative (10^{-5}, n=3; 10^{-6}, n=2) with further deepening of responses over time (**Figure 2**). At the time of last data-cut, 5 subjects were MRD negative at 10^{-6}, 2 at 10^{-5}. Of those who achieved MRD negativity at 10^{-6} (n=5), none have had progressive disease (PD).

Disease progression was observed in 3 subjects. One subject treated on DL1 had progression at day +115 after a best response of PR at day+28. The subject was retreated with CART-ddBCMA at DL2 on day +136 and had further progression at day +205 from initial CAR-T infusion. The second subject with disease progression was treated on DL2, reached PR at day 28, VGPR at month 4, and sCR at month 9 (concurrently MRD negative at 10^{-5}) but had progressive disease at day +320 with new lymphadenopathy and rising M-protein (**Figure 2**). This subject had received a BCMA ADC prior to

enrollment in the study. After progression, the subject was re-treated at DL1. The subject had an ongoing PR at the time of reporting following re-infusion. The third subject with disease progression was treated on DL1 and had a PR, which was maintained for almost one year but had disease progression by day +336. The subject did not receive any re-treatment at the time of reporting.

CAR-T cell expansion and persistence

CART-ddBCMA expansion was measured by transgene vector copy number in whole blood. The median time to peak expansion of CART-ddBCMA after infusion was 14 days (range 9–21) in DL1, 10 days (range 7–14) in DL2, and 11 days (range 7–21) in all subjects. The median copies of vector transgene per microgram of genomic DNA at the peak level was 71,992 (range 10,068–204,300) in DL1, 91,829 (range 43,785–351,000) in DL2, and 90,147 (range, 10,068–351,000) in all subjects. Median area under the curve (AUC0-28, days × VCN/microgram of genomic DNA) for CART-ddBCMA was 514,374 (range, 76,916–3,026,634) in DL1, 644,965 (range, 42,7583–1,777,748) in DL2, and 644,965 (range, 76,916–3,026,634) in all subjects. Median persistence of CART-ddBCMA was 59 days (range, 21–180) in DL1, 42 days (range, 28–180) in DL2, and 42 days (range, 21–180) in all subjects. CART-ddBCMA kinetics including peak level, time to peak expansion, and persistence were similar for DL1 and DL2 (**Figure 3**).

Soluble BCMA (s-BCMA) levels in the serum, a marker for plasma cells and myeloma cells[9,11] decreased in all subjects following CART-ddBCMA treatment. The fall in s-BCMA levels in the peripheral blood continued even after the CART-ddBCMA were undetectable in the peripheral blood (**Supplementary Figure S2 and S3**). The recovery of s-BCMA levels was relatively slow in patients with ongoing response, and the majority of patients had lower s-BCMA levels for over 6 months suggesting a slower recovery of plasma cells.

DISCUSSION

This study demonstrated that the maximally tolerated dose of CART-ddBCMA was not exceeded at a flat dose of $300x10^6$ CAR^+ cells. Evaluation of secondary endpoints indicates an ORR of 100%, with 75% of those responses being CR or better collectively and ≥67% CR or better in each dose level. The adverse events observed in this trial were consistent with previously observed AEs in BCMA CAR T cell trials,[28] including the pivotal study that led to ide-cel approval.[23] In this study, only 1 patient (8.3%) had grade 3 neurotoxicity occurring at DL2 within the first week of treatment, which was the only DLT observed on study. Importantly, no grade ≥3 CRS or ICANS occurred in DL1 and there were no cases of delayed onset Parkinson's-like progressive movement disorders[53,54] observed in either dose levels. At DL1, the lack of grade ≥ 3 CRS and ICANS occurred in the context of 100% ORR (6/6) and 66.7% (4/6) sCR. No patients experienced atypical neurotoxicity despite a median follow-up of 12.6 months. Ten of the 12 subjects dosed with CART-ddBCMA (83.3%) remained in ongoing response at time of data cut (median follow-up 395 days). Additionally, of the patients that were evaluable, 88.9% were MRD-negative within one month of treatment and many (5/6 patients that were tested multiple times) maintained or developed a deeper response to treatment over time, based on their MRD status.

These responses occurred in patients with relatively poor prognostic indicators, including 7 of 12 (58.3%) with high tumor burden (BMPC >50%), 7 of 12 (58.3%) with extra-medullary disease, and 9 of 10 evaluable (90%) with high-risk cytogenetics. They were also heavily pretreated, with 7 of 12 (58.3%) patients having prior hematopoietic stem cell transplant and 10 of 12 (83.3%) having penta-refractory disease. Given the comparable ORRs between DL1 and DL2, and the comparatively lower CAR-T-related toxicities in patients treated with $100x10^6$ CART-ddBCMA we have continued enrollment of the expansion cohort at DL1. If the response rate observed in this study continues in a larger cohort, this dose level will be employed in a pivotal trial which is currently in development.

CART-ddBCMA kinetics, including median time to reach peak expansion (10 days) and median time to onset of response (28 days), were similar and consistent with kinetics of CAR-T cell therapies, including ide-cel[23] and cilta-cel [25]. The ORR and CR observed with CART-ddBCMA was comparable to ORR observed with ide-cel and cilta-cel. [23,26,27,55] These results are promising when compared to ide-cel and cilta-cel given the higher rates of high-risk cytogenetics (90% vs 35% and 24% respectively), EM involvement (58% vs 39% and 13% respectively) and penta-refractory disease (83% vs 26% and 42% respectively). [23,26,27,55] After a median follow-up of 12.3 months, median duration of response, PFS, and OS have not been reached at either dose level. More importantly, CART-ddBCMA responses deepened over time, and 6 subjects (of 8 evaluable) remained relapse-free beyond 12-month evaluation, including 3 subjects remaining relapse-free beyond 20 months (**Figure 2A**), indicating the durability of the efficacy.

The persistence of CART-ddBCMA cells in the peripheral blood was also similar to majority of BCMA targeting CAR-T cell therapies, which noted a drop in peripheral CAR+ cells within 60 days and lack of detectable CAR+ cells in peripheral blood within 120 days in majority of subjects.[26,56,57] We believe the drop in CART-ddBCMA levels is mainly due to lack of antigen stimulation following tumor elimination. Intriguingly, durability of efficacy was not found to correlate with presence of detectable CAR-T cells in multiple myeloma in previous studies.[26,57] In our study, even though CART-ddBCMA cells were not detectable after 120 days, responses were durable for over 12 months in 6 out 8 evaluable subjects. Furthermore, s-BCMA levels remained low in all subjects with ongoing response and the recovery rate was slow suggesting a slower recovery of BCMA expressing plasma cells in the peripheral blood. Further studies and additional data are needed to verify if slower recovery of BCMA expressing plasma cells is due to ongoing immunosurveillance against BCMA expressing plasma cells by CART-ddBCMA cells.

This trial is the first to demonstrate the utility of D-domain antigen binding domain-based CAR T cells. D-domains have distinct advantages, such as triple α-helical bundle stabilized by a hydrophobic core with no disulfide bonds or N-linked glycosylation sites,[44] and are easily manipulatable, allowing for removal of immunogenic epitopes and modulation of the target binding specificities. Therefore, the production of D-domain based CAR-T cells is expected to provide consistent manufacturing with lower inter-patient variability, and decreased tonic signaling which may improve the durability of BCMA CAR-T responses. The current study provides the first evidence on clinical application of D-domains. The durable responses, consistent CAR^+ expression rate per cell (median VCN of 2.33, range 1.33–3.55), and low inter-patient variability (median CAR^+CD3^+ cells in the product of 74%, range 61%–87%) noted in the current study are encouraging and support the development of binding domains for other targets.

This study is limited by a small sample size and is mainly designed to evaluate the initial safety of CART-ddBCMA administration. This limitation of the study should be considered during the interpretation of the findings on safety and efficacy. Further studies in larger cohort are needed to confirm the safety and efficacy of CART-ddBCMA cells for treatment of relapsed/refractory MM.

In conclusion, we characterized the safety of CART-ddBCMA at doses of 100 and 300×10^6 cells per patient. We further showed that CART-ddBCMA administration can induce deep and durable responses in patients with high-risk relapsed/refractory MM.

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AUTHORSHIP STATEMENT

Firgault, Bishop, Rosenblatt, O'Donnell, Raje, Cook, Yee, Logan, Avigan, Jakubowiak, Shaw, Daley, and Nikiforow contributed to the study design, collection of data, analyses and interpretation of data. Griffin and Cornwell contributed to study design and data analyses. Shen, Heery and Maus contributed to the study design and interpretation of data.

CONFLICTS STATEMENT

Frigault: Celgene: Consultancy; Novartis: Consultancy, Research Funding; Arcellx: Consultancy; Gilead/Kite: Consultancy, Research Funding. **Bishop**: Kite: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; Incyte: Honoraria, Speakers Bureau; Autolus: Membership on an entity's Board of Directors or advisory committees; Novartis: Membership on an entity's Board of Directors or advisory committees, Research Funding; CRSPPR Therapeutics: Membership on an entity's Board of Directors or advisory committees, Research Funding; BMS: Honoraria, Speakers Bureau. O'Donnell: Celgene: Consultancy. **Rosenblatt**: Attivare Therapeutics: Consultancy; Bristol-Myers Squibb: Research Funding; Parexel: Consultancy; Wolters Kluwer Health: Consultancy, Patents & Royalties; Imaging Endpoints: Consultancy; Karyopharm: Membership on an entity's Board of Directors or advisory committees. **O'Donnell**: Celgene: Consultancy. **Raje**: Celgene: Consultancy. **Yee**: Adaptive: Consultancy; Bristol Myers Squibb: Consultancy; GSK: Consultancy;

Oncopeptides: Consultancy; Karyopharm: Consultancy; Amgen: Consultancy; Takeda: Consultancy; Sanofi: Consultancy; Janssen: Consultancy. **Shen**: Arcellx: Former Employment, Current equity holder in private company. **Avigan**: Celgene: Membership on an entity's Board of Directors or advisory committees, Research Funding; Pharmacyclics: Research Funding; Kite Pharma: Consultancy, Research Funding; Juno: Membership on an entity's Board of Directors or advisory committees; Partner Tx: Membership on an entity's Board of Directors or advisory committees; Karyopharm: Membership on an entity's Board of Directors or advisory committees; Bristol-Myers Squibb: Membership on an entity's Board of Directors or advisory committees; Aviv MedTech Ltd: Membership on an entity's Board of Directors or advisory committees; Takeda: Membership on an entity's Board of Directors or advisory committees; Legend Biotech: Membership on an entity's Board of Directors or advisory committees; Chugai: Membership on an entity's Board of Directors or advisory committees; Janssen: Consultancy; Parexcel: Consultancy; Takeda: Consultancy; Sanofi: Consultancy. **Jakubowiak**: BMS: Membership on an entity's Board of Directors or advisory committees; Celgene: Membership on an entity's Board of Directors or advisory committees; Abbvie: Membership on an entity's Board of Directors or advisory committees; Gracell: Membership on an entity's Board of Directors or advisory committees; GSK: Membership on an entity's Board of Directors or advisory committees; Janssen: Membership on an entity's Board of Directors or advisory committees; Karyopharm: Membership on an entity's Board of Directors or advisory committees; Amgen: Membership on an entity's Board of Directors or advisory committees; Sanofi: Membership on an entity's Board of Directors or advisory committees. **Shaw**: Orchard Therapeutics, Ltd: Current equity holder in publicly-traded company. **Nikiforow**: Kite/Gilead: Other: ad HOC Advisory Boards; Novartis: Other: ad Hoc Advisory Boards; Iovance: Other: ad Hoc Advisory Boards; Glaxo Smith Kline (GSK): Other: ad Hoc Advisory Boards. **Griffin**: Arcellx: Current Employment, Current equity holder in private company. **Cornwell**: Arcellx: Current Employment, Current equity holder in private company. **Heery**: Arcellx: Current Employment, Current equity holder in private

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TABLES

Table 1: Patient Demographics

Characteristics	**Dose Level 1 100 million CAR-T (n=6)**	**Dose Level 2 300 million CAR-T (n=6)**
Age, median (min–max)	73 (66–75)	60 (53–65)
Gender	3 Male 3 Female	5 Male 1 Female
BMPC >50%	3/6	4/6
Extra-medullary disease	4/6	3/6
High-risk cytogenetics per IMWG	5/5*	4/5*
Prior Lines of Therapy, median (min-max)	5 (5–7)	4 (3–16)
Prior HSCT	3/6	4/6
Penta-refractory†	6/6	4/6
IgG myeloma IgA myeloma Light chain only	1 3 2	5 0 1

BMPC, bone marrow plasma cell; IMWG, International Myeloma Working Group; HSCT, hematopoietic stem cell transplant; †penta-refractory patients are refractory to bortezomib, carfilzomib, daratumumab, lenalidomide, and pomalidomide; *some subjects were not evaluable or data were not available at time of data cut-off.

Table 2: Adverse Events Following CART-ddBCMA Infusion

	Cohort		
Event	**100x10^6 (N=6) n (%)**	**300x10^6 (N=6) n (%)**	**Total (N=12) n (%)**
Subjects with at least one ≥ grade 3 AE	6 (100%)	6 (100%)	12 (100%)
Neutropenia	6 (100%)	5 (83.3%)	11 (91.7%)
Anemia	5 (83.3%)	5 (83.3%)	10 (83.3%)
Lymphocytopenia	5 (83.3%)	3 (50.0%)	8 (66.7%)
Thrombocytopenia	2 (33.3%)	4 (66.7%)	6 (50.0%)
Leukopenia	3 (50.0%)	2 (33.3%)	5 (41.7%)
Hyponatremia	2 (33.3%)	0	2 (16.7%)
Febrile neutropenia	3 (50.0%)	1 (16.7%)	4 (33.3%)
Hypertension	2 (33.3%)	1 (16.7%)	3 (25.0%)

AE, adverse event

Table 3: CAR-T-associated Adverse Events

CAR-T-associated AEs Per ASTCT criteria	**100 million (N=6)**		**300 million (N=6)**	
Cytokine Release Syndrome (CRS)	**grade 1/2**	**grade 3**	**grade 1/2**	**grade 3**
	6	0	5	1
Median onset (min–max)	2.5 days (0–4 days)		< 24 hours (0–1 day)	
Median duration (min–max)	5 days (2–7 days)		3 days (1–9 days)	
Neurotoxicity (ICANs)	**grade 1/2**	**grade 3**	**grade 1/2**	**grade 3**
	1	0	0	1
Onset	2 days		6 days	
Duration	2 days		14 days	
Toxicity Management				
Tocilizumab	4		5	
Dexamethasone	3		2	
Anakinra	0		1	

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; ICANS, immune effector cell-associated neurotoxicity

FIGURE LEGENDS

Figure 1: Study CONSORT diagram.

Figure 2: Objective responses in patients treated with CART-ddBCMA.

Responses were assessed according to the International Myeloma Working Group (IMWG) consensus criteria. Minimal residual disease (MRD) status is also indicated along with extent of MRD, presented as the number of multiple myeloma cells detected in the bone marrow per $1x10^4$, $1x10^5$, or $1x10^6$ total nucleated cells. An MRD of $1x10^{-4}$ or less is considered MRD-negative. A. The best responses for each patient are shown, grouped by dose cohorts. B. OR and sCR/CR rate over time.

Figure 3: CART-ddBCMA expansion and persistence in patients.

The kinetics of CART-ddBCMA over time is shown for each patient as measured by the copies of vector transgene per microgram of genomic DNA.

Figure 1

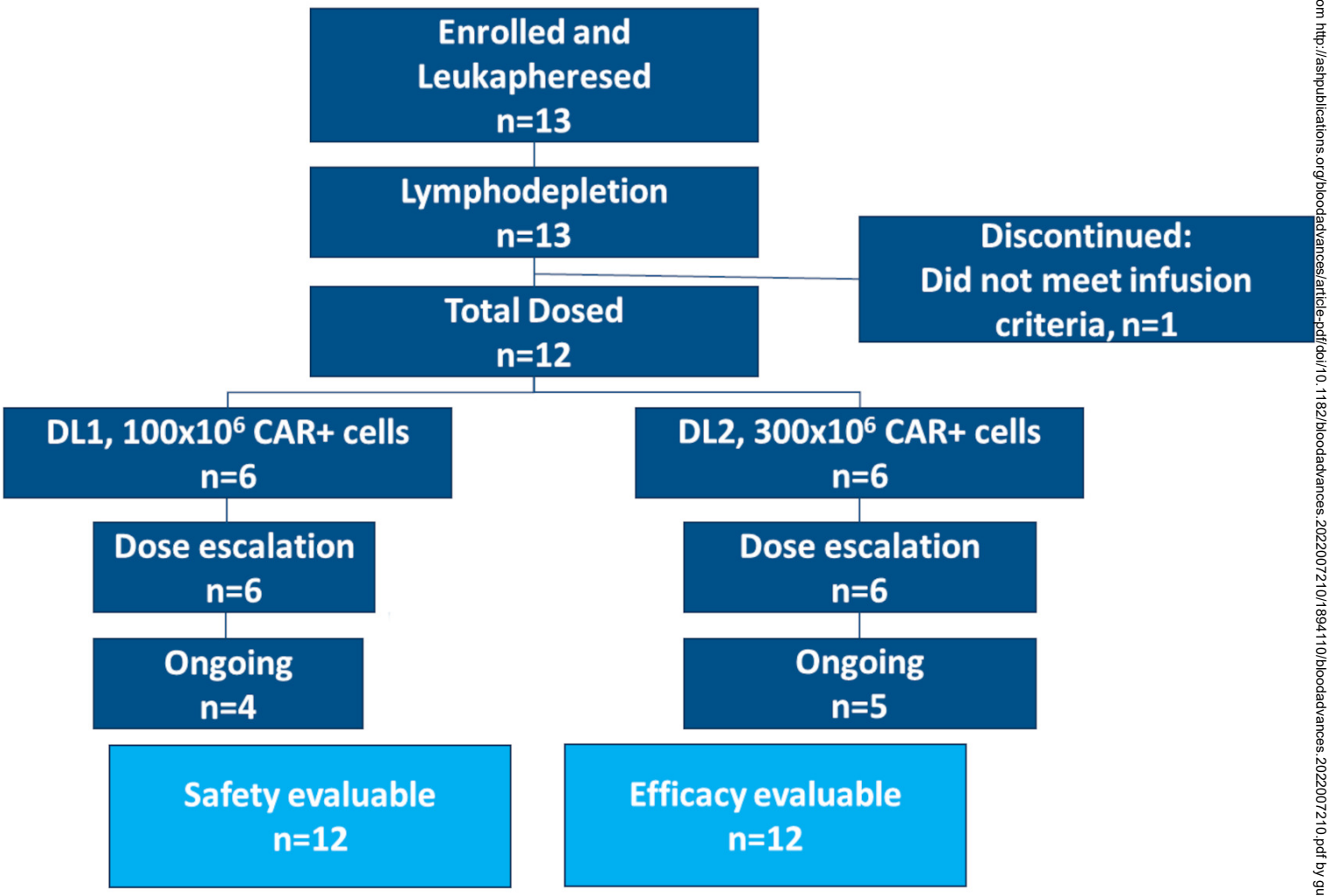
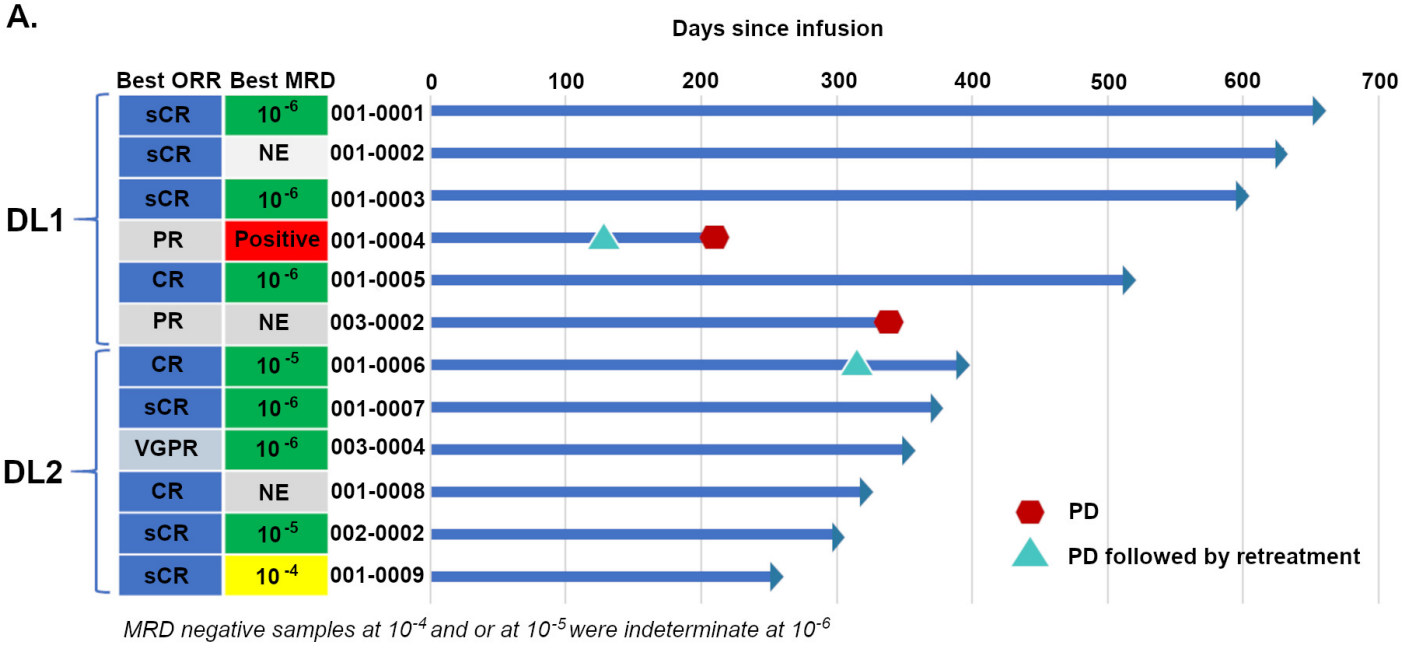


Figure 2



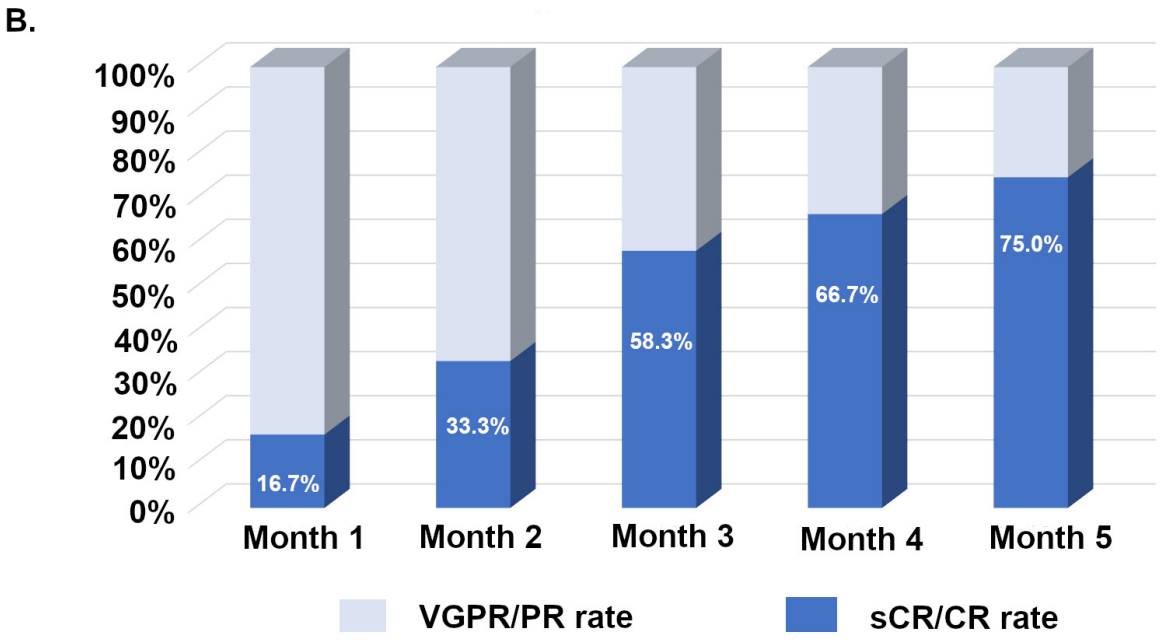


Figure 3

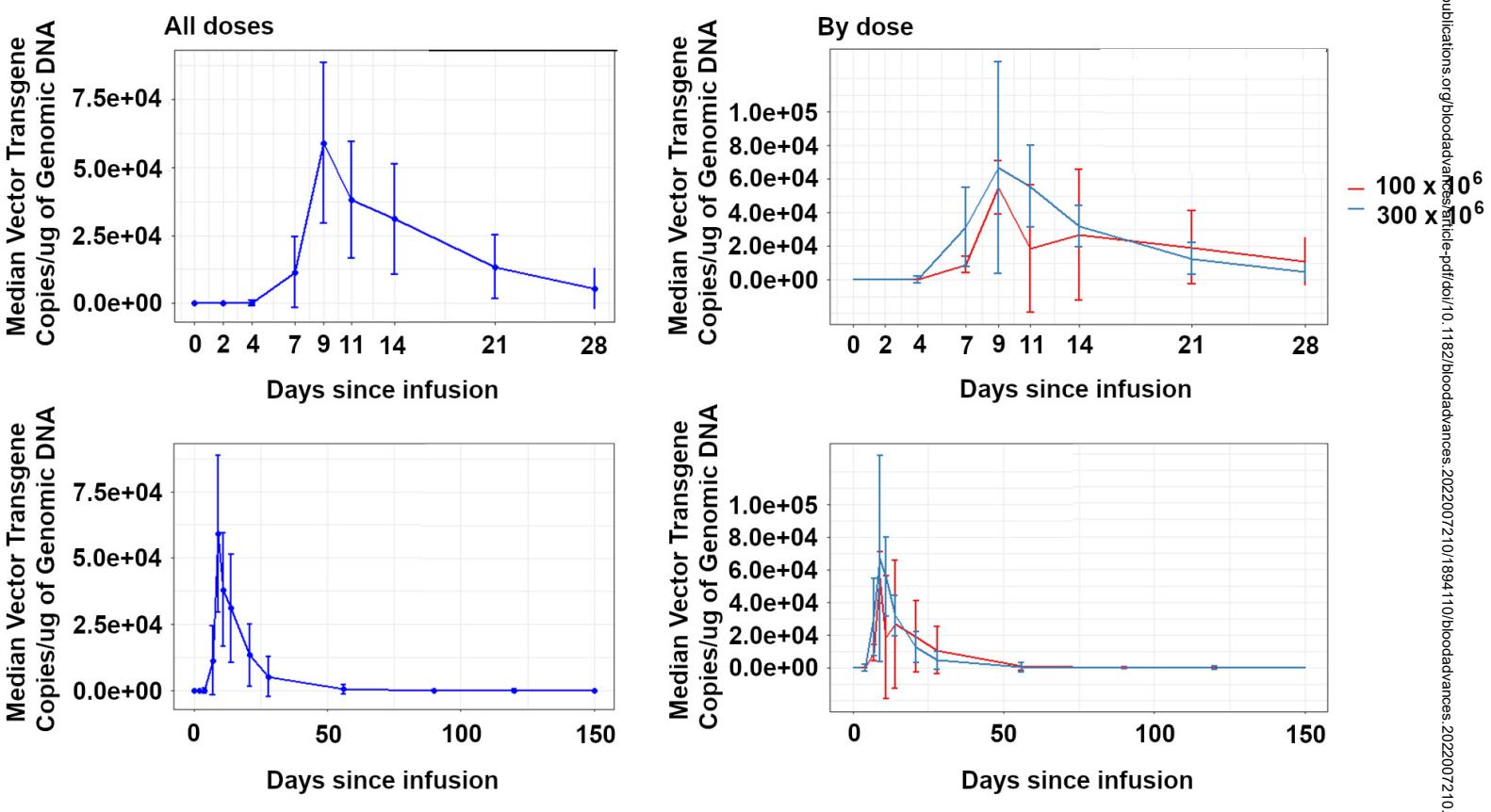


Figure 3