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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Long Term Follow-up after Treatment with Allogeneic Off-the-Shelf CAR T Cell Therapy for Relapsed or Refractory B-Cell Malignancies

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CAR T cells provide benefit in patients with relapsed/refractory (R/R) hematologic malignancies. However, limitations of autologous products include cost, production complexity, quality of T cells, and life-threatening toxicity. To overcome these limitations, we developed allogeneic, "off-the-shelf" CD19-specific CAR T cells by transducing our institutional second-generation CD28-containing CAR (19-28z) into Epstein-Barr Virus (EBV)-specific cytotoxic lymphocytes (19-28z CAR EBV-CTLs).
Patients with R/R B-cell malignancies were stratified into 3 treatment cohorts: cohort 1 (disease recurrence after allogeneic or autologous hematopoietic cell transplant (HCT)), cohort 2 (19-28z CAR EBV-CTLs as consolidative therapy after autologous HCT), or cohort 3 (19-28z CAR EBV-CTLs as consolidative therapy after allogeneic HCT). The objectives were determining dose limiting toxicity (DLT; primary endpoint) and optimal dose for multiple infusions.
Sixteen patients were treated with 19-28z CAR EBV-CTLs with 8 in cohort 1 (B-ALL n=6; Burkitt lymphoma n=1; CLL n=1), 6 in cohort 2 (PMBCL n=2; DLBCL n=3; marginal zone lymphoma n=1), and 2 in cohort 3 (DLBCL n=2). Median age at treatment was 30 years (range 1-71 years). All patients were heavily pretreated, receiving a median of 5 lines of therapy (including any HCT received; range 3-11 lines of therapy) prior to 19-28z CAR EBV-CTLs. Dosing on this protocol was based off T cells/kg: median dose infused was $3x10^6$ T cells/kg (range 1-$10x10^6$ T cells/kg). Twelve patients received multiple doses (overall median 2.5; range 1-3) with $3x10^6$ T cells/kg determined to be the optimal dose enabling multiple treatments per manufactured cell line. Products had variable transduction efficiencies with a median of 28.7% (range 7.4-41%), and median 19-28z CAR EBV-CTL dose was $0.7x10^6$/kg (range 0.05-$2.7x10^6$/kg). 19-28z CAR EBV-CTL sources were primary HCT donors (n=4) and third-party donors (n=12). HLA matching between patients and donors was 10/10 (n=3), 6/10 (n=2), 5/10 (n=1), 4/10 (n=3), and 2/10 (n=7). Ten of the patients were EBV-seropositive, four were seronegative, and two were serostatus unknown.
Severe cytokine release syndrome (CRS) or neurotoxicity did not occur post-infusion, and no DLT was noted in the trial. Six patients developed diffuse skin rash with 3 patients' rashes deemed to be graft-versus-host disease (n=1 HLA-matched HCT donor; n=2 third-party donor), which resolved with topical steroids (n = 3). Median follow-up was 53.3 months (range 4.2-135 months) with 4 deaths due to disease progression. Overall survival of all patients was 81% at 12 months and 74% at 24 months (**Figure 1**).
In summation, we successfully treated 16 patients with an allogeneic, "off-the-shelf" 19-28z CAR EBV-CTL product without significant toxicity. The manufacturing platform effectively overcomes many of the limitations of autologous CAR T cell products including cost, need for patient-specific manufacturing, and life-threatening toxicity. CAR EBV-CTLs also broaden the applicability of CAR T cell therapy for patients with insufficient circulating T cells to generate autologous products. This trial

determined an optimal manufacturing dose of allogeneic CAR T cells to enable repeated dosing. In the cohort of heavily pre-treated patients, long-term outcomes following multiple infusions of 19-28z CAR EBV-CTLs were excellent. Allogeneic, "off-the-shelf" CAR EBV-CTLs provide a readily available therapy for patients with limited therapeutic options, and this trial demonstrates the safety of CAR T cell infusions as consolidation after HCT. This trial was registered at www.clinicaltrials.gov as NCT01430390.

Figure 1: Overall survival following 19-28z CAR EBV-CTLs of all patients by disease (A) and donor source (B).

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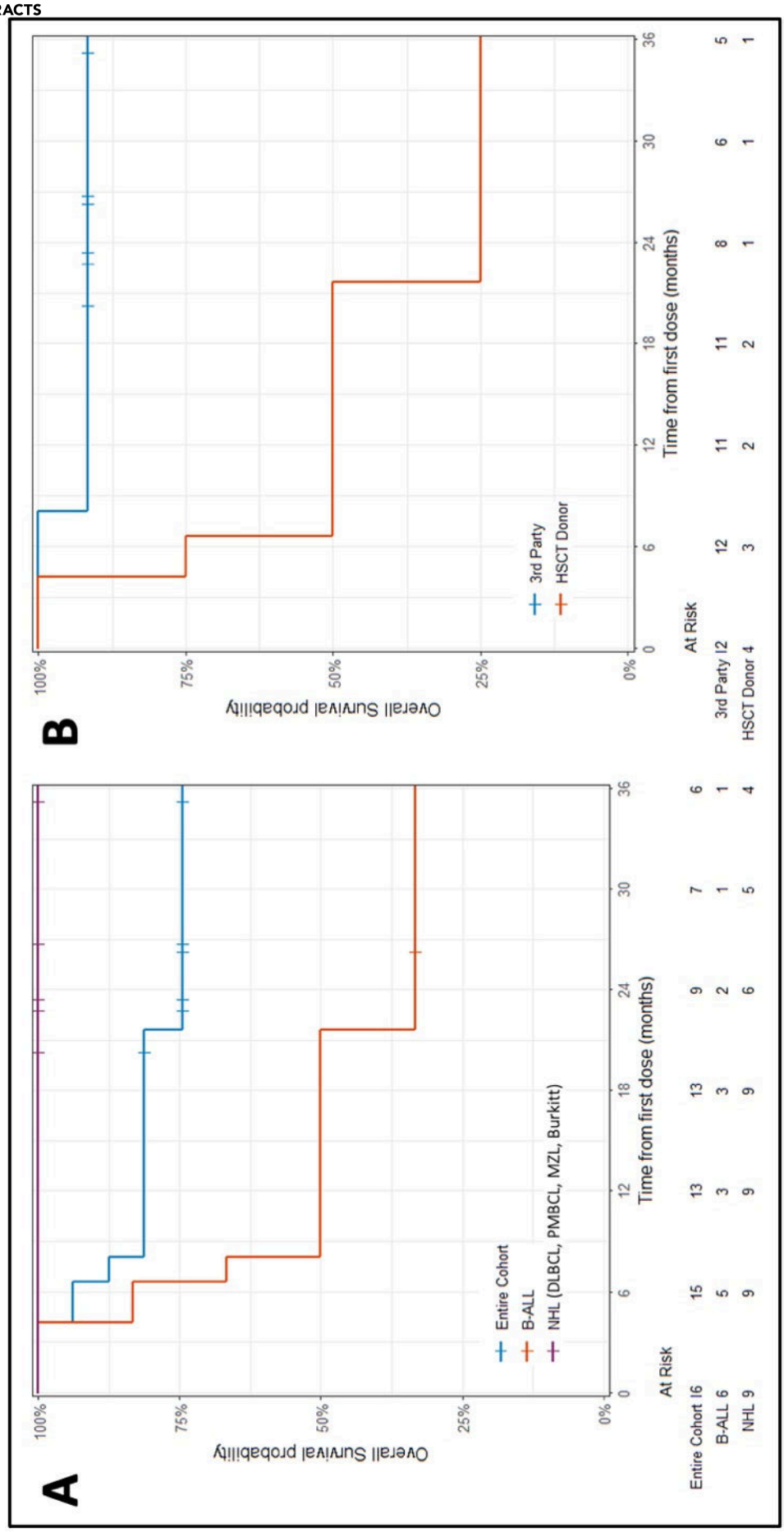

Figure 1