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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Expansion, Persistence, and Characteristics of Autologous, Bhv-1100 Armored Memory-like NK Cells Infused Prior to Autologous Stem Cell Transplant in MRD+ Multiple Myeloma Patients: A First-in-Human Trial

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Introduction/Background

Autologous stem cell transplant (ASCT) improves MRD negativity and prolongs progression-free survival in patients with multiple myeloma (MM) in their first or second remission following induction chemotherapy. MM NK cells are dysfunctional, negatively impacting outcomes. BHV-1100, a novel Antibody Recruiting Molecule (*ARM*), binds to CD38 and recruits NK cells for antibody-dependent cell cytotoxicity (ADCC) without inducing fratricide. Allogeneic, cytokine induced memory-like (CIML) NK cells effectively treat myeloid disorders, however, it is not known if autologous CIML NK cells, when coated with BHV-1100, would further improve ASCT outcomes in MM.

Methods

We designed a first-in-human study of autologous CIML NK cells coated *ex-vivo* with BHV-1100 for MRD+, MM patients undergoing ASCT following first or second remission. NK cells were isolated from non-mobilized leukapheresis on day -1 (prior to melphalan for HCT) using CD3 depletion followed by CD56 positive selection with Miltenyi's CliniMACS. The NK cells were incubated overnight (12-16 hours) with IL-12 (10ng/ml), IL-15 (100ng/ml), and IL-18 (50ng/ml) to induce CIML differentiation, washed and subsequently coated with BHV-1100 for one hour prior to infusion. The product was infused fresh on D0 after standard melphalan 200 mg/m2 myeloablative conditioning and followed by stem cell infusion. Low dose IL2 (1 mIU/m ^{2}) was administered SQ starting on D+1, QOD for a total of 7 doses.

Results

This is an ongoing trial (NCT04634435) with a median follow-up of 191 days. We are herein reporting data on the *in vivo* expansion and functional characterization of ARMored CIML NK for the first 5 patients. CIML NK cells were manufactured with a 100% success rate and infused at a target dose of 5-10x10 ^{6} cells/kg-body weight, 24 hours after 200 mg/m ^{2} melphalan administration. Patients received between 3.9-6.0x10 ^{6}/Kg stem cells. Engraftment based on recovery of neutrophil count occurred on D+12-D+14. There was a 3-fold expansion of NK cells in the peripheral blood from D+7 (from 12% to 42%) to D+28 that persisted until D+60 (25% total PBMC, Fig. 1A). Most expanded NK cells were CD56 ^{dim}, CD16 ^{high}, KIR ^{high} and CD57 ^{high}. CD57 and KIR expression increased over time from D+7 to D+60, whereas NKG2A expression decreased, indicating the expansion of mature, activated, and cytotoxic NK cells. Regulatory T cells increased by D+7 (3% vs 15% total PBMC) and returned to baseline after D+14 most likely reflecting the effect of IL-2 treatment. The functional capacity of the infused product was tested *in vitro* against MOLP8 MM cell line. The BHV-1100 ARMored CIML NK cells showed increased IFN (53% vs 48% at 0H and 53% vs 44% at 24H) and CD107a (Fig.1B) (26% vs 13% at 0H and 34% vs 15% at 24H) production compared to untreated CIML NK cells and the product was stable for 24 hours.

Conclusion

Autologous, BHV-1100 ARMored CIML NK cells have enhanced anti-MM activity as well as expand and persist *in vivo* peaking at D+28 after infusion. This represents an innovative approach to boost autologous cancer immunosurveillance in the context of ASCT. Aside from anticipated infusion reactions, no severe/unexpected adverse events were noted; longer follow-up is required to assess safety and efficacy.

Disclosures Vergara-Cadavid: *Senti Bio:* Current Employment. **Sperling:** *Novartis:* Consultancy; *Roche:* Consultancy. **Nadeem:** *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Membership on an entity's Board of Directors or advisory committees; *GPCR Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Rybicki:** *Biohaven Pharmaceuticals:* Current Employment. **Schnittman:** *Biohaven Pharmaceuticals:* Current Employment. **Stock:** *Biohaven Pharmaceuticals:* Current Employment. **Nikiforow:** *A2 Bio:* Other: Participation in ad hoc advisory board; *GlaxoSmithKline:* Other: Participation in ad hoc advisory board; *Iovance:* Other: Participation in ad hoc advisory board; *Kite/Gilead:* Other: Participation in ad hoc advisory board; *Sobi:* Other: Participation in ad hoc advisory board. **Ritz:** *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Clade Therapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Garuda Therapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Smart Immune:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *LifeVault Bio:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *TScan Therapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Equillium:* Research Funding; *Kite/Gilead:* Research Funding; *Oncternal:* Research Funding; *Avrobio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Akron Biotech:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Soiffer:** *Juno Therapeutics/ BMS/Celgene USA:* Other: Data Safety Monitoring Board; *Vor Bipharma:* Consultancy; *Neovii:* Consultancy; *Astellas:* Consultancy; *Smart Immune:* Consultancy; *Jasper:* Consultancy; *Bluesphere Bio:* Consultancy; *NMPD - Be the Match, USA:* Membership on an entity's Board of Directors or advisory committees. **Romee:** *Biohaven:* Research Funding; *Inndura:* Consultancy.

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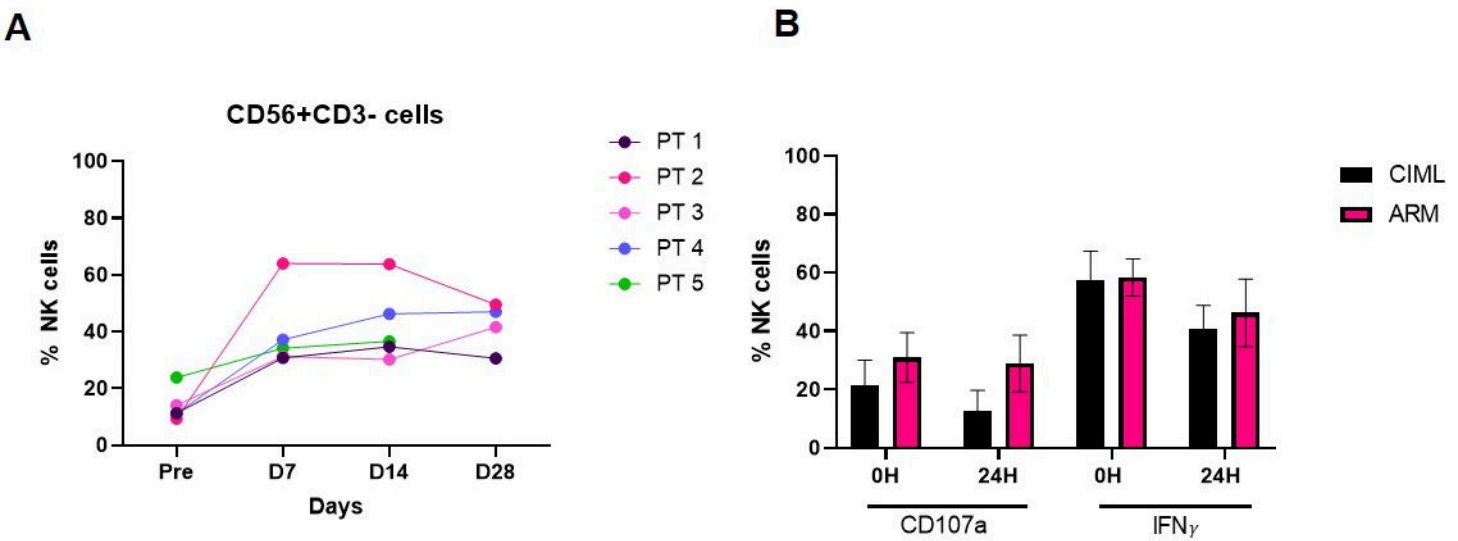

Figure 1: ARMored NK cells expand and persist for up to 60 days after infusion. A) Percentage of PBMC that are NK cells (CD56+CD3-), each line represents an individual patient. B) CD107a and IFNγ producing NK cells following 6-hour co-culture with MOLP8 target cells at the time of infusion (0H) and after 24H hold at 4 degrees. Data presented is mean + SEM (n=4).

Figure 1