# 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

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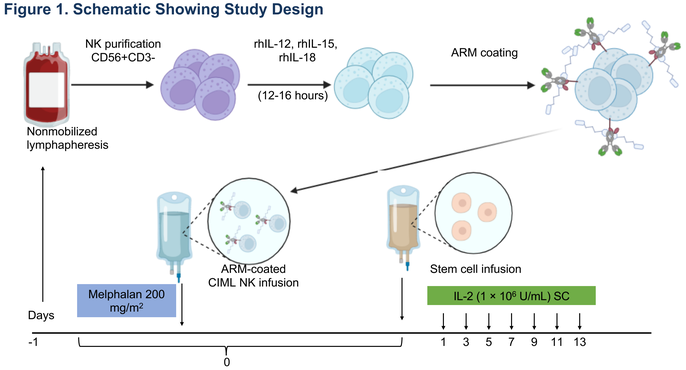
## INTRODUCTION

- Autologous stem cell transplant (ASCT) improves minimal residual disease (MRD) negativity and prolongs progression-free survival in patients with newly diagnosed multiple myeloma[1,2]
- Multiple myeloma natural killer (NK) cells are dysfunctional, negatively impacting outcomes [3,4]
- BHV-1100 is an **antibody recruiting molecule (ARM)** that binds to CD38 target cell antigen and recruits NK cells for antibody-dependent cellular cytotoxicity (ADCC) without inducing fratricide
- Cytokine-induced memory-like (CIML) NK cells effectively treat myeloid disorders[5]
- We designed a first-in-human study of autologous CIML NK cells coated *ex vivo* with BHV-1100 for MRD+ patients with newly diagnosed multiple myeloma undergoing ASCT

## METHODS

- In the ongoing phase 1 study (NCT04634435), eligible patients had newly diagnosed MRD+ multiple myeloma and were in first or second remission without prior ASCT or allogeneic stem cell transplant
- The study schematic (**Figure 1**) shows an overview of ASCT with BHV-1100

**Figure 1. Schematic Showing Study Design**




**Day -1:** Patients underwent nonmobilized lymphapheresis. Cells were manufactured in house from lymphapheresis (CD3 depletion, CD56 enrichment using Miltenyi CliniMACS®). NK cells were incubated overnight with IL-12 (10 ng/mL), IL-15 (100 ng/mL), and IL-18 (50 ng/mL) and subsequently coated with BHV-1100; **Day 0:** Patients received standard melphalan 200 mg/m$^2$ myeloablative conditioning, followed by CIML NK cell and then stem cell infusion. Low dose IL-2 (1 × 10$^6$ U/m$^2$) was administered SC (total of 7 doses).
IL, interleukin; rhIL, recombinant human interleukin; SC, subcutaneously.

## PATIENTS AND TREATMENT

- Data from first 5 enrolled patients are presented; median follow-up was 191 days
- CIML NK cells were manufactured with a 100% success rate and infused at target dose of 5-10 × 10$^6$ cells/kg body weight 24 hours after melphalan 200 mg/m$^2$
- Patients received 3.9-6.0 × 10$^6$/kg body weight stem cells
- Engraftment based on recovery of neutrophil count occurred on days 12-14
- Aside from anticipated infusion reactions, no severe or unexpected adverse events were noted
- Longer follow-up is required to assess safety and efficacy

## IN VIVO RESULTS

### NK Expansion and Persistence

- There was a 3.5-fold expansion of NK cells in the peripheral blood from day 7 (from 11.1% to 41%) to day 28 that persisted until day 60 (25% total peripheral blood mononuclear cells [PBMC]) (**Figure 2**)
- Most expanded NK cells were CD56$^{dim}$, CD16+, killer cell immunoglobulin-like receptor KIR+, and CD57+ (**Figure 3**)
- CD57 and KIR expression increased over time from day 7 to day 60 (**Figure 3C, D**), whereas NKG2A expression decreased (**Figure 3E**), indicating the expansion of mature, activated, and cytotoxic NK cells
- Regulatory T cells increased by day 7 (3% vs 15% total PBMC) and returned to baseline after day 14, most likely reflecting the effect of IL-2 treatment

**Figure 2. ARMored NK Cells Expand After Infusion**

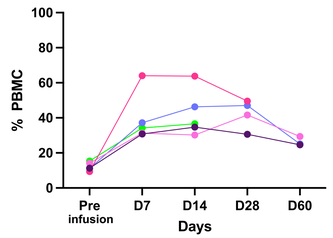



**Figure 3. ARMored Cells Exhibit an Activated, Mature Cell Surface Signature**




## KEY POINTS

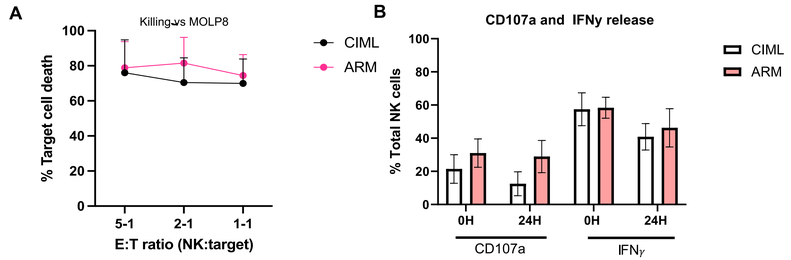
- ❑ BHV-1100 is an antibody-recruiting molecule (ARM) that binds to CD38 target cell antigen and recruits NK cells for ADCC
- ❑ Autologous, BHV-1100 ARMored CIML NK cells have enhanced anti–multiple myeloma activity in vitro and expand and persist in vivo, peaking at 28 days after infusion
- ❑ In a first-in-human study in patients with multiple myeloma undergoing ASCT, no severe or unexpected adverse events were noted with BHV-1100 ARMored CIML NK cells; longer follow-up is required
- ❑ BHV-1100 ARMored CIML NK cells represent an innovative approach to boost autologous cancer immunosurveillance in the context of ASCT for multiple myeloma

## CORRELATIVE IN VITRO RESULTS

### Functional capacity of ARMed CIML NK cells

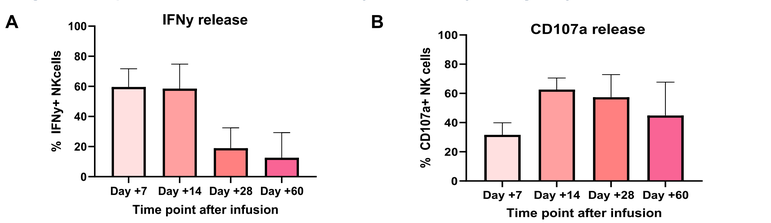
- BHV-1100 ARMored CIML NK cells were stable for up to 24 hours at 4°C
- The BHV-1100 ARMored CIML NK cells had a higher killing capacity towards MOLP8 multiple myeloma cell lines compared with untreated CIML NK cells at baseline (**Figure 4A**)
  - 90.8% vs 81% target cell death at both 4 hours and 24 hours (2:1 ratio)
- ARMored CIML NK cells showed increased CD107a expression (26% vs 14.9%) and IFNγ production (53% vs 37.5%) compared with untreated CIML NK cells at 24 hours (**Figure 4B**)

**Figure 4. ARMored NK Cells Have Enhanced Activity Against Multiple Myeloma cell lines**




- The functional capacity of peripheral blood NK cells was tested at correlative time points after infusion: (**Figure 5**)
  - IFNγ release was very high at day +7 and day +14 but drops after this, coinciding with the last dose of IL-2 (**Figure 5A**)
  - CD107a release after co-culture with K562 cells was very high at all time points indicating functional capacity of PB NK cells (**Figure 5B**)

**Figure 5. Peripheral Blood NK Cells Maintain Cytotoxic Ability Through Day + 60 After Infusion**

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