Expansion, Persistence, and Characteristics of Autologous, BHV-1100 ARMored Memory-Like NK Cells Infused Prior to Autologous Stem Cell Transplant MRD+, Newly Diagnosed Multiple Myeloma Patients

Introduction

- Autologous stem cell transplant (ASCT) improves minimal residual disease (MRD) negativity and prolongs progression-free survival in patients with newly diagnosed multiple myeloma.
- Monoclonal natural killer (NK) cells are dysfunctional, negatively impacting outcomes in patients with multiple myeloma.
- BHV-1100 is an ARM that binds to CD38 target cell antigen and recruits NK cells for antibody-dependent cellular cytotoxicity (ADCC) without inducing NK cell fratricide.

**Methods Overview**

- In the ongoing phase 1 study (NCT04694435), 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.
- The percentage of NK cells (CD56+CD3+) and CD57+, KIR+, and NKG2A+ NK subsets in patients' peripheral blood was assessed using flow cytometry.
- Target cell death, CD107a expression, and interferon gamma (IFNγ) production were assessed following a 6-hour culture with MelD17 target cells and the infused product vs untreated CIML (1:1, 2:1, and 5:1 effector:target ratios), both at the time of infusion and after 24 hours at 4°C.

**RESULTS**

- **Patients and Treatment**
  - The in vivo expansion and functional characterization of ARMored CIML NK cells for the first 5 enrolled patients are presented; median follow-up was 191 days.
  - CIML NK cells were manufactured in house from lymphapheresis of patients undergoing ASCT for multiple myeloma.

**IN VIVO RESULTS**

- There was a 3.5-fold expansion of NK cells in the peripheral blood from day 7 (11.1% to 41.1%) to day 28 that persisted until day 60 (25% total peripheral blood mononuclear cells [PBMCs]) (Figure 2).
- Monoclonal expanded NK cells were CD56bright, CD16+, KIR+, and CD57+ (Figure 3).
- CD57 and killer cell immunoglobulin-like receptor (KIR) expression increased over time from day 7 to day 60, whereas NKG2A expression decreased, indicating the expansion of mature, activated, and cytotoxic NK cells (Figure 3).
- 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.

**IN VITRO RESULTS**

- The functional capacity of the infused product was tested in vitro against the K562 multiple myeloma cell line.
- Samples of non-infused BHV-1100 ARMored cells were stable for up to 24 hours at 4°C.
- The BHV-1100 ARMored cells had a higher killing capacity compared with untreated CIML NK cells.
- ARMCIML NK cells also showed increased CD107a expression (26% vs 14.9%) and IFNγ production (33% vs 53%) compared with CIML NK cells at 24 hours (Figure 4).

**CONCLUSIONS**

- BHV-1100 is an antibody-recruiting molecule (ARM) that binds to CD38 target cell antigen and recruits NK cells for ADCC.
- Autologous, BHV-1100 ARMed CIML NK cells have enhanced anti-multiple myeloma activity in vitro and expanded and persist in vivo, peaking at 28 days after infusion.
- A first-in-human study in patients with multiple myeloma undergoing ASCT; no severe or unexpected adverse events were observed with BHV-1100 ARMed CIML NK cells; longer follow-up is required.

**DISCLOSURES**

- The study was supported by Biohaven Pharmaceuticals, and the study was conducted in accordance with the Declaration of Helsinki.

**REFERENCES**

3. Davis of Apollo Medical Communications, part of Helios Global Group, and funded by Biohaven Pharmaceuticals.

**Figure 1. Study Schematic**

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

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

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

% NK cells (%): the proportion of total lymphocytes that are CD56+CD3+ NK cells.

<table>
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<th>NK cells (%)</th>
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<th>Pre-infusion</th>
<th>Day 24</th>
<th>Day 120</th>
<th>0h 24H 0H 24H</th>
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