PA-058
BP2202: An Off-the-Shelf iPSC-Derived BCMA-Targeted Cellular Therapy for Multiple Myeloma

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INTRODUCTION

BCMA-targeted CAR-T cells and T-cell engagers have shown meaningful activity in relapsed/refractory multiple myeloma (RRMM), but relapse remains common. Autologous CAR-T therapy is limited by manufacturing complexity, long vein-to-vein time, and product variability, while conventional allogeneic CAR-T approaches have shown limited persistence. Thus, off-the-shelf allogeneic therapies with durable efficacy are needed.

Invariant natural killer T (iNKT) cells are a rare T-cell subset with potent direct and indirect anti-tumor activity through activation of CD8+ T cells and other immune populations. iPSC technology enables scalable generation of this otherwise rare cell population while preserving its functional properties.

BP2202 is an off-the-shelf, iPSC-derived BCMA CAR-iNKT cell therapy that leverages both CAR-mediated cytotoxicity and the intrinsic anti-tumor functions of iNKT cells, while enabling scalable, master cell bank-based manufacturing.

AIM

1. *In vitro* characterization
Anti-tumor activity and functional properties against BCMA-expressing myeloma cells

2. *In vivo* efficacy
Anti-tumor activity

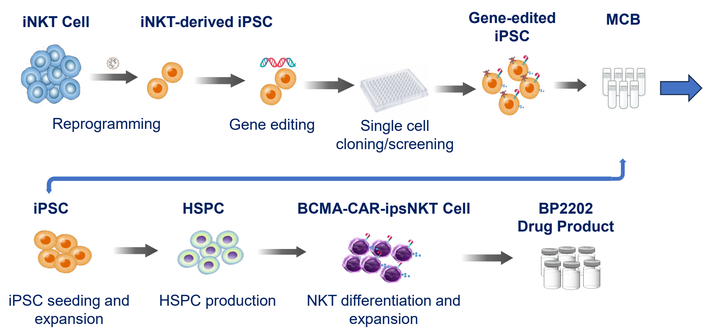
3. Clinical translation
Design of a Phase 1 study evaluating the safety and preliminary efficacy of BP2202 in RRMM

METHOD

- BP2202 was evaluated for phenotype, CAR expression, antigen-specific cytotoxicity, and cytokine production.
- Cytotoxicity was assessed by luciferase-based killing assay (RPMI8226, BCMA-positive; SK-OV-3, BCMA-negative) and by xCELLigence assay (U-2OS, CD1d-positive, ± α-GalCer). Anti-tumor activity was evaluated in MM.1S xenograft mouse models by bioluminescence imaging.
- Genomic safety of the gene-edited iPSC was assessed by karyotyping, optical genome mapping, whole genome sequencing, and off-target analysis.
- The phase 1 study is an open-label, multicenter, dose-escalation trial in RRMM patients after ≥ 3 prior lines of therapy.

RESULTS

1. Overview of BP2202 manufacturing

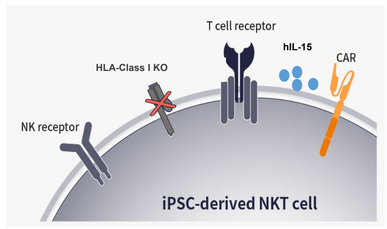


Genomic safety assessment

- **Karyotyping (G-banding)** ⇒ Normal
- **Optical genome mapping** ⇒ No unintended structural abnormalities
- **Whole genome sequencing** ⇒ No unintended genomic alterations
- **Off-target analysis** ⇒ No off-target events

Figure 1. iNKT cells were reprogrammed into iPSCs, followed by insertion of the BCMA-CAR and IL-15 genes into the iPSC genome using gene-editing technology. After single-cell cloning and screening, a CAR-iPSC clone was established and used to generate the master cell bank (MCB). The MCB underwent extensive quality control, including genomic safety assessment. Manufacturing of BP2202 begins with iPSC expansion, followed by primary differentiation into Hematopoietic Stem and Progenitor Cells (HSPCs) and subsequent differentiation into BP2202.

2. Key features of BP2202



- **BCMA-CAR Knock-in** ⇒ Enables targeted killing of BCMA⁺ tumor cells
- **Soluble hIL-15 expression** ⇒ Enhances iNKT cell survival and persistence
- **HLA-class I Knock-out** ⇒ Reduces immunogenicity and promotes persistence
- **Invariant TCR expression** ⇒ Enables CD1d-restricted cytotoxicity, Promotes DC maturation, Facilitates M1φ polarization
- **NK receptor expression** ⇒ Boost innate cytotoxicity

3. Phenotype and CAR expression

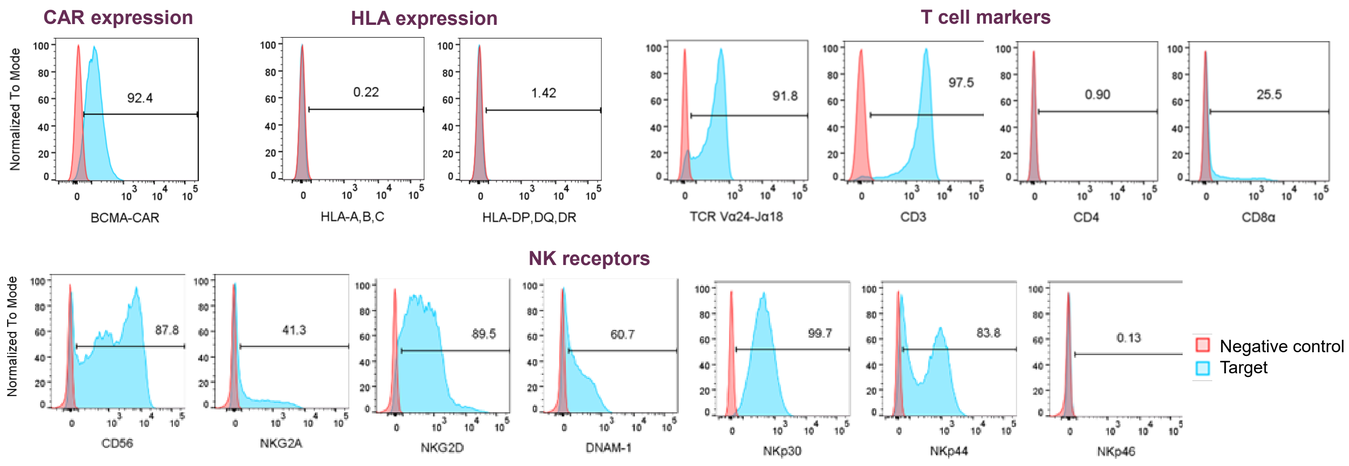
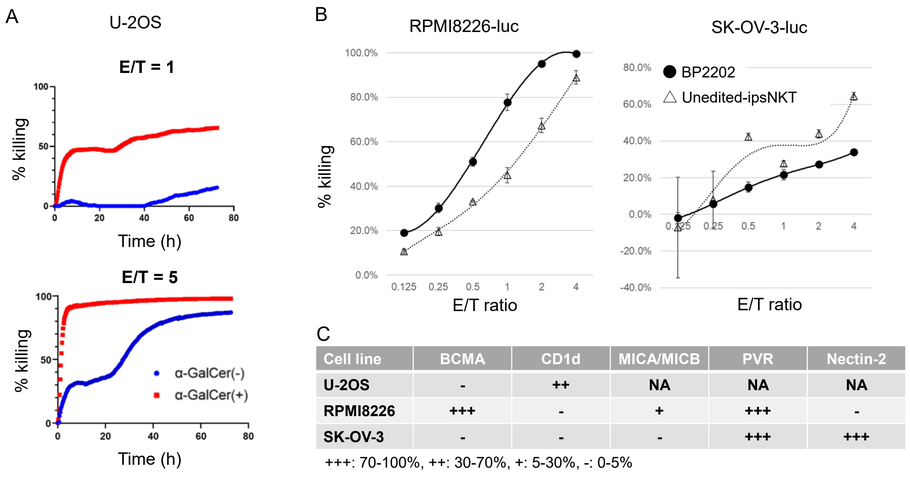


Figure 2. Surface marker expression of BP2202 by Flow cytometry. Histograms show the expression of CAR and HLA molecules (HLA-ABC and HLA-DP/DR/DQ) in the live cell population. The expression of the iNKT TCR (Vα24-Jα18), CD3, CD4, and CD8α, as well as the NK-associated markers CD56, NKG2A, NKG2D, DNAM-1, NKp30, NKp44, and NKp46, was analyzed.

4. Killing activity and cytokine production



C

Cell line	BCMA	CD1d	MICA/MICB	PVR	Nectin-2
U-2OS	-	++	NA	NA	NA
RPMI8226	+++	-	+	+++	-
SK-OV-3	-	-	-	+++	+++

+++: 70-100%, ++: 30-70%, +: 5-30%, -: 0-5%

Figure 3. (A) BP2202, with or without 100 ng/mL α-GalCer, was co-cultured with 1×10^4 U-2OS cells/well at various E/T ratios for 72h, and cytotoxic activity was evaluated using the real-time cell analyzer xCELLigence. (B) BP2202 was co-cultured with 3×10^4 target cells/well at various E/T ratios for 24h, and cytotoxic activity was evaluated using a luciferase assay. Cytotoxicity was calculated as follows: % cytotoxicity = [1 − (RFU of co-cultured cells/RFU of target cells alone)] × 100. Data are presented as mean ± SEM (n = 3). (C) Expression pattern of BCMA, CD1d and NK receptors ligands using flowcytometry analysis. NA: Not Assessed (D) BP2202 was co-cultured with 1×10^5 target cells/well at an E/T ratio of 1 for 24 h, and IFN-γ and TNF-α levels in the culture supernatant were measured using a Cytometric Bead Array. Data are presented as mean ± SEM (n = 3).

5. *In vivo* anti-tumor effect

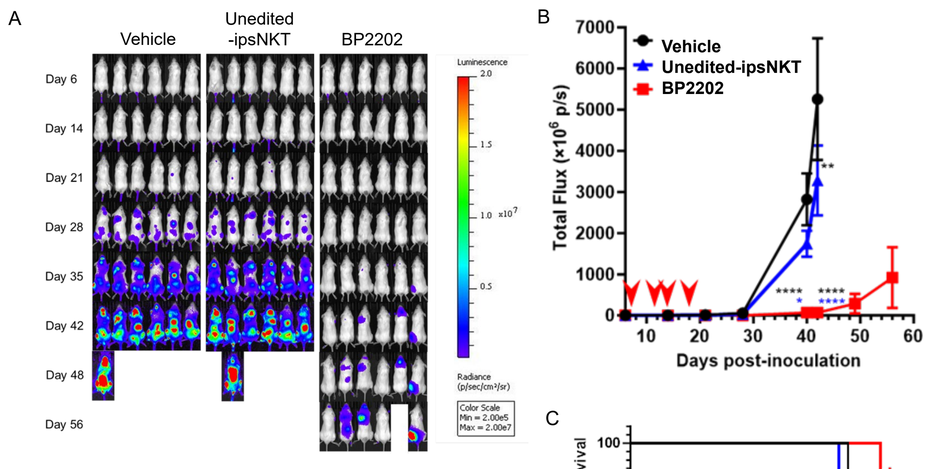


Figure 4. Vehicle (HBSS), 1×10^7 cells/body Unedited-ipsNKT or 1×10^7 cells/body BP2202 were administered intravenously to MM.1S-luc bearing NOG-hIL15Tg mice on Day 7, 11, 14 and 18. (A) Bioluminescence images of MM.1S-luc bearing NOG-hIL15Tg mice. (B) Changes in total flux values derived from bioluminescence images. Data are presented as mean ± SD. Two-way ANOVA followed by Tukey's multiple comparison was used to assess significance. Significance level indicated by *: P<0.05 or ****: P<0.0001 (black: v.s. vehicle group or blue: v.s. unedited ipsNKT group). (C) Survival rate. Survival rate (n = 6 per group) for MM.1S-luc inoculated mice shown as Kaplan–Meier survival curves. Survival estimates were assessed by log-rank tests. Significance level indicated by ***: P<0.001.

6. Study design for Phase 1 clinical trial (BP2202-001)

Primary Endpoint
•Incidence, severity, and relationship to BP2202 of AEs and DLTs

Secondary Endpoints
•RP2D determination (Part A)
•Preliminary anti-tumor activity: ORR, DoR, DCR

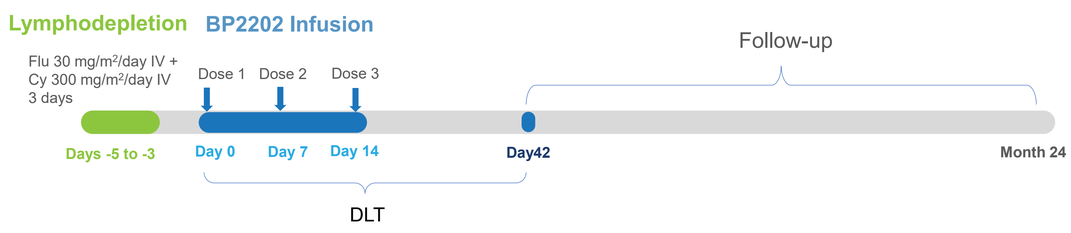
Part A Dose Escalation: 3 + 3 dose escalation

Dose Level (DL)	Total Fixed Dose of BP2202 cells	N
3	6×10^8 cells/body (× 3 doses)	3-6
2	4×10^8 cells/body (× 3 doses)	3-6
1 (Starting Dose)	2×10^8 cells/body (× 3 doses)	3-6
-1	1×10^8 cells/body (× 3 doses)	3-6

Part B Dose Expansion: RP2D

RP2D is administrated to all participants in Part B

N=Up to 12 including participants treated at RP2D in Part A



Key inclusion criteria

- Age ≥18 years
- ECOG Performance Status of 0 or 1
- Diagnosis of Multiple myeloma (MM) with ≥3 prior lines of therapy, including:
  - Proteasome inhibitor (PI)
  - Immunomodulatory drug (IMiD)
  - Anti-CD38 antibody
- Adequate organ function
- Measurable disease

Key exclusion criteria

- HIV, active HBV, or HCV infection
- Other active or recently treated malignancy (except specified low-risk cancers)
- History of Grade 2–4 GvHD
- Pregnancy or lactation Active CNS involvement of multiple myeloma
- Clinically significant hepatic, renal, cardiac, or bone marrow dysfunction
- Significant coagulopathy
- Active infection prior to lymphodepletion
- Significant comorbidities that may increase study risk or interfere with study participation

CONCLUSIONS

- **BP2202 retains key iNKT characteristics, including NK receptors and invariant TCR expression, supporting multi-MOA activity.**
- **BP2202 mediates anti-tumor activity through CAR-, NK receptor-, and CD1d/TCR pathways.**
- **No unintended structural or genomic abnormalities or off-target events were detected.**
- **BP2202 demonstrated potent anti-tumor activity in vitro and significant tumor growth inhibition in vivo.**
- **These findings support the clinical development of BP2202 as a promising off-the-shelf therapy for R/R MM.**

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