A Phase I Study of PNK-007, an Allogeneic, Off the Shelf NK cell in relapsed/refractory Acute Myeloid Leukemia (NCT02781467)

#CT079

Sarah Cooley[1], Parameswaran Hari[2], James McCloskey[3], Michael Byrne[4], Eunice Wang[5], Mohamad Hussein[6], Erica Giarritta[7], Xiaokui Zhang[7], Robert Hariri[7], Jeffrey S. Miller[1]

[1]University of Minnesota, Minneapolis, MN, [2]Medical College Wisconsin, Milwaukee, WI, [3]Hackensack University Medical Center, Hackensack, NJ, [4]Vanderbilt Ingram Cancer Center, Nashville, TN, [5]Roswell Park Comprehensive Cancer Center, Buffalo, NY, [6]Celgene Corporation, Summit, NJ, [7]Celularity, Inc., Warren, NJ,

INTRODUCTION

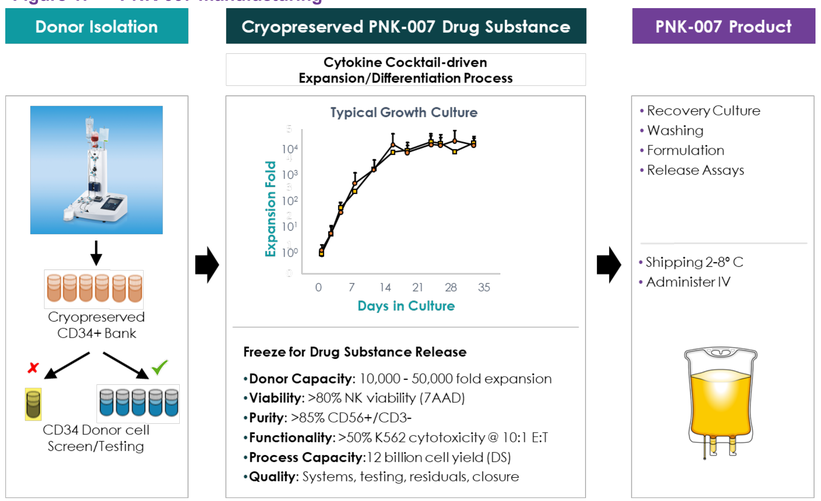
Background

- Natural Killer (NK) cells are innate immune cells which play an important role in host immune surveillance against pathogenic infection and cell transformation. Multiple studies adoptively transferring NK cells in clinical settings have demonstrated the potential of NK cells to induce remissions for hematological indications with a consistent safety profile.[1,2,3]
- Celularity has developed a GMP procedure for generating Placental Hematopoietic Stem Cell Derived Natural Killer cells (PNK-007). This technology platform enables the scalable production of an off the shelf, allogeneic NK cell therapy.
- PNK-007 shows cytotoxic activity against various cancer cell lines and secrete cytokines such as interferon gamma (IFN-g) during co-culture with cancer cells.
- PNK-007 has been evaluated for the treatment of multiple myeloma patients post-autologous transplant in a Phase I study (PNK-007-MM-001). The completed study is presented in Poster #CT108.
- Immune monitoring of AML patients treated with PNK-007 under this study was performed. Results are presented in Poster #LB-070.
- Here, we present results of the Phase I first-in-man study in relapsed/refractory (r/r) acute myeloid leukemia (AML) patients (PNK-007-AML-001).

PNK-007 manufacturing process overview

- Placental CD34+ cells were cultivated in the presence of cytokines including thrombopoietin (Tpo), stem cell factor (SCF), Flt3 ligand, IL-7, IL-15 and IL-2 for 35 days to generate PNK-007 under the cGMP standards followed by release testing.
- PNK-007 was >95% pure for CD56+/CD3- cells that exhibited in vitro cytotoxicity against K562 cells.

Figure 1: PNK-007 manufacturing



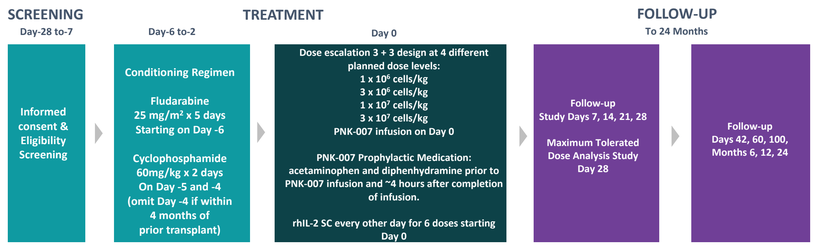
CD34 donor cells are screened and tested for use in PNK-007 manufacturing. Cells are harvested following a 35 day expansion and differentiation process, then frozen as Drug Substance. Qualified Drug Substance undergoes a final formulation and release process and is distributed as a fresh formulated product.

Objectives

- **Primary**: To assess the safety and determine the maximum tolerated dose (MTD) of PNK-007.
- **Secondary**: To explore potential clinical efficacy by CRp or CR at 42 days and OS at 24 months.
- **Exploratory**: To measure in vivo expansion of PNK-007, evaluate safety by Treatment-Related Mortality (TRM), and correlate CR/CRp incidence with in vivo expansion.

Methods

Figure 2: Overview of PNK-007-AML-001 clinical protocol



***Recombinant human IL-2 (rhIL-2) to facilitate NK cell survival and expansion**[4]: rhIL-2 at 6 million units subcutaneously beginning Day 0, every other day for 6 total doses.*

***Pre- and Post-medication**: Acetaminophen 650 mg PO and diphenhydramine 25 mg PO prior to PNK-007 infusion and 4 hours after PNK-007 and rhIL-2.*

Study Design

- This is a Phase I, multicenter, open label, study evaluating the dose of PNK-007 infusion using 3+3 design.
- No HLA matching or KIR mismatching was used.

Key Inclusion Criteria

- Relapsed/refractory patients, including:
  - Primary AML induction failure, relapsed AML who failed standard re-induction therapy, or Secondary (MDS or Treatment-related) AML who have undergone 1 prior AML therapy
- Age 18 to 70 years
- KPS ≥ 50%
- Ability to be off immunosuppressive drugs for at least 3 days prior to PNK-007 infusion.

Key Exclusion Criteria

Patients were excluded if they had any of the following:

- biphenotypic acute leukemia
- graft vs host disease (GvHD)
- aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 x the upper limit of normal (ULN) within 3 days prior to PNK-007.
- new or progressive pulmonary infiltrates or pleural effusion within 2 weeks of PNK-007 infusion.
- untreated chronic infection or new infection requiring systemic antibiotics 2 weeks prior to treatment.
- body weight exceeding 120 kg.

Results

Demographics

- Enrolled 10 patients, age range 30-70 years (median 66 years), KPS ≥ 70%
- 50% male, 50% female
- 90% White, Non-Hispanic/Latino, 10% not reported
- WHO Classifications:
  - Recurrent genetic abnormalities (n=4)
  - MDS-related changes (n=4)
  - Not otherwise specified (n=2)
- Median 3 prior lines of therapy (min 1; max 5)
- 5 patients with history of MDS
- 5 patients with prior allogeneic SCT

Results

Safety Results

- Ten patients received a single PNK-007 infusion: 3 patients at 1 x 10^6 cells/kg, 3 patients at 3 x 10^6 cells/kg, and 4 patients at 10 x 10^6 cells/kg.
- Patients received 5 to 6 total rhIL-2 injections SC.
- One patient experienced Grade 4 Cytokine Release Syndrome (CRS) 14 days after PNK-007 infusion which was effectively managed with tocilizumab. This CRS event was considered a dose-limiting toxicity.
- The other 9 patients did not experience CRS symptoms and PNK-007 was well tolerated with no infusion reactions or GvHD.
- No deaths were attributed to PNK-007. All 10 patients died during the follow-up period of the study; 80% due to progressive AML and 20% due to AML-related complications.
- The MTD of PNK-007 was not identified during the course of this study. Of note, this study was terminated early due to a business decision and not due to safety concerns.

Efficacy Results

- 8 of 10 patients were efficacy evaluable; the other 2 patients were not due to inadequate BM for evaluation.
- 2 of 8 efficacy evaluable patients had evidence of clinical benefit.
  - The first patient achieved a complete response with incomplete platelet recovery (CRp) on Day 21. Of note, this is the same patient who experienced CRS.
  - The second patient, treated at 10M cells/kg, was observed to achieve MLFS on Day 14.
  - Day 42 bone marrow biopsy could not be performed in either patient.
- Median OS was 2.4 months (95% CI: 1.3, 4.3).

Exploratory Results

- Flow cytometric analysis of patient peripheral blood showed in vivo persistence, proliferation as measured by Ki67 expression, and maturation of PNK-007 at dose levels 3 x 10^6 cells/kg and 10 x 10^6 cells/kg between 7 and 28 days after PNK-007 infusion.
- Ex vivo functional analysis of PNK-007 from 1 patient showed NK cell effector activity.
- See Poster #LB-070 for more in-depth Immune Monitoring results

CONCLUSIONS

PNK-007 is a fully allogeneic, off the shelf CD34+ derived NK cell product.

A single infusion of PNK-007 up to 10 x 10^6 cells/kg with rhIL-2 following Cy-Flu conditioning was safe and well tolerated, with one manageable CRS event observed.

Two of 10 patients treated achieved clinical response, assessed by the investigators using the International Working Group AML Response Criteria as CRp and MLFS.

Observed clinical data warrant further evaluation of PNK treatment in AML.

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