Safety and Tolerability of Allogeneic, Off-the Shelf Placental Natural Killer Cells (PNK-007) in Phase 1 Multiple Myeloma (NCT02955550) and Acute Myeloid Leukemia (NCT02781467)

Sharmila Koppisetti[1], Catherine Balint[1], Erica Giarritta[1], Nassir Habboubi[1], Robert Hariri[1]
[1]Celularity, Inc., Warren, NJ

EHA-3239

INTRODUCTION

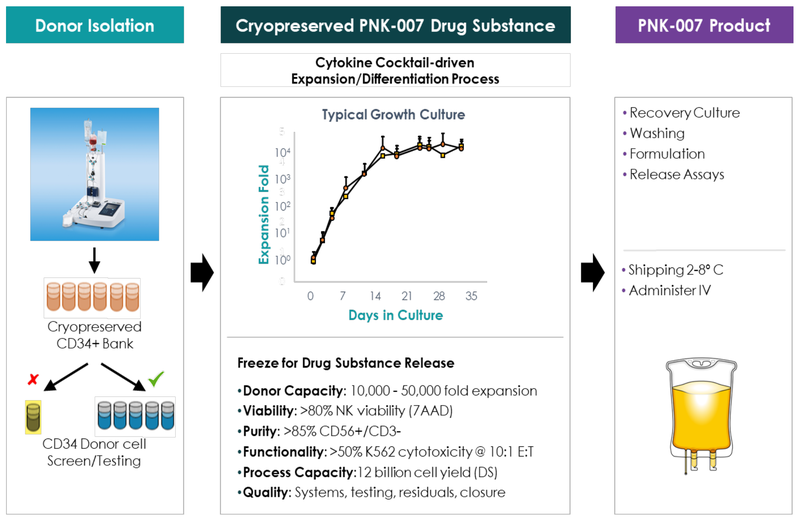
Background

- 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 is a fully allogeneic, off-the shelf CD34+ derived NK cell product which is not genetically modified. It shows cytotoxic activity against various cancer cell lines and secrete cytokines such as interferon gamma (IFN-g) during co-culture with cancer cells.
- Here, we present results of the safety and tolerability of PNK-007 during the 28 day Dose Limited toxicity (DLT) period in both the Phase I first-in-man study in relapsed/refractory (r/r) acute myeloid leukemia (AML) patients (PNK-007-AML-001) which is completed, and the Phase I study in multiple myeloma (MM) patients after autologous stem cell transplant (ASCT) (PNK-007-MM-001) which is active and not recruiting.

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



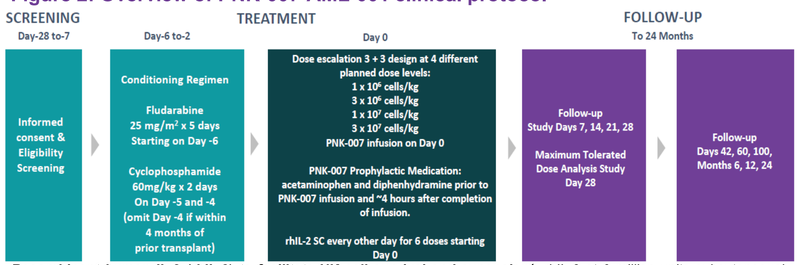
CD34 donor cells are screened and tested for use in PNK-007 manufacturing. Cells are harvested following a 35 day expansion and differentiation process, then frozen as Drug Substance. Qualified Drug Substance undergoes a final formulation and release process and is distributed as a fresh formulated product.

ACUTE MYELOID LEUKEMIA (AML) STUDY -OBJECTIVES

- **Primary**: To assess the safety and determine the maximum tolerated dose (MTD) of PNK-007.
- **Secondary**: To explore potential clinical efficacy by complete remission (CR) or CR with incomplete platelet recovery (CRp) at 42 days and overall survival at 24 months.

AML STUDY SCHEMA

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



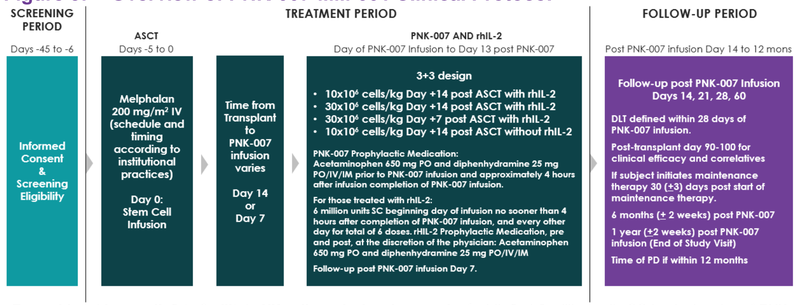
Recombinant human IL-2 (rhIL-2) to facilitate NK cell survival and expansion[4]*: rhIL-2 at 6 million units subcutaneously beginning Day 0, every other day for 6 total doses.*
***Pre- and Post-medication**: Acetaminophen 650 mg PO and diphenhydramine 25 mg PO prior to PNK-007 infusion and 4 hours after PNK-007 and rhIL-2.*

MULTIPLE MYELOMA (MM) STUDY -OBJECTIVES

- **Primary**: To assess the safety and determine the feasibility of infusing PNK-007 at various doses and timepoints following ASCT in subjects (subjs) with MM.
- **Secondary**: To explore potential clinical efficacy at Day 90-100 post ASCT. Determine if rhIL-2 is needed for PNK-007 therapy. Determine dosing required to achieve minimal residual disease negativity.

MM STUDY SCHEMA

Figure 3: Overview of PNK-007-MM-001 Clinical Protocol



Recombinant human IL-2 to facilitate NK cell survival and expansion[4]***:** rhIL-2 at 6 million units SC beginning day of PNK-007 infusion, every other day for 6 total doses.*

Table 1: Overview of PNK-007-AML and PNK-007 MM-001 Study Design

	AML	MM
Study Design	Phase 1, multicenter, open label study evaluating the dose of PNK-007 infusion using 3+3 design. HLA mismatching/KIR mismatching was not used.	Phase 1, multicenter, open label study evaluating the dose and timing of infusion of PNK-007 post ASCT in MM using 3+3 design
Key Inclusion Criteria	▪ Relapsed/refractory pts 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. ▪ Aged 18 to 70 years	▪ Newly diagnosed MM undergoing induction therapy prior to undergoing first ASCT. (Prior to amendment pts who had prior anti-MM therapy and had relapsed were eligible to participate). ▪ Aged 18-70 years
Key Exclusion Criteria	▪ Pt has biphenotypic acute leukemia ▪ Body weight exceeding 120 kg ▪ Pt has graft vs host disease	▪ Plasma cell leukemia or non secretory MM ▪ Body weight exceeding 120 kg ▪ Previously undergone allogeneic stem cell transplant

RESULTS

Table 2: Demographics

	AML	MM
Median Age, years (range)	66 (30-70 years)	58 (44-69 years)
Gender Male/Female	5/5	7/8
Race White; Black/African American; Other	9/0/1	13/1/1
Diagnosis & Disease History	▪ Five (5) patients with prior allogeneic stem cell therapy ▪ Five (5) patients with history of Myelodysplastic syndrome (MDS) ▪ Median of 3 prior lines of therapy with min of 1 and max of 5	▪ Twelve (12) Newly Diagnosed myeloma undergoing 1st ASCT ▪ One (1) Myeloma with prior relapse undergoing 1st ASCT ▪ Two (2) Myeloma with relapsed disease after 1st ASCT who are undergoing second ASCT

AML: A total of 5 subjs reported serious adverse events (SAEs) with one Cytokine Release Syndrome (CRS) event attributed to PNK-007. This DLT of CRS occurred on day 14 after PNK-007 infusion that was managed with tocilizumab. No GvHD, infusion-related toxicity, or neurotoxicity reported. Metabolic disorders was the common system organ class (SOC) with hypokalemia observed in 7 subjs. The common Infections noted were sinusitis, klebsiella, cytomegalovirus, pneumonia, sepsis, bacteremia, and clostridium difficile; all unrelated to PNK-007. Within Cardiac disorders SOC, a grade 5 unrelated cardiac arrest event was reported. Within Gastrointestinal SOC, 4 subjs experienced nausea; one PNK-007 related.
MM: No dose-limited toxicities were reported in this study. Gastrointestinal disorders was the common SOC with one event of vomiting and diarrhea related to PNK-007 was reported. Four subjs reported maculo-popular rash; unrelated to PNK-007. Common Infections noted were oral candidiasis, soft tissue infection, staphylococcus abscess, streptococcal pneumonia; all unrelated to PNK-007. Four subjs noted SAEs; unrelated to PNK-007.

Table 3: Number of subjs with at least one event of interest within 28 days of DLT period (by PNK-007 relatedness)

ALL GRADES	AML (N=10)		MM (N=15)	
EVENTS	**RELATED**	**UNRELATED**	**RELATED**	**UNRELATED**
CRS	1	0	0	0
GvHD	0	0	0	0
Infusion related toxicity	0	0	0	0
Febrile neutropenia	0	4	0	2
Diarrhea	0	3	1	5
Nausea	1	3	0	6
Vomiting	0	1	1	5
Hypotension	2	4	0	2
Infections and infestations SOC	0	6	0	4
Hypokalemia	0	7	0	7
SAEs	1	4	0	4

CONCLUSIONS

- A single infusion of PNK-007 up to 10M cells/kg with rhIL-2 following Cy-Flu conditioning was safe and well tolerated in AML subjs with one treatable CRS event observed.
- A single infusion of PNK-007 up to 30M cells/kg following ASCT was safe and well tolerated in MM subjs.
- Overall, PNK-007 demonstrated a favorable safety and tolerability profile with CRS incidence in 1 out of 25 subjs.
- The Placental Natural Killer cells are under evaluation through multi-dosing in both hematological malignancies and solid tumors.

REFERENCES

1. Geller MA, Cooley S, Judson PL, Ghebre R, Carson LF, Argenta PA, et al. A phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer. Cytotherapy 2011;13:98-107.
2. Miller JS, Soignier Y, Panoskaltsis-Mortari A, McNearney SA, Yun GH, Fautsch SK, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. Blood 2005;105:3051-7.
3. Shah N, Li L, Kaur I, McCarty J, Yvon E, Shaim H, et al. Infusion of ex vivo expanded allogeneic cord blood-derived natural killer cells in combination with autologous stem cell transplantation for multiple myeloma: results of a phase I study. Blood 2015 126 (23):929.
4. Miller JS, Tessmer-Tuck J, Pierson BA, Weisdorf D, McGlave P, Blazar BR, et al. Low dose subcutaneous interleukin-2 after autologous transplantation generates sustained in vivo natural killer cell activity. Biol Blood Marrow Transplant 1997;3:34-44.

ACKNOWLEDGEMENTS

- We thank the patients, care givers, sites and research staff for contributing to this research study.
- www.celularity.com