Results of a Phase I Study of PNK-007, Allogeneic, Off the Shelf NK cell, Post Autologous Transplant in Multiple Myeloma (NCT02955550)

4451

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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 novel proprietary GMP procedure that enables the scalable production of an off-the-shelf, allogeneic NK cell therapy. Using this technology platform, Celularity developed PNK-007, a Placental Hematopoietic Stem Cells Derived Natural Killer cell therapy.

PNK-007 shows cytotoxic activity against various cancer cell lines and secretes cytokines such as IFN-γ during co-culture with cancer cells.

PNK-007 has been evaluated for the treatment of relapsed/refractory acute myeloid leukemia (AML) subjects in a Phase I study (PNK-007-AML-001).

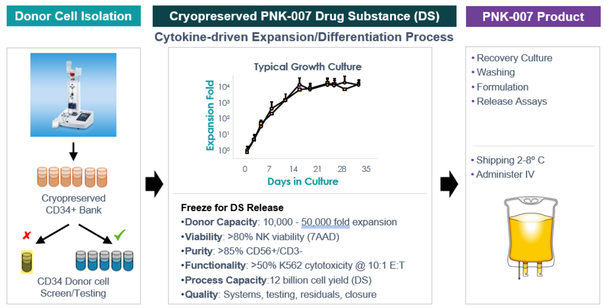
Here, we present final results of the Phase I study in multiple myeloma (MM) after autologous stem cell transplant (ASCT).

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.

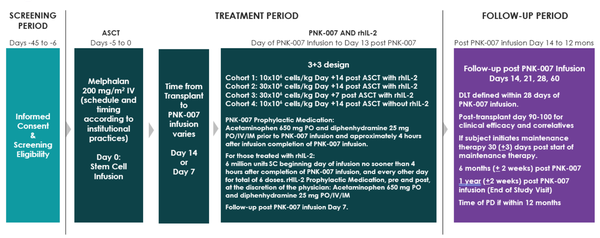
Figure 1: PNK-007 Manufacturing



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.

METHODS

Figure 2: Overview of PNK-007-MM-001 Clinical Protocol



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

OBJECTIVES

Primary: Assess the safety and determine the feasibility of infusing PNK-007 at various doses and timepoints following ASCT in subjects with MM.

Secondary: 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 (MRD) negativity.

Exploratory: Determine time to engraftment post ASCT, persistence and in vivo expansion of PNK-007, correlate PNK-007 to MRD, and evaluate PNK-007 effects on immune system.

METHODS

Study Design

- This is a Phase I, multicenter, open label, study evaluating the dose and timing of infusion of PNK-007 post ASCT in MM.
- Eligible subjects were undergoing or had completed (re)/induction therapy for the purposes of ASCT for MM.
- Pre-transplant induction therapy was not specified.
- Two dose levels of PNK-007 have been evaluated: 10 x 10^6 cells/kg and 30 x 10^6 cells/kg.
- Two timepoints post ASCT have been evaluated: Day 14 post ASCT and Day 7 post ASCT.
- Clinically appropriate maintenance therapy was permitted after the Day 90-100 visit (D90).
- Initially this study was open to both newly diagnosed (NDMM) and relapsed/refractory (RRMM) MM subjects but was later limited to the enrollment of NDMM subjects.
- Initially all subjects were to receive treatment with rhIL-2, but later was amended to evaluate if rhIL-2 was needed for PNK-007 survival and/or expansion or for anti-myeloma activity.
- Cohort 1 has 6 subjects enrolled due to repeating the 10 x 10^6 cell/kg at Day 14 post-ASCT inclusive of only the amended NDMM subject population.

Key Inclusion Criteria

- Newly diagnosed MM undergoing induction therapy prior to undergoing first ASCT (Prior to amendment subjects who had undergone prior anti-MM therapy and had relapsed, or refractory were eligible to participate).
- Aged 18 to 70.
- ECOG < 2 or KPS ≥ 70.
- Ability to be off immunosuppressive drugs for at least 3 days prior to PNK-007 infusion.

Key Exclusion Criteria

- Plasma cell leukemia or non-secretory MM.
- Previously undergone allogeneic stem cell transplant.
- 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/pleural effusion within 2 weeks prior to PNK-007.
- Body weight exceeding 120 kg.

RESULTS

The first subject enrolled February 2017. The study is closed to enrollment.

Table 1: Demographics

Category		Total (n=15)
Age	Median age, years (range)	58 (44-69)
Gender	Female	8
	Male	7
Race	White	13
	Black/African American	1
	Other	1
Type of Disease	Newly diagnosed myeloma undergoing first ASCT	12
	Myeloma with prior relapse undergoing first ASCT	1
	Myeloma with relapsed disease after first ASCT who are undergoing second ASCT	2
ECOG / Karnofsky Performance Status	ECOG 0	2
	Karnofsky 100%	1
	ECOG 1	9
	Karnofsky 90%	1
	Karnofsky 80%	2
Prior lines of MM treatment	0	12
	1	1
	2	1
	5	1

RESULTS CONTINUED

Table 2: Study Disposition

Reason for end of study	Total (n=15)
Completed 1-year follow-up	13
Physician Decision	1
Voluntary withdrawal	1

No subjects died or noted disease progression during study participation.

Table 3: Events of Interest by PNK-007 Relatedness within 28 Day DLT Period

All Grades	MM (N=15)		
Events	**Related and Non-Serious**	**Unrelated and Non-Serious**	**Unrelated and Serious**
Anemia	1	4	0
Febrile neutropenia	0	0	2
Diarrhea	1	5	0
Nausea	0	6	0
Vomiting	1	4	0
Hypotension	0	2	0
Infections and infestations SOC	0	2	1
Hypokalemia	0	7	0
Pyrexia	0	6	1
Rash	0	3	2

Data extracted 02Dec2019

- There were no DLT events identified in the 28 days following PNK-007 infusion.
- No GvHD, Cytokine Release Syndrome, or PNK-007 infusion related toxicities were identified.

Table 4: Subject Response Assessments

	Subject	LOT*	Baseline		Day 90		1 Year		Mtn Therapy
			IMW	MRD	IMW	MRD	IMW	MRD	
Cohort 1	002-1001	1	VGPR	+	VGPR	-	VGPR	NE	Y
	002-1002	2	PR	+	VGPR	-	VGPR	-	Y
	002-1003	1	PR	+	PR	+	VGPR	-	Y
	002-1008	1	VGPR	+	VGPR	-	CR	-	Y
	002-1005	1	Unk	+	SD	+	DD	DD	DD
Cohort 2	003-1001	1	VGPR	+	VGPR	+	VGPR	+	N
	005-1001	3	PR	NE	VGPR	+	PR	+	Y
	008-1001	1	VGPR	+	VGPR	-	sCR	-	Y
	008-1002	1	VGPR	+	sCR	-	VGPR	-	Y
Cohort 3	001-1001	1	VGPR	-	sCR	-	ND	ND	Y
	009-1001	1	CR	+	sCR	-	ND	ND	Y
	009-1002	6	Unk	+	PR	+	WD	WD	Y
Cohort 4	002-1006	1	VGPR	-	VGPR	-	VGPR	NE	Y
	008-1003	1	VGPR	-	sCR	-	CR	-	Y
	002-1007	1	VGPR	-	CR	-	CR	-	Y

Minimal Residual disease (MRD) assay performed on fresh bone marrow aspirate at LOD < 10-5 according to EuroFlow guidance. Subjects in green indicate conversion from MRD(+) to MRD(-) by 1 year, orange indicates unchanged MRD(+) status, gray indicates MRD(-) status at time of enrollment. CR = Complete response; DD = Discontinued due to Physician Decision; IMW = International Myeloma Working Group Response Assessment; LOT = Current Line of Therapy that the subject was being treated with as Induction to ASCT; Mtn = Maintenance; ND = Not Done as procedure not performed; NE = Not Evaluable due to insufficient sample; PR = Partial Response; sCR = Stringent complete response; SD = Stable disease; Unk = Unknown; VGPR = Very Good Partial Response; WD = Subject withdrawal*

- Pre-ASCT induction therapy was variable. All subjects had been exposed to Immunomodulatory drug (IMiDs) and Proteasome Inhibitors (PI).
- Clinically appropriate maintenance therapy was permitted after the Day 90-100 visit (D90), unless otherwise clinically indicated.
  - Maintenance therapy for subjects included IMiDs either alone or in combination with steroids, PI and/or monoclonal antibodies.
- Response assessment was based on IMWG criteria and based on physician assessment:
  - Pre-ASCT response is identified as the Best response to Pre-ASCT Induction therapy.
- Using a validated Euro-flow minimal residual disease (MRD) assay of bone marrow aspirate (BMA):
  - Pre-ASCT: 4/15 subjects were MRD negative (MRD-).
  - D90 post-ASCT: 10/15 subjects were MRD-, with 6 subjects converting to MRD-.
  - 1 Year post-ASCT: 7/9 subjects were MRD-, with 1 subject converting to MRD- following D90.

EXPLORATORY RESULTS

- PNK-007 infusion did not interfere with immune reconstitution kinetics. Platelet, neutrophil, and absolute lymphocyte counts recovered by day 28 post-ASCT in 12/15 subjects. The 3/15 subjects did reconstitute prior to Day 90 and were all NDMM subjects.
- rhIL-2 administration did not significantly affect reconstitution of subjects' NK cells. rhIL-2 transiently enhanced levels of T_{reg} (p=0.0075) relative to pre-rhIL-2 levels. There were not differences in T_{reg} in subjects not receiving rhIL-2.
- Subjects' CD4 and CD8 T cell populations showed inhibited effector response 7-14 days post-ASCT, potentially due to increased numbers of T_{reg}. At all timepoints, however, activated T cells primarily secreted IL-2 and IFNγ with minimal levels of IL-4 and IL-17.
- HLA matching was not required for selection of PNK-007, however, HLA type was collected for evaluation purposes. Serum analysis of serial sampling up to 1 year following PNK-007 demonstrated absence of allo-HLA antibodies (by flow cytometry) in all subjects.
- PNK-007 cell persistence was not detectable by flow cytometry in subjects at day +7 post PNK-007, the earliest post-infusion timepoint measured.
- Please see **Poster 4457**, "Immune Monitoring of CD34+ Placental Cell Derived Natural Killer Cell Therapy (PNK-007) in Phase I Study of Multiple Myeloma," in this poster session for additional information on exploratory analyses.

CONCLUSIONS

- PNK-007 is the first fully allogeneic, off-the-shelf placental CD34+ derived NK cell product in MM clinical trials.
- 15 subjects with MM have been treated with PNK-007 as a single infusion following ASCT.
- No Dose Limiting Toxicities have occurred with no negative impact on bone marrow recovery (at both dose schedules) as well as no evidence of GvHD.
- MRD assessment by EuroFlow showed MRD- observed in 10/15 subjects at D90 post-ASCT, 1 subject being relapsed refractory.
- MRD- was observed in 7/9 subjects at 1 Year post-ASCT.
- No MRD- subjects reverted to MRD+ during participation in the study.
- These clinical responses are encouraging and warrant further evaluation in a randomized setting as part of front-line MM therapy.

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.

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DISCLOSURES

Holstein: Oncopeptides: Membership on an entity's Board of Directors or advisory committees, Research Funding; Genentech: Membership on an entity's Board of Directors or advisory committees; Celgene: Consultancy; Takeda: Membership on an entity's Board of Directors or advisory committees; Adaptive Biotechnologies: Membership on an entity's Board of Directors or advisory committees; Sorrento: Consultancy; GSK: Consultancy. **Cooley:** Fate Therapeutics, Inc: Employment, Equity Ownership. **Hari:** Celgene: Consultan:cy, Honoraria, Research Funding; GSK: Other: Grant; BMS: Consultancy, Research Funding; Janssen: Consultancy, Honoraria; Kite/Gilead: Consultancy, Honoraria; Amgen: Research Funding; Spectrum: Consultancy, Research Funding; Sanofi: Honoraria, Research Funding; Cell Vault: Equity Ownership; AbbVie: Consultancy, Honoraria; Takeda: Consultancy, Honoraria, Research Funding. **Jagannath:** BMS: Consultancy; Merck: Consultancy; Celgene: Consultancy; Novartis: Consultancy; Medicom: Speakers Bureau; Multiple Myeloma Research Foundation: Speakers Bureau. **Balint:** Celgene: Equity Ownership; Celularity, Inc: Employment. **van der Touw:** Celularity, Inc: Employment. **Zhang:** Celularity Inc: Employment. **Hariri:** Celularity Inc: Employment. **Vij:** Bristol-Myers Squibb: Honoraria, Research Funding; Celgene: Honoraria, Research Funding; Genentech: Honoraria; Janssen: Honoraria; Karyopharm: Honoraria; Sanofi: Honoraria; Takeda: Honoraria, Research Funding.