First-in-Human Phase I Study of Nicotinamide-Expanded Related Donor Natural Killer Cells for the Treatment of Relapsed/Refractory Non-Hodgkin Lymphoma and Multiple Myeloma

Veronika Bachanova[1], David H. McKenna[1], Jr., Xianghua Luo[1], Todd E. Defor[1], Sarah A. Cooley[1], Erica Warlick[1], Daniel W. Weisdorf[1], Guy Brachya[2], Tony Peled[2], Jeffrey S. Miller[1]

[1]University of Minnesota, Minneapolis, Minnesota, [2]Gamida Cell, Jerusalem

Background

Natural Killer (NK) Cells

- Adoptive transfer of cytolytic NK is an attractive immunotherapeutic approach to the treatment of lymphoma and other malignancies
- Previous clinical success has been modest due to limited in vivo persistence of NK cells and their impaired effector function
- Nicotinamide (NAM)-based technology, previously used for hematopoietic stem cells, has been adapted for adult donor NK cells, modulating the characteristics and function of NK cells expanded ex vivo[1]
- In preclinical studies, NAM-NK demonstrated cytotoxicity as well as increased homing, proliferation and persistence[2]
- We report preliminary results of a Phase I NAM-NK study in patients with lymphoma and multiple myeloma

Figure 1. NK Cell Functions

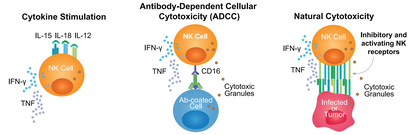
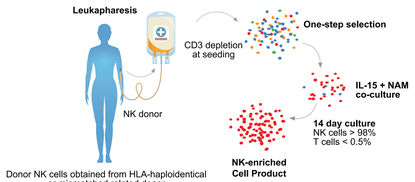


Figure 2. NAM-NK Expansion Process



Phase I Study Design

Objectives

Dose escalation phase: Determine maximum tolerated dose of NAM-NK
Expansion phase: Overall disease response in multiple myeloma and lymphoma

Key Inclusion Criteria

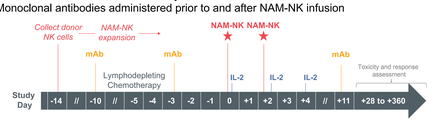
- **Age:** ≥ 18 to ≤ 80 years
- **Acceptable organ function**
- **Lymphoma:** Confirmed CD20-positive B-cell Non-Hodgkin Lymphoma (NHL) with measurable disease > 1.5cm; relapsed/refractory disease that has failed conventional therapy and/or transplant

OR

- **Myeloma:** Relapsed/refractory disease after two lines of therapy including proteasome inhibitor and immunomodulatory drug, or relapse after autologous or allogeneic transplant; measurable disease by M spike, light chains, plasmacytoma, or measurable soft tissue or bone disease

Study Schema

- Donor NK cells are expanded *ex-vivo*
- Patient undergoes lymphodepleting regimen of cyclophosphamide and fludarabine
- Patient receives NAM-NK followed by short course IL-2
- Monoclonal antibodies administered prior to and after NAM-NK infusion



- Monoclonal antibodies (mAb): Elotuzumab (10 mg/kg IV) for multiple myeloma, rituximab (375 mg/m^2 IV) for B-cell lymphoma
- Lymphodepleting chemotherapy: Cyclophosphamide (400 mg/m^2 IV) x 3d and fludarabine (30 mg/m^2 /d IV x 3d)
- IL-2: 6 million units sc

Results

Patient Demographics

Table 1. Demographics and Disease Characteristics

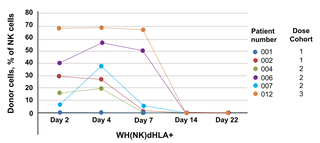
Patient and Disease Characteristics	Number of Patients (N=14)
Age [median (range)]	62 (47-75 years)
Gender: male/female	9/5
Diagnosis	
Multiple myeloma	8
Follicular lymphoma	3
Transformed Lymphoma	2
Diffuse Large B Cell Lymphoma	1
Disease status	
Relapsed	10
Refractory	4
Prior Therapies	
Number of lines of prior therapy [median (range)]	5 (3-10)
Prior Autologous Transplant	7
Prior Allogeneic Transplant	1
Time from Diagnosis to Treatment [median (range)]	4.5 (1-26 years)

Table 2. NAM-NK Dose Cohorts.

Cohort	Target TNC Dose (99% NK)	Total Dose NAM-NK Infused Median (Range)
1	2.0 x 10^7	4.4 x 10^7 (1.9-7.3 x 10^7)
2	1.0 x 10^8	9.3 x 10^7 (8.7 x 10^7-1.2 x 10^8)
3	2.0 x 10^8	1.7 x 10^8 (1.6-2.0 x 10^8)

Persistence and Expansion of Donor NAM-NK

Figure 3. Donor NAM-NK Cells Detected in Peripheral Blood of 6 Subjects with Donor-Specific HLA



- Donor NAK-NK cells in peripheral blood express high levels of CD16 and Ki-67 (not shown)

Figure 4. Patient 007 (MM): Donor Cells Detected in Blood and Bone Marrow by Flow Chimerism (Donor is HLA-A2+). Flow plots are gated on CD56+CD3- NK Cells

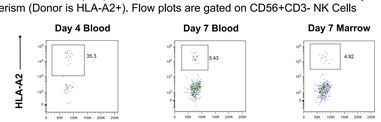
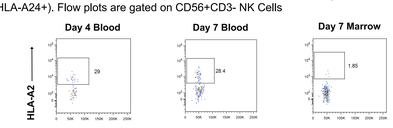


Figure 5. Patient 002 (NHL-follicular): Donor Cells Detected in Blood by Flow Chimerism (Donor is HLA-A24+). Flow plots are gated on CD56+CD3- NK Cells



Safety

- No Dose Limiting Toxicities
- No GVHD, tumor lysis syndrome, or neurotoxicity reported
- Hematologic toxicities: grade 3 (n=3) and grade 4 (n=1)
- Non-hematologic toxicities attributed to cyclophosphamide/fludarabine, most grade 1/2
- Bradycardia reported in one patient, attributed to elotuzumab
- Cytokine release syndrome (grade 3) in one patient with MM, presented on d18 with fever, hypoxemia and hypotension, promptly responded to tocilizumab
- One patient death due to E. coli sepsis

Table 3. Adverse Events

Event	All Grades (n)	Grade 3/4 (n)
Hypertension	7	4
Neutrophil count decreased	4	4
Anemia	4	3
Platelet count decreased	4	3
White blood cell decreased	3	3
Fever	8	2
Dyspnea	5	2
Hypophosphatemia	3	2
Hypoxia	2	2
Hypotension	5	1
Upper respiratory infection	5	1
Edema	3	1
Sinus tachycardia	3	1
Hyponatremia	2	1
Abdominal pain	1	1
Atrial fibrillation	1	1
Cytokine release syndrome	1	1
E. coli Pneumonia	1	1
Febrile neutropenia	1	1
Hyperkalemia	1	1
Pulmonary edema	1	1

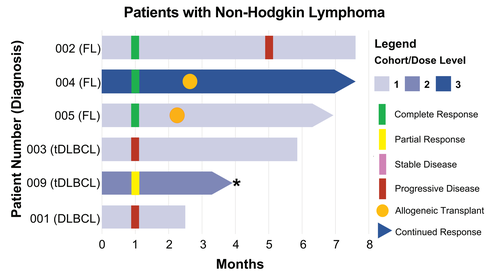
Grade 3/4 adverse events possibly, probably or definitely related to therapy reported in at least one patient

Efficacy

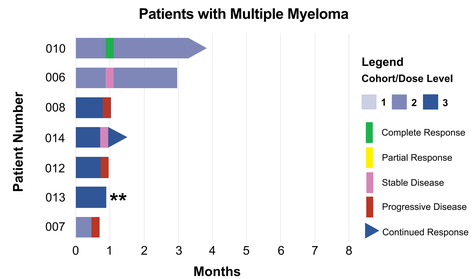
6 patients with NHL evaluable for response:
- 3 patients with complete response (CR) (2 FL, 1 TL); 2 patients subsequently underwent allogeneic stem cell transplant
- 1 patient with partial response (~75% reduction) (DLBCL)
- 2 patients with progressive disease (PD) (tDLBCL, DLBCL)

6 patients with MM evaluable for response: heavily pretreated with extensive disease
- 1 patient with CR (extramedullary disease)
- 2 patients with stable disease
- 3 patients with progressive disease (PD)
- 1 patient not evaluable
- 1 patient pending response assessment

Figure 6. Swimmer Plots

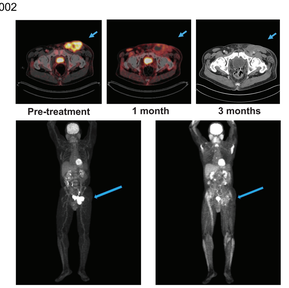


Each bar represents one patient from NAM-NK infusion to last follow-up.
FL: Follicular lymphoma; tDLBCL: transformed diffuse large B cell lymphoma; DLBCL: diffuse large B cell lymphoma
1 additional patient with MM pending d28 evaluation
*Continued tumor shrinkage



**Patient discontinued prior to evaluation
1 additional patient pending d28 evaluation

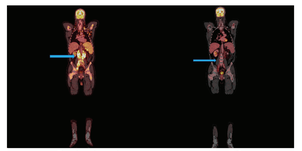
Figure 7. Patient 002



Pt 002: 67-year-old man with Stage IVA follicular lymphoma diagnosed in 2012, previously treated with multiple rituximab-containing regimens (R-CVP, R-bendamustine, R-ICE, R-EPOCH) presented with bulky adenopathy in upper and lower abdomen and bone marrow involvement

Received NAM-NK dose level 1: complete response, confirmed by biopsy

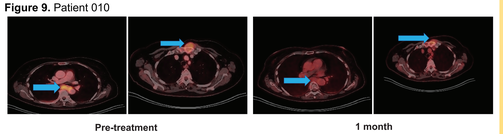
Figure 8. Patient 004



Pt 004: 60-year-old man with Stage IV follicular lymphoma diagnosed in 2015, previously treated with R-bendamustine, R-CHOP, and R-ICE.

Received NAM-NK dose level 2: complete response. Went on to allogeneic bone marrow transplant.

Figure 9. Patient 010



Pt 010: 70-year-old woman with multiple myeloma diagnosed in 2012, previously treated with lenalidomide/bortezomib/dexamethasone; lenalidomide/bortezimib; pomalidomide/dexamethasone, and autologous stem cell transplant; presented with extramedullary disease.

Received NAM-NK dose level 2: complete response

Conclusions

- NAM-NK was well-tolerated without infusion toxicity or DLTs
- Maximum target dose of 2 x 10^8 cells/kg was achieved
- NAM-NK cells were detectable in blood and bone marrow, and exhibited proliferative phenotype and cytotoxic function
- Clinical activity was observed, including complete responses in patients with lymphoma and myeloma
- Additional patients will be treated at the MTD to further evaluate safety and efficacy
- Future directions include cryopreservation and exploration of multiple treatment cycles

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1. Horwitz, M., et al JCI 12:3121, 2014.
2. Peled, T., Brachya, G., et al: Blood 2017, 130:657.