GDA-201, A Novel Metabolically Enhanced Allogeneic Natural Killer (NK) Cell Product Yields High Remission Rates in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL): 2-Year Survival and Correlation With Cytokine IL-7

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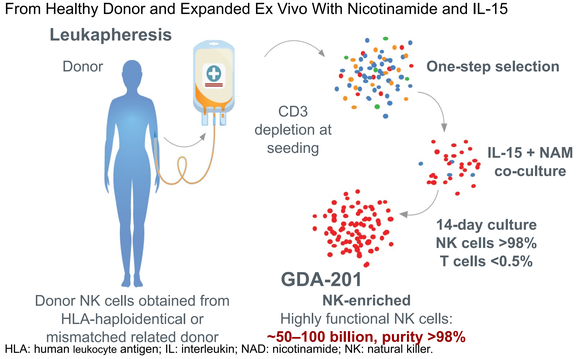
INTRODUCTION

- The innate capacity of natural killer (NK) cells to kill tumor targets has been translated into cancer immunotherapy, with the adoptive transfer of cytolytic NK cells an attractive immunotherapeutic approach
- However, previous clinical success has been modest due to the limited in vivo persistence of NK cells resulting in impaired effector function
- Nicotinamide (NAM) can expand any cell type, including stem cells and NK cells. NAM plays a key role in:
  - Metabolic reprogramming of cells
  - Nicotinamide adenine dinucleotide–related signaling pathways
  - Preservation of cellular functionality and phenotype during expansion
- In preclinical models, NAM significantly enhanced[1]:
  - Anti-tumor function of ex vivo expanded NK cells
  - Trafficking to tissues
  - Antibody-dependent cell-mediated cytotoxicity
  - Tolerance to oxidative stress
- GDA-201 represents a novel class of metabolically enhanced ex vivo expanded allogeneic NK cells with acquired capacity for improved organ trafficking, augmented resistance against exhaustion and in vivo proliferation (**Figure 1**)

Figure 1. GDA-201 is a Novel Ex Vivo Expanded Allogeneic NK Cell Product Derived From Healthy Donor and Expanded Ex Vivo With Nicotinamide and IL-15



HLA: human leukocyte antigen; IL: interleukin; NAD: nicotinamide; NK: natural killer.

- Objective responses in patients with lymphoma were previously presented.[2] We now report 2-year follow-up of patient outcomes

OBJECTIVE

- To evaluate outcomes of GDA-201 in combination with rituximab in patients with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL)

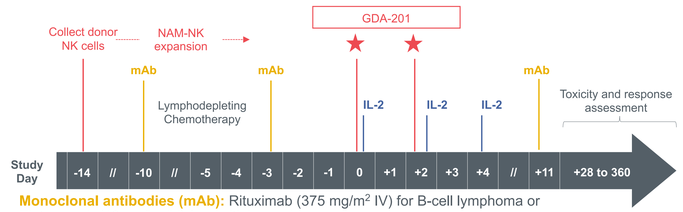
METHODS

Study Design

- This phase 1 trial (NCT03019666) evaluated the safety and efficacy of GDA-201 in patients with R/R multiple myeloma and R/R NHL
- Following donor apheresis, CD3-depleted mononuclear cells were cultured for 14–16 days with NAM (5 mM) and interleukin (IL)-15 (20 ng/mL), resulting in a 40-fold increase in NK cells and increased expression of CD62L from 2.9% to 21%
- GDA-201 contained ~98% NK cells, and CD3 content was low at <0.5% (<5×10^5/kg/dose)
- Patients received 2 doses rituximab and lymphodepleting chemotherapy, before receiving GDA-201 followed by low-dose IL-2 and 3rd dose of rituximab (**Figure 2**)
- Patients and donors provided written informed consent, and ethics approval was obtained

Figure 2. Study Design

GDA-201 Cohort	Target TNC Dose (cells/kg)
1	2.0 × 10^7
2	1.0 × 10^8
3	2.0 × 10^8



Monoclonal antibodies (mAb): Rituximab (375 mg/m^2 IV) for B-cell lymphoma or Elotuzumab (10 mg/kg IV) for multiple myeloma

Lymphodepleting chemotherapy: Cyclophosphamide (400 mg/m^2 IV × 3d) and fludarabine (30 mg/m^2 /d IV × 3d)

IL-2: 6 million units SC

IL: interleukin; IV: intravenous; mAb: monoclonal antibody; NAM: nicotinamide; NK: natural killer; SC: subcutaneous; TNC: total nucleated cell.

Study Population

- Inclusion criteria:
  - ≥18 years of age with CD20-positive B-cell NHL
  - CD20 expression confirmed by flow cytometry or immunohistochemistry
  - Evidence of R/R disease that has failed conventional therapy
  - Measurable disease >1.5 cm in diameter
  - Human leukocyte antigen (HLA)–haploidentical or mismatched related donor (12–70 years of age)
  - Karnofsky Performance Scale score ≥60%
- Exclusion criteria
  - Active, untreated central nervous system (CNS) involvement
  - Active autoimmune disease requiring immunosuppressive therapy
  - High donor-specific anti-HLA antibodies titer (mean fluorescence intensity >1000)

Endpoints

- Safety, dose-limiting toxicities
- Overall response rate, complete response, partial response, duration of response, progression-free survival (PFS), overall survival (OS)
- Biomarker: IL-7 and IL-15 levels

RESULTS

Patients

- 16 patients with NHL received the maximum target dose (median dose, 12.4 [range 2.0–26.0] × 10^7 GDA-201 cells/kg)

Table 1. Patient Demographics

	Total (N=36)	NHL cohort (n=20)
Age, median (range), years	61 (46–83)	60 (46–83)
Sex: male/female, n	21/14	11/9
Multiple myeloma, n NHL, n	16 20	– 20
Diffuse large B-cell lymphoma	–	9
Follicular lymphoma	–	10
Mantle cell lymphoma	–	1
Disease status, n (%)		
Relapsed	28 (80)	17 (85)
Refractory	7 (20)	3 (11)
Stage III–IV (NHL only), n (%)	–	16 (80)
Number of lines of therapies, median (range)	4.5 (1–10)	3 (1–8)
Prior autologous transplant, n (%)	16 (47)	3 (17)
Prior allogeneic transplant, n (%)	1 (3)	1 (5.6)
KPS 80 or less, n (%)	16 (47)	8 (45)
GDA-201 cell dose, median in 10^7/kg (range)	**14.3 (2.0–26.0)**	**10.2 (2.0–26.0)**

KPS: Karnofsky Performance Scale; NHL: non-Hodgkin lymphoma.

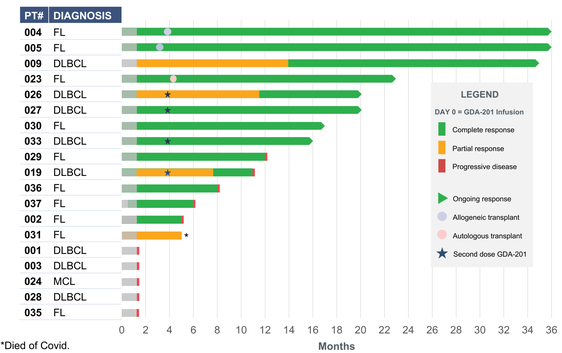
Safety

- The most common grade 3/4 treatment-emergent adverse events were thrombocytopenia (n=9), hypertension (n=9), neutropenia (n=4), febrile neutropenia (n=4), and anemia (n=3)
- Adverse events of special interest (cytokine release syndrome, neurotoxic events, graft-versus-host disease, or bone marrow aplasia) were not observed
- One patient died of *Escherichia coli* sepsis

Efficacy

- Nineteen patients were evaluable for response
- **Overall response rate (ORR) was 74%**
- **Complete response rate (CR) 65% (n=13)**
- **Among patients with CR, there were 5 with DLBCL and 8 with FL**
- **1 patient had partial response (PR)**
- Four patients underwent re-treatment with GDA-201 without LD chemotherapy; two patients (FL and transformed DLBCL) had further deepening of response from PR to CR

Figure 3. Objective Responses in Patients With NHL Treated With GDA-201

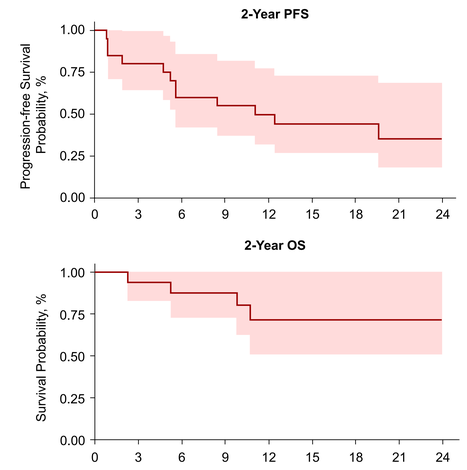


*Died of Covid.

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; LD: lymphodepleting; MCL: mantle cell lymphoma.

- At a median follow-up of 11 (range, 1–36) months:
  - 1- and 2-year PFS were 50% (95% confidence interval [CI], 27%–69%) and 35% (95% CI, 14%–58%), respectively
  - 2-year OS was 78% (95% CI, 51%–91%)

Figure 4. OS and PFS in Patients With NHL Treated With GDA-201



CI: confidence interval; NHL: non-Hodgkin lymphoma; OS: overall survival; PFS: progression-free survival.

Biomarker Analysis: IL-7 level correlated with PFS and OS

- Persistence of donor NAM-NK in peripheral blood demonstrated up to days 7–14 (day 7 range, 2%–92% GDA-201 cells)
  - Median IL-7 plasma levels at baseline, day 7, and day 14 were 5.12 pg/dL (range, 1.7–16.0), 11.7 pg/dL (3.5–20.0) and 9.66 pg/dL (5.4–18.5)
- Increased ΔIL-7 (day 0-14) correlated with survival:
- Increased in ΔIL-7 serum levels of 1 pg/dL was associated with:
  - A 37% improvement in 1-year PFS (hazard ratio, 0.63; 95% CI, 0.41–0.96; *P*=0.03)
  - A 58% improvement in 1-year OS (hazard ratio, 0.42; 95%CI, 0.40–0.85; *P*=0.02)

CONCLUSIONS

- Cellular therapy using GDA-201 with rituximab was well tolerated and demonstrated significant clinical activity in patients with advanced DLBCL and FL.
  - Durable complete remissions have been observed in patients with relapsed and refractory NHL
  - A cytokine surge following lymphodepleting chemotherapy appears to be associated with clinical activity
- **Phase 2 studies in aggressive and indolent NHL cohorts are planned using cryopreserved GDA-201 product**

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2. Bachanova V, et al. *Blood.* 2019;134(Suppl 1):777.