A PHASE 1/2 STUDY OF GDA-201 (NADRAVALEUCEL), CRYOPRESERVED NICOTINAMIDE-ENHANCED ALLOGENEIC NATURAL KILLER CELLS, IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL LYMPHOMA

Poster #255

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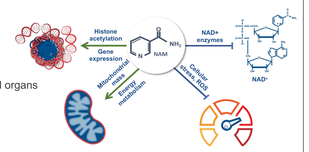
BACKGROUND

- Natural killer (NK) cells are cytotoxic lymphocytes that have drawn considerable attention in recent years as a promising immunotherapy for cancer. However, limited NK persistence in vivo has been a barrier to clinical success
- GDA-201 (nadravaleucel) consists of metabolically enhanced ex-vivo expanded allogeneic NK cells, manufactured using nicotinamide (NAM)-based expansion technology
- GDA-201 cells exhibit improved homing to lymphoid organs, decreased expression of inhibitory checkpoints, augmented resistance to oxidative stress and competent cytotoxicity (**Figure 1**)
- In a previous phase 1 study, we have shown that a fresh formulation of GDA-201 in combination with rituximab was well tolerated and demonstrated clinical efficacy with long-term responses in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (R/R B-NHL)[1]
  - We now report results of the phase I dose escalation portion of a phase 1/2, open-label, multicenter study evaluating the safety and efficacy of allogeneic cryopreserved GDA-201 in patients with R/R B-NHL (NCT05296525).

FIGURE 1. NAM ADVANTAGE IN NK CELL CULTURE

NAM effect on NK cells:

- Master regulator of **NAD**-related signaling pathways
- Increases **metabolic fitness**
- Plays a key role in the **metabolic reprogramming** of cells
- Enhances cellular **functionality** and **phenotype**
- Improves **homing** and **retention** of GDA-201 in the lymphoid organs
- Maintains competent direct **cytotoxicity & ADCC functions**
- Downregulates the expression of **inhibitory checkpoints**
- Preserves a **non-exhausted phenotype**
- Protects against **oxidative stress**

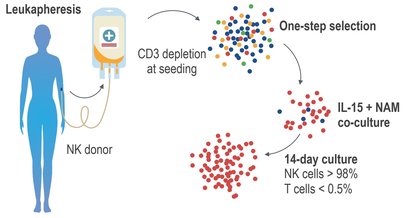


ADCC, antibody-dependent cellular cytotoxicity; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; NK, natural killer; ROS, reactive oxygen species.

METHODS

- This is a phase 1/2, open-label, multicenter study evaluating the safety and efficacy of cryopreserved GDA-201 in patients with R/R B-NHL
- Adult patients with R/R follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBCL), mantle cell (MCL), and marginal-zone B-cell lymphomas (MZL) are eligible for phase I
- Patients received at least 2 lines of therapy and either failed or were considered ineligible for chimeric antigen receptor T-cell-based therapy (CAR-T per the investigator's discretion
- Phase I was a standard 3+3 dose escalation design comprising 4 dose cohorts of up to 2 X 10^8 cells/kg.
- Administration of GDA-201 was preceded by 2 doses of rituximab, as well as fludarabine and cyclophosphamide based lymphodepletion. After GDA-201, patients received IL-2 cytokine support and an additional dose of rituximab (**Figure 3**)
- The goal was to determine the maximal tolerated dose (MTD) and recommended phase II dose (RP2D) based on dose-limiting toxicities (DLTs) as monitored over 28 days post–GDA-201 infusion
- The study is currently enrolling patients at 6 US sites (Memorial Sloan Kettering Cancer Center, NY; Massachusetts General Hospital, MA; University of Minnesota, MN; Loyola University, IL; Henry Ford Hospital, MI; Mayo Clinic, FL)

FIGURE 2. PRODUCTION OF GDA-201



- Apheresis material collected from healthy donor volunteers
- Cells undergo T-cell depletion. T cells are irradiated and re-introduced into the culture system as feeder cells
- Cells are cultured for 14 days in the presence of IL-15 and NAM
- NK enriched cell product is obtained with NK cell content of >98% and T-cell content of <0.5%

IL-15, interleukin 15; NAM, nicotinamide; NK, natural killer.

RESULTS

FIGURE 3. PATIENT DISPOSITION & STUDY SCHEMATICS

A

Patient #	GDA-201 Dose (cells/kg)	Age	Sex	Histology	Subtype	Stage	No. of Prior lines	Prior CAR-T	Prior HSCT
10501	2.5 X 10^7	40	F	FL > DLBCL	NOS	2	6	N	N
10301	2.5 X 10^7	47	M	DLBCL > FL	ABC	3	6	Y	Auto
10402	2.5 X 10^7	65	M	DLBCL	GCB	2	7	Y	N
10403	2.5 X 10^7	68	F	HGBCL	NOS	4	8	Y	Auto, Allo
10502	5.0 X 10^7	69	F	MZL	NOS	4	5	N	N
10801	5.0 X 10^7	63	M	HGBCL	NOS	2	7	Y	Auto
10404	5.0 X 10^7	62	M	DLBCL	ABC	3	3	Y	N
10406	1.0 X 10^8	67	M	MCL	NOS	4	10	N	Auto, Allo
10201	1.0 X 10^8	64	F	FL > DLBCL	NOS	4	5	Y	N
10701	1.0 X 10^8	78	F	MZL	NOS	3	3	N	N
10504	2.0 X 10^8	69	M	DLBCL	GCB	3	4	N	N
10506	2.0 X 10^8	68	F	FL	NOS	4	2	N	Allo

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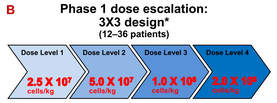

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Figure 3. Patient Disposition and Study Schematics
(**A**) Patient disposition table
(**B**) GDA-201 phase 1 dose escalation: 3X3 design
(**C**) GDA-201 phase 1 dose escalation: schedule of interventions and events in the GDA-201 study

ABC, activated B-cell type; Allo, allogeneic; Auto, autologous; CAR-T, chimeric antigen receptor T-cell based therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; F, female; FL, follicular lymphoma; GCB, germinal center B-cell type; HGBCL, high grade B-cell lymphoma; HSCT, hematopoietic stem cell transplant; M, male; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; PD, progression of disease; PR, partial response; SD, stable disease.

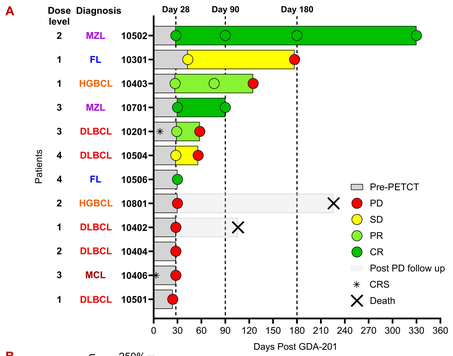
FIGURE 4. SAFETY & EFFICACY SUMMARY

Patient #	GDA-201 Dose (cells/kg)	Infusion Reactions to GDA-201	DLTs	CRS	ICANS	GVHD	Related Grade 3/4 AEs	Related SAEs	Best Overall Response	Follow-up Period (Days)
10501	2.5 X 10^7	N	N	N	N	N	N	N	PD	24
10301	2.5 X 10^7	N	N	N	N	N	N	N	SD	177
10402	2.5 X 10^7	N	N	N	N	N	N	N	PD	28
10403	2.5 X 10^7	N	N	N	N	N	N	N	PR	125
10502	5.0 X 10^7	N	N	N	N	N	N	N	CR	330
10801	5.0 X 10^7	N	N	N	N	N	N	N	PD*	30
10404	5.0 X 10^7	N	N	N	N	N	N	N	PD	28
10406	1.0 X 10^8	N	N	Gr1	N	N	N	N	PD	29
10201	1.0 X 10^8	N	N	Gr2	N	N	N	N	PR	58
10701	1.0 X 10^8	N	N	N	N	N	N	N	CR	90
10504	2.0 X 10^8	N	N	N	N	N	N	N	SD	28
10506	2.0 X 10^8	N	N	N	N	N	N	N	CR	30

*Per response assessment using Lugano classification,[2] this patient was categorized as PD due to progression of one non-target lesion.
AEs, adverse events; CR, complete response; CRS, cytokine release syndrome; DLTs, dose-limiting toxicities; Gr, grade; GVHD, graft-versus-host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; PD, progression of disease; PR, partial response; SAEs, serious adverse events; SD, stable disease.

FIGURE 5. PRELIMINARY EFFICACY RESULTS

A



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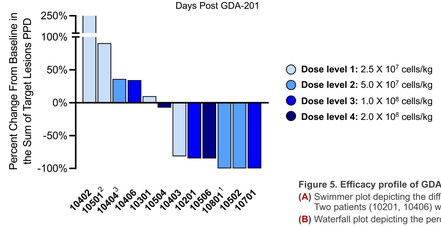

[1]PD determined by progression of one non-target lesion
[2]Based on day 24 CT.
[3]Based on day 21 CT.

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Figure 5. Efficacy profile of GDA-201 in R/R B-NHL patients
(**A**) Swimmer plot depicting the different responses among GDA-201 R/R B-NHL patients. Dose level and histology appear adjacent to the Y axis. Two patients (10201, 10406) who presented with grade 1 / 2 cytokine release syndrome (CRS) following GDA-201 are labelled with an asterisk (*).
(**B**) Waterfall plot depicting the percent change from baseline in the sum of products of the perpendicular diameters (PPD) as measured for all target lesions.
(**C**) Fusion PET/CT images of R/R B-NHL patients before and 28 days after GDA-201 infusion. Dashed lines encircle lesions of suspected lymphomatous origin. **Top row**: Axial PET/CT sections at the level of the mediastinum of patient 10801. Two target lesions regress completely following GDA-201 administration. Per response assessment using Lugano classification,[2] this patient was categorized as PD due to progression of one non-target lesion. **Bottom row**: Coronal PET/CT sections of patient 10201. Multifocal lymphomatous involvement markedly regress following GDA-201 administration.

CR, complete response; CRS, cytokine release syndrome; diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high grade B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progression of disease; PPD, perpendicular diameter; PR, partial response; R/R B-NHL, relapsed/refractory B-cell non-Hodgkin lymphoma; SD, stable disease.

CONCLUSIONS

- In this phase 1 study, cryopreserved GDA-201 at doses of up to 1.0 X 10^8 cells/kg plus rituximab was well tolerated in patients with B-cell NHL
  - No GDA-201-related infusion reactions, dose-limiting toxicities, GDA-201-related grade 3/4 AEs, or serious AEs were observed
  - No cases of GVHD/ICANS were reported
  - Two cases of CRS (1 patient with grade 1 and 1 patient with grade 2) were noted
  - The most common grade 3/4 AE was transient neutropenia in all patients, related to lymphodepleting therapy
- Seven patients experienced a decrease in tumor burden following GDA-201 administration (2 SD, 2 PR, 3 CR)
  - Among responders (PR, CR), target lesion dimensions decreased by a mean of 90.2% (range: 81.5–100%)
  - Of the 6 patients who previously progressed on CAR-T cell therapy, 3 patients showed clinical benefit from GDA-201 treatment (1 SD, 2 PR)
- Overall, preliminary evidence from this phase 1 study suggests GDA-201 may have potential efficacy in the post CAR-T cell setting, and the study is continuing to enroll patients at the 2.0 X 10^8 cells/kg dose level

REFERENCES

1. Cichocki F, et al. *Science Translational Medicine* 2023;19;15(705). 2. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068

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