Tumor Microenvironment Spatial Analysis after Adoptive NK Cell Therapy for Lymphoma Revealed Cross-Talk with Adaptive T-Cell Immunity

Veronika Bachanova, Jeffrey S. Miller, Joseph E. Maakaron, Yvette Soignier, Rose Wangen, Ronit Simantov, Dr. Roei Mazor, Ashenafi Tilahun, Martin Felices and

Bartosz Grzywacz

UNIVERSITY OF MINNESOTA
Driven to Discover®

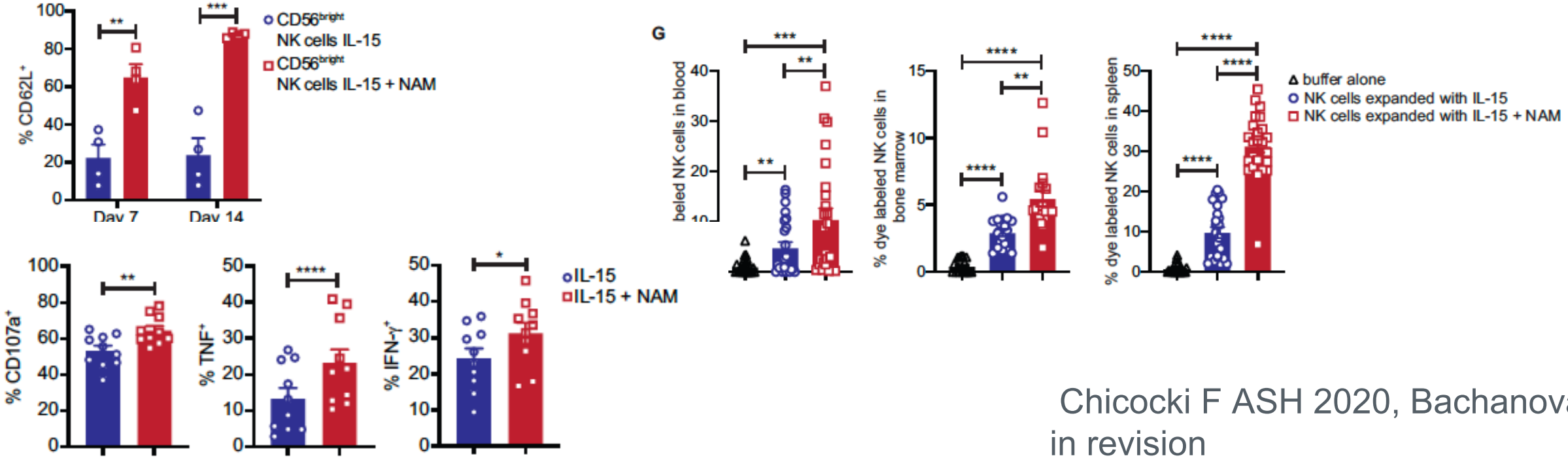
Disclosures

- Trial Sponsor (NCT03019666). : Gamida Cell
- Research Funding: Gamida Cell, Incyte, BMS, Citius, FATE Therapeutics
- Advisory Board: Astra Zeneca, ADC, Karyopharma, Takeda

NK cell adoptive therapy can be enhanced with nicotinamide to improve effector function and tissue retention

Natural killer (NK) immune effectors are increasingly being explored for cancer immunotherapy.

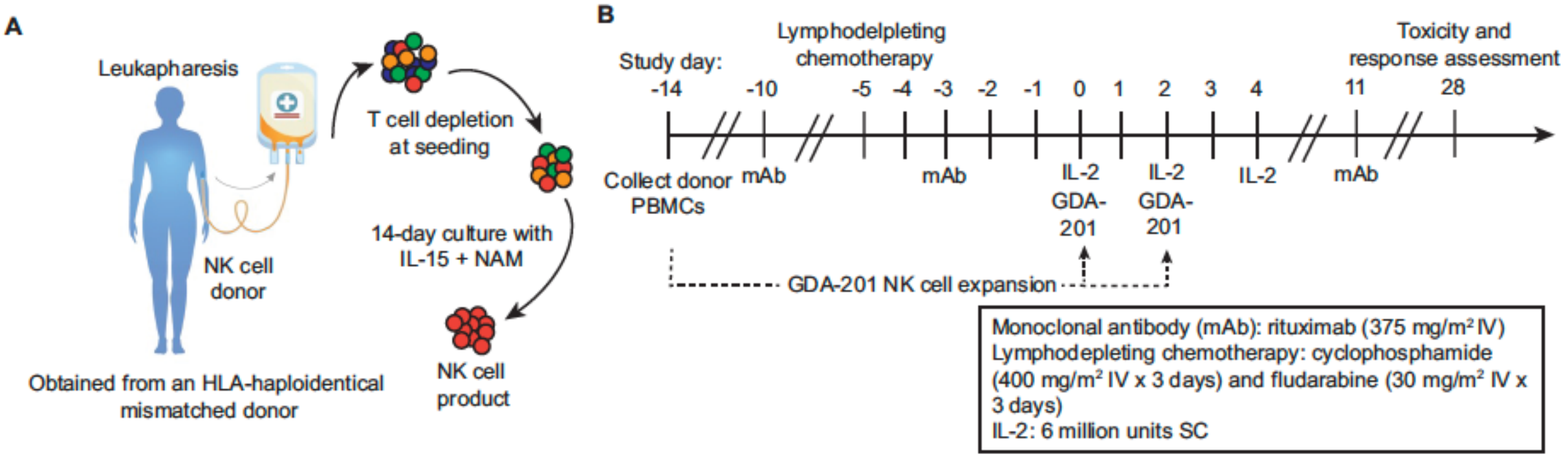
GDA-201 is a novel **nicotinamide ex-vivo expanded metabolically fit allogeneic NK** cell product with augmented resistance against exhaustion



Chicocki F ASH 2020, Bachanova in revision

GDA-201 is Novel Allogeneic NK cell Product Derived from Healthy Donor and Expanded Ex-Vivo with Nicotinamide and IL-15

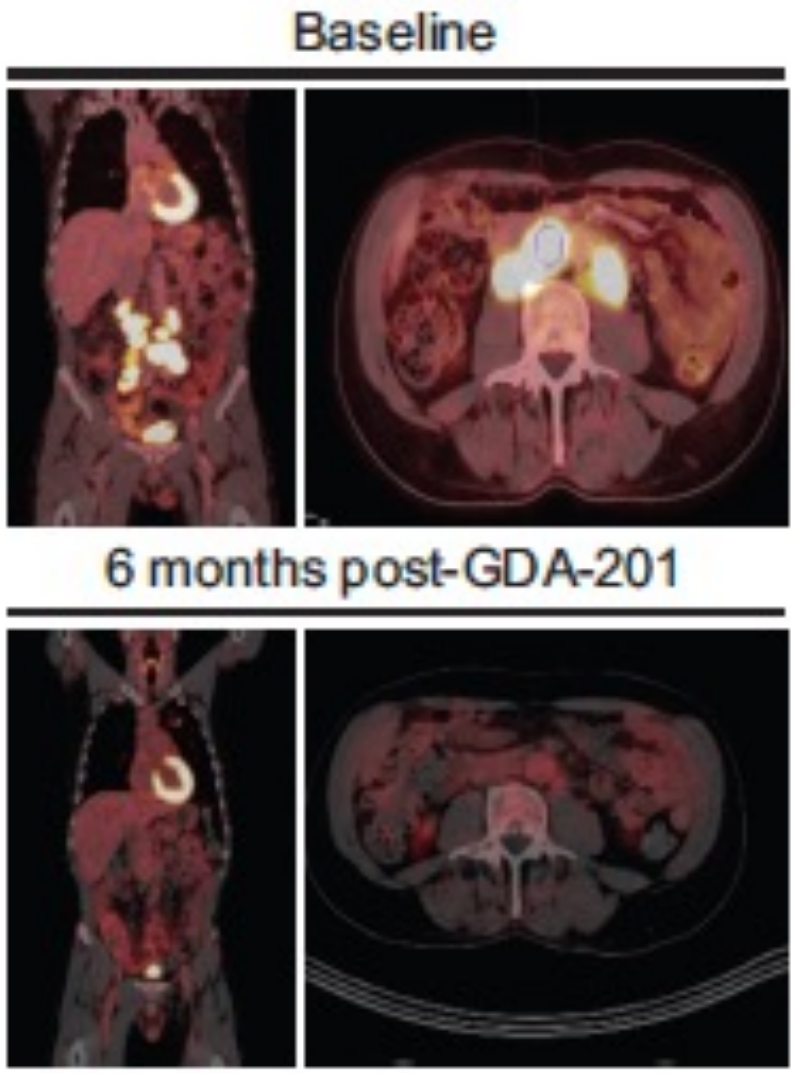
Phase 1 trial



ClinicalTrials.gov Identifier NCT03019666

Bachanova, ASH 2021

Durable responses were observed in patients with B-cell lymphoma



19 patients with NHL treated (8 had LBCL, 1 MCL, 10 FL)

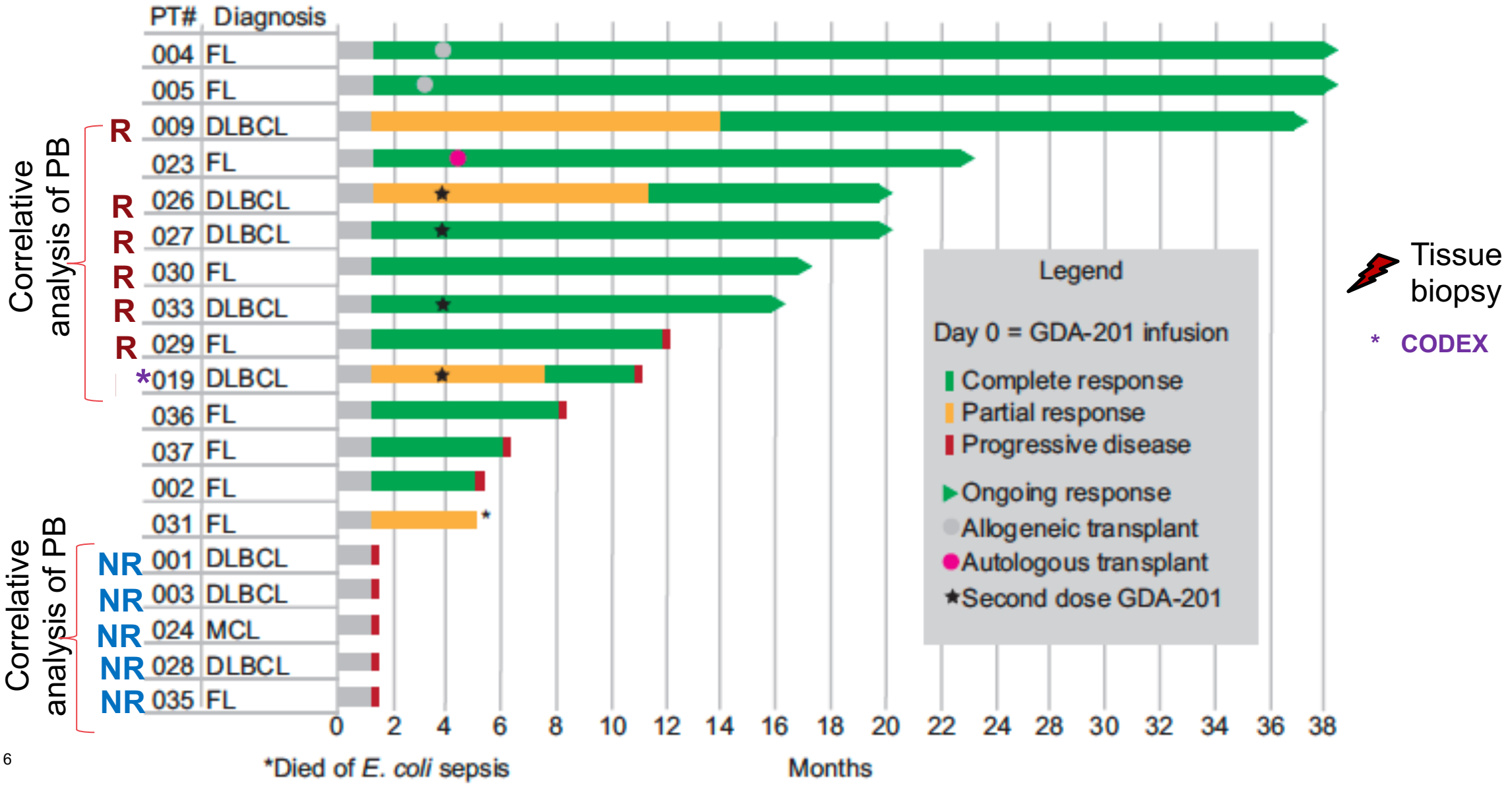
- 13 CR
- 1 PR
- 5 PD
- ORR: 74%

- **FL: 8 CR, 1PR, 1PD**
- **DLBCL: 5 CR, 3 PD**
- **MCL: 1 PD**

The median duration of response was 16 months (range 5-36 months)

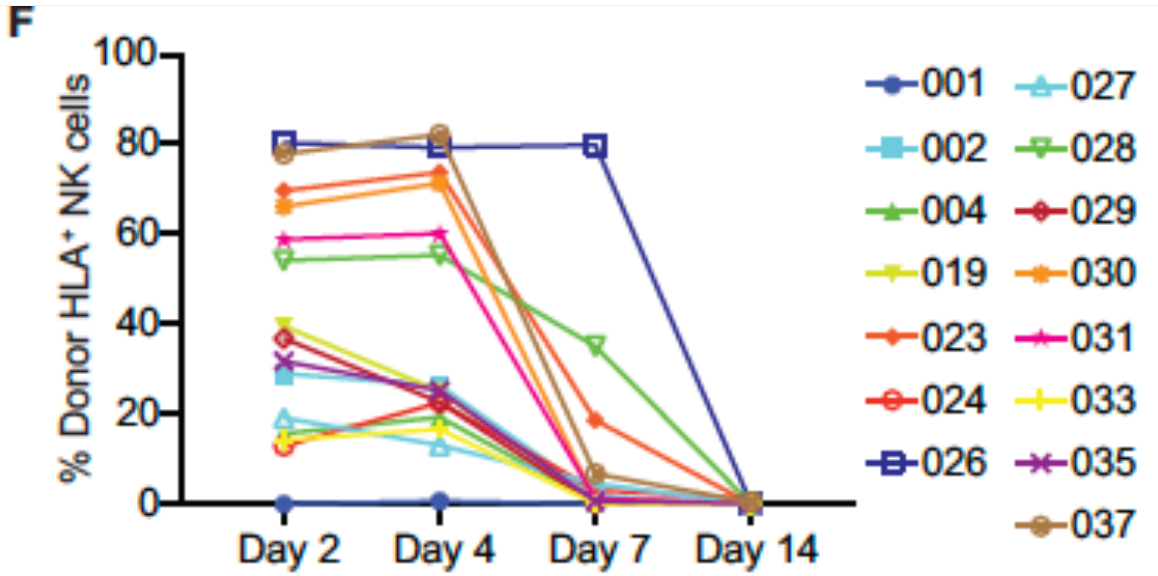
Bachanova, ASH 2020,ASCTC 2021
Chicocki F, Bachanova STM in review

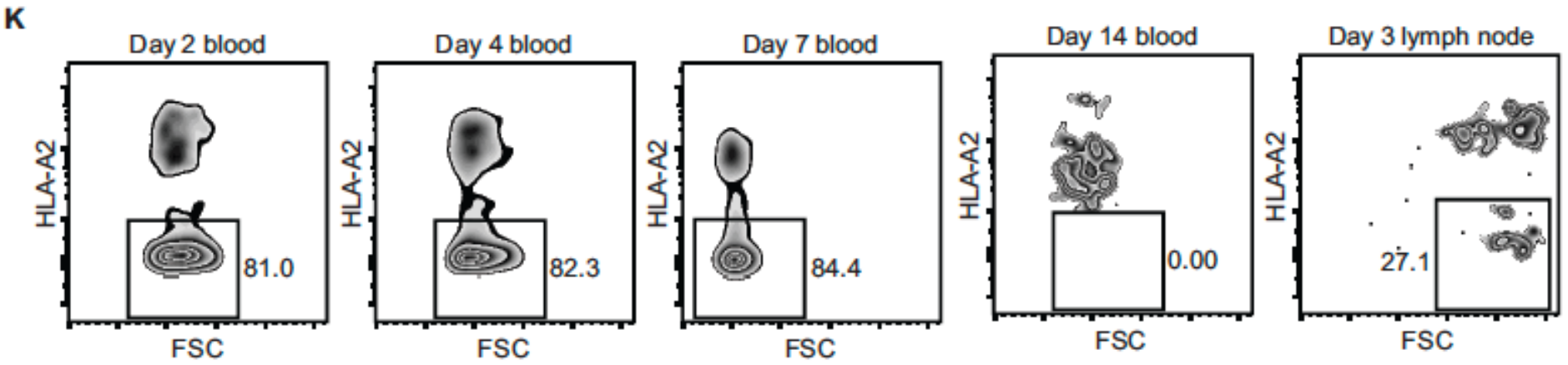
Disease Type and Duration of Response For the R/R NHL



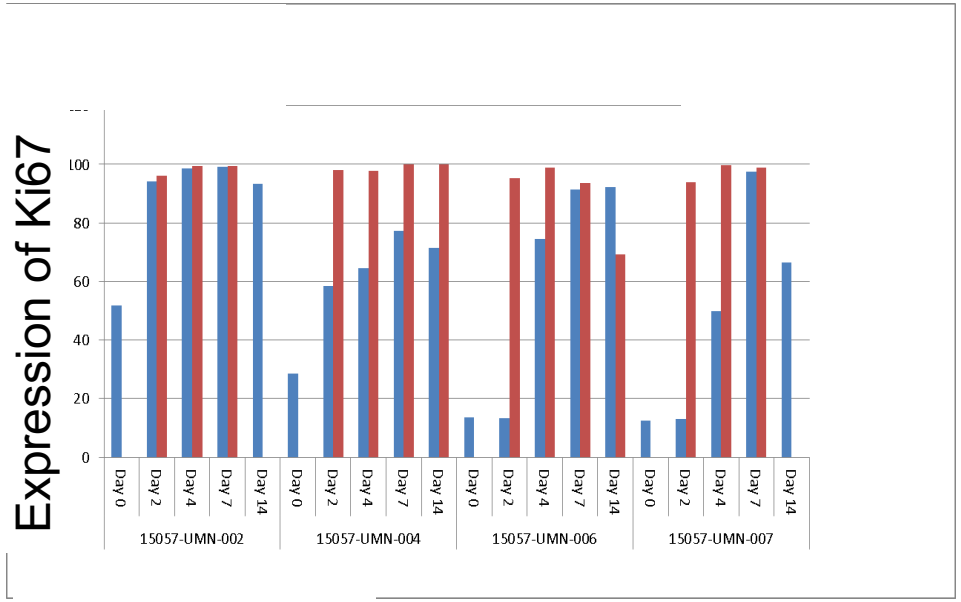
Donor NK cells (GDA-201) detection in blood and lymph nodes

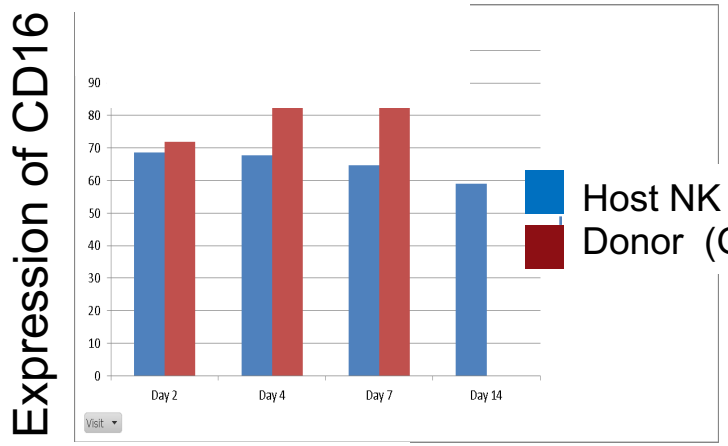
Day 7 NK absolute count:
96.54 (39 - 151)]

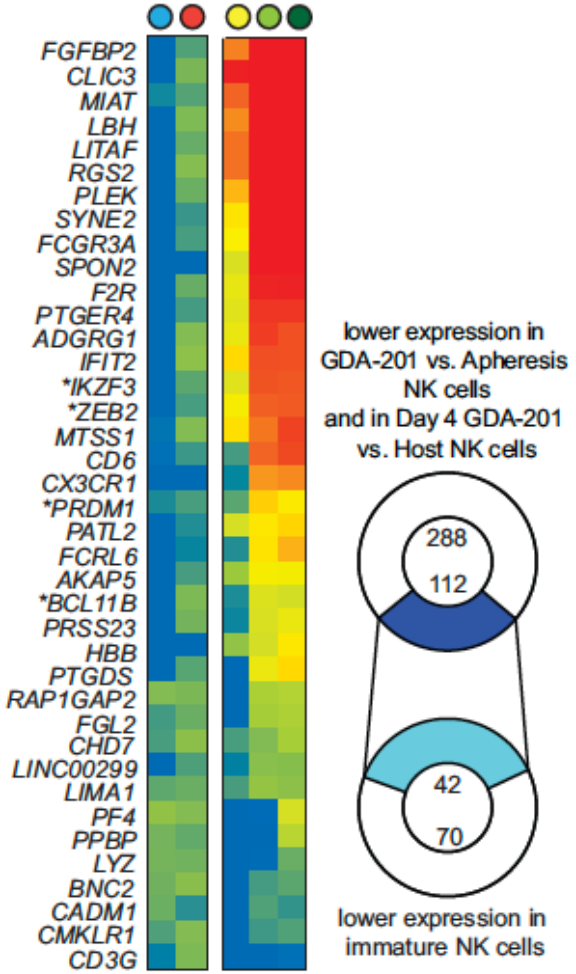


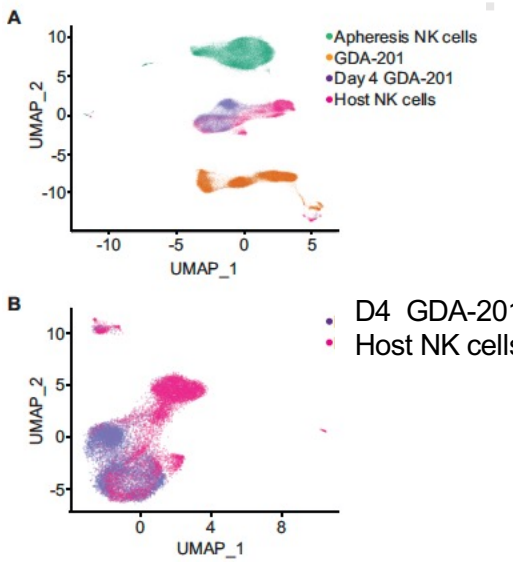


GDA-201 cells proliferate in blood and maintain gene expression profile









CD56^{bright} NK cells
CD56^{dim}CD94^{high} NK cells
CD56^{dim}CD94^{low} NK cells
RNA-seq

GDA-201 vs. Apheresis NK cells
Day 4 GDA-201 vs. Host NK cells
scRNA-seq

Transcriptome profiling suggest maintained gene expression of GDA201 in vivo which resembles CD56bright NK cells

NK cells and T cells subsets in PB are more abundant in responders

Responders

Pre-LD

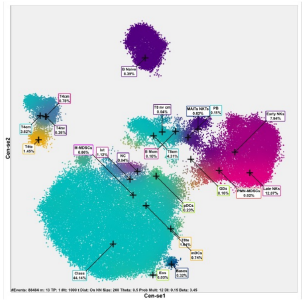
Day +7

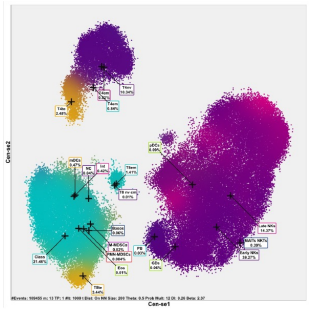
Non-responders

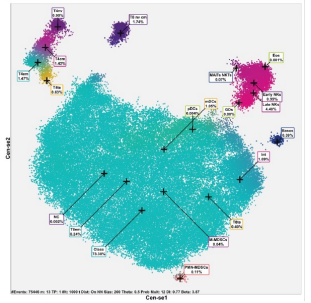
Pre-LD

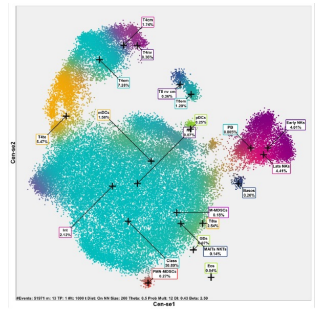
Day +7

Pt 026



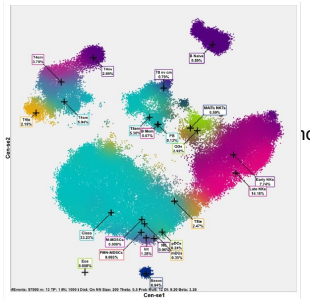


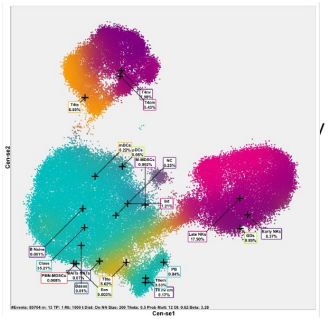


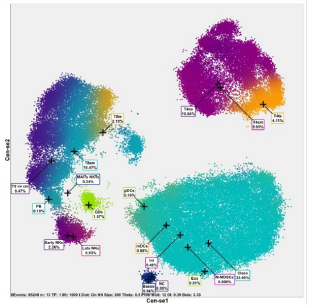


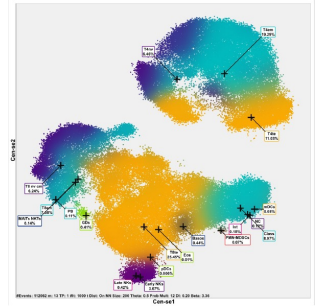
Pt 028

Pt 027





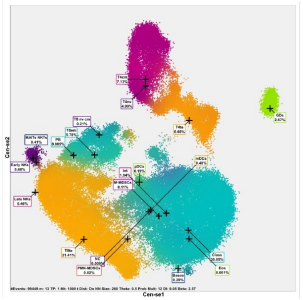


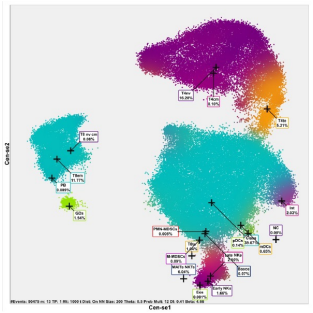


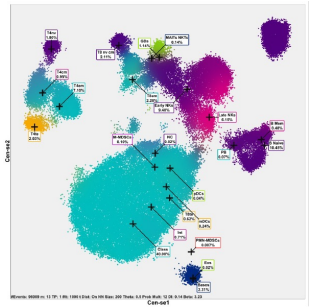
Pt 024

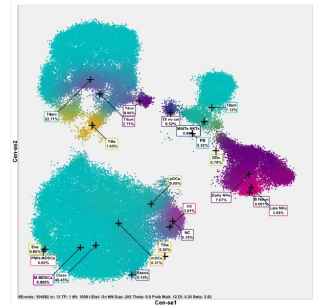
- monocytes
- CD4 CM
- NK
- T TE
- CD8 CM
- CD8 EM

Pt 002





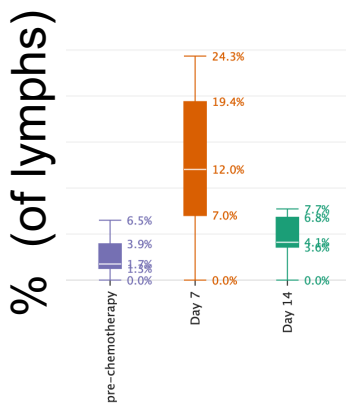




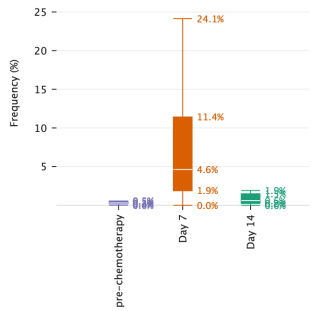
Pt 035

Transient host T cells (predominantly CD8 and Treg) proliferation in blood

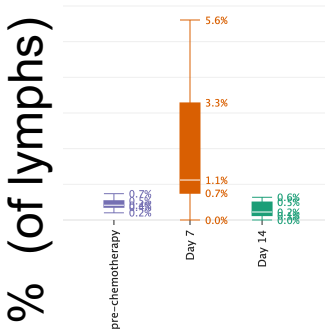
T regs Ki67 high



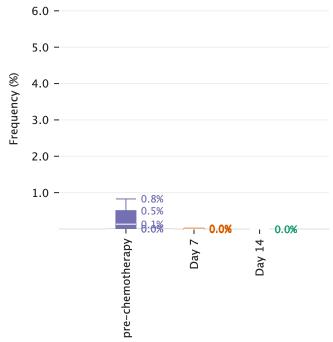
CD8 Ki67 high



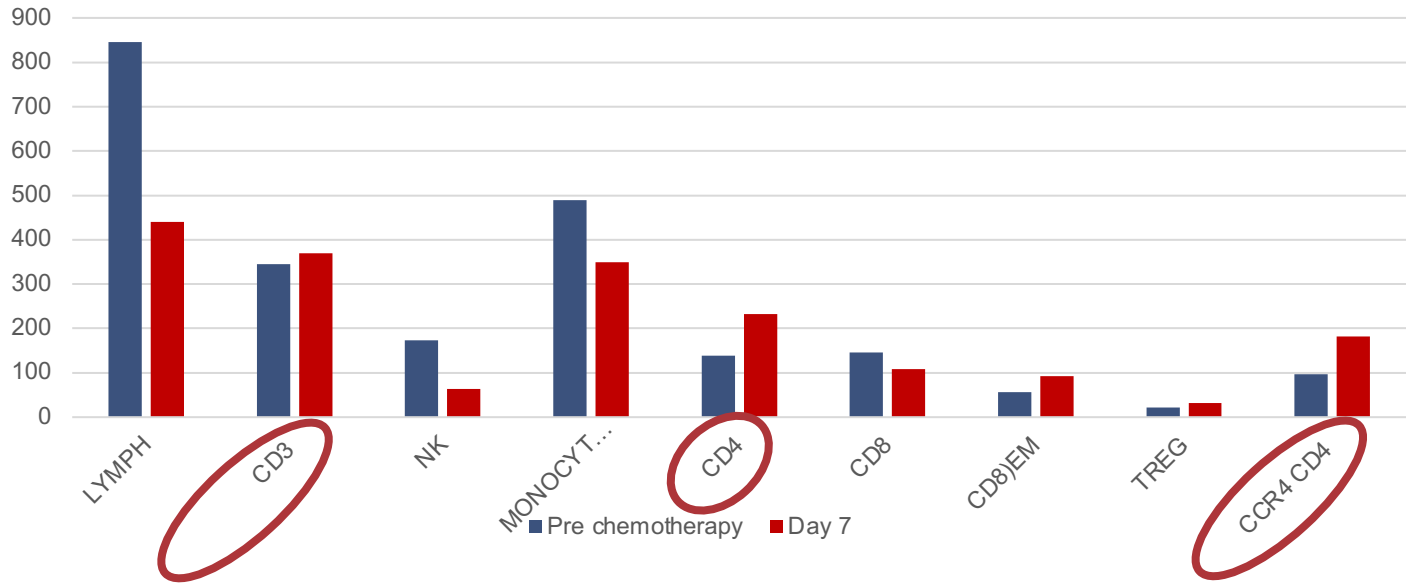
CD4 Ki67 high



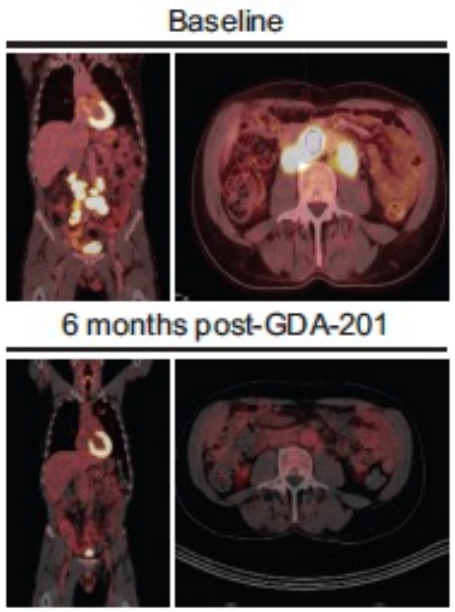
NKT Ki67 high



Absolute count (median) at day 7 in PB

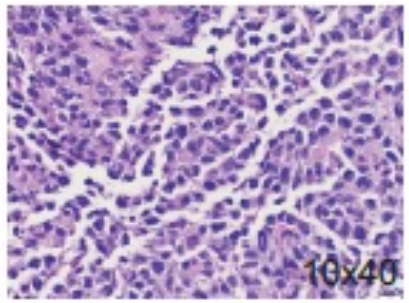


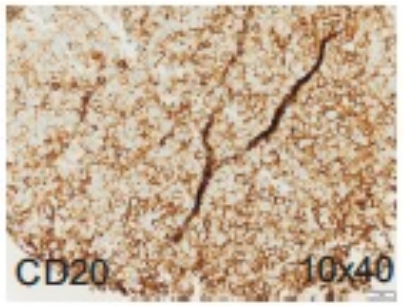
Pre and Post-treatment lymph node biopsy (LBCL)

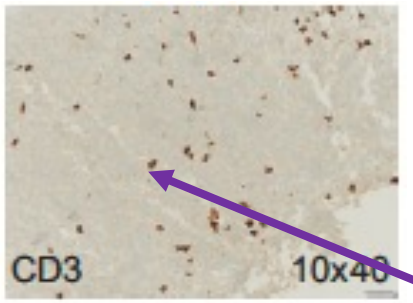


Native stain | CD20 Lymphoma | CD3 T cells

Pre-treatment lymph node biopsy

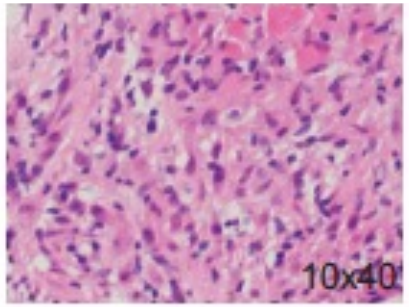


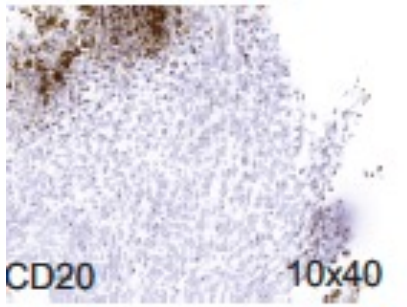


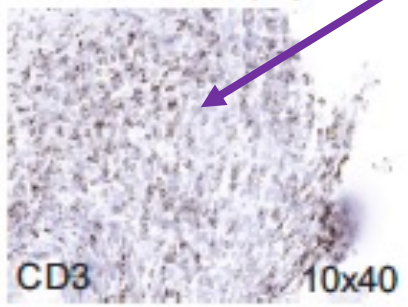


T cells

Day 16 post GDA-201 infusion biopsy

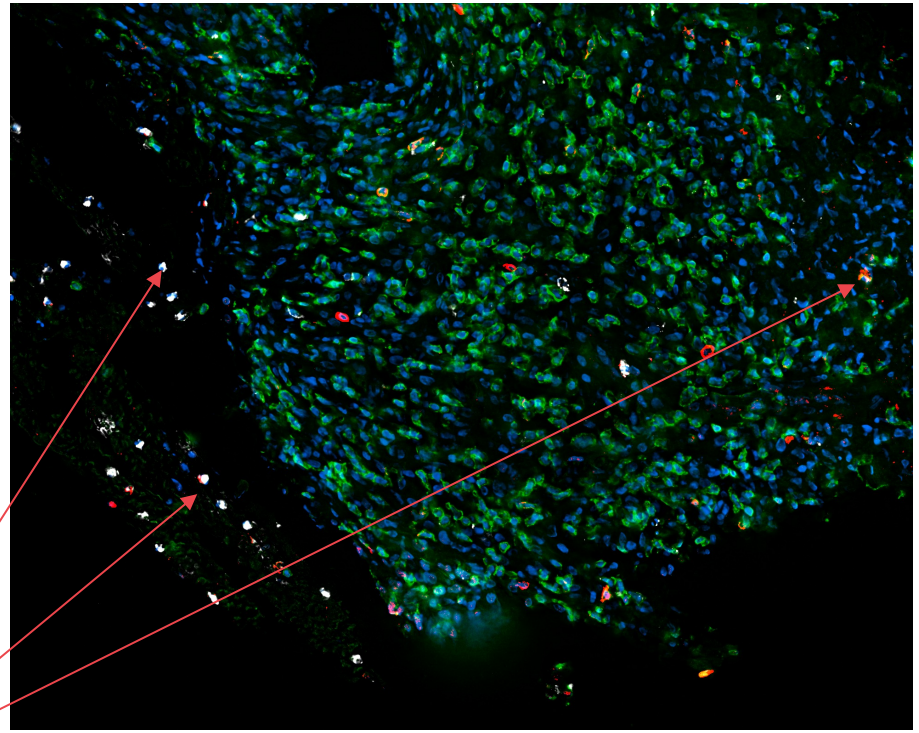






Tumor tissues after GDA-201 lack lymphoma B-cells and harbor dense T cell infiltrate and scattered granzyme+ NK cells

Day 16 post-NK cell infusion
lymph node biopsy



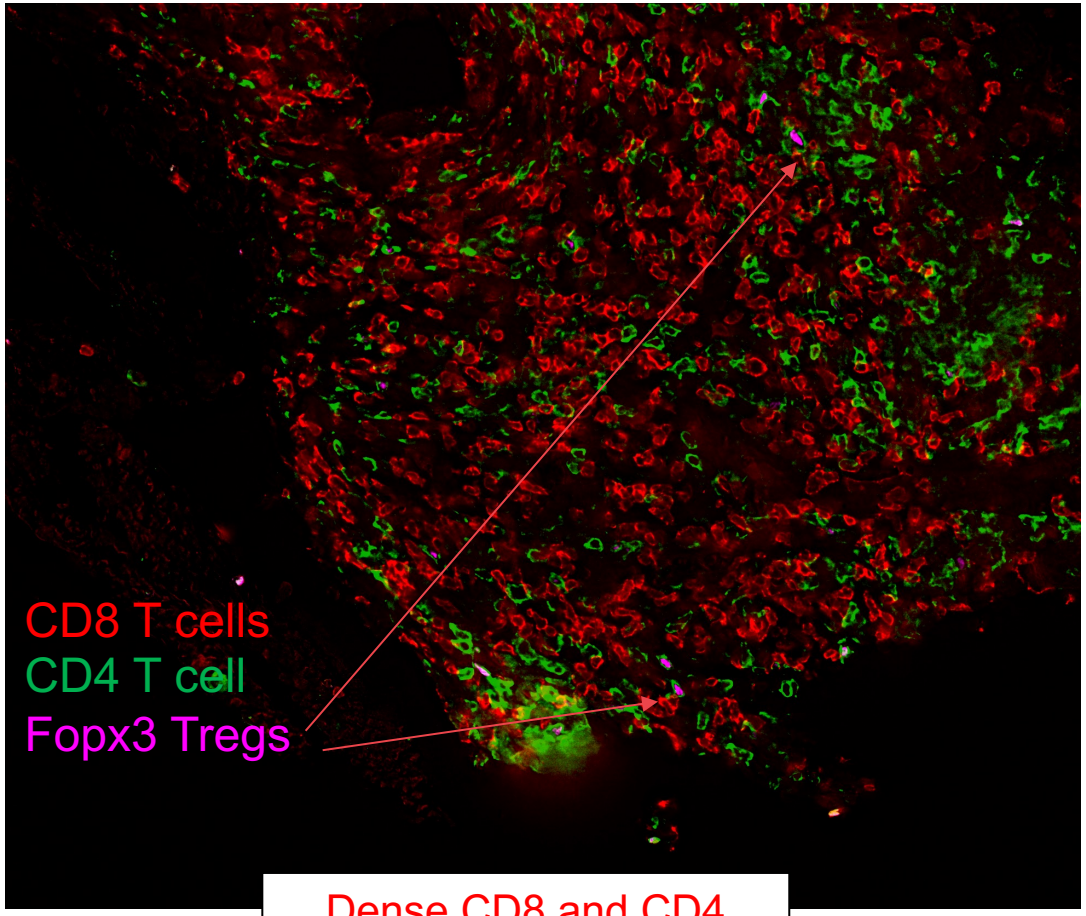
No viable lymphoma left,
B cell markers: CD19, CD20,
PAX5 are <u>all negative</u>

NK cells

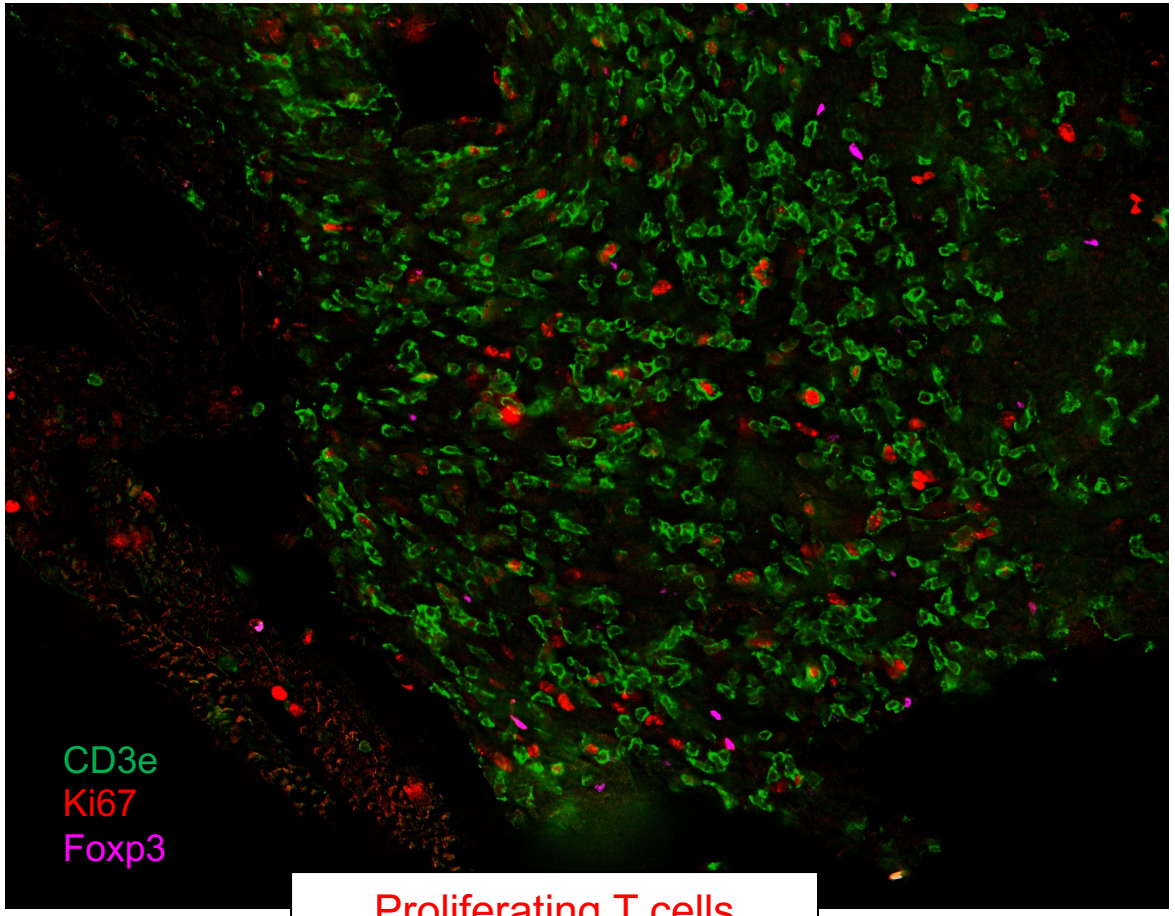
CD56 NK cells
Granzyme B (NK cells; white)
CD3 (T cells)

Grzywacz B,
unpublished

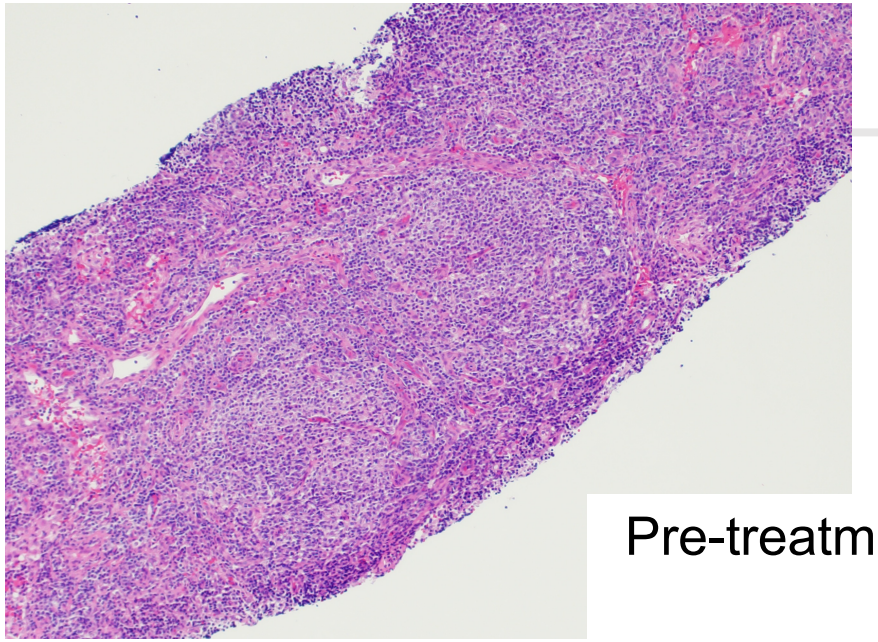
Tumor tissue after GDA-201 harbors dense CD8 and CD4 cell infiltrate



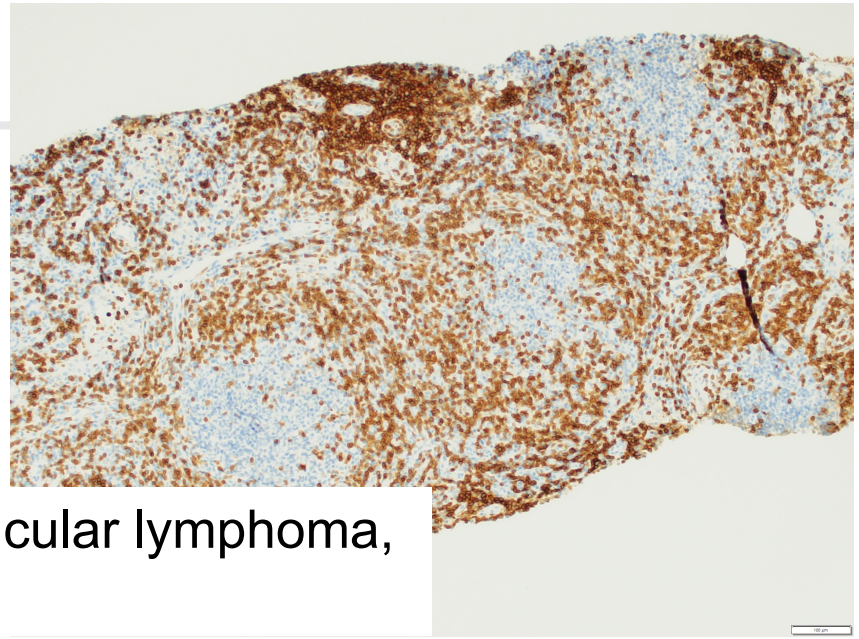
Dense CD8 and CD4 inhiltrate



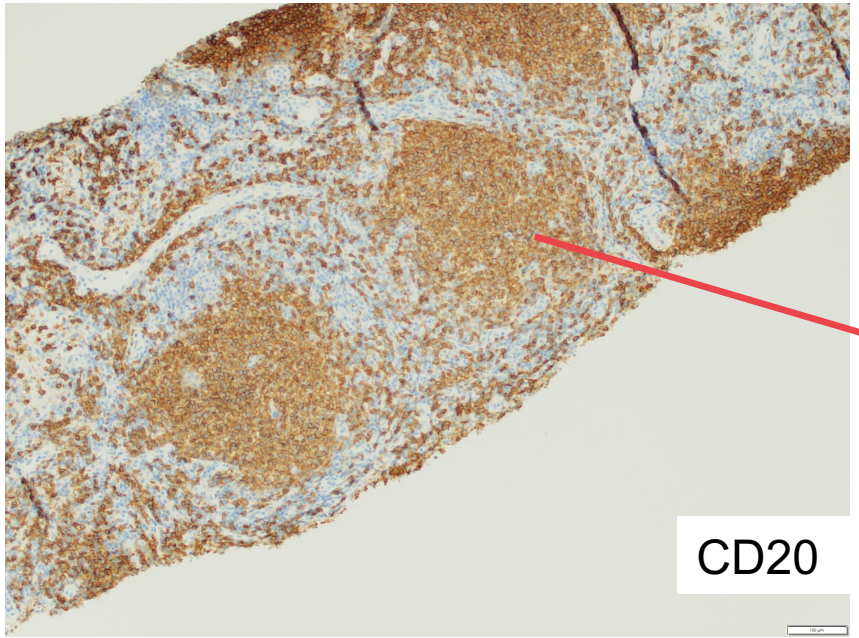
Proliferating T cells in lymph node



Pre-treatment biopsy shows follicular lymphoma, low grade

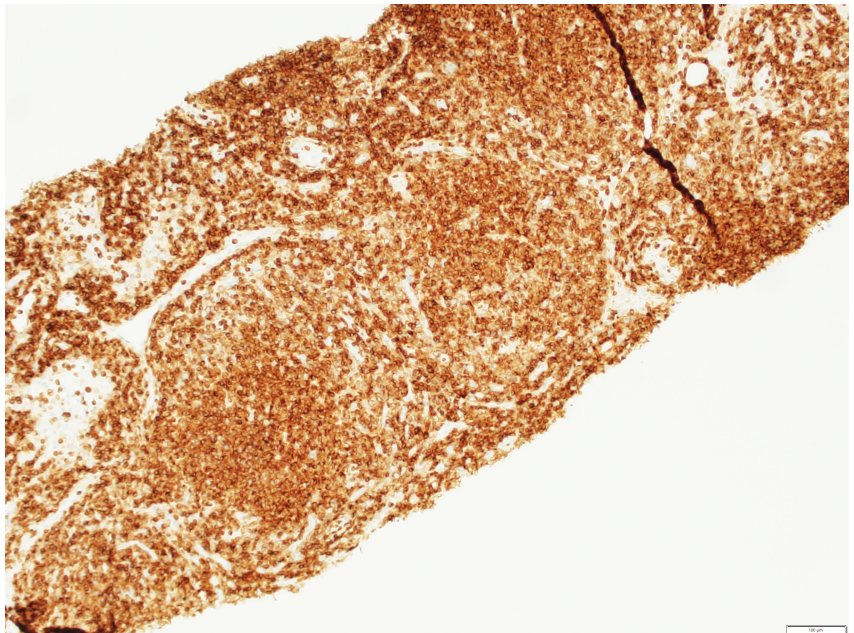


CD3



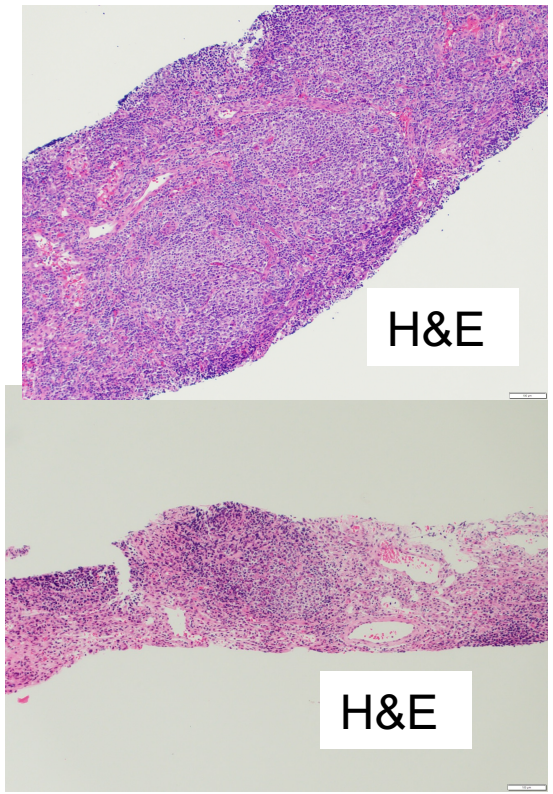
B-tumor cells

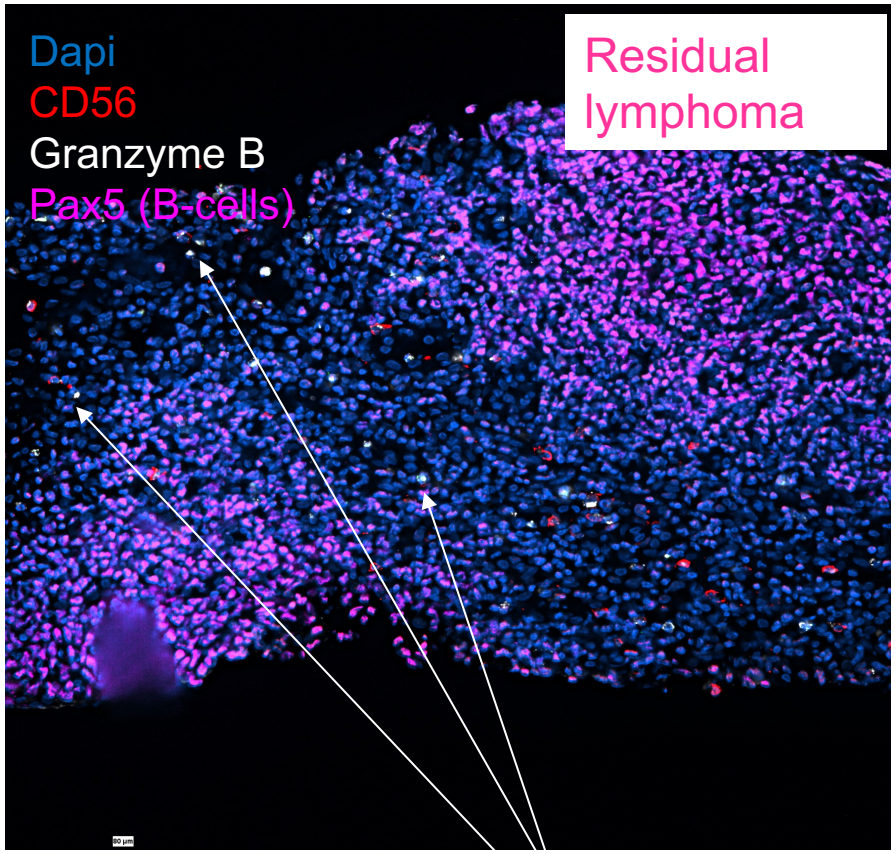
CD20

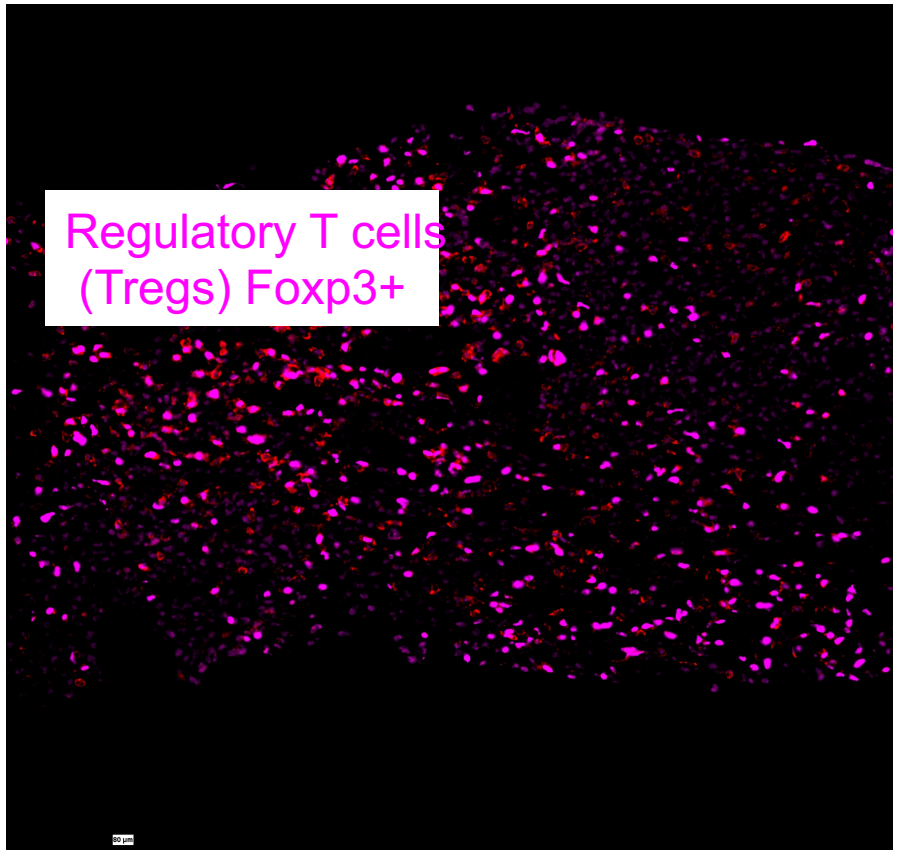


BCL2

Follicular lymphoma tissue (responder): day +3 post infusion shows residual lymphoma, increased NK cells and CD8 T cells and persistence of Tregs

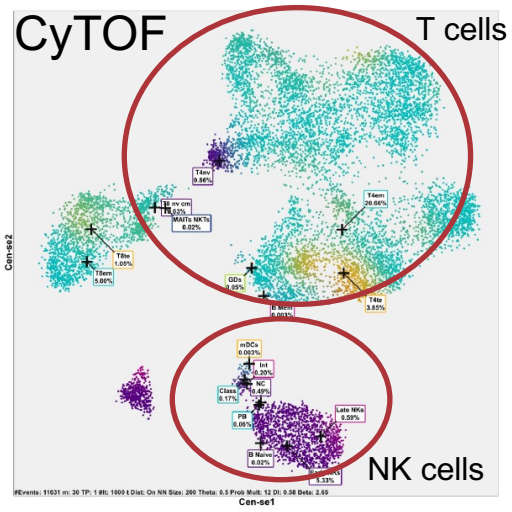






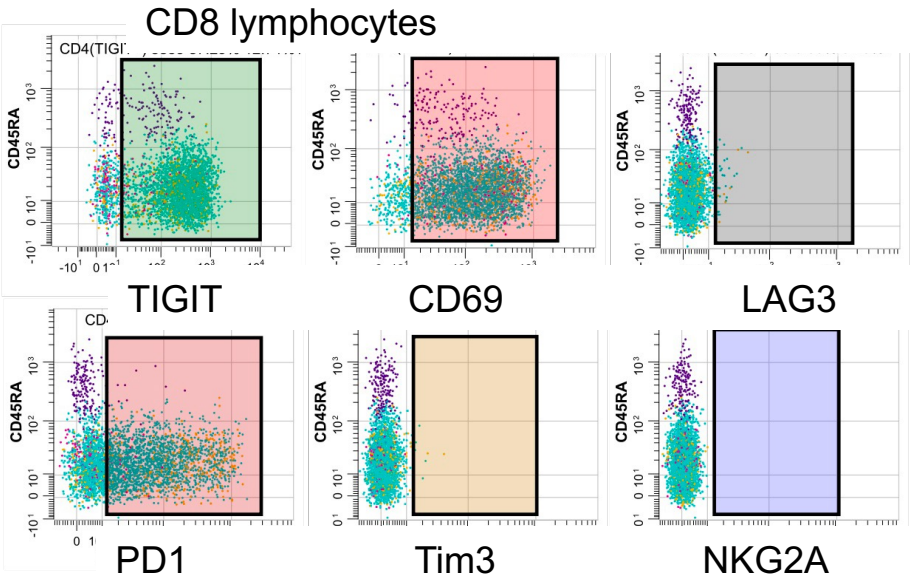
NK cells

Lymph node cell composition analysis from responders



	Pt 026 (day +16)	Pt 009 (day +3)
Dg	LBCL	FL
T cells	**78% (lymph)**	**62% (lymph)**
NK cells	**10%**	**13%**
CD8	35%	97%
-Eff Mem	73%	1%
-Term Eff	25%	98%
-Cen M	1%	1%
CD4	63%	3%
-EM	80%	32%
-TE	11%	41%
-Naïve	4%	0%
Treg	23%	10%
B cells	5%	0%

	CD8 (%)	CD4 (%)
CXCR3	**75**	**52**
CXCR5	3	27
CCR4	**36**	**61**
CCR6	7	10
CCR7	3.5	2.6



Tumor infiltrating T cells are predominantly characterized by:

- Terminal Effector or Effector Memory phenotype and activation (↑ HLA-DR, CD69)
- ↑ expression of suppressive receptors (TIGIT, PD1)
- Expression of chemokine receptors CXCR3 and CCR4 is increased on CD8 and CD4 in both tissue and blood compartments

Conclusions

- Spatial analysis of “on treatment” tumor biopsies suggests NK cells trafficking to tumor microenvironment (10-15 % of all cells)
- T cells were the predominant population infiltrating tumor sites with variable proportion between 60-80% of cellularity
-
- Both CD8 and CD4 subsets have been detected, including CD4+CD25+ regulatory T cells; predominance for CD3 TE and CD3 EM cells, however the variability in composition among patients was significant
- T cells in blood and tissues have increased expression of chemokine CXCR3 and CCR4
- Overall, data support a model in which adoptive NK cell infusion and cytokines enhance immune microenvironment changes which support the influx of host T cells. This occurs early post GDA-201 infusion concurrent with limited blood compartment persistence.
- Contribution of adaptive immunity in effective tumor elimination after NK cell therapy requires further study

Acknowledgments

Masonic Cancer Center
University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute

- Patients and their families
- University of Minnesota BMT and Cellular Therapy Program

BMT/CT Program at University of Minnesota
Jeffrey Miller-director
Mark Juckett
Joseph Maakaron
Daniel Weisdorf
Shernan Holtan
Najla El Jurdi
Brian Betts
Roy Kao
Daniel O'Leary
Veronika Bachanova

Lymphoma/Myeloma Program:
Maire Hu
Sanjal Desai
Aimee Merino
Sean Tracy
Jeremy Allread

MCT Facility
David McKenna

Clinical Trial Office
Ashley Lyle

Pathology Division UM

gamida cell

NIH

American Society of Hematology

Marrow on the Move