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Single Cell Profiling Reveals a CD8$^+$ Continuum and Adaptive T Cell Plasticity in Response to PD-1 Blockade-based Therapy in Acute Myeloid Leukemia

Hussein A. Abbas, Dapeng Hao, Katarzyna Tomczak, Praveen Barrodia, Jin Seon Im, Patrick K. Reville, Zoe Alaniz, Wei Wang, Ruiping Wang, Feng Wang, Gheath Al-Atrash, Koichi Takahashi, Jing Ning, Maomao Ding, Jairo T. Matthews, Latasha Little, Jianhua Zhang, Sreyashi Basu, Marina Konopleva, Guillermo Garcia-Manero, Michael R. Green, Padmanee Sharma, James P. Allison, Steven M. Kornblau, Kunal Rai, Linghua Wang, Naval Daver and Andrew Futreal

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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Disclosure Information

I have no financial relationships to disclose.

Relapsed/Refractory (R/R) AML Patients Have Poor Prognosis

- 30-40% of AML patients fail to achieve remission with induction chemotherapy; 50-70% of patients who achieve remission will eventually relapse

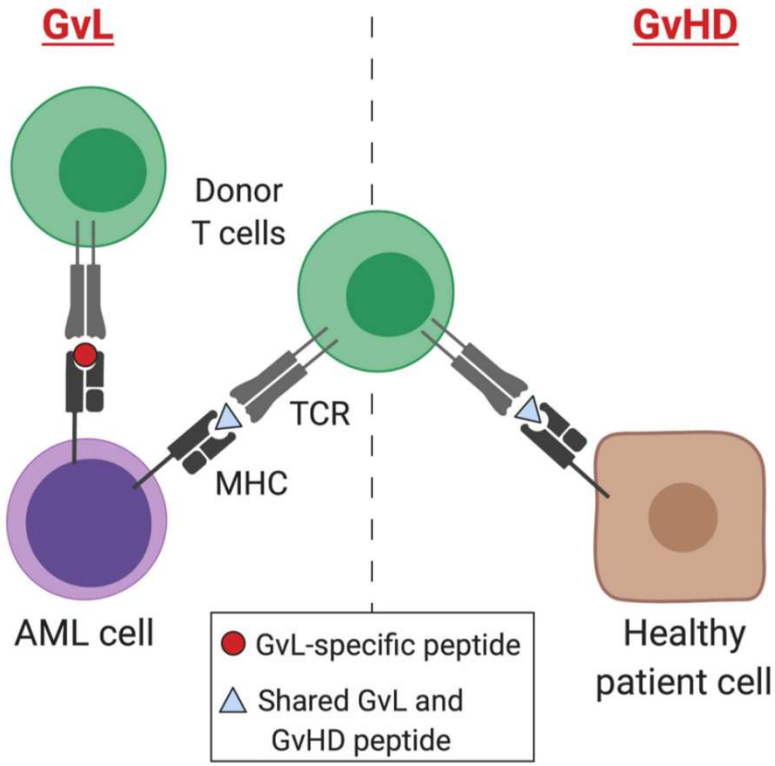
- Hypomethylating agents (HMA) based therapy has an overall response rate of 15-20% and median OS of 6 months in R/R AML[1]

- Increased PD1/PDL1 expression during AML progression is an independent adverse prognostic factor[2,3]

- AML proliferate in an immune-rich microenvironment with complex interaction with its immune milieu

[1]Stahl et al Blood Adv 2018; [2]Schnorfeil et al J of Hem & Onc 2015; [3]Chen et al Cancer Biology & Therapy; 2014

Allogeneic Stem cell Transplantation Cures AML via T cell-mediated antileukemic Effect



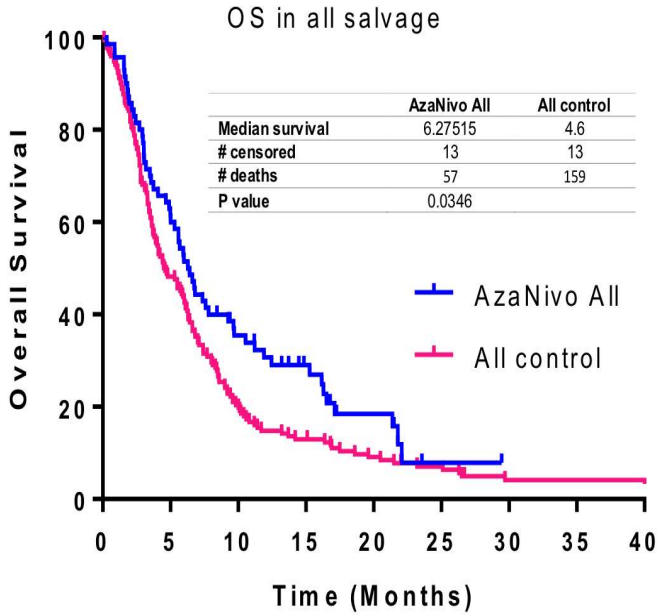
- R/R AML patients are frail and older
- Significant transplantation-related morbidities
- Not all patients are candidates due to cost, age, lack of donors, among other reasons
- ***How can we empower the immune system to eradicate leukemia?***

Sweeney et al Front Onc 2019; Horowitz et al Blood 1990

HMA + nivolumab elicited improved OS compared to HMA-based therapy in R/R AML

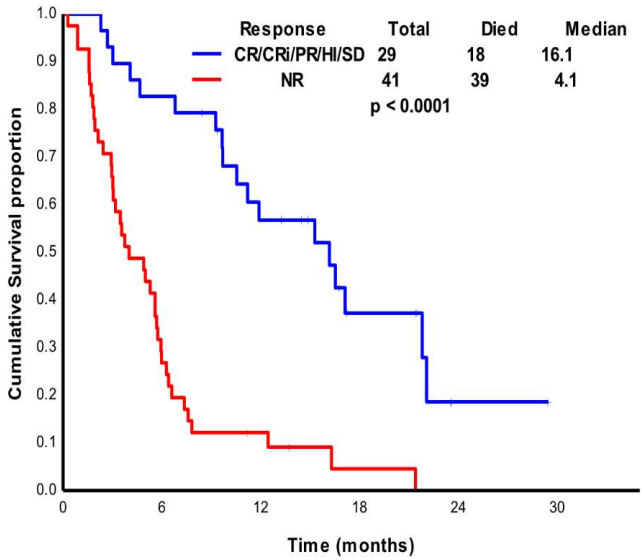
- 70 pts with R/R AML (median age 70 years); RR=33%

OS among all patients vs Aza-Based Control



	AzaNivo All	All control
Median survival	6.27515	4.6
# censored	13	13
# deaths	57	159
P value	0.0346	

OS by response vs no response to AZA+Nivo

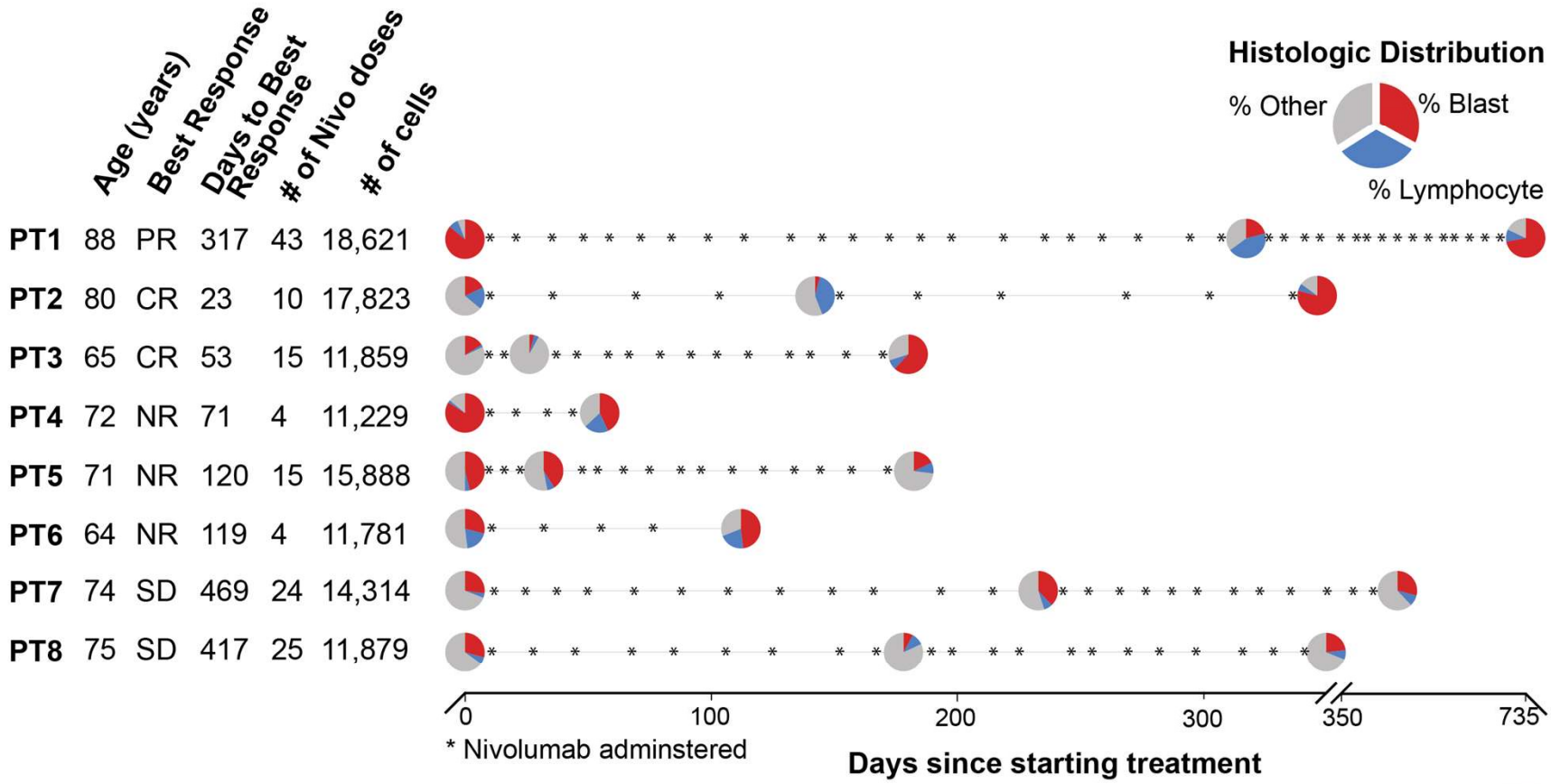


Daver N, et al. Cancer Discovery 2019

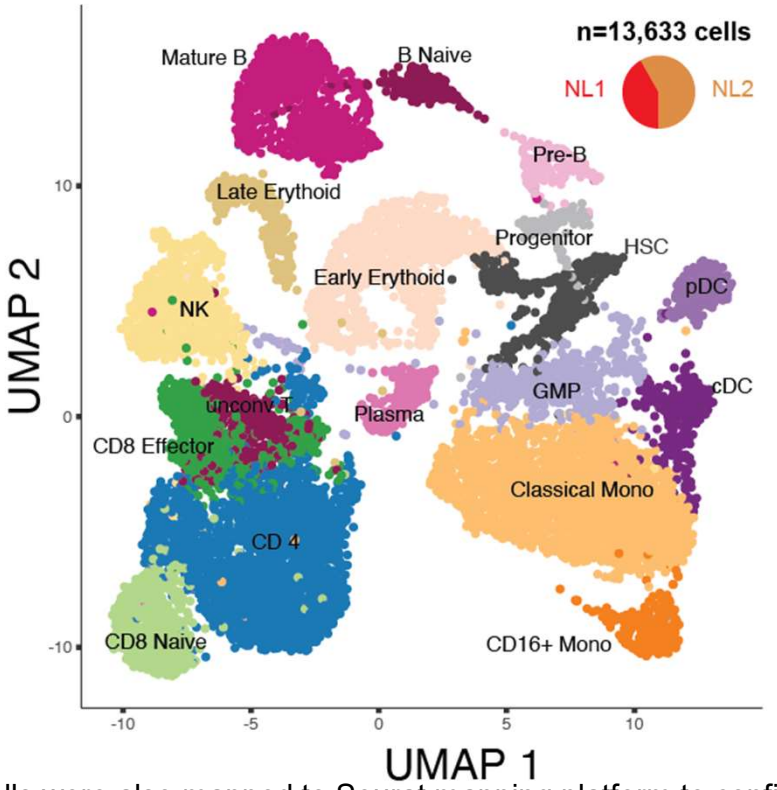
Key Questions

- Is the TCR repertoire augmented following PD-1 blockade therapy in AML similar to what is seen in solid cancers?
- What is the T cell landscape of AML before and after treatment with PD-1 blockade therapy?
- Are there distinct T cell subsets that are associated with responses or resistance?

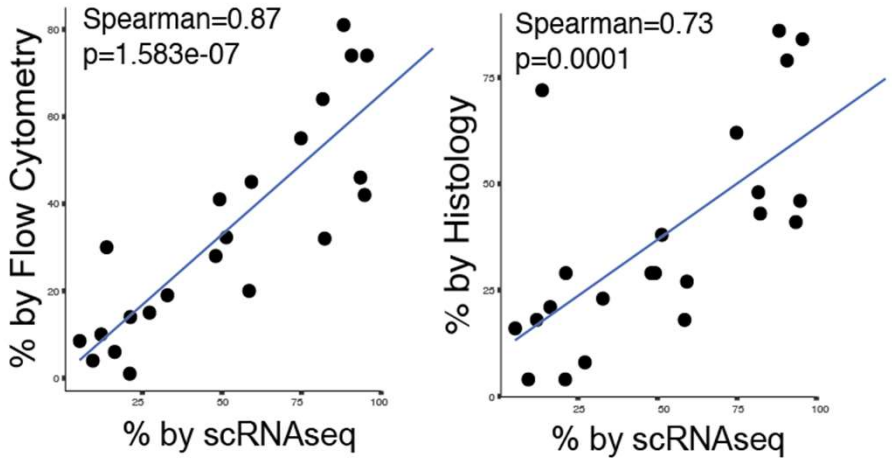
Study Design: Longitudinal scRNA and scTCR Assessment of T cells



Pseudotemporal Trajectory Analysis Recapitulates Normal Hematopoiesis in Healthy Donor BMs

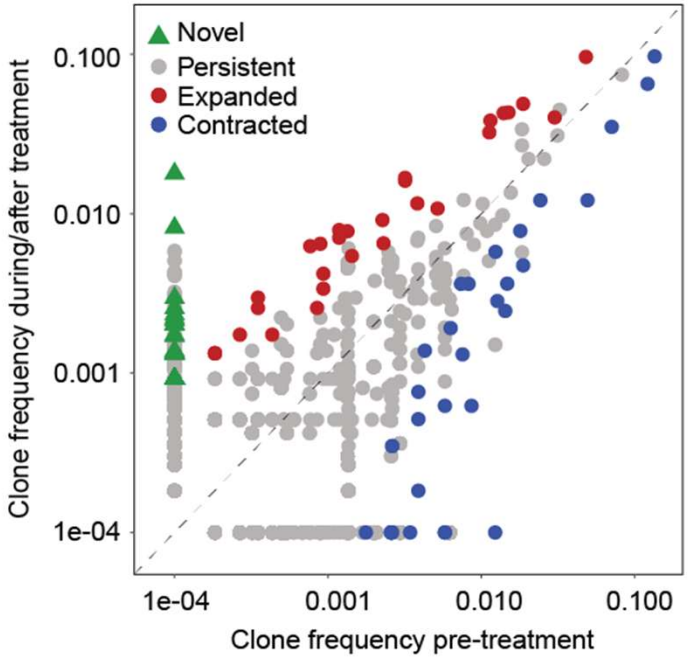


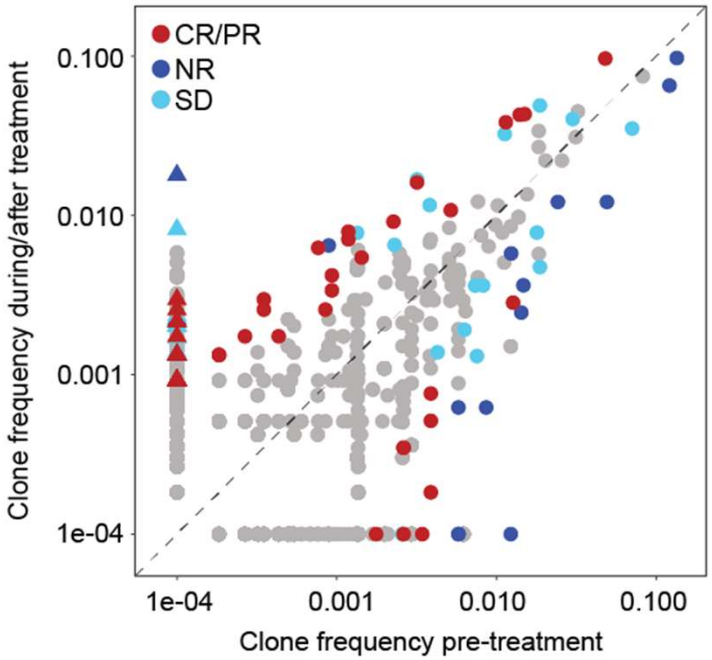
Correlation of AML Cell Number Identified with Flow Cytometry and Histopathology

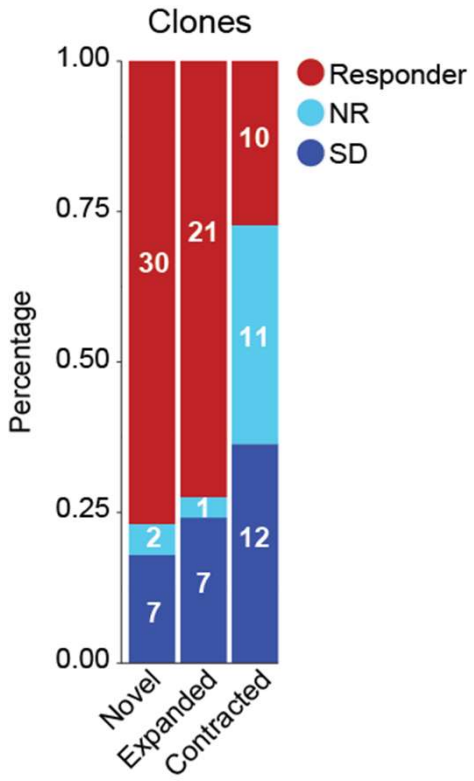


*All cells were also mapped to Seurat mapping platform to confirm annotation

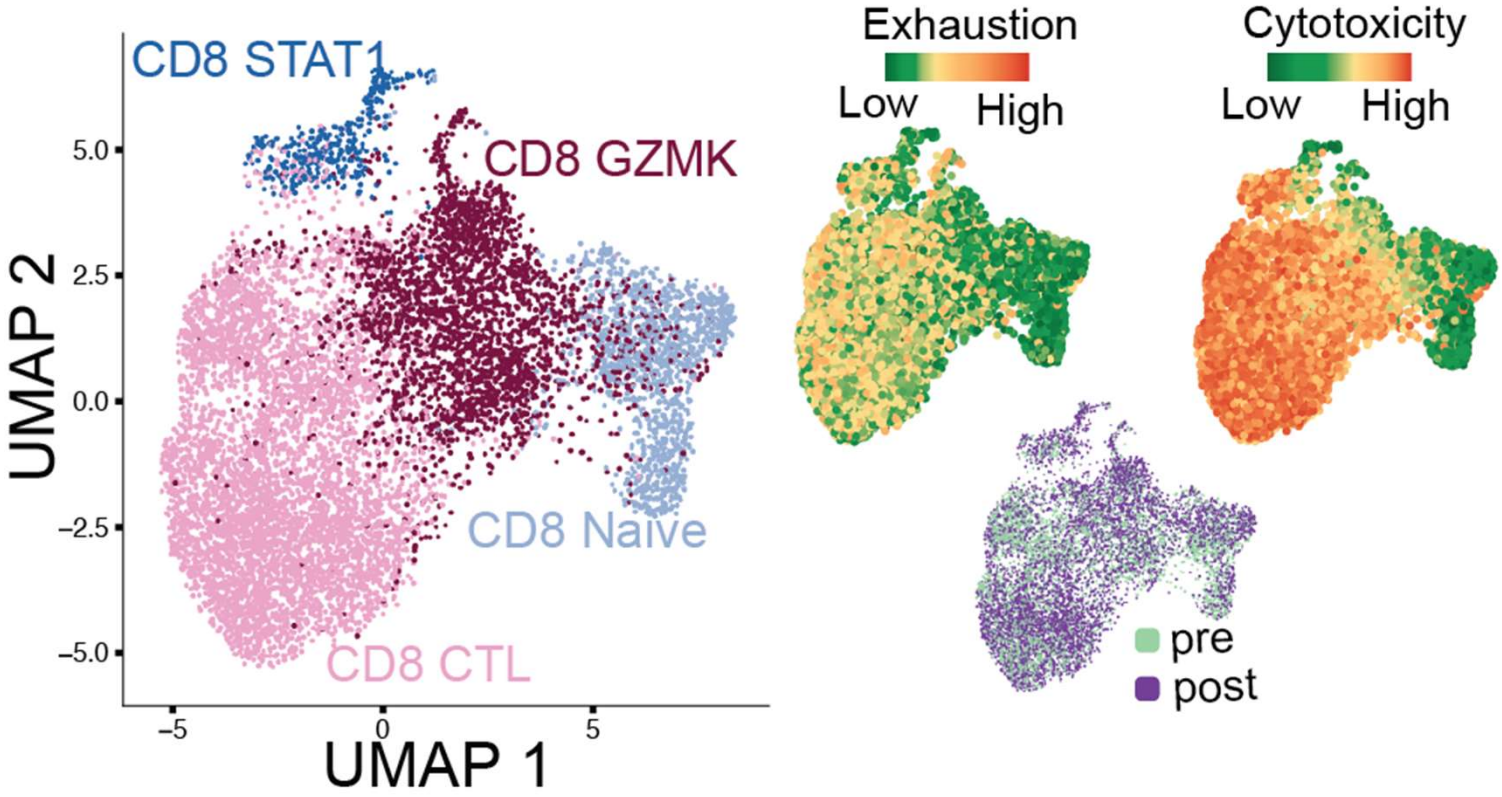
Augmented (novel and expanded) clonotypes in responders and stable disease patients, versus contracted clonotypes in non-responders





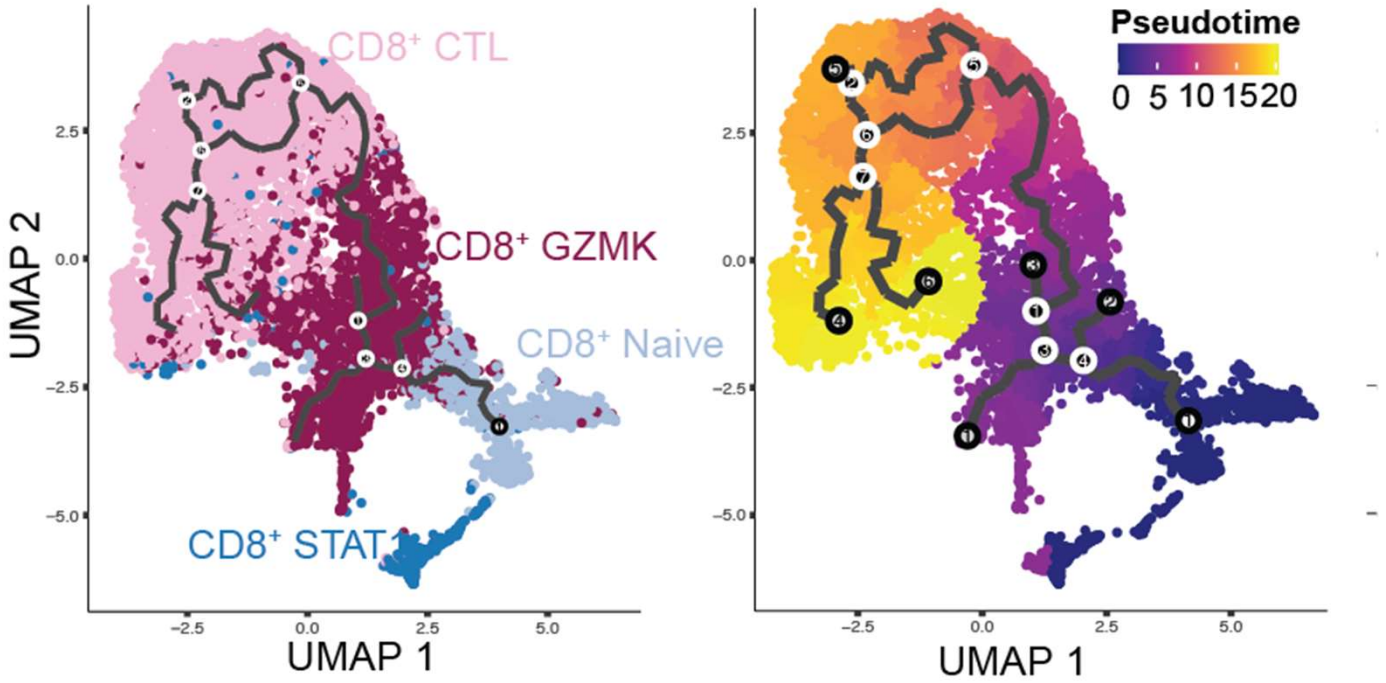


CD8+ T Cells Phenotypic Subsets

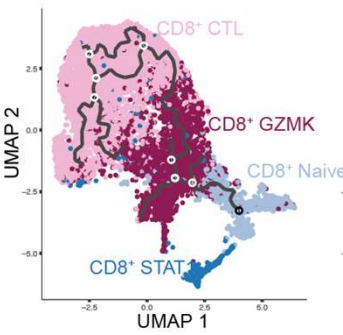


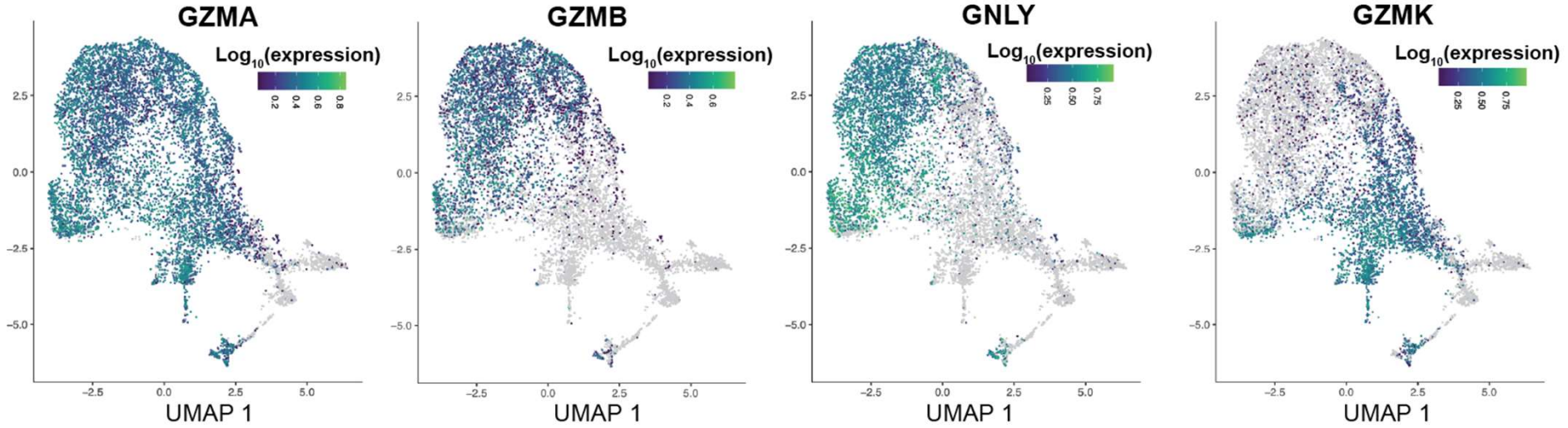
Hanzelmann et al BMC Bioinformatics 2013; van der Leun et al Nature Reviews Cancer 2020

Trajectory Analysis of CD8⁺ T Cells Define a Continuous Phenotypic Spectrum



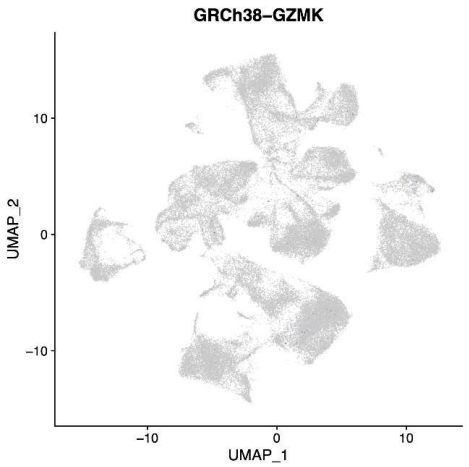
Differential Expression of Granzyme and Cytolytic Genes In CD8+ T Cells

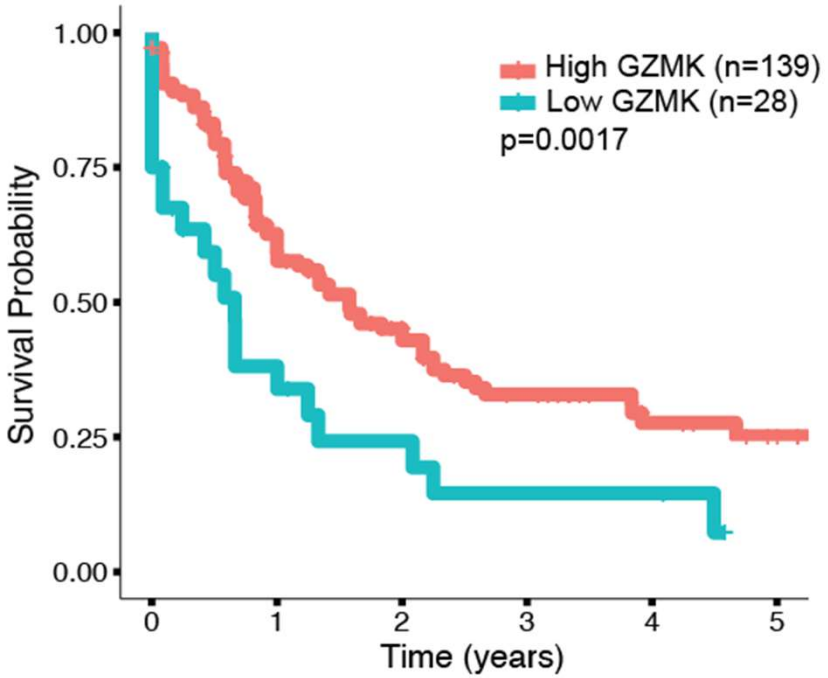




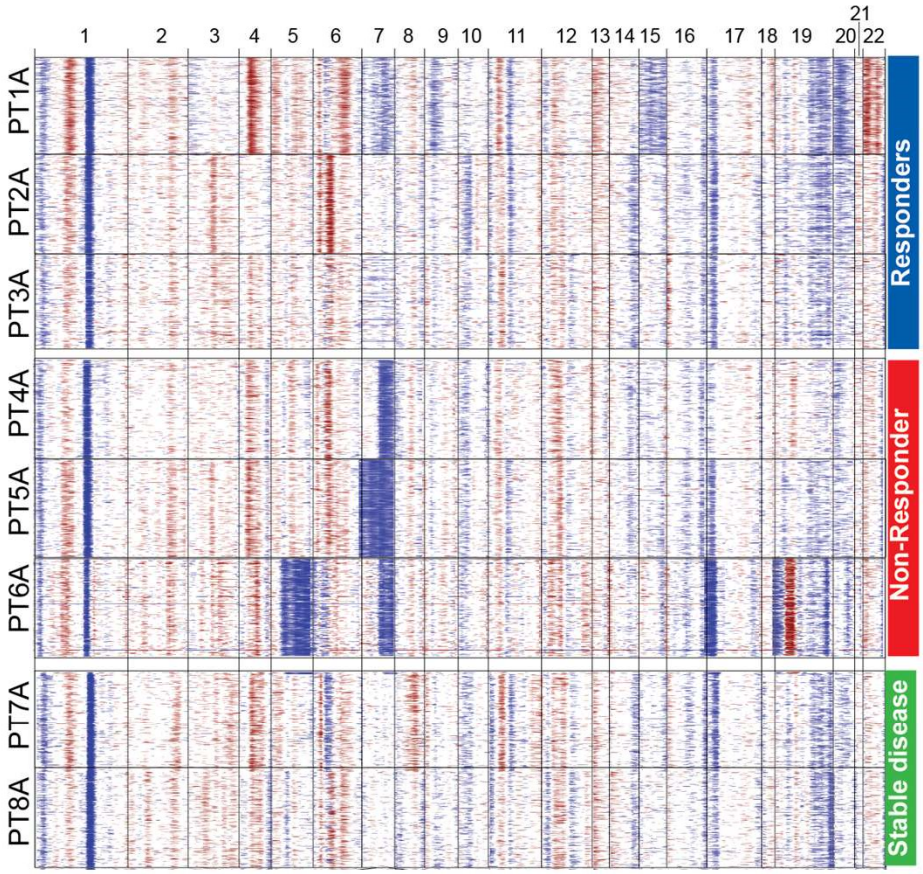
GZMK was expressed on immune cells only and associated with better outcomes in TCGA AML Cohort

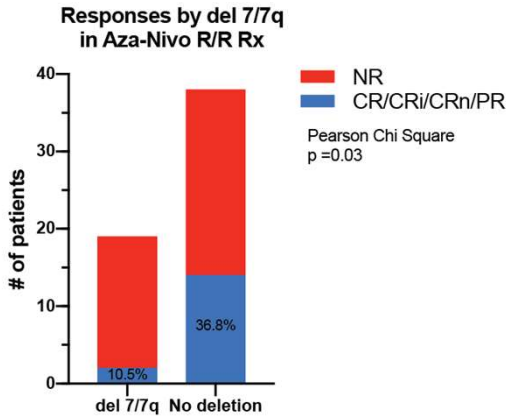
GZMK is not expressed in AML Cells

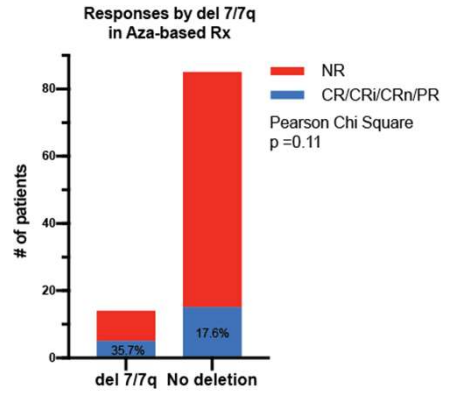




Are there genomic characteristics that are associated with response?







Conclusions

- Emergence of an adaptive T cell response (expanded and novel T cell clones) in response to PD-1 blockade therapy in AML
- Complex T cell components with significant interpatient heterogeneity
- GZMK is a marker of $CD8^+$ T cells that is associated with memory characteristics, and its expression is mutually exclusive with GZMB
- Chromosome 7/7q loss may be associated with resistance to checkpoint inhibitor based therapies in AML