Therapy-related myeloid neoplasms

Defining genetic characteristics

EHA-SWG Scientific Meeting on sAML
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Coleman Lindsley, MD, PhD
Associate Professor of Medicine
Director, Edward P. Evans Center for MDS
Dana-Farber Cancer Institute
https://lindsleylab.dana-farber.org

Dana-Farber Cancer Institute

Disclosures

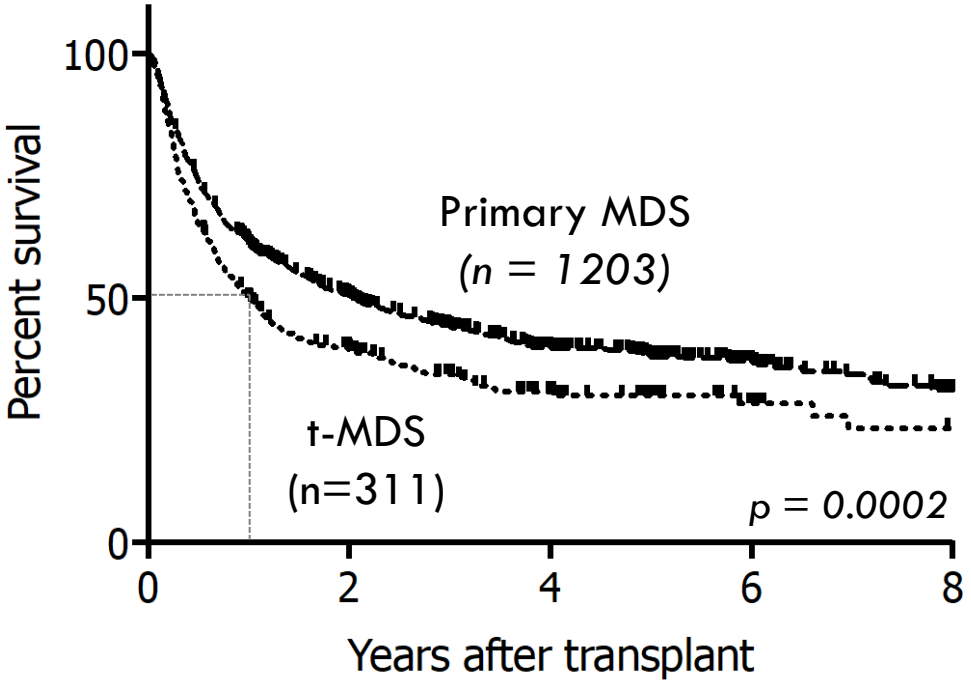
Qiagen
bluebird bio
Vertex Pharmaceuticals
Verve Therapeutics
Geron Corporation
Takeda Pharmaceuticals
Jazz Pharmaceuticals

Therapy-related Myeloid Neoplasms

Poor survival

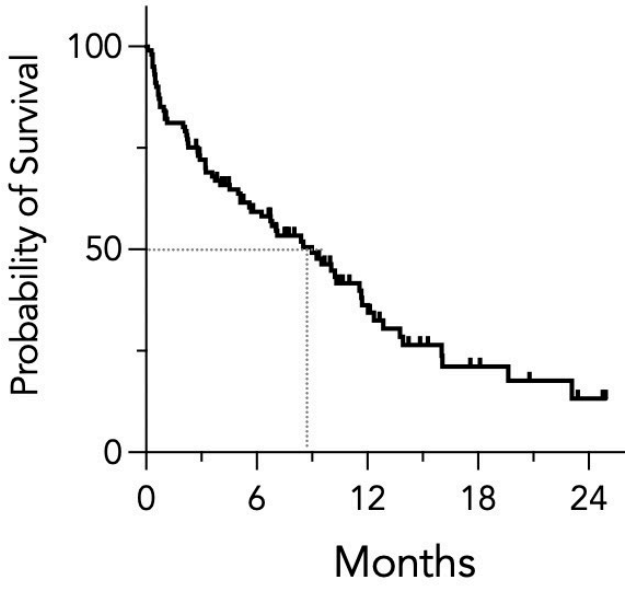
MDS

CIBMTR HCT

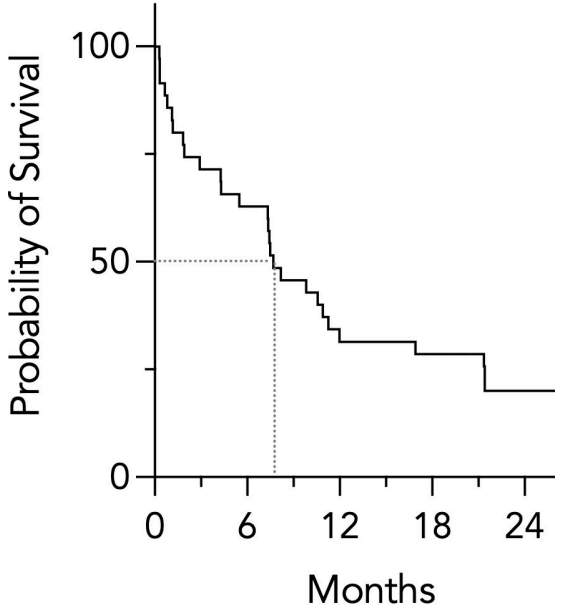


AML

Ph3 Amonafide

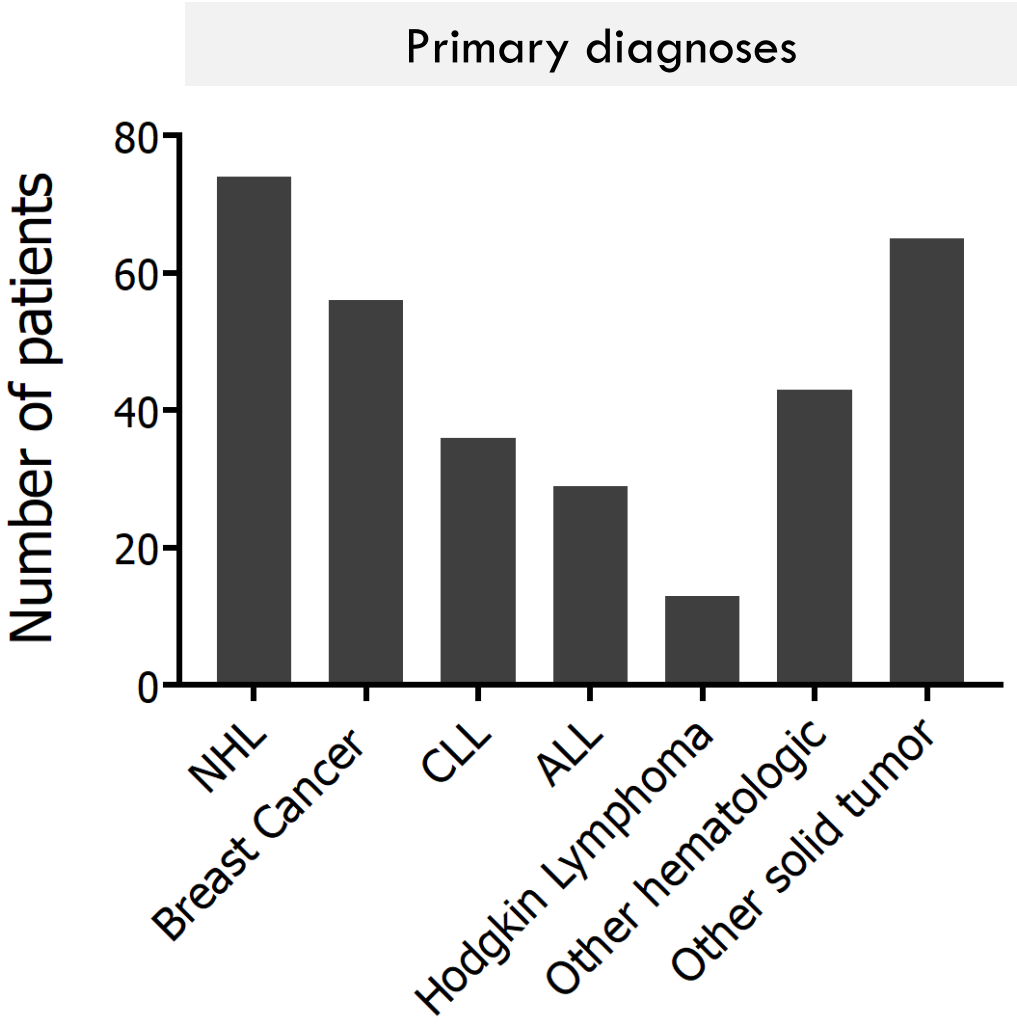


Ph3 CPX-351



Therapy-related Myeloid Neoplasms

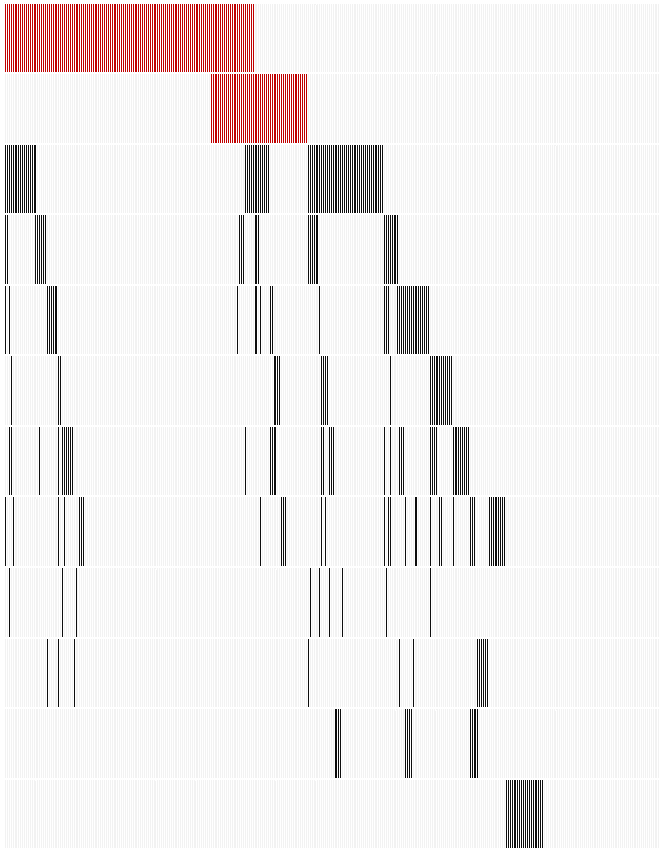
Clinical heterogeneity



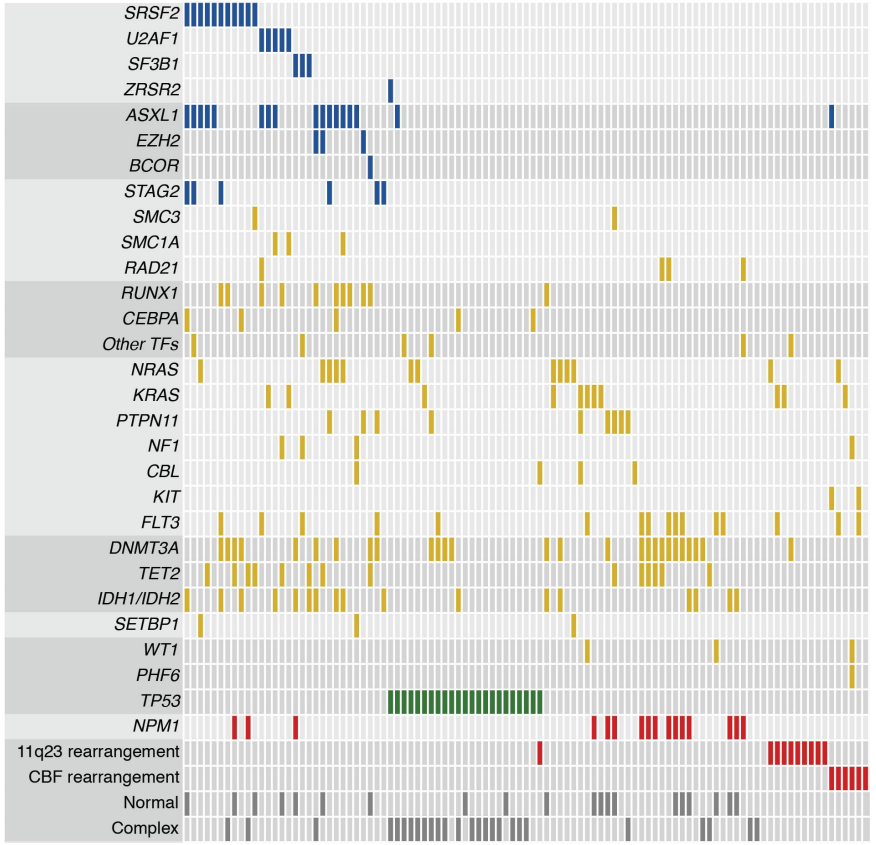
Therapy-related Myeloid Neoplasms

Genetic heterogeneity

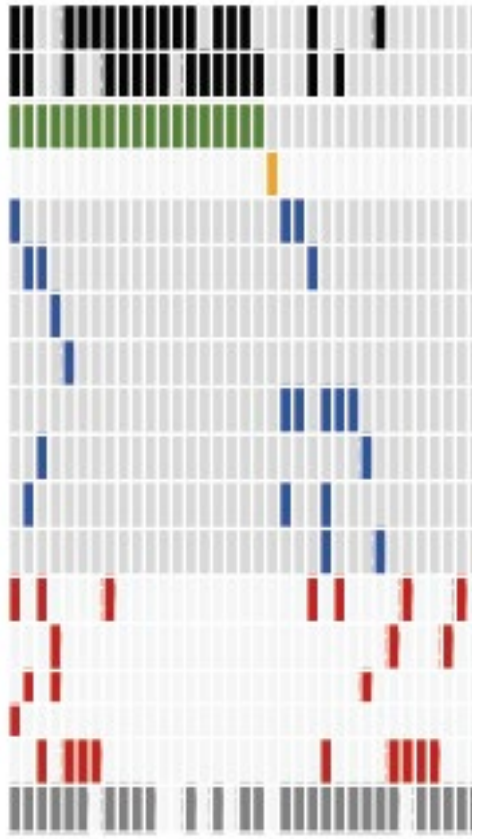
CIBMTR HCT



Ph3 Amonafide

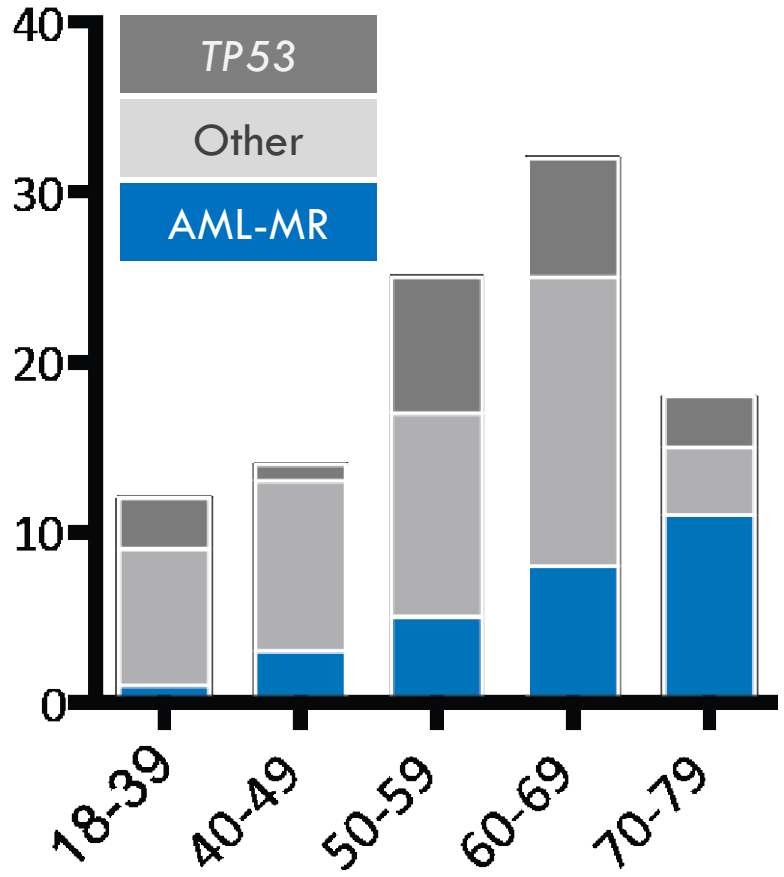


Ph3 CPX-351

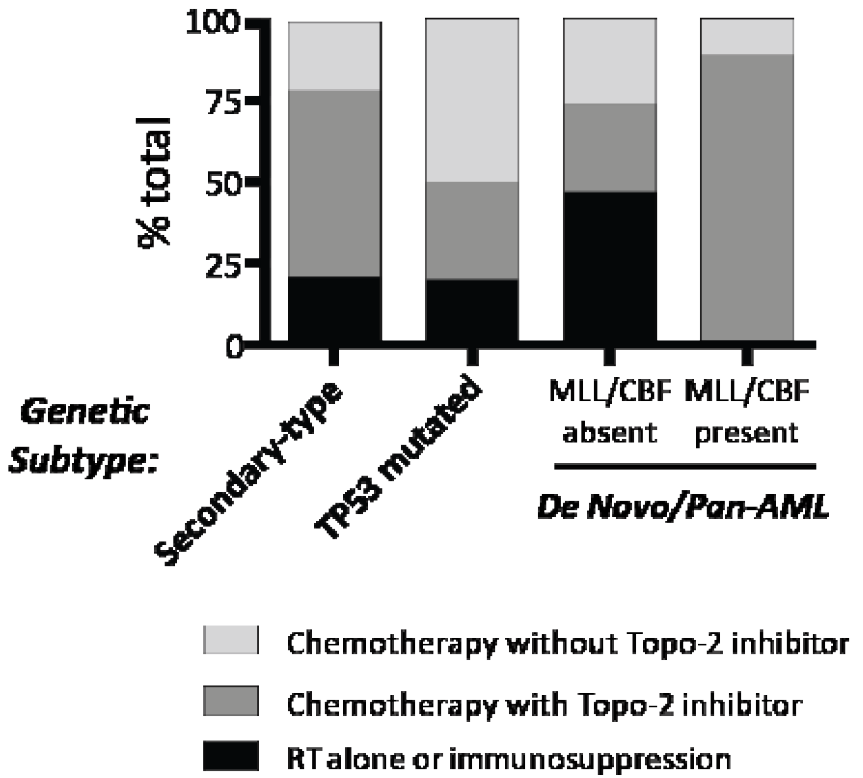


t-AML genetics depends on the population

Impact of Age

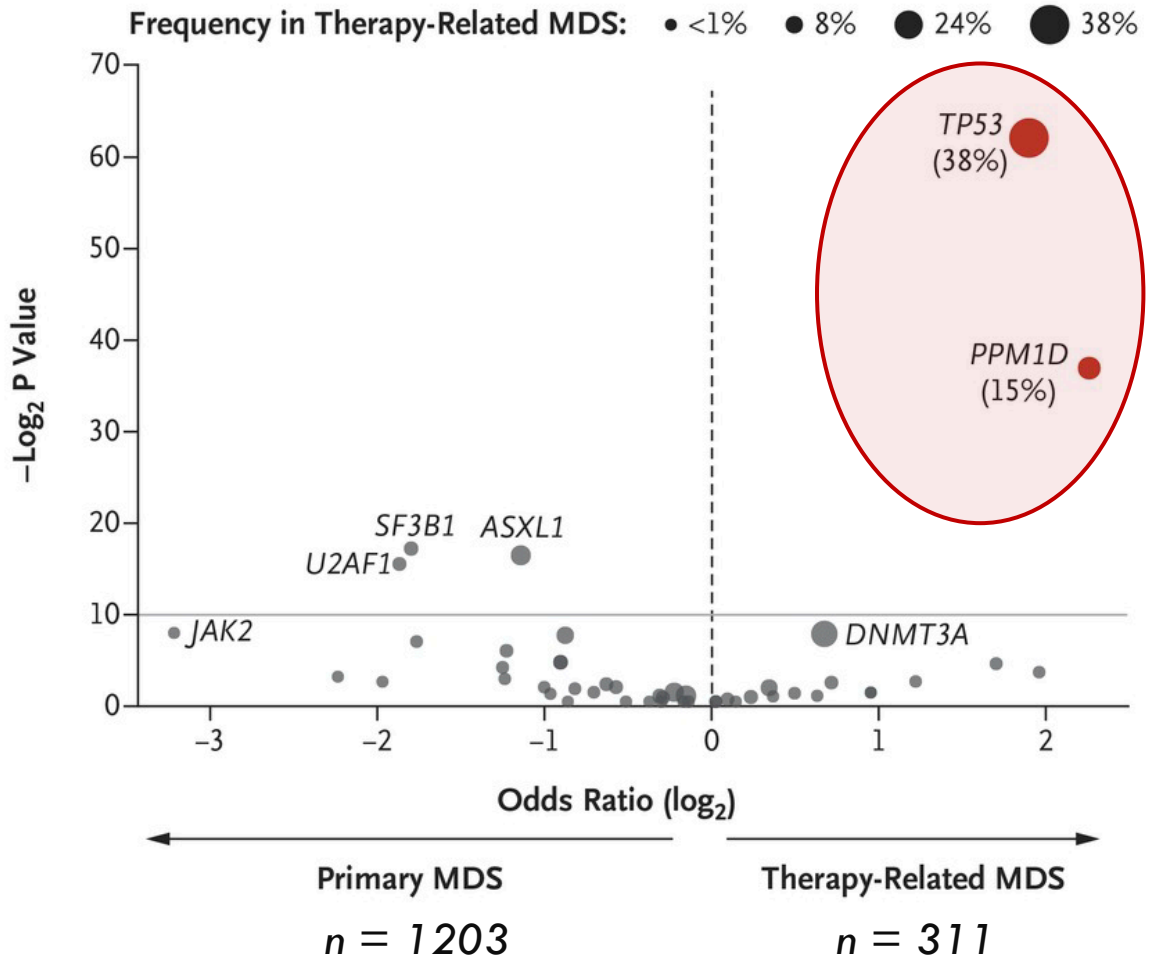


Impact of Exposure

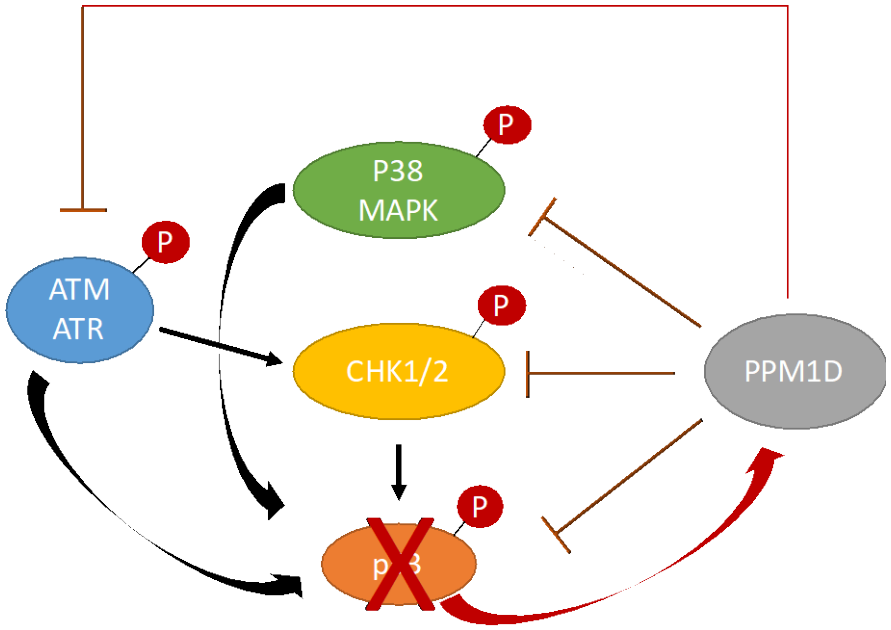


What's different about t-MNs?

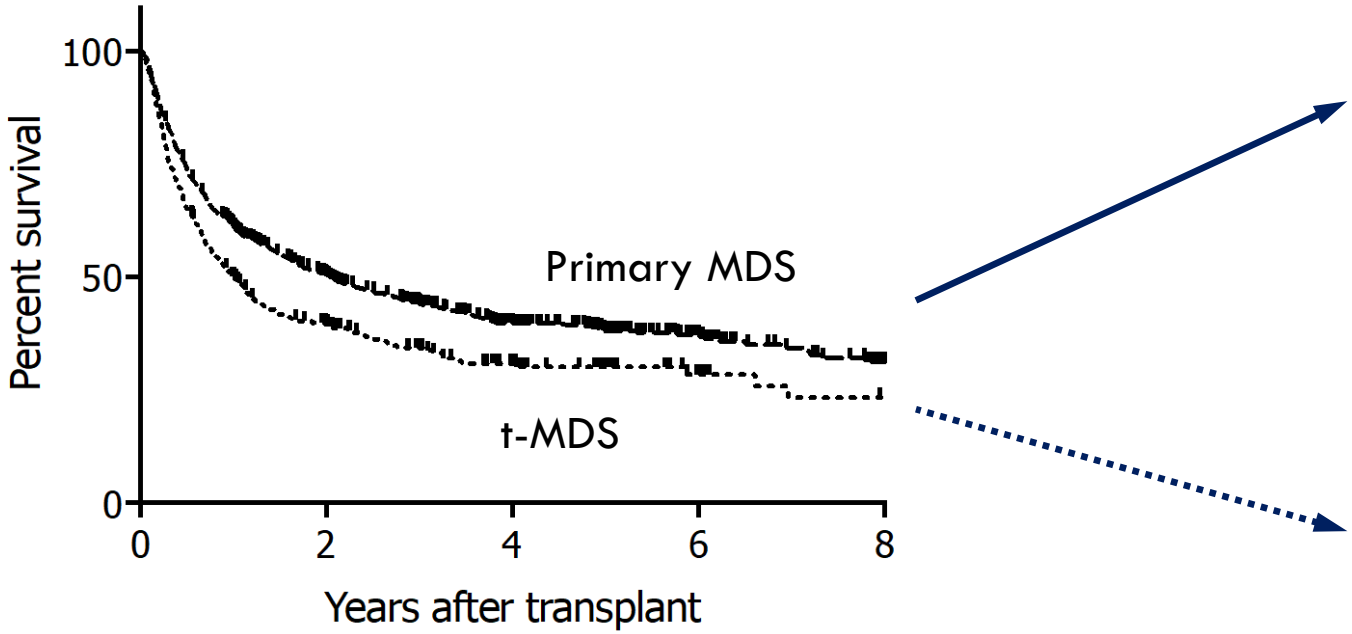
DDR pathway mutations

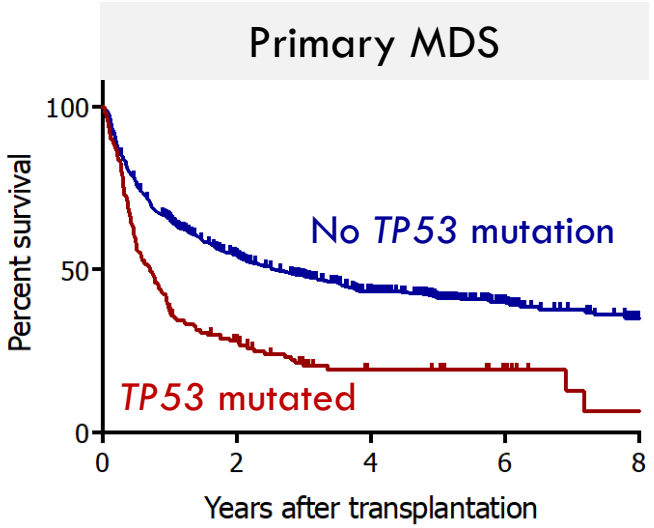


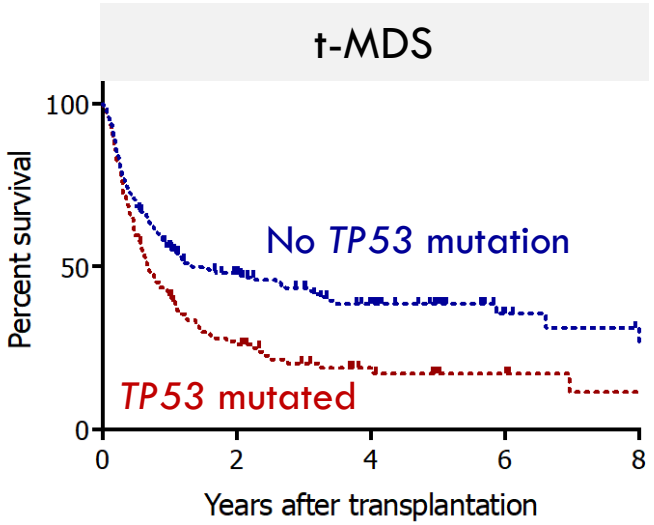
TP53 and *PPM1D* mutations Attenuate DDR



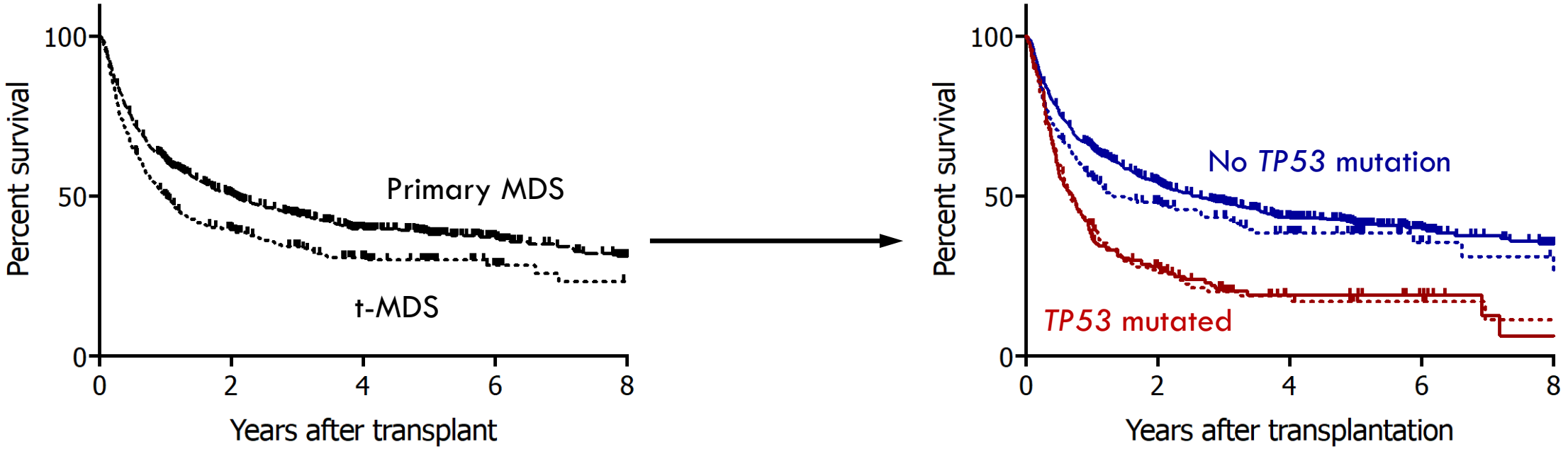
TP53 mutations drive adverse prognosis of t-MDS





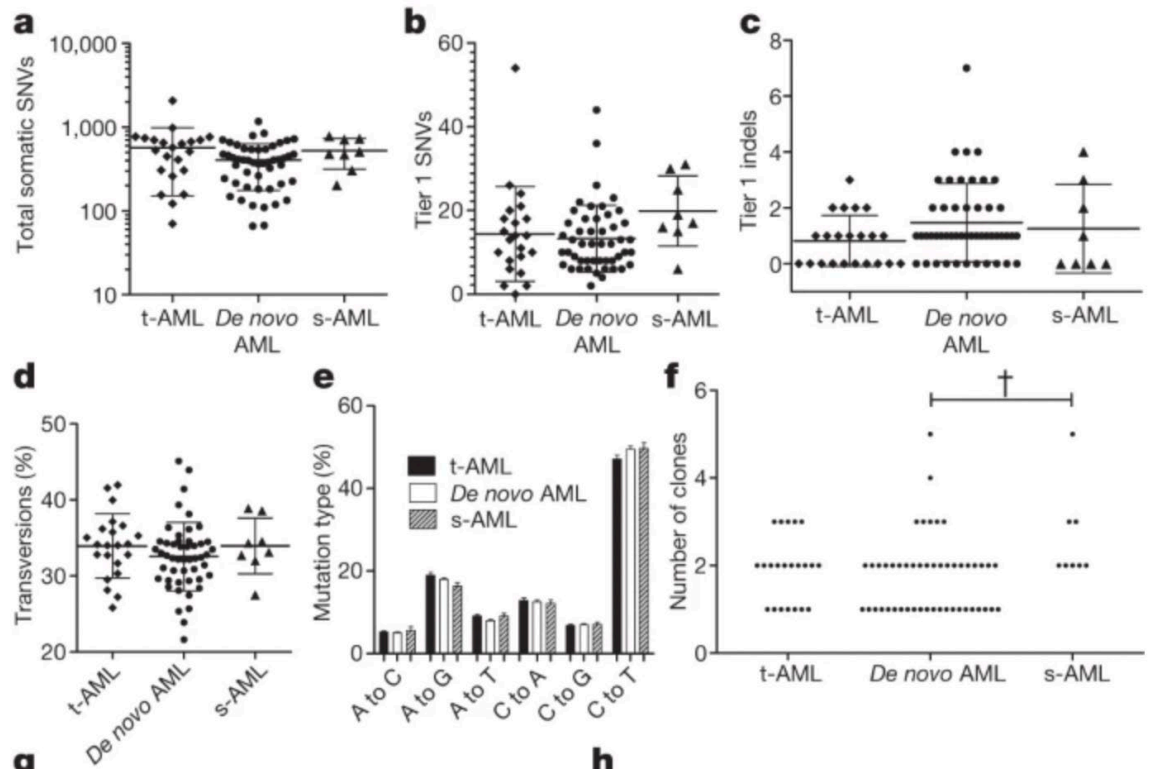


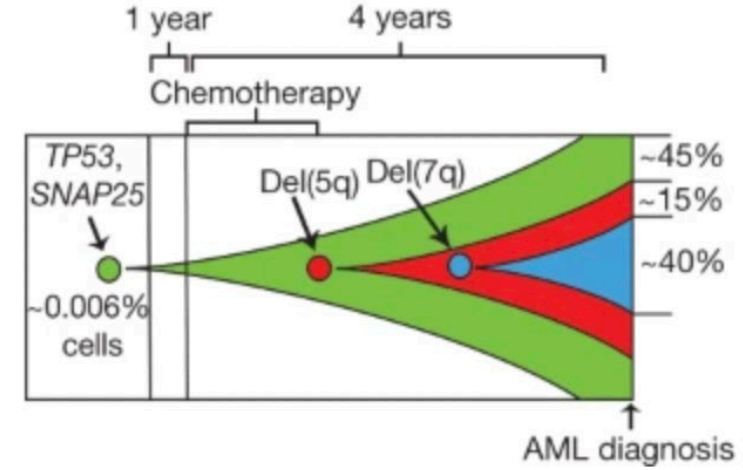
TP53 mutations drive adverse prognosis of t-MDS

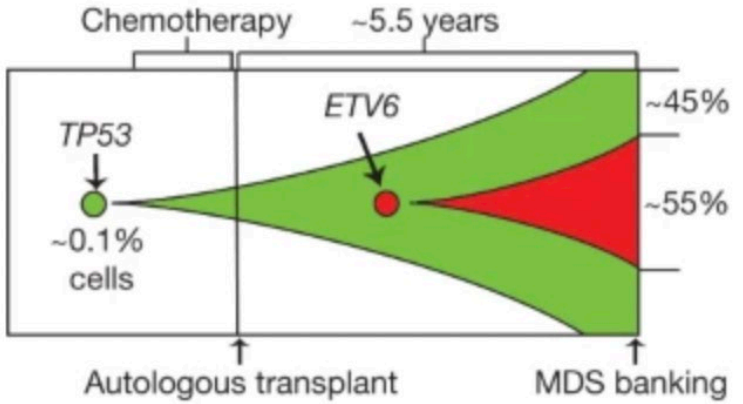


Cytotoxic therapy exposure

selectogenic >> mutagenic





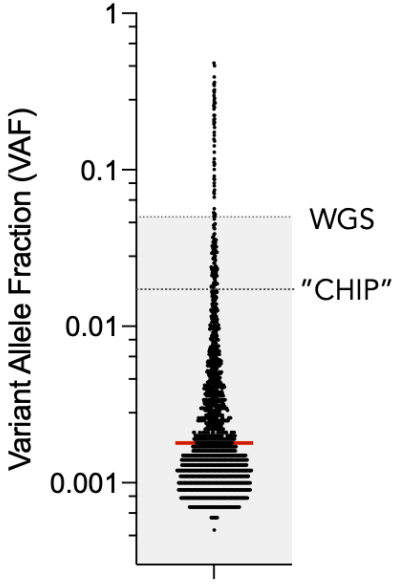


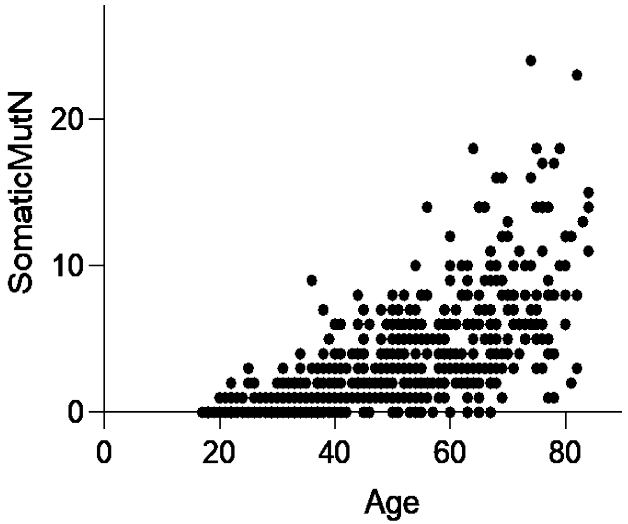
Wong, et al. 2015

Goal: Define the substrate of clonal selection

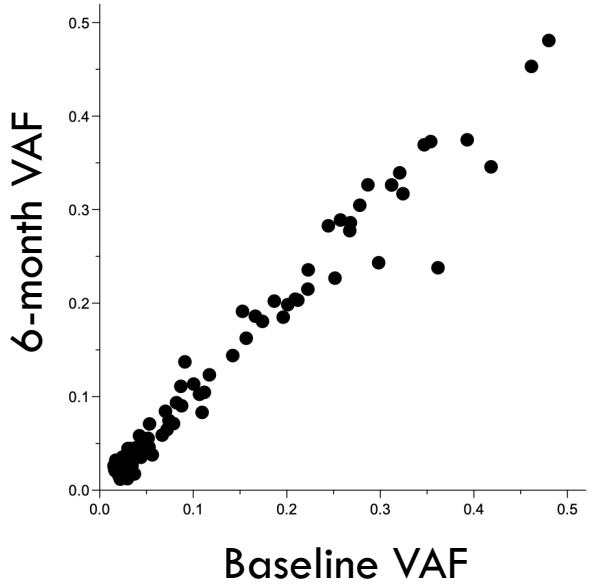
Ultrasensitive CH detection using targeted duplex sequencing

VAF	*# mutations per individual*	Controls – peds	6-month interval concordance





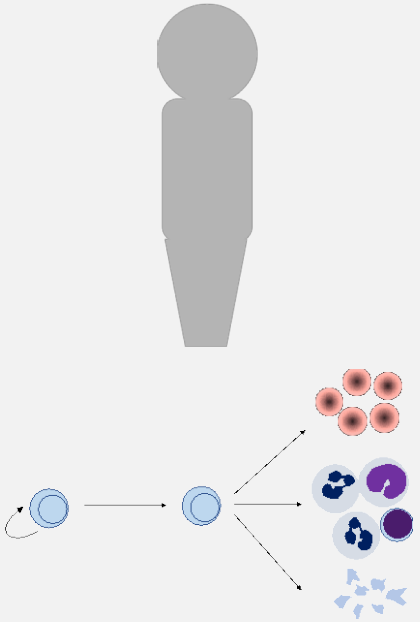
Neuroblastoma cohort (n=112)
DNMT3A
TET2
PPM1D
ASXL1
TP53
GNB1
ATM



Curative therapies for sickle cell disease

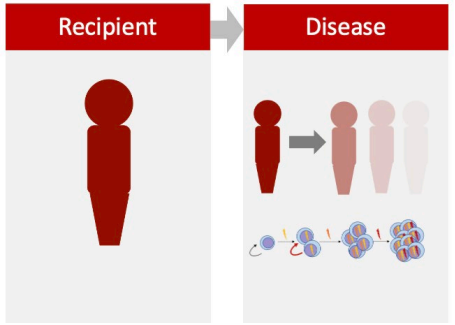
Modifying substrate and constraint

SCD



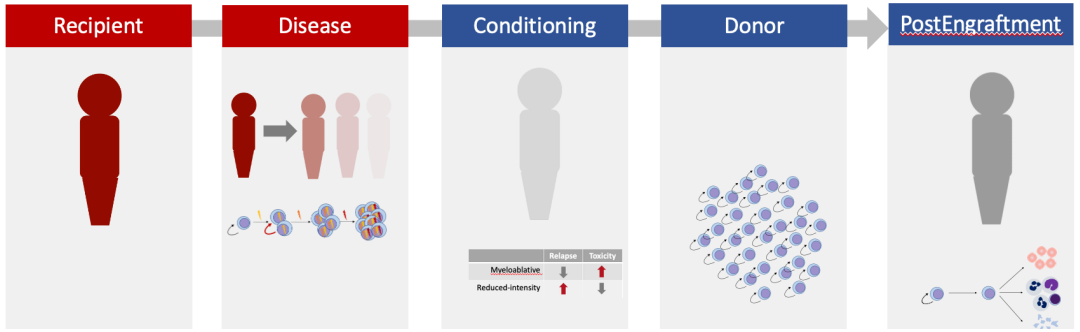
Disease-specific risk of somatic clonal expansion?

Systemic disease manifestations

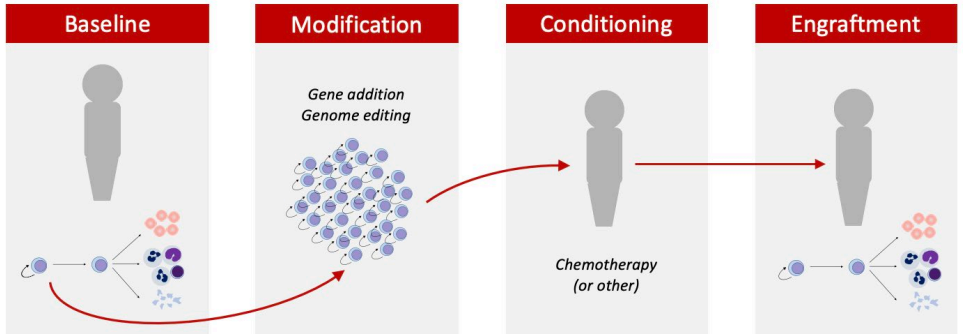


leukemia, organ-specific risks (CVD, infection, etc)

Hematopoietic cell transplantation (*allogeneic HSCs*)



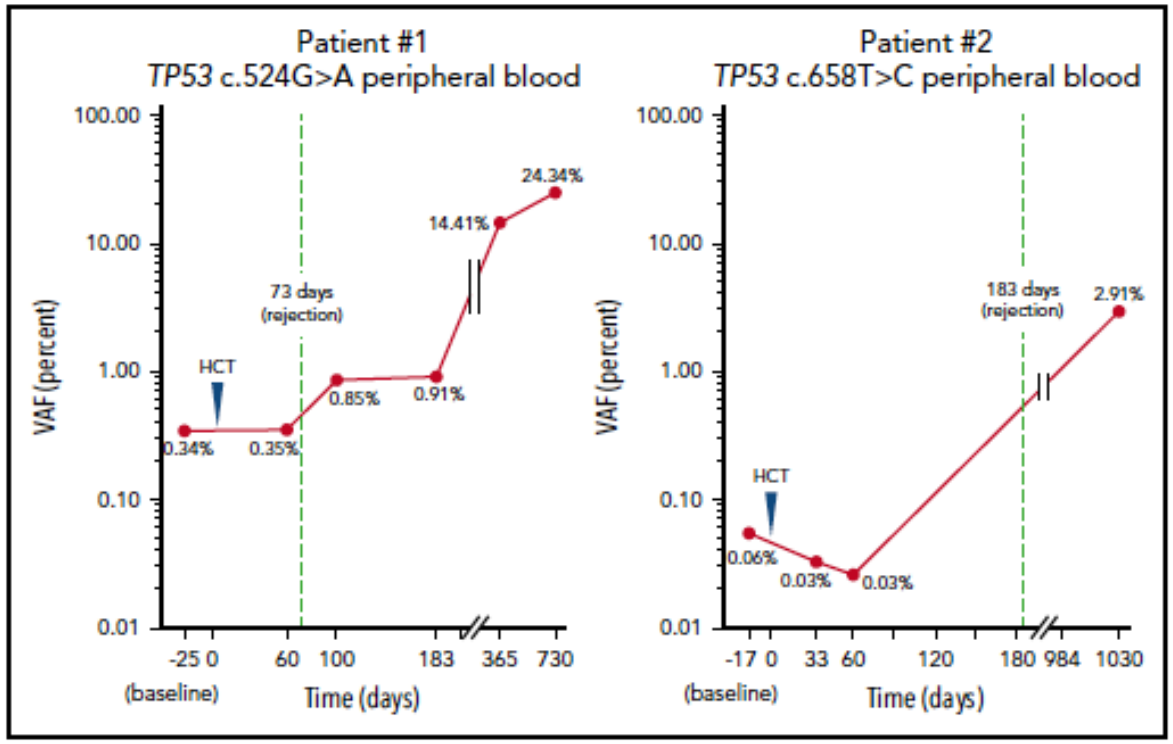
Gene therapy (*autologous HSCs*)
Gene addition
Gene editing



Curative therapies for sickle cell disease

Therapy-related leukemias

SCD patients who develop MDS/AML post NMA allo-HCT
TP53 mutations in pre-HCT recipient samples



BRIEF REPORT

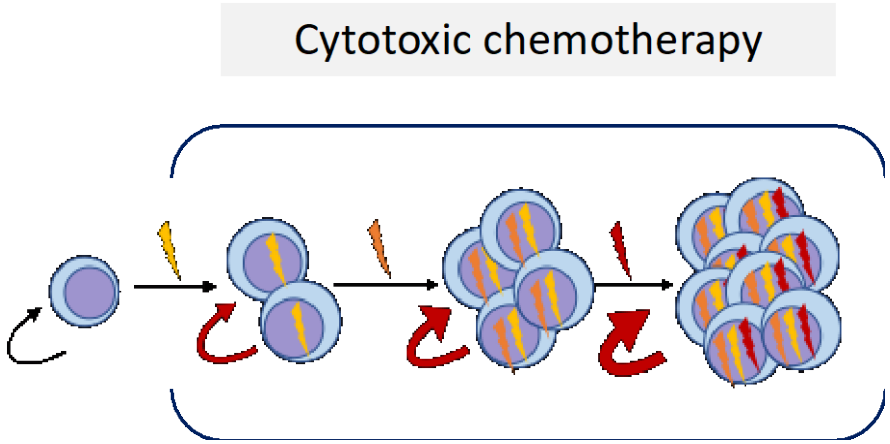
Acute Myeloid Leukemia Case after Gene Therapy for Sickle Cell Disease

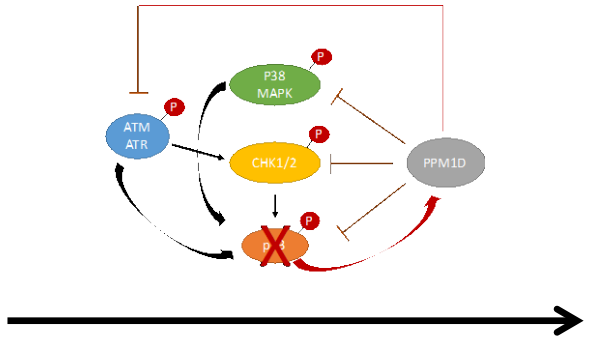
Sunita Goyal, M.D., John Tisdale, M.D., Manfred Schmidt, Ph.D., Julie Kanter, M.D., Jennifer Jaroscak, M.D., Dustin Whitney, Ph.D., Hans Bitter, Ph.D., Philip D. Gregory, Ph.D., Geoffrey Parsons, Ph.D., Marianna Foos, M.S., Ashish Yeri, Ph.D., Maple Gioia, A.L.M., Sarah B. Voytek, Ph.D., Alex Miller, B.S., Jessie Lynch, M.S., Richard A. Colvin, M.D., Ph.D., and Melissa Bonner, Ph.D.

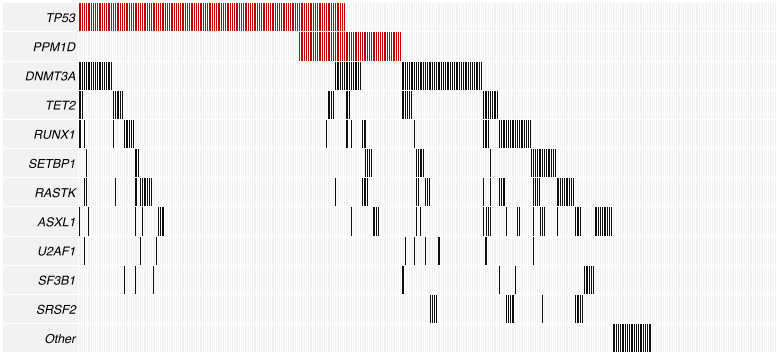
Commercial lab: RUNX1, PTPN11, KRAS mutations
AML did NOT have viral integration

Ghannam et al. Blood 2020; 135(14)

1. *TP53* and *PPM1D* mutations are highly selected by chemotherapy
2. TP53 mutations drive adverse prognosis of t-MDS
3. Therapy exposure confers a population-level risk because it selects for high-risk *TP53* clones in individuals.
4. t-MN without TP53 may not carry disease-intrinsic adverse risk.







Dana-Farber Cancer Institute

Rahul Vedula
Moses Murdock
Naomi Kawashima
Chris Reilly
Fred Tsai
Andrew Gehrke
Amelia Grosskopf
Jessica Knapp
Deirdra Venney
Kornelia Gladysz
Felicia Lim
Danielle Morrow
Rishi Thakur
Harrison Tsai
Eva Schaefer

Jianwe Che
Demetris Gazgalis

DFCI Leukemia
Rich Stone
Dan DeAngelo
Marlise Luskjin
Jacqueline Garcia

BROAD INSTITUTE

Niall Lennon
Carrie Cibulskis
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Chris Hourigan

Fred Hutch Cancer Center

Jerry Radich

UNIVERSITY OF CAMBRIDGE

George Vassiliou
Margarete Fabre
Sean Wen

Boston Children's Hospital

Suneet Agarwal
Akiko Shimamura