Hello, Goodbye

Classification of Secondary leukemia

EHA-SWG Scientific Meeting on sAML
April 25, 2025

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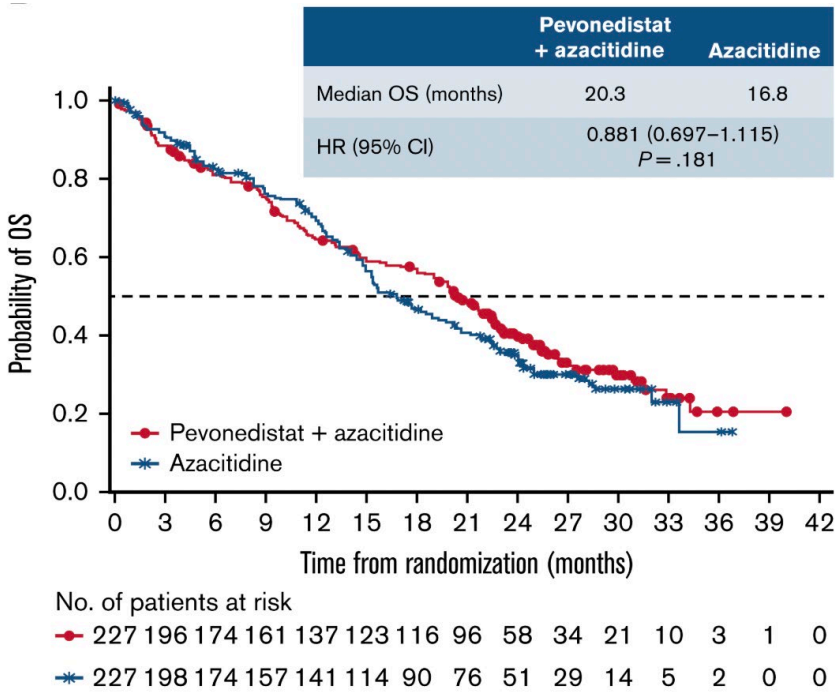
Dana-Farber
Cancer Institute

The Problems

Problem 1:

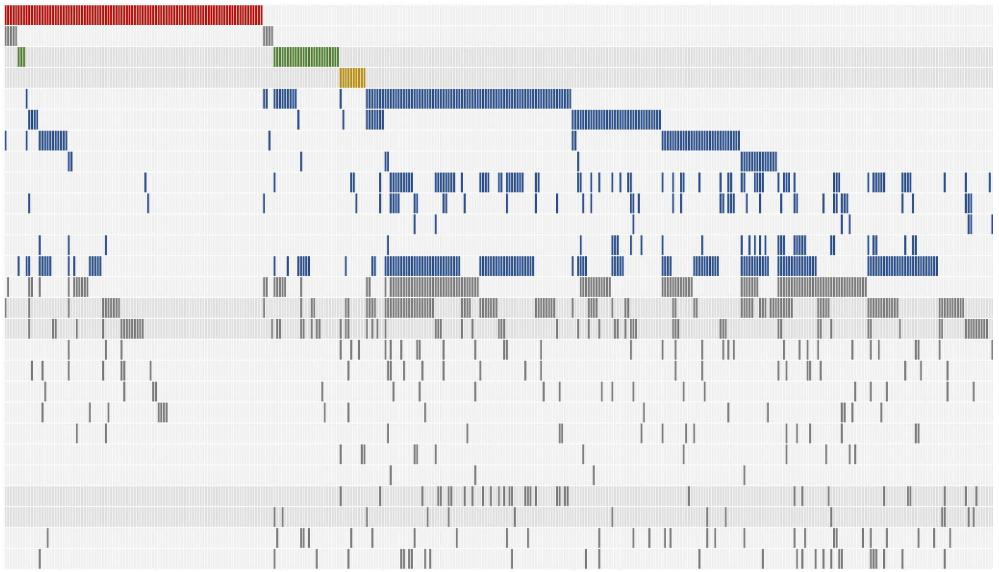
Negative Phase 3 study

Pevonedistat plus AZA vs *AZA alone*



Problem 2:

Limited understanding of link between disease biology and treatment outcomes



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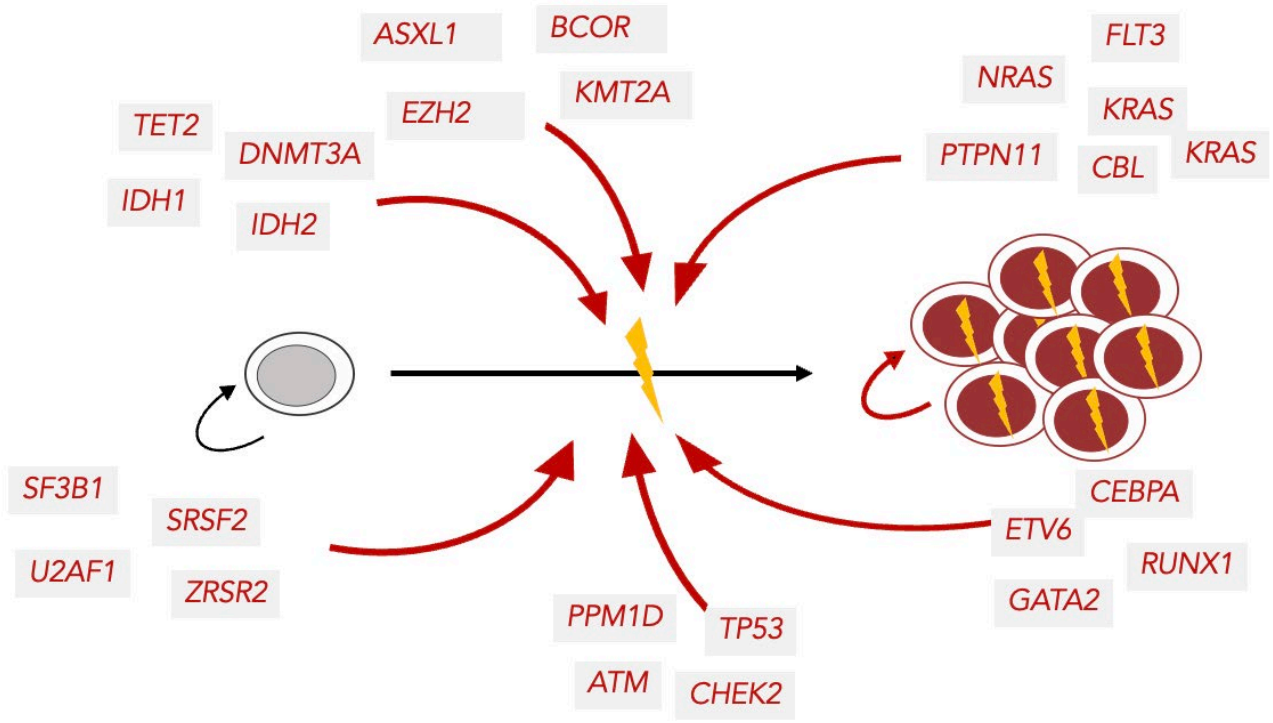
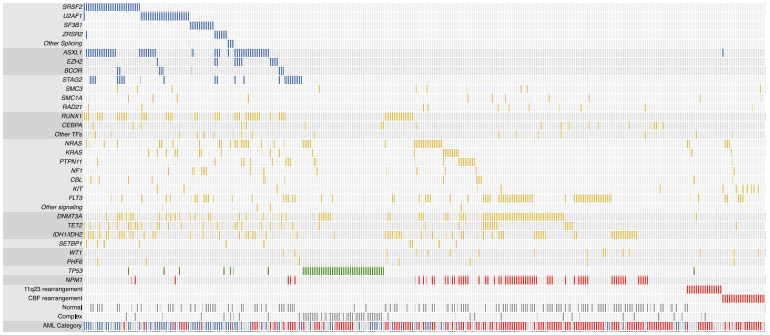
Problem 2, expanded…

The Parts List of myeloid driver mutations



Combinatorial diversity



Temporal dynamics

Classification

Simplify

through core principles

Focused reductionism

Embrace heuristic rules that predict clinical/biological characteristics (OS, response/resistance)

Iterative refinement

Begin with a simplified heuristic model; refine it iteratively as new data emerges.

Regularly test heuristic rules against clinical data, updating rules based on observed discrepancies.

Pragmatic optimism

Emphasize actionable insights rather than comprehensive solutions.

Acknowledge complexity… but prioritize simplifying assumptions that lead to clinical action.

Demonstrate clinical scenarios where heuristic models directly improve patient stratification or therapeutic decision making

Acute Myeloid Leukemia

Clinical heterogeneity and risk stratification circa 2010

Cytogenetics

Genetics

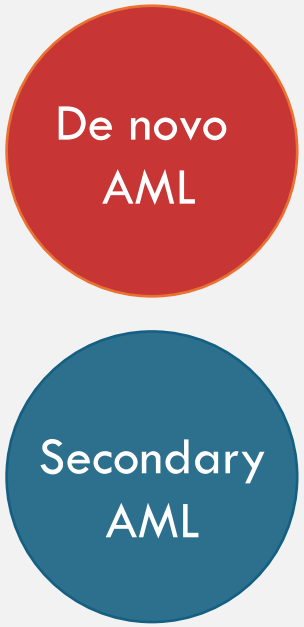
Age

Ontogeny

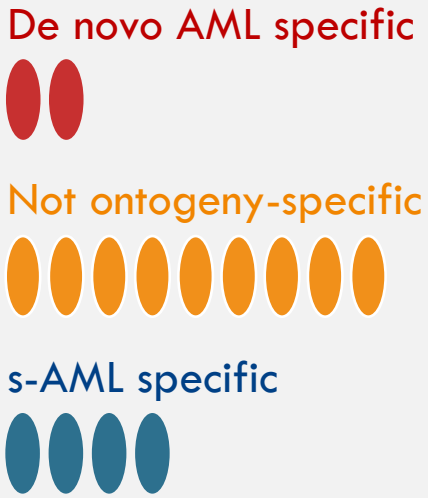
- "Therapy-related AML"
  - prior leukemogenic exposure
- "Secondary AML"
  - antecedent MDS
- "De novo AML"
  - no MDS or exposure identified

Define an objective, highly-specific genetic ontogeny classifier that resolves AML heterogeneity independent of clinical history.

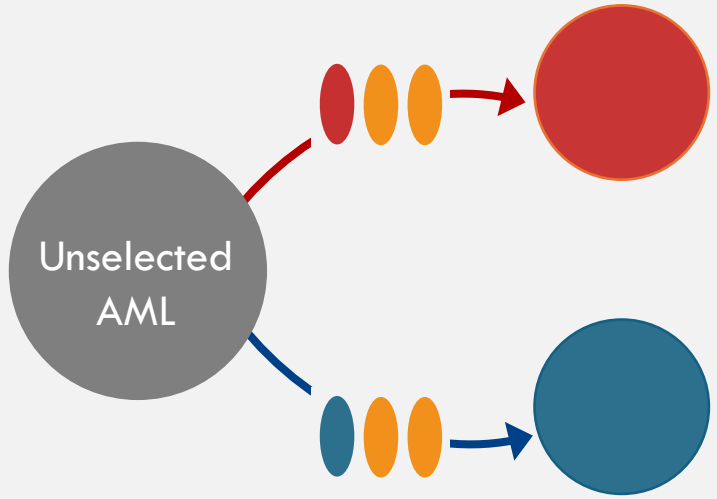
1. Define mutation spectrum



2. Determine specificity



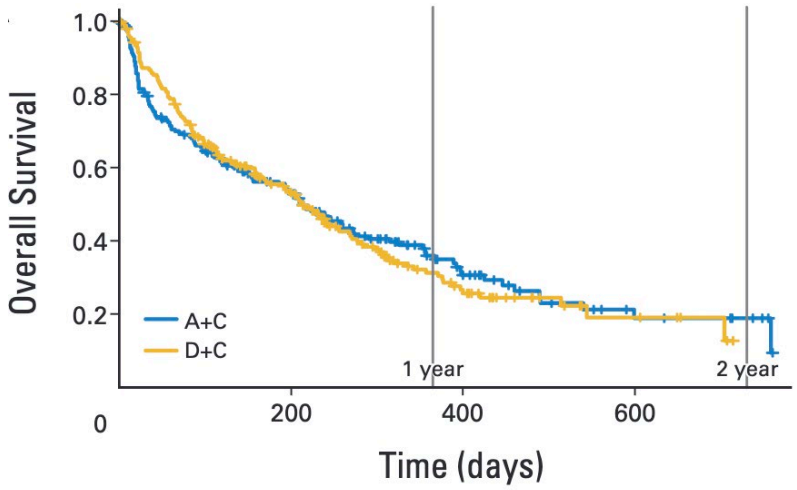
3. Validate



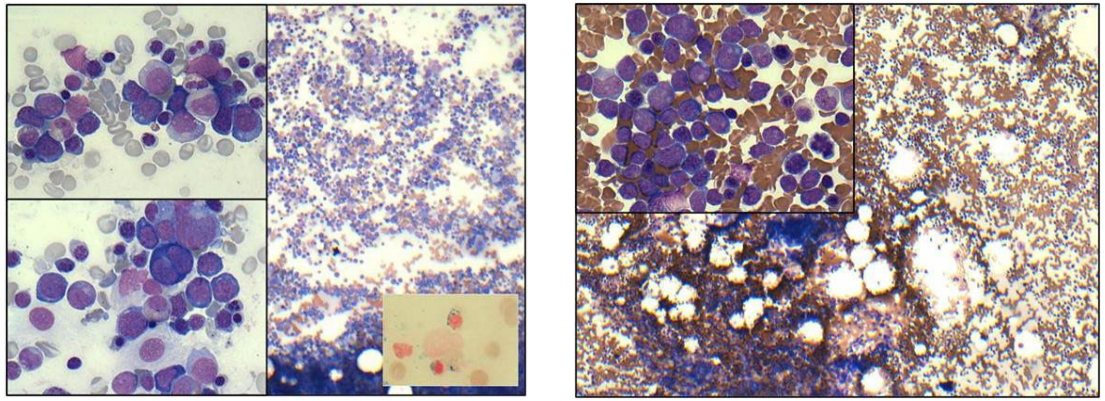
Randomized phase III trial in s-AML and t-AML

Cytarabine in combination with Amonafide L-Malate or Daunorubicin

Clinical study was negative



DNA extracted from bone marrow aspirate slides



Rigorous eligibility criteria

- s-AML with histologically confirmed history of MDS/CMML

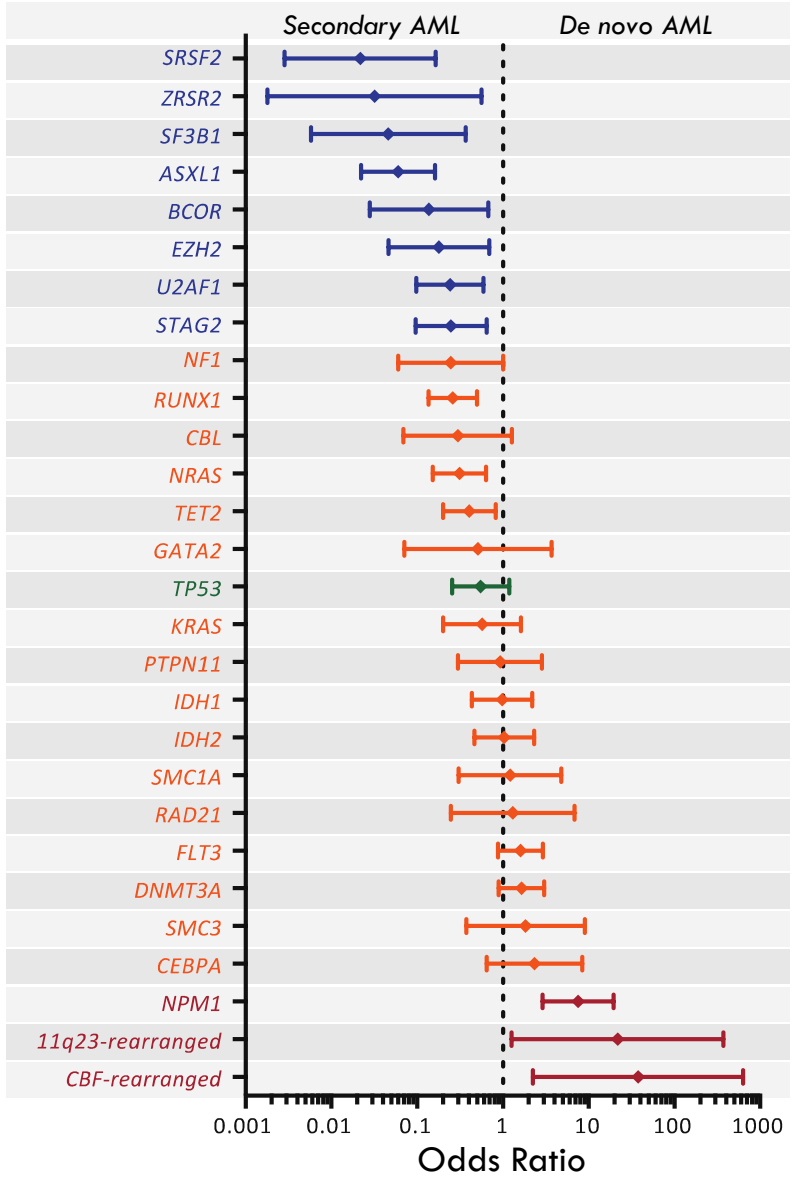
Uniform treatment, response adjudication, outcomes

- Comparison of two intensive induction regimens

Targeted sequencing

Mutations have ontogeny-specificity

s-AML versus TCGA de novo AML



>95% specific for s-AML (AML-MR)

- *SRSF2, ZRSR2, SF3B1, U2AF1*
- *EZH2, ASXL1, BCOR*
- *STAG2*

Not specific

- DNA methylation, RAS/MAPK, myeloid TF
- *TP53*

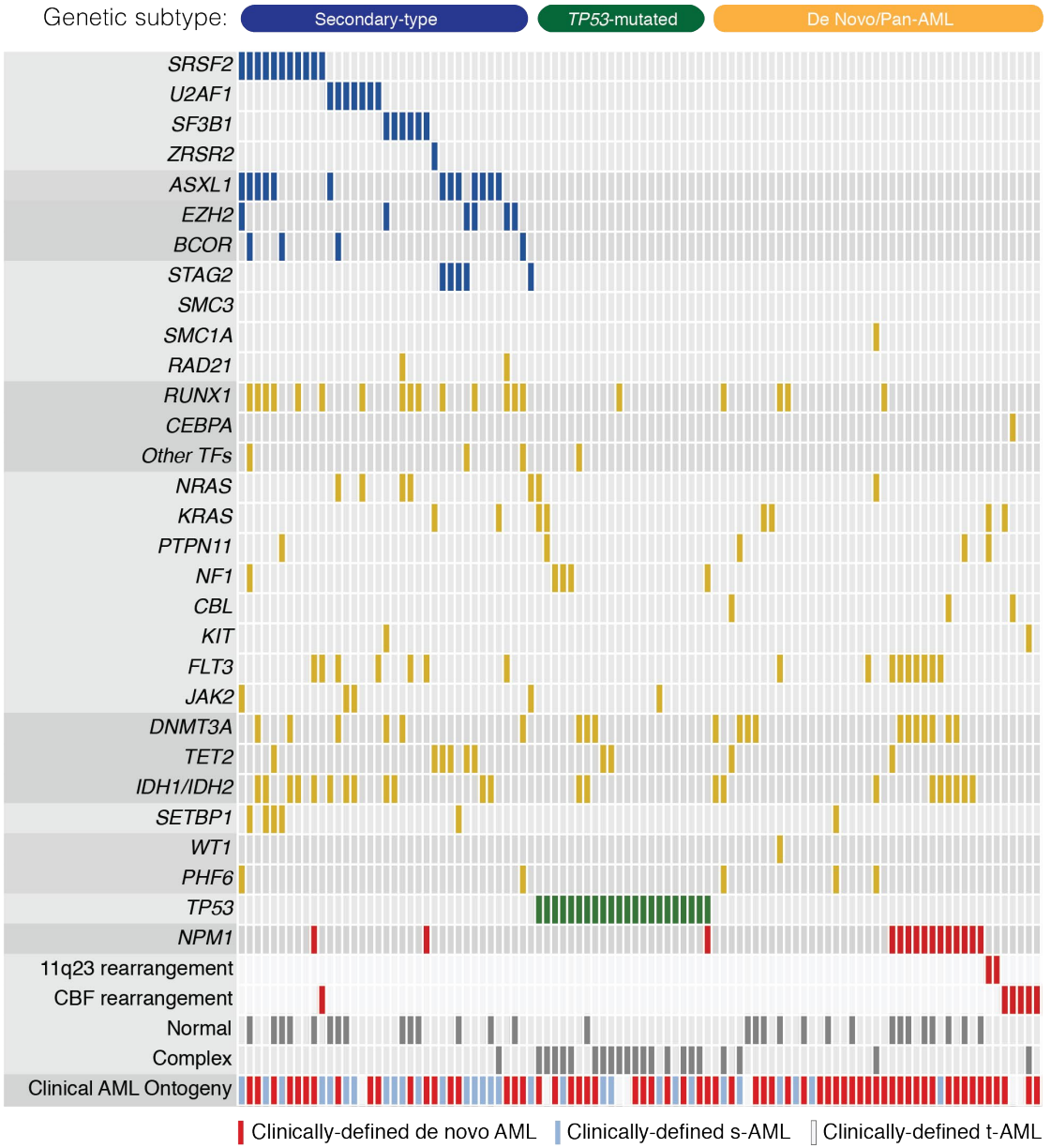
>95% specific for de novo AML

- NPM1
- CBF, KMT2A-rearranged

Resolving heterogeneity in an unselected AML cohort

DFCI AML Cohort

- Consecutive cases (~1 year)
- Median age: 65 years
- Clinical ontogeny
  - 64% de novo AML
  - 30% secondary AML
  - 6% therapy-related AML

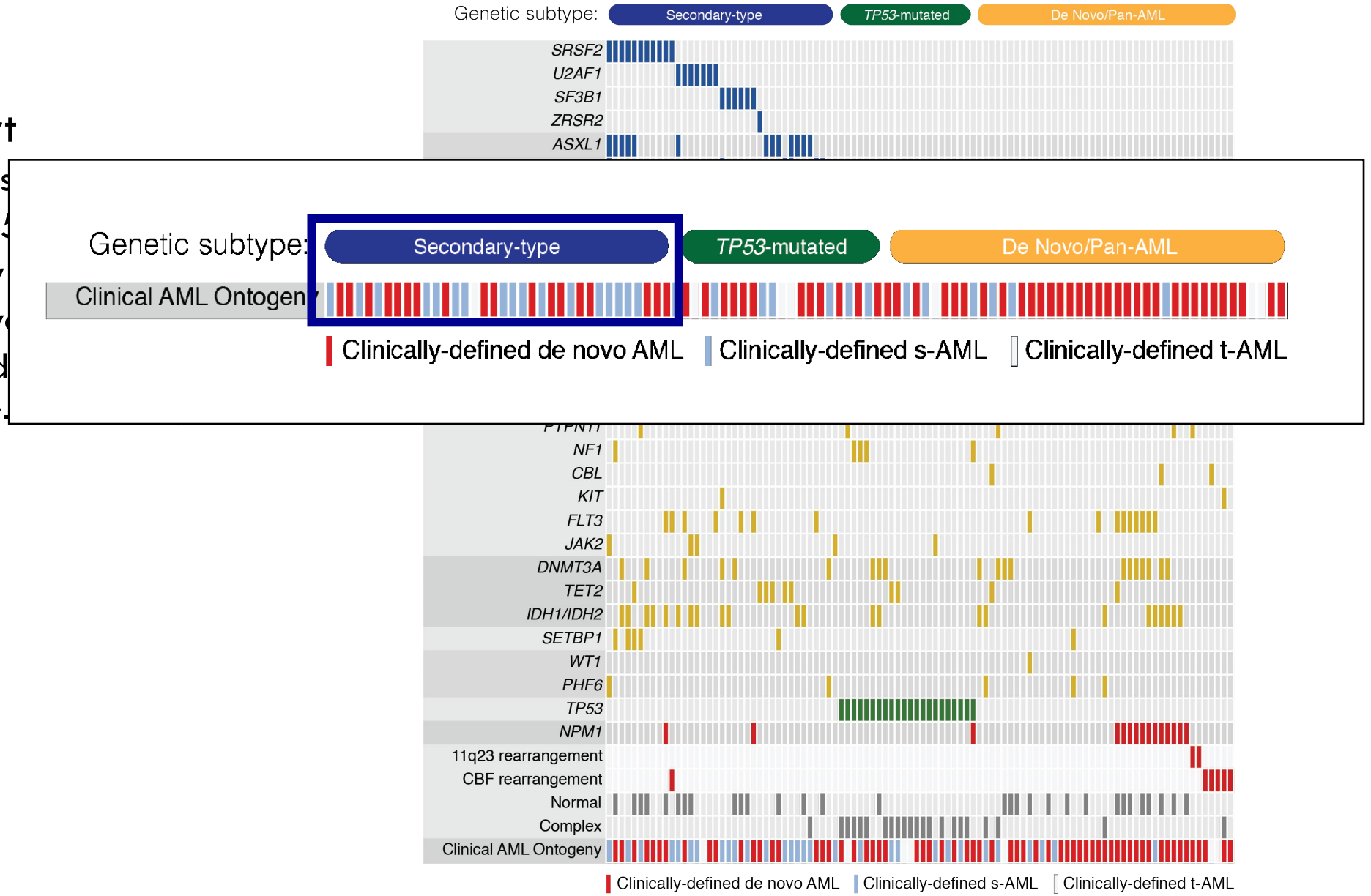


Resolving heterogeneity in an unselected AML cohort

Validation cohort

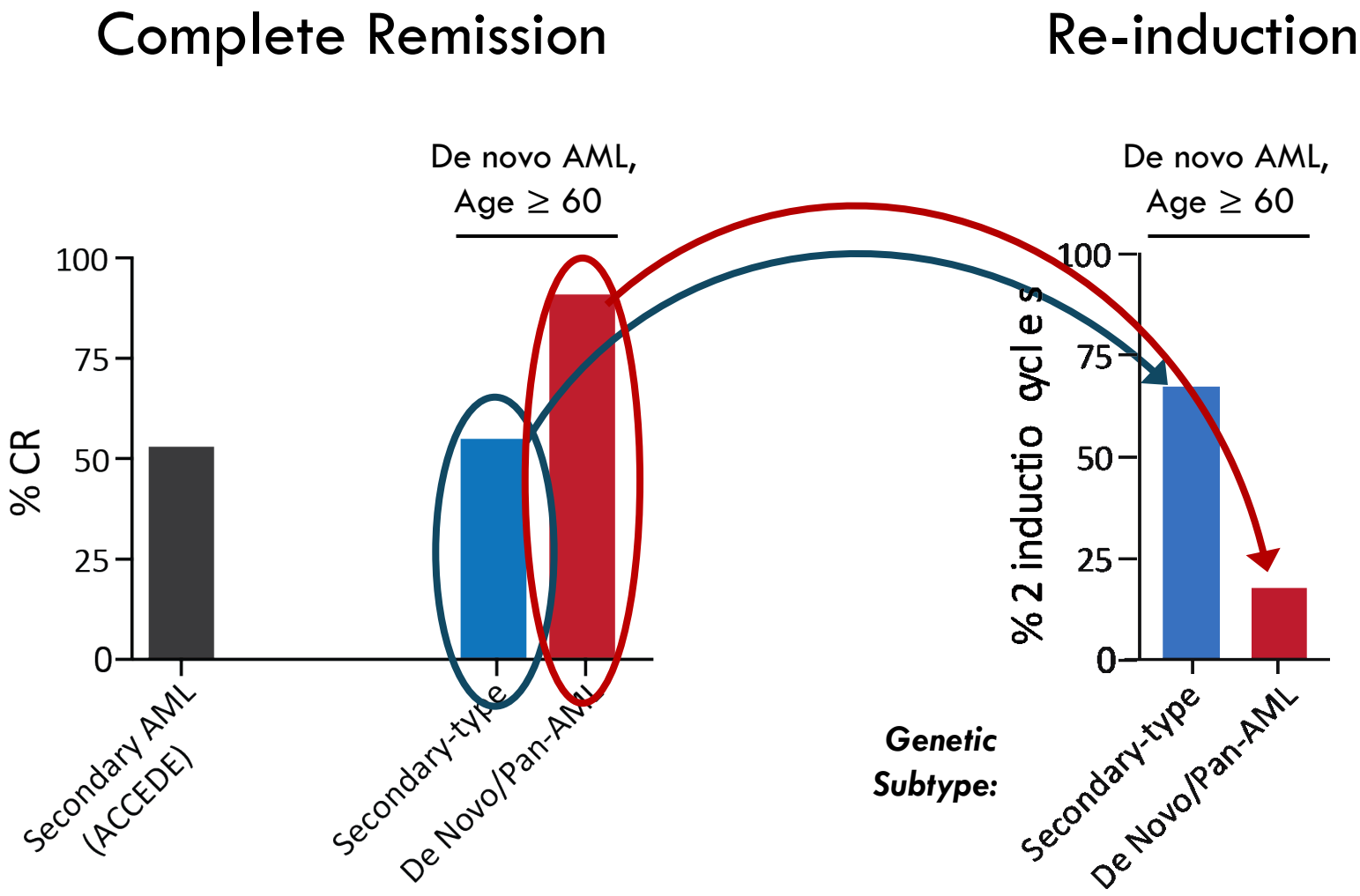
DFCI AML Cohort

- Consecutive cases
- Median age = 6
- Clinical ontogeny
  - 64% De nov
  - 30% Second
  - 6% Therapy-



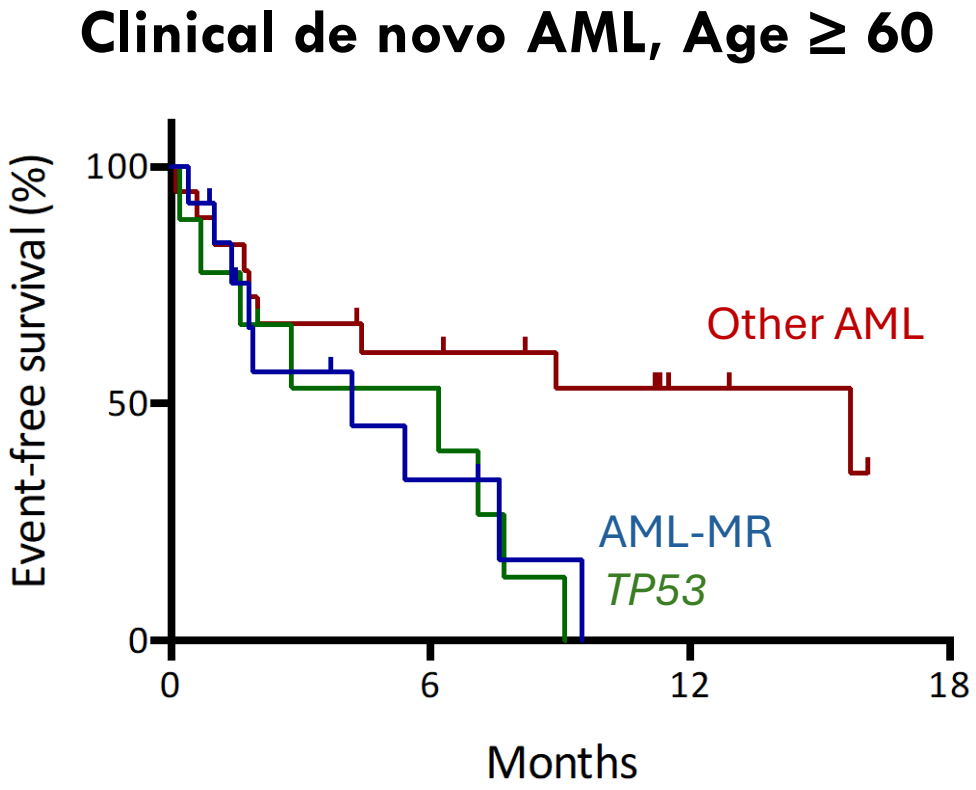
AML-MR mutations

chemo-resistance in older de novo AML patients



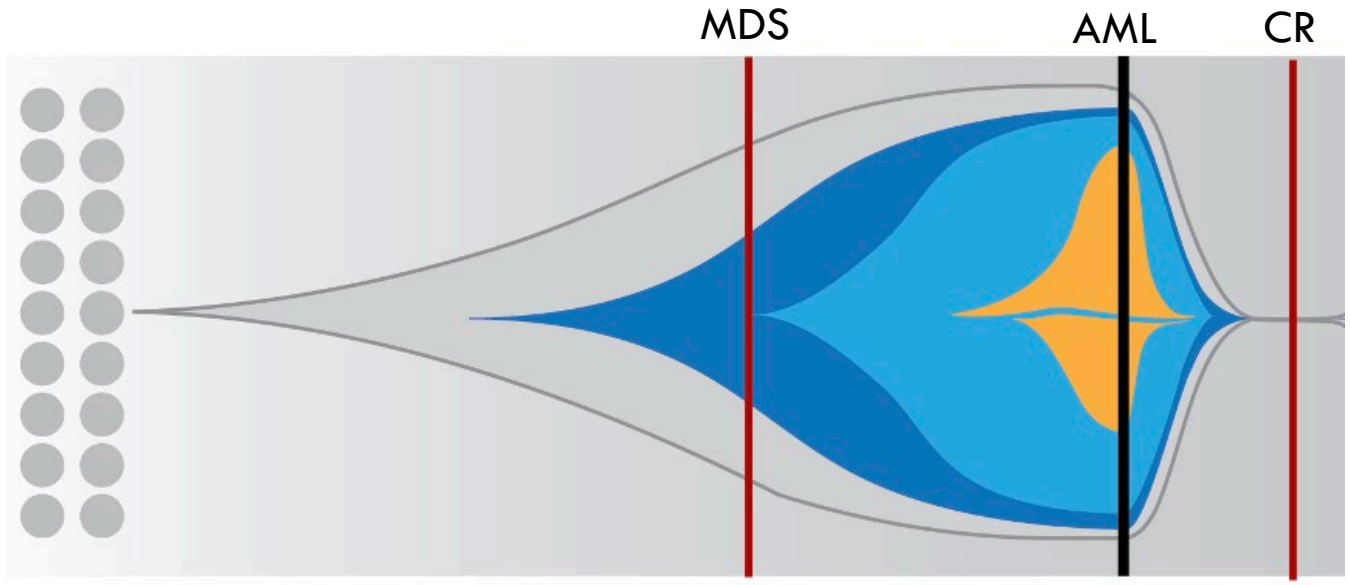
Older patients with *de novo* AML,

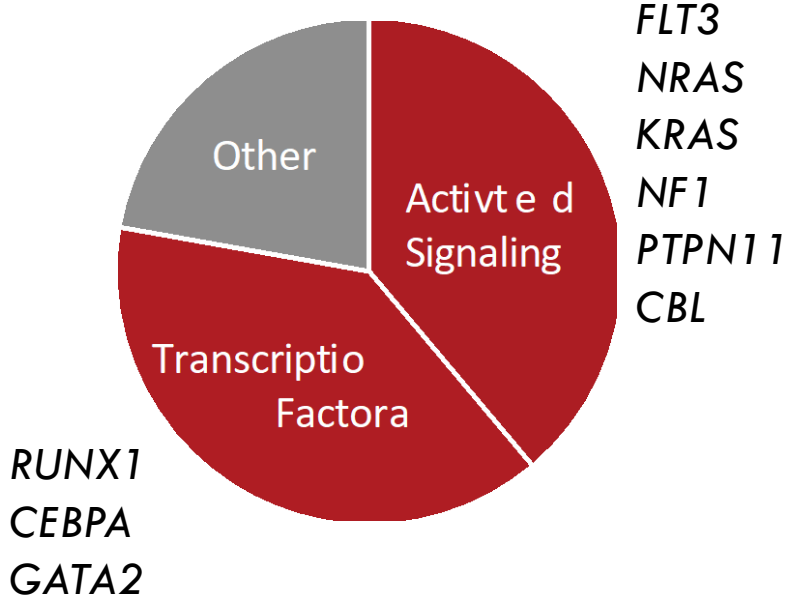
AML-MR mutations associated with adverse outcomes



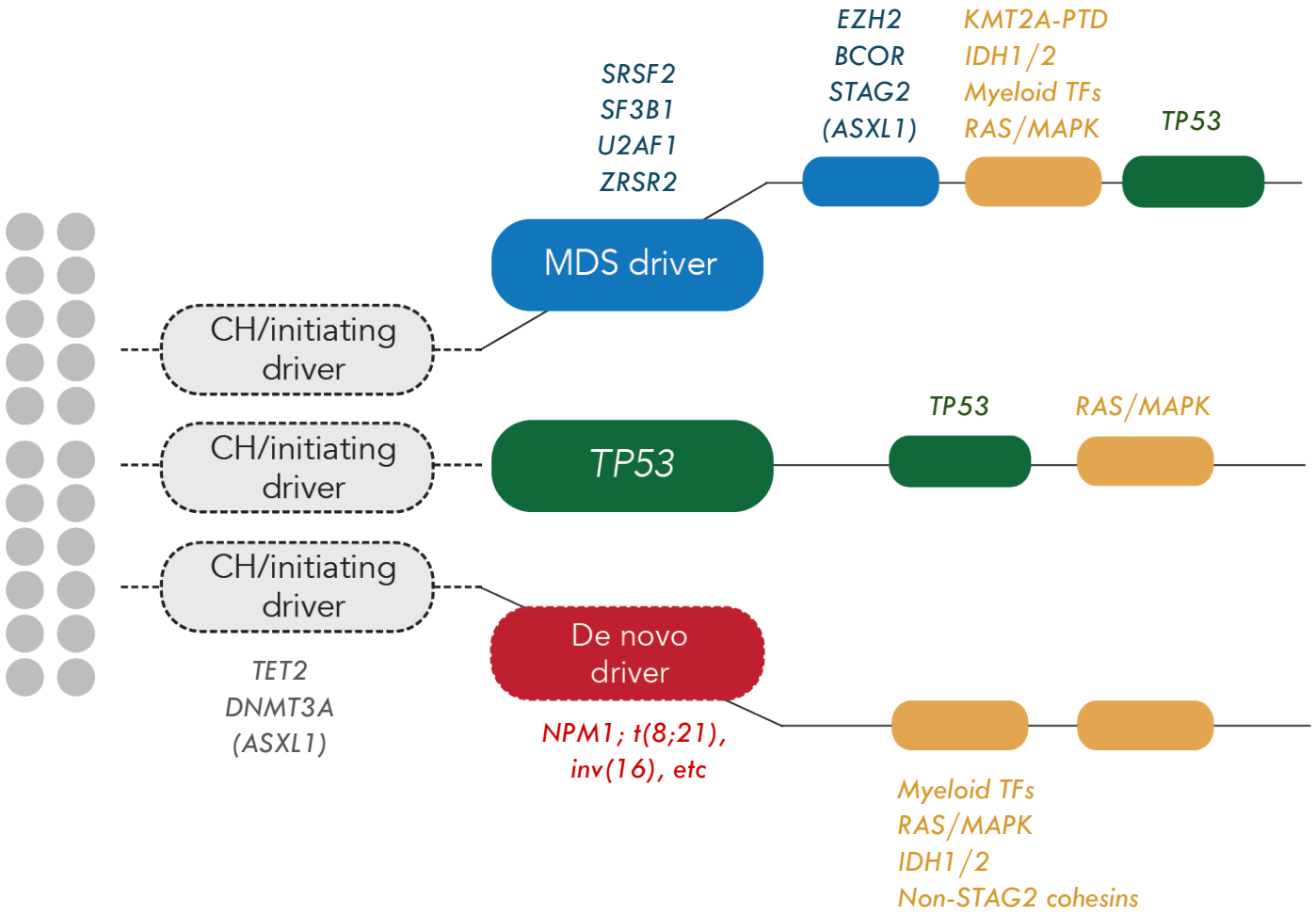
Evolution and treatment resistance

Defining order of mutations (prior to the single-cell era)





AML ontogeny: a reductionist model



Secondary AML (AML-MR)

TP53 AML

De novo/Other AML

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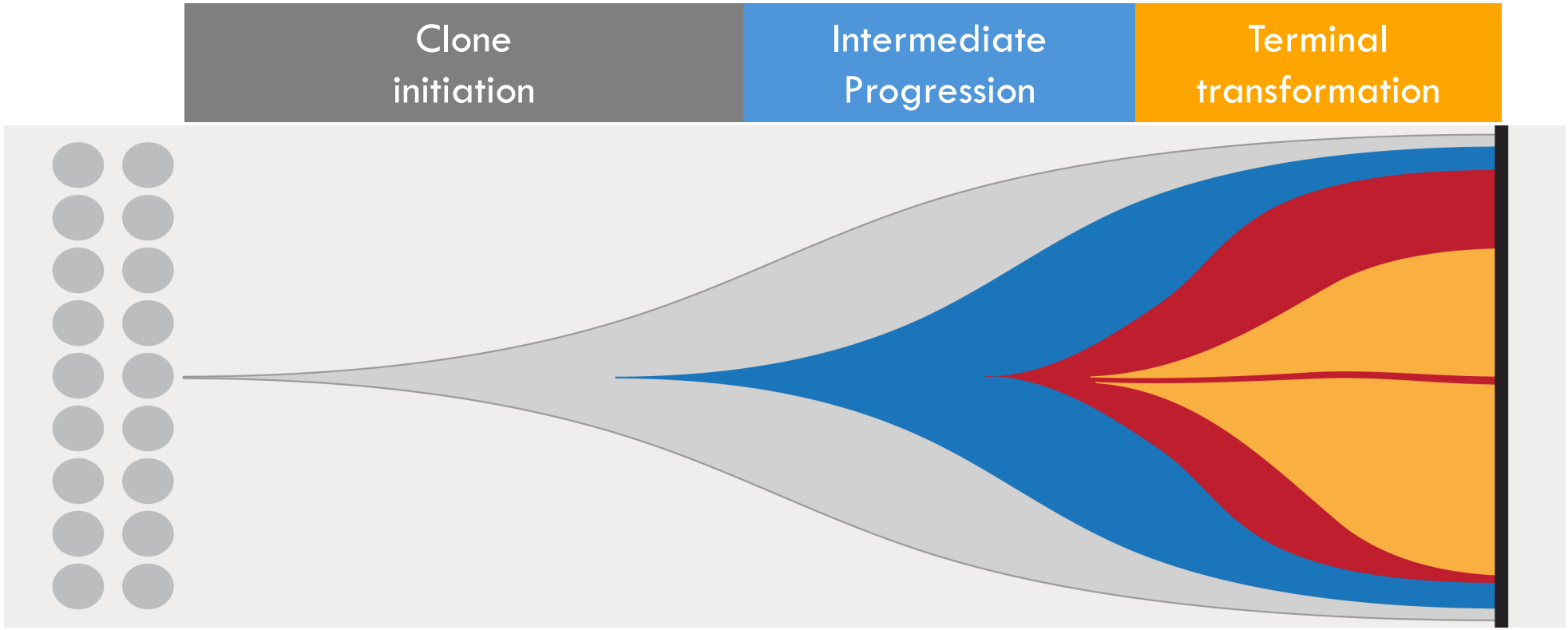
Temporal heuristic

Defining the order of operations



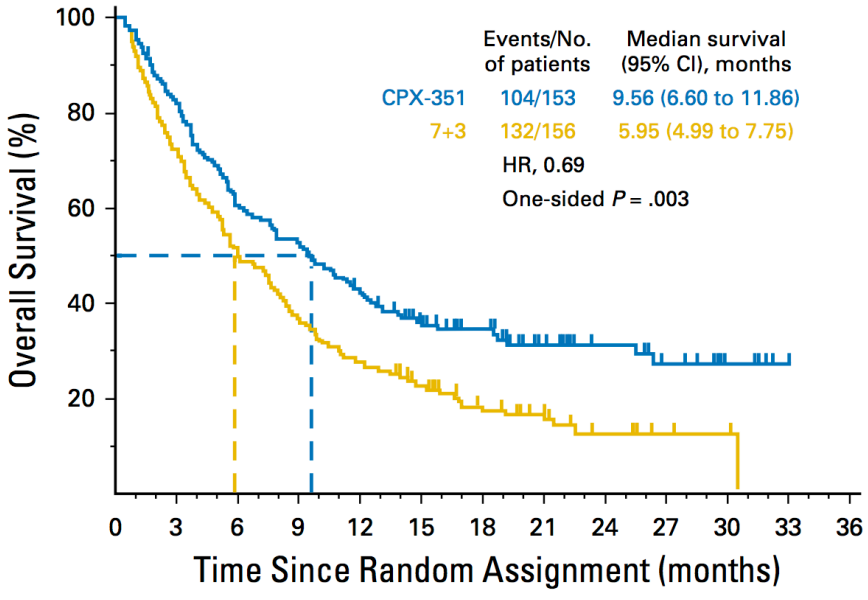
Phase 3 CPX-351 vs. 7+3 in secondary/therapy related AML

Regulatory approval based on outdated trial enrollment criteria

Inclusion criteria

1. AML-MRC with Prior MDS/CMML
2. AML-MRC with MDS-related cytogenetic changes*
3. Post-cytotoxic therapy exposure

*Defined by 2008 WHO 4th edition




Shai Shimony


Moses Murdock

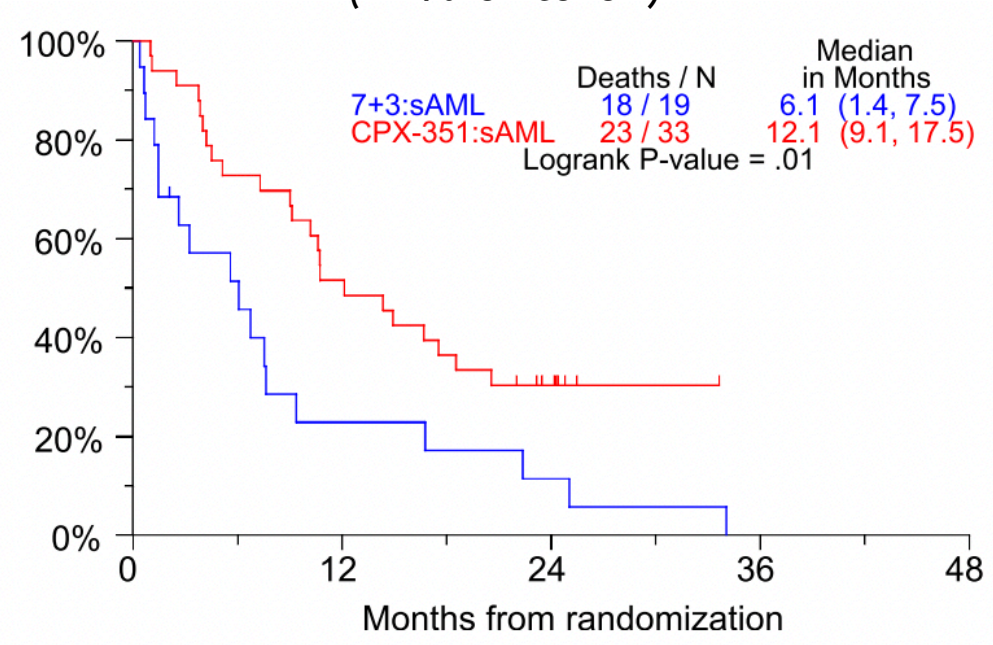
NCT01696084; Lancet, et al. *J Clin Oncol*, 2018.; Lancet, et al. *Lancet Haem*, 2021

Phase 2 CPX-351 vs. 7+3

Planned subgroup analysis

"Secondary AML"

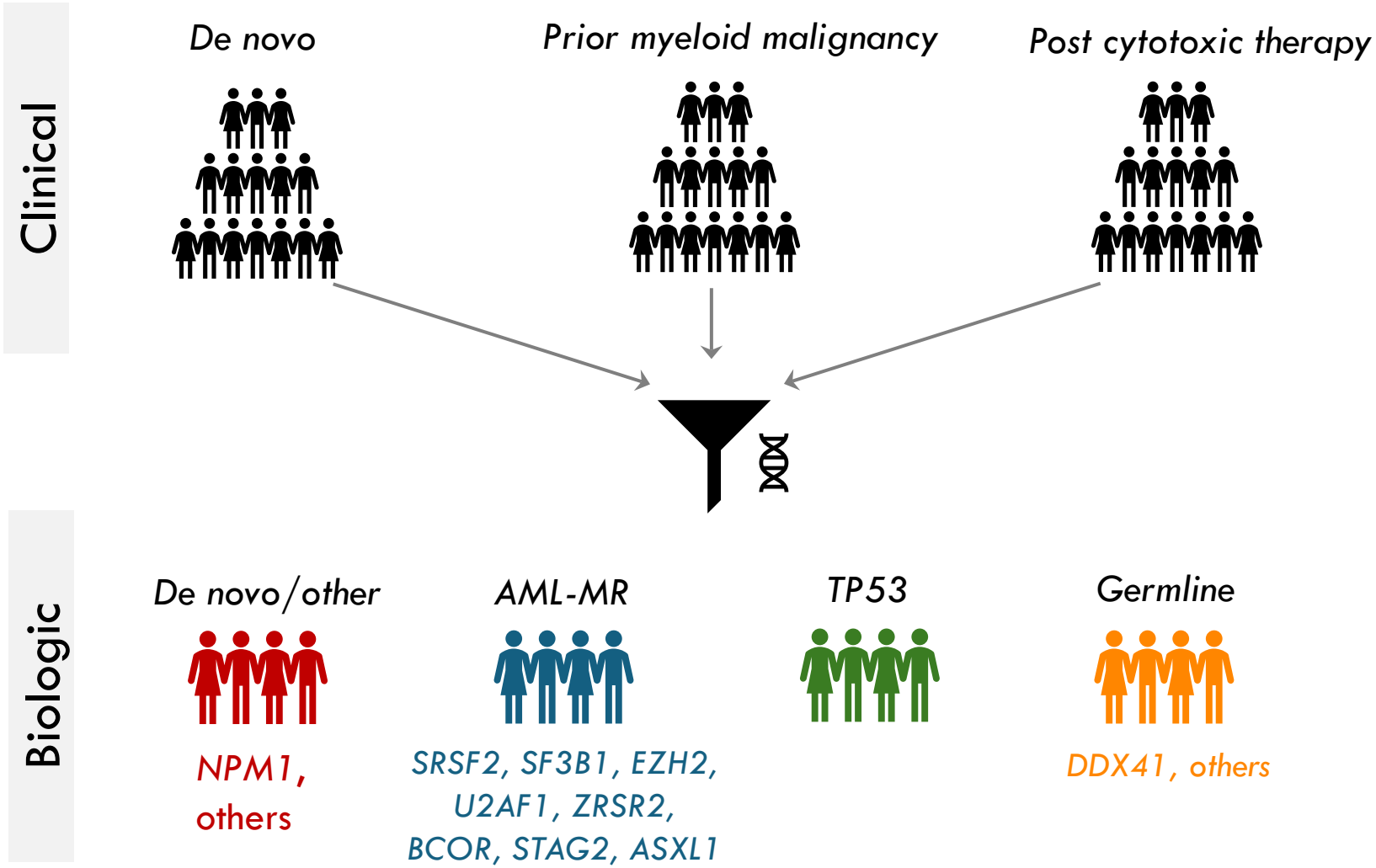
(41% of cohort)



Definition of secondary AML in the Phase 2 study:

- Secondary AML: a history of antecedent hematologic disorder (MDS or MPN)
- Therapy-related AML: a history of cytotoxic treatment for non-hematologic malignancy

AML ontogeny → now drives AML classification and prognostic models



Phase 3 CPX-351 vs. 7+3 in secondary/therapy related AML

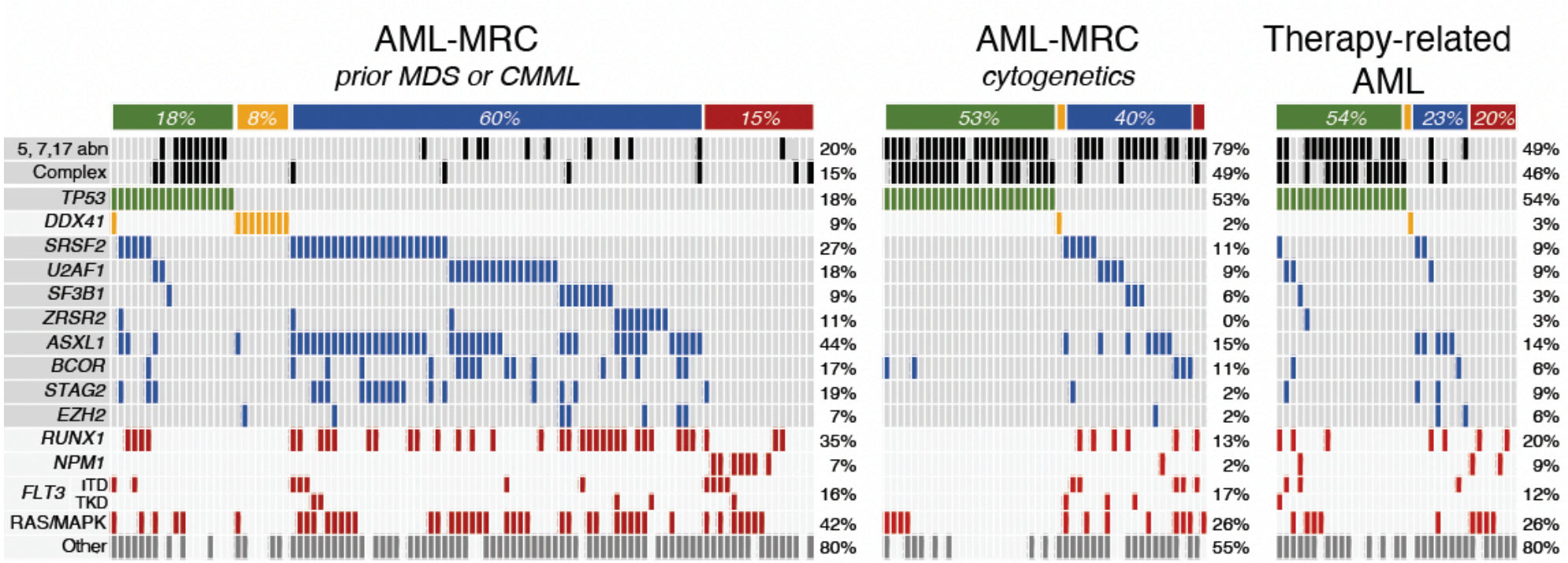
Re-classification of clinical group based on biology

TP53

AML-MR

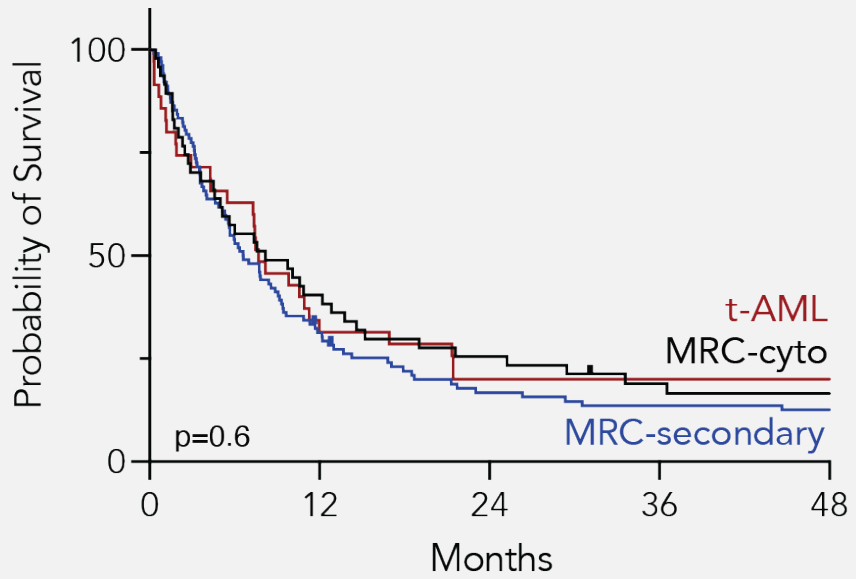
Other/de novo

DDX41

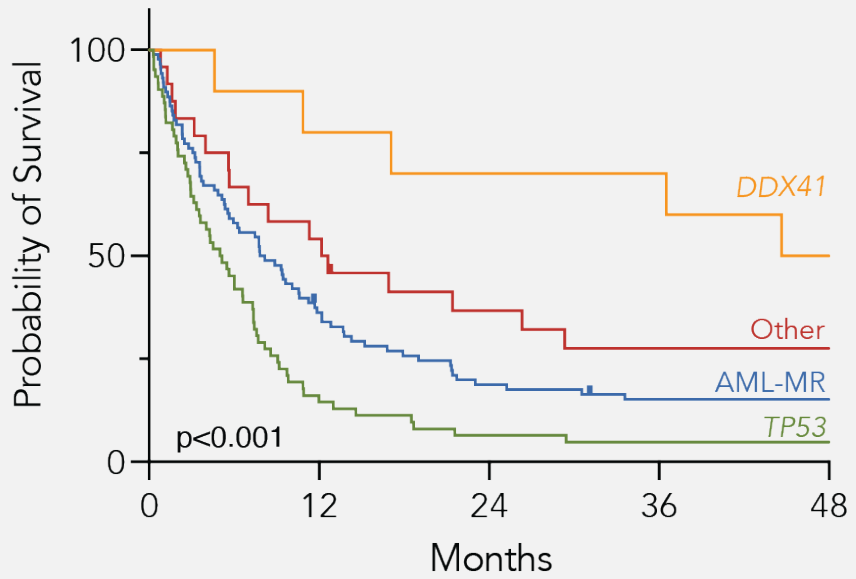


Genetic grouping stratifies better than trial inclusion groups

Clinical classification
(trial inclusion groups)

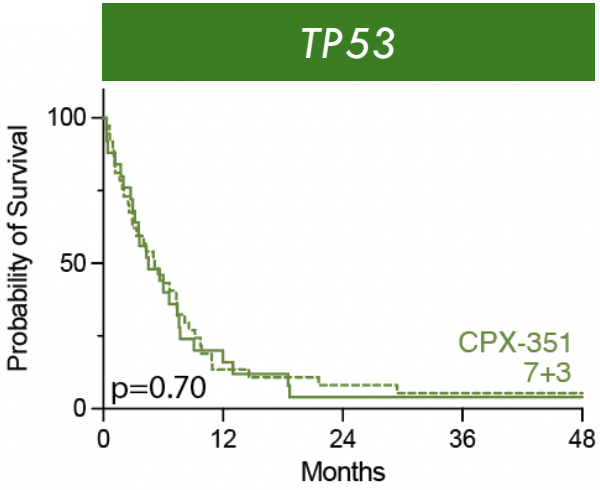


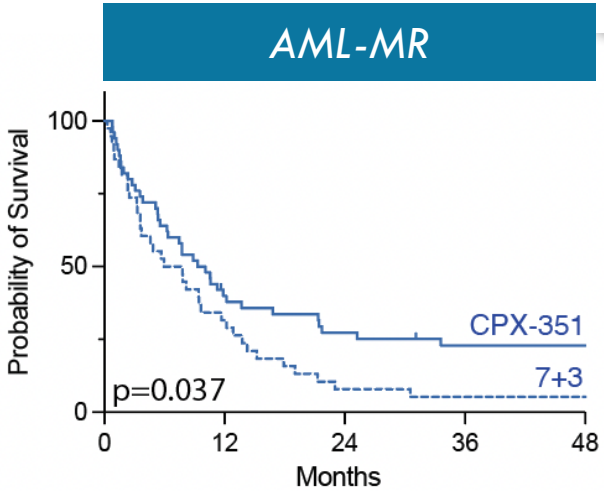
Molecular classification
(ontogeny-based)

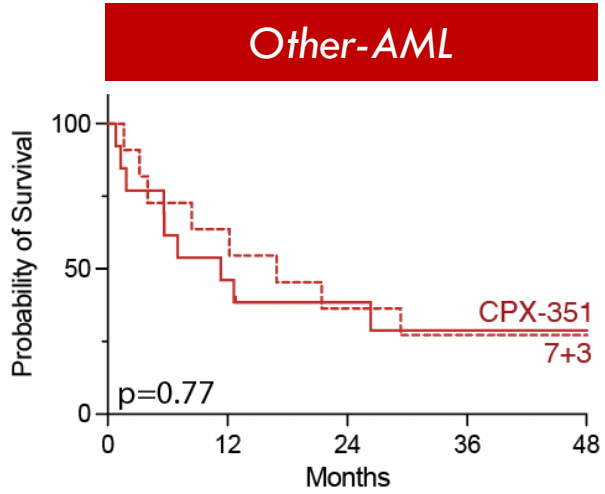


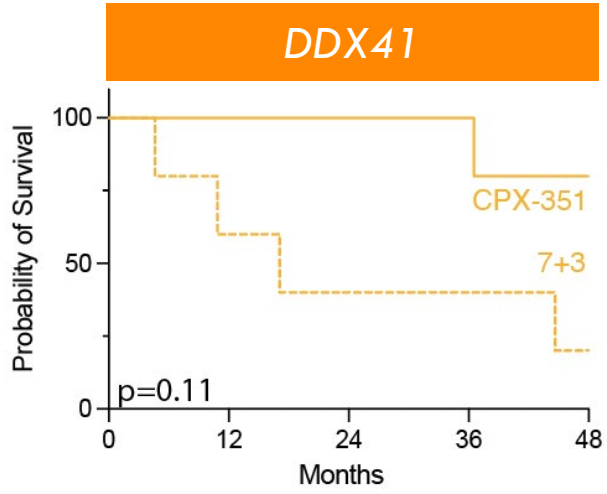
Phase 3 CPX-351 vs. 7+3 in secondary/therapy related AML

Overall survival according to molecular groups





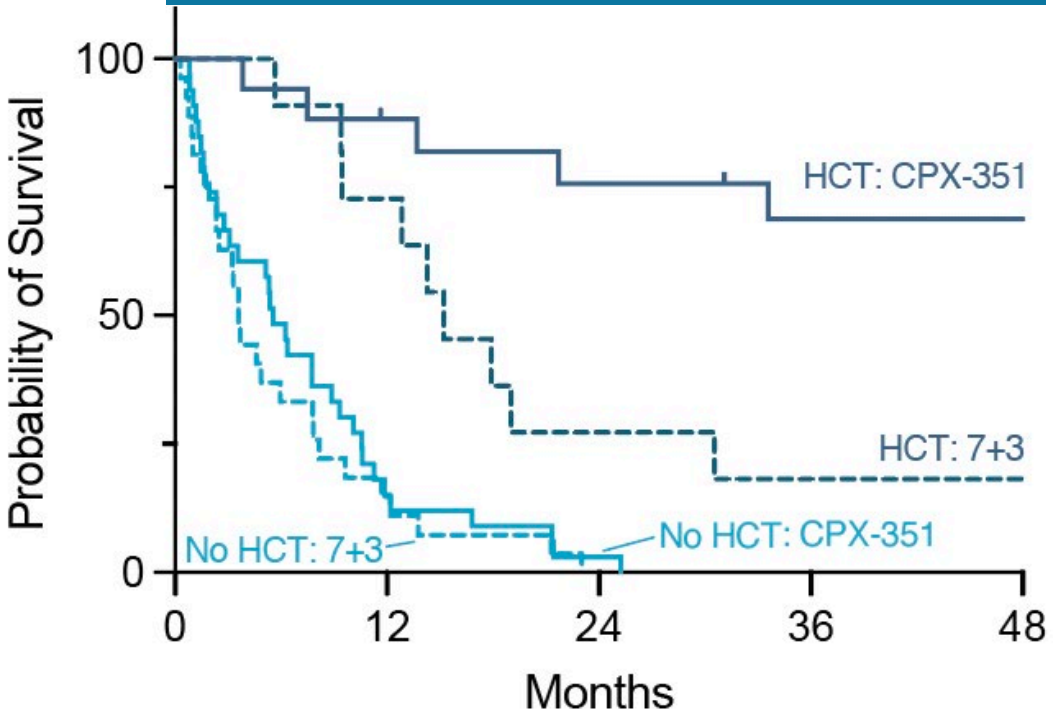




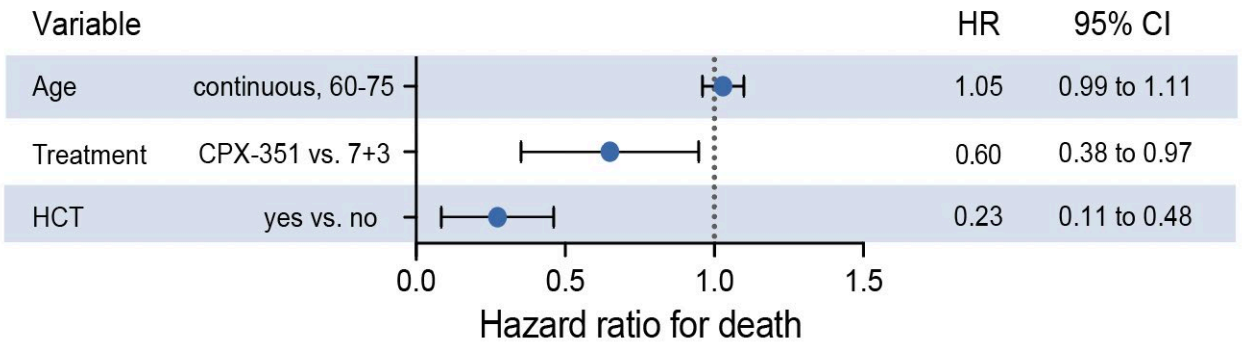
CPX-351 *vs.* 7+3 in AML-MR

Beneficial effect of CPX-351 driven by HCT

AML-MR
OS by HCT and treatment arm

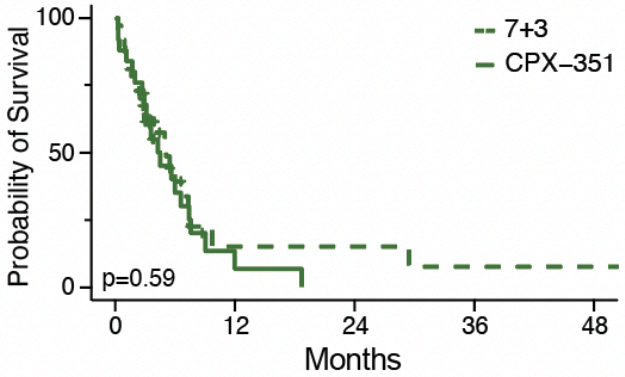
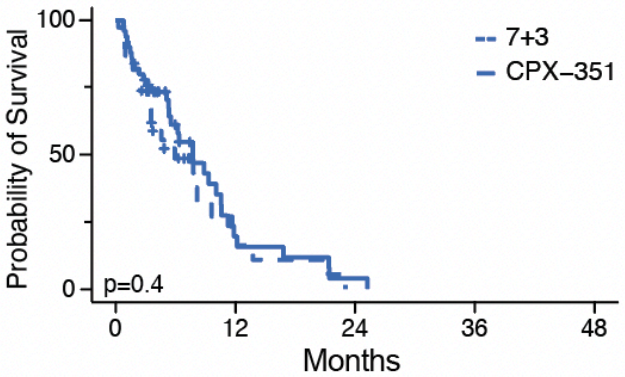
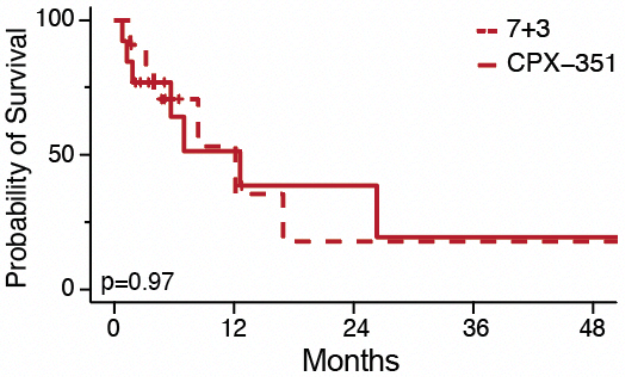
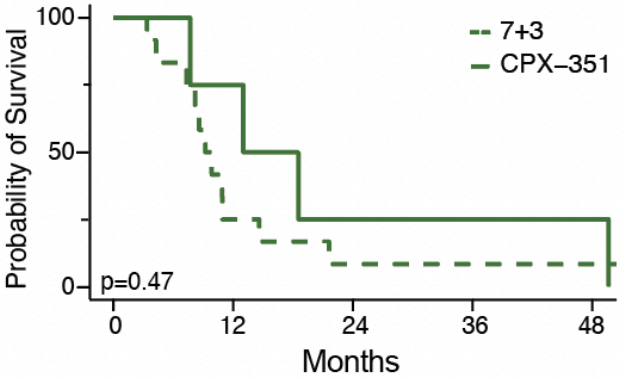
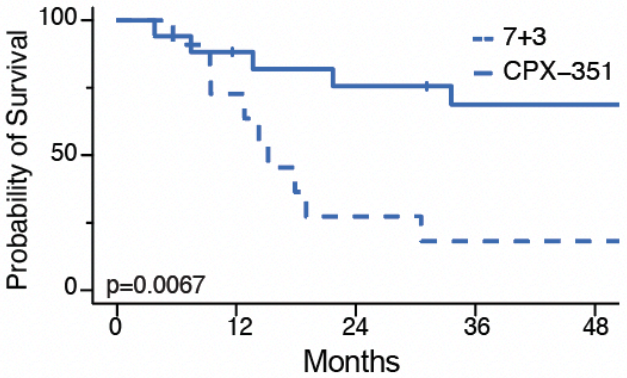
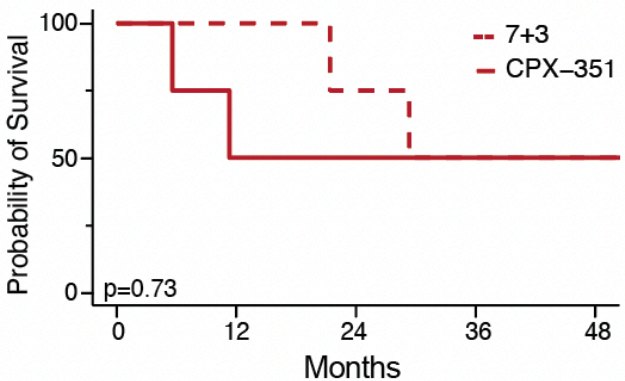


MV model
OS with HCT as time-dependent covariate



No benefit of CPX-351

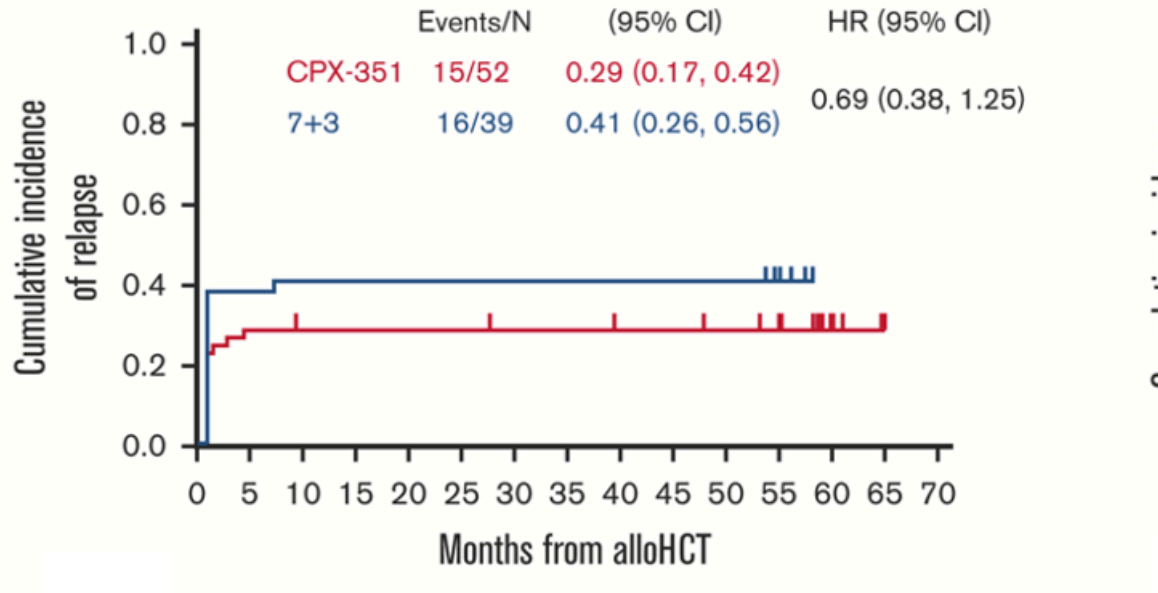
No beneficial effect of CPX-351 in any group

	TP53	*AML-MR*	*Other-AML*
Censored at HCT			
Transplant patients			

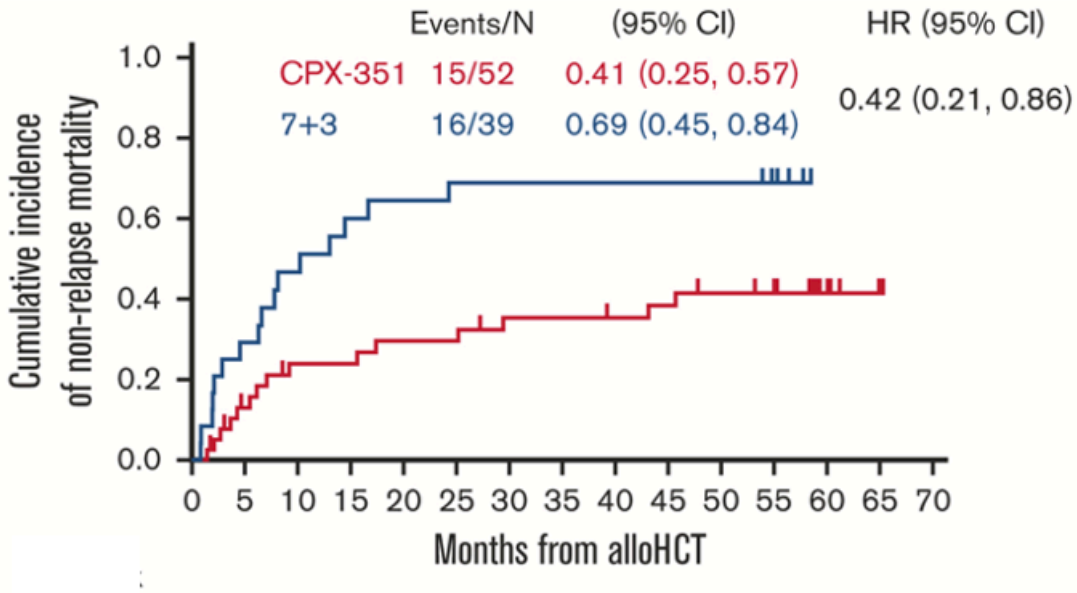
Post-HCT outcomes on Ph3 CPX-351 *vs.* 7+3 trial

Beneficial effect of CPX-351 driven by decreased NRM

Relapse



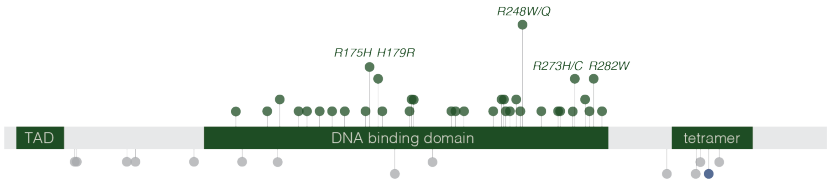
Non-relapse mortality

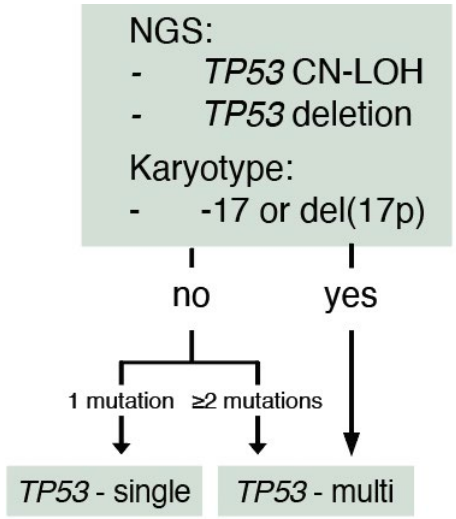


Uy, 2022
PMID: 35443022

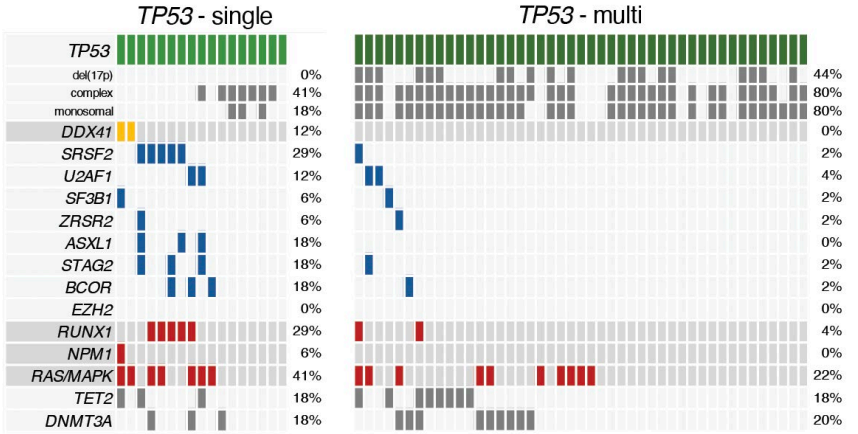
TP53 AML

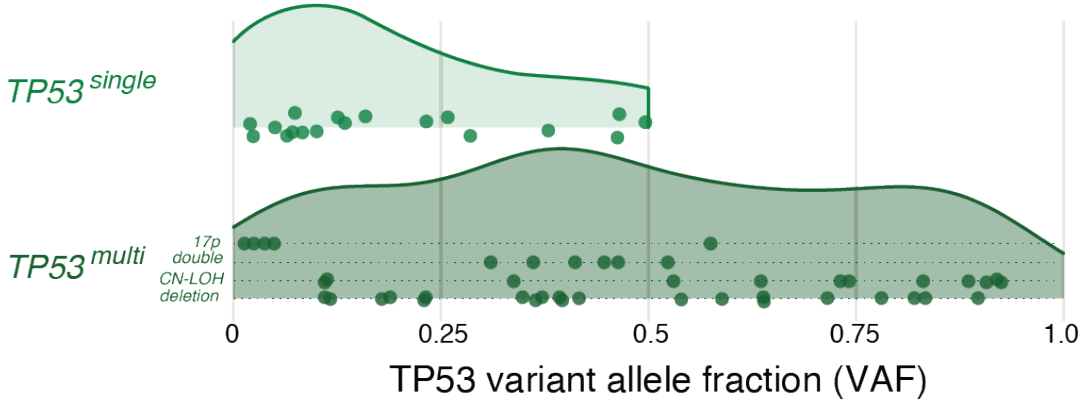
TP53 mutations and allelic state determination





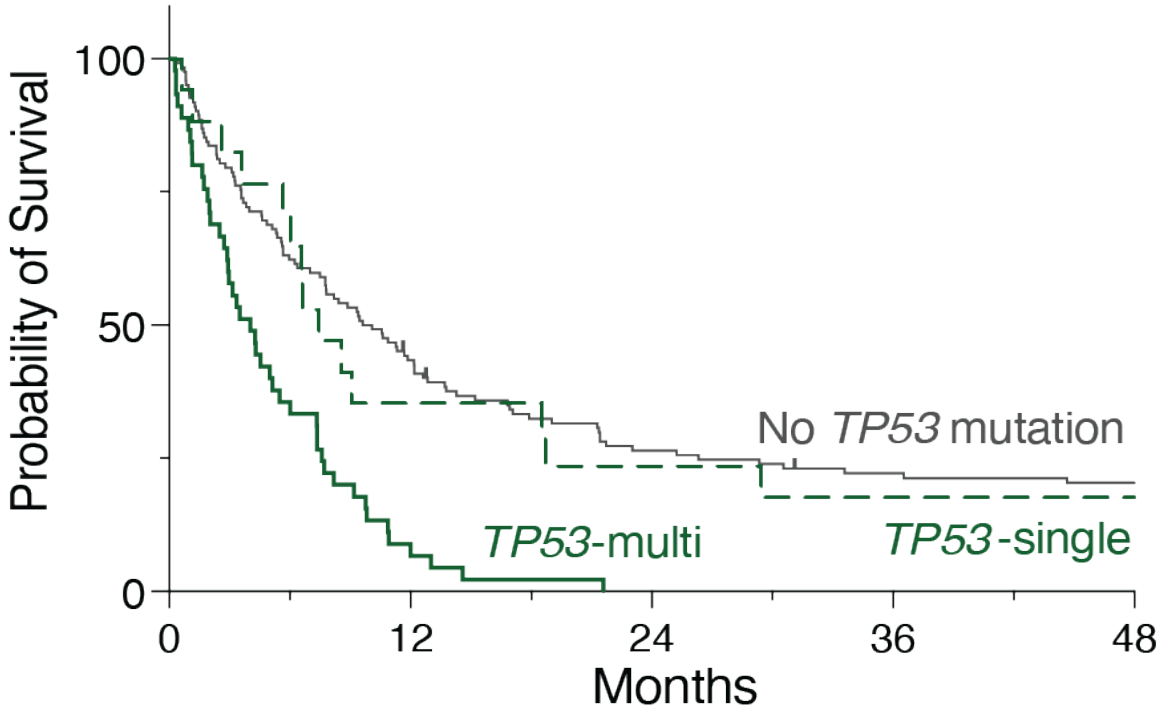
Genetic characteristics based on allelic state





TP53 AML

TP53: overall survival



Phase 3 CPX-351 vs. 7+3 in secondary/therapy related AML

Conclusions from genetic re-classification

1. AML-MR drives the benefit of CPX-351 over 7+3
   - Effect appears only with HCT consolidation

2. Allelic status underlies outcomes in TP53-AML
   - No difference between CPX-351 vs 7+3

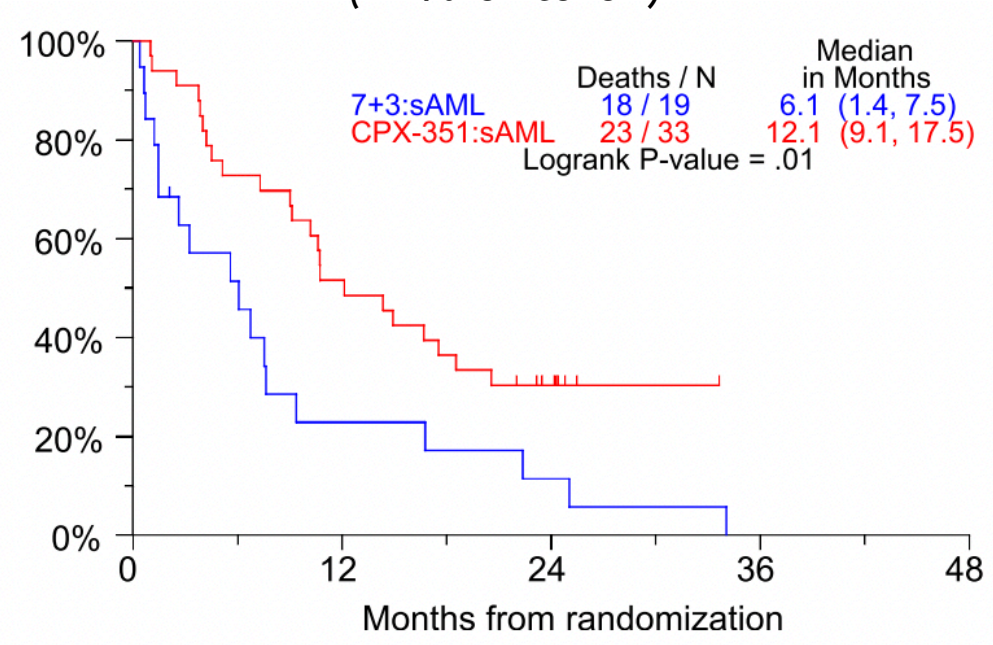
3. DDX41 AML: favorable induction outcomes even in HR-AML
   - Better with CPX-351 than 7+3? (cohort too small)

Phase 2 CPX-351 vs. 7+3

Planned subgroup analysis

"Secondary AML"

(41% of cohort)



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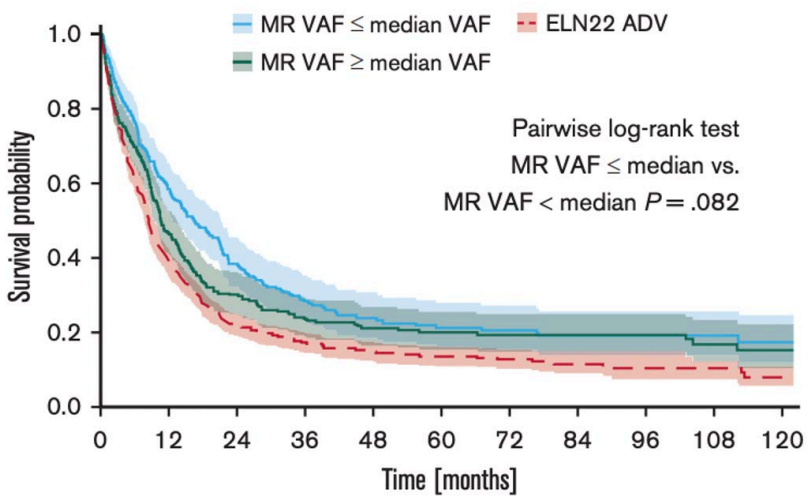
Iterative refinement of the AML-MR heuristic

Which heterogeneity is meaningful?

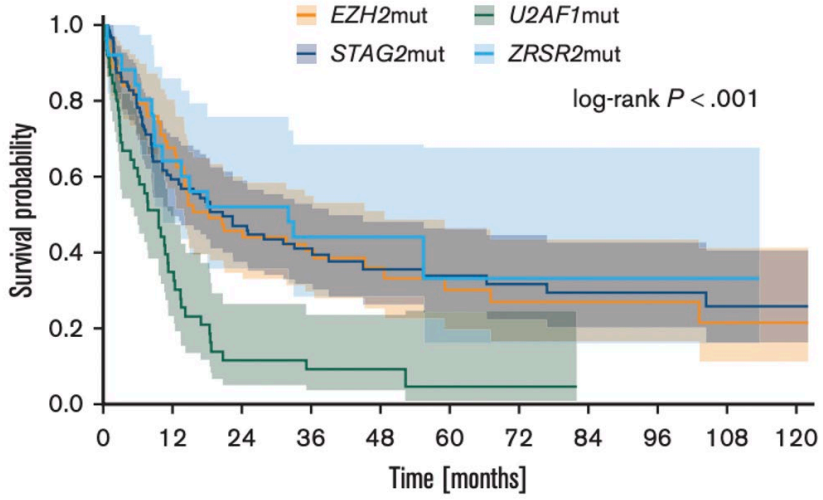
1570 intensively treated adult AML patients (AML96, AML60+, AML2003, SORAML)

PMID: 39504561

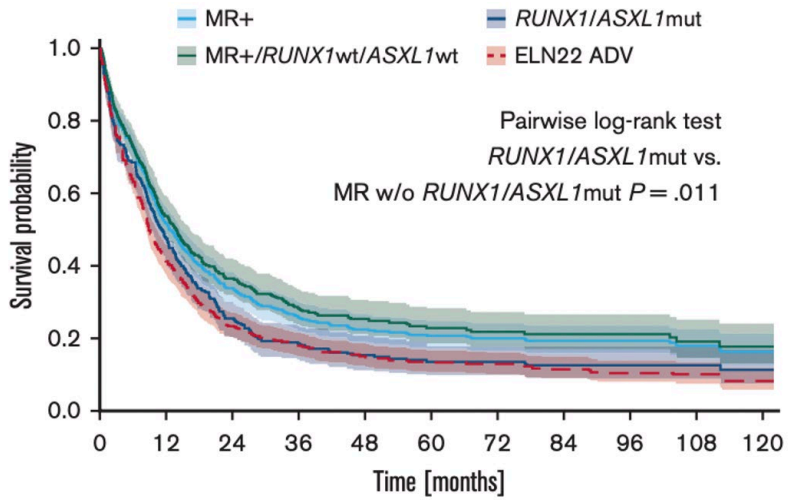
Position in clonal hierarchy



Subgroups



Co-mutations



Classification… moving forward?

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through core principles

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IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

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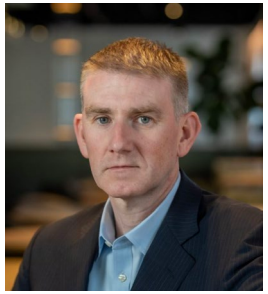
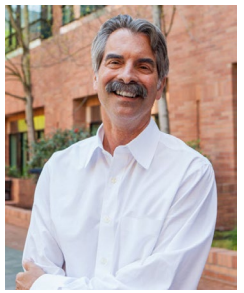

Chris Hourigan


Coleman Lindsley


Jerry Radich

Dana-Farber Cancer Institute

FRALIN BIOMEDICAL RESEARCH INSTITUTE AT VTC
CANCER RESEARCH CENTER (D.C.)
VIRGINIA TECH

Fred Hutch Cancer Center

Standards	Methods development	Clinical Trial Cohort Analysis & Regulatory Engagement	myeloMATCH Collaboration

Private sector financial support

Donated services and materials

Academic Partners
Dana-Farber Cancer Institute
Virginia Tech (Fralin Biomededical Research Institute)
Fred Hutchinson Cancer Research Center

Public-Sector Partners
National Cancer Institute (NCI)
National Heart Lung and Blood Institute (NHLBI)
U.S. Food and Drug Administration (FDA)

Private-Sector Partners
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Syndax Pharmaceuticals
Sysmex Inostics, Inc.
10x Genomics, Inc.
Takeda Pharmaceuticals
Thermo Fisher Scientific
TwinStrand Biosciences, Inc
Twist Bioscience Corporation

Clinical Trial Cohort Analysis & Regulatory Engagement

Serial molecular assessment using custom duplex NGS

Non-transplant

Phase 3

- P3001/PANTHER: AZA vs. AZA+Pevonedistat *(frontline HR-MDS and low-blast AML)*
- ENHANCE: AZA+magro vs. AZA+placebo *(frontline HR-MDS)*
- ENHANCE-2: AZA/Magro vs. AZA/Ven or intensive chemo *(frontline AML with ≥1 TP53 mutation)*
- ENHANCE-3: AZA/Ven+magrolimab vs. AZA/Ven+placebo *(frontline AML, unfit)*

Phase 1/2

- BLAST MRD AML-1: Phase 2 intensive chemo +/- pembrolizumab *(frontline AML, 18-75)*
- BLAST MRD AML-2 : Phase 2 AZA/Ven + pembrolizumab *(frontline AML, unfit ≥60)*
- SWOG 1612: Phase 2/3 AZA vs AZA+nivolumab *(AML ≥60)*
- P2002/PEVENAZA: Rando phase 2 AZA/Ven vs. AZA/Ven+pevonedistat *(frontline AML, unfit)*
- DFCI #19-263: Phase 1 LY3214996 (ERKi) monotherapy *(R/R AML)*
- DFCI #24-021: Phase 1 7+3+midostaurin+ revumenib *(frontline AML with NPM1 and FLT3)*
- DFCI #23-534: Phase 1 CIML NK cells + venetoclax as consolidation *(AML)*
- DFCI #18-351: Phase 1b 7+3 plus Venetoclax *(frontline AML)*
- NCT05342584 (Mantzaris): Phase 1b 7+3 plus Venetoclax *(frontline AML)*

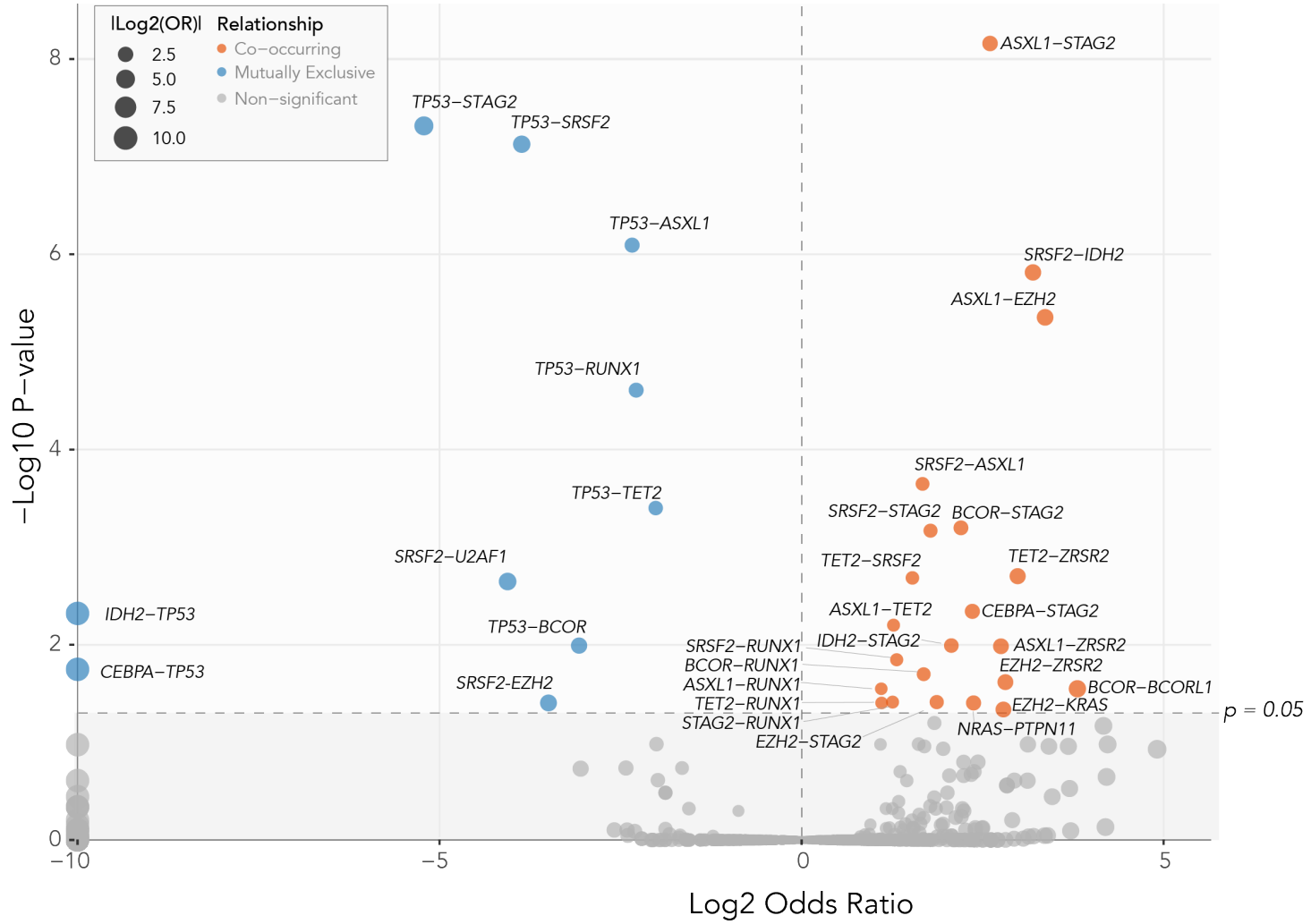
Transplant

- CTN1202: Pre-/Post-HCT *(AML/MDS)*
- CTN1703/1801: Pre-/Post-HCT - PTCy vs Tac/MTX *(AML/MDS)*
- ABA2: Pre-/Post-HCT - Tac/MTX +/- abatacept *(AML/MDS)*
- DFCI #18-283: Ven/FluBu2 +/- maintenance *(high risk MN)*
- DFCI #20-336: IS-free Treg engineered HaploHCT *(active RR ultra-HR-MDS/AML)*
- Ivo Maintenance: Rando Phase 2 ivosidenib vs. placebo as maintenance therapy *(AML, IDH1)*

The problem with pairs

Gene-gene diads → a need for triads, tetrads, …

390 patients on randomized Phase 3 HR-MDS/AML



The problem with pathways

RAS-MAPK subnetwork analyses

390 patients on randomized Phase 3 HR-MDS/AML

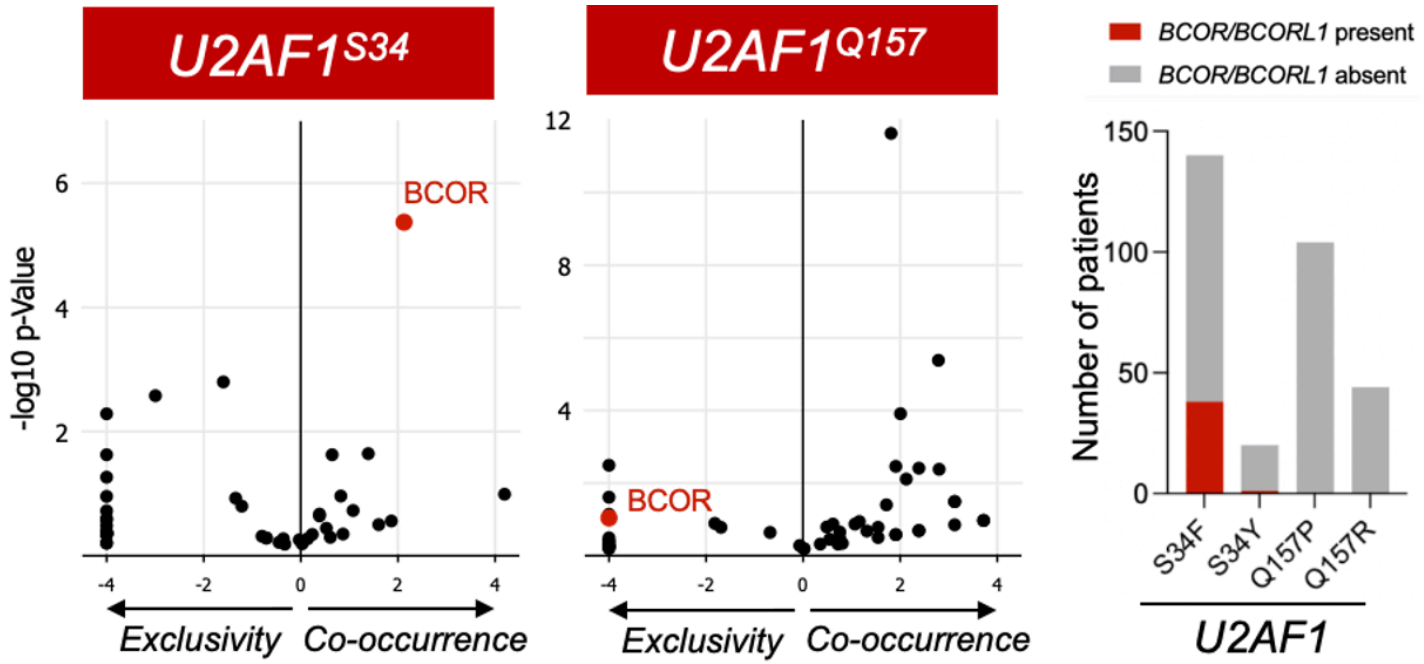
The problem with pathways

NRAS/KRAS codon specific biology?

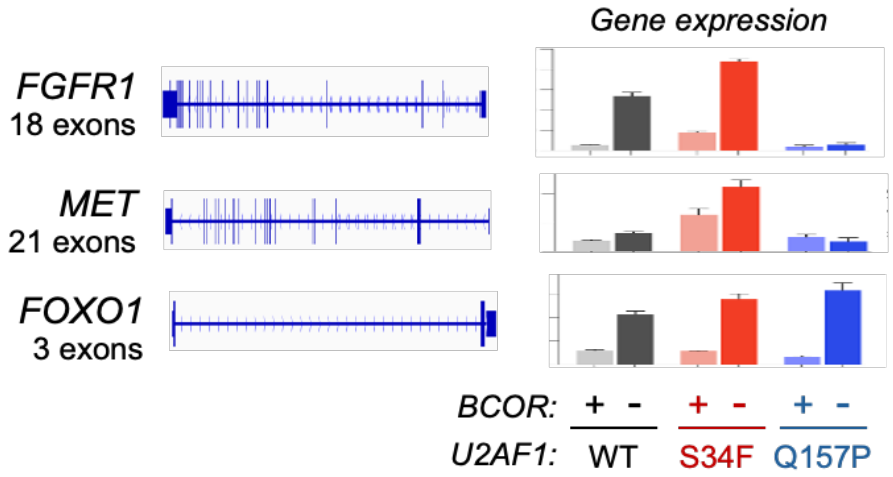
The problem with genes

U2AF1 codon specific biology?

U2AF1 has codon-specific co-mutation associations



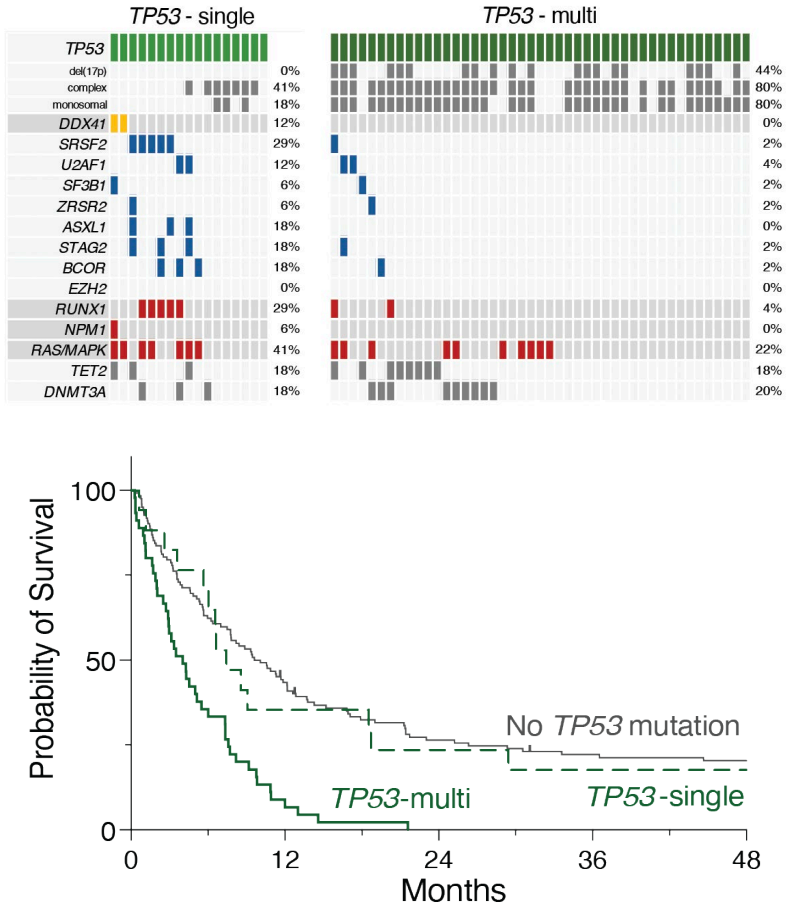
Differential impact of S34F and Q157P on impact of BCOR mutation



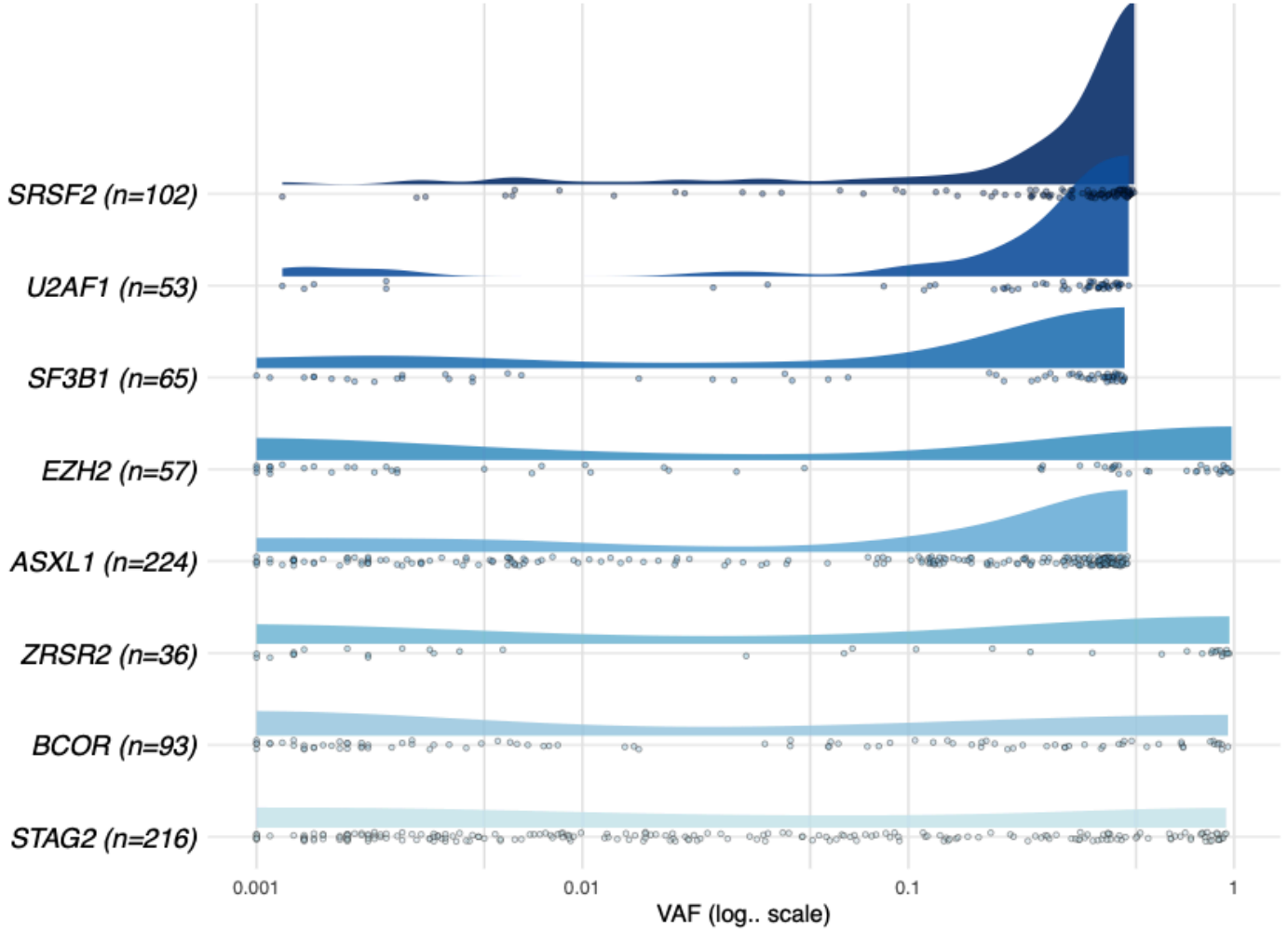
The challenge of categorical assignment

Defining meaningful subgroups → VAF is never 'the thing'

TP53
Allelic state subgroups



AML-MR
VAF heterogeneity



Everyone has an origin story?

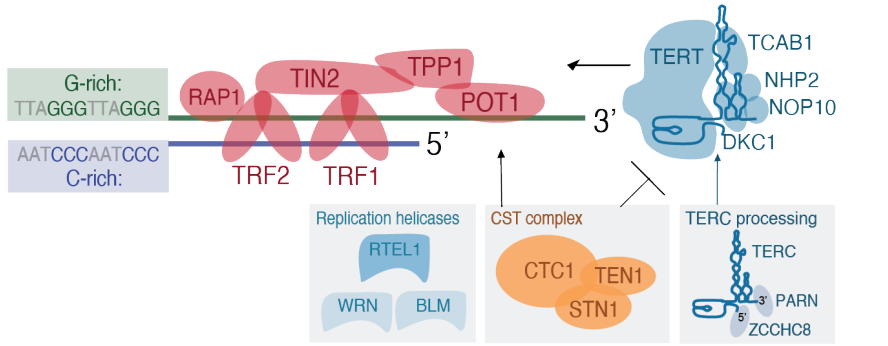
Defining meaningful subgroups

CPX-351 trial: additional germline P/LP variants

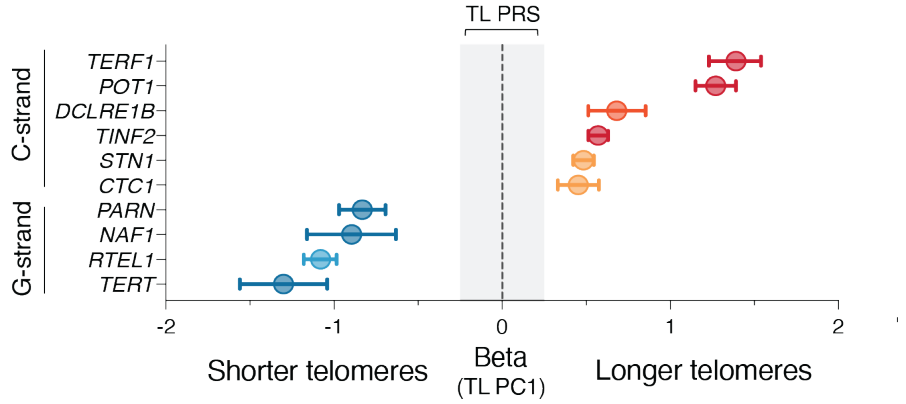
- *BRIP1 → TP53-multi*
- *CHEK2 → poor risk cyto + NRAS*
- *ATM → TP53-multi*
- *ATM → DNMT3A, BCOR, RUNX1, RASx4, ITD*
- *ATM → DNMT3A, SRSF2, TP53*
- *PARN → RAS x 5*
- *RTEL1 → TP53, ATMx2*
- *RTEL1 → U2AF1-S34F, BCORx2, NF1, PTPN11*

Defining "missing heritability"

Telomere maintenance machinery



UK Biobank
Germline rare variants and telomere length

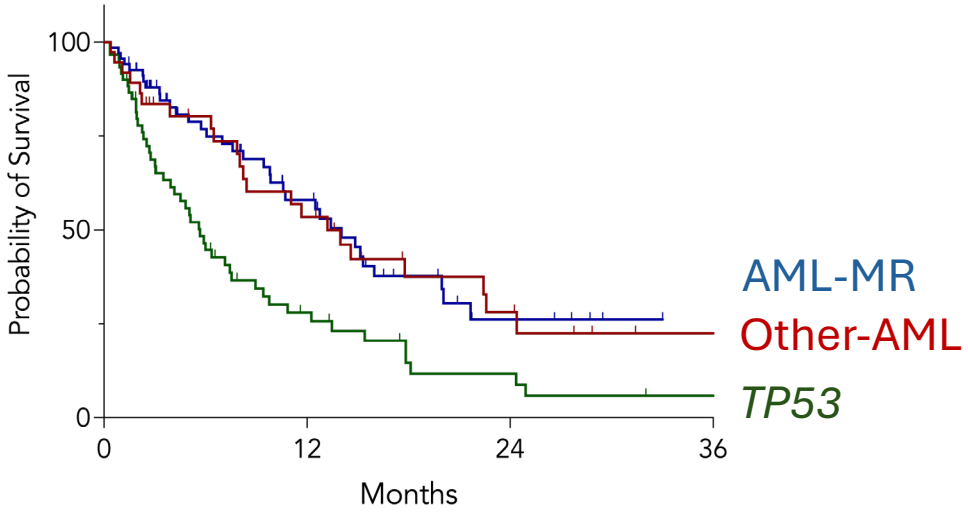


Context inflects meaning

Treatment can alter clinical impact of group

HMA + Venetoclax

Neutralizes the negative effect of AML-MR



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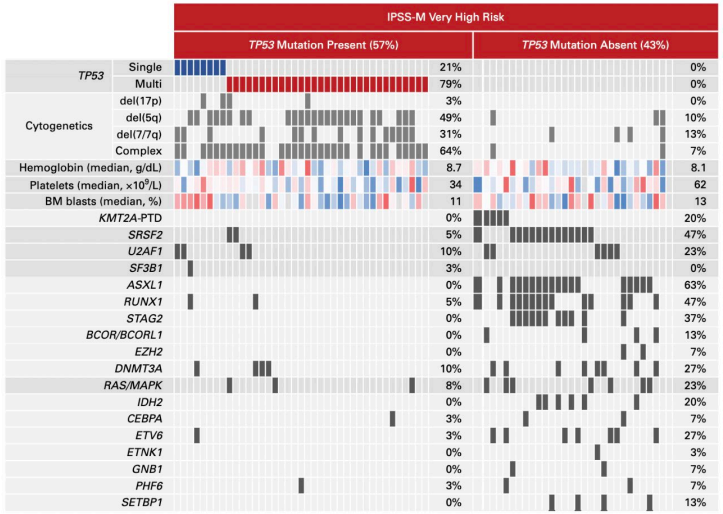
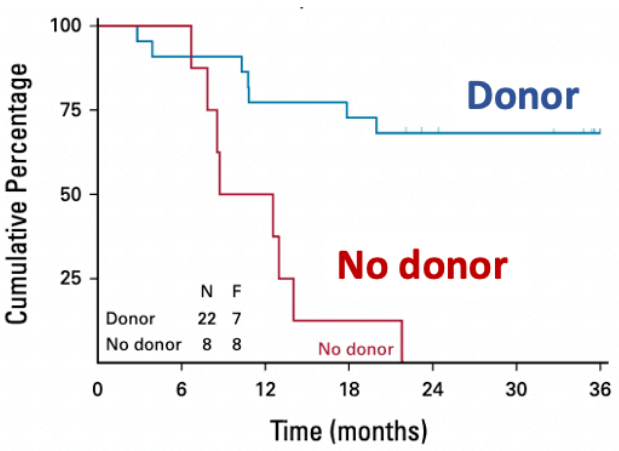
Allo HCT

Neutralizes negative effect of TP53-WT IPSS-M VH





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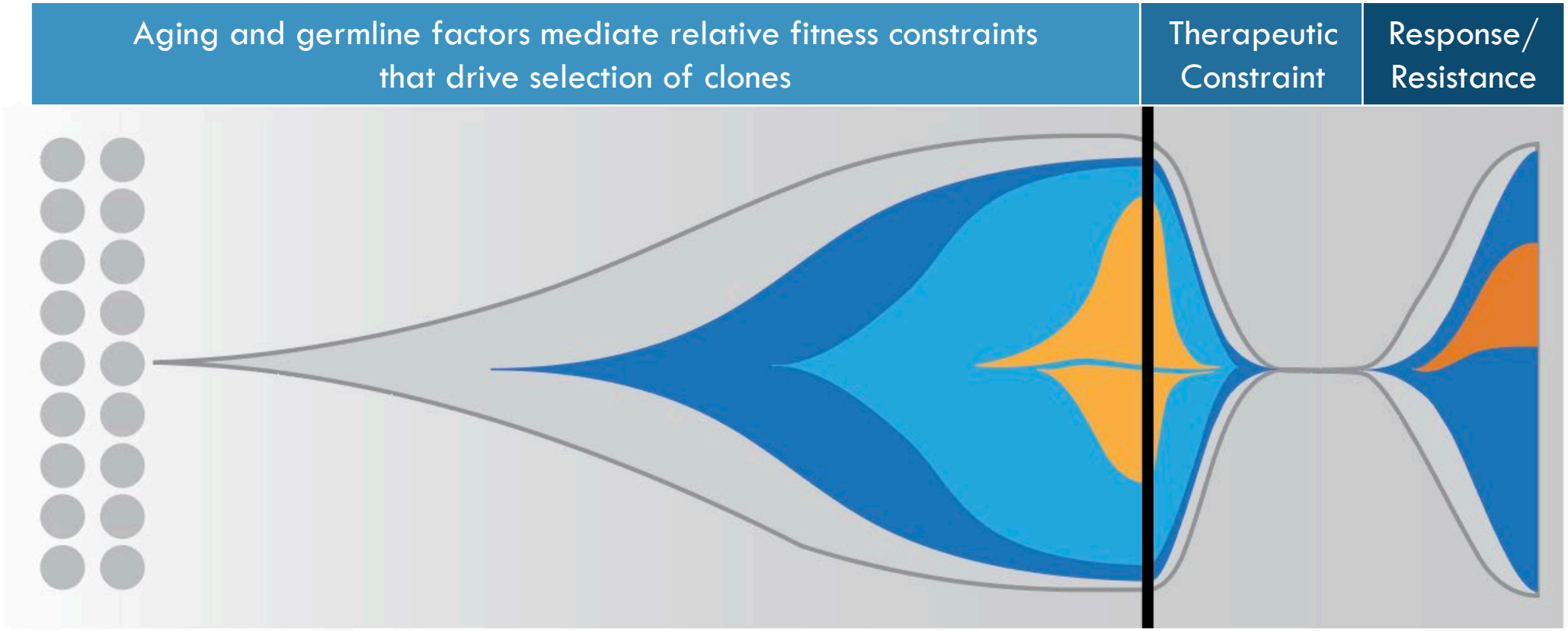
Pathogenesis and disease genetics

Reflect mechanism and magnitude of fitness constraint



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