Molecular prognostic scoring (IPSS-M) – How does it improve patient management?

Elizabeth A. Griffiths, MD
Roswell Park Comprehensive Cancer Center
State University of NY at Buffalo

ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Disclosures

- Advisory Board/Honoraria: AbbVie, Alexion Pharmaceuticals, Apellis, Celgene/BMS, CTI Biopharma, Genentech, Novartis, Picnic Health, Takeda Oncology, Taiho Oncology

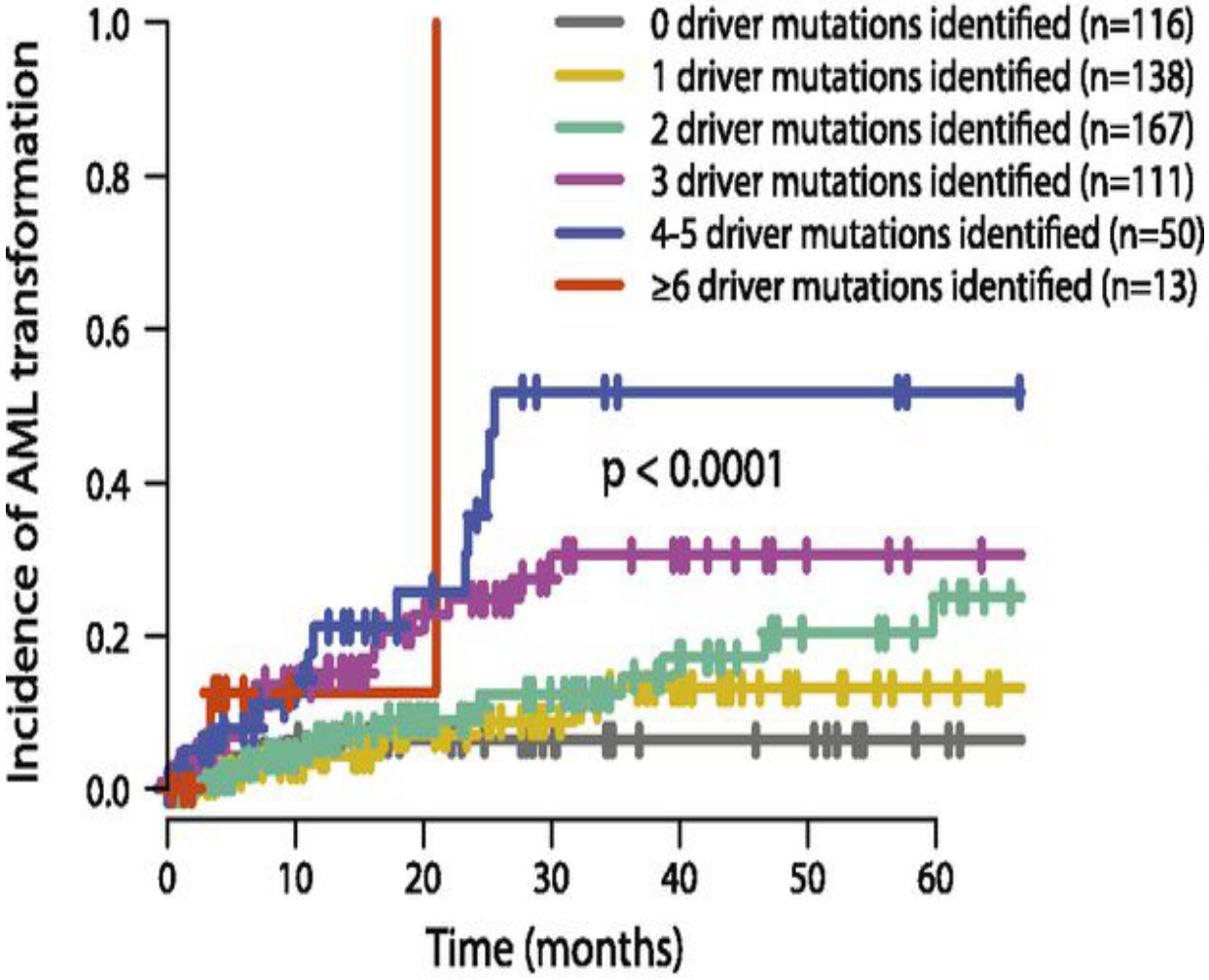
- Research Funding: Astex Pharmaceuticals, AstraZeneca Rare Disease, Alexion Pharmaceuticals, Apellis Pharmaceuticals, Blueprint Medicines, Genentech Inc,

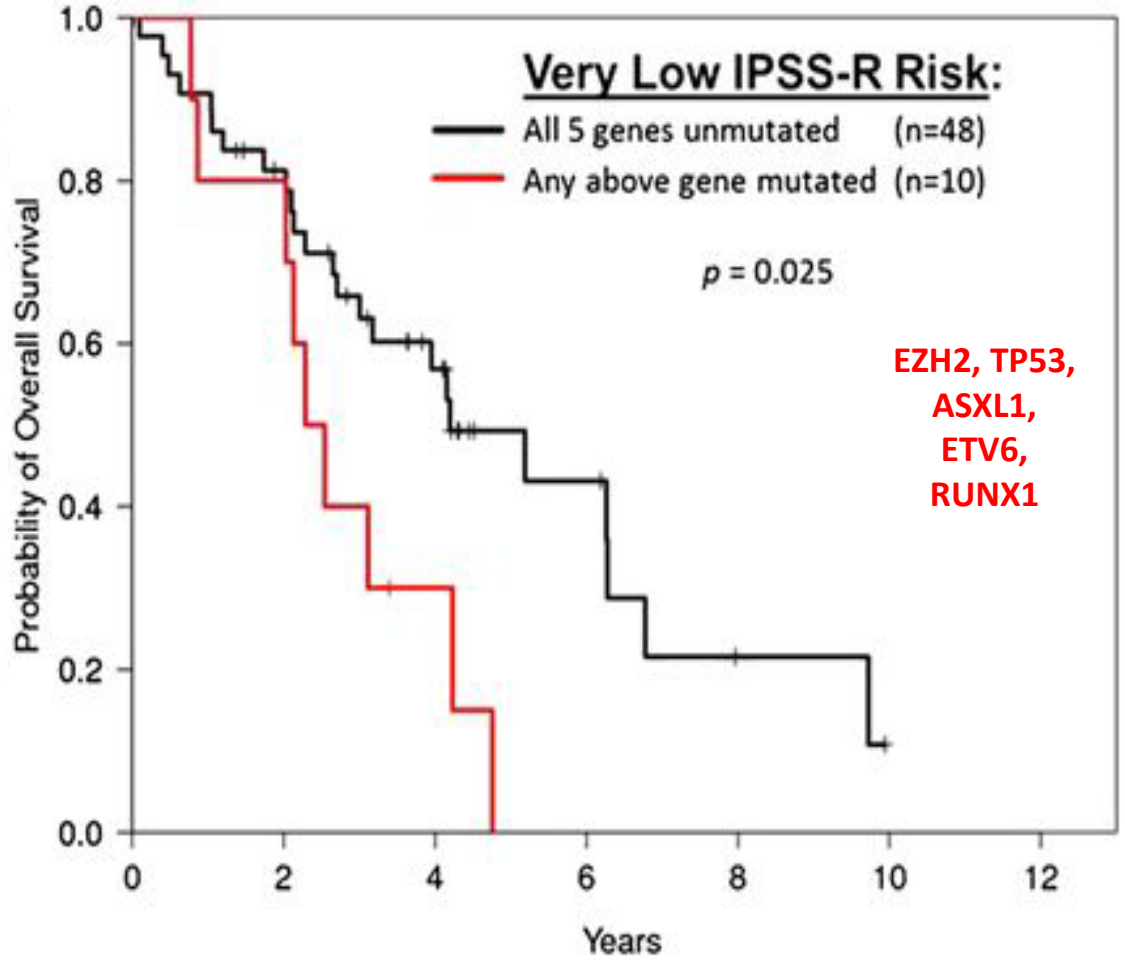
- CME/Honoraria: Physicians Educational Resource, MediCom Worldwide, American Society of Hematology, AAMDS International Foundation

Clinical Case: JC

- 76yowf, well, no ca hx, presents with pancytopenia
  - Baseline WBC 2.9, ANC 1.3, plts 78, hg 11.3.
  - BM: trilineage dysplasia, 8% blasts, NK in 20 cells
- Pt is asymptomatic and non-transfusion dependent
  - IPSS-R calculation is performed, score is 3.5- intermediate risk
- Referral to transplant, initial rx-> watchful waiting Q3m
- NGS: *TP53* R248W (VAF 42%), *ASXL1* G646fs*12, *IDH2* R140Q, *FANCA* loss exons 3-6, *NOTCH1* N2143fs*99, *RUNX1* E80*, R166Q-subclonal, *SRSF2* P95T, *U2AF1* S34T, *STAG2* R953*
- What to do?

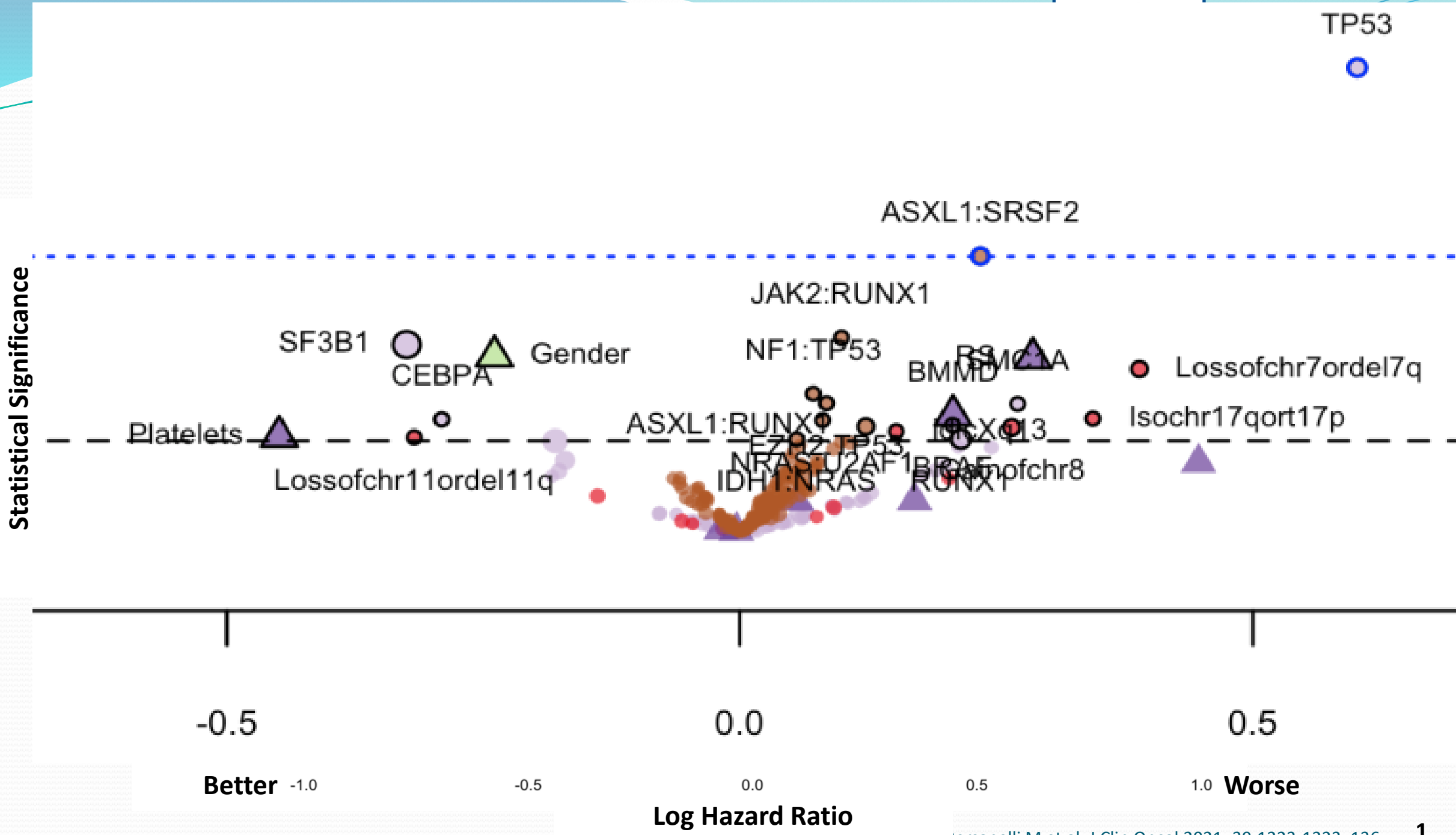
Mutations Are Common & Prognostic in MDS





Papaemmanueuil et al, *Blood* 2013; 122:3616-27
Bejar, ASH Educ Program, 2013: 504-10.

Malcovati et al, Blood 2015; 126:233–41.
Malcovati et al, Blood 2017; 129: 3371-8.
Tsaknakis et al, Blood 2021; 138:1249–57.


TP53
ASXL1:SRSF2
JAK2:RUNX1
SF3B1
CEBPA
Gender
NF1:TP53
BMMD
Lossofchr7ordel7q
Platelets
ASXL1:RUNX1
Isochr17qort17p
Lossofchr11ordel11q
IDH1:NRAS
RUNX1
-0.5
0.0
0.5
Statistical Significance
Better
-1.0
-0.5
0.0
0.5
1.0
Worse
Log Hazard Ratio

Until Recently, no molecular prognostic standard

- We knew:
  - More mutations-> worse
  - *TP53* mutations-> bad
  - Complex karyotypes, chromosome 7-> bad

- How to integrate all of this in the face of patients presenting at a range of age, comorbidity, performance status?

- Given the potential toxicity of allo Tx, who should proceed?

What did the IPSS-M Cohort Teach Us?

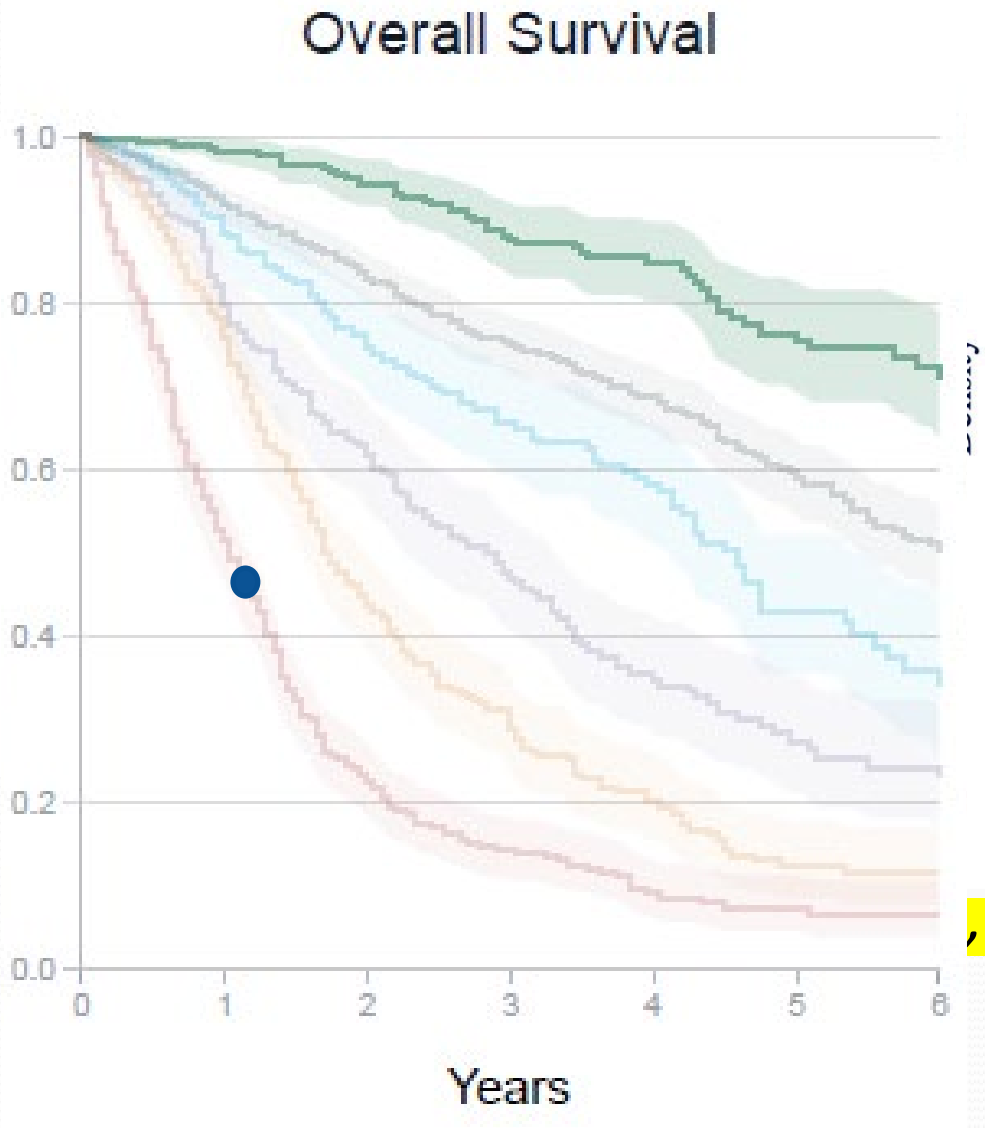
- *TP53*$^{\text{multi-hit}}$, *FLT3*-ITD/TKD, & *KMT2A* (MLL) PTDs (NEW)
  - Predict worst risk

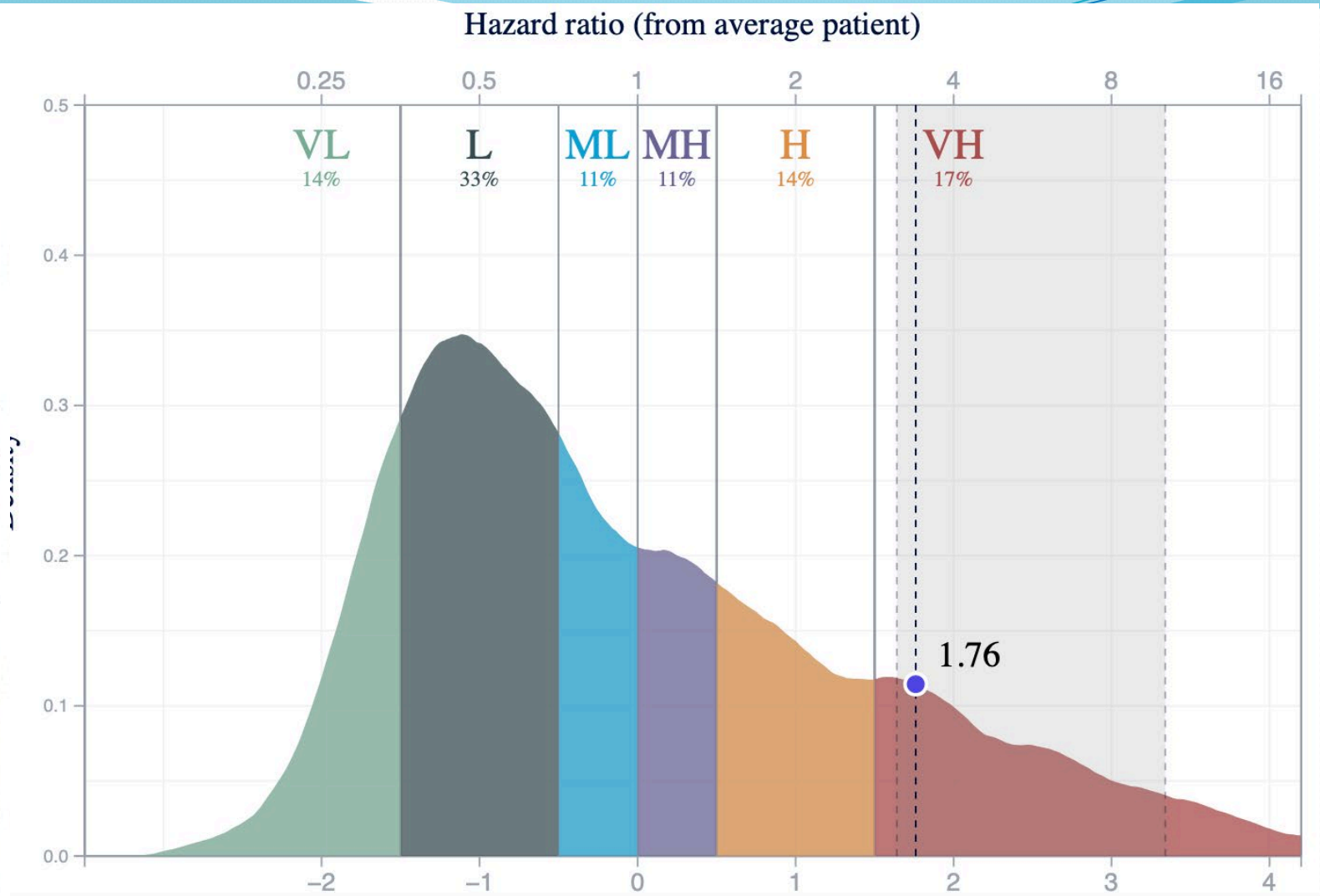
- Mutations in *ASXL1*, *CBL, DNMT3A, ETV6, EZH2, IDH2, KRAS, NPM1, NRAS*, *RUNX1*, *SRSF2*, and *U2AF1*
  - Individually-> worsen risk

- Add'l risk by counting mutations (0,1,≥2):
  - *BCOR/1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*
  - *https://www.mds-risk-model.com/*

Bernard E et al. NEJM Evidence 2022; 1 (7).

Clinical Case: IC



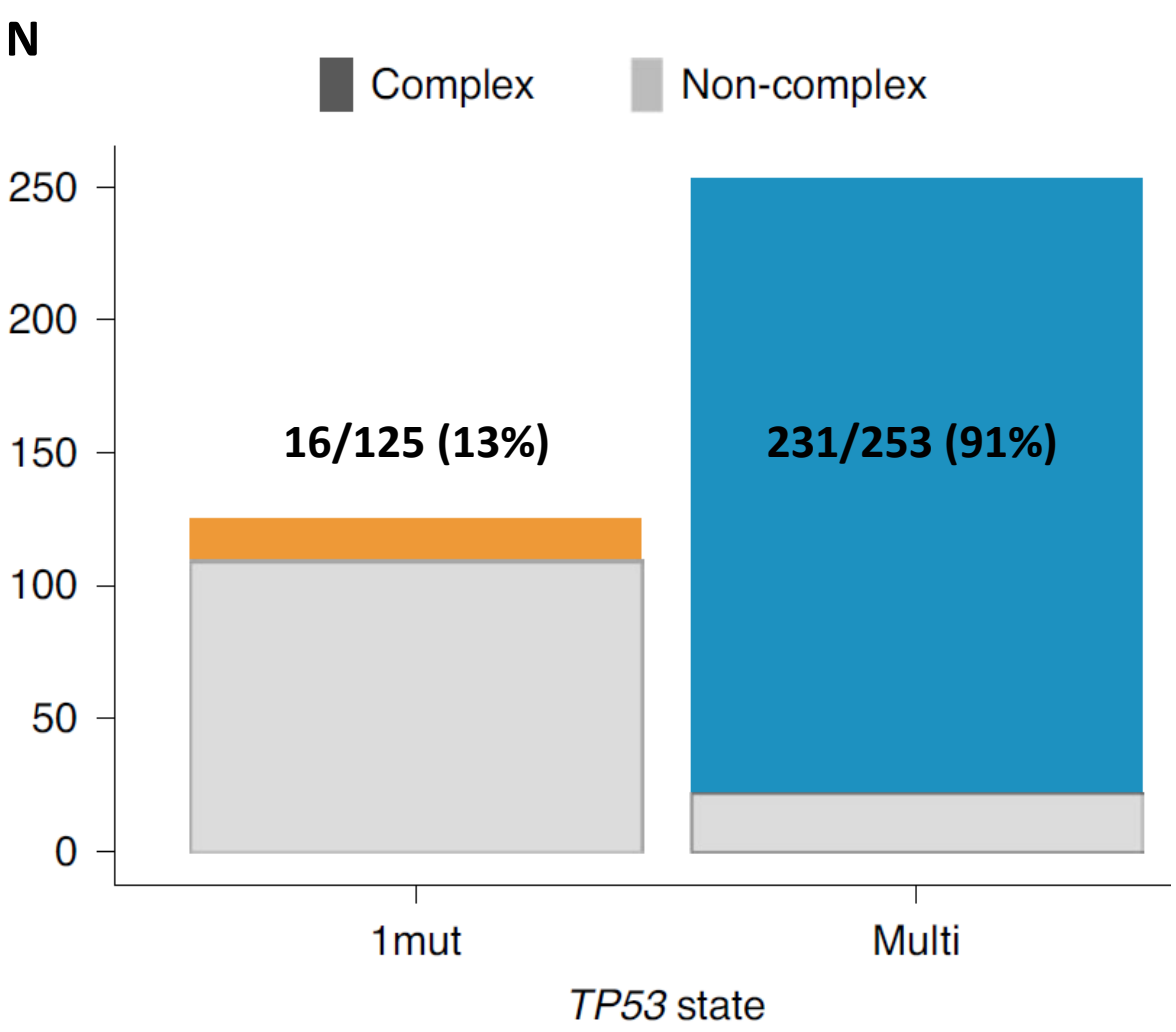


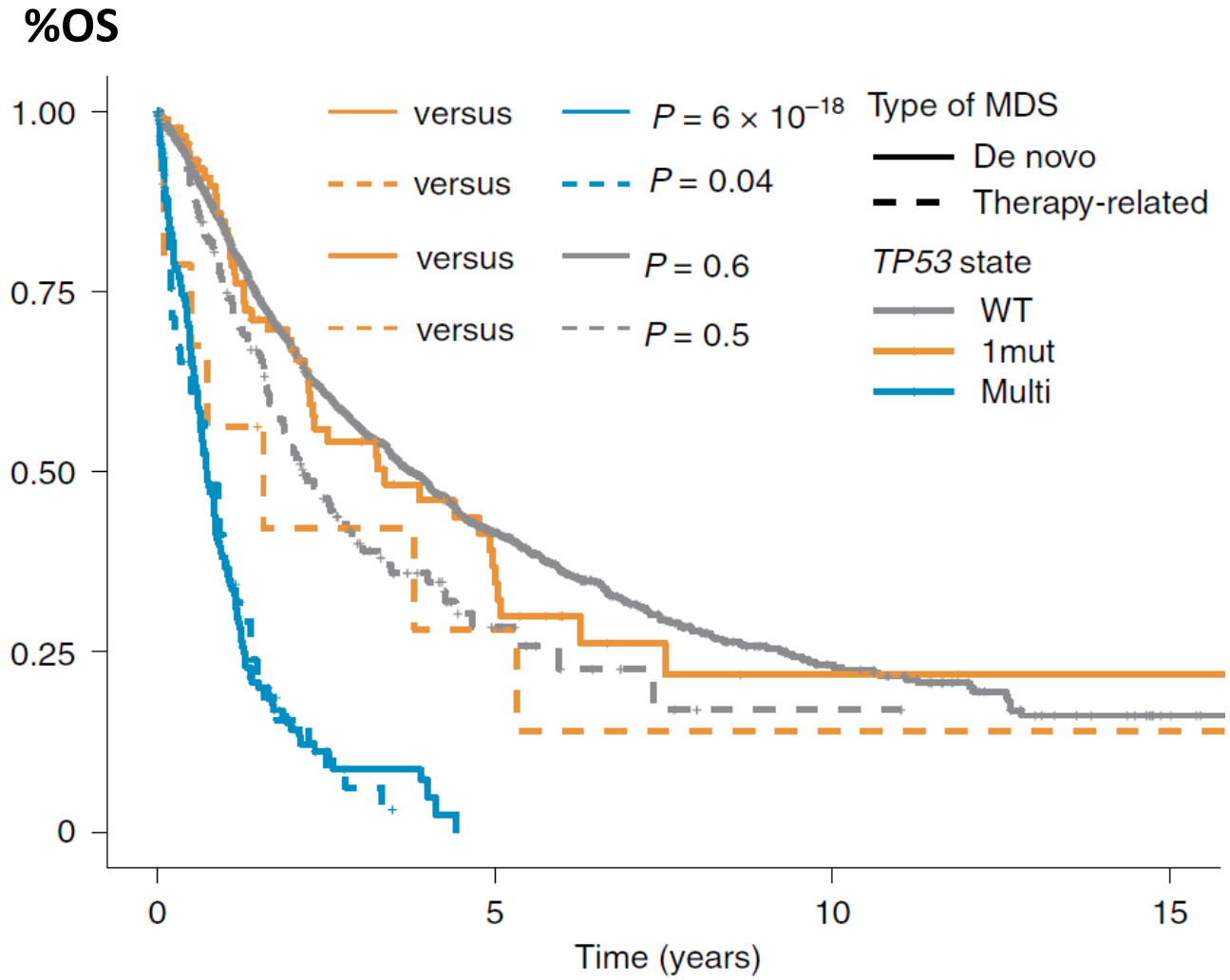
, STAG2

https://www.mds-risk-model.com/

Bernard et al. NEJM Evidence 2022

What is Multi-hit TP53?

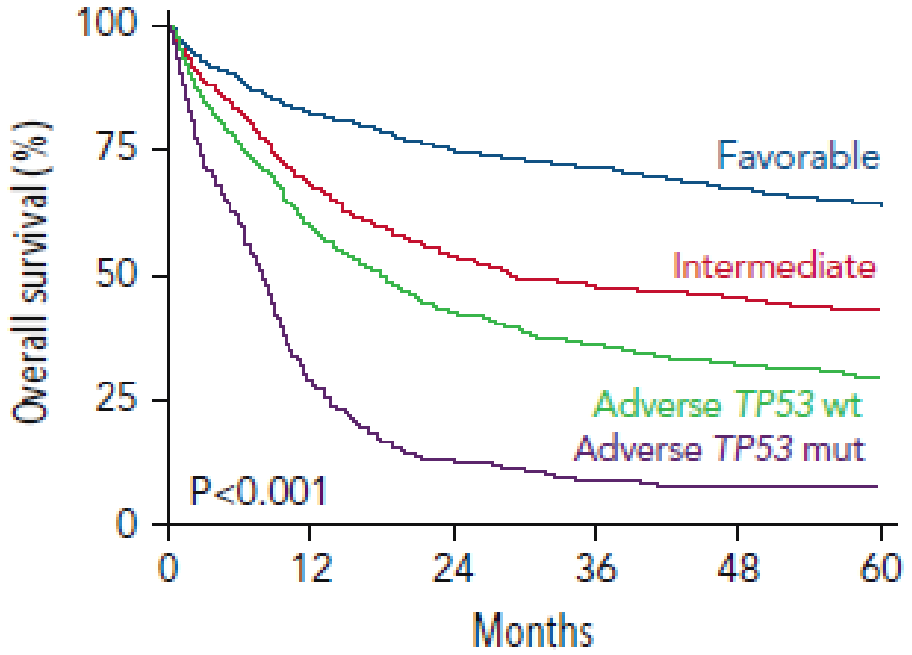




Bernard et al, Nat Med (2021) 26:1549-56.

TP53^{mut} MDS/AML-> Even MRD(-) & AlloTx

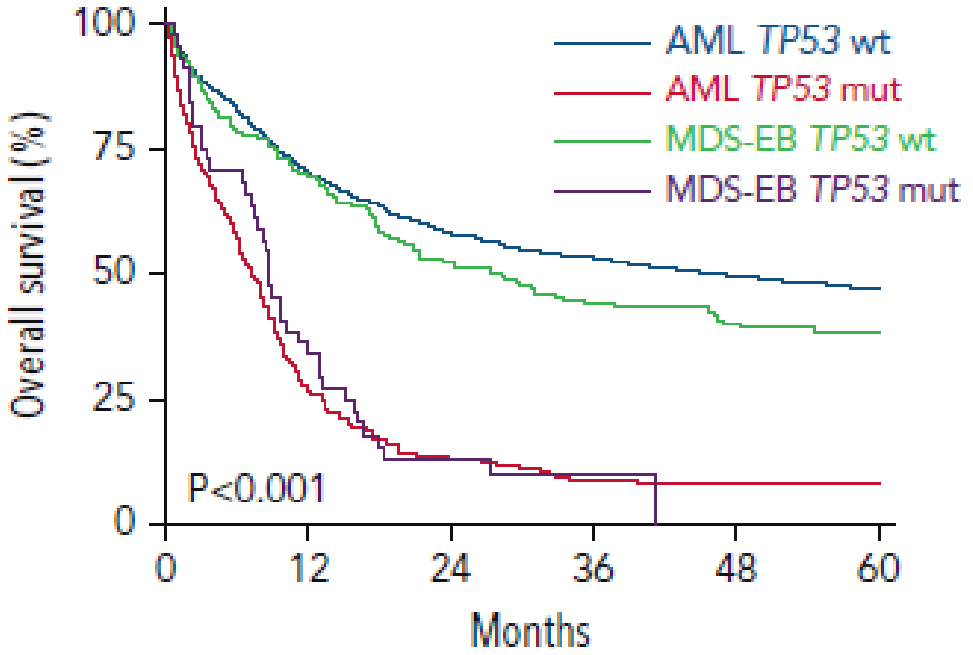
A



No. at risk:

Favorable	713	581	520	432	313	228
Intermediate	602	402	308	236	162	115
Adverse *TP53* wt	655	386	267	201	142	89
Adverse *TP53* mut	230	65	28	15	9	5

B



No. at risk:

AML *TP53* wt	1805	1255	1014	807	572	397
AML *TP53* mut	186	50	23	14	9	5
MDS-EB *TP53* wt	165	114	81	62	45	35
MDS-EB *TP53* mut	44	15	5	1	0	0

Grob T et al. Blood (2022) 139:2347-54.

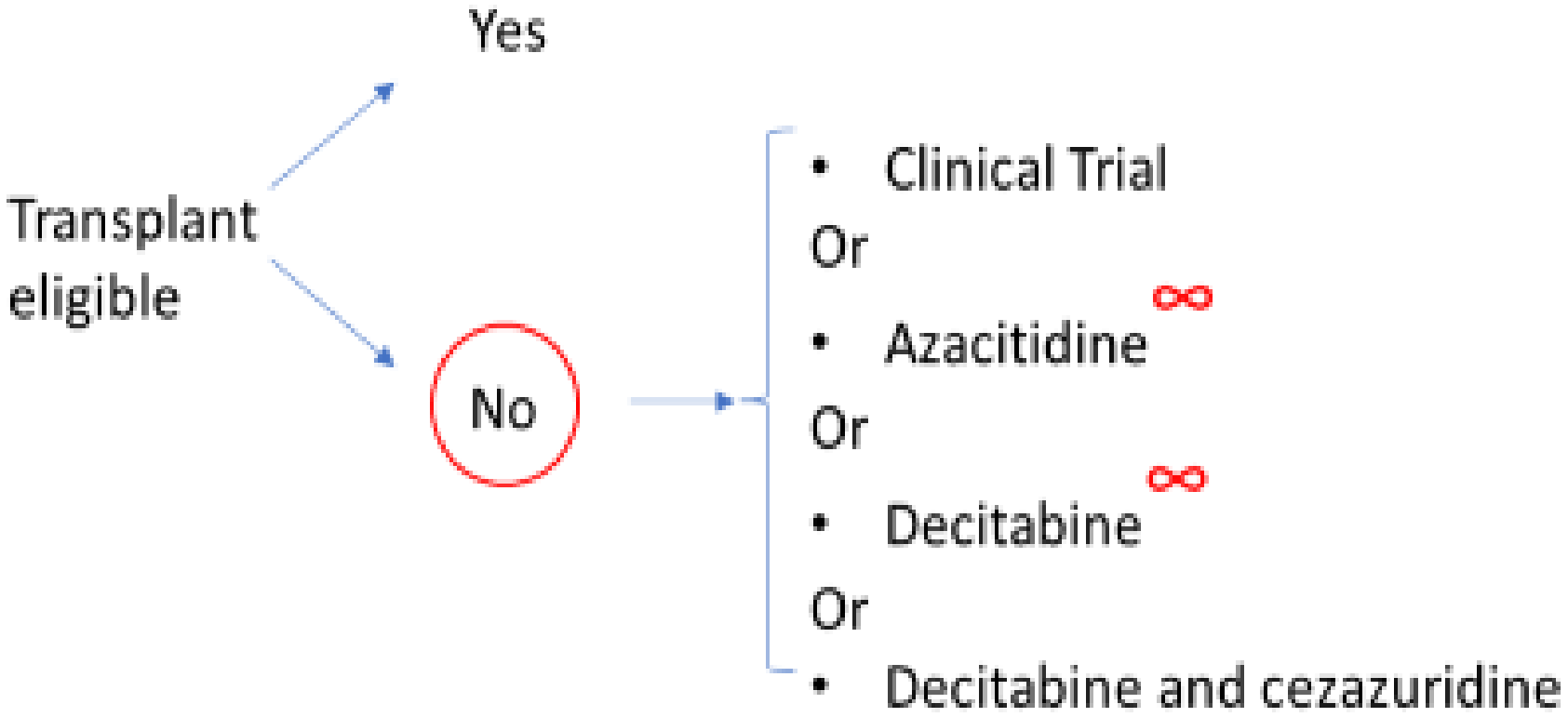
JC- Continued

- Equivocally fit for transplant, but isn't interested
- Progressive count decline over 6 months->
- Enrolls on trial of novel oral HMA
  - Serial marrows show blasts 13-15%, developing -17
- Currently s/p cycle 10- non-transfusion dependent w/ good QOL

- At the time of decision for no transplant- initiated honest discussion of prognosis, pts designated herself DNR/DNI
  - Does not want to die in the hospital

US Guidelines suggest HMAs for all high-risk patients

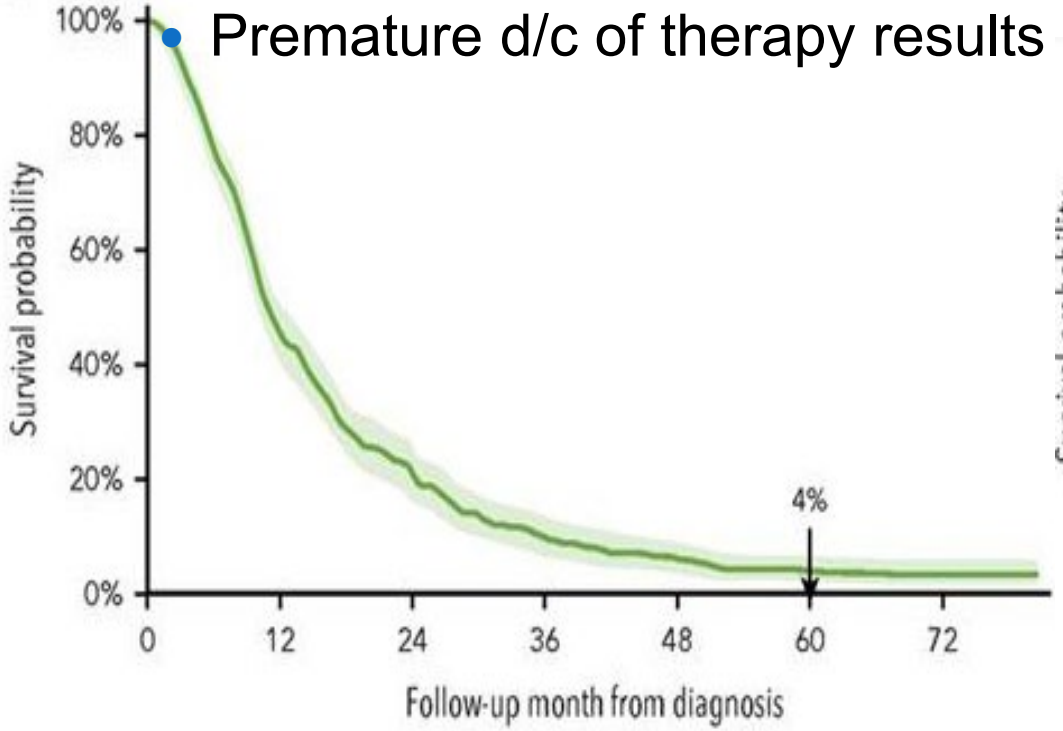
- NCCN Guidelines for high-risk disease:

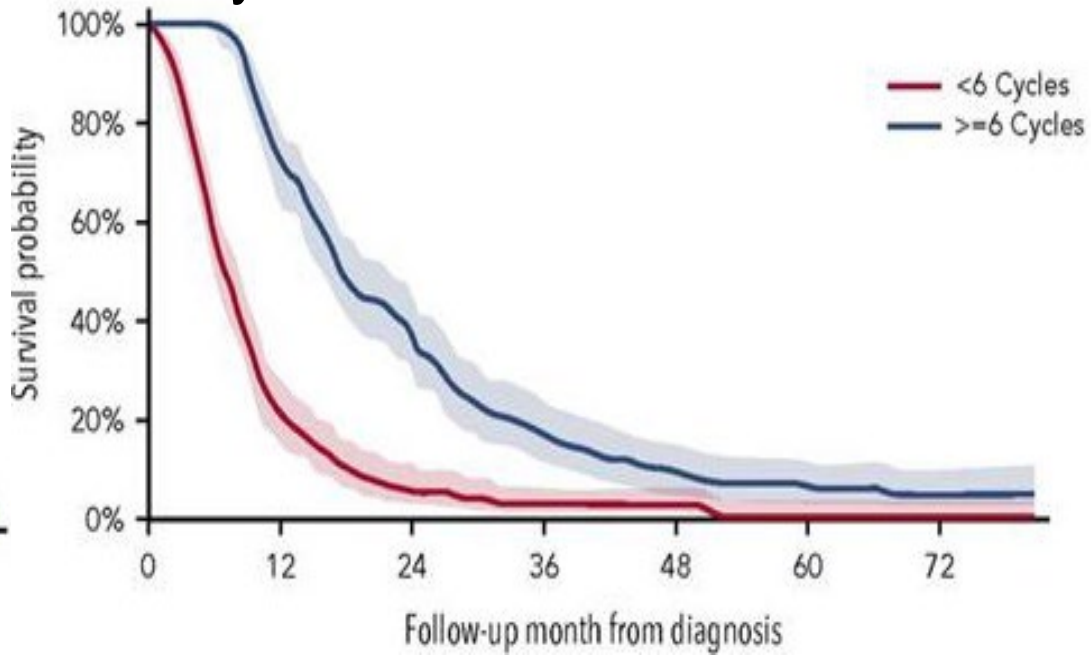


∞ = azacitidine or decitabine should be continued for at least 4-6 cycles to determine response and continued as maintenance.

HMA benefit less clear for oldest old

- HMA survival benefit ~3m for those >79
- Pts getting <6 cycles derive less benefit
  - Early discontinuation (<4cy) more common in older pts w poor PS
  - Premature d/c of therapy results in toxicity w/o OS benefit





Davidoff AJ et al. Leuk Lymph 2020;61:1178-87.
Zeidan AM et al. Clin Lymph Myel Leuk 2022;22:670-9.
Shallis RM et al. Drugs & Aging 2021:38;751–67.

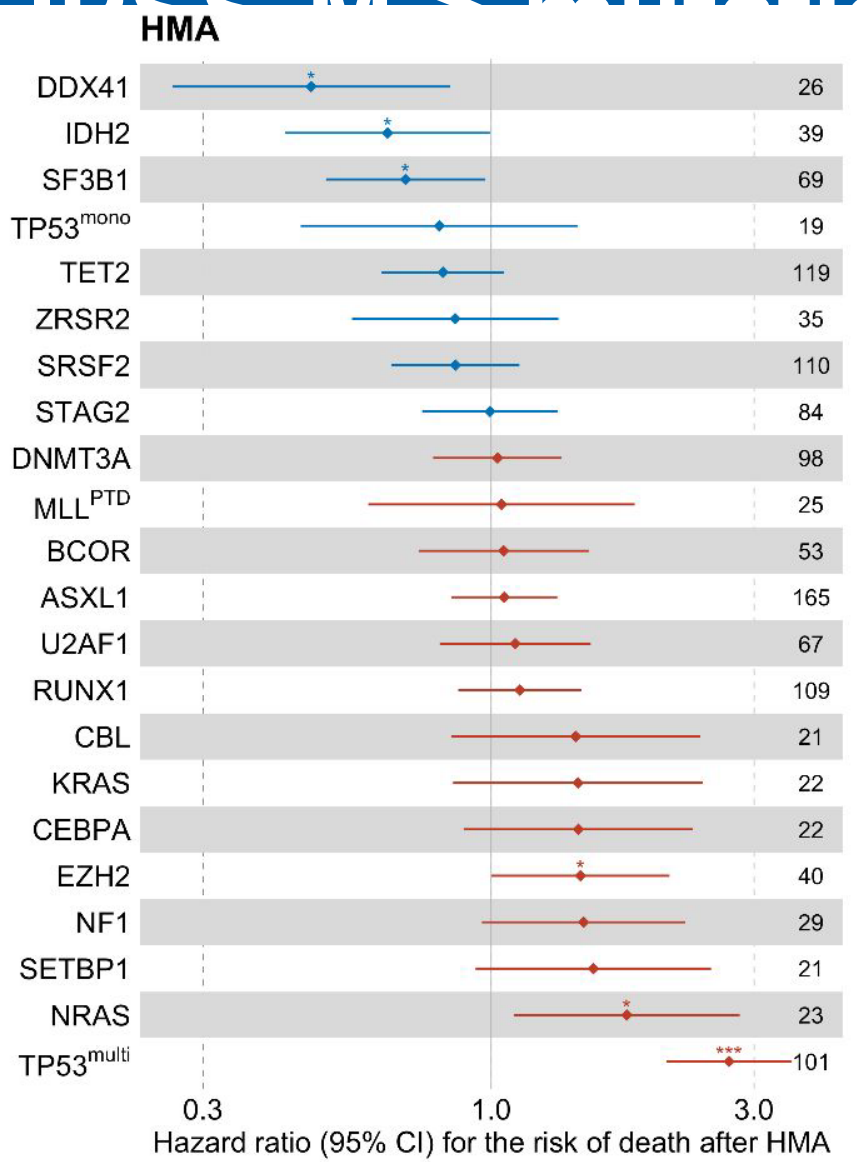
Zeidan AM et al. Blood 2018;131: 818–821.

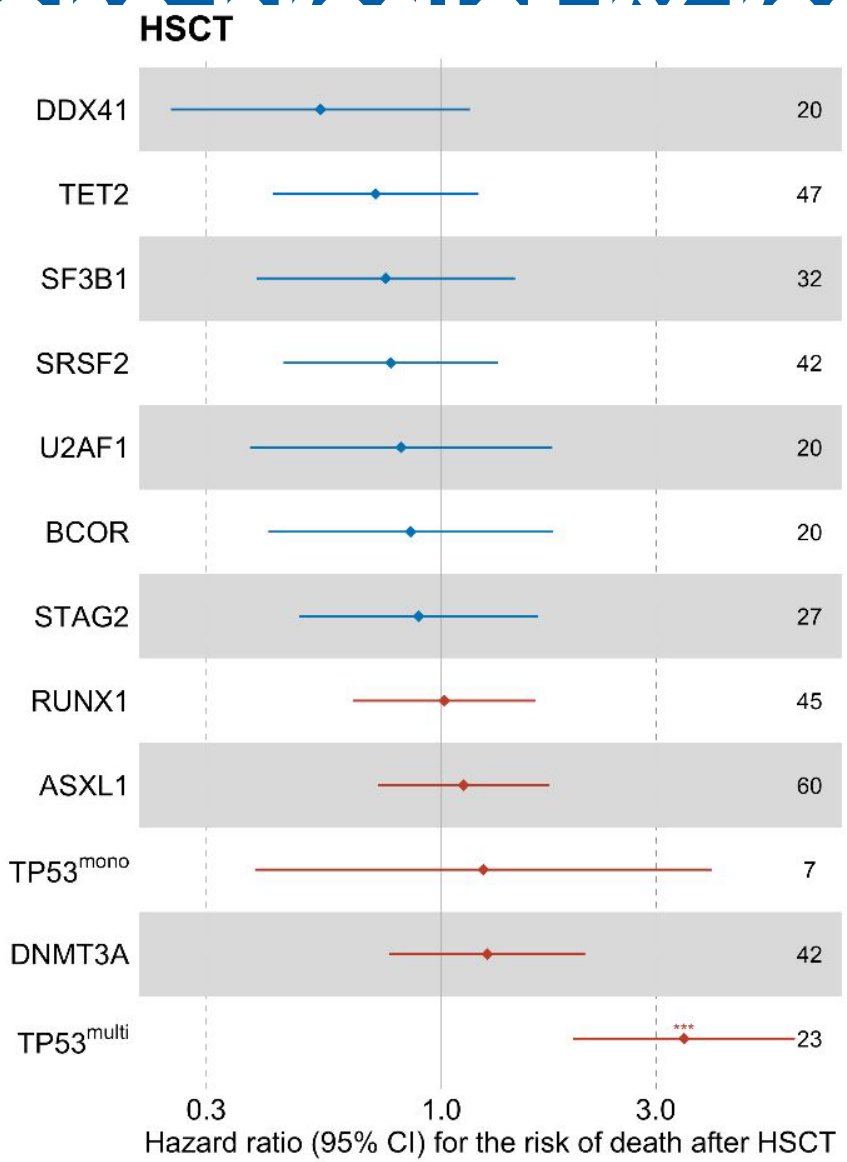
Optimized Symptom Management

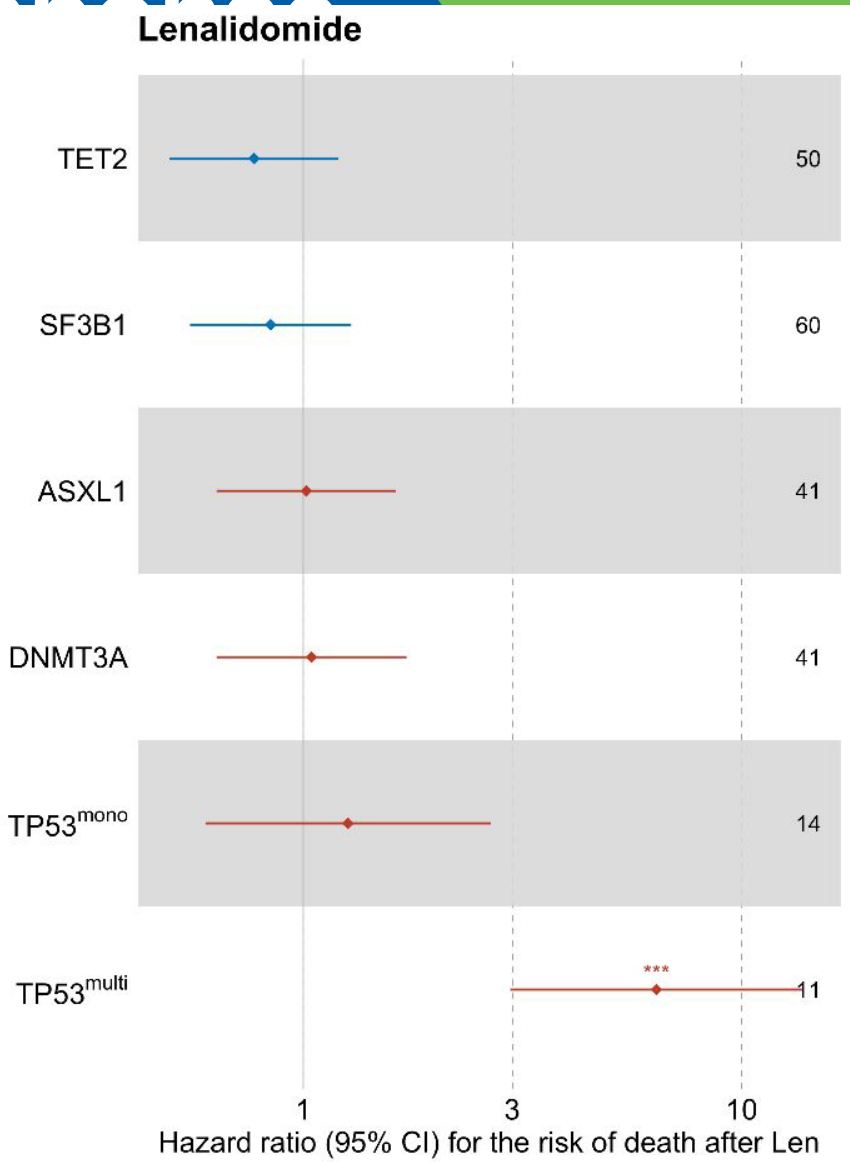
- WHO: consider palliative care for all w/ life-threatening disease
- Early Goals of Care discussions:
  - >30d prior, w/hematologist-> Less ICU admissions, less in-hospital death, increased hospice utilization
- Optimized geriatric assessments-> helps treatment selection
- Inclusion of HRQoL endpoints in clinical trials (esp for older pts)
- Re-imagine hospice care with inclusion transfusions

WHO. Palliative care. 2021. https://www.who.int/newsroom/fact sheets/detail/palliativecare (accessed Oct 3, 2021).
Odejide OO et al. Cancer 2020;126:515-522.
Odejide OO and Steensma DE. Lancet Haematol 2020; 7: e418–24.
Fletcher SA et al. Cancer 2016;122:1209-15.
Wedding U. Lancet Healthy Longev 2021; 2: e746–53.

IPSS-M > mutations predict rx response







What else does IPSS-M Teach Us?

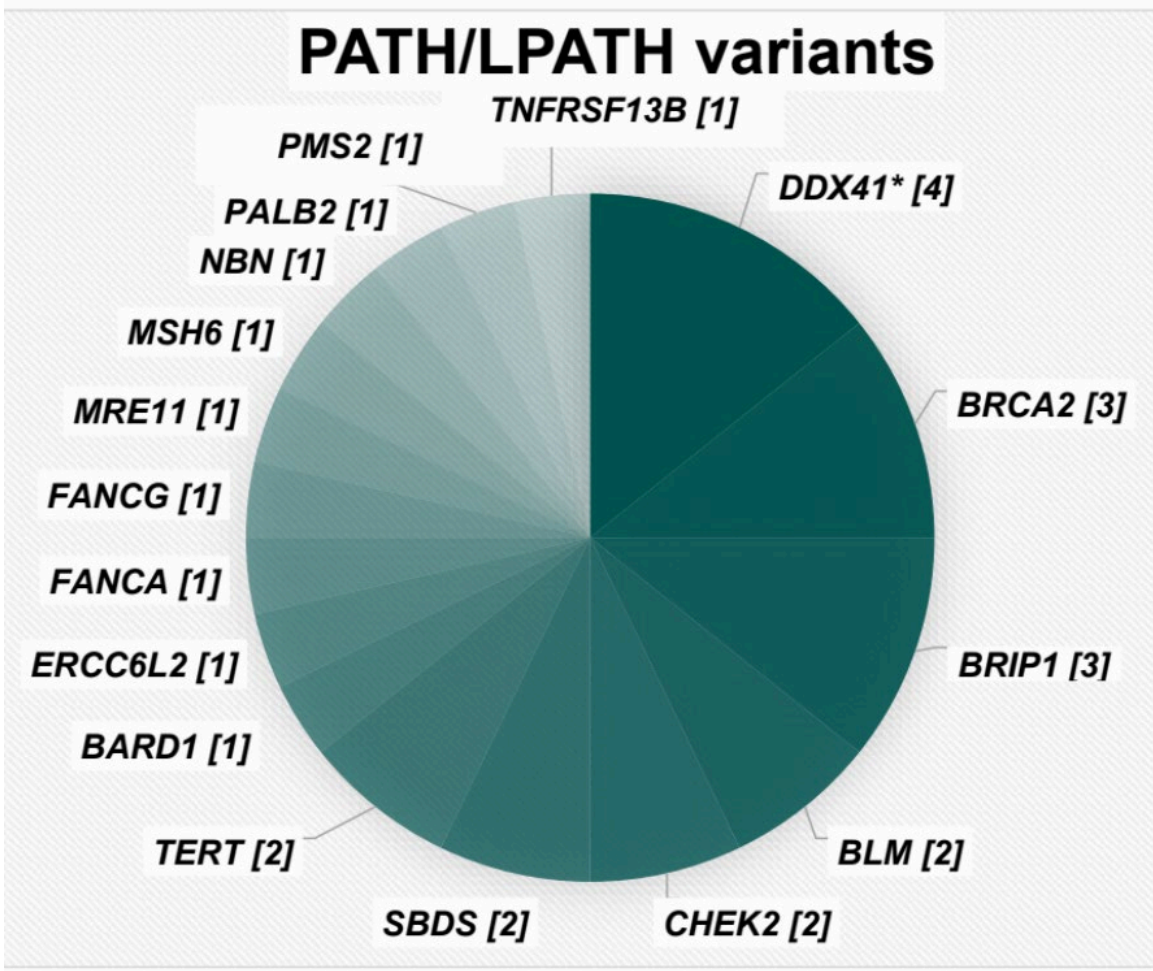
- Germline DDX41-> not uncommon in MDS!
- *DDX41*^{mut}-> Predicts for AML Tx, but favorable OS
  - Cohort had 2957 pts; 90 had *DDX41mut* (3%)
  - both germline (87%) and acquired events (2nd hit)
  - Most common co-mutation was second-hit *DDX41*
  - Age at dx equivalent to the whole cohort
  - Good responses to HMAs & transplant

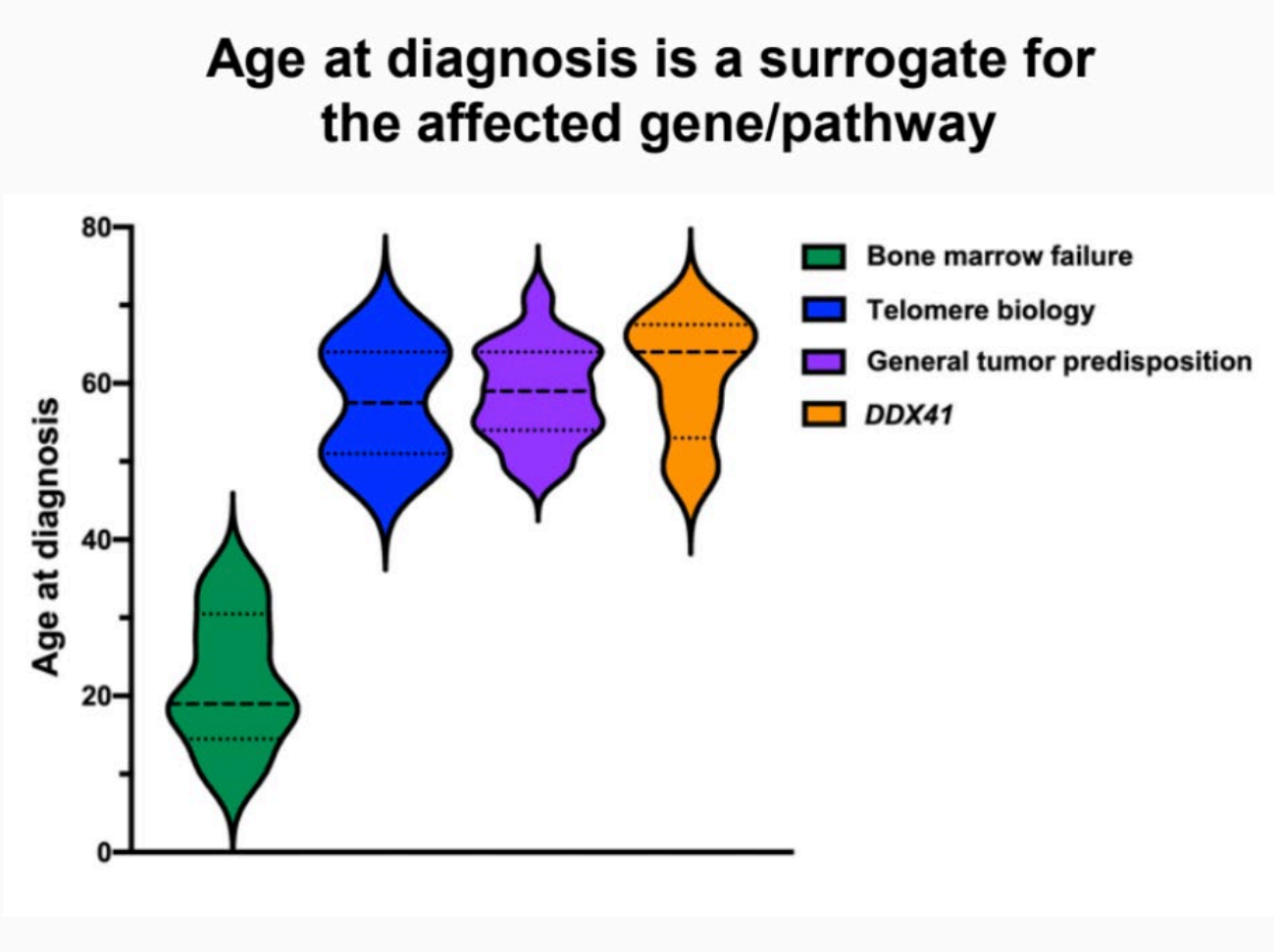
Bernard E et al. NEJM Evidence 2022; 1 (7).

Germline Predisposition: CIBMTR MDS Pt/Donor Pairs

7% (28/404) had germline events!

Variants across the age spectrum

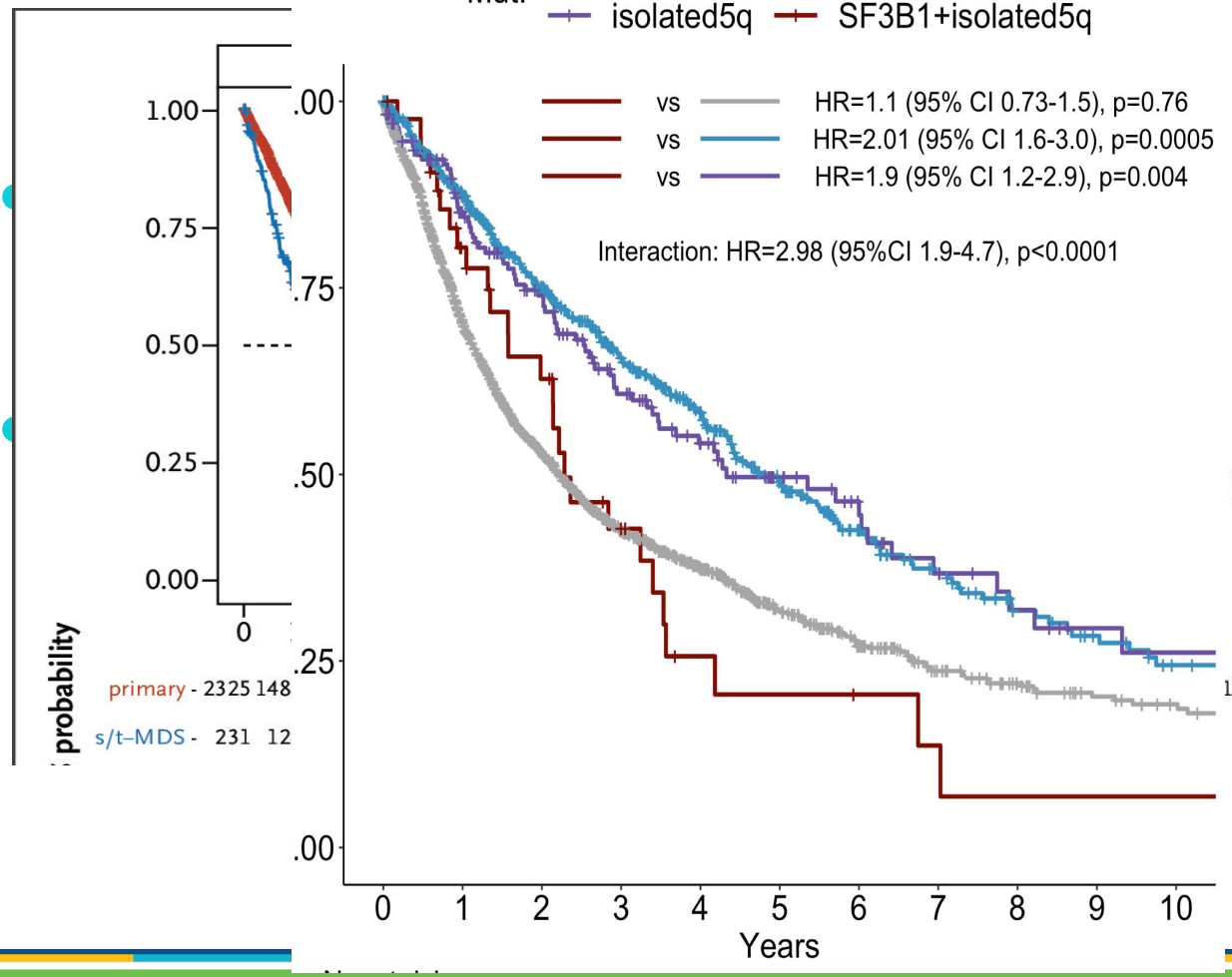


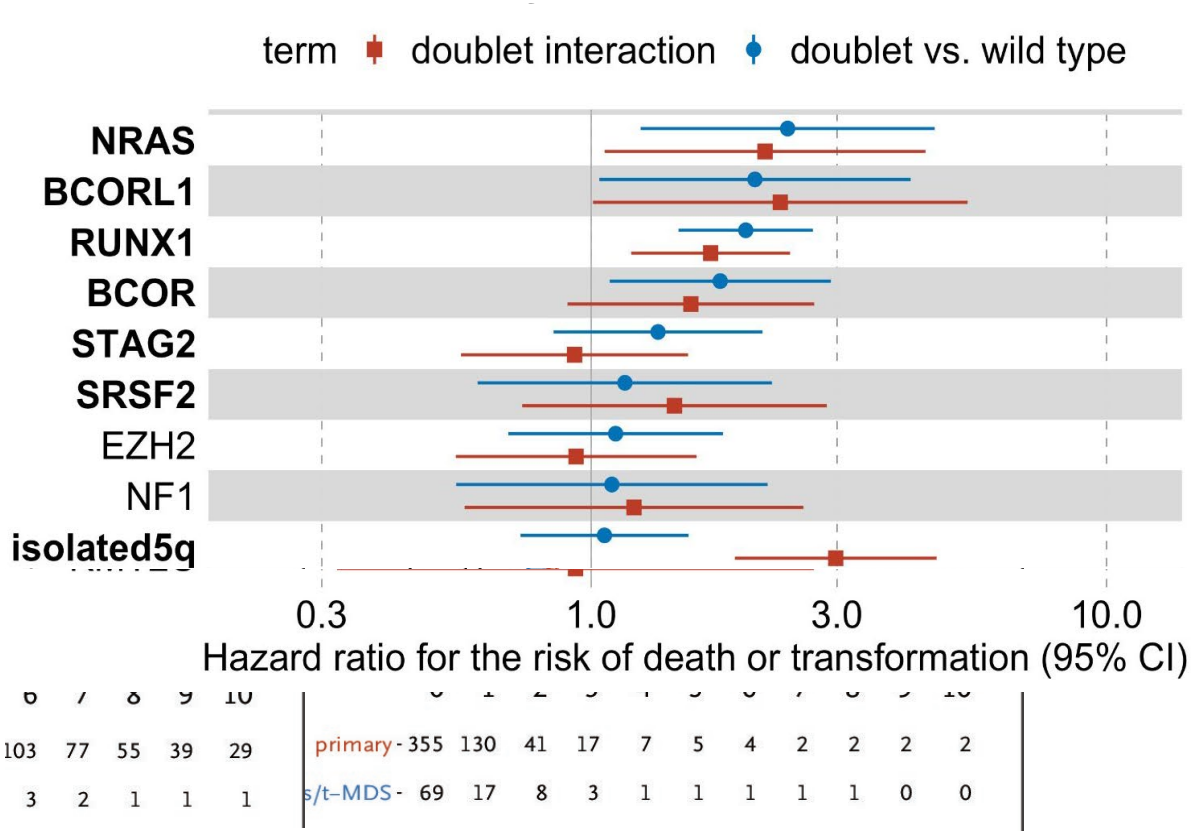


Feurstein SK et al. Blood (2021) 138 (Supplement 1): 320.

What else does IPSS-M Teach Us?

- Second





Bernard E et al. NEJM Evidence 2022; 1 (7).

Thank You!
Questions

elizabeth.griffiths@roswellpark.org
443-676-4701