Myelodysplastic Syndromes: Molecular & Clinical Classifications

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Disclosures

- Novartis—Advisory Group
- Celgene-Research funds
- H3 Biotech "
- Aprea "
- Notable Labs "

MDS Classification: Trajectory

- Prior systems
  - Characterization: Morphology—dysplasia, marrow blast %
    - FAB 1982; WHO 2001, 2008, 2016
  - Classification: Clinical prognostic risk-based analyses
    - Morphology/CBC/Cytogenetics codified/quantified
    - IPSS 1997; IPSS-R 2012; WPSS-R 2015
  - Mutations 2011 – present
    - Type, number, allelic status, co-mutations
- Molecular variables as complement to clinical features
  - Cytogenetic abnormalities in only ~50% MDS patients
  - Numerous mutational subtypes often with low incidence
  - Multiple co-mutations influencing clinical outcomes

→IPSS-R/Molecular project

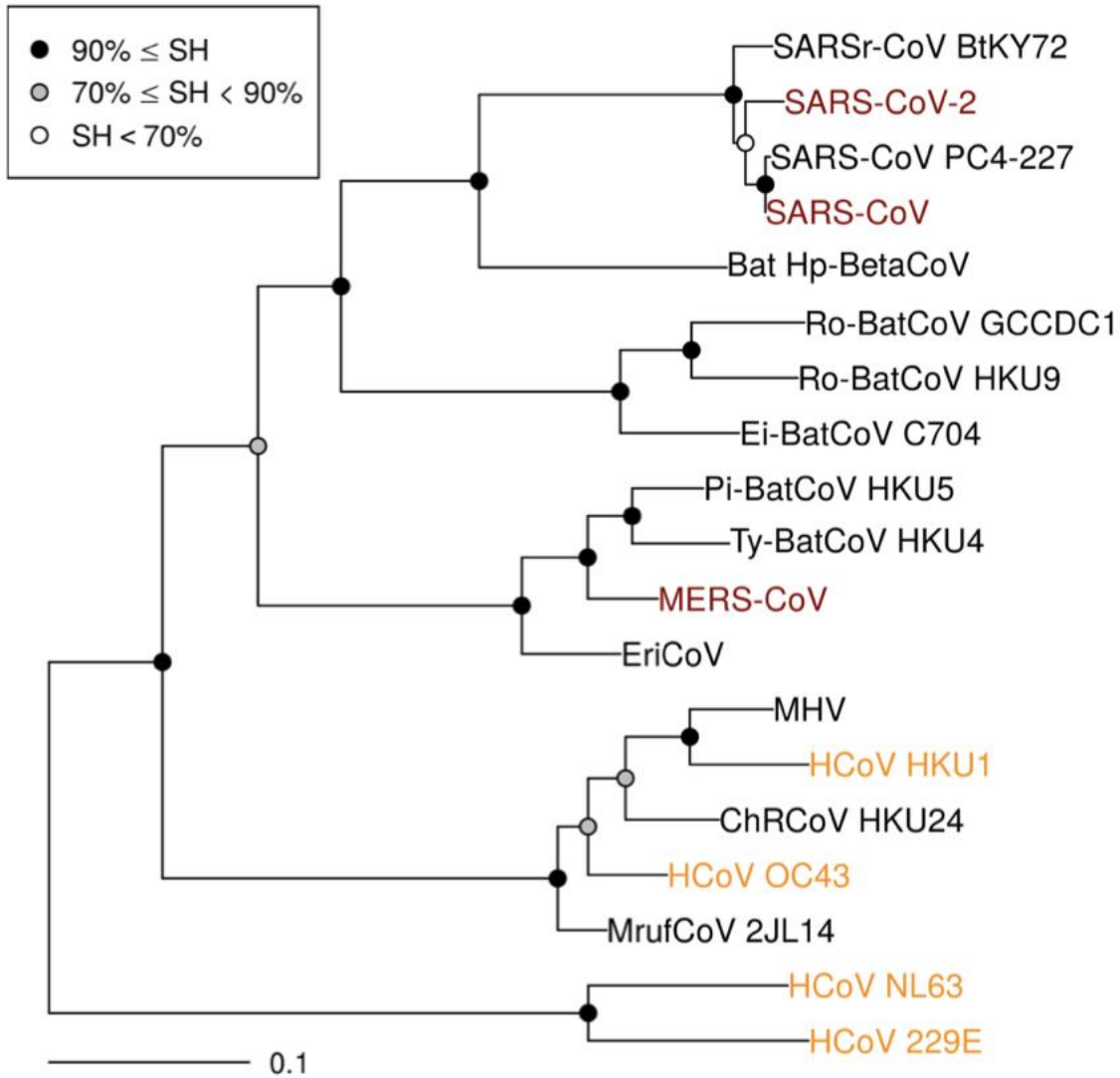
MDS Classifications 1982-97

System	BM Blasts	Cytopenias	Cyto-genetics	Age	LDH
Bennett ‘82, FAB	+	-	-	-	-
Mufti ‘85,UK	+	+, 3	-	-	-
Sanz ‘89, Spain	+	+, 3	-	+	-
Aul ‘92, Germany	+	+, 2	-	+	+
Morel ‘93, France	+	+, 1	+	-	-
Toyama ‘93, Japan	+	+, 3	+	+	-
Greenberg ‘97, IPSS	+	+, ’3’	+	+	-

Classification:
Virus Taxonomy

Category	Virus
Realm	*Riboviria*
Order	*Nidovirales*
Suborder	*Cornidovirineae*
Family	*Coronaviridae*
Subfamily	*Coronavirinae*
Genus	*Betacoronavirus*
Subgenus	*Sarbecovirus*
Species	*Severe acute respiratory syndrome-related coronavirus*
Individuum	SARS-CoV SARS-CoV_PC4-227 SARSr-CoV_BtKY72 SARS-CoV-2/X1/Human/2019/Wuhan_XYZ12345

Severe acute respiratory syndrome-related coronavirus: Species & its Viruses



Gorbalenya AE, Baker SC, et al, bioRxiv preprint doi: https://doi.org/10.1101/2020.02.07.937862

Coronavirus Study Group

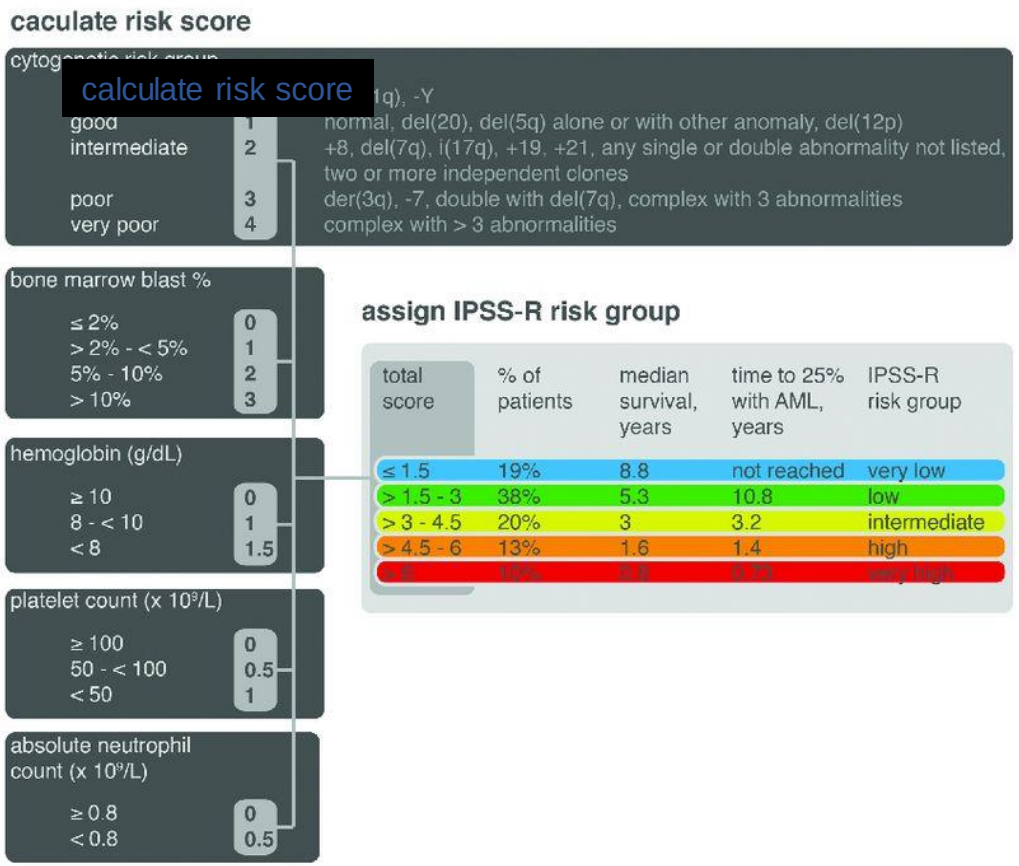
Prognostic Classification Systems for MDS & CMML 1997-2013

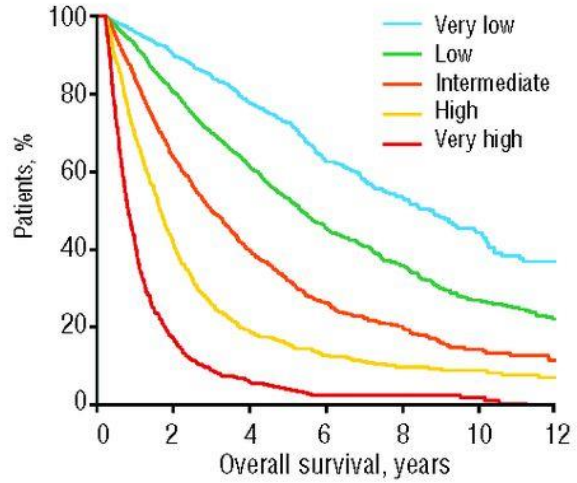
	Blasts	Cyto	Hgb	Plts	ANC	Age	RBC txn	PS
IPSS	+	+	+	+	+	+		
WPSS	+[1]	+	+				+[2]	
MDA-LR	+	+	+	+		+		
MDAS	+	+	+	+	+[3]	+	+	+
FPSS	+(PB)	+					+	+
CPSS[4]	+	+	+		+[3]		+[2]	
IPSS-R[5]	+	+	+	+	+	+		+

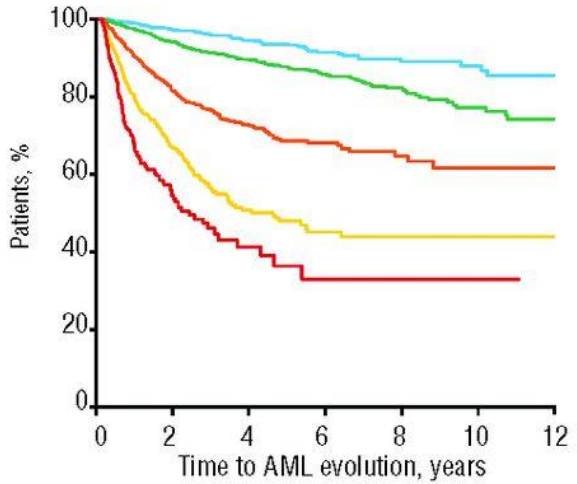
[1] WHO MDS subtype
[2] RBC transfusion dependency can be substituted by hemoglobin (Hgb) level
[3] Leukocytosis
[4] CMML: FAB and WHO MDS subtypes
[5] Plus other variables: LDH, ferritin, β2-microglobulin, fibrosis

Jonas & Greenberg, 2015

Revised International Prognostic Scoring System (IPSS-R)
Cytopenias, Cytogenetics, Marrow blasts

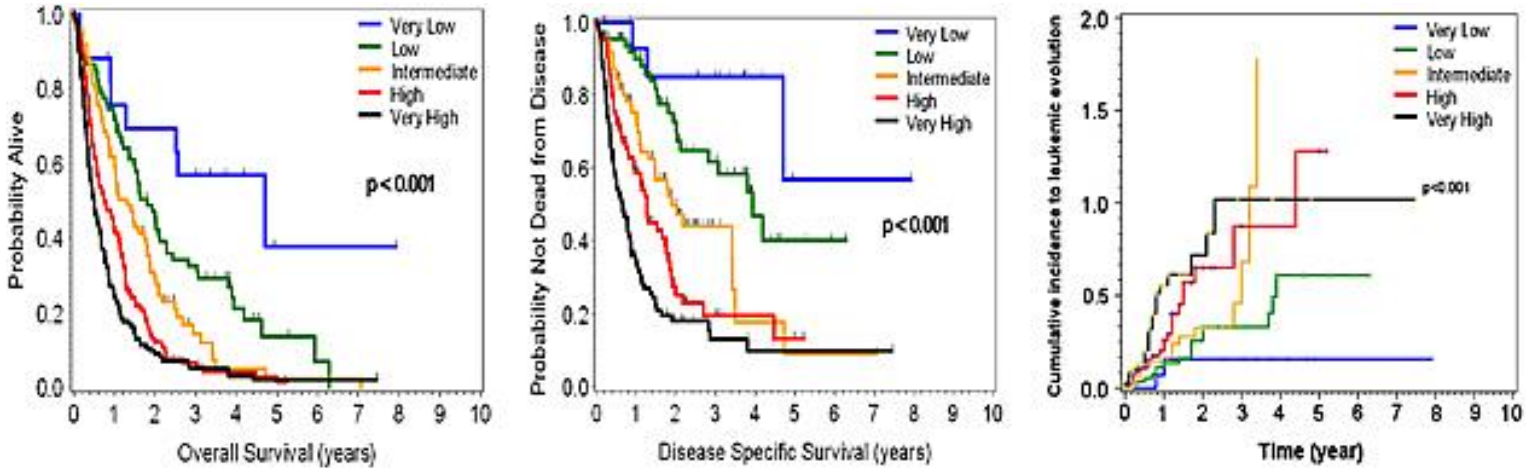






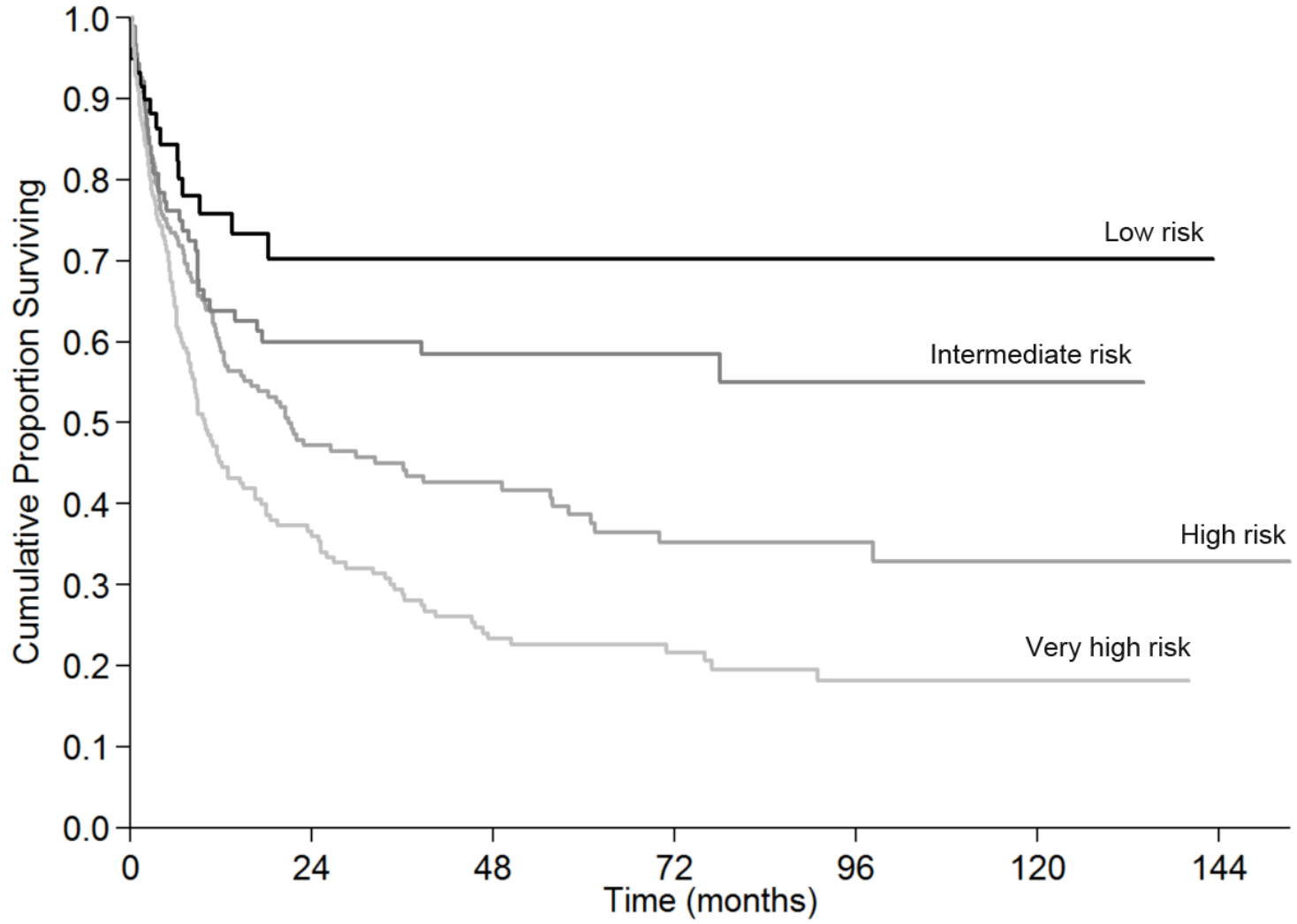
Greenberg et al, IWG-PM, Blood 2012, n=7012

t-MDS & IPSS-R: Clinical Outcomes



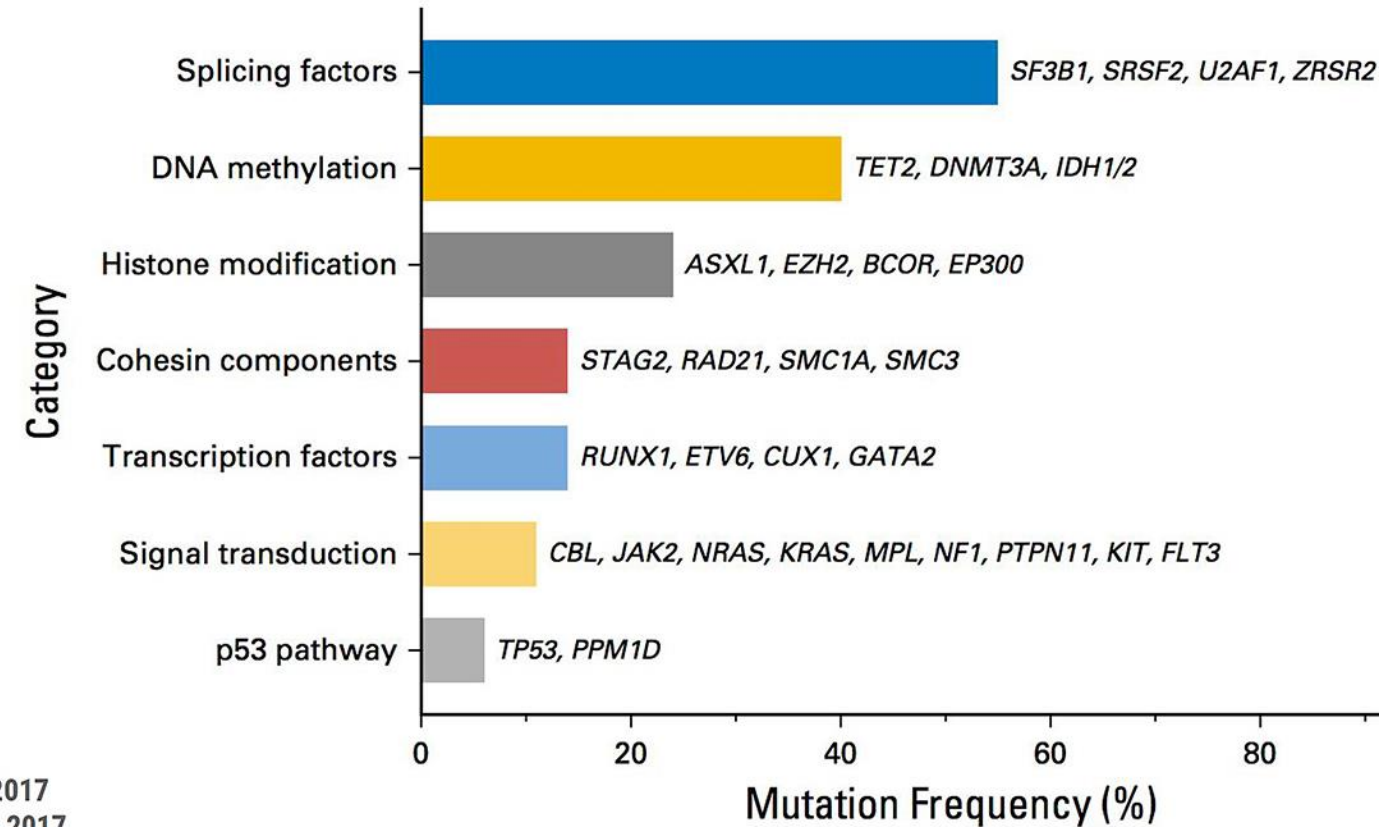
Ok CY et al, Leukemia 28:185, 2014; n=411 (MDA & MGH)

MDS: Post-Allogeneic HSC Transplant Outcome:
OS Relation to Pre-Transplant IPSS-R Risk Category



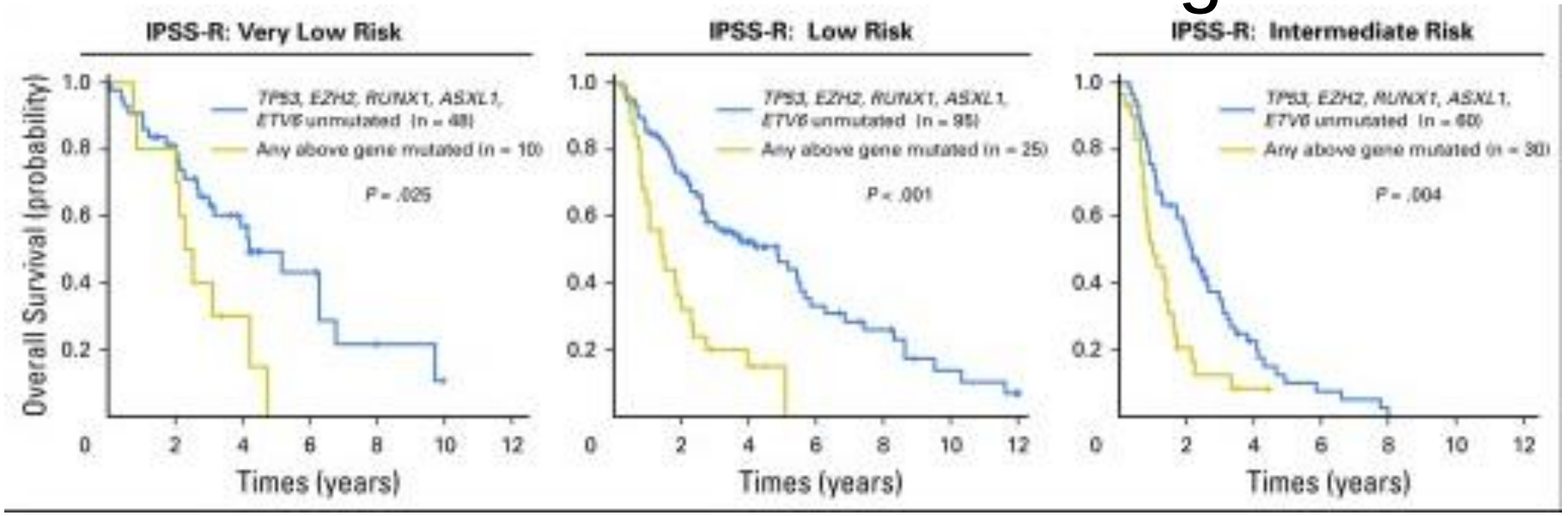
GITMO study, n=519, Della Porta et al, Blood 2014

MDS mutations across pathways



Kennedy and Ebert JCO 2017
Sperling et al Nature Rev 2017
Saez et al Blood 2017
Haferlach at al Leukemia 2014
Yoshida et al Nature 2011
Papaemmanuil et al NEJM 2011

Mutation Impact on Survival in MDS --additive to IPSS-R categories*

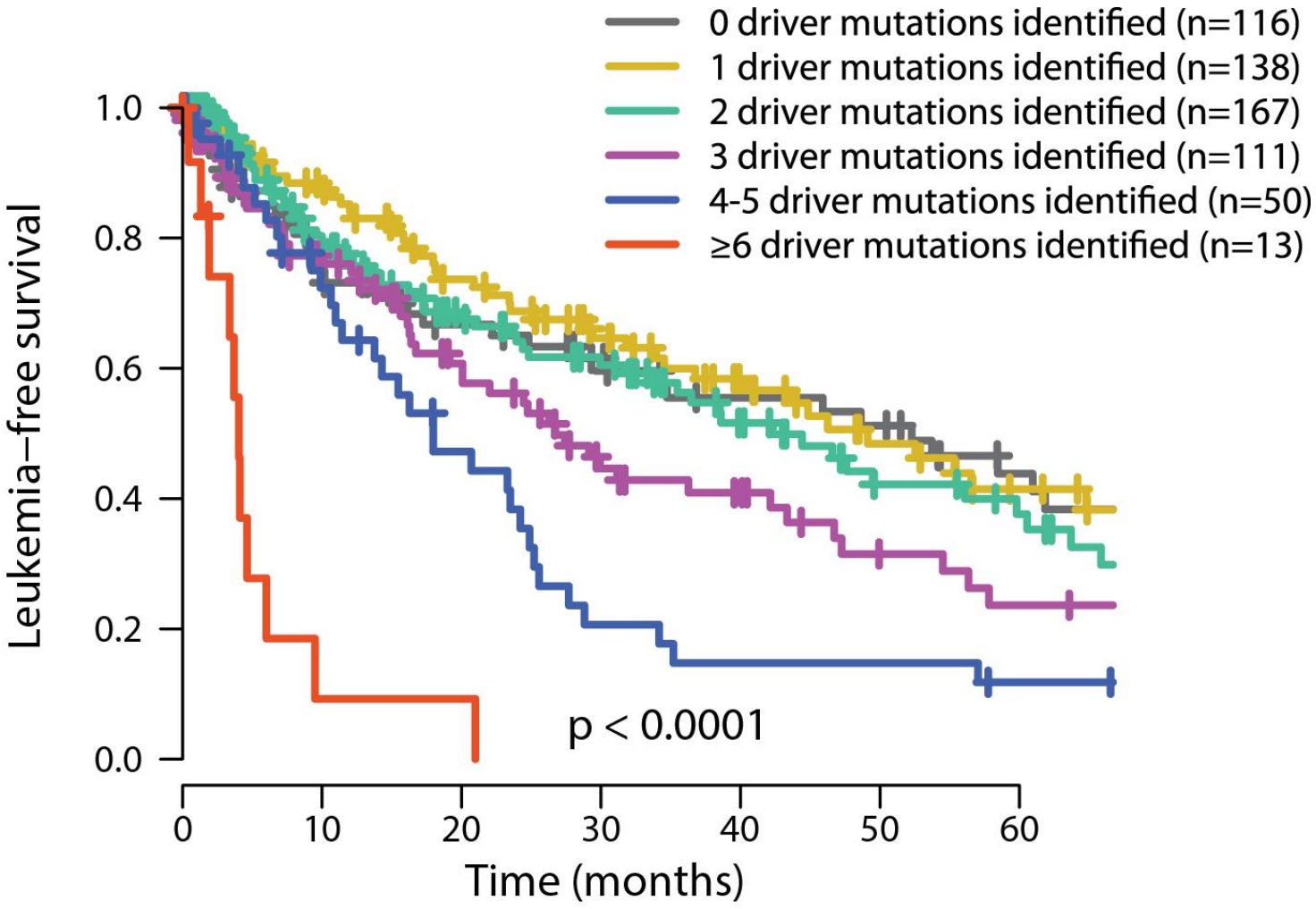


**TP53, ASXL1, RUNX1, EZH2, ETV6*

Bejar et al, Haematologica 2014

LFS Relative to Number of Oncogenic Mutations

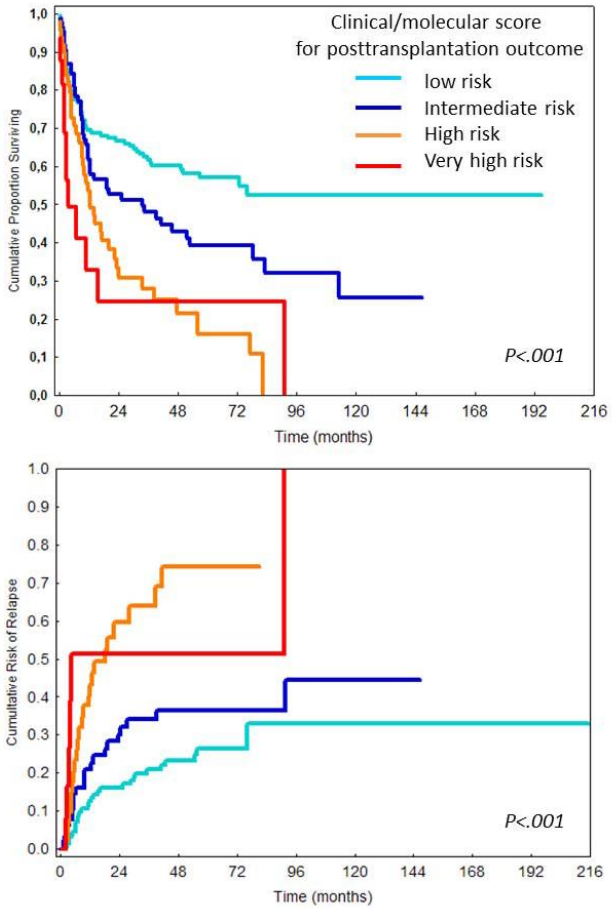
Papaemannuil et al, Blood 2013; n= 595



Genomic population studies identify molecular prognostic markers

Patient Number	Authors	Year	Prognostic genes in multivariate model
439	Bejar et al.	2011	***ASXL1***, *ETV6*, ***EZH2***, ***RUNX1***, ***TP53***
738	Papaemmanuil et al.	2013	***EZH2,*** *DNMT3A*, ***SF3B1, SRSF2, RUNX1***, *TET2*, ***TP53***
944	Haferlach et al.	2014	***ASXL1***, *KRAS*, *LAMB4*, ***NPM1***, *PRPF8*, ***RUNX1, TP53***
508	Nazha et al.	2017	*CBL*, *NRAS*, ***TP53***
685	Tefferi et al.	2018	***ASXL1, SF3B1, RUNX1***

Post Allo-Transplant Clinical/Molecular Model



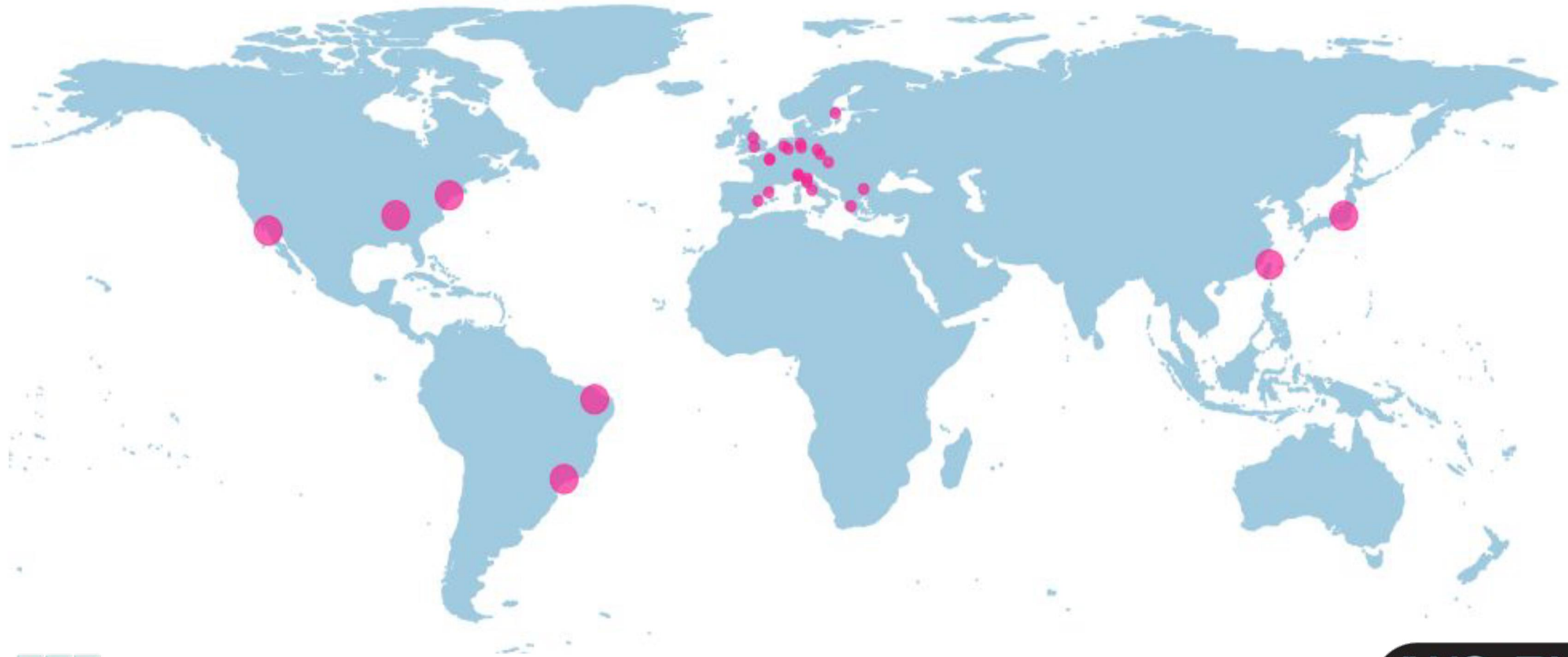
Della Porta et al, J Clin Oncol '16, GITMO, n=401 MDS/AML-MRC
5 Independent Predictors including ***ASXL1,RUNX1,TP53*** *mutations*

MDS Classification: Project update

- Biologic variables needed to complement clinical features
  - Cytogenetic abnormalities in only ~50% MDS patients
  - Numerous mutational subtypes often with low incidence
  - Multiple co-mutations influencing clinical outcomes
- Robust integrated clinical-molecular database and sequencing program required
  - IPSS-R/Molecular project through the IWG-PM under the aegis of the MDS Foundation, n = 3000+ samples
  - Sequencing @ Memorial Sloan Kettering—*E Papaemmanuil, E Bernard*
    - Coordinating Committee: *Bejar, Cazzola, Ebert, Greenberg, Hellstrom, Malcovati, Ogawa*

International Working Group for the prognosis of MDS

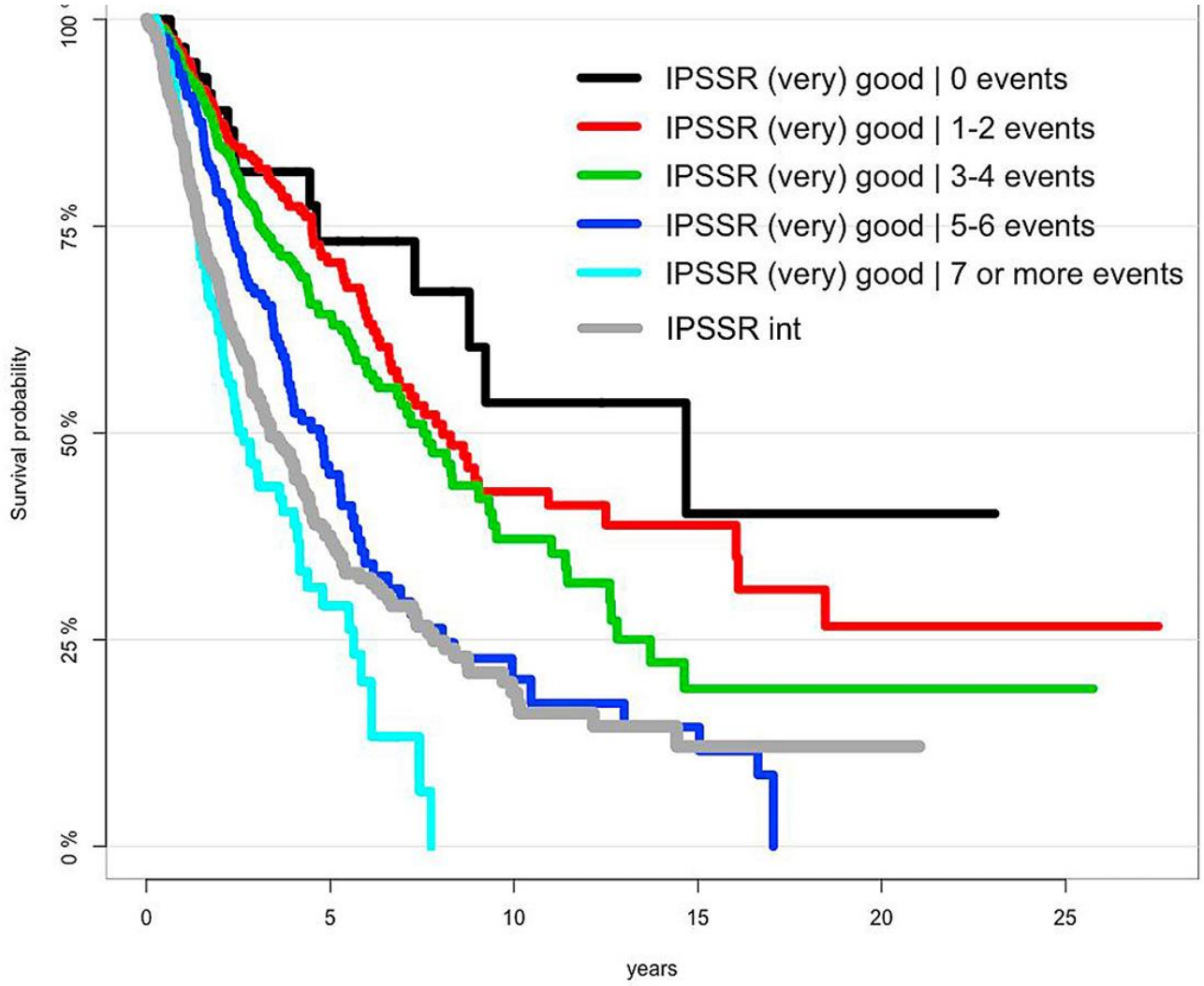
13 countries | 25 centers



mds foundation
the myelodysplastic syndromes foundation, inc.

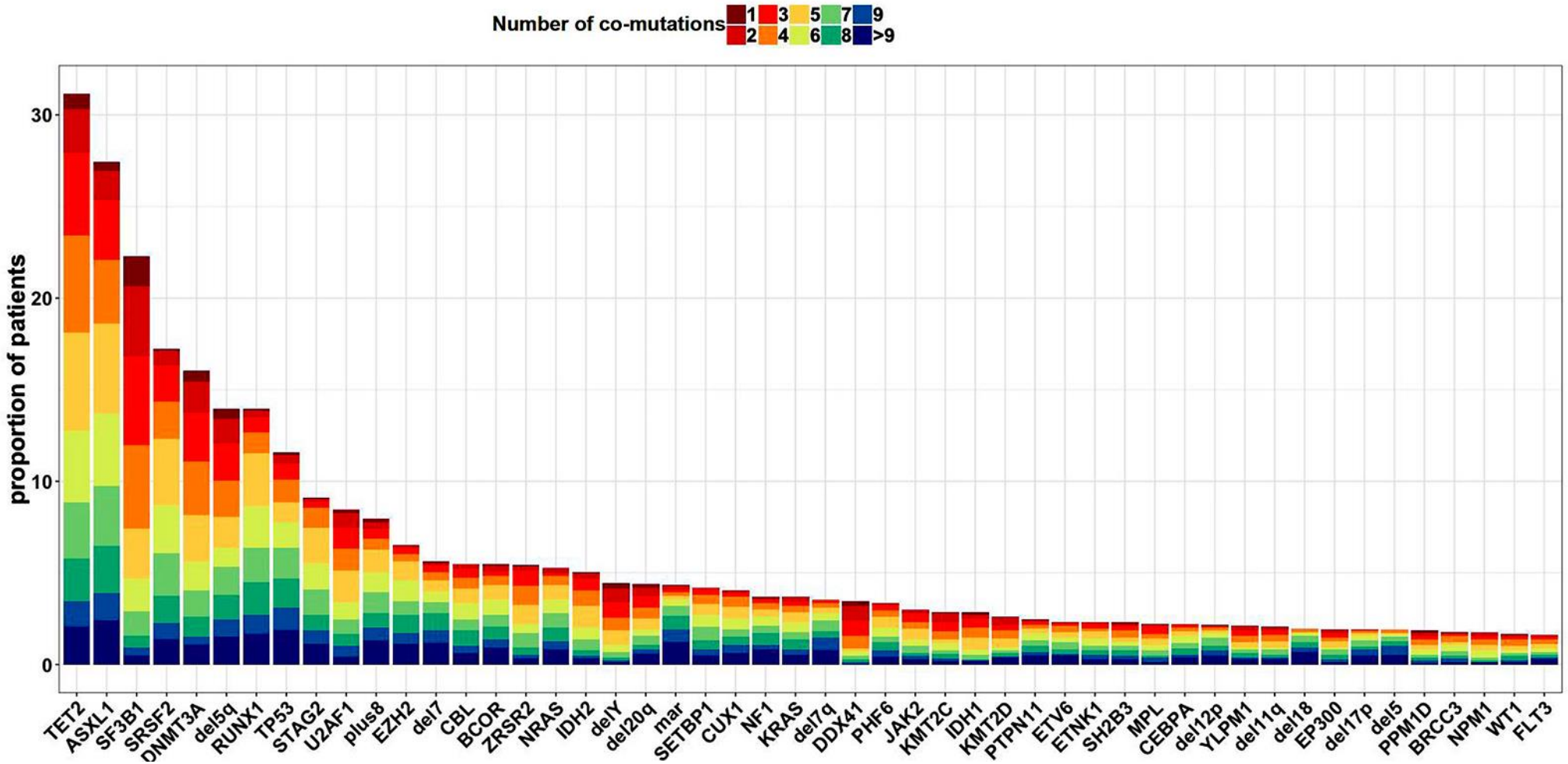
IWG-PM
INTERNATIONAL WORKING GROUP
FOR THE PROGNOSIS OF MDS

Survival Impact of Mutant Driver Numbers



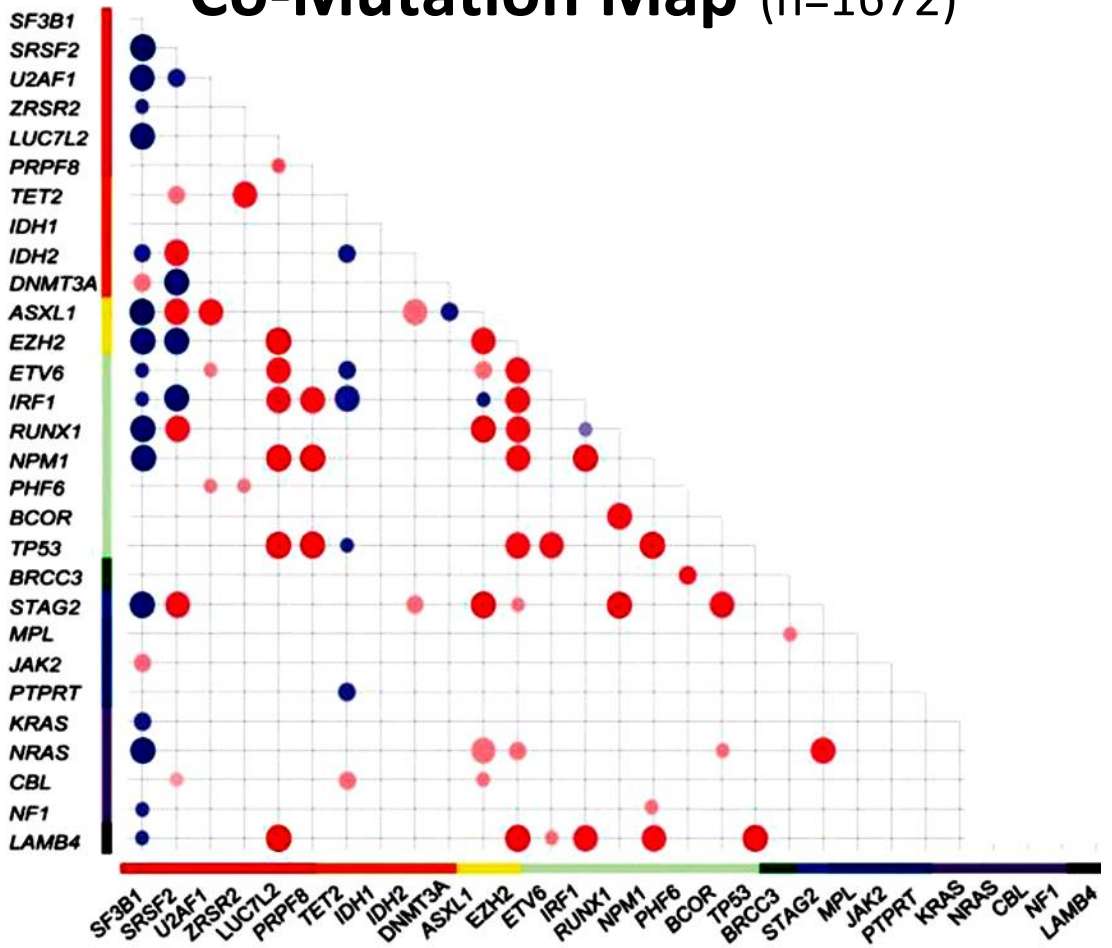
E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018

Long tail of gene frequency with co-mutators



E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018

MDS Mutational Analyses:
Co-Mutation Map (n=1672)



Haferlach at al Leukemia 2014
Papaemmanuil et al Blood 2013

Incorporation of *SF3B1* status in WHO 2016

MYELOID NEOPLASIA

SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts

Luca Malcovati,[1,2] Mohsen Karimi,[3] Elli Papaemmanuil,[4] Ilaria Ambaglio,[2,5] Martin Jädersten,[3] Monika Jansson,[3] Chiara Elena,[1,2] Anna Gallì,[2] Gunilla Walldin,[3] Matteo G. Della Porta,[2,5] Klas Raaschou-Jensen,[6] Erica Travaglino,[2] Klaus Kallenbach,[7] Daniela Pietra,[2] Viktor Ljungström,[8] Simona Conte,[3] Emanuela Boveri,[9] Rosangela Invernizzi,[5,10] Richard Rosenquist,[8] Peter J. Campbell,[4] Mario Cazzola,[1,2] and Eva Hellström Lindberg[3]

BLOOD, 8 DECEMBER 2011 • VOLUME 118, NUMBER 24

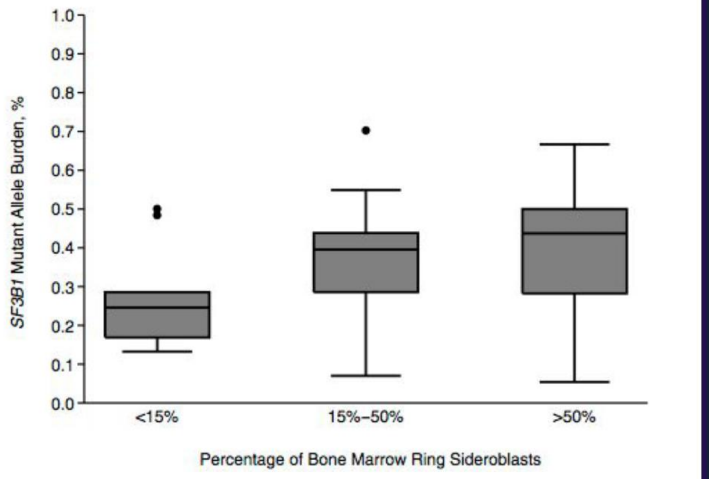
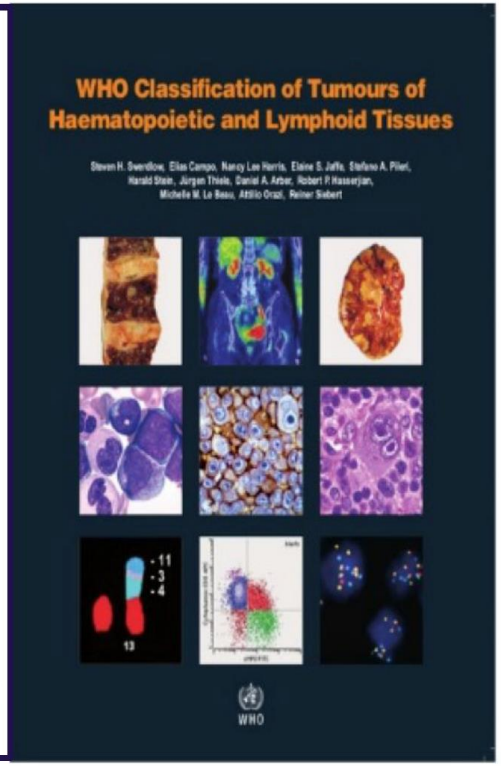


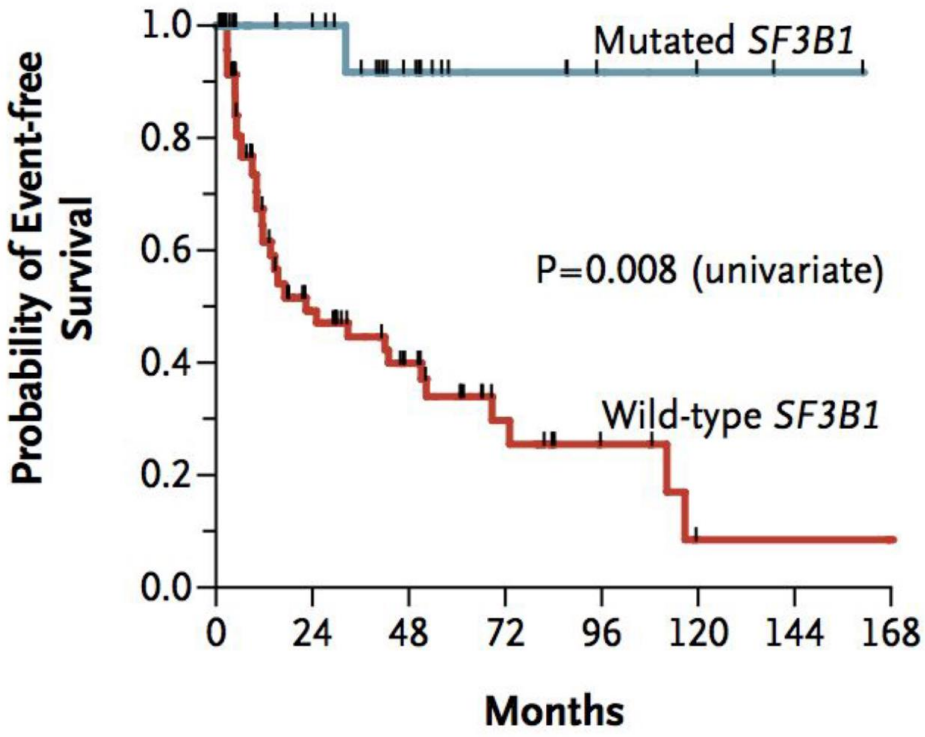
Figure 2. Relationship between *SF3B1* mutant allele burden and proportion of ring sideroblasts. Values for percentage of ring sideroblasts are grouped here in 3 arbitrary categories: < 15% (n = 183), 15% to 50% (n = 85), and > 50% (n = 57). Data are shown in a box plot depicting the smallest and largest observation (lowest and highest horizontal line, respectively), lower and upper quartile with median value (box), and outliers (dots).



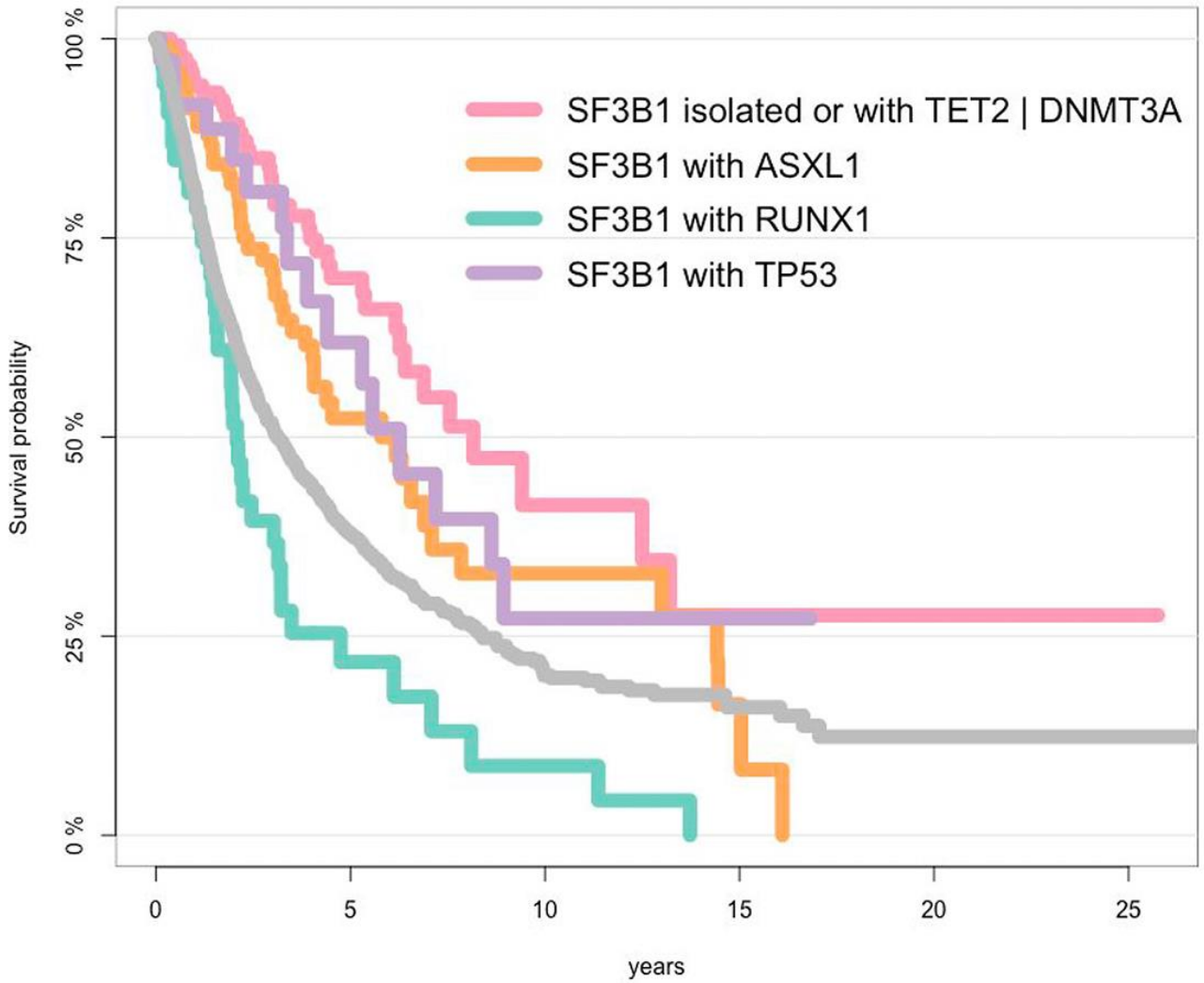
Malcovati et al Blood 2011
Papaemmanuil et al NEJM 2011

WHO 2016 MDS-RS:

more than 15% ringed sideroblasts
or
more than 5% of ringed sideroblasts and *SF3B1* mutation



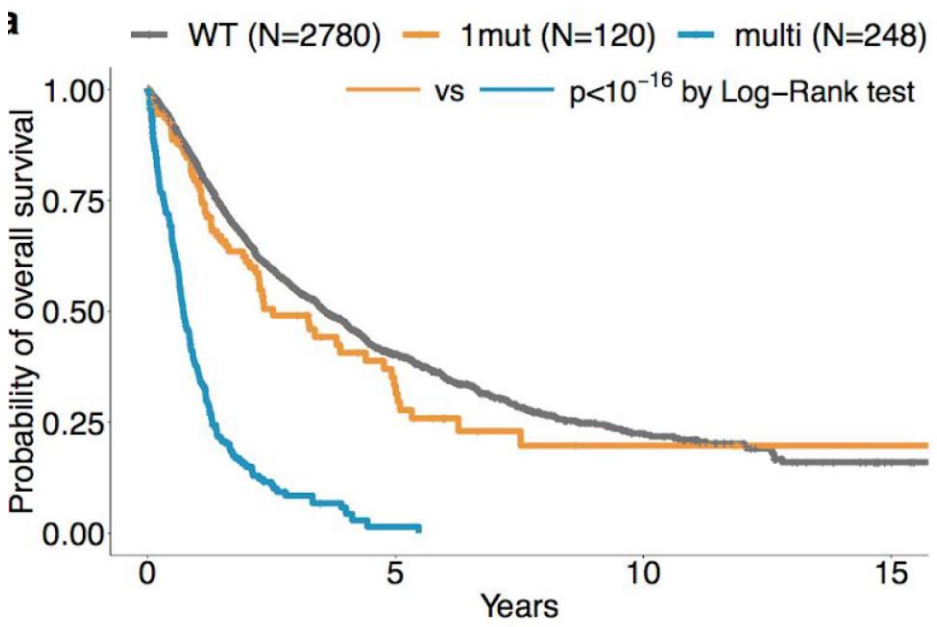
mSF3B1 Outcome Shift with Co-Mutators

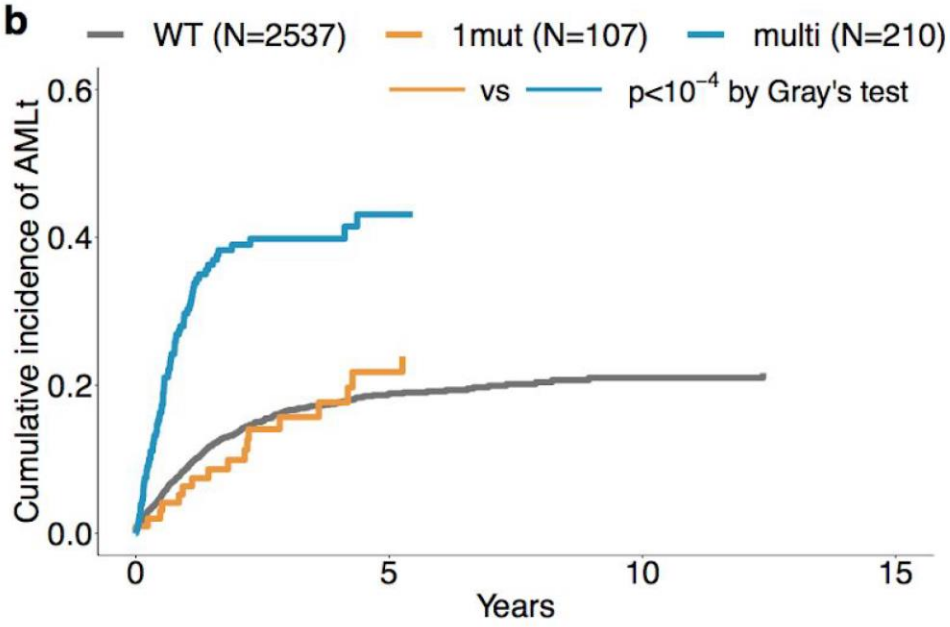


E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018

TP53 Allelic State Shapes 1º MDS Clinical Outcomes

68% multi-hit/bi-allelic m*TP53*



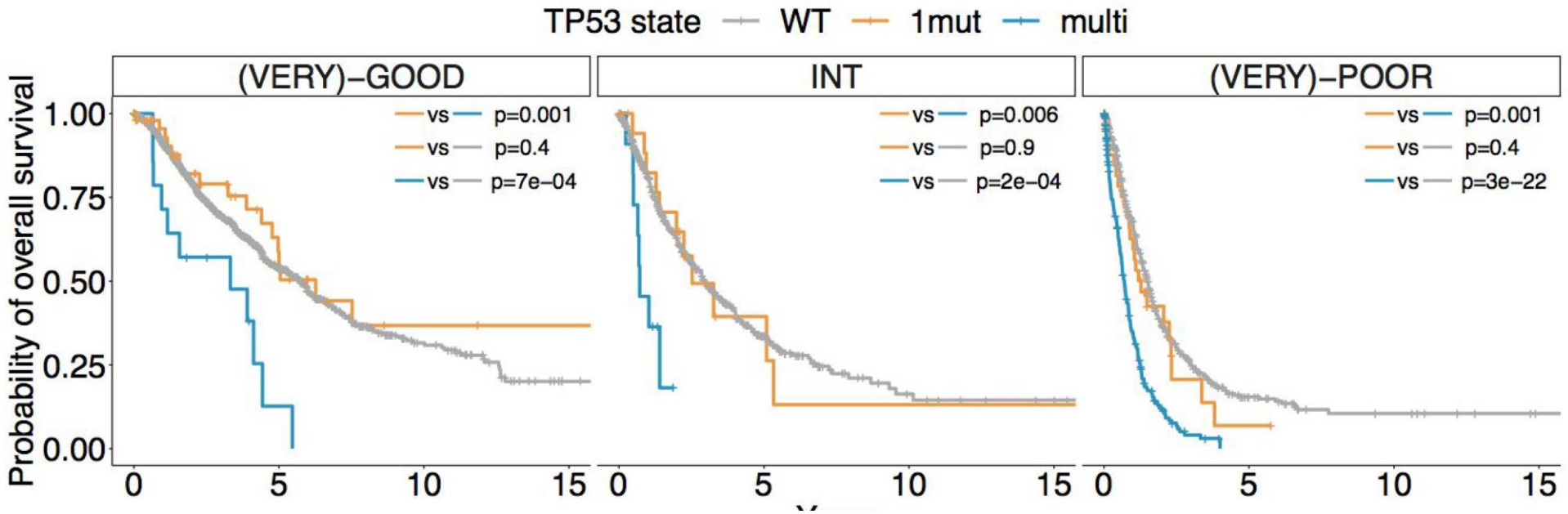


mTP53 n=368 pts

mTP53 n=317 pts

Bernard et al, for IWG-PM, ASH 2019, #675

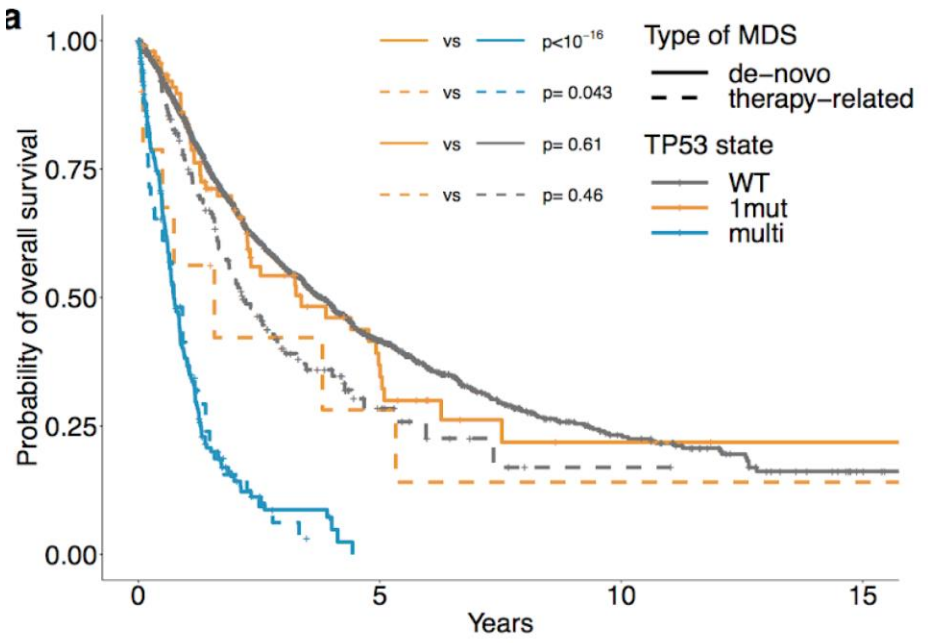
TP53 Allelic State Impacts IPSS-R Risk Group Survival Outcomes

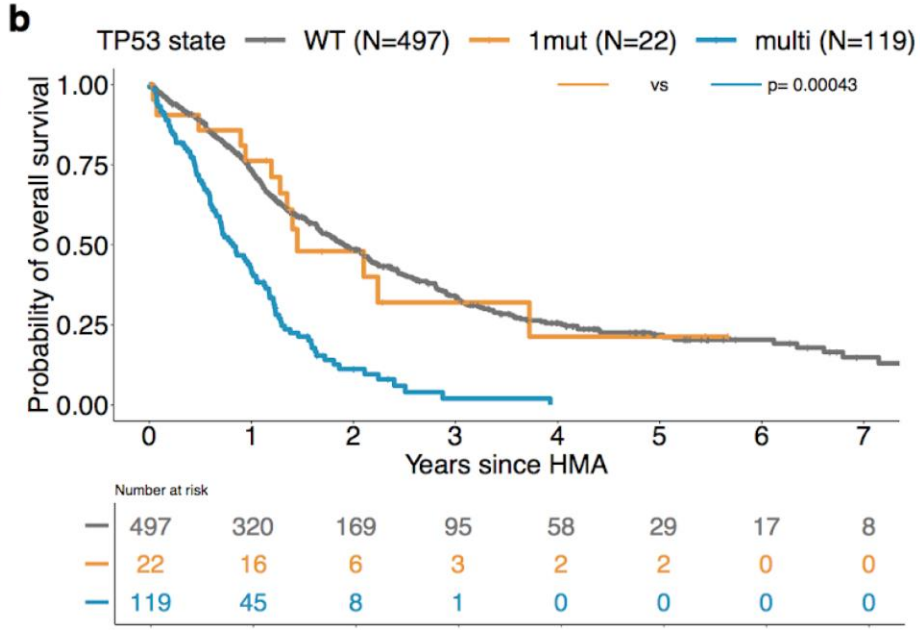


Bernard et al for IWG-PM, ASH2019 #675

Patient TP53 Status: 368 mutated, 2780 Wild-type

TP53 Allelic State Shapes Clinical Outcomes in Therapy-Related MDS & HMA Response





1º & Therapy-Related MDS

Impact of HMA Therapy

Bernard et al for IWG-PM, ASH 2019, #675

MDS Molecular and Clinical Classification Summary

- Better defined:
  - Molecular heterogeneity
  - Mutations: critical nature of allele status, number and co-mutators
  - Impact on survival, AML evolution, HMA responses
  - Both p- and TR-MDS evaluated
- IPSSR-Molecular classification project progressing
  - Genotype-Phenotype associations for clinical subtypes
  - Identifying VUSs as now being pathogenic
  - Prognostic classification
  - Ongoing analysis of potential therapeutic targets
  - Other features to be integrated (e.g., gene expression)