Somatic mutations in diagnosis and prognosis of MDS

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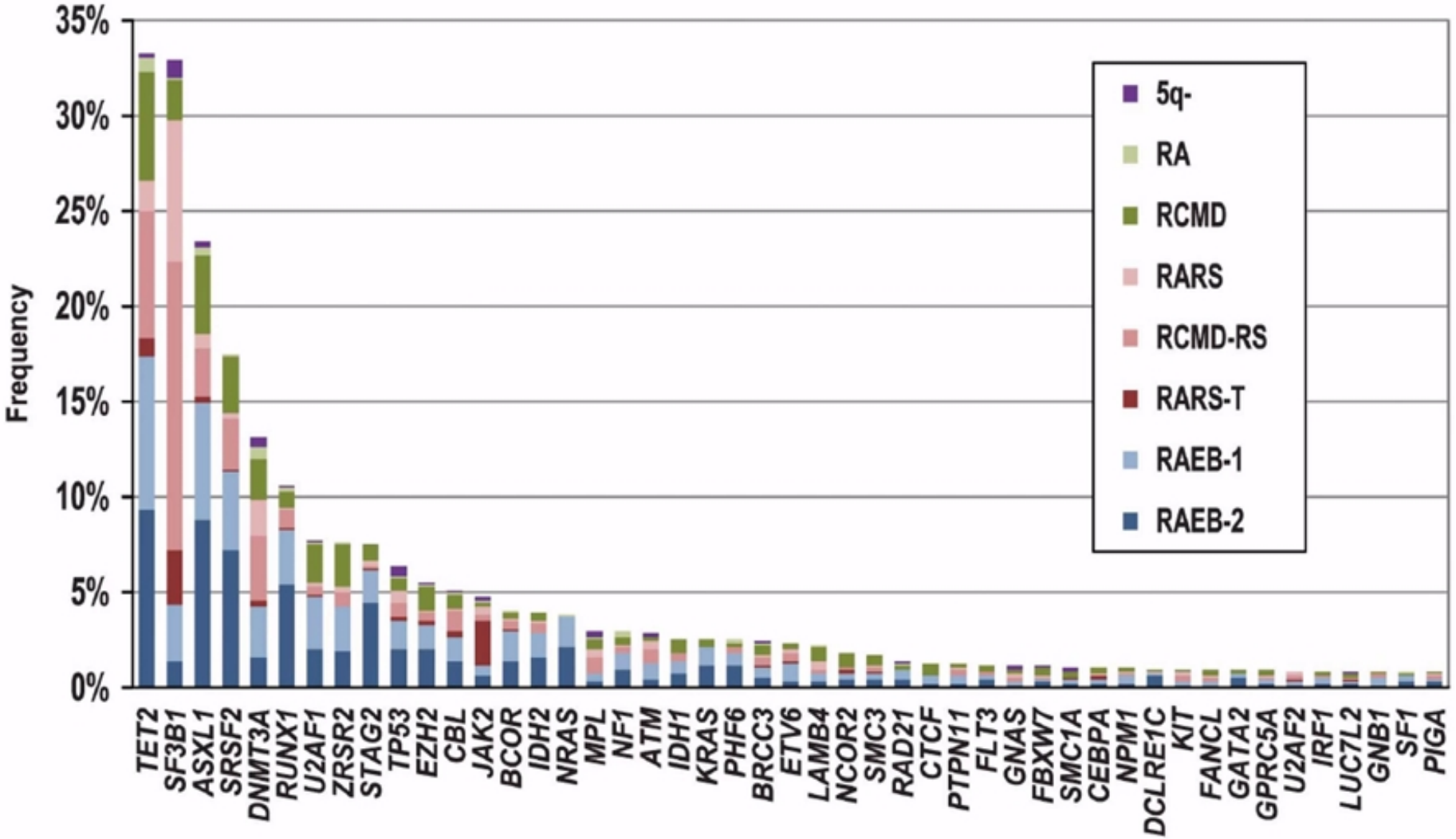
7th INTERNATIONAL SYMPOSIUM ON ACUTE PROMYELOCYTIC LEUKEMIA

Rome, NH Collection Vittorio Veneto Hotel
September 24 - 27, 2017

Recurrently mutated genes in MDS



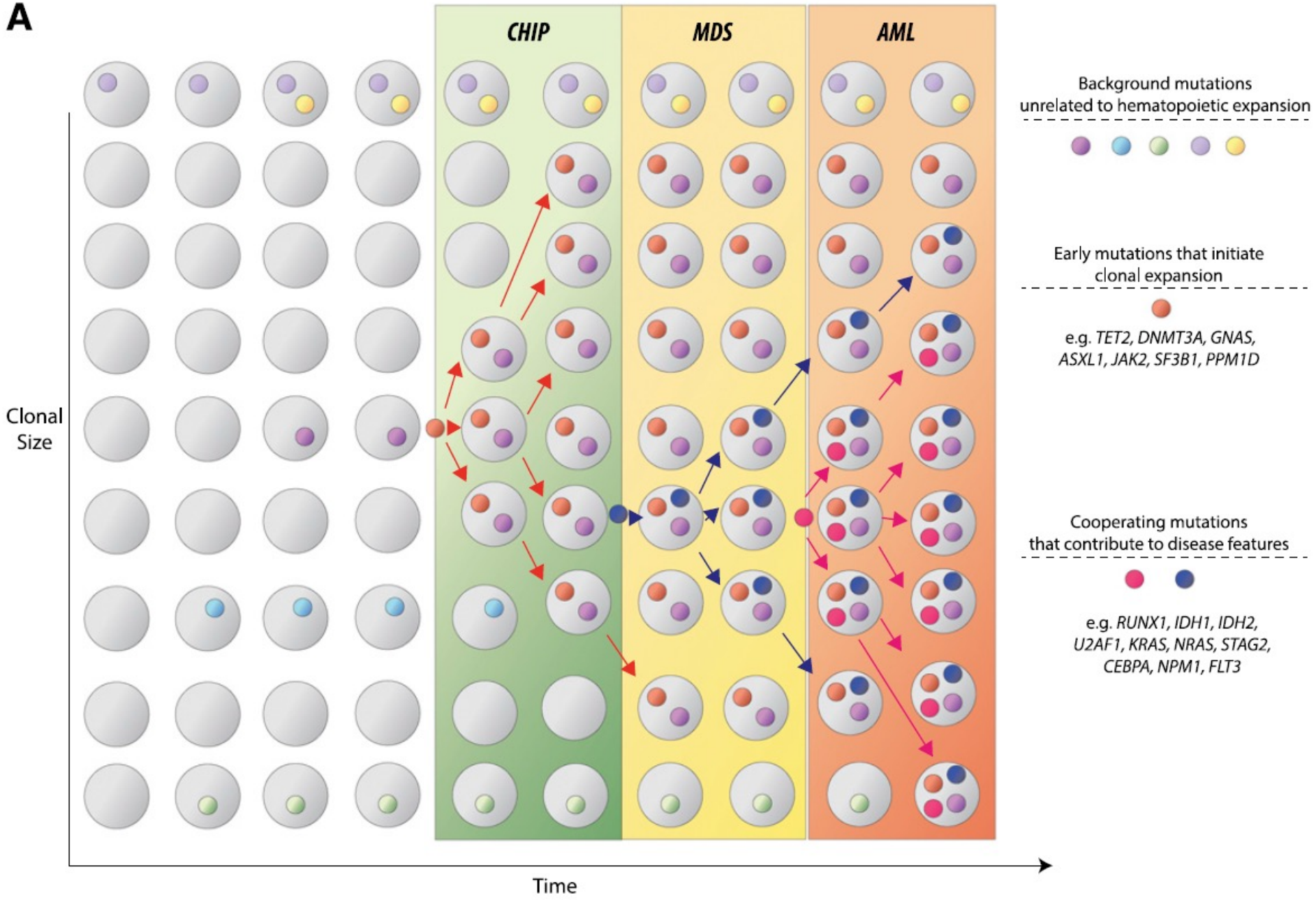
Haferlach T et al, Leukemia 2014

Gene	Frequency	Gene function
TET2	30%	Epigenetic regulation
SF3B1	28% (up to 80% in RARS-T)	Splicing Factor
ASXL1	19%	Epigenetic regulation
RUNX1	10%	Transcription Factor
NRAS (KRAS)	10-15%	Signal Transduction
TP53	10 %	Transcription factor, apoptosis
U2AF35	10 %	Splicing Factor
SRSF2	10%	Splicing Factor
EZH2	5-10%	Epigenetic regulation
DNMT3A	5-8%	Epigenetic regulation
IDH1	5-7 %	Epigenetic regulation
ATRX	5%	Epigenetic regulation
JAK2	5%	Signal Transduction
C/EBPa	5%	Transcription Factor
NPM1	3-5%	Nuclear import, apoptosis
IDH2	3-5%	Epigenetic regulation
MLL	3%	Epigenetic regulation
ETV6	3%	Transcription Factor
UTX	3%	Epigenetic regulation
FLT-3	2%	Growth factor receptor
ZRSR2	1-3%	Splicing Factor
PRPF40B	2%	Splicing Factor
SF3A1	1-2%	Splicing Factor
SF1	1-2%	Splicing Factor

Biological classification of somatic mutations in MDS

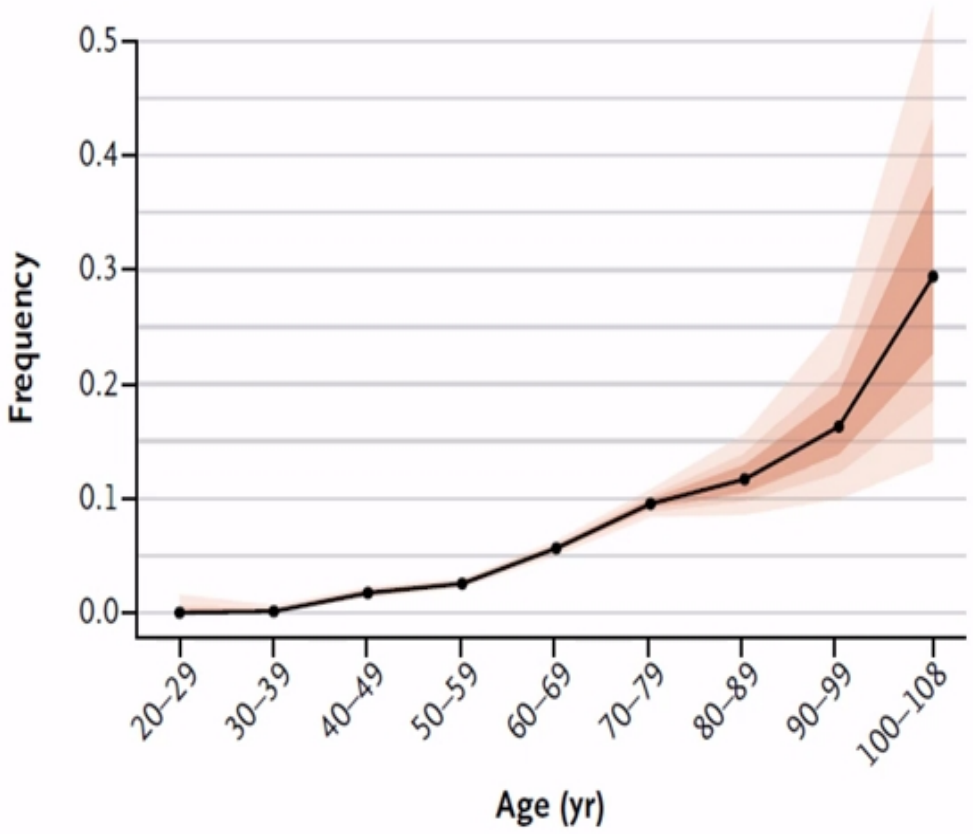
1. Epigenetic regulators
2. RNA-splicing factors
3. Signal transduction
4. Transcription factors
5. Apoptotic factors
6. Growth factor receptor

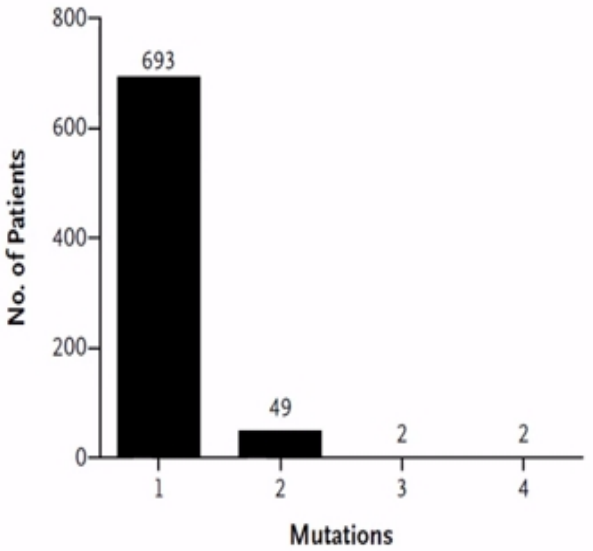
Clonal Evolution in MDS/AML



Steensma D et al, Blood 2015

Clonal Hematopoiesis of Indetermined Potential (CHIP)



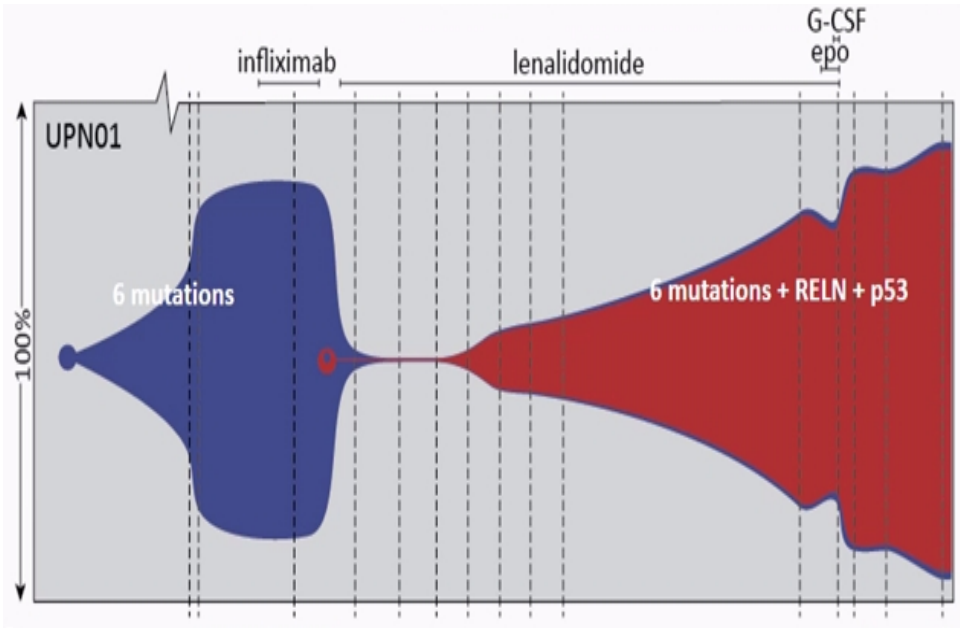


- ✓ Above the age of 70, over 10% of individuals have hematopoietic clones
- ✓ CHIP is associated to: - probability to develop a hematologic disease (HR:11)
  - all-cause mortality (HR 1.4)
  - probability of atherosclerosis/myocardial infaction (HR: 3-4)

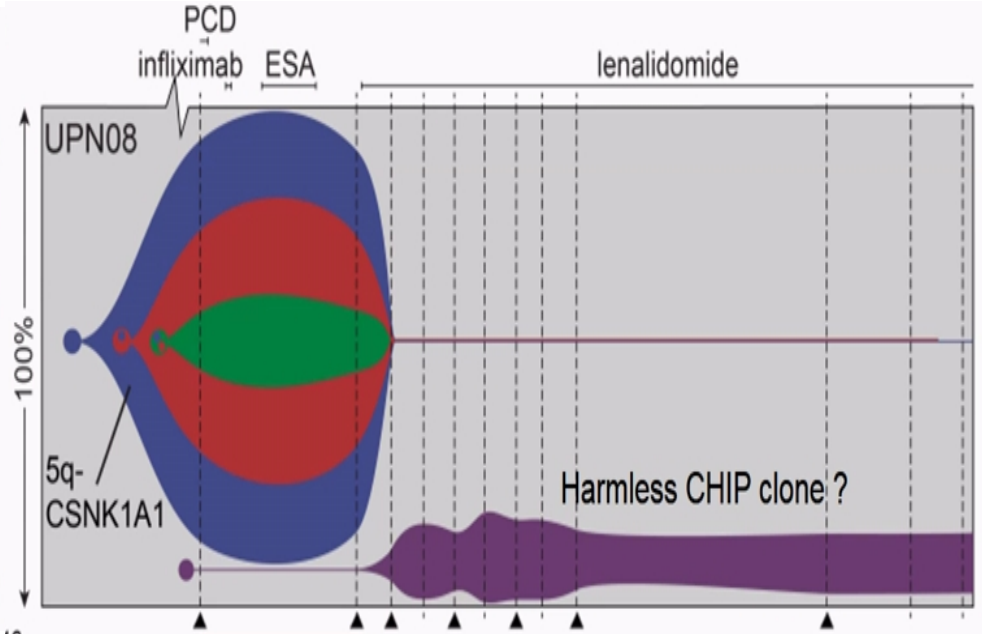
Jaiswal, Genovese, NEJM 2014

Models of MDS progression

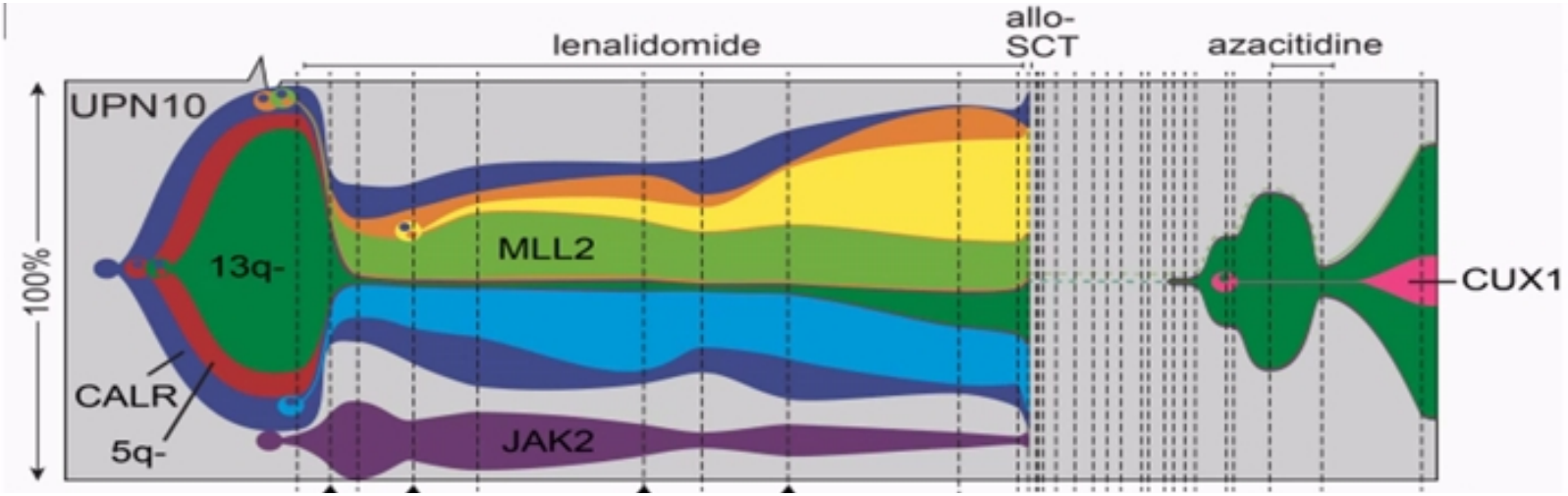
A) Expansion of a pre-existing clone



B) Expansion of a by-stander clone



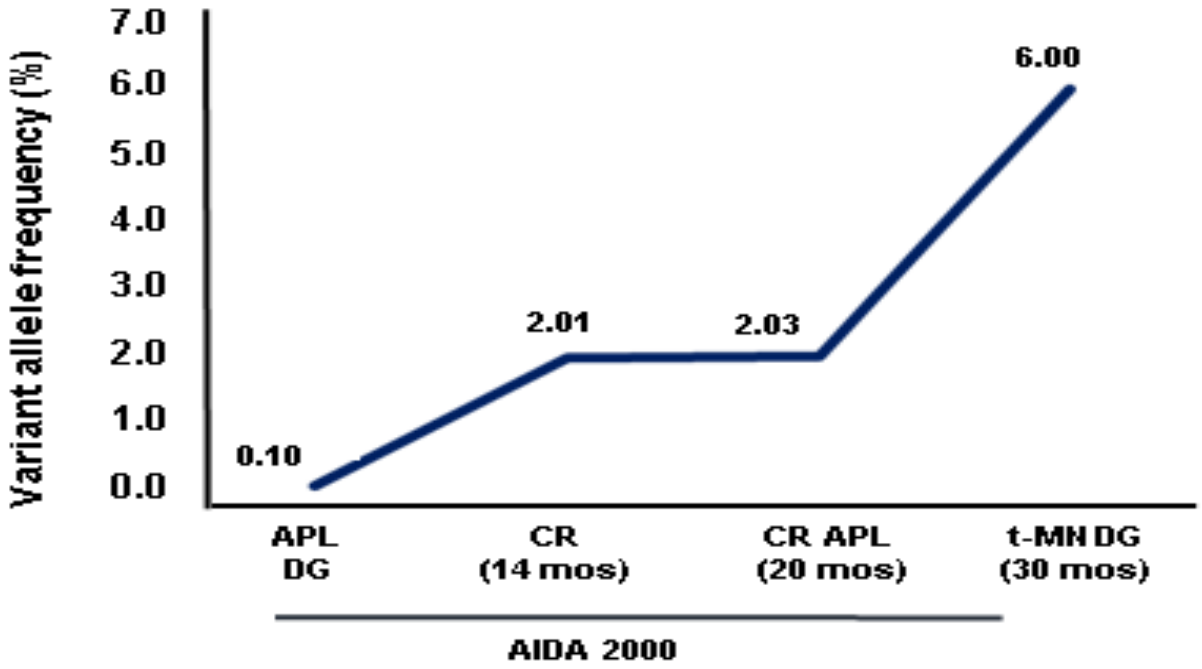
C) Appearance of new clones



Da Silva-Coelho et al , Nature Communications 2017

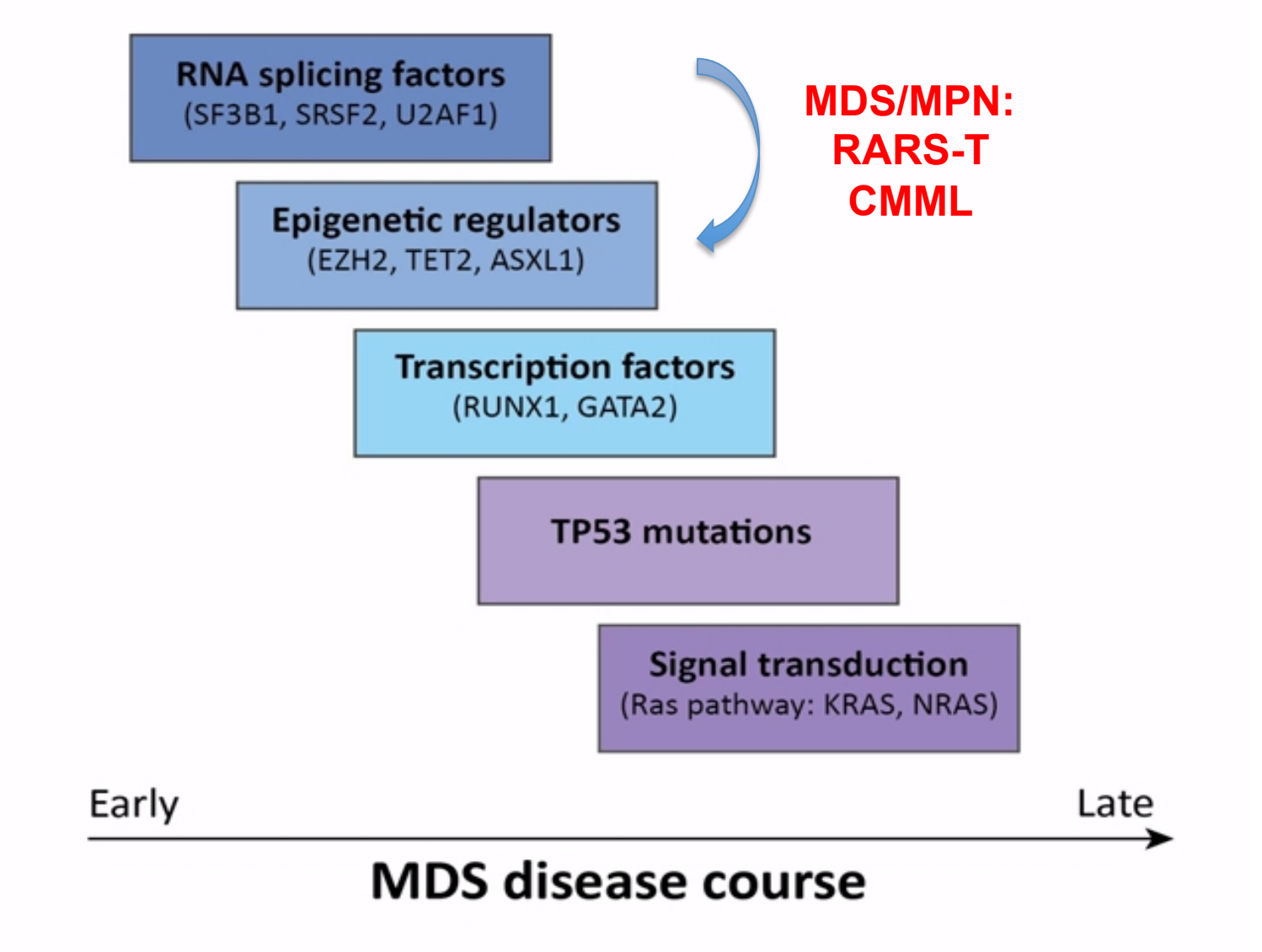
Clonal evolution in therapy-related myeloid neoplasms

UPN2: TP53Y220C



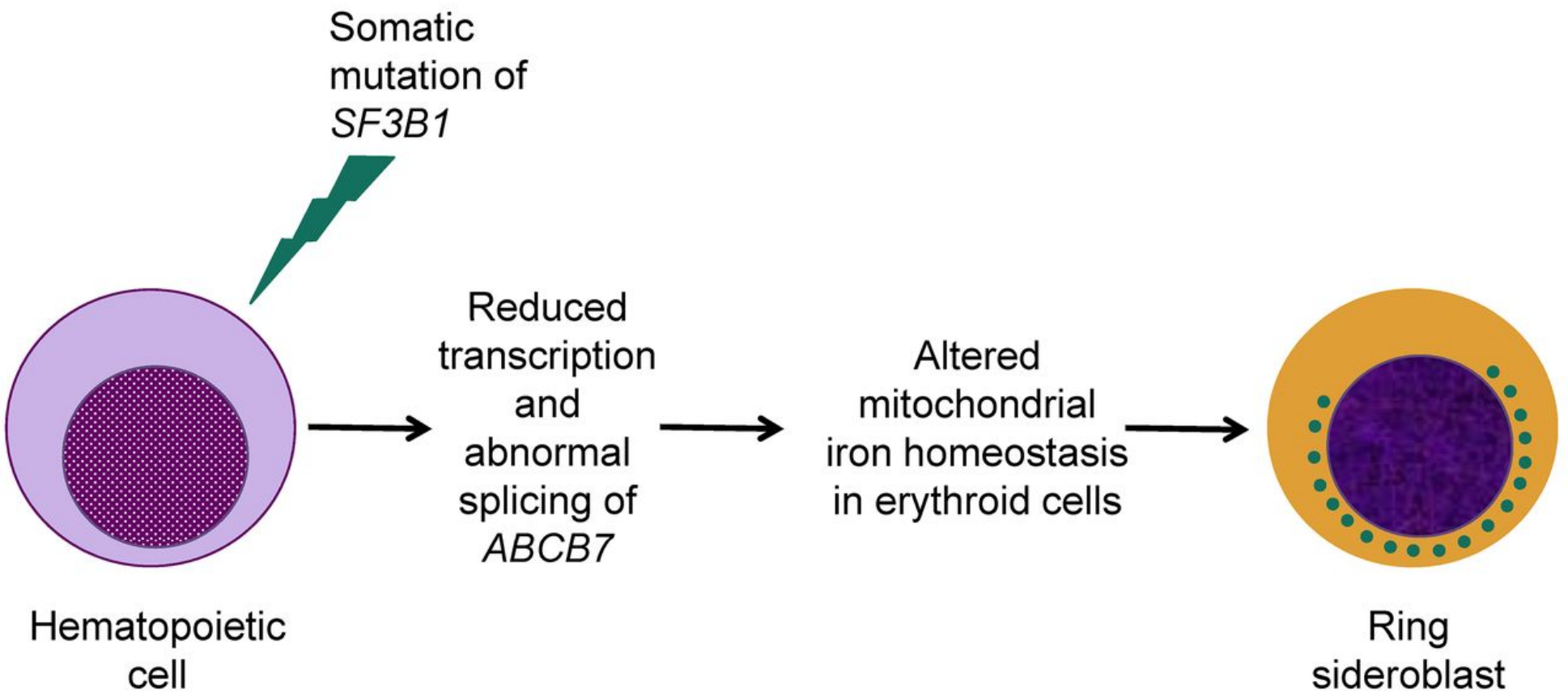
Fabiani et al , Oncoarget 2017

Order of mutations during MDS progression



Bejar & Abdel-Wahab, Blood 2013

SF3B1 and MDS-RS

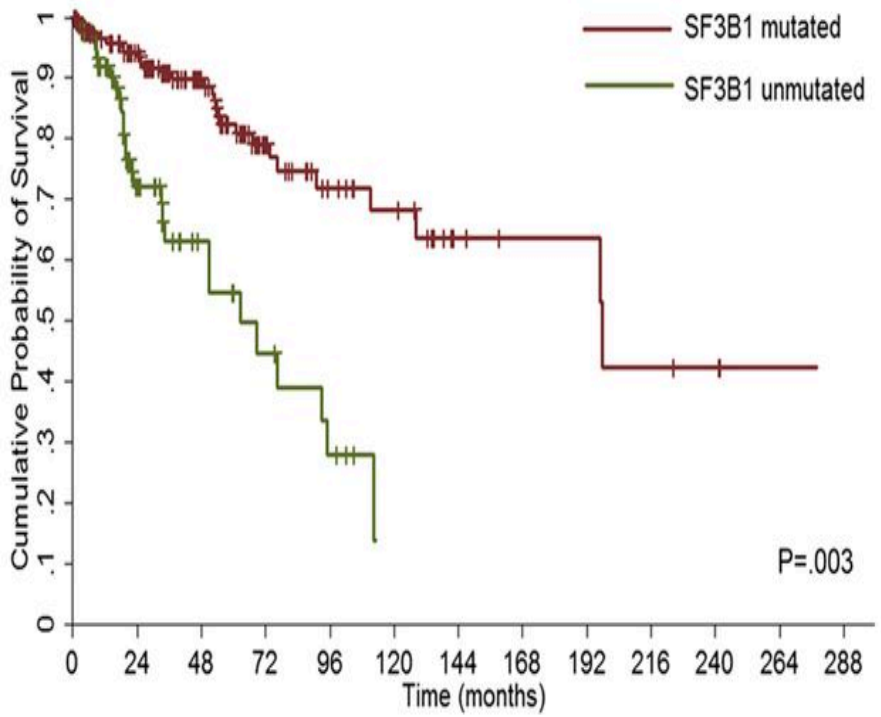


Cazzola et al , Blood 2013

SF3B1Mutations

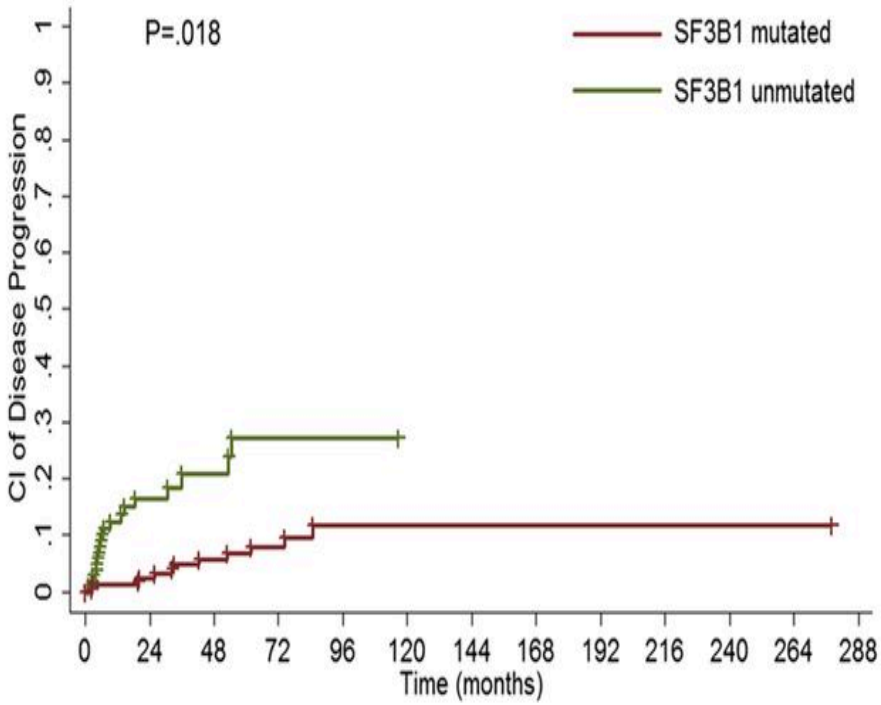
A

Overall Survival



B

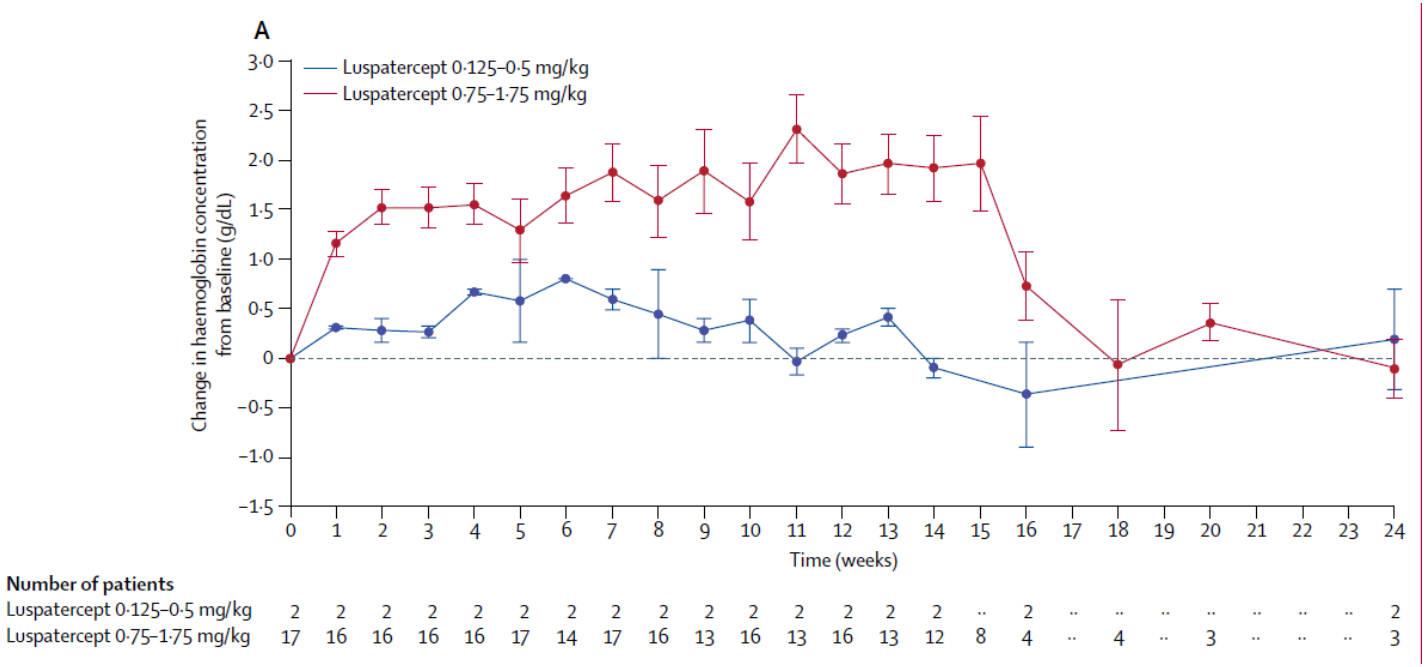
Risk of disease progression



Malcovati el al, Blood 2015

Luspatercept in LR-MDS

- Luspatercept (ACE-536) is a novel fusion protein that blocks TGF β superfamily inhibitors of erythropoiesis
- 58 patients with MDS were enrolled in the 12 week base study at 9 treatment centres in Germany
- 32 of 51 patients (63%) receiving higher dose luspatercept (0·75–1·75 mg/kg) achieved HI-E versus 2 of 9 (22%) receiving lower dose (0·125–0·5 mg/kg)



Platzbecker et al, Lancet Oncol 2017

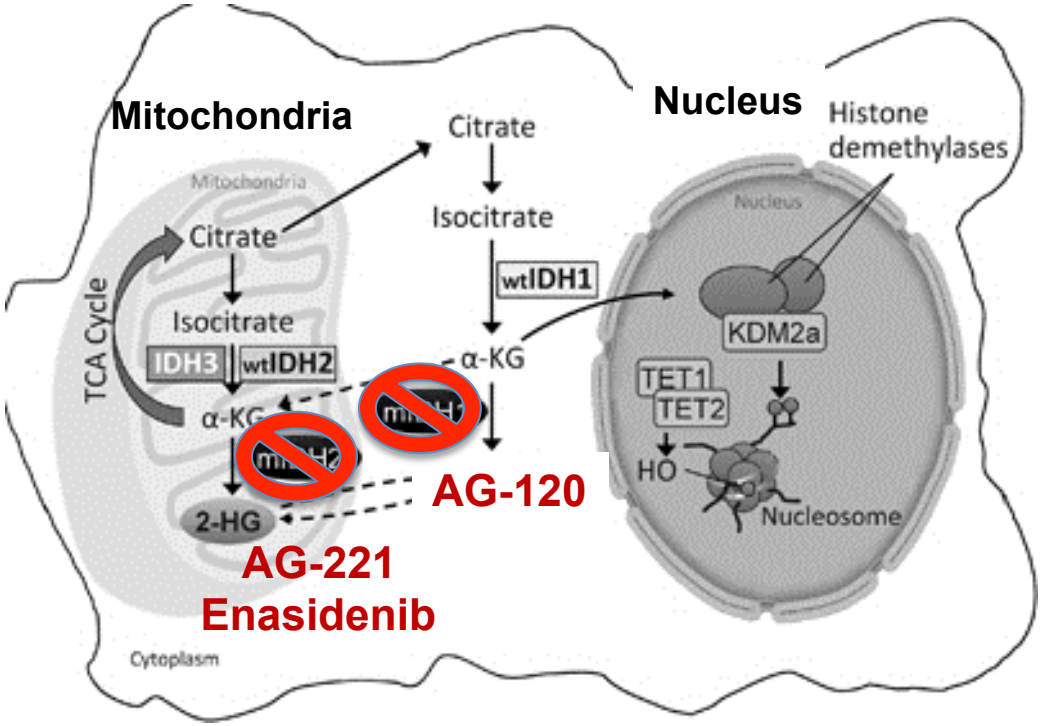
Prognostic Factors for Erythroid Response

		IWG HI-E	RBC-TI
Transfusion Burden	Low (< 4 RBC/8w) High	65% 62%	75% 29%
Previous use of ESA	Yes No	62% 65%	38% 39%
Previous Lenalidomide	Yes no	63% 63%	13% 44%
Serum EPO	<200 IU/L 200-500 IU/L > 500 IU/L	76% 58% 43%	53% 44% 14%
Ring-sideroblasts	Positive (>15%) Negative	69% 43%	42% 29%
SF3B1 mutation	Positive Negative	77% 40%	44% 39%
Any splicing factor mutation	Positive negative	73% 36%	50% 8%
IPSS-R	V. low to low Intermediate High to V. high	65% 59% 67%	48% 31%

Platzbecker et al, Lancet Oncol 2017

IDH mutations in MDS & AML

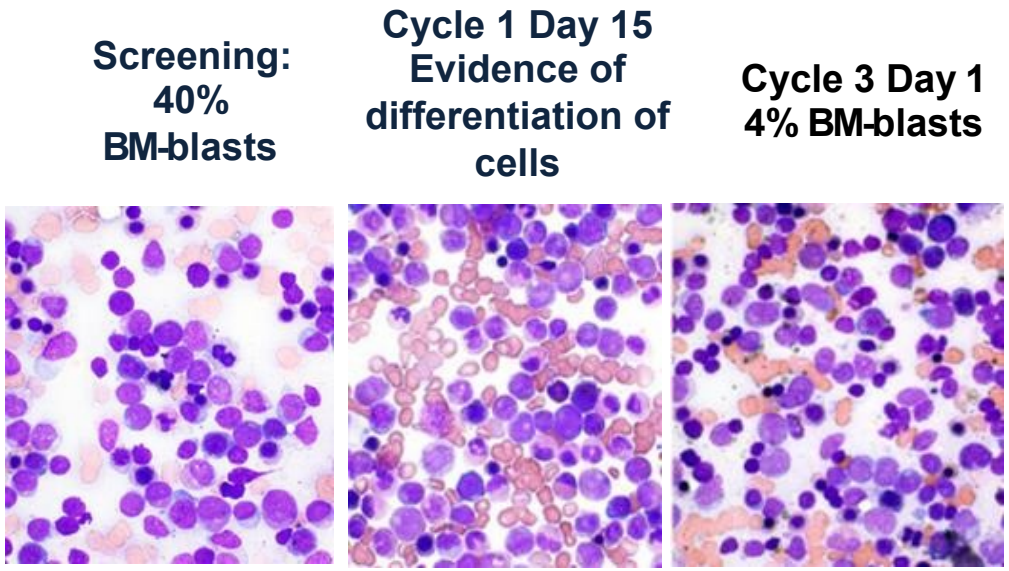
Mutated gene	AML	MDS
IDH1	7-14%	3%
IDH2	8–19%	~5%



- IDH enzymes catalyze citrate to α-ketoglutarate (α-KG)
- α-KG catalyzes histone demethylases and TET hydroxylation of 5-methylcytosine
- **Mutant IDH1/ IDH2** result in an increase of the oncometabolite, 2-hydroxyglutamate (2-HG)
- 2-HG induces a block of cell differentiation by inhibiting the chromatin-modifying enzymes, DNA and histone demethylases, which results in hypermethylated DNA, blocking cell differentiation
- AML with mutated IDH is associated with extensive hypermethylation

Medeiros et al, Leukemia 2016

AG-221 (Enasidenib) promotes cell differentiation

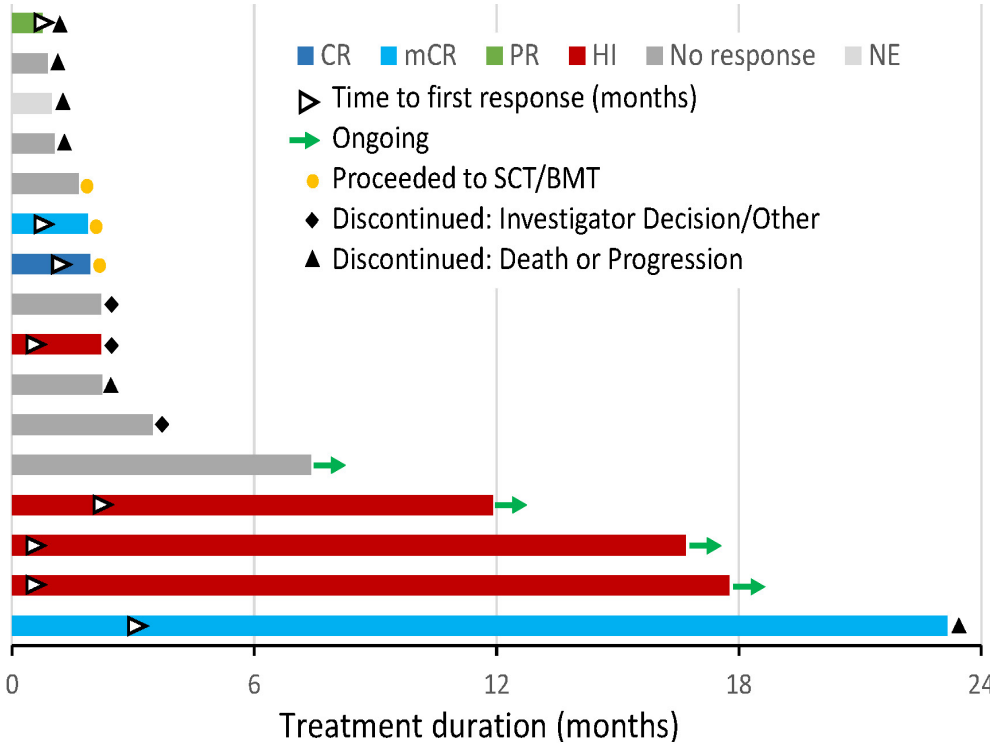


- Differentiation effects: BM-blasts reduced from 40% to 4%
- Evidence of differentiation as early as cycle 1
- Full neutrophil recovery at cycle 2
- Achieved CR by start of cycle 4

Stein et al, Blood 2017

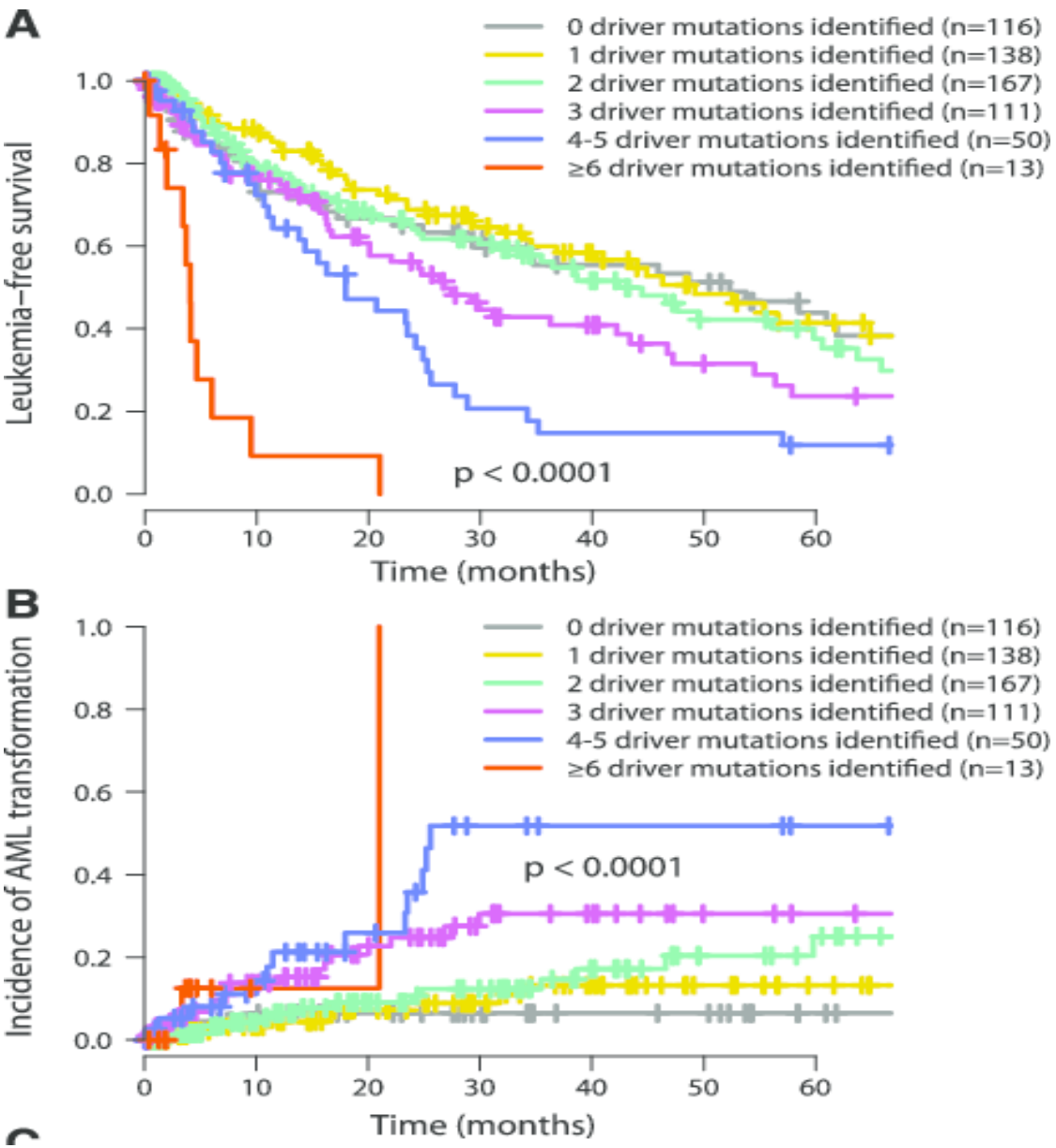
❖ Daily oral enasidenib 100 mg QD in 28-day cycles in16 MDS patients

	MDS Patients (N=16) n (%)
Overall response rate (CR + PR + mCR + HI)	**8/15 (53)**
Best response	
Complete Remission*	1/9 (11)
Partial Remission*	1/9 (11)
Marrow CR*	2/9 (22)
Hematologic Improvement	4/15 (27)
Not Evaluable†	1 (6)



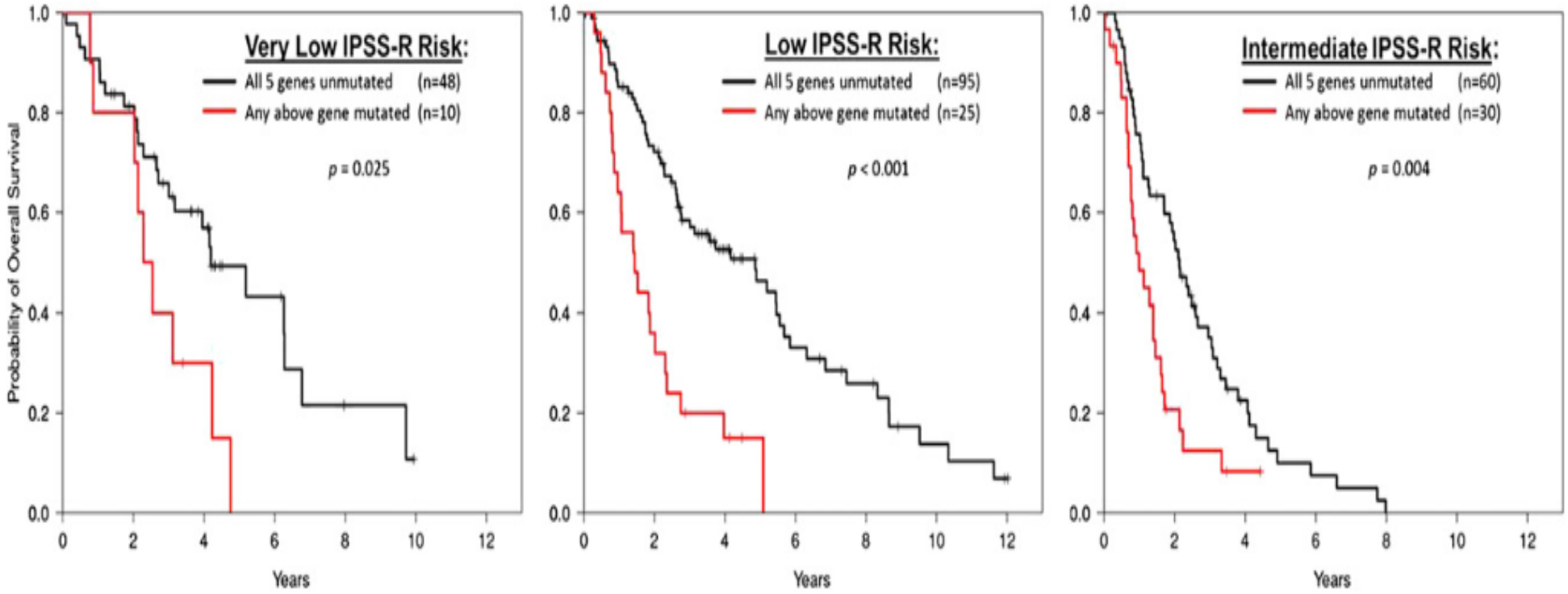
Stein et al, ASH Meeting 2016

Mutation burden



Papaemmanuil et al, Blood 2013

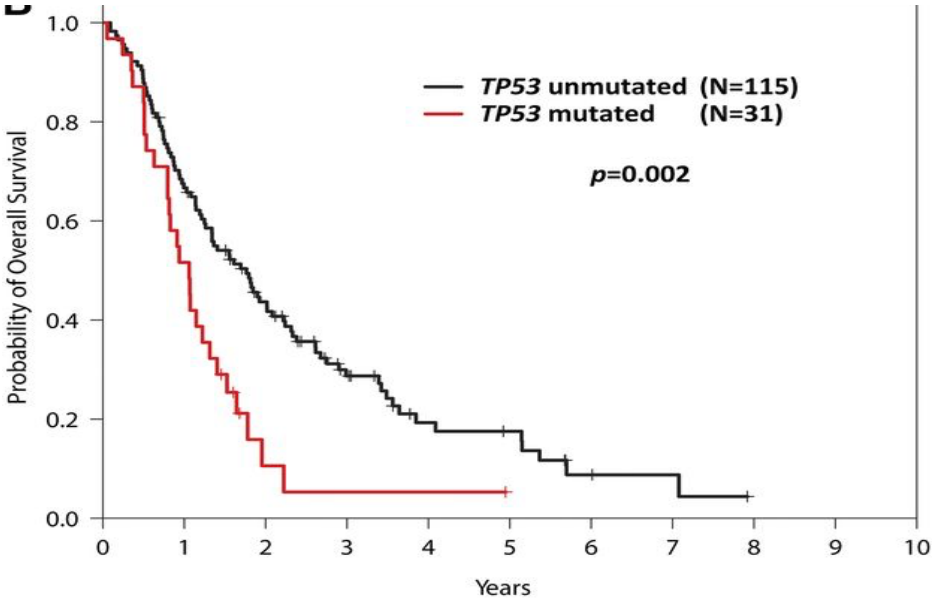
TP53, EZH2, RUNX1, ASLX1, or ETV6 Mutations

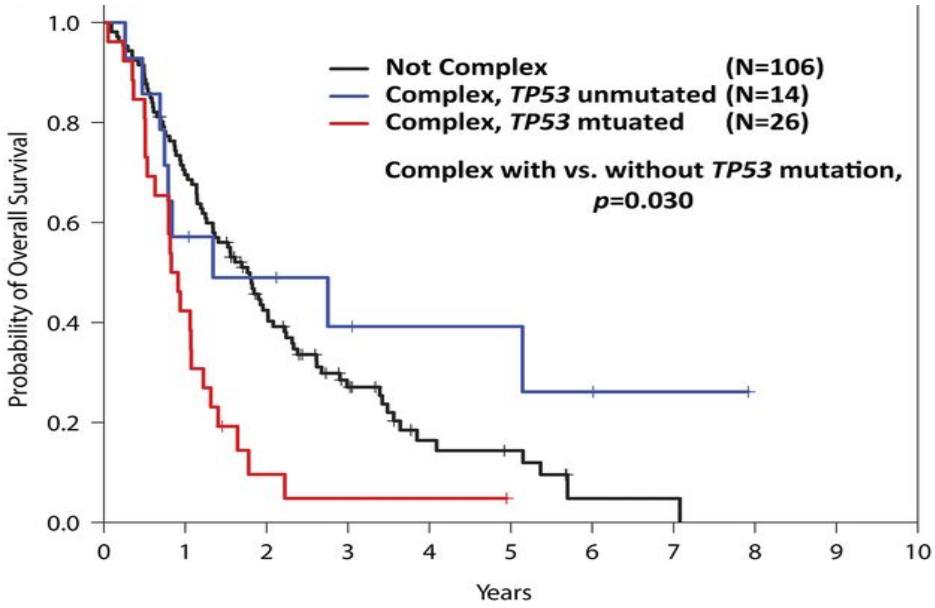


Bejar & Steensma, Blood 2014

TP53 Mutations

MDS

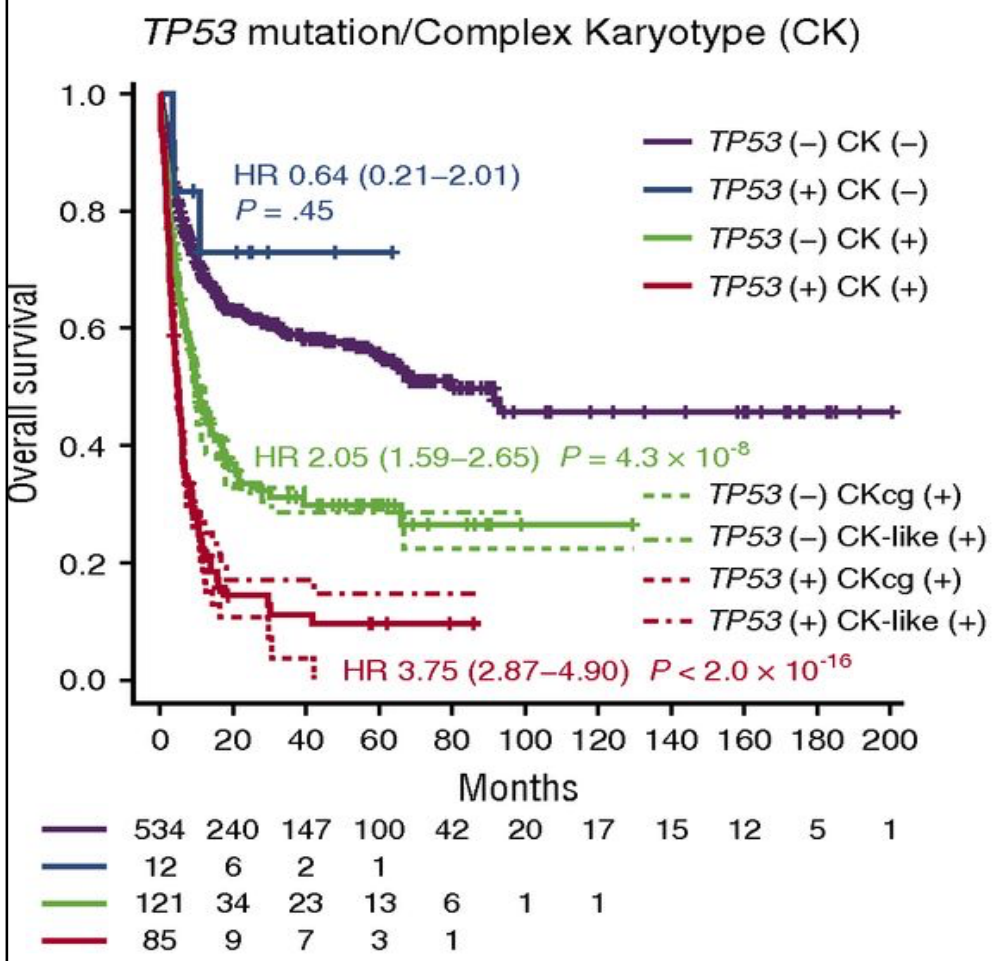


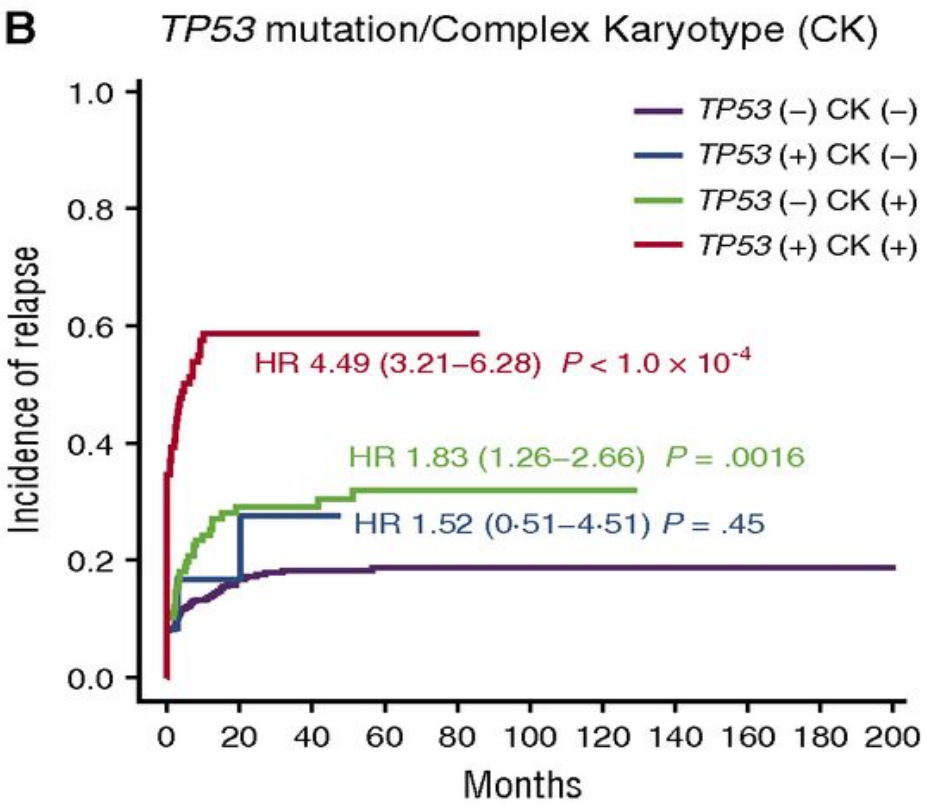


Mut-TP53 significantly contributes to dismal survival in MDS and AML with complex karyotype

Bejar et al, Blood 2014, Papaemmanuil et al, NEJM 2016

TP53 and HSCT in MDS

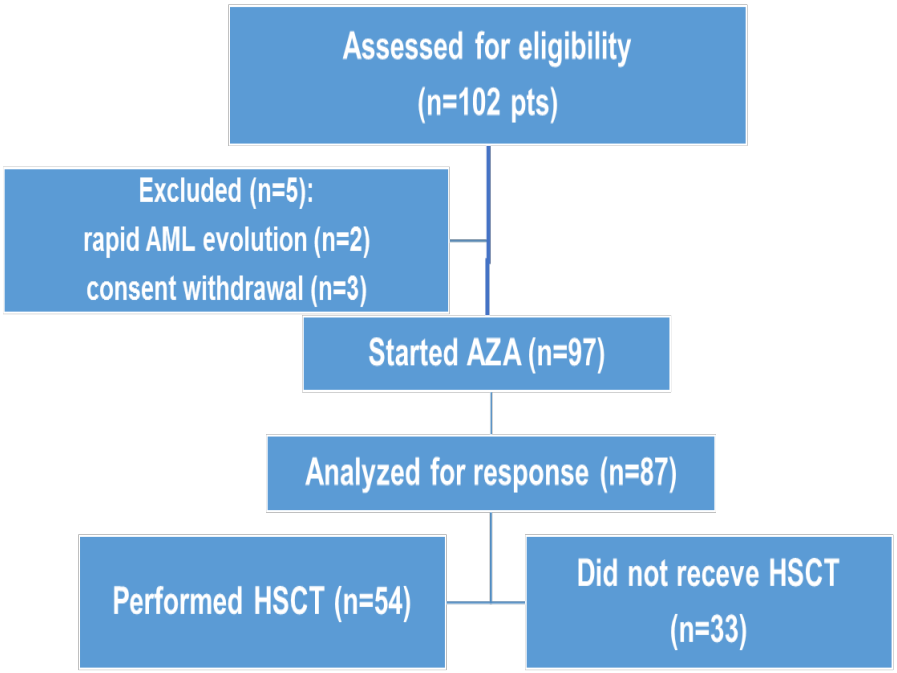




Yoshizato et al, Blood 2017

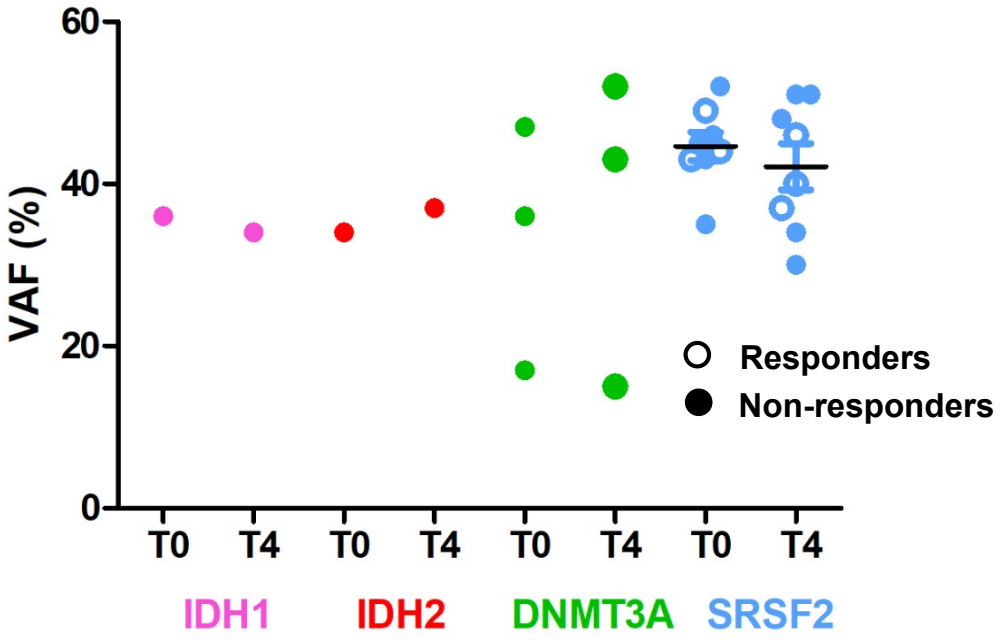
Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study

M. T. Voso[1*], G. Leone[2], A. Piciocchi[3], L. Fianchi[2], S. Santarone[4], A. Candoni[5], M. Criscuolo[2], A. Masciulli[6], E. Cerqui[7], A. Molteni[8], C. Finelli[9], M. Parma[10], A. Poloni[11], A. M. Carella[12], F. Spina[13], A. Cortelezzi[14], F. Salvi[15], E. P. Alessandrino[16], A. Rambaldi[6] & S. Sica[2]



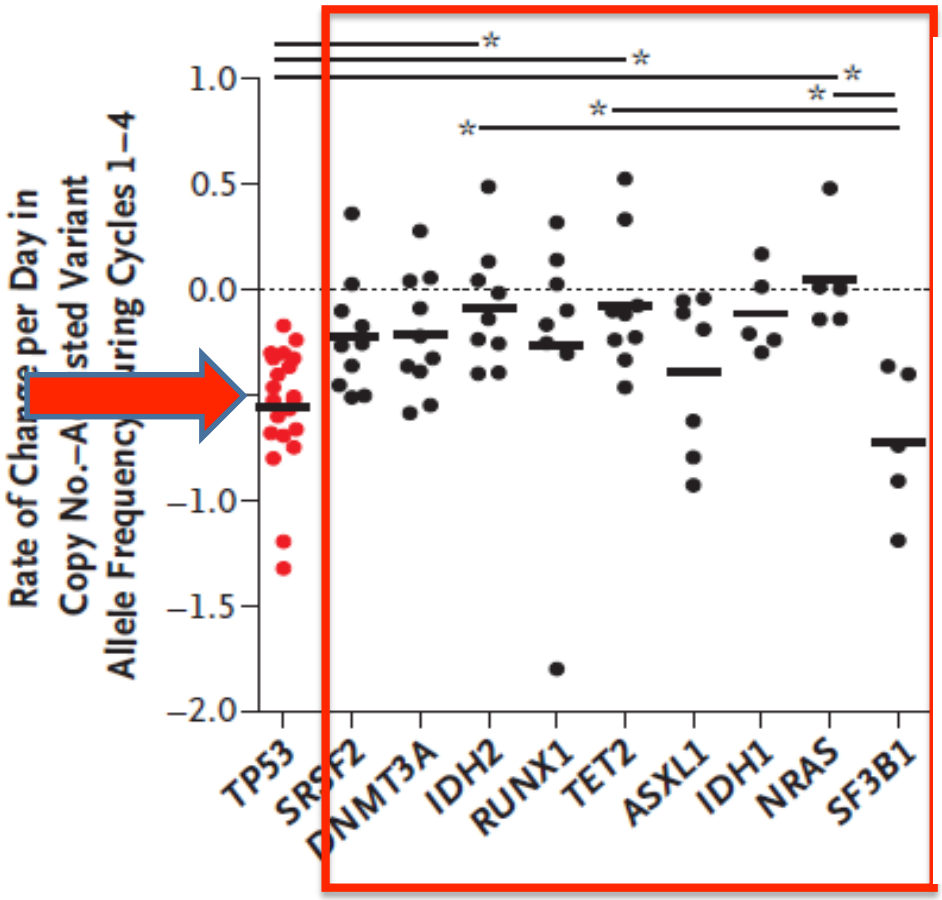
74% of pts with a donor

Ann Oncol 2017

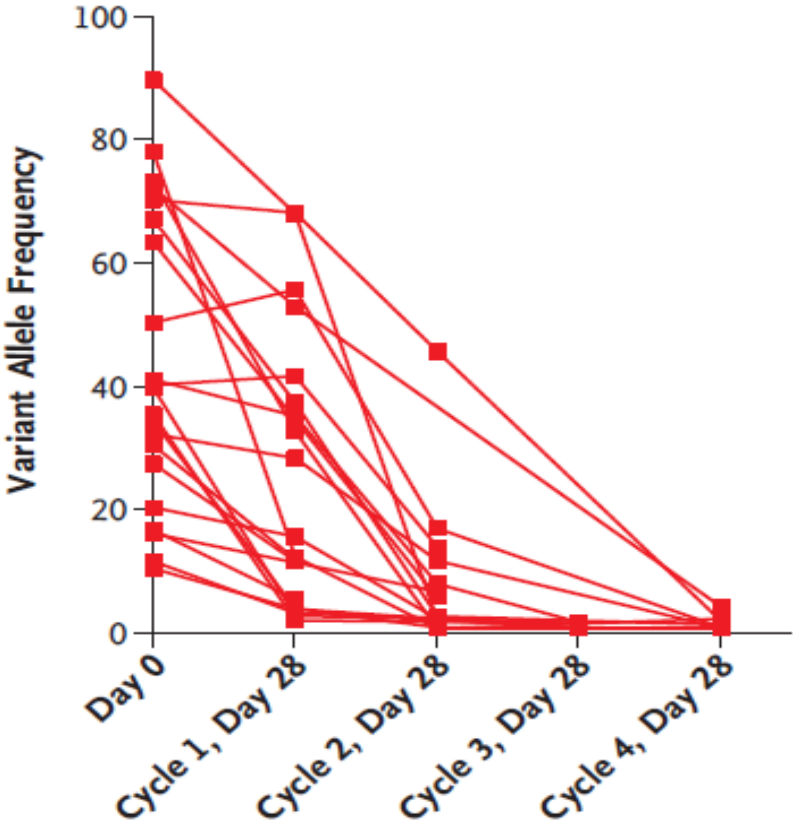


Falconi G., Fabiani E., unpublished

Clearance of TP53 Mutations during Hypomethylating Treatment (DAC, 20 mg/m^2/day for 10 days)



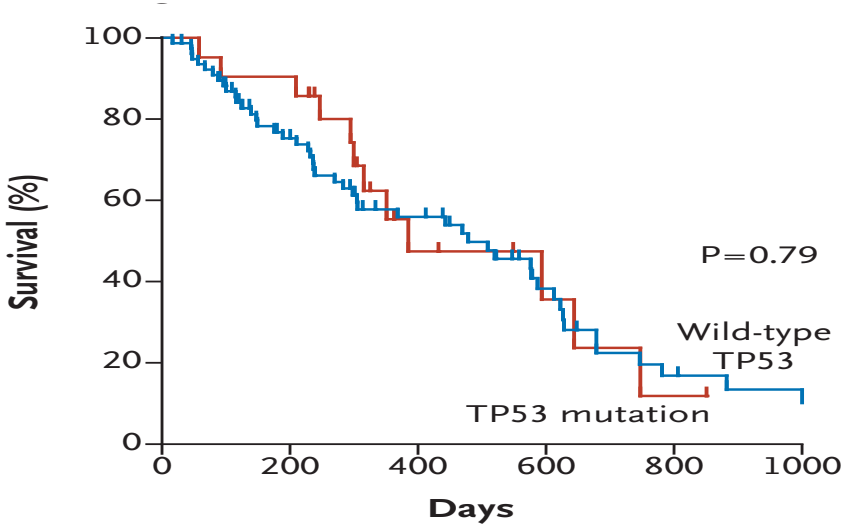
TP53-mut, n=21 pts



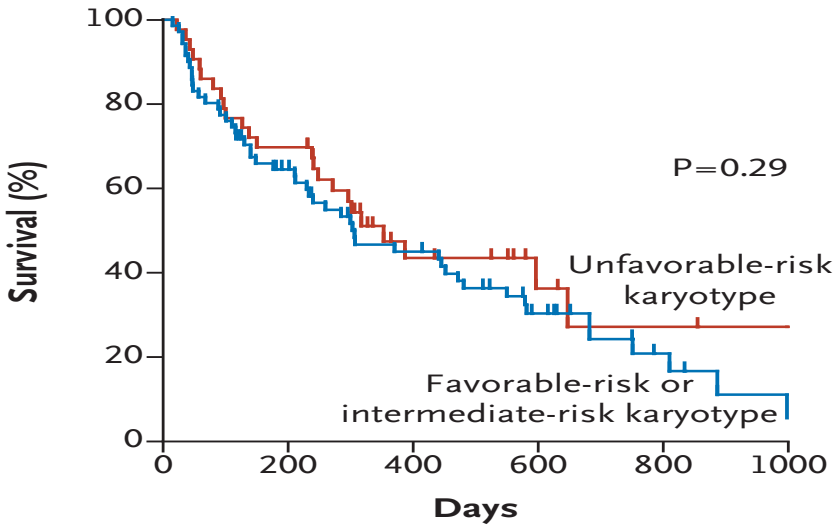
Welch et al, NEJM 2016

Survival

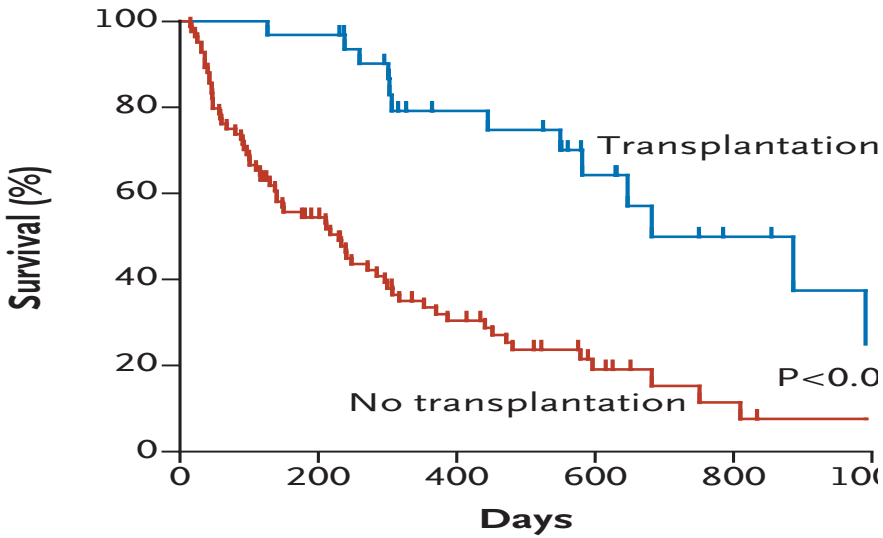
TP53 mutation



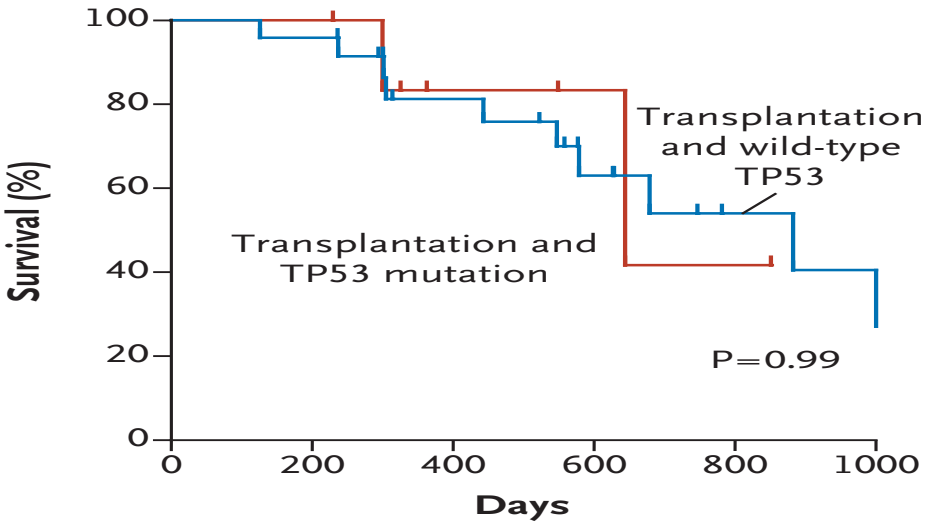
Karyotype



HSCT



TP53 in HSCT



Welch et al, NEJM 2016

Acknowledgements

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Francesco Lo Coco

Sergio Amadori
William Arcese

Valentina Alfonso
Laura Cicconi
M. Domenica Divona
Emiliano Fabiani
Giulia Falconi
Licia Iaccarino
Serena Lavorgna
Nelida Noguera
Tiziana Ottone

Francesco Buccisano
Eleonora De Bellis
Iliaria Del Principe
Luca Maurillo
Adriano Venditti

AIRC