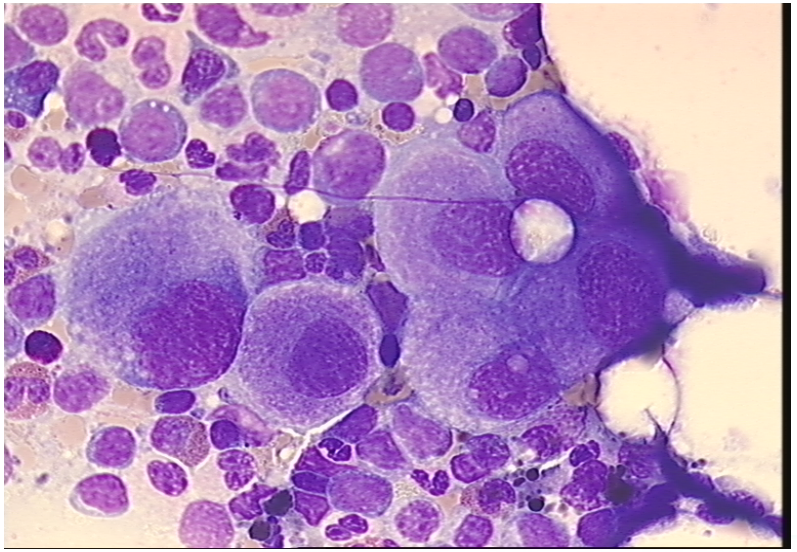
Le mielodisplasie oggi: inquadramento dell'argomento

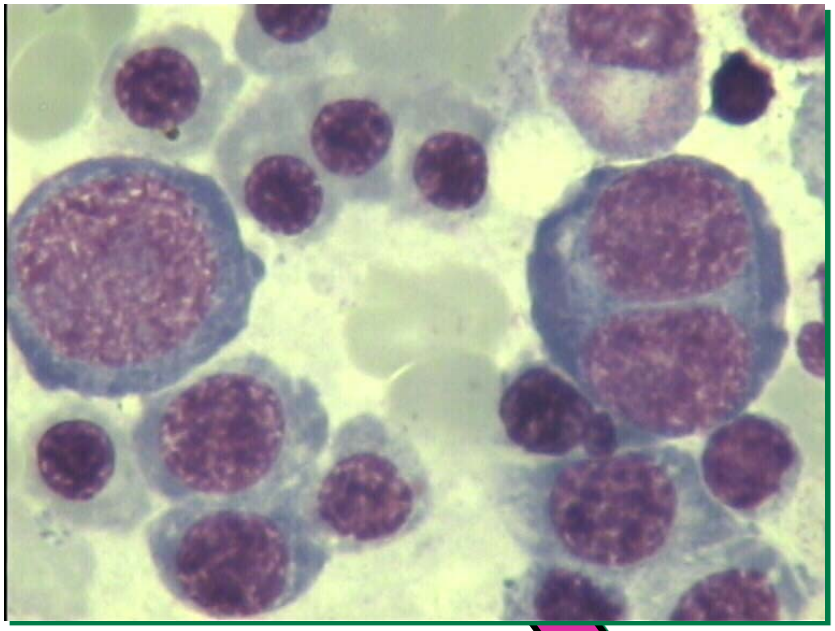


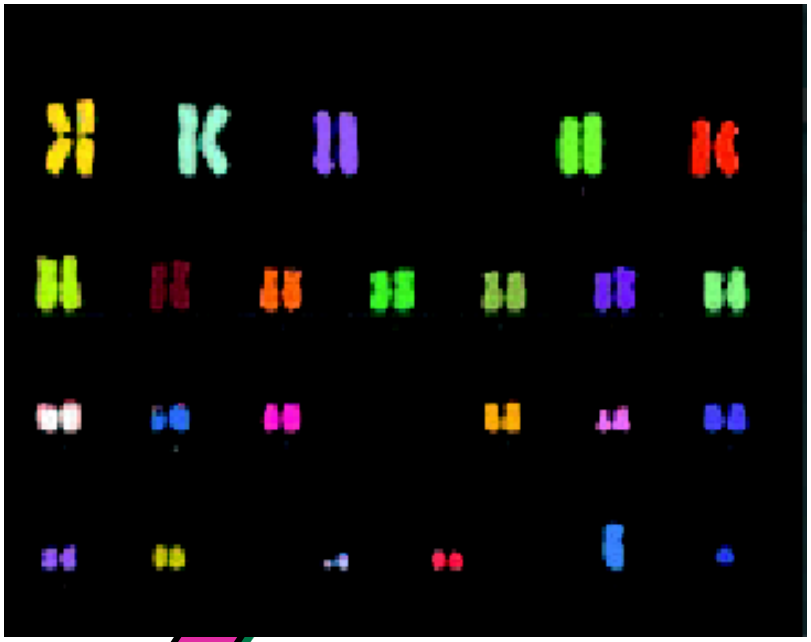
Valeria Santini

MDS UNIT

Ematologia, Università di Firenze

Myelodysplastic syndromes are a constellation of diseases with difficult diagnosis





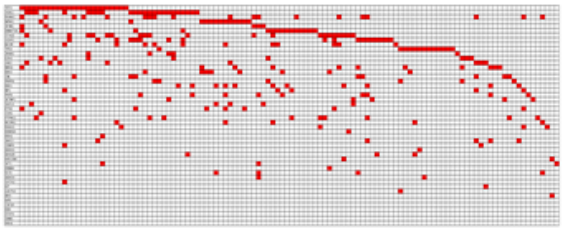
An accurate diagnosis is the basis for successful prognostic stratification (and treatment) of MDS

Criteria: presence and number of dysplastic lineages , percentage of bone marrow blasts, cytogenetic abnormalities

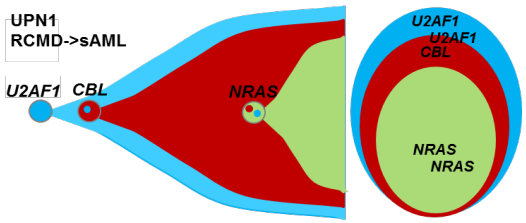
MDS MOLECULAR PATHOGENESIS

Somatic discovery

Germ line discovery



Clonal hierarchy



Clinical applications

Targeted deep NSG panels

- Diagnosis
- Prognosis
- MRD

Somatic diversity

- mutations
- chromosomal defects

MOLECULAR DIVERSITY

- Germline variants
- Epigenetic defects
- Intra-tumor heterogeneity (clonal architecture)

Courtesy J Maciewiesky

How to evaluate MDS clinically? how to determine prognosis?

New classification of cytogenetic risk

Very good	Good	Intermediate	Poor	Very poor
Isolated: del(11q) -Y	Normal **Isolated:** der(1;7) del(5q) del(12p) del(20q)	**Isolated:** 7q- +8 i(17p) +21 +19 Other single	**Isolated:** der(3)(q21q26) -7	**Complex** >3 anomalies
	Double with 5q-	Other double	**Complex** 3 anomalies	
			Double with –7/7q-	

Schanz J et alJ Clin Oncol. 2012 Mar 10;30(8):820-9.

International prognostic scoring system (IPSS-R) variables and weighted scores

Cytogenetics	Very good	Good	Intermediate	Poor	Very poor
Score	0	1	2	3	4
BM blasts, %	≤ 2	> 2–< 5	5–10	> 10	
Score	0	1	2	3	
Hb, g/dL	≥ 10	8–9.9	< 8		
Score	0	1	1.5		
ANC, x 10^9/L	≥ 0.8	< 0.8			
Score	0	0.5			
Platelets, x 10^9/L	≥ 100	50–99	< 50		
Score	0	0.5	1		

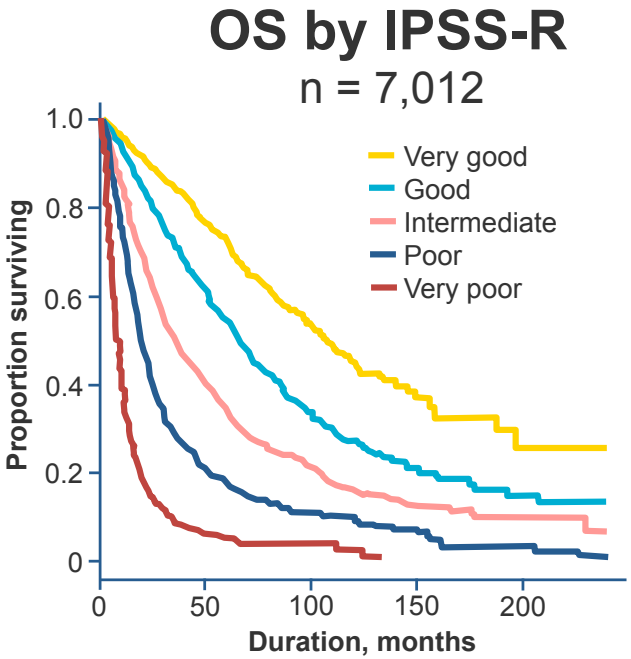
* Regression analysis for survival and AML evolution.
ANC, absolute neutrophil count; BM bone marrow.

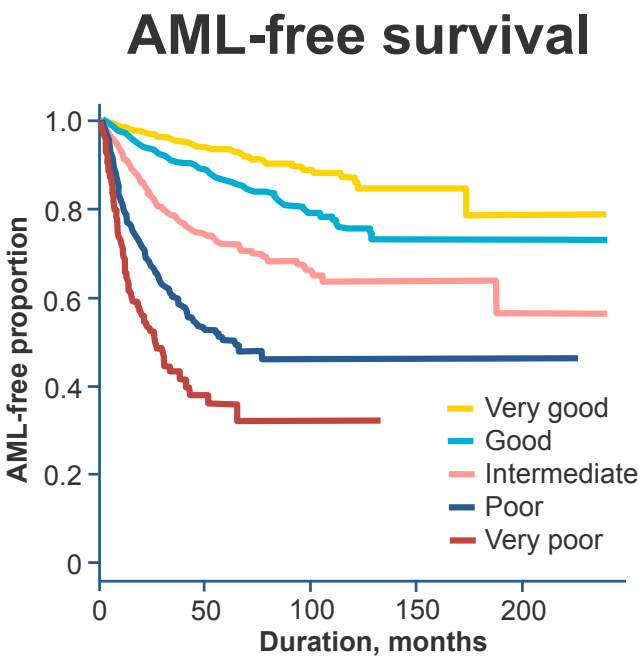
Greenberg PL, et al. Blood. 2012;120:2454-65.

IPSS-R: prognostic scores and risk groups

* Values for 70-year-old patient (for consideration of age: [age in years − 70] x 0.04, add result to sum of other variables). Age, PS, ferritin, and LDH were significant additive features for OS but not for AML transformation.

Risk category	Score
Very low	≤ 1.5
Low	> 1.5–3
Intermediate	> 3–4.5
High	> 4.5–6
Very high	> 6



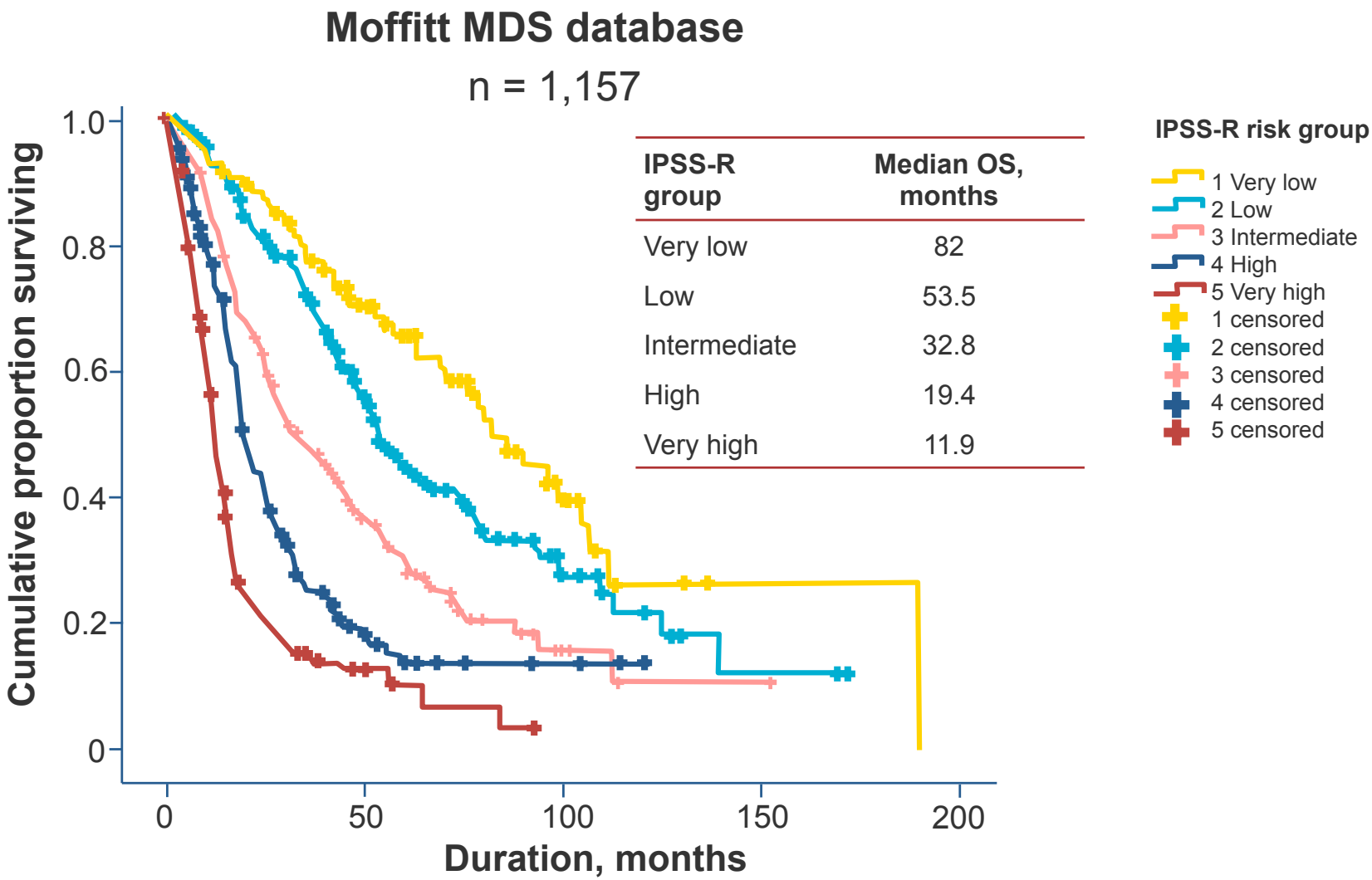


	Very low	Low	Intermediate	High	Very high
Median OS, years	8.8	5.3	3.0	1.6	0.8
AML 25%, years	NR	10.8	3.2	1.4	0.73

NR, not reached.

Greenberg PL, et al. Blood. 2012;120:2454-65 and updated data.

Critical point for sequential therapy: Is the IPSS-R valid for treated patients?



IPSS-R group	Median OS, months
Very low	82
Low	53.5
Intermediate	32.8
High	19.4
Very high	11.9

Mishra A, et al. Blood. 2012;120:abstract 2816.

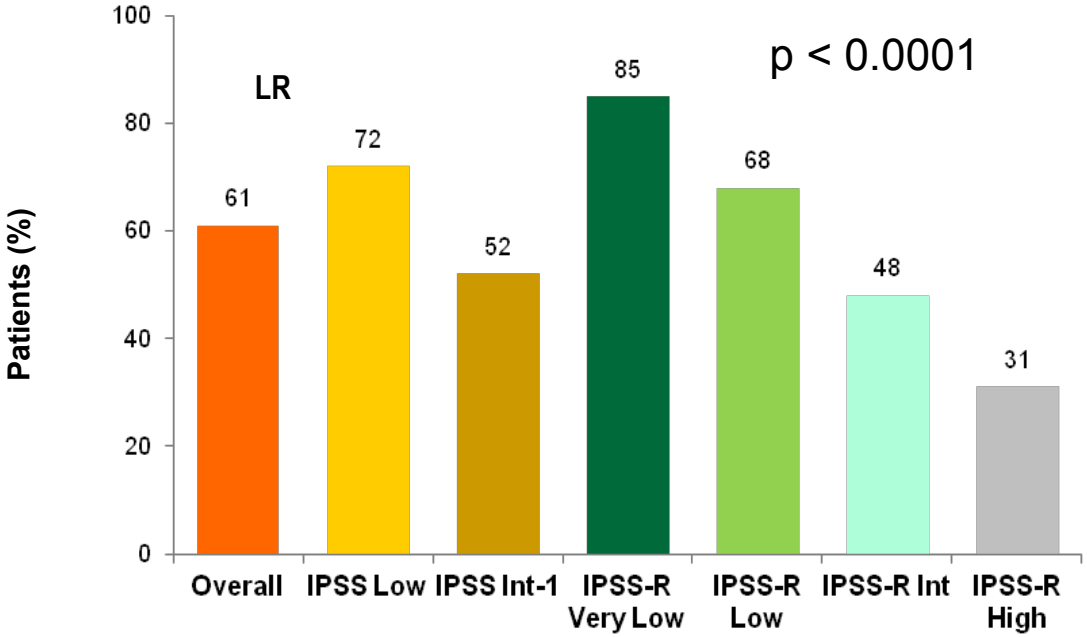
IPSS-R, sEPO levels, ferritin but no specific mutation predict response to ESAs

Factor	Value	Score	Value	Score
Transfusion requirement*	<2 U/ month	0	≥2 U/ month	1
Serum EPO*	<500 U/ L	0	≥500 U/ L	1

serum Ferritin associated with EPO response

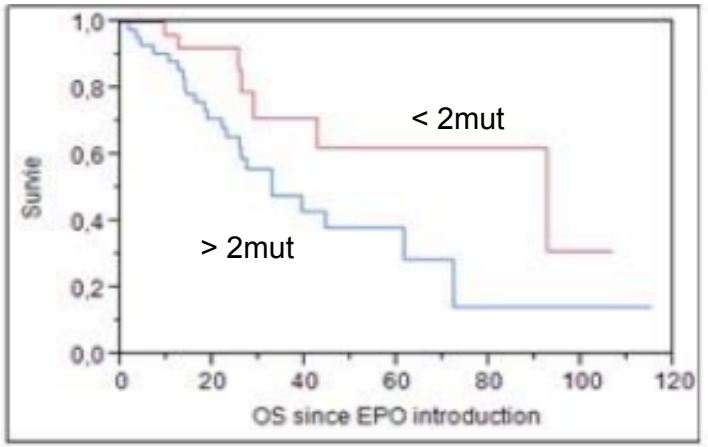
Predicted response
Score = 0: 74%
Score = 1: 23%
Score = 2: 7%

Hellström-Lindberg E et al. Br J Haematol. 1997;99(2):344-51.



Santini V, et al. Blood. 2013;122:2286-8.

Number of mutations predicts OS after ESAs (79 pts-)

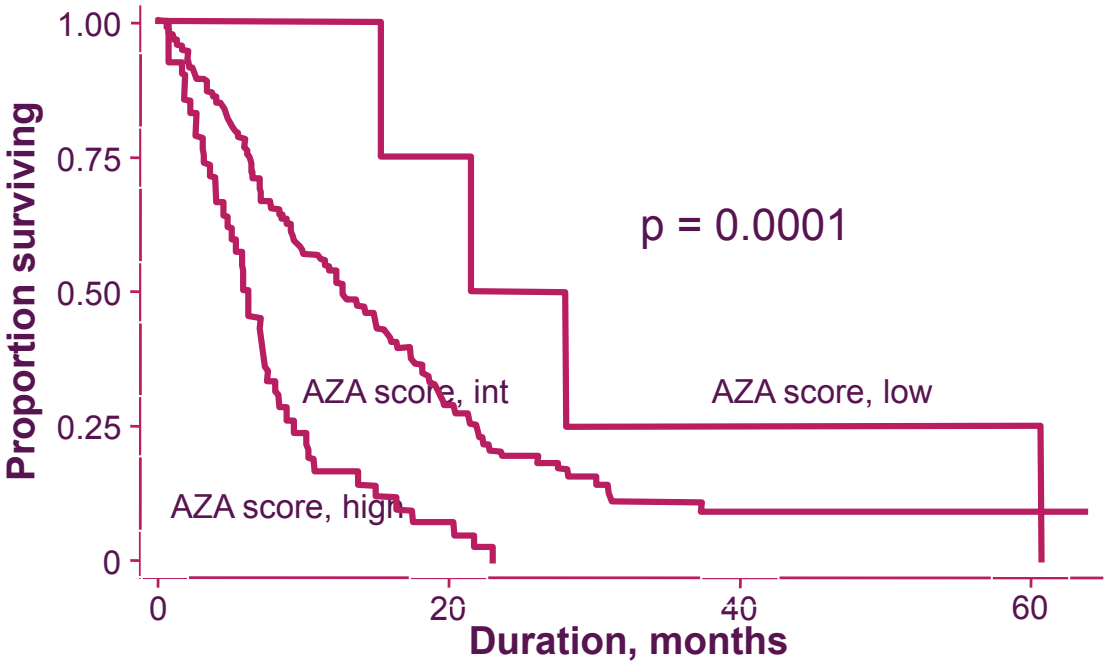


P=0.04

Kosmider O. et al Haematologica 2016; 101: e280-3.

Clinical and IPSS-R heterogeneity: OS in IPSS-R very high-risk group according to French AZA scoring system

IPSS-R very high-risk MDS



French AZA scoring system

Risk factor	Score
ECOG performance status ≥ 2	1
Intermediate-risk cytogenetics	1
Poor-risk cytogenetics	2
Transfusion dependence ≥ 4 U/8 wks	1
Peripheral blood blasts present	1

Ades L, et al. Blood. 2012;120:abstract 422 and data presented at ASH 2012.

ECOG, Eastern Cooperative Oncology Group.

Itzykson R, et al. Blood. 2011;117:403-11.

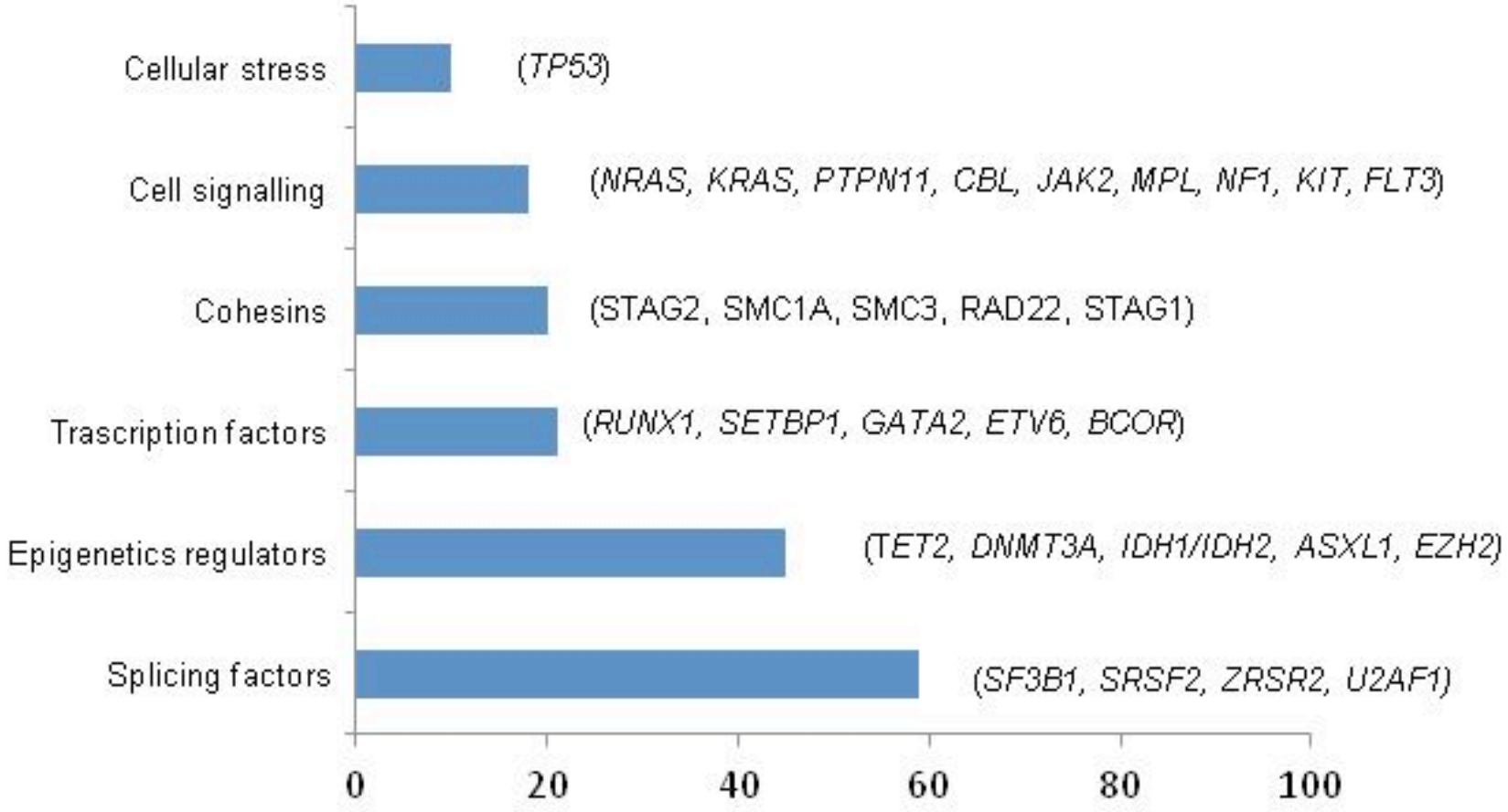
Is IPSS-R enough?

Molecular variables: mutations and DNA methylation

Molecular variables: somatic mutations

- IPSS-R does not consider somatic mutations
- Somatic mutations are present in nearly 90% of MDS
- Several mutated genes have prognostic significance independent of the IPSS-R
- How to weigh prognostic mutations in clinical practice remains unclear

Recurrent somatic mutations are found in > 80% of MDS cases



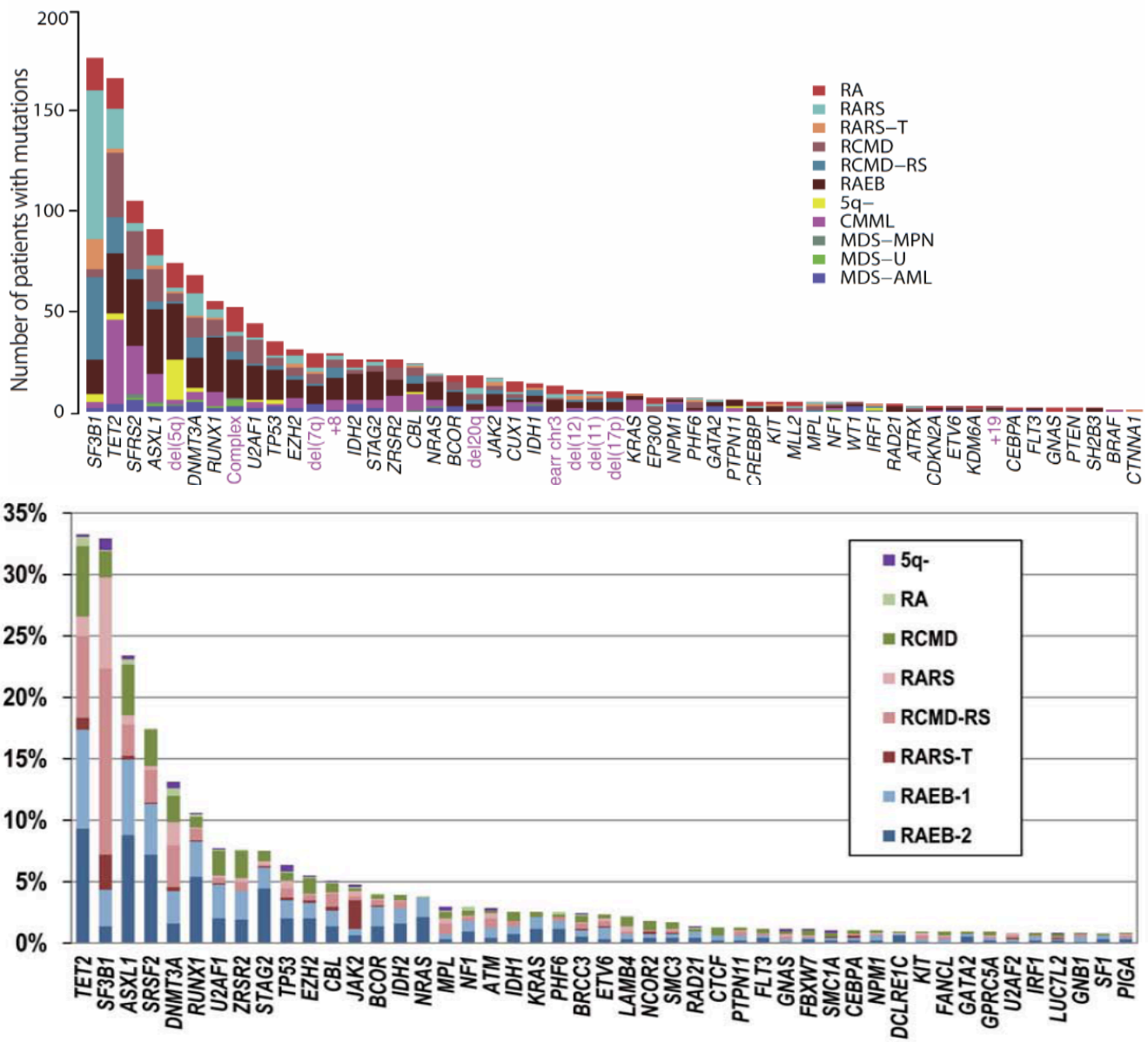
Somatic mutations in MDS:

prognostic value

possible therapeutic target

confirm diagnosis (?)

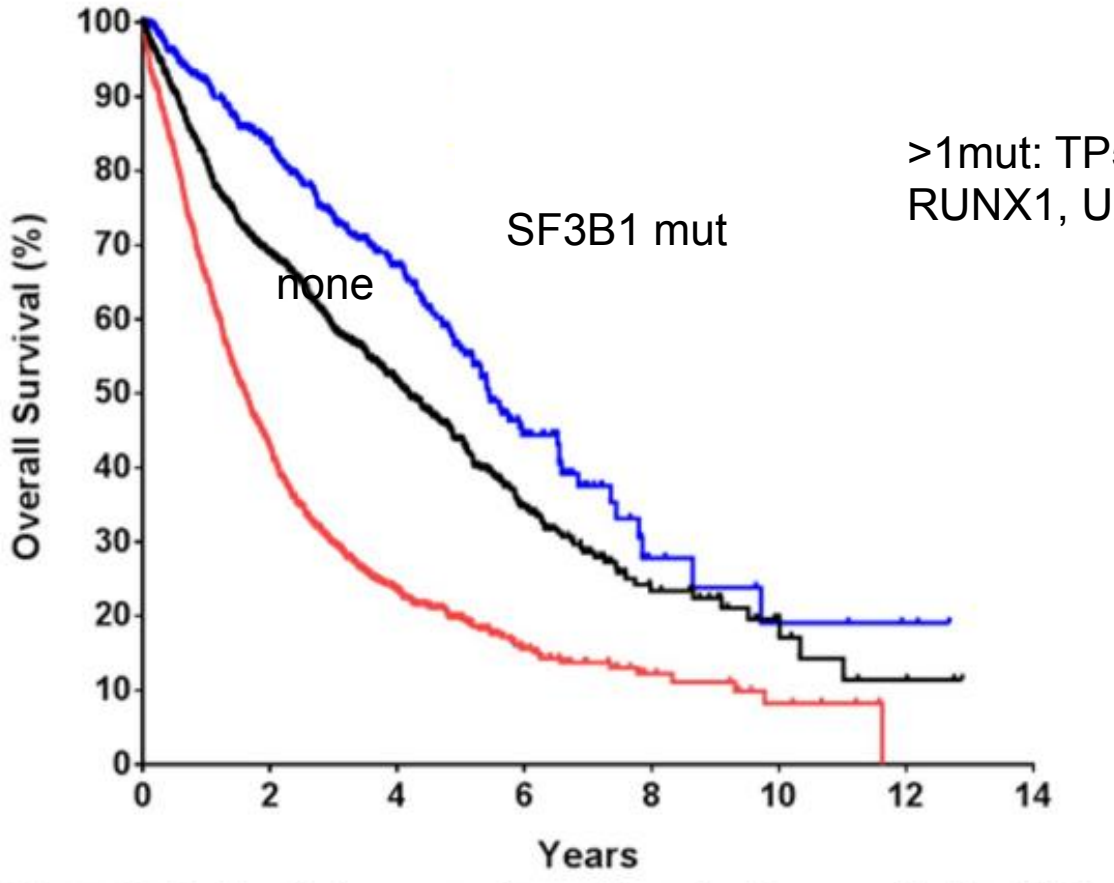
Somatic Mutations in MDS



Papaemmanuil et al. *Blood*. 2013.

Haferlach et al. *Leukemia*. 2014.

Somatic gene mutations in MDS are independent prognostic indicators

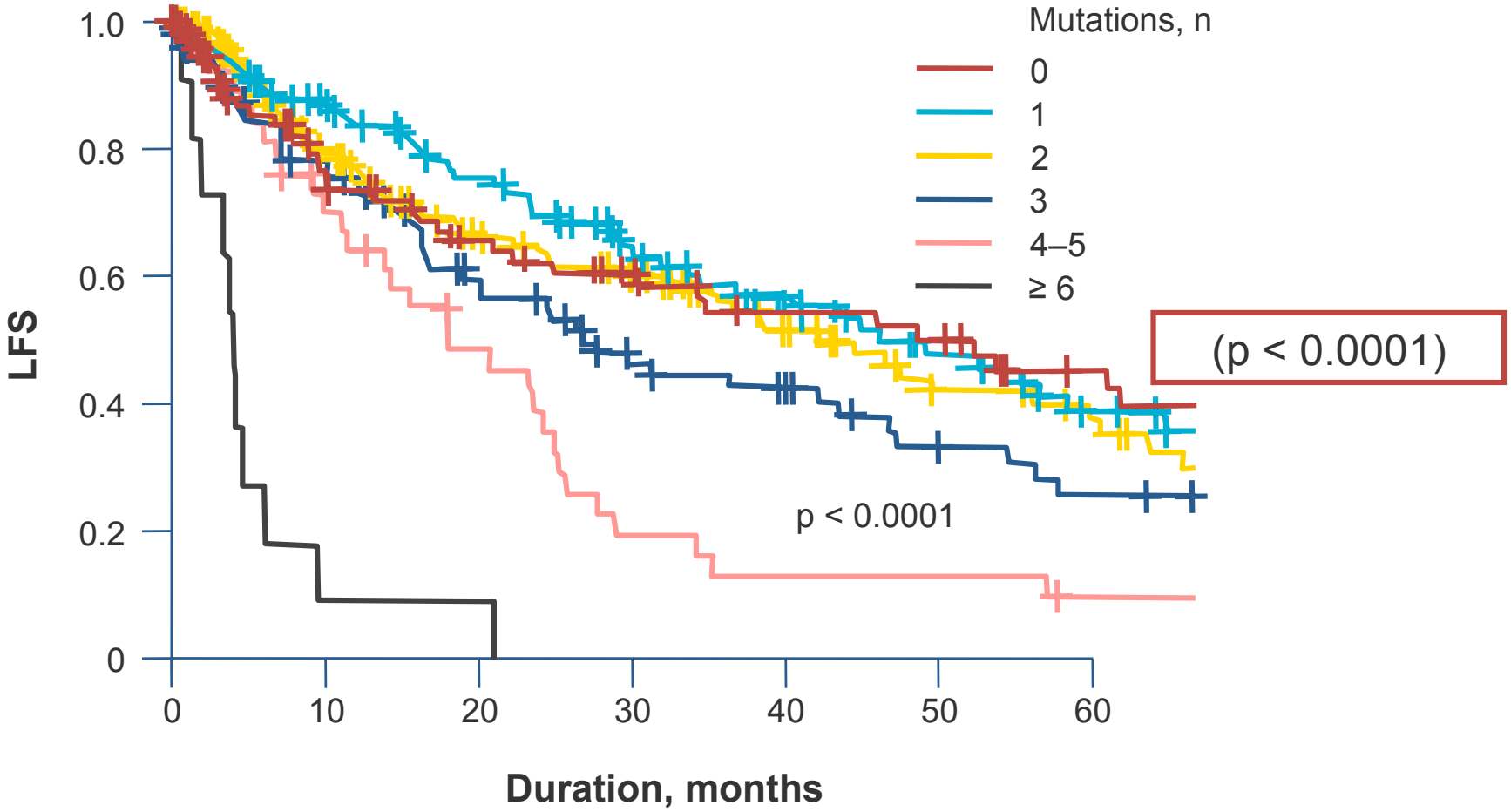


>1mut: TP53, CBL, EZH2, RUNX1, U2AF1, ASXL1

Rafael Bejar et al. Blood 2015;126:907

blood

Leukaemia-free survival in MDS inversely correlates with number of driver mutations



Papaemmanuil E, et al. Blood. 2012;120:abstract 5.

Impact of Mutations by IPSS-R Group

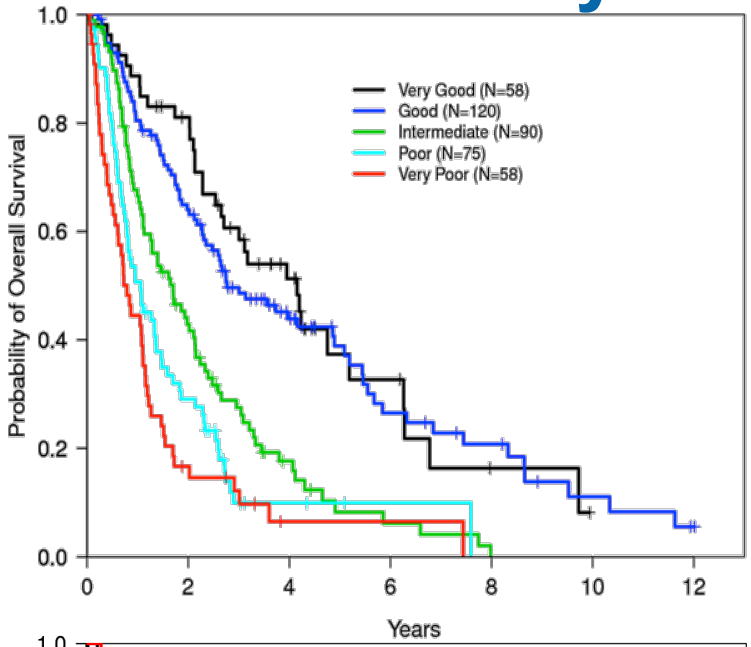
TP53

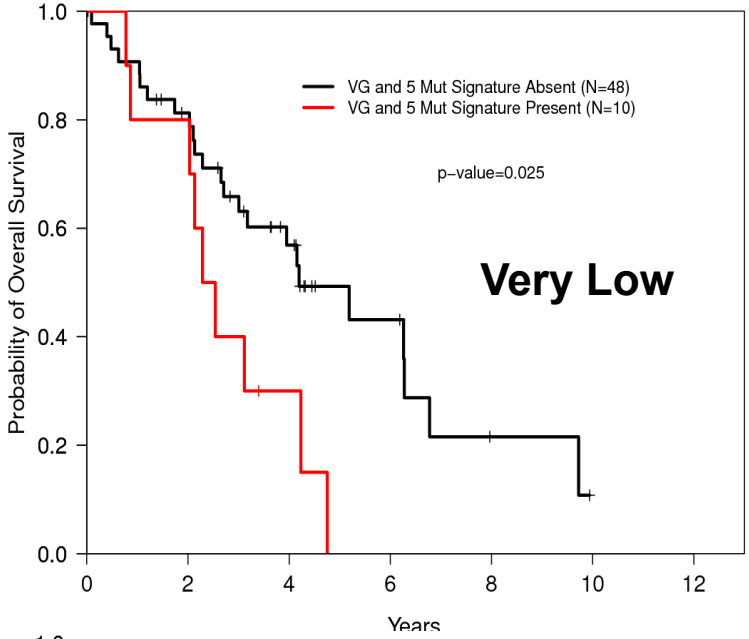
ETV6

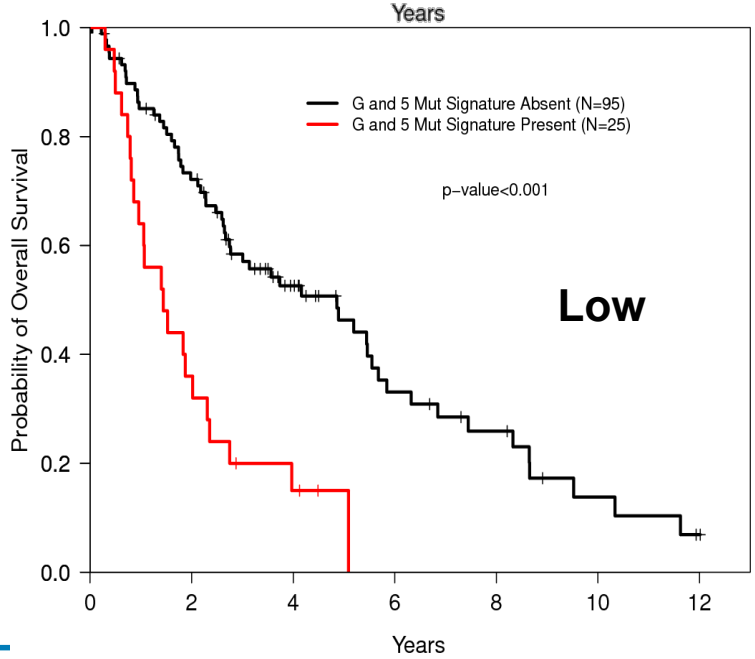
ASXL1

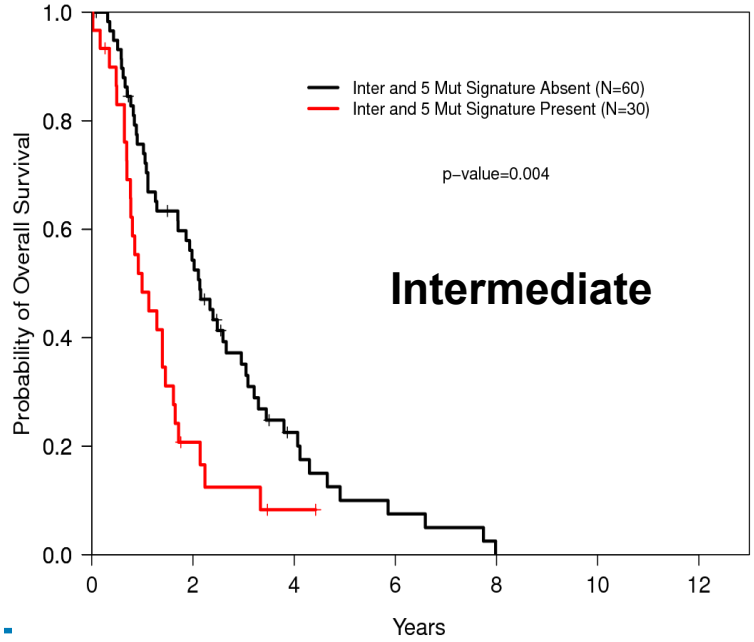
EZH2

RUNX1



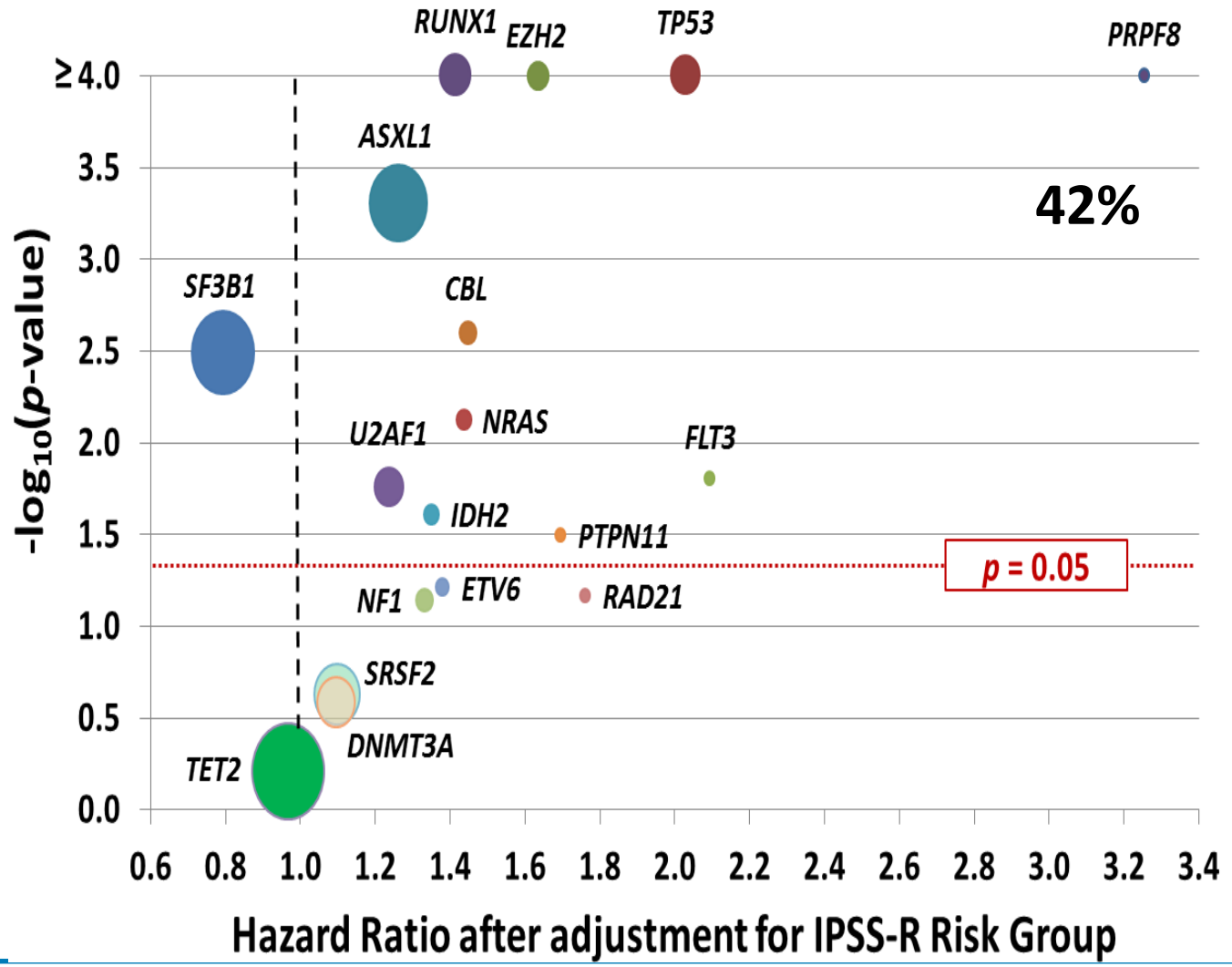




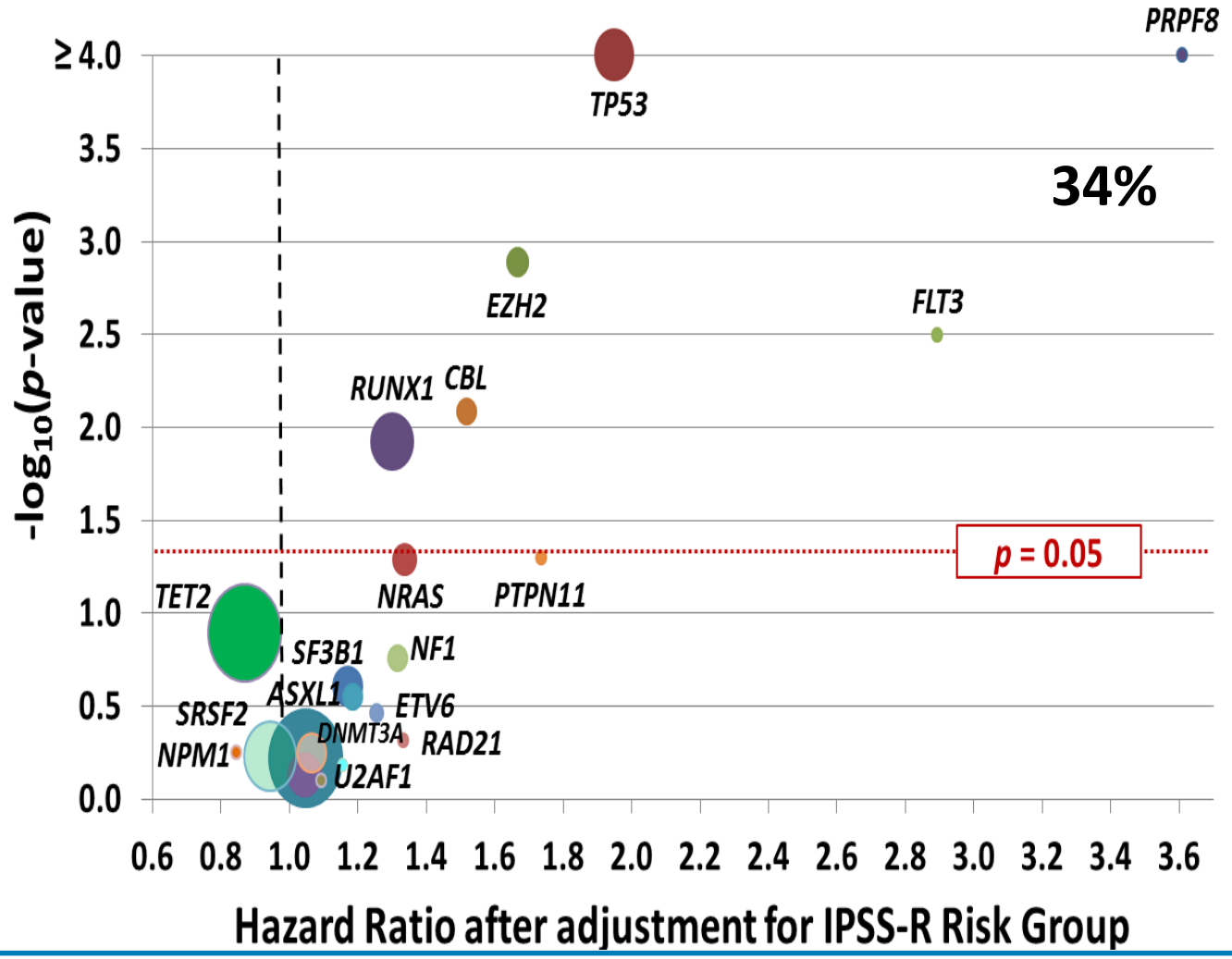


- Bejar R, et al. N Engl J Med. 2011;364:2496-506.

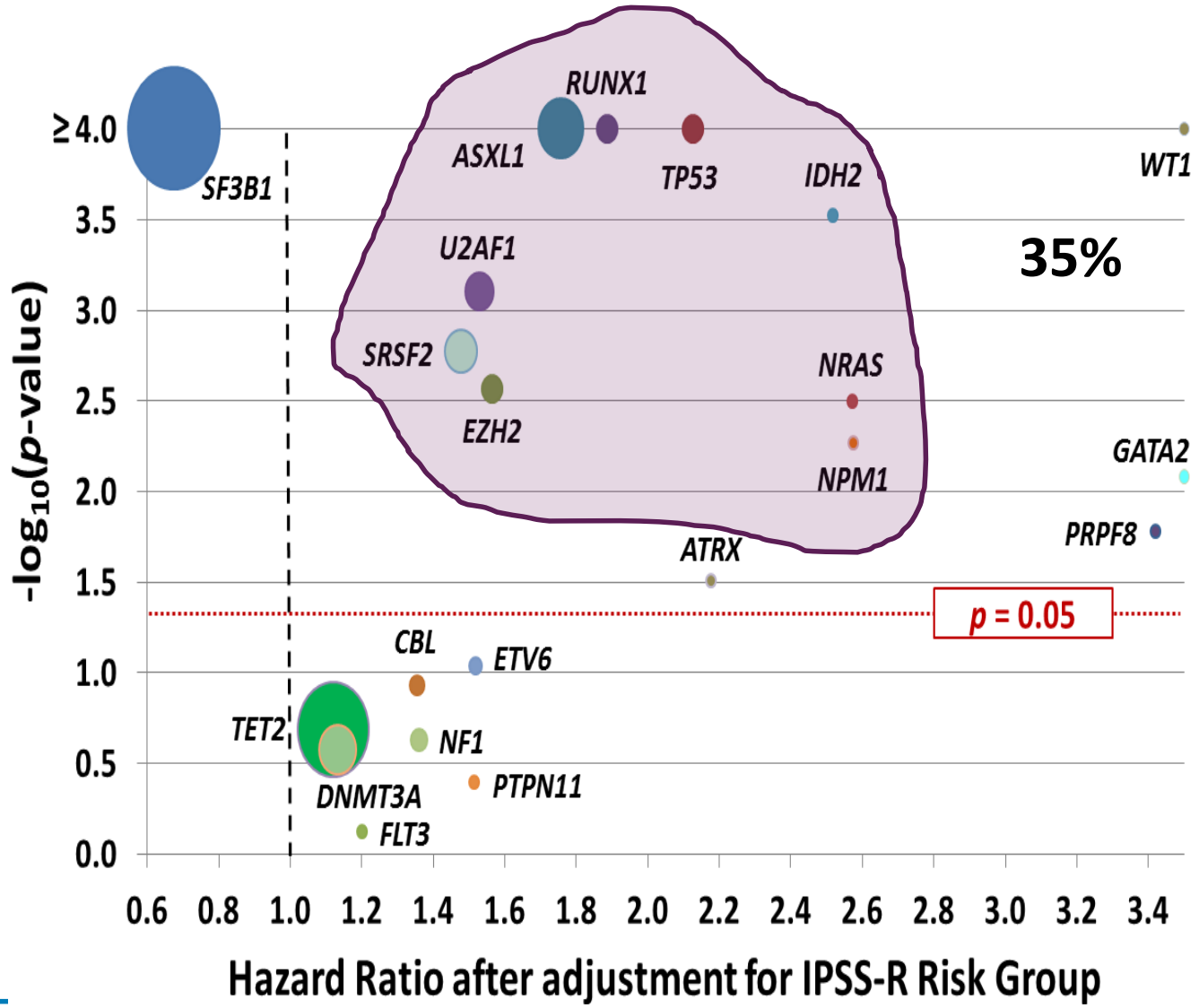
IPSS-R Adjusted Hazard Ratios for Mutated Genes



Division by Blast Proportion (5-30%)

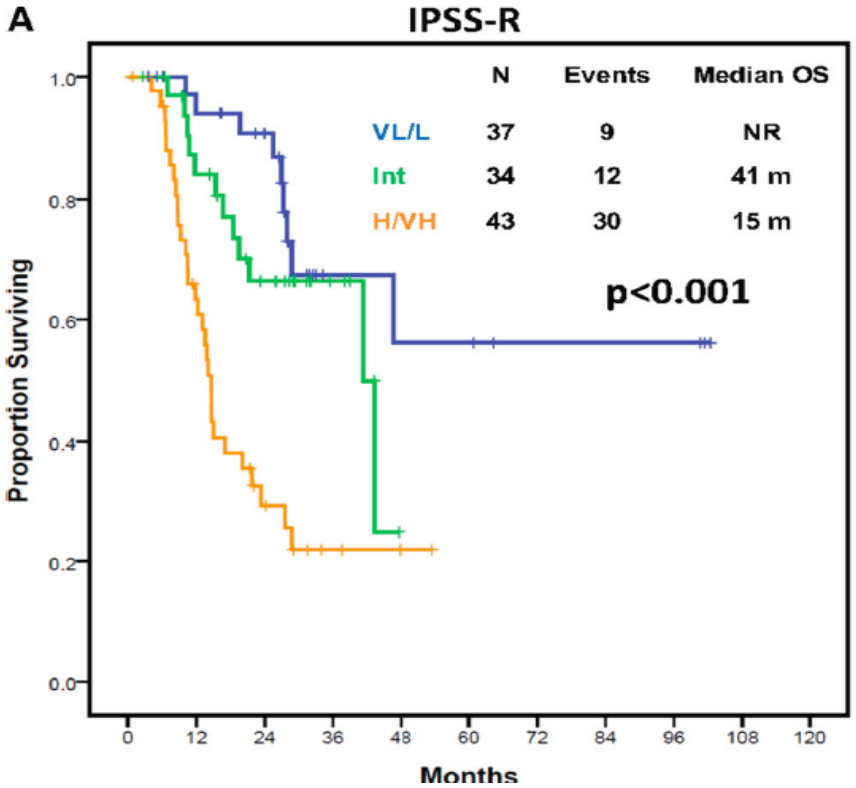


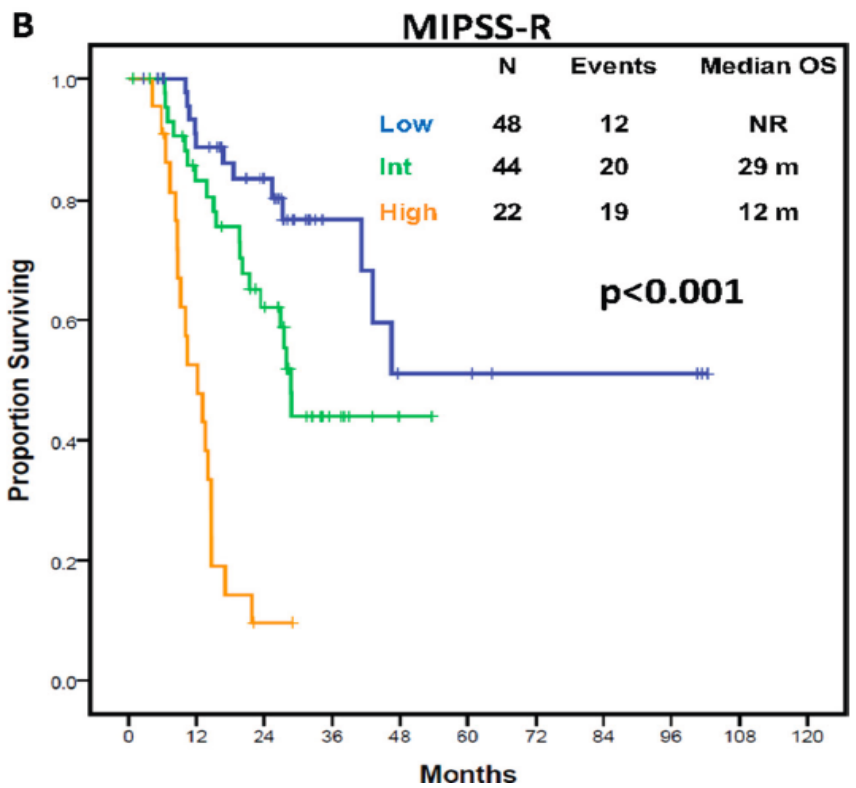
Division by Blast Proportion (<5%)



IPSS-R integrated model with molecular variables (83 pts)

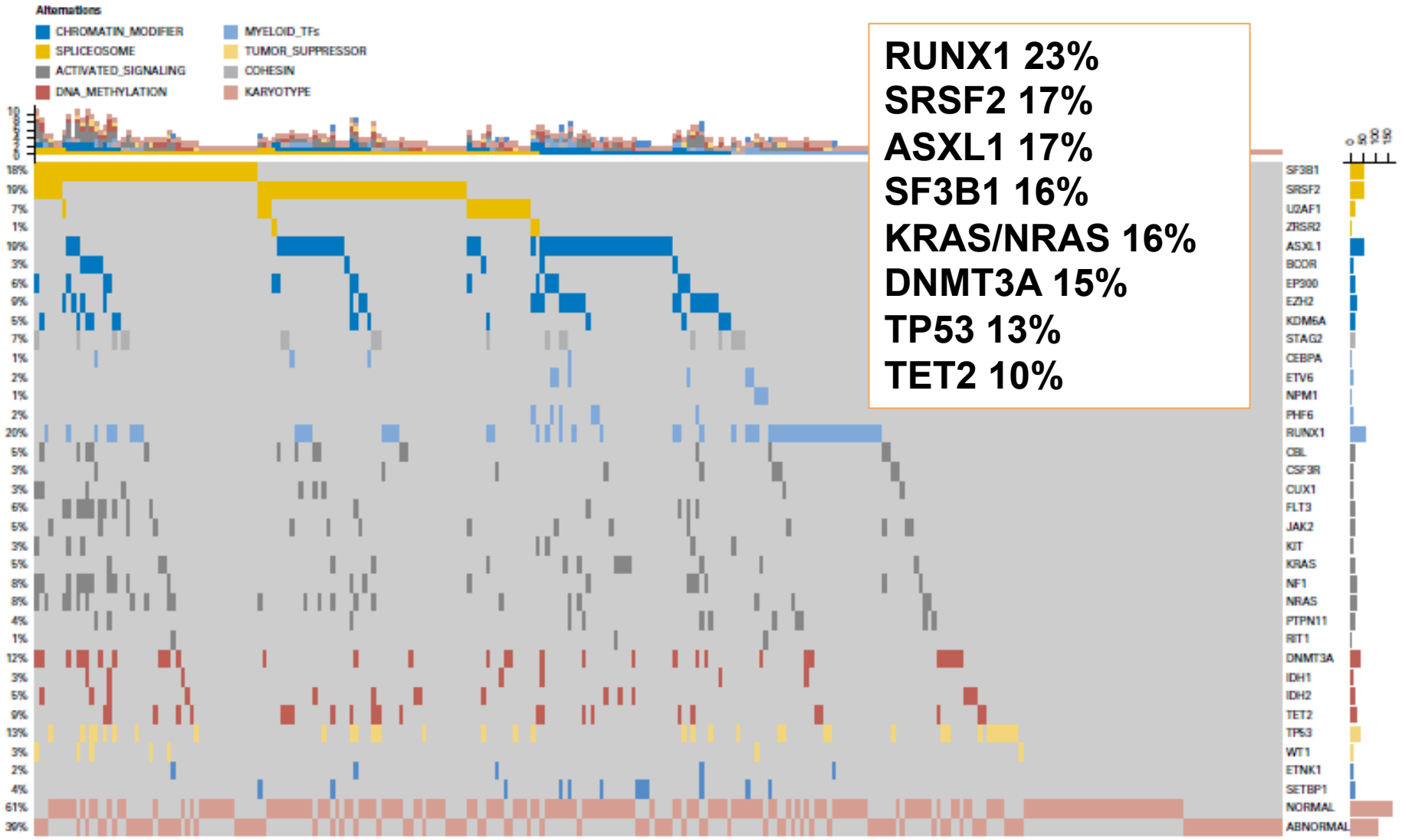
Variable	Hazard Ratio	95% CI	*p* value	Score
IPSS-R				
Intermediate	1.45	0.56–3.77	0.45	0.5
High/Very high	4.66	2.01–10.84	< 0.001	1.5
TP53	3.12	1.3–7.49	0.011	1
Mutations 3 or more	2.51	1.32–4.76	0.005	1





Montalban-Bravo G et Al,, Oncotarget 2018, Vol. 9, (No. 11), pp: 9714-9727

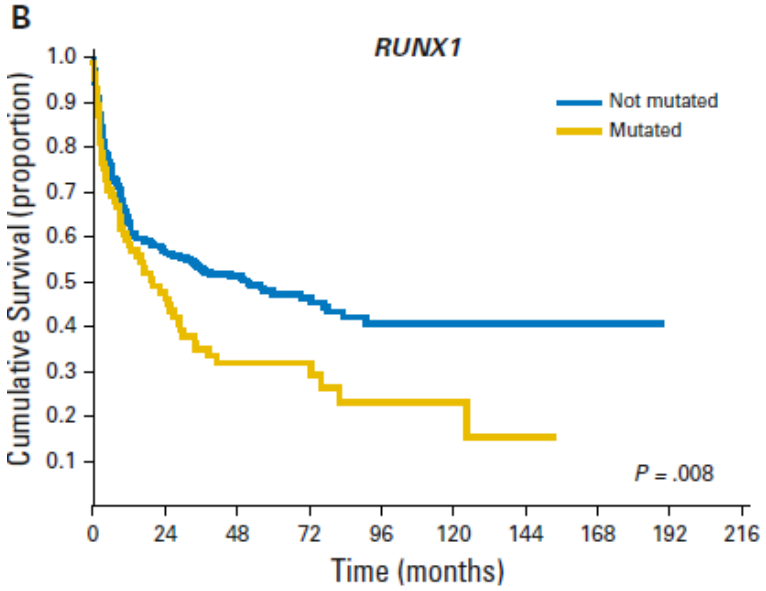
Mutation patterns observed in MDS treated with allo-HSCT

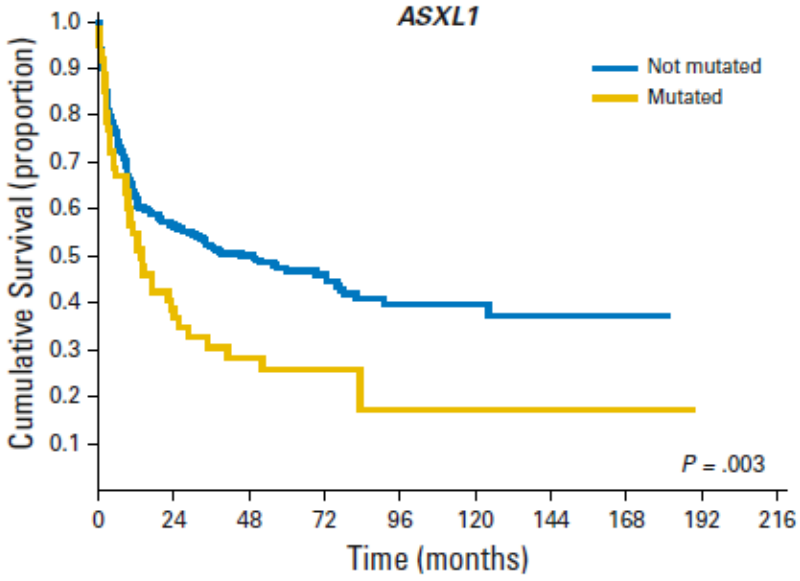


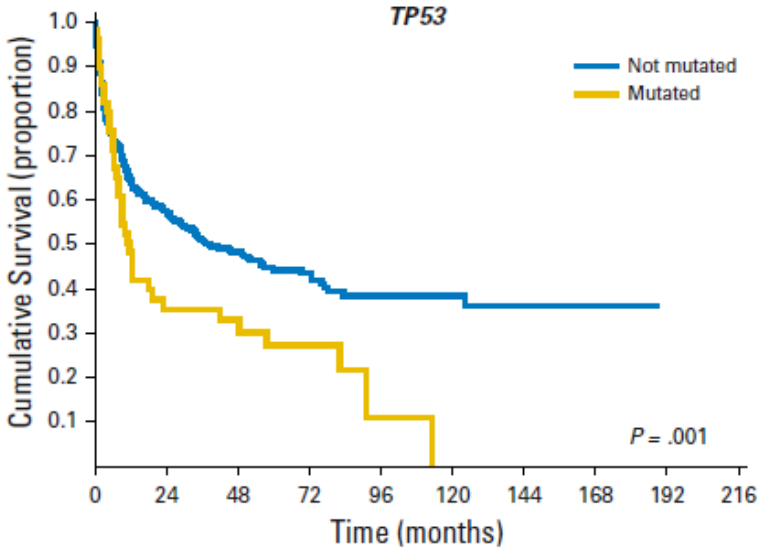
JCO doi:10.1200/JCO.2016.67.3616

GITMO

Relationship between type of oncogenic mutations and overall survival of MDS receiving allo-HSCT





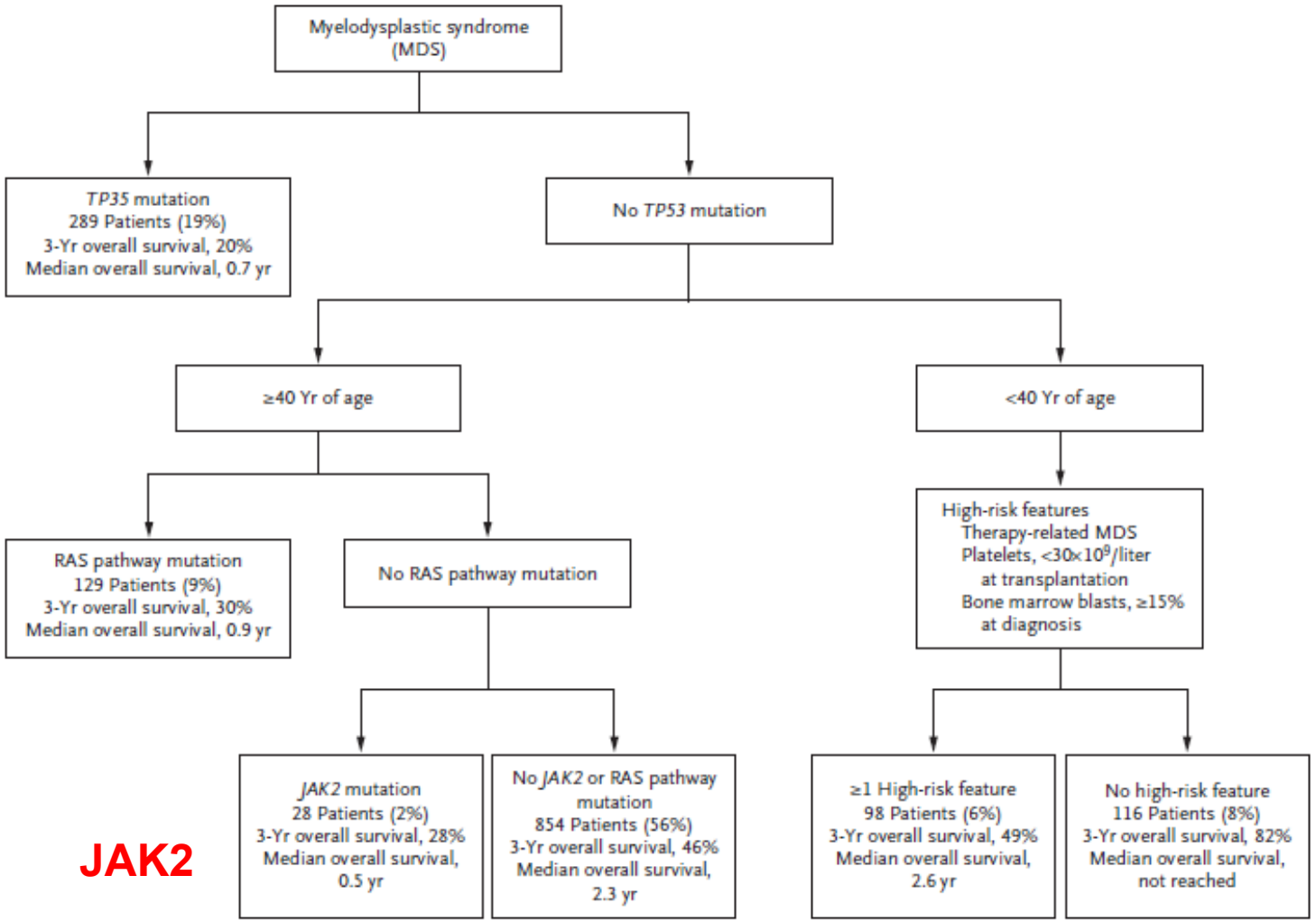


Multivariable analysis				
MDS patients	**Probability of relapse**		**Overall Survival**	
Variable	HR	P	HR	P
ASXL1	1.89	.003	1.72	.008
RUNX1	1.67	.02	1.59	.035
TP53	1.90	.019	1.82	.022

Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

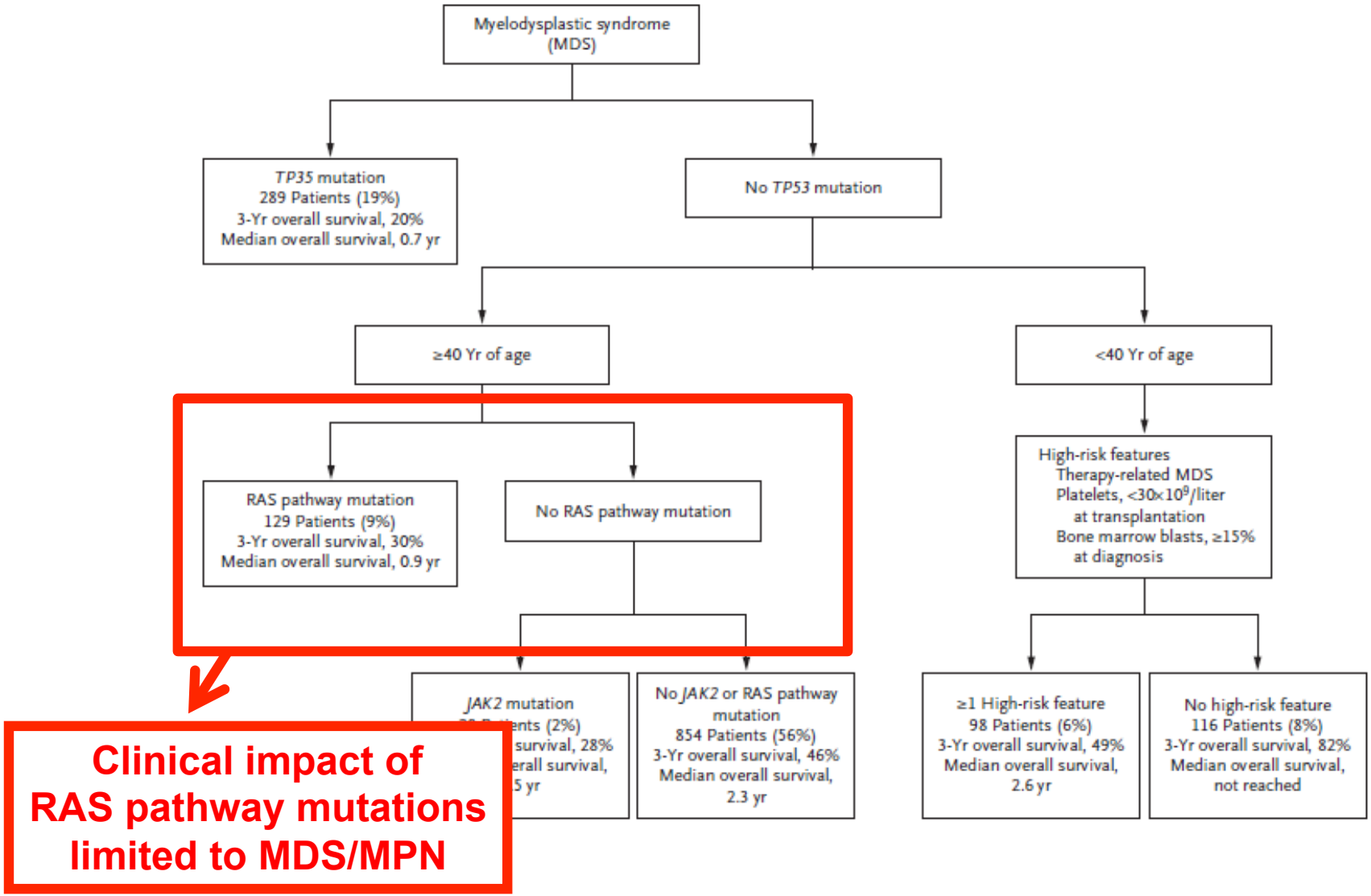
Prognostic Mutations in Myelodysplastic Syndrome patients treated with HSCT.

TP53 mutations are the strongest predictor



Lindsley, RC et al. N Engl J Med 2017;376:536-47.

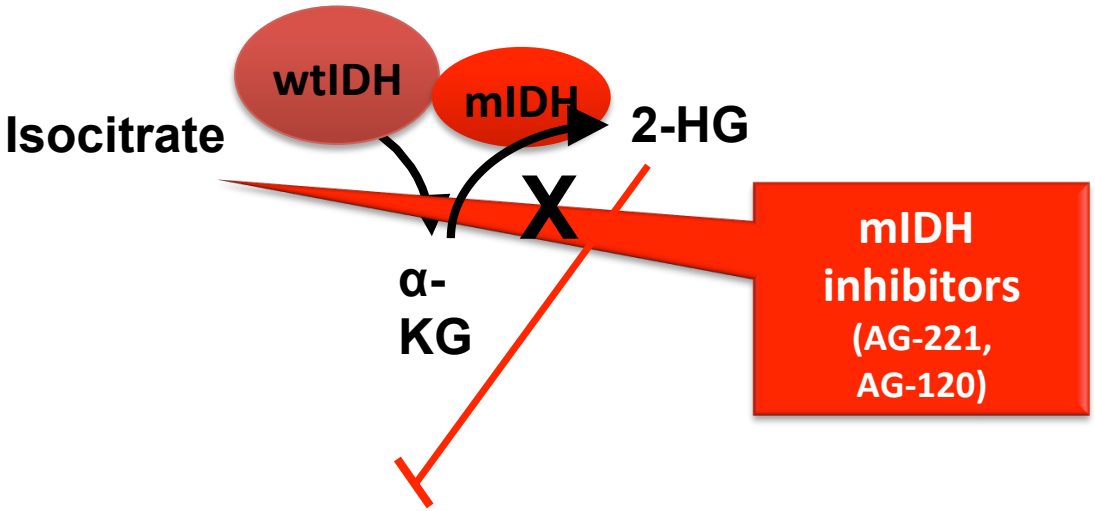
Prognostic Mutations in Myelodysplastic Syndrome patients treated with HSCT

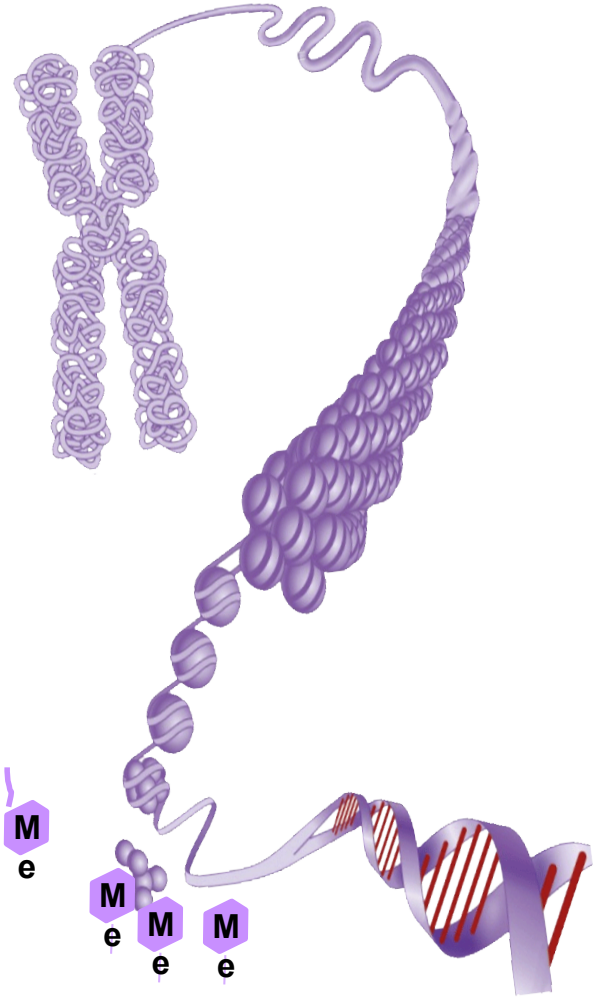


Yoshizato et al et al. Blood. 2017 Apr 27;129(17):2347-2358

Somatic mutations in MDS: possible therapeutic target

Mutant IDH1/2 (5-10% in MDS) inhibitors reduce production of 2-HG and promote cellular differentiation



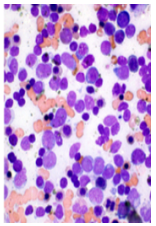


DNA and Histone Demethylases

1. Hypermethylation

2. Modulation of gene expression

Leukemic blast cells

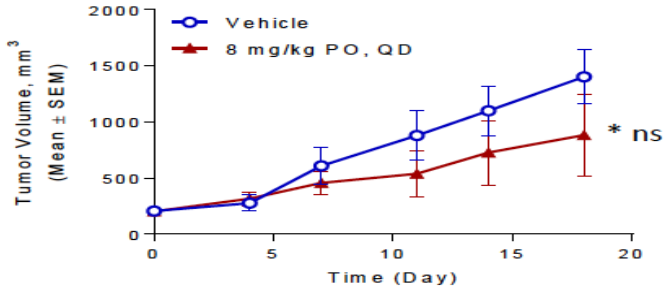


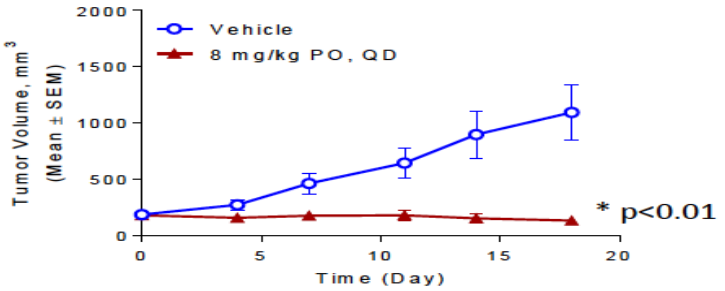
Blocked differentiation

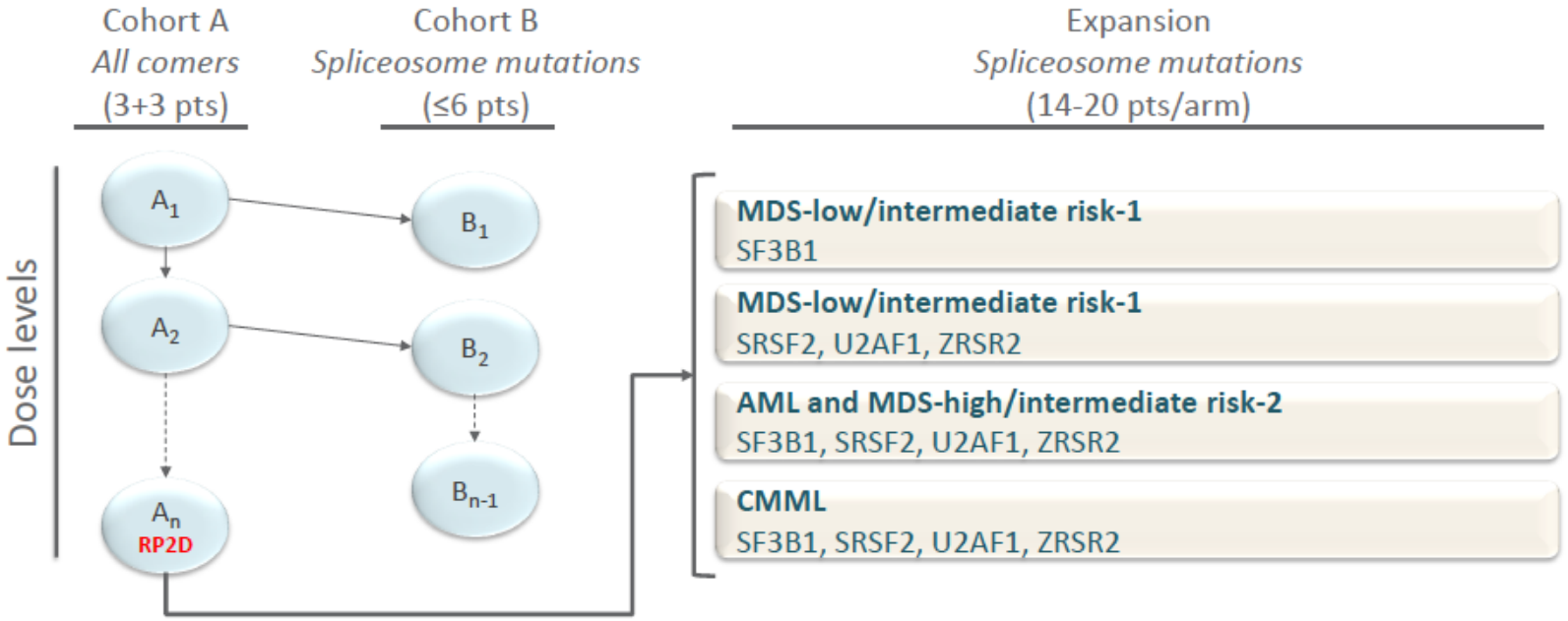
Differentiated myeloid cells

mIDH inhibitors are epigenetic modifiers
Not cytotoxic
Can induce responses <u>without eliminating m*IDH* clone</u>

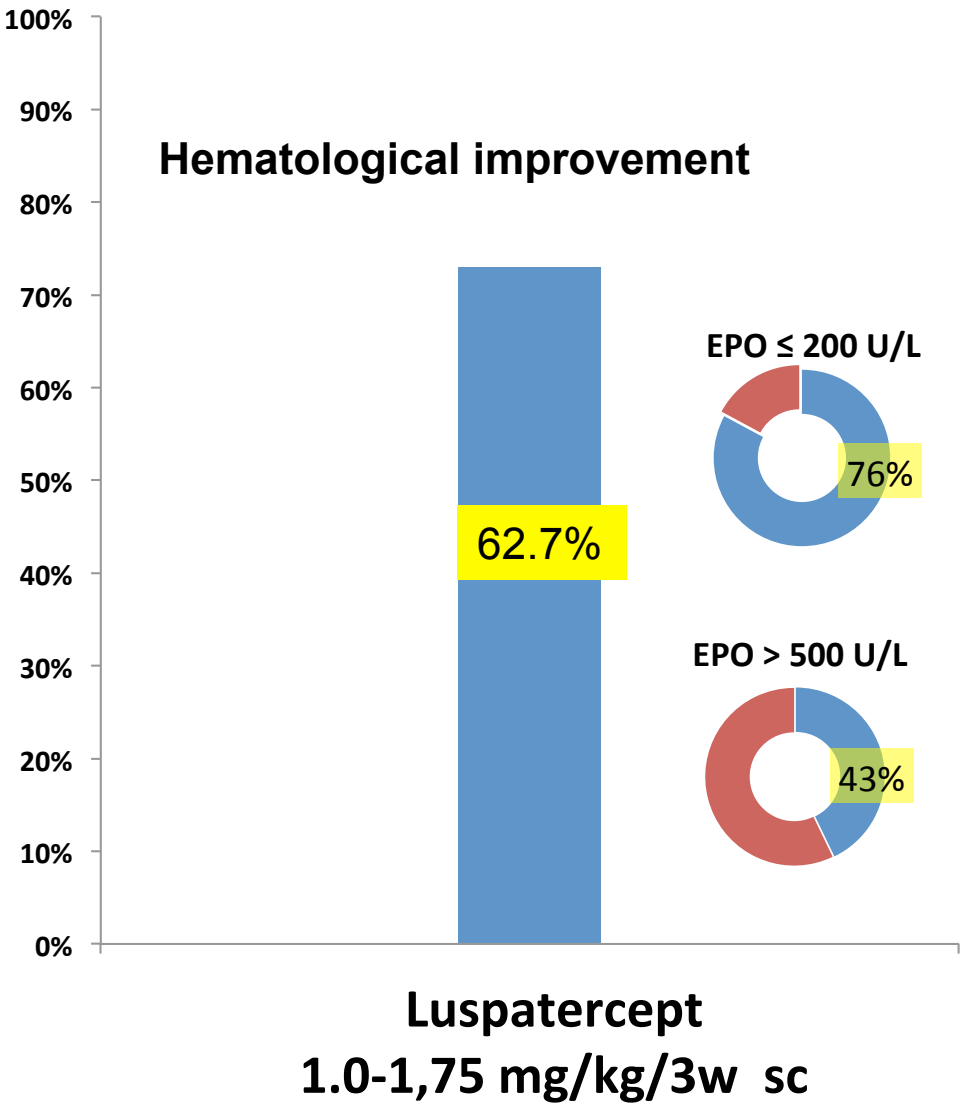
Preclinical and clinical studies of oral H3B-8800 for MDS carrying mutations in spliceosome genes

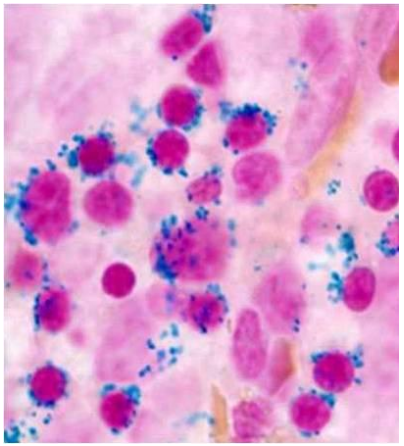




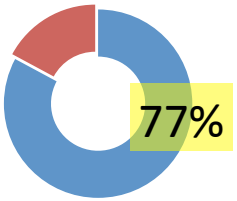


SF3B1 mutation is a possible predictor of response to TGFbeta-pathway inhibition in LR-MDS pts





SF3B1 mut

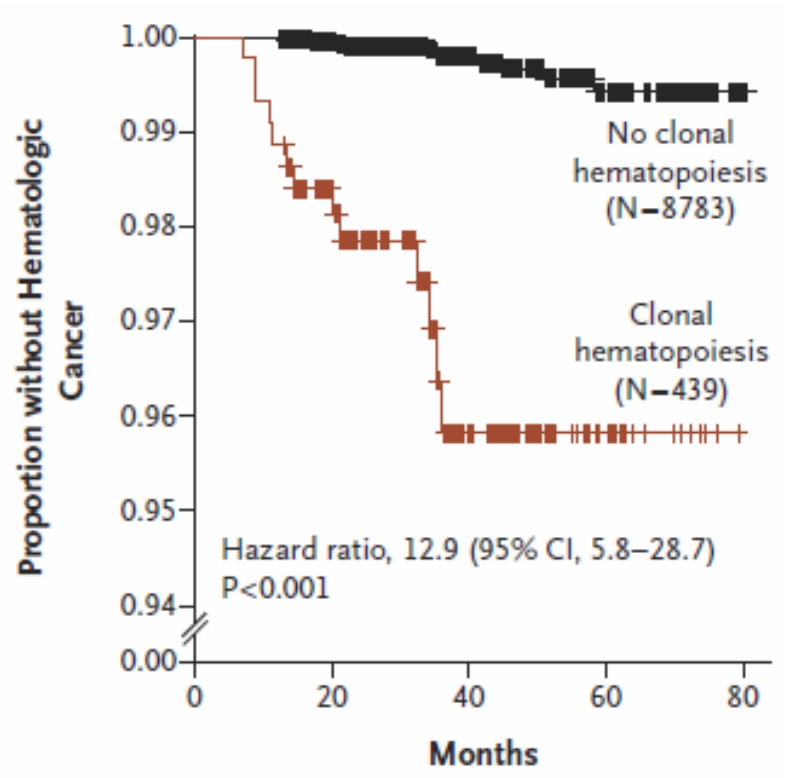


Platzbecker et al, Lancet Oncol 2017

ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S.,

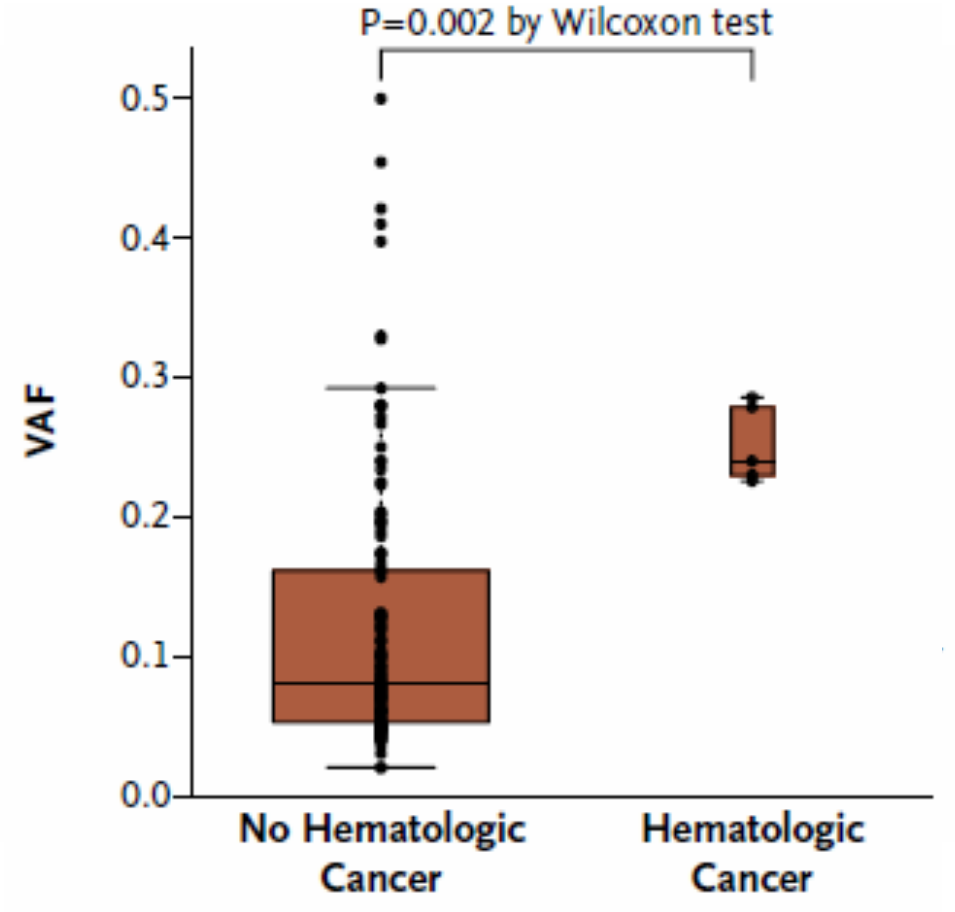


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,



Inherited predisposition to myelodysplastic syndromes and other haematological malignancies

WHO 2016 classification of myeloid neoplasms with germ line predisposition

Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunctior
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or
Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

*Lymphoid neoplasms also reported.

Arber et al Blood 2016 : 127:2391

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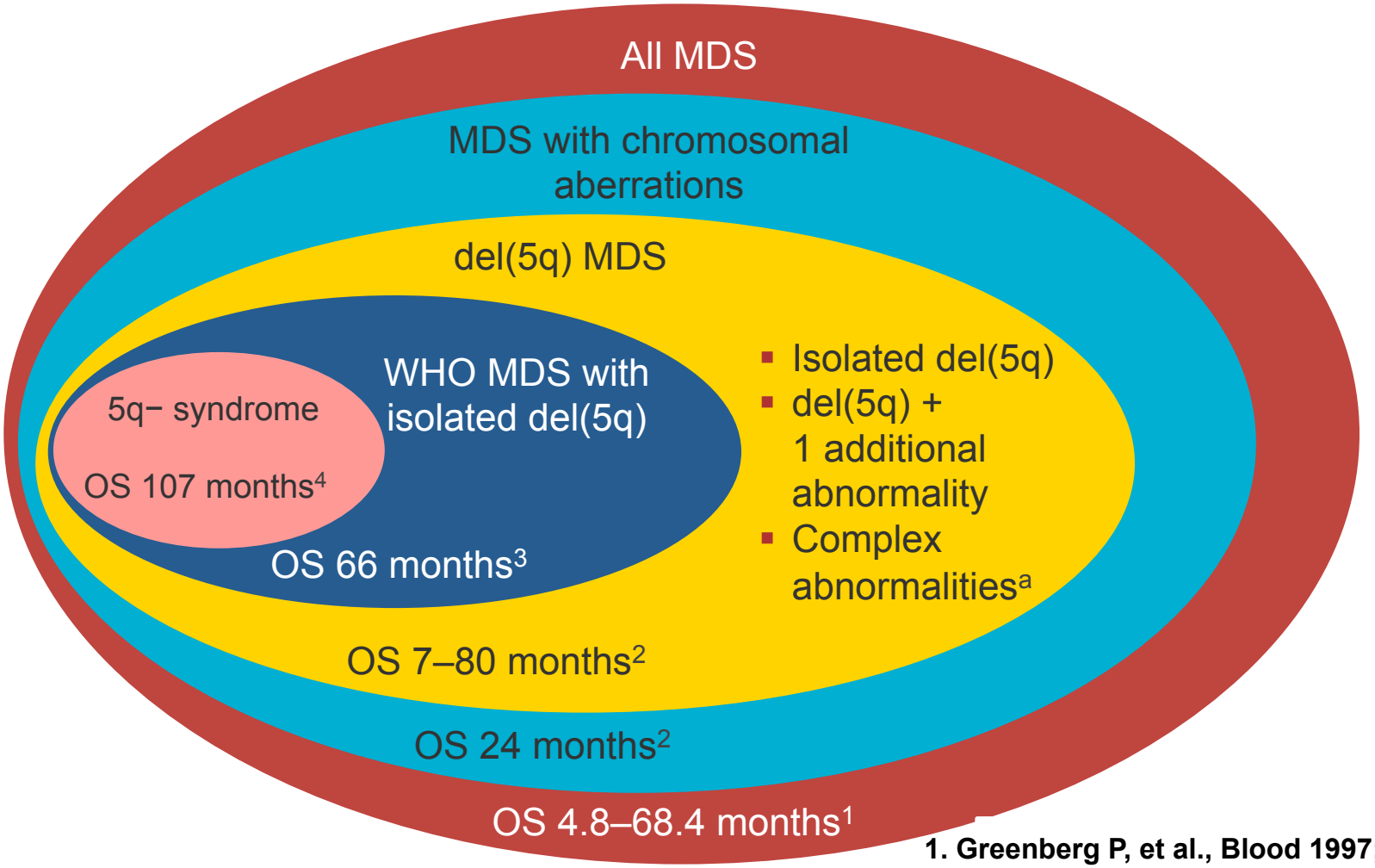
Arber et al Blood 2016 : 127:2391

- **Patient with de novo MDS *at a younger age* (< 50yrs)**
- **Patient with MDS and familial history of AML**
- **Patient with MDS and peculiar extra hematological symptoms:**

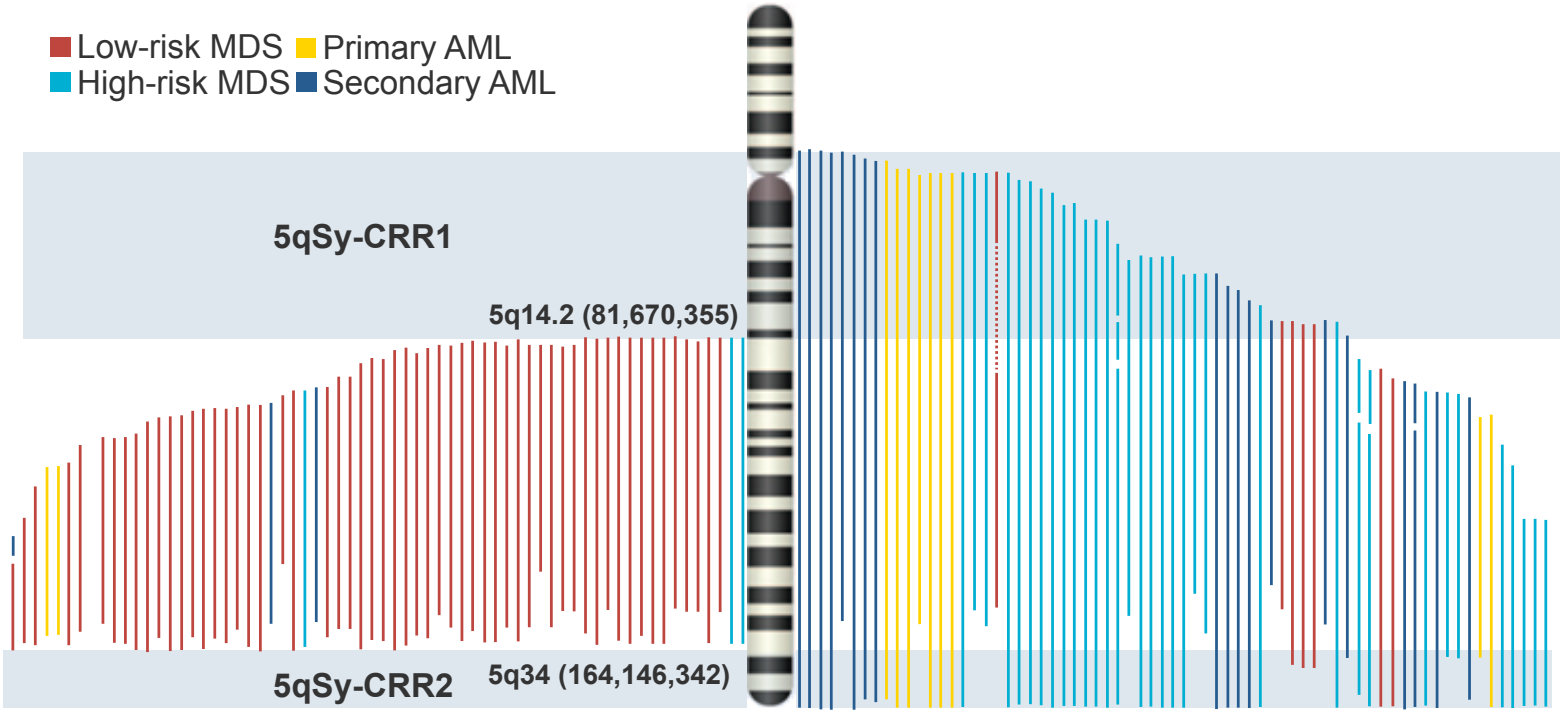
1. **Perform an accurate family and personal history**
2. **Search for signs and symptoms of congenital syndromes**
3. **Perform mutational analysis for genes involved in inherited predisposition**
4. **Select accurately HSCT donor (completely avoid related matched donor?) Slow engraftment, donor derived leukemia**
5. **Familial genetic counseling (anticipation of onset through generations)**

del(5q) MDS is not always 5q− syndrome



1. Greenberg P, et al., Blood 1997;89:2079–88
2. Haase D, et al., Blood 2007;110:4385–95
3. Mallo M, et al., Leukemia 2011;25:110–2
4. Giagounidis A, et al., Hematology 2004;9:271–7

CRR vs CDRs in del(5q) MDS: impact on prognosis



- In patients who had intact CRRs vs those who had lesions that occurred in the CRRs
  - OS was longer (32 vs 14 months; p = 0.04)
  - baseline platelet count was higher (171 vs 84 x 105/μL; p ≤ 0.001)
- Less AML progression occurred in patients with smaller lesions than in those with lesions involving the distal ends of 5q (p = 0.002)

AML, acute myeloid leukaemia; CRR, commonly retained region.

Jerez A, et al. J Clin Oncol. 2012;30:1343-9.

TP53 mutations in MDS and their impact on patient outcomes

Retrospective analysis of the incidence and prognostic impact of *TP53* mutations in patients with del(5q) by using next-generation sequencing

Patient characteristics (n = 318)

- Median age, years (range): **65 (17–72)**
- IPSS risk, n (%)
  - Low: **71 (24)**
  - Int-1: **101 (32)**
  - Int-2: **58 (18)**
  - High: **29 (9)**
- 40 patients (12%) received BM transplantation, intensive chemotherapy, azacitidine, or lenalidomide

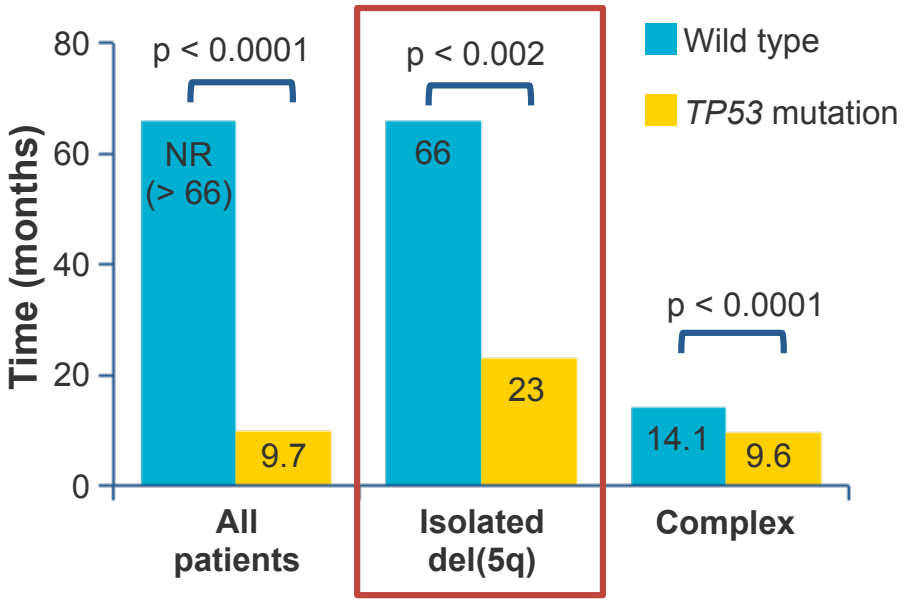
Multivariate analysis:[b] *TP53* mutational status was the strongest predictor for OS and PFS (p < 0.0001 for both)

***TP53* mutations are an independent prognostic marker in patients with del(5q) MDS**

_TP53_ mutational status

- Patients with mutation, n (%): **30 (9.4)**
- Median clone size, % (range): **42 (2.5–93)**

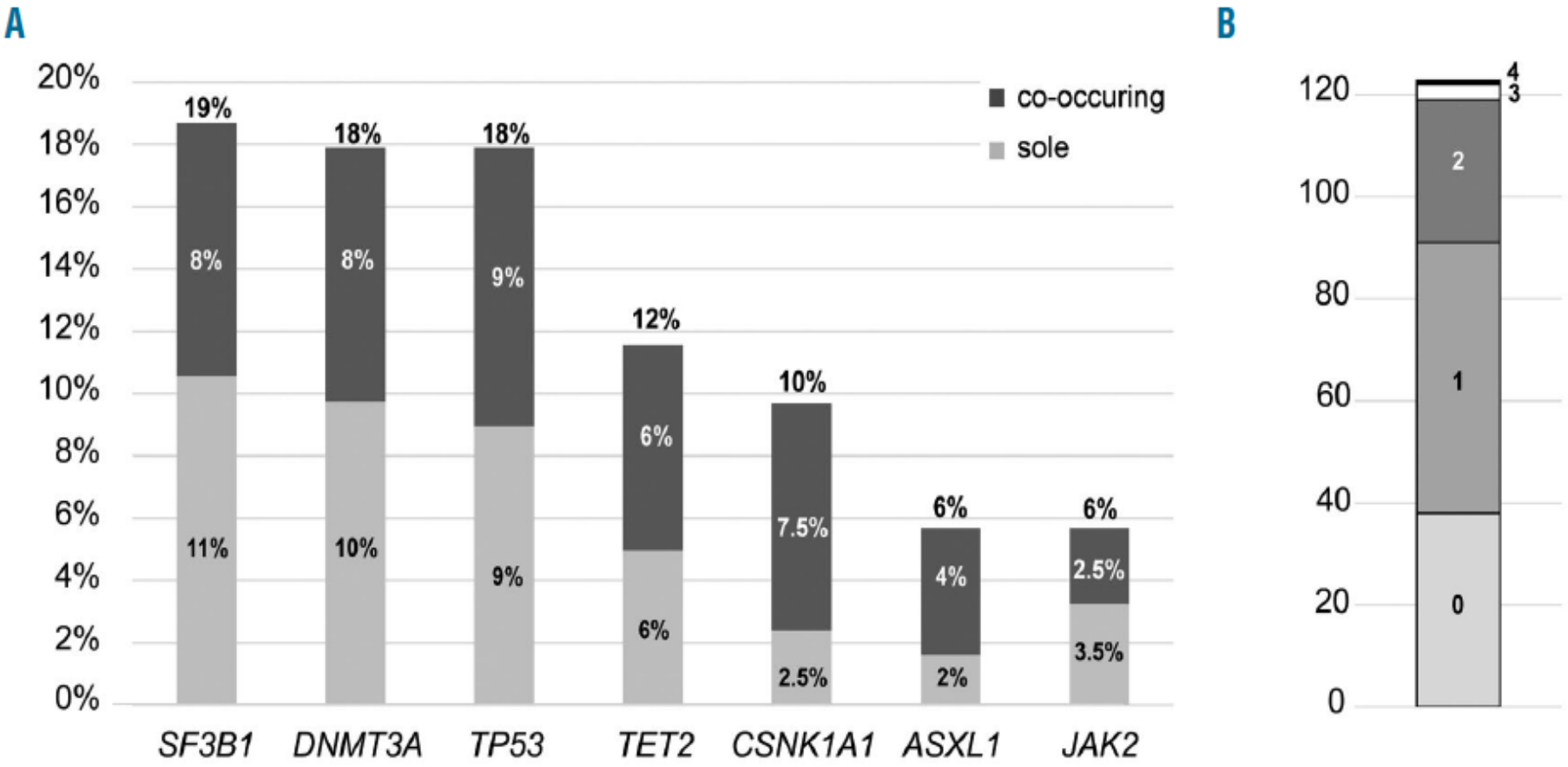
OS by *TP53* mutational status[a]



[a] Survival analysis was censored at treatment date.
[b] Co-variables: age; sex; WHO subtype; IPSS risk; ± mutations.
IPSS, International Prognostic Scoring System; PFS, progression-free survival.

Kulasekararaj AG, et al. Blood. 2011;118:abstract 792.

Most frequently mutated genes in MDS with isolated del5q



Meggendorfer et al . Hameatologica 2017 ; 102(9):1502-1510

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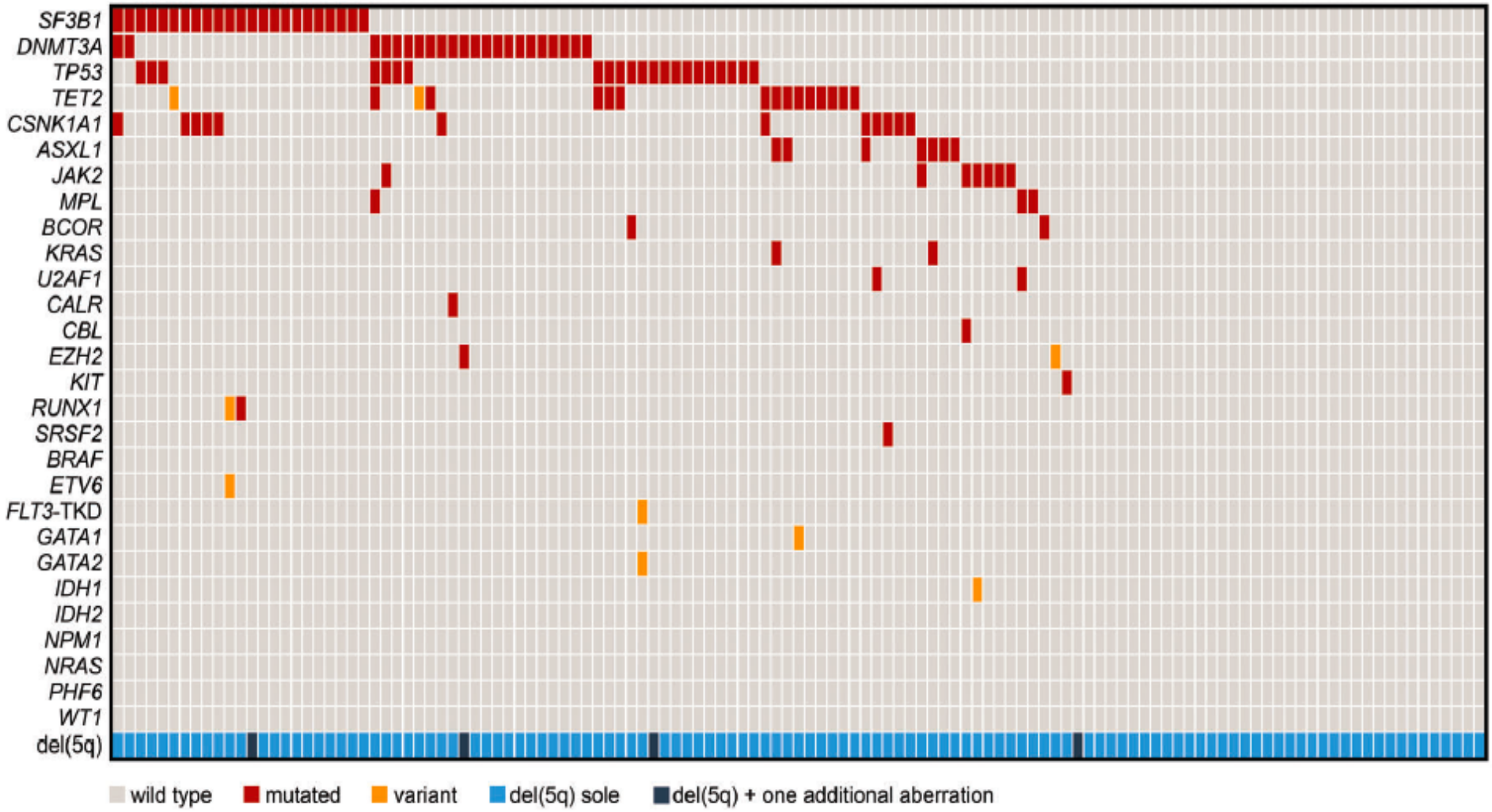
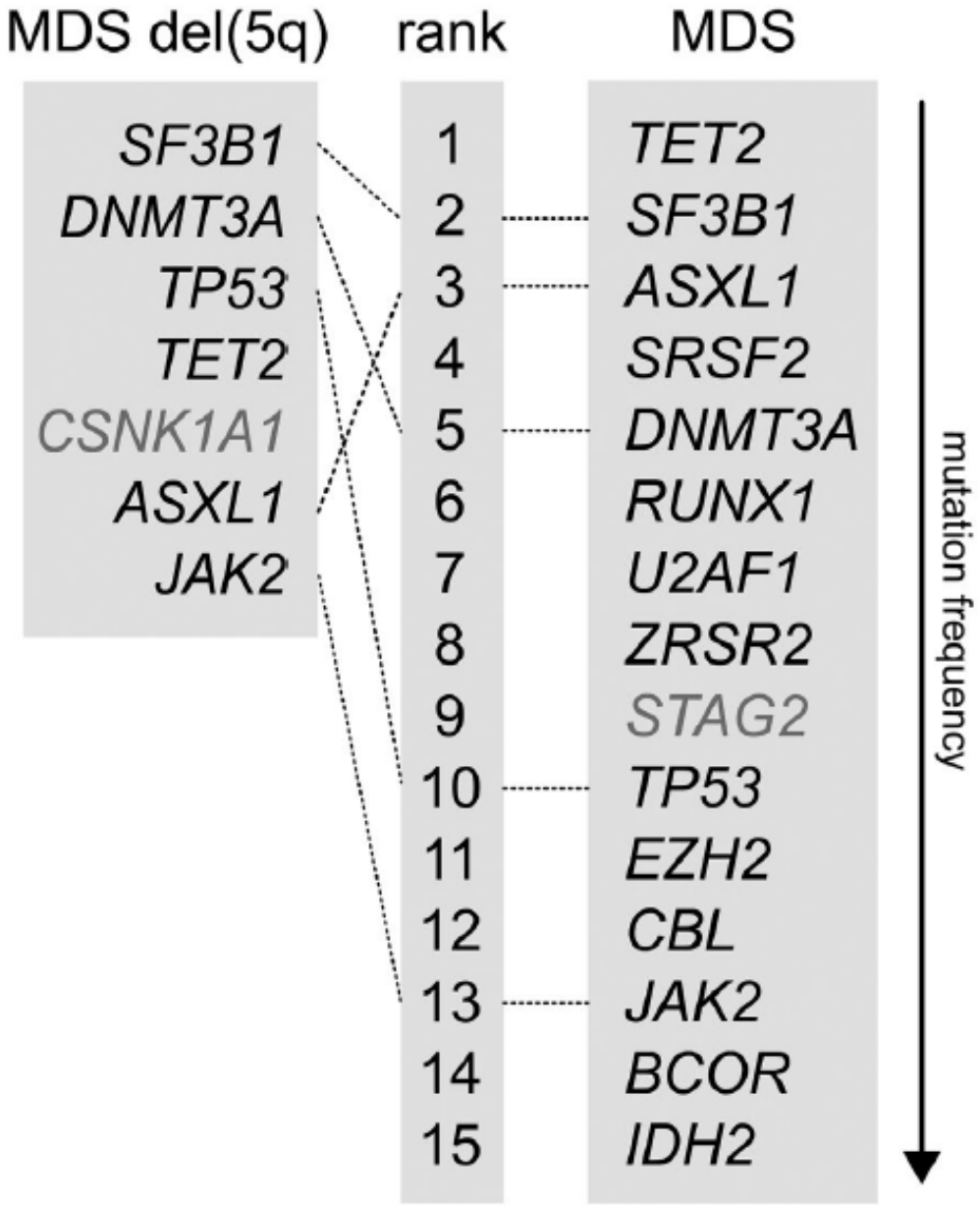


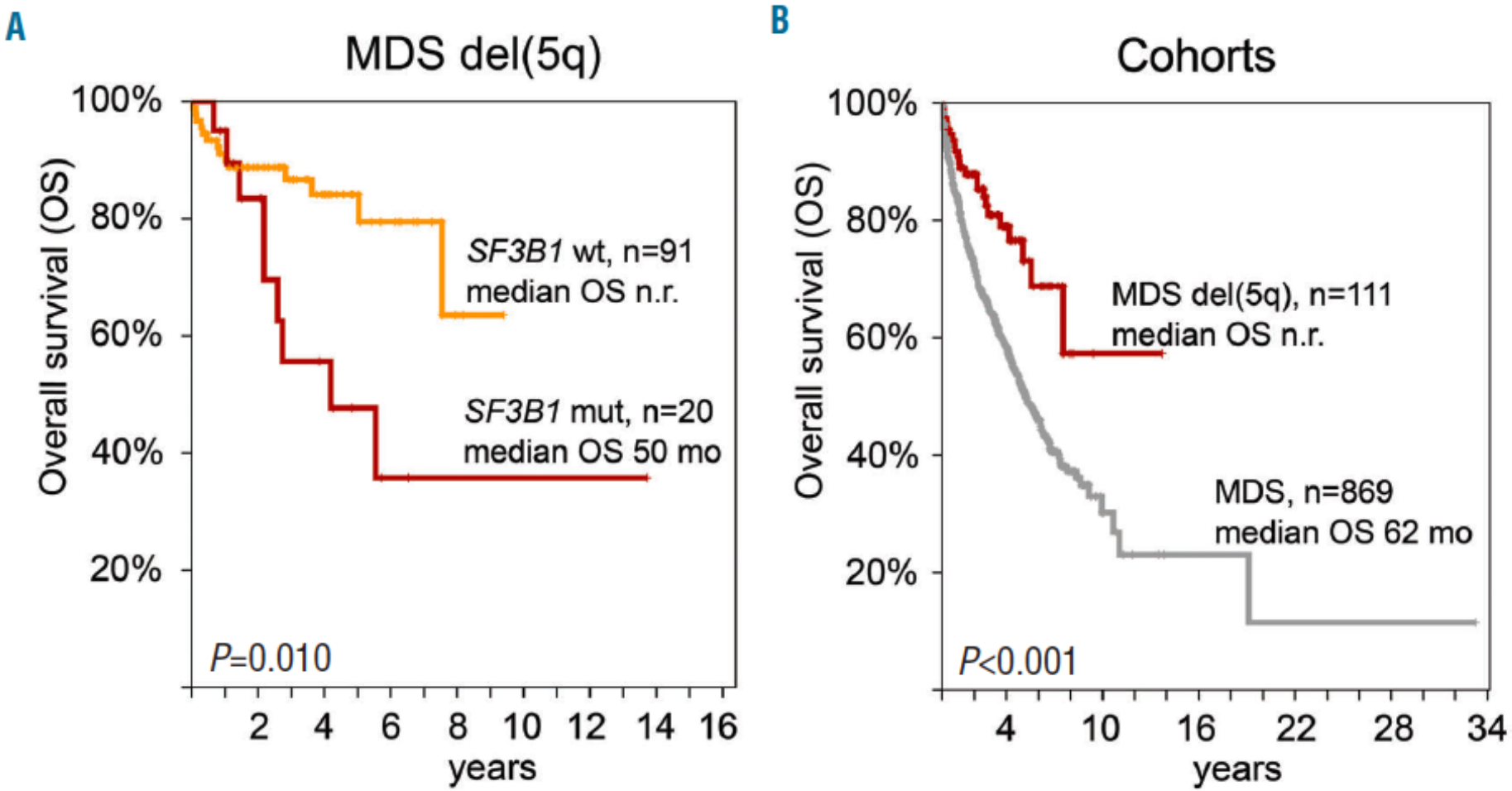
Meggendorfer et al . Hameatologica 2017 ; 102(9):1502-1510

Most frequently mutated genes in MDS with isolated del5q and comparison with nondel5q MDS



a 2017 ; 102(9):1502-1510

SF3B1 mutations are not a good prognostic factor In MDS with isolated del5q



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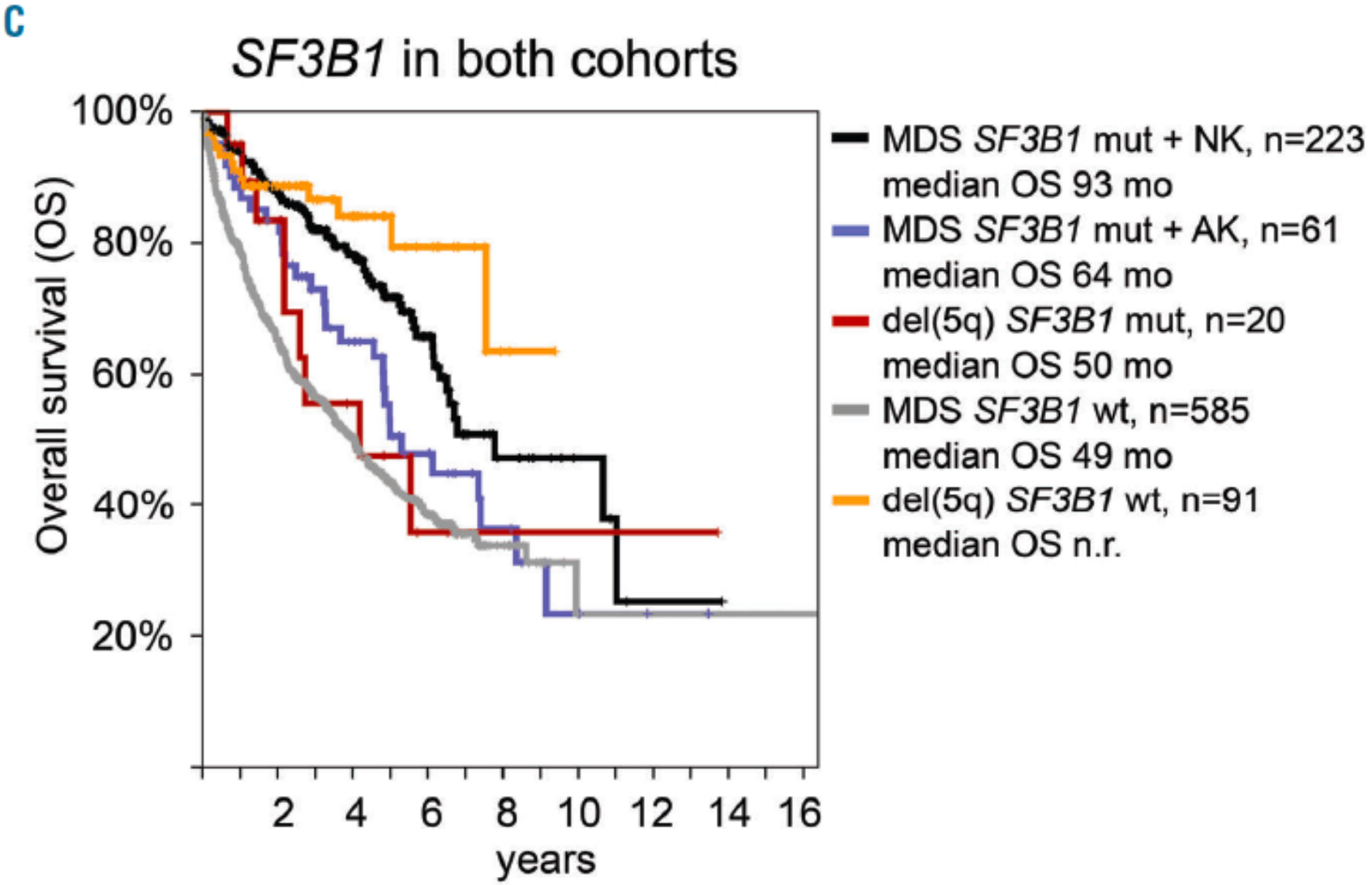


Meggendorfer et al . Hameatologica 2017 ; 102(9):1502-1510

Somatic mutation evaluation in MDS

1. Help refining diagnosis according to WHO for MDS with RS
2. Indicate possibility of experimental target therapy
3. Prompt to earlier intervention in presence of multiple or prognostically negative mutations
4. Prognostic value in MDS with del5q (TP53 mut)
5. Prognostic value in HSCT
6. No indication to select or exclude from HMA therapy or from HSCT on the basus of mutations

Somatic mutations in suspect of MDS:
a help in diagnosis?

Dysplasia can be induced by other causes than MDS

Cytopenias without dysplasia may be tricking

…

and definite diagnosis is often a challenge

ICUS idiopathic cytopenia of unknown significance

IDUS
idiopathic dysplasia of unknown significance

CHIP/ARCH
clonal hemopoiesis of indeterminate potential/ age related clonal hemopoiesis

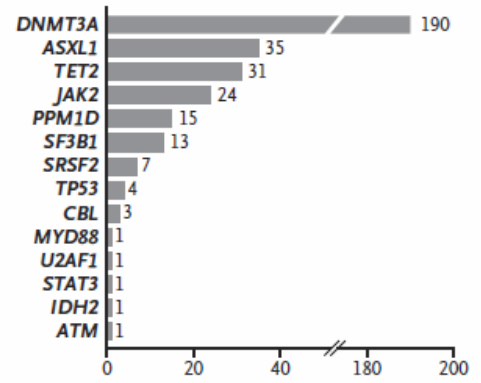
CCUS
clonal cytopenia of unknown significance

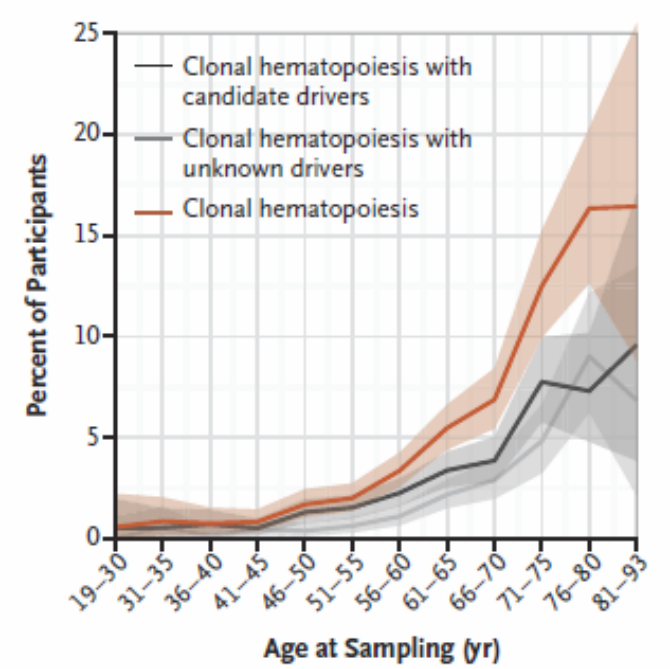
Clonal hemopoiesis in the era of deep sequencing

ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S.,





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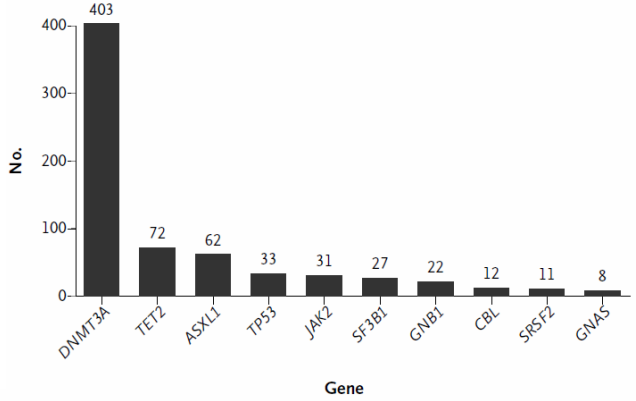

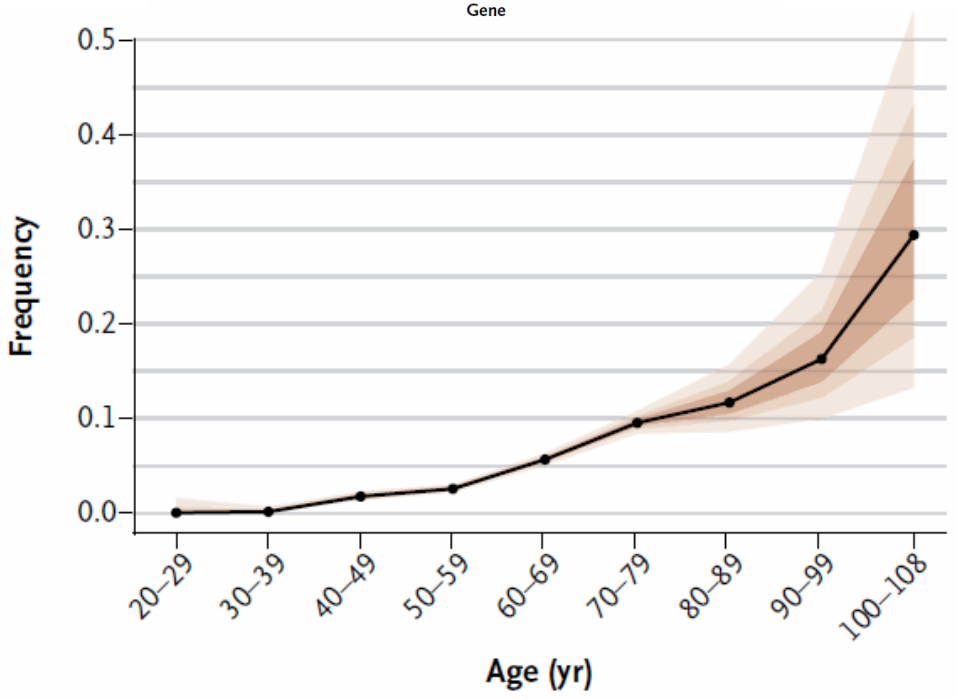

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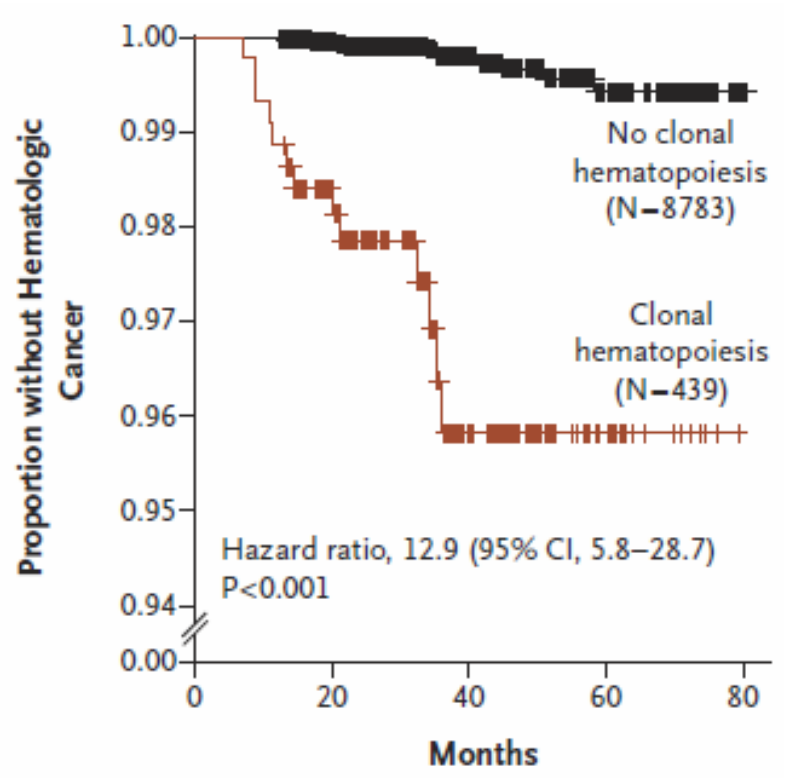

The NEW ENGLAND JOURNAL of MEDICINE

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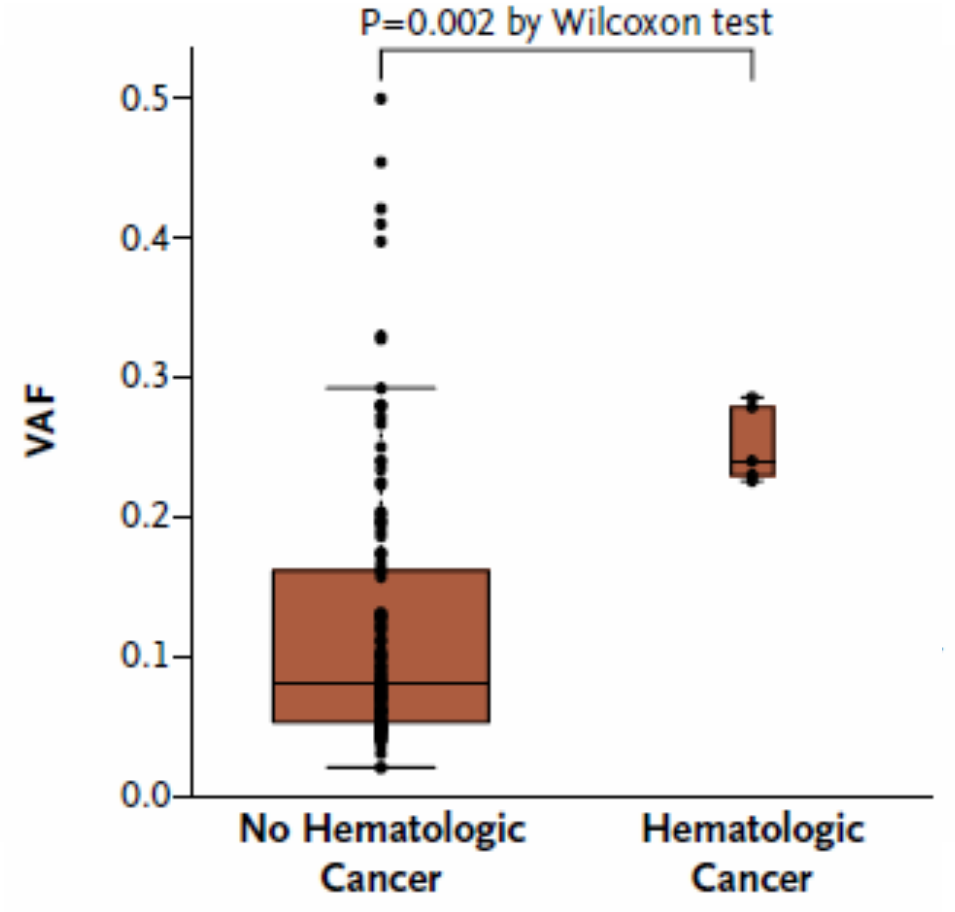


Clonal hemopoieis of indeterminate potential (CHIP)

- Clonality defined by presence of MDS-associated genes:

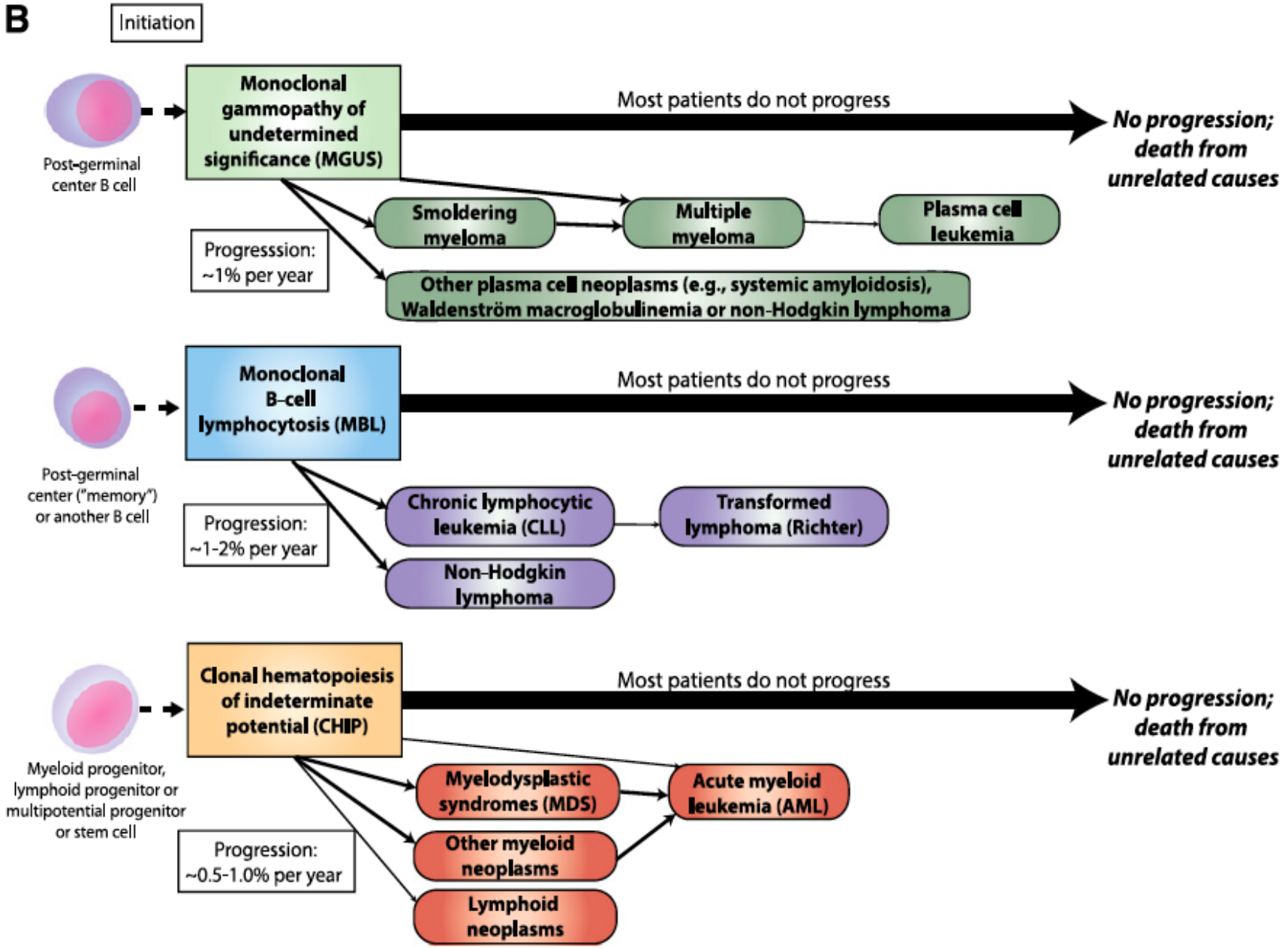
DNMT3A, ASXL1, TET2, (JAK2) with loss of function

- Little propensity to develop MDS (0,5-1% /year)
- Present in 15% of persons aged > 70yrs

Triggered by (?) :

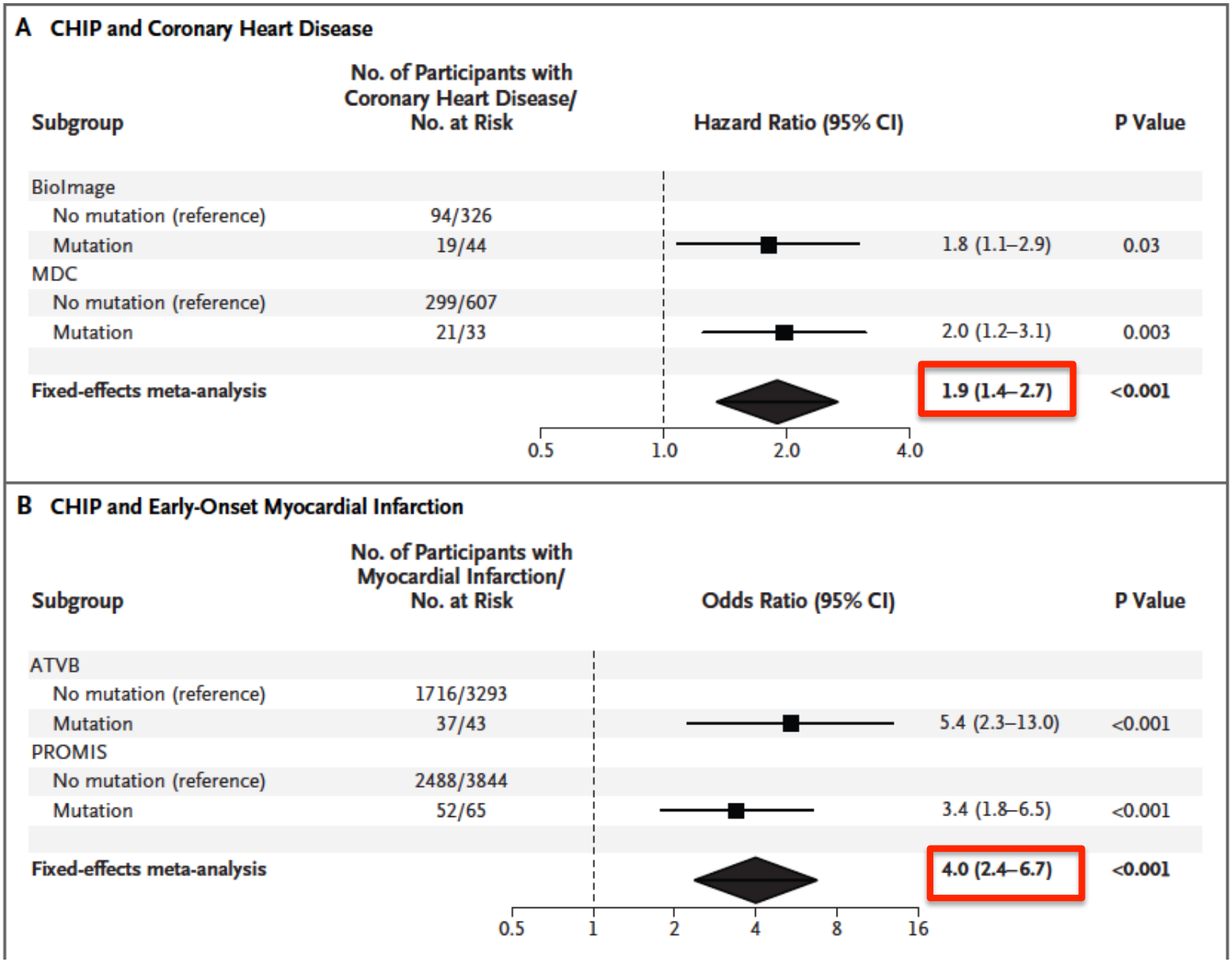
Stochastic event
Environment (smoke, radiation, chemotherapy, inflammation)
Hereditary/predisposition conditions

Is CHIP so *innocent* ??



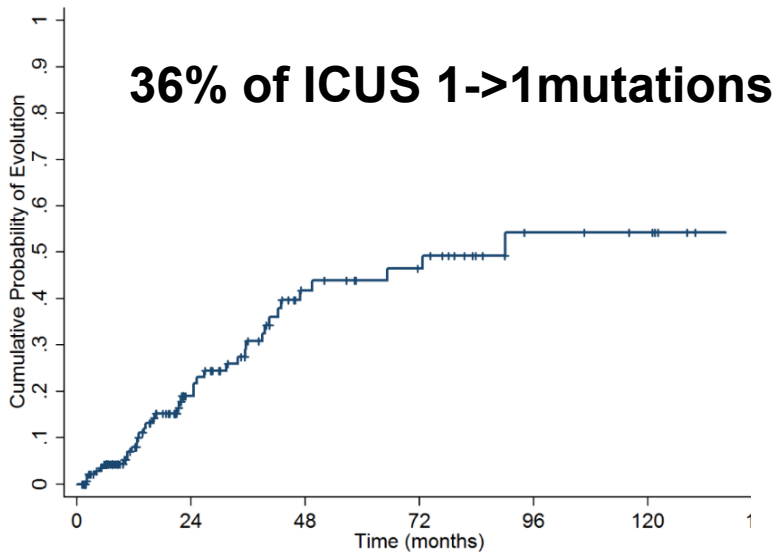
Steensma DP, Blood 2015; 126:9

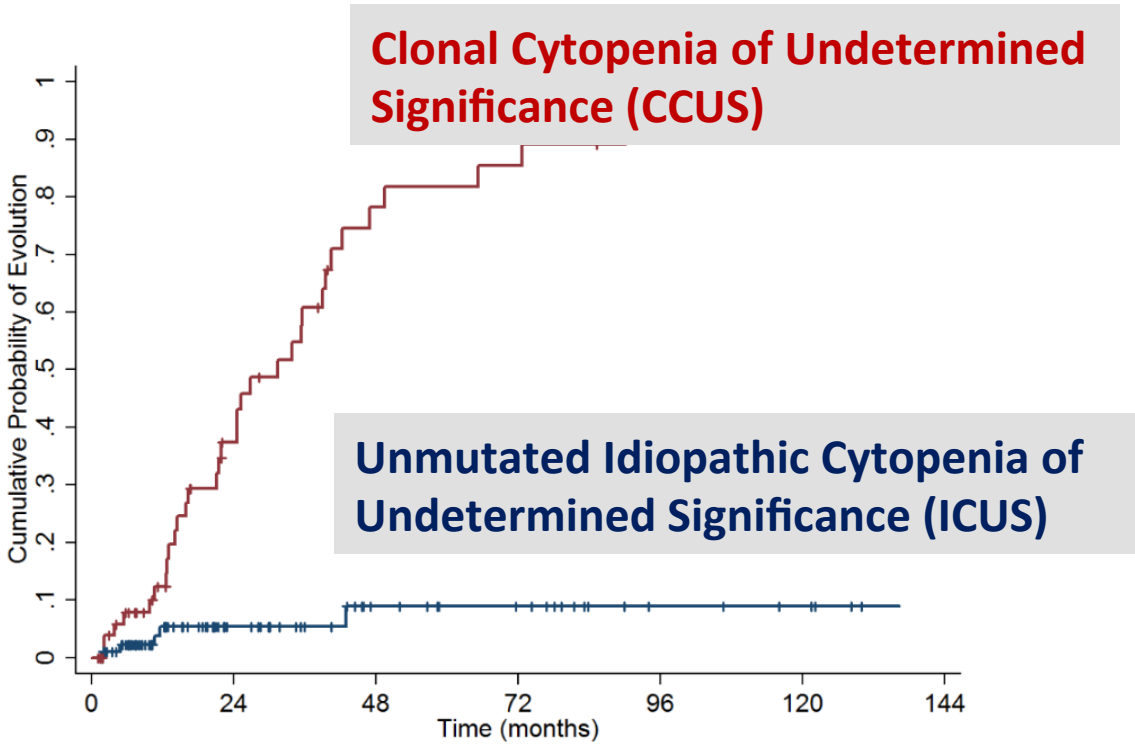
CHIP correlates with coronary heart disease



Jaiswal S et al NEJM June 21, 2017

Mutations in patients with CCUS predict evolution compared to ICUS





Malcovati L et al; Blood 2017 ;129: 3371

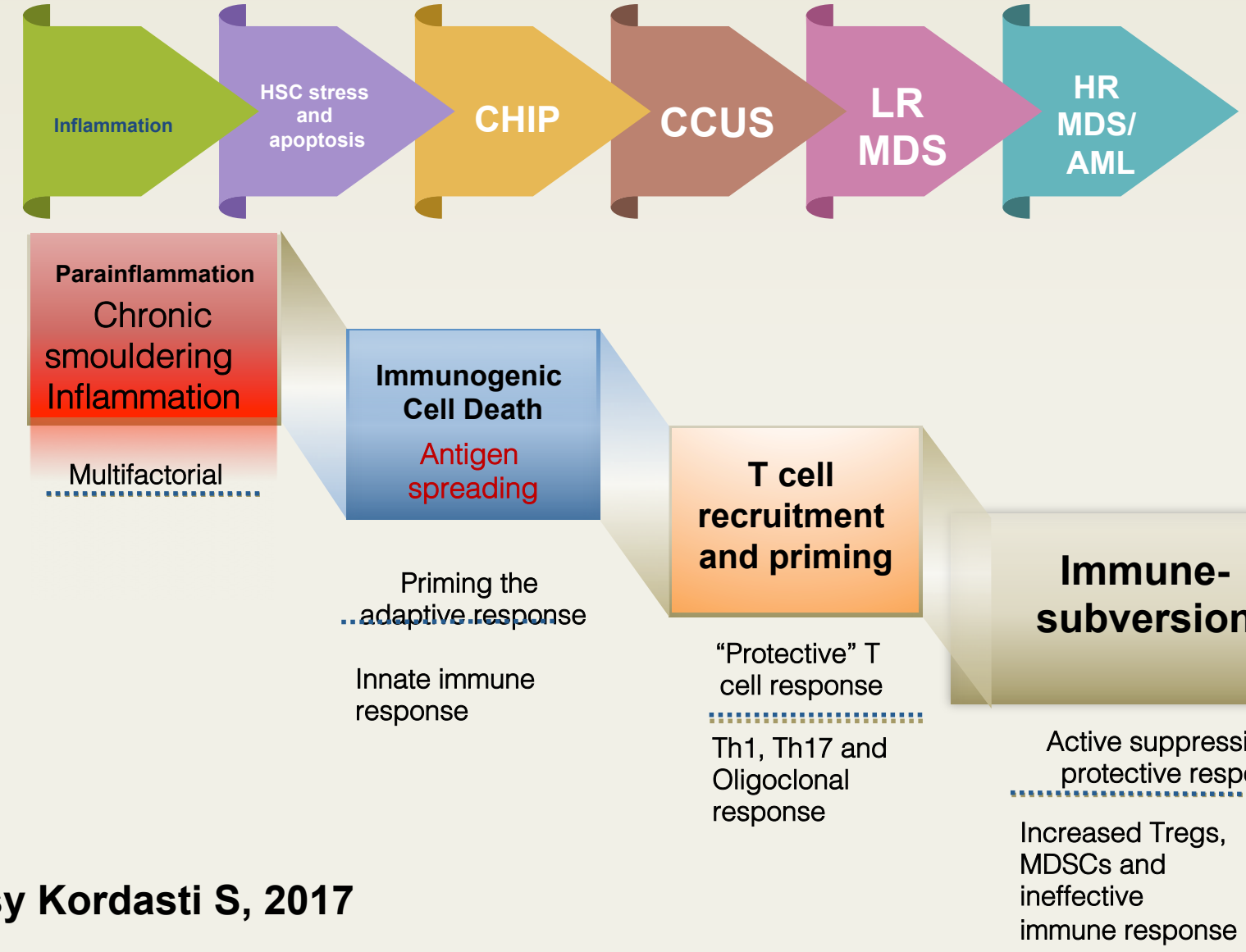
Exposure to Radiation Therapy or Tobacco Use Increases Risk of Clonal hemopoiesis More Than Chemotherapy Exposure

	Clonal Hematopoiesis			
	Overall	**No**	**Yes**	***P*-value**
Sample size (% of total cohort)	5649	4296	1353	
Prior Chemo *, N%	64%	64%	64%	0.89
Prior radiation*, N%	37%	35%	41%	<0,001
Current/former smoker, N%	46%	44%	53%	<0,001

CHIP in 25% of solid tumor patients, with 4.5% harboring presumptive leukemia driver mutations (CH-PD). Most frequent DNMT3A.
PPM1D and TP53 mutations were associated with prior exposure to chemotherapy.

Coombs et al., 2017, Cell Stem Cell 21, 1–9

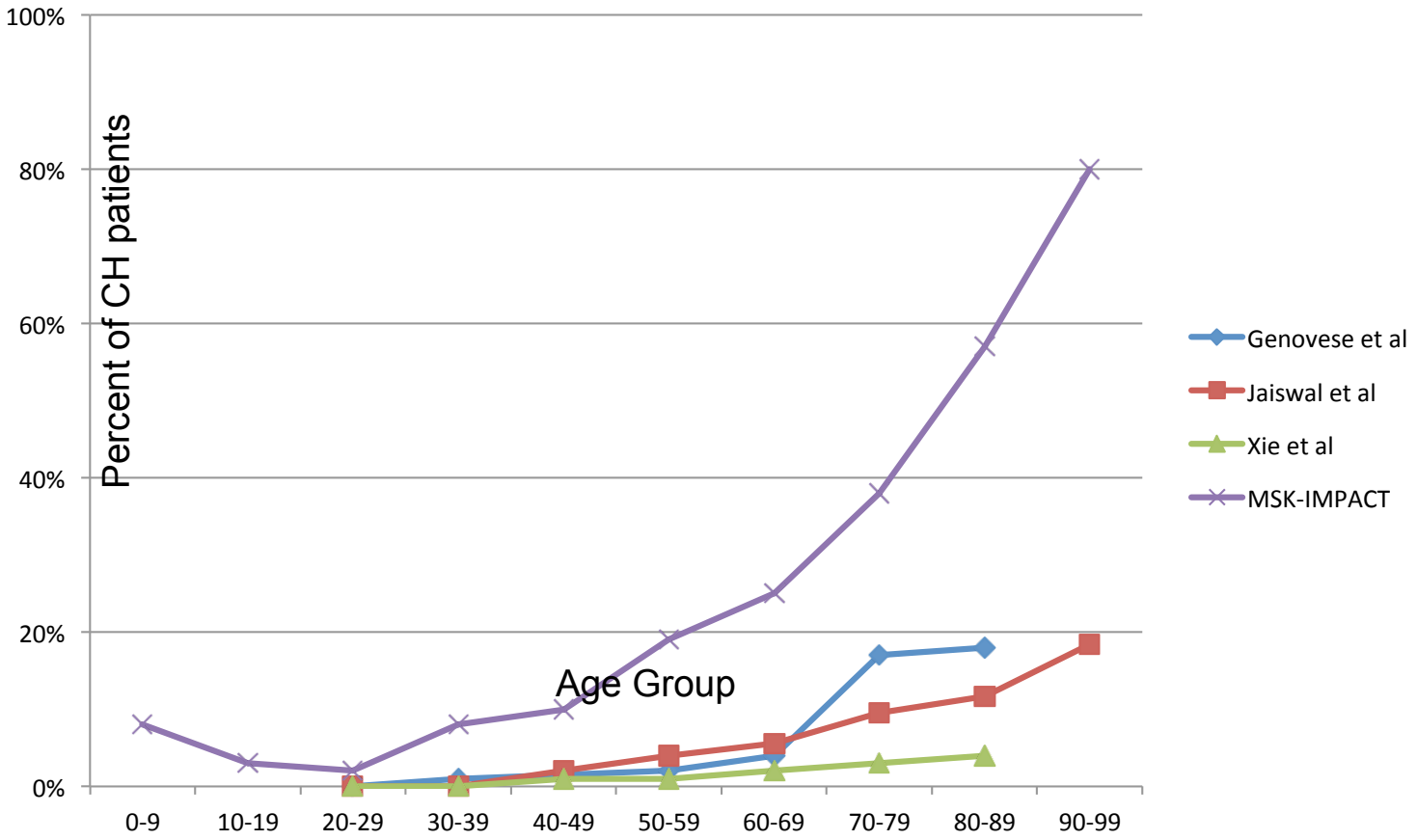
inflammation could be a trigger for clonal hemopoiesis



Courtesy Kordasti S, 2017

Age-dependent clonal hemopoiesis is More Common Than Reported in Hotspot Focused Studies

Senectus ipsa morbus est



Coombs et al., 2017, Cell Stem Cell 21, 1–9
Genovese G. et al NEJM. 2014;371(26):2477-87
Jaiswal S et al NEJM. 2014 ;371(26):2488-98
Xie et al; Nat Med. 2014 ;20(12):1472-8.

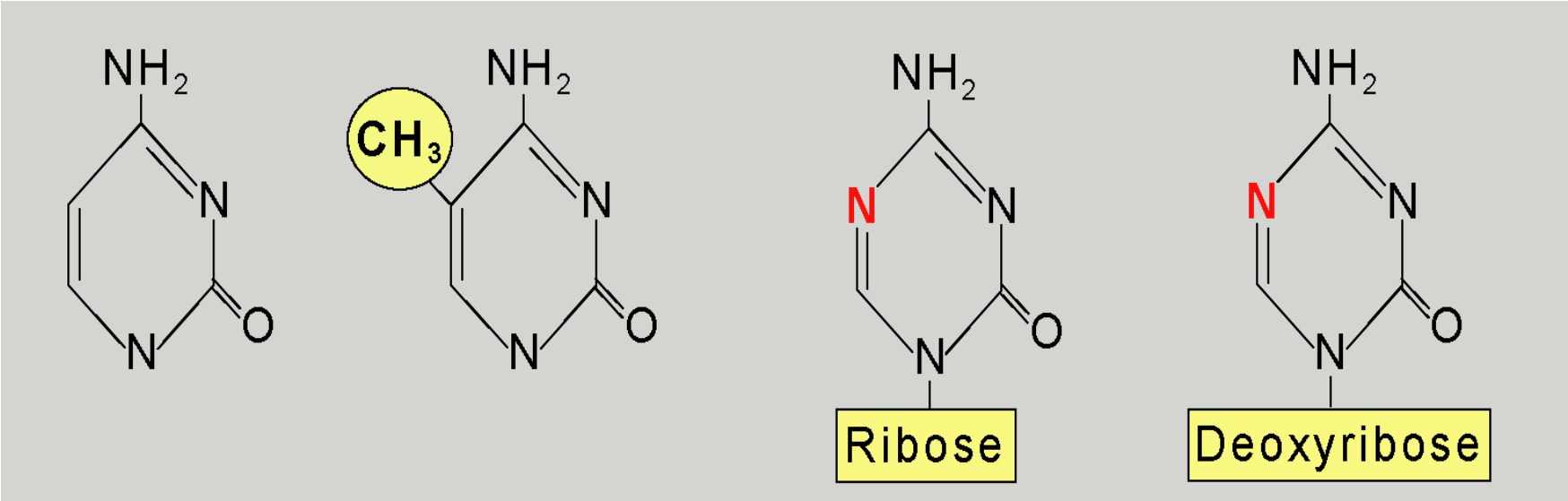
'YOU'RE DELIBERATLY PUTTING YOURSELF AT RISK OF ILL HEALTH BY BEING OVER 65...'

	ICUS	ARCH	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	-	+	+	+	+	+
Dysplasia	-	-	-	-	+	+
Cytopenia	+	-	-	+	+	+
BM Blast %	<5%	<5%	<5%	<5%	<5%	<19%
AML Overall Risk	Very low	Very low	Very low but cardiopathy	Low / intermediate	Low	High
Median Num of mutations	0	1	1	>1<2	>2	>2
Typical VAF	-	1-10%	9-12% (>10)	30-40% (40)	>50%	>50%
Types of mutations		*DNMT3A, TET2,ASXL1, JAK2, TP53*	*DNMT3A, TET2,ASXL1, JAK2, TP53*	*TET2, DNMT3A,ASXL1, SRSF2, TP53* ***Later*** *TET2, SRSF2, ASXL1, U2AF1, DNMT3A*	***SF3B1, TET2, ASXL1, SRSF2, DNMT3A*** *and all the less frequent*	

Modified from Steensma et al, *Blood* 2015 and Bejar R Leukemia, 2017 online

Molecular variables: DNA methylation

Azanucleosides, Cytosine Analogues with hypomethylating properties



Cytosine

5-methyl-cytosine

5-aza-cytidine

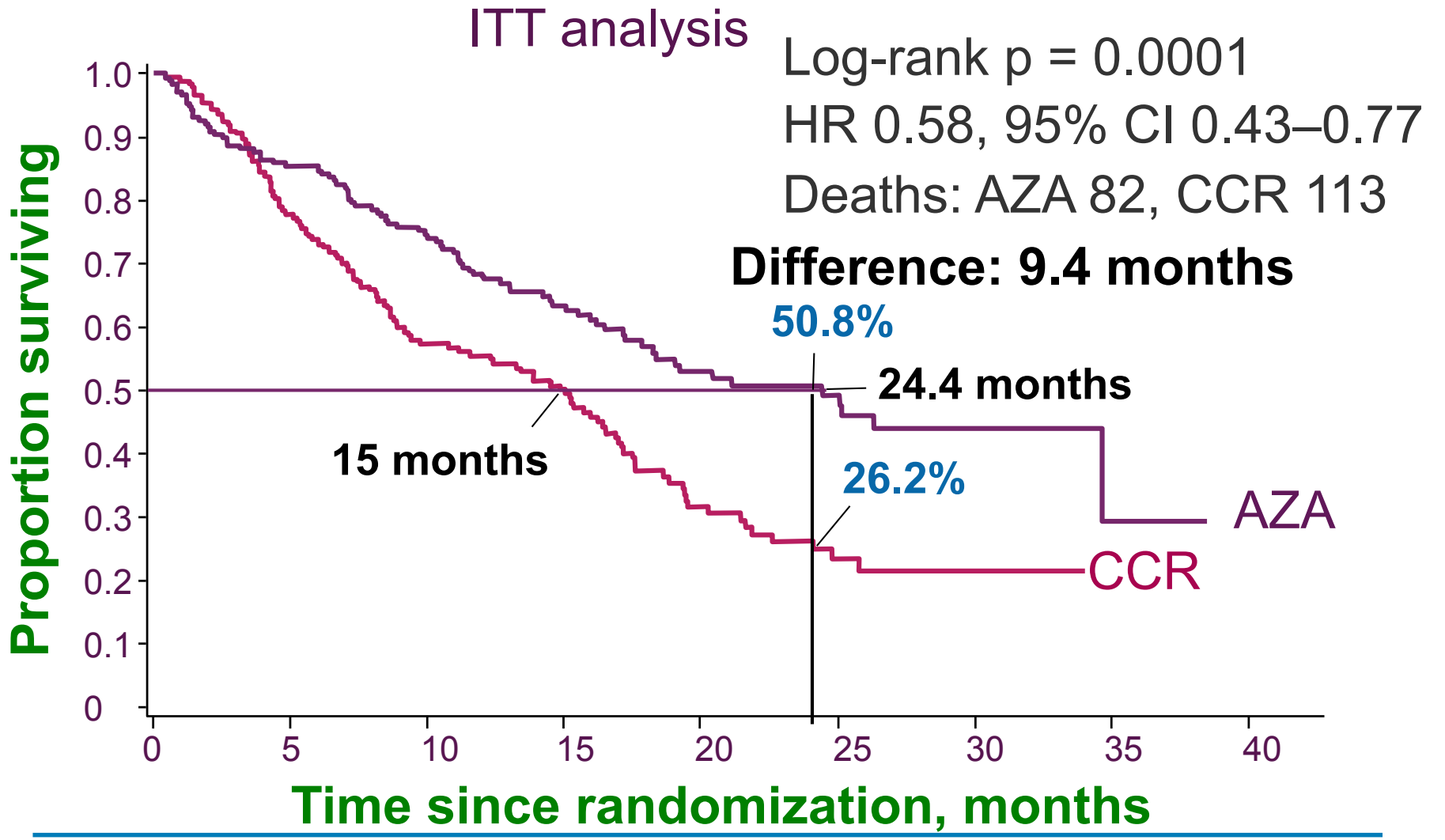
Azacitidine

5-aza-2’-deoxy-cytidine

Decitabine

Santini et al, Ann Int Med 2001

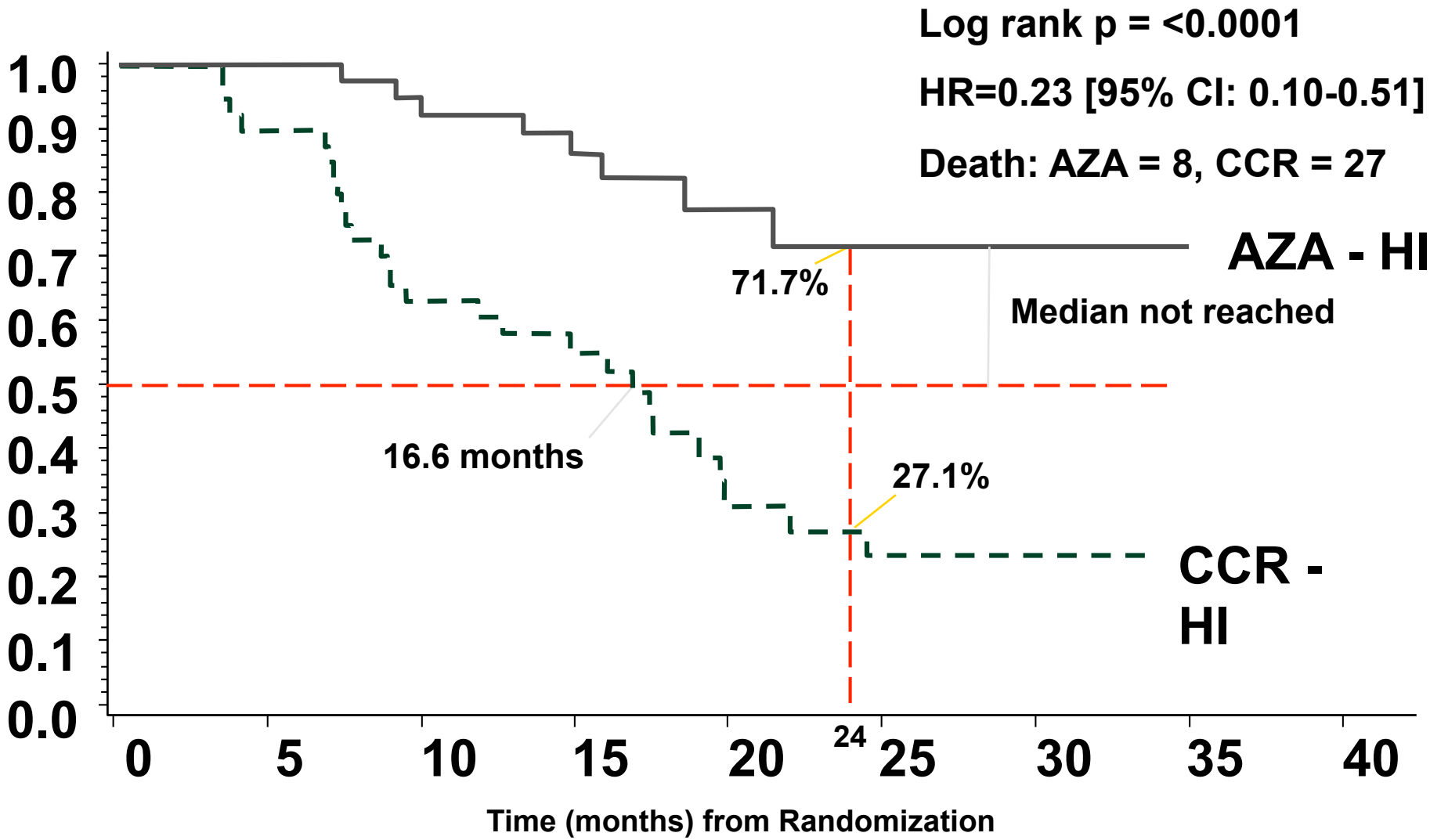
Overall survival: AZA vs CCR



CI, confidence interval; ITT, intention-to-treat.

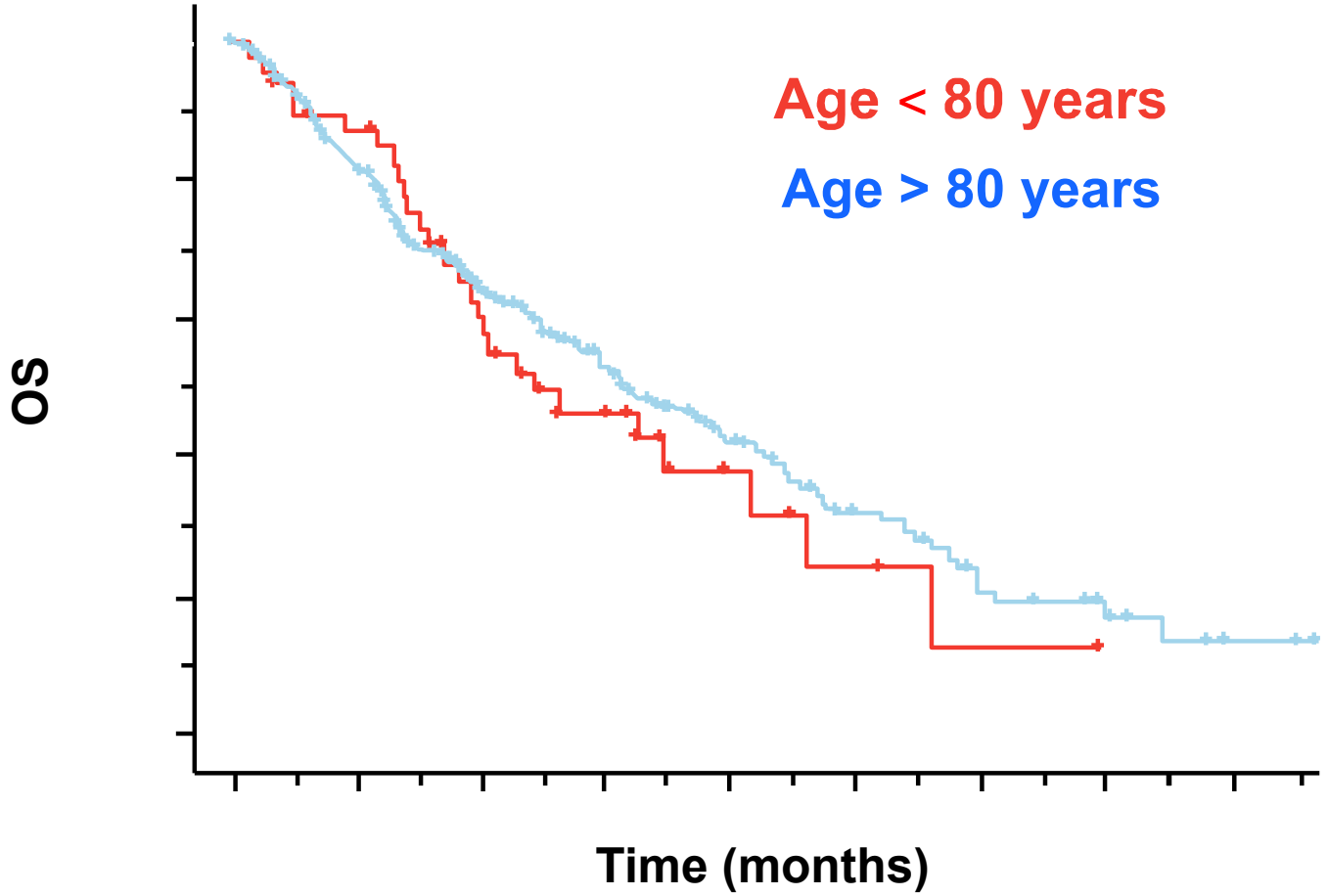
Fenaux P, et al. Lancet Oncol. 2009;10:223-32.

AZA vs CCR: OS in Pts with Best Response of HI



Gore S, et al, Haematologica. 2013 Jul;98(7):1067-72.

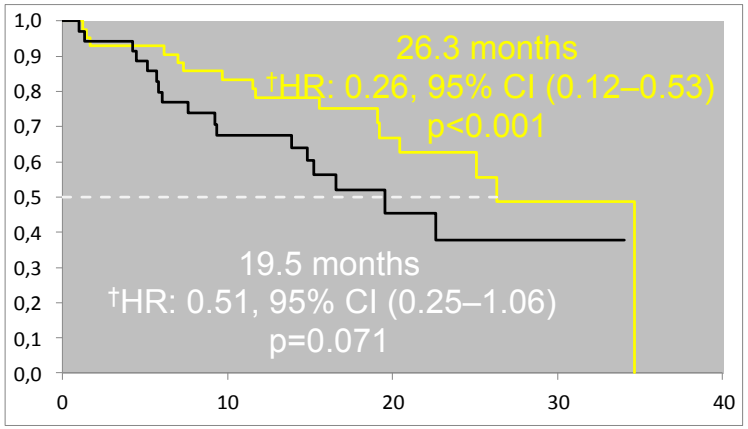
Azacitidine (AZA) in Higher Risk MDS Patients (pts) Aged ≥ 80 Years : OS



- OS similar in patients aged < 80 and ≥ 80 years (*P* = .6)
- Median OS 12.1 months; 1- and 2-year OS: 50% and 23.2%

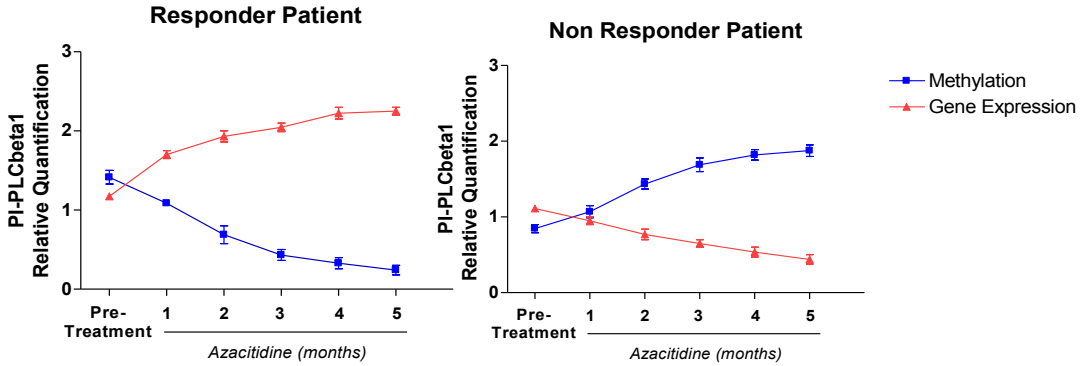
Itzykson, R., et al. *Blood*. 2009;114(22):705.

Methylation pattern and response to therapy

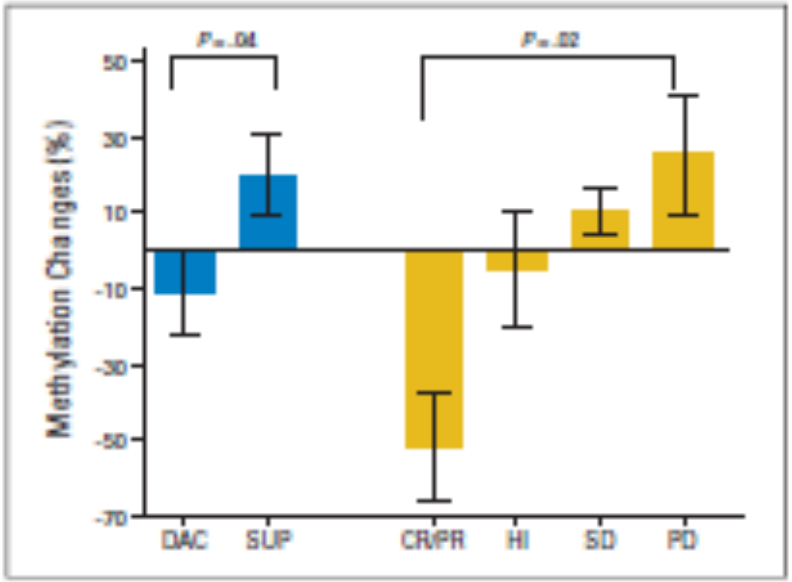


OS after AZA according to CDH1 methylation levels

Herman JG, et al. Presented at AACR 2009 [Abstract 4746]



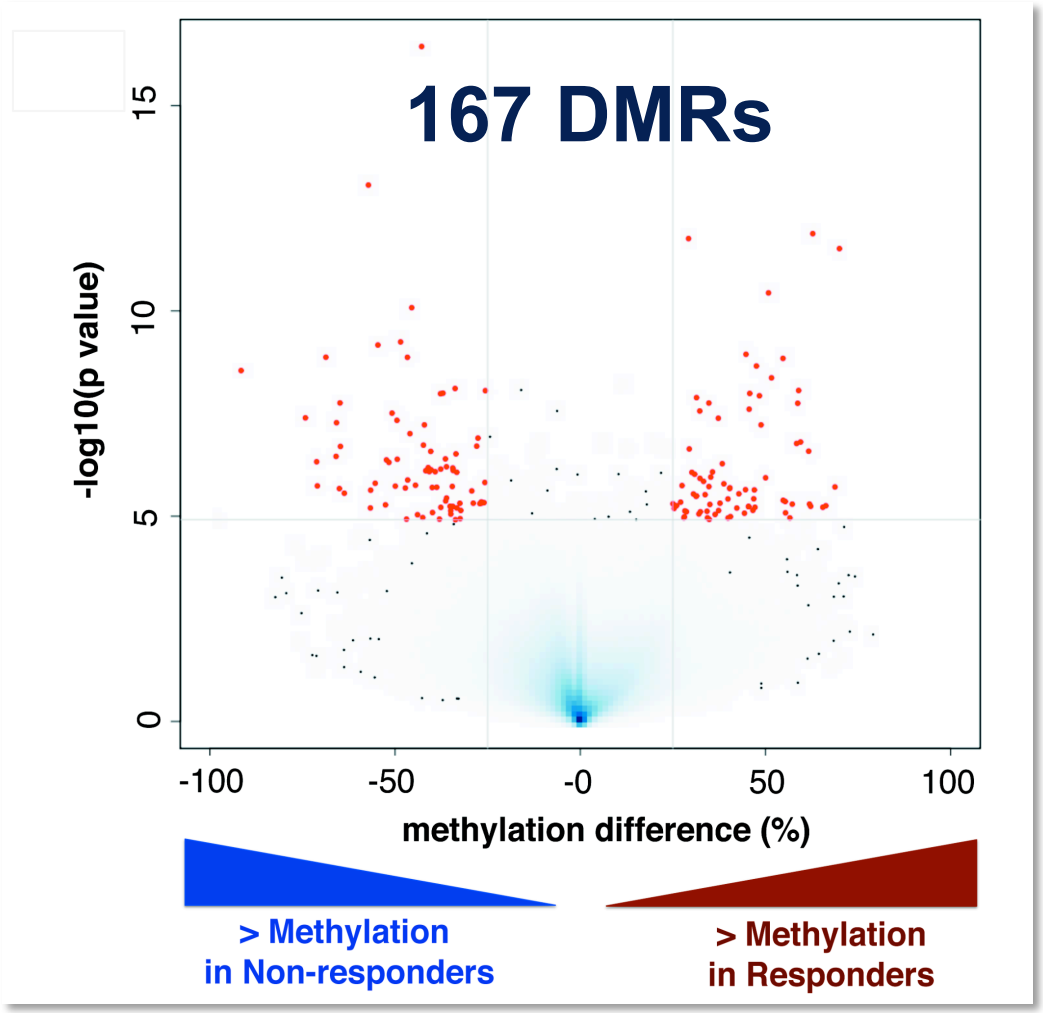
PI-PLCbeta1 promoter methylation and gene expression correlate with response to azacitidine
Follo et al PNAS 2009 29;106(39):16811-6



Global methylation and response to Decitabine

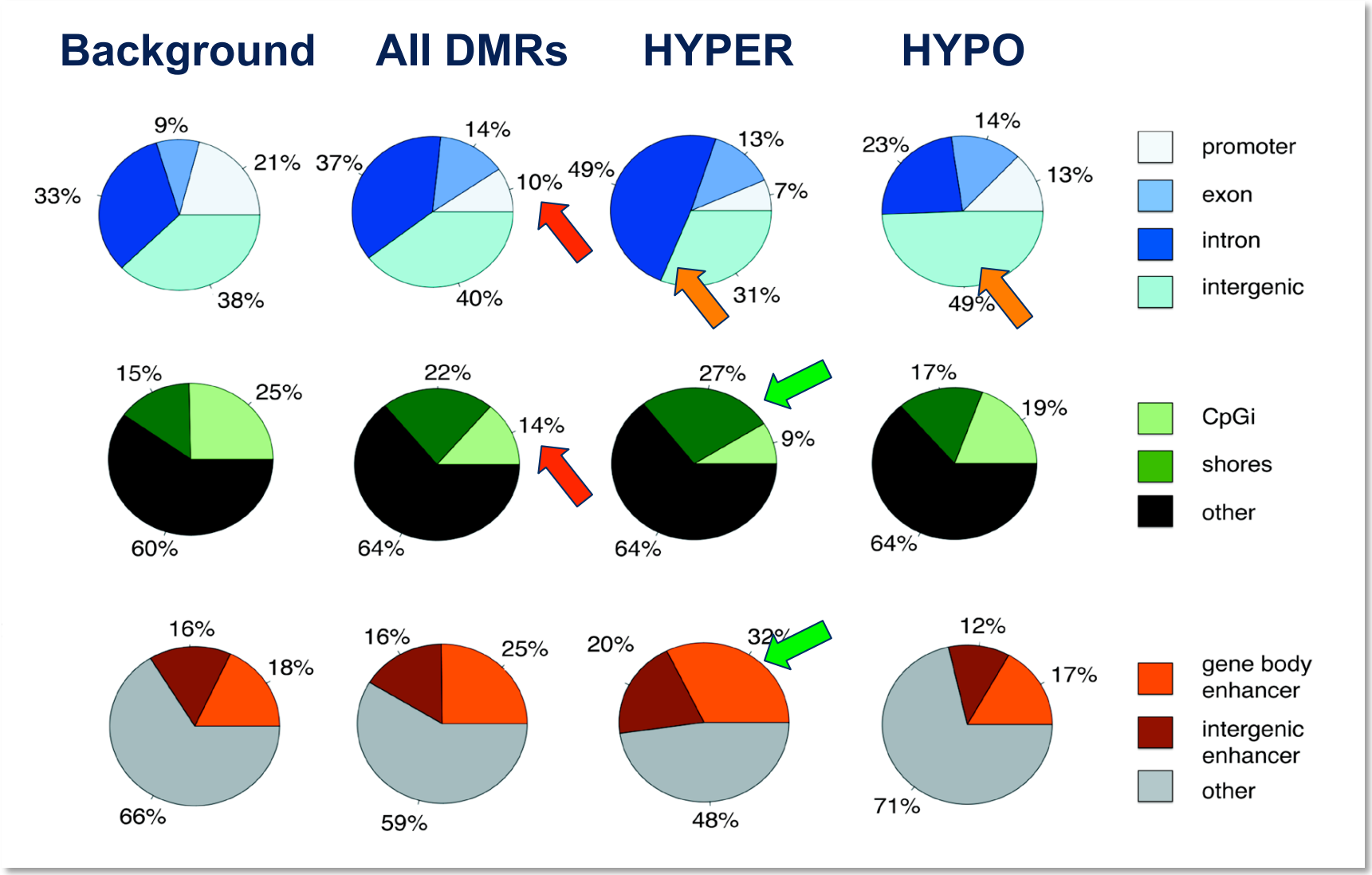
Shen, J Clin Oncol. 2010 1;28(4):605-13

Distinct DNA methylation profiles at diagnosis of CMML is associated with response to decitabine



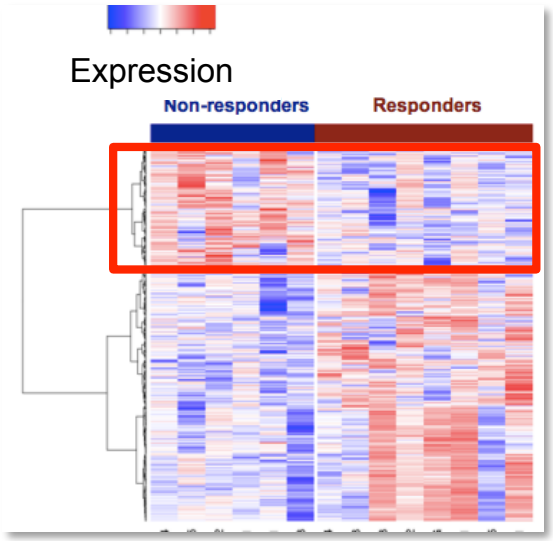
Meldi, et al. JCI 2015

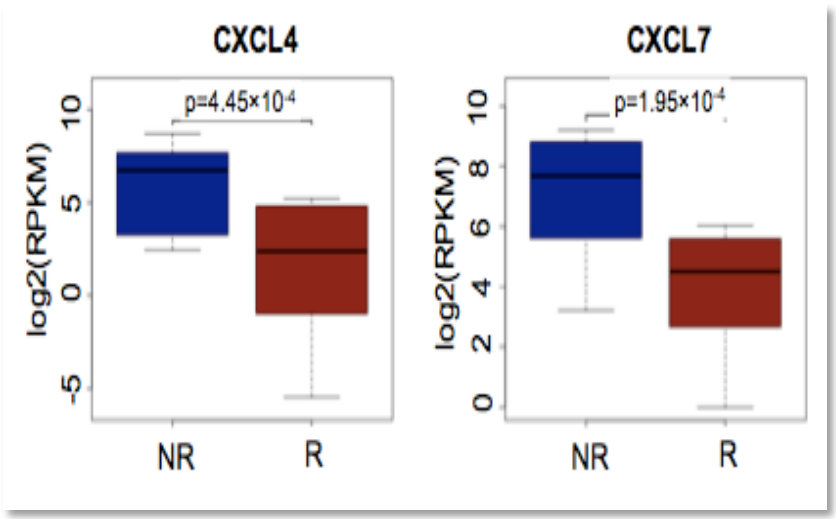
Differentially methylated regions are enriched at distal intergenic regions and enhancers

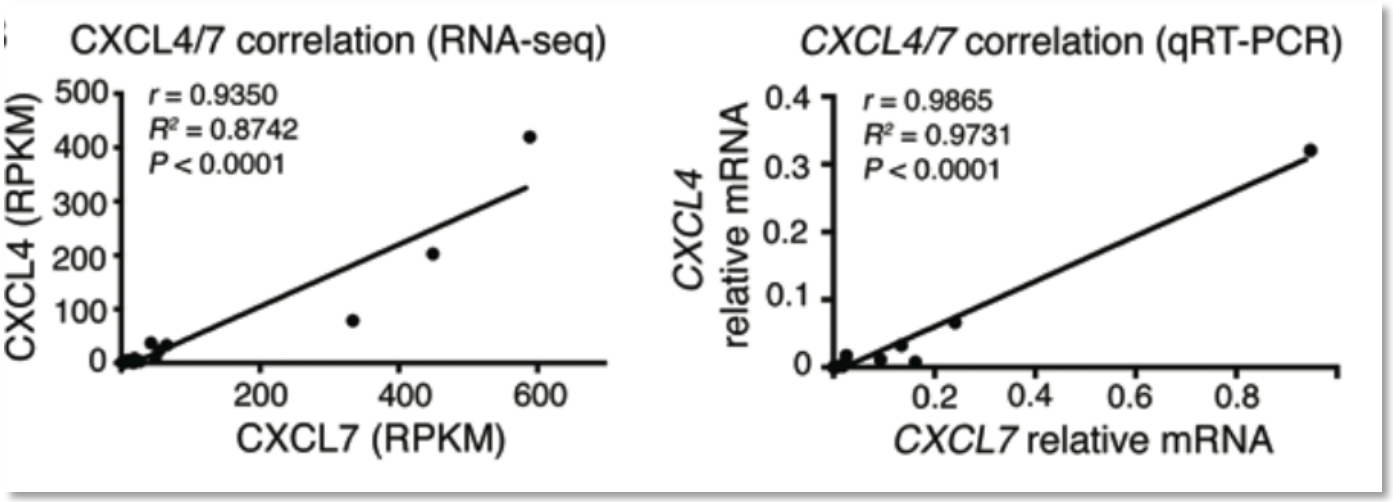


Meldi, et al. JCI 2015

CXCL4 and CXCL7 are up-regulated in the bone marrow of non-responders



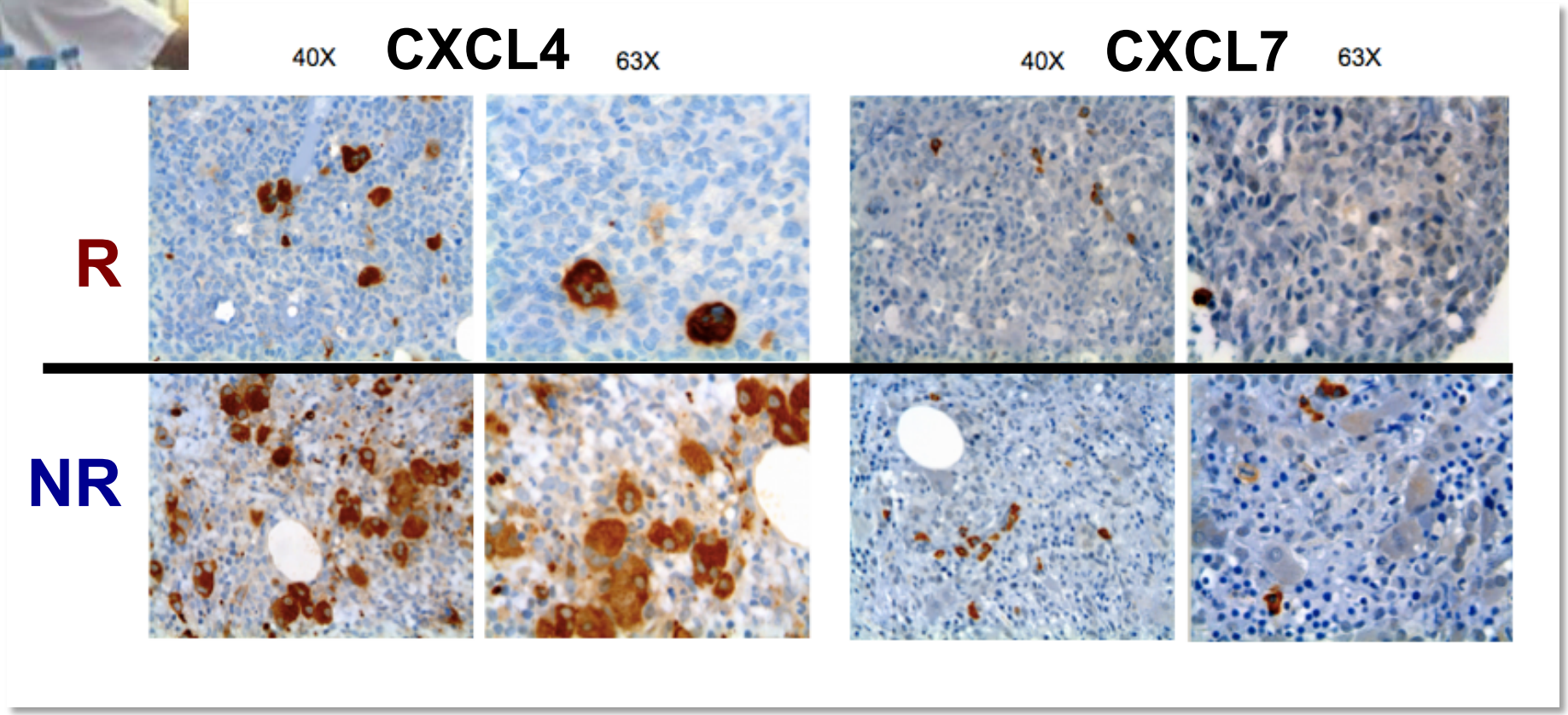




Meldi, et al. JCI 2015

CXCL4 and CXCL7 are up-regulated in the bone marrow of non-responders

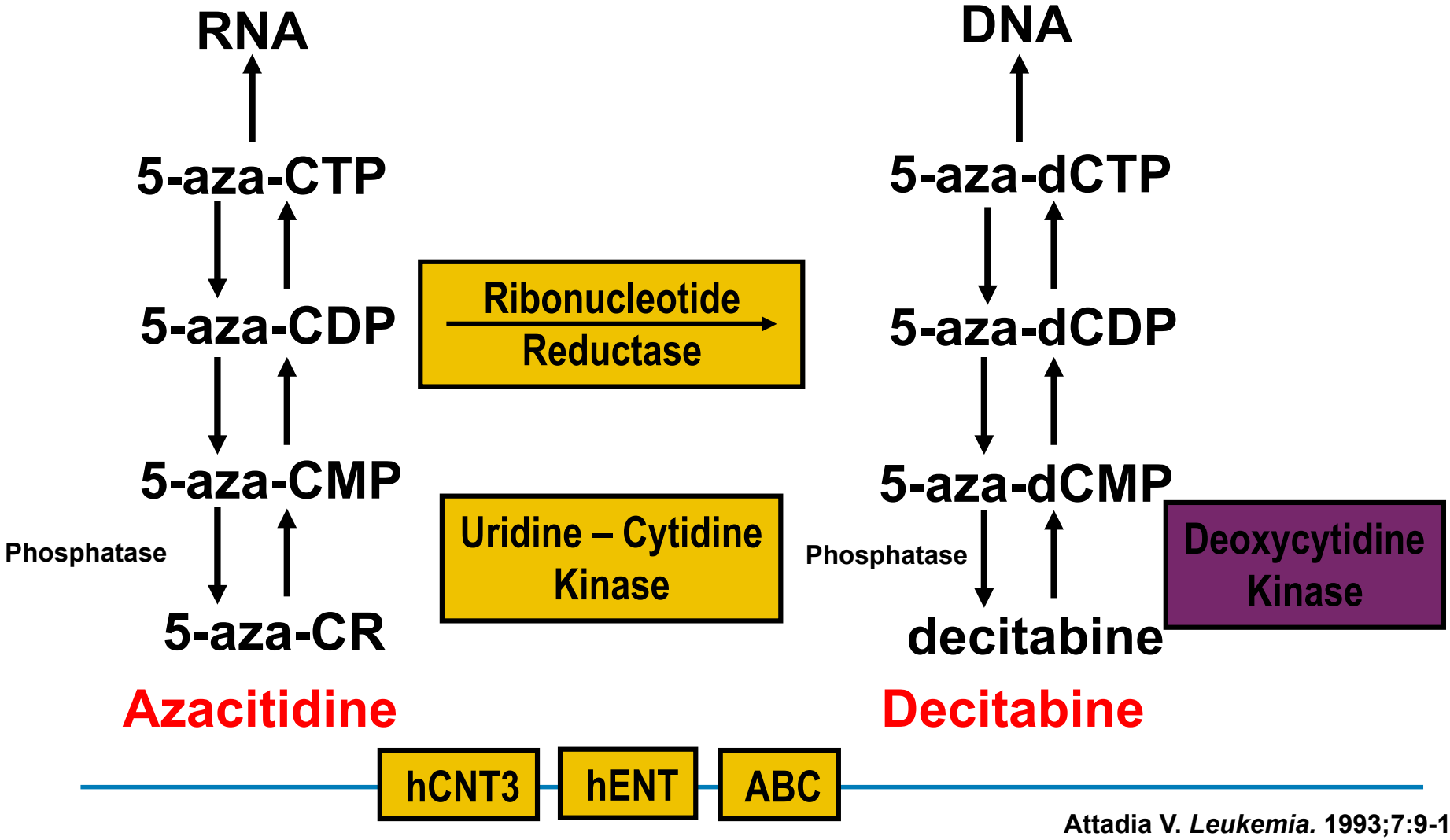
Francesca Buchi



Meldi, et al. JCI 2015

Uptake and metabolism of drugs may be impaired genetically and alter outcome

RNA/DNA uptake of hypomethylating agents



Attadia V. *Leukemia.* 1993;7:9-16.

UCK1 hyperexpression modulates response to Azacitidine in HR-MDS

Ana Valencia et al, Leukemia 2013

57 MDS pts

↓

Azacitidine

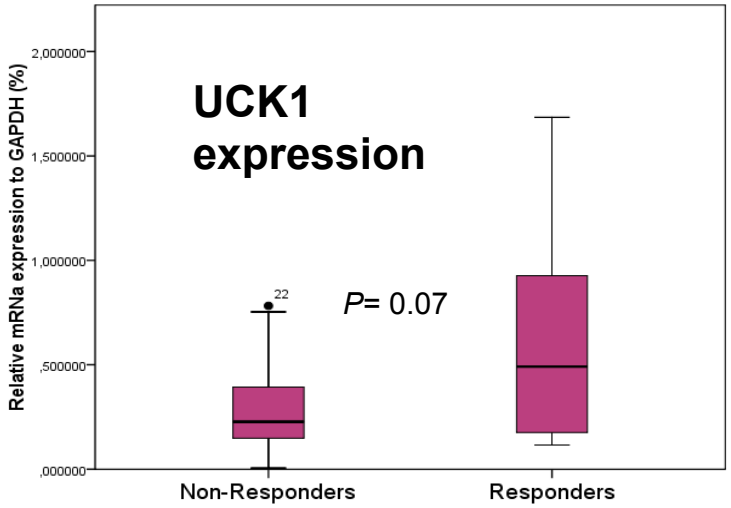
75mg/m^2/7 days
every 28 gg

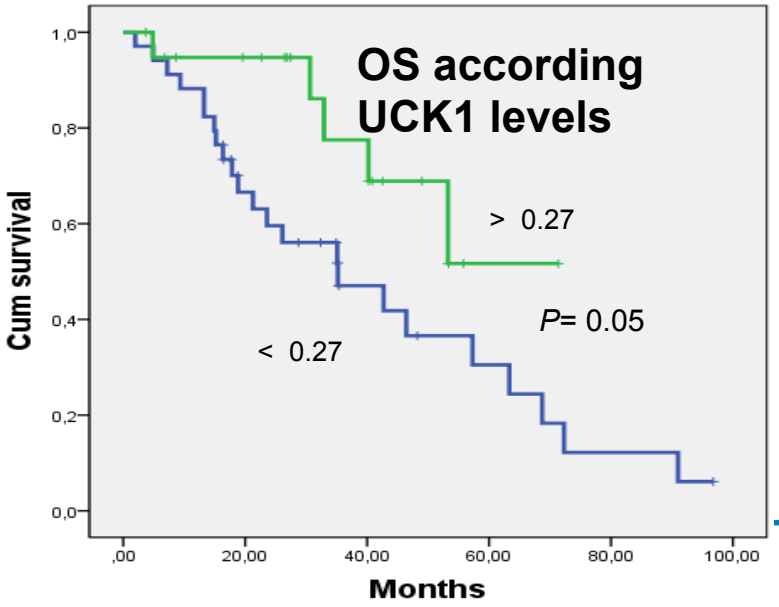
UCK1/2

Gene expression

Promoter methylation

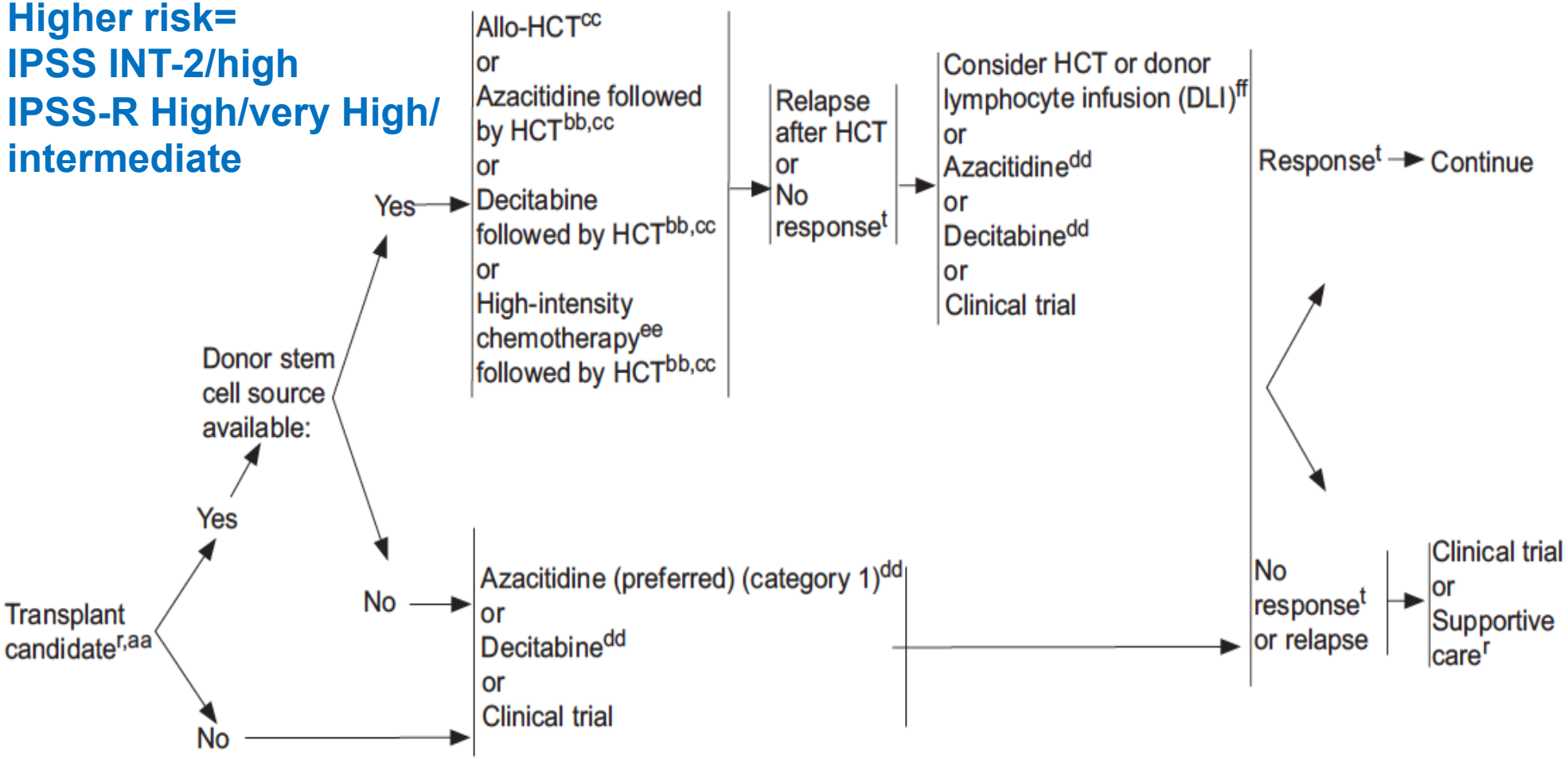
Gene sequence





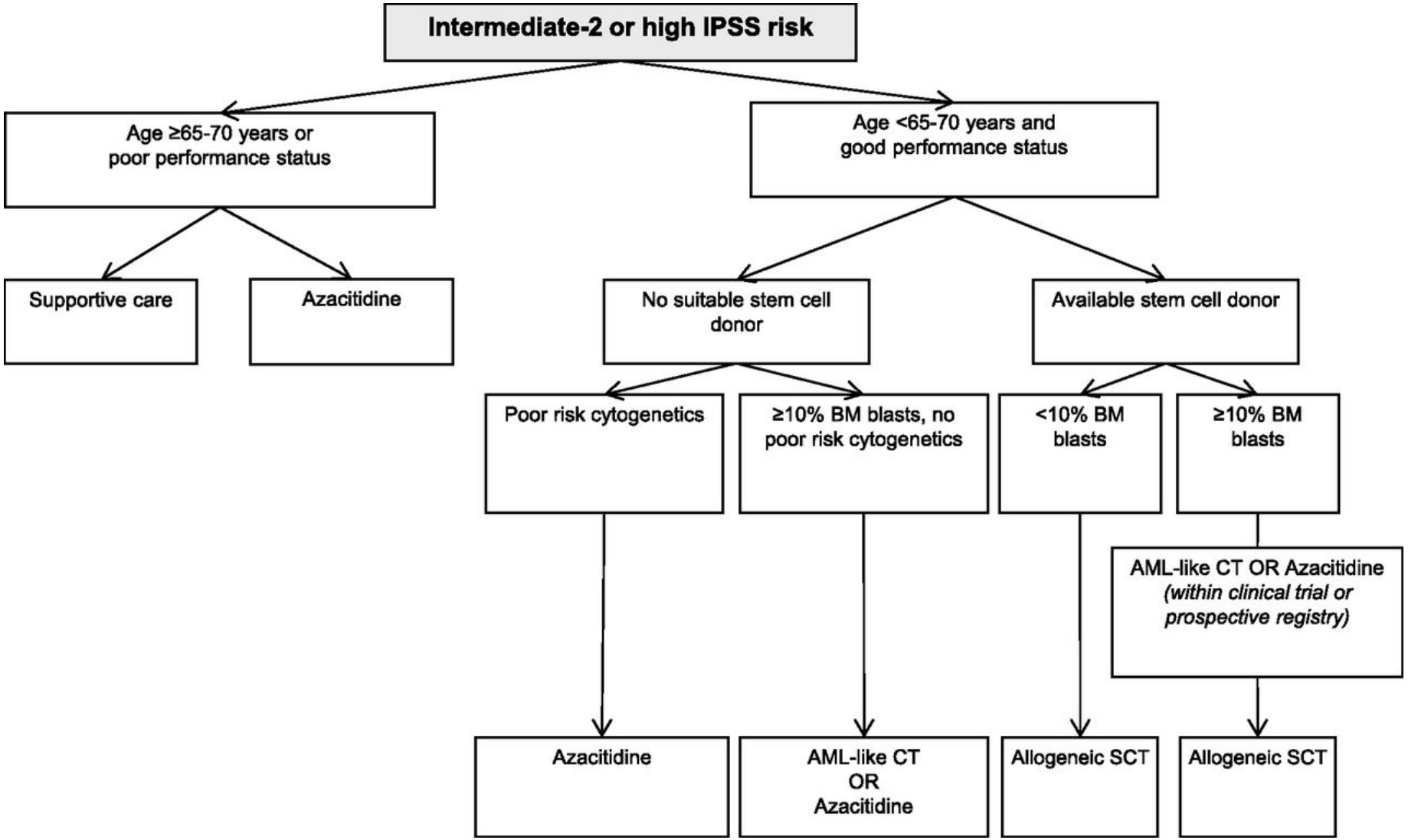
Myelodysplastic Syndromes, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology.

Higher risk=
IPSS INT-2/high
IPSS-R High/very High/ intermediate



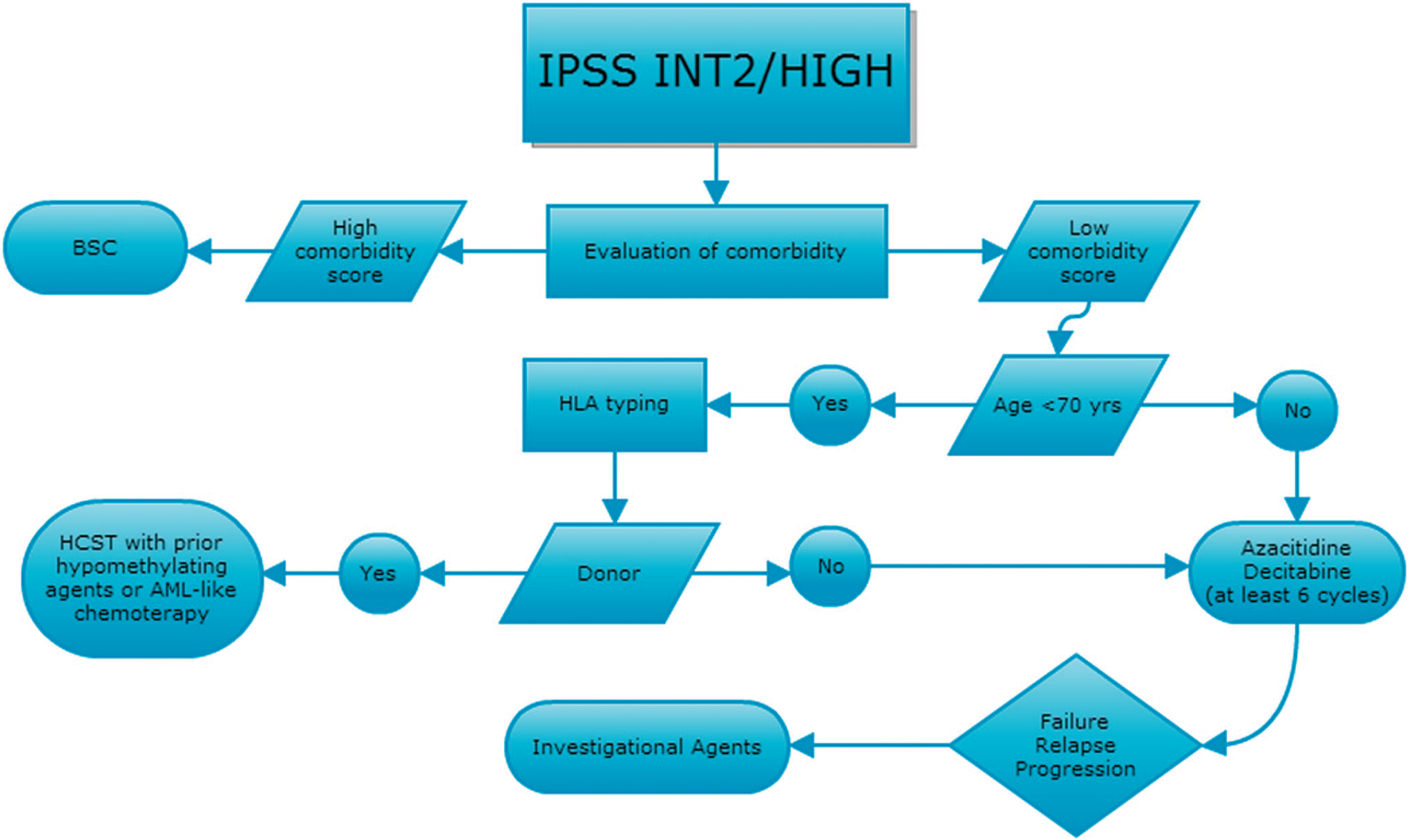
Greenberg PL et al. J Natl Compr Canc Netw. 2017 Jan;15(1):60-87

Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score.



Luca Malcovati et al. Blood 2013;122:2943-2964

Therapeutical options for higher risk MDS



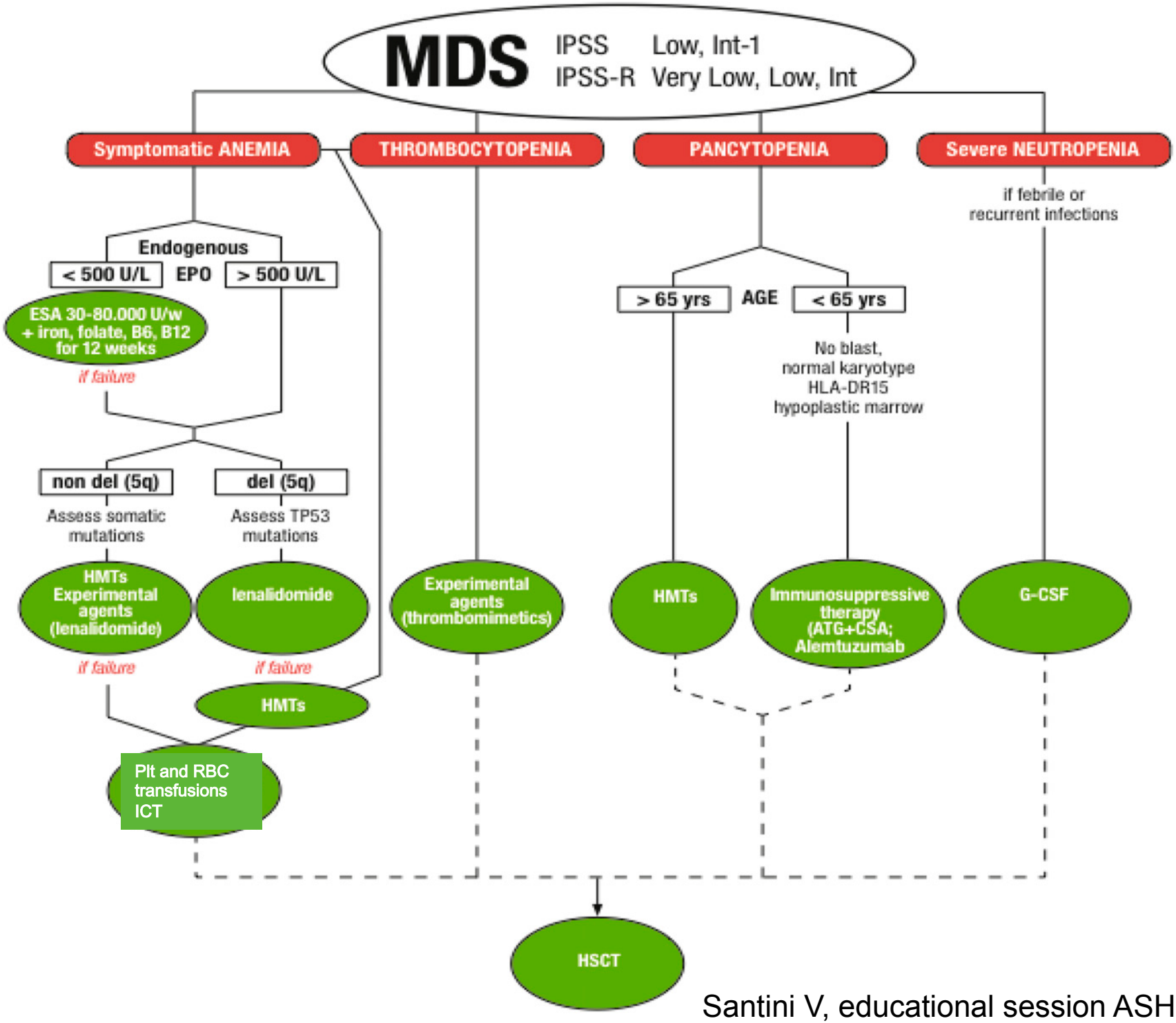
Santini V.
Hematology Am Soc Hematol Educ Program. **2012**;**2012**:65-73.

SIE-Italian Guideline Recommendations

Patients belonging to the IPSS int 2-high groups and not eligible to allogeneic HSCT, or eligible to allogeneic HSCT but lacking an immediately available donor, are recommended to receive hypomethylating therapy .

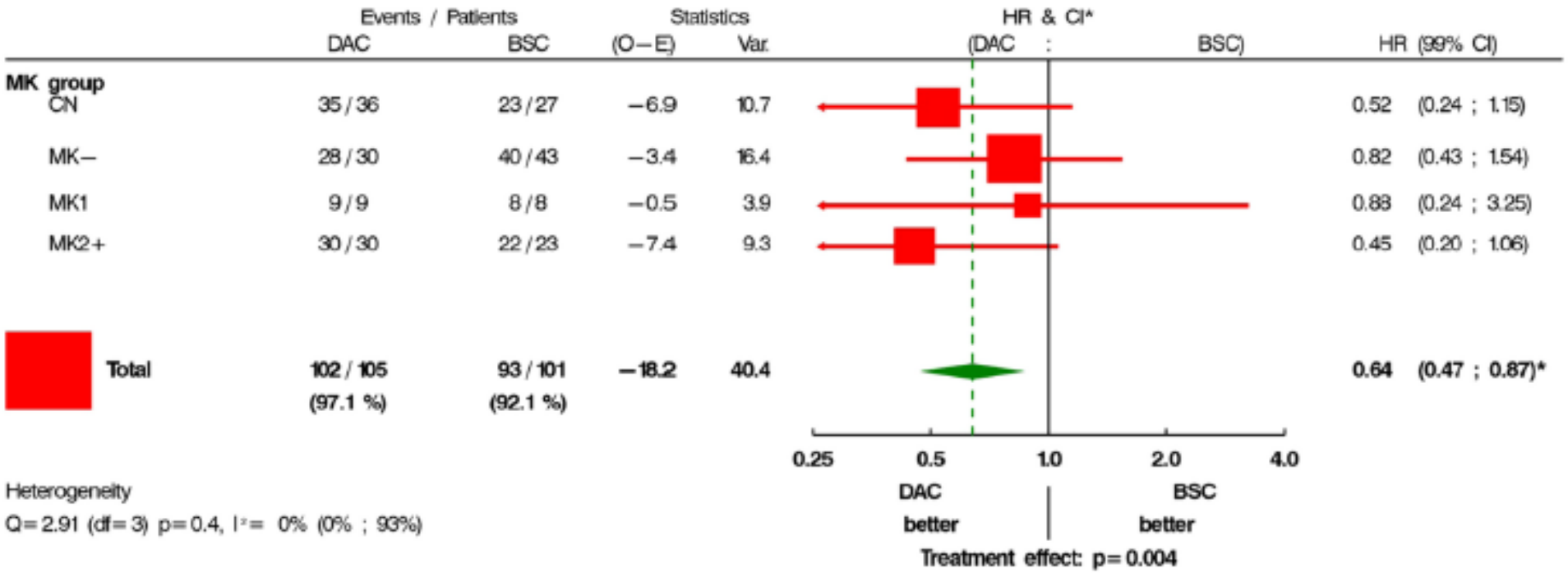
(grade A)

Santini et al, Leuk Res 2010



Santini V, educational session ASH 2016

Progression-free survival after decitabine is strikingly prolonged in the presence of 2 or more monosomies



Lübbert, Suciu et al., 2016

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TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

J.S. Welch, A.A. Petti, C.A. Miller, C.C. Fronick, M. O'Laughlin, R.S. Fulton, R.K. Wilson, J.D. Baty, E.J. Duncavage, B. Tandon, Y.-S. Lee, L.D. Wartman, G.L. Uy, A. Ghobadi, M.H. Tomasson, I. Pusic, R. Romee, T.A. Fehniger, K.E. Stockerl-Goldstein, R. Vij, S.T. Oh, C.N. Abboud, A.F. Cashen, M.A. Schroeder, M.A. Jacoby, S.E. Heath, K. Luber, M.R. Janke, A. Hantel, N. Khan, M.J. Sukhanova, R.W. Knoebel, W. Stock, T.A. Graubert, M.J. Walter, P. Westervelt, D.C. Link, J.F. DiPersio, and T.J. Ley

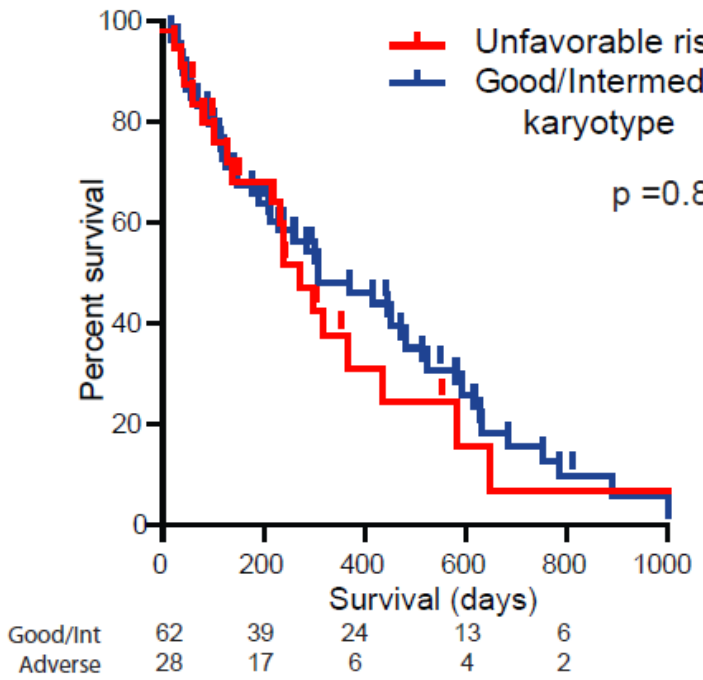
Welch JS et al. N Engl J Med 2016;

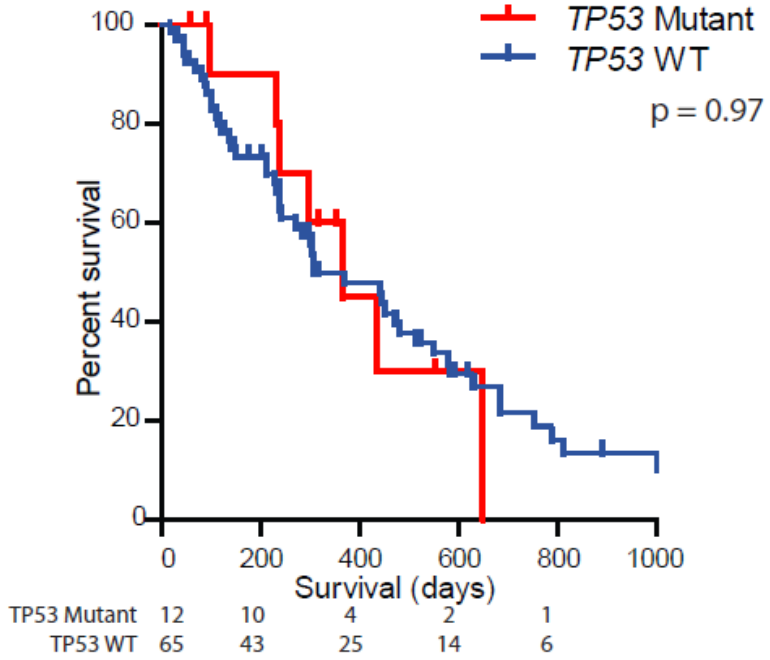
100% patients *TP53* mutations respond to Decitabine

Characteristic	All Patients (N=116)	*TP53* Mutations (N=21)	Wild-Type *TP53* (N=78)	*TP53* Not Evaluated (N=17)	P Value†
Response — no. (%)					
Bone marrow blast clearance <5% blasts	53 (46)	21 (100)	32 (41)	0	<0.001
Complete remission					
With recovery of peripheral-blood counts	15 (13)	4 (19)	11 (14)	0	0.73
With incomplete count recovery	24 (21)	9 (43)	15 (19)	0	0.04
Morphologic complete remission					
With hematologic improvement	6 (5)	5 (24)	1 (1)	0	0.002
Without hematologic improvement	8 (7)	3 (14)	5 (6)	0	0.36
No bone marrow blast clearance	63 (54)	0	46 (59)	5 (29)	<0.001
Partial response	9 (8)	0	9 (12)	0	0.05
Stable disease	23 (20)	0	18 (23)	5 (29)	0.006
Progressive disease	19 (16)	0	19 (24)	0	0.003
Samples not available for evaluation	12 (10)	0	0	12 (71)	

Welch JS et al. N Engl J Med

OS according to risk karyotype and TP53 profile with decitabine



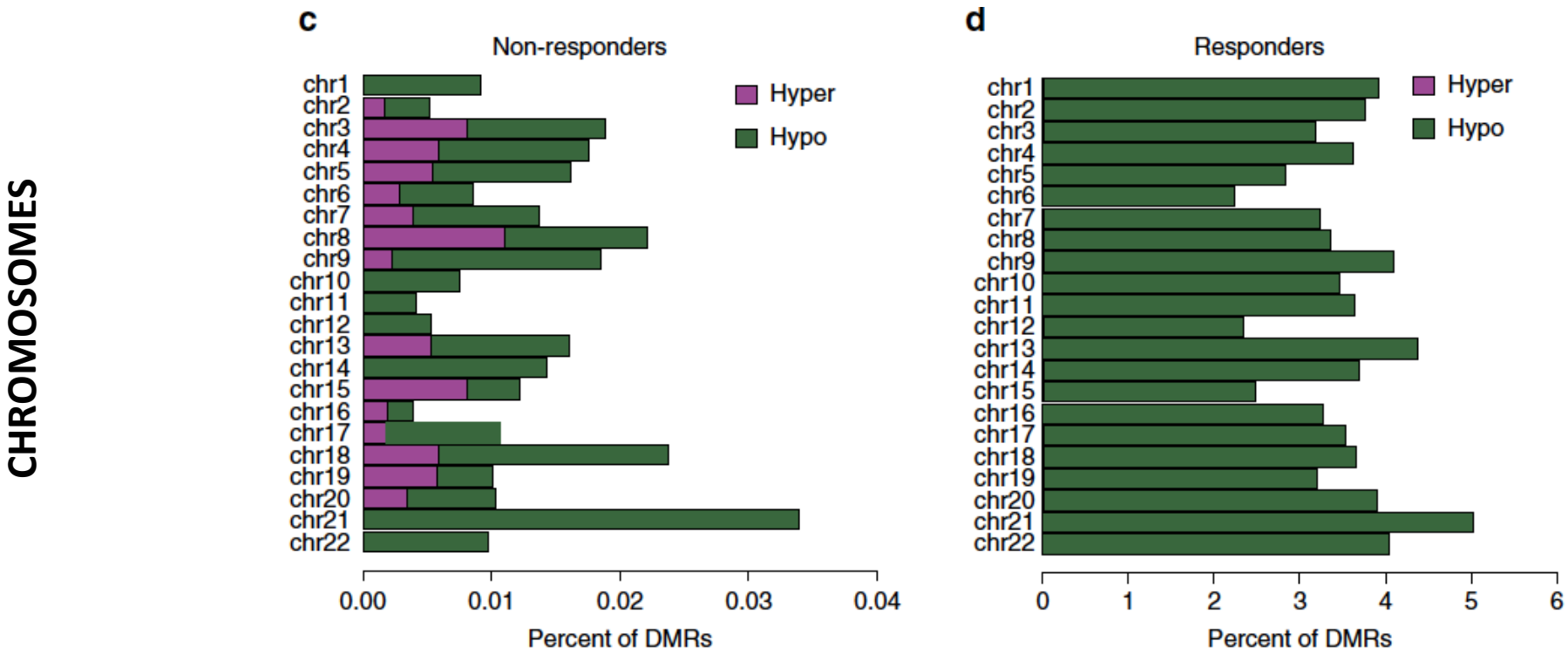


No differences between unfavourable and favourable risk karyotype
No differences between per status TP53 mutant and wild type

Welch et al. NEJM 2016;375:2023–36

Response to DAC is associated with reversal of hypermethylation

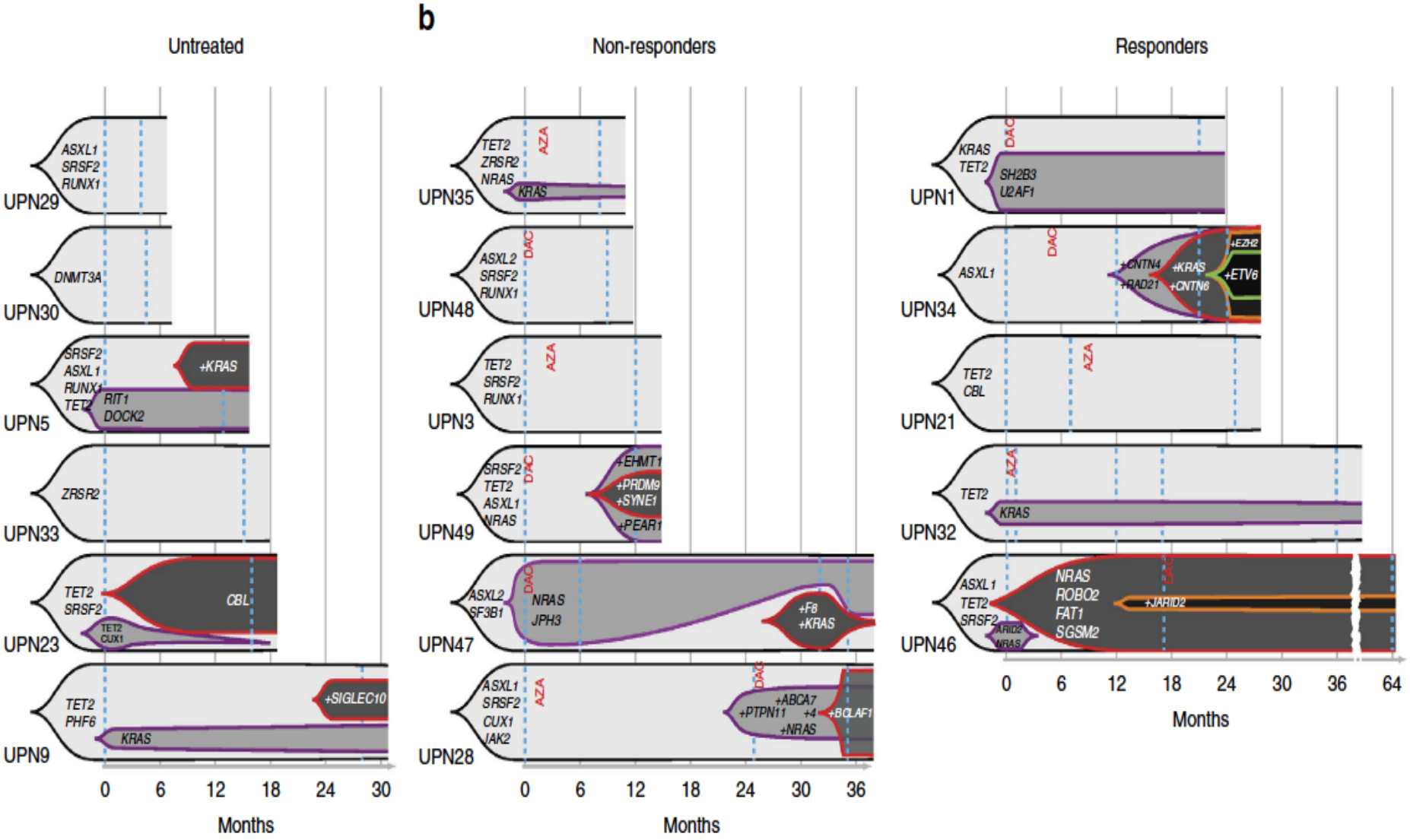
Before DAC – After DAC



- **Loss of mC ≥ 25% after DAC**
- **Gain of mC ≥25% after DAC**

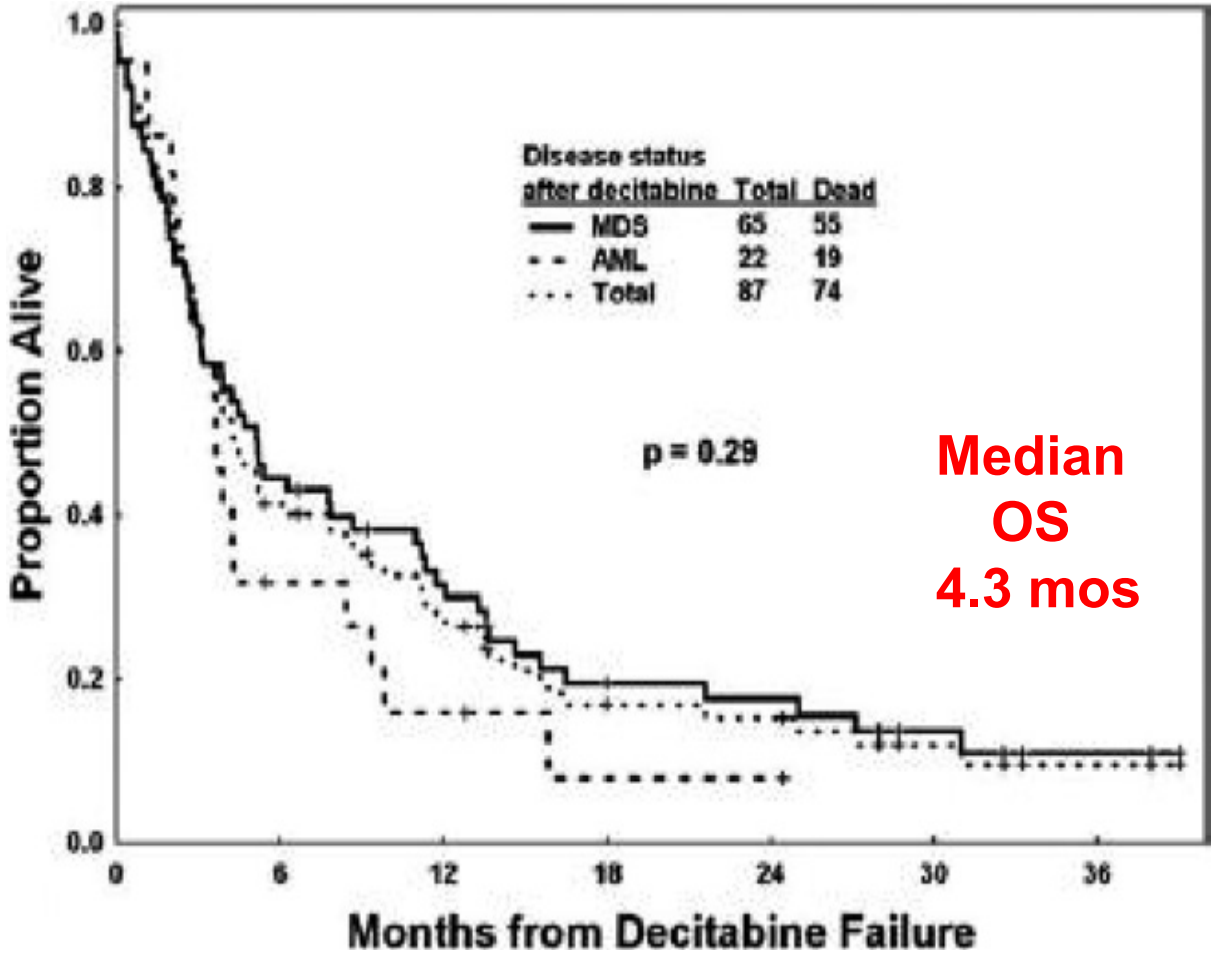
Merlevede et al Nat Commun. 2016 Feb 24;7:10767.

Mutation allele burden remains unchanged after DAC



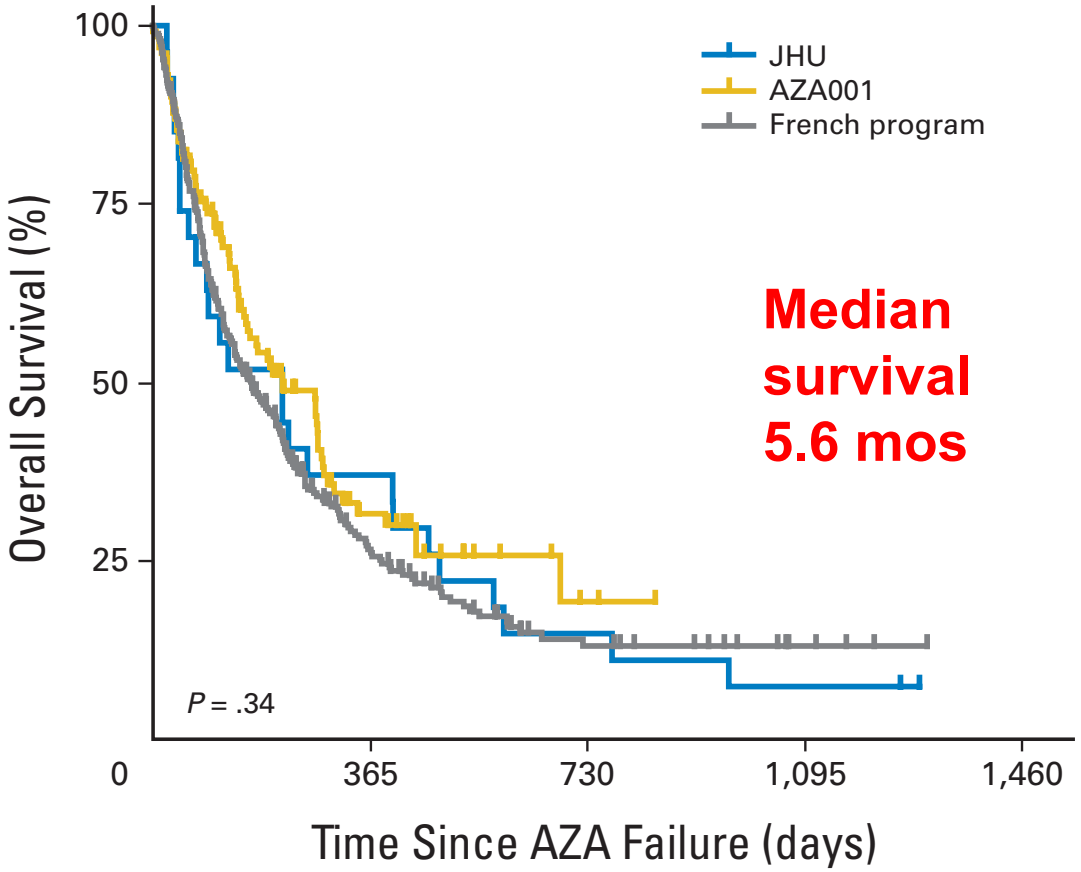
Merlevede et al Nat Commun. 2016 Feb 24;7:10767.

Survival after decitabine failure in MDS/AML patients



Jabbour et al, Cancer 116:3830(2008)

Survival after azacitidine failure in MDS/AML patients



Prebet et al, JCO 29:3322 (2011)

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DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

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