Myelodysplastic Syndromes: Is It Time to Incorporate NGS and What Is New in Terms of Therapy?

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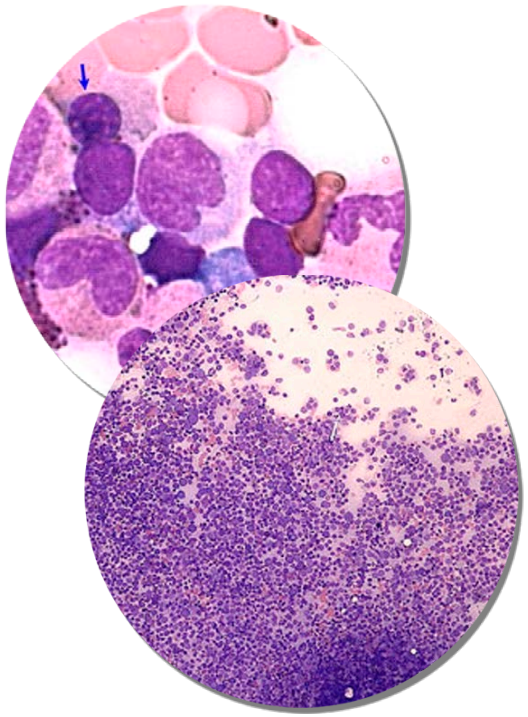
Myelodysplastic Syndromes (MDS)

- A group of malignant hematopoietic neoplasms characterized by[1]
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations.
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000[2]
  - In US (true estimates ≈37,000-48,000)
- Median age: 70 yrs; incidence: 34-47/100,000 >75 yrs[3]



AML = acute myeloid leukemia.

1. Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, eds. *Clinical Oncology*. New York, NY: Churchill Livingstone; 2004:2849-2881. 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.

Minimal Diagnostic Criteria

Cytopenia(s):

- Hb <11 g/dL, *or*
- ANC <1500/µL, *or*
- Platelets <100 x 10^9/L

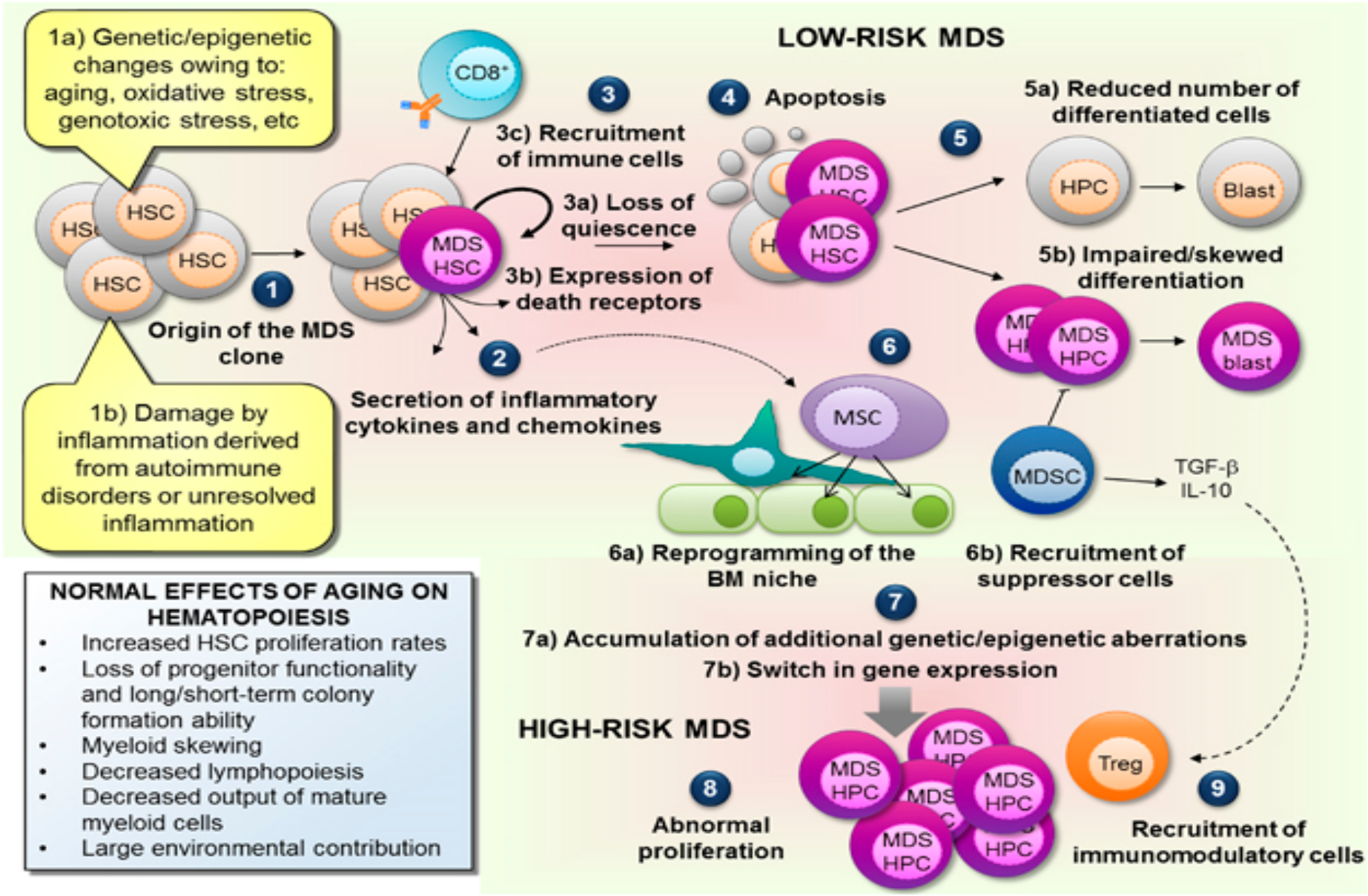
MDS "decisive" criteria:

- >10% **dysplastic cells** in 1 or more lineages, *or*
- 5-19% **blasts**, *or*
- Abnormal **karyotype** typical for MDS, *or*
- Evidence of **clonality**

EXCLUDE other causes of cytopenias and morphological changes:

- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE etc.)*
- *Congenital syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

MDS pathogenesis model



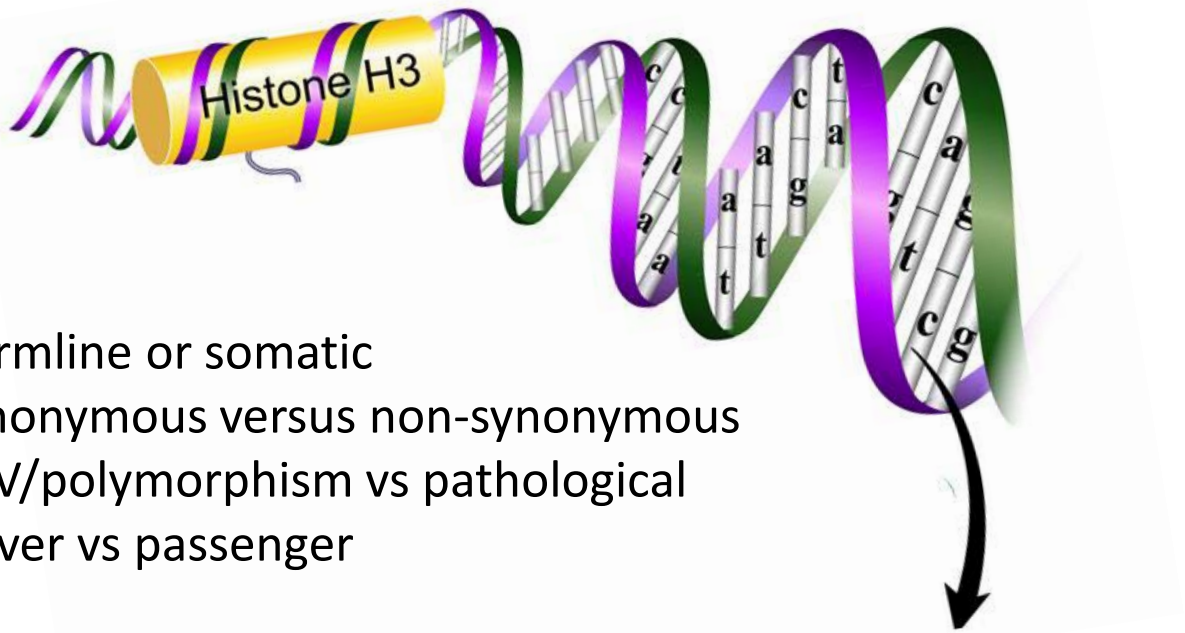
Genetic Abnormalities in MDS

Translocations/ Rearrangements	Uniparental Disomy/ Microdeletions	Copy Number Change	Point Mutations
Rare in MDS	Rare – often at sites of point mutations	About 50% of cases	Most common
t(6;9) i(17q) t(1;7) t(3;?) t(11;?) inv(3) idic(X)(q13)	4q - *TET2* 7q - *EZH2* 11q - *CBL* 17p - *TP53*	del(5q) -7/del(7q) del(20q) del(17p) del(11q) +8 -Y	Likely in all cases ~80% of cases have mutations in a known gene
Karyotype	**Array CGH SNP Array**	**Karyotype/FISH**	**Genotyping Sequencing**

Observed Frequency in MDS

Vardiman,JW, et al. Blood. 2009;114(5): 937-951. Tiu R, et al. Blood. 2011;117(17):4552-4560. Schanz, J, et al. J Clin Oncol. 2011; 29(15):1963-1970. Bejar R, et al. N Engl J Med. 2011;364(26):2496-2506. Bejar R, et al. J Clin Oncol. 2012;30(27):3376-3382.

What is a mutation?



- Germline or somatic
- Synonymous versus non-synonymous
- SNV/polymorphism vs pathological
- Driver vs passenger

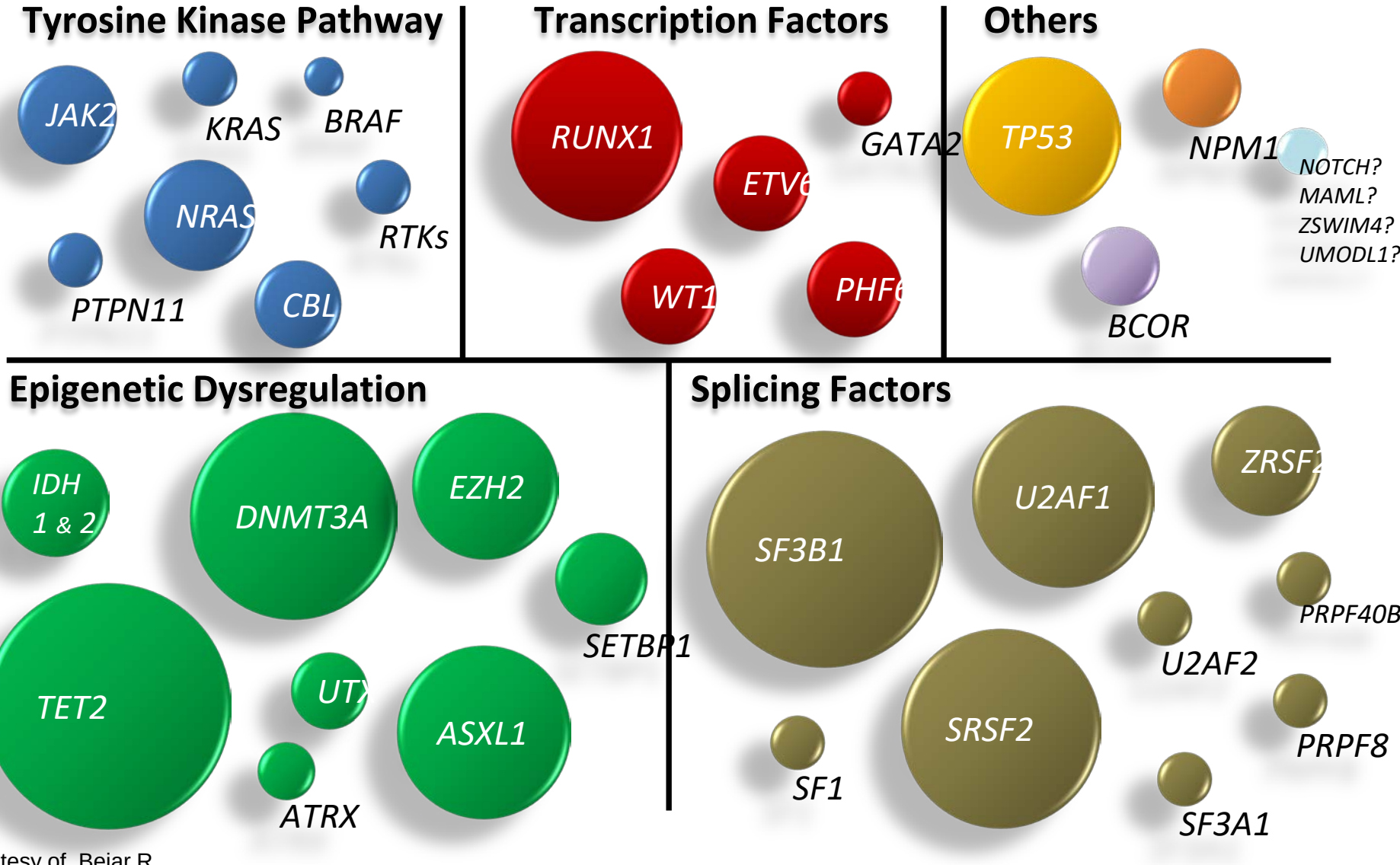
Type of mutations

- Missense
- Non-sense
- Insertion
- Deletion
- Frame shift
- duplication

…TTGAGTCG….

…TTGAGTAG….

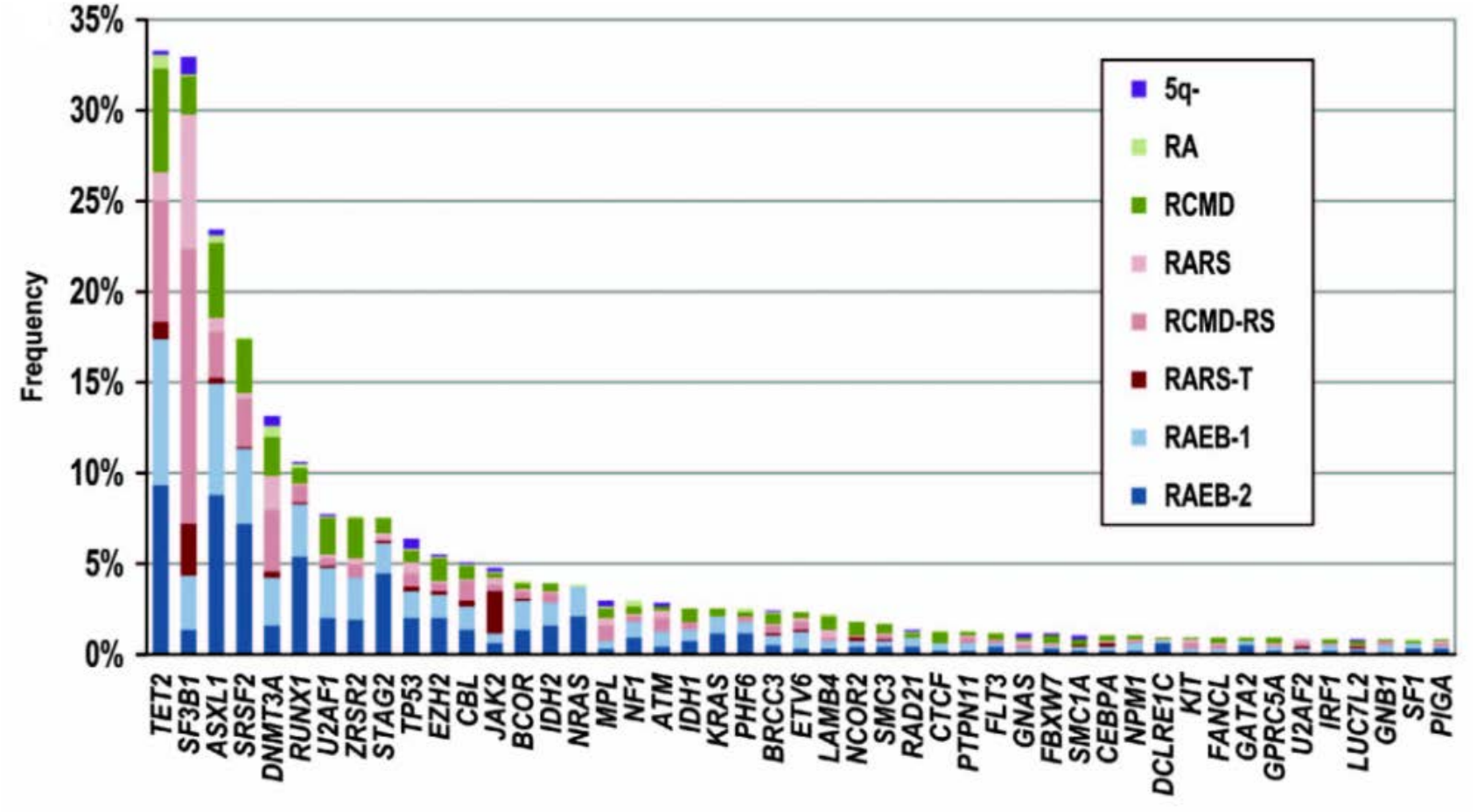
Genes Recurrently Mutated in MDS



Courtesy of Bejar R.

Recurrent Genetic Mutations in MDS

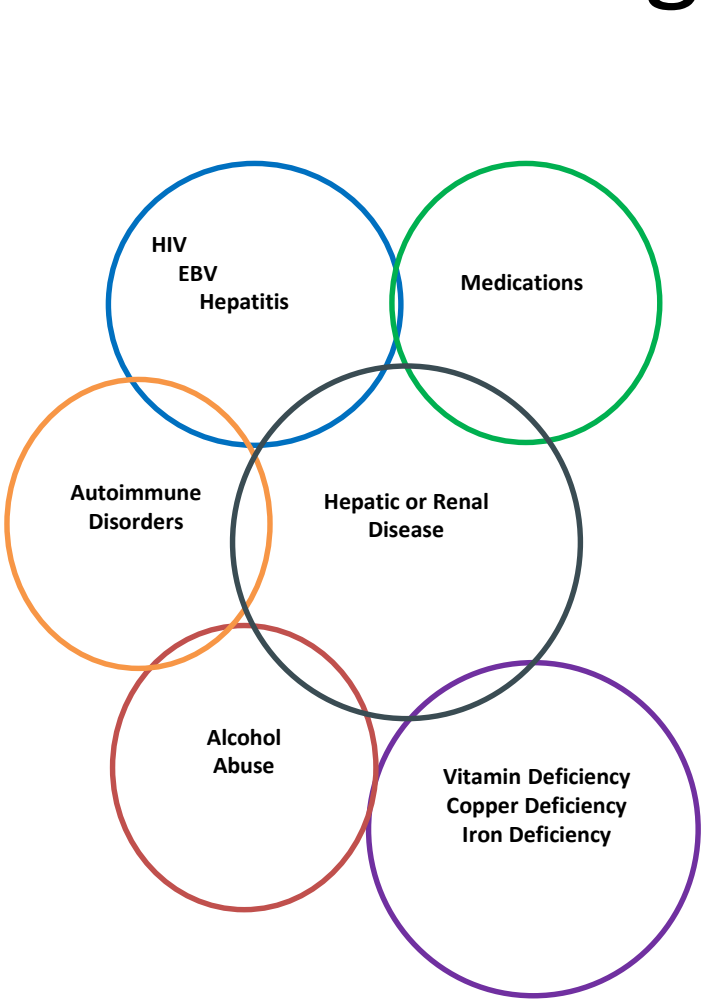
~89% of patients had a mutation by NGS



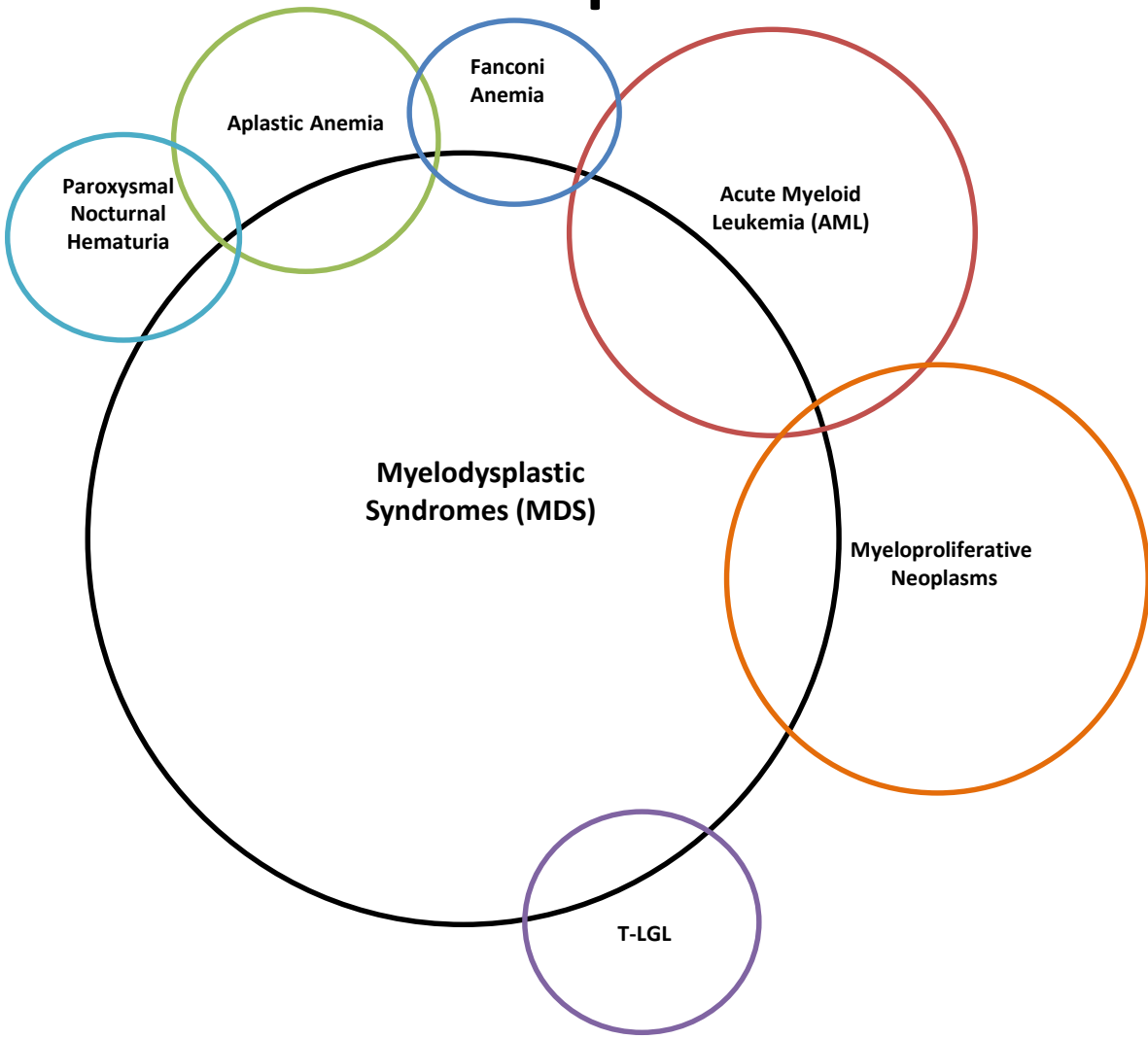
Haferlach et al., *Leukemia* (2014) 28**,** 241–247; doi:10.1038/leu.2013.336.

MDS DIAGNOSIS

Diagnostic Overlap



Non-Clonal



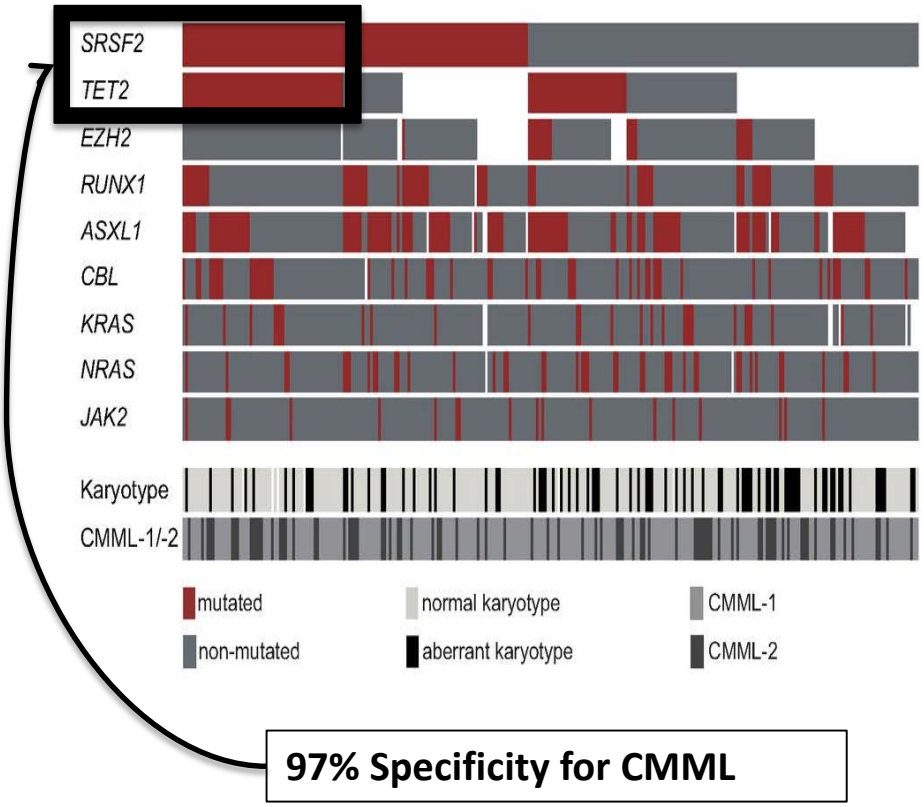
Clonal

Mutations in MDS

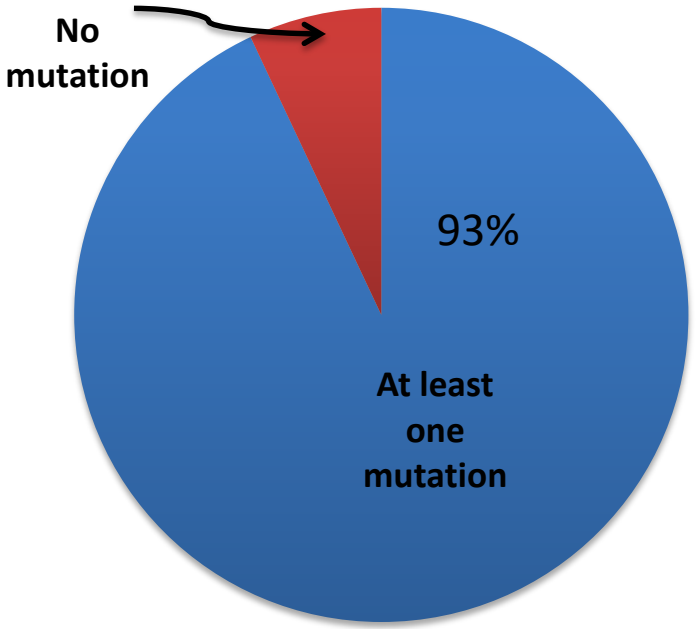
- MDS-associated gene mutations can establish the presence of clonal hematopoiesis, which can help exclude benign causes of cytopenias in cases with non-diagnostic morphology
- Mutations may not establish a diagnosis of MDS in the absence of clinical diagnostic criteria
- In the appropriate context (e.g., cytopenias present without AML defining criteria, no evidence of other malignancy), they could aid in the determination of diagnosis

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. v2.2015.

NGS Myeloid Panels can efficiently identify clonality



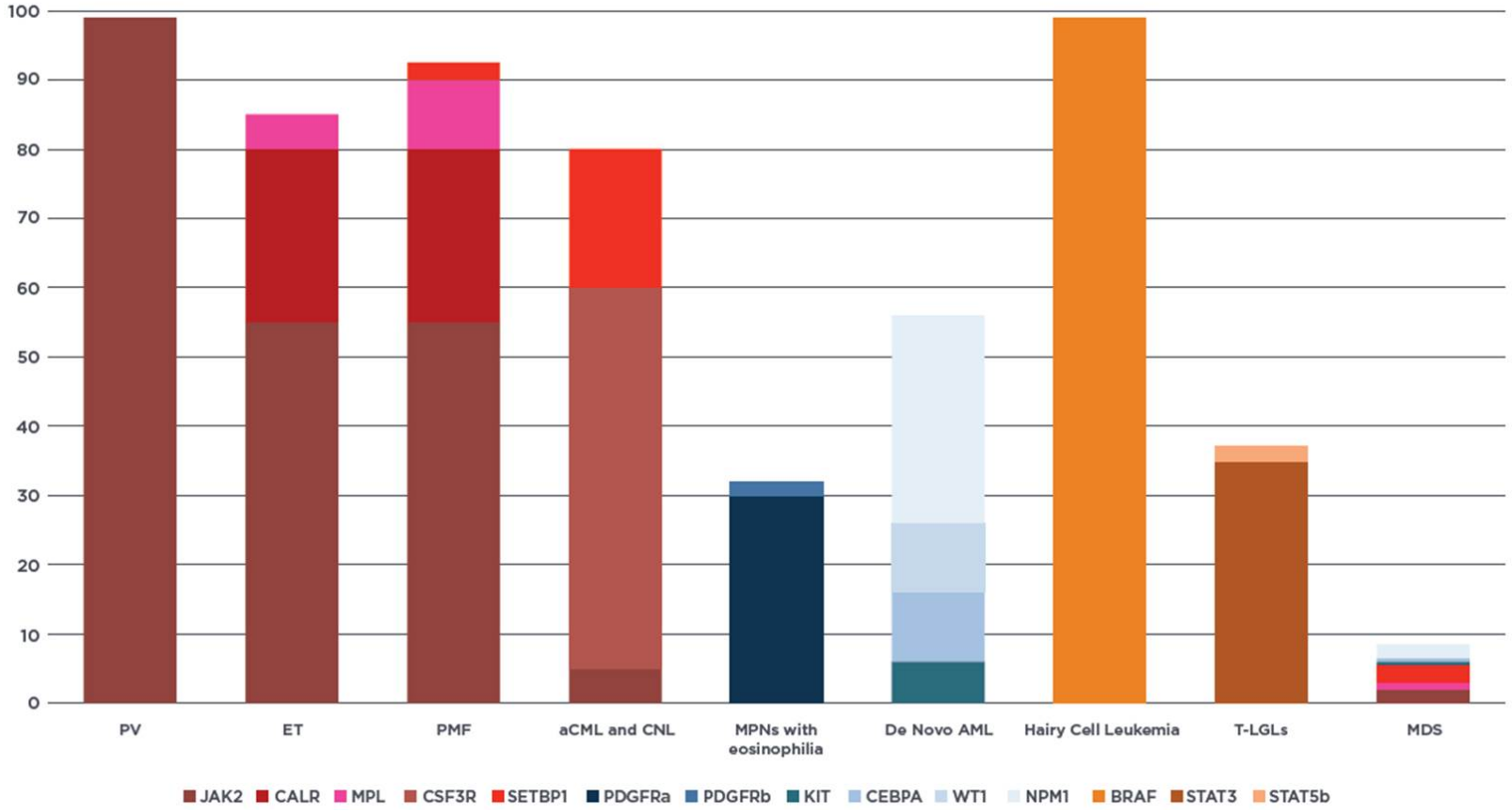
Malcovati L Blood 2014



Meggendorfer et al Blood 2013

MOFFITT CANCER CENTER

Mutations in certain genes may favor related myeloid neoplasms or possible mimics of MDS

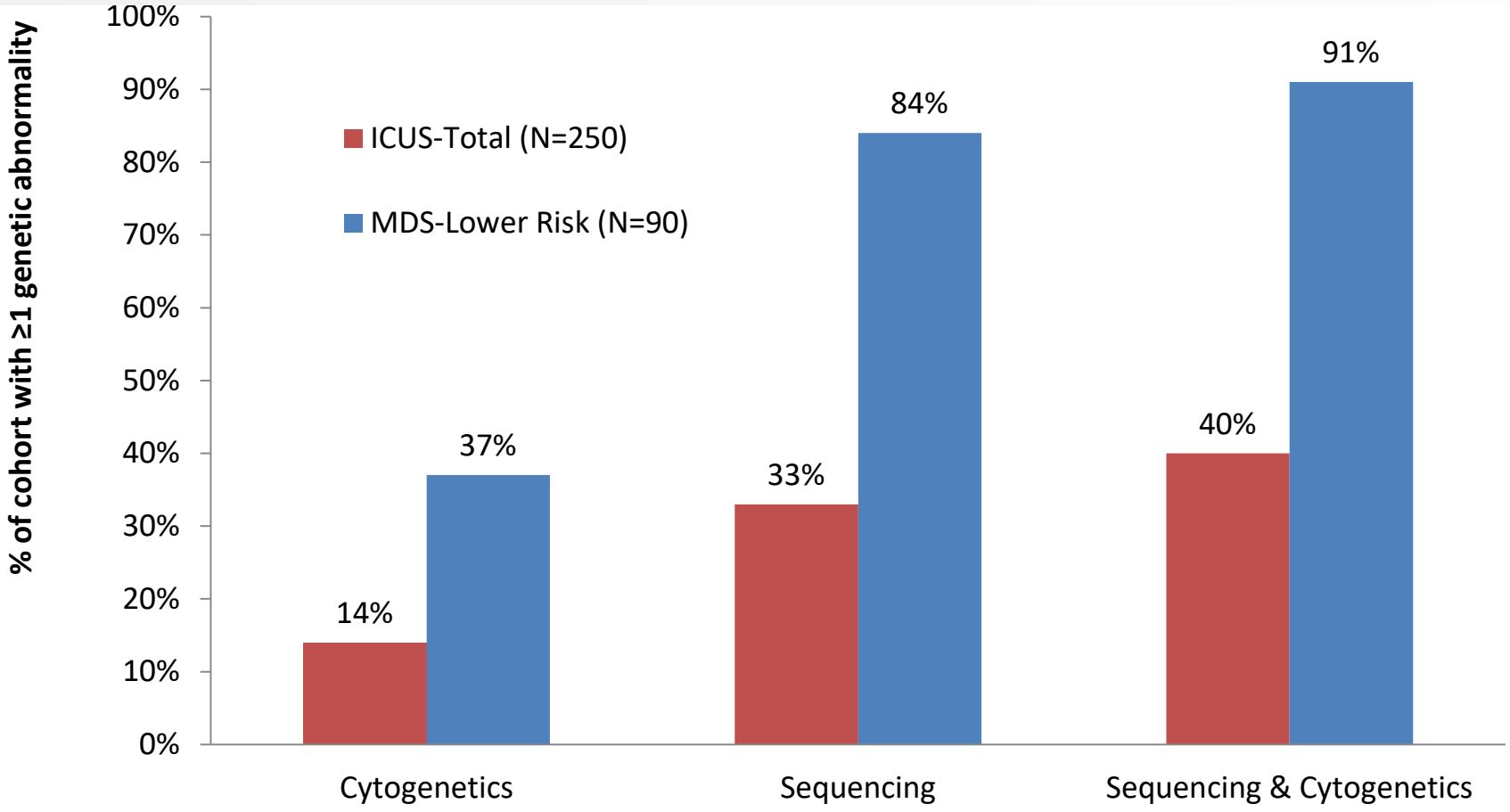


Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med.* 2013;369(25):2379-2390.; Kiladjian JJ. The spectrum of JAK2-positive myeloproliferative neoplasms. Hematology Am Soc Hematol Educ Program. 2012;2012:561-6. ; Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. *Leukemia.* 2010;24:1128-1138.; Damm F, Itzykson R, Kosmider O, et al. SETBP1 mutations in 658 patients with myelodysplastic syndromes, chronic myelomonocytic leukemia and secondary acute myeloid leukemias. *Leukemia.* 2013;27:1401-1403.; Thol F, Suchanek KJ, Koenecke C, et al. SETBP1 mutation analysis in 944 patients with MDS and AML. *Leukemia.* 2013;27:2072-2075.; Tefferi A, Thiele J, Vannucchi AM, et al. An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. *Leukemia.* 2014;28:1407-1413.

MDS CLASSIFICATION

SOMATIC MUTATIONS INDICATIVE OF CLONAL HEMATOPOIESIS ARE PRESENT IN A LARGE FRACTION OF CYTOPENIC PATIENTS WHO LACK DIAGNOSTIC EVIDENCE OF MDS

Jeff M Hall[1], Jenan Al Hafidh[1], Emily Balmert[1], Bashar Dabbas[1], Christine Vaupel[1], Carlos El Hader[1], Matthew McGinniss[1], Shareef Nahas[1], Julie Kines[1], Sue Beruti[1], and Rafael Bejar[2]
[1]Genoptix, Inc., a Novartis company; [2]UC San Diego, San Diego, CA



Hall J, et al. ASH 2014, Abstract 3272

ANALYSIS

nature medicine

Age-related mutations associated with clonal hematopoietic expansion and malignancies

Mingchao Xie[1,2,7], Charles Lu[1,7], Jiayin Wang[1,2,7], Michael D McLellan[1], Kimberly J Johnson[3], Michael C Wendl[1,4,5], Joshua F McMichael[1], Heather K Schmidt[1], Venkata Yellapantula[1,2], Christopher A Miller[1], Bradley A Ozenberger[1,2], John S Welch[2,6], Daniel C Link[2,6], Matthew J Walter[2,6], Elaine R Mardis[1,2,4,6], John F Dipersio[2,6], Feng Chen[2,6], Richard K Wilson[1,2,4,6], Timothy J Ley[1,2,4,6] & Li Ding[1,2,4,6]

The NEW ENGLAND JOURNAL of MEDICINE

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., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhoum, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svantesson, M.S., Mikael Landén, Ph.D., Martin Höglund, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.

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Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

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Risk of acquiring mutations increases with age

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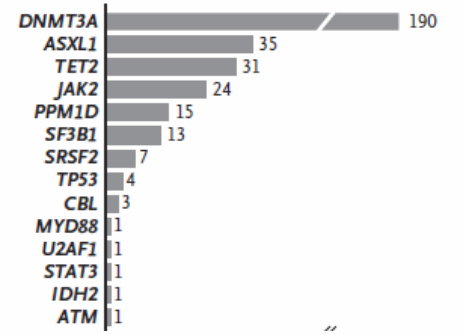

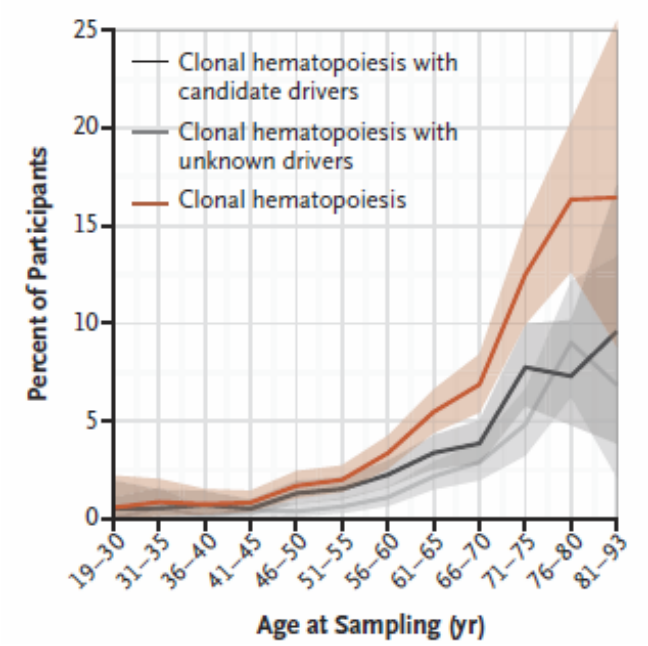

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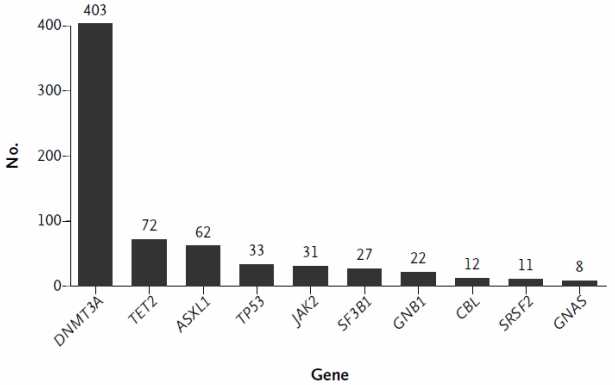

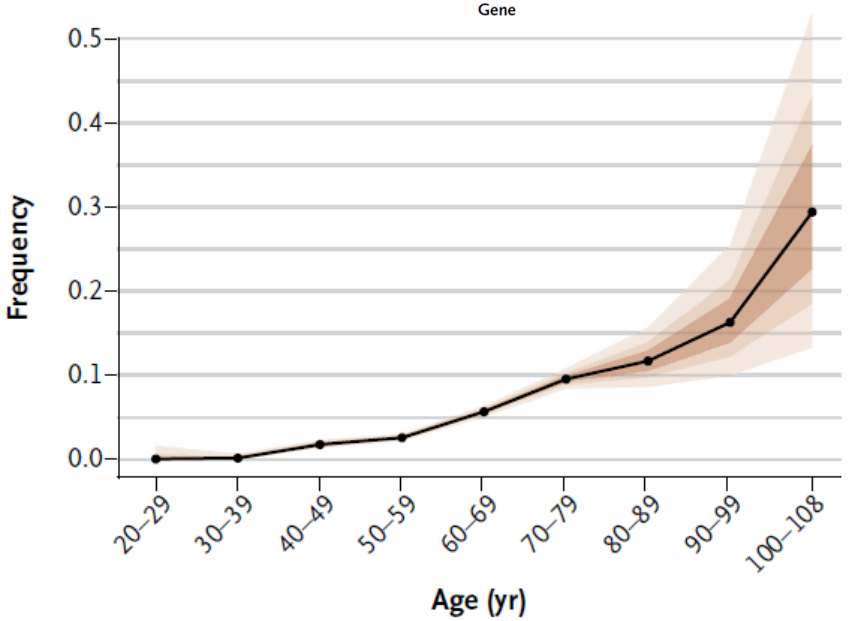

Allele frequency is rarely over 20%

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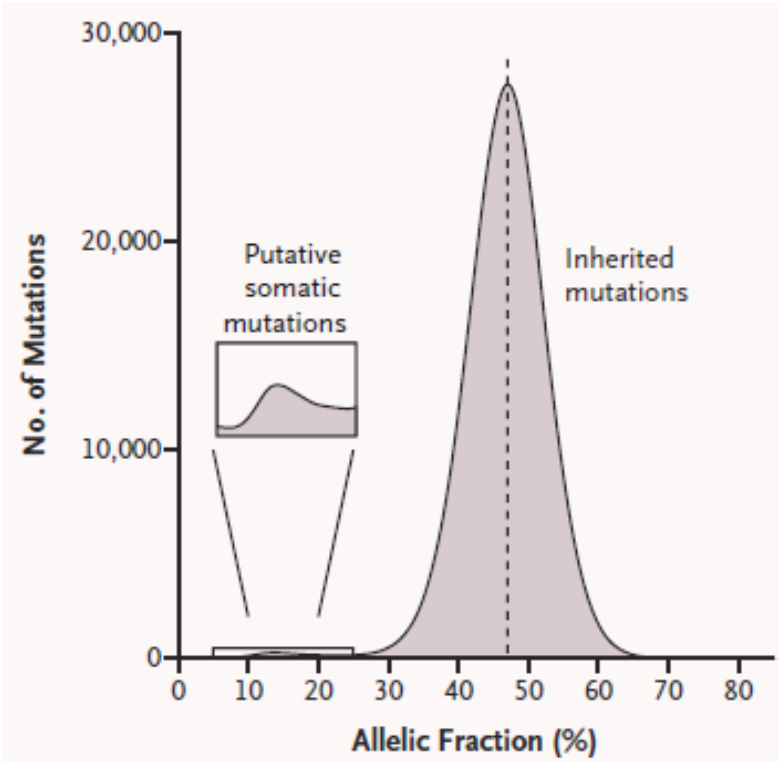

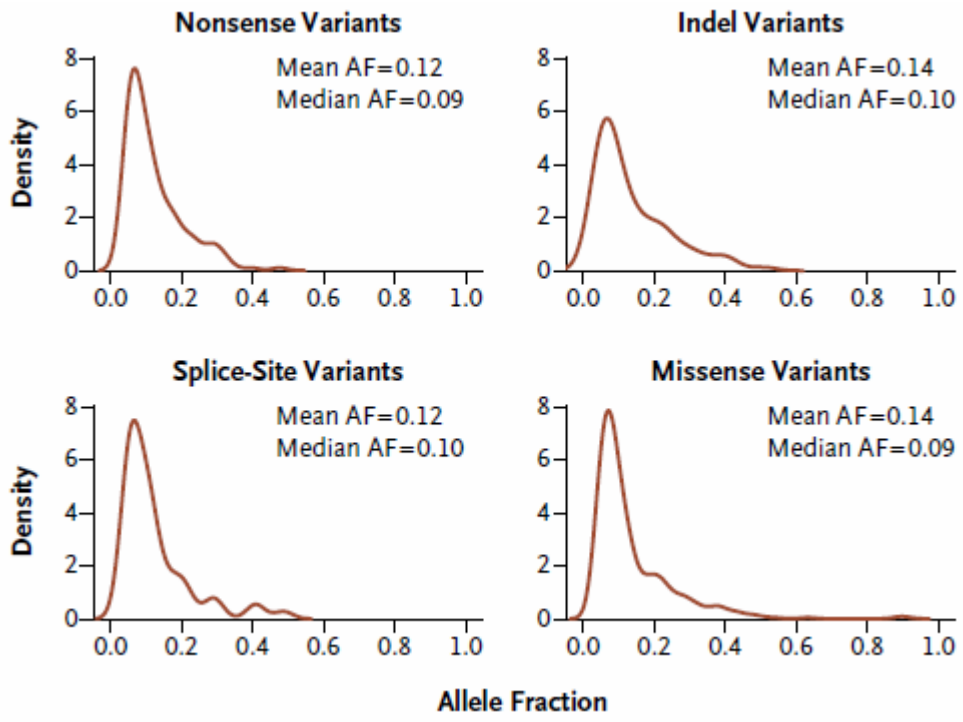

Acquisition of somatic clones is not benign

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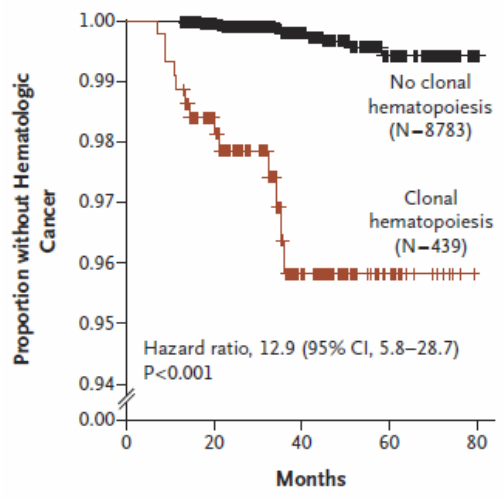

Category	No. of Patients	Hazard Ratio for Hematologic Cancer (95% CI)
No mutations	8783	1.00 (1.00–1.00)
One mutation	1122	0.47 (0.06–3.56)
Two mutations	237	1.99 (0.26–15.27)
CH-UD	170	11.34 (3.44–37.41)
CH-CD	269	13.73 (5.74–32.83)
CH	439	12.89 (5.78–28.72)

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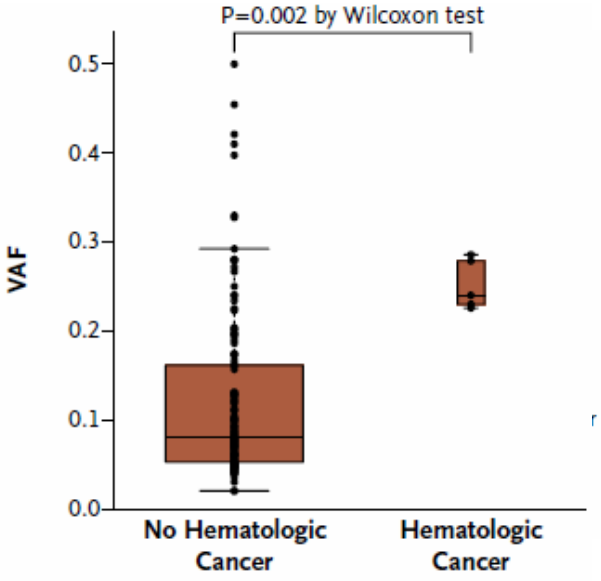
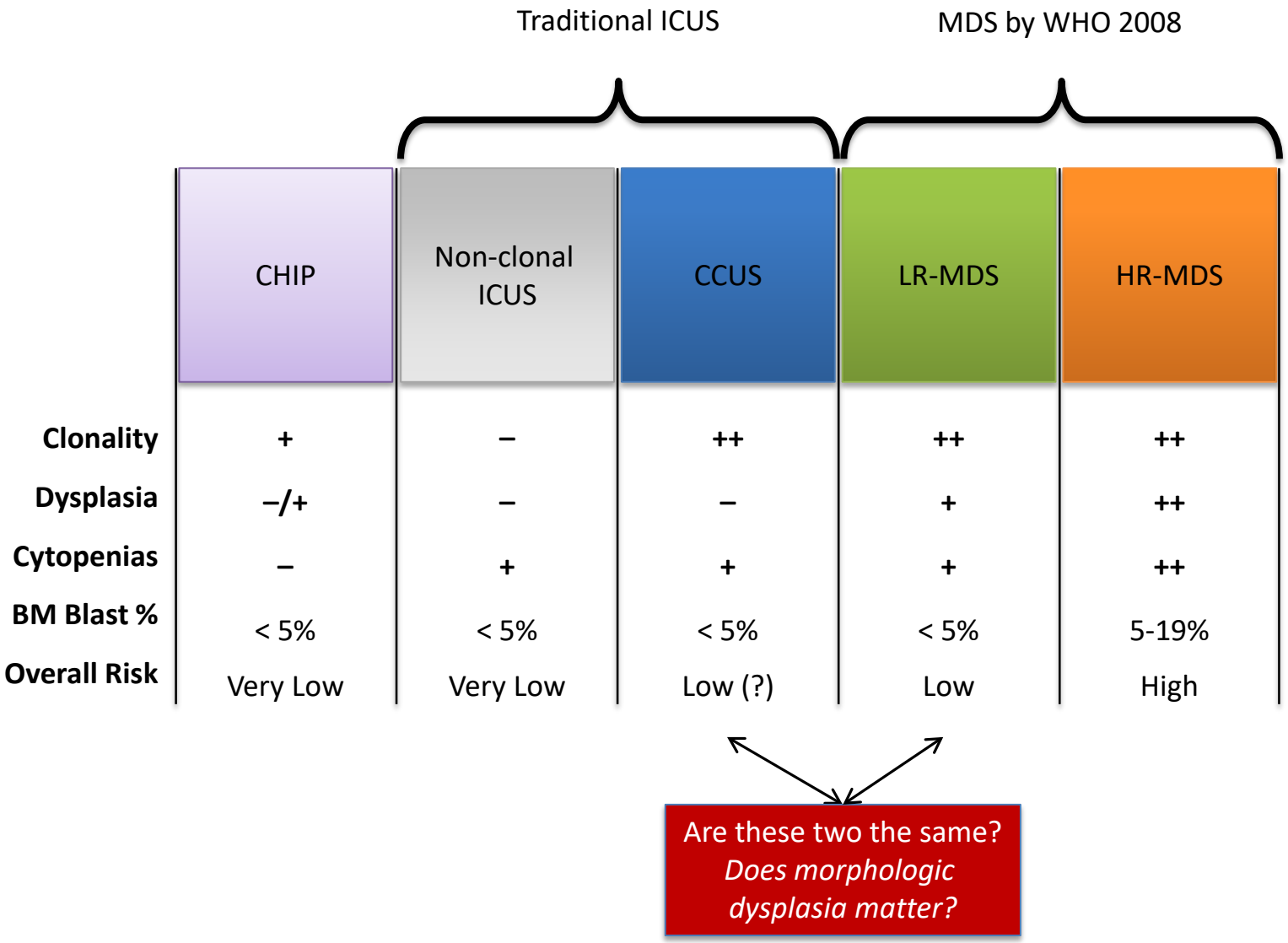


No mutation (referent)	11/3208		
JHS	10/2326		
MEC	1/882		
Mutation	5/134	11 (3.9–33)	<0.001
JHS	3/83	7.1 (2.0–25)	0.002
MEC	2/51	36 (4.9–270)	<0.001
Mutation, VAF ≥0.10	5/57	49 (21–120)	<0.001
JHS	3/34	21 (5.7–80)	<0.001
MEC	2/23	90 (29–280)	<0.001

How do we classify these patients?



CCUS = clonal cytopenias of undetermined significance; ICUS = idiopathic cytopenias of undetermined significance; CHIP = clonal hematopoiesis of indeterminate potential; LR = lower risk, HR = higher risk

New Proposed WHO classification

Table 1. Proposed nomenclature changes for MDS categories

Proposed Category	Current or prior WHO category
MDS with single lineage dysplasia (MDS-SLD)	Refractory cytopenia with unilineage dysplasia (RCUD; encompassing refractory anemia, refractory thrombocytopenia, and refractory neutropenia)
MDS with multilineage dysplasia (MDS-MLD)	Refractory cytopenia with multilineage dysplasia (RCMD)
MDS with single lineage dysplasia and ring sideroblasts (MD-RSSLD)	Refractory anemia with ring sideroblasts (RARS)
MDS with multilineage dysplasia and ring sideroblasts (MDS-RSMLD)	Refractory cytopenia with multilineage dysplasia and ring sideroblasts* (RCMD-RS)
MDS with excess blasts-1 (MDS-EB1)	Refractory anemia with excess blasts-1 (RAEB1)
MDS with excess blasts-2 (MDS-EB2)	Refractory anemia with excess blasts-2 (RAEB2)

* RCMD-RS was an entity in the 2001 WHO Classification, but was merged with RCMD in the 2008 Classification.

- Eliminate non-erythroid blast count if erythroid cells > 50%
- RS > 5% and SF3B1 mutation MDS-RS-SLD

ASH 2015 Educational book

MDS RISK STRATIFICATION

Impact of Mutations by IPSS Group

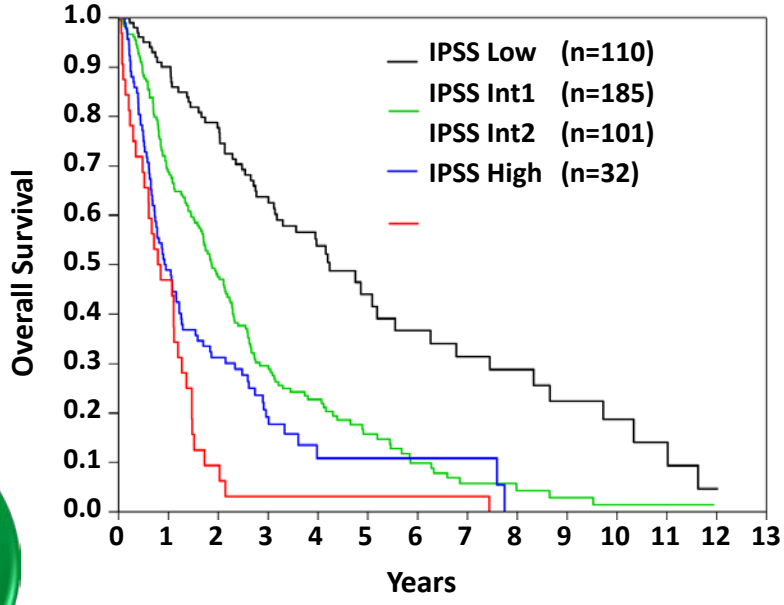
TP53

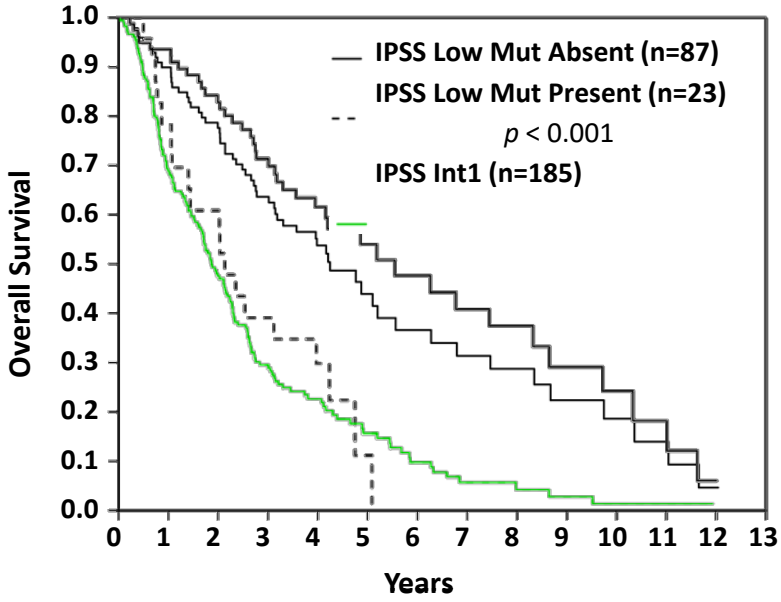
ETV6

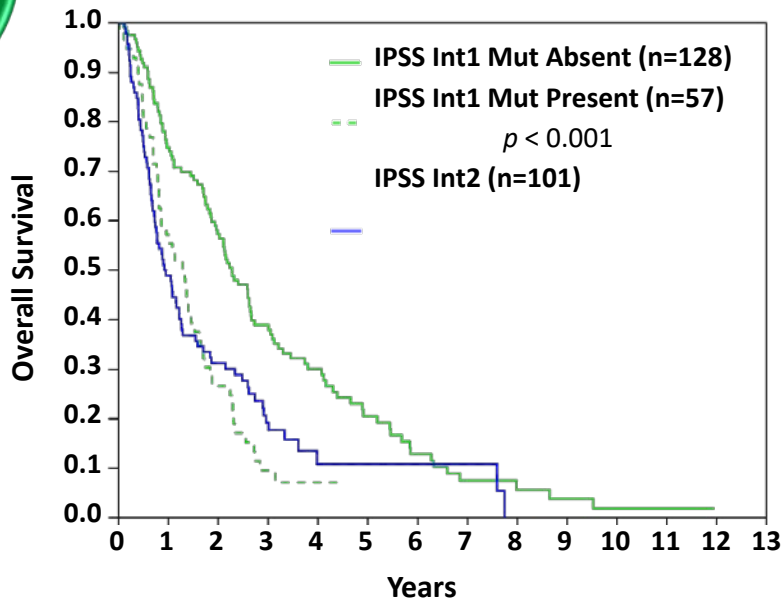
ASXL1

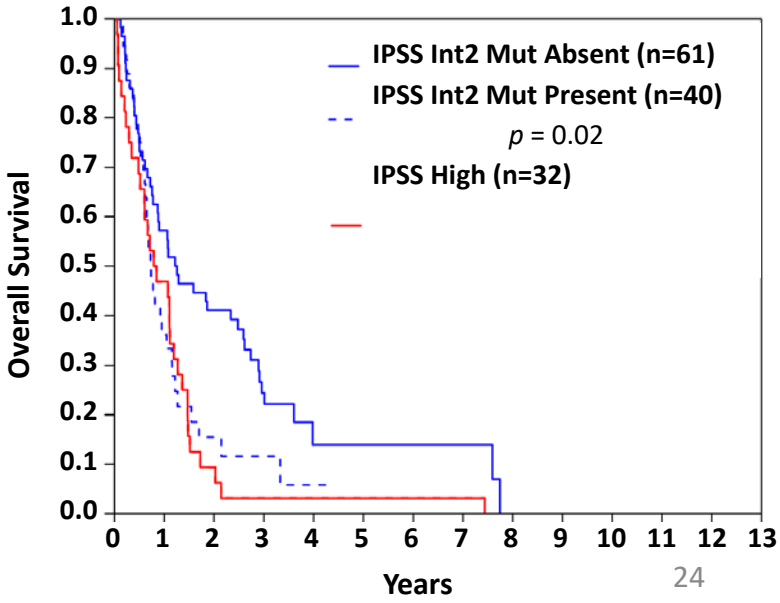
EZH2

RUNX1

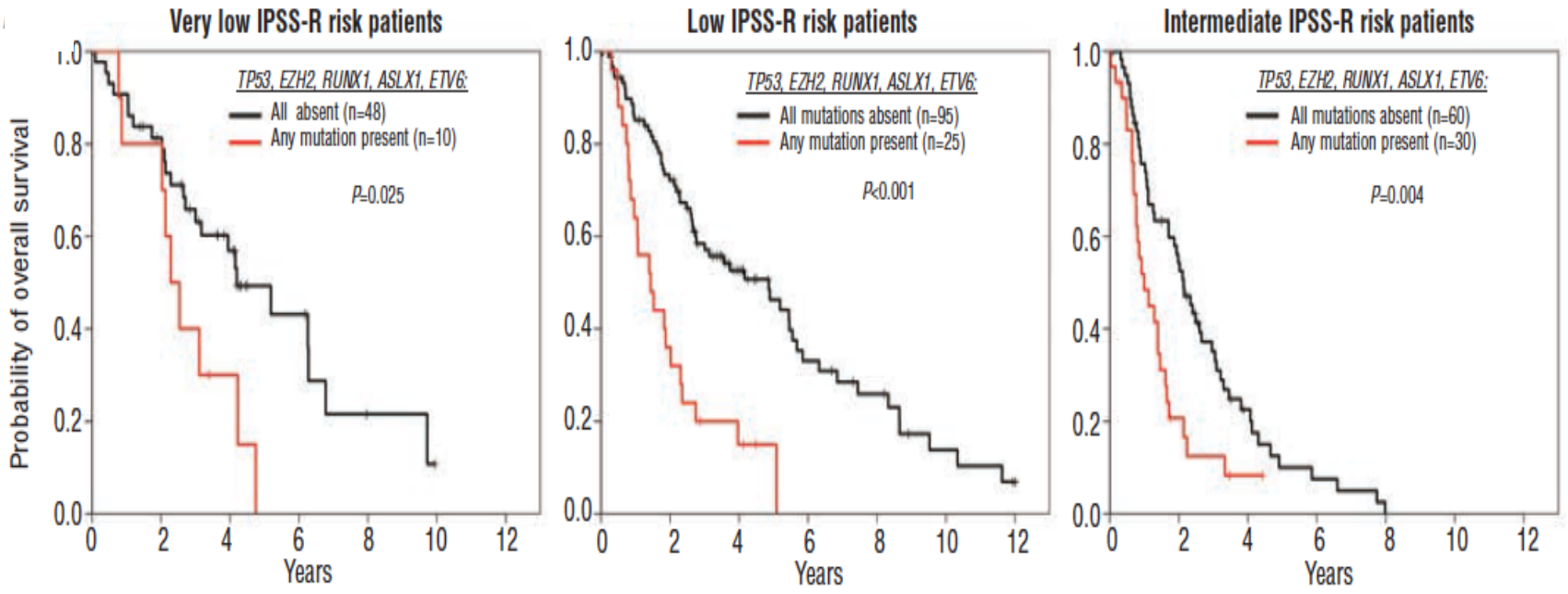








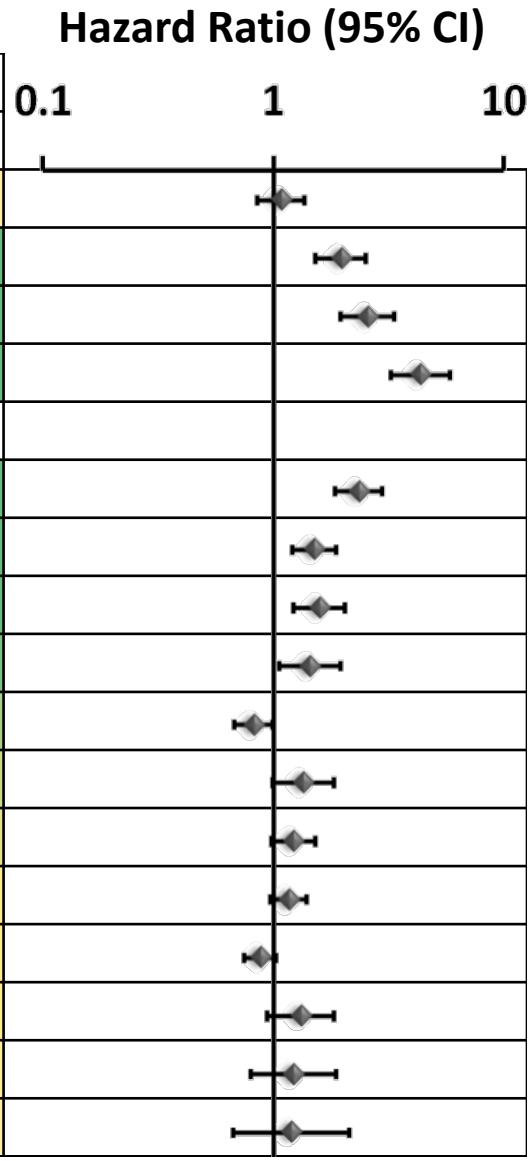
Somatic Gene Mutations Improve Precision of the IPSS-R



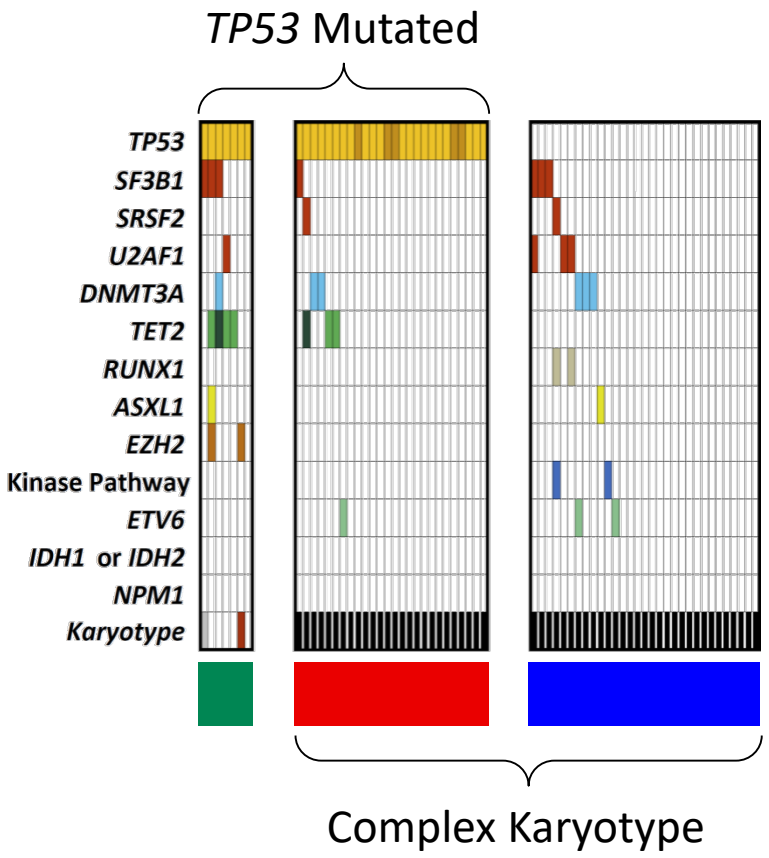
Bejar R. Haematologica 2014; 99: 956.

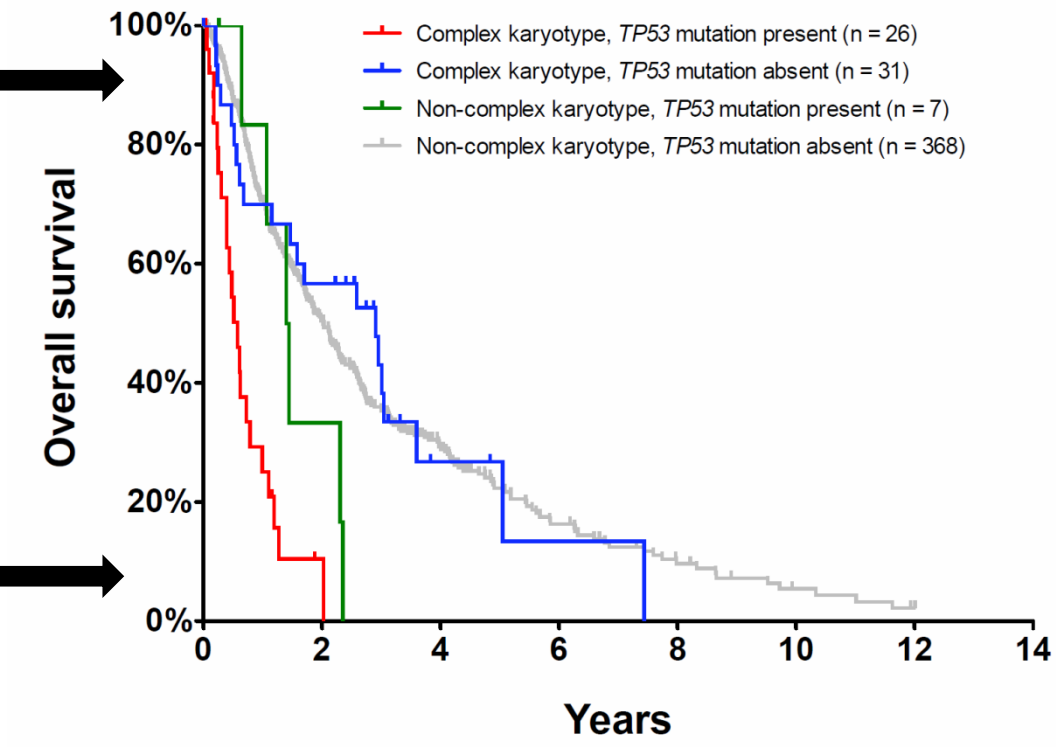
IWG Molecular analysis

	HR	*p*-value
IPSS-R Risk Groups (vs. Very Low)		
Low	1.08	0.542
Intermediate	1.97	<0.0001
High	2.56	<0.0001
Very High	4.36	<0.0001
Mutated Genes (vs. Unmutated)		
TP53	2.35	<0.0001
RUNX1	1.51	0.0002
EZH2	1.58	0.0006
NRAS	1.44	0.019
SF3B1	0.82	0.041
CBL	1.35	0.056
U2AF1	1.22	0.069
ASXL1	1.17	0.090
TET2	0.88	0.104
IDH2	1.31	0.111
KRAS	1.22	0.362
NPM1	1.2	0.546



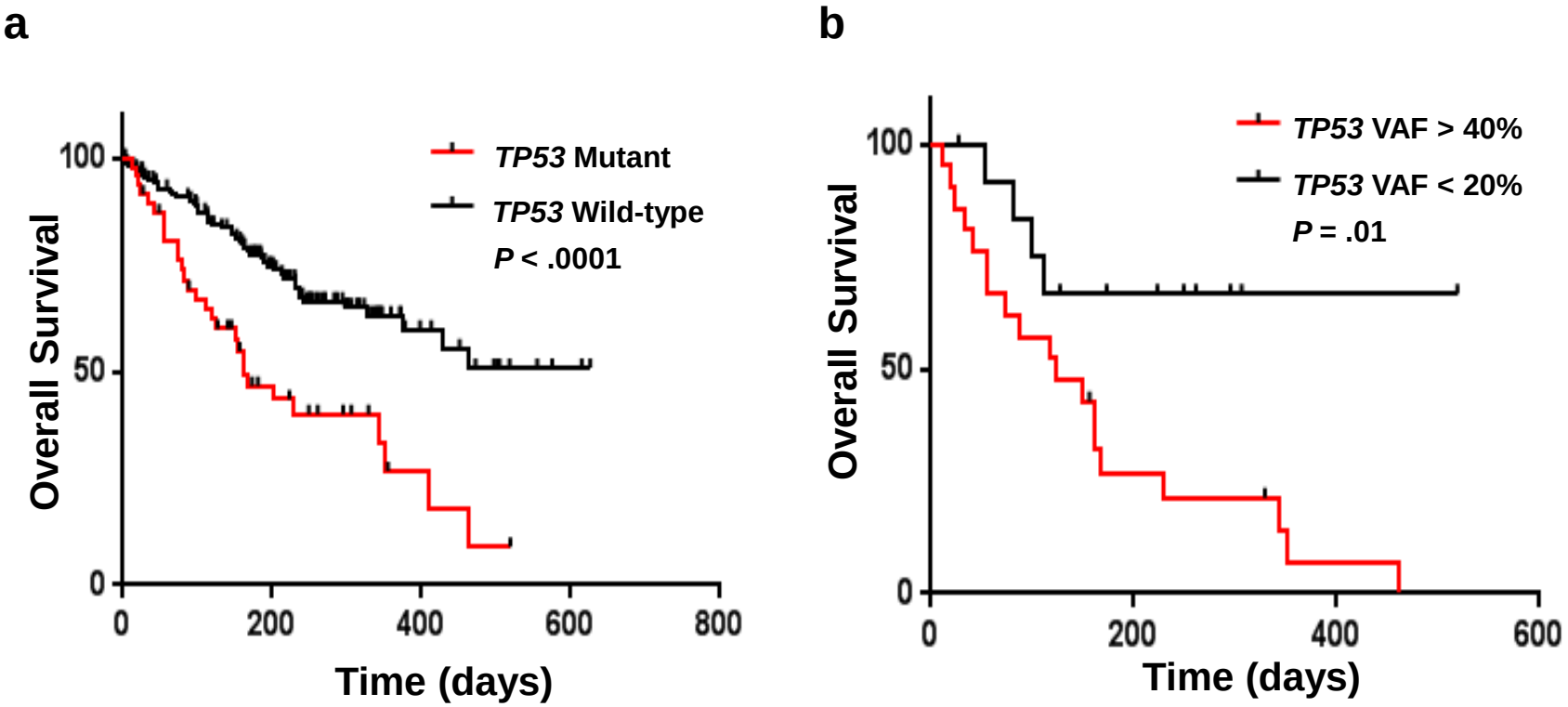
TP53 Mutations and Complex Karyotypes





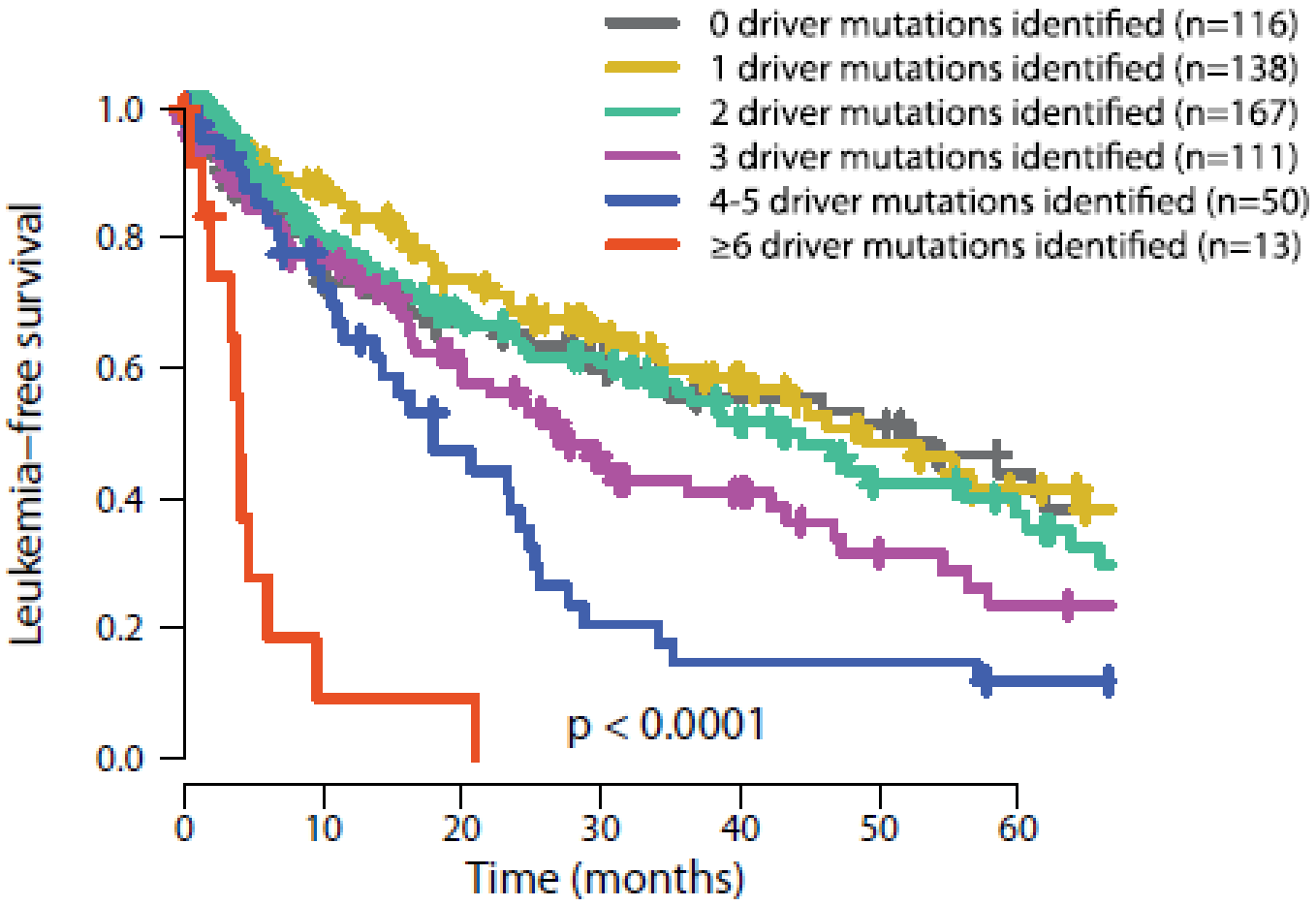
The adverse prognostic impact of the complex karyotype is entirely driven by its frequent association with mutations of *TP53*

Clonal burden of *TP53* Mutation Predicts for Inferior Survival



Sallman et al., Leukemia journal

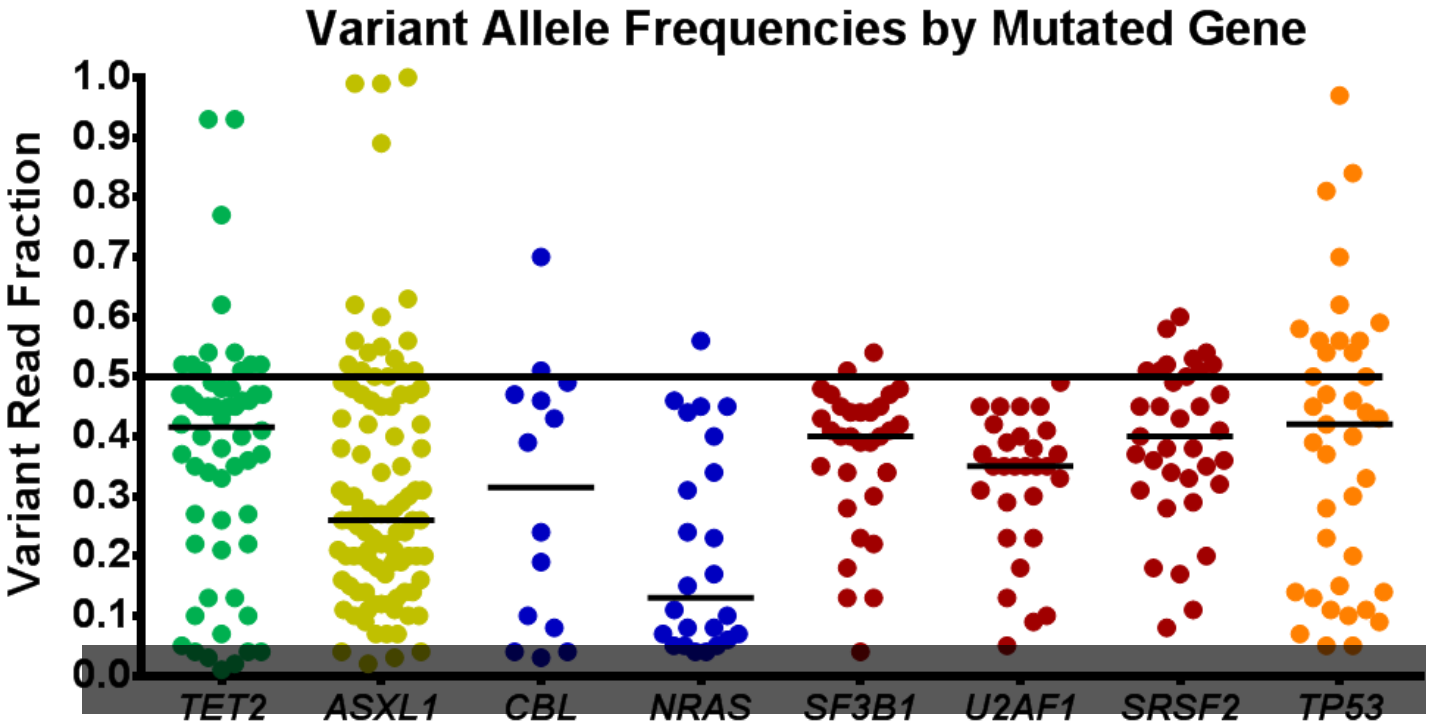
Number of Mutations and Prognosis



Papaemmanuil E, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013.

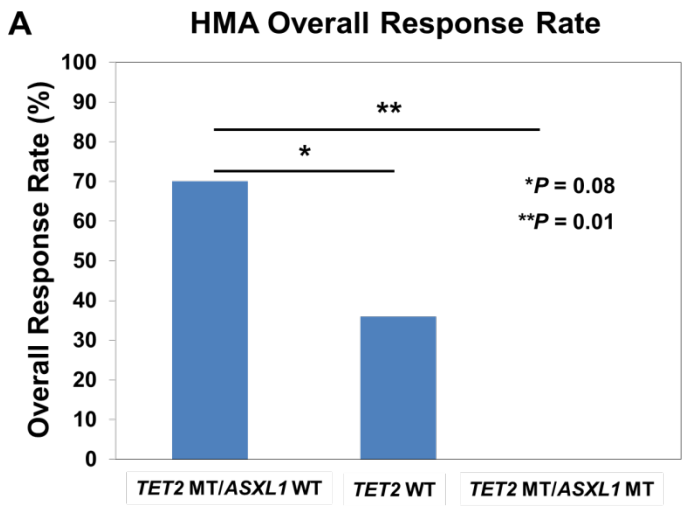
THERAPEUTIC IMPLICATIONS

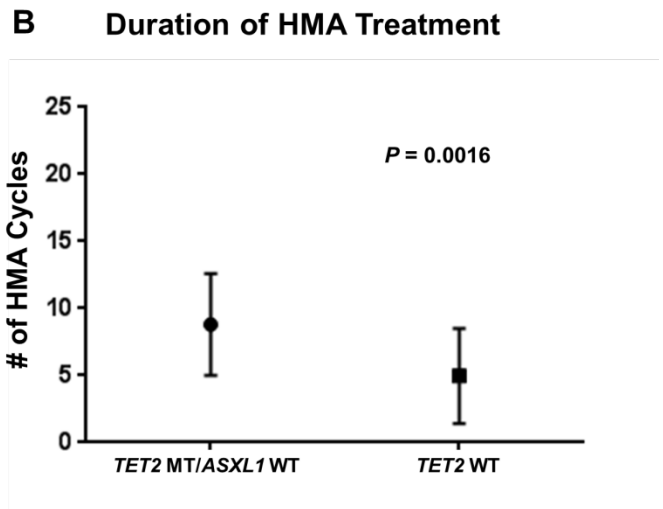
Response by Variant Abundance

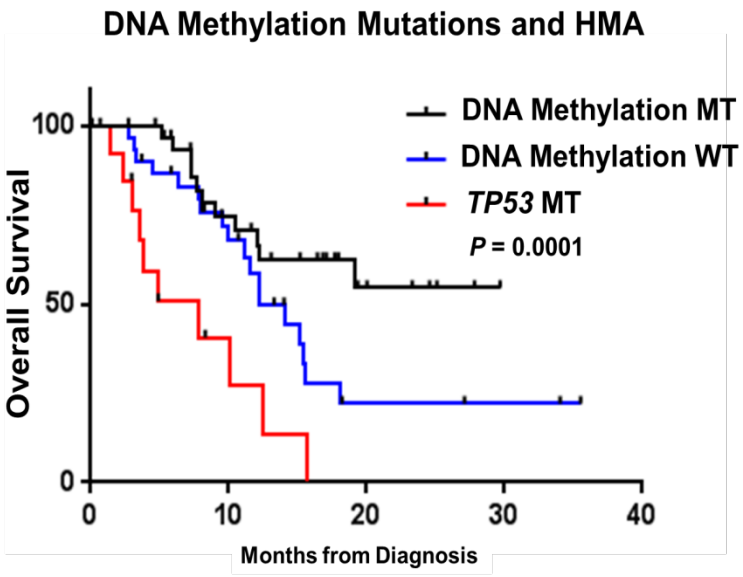


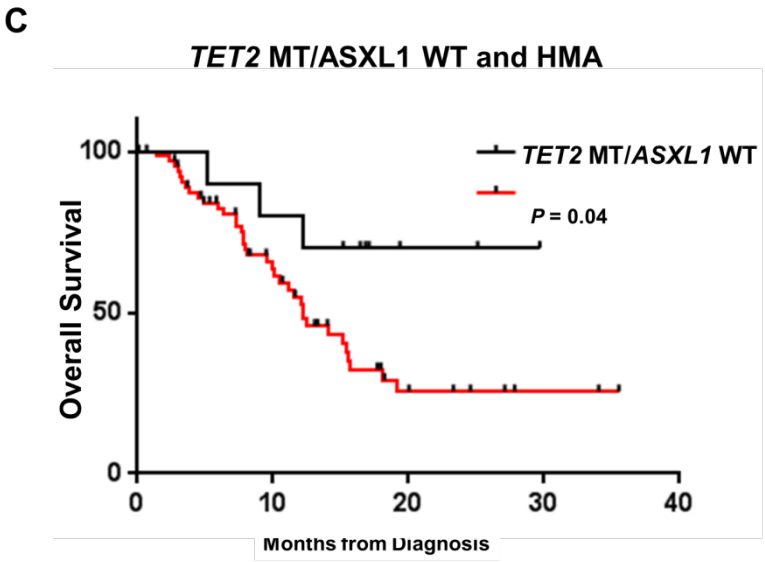
Gene (n) *VAF ≥ 0.1*	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
TET2 (50)	**1.99** (1.05, 3.80)	**0.036**	**1.98** (1.02, 3.85)	**0.044**
TET2 mut + *ASXL1* wt (23)	**3.65** (1.38, 9.67)	**0.009**	**3.64** (1.35, 9.79)	**0.011**

Can we tailor therapy accordingly?









Sallman, et. al. ASH 2016

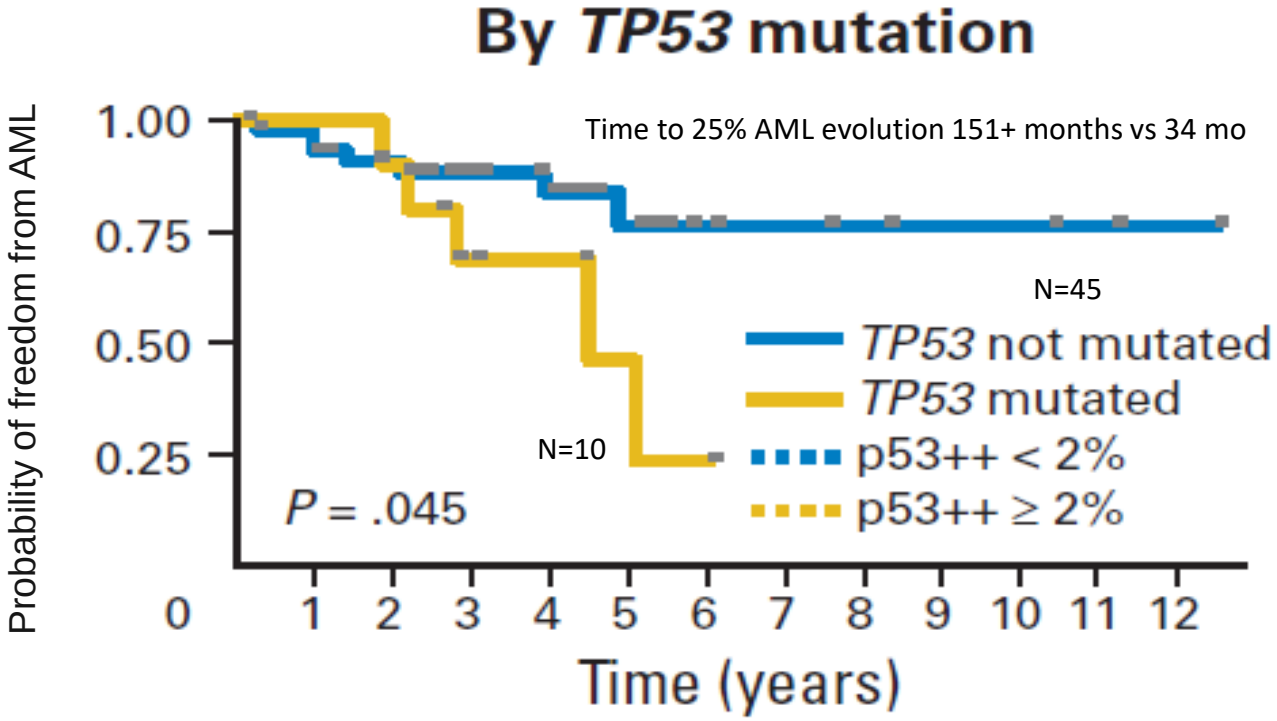
MDS with Founder *TP53* Mutations are Highly Responsive to Decitabine

- **Welch JS, et. al. *NEJM* 2016; 375:2023.**
  - 116 MDS/AML treated with decitabine 20 mg/m^2/d x 10d q 28d
  - exome sequencing pretreatment & serially
  - Higher ORR in *TP53* mutant vs. Wt (21/21 [100%] vs. 32/78 [41%], *P* <0.001)
  - CR/Cri higher in *TP53* mutant vs. Wt (13/21 [62%] vs. 26/78 [33%], *P*=0.04)

- **Chang CK, et. al. *Brit J Haematol* 2016; Epub.**
  - 109 MDS treated with decitabine 20 mg/m^2/d x 5d q 28d
  - exome sequencing pretreatment
  - CR rate higher in *TP53* mutant vs. Wt (10/15 [66.7%] vs. 20/94 [21%], *P* =0.001)
  - No difference in ORR (*TP53* mutant, 11/15 [73%] vs. 63/94 [67%] Wt)
  - Poor OS in *TP53*$_{mu}$ MDS (median, 14 vs. 39 mos; *P*=0.012)

Probability of AML Progression in Low/Int-1 del(5q) MDS by *TP53* mutation

[n=55]



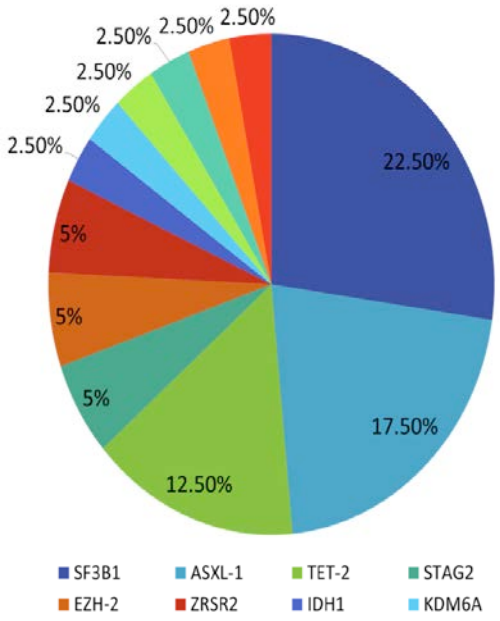
Median follow-up: 40 months
Progression = blasts >10% or complex karyotype.

- TP53 with median clone size of 11% was detected in 18% of pts.
- 5 out of 12 patients who progressed to AML had TP53 mutation.
- 8 out of 10 mutated Tp53 patients received lenalidomide where a trend toward AML progression was noted.
- no complete CCR observed among p53 mutated pts.

Jädersten M, et. al. JCO April 2011 epub

Somatic Gene Mutations (SGM) as Biomarkers for Response to Immunosuppressive Therapy (IST)

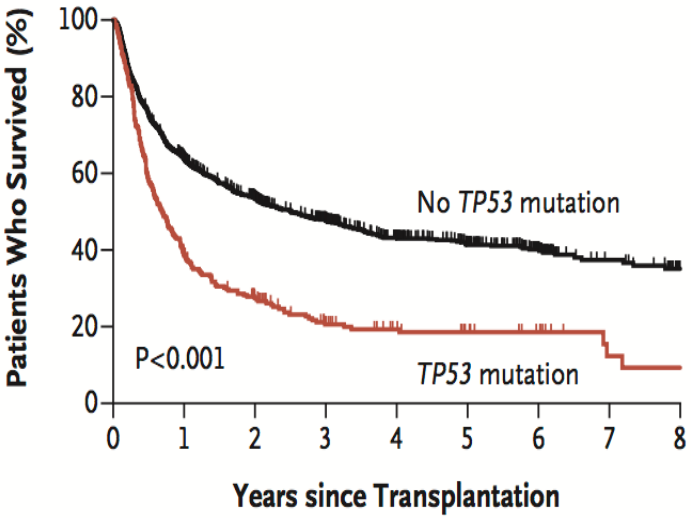
- Independent clinical covariates for response to ATG ± CsA include age, HLA-DR15^{+} & duration of transfusion dependence in the NIH model
- 66 IPSS Low/Int risk MDS pts treated with ATG ± CsA with 42% (n=28) ORR
- No SGM in detected 50% of patients.
- Absence of SGM associated with higher **IST ORR** (**70% vs 40%**, *P*=0.16) with a mean response duration of 12 mos in SGM^{-} vs 9 mos in SGM^{+}pts (*P*=0.09).
- *SF3B1* mutation was associated with **IST nonresponse (11% *SF3B1Mu*$^{+}$ vs 68% WT, p=0.01**)
- Rate of **AML transformation** in pts with non-*SF3B1* SGM > SGM^{-}, p=0.023 with reduced OS.



Komrokji R, et al. ASH 2015; 1664a.

Impact of *TP53* Mutation & Age on AlloHCT

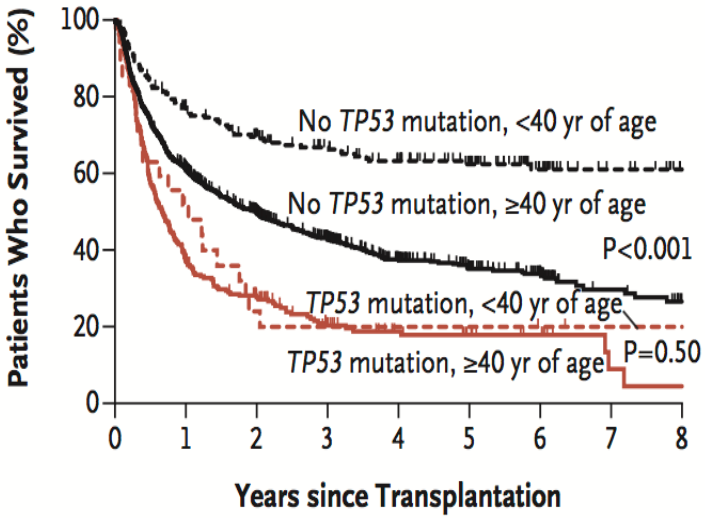
OS by TP53 Mutation Status & Age



No. at Risk

No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

OS by TP53 Mutation



No. at Risk

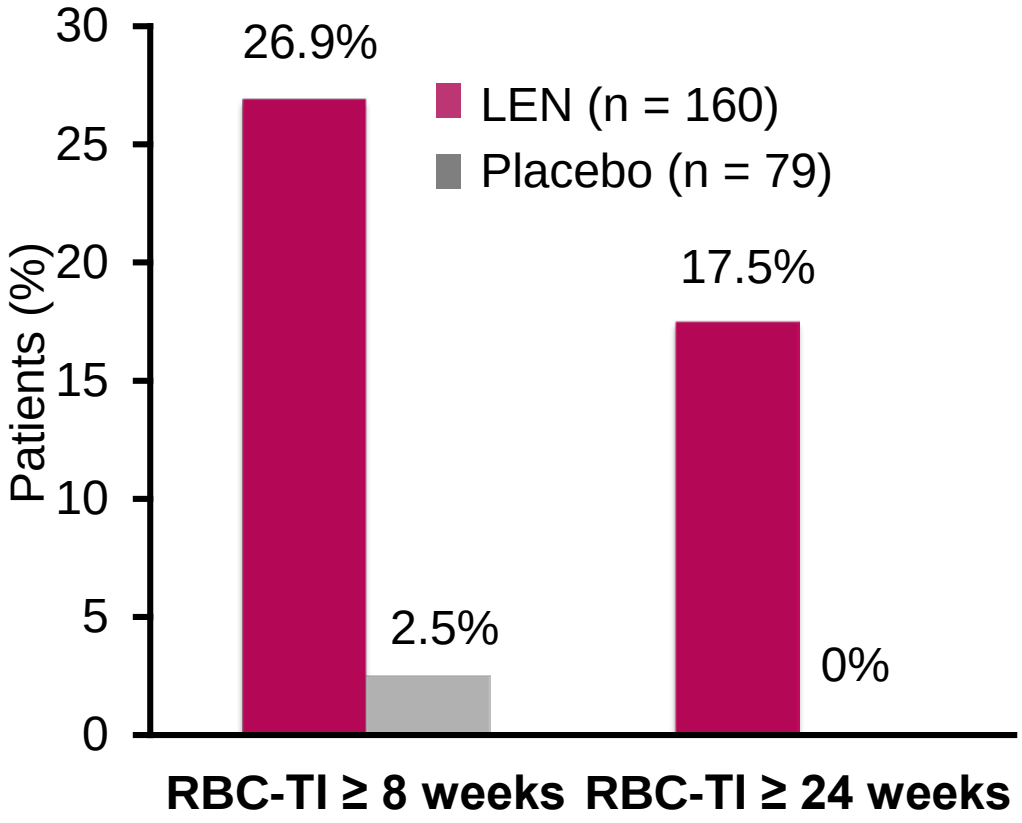
No *TP53* mutation									
<40 yr of age	214	159	133	115	100	78	42	23	13
≥40 yr of age	1010	598	396	255	161	105	67	30	19
TP53 mutation									
<40 yr of age	27	14	7	5	5	5	4	4	3
≥40 yr of age	262	95	59	34	21	15	10	3	2

Lindsley RC, et. al. NEJM 2017; 376: 536.

LRMDS

Would you use lenalidomide or HMAs?

Lenalidomide



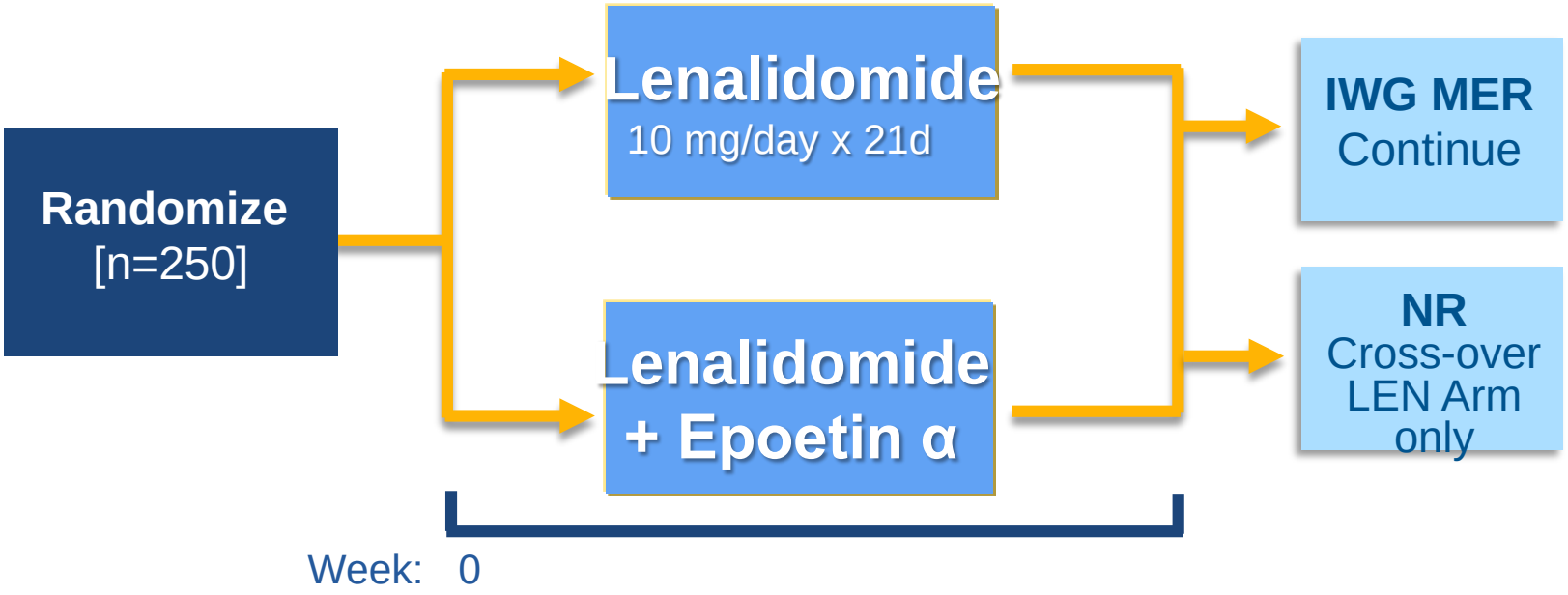
Median duration of response 32.9 weeks (95%CI, 20.7–71.1) among RBC-TI ≥ 8 weeks

Azacitidine

Lineage HI in Evaluable Pts,* n/N (%)	5-2-2 (n = 50)	5-2-5 (n = 51)	5d (n = 50)
Erythroid $_{Ma}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	12/24 (50)	12/22 (55)	15/25 (64)
Platelet$_{Ma}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
Neutrophi l$_{Ma}$	4/23 (17)	4/23 (17)	9/24 (38)

Santini V, et al. JCO 2016; Lyons RM, et al. J Clin Oncol. 2009;27:1850-1856.

Phase III Intergroup Study of Lenalidomide ± Epoetin Alpha After ESA Failure [ECOG 2905]



- Eligibility: Low/Int-1 IPSS, ESA failure or low response profile, Hgb <9.5 g/dL
- Stratification: serum EPO (> vs. <500mU/ml), prior ESA (EA vs. DA vs. None)
- Epoetin alfa 60,000 units SC weekly
- Primary Endpoint (EP): MER
- Secondary EP: Time to MER, MER duration, LEN cross-over response, candidate response biomarkers (CD45 isoform profile)

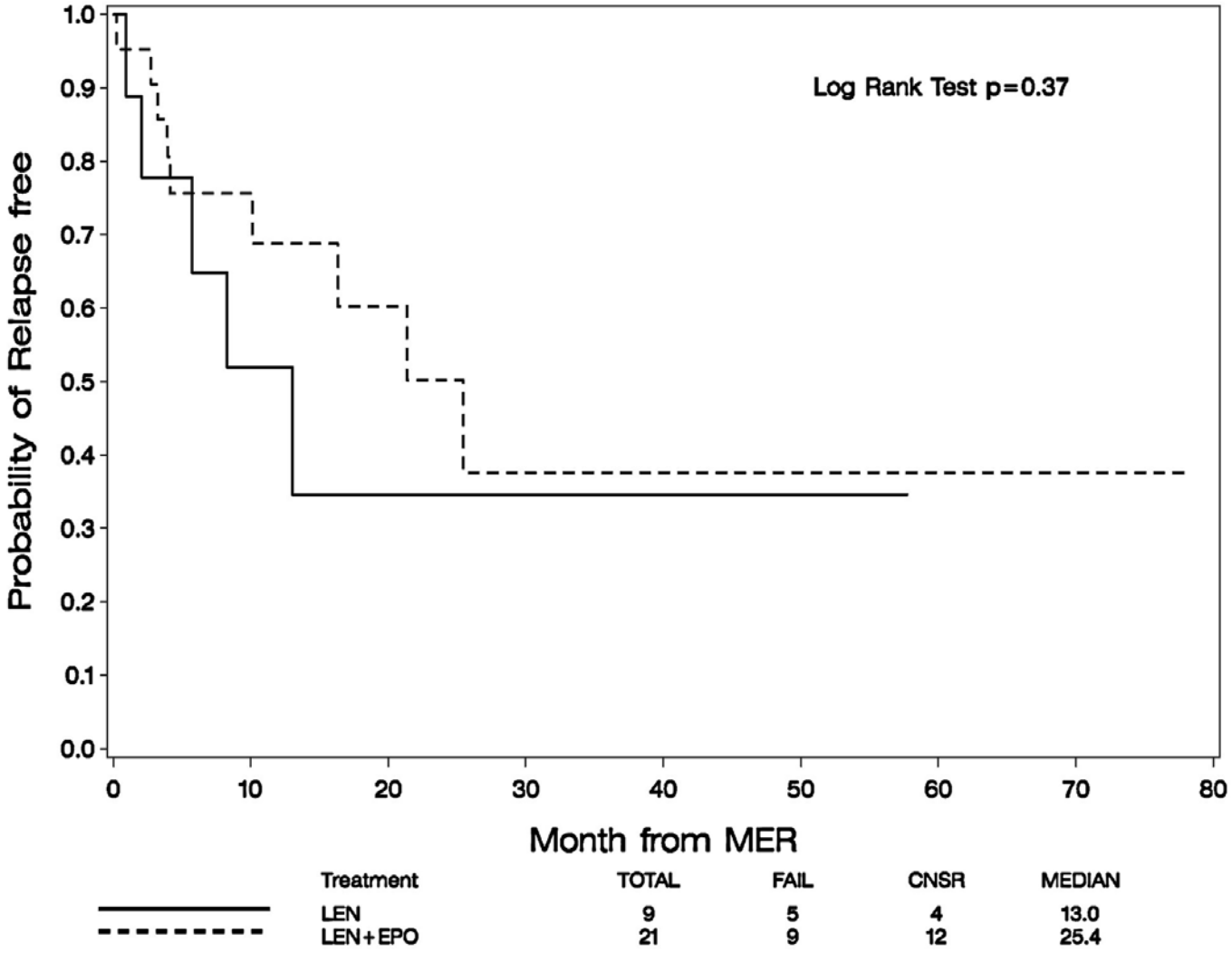
List A, et. al. ASH 2016; #223a.

Response Analysis

Response & Cohort	Arm A (%) LEN	Arm B (%) LEN+Epo	*P* value
ITT Analysis [n=163]	N=81	N=82	
MER	9 (11.1)	21 (25.6)	*P*=0.025
Minor ER	15 (18.5)	13 (15.9)	P=0.68
Overall ER	24 (29.6)	34 (41.5)	P=0.14
Arm A Crossover MER	N=34	7 (21%)	
Week 16 Evaluable [n=117]	N=56	N=60	
MER	8 (14.3)	20 (32.8)	*P*=0.029
Minor ER	13 (23.1)	13 (21.3)	P=0.83
Overall ER	21 (37.5)	33 (54.1)	P=0.09

List A, et. al. ASH 2016; #223a.

Duration of MER



List A, et. al. ASH 2016; #223a.

Low-Dose HMAs in LR MDS: Response Rates

Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	*P* Value
ORR	70	49	.03
▪CR	37	36	.90
▪mCR	9	5	NR
▪HI	24	8	NR
▪SD	26	44	NR
▪PD	4	8	NR
CCyR	25	6	.12
PCyR	36	19	
▪CCyR + PCyR	61	25	.02

*Median treatment cycles (range): 9 (1-41).

Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	*P* Value
Blasts ≥ 5%	(n = 21)	(n = 11)	
▪ORR	100	36	< .001
▪CR	52	18	.06
Blasts < 5%	(n = 45)	(n = 27)	
▪HI - ≥ 1 lineage	36	48	.29
▪HI - all lineages	22	26	.72
TI at response	32	16	.20

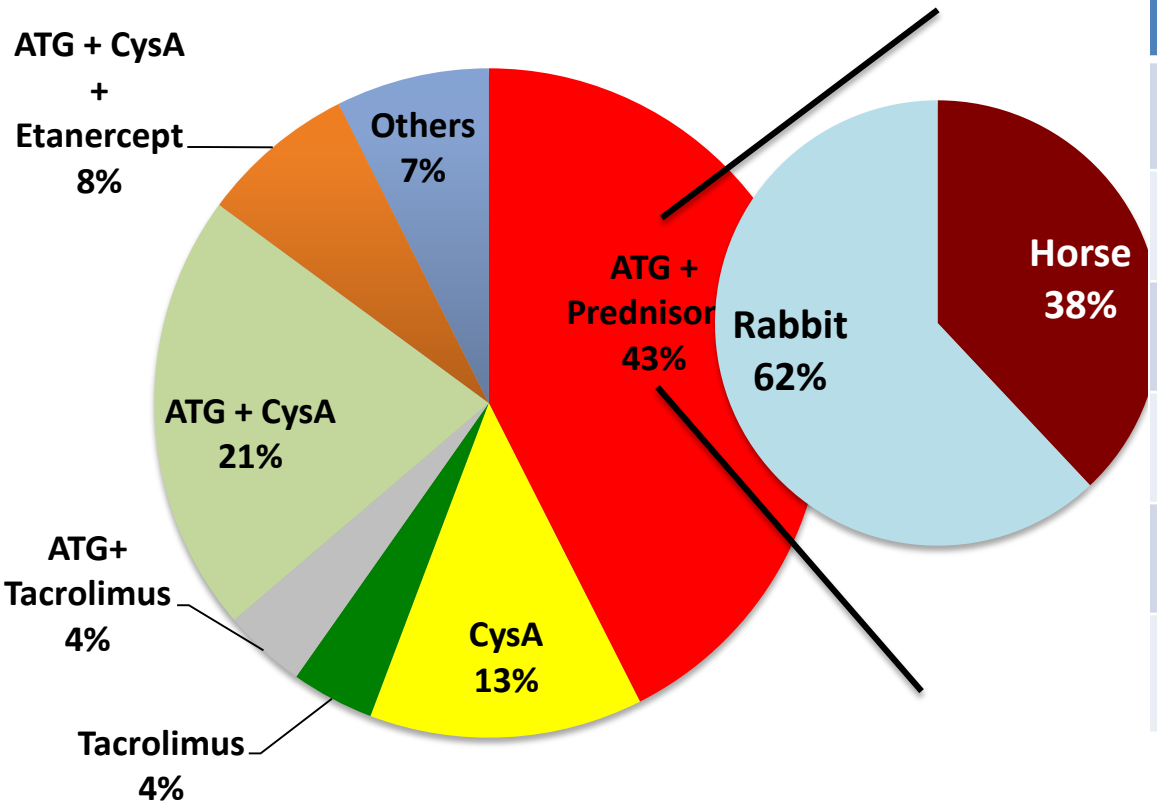
- Strongest predictors of response included BM blasts ≥ 5%, MDS/MPN or CMML diagnosis, high MDA LR MDS score, and IPSS intermediate-1 risk

Jabbour EJ, et al. ASH 2016. Abstract 226.

Slide credit: clinicaloptions.com

Type of IST used (N=217) and responses

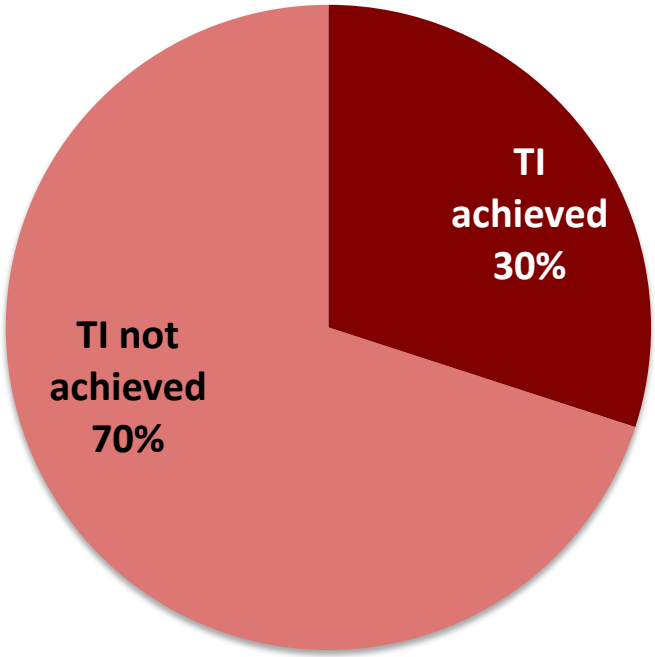
Prednisone only: 150 (41%) patients -> Excluded from analysis

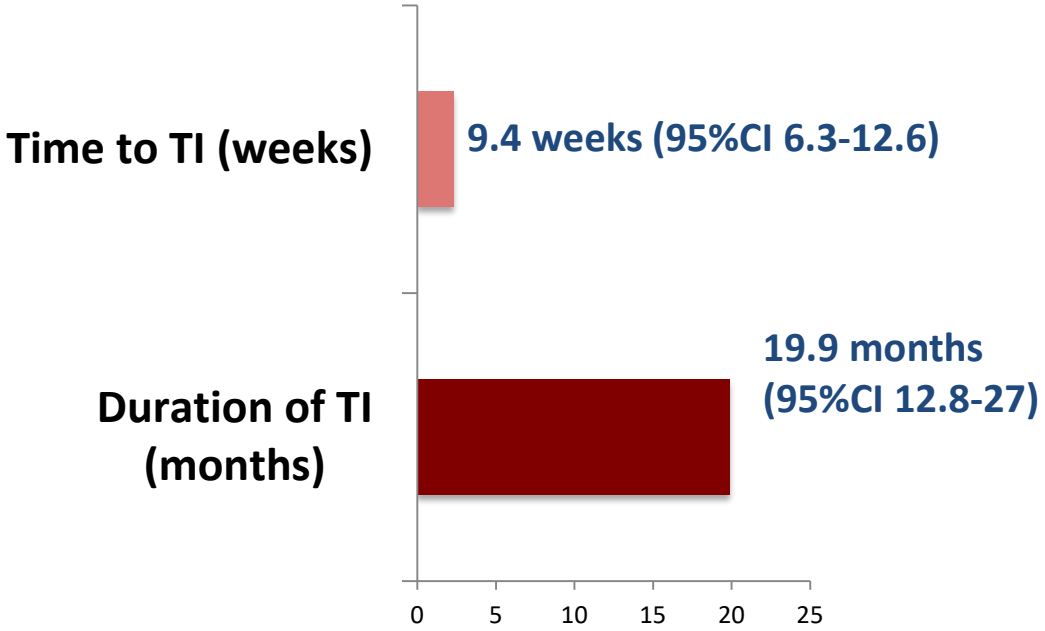


Response	%	95%CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR	48.8	39.8-57.9

Stahl M et al. ASH 2017 [Abstract # 422]

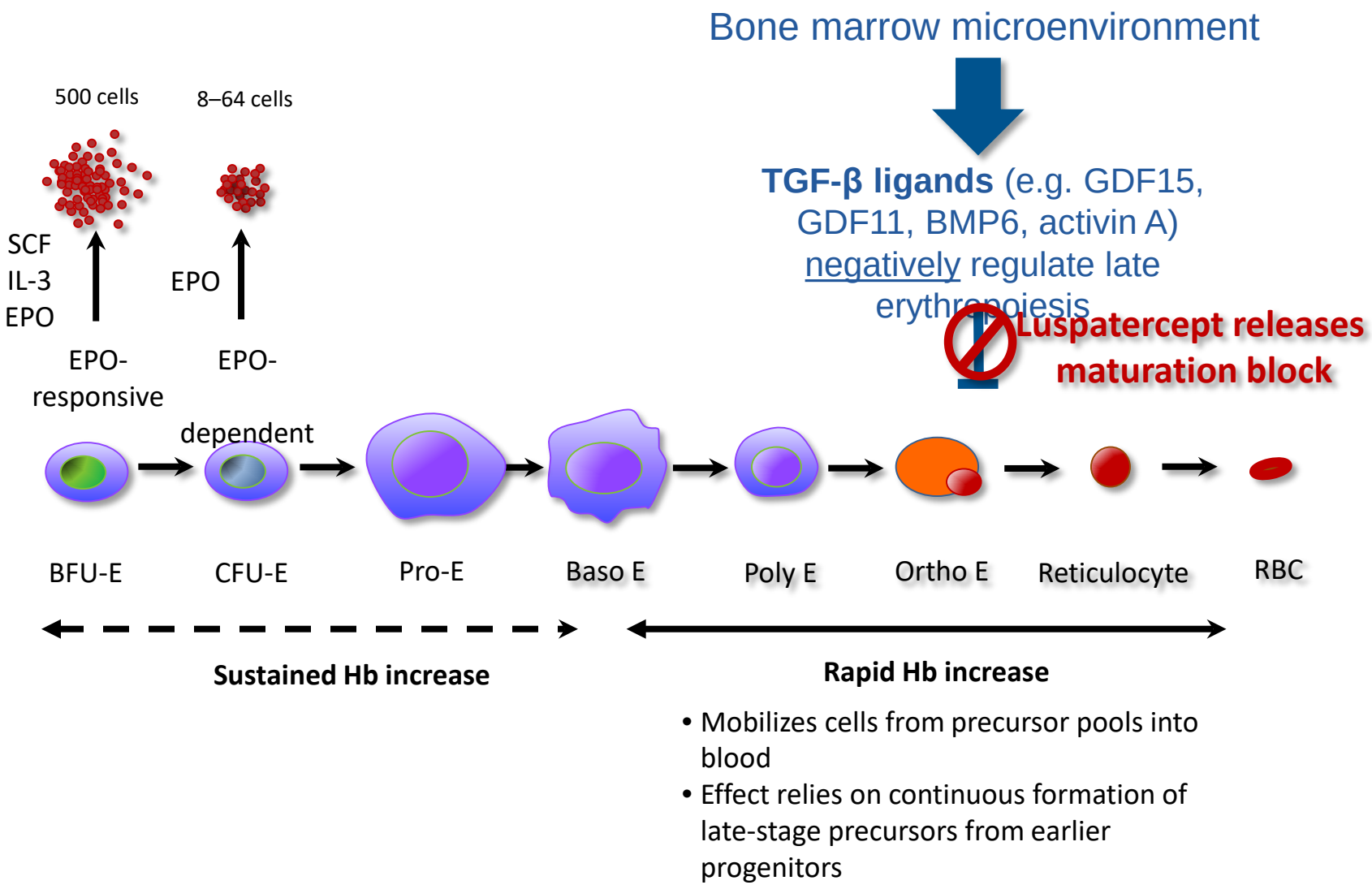
Transfusion independence (TI)





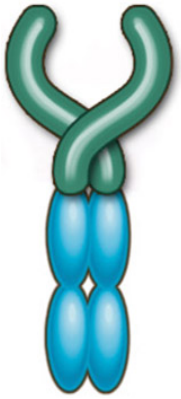
Stahl M et al. ASH 2017 [Abstract # 422]

Excess Smad2/3 Signaling Suppresses Late-Stage RBC Maturation in MDS



ACE-011 (Sotatercept) and ACE-536 (Luspatercept)

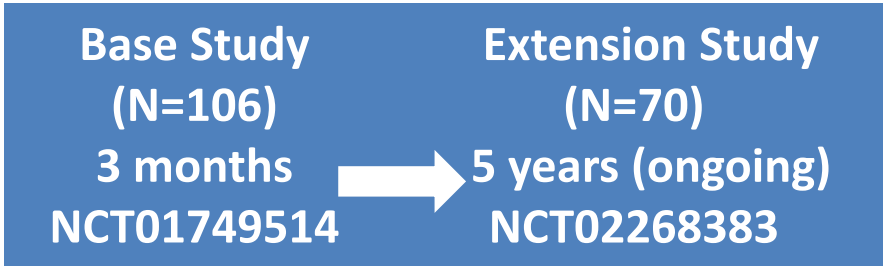
Novel Ligand Traps for TGFβ Superfamily Ligands

	ACE-011 (Sotatercept)	ACE-536 (Luspatercept)
Fusion protein with ligand trap activity	 Extracellular Domain of **ActRIIA**	 Modified Extracellular **ActRIIB** Domain
Receptor ligand interaction	GDF11, Activin-A	GDF11, GDF8, Activin-B, BMP6, BMP10
Heme effect	+	+
Bone effect	+	−

Suragani R, et. al. Nat Med 2014; 20: 408.

Luspatercept PACE-MDS Phase 2 Clinical Trials Overview

A Phase 2, multicenter, open-label, 3-month dose-escalation study in adults with lower-risk MDS followed by a 5-year extension study



Patient Population	**Efficacy Endpoints**

Multiple cohorts enrolling low/intermediate-1 risk (IPSS) MDS patients including:
• Non-transfusion dependent and transfusion dependent patients
• ESA-naïve and ESA-experienced patients
• Patients with a range of baseline EPO levels
• RS+ and non-RS patients
	• IWG (2006) HI-E:
	  • Hb increase ≥ 1.5 g/dL for all values over 8 weeks for patients with < 4 units/8 wk and Hb < 10 g/dL
	  • ≥ 4 RBC unit decrease over 8 weeks for patients with ≥ 4 units/8 wk

Treatment	**Other Efficacy Endpoints**
• Luspatercept 0.125 – 1.75 mg/kg (base study); 1.0 – 1.75 mg/kg (extension) SC q3 weeks • All patients followed up for 2 months post last dose or early discontinuation	• RBC-TI: RBC-transfusion independence ≥ 8 weeks (RBC evaluable patients, ≥2U/8 weeks) • Time to/duration of HI-E response

Platzbecker U et al. ASH 2017 [Abstract # 2982]

IWG HI-E and RBC-TI Response Rates by ESA, EPO, RS Status

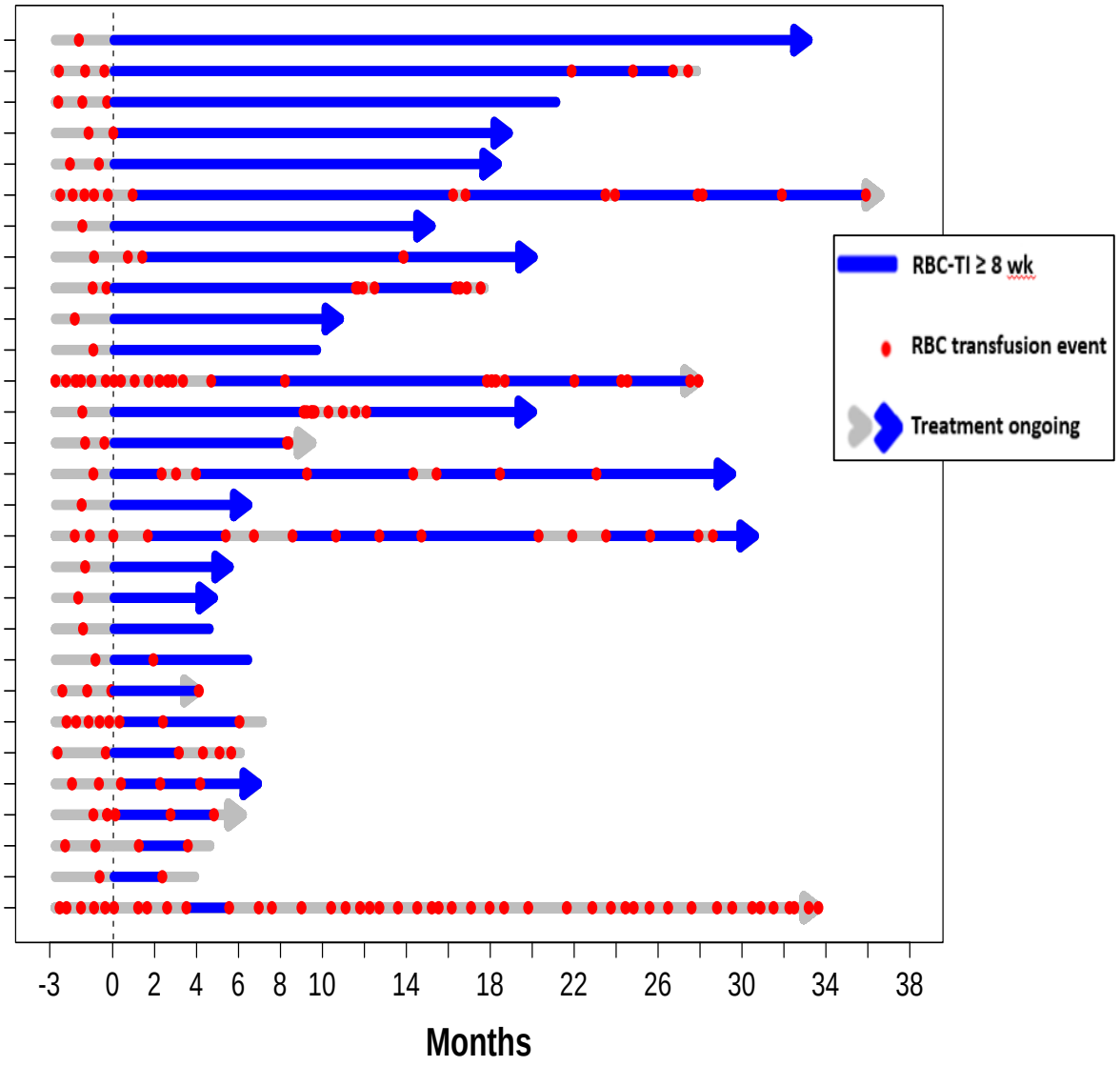
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Response Rates	IWG-HI-E, n/N (%) (N=99)	RBC-TI, n/N (%) (N=67)
All patients	52/99 (53%)	29/67 (43%)
ESA-naïve	28/53 (53%)	17/31 (55%)
Prior ESA	24/46 (52%)	12/36 (33%)
Baseline EPO <200 U/L		
RS+	25/39 (64%)	16/24 (67%)
Non-RS	7/13 (54%)	3/7 (43%)
Baseline EPO 200-500 U/L		
RS+	10/14 (71%)	4/9 (44%)
Non-RS	4/8 (50%)	3/5 (60%)
RS Status		
RS+	40/62 (65%)	22/42 (52%)
Non-RS	12/35 (34%)	7/23 (30%)
Unknown	0/2 (0%)	0/2 (0%)

Platzbecker U et al. ASH 2017 [Abstract # 2982]

Durability of Response in RBC-TI Responders

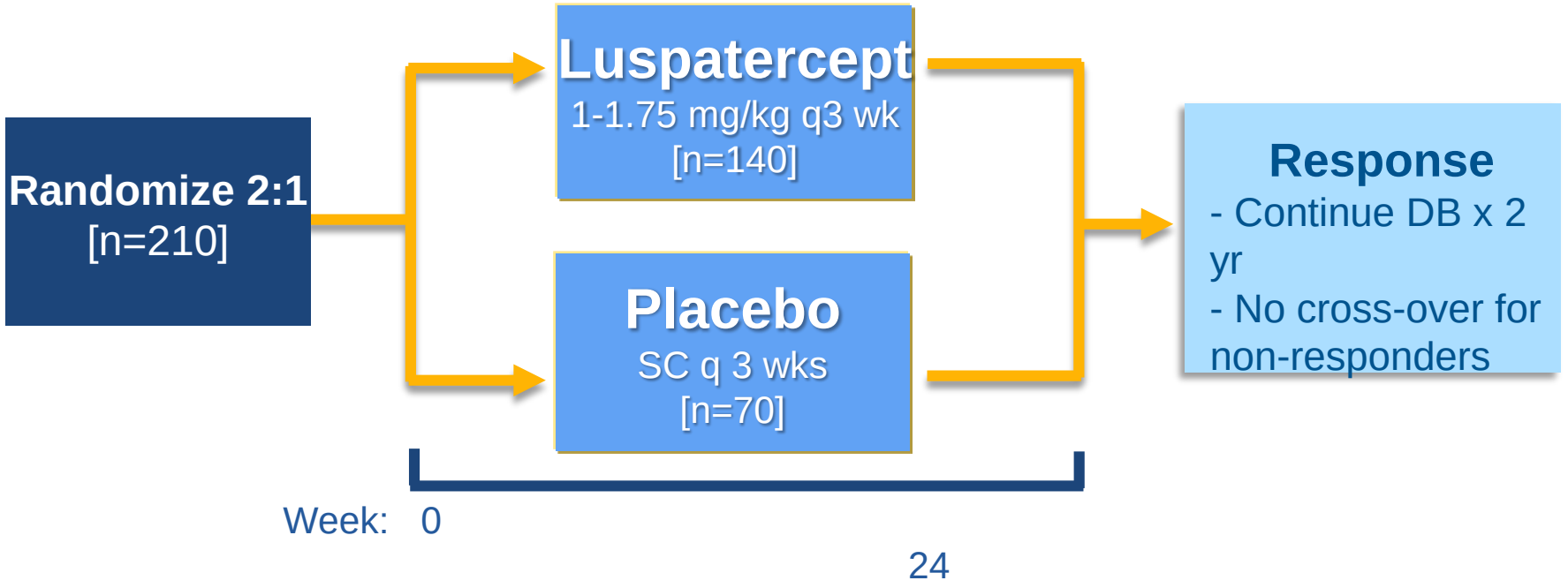
Patients Treated at ≥ 0.75 mg/kg with Baseline RBC ≥2U/8 weeks



Platzbecker U et al. ASH 2017 [Abstract # 2982]

Data as of 08 Sept 2017

MEDALIST: Phase 3 Randomized Double-blind Study of Luspatercept vs Placebo in Transfusion-Dependent LR-MDS With Ring Sideroblasts [ACE-536-MDS-001]



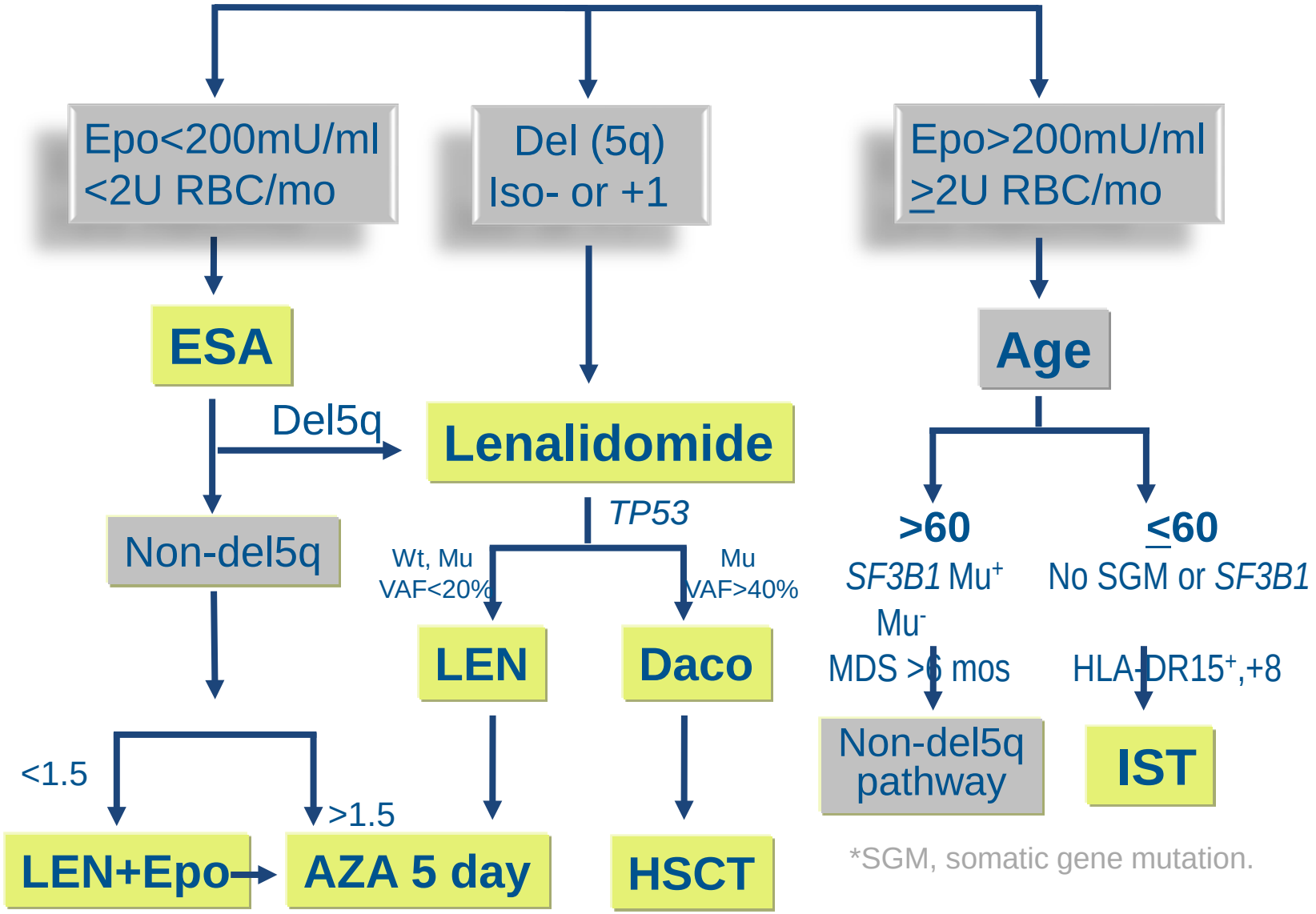
Eligibility: Non-del(5q) MDS with ≥15% RS, VL-Int. IPSS-R, □ 2 U PRBC/8 wks, prior ESA

Key Exclusions: Prior treatment with IMiDs, azanucleosides or IST; ANC < 500, plat<50K

Stratification: RBC transfusion burden (< 6 vs ≥6 U/8wk), IPSS-R VL/Low vs. Int.

Primary end-point: Transfusion Independence x ≥ 8 weeks

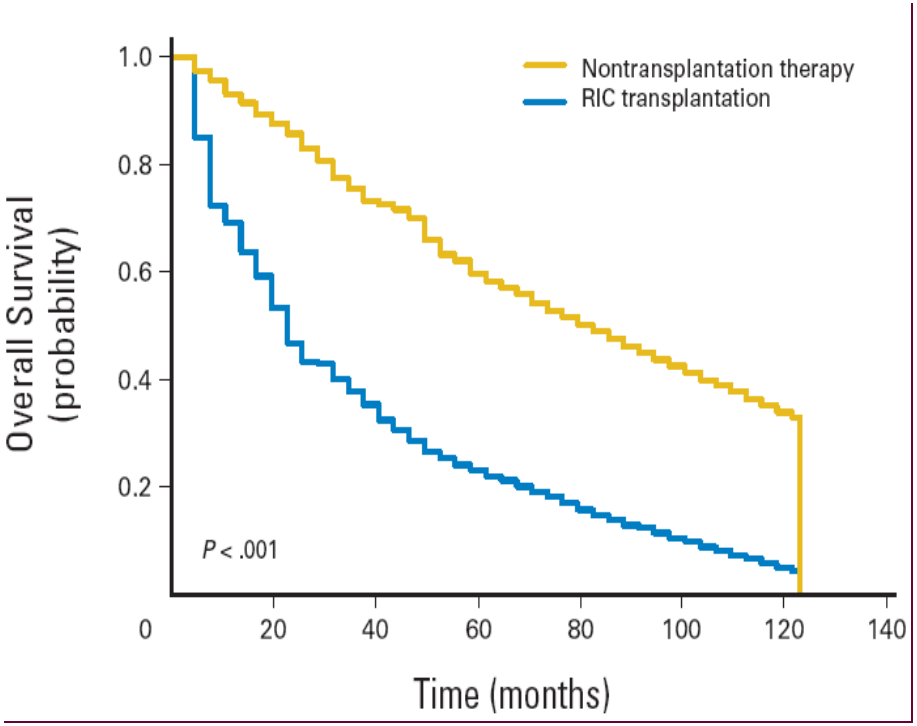
Anemia Management Algorithm in LR-MDS

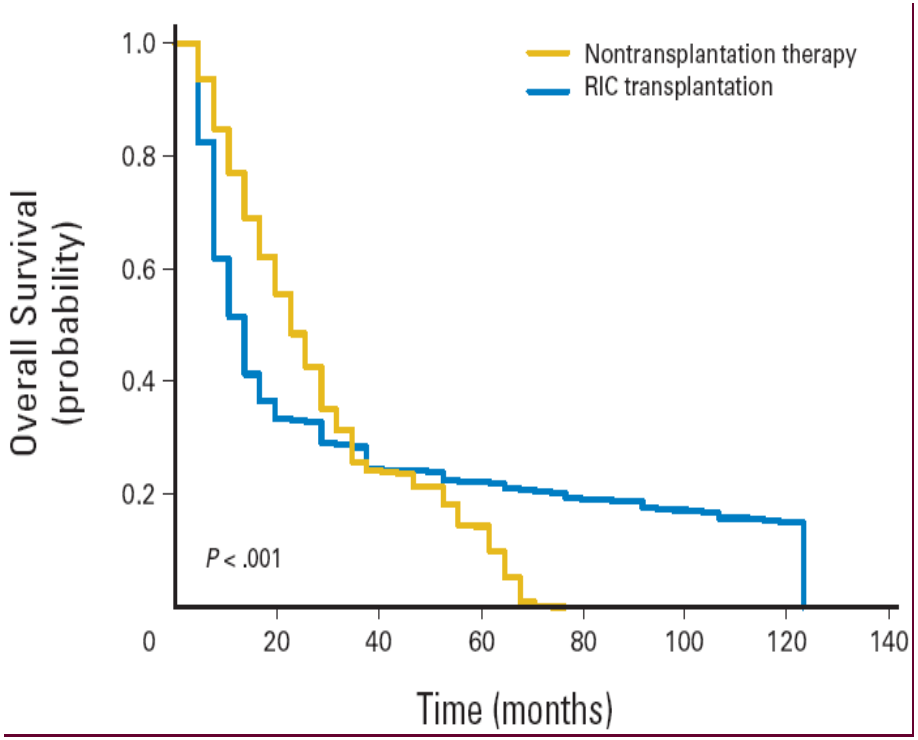


*SGM, somatic gene mutation.

HR-MDS

Allogeneic Hematopoietic Stem Cell Transplantation remains the only curative option for MDS patients

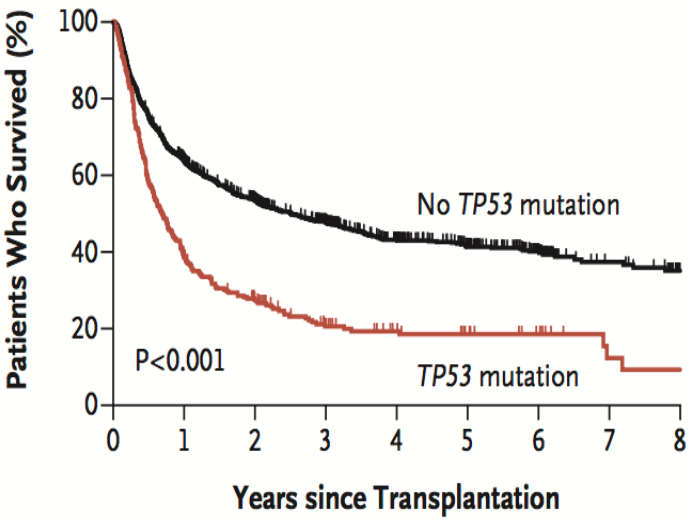




Koreth J, et al. J Clin Oncol. 2013;31:2662-2671.

Impact of *TP53* Mutation & Age on AlloHCT

OS by TP53 Mutation Status & Age



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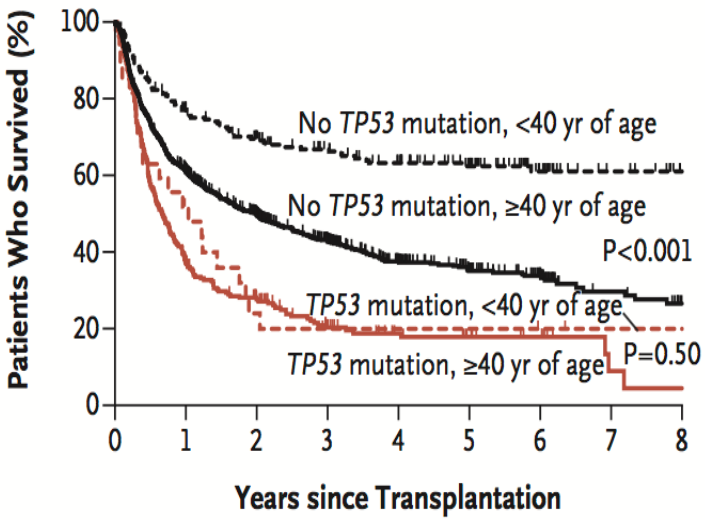

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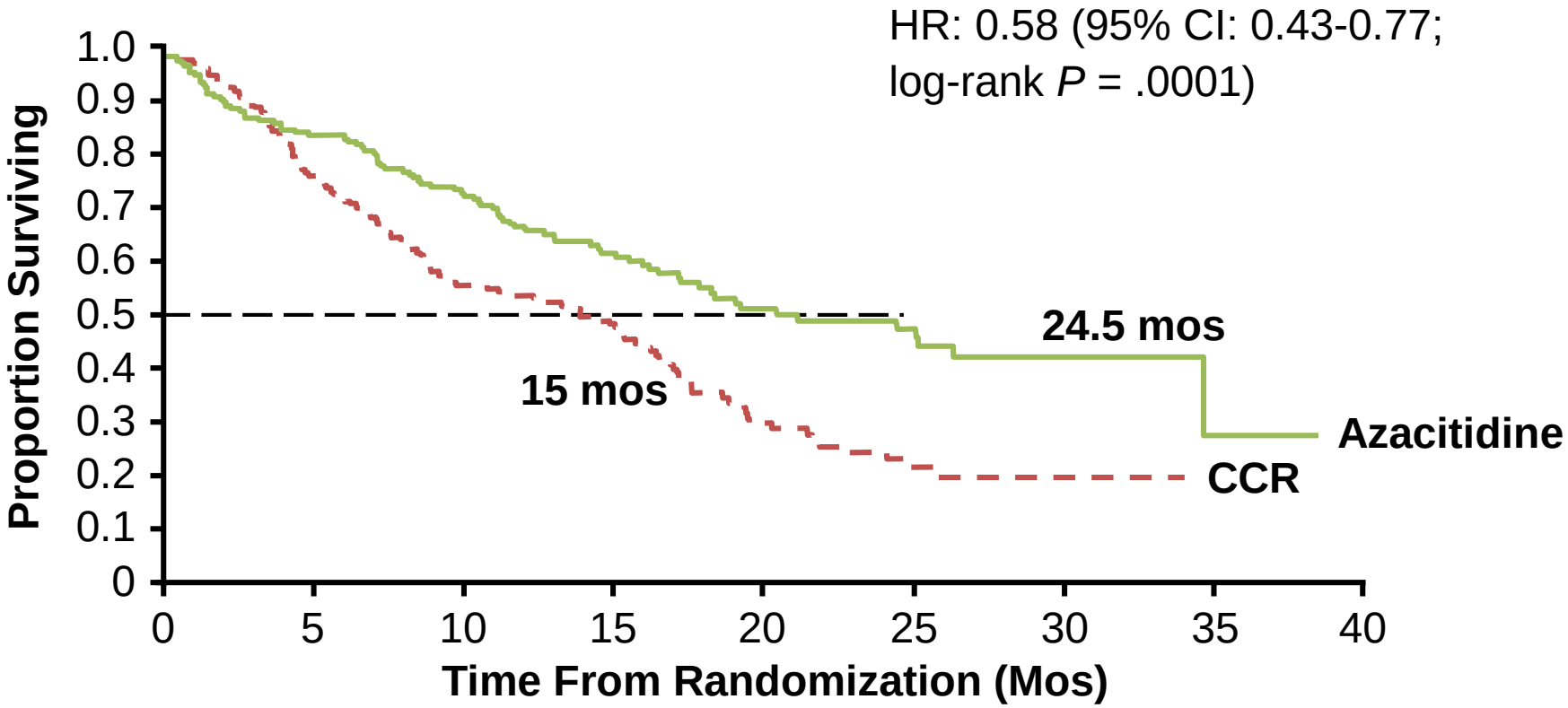
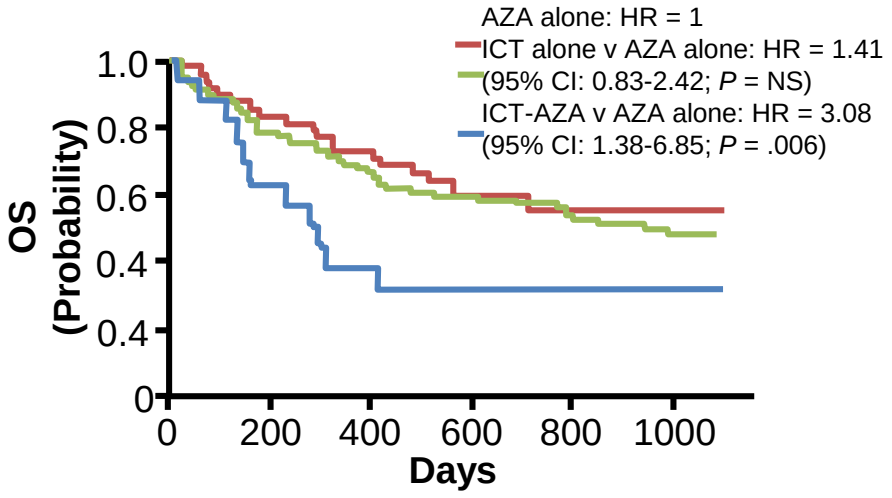
Lindsley RC, et. al. NEJM 2017; 376: 536.

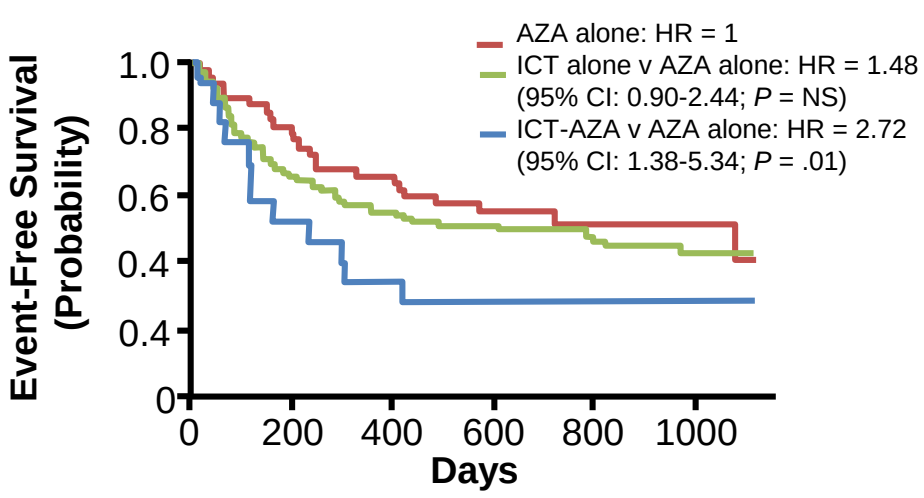
AZA-001 Trial: Azacitidine Significantly Improves Overall Survival

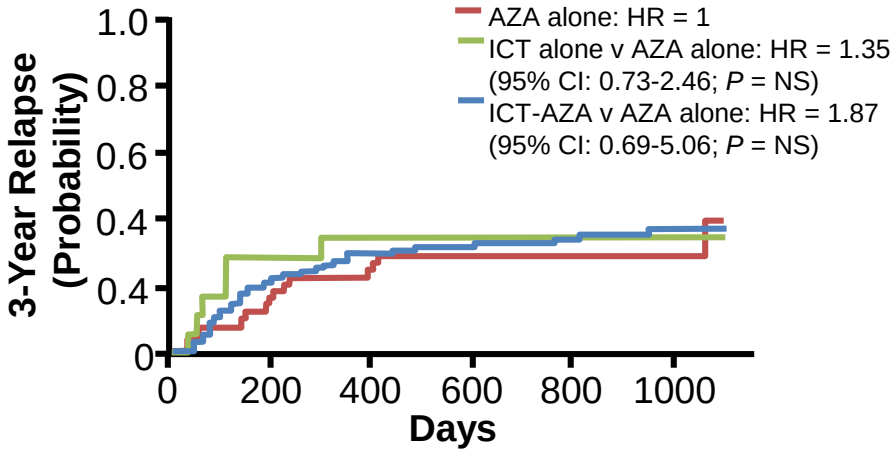


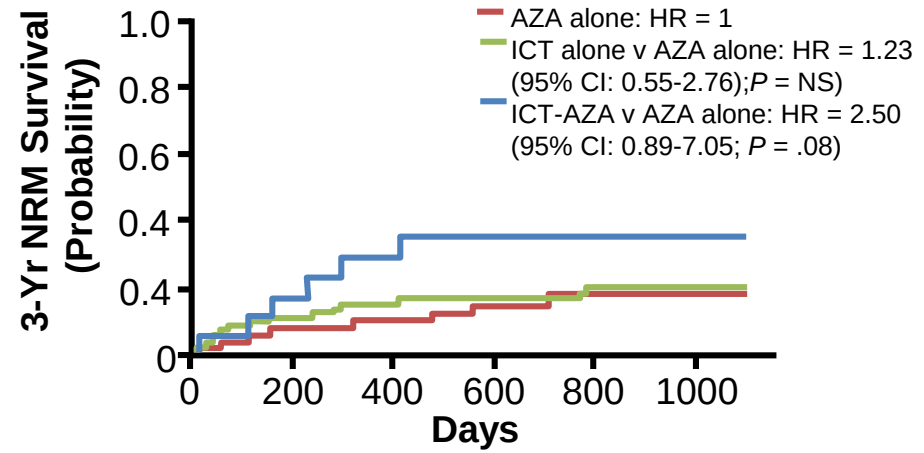
Fenaux P, et al. Lancet Oncol. 2009;10:223-232

Treatment With AZA OR ICT Prior AHSCT







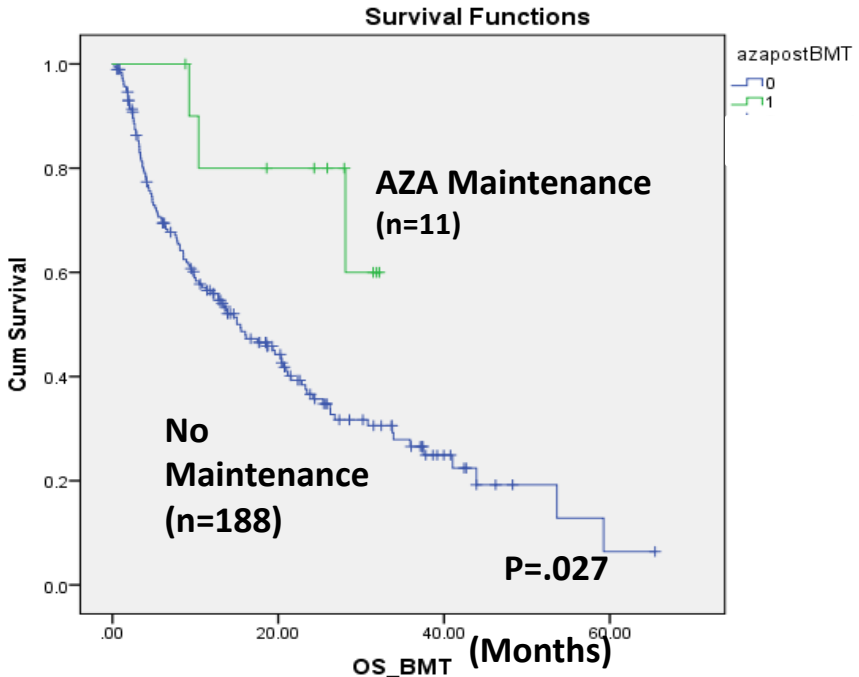


Damaj G, et al. J of Clin Oncol. 2012;30:4533-4540.

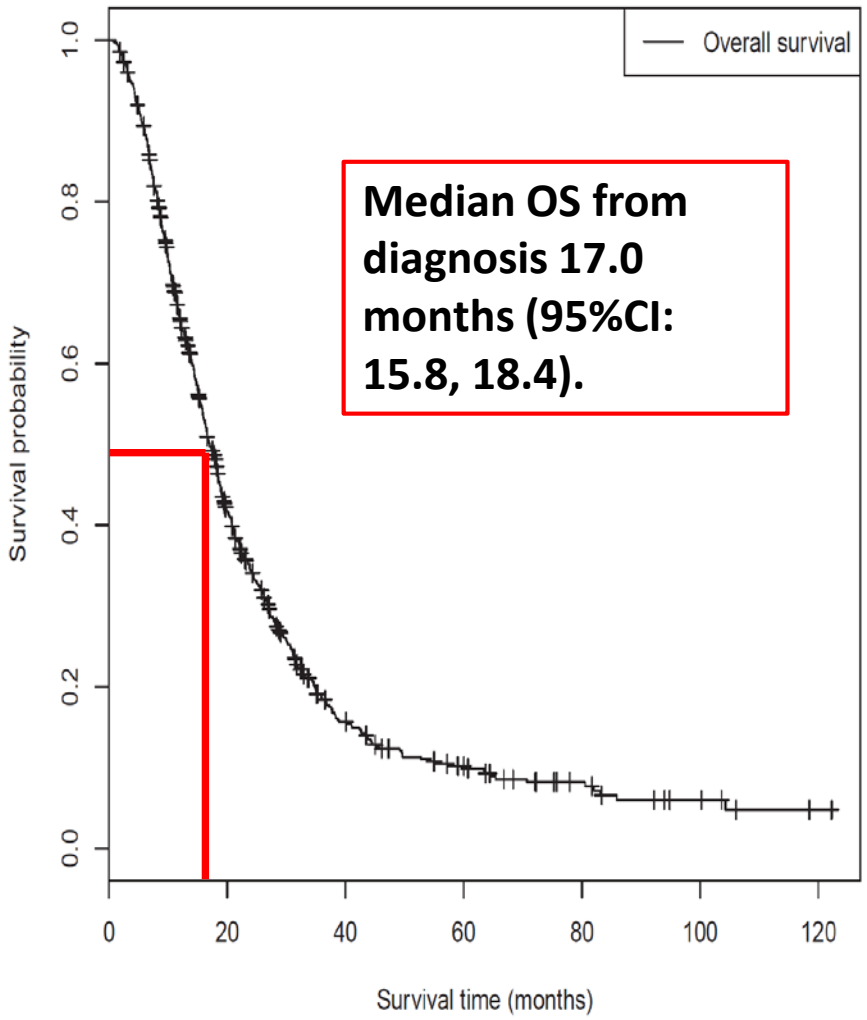
Azacitidine Maintenance after AHSCT

- **De Lima, et al. Cancer 2010; 116(23)**
  - N= 45, majority AML patients (n=37).
  - Excluded active disease, active GVHD, active infections.
  - MTD AZA 32mg/m^2 SQ for 5 days SQ X 4 cycles.
  - Median EFS 18.2 mo (95% CI: 11.9-NR), One year EFS and OS 58% and 77%

- **Mishra et al. Leukemia Research, vol 55, S1, April 2017, Page S48**



How do HMAs perform in the real-life setting?



- A retrospective analysis of 636 HR-MDS in the MDS Clinical Research Consortium database (6 tertiary centers, no single center accounted for > 39%).
- 69.6% INT-2, 30.4% high IPSS
- Median follow-up 15.7 months (95% CI: 14.6, 16.8).
- Median time from diagnosis to HMA initiation 0.95 months (95%CI: 0.86, 1.06).
- 67.9% azacitidine, 32.1% decitabine.
- Median number of cycles 5.0 (IQR: 3.0, 8.0)
- 72.2% received ≥ 4 cycles.

Zeidan et al, Leukemia, 2016

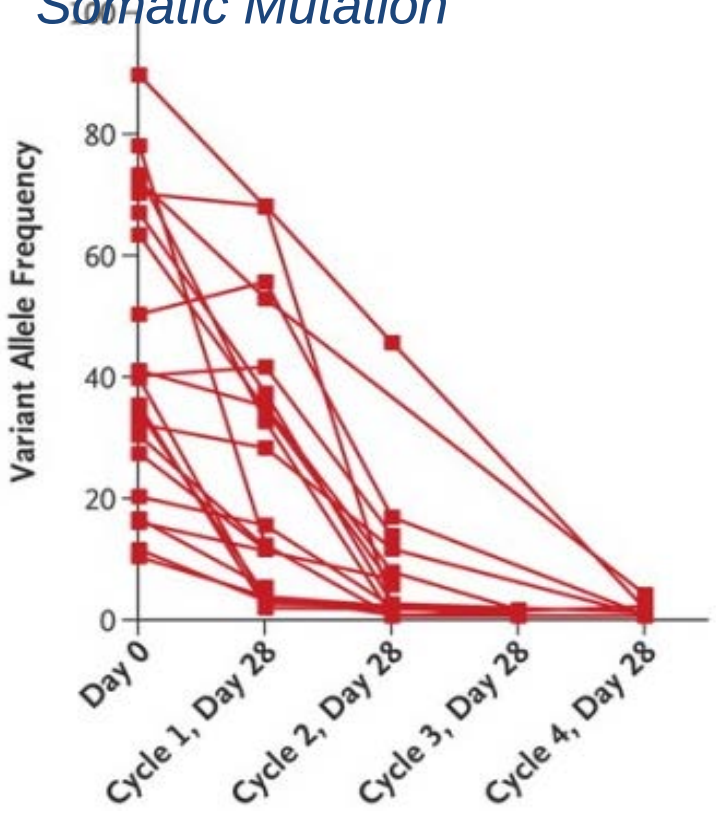
MDS with Founder *TP53* Mutations are Highly Responsive to Decitabine

- **Welch JS, et. al. *NEJM* 2016; 375:2023.**
  - 116 MDS/AML treated with decitabine 20 mg/m^2/d x 10d q 28d
  - exome sequencing pretreatment & serially
  - ORR higher in fav/int cytogenetic risk vs. unfavorable (29/43 [67%] vs. 24/71 [34%], *P* <0.001)
  - Higher ORR in *TP53* mutant vs. Wt (21/21 [100%] vs. 32/78 [41%], *P* <0.001)
  - CR/Cri higher in *TP53* mutant vs. Wt (13/21 [62%] vs. 26/78 [33%], *P*=0.04)
  - No relation between response & change in cytosine methylation or subclonal *TP53* mutation

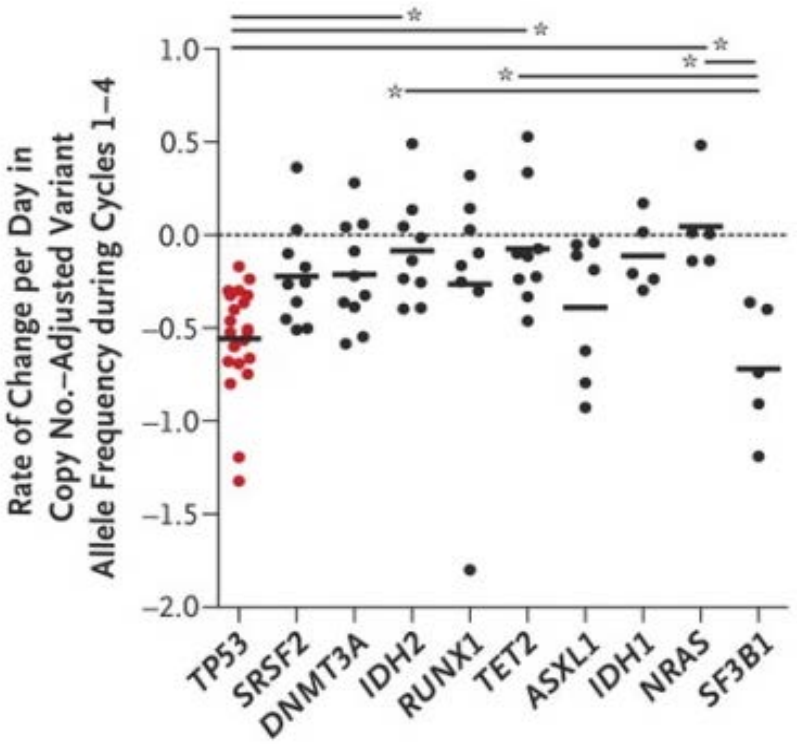
- **Chang CK, et. al. *Brit J Haematol* 2016; Epub.**
  - 109 MDS treated with decitabine 20 mg/m^2/d x 5d q 28d
  - exome sequencing pretreatment
  - CR rate higher in *TP53* mutant vs. Wt (10/15 [66.7%] vs. 20/94 [21%], *P* =0.001)
  - No difference in ORR (*TP53* mutant, 11/15 [73%] vs. 63/94 [67%] Wt)
  - Poor OS in *TP53*$_{mu}$ MDS (median, 14 vs. 39 mos; *P*=0.012)

Rate of Clearance of Somatic Gene Mutations in Decitabine Treated Patients

Clearance of $TP53_{mu}$ Clones



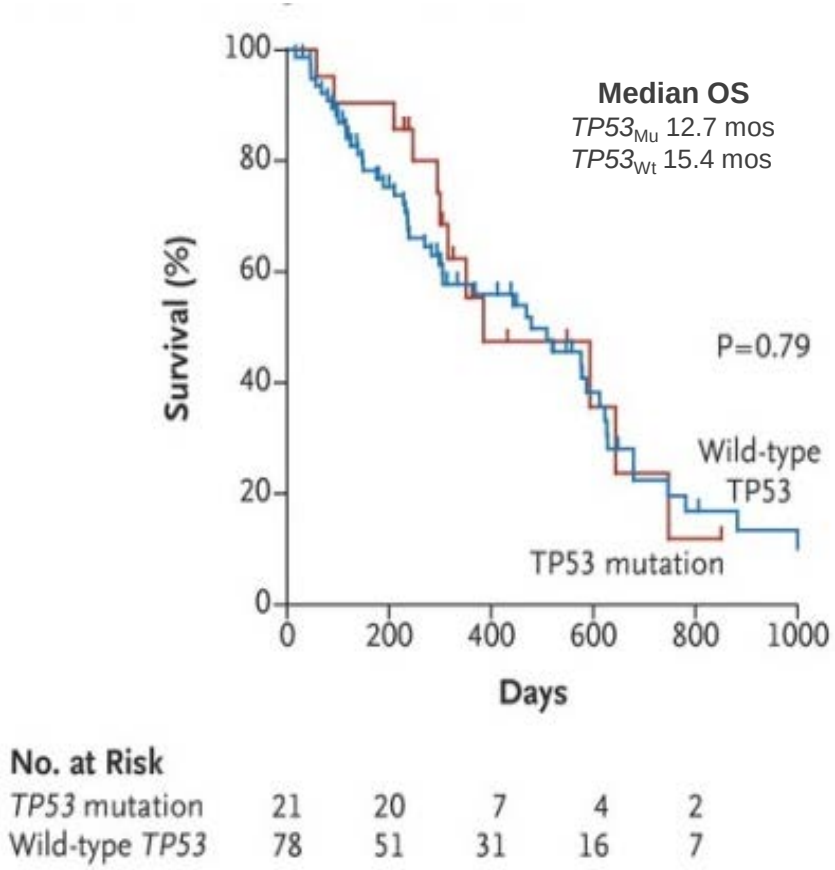
Change in VAF by Somatic Mutation



Welch JS, et. al. NEJM 2016; 375:2023.

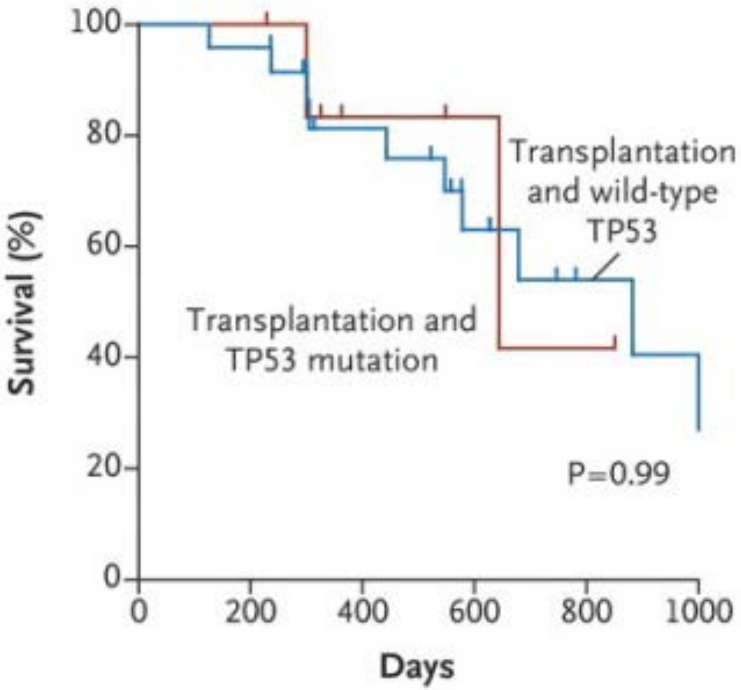
Overall Survival by TP53 Mutation Status

OS in $TP53_{mu}$ vs. Wt



No. at Risk					
TP53 mutation	21	20	7	4	2
Wild-type *TP53*	78	51	31	16	7

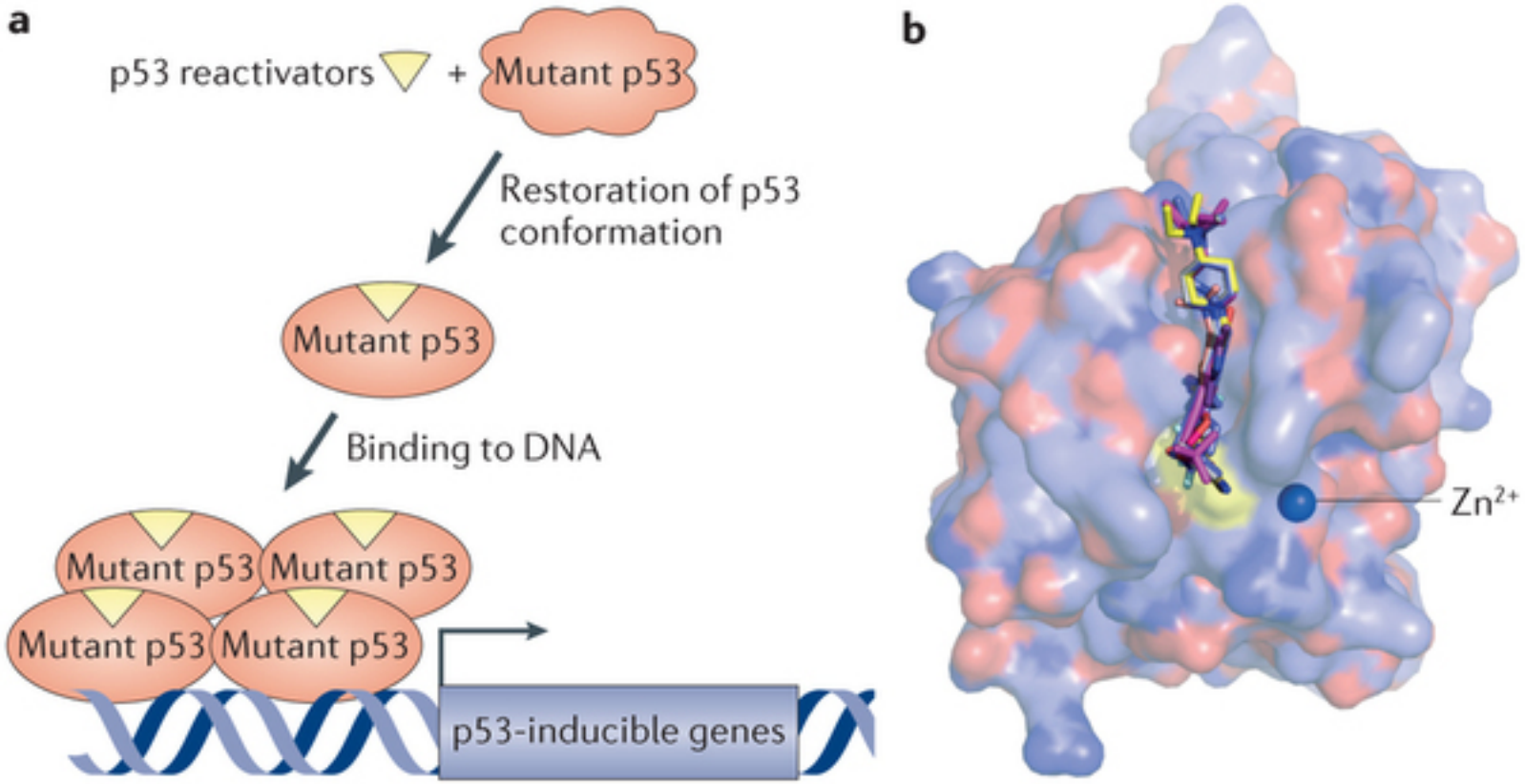
OS with HSCT by TP53



	7	7	4	3	2
	24	24	16	10	5

Welch JS, et. al. NEJM 2016; 375:2023.

APR-246 Restores Wild-type p53 Function



Khoo et al., *Nature Reviews Drug Discovery*; 2014, 13, 217-36

Enasidenib in m*IDH2* MDS: Response

Response, n/N (%)	MDS Pts (N = 17)
ORR*	10/17 (59)
CR†	1/11 (9)
PR†	1/11 (9)
mCR†	3/11 (27)
Any HI	
▪Erythrocytes	5/17 (29)
▪Platelets	3/15 (20)
▪Neutrophils	4/12 (33)
▪Trilineage improvement	4/10 (40) 2/5 (40)
▪Bilineage improvement	2/5 (40)

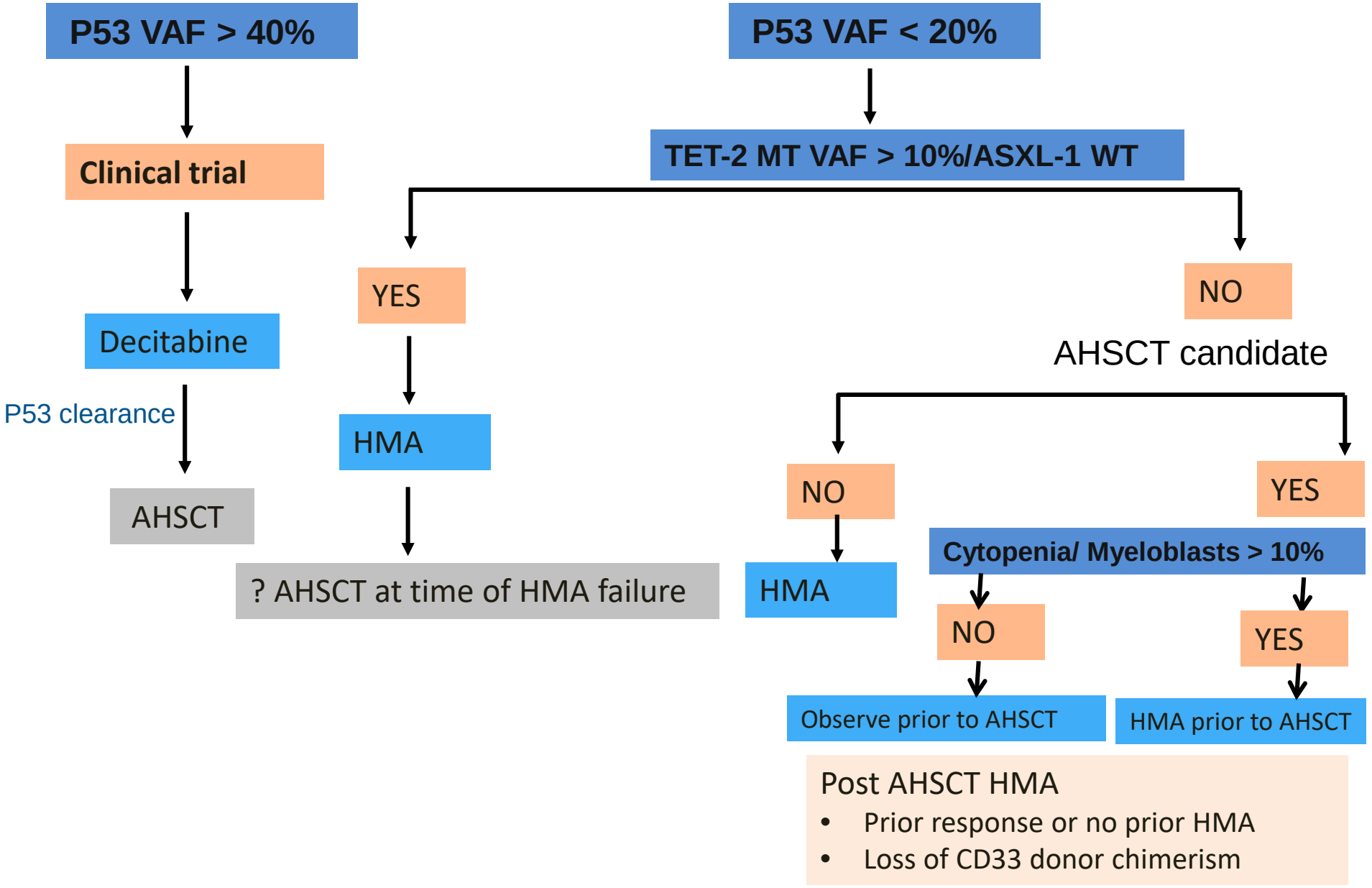
- 7 of 13 pts (54%) with prior HMA responded to enasidenib
- Median time to response: 21 days (range: 10-87)

*CR + PR + mCR + HI.
†Investigator-assessed; pts had ≥ 5% BM blasts at BL.

Stein EM, et al. ASH 2016. Abstract 343.

Slide credit: clinicaloptions.com

Proposal for HR-MDS Treatment Algorithm



Post AHSCT HMA

- Prior response or no prior HMA
- Loss of CD33 donor chimerism


only perfect counts
Moffitt MDS Team