Emerging Treatment Options for Myelodysplastic Syndromes

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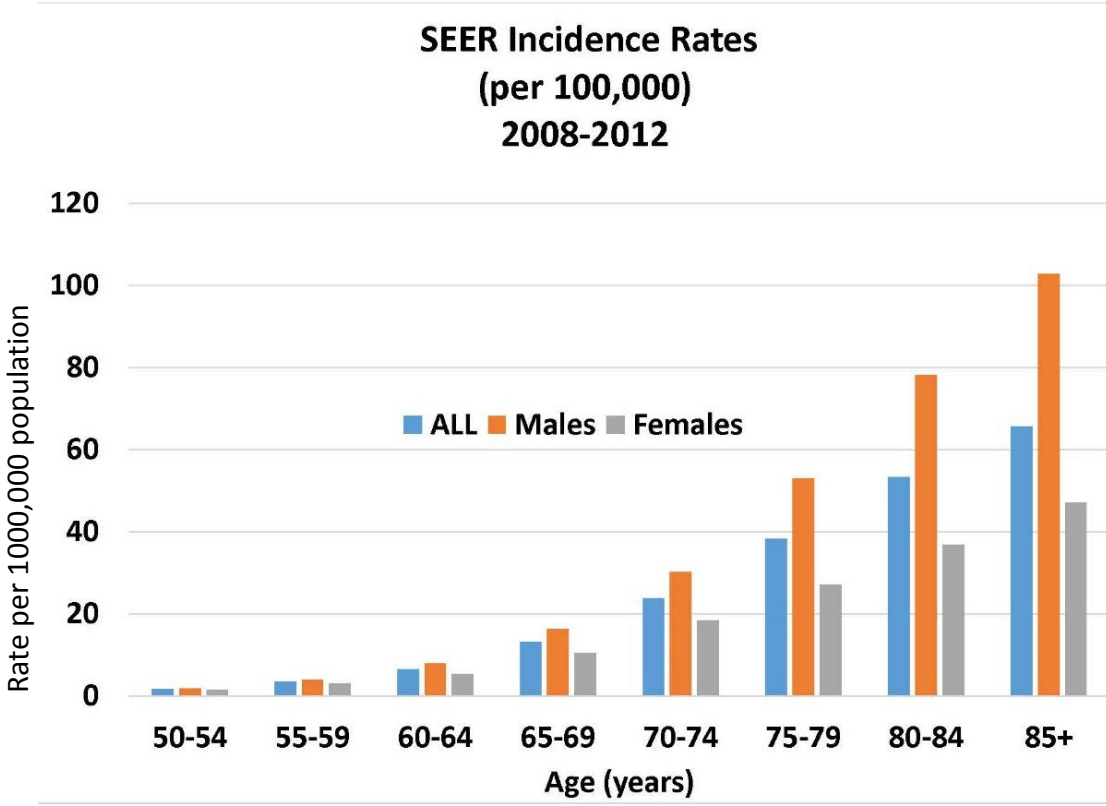
Please note that some of the studies reported in this presentation were presented as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

Age Related Incidence of MDS

- A group of heterogeneous clonal hematopoietic cell **neoplasms**
- Overall incidence 5 per 100,000
  Most common myeloid neoplasm
- Peripheral blood cytopenias
- Variable risk of progression to AML (1 in 3)



SEER data 2008-2012 and Greenberg, et al 1997

Reproduced with permission, H. Carraway

Making a diagnosis of Myelodysplastic syndromes (MDS)

At least one cytopenia:

- **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

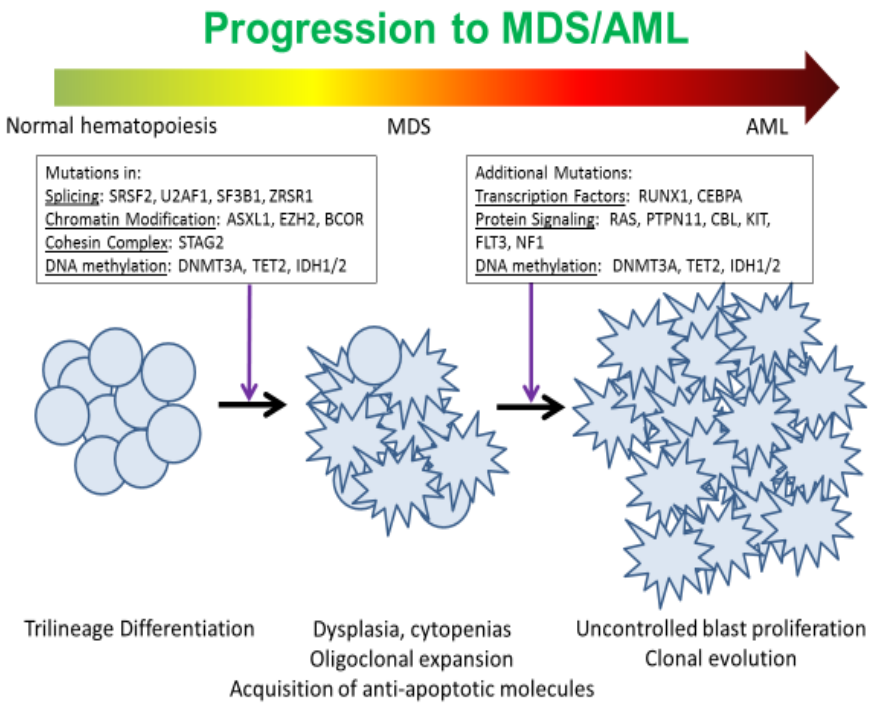
EXCLUDE other causes of cytopenias and morphological changes:

- ***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.)***

Slide courtesy of R. Komrokji (modified)

CHIP: Clonal Hematopoiesis of Indeterminate Potential

- Absence of definitive morphologic criteria of a heme malignancy
- Not meeting diagnostic criteria for MGUS, MBL, or PNH
- Detection of a recurrent hematologic malignancy-associated somatic molecular mutation at a VAF of ≥ 2% (e.g. TET2, DNMT3A, etc.)
- Prevalence increase with age
- Approximately 10% of people >65-70 years
- ⇧ progression to overt malignancy (0.5-1%/year, similar to MGUS)
- Higher risk of CAD (HR= 2) and ischemic strokes (HR=2.6)
- Higher risk of all-cause mortality (HR=1.4)



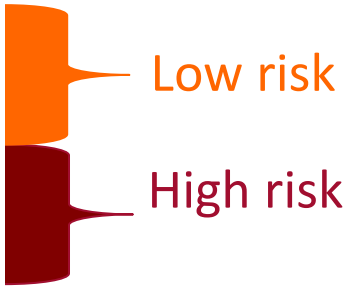
Steensma D et al, Blood, 2015; Jaiswal et al, NEJM, 2015, Genovese G et al, NEJM, 2015

Slide reproduced from the American Society of Hematology

IPSS: First Tool for Risk Stratification of MDS

	Score Value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	**< 5%**	**5% to 10%**	**--**	**11% to 20%**	**21% to 30%**
Karyotype*	**Good**	**Intermediate**	**Poor**	**--**	**--**
Cytopenias†	**0/1**	**2/3**	**--**	**--**	**--**

Risk Group	Risk Score
Low	0
Intermediate 1	0.5-1
Intermediate 2	1.5-2
High	>/= 2.5



***Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.**
†Hb < 10 g/dL; ANC < 1800/μL; platelets < 100,000/μL.

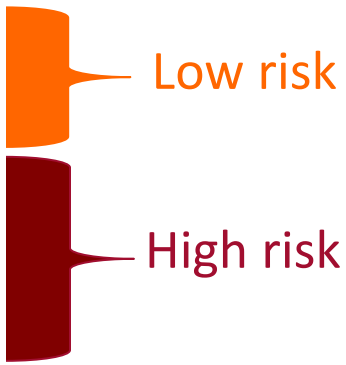
Greenberg P, et al. Blood. 1997;89:2079-2088.

IPSS-R: Used to Determine Prognosis/Risk

P. Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

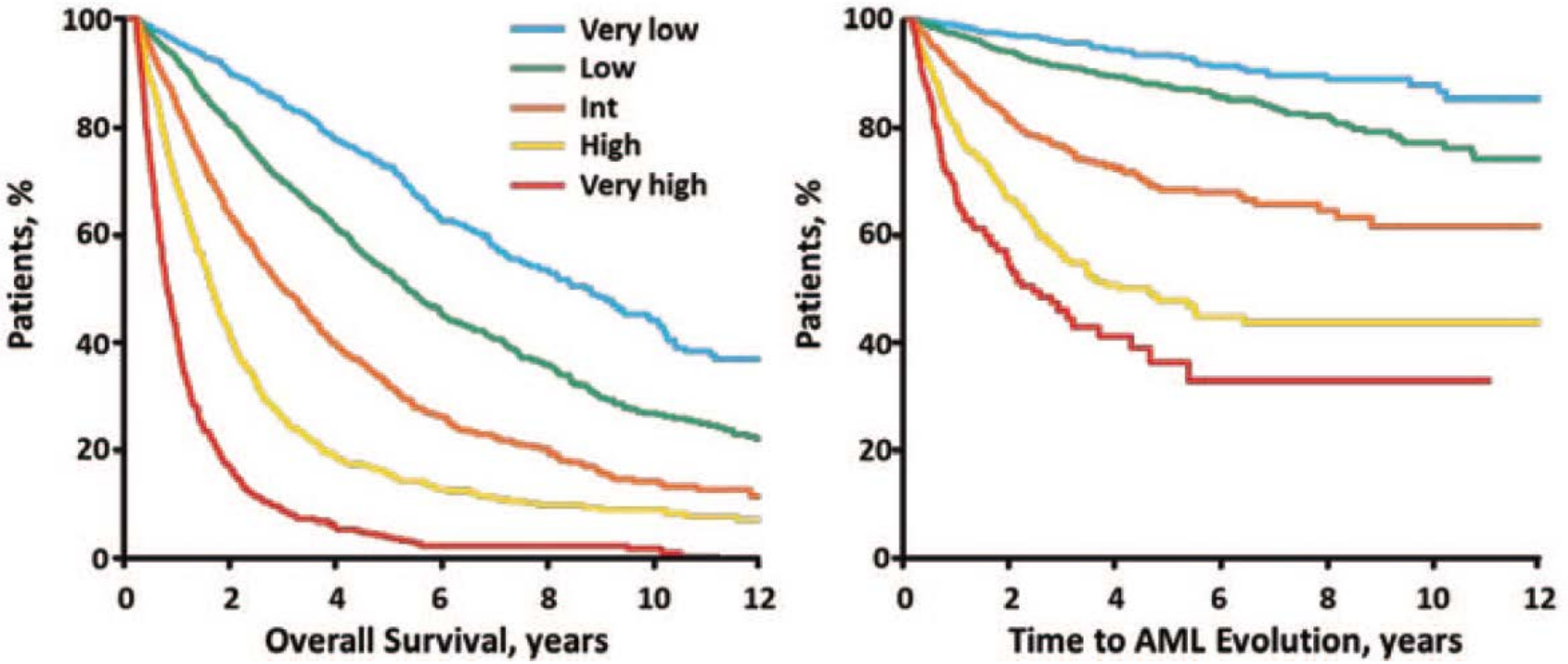
IPSS-R: Prognostic Risk Categories/Scores

Risk Group	Risk Score
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

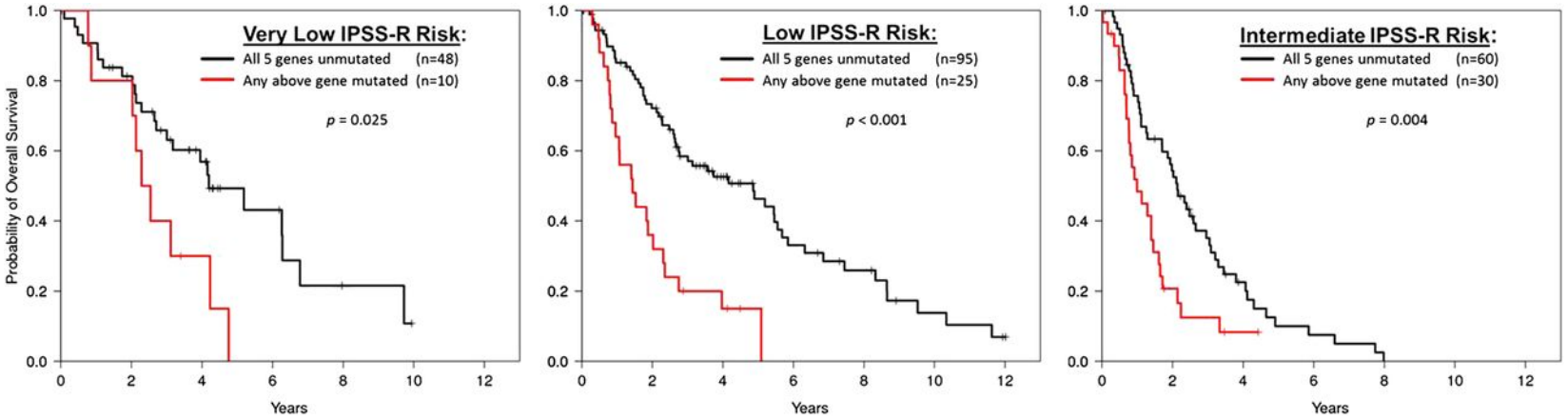


Greenberg et al. Blood 2012;120:2454-65.

Prognosis: IPSS-R



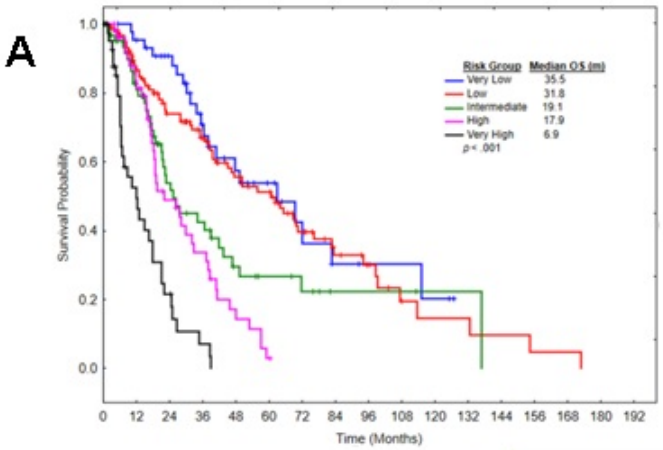
Somatic mutation in any of the 5 genes (TP53, EZH2, RUNX1, ASLX1, or ETV6) shown in Bejar et al, NEJM 364, 2011 to have prognostic significance independent of the International Prognostic Scoring System (IPSS) identifies patients from that same cohort with shorter overall survival than predicted by the IPSS-R for the 3 lowest IPSS-R risk groups.



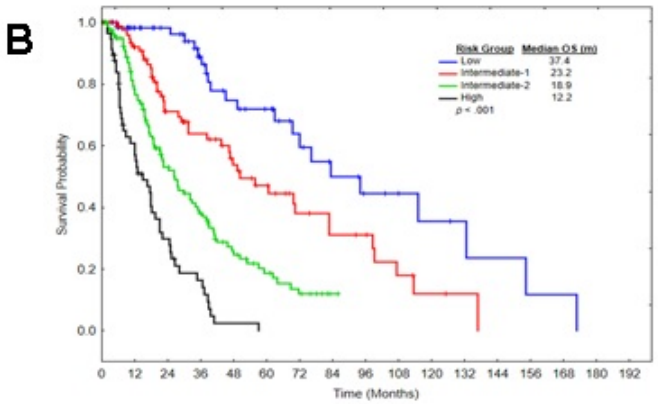
Bejar R , and Steensma D P Blood 2014;124:2793-2803

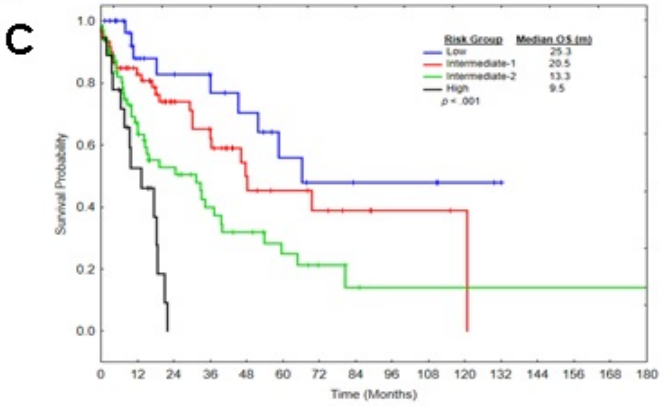
IPSS-Rm

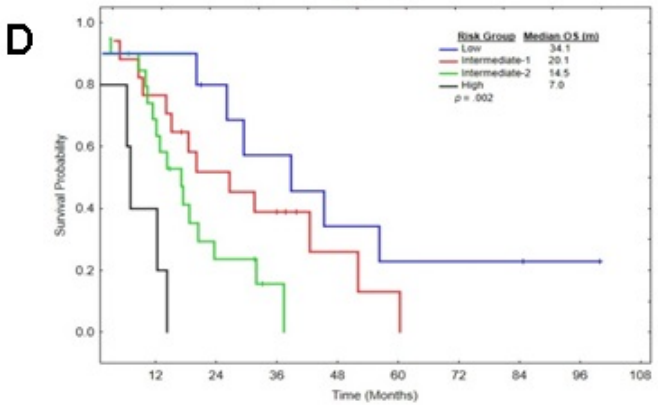
ASH abstract 607 2015, Aziz Nazha Et al.

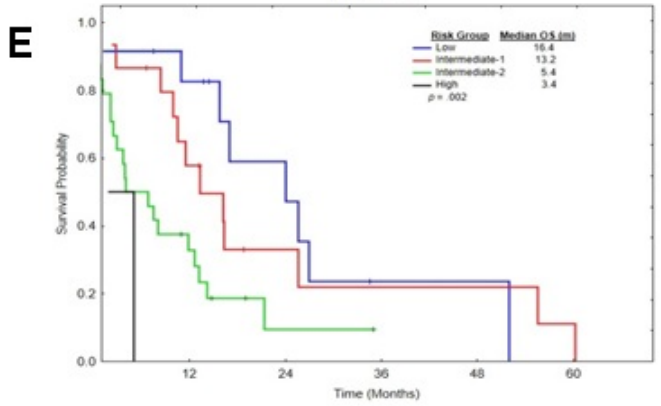


508 patients. Three genes were found to be prognostic: EZH2, p53, SF3B1.









A = IPSS-R, **B** = IPSS-Rm (training cohort), **C** = IPSS-Rm (validation cohort), **D,E** = IPSS-Rm (Paired samples at each time point)

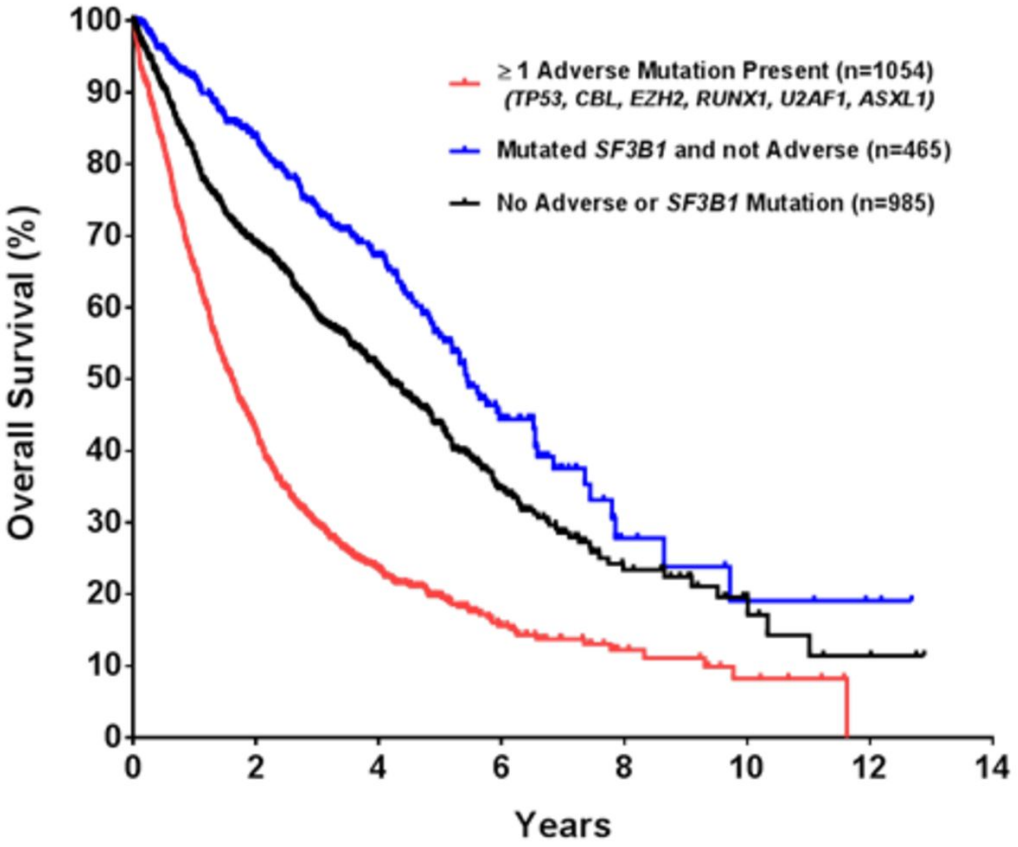


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Rafael Bejar et al. Blood 2015;126:907

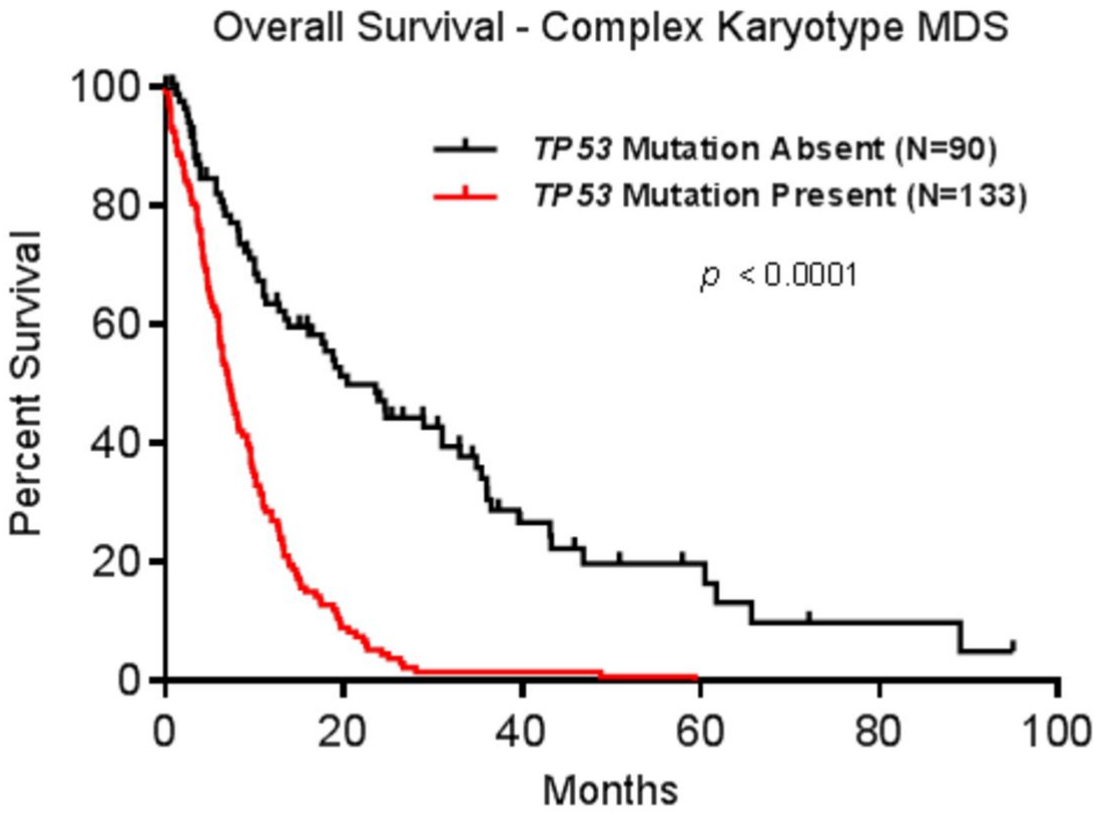


Figure: Overall survival of 223 patients with MDS and complex disease karyotypes stratified by their *TP53* mutation status.

Bejar R et al. Blood 2014;124:532

Treatment Goals in MDS

- Cure
- Improve overall survival
- Lower the risk of transformation to AML
- Complete remission, partial remission, stable disease
- Improve tri-lineage hematopoiesis and function
  - Decrease infections by resolving neutropenic state/dysfunction
  - Decrease PRBC/PLT transfusion burden

- Supportive care
  - Decrease symptoms that impair quality of life

Therapies for Lower Risk MDS

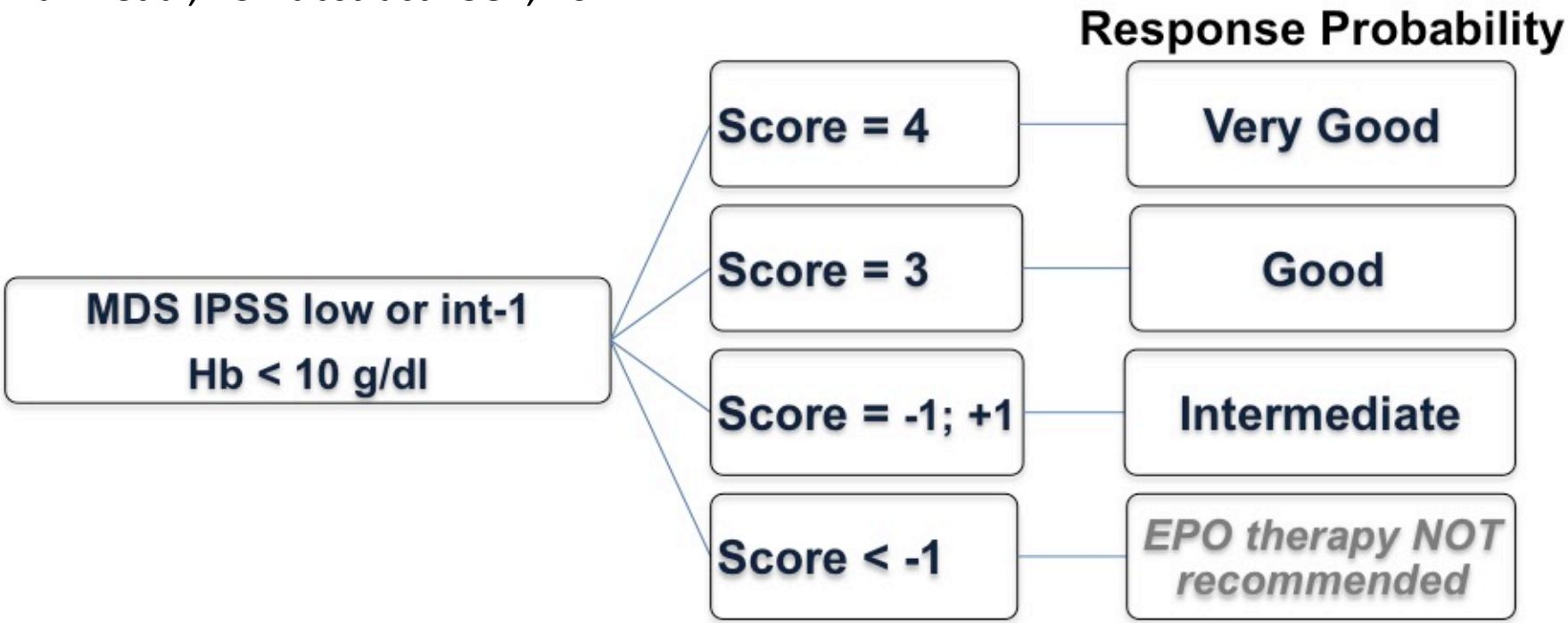
ESAs: Work well in patients with low transfusion Requirements (<2 units PRBCs/month) and EPO level (<500): 74% response rate.

Work poorly in patients with high transfusion Requirements and EPO >500: 7% response rate (Hellstrom-Lindberg et al, BJH 120, 2003).

Also clearly inferior responses in higher risk disease.

"Revised HLS"

Riva M et al, ASH abstract 2981, 2017.



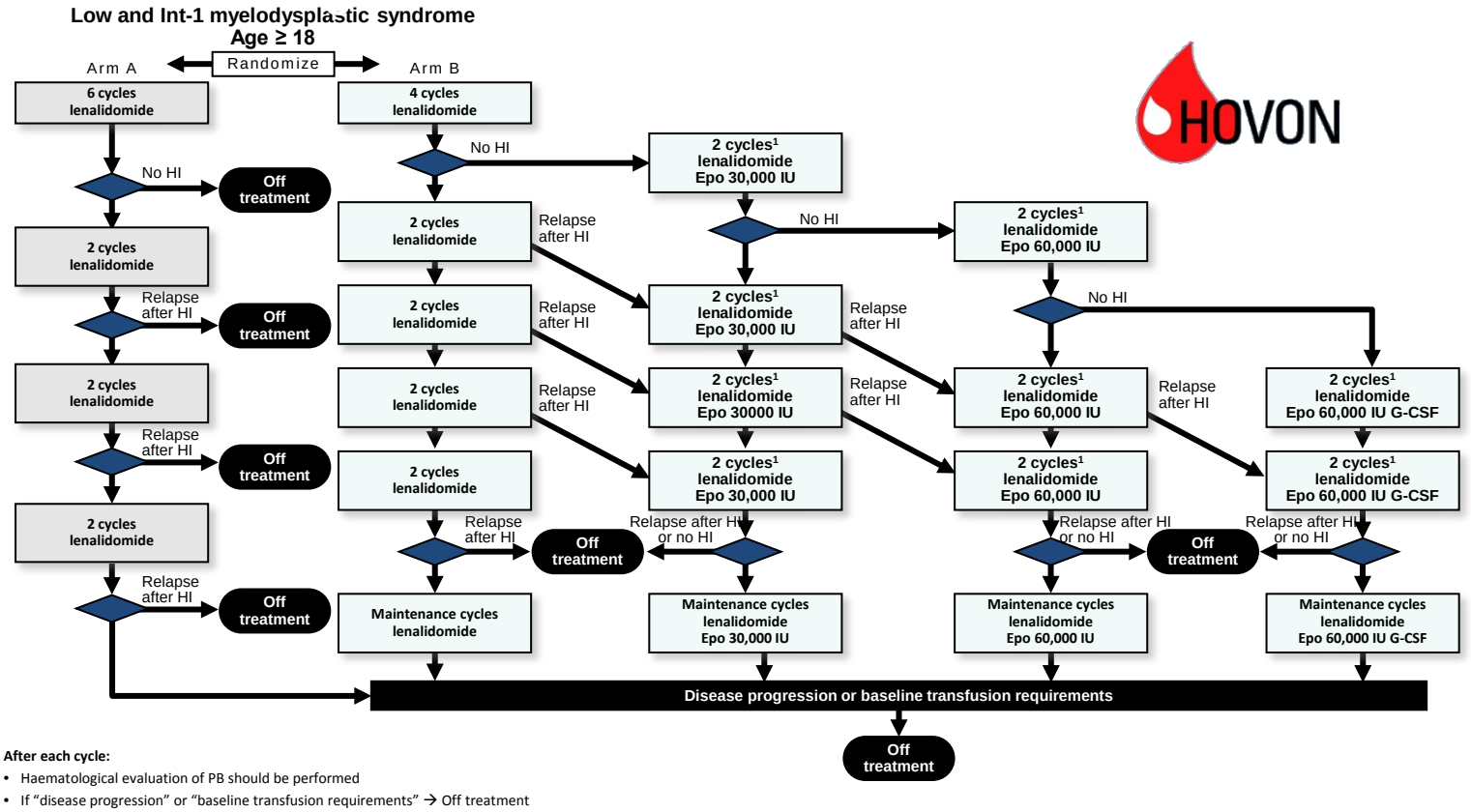
Treatment Response Criteria

(responses must last at least 8 weeks)

- Hb increase by 1.5 g/dL
- Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.

Treatment Response Score

S-EPO mU/mL	<100	+2
	100-500	+1
	>500	-3
Transf RBC units/m	<2	+2
	≥2	-2



[1]For Epo and/or G-CSF reduction in case of HI, see protocol 9.2.2 and 9.2.3.

Van DeLoosdrecht et al. ASH 2016; Abs 224

HOVON89 Results: Primary and Secondary Endpoints

- **Hematological Improvement-Erythroid*: 41%**
  - 39% and 42% for the pts in arm A and B, respectively (p = 0.45)

- **Hematological Improvement-Erythroid*:**
  - non-del5q *versus* del5q: 34% vs 79%

- **Time-to-HI-E**: 3.1 months (median; range 1.6-12.3) for both arms

- **Duration of HI-E:** 10.6 months (range 1.4 – 76.1)

*According to IWG criteria

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HOVON

Van DeLoosdrecht et al. ASH 2016; Abs 224

Results: NGS and Response to Lenalidomide

- Presence of 2 or more mutations are inversely related to HI-E (p=0.004)
- Presence of 1 or more splicing factor mutations are inversely related to HI-E (p<0.0001)
- Of the 7 most frequently mutated genes (i.e.) TET2, ASXL1, DNMT3, ATRX, RUNX1, ***only*** SRSF2 (p=0.021) ***and*** SF3B1 (p=0.004) are significantly associated with lack of response to lenalidomide (HI-E)

Van DeLoosdrecht et al. ASH 2016; Abs 224

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

Base Study (N=106)
3 months
NCT01749514

→

Extension Study (N=70)
5 years (ongoing)
NCT02268383

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

EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; HI-E: hematologic improvement erythroid; RS: ring sideroblast

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

Data as of 08 Sept 2017

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]

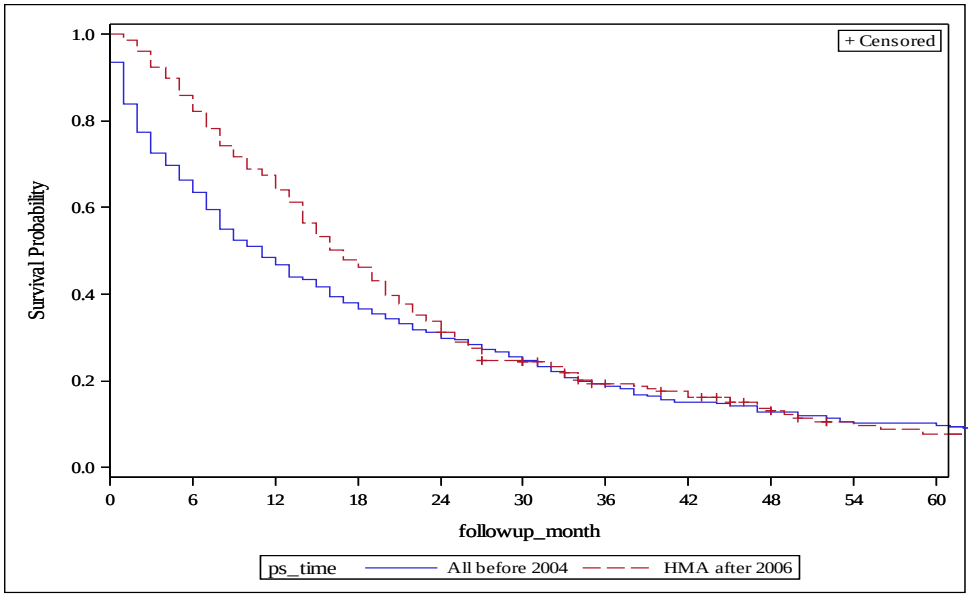
Data as of 08 Sept 2017

67% HI-E in SF3B1 mutated (N= 43)vs 32% in WT (N=31)

48% RBC-TI in SF3B1 mutated (N= 29)vs 36% in WT (N= 22)

HMAs might improve survival in some CMML patients

Pre-HMA (N=395)		HMA (N=225)		HMA vs non-HMA (ref)	
N died	Median survival (95% CI)	N died	Median survival (95% CI)	HR (95% CI)	P-value
385	11 [8-13]	200	17 [14-19]	0.72 (0.58-0.91)	.005



Zeidan A et al, Cancer, 2017

Study Design: Phase 1/2 Ruxolitinib CMML Study

Rolling-Six Design 8 weeks between cohorts

Second Stage of Phase if 1 of 10 respond

- **All CMML WHO subtypes were included without regard to previous therapy.**
- **Key exclusion criteria included an ANC < $0.25x10^3$ c/dL and a platelet count < $35x10^3$c/dL.**
- **Phase 1 completed, n=20 pts (Padron, et al Clinical Cancer Res 2016)**
- **Deep Sequencing of recurrent gene mutations in CMML before and after therapy.**
- **Comprehensive Cytokine profiling**

Padron et al for MDS CRC, ASH 2017, Abstract # 162

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Summary of Responses

- Three bi- and tri- lineage hematologic responses by MDS IWG 2006 (i.e. 2 HI-E, 2 HI-P, 1 HI-N)
- One bone marrow complete response identified
- One partial marrow response identified
- 6 of 13 patients (46%) with splenomegaly had a ≥ 50% reduction by physical exam
- When using 'clinical benefit' as defined by the MDS/MPN-IWG response criteria 11 of 24 (46%) evaluable patients responded
- ***Most common reason for discontinuation was disease progression (n=10)***

Padron et al for MDS CRC, ASH 2017, Abstract # 162

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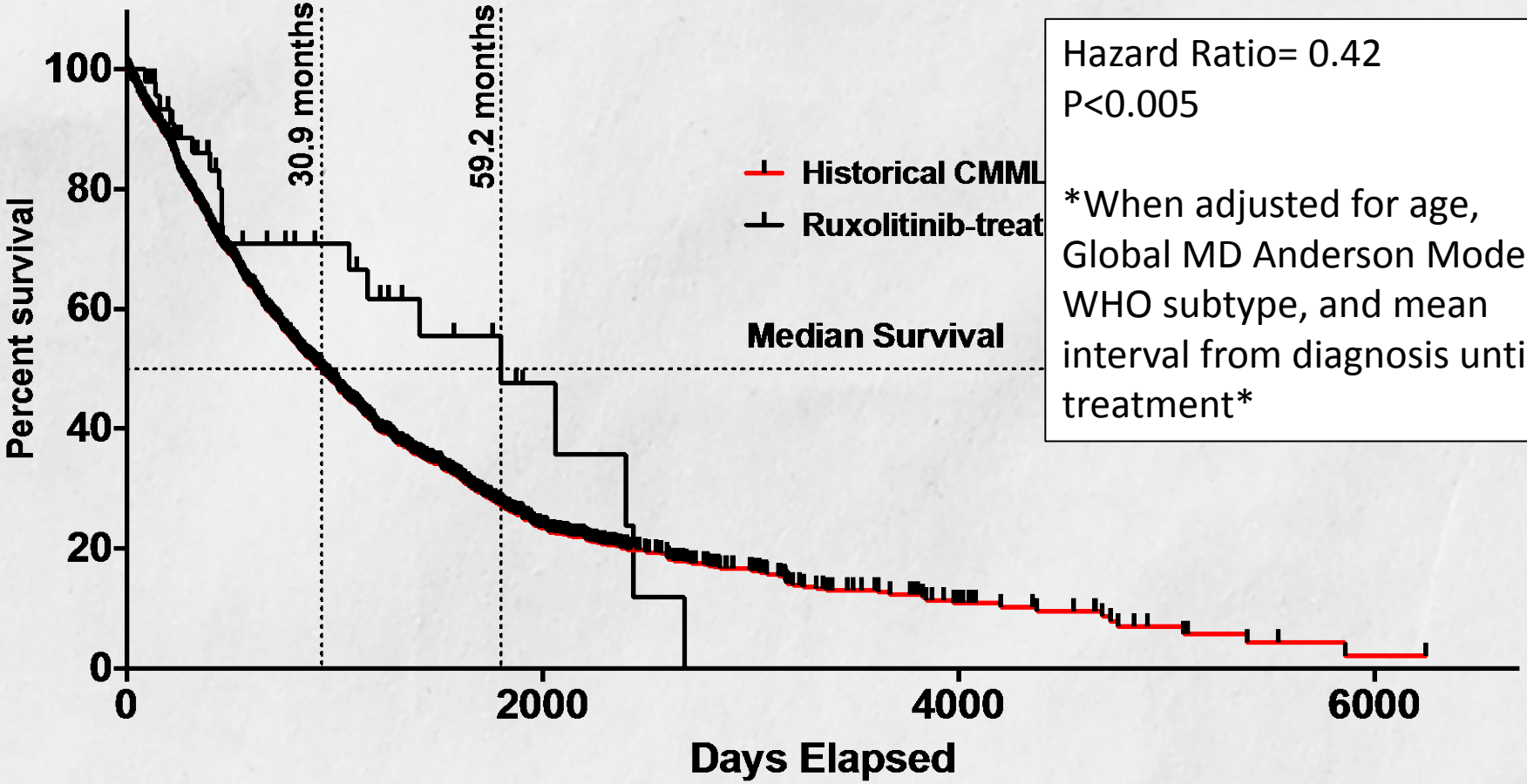
Ruxolitinib-treated CMML compared to historical controls



Hazard Ratio= 0.42
P<0.005

When adjusted for age, Global MD Anderson Model, WHO subtype, and mean interval from diagnosis until treatment

Padron et al for MDS CRC, ASH 2017, Abstract # 162

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Other Agents in CMML

Tipifarnib: Farnesyltransferase inhibitor. FTs are necessary for proper Localization of RAS molecules to the inner cell membrane, hypothesized to be more effective in WT RAS patients.

15 patients treated, 11 with CMML-1 and 4 with CMML-2.
Commons AEs were thrombocytopenia, diarrhea, nausea

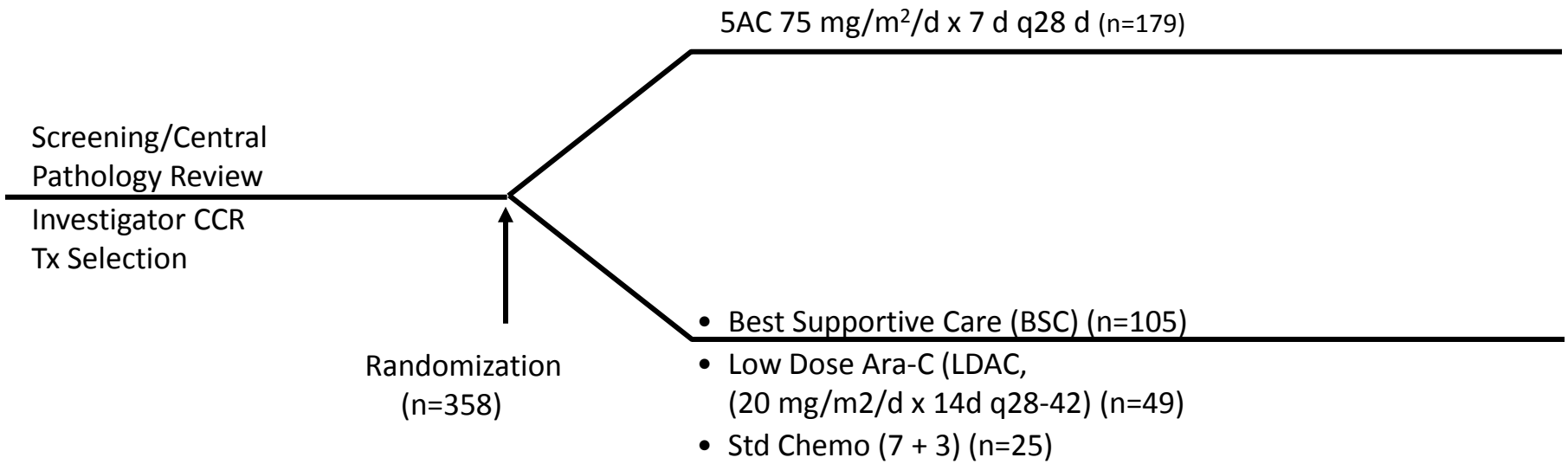
Only 1 of 7 patients evaluable for response had marrow response.

Patnaik M, ASH abstract 2963, 2017.

Eltrombopag: Tested in 25 CMML patients with lower risk features and platelets <50,000. Itzykson R, ASH Abstract 4266, 2017.

63% had HI-Platelets with median duration of response of 8 months.

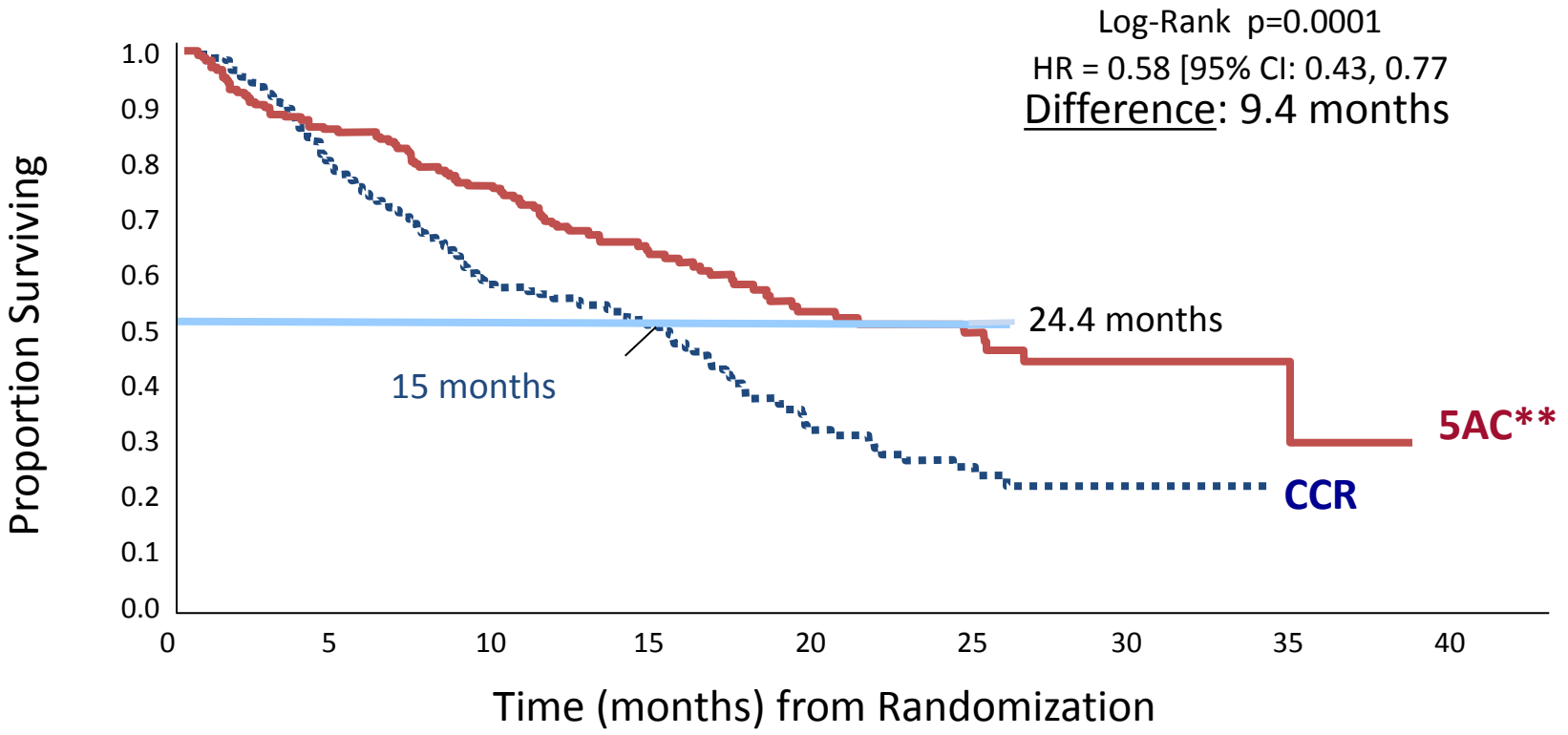
Azacitidine Survival Study (AZA-001)



BSC was included with each arm.
Tx continued until unacceptable toxicity, AML transformation, or disease progression

Fenaux et al. Lancet Oncology 2009;10:223.

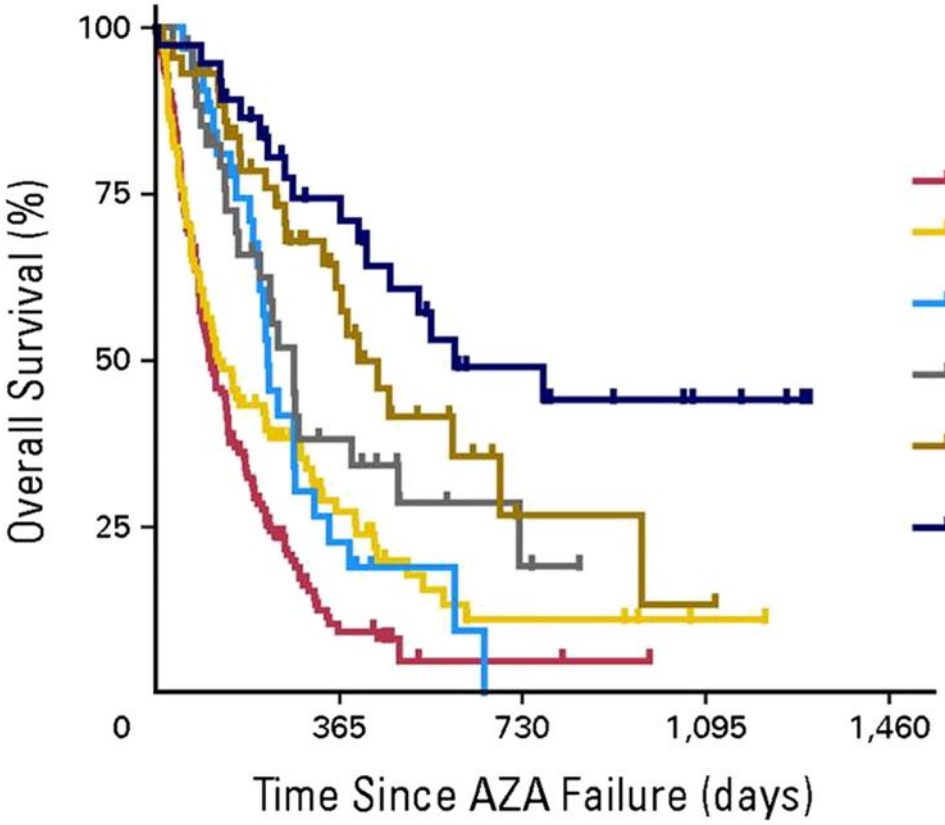
Overall Survival: Azacitidine vs CCR



**Improved OAS also seen for low blast count AML

Fenaux et al. Lancet Oncology 2009;10:223.

Patients with MDS for whom hypomethylating agents have failed have poor outcomes overall.



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Bejar R , and Steensma D P Blood 2014;124:2793-2803

There remains no standard of care after hypomethylating agent failure:

Omecetaxine phase II (Short et al, ASH abstract 2967, 2017).
35 patients, median BM blasts 10%

OM given at 1.25 mg/m2 SQ q 12 hours x 3 days on 28 day cycle

12/35 patients responded: 3 CRp and 9 Cri
Fatigue and nausea were most common Aes

Median OS was 7.6 months

NOVEL APPROACHES IN MDS

CC-486: Oral Vidaza, ongoing trials.

ASTX727 (oral decitabine) paired with E7727 an oral cytidine deaminase inhibitor. The pairing Assures that oral decitabine will not be degraded, favorable PK have been reported (Garcia-Manero, ASH Abstract 4274, 2017).

SGI-110 (guadecitabine): Phase III is ongoing.

Rigosertib (Multikinase inhibitor in HMA failure). We are participating in a large phase III trial. Randomized versus investigator choice.

LSD1 inhibitors: We are participating in a phase I in AML, run by lung cancer group.

IDH1/IDH2 inhibition: These mutations present in 15% of AML but only 6% of MDS. They lead to aberrant hypermethylation. In the phase I/II study in advanced myeloid malignancies 6/16 MDS patients had a response (1 CR, 1 PR, and 4 HI). Stein E, ASH abstract 343, 2016.

Venetoclax (BCL2 inhibition): Ongoing clinical trials in up front and HMA failure settings.

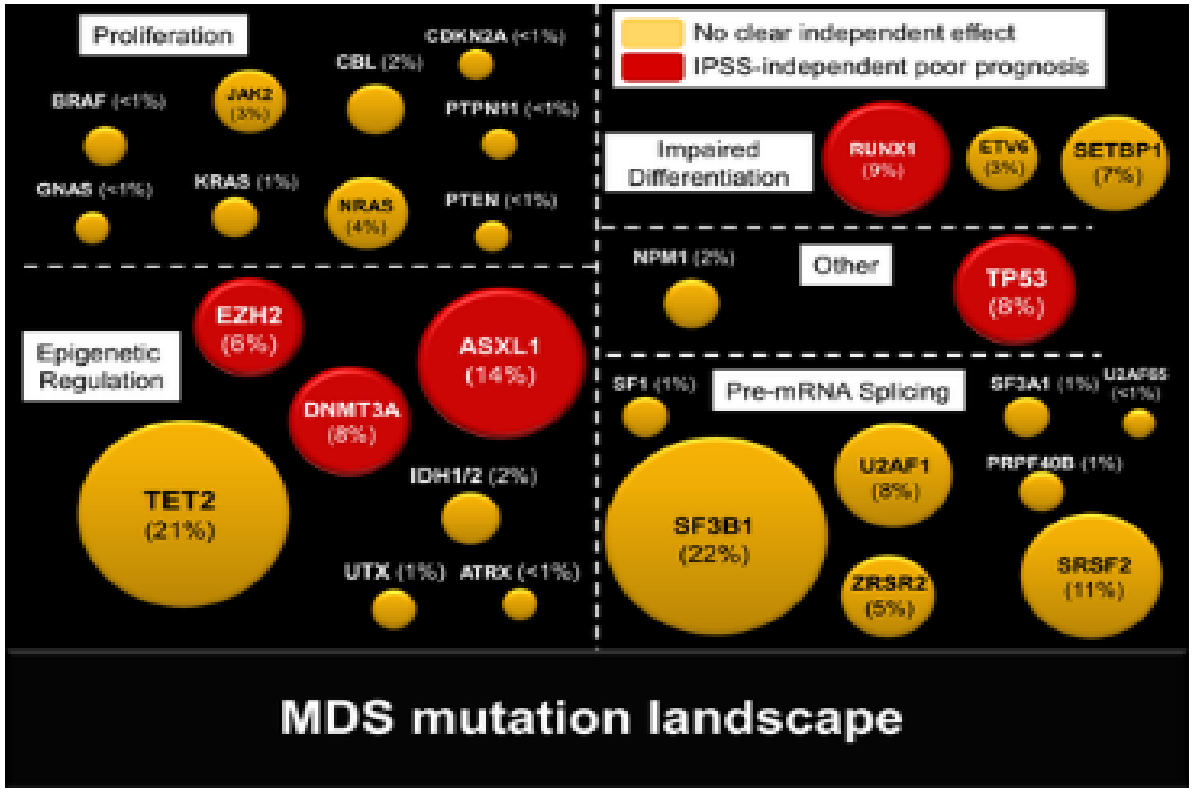
Clinical Trials for MDS Open At Penn

Up front: Azacitadine plus pracinostat. IV Vidaza (7 day dosing) plus oral pracinostat.

HMA failure: Rigosertib 2:1 randomization versus best available therapy.

BMT-CTN 1102: Hypomethylating agent/best supportive care versus reduced intensity conditioning allo SCT for MDS ages 50-75 IPSS 1.5 or greater.

- *Observational only
- *Biological randomization based on presence or absence of matched sibling or 10/10 unrelated donor.


Proliferation
CDKN2A (<1%)
CBL (2%)
JAK2 (3%)
BRAF (<1%)
PTPN11 (<1%)
GNAS (<1%)
KRAS (1%)
NRAS (4%)
PTEN (<1%)
No clear independent effect
IPSS-independent poor prognosis
Impaired Differentiation
RUNX1 (9%)
ETV6 (3%)
SETBP1 (7%)
NPM1 (2%)
Other
TP53 (8%)
Epigenetic Regulation
EZH2 (6%)
ASXL1 (14%)
DNMT3A (8%)
TET2 (21%)
IDH1/2 (2%)
UTX (1%)
ATRX (<1%)
SF1 (1%)
Pre-mRNA Splicing
SF3A1 (1%)
U2AF65 (<1%)
U2AF1 (8%)
PRPF40B (1%)
SF3B1 (22%)
ZRSR2 (5%)
SRSF2 (11%)
MDS mutation landscape