Myelodysplastic Syndromes: How Much Further Do We Have to Go?

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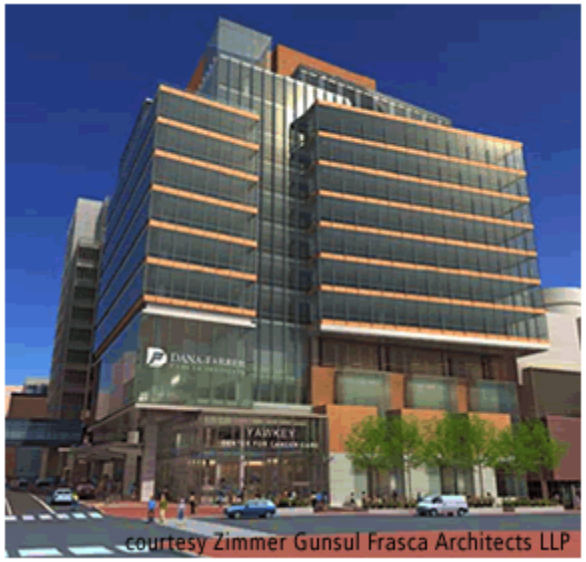
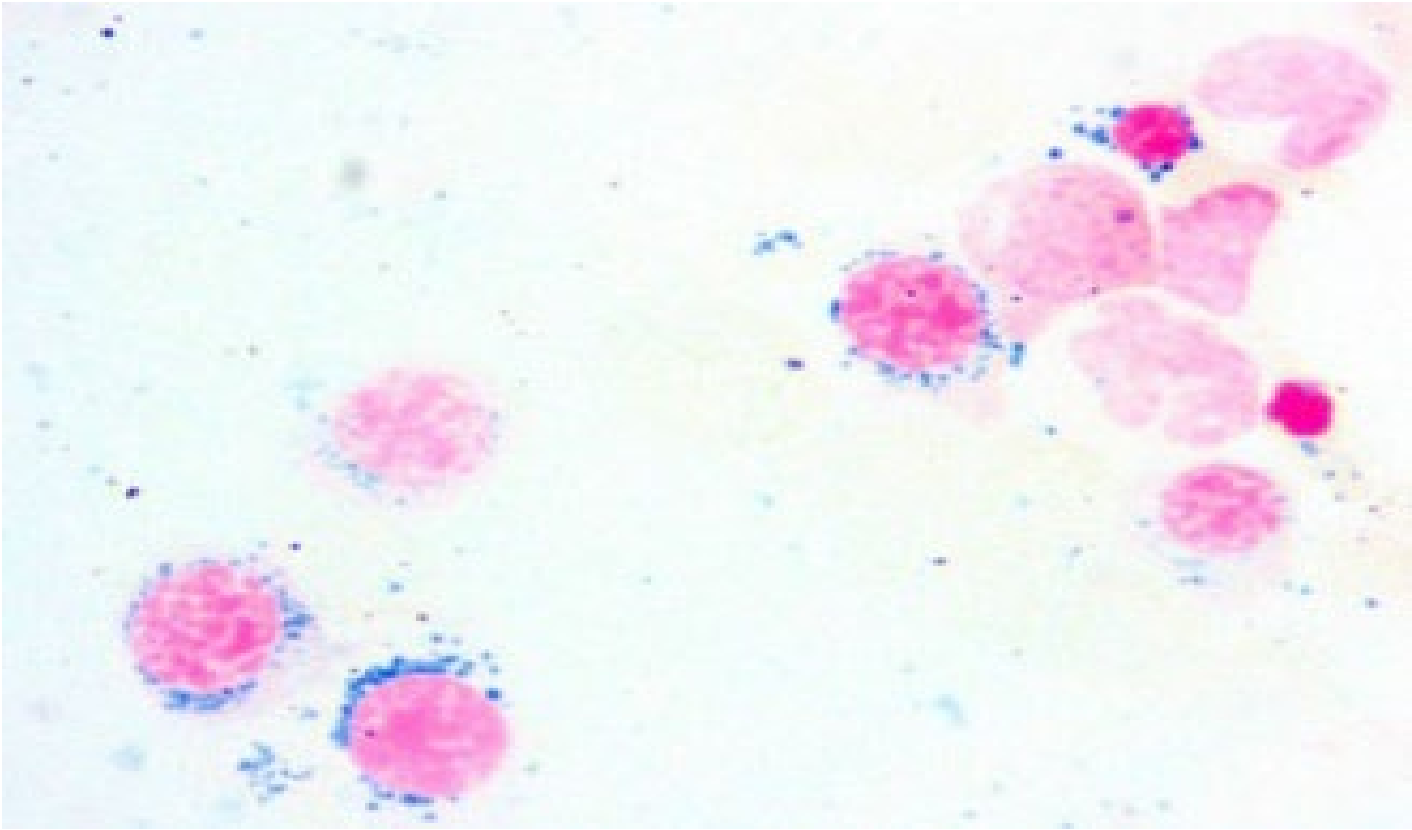


Yawkey Center (Clinic)

MDS: Prognosis and Therapy



Myelodysplastic Syndromes: Outline

- Genetics and Prognosis
- Therapy of lower risk disease
  - Standard approach
    - Lenalidomide in 5q-
    - Lenalidomide +EPO
  - Low dose HMA
  - Luspatercept
  - ?Spliceosome inhibitors
- Therapy of Higher risk disease
  - HMA remains the standard
  - Add ? Venetoclax ? CPI
- Other Questions
  - ? Iron Chelation
  - ? When to transplant

Changes in World Health Organization MDS terminology:

2008 Name	Abbrev.	2016 Name	Abbrev.
Refractory cytopenia with unilineage dysplasia	RCUD (includes RA, RN and RT)	**MDS with single lineage dysplasia**	MDS-SLD
Refractory anemia with ring sideroblasts	RARS	**MDS with ring sideroblasts***	MDS-RS
MDS with isolated del(5q)	Del(5q)	*unchanged*	*unchanged*
Refractory cytopenia with multilineage dysplasia	RCMD	**MDS with multilineage dysplasia**	MDS-MLD
		(with ring sideroblasts*)	MDS-RS-MLD
Refractory anemia with excess blasts, type 1	RAEB-1	**MDS with excess blasts, type 1**	MDS-EB-1
Refractory anemia with excess blasts, type 2	RAEB-2	**MDS with excess blasts, type 2**	MDS-EB-2
MDS, unclassifiable	MDS-U	*unchanged*	*unchanged*
Refractory cytopenia(s) of childhood	RCC	*unchanged*	*unchanged*

* - now includes <15% ring sideroblasts if *SF3B1* mutation is present

References: WHO Tumour Classification 4th edition, IARC 2008. Arber D et al, Blood *May 2016.*

Risk Assessment in Myelodysplastic Syndromes

Key Information for MDS Risk Assessment in 2019
Host Factors
• **Age**
• **Comorbid** conditions
• **Performance status**
Disease Factors
• Proportion of marrow **blasts**
• Number and degree of peripheral blood **cytopenias**
• **Cytogenetics** / karyotype
• **Transfusion** burden
• Other marrow features: presence of heavy marrow **fibrosis**, ring sideroblasts (if low risk/only anemic – to distinguish RA from RARS)

While not yet routinely part of risk assessment, molecular features will become critical soon.

IPSS (1997) Risk Stratification

	Score				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5%	5%-10%	--	11%-20%	21%-30%
Karyotype class*	Good	Intermediate	Poor	--	--
# of cytopenias**	0 or 1	2 or 3	--	--	--

*** Karyotype class: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes; ** Cytopenias: Hb < 10 g/dL, ANC < 1800/uL, platelets < 100,000/uL**

Risk Groups				
	Low	Int-1	Int-2	High
IPSS	0	0.5-1.0	1.5-2.0	2.5-3.5

Adapted from Greenberg P, et al. *Blood*. 1997:89(6):2079-2088.

MDS IPSS-R Components (Greenberg P et al 2012)

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Cytogenetic Risk group	Included karyotypes	Median survival, mo	% Patients
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Karyotypes for use in IPSS-R

Risk group	Included karyotypes	Median survival, years	25% of patients to AML, years	Proportion of patients in this group
Very good	del(11q), -Y	5.4	N/R	4%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4	72%
Intermediate	+8, del(7q), i(17q), +19, any other single or double abnormality not listed	2.7	2.5	13%
Poor	Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities	1.5	1.7	4%
Very poor	Complex with >3 abnormalities	0.7	0.7	7%

From: Greenberg P et al *Blood* 2012 Sep 20;120(12):2454-65.

IPSS-R

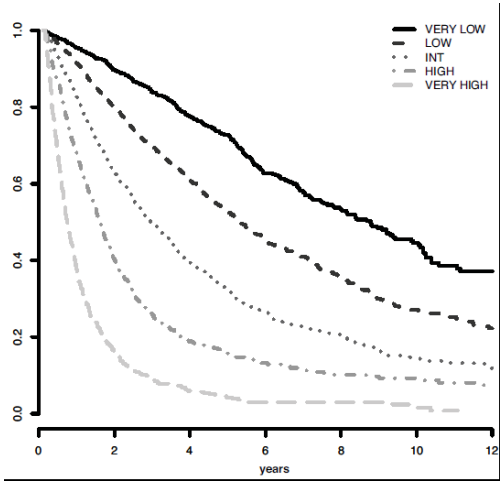
Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤2%	>2 - <5%	5 - 10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	0	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	0	0.5	1		

Possible range of summed scores: 0-10

Greenberg P et al *Blood* 2012 Sep 20;120(12):2454-65.

IPSS-R

Risk group	Points	% patients (n=7,012; AML data on 6,485)	Median survival, years	Median survival for pts under 60 years	Time until 25% of patients develop AML, years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermed	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

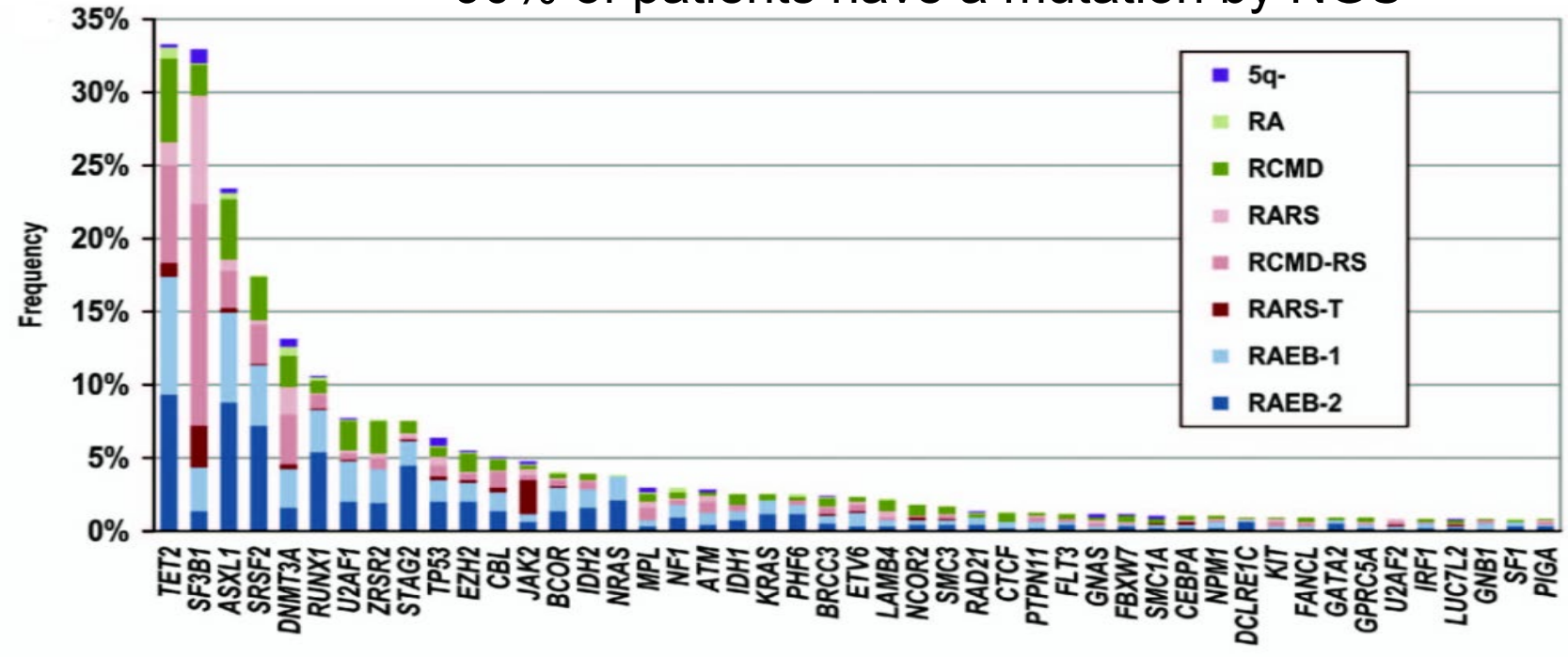


Using IPSS-R:
27% of IPSS lower risk "upstaged"
18% of IPSS higher risk "downstaged"

Greenberg P et al *Blood* 2012 Sep 20;120(12):2454-65.

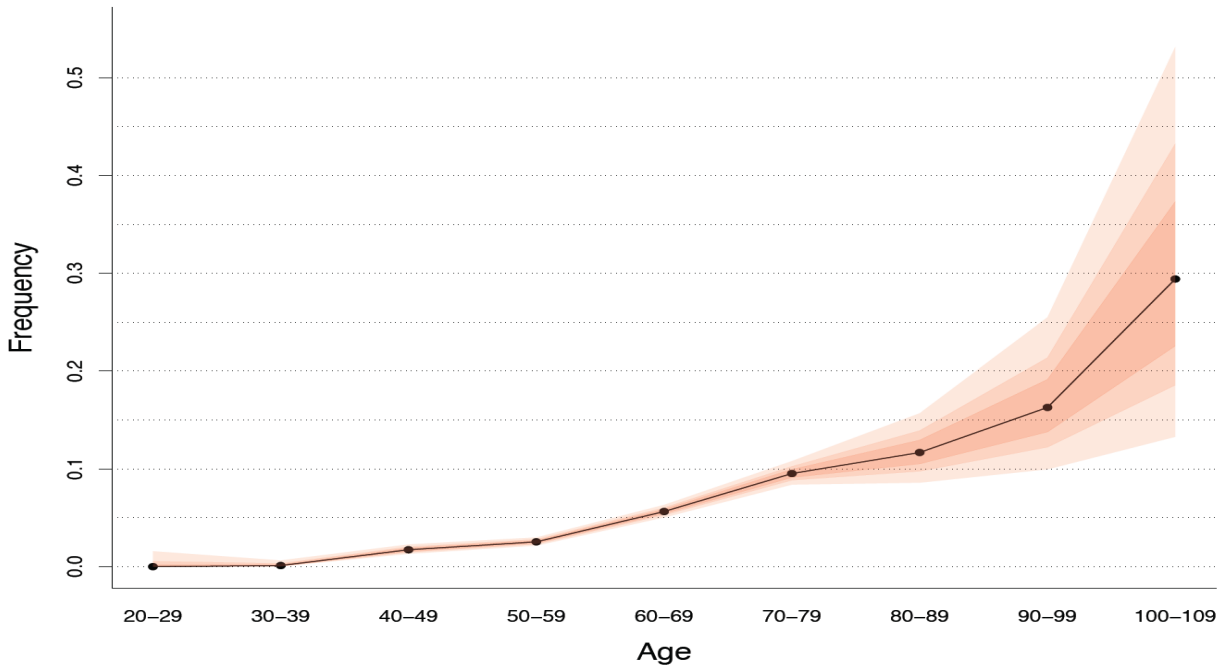
Recurrent Genetic Mutations in MDS

~90% of patients have a mutation by NGS



Haferlach et al., *Leukemia* (2014) 28, 241–247

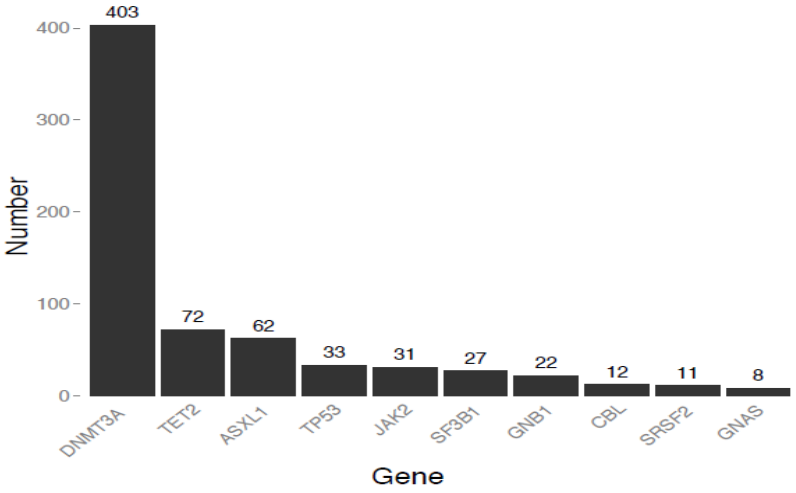
Frequency of Mutations by Age

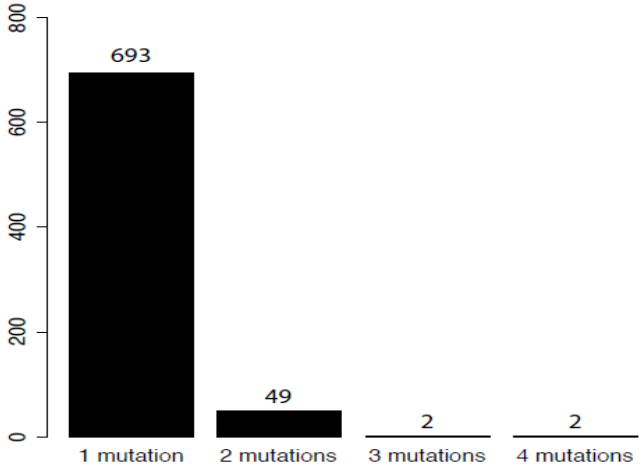


No. with mutation	0	1	50	138	282	219	37	14	5
Total	240	885	2894	5441	5002	2300	317	86	17

Jaiswal S et al *N Engl J Med* 2014

Mutation Distribution





Jaiswal S et al *N Engl J Med* 2014

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

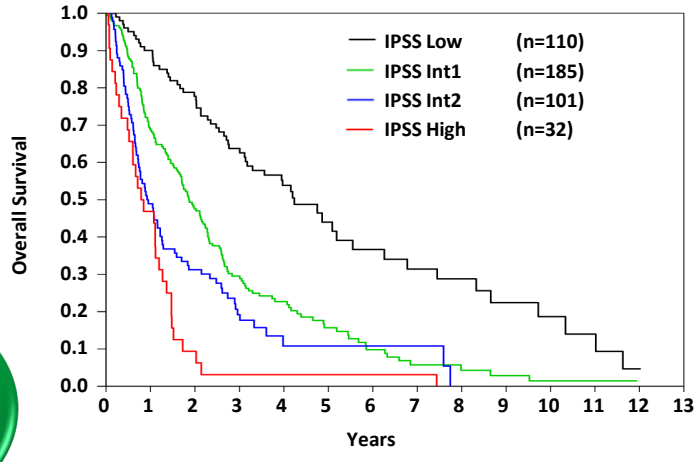
Traditional ICUS

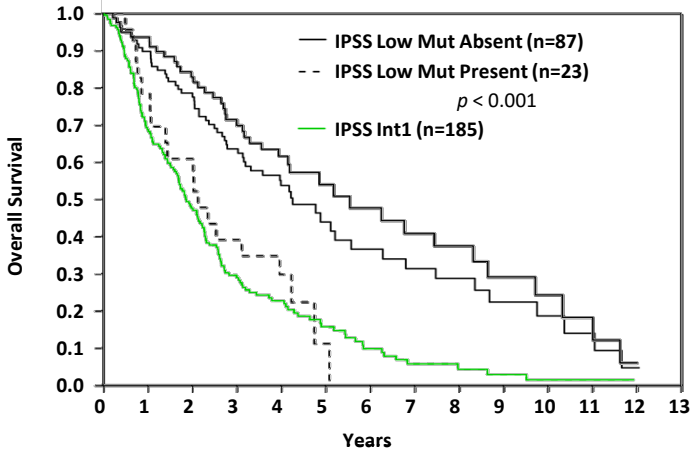
MDS by WHO 2008

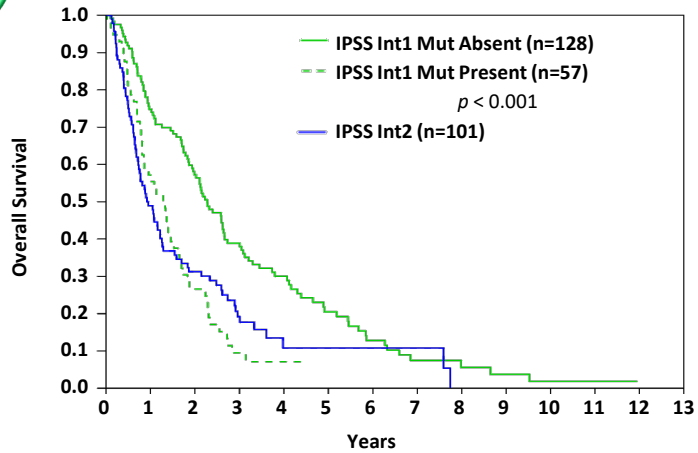
	'Non-clonal' ICUS	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	–	+	+	+	+
Dysplasia	–	–	–	+	+
Cytopenias	+	–	+	+	+
BM Blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall Risk	Very Low	Very Low	Low (?)	Low	High
Treatments	Obs/BSC	Observation	Obs/BSC/GF	Obs/BSC/GF IMiD/IST	HMA/HCST

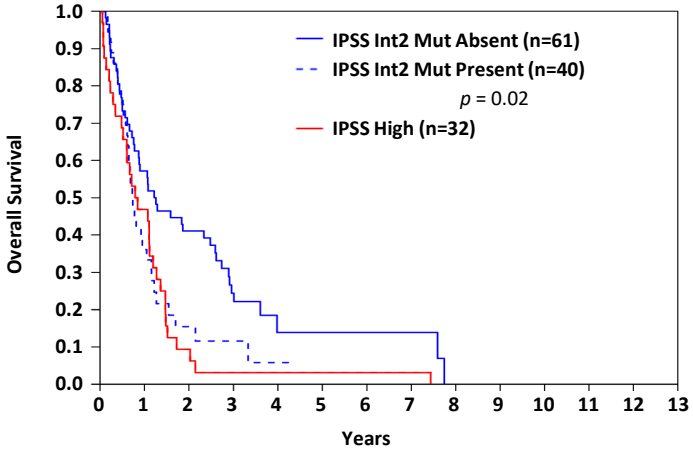
Clonal Cytopenias

Impact of Mutations by IPSS Group









Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

Lenalidomide Clinical Trials in MDS

Eligibility:

>2 U pRBCs/8 weeks

Platelet >50 x 10^9/L

ANC >500/uL

MDS-001

N = 43, Phase I/II initiated Feb 2002

List A et al *NEJM* 2005

Del(5q)

MDS-003

N=148, Phase II initiated July 2003

List A et al *NEJM* 2006

67% transfusion independence

Median duration of response >2 years

45% complete cytogenetic remission

MDS-004

N=205, Phase III initiated July 2005

Fenaux et al *Blood* 2011

No difference in dose reductions w/ 5 vs 10 mg.
↑cytogenetic CR with 10 mg 21/28 d vs 5 mg/d

Non-del(5q)

MDS-002

N = 214, Phase II initiated July 2003

Raza A et al *Blood* 2008

26% transfusion independence

Median duration of response 41 weeks

9% complete cytogenetic remission

MDS-005

N = 239, Phase III initiated Nov. 2009

Santini et al J Clin Oncol 2016

27% v 3% TI, 31 wk resp duration
No diff in QOL overall, but resp assoc w imp QOL

MDS: ?New Approaches for Lower Risk

- **Len (10 mg/d x 21d)+EPO (60k/wk) higher major 4 week erythroid response (26%) than Len alone (10%) in non del 5q- (p=0.018); E2905**
  - List et al., ASH 2016, abstract 223; Toma A, et al, Leukemia 2016, 30: 897-905.

- **Activin trap: luspateracept**
  - Fenaux et al., ASH 2018, abstract 1

- **Short course hypomethylating agents for lower risk pts**
  - 3d decitabine higher ORR (70)% than 3d azacytidine (33%)
  - Jabbour et al., Blood. 2017 130(13):1514-1522
  - Ongoing MDS consortium rand trial of 3 low dose HMA arms

- **Splicesome inhibitors in those with U2AF1, SF3B1, SRSF2, ZRSR2 mutations**

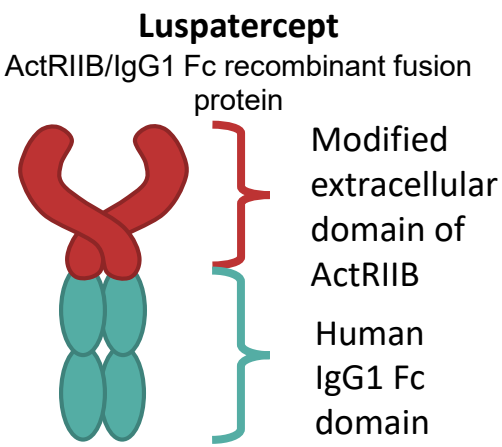
The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients with Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

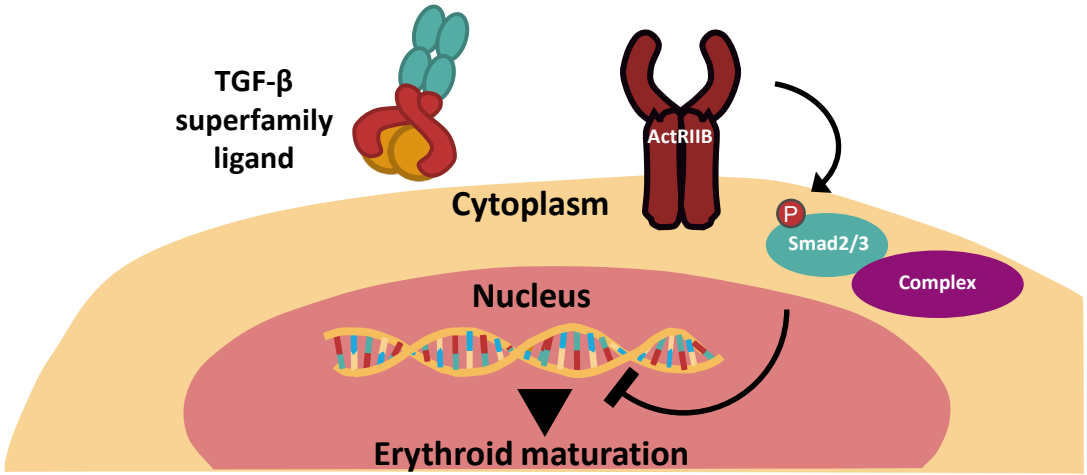
Pierre Fenaux, Uwe Platzbecker, Ghulam J. Mufti, Guillermo Garcia-Manero, Rena Buckstein, Valeria Santini, María Díez-Campelo, Carlo Finelli, Mario Cazzola, Osman Ilhan, Mikkael A. Sekeres, José F. Falantes, Beatriz Arrizabalaga, Flavia Salvi, Valentina Giai, Paresh Vyas, David Bowen, Dominik Selleslag, Amy E. DeZern, Joseph G. Jurcic, Ulrich Germing, Katharina S. Götze, Bruno Quesnel,
Odile Beyne-Rauzy, Thomas Cluzeau, Maria Teresa Voso, Dominiek Mazure, Edo Vellenga, Peter L. Greenberg, Eva Hellström-Lindberg, Amer M. Zeidan, Abderrahmane Laadem, Aziz Benzohra, Jennie Zhang, Anita Rampersad, Peter G. Linde, Matthew L. Sherman,
Rami S. Komrokji and Alan F. List

Fenaux P, et al, ASH 2018, abstract 1

MEDALIST Luspatercept Trial

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion-reduction or RBC-TI in patients with MDS-RS (52%) vs. other subtypes (30%)[2]





1. Suragani RN, et al. *Nat Med*. 2014;20:408.;
2. Platzbecker U, et. A. Lancet Oncol 2017; 18:1338.

ActB, activin B; ActRIIB, human activin receptor type IIB; BMP, bone morphogenetic protein; GDF, growth differentiation factor; IgG1 Fc, immunoglobulin G1 fragment crystallizable; LR, lower-risk; MDS, myelodysplastic syndromes; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor-beta.

MEDALIST Trial

Study Design - A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO 2008): ≥ 15% ring sideroblasts or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Int-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naïve: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease modifying agents (e.g., iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 d
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

Disease & Response Assessment week 24 & q 6 months Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; No crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Data cutoff: May 8, 2018 Includes Last Subject Randomized + 48 weeks.
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agents; iMID, immunomodulatory drug; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; RBC, red blood cell; s.c., subcutaneously; SF3B1, splicing factor 3b subunit 1; WHO, World Health Organization.

MEDALIST Trial
Study Endpoints

Primary endpoint:

- Red Blood Cell – Transfusion Independence ≥ 8 weeks (Weeks 1–24)

Key secondary endpoints:

- Red Blood Cell – Transfusion Independence ≥ 12 weeks, Weeks 1–24
- Red Blood Cell – Transfusion Independence ≥ 12 weeks, Weeks 1–48

Additional secondary endpoints:

- HI-E (IWG 2006 criteria[1]) for any consecutive 56-day period
  - Reduction in transfusion burden ≥ 4 RBC units/8 weeks[a] or
  - Mean Hb increase of ≥ 1.5 g/dL/8 weeks[b]
- Duration of response
- Hb change from baseline
- Mean serum ferritin

[a] In patients with baseline RBC transfusion ≥ 4 units/8 weeks. [b] In patients with baseline RBS transfusion burden < 4 units/8 weeks.
AE, adverse event; IWG, International Working Group; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; RBC-TI, red blood cell transfusion independence.

1. Cheson B, et al. Blood 2006;108:419–25.

MEDALIST Trial

Primary Endpoint Achieved: Red Blood Cell – Transfusion Independence) ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval; RBC-TI, red blood cell transfusion independence.

MEDALIST Trial

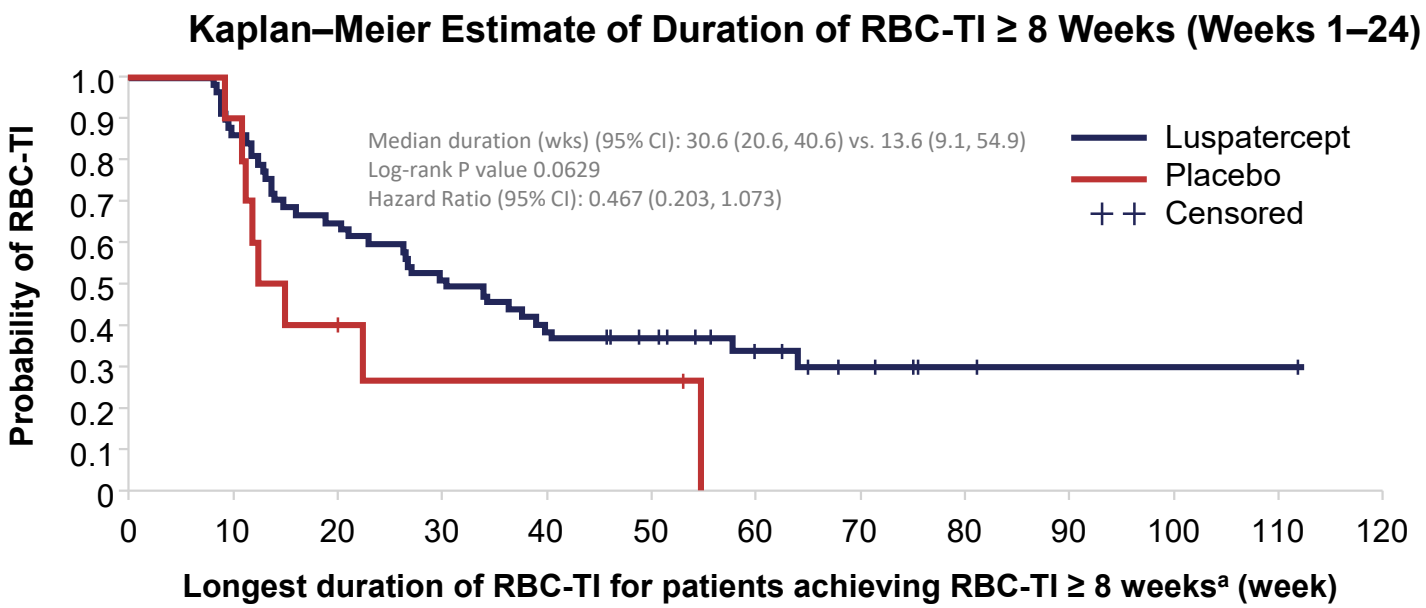
Key Secondary Endpoints: Red Blood Cell – Transfusion Independence ≥12 Weeks

RBC-TI ≥ 12 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

[a] Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval; IPSS-R, Revised International Prognostic Scoring System; RBC-TI, red blood cell transfusion independence.

MEDALIST Trial

Duration of RBC-TI Response



Number of patients													
Luspatercept	58	49	37	29	23	18	11	6	3	1	1	1	0
Placebo	10	9	4	2	2	2	0						

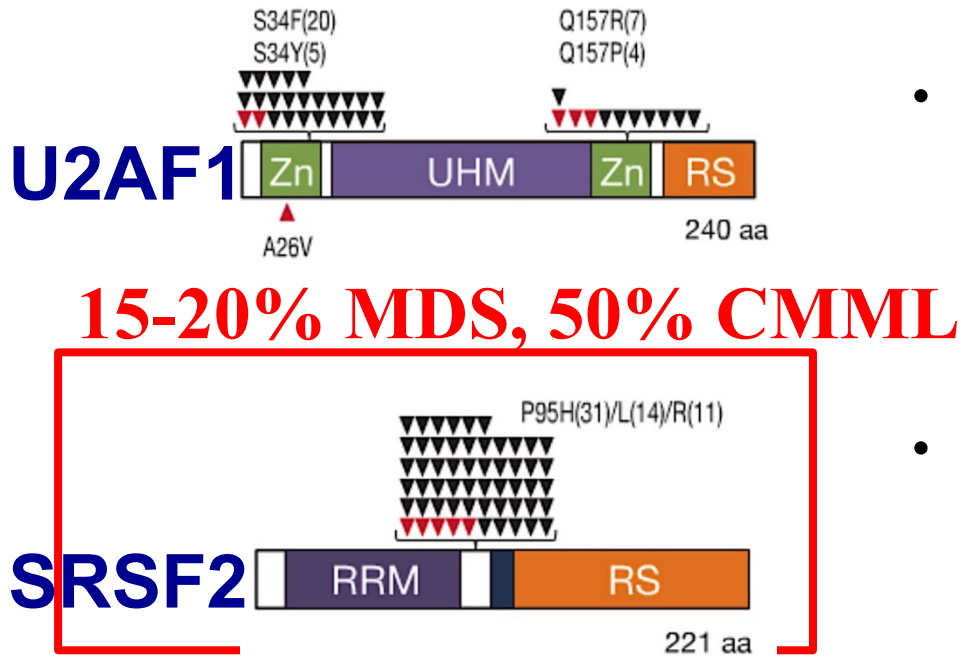
[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.
IPSS-R, Revised International Prognostic Scoring System; HR, hazard ratio; RBC-TI, red blood cell transfusion independence.

MEDALIST Trial
Safety Summary

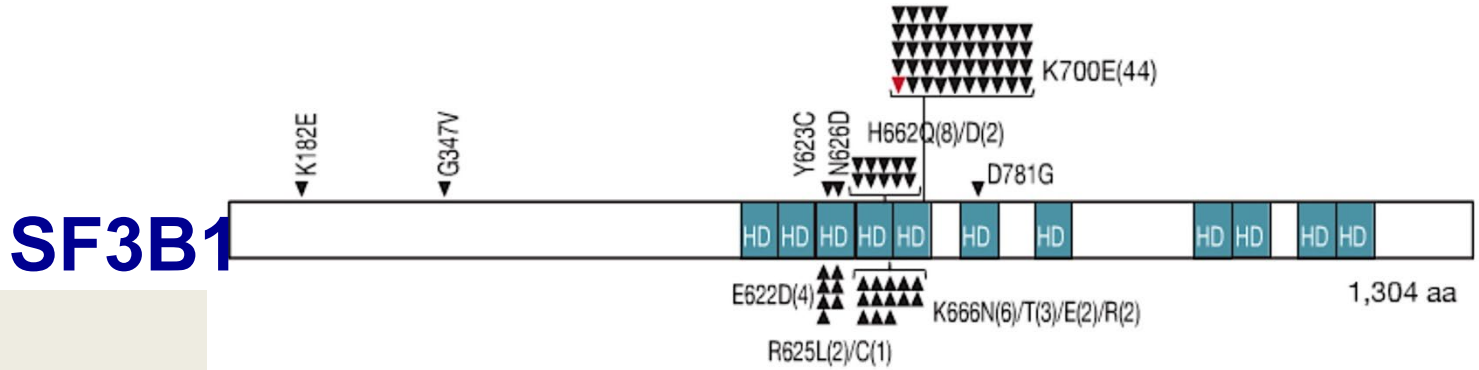
	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE, n (%)	**150 (98.0)**	**70 (92.1)**
Patients with ≥ 1 suspected related TEAE	67 (43.8)	27 (35.5)
Patients with ≥ 1 serious TEAE	48 (31.4)	23 (30.3)
Patients with ≥ 1 Grade 3 or 4 TEAE	65 (42.5)	34 (44.7)
Patients with TEAEs leading to death[a]	5 (3.3)	4 (5.3)
Patients with ≥ 1 TEAE causing discontinuation, n (%)	**13 (8.5)**	**6 (7.9)**

[a] In luspatercept arm: sepsis (2), multiple organ dysfunction syndrome, renal failure, hemorrhagic shock; in placebo arm sepsis, urosepsis, general physical health deterioration, respiratory failure
TEAE, treatment-emergent adverse event.

Splicing factor mutations in hematologic malignancies

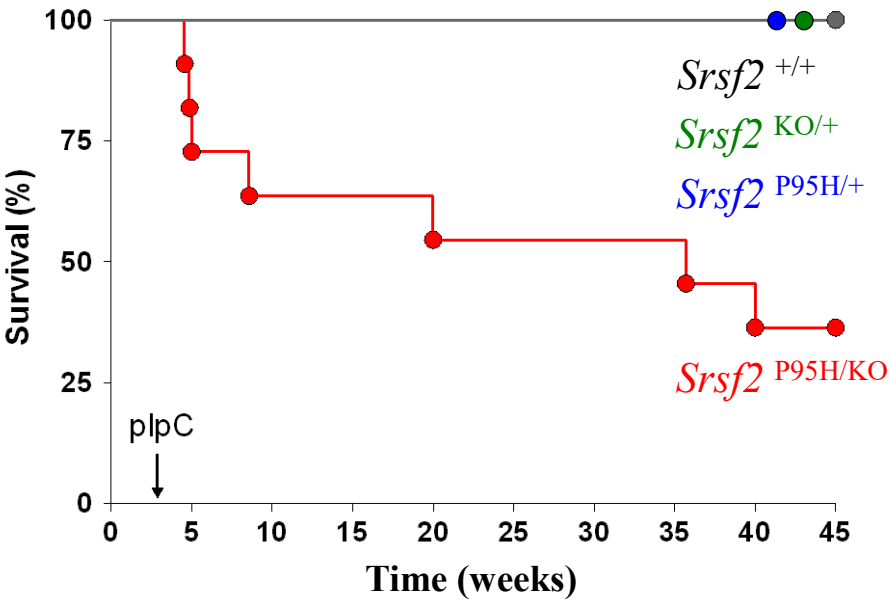


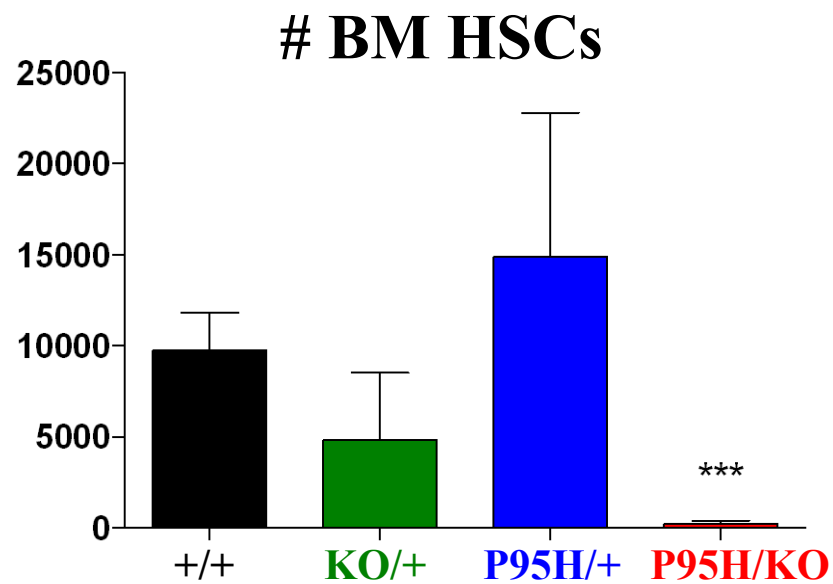
- Spliceosomal mutations occur almost entirely as **heterozygous point mutations** at specific residues
- These mutations occur in a **mutually exclusive manner** with one another

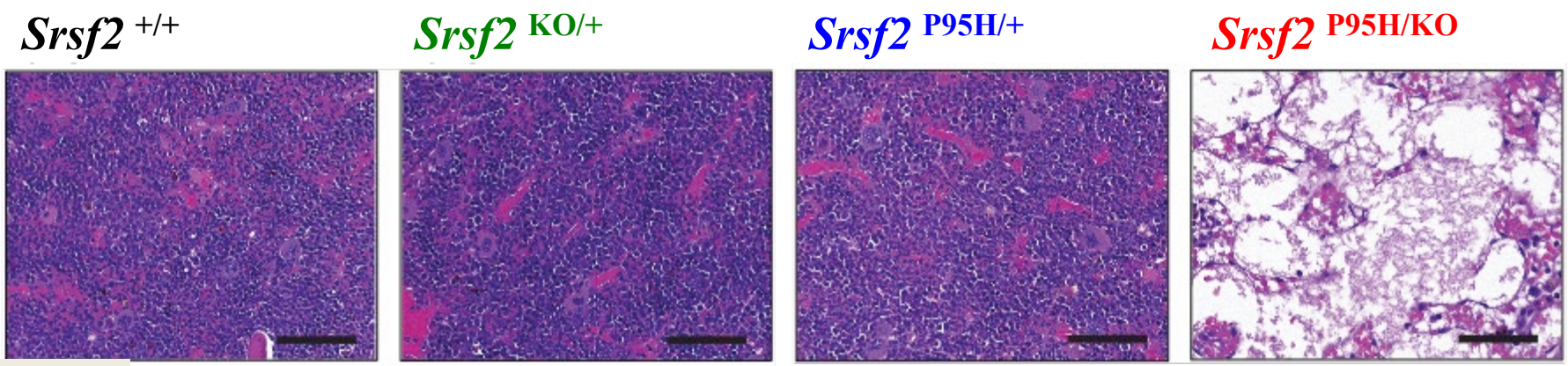


Yoshida et al. *Nature* 2011; Wang et al. *NEJM* 2011; Papaemmanuil *et al. NEJM* 2011; Graubert et al. *Nat Genetics* 2012

Srsf2^{P95H} cells require wildtype *Srsf2* for survival







Lee et al. Nature Medicine (2016) 22: 672-678

Azacitidine Survival Study

AZA-001 Survival Study Design

Higher-risk MDS (FAB)
1:1 Randomization

Azacitidine SC 75 mg/m^2 × 7 days, Repeated every 28 days

N=358

Standard of Care
Options:
1. Best supportive care
2. Low-dose cytarabine
3. 3&7 chemotherapy

Fenaux P, et al. *Lancet Oncol.* 2009;10(3):223-232.

AZA-001 MDS Study Results

- **Median survival improved with azacitidine**
  - **24.4 mos for azacitidine vs. 15 mos for conventional care regimens (CCR) (stratified log-rank *P*-value = 0.0001)**
  - **9.4 months median survival benefit for patients on azacitidine compared with CCR**
  - **CR not needed to note survival benefit**

- **Two-year survival rate:**
  - **50.8% for azacitidine vs 26.2% for CCR ($P < 0.0001$)**
  - **Note: alternative dosing/scheduling strategies and IV formulation may be equivalent to 7 day SC**

Fenaux P, et al. *Lancet Oncol.* 2009;10(3):223-232.

Outcomes After Azacitidine Failure Are Poor

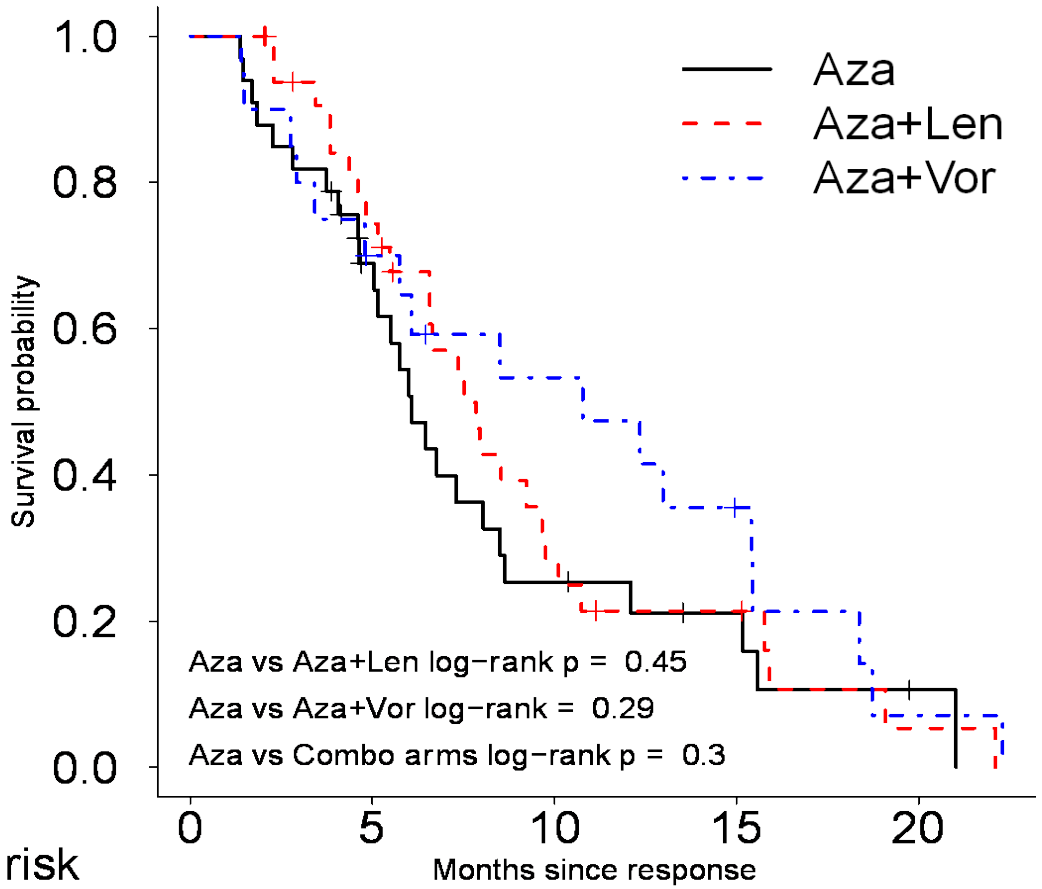
- Data available on 350 pts (median survival 3.6 months for those without known treatment)

Subsequent therapy	Number of patients (%)	Median survival (range)
Allogeneic transplant	**50 (14%)**	18.3 months **(3-55+)**
Investigational therapy **(e.g. IMiD, HDACi, other)**	**56 (16%)**	13.2 months **(1-36+)**
Conventional cytotoxic therapy **(e.g., 3&7, LDAC, 6-MP etc)**	**84 (24%)**	7.6 months
Palliative care	**160 (46%)**	3.3 months

Even in LR MDS, HMA failure=15 mon med OS, Jabbour ASH 2013

Prebet T et al, *JCO* 2011; 29:3322

North American Intergroup Randomized Phase 2 MDS Study S1117: Relapse-free Survival (I) All Responders



N at risk

Aza	33	19	7	4	1
Aza+Len	34	23	8	5	1
Aza+Vor	20	13	9	5	1

Sekeres et al. JCO 201735: 2745-2753

A Phase II Study of Nivolumab or Ipilimumab with or without Azacitidine for Patients with Myelodysplastic Syndrome

Guillermo Garcia-Manero, Koji Sasaki, Guillermo Montalban-Bravo, Naval G. Daver, Elias J. Jabbour, Yesid Alvarado, Courtney D. DiNardo, Farhad Ravandi, Gautam Borthakur, Prithviraj Bose, Naveen Pemmaraju, Kiran Naqvi, Jorge E. Cortes, Tapan M. Kadia, Marina Y. Konopleva, Simona Colla, Hui Yang, Caitlin R. Rausch, Yvonne Gasior, Carlos E. Bueso-Ramos, Rashmi Kanagal-Shamanna, Keyur P. Patel, Hagop M. Kantarjian

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Garcia-Manero, G et al, ASH 2018, abstract 465

ICPI in MDS: Introduction

- **MDS CD34+ cells express PD1, PDL1 and CTLA4**
- **Exposure to HMA results in overexpression of PD1, PDL1 and CTLA4 both in vitro and in vivo**
- **Immune check point inhibitors (ICPI) significant activity in multiple malignancies**
- **Need for new therapies in front line and HMA failure MDS**
- **Hypothesis: Treatment of patients with MDS with ICPI alone or in combination with HMA safe and clinically active in MDS**

Yang et al: Leukemia 2014

ICPI in MDS: Eligibility Criteria

- **Age ≥ 18 years with WHO MDS**
- **Both untreated and HMA failure disease**
- **Acceptable PS, renal and hepatic functions**
- **No prior hx of inflammatory or autoimmune disease**
- **HIV disease or active hepatitis C**
- **For HMA failure cohort:**
  - **No more than 4 months since last cycle of HMA**
  - **No other therapy after HMA exposure**

ICPI in MDS: Study design

HMA failure cohorts	Previously untreated cohorts
Cohort #1: Single agent nivolumab	Cohort #4: 5-azacitidine +nivolumab
Cohort #2: Single agent ipilimumab	Cohort #5: 5-azacitidine + ipilimumab
Cohort #3: Ipilimumab+nivolumab	Cohort #6: 5-azacitidine + ipilimumab+nivolumab

- Each cohort max of N=20 patients
- In HMA failure cohorts: add back azacitidine after 6 cycles of ICPI if no response
- Stopping rules for toxicity and response

ICPI in MDS: Treatment

Cohort	Therapy
Cohort #1	Nivolumab 3 mg/kg IV q2 weeks
Cohort #2	Ipilimumab 3 mg/kg IV q3 weeks
Cohort #4	Azacitidine 75 mg/m^2 IV x 5 days q 28 Nivolumab 3 mg/kg IV on day 6 and 20
Cohort #5	Azacitidine 75 mg/m^2 IV x 5 days q28 Ipilimumab 3 mg/kg IV on day 6

ICPI in MDS
Toxicities

	Frontline				HMA failure			
	Nivo + AZA N = 20		Ipi + AZA N = 21		Nivo N = 15		Ipi N = 20	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Infection	6 (30)	5 (25)	5 (24)	4 (19)	6 (40)	6 (40)	7 (35)	6 (30)
Rash	5 (25)	0	8 (38)	1 (5)	1 (7)	0	7 (35)	1 (5)
Fatigue	6 (30)	0	1 (5)	0	6 (40)	0	5 (25)	0
Musculoskeletal pain	7 (35)	0	4 (19)	2 (10)	0	0	4 (20)	0
Pruritus	1 (5)	0	4 (19)	0	1 (7)	1 (7)	5 (25)	0
Transaminitis	2 (10)	2 (10)	2 (10)	2 (10)	1 (7)	0	3 (15)	2 (10)
Constipation	3 (15)	0	4 (19)	0	1 (7)	0	0	0
Diarrhea	1 (5)	0	3 (14)	0	1 (7)	0	2 (10)	0
Nausea	2 (10)	0	3 (14)	0	1 (7)	0	1 (5)	0
Anorexia	3 (15)	0	1 (5)	0	0	0	2 (10)	0

- Other G3/4: AKI, 2 in Ipi; hemolysis, 1 in Ipi; colitis, 1 in Nivo
- Grade 2 hypophysitis: 1 in Ipi, Ipi+AZA, and Novo+AZA, respectively

ICPI in MDS: Response Rates

	Frontline		HMA failure	
	Nivo + AZA N = 20	Ipi + AZA N = 21	Nivo N = 15	Ipi N = 20
Response				
ORR	14 (70)	13 (62)	0 (0)	6 (30)
CR	8 (40)	3 (14)	0 (0)	0 (0)
mCR+HI	2 (10)	0 (0)	0 (0)	1 (5)
mCR	3 (15)	7 (33)	0 (0)	3 (15)
HI	1 (5)	3 (14)	0 (0)	3 (15)
SD	0 (0)	1 (5)	0 (0)	0 (0)
NR	5 (25)	5 (24)	15 (100)	13 (65)

- Not evaluable: 3 pts
- Median number of cycles: 4 (range 1-29)
- Median number of cycles to response: 3 (range 1-15)

Allogeneic Transplant in MDS: Approximation of Life Expectancy (Years)

	Immediate Transplant	Transplant in 2 Years	Transplant at Progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

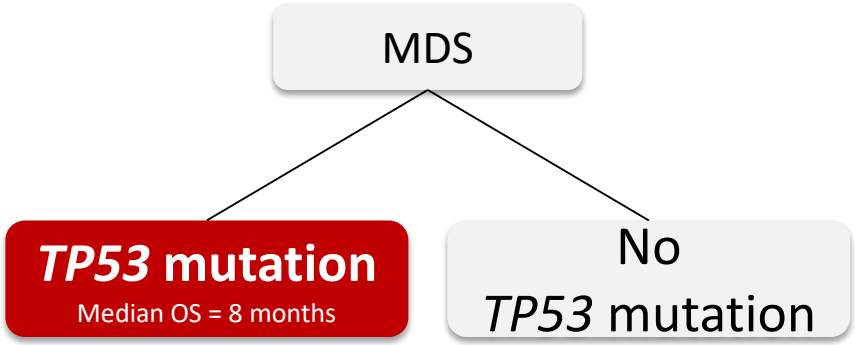
*This is for fully HLA matched T cell replete **myeloablative** SCT*

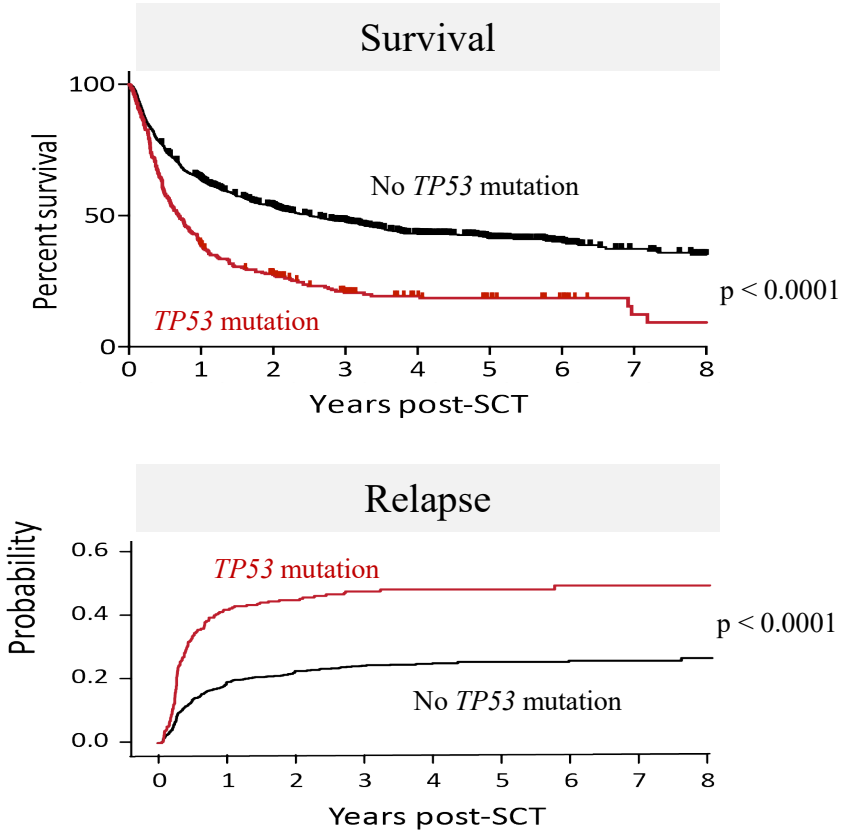
Cutler CS, et al. *Blood.* 2004;104(2):579-585.

Update: Koreth J et al JCO 2013: *Same applies in era of RIC allo SCT among patients 60-70 years old*

TP53 mutated MDS

Poor prognosis Post-SCT due to early relapse





Lindsley C, et al. *N Engl J Med.* 2017;376(6):536-547.

Safety and Efficacy, Including Event-free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients with Low- and Int-1-Risk Myelodysplastic Syndromes (MDS): Outcomes from the Randomized, Double-Blind TELESTO Study

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Angelucci E, et al, ASH 2018, abstract 234

Background and study rationale

- Although iron chelation therapy (ICT) has been shown to improve outcomes in lower-risk MDS patients, the studies were mainly retrospective analyses and registry studies[1–6]
- However, considerable debate remained on the clinical utility of ICT in this patient population, and the need for a randomized trial has long been recognized[8]

Aims

The TELESTO (NCT00940602) study prospectively evaluated event-free survival (EFS) and the safety of ICT with deferasirox versus placebo in patients with Low/Intermediate (Int)-1-risk MDS

AML, acute myeloid leukemia;
MDS, myelodysplastic syndromes; RBC, red blood cell

1. Delforge M *et al. Leuk Res* 2014;38:557–563;
2. Leitch HA *et al. Clin Leukemia* 2008;2:205–211; 3. Lyons RM *et al. Leuk Res* 2017;56:88–95;
4. Neukirchen J *et al. Leuk Res* 2012;36:1067–1070; 5. Remacha AF *et al. Ann Hematol* 2015;94:779–787;
6. Rose C *et al. Leuk Res* 2010;34:864–870; 7. Meerpohl JJ *et al. Cochrane Database Syst Rev* 2014:CD007461

TELESTO study design

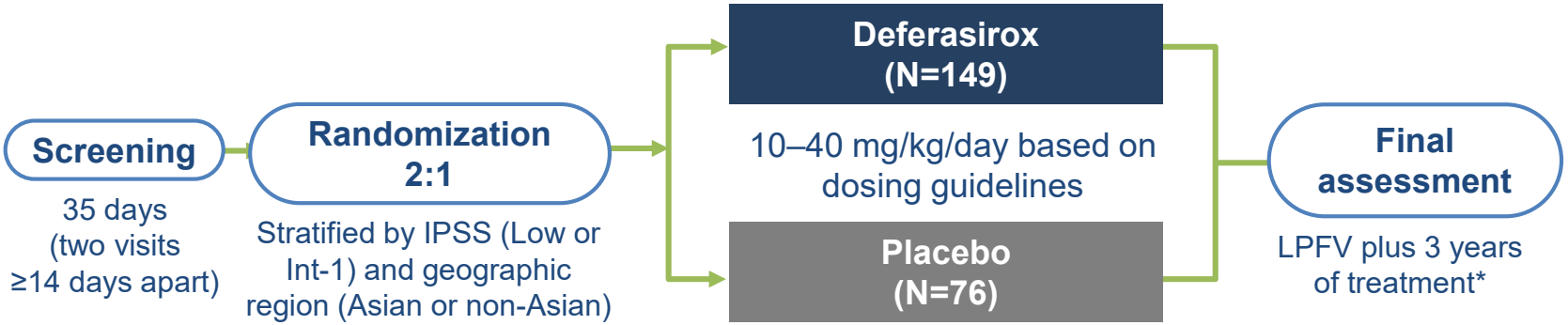
Designed as a **Phase III trial** with a target enrolment of **630** patients

Because of low enrolment, the target sample size was reduced, based on the feasibility of enrolling patients and consultations with the health authorities

Changed a to **Phase II trial** with target enrolment of **210** patients

Trial was therefore not designed to make statistical comparisons

TELESTO – a Phase II, randomized, double-blind study



*Patients who experienced a non-fatal event were discontinued and followed up for 28 days; patients were then followed up every 3–6 months (for evaluation or survival)

Key inclusion criteria:

- Hematologically stable IPSS Low or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
- Serum ferritin >1000 ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF ≥50% by echocardiography
- ALT or AST ≤3.5×ULN, total bilirubin ≤1.5×ULN, no previous diagnosis of liver cirrhosis; CrCl ≥40 mL/min
- ECOG performance status ≤2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LPFV, last patient first visit; LVEF, left ventricular ejection fraction; pRBC, packed red blood cell; ULN, upper limit of normal

TELESTO – study objectives

Primary

To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an **independent adjudication committee**, or death, whichever occurred first

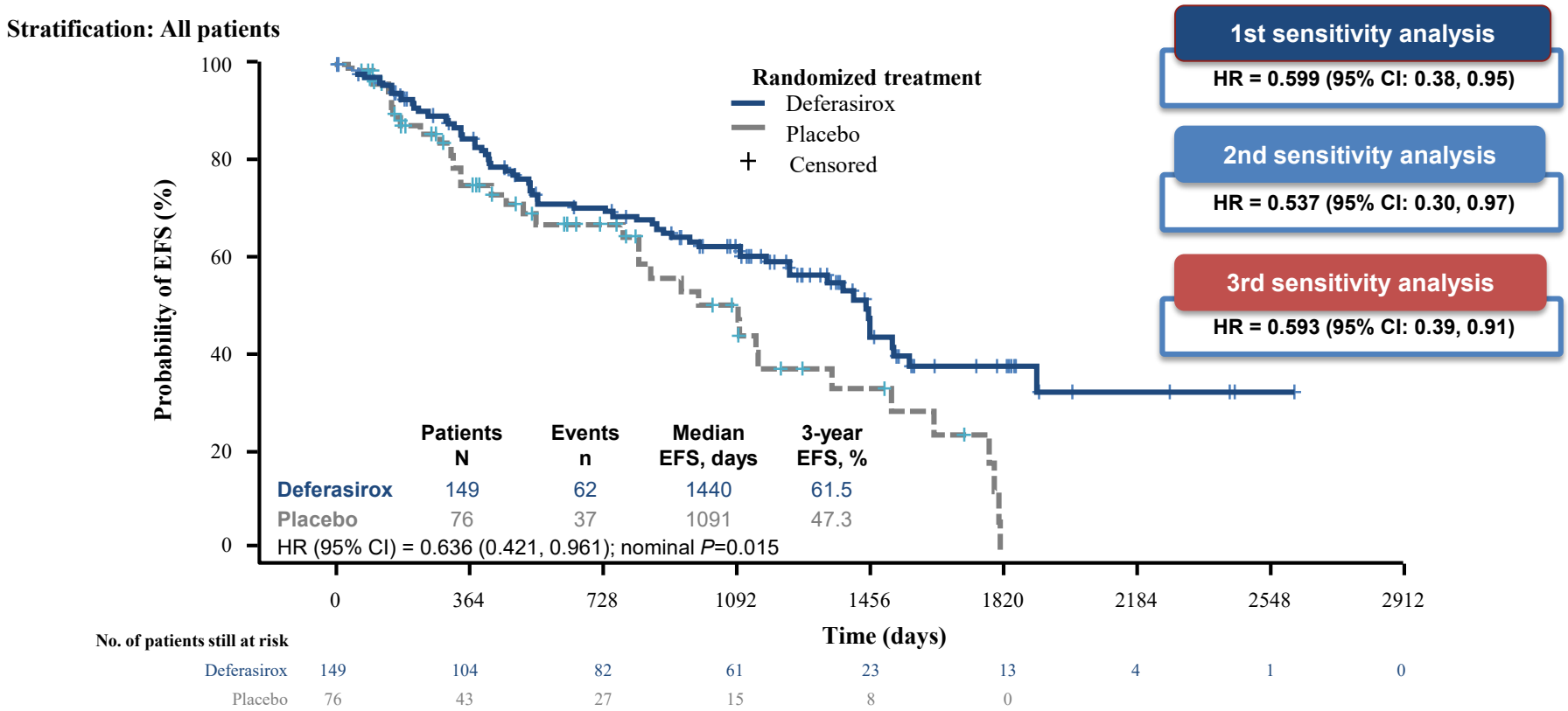
Key secondary

To assess:

- Overall survival
- Change in serum ferritin level
- Hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria[1])
- Change in endocrine function (thyroid and glycemic control)
- Safety

1. Cheson BD *et al. Blood* 2006;108:419–425

Kaplan–Meier plot of EFS



EFS events (non-fatal events or deaths) that occurred first as confirmed by the EAC (adjudication rate 44%)

Parameter	Patients with events†		
	Deferasirox N=149 n (%)	Placebo N=76 n (%)	All patients N=225 n (%)
Non-fatal events confirmed by EAC*	14 (9.4)	12 (15.8)	26 (11.6)
Progression to AML	10 (6.7)	6 (7.9)	16 (7.1)
Hospitalization for CHF	1 (0.7)	3 (3.9)	4 (1.8)
Liver cirrhosis	0	0	0
Liver function impairment	1 (0.7)	1 (1.3)	2 (0.9)
Worsening of cardiac function	2 (1.3)	2 (2.6)	4 (1.8)
Deaths during treatment	48 (32.2)	25 (32.9)	73 (32.4)

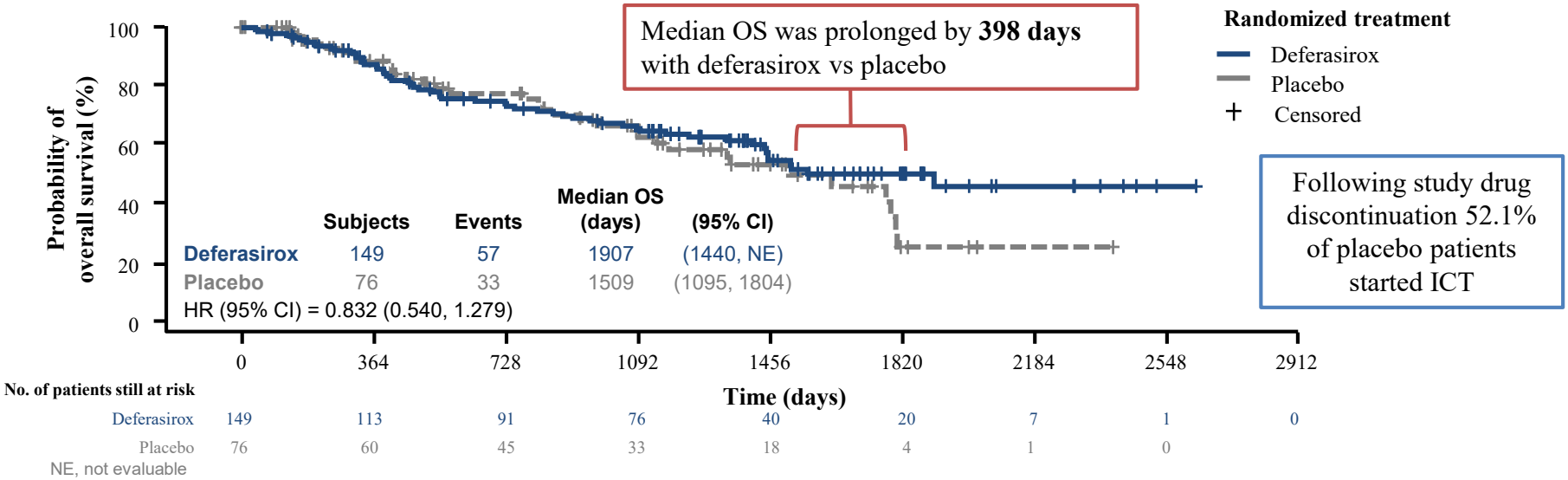
*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included;
†A patient with multiple occurrences of the same event is counted only once in the component category

TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS

Summary of overall survival

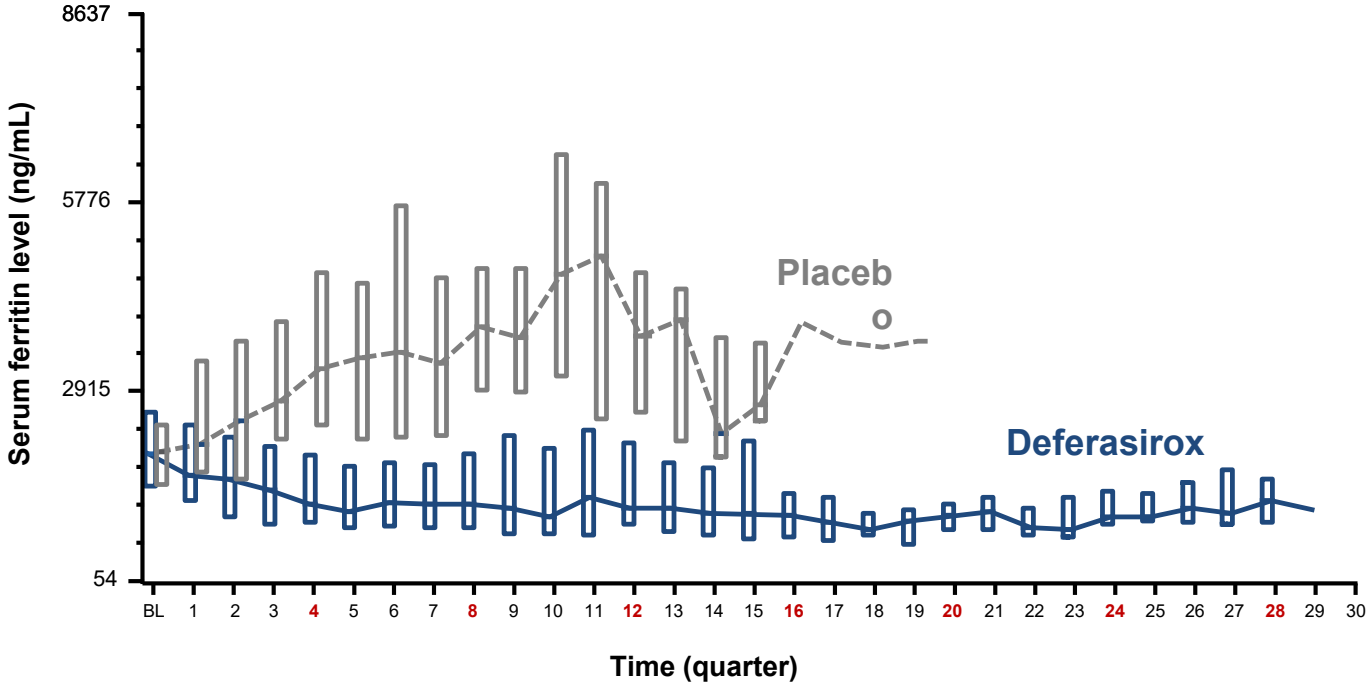
All patients*	Log-rank test			Cox model
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	1907 (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	1509 (1095, 1804)		

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



NE, not evaluable

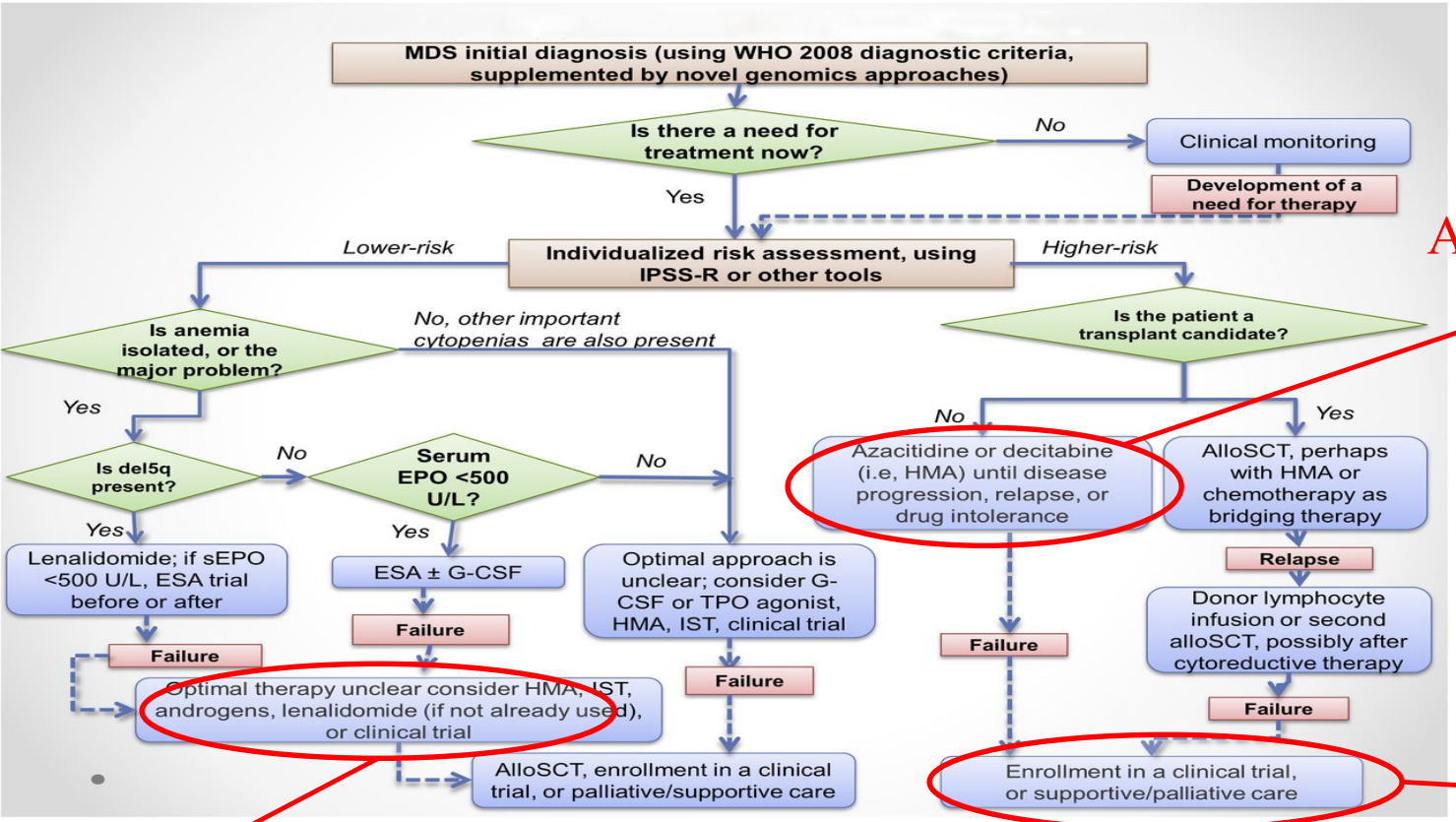
Serum ferritin trends



	BL	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Deferasirox	146	141	123	108	94	89	83	76	70	63	60	55	49	39	29	26	22	16	12	10	8	8	4	4	4	4	3	3	2	1	
Placebo	76	76	69	56	49	37	30	24	24	18	11	10	9	5	3	3	1	1	1	1											

Boxes show lower and upper quartiles, horizontal line shows the median

Current MDS Therapeutic Algorithm



AZA-plus studies

Luspatercept (ACE-536)

Rigosertib, PDL1 antagonists, many others

Bejar R, Steensma D. *Blood* 2014.

Myelodysplastic Syndrome: Conclusions

- Myelodysplastic Syndrome:
  - Mutations matter!
  - Clonal hematopoietic disorder vs MDS
  - Prognosis: IPSS, R-IPSS, genetic mutations, comorbid disease, PS
    - Beware of TP53 mutations
  - Lower risk MDS:
    - ESA, lenalidomide, (Luspatercept)
    - TPO-mimetic agents (safe, perhaps effective in Low risk (Oliva et al Lancet Hematol 2017) , but worse than placebo in higher risk (Dickenson et al , Blood 2019)
    - HMA
  - Higher risk MDS:
    - HMA (azacitidine, decitabine)
    - Immune suppression
    - Addition of second agent has not proven beneficial, thus far (watch for venetoclax) (Ongoing aza +ven in HR ds, and Aza +ven in Aza failure)

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  - **Worldwide: C Schiffer, T Fischer, H Dohner, K Dohner, C Thiede, R Schlenk, and others**
- **Slides**
  - **N Daver, D Sallman, C Burchart, D Pollyea, J Cortes, D DeAngelo, O Ottman, M Wieduwilit, A Advani, M Konopleva, A Maiti**

The End

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