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Myelodysplastic Syndromes (Neoplasms)

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speaker

Olatoyosi Odenike, MD

Disclosures

Consultancy: ABBVIE; Bristol Myers Squibb; Celgene; Impact Biomedicines; Kymera Therapeutics; Novartis; Taiho

Research Funding: ABBVIE; Agios; Aprea Therapeutics; Astex; AstraZeneca; Bristol Myers Squibb; Celgene; CTI/Baxalta; Daiich; Incyte; Janssen; Kartos Pharmaceuticals; Loxo; Novartis; NS-Pharma; Oncotherapy Science

Membership on a Board or Advisory Committee: ABIM; Aplastic Anemia MDS International Foundation; Threadwell Therapeutics

Discussion of off-label drug use: N/A



Case 1: Mr Low Dysplasio

- 73-year-old male presented with fatigue
- Exam: pallor; no organomegaly
- CBC: Hb 7 g/dL, MCV 103 fL, ANC $1.2 \times 10^9/L$, platelets $120 \times 10^9/L$
- Red blood cell transfusions 2-3 units per month
- B12/folate/iron studies unremarkable. Serum EPO: 510 U/L
- Bone marrow: 60% cellular, with multilineage dysplasia with 2% blasts and 35% ring sideroblasts. Karyotype: XY, +8 NGS: **TET2** (VAF 35%) and **SF3B1** (VAF 52%)

Patient wants information about his diagnosis and prognosis.

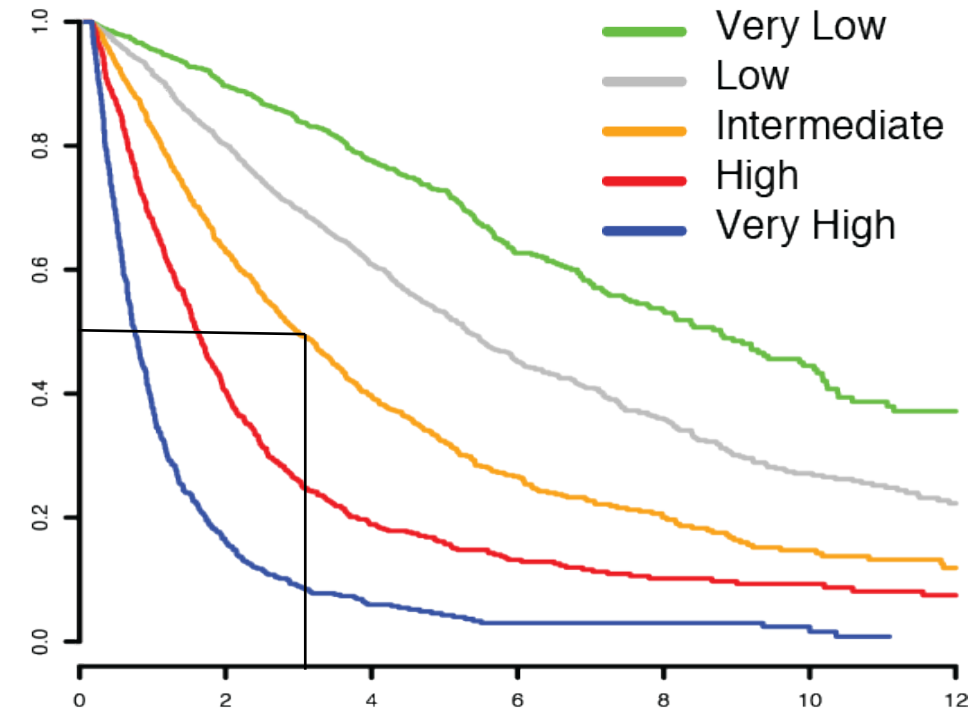


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- a) Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS); IPSS-R intermediate risk
- b) MDS with SF3B1; IPSS-M moderate low
- c) Refractory anemia; low risk disease
- d) a+b
- e) None of the above

Prognosis by the Revised IPSS (IPSS-R)

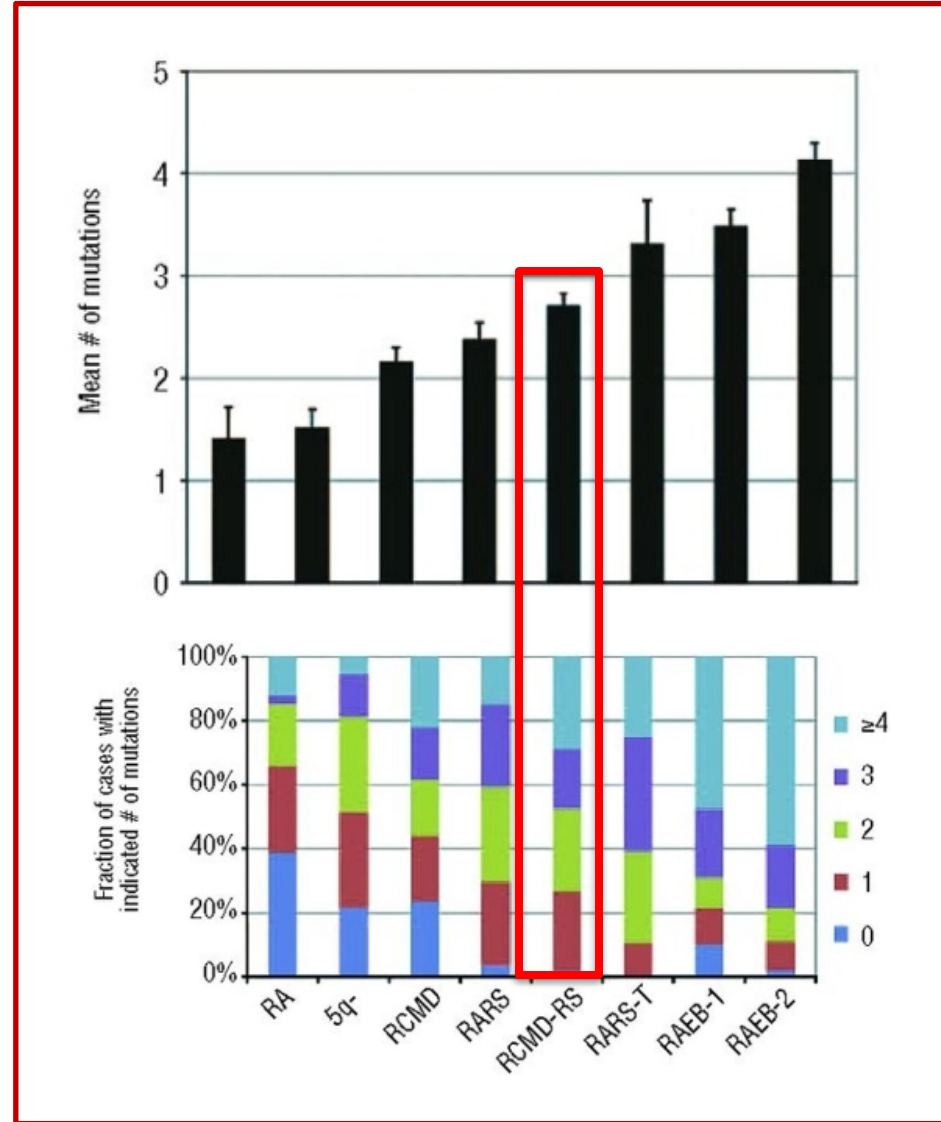
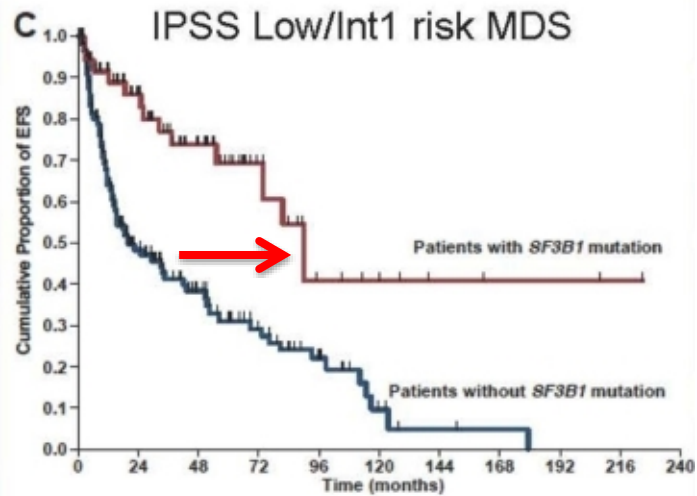
Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		INT	Poor	Very Poor
BM blast %	≤ 2		>2 <5		5 - 10	>10	
Hemoglobin	≥ 10		8 - <10	< 8			
Platelets	≥ 100	50– <100	< 50				
ANC	Risk Category						
	Very Low		≤ 1.5				
	Low		> 1.5 - 3				
	Intermediate		> 3 – 4.5				
	High		> 4.5 - 6				
	Very High		>6				



IPSS: Int-1, median OS: 42 months

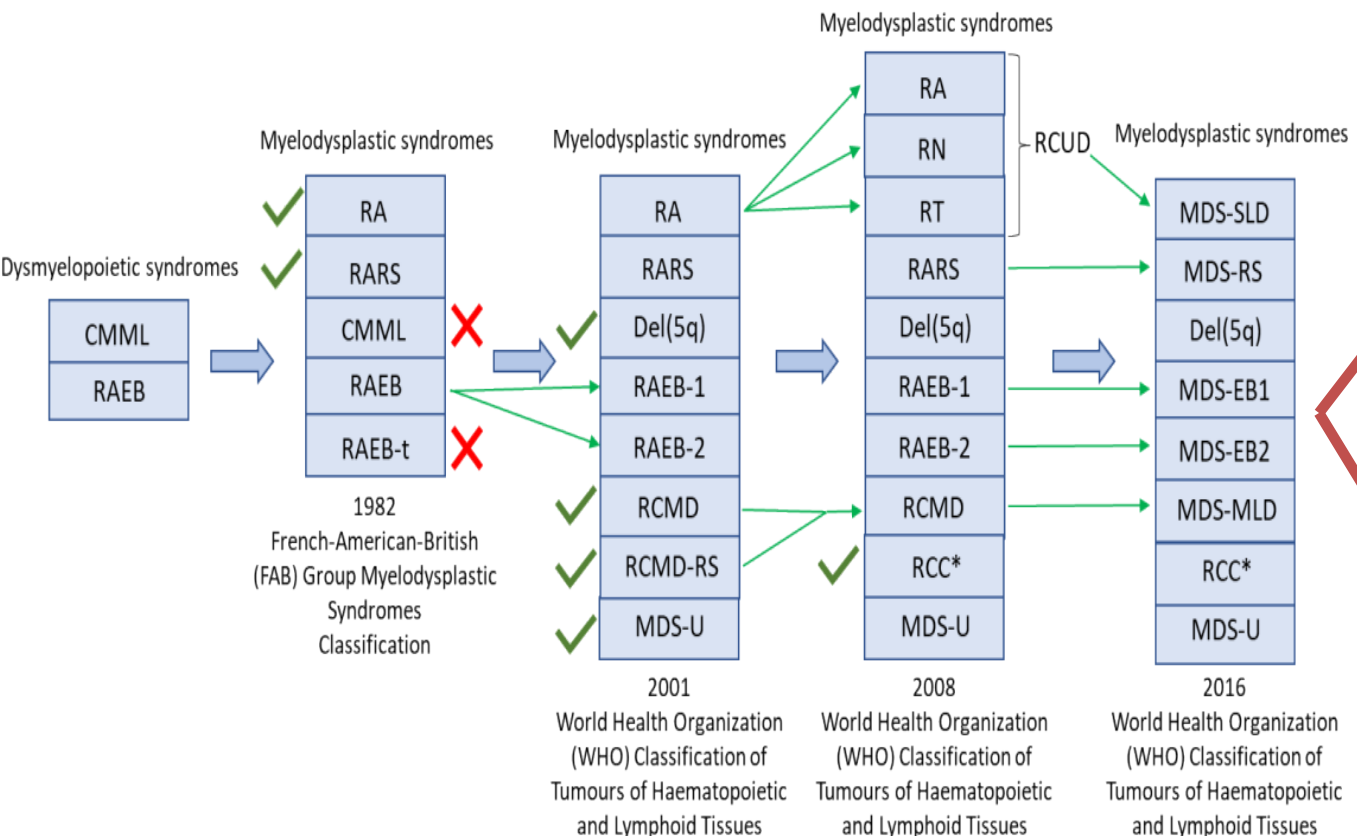
IPSS-R score 3.5 (INT), median OS: 36 months

Clinical-Genotype Associations in MDS



MDS classification has evolved over time

WHO 2022



Key
 ✓ = new addition to respective classification
 ✗ = removed from subsequent classification



ICC 2022

The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data

Daniel A. Arber, Attilio Orazi, Robert P. Hasserjian, Michael J. Borowitz, Katherine R. Calvo, Hans-Michael Kvasnicka, Sa A. Wang, Adam Bagg, Tiziano Barbui, Susan Branford, Carlos E. Bueso-Ramos, Jorge E. Cortes, Paola Dal Cin, Courtney D. DiNardo, Herve' Dombret, Eric J. Duncavage, Benjamin L. Ebert, Elihu H. Estey, Fabio Facchetti, Kathryn Foucar, Naseema Gangat, Umberto Gianelli, Lucy A. Godley, Nicola Gökbuget, Jason Gotlib, Eva Hellström-Lindberg, Gabriela S. Hobbs, Ronald Hoffman, Elias J. Jabbour, Jean-Jacques Kiladjian, Richard A. Larson, Michelle M. Le Beau, Mignon L-C. Loh, Bob Löwenberg, Elizabeth Macintyre, Luca Malcovati, Charles G. Mullighan, Charlotte Niemeyer, Olatoyosi M. Odenike, Seishi Ogawa, Alberto Orfao, Elli Papaemmanuil, Francesco Passamonti, Kimmo Porkka, Ching-Hon Pui, Jerald P. Radich, Andreas Reiter, Maria Rozman, Martina Rudelius, Michael R. Savona, Charles A. Schiffer, Annette Schmitt-Graeff, Akiko Shimamura, Jorge Sierra, Wendy A. Stock, Richard M. Stone, Martin S. Tallman, Jürgen Thiele, Hwei-Fang Tien, Alexandar Tzankov, Alessandro M. Vannucchi, Paresh Vyas, Andrew H. Wei, Olga K. Weinberg, Agnieszka Wierzbowska, Mario Cazzola, Hartmut Döhner and Ayalew Tefferi





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Abstract #463



“Clash of Titans”: Taking the Best of Both Worlds Validation of 2022 WHO and ICC Classifications in Myelodysplastic Syndromes: An Analysis on Behalf of the International Consortium for MDS (icMDS)

Somedeb Ball*, Avani M Singh*, Najla Al Ali, Luis E Aguirre, Akriti G Jain, Sara M Tinsley, Zaker I Schwabkey, Onyee Chan, Zhuoer Xie, Andrew Kuykendall, Andrew Brunner, John Bennett, Rena Buckstein, Rafael Bejar, Jan Philipp Bewersdorf, Hetty Carraway, Matteo Della Porta, Amy E. DeZern, Elizabeth Griffiths, Stephanie Halene, Robert Hasserjian, Sanam Loghavi, Olatoyosi Odenike, Mrinal Patnaik, Gail Roboz, Valeria Santini, Maximilian Stahl, Mikkael A Sekeres, David Steensma, Justin Taylor, Mina Xu, Kendra Sweet, Jeffrey lancet, Alan List, Eric Padron, David A Sallman, **Amer M Zeidan#**, **Rami S Komrokji#**

*To be considered co-first authors #To be considered co-senior authors

Similarities and Differences: WHO and ICC for MDS

Ring Sideroblasts	RS \geq 15%	MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD) and multi-lineage dysplasia (MDS-RS-MLD)	MDS with ring sideroblasts (MDS-RS): Low blast, <i>SF3B1</i> wild-type	No RS specific category
Number of Dysplastic Lineages	1 vs. >1	MDS with single lineage dysplasia (MDS-SLD) and multi-lineage dysplasia (MDS-MLD)	Dysplastic lineages are removed MDS with low blasts (MDS-LB): <5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD) and multi-lineage dysplasia (MDS, NOS-MLD)
Blasts	5-9%	MDS with excess blasts-1 (MDS-EB1): 5-9% BM blasts	MDS with increased blasts-1 (MDS-IB1): 5-9% BM and/or 2-4% PB blasts	MDS with excess blasts (MDS-EB ; 5-9% BM and/or 2-9% PB blasts or Auer rods)
	10-19%	MDS excess blasts-2 (MDS-EB2): 10-19% BM or PB blasts or Auer rods	MDS with increased blasts-2 (MDS-IB2): 10-19% BM or 5-19% PB blasts or Auer rods	MDS/AML (10-19% BM or PB blasts)
Added Subgroup	WHO	Not included	MDS, hypoplastic (MDS-h): Hypocellular marrow (age-adjusted)	Not included
		Not included	MDS with fibrosis (MDS-f): BM blasts 5-19%, PB blasts 2-19%; BM Fibrosis- grade \geq 2	Not included
Removed		MDS unclassifiable	Not included	Not included

Arber et al. Blood. 2016; Khoury et al. Leukemia. 2022; Arber et al. Blood. 2022 .

Similarities and Differences: WHO and ICC for MDS

GENETICS		WHO 2016	WHO 2022	ICC 2022
Common Genetically Defined Subgroups	<i>SF3B1</i>	No specific category	MDS-<i>SF3B1</i> : MDS with low blasts (BM <5%, PB <2%) and <i>SF3B1</i> mutation - No del 5q, -7, complex karyotype - No <i>TP53</i> , <i>RUNX1</i> , <i>EZH2</i> , or <i>NPM1</i> mutations	MDS-<i>SF3B1</i> : MDS with low blasts (BM <5%, PB <2%) and <i>SF3B1</i> mutation - <i>SF3B1</i> VAF ≥10% - No del 5q, -7, complex karyotype - No multi-hit <i>TP53</i> or <i>RUNX1</i> mutations
	5q	MDS with isolated del(5q)	MDS-5q : MDS with low blasts and isolated del 5q	MDS del(5q) : MDS with isolated Del 5q or with 1 other cytogenetic abnormality except -7/del(7)
	<i>TP53</i> mutation (supersedes all other MDS categories)	Not included	MDS-bi<i>TP53</i> : MDS with biallelic <i>TP53</i> inactivation - ≥2 <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> copy number loss or cnLOH	MDS with mutated <i>TP53</i> MDS/AML with mutated <i>TP53</i> - MDS (blast <10%): Criteria same as WHO or, 1 <i>TP53</i> mutation plus complex karyotype - MDS/AML (blast 10-19%): Any <i>TP53</i> mutation (VAF ≥10%)
Other genetic Subgroups	MDS-related gene mutations and cytogenetic abnormalities	Not included	MDS with low or excess blasts with other defined gene alterations	MDS/AML with myelodysplasia related gene mutations MDS/AML with myelodysplasia related cytogenetic abnormalities

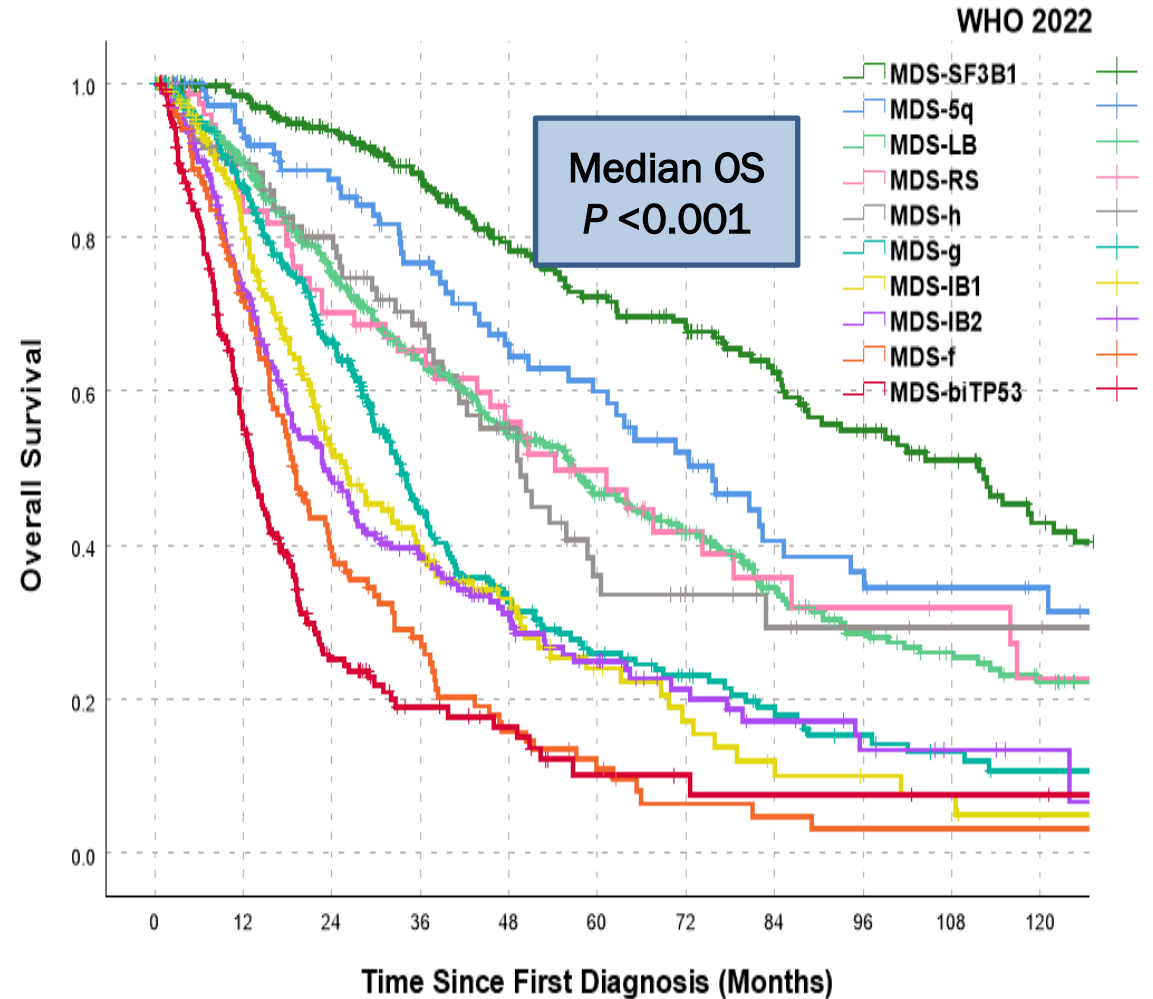
Materials and Methods

- Institutional **MDS Database of Moffitt Cancer Center**
- Confirmed diagnosis of **MDS (WHO 2016 criteria)** with available **myeloid NGS** results at diagnosis
- Reclassified by **WHO 2022** and **ICC 2022** proposed criteria
- **“Multi-hit” TP53 state:** *TP53*-VAF $\geq 50\%$ or, ≥ 2 *TP53* mutations (VAF $\geq 10\%$ each) or, 1 *TP53* mutation plus loss of 17p (by karyotype or FISH)
- **2231** molecularly annotated MDS cases: Median follow up duration of **60.2** months
- Kaplan Meier statistics (log rank test) for survival endpoints and Cox regression for multivariate analysis (SPSS)



WHO 2022 Subgroups with Survival

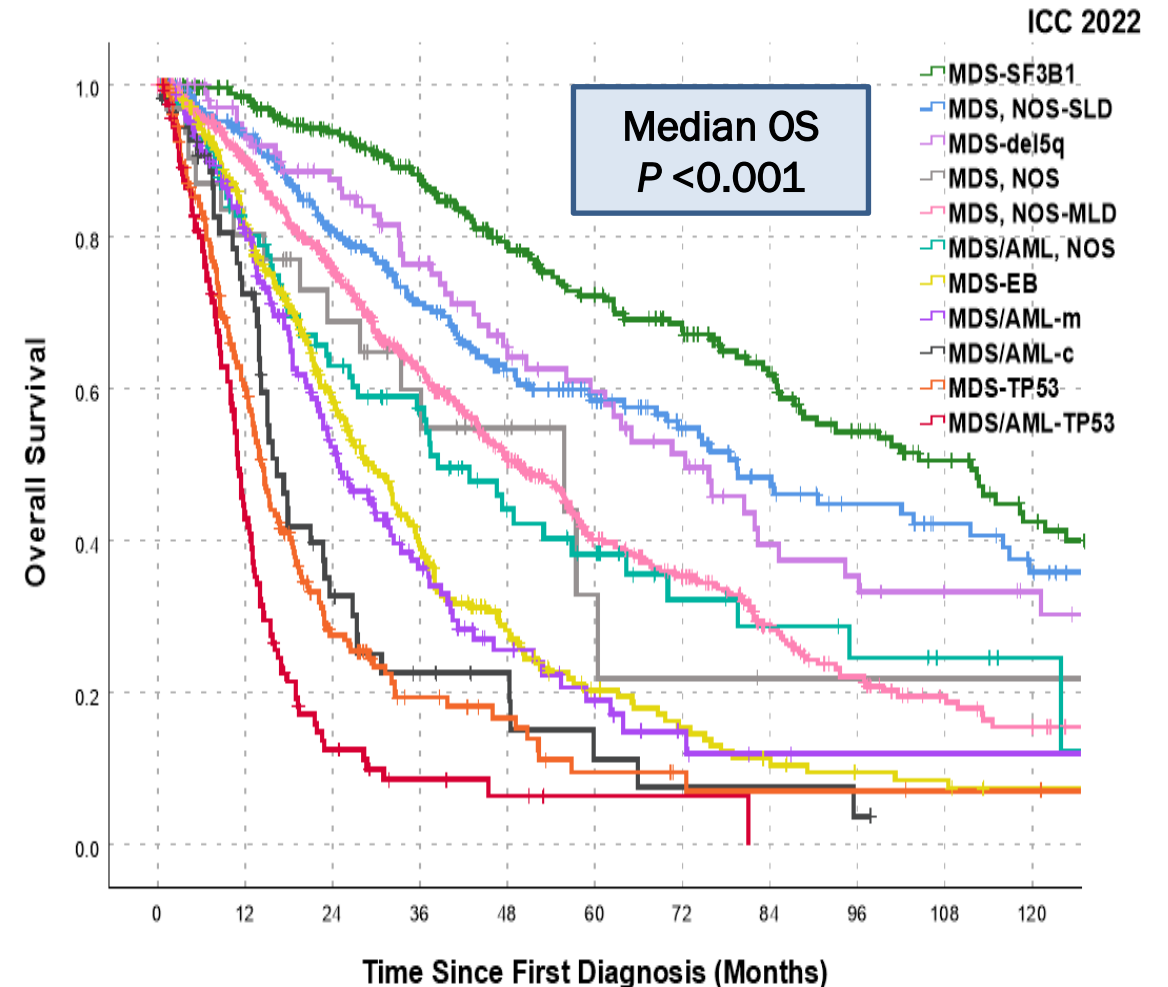
Subgroups	No. (%)	mLFS	mOS
Overall	2231 (100%)	30.9 mo	40.9 mo
MDS-SF3B1	276 (12%)	109.4 mo	111.6 mo
MDS-5q	110 (5%)	62.9 mo	75.6 mo
MDS-LB	595 (27%)	47.8 mo	56.8 mo
MDS-RS	82 (4%)	50.5 mo	54.3 mo
MDS-h	98 (4%)	42.3 mo	49.6 mo
MDS -g *	325 (15%)	22.1 mo	33.3 mo
MDS-IB1	193 (9%)	21.0 mo	25.9 mo
MDS-IB2	224 (10%)	10.0 mo	22.9 mo
MDS-f	118 (5%)	13.7 mo	18.9 mo
MDS-biTP53	210 (9%)	10.0 mo	13.2 mo



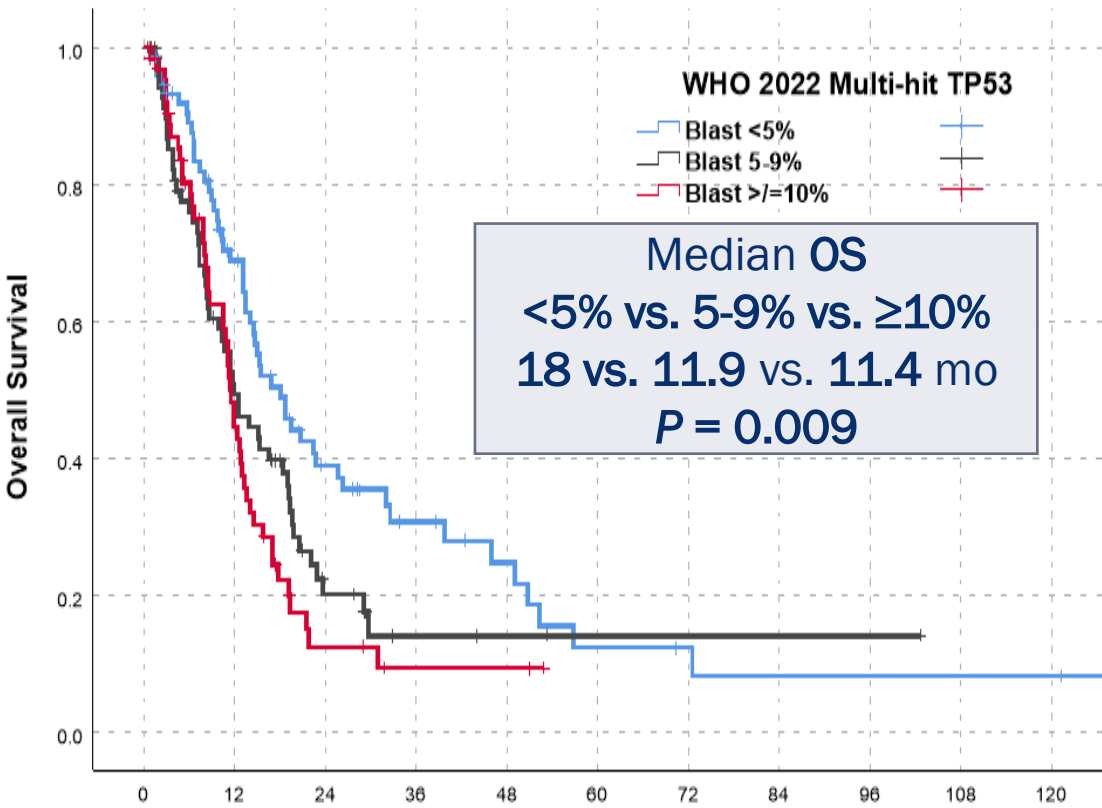
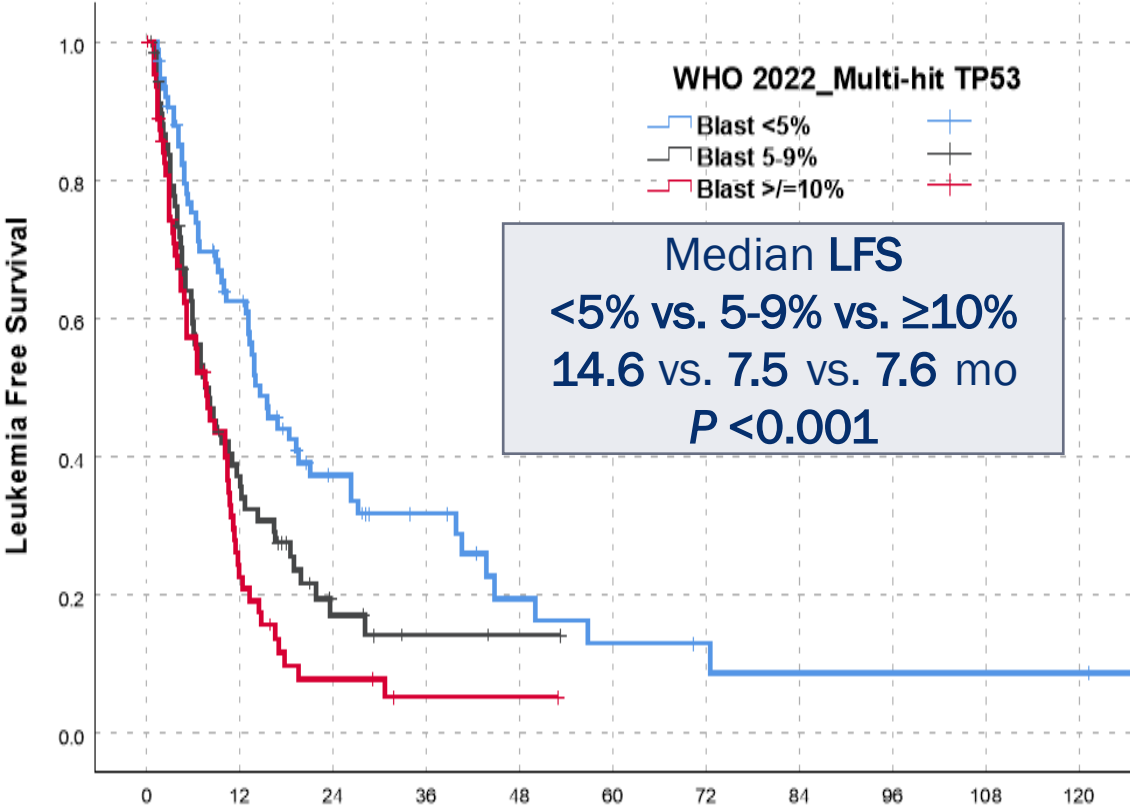
* Low or increased blasts with *RUNX1*, *IDH1/2*, Cohesin complex mutations, *SF3B1* with blast $\geq 5\%$; [LFS- Leukemia free survival, OS- Overall survival]

ICC 2022 Subgroups with Survival

Subgroups	No. (%)	mLFS	mOS
Overall	2202 (100%)	31.6 mo	41.2 mo
MDS-SF3B1	276 (13%)	105.7 mo	111.6 mo
MDS, NOS-SLD	248 (11%)	74.2 mo	79.4 mo
MDS-del5q	110 (5%)	62.9 mo	75.6 mo
MDS, NOS	32 (1%)	55.8 mo	55.8 mo
MDS, NOS-MLD	606 (27%)	41.5 mo	49.6 mo
MDS/AML, NOS	83 (4%)	14.0 mo	38.4 mo
MDS-EB	324 (15%)	21.0 mo	29.4 mo
MDS/AML with MDS-Related Mutations	163 (7%)	11.5 mo	24.7 mo
MDS/AML with MDS-Related Cytogenetic Abnormalities	55 (3%)	11.2 mo	16.3 mo
MDS-mTP53	191 (9%)	11.5 mo	14.5 mo
MDS/AML-mTP53	115 (5%)	6.4 mo	11 mo



Multi-hit *TP53**- MDS (WHO 2022): Survival by Blast %



Number at Risk

	0	12	24	36	48	60	72	84	96	108	120
<5%	75	42	20	12	6	4	3	2	2	2	2
5-9%	70	22	7	2	1	0	0	0	0	0	0
≥10%	65	13	4	1	1	0	0	0	0	0	0

Number at Risk

	0	12	24	36	48	60	72	84	96	108	120
<5%	75	46	22	12	8	4	3	2	2	2	2
5-9%	70	31	9	3	2	1	1	1	1	0	0
≥10%	65	25	5	2	2	0	0	0	0	0	0

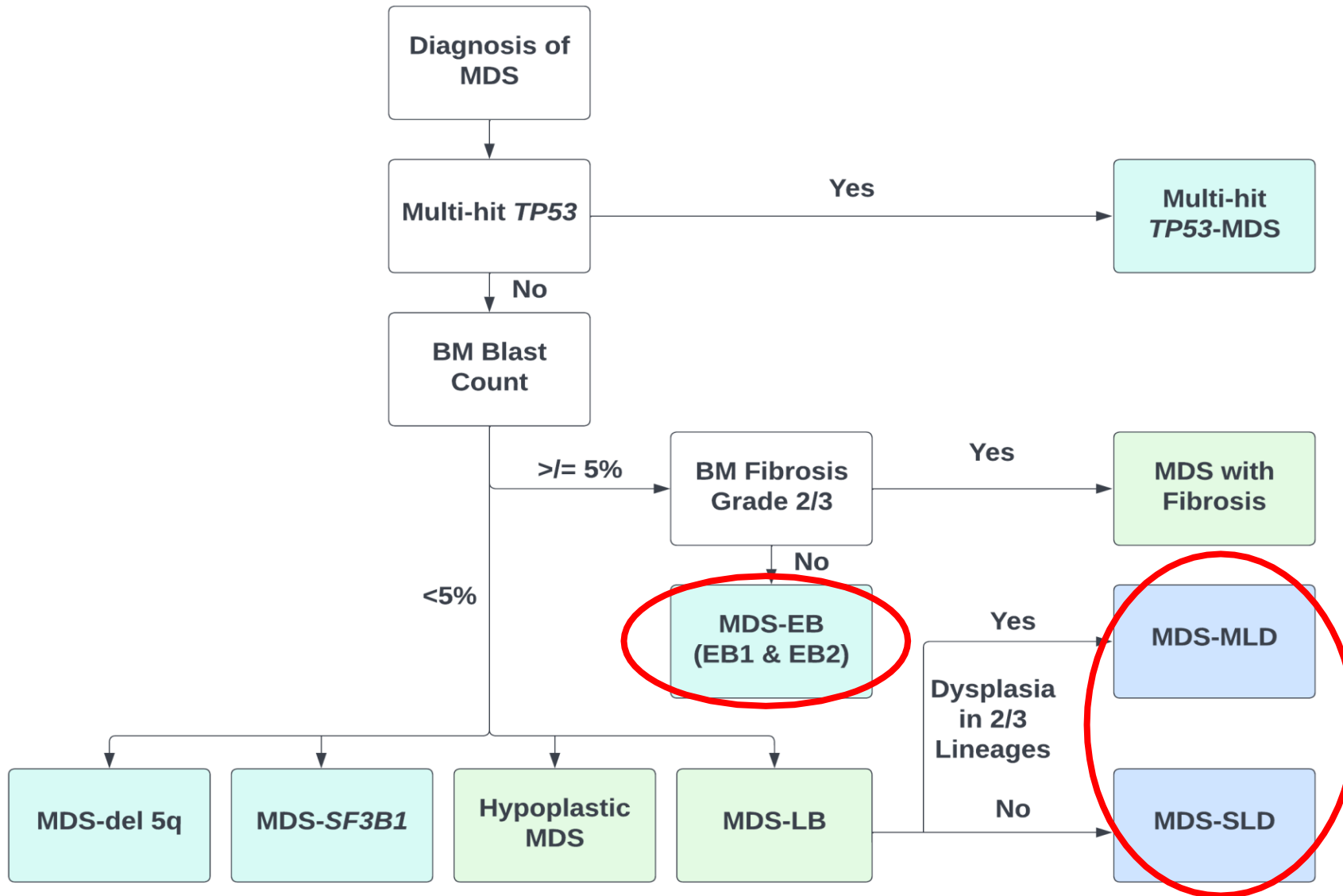
**TP53*-VAF ≥ 50% or, ≥ 2 *TP53* mutations (VAF >10% each) or, 1 *TP53* mutation plus loss of 17p (by Karyotype or FISH)

Conclusions and Future Directions

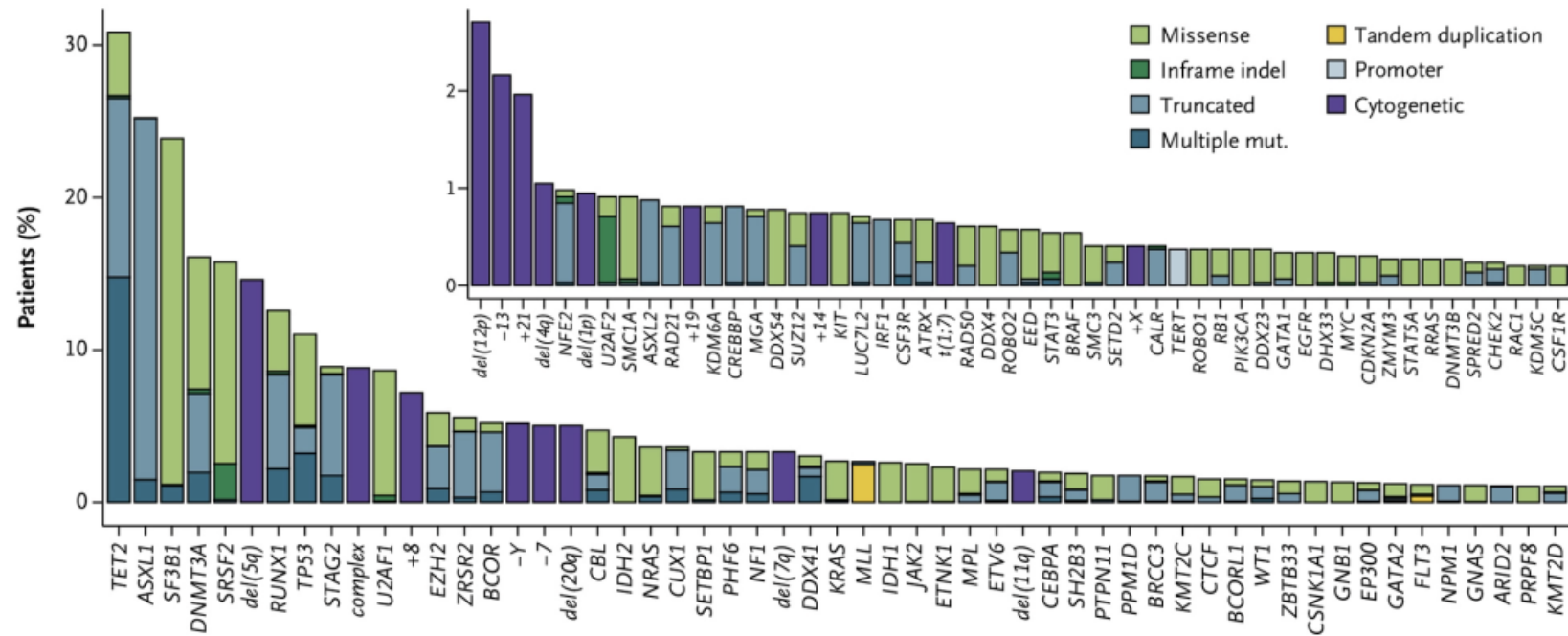
- Both WHO and ICC classification systems for MDS has room for improvement
- Molecularly defined entities (*SF3B1*, deletion 5q, and “multi-hit” *TP53*) are clearly unique
- *TP53* mutation predicted most dismal LFS and OS in both WHO and ICC systems, and “multi-hit *TP53* state” remained independent predictor of survival
- Survival of MDS-RS (*SF3B1*-WT) was similar to MDS-LB, and MDS-MLD had worse outcomes than MDS-SLD
- Blast $\geq 5\%$ correlated better with OS than $\geq 10\%$; however, precise blast cut-off needs to be further examined
- Grade 2/3 fibrosis was associated with worse OS in MDS-IB group, and was independent predictor of OS
- Future validation in multicenter dataset (VALIDATE) within icMDS is planned to support findings



A Proposal for Unified Classification for MDS



Wide Genetic heterogeneity in MDS



- 2957 MDS patients
- 3186 cytogenetic alterations in 41% of patients
- **9254 oncogenic mutations across 121 genes in 90% of pts**

Slide from M Cazzola ASH Education talk 2022

The IPSS-M model

Model fit with a robust Cox multivariable regression adjusted for confounder variables

Category	Variable	Multivariable model: hazard ratio ^a (95% CI)	Weight w	Scaling x^{mean}
confounder	% Age, in years	1.23 (1.05 - 1.43)	N/A	N/A
	Sex: Male	1.22 (1.06 - 1.41)	N/A	N/A
	Type: Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A	N/A
clinical	% Bone Marrow Blasts, in %	1.42 (1.30 - 1.55)	0.352	0.922
	% min(Platelets, 250), in $\times 10^9/L$	0.80 (0.72 - 0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171	9.87
cytogenetics	IPSS-R category vector ^a	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects 17 variables, 16 genes	<i>TP53</i> ^{multi}	3.27 (2.38 - 4.48)	1.18	0.0710
	<i>MLL</i> ^{PTD}	2.22 (1.49 - 3.32)	0.798	0.0247
	<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11 - 4.45)	0.798	0.0108
	<i>SF3B1</i> ^{sq}	1.66 (1.03 - 2.66)	0.504	0.0166
	<i>NPM1</i>	1.54 (0.78 - 3.02)	0.430	0.0112
	<i>RUNX1</i>	1.53 (1.23 - 1.89)	0.423	0.126
	<i>NRAS</i>	1.52 (1.05 - 2.20)	0.417	0.0362
	<i>ETV6</i>	1.48 (0.98 - 2.23)	0.391	0.0216
	<i>IDH2</i>	1.46 (1.05 - 2.02)	0.379	0.0429
	<i>CBL</i>	1.34 (0.99 - 1.82)	0.295	0.0473
	<i>EZH2</i>	1.31 (0.98 - 1.75)	0.270	0.0588
	<i>U2AF1</i>	1.28 (1.01 - 1.61)	0.247	0.0866
	<i>SRSF2</i>	1.27 (1.03 - 1.56)	0.239	0.158
	<i>DNMT3A</i>	1.25 (1.02 - 1.53)	0.221	0.161
	<i>ASXL1</i>	1.24 (1.02 - 1.51)	0.213	0.252
	<i>KRAS</i>	1.22 (0.84 - 1.77)	0.202	0.0271
	<i>SF3B1</i> ^{tr}	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals ^b 1 variable, 15 genes	min(Nres, 2) Possible values are 0, 1 or 2	1.26 (1.12 - 1.42)	0.231	0.388

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin (NO ANC)

IPSS-R cytogenetic categories

31 Genes included in final set

17 genetic variables from 16 main effect genes

Individual weights attributed to each variable

1 genetic variable from 15 residual genes[^]

Number of mutated genes (0, 1 or 2)

^aresidual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

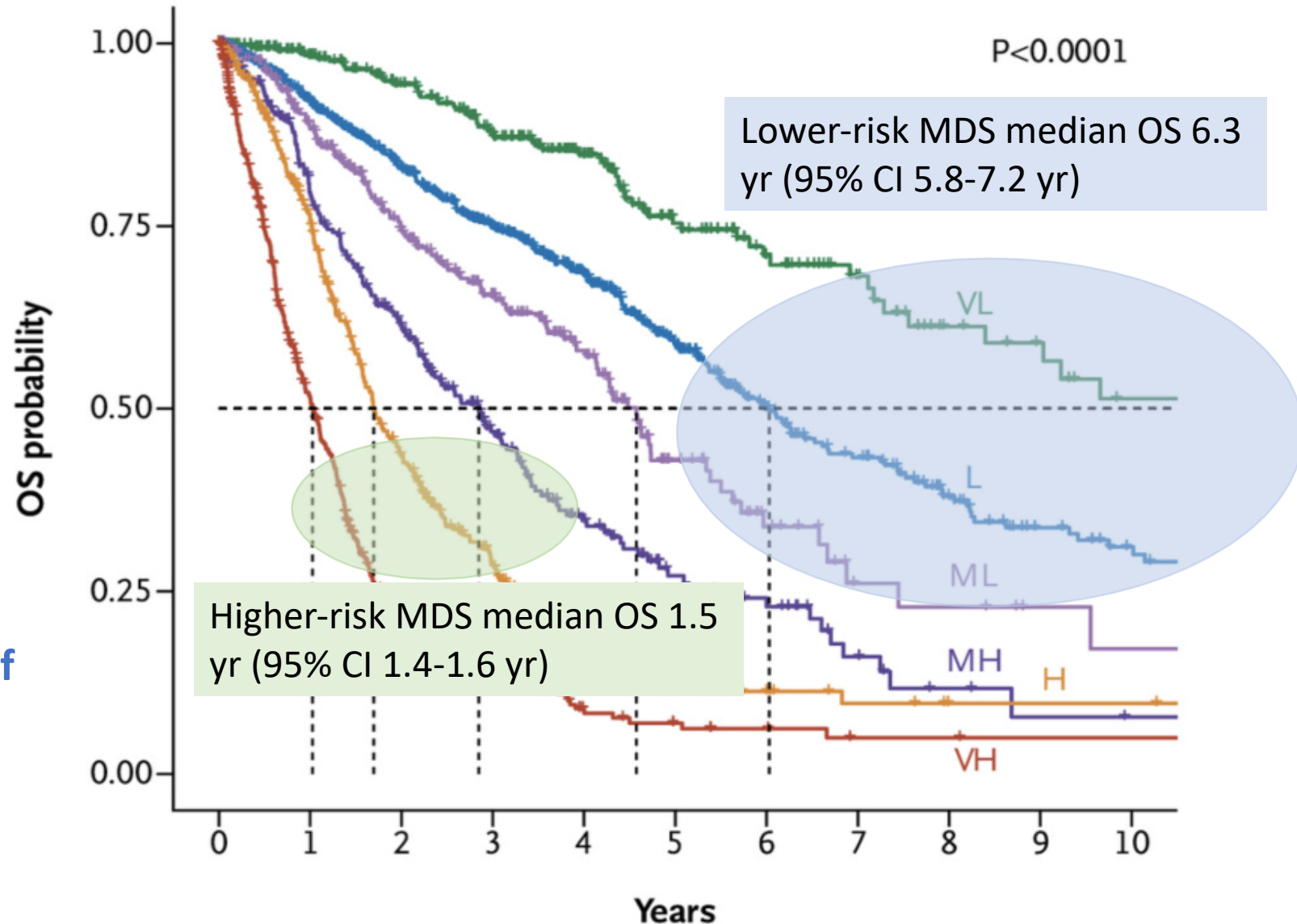
The IPSS-M risk categories

IPSS-M risk categories:

- Very Low (VL)
- Low (L)
- Moderate Low (ML)
- Moderate High (MH)
- High (H)
- Very High (VH)

Compared with IPSS-R,
IPSS-M re-stratified 46% of
patients

www.MDS-risk-model.com





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Abstract #464



Real-World Validation of Molecular International Prognostic Scoring System (IPSS-M) for Myelodysplastic Syndromes

Elisabetta Sauta, PhD

Robin M, Bersanelli M, Travaglino E, Meggendorfer M, Zhao LP, Berrocal JCC, Sala C, Maggioni G, Bernardi M, Di Grazia C, Vago L, Rivoli G, Borin L, D'Amico S, Tentori CA, Ubezio M, Campagna A, Russo A, Mannina D, Lanino L, Chiusolo P, Giaccone L, Voso MT, Riva M, Oliva E, Zampini M, Riva E, Nibourel O, Bicchieri M, Bolli N, Rambaldi A, Passamonti F, Savevski V, Santoro A, Germing U, Kordasti S, Santini V, Campelo MD, Sanz G, Solé F, Kern W, Platzbecker U, Ades L, Fenaux P, Haferlach T, Castellani G and Della Porta MG

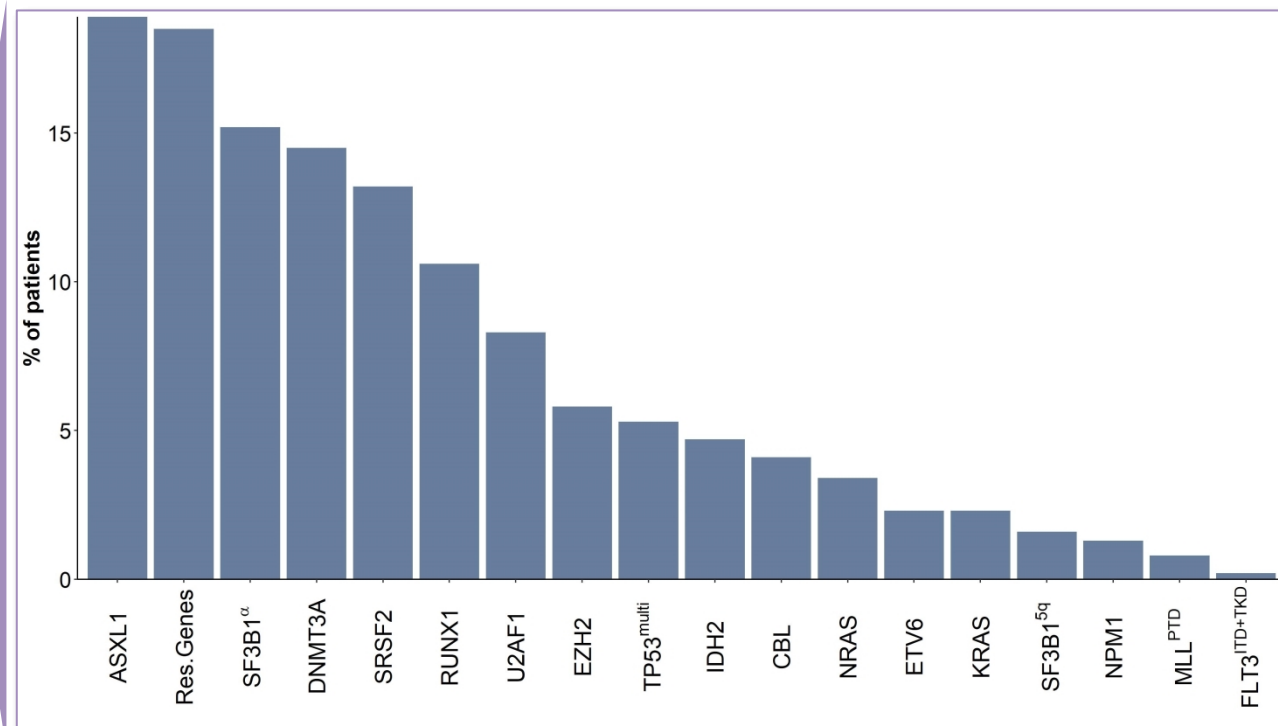
on behalf of GenoMed4All consortium (Genomics and Personalized Medicine for all through Artificial Intelligence in Haematological Diseases - www.genomed4all.eu)

Study Population

- 2,876 patients with primary MDS from GenoMed4All consortium with clinical and molecular data available from 21 European affiliated centers (retrospective analysis)

Genomed4All Cohort Characteristics	All Patients (n = 2,876)
Age (yrs), median (range)	68 (18-96)
Gender (Male/Female), %	1133/1743, 39% ; 61%
Median follow-up (months)	37.5 (36.2-38.8)
≥1 somatic mutations on 31 IPSS-M genes, %	82.4
≥1 oncogenic lesions, %	84
Number oncogenic lesions per patient, median (range)	3 (0-12)

DISTRIBUTION OF MUTATIONS ON THE IPSS-M GENES IN THE STUDY POPULATION

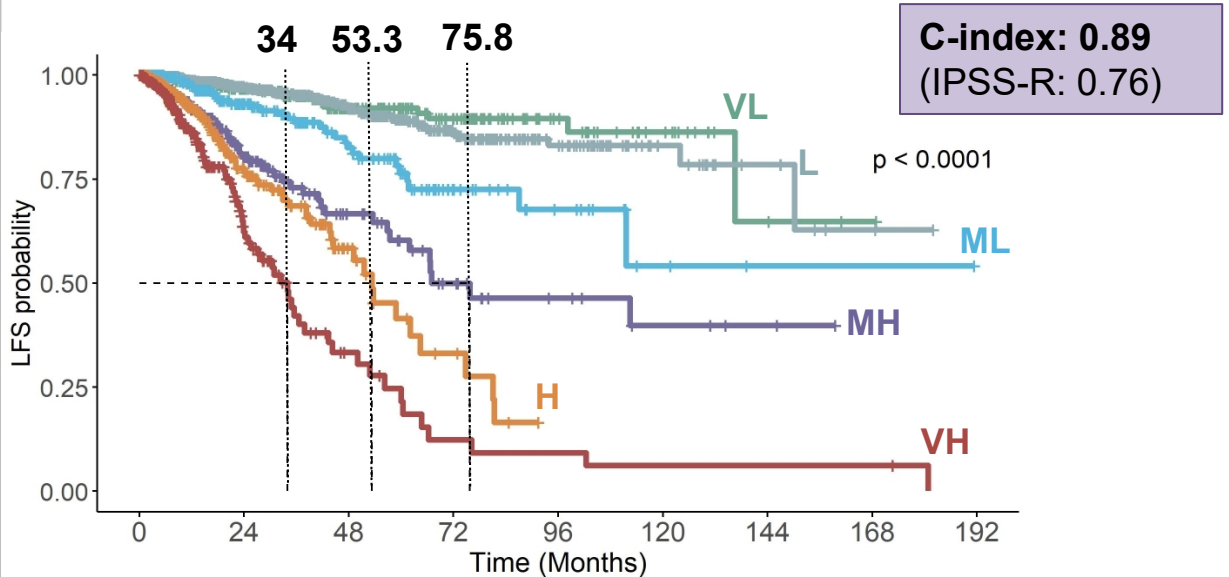
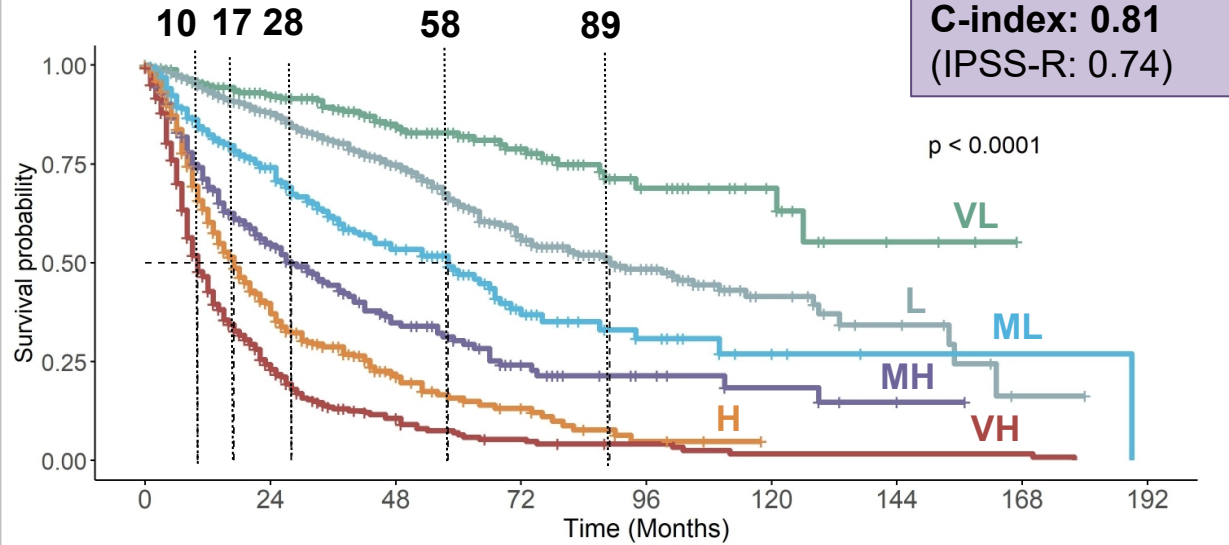


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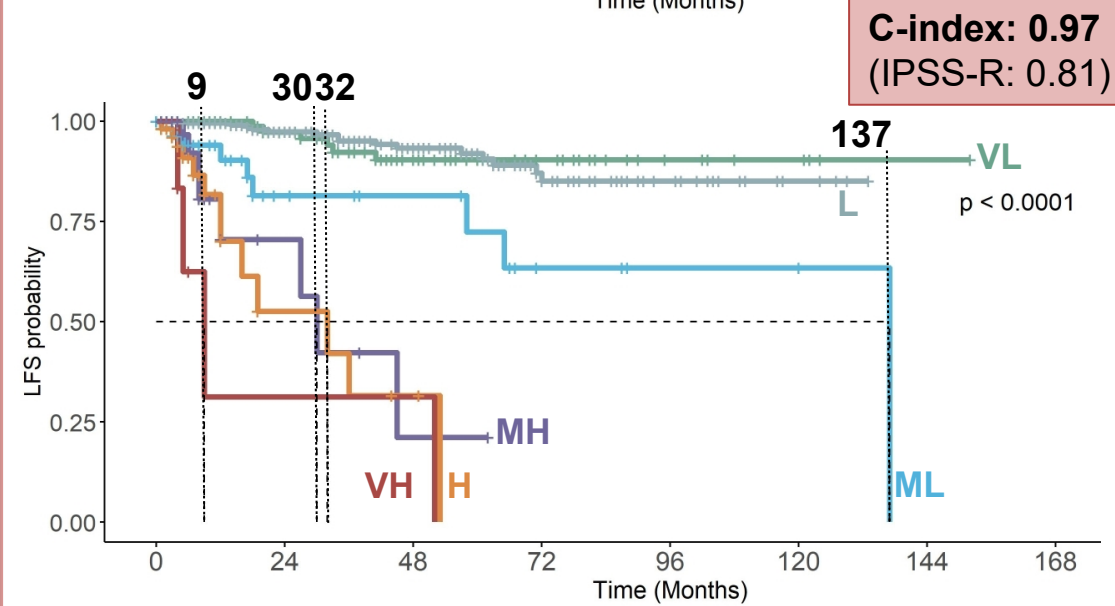
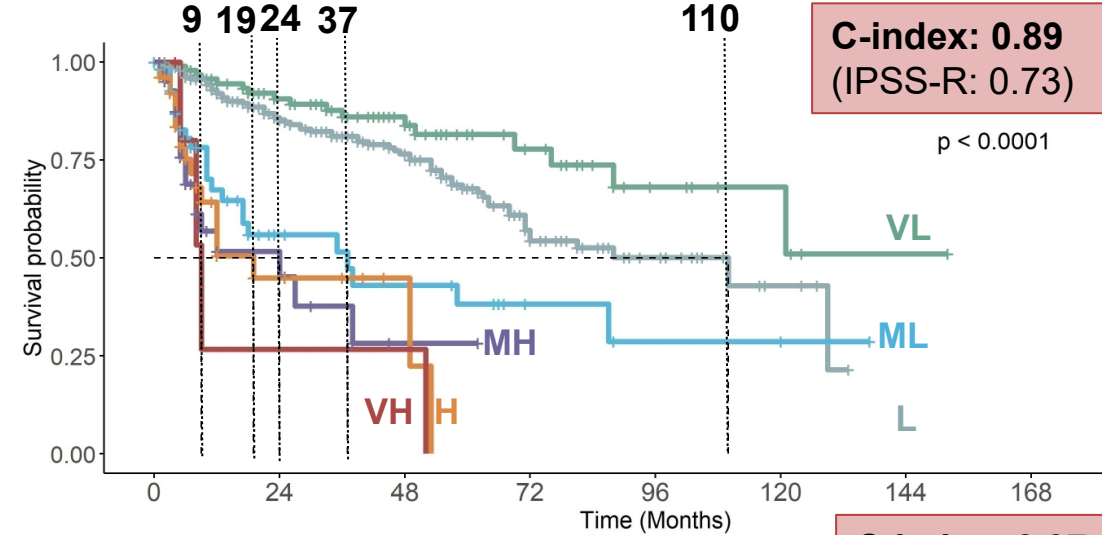
- a) Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS); IPSS-R intermediate risk
- b) MDS with SF3B1; IPSS-M moderate low
- c) Refractory anemia; low risk disease
- d) a+b
- e) None of the above

AIM 1: Extensive Real-World Validation

GENOMED4ALL COHORT

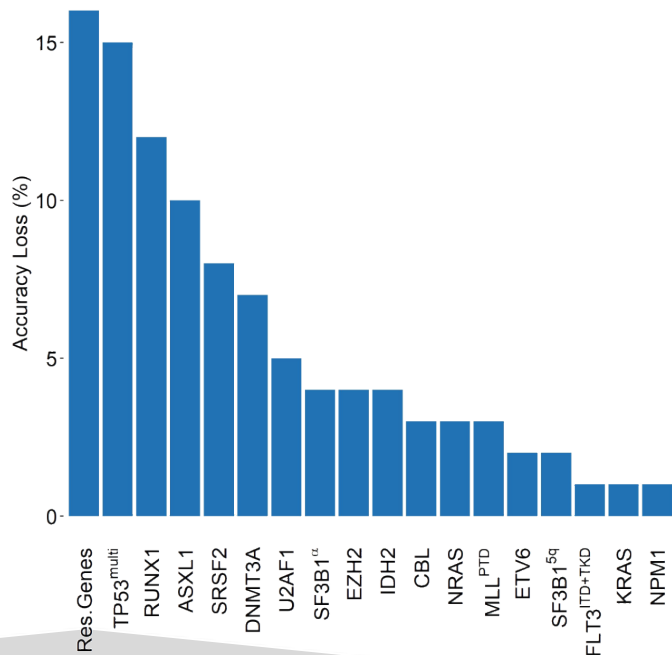


PATIENTS WITHOUT DETECTABLE IPSS-M MUTATIONS



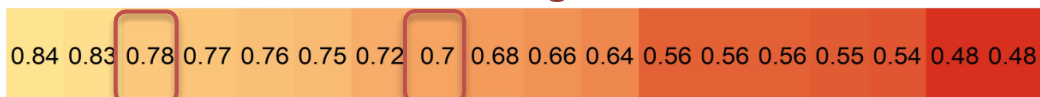
AIM 3: Testing Accuracy of IPSS-M with Missing Genomic Data

GenoMed4All Cohort



Set of 15 genes

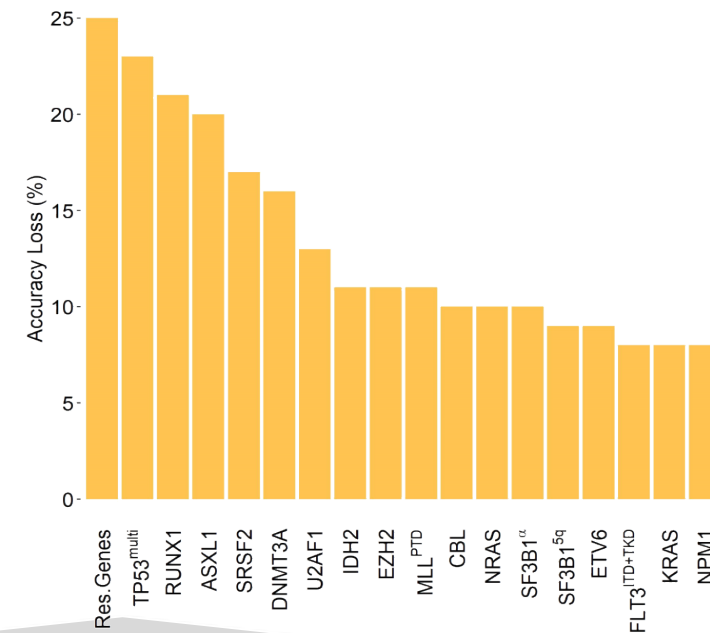
Set of 10 genes



ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH2, MLL^{PTD}, NPM1, NRAS, RUNX1, SF3B1, SRSF2, TP53^{multi} and U2AF1

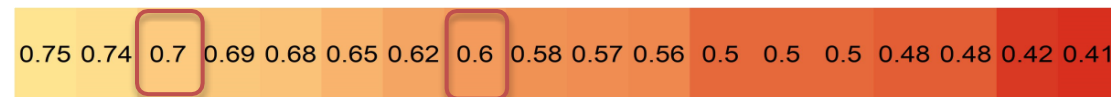
IWG-PM Cohort*

*Bernard E et al, NEJM Evid 2022



Set of 15 genes

Set of 10 genes



Conclusions

In this study, we **provided an extensive validation** of the recently developed IPSS-M:

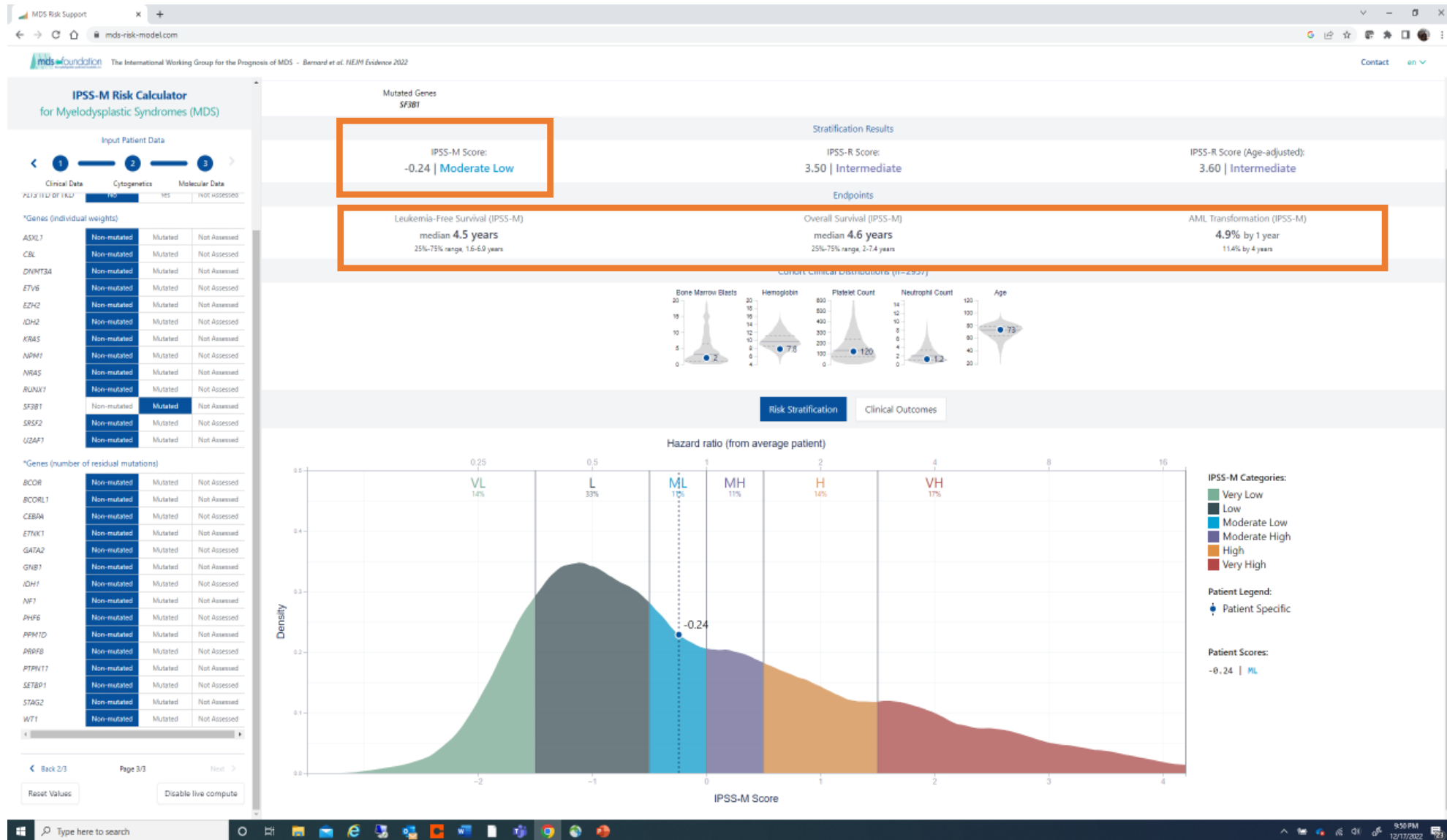
- Compared to IPSS-R, the **IPSS-M resulted in improved prognostic accuracy** across all clinical endpoints, even in *patients without not detectable mutations* on IPSS-M related genes.
- **In patients treated with allo-HSCT**, IPSS-M significantly improved the risk prediction of disease relapse and of the probability of post-transplantation survival, helping the **identification of patients with high risk of transplantation failure**.
- **Testing the robustness of IPSS-M** when molecular information was missed, **we defined a minimum set of 15 relevant genes ensuring a risk prediction accuracy greater than 70%**.

Back to Patient: WHO & ICC 2022 classifications & IPSS-M risk

Classification:
WHO 2022 and
ICC 2022:
MDS-SF3B1

www.MDS-risk-model.com

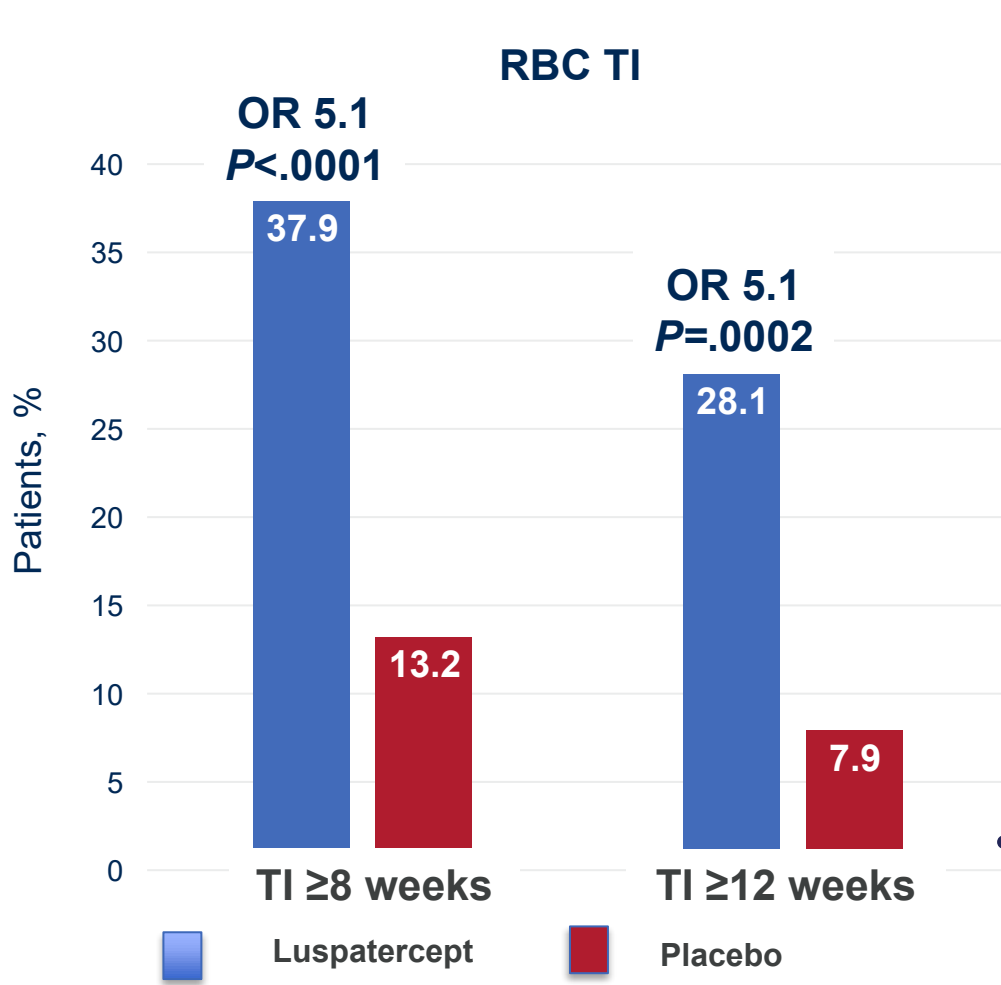
Prognosis:
IPSS-M
Moderate Low



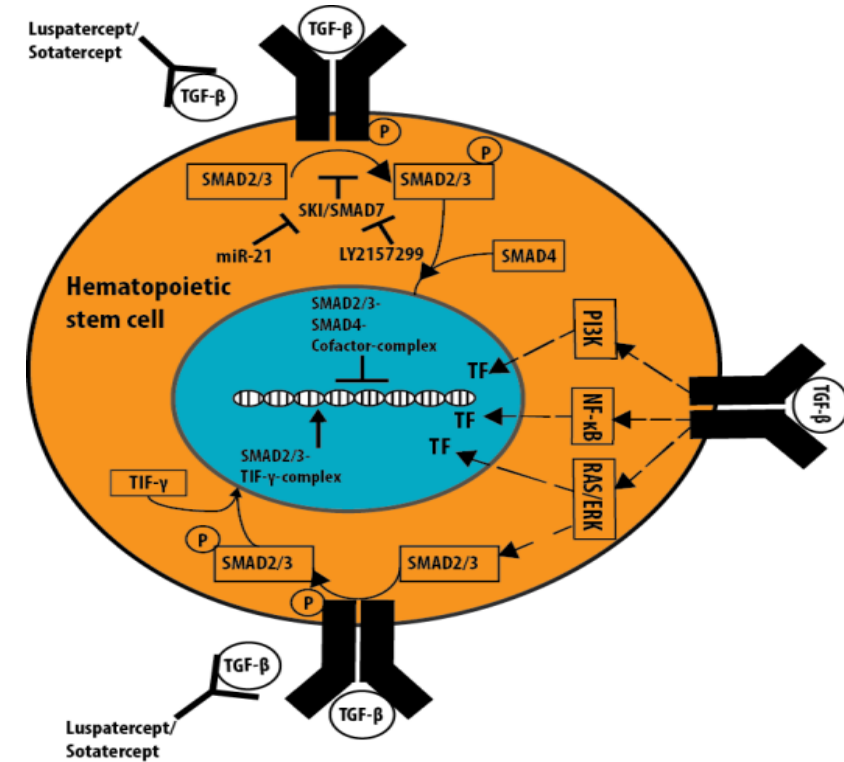
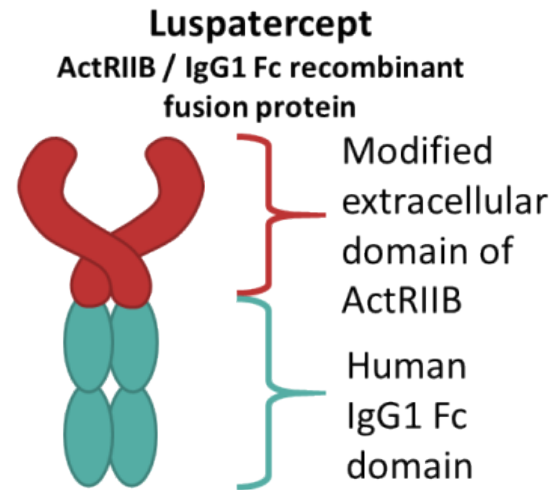
Case 1:
How would you treat this patient?

- a) Erythropoietin stimulating agent
- b) lenalidomide
- c) luspatercept
- d) Immunosuppressive therapy
- e) None of the above

The MEDALIST trial: Luspatercept significantly improved RBC TI rate compared to placebo



^aDefined as a reduction in transfusion of ≥4 RBC units/8 weeks or a mean Hb increase of ≥1.5 g/dL/8 weeks in the absence of transfusions (achieved in 53% Luspatercept vs 9% placebo).



- Luspatercept is a first-in-class erythroid maturation agent (EMA) that neutralizes select TGF- β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis



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Investigational approaches: Lower risk MDS



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Abstract #459

Imetelstat Achieved Prolonged, Continuous Transfusion Independence in Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents Within the IMerge Phase 2 Study

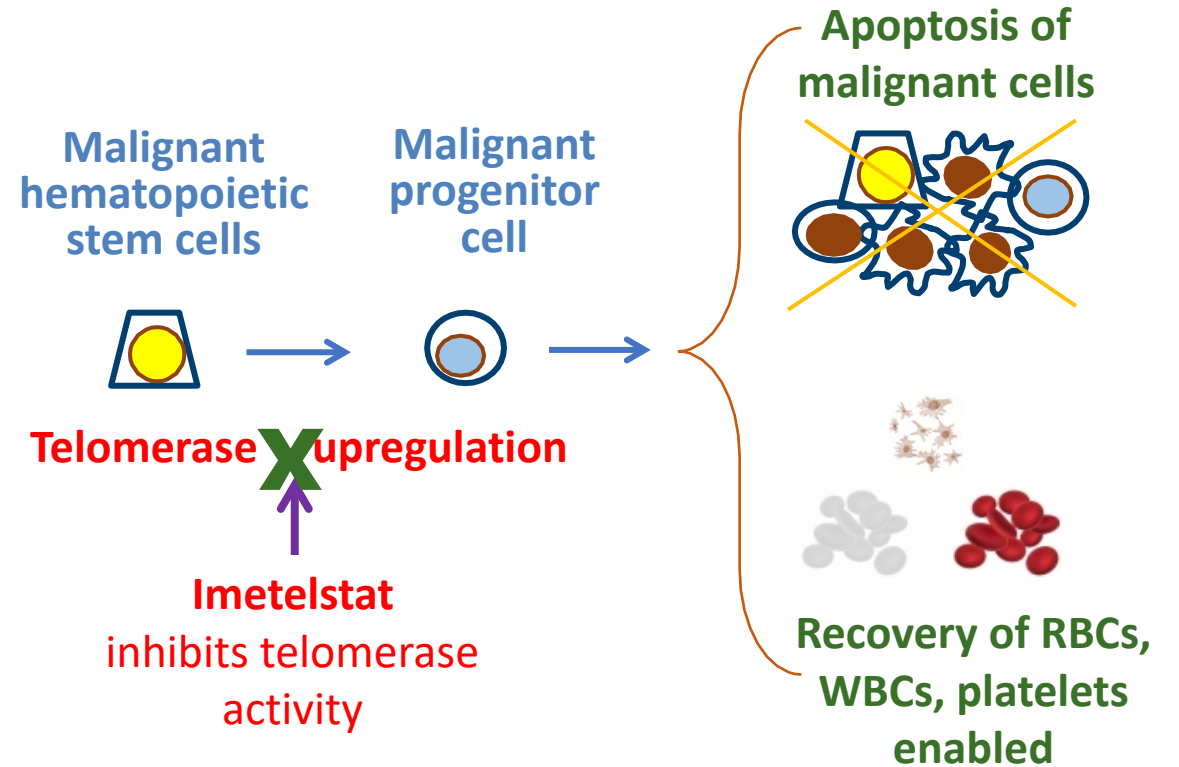
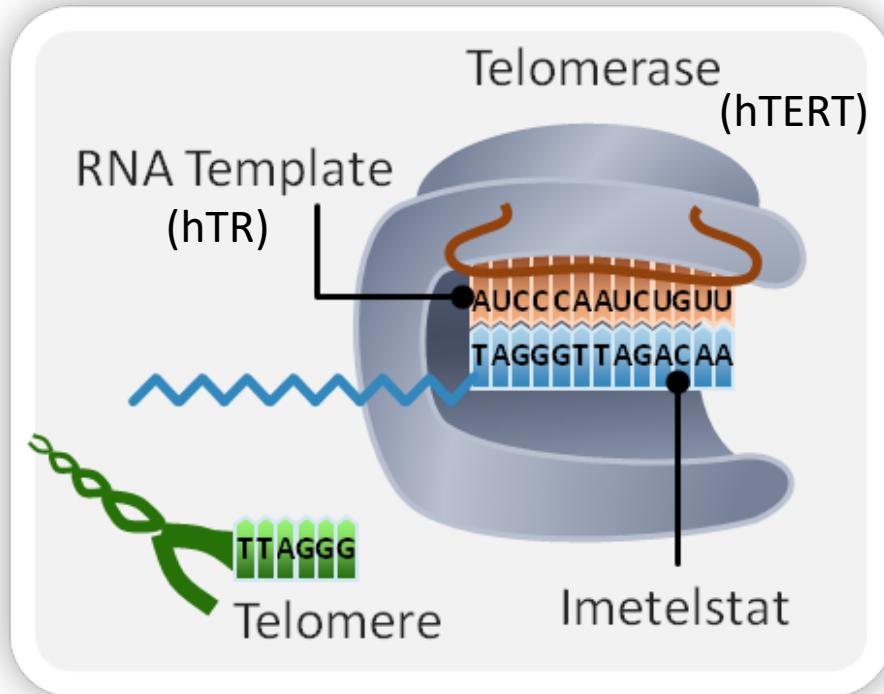
Uwe Platzbecker, MD,¹ Rami Komrokji, MD,² Pierre Fenaux, MD, PhD,³ Mikkael A. Sekeres,⁴ Michael Robert Savona,⁵ Yazan F. Madanat, MD,⁶ Koen Van Eygen, MD,⁷ Azra Raza, MD,⁸ Ulrich Germing, MD,⁹ Laurie Sherman, BSN,¹⁰ Tymara Berry, MD,¹⁰ Souria Dougherty, MBA,¹⁰ Sheetal Shah, PhD,¹⁰ Libo Sun, PhD,¹⁰ Ying Wan, MD, PhD,¹⁰ Fei Huang, PhD,¹⁰ Annat Ikin, PhD,¹⁰ Faye Feller, MD,¹⁰ Amer Zeidan, MHS,¹¹ and Valeria Santini¹²

¹University Clinic Leipzig, Leipzig, Germany; ²Moffitt Cancer Center, Tampa, FL, USA; ³Hôpital Saint-Louis, Université Paris Diderot, Paris, France; ⁴Sylvester Cancer Center, University of Miami, Miami, FL, USA; ⁵Vanderbilt University Medical Center, Nashville, TN, USA; ⁶University of Texas Southwestern Medical Center, Dallas TX, USA; ⁷Algemeen Ziekenhuis Groninge, Kortrijk, Belgium; ⁸Columbia University Medical Center, New York, NY, USA; ⁹Klinik für Hämatologie, Onkologie, and Klinischimmunologie, Universitätsklinik Düsseldorf, Heinrich-Heine-Universität, Düsseldorf, Germany; ¹⁰Geron Corporation, Parsippany, NJ, USA; ¹¹Yale School of Medicine, New Haven, CT, US; ¹²MDS Unit, AOU Careggi-University of Florence, Florence, Italy

Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity^{1,2}

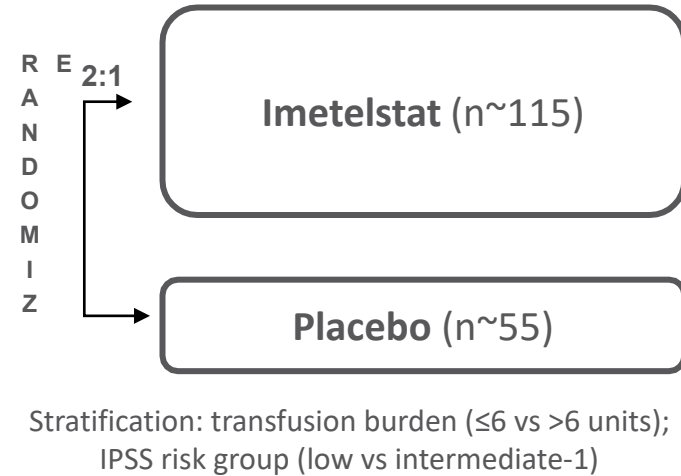
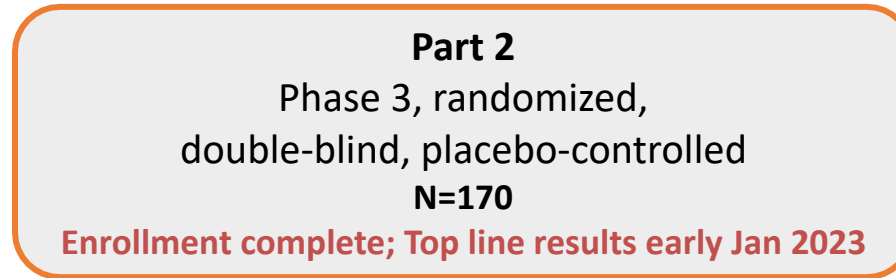
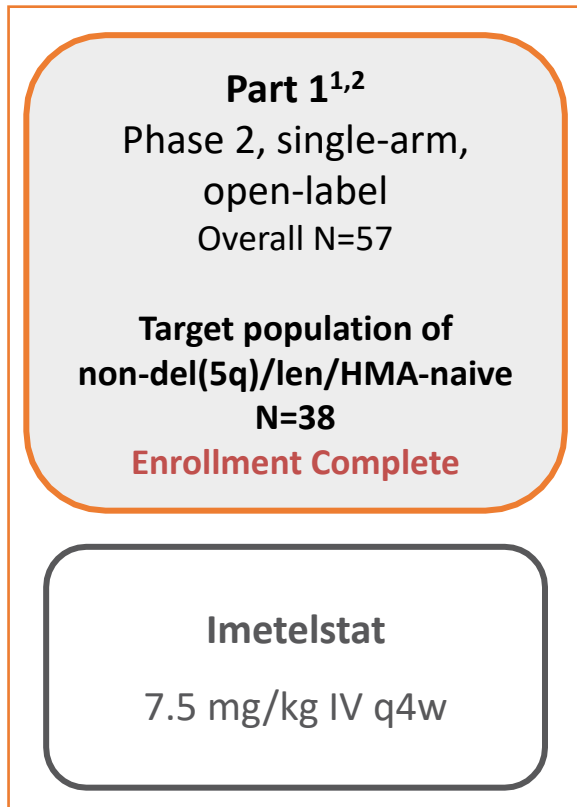
- Imetelstat has disease-modifying potential to selectively kill malignant stem and progenitor cells, enabling recovery of blood cell production^{3,4}



hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X et al. *Blood Adv.* 2018;25;2(18):2378-2388.

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design



- **Patients with LR-MDS^{1,2}**
 - IPSS low or intermediate-1
 - Relapsed/refractory to ESA or sEPO >500 mU/mL
 - Transfusion dependent:
≥4 units RBC/8 weeks over the 16-week prestudy period
 - Non-del5(q), len/HMA-naive
- **Primary endpoint:** ≥8-week RBC TI
- **Key secondary endpoints:** safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent
Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)
Supportive care: transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.
1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113.

Meaningful and Durable TI With Imetelstat Treatment

- Of 57 patients treated in the phase 2 study, 38 patients were non-del(5q) and lenalidomide/HMA naive (target patient population)^{1,2}
 - Longer duration of TI was seen in the target population (median, 88 weeks) vs all 57 treated patients (median, 65 weeks)

Efficacy parameters	Target population N=38 ²
8-week TI, n (%)	16 (42)
Median duration of TI, weeks (95% CI) ^a	88.0 (23.1-140.9)
24-week TI, n (%)	12 (32)
TI ≥1 year, n (%)	11 (29)

- **The analysis in this presentation describes the characteristics and clinical benefits of the 11 patients within the target patient population who had continuous TI for ≥1 year while on imetelstat after 57 months of follow-up**
- The 29% of patients who achieved sustained TI ≥1 year² represent:
 - 69% of the ≥8-week TI responders
 - 92% of the ≥24-week TI responders
 - 37% (10 of 27) of MDS-RS+ patients treated

^aBased on the Kaplan Meier method. HMA, hypomethylating agent; MDS, myelodysplastic syndromes; RS+, ring sideroblast-positive; TI, transfusion independence.

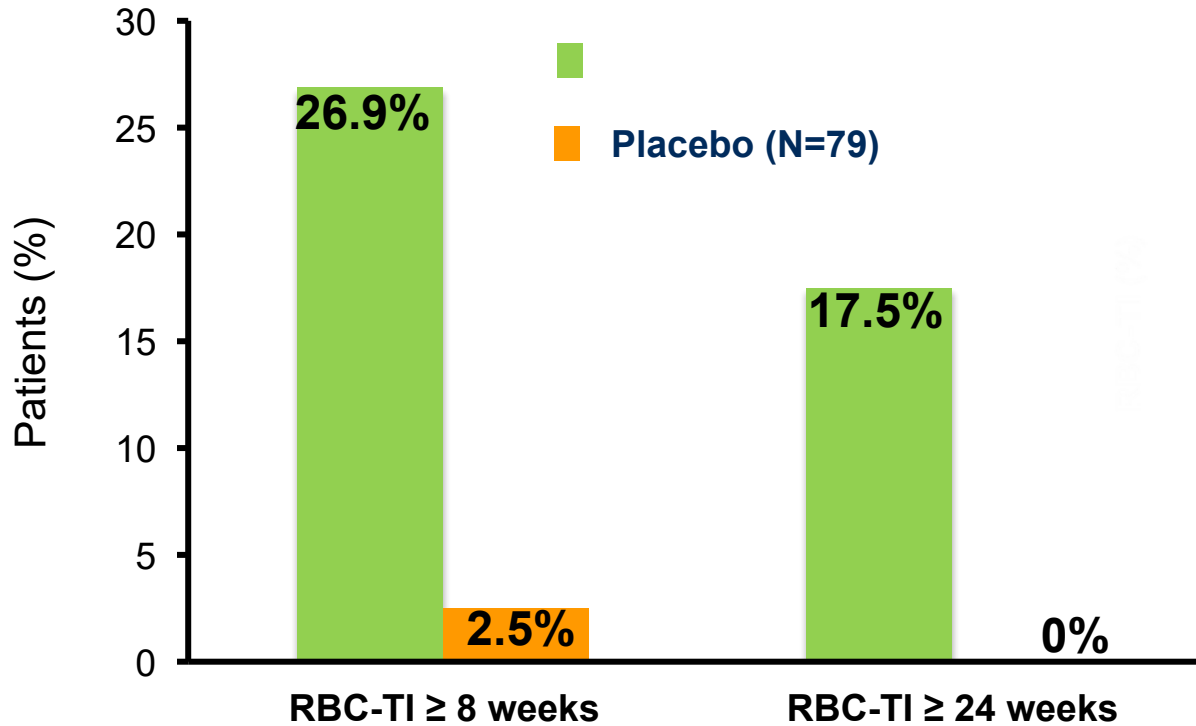
1. Steensma DP, et al. *J Clin Oncol*. 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 658.

Conclusions

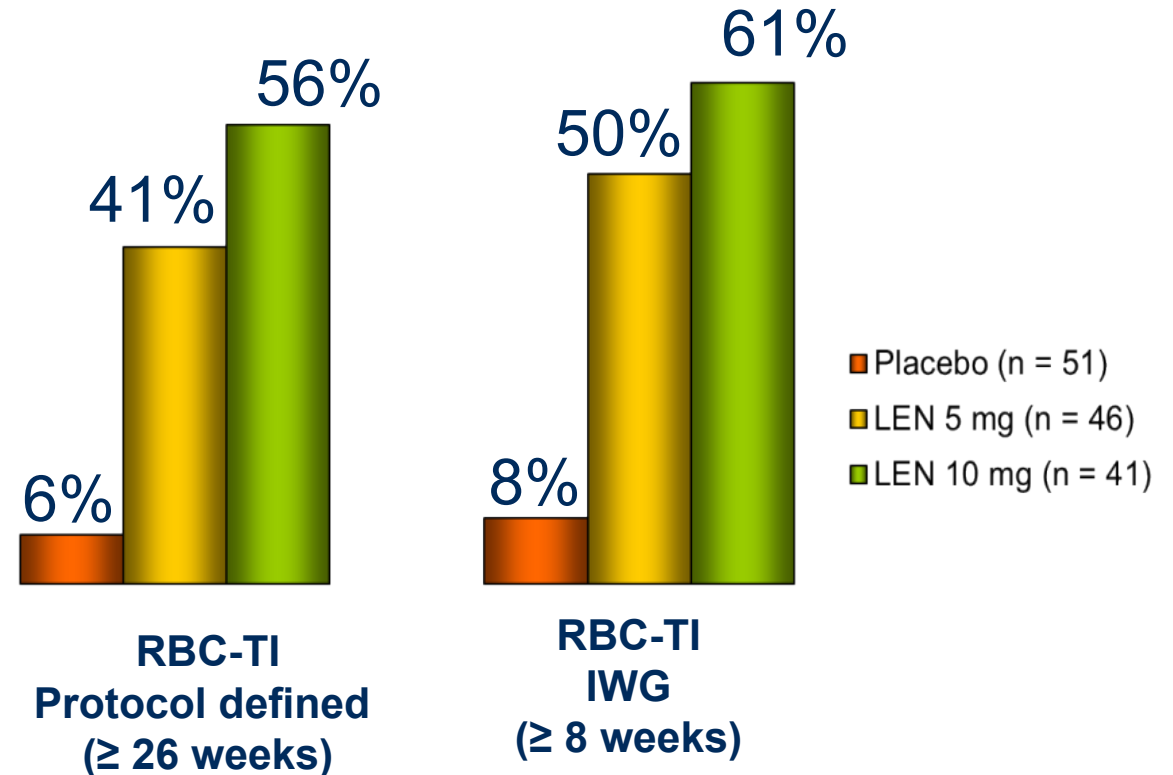
- Imetelstat demonstrated ≥ 1 year sustained, continuous TI in 29% of patients with transfusion dependent, non-del(5q) LR-MDS relapsed/refractory to ESAs and lenalidomide/HMA naive
 - Attainment of 24-week TI was indicative of the likelihood to achieve TI ≥ 1 year
- Evidence of disease-modifying activity for imetelstat mechanism of action:
 - Durable TI with median duration of TI of 92.4 weeks and robust increase in Hgb by ≥ 3 g/dL
 - Notable survival post-ESA (median OS, 56 months)
 - Meaningful reduction in mutational burden that correlated with longer TI and shorter time to onset of TI
- Safety findings were consistent with those of the overall target population and previous reports
- Enrollment is complete for the phase 3 part of IMerge, a randomized (2:1), double-blind, placebo-controlled trial to compare efficacy of imetelstat versus placebo in transfusion dependent, ESA-relapsed/refractory, non-del(5q), lenalidomide/HMA-naive LR-MDS
 - Results from the primary analysis are expected in early January 2023

Lenalidomide in LR-MDS

Len vs. placebo in non-del5q LR-MDS MDS-005



Len vs. placebo in del5q LR-MDS MDS-004



Median duration of TI: 32.9 weeks (95%CI 20.7–71.1) among TI ≥ 8 weeks LEN responders

Abstract #460

64th ASH Annual Meeting



Evaluation of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent LR-MDS del(5q) patients: Final results of Sintra-REV Phase III international multicenter clinical trial

Félix López-Cadenas, Eva Lumbreras, Teresa González, Blanca Xicoy, Joaquín Sánchez-García, Rosa Coll, Bohrane Slama, Jose Ángel Hernández-Rivas, Sylvain Thepot, Teresa Bernal, Agnés Guerci-Bresler, Guillermo Sanz, Joan Bargay, María Luz Amigo, Raquel de Paz Arias, Claude Preudhomme, Aristoteles Giagounidis, Uwe Platzbecker, Stefan Wickenhauser, Katharian S Goetze, Ali Arar, Jesus M Hernández-Rivas, Sofia M Toribio Castelló, Pierre Fenaux, Consuelo del Cañizo and María Díez-Campelo

M. Díez-Campelo, MD, PhD
mdiezcampelo@usal.es



Low Risk MDS (LR-MDS) with del(5q)

➤ LR-MDS patients with del(5q):

- Presented with anemia 68%, 42% transfusion dependency (TD)¹
- Median time to TD in anemic non-TD LR-MDS is 1.7y^{2, 3}

➤ Len at 10 mg/d in patients with transfusion requirements:

- Transfusion Independency (TI): 67%⁴ and 61%⁵
- Cytogenetic Responses (CyR): 73%⁴ and 50%⁵
- Improve outcome among responders^{5, 6}: OS and AML evolution
- Target clonal cells, nevertheless, did not eliminate malignant stem cells⁷

***Could early Lenalidomide at low doses
prolong time until TD and improve outcome?***

1. Germing, *Leukemia* 2012

2. Rojas, *Leuk Res* 2014

3. López-Cadenas, *ASH* 2016

4. List, *NEJM* 2006

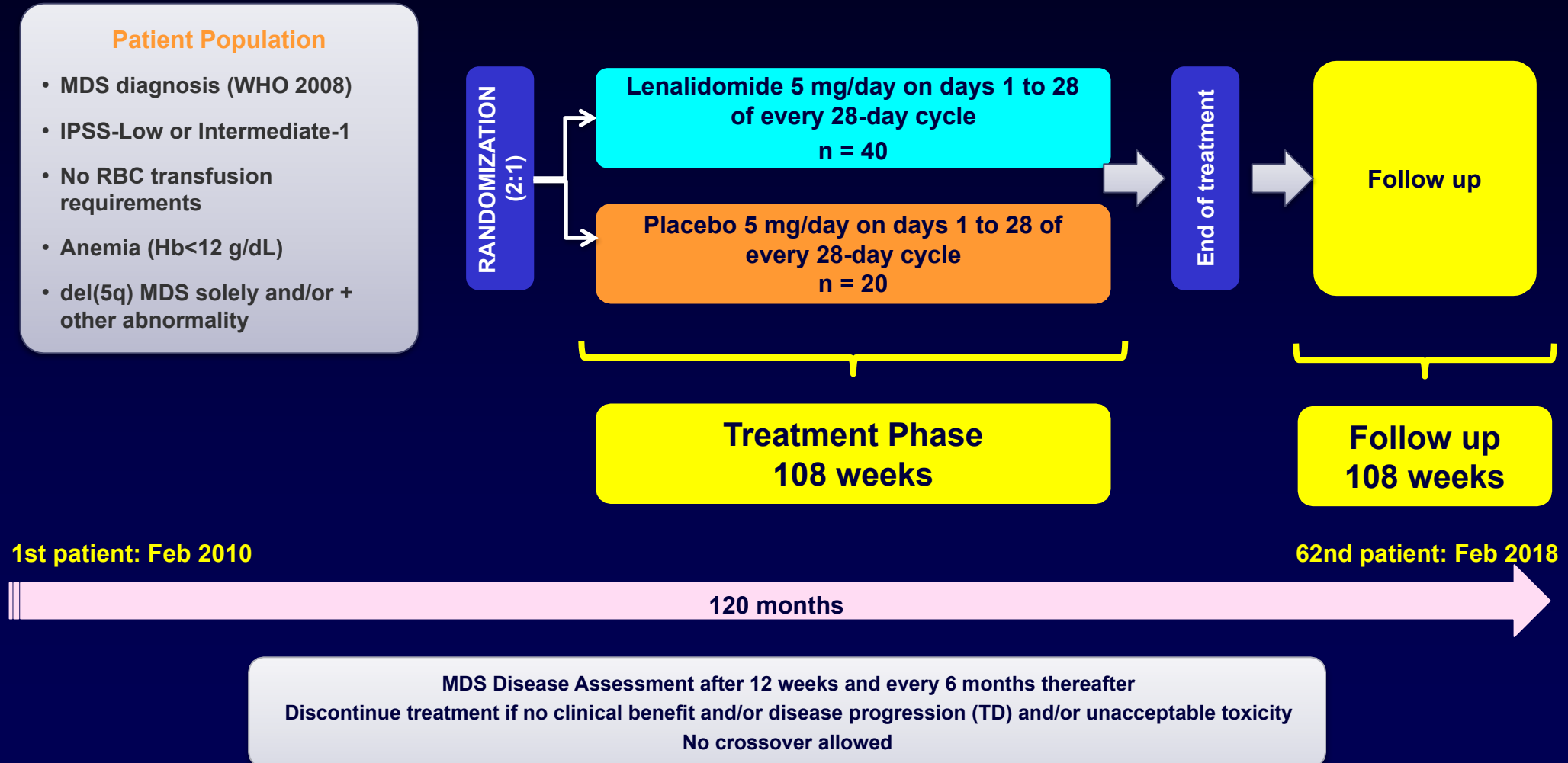
5. Fenaux, *Blood* 2011

6. List et al. *Leukemia* 2014

7. Tehrani, *NEJM* 2010

Design

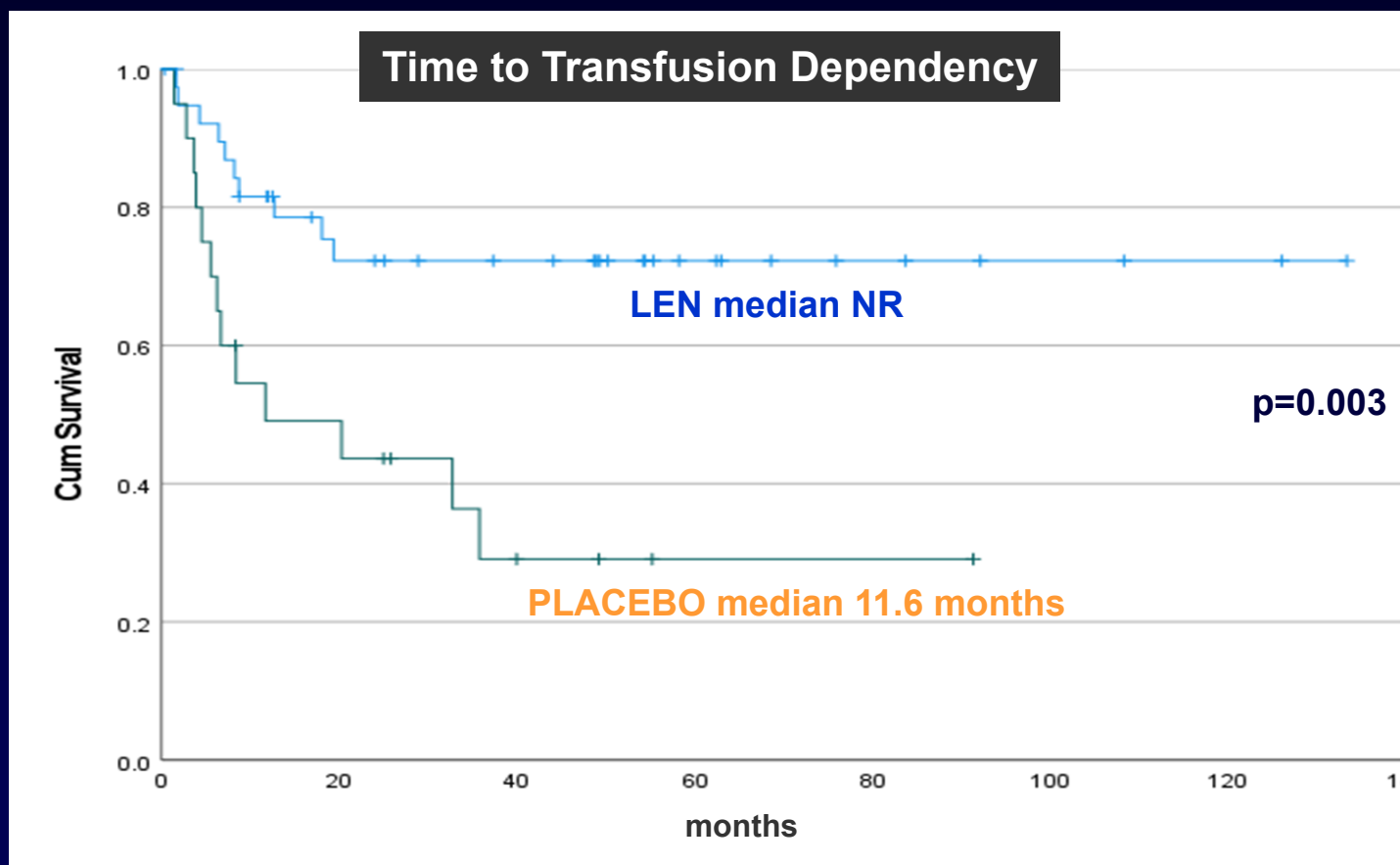
The Sintra-Rev trial is a phase 3, double-blind, randomized, placebo-controlled, multicenter study



Primary objective: Efficacy (ITT, N=61)

Low doses of Len delayed and decreased transfusion dependency

- TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)
- ✓ Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692), p=0.005



Median follow up 5.05y (0.3-11): 5.2 vs 4.85, p=ns

Summary

- **Early treatment with Lenalidomide at low doses (5mg)**
 - **Prolongs the time to and decreased the risk of transfusion dependency**
 - Reached **erythroid responses in 77.8%** of patients
 - Achieved **cytogenetic responses in 94.1%** of patients (87.5% completed)
 - **Acceptable safety profile**, hematological toxicities not clinically relevant
 - Did **not promote clonal evolution**, even in *TP53* mut patients
- **Any impact on long term outcome?**

Case 2: Ms High Dysplasia

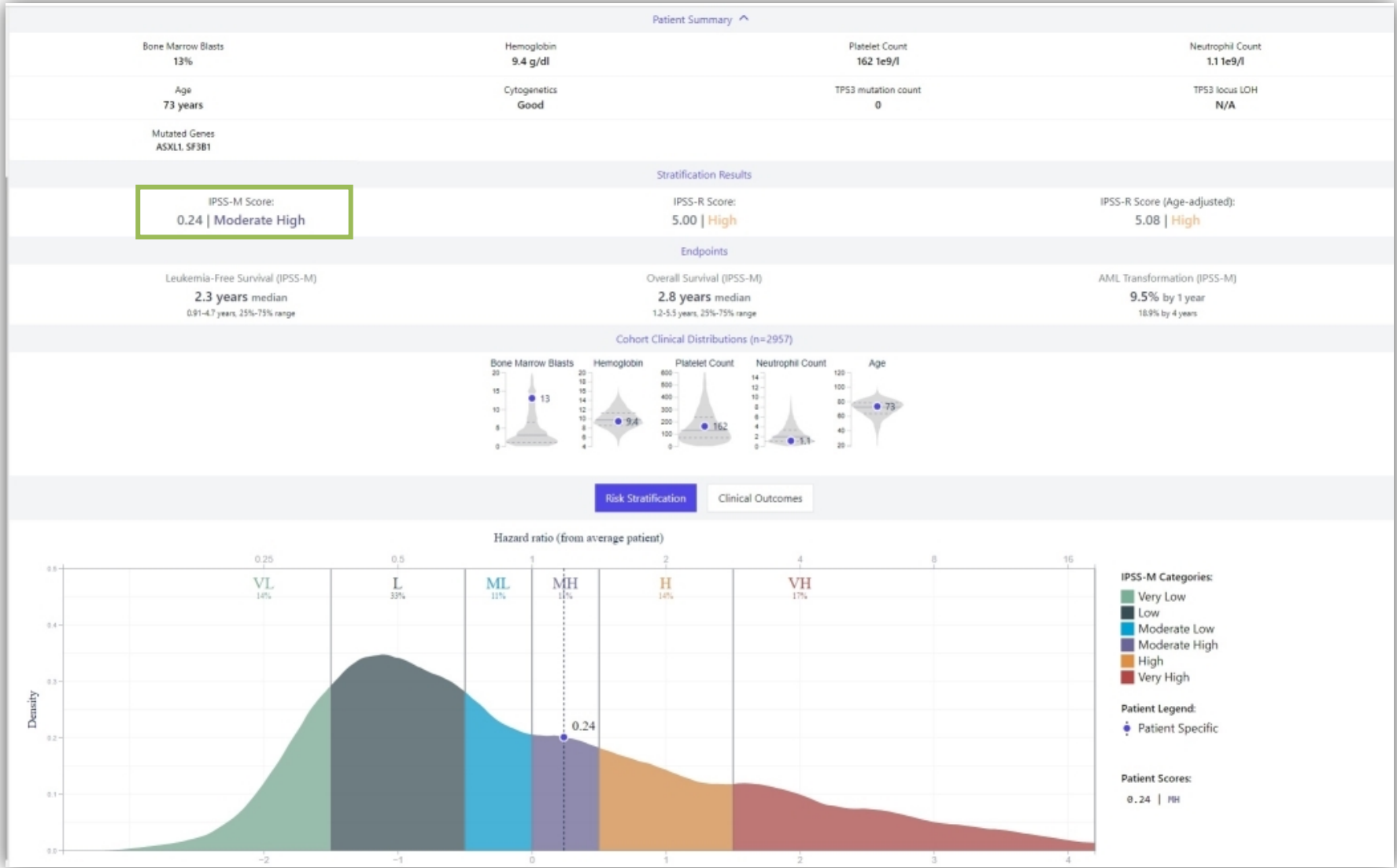
- 71-year-old female presents with fatigue
- Exam: Pale, no organomegaly or adenopathy
- CBC: Hb 9.4 g/dL, MCV 108 fL, ANC $1.1 \times 10^9/L$, platelets $162 \times 10^9/L$
- BM aspirate/Bx: 80% cellular, 13% blasts, +1 fibrosis Karyotype: 46, XX Molecular panel: *SF3B1* (VAF 35%) and *ASXL1* (VAF 52%) mutations

How would you approach prognosis and management?

Patient wants to know her chances of long-term survival if she does not want to undergo allogeneic stem cell transplantation

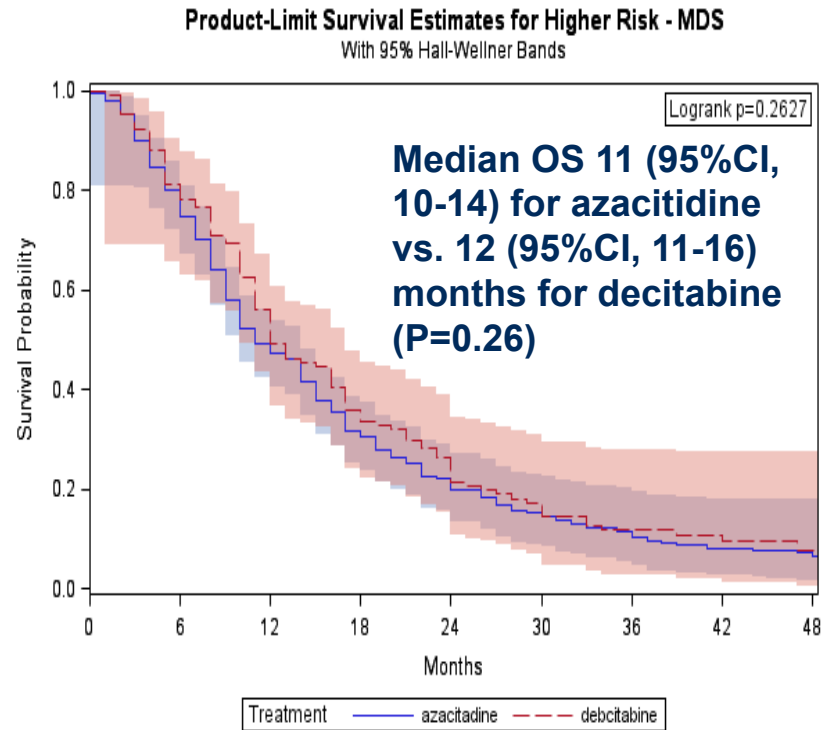


What Is the IPSS-M Score and Risk Group for This Patient?

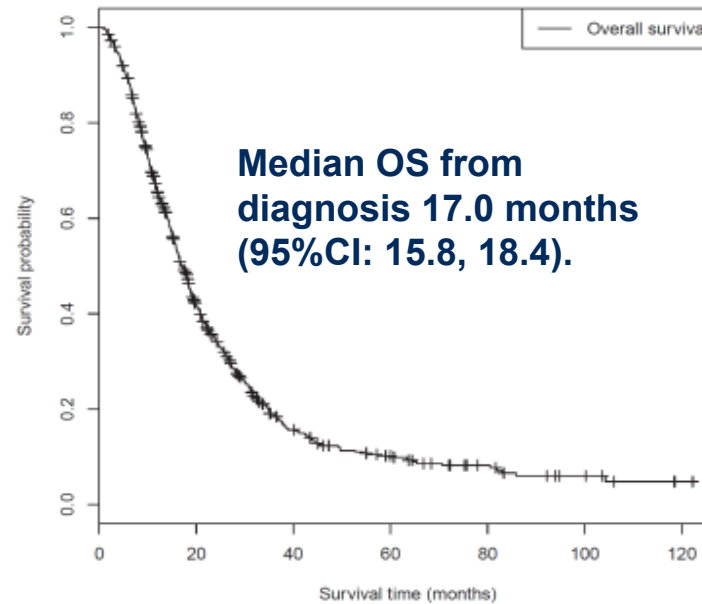


mds-risk-model.com

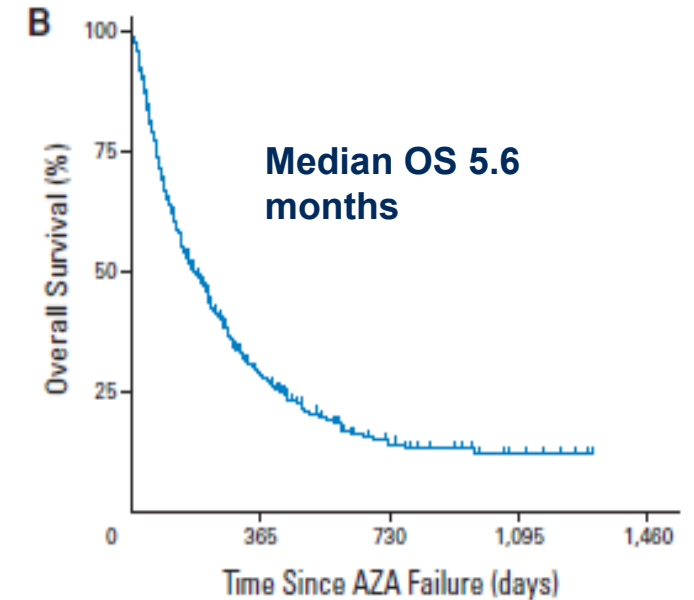
Survival of patients with HR-MDS remains poor despite use of hypomethylating agents



532 patients ≥ 66 years at diagnosis who received ≥ 10 days of HMA therapy

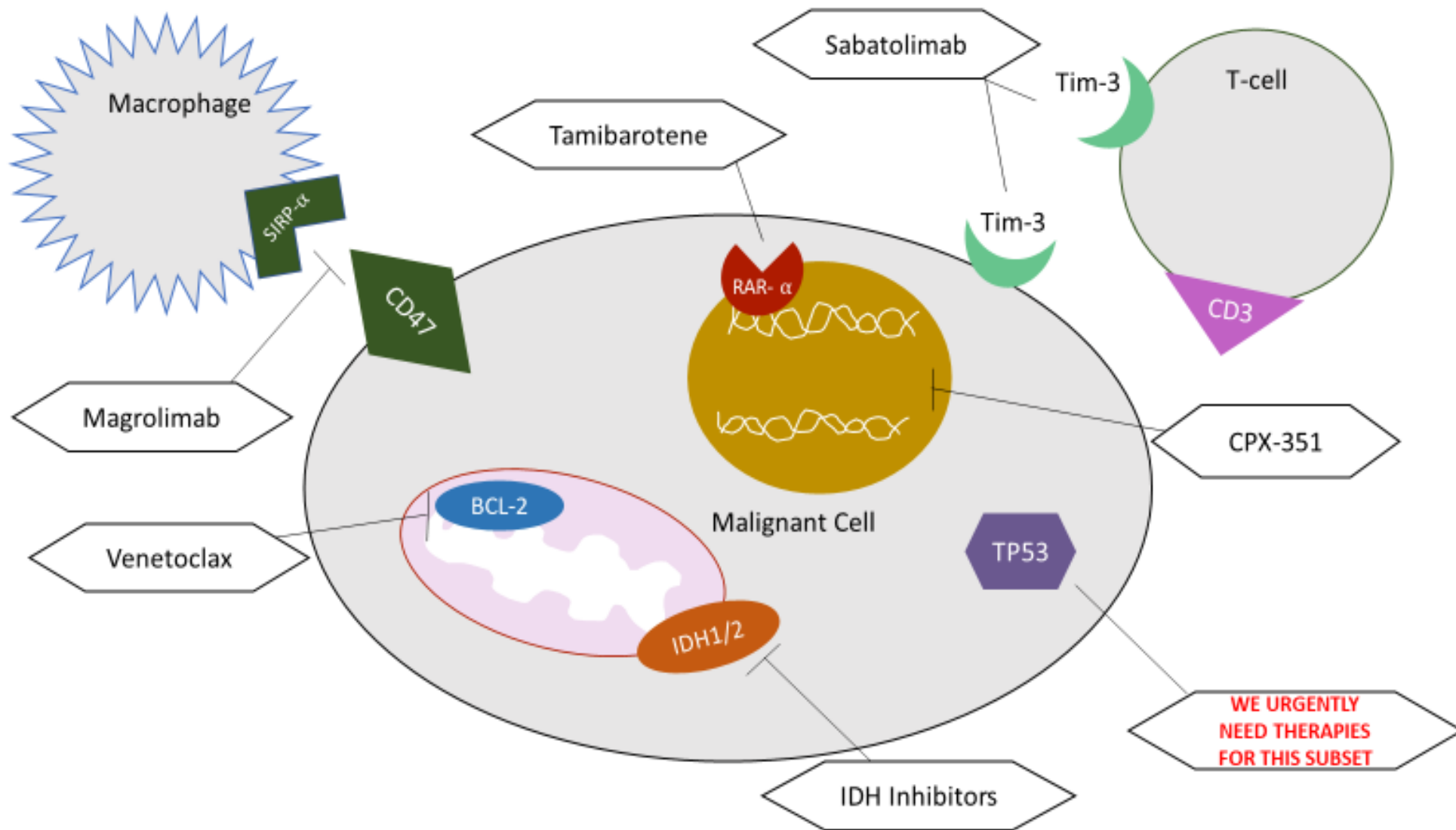


636 HR-MDS of all ages in the MDS Clinical Research Consortium who received HMA (median 5 cycles), 72% received ≥ 4 cycles. 68% received aza.



Survival post azacitidine failure for patients with HR-MDS

Mechanisms of action of late phase novel therapies for higher risk MDS



Selected Randomized Phase III Trials in frontline management of HR-MDS

Drug	NCT	Patient characteristics	Intervention	Study outcomes
Venetoclax	NCT04401748 (VERONA) Estimated primary completion date: 02/2025	Newly-diagnosed HR-MDS Estimated enrollment: 500	Venetoclax + AZA vs. placebo + AZA	Primary Outcome: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 36 Months) - Overall survival (OS) (Up to 5 years)
MBG453 (Sabatolimab)	NCT04266301 (STIMULUS-MDS2) Estimated primary completion date: 05/2027	Newly-diagnosed HR-MDS or CMML-2 Estimated enrollment: 500	MBG453+ AZA vs. placebo + AZA	Primary Outcome: - Overall Survival (Up to 5 years after last patient randomized)
Pevonedistat	NCT03268954 (PANTHER) Estimated Primary completion date: 07/2023	Newly-diagnosed HR-MDS, CMML, or Low-Blast AML Estimated enrollment: 502	Pevonedistat + AZA vs. AZA alone Open-label	Primary Outcome: - Event-Free Survival (From randomization until transformation to AML, or death due to any cause; up to 6 years)
Magrolimab	NCT04313881 (ENHANCE) Estimated primary completion date: 08/2022	Newly-diagnosed HR-MDS Estimated enrollment: 520	Magrolimab + AZA vs. AZA + placebo	Primary Outcomes: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 24 Months) - Overall survival (OS) (Up to 5 years)
APR-246	NCT03745716 Actual primary completion date: 11/2020	Newly-diagnosed TP53-mutated HR-MDS Estimated enrollment: 154	APR-246 + AZA Vs. AZA alone Open-label	Primary Outcome: - Complete response rate (CR) with APR 246 + azacitidine vs. azacitidine only
SY-1425 (Tamibarotene)	NCT04797780 Estimated Primary completion date: 07/2023	Newly-diagnosed RARA-positive HR-MDS Estimated enrollment: 190	SY-1425 + AZA Vs. placebo + AZA	Primary outcome: - Complete response rate (CR) with SY-1425 + azacitidine vs. azacitidine only

Conclusions for MDS at ASH 2022

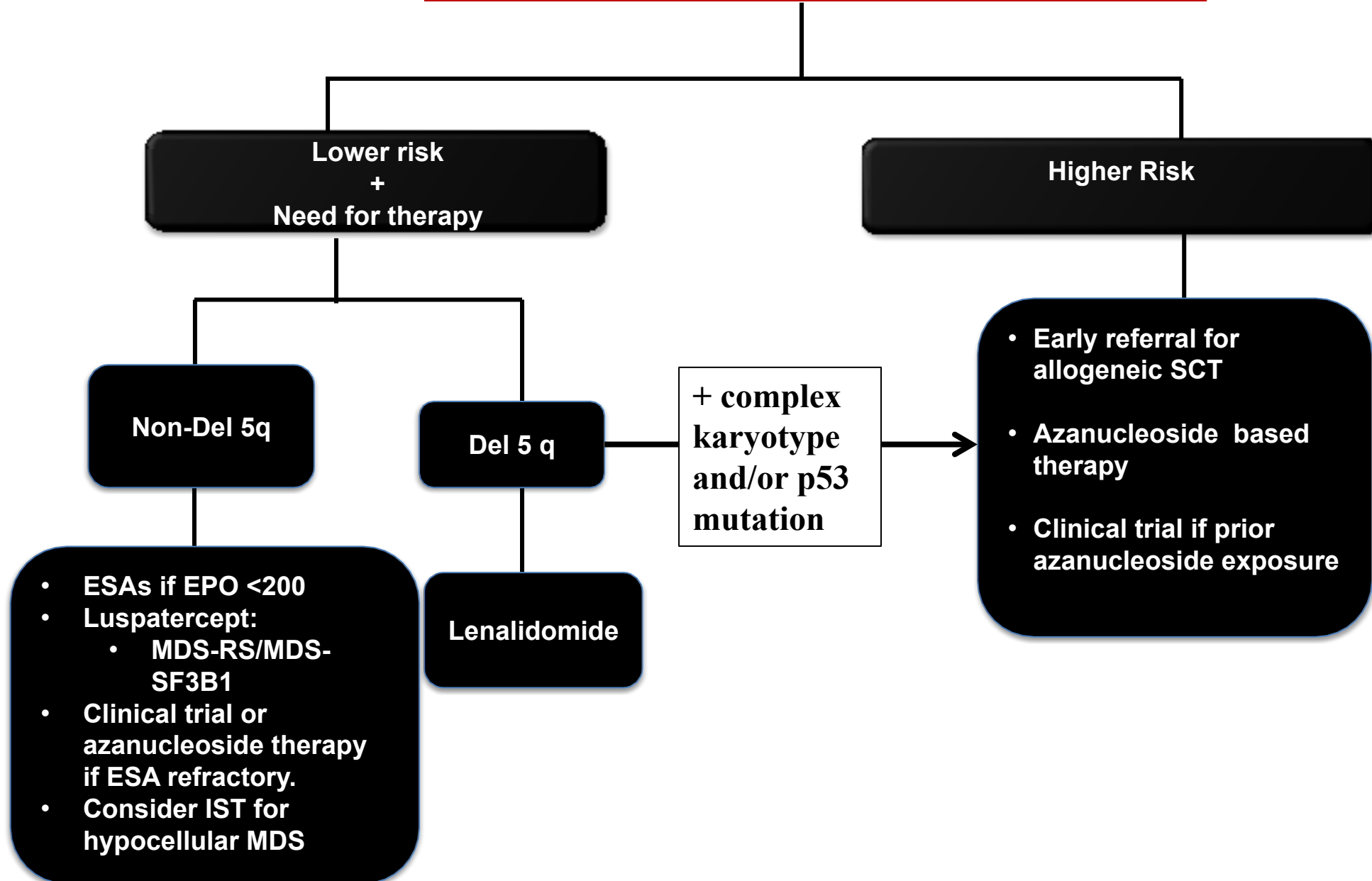
- Myelodysplastic syndromes/neoplasms (MDS) are highly heterogenous
 - in biology and clinical outcomes (even within IPSS-R)
- IPSS-M accounts for prognostic impact of molecular mutations
 - improves accuracy of risk stratification
 - External validation at ASH
- Two new MDS classification systems (WHO 2022 and ICC 2022)
 - add genetically-defined disease subsets and improve disease classification
 - require harmonization for clinical care
 - External validation at ASH
- TP53 mutations, especially biallelic, remain most challenging to overcome



Conclusions for MDS at ASH 2022

- Imetelstat: Phase 2 extended follow-up of anemic lower-risk MDS
 - suggests sustained transfusion independence; P3 results ~ 2023
- Results of other randomized phase 3 trials (venetoclax, Magrolimab, sabatolimab and tamibarotene) are expected 2023 and beyond
- Clinical trial enrollment should be encouraged in all patients with MDS


Risk Stratification by R-IPSS/IPSS-M





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Thank You