MDS

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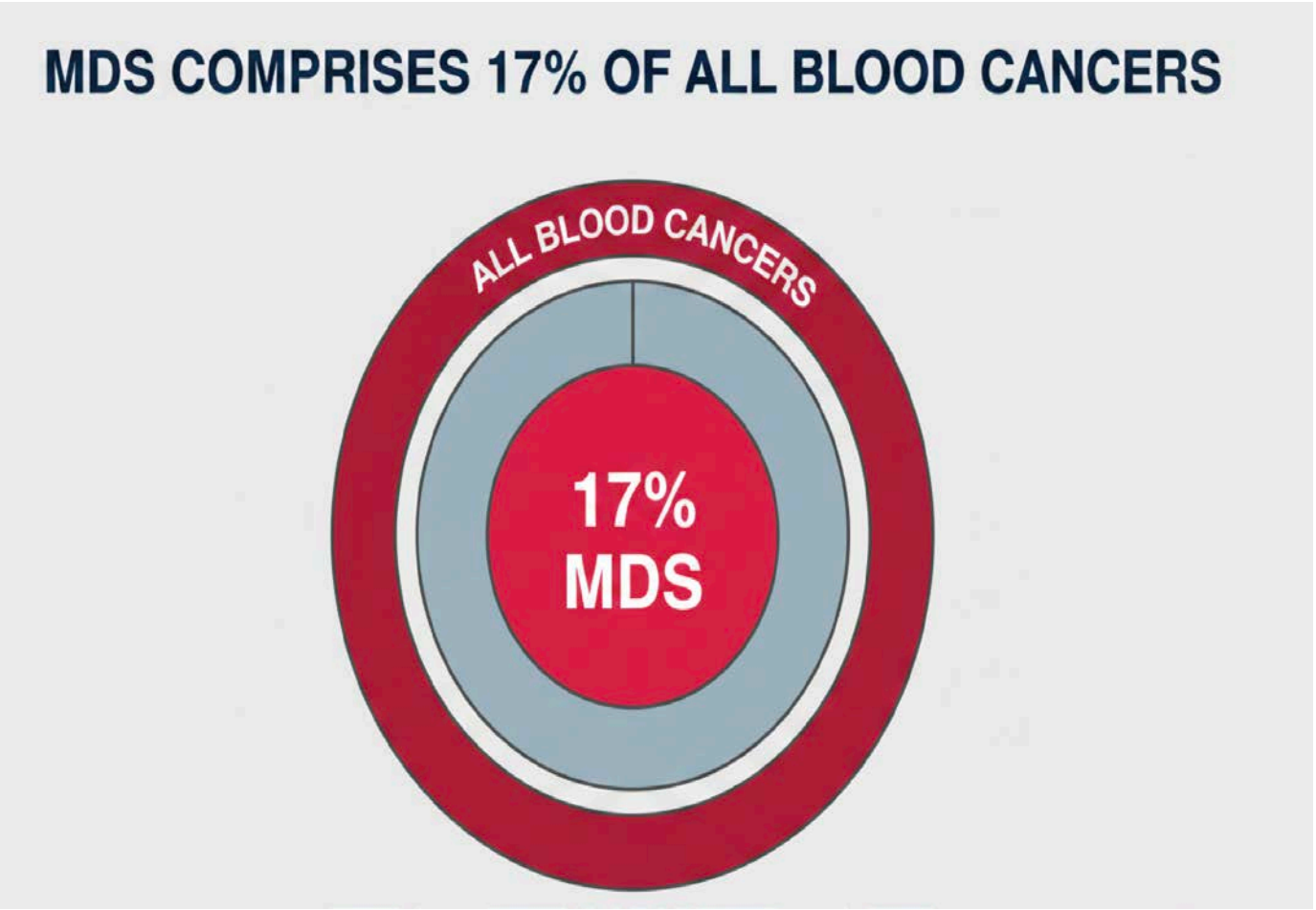
Chair MDS-CAN

MDS-CAN

Objectives

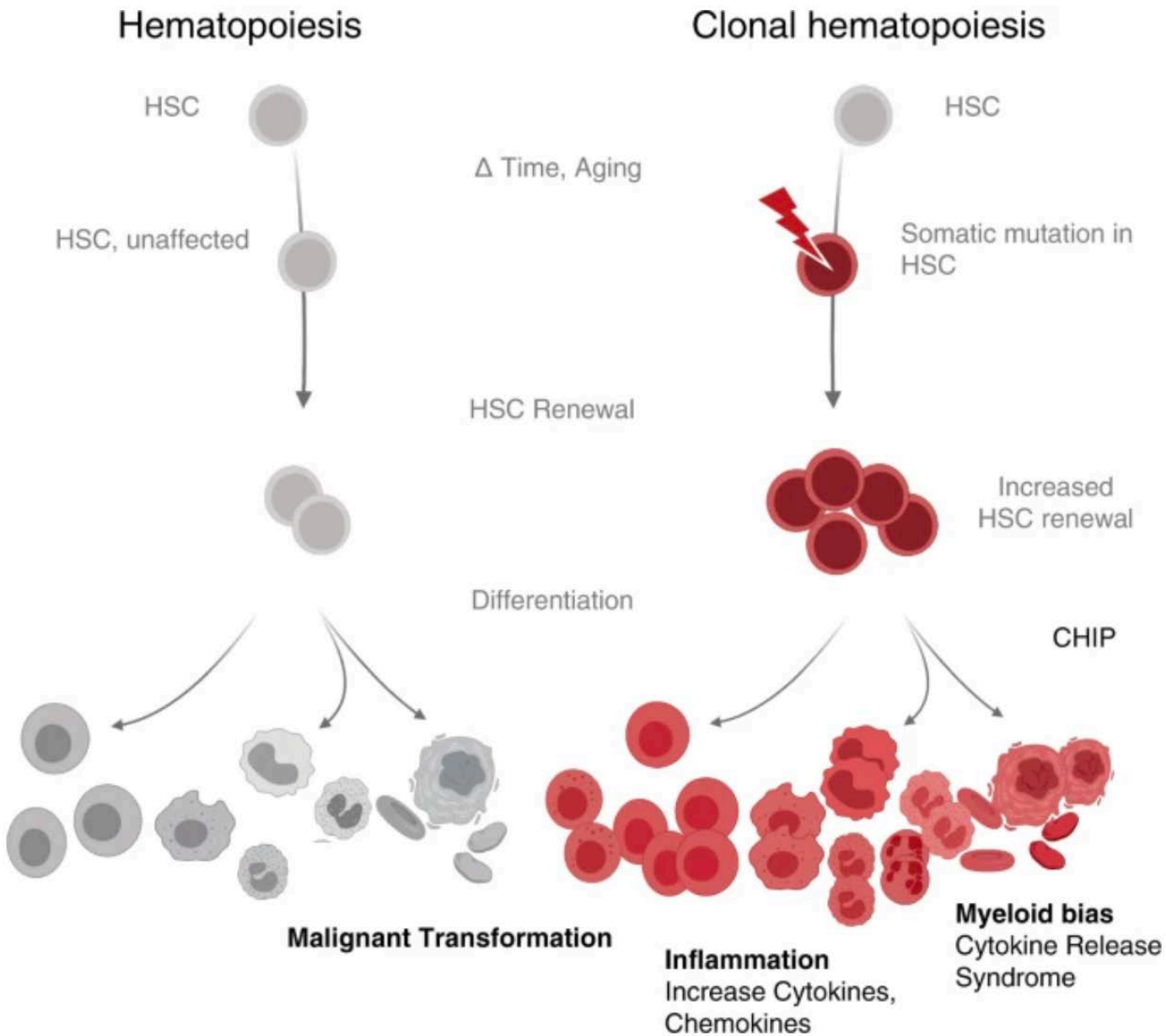
- Trajectory of disease: from innocent clones to full blown MDS to leukemia
- Prognosis updates
- Treatment update
- MDS registry updates
- Clinical trials you might consider now and in the near future

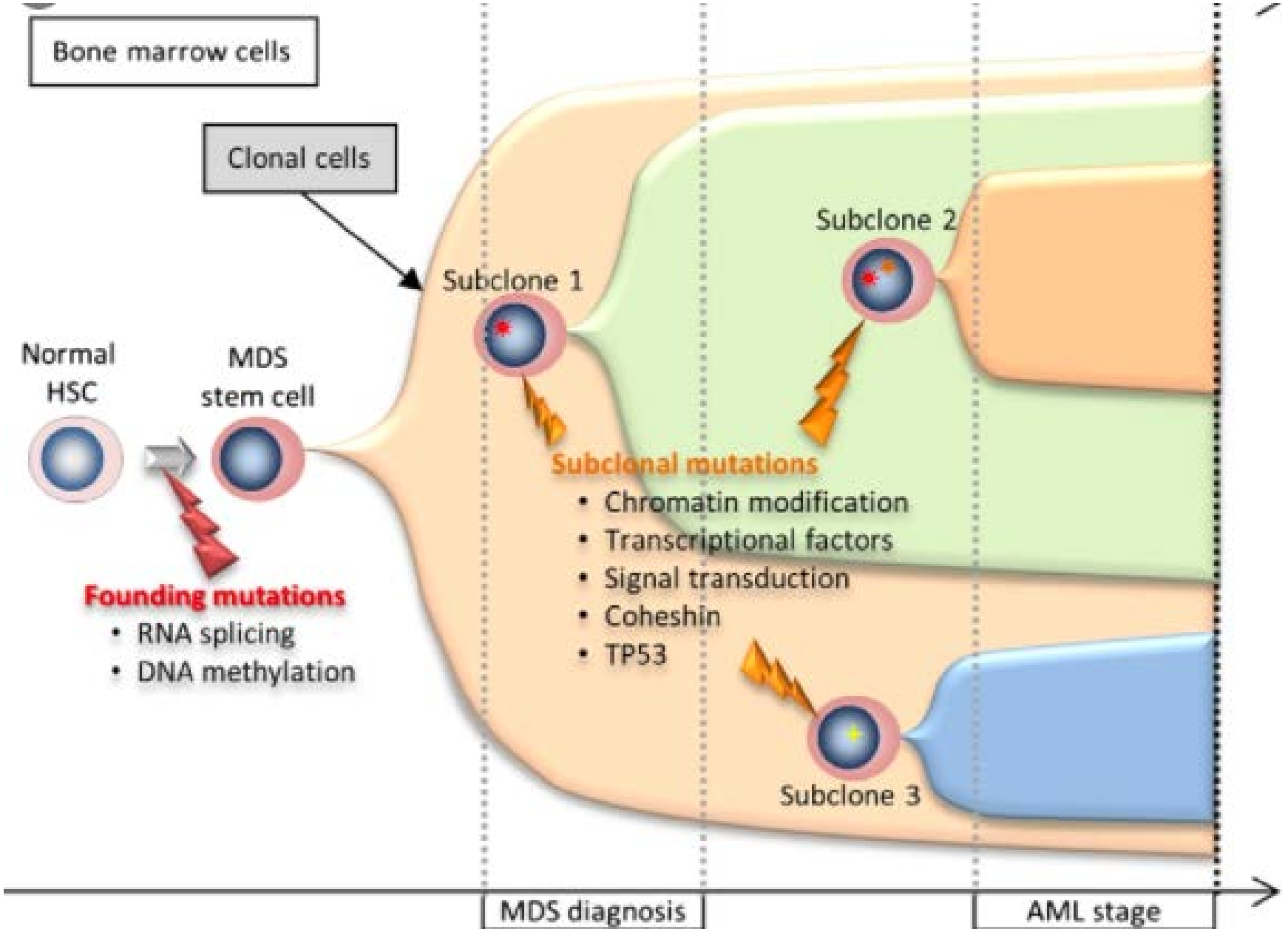
MDS STATS



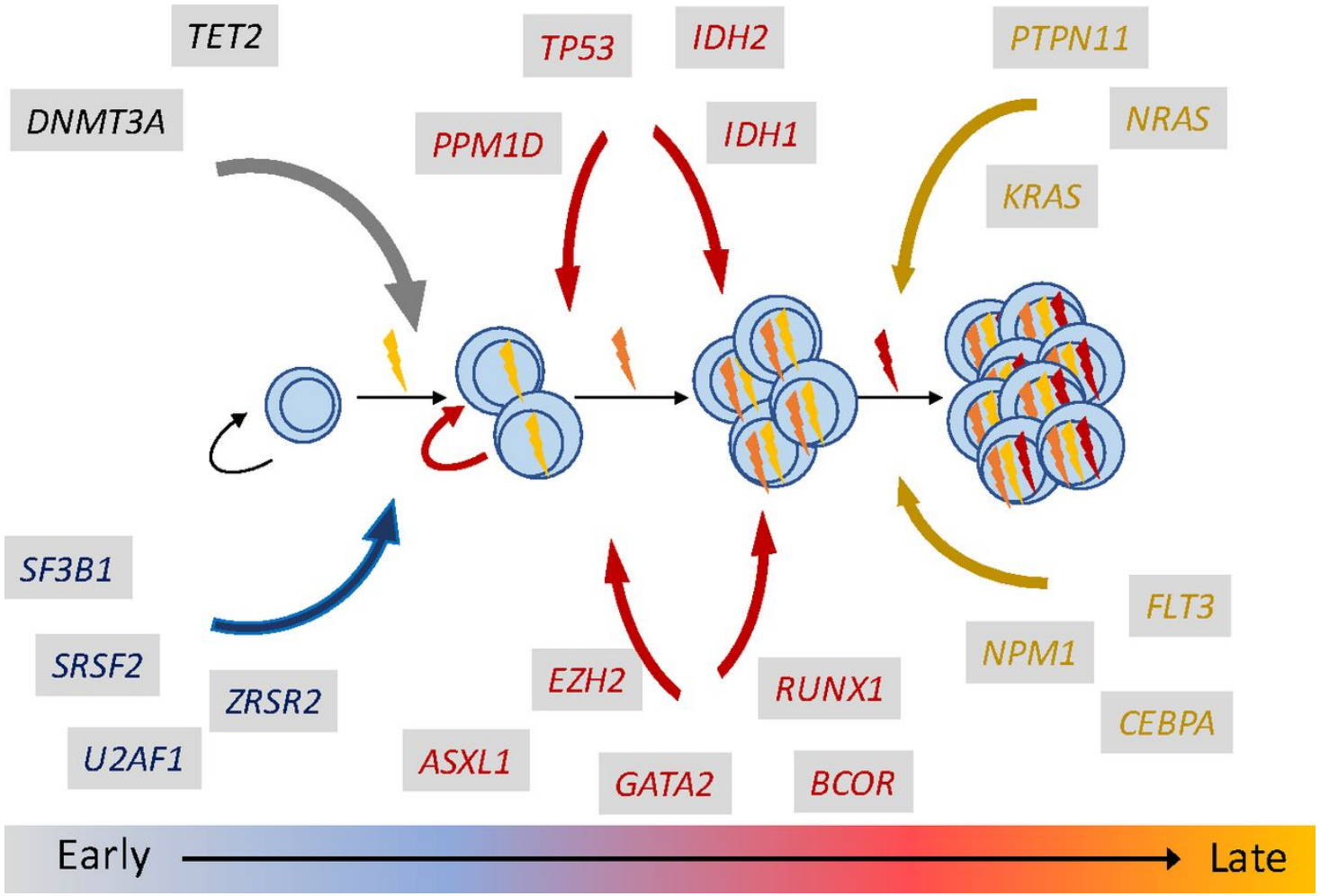
- **Annual Cases:** Roughly 5,900 new cases are diagnosed every year.
- **Incidence Rate:**
  - 4 cases per 100,000: increases with age
- **Demographics:** Predominantly affects older adults, with a median age at diagnosis of 75–76 years.
- **Gender:** Higher incidence in men, with a male-to-female ratio of 1.35.

Fig. 1: Contrasting hematopoiesis with clonal hematopoiesis.




Bone marrow cells
Clonal cells
Normal HSC
MDS stem cell
Subclone 1
Subclone 2
Subclone 3
Founding mutations
• RNA splicing
• DNA methylation
Subclonal mutations
• Chromatin modification
• Transcriptional factors
• Signal transduction
• Cohesin
• TP53
MDS diagnosis
AML stage

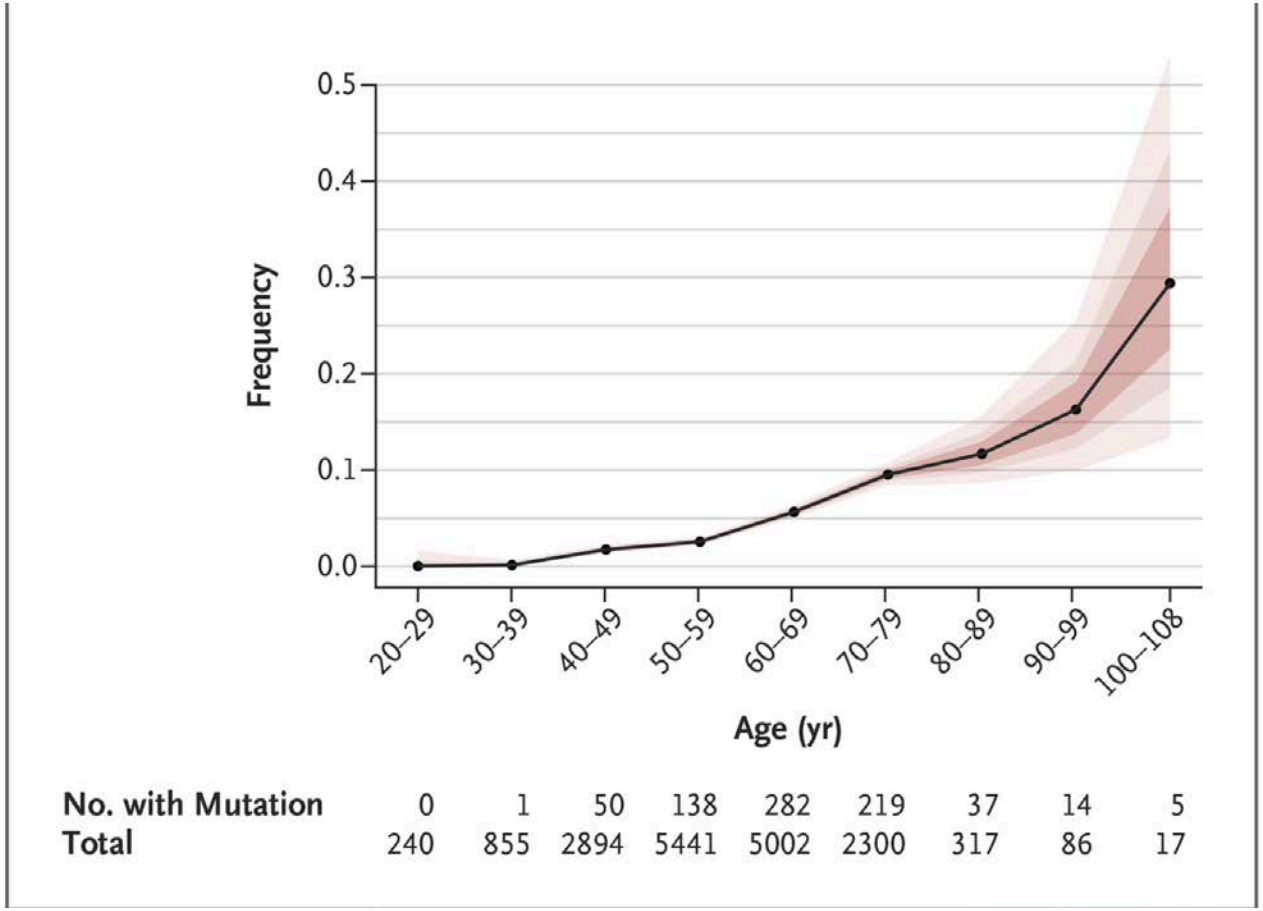
MDS occurs because of progressive genetic mutations



Pathways and genes	Frequency, %
RNA Splicing	
SF3B1	15–30
SRSF2	10–20
U2AF1	<10
ZRSR2	<10
DNA methylation	
TET2	20–30
DNMT3A	10–15
IDH1/IDH2	5
Chromatin modification	15–20
ASXL1	
EZH2	5
RAS pathway	
CBL	<5
NRAS/KRAS	<5
Transcription	
RUNX1	10
BCOR	<5
Tumor suppressor	
TP53	5

R. Coleman Lindsley, Am Soc Hematol Educ Program, 2017, Figure 2.

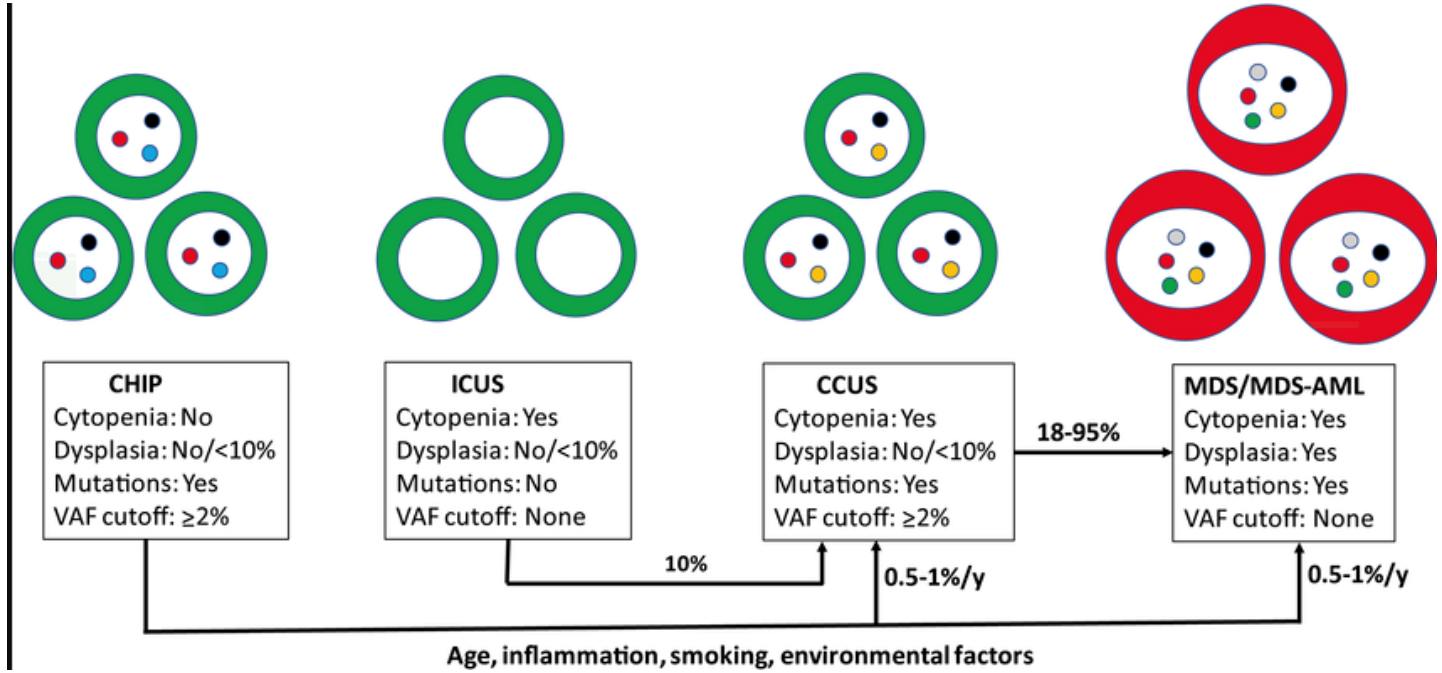
These same mutations can be found in healthy people and increase with age: 10% above age 70

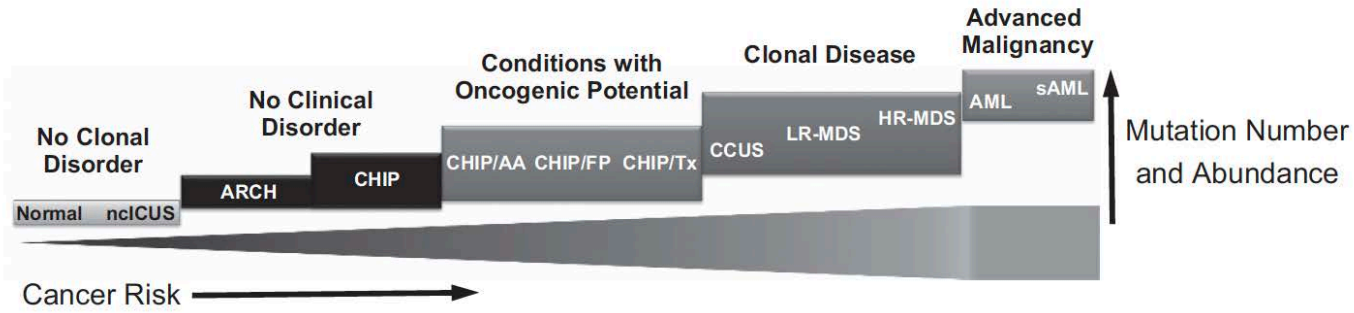


No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

CHIP

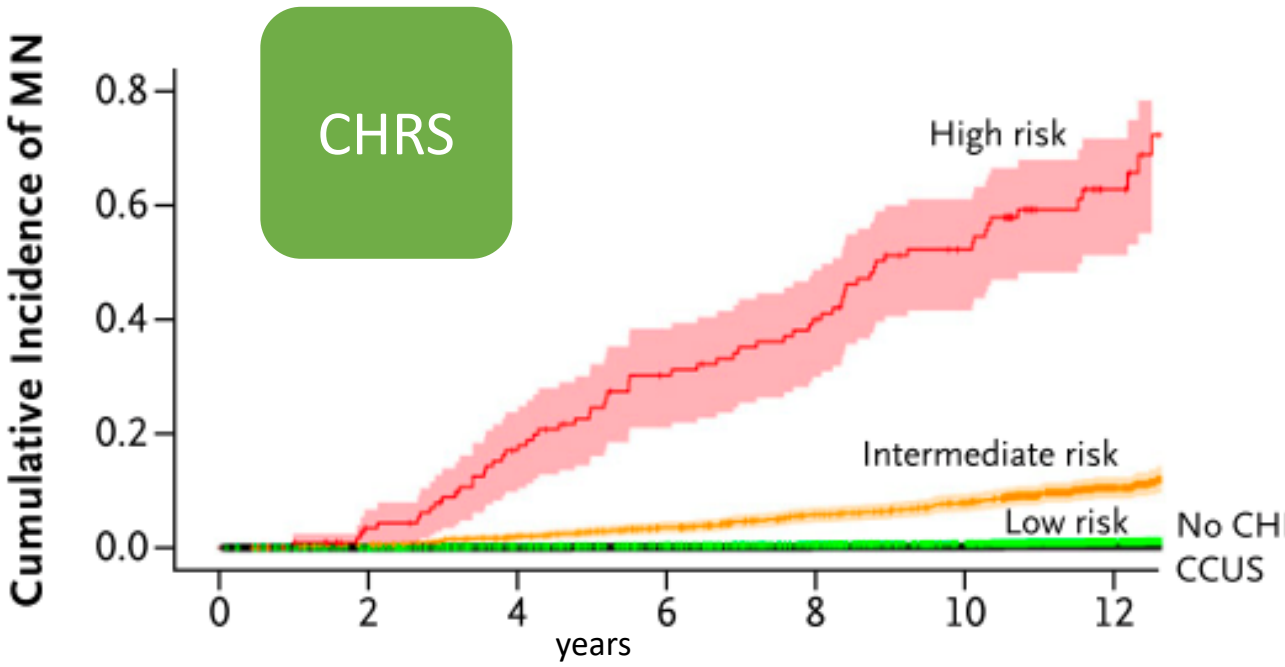
Jaiswal, NEJM 2014

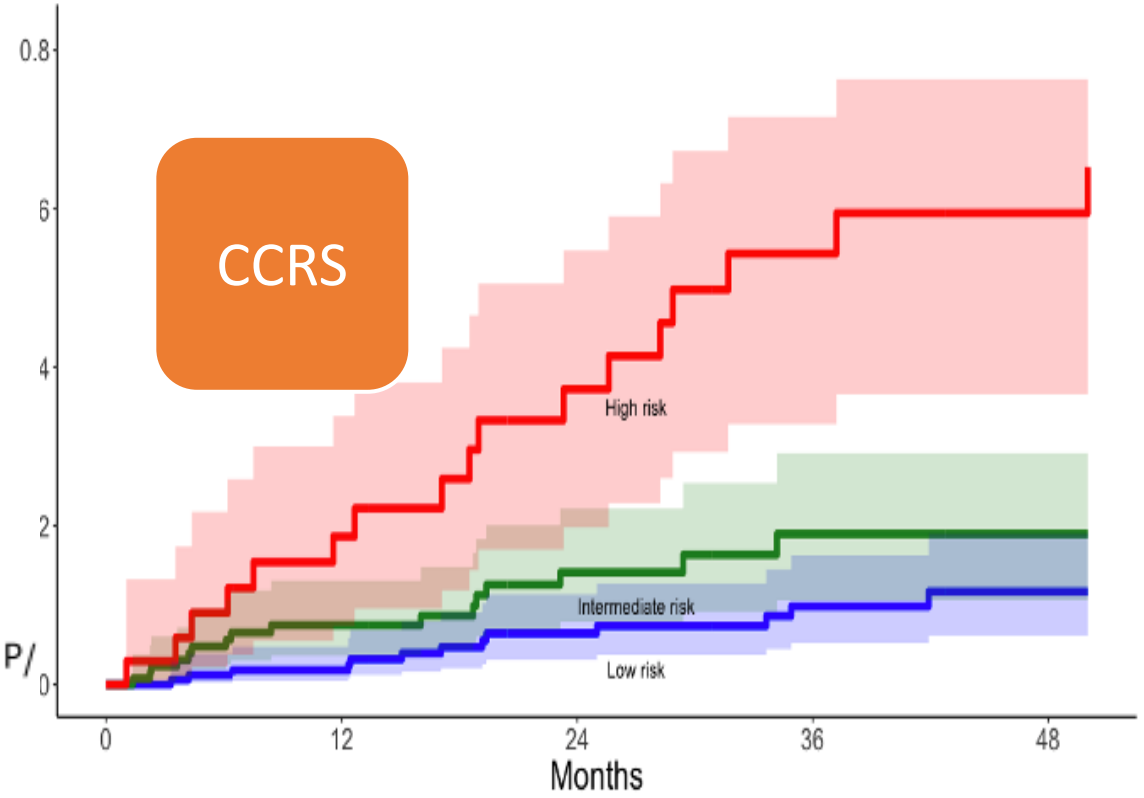




Falini B Am J Haematol 2023
Bejar R. Leukemia 2017

Risk stratification tools for CHIP and CCUS





Clonal Hematopoiesis Risk Score

- **Population based study**
- **Variables: age, MCV, RDW, clonality, high-risk mutations, mutation numbers, and clonal burden**
- **Predict risk of myeloid neoplasm, not OS**

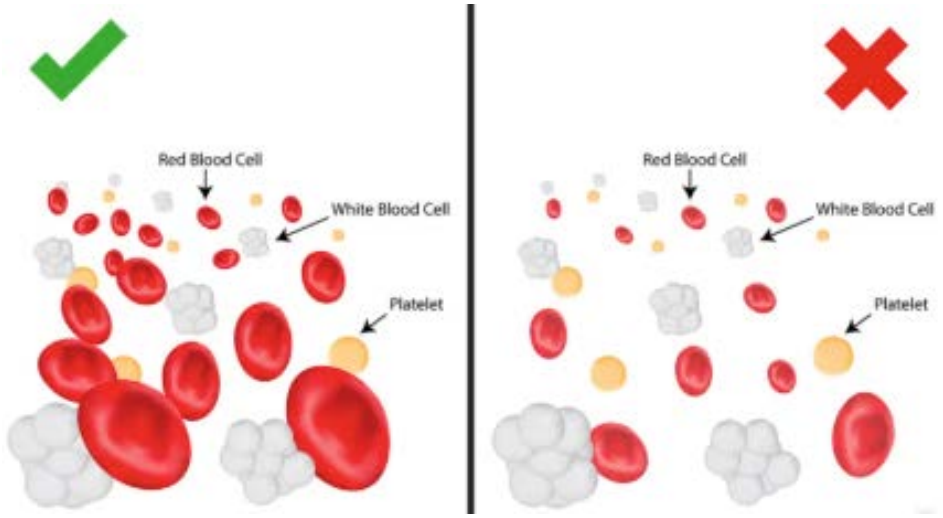
Clonal Cytopenia Risk Score

- **Real world data**
- **Variables: splicing mutations, mutation numbers, and thrombocytopenia**
- **Predict risk of myeloid neoplasm, not OS**

Weeks, et al. NEJM evidence 2023; Xie et al., Blood 2024

Clinical Presentations of MDS

- Asymptomatic:



- Symptomatic:

SUMMARY: MDS Diagnosis and Natural History

- To diagnose MDS, you need at least 1 reduced blood count AND one of:
  - Dysplasia: abnormal appearance under microscope
  - Too many immature cells (blasts)
  - MDS defining cytogenetic abnormality

- MDS leads to complications:
  - Marrow failure → low blood counts → transfusions, bleeding, infections
  - Iron overload
  - Transformation to AML (25%)
  - Cardiovascular disease

Conceptual Classification of MDS: Risk Classification

Chronic Phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB- no adverse mutations

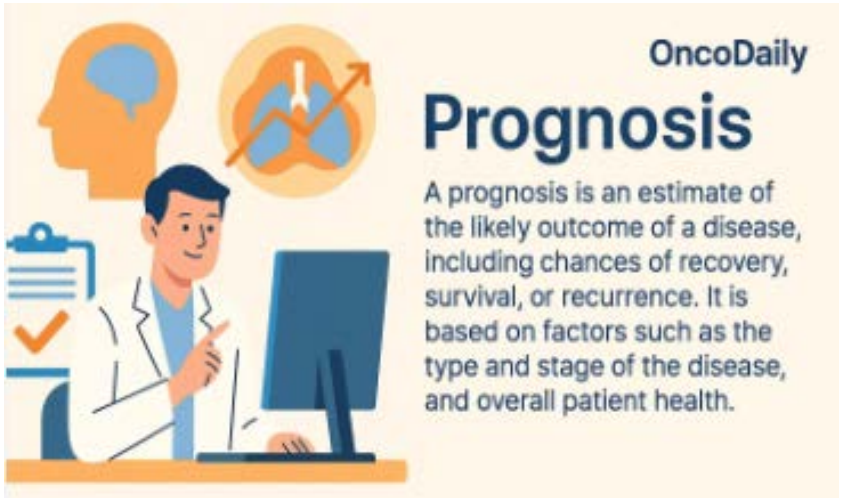
Accelerated Phase MDS

- MDS-EB (5-9% myeloblasts)
- Bi-allelic *TP53* MDS
- MDS-fibrosis

MDS-AML

- ≥10-20% myeloblasts

AML, Acute Myeloid Leukemia; LB, low blasts; MDS, Myelodysplastic syndrome; MR, myelodysplasia-related; SF3B1, Splicing Factor 3B Subunit; TP, Tumour Protein



IPSS

IPSS
Greenberg et al. Blood 1997

Blast:
- <5% (0)
- 5-10% (0.5)
- 11-20% (2.5)
- 21-30% (2)

Cytopenia:
- Hb<10 g/dl
- ANC<1.5/μL
- PLT<100/μL

0-1 score:0; 2-3: score 0.5

Cytogenetics:
- Good (0)
- Intermediate (0.5)
- Poor (2)

Risk group
- Low: 0
- Int-1: 0.5-1
- Int-2: 1.5-2
- High:≥2.5

Improvements from IPSS->IPSS-R
- Add specific strata to include the depth of cytopenia;
- Revised BM blasts cutoff;
- Incorporate additional cytogenetic abnormalities and give more weight on this

IPSS-R

IPSS-R
Greenberg et al. Blood 2012

Blasts:
- <2% (0)
- 2-5% (0.5)
- 5-10% (1.5)
- >10% (2)

Cytopenias:
- Hb: 8-10 g/dl (1)
- Hb:<8 g/dl (1.5)
- ANC:<0.8/μL (0.5)
- PLT: 50-<100/μL (0.5)
- PLT:<50 (1)

Cytogenetics[a]:
- Very Good (0)
- Good (0.5)
- Intermediate (2)
- Poor (3)
- Very poor (4)

Risk group
- Very low≤1.5
- Low: 1.5-3
- Int: 3.5-4.5
- High: 5-6
- Very high:>6

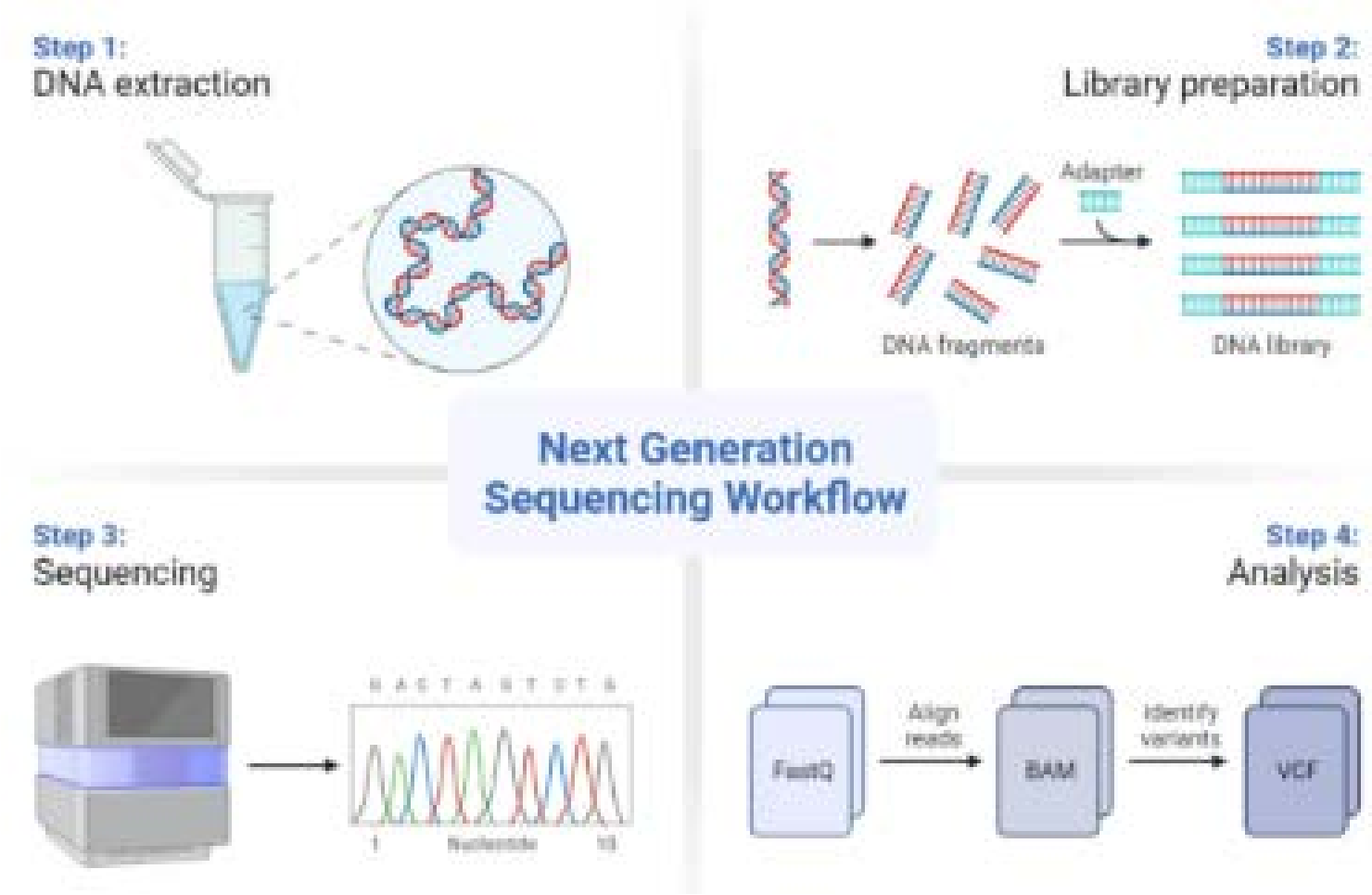
IPSS-M

Bernard et al. NEJM Evidence 2022
IPSS-M

Online calculator:
https://mds-risk-model.com/

Model input include:
age, sex, Hb, PLT, BM blasts%, IPSS-R cytogenetic risk, and 31 gene panel
(-*TP53* allelic status, *SF3B1*^{5q}, *SF3B1*^{a}, *SF3B1*$^{\beta-}$
Number of additional mutations in *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*
&
-Binary (Yes/No): *ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH2, KRAS, KMT2A, NPM1, NRAS, RUNX1, SRSF2,* and *U2AF1)*

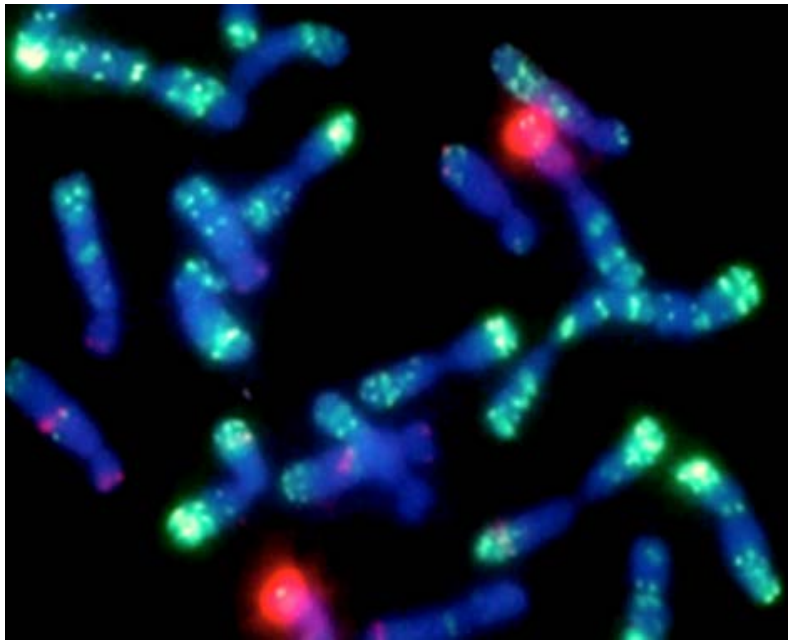
Next Generation Sequencing (NGS)



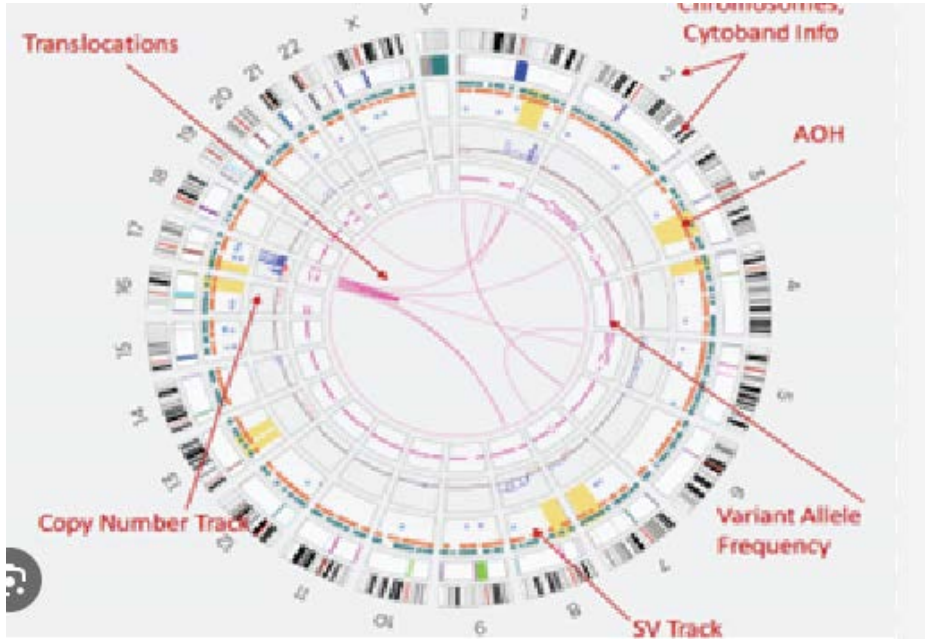
Improved techniques in identifying chromosome abnormalities

Metaphase Cytogenetics

FISH



Optical Genome Mapping



*Bone Marrow Blasts

Percentage: 2 [0-30%]

*Hemoglobin

g/dL | Change: 10.8 [4-20 g/dL]

*Platelet Count

1e9/L: 470 [0-2000 1e9/L]

OPTIONAL IPSS-R DATA

Absolute Neutrophil Count

1e9/L: 3 [0-15 1e9/L]

Age

Years: 58 [18-120 years]

CYTOGENETICS

*Presence of

del(5q)	No	Yes
-7/del(7q)	No	Yes
-17/del(17p)	No	Yes
Complex Karyoptype	No	Yes

*Cytogenetics Category

Very Good	-Y, del(11q).
Good	Normal, del(5q), del(12p), del(20q), double including del(5q).

MOLECULAR DATA

*Number of TP53 mutations

Mutation Count	0	1	2+

* Maximum TP53 VAF

Percentage: 13 [0-100%]

*Loss of heterozygosity at TP53 locus (if known)

TP53 LOH	No	Yes	N/A

Bernard et al. NEJM Evidence 2022
IPSS-M

Online calculator:
https://mds-risk-model.com/

Model input include:
age, sex, Hb, PLT, BM blasts%, IPSS-R cytogenetic risk, and 31 gene panel (-*TP53* allelic status, *SF3B1*^{5q}, *SF3B1*^{a}, *SF3B1*$^{\beta-}$ Number of additional mutations in *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*
&
-Binary (Yes/No): *ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH2, KRAS, KMT2A, NPM1, NRAS, RUNX1, SRSF2,* and *U2AF1*)

IPSS-M Risk Calculator

PATIENT SUMMARY

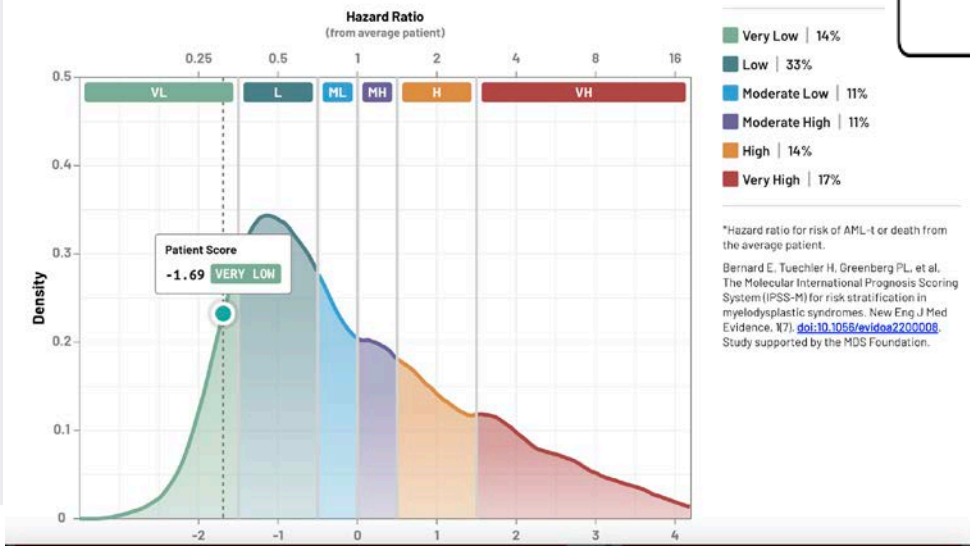
STRATIFICATION RESULTS

IPSS-M Score:	IPSS-R Score:	IPSS-R Score (Age-adjusted):
-1.69 VERY LOW	**1.00** VERY LOW	**0.46** VERY LOW

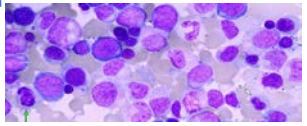
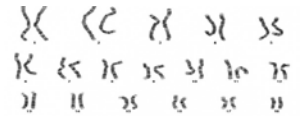
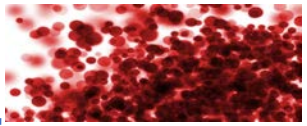
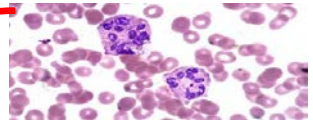
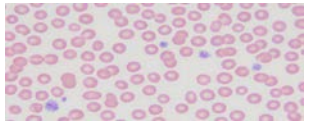
ENDPOINTS

Leukemia-Free Survival (IPSS-M):	Overall Survival (IPSS-M):	AML Transformation (IPSS-M):
9.7 years median	**10.6 years** median	**0%** by 1 year
5-17.4 years, 25%-75% range	5.1-17.4 years, 25%-75% range	2.8% by 4 years

Graph | Table



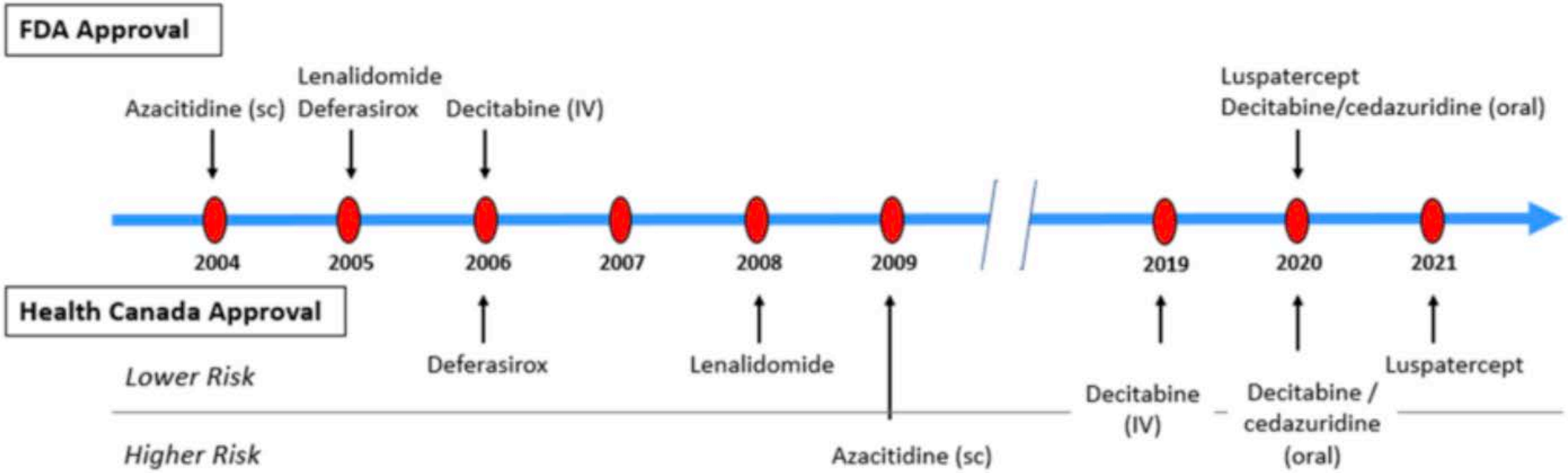
Risk Stratification and Clinical Decisions in MDS – IPSS-M 58% of MDS is Lower risk

	Diagnosis[1]	Classification[1]	Incidence (%)[1]	Median OS (yrs)[1]	Progression risk (% at 4 yrs)*,[1]	Treatment goal[2]	Current SoC[2]
Low risk		Very low *(Very low/low)*	14	10.6	2.8	Hematologic improvement (lower risk of infection & bleeding)	Transfusion ESAs Lusptaercept HMAs Watch & wait
		Low *(Very low/low/int)*	33	6.0	5.1		
		Moderate low *(Low/int)*	11	4.6	11.4		
						?	
High risk		Moderate high *(Low/int/high)*	11	2.8	18.9	Alter disease natural history (higher risk of infection & bleeding)	HMAs/ICT +/- ASCT
		High *(Int/high/very high)*	14	1.7	29.2		
		Very high *(High/very high)*	17	1.0	42.8		

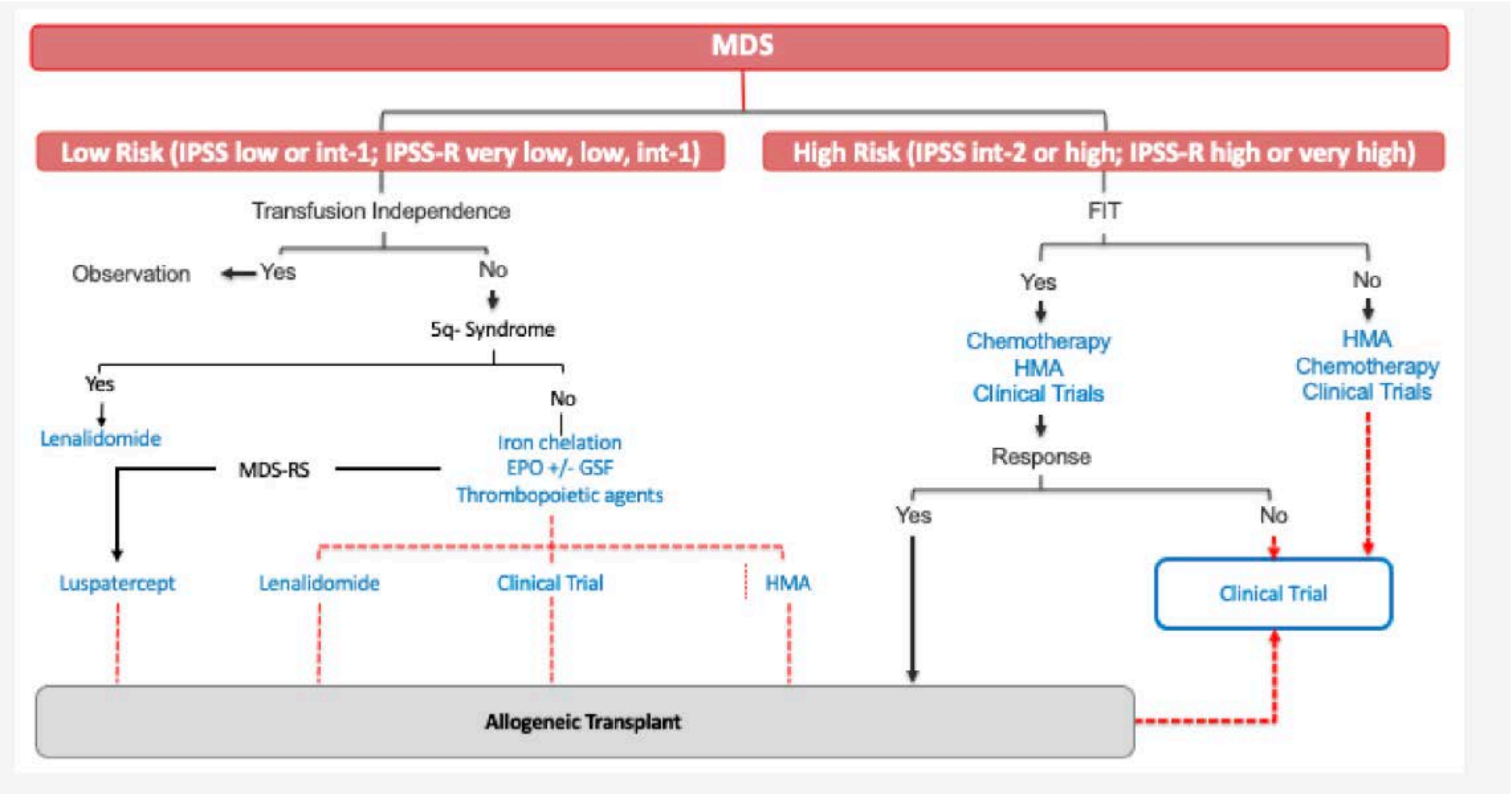
ASCT, Autologous stem cell transplant; ESA, Erythropoietin stimulating agents; HMA, Hypomethylating agents; iron chelation therapy; IDH, isocitrate dehydrogenase; IPSS, International Prognostic; MDS, Myelodysplastic syndrome; OS, overall survival; SoC, standard of care

1.Bernard E, *et al. NEJM Evid* 2022; 1:7; 2.Fenaux P, *et al. Ann Oncol* 2021;32:142–156.

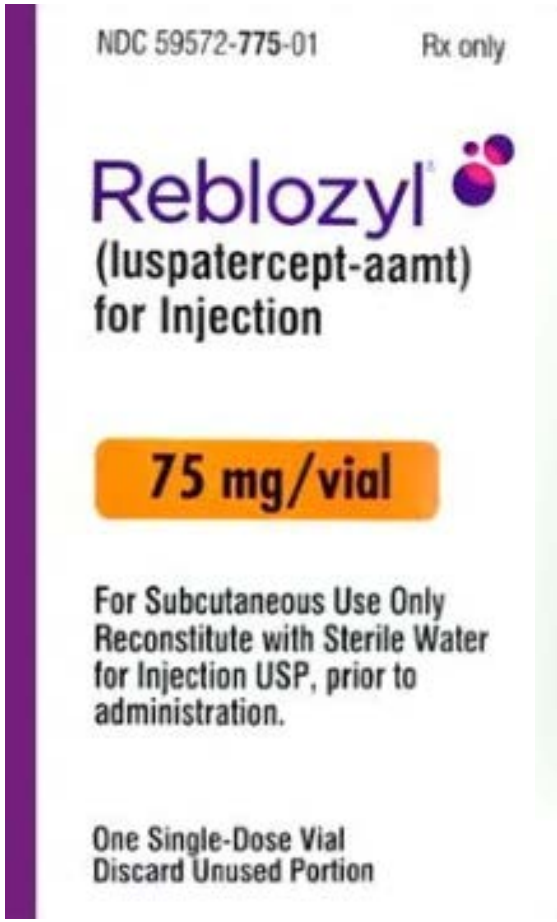
Drug approvals in Canada: Too few

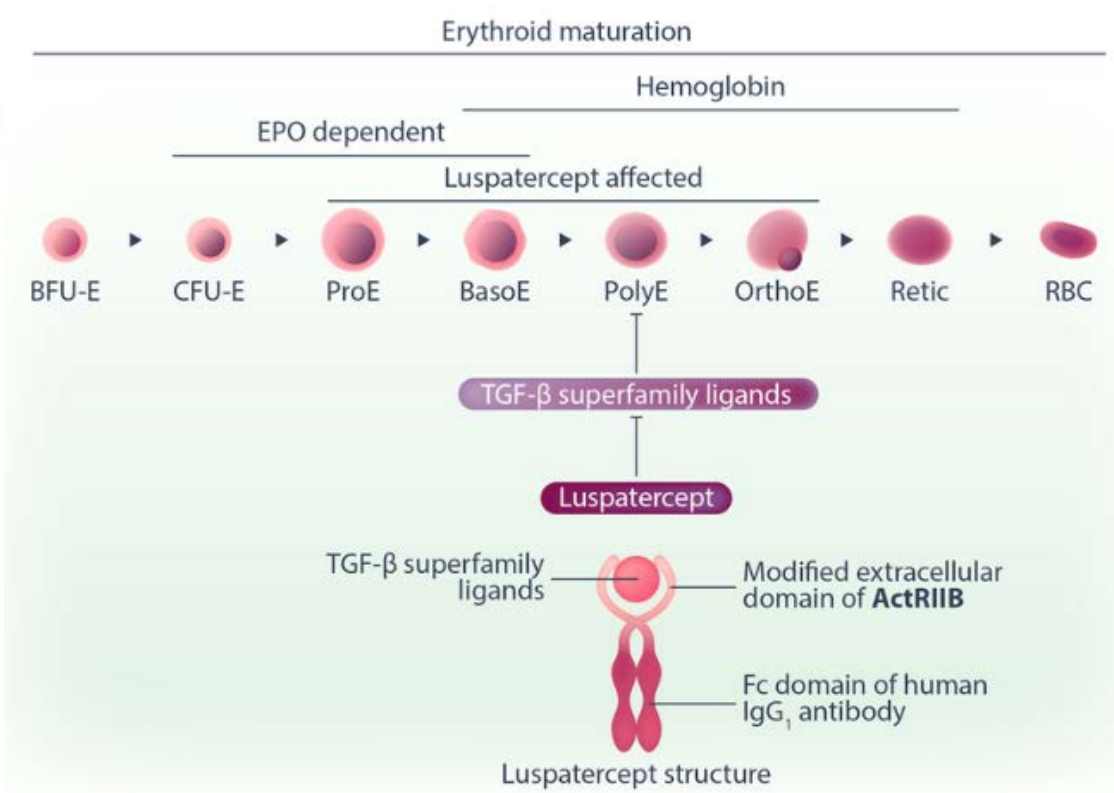


Treatment algorithm



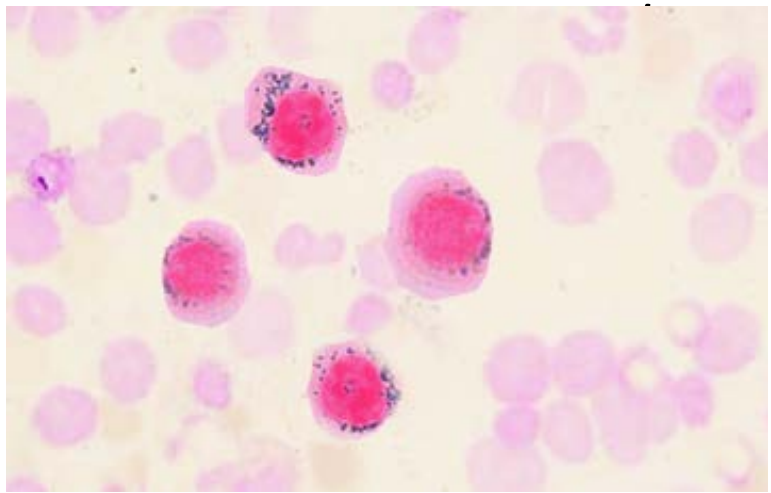
Luspatercept: maturation agent



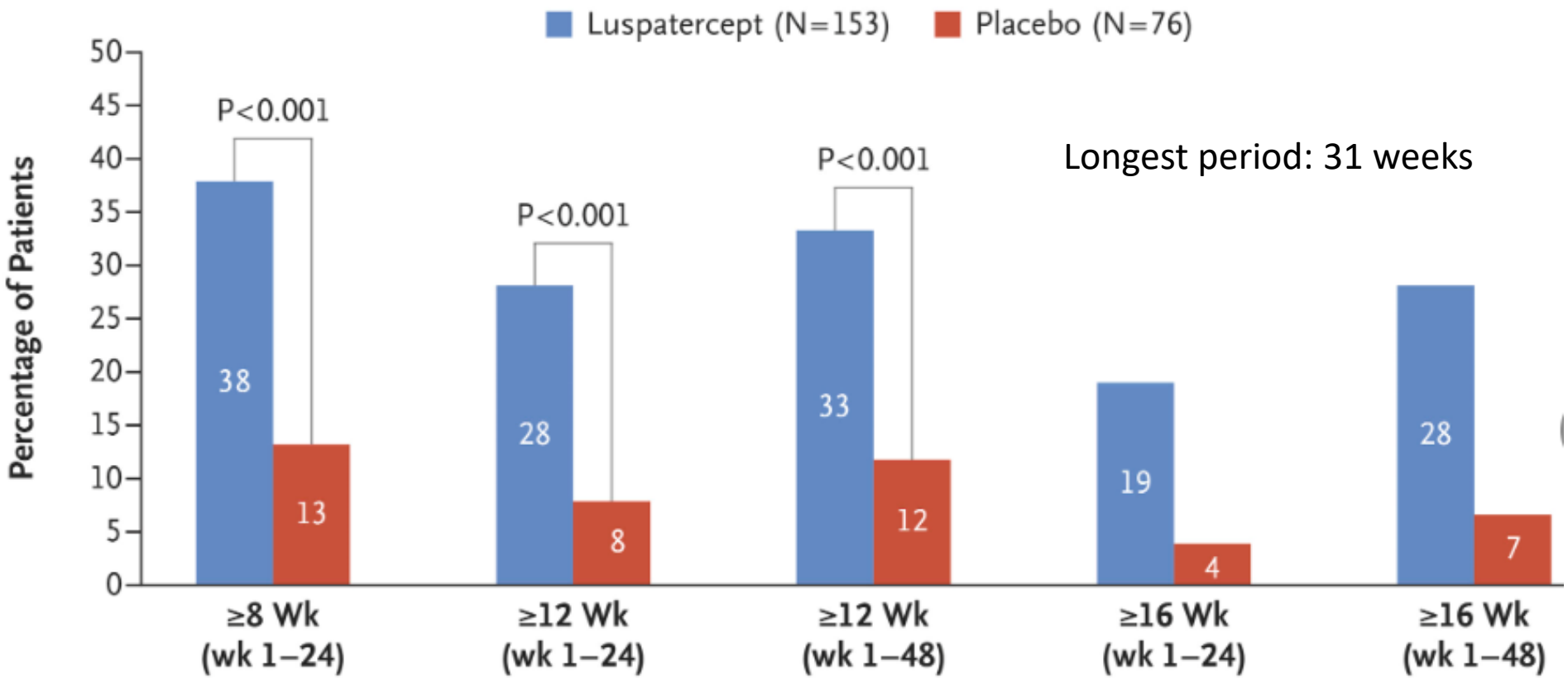


Reimbursed for:

- Lower risk MDS
- MDS with ring sideroblasts
- Transfusion dependent
  - > 2 UNITS/8w x 16w
- EPO stimulating agents failed



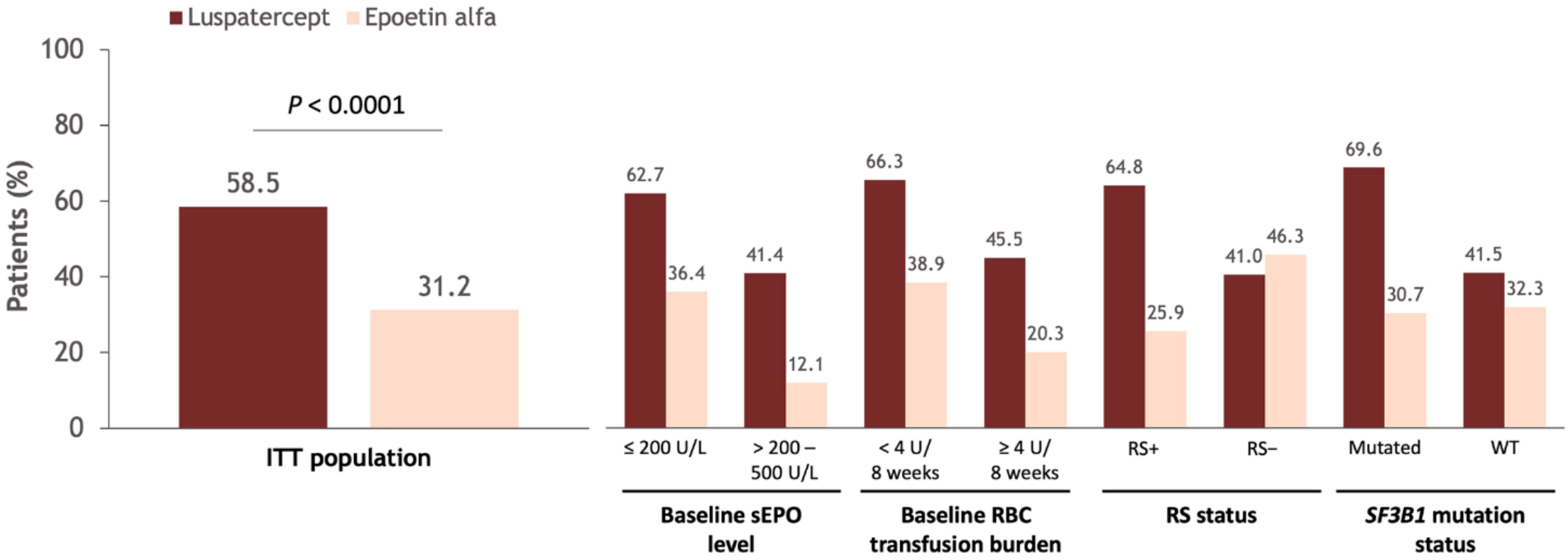
MEDALIST study: transfusion independence



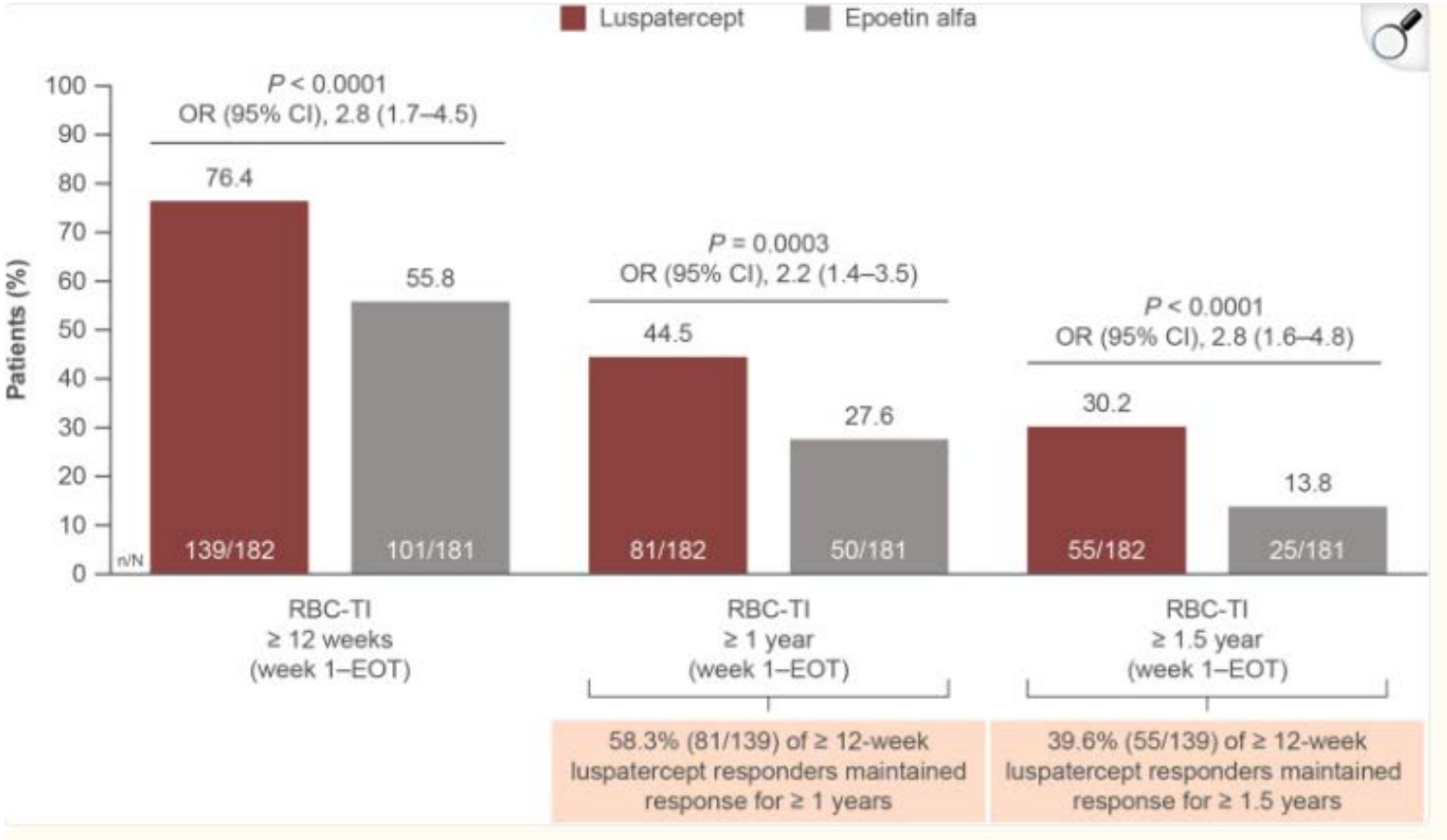
Longest period: 31 weeks

Fenaux P. NEJM 2020

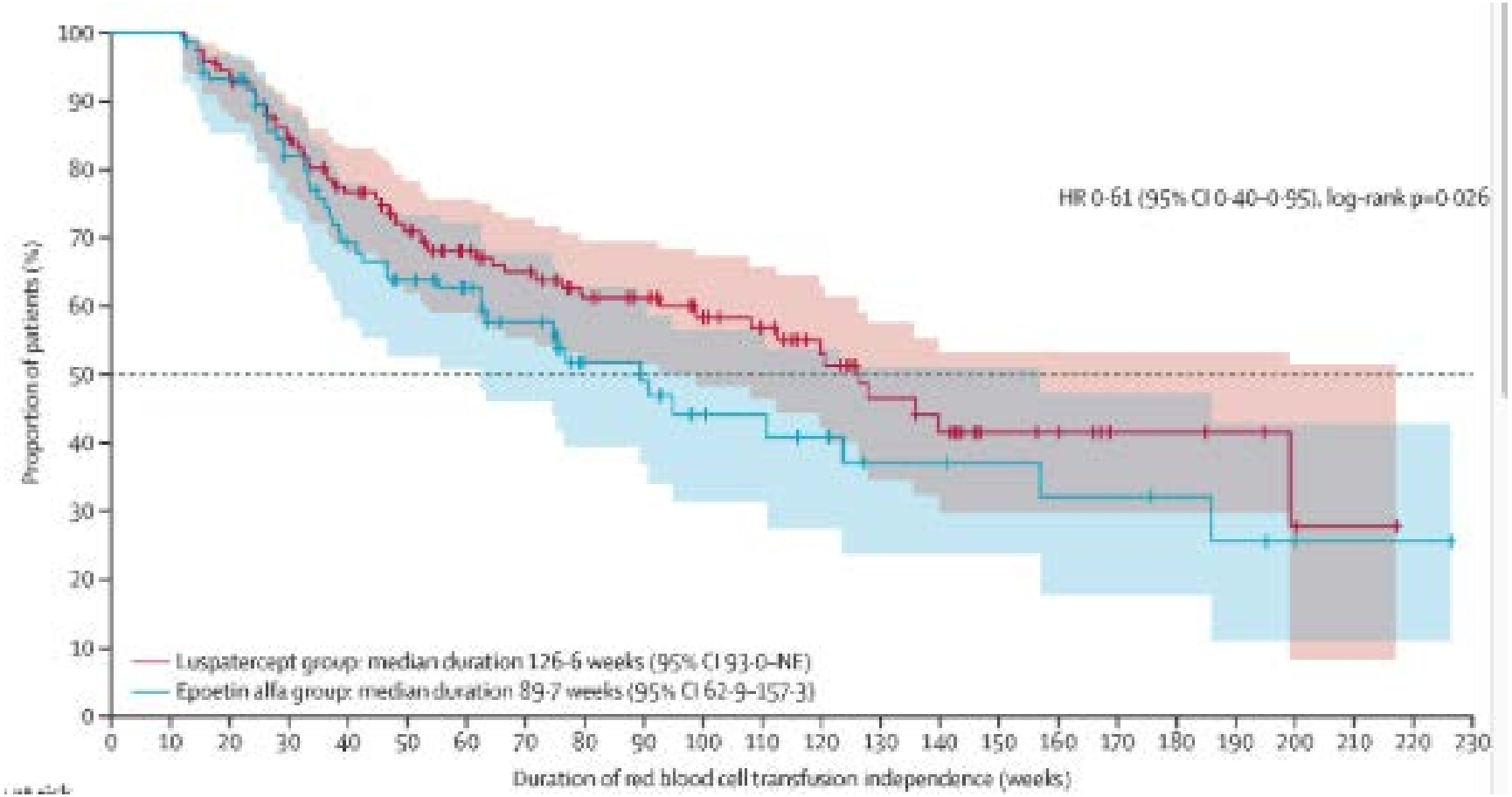
COMMANDS study: Luspatercept better than Erythropoietin when used front line at eliminating transfusion independence



Luspatercept works longer than EPREX

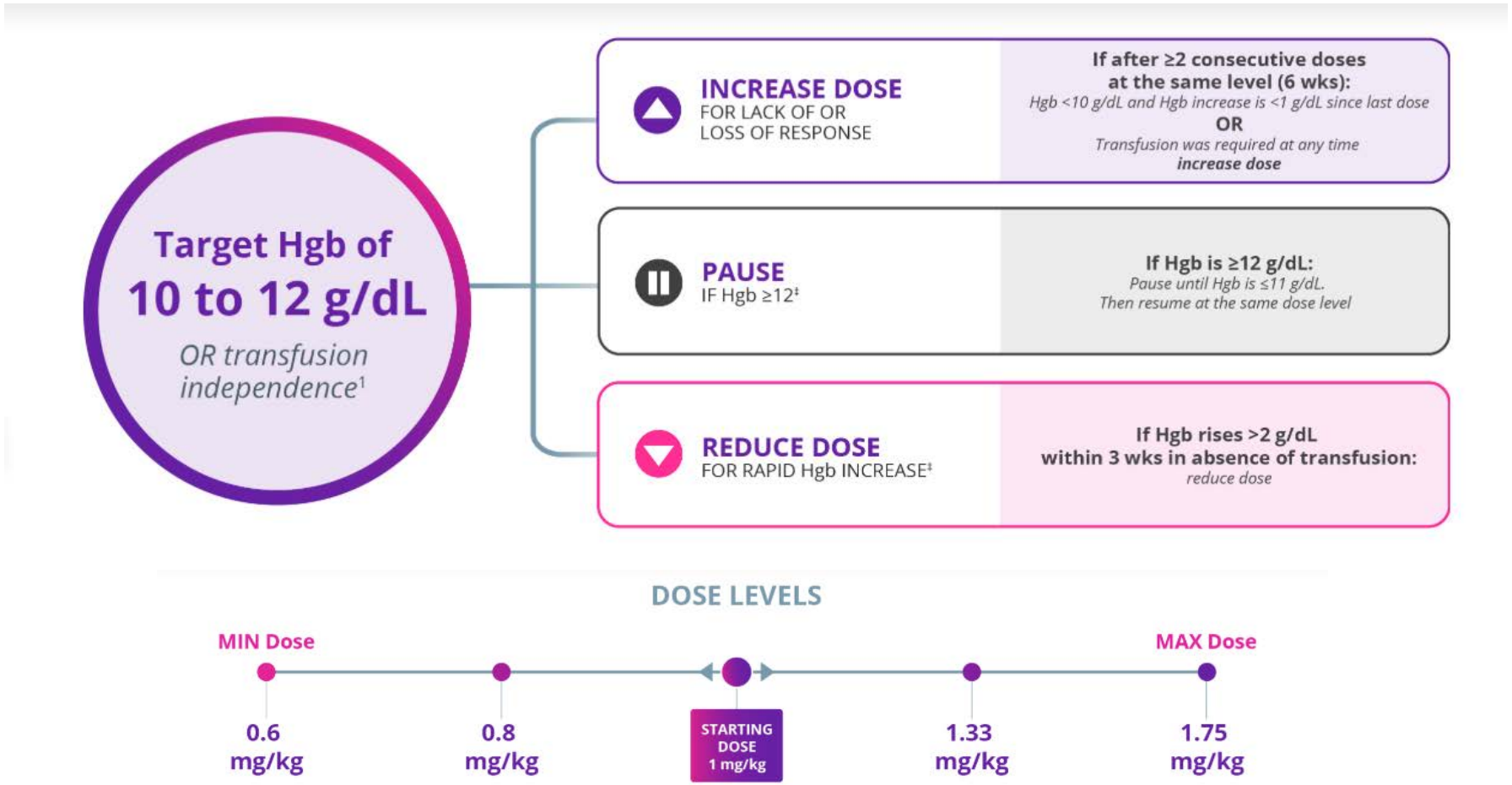


Luspatercept versus EPO: Transfusion independence of 126 weeks versus 90 weeks



Dose adjust to target hemoglobin of 10 to 12 g/dL

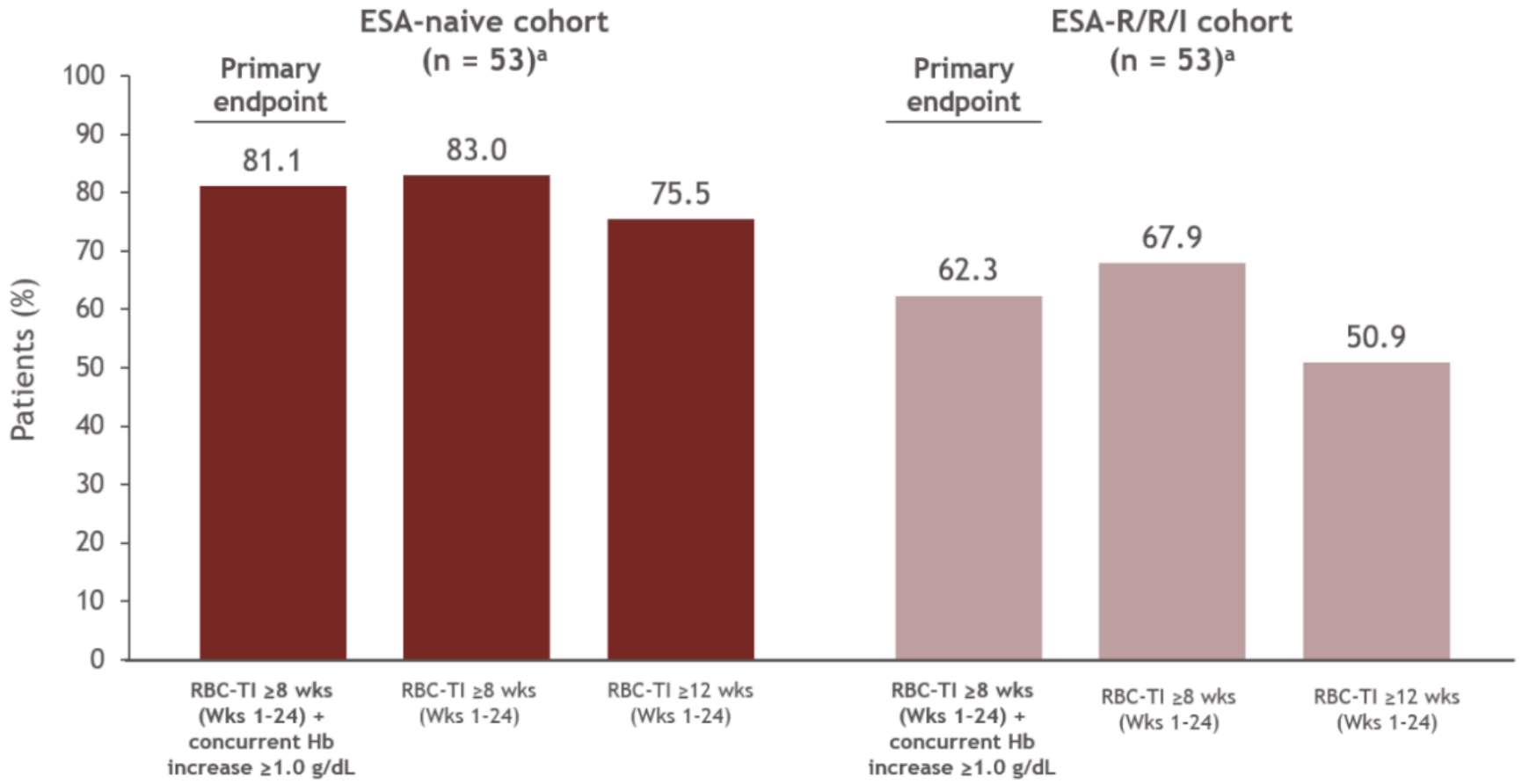
65% of patients treated in COMMANDS required the maximum dose of 1.75 mg/kg[2†]



Administer once every 3 weeks by subcutaneous injection. Wait a minimum of 6 weeks between dose increases.[1]

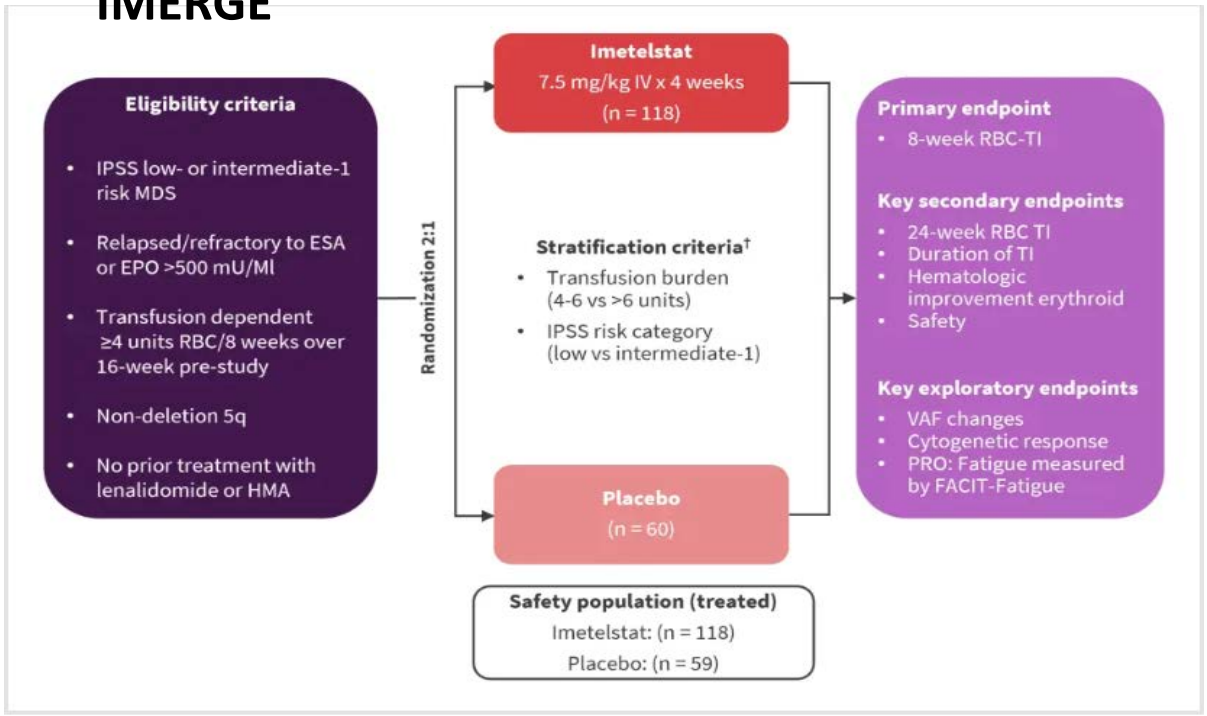
MAXILLUS study: starting at 1.75 mg/kg Dose matters!

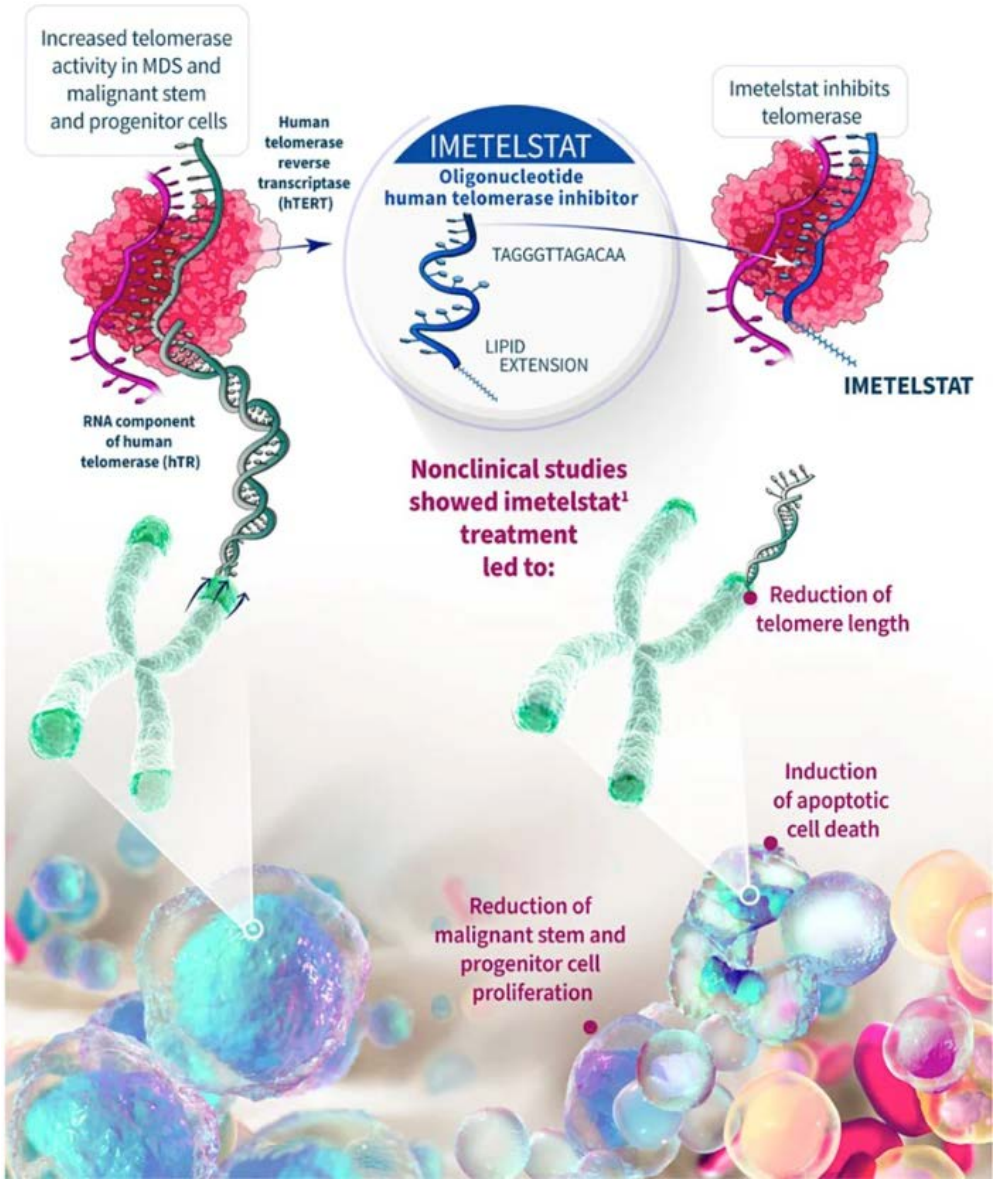
Figure: Primary Analysis of RBC-TI ± Hb Increase ≥8 Wks and RBC-TI ≥12 Wks for LUSPA Tx in the MAXILUS Study Among the ESA-naive Cohort and the ESA-R/R/I Cohort



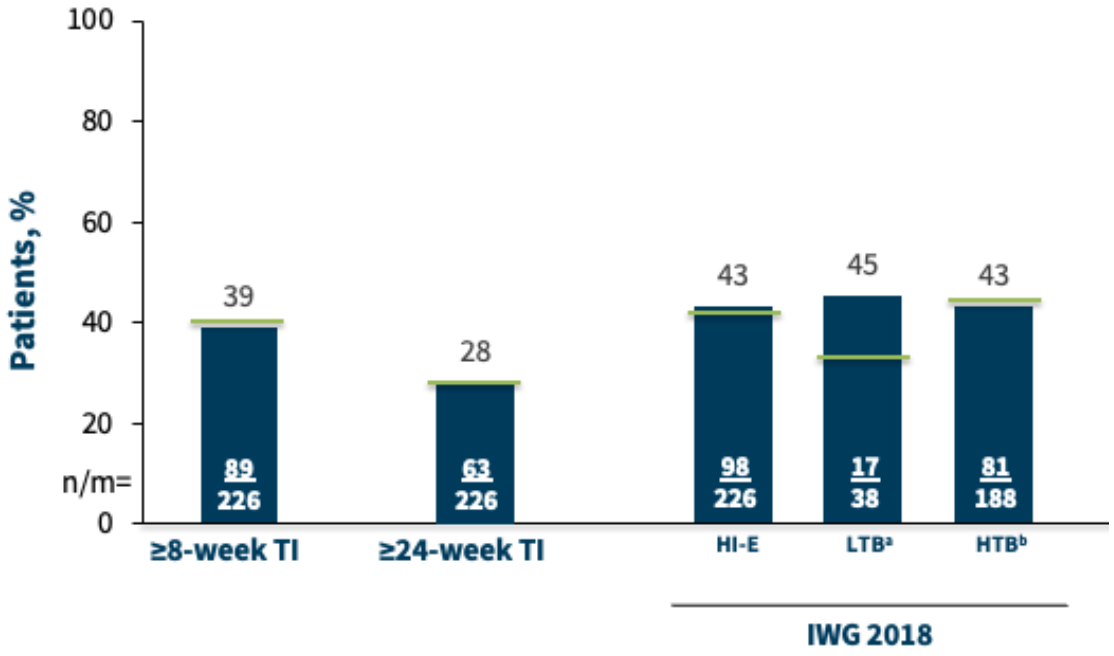
Imetelstat
Blocks telomerase and leads to cancer cell death

IMERGE





Imetelstat Results

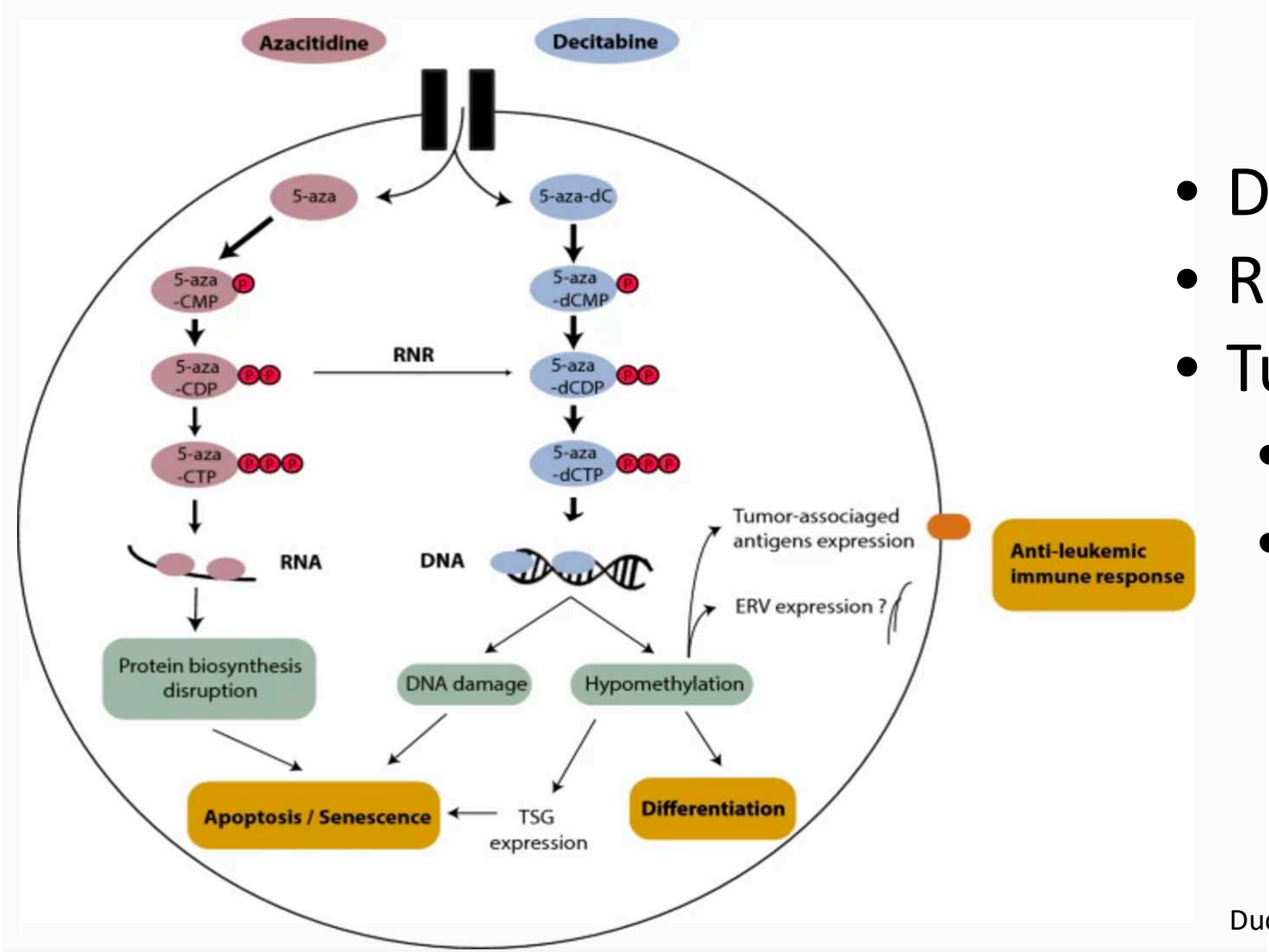


- Worked in very heavily transfusion dependent population regardless of prior exposure
- Worked for all types of MDS (lower risk)
- Reduced the malignant clone
- Improved fatigue levels

Higher risk disease

- Typically treated with hypomethylating agents
- Two kinds:
  - Azactidine- injection x 7 days/28 d
  - Decitabine: oral x 5 days

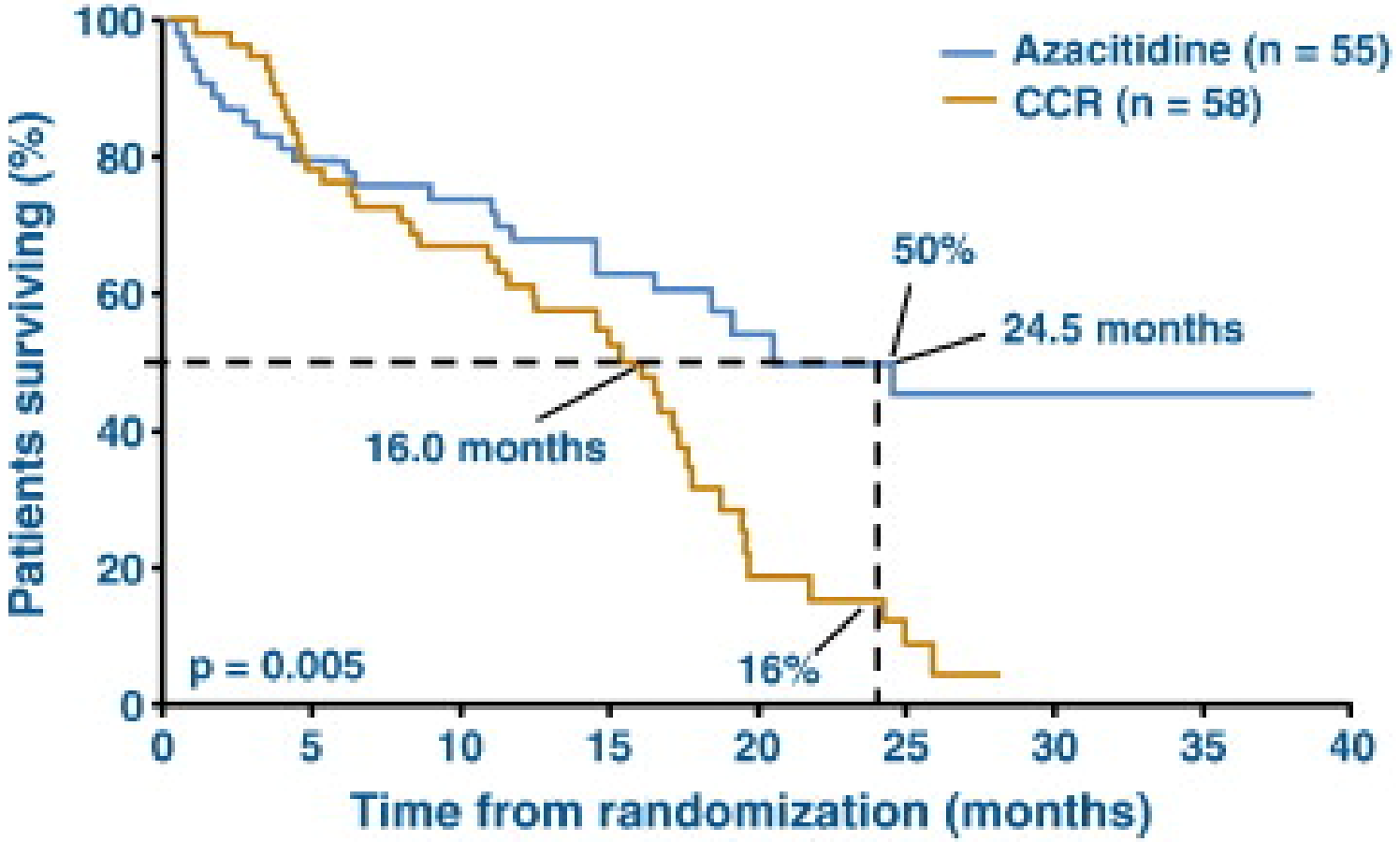
Mechanism of action of HMAs



- DNA damage
- RNA damage (AZA)
- Turn on silenced gene
  - Maturation
  - Induce Immune Responses

Duchmann M et al. Progress in Hematology 2019

What have hypomethylating agents been shown to do? Improve overall survival

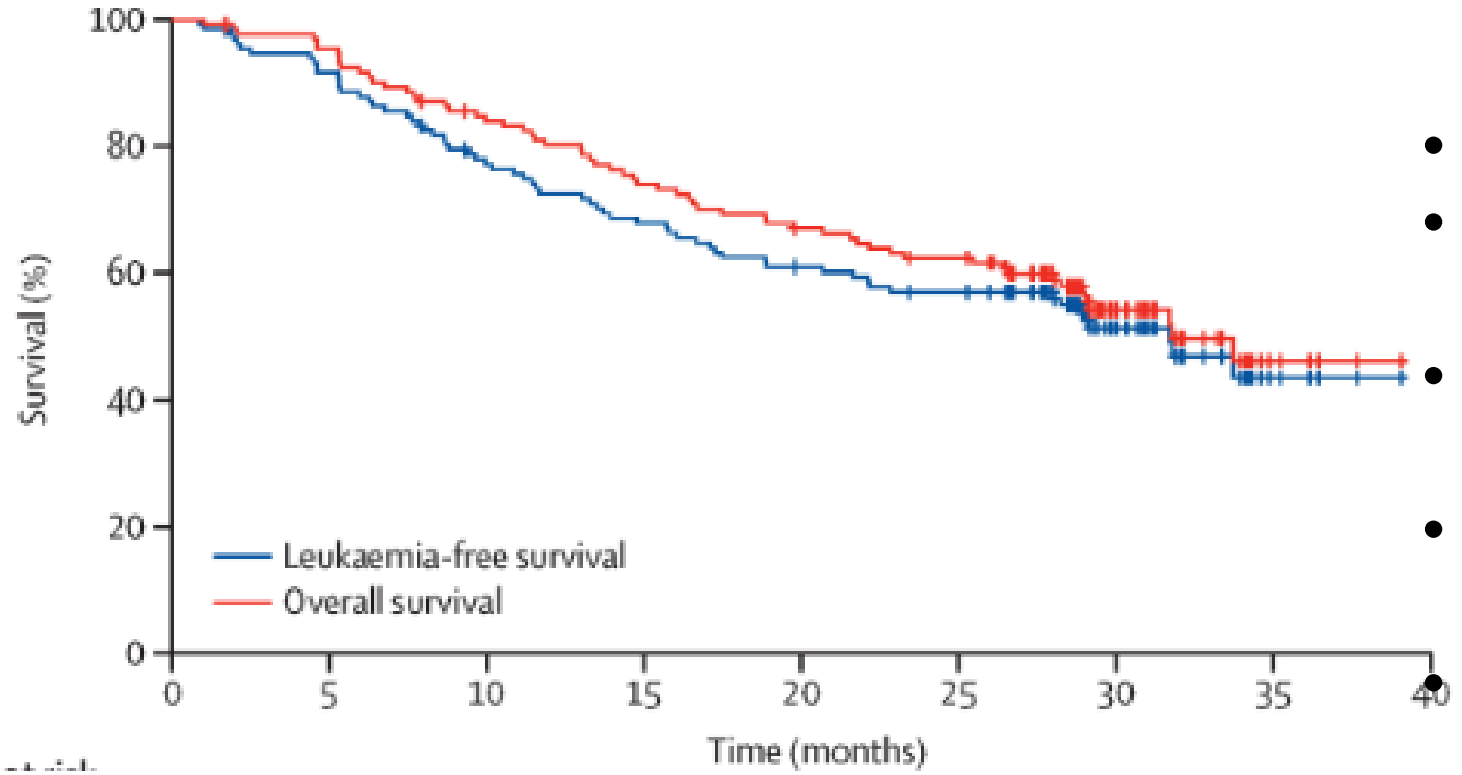


- **Reduce risk of leukemia**
- **Transfusion independence in 45%**

	PANTHER		STIMULUS	ENHANCE	SELECT-MDS-1	VERONA
	Pevonedistat	Eprenetapopt	Sabatolimab	Magrolimab	Tamibarotene	Venetoclax
Target	NEDD8 inhibitor	TP53 reactivator	TIM3 inhibitor	CD47 mAb	Selective RARα agonist	BCL2 inhibitor
Population	Intermed High Very High	TP53 mutant	Intermed High Very High CMML-2	Intermed High Very High	RARα positive 5% blasts Intermed High Very High	Intermed High Very High
Number Recruited	454	154	127	520	190	509
Randomization	2:1	1:1	1:1	1:1	2:1	1:1
Endpoint	EFS	CR	CR and PFS	CR and OS	CR	OS
Result	Did not meet primary endpoint	Did not meet primary endpoint	Did not meet primary endpoint	Futility	Did not meet primary endpoint	Did not meet primary endpoint
Publication	Adès L, et al., *Blood Adv,* 2022	Pending	Zeidan AM, et al., *Lancet Haematol,* 2024	Pending	DeZern AE, et al., *Blood Adv*, 2025	Pending

Abbreviations: CMML-2, chronic myelomonocytic leukemia-2; CR, complete remission; EFS, event-free survival; mAb, monoclonal antibody; OS, overall survival; PFS, progression-free survival; RARα, retinoic acid receptor alpha.

ASCERTAIN: Oral Decitabine just as good as IV decitabine



- **Drug levels the same**
- **Impact on methylation, the same**
- **Suppresses blood counts more than azacitidine**
- **45% achieve transfusion independence**
- **Also works for CMML**

Garcia-Manero G. Lancet hematology 2024

Rena Buckstein MD FRCPC

Founder and Chair, MDS-CAN

Sunnybrook Health Science Center

Toronto, Ontario

BRIEF HISTORY

- Initiated in 2005 by Dr. Rena Buckstein & Dr. Richard Wells at the Sunnybrook Health Sciences Centre – Odette Cancer Centre

- Began as a single-center initiative that collected quality of life and disease characteristics of patients with myelodysplastic syndromes, chronic myelomonocytic leukemia, and low-blast AML.

- Academic medical centers of MDS excellence across Canada started contributing to the MDS-CAN in 2012

- 14 years of real-world data collection.

- To date, the database involves the collaboration of 15 centers/9 provinces across Canada and has enrolled 1558 patients.

MDS-CAN

OBJECTIVES

1. To track quality of life over time and predictors of this
2. Evaluate the effects of patient related factors such as frailty, comorbidity, disability and physical performance on quality of life, overall survival and treatment toxicity.
3. Evaluate any differences in disease across 3 regions of Canada
4. Provide samples to basic scientists for ‘translational research’
5. Health economic research
6. ‘Real-world ‘evaluation of therapies in MDS and disease natural history

MDS-CAN

Investigations:

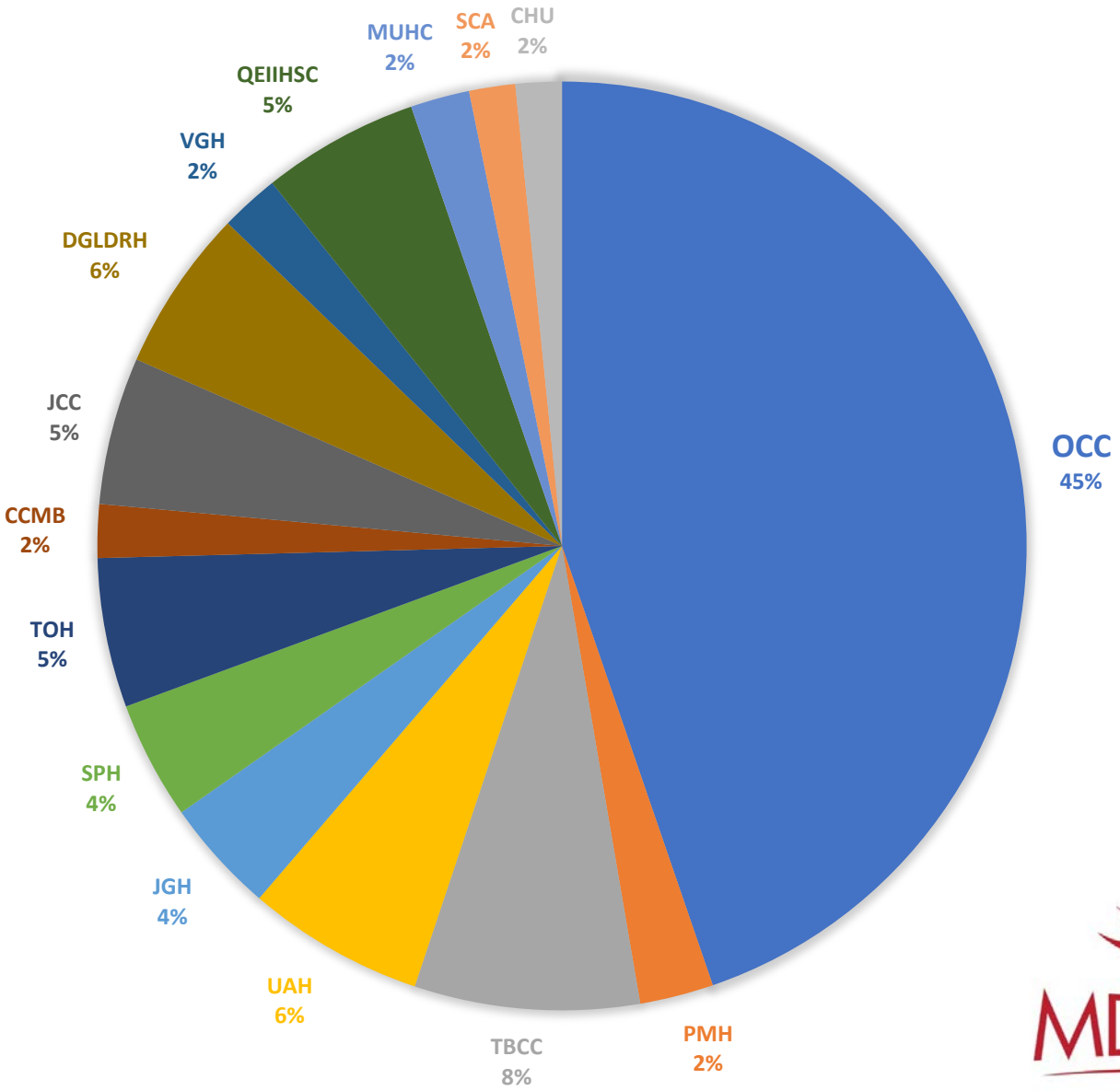
- **Yearly:** frailty, physical performance (stand sit x 10, 4 M walk, grip strength), LB SIADL, comorbidity (MDS-CI, CCI)
- **Twice yearly:** QOLs: ESAS GFS, QLQ C30, QUALMS
- **Twice yearly:** review of meds, transfusions, blood counts, treatments and response, leukemia, survival, complications

MDS-CAN

PATIENT ACCRUALS PERCENTAGE

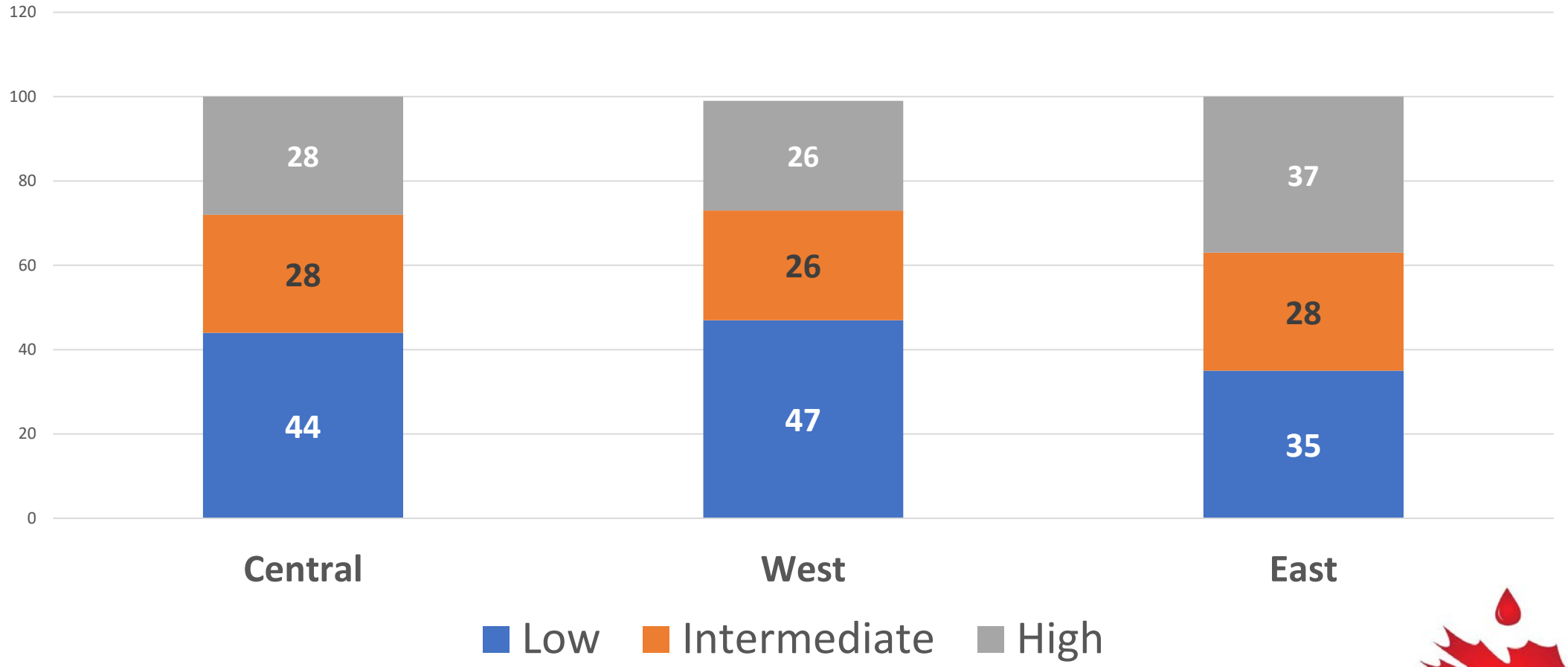
By Site *(n=1589)*

57% from Ontario
45% from OCC



MDS-CAN

IPSS-R by Region: Higher Risk Out East

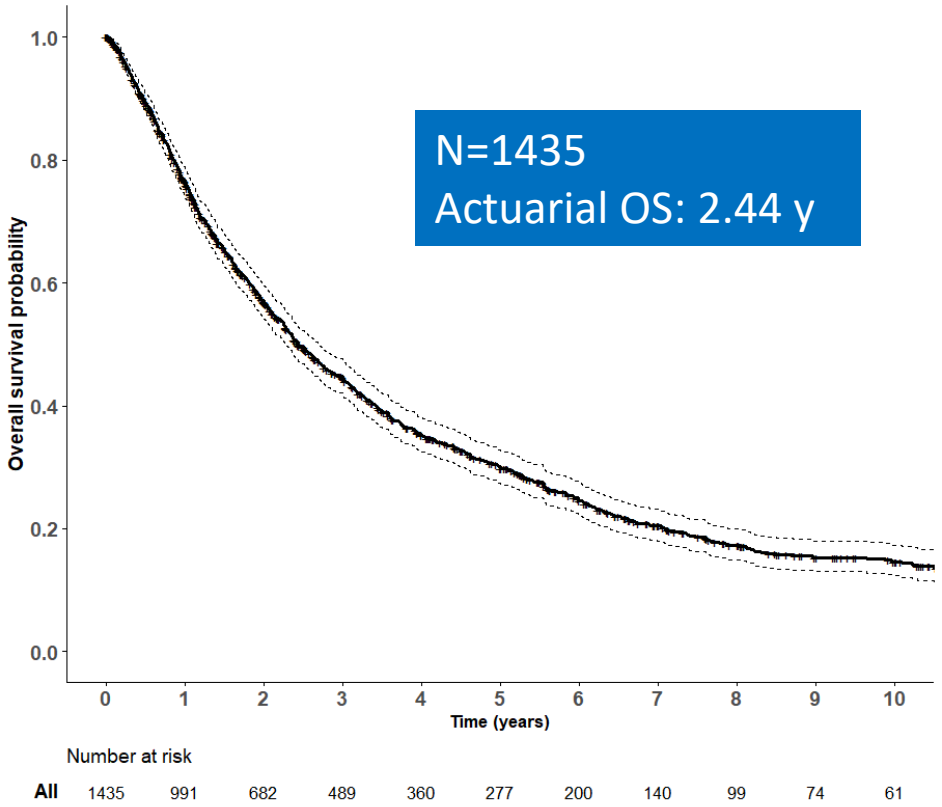


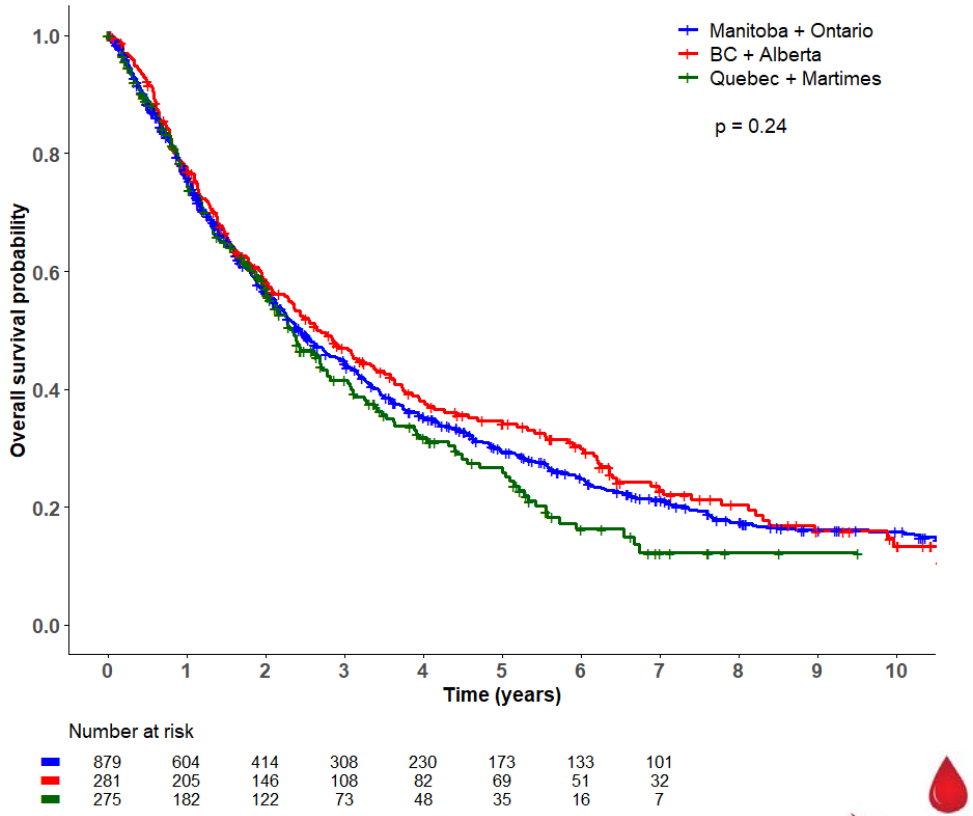
MDS-CAN

Characteristics	BC + Alberta N=281	Manitoba + Ontario + SASK N=879	Quebec+ Maritimes N=275	P value
Age	73	73	73	0.8
Gender male	68%	64%	64%	0.4
MDS secondary	6%	10%	9%	0.2
BMI	28	28	28	0.8
Time from Dx (m)	**5**	**4**	**3**	**.002**
Follow up (m)	**37**	**36**	**26**	**.005**
Dead	70%	70%	62%	NS
LTFU > 18 m	7.8%	11%	16%	.03
Developed AML	16%	18%	12%	.08
Transfusion dependence	**21%**	**27%**	**19%**	**.009**
Blasts	**5%**	**6%**	**7%**	**.007**

Characteristics	BC + Alberta N=281	Manitoba + Ontario + SASK N=879	Quebec+ Maritimes N=275	P value
Rockwood frailty				**.0003**
1-2	**53%**	37%	44%	
3	30%	35%	34%	
4-5	14%	25%	17%	
6+	4%	3%	4%	
FS-15				**<.0001**
Not frail	47%	20%	16%	
Prefrail	20%	36%	27%	
Frail	33%	44%	47%	
4 meter walk test				**.03**
> 6.67 s	7%	13%	11%	
Lawton Brody disability (any)	33%	45%	41%	**.01**
ESA	30%	37%	**26%**	**.001**
ICT	13%	15%	8%	**.02**
HMA	36%	36%	35%	0.96
Lenalidomide	5%	**10%**	4%	**.001**
Luspatercept	2%	1%	1%	0.36

Overall survival does not differ by region





MDS-CAN

MDS-CAN Research

Publications

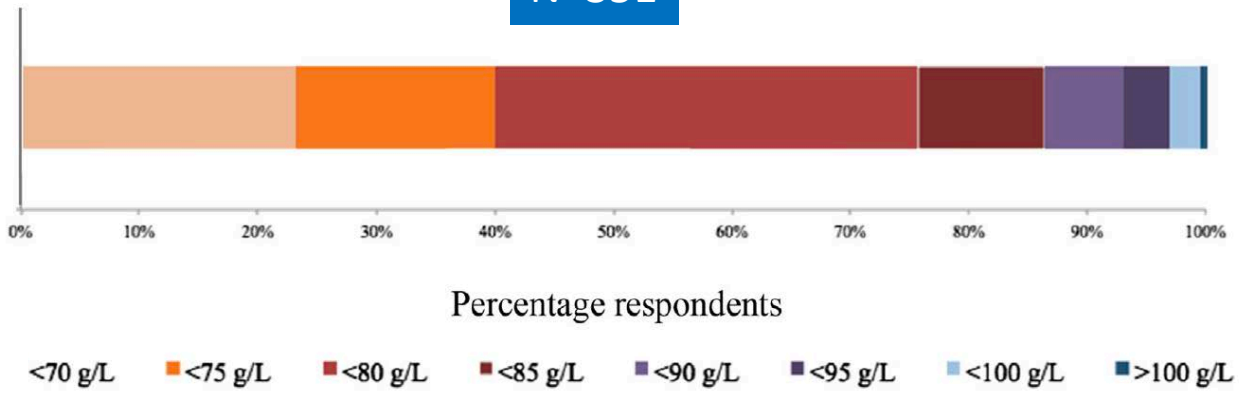
TRANSFUSION PRACTICE

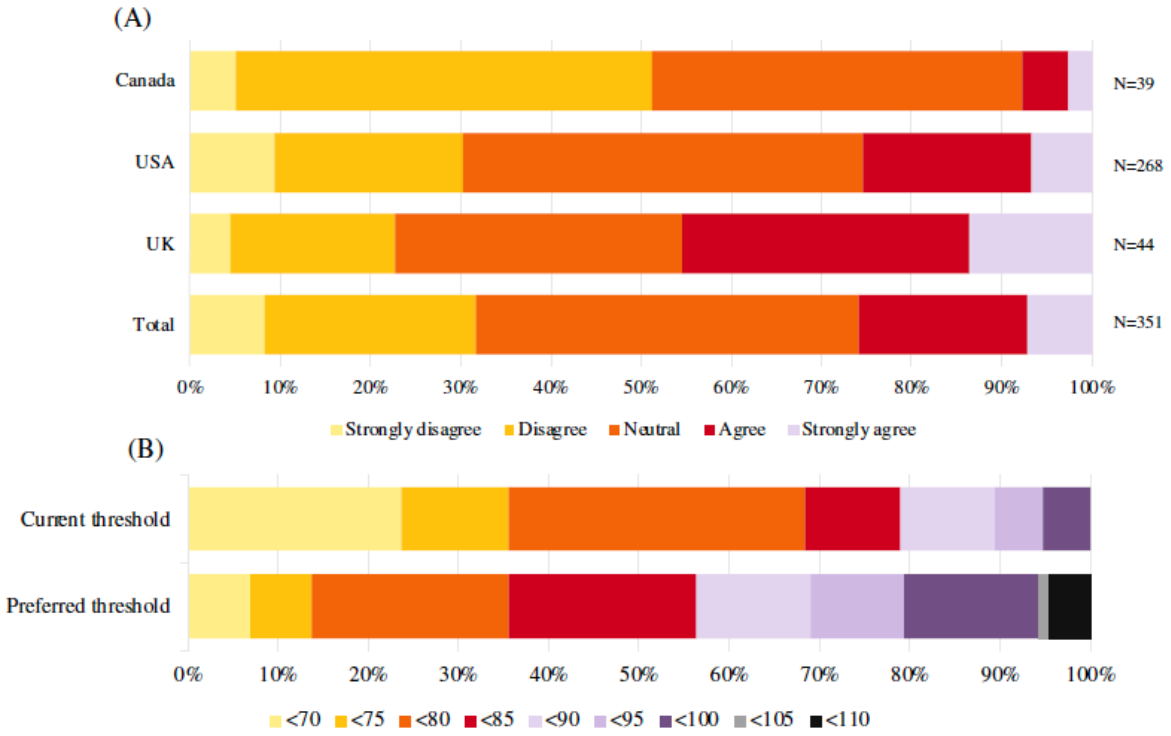
TRANSFUSION

Multi-national survey of transfusion experiences and preferences of patients with myelodysplastic syndrome

Abi Vijenthira[1] | Rebecca Starkman[2] | Yulia Lin[3,4] | Simon J. Stanworth[5,6,7,8] | David Bowen[9] | Lea Harrison[10] | Sophie Wintrich[11] | Jeannie Callum[3,4] | Rena Buckstein[12]

N=351





Key Learnings:

- 27% USA patients transfused @ Hgb < 70 g/L; 57% @ 70-80 g/L
- 75% felt symptomatic relief > 1 day later
- 7% never felt better post Tx
- 31% endorsed economic hardship

- 26% wished they were transfused at a higher Hgb threshold
- (45% in the UK, 8% Canada)
- 62% wanted a threshold of 85 g/L

Vijenthira A et al. Transfusion 2022

Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS)

Gregory A. Abel,[1,2] Fabio Efficace,[3] Rena J. Buckstein,[4] Sara Tinsley,[5] Joseph G. Jurcic,[6] Yolanda Martins,[1] David. P Steensma,[2] Corey D. Watts,[1] Azra Raza,[6] Stephanie J. Lee,[7] Alan F. List,[5] and Robert J. Klaassen[8]

[1]Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Center for Leukemia, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, Rome, Italy; [4]Department of Medical Oncology/Hematology, Odette Cancer and Sunnybrook Health Sciences Center, Toronto, Canada; [5]Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [6]Division of Hematology/Oncology, Department of Medicine, Columbia University Medical Center, New York, NY, USA; [7]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; and [8]Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Haematologica 2016
Volume 101(6):781-788

Table 3. Correlations between overall QUALMS scores, EORTC QLQ30 and FACT-An.

	Correlation with QUALMS (r)*
EORTC QLQ-C30	
Global health	0.59
Physical function	0.58
Role function	0.61
Emotional function	0.68
Cognitive function	0.60
Social function	0.61
Fatigue	-0.65
Nausea	-0.37
Pain	-0.43
FACT-An	
Fact-An total score	0.79
Anemia Subscale (AnS)	0.74
Trial Outcome Index (TOI)	0.78

*All correlations were significant at P<0.001 (two-tailed test).

255 MDS patients/5 centers

Columbia, DFCI, GIMEMA, MOFFITT, Odette

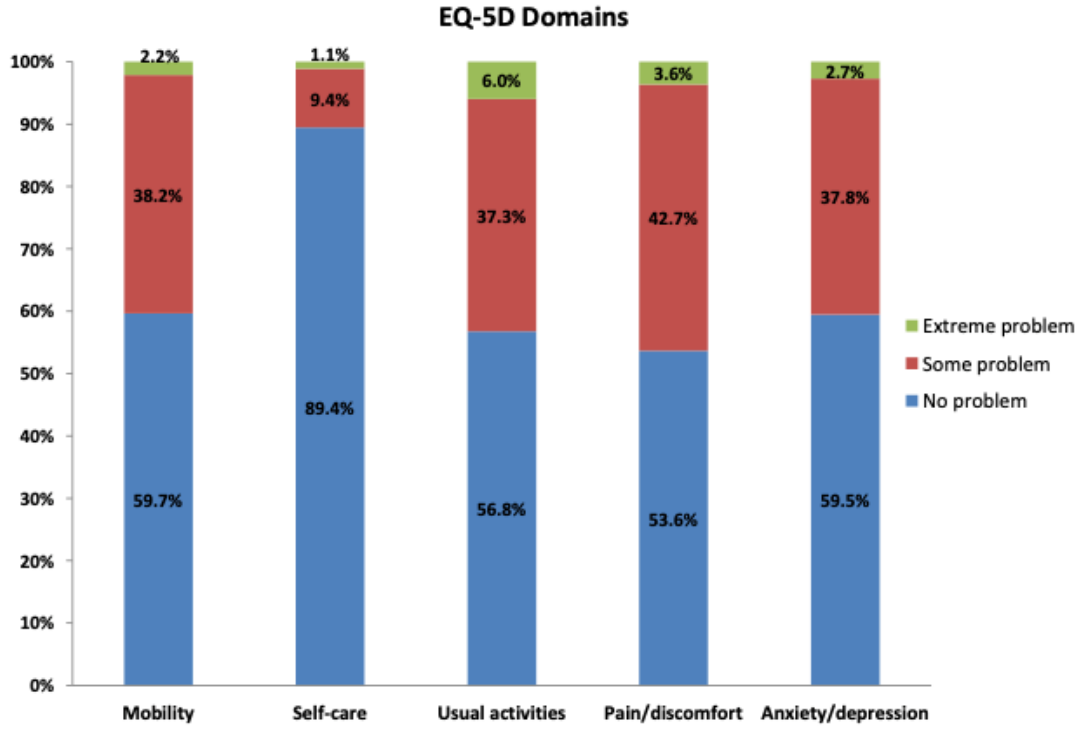
- Assess QUALMS internal consistency, reliability, concurrent validity, stability and reliability
- Compare with other scales, anemia, TD, clinical events like bleeding, infection or hospitalization

Findings:

- **High internal consistency reliability found using 33 items of QUALMS**
- Mean score was 67 (SD 15) and was not too dissimilar in all other centers
- 3 factors (physical burden, benefit finding and emotional burden explained 43% of the variance
- **Good correlation between QUALMS and QLQ-C30 and FACT-An**
- **Good groups validity wrt TD, Hgb, risk score, albumin, comorbidity**
- **Good test-retest reliability**
- **Responsive in those that had infection, hospitalization,**
- **MCID: 7**

Abel G et al. Haematologica 2016

QUALITY of LIFE is impaired and worse compared with age matched controls



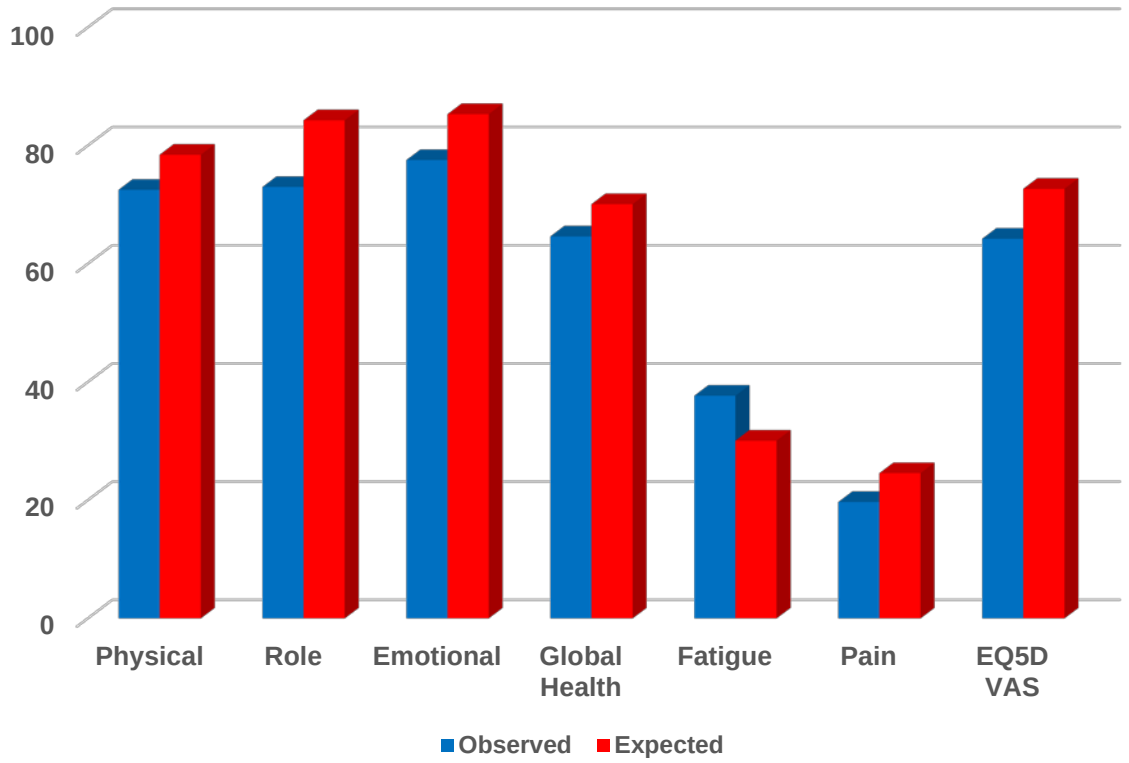
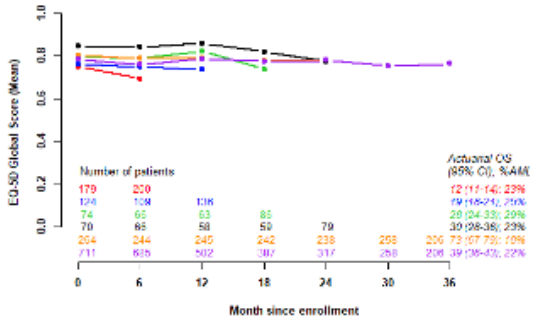
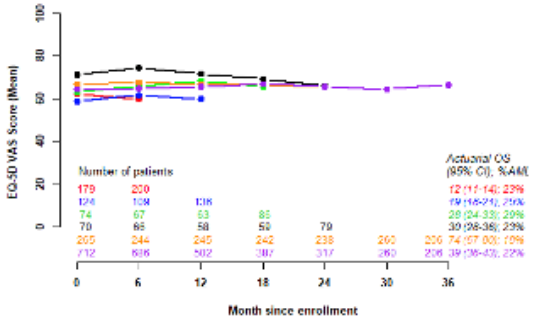
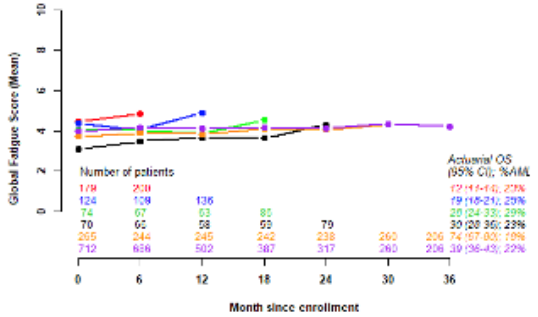
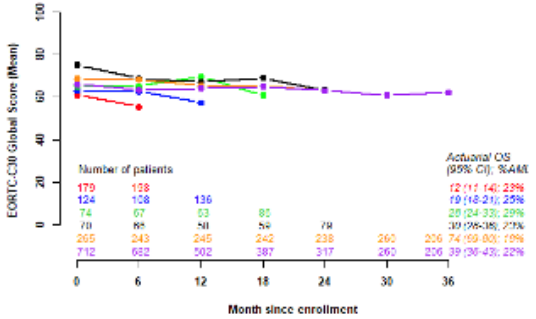


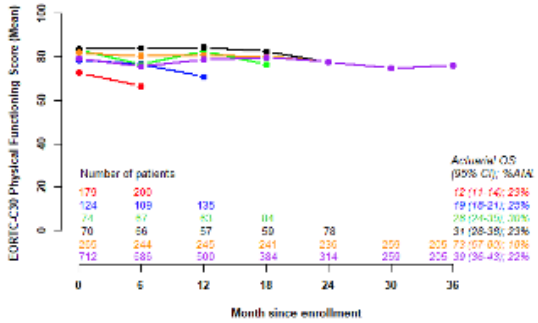
Figure 1. EQ-5D domains at enrollment.

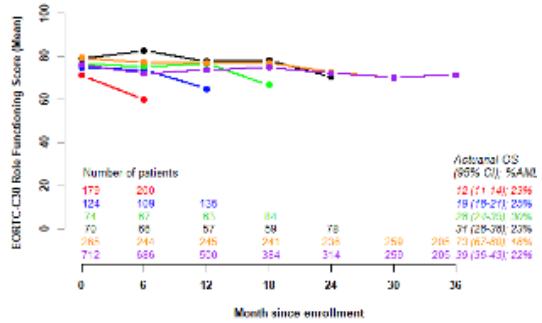


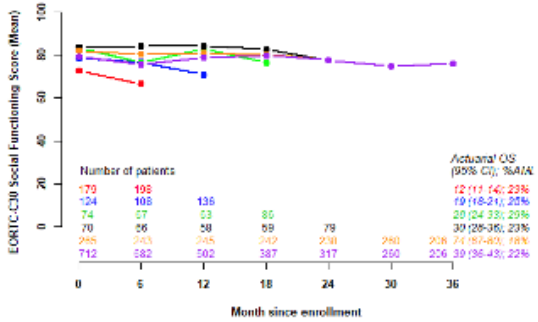












- **Quality of life declines over time slowly**
- **Predicted by hemoglobin, transfusion dependence, frailty and disability**

bjh research paper

Patient-related factors independently impact overall survival in patients with myelodysplastic syndromes: an MDS-CAN prospective study

Rena Buckstein,[1] Richard A. Wells,[1] Nancy Zhu,[2] Heather A. Leitch,[3] Thomas J. Nevill,[4] Karen W. L. Yee,[5] Brian Leber,[6] Mitchell Sabloff,[7] Eve St. Hilaire,[8] Rajat Kumar,[9] Michelle Geddes,[10] April Shamy,[11] John Storring,[12] Andrea Kew,[13] Mohamed Elemary,[14] Max Levitt,[15] Martha Lenis,[1] Alex Mamedov,[1] Liying Zhang,[16] Ken Rockwood[17] and Shabbir M. H. Alibhai[18]

Summary

Little is known about the effects of frailty, disability and physical functioning on the clinical outcomes for myelodysplastic syndromes (MDS). We investigated the predictive value of these factors on overall survival (OS) in 445 consecutive patients with MDS and chronic monomyelocytic leukaemia (CMML) enrolled in a multi-centre prospective national registry. Frailty, comorbidity, instrumental activities of daily living, disability, quality of life, fatigue and physical performance measures were evaluated at baseline and were added as covariates to conventional MDS-related factors as predictors of OS in Cox proportional hazards models. The median age was 73 years,

Leukemia (2020) 34:1394–1406
https://doi.org/10.1038/s41375-019-0666-7

ARTICLE

Myelodysplastic syndrome

An MDS-specific frailty index based on cumulative deficits a independent prognostic information to clinical prognostic scoring

R. Starkman[1] · S. Alibhai[2] · R. A. Wells[1] · M. Geddes[3] · N. Zhu[4] · M. M. Keating[5] · B. Leber[6] · L. Chodirker[1] · M. Sabloff[7] · G. Christou[7] · H. A. Leitch[8] · E. St-Hilaire[9] · N. Finn[9] · A. Shamy[10] · K. Yee[11] · J. Storring[12] · T. Nevill[13] · R. Delage[14] · M. Elemary[15] · V. Banerji[16] · M. Lenis[17] · A. Kirubananthaan[17] · A. Mamedov[17] · L. Zhang[1] · K. Rockwood[18] · R. Buckstein[1]

Received: 31 July 2019 / Revised: 30 October 2019 / Accepted: 17 November 2019 / Published online: 6 December 2019

Leukemia (2020) 34:3434–3438
https://doi.org/10.1038/s41375-020-01026-y

CORRESPONDENCE

Myelodysplastic Syndrome

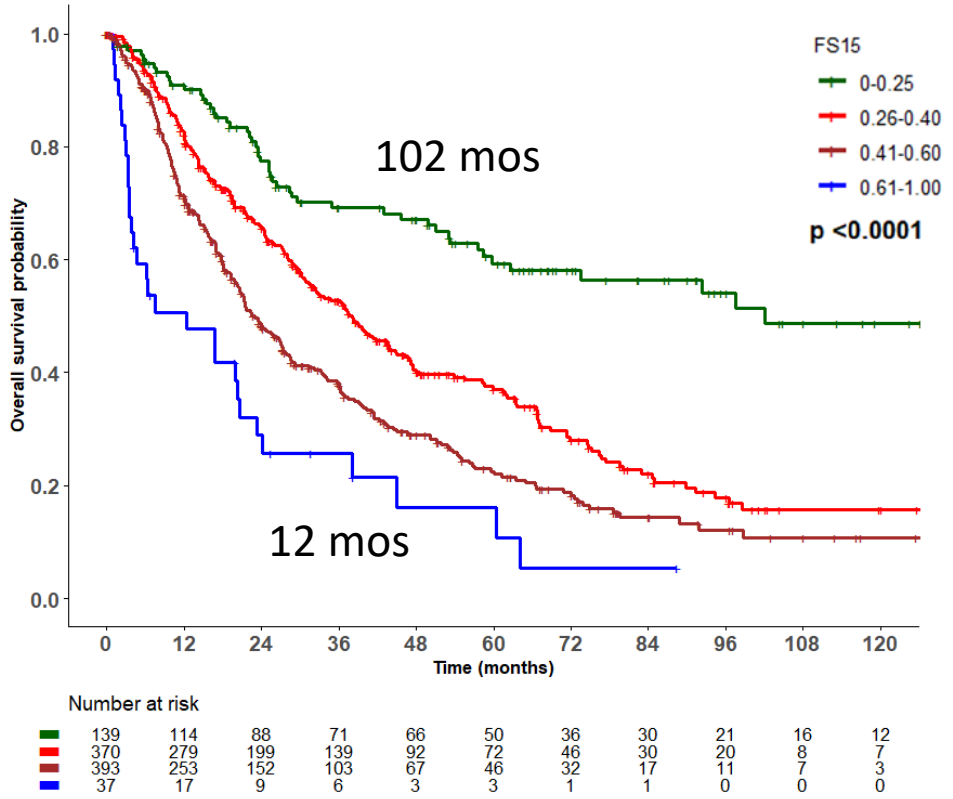
Revised 15-item MDS-specific frailty scale maintains prognostic potential

Bo A. Wan[1] · Aziz Nazha[2] · Rebecca Starkman[1] · Shabbir Alibhai[3] · Richard. A. Wells[1] · Michelle Geddes[4] · Nancy Zhu[5] · Mary-Margaret Keating[6] · Brian Leber[7] · Lisa Chodirker[1] · Mitchell Sabloff[8] · Grace Christou[8] · Heather A. Leitch[9] · Eve St-Hilaire[10] · Nicholas Finn[10] · April Shamy[11] · Karen W. L. Yee[12] · John Storring[13] · Thomas J. Nevill[14] · Robert Delage[15] · Mohamed Elemary[16] · Versha Banerji[17] · Anne Parmentier[18] · Mohammad Siddiqui[18] · Aksharh Kirubananthaan[18] · Alexandre Mamedov[18] · Liying Zhang[1] · Rena Buckstein[1]

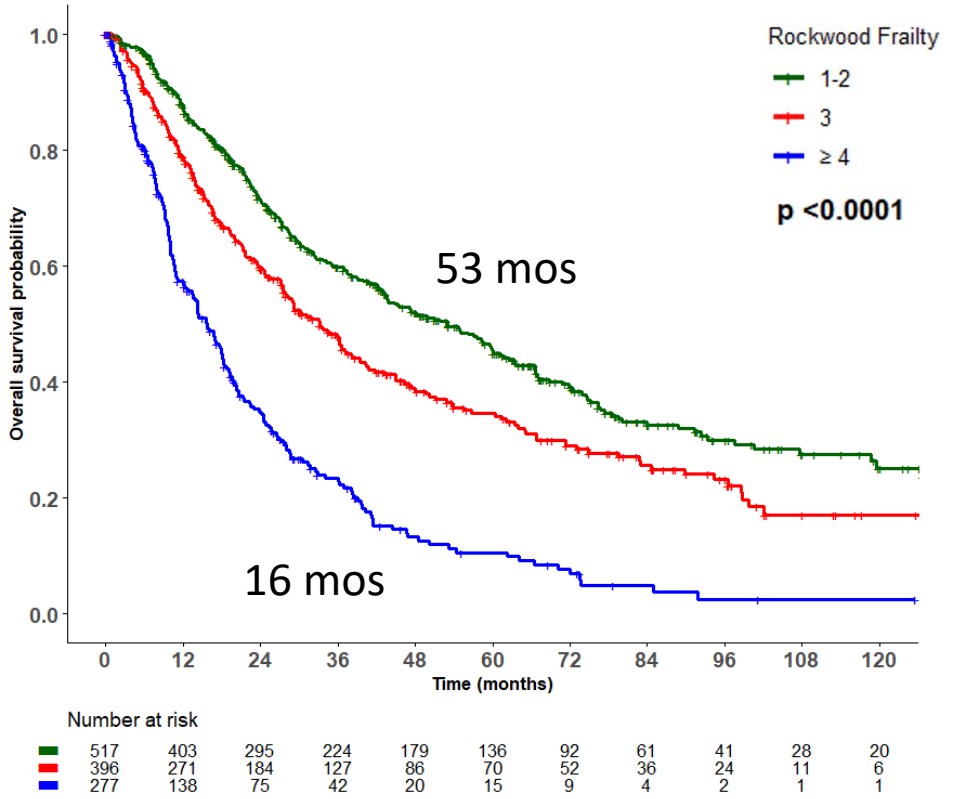
Received: 30 April 2020 / Revised: 29 July 2020 / Accepted: 7 August 2020 / Published online: 28 August 2020

Overall survival by frailty

FS-15



Rockwood Frailty



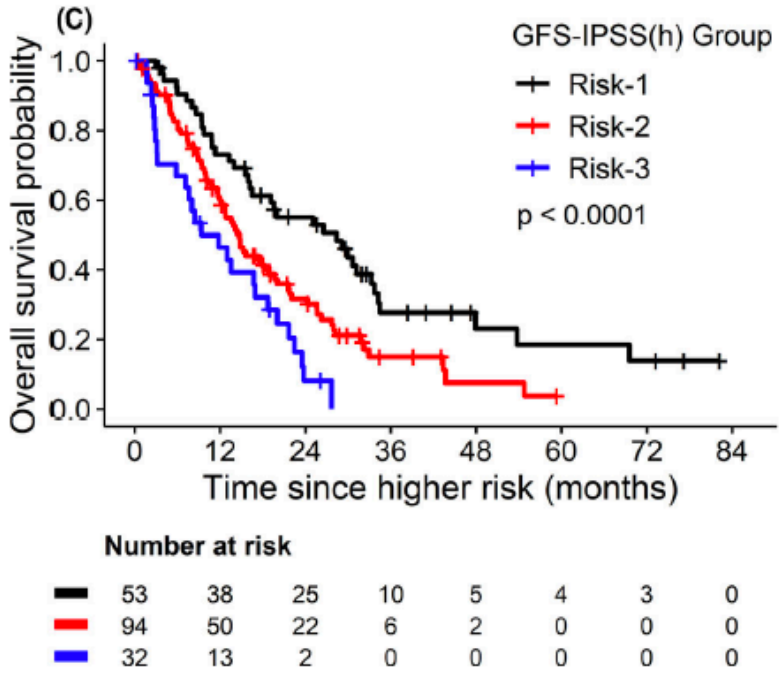
<DS GRIP Strength

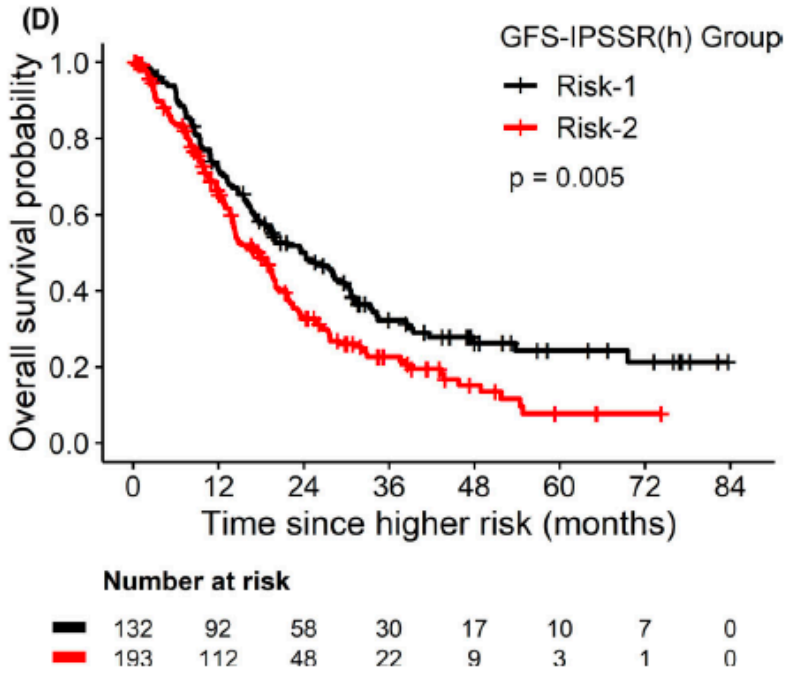
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

Short Report

Patient-reported fatigue refines prognosis in higher-risk myelodysplastic syndromes (MDS): a MDS-CAN study

Irina Amitai, Michelle Geddes, Nancy Zhu, Mary-Margaret Keating, Mitchell Sabloff, Grace Christou, Brian Leber, Dina Khalaf, Heather A. Leitch, Eve St-Hilaire, Nicholas Finn, April Shamy ... See all authors





IPSS-R ≥ 3.5
Risk 1: GFS < 4
Risk 2: GFS ≥ 4

Risk 1: IPSS-Int-2 and GFS < 4
Risk 2: IPSS-High and GFS < 4 or INT-2 and GFS ≥ 4
Risk 3: IPSS- High and GFS ≥ 4

Amitai, I et al. BJH 2021

LEUKEMIA & LYMPHOMA
2022, VOL. 63, NO. 13, 3165–3174
https://doi.org/10.1080/10428194.2022.2109154

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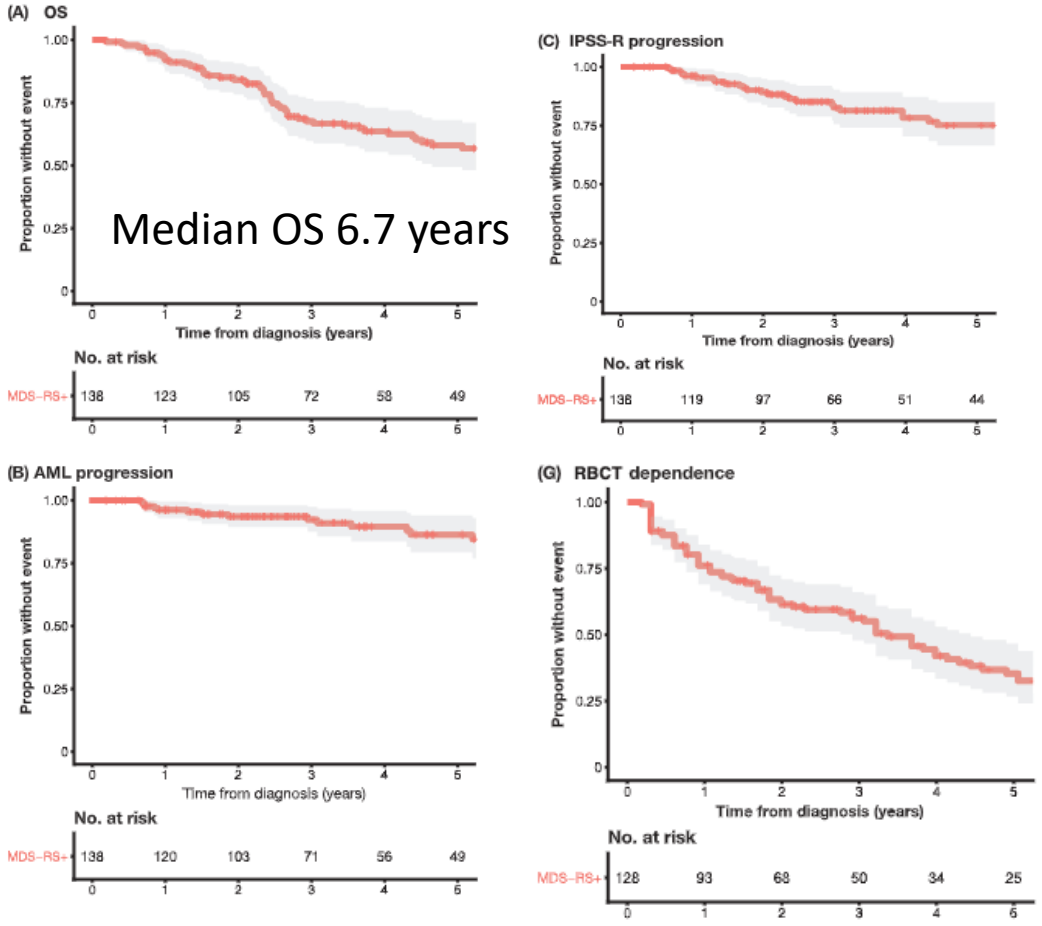
ORIGINAL ARTICLE

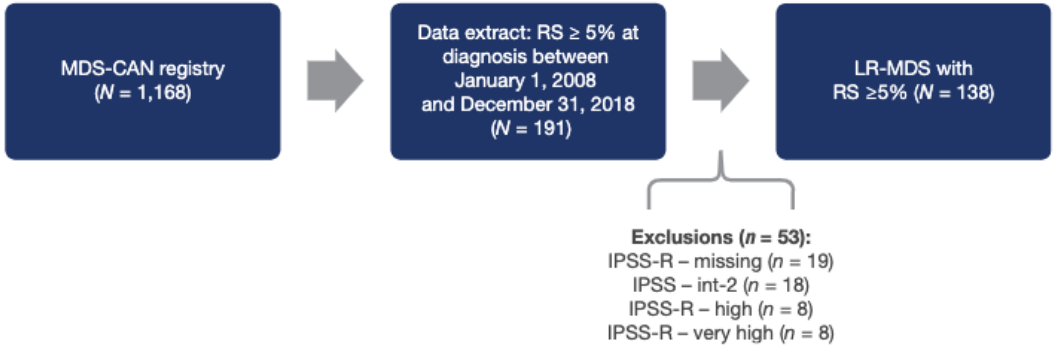
OPEN ACCESS Check for updates

A natural history of lower-risk myelodysplastic syndromes with ring sideroblasts: an analysis of the MDS-CAN registry

Rena Buckstein[a,b], Lisa Chodirker[a,b], Lee Mozessohn[a,b], Karen W.L Yee[b,c], Michelle Geddes[d], Nancy Zhu[e], April Shamy[f], Heather A. Leitch[g], Grace Christou[h], Versha Banerji[i], Leber Brian[j], Dina Khalaf[j], Eve St-Hilaire[k], Nicholas Finn[k], Thomas Nevill[l], Mary-Margaret Keating[m], John Storring[n], Robert Delage[o], Anne Parmentier[a], Aksharh Thambipillai[a], Mohammed Siddiqui[a], Christopher Westcott[p], Chris Cameron[q], Alexandre Mamedov[a], Paul Spin[q] and Derek Tang[r]



Median OS 6.7 years



76% deaths MDS related

Within 5 years:

- **14% → AML**
- **25% → risk score increased**
- **12%→ hospitalized or died from CVD**

Cumulative probability of RBC TD

- **24% @ 1 years**
- **65% @ 5 years**

Buckstein R et al. Leuk Lymph 2022

LEUKEMIA & LYMPHOMA
2023, VOL. 64, NO. 3, 651–661
https://doi.org/10.1080/10428194.2022.2156793

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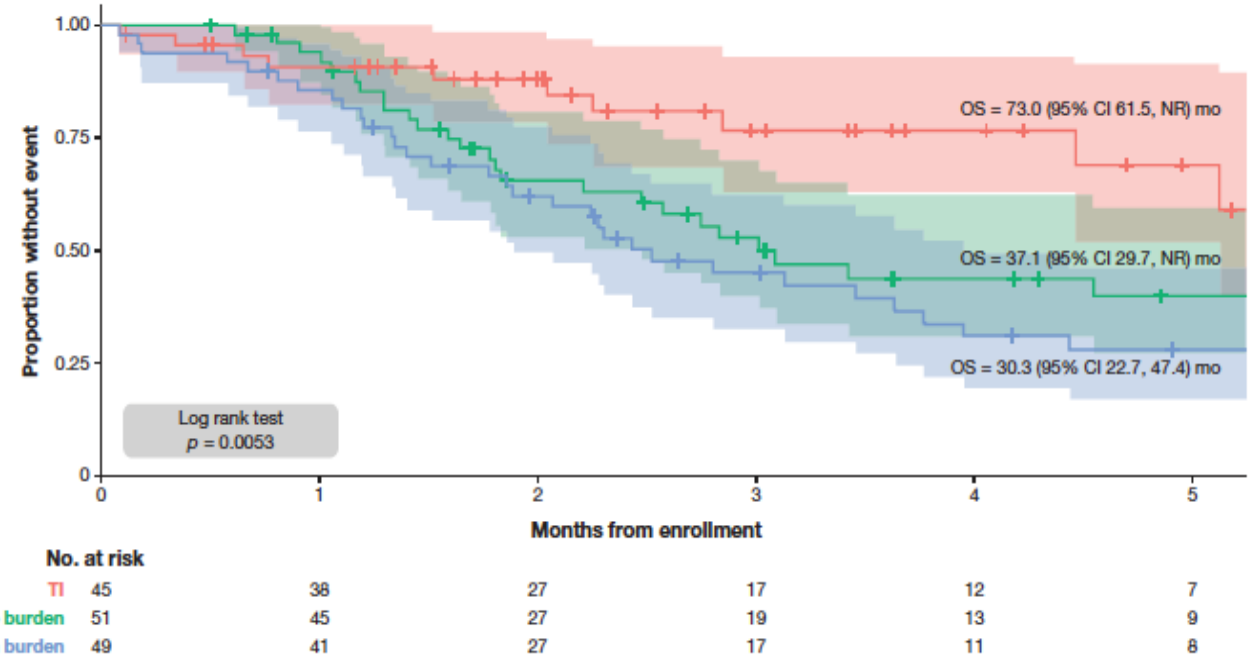
ORIGINAL ARTICLE

OPEN ACCESS Check for updates

The burden of red blood cell transfusions in patients with lower-risk myelodysplastic syndromes and ring sideroblasts: an analysis of the prospective MDS-CAN registry

Rena Buckstein[a,b], Lisa Chodirker[a,b], Karen W.L. Yee[b,c], Michelle Geddes[d], Heather A. Leitch[e], Grace Christou[f], Versha Banerji[g], Brian Leber[h], Dina Khalaf[h], Eve St-Hilaire[i], Nicholas Finn[i], Thomas Nevill[j], Mary-Margaret Keating[k], John Storring[l], Anne Parmentier[a], Aksharh Thambipillai[a], Derek Tang[m], Christopher Westcott[n], Chris Cameron[o] and Paul Spin[o]



LTB: < 1 U/4w); HTB ≥ 1 U/4W)

- 145 lower risk MDS with RS
- Median OS 44 m
- Mean RBC dose density was 0.95 u/m
- 69% required 1+ transfusions (median time 26 months)

Cumulative density of RBCs associated with greater

- Mortality
- Hospitalization
- Inferior HRQOL

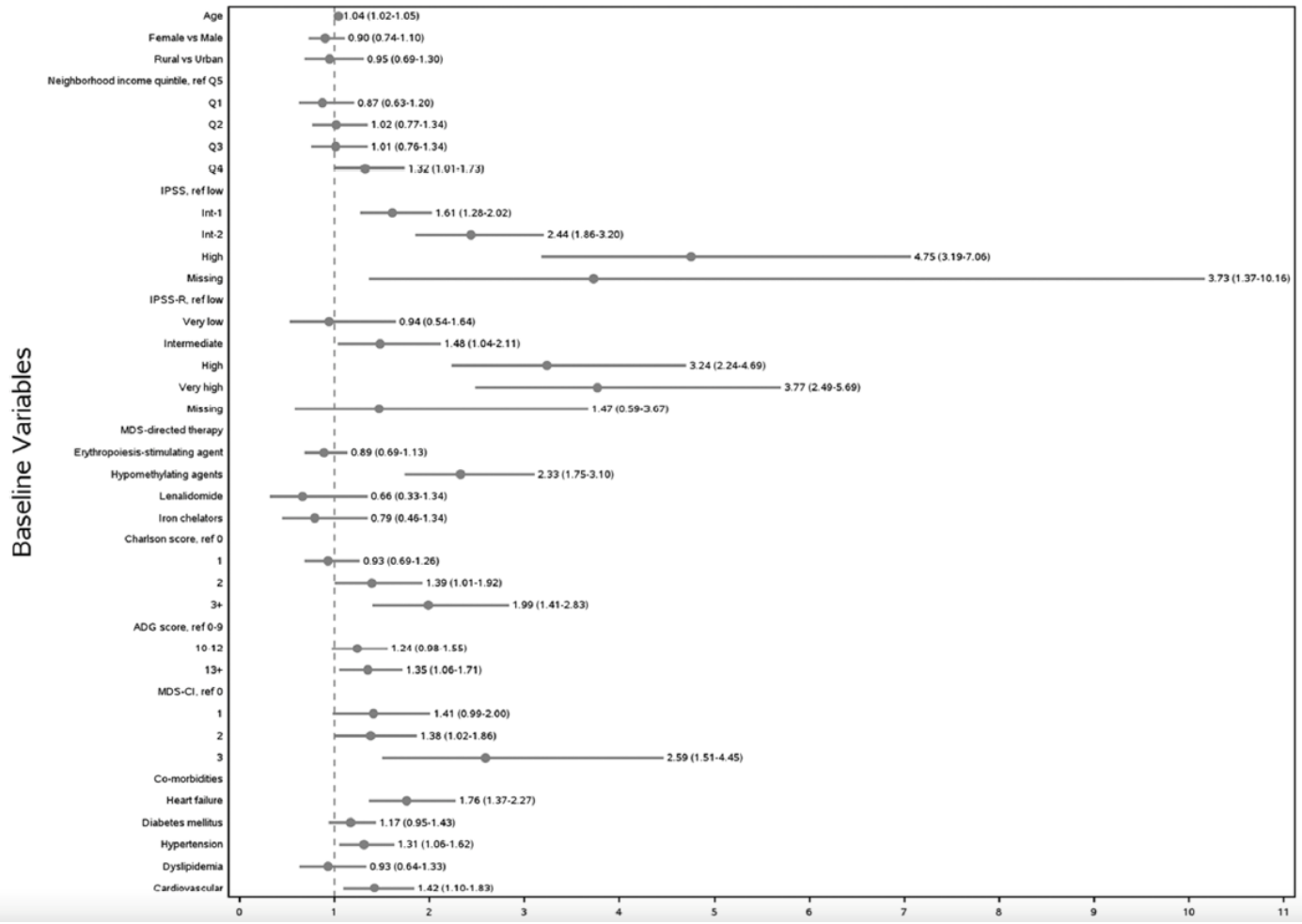
Buckstein R Leuk Lymphoma 2023

Annals of Hematology (2022) 101:1023–1030
https://doi.org/10.1007/s00277-022-04802-1

ORIGINAL ARTICLE

The impact of oral hypoglycemics and statins on outcomes in myelodysplastic syndromes

Eugene Brailovski[1,2] · Qing Li[3] · Ning Liu[3] · Brian Leber[4] · Dina Khalaf[4] · Mitchell Sabloff[5] · Grace Christou[5] · Karen Yee[1,6] · Lisa Chodirker[1,2] · Anne Parmentier[2] · Mohammed Siddiqui[2] · Alexandre Mamedov[2] · Liying Zhang[2] · Ying Liu[3] · Craig C. Earle[1,2,3] · Matthew C. Cheung[1,2,3] · Nicole Mittmann[7,8] · Rena J. Buckstein[1,2] · Lee Mozessohn[1,2,3]



Ontario MDS CAN patients/ICES

- N=533 over age 66
- 74% lower risk
- Statins: 49%
- Metformin: 19%
- Sulfonylureas: 9%
- DPP4i: 6.4%

- DPP4 is elevated in the exosomes of leukemia blasts and myelosuppressive
- DPP4 inactivate GMCSF
- High dose sitagliptin improves umbilical cord transplantation
- Observational studies: DPP4i + impact in solid tumours (GI, lung, prostate)

UVT analysis: DPP4i associated with Improved OS in lower risk MDS (HR 0.98 (0.95-1.0, p=.05) but not MVT (p=.06)

? Insufficient dosing, follow up, cohort size??

Brailovski E et al. Annals of Hematol 2022

High transferrin saturation predicts inferior clinical outcomes in patients with myelodysplastic syndromes

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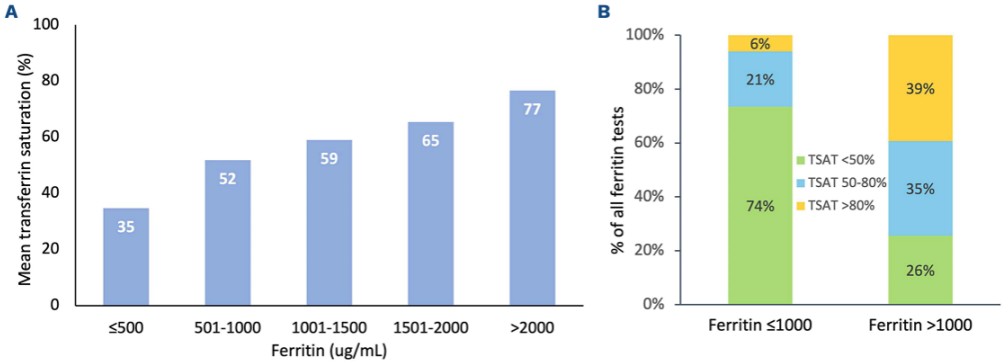
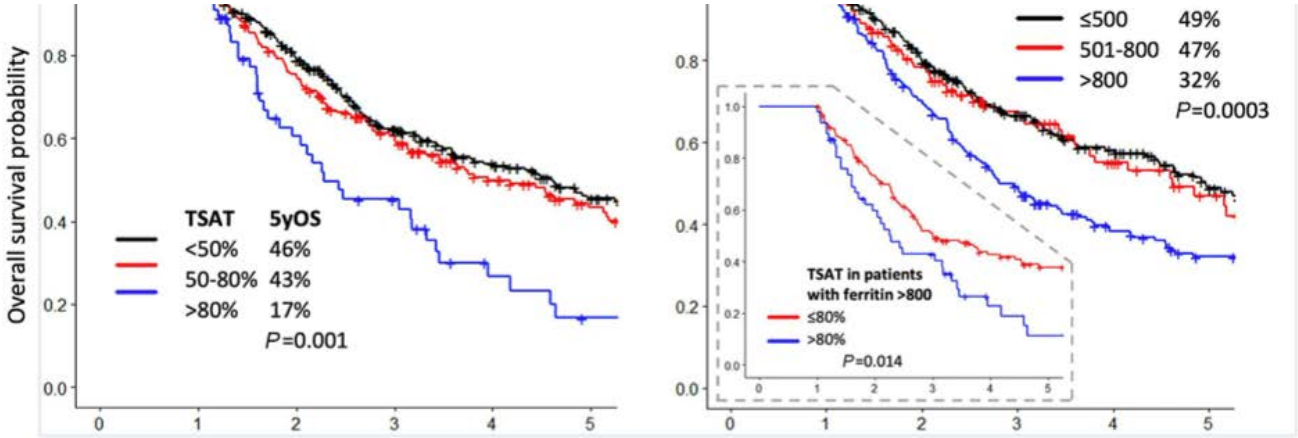
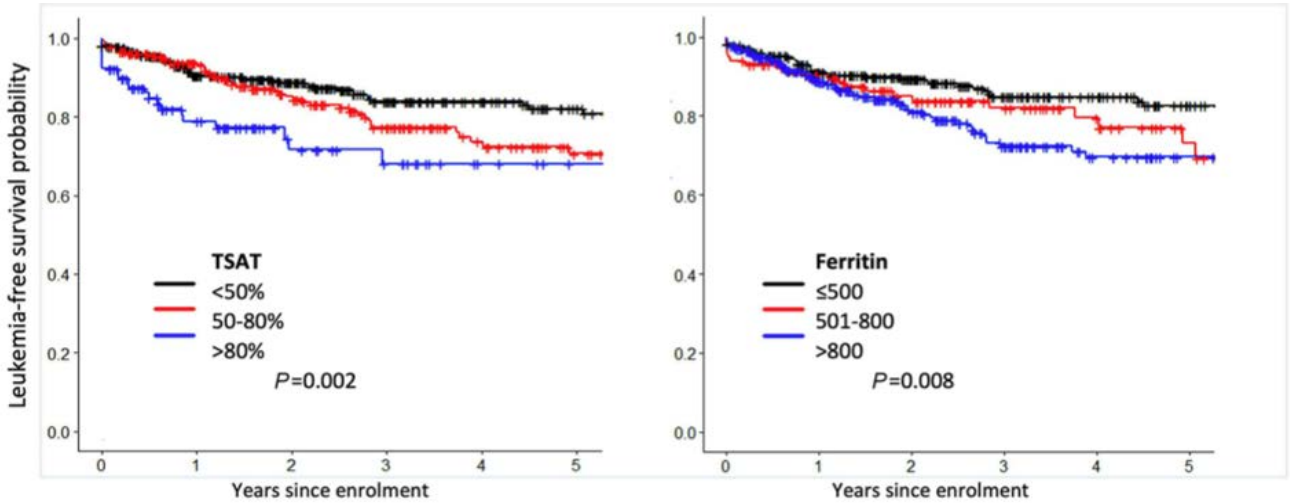
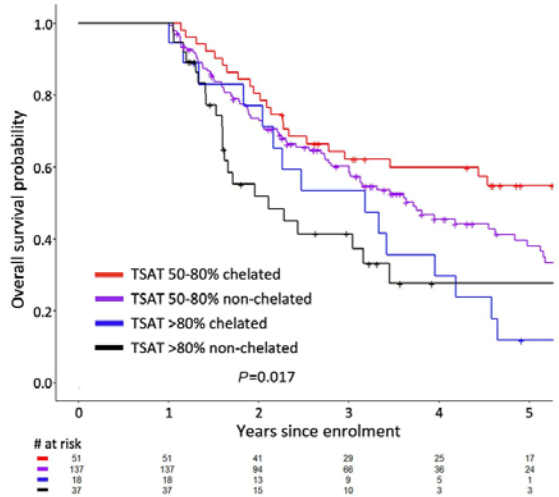






- 718 patients with ferritin and TSAT serially
- TSAT increased over time only in TD patients
- Ferritin and TSAT moderately correlated: r=0.63 (p < .0001)
- TSAT > 80% associated with inferior cardiac death-free survival; P=.053



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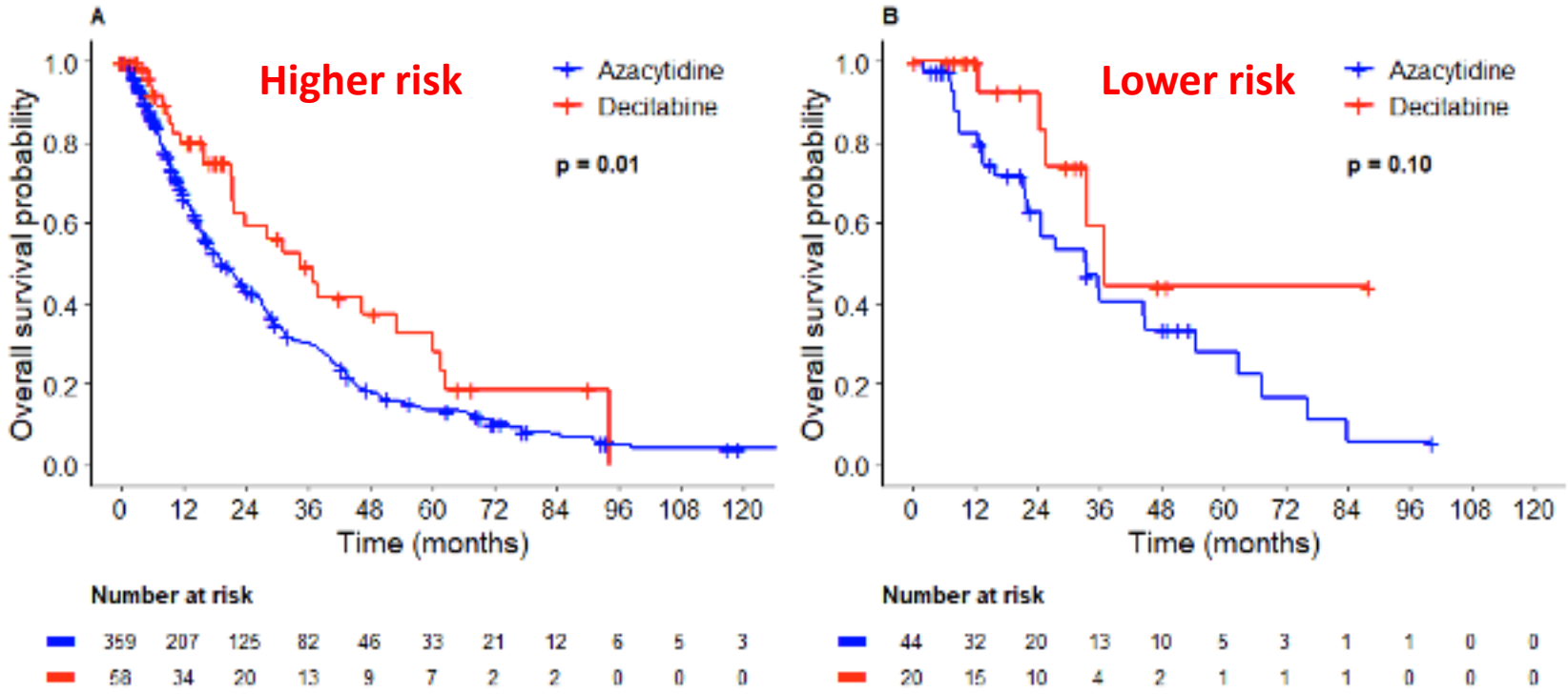
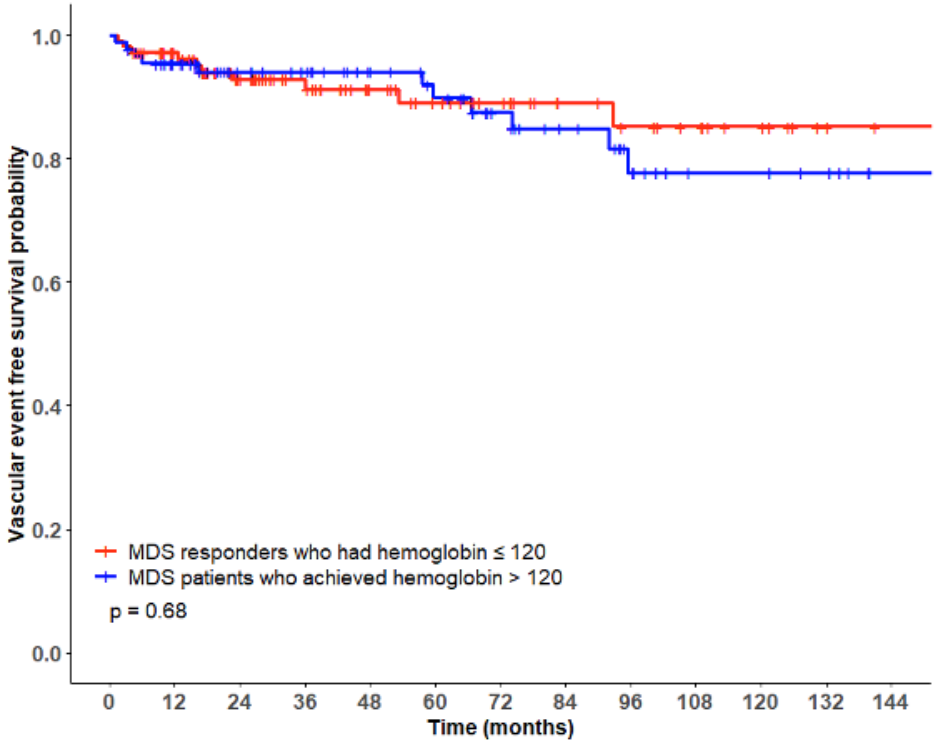
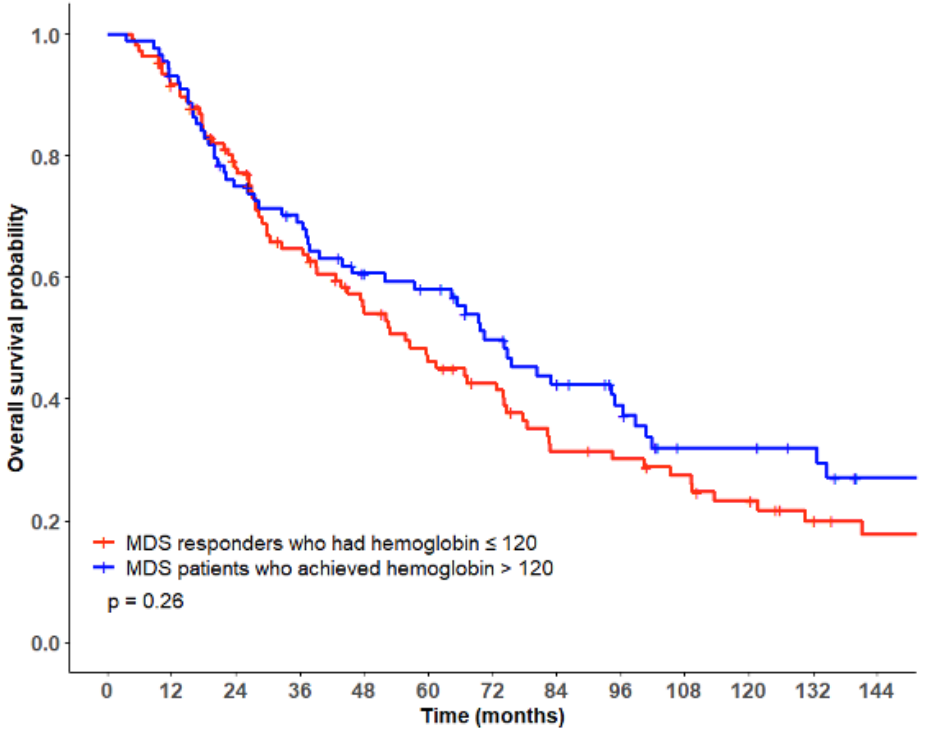
Decitabine non-inferior to AZACITIDINE



Going above a Hgb of 120 g/L with EPO does not increase risk of blood clots or cardiac events and patients may live longer!

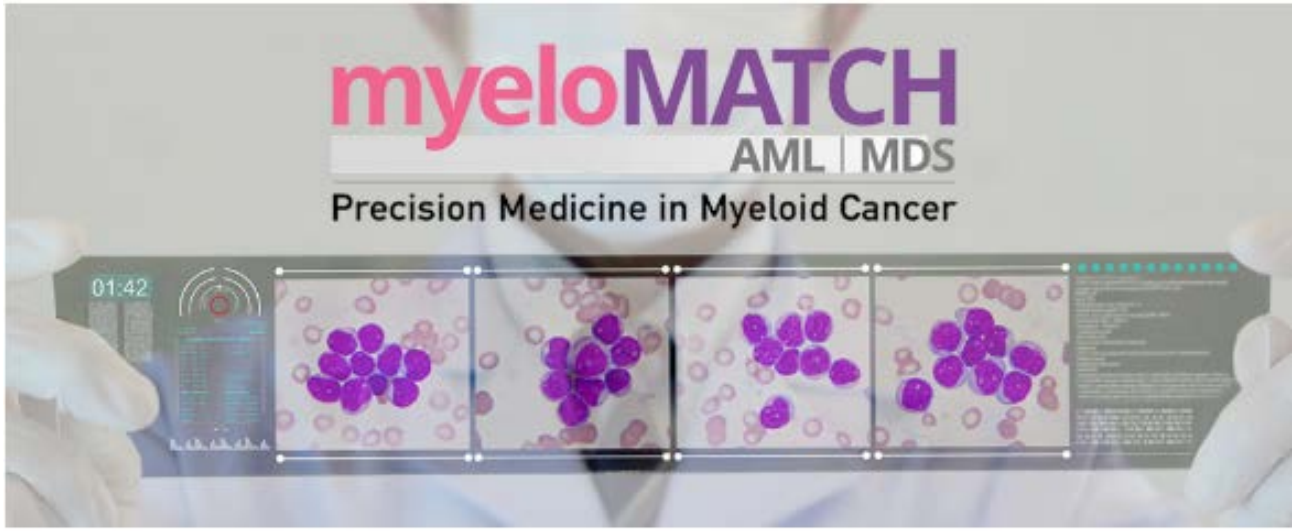




MDS Clinical trials at Odette Cancer Center

- **Keros study**: randomized trial of Elritercept versus placebo in transfusion dependent lower risk MDS having failed erythropoietin stimulating agents (EPREX or ARANESP)
- **GSK study** (June): A Phase 2, Randomized, Open-label, Study of Momelotinib in Participants with transfusion dependent anemia due to Low-Risk Myelodysplastic Syndrome (1 prior line of therapy)
- **OURA study**: an open label 12-week wearable study in all patients with MDS (30 who are dependent on transfusions and 30 who are not)
- **MDS-CAN** registry: all comers within 12 months of diagnosis


COMING
SOON


myeloMATCH
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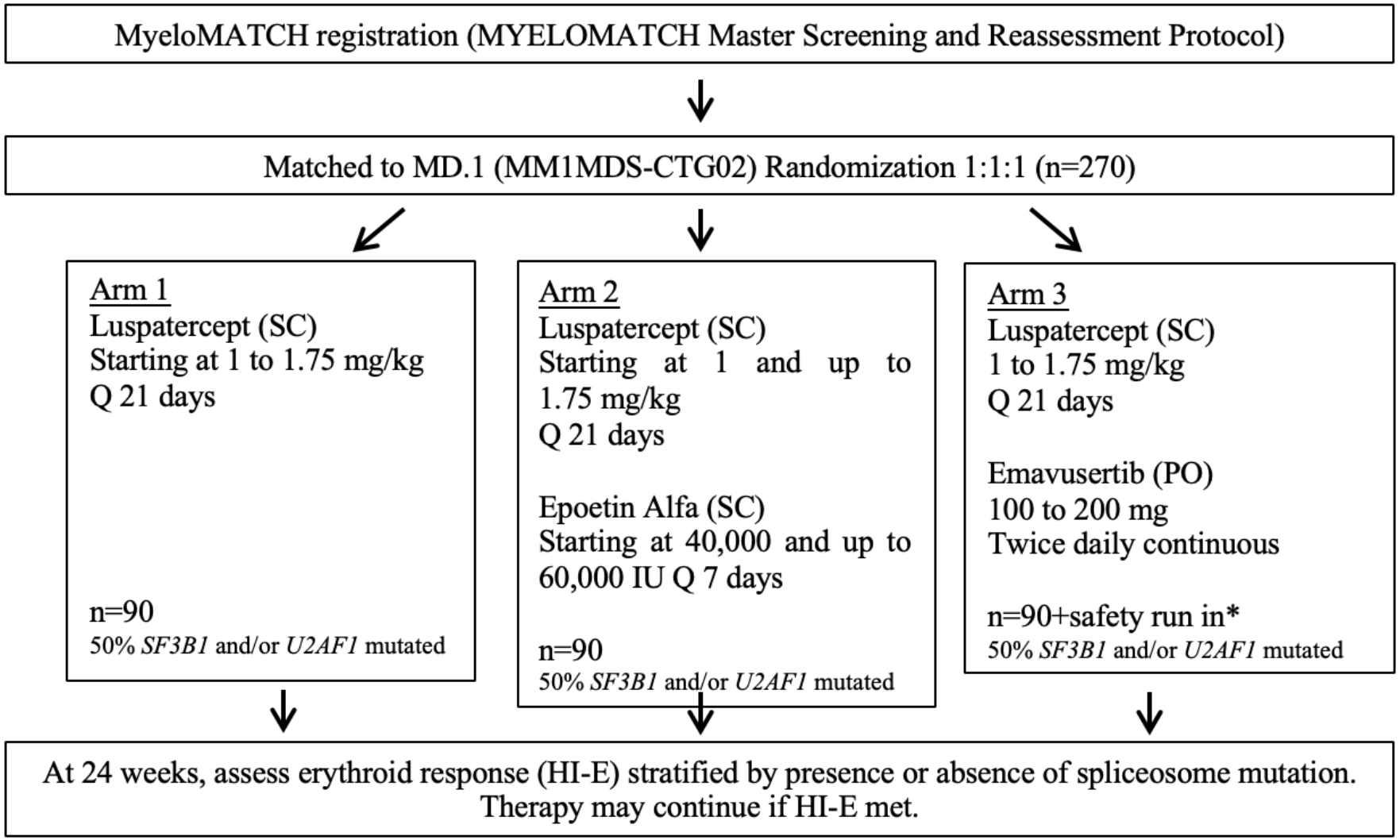
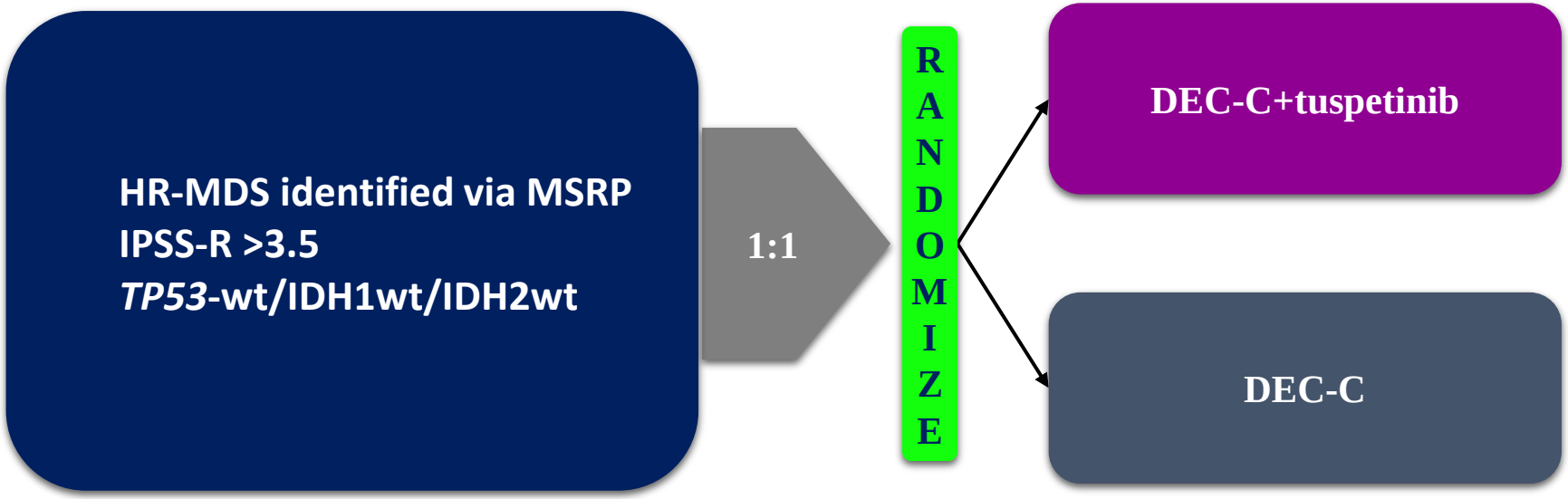


*Prior to the randomized component, 6-24 participants will be accrued to arm 3 to ensure safety and tolerability of the combination of emavusertib and luspatercept, and confirm selection of the emavusertib dose for the randomized component.

Randomized Phase 2 Study of tuspetinib based combination therapy in *TP53* wildtype higher risk MDS (N=88)



Primary endpoint : CR within the first 4 cycles of therapy by IWG2023 criteria

Cycle length=28 days. Safety run in phase (n=6) of the combination arm, prior to randomization (n=88)

Bone marrow biopsy at end of 2 cycles (if clinically indicated), 4 and 6 cycles and at progression or relapse

Treatment may continue until disease progression or enrollment to an appropriate tier of myeloMATCH

Stratification factors: IPSS-R score 4-6vs>6; activated signaling pathway (N-RAS/K-RAS/KIT) mutated vs not mutated

Thank-you for listening!

Any Questions?