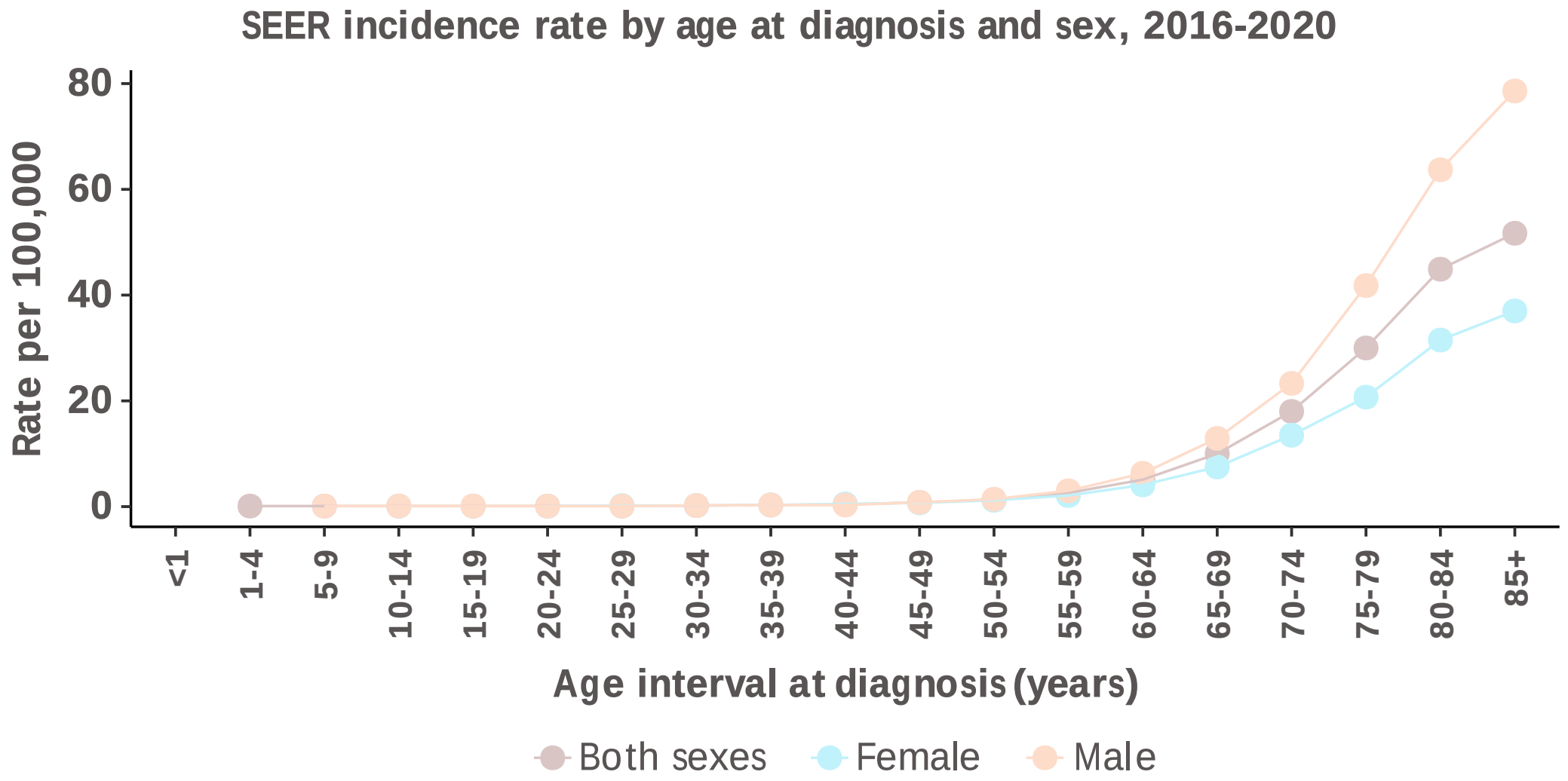
WHAT's NEW IN MDS?

Rena Buckstein MD FRCPC
Chair of MDS-CAN
Head, Hematology Clinical Trials Odette Cancer Center
Sunnybrook Health Sciences Center

Agenda

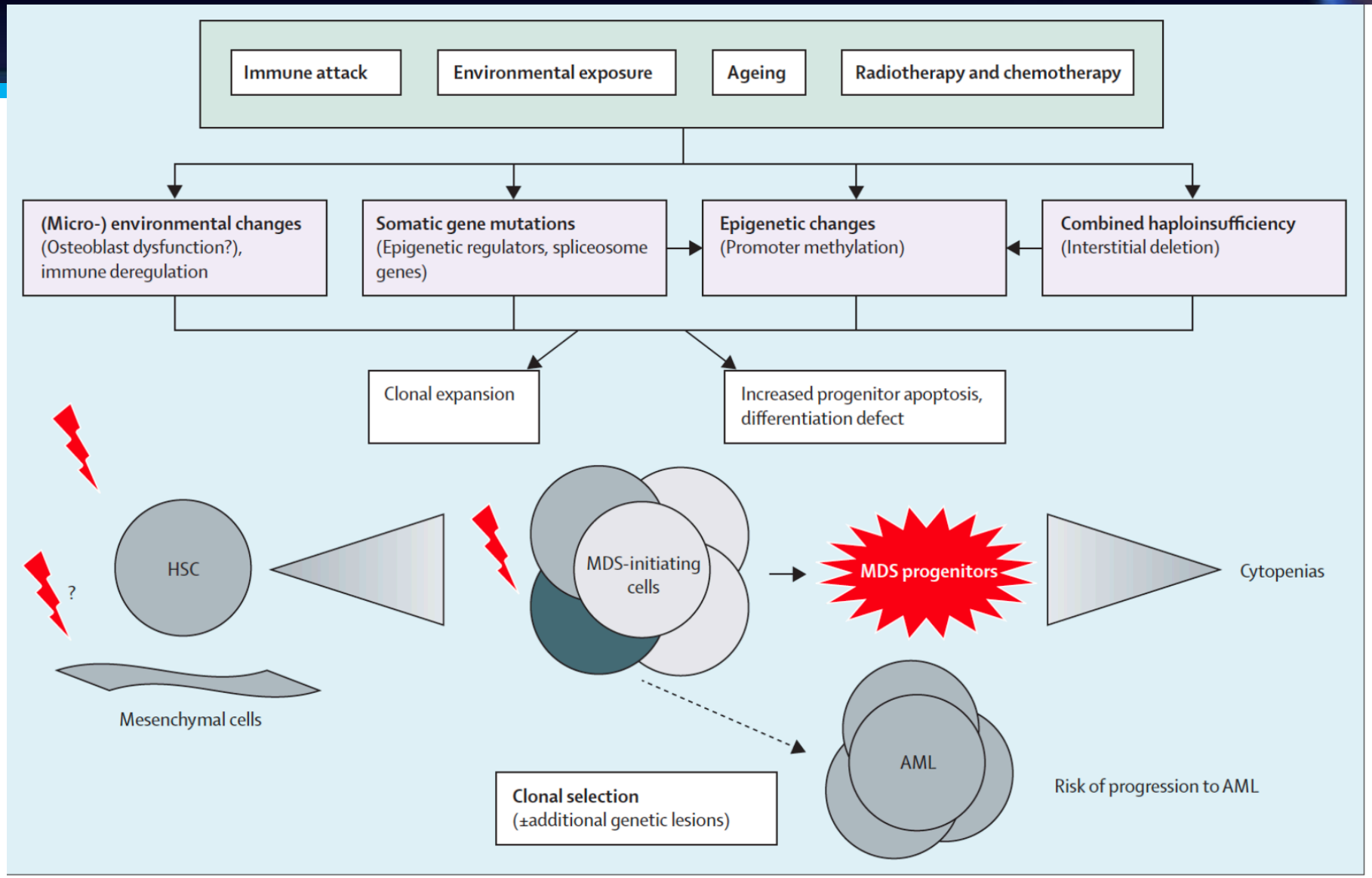
- New classification
- New prognosis
- New treatment in lower risk disease
- New treatment in higher risk disease
- Ongoing or pending clinical trials in Toronto

Figure 1. MDS incidence rate in the USA by age at diagnosis and sex (2016–2020)



MDS, myelodysplastic syndromes; SEER, Surveillance, Epidemiology, and End Results.

MDS pathogenesis



Ades et al. Lancet 2014.

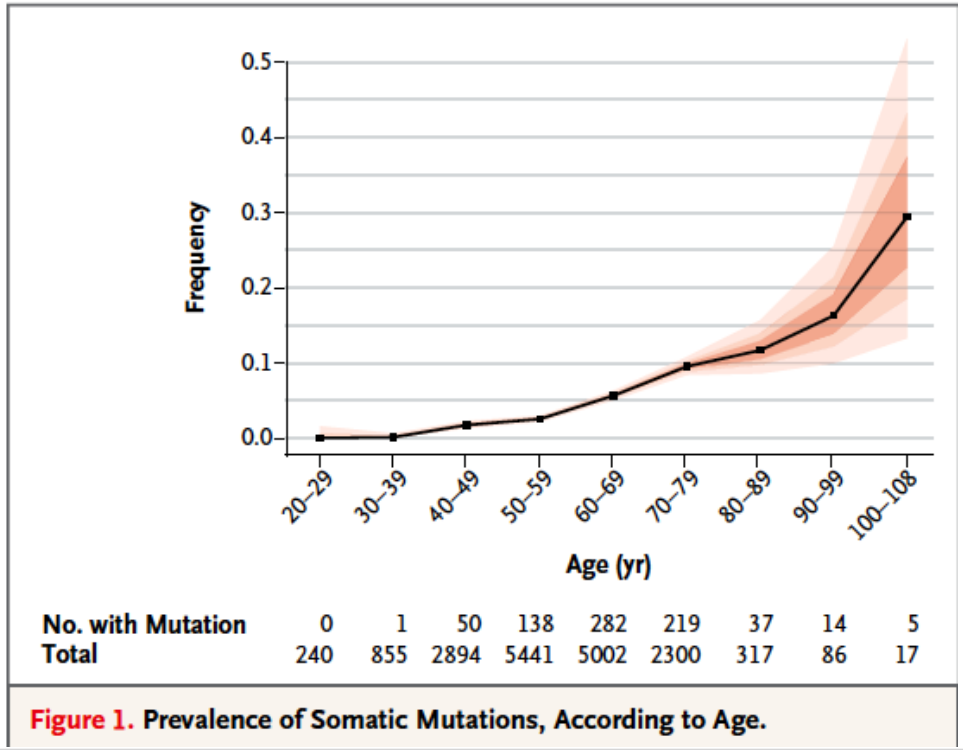
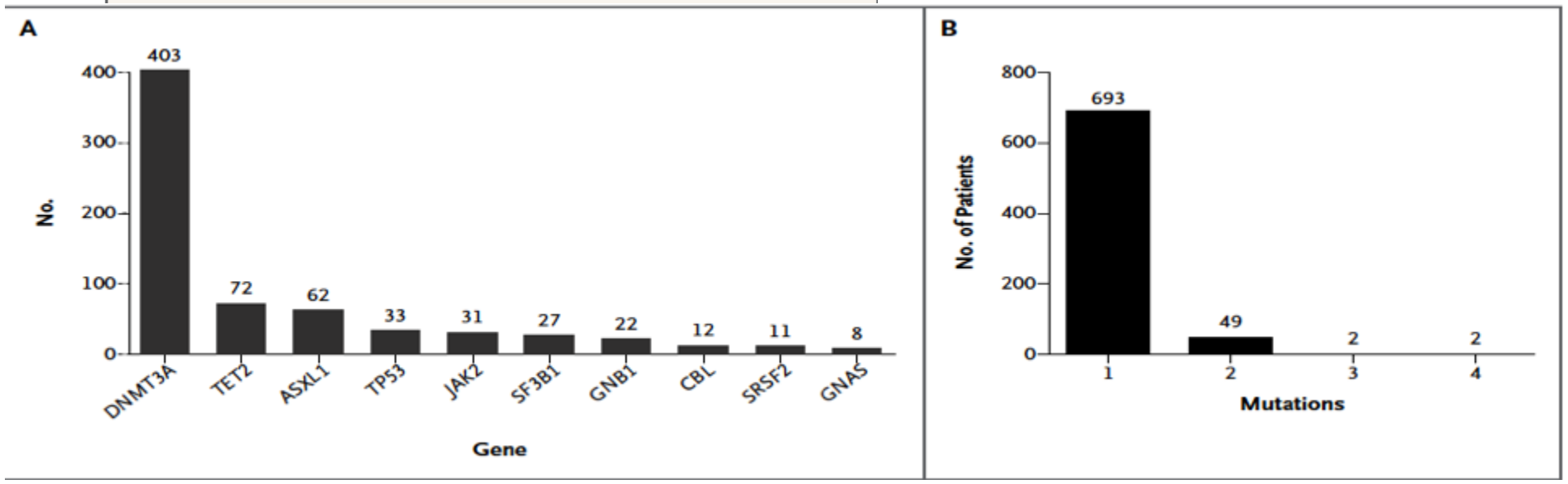
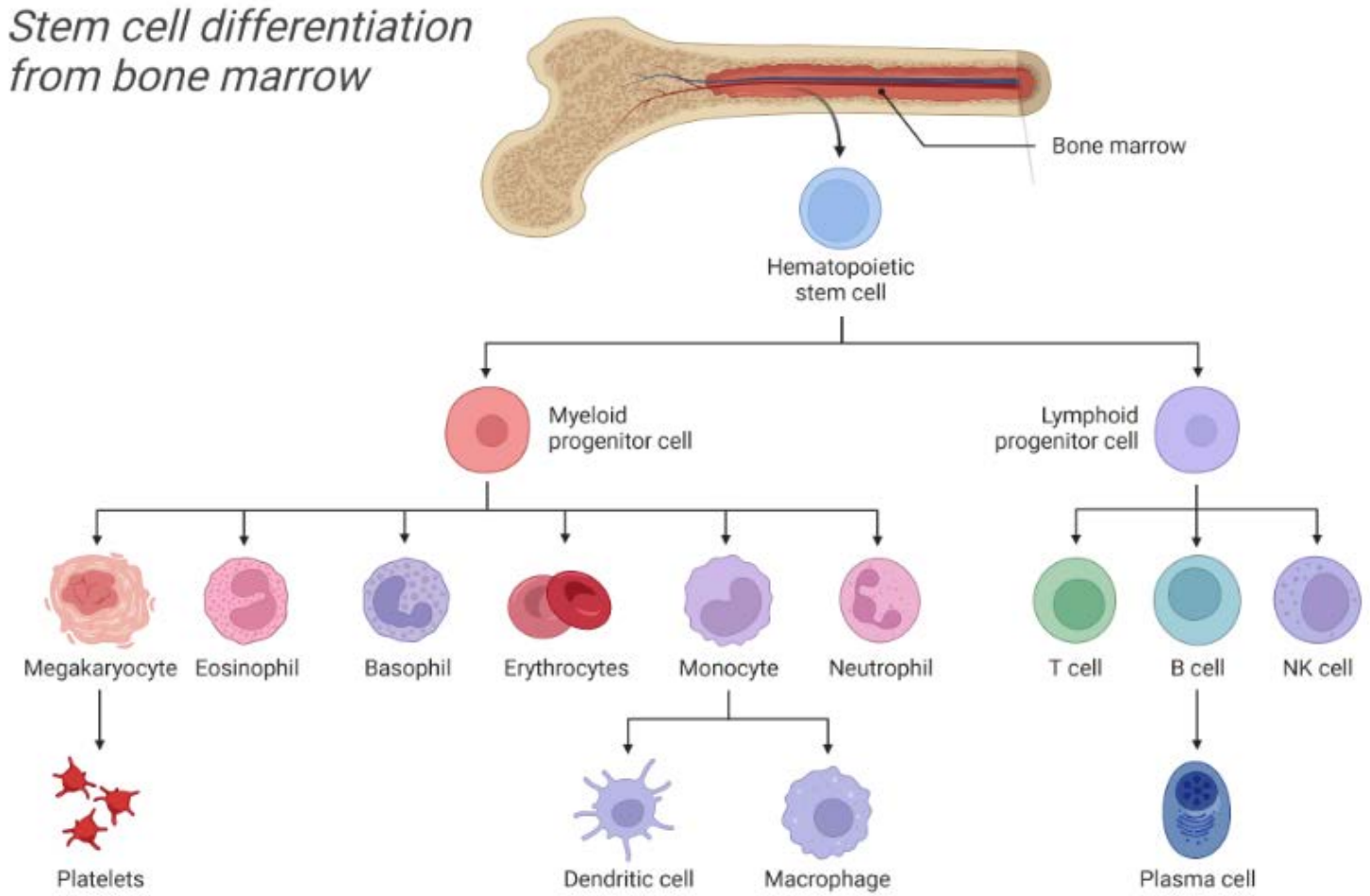


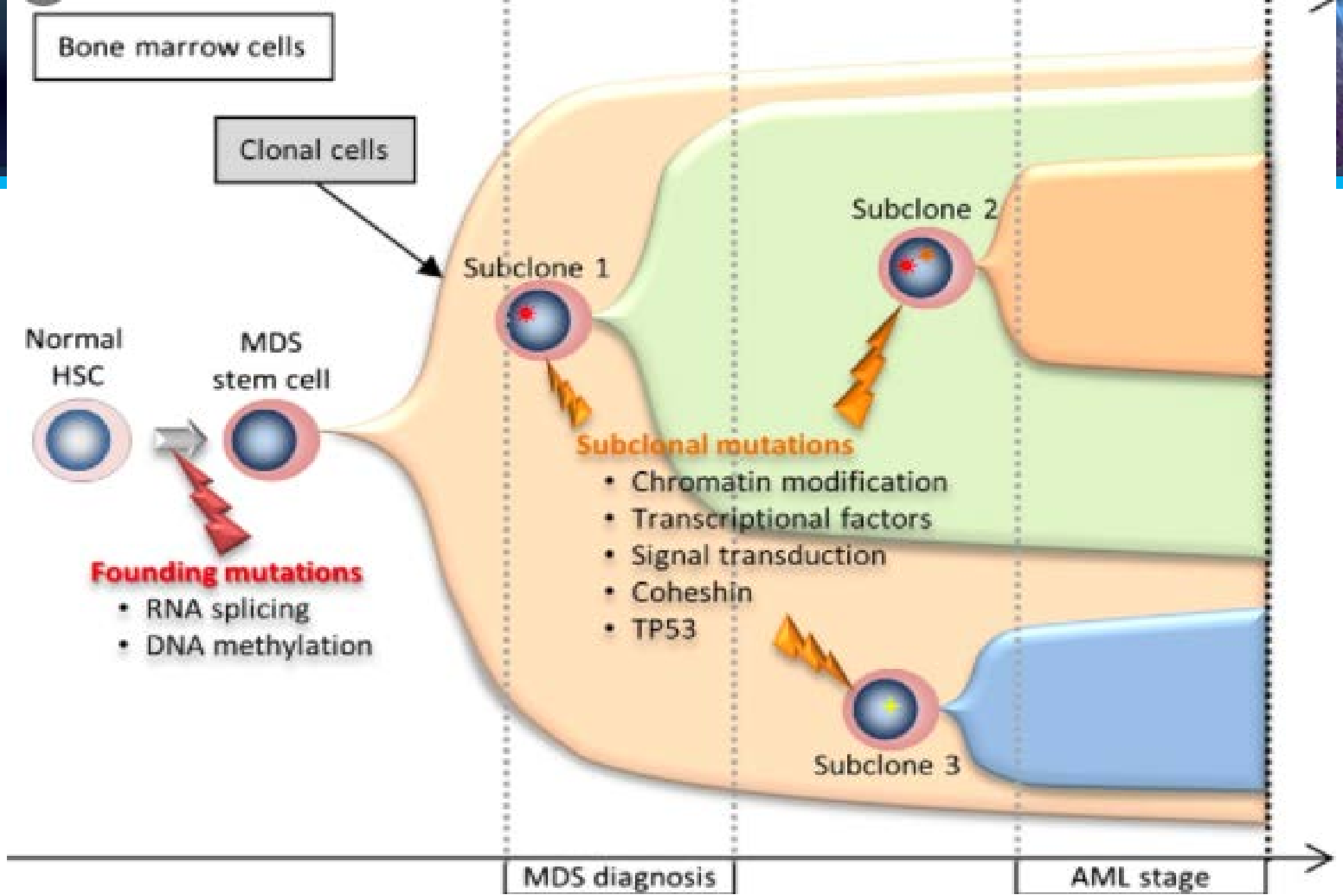
Figure 1. Prevalence of Somatic Mutations, According to Age.

These rates far exceed the incidence of clinically diagnosed hematologic cancer in the general population

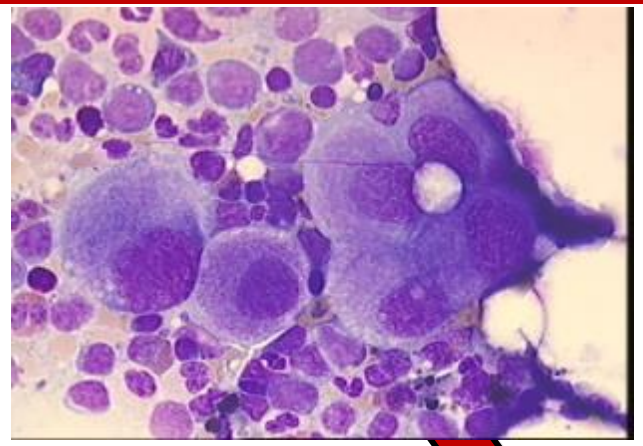


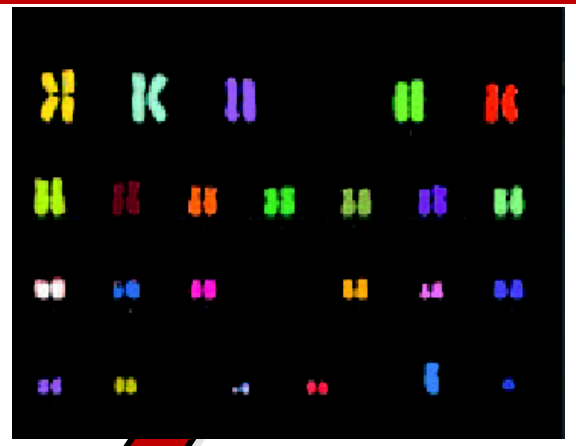
How normal blood is made




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

Myelodysplastic Syndromes are a Constellation of Diseases with Difficult Diagnosis





An accurate diagnosis is the basis for successful treatment of MDS

WHO qualitative and quantitative recommendation for morphological diagnosis :

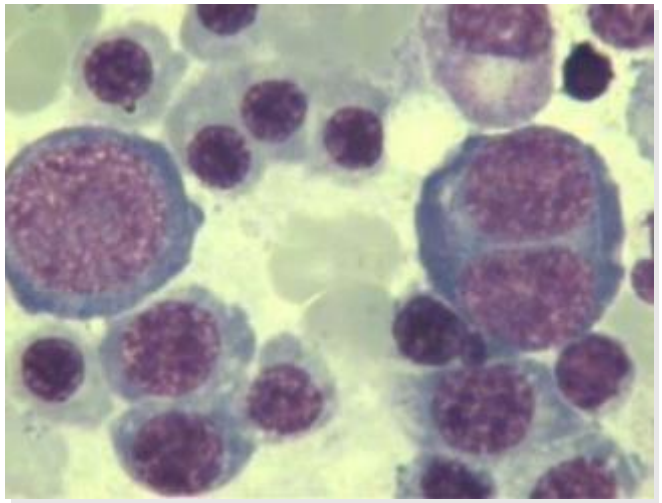
presence and number of lineages with > 10% dysplasia

description of dysplasia

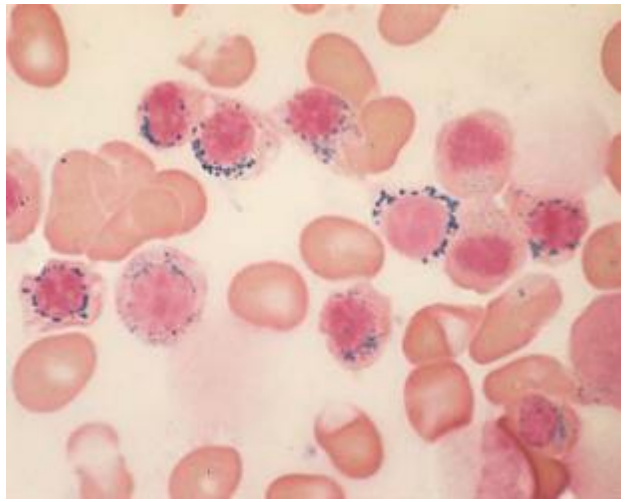
percentage of bone marrow blasts at aspirate

cytogenetic abnormalities

Perls staining

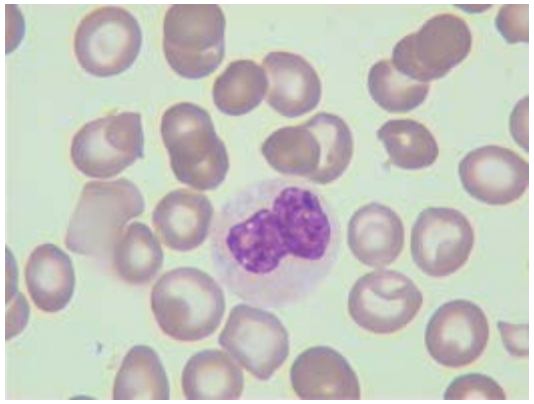


Morphology at BM aspirate and blast count

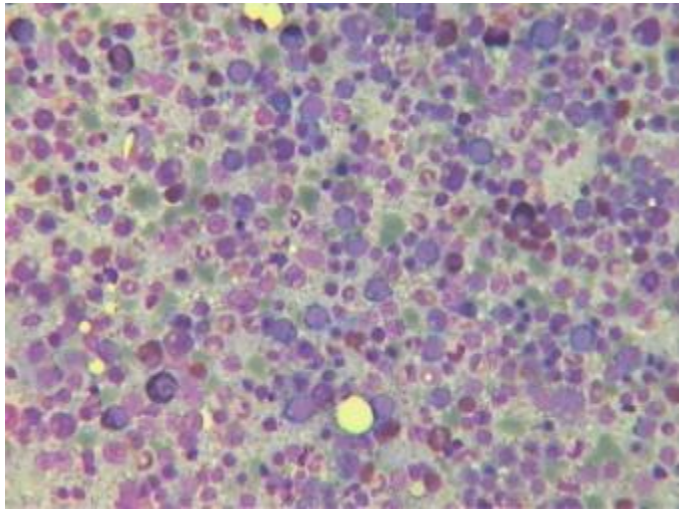


BM Perls staining for iron

PB cytology



ALWAYS !

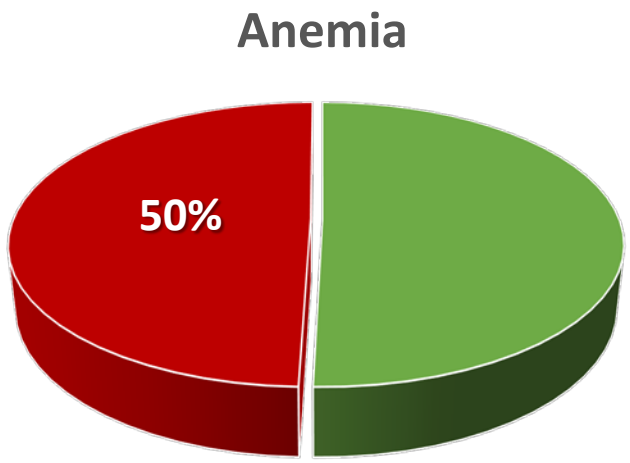


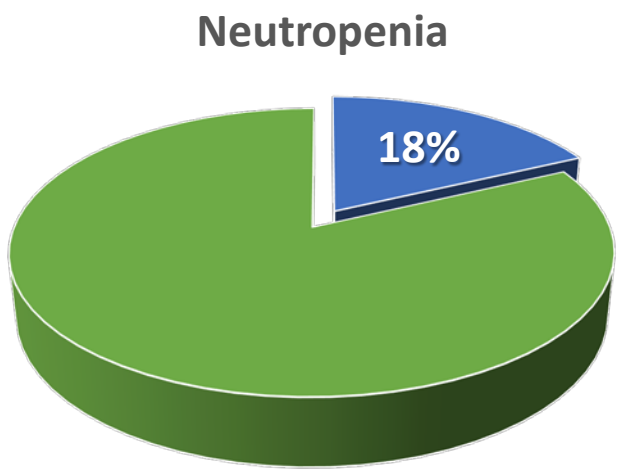
BM trephine biopsy for evaluation of cellularity and fibrosis

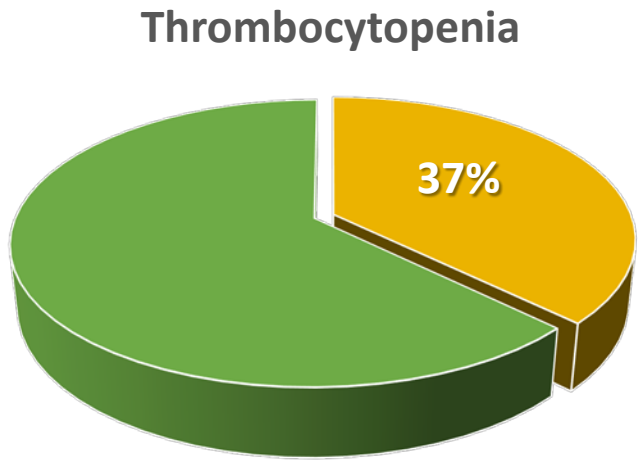
CD34/CD117 cells should not be counted as blasts, except in absence of marrow blood aspiration (fibrosis)

Malcovati et al , ELN Guidelines-Blood 2013- Valent P et al Leuk Res 2007

Incidence of Cytopenias in MDS Patients
Italian MDS Registry FISIM cases







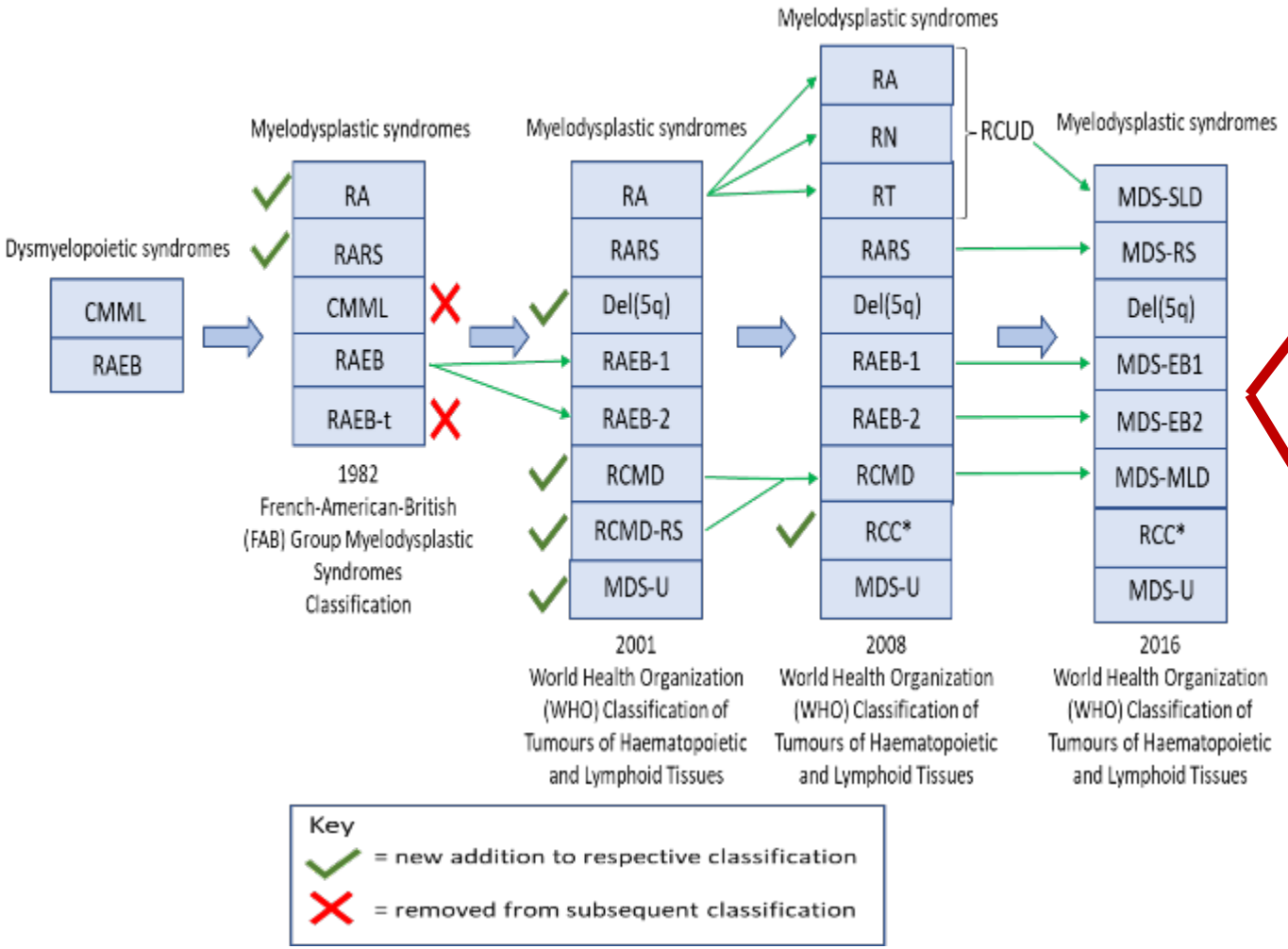
Hb < 10 gr/dl

ANC <800/uL

plt < 100000/uL

FISiM
FONDAZIONE
ITALIANA
SINDROMI
MIELODISPLASTICHE

MDS Classification Has Evolved Over Time



WHO 2022

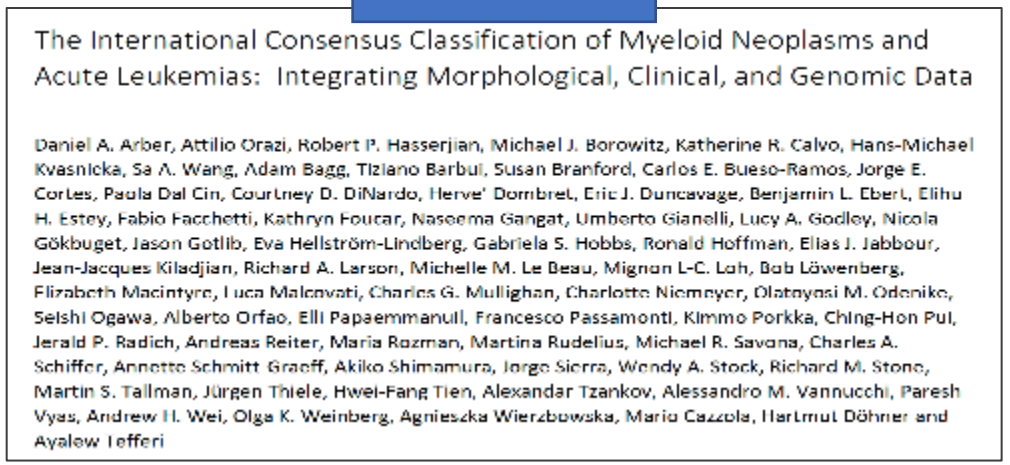
Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury, Eric Solary, Oussama Abla, Yassmine Akkari, Rita Alaggio, Jane F. Apperley, Rafael Bejar, Emilio Berti, Lambert Busque, John K. C. Chan, Weina Chen, Xueyan Chen, Wee-Joo Chng, John K. Choi, Isabel Colmenero, Sarah E. Coupland, Nicholas C. P. Cross, Daphne De Jong, M. Tarek Elghetany, Emiko Takahashi, Jean-Francois Emile, Judith Ferry, Linda Fogelstrand, Michaela Fontenay, Ulrich Germing, Sumeet Gujral, Torsten Haferlach, Claire Harrison, Jennelle C. Hodge, Shimin Hu, Joop H. Jansen, Rashmi Kanagal-Shamanna, Hagop M. Kantarjian, Christian P. Kratz, Xiao-Qiu Li, Megan S. Lim, Keith Loeb, Sanam Loghavi, Andrea Marcogliese, Soheil Meshinchi, Phillip Michaels, Kikkeri N. Naresh, Yasodha Natkunam, Reza Nejati, German Ott, Eric Padron, Keyur P. Patel, Nikhil Patkar, Jennifer Picarsic, Uwe Platzbecker, Irene Roberts, Anna Schuh, William Sewell, Reiner Siebert, Prashant Tembhare, Jeffrey Tyner, Srdan Verstovsek, Wei Wang, Brent Wood, Wenbin Xiao, Cecilia Yeung and Andreas Hochhaus

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

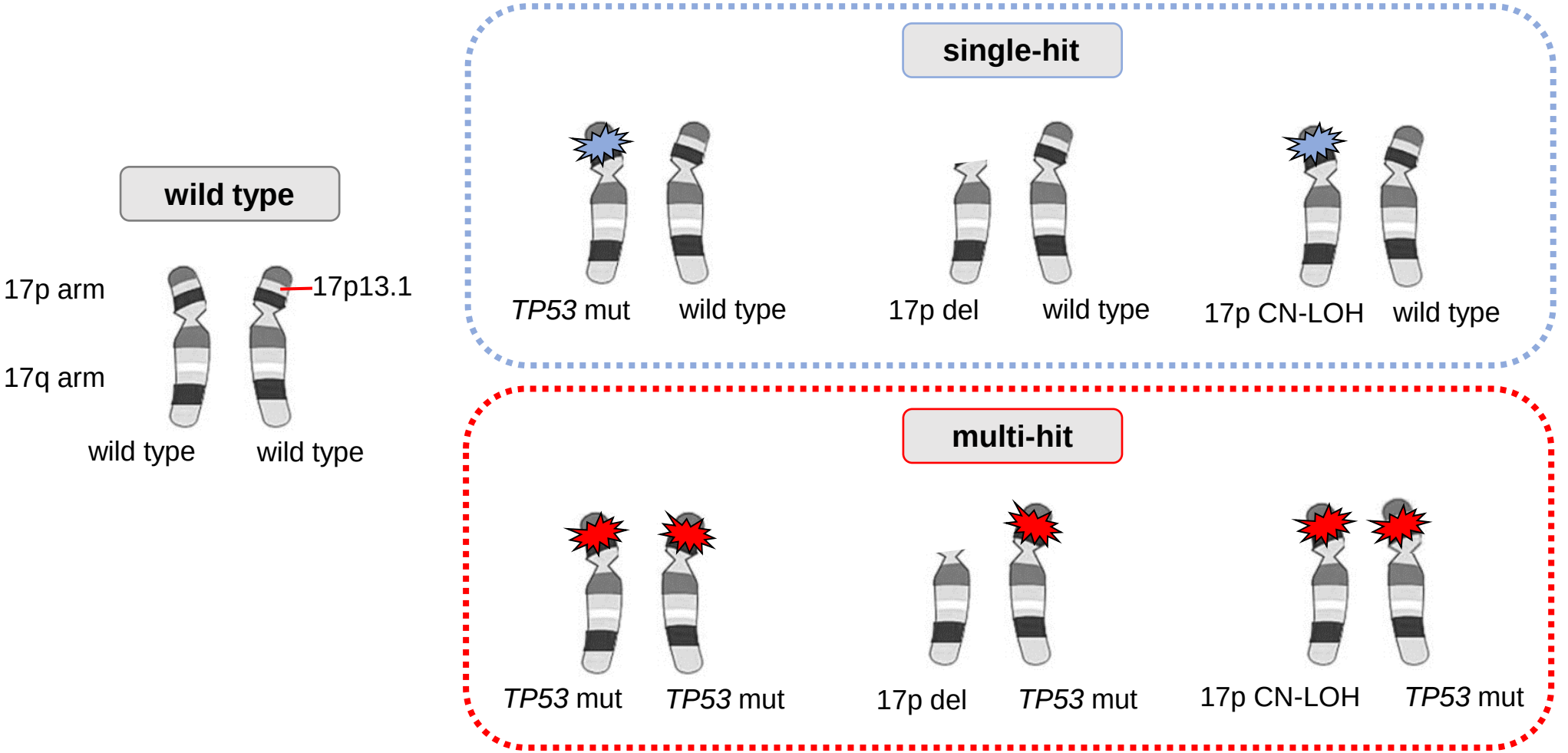
Zeidan A et al, Blood Reviews, 2019; Khoury J et al, Leukemia; Arber D et al, Blood 2022

Komrokij et al , EHA 2023

ICC versus WHO

- Where they agree (for the most part):
- CCUS: clonal cytopenias with uncertain significance
- MDS with defining cytogenetic abnormalities
  - Del5q-
  - *SF3B1* mutations
  - *TP53* mutations (double hit)
- Where they disagree
  - Does # lineages dysplastic matter?
  - Should fibrosis or low cellularity be considered separate entities?
  - Should blasts of 10-19% be lumped with AML?
  - Should MDS with ring sideroblasts (without *SF3B1* mutations) still be its own category?
  - What mutational frequencies are considered significant?
  - Neoplasms or Syndromes?

TP53 Loss


wild type
17p arm
17q arm
17p13.1
wild type
wild type
single-hit
TP53 mut
wild type
17p del
wild type
17p CN-LOH
wild type
multi-hit
TP53 mut
TP53 mut
17p del
TP53 mut
17p CN-LOH
TP53 mut

Conceptual classification of MDS

Chronic phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB

Accelerated phase MDS

- MDS-EB (5-19% myeloblasts) (cutoff to be refined)
- Bi-allelic *TP53* MDS
- MDS-f

AML-MDS related (AML-MR)

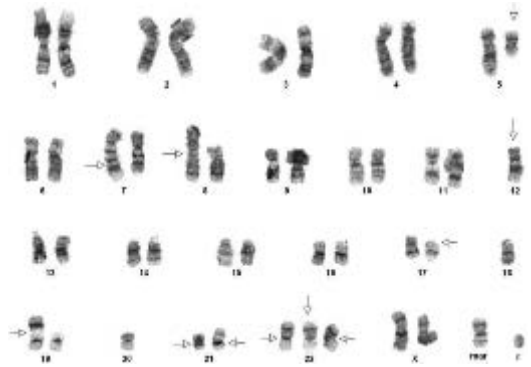
- ≥20% myeloblasts (cutoff to be refined) with prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations.

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes (IPSS-M)

IWG-PM cohort for IPSS-M development

n=2,957
diagnostic MDS

3,186 cytogenetic alterations
in 41% of patients

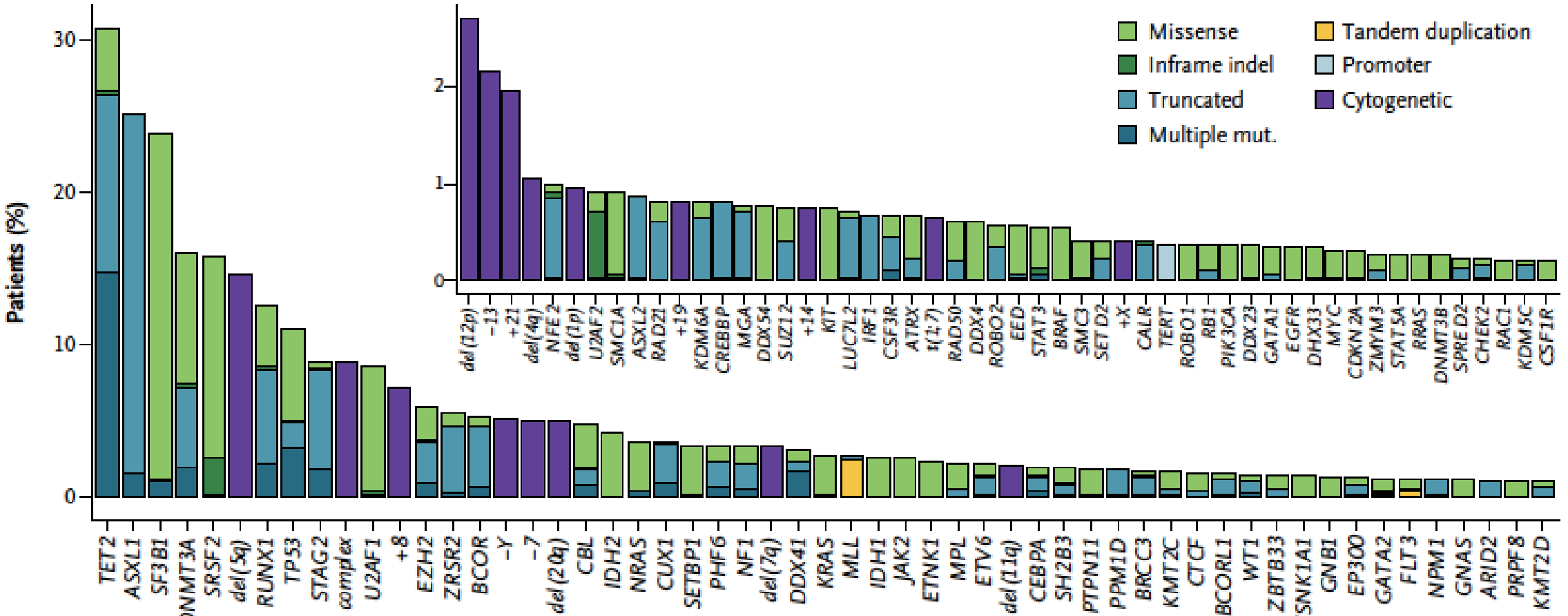


9,254 mutations in 121 genes
in 90% of patients

94% of patients had oncogenic alterations (either cytogenetic abnormalities, gene mutation, or both)

Bernard E et al, NEJM Evid 2022;1(7) June 12.

Frequency of Mutated Genes, Type of Mutation, and Cytogenetic Alterations in 2957 MDS Cases Analyzed



Bernard E et al, NEJM Evid 2022;1(7) June 12.

IPSS-M

The model consisted of:

1) Hemoglobin, platelets, and bone marrow blasts (neurophil number not significant)

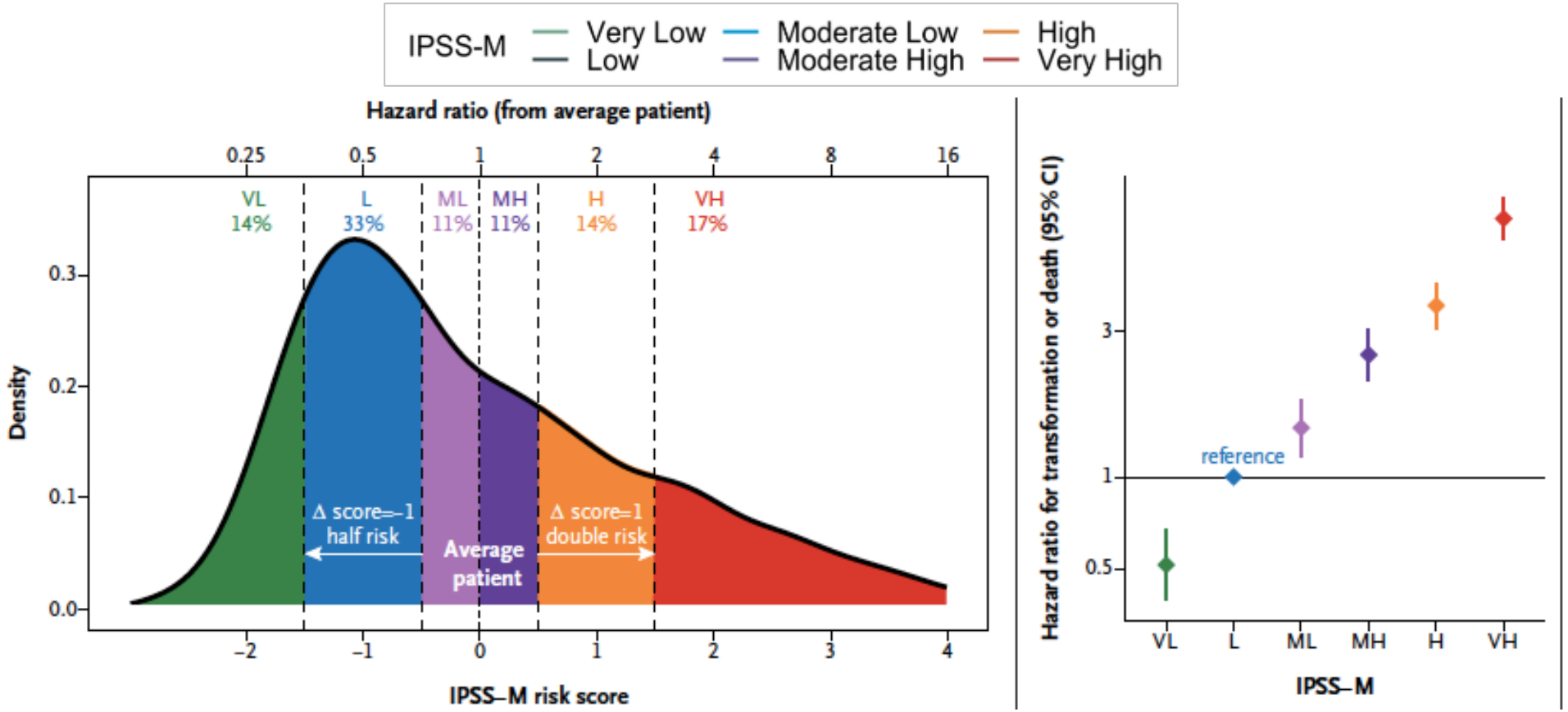
2) IPSS-R cytogenetic category

3) 17 binary features derived from the presence of mutations in 16 predictive genes
   - *ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *IDH2*, *KRAS*, *MLL*^{PTD}, *NPM1*, *NRAS*, *RUNX1*, *SF3B1*^{5q}, *SF3B1*$^{\alpha}$, *SRSF2*, *TP53*^{multihit}, and *U2AF1*

4) One feature representing the number of mutations from a group of 15 genes
   - 15 additional genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*) on the basis of adverse effects

Bernard E et al, NEJM Evid 2022;1(7) June 12.

IPSS-M Patient-Specific Risk Score & Risk Categories



Score value of 0 represented the average patient
(i.e., a hypothetical patient with mean values for all variables)

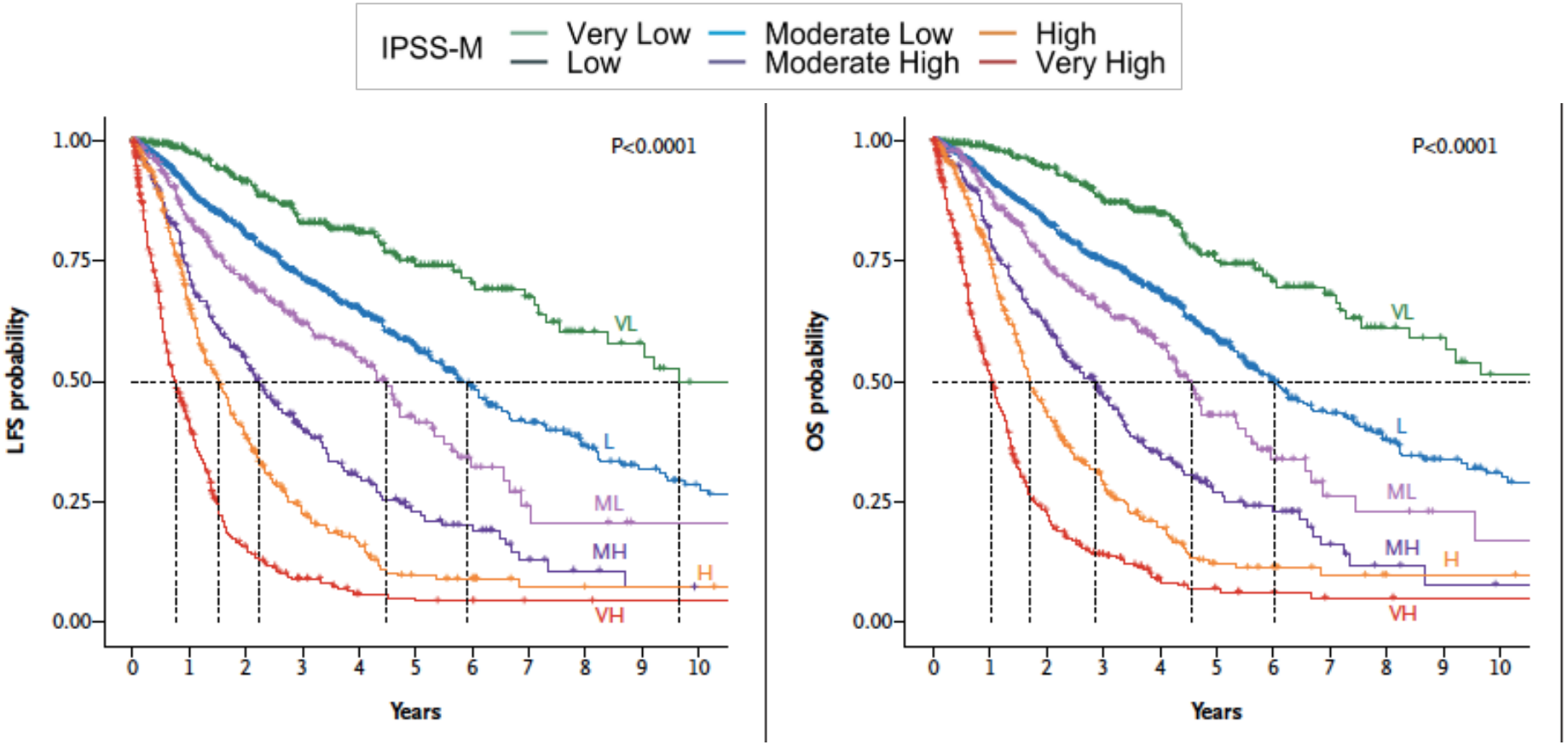
Continuous risk score

Patient-specific score

Reproducible and Interpretable

Bernard E et al, NEJM Evid 2022;1(7) June 12.

IPSS-M Patient-Specific Risk Score & Risk Categories



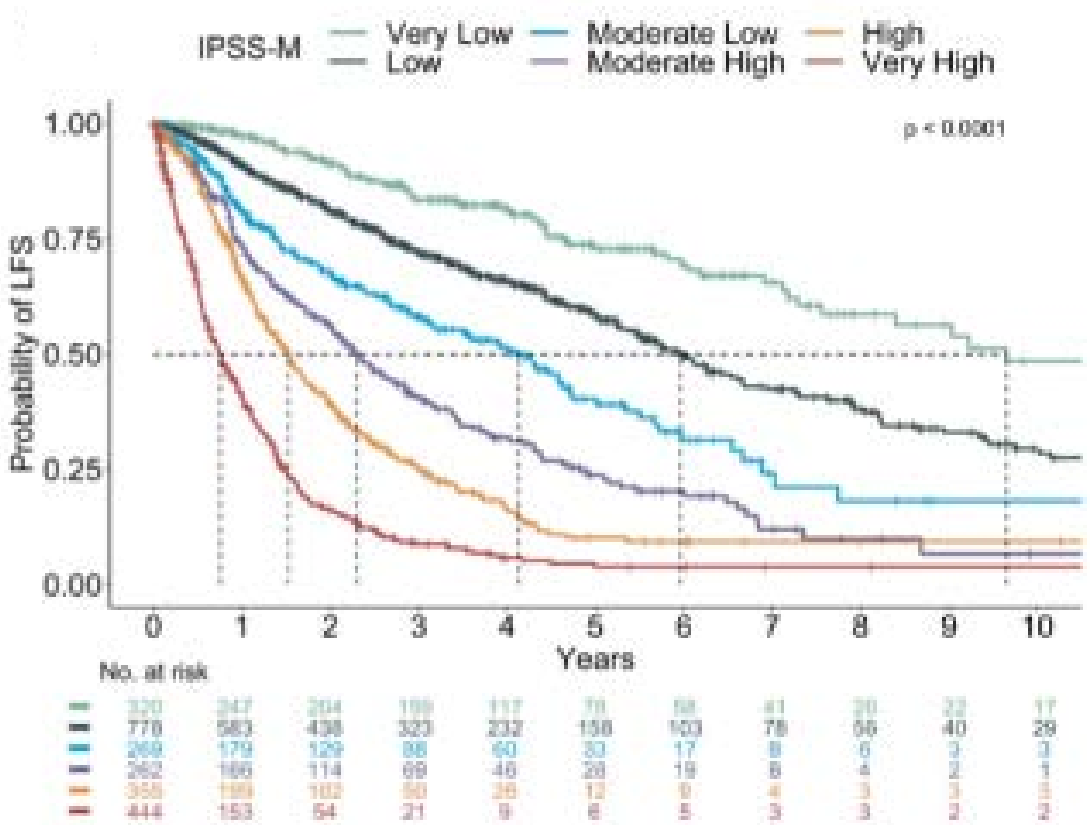
A six-category risk schema

Prognostic separation

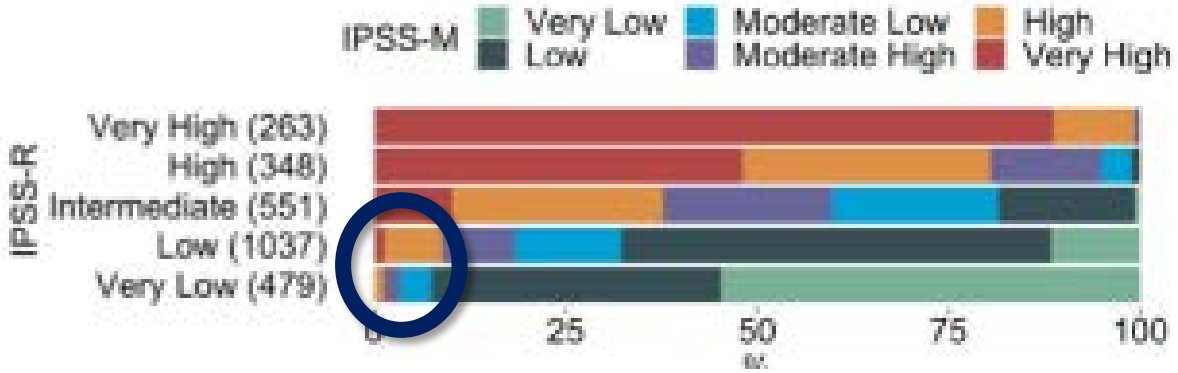
Therapeutic decisions & clinical trial design

Bernard E et al, NEJM Evid 2022;1(7) June 12.

IPSS-M Upgrades and Downstages MDS



Upstages 34%
Downstages 12%



Bernard E et al, NEJM Evid 2022;1(7) June 12.

IPSS-M calculator: https://mds-risk-model.com/

IPSS-M Risk Calculator

Risk Stratification | Clinical Outcomes

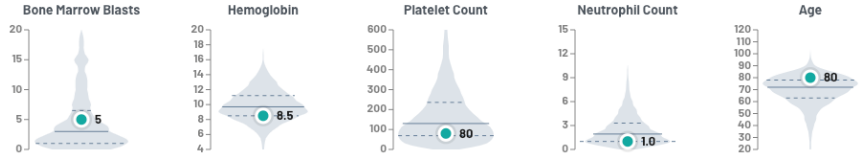
PATIENT SUMMARY

Bone Marrow Blasts:	Hemoglobin:	Platelet Count:	Neutrophil Count:	Age:
5 %	8.5 g/dL	80 1e9/L	1.0 1e9/L	80 years

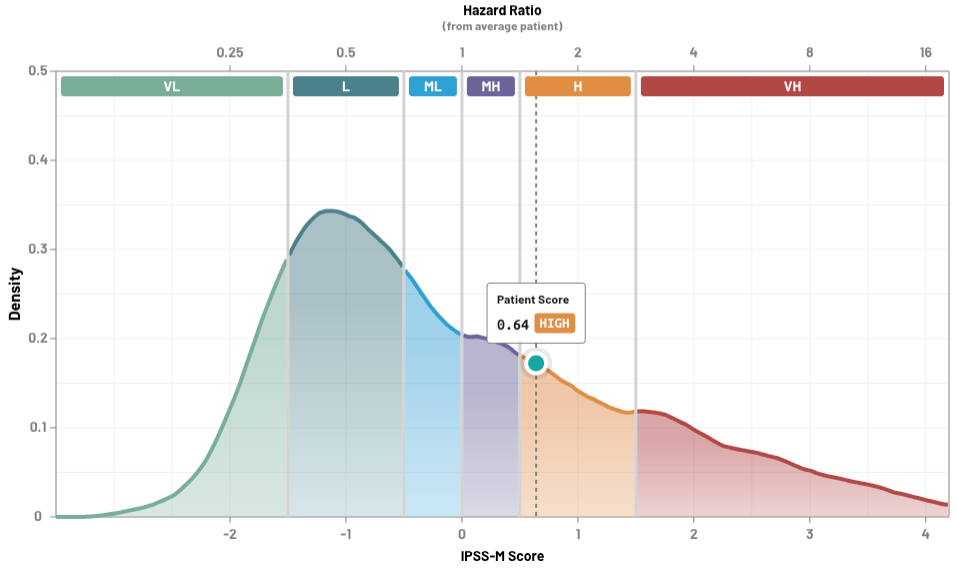
Cytogenetics Category:	TP53 Mutation Count:	TP53 Maximum VAF:	TP53 locus LOH:
Good	0	N/A	No

Mutated Genes:	Missing Genes:
ASXL1, RUNX1	0

Cohort Clinical Distributions (n=2957)



Graph | Table



*Hazard ratio for risk of AML-t or death from the average patient.

Bernard E, Tuechler H, Greenberg PL, et al, The Molecular International Prognosis Scoring System (IPSS-M) for risk stratification in myelodysplastic syndromes. New Eng J Med Evidence, 1(7). doi:10.1056/evidoa2200008. Study supported by the MDS Foundation.

STRATIFICATION RESULTS

IPSS-M Score:	IPSS-R Score:	IPSS-R Score (Age-adjusted):
0.64 HIGH	4.50 INT	4.78 HIGH

ENDPOINTS

Leukemia-Free Survival (IPSS-M):	Overall Survival (IPSS-M):	AML Transformation (IPSS-M):
1.5 years median	1.7 years median	14.3% by 1 year
0.8-2.8 years, 25%-75% range	1-3.4 years, 25%-75% range	29.2% by 4 years

What Defines RISK category

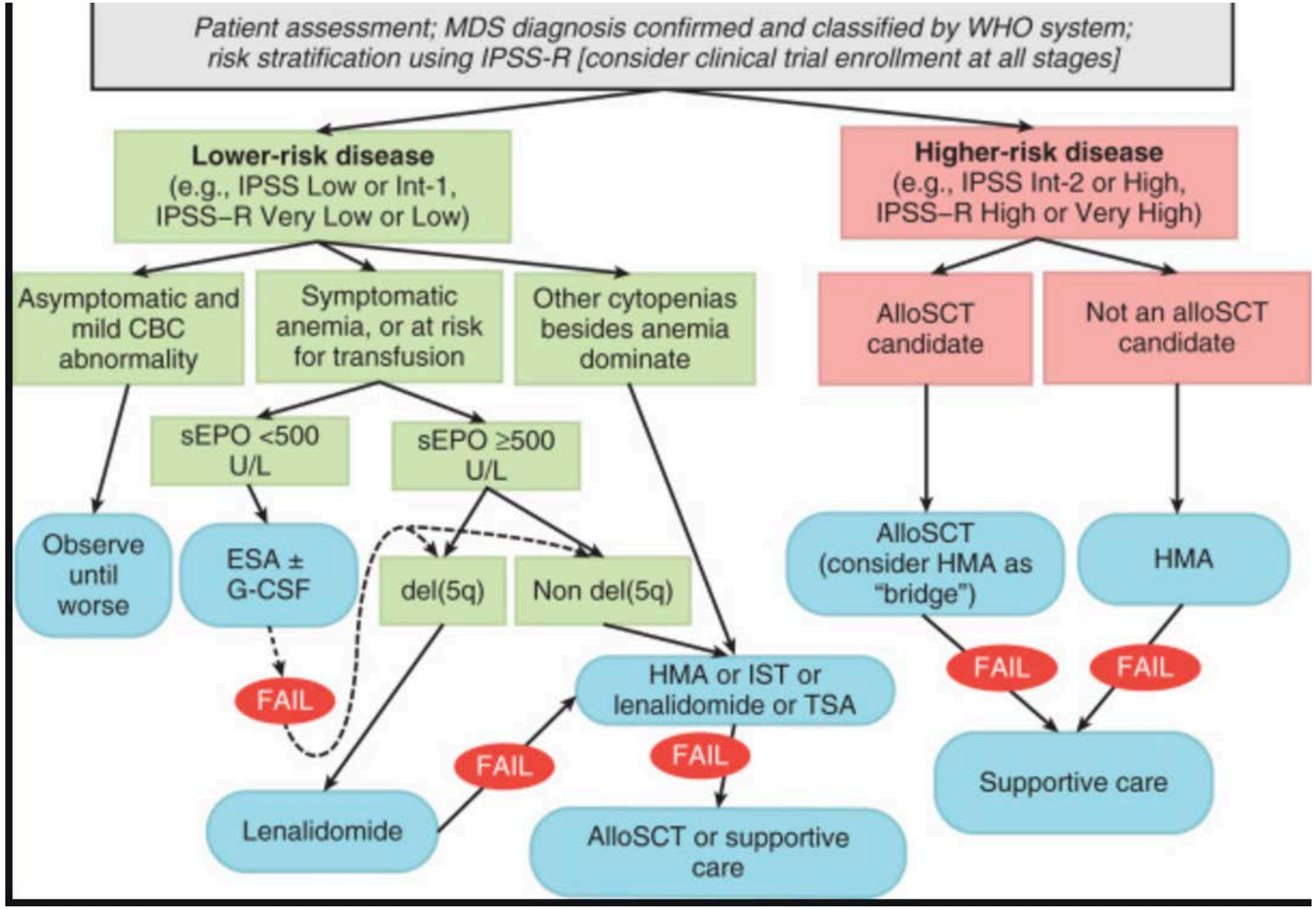
- Risk: of developing leukemia and shorter survival
- **Higher risk:**
  - Transfusion dependent (non MDS-with SF3B1)
  - IPSS-R score of > 3.5
  - IPSS-M: MH, H and VH
- **Lower risk:**
  - Non transfusion dependent
  - IPSS-R score of <=3.5
  - IPSS-M: VL, L and ML

Goals of therapy: tailored to patient needs

- **Lower risk:**
  - Improve BM function
  - Relieve symptoms of anemia or other low blood counts
  - Improve QOL
  - Eliminate dependence on transfusions
  - Prevent iron overload
  - Prevent cardiac complications

- **Higher risk:**
  - Delay or avoid leukemia
  - Improve overall survival
  - Eliminate dependence on transfusions
  - Improve or maintain QOL
  - Cure?

Algorithm for Treatment



Steensma D and Stone R. Abeloff's Clinical Oncology 2020, Pages 1798-1820.e1

New drugs Lower Risk:

- **Lower Risk:**
  - Luspatercept relapsed RS+: now in Canada
  - Luspatercept front-line: now in USA and EU
  - Imetelstat: soon in USA
  - Oral DEC-C (decitabine –cedazuridine): now in Canada

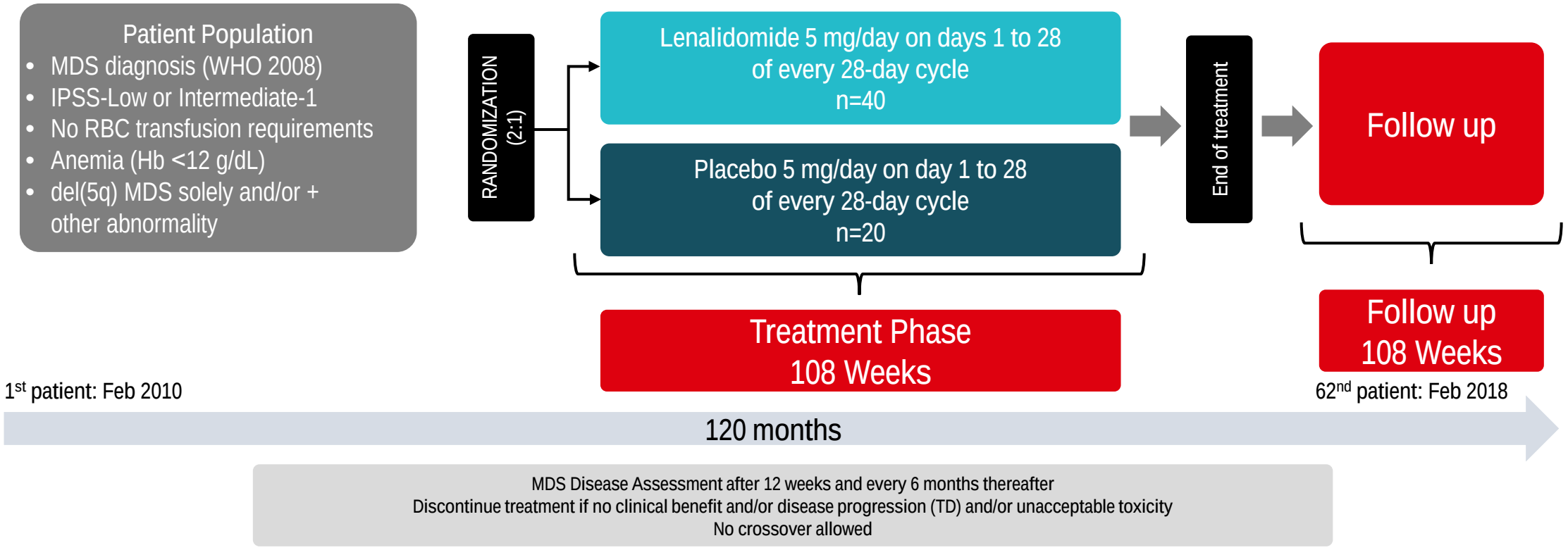
Combination Approaches Higher risk: more failures than successes….

- HMA +
  - Pevonedistat (PANTHER)
  - Eprenetopt
  - Magrolimab (ENHANCE)
  - Sabatolimab (STIMULUS)
  - Venetoclax (VERONA)
  - **Ivosidenib (IDH1)**
  - **Enasidenib. (IDH2)**
  - PD-1 and PDL1 inhibitors
  - Tamibarotene (SELECT-MDS-1)

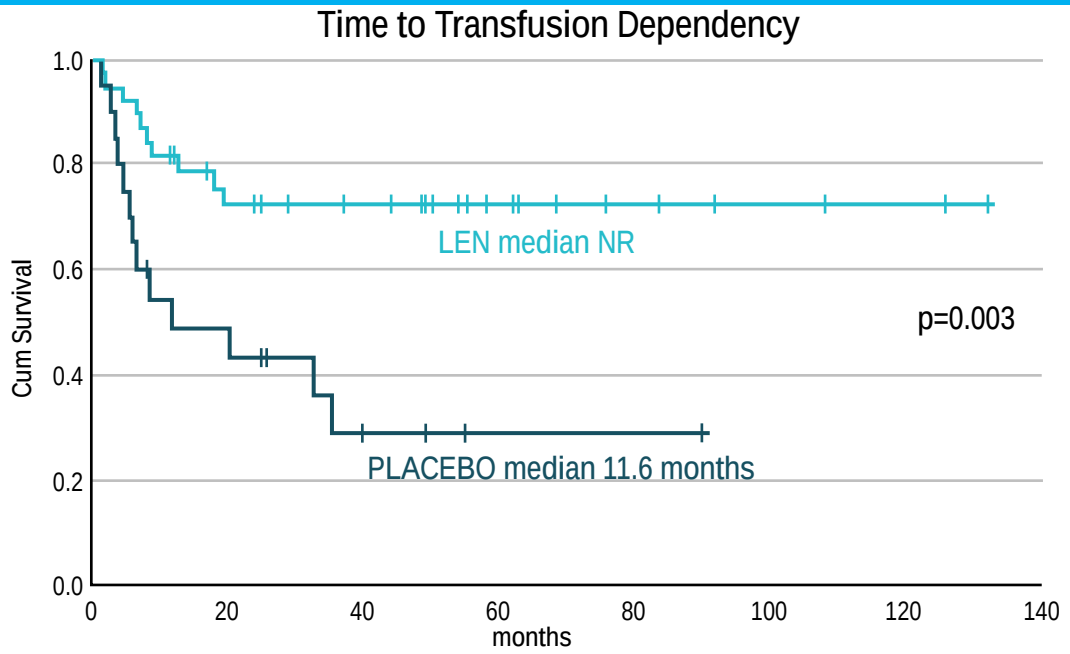
#460 Evaluation of Lenalidomide vs Placebo in Non-Transfusion Dependent Low Risk Del(5q) MDS Patients. Final Results of Sintra-REV Phase III International Multicenter Clinical Trial (López Cadenas F, et al.)

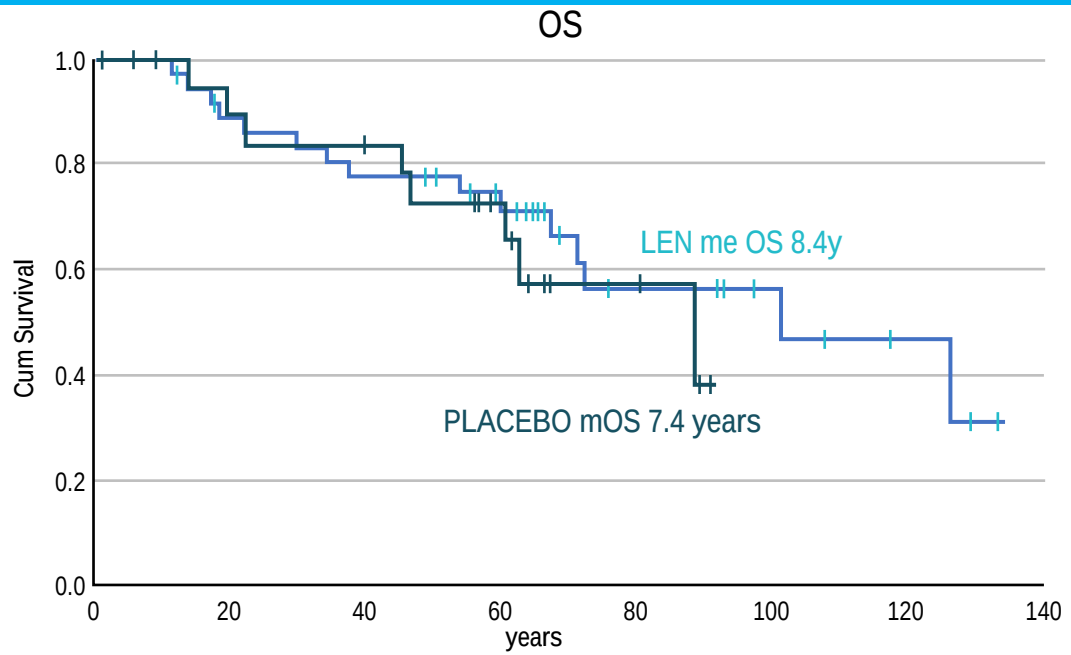
JB

- Sintra-Rev is a phase 3 multicenter trial in low-risk MDS-del(5q) patients with anemia without transfusion dependency.
- Patients were randomized (2:1) in a double-blind design to LEN (5 mg/day continuously) vs placebo for 2 years of treatment and 2 years of follow-up. The primary endpoint was the time to transfusion dependency



#460 Evaluation of Lenalidomide vs Placebo in Non-Transfusion Dependent Low Risk Del(5q) MDS Patients. Final Results of Sintra-REV Phase III International Multicenter Clinical Trial (López Cadenas F, et al.)





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

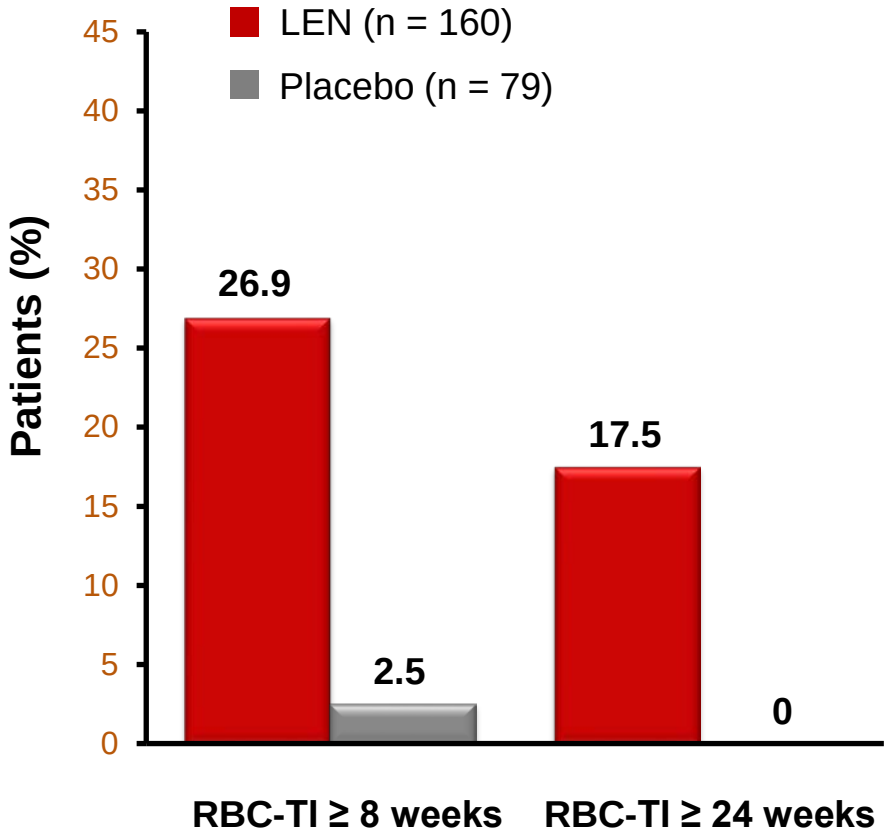
TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)

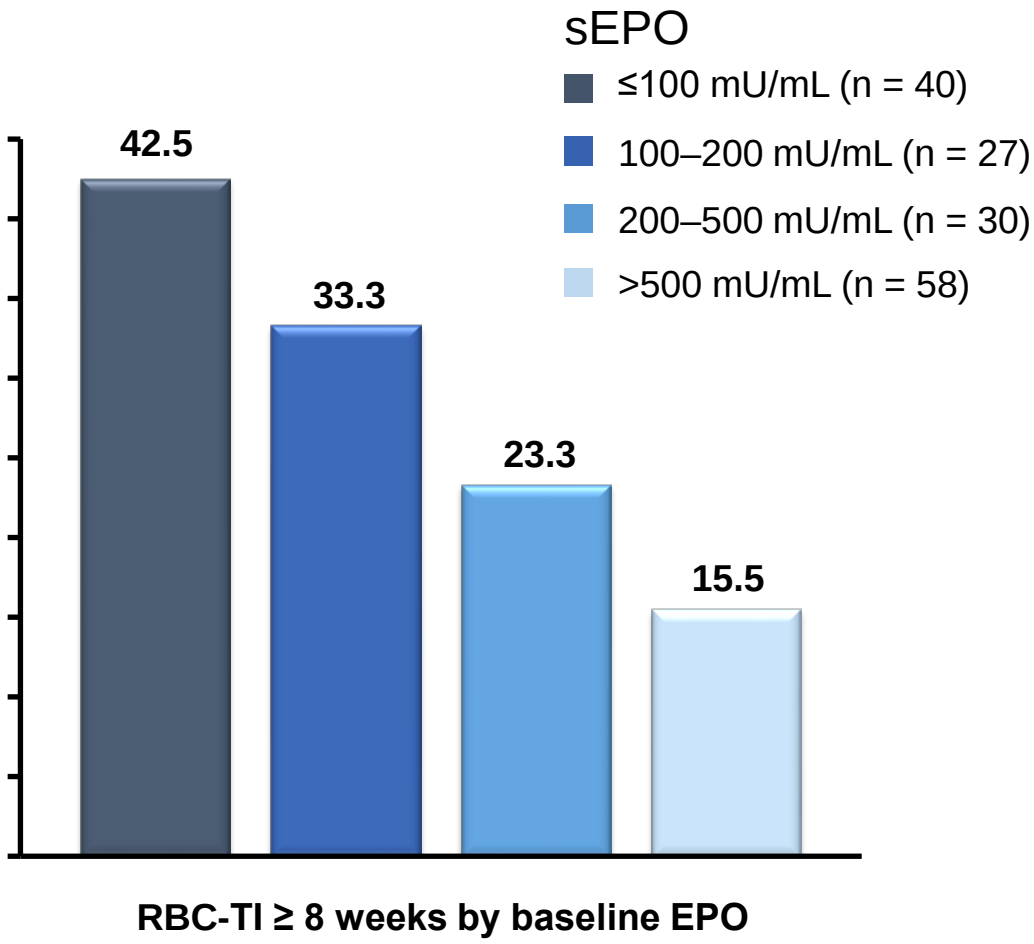
Low doses of LEN reached erythroid and CG responses

Erythroid response	28/36 (77.8%)
CG response	32/34 (94.1%)

- AML evolution was identified in 6/40 (15%) and 5/21 (23.8%) for LEN and placebo patients, respectively (p=0.488).

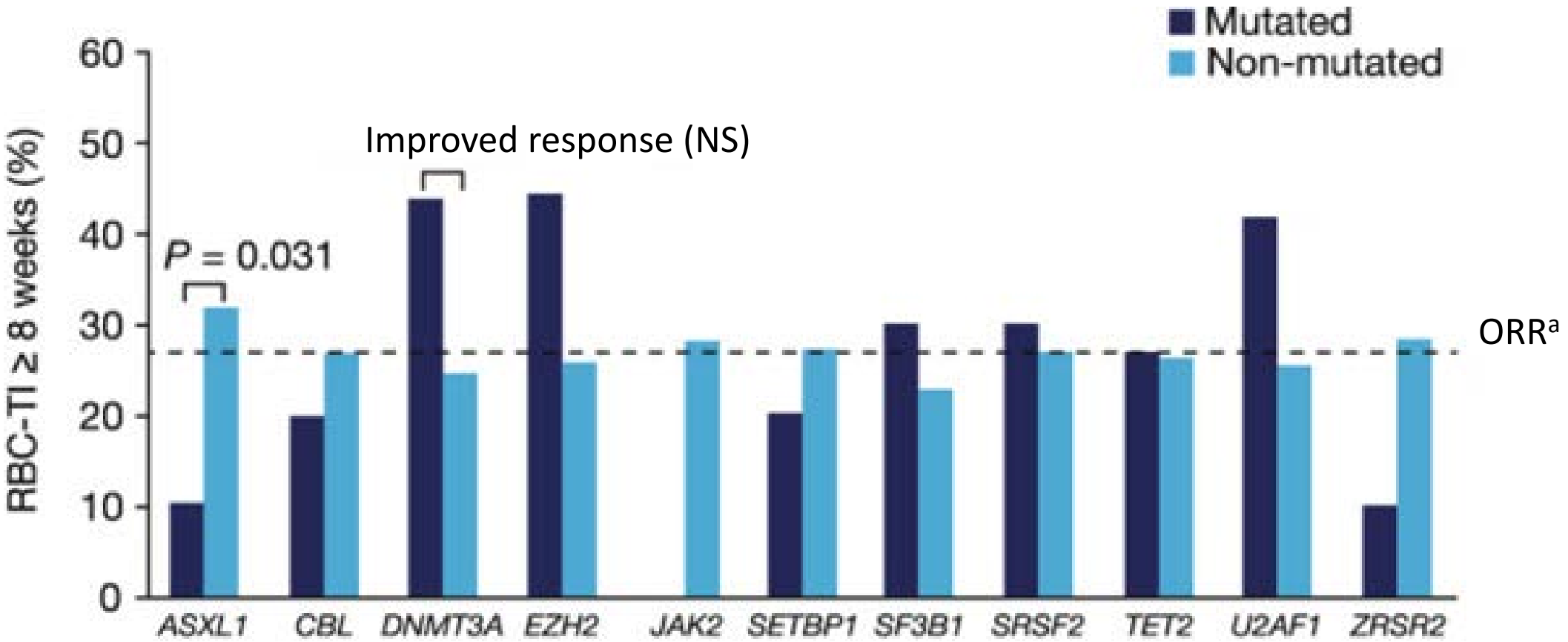
An Old Story: Lenalidomide in non-del5q MDS





Santini V J Clin Oncol. 2016 Sep 1;34(25):2988-96.

ASXL1 Mutation is Associated with Lower RBC-TI ≥8 Weeks Response While DNMT3a and EZH2 Mutations Tend to Have Major Responses in LEN-Treated non-del 5q Patients



[a]Dotted line represents the RBC-TI ≥ 8 weeks response rate in the overall population (26.9%)

Santini V et al. Leukemia. 2021 Mar;35(3):897-900.

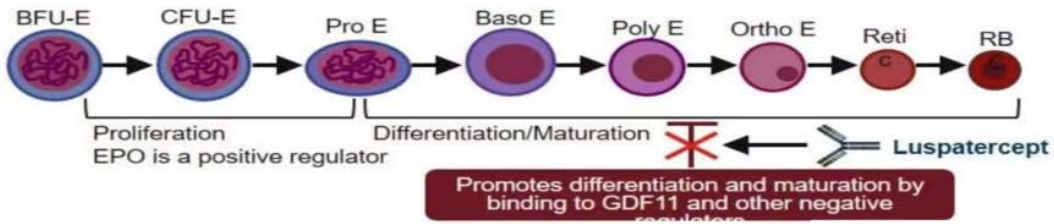
Luspatercept (ACE-536)

Structure

Luspatercept

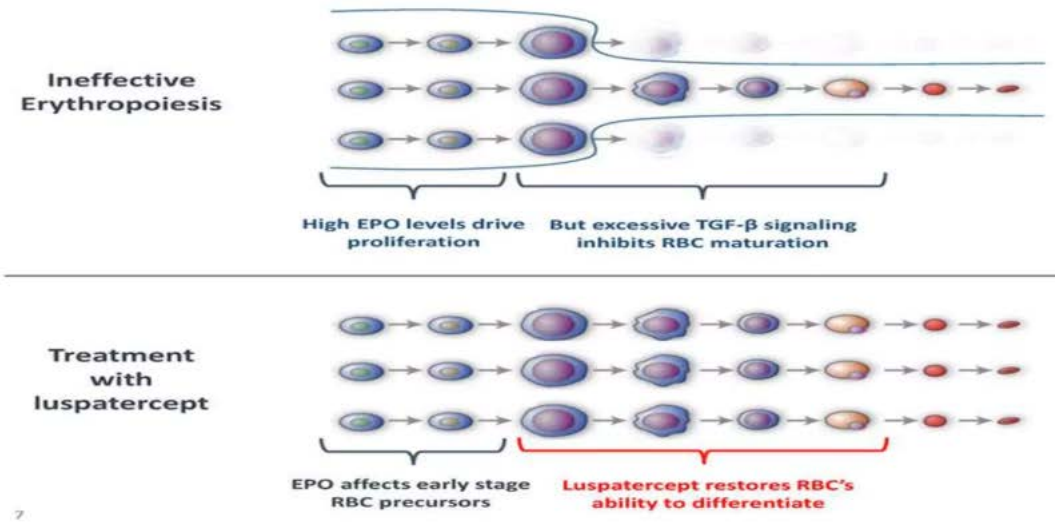
- Luspatercept is a modified activin receptor type IIB (ActRII fusion protein
- Acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 signaling; increased hemoglobin in healthy volunteers[a]
- In a murine model of β-thalassemia and MDS, murine analog RAP-536 promoted late-stage erythropoiesis, increased hemoglobin, and reduced disease burden[]

Mechanism of Action

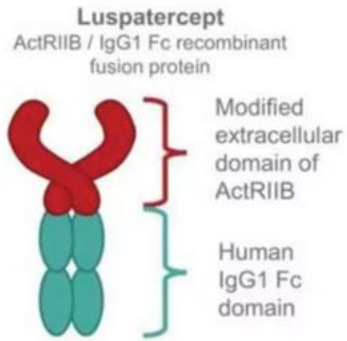


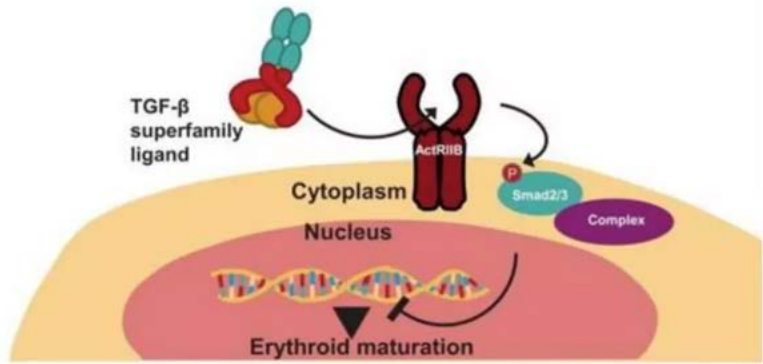
Luspatercept's Novel Mechanism to Treat Anemia

MDS, β-Thalassemia and Myelofibrosis



- First-in-class erythroid maturation agent
- Targets TGF-β ligands to block aberrant Smad2/3 signaling and augment late-stage erythropoiesis[1]





Camaschella. Br J Haematol. 2016;172:512.

MEDALIST Trial: Luspatercept in MDS RS with Transfusion Dependency

Inclusion Criteria

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

Randomized 2:1

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

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 3 weeks (n = 76)

Disease and response assessment
Week 24 and every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria

Patients followed ≥ 3 years post-final dose for AML progression, subsequent MDS treatment, and overall survival; crossover between groups was not allowed

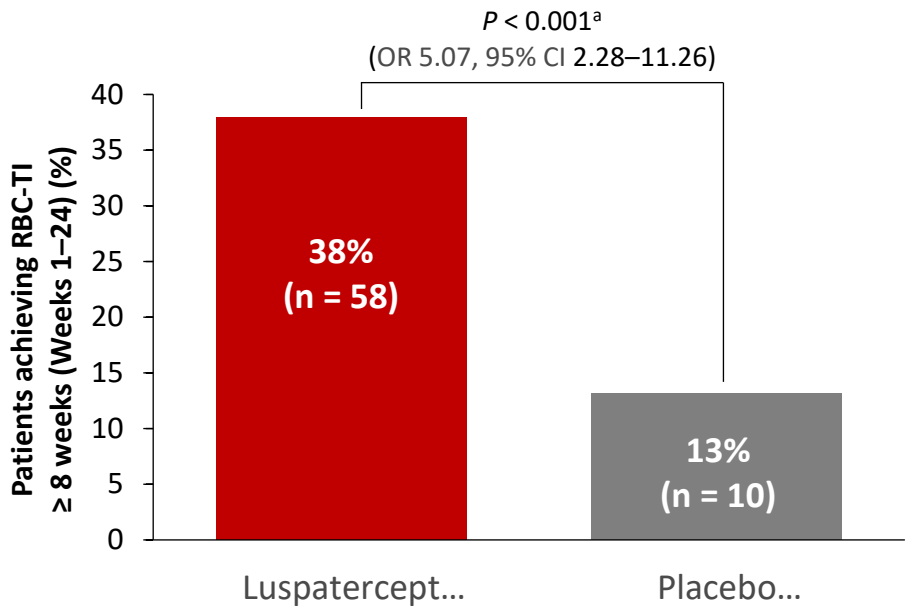
Primary analysis data cutoff date May 8, 2018; current data cutoff date July 1, 2019.

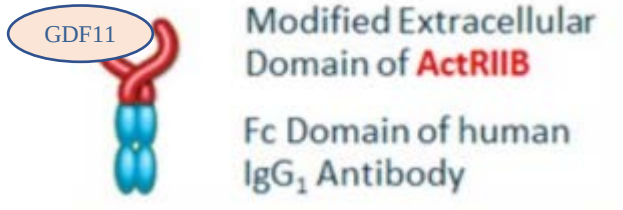
Patients were randomized between March 2016 and June 2017 at 65 sites in Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, Turkey, UK, and USA.

AML, acute myeloid leukemia; EPO, erythropoietin; HMA, hypomethylating agent; IMiD, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; WHO, World Health Organization.

Fenaux P et al. *N Engl J Med*. 2020;382:140-151.

Luspatercept Induces Transfusion Independence in *RS(+)* LR-MDS





n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Primary endpoint responders[b]	58 (37.9)	10 (13.2)
Responders with 1 response	22 (14.4)[c]	6 (7.9)
Responders with 2 responses	23 (15.0)	4 (5.26)
Responders with ≥ 3 responses	13 (8.5)	0

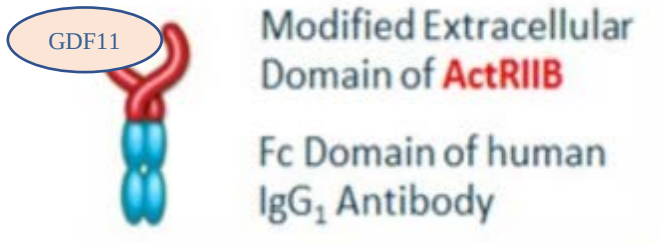
- Response rates were similar regardless of *SF3B1* allelic burden and total number of baseline somatic mutations
- The median duration of the longest single period of RBC-TI (by primary endpoint) was 30.6 weeks in the luspatercept arm compared with 13.6 weeks in the placebo arm

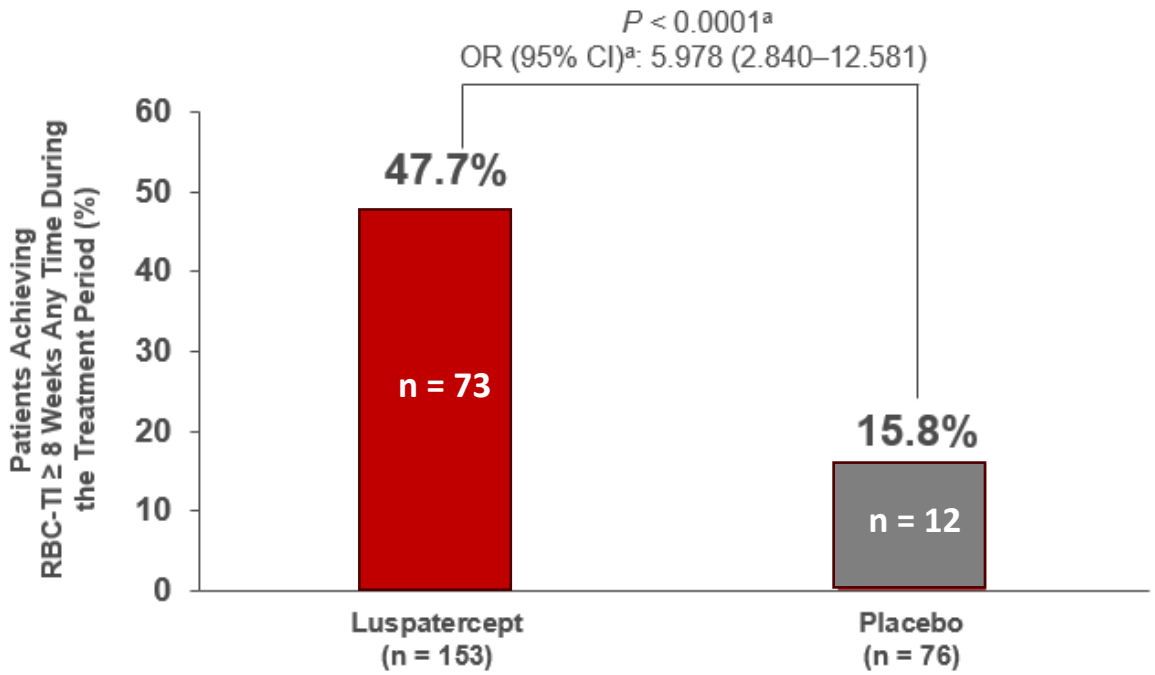
[a]Determined using a Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 vs < 6 units/8 weeks) and baseline IPSS-R score (Very low or Low vs Intermediate).
[b]Defined as the absence of any RBC transfusion during any consecutive 56-day period during Weeks 1–24. [c]Eleven patients were transfusion-free during the entire post-treatment period.

IPSS-R, International Prognostic Scoring System-Revised; OR, odds ratio; RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence.

Fenaux P et al. *N Engl J Med*. 2020;382:140-151.

Luspatercept Induces Transfusion Independence in *RS(+)* LR-MDS



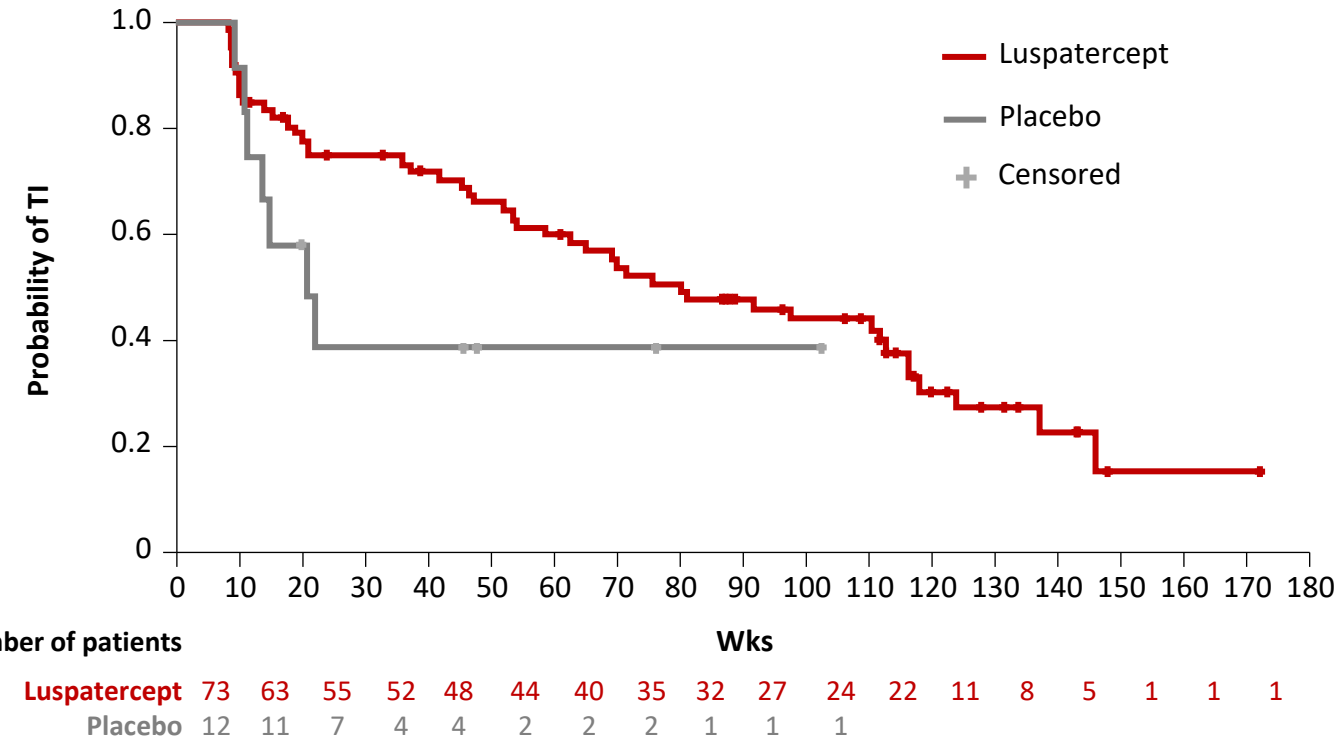


- When assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥ 8 weeks compared with placebo than previously reported (37.9% of patients receiving luspatercept achieved RBC-TI ≥ 8 weeks during Weeks 1–24 of treatment vs 13.2% of placebo-treated patients; P < 0.0001)

Luspatercept has been approved by FDA and EMA in 2020 (and Health Canada in 2021) for TD MDS-RS

Fenaux P et al. *N Engl J Med*. 2020;382:140-151.

MEDALIST Updated Analysis: Cumulative Duration of RBC-TI ≥ 8 Wks*

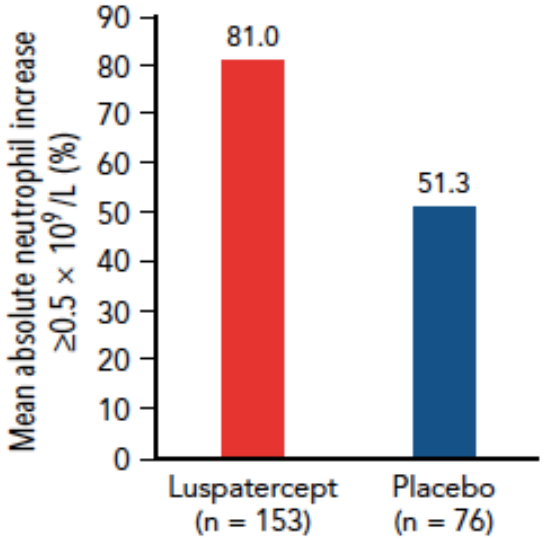


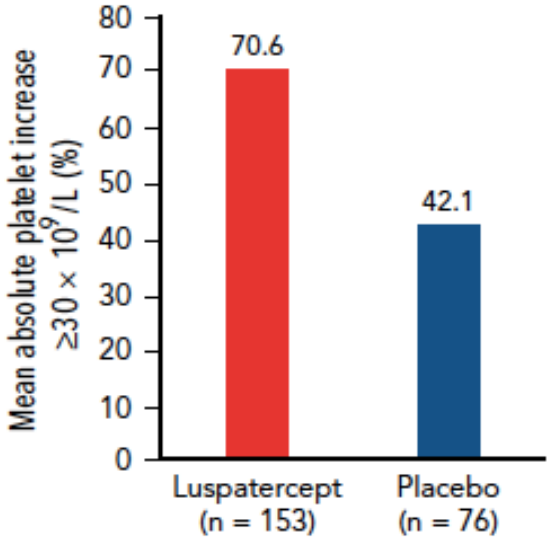
	Luspatercept (N = 73)	Placebo (N = 12)
Median duration	79.9 weeks	21.0 weeks
HR (95% CI)	0.485 (0.205-1.149)	

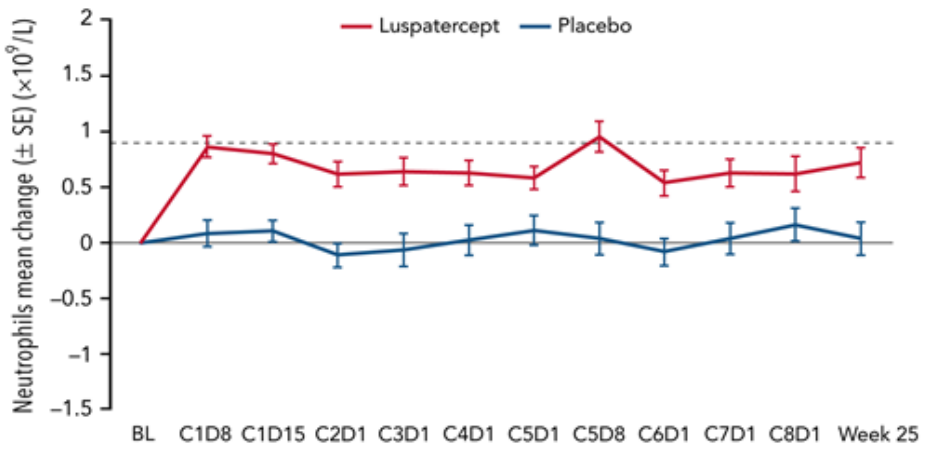
*Cumulative duration of RBC-TI ≥ 8 wks defined as sum of all periods of RBC-TI for pts attaining RBC-TI ≥ 8 wks during entire treatment period.

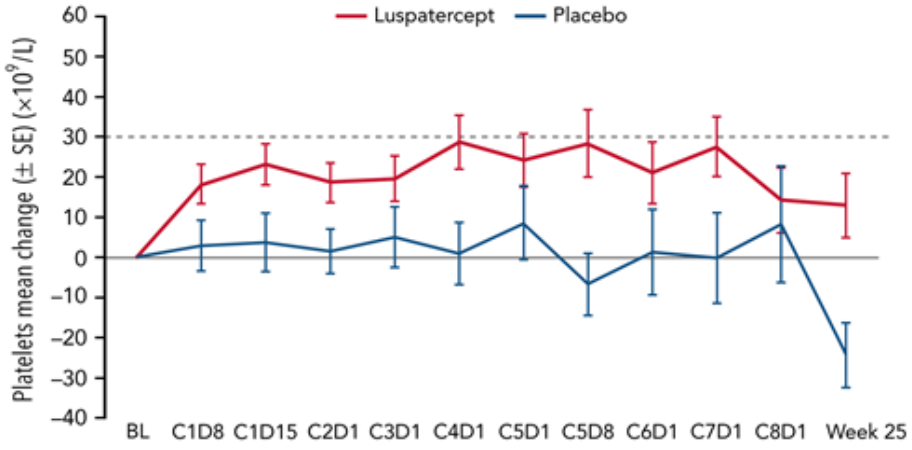
Fenaux. ASH 2019. Abstr 841.

Neutrophil and Platelet Increase During Luspatercpt Treatment



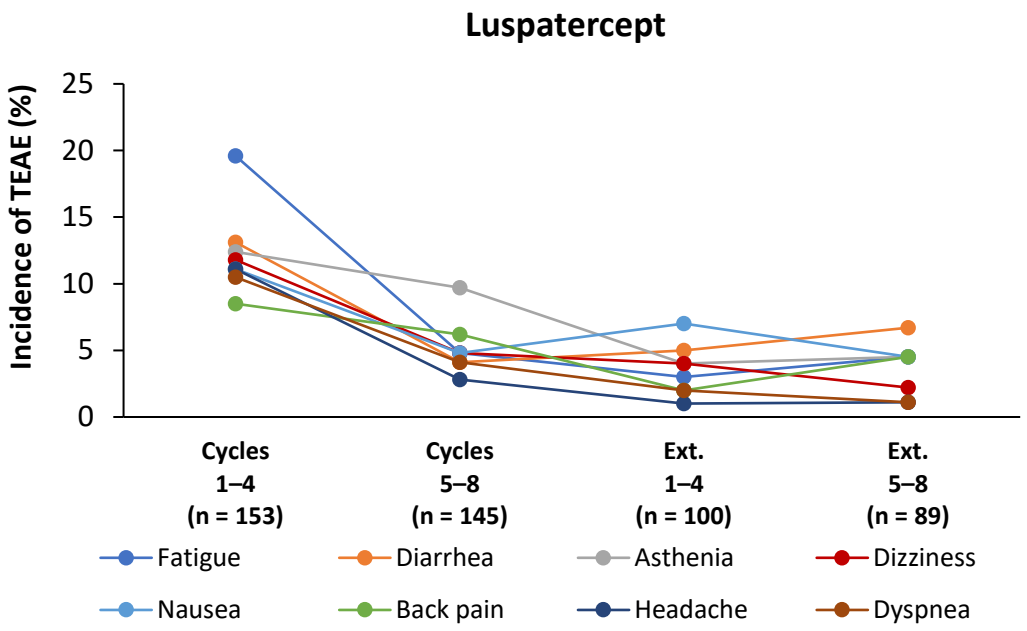


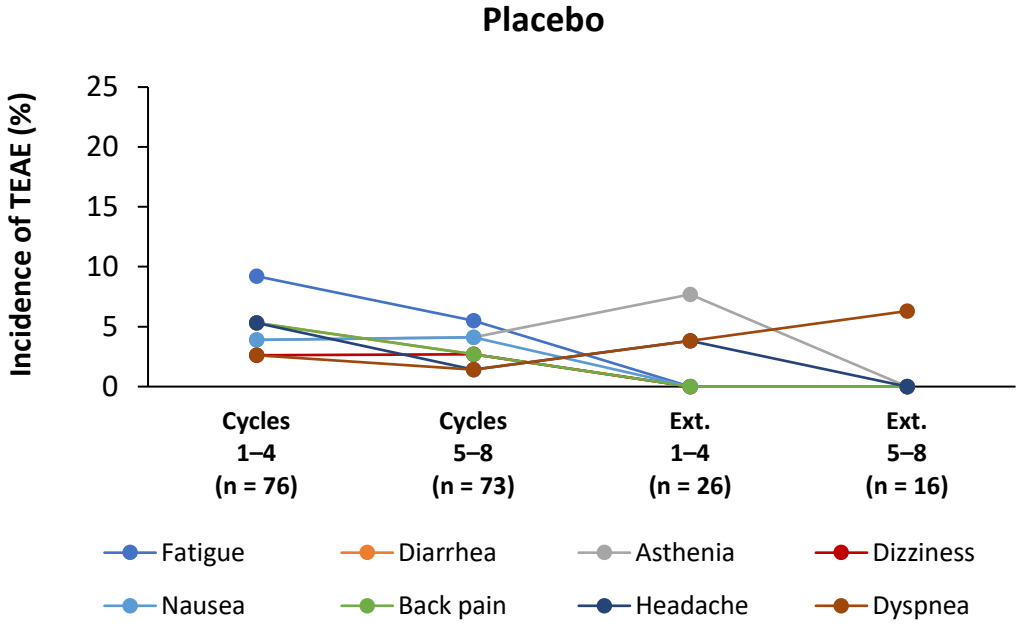




Garcia Manero et al. Blood. 2022;139(4):624-629.

SAFETY: Frequent TEAEs (ANY GRADE) by Treatment Cycle



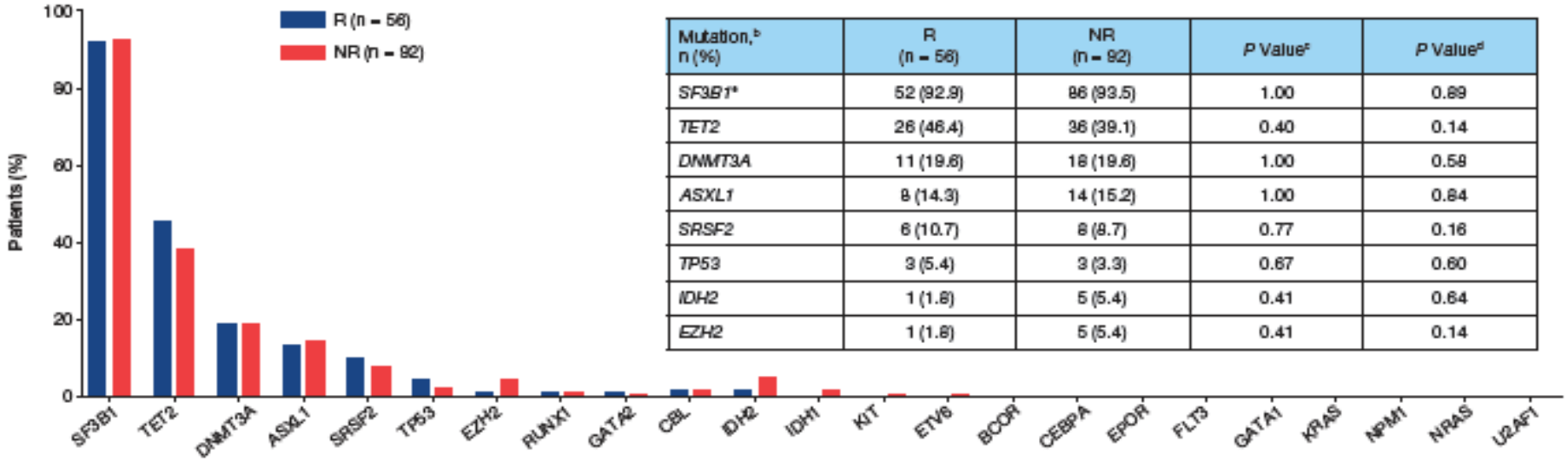


- New onset of TEAEs generally decreased over time in both treatment arms during the first 24 weeks of the study

Data cutoff: July 1, 2019.

Luspatercept Significantly Reduces RBC TB, Regardless of Gene Mutation Frequency, Spectrum, and Prognostic Significance Among LR MDS Patients Enrolled in the MEDALIST Trial

Figure 3. Frequency of Mutations at Baseline for Patients Treated With Luspatercept in the MEDALIST Trial, Classified by Response[a]



Mutation,[b] n (%)	R (n = 56)	NR (n = 92)	*P* Value[c]	*P* Value[d]
SF3B1[e]	52 (92.9)	86 (93.5)	1.00	0.89
TET2	26 (46.4)	36 (39.1)	0.40	0.14
DNMT3A	11 (19.6)	18 (19.6)	1.00	0.58
ASXL1	8 (14.3)	14 (15.2)	1.00	0.84
SRSF2	6 (10.7)	8 (8.7)	0.77	0.16
TP53	3 (5.4)	3 (3.3)	0.67	0.60
IDH2	1 (1.8)	5 (5.4)	0.41	0.64
EZH2	1 (1.8)	5 (5.4)	0.41	0.14

Figure 4. Frequency of Number of Mutations at Baseline in Responders and Non-Responders Treated With Luspatercept in the MEDALIST Trial[a]

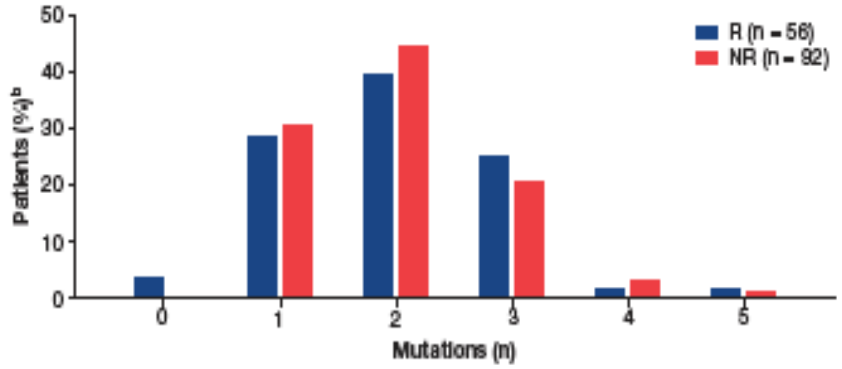
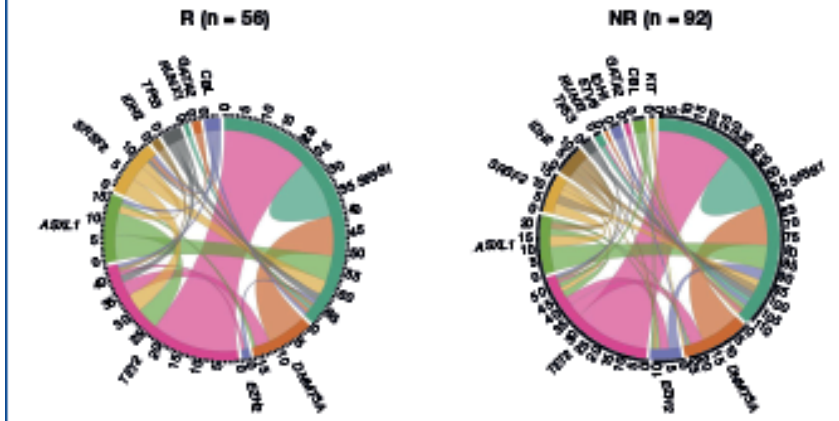


Figure 6. Co-Occurrence of Mutations for Patients Treated With Luspatercept in the MEDALIST Trial, Classified by Response[a]



Platzbecker et al. ASH 2019.

The COMMANDS Study

The COMMANDS study (NCT03682536) is a phase 3, global, open-label, randomized trial comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R LR-MDS in ESA-naive patients who require RBC transfusions

Key eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low, or intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2–6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline sEPO level
- Baseline RBC transfusion burden
- RS status

Randomized 1:1

Luspatercept (N = 178)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 178)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG criteria

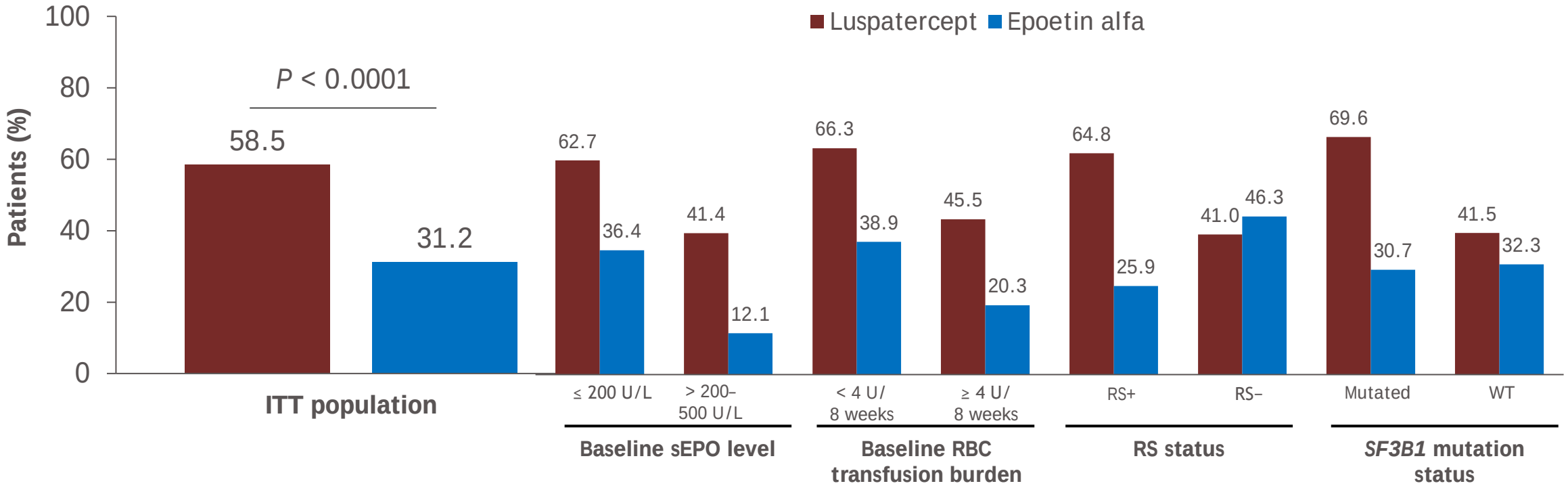
Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

[a]MDS with del(5q) were excluded. [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline; AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndromes; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Primary Endpoint: Luspatercept Superior to Epoetin Alfa

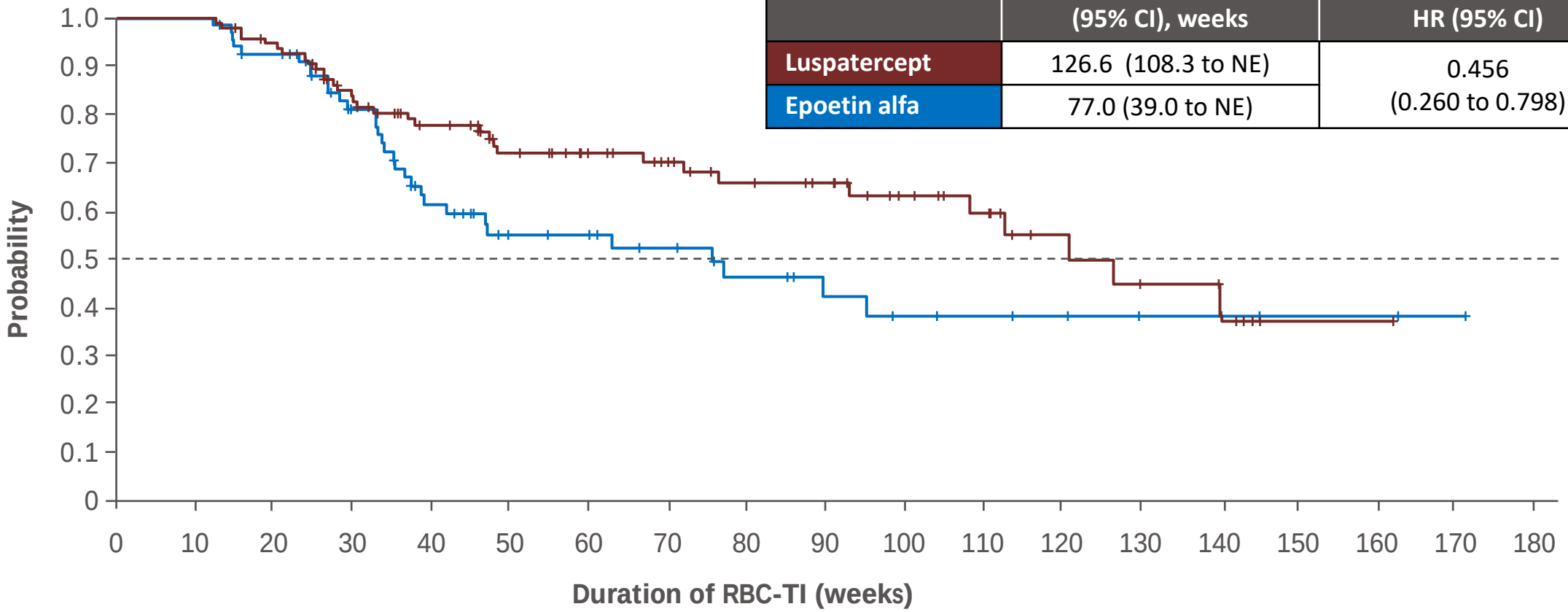
- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
  - Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed



This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment.

Duration of RBC-TI ≥ 12 weeks[a]

	Median duration (95% CI), weeks	HR (95% CI)
Luspatercept	126.6 (108.3 to NE)	0.456 (0.260 to 0.798)
Epoetin alfa	77.0 (39.0 to NE)	



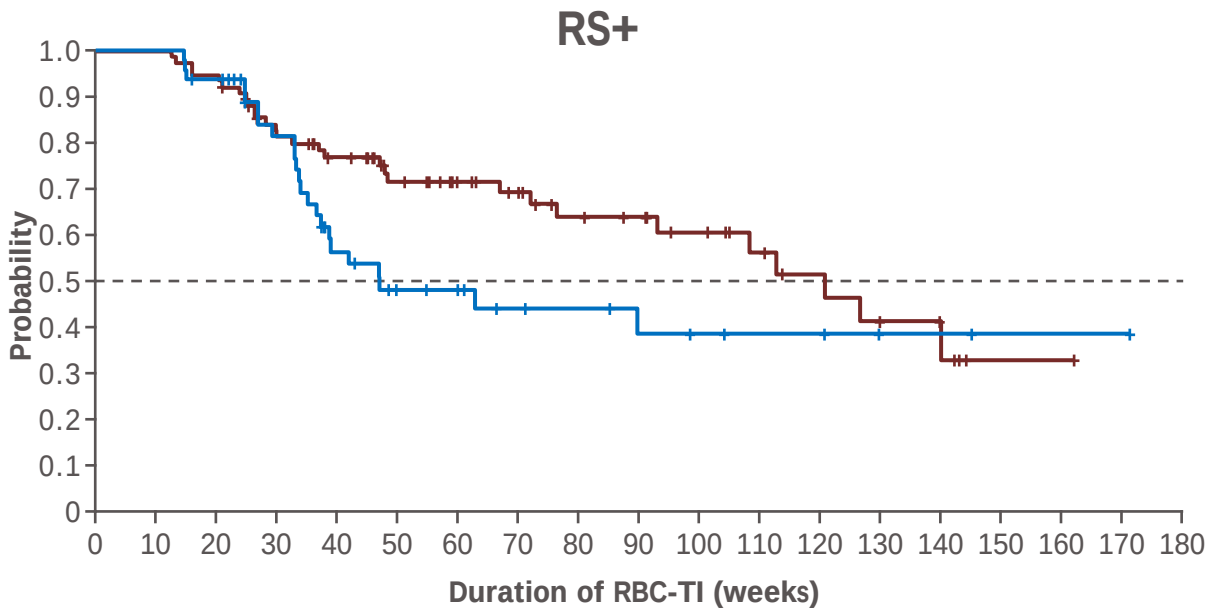
No. at risk

Luspatercept	98	98	91	74	61	49	42	37	31	28	21	17	11	8	6	1	1	0	
Epoetin alfa	71	71	63	47	33	24	23	19	15	11	9	8	7	5	5	2	2	1	0

EOT, end of treatment; NE, not estimable; RBC-TI, red blood cell transfusion independence.
[a]In ITT responders during weeks 1–EOT.

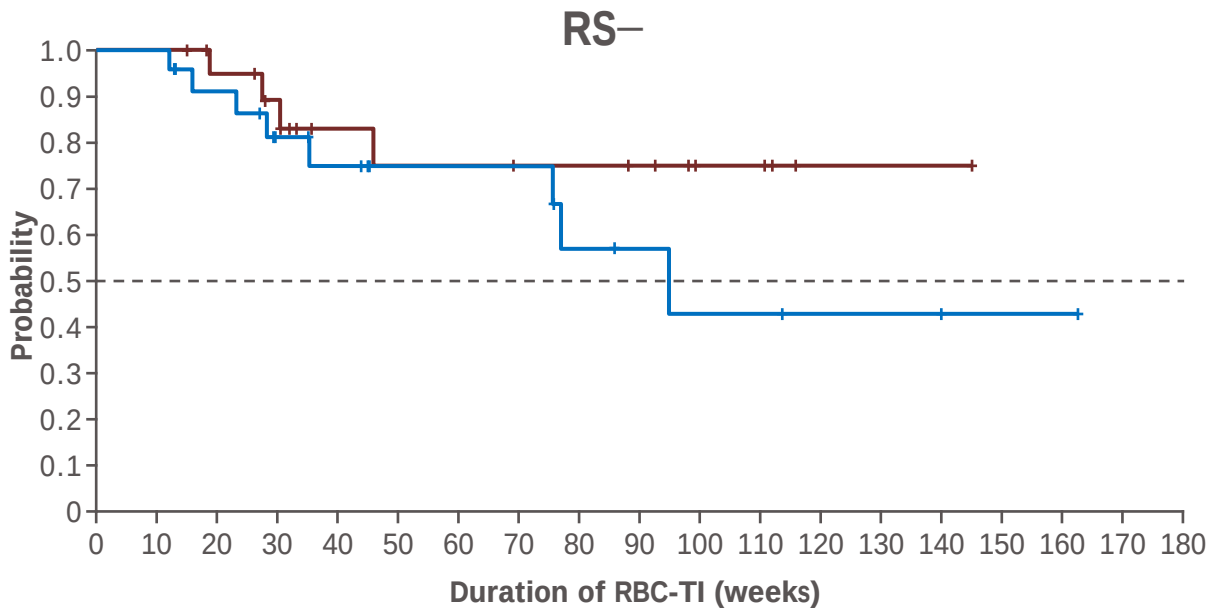
Duration of RBC-TI ≥ 12 weeks[a]: RS subgroups

Median duration (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
RS+	120.9 (76.4 to NE)	47.0 (36.6 to NE)	**0.626 (0.361 to 1.085)**
RS–	NE (46.0 to NE)	95.1 (35.3 to NE)	**0.492 (0.148 to 1.638)**



No. at risk

Luspatercept	77	77	73	59	51	40	33	29	23	21	17	13	10	7	5	1	1	0	
Epoetin alfa	48	48	44	33	21	15	14	10	9	7	6	5	5	3	3	1	1	1	0



No. at risk

Luspatercept	21	21	18	15	10	9	9	8	8	7	4	4	1	1	1	0			
Epoetin alfa	23	23	19	14	12	9	9	9	6	4	3	3	2	2	2	1	1	0	

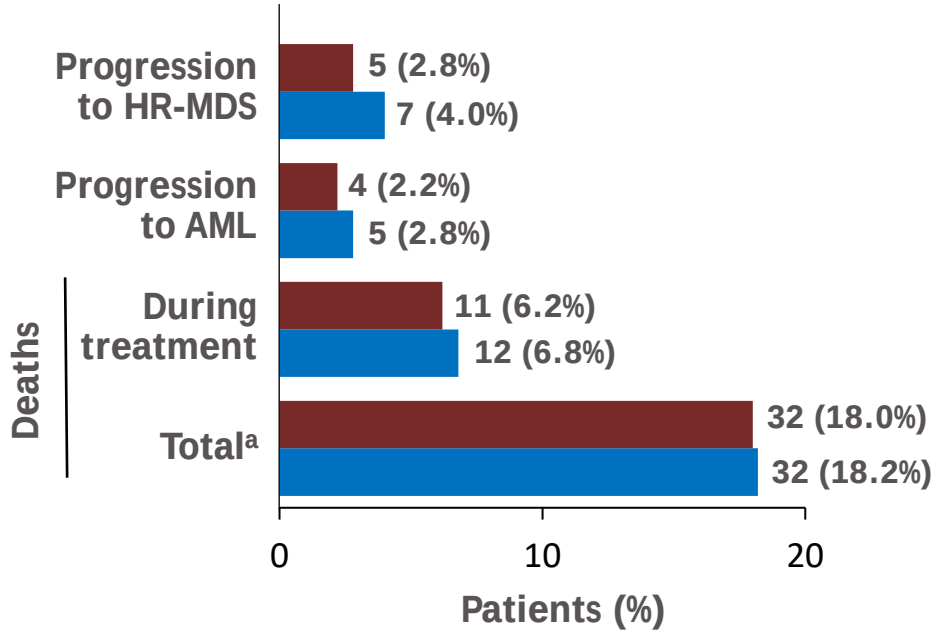
EOT, end of treatment; NE, not estimable; RBC-TI, red blood cell transfusion independence.
[a]In ITT responders during weeks 1–EOT.

Safety

	Luspatercept (N = 178)		Epoetin alfa (N = 176)	
Patients, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

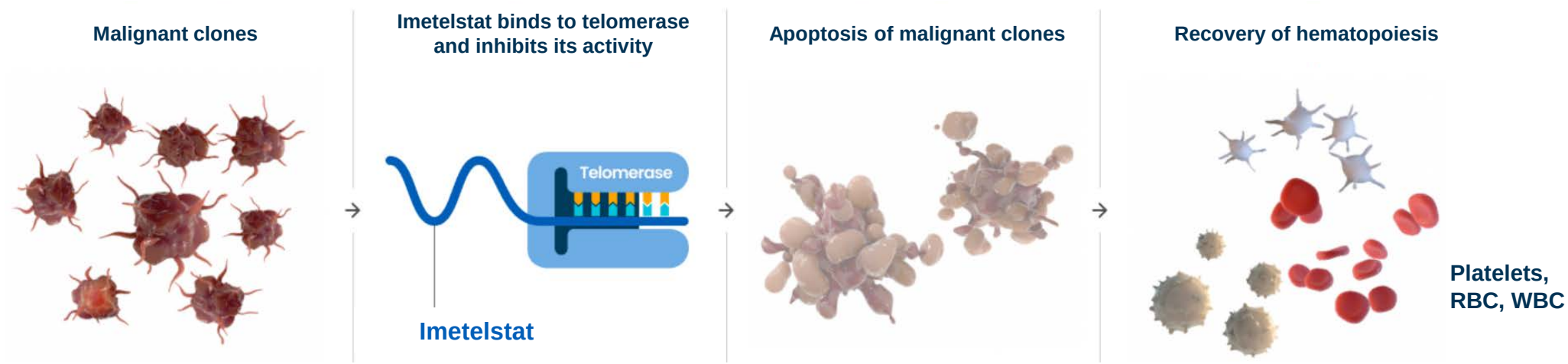
TEAEs of any grade
164 (92.1%) luspatercept
150 (85.2%) epoetin alfa

Treatment duration, median (range), weeks
41.6 (0–165) luspatercept
27.0 (0–171) epoetin alfa



Safety data are not exposure-adjusted.
[a]Deaths during treatment period and post-treatment period. TEE, thromboembolic event.

Imetelstat in Lower Risk MDS



- Imetelstat is a first-in class direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[1-4]
- In the phase 2 part of the IMerge study (NCT02598661), patients with LR-MDS who were heavily RBC transfusion dependent, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA achieved durable and continuous RBC-TI when treated with imetelstat[5]
  - Specifically, 8-week RBC-TI rates were 42% with a median TI duration of 86 weeks
- This analysis reports phase 3 results from IMerge in the same patient population

Platzbecker U et al. EHA 20223

IMerge Subgroup Analysis: Study Design

- International, double-blind, randomized phase III trial

Stratified by transfusion burden (4-6 vs >6 U) and IPSS-R category (low vs intermediate-1)

Patients with low-risk or intermediate-1–risk MDS (IPSS-R); R/R* to ESA or EPO >500 mU/mL (ESA ineligible); RBC transfusion dependent (≥4 U/8 wk over 16 wk prestudy); non-del(5q); no prior lenalidomide or HMAs
(N = 178)

2:1

Imetelstat
7.5 mg/kg IV Q4W
(n = 118)

Placebo
(n = 60)

Supportive Care
RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy as needed at discretion of investigator

Primary endpoint: 8-wk RBC-TI

Secondary endpoints: 24-wk RBC-TI, TI duration, HI-E, safety

This analysis

Subgroup analysis: rates of RBC-TI vs placebo across IPSS, IPSS-R, IPSS R cytogenetic, and IPSS-M risk categories

*Received ≥8 wk of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per wk) without Hgb rise ≥1.5 g/dL or decrease in RBC transfusion requirement ≥4 U/8 wk, transfusion dependence, or reduction of Hgb by ≥1.5 g/dL after hematopoietic improvement from ≥8 wk of ESA treatment.

NCT02598661. Platzbecker. Lancet. 2023;[Epub]. Komrokji. ASH 2023. Abstr 194.

IMerge Subgroup Analysis: Rates of Durable Transfusion Independence

RBC-TI Response, %	Rates of Durable RBC-TI Over Time		
	Imetelstat	Placebo	*P* Value
≥ 8-Wk RBC-TI*	40	15	<.0008
≥ 16-Wk RBC-TI	31	7	<.0002
≥ 24-Wk RBC-TI	28	3	<.0001
≥ 1-Yr RBC-TI	18	2	<.0023

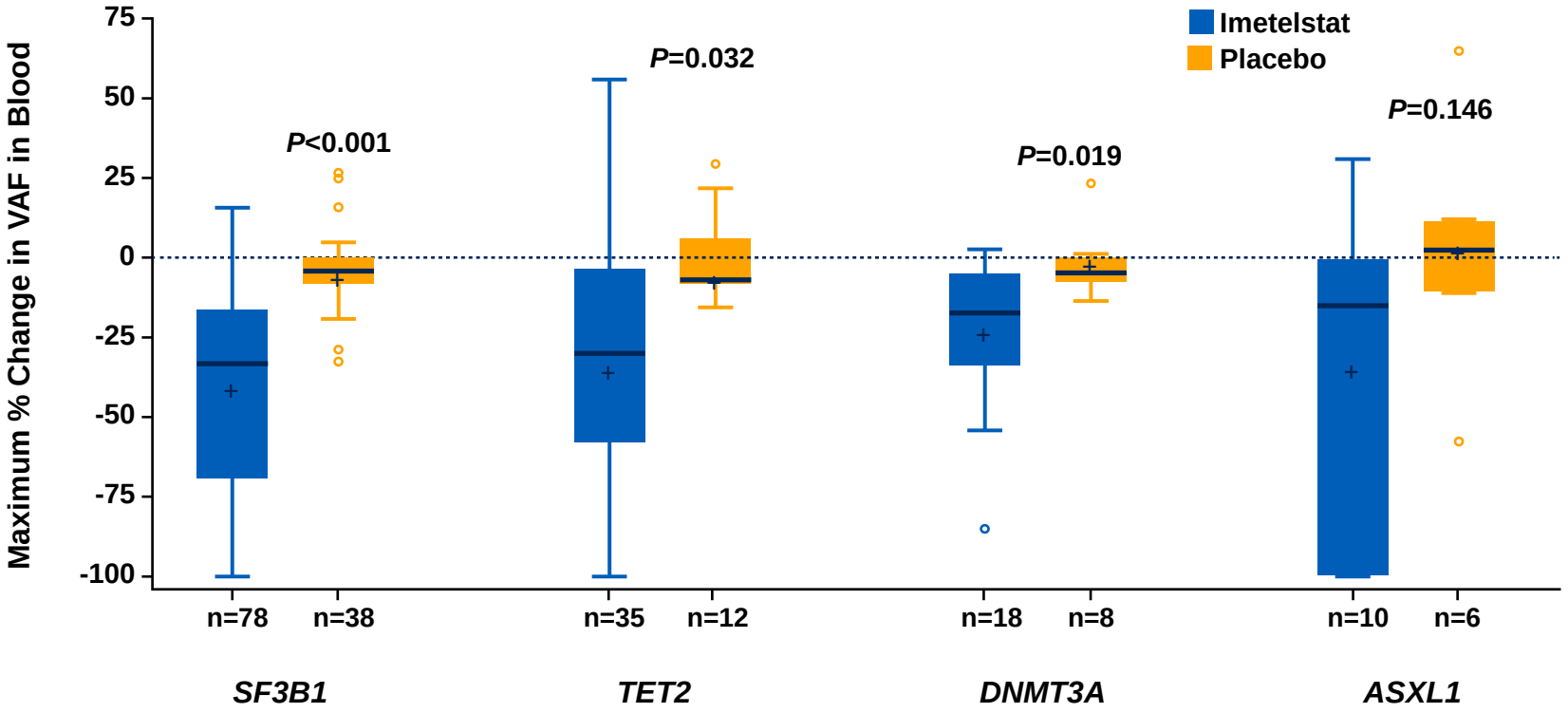
*Primary endpoint.

- Single continuous RBC-TI period was achieved by most 8-wk responders to imetelstat (83%)

Platzbecker. Lancet. 2023;[Epub]. Komrokji. ASH 2023. Abstr 194.

Reductions in VAF of Genes Frequently Mutated in MDS Were Greater With Imetelstat vs Placebo

- Mutations on 36 genes associated with MDS was tested by NGS on samples taken from baseline and post-treatment
- Among patients with evaluable mutation data, the maximum reductions in VAF of the *SF3B1*, *TET2*, *DNMT3A, and ASXL1* genes were greater with imetelstat than placebo

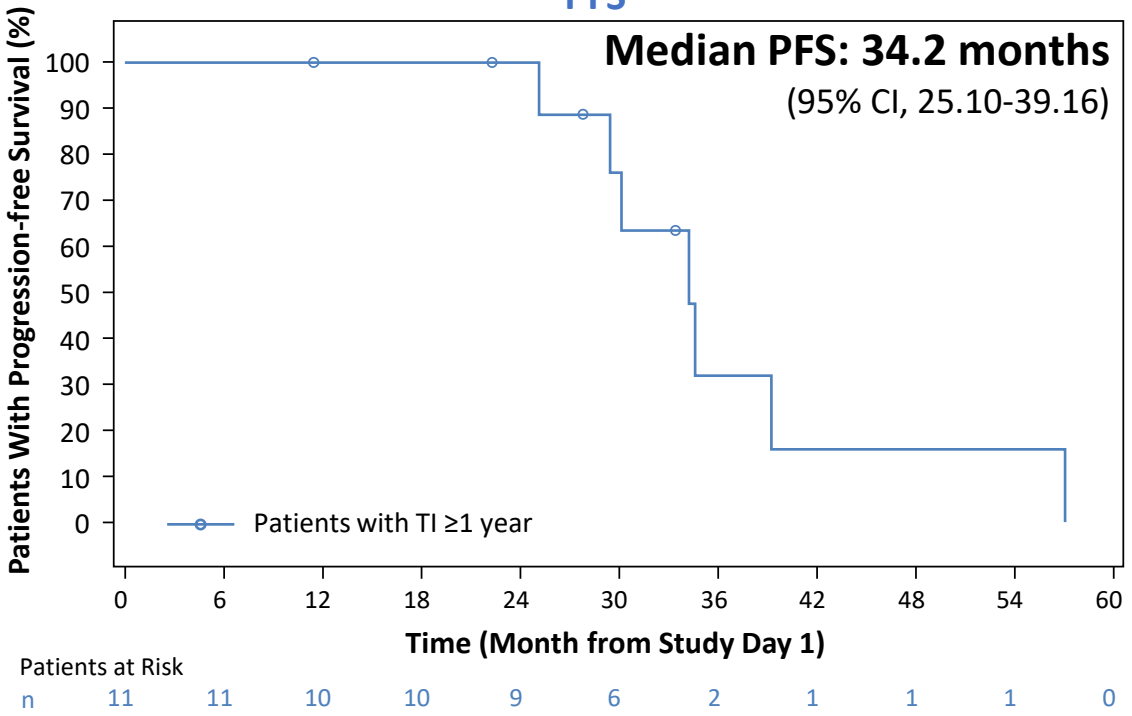


Some patients had 100% reduction/complete disappearance

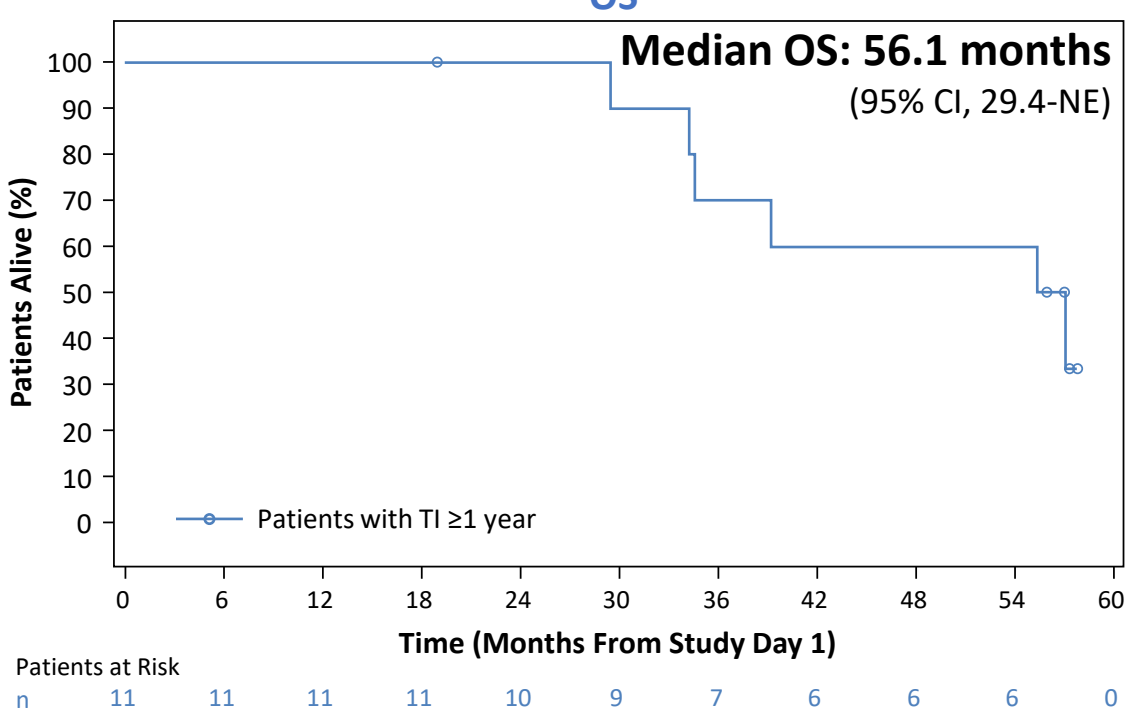
Platzbecker U et al. EHA 20223

Robust PFS and Survival of Imetelstat-Treated Patients With TI ≥1 Year

PFS



OS



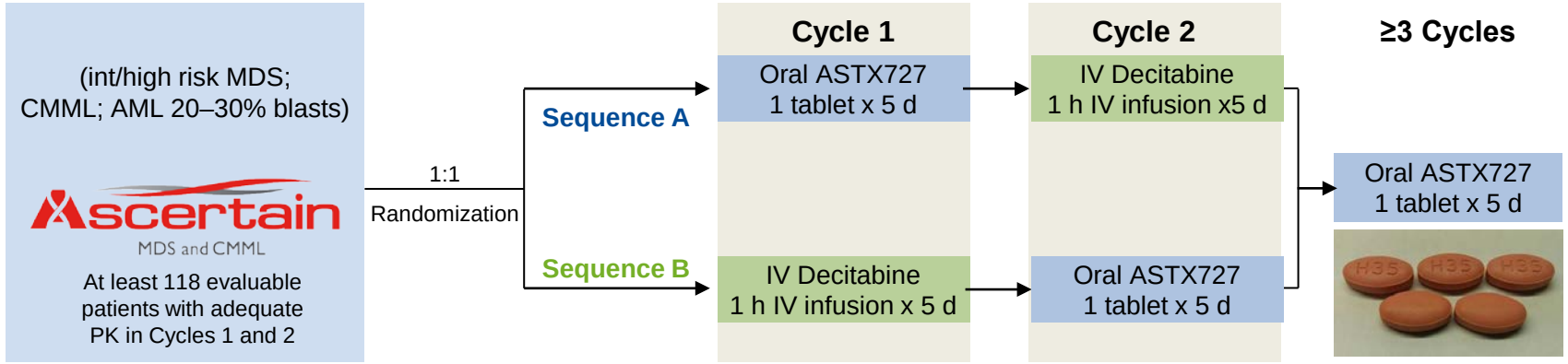
- After a median follow-up of 57 months, no progressions to AML were observed among the ≥1-year TI responders

Parameter	Patients with TI ≥1 year (n=11)	Others (n=27)	Target population (N=38)
Median PFS, months (95% CI)	34.2 (25.1, 39.2)	25.5 (11.5, 44.2)	34.2 (25.1, 41.4)
Median OS, months (95% CI)	56.1 (29.4, NE)	47.1 (38.1, NE)	55.2 (38.1, 67.1)

Data cutoff: October 13, 2022.
Based on the Kaplan-Meier method.
AML, acute myeloid leukemia; NE, not evaluable; OS, overall survival; PFS, progression-free survival; TI, transfusion independence.

Platzbecker et al. ASH 2022 Abstract #459.

ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML
Trial Design: Randomized Cross-Over



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

ASTX727 Phase 3 Baseline Characteristics Randomized Treated Population

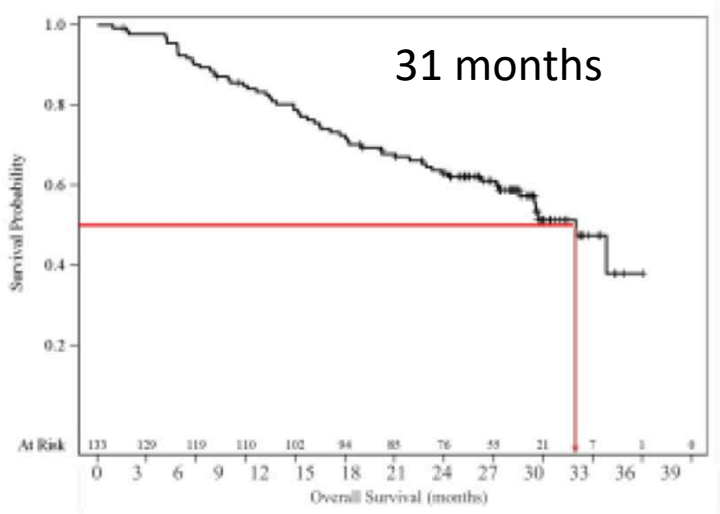
[1] Oral ASTX727 in Cycle 1 IV decitabine in Cycle 2
[2] IV decitabine in Cycle 1 Oral ASTX727 in Cycle 2

		Sequence A[1] N=66	Sequence B[2] N=67	Total Treated N=133
Median age, y (range)		70 (44-85)	72 (49-88)	71 (44–88)
Sex	Male	64%	67%	65%
	Female	36%	33%	35%
Median weight, kg (range)		79 (45-158)	85 (51-127)	83 (45 -158)
Median BSA, m^2 (range)		1.93 (1.4-2.9)	2.0 (1.5-2.6)	1.99 (1.4 - 2.9)
CMML		8%	16%	12%
MDS, IPSS classification	High risk	21%	11%	16%
	Int-1 and 2	65%	63%	64%
	Low risk	6%	10%	8%
Transfusion dependent	RBCs	39%	39%	39%
	Platelets	9%	6%	7.5%
ECOG PS	0	38%	45%	41%
	1	62%	55%	59%

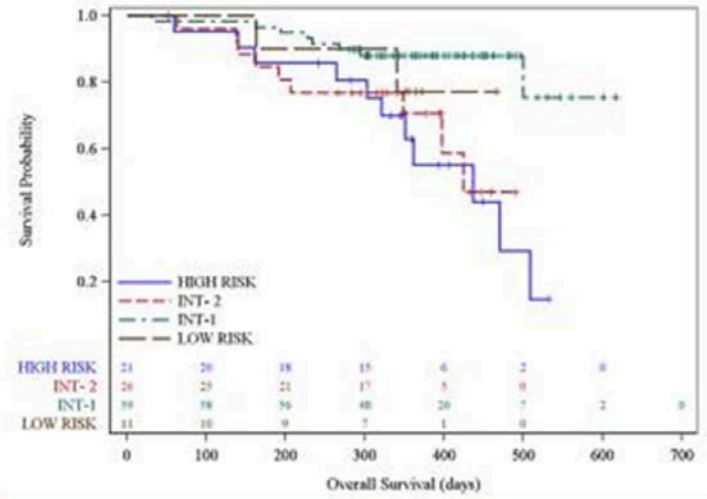
Table 4. Response analysis from ASTX727-02 (Phase 3)[4]

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22%)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)
HI-erythroid	2 (1.5%)	(0.2,5.3)
HI-neutrophils	1 (0.8%)	(0.0,4.1)
HI-platelet	7 (5.3%)	(2.1,10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7%)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

OS



7. ASCERTAIN (ASTX727-02/Phase 3) Overall Survival by IPSS [120-day Safety Update Data – November 1, 2019]



ASCERTAIN Results for LOWER risk MDS

- 69/133 (52%) patients had lower risk MDS
- 40% were transfusion dependent of red cells
- 9% were transfusion dependent of plts

- Results:
  - Overall response rate 56%
  - CR duration 15 months
  - Median time to best response 4 months
  - 26% proceeded to stem cell transplant

Results: Transfusion Independence

Place video here

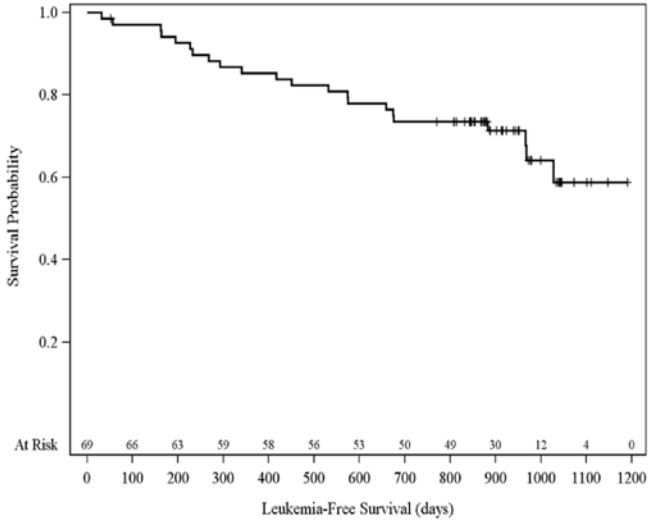
	RBC Transfusion Dependent on Entry (N=27)	Platelet Transfusion Dependent on Entry (N=6)
Transfusion independent at 56-days	13 (48.1%) (28.7, 68.1)	4 (66.7%) (22.3, 95.7)
Transfusion independent at 84-days	11 (40.7%) (22.4, 61.2)	2 (33.3%) (4.3, 77.7)

Garcia-Manero G, ASH 2021

OS and LFS not Reached in Lower Risk Subset

Results: ASCERTAIN Leukemia-Free Survival in Lower Risk Patients

Place video here

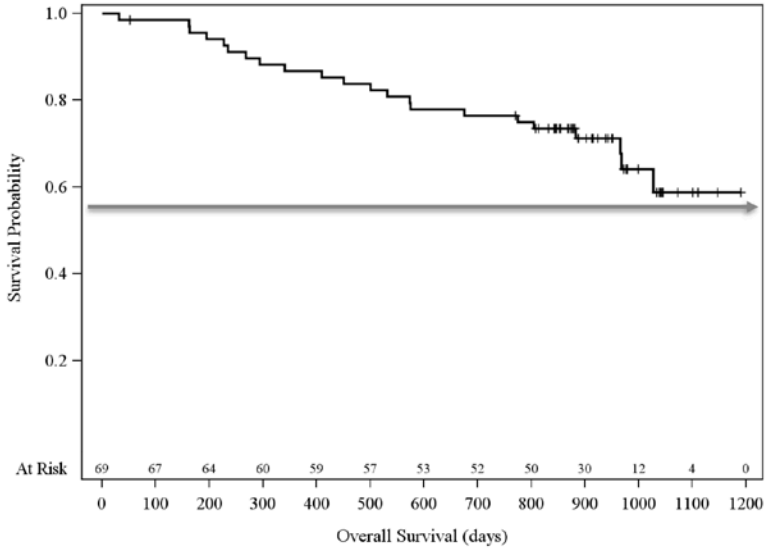


- Median follow up is ~32 months.
- For events of leukemia or death, median time has not yet been reached.
- 95% CI (31.7 months, NE).

NE = not estimable

Results: ASCERTAIN Overall Survival in Lower Risk patients (N=69)

Place video here



- Median follow up is ~32 months.
- mOS has not yet been reached.
- 95% CI (31.7 months, NE).

NE = not estimable

Garcia-Manero, ASH 2021

Higher Risk Disease

Study Design for M15-531

Phase 1b Study of Venetoclax Plus Azacitidine in Patients With Treatment-Naive Higher-Risk Myelodysplastic Syndromes[1]

Patients (N=107)

- Adult patients with de novo treatment-naive HR MDS defined by IPSS/IPSS-R risk categories (IPSS score ≥1.5 or IPSS-R score >3)
- BM blasts <20% at baseline
- ECOG PS ≤2
- No prior therapy for MDS or with a BH3 mimetic
- No prior SCT or solid organ transplantation
- No history of an active malignancy within the past 2 years prior to study entry[a]

Primary End Point

- CR per IWG 2006

Venetoclax 400 mg orally daily on Days 1–14 of each 28-day cycle[b]
+
Azacitidine 75 mg/m^2 IV or SC on Days 1–7 or Days 1-5, 8, 9

Treatment until progression

Key Secondary End Points

- mCR, ORR, DOR, DoCR: per IWG 2006
- TTNT, overall survival
- Safety
- Hematologic improvement
- Postbaseline RBC and platelet TI
- Rate, time to AML transformation

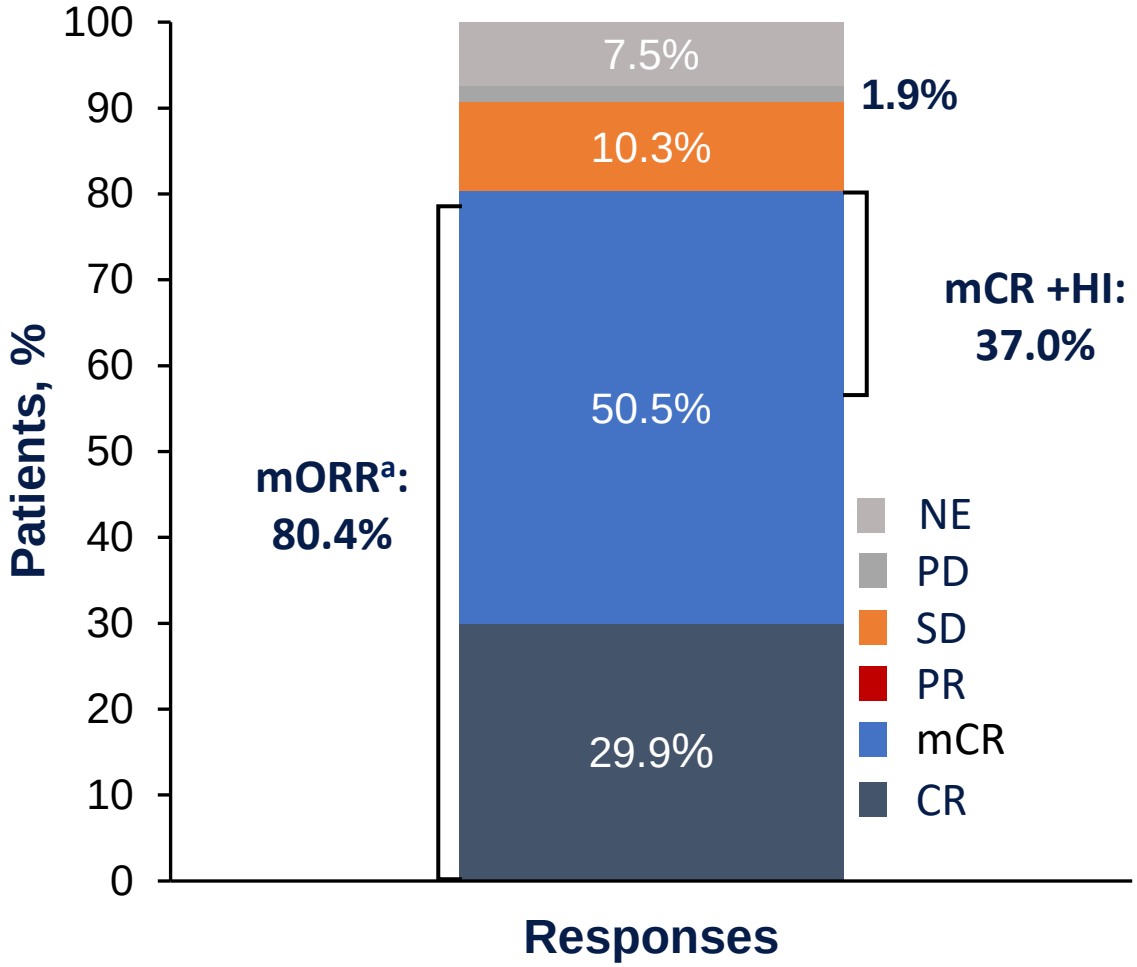
[a]With the exception of asymptomatic prostate cancer without known metastases and no requirement for therapy; adequately treated in situ carcinoma of the cervix uteri; adequately treated basal cell/localized squamous cell carcinoma of the skin. [b]Prophylactic antibiotics were mandated in Cycle 1 and for patients with grade ≥3 neutropenia thereafter.

1. ClinicalTrials.gov. Accessed August 15, 2023. https://www.clinicaltrials.gov/study/NCT02942290

AML, acute myeloid leukemia; BH3, BCL-2 Homology 3; BM bone marrow; CR, complete remission; DOR, duration of response; DoCR, duration of CR; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS-R, International Prognostic Scoring System-Revised; IV, intravenous; IWG, International Working Group; mCR, marrow complete remission; MDS, myelodysplastic syndromes; ORR, overall response rate; RBC, red blood cell; SC, subcutaneous; SCT, stem cell transplantation; TTNT, time to next treatment, TI, transfusion independence.

Best Responses for Ven 400 mg + Aza

>80% of Patients Who Received Ven + Aza Responded

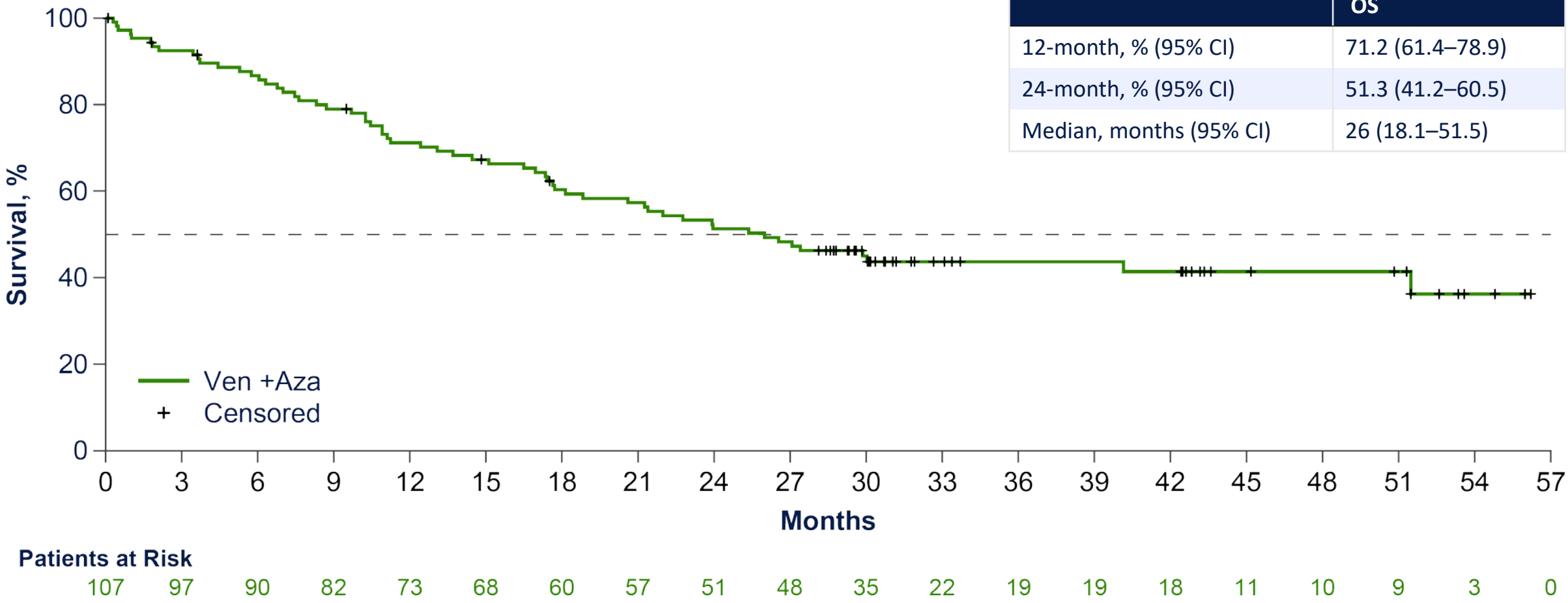


- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

[a]mORR=CR+mCR+PR; PR, n=0; response rates based on International Working Group 2006 response criteria.
AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; MDS, myelodysplastic syndromes; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

Overall Survival[a] for Patients Who Received Ven 400 mg + Aza

	OS
12-month, % (95% CI)	71.2 (61.4–78.9)
24-month, % (95% CI)	51.3 (41.2–60.5)
Median, months (95% CI)	26 (18.1–51.5)



[a]Overall survival was defined as the number of months from the date of the first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Aza, azacitidine; OS, overall survival; Ven, venetoclax.

Transfusion Independence and Hematologic Improvement

	N=107
TD to TI conversion rate, n/N (%)	
RBC	26/56 (46.4)
Platelets	7/18 (38.9)
RBC and platelets	24/59 (40.7)
Postbaseline TI, n (%) [95% CI]	
RBC	66 (61.7) [51.8–70.9]
Platelets	77 (72.0) [62.5–80.2]
RBC and platelets	61 (57.0) [47.1–66.5]
Median maximal duration of TI achieved, months (range)	
RBC	5.4 (1.8–50.8)
Platelets	5.4 (1.9–56.0)
Postbaseline hematologic improvement, n/N (%) [95% CI]	51/104 (49.0) [39.1–59.0]
Erythroid	40/93 (43.0) [32.8–53.7]
Platelet	31/74 (41.9) [31.8–55.3]
Neutrophil	10/57 (17.5) [8.7–29.9]

RBC, red blood cells; TD, transfusion dependence; TI, transfusion independence.

Other agents under investigation but not yet available

- **IDH1 inhibitor (ivosedinib)**
- **IDH2 inhibitor (enasidinib)**

- **Being tested alone (after AZA or DEC stops working) or front line in combination with HMA.**

Clinical trials in MDS in Ontario

- MDS-CAN registry
- MDS-CVD: screening cardiac CT and 2DECHO, correlation with somatic mutations
  - For whom: diagnosed at Sunnybrook within last year, banked BM DNA
- ELEMENT study: Anemic (Hgb < 95) but symptomatic and not yet transfusion dependent, untreated lower risk MDS: RCT Luspatercept vs EPREX. OPEN
- Maxillus study: TD untreated lower risk MDS: maximal dose of luspatercept vs EPREX COMING

Thank you!

Questions