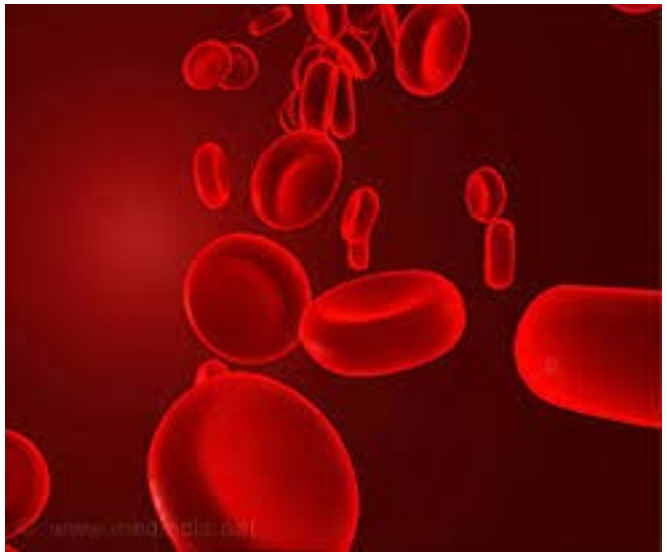

The Old And The New In MDS management

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FEB 9, 2023

Disclosures

Honoraria and consultancy:
- Novartis
- Pfizer
- Paladin
- Astellas
- Jazz
- Taiho
- Abbvie
- BMS

Slide deck derived from previous training deck by BMS

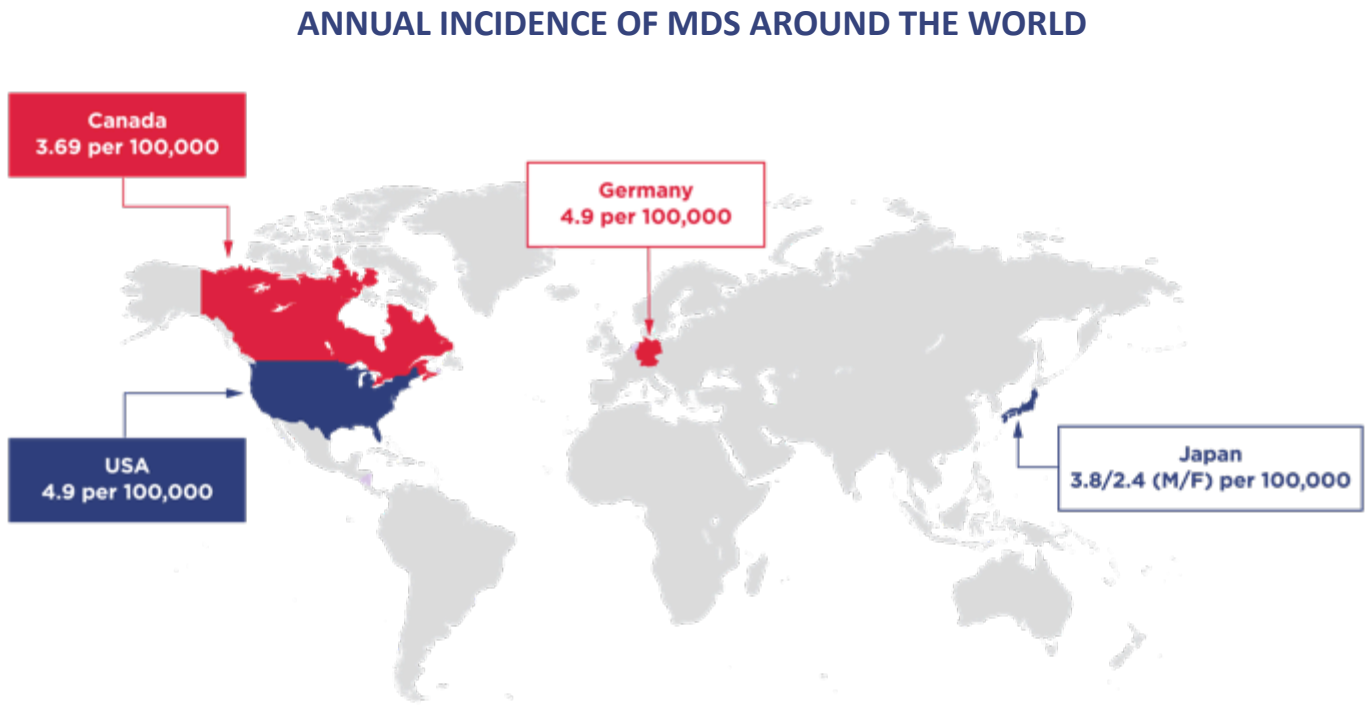
Canadian and Global Incidence of MDS

> 350,000 patients have MDS worldwide[1]

In Canada, it is estimated that there are 10,000 – 40,000 patients who have been diagnosed with MDS[2]

- Approximately 1,800 – 5,900 new cases are diagnosed each year in Canadians >65 years[2]

The highest incidence rates are found in the U.S, Japan, and Germany[3]



MDS, myelodysplastic syndromes.

[1]Research and Markets. Global Myelodysplastic Syndrome (MDS) Market 2017-2027: Prevalence Forecast, Licensing and Acquisition Deals & Drug-Specific Revenue Forecasts. Available at: https://www.globenewswire.com/news-release/2018/01/22/1298306/0/en/Global-Myelodysplastic-Syndrome-MDS-Market-2017-2027-Prevalence-Forecast-Licensing-and-Acquisition-Deals-Drug-Specific-Revenue-Forecasts.html. [2]Leukemia & Lymphoma Society of Canada. Blood Cancer in Canada. 2016. [3]Slack J, et al. Journal of Applied Laboratory Medicine. 2018;03:378-383.

Incidence of MDS

MDS is a heterogeneous disease and can be categorized broadly as lower-risk or higher-risk using prognostic scoring systems

The International Prognostic Scoring System – Revised (IPSS-R) is the most commonly used for newly diagnosed MDS patients[1*]

The IPSS-R considers cytogenetics, bone marrow blasts, and hemoglobin, platelet, and ANC levels in determining prognostic risk[1]

Using the IPSS-R:

- **~77%** of MDS patients are considered lower-risk (19% very low, 38% low, 20% intermediate)[1,2]
- **~23%** of MDS patients are considered higher-risk (13% high, 10% very high)[1,2]
- In clinical practice, an IPSS-R cut-off of 3.5 is often used to classify patients into lower- (≤3.5) and higher-risk (>3.5) MDS, thus dividing patients with intermediate-risk[3,4]

Incidence of MDS

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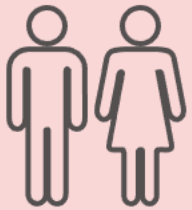
*A prognostic calculator for MDS may be accessed here: http://www.mdsclearpath.org

ANC, absolute neutrophil count; IPSS-R, International Prognostic Scoring System – Revised; MDS, myelodysplastic syndromes.

[1]Greenber P, et al. Blood. 2012;120(12):2454-2465. [2]Santini V. Hematology. 2016;2016(1):462-469. [3]Pfeilstöcker M, et al. Blood. 2016;128(7):902-910. [4]Expert opinion.

DEMOGRAPHICS OF MDS

The incidence of MDS varies depending on:



Sex

MDS affects more males than females[1]

Race

MDS affects individuals of all races but the incidence rate is highest in White individuals[1]

Age

The median age of diagnosis for MDS is 76 years[2]
Incidence rates increase drastically in individuals >80 years[3]

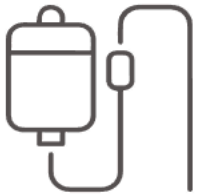
*Based on data from the United States
MDS, myelodysplastic syndromes.
[1]Rollison DE, et al. Blood. 2008;112;45-52. [2]Wells R, et al. Canadian Medical Association Journal. 2016;188(10):751. [3]SEER Cancer Statistics Review 1975-2016. Section 30. National Cancer Institute. Available at https://seer.cancer.gov/csr/1975_2016/results_merged/sect_30_mds.pdf#search=mds.

RISK FACTORS FOR DEVELOPING MDS

Most cases of MDS occur *de novo* but a number of risk factors have been identified:

Environmental/ Lifestyle

Occupational benzene exposure (e.g., petrochemical industry), or through cigarette smoke (increases MDS risk for as long as 15 years from time of quitting)[1,2]



Therapy-Related*

Therapy-related MDS (t-MDS) constitutes **10 – 15%** of all MDS cases[3] T-MDS is typically considered higher-risk, with greater resistance to treatment, and worse prognosis[4]

Other

Family history of hematopoietic cancers, certain inherited blood disorders†, and a BMI >25 increase an individual's risk of developing MDS[1,3,5]

*Developed after chemotherapy and/or radiotherapy treatment for other cancers. †Such as Fanconi anemia, congenital neutropenia.
BMI, body mass index; MDS, myelodysplastic syndromes; t-MDS, therapy-related MDS.
[1]Strom SS, et al. Leukemia. 2005;19:1912-1918. [2]Schnatter AR, et al. J Natl Cancer Inst 2012. 104:1724-1737. [3]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [3]Fukumoto JS, Greenberg PL. Critical Reviews in Hematology Oncology. 2005;56:179-192. [5]Ma X, et al. American Journal of Epidemiology. 2009;169:1492-1499.

ABNORMAL HEMATOPOIESIS IN MDS

- MDS are a group of clonal diseases characterized by dysplasia of hematopoietic progenitor cells resulting in impaired hematopoiesis and peripheral cytopenias[1-3]

- The core pathology of MDS lies in the loss of ability of the abnormal MDS clone to mature, resulting in dysplasia of erythroid progenitors[3]
  - Causes chronic, worsening cytopenias, including anemia, for MDS patients

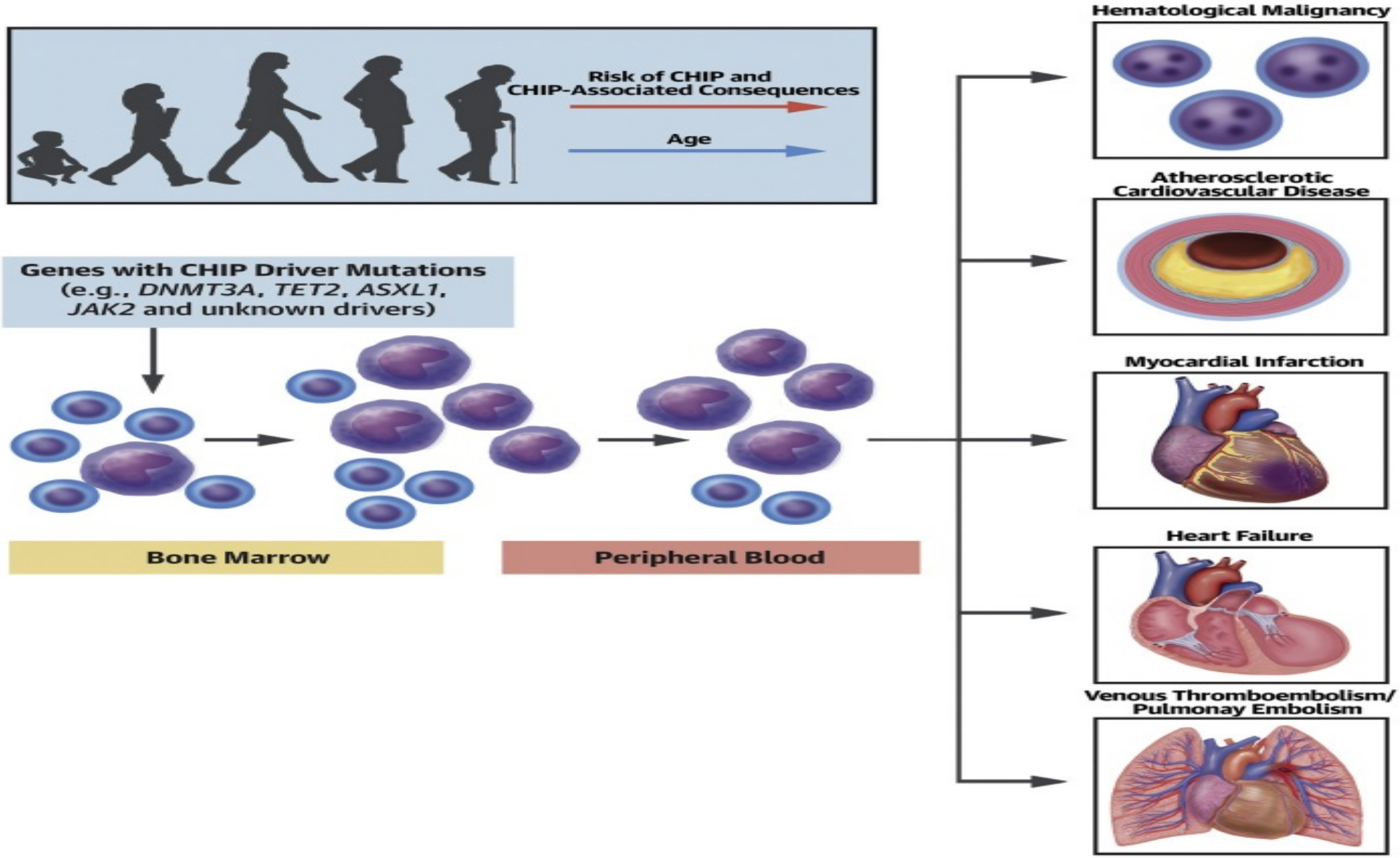
- Up to **90%** of MDS patients have ≥1 mutation within coding regions of the genome that impact distinct cellular pathways, although the precise mechanism of these mutations has not been fully elucidated[4,5]

Clonal mutation is the trigger for MDS development[6]

MDS, myelodysplastic syndromes.

[1]Fontenay-Roupie M, et al. British journal of Haematology. 1999;106:464-473. [2]Santini V. Seminars of Haematology. 2015;52:348-356. [3]Spaulding TP, et al. British Journal of Haematology. 2019. [4]Sanz GF, et al. Blood Advances. 2019;3(21):3454-3460. [5]Ogawa S. Blood. 2019;133:1049-1059. [6]Mohammad AA. Oncology Reviews. 2018;12(397):34-142.

CENTRAL ILLUSTRATION: Clonal Hematopoiesis of Indeterminate Potential as an Age-Related Phenomenon Predisposing to Multiple Cardiovascular Phenotypes



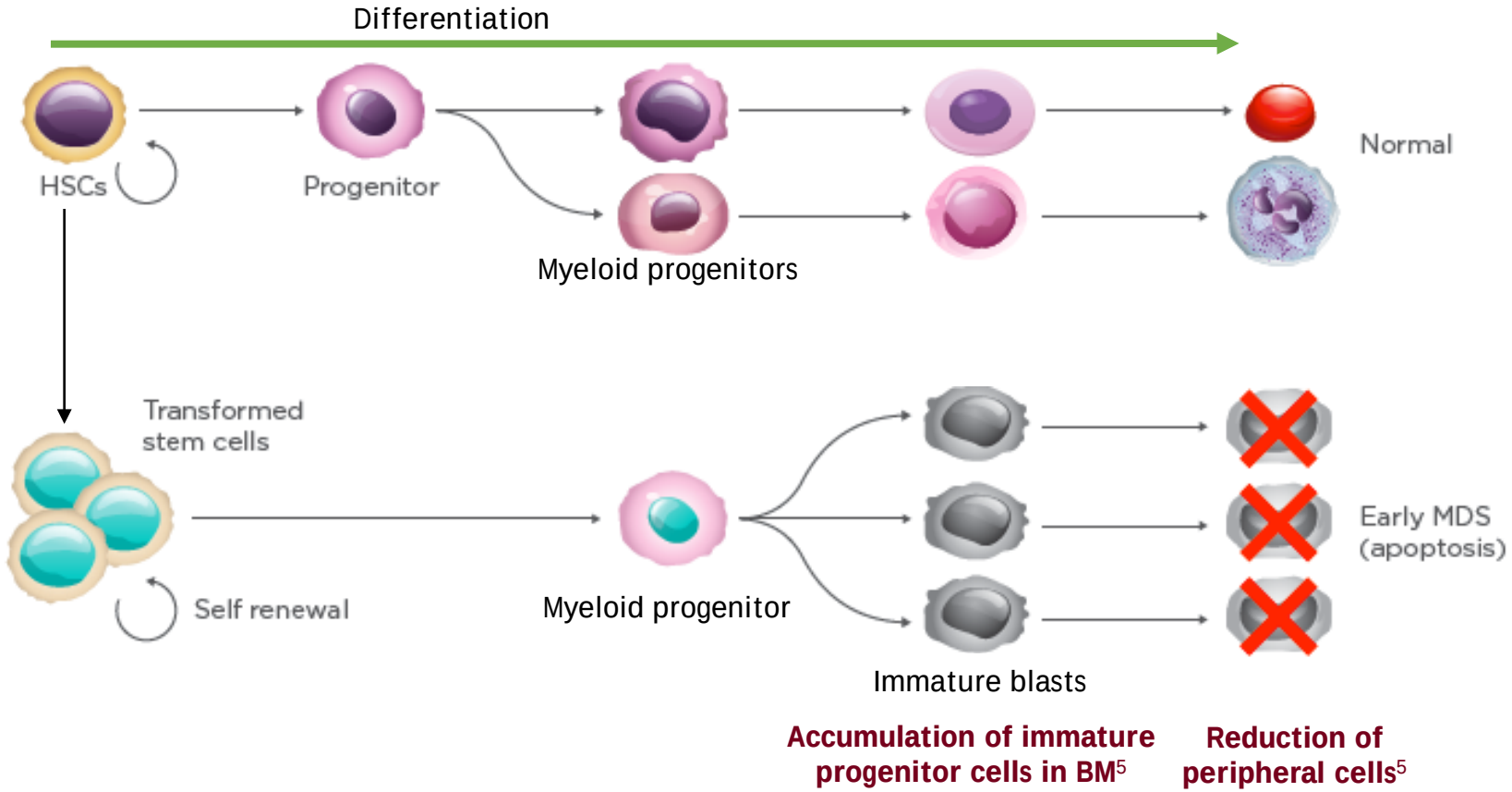
Khetarpal, S.A. et al. J Am Coll Cardiol. 2019;74(4):578–86.

ABNORMAL HEMATOPOIESIS IN MDS (CONT'D)

The clonal transformation in MDS occurs at the level of the myeloid stem cells[1]

The transformation suppresses normal stem cells, resulting in the inability to regulate self-renewal and differentiation[2]

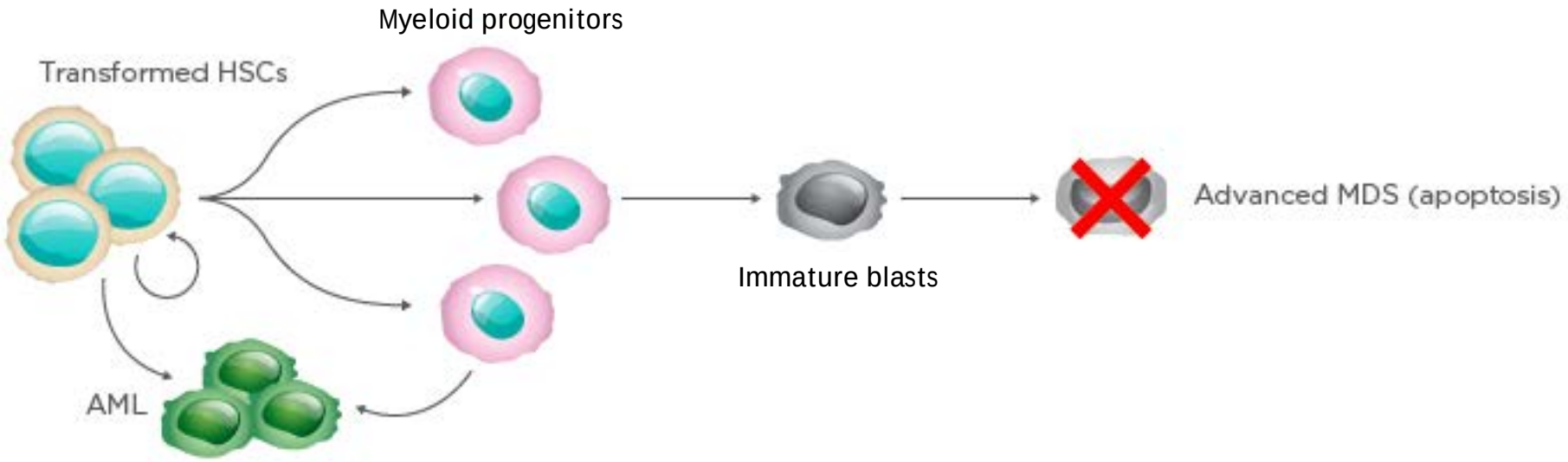
- One theory suggests that in MDS patients, a partially differentiated blast cell arises from the HSC that impedes further differentiation into mature cells[3,4]



BM, bone marrow; HSC, hematopoietic stem cell; MDS, myelodysplastic syndromes.

[1]Cazzola M, Malcovati L. New England Journal of Medicine. 2005;352(6):536-538. [2]Mohammad AA. Oncology Reviews. 2018;12(397):34-142. [3]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [4]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19. 5Cazzola M. New England Journal of Medicine. 2020;383:1358-1374.

ABNORMAL HEMATOPOIESIS IN MDS (CONT'D)



As MDS progresses, the undifferentiated blasts undergo proliferation rather than apoptosis by up-regulating survival pathways causing dysplasia[1]

Cells are also continually being stimulated by growth factors in an attempt to generate terminally-differentiated blood cells[2]

These processes contribute to the transformation of MDS to AML[2]

AML, acute myeloid leukemia; HSC, hematopoietic stem cell; MDS, myelodysplastic syndromes.

[1]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [2]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19.

COMMON SIGNS AND SYMPTOMS OF MDS

MDS can be asymptomatic and discovered during routine blood work[1]

Cytopenias associated with MDS may manifest as signs and symptoms leading to a diagnosis[1]

Common Signs and Symptoms of MDS[1,2]
Fatigue, weakness
Loss of sense of well-being
Pallor
Exertional dyspnea
Frequent severe infections
Easy bruising and/or bleeding (e.g., nosebleeds, gum bleeds)
Arthralgia
Weight loss
Loss of appetite
Fever

MDS, myelodysplastic syndromes.

[1]Mayo Clinic. Myelodysplastic Syndromes. Available at: https://www.mayoclinic.org/diseases-conditions/myelodysplastic-syndrome/symptoms-causes/syc-20366977. [2]Canadian Cancer Society. Myelodysplastic Syndromes. Available at: https://www.cancer.ca/en/cancer-information/cancer-type/leukemia/leukemia/myelodysplastic-syndromes/?region=on.

SYMPTOMS ASSOCIATED WITH CYTOPENIAS

MDS is characterized by cytopenias

- **Anemia** is the most common cytopenia in MDS[1]
- **Thrombocytopenia** is observed in ~50% of lower risk MDS cases[2]
- **Neutropenia** is observed in ~50% of MDS cases[3]

Anemia[4,7]	Thrombocytopenia[5,7]	Neutropenia[6,7]
Fatigue Weakness Presyncope* Dyspnea Rapid heartbeat Pallor Chest pain Confusion	Petechiae Easy or excessive bruising Abnormal or excessive bleeding from nose or mouth Unusually heavy menstrual flow Blood in urine or stool Bleeding in the gastrointestinal tract Neurological symptoms including headache, confusion or balance difficulties in severe cases	Fever Frequent, severe or unusual infections

*Presyncope: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.[8]
MDS, myelodysplastic syndromes.

[1]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [2]Kantarjian H, et al. Cancer. 2007;109:1705-1714. [3]Toma A, et al. Hematologica. 2012;97:1459-1470. [4]Braunstein EM. Overview of Anemia. Available at: https://www.merckmanuals.com/en-ca/home/blood-disorders/anemia/overview-of-anemia. [5]Harvard Health Publishing. Thrombocytopenia. Available at: https://www.health.harvard.edu/a_to_z/thrombocytopenia-a-to-z. [6]Territo M. Neutropenia. Available at: https://www.merckmanuals.com/en-ca/home/blood-disorders/white-blood-cell-disorders/neutropenia. [7]Expert opinion. [8]Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

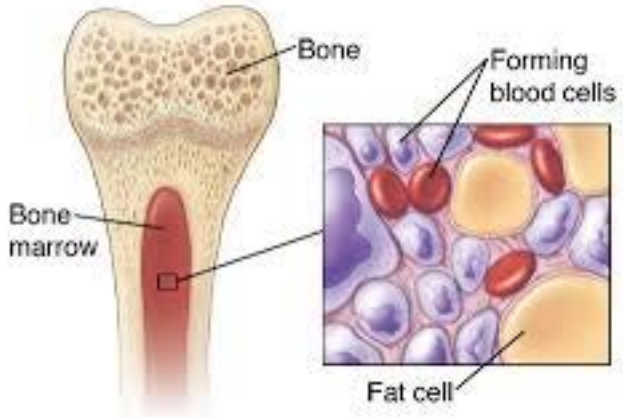
DIAGNOSING MDS

Initial Exam → **Blood Tests** → **Bone Marrow Biopsy** → **Cytogenetic & Mutation Testing**

Dysplasia, as seen in MDS, can be the result of factors other than a clonal disorder[1]

Differential diagnosis includes[1-4]:

- Vitamin B_{12} or folate deficiency
- Exposure to heavy metals
- Drugs/recent cytotoxic therapy
- Autoimmune diseases
- Chronic liver diseases and/or chronic alcohol use
- Fanconi syndrome



HIV, human immunodeficiency virus; MDS, myelodysplastic syndromes.

[1]Alberta Health Services. Myelodysplastic Syndromes. Clinical Practice Guideline LYHE-004 Version 2. 2009. [2]Buckstein R, Wells R. Sunnybrook Hospital. 2008. 3Killick SB, et al. British Journal of Haematology. 2014;164:503-525. [4]Expert opinion.

BLOOD TESTS

	Complete Blood Count (CBC)	Blood Chemistry	Blood Smear	Other
Parameters	• White blood cell (WBC) – count and differential • Platelet count • Hemoglobin (Hgb) or hematocrit (HCT) level	• Iron • Ferritin • Total iron binding capacity (TIBC) • Transferrin saturation • Folate • Vitamin B_{12}	• Dysplastic RBCs • Presence of macrocytes • Neutrophils – level of nuclear segmentation • Hypolobated or dysplastic neutrophils • Hypogranular platelets	• Serum EPO • Beta-2 microglobulin • Lactate dehydrogenase • Type and screen • Hemolysis workup
Reason	Confirm cytopenias	Exclude non-clonal causes of cytopenias	Examine morphology of cells to confirm dysplasia	Decide on prognosis and treatment options for patient

CBC, complete blood count; EPO, erythropoietin; Hgb, hemoglobin; HCT, hematocrit; MDS, myelodysplastic syndromes; RBC, red blood cell; TIBC, total iron binding capacity; WBC, white blood cell.

[1]Alberta Health Services. Myelodysplastic Syndromes. Clinical Practice Guideline LYHE-004 Version 2. 2009. [2]Wimazal F, et al. Leukemia Research. 2001;25:287-294. [3]Killick SB, et al. British Journal of Haematology. 2014;164:503-525. [4]Expert opinion.

BONE MARROW BIOPSY

Characteristic	MDS Criteria
Type and degree of dysplasia	>10% of dysplasia in any lineage upon BM aspirate or biopsy
Percentage of blast cells	Presence of blasts, >20% blasts could indicate leukemia
Cellularity	Typically normal or hypercellular bone marrow; ~15% hypocellular
Ring sideroblasts	For MDS-RS-SLD or MDS-RS-MLD diagnosis, ≥15% ring sideroblasts or ≥5% if *SF3B1* mutation is also present

BM, bone marrow; MDS, myelodysplastic syndromes; MDS-RS-SLD, MDS with ring sideroblasts with single lineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts with multi-lineage dysplasia; RBC, red blood cell.

[1]Arber DA, et al. Blood 2016. 127(20):2391-2405. [2]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [3]Schemenau J, et al. Eur J Hematol 2014. 95:181-189. [4]Expert opinion.

CYTOGENETIC TESTING

Karyotype analysis is performed during MDS diagnosis because cytogenetic features significantly impact prognosis and treatment, and can be used to confirm MDS diagnosis in cases where morphologic changes are subtle[1-4]

~50%

of *de novo* MDS patients have ≥1 cytogenetic abnormality[5]

The majority of chromosomal aberrations in MDS are unbalanced, resulting in the loss or gain of chromosomal material[6]

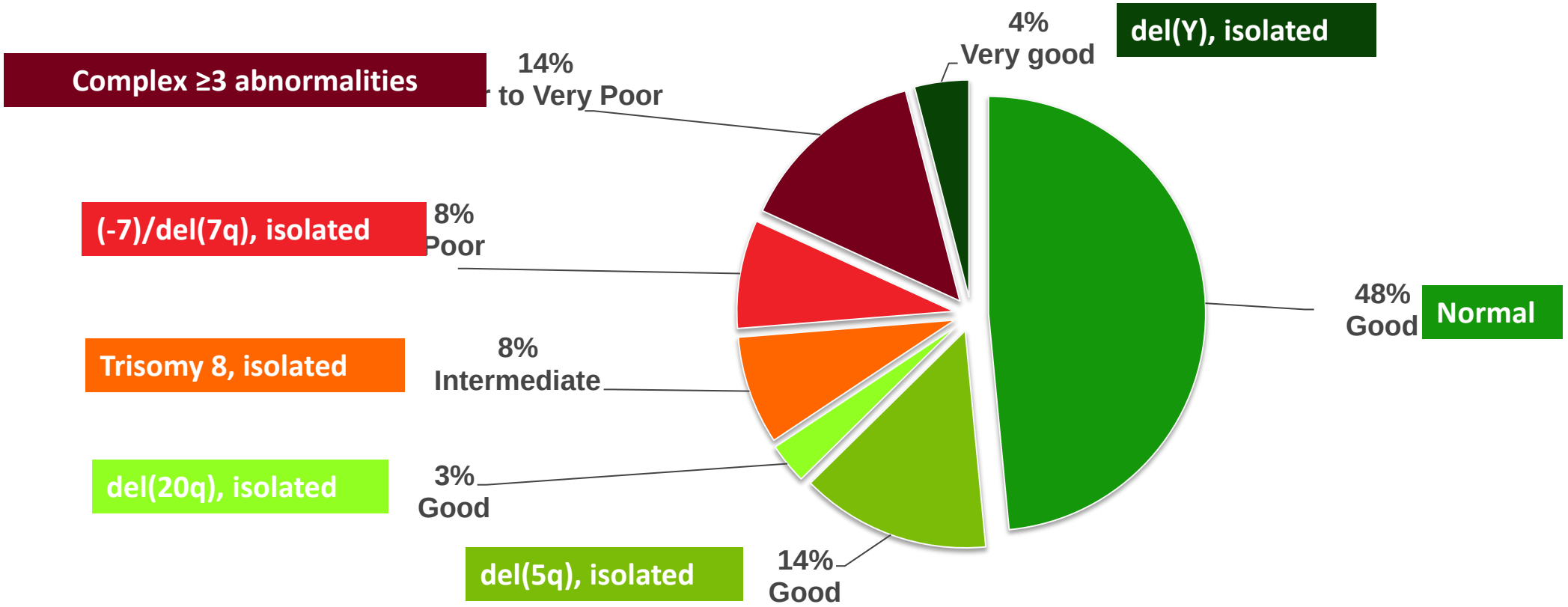
The loss or gain of chromosomes impacts the production of gene products that are important in MDS-related pathways[7]

MDS, myelodysplastic syndromes.

[1]Greenberg P, et al. Blood. 1997;89(6):2079-2088. [2]Greenberg P, et al. Blood. 2012;120(12):2454-2465. [3]Fenaux P, et al. Blood. 2011;118:3765-3776. [4]Expert opinion. [5]Haase D, et al. Blood. 2007;110:4385-4395. [6]Ogawa S. Blood. 2019;133:1049-1059. [7]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19.

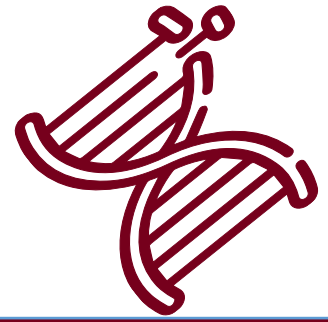
MOST COMMON CYTOGENETIC ABNORMALITIES

Incidence and Prognosis of Cytogenetic Abnormalities in MDS*[1,2]



*Primarily in de novo MDS (93.3% primary vs. 6.7% secondary).
MDS, myelodysplastic syndromes.
[1]Haase D, et al. Blood. 2007;110:4385-4395. [2]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19.

MOST COMMON GENETIC MUTATIONS



Gene	Frequency (%)	Pathway	Prognostic Implication	Common Attributes
SF3B1	20 – 25	RNA Splicing	Favourable	• Found in ~75% of patients with MDS-RS • Commonly occurs with *DMNT3A* mutations
TET2	20 – 25	DNA Methylation	Neutral	• Associated with 4q microdeletion in elderly patients • Moderate risk of AML
TP53	~20	DNA Repair, Cell Division, Apoptosis	Adverse	• Commonly occurs with del(5q) or complex karyotypes with -5/5q- • Increased risk of AML • Poor overall survival and response to treatment
ASXL1	10 – 20	Chromatin Modification	Adverse	• Common in MDS-EB • Shorter overall survival • Increased risk of AML
SRSF2	10 – 15	RNA Splicing	Adverse	• Occurs most often in males, advanced age • Most common mutation in CMML
DNMT3A	10 – 15	DNA Methylation	Adverse	• Associated with abnormal karyotype • Faster transformation to AML
RUNX1	10 – 15	Transcription	Adverse	• Common in high risk MDS and t-MDS • Associated with thrombocytopenia • Increased risk of AML

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; MDS-EB, MDS with excess blasts; MDS-RS, MDS with ring sideroblasts; t-MDS, therapy-related MDS.

[1]Ogawa S. Blood. 2019;133:1049-1059. [2]Ganguly BB, Kadam NN. Mutation Research. 2016;769:47-62. [3]Hunter A, Sallman DA. Hematol Oncol Clin North Am 2020. 34:421-440. [4]Cumbo C, et al. Int J Mol Sci 2020. 21:3432.

PROGNOSTIC SCORING SYSTEMS – IPSS AND IPSS-R

The IPSS was developed through an International MDS Risk Analysis Workshop in 1997[1]

The group identified major variables that impact disease progression to AML[1]:

- Cytogenetic abnormalities
- Percentage of BM blasts
- Number of cytopenias

In 2012, the IPSS was revised (IPSS-R)* to include the following changes[2]:

- Five prognostic categories rather than 4
- Refinement of BM blast count categories
- Evaluation of depth of cytopenias, as well as the number
- Expanded cytogenetic analysis categories
- Inclusion of features affecting survival such as age, performance status, serum ferritin, LDH, and beta-2 microglobulin

The database to develop the IPSS included 816 patients vs. 7012 patients for the IPSS-R[1,2]

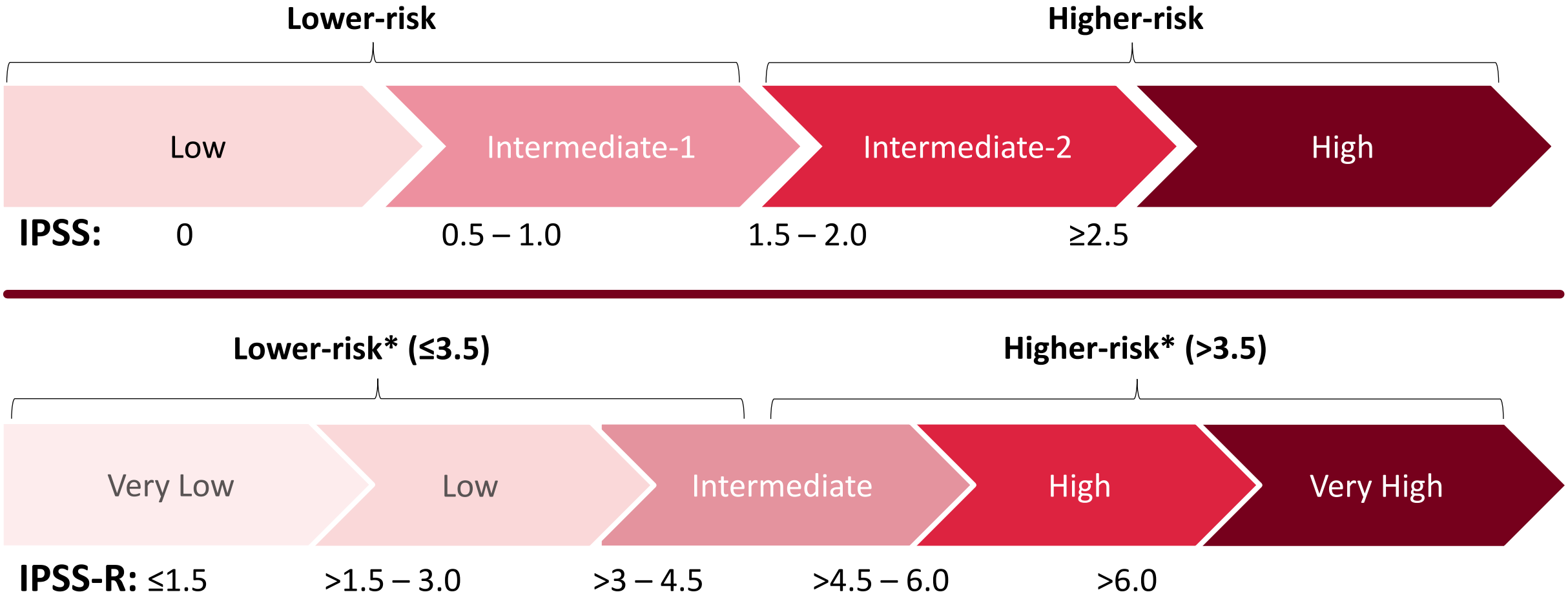
An IPSS and IPSS-R calculator can be accessed here: http://www.mdsclearpath.org

*Applicable only to primary disease

AML, acute myeloid leukemia; BM, bone marrow; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System – Revised; MDS, myelodysplastic syndromes.

[1]Greenberg P, et al. Blood. 1997;89(6):2079-2088. [2]Greenberg P, et al. Blood. 2012;120(12):2454-2465.

IPSS AND IPSS-R RISK CATEGORIES[1-5]



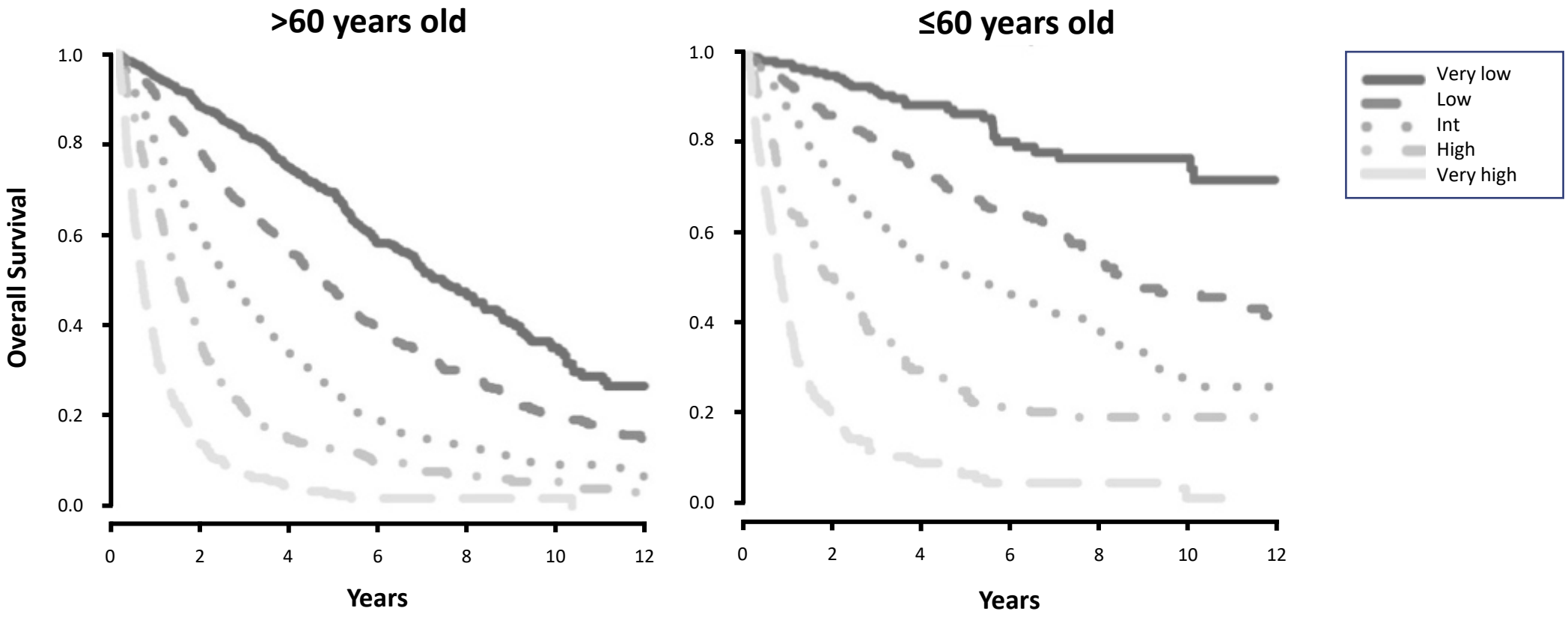
*In clinical practice, an IPSS-R cut-off of 3.5 is often used to categorize patients into lower- and higher-risk MDS[3–5]

IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System – Revised.

[1]Greenberg P, et al. Blood. 1997;89(6):2079-2088. [2]Greenberg P, et al. Blood. 2012;120(12):2454-2465. [3]Pfeilstöcker M, et al. Blood. 2016;128(7):902-910. [4]Montoro JM, et al. ASH 2020. Abstract 3108. [5]Expert opinion.

OVERALL SURVIVAL ACCORDING TO IPSS-R SCORE

Overall Survival According to IPSS-R Score in Patients with MDS Aged >60 Years and ≤60 Years[1]



IPSS-R, International Prognostic Scoring System – Revised; MDS, myelodysplastic syndromes.

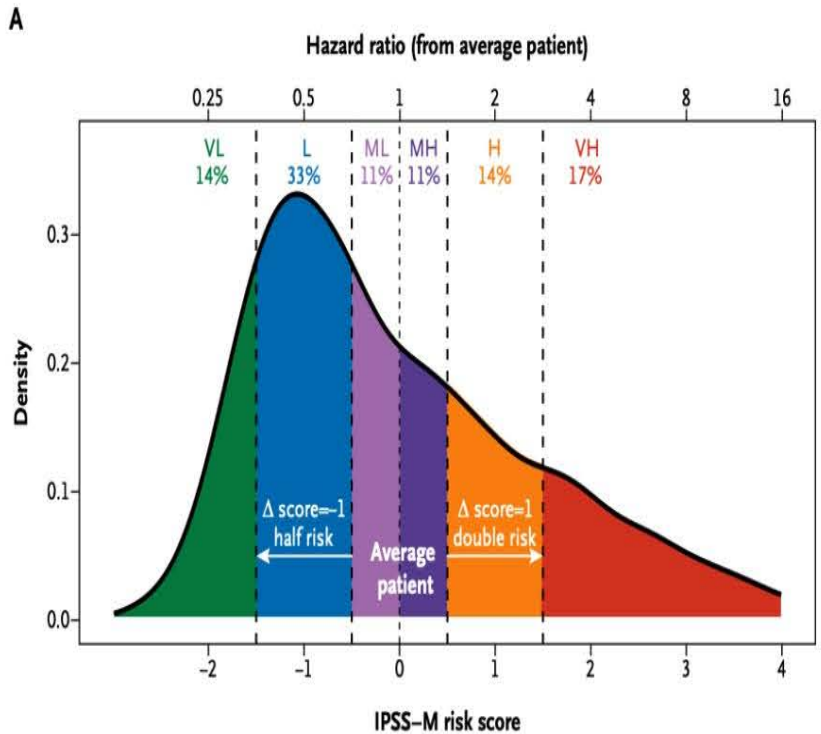
[1]Greenberg P, et al. Blood. 2012;120(12):2454-2465.

IPSS-M model

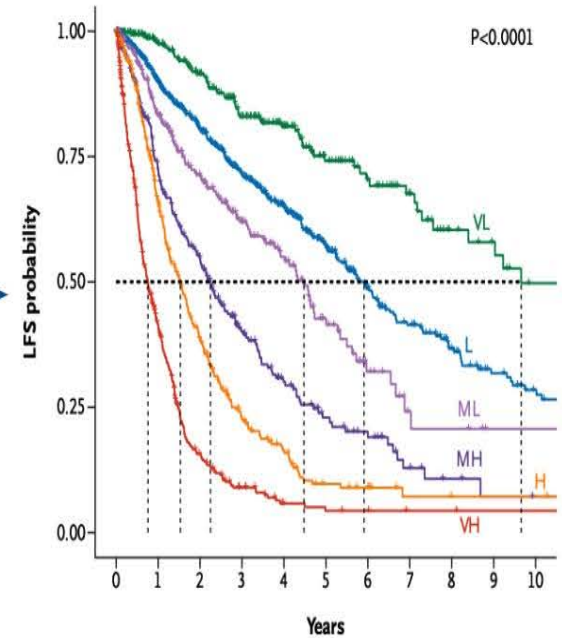
Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{Sq}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

IPSS-M risk score and strata



Risk discrimination



MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

MDS/MPN includes myeloid neoplasms with clinical, laboratory, and morphological features that overlap between MDS and MPN[1]

Included in the 2016 WHO MDS/MPN category are[1]:

1. **Chronic myelomonocytic leukemia (CMML)***
2. Atypical CML, *BCR-ABL1*$^{-}$
3. Juvenile myelomonocytic leukemia (JMML)
4. MDS/MPN with ring sideroblasts associated with marked thrombocytosis (MDS/MPN-RS-T; previously known as RARS-T)

MDS/MPN-RS-T was accepted as a full entity in the 2016 WHO classification after the discovery that it is frequently associated with mutations in *SF3B1*[1]

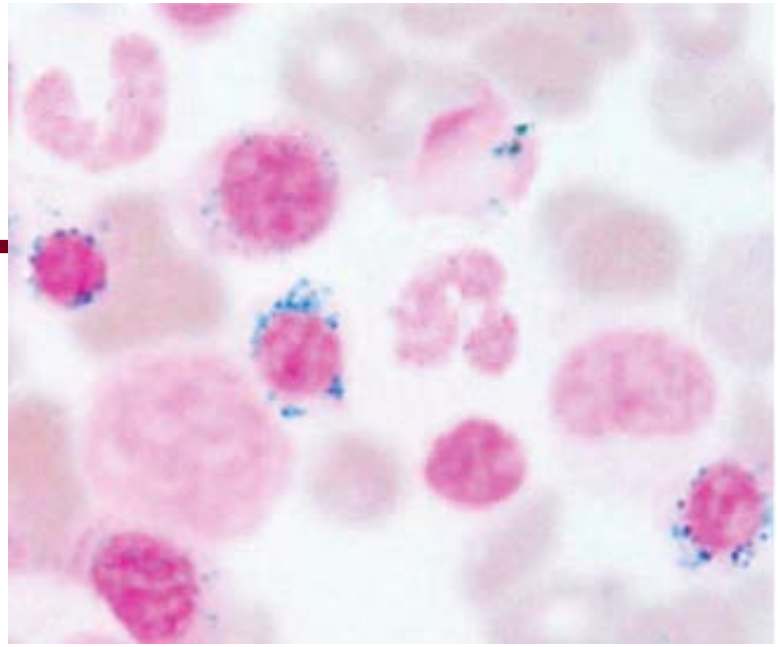
*CMML-0, a category for cases with <2% blasts in PB and <5% blasts in BM; CMML-1 for cases with 2% to 4% blasts in PB and/or 5% to 9% blasts in BM; CMML-2 for cases with 5% to 19% blasts in PB, 10% to 19% in BM, and/or when any Auer rods are present

MPN, myeloproliferative neoplasms; MDS, myelodysplastic syndromes; WHO, World Health Organization.

[1]Arber DA, et al. Blood. 2016;127(20):2391-2405.

RING SIDEROBLASTS IN MDS

As many as 33% of MDS patients have >15% ring sideroblasts in the bone marrow[1]



Ring sideroblasts are characterized by a build-up of iron in the mitochondria of erythroblasts[2]

- They are visualized as a perinuclear ring of granules using Prussian blue
- staining (Perls reaction)

There are 2 MDS subtypes within the 2016 WHO classification system specific to ring sideroblasts[3]:

- MDS-RS-SLD
- MDS-RS-MLD

Ring sideroblasts may also occur at any level within other MDS subtypes and are found in patients with MDS/MPN-RS-T[3,4]

MDS, myelodysplastic syndromes; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts associated with marked thrombocytosis; MDS-RS-MLD, MDS with ring sideroblasts with multi-lineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts with single lineage dysplasia; WHO, World Health Organization.

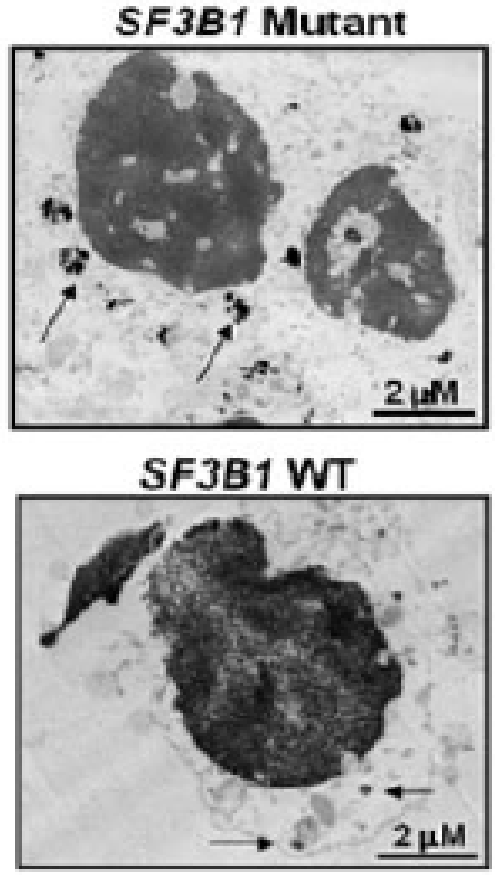
[1]Papaemmanuil E, et al. Blood. 2013;122(22):3616-3627. [2]Cazzola M, Invernizzi R. Haematologica. 2011;96(6):789-792. [3]Arber DA, et al. Blood. 2016;127(20):2391-2405. [4]Malcovati L, Cazzola M. British Journal of Haematology. 2016;174(6):847-858.

RING SIDEROBLASTS AND *SF3B1* IN MDS

Ring sideroblasts in mutated *SF3B1* patients shows altered iron distribution characterized by coarse iron deposits[1]

In recent studies of MDS patients with any ring sideroblasts, the percentage of ring sideroblasts was found not to be prognostically relevant[2]

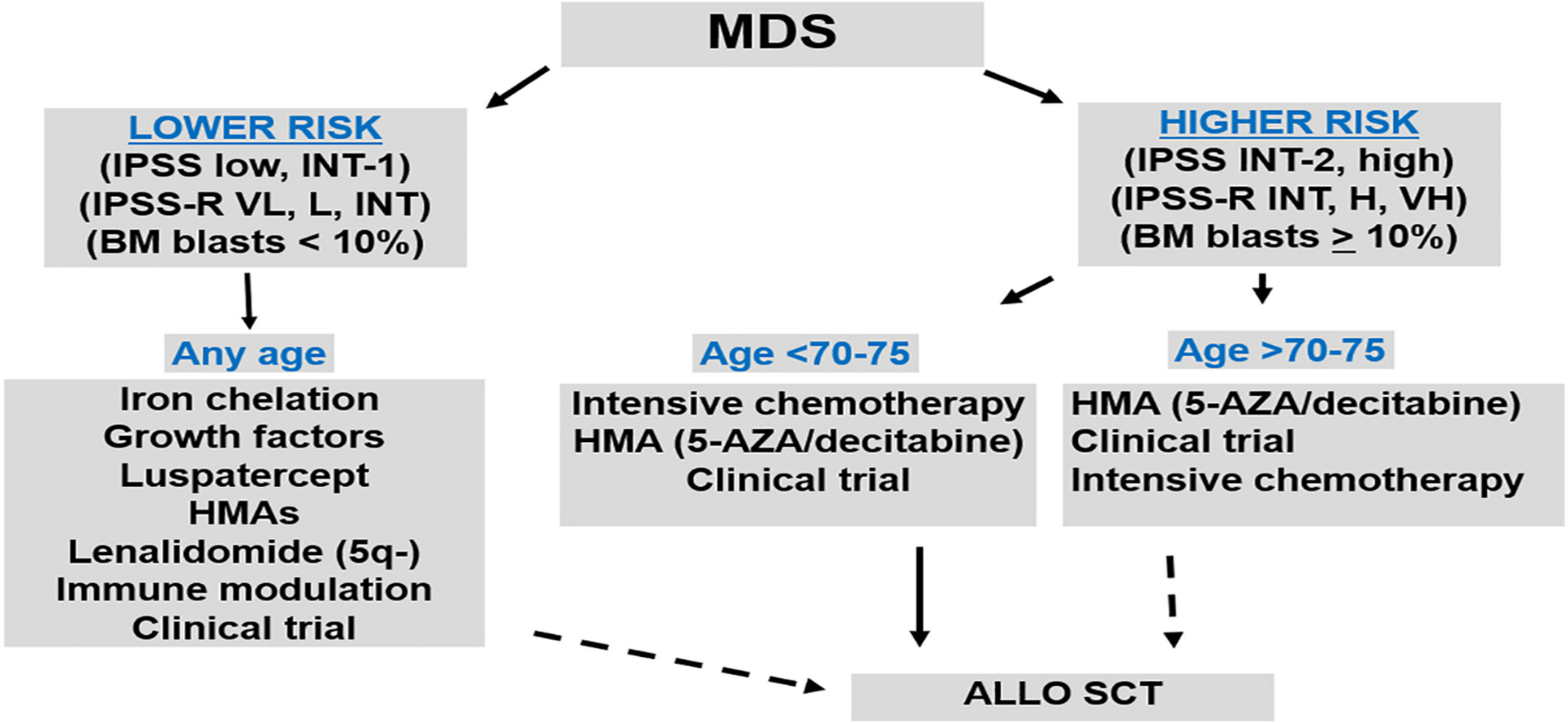
- A diagnosis of MDS-RS can be made with ≥5% ring sideroblasts if a *SF3B1* mutation is identified[3]
- Unlike MDS-RS, the number of ring sideroblasts for a diagnosis of MDS/MPN-RS-T is not dependent on *SF3B1* mutational status[3]



Transmission electron microscopy of BM cells from a representative wildtype and a MDS-RS patient. Arrows indicate the presence of abundant perinuclear iron deposits in the mutant compared with the wildtype patient. Specimens' cuts are 2 µm-thick sections. Adapted from Visconte V, et al. Blood 2012;1(16):3173-3186)

MDS, myelodysplastic syndromes; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts associated with marked thrombocytosis; MDS-RS, myelodysplastic syndromes with ring sideroblasts.

[1]Dolatshad H, et al. Leukemia. 2015;29:1092-1103. [2]Patnaik MM, et al. Blood. 2012;119(24):5674-5677. [3]Arber DA, et al. Blood. 2016;127(20):2391-2405.



Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management
Guillermo Garcia-Manero, Kelly S. Chien, Guillermo Montalban-Bravo
First published: 03 August 2020
https://doi.org/10.1002/ajh.2595

TREATMENT OPTIONS FOR MDS

Treatment approaches for MDS evolve over the course of the disease, and may vary depending on[1]:

- Risk score
- Age
- Performance status

Active management of MDS patients can be achieved through the use of the following drug classes[1-3]:

- Hypomethylating agents
- Hypomethylating agents+ BCL2i
- Immunomodulating agents
- Immunosuppressive agents
- Hematopoietic growth factors
- Iron chelators

These therapies do not cure MDS but can reduce transfusion needs, improve quality of life, and extend survival[4]

The only curative therapeutic option for MDS is allogeneic hematopoietic stem cell transplantation (allo-HSCT)[4]

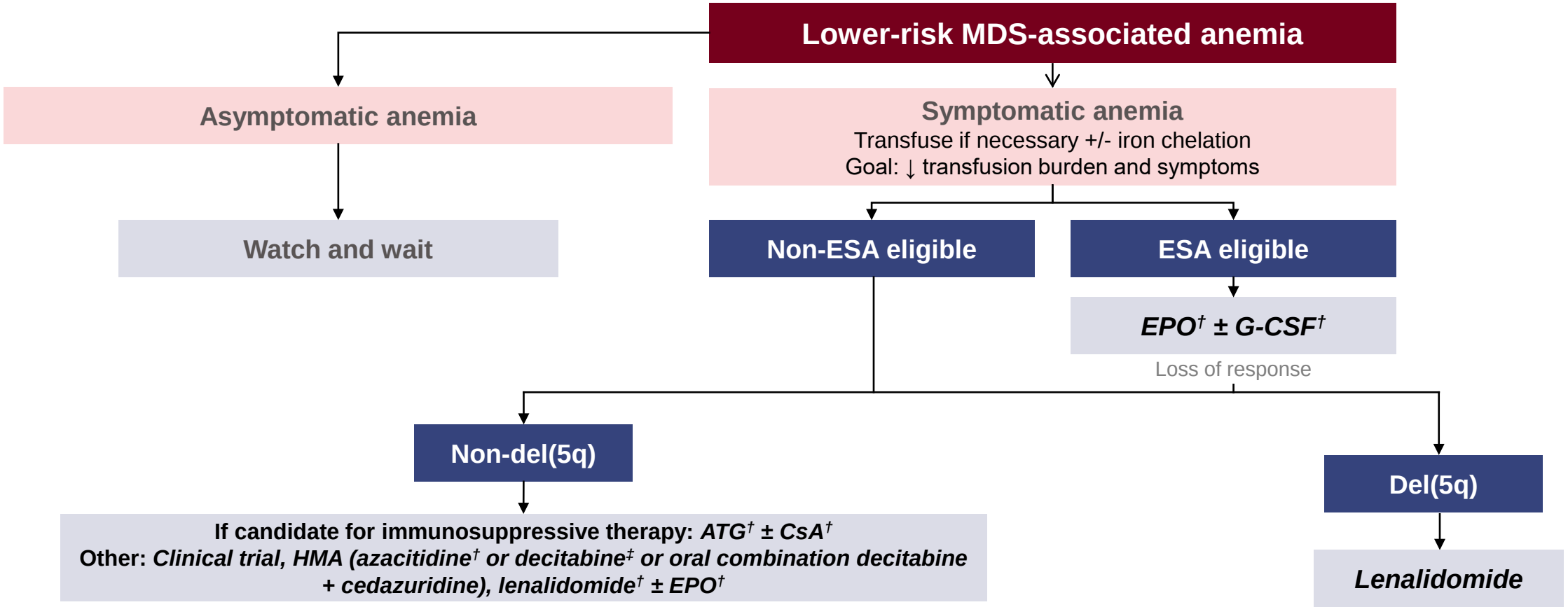
Supportive care measures are also essential to the care and management of patients with MDS as they mitigate the impact of cytopenias and transfusion of blood products[5]

Further information can be accessed here: http://www.mdsironroad.org (UN: ironroad, PW: makeirongreatagain)

Allo-HSCT; allogeneic hematopoietic stem cell transplantation; MDS, myelodysplastic syndromes; PW, password; UN, username

[1]NCCN Guidelines. Myelodysplastic Syndromes. Version 2.2020. [2]Killick SB, et al. British Journal of Haematology. 2014;164:503-525. [3]Expert opinion. [4]Wells RA, et al. CMAJ. 2016;188:751.
[5]Leitch HA, Vickars LM. Hematology Am Soc Hematol Educ Program 2009. 2009:664-672.

MANAGING LOWER-RISK MDS PATIENTS



†Unapproved Health Canada indication; ‡Health Canada approved indication in lower risk MDS limited to intermediate-1 (by IPSS) MDS - not currently marketed
ATG anti-thymocyte globulin, CsA cyclosporine, Del(5q) MDS with chromosome 5q deletion, EPO erythropoietin, ESA erythropoiesis-stimulating agent, G-CSF granulocyte colony stimulating factor, HMA hypomethylating agent, IPSS, International Prognostic Scoring System; MDS myelodysplastic syndromes, RBC red blood cell, RS+ ring sideroblasts.
Source: Canadian Expert Opinion.

INADEQUATE RESPONSE OR DISEASE PROGRESSION IN LOWER-RISK MDS

Inadequate/loss of response *without* disease progression:

- Patients should be treated with alternative therapies, best supportive care, or enrollment in a suitable clinical trial[1-4]

In cases of inadequate/loss of response:	Try:*
Lenalidomide and have MDS(del5q)	Adding ESA
ESA and have MDS(del5q)	Lenalidomide
ESA and are **not** MDS(del5q)	IST (if eligible), or HMA, or lenalidomide, or best supportive care
IST	Lenalidomide, or ESA, or HSCT, or best supportive care

Loss of response *with* disease progression:

- Patient management should shift to reflect that of higher-risk MDS patients[2,3]

*Access varies between provinces

ESA, erythropoiesis-stimulating agents; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IST, immunosuppressive therapy; MDS, myelodysplastic syndromes.

[1]Buckstein R, et al. A Quality program initiative of the Pn Evidence-Based Care (PEBC), Cancer Care Ontario (CCO). 2018. [2]Alberta Health Services. Myelodysplastic Syndromes. Clinical Practice Guideline LYHE-004.2009. [3]NCCN Guidelines. Myelodysplastic Syndromes. Version 2.2020. [4]Canadian Expert Opinion.

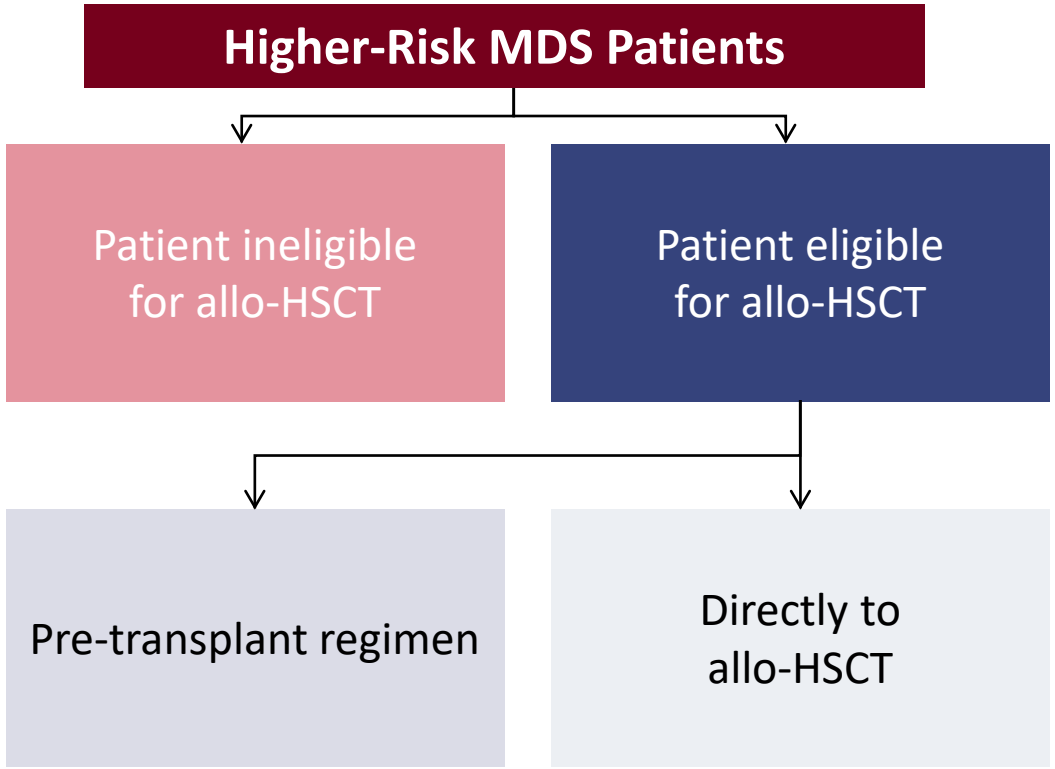
MANAGING HIGHER-RISK MDS PATIENTS

For higher-risk MDS patients, allo-HSCT should be considered at diagnosis[1]

Treatment options include[2-3]:

- Allo-HSCT
- Hypomethylating agents =/- BCL2i
- Cytoreductive chemotherapy

Enrollment in a suitable clinical trial should also be considered for higher-risk MDS patients when applicable[4]



Allo-HSCT, allogeneic hematopoietic stem cell transplantation; MDS, myelodysplastic syndromes.

[1]Cutler C, et al. Blood. 2004;104:579-585. [2]Alberta Health Services. Myelodysplastic Syndromes. Clinical Practice Guideline LYHE-004.2009. [3]Buckstein R, Wells R. Myelodysplastic Syndromes. 2008. Available at: https://sunnybrook.ca/uploads/Myelodysplastic_Syndromes.pdf. [4]NCCN Guidelines. Myelodysplastic Syndromes. Version 2.2020.

MANAGING ANEMIA WITH ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

There are 2 ESAs currently available for use in Canada:

1. Epoetin alfa (Eprex®)[1]
2. Darbepoetin alfa (Aranesp®)[2]

These ESAs do not have an MDS-specific indication

Their use in MDS-associated anemia are recommended for[3,4]:

- IPSS-R: Very low, low, or intermediate-risk MDS
- Moderate-to-severe anemia (Hgb < 10 g/dL)
- Serum EPO < 500 mU/mL
- RBC transfusion requirement < 2 RBC units/month (not transfusion-dependent)
- Absence of excess blasts

The guidelines also suggest the addition of G-CSF for patients with ≥15% ring sideroblasts[3-5]

EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; G-CSF, granulocyte colony stimulating factor; Hgb, hemoglobin; IPSS-R, International Prognostic Scoring System - Revised; MDS, myelodysplastic syndromes; RBC, red blood cell.

[1]Eprex Product Monograph. Janssen Incorporated. 2017. [2]Aranesp Product Monograph. Amgen Canada Incorporated. 2018. [3]Buckstein R, et al. A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO). 2018. [4]Alberta Health Services. Myelodysplastic Syndromes. Clinical Practice Guideline LYHE-004.2009. [5]NCCN Guidelines. Myelodysplastic Syndromes. Version 2.2020.

RESPONSE TO ESAs

Response to ESAs is largely dependent on serum EPO levels and RBC transfusion dependency[1]

The efficacy of ESAs is highest in patients with serum EPO < 200 mU/mL[1]

ESA efficacy is lowest, and therefore not recommended, in patients with serum EPO > 500mU/mL[2,3]

A predictive model for patient response to ESAs was validated in 2003 and takes 3 variables into account that were found to be significantly correlated to ESA response in univariate and multivariate analyses:[4]

- Serum EPO
- Serum ferritin
- IPSS-R risk score

EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; IPSS-R, International Prognostic Scoring System - Revised; RBC, red blood cell.

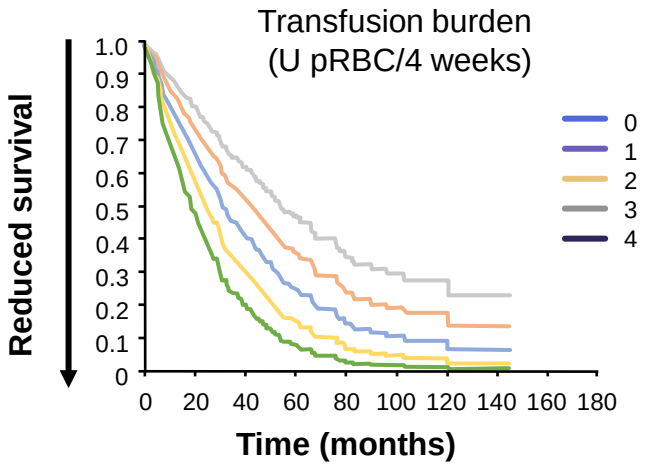
[1]Hellstrom-Lindberg E. Leukemia and Lymphoma. 2010;51:1155-1156. [2]Santini V, et al. Blood. 2013;122:2286-2288. [3]Hellstrom-Lindberg E, et al. British Journal of Hematology. 1997;99:344-351.
[4]Hellstrom-Lindberg E, et al. British Journal of Hematology. 2003;120:1037-1046.

IMPACT OF TRANSFUSIONS ON PROGNOSIS

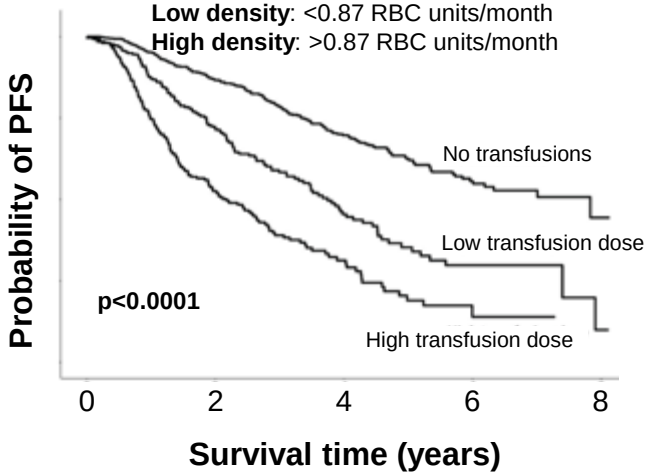
Transfusion dependency in LR-MDS is associated with inferior OS[1]

The effect of transfusion dependency is more noticeable in patients with LR MDS and is associated with the severity of transfusion requirement[1]

Overall survival[1]



Progression-free survival[2]



EUMDS: European LeukemiaNet MDS Registry; LR, low risk; PFS: progression-free survival; pRBC: packed red blood cells

[1]Malcovati L, et al. Haematologica 2006;91:1588–90; [2]de Swart L, et al. Haematologica. 2020;105(3):632–639.

IMPACT OF TRANSFUSIONS ON QUALITY OF LIFE (QOL)

RBC transfusion dependence in patients with MDS is associated with impaired HRQoL[1]

One study assessed 1690 patients with MDS (median age 74 years) using EQ-5D, a validated, generic, patient-reported HRQoL questionnaire[1,2]

HRQoL was significantly impaired in patients who were transfusion dependent in uni- and in multivariate analyses[1]:

EQ-5D Index (n = 1683)	Univariate				Multivariate*			
Red blood cell transfusion†	Coef.	95% CI		P-value	Coef.	95% CI		P-value
No								
Yes	-0.07	-0.10	-0.05	**<0.001**	-0.04	-0.07	-0.02	**<0.001**

*Adjusted for all other variables; †As assessed in the year prior to initial diagnosis
HRQoL, health-related quality of life; MDS, myelodysplastic syndromes; RBC, red blood cell
[1]Stauder R, et al. Leukemia 2018. 32:1380–1392; [2]Brooks R. Health Policy 1996. 37(1):53–72.

MINIMIZING IRON OVERLOAD

The body has no way to excrete excess iron[1]

When possible, transfusions should be minimized with the use of medications (eg. ESA)[1]

Excess iron is reduced through the use of iron chelators, which capture non-transferrin bound iron and labile plasma iron[2]

Iron chelators can also remove excess iron by mobilizing it from organs, forming a complex with it, and then getting excreted[3]

In Canada, there are 2 drugs that are indicated for iron overload in MDS:

- Deferoxamine (DFO)[4]
- Deferasirox (DFX)[5]

Deferiprone (DFP) has been shown to increase iron excretion but has been mainly used in hemoglobinopathies (e.g., β-thalassemia) and not in MDS[6]

- Deferiprone does not currently have a Health Canada approved indication in MDS[7]

MDS, myelodysplastic syndromes. [1]Expert opinion. [2]Leitch HA, et al. Leukemia Research. 2018;74:21-41. [3]Mobarra N, et al. International Journal of Hematology-Oncology and Stem Cell Research. 2016;10:239-247. [4]Desferal Product Monograph. Pfizer Canada Incorporated. 2017. [5]Exjade Product Monograph. Novartis Pharmaceuticals Canada. [6]Wells RA, et al. Leukemia Research. 2008;32:1338-1352. [7]Ferriprox Product Monograph. ApoPharma Incorporated. 2019.

CANADIAN RECOMMENDATIONS FOR IRON CHELATION THERAPY

Transfusion-dependent, ICT-eligible MDS patients should begin treatment when:

- SF > 1000 µg/L consistently elevated over time, preferably with fasting transferrin saturation > 50%, or with evidence of organ damage from IOL
- Expected ongoing transfusion requirement (actual/predicted ≥ 20 units PRBC)
- Life expectancy > 1-2 years
  - IPSS low or int-1
  - IPSS-R ≤ 4.5
  - MDS-SLD/MDS-RS-SLD/MDS (del)5q
  - Candidate for SCT
  - Candidate for/responder to potentially disease modifying therapies

- Reduce dose of DFO when SF < 2000 µg/L; discontinue DFO when SF < 1000 µg/L
- Discontinue DFX when SF < 500 µg/L; follow PM when creatinine is elevated

Monitor iron intake rate to assess IOL at each transfusion

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; DFO, deferoxamin; DFX, deferasirox; ICT, iron chelation therapy; IOL, iron overload; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-SLD, MDS with single lineage dysplasia; PM, product monograph; PRBC, packed red blood cells; SCT, stem cell transplant; SF, serum ferritin

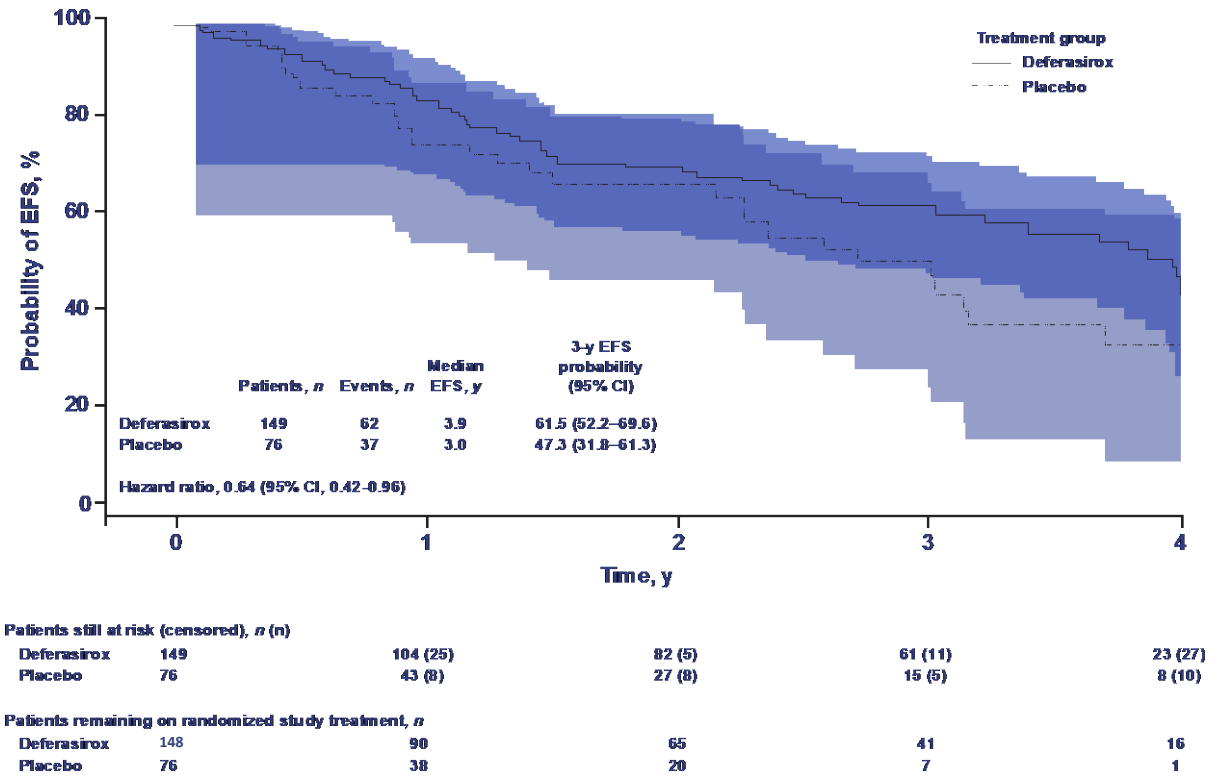
Leitch HA, et al. Leuk Res. 2018;74:21-41

BENEFIT OF IRON CHELATION THERAPY (ICT)

A recent randomized, double-blind, placebo-controlled trial (TELESTO) evaluated the effect of ICT on the outcomes of patients with low- to intermediate-1 risk MDS[1]

Patients receiving deferasirox had a significantly longer event-free survival (EFS)* compared to those receiving placebo (3.9 years [95% CI, 3.2 to 4.3 years] vs. 3.0 years [CI, 2.2 to 3.7 years], respectively) [1]

Event-free survival of patients on deferasirox vs. placebo with 95% Hall-Wellner bands[1]



EFS was defined as the time from the date of randomization to the date of first documented and confirmed nonfatal event (e.g., worsening cardiac function, hospitalization for heart failure, liver function impairment, cirrhosis, transformation to acute myeloid leukemia) or death, whichever occurred first

CI, confidence interval; EFS, event free survival; ICT, iron chelation therapy; MDS, myelodysplastic syndromes

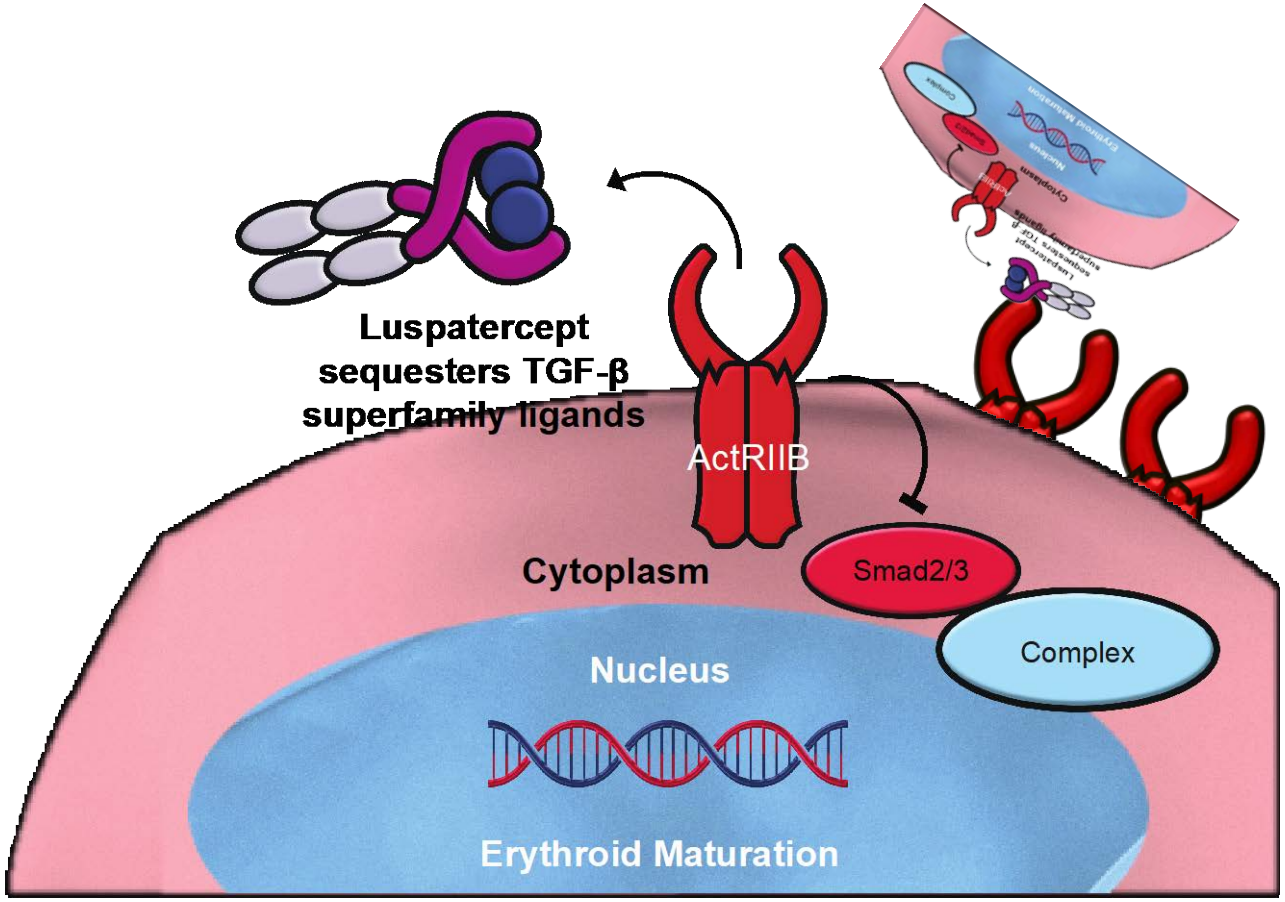
[1]Angelucci E, et al. Ann Intern Med 2020. 172:513-522.

LUSPATERCEPT MECHANISM OF ACTION

Luspatercept is an ActRIIB/IgG1 Fc recombinant fusion protein[1]

Luspatercept binds select members of the TGF-β superfamily to inhibit aberrant Smad2/3 signaling[1]

In MDS models, inhibiting Smad2/3 signaling improves erythroid maturation via late-stage erythropoiesis[1]



ActRIIB, activin receptor type IIB; MDS, myelodysplastic syndromes; TGF-β, transforming growth factor β.

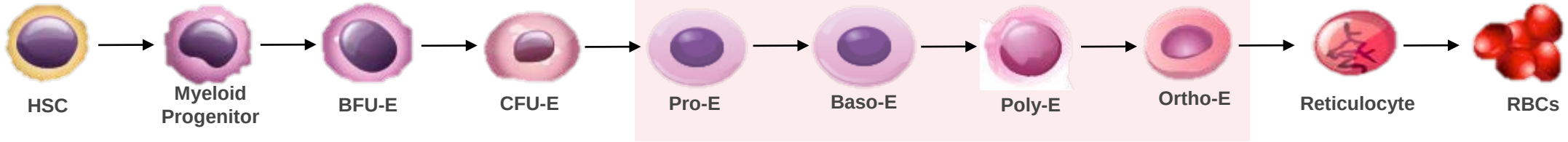
[1]Platzbecker U, et al. *Lancet Oncology*. 2017;18:1338-1347.

LUSPATERCEPT TARGETS LATE-STAGE ERYTHROPOIESIS

Early-stage erythropoiesis[1]
Erythroid proliferation
EPO-dependent

Late-stage erythropoiesis[1]
Erythroid maturation

Luspatercept Responsive[1]



Luspatercept is a potential **first-in-class erythroid maturation agent** that binds to select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signalling and **enhance late-stage erythropoiesis[2]**

Baso-E, basophilic erythroblast; BFU-E, burst-forming unit erythroid progenitor; CFU-E, colony-forming unit erythroid progenitor; EPO, erythropoietin; HSC, hematopoietic stem cell; Ortho-E, orthochromatic erythroblast; Poly-E, polychromatophilic erythroblast; Pro-E, proerythroblast; RBC, red blood cell.

[1]Suragani RNVS, et al. *Nature Medicine*. 2014;20:408-414; [2]Platzbecker U, et al. *Lancet Oncology*. 2017;18:1338-1347

MEDALIST STUDY DESIGN[1,2]

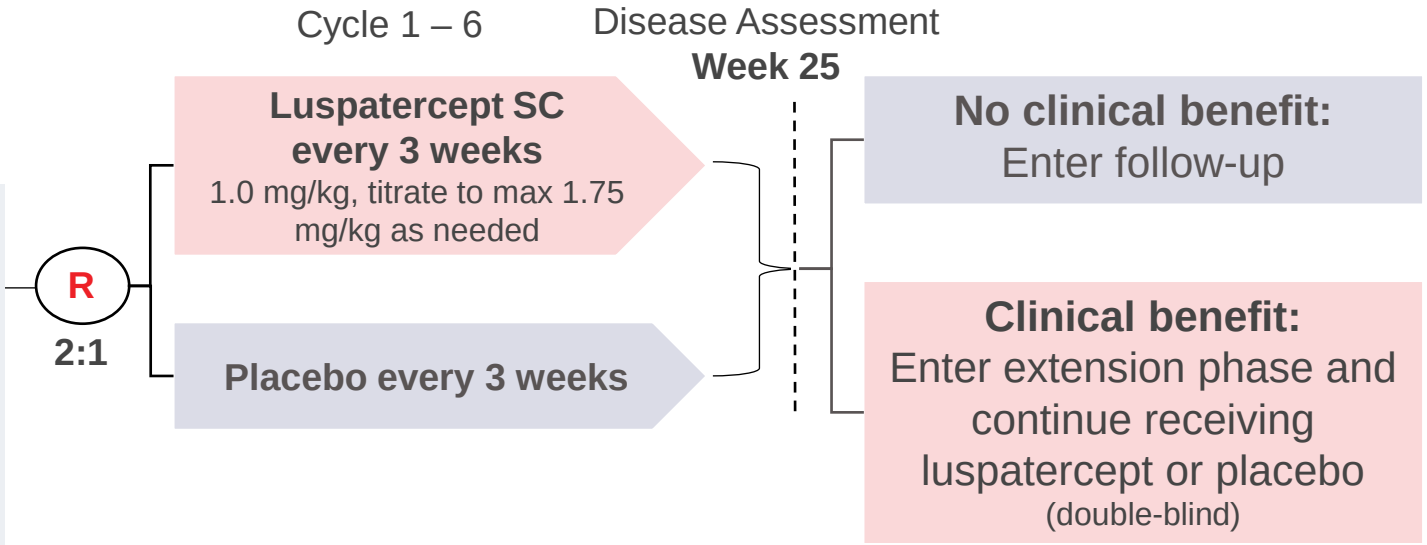
MEDALIST was a double-blind, randomized, placebo-controlled, phase 3 study

Key Eligibility Criteria:

- Age ≥ 18 years
- MDS with ring sideroblasts according to WHO criteria
- IPSS-R very low- to intermediate risk
- Require regular RBC transfusions ≥2 units/8 weeks
- No transfusion-free period >56 days 16 weeks before randomization
- Prior treatment with ESAs (refractory or intolerant), or unlikely to respond to ESA with serum EPO >200 U/L

Exclusion Criteria:

- del(5q) MDS
- WBC count: ≥ 13 x 10^9/L
- Neutrophil <0.5 x 10^9/L
- Platelets <50 x 10^9/L
- Prior use of a disease-modifying agents for MDS



All patients were eligible to receive best supportive care as needed, including:

- RBC transfusions
- Iron chelating agents
- Use of antibiotic, antiviral, and antifungal therapy
- Nutritional support

EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; HMA, hypomethylating agent; iMID, immunomodulatory imide drug; IPSS-R, International Prognostic Scoring System = Revised; MDS, myelodysplastic syndromes; MDS-RS, MDS with ring sideroblasts; RBC, red blood cell; RS, ring sideroblasts; SC, subcutaneous; WHO, World Health Organization.

[1]Celgene Incorporation. REBLOZYL® Product Monograph. February 11, 2021. [2]Fenaux P, et al. NEJM 2020;382(2):140-151.

MEDALIST BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS[1]

	Luspatercept (N=153)	Placebo (N=76)
Median age (min, max), years	71 (40, 95)	72 (26, 91)
Age categories, n (%)		
< 65 years	29 (19.0)	16 (21.1)
65 – 74 years	72 (47.1)	29 (38.2)
≥ 75 years	52 (34.0)	31 (40.8)
Time since diagnosis of MDS[a], months		
Mean (SD)	57.8 (56.6)	52.7 (42.3)
Median (Min, Max)	44.0 (3, 421)	36.1 (4, 193)
MDS Classification[b], n (%)		
MDS with refractory anemia with ring sideroblasts (RARS)	7 (4.6)	2 (2.6)
MDS with refractory cytopenia with multilineage dysplasia (RCMD-RS)	145 (94.8)	74 (97.4)
Other[c]	1 (0.7)	0 (0.0)
≥15% ring sideroblasts, n (%)	153 (100.0)	76 (100.0)
***SF3B1*, n (%)**		
Mutated	141 (92.2)	65 (85.5)
Nonmutated	12 (7.8)	10 (13.2)
Missing	0 (0.0)	1 (1.3)
Hemoglobin (g/dL)		
Mean (SD)	7.7 (0.8)	7.7 (0.8)
Median (Min, Max)	7.6 (6, 10)	7.6 (5, 9)

[a]Time since original MDS diagnosis was defined as the number of years from the date of original diagnosis to the date of informed consent. [b]Per the WHO 2008 criteria.
[c]Locally diagnosed MDS-RS and multilineage dysplasia. MDS, myelodysplastic syndromes; WHO, World Health Organization.
[1]Celgene Incorporation. REBLOZYL® Product Monograph. February 11, 2021.

MEDALIST BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS[1]

	Luspatercept (N=153)	Placebo (N=76)
IPSS-R Classification Risk Category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
High	1 (0.7)	0 (0.0)
ECOG performance status, n (%)		
0	54 (35.3)	33 (43.4)
1	91 (59.5)	32 (42.1)
2	8 (5.2)	11 (14.5)
Serum EPO (U/L) categories[a], n (%)		
< 100	51 (33.3)	31 (40.8)
100 to < 200	37 (24.2)	19 (25.0)
200 to 500	43 (28.1)	15 (19.7)
> 500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0 (0.0)
RBC transfusions/8 weeks over 16 weeks categories, n (%)		
≥ 6 units	66 (43.1)	33 (43.4)
< 6 units	87 (56.9)	43 (56.6)
≥ 4 and < 6 units	41 (26.8)	23 (30.3)
< 4 units	46 (30.1)	20 (26.3)
Prior ESA, n (%)	148 (96.7)	70 (92.1)

[a]Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug. ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; IPSS-R, International Prognostic Scoring System – Revised; MDS, myelodysplastic syndromes; RBC, red blood cell.

[1]Celgene Incorporation. REBLOZYL® Product Monograph. February 11, 2021.

MEDALIST – TREATMENT EXPOSURE[1]

Treatment exposure	Luspatercept (N=153)	Placebo (N=76)
Median treatment duration, weeks (range)*	49 (6–114)	24 (7–89)
Median number of doses received, weeks (range)	16 (2–37)	8 (3–30)
Patients completing 24 weeks of treatment, n (%)	128 (83.7)	68 (89.5)
Patients completing 48 weeks of treatment, n (%)	78 (51.0)	12 (15.8)
Patients remaining on treatment at data cutoff, n (%)	70 (45.8)	6 (7.9)
Maximum dose received, n (%)		
1.0 mg/kg	35 (22.9)	5 (6.6)
1.33 mg/kg	28 (18.3)	8 (10.5)
1.75 mg/kg	90 (58.8)	63 (82.9)

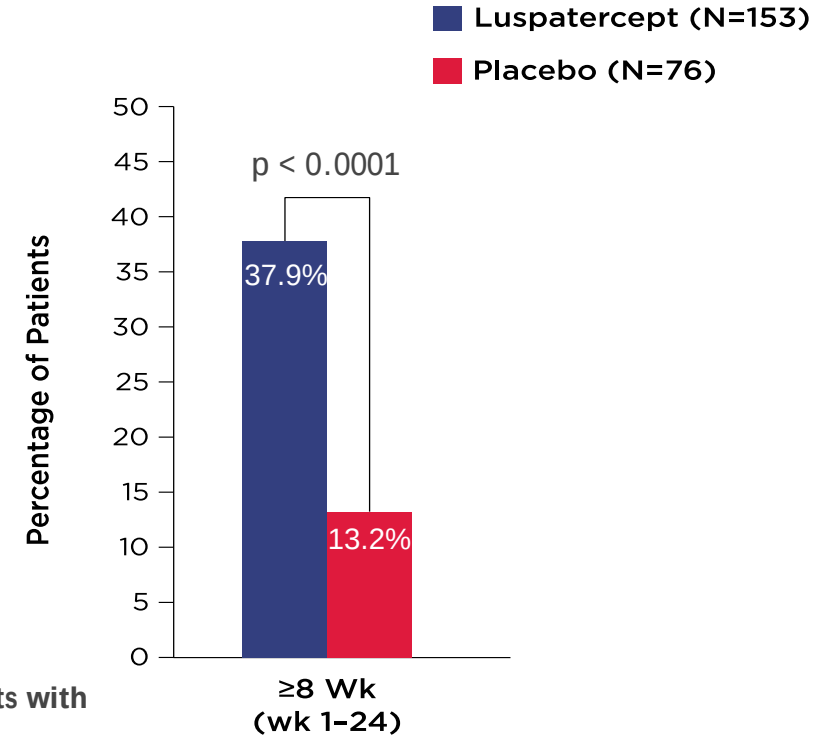
*Calculated as ([treatment end date] – [date of first dose] + 1)/7. Treatment end date was the date of last dose plus 20 days, date of study discontinuation or death, whichever occurred earlier.
Data cutoff: May 8, 2018. [1]Fenaux P, et al. *New England Journal of Medicine*. 2020;382:140-151.

PRIMARY ENDPOINT: RBC TRANSFUSION INDEPENDENCE (RBC-TI) ≥8 WEEKS[1]

37.9% of patients receiving luspatercept as opposed to 13.2% of patients receiving placebo reached RBC-TI* for ≥8 weeks (*p*<0.0001†, risk difference 24.6; 95% CI 14.5, 34.6)

Of the patients who achieved the primary endpoint, 62% (36/58) had more than 1 episode of RBC-TI during the treatment period

- 22 patients (14%) in the luspatercept group, who met the primary endpoint‡ had maintained their response at 1 year



No. of patients with Response (%)	≥8 Wk (wk 1–24)
Luspatercept	58 (37.9)
Placebo	10 (13.2)

*Defined as the absence of any RBC transfusion during any consecutive 56-day (8-week) period during the primary phase of the treatment period (first 24 weeks of double-blind treatment). †2-sided p-value from Cochran-Mantel-Haenszel (CMH) test stratified for average baseline RBC transfusion requirement (≥6 units vs. <6 units for RBC per 8 weeks), and baseline IPSS-R score (very low or low vs. intermediate); ‡The primary endpoint was TI for 8 weeks or longer during weeks 1-24

EPO, erythropoietin; CI, confidence interval; RBC, red blood cell; RBC-TI, red blood cell transfusion independence.

[1]Celgene Incorporation. REBLOZYL® Product Monograph. February 11, 2021.

MEDALIST – NUMBER OF RESPONSES FOR RBC-TI ≥8 W

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

36 of 58 patients (62%) in the luspatercept group who had a response had at least 2 response intervals of TI ≥8 weeks during treatment

All the patients with a response in the placebo group had two or fewer response intervals

* Primary endpoint is defined as the absence of any red blood cell transfusion during any consecutive 56-day period during weeks 1–24; † Eleven patients were transfusion-free during the entire post-treatment period.
TI, transfusion independence.
Data cutoff: May 8, 2018. [1]Fenaux P, et al. *New England Journal of Medicine*. 2020;382:140-151.

MEDALIST – NUMBER OF RESPONSES FOR RBC-TI ≥8 WEEKS

n / total n of responders (%)	Dose level*		
	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg
RBC-TI ≥8 weeks (weeks 1–24)	52/58 (89.7)†	2 (3.4)	2 (3.4)
RBC-TI ≥8 weeks (weeks 1–48)	47/69 (68.1)	5/69 (7.2)	7/69 (10.1)
RBC-TI ≥12 weeks (weeks 1–48)	33/51 (64.7)	3/51 (5.9)	4/51 (7.8)

52 of 58 patients (90%) had their first response at 1.0 mg per kilogram

4 patients (7%) had their first response after dose increases
2 patients increased to 1.33 mg/kg
2 patients increased to 1.75 mg/kg

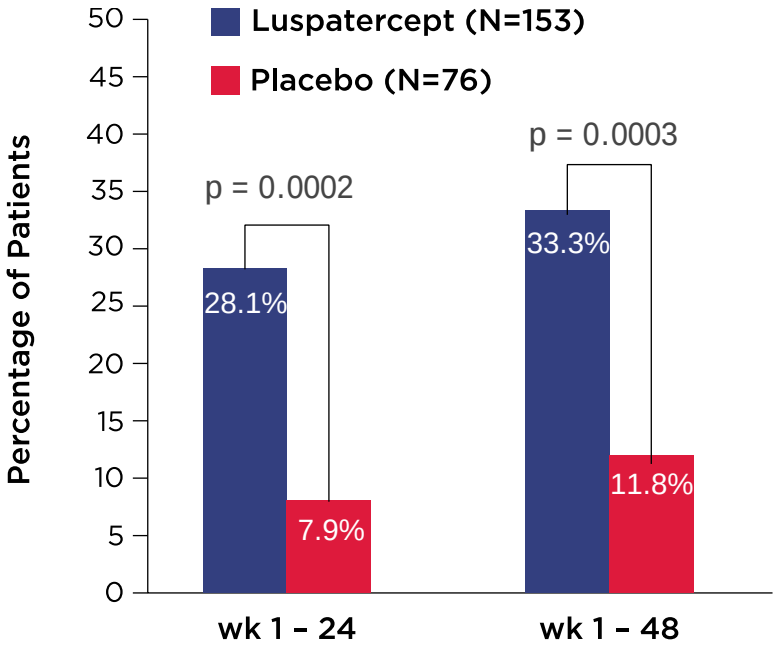
* First responses at 0.8 mg/kg not shown; † 15/58 (25.9%) patients initially responded at 1.0 mg/kg luspatercept and had subsequent responses at the same dose level; 14/58 (24.1%) patients initially responded at 1.0 mg/kg luspatercept and had subsequent responses at higher dose levels.
RBC, red blood cell; TI, transfusion independence.
Data cutoff: May 8, 2018. [1]Fenaux P, et al. *New England Journal of Medicine*. 2020;382:140-151.

MEDALIST – RBC-TI FOR ≥12 WEEKS[1]

A key secondary endpoint during the MEDALIST trial included RBC-TI for ≥12 during weeks 1 – 24* and during weeks 1 – 48†

During weeks 1 – 24, 28.1% of patients treated with luspatercept and 7.9% receiving placebo achieved RBC-TI for ≥12 weeks (*p*=0.0002‡; risk difference 20.0; 95% CI 10.9, 29.1)

During weeks 1 – 48, 33.3% of patients on luspatercept and 11.8% of patients on placebo achieved RBC-TI for ≥ 12 weeks (*p*=0.0003‡; risk difference 21.4; 95% CI 11.2, 31.5)



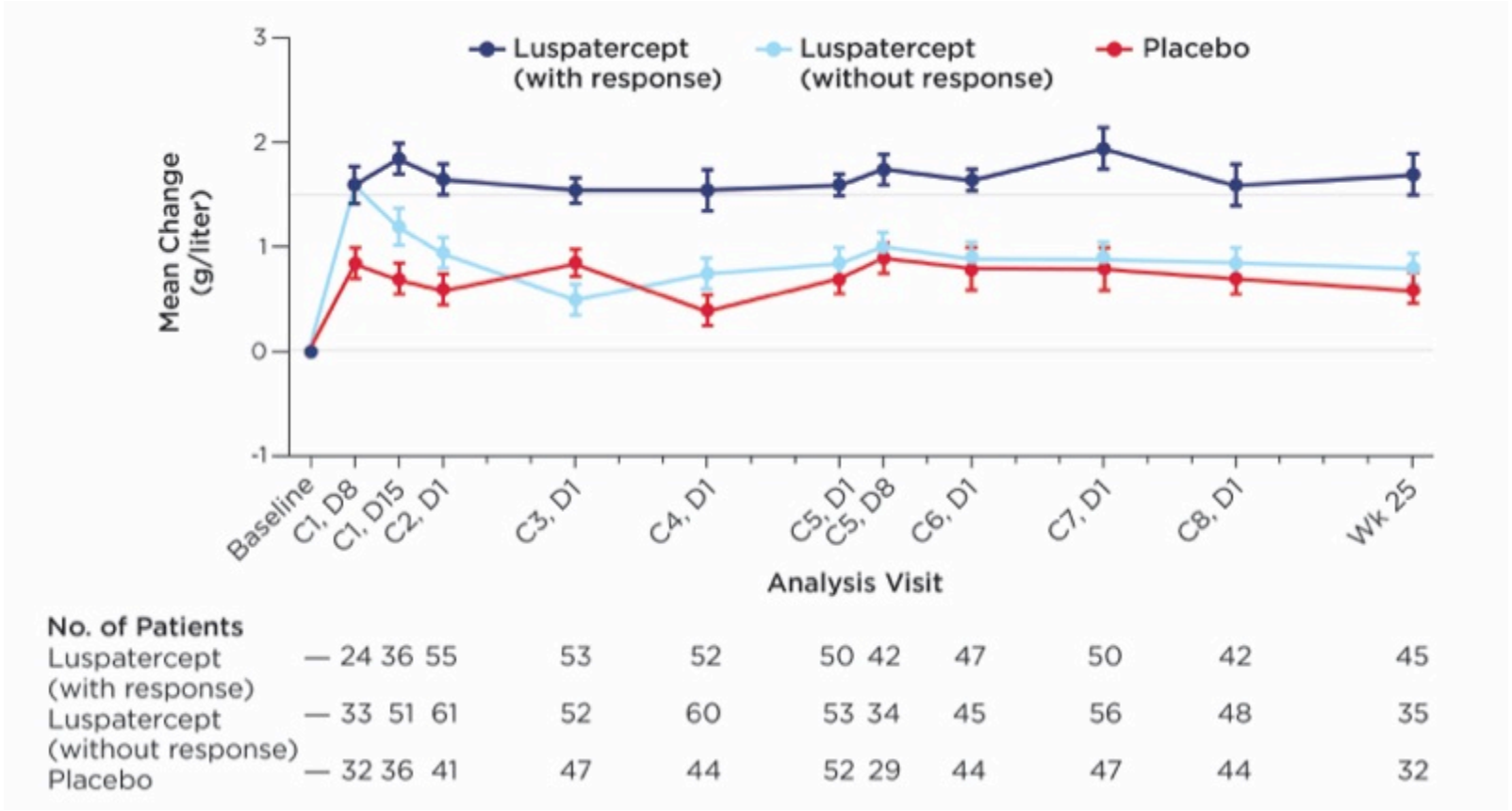
No. of patients with Response (%)	wk 1 – 24	wk 1 – 48
Luspatercept	43 (28.1)	51 (33.3)
Placebo	6 (7.9)	9 (11.8)

*Defined as the absence of any RBC transfusion during any consecutive 84-day (12 week) period during the primary phase of the treatment period (first 24 weeks of double-blind treatment). †Defined as the absence of any RBC transfusion during any consecutive 84-day (12 week) period during Week 1 to Week 48. ‡2-sided p-value from Cochran-Mantel-Haenszel (CMH) test stratified for average baseline RBC transfusion requirement (≥6 units vs. <6 units for RBC per 8 weeks), and baseline IPSS-R score (very low or low vs. intermediate). CI, confidence interval; RBC-TI, red blood cell transfusion independence.

[1]Celgene Incorporation. REBLOZYL® Product Monograph. February 11, 2021.

MEDALIST – HEMOGLOBIN RESPONSE[1]

Change from baseline in hemoglobin level



No. of Patients										
Luspatercept (with response)	—	24	36	55	53	52	50	42	47	50	42	45
Luspatercept (without response)	—	33	51	61	52	60	53	34	45	56	48	35
Placebo	—	32	36	41	47	44	52	29	44	47	44	32

In the luspatercept group, increases in the hemoglobin level were greater over time among patients who had a response regarding transfusion independence

Among those who had a response, the median peak increase in the hemoglobin level was 2.55 g/dL (range, 1.0 – 4.1)

Data cutoff: May 8, 2018. [1]Fenaux P, et al. *New England Journal of Medicine*. 2020;382:140-151.

MEDALIST – EFFECT ON IRON OVERLOAD[1]

Patients in the luspatercept group had a greater reduction in mean serum ferritin level from baseline compared to those receiving placebo (averaged over weeks 9 – 24)[1]

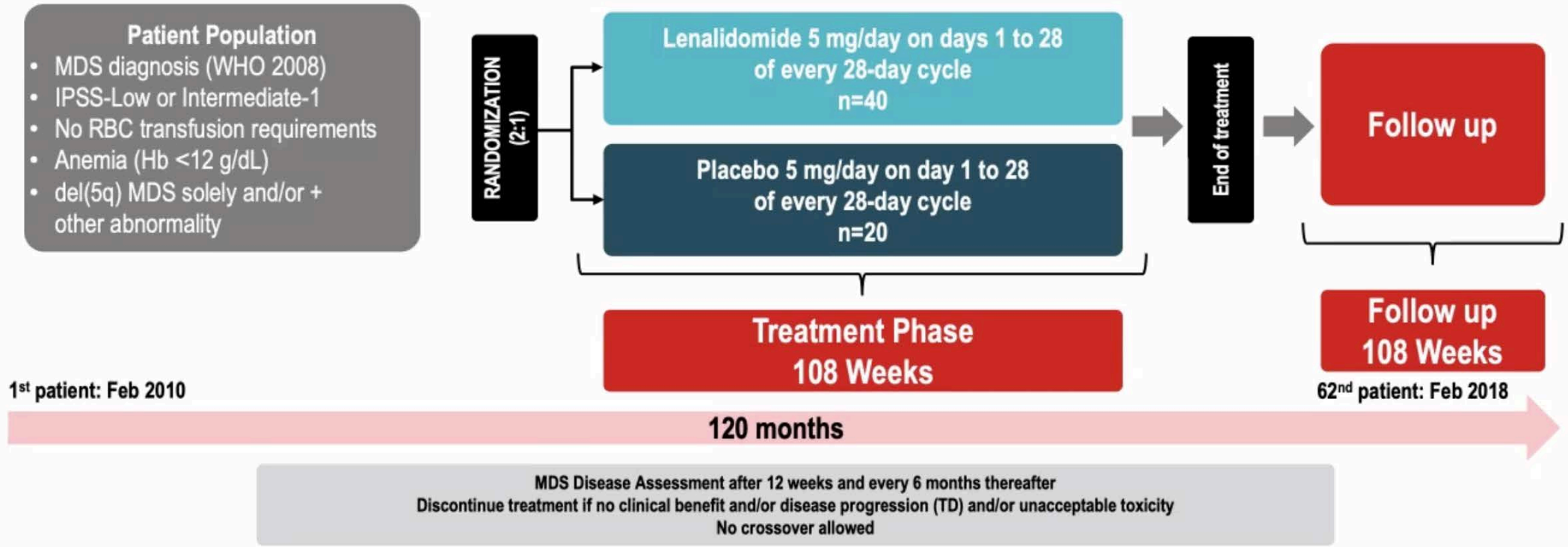
Mean Serum Ferritin Change from Baseline[1]	Luspatercept (N=153)	Placebo (N=76)
Averaged over weeks 9 – 24		
No.	148	74
Least-squares mean (SE), µg/L	-2.7 (54.05)	226 (68.02)
Least-squares mean differences (luspatercept vs. placebo) (SE) (95% CI)	-229.1 (74.43) (-375.8, -82.4)	
Averaged over weeks 33 – 48		
No.	89	16
Least-squares mean (SE), µg/L	-72.0 (74.76)	247.4 (140.96)
Least-squares mean differences (luspatercept vs. placebo) (SE) (95% CI)	-319.5 (144.57) (-606.3, -32.7)	

CI, confidence interval; No., number; SE, standard error.
Data cutoff: May 8, 2018. [1]Fenaux P, et al. New England Journal of Medicine. 2020;382:140-151.

#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.)

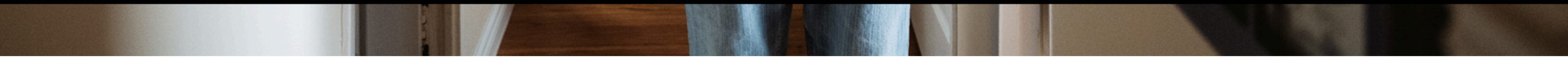
JB

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



Hb, hemoglobin; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndrome; RBC, red blood cell; TD, transfusion dependency; WHO, World Health Organization

López Cadenas F, et al. Presented at ASH 2022; Abstract 460; Oral presentation; Session: 637. Myelodysplastic Syndromes – Clinical and Epidemiological III. Sunday, December 11, 2022: 5:15 PM.



Reflections on a rich and remarkable life

In 2019, an MDS diagnosis stopped Bob Markovich in his tracks. With his condition now under control, he's able to look back on a life well-lived while remaining focused on the future

Tania Amardeil
October 25, 2022

https://www.macleans.ca/longforms/reflections-on-a-rich-and-remarkable-life/