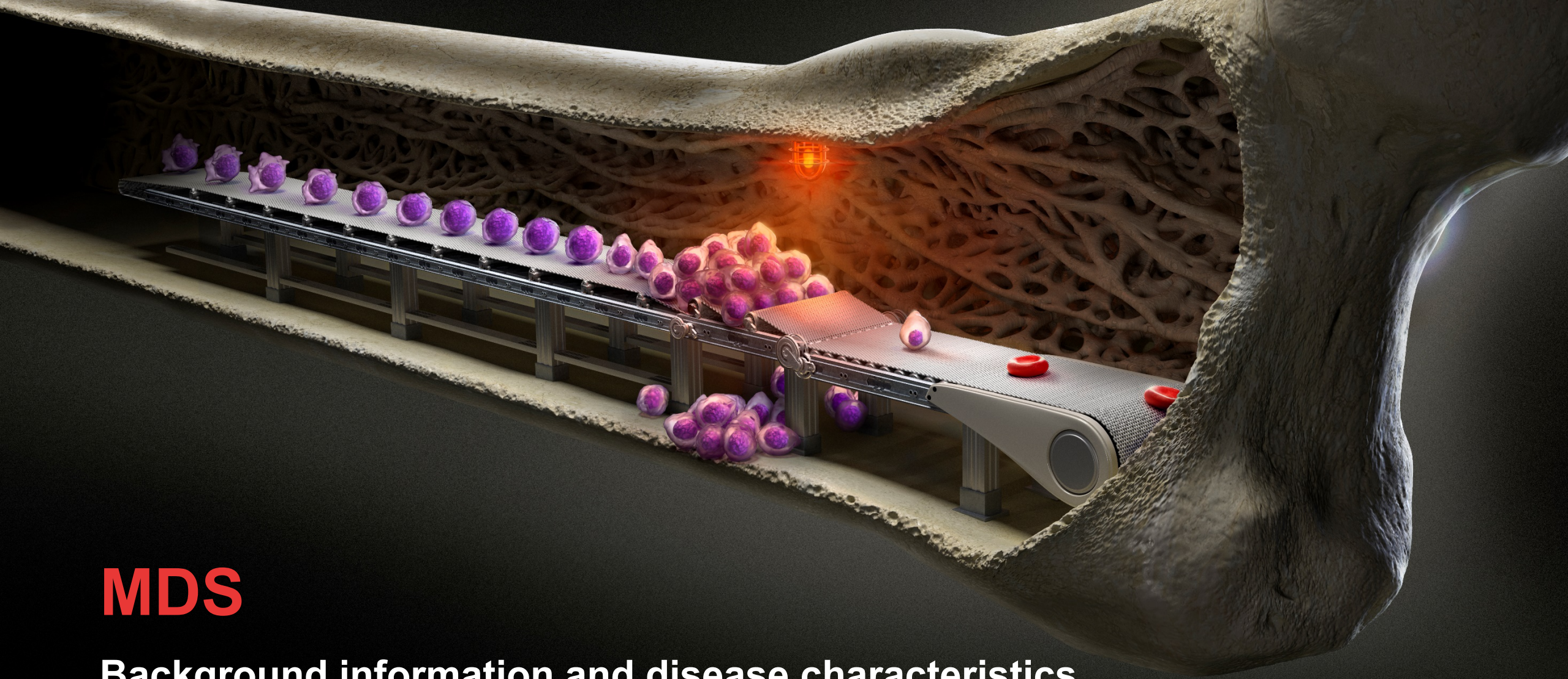


MDS

Background information and disease characteristics

Enter

Contents

Myelodysplastic syndromes (MDS)

MDS are a diverse and heterogeneous group of malignant disorders[1,2]

- MDS are characterized by ineffective hematopoiesis, dysplasia in hematopoietic cells, cytopenias, and increased risk of progression to AML

MDS are frequently underdiagnosed[3]

- Many patients are asymptomatic or have relatively mild cytopenias, leading to under-recognition of MDS
- Anemia is not a normal consequence of aging and is recommended that elderly patients with unexplained anemia should be evaluated for MDS

MDS are myeloid malignancies, which are clonal HSC diseases comprising chronic and acute disorders[4]

AML is an aggressive myeloid malignancy, which can either occur *de novo* or arise from a previous chronic stage with additional alterations[4]

Chronic myeloid disorders include:

- MPN
- MDS
- CMML

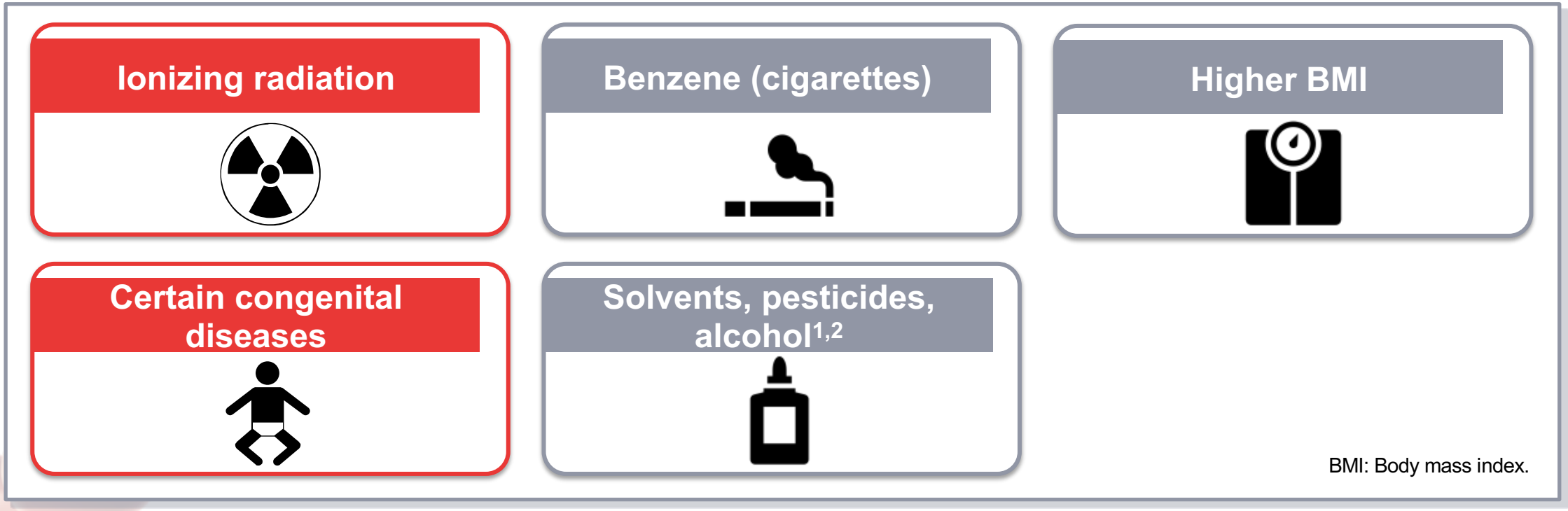
1. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. *Blood* 2013;121:4280–4286.
2. Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.
3. Zeidan AM, Faltas B, Smith D, *et al*. Myelodysplastic syndromes: what do hospitalists need to know? *J Hosp Med* 2013;8:351–357.
4. Murati A, Brecqueville M, Devillier R, *et al*. Myeloid malignancies: mutations, models and management. *BMC Cancer* 2012;12:304.

AML: Acute myeloid leukemia.
HSC: Hematopoietic stem cell.
MPN: Myeloproliferative neoplasms.
CMML: Chronic myelomonocytic leukemia.

HE-CA-2100003E

Causes of MDS

- Most cases of MDS are primary (*de novo*) with unknown origin[1]
- Some factors, such as environmental and occupational exposures, genetic syndromes, and obesity may increase the risk of developing MDS[1,2]



1. Bowen DT. Occupational and environmental etiology of MDS. *Best Pract Res Clin hematol* 2013;26:319–326.
2. Zeidan AM, Faltas B, Smith D, *et al*. Myelodysplastic syndromes: what do hospitalists need to know? *J Hosp Med* 2013;8:351–357.

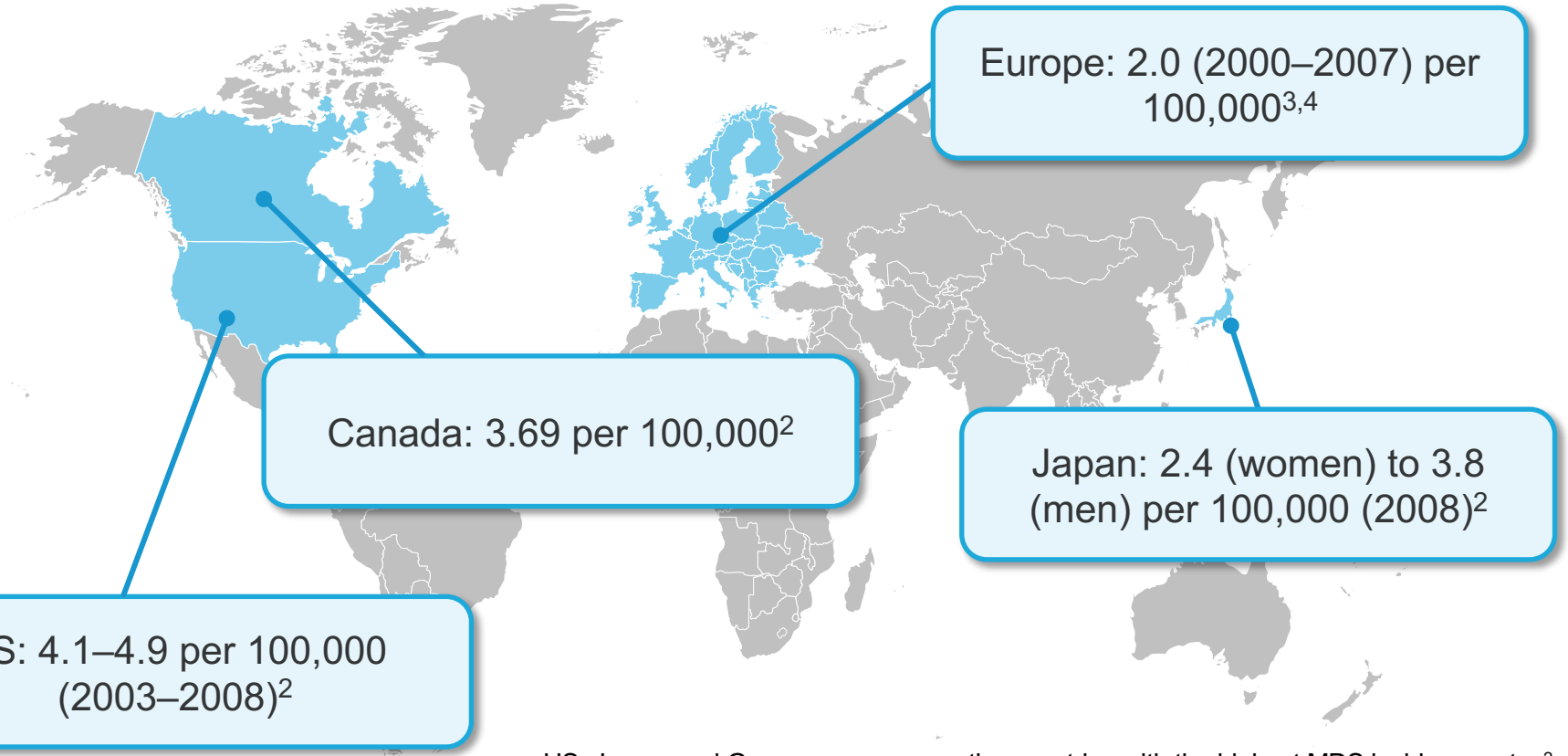
Epidemiology: Incidence and prevalence

MDS affects more than 350,000 people worldwide[1]

Prevalence and incidence in Canada[5]

- It is estimated that 10,000–40,000 patients in Canada have been diagnosed with MDS
- Approximately 1,800–5,900 new cases are diagnosed each year in Canadians >65 years

Incidence



US, Japan, and Germany are among the countries with the highest MDS incidence rates[2]

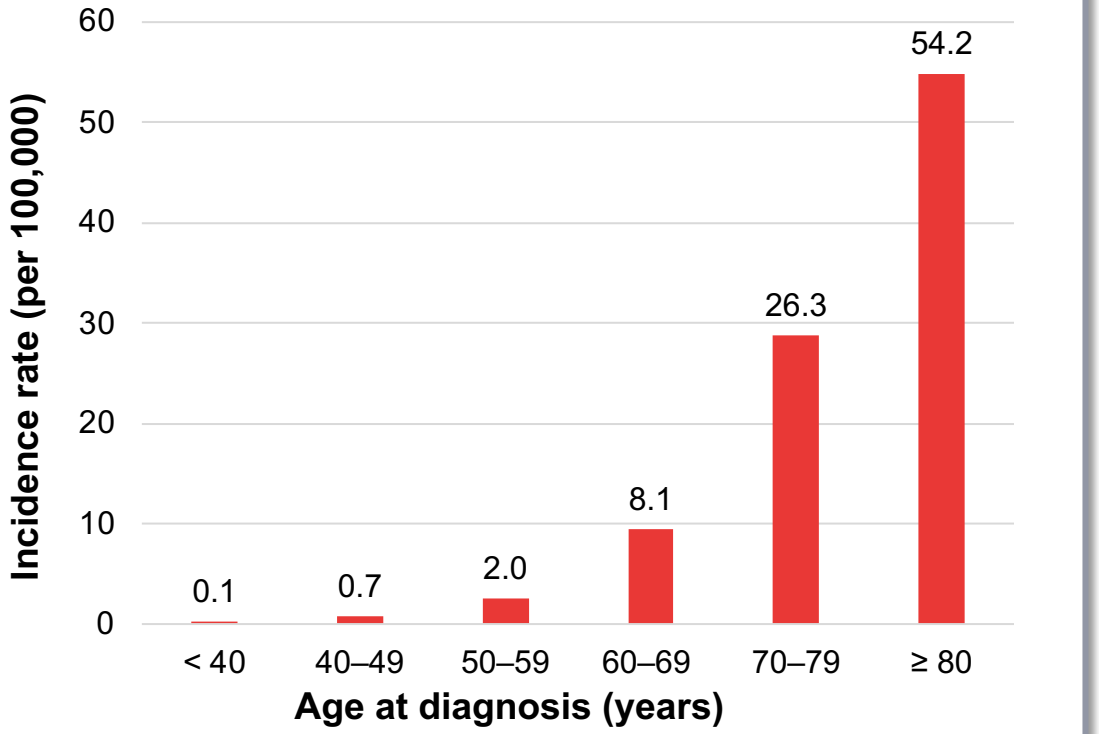
1. Research and Markets. Global Myelodysplastic Syndrome (MDS) Market 2017-2027: Prevalence Forecast, Licensing and Acquisition Deals & Drug-Specific Revenue Forecasts. Accessed September 2020 at: https://www.globenewswire.com/news-release/2018/01/22/1298306/0/en/Global-Myelodysplastic-Syndrome-MDS-Market-2017-2027-Prevalence-Forecast-Licensing-and-Acquisition-Deals-Drug-Specific-Revenue-Forecasts.html 2. Slack J, Nguyen L, Naugler C, *et al*. Incidence of myelodysplastic syndromes in a major canadian metropolitan area. *JALM* 2018;3:378-383. 3. Visser O, Trama A, Maynadie M, *et al*. Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer* 2012;48:3257-3266. 4. Executive Agency for Health and Consumers. Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases. Accessed September 2020 at: http://www.rarecarenet.eu/fact_sheets.php 5. Leukemia and Lymphoma Society of Canada. Facts and Statistics. Accessed September 2020 at: https://www.llscanada.org/disease-information/facts-and-statistics

Epidemiology: Incidence according to age

Age is the greatest risk factor for developing MDS[1]

- The median age of diagnosis for MDS is 76 years[2]
- Incidence rates increase drastically in individuals >80 years[3]
- The prevalence of MDS is expected to increase with the aging population even if the age-specific incidence rates and survival remain stable[2,3]

Age-adjusted US incidence rates for MDS (2013–2017)[4]

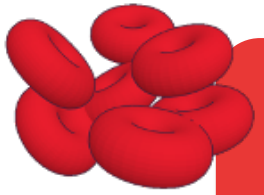


1. Sekeres M. Epidemiology, natural history, and practice patterns of patients with myelodysplastic syndromes in 2010. *J Natl Compr Canc Netw* 2011;9:57–63.
2. Ma, X. Epidemiology of myelodysplastic syndromes. *Am J Med* 2012;125:S2–S5.
3. Zeidan AM, Faltas B, Smith D, *et al*. Myelodysplastic syndromes: what do hospitalists need to know? *J Hosp Med* 2013;8:351–357.
4. National Cancer Research Institute. SEER Cancer Statistics Review 2013–2017. Accessed September 2020 at: https://seer.cancer.gov/csr/1975_2017/results_merged/sect_30_mds.pdf

HE-CA-2100003E

Clinical presentation of MDS

- Almost all patients with MDS present symptoms related to underlying cytopenias[1]
- Anemia is the most common cytopenia and is observed in > 80% of patients with MDS[1]



Anemia[1]

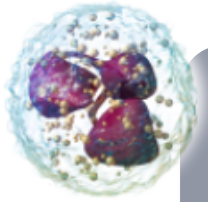
Fatigue

Shortness of breath

Pale skin

Weakness

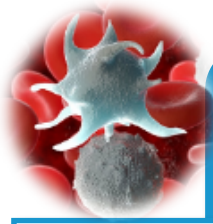
Cardiovascular symptoms (chest pain, heart palpitations)



Neutropenia[1–3]

Infections and related symptoms

Fever



Thrombocytopenia[1–3]

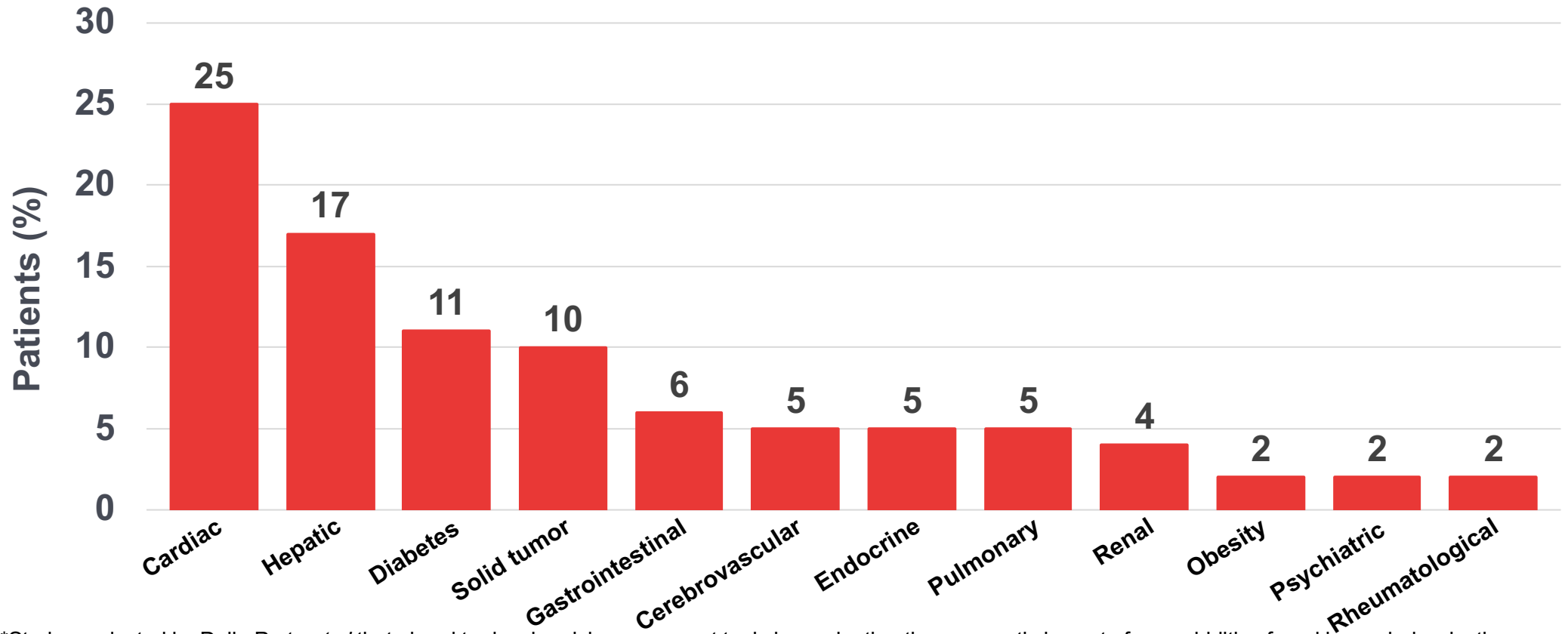
Increased bruising

Bleeding

1. Balducci L. Transfusion independence in patients with myelodysplastic syndromes. *Cancer* 2006;106:2087–94.
2. Bryan J, Jabbour E, Prescott H, *et al*. Thrombocytopenia in patients with myelodysplastic syndromes. *Semin Hematol* 2010;47:274–280.
3. Canadian Cancer Society. Myelodysplastic syndromes. Accessed September 2020 at: https://www.cancer.ca/en/cancer-information/cancer-type/leukemia/leukemia/myelodysplastic-syndromes/?region=on

Clinical presentation: Comorbidities

The prevalence of comorbidities at time of MDS diagnosis (N = 840)[1]*

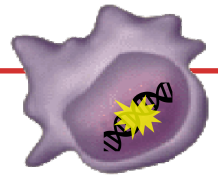


*Study conducted by Della Porta *et al* that aimed to develop risk assessment tools by evaluating the prognostic impact of comorbidities found in myelodysplastic syndromes through a learning cohort (N=840) from Pavia, Italy.

1. Della porta MG, Malcovati L, Strupp C, *et al*. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *hematologica* 2011; 96: 441–449.

Ineffective erythropoiesis in MDS[1,2]

Mutations in the hematopoietic stem cells

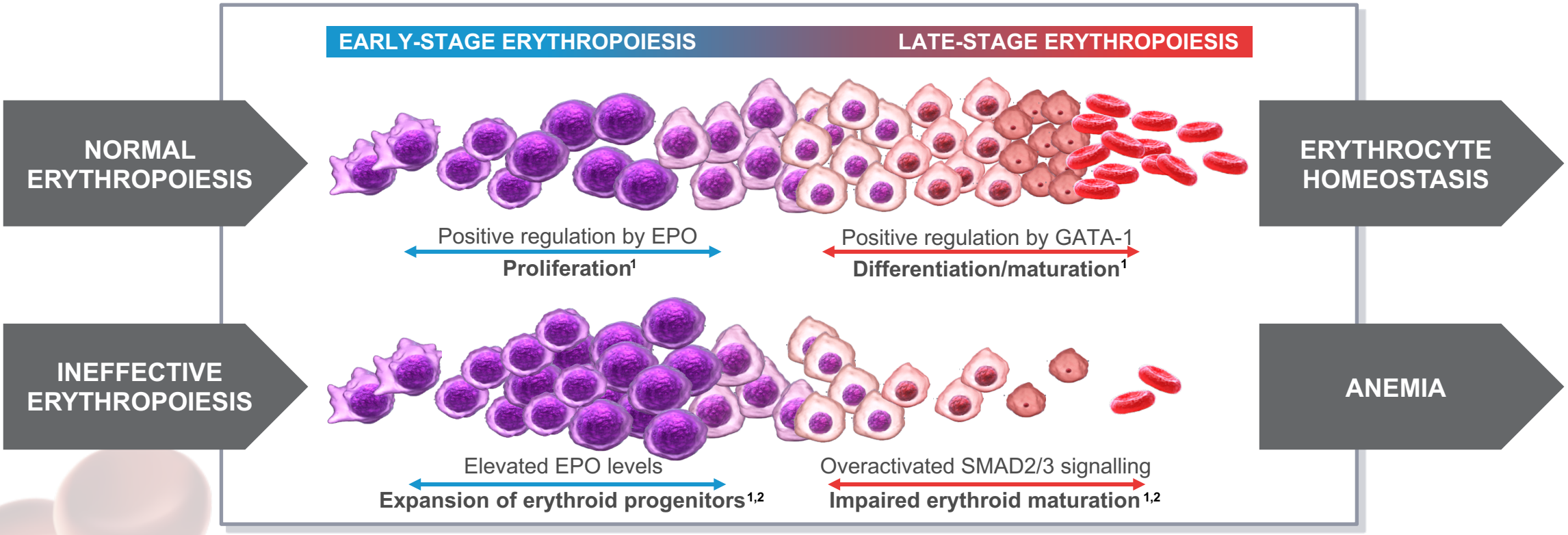


→ Impaired differentiation of precursor cells → **Ineffective hematopoiesis and erythropoiesis** → Anemia and other cytopenias

1. Zeidan AM, Faltas B, Smith D, *et al*. Myelodysplastic syndromes: what do hospitalists need to know? *J Hosp Med* 2013;8:351–357.
2. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). *Int J Hematol* 2018;107:55–63.

Ineffective erythropoiesis (IE)

IE is characterized by the proliferation of erythroid progenitors, increased apoptosis of erythroblasts and impaired maturation[1]



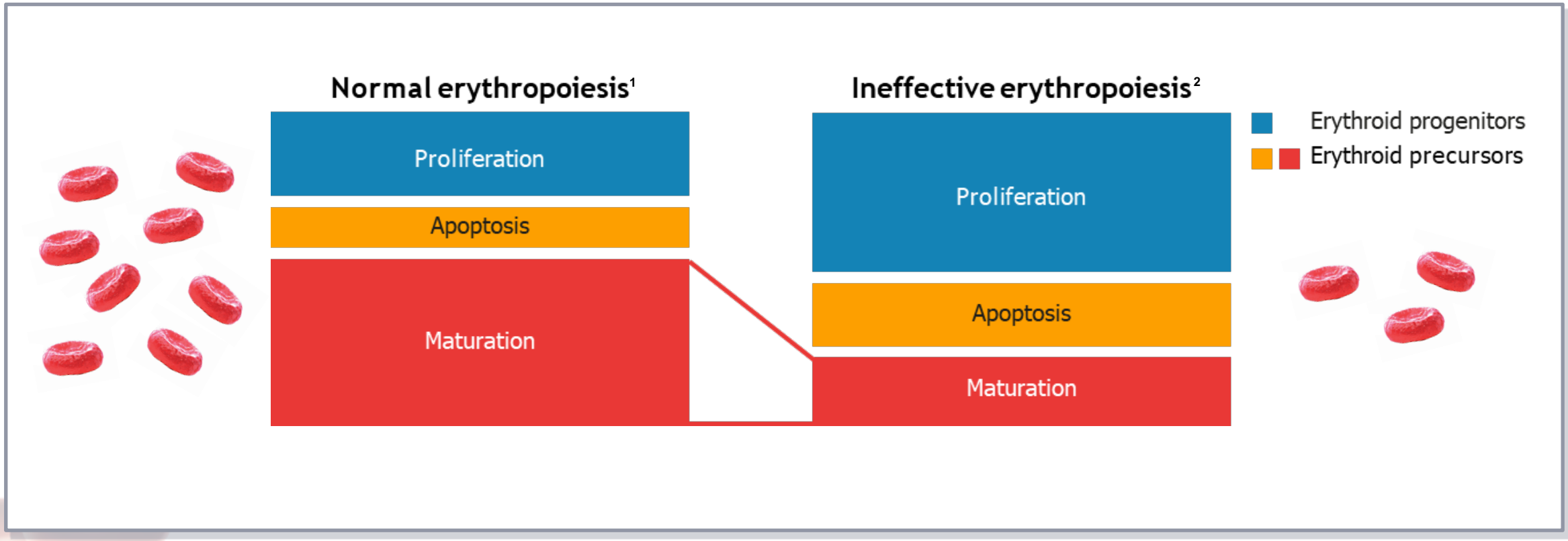
EPO: Erythropoietin.

1. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130–143.
2. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *hematologica* 2018;103:1593–1603.

HE-CA-2100003E

Characteristics of IE

IE is an ongoing pathological state where increased erythroid proliferation is unable to restore red blood cell counts[1,2]

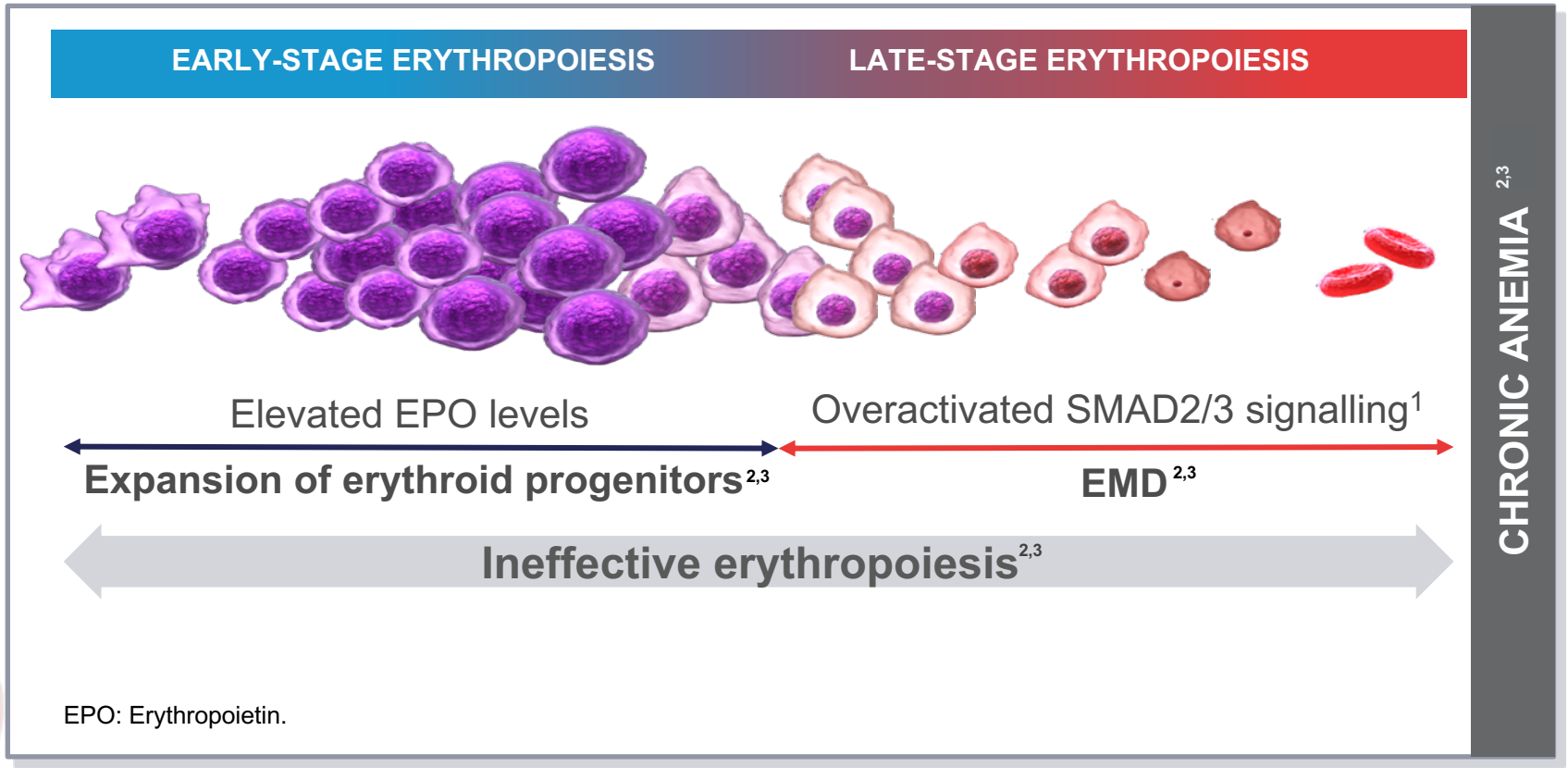


1. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J hematol* 2016;172:512–523.
2. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J hematol* 2016;174:661–673.

Erythroid maturation defects (EMDs)

EMDs form the underlying mechanism of ineffective erythropoiesis[1]

These defects occur in late-stage erythropoiesis and contribute to IE and chronic anemia observed in MDS[1,2]



EPO: Erythropoietin.

1. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J hematol* 2016;174:661–673.
2. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *hematologica* 2018;103:1593–1603.
3. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130–143.

HE-CA-2100003E

EMDs: Dysregulation of TGF-β signalling

Overactivated TGF-β superfamily signalling via SMAD2/3 contributes to impaired erythroid maturation in select hematologic diseases[1,2]

Elevated levels of select TGF-β superfamily ligands lead to increased activation of the SMAD2/3 signalling pathway via the ActRII receptor[4]

↓

Increased phosphorylation of SMAD2/3 and translocation of signalling complexes into the nucleus[2]

↓

SMAD2/3 signalling complexes negatively regulate late-stage differentiation of erythroblasts

↓

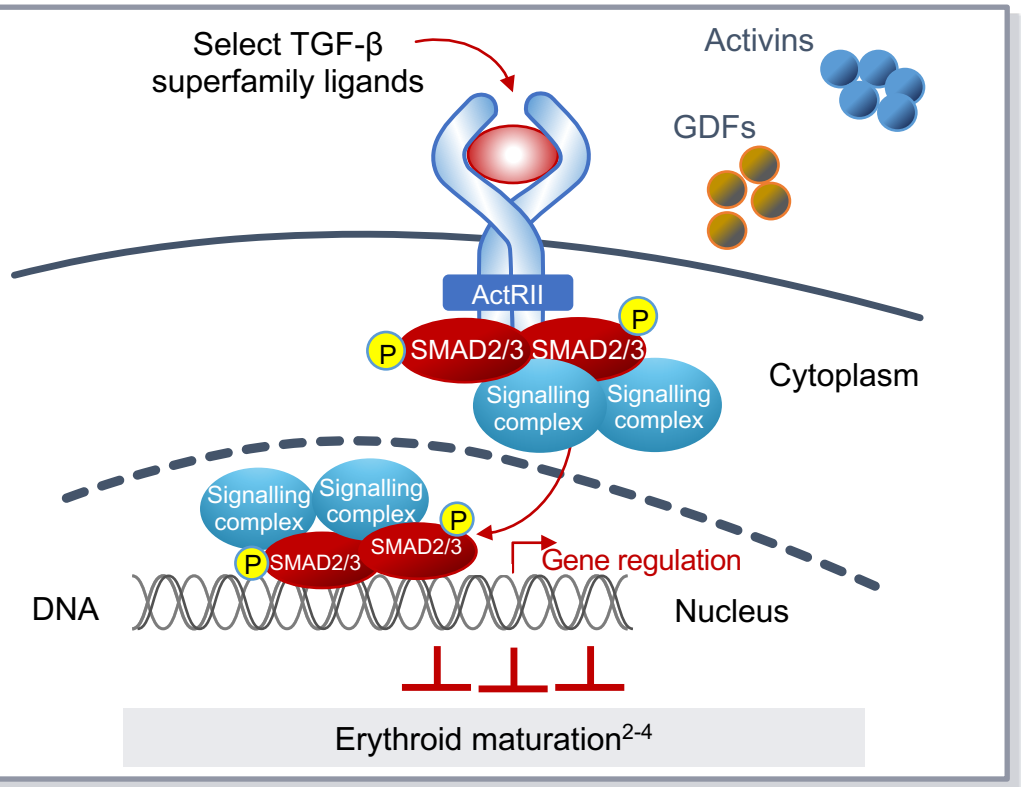
Impaired maturation of erythroblasts into terminally-differentiated erythrocytes[2]

↓

Fewer mature erythrocytes released into the bloodstream[2,5]

↓

IE and chronic anemia[6]



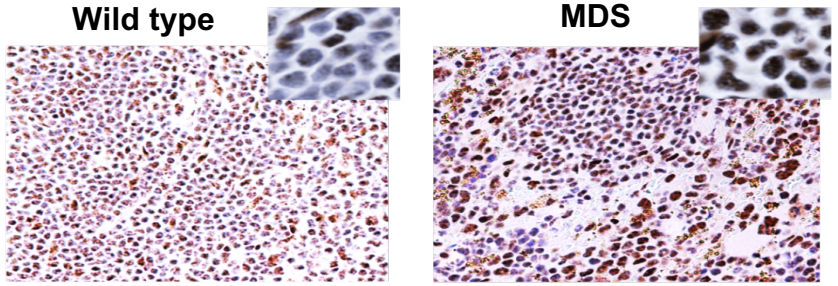
TGF: Transforming growth factor.
GDF: Growth differentiation factor.
DNA: Deoxyribonucleic acid.

1. Torres LDS, Okumura JV, da Silva DG, *et al*. Plasma levels of TGF-β1 in homeostasis of the inflammation in sickle cell disease. *Cytokine* 2016;80:18–25.
2. Zhou L, Nguyen AN, Sohal D, *et al.* Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. *Blood* 2008;112:3434–3443.
3. Suragani RN, Cadena SM, Cawley SM*, et al*. Transforming growth factor-beta superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med* 2014;20:408–414.
4. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130–143.
5. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J hematol* 2016;172:512–523.
6. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J hematol* 2016;174:661–673.

EMDs: Dysregulation of TGF-β signalling

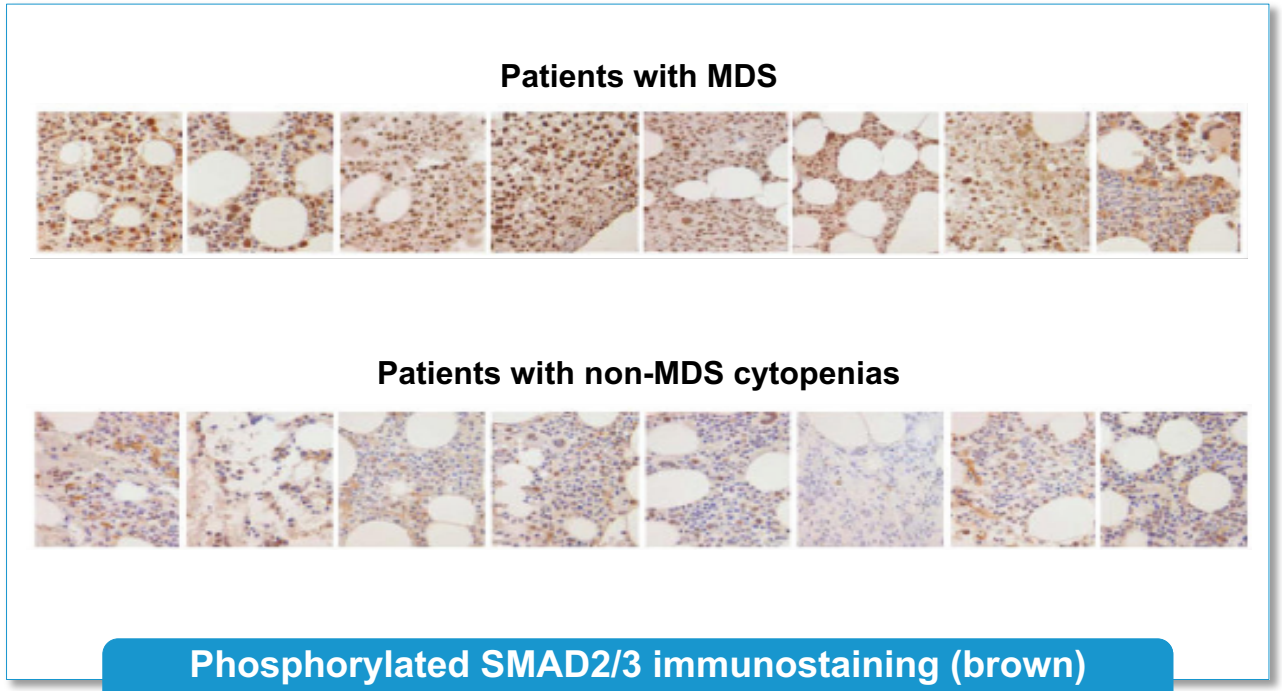
Increased TGF-β superfamily signalling via SMAD2/3 is commonly observed in MDS[1]

IN MICE



Phosphorylated SMAD2/3 immunostaining (brown) in spleen sections[1]

IN HUMANS



Phosphorylated SMAD2/3 immunostaining (brown) of bone marrow biopsies[2]

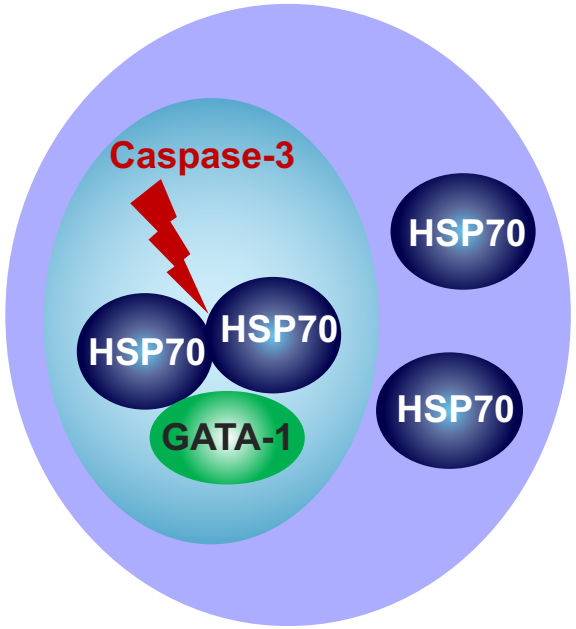
1. Suragani RN, Cawley SM, Li S, *et al.* Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine b-thalassemia. *Blood* 2014;123(25):3864–3872.
2. Zhou L, Nguyen AN, Sohal D, *et al.* Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. *Blood* 2008;112:3434–3443.

HE-CA-2100003E

EMDs: GATA-1 degradation

Low levels of GATA-1 contribute to EMDs and IE, which are commonly seen in MDS[1]

NORMAL ERYTHROPOIESIS

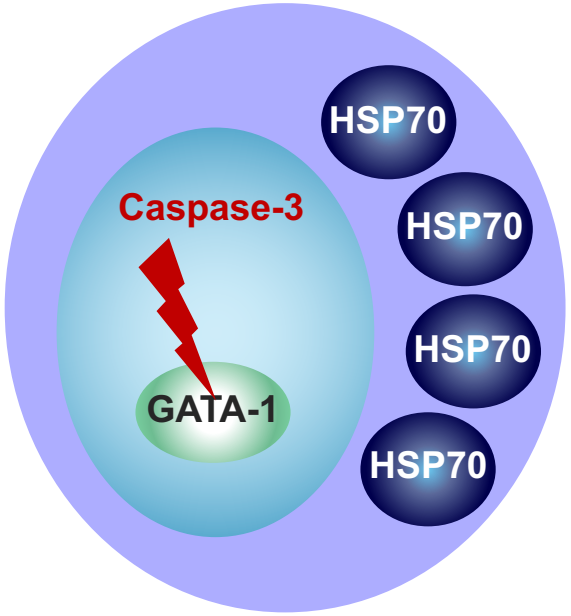


Healthy adult: HSP70 translocates into the nucleus and **protects GATA-1** from cleavage by caspase-3[1]

GATA-1 available to induce differentiation and maturation of erythroid progenitors[1]

MATURATION

EMD



MDS: GATA-1 expression is decreased and HSP70 does not accumulate in the nucleus[2]

GATA-1 is cleaved by caspase-3 and is not available to exert anti-apoptotic effects or induce differentiation and maturation[1]

APOPTOSIS / MATURATION ARREST

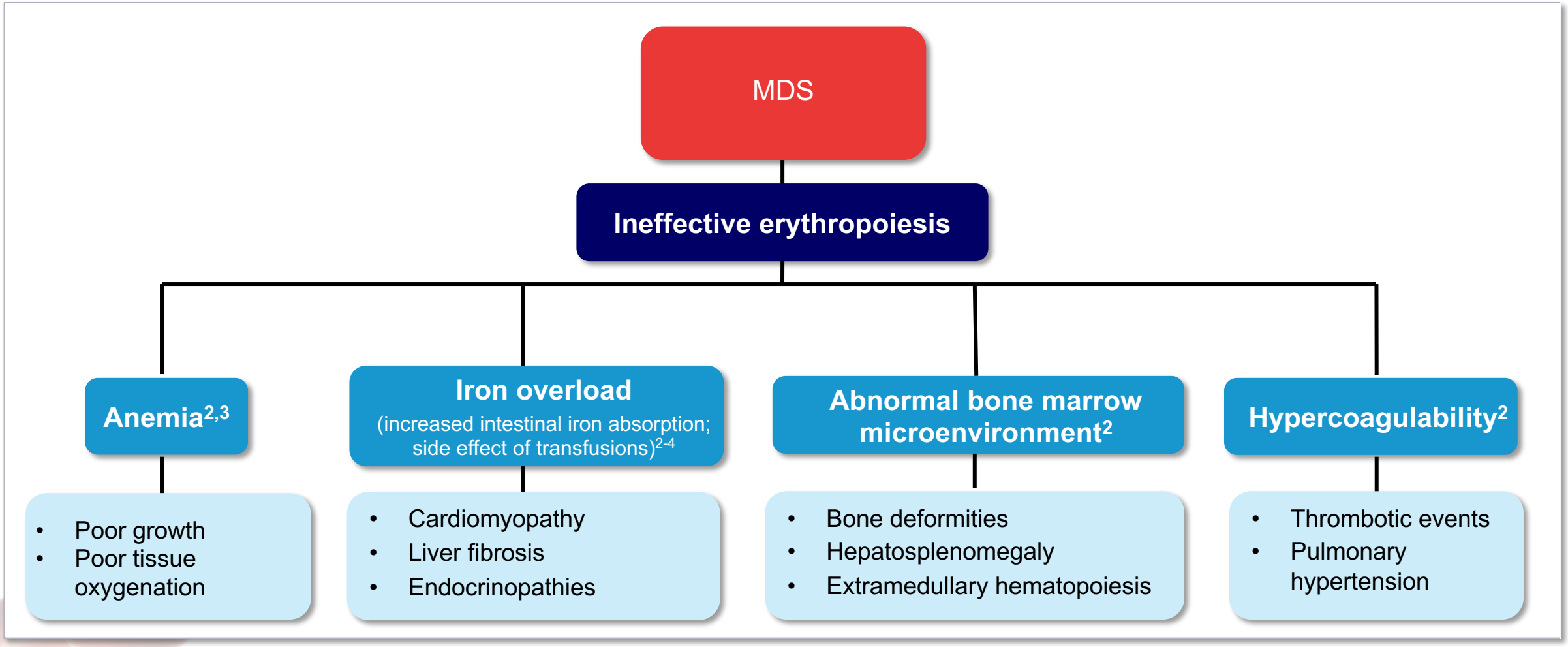
HSP: Heat shock protein.

1. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *hematologica* 2018;103:1593–1603.
2. Frisan E, Vandekerckhove J, de Thonel A, *et al*. Defective nuclear localization of Hsp70 is associated with dyserythropoiesis and GATA-1 cleavage in myelodysplastic syndromes. *Blood* 2012;119(6):1532–1542.

HE-CA-2100003E

Implications of IE

IE may contribute to a range of symptoms and complications in patients with MDS[1]



1. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J hematol* 2016;172:512–523.
2. Sleiman J, Tarhini A, Bou-Fakhredin R, *et al*. Non-transfusion-dependent thalassemia: An update on complications and management. *Int J Mol Sci* 2018;19: 182.
3. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). *Int J Hematol* 2018;107:55–63.
4. Munoz M, Villar I, Garcia-Erce JA. An update on iron physiology. *World J Gastroenterol* 2009;15:4617–4626.

HE-CA-2100003E

Anemia is an underlying condition of MDS

Anemia is characterized by the shortage of functional hemoglobin or red blood cells that reduces oxygen delivery to tissues[1]

Ineffective erythropoiesis (IE) is a pathological state that results in low RBC count and contributes to anemia[1,2]

Anemia results in lower[1,2]

Number of circulating RBCs

Hb levels

- According to the WHO, Hb levels <12 g/dL in women or <13 g/dL in men are indicative of anemia

Hematocrit levels

- Percentage volume of packed RBCs in a blood specimen

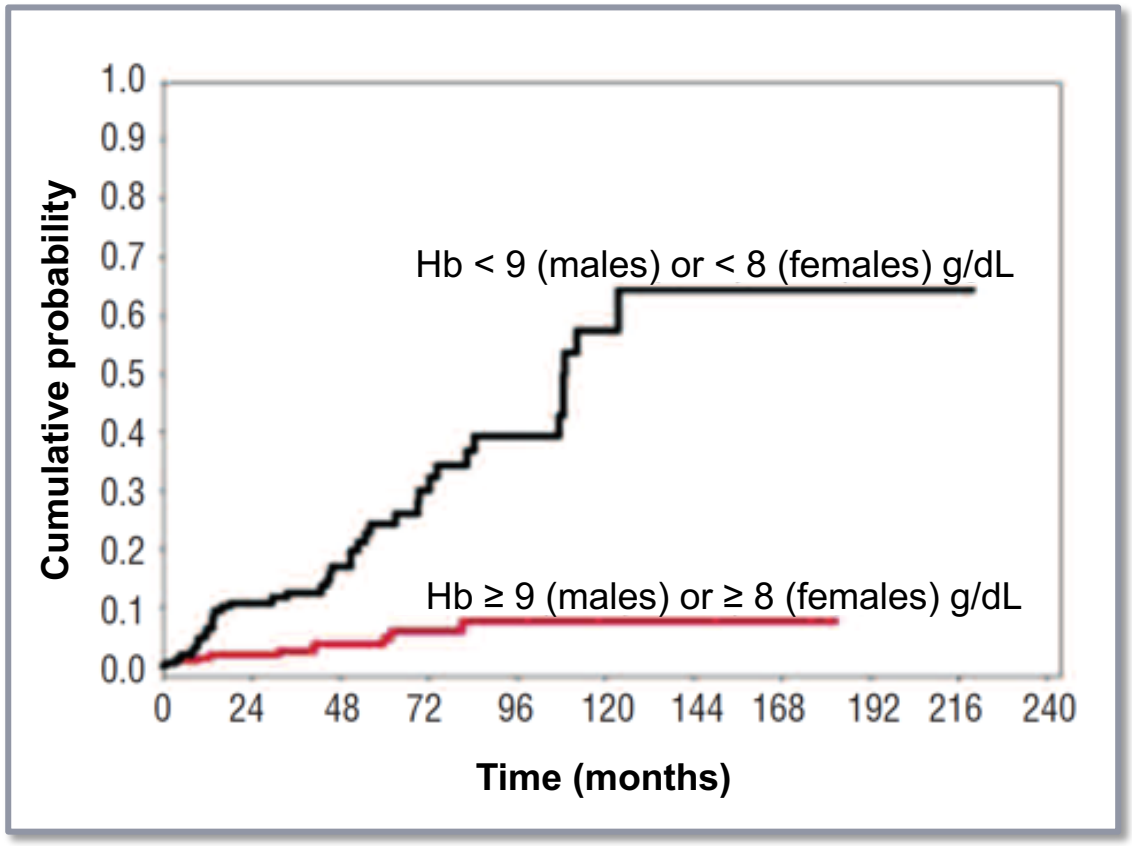
This condition may develop into chronic, severe anemia, which is frequently observed in a range of hematological disorders, often as a result of ineffective erythropoiesis.[3,4]

WHO: World Health Organization.
RBC: Red blood cell.

1. Kassebaum NJ. The global burden of anemia. *Hematol Oncol Clin N Am* 2016;30:247–308.
2. Smith RE. The clinical and economic burden of anemia. *Am J Manag Care* 2010;16:S59–S66.
3. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130–143.
4. Balducci L. Transfusion independence in patients with myelodysplastic syndromes. *Cancer* 2006;106:2087–94.

Anemia is correlated with reduced survival in MDS

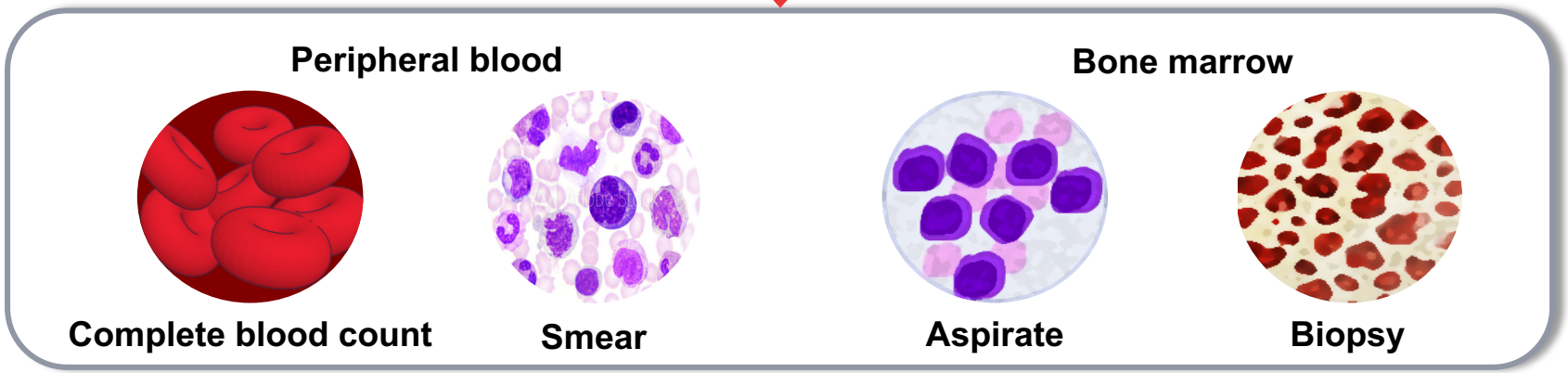
Probability of developing cardiac disease and death according to degree of anemia in patients with MDS (n = 840)[1]



1.Malcovati L, Della Porta MG, Strupp C, *et al*. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *hematologica* 2011;96:1433–1440.

Diagnosis of MDS

Dysplastic features found in blood cells should be morphologically examined to diagnose MDS[1]



The assessment of dysplasia on peripheral blood and bone marrow smears is the mainstay for MDS diagnosis[1]

1. Malcovati L, Hellstrom-Lindberg E, Bowen D, *et al*. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; 122: 2943–2964.

Diagnostic approaches to MDS

Blood tests[1]	• Complete blood counts and blood biochemistry; also test for alternative causes of cytopenia such as viral infections, and low levels of iron, vitamin B12 or folate
Cell morphology[1]	• Assessment of dysplasia is the mainstay for an MDS diagnosis • Enumeration of blasts is critical for an accurate MDS classification
Cytogenetic analysis[1]	• Detecting clonal chromosomal abnormalities allows conclusive diagnosis and prognostic classification, and should be performed in all patients with suspected MDS
Mutational analysis[1]	• Detection of somatic mutations can allow conclusive diagnosis and reliable prognosis • *SF3B1* mutations are the only mutations included in the MDS WHO 2016 classification

WHO: World Health Organization.

1. Malcovati L, Hellstrom-Lindberg E, Bowen D, *et al*. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; 122: 2943–2964.

Genetic defects including cytogenetic abnormalities and mutations are common in MDS[1]

Cytogenetic abnormalities[1-3]

- Cytogenetic abnormalities are observed in 50–60% of patients with MDS
- Clonal and recurrent cytogenetic abnormalities are often present at disease presentation

Most common **single cytogenetic abnormalities** include:

- del(5q)
- monosomy 7 or del(7q)
- trisomy 8
- del(20q)[2]

Genetic mutations[3]

- MDS patients carry a median of 9 mutations in coding regions of the genome
- Despite the prevalence of certain mutations, there is no unique mutation signature associated with MDS

Genes most commonly implicated in MDS are involved in distinct cellular pathways including:

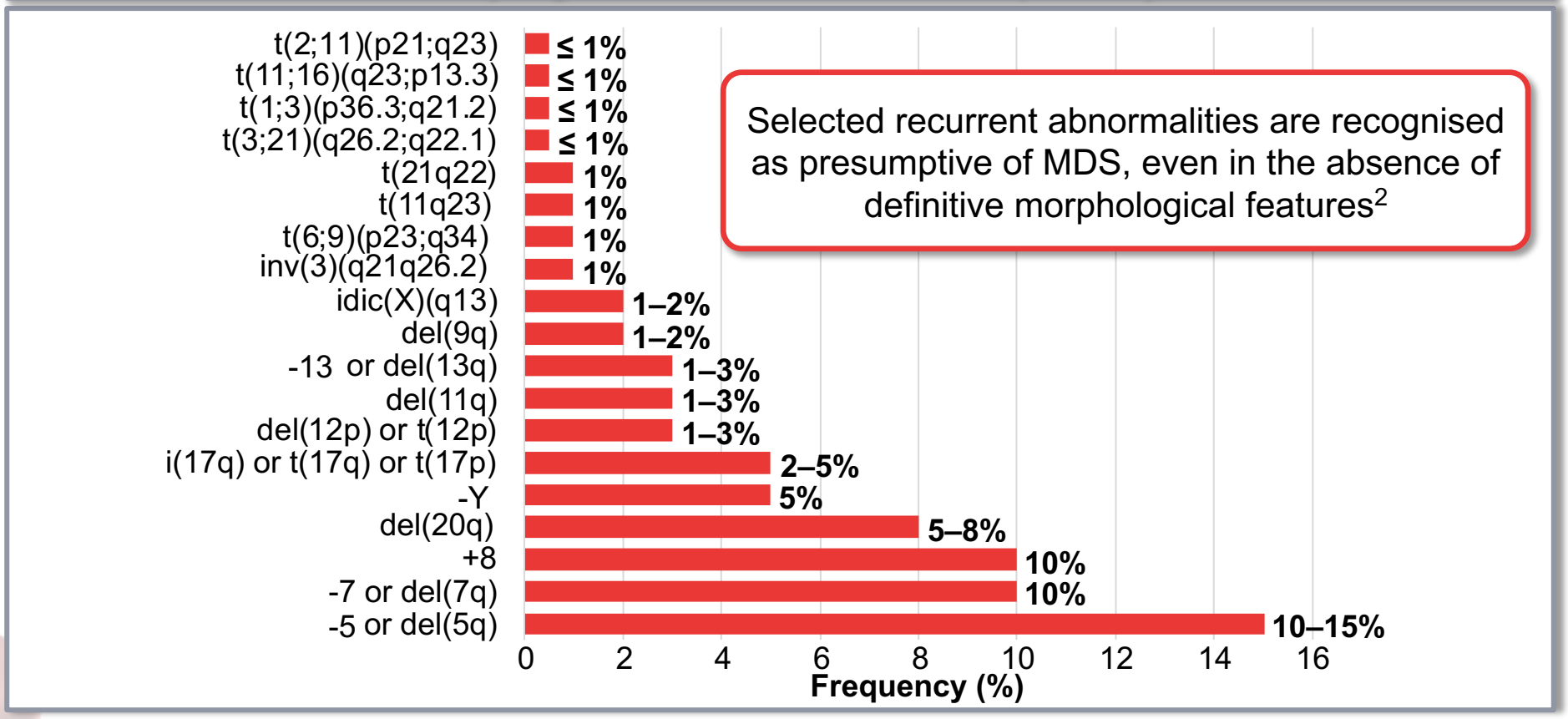
- Epigenetic regulation (DNA methylation, chromatin modification)
- RNA splicing
- Transcription[3]

del: Deletion.

1. Visconte V, Tiu RV, Rogers HJ. Pathogenesis of myelodysplastic syndromes: an overview of molecular and non-molecular aspects of the disease. *Blood Res* 2014; 49: 216–227.
2. Malcovati L, Hellstrom-Lindberg E, Bowen D, *et al*. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; 122: 2943–2964. 3.Ogawa S. Genetics of MDS. *Blood* 2019;133:1049–1059.

Cytogenetic abnormalities

Recurrent cytogenetic abnormalities in primary MDS[1,2]



del: Deletion.

1. Visconte V, Tiu RV, Rogers HJ. Pathogenesis of myelodysplastic syndromes: an overview of molecular and non-molecular aspects of the disease. *Blood Res* 2014; 49: 216–227.
2. Malcovati L, Hellstrom-Lindberg E, Bowen D, *et al*. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; 122: 2943–2964.

HE-CA-2100003E

Genetic mutations

Distribution of recurrent mutations and karyotypic abnormalities in MDS[1]

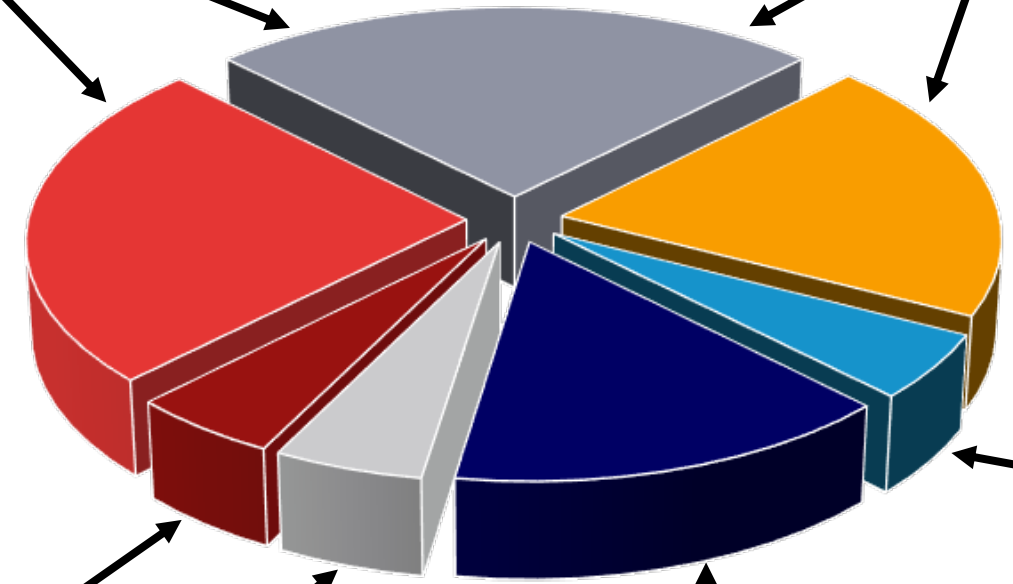
Splicing factors (~50%)
- *SF3B1* (18%)
- *U2AF1* (12%)
- *SRSF2* (12%)
- *ZRSR2* (5%)
- Others (5%)

Rarely co-occur with each other

Overlap in splicing factor and epigenetic regulator (25%)

Epigenetic regulators (~45%)
- *TET2* (20%)
- *ASXL1* (15%)
- *DNMT3A* (12%)
- *EZH2* (5%)
- *IDH1/2* (5%)
- Others (5%)

Often co-occur except for *TET2* and *IDH*



TP53 and no splicing factor or epigenetic regulator (~5%)
Often complex karyotypes with frequent del(5q), abnormal chromosome 7 and monosomies. Other mutations less frequent

No common abnormality (~5%)

Karyotype abnormality (~5%)

Mutations in other genes (~15%)
- Transcription factors (*RUNX1, ETV6, PHF6, GATA2*)
- Kinase signalling (*NRAS, KRAS, JAK2, CBL)*
- Cohesins (*STAG2, SMC3, RAD21*)
- DNA repair

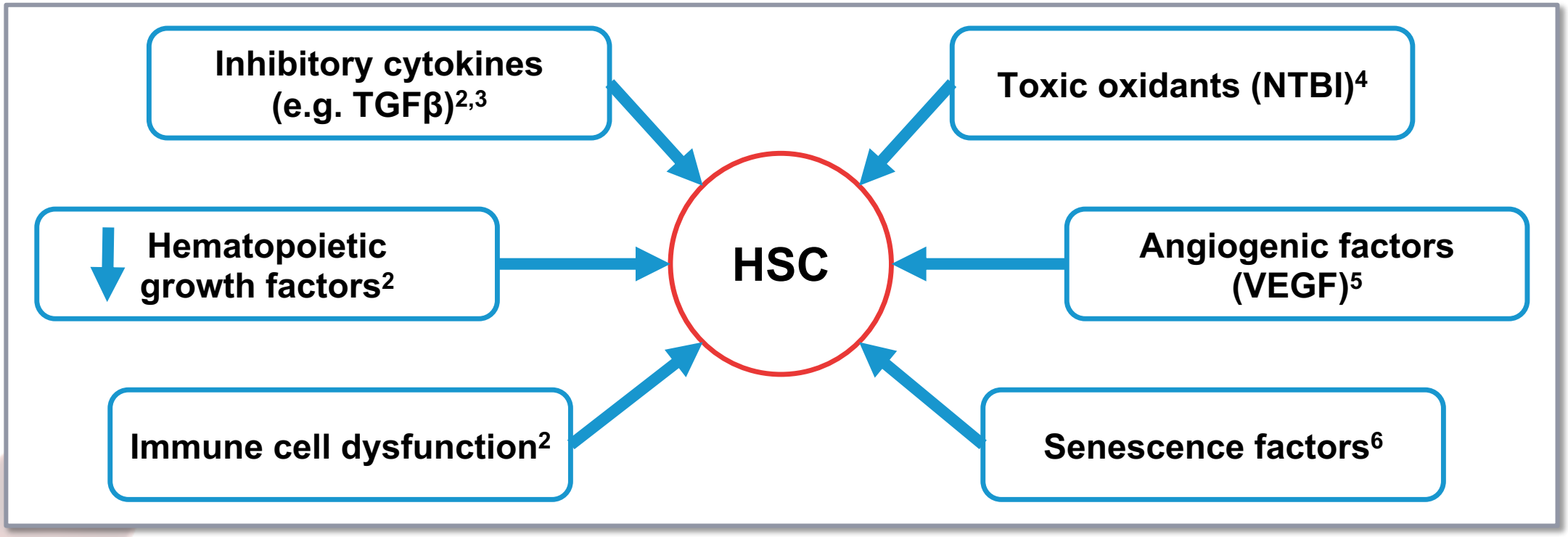
Adapted from Bejar R and Steensma DP.

del: Deletion.

1. Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood* 2014;124:2793–2803.

Marrow microenvironmental factors in MDS

- Bone marrow contains HSCs that exist within a complex and dynamic microenvironment with cellular and molecular factors to regulate hematopoiesis[1]
- Aberrant interactions between hematopoietic stem cells and the microenvironment may contribute to MDS pathogenesis[1]



HSC: Hematopoietic stem cell. TGFβ: Transforming growth factor beta. NTBI: Non-transferrin-bound iron. VEGF: Vascular endothelial growth factor.

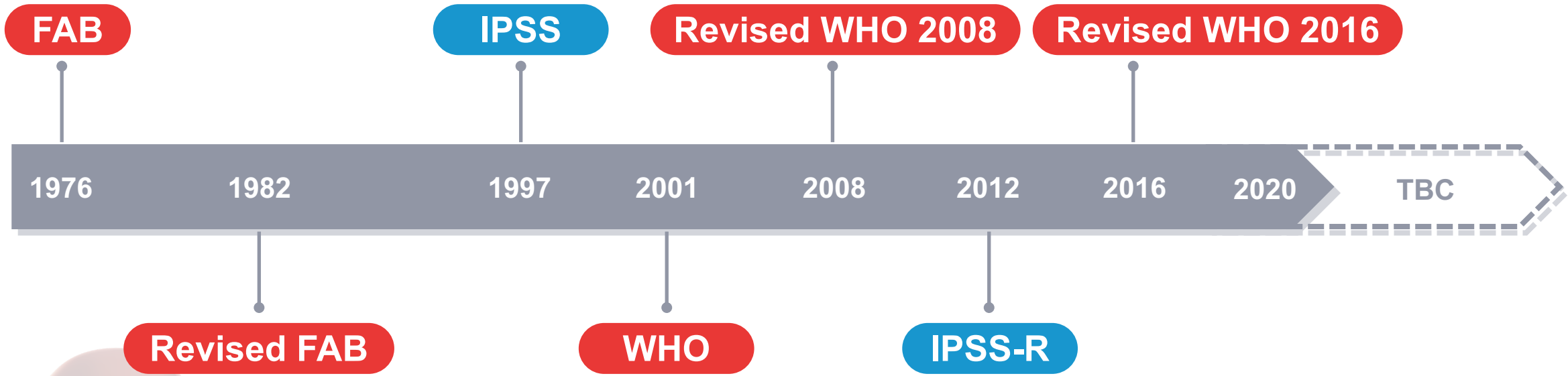
1. Rankin EB, Narla A, Park JK, *et al.* Biology of the bone marrow microenvironment and myelodysplastic syndromes. *Mol Genet Metab* 2015;116:24–28. 2. Barreyro L, Chlon TM, Starczynowski DT. Chronic immune response dysregulation in MDS pathogenesis. *Blood* 2018;132:1553–1560. 3. Teodorescu P, Pasca S, Dima D, *et al.* Targeting the microenvironment in MDS: The final frontier. *Front Pharmacol* 2020;11:1044. 4. de Swart L, Reiniers C, Bagguley T, *et al.* Labile plasma iron levels predict survival in patients with lower-risk myelodysplastic syndromes. *hematologica* 2018;103:69–79. 5. Wimazal F, Krauth MT, Vales A, *et al.* Immunohistochemical detection of vascular endothelial growth factor (VEGF) in the bone marrow in patients with myelodysplastic syndromes: correlation between VEGF expression and the FAB category. *Leuk Lymphoma* 2006;47:451–460. 6. Wang YY, Jian-nong C, Jun H, *et al.* Accelerated cellular senescence in myelodysplastic syndrome. *Exp Hematol* 2009;37:1310–1317.

HE-CA-2100003E

Classification systems

A number of systems have been developed to diagnose patients, classify disease subtypes, and determine prognosis[1,2]

Timeline of key diagnostic and prognostic scoring systems for MDS



FAB: French-American-British.
IPSS: International Prognostic Scoring System.
WHO: World Health Organization.
IPSS-R: International Prognostic Scoring System (revised).

1. Lorand-Metze I, Niero-Melo L, Buzzini R, *et al*. Guidelines part 2: Myelodysplastic syndromes – classification systems. *Hematol Transfus Cell Ther* 2018; 40: 262–266.
2. Bennett JM, Komrokji RS. The myelodysplastic syndromes: Diagnosis, molecular biology and risk assessment. *Hematology* 2005;10 Suppl 1:258–269.

WHO 2016 classification: MDS

MDS subtype	Dysplastic lineages	Cytopenias*	Ring sideroblasts	Blasts	Cytogenetics
MDS-SLD	1	1 or 2	< 15% or < 5% if *SF3B1* mutation is present	BM < 5%; PB < 1%; no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-MLD	2 or 3	1–3			
MDS-RS					
MDS-RS-SLD	1	1 or 2	≥ 15% or ≥ 5% if *SF3B1* mutation	BM < 5%; PB < 1%; no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS-MLD	2 or 3	1–3			
MDS with isolated del(5q)	1–3	1–2	None or any	BM < 5%; PB < 1%; no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del(7q)
MDS-EB					
MDS-EB-1	0–3	1–3	None or any	BM 5–9% or PB 2–4%; no Auer rods	Any
MDS-EB-2				BM 10–19% or PB 5–19% or Auer rods	
MDS-U					
With 1% blood blasts	1–3	1–3	None or any	BM < 5%; PB = 1%†; no Auer rods	Any
With SLD and pancytopenia	1	3	None or any	BM < 5%; PB < 1%; no Auer rods	Any
Based on defining cytogenetic abnormality	0	1–3	< 15%‡	BM < 5%; PB < 1%; no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1–3	1–3	None	BM < 5%; PB < 2%	Any

WHO: World Health Organization.
MDS-SLD: Myelodysplastic syndrome with single lineage dysplasia.
MDS-MLD: Myelodysplastic syndrome with multi lineage dysplasia.
PB: Peripheral blood.
BM: Bone marrow.
del: Deletion.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts.
MDS-RS-SLD: Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia.
MDS-RS-MLD: Myelodysplastic syndrome with ring sideroblasts and multi lineage dysplasia.
MDS-EB: Myelodysplastic syndrome with excess blasts.
MDS-U: Myelodysplastic syndromes unclassifiable.
SLD: Single lineage dysplasia.
ANC: Absolute neutrophil count.
*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 X 10^9/L; and ANC, <1.8 X 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 X 10^9/L.
†One percent PB blasts must be recorded on at least two separate occasions.
‡Cases with ≥15% ring sideroblasts have significant erythroid dysplasia and are classified as MDS-RS-SLD.

Adapted from Aber *et al.*

1. Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.

WHO classification: MDS-RS

- The hallmark of MDS-RS is the presence of ring sideroblasts (RS) – erythroid precursors in the bone marrow characterized by iron-rich mitochondria around the nucleus[1]
- RS can be detected in both clonal and non-clonal hematological disorders
  - Clonal hematological disorders include myeloid neoplasms such as MDS, MPN, MDS/MPN
  - Non-clonal hematological disorders include inherited or acquired sideroblastic anemia[2]

Ring sideroblasts can be visualized with Prussian blue staining (Perls reaction) and are characterized by a minimum of five siderotic granules across the nuclear circumference[1]

MDS-RS is classified as lower-risk MDS

A sub-type of MDS-RS-SLD, accounts for ~3–10% of all MDS cases[2]

WHO: World Health Organization.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts.
MPN: Myeloproliferative neoplasms.
MDS-RS-SLD: Myelodysplastic syndrome with single lineage dysplasia.

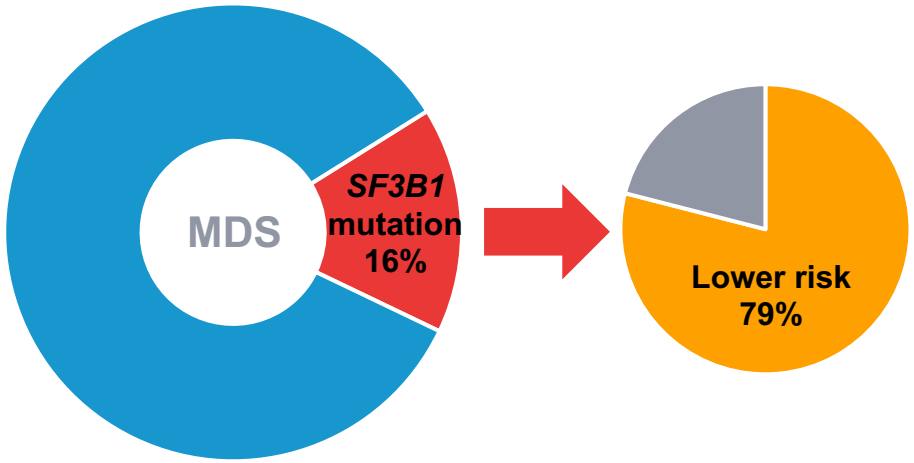
1. Malcovati L, Cazzola M. Recent advances in the understanding of myelodysplastic syndromes with ring sideroblasts. *Br J hematol* 2016 Sep;174(6):847–858.
2. Patnaik MM, Tefferi A. Refractory Anemia with Ring Sideroblasts (RARS) and RARS with Thrombocytosis (RARS-T) – "2019 update on diagnosis, risk-stratification, and management". *Am J Hematol* 2019 Apr;94(4):475–488.

WHO classification: MDS-RS and *SF3B1* mutations

Recurrent mutations in *SF3B1* are frequent in MDS and are associated with the presence of RS[1]

In one study, 16% of patients with MDS had *SF3B1* mutations.

The majority of patients with mutated *SF3B1* were found to have lower-risk MDS (79%)[4]



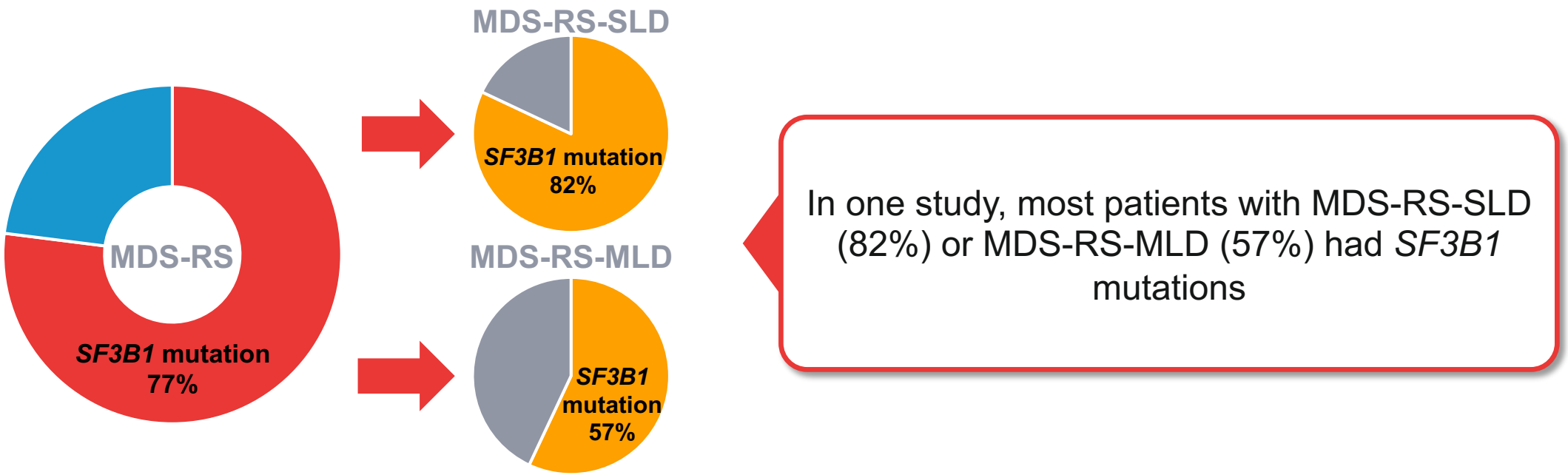
- Mutations in the spliceosome gene, *SF3B1*, may be associated with blocking late-stage erythropoiesis[2]
- These are the only mutations currently included in the WHO (2016) diagnostic classification for MDS[1]
- *SF3B1* mutations are seen in approximately 25–30% of all MDS[3]

WHO: World Health Organization.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts.

1. Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.
2. Obeng EA, Chappell RJ, Seller M, *et al*. Physiologic expression of Sf3b1K700E causes impaired erythropoiesis, aberrant splicing, and sensitivity to therapeutic spliceosome modulation. *Cancer Cell* 2016;30:404–417.
3. Cazzola M, Rossi M, Malcovati L. Biologic and clinical significance of somatic mutations of SF3B1 in myeloid and lymphoid neoplasms. *Blood* 2013;121:260–269.
4. Migdady Y, Barnard J, Al Ali N, *et al*. Clinical outcomes with ring sideroblasts and SF3B1 mutations in myelodysplastic syndromes: MDS clinical research consortium analysis. *Clin Lymphoma Myeloma Leuk* 2018;18:528–532.

WHO classification: MDS-RS and *SF3B1* mutations

SF3B1 mutations occur frequently in both subtypes of MDS-RS[1]

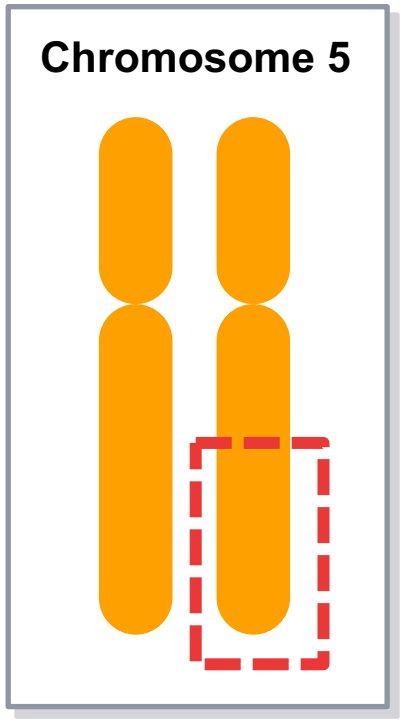


In one study, most patients with MDS-RS-SLD (82%) or MDS-RS-MLD (57%) had *SF3B1* mutations

WHO: World Health Organization.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts.
MDS-RS-SLD: Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia.
MDS-RS-MLD: Myelodysplastic syndrome with ring sideroblasts and multi lineage dysplasia.

1. Mangaonkar AA, Lasho TL, Finke CM, *et al*. Prognostic interaction between bone marrow morphology and SF3B1 and ASXL1 mutations in myelodysplastic syndromes with ring sideroblasts. *Blood Cancer J* 2018;8:18.

WHO classification: MDS with isolated del(5q)



Most common cytogenetic abnormality in MDS

- Deletions of the long arm of chromosome 5 [del(5q)] are found in approximately 10–15% of all patients with primary MDS[1]
- MDS with isolated del(5q) is the only cytogenetic abnormality that defines a specific MDS subtype (WHO 2016)[2]

MDS with isolated del(5q) and <5% BM blasts is a distinct disease subtype that is characterized by a relatively good prognosis[1]

WHO: World Health Organization.
del: Deletion.
BM: Bone marrow.

1. Giagounidis A, Mufti GJ, Mittelman M, *et al*. Outcomes in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with isolated deletion 5q treated with lenalidomide: a subset analysis from the MDS-004 study. *Eur J hematol* 2014;93:429–438.
2. Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.

IPSS and IPSS-R classification

These prognostic classification systems evaluate the expected survival and risk of progression for MDS in each risk category[1]

- In 1997, the IPSS was created to evaluate the prognosis in MDS by assigning weighted scores to specific prognostic features
- In 2012, the IPSS was revised (as the IPSS-R) to refine its prognostic utility

After the IPSS-R was developed[1]

27% of IPSS lower-risk categories were reclassified into higher-risk IPSS-R categories

18% of IPSS higher-risk categories were reclassified into lower-risk IPSS-R categories

IPSS: International Prognostic Scoring System.
IPSS-R: International Prognostic Scoring System (revised).

1. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.

IPSS and IPSS-R classification

IPSS[1,3]

- Based on the percentage of BM blasts, number of cytopenias and marrow cell karyotype
- Risk categories (scores):
  - ✓ Low (0)
  - ✓ Intermediate-1 (0.5–1.0)
  - ✓ Intermediate-2 (1.5–2.0)
  - ✓ High (≥2.5)

Refinements[1]

- New BM blast categories
- Refined cytogenetic abnormalities and risk groups
- Evaluation of cytopenia depth
- Inclusion of differentiating features: age, performance status, serum ferritin, LDH, β_2-microglobulin
- Prognostic model with 5 risk factors

IPSS-R[1]

- Further stratifies patients into 5 risk groups with different outcomes associated with of AML evolution and survival
- Risk categories (scores):
  - ✓ Very low (≤1.5)
  - ✓ Low (>1.5–3)
  - ✓ Intermediate (>3–4.5)
  - ✓ High (>4.5–6)
  - ✓ Very high (>6)

IPSS: International Prognostic Scoring System.
IPSS-R: International Prognostic Scoring System (revised).
BM: Bone marrow.
LDH: Lactate dehydrogenase.
AML: Acute myeloid leukemia.

1. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.
2. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. *Blood* 2013;121:4280-4286. 3. Greenberg P, Cox C, LeBeau MM, *et al.* International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89: 2079–2088.

IPSS and IPSS-R classification

IPSS for MDS[1]

	Risk score value				
Prognostic factor	0	0.5	1.0	1.5	2.0
Karyotype*	Good	Intermediate	Poor		
BM blasts, %	< 5	5 to 10	–	11 to 20	21 to 30
Cytopenias, n	0/1	2/3	–	–	–

IPSS-R for MDS[2]

	Risk score value						
Prognostic factor	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	–	Good	–	Intermediate	Poor	Very poor
BM blasts, %	≤ 2	–	> 2 to < 5	–	5 to 10	> 10	–
Hb (g/dL)	≥ 10	–	8 to < 10	< 8	–	–	–
Platelets (x 10^9/L)	≥ 100	50 to < 100	< 50	–	–	–	–
ANC (x 10^9/L)	≥ 0.8	< 0.8	–	–	–	–	–

IPSS: International Prognostic Scoring System.
IPSS-R: International Prognostic Scoring System (revised).
BM: Bone marrow.
Hb: Hemoglobin.
ANC: Absolute neutrophil count.
del: Deletion.
*Good, normal, -Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

1. Greenberg P, Cox C, LeBeau MM, *et al.* International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89: 2079–2088.
2. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.

IPSS-R risk categories

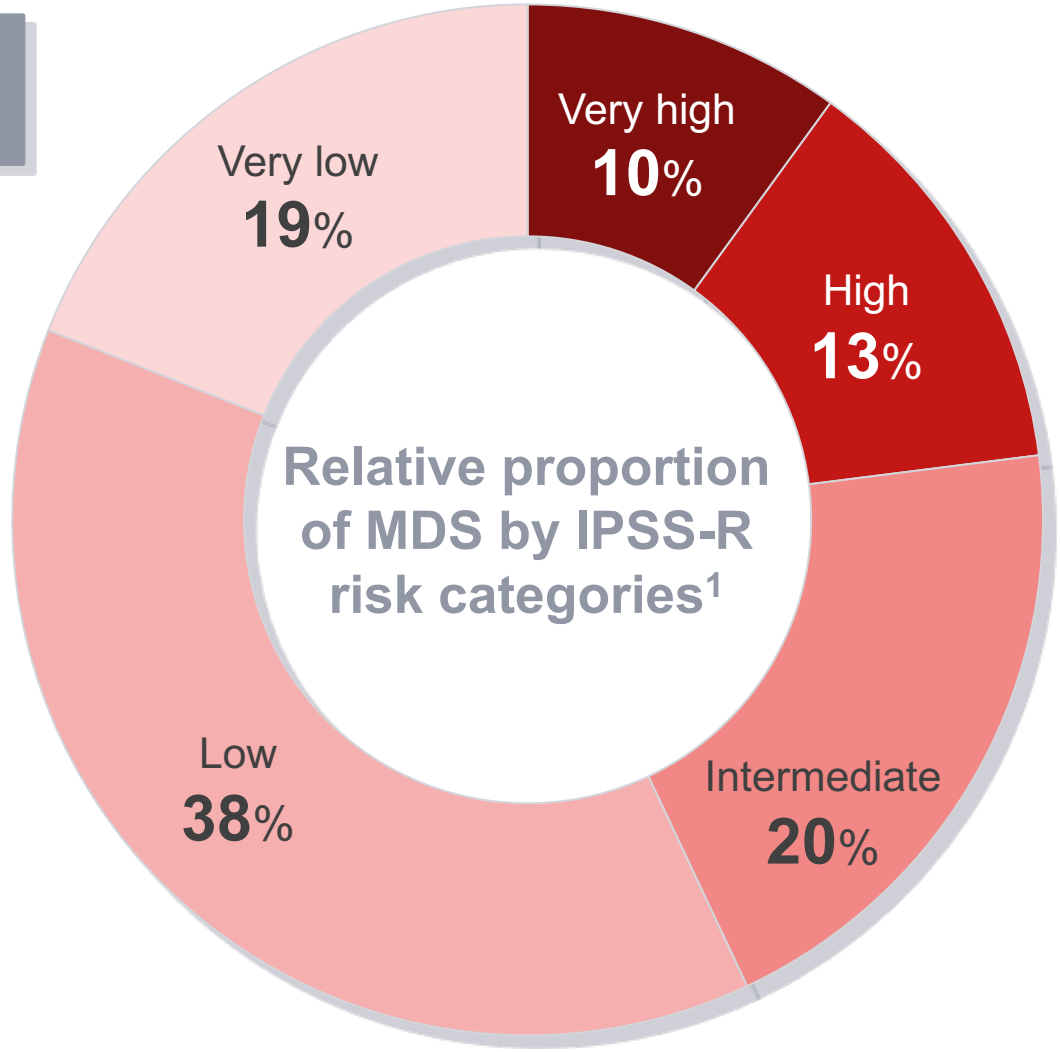
Generally, IPSS-R categories are grouped as[1]

Lower-risk MDS (IPSS-R score ≤ 3.5)

Composed of very low-, low-, and some intermediate-risk patients

Higher-risk MDS (IPSS-R score ≥ 4.0)

Composed of very high-, high-, and some intermediate-risk patients



IPSS-R: International Prognostic Scoring System (revised).

1. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.

Prognosis by IPSS-R classification

Prognosis of MDS is highly variable and depends on the risk classification[1]

- MDS is associated with reduced survival
- Survival rates and time of MDS progression into AML may range from a few months to several years

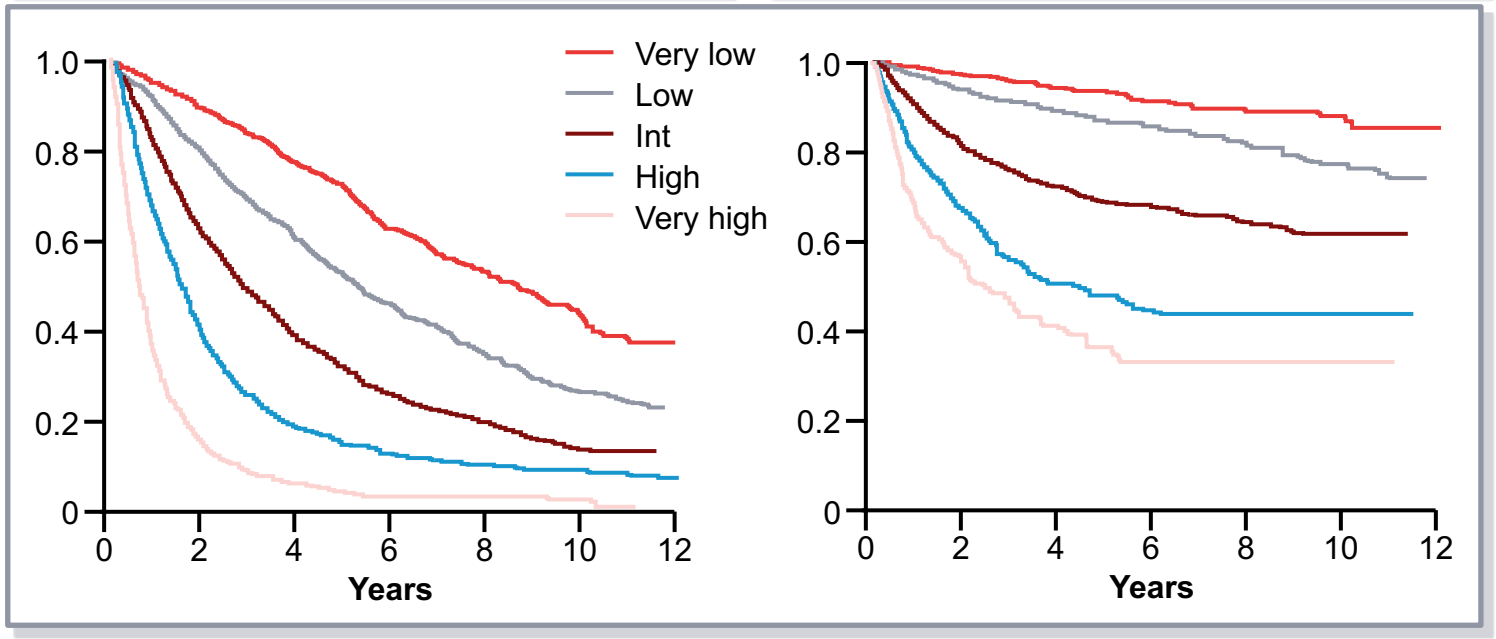
	IPSS-R risk categories				
	Very low	**Low**	**Intermediate**	**High**	**Very high**
Overall survival (years)*	8.8	5.3	3.0	1.6	0.8
AML/25%† (years)	NR	10.8	3.2	1.4	0.73

IPSS-R: International Prognostic Scoring System (revised) .
AML: Acute myeloid leukemia.
*Medians, years (95% CI) , P≤0.001.
†Median time to 25% AML evolution (95% CIs) , P≤0.001.

1. Greenberg PL, Tuechler H, Schanz J, *et al*. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.

Prognosis by IPSS-R classification

MDS survival based on IPSS-R prognostic risk categories
(N = 7012)[1]



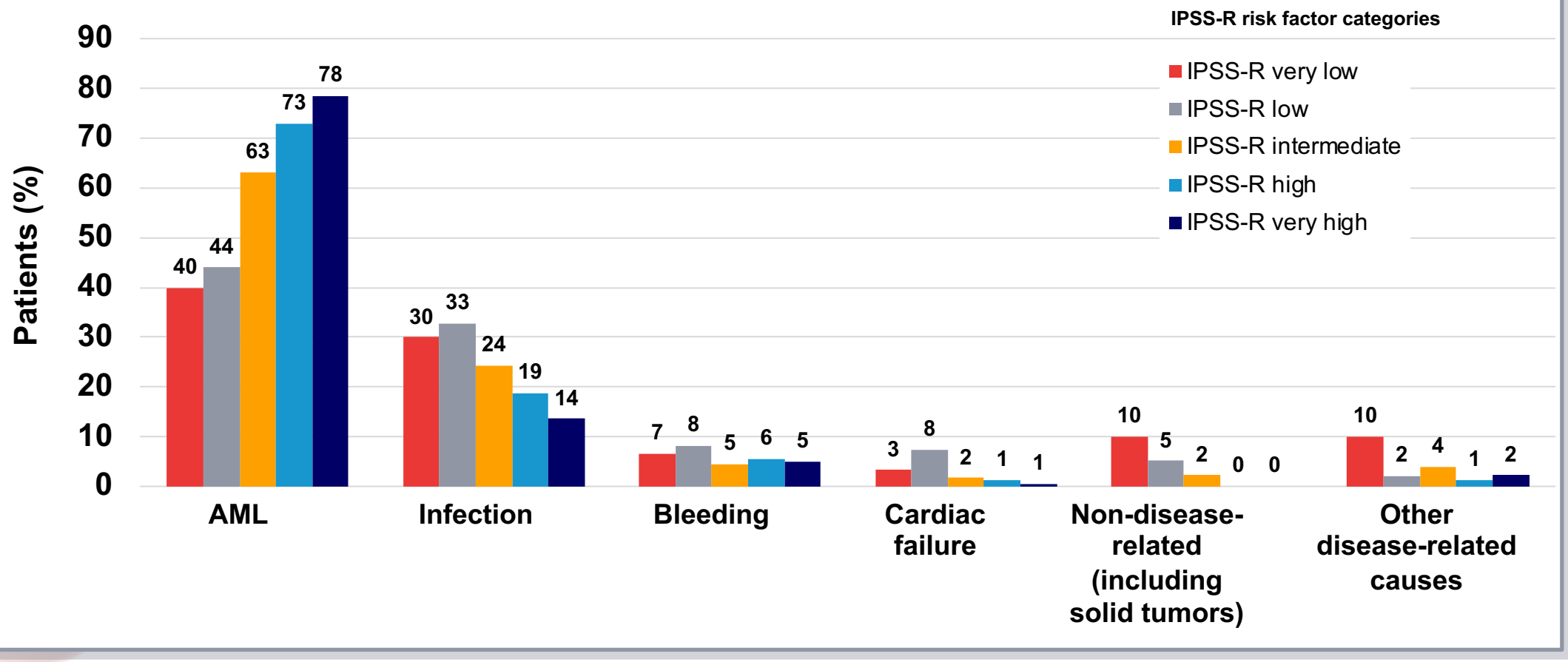
MDS to AML evolution based on IPSS-R prognostic risk categories
(N = 6485)[1]

IPSS-R: International Prognostic Scoring System (revised) .
AML: Acute myeloid leukemia.

1. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.

Prognosis: Causes of death by IPSS-R classification

Causes of death in patients with MDS (N = 660) according to IPSS-R risk categories[1]



IPSS-R: International Prognostic Scoring System (revised) .
AML: Acute myeloid leukemia.

1. Nachtkamp K, Stark R, Strupp C, *et al*. Causes of death in 2877 patients with myelodysplastic syndromes. *Ann Hematol* 2016;95:937–944.

MDS
Summary

MDS are a heterogeneous group of myeloid malignancies[1,2]

They are clonal myeloid malignancies characterized by:
- Ineffective hematopoiesis
- Dysplasia in hematopoietic cells
- Cytopenias
- Increased risk of progression to AML

The incidence of MDS progressively increases with age[3]: **76 years** is the median age at diagnosis

Most patients show symptoms related to underlying blood-cell deficiencies[4-7]

- Disease-related anemia is observed in >80% of cases
- Anemia is correlated with reduced survival in MDS and is mainly driven by ineffective erythropoiesis
- Prognosis for MDS patients is highly variable
  - Survival rates and progression to AML can range from a few months to several years

The IPSS-R prognostic system is an important standard for assessing prognosis and predicting outcomes of patients with MDS[5]

AML: Acute myeloid leukemia.
IPSS-R: International Prognostic Scoring System (revised).

1. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. *Blood* 2013;121:4280-4286.
2. Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–2405.
3. Ma, X. Epidemiology of myelodysplastic syndromes. *Am J Med* 2012;125:S2-S5.
4. Balducci L. Transfusion independence in patients with myelodysplastic syndromes. *Cancer* 2006;106:2087-2094.
5. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.
6. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anemias. *Br J hematol* 2016;172:512–523.
7. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J hematol* 2016;174:661–673.

Bristol Myers Squibb™

HE-CA-2100003E