# Latest Research on MDS

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# Disclosures

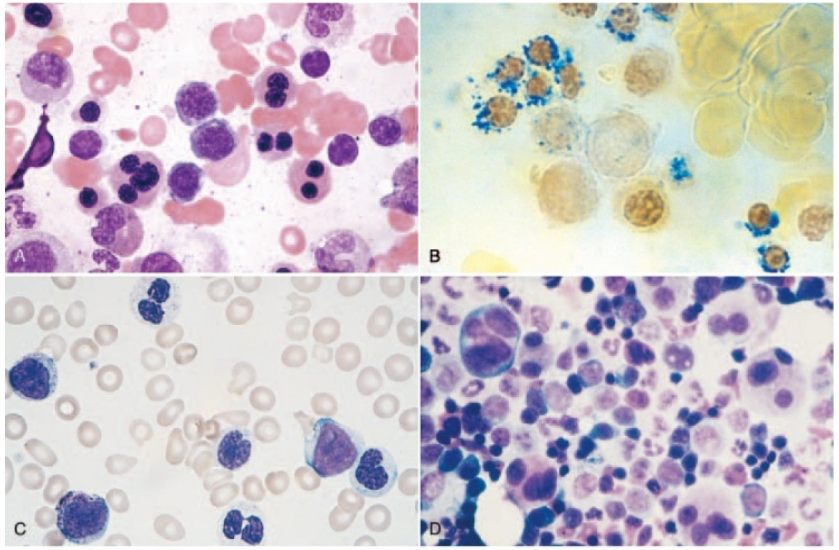
| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Abbvie | x | | | | | | |
| Alexion | x | | x | | | | |
| Celgene | x | | x | | x | | |
| Novartis | x | | x | | x | | |
| Otsuka | x | | | | | | |
| | | | | | | | |

# Agenda

1. MDS; introduction
2. Management of anemia in MDS
   - Complications of anemia
   - RBC transfusions & their burden
   - Clinical benefit of reducing transfusions in lower risk MDS
   - New approaches to reducing transfusion dependence
3. Case study; management of anemia & iron overload
4. Conclusions and future directions

# Introduction: MDS

- MDS is a heterogeneous group of clonal bone marrow failure syndromes
- Characterized by ineffective hematopoiesis & the potential for progression to AML
- Overall survival & AML progression are predicted by the IPSS, IPSS-R, WPSS & newer scores (eg the IPSS-RM in development)[1-5]





1. Greenberg P, et al. Blood. 1997 Mar 15;89(6):2079-88. 2. Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65. 3. Malcovati L, et al. Clin Oncol. 2007 Aug 10;25(23):3503-10. 4. Schanz J, et al. J Clin Oncol. 2012 Mar 10;30(8):820-9. 5. Kantarjian H, et al. Cancer. 2008;113:1351–1361.

Image from: Robbins SL, Cotran RS. Pathologic basis of disease. 7th ed. St Louis, MO: WB Saunders; 2004.

# Introduction: MDS

- For current and future approaches to optimal MDS management, proper classification & risk stratification is needed
- This includes documentation of cytopenias, morphologic abnormalities, marrow blast count, cytogenetic changes & molecular abnormalities where possible
- Division of patients into lower & higher risk generally determines management approach

Risk stratification of MDS

| | Lower risk | Higher risk |
|---|---|---|
| IPSS | Low or intermediate-1 | Intermediate-2 or high |
| IPSS-R | ≤4.5 | >4.5 |
| WPSS | ≤2 | >2 |
| MPSS | ≤6 | >6 |
| WHO | MDS-SLD, MDS-SLD-RS, MDS with isolated del(5q) | MDS-EB-2 |
| Molecular | Eg SF3B1 | Eg TP53, ASXL1 |

1. Greenberg P, et al. Blood. 1997 Mar 15;89(6):2079-88. 2. Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65. 3. Malcovati L, et al. Clin Oncol. 2007 Aug 10;25(23):3503-10. 4. Kantarjian H, et al. Cancer. 2008;113:1351–1361. 5. Arber DA, et al. Blood. 2016 May 19;127(20):2391-405.

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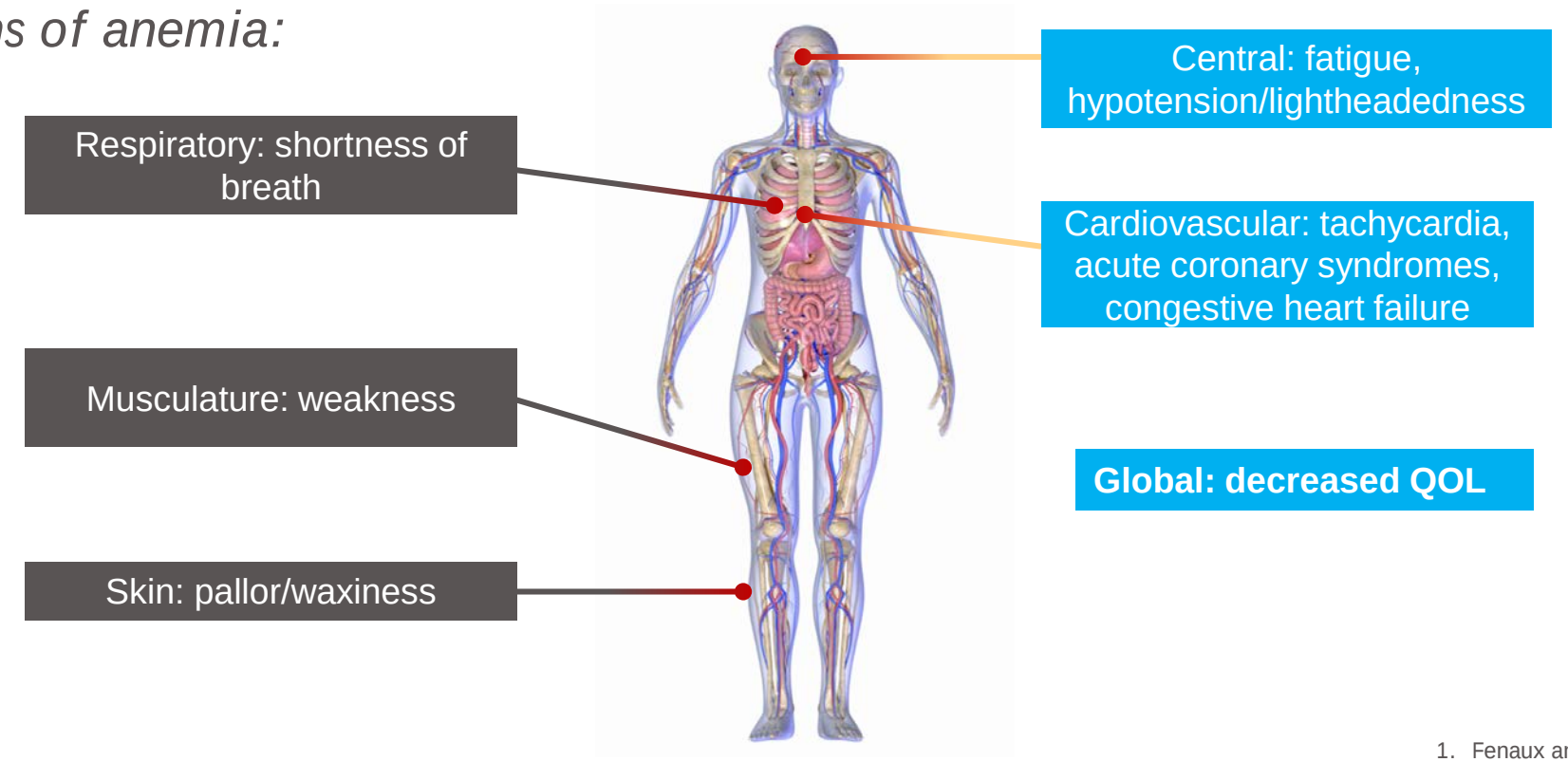
# MDS and Anemia

- Anemia is a hallmark of MDS that can be challenging to manage; most patients will require RBC transfusions[1]

*Signs & symptoms of anemia:*




1. Fenaux and Adès. Blood. 2013;121:4280–6

# Treatment options for lower risk MDS

**Therapeutic options are determined by risk score – LR-MDS**
**Objective: decrease transfusion burden & symptoms**

| Treatment | Comment |
|---|---|
| ESAs[1–3] | Most effective in patients with low serum erythropoietin (EPO) level and low transfusion burden |
| Lenalidomide[1,4] | Transfusion-dependent patients with LR-MDS and del(5q) after ESA failure |
| IST[2] | For patients with features indicating a high probability of response to IST |
| HMAs[2] | May be a second-line option for selected cytopenic LR patients in some jurisdictions |
| Supportive care[2] | RBC transfusions (+ iron chelation)*, platelet transfusions, growth factors |

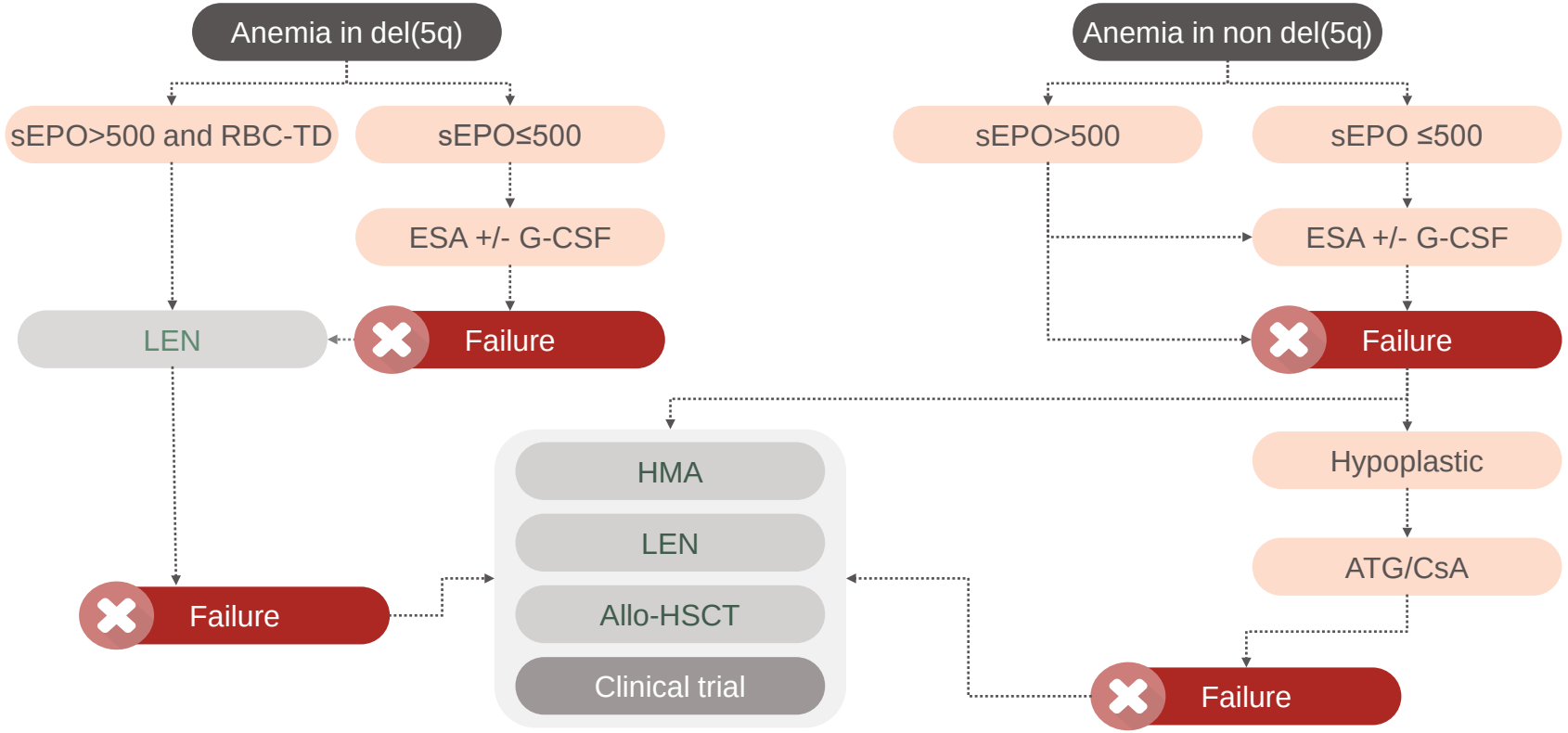
*Management of iron overload should be a consideration in all treatment groups

EPO: epoetin; HMAs: hypomethylating agents; IST: immunosuppressive therapy

1. Fenaux P, et al. Br J Haematol 2019. doi: 10.1111/bjh.16206. Epub ahead of print; 2. Raj K, et al. Postgraduate Haematology. John Wiley & Sons, Ltd., 2016. p.438–73; 3. Hellstrom-Lindberg, E. 2008. Myelodysplastic Syndromes. 1st ed. Remedica. London; 4. Fenaux P, et al. Blood 2011;118:3765–76

# Treatment options for LR-MDS patients are limited

**Symptomatic anemia:** transfuse if necessary +/- iron chelation. **Goal:** ↓ transfusion burden and symptoms



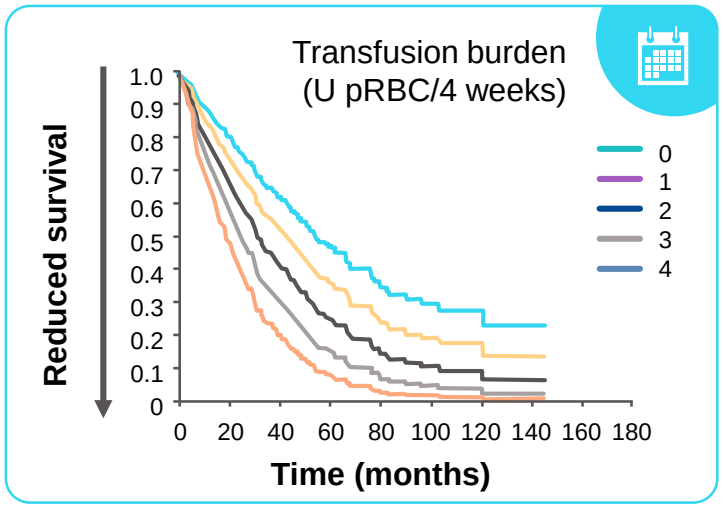

ATG: Anti-Thymocyte Globulin; Allo: allogeneic; CsA: cyclosporine A; sEPO: serum erythropoietin; G-CSF: granulocyte colony-stimulating factors; LEN: lenalidomide; RBC-T: red blood cell transfusion

1. Platzbecker U. Blood 2019;133:1096–1107

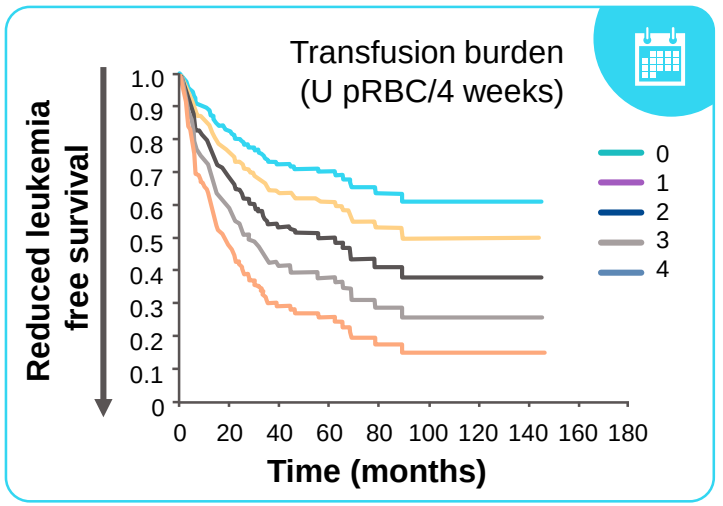
# Transfusion dependency in LR-MDS is associated with inferior OS

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

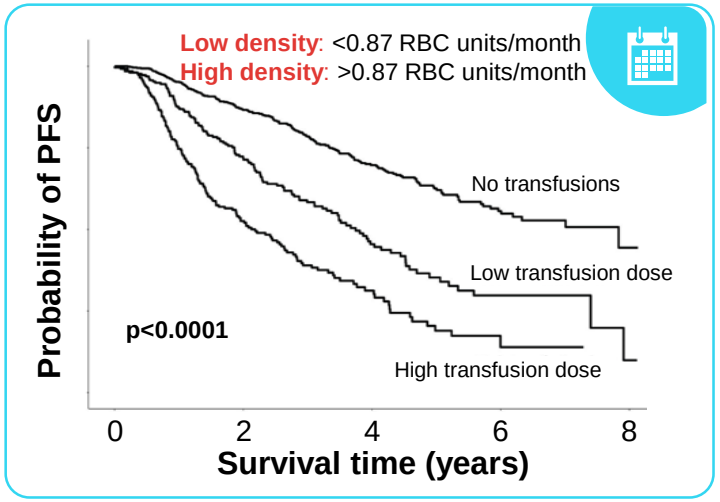
**Overall survival (HR=1.36; p<0.001)[1]**




**Leukemia free survival (HR=1.40; p<0.001)[1]**




**Progression-free survival[2]**




Malcovati et al.

EUMDS

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

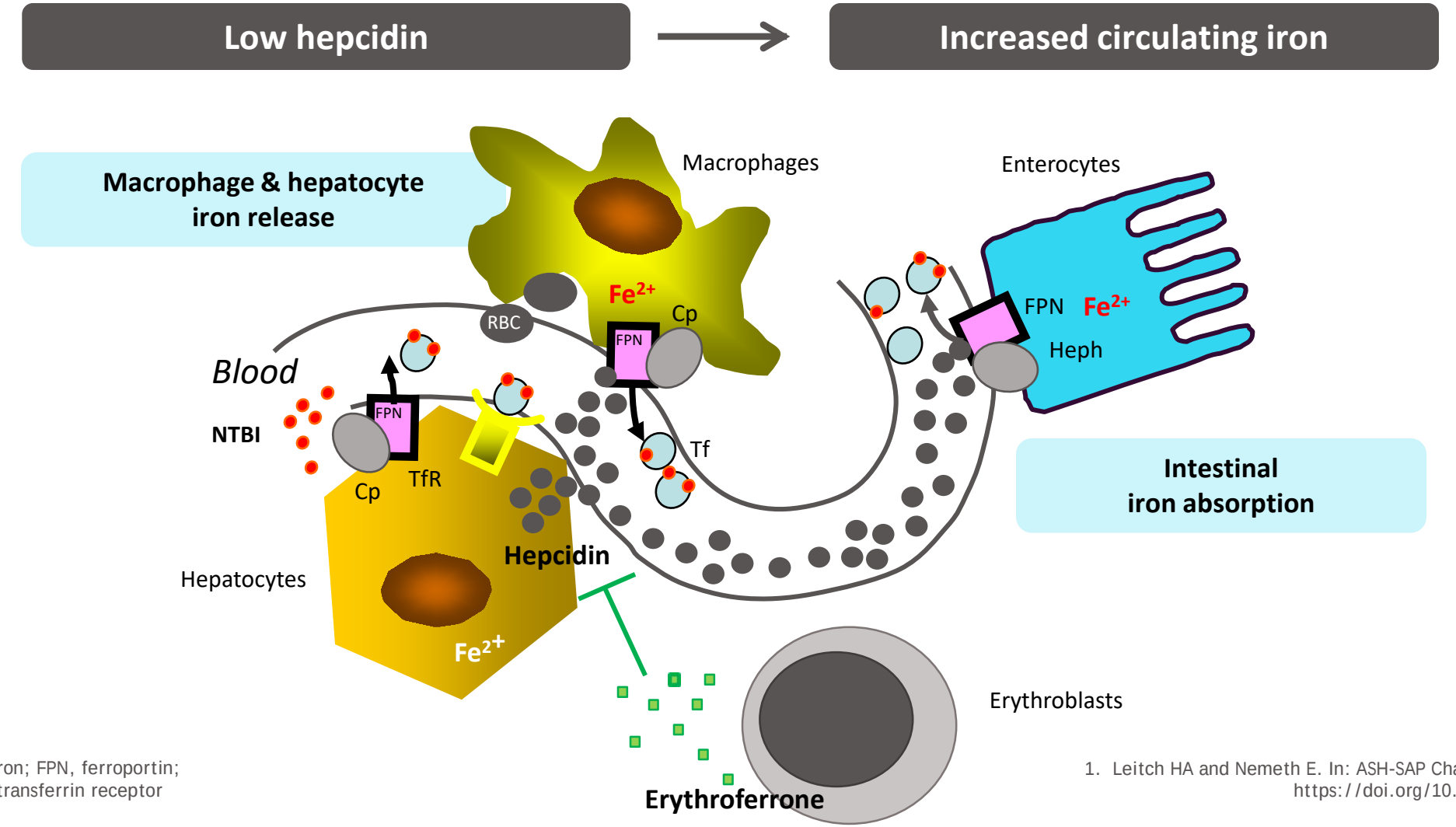
1. Malcovati L, et al. Haematologica 2006;91:1588-90; 2. de Swart L, et al. Haematologica 2019;104. Epub ahead of print

# MDS patients who achieve transfusion independence have reduced mortality vs patients who remain TD

- A systematic review and meta-analysis investigated OS in MDS patients who were transfusion independent compared to transfusion dependent
  - Included were studies that recruited adults with MDS & reported OS for TI vs TD patients
- 89 articles were included in the review, with 55 separate data sets
- The analysis showed:
  - a consistent OS benefit in TI vs TD patients
  - TI was associated with a 59% reduction in risk of death compared with TD (HR 0.41; 95% credible interval [CrI] 0.29–0.56)
  - the OS benefit was independent of MDS severity (interaction coefficient HR 1.38; 95% CrI 0.62–3.41)

1. Harnan S, et al. *Acta Haematol* 2016;136:23–42

# Iron overload is a consequence of RBC transfusion

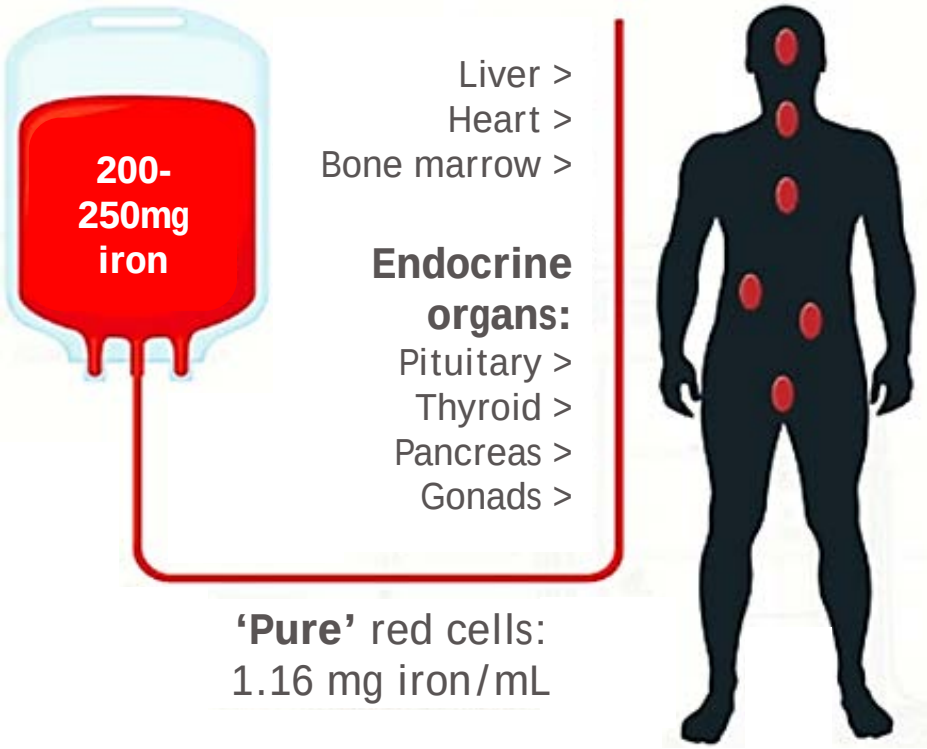



Cp, ceruloplasmin; Fe, iron; FPN, ferroportin; Heph, hephaestin; TfR, transferrin receptor

1. Leitch HA and Nemeth E. In: ASH-SAP Chapter 5, 2019, June. Doi: https://doi.org/10.1182/ashsap7.chapter05

# Iron accumulation from transfusion therapy

- Moderate transfusion requirement:
  - 2 units/month
  - **~100 units/4 years**
  - **100 units:** ≥20g iron
  - **Iron is deposited in tissues and organs and causes toxicity**
  - **IOL results in the presence of toxic redox-active iron**

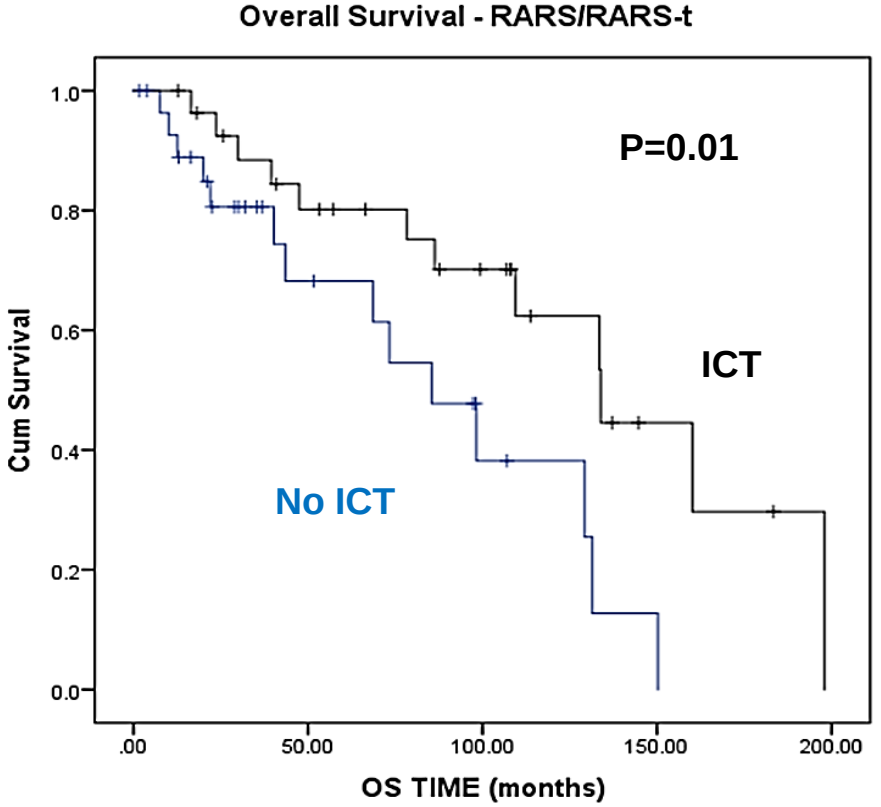



EUMDS, European LeukemiaNet MDS Registry

# MDS-RS patients are more likely to develop iron overload

- Compared to other MDS subtypes:
  - Hepcidin levels are lowest in MDS-RS. Low hepcidin stimulates GI absorption of iron[1,2]
  - Iron loading is highest in MDS-RS[2]
  - RARS patients have the highest levels of (toxic) non-transferrin bound iron[1,2]
  - MDS-RS patients have relatively long survival; there is more time for transfusional iron to accumulate to toxic levels[3]
  - Iron overload in MDS is associated with increased morbidity, exacerbation of pre-existing morbidity and impaired survival[4]

**OS of TD MDS patients with RS according to receipt of iron chelation therapy[5]**




1. Lyle L, et al. J Adv Pract Oncol 2018;9:392-405; 2. Santini V, et al. PLoS One 2011;6:e23109; 3. Shenoy N, et al. Blood 2014;124:873–81; 4. Remacha AF, et al. Ann Hematol 2015;94:779–87; 5. Wong SA, Leitch HA. Leuk Res. 2018 Jan;64:24-29. doi: 10.1016/j.leukres.2017.11.005.

# Measures of iron overload

**Currently available measures of iron overload in clinical practice.**

| Diagnostic tool | Characteristics | Advantages | Disadvantages |
|---|---|---|---|
| Calculation of transfusion iron burden | Provide a direct quantitative estimate of the body iron burden | Easy to calculate, inexpensive | Unreliable in patients with bleeding or chelation therapy |
| Serum ferritin level | Indirect serologic estimation of body iron burden | Widely available; easy to perform; low-cost; repeatable | Unreliable in patients with inflammation, liver function deficiency, and ascorbate deficiency |
| Serum ferritin saturation | High sensitivity and specificity in untransfused patients | Widely available; easy to perform; low-cost; repeatable | No quantitative correlation to iron burden |
| SQUID | Direct instrumental estimation of hepatic iron concentration | Noninvasive, repeatable | Expensive; not widely available; not validated; significant underestimation; not applicable to the heart |
| MRI R2 | Indirect instrumental estimation of tissue iron concentration | Noninvasive, repeatable; validated in the liver | Expensive; not widely available; reliable up to LIC of 15mg/gDW; not applicable for cardiac assessment |
| MRI T2* | Indirect instrumental estimation of tissue iron concentration | Noninvasive, repeatable; validated in the heart; provides cardiac functional information | Expensive; not widely available; complex, requires skilled radiologist |
| Liver biopsy | Provides a direct estimation of iron overload | Validated and quantitative method to estimate hepatic iron concentration (gold standard) | Invasive (cannot be employed in many patients with hematologic malignancies) |
| Non-transferrin bound iron (NTBI)[1] | Research tool at present | Noninvasive method; estimates generation of the toxic iron fraction | Not validated and not widely available. Not currently useful in clinical practice |
| Serum hepcidin level | Research tool at present | Noninvasive method that identifies patients at high risk of iron loading | Not widely available. Not currently useful in clinical practice |

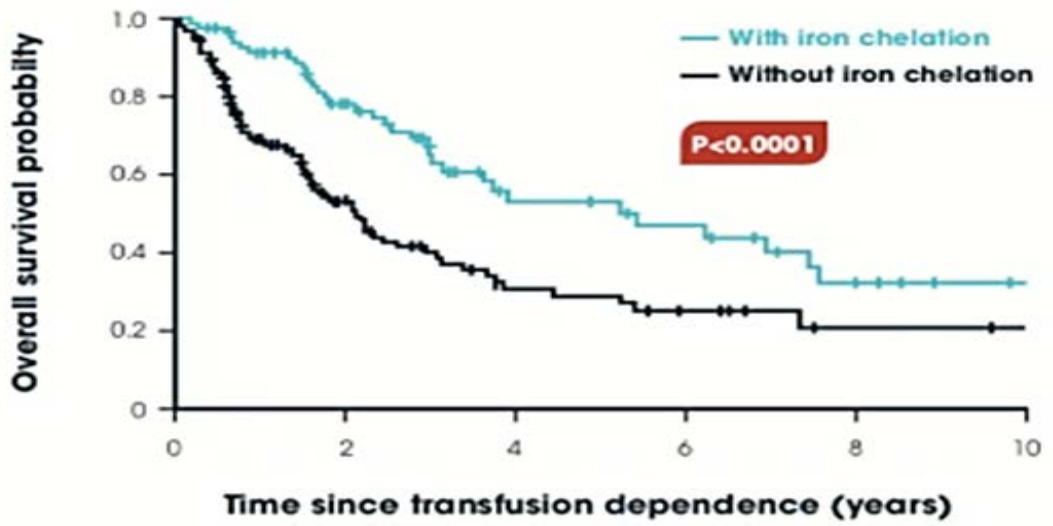
IOL, iron overload; MRI, magnetic resonance imaging; SQUID, superconducting quantum interference device.
[1]other measures of oxidative stress include labile plasma iron (LPI), enhanced LPI (eLPI), reactive oxygen species (ROS) and long lasting cellular results of oxidative damage such as DNA oxidation products & lipid peroxidation products.
Reprinted from Alessandrino EP, et al. Am J Hematol. 2011;86:897-902, with minor modifications; from Leitch HA, et al. Crit Rev Oncol Hematol. 2017;113:156-70 and from Leitch HA, et al. Leuk Res. 2018;74:21-41.

# Reducing IOL in MDS

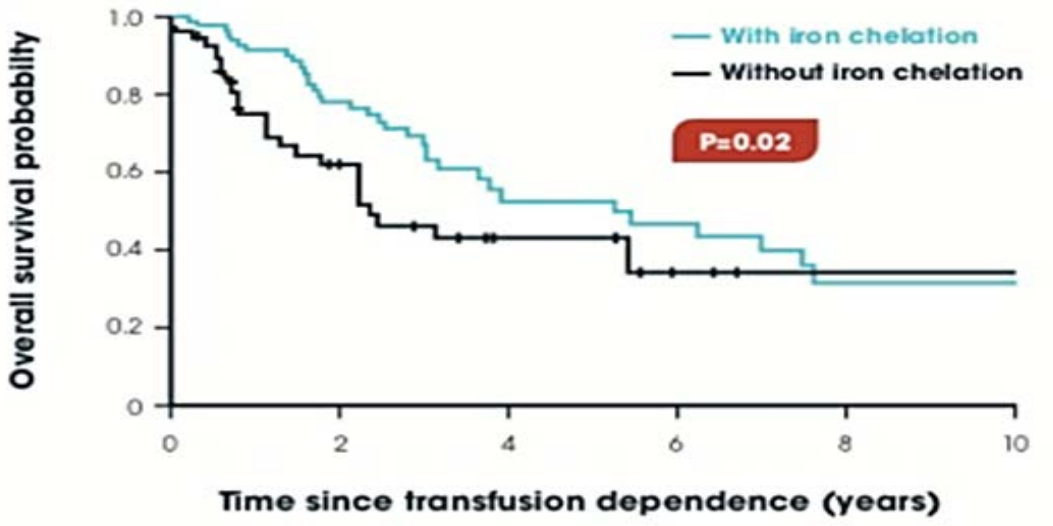
- Historically, the importance of IOL management in MDS has been controversial
- An analysis from the Canadian MDS registry controlled for 4 measures of patient performance status & evaluated OS from time of first RBC TD
- This showed superior OS in patients receiving ICT
- Several analyses matching for characteristics thought to affect prognosis supported these findings

**OS in IPSS lower-risk MDS from RBC TD by receipt of iron chelation therapy**

All patients




Matched-pair analysis*



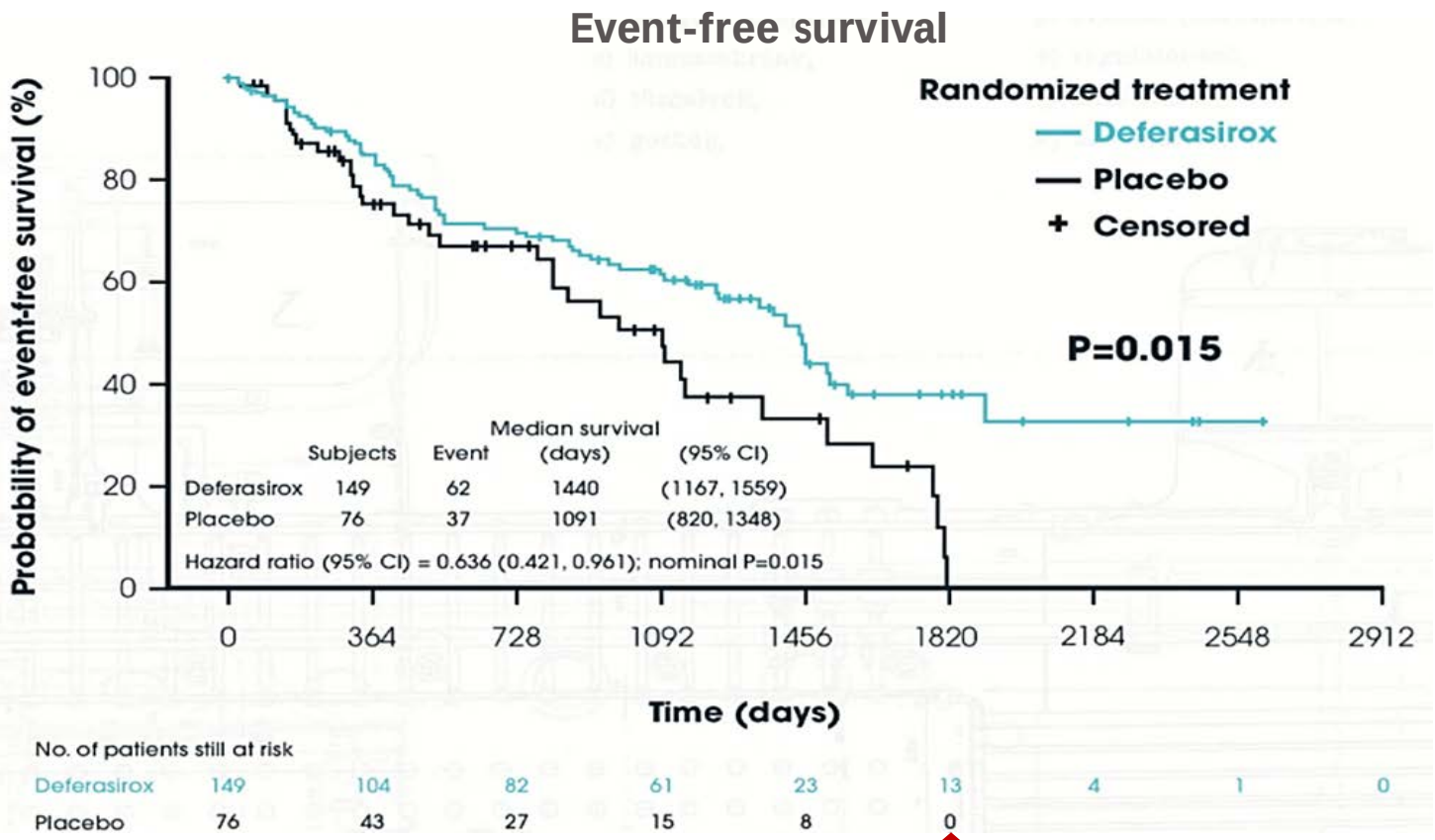

*Patients matched 1:1 for age (≤50, 51-60, 61-65, 66-70, 71-75, 76-80 and >80 years), IPSS-R score (very low + low, intermediate, and high + very high), number of RBC units/month transfused (0, >0-≤2, >2-≤4, >4-≤6 and >6), and time from MDS diagnosis until RBC TD (0, 0-<6, >6-36, >36 months)

1. Leitch HA, et al. Brit J Haematol 2017;179:83-97

# Event-free survival: TELESTO

- The RCT of DFX vs placebo was recently reported
- Despite target enrollment being reduced by 2/3, making the study not powered to detect its endpoint
- Despite half of placebo patients withdrawing from study & subsequently receiving chelation
- Despite the mean age of study patients being 10-15 years younger than most MDS
- There was significantly superior EFS in patients receiving ICT
- This study might underestimate an impact of IOL reduction in MDS

**Randomized trial of deferasirox versus placebo in IPSS lower-risk MDS**

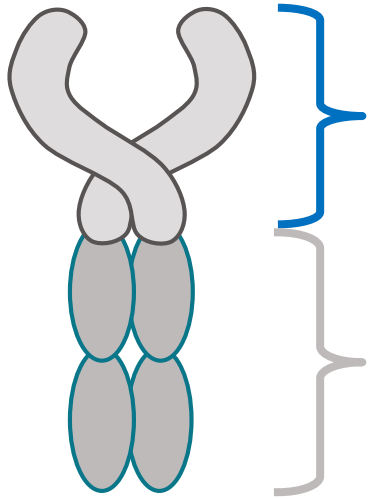



1. Angelucci E, et al. Ann Intern Med. 2020 Mar 24. doi: 10.7326/M19-0916. Online ahead of print.

# Novel approaches to reduce transfusion dependence in LR MDS

# Luspatercept*: an erythroid maturation agent (EMA) for treatment of anemia in LR MDS

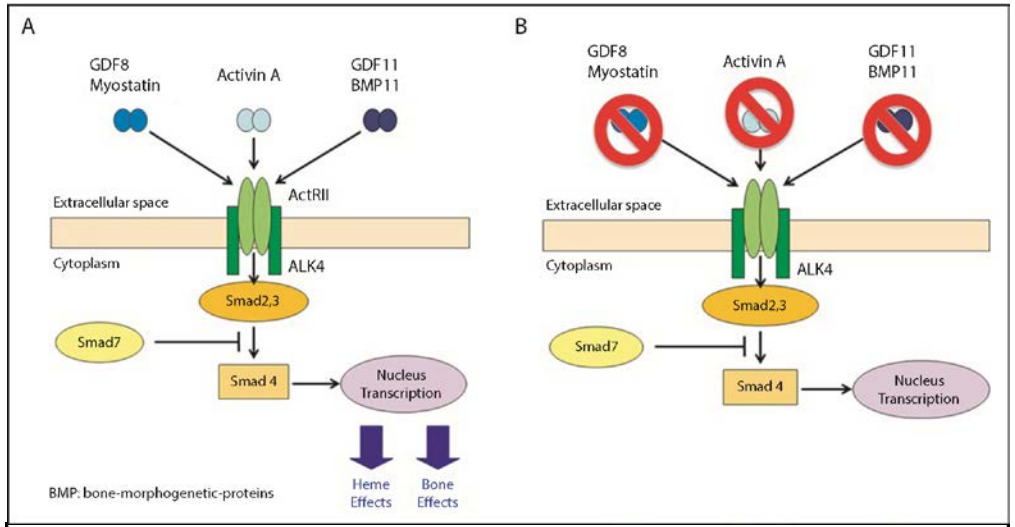
**Binds select TGF-ß superfamily ligands**

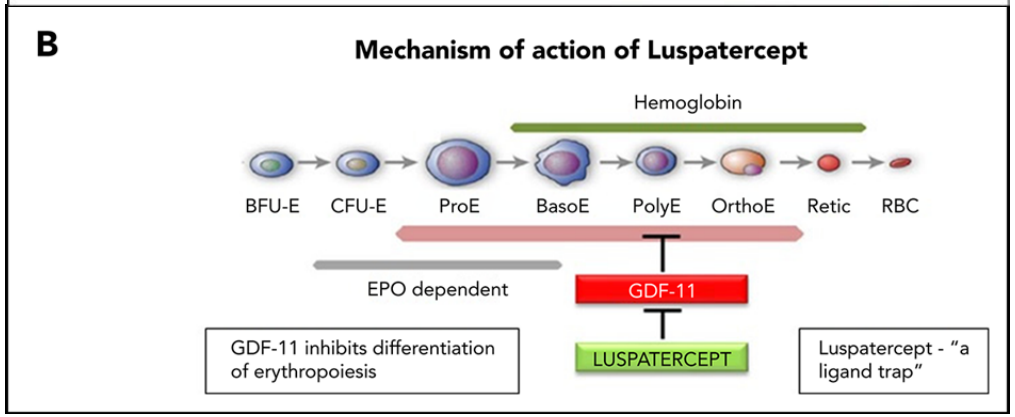


**Modified extracellular domain of ActRIIB**

**Human IgG1 Fc domain**

**Reduces aberrant SMAD2/3 signalling, allowing erythroid maturation in late-stage erythropoiesis**

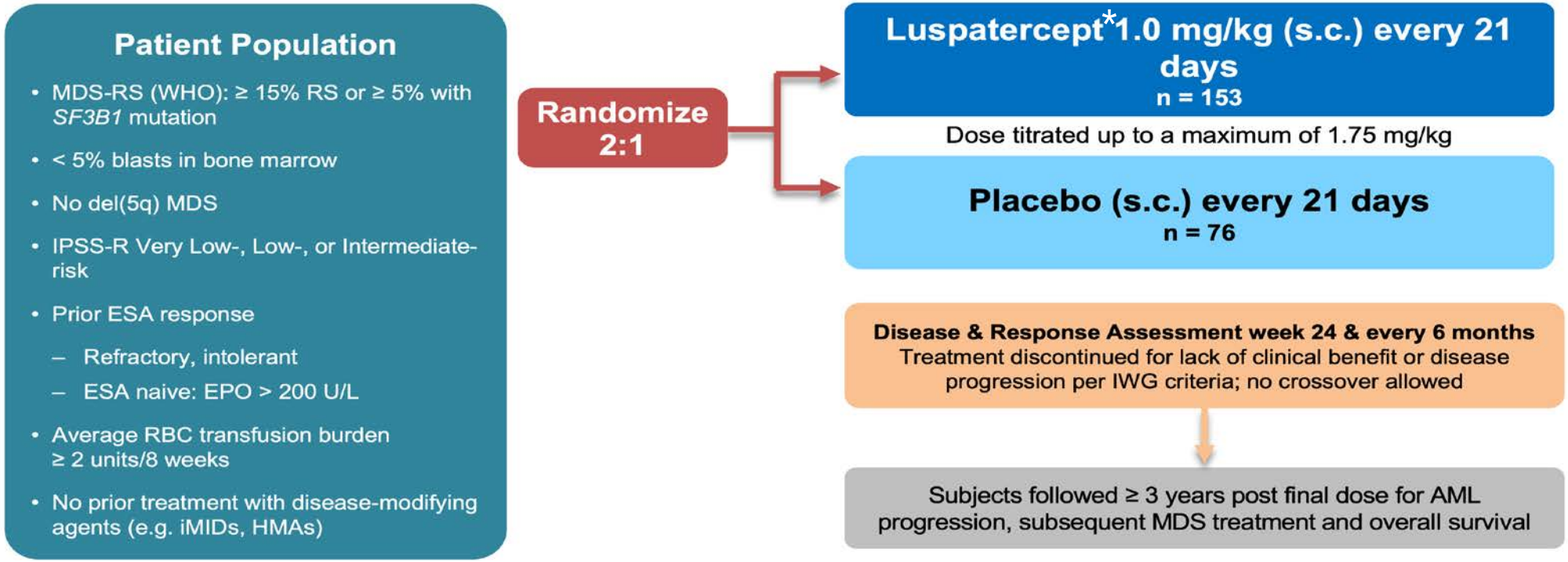



*Luspatercept is not currently licensed for this indication in the European Union

1. Fenaux P et al. Blood, 2019 133(8):790-4.

# MEDALIST TRIAL study design – a randomized, double-blind, placebo-controlled, phase 3 study




**Primary endpoint:** RBC transfusion independence ≥8 weeks (weeks 1–24)
**Key secondary endpoint:** RBC transfusion independence ≥12 weeks (weeks 1–24 and weeks 1–48)

Data cutoff: May 8, 2018. Includes last subject randomised + 48 weeks
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization

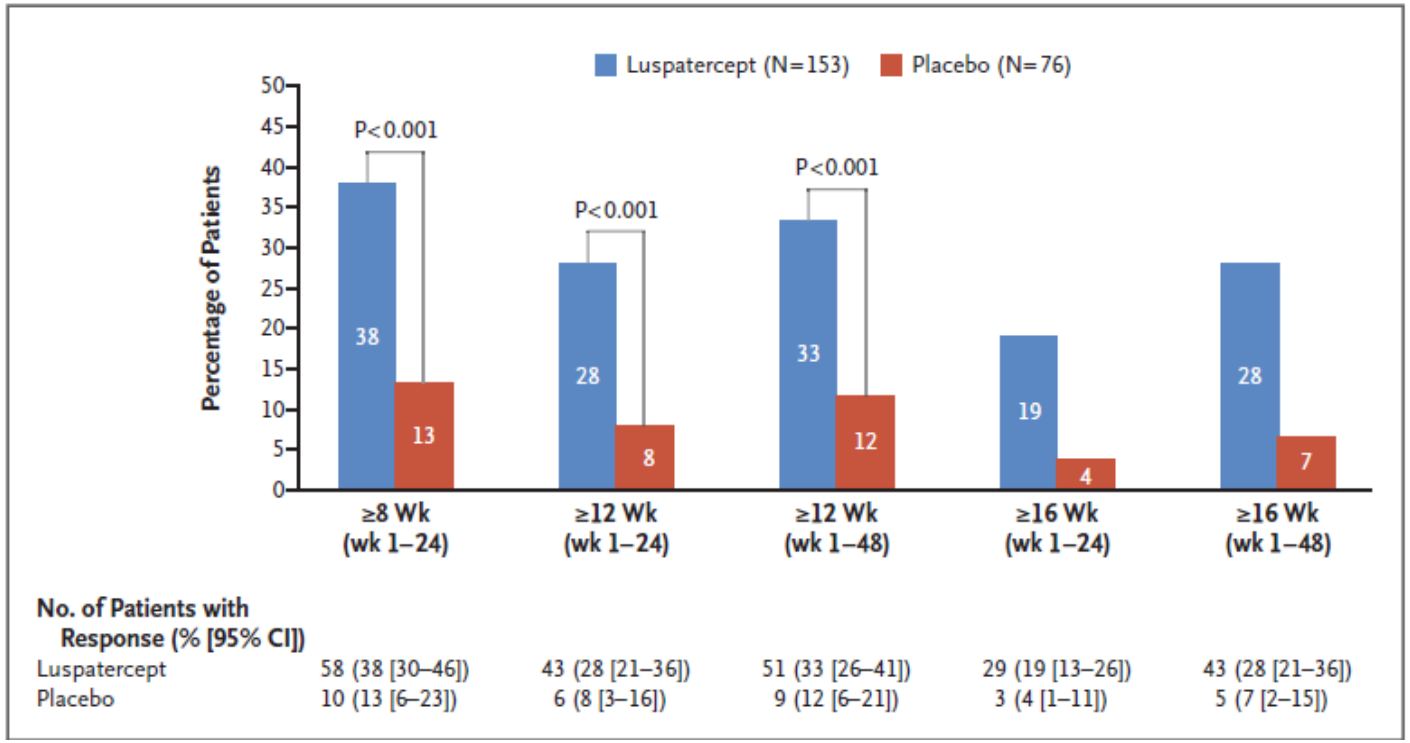
*Luspatercept is not currently licensed in this indication in the European Union

1. Fenaux P et al. Oral presentation at ASH 2018. Abstract 1.

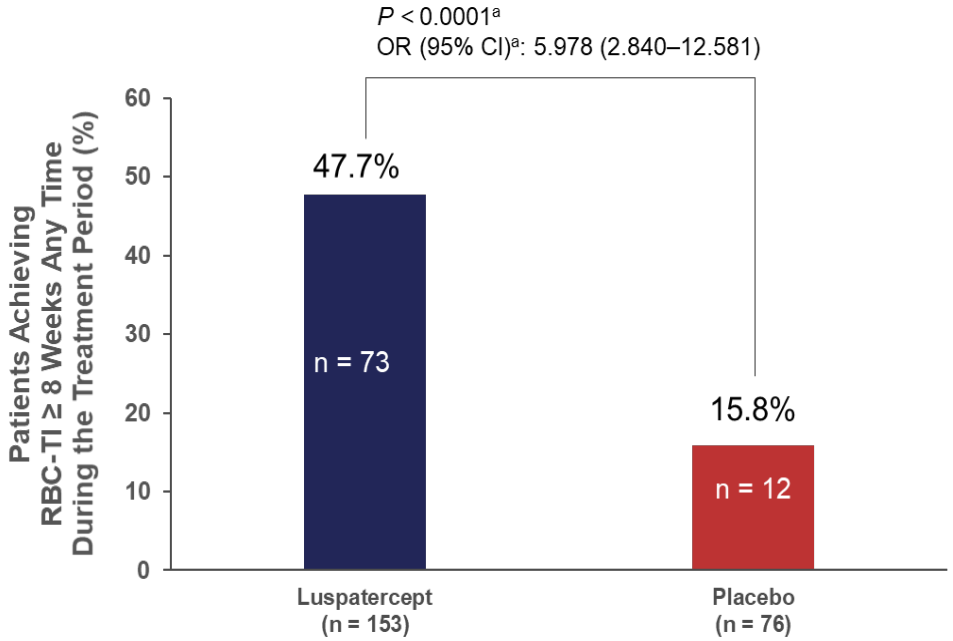
Data cutoff: May 8, 2018

# MEDALIST:

## Responses




## RBC-TI ≥8 Weeks Achieved Any Time During Treatment Period




*Luspatercept is not currently licensed for this indication in the European Union

1. Fenaux P, et al. New Engl J Med. 2020;382:140-151.

# MEDALIST: Effects of luspatercept on serum ferritin in patients with LR MDS with ring sideroblasts

## EHA 2020 submission: EHA-1260

**Aims:** To assess changes from baseline (BL) in serum ferritin and iron chelation therapy (ICT) use in pts in the MEDALIST trial

**Results:** A decrease from BL in mean serum ferritin was observed with luspatercept vs PBO in Wks 9–24 (least squares [LS] mean −2.7 vs +226.5 µg/L; P=0.0024) and Wks 33–48 (LS mean −72.0 vs +247.4 µg/L; P=0.0294)

**Summary/Conclusion:** Luspatercept treatment resulted in serum ferritin decreases, particularly in pts with higher BL transfusion burden and in those with high BL serum ferritin who experienced significant RBC transfusion reduction. This suggests that the effect of luspatercept on serum ferritin may be due not only to transfusion reduction, but also potentially to a more direct effect of the drug on ineffective erythropoiesis and/or iron metabolism. Overall, ICT use was reduced with luspatercept

**The magnitude in SF reduction observed is similar to that seen in the 1-yr EPIC study of the oral iron chelator, deferasirox[1, 2].**

# COMMANDS Study Design

## Randomized, Open-label Phase 3 Study

### Patient population

- **MDS diagnosis** (WHO 2016)
- **IPSS-R VL, L, INT risk**
- **RS(+) and RS(-) patients** [cap 40% - 60% RS(+)]
- **ESA naïve** (2 EPO doses allowed)
- **Endog. sEPO < 500 U/L**
- **Requiring RBC transfusions**:
  - **2 – 6 pRBCs units within 8 wks prior to randomization**
  - for Hgb ≤ 9 g/dL with symptoms or Hgb ≤ 7 g/dL without symptoms
- No prior treatment with disease modifying agents (e.g HMA)
- Not eligble for or treated with Lenalidomide (del5q)

**Stratification:**

RBC Transfusion Burden
- 2-3 / 4-6 units

RS status:
- RS(+) / Non RS

EPO level:
- ≤ 200 / > 200

1

1

**Luspatercept (ACE-536) 1.0 mg/kg s.c. Q3W** with titration up to max 1.75 mg/kg (n= 175)

**Epoetin alfa* 450 IU/kg s.c. QW** max. total dose 40K IU titration up to 1050 IU/kg max. total dose 80K IU (n= 175)

- 350 subjects
- RBC TI 12wks + Hb 20% → 36% (Δ16%)
- Power 90%

**MDS Disease Assessment after 24 wks and q6 months thereafter**

Discontinue if no clinical benefit or progression as per IWG

**Follow-Up**

at least 5 years post first dose or 3 years from last dose (whichever occurs later) for:

- AML
- Other (pre-) malignancies
- Subsequent MDS treatment
- and OS

- **1° Endpoint:**
  - 12 week RBC-Transfusion Independence + mean Hgb increase 1.5g/dL over the first 24 wks
- **2° Endpoints:**
  - Multiple secondary efficacy endpoints relating to response and duration

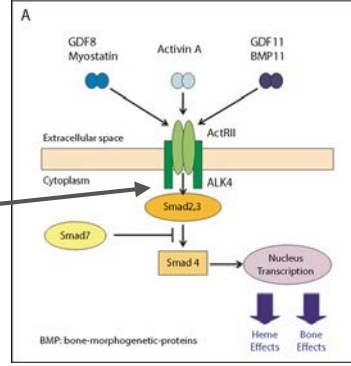
Individual doses according to body weight will be rounded up to the next 2,000 IU dose level or up to the next 4,000 IU dose level for doses exceeding a calculated dosing of 56,000 IU according to body weight.

*Luspatercept is not currently licensed for this indication in the European Union

* Individual doses according to body weight will be rounded up to the next 2,000 IU dose level or up to the next 4,000 IU dose level for doses exceeding a calculated dosing of 56,000 IU according to body weight.

NCT03682536

# Phase II study of the ALK5 inhibitor galunisertib in very low-, low-, and intermediate-risk MDS

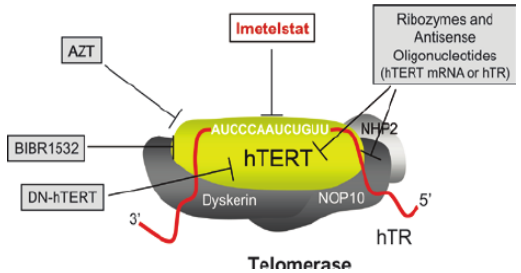



- Overactivation of TGF-ß signaling occurs in MDS.
- Galunisertib*, an oral inhibitor of the TGF-ß receptor type 1 kinase (ALK5) is effective in preclinical MDS models & has acceptable toxicity in phase I studies of solid tumours.
- A phase II multicenter study of galunisertib treated very low-, low-, or intermediate- IPSS-R risk MDS with Hb ≤10.0 g/dL with galunisertib 150 mg PO BID 14/28 days.
- 10/41 evaluable patients (24.4%) had HI-e by IWG 2006 criteria including 9/28 (32.1%) of TD.
- 18/41 (44%) had significant reduction in fatigue.
- Median response duration was 90 days.
- Galunisertib has an acceptable safety profile and was associated with HI in lower- & intermediate-risk MDS, with responses in heavily TD patients.
- A phase III study has completed enrolment.

*Galunisertib is not currently licensed for this indication in the European Union

1. Santini V et al. Clin Cancer Res . 2019 Dec 1;25(23):6976-6985.

# Imerge: imetelstat (GRN163L) in TD IPSS Low or Int-1 Risk MDS Relapsed/Refractory to ESA




- Imetelstat* is a 13-mer lipid-conjugated oligonucleotide that targets the RNA template of human telomerase & competitively inhibits enzymatic activity.
- A phase 2 study in TD LR MDS demonstrated an 8-week RBC-TI rate of 42%; & 68% HI-E in 38 heavily TD patients (median 8U/8 wk). Median response duration was 85.9 wk.
- IMerge (ClinicalTrials.gov: NCT02598661) is enrolling adults with IPSS low or int-1 risk, non-del(5q) MDS, TD, R/R to ESAs, & not received lenalidomide or HMA. Randomized (2:1) double-blind, placebo-controlled & will enroll 170 patients in 90 centers.
- Imetelstat is a 2h IV infusion Q4 weeks at 7.5 mg/kg.
- Primary endpoint is the rate of RBC-TI ≥8 weeks.

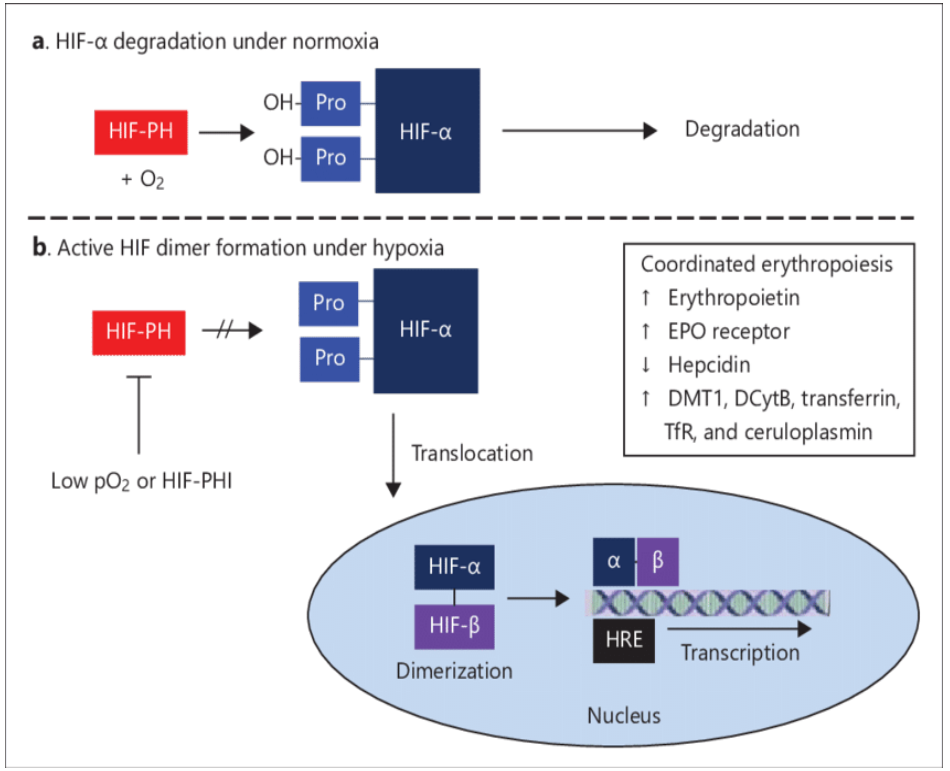
*Imetelstat is not currently licensed for this indication in the European Union

1. Platzbecker U et al. Blood (2019) 134 (Supplement_1): 4248

# Efficacy and safety of FG-4592 for treatment of anemia in subjects with lower risk MDS

- Roxadustat* (FG-4592) is an orally administered HIF prolyl hydroxylase inhibitor in development to treat anemia in MDS & chronic kidney disease[1]
- Roxadustat increases endogenous EPO levels by stabilization of HIF & improves iron regulation by modulation of hepcidin levels[1]
- In preclinical models roxadustat improves Hb levels[1]
- Roxadustat is in a phase 3 randomized double-blind placebo-controlled study of efficacy & safety to treat anemia in lower-risk, ESA-naive MDS with low RBC transfusion burden (NCT03263091)[1]
- Other treatments: HMAs, lenalidomide, spliceosome inhibitors[1,2]

**HIF activity under normoxic and hypoxic conditions[3]**




*Roxadustat is not currently licensed for this indication in the European Union

1. Kubasch & Platzbecker. Int J Mol Sci 2019 Aug 7;20(16):3853; 2. NCT03263091. Available from: https://clinicaltrials.gov/ct2/show/NCT03263091 Accessed: May 2020; 3. Locatelli F, et al. Am J Nephrol 2017;45:187–99

# Another upcoming lower risk MDS study - JNJ-64619178, an Inhibitor of Protein Arginine Methyltransferase 5 (PRMT5)

| Lower Risk Myelodysplastic Syndrome |
| --- |
| • A diagnosis of lower risk MDS according to World Health Organization 2016 criteria, confirmed by bone marrow aspirate and biopsy.[2] |
| • IPSS low risk or intermediate-1 risk (Attachment 13). |
| • RBC transfusion dependent. Received at least 4 units of RBCs over any 8 consecutive weeks during the 16 weeks prior to first dose of study drug. Pre-transfusion hemoglobin must have been ≤9.0 g/dL. |
| • Relapsed/refractory to ESA treatment or endogenous serum EPO level >500 mU/mL. |
| • Del(5q) karyotype is allowed, provided prior treatment with lenalidomide has failed or subject was ineligible to receive lenalidomide. |

- Oral, once daily 14/21
- Roxadustat (also oral) can be ESA naïve or R/R to ESA

# Agenda

1. MDS; introduction
2. Management of anemia in MDS
    1. Complications of anemia
    2. RBC transfusions & their burden
    3. Clinical benefit of reducing transfusions in lower risk MDS
    4. New approaches to reducing transfusion dependence
3. **Case study; management of anemia & iron overload**
4. Conclusions and future directions

# Case

- 56 year old man presented with fatigue
- Physical examination normal
- WBC 5.3, ANC 2.7, Hb 99 MCV 102, platelets 336
- Ferritin 800 (ULN 370), transferrin saturation 70%
- EPO level 168.1 IU/mL
- Smear showed macrocytosis
- Bone marrow aspirate showed increased cellularity, blasts 1%, erythroid dysplasia, ringed sideroblasts
- Cytogenetics, normal male karyotype
- Diagnosis:  RARS, IPSS low risk
- Requiring transfusion of 2U PRBC every 3 weeks

# Is he eligible for agents that induce transfusion independence?

- Why ESA?

- LEN not approved for normal karyotype
- lived remotely so IST would be difficult
- Azacitidine is not approved for lower risk MDS
- SCT considered but deferred because of good prognosis MDS & no sibling donor
- ICT – use active treatment + phlebotomy (if reasonable Hb) to reduce IOL
- Consider a clinical trial

# MDS CLEAR PATH

This tool is designed to help streamline the continuum of care for MDS patients, from diagnosis and staging through to treatment.

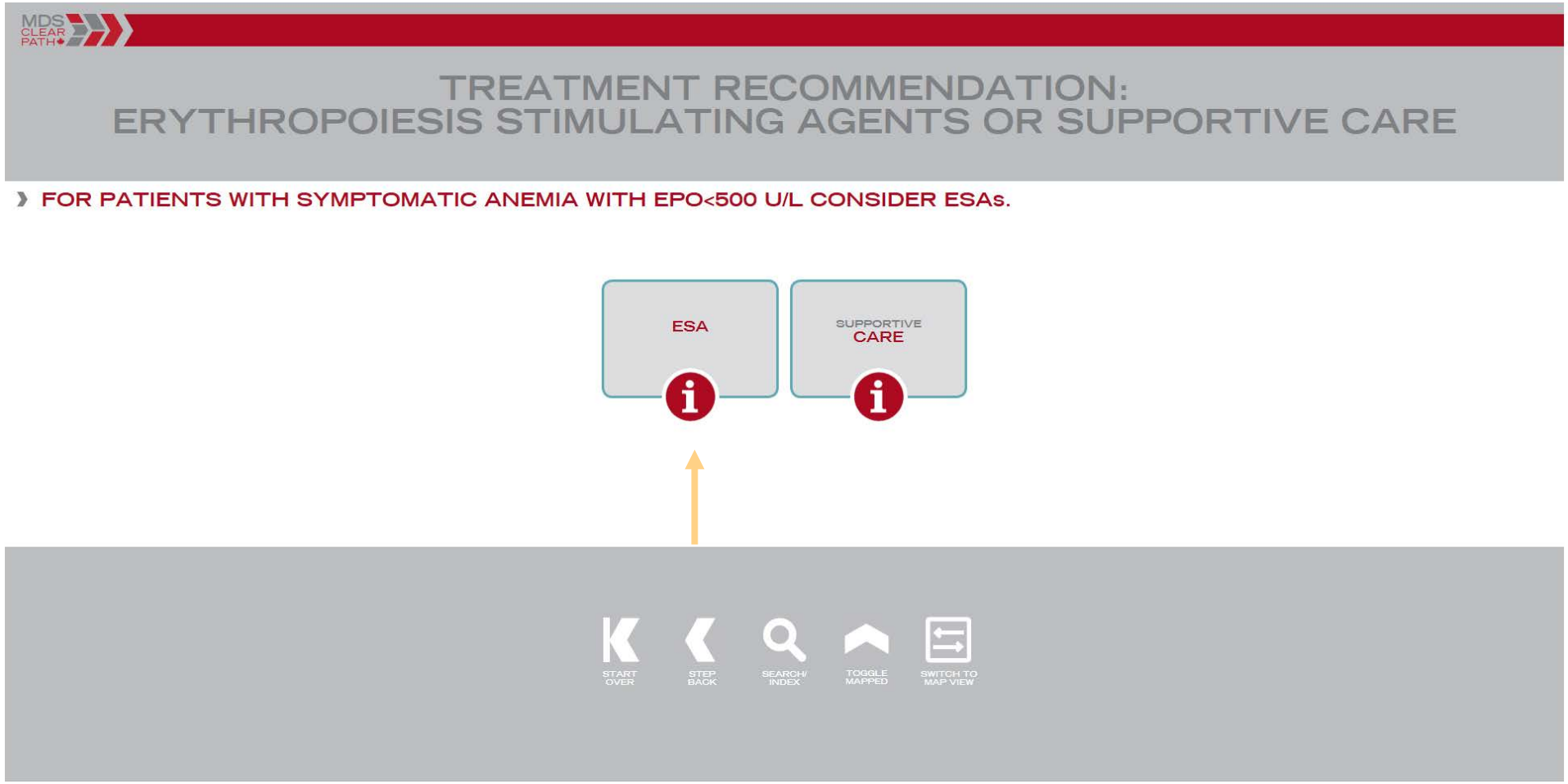
It features a comprehensive algorithm, which is the outcome of a Canada-wide physician consensus on best practices in MDS management. Ultimately it will serve to support physicians at key decision points in their treatment of MDS patients.

START FRANÇAIS

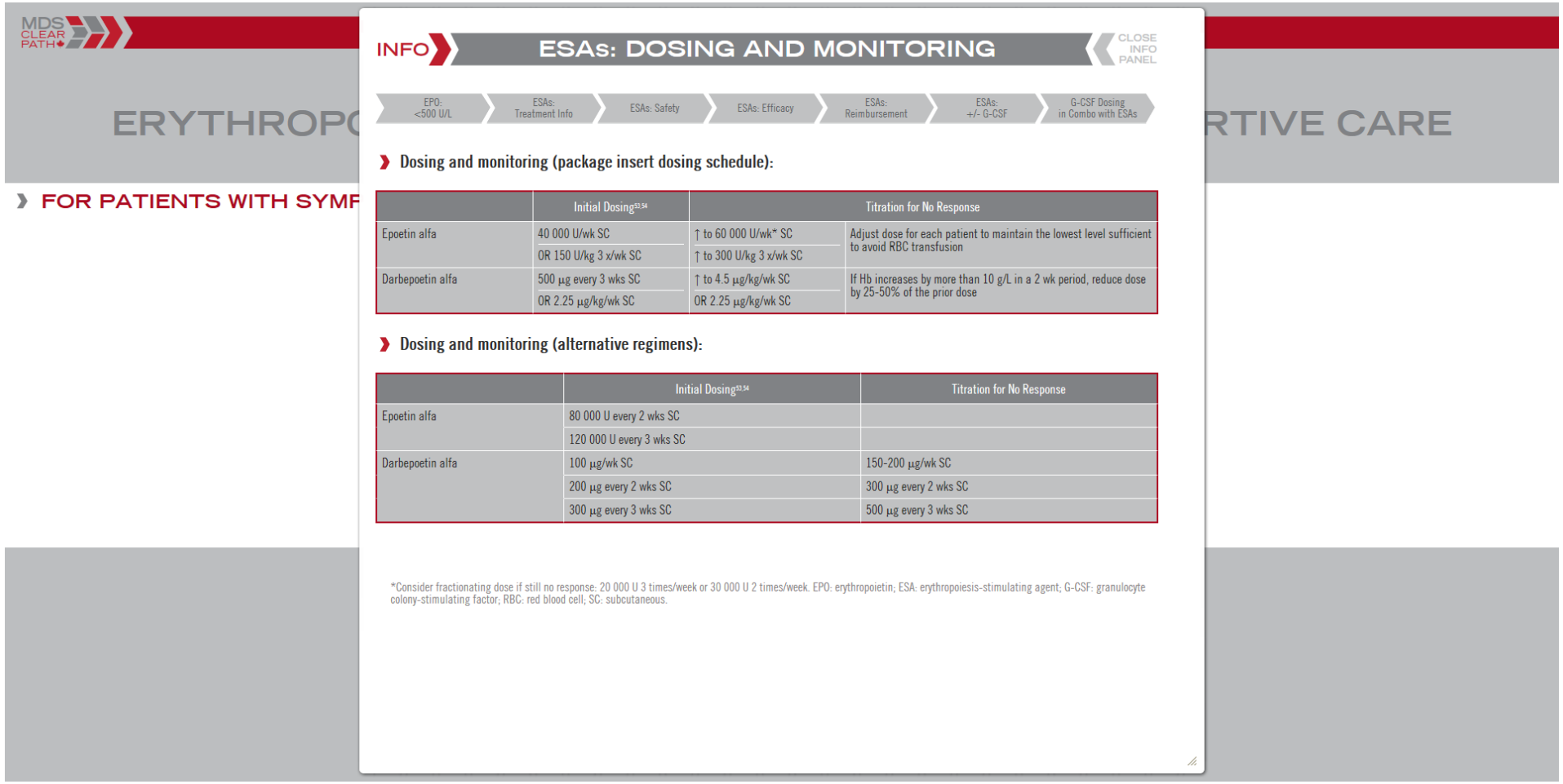
The content of this program is supported by an unrestricted educational grant from Celgene Inc.

The MDS Clear Path has been developed and approved by a Steering Committee with the input of over 60 Canadian physicians. Members of this Steering Committee are Dr. Richard Wells, Dr. Heather Leitch, Dr. Harold Olney and Dr. April Shamy. The opinions expressed are solely those of the Steering Committee members. The content is specifically intended to be used by qualified physicians/medical professionals, to assist them in the management of MDS patients. The MDS Clear Path does not substitute, nor is it intended to substitute for the medical advice of an appropriately qualified and licensed physician or other healthcare provider. Use of the application is undertaken entirely on your own responsibility as a healthcare professional. The information provided here is for educational and informational purposes only. In no way should it be considered as offering medical advice. The digital formats of the MDS Clear Path have been completed by The Adpharm Inc. (a healthcare communications company) through funding from Celgene Inc. The sole purpose was to deliver the content of the original MDS Clear Path in a user friendly, digital format. No content was modified in the transition to a digital format. All digital formats are the property of Celgene Inc. This presentation may include indications and treatment regimens which are not authorized in Canada. Please refer to current product monographs for complete indication and safety information.

# MDS ClearPath Treatment Wizard: treatment recommendation for Int-1 MDS with symptomatic anemia



# ESAs: dosing and monitoring




| | Initial Dosing[53,54] | Titration for No Response | |
|---|---|---|---|
| Epoetin alfa | 40 000 U/wk SC<br>OR 150 U/kg 3 x/wk SC | ↑ to 60 000 U/wk* SC<br>↑ to 300 U/kg 3 x/wk SC | Adjust dose for each patient to maintain the lowest level sufficient to avoid RBC transfusion |
| Darbepoetin alfa | 500 µg every 3 wks SC<br>OR 2.25 µg/kg/wk SC | ↑ to 4.5 µg/kg/wk SC<br>OR 2.25 µg/kg/wk SC | If Hb increases by more than 10 g/L in a 2 wk period, reduce dose by 25-50% of the prior dose |

| | Initial Dosing[53,54] | Titration for No Response |
|---|---|---|
| Epoetin alfa | 80 000 U every 2 wks SC | |
| | 120 000 U every 3 wks SC | |
| Darbepoetin alfa | 100 µg/wk SC | 150-200 µg/wk SC |
| | 200 µg every 2 wks SC | 300 µg every 2 wks SC |
| | 300 µg every 3 wks SC | 500 µg every 3 wks SC |

# Canadian guidelines for the management of iron overload in MDS

Leukemia Research 74 (2018) 21–41

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

## Iron overload in myelodysplastic syndromes: Evidence based guidelines from the Canadian consortium on MDS

Heather A. Leitch[a,*], Rena Buckstein[b], Nancy Zhu[c], Thomas J. Nevill[d], Karen W.L. Yee[e], Brian Leber[f], Mary-Margaret Keating[g], Eve St. Hilaire[h], Rajat Kumar[i], Robert Delage[j], Michelle Geddes[k], John M. Storring[l], April Shamy[m], Mohamed Elemary[n], Richard A. Wells[b]

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[j] Hematology Department, Centre Hospitalier Universitaire, Laval University, Quebec, QC, Canada
[k] Department of Medicine/Hematology, Foothills Medical Centre, Calgary, Alberta, Canada
[l] McGill University Health Centre, Montreal, Quebec, Canada
[m] Sir Mortimer B Davis Hospital, McGill University, Montreal, Quebec, Canada
[n] Saskatoon Cancer Center, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

1. Leitch HA, et al. Leukemia Research 2018;74:21–41.
Ex-Canadian guidelines: NCCN Clinical Practice Guidelines in Oncology. Myelodysplastic syndromes. Version 1.2020; Malcovati L, et al. Blood 2013;122:2943–64

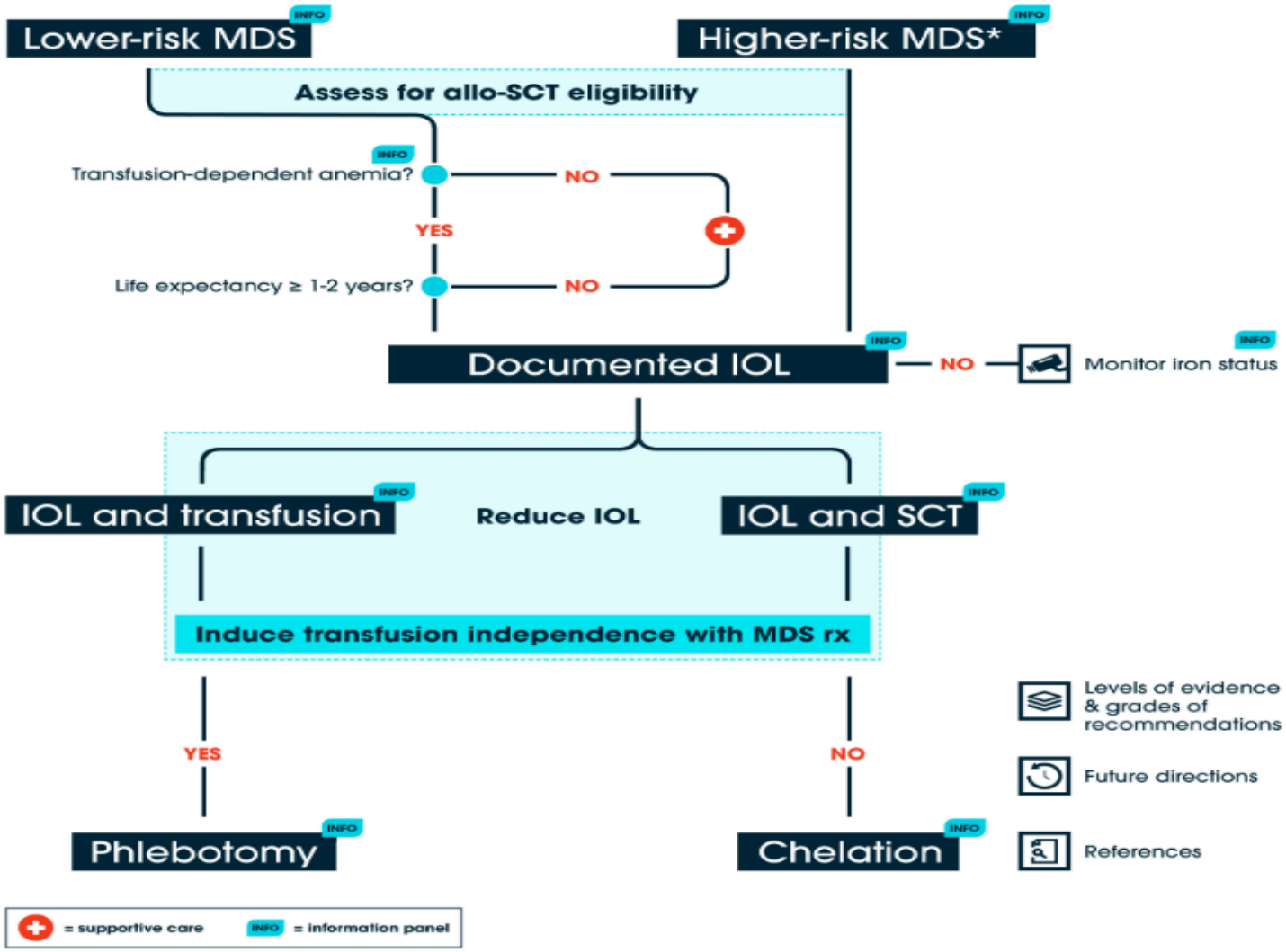

This tool is designed to help streamline the care of MDS patients with iron overload (IOL). It features comprehensive information on clinical endpoints impacted by and IOL reduction, the outcome of a Canada-wide physician consensus on best practices in IOL management in MDS. It will support physicians in their treatment of MDS patients with IOL.

CCMDS|CCSMD

1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

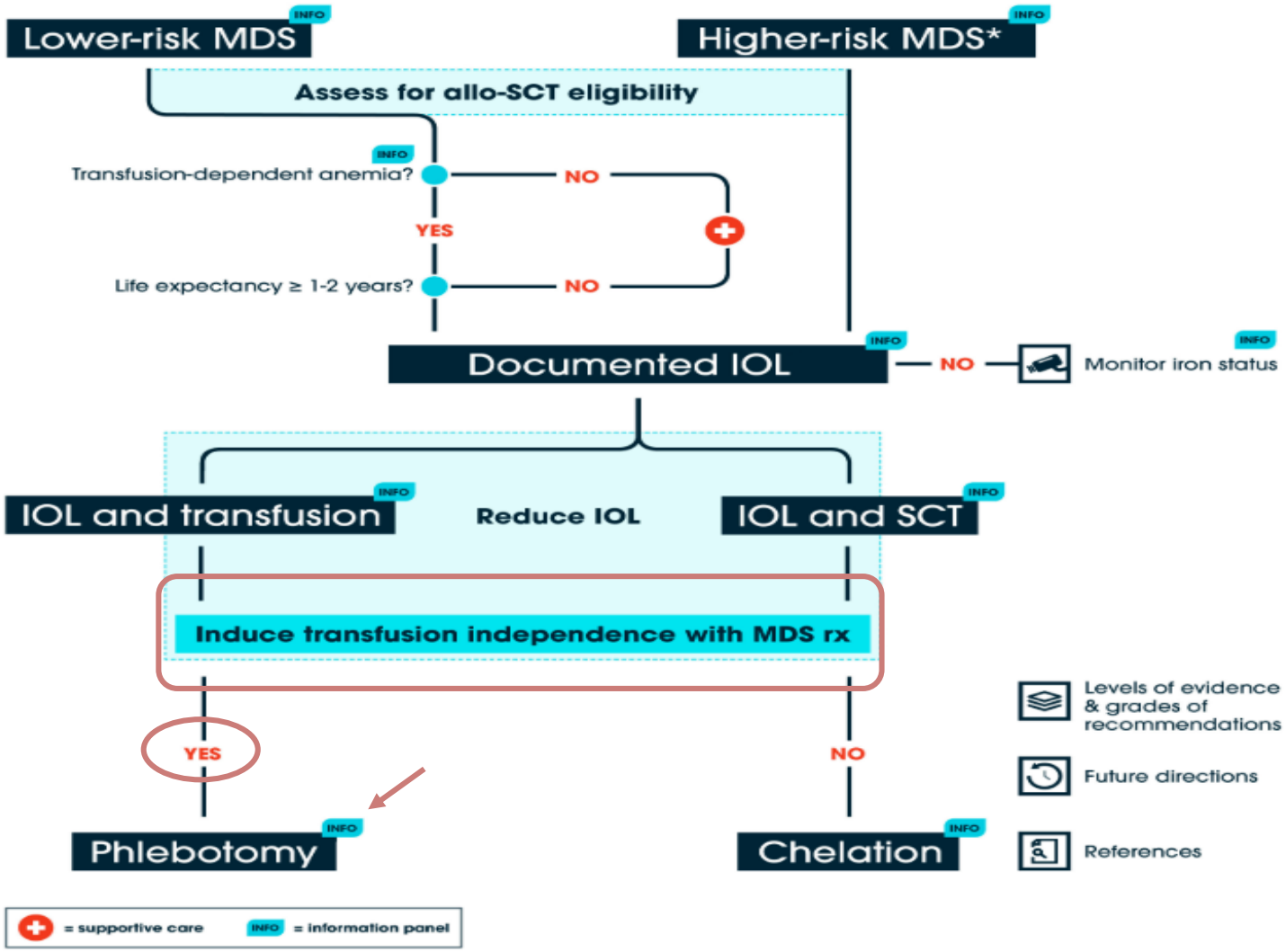
# Canadian guidelines for the management of iron overload in MDS

Modes:
- Iron Road
- IR express




1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

# Canadian guidelines for the management of iron overload in MDS

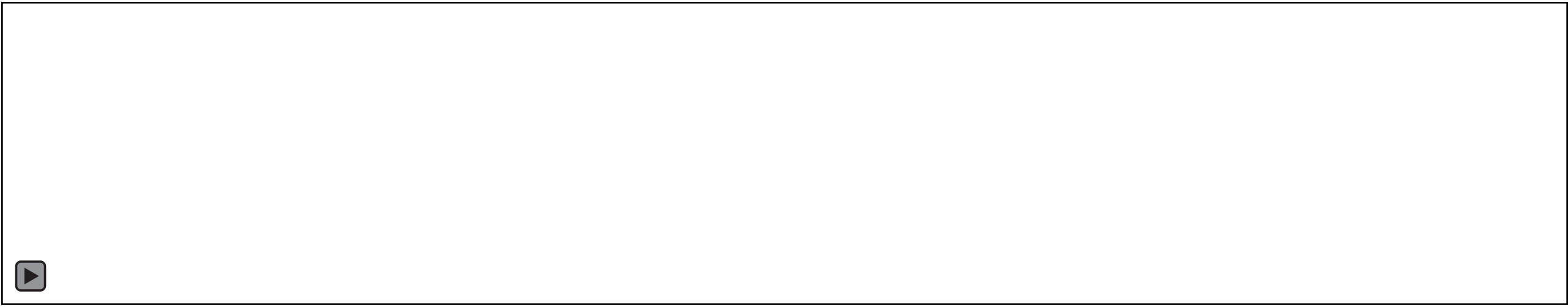



1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

# Eligible for therapies that induce transfusion independence?


1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

# Transfusion independence with a reasonable hemoglobin achieved?



1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

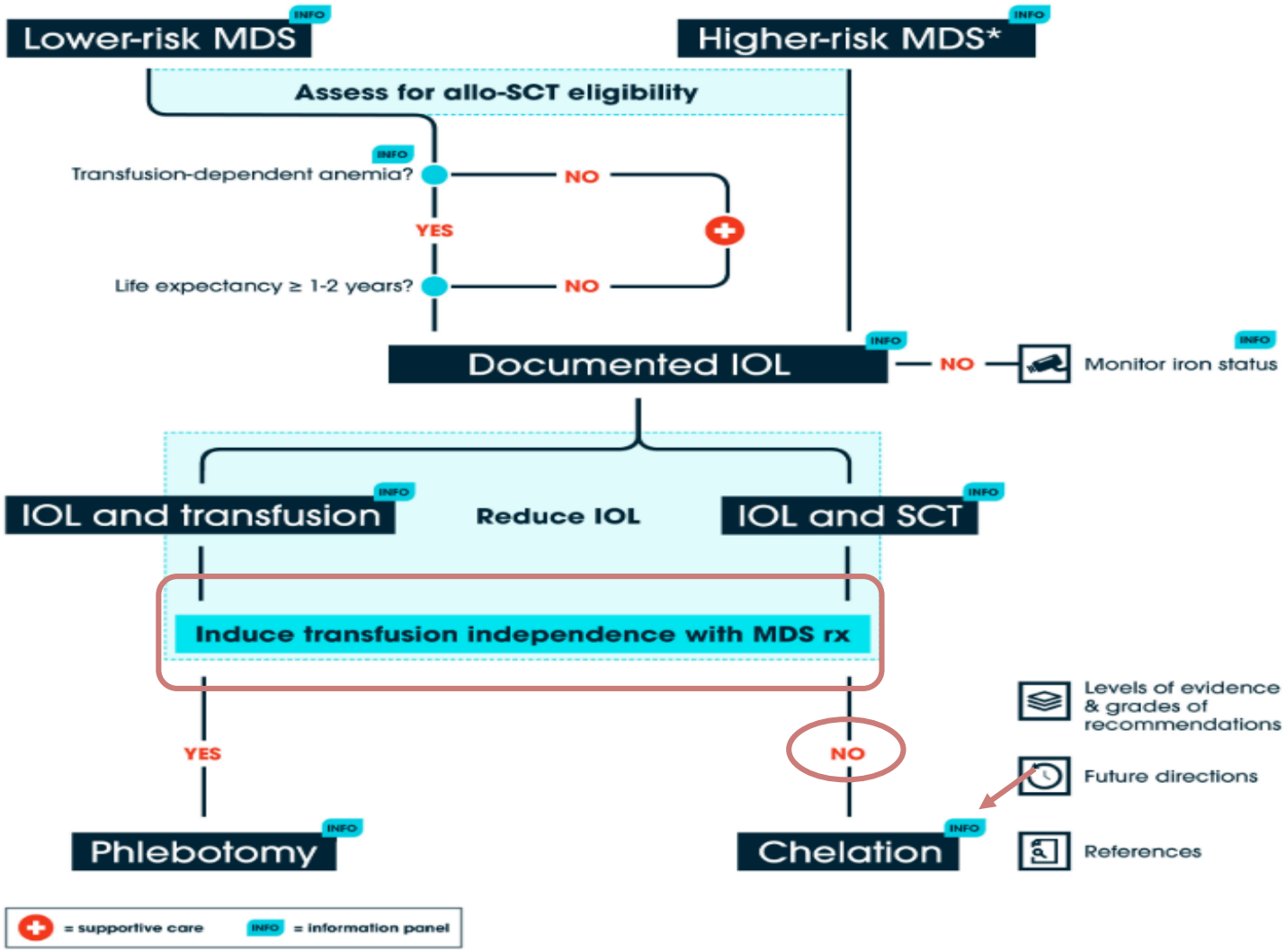
# Case

- With EPO 60,000U weekly
  - Hgb 110-120
  - ferritin 1115, transferrin saturation 81%
  - (here is where I could have started serial phlebotomy)
- 1 year later, remained transfusion independent
  - ferritin 896, tsat 70%
- 6 years of transfusion independence & improved QOL

# Case

- 6 years later presented with exacerbation of anemia
- Repeat BMBx showed stable MDS
- Developed a regular transfusion requirement
  —Initially 2U every 4 weeks
- Ferritin increased to >2500, tsat 90%

# Canadian guidelines for the management of iron overload in MDS




1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

# Case

- Started on DFX (dispersible formulation) 20mg/kg/day
  - Creatinine rose to 300
- DFX stopped
  - Creatinine dropped to 150
- Started on DFO 30mg/kg/day by continuous SQ infusion12 h/day, 7 days/week
  - Routine audiology tests 2 years later showed severe sensorineural hearing loss
  - DFO stopped
- Started lenalidomide (off-label)
  - Developed sepsis requiring ICU admission

# Case

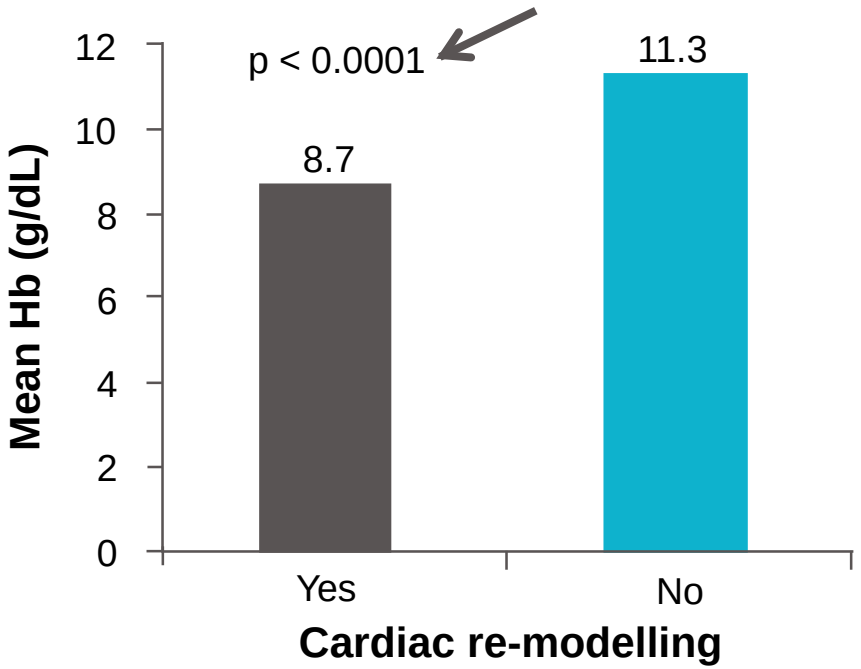
- While waiting for luspatercept*, started DFP*
  - Developed arthralgias requiring narcotic medications
  - DFP stopped
- Started ELT*
  - In second month of treatment died of refractory CHF & infections (from IOL) at age 70

*These compounds do not have a marketing authorization for this indication in the European Union

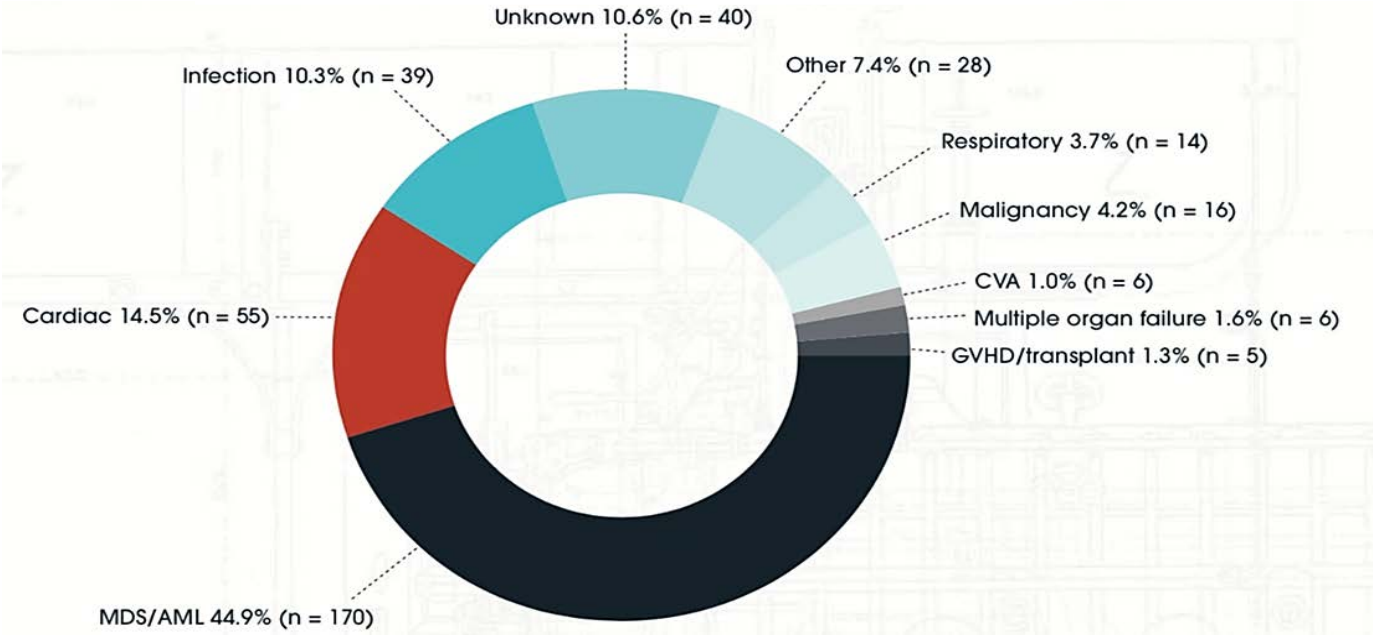
# Cardiac events in MDS patients

1. MDS patients with Hb < 10.7 g/dL have an increased incidence of cardiac remodeling[1]
2. IOL is associated with development of cardiac events[2]
3. Cardiac events are the leading cause of non-leukemic death in MDS[2]

**Hb levels in patients with evidence of cardiac remodelling[1]**




**Cardiac events are the leading cause of non-leukemic death in MDS patients[2]**




CI, confidence interval; LVH, left ventricular hypertrophy.

1. Oliva EN, et al. Leuk Res. 2005;29:1217-9; 2. Marek BJ, et al. Blood. 2013;122:abstract 2775.

# Cardiac events in transfused lower IPSS risk MDS

- Cardiac events included clinical episodes of CAD, CHF & ARR[1]
- Median TTCE was 7 & 20 months for ICT & non-ICT patients[1]
- In MVA, receiving ICT remained significant for TTCE (**p=0.03**)[1]
- For a detailed discussion on the contribution of IOL to atherosclerosis, see Vinchi et al (2014)[2]

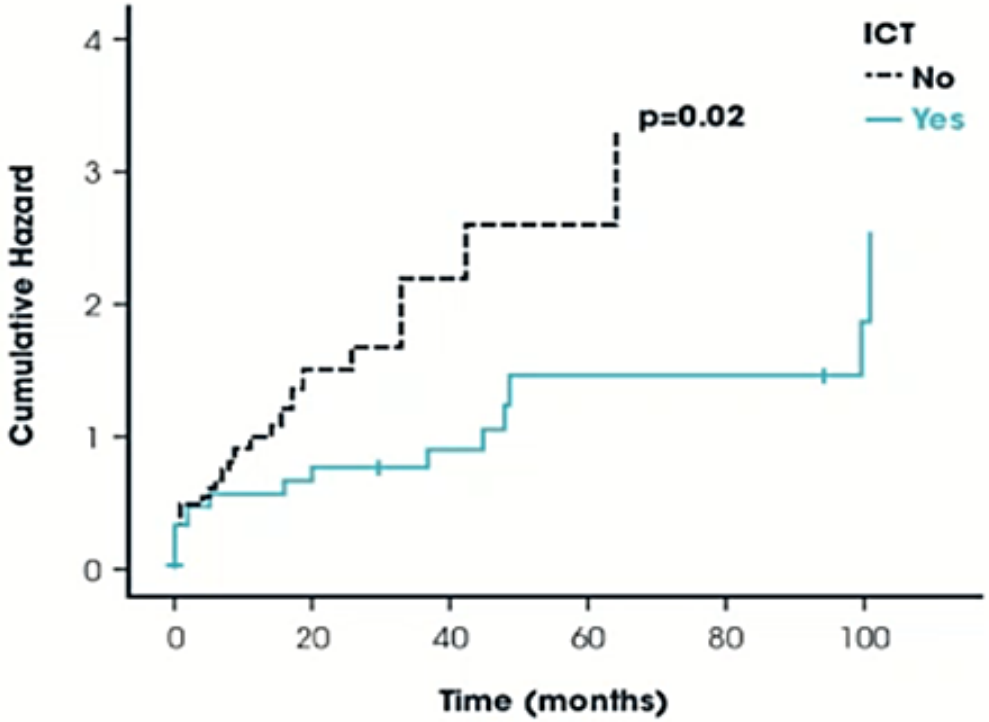



**Figure** Delayed time from RBC transfusion dependence to first cardiac event in lower IPSS risk MDS patients receiving iron chelation therapy[1]

ARR, arrythmia; CAD, coronary artery disease; CHF, congestive heart failure; ICT, iron chelation therapy; MVA, multivariate analysis; TD, transfusion dependent; TTCE, time to cardiac event.

1. Wong CAC & Leitch HA. Leuk Res. 2019;83:106170. 2. Vinchi F, et al. Front Pharmacol. 2014;5:1-20.

# Infections

- An iron rich environment enhances the growth of microorganisms. IOL leads to functional impairment of neutrophils, macrophages & natural killer cells[1-7]
- In SCT for hematologic malignancies, IOL (elevated pre-SCT SF, hepcidin level, or LIC) is a risk factor for significant infections[8]
- An analysis from the US Medicare Registry indicated that TD MDS had a higher rate of infections than TI (81 vs 55.7%, p<0.001)[9]
- In 138 RBC TD lower IPSS risk MDS, median time to first infection (TTI) in patients not receiving ICT was shorter (7.8 vs 27 months for ICT patients, p<0.0001)[10]

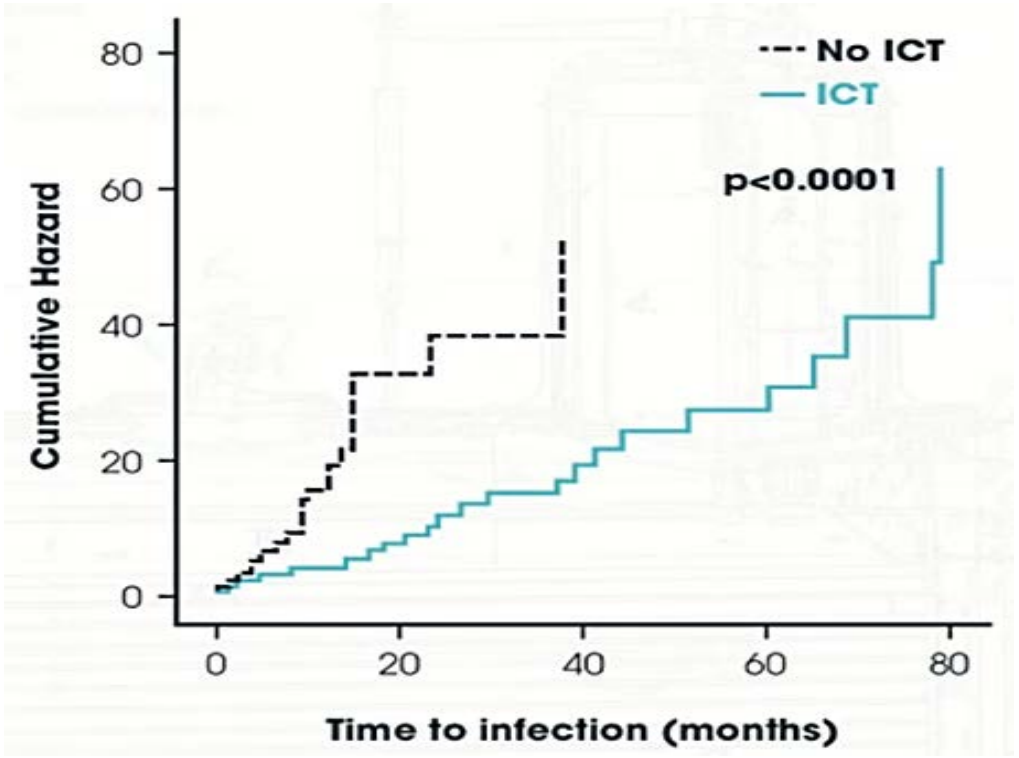
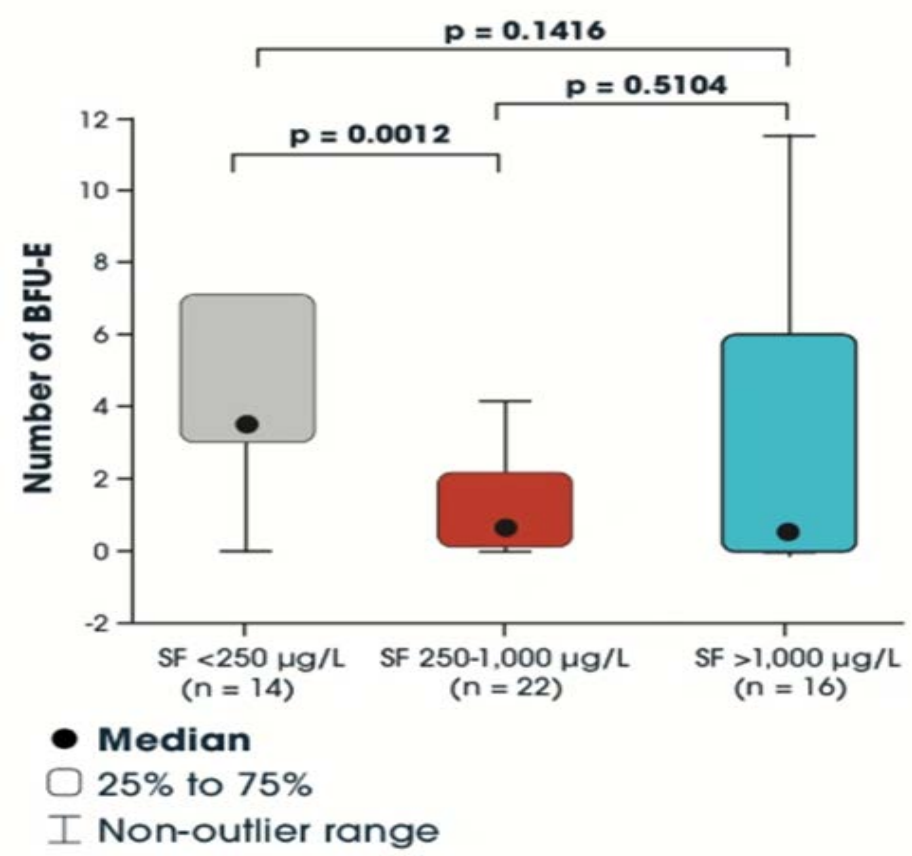



**Figure** Time from first RBC transfusion to first infection in patients with lower IPSS risk MDS not receiving or receiving iron chelation therapy[9]

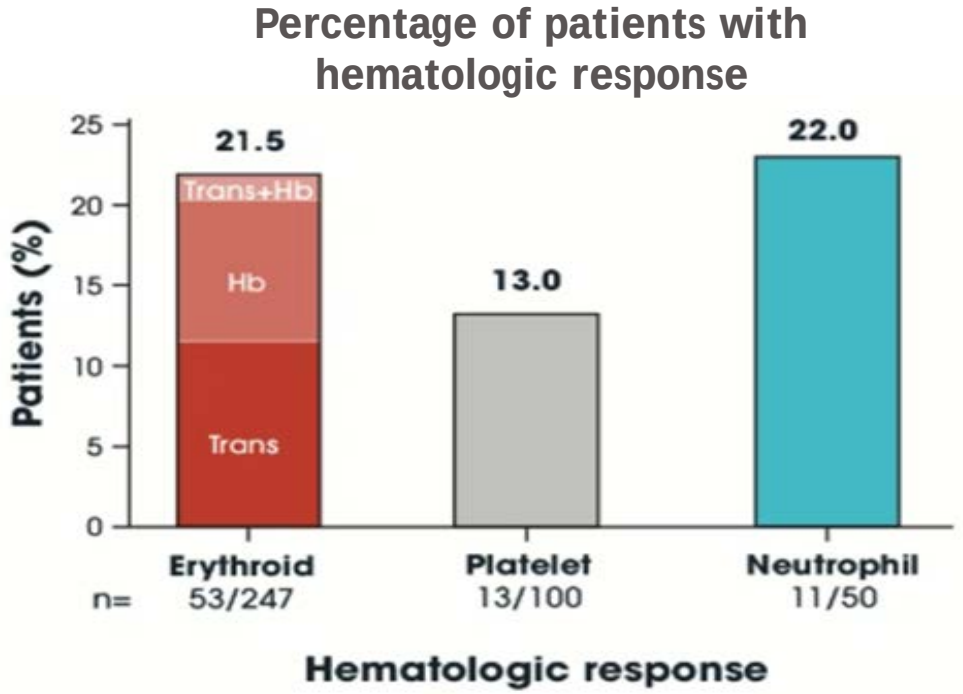
ICT, iron chelation therapy; IOL, iron overload; LIC, liver iron concentration; SCT, stem cell transplantation; SF, serum ferritin; TD, transfusion dependent; TI, transfusion independent; TTI, time to infection.

[1]Cantinieaux B, et al. J Lab Clin Med. 1998;111:524-8. [2]Barton Pai A, et al. Am J Nephrol. 2006;26:304-9. [3]Cantinieaux B, et al. Eur J Haematol. 1987;39:28-34. [4]Cantinieaux B, et al. J Lab Clin Med. 1999;133:353-61. [5]van Asbeck BS, et al. J Immunol. 1984;132:851-6. [6]van Asbeck BS, et al. J Infect. 1984;8:232-49. [7]Nairz M, et al. Front Pharmacol. 2014;5:152. [8]Leitch HA, et al. Crit Rev Oncol Hematol. 2017 May;113:156-170. [9]Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52. [10]Wang CAC, et al. Leuk Res. 2018;67:75-81.

# Bone marrow failure




1. Hartmann J, et al. Leukemia Research. 2013 Mar;37(3):327-32.




Hematologic improvement by IWG 2006 criteria in the EPIC study

2. Gattermann N, et al. Haematologica. 2012;97:1364-71.
3. Cheson BD, et al. Blood. 2006;108:419-25.

BFU-E, burst-forming units erythroid; EPIC, Evaluation of Patients' Iron Chelation with Exjade; IWG, International Working Group; SF, serum ferritin.

# Agenda

1. MDS; introduction
2. Management of anemia in MDS
    1. Complications of anemia
    2. RBC transfusions & their burden
    3. Clinical benefit of reducing transfusions in lower risk MDS
    4. New approaches to reducing transfusion dependence
3. Case study; management of anemia & iron overload
4. **Conclusions and future directions**

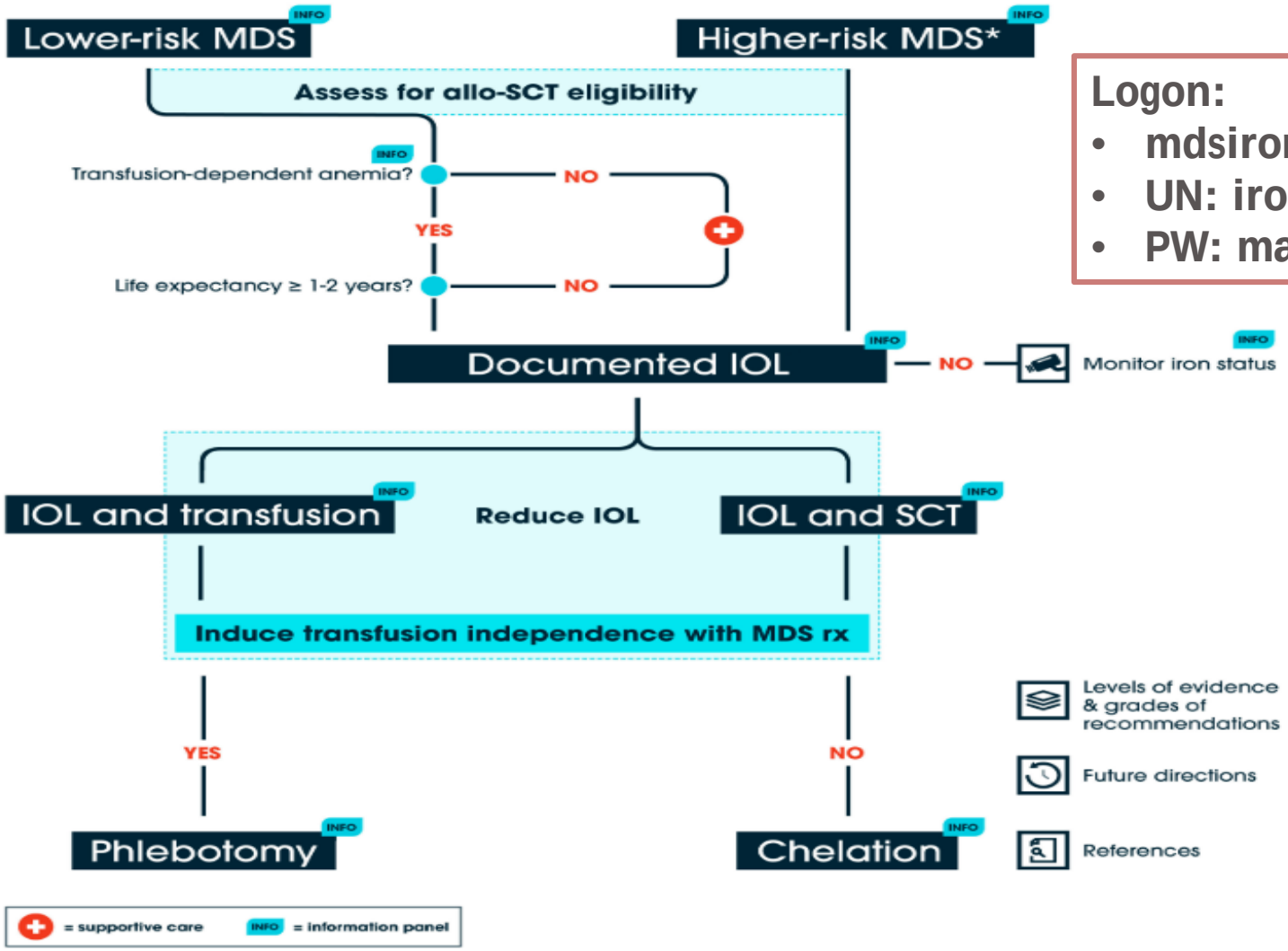
# Summary/Conclusions:

- Transfusion independence is associated with superior OS and QOL in LR MDS[1,2]
- Following ESA failure the treatment options in LR MDS have to date been limited[3]
- Transfusion dependence leads to IOL, associated with inferior clinical endpoints[4]
  - —The number of chelators we have access to is limited
  - —Use of these chelators may be limited by side effects
- In future, we will hopefully have access to more therapeutic options to modify disease course in MDS and induce transfusion independence. This will optimize OS & QOL
- Wherever possible, IOL should be delayed, minimized or reversed using novel agents +/- phlebotomy[5]. When this is not possible, reducing IOL with ICT should be considered.[5]

BFU-E, burst-forming units erythroid; EPIC, Evaluation of Patients' Iron Chelation with Exjade; IWG, International Working Group; SF, serum ferritin.

1. Malcovati L, et al. Haematologica 2006;91:1588–90; 2. Fenaux P, et al. Br J Haematol 2019; 3. Platzbecker U. Blood 2019;133:1096–1107; 4. de Swart L, et al. Haematologica 2019;104. Epub ahead of print; 5. Fenaux P, et al. Br J Haematol 2019. doi: 10.1111/bjh.16206. Epub ahead of print

# Canadian guidelines for the management of iron overload in MDS




**Logon:**

- **mdsironroad.org**
- **UN: ironroad**
- **PW: makeirongreatagain**

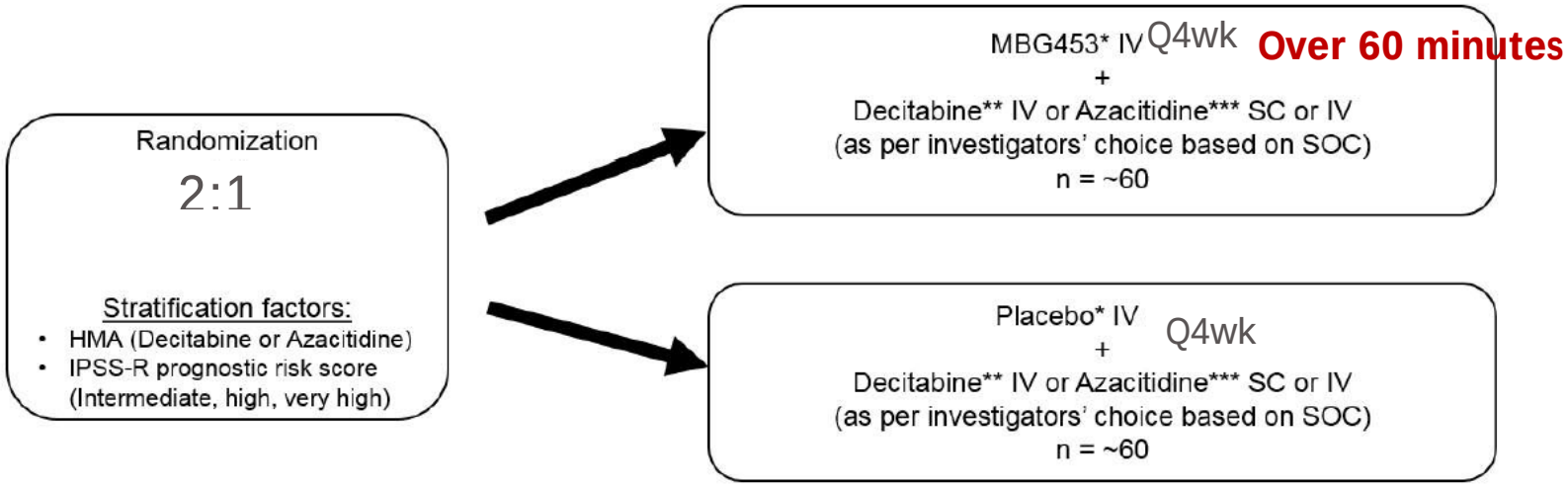
1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

# Higher risk MDS; TIM-3, MBG

- T-cell immunoglobulin and mucin domain-containing 3 (TIM-3) is a negative regulator of T cells (immune checkpoint).
- TIM-3+ HSC from patients with MDS display aberrant differentiation, increased proliferation and decreased apoptosis (Sakuishi et al 2011).
- TIM-3 is overexpressed in MDS patients & detection on blasts increases as MDS progresses.
- Therefore blockade of this immune checkpoint constitutes a target for therapy in MDS.
- MBG453 is a high-affinity, ligand-blocking, humanized anti-TIM-3 antibody which blocks the binding of TIM-3 to phosphatidylserine (PtdSer, a cell membrane component).
- Human trials have shown that MBG453 can be safely administered with HMA (azacytidine) in MDS/AML.
- Clinical activity has been observed in high and very high risk MDS.

# Study design

**Figure 3-1 Study design**




*MBG453 or placebo: 400 mg on D8 and D22
**Decitabine: 20 mg/m$^2$ from D1 to D5
***Azacitidine: 75 mg/m$^2$ from D1 to D7 or D1 to D5 + D8 to D9

# Thank you

Questions? hleitch@providencehematology.com