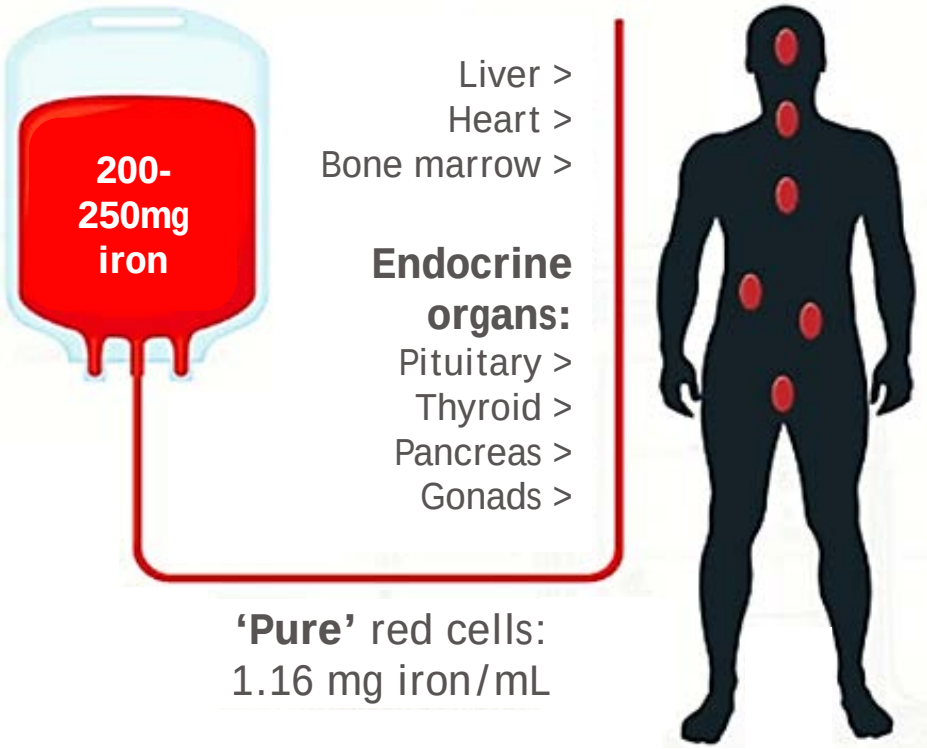
Iron accumulation from transfusion therapy

- 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**



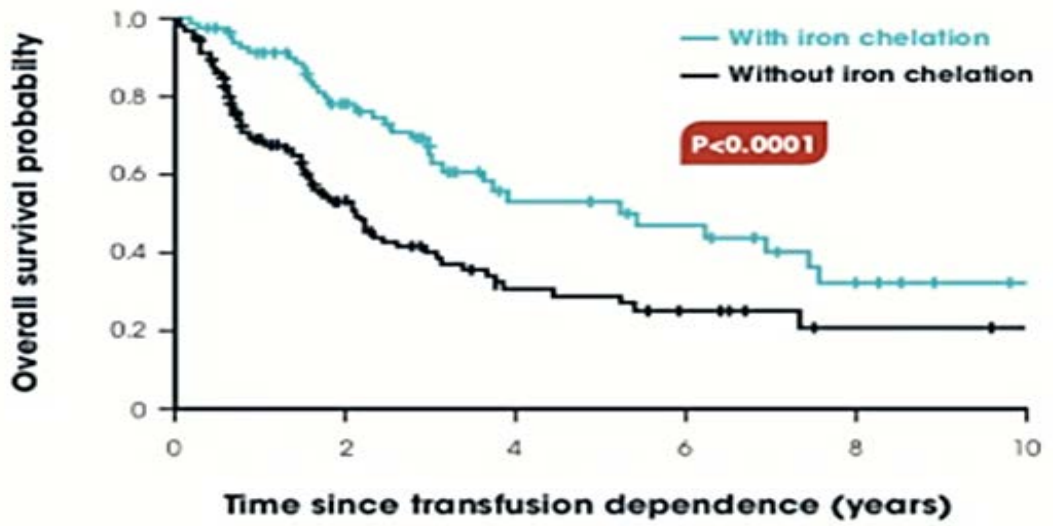
EUMDS, European LeukemiaNet MDS Registry

Reducing IOL in MDS

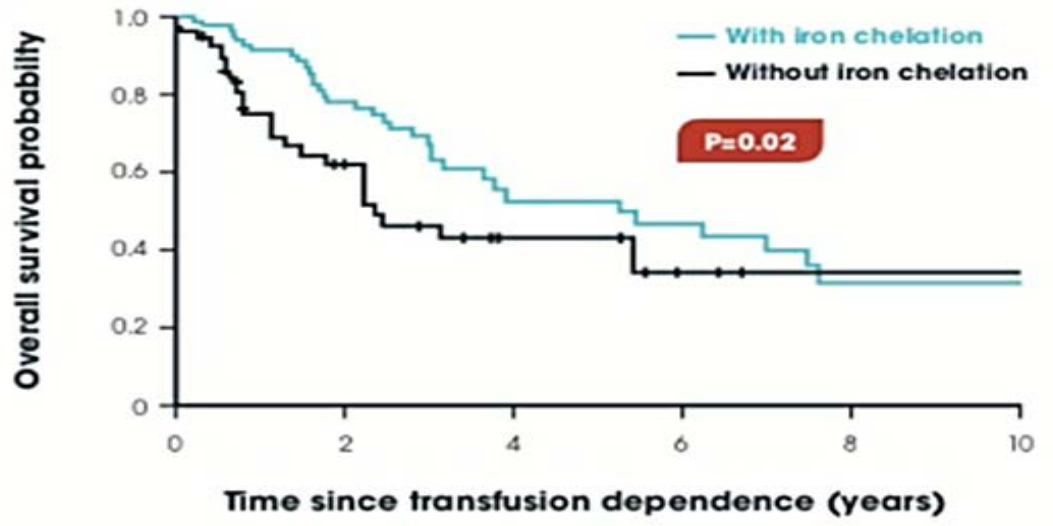
- Historically, the importance of IOL management in MDS has been controversial
- An analysis from the Canadian MDS registry controlled for 4 measures of patient performance status & evaluated OS from time of first RBC TD
- This showed superior OS in patients receiving ICT
- Several analyses matching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

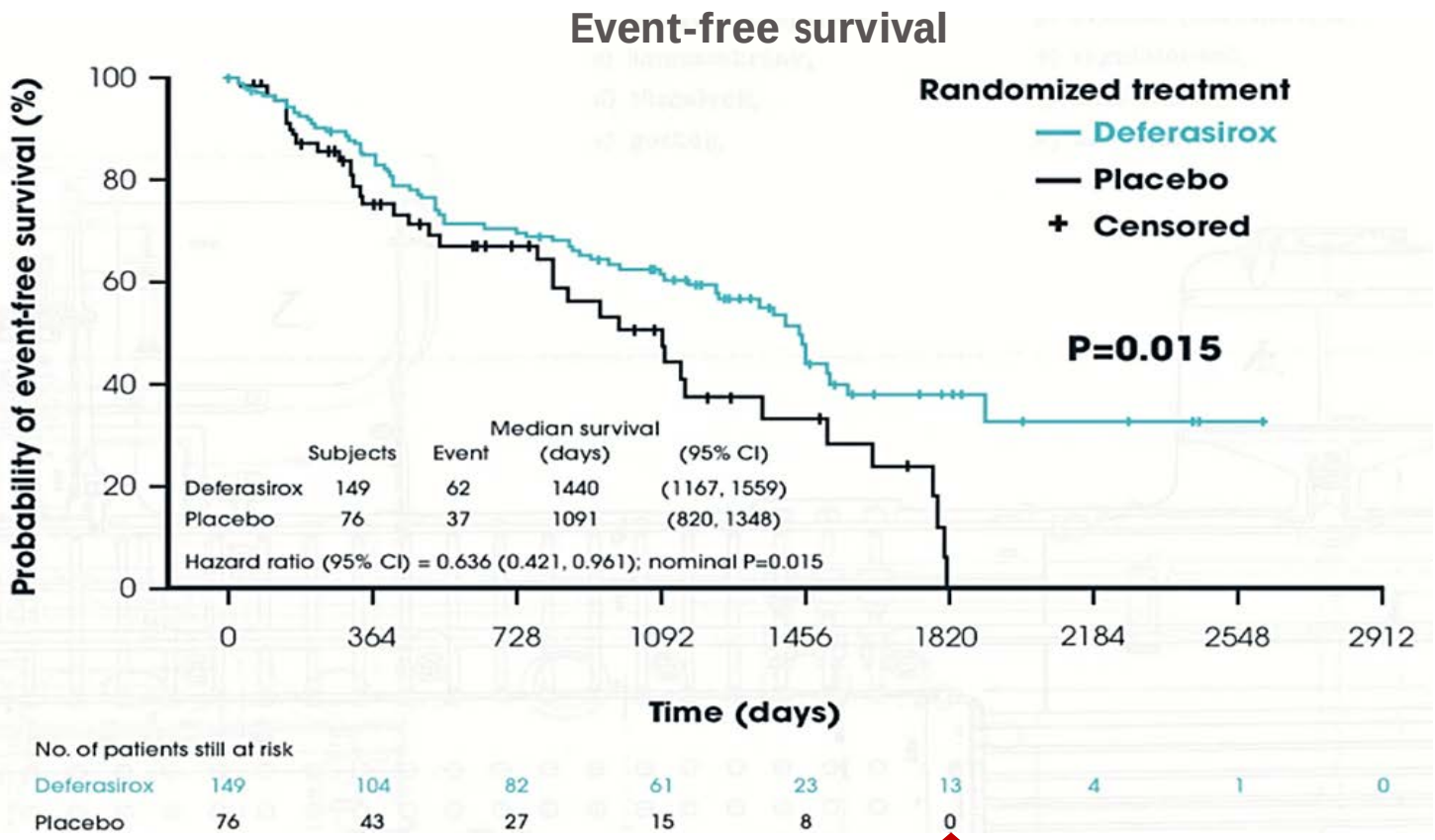
1. Leitch HA, et al. Brit J Haematol 2017;179:83-97

Event-free survival: TELESTO

Reference added

- 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.

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

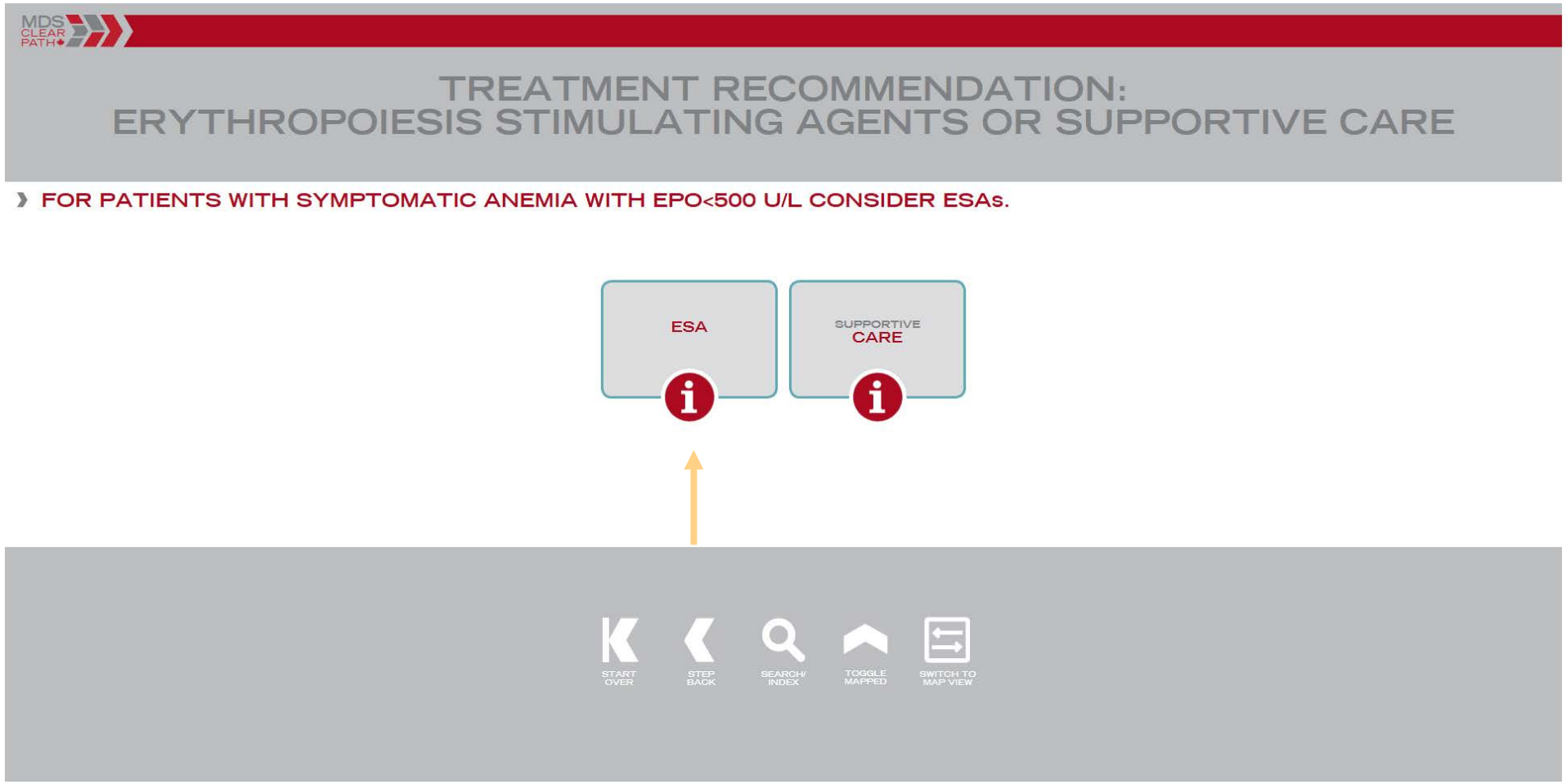
This tool is designed to help streamline the continuum of care for MDS patients, from diagnosis and staging through to treatment.

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.

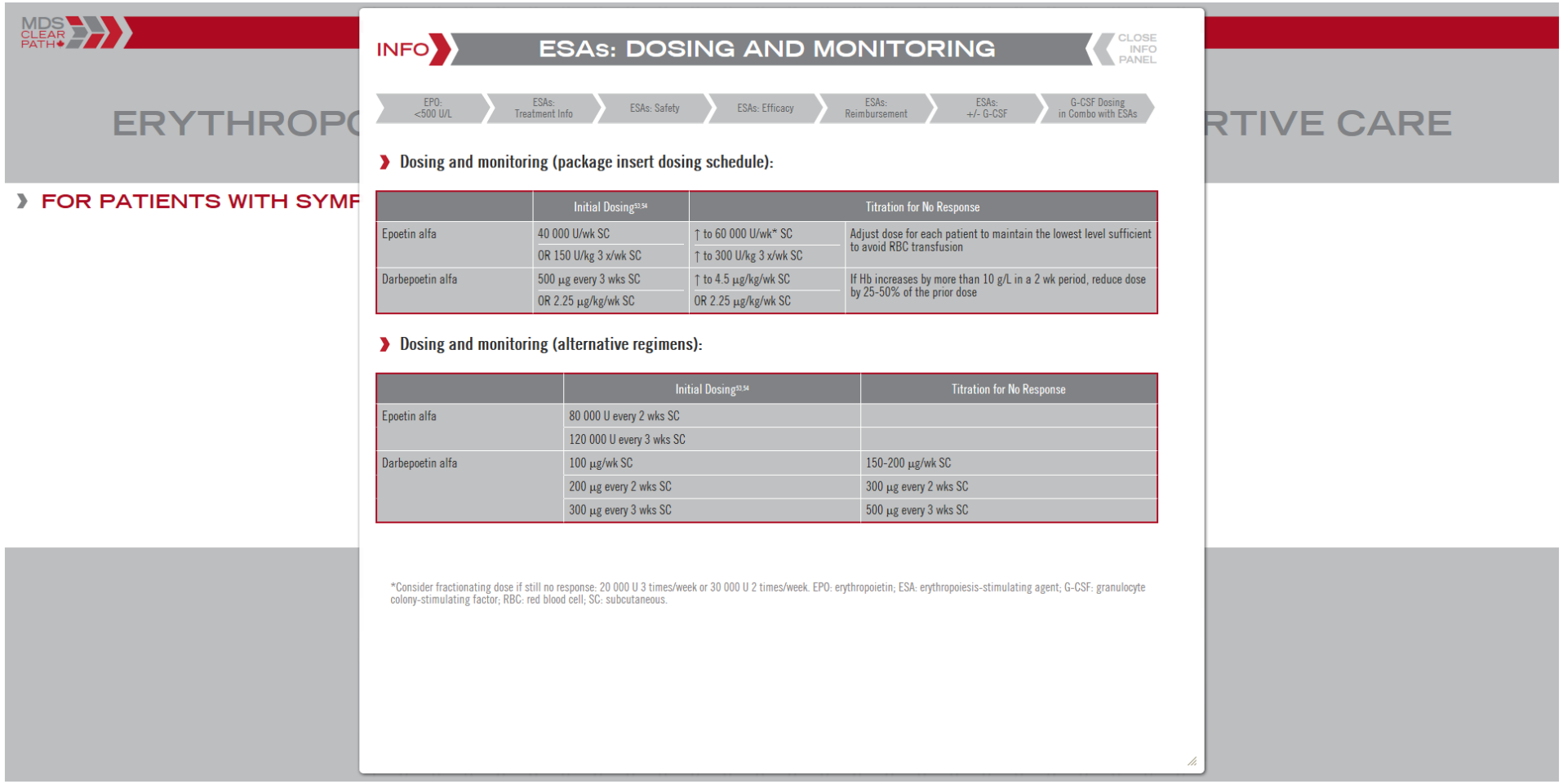
START FRANÇAIS

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



Dosing and monitoring (package insert dosing schedule):

	Initial Dosing[53,54]	Titration for No Response	
Epoetin alfa	40 000 U/wk SC OR 150 U/kg 3 x/wk SC	↑ to 60 000 U/wk* SC ↑ 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 OR 2.25 µg/kg/wk SC	↑ to 4.5 µg/kg/wk SC 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

Dosing and monitoring (alternative regimens):

	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

*Consider fractionating dose if still no response: 20 000 U 3 times/week or 30 000 U 2 times/week. EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte colony-stimulating factor; RBC: red blood cell; SC: subcutaneous.

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

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[j] Hematology Department, Centre Hospitalier Universitaire, Laval University, Quebec, QC, Canada
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[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

The original Iron Road

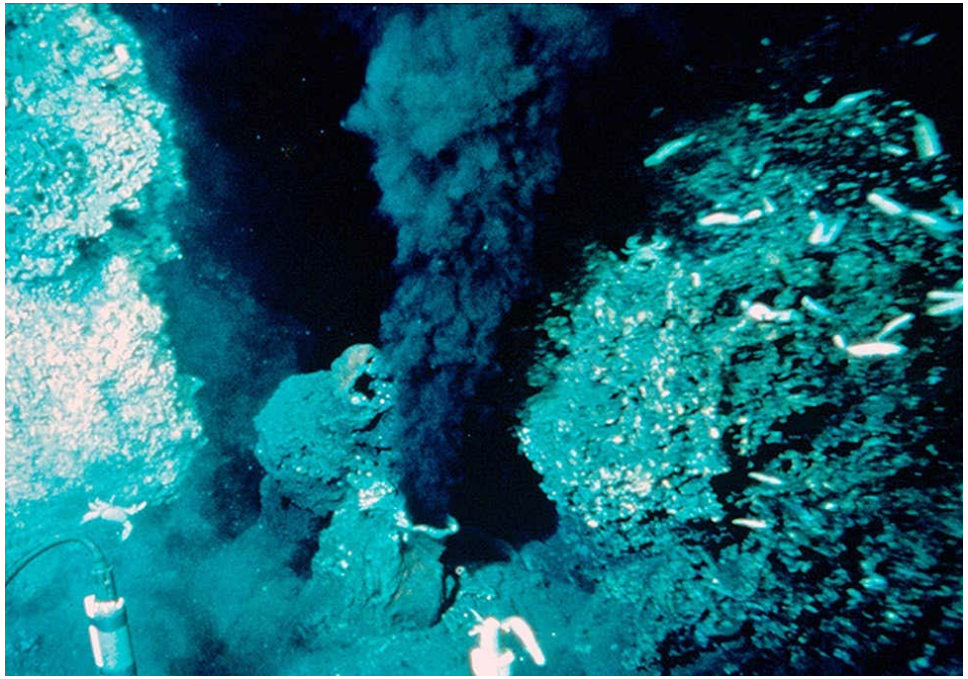
- The Last Spike of the Canadian Pacific Railway was driven at Craigellachie, British Columbia, at 9:22AM on November 7, 1885.
- It was driven by CPR financier Donald Smith (Lord Strathcona), marking the completion of a transcontinental railroad.
- The railway's completion fulfilled an 1871 commitment made by the Canadian federal government to BC, which stipulated that a railroad be built joining the Pacific province to Central Canada.
- The transcontinental railway was a major factor in BC's decision to join the Canadian Confederation.


The Last Spike at Craigellachie BC

From: Wikipedia
https://en.wikipedia.org/wiki/Last_Spike_(Canadian_Pacific_Railway)

General Comments on Iron Overload

- "Iron is the new cholesterol"[1]
  - Iron is central to many processes & disorders.
  - "Such is the Faustian bargain that has been struck by life on this planet. Oxygen & iron are essential for energy production, but may also conspire to destroy the delicate order of our cells. 'Life was designed to exist at the very interface between iron sufficiency and deficiency.'"
- Iron is an ancient signaling molecule[2]
  - Iron was involved in signaling billions of years before the existence of ATP
  - "Environmental conditions in porous hydrothermal vents — where heated, mineral-laden seawater spews from cracks in the ocean crust — created a gradient in positively charged protons that served as a 'battery' to fuel the creation of organic molecules & proto-cells."



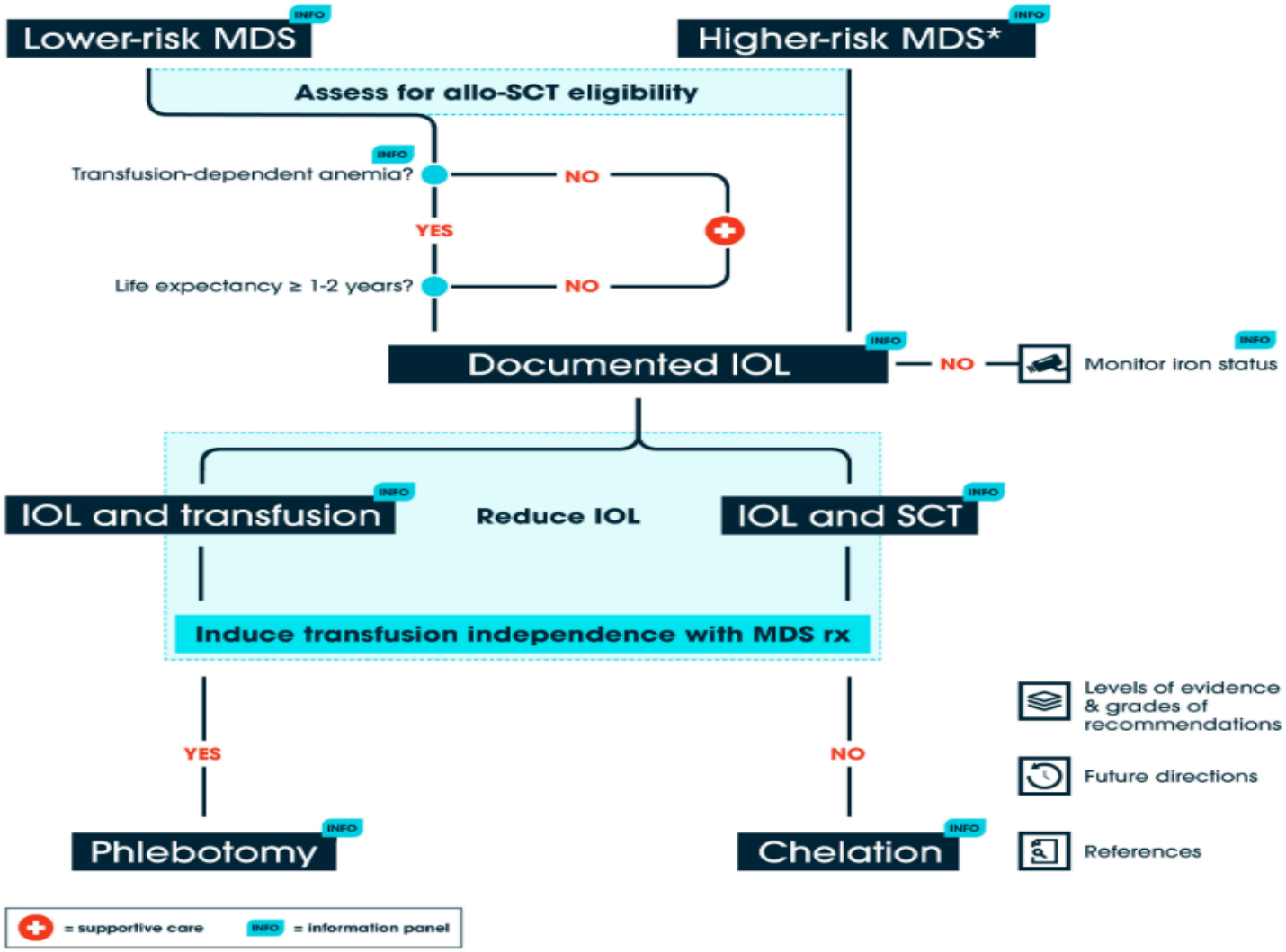
"Life on earth probably originated in deep sea vents"

https://www.google.com/search?q=image+of+hydrothermal+vents&rlz=1C1GCEA_enCA884CA884&sxsrf=ALeKk02zcF5KxPIQdIRBAeGGpxkqWq6riw:1584219300213&tbm=isch&source=iu&ictx=1&fir=E-8kF5DdT63piM%253A%252C47OIKi0pQGQH1M%252C_&vet=1&usg=AI4_-kTdoR7jrkyj0uRI2G3chR_g728qWw&sa=X&ved=2ahUKEwi5q4rI7JroAhW-GzQIHUtCDVkQ9QEwAXoECAsQHA#imgrc=Pn8kpMd3YvS-WM&imgdii=zamZx1K0N4kwUM

[1]Dalton C. 2018 **http://getpocket.com/explore/item/iron-is-the-new-cholesterol**. [2]Ghose T. 2013 **https://www.livescience.com/26173-hydrothermal-vent-life-origins.html**.

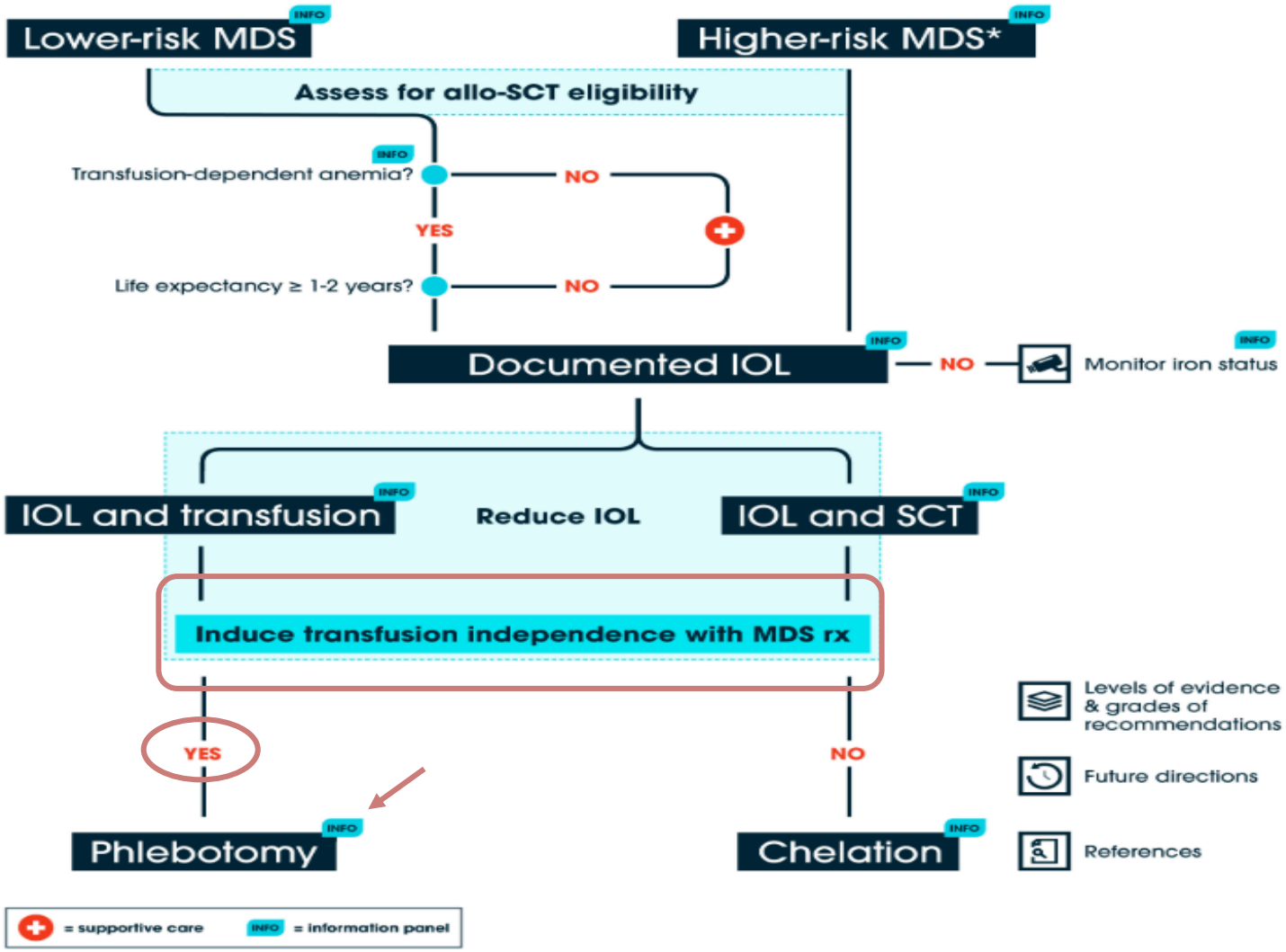
Canadian guidelines for the management of iron overload in MDS

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

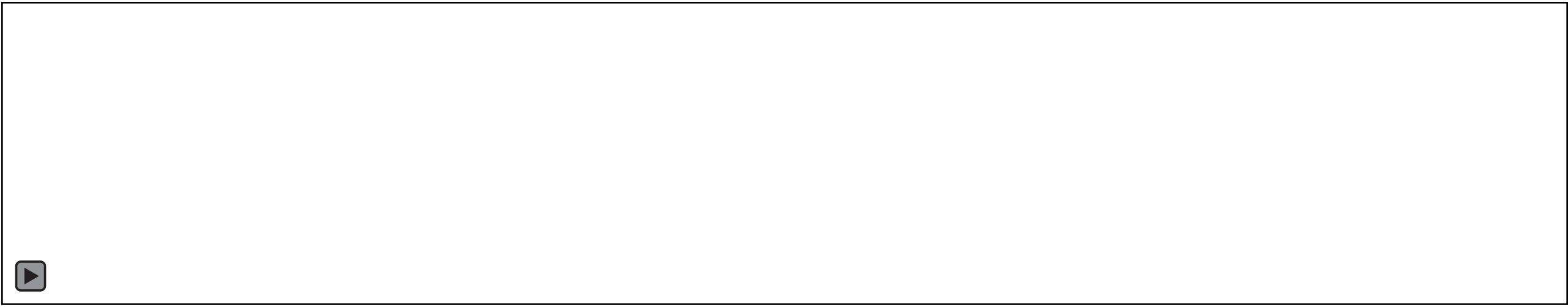


1. Leitch HA, et al. EHA 2020, abstract code EHA 1089

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

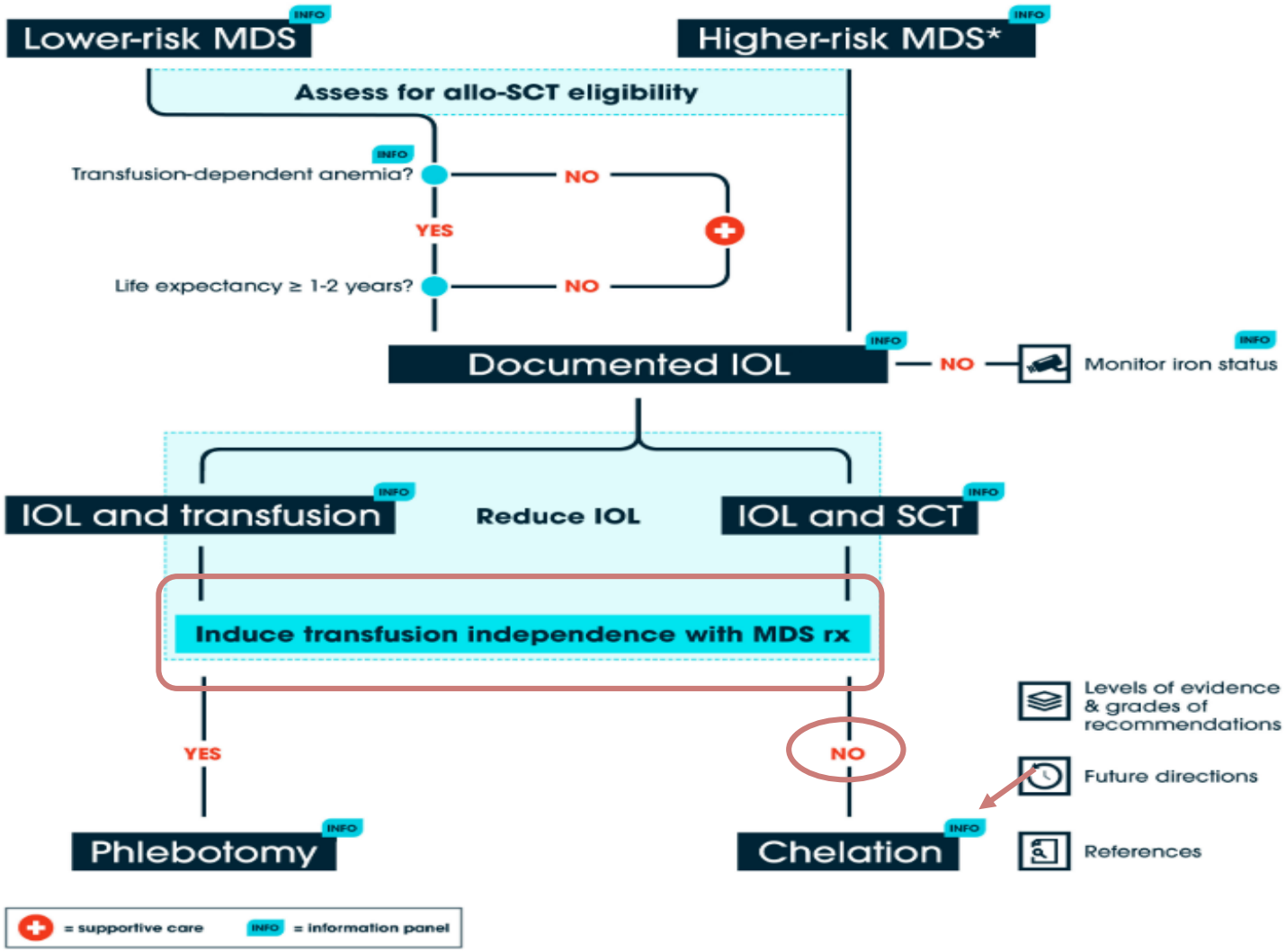
Case

- 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

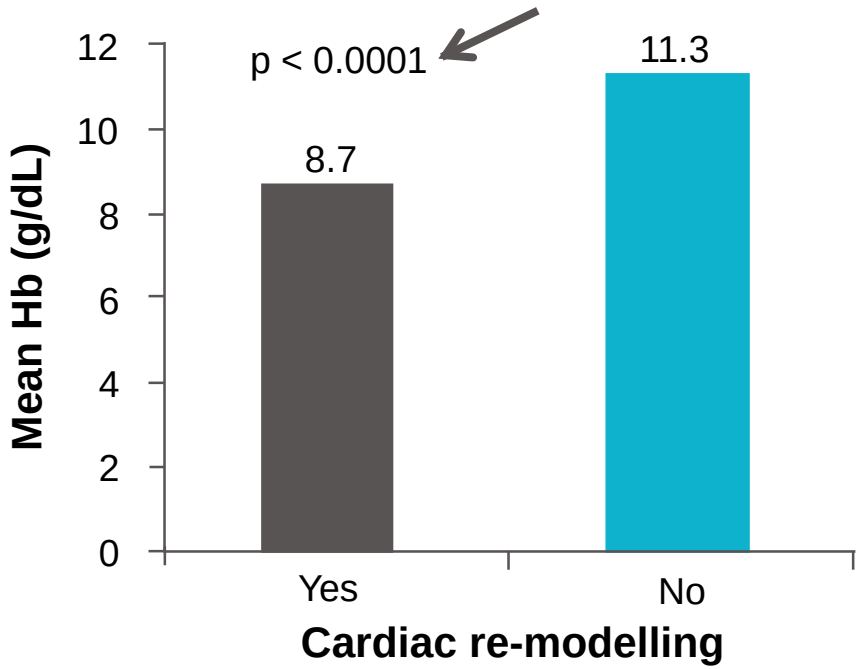
*These compounds do not have a marketing authorization for this indication in the European Union

I've substituted some more harmonious colours

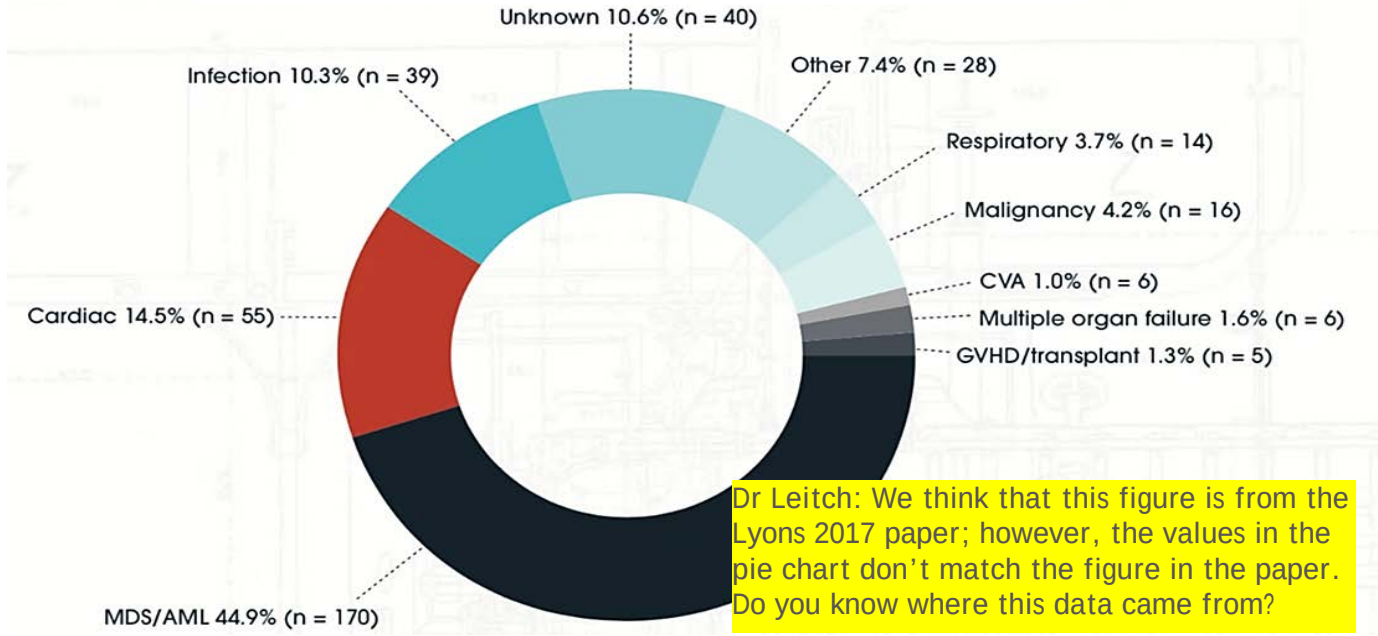
Cardiac events in MDS patients

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]



Dr Leitch: We think that this figure is from the Lyons 2017 paper; however, the values in the pie chart don't match the figure in the paper. Do you know where this data came from?

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.

I think the Lyons is the update of the Marek but Marek is what the agency that put together the IronRoad used to make this figure, so I've substituted that reference here

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]

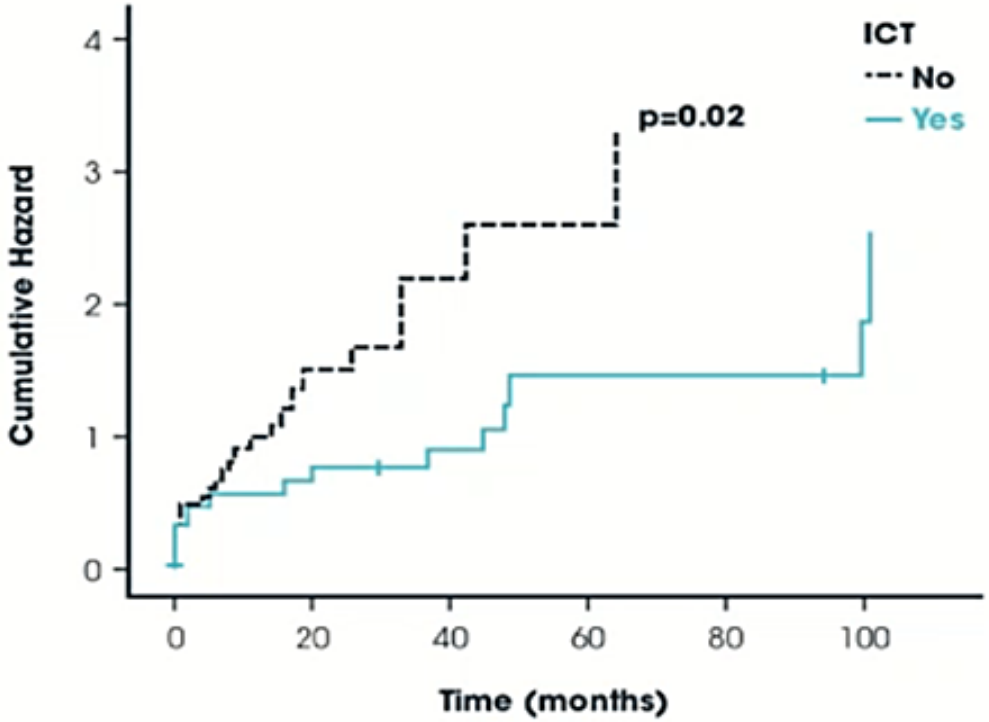


Figure Delayed time from RBC transfusion dependence to first cardiac event in lower IPSS risk MDS patients receiving iron chelation therapy[1]

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]

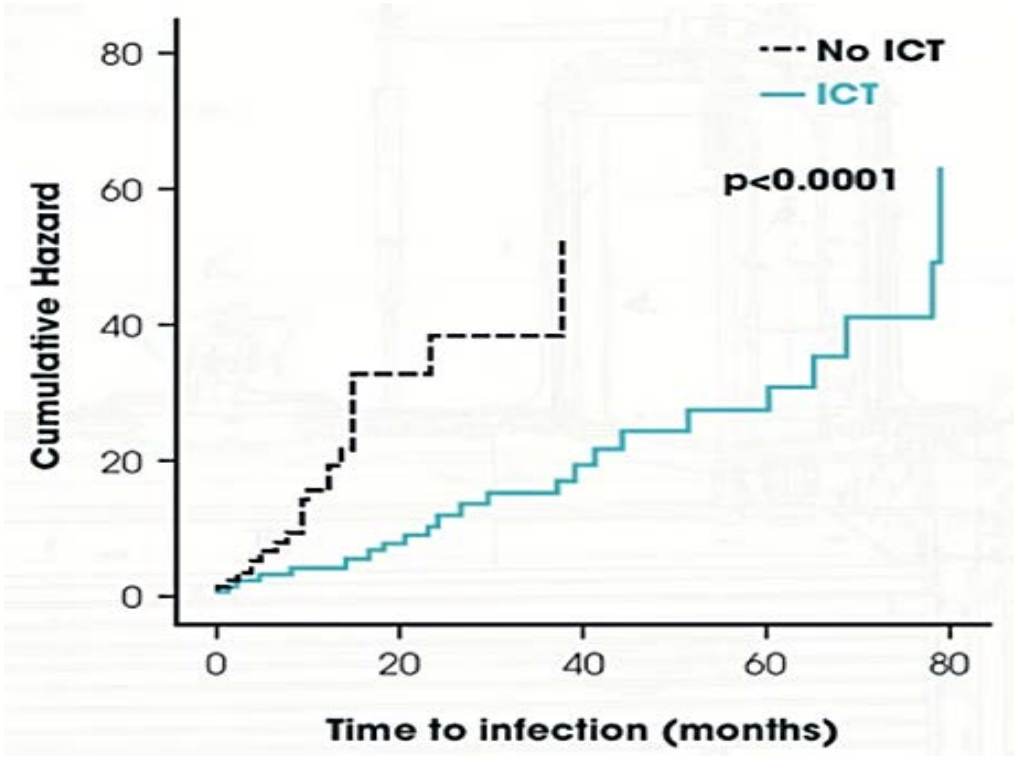
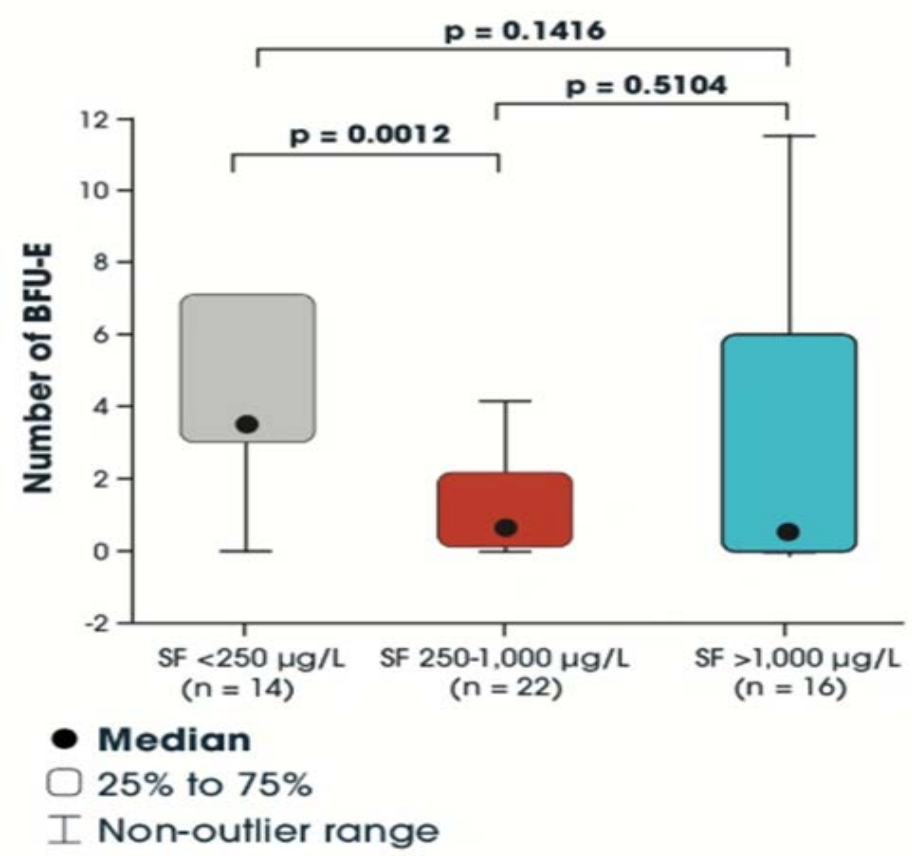


Figure Time from first RBC transfusion to first infection in patients with lower IPSS risk MDS not receiving or receiving iron chelation therapy[9]

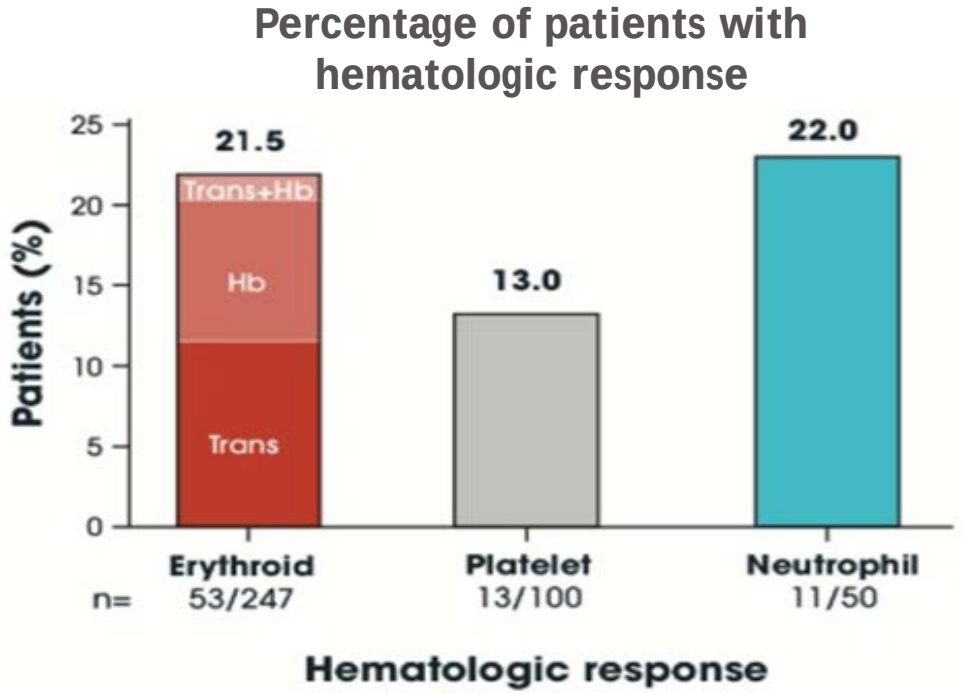
ICT, iron chelation therapy; IOL, iron overload; LIC, liver iron concentration; SCT, stem cell transplantation; SF, serum ferritin; TD, transfusion dependent; TI, transfusion independent; TTI, time to infection.

[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.

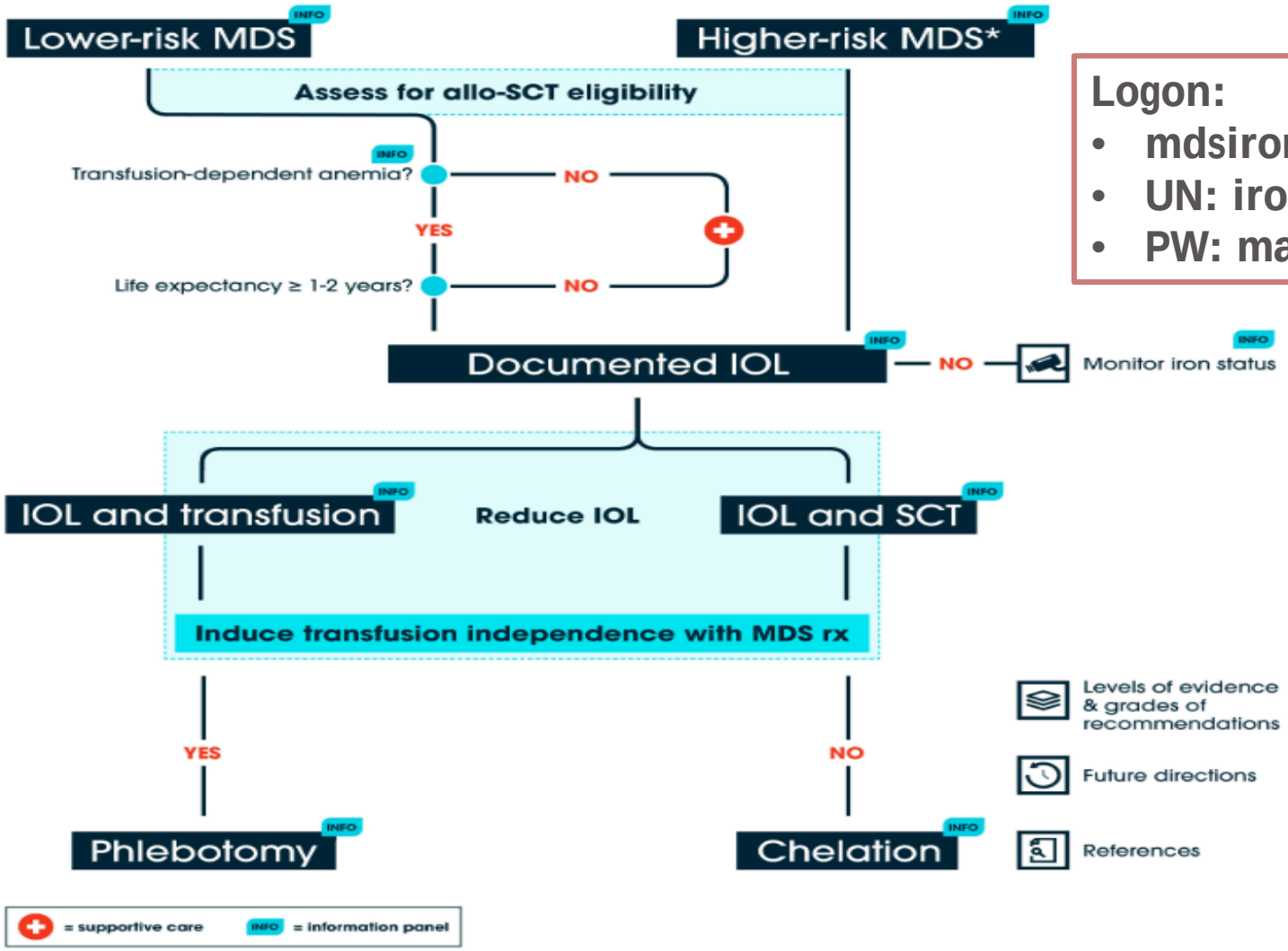
Summary/Conclusions:

- 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

Thank you

Questions? hleitch@providencehematology.com