Multidisciplinary Approaches to Cancer Symposium

Myelodysplastic Syndrome: How to Treat & When to Send?

Azra Borogovac, MD, MS

Assistant Clinical Professor

City of Hope, Orange County

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Significant increase in donor availability for all racial/ethnic groups, with improvements in doing haplo transplants.*
- *Bias/barriers for transplant referrals based on age/race.*

Progression of clonal cytopenias

*Exclude other causes of dysplasia based on history and/or lab testing: deficiencies in B12, folate, or copper; excess alcohol, toxic exposures, medications, HIV infection, sideroblastic anemia, genetic disorders.

2022 Classification: WHO and ICC

- WHO: Myelodysplastic syndromes renamed to **Myelodysplastic Neoplasms** (MDS)
- Both: Added **genetically defined** and **morphologically defined** classifications

Defining genetic abnormalities	WHO 2022[1]	ICC 2022[2]
5q deletion	MDS with low blasts and isolated del(5q) *can have 1 other abnormality other than -7 or del(7q)	MDS with del(5q). *can have 1 other abnormality other than -7 or del(7q) or multi-hit TP53
SF3B1 mutation	MDS with low blasts and SF3B1 mutation OR ≥15% Ringed sideroblasts *No del(5q), -7, or complex karyotype	MDS with mutated SF3B1 (≥10%VAF) No del(5q), -7/del(7q), or complex No multi-hit TP53 or RUNX1
TP53 mutation	MDS with biallelic TP53 inactivation <20% blasts Not AML defining	Multi-hit TP53 or TP53 (≥10%VAF) and complex karyotype (blasts <10%) AML defining if blasts ≥10%

1. Khoury, et al. Leukemia 2022; 2. Arber, et al. Blood 2022.

Cell morphology	WHO 2016[1]	WHO 2022[2]	ICC 2022[3]
Ringed sideroblasts (RS)	MDS-RS-single lineage dysplasia (SLD) MDS-RS-multilineage dysplasia (MLD)	MDS-RS, low blast, SF3B1 wildtype	No RS category
Number of dysplastic lineages	MDS-SLD, MDS-MLD	Dysplastic lineages removed MDS with low blasts <5% BM and <2% PB	MDS, NOS-SLD MDS, NOS-MLD
Blasts 5-9%	MDS with excess blasts-1 (MDS-EB-1): 5-9% BM	MDS with increased blasts -1 (MDS-IB1) 5-9% BM, 2-4% PB	MDS-EB: 5-9% BM, 2-9%PB or Auer rods
Blasts 10-19%	MDS-EB-2: 10-19%BM or PB blasts or Auer rods	MDS-IB2: 10-19% BM or 5-19% PB or Auer rods *Can be treated as AML	MDS/AML (10-19% BM or PB blasts) except AML defining mutations (NPM1, bzip CEPBA, and TP53)
New	Not included	MDS, hypoplastic (MDS-h) Hypocellular marrow	Not included
New	Not included	MDS with fibrosis (MDS-f) BM blasts 5-19%, PB blasts 2-19%, fibrosis grade≥2	Not included
Removed	MDS, unclassifiable	Not included	Not included

1. Arber, et al. Blood. 2016; 2. Khoury, et al. Leukemia 2022; 3. Arber, et al. Blood 2022.

- Survival based on WHO 2022 subgroups

Subgroups	No. (%)	mLFS	mOS
Overall	2228 (100%)	30.9 mo	40.9 mo
MDS-*SF3B1*	294 (13%)	100.6 mo	101.8 mo
MDS-5q	107 (5%)	65 mo	75.6 mo
MDS-LB	704 (31%)	46.2 mo	56.1 mo
MDS-RS	78 (4%)	50.5 mo	54.3 mo
MDS-h	94 (4%)	42.3 mo	49.6 mo
AML*	51 (2%)	NA	30.8 mo
MDS-IB1	281 (13%)	20.5 mo	28.1 mo
MDS-IB2	291 (13%)	11 mo	23.7 mo
MDS-f	114 (5%)	13.8 mo	18.9 mo
MDS-bi*TP53*	214 (10%)	10.0 mo	13.2 mo

* Cases with AML-defining genetic abnormalities per WHO 2022
[mLFS- Median Leukemia free survival, mOS- Median Overall survival]

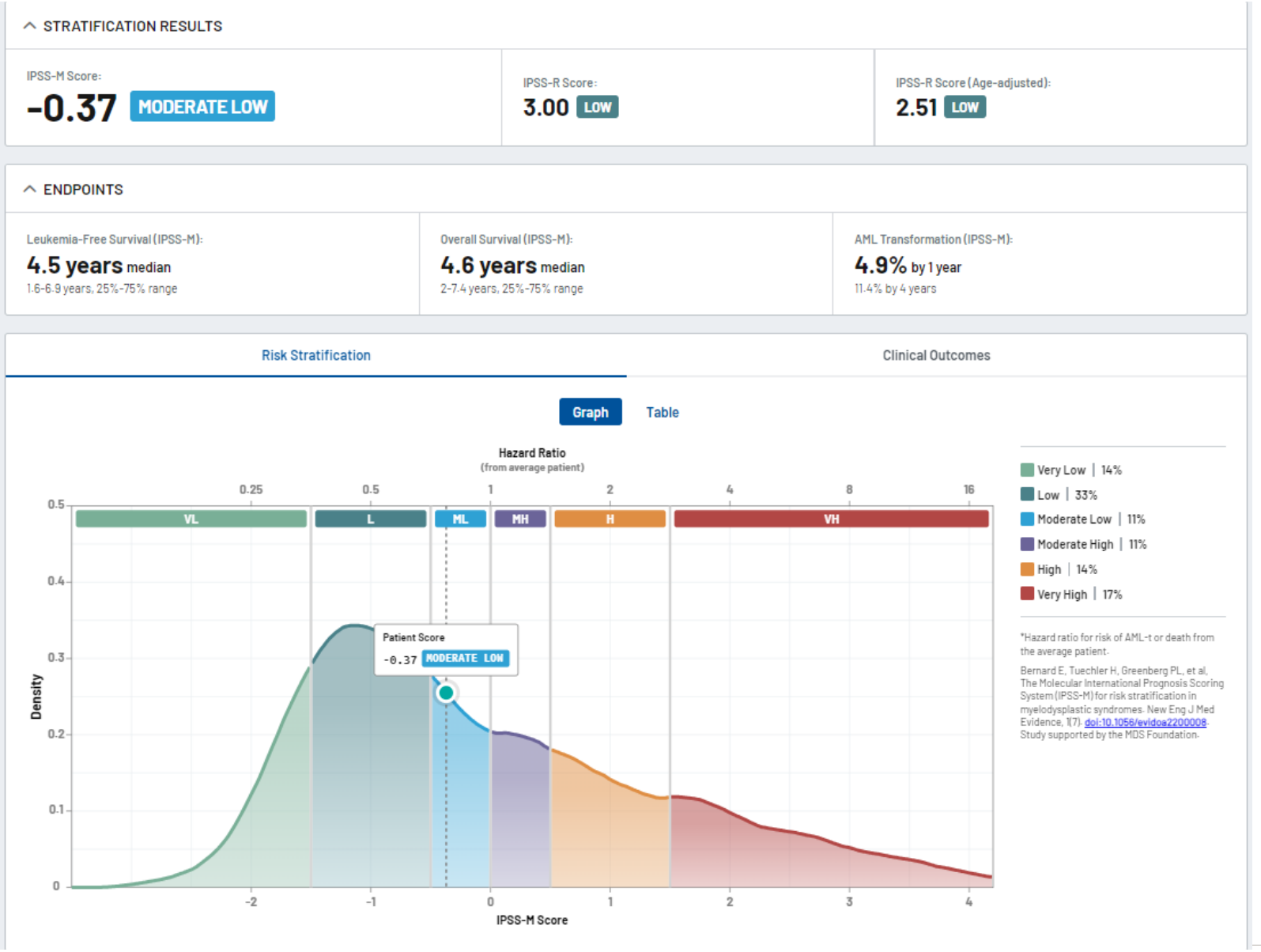
- Survival based on ICC 2022 subgroups

Subgroups	No. (%)	mLFS	mOS
Overall	2227 (100%)	30.9 mo	40.9 mo
MDS-*SF3B1*	277 (12%)	109.4 mo	111.6 mo
MDS, NOS-SLD	247 (11%)	74.2 mo	79.4 mo
MDS-del5q	108 (5%)	65 mo	75.6 mo
MDS, NOS	31 (1%)	55.8 mo	55.8 mo
MDS, NOS-MLD	610 (28%)	41.4 mo	49.5 mo
MDS/AML, NOS	80 (4%)	14.1 mo	42.7 mo
MDS-EB	324 (15%)	21.0 mo	28.6 mo
AML*	27 (1%)	NA	26.3 mo
MDS/AML-m	161 (7%)	11.5 mo	24.7 mo
MDS/AML-c	54 (2%)	11.3 mo	16.3 mo
MDS-*TP53*	194 (9%)	11.5 mo	14.2 mo
MDS/AML-*TP53*	115 (5%)	6.4 mo	11.1 mo

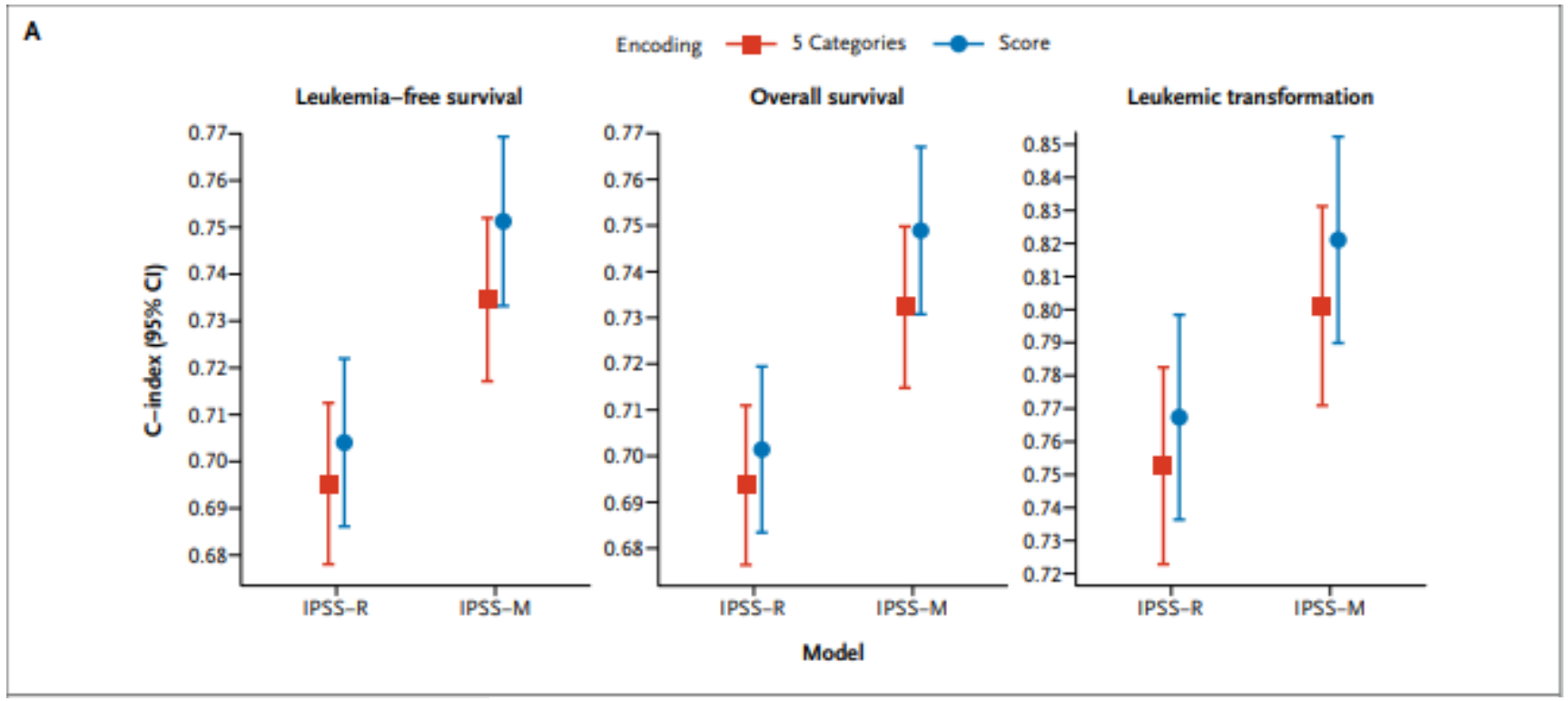
* Cases with AML-defining genetic abnormalities per ICC 2022
[mLFS- Median Leukemia free survival, mOS- Median Overall survival]

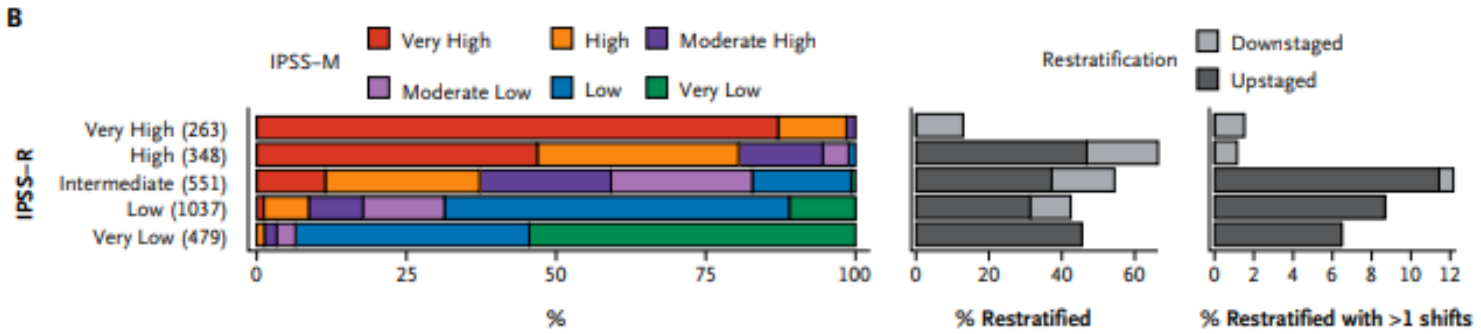
Ball, et al. ASH 2022.

- Online IPSS-M calculator available: https://mds-risk-model.com/
- Can be used with secondary/treatment-related MDS
- Caveat: Developed using only untreated patients



IPSS-M vs IPSS-R





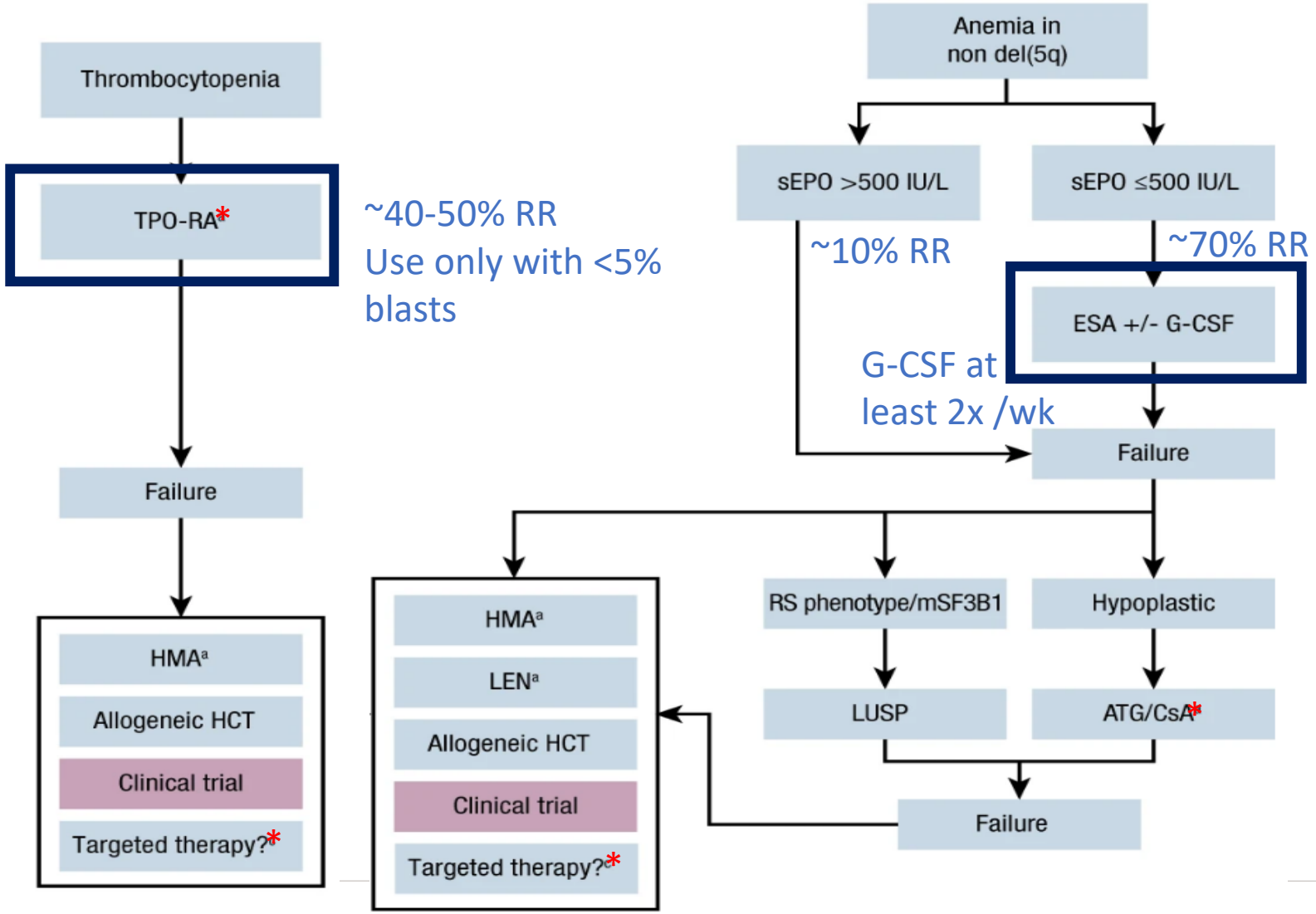
- 46% of patients has reclassification of risk
  - 74% were upstaged
  - 26% were downstaged

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

Treatment approach: Low-risk MDS

The goal of therapy is to improve quality of life:

- **Reduced symptoms**
- **Transfusion independence**



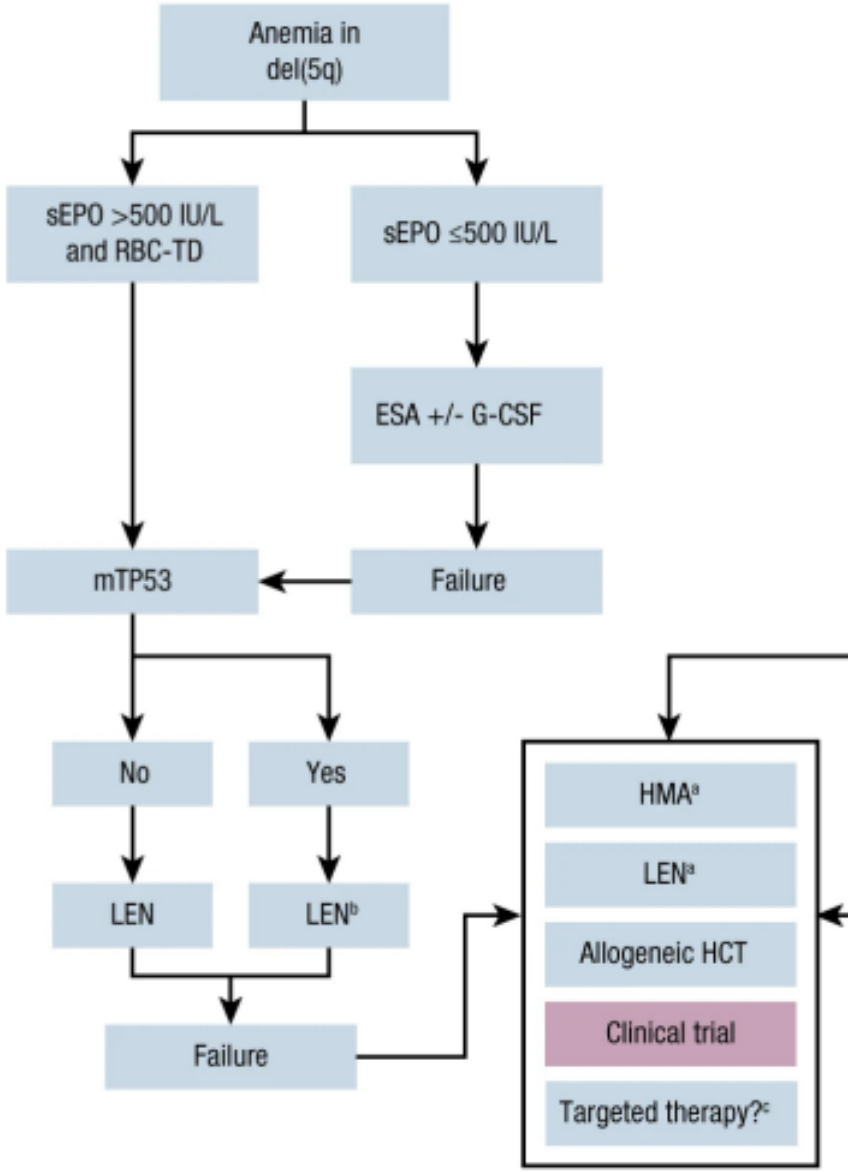
*Not FDA approved

Flowchart adapted from Platzbecker, et al. Leukemia (2021): 35, 2182-2198.

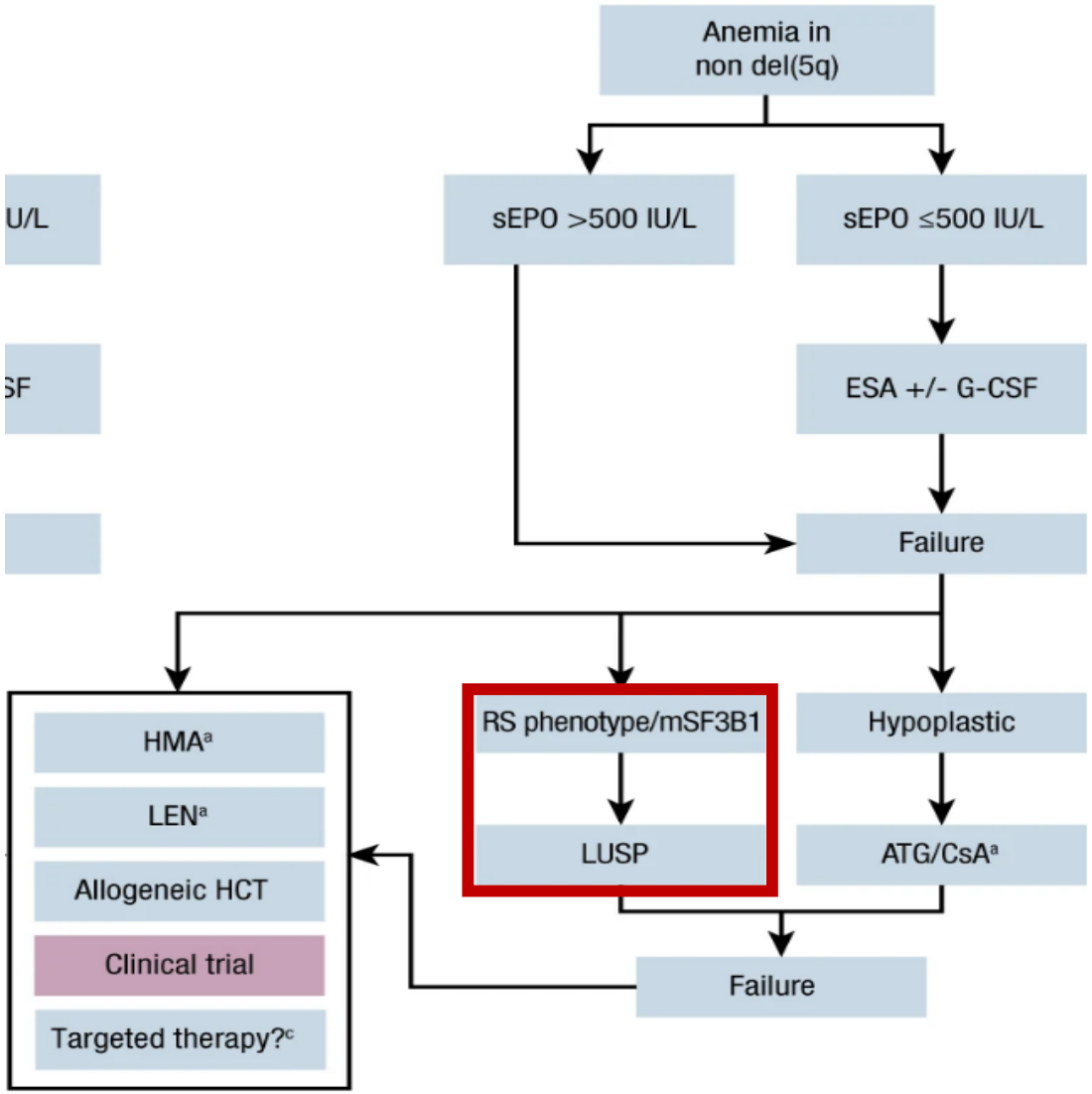
Lenalidomide

- **Approved** for transfusion-dependent anemia in low to int-1 risk MDS patients with del(5q) with or without additional cytogenetic abnormalities (except chr. 7 abnormalities).
    - Decreases transfusion needs in 2/3 of patients

- **Off label:** Sometimes used in patients without del(5q) if failed ESA.
    - Decreases transfusion needs in ¼ of patients.



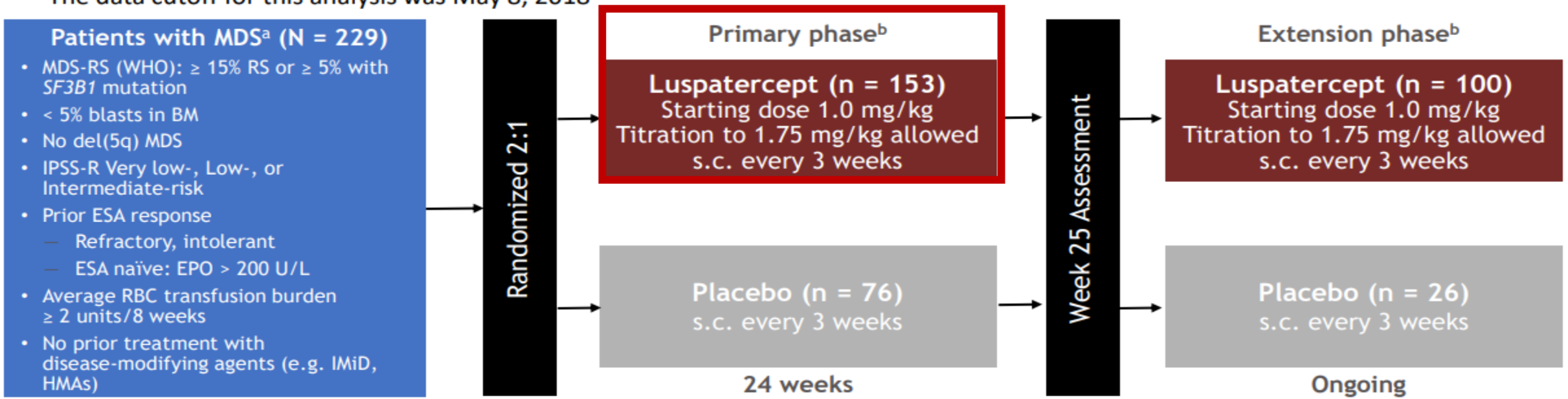
Flowchart adapted from Platzbecker, et al. Leukemia (2021): 35, 2182-2198.



Flowchart adapted from Platzbecker, et al. Leukemia (2021): 35, 2182-2198.

MEDALIST Trial

- The objective of this phase 3, randomized, double-blind, placebo-controlled trial was to evaluate the efficacy and safety of luspatercept in patients with IPSS-R-defined LR-MDS who have RS and require RBC transfusions and who were refractory to, intolerant of, or unlikely to respond to ESAs
- The data cutoff for this analysis was May 8, 2018



- [a]During the 16 weeks prior to randomization. [b]Disease & Response Assessment Week 24 & every 6 months: Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed. Subjects followed ≥ 3 years after the final dose for AML progression, subsequent MDS treatment, and overall survival.
- **AML, acute myeloid leukemia; BM, bone marrow; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IPSS-R, International Prognostic Scoring System-Revised; IWG, International Working Group; LR, lower risk;** MDS, myelodysplastic syndromes; RBC, red blood cell; **RS, ring sideroblasts;** s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

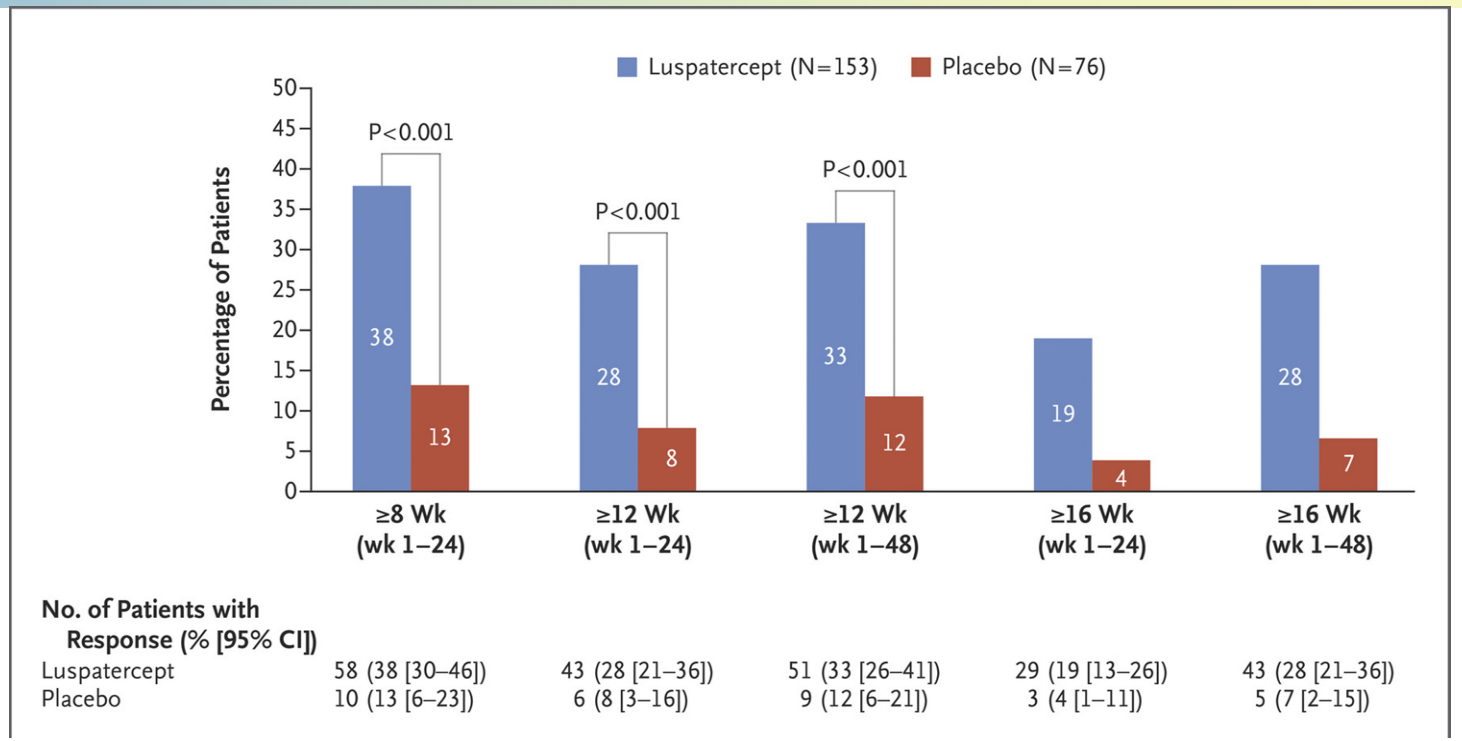
Fenaux et al. NEJM 2020

Slide from Dr. Uwe Platzbecker's presentation at SOHO 2023

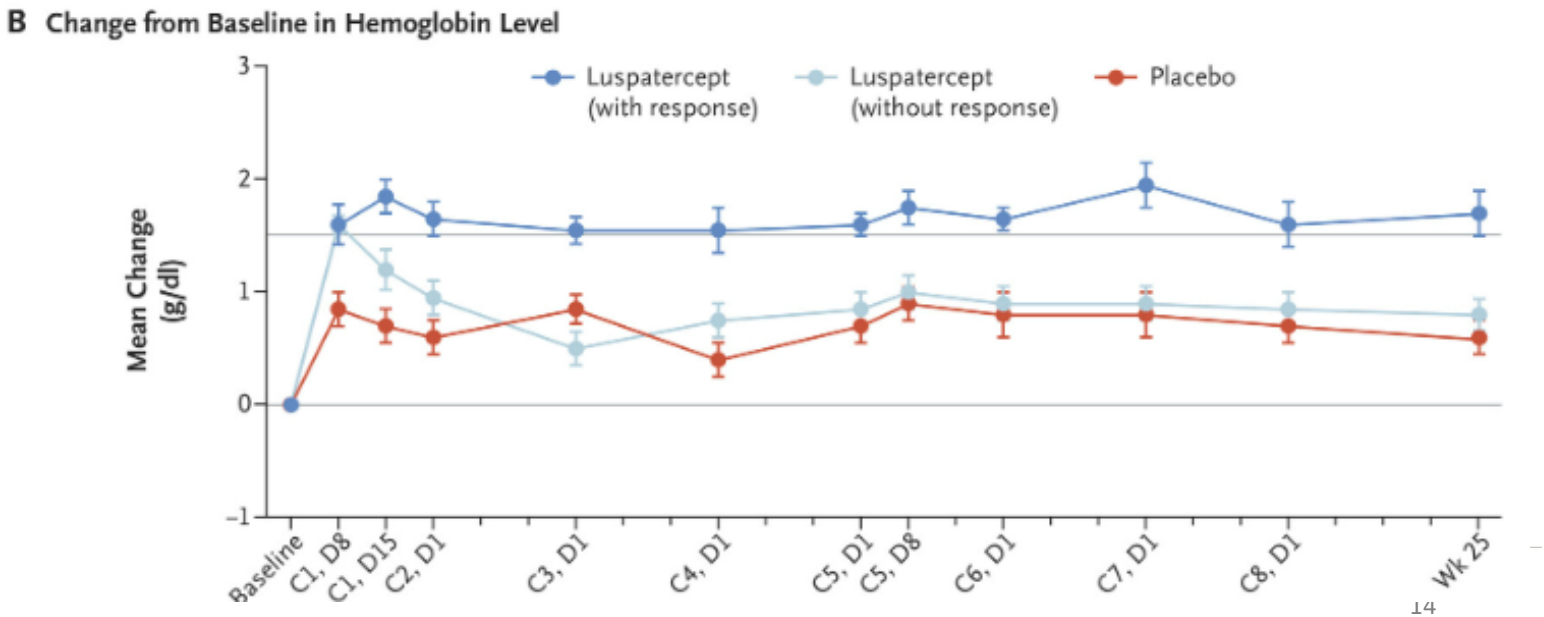
Results

- 38% vs 13% transfusion independence at 8 weeks.
- Responders improved ~2gm/dl hgb.

Approved for transfusion-dependent LR-MDS with RS ≥15% or ≥5% with SF3B1 mutation in those not responding to ESAs.



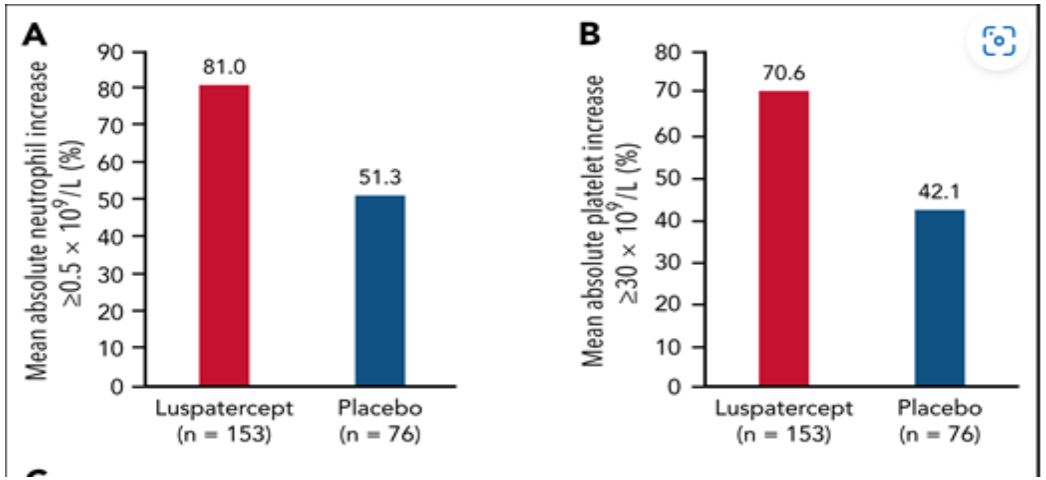
No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

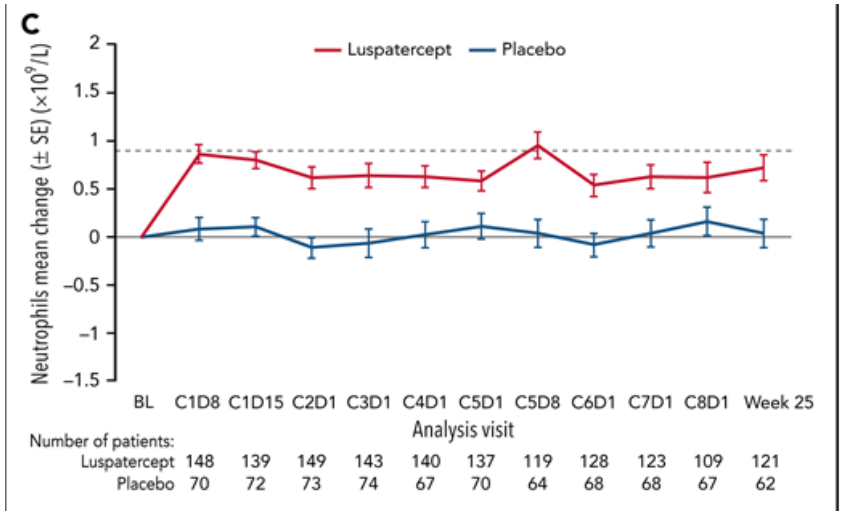


Fenaux, P, et al. NEJM 2020; 382:140-151.

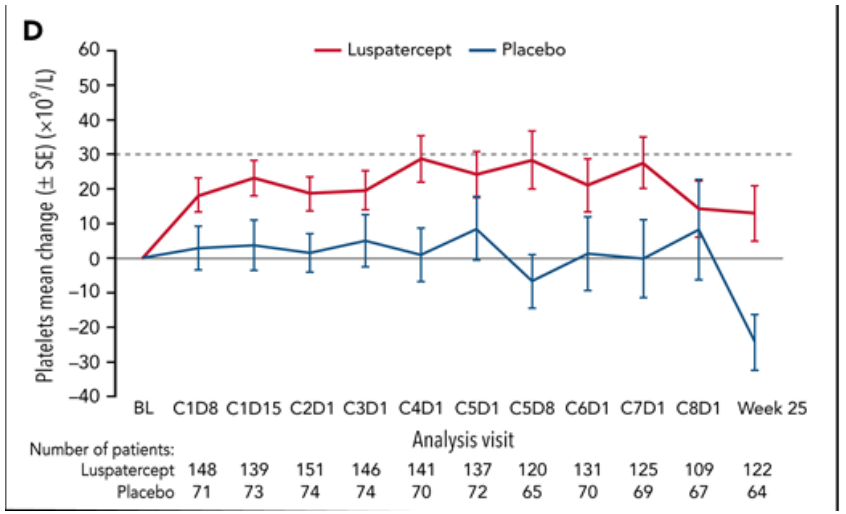
Neutrophils and platelets?

- 81% vs 51% increase in neutrophils of ≥0.5 × 10^9/L for 56 consecutive days.
- 70.6% vs 42.1% increase in platelets of ≥30 × 10^9/L maintained through week 25.





- Mean change: 0.95 × 10^9/L vs 0.04 × 10^9/L



- Mean change: 28.7 × 10^9/L vs 0.9 × 10^9/L

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

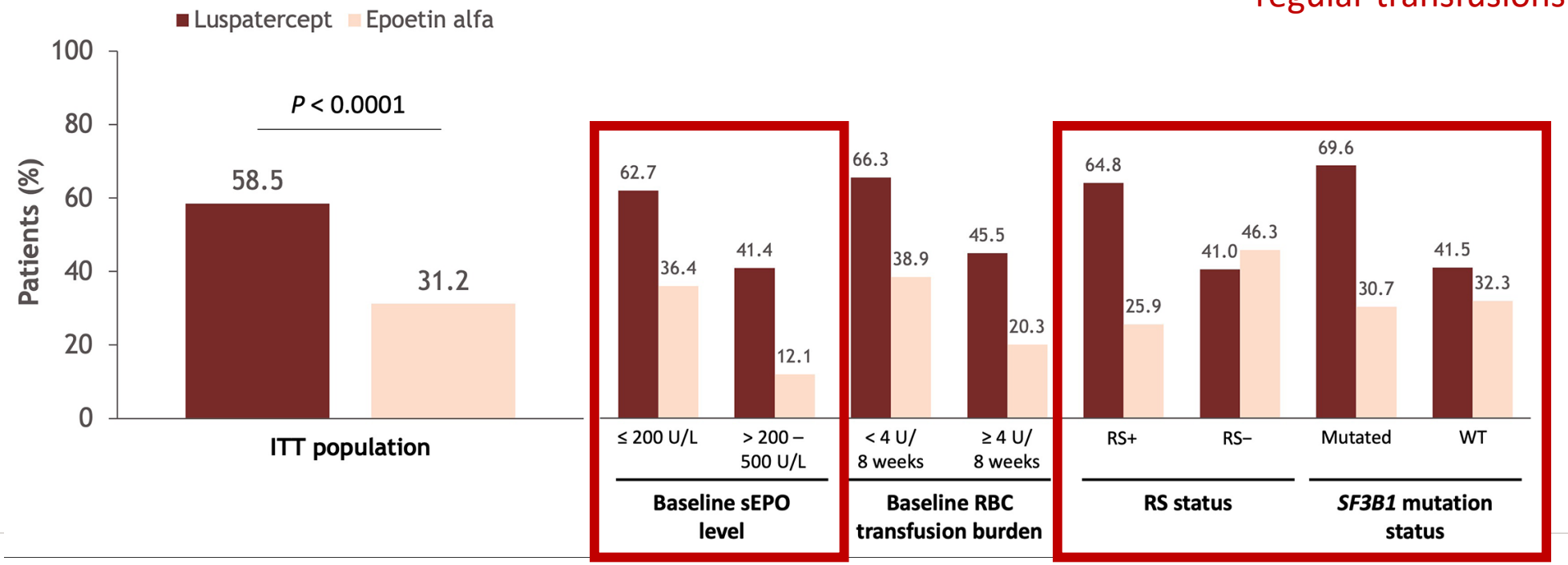
Most common* TEAEs (any grade)	Luspatercept			Placebo		
	Overall (N = 153)	LTB (n = 87)	HTB (n = 66)	Overall (N = 76)	LTB (n = 43)	HTB (n = 33)
Fatigue	46 (30.1)	29 (33.3)	17 (25.8)	11 (14.5)	8 (18.6)	3 (9.1)
Diarrhea	43 (28.1)	33 (37.9)	10 (15.2)	8 (10.5)	3 (7.0)	5 (15.2)
Asthenia	39 (25.5)	23 (26.4)	16 (24.2)	9 (11.8)	2 (4.7)	7 (21.2)
Edema peripheral	37 (24.2)	20 (23.0)	17 (25.8)	13 (17.1)	6 (14.0)	7 (21.2)
Cough	34 (22.2)	20 (23.0)	14 (21.2)	10 (13.2)	5 (11.6)	5 (15.2)
Dizziness	34 (22.2)	23 (26.4)	11 (16.7)	4 (5.3)	1 (2.3)	3 (9.1)
Nausea	34 (22.2)	22 (25.3)	12 (18.2)	6 (7.9)	3 (7.0)	3 (9.1)
Back pain	33 (21.6)	17 (19.5)	16 (24.2)	5 (6.6)	4 (9.3)	1 (3.0)
Dyspnea	29 (19.0)	19 (21.8)	10 (15.2)	5 (6.6)	2 (4.7)	3 (9.1)
Headache	27 (17.6)	17 (19.5)	10 (15.2)	5 (6.6)	2 (4.7)	3 (9.1)
Constipation	21 (13.7)	11 (12.6)	10 (15.2)	7 (9.2)	3 (7.0)	4 (12.1)
Urinary tract infection	21 (13.7)	14 (16.1)	7 (10.6)	4 (5.3)	0 (0.0)	4 (12.1)
Pyrexia	20 (13.1)	13 (14.9)	7 (10.6)	7 (9.2)	3 (7.0)	4 (12.1)
Bronchitis	19 (12.4)	13 (14.9)	6 (9.1)	1 (1.3)	1 (2.3)	0 (0.0)
Upper respiratory tract infection	19 (12.4)	15 (17.2)	4 (6.1)	4 (5.3)	4 (9.3)	0 (0.0)
Anemia	17 (11.1)	9 (10.3)	8 (12.1)	6 (7.9)	4 (9.3)	2 (6.1)
Viral upper respiratory tract infection	17 (11.1)	9 (10.3)	8 (12.1)	4 (5.3)	2 (4.7)	2 (6.1)
Hypertension	16 (10.5)	13 (14.9)	3 (4.5)	6 (7.9)	2 (4.7)	4 (12.1)
Decreased appetite	14 (9.2)	10 (11.5)	4 (6.1)	3 (3.9)	1 (2.3)	2 (6.1)
Vomiting	14 (9.2)	11 (12.6)	3 (4.5)	5 (6.6)	2 (4.7)	3 (9.1)
Epistaxis	13 (8.5)	12 (13.8)	1 (1.5)	3 (3.9)	2 (4.7)	1 (3.0)

Zeidan, et al. Blood (2022) 140 (20):2170-2174.

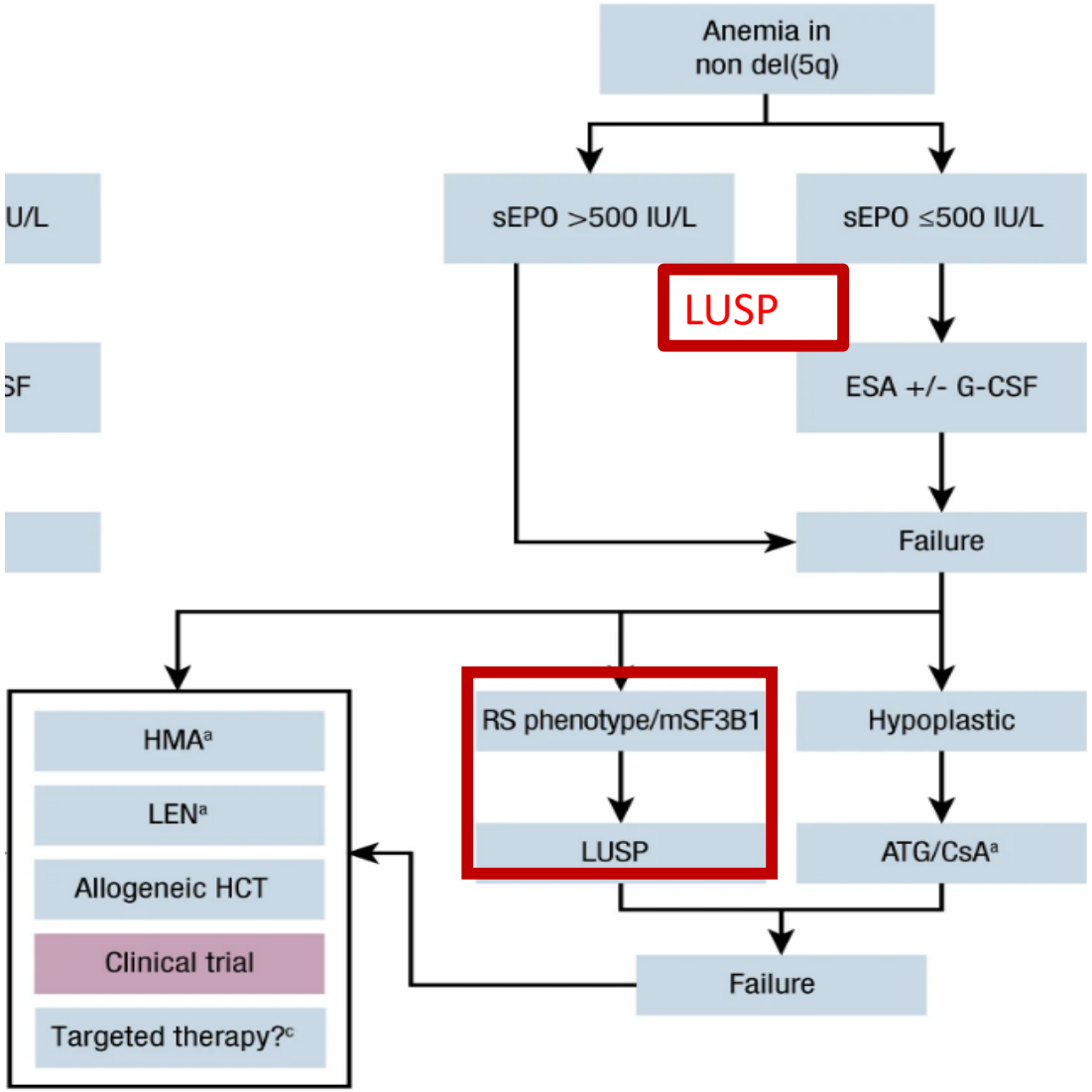
COMMANDS trial

- Phase 3 trial comparing efficacy/safety of Luspatercept vs epoietin in **ESA naïve** patients with LR-MDS.
- Transfusion independence: 58.5% vs 31.2%
- Time to first transfusion: 168 days vs 42 days
- Duration of response: 2.43 years vs 1.48 years

Approved as first-line treatment of anemia without prior ESA use in low-to intermediate-risk MDS and who may require regular transfusions.



Platzbecker, et al. Lancet 2023; 10399 (402):373-385

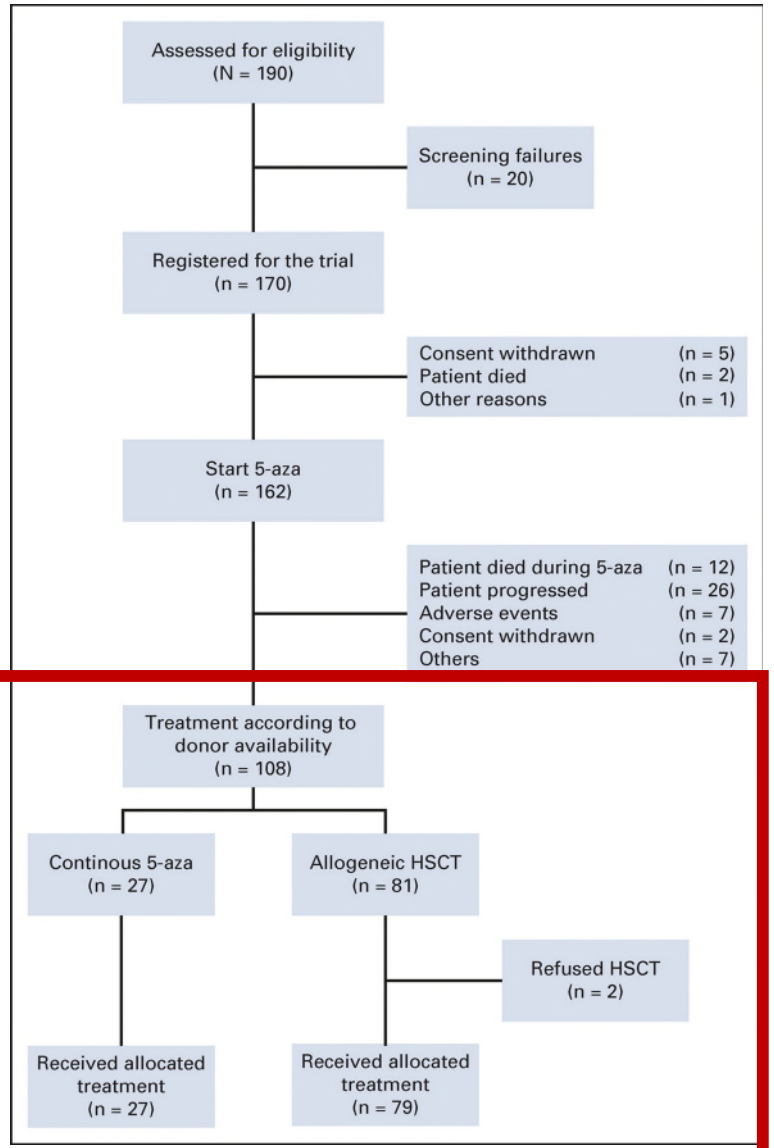


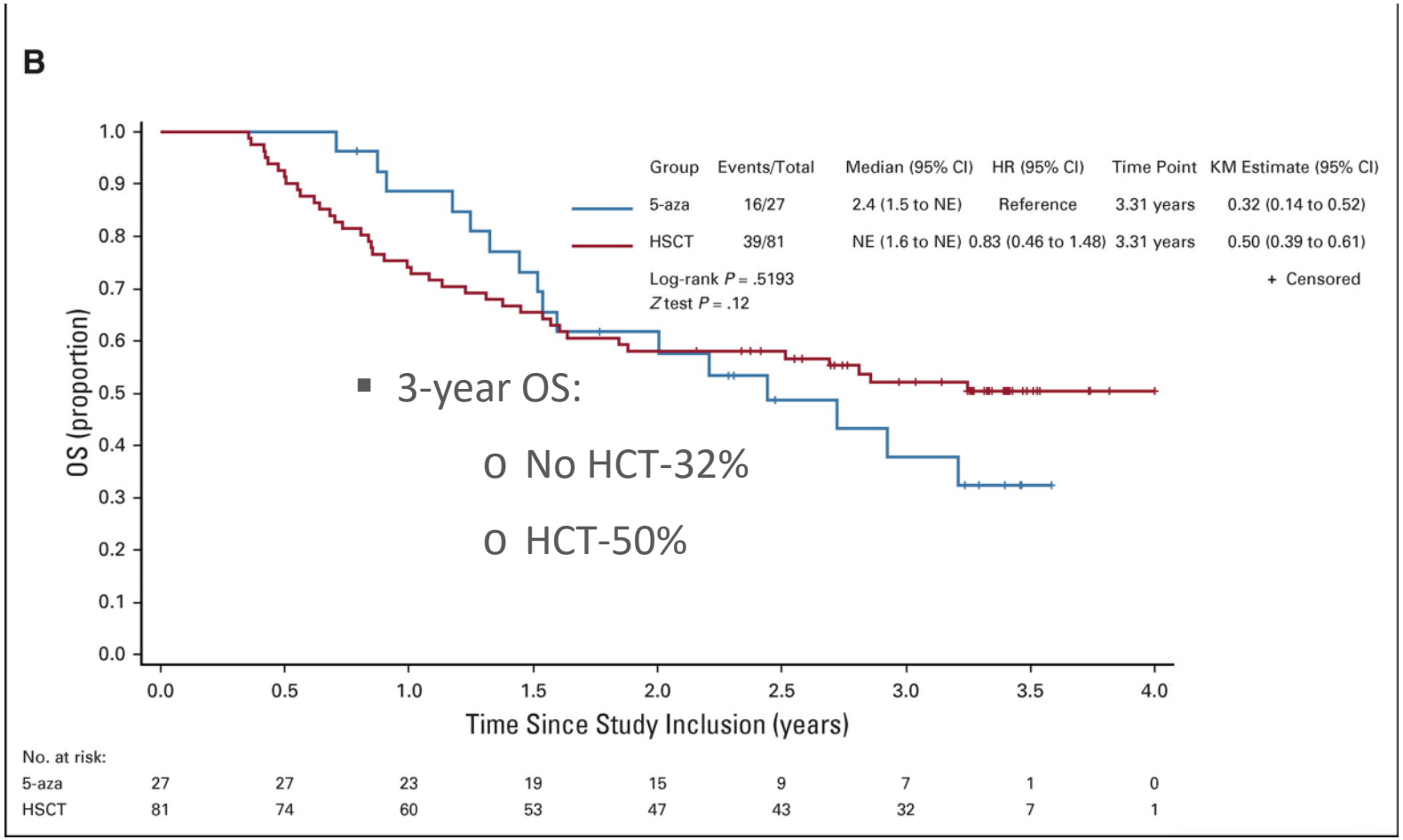
Flowchart adapted from Platzbecker, et al. Leukemia (2021): 35, 2182-2198.

High/Very high-risk MDS

- Goals: change the disease course, prolong life, and improve symptoms
  - Early transplant evaluation
  - Clinical trials
  - Hypomethylating agents (azacytidine IV/SQ or decitabine IV)
    - Oral decitabine-cedazuradine approved in 2020
    - Addition of venetoclax (off-label)
    - Oral azacytidine **not** approved or recommended in MDS
  - Targeted agents (off-label)
    - Ivosidenib (IDH1 mutation) or enasidenib (IDH2 mutation)
  - Supportive care

VidazaAllo Study, New MDS 55-70

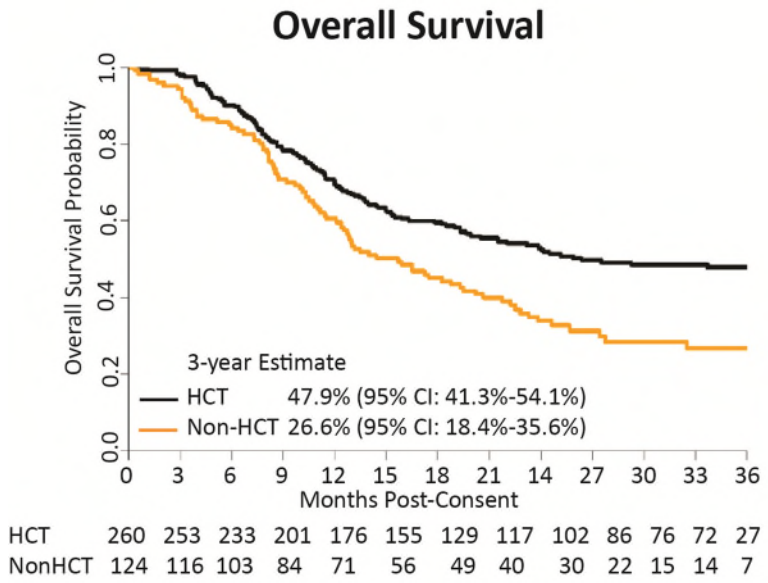


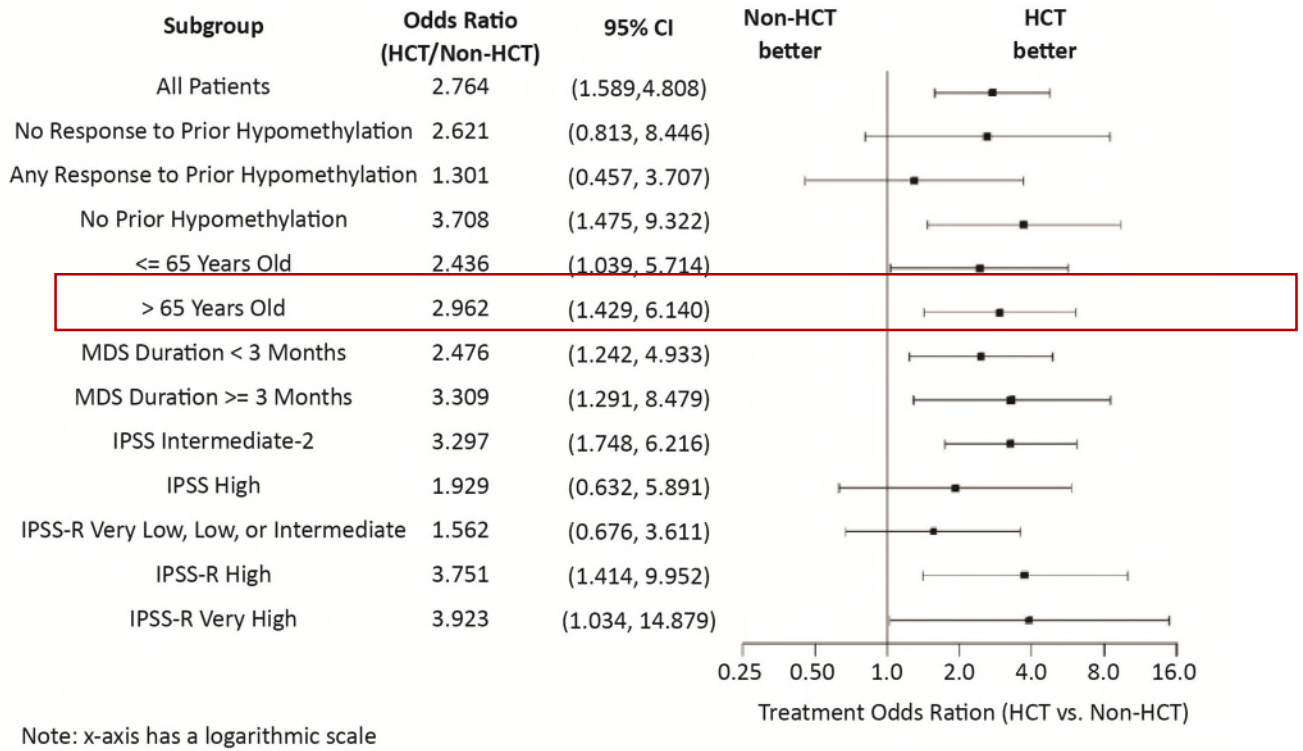


- 3-year OS:
  - No HCT-32%
  - HCT-50%

Kröger N, et al. *J Clin Oncol*. 2021;39(30):3318-3327.

Matched donor vs No donor, Ages 50-75



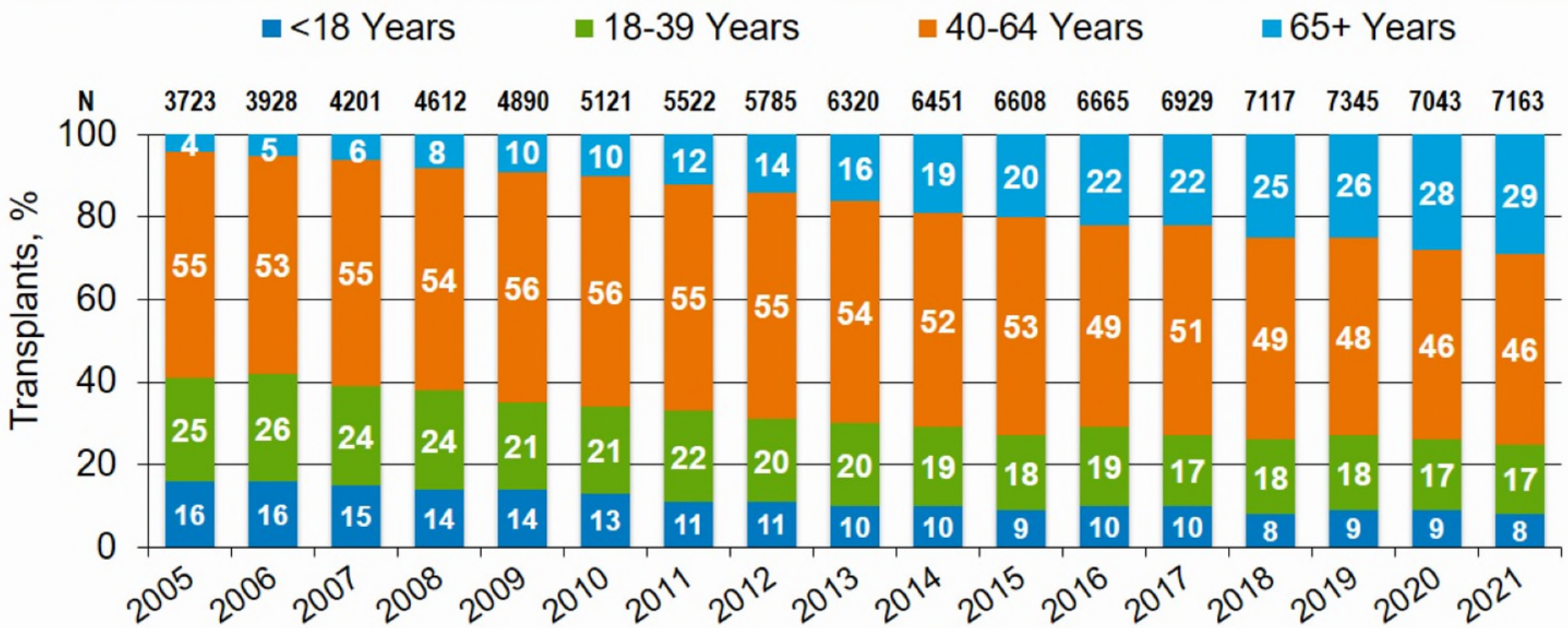


Note: x-axis has a logarithmic scale

- 3-year OS:
  - No HCT-27%
  - HCT-48%

Nakamura R, et al. *J Clin Oncol*. 2021;39(30):3328-3339.

Recipient Age of Allogeneic HCTs for Malignant Diseases in the U.S.



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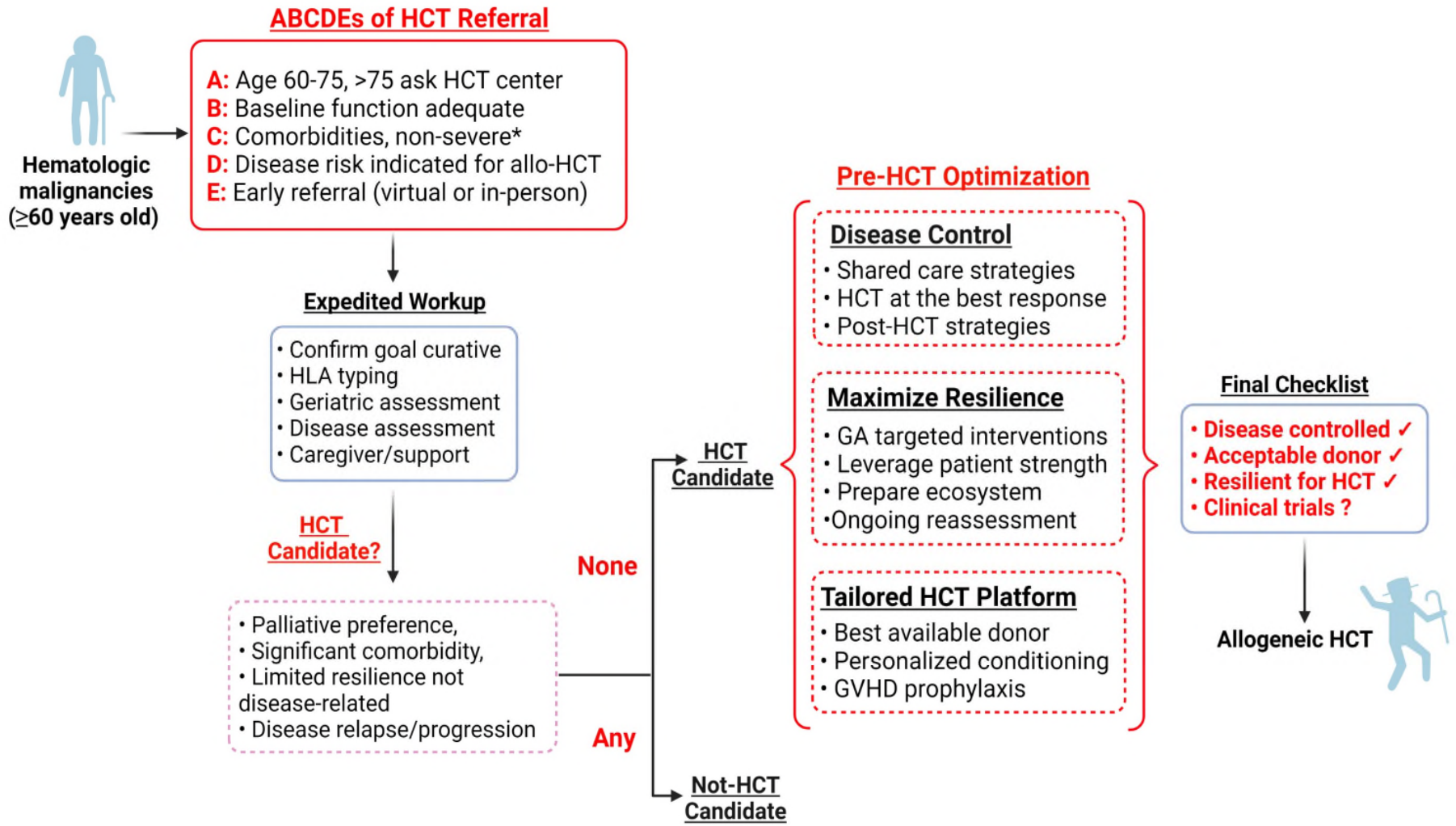
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

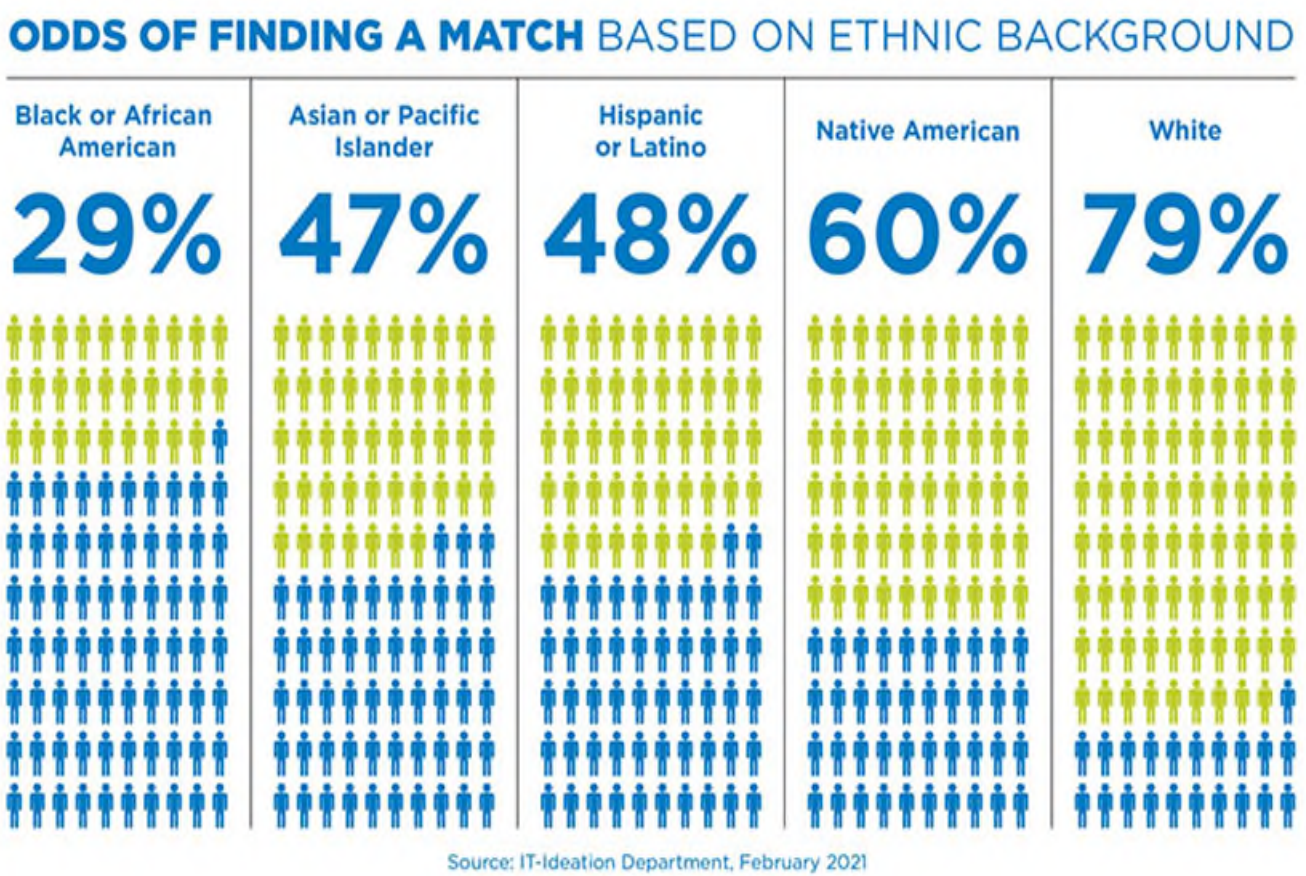
Includes Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Myelodysplastic Syndromes/Myeloproliferative Neoplasms, Non-Hodgkin Lymphoma, Hodgkin Lymphoma.

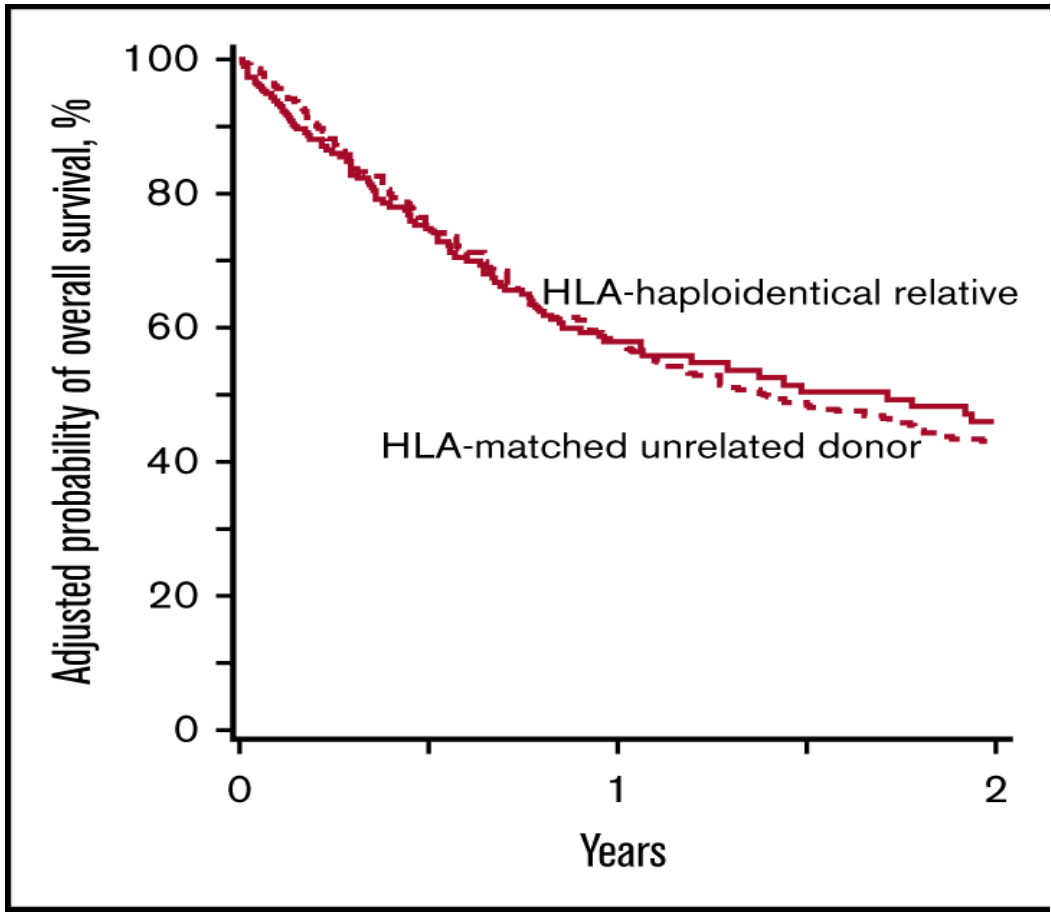
Transplant assessment/optimization for older adults



Lin RJ and Artz AS. Hematology Am Soc Hematol Educ Program. 2021;2021(1):254-263

Race/ethnic barriers to transplant





- Haploidentical donor transplants allow for increased donor availability.

Be The Match [https://bethematch.org]. Accessed May 21, 2022. https://bethematch.org/.
Grunwald MR, et al. *Blood Adv*. 2021;5(4):975-983

Conclusions

- The latest revisions to MDS classifications by both the WHO and ICC underscore the significance of molecular mutations and highlight a nuanced boundary between MDS and AML, particularly in cases with elevated blast counts.
- The IPSS-M emerges as a highly predictive risk stratification tool, recommended for application in every MDS patient at the time of diagnosis.
- Luspatercept has a role in low-int risk MDS patients who may be transfusion dependent in both the upfront and ESA-refractory settings.
- Timely referrals for transplantation significantly enhance long-term survival outcomes.
- As the field progresses, barriers to transplant such as age/race diminish.

Thank you for your attention!

City of Hope | ORANGE COUNTY

Questions?

aborogovac@coh.org
Twitter: Azraboro88