MDS Foundation's Educational Patient-Caregiver Forum

UT Southwestern™
Simmons Cancer Center

Navigating Lower-risk MDS

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Conflict of interest disclosure

- I have no conflicts of interest to disclose

- I WILL include discussion of investigational or off-label use of a product in my presentation

Attendees… By show of Hands

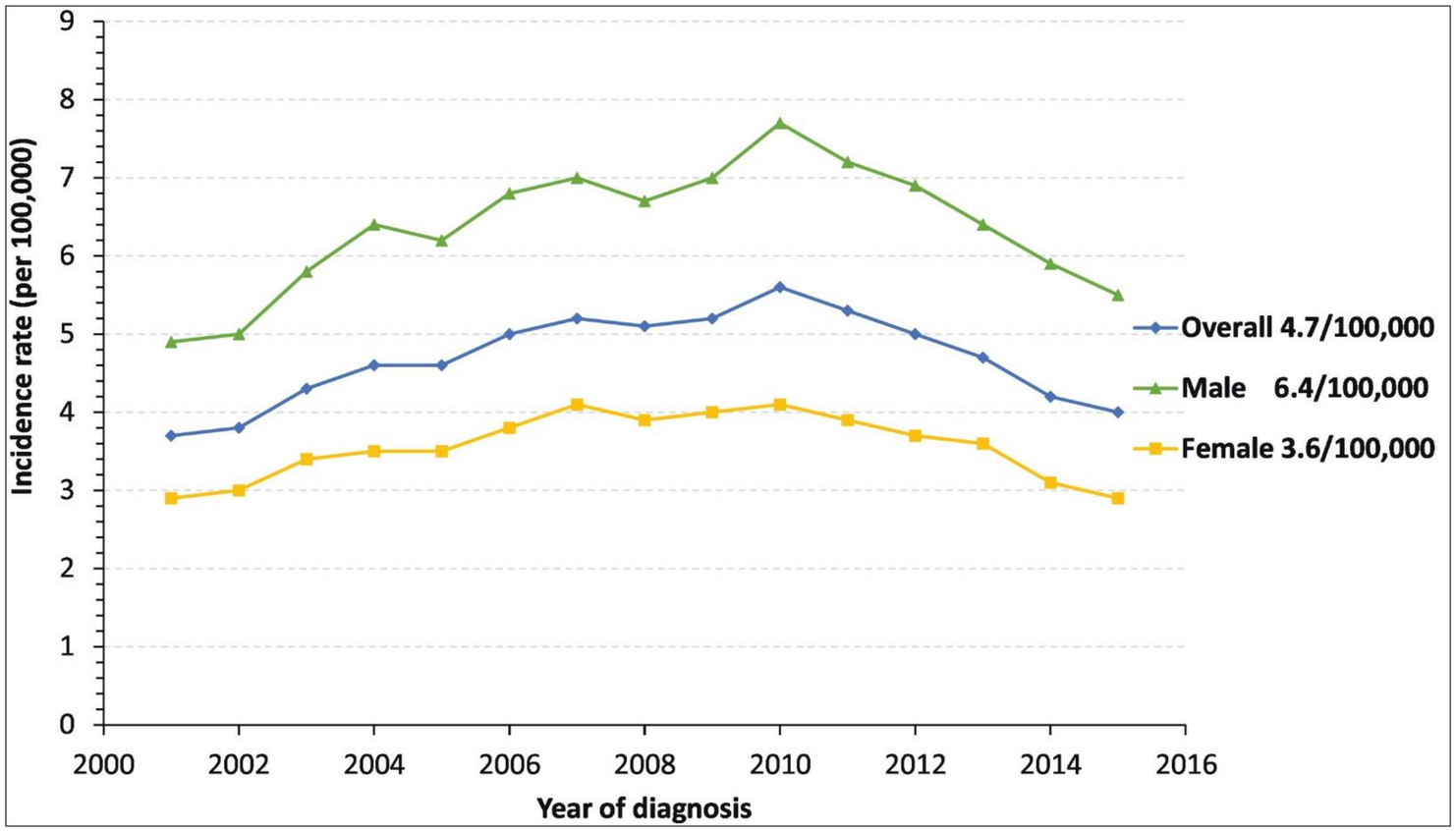
- How many patients are in the audience?
- Patient caregivers or patient advocates?
- Pharmaceutical company representatives?
- None of the above?

For the patients in the audience….

- Please raise your hand if MDS was first described to you as a cancer?

Epidemiology of MDS – Surveillance, epidemiology and end results (SEER) DATA

- Captured as “cancer” – 2001
- 13,400 new cases per year
- Incidence Rate 4.7/100,000
- Male preponderance (M:F 1.5-2.0)

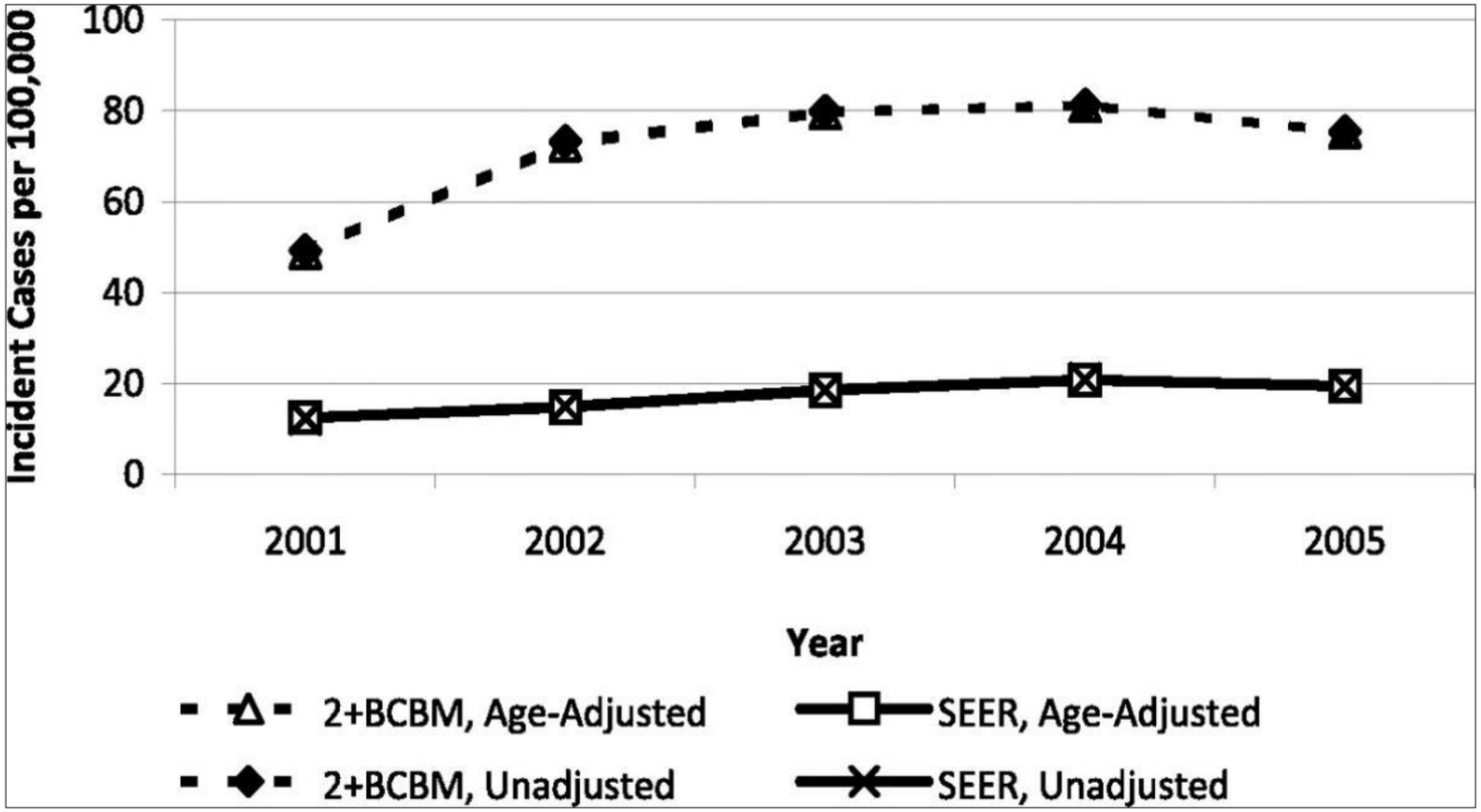


Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)

Incidence Rates Based on a claims-based Algorithm

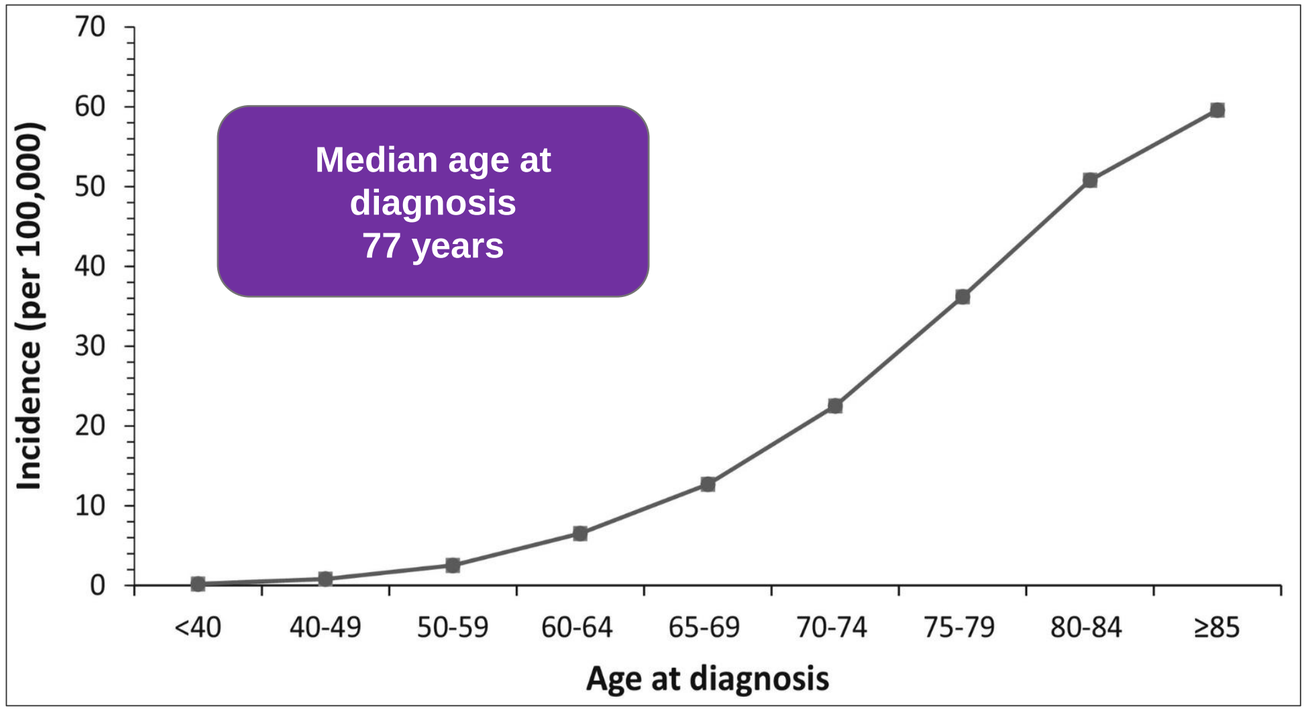
- Patients ≥65 years
- Incidence of 75/100,000

vs. 20/100,000 reported by SEER

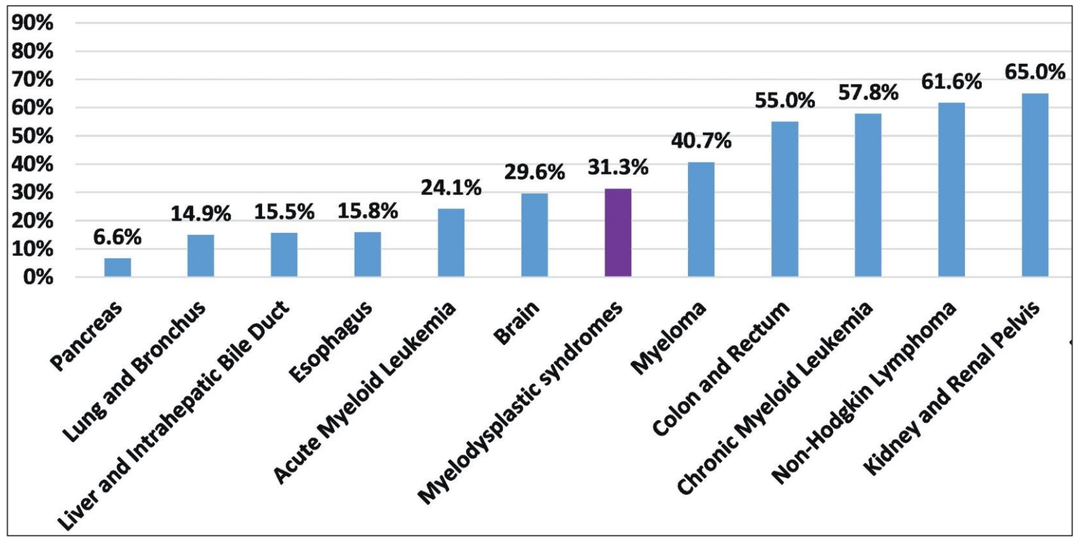


Cogle CR et al. Blood 2011

Age at diagnosis and Overall Survival



5 year overall survival rate in MDS ~ 31%

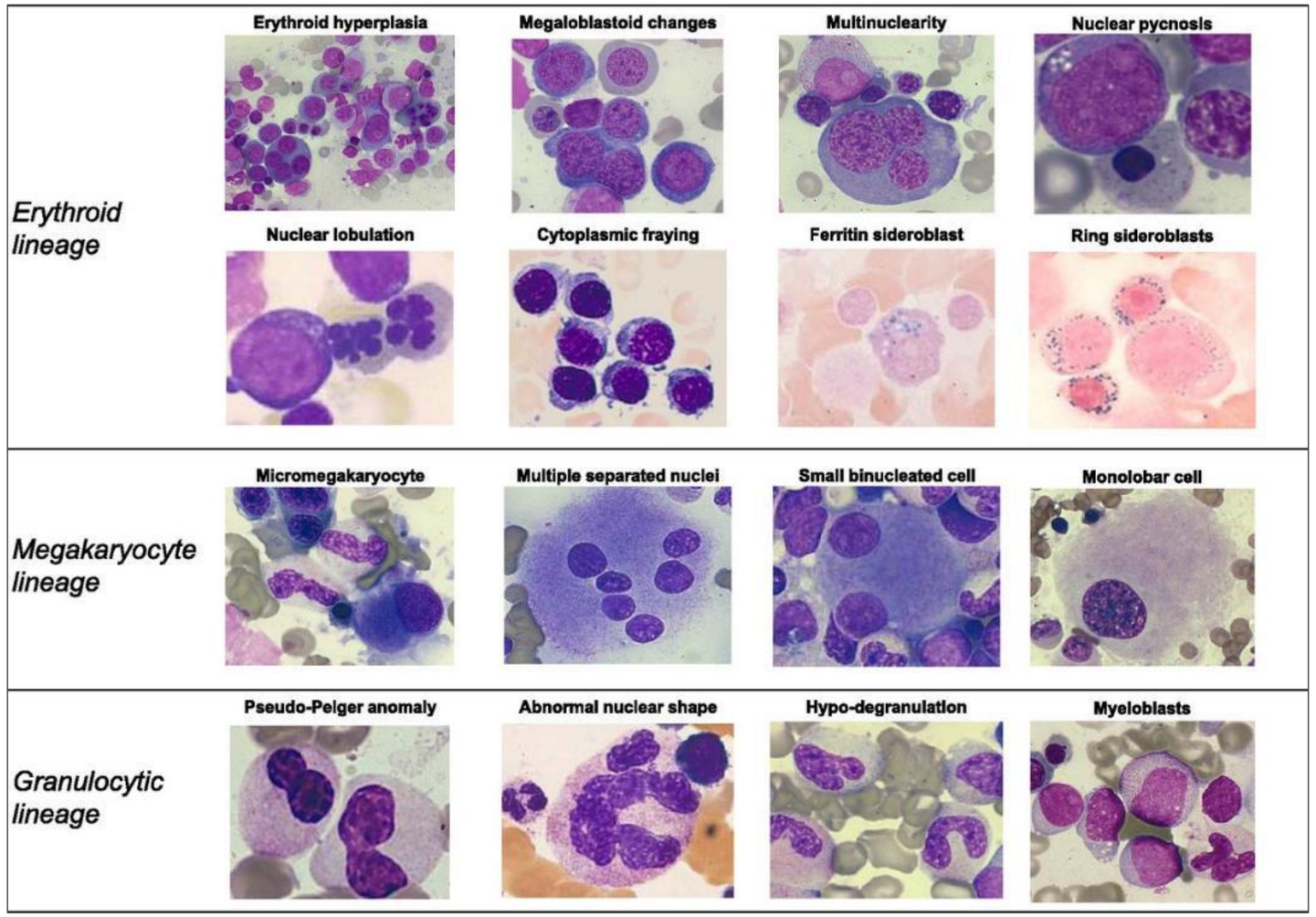


Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)

Diagnosis and Marrow Dysplasia

- Dysplastic changes in > 10% of cells
  - ➢ Peripheral cytopenias
  - ➢ Increased blasts
  - ➢ Increased ring sideroblasts

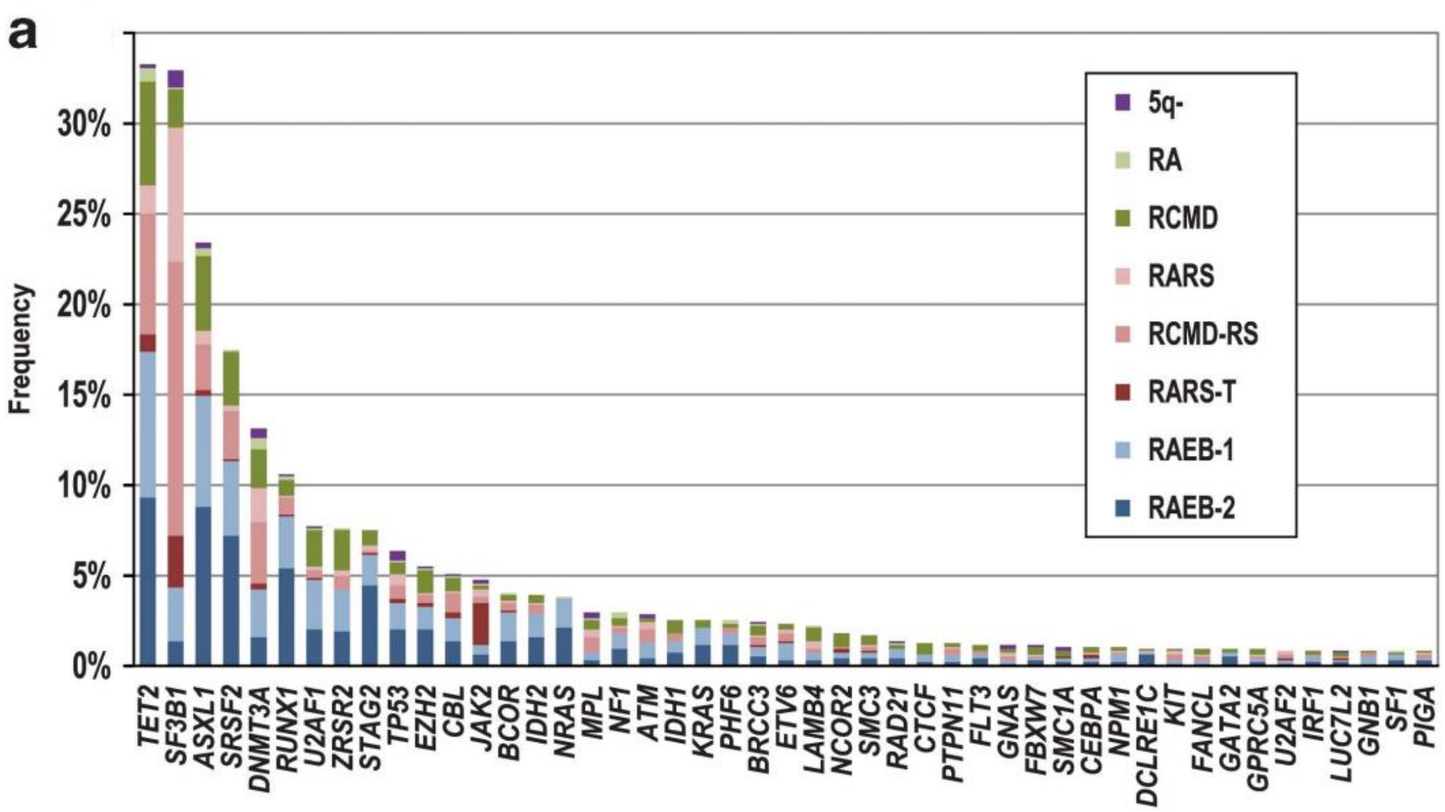
- Defining karyotype/genomic abnormality

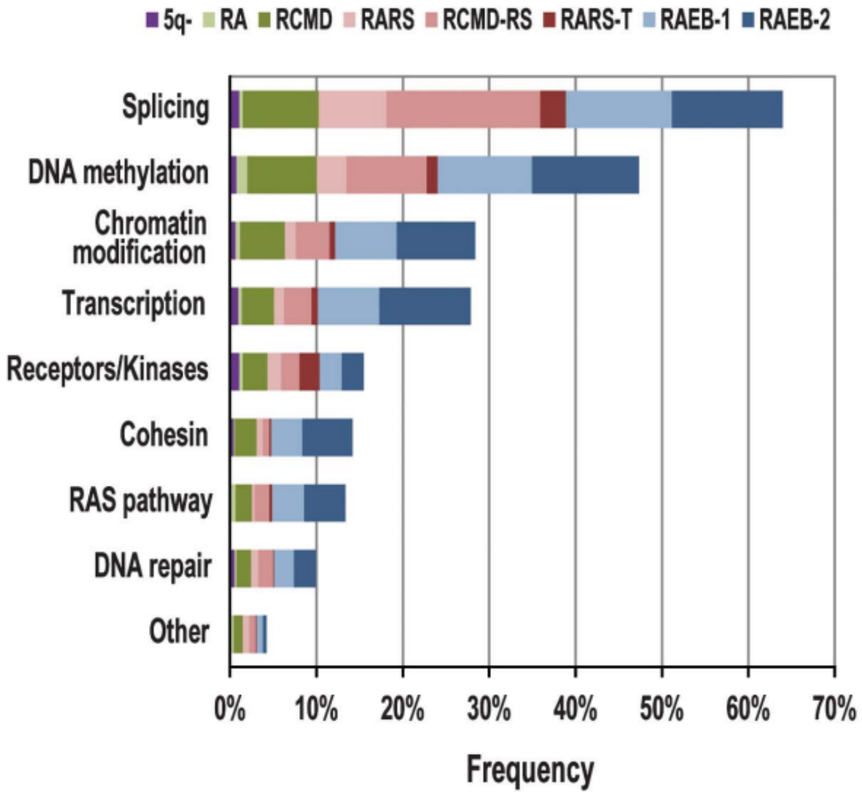


Cazzola M, et al. Blood 2013

Genomic Landscape of MDS: 944 patients

- 90% had 1 or more driver mutations (median: 3/pt, [0-12])





Haferlach et al. Leukemia 2014

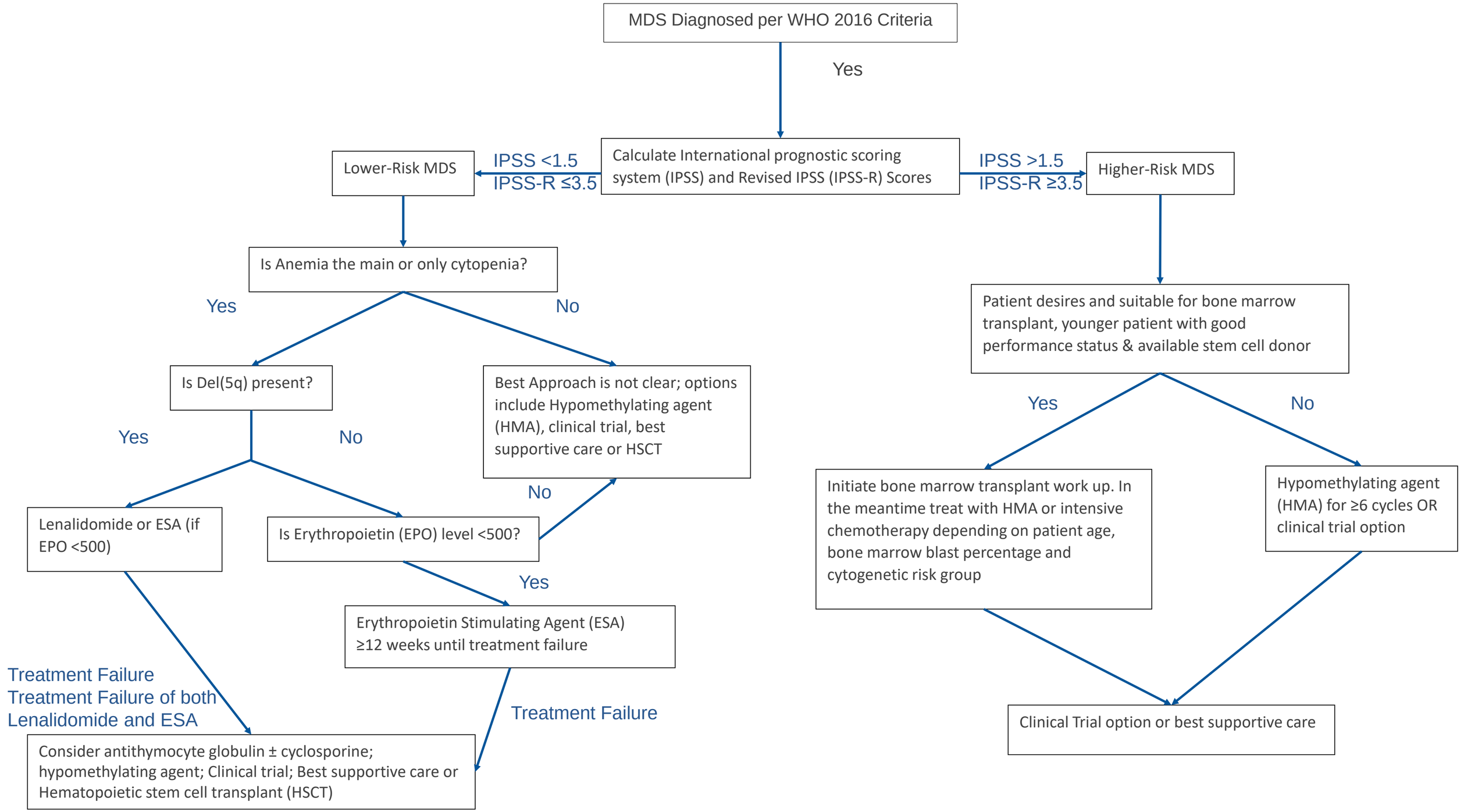
Lower-Risk Myelodysplastic Syndrome

- **Lower Risk Definition??**
  - Prognostic scoring systems:
  - International prognostic scoring system (IPSS) Low-risk, Intermediate-1 risk (0-1.0)
  - Revised-IPSS: Very low risk, low-risk and intermediate risk (≤3.5)
  - Morphology: MDS without excess blasts

Treatment Goals in Lower-risk MDS

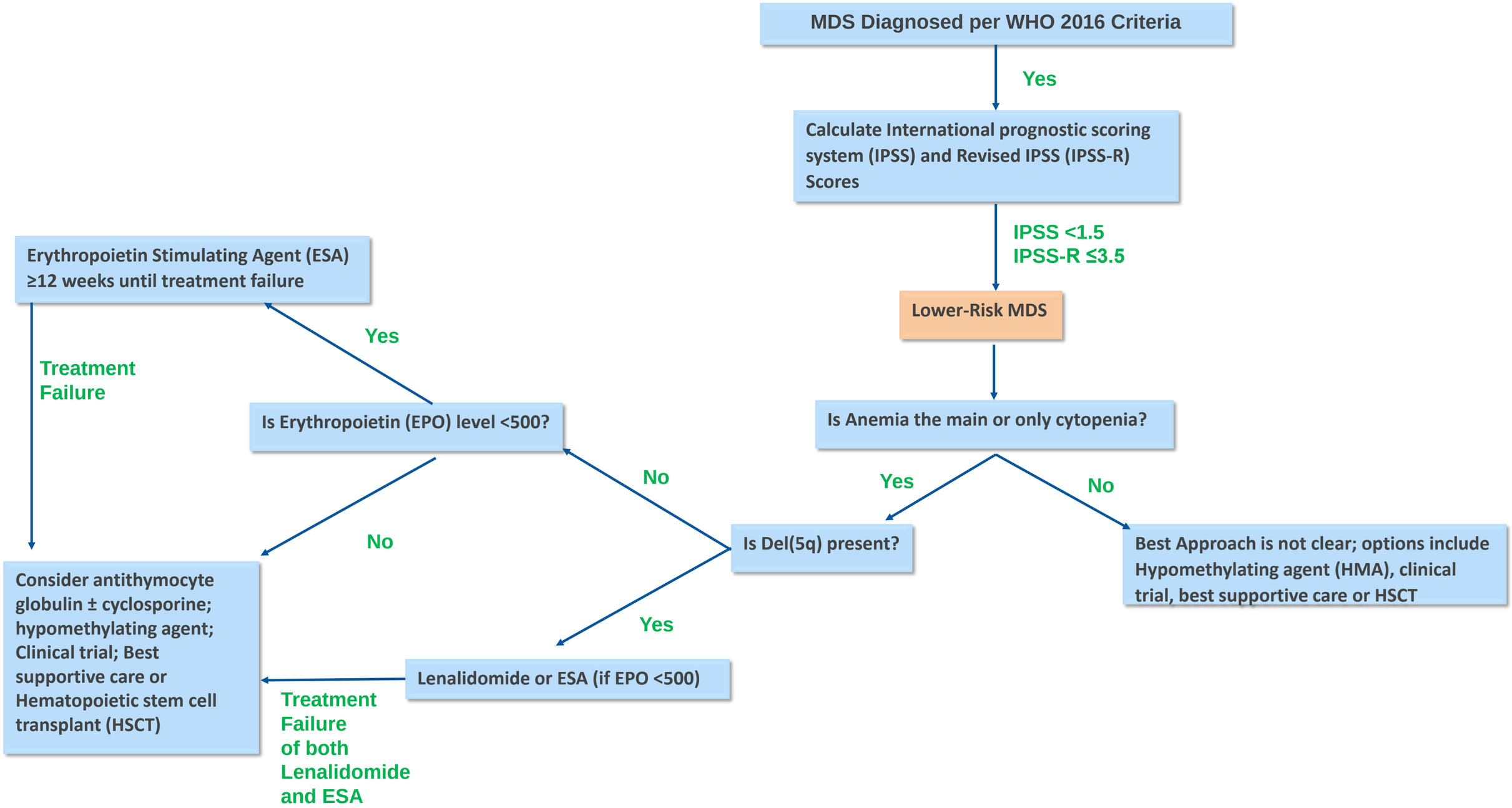
- Improve blood counts and decrease transfusion requirements
- Improve quality of life and symptom burden
- Only curative option is by an allogeneic cell transplant
- Timing to initiate treatment is key ---- 2 factors: blood counts and patient symptoms

Treatment algorithm for MDS



Madanat Y.F., Sekeres M.A. (2019) Myelodysplastic Syndromes (MDS). Concise Guide to Hematology. Springer, Cham

Treatment algorithm for lower-risk MDS



Madanat Y.F., Sekeres M.A. (2019) Myelodysplastic Syndromes (MDS). Concise Guide to Hematology. Springer, Cham

FDA Approved treatments in MDS

- Lenalidomide for deletion 5q MDS
- Hypomethylating agents (Azacitidine and Decitabine)

- Commonly used off-label:
  - Erythropoietin stimulating agents (erythropoietin and darbopoetin)
  - Lenalidomide for non-del(5q) MDS
  - Immunosuppressive therapy (Antithymocyte globulin (ATG) and cyclosporine)

Erythropoietin Stimulating Agent Response Model in MDS

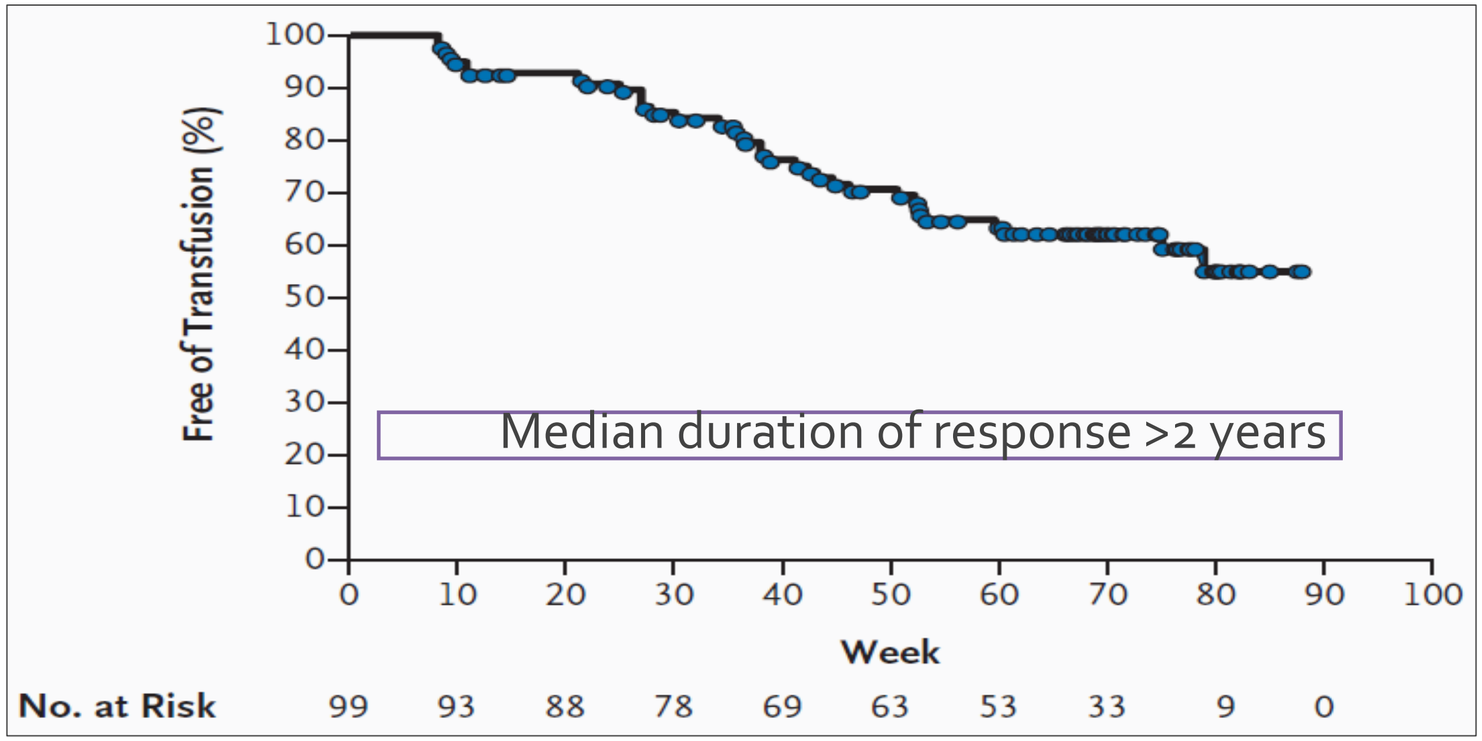
- Serum erythropoietin level (EPO) Level (U/L)
- Red blood cell transfusion requirements (# of units/month)

High response rate 74% (n=34)	Intermediate response rate 23% (n=31)	Low response rate 7% (n=39)
EPO ≤500 & <2U/mo	EPO ≤500 & ≥2 U/mo	EPO >500 & ≥2 U/mo
	EPO >500 & <2 U/mo	

Hellström-Lindberg E, et al. Br J Haematol. 2003

Lenalidomide response in Deletion 5q in MDS

Response Rate 67% of patients with deletion 5(q) MDS

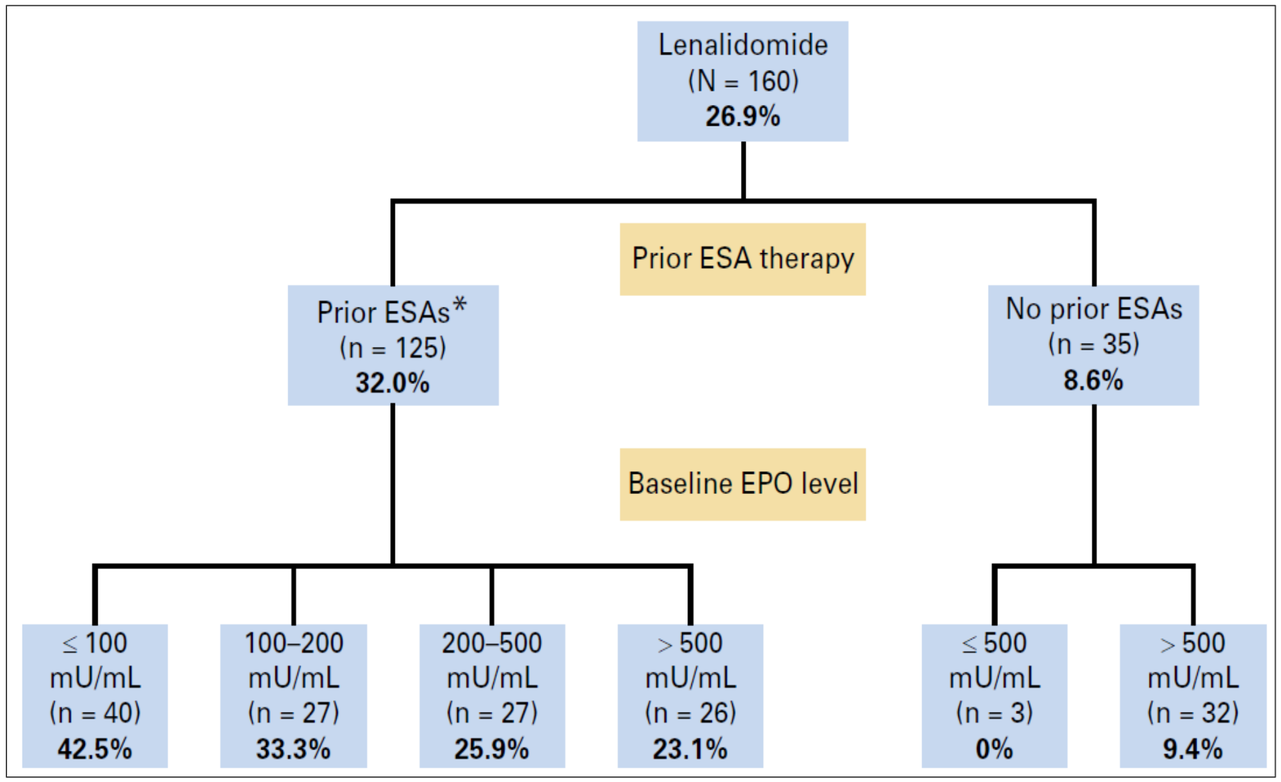


Median duration of response >2 years

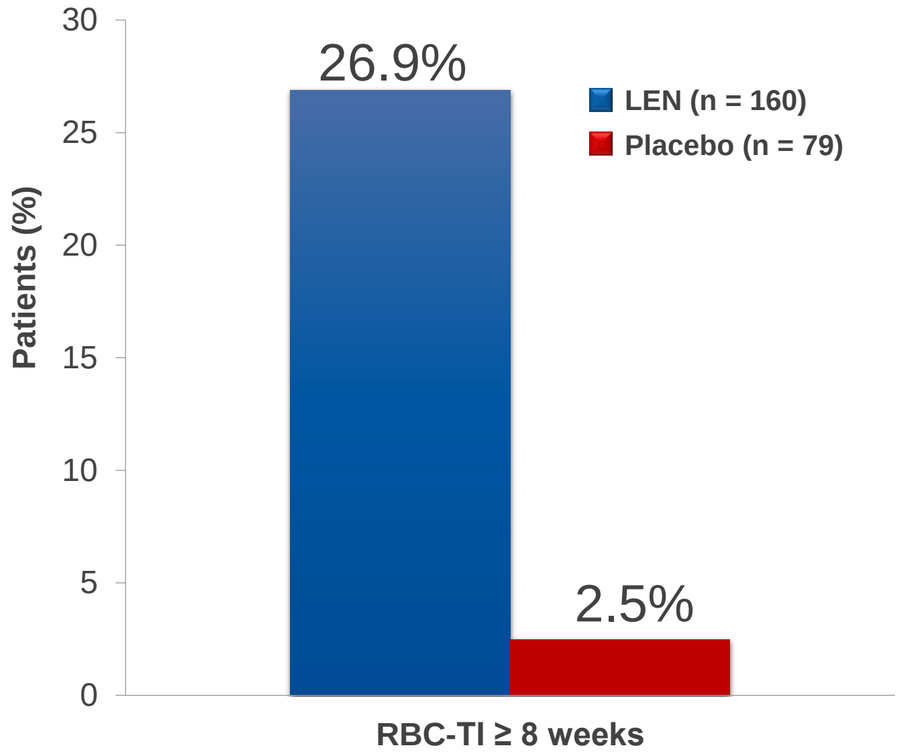
List et al. N Engl J Med 2006

Lenalidomide in non-deletion 5q

Response rate 27% with non-deletion 5(q) MDS



Significantly more patients on LEN achieved RBC-TI ≥ 8 weeks versus placebo (*P* < 0.001)



Santini V. et al. J Clin Oncol 2016

Conclusions 1 - 3 (For patients with anemia)

- Use erythropoietin stimulating agents (ESA's) if serum erythropoietin <500 with low transfusion requirements

- Use lenalidomide in deletion 5q MDS upfront or after failure of ESA

- Consider using lenalidomide in non-deletion 5q MDS after failure of ESAs (Off label)

- However….

Combined Treatment with Lenalidomide and Epoetin Alfa Leads to Durable Responses in Patients with Epo-Refractory, Lower Risk Non-Deletion 5q [Del(5q)] MDS: Final Results of the E2905 Intergroup Phase III Study - *an ECOG-ACRIN Cancer Research Group Study, Grant CA180820, and the National Cancer Institute of the National Institutes of Health*

- Low/Intermediate 1 risk IPSS
- Hemoglobin <9.5 g/dl
- Unresponsive to EPO or TD ≥2 Units/mo + EPO >500mU/ml

205 patients randomized

14 excluded
Interruption in drug supply for 4 mo

96 patients
Arm A (LEN alone)
10 mg PO 21/28 days

99 patients
Arm B (LEN + EA
60,000 U SQ/wk)

Primary endpoint:
Major erythroid response (MER) at week 16

1) RBC-TI for ≥ 8 consecutive weeks AND a sustained ≥1 g/dL hemoglobin rise compared to mean pre-transfusion baseline value in TD patients

2) >2 g/dL rise in hemoglobin without transfusion for ≥ 8 consecutive weeks in non-TD patients (<4U RBC/8 wks)

List A, et al. ASH 2019. Oral Abstract 842

Combined Treatment with Lenalidomide and Epoetin Alfa Leads to Durable Responses in Patients with Epo-Refractory, Lower Risk Non-Deletion 5q [Del(5q)] MDS: Final Results of the E2905 Intergroup Phase III Study - *an ECOG-ACRIN Cancer Research Group Study, Grant CA180820, and the National Cancer Institute of the National Institutes of Health*

- Heavily transfusion dependent population with 85% of patients – received a median of 4 units/8 weeks
- 93% of patients received prior treatment with Epo and 18% azanucleosides.

	Arm A (Len alone)	Arm B (Len plus EA)	P value
MER	11.5%	28.3%	0.004
MER if on treatment for 16 wks	15.6%	38.9%	0.004
Cross over MER (44 patients)	25%		
mDOR	13 months	23.8 months	

Concludions: The addition of LEN to EA treatment is an effective strategy for the management of Epo-refractory patients with a potential duration of benefit extending to years.

List A, et al. ASH 2019. Oral Abstract 842

Low-dose HMAs in LR-MDS: Treatment

- Regimens:
  - DAC 20 mg/m^2 IV D1-3 every 4 weeks
  - AZA 75 mg/m^2 IV/SC D1-3 every 4 weeks

- Response assessment by modified IWG 2006

- Between 11/2012 and 10/2015, 91 pts with LR-MDS treated and evaluable for response

- Median duration of follow-up = 14 months (range: 2-30 months)

Short et al. for MDS CRC Blood 2017

Low-dose Hypomethylating agents in LR-MDS: Response

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	**54 (59)**
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Short et al. for MDS CRC Blood 2017

Sequence of therapy: Azacitidine vs LEN in Lower-risk MDS

- Lenalidomide is widely used off-label in the non-del5q setting
- NCCN clinical guidelines list LEN as a 2nd treatment option for TD anemia in lower-risk non-del 5q MDS after hypomethylating agents (HMAs)
- Led to wide use of HMAs as frontline therapy after erythroid stimulating agents (ESA) failure in LR-MDS
- Response rate to LEN after HMA failure is not known, as MDS-002 and MDS-005 excluded patients previously treated with HMAs
- Examined response rates to each drug when treatment order (LEN followed by HMA or HMA followed by LEN) differed

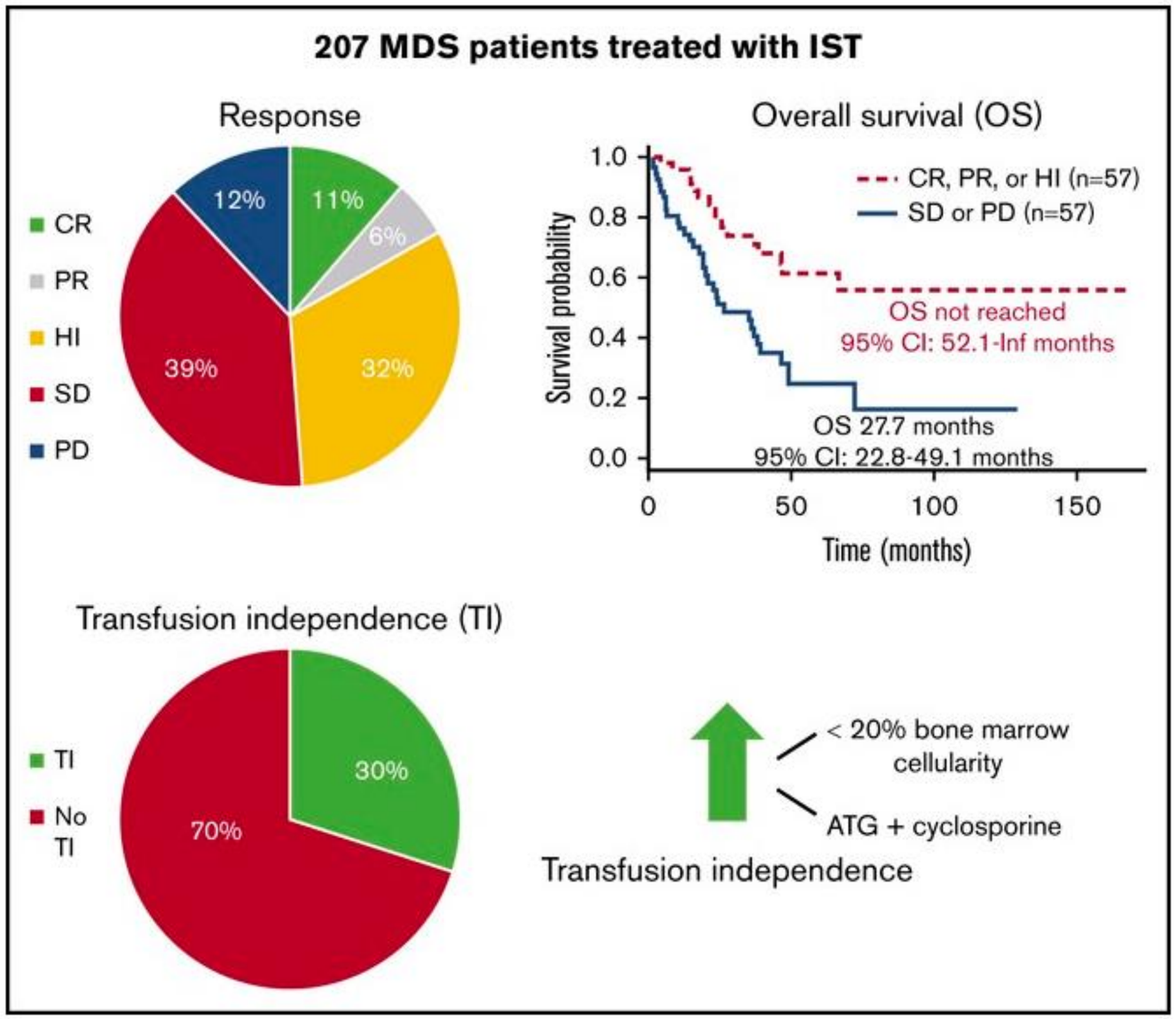
	LEN Response Rates (HI+)	AZA Response Rates (HI+)
LEN 1st line n= 80	20% (n=16)	30% (n=24)
Len 2nd line n= 64	11% (n=7)	39% (n=25)
P value	**0.046**	0.20

Komrojki et al. for MDS CRC ASH 2016; abstract 4322

Immunesuppressive therapy

Achievement of RBC TI was associated with a hypocellular bone marrow (cellularity < 20%); horse ATG plus cyclosporine was most effective

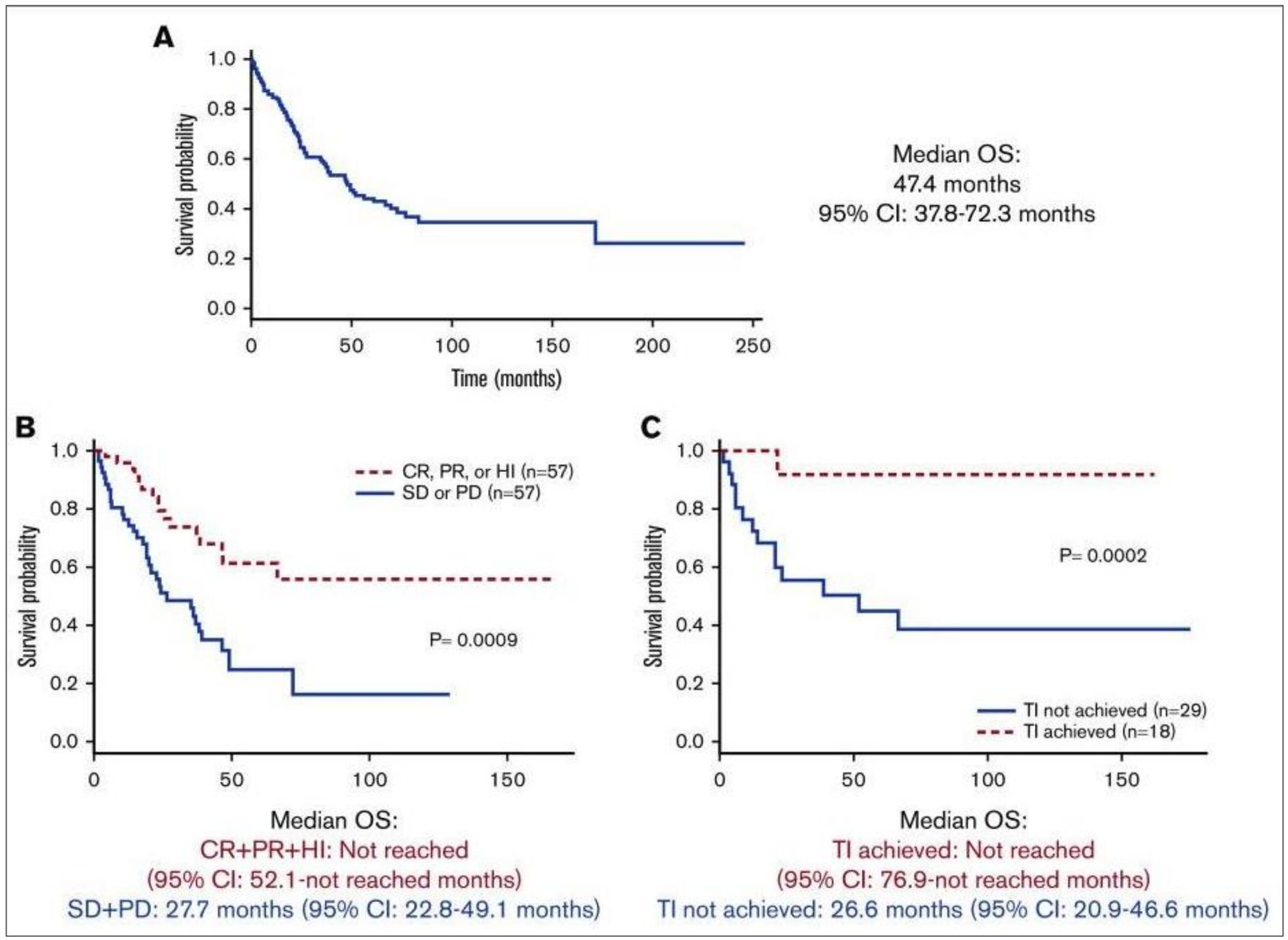
For TI, only a hypocellular bone marrow remained a significant predictor of achieving RBC TI (<20% vs >20%: OR, 4.0; 95% CI, 1.2-13; *P* = .03).



Stahl et al. Blood Adv. 2018 Jul 24; 2(14): 1765–1772

Outcomes of IST in MDS

Response	Percentage	95% CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR (CR+PR+HI)	48.8	39.8-57.9
TI	30	22.3-39.5



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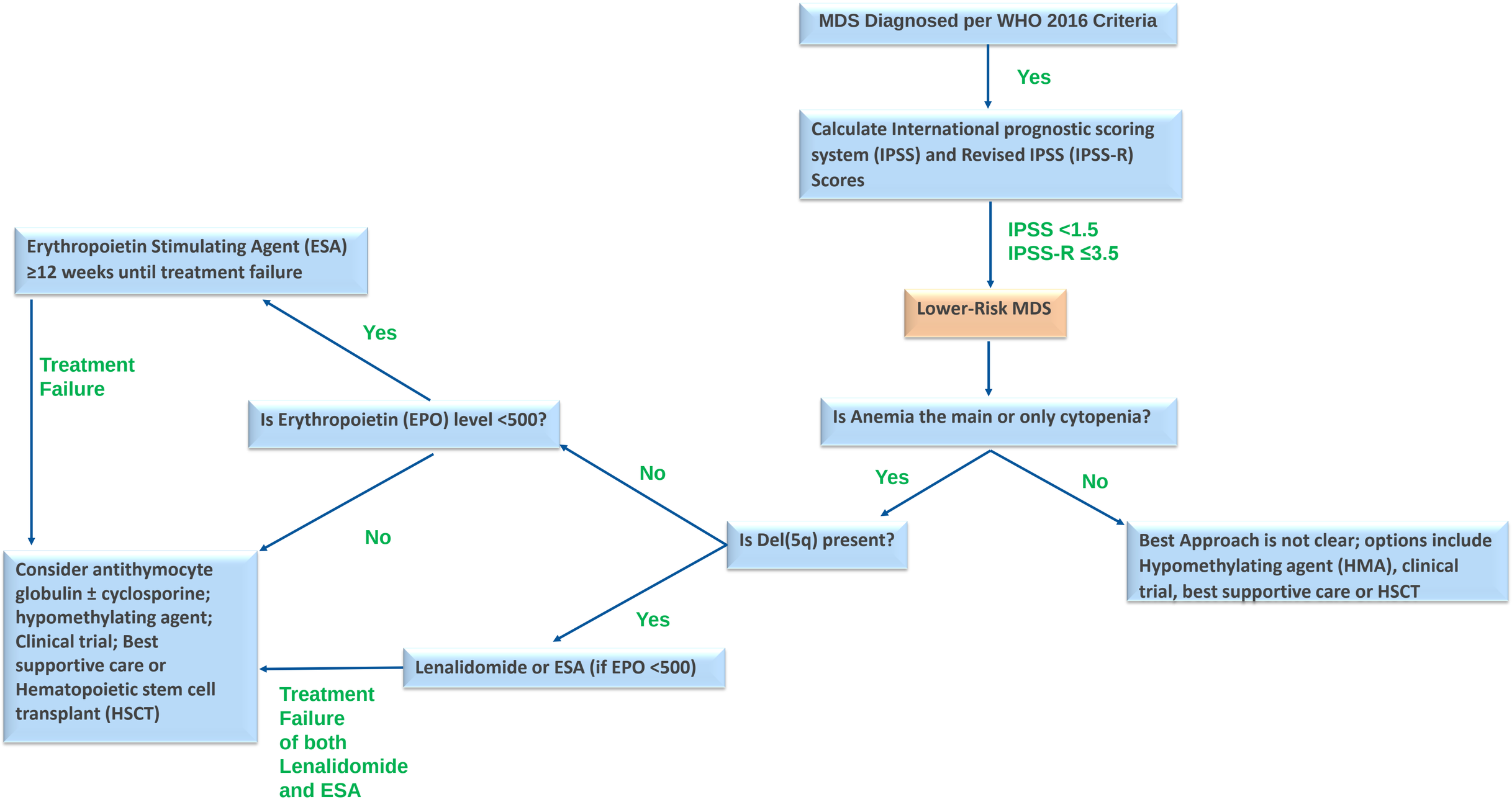
Treatment algorithm for lower-risk MDS



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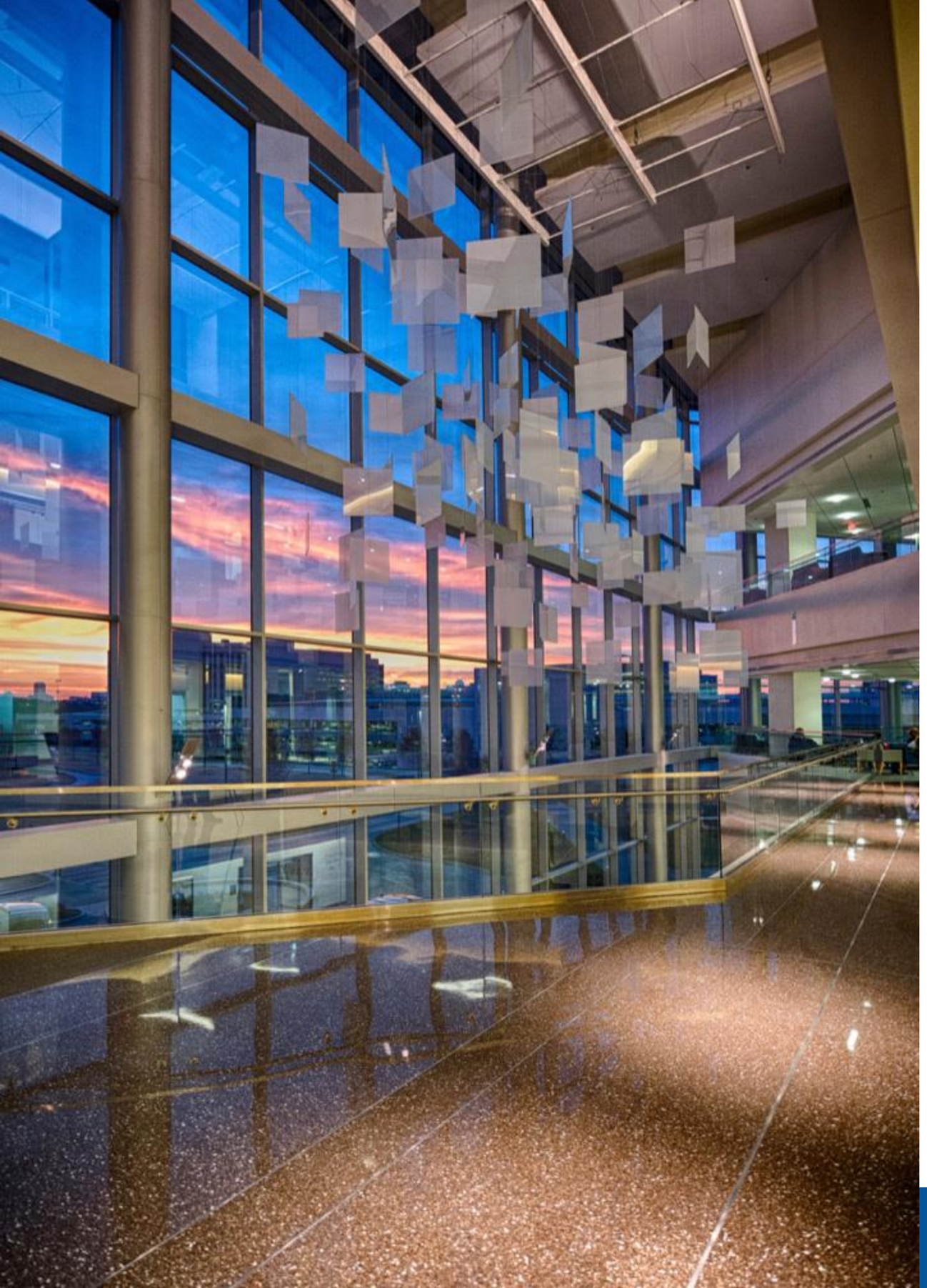

Our patients, caregivers and patient advocates

mds foundation
the myelodysplastic syndromes foundation, inc.

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