Kezelési lehetőségek myelodysplasiában

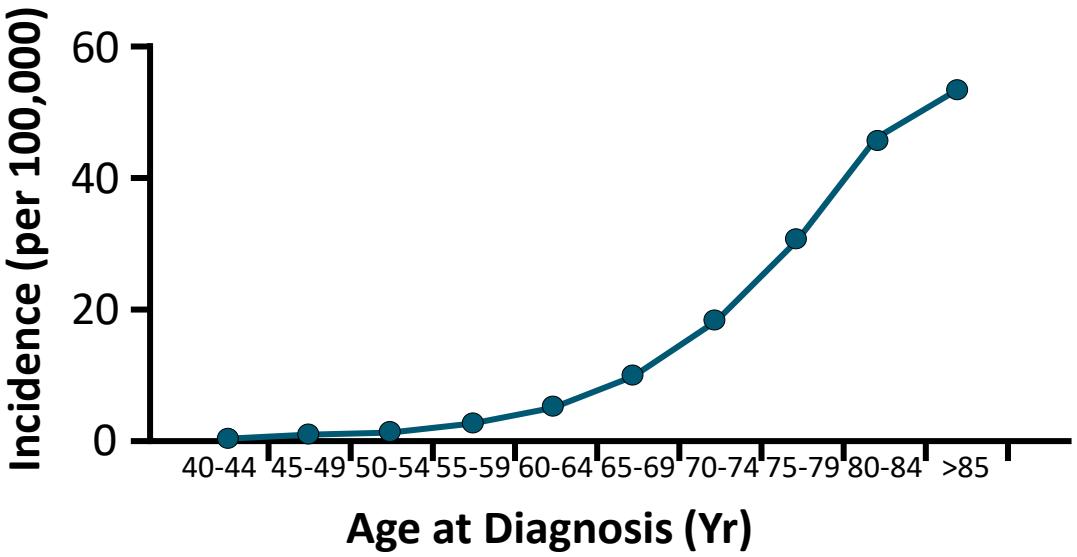
Dr Borbényi Zita

SZTE, Hematológia Centrum

MDS Epidemiology

- **Overall incidence:** 4.0/100,000
- **In US:** 34,118
- **Median age:** 77 yr

Incidence Rates of MDS Increase With Age



More than 86% of patients were diagnosed at age ≥60 yr

Epidemiology of Hematologic and Nonhematologic Malignancies in US (SEER Database, 2012-2018)	Incidence*	5-Yr OS (2012-2018), %
Hematologic malignancies		
Hodgkin lymphoma	2.6	89.1
MDS	**4.0**	**36.9**
Myeloma	7.1	57.9
Leukemia	14.1	65.7
Non-Hodgkin lymphoma	19.0	73.8
Selected nonhematologic malignancies		
Lung and bronchus	52.0	22.9
Colon and rectum	37.7	65.1
Breast	128.3	90.6

*Age-adjusted incidence rate per 100,000 men and women per yr between 2012 and 2108.

Zeidan. Blood Rev. 2019;34:1. seer.cancer.gov/statistics-network. Ma. Am J Med. 2012;125:S2.

MDS Minimal Diagnostic Criteria

Prerequisite criteria: *both 1 and 2 must be fulfilled*

1. Persistent cytopenia(s)

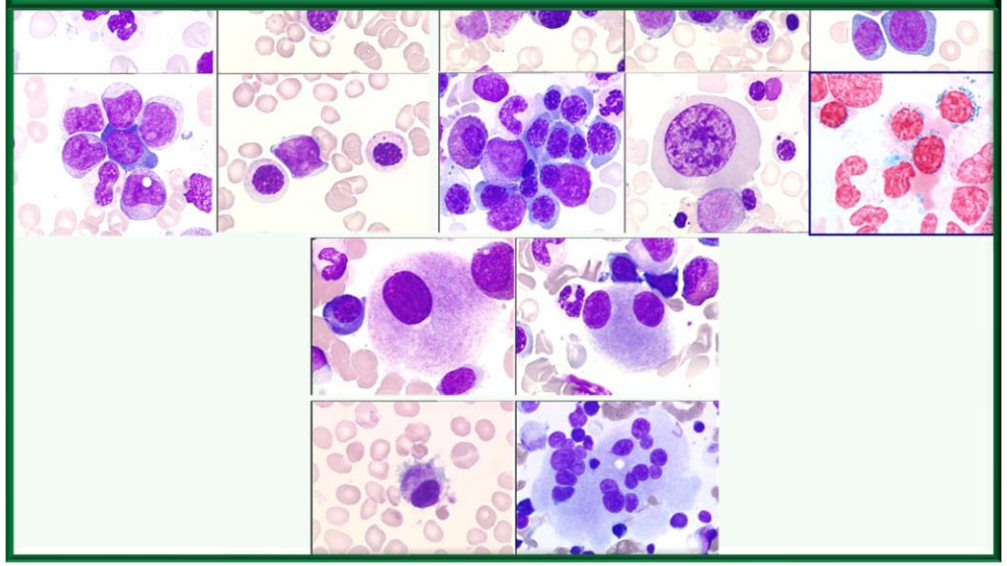
2. EXCLUDE other causes of cytopenias and morphological changes

- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE, etc)
- Hereditary BMF syndromes (Fanconi anemia, etc)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN, etc)

MDS major criteria

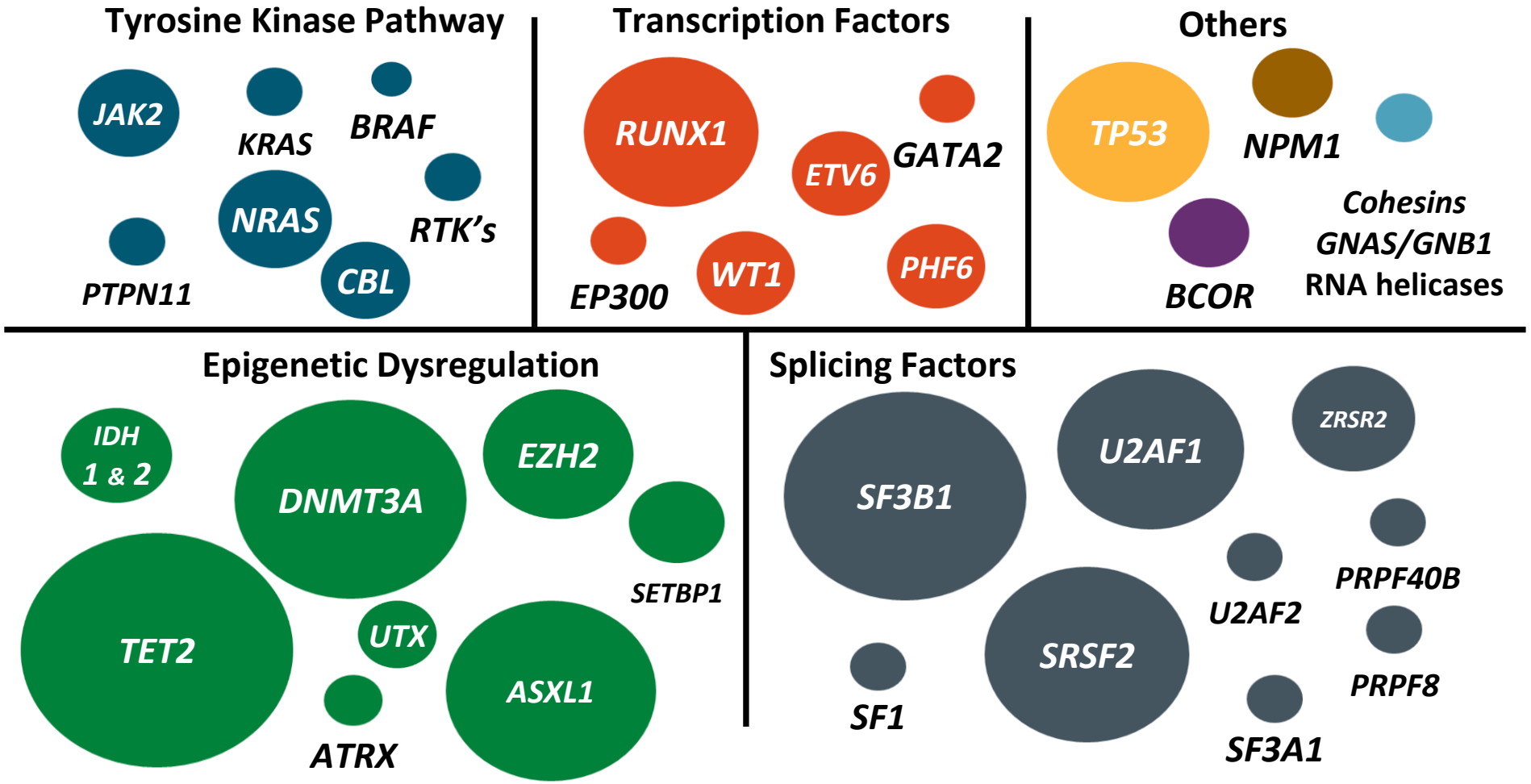
i. Dysplasia of ≥10% of cells in 1 or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in RS of ≥15% (or ≥5% in the presence of a *SF3B1* mutation)
ii. An increase in myeloblasts of 5%-19% in dysplastic BM smears (in the absence of AML-specific gene rearrangements) or 2%-19% myeloblasts in peripheral blood smears
iii. An MDS-related (5q-, -7, complex…) karyotype

≥1 of these major MDS criteria has to be met (together with prerequisite criteria) to arrive at diagnosis of MDS



Valent. Oncotarget. 2017;8:73483. NCCN. Clinical practice guidelines in oncology: myelodysplastic syndromes. v.1.2023. nccn.org.

Oncogenic Gene Mutations in MDS



Bejar. Blood. 2014;124:2793. Ogawa. Blood. 2019;133:1049. Slide courtesy of D. Steensma (modified).

Validation of MDS Classification Systems

- Investigators concluded that improvements are possible for both WHO 2022 and ICC 2022 MDS classification systems
  - Molecularly defined subtypes (*SF3B1,* del5q, and multihit *TP53*) are unique
  - *TP53* mutation predicted poor survival, and multihit *TP53* independently predicted survival
  - MDS-RS (*SF3B1* wild-type) and MDS-LB subtypes showed similar survival
  - Outcomes were worse for MDS-MLD vs MDS-SLD
  - Blast percentage correlated with OS, but precise cutoffs should be examined further
  - Grade 2/3 fibrosis was associated with decreased OS and was independent predictor of OS within MDS-IB
- Investigators proposed unified classification algorithm for MDS and plan analysis of multicenter dataset (VALIDATE study)

Ball. ASH 2022. Abstr 463.

Genetically Defined Subtypes in 2022: ICC and WHO

Lower-risk MDS subtypes: <5% BM and <2% PB blasts

- MDS with mutated *SF3B1*
- MDS with del(5q)

- MDS with low blasts and *SF3B1* mutation
- MDS with low blasts and del(5q)

Higher-risk MDS subtype: any blast percentage up to 20%

- MDS with mutated *TP53* (blasts 0%-9%)
- MDS/AML with mutated *TP53* (blasts 10%-19%)

- MDS with biallelic *TP53* inactivation

Diverted to AML: cases with AML-defining genetic abnormalities (ICC: only if ≥10% blasts)

- *PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, KMT2A* rearranged, *DEK::NUP214, MECOM* rearranged, *NUP98* rearranged, *NPM1* mutated, *CEBPA* mutated, *bZIP CEBPA**

*ICC only.

Arber. Blood 2022;140:1200. Khoury. Leukemia 2022;36:1703.

Morphologically Defined Subtypes in 2022: ICC and WHO

Lower-risk MDS subtypes: <5% BM and <2% PB blasts

- MDS-NOS with single-lineage dysplasia
- MDS-NOS with multilineage dysplasia
- MDS-NOS without dysplasia

- MDS with low blasts
- MDS with low blasts and ring sideroblasts
- Hypoplastic MDS

Higher-risk MDS subtypes: ≥5% BM/≥2% PB blasts or Auer rods

- MDS with excess blasts

- MDS with increased blasts: 1
- MDS with increased blasts: 2
- MDS with fibrosis

Diverted to new entity intermediate between MDS and AML: 10%-19% blasts

- MDS/AML

Effort to acknowledge continuum between MDS and AML, expand patient treatment options, and stimulate research to achieve more rational (likely genetic) distinction between MDS and AML than arbitrary blast cutoff

Arber. Blood 2022;140:1200. Khoury. Leukemia 2022;36:1703. Estey. Blood. 2022;139:323. DiNardo. Cancer. 2022;128:1568.

IPSS-Revised

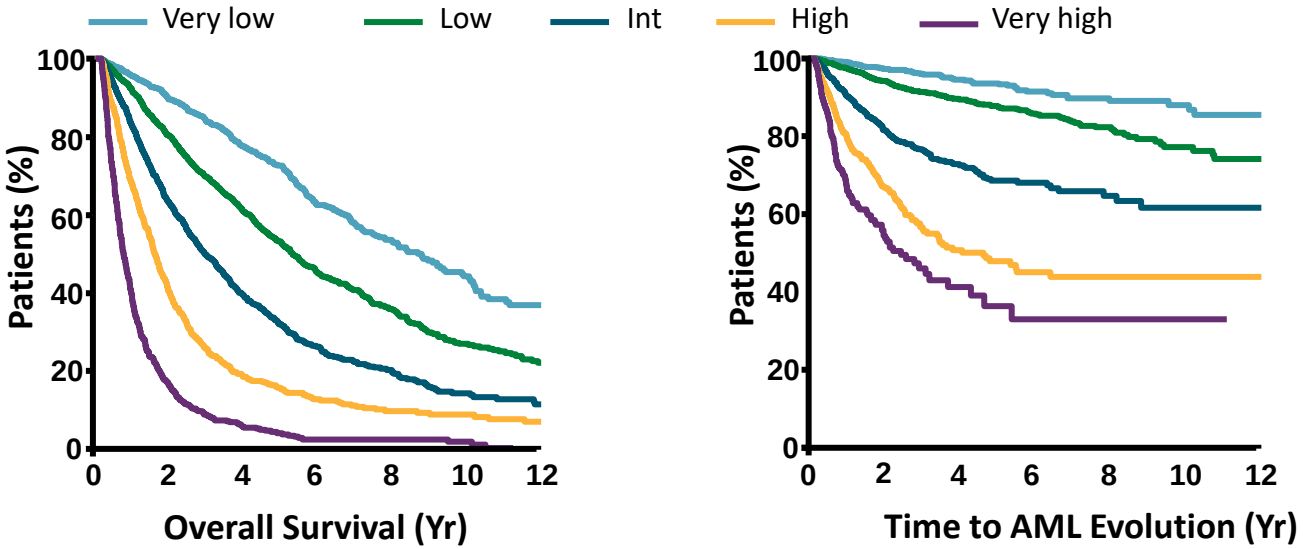
	Score Value						
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3**	**4**
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
BM blast, %	≤2	--	>2-<5	--	5-10	>10	--
Hemoglobin, g/dL	≥10	--	8-<10	<8	--	--	--
Platelets, x 10^9/L	≥100	50-<100	<50	--	--	--	--
ANC, x 10^9/L	≥0.8	< 0.8	--	--	--	--	--

Risk	Score
Very low	≤1.5
Low	>1.5-3.0
Intermediate	>3.0-4.5
High	>4.5-6.0
Very high	>6.0

Greenberg. Blood. 2012;120:2454.

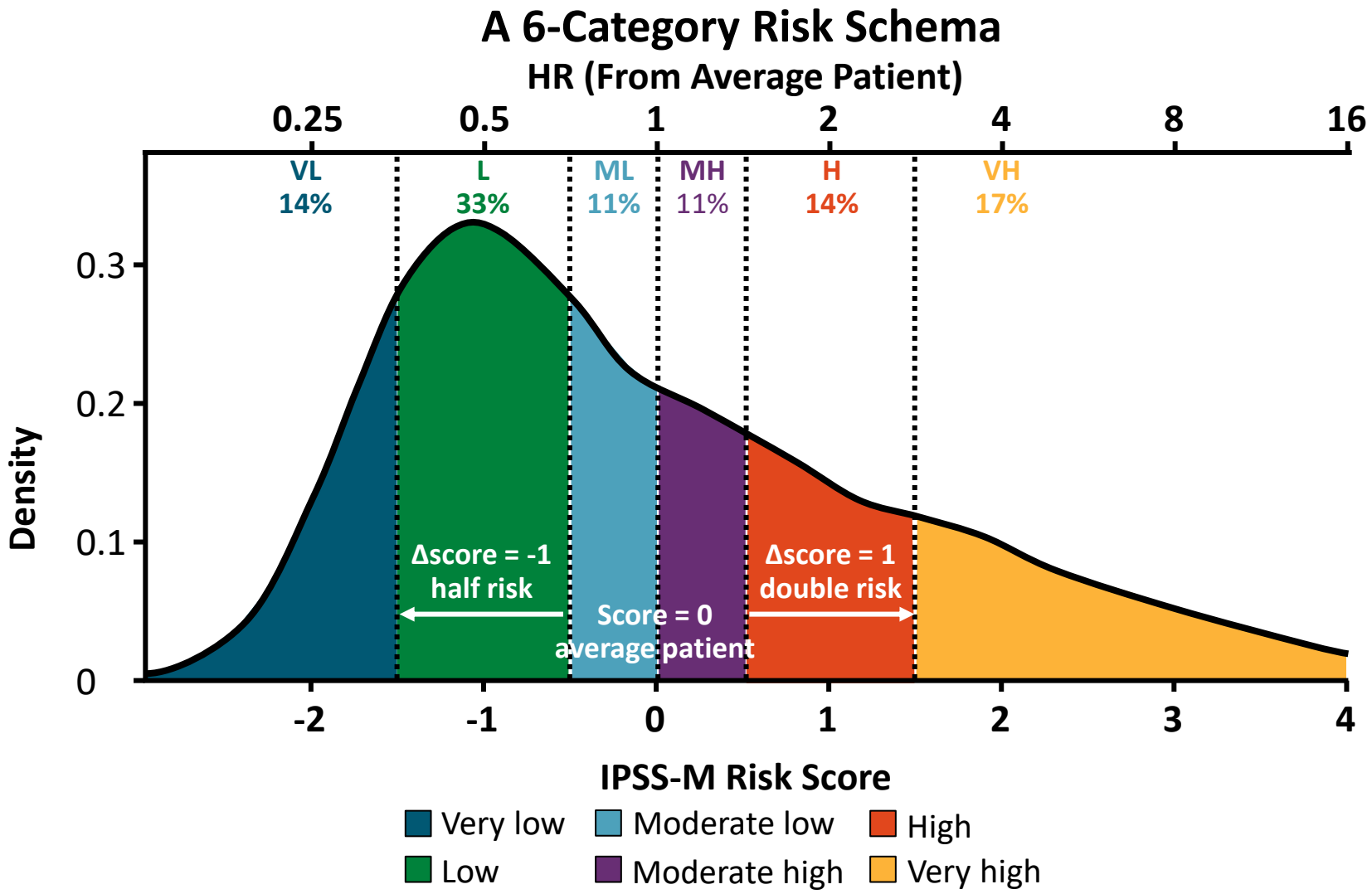
Risk Groups for the IPSS-R

Risk Group	Points	Patients, %	Median Survival, Yr	Time Until 25% of Patients Develop AML, Yr
Very low	≤1.5	19	8.8	Not reached
Low	>1.5-3	38	5.3	10.8
Intermediate	>3-4.5	20	3.0	3.2
High	>4.5-6	13	1.6	1.4
Very high	>6	10	0.8	0.73



Bejar. Haematologica. 2014;99:956.

IPSS-M Risk Categories

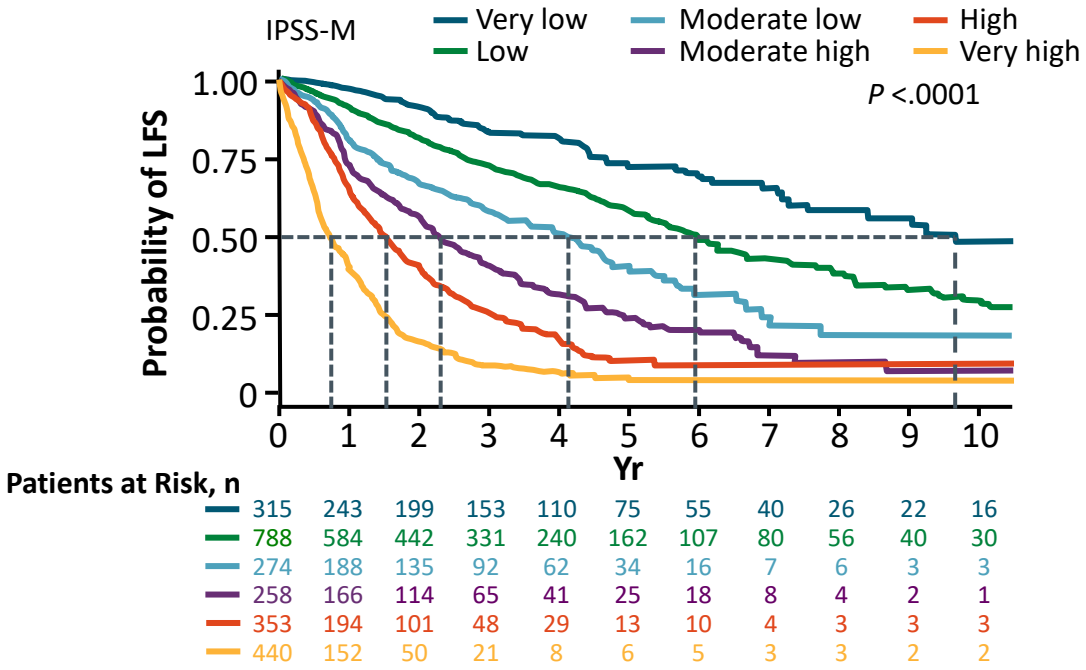


Bernard. NEJM Evidence. 2022;1.

Molecular IPSS for MDS

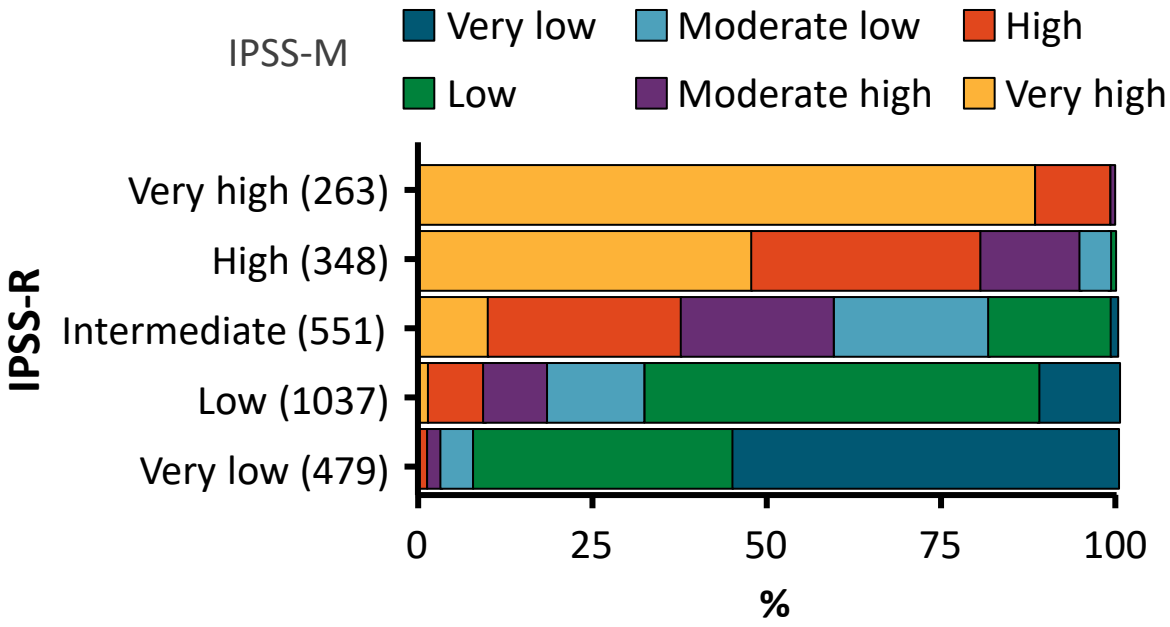
- Discovery cohort: diagnostic MDS samples (N = 2957) with <20% blasts and WBC <13 x 10^9/L were profiled for mutations in 152 driver genes
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders

Leukemia-Free Survival



Restratification of Patients From IPSS-R to IPSS-M Categories

- 46% (n = 1223) of patients were restratified
- 7% (n = 196) of patients were restratified by more than 1 strata

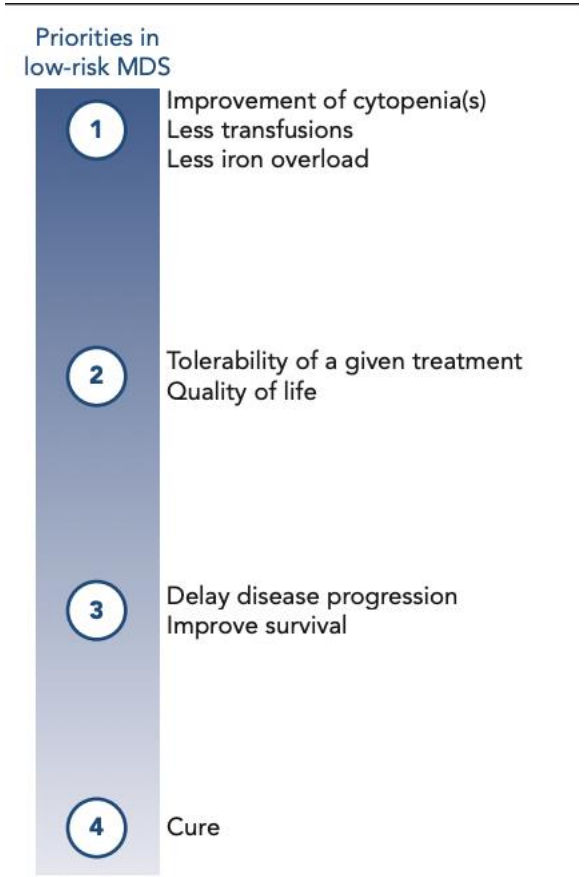


Bernard. NEJM Evidence. 2022;1.

Conclusions

- MDS are heterogenous group of neoplastic stem cell neoplasms
- MDS are interplay between genetic abnormalities and inflammatory milieu
- Clonal hematopoiesis is a spectrum
- Modern classification and risk stratification should include clinical, molecular, and host-related variables

Lower-Risk MDS Treatment Goals



- ***Improve quality of life***
- Improve cytopenia (mostly anemia)

- Prolong overall survival
- Reduce risk of progression

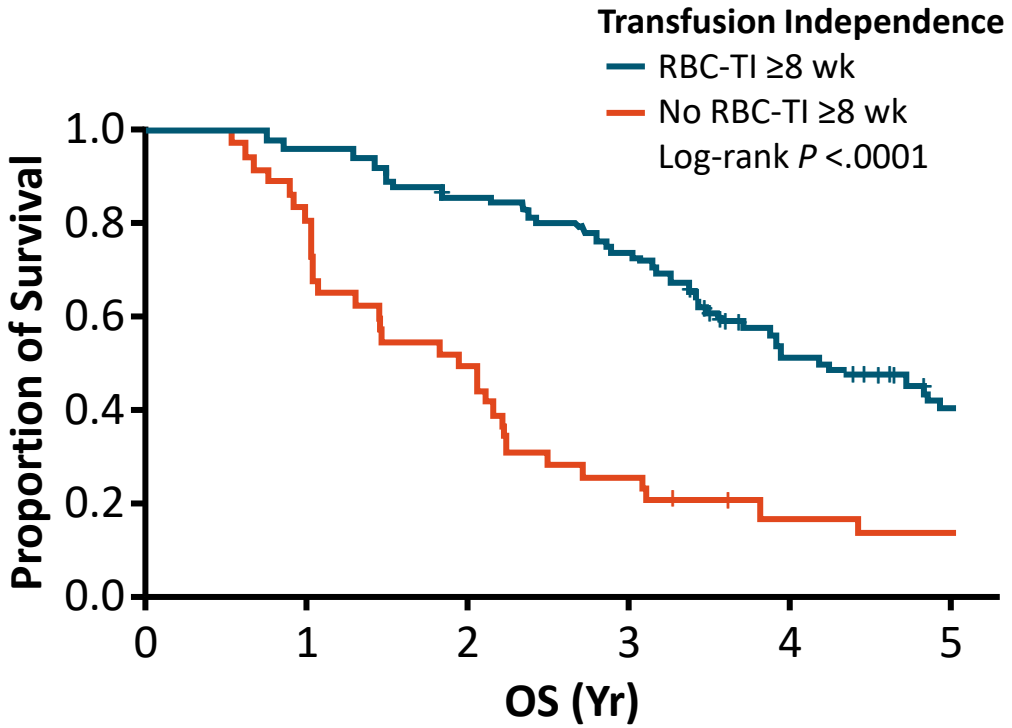
Scalzulli. Blood Rev. 2021;45:100689. Platzbecker. Blood. 2019;133:1096.

Lower-Risk MDS Treatment Goals

Disease-Modifying Therapy in Lower-Risk Setting[1]

- Lenalidomide in MDS del(5q)[2,3]
  - Eliminate del(5q) clone, not stem cells
  - Transfusion independence and cytogenetic responses
  - Improved outcome among responders (OS and EFS)
- Allogeneic stem cell transplant[4]
  - Curative
  - Increased morbidity, mortality
  - Delay until disease evolution, not as first line?

Survival by RBC-TI Duration[2]



Patients at Risk, n

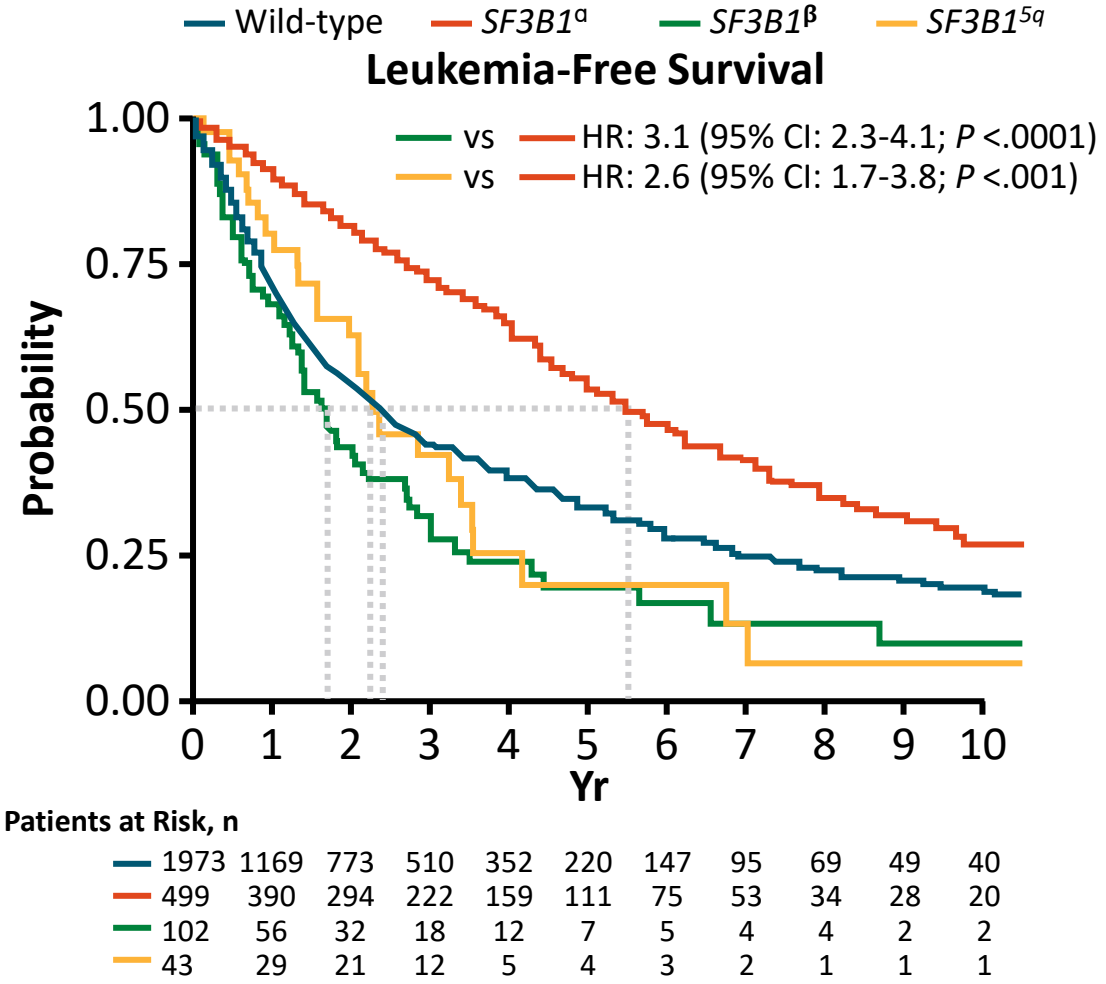
RBC-TI ≥8 wk	94	91	80	69	43	29
No RBC-TI ≥8 wk	38	31	19	10	5	4

1. List. Leukemia. 2018;32:1493. 2. List. Leukemia. 2014;28:1033.
3. Fenaux. Blood. 2011;118:3765. 4. De Witte. Blood. 2017;129:1753.

Disease-Modifying Drug in Lower-Risk MDS: Lenalidomide in del(5q)

Lenalidomide (10 mg/day orally, 21/28 days)

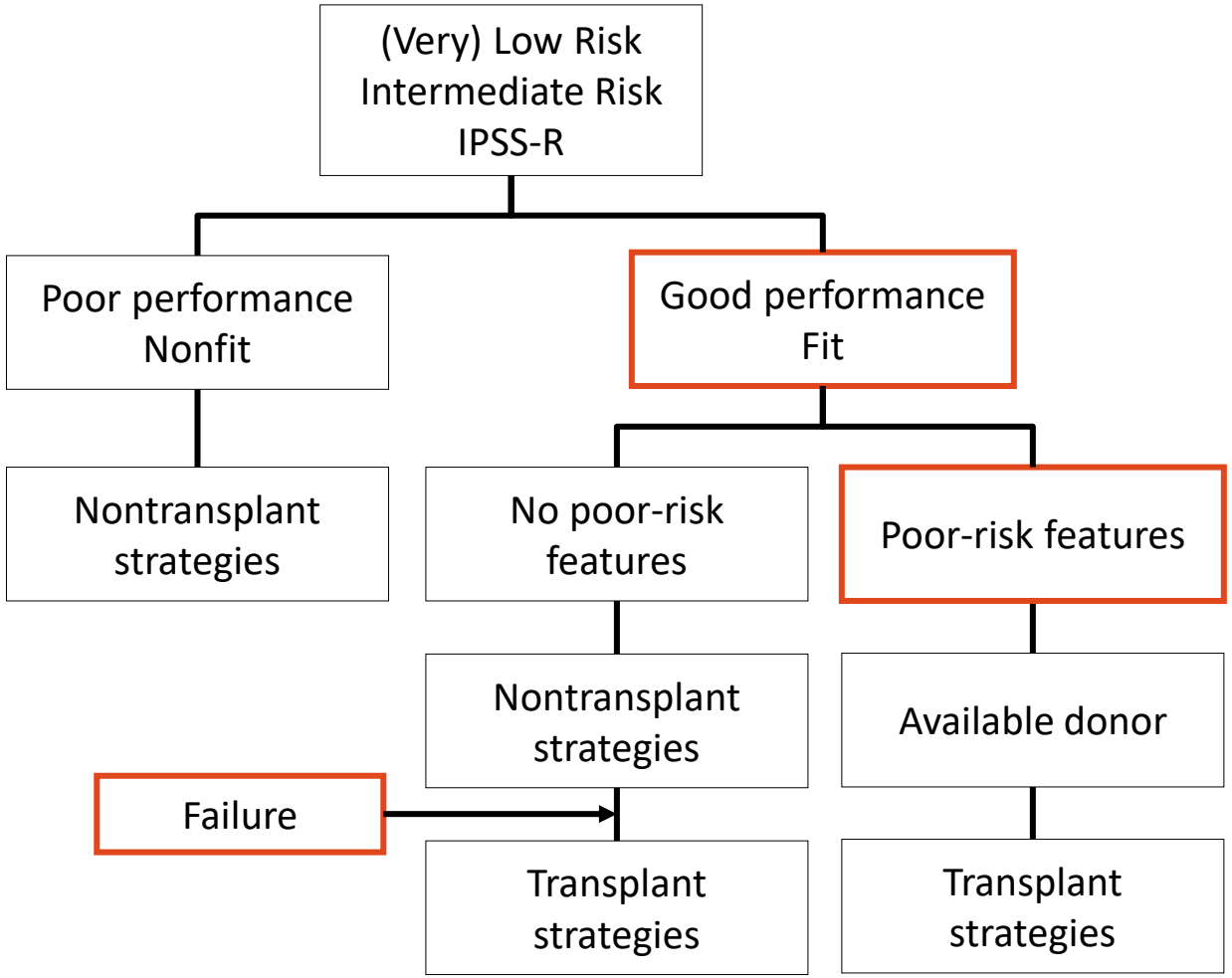
- **Del(5q) transfusion dependent**
  - Median Hgb increase 5.4 g/dL, median time to response 4.6 wk
  - 76% ER, 60% TI, and 50% cytogenetic responses
  - Myelosuppression, rash, diarrhea
  - Improved outcome among responders
  - **Mandatory *TP53* status**
    - Increased AML evolution if mutated: 5yr 77% *TP53mut* vs 24% *TP53wt*
    - Other adverse genes: *TET2*, *RUNX1*, *SF3B1*???



List. NEJM. 2006;355:1456. Fenaux. Blood. 2011;118:3765. Jädersten. JCO. 2011;29:1971. Bernard. NEJM Evid. 2022;1.

Disease-Modifying Approach in MDS: Allogeneic Transplant

Indications in Patients With Lower-Risk MDS



- Poor-risk features defined as:
  - **Poor-risk cytogenetic** characteristics
  - **Persistent blast increase** (>50% or with >15% BM blasts)
  - **Life-threatening cytopenia** (ANC <0.3 x 10^9/L; PLTs <30 x 10^9/L)
  - **High transfusion intensity** (≥2 units per mo for 6 mo)
  - **Molecular testing** should be seriously considered in case of absence of poor-risk cytogenetic characteristics or persistent blast increase

De Witte. Blood. 2017;129:1753.

First-line Treatment in Symptomatic Anemia: ESAs

- **ESAs (high doses + G-CSF; if no responders, 20% rescue, MDS-RS)**
- **Symptomatic anemia**
- Phase III clinical trials (erythroid response: 14.7% darbepoetin and 31.8% epoetin-α)[1,2]
- Real-world evidence[3]:
  - 59% of erythroid responses
  - Median duration of response: 18-24 mo
  - No increased risk of AML
- No relevant adverse events

- Predicted score of response[4]:

Transfusion Need	
Value	Score
<2 U/mo	0
≥2 U/mo	1

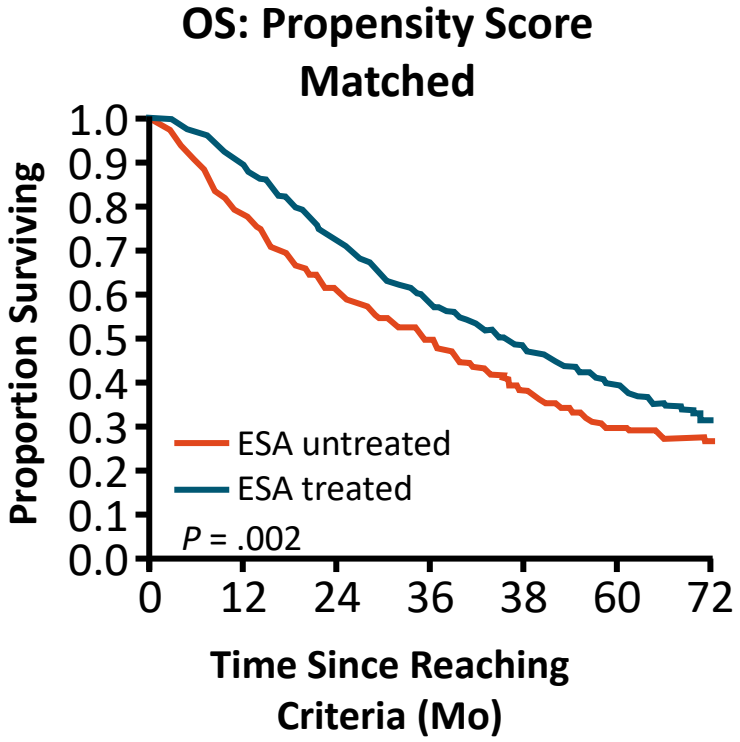
Serum Epo	
Value	Score
<500 U/L	0
≥500 U/L	1

Predicted Response Rate, %	
Score 0	74
Score 1	23
Score 2	7

1. Fenaux. Leukemia. 2018;32:2648. 2. Platzbecker. Leukemia. 2017;31:1944.
3. Diez Campelo. EHA. 2015. Abstr P244. 4. Hellstrom-Lindberg. Best Pract Res Clin Haematol. 2013;26:401.

First-line Treatment in Symptomatic Anemia: ESAs

- EUMDS: prospective registry since 2008
- LR-MDS, Hgb <10 g/dL, propensity score matching
- n = 426 untreated vs n = 742 treated with ESAs
- Median OS: 34.8 mo untreated vs 44.9 mo treated



Garelius. Hemasphere. EHA 2022. Abstr S168.

Second-line Treatment for Patients With RS-LR-MDS

- **Luspatercept (1-1.75 mg/kg SC every 3 wk)**
- **Transfusion-dependent MDS with RS/*SF3B1*mut**
- TI 38%, ER 53%, median duration of response 30 wk
- Median peak Hgb increase level 2.55 g/dL
- Favorable safety profile and administration (SC/3 wk)

1. Fenaux. NEJM. 2020;382:140. 2. Garcia Manero. EHA. 2021. Abstr EP920.
3. Garcia Manero. Blood. 2022;139:624. 4. Komrokji. ASH. 2020. Abstr 3111.

Real World Data on Luspatercept

- Retrospective review, N = 114[1]
  - RBC HTB: 47%
  - Dose escalation: 55%
- Higher responses correlated with lower TB at baseline and with *SF3B1* mutations

Outcome	Luspatercept (N = 114)
HI, % ▪ HMA failure vs HMA naive	39.5 30 vs 50
ORR, % ▪ *SF3B1* mut vs wt ▪ RS vs non-RS ▪ MDS/MPN-RS-T	45 48 vs 16 49 vs 28 79
mDOR, mo (range)	15.6 (2.6-27.3)

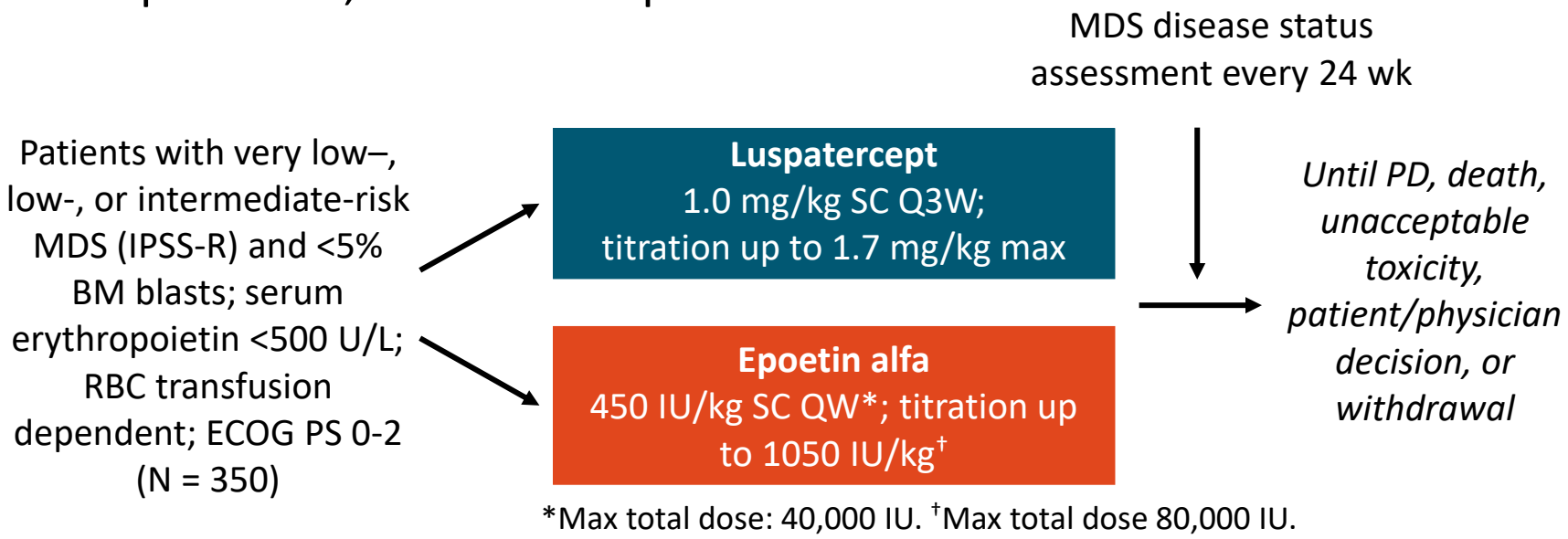
- Retrospective review, N = 184[2]
- Patients with higher TB significantly associated with lower probability of TI

Outcome	Luspatercept (N = 184)
≥8 wk TI in Weeks 1-24, %	32
≥8 wk TI in Weeks 1-48, %	38.6
Median duration TI, wk	27.9
≥1 Maximum approved dose, n (%)	144 (81)

1. Komrokji. ASH 2022. Abstr 1757. 2. Lanino. ASH 2022. Abstr 3088.

COMMANDS: Upfront Luspatercept vs Epoetin Alfa

- Open-label, randomized phase III trial



*Max total dose: 40,000 IU. †Max total dose 80,000 IU.

Post Tx Follow-up:

- **42-day follow-up:** AE reporting
- **Collection of transfusion data:** ≥8 wk after last dose or until end of trial, whichever is later
- **Long term:**
  - Malignancy/premalignancy monitoring
  - Progression to AML
  - Subsequent therapies
  - 5-yr survival from last dose or 3-yr survival from last dose (whichever is later) unless the patients withdraws, dies, or is lost to follow-up

- **Primary endpoint:** 12-wk RBC-TI with mean Hgb increase ≥1.5 g/dL
- **Key secondary endpoints:** 24-wk RBC-TI, Hgb change, HI-E, RBC-TI for ≥12 wk, time to first RBC transfusion, safety

Della Porta. ASH 2020. Abstr 2198. NCT03682536.

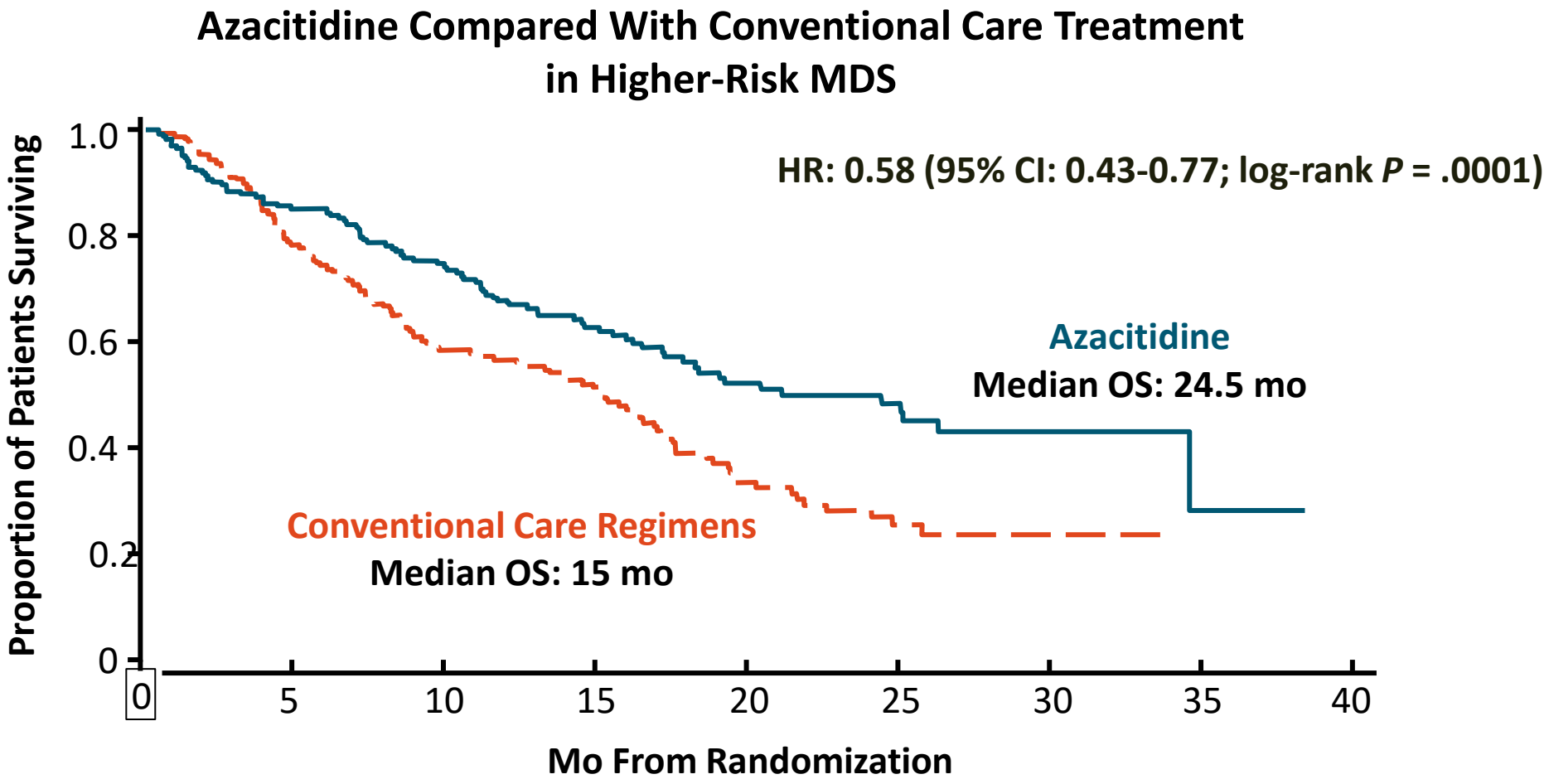
Novel Investigational Therapies in R/R TD LR-MDS: Imetelstat

- **Imetelstat (7.5 mg/kg IV/28 days)**
- **Transfusion dependent after ESA failure**
- Telomerase inhibitor targeting cells with short telomere lengths and active telomerase
- Phase II IMerge trial
  - 38% TI, median duration of response 1.3 yr[1]
  - Disease modifier: VAF decreased among responders[1-3]
  - Not clinically relevant hematologic toxicities (grade 3/4 neutropenia/thrombopenia: ~60%)[1]
  - On-target activity (hTERT reduction >50%) correlates with durable TI[4]
- Phase III completed
- Target malignant megakaryocytes

1. Steensma. JCO. 2021;39:48. 2. Fenaux. EHA 2019. Abstr S837.
3. Platzbecker. EHA 2020. Abstr S183. 4. Santini. ASH 2021. Abstr 2598.

Higher Risk MDS

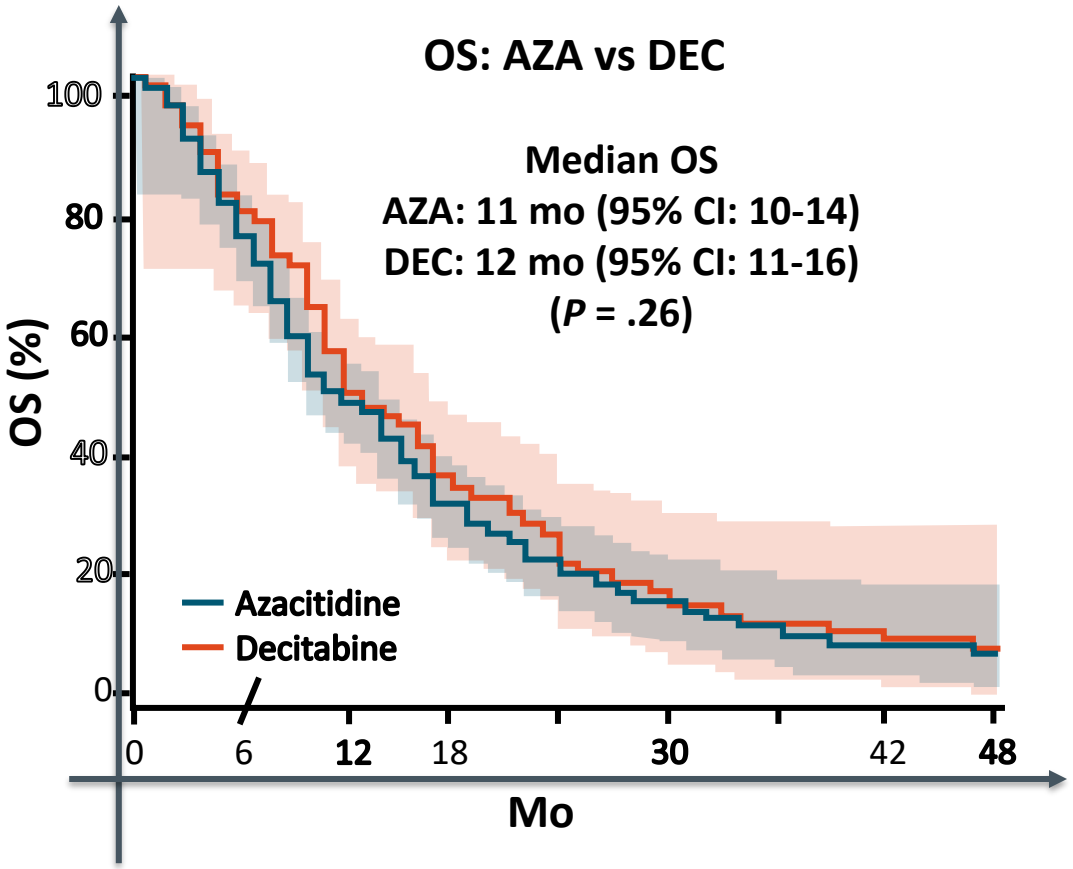
AZA-001: Azacitidine Efficacy in Higher-Risk MDS



Fenaux. Lancet Oncol. 2009;10:223.

Which HMA Would You Use?

Retrospective Analysis of HMA-Treated Patients With RAEB From SEER-Medicare Database

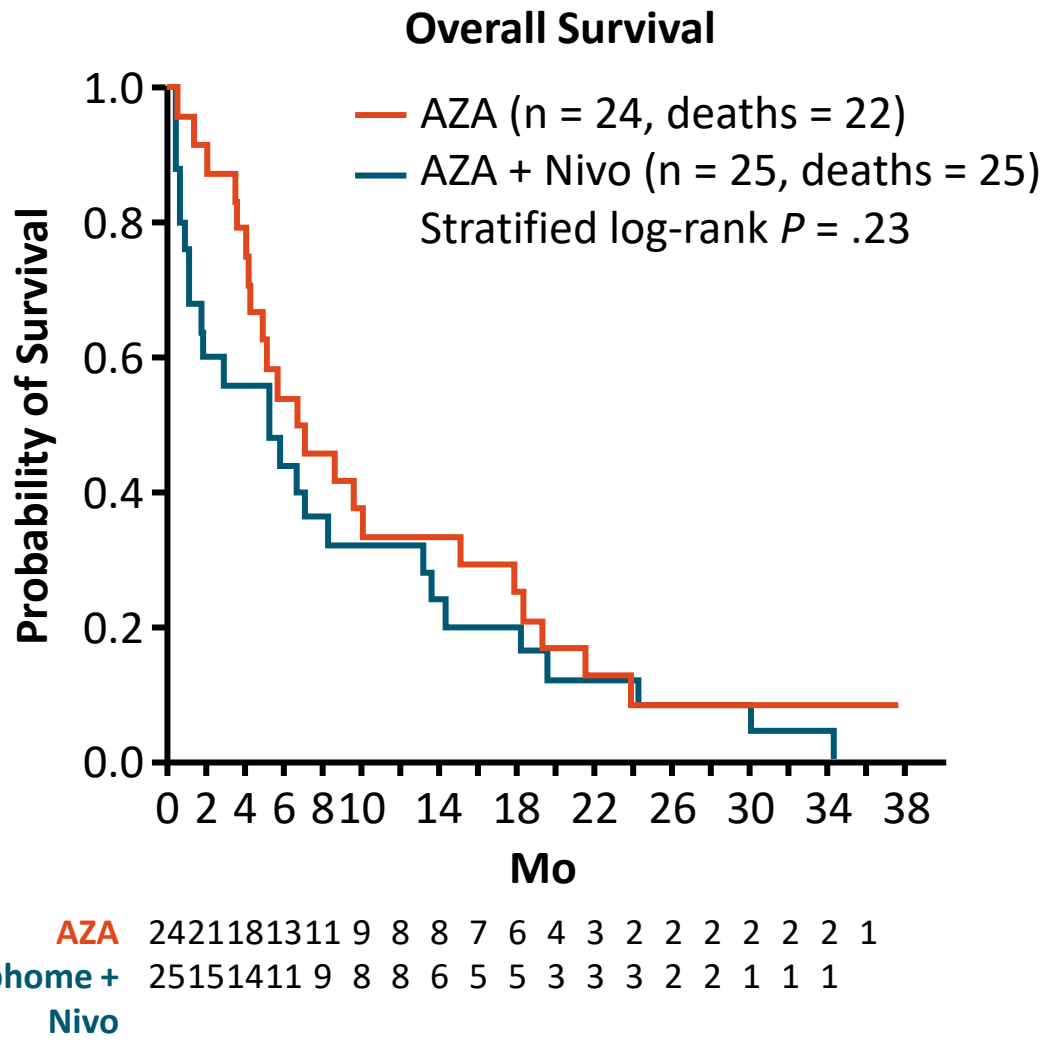


- 532 patients who received ≥10 days of therapy; ≥66 yr of age
- 78% received azacitidine, and 22% received decitabine
- Median OS for HMA-treated patients with RAEB: 12 mo (95% CI: 11-14)
- In multivariate analysis of OS, HR: 0.99 (95% CI: 0.78-1.24) indicating no significant improvement (or decrement) for decitabine compared with azacitidine

S1612: Azacitidine and Nivolumab vs Azacitidine in Newly Diagnosed Older Patients With AML or HR-MDS

- Randomized, phase II/III study; primary endpoint: OS
- Early study closure after 49 patients enrolled due to a higher 28-day mortality in the azacitidine-nivolumab arm
- SAEs: 93 AZA + Nivo vs 21 AZA
- Immune adverse events: pneumonitis (n = 2); diarrhea (n = 1); elevated AST (n = 2)

	AZA (n = 24)	AZA + Nivo (n = 25)	*P* Value
Early death			
▪ Alive >28 days	23 (96)	19 (76)	.098
▪ Died within 28 days	1 (4)	6 (24)	
Best response			
▪ CR	3 (12)	4 (16)	.66
▪ CRp/CRi	3 (12)	1 (4)	
▪ HE-E and HI-N and HI-P	1 (4)	0	
▪ HI-P only	0	1 (4)	
▪ MLFS	1 (4)	0	
▪ Stable disease	7 (29)	6 (24)	
▪ No response	9 (38)	13 (52)	



Assouline. Leuk Lymphoma. 2023;64:473.

VERONA: Venetoclax + Azacitidine in Treatment-Naive Patients With Higher-Risk MDS

- Randomized phase III trial

Patients with newly diagnosed HR MDS, IPSS-R >3 (intermediate, higher, very high risk); HSCT eligible; no previous HMA or venetoclax therapy; ECOG PS ≤2 (planned N = 500)

Venetoclax 400 mg QD (Days 1-14) + + Azacitidine 75 mg/m^2 (7 days within 9 calendar days/28-day cycle)

Placebo + Azacitidine 75 mg/m^2 (7 days within 9 calendar days/28-day cycle)

→ *Until relapse, disease progression, unacceptable toxicity, or HSCT*

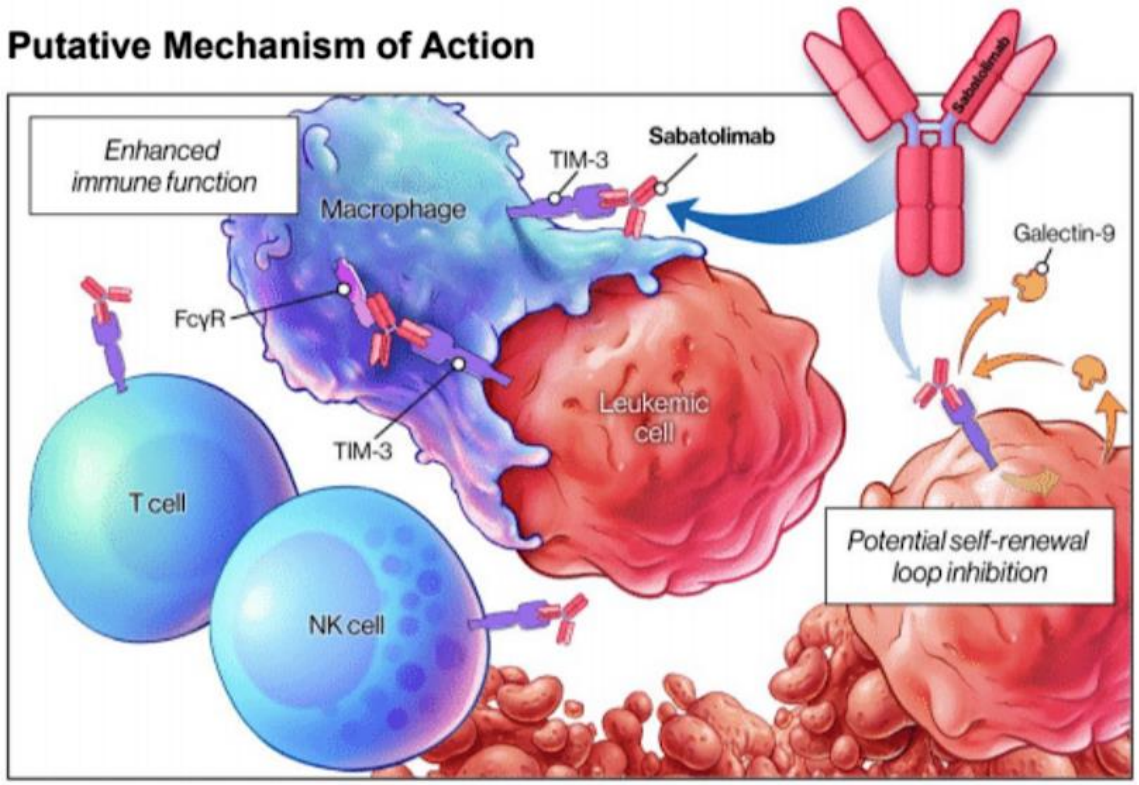
- **Primary endpoints:** CR, OS
- **Secondary endpoints:** transfusion independence, ORR, modified ORR, QoL, PRO

Zeidan. ASCO 2021. Abstr TPS7054. NCT04401748.

Primary results of Stimulus-MDS1: A randomized, double-blind, placebo-controlled Phase II study of TIM-3 inhibition with sabatolimab added to hypomethylating agents (HMAs) in HR-MDS

Sabatolimab is a novel immunotherapy targeting the immuno-myeloid regulator TIM-3

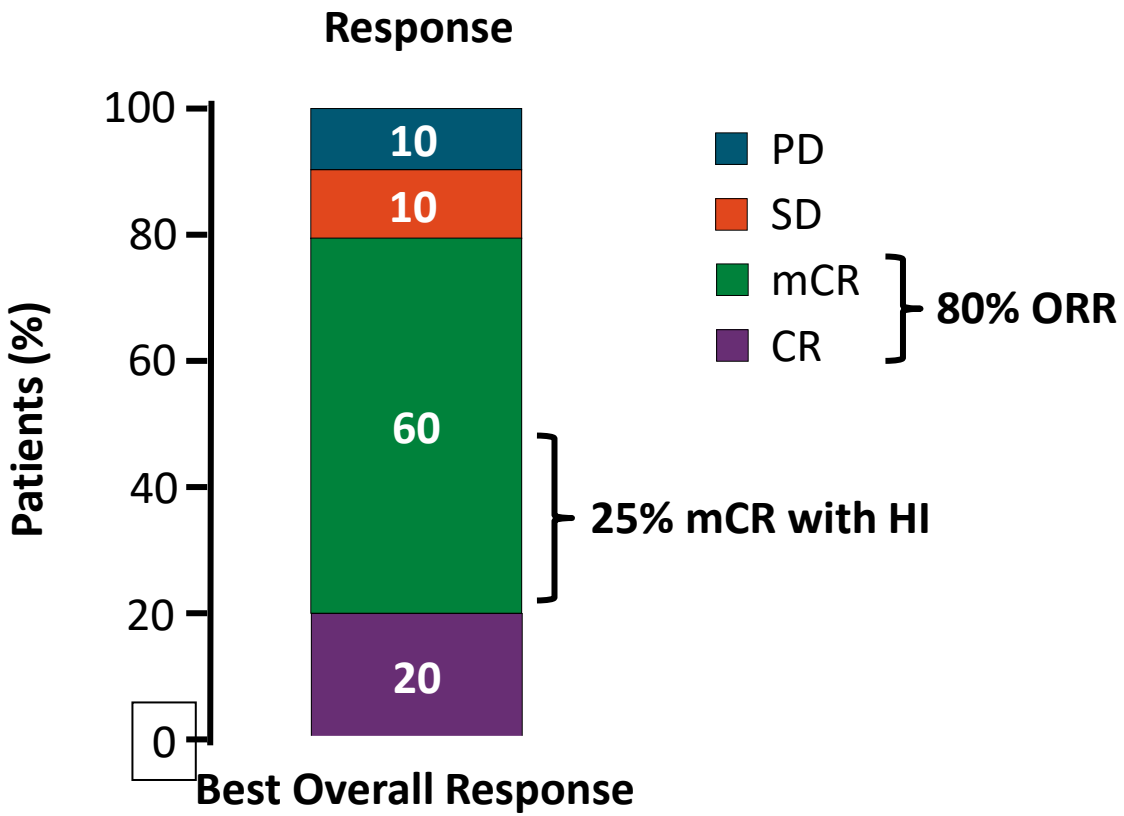
- TIM-3 is expressed on LSCs and blasts, but not on normal HSCs[1-5]
- As an inhibitory receptor, TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- Preclinical studies show that sabatolimab has a potential dual mechanism to combat myeloid malignancies by reactivating the immune system[6]
- Sabatolimab + HMAs demonstrated clinical benefit with favorable tolerability in a Phase Ib study in patients with HR/vHR-MDS[7]



Zeidan AM et al. ASH 2022; Abstract 853

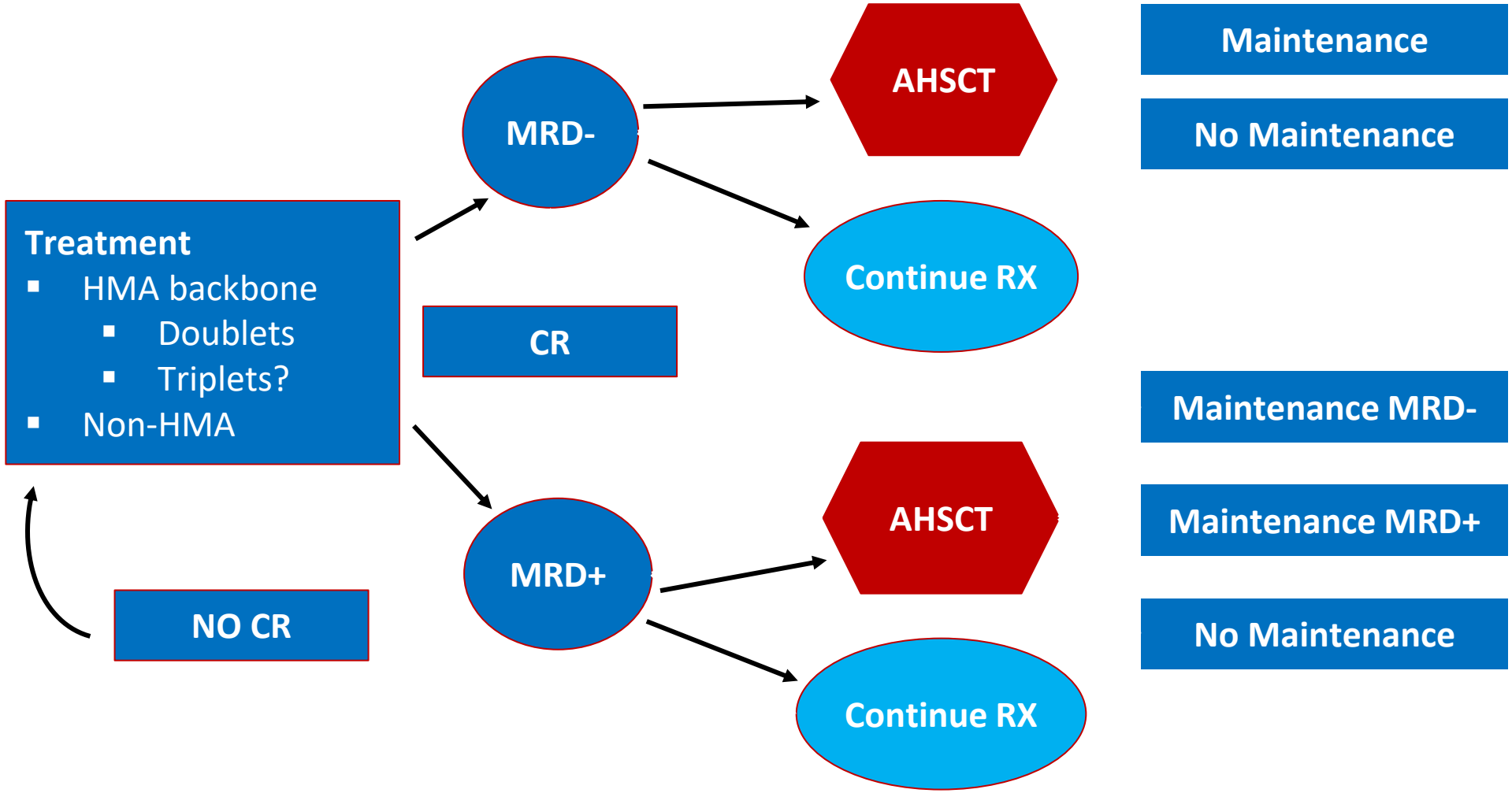
CPX-351 in HR-MDS

- Multicenter, dose-escalation, safety-expansion phase I study (N = 20)
- 75% of patients proceeded to allo-HCT; 15% pending allo-HCT
- 0 deaths within 30 days of induction
- 1 patient died from PD to sAML within 60 days of induction
- 1 patient did not proceed to allo-HCT due to poor performance status post induction and was taken off study



Jacoby. ASH 2021. Abstr 540.

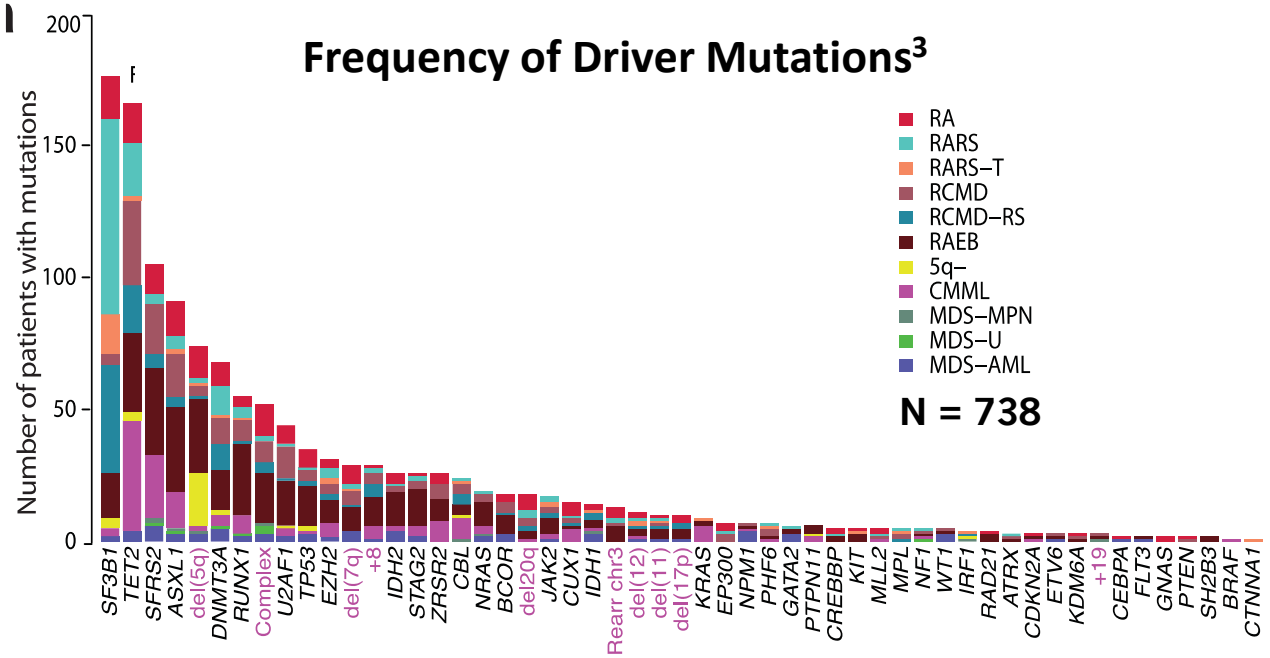
Total Therapy in HR-MDS



Clinical Drug Development for HR-MDS, Especially Post HMA Failure, Has Proven Very Challenging: Exiting the Black Hole

Challenges[1,2]

- Biological and molecular heterogeneity of disease
- Poor understanding of mechanisms of resistance, including primary vs secondary failure
- Poor condition of most patients at time of HMA failure
- Typical MDS patient is frail, late 70s in age, many with limited social support, live far from tertiary centers where trials are typically conducted



- >85% to 90% of patients have ≥1 mutation[3,4]
- >45 mutations, none specific to MDS[3,4]
- Only 5-6 mutations seen >10% cases[3,4]
- Average number of mutations per patient is 2-4[3,4]