Multidisciplinary Approaches to Cancer Symposium

Myelodysplastic Syndrome and Myeloproliferative Neoplasm: Molecular Markers & Management with Novel Drugs

Subheading: Myelodysplastic Syndrome: An Update on Diagnosis & Treatment

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Disclosures

- On the Speakers Bureau for Sanofi

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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

This presentation has been peer-reviewed and no conflicts were noted.

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:

- *Impact of race/ethnicity on prognosis of patients with myelodysplastic syndrome.*
- *Correlation of socioeconomic status and survival of elderly patients with MDS .*

MDS is now Myelodysplastic Neoplasms

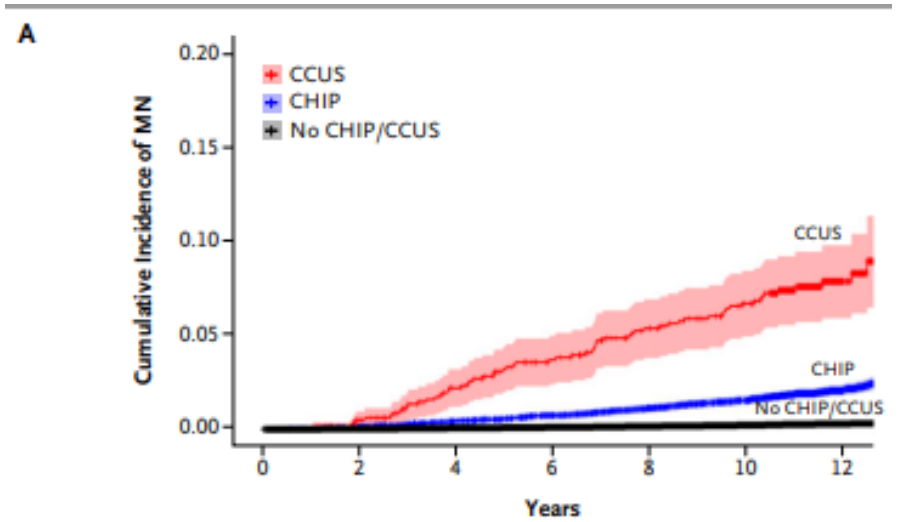
WHO 2022			ICC 2022		
MDS Defining Genetic Abnormalities	Blasts	MDS with Morphologically Defined		Cytopenia	Mutations
Low Blasts and Isolated 5q del (MDS-5q)	< 5% BM and < 2% PB	Low Blasts (MDS-LB)	MDS-del(5q)		Any, except multi hit TP53
Low Blasts and SF3B1 (MDS-*SF*3B1)		MDS hypoplastic (MDS-h)	MDS-*SF*3B1	≥ 1	Any except isolated del(5q), -7, del (7q), abn 3q.26.2 or complex
Biallelic TP53 inactivation (MDS-*bi*TP53)	< 20% BM and PB				
		MDS with increased blasts (MDS-IB)			
	5%-9% BM or 2%-4%PB	MDS-IB1	MDS-EB		Any, except multi-hit *TP53*
	10%-19% or 5%-19% PB or Auer Rods	MDS-IB2	MDS/AML		Any, except *NPM1* bZIP, CEBPA, or T*P53*

Adapted from
Khoury JD, et al. Leukemia 2022
Arber DA, et al. Blood 2022

CHIP: Clonal Hematopoiesis of Indetermined Potential
CCUS: Clonal Cytopenia of Undetermined Significance

- CHIP and CCUS
  - CHIP: Acquired mutations in BM stem cells leading to a mutated clonal population in peripheral blood. No Dx of myeloid disorder.
  - CCUS: CHIP with ≥ 1 persistent idiopathic cytopenia.

- CCUS - 10-fold increased risk of hematologic malignancy
  - Increased risk of cardiovascular disease.



Number at Risk

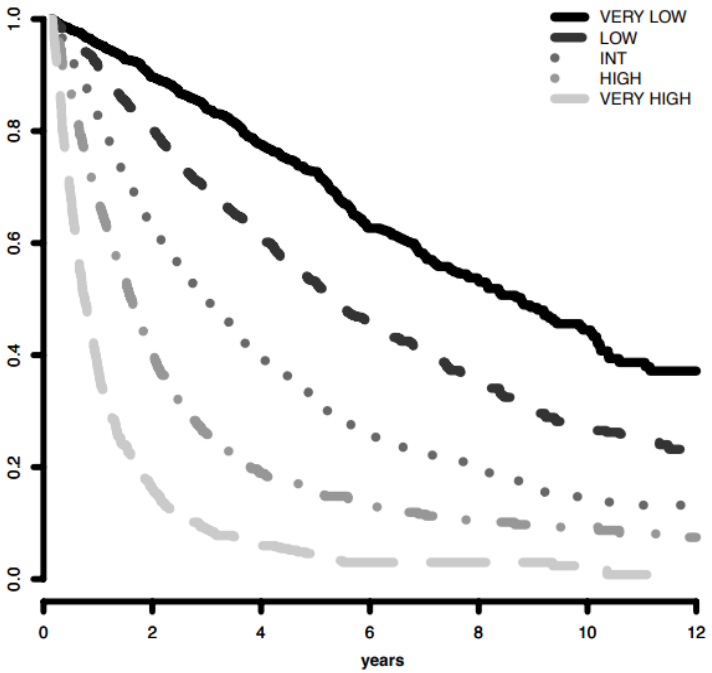
Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254

Weeks LD, et al; NEJM 2023

Revised International Prognostic Scoring System (IPPS-R) for MDS

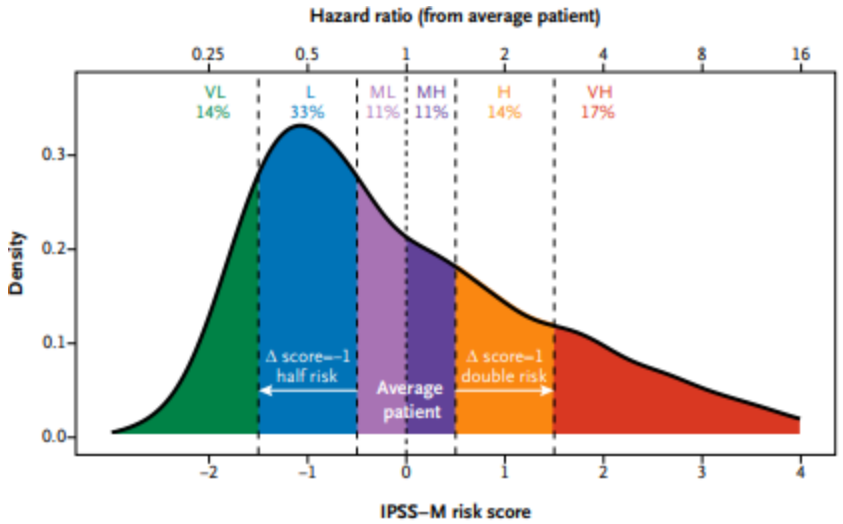
Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM blasts %	≤ 2		> 2% - < 5%		5% - 10%	> 10%	
Hemoglobin	≥ 10		8 - < 10	< 8			
Platelets	≥ 100	50 - < 100	< 50				
ANC	≥ 0.8	< 0.8					

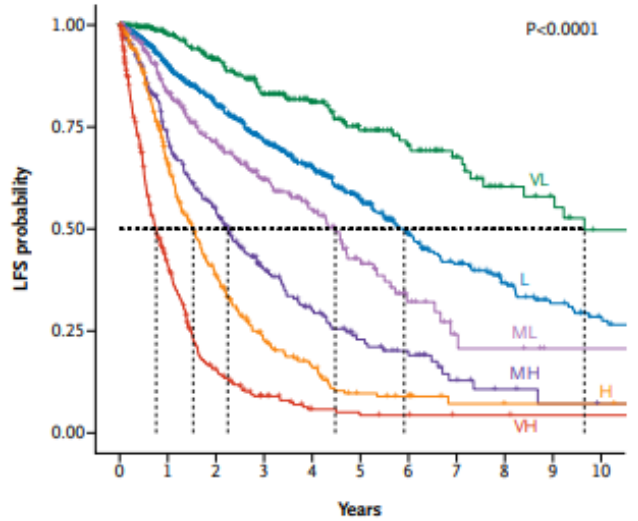
Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival (years)	Median AML evolution, 25% (years)	Hazard ratios OS/AML	Hazard ratios OS/AML
Very good (4%/3%)	-Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (72%/66%)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13%/19%)	Del(7q), +8, +19, i(17q), any other single or double	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4%/5%)	-7, inv(30/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very Poor (7%/7%)	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9



Greenberg PL, Blood. 2012;120(12): 2454-2465

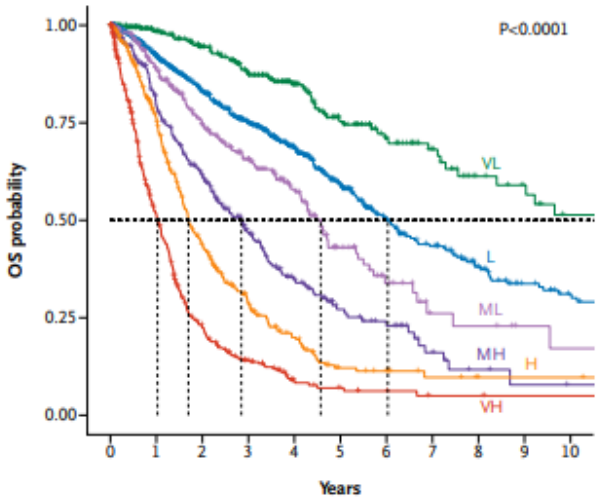
Molecular International Prognostic Scoring System for MDS (M-IPSS)





No. at risk

VL	315	243	199	153	110	75	55	40	26	22	16
L	788	584	442	331	240	162	107	80	56	40	30
ML	274	188	135	92	62	34	16	7	6	3	3
MH	258	166	114	65	41	25	18	8	4	2	1
H	353	194	101	48	29	13	10	4	3	3	3
VH	440	152	50	21	8	6	5	3	3	2	2



No. at risk

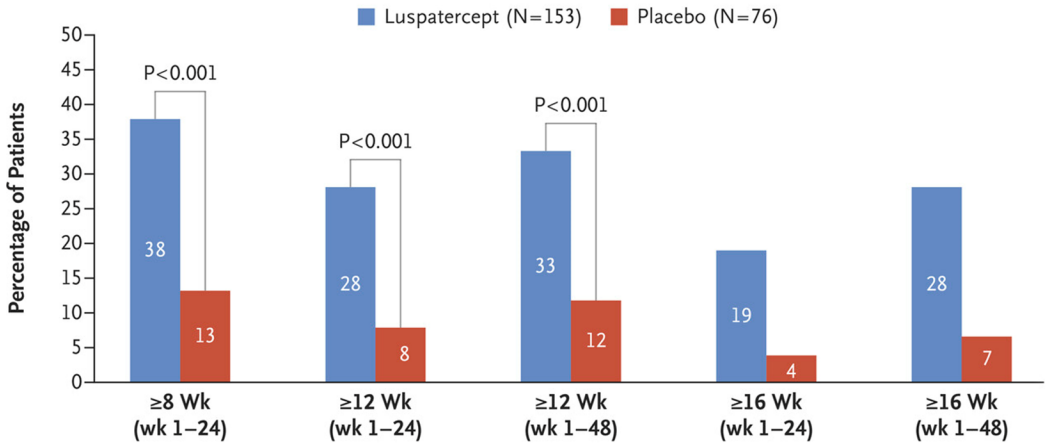
VL	344	267	224	180	126	82	57	42	28	24	18
L	852	640	496	382	270	176	112	83	57	40	31
ML	295	214	152	111	72	35	18	8	7	4	3
MH	278	191	134	80	48	27	20	9	4	2	1
H	367	235	121	65	37	15	12	6	3	3	3
VH	460	200	77	37	14	9	6	3	3	2	2

Bernard E; NEJM, 2022

Luspatercept in Patients with Lower-Risk MDS after ESAs

*Recombinant fusion protein that binds transforming growth factor β superfamily ligands to reduce SMAD2 and SMAD3 signaling

- **Phase 3 trial**
  - Patients **with very-LR, LR, or intermedediate-risk MDS** with ring sideroblasts, transfusion dependent.
  - **Luspatercept vs Placebo**.
  - Primary end point **TI for ≥ 8 during** weeks 1 through 24.
  - Secondary end point was TI **for ≥ 12 weeks**.



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. 382:140-51

Imetelstat in patients with lower-risk MDS who have R/R to ESA (IMerge Trial)

- Phase 3, double-blind, placebo-controlled trial.
- ESA-relapsed, ESA-refractory, or ESA-ineligible.
- Low or Intermediate-1 risk disease.
- Imetelstat vs placebo Q4W until progression or toxicity.
- Primary endpoint: **8-week RBC-TI**

	Imetelstat (n/%)	**Placebo (n/%)**
Patients	118	60
RBC-TI ≥ 8 wks	47 (40%)	9 (15%) (p = 0.0008)
Grade 3-4	107/118 (91%)	28/59 (47%)
Neutropenia	68%	3%
Thrombocytopenia	62%	8%

Platzbecker, U et al. *The Lancet*, Vol 403, Iss 10423, 249 – 260. Jan. 2024

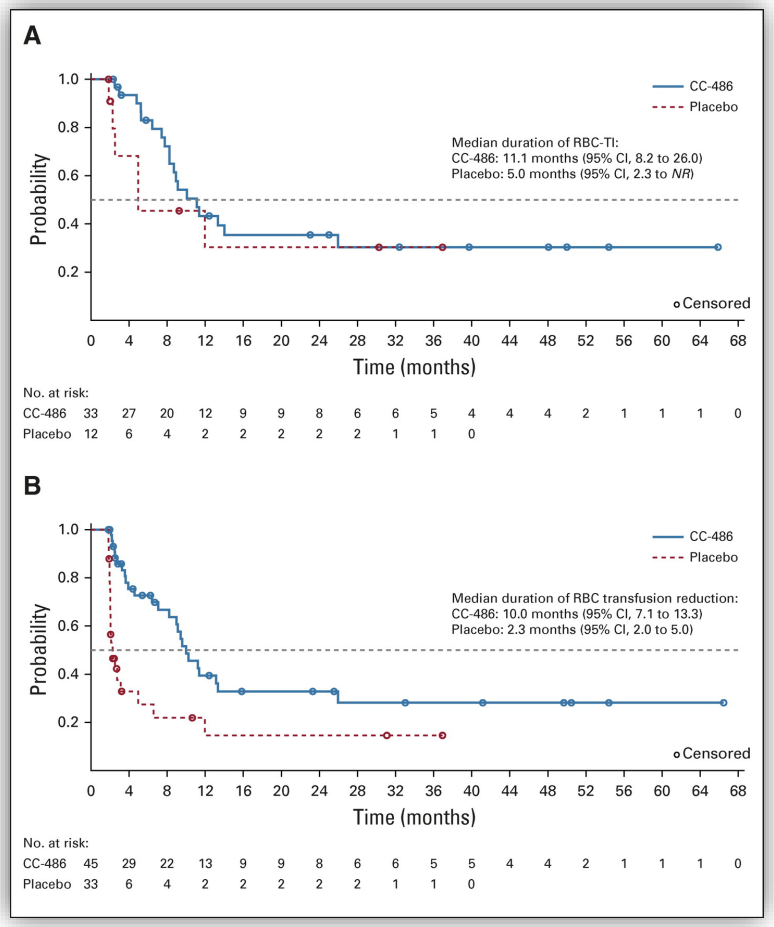
Oral Azacitidine in Patients With Lower-Risk MDS (Phase 3, Placebo Controlled)

CC-486 300-mg (107 pts) vs placebo (109 pts)

Primary end point: RBC TI

Median age: 74 years, mANC was 1.3 × 10^9/L.

	RBC-TI
CC-486 300mg	31%
Placebo	11%



Imbalance in deaths during the first 56 days.

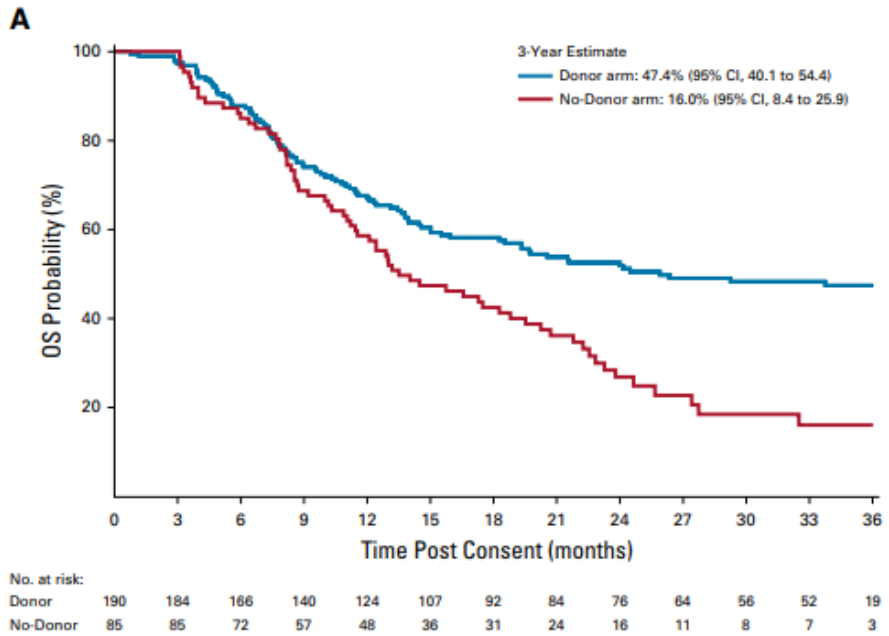
CC-486, n = 16; placebo, n = 6

Main cause: infections

Oral Aza is NOT IV Aza

Garcia-Manero, et al; J Clin Oncol 39:1426-1436. 2021

Hematopoietic Cell Transplantation in Patients 50-75 Years of Age With High Risk-MDS



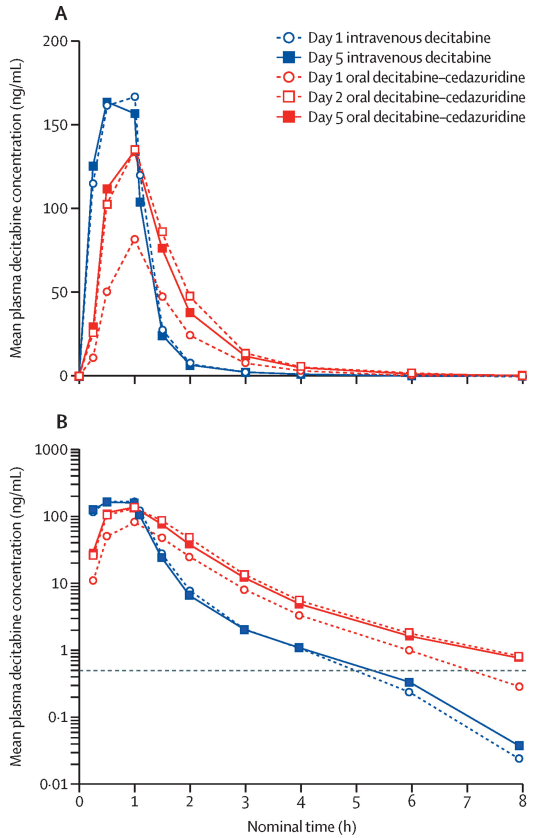
@ 3 years	Transplant	No Transplant
Overall Survival*	47.9%	26.6%
Leukemia-free survival	35.8%	20.6%
* absolute difference 21.3%		

Significant survival advantage in **older subjects** with higher-risk MDS who underwent RIC HCT vs no HCT.

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

Oral decitabine–cedazuridine versus IV decitabine for MDS and CMML (ASCERTAIN)

- 133 patients
  - 121 (91%) White
  - 4 (3%) Black or AA
  - 3 (2%) Asian
  - 5 (4%) not reported



CONCLUSION:
Oral decitabine–cedazuridine was pharmacologically and pharmacodynamically equivalent to intravenous decitabine.

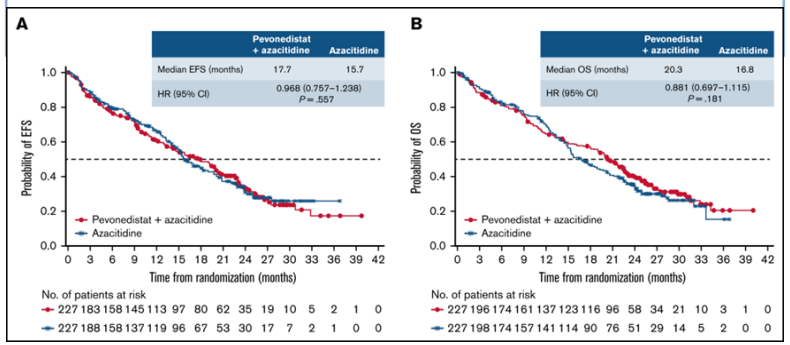
Garcia-Manero, Guillermo et al. *The Lancet Haem*, Vol 11, Iss 1, e15 - e26

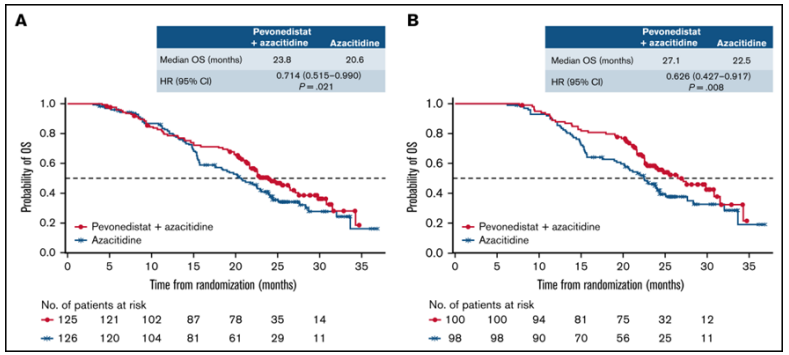
Combination Therapies for HR-MDS

	CR	Drug D/C
Aza	24%	8%
Aza + Len	24%	20%
Aza + Vor	17%	21%
Aza + Sabatolimab	19.6%	Phase 3
Aza + Magrolimab	33%	Phase 1B

Pevonedistat + Aza vs Aza in HR-MDS

mEFS and mOS not statistically different.





OS	Pevo + Aza	AZA
> 3 cycles	23.8	20.6 (p=0.021)
> 6 cycles	27.1	22.5 (p=0.008)

Sekeres et al; JCO 2017;35: 2745 – 53
Sallman et al: JCO. 2023;41:2815-2826.
Zeidan, A. M; EHA 2024
Ades, L et al; *Blood Adv* (2022) 6 (17): 5132–5145

Venetoclax and Azacitidine for Patients with High-Risk MDS

Ven 400 mg PO QD on Days 1-14 and Aza 75 mg/m ^{2} IV on D1-7 (or D 1-5, 8, and 9); on 28-day cycle.

Responses*	107 patients IPSS-R of > 3
CR	29.9% (95% CI, 21.4-39.5)
Median CR duration	16.6 mo (95% CI, 10.0-NR)
Median OS	26 mo (95% CI, 18.1-51.5)
Median TTNT	6.8 mo (95% CI, 5.6-8.3)
Subsequent treatment	57.9%
Subsequent HCT	39.3%
CR + PR + mCR	> 80%

*by International Working Group 2006 criteria

Garcia, et al; Vol. 142, Iss. Supp. 1 Nov. 2 2023.

FDA approves Ivosidenib for R/R MDS with mIDH1. Oct. 2023

- Open-label, single-arm.
- 18 adult patients
- 500 mg PO QD for 28-day cycles until progression, toxicity, or HCT.
- Median tx duration: 9.3 mo.

	18 Patients
CR	38.9% (95% CI: 17.3, 64.3)
Median time-to-CR	1.9 mo. (range, 1.0 to 5.6 mo.)
Median CR duration	Not estimable (range 1.9, 80.8+ mo.)
9 patients RBC or PLT TD	6/9 (67%) TI during any 56 days period
9 patients RBC or PLT TI	7/9 (78%) TI during any 56 days period

Box Warning:
Risk of differentiation syndrome - May be life-threatening or fatal.

Comparison of Demographics, Disease characteristics, and Outcomes between African Americans patients and White patients with MDS: A population-based study.

- SEER* (18 Registries, 2000-2018, Nov 2020 submission)
- 37,564 pats with confirmed MDS
- age ≥ 20
- Dx between 2000-2013
- MDS sub-types: low, intermediate, and high-risk disease.

	AA	W
3,7564	8%	92%
Males	49%	58%
Median Age	71	76
Metropolitan Areas	66.8%	60.2%
mOS	33 mo	26 mo

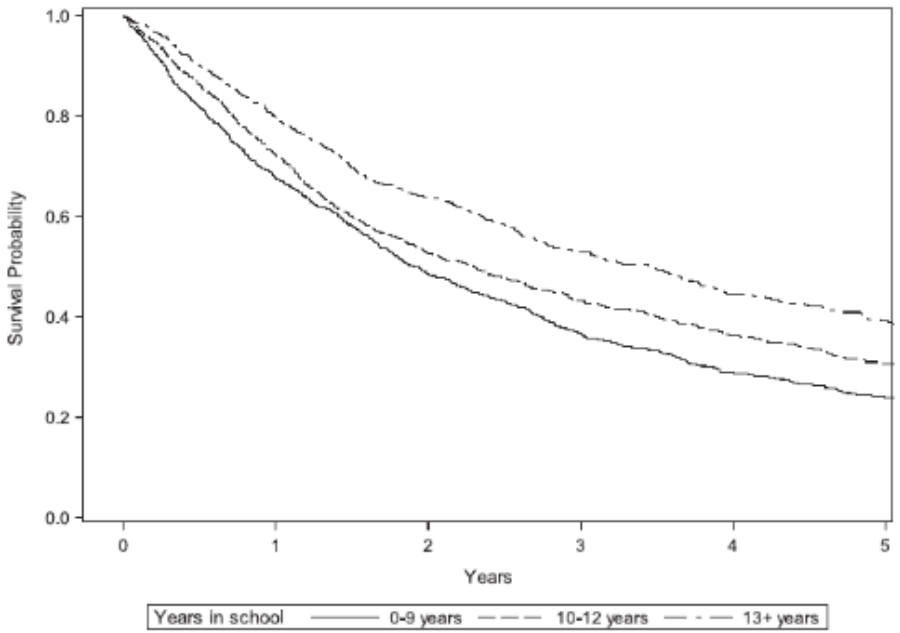
Multivariate Cox-PH model, HR for OS after adjusting for sex, age at diagnosis, histology, urban-rural continuum, income group was: 0.90 (95%CI 0.86-0.94), $p < 0.001$.

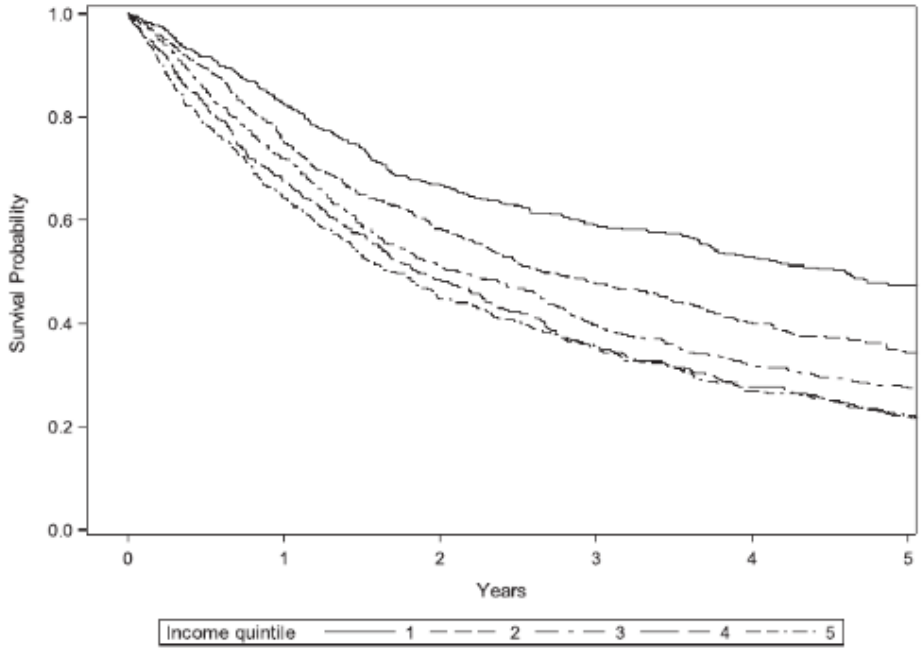
Limitations: retrospective nature, reliance on data only available in SEER, and the lack of data on subtypes of MDS.

*Surveillance, Epidemiology, and End Results

Lesegretain et al, J Clin Oncol 40, 2022 (suppl 16; abstr 7051)

Income, education and their impact on survival in patients with MDS.





Age at Diagnosis n= 2945	
≥ 75 y/o	1574 (53%)
< 75 y/o	1371 (47%)

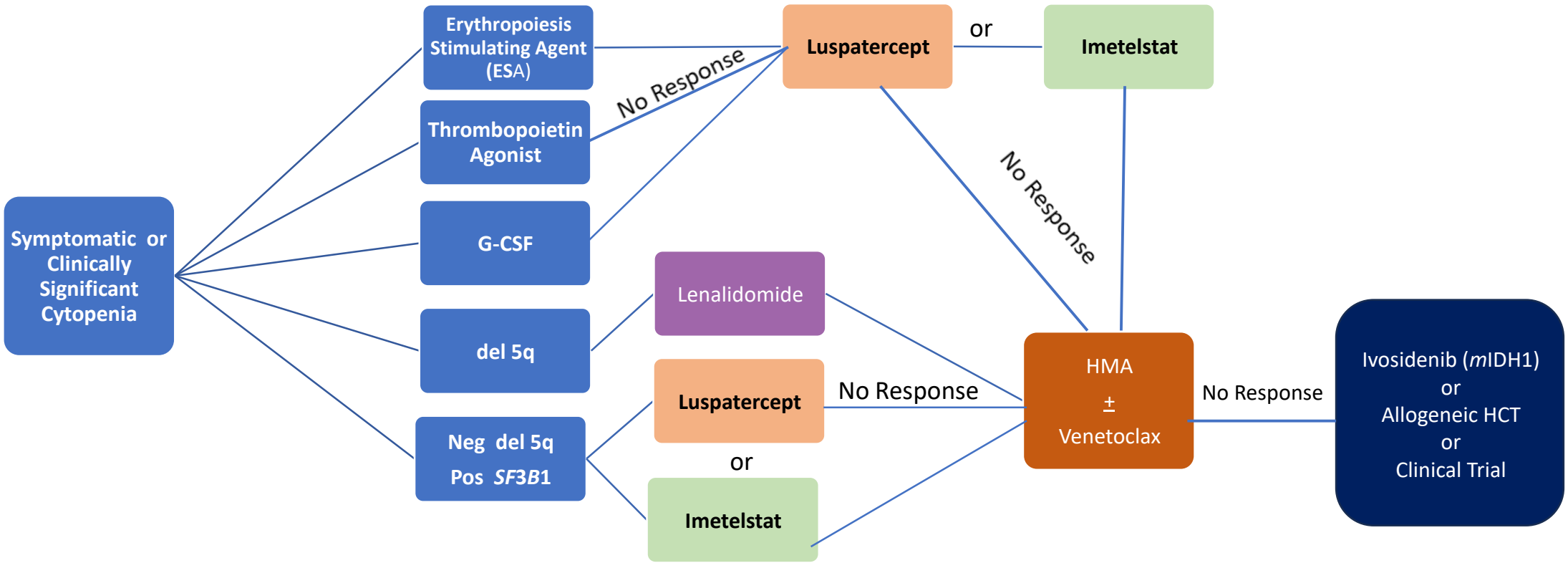
Mortality

- **50% higher** among patients in the **lowest income** category
- **40% higher** in patients with **mandatory school education** only compared to college or university education.

Larfors G, et al. Eur J Haematol. 2021.

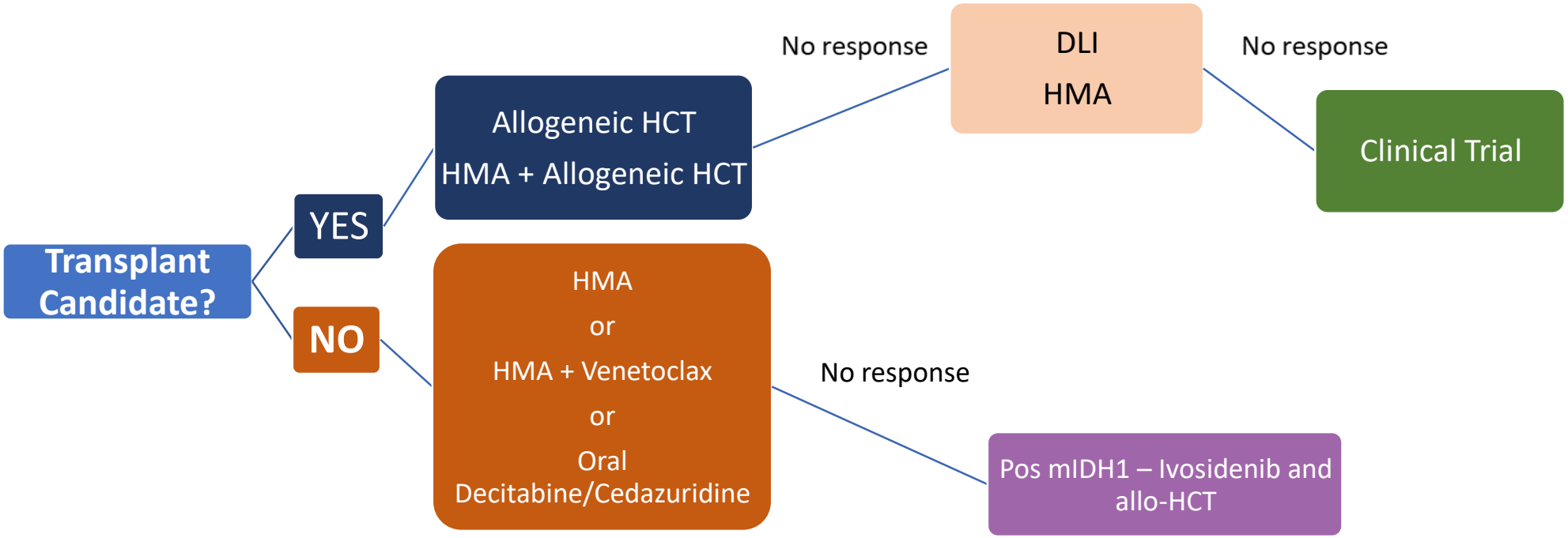
Mahalo (*Thank you*)

Low Risk MDS
(IPSS-R VERY-LOW-, LOW-, INTERMEDIATE-RISK DISEASE)



Adapted NCCN Guidelines Version 3.2024

High Risk MDS
(IPSS-R Intermediate, High, Very High-Risk Disease)



Adapted NCCN Guidelines Version 3.2024