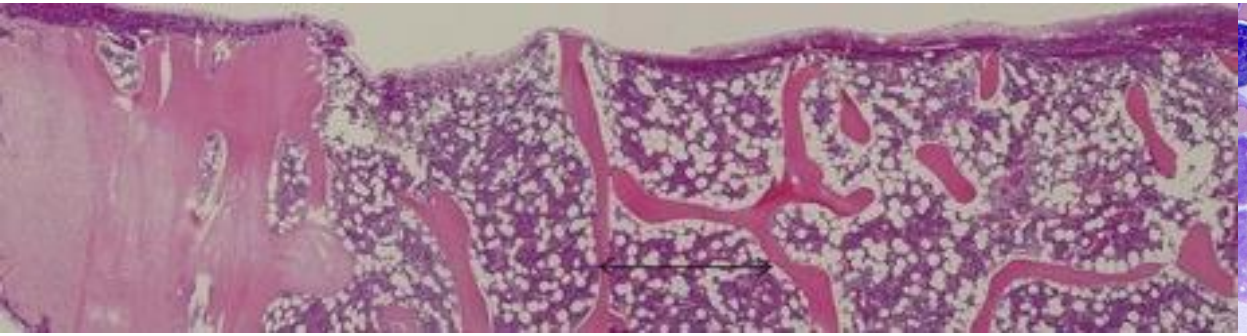
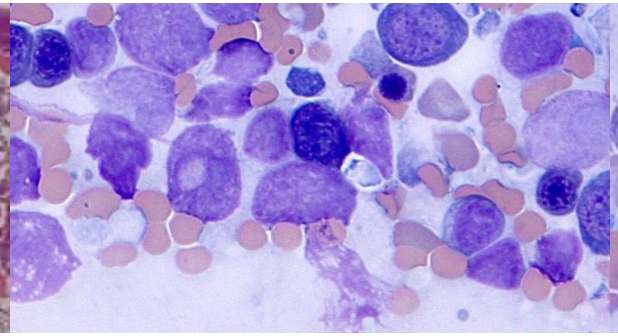
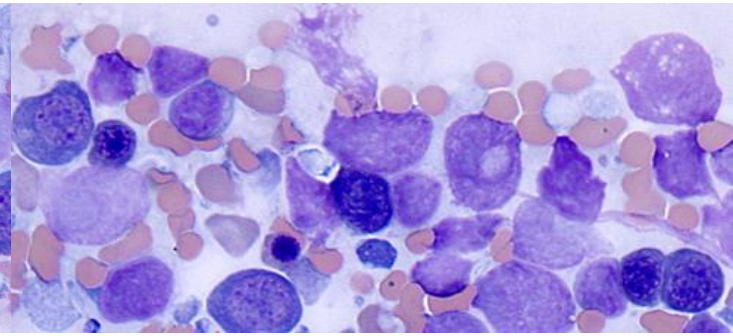
Myelodysplasia







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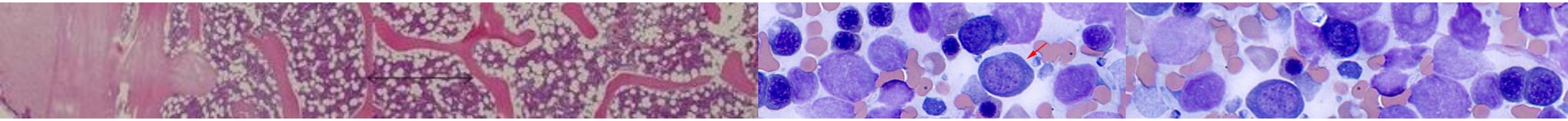
UNIVERSITY OF MIAMI HEALTH SYSTEM

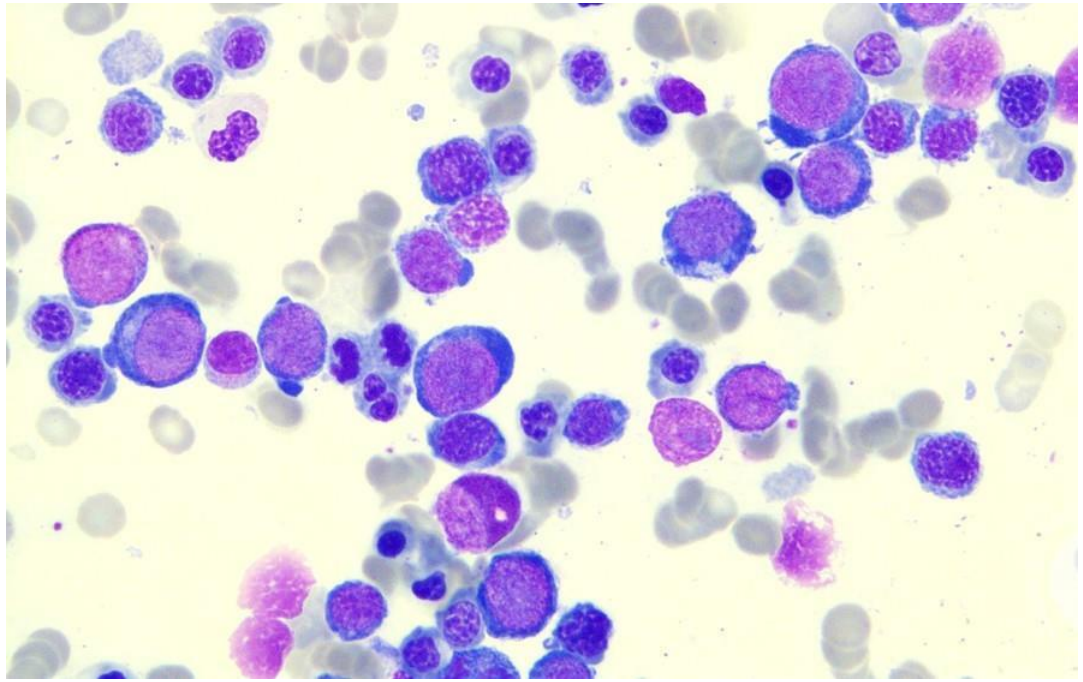
Presentation Roadmap



- Defining MDS
- Classification and Risk Stratification
- Lower Risk MDS
- Higher Risk MDS

MDS

- A group of malignant hematopoietic neoplasms characterized by:
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000
  - In US, true estimates ≈37,000-48,000
- Median age: 70 yr; incidence: 34-47/100,000 >75 yr



Haferlach. Pathobiology. 2019
SEER data. 2000-2009.

This Definition Maybe Challenged in the Future…

CCUS: Clonal Cytopenia of Undetermined Significance

The primary distinction between CCUS and lower-risk (LR)-MDS is the presence of pathologically defined dysplasia in >10% of any lineage.

High risk CCUS v. LR MDS… Are they similar?

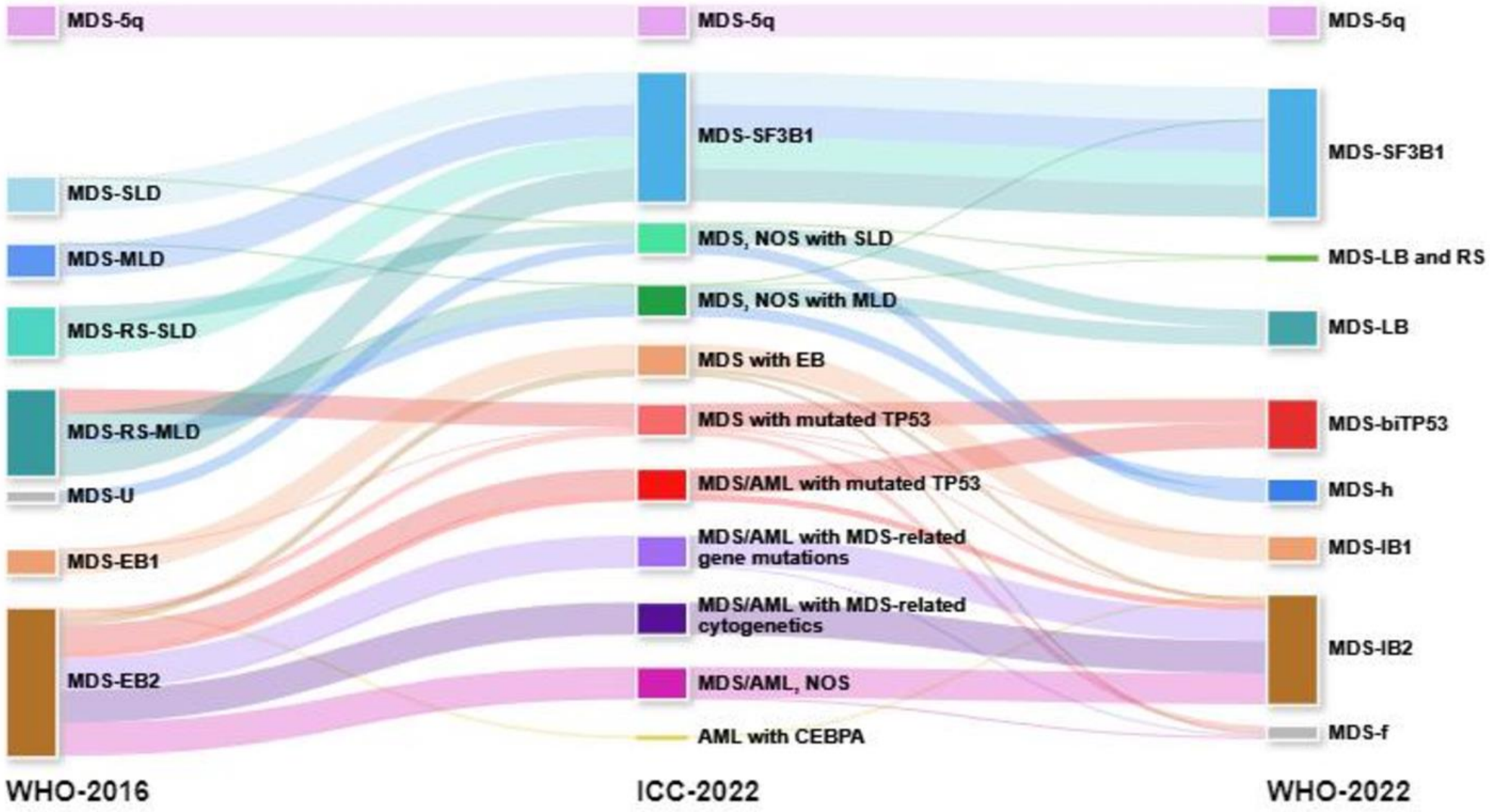
Xie et al. ASH Abstract 354, 2024

MDS Classification Systems

MDS WHO Classification	MDS ICC Classification
MDS w. Biallelic TP53 inactivation	
MDS with Increased Blasts	**MDS with Excess Blasts**
MDS IB-1 Peripheral Blood: 2-4% Bone Marrow: 5-9%	MDS EB Peripheral Blood: 2-9% Bone Marrow: 5-9%
MDS IB-2 Peripheral Blood: 5-19% Bone Marrow: 10-19%	MDS/ AML Peripheral Blood: 10-19% Bone Marrow: 10-19%
MDS with Fibrosis (MDS IB+ F)	

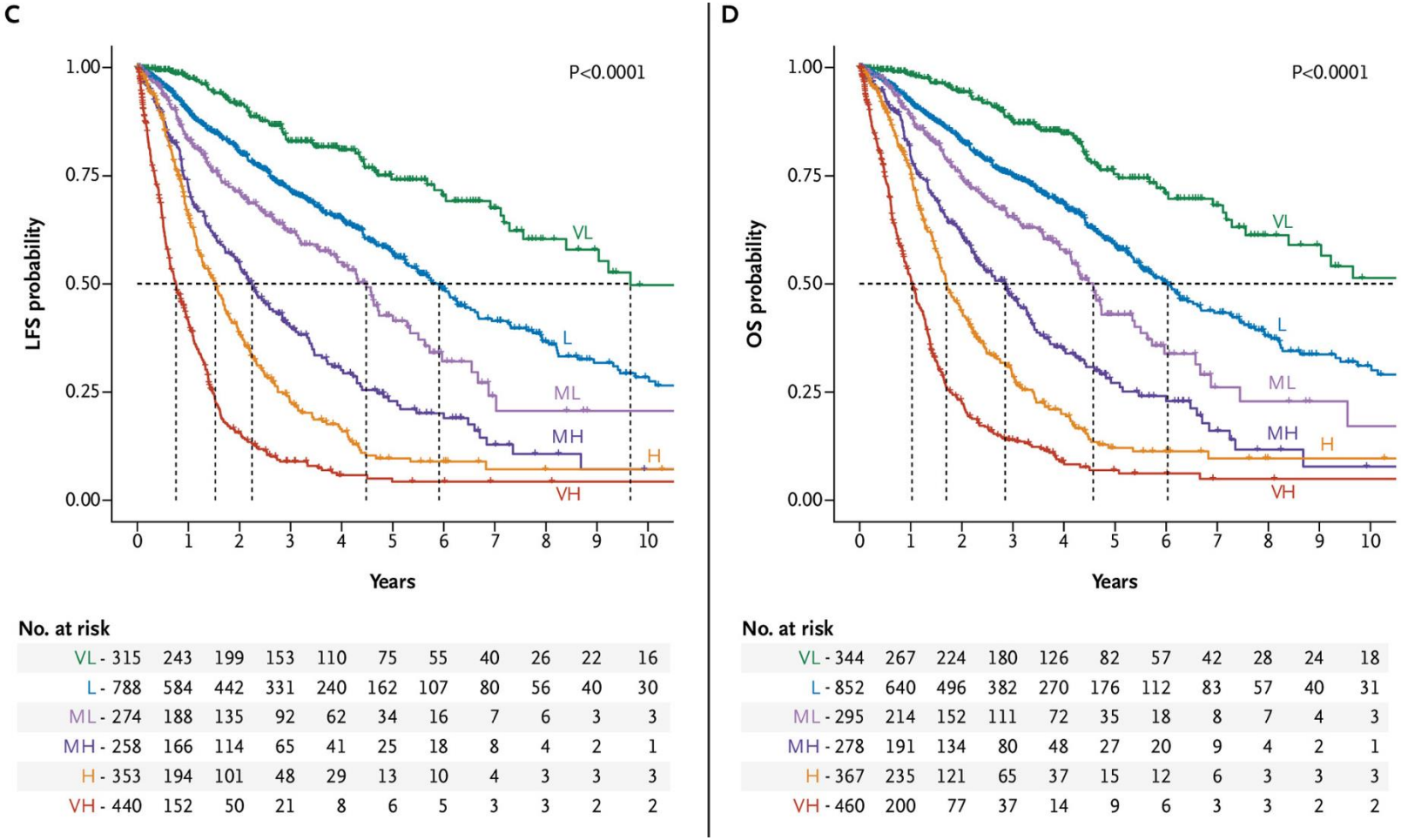
Data from Khoury et al. Leukemia 2022 and Arber et al Blood 2022

Having 2 systems is Confusing!



Lee et al. Blood Cancer Journal 2023

Prognostic Scoring: Use of IPSS-M



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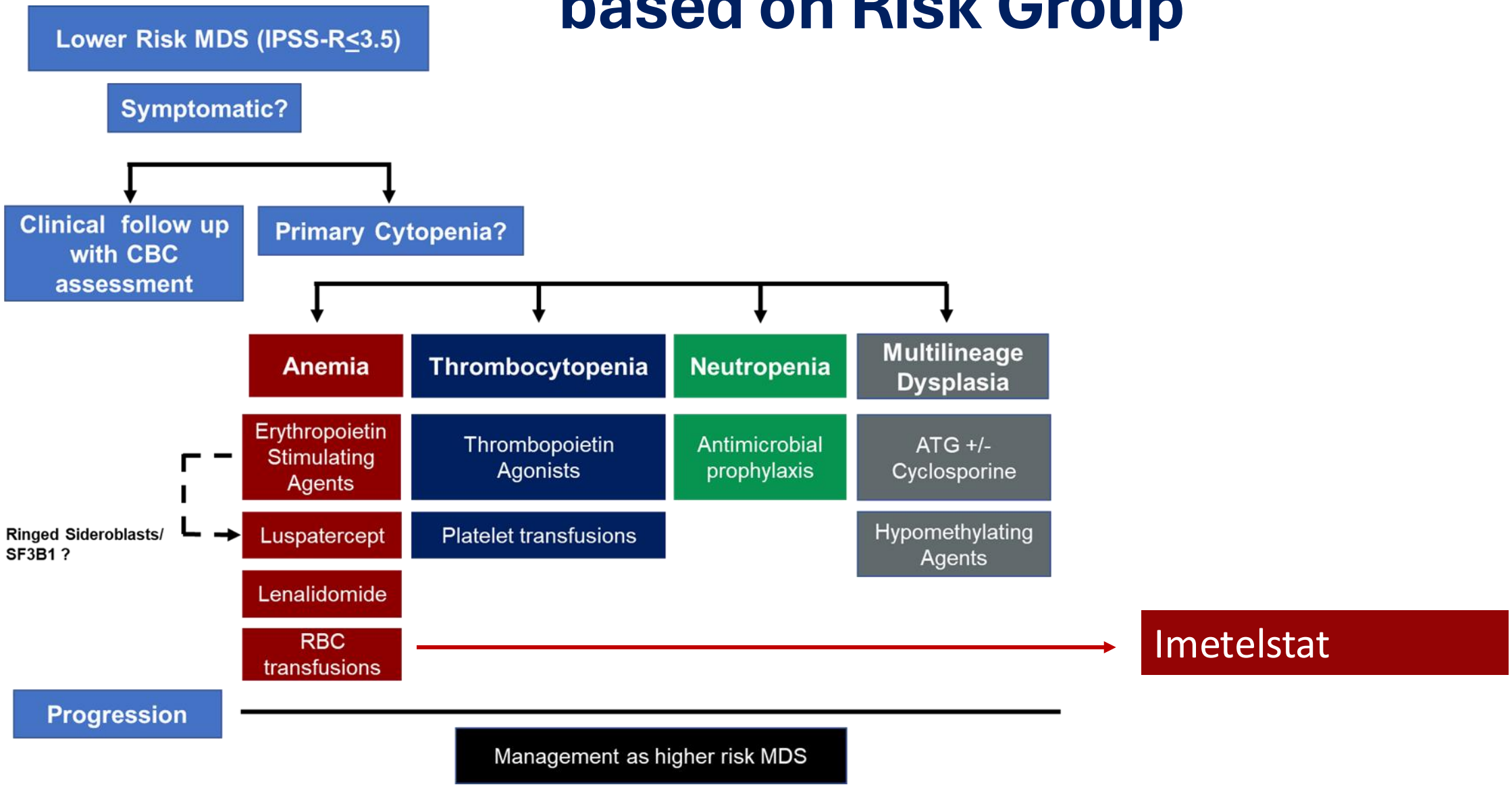
IPSS-R v. IPSS-M

- Many presentations over the past 2-3 years!
- Reclassification/ reorganization of trial data

Standard Treatment Options based on Risk Group



Adapted from Chandhok and Sekeres, Wintrobes Hematology Textbook

Erythropoiesis-Stimulating Agent (ESA) Treatment of MDS

- **When is the best time to start this treatment?**
  - At Diagnosis?
  - Transfusion Dependence?
  - Study Presented: GFM Randomized Phase III EPO-Pretar Trial

- **Should this be a single agent or combination**
  - Add back strategy or upfront
  - Non-RS patients with ESA failure Study Presented: GFM Combola Study

Park et al. Abstract 349 ASH 2024
Komrokji et al. Blood Advances 2023
Ades et al. Abstract 351 ASH 2024

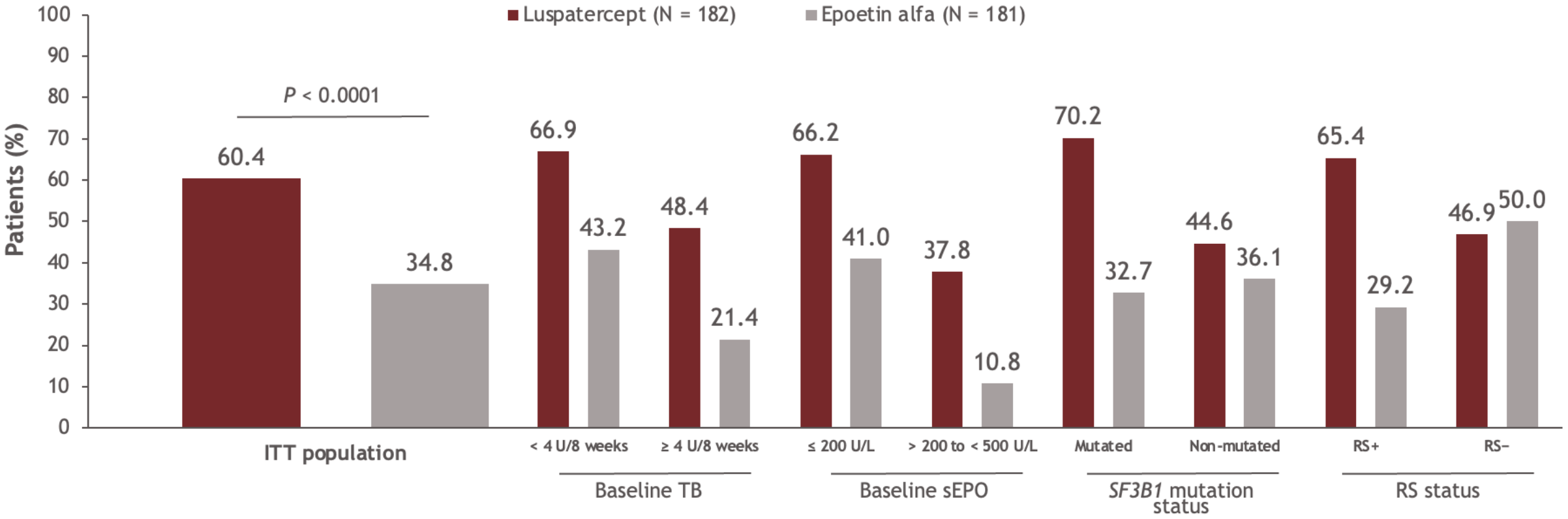
Approvals for Anemia in Lower Risk MDS

- **Luspatercept→ Key Trial: COMMANDS**

- Initial Approval was for SF3B1 MDS

FDA Label Expansion in 2023: "Treatment of anemia without prior erythropoiesis-stimulating agent (ESA) use in adult patients with very low– to intermediate-risk myelodysplastic syndrome (MDS) who may require regular red blood cell (RBC) transfusions."

COMMANDS:Primary Endpoint (RBC-TI ≥12w +Hb increase 1.5g/dL)



Durability of Response:

RBC-TI period ≥ 1 year (44.5% Luspatercept v. 27.6% w. ESA (P = 0.0003)

RBC-TI ≥ 1.5 years (30.2% Luspatercept v 13.8% ESA (P < 0.0001))

Subgroup Benefits: Luspatercept showed superior RBC-TI across subgroups, including RS-negative status, low baseline erythropoietin levels, and non-mutated SF3B1.

Progression Rates to HR MDS or AML: Similar

Garcia Manero, ASH 2023, Abstract 193
Garcia Manero, ASH 2024 Abstract 350

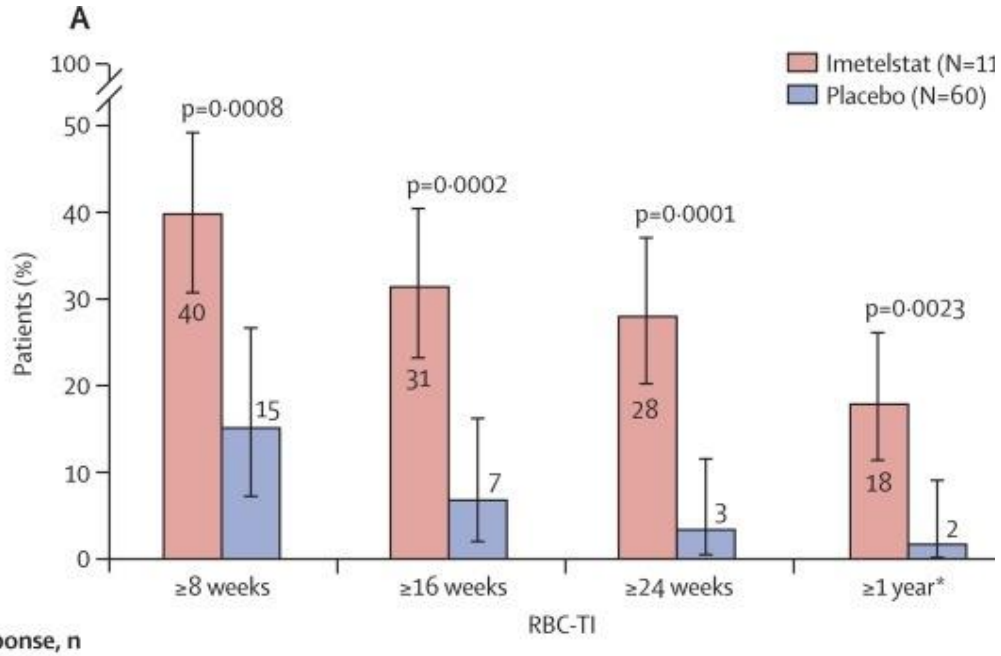
Approvals for Anemia in Lower Risk MDS

Imetelstat→ Key Trial: IMerge

FDA Approval in 2024

“For adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring four or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs).”

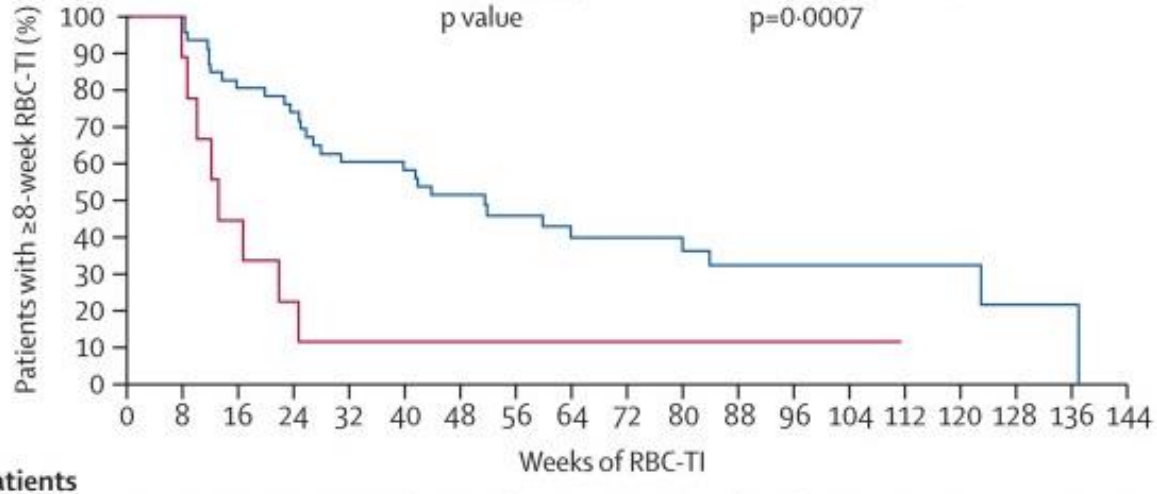
IMerge: Imtelstat



Patients with response, n (% [95% CI])	≥8 weeks	≥16 weeks	≥24 weeks	≥1 year*
Imetelstat	47 (40% [31–50])	37 (31% [23–41])	33 (28% [20–37])	21 (18% [11–26])
Placebo	9 (15% [7–27])	4 (7% [2–16])	2 (3% [0·4–12])	1 (2% [0·04–9])

B

Patients with 8-week transfusion independence	Weeks of RBC-TI, median (95% CI)
Imetelstat (n=47)	51·6 (26·9 –83·9)
Placebo (n=9)	13·3 (8·0–24·9)
HR (95% CI)	0·23 (0·09–0·57)
p value	p=0·0007



Number of patients																				
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0

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Platzbecker et al. Lancet December 2023
Komrokji, ASH 2023, Abstract 194

Imtelstat Update

Reduced Transfusion Burden

Quality of Life (QOL):

Imetelstat improved fatigue (FACIT-Fatigue scores)

Maintained QOL and anemia symptom control, while placebo showed worsening.

Impact of Prior Therapy:

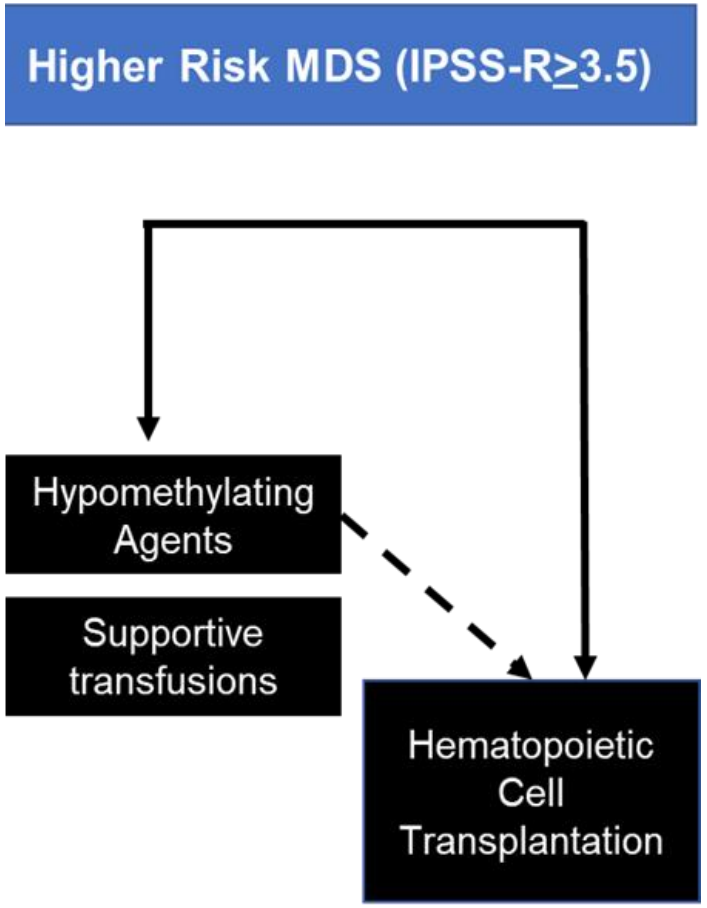
Small numbers, but efficacy seen in ESA treated or ineligible, Lenalidomide treated, Luspatercept treated, and HMA treated patients

Platzbecker, Abstract 352, ASH 2024
Sekeres et al. Abstract 3210 ASH 2024

Big Picture Questions

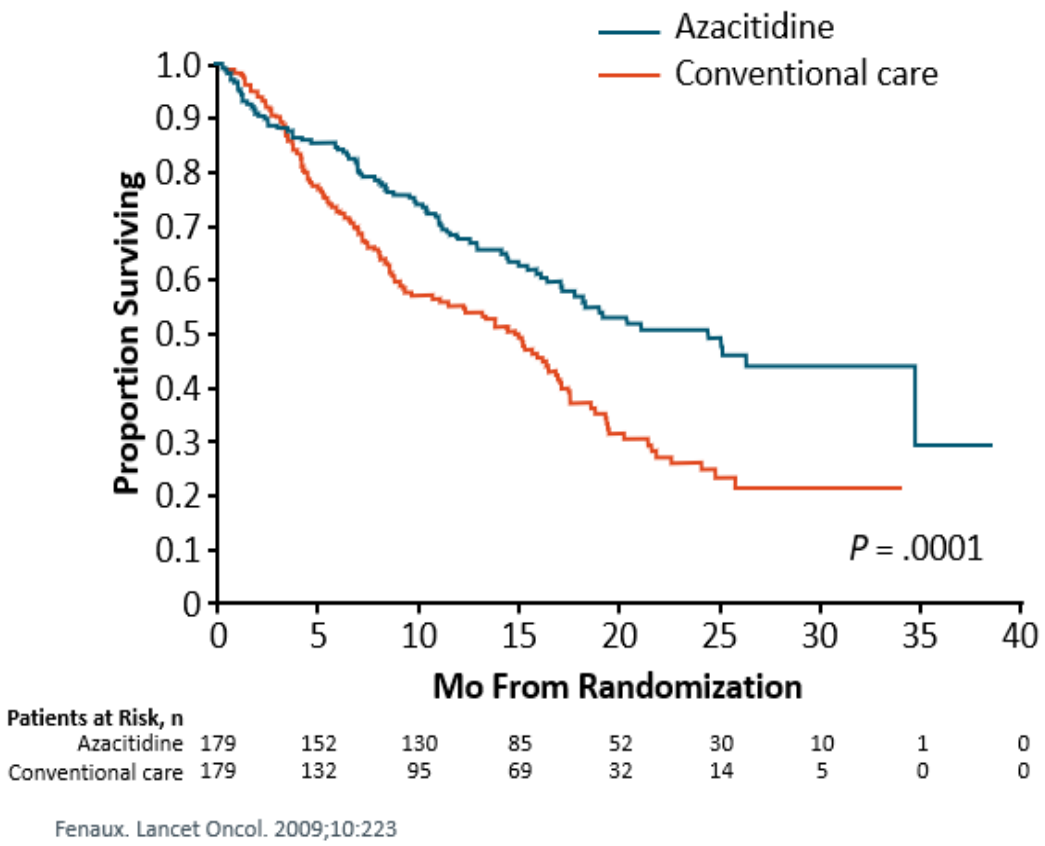
- How to optimize sequencing therapies?
- How do we best utilize these therapies?
- To start earlier or later?

Standard Treatment Options Based on Risk Group



Chandhok and Sekeres, Wintrobes Hematology Textbook

Higher Risk MDS



Fenaux. Lancet Oncol. 2009;10:223

We are desperately waiting for new agents!

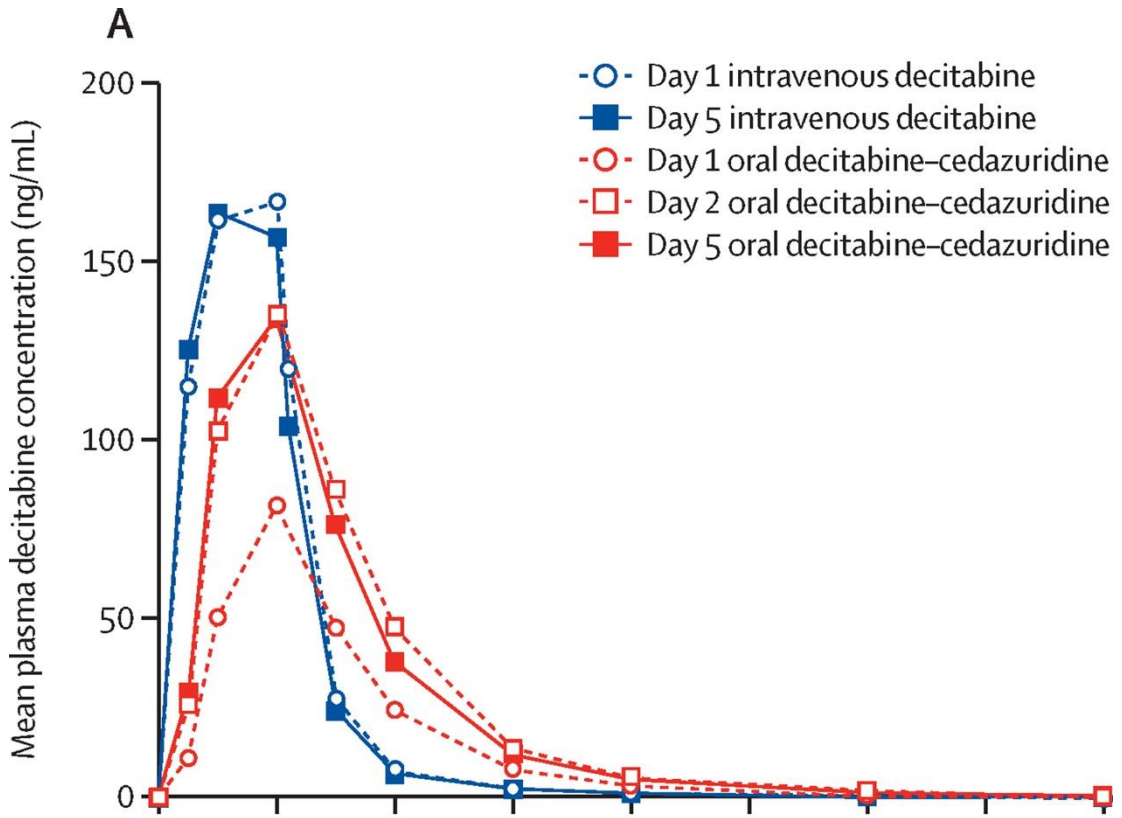
HMAs still win

- **Phase III AZA-001 study (N = 358)**
  - Subset analysis in patients >75 yr of age (n = 87; ~1/4 of randomized patients)
- **2-yr OS superior with azacitidine (*P* = .0003)**
  - Azacitidine: 55%
  - Conventional care: 15%
- **No significant difference in the rate of bleeding or infections**

Oral HMA: Decitabine and Cedazuridine

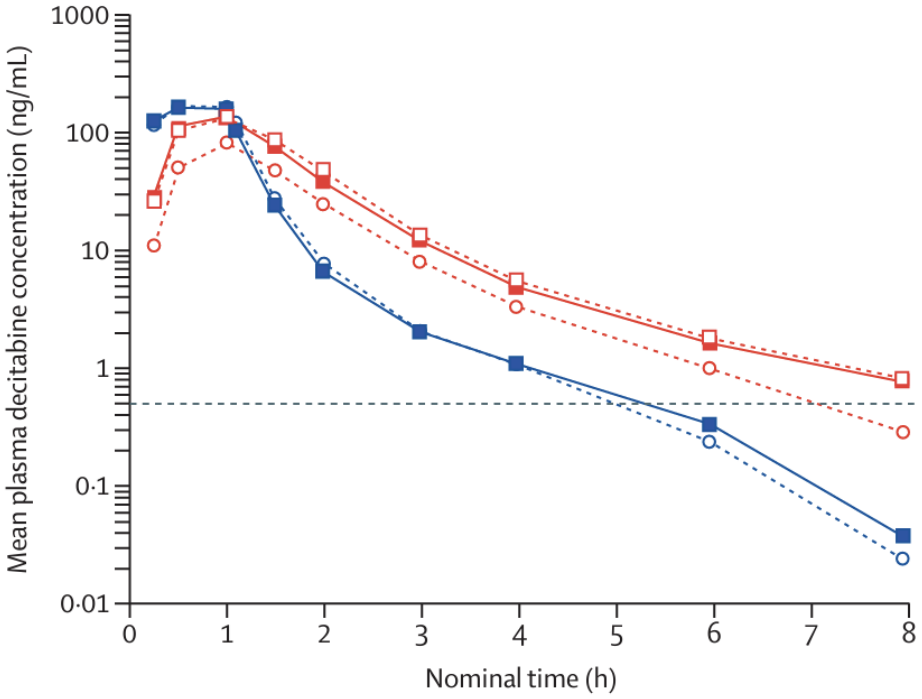
- FDA Approval in 2020→ **Key Trial: ASCERTAIN**

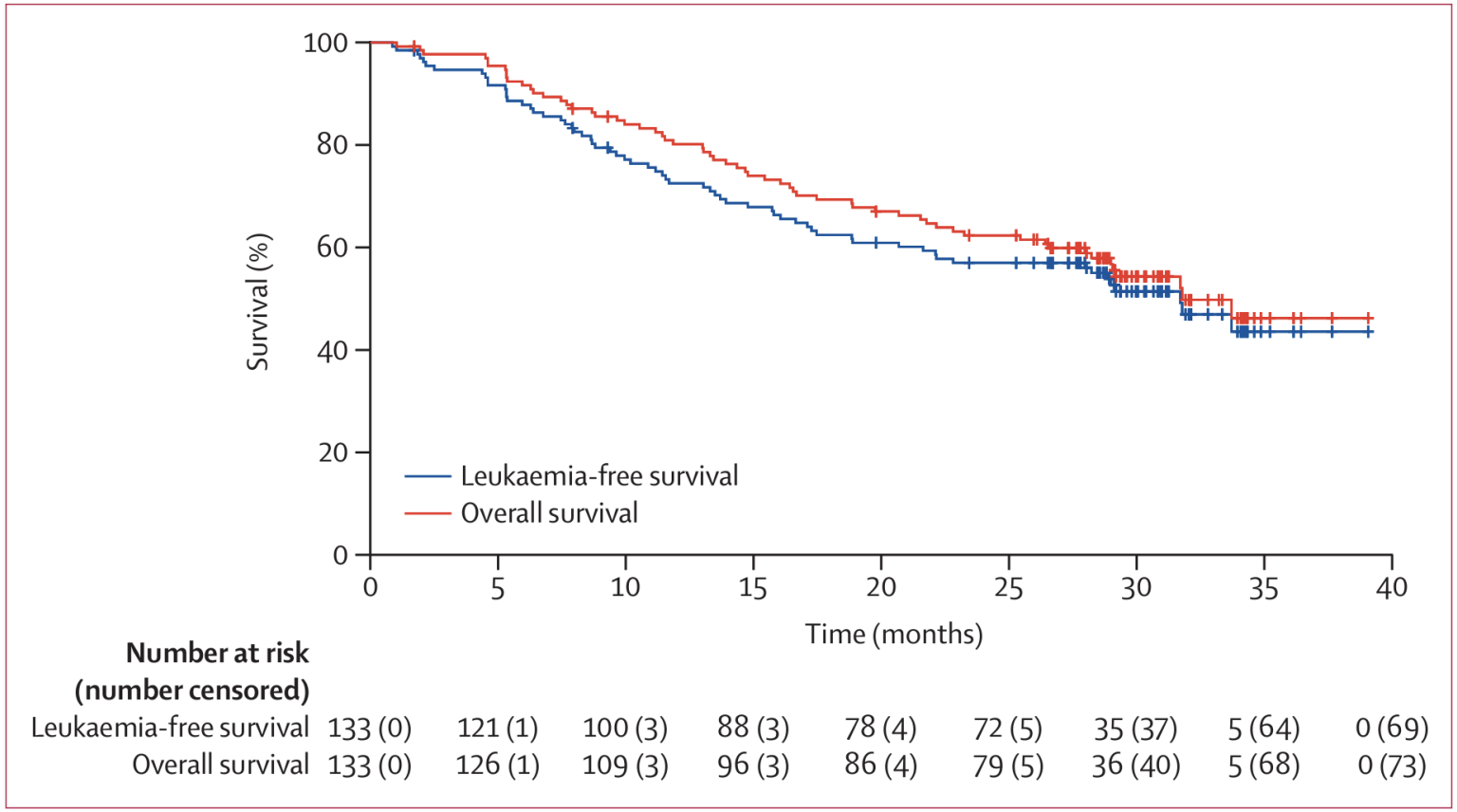
Trial based on pharmacokinetics



Garcia Manero et al. Lancet 2024

Ascertain Trial: Oral Decitabine- Cedazuridine





Number at risk (number censored)									
Leukaemia-free survival	133 (0)	121 (1)	100 (3)	88 (3)	78 (4)	72 (5)	35 (37)	5 (64)	0 (69)
Overall survival	133 (0)	126 (1)	109 (3)	96 (3)	86 (4)	79 (5)	36 (40)	5 (68)	0 (73)

Figure 3: **Leukaemia-free survival and overall survival**

Garcia Manero et al. Lancet Haem. January 2024

Combinations: Some Recent Disappointing results

- Eprenetapopt (APR-246) + AZA
- Magrolimab+AZA (ENHANCE trial)
- Pevonidostat+AZA v. AZA (PANTHER trial)
- Sabatolimab+HMA vs. HMA+placebo (STIMULUS trial)

Most Recent:

- Tamibarotene+ AZA v. Placebo+ AZA (SELECT-MDS-1 Phase 3 trial)

Anticipated: VERONA Study

Venetoclax + AZA versus AZA monotherapy
Phase 3 study

Primary Endpoint: Overall Survival

More to Come…

Thank you for your Attention!