How Do We Treat MDS?

MDS Foundation MDS Patient & Family Forum Agenda

May 11, 2024

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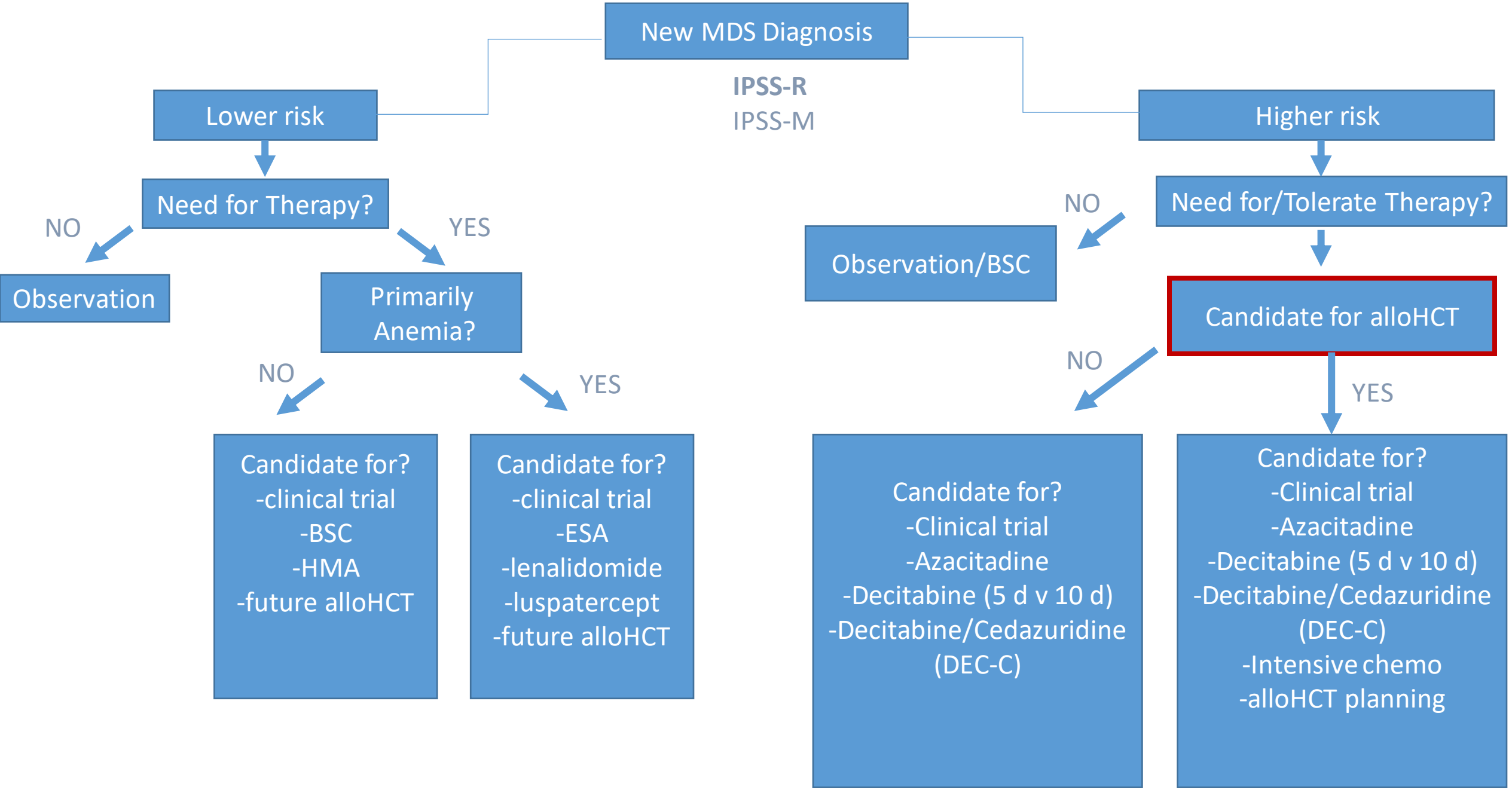
New MDS Diagnosis
IPSS-R
IPSS-M
Lower risk
Higher risk
Need for Therapy?
NO
YES
Observation
Primarily Anemia?
NO
YES
Candidate for?
-clinical trial
-BSC
-HMA
-future alloHCT
Candidate for?
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-ESA
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-luspatercept
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Observation/BSC
Need for/Tolerate Therapy?
Candidate for alloHCT
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Candidate for?
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-Azacitadine
-Decitabine (5 d v 10 d)
-Decitabine/Cedazuridine (DEC-C)
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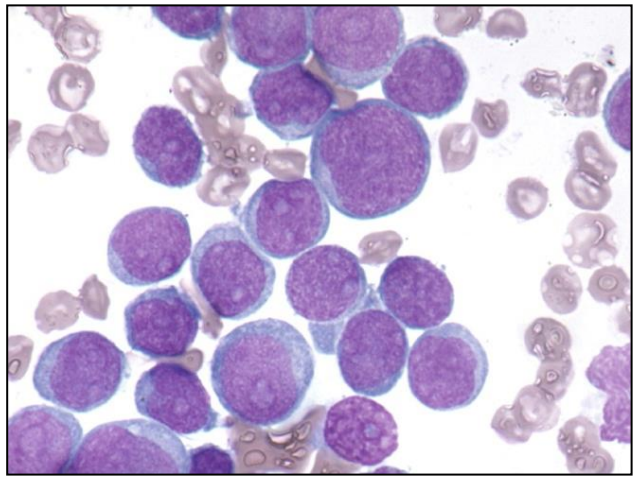
-Intensive chemo
-alloHCT planning

How do we decide on therapy?

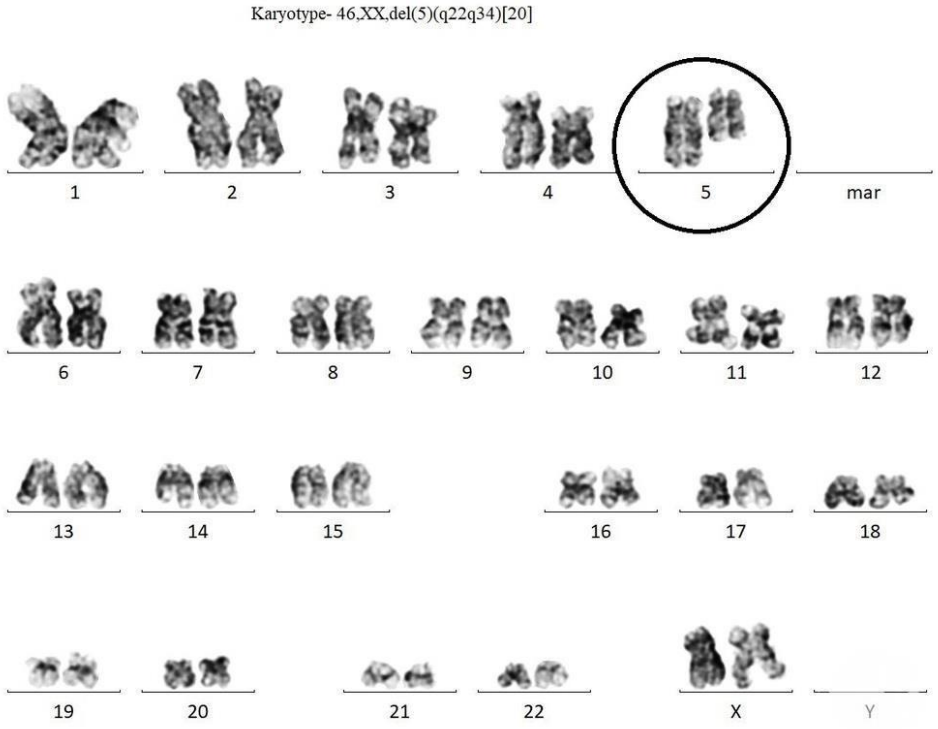
- WHO classification (blasts, cytogenetics, gene mutations)
- Low-risk or high-risk disease: IPSS Prognostic Score
- Need for upfront treatment versus watchful waiting
- Availability of therapies and clinical trials
- Medical co-morbidities of patients
- Shared decision making of patient and physician

How is MDS Classified?

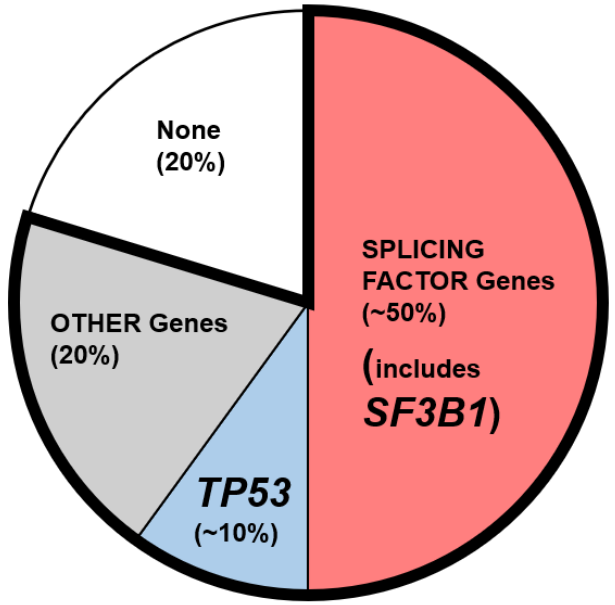
Blasts



Cytogenetics



Gene Mutations



How is MDS Classified?

WHO 2022 Classification of Myelodysplastic Neoplasms (MDS)

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

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Merge MDS-IB2 with AML?

- "MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations and clinical trial design"
- International Consensus Classification (ICC) uses a new MDS/AML category for MDS-EB2

https://doi.org/10.1182/blood.2022015850

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What is my prognosis? Revised International Prognostic Scoring System (IPSS-R)

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermed	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
ANC	≥0.8	<0.8					

Risk group	IPSS-R score	Median OS (years)	Time to 25% AML (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
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Good: Normal, del(5q), del(12p), del(20q), double including del(5q).
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Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abn
Very poor: Complex: >3 abnormalities

Greenberg et al, Blood 2012

Have any updates been made to scoring systems to incorporate more gene mutations?

IPSS-M Calculation https://mds-risk-model.com/

So which treatment is right for me?

- Shared decision making based on symptoms, risk-stratification, and patient age/medical issues

- Clinical trial participation

MDS Alliance MDS Global Patient Survey 2022

Clinical Trial Awareness

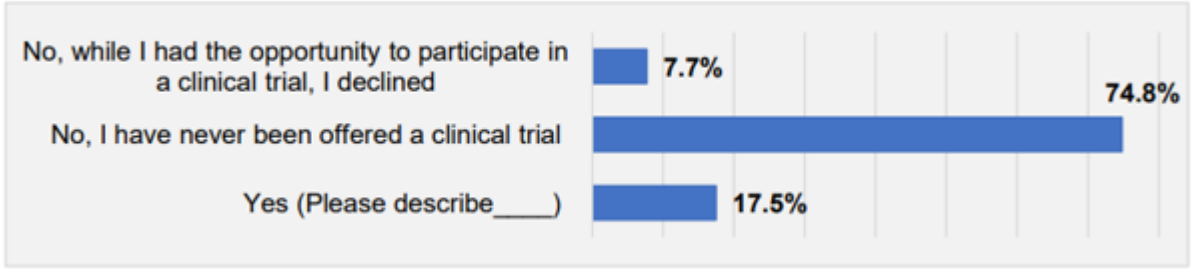
Participation in Clinical Trials (N = 610)

Respondents were also asked, "*Have you participated in any clinical trials?*"

While 82.5% of respondents reported they have not participated in a clinical trial, over three-quarters (74.8%) reported they had never been offered a clinical trial.

74.8%

Percent of respondents reporting they have NEVER been offered a clinical trial



Data collected by the MDS Alliance. https://www.mds-alliance.org/the-mds-global-patient-survey-2022/

key provider takeaways from the 2022 MDSA Global Survey, Ashley Moncrief, Director of Patient care, MDS Foundation, Inc

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- **CBC** = WBC 5.1, hemoglobin 8.1 (ANC 3.6), platelets 278K
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- **WHO diagnosis : MDS with SF3B1**
- **IPSS-R** ?
- **Treatment** ?

Patient #2

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Risk Group and Survival Predictions for Pt #1

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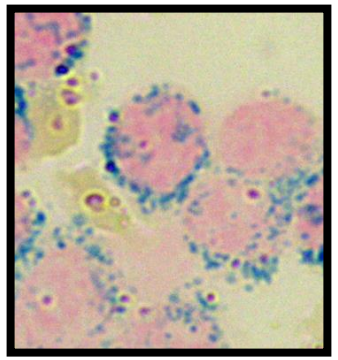
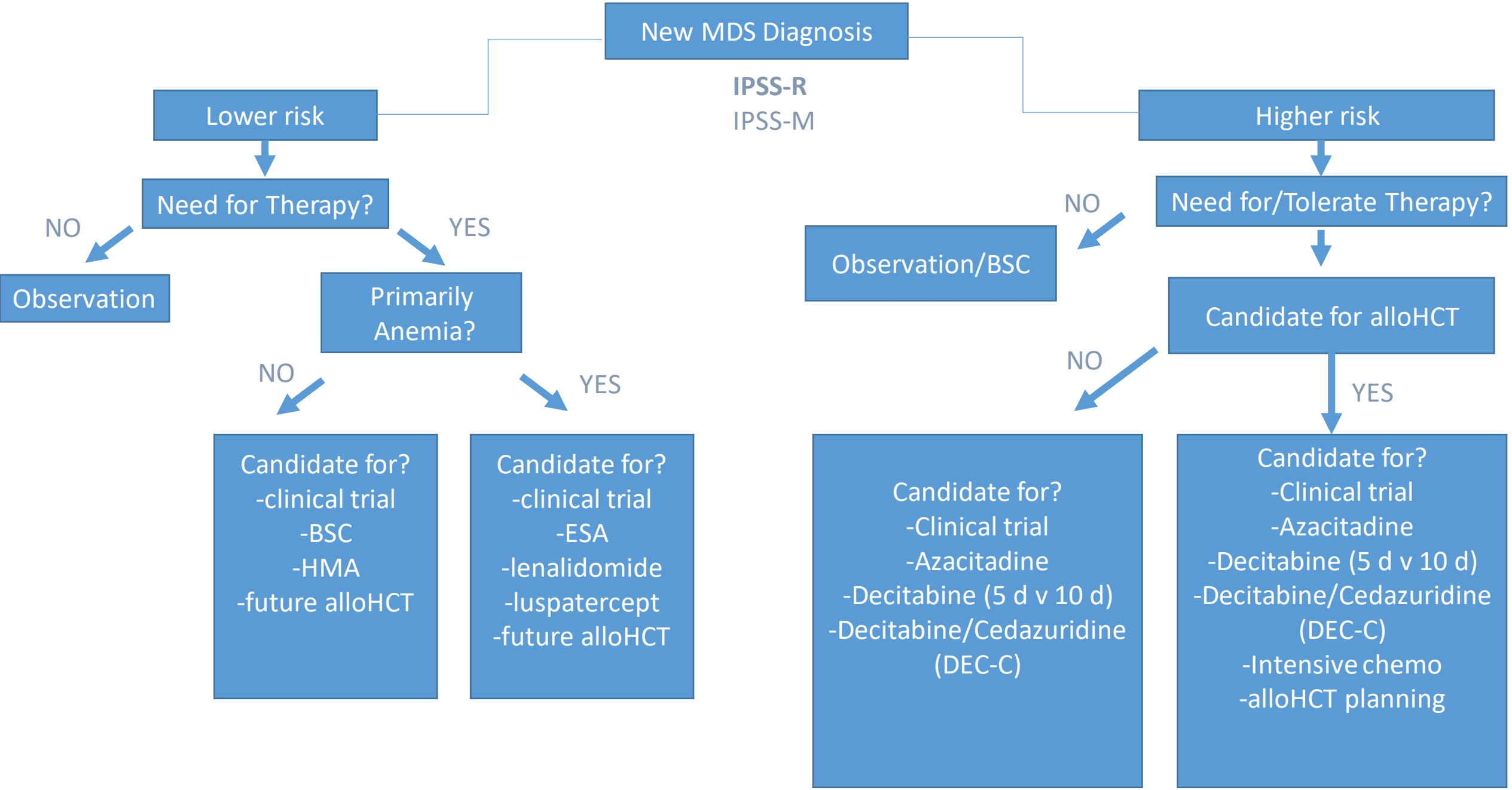
Ring Sideroblasts



SF3B1 mutation

Greenberg et al, Blood 2012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Treatment: Erythropoietin for symptomatic anemia in MDS

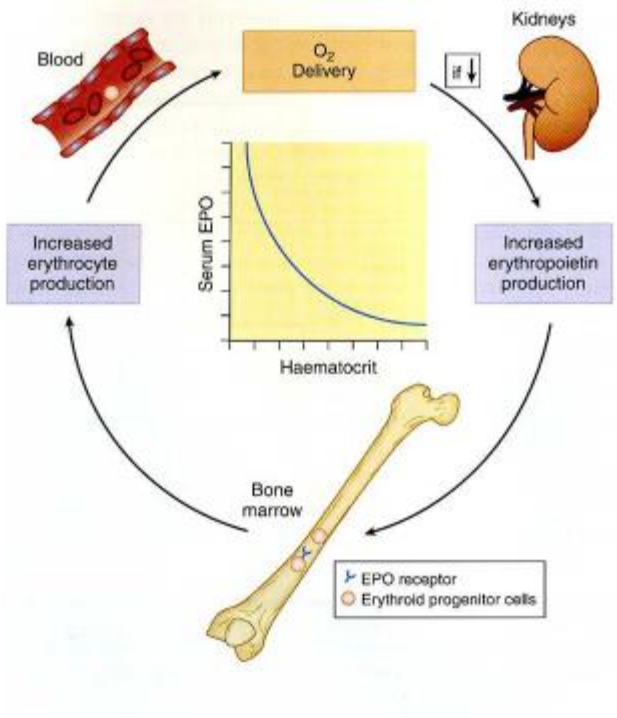
Table 1. Predictive variables for ESA response in MDS

Biological	
Endogenous erythropoietin levels <500 U/L	
Marrow blast <10%	
IPSS low-INT-1	
Diagnosis of refractory anemia	
Normal karyotype	
Clinical	
Transfusion independence	
Short duration of disease	

Abbreviations: ESA, erythropoietic stimulating agents; INT-1, intermediate-1; IPSS, International Prognostic Score System; MDS, myelodysplastic syndromes.

The Oncologist 2011;16(suppl 3):35–42 www.TheOncologist.com

Pt#1 18.9 U/L



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Response rates 45-73%

Median time to response 5 weeks (4-9)

Duration of response 8-48 months

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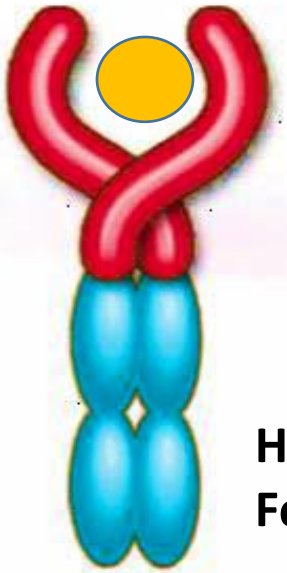
Luspatercept for lower-risk MDS

LUSPATERCEPT

TGF-B superfamily ligand



Modified ActRIIB fusion protein

Human IgG Fc domain

Soluble "Cytokine sink" to prevent signaling at cell surface

- "Ligand trap" binds TGF beta ligands and modulates TGF beta signaling pathway
- Targets late stage erythropoiesis
- "First in class maturation agent" (EMA)
- **Approved in April 2020 for LR-MDS patients with RS who are transfusion dependent and refractory to ESA therapy**
- **COMMANDS:** First study in ESA-naïve LR-MDS pts to compare ESA to investigational therapy for transfusion dependent anemia in upfront therapy

COMMANDS Trial

Key Eligibility

- IPSS–R Score VL, L, Intermediate
- Transfusion dependent
- ESA agent naïve
- EPO < 500 U/L
- Non del 5(q)

RANDOMIZE

1:1

Luspatercept
SQ Q 21 D

Epoetin alfa
SQ Q week

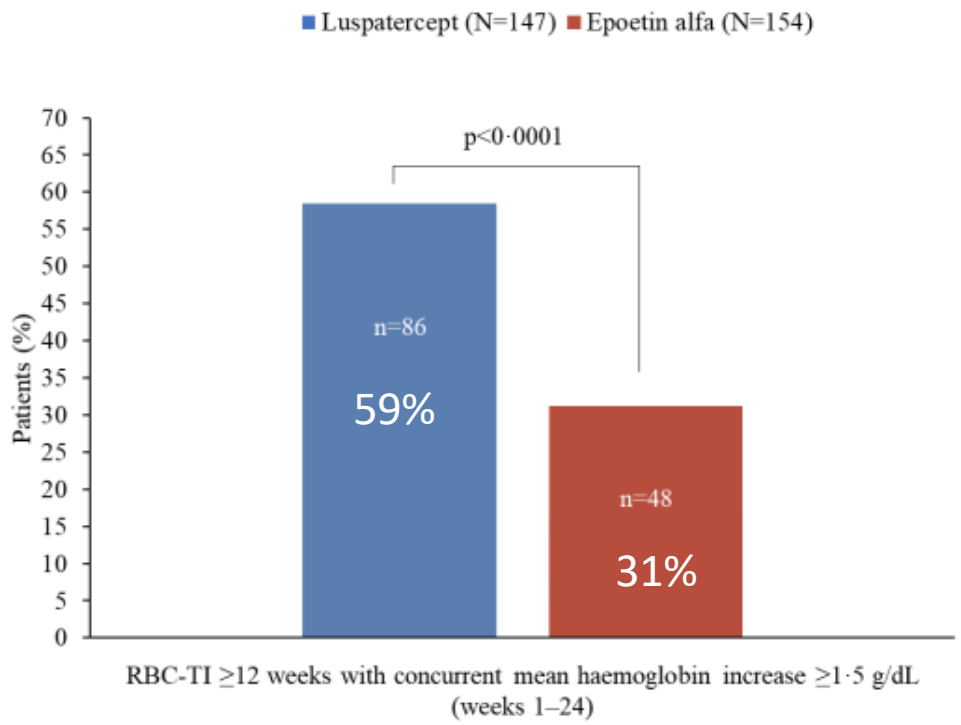
STRATIFIED
-Transfusion burden <4 or ≥ 4U/8 wks
-EPO levels ≤ 200 vs <200 to <500
-Ringed sideroblasts (pos vs neg)

Endpoints

- Primary: RBC-TI ≥ 12 wks with a concurrent Hgb increase ≥ 1.5 g/dl
- Secondary:
  - RBC-TI ≥ 12 wks
  - RBC-TI ≥ 24 wks
  - HI-E

COMMANDS Trial Interim Analysis

Primary Endpoint



- **Median duration of TI was 127 weeks vs 77 weeks, respectively p=0.005**
- **Received FDA approval in August 2023**

Lancet 2023; 402: 373–85

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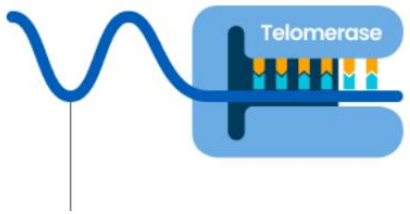
Imetelstat in Lower Risk MDS

Malignant clones

Constitutively High telomerase activity

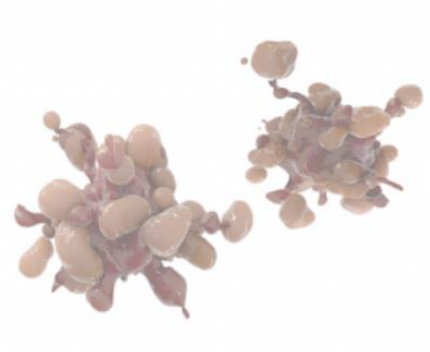
Imetelstat binds to telomerase and inhibits its activity



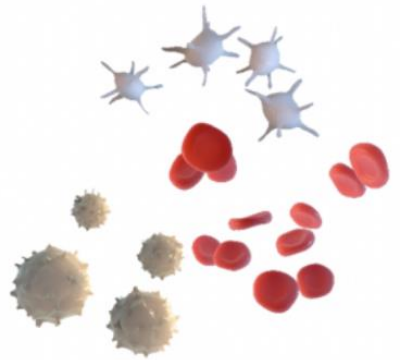
Imetelstat

Imetelstat is a 13-mer oligo that binds RNA template of telomerase

Apoptosis of malignant clones



Recovery of hematopoiesis



Platelets, RBC, WBC

Slide courtesy of Amer Zeidan, MBBS MHS, Associate Professor of Internal Medicine (Hematology)

IMerge Phase 3 Trial Design

Phase 3
Double-blind, randomized
118 clinical sites in 17 countries

Patient population (ITT; N = 178)

- IPSS low-risk or intermediate-1–risk MDS
- R/R[a] to ESA or EPO >500 mU/mL (ESA ineligible)
- Transfusion-dependent: ≥4 U RBCs/8 wk over 16 wk before study
- Non-del(5q)
- No prior treatment with lenalidomide or HMAs

R 2:1

Imetelstat
7.5 mg/kg IV every 4 wk
(n = 118)

Stratification
- Transfusion burden (4-6 U vs >6 U)
- IPSS risk category (low vs intermediate-1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

Placebo
(n = 60)

Safety population (treated; N = 177)
Imetelstat (n = 118)
Placebo (n = 59)

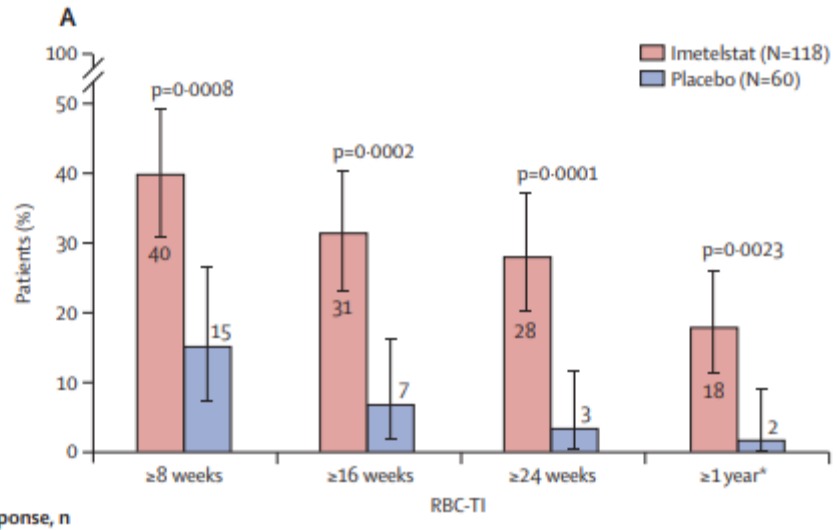
Primary end point
- 8-wk RBC-TI[b]

Key secondary end points
- 24-wk RBC-TI[b]
- Duration of TI
- HI-E
- Safety

Key exploratory end points
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

Slide Courtesy of Dr. Komrok

Results



Patients with response, n (% [95% CI])				
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])

FDA ODAC Committee Votes In Favor of Benefit-Risk Profile of Imetelstat in Lower-Risk MDS

March 14, 2024

https://www.fda.gov/media/176966/download

https://www.onclive.com/view/fda-odac-committee-votes-in-favor-of-benefit-risk-profile-of-imetelstat-in-lower-risk-mds

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Revised International Prognostic Scoring System (IPSS-R) Pt #2

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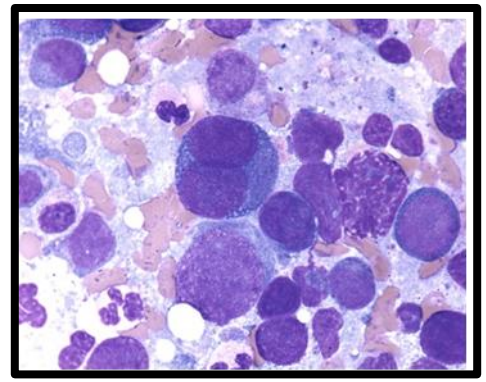

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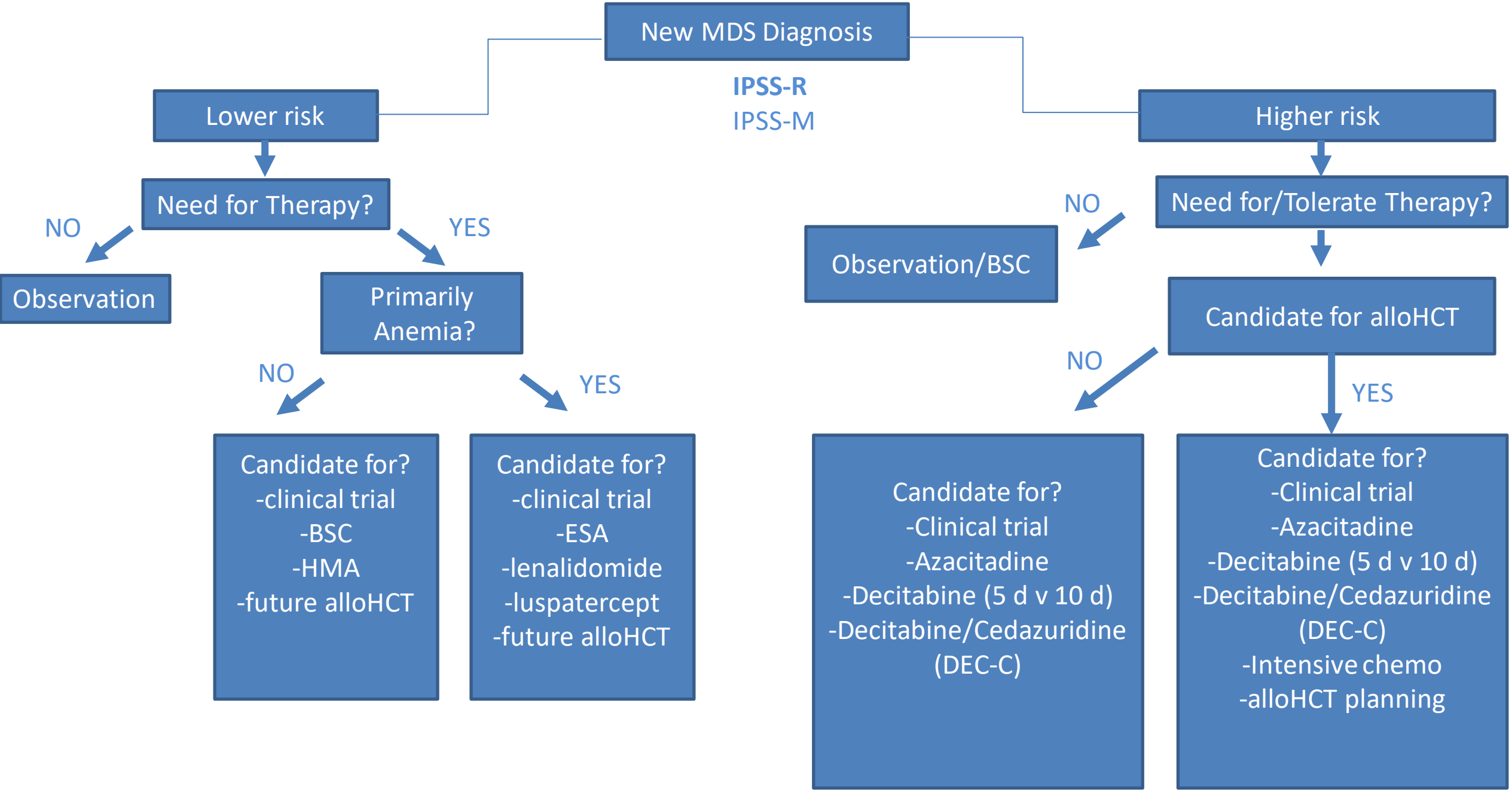
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Candidate for?
-clinical trial
-ESA
-lenalidomide
-luspatercept
-future alloHCT
NO
Observation/BSC
Need for/Tolerate Therapy?
Candidate for alloHCT
NO
YES
Candidate for?
-Clinical trial
-Azacitadine
-Decitabine (5 d v 10 d)
-Decitabine/Cedazuridine (DEC-C)
Candidate for?
-Clinical trial
-Azacitadine
-Decitabine (5 d v 10 d)
-Decitabine/Cedazuridine (DEC-C)
-Intensive chemo
-alloHCT planning

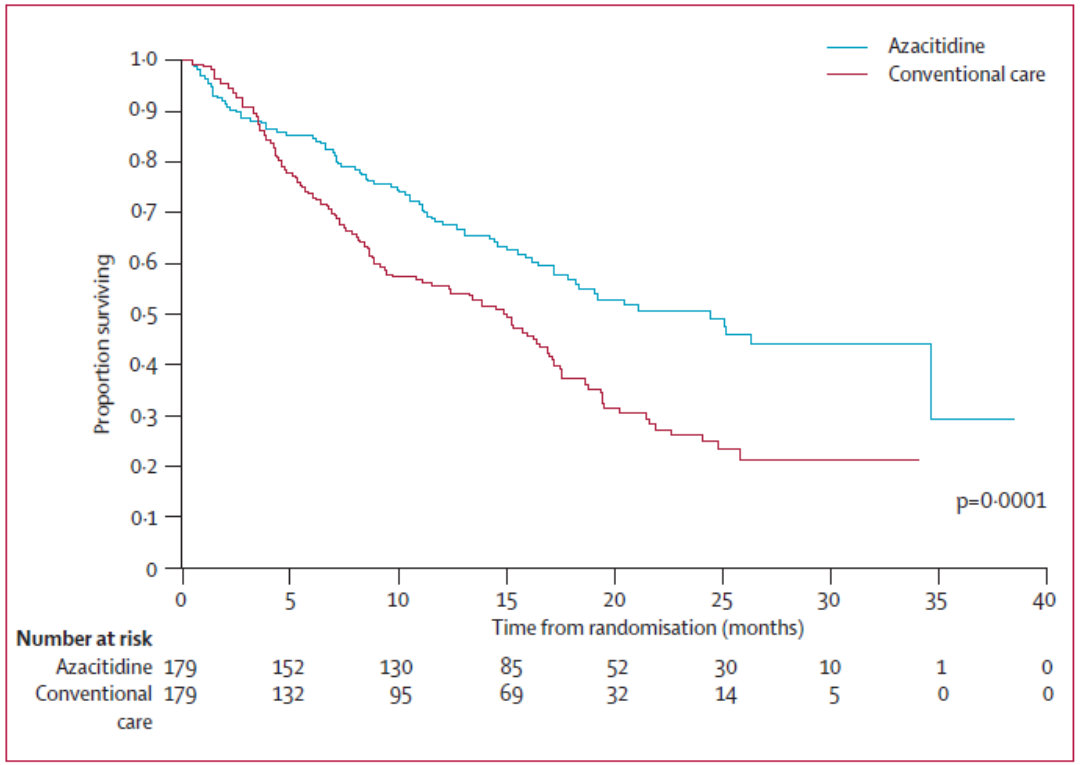
What Are Current Standard of Care Options?

- Hypomethylating agents:
  - Azacitadine 75 mg/m^2 X 7 days every 28 days
  - Decitabine 20 mg/m^2 X 5 days every 28 days
  - Decitabine 20 mg/m^2 X 10 days every 28 days (n engl j med 375;21)

- Oral decitabine and cedazuridine (DEC-C) recently FDA approved as a substitute for IV decitabine (Blood 2020 Aug 6;136(6):674-683)

DNA Hypomethylating Agents Improve Survival: AZA-001

Azacitidine vs conventional care



- Median OS 24.5 vs 15 months
- Median time to AML 17.8 vs 11.5 mo
- **Can we do better?**

Fenaux et al. Lancet Oncology 2009; 10:223

Azacitidine Responses in Select Major Trials and a Meta-Analysis

Endpoint	Fenaux (2009)	Itzykson (2011)	SWOG S1117 (2015)	Panther Sekeres (2021)	Review Garcia (2021)
	Aza n= 179	Aza n= 282	Aza n= 92	Aza n =35[#]	Aza 237 studies
median OS, months	24.5 (9.9-NR)	13.5	15	19.1	18.6 (15.3-21.9)
median relapse free survival	NR	NR	6		
median progression free survival	*14.1 (IQR 4.2-27.6)	NR	NR	14 [##]	12
ORR (CR+PR+HI)	35%	38%	37%	57%	
ORR (CR+PR+ mCR + HI)	mCR NR	43%	NR	NR	
CR	17%	14%	24%	26.7%	17%
PR	12%	3%	0	13%	
HI (Any, includes CR , PR, SD)	49%	NR	13%	17%	
mCR + HI	mCR NR	5.60%	NR	NR	
mCR, no HI	mCR NR	5.60%	NR	NR	
SD (both with and without HI)	42%	38%	NR	NR	
median time to AML	15.0 (8.8-27.6)	NR	NR		
median duration of response** (CR+PR+HI)	13.6,(IQR 5.9-26.4)	9.5	9.0	13.1	

*defined as median time to disease progression,relapse after CR or PR, or death

** CR+PR+HI (Fenaux, Sekeres 2021) or (CR + PR + mCR + HI (Itzykson) ; [#] higher-risk MDS cohort only;[##]event-free survival

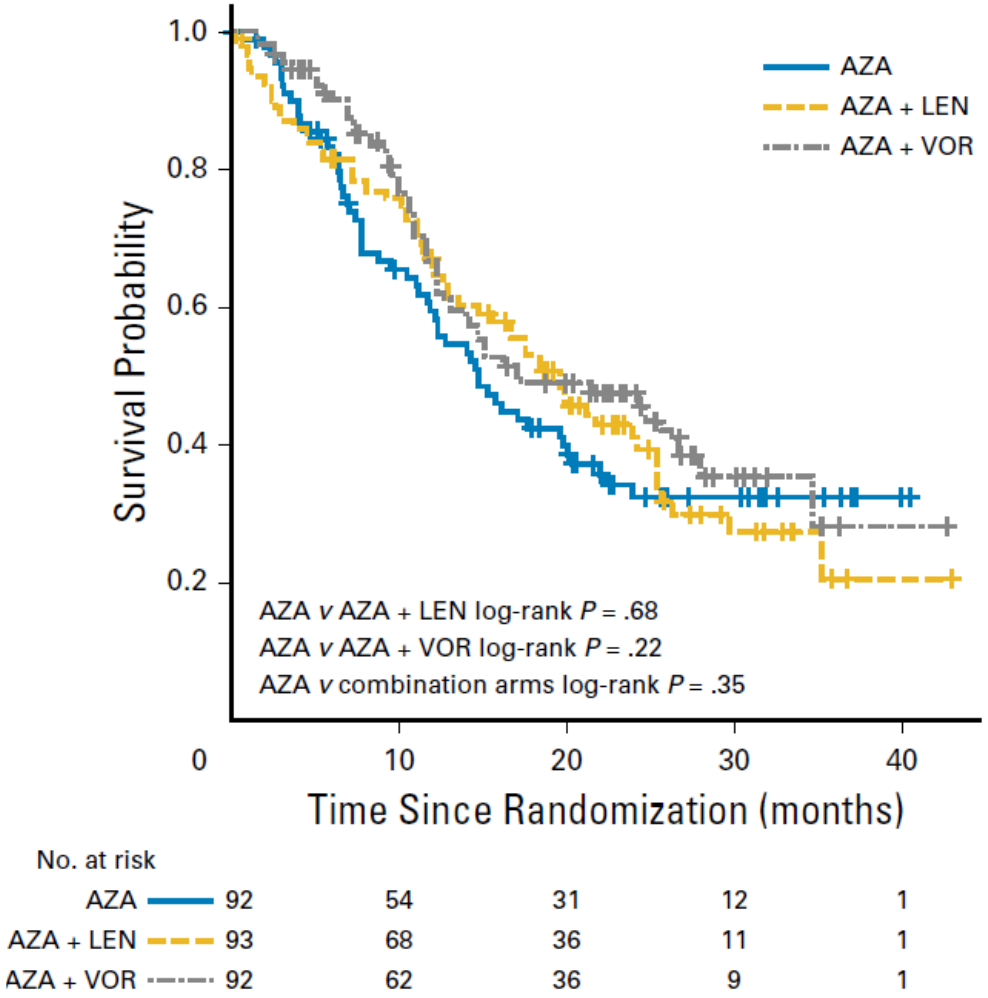
NR, not reported

Clinically Unmet Need: Improving Response and Survival over single agent Azacitidine

Fenaux et al. Lancet Oncology 2009; 10:223
Itzykson et al. Blood . 2011; 117:403.
Sekeres, et al. Blood 2015;126:908

Sekeres, et al. Leukemia 2021;35:2119-2142
Garcia, et al. Leukemia Research .2021 104

Historically, Azacitadine "Doublets" Have Been Disappointing



Sekeres, et al. J Clin Oncol 2017;2745

- Clinically unmet need
- Recent doublets with novel compounds have not met primary endpoints:
- APR-246 (acts on *TP53*)
- Pevonedistat (acts on ubiquitination)
- Magrolimab (CD47 macrophage checkpoint inhibitor
- Sabatolimab (immunomodulary)

https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3

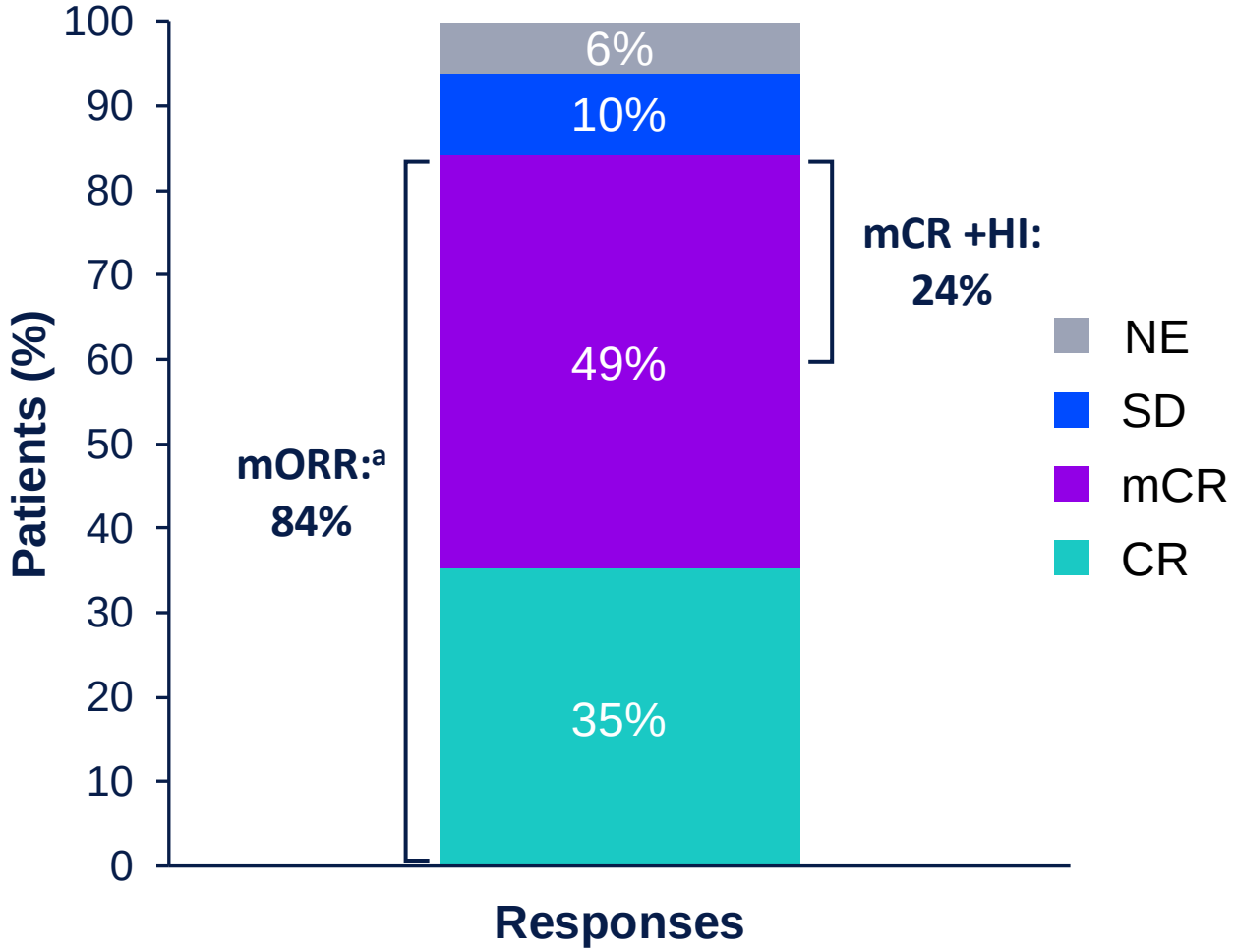
Sekeres, et al. Leukemia 2021;35:2119-2142

P3 VERONA Study

- Phase 3 randomized, double-blind study of patients with treatment-naïve HR-MDS study of venetoclax with azacitidine to assess change in complete remission and overall survival (VERONA) (NCT04401748)
- Patients 1:1 to receive placebo or Ven 400 mg oral tablet once daily on Days 1-14, both in combination with Aza 75 mg/m2 (intravenous or subcutaneous) on Days 7-0-0 or Days 5-2-2 per 28-days
- Planned enrollment is approximately 500 patients, which began in 2020

DOI: 10.1200/JCO.2021.39.15_suppl.TPS7054 Journal of Clinical Oncology - published online before print May 28, 2021

Azacitidine + Venetoclax: Early Phase Data



- Median time to response:

0.9 months (95% CI, 0.7–5.8)

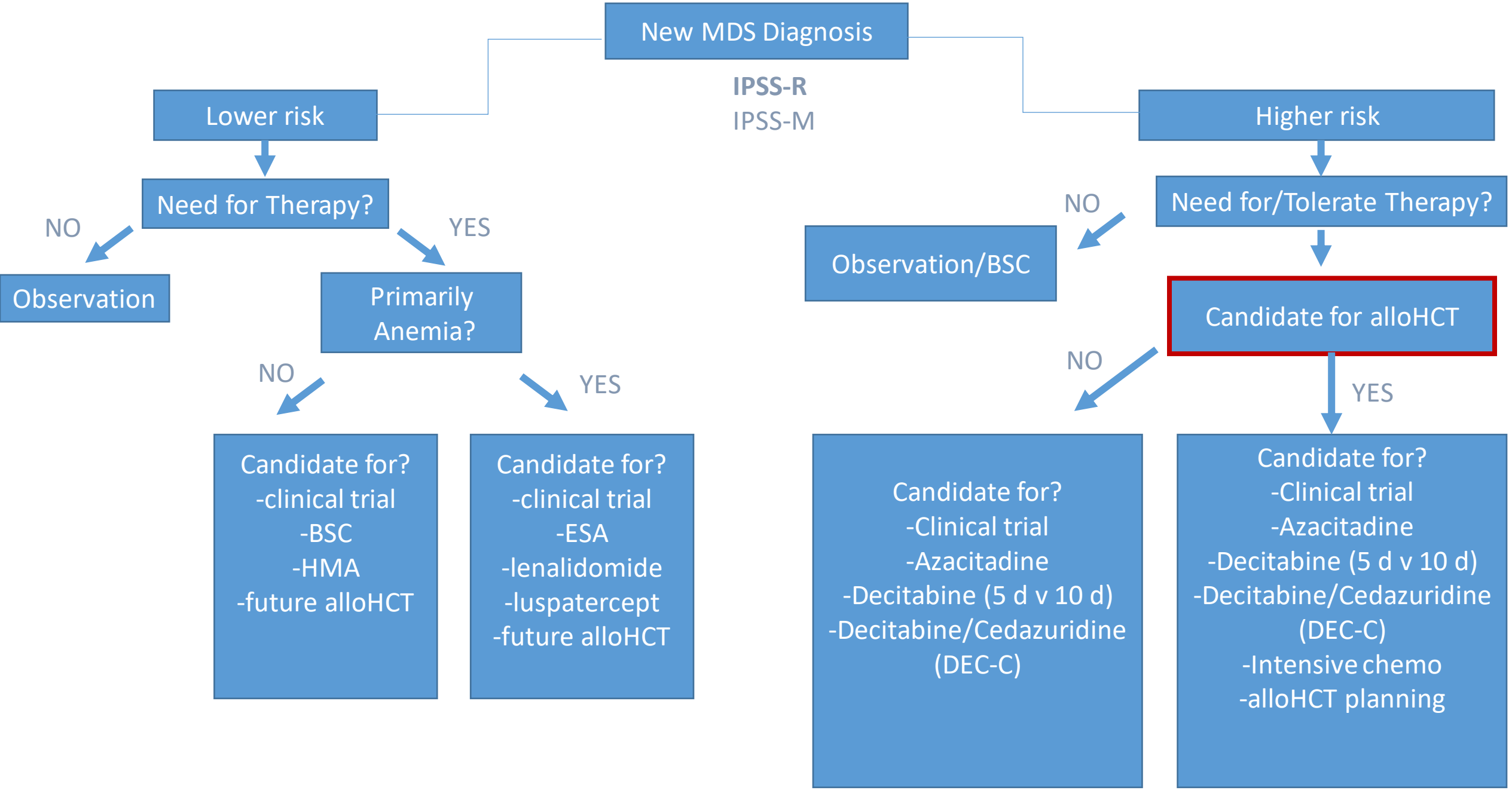
- Median duration of response:

12.4 months (95% CI, 9.9–NR)

ASH 2021, Abstract 241

Slide courtesy of Dr. Jacqueline Garcia

Data cutoff: Dec 15, 2020


New MDS Diagnosis
IPSS-R
IPSS-M
Lower risk
Higher risk
Need for Therapy?
NO
YES
Observation
Primarily Anemia?
NO
YES
Candidate for?
-clinical trial
-BSC
-HMA
-future alloHCT
Candidate for?
-clinical trial
-ESA
-lenalidomide
-luspatercept
-future alloHCT
NO
Observation/BSC
Need for/Tolerate Therapy?
Candidate for alloHCT
NO
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Candidate for?
-Clinical trial
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Candidate for?
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-Decitabine (5 d v 10 d)
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-Intensive chemo
-alloHCT planning

Fitness of Patient: HCT-Specific Comorbidity Score (HCT-CI) (Sorror Score)

Table 1. HCT-CI

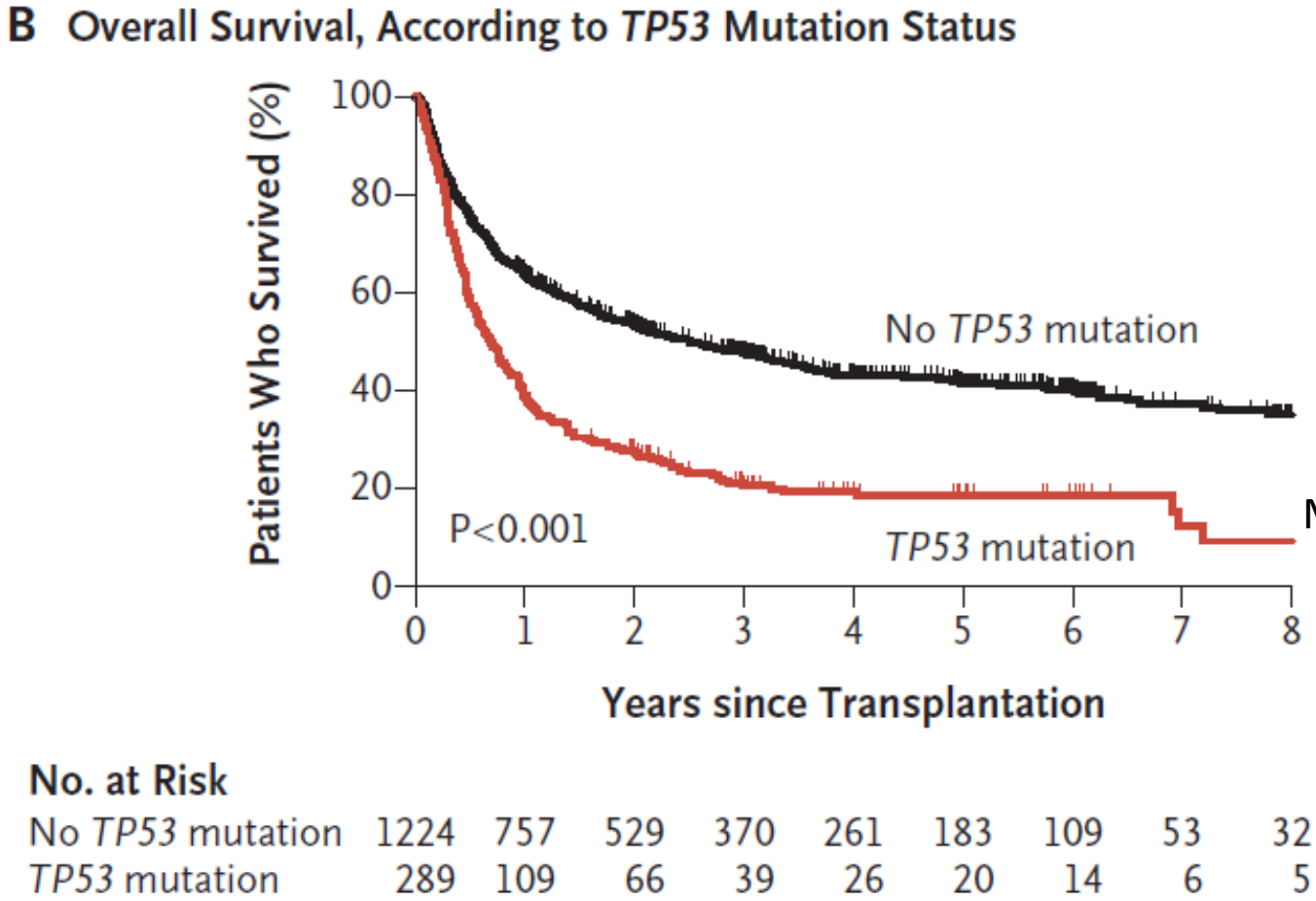
Comorbidities	HCT-CI scores
Arrhythmia	1
Cardiovascular comorbidity	1
Inflammatory bowel disease	1
Diabetes or steroid-induced hyperglycemia	1
Cerebrovascular disease	1
Psychiatric disorder	1
Mild hepatic comorbidity	1
Obesity	1
Infection	1
Rheumatologic comorbidity	2
Peptic ulcer	2
Renal comorbidity	2
Moderate pulmonary comorbidity	2
Prior malignancy	3
Heart valve disease	3
Moderate/severe hepatic comorbidity	3
Severe pulmonary comorbidity	3
	Total score = _____

NRM		NRM	
Score	**Patients, %**	**HR*(95% CI)**	**2-year, %**
0	38	1	9
1	17	1.66 (0.9-3.1)	14
2	17	3.48 (2.0-6.0)	27
3	17	6.09 (3.7-10.1)	41
4 or more	11	6.93 (4.0-12.0)	43

Blood. 2005;106(8):2912-2919.

http://www.hctci.org/

Biological characteristics of the disease: *TP53* Mutation Confers Poor Prognosis After Stem Cell Transplant



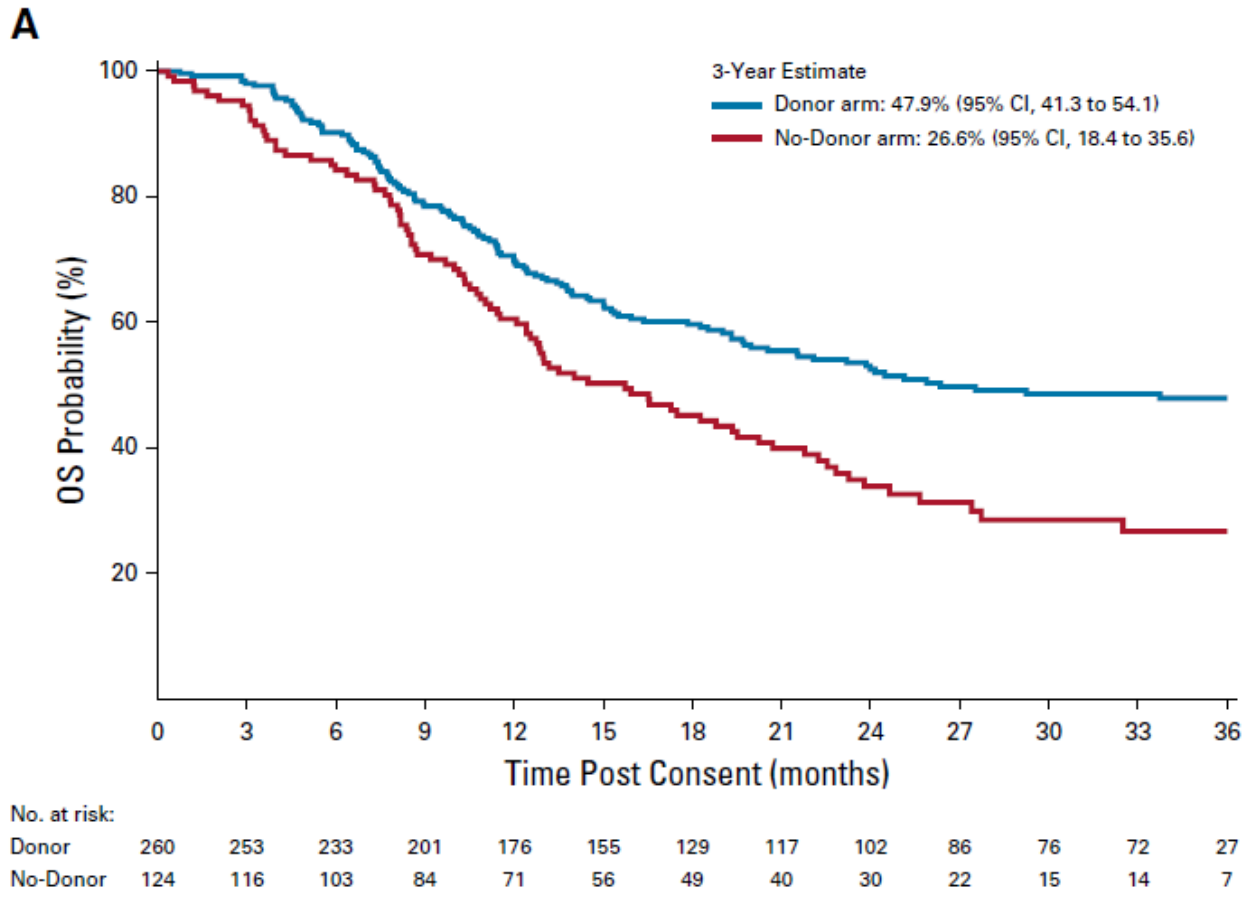
Median OS 0.7 years

Lindsley, et al. NEJM 2017;376;6

Am I too old to get a transplant?

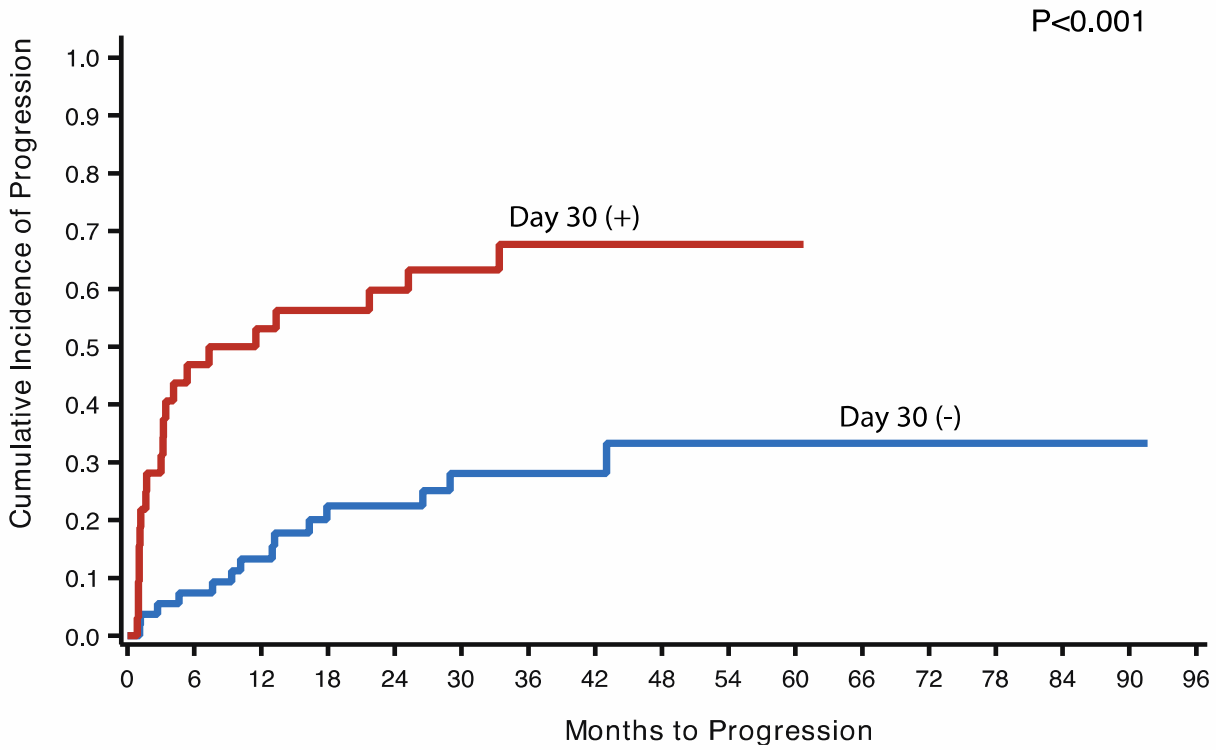
Survival advantage of allogeneic stem cell transplant in older patients: BMT CTN 1102

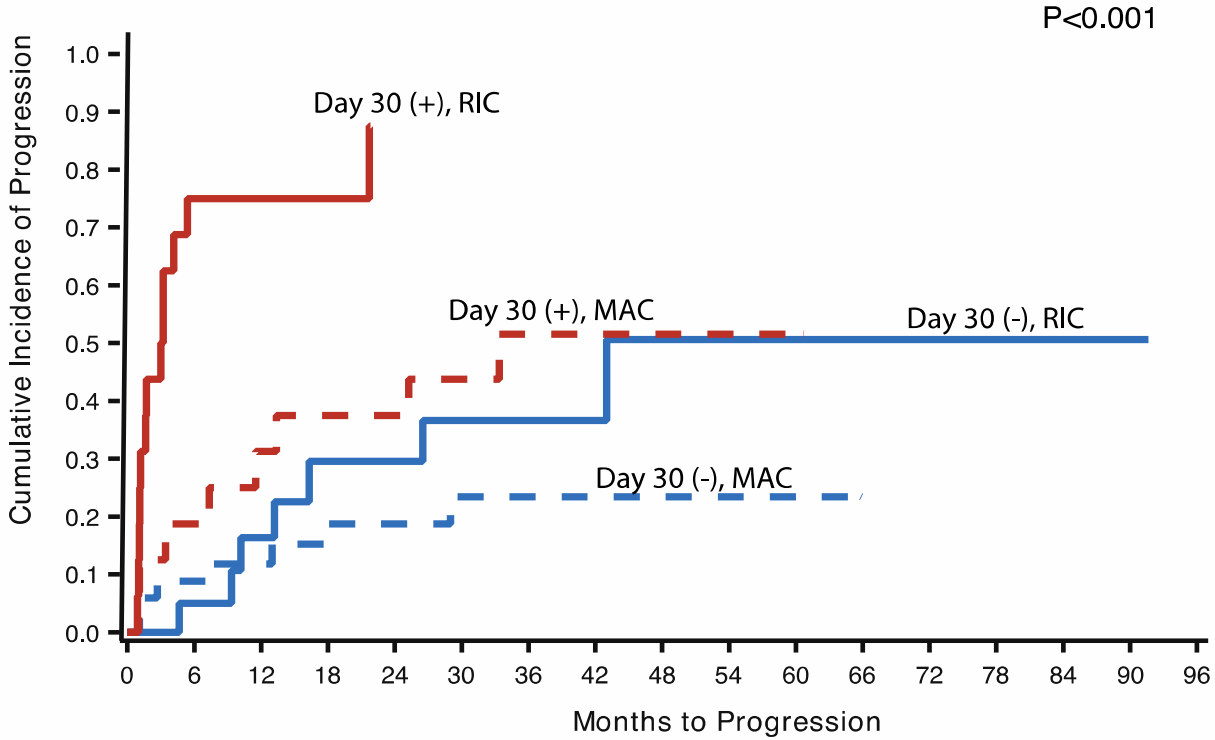
- Key eligibility:
  - Age 50-75 (median 66.7 [50.1-75.3])
  - higher risk MDS (69% High or Very High)
  - Suitable for reduced-intensity conditioning
- Primary endpoint 3 year OS in ITT analysis



J Clin Oncol 39:3328-3339. © 2021

Persistent mutations at Day 30 Post Transplant **is Associated with Increased Risk of Progression**





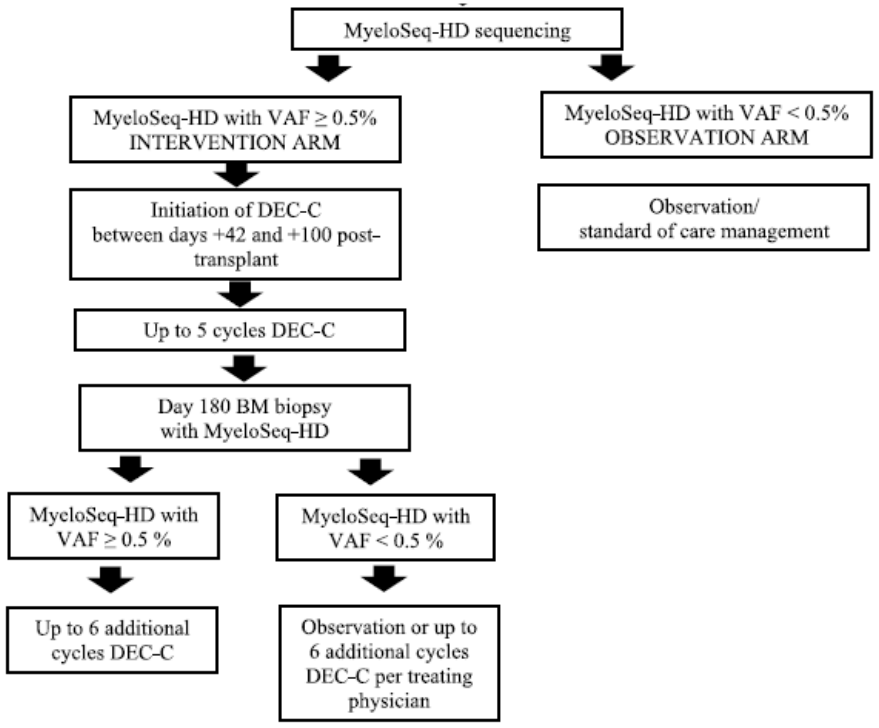
(HR 4.48; 95% confidence interval [CI], 2.21 to 9.08; P<0.001) independent of IPSS-R and conditioning regimens. Could detect relapse by sequencing a median of 67 days before clinical relapse

Duncavage E, Jacoby M, et al, NEJM, 2018

A Trial of Pre-emptive Therapy with DEC-C to Improve Outcomes in MDS Patients with Measurable Residual Disease Post Allogeneic Hematopoietic Cell Transplant (NCT04742634)

Trial Design

Day 30 post-transplant



MDS Clinical Trials at Washington University/Siteman Cancer Center

	Mechanism	Study Population	Clinical trial
(AZD9829)	Anti-CD123 ADC	R/R CD123 Positive heme malignancies	NCT06179511
DEC-C in MDS w/MRD post-alloHCT	Decitabine and Cedazuridine (DEC-C)	molecular MRD Day 30 post-transplant	NCT04742634
ChromoSeq AML/MDS	Whole genome sequencing	New AML or MDS	NCT05434598 NCT04986657

Coming soon: A Phase3b trial of luspatercept for LR-MDS