The Myelodysplastic Syndromes

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Taussig Cancer Institute

L&MD
Leukemia & Myeloid Disorders Program

Disclosures

“It troubles me that we’re being led into battle by a person wearing a bow tie.”

-New Yorker | September 10, 2018

Overview – Myelodysplastic Syndromes

1. Organization, in general
2. Diagnosis and Classification
3. Epidemiology
4. Pathogenesis
    a. Clonal Process
    b. Secondary MDS
5. Risk stratification
    a. IPSS-R
6. Treatment of Lower-risk MDS
    1. ESAs
    2. IMIDS
    3. Immunosuppressive therapy
7. Treatment of Higher-risk MDS
    1. Hypomehtylating agents
8. Transplantation for MDS
9. Discussion

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What is MDS?

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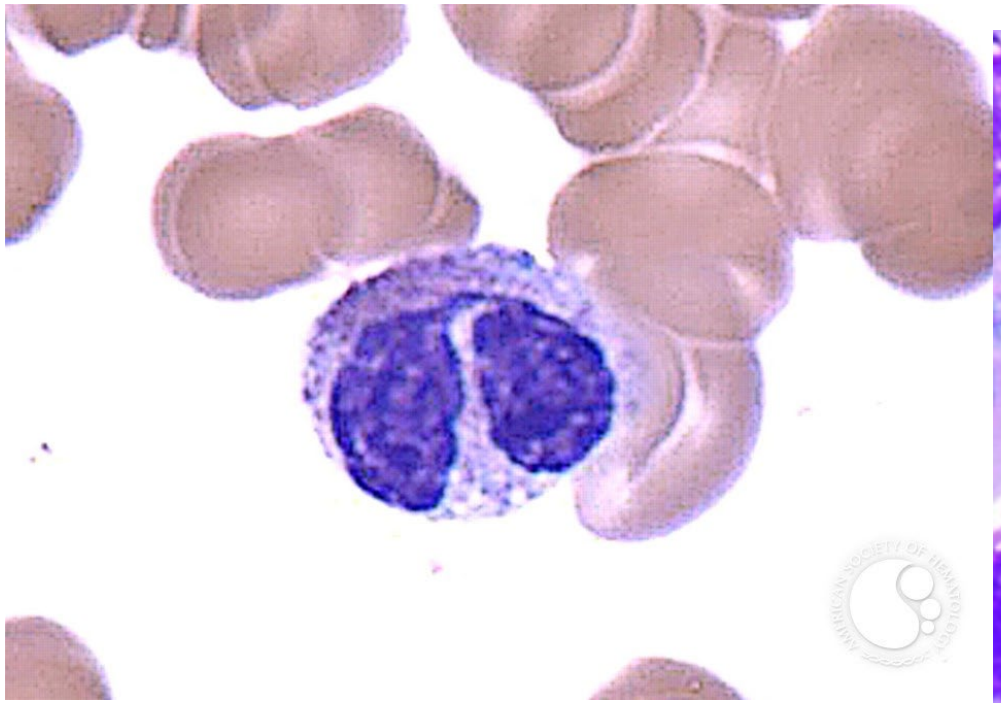
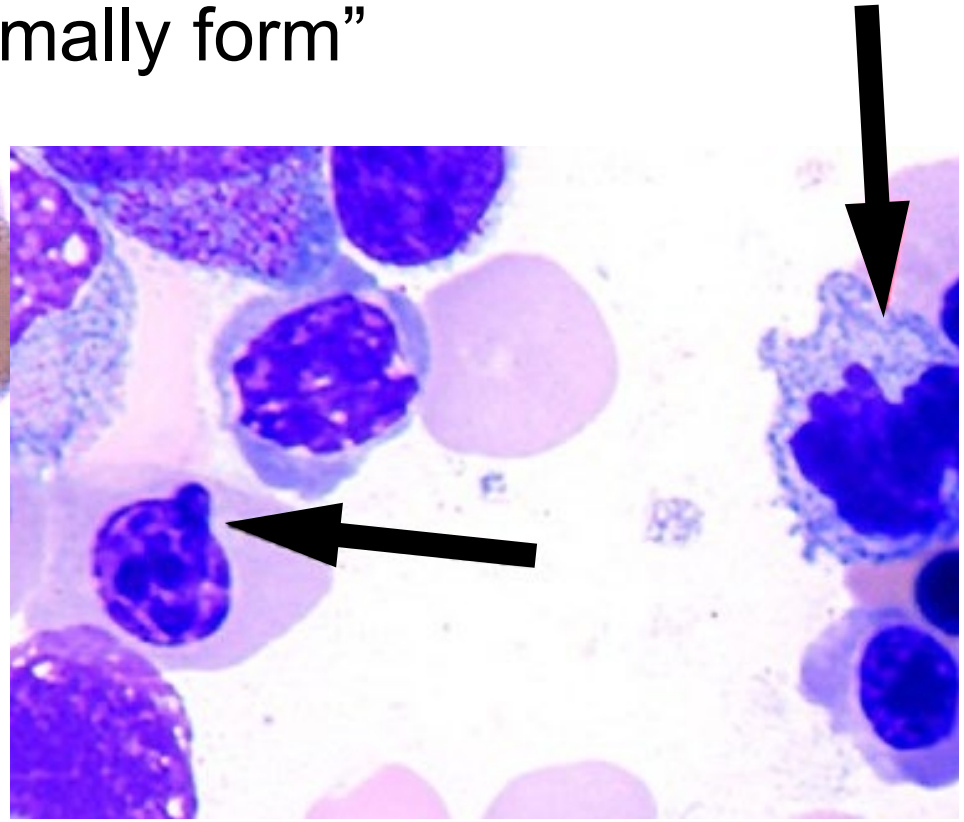
The Myelodysplastic Syndromes

- Gr. *myelos* – “marrow”
- Gr. *dys* + *plassein* – “abnormally form”





Maslak P, Pelger Huet Cell - 1. ASH Image Bank. 2011; 2011-2117.

Maslak P, Dysplastic Red Cell Changes (Bone Marrow Aspirate) I - 2. ASH Image Bank. 2011; 2011-3269.

MDS is a cancer?

Oxford dictionary: The disease caused by an uncontrolled division of abnormal cells in a part of the body (from Latin *cancr* meaning crab)

Mural Study for Cancer, 1948; Clarence Van Duzer (1920-2009)

Diagnosis and Classification of MDS

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WHO Diagnostic Criteria

Minimal Morphologic Criteria

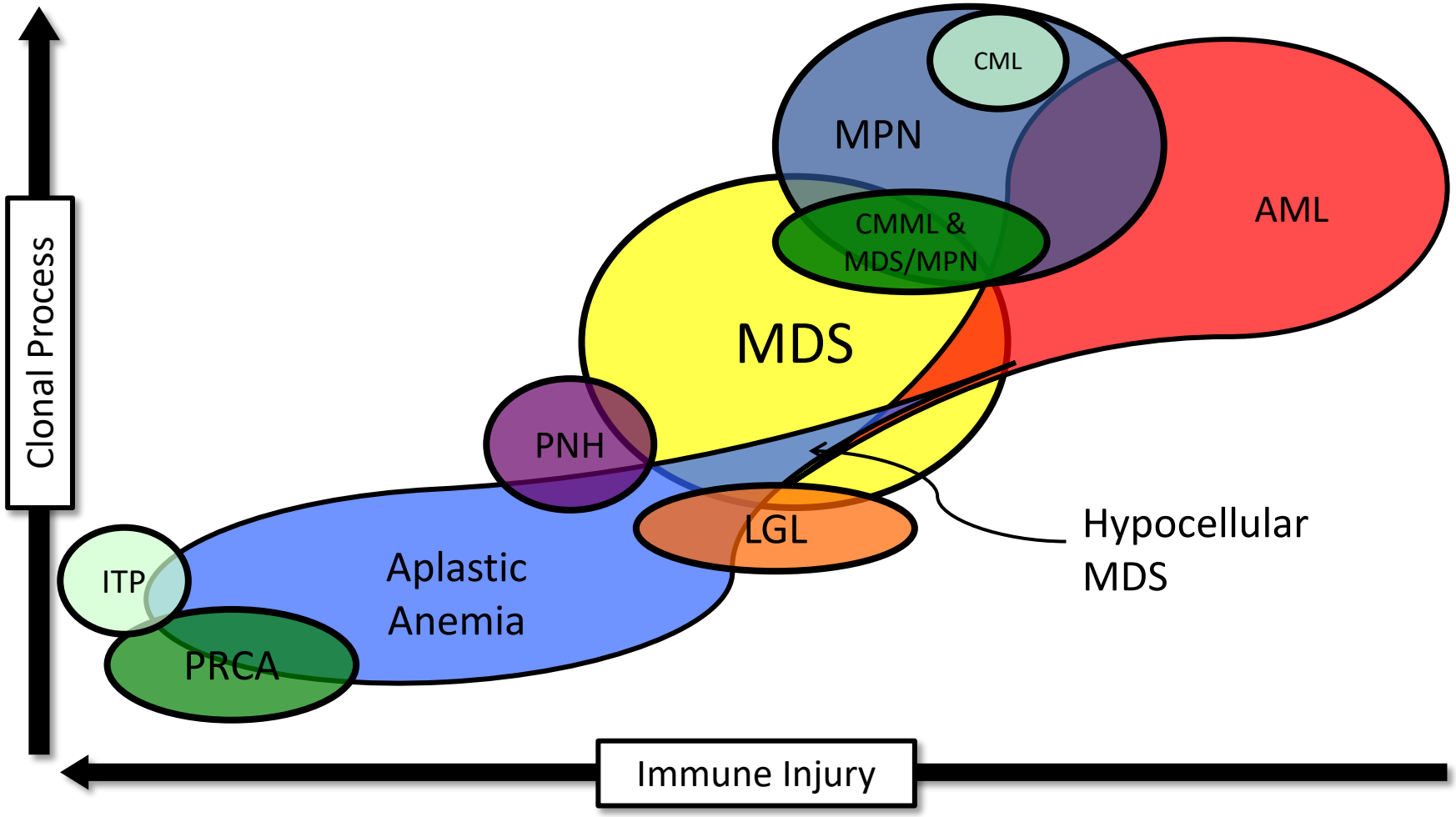
- ≥10% of the cells ≥1 lineage must show dysplasia
- Dysplasia not required if:
  - Defining cytogenetics
  - BM blasts ≥ 5%, PB blasts ≥ 2%, or Auer rods
- At least one cytopenia present
- Causes of secondary dysplasia must be excluded

Defining Cytogenetics

- -7 or del(7q)
- -5 or del(5q)
- del(13q)
- del(11q)
- del(12p) or t(12p)
- del(9q)
- idic(X)(q13)
- t(17p) or i(17q)
- t(11;16
- t(3;21)
- t(1;3)
- t(2;11)
- inv(3)
- t(6;9)
- Complex

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

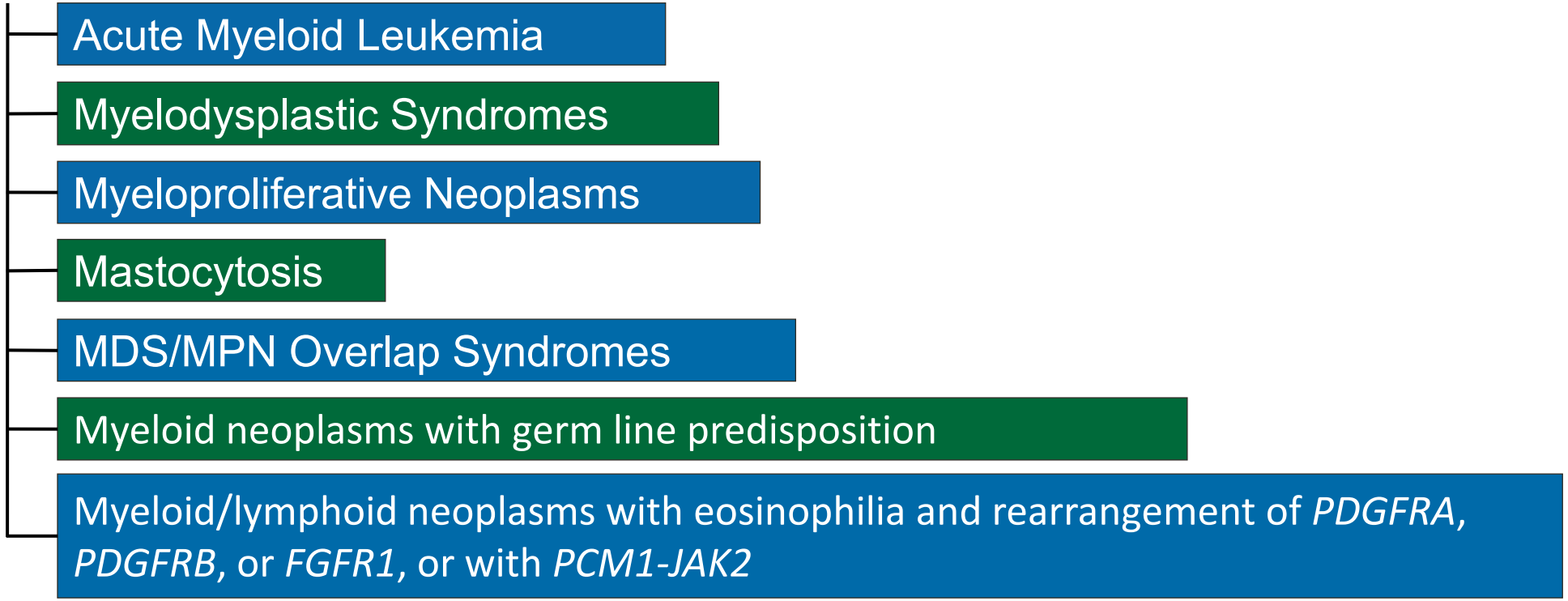
Spectrum of Marrow Failure



Gerds, AT. *Curr Hematol Malig Rep*. 2014 Dec;9(4):400-6

WHO Classification

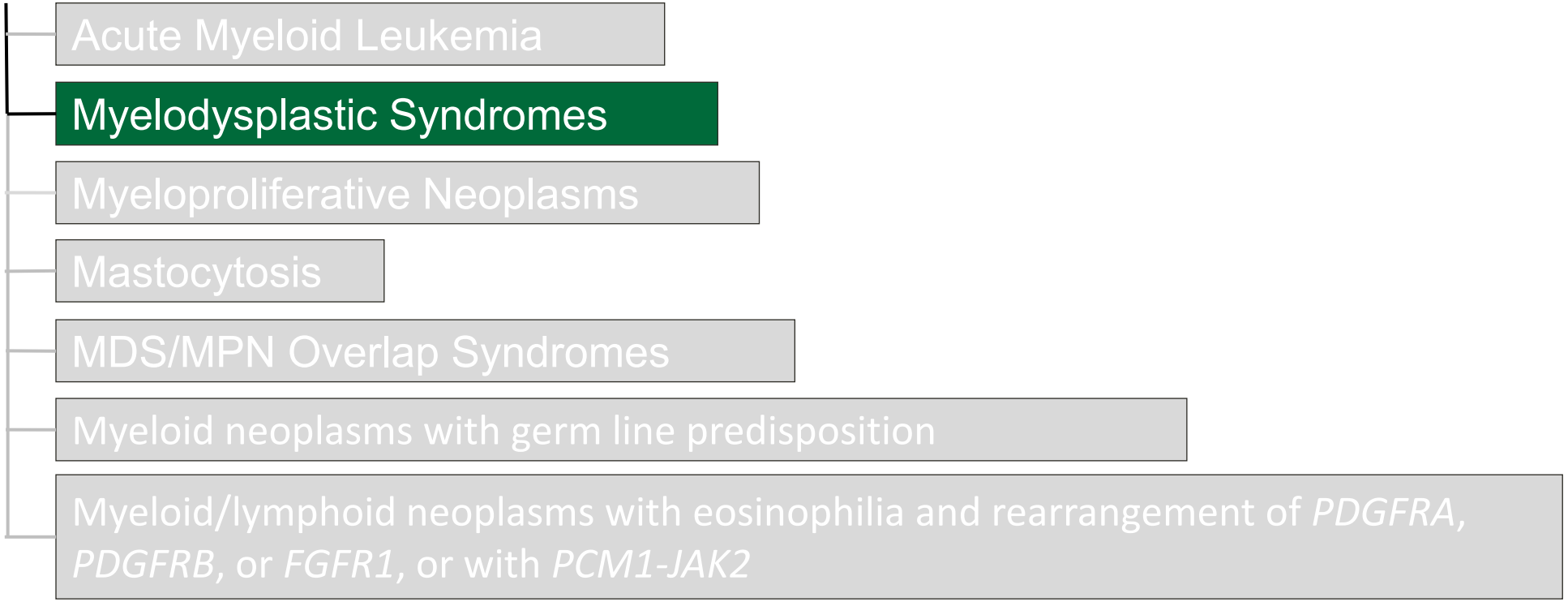
Myeloid Neoplasms



Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

WHO Classification

Myeloid Neoplasms



Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Name	Dysplastic lineages	Cytopenias*	Ringed sideroblasts as % of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) ± 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Name	Dysplastic lineages	Cytopenias*	Ringed sideroblasts as % of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis

MDS with < 5% blasts

MDS with excess (≥ 5%) blasts

MDS, unclassifiable

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Epidemiology of MDS

MDS Epidemiology

Age-Adjusted Incidence Rates[a] for the 18 SEER Geographic Areas by Age and Race, 2009-2013

Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
Myelodysplastic Syndromes (MDS)						
By age						
Ages <40	0.1	335	0.1	164	0.1	171
Ages 40-49	0.7	459	0.8	233	0.7	226
Ages 50-59	2.4	1,406				
Ages 60-69	9.3	3,653				
Ages 70-79	30.2	6,539				
Ages 80+	59.8	8,946				
By race						
All Races	4.9	21,338				
White	5.1	17,978				
Black	4.1	1,617				
Asian/Pacific Islander	3.7	1,420				
American Indian/Alaska Native[b]	3.4	76	3.6	38	3.2	38
Hispanic[c]	3.5	1,644	4.4	866	2.9	778

Incidence Rate = 4.9/100,000 per year

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

MDS Epidemiology

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Ages 40-49	0.7	459	0.8	233	0.7	226
Ages 50-59	2.4	1,406	2.7	781	2.0	625
Ages 60-69	9.3	3,653	11.5	2,131	7.4	1,522
Ages 70-79	30.2	6,539	40.3	3,861	22.2	2,678
Ages 80+	59.8	8,946	90.0	4,928	42.3	4,018
By race						
All Race		21,338	6.7	12,098	3.7	9,240
White		17,978	7.0	10,351	3.8	7,627
Black	4.1	1,617	5.3	806	3.4	811
Asian/Pacific Islander	3.7	1,420	4.8	777	2.8	643
American Indian/Alaska Native[b]	3.4	76	3.6	38	3.2	38
Hispanic[c]	3.5	1,644	4.4	866	2.9	778

Men > Women

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

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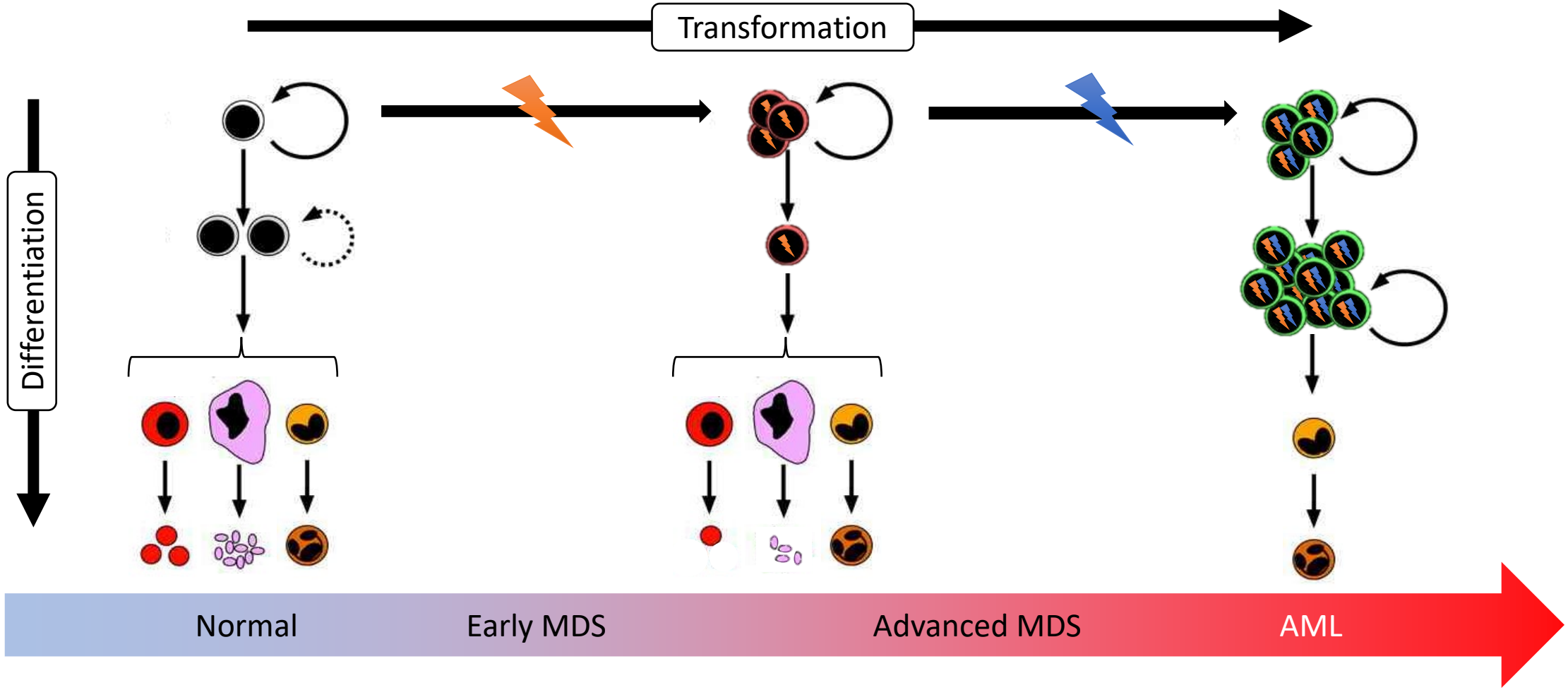
White > African-American

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

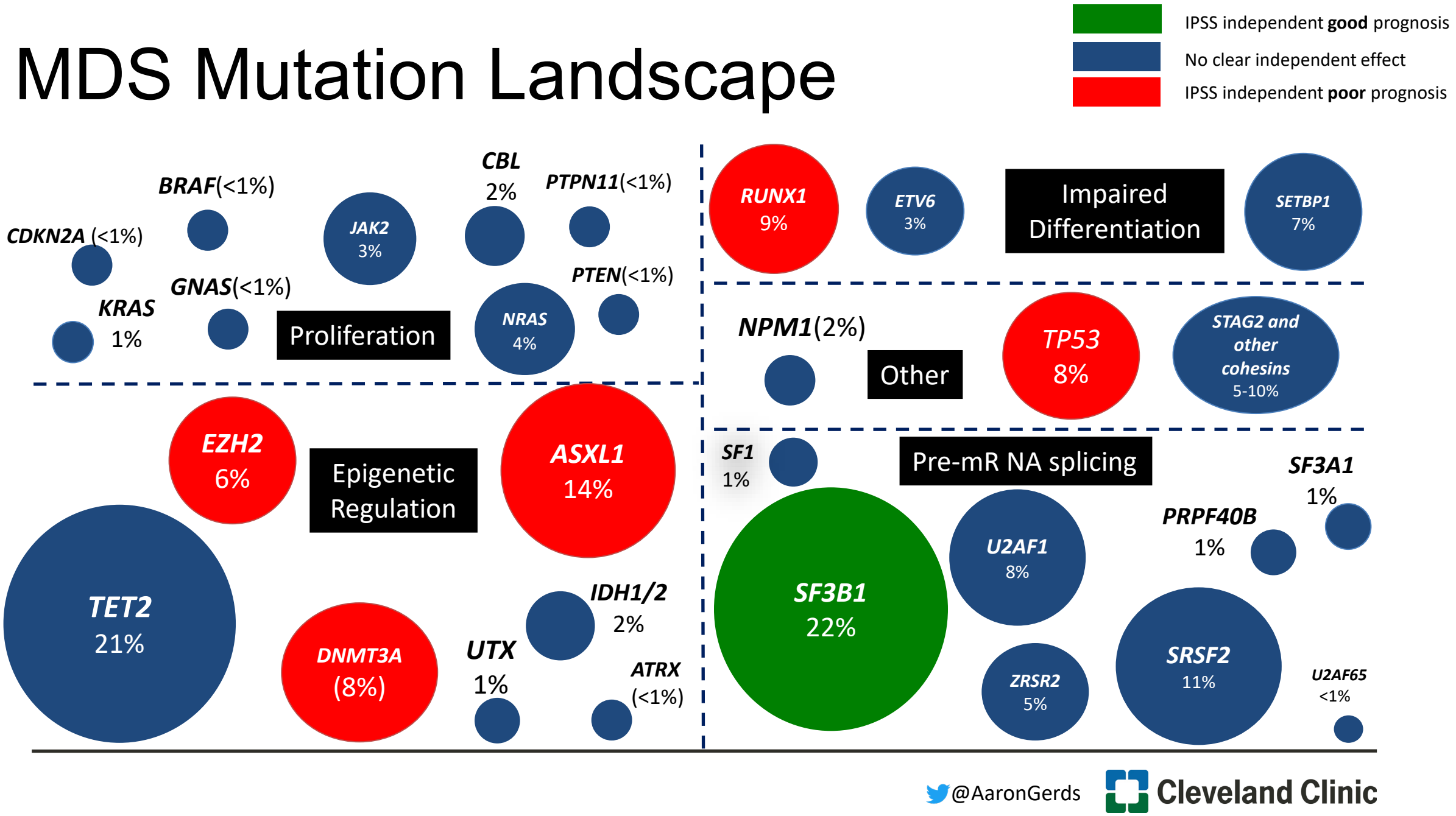
Pathogenesis of MDS

Pathogenesis of MDS



Adapted from: Passegué E, et al., Proc Natl Acad Sci. 2003 Sep 30;100 Suppl 1:11842-9.

MDS Mutation Landscape



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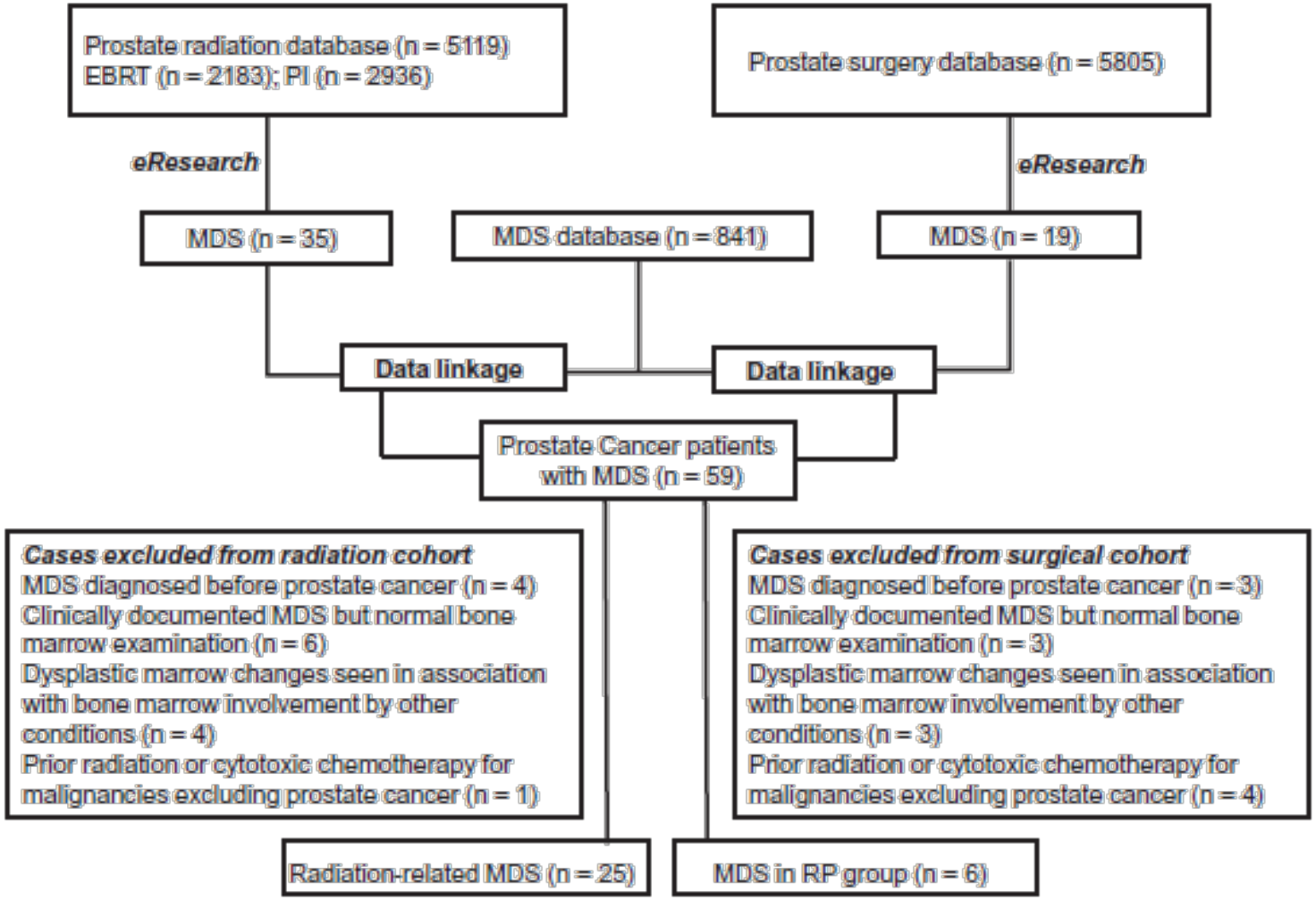
Cross-sectional analysis of 4,514 MDS patients in the U.S. in 2005-2007

Age (Median)	**Newly diagnosed**	**71 years**
	Established	**72-75 years**
Sex (Mean)	**Male (Newly diagnosed)** **(Established)**	**55%** **51-57%**
Duration of MDS (Median)		**13-16 months**
MDS Status	**Primary**	**88 – 93%**
	Secondary	**7 – 12%**
Secondary	**Chemotherapy**	**55 – 80%**
Cause	**Radiation**	**6 – 21%**
	Chemical exposure	**2 – 9%**

Sekeres et al. *J National Cancer Inst* 2008;100:1542.

MDS and Prostate Cancer Radiotherapy



Mukherjee et al. J National Cancer Inst 2014;106:462

MDS and Prostate Cancer Radiotherapy

	Risk regression model 2§		Risk regression model 4ll	
Age	1.13 (1.06 to 1.19)	<.001	1.20 (1.12 to 1.29)	<.001
BMI			1.12 (1.03 to 1.23)	.01
Radiation vs RP	1.63 (0.59 to 4.53)	.35	1.40 (0.26 to 7.67)	.70

Mukherjee et al. J National Cancer Inst 2014;106:462

MDS Risk Stratification

IPSS-R Cytogenetic Classification

Risk Group	Included karyotypes (19 categories)	Patients in group	Median survival (months)
Very good	del(11q), -Y	2.9%	60.8
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	65.7%	48.6
Intermediate	+8, del(7q), i17(q), +19, +21, any single or double anomaly not listed, two or more independent clones	19.2%	26.1
Poor	der(3q), -7, double with del(7q), complex (3 abnormalities)	5.4%	15.8
Very poor	Complex with ≥ 4 abnormalities	6.8%	5.9

Schanz J, et al., J Clin Oncol. 2012 Mar 10;30(8):820-9.; Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

Scoring the IPSS-R

Parameter	Categories and associated score				
Cytogenetic risk group	Very Good	Good	Int	Poor	Very Poor
	0	1	2	3	4
Marrow blasts	≤ 2%	> 2% - < 5%	5% - 10%	>10%	
	0	1	2	3	
Hemoglobin	≥ 10 g/dL	8 - < 10 g/dL	< 8 g/dL		
	0	1	2		
Platelet count	≥ 100	50 - < 100	< 50		
	0	0.5	1		
ANC	≥ 0.8	< 0.8			
	0	0.5			

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

Scoring the IPSS-R

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Int	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

IPSS-R Risk Groups

Risk group	Points	Patients	Median Survival (years)	Time until 25% develop AML (yr)
Very low	0 - 1.5	19%	8.8	NR
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

http://www.ipss-r.com

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

MDS Prognosis Made Easy!

- **Lower Risk**
  - MDS-SLD/MLD (*RA, RCMD, RCUD*)
  - MDS-RS (*RARS*)
  - MDS del (5q)
  - MDS-U
  - IPSS Low/Intermediate-1 (0-1.0)
  - IPSS-R Very Low/Low/Intermediate (<3.5)

- **Higher Risk**
  - MDS-EB-1, MDS-EB-2 (*RAEB-1, RAEB-2*)
  - IPSS Int-2/High (>1.5)
  - IPSS-R Intermediate/High/Very High (>3.5)

Slide courtesy of Mikkael Sekeres

Treatment of Lower-risk MDS

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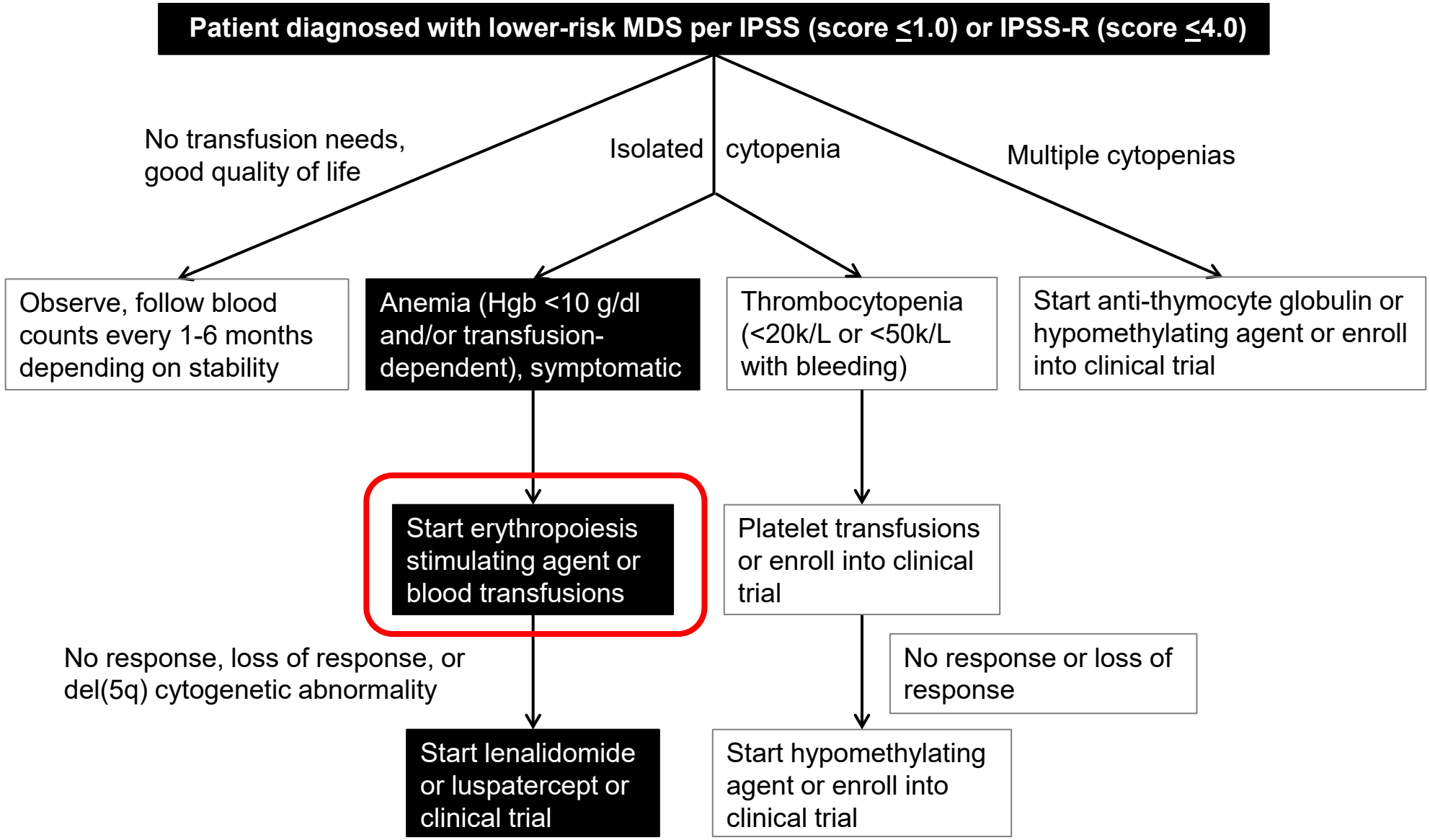


Adapted from Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Erythropoiesis Stimulating Agents

- Number of published regimens:
  - Erythropoietin 150 to 300 U/kg daily
  - Erythropoietin ≥150 U/kg three times weekly
  - Erythropoietin 40,000 U once per week
  - Darbepoetin alpha 75-400 mcg once/week
  - Darbepoetin alpha 500 mcg every 2-3 weeks

- Higher doses may be more effective than lower doses
- Responses may take up to 12-26 weeks

Mundle S, et al., Cancer. 2009 Feb 15;115(4):706-15.
Terpos E, et al., Br J Haematol. 2002 Jul;118(1):174-80.

ORR for ESAs in MDS

	Patients (%)	Response rate	IWG response			Duration of response (median months, range)
			CR/PR	HI-E	HI-N/P	
Growth factors	100	39·5	9·1	66·8	24·1	18 (1–116)
EPO	57·3	39·4	6·1	93·9	–	17 (1–93)
EPO + GCSF	23·4	47·8	23·2	60·6	7·1	19 (2–62)
GMCSF	6·2	37·8	–	–	100	6 (1–18)
EPO + GMCSF	5·8	33·7	–	81·3	18·7	24 (1–116)
GCSF	3·0	47·9	–	4·5	95·5	3 (1–6)
IL3	3·0	17·0	–	–	100	3 (1–12)
IL6	1·3	38·1	–	–	100	5 (2–14)

Overall Response Rate ~40%

Golshayan AR. et al. Br J Haematol. 2007 Apr;137(2):125-32.

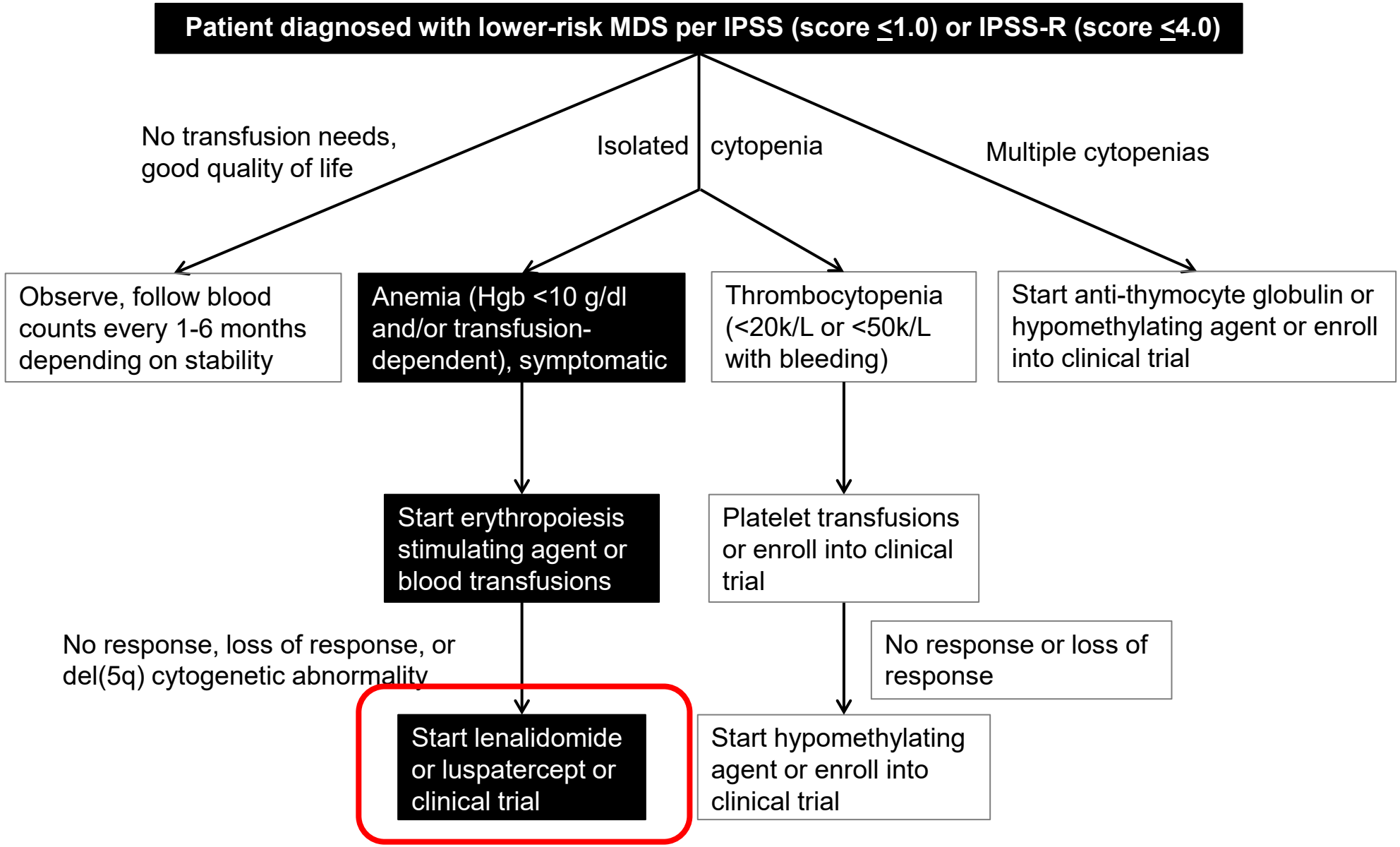
Predictive Model for ESA + GCSF

- Nordic MDS Group [N = 98]

Parameter	Points			
	+2	+1	-2	-3
Serum Epo (mU/mL)	< 100	100 - 500		> 500
RBC Transfusions	< 2 units/mo		≥ 2 units/mo	

Points	Patients	% Response
≥ 2	29	74%
-1 to 1	31	23%
< -1	34	7%

Hellstrom-Lindberg et al, Br J Haematol 1997; 99: 344.



Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Luspatercept (Approved 4/3/2020)

- For the treatment of anemia
  - After ESA *AND*
  - Requiring >/=2 RBC units over 8 weeks *IN*
  - Very low- to intermediate-risk MDS-RS *OR* MDS/MPN-RS-T

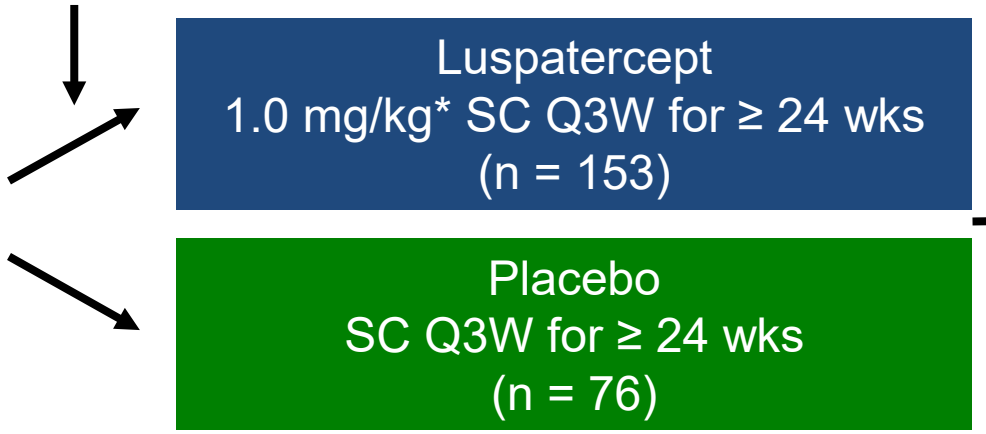
Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

MEDALIST: Study Design

- ≥ 18 yrs of age with non-del(5q) MDS and ring sideroblasts
- IPSS-R: very low/low/intermediate
- Refractory, intolerant, or ineligible for ESAs
- RBC transfusion dependent

(N = 229)

Randomized 2:1



*Could be titrated up to 1.75 mg/kg if needed.

Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24

Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

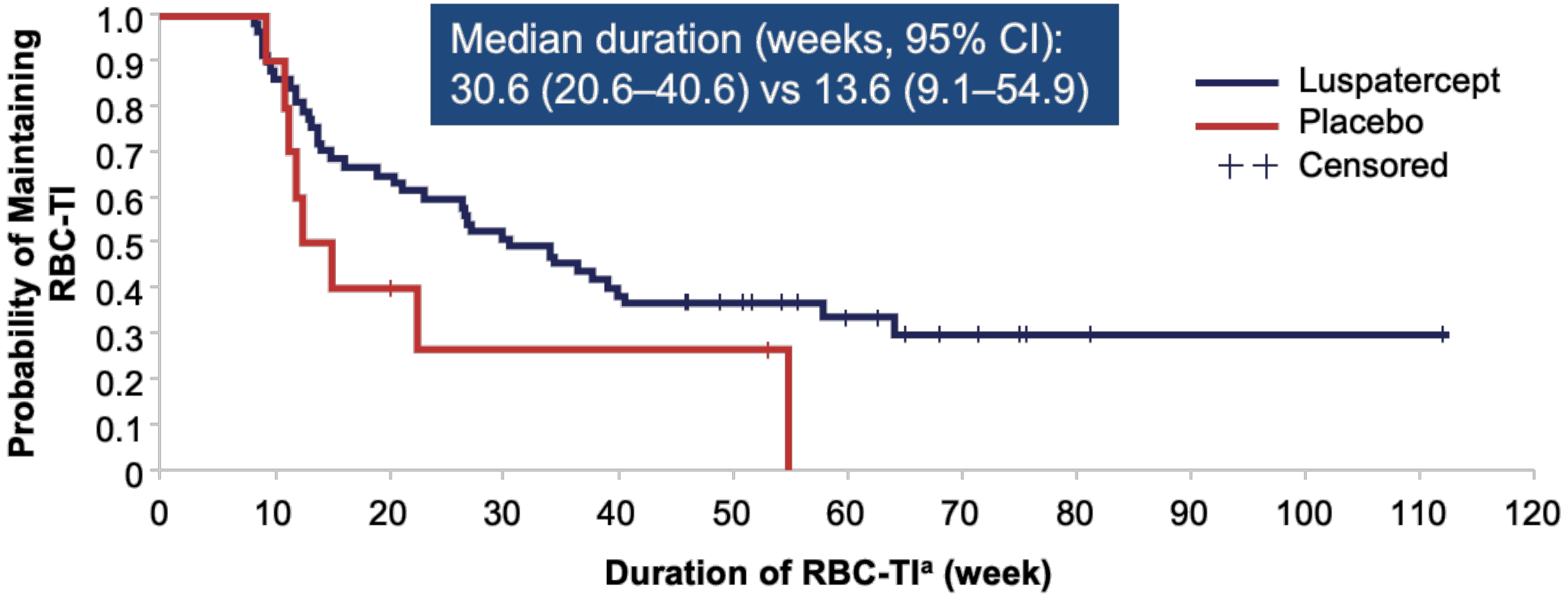
MEDALIST Trial: Primary Endpoint: RBC Transfusion Independence ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P-value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

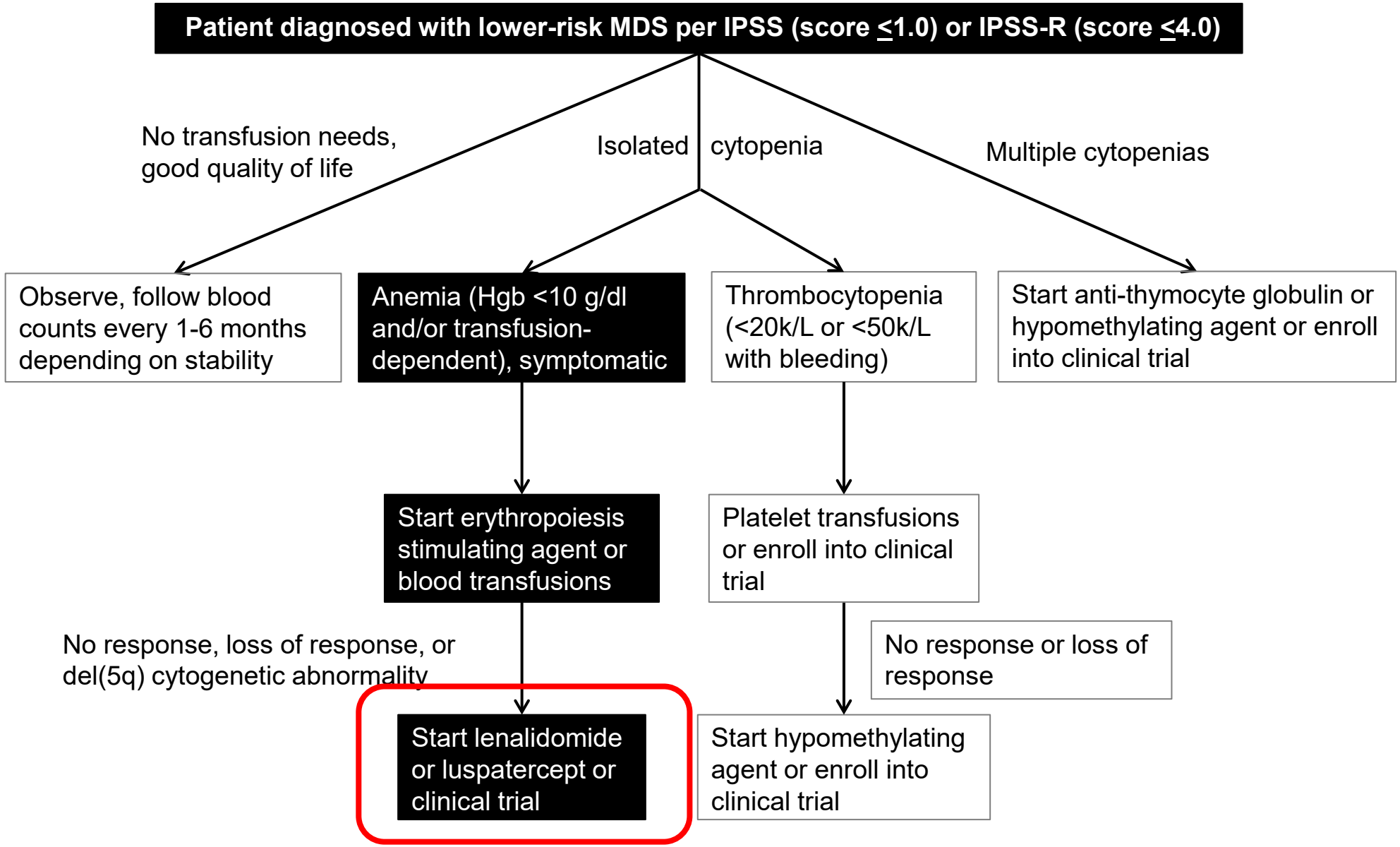
Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

MEDALIST Trial: Duration of RBC-TI Response in Primary Endpoint Responders



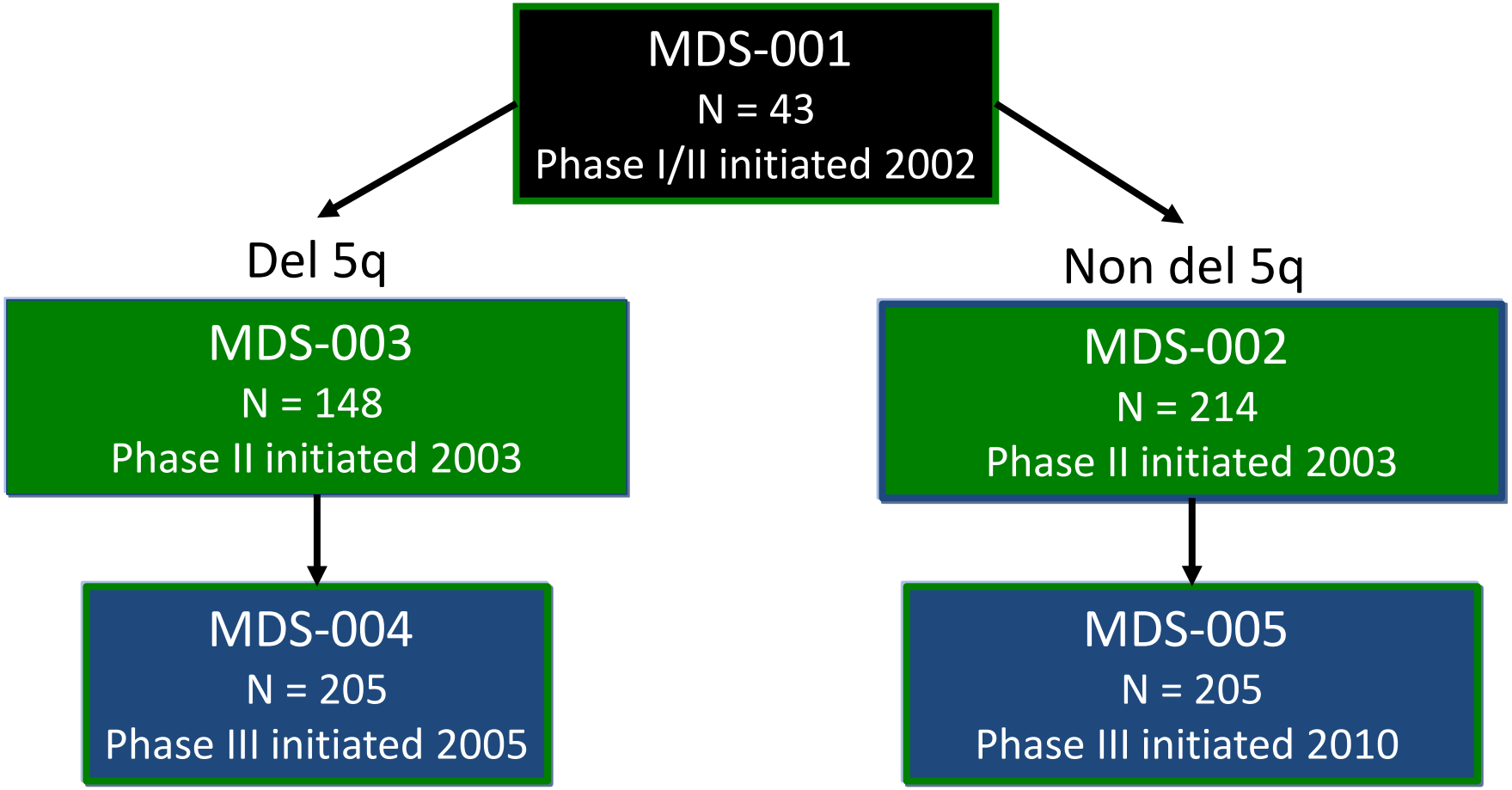
Number of patients												
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.
Fenaux P et al. ASH 2018. Abstr 1. NCT02631070.



Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Development of IMIDs for MDS



US FDA Indication for Lenalidomide

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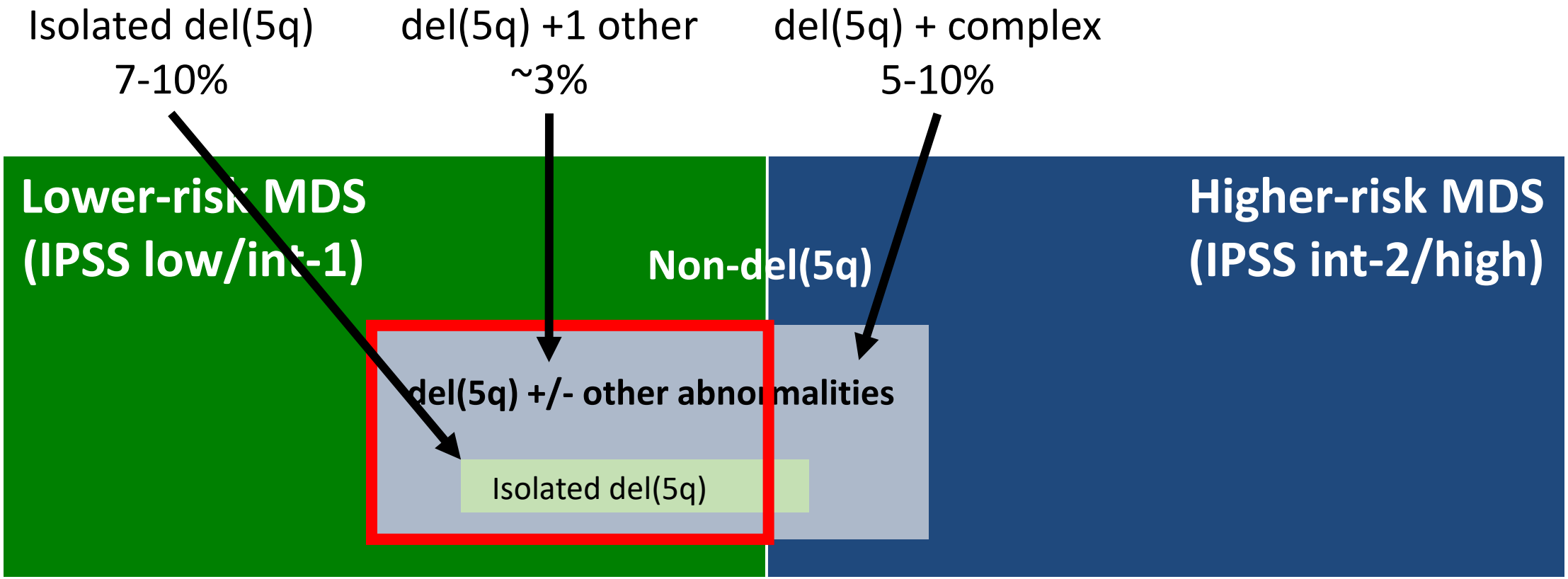
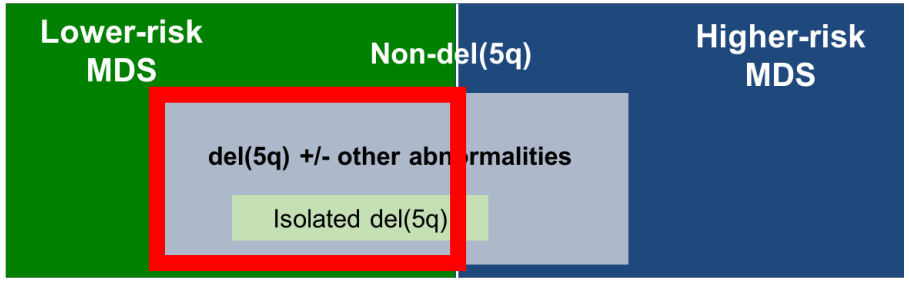


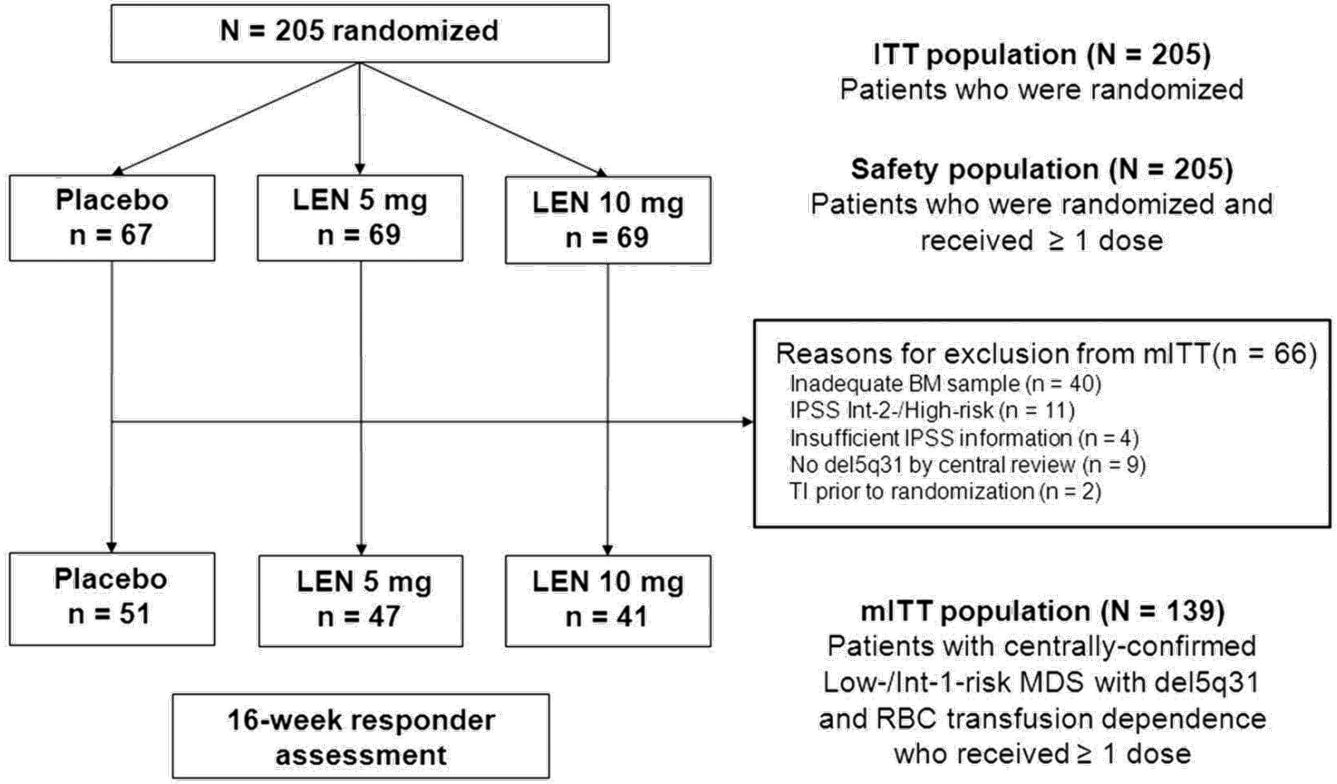
Schanz J et al. J Clin Oncol. 2012 Mar 10;30(8):820-9.
Komrokji RS, Padron E, Ebert BL, List AF. Best Pract Res Clin Haematol. 2013 Dec;26(4):365-75

MDS-004 Study



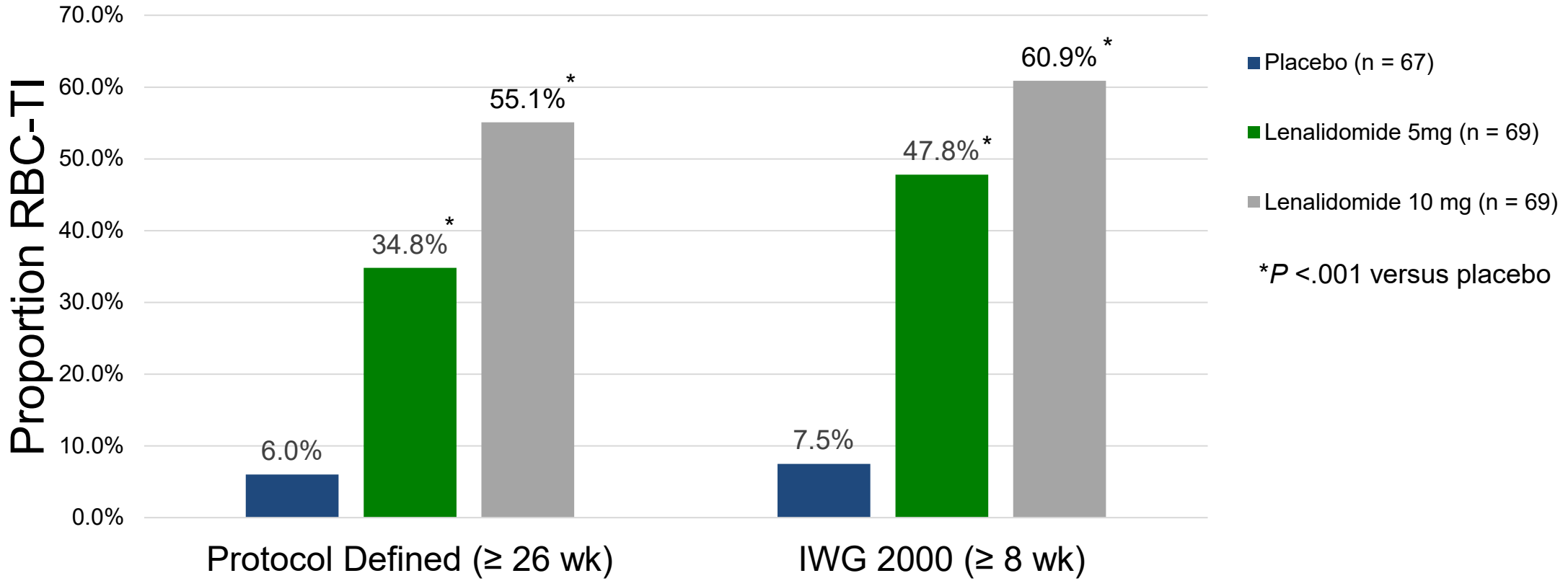
- RBC-Transfusion dependent anemia

- Lenalidomide
  - 10 mg/day days 1 - 21
  - 5 mg/day days 1 - 28
  - Placebo



Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-004 Study: Erythroid Response by RBC-TI

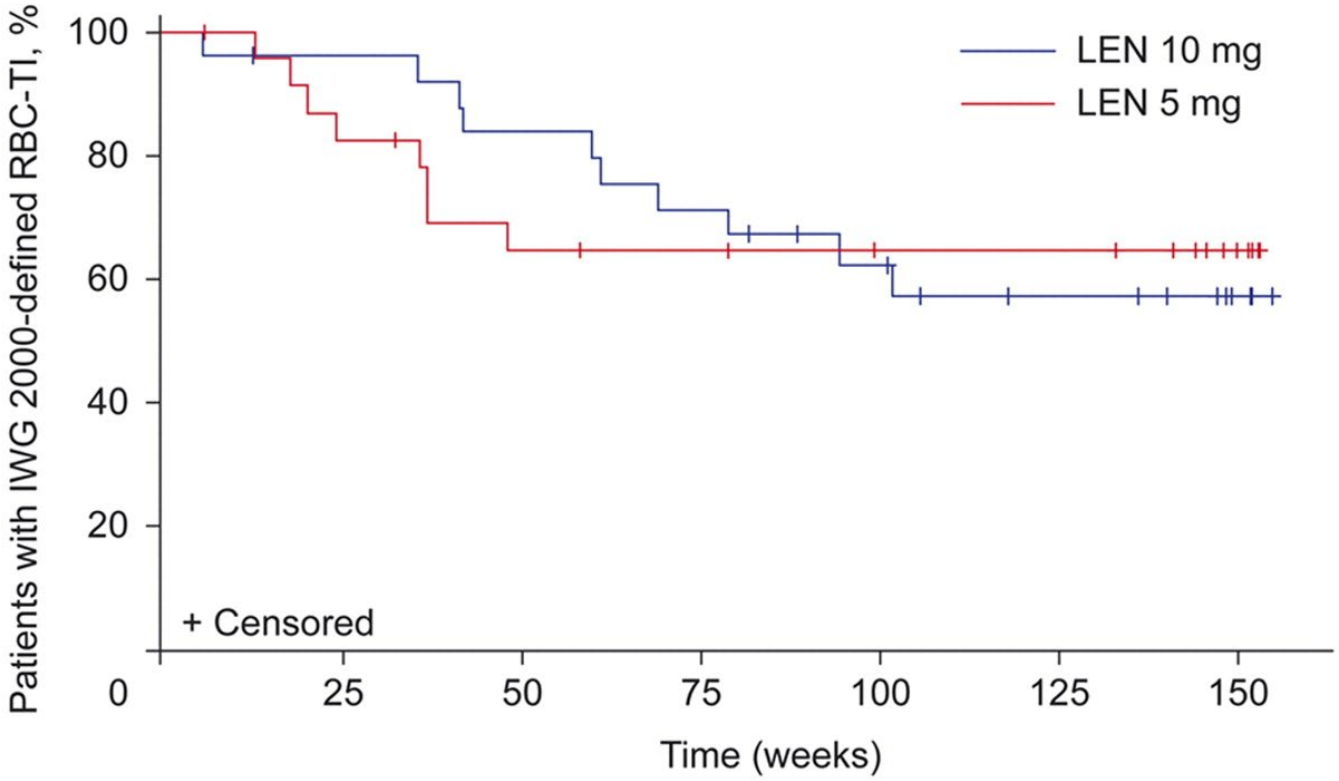


52% pre-treated with ESA, median time from diagnosis to enrolment 2.7 years (0.2-17.2)

Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-004 Study: Response Duration

- Median (95% CI) duration of RBC-TI:
  - LEN 5mg: NR weeks (41.3-NR)
  - LEN 10mg: NR weeks (82.9-NR)
- 30% patients on LEN 10mg had a major cytogenetic response (20% minor)

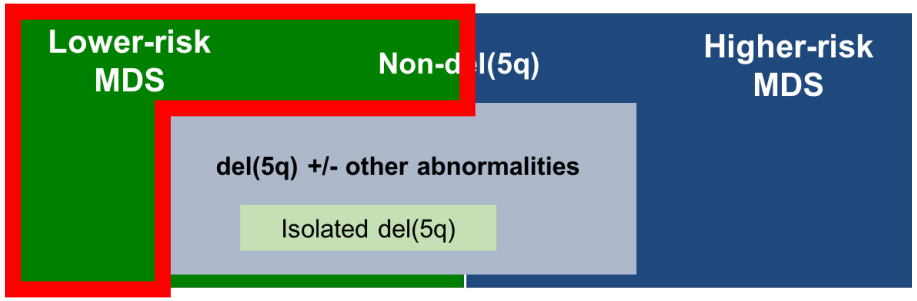


Patients at risk, n

LEN 10 mg	25	23	20	17	13	9	7
LEN 5 mg	24	20	15	13	12	11	7

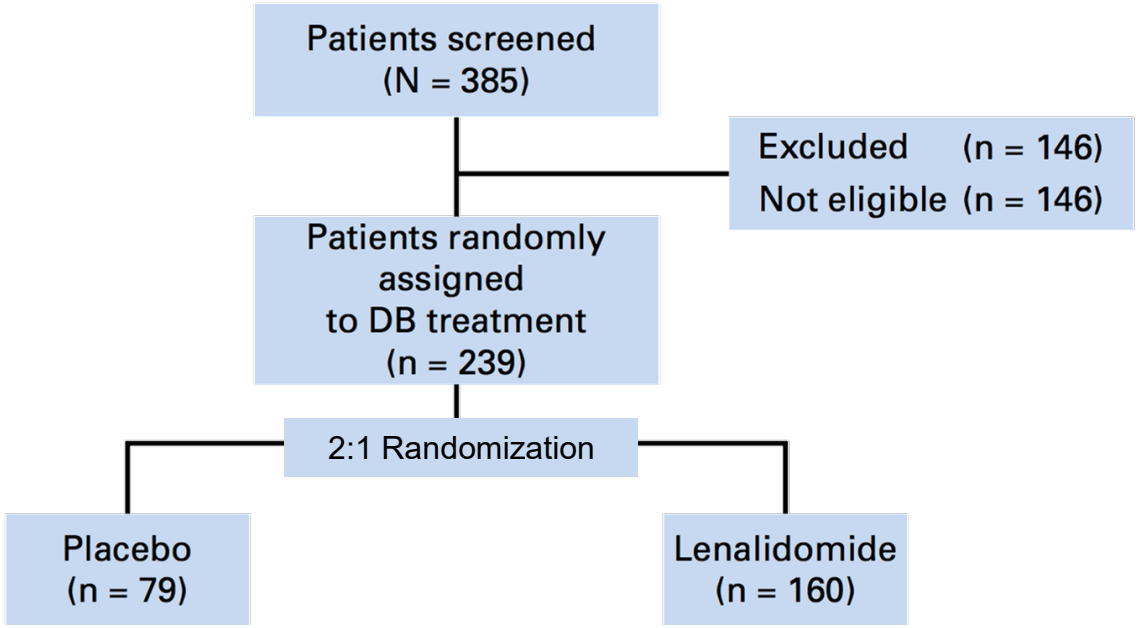
Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-005 Study



- RBC-Transfusion dependent anemia
- R/R or unlikely to respond to ESA

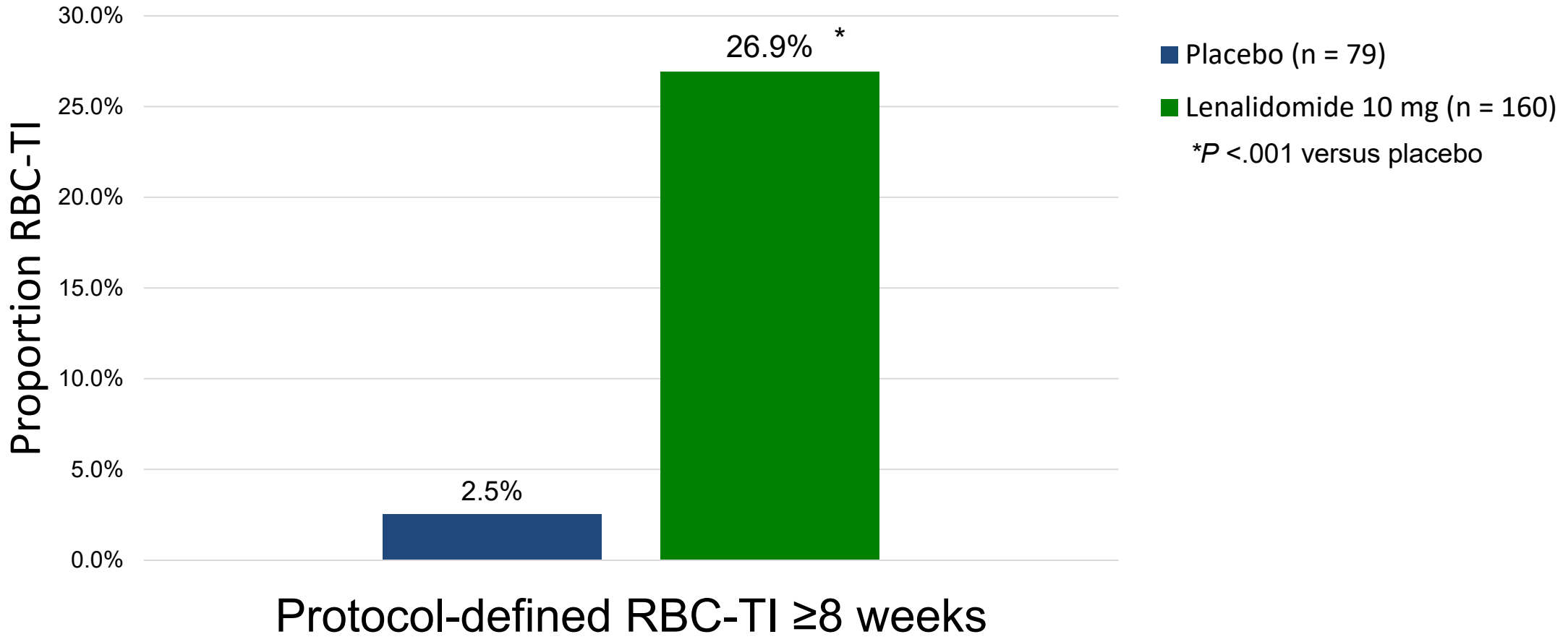
- Lenalidomide
  - 10 mg/day days 1 - 28
  - Placebo



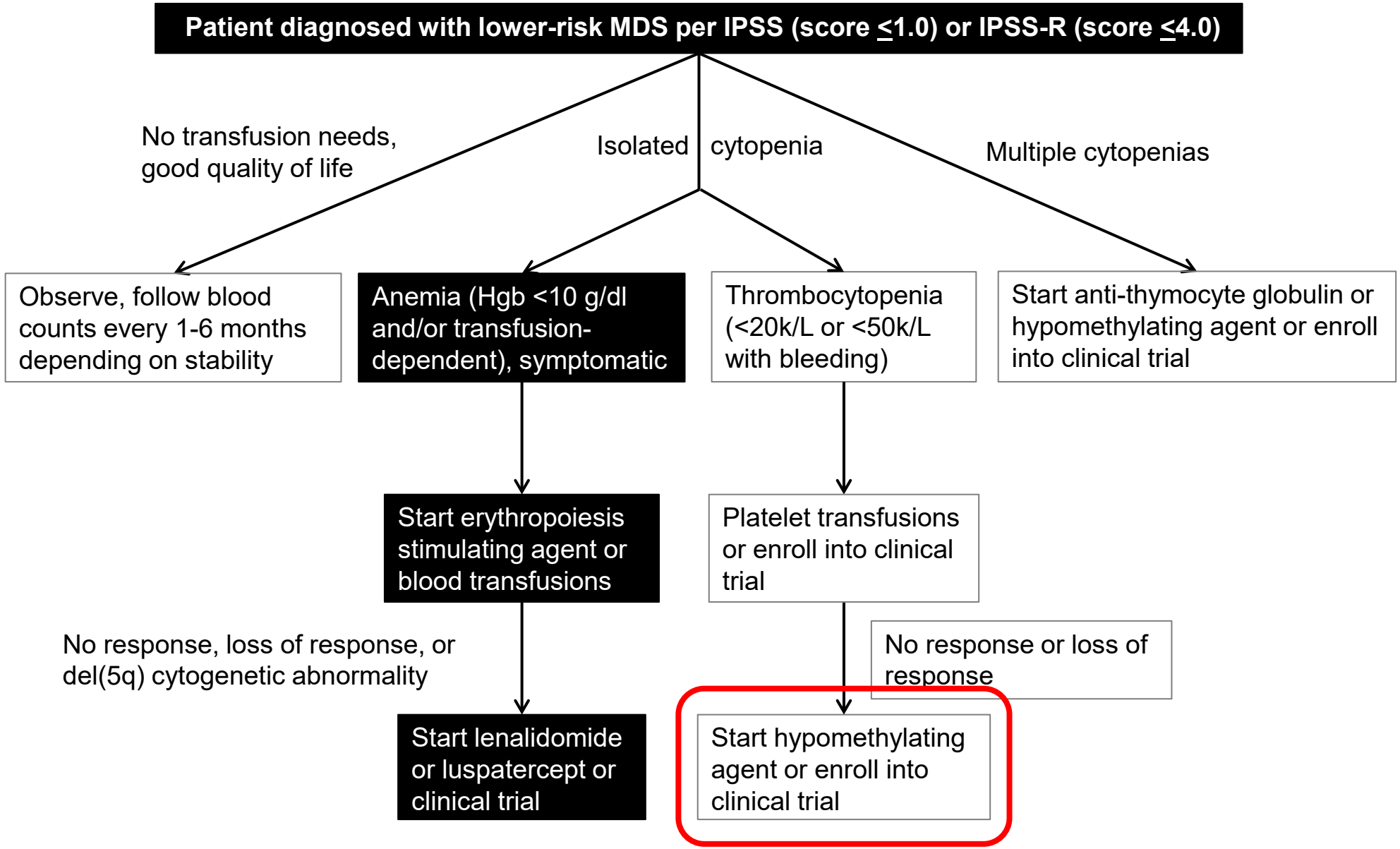
Somatic mutations (n = 198)	
SF3B1	58.6%
TET2	33.3%
ASXL1	23.2%
DNMT3A	13.6%

Santini V et al. J Clin Oncol. 2016 Sep 1;34(25):2988-96.

MDS-005 Study: Erythroid Response by RBC-TI



Santini V et al. J Clin Oncol. 2016 Sep 1;34(25):2988-96.



Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Low-Dose HMA for LR-MDS

- Regimens:
  - DAC 20 mg/m2 IV D1-3 every 4 weeks
  - AZA 75 mg/m2 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)

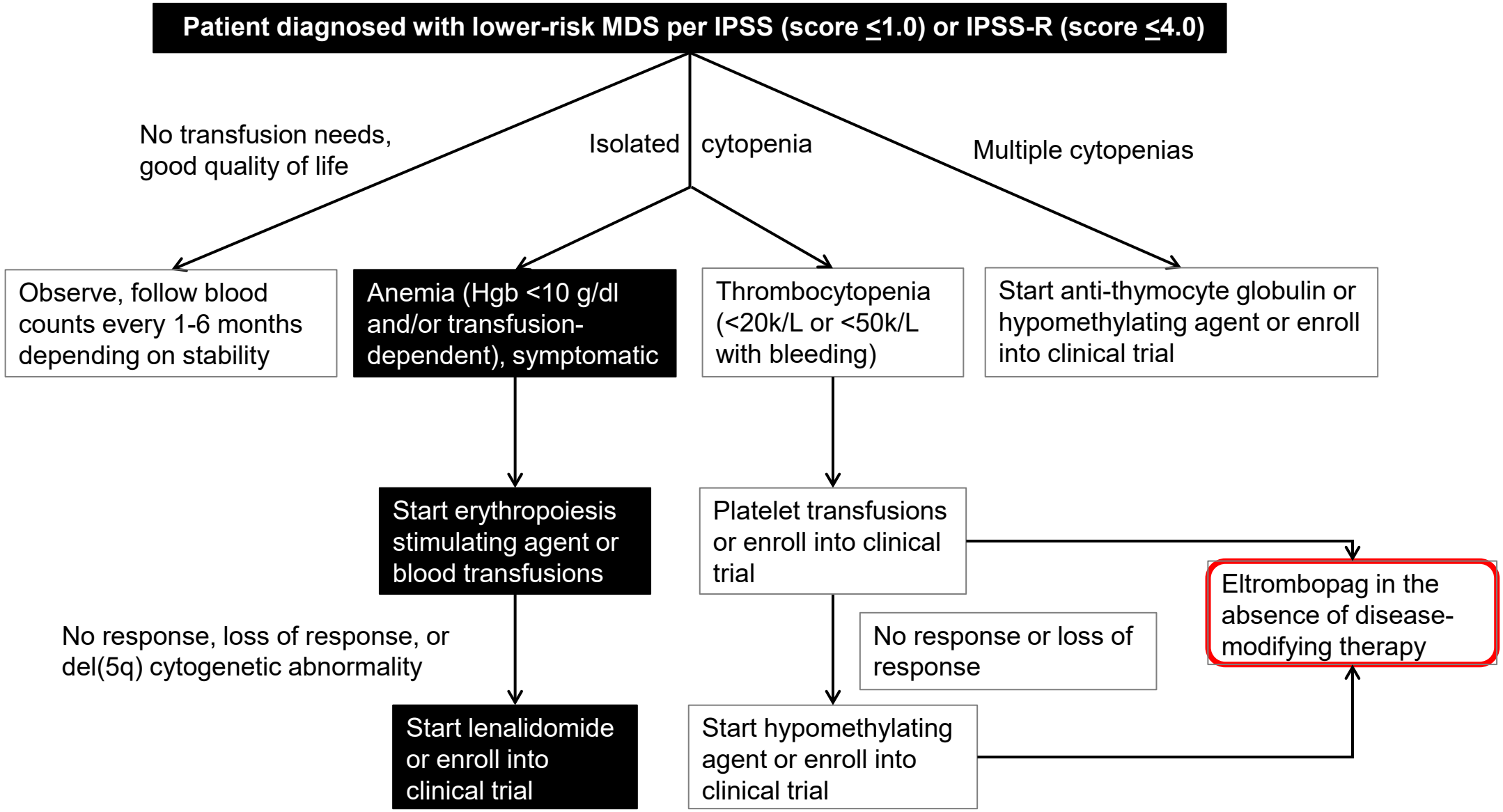
Jabour and Short et al. Blood. 2017 Sep 28;130(13):1514-1522.

Low-Dose HMA for LR-MDS

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)

Jabour and Short et al. Blood. 2017 Sep 28;130(13):1514-1522.

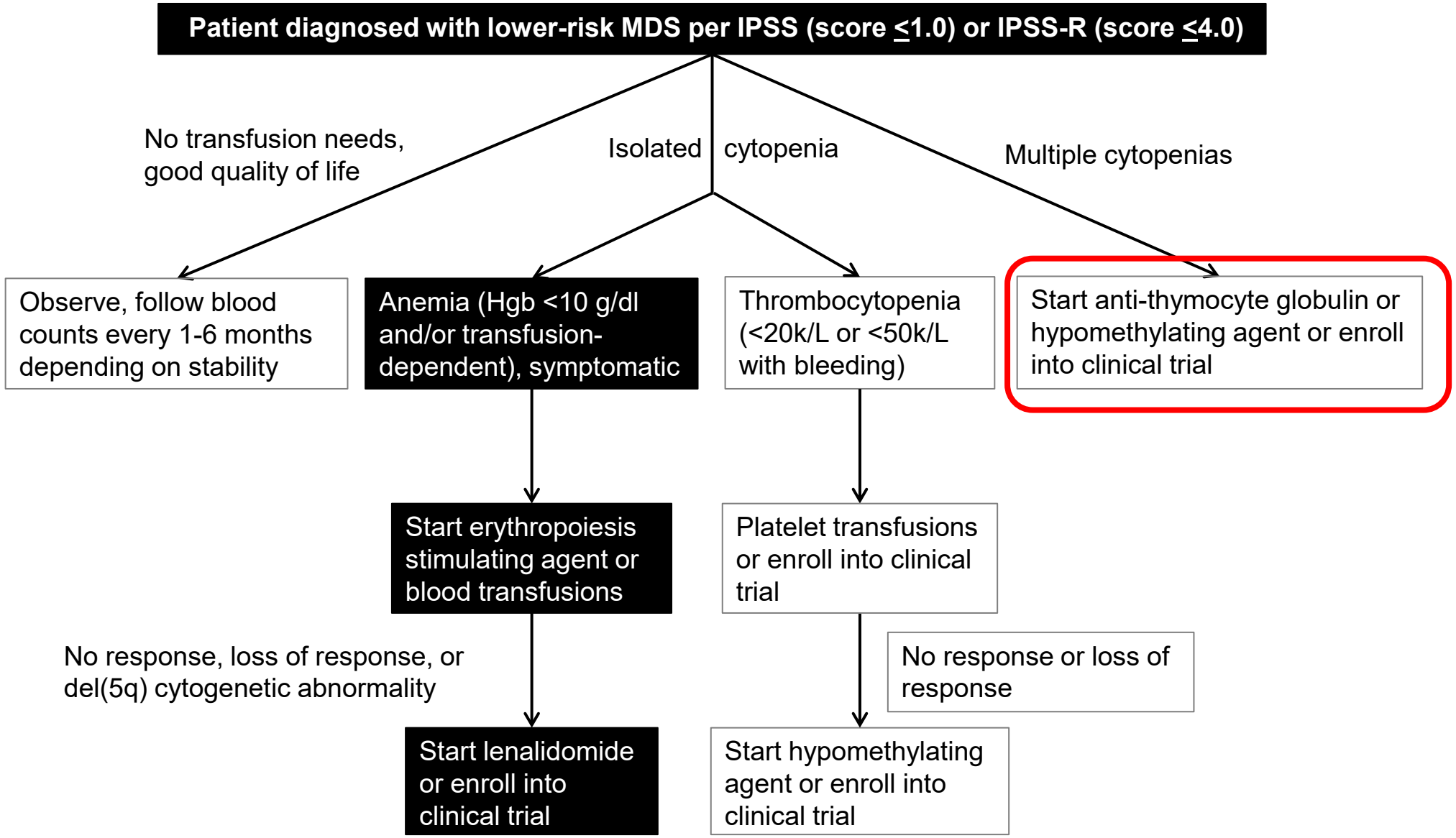


Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Eltrombopag for MDS

- ASPIRE randomized (2:1), placebo-controlled, phase 2 trial
  - High-risk MDS/AML (145 patents randomized)
  - Primary endpoint: Clinically relevant thrombocytopenic events (CRTE)
    - Grade 3 hemmorhage
    - Transfusion for platelets <10K
  - Average weekly CRTE proportions from weeks 5–12 were significantly lower with eltrombopag (54%) than with placebo (69%, OR 0.20, 95% CI 0.05–0.87; p=0·032).
  - Did not show disease progression
- Low-risk MDS (n=30)
  - 11 (44%) of 25 patients evaluable for response responded
    - 6 with bi-lineage responses
  - Liver enzyme elevations were seen that required dose interruption
  - The most frequent treatment-related AE's were nausea and vomiting (20%), skin lesions (20%), headaches (17%), and discoloration of the sclerae (17%)

Mittelman M, et al. Lancet Haematol. 2018 Jan;5(1):e34-e43.
Vincente A, et al. Haematologica 2020;105(12):2785-2794

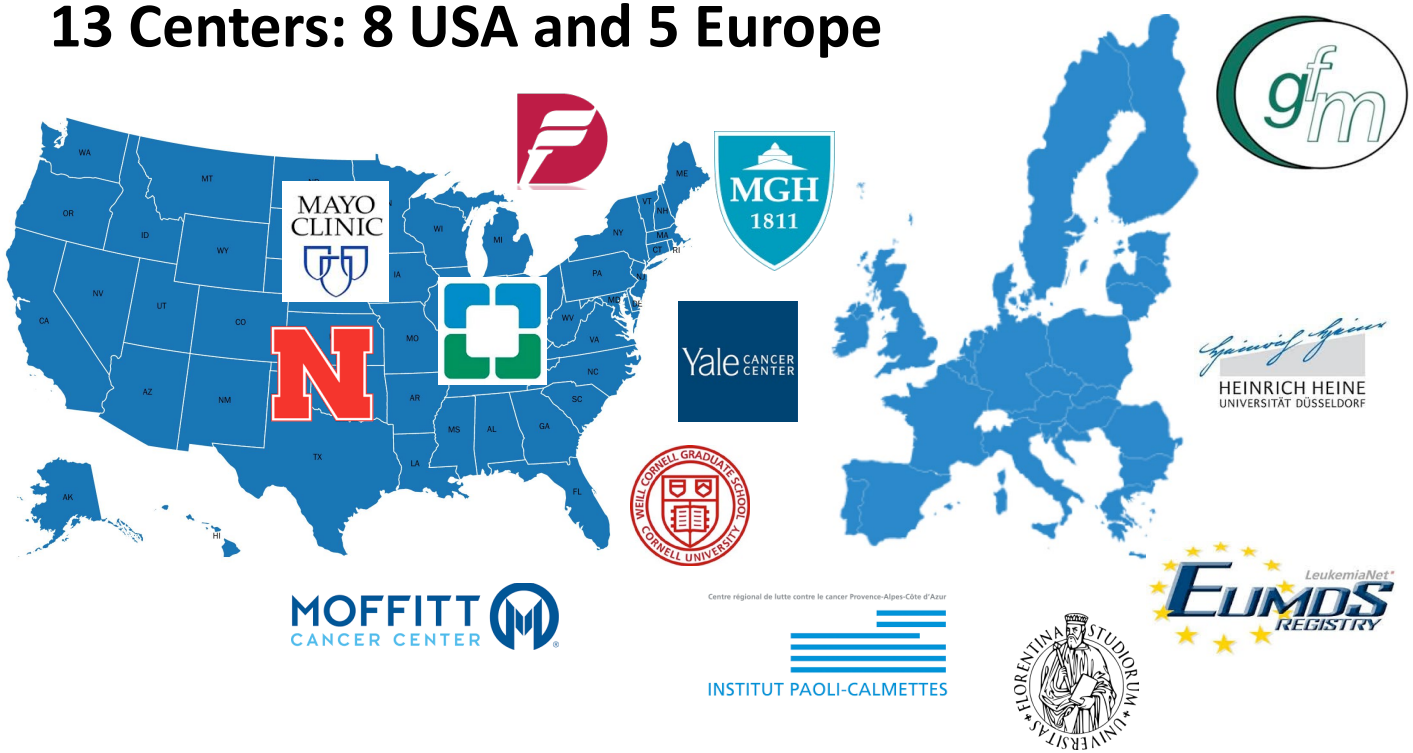


Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Anti-thymocyte Globulin for MDS

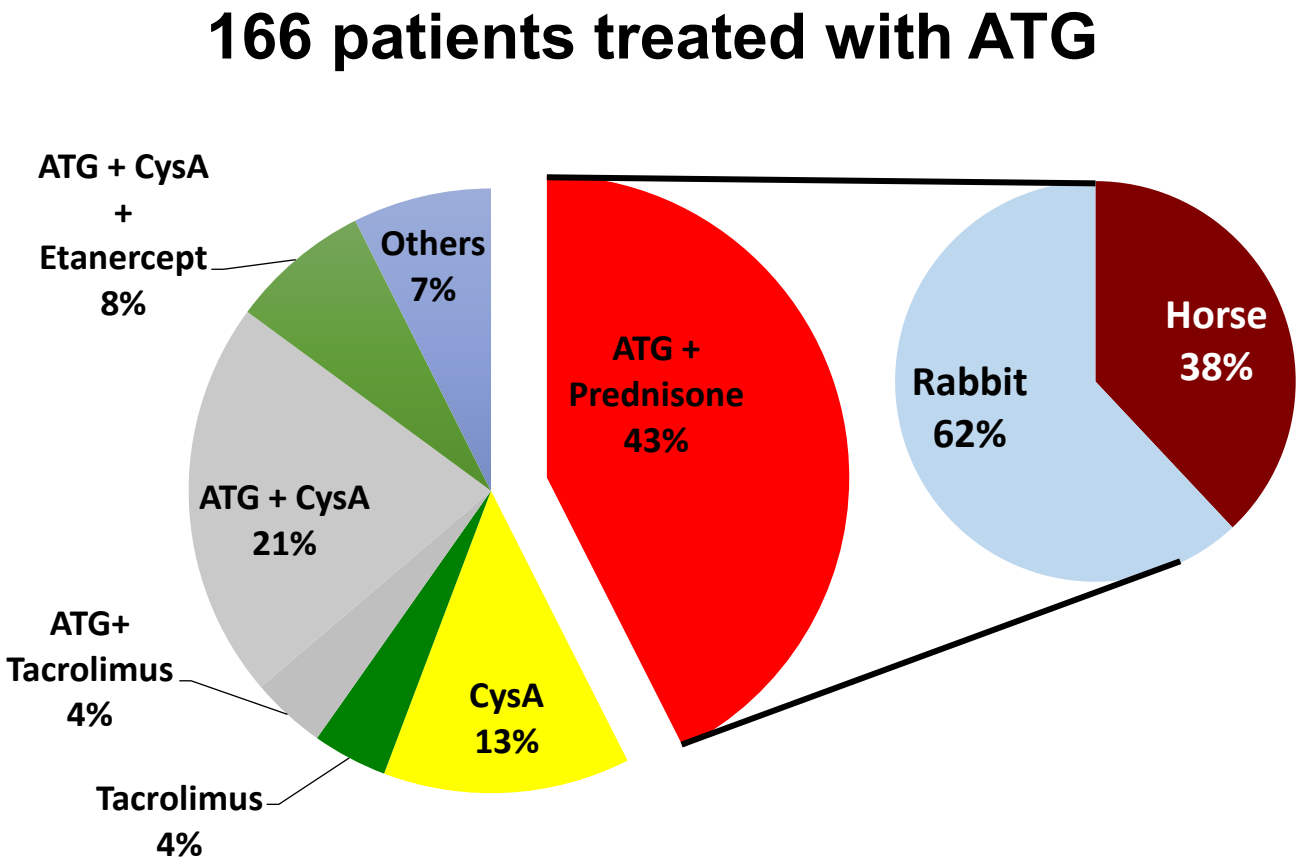
A retrospective cohort, International, multi-center, study

13 Centers: 8 USA and 5 Europe



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

Anti-thymocyte Globulin for MDS



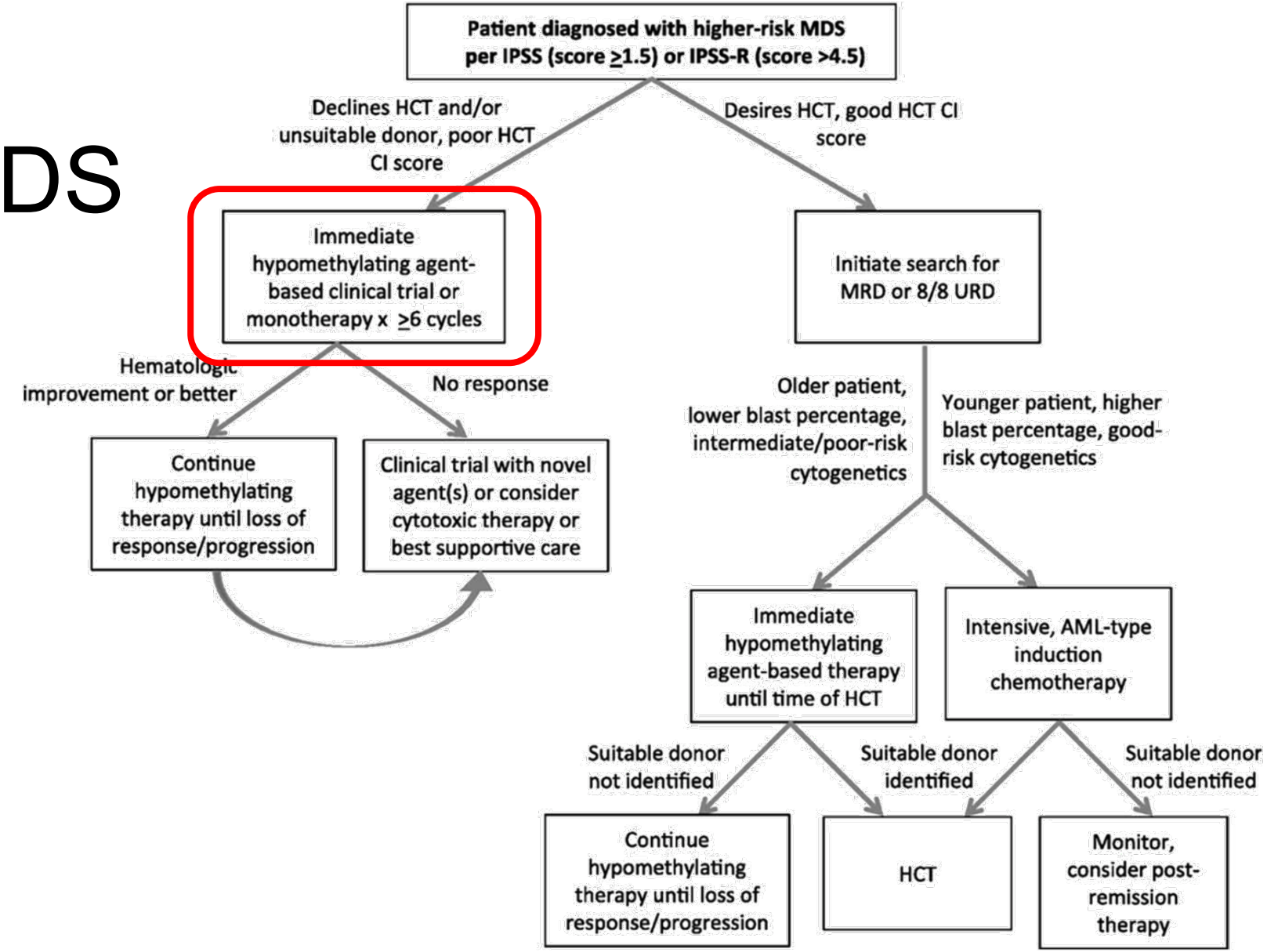
Response	%	95%CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR	48.8	39.8-57.9

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

Treatment of Higher-risk MDS

Cleveland Clinic
Taussig Cancer Institute

Treatment of Higher-risk MDS

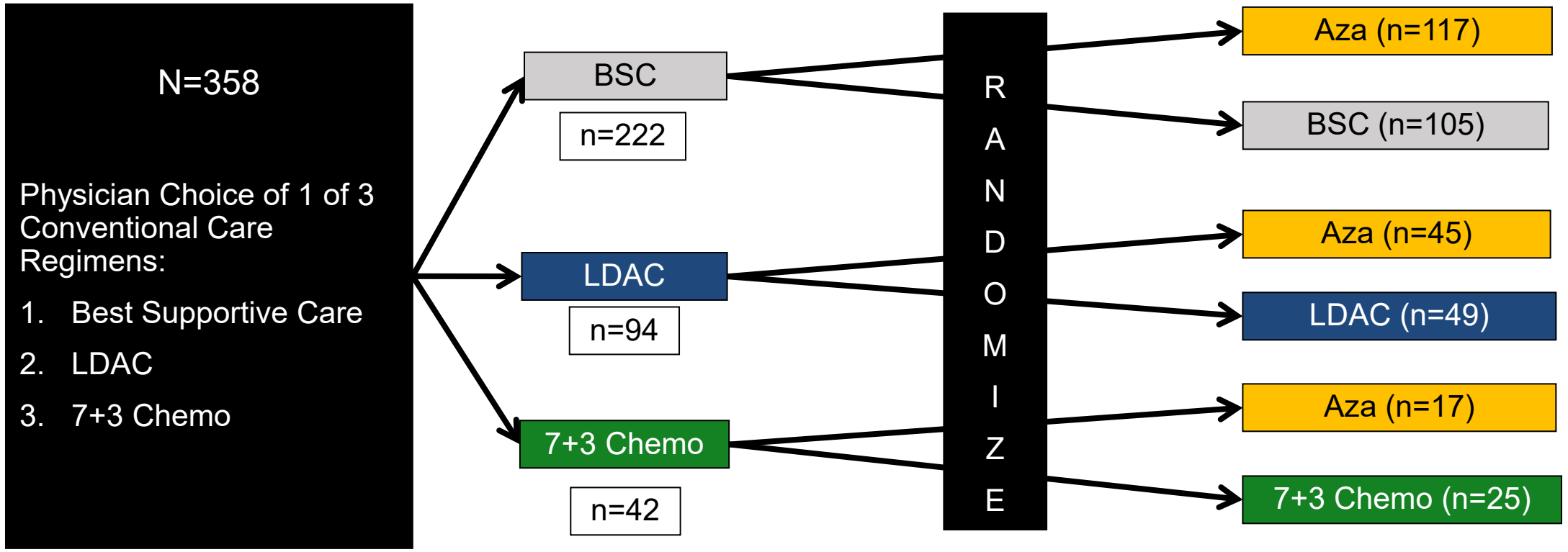


Sekeres MA., Cutler C. *Blood*. 2014 Feb 6;123(6):829-36.

Hypomethylating Agents

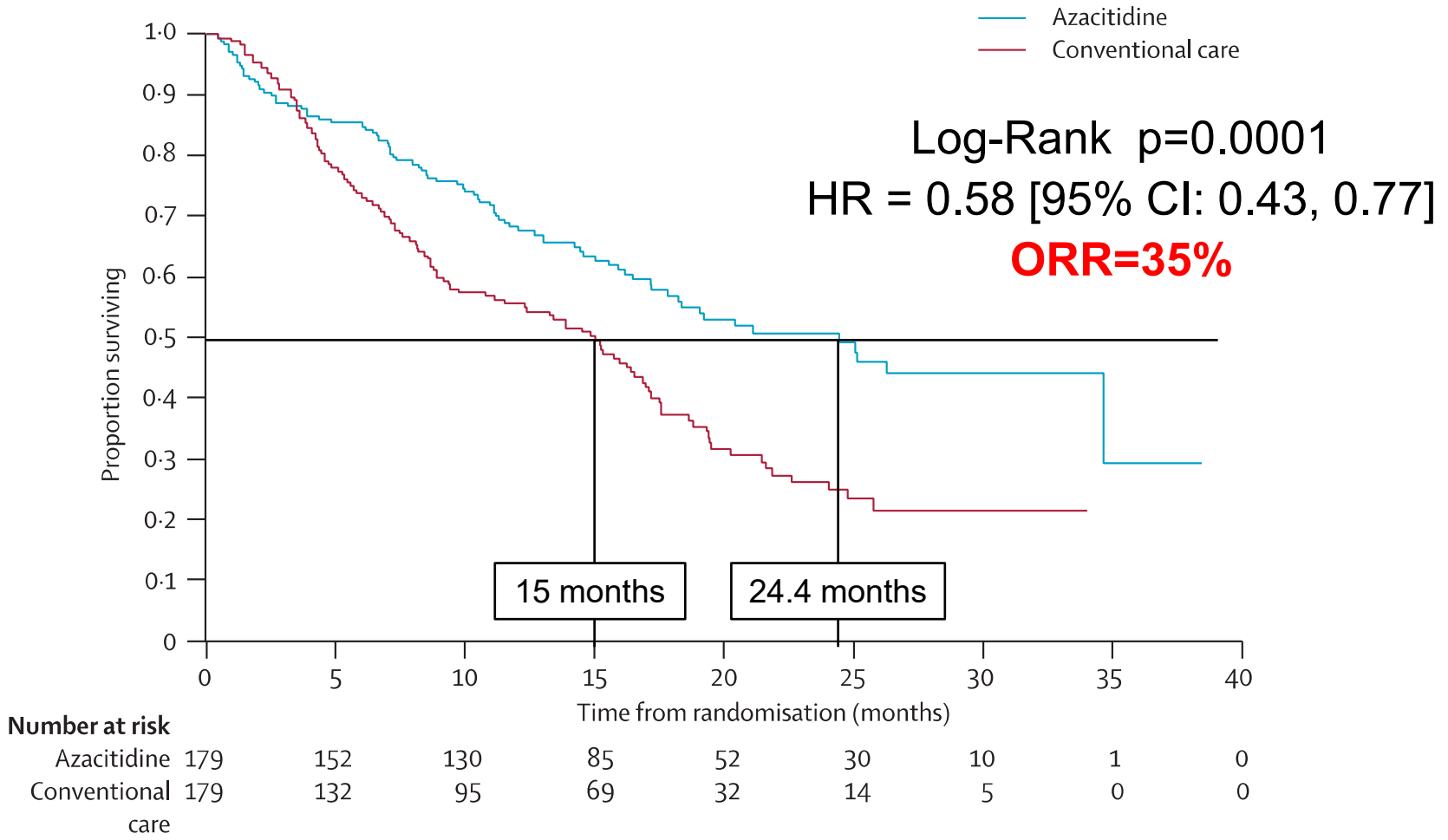
- Azacitidine and decitabine
  - Favorable toxicity profile
  - Outpatient administration
  - Delay progression of MDS to AML
  - Shown survival advantage over conventional care (azacitidine)

AZA-001 Randomization Schema



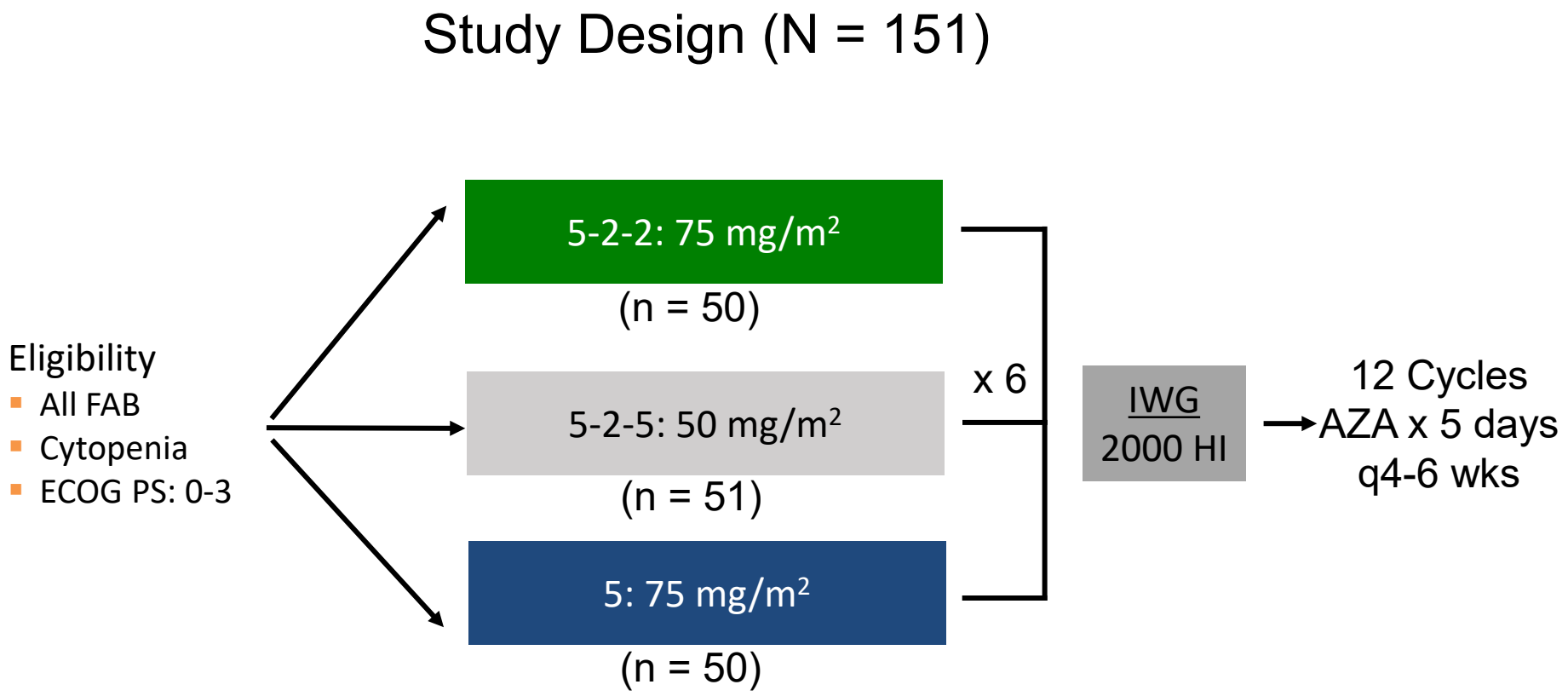
Fenaux P, et al. Lancet Oncol. 2009 Mar;10(3):223-32.

AZA-001 Overall Survival



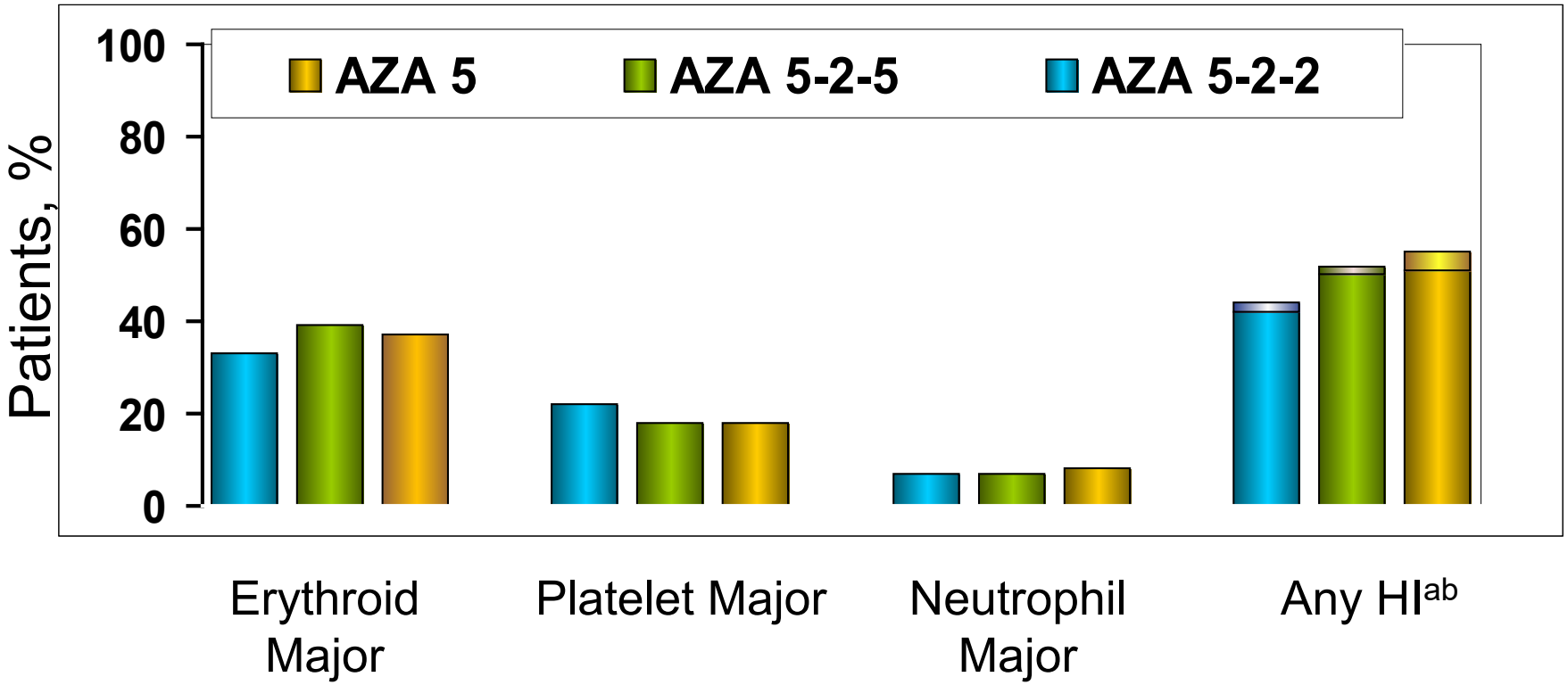
Fenaux P, et al. Lancet Oncol. 2009 Mar;10(3):223-32.

Randomized Phase II Study of Alternative AZA-002 Dose Schedules



Lyons RM et al. *J Clin Oncol.* 2009;27:1850-1856.

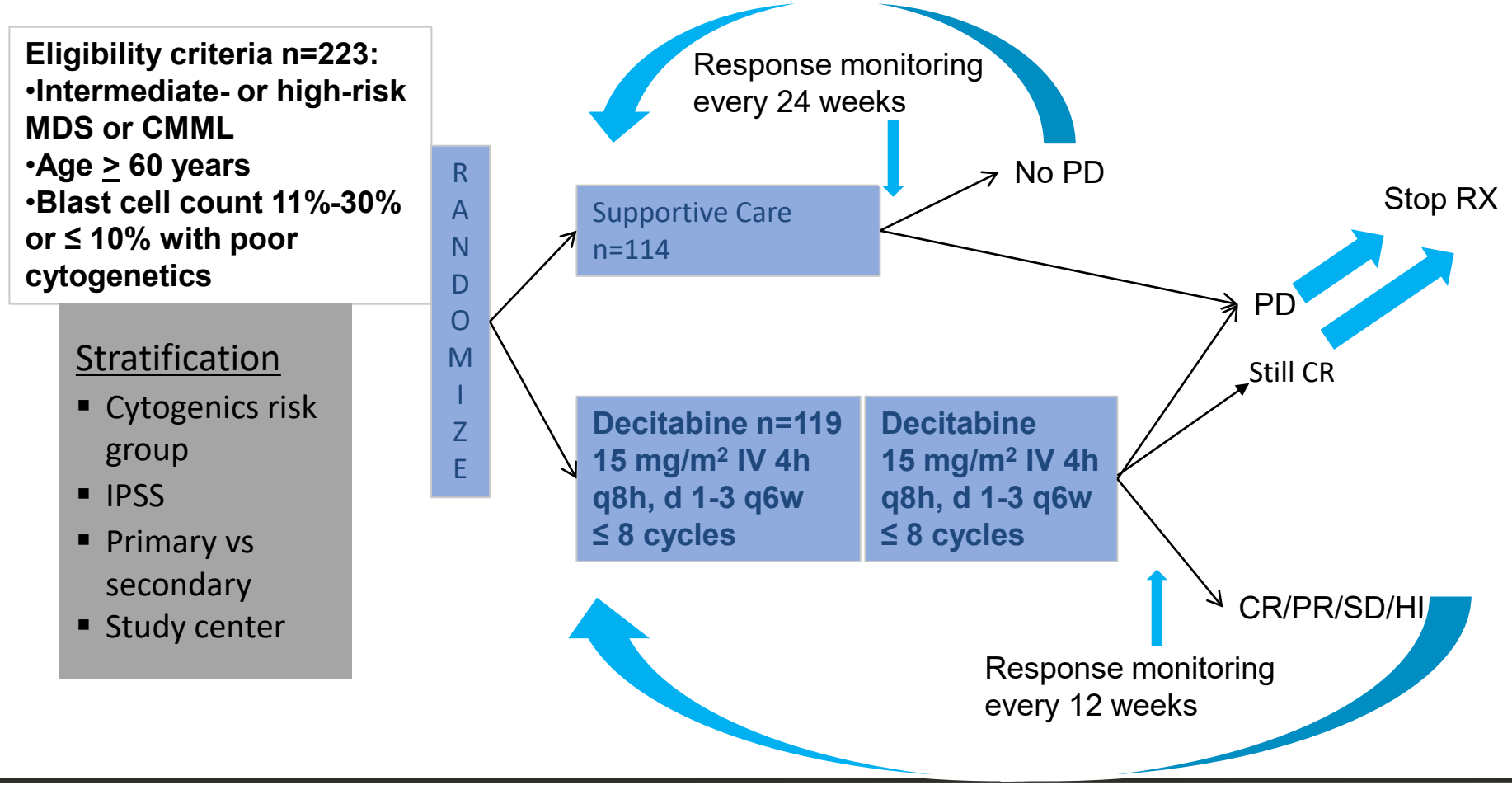
AZA-002: Hematologic Improvement



[a] Patients counted only once for best response in an improvement category.
[b] Minor improvement at top of HI columns.

Lyons RM et al. *J Clin Oncol.* 2009;27:1850-1856.

Randomized Phase III Study of Low-Dose Decitabine for Patients With Higher-Risk MDS EORTC-06011



Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

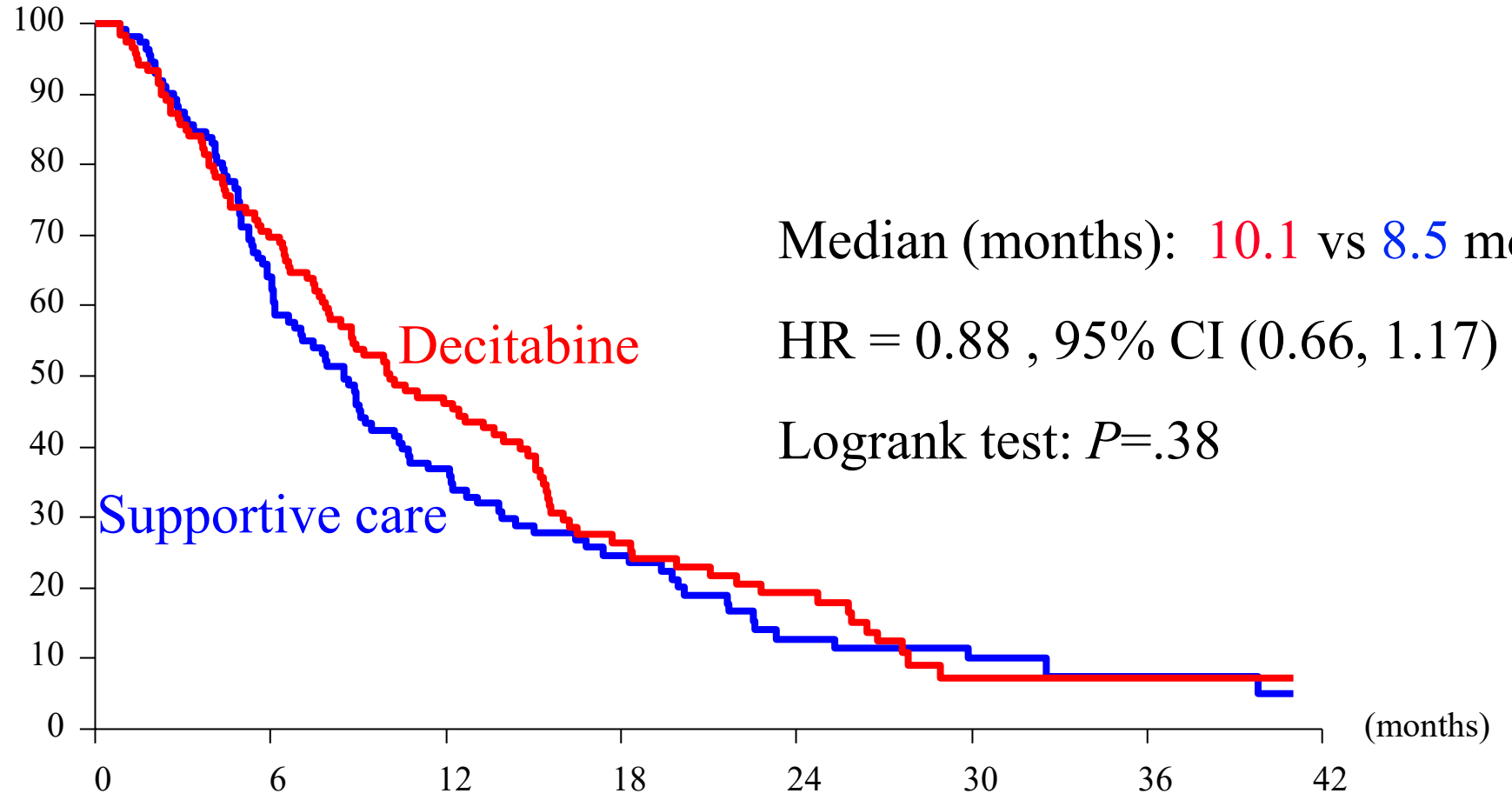
EORTC-06011 Reason for going off-protocol

	Supportive care N=114 (100%)	Decitabine N=119 (100%)
Normal completion	19 (16.7%)	31 (26.1%)
Progression of disease	55 (48.2%)	40 (33.6%)
Toxicity	NA	19 (16.0%)
Prolonged cytopenia	NA	5 (4.2%)
Death	17 (14.9%)	11 (9.2%)
Refusal	14 (12.3%)	6 (5.0%)
Protocol violations	5 (4.4%)	3 (2.5%)
Ineligible	1 (0.9%)	1 (0.8%)
Other	3 (2.6%)	3 (2.5%)

Median time to off-study: 112 days vs 180 days

Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

EORTC-06011 Overall Survival



Median (months): 10.1 vs 8.5 months

HR = 0.88 , 95% CI (0.66, 1.17)

Logrank test: *P*=.38

O	N	Number of patients at risk :					
96	114	71	38	22	10	6	3
99	119	83	53	24	15	4	4

Supportive care

Decitabine

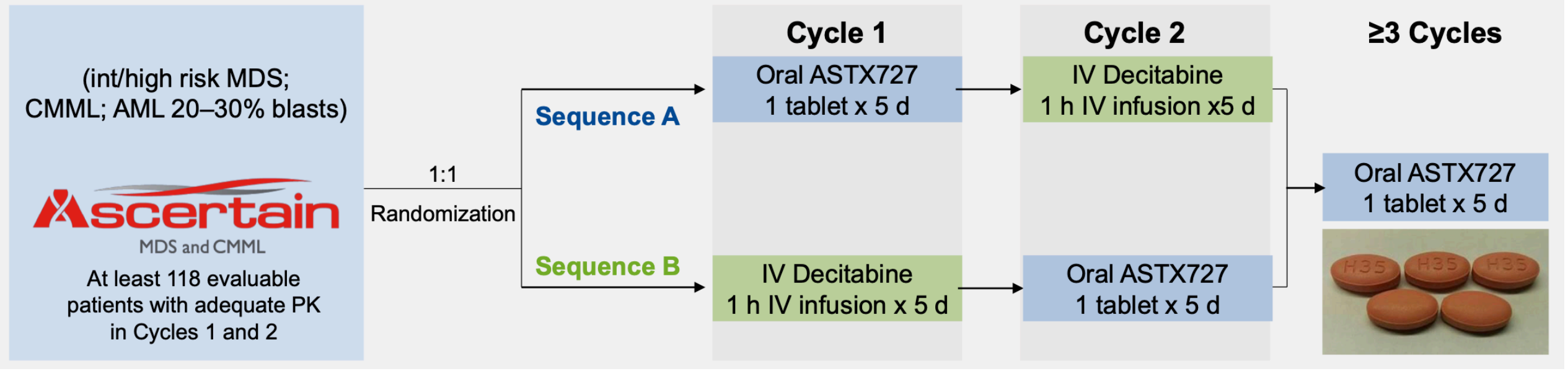
Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

No survival advantage for DAC?

- Number of treatments courses given
- Different populations and comparator groups
  - MDS duration
  - Cytogenetic risk groups
  - Performance status
- How the drug was given
- There is a true difference between aza and dac

Oral Decitabine (Approval 7/7/2020)

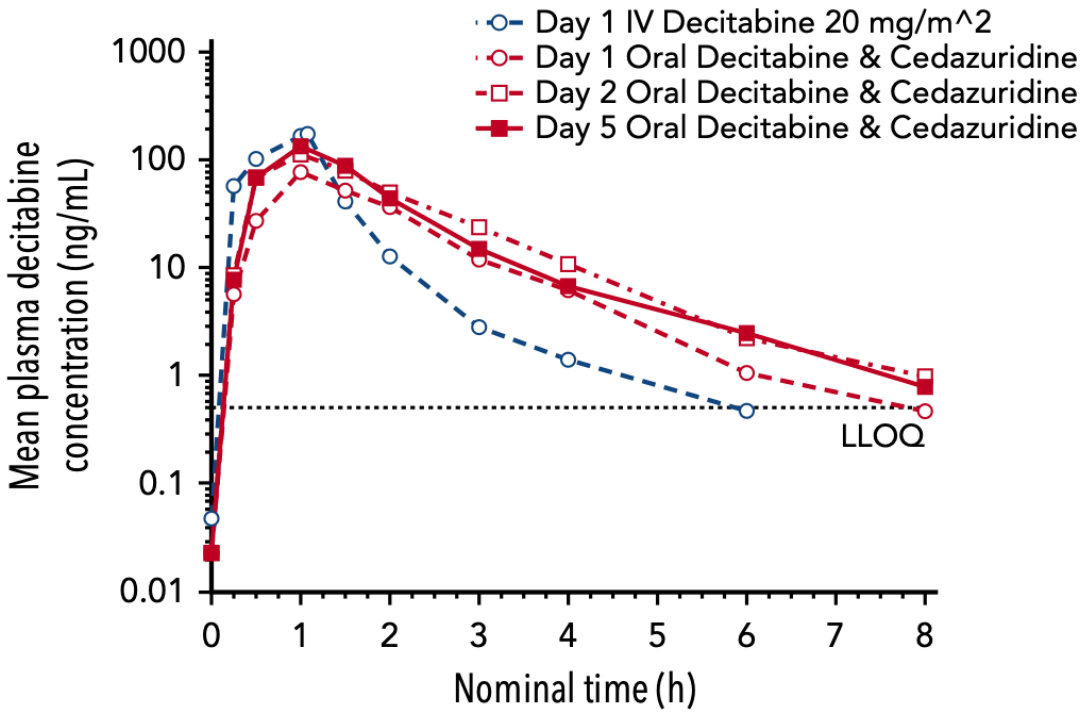
- 35mg decitabine/100mg cedazuridine vs deciatibine (20 mg/m^2)
  - ASTX727-01-B (N=80) – Phase 1/2
  - ASTX727-02 (N=133) – Phase 3



Savona M, et al. *Lancet Haematol*. 2019 Apr;6(4):e194-e203.
Garcia-Manero, G et al. *Blood*. 2020 Aug 6;136(6):674-683.

Oral Decitabine

- ASTX727-01-B
  - CR rate of 18% (95% CI, 10%-28%)
  - Median duration of CR 8.7 (range, 1.1-18.2) months
- ASTX727-02 (Ascertain)
  - CR rate of 21% (95% CI, 15%-29%)
  - Median duration of CR 7.5 (range, 1.6-17.5) months
- Both studies showed similar:
  - Side effect profiles/toxicity
  - PK data between oral and IV formulation

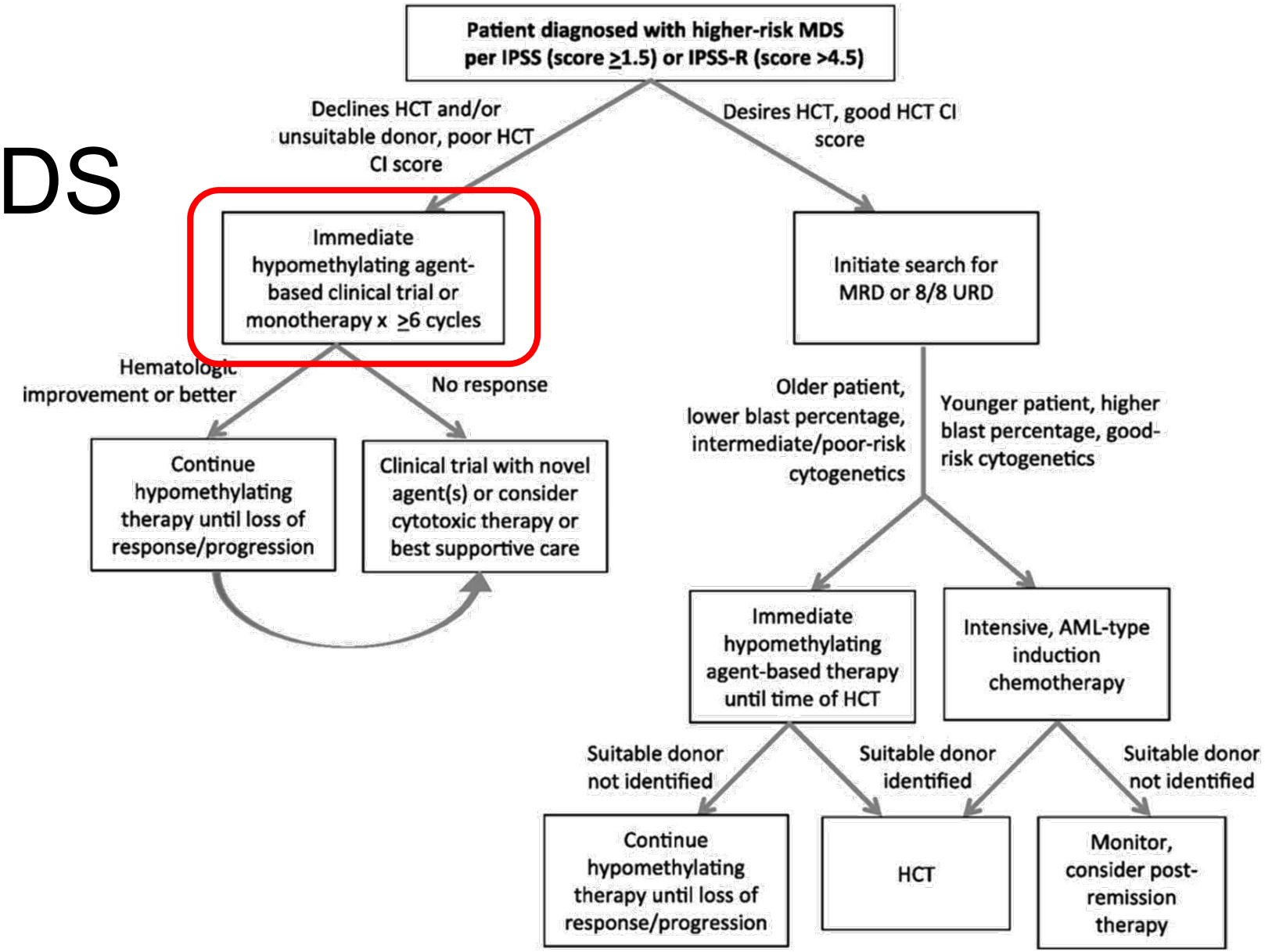


- Comparison of disease response between oral and IV was not possible because all patients received decitabine-cedazuridine starting in cycle 3

Savona M, et al. *Lancet Haematol*. 2019 Apr;6(4):e194-e203.
Garcia-Manero, G et al. *Blood*. 2020 Aug 6;136(6):674-683.

Treatment of Higher-risk MDS

Oral C-DEC?



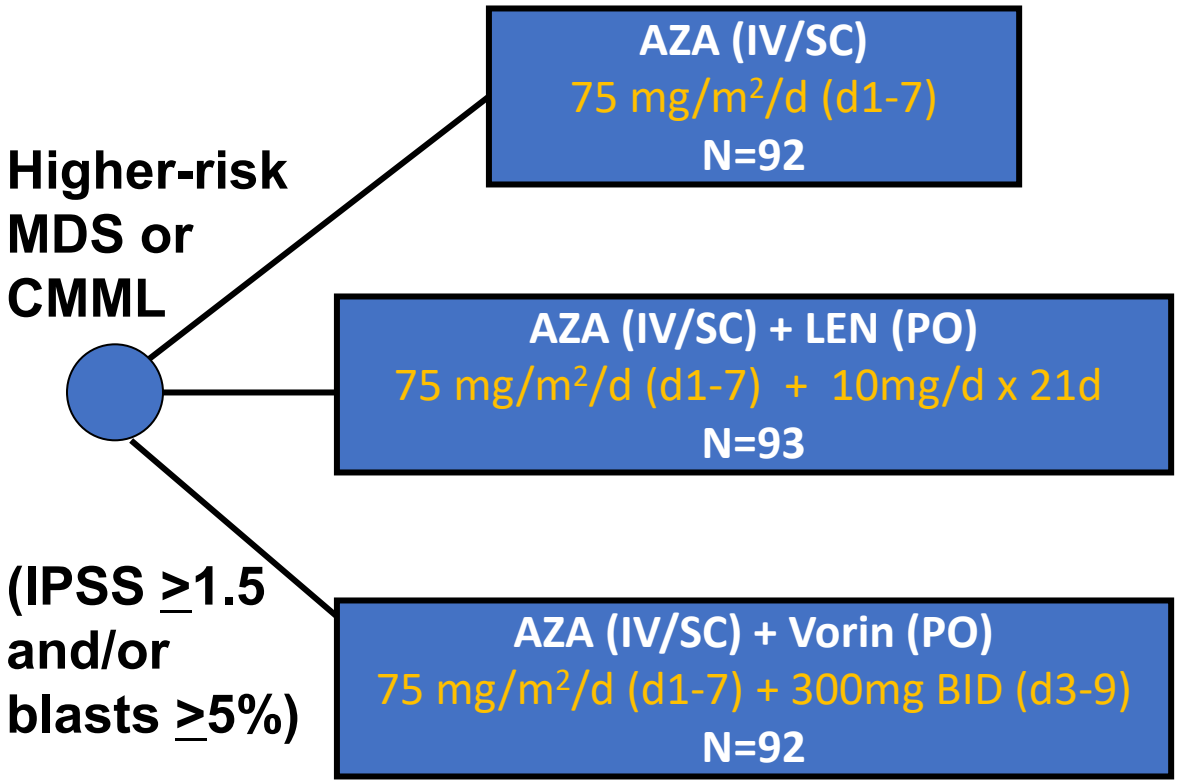
Sekeres MA., Cutler C. *Blood*. 2014 Feb 6;123(6):829-36.

!WARNING!

- Oral azcitidine (ONUREG®) is not IV/SQ azacitidine (Vidaza®)
- Oral aza is approved for maintenance therapy in AML
- There is a randomized phase III trial in lower-risk MDS
  - 216 patients with lower-risk MDS and RBC transfusion–dependent anemia.
  - RBC transfusion independence was achieved in 30.8% of the oral azacitidine group vs 11.1% of the placebo group (*P* = .0002)
  - Early excess death was observed in the oral azacitidine group in association with baseline severe neutropenia

Garcia-Manero G, et al. *J Clin Oncol* 2021 39:13, 1426-1436

North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design



Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 282/277

Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

06/2012 – 06/2014

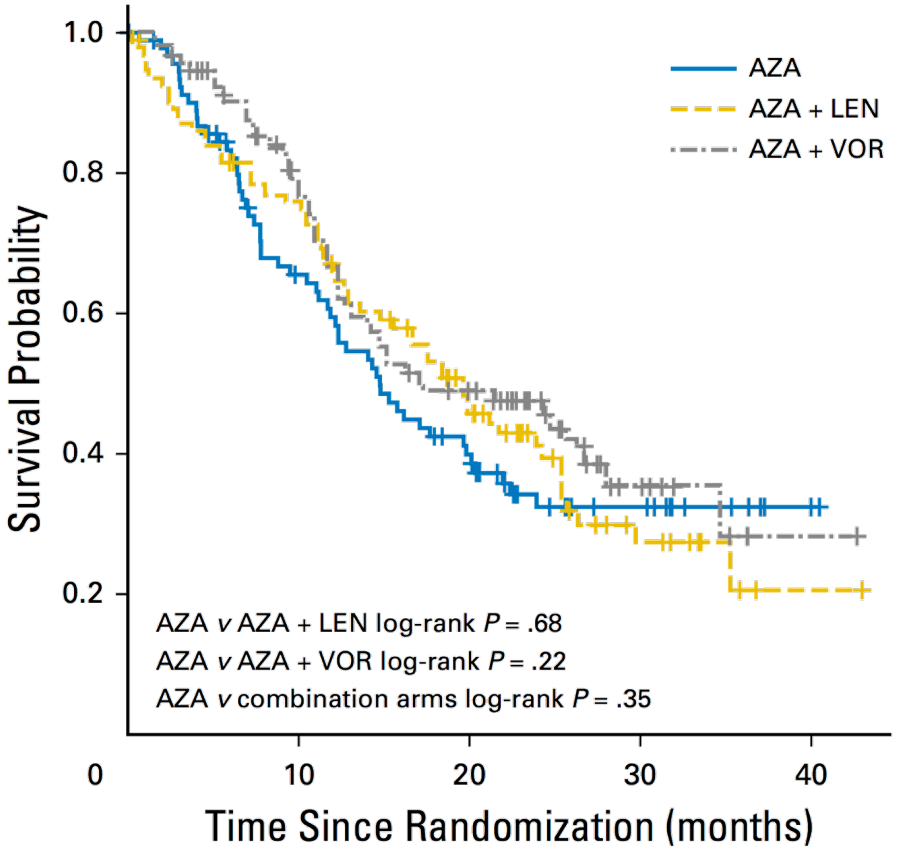
Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

North American Intergroup Randomized Phase 2 MDS Study S1117: Response

Response Variable	AZA	AZA+LEN (P-value vs. AZA)	AZA+VOR (P-value vs. AZA)	Total n=277
Median Tx Duration (Wks)	25	24	20	22
Overall Response Rate (%)	38	49 (.16)	27 (.16)	38%
CR/PR/HI (%)	24/0/14	24/1/25	17/1/9	22/1/16%
CMML ORR (%)	5 (28)	13 (68) (.02)	2 (12) (.41)	37%
ORR Duration (median)	10 months	14 months (.41)	15 months (.31)	14 months

Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

North American Intergroup Randomized Phase 2 MDS Study S1117: OS All Patients



Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

Azacitidine and…

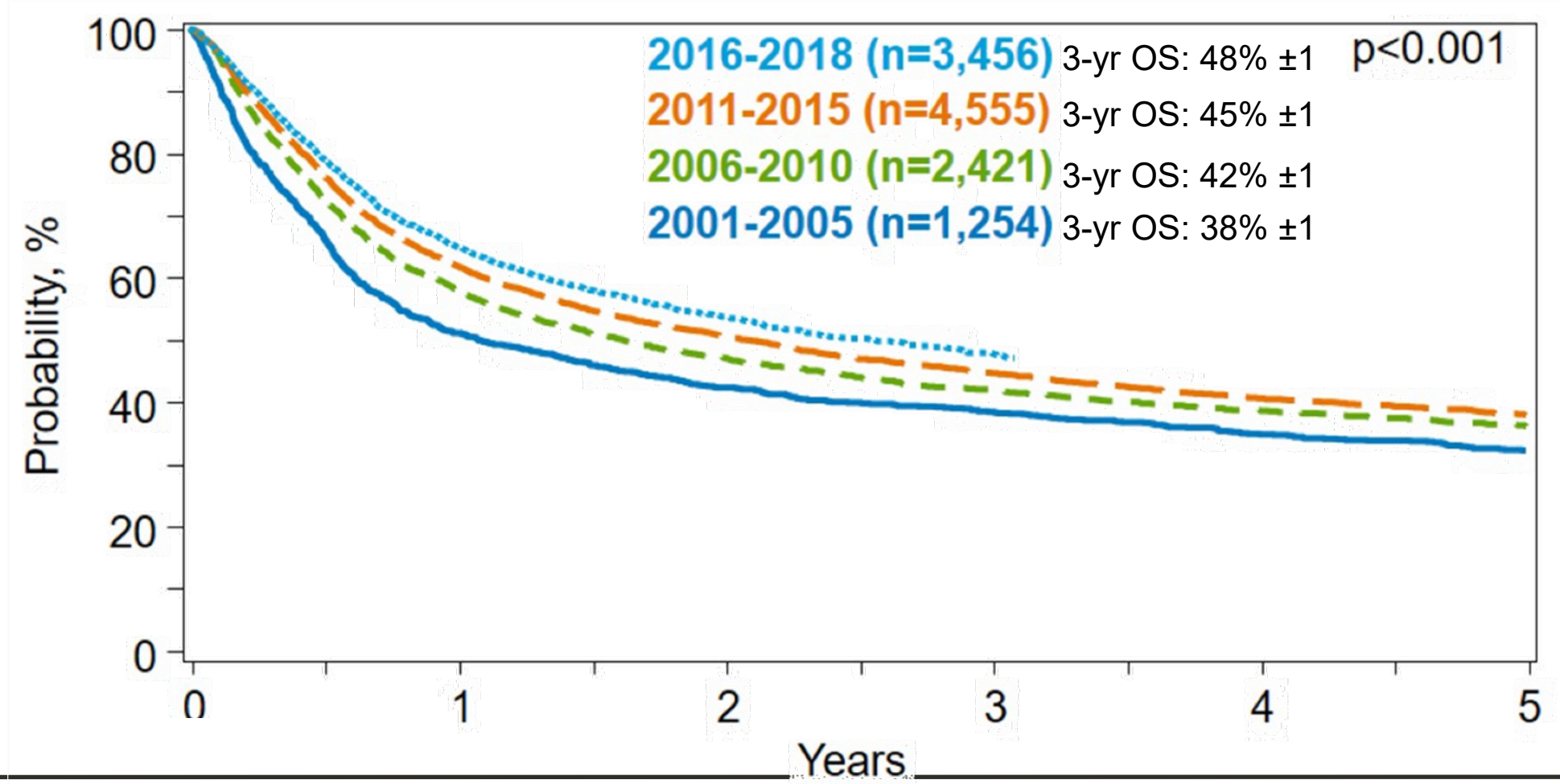
- Venetoclax
  - Phase 1b in78 patients with treatment-naïve MDS
  - Median age was 70 years, and 91% had an ECOG score of 0 to 1
  - Serious AEs were reported in 73% of patients. These included neutropenia (49%), pneumonia (6%), and diverticulitis (5%)
  - 39.7% CR and 39.7% with marrow CR
  - Median time to CR was 2.6 months
  - Median duration of response was 12.9 months
  - Phase III, placebo-controlled VERONA trial is ongoing
- Enasidenib/Ivosidenib
- Others!

Garcia JS et al. Abstract #656. Presented at the 2020 ASH Annual Meeting, December 7, 2020.
Richard-Carpentier G, *Blood* (2019) 134 (Supplement_1): 678.
Lachowiez CA, et al. J Clin Oncol. 2021;39:(suppl 15; abstr 7012).

Blood and Marrow Transplantation for MDS

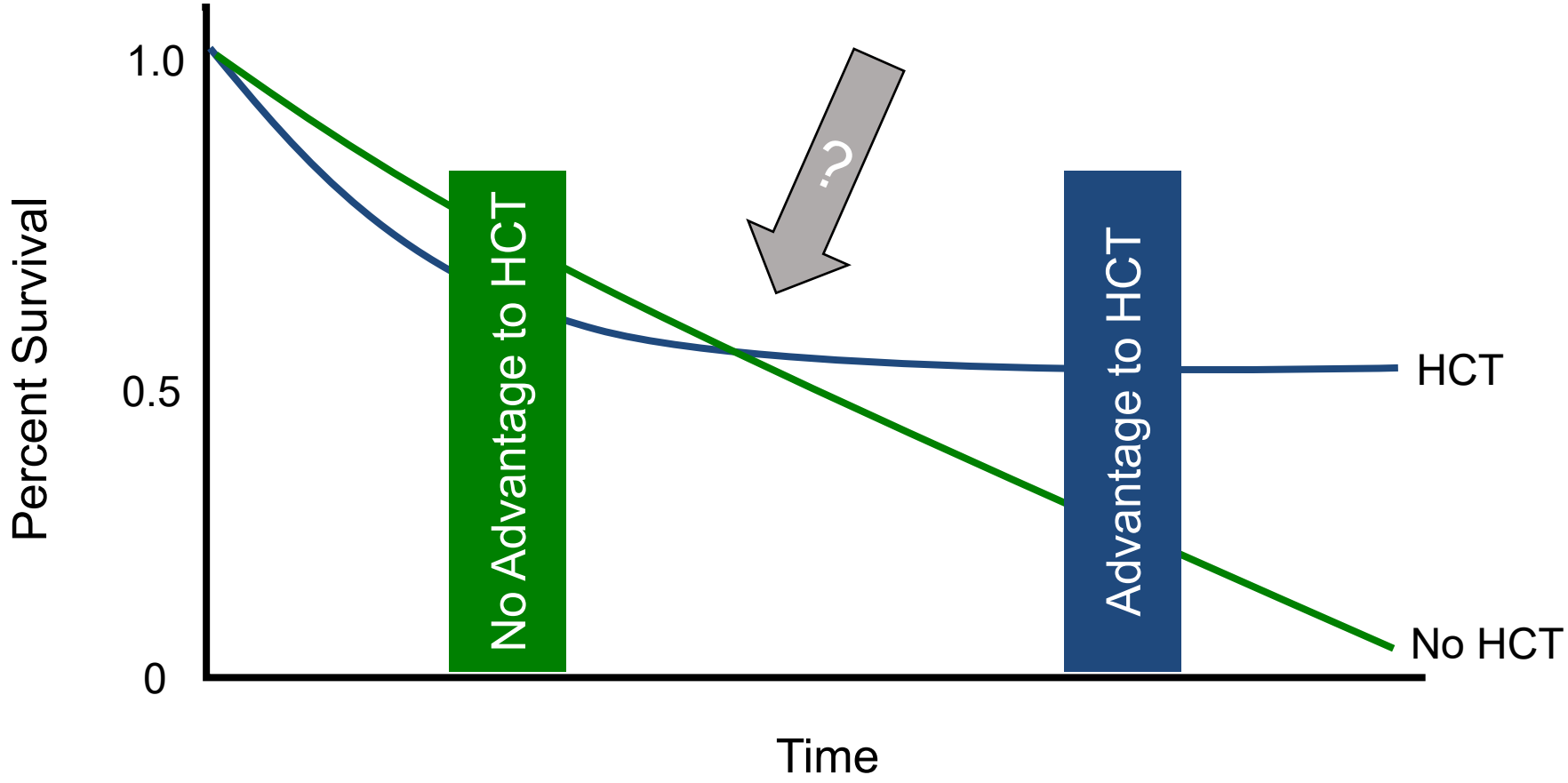
Cleveland Clinic
Taussig Cancer Institute

OS after HCT for MDS, 2001-2018

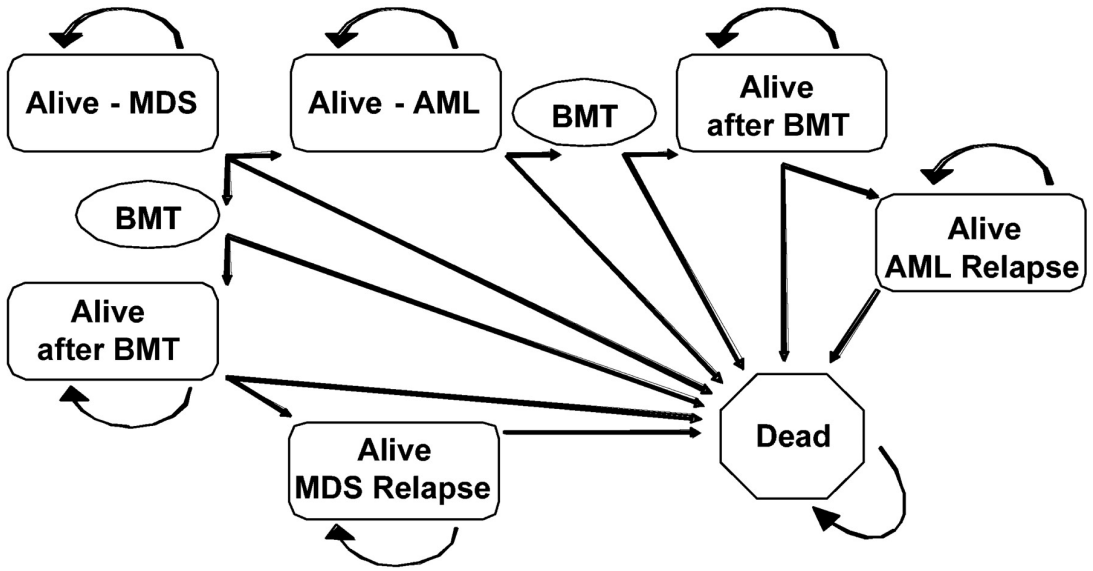


Phelan, R., Arora, M., Chen, M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020. Available at https://www.cibmtr.org

Allogeneic HCT for MDS



Markov Modeling in HCT



- Retrospective comparison
  - All Primary MDS
  - Marrow Grafts
  - HLA-identical donors
  - Myeloablative
- 184 Delayed transplant MDS
- 260 Transplant MDS at time of diagnosis
- 230 Transplant at progression to tAML

Cutler C, et al. Blood. 2004 Jul 15;104(2):579-85.

Decision Analysis

Estimated Life expectancy (years) after HCT for MDS (age < 60)

IPSS RISK	Immediate HCT	HCT in 2 years	HCT at progression
Low	6.51	6.88	**7.21**
Int-1	4.61	4.74	**5.16**
Int-2	**4.93**	3.21	2.84
High	**3.20**	2.75	2.75

Cutler C, et al. Blood. 2004 Jul 15;104(2):579-85.

Decision Analysis

Estimated Life expectancy (years) after RIC-HCT for MDS (age ≥ 60)

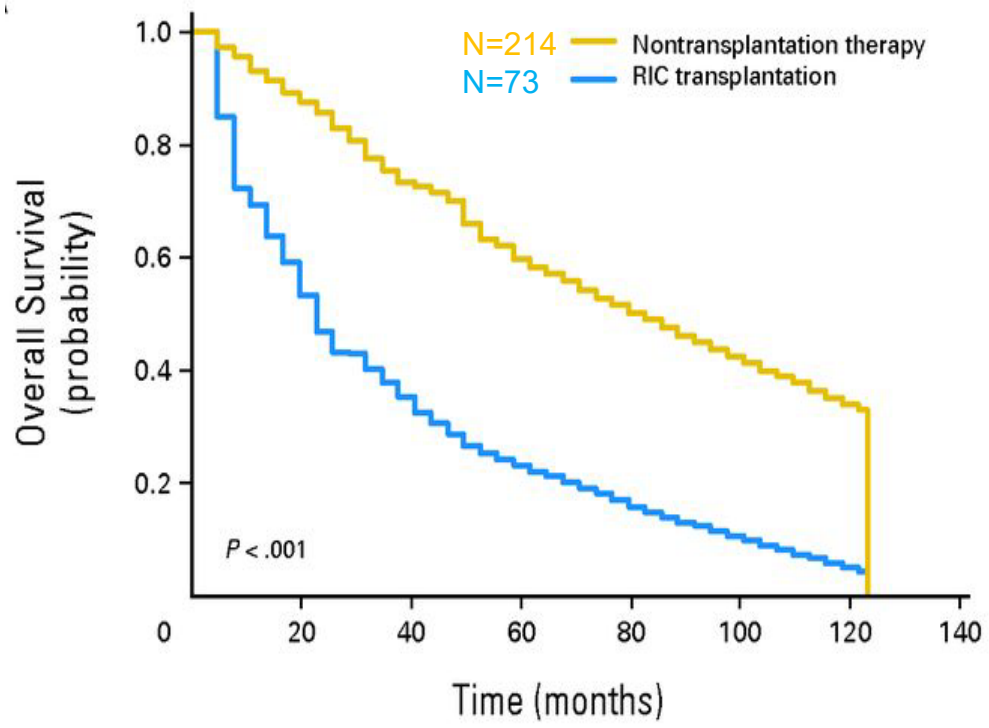
IPSS RISK		Non-HCT	Early HCT
Low/Int-1	Overall LE	6.42	3.17
	QALE: TI	5.42	2.92
	QALE: TD	3.83	2.92
Int-2/High	Overall LE	0.24	3.00
	QALE: HR-MDS	1.25	2.75
	QALE: GvHD	1.25	1.83

Koreth J, et al. Blood 2011; ASH Annual Meeting Abstracts 2011 118: 115.

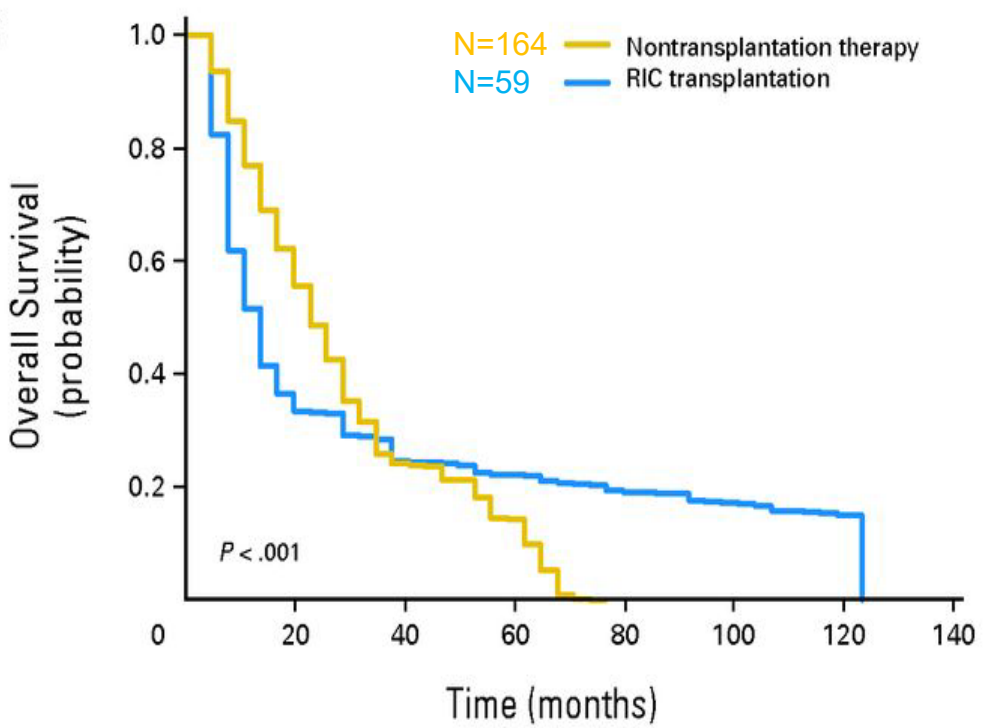
Timing of HCT by IPSS Using RIC

- *de novo* MDS 60-70 years of age
- Survival measured from start of therapy
- HLA Matched Donors
- Bu x 2 days or 2-4 Gy TBI (no T-cell depletion)

Low/Int-1



Int-2/High



Koreth et al. *J Clin Oncol* 2013;31:2662-2670

Summary – Myelodysplastic Syndromes

1. Organization, in general
2. Diagnosis and Classification
3. Epidemiology
4. Pathogenesis
    a. Clonal Process
    b. Secondary MDS
5. Risk stratification
    a. IPSS-R
6. Treatment of Lower-risk MDS
    1. ESAs
    2. IMIDS
    3. Immunosuppressive therapy
7. Treatment of Higher-risk MDS
    1. Hypomehtylating agents
8. Transplantation for MDS
9. Discussion

Discussion

Cleveland Clinic
Taussig Cancer Institute

Thanks!

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Olivia Kodramaz
Caitlin Swann, PharmD
Madeline Waldron, PharmD
Kelly Gaffney, PharmD
Jenna Thomas, PharmD

And Our Patients!!!