Non-transplant Therapy for MDS

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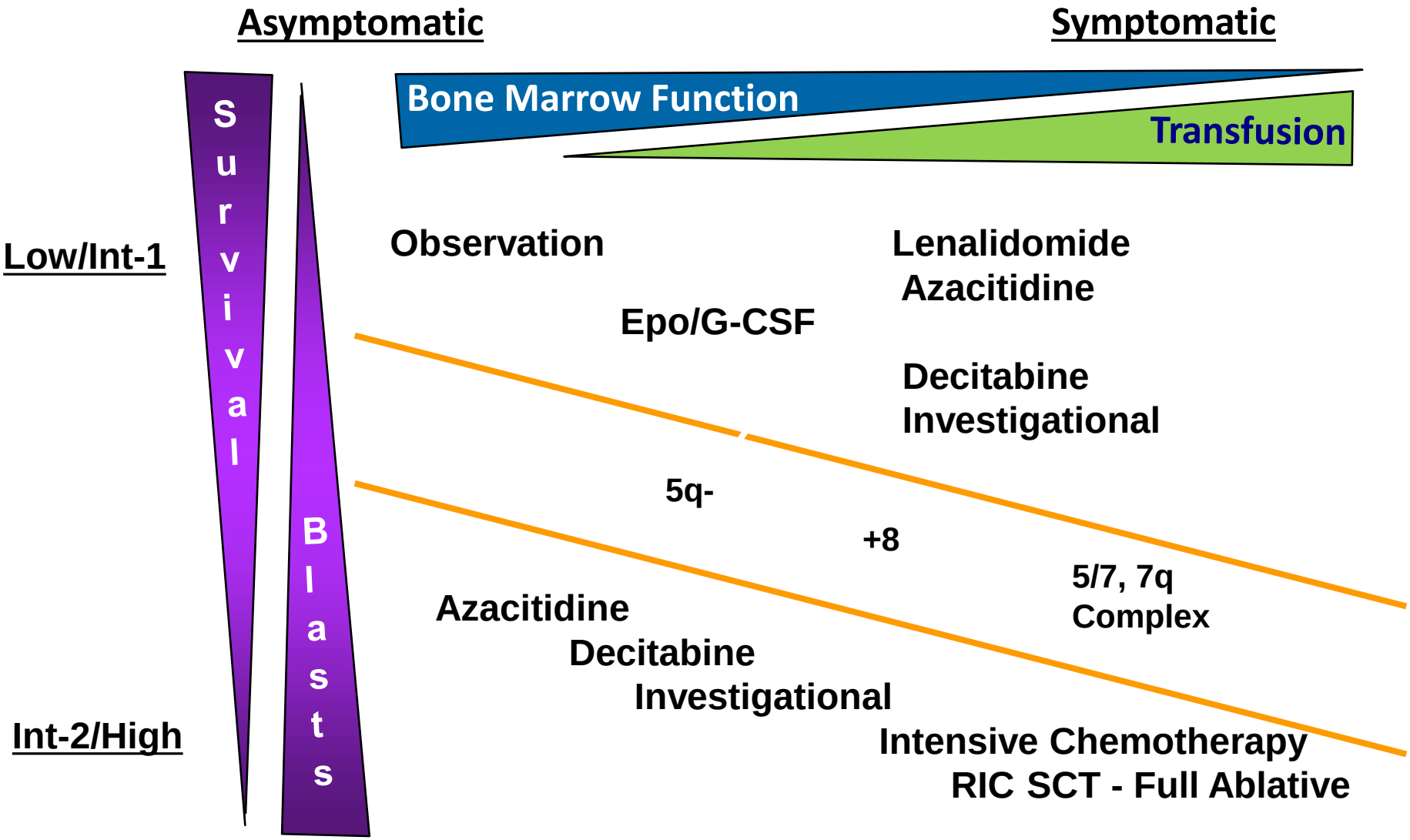
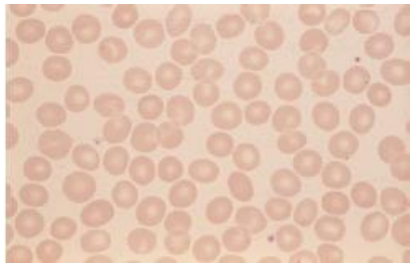
MDS Treatment Algorithm



Treatment Options for Lower-risk MDS

- Transfusion Support
- Growth Factors
- Lenalidomide/Revlimid
- Azacitidine
- Clinical Trial

MDS: Transfusion Therapy



Anemia

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Packed red blood cells

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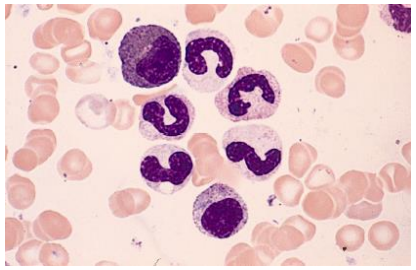
Adverse effects due to immune mechanisms

Iron overload

Volume overload



Neutropenia

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Granulocyte transfusion

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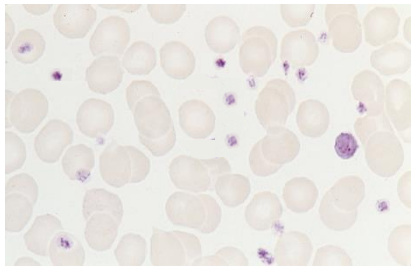
Laborious, short-lived effect, not widely available, Clinical utility unproven



Thrombocytopenia

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Platelet transfusion

↓

Transfusion reactions, HLA sensitization

Growth Factors

Red cell growth factors

Medicare only pays for these if Hb <10 g/dL
Safety concerns in solid tumors, not (yet) in MDS

- Epoetin alfa (Procrit ™)
- Darbepoetin alfa (Aranesp ™)

White cell growth factors

No survival benefit but may help decrease infx.
Sometimes combined with red cell factors

- Filgrastim, G-CSF (Neupogen ™)
- Pegfilgrastim (Neulasta ™)

Platelet growth factors

New; risks still being defined in MDS
Reports of increased blasts in a few patients
Only FDA-approved for immune thrombocytopenia and AA

- Romiplostim (NPLate ™)
- Eltrombopag (Promacta ™)

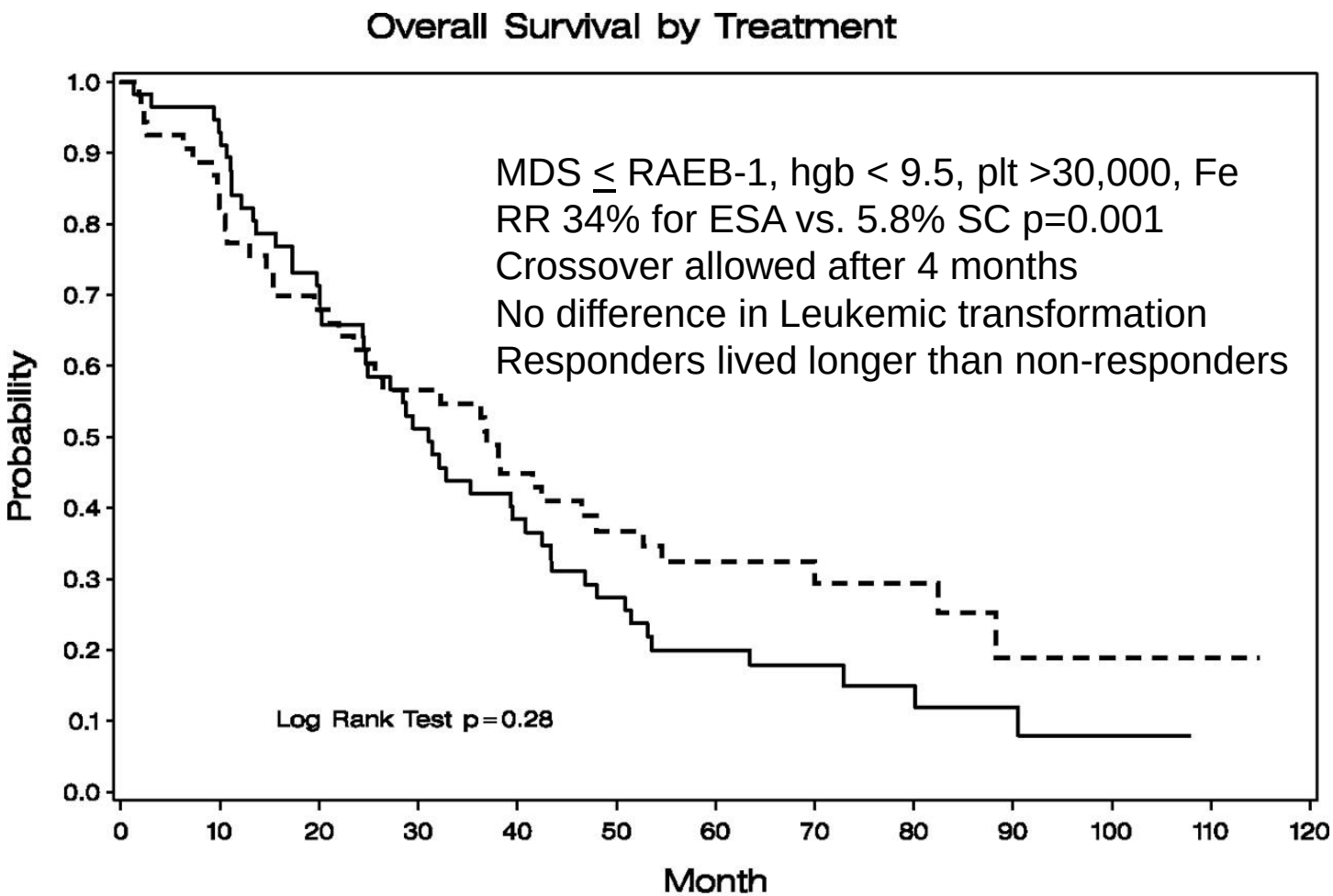
Growth Factors in MDS

Patient Criteria	Probability of Response[1]
Transfusion need < 2 units per mo and serum EPO < 500 units/L	74%
Only one of the above criteria	23%
Neither criteria	7%

- Epo 10,000 u/day x 5 days + GCSF 75-300 mcg/day 3 x week[1]
- Other studies suggest no benefit with adding GCSF[2]
- 10% marrow myeloblasts no benefit[2]
- GSCF not recommended for neutropenic prophylaxis[3]
  - Intermittent use in patients with severe infection and neutropenia
- Tepo-mimetics under investigation[4]
  - 46% platelet response, 2 patients progressed to AML

[1]Hellstrom-Lindberg E., et al. *Br J Haematol.* 2003;120:1037-1046
[2]Park, et al. *Blood.* 2008;111:574-582
[3]Negrin et al. *Ann Intern Med*. 1989;110:976-984
[4]Kantarjian et al. *J Clin Onc* 2010 Jan 20;28(3):437-44

Epo-G vs. S.C.

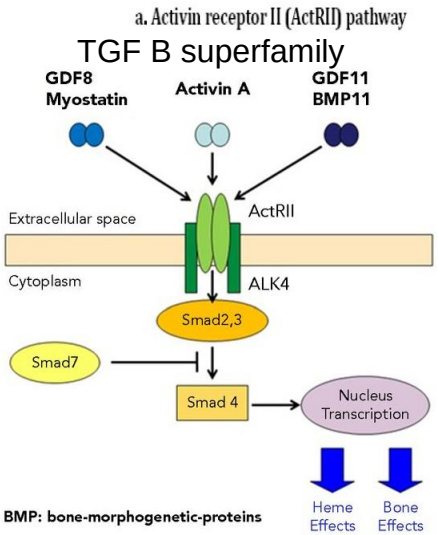


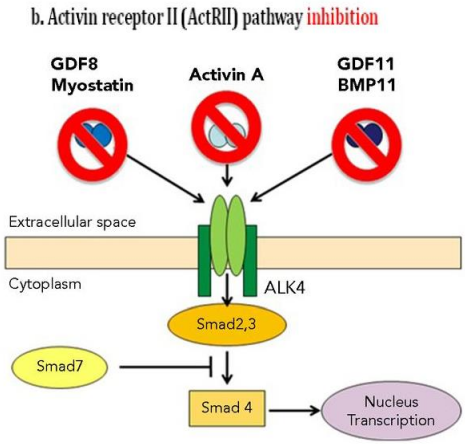
MDS ≤ RAEB-1, hgb < 9.5, plt >30,000, Fe
RR 34% for ESA vs. 5.8% SC p=0.001
Crossover allowed after 4 months
No difference in Leukemic transformation
Responders lived longer than non-responders

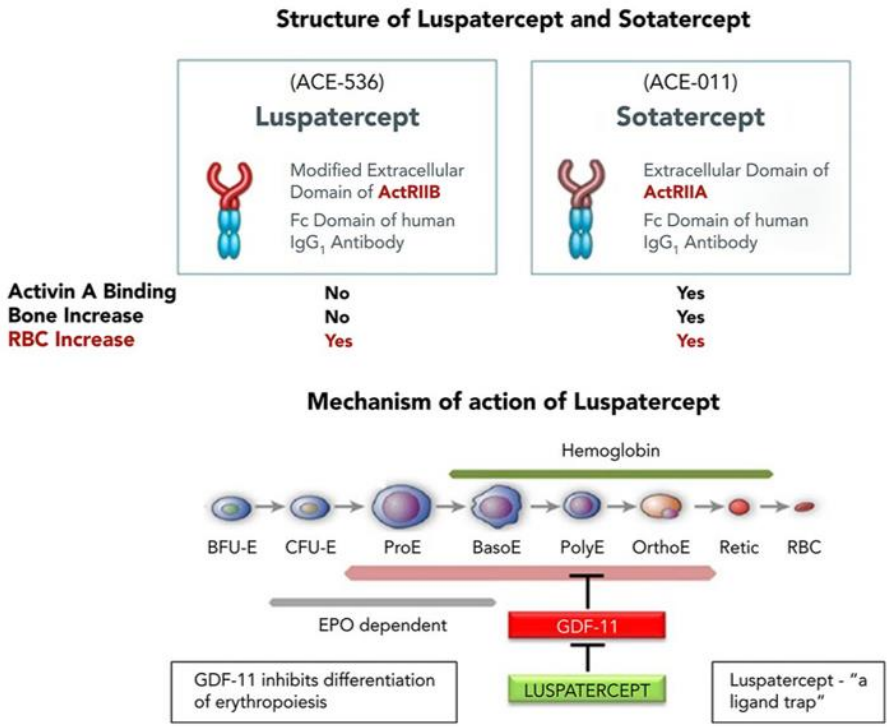
Treatment	TOTAL	FAIL	CNSR	MEDIAN
Supportive Care	57	48	9	31.0
EPO 150u/Kg/d	53	38	15	37.0

Greenberg P., et al. *Blood.* 2009;114:2393-1400

ACTRII Ligand Traps







Pierre Fenaux et al. *Blood* 2019;133:790-794

Phase 3 MEDALIST Study of Luspatercept* for Patients With Lower-Risk MDS-RS Requiring RBC Transfusions: Study Design and Patients

Key eligibility criteria

- Age ≥18 years
- IPSS-R very low-, low-, or intermediate-risk MDS with ringed sideroblasts (RS)
- Refractory, intolerant, or ineligible to receive ESAs
- Require RBC transfusions

RANDOMIZED 2:1

Luspatercept (n=153)
1.0 mg/kg titrated up to 1.75 mg/kg, if needed, SC q3w for ≥24 weeks

Placebo (n=76) q3w

Primary endpoint: RBC-TI for ≥8 weeks between week 1 and 24
Secondary endpoints: RBC-TI for ≥12 weeks between week 1 and 24, mHI-E (IWG 2006) for consecutive 56days

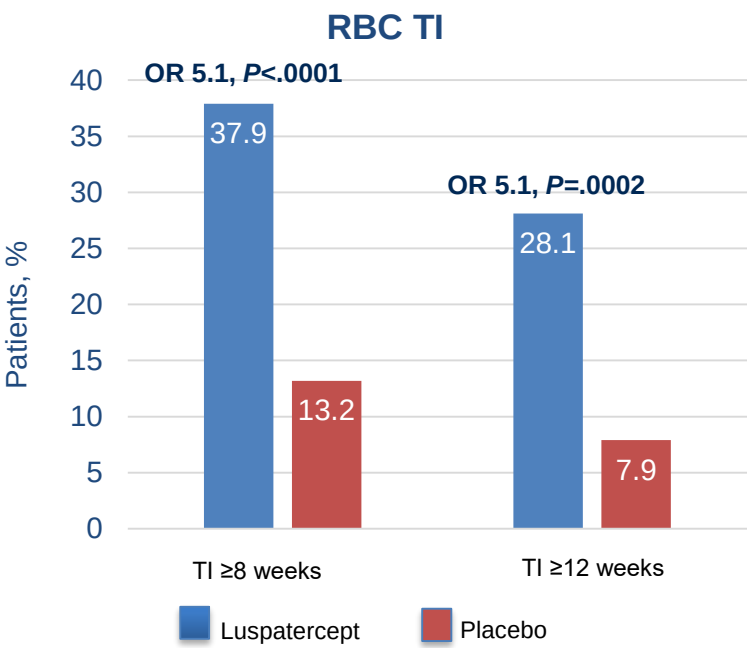
mHI-E, modified hematologic improvement-erythroid.

*Luspatercept is investigational and not currently approved as part of any oncology regimen

Patient Characteristics		Luspatercept (n=153)	Placebo (n=76)
Median age, years (range)		71 (40-95)	72(26-91)
Median time from diagnosis, months (range)		44.0 (3-421)	36.1 (4-193)
Male, n (%)		94 (61.4)	50 (65.8)
Median RBC units transfused over 8 weeks in the 16 weeks prior to treatment, n (range)		5 (1-15)	5 (2-20)
RBC units/8 weeks, %	<6	87 (56.9)	43 (56.6)
	≥6	66 (43.1)	33 (43.4)
Baseline serum erythropoietin, n (%)	<200 IU/L	88 (57.5)	50 (65.8)
	≥200 IU/L	64 (41.8)	26 (34.2)
Pre-transfusion Hb, median (range), g/dL		7.6 (6-10)	7.6 (5-9)
SF3B1 mutation, n (%)		141 (92.2)	65 (85.5)

Fenaux P, et al. Abstract 1.

Phase 3 MEDALIST Study of Luspatercept for Patients With Lower-Risk MDS-RS Requiring RBC Transfusions: Results and Summary



[a]Defined as a reduction in transfusion of ≥4 RBC units/8 weeks or a mean Hb increase of ≥1.5 g/dL/8 weeks in the absence of transfusions.

- Compared with placebo, patients receiving luspatercept were more likely to achieve an mHI-E response[a] (52.9% vs 11.8% during weeks 1–24; *P*<0.0001)

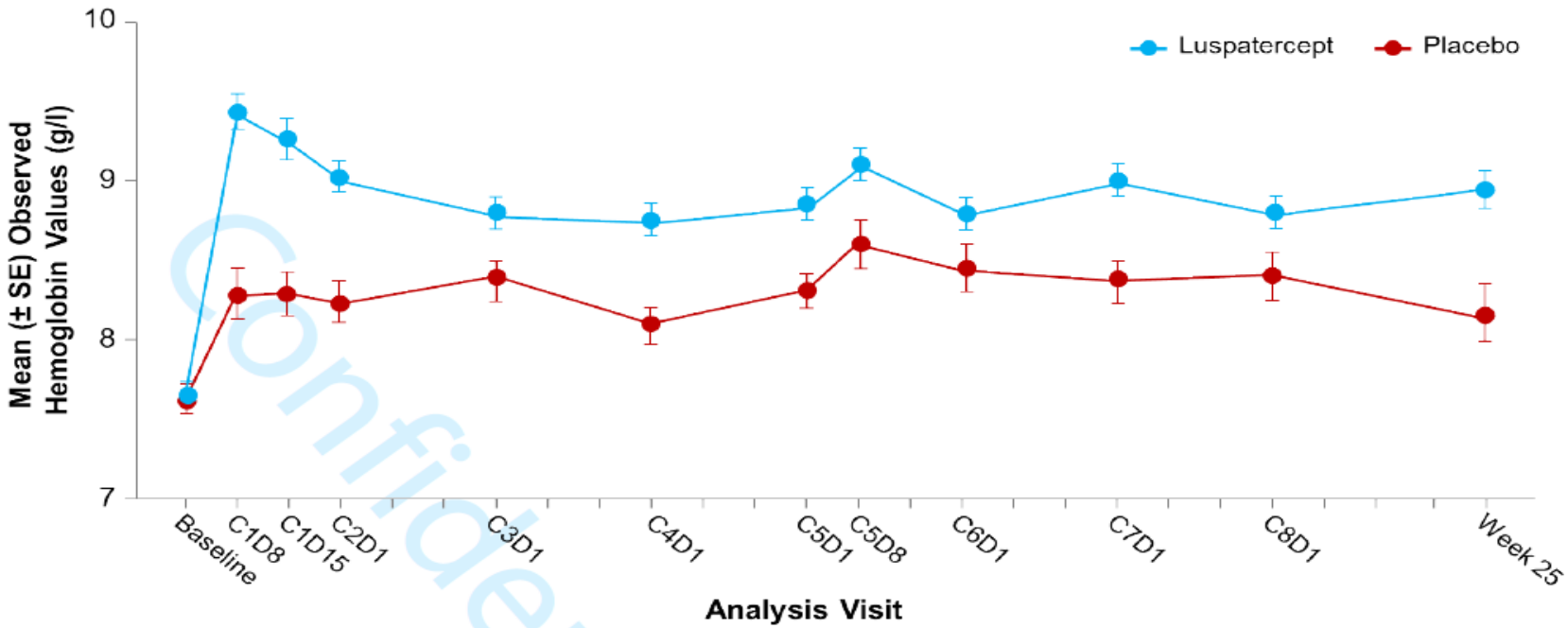
Selected TRAEs, n (%)	Luspatercept (n=153)	Placebo (n=76)
Fatigue	41 (26.8)	10 (13.2)
Diarrhea	34 (22.2)	7 (9.2)
Asthenia	31 (20.3)	9 (11.8)
Nausea	31 (20.3)	6 (7.9)
Dizziness	30 (19.6)	4 (5.3)

Summary

- Compared with placebo, luspatercept significantly reduced transfusion burden for patients with anemia and very low-, low-, and intermediate-risk MDS-RS requiring transfusions
- The safety profile for luspatercept was manageable in this patient population

Fenaux P, et al. Abstract 1.

Medalist Study



Number of Patients												
Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

Phase 2 Pilot Study of Eltrombopag* for Patients With Low- to Intermediate-2-Risk MDS: Study Design and Patients

Key eligibility criteria

- Age ≥18 years
- MDS, with RCUD, RARS, RCMD-RS, or RCMD (by WHO)
- IPSS risk: low or intermediate-1/2
- Platelet count ≤30,000/uL or platelet-transfusion-dependence (requiring ≥4 platelet transfusions in 8 weeks prior to study), or Hb ≤9.0 g/dL or RBC transfusion-dependence (requiring ≥4 units of PRBCs in 8 weeks prior to study), or ANC ≤500

Eltrombopag (n=30)
50 mg/day, up to 150 mg/day, with dose increases of 25 mg q 2 weeks

Responders → **Extension arm**

Primary endpoint: Hematologic response at 16 or 20 weeks [Defined as either (1) an increase in platelet counts ≥20,000/uL or TI for ≥8 weeks, or (2) Hb increase of ≥1.5g/dL from baseline, or a reduction in RBC transfusions ≥50%, or (3) an increase in ANC ≥0.5×10^9/L or by ≥100% in patients with a baseline ANC <0.5×10^9/L]

*Eltrombopag is not currently approved for treatment of MDS/AML

Vicente A, et al. Abstract 229. https://www.clinicaltrials.gov/ct2/show/NCT00961064.

Patient Characteristics		(N=30)
Median age, years (range)		65 (35-85)
Diagnosis, %	AA	43
	Hypoplastic MDS	17
	Primary MDS	40
WHO Subtype, n (%)	RCUD	11 (37)
	RCMD	11 (37)
	MDS-U	6 (20)
	RARS	2 (6)
IPSS, n (%)	Good	16 (53)
	Intermediate	13 (43)
	Poor	1 (4)
Lines of treatment, n (%)	≥2	12 (40)

Phase 2 Pilot Study of Eltrombopag for Patients With Low- to Intermediate-2-Risk MDS: Results and Summary

Efficacy

- 47% of patients (14/30) met the primary endpoint of hematological response; all responders continued eltrombopag on the extension arm
  - 10/14 responding patients achieved a robust response[a] (RR) after a median treatment duration of 15 months (range 7-27 months)
  - PB cell counts significantly declined in 5/10 RR and eltrombopag was restarted per protocol
    - In 4 of these patients PB cell counts recovered
    - 1 patient did not achieve a second response
- Based on IPSS, 4/30 (13%) had PD, including 2 non-responders and 2 responders, at a median follow-up of 4 months (range, 3-35 months)
- NGS for somatic variants was performed in 29/30 patients
  - At baseline, 22/29 (76%) patients had ≥1 mutation: *TET2 (14.5%), ASXL1 (12.5%), SF3B1 (8.3%), SETBP1 (8.3%), ATM (8.3%),* and *ZRSR2 (8.3%)*
  - After eltrombopag, additional somatic variants in different genes were detected in 4/14 responders and 7/16 non-responders
    - The VAF of variants detected at both time points were similar

[a]RR: stable hematopoiesis with Hb ≥10 g/dL, thrombocytes ≥50.000/L, and ANC ≥ 1000/L.

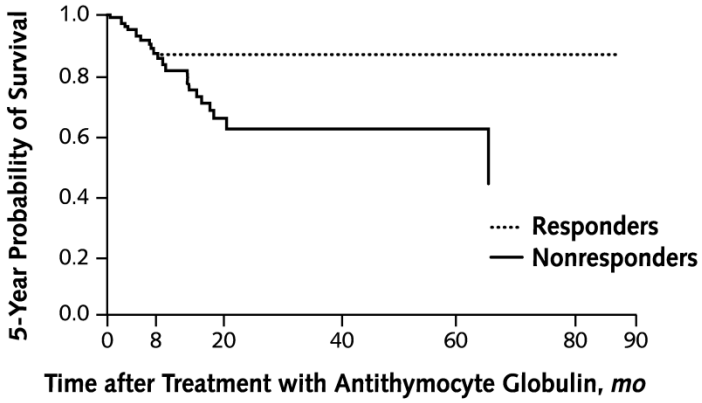
TRAEs (in >5% of patients), n (%)	Any Grade	Grade 3/4
Increased liver transaminases	3 (10)	3 (10)
Nausea and vomiting	5 (17)	–
Headache	4 (13)	–
Jaundice	8 (27)	–
Abdominal pain	4 (13)	–
Myalgia	3 (10)	–
Skin rash and pruritis	4 (13)	–

Summary

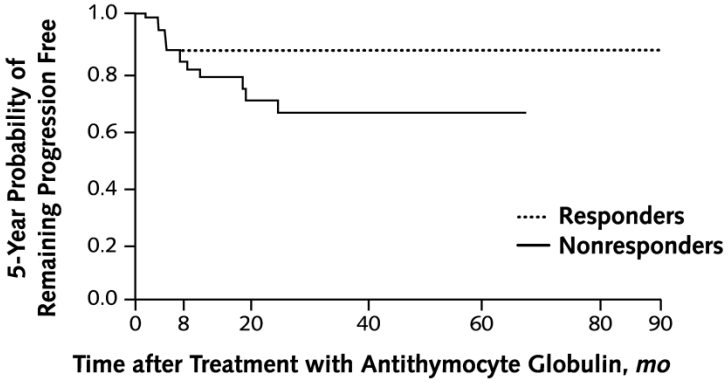
- Hematologic response with eltrombopag was achieved in 47% of patients
- Although there were no AML transformations observed on eltrompopag, 4 patients had progression of MDS
- 5/20 patients acquired new cytogenetic abnormalities with eltrombopag

Vicente A, et al. Abstract 229.

ATG Therapy in MDS



Patients at Risk, *n*							
Responders	21	20	20	10	6	1	0
Nonresponders	40	30	18	7	3	0	0

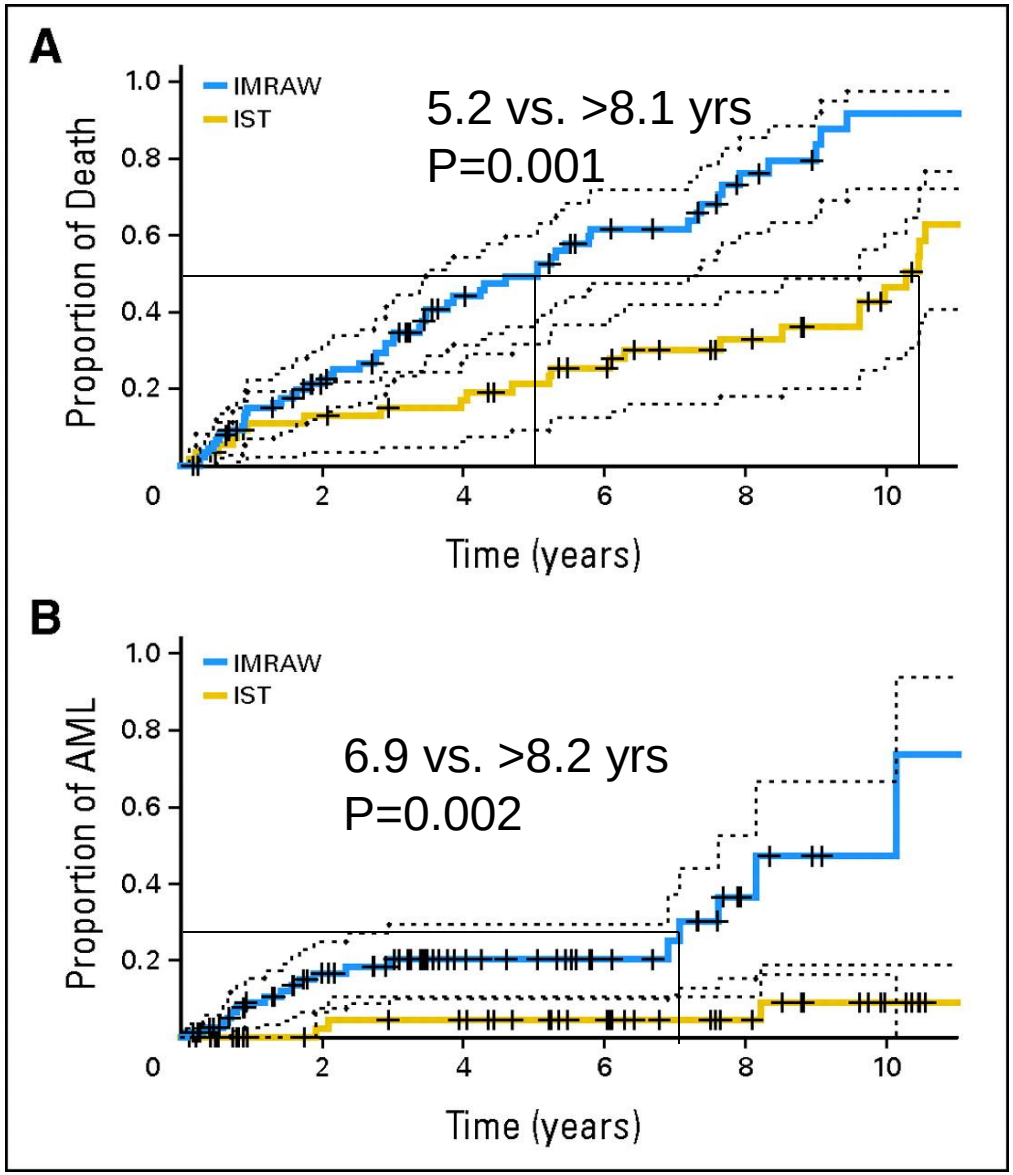


Patients at Risk, *n*							
Responders	21	20	20	10	6	1	0
Nonresponders	40	27	15	7	2	0	0

- Phase II study of ATG
  - 61 RA, RARS,RAEB (FAB)
  - Transfusion dependent
  - 40 mg/kg/day x 4 days
- 21/61 (34%) patients with major HI-E
  - Younger age <58
  - HLA - DR 15
  - Shorter duration of RBC tfn

Molldrem JJ, et al. *Ann Int Med.* 2002;137:156-163;
Sauntharajah Y. *Blood*. 2003;102:3025-3027

Survival and AML evolution after ATG



Int-1 MDS
≤60 years

IST=ATG 40 mg/kg/day x 4 days + CSA 5-12 mg/kg/day

89 IST
55 IMRAW

Sloand, E. M. et al. *J Clin Oncol*; 26:2505-2511 2008

Immunosuppressive Therapy (IST): Summary

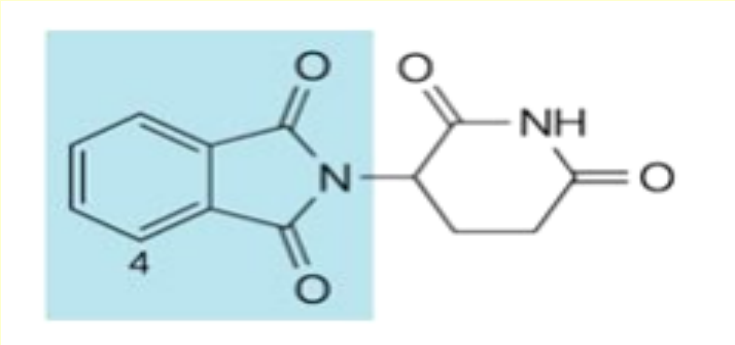
- Age is the strongest variable for IST response[1,2]
  - Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-TI on OS[2]
- Karyotype may influence IST response and disease biology
  - Low frequency of IST response in del(5q)[2]
  - High response rate in trisomy 8[3]
    - NIH 8/17 (47%)
    - WT1 amplification with specific cellular response
    - Autoimmune hematopoietic suppression may select for +8 expansion

1. Saunthararajah Y, et al. Blood. 2002;100:1570-1574. 2. Sloand EM, et al. J Clin Oncol. 2008;26:2505-2511.
3. Sloand E, et al. ASH 2004. Abstract 1431.

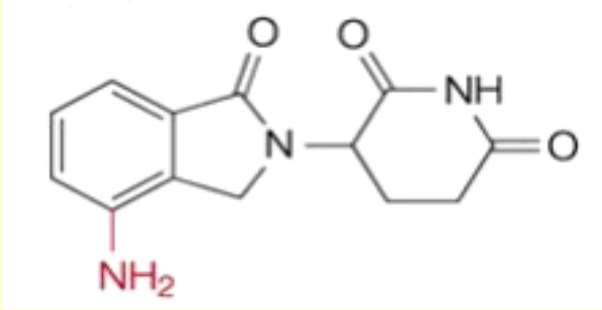
Lenalidomide (REVLIMID®, Celgene)

- No significant neurotoxicity, somnolence, or constipation
- Potent modulator of myelosuppressive properties

Thalidomide



Lenalidomide



List A. *New Eng J Med. 2005;*352(6):549-557.

Lenalidomide in Transfusion-Dependent Patients With Low/Int-1 MDS (MDS-002/003)

Multicenter Phase II Studies

Eligibility

RBC transfusion ≥ 2 U/8 wk
16 wk transfusion Hx
ANC > 500/μL
Platelets > 50,000/μL
de novo MDS
Low/Int-1 MDS

MDS-003: del 5q31.1 (n=148)

MDS-002: other (n=214)

REGISTER

Lenalidomide Dosing

10 mg po × 21/28 d
10 mg po qd

Week: 0 6 12 18 24

RESPONSE

Yes → Continue

No → Off Study

MDS-003:80%
MDS-002: 55%
Dose Reduction
5 mg qd
5 mg qod

Primary endpoint: transfusion independence
Secondary endpoints: cytogenetic response, pathologic response, safety

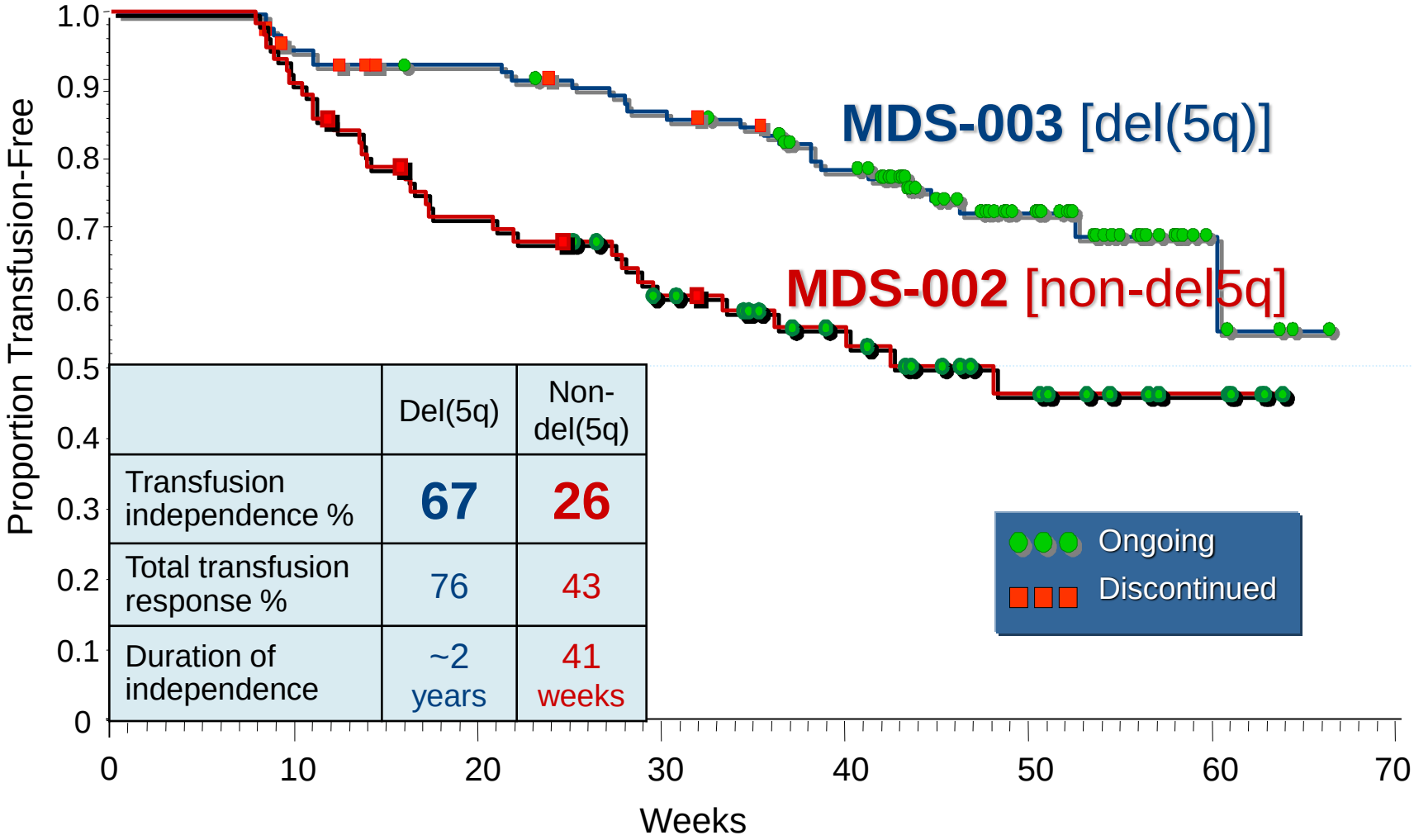
List et al. *N Engl J Med* 2006;355:1456-1465
Raza et al. *Blood* 2008;111:86-93

MDS-002/003: Treatment-Related Adverse Events

Grade ≥ 3 Adverse Events, %	Non-del(5q)	del(5q)
Thrombocytopenia	**20**	**44**
Neutropenia	**25**	**55**
Pruritus	1	3
Rash	4	6
Diarrhea	1	3
Fatigue	4	3

List AF, et al. *N Engl J Med.* 2006;355:1456-1465
Raza A, et al. *Blood*. 2008;111:86-93.

Lenalidomide: Duration of Transfusion Independence



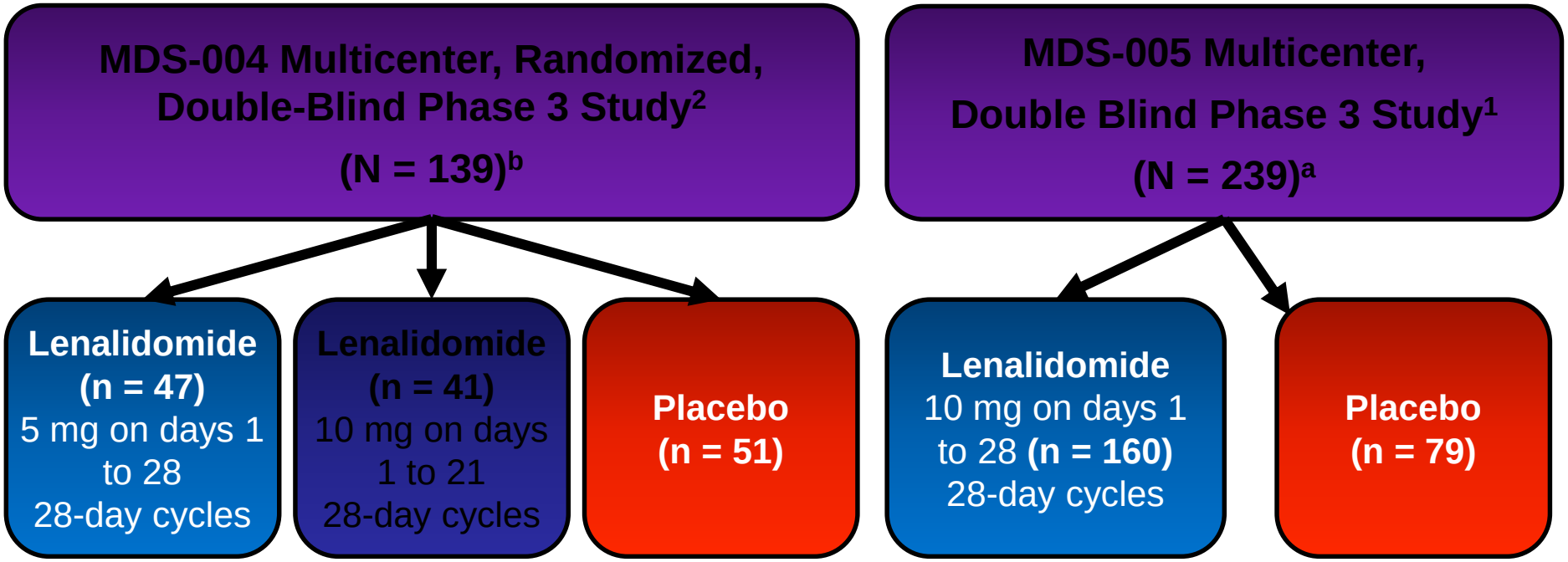
	Del(5q)	Non-del(5q)
Transfusion independence %	**67**	**26**
Total transfusion response %	76	43
Duration of independence	~2 years	41 weeks

List et al. *N Engl J Med* 2006;355:1456-1465
Raza et al. *Blood* 2008;111:86-93

Lenalidomide in Transfusion-Dependent Patients With Low/Int-1 MDS MDS-004/005

Double-Blind Randomized Placebo Control Trial

- 2 randomized trials using lenalidomide for the treatment of patients with primary, lower-risk (IPSS low/Int-1–risk), del(5q)[b] and non-del (5q)[a] MDS with RBC-TD



Primary endpoint: RBC-TI (≥ 26 weeks)

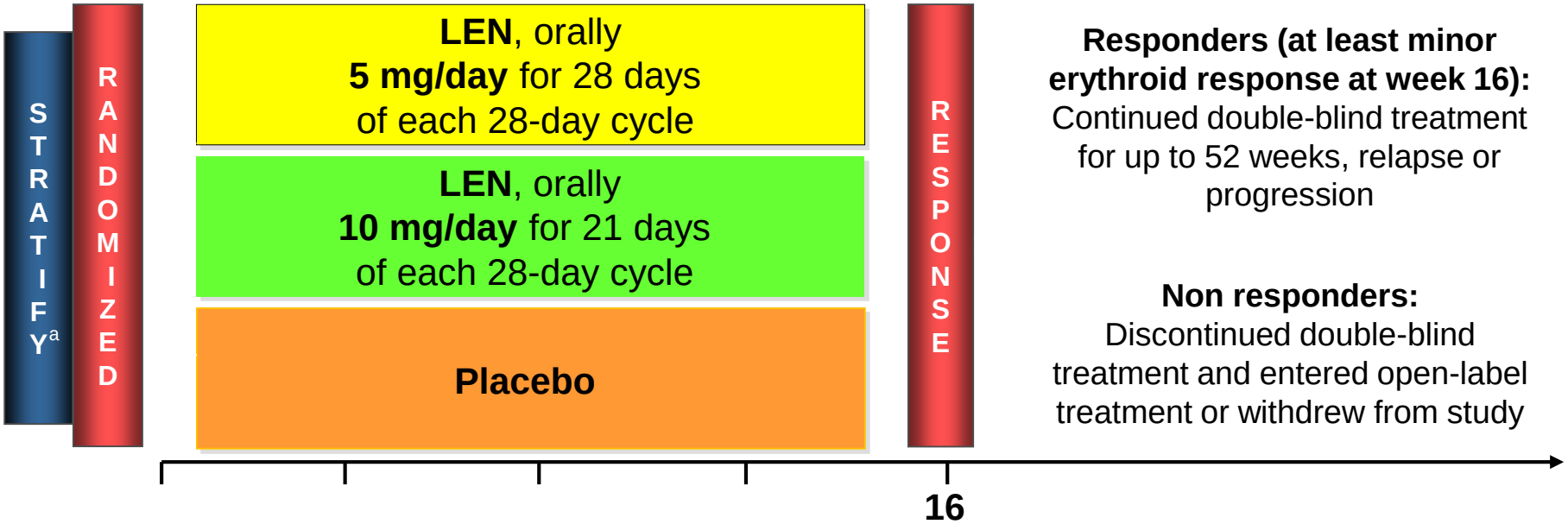
Primary endpoint: RBC-TI (≥ 8 weeks)

[a] With or without additional chromosomal abnormalities. [b] Modified intent-to-treat population.
del, deletion; Int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependence; TI, transfusion independence.

1. Santini, et al. *Jnl Clin Oncol.* 2016;34:2988-2996.
2. Fenaux P, et al. *Blood.* 2011;118:3765-3776.

MDS-004 Study Design

Double-blind phase[b]: Len 5 mg or 10mg vs PBO

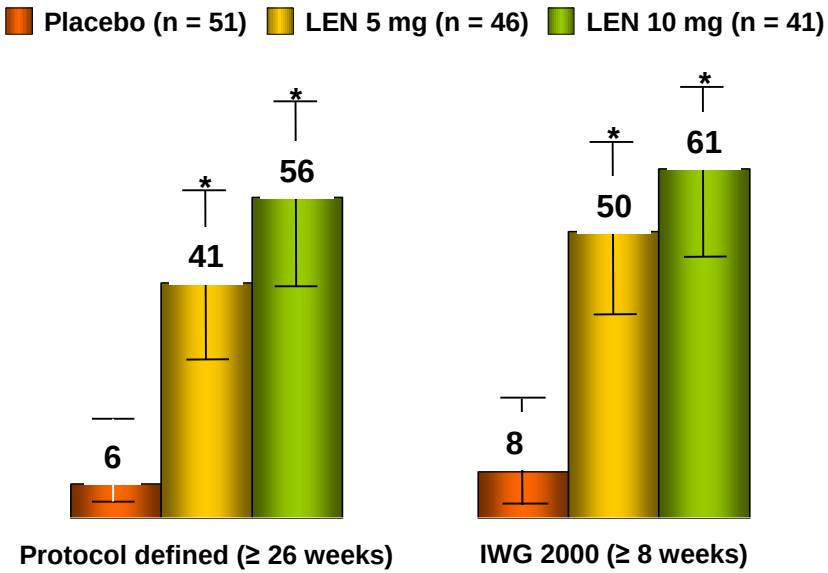


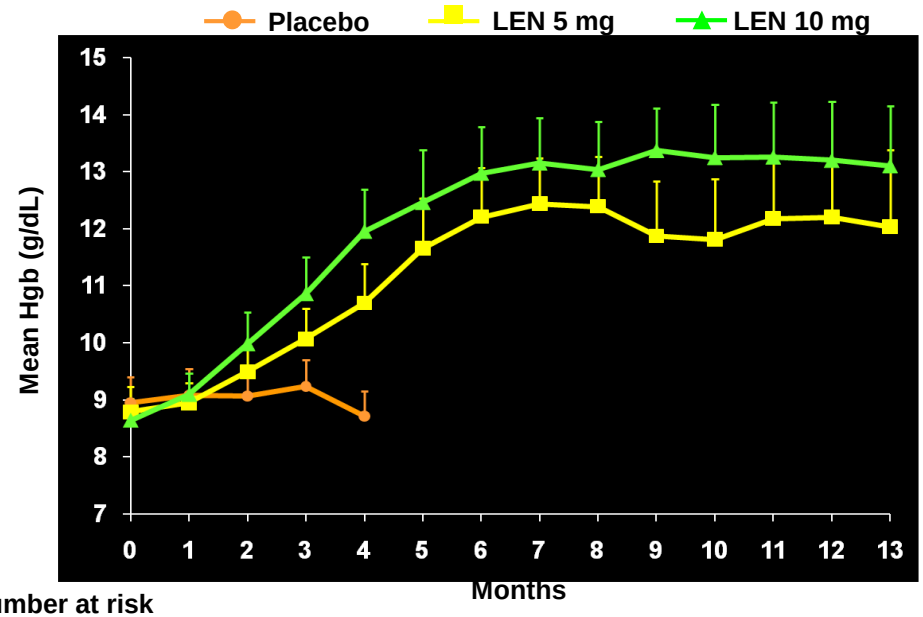
- Key inclusion criteria: centrally-confirmed IPSS-defined Low- or Int-1-risk MDS with del(5q) +/- additional cytogenetic abnormalities, and RBC-transfusion dependency (no consecutive 56 days without transfusion within last 112 days)
  - Patients with ANC < 500 cells/mcL or platelet count < 25,000/mcL were excluded
- Primary endpoint: RBC-TI for ≥ 26 weeks (absence of transfusions during consecutive 26 weeks on treatment and increase hemoglobin > 1 g/dL from baseline
- Secondary endpoints: erythroid response, duration of RBC-TI, cytogenetic response, time to AML progression from randomization, and adverse events

[a] Patients stratified by IPSS score and cytogenetic complexity prior to randomization.
[b] Bone marrow assessments were performed at baseline, 12 weeks, and every 24 weeks thereafter.
ANC, absolute neutrophil count; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndromes; PBO, placebo; RBC-TI, red blood cell transfusion independence.

Fenaux P, et al. *Blood.* 2011;118:3765-3776

MDS-004-Efficacy: RBC-TI and Hemoglobin Over Time (mITT Population[a])





Number at risk														
Placebo	51	51	50	49	47									
LEN 5 mg	46	46	45	42	42	28	23	22	22	22	21	19	17	10
LEN 10 mg	41	40	38	37	37	29	26	24	24	24	24	23	23	19

*$P < 0.001$ vs placebo.
Bars represent 95% CI.

- Consistent results were observed in the ITT population (N = 205)
- Achievement of RBC-TI for ≥ 26 weeks was not affected by age, gender, FAB classification, IPSS risk, time from diagnosis, cytogenetic complexity, baseline platelet counts, or number of cytopenias at baseline
- Hemoglobin increased over time with a maximum median Hgb change in responders of LEN 5 mg of 5.1 g/dL and LEN 10 mg of 6.3 g/dL

[a] mITT population defined as patients with centrally-confirmed MDS who received ≥ 1 dose (N = 138).
CI, confidence interval; FAB, French-American-British; IPSS, International Prognostic Scoring System; Hgb, hemoglobin; IWG, International Working Group; LEN, lenalidomide; mITT, modified intent-to-treat; RBC-TI, red blood cell transfusion independence.

.Fenaux P, et al. *Blood.* 2011;118:3765-3776

MDS-005 Lenalidomide in non-del 5q MDS

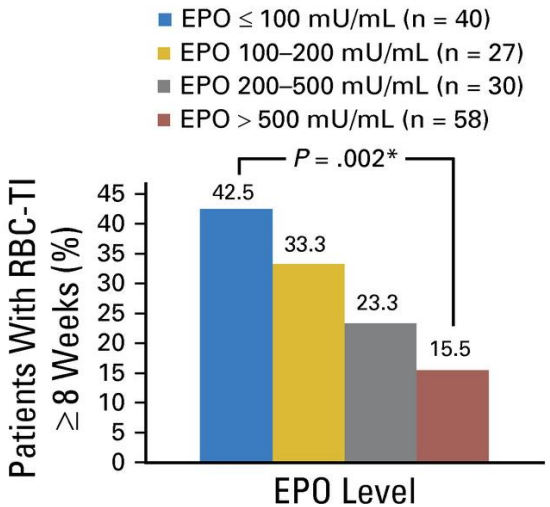
Table. Key efficacy data.

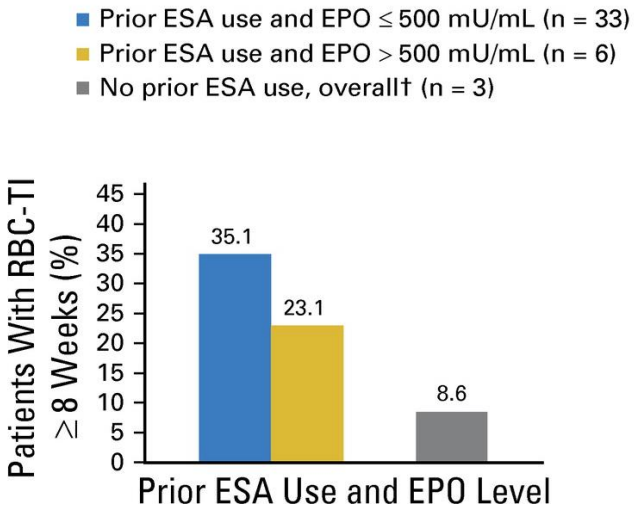
Response	LEN (n = 160)	PBO (n = 79)
RBC-TI ≥ 56 days, n (%)	43 (26.9)*	2 (2.5)
Duration of RBC-TI ≥ 56 days, median (95% CI), weeks[a]	32.9 (20.7–71.1)	NE (NE–NE)
RBC-TI ≥ 168 days, n (%)	28 (17.5)	0

[a]Responding pts only.

*$P < 0.001$.

NE, not estimable.





Santini, et al. *Jnl Clin Oncol.* 2016;34:2988-2996

Summary: Lenalidomide Treatment in Low-/ Intermediate-1–Risk MDS

- MDS-004/005 confirmed results of MDS-003/002[1,2]
  - Efficacy of 10 mg comparable between studies
    - Transfusion independence by IWG (61% vs 67%)
  - MDS-004 supports 10 mg as appropriate starting dose
    - Higher TI for 10 mg
    - Mean duration of TI: 106 wks
    - Greater proportion of cytogenetic responses vs 5 mg (41% vs 17%)
    - No significant differences in hematological toxicity
  - The rate of transformation to AML is comparable to the literature
- MDS-002/005 provided evidence that lenalidomide could be a choice for anemia treatment in lower-risk non-del(5q) pts with adequate platelets and neutrophil count[3,4]
- Lenalidomide mechanism of action is karyotype dependent, suppressing the clone in del(5q) and promoting erythropoiesis in non-del(5q)[5]

1. Fenaux P, et al. Blood. 2011;118:3765-3776. 2. List AF, et al. N Engl J Med. 2006;355:1456-1465. 3. List AF, et al. N Engl J Med. 2005;352:549-557. 4. Raza A, et al. Blood. 2008;111:86-93. 5. Sekeres MA, et al. J Clin Oncol. 2008;26:5943-5949.

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

5-2-2: 75 mg/m²
(n = 50)

5-2-5: 50 mg/m²
(n = 51)

5: 75 mg/m²
(n = 50)

x 6

IWG 2000 HI

12 Cycles
AZA x 5 days
q4-6 wks

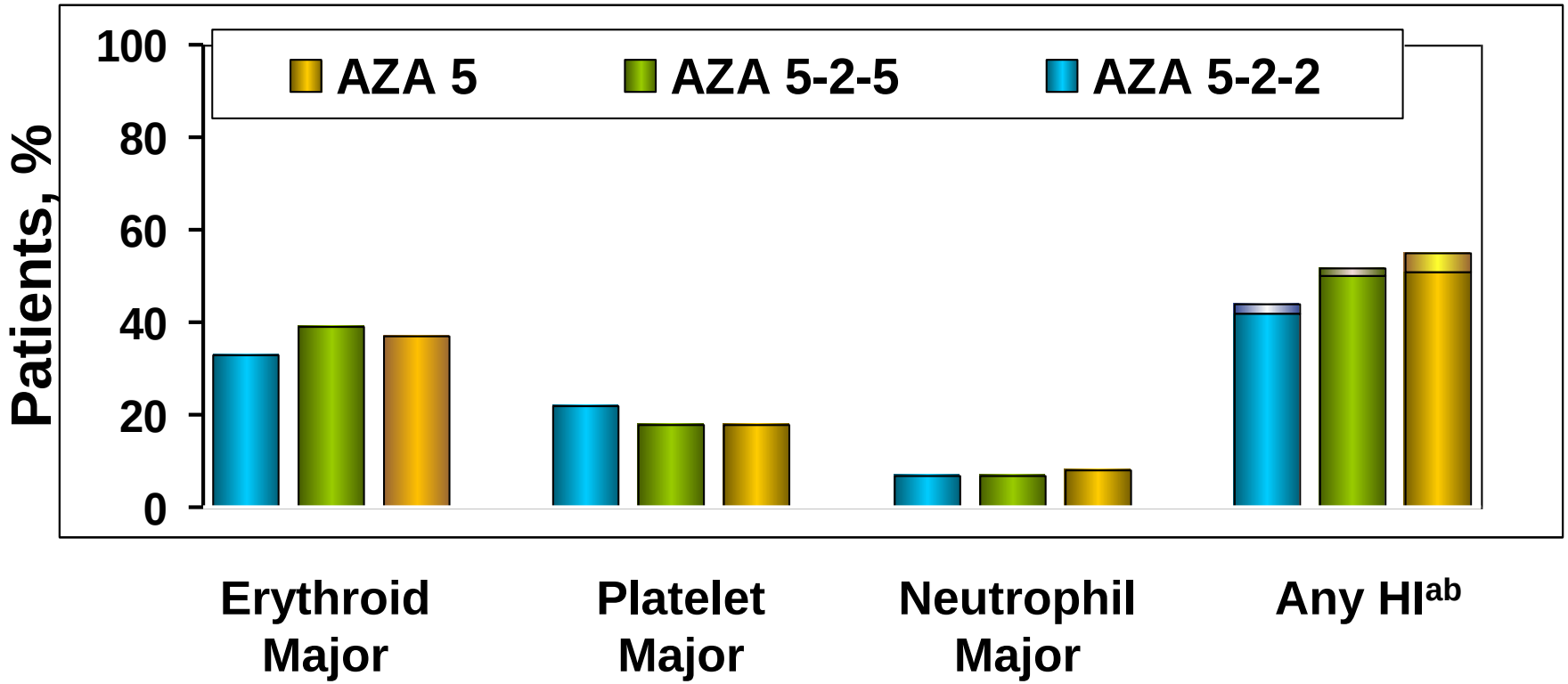
Lyons RM et al. *J Clin Oncol.* 2009;27:1850-1856.

Baseline Demographics/Disease Characteristics for All Randomized Patient (N = 151)

Characteristic	AZA 5-2-2 N = 50	AZA 5-2-5 N = 51	AZA 5 N = 50
Age, median (range)	73 (37-88)	76 (54-91)	76 (47-93)
Gender, %			
Male	56	73	66
RBC transfusion dependent, %	44	39	48
FAB, %			
RA	44	41	44
RARS	14	14	14
RAEB	28	33	28
RAEB-T	2	2	4
CMMoL	12	10	10

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

Hematologic Improvement

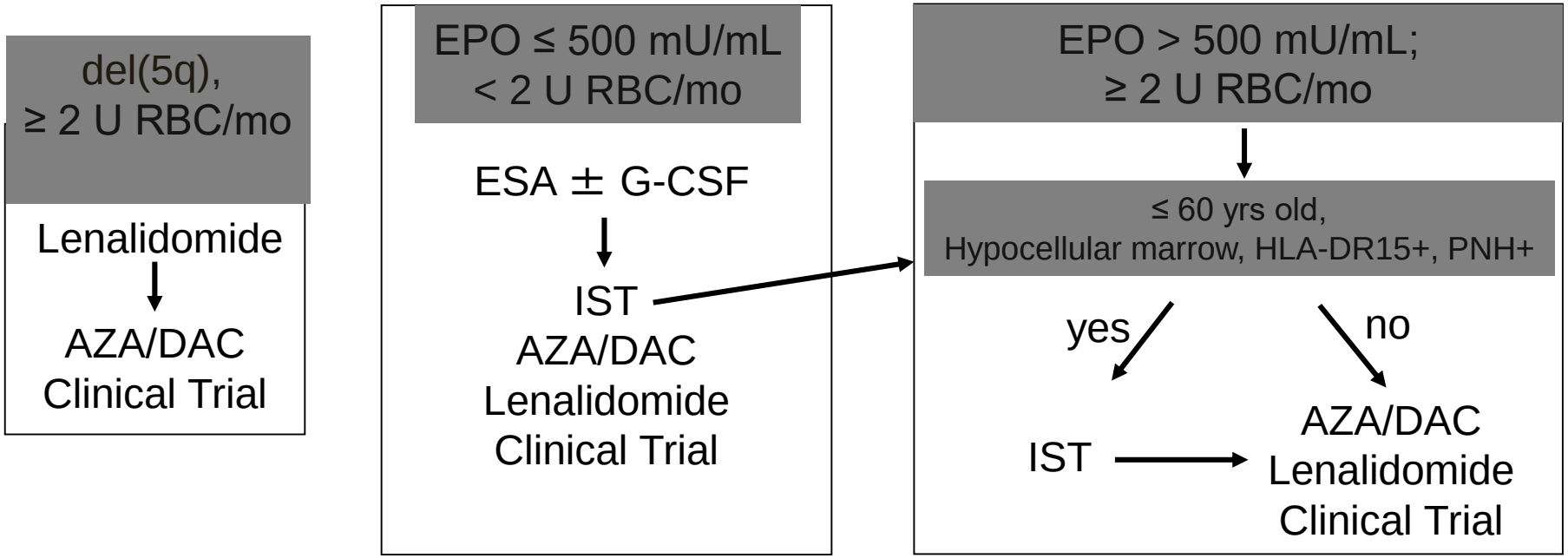


[a] Patients counted only once for best response in an improvement category.
[b] Minor improvement at top of HI columns.

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

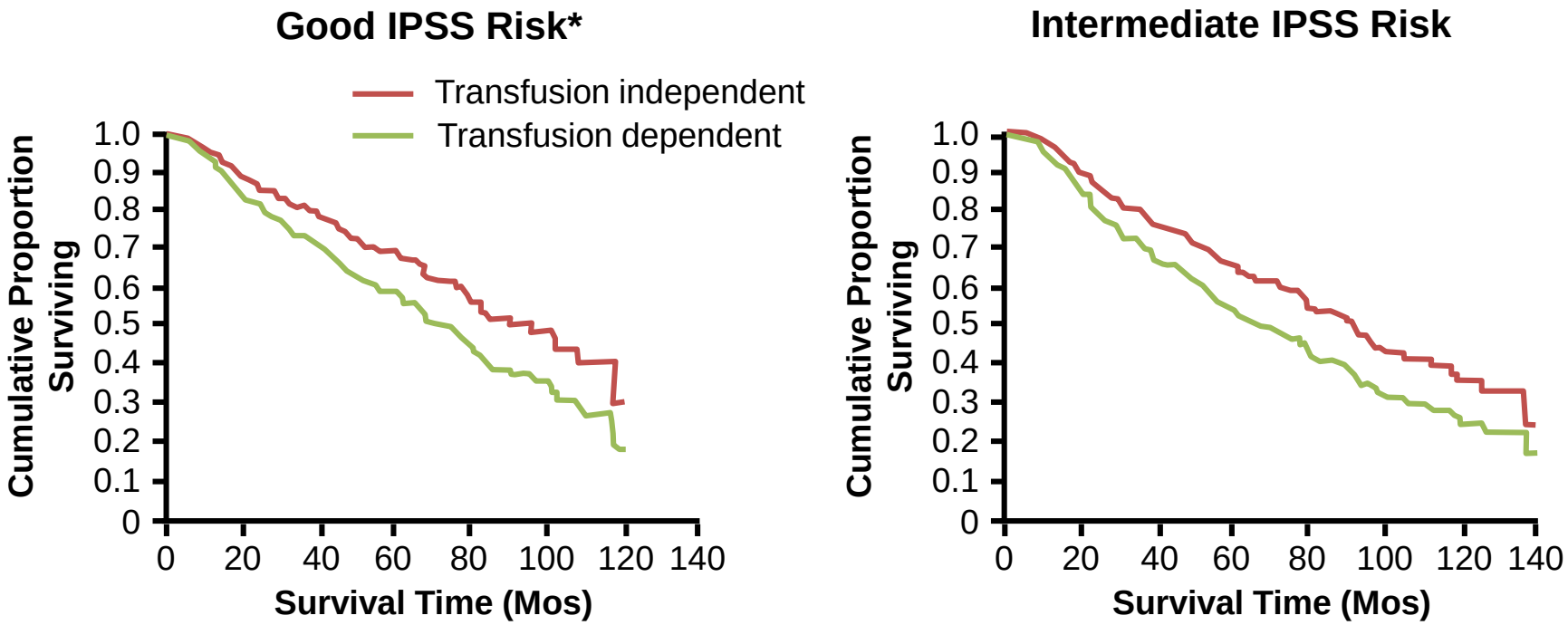
Anemia Management Algorithm Low- or Intermediate-1 Risk MDS

- Assess potential causes of anemia
- Supplement with iron, folate, vitamin B as needed
- RBC transfusion support for symptomatic patients



Adapted from NCCN. Clinical practice guidelines in oncology. MDS. v.2.2015.

Is Transfusion Dependency an Issue in MDS?

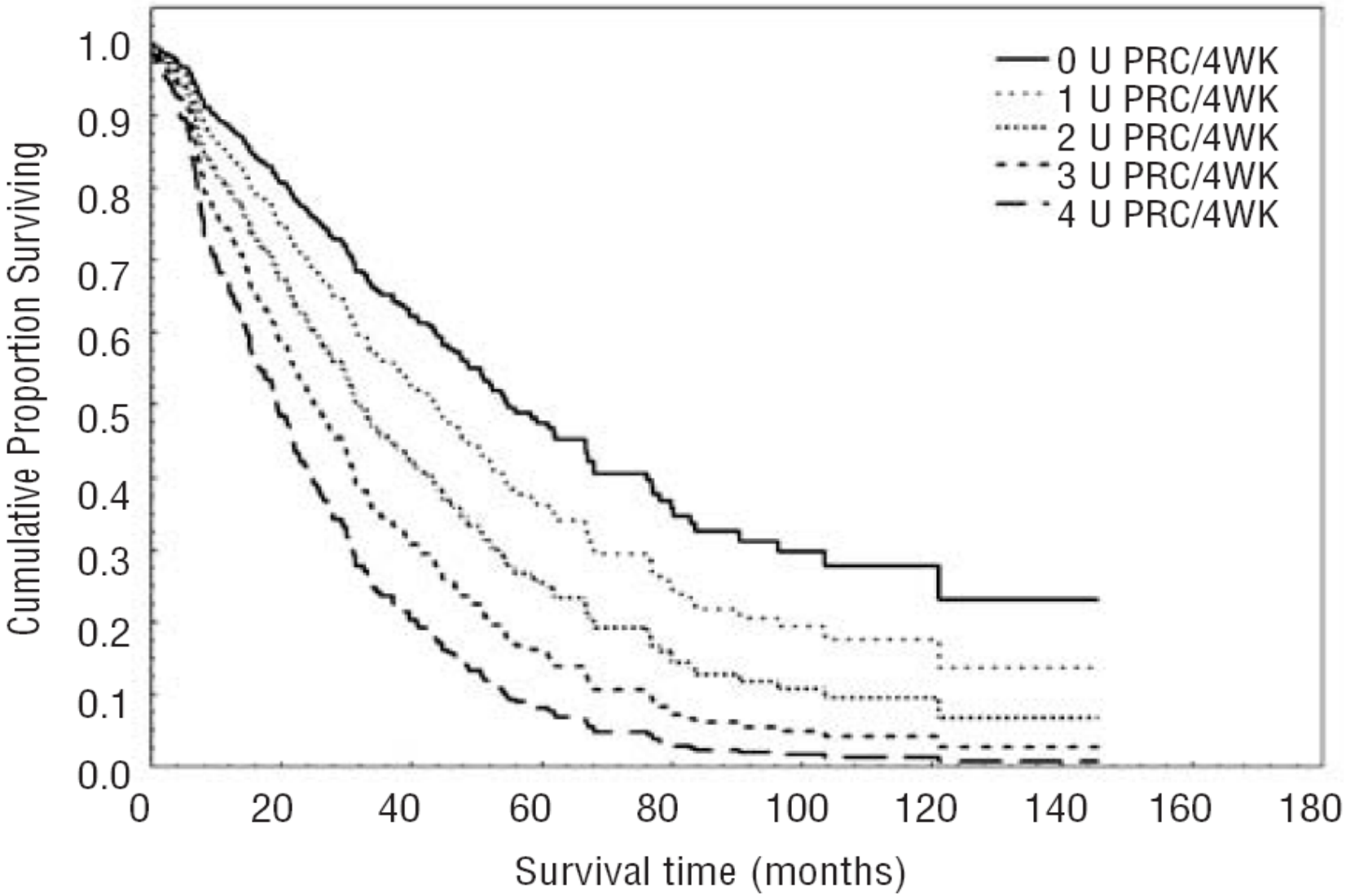


*Excludes isolated 5q-

- Transfusion-dependent patients had a significantly shorter OS than transfusion-independent patients (HR: 2.16; $P < .001$ overall)

Malcovati L, et. al. *J Clin Oncol*. 2005;23:7594-7603.

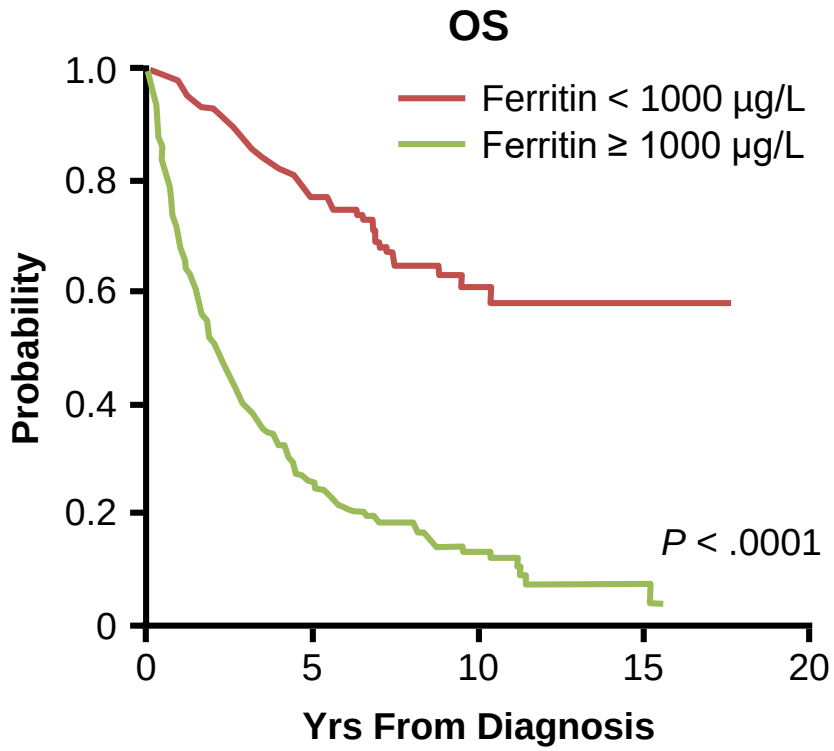
Survival by Transfusion Burden

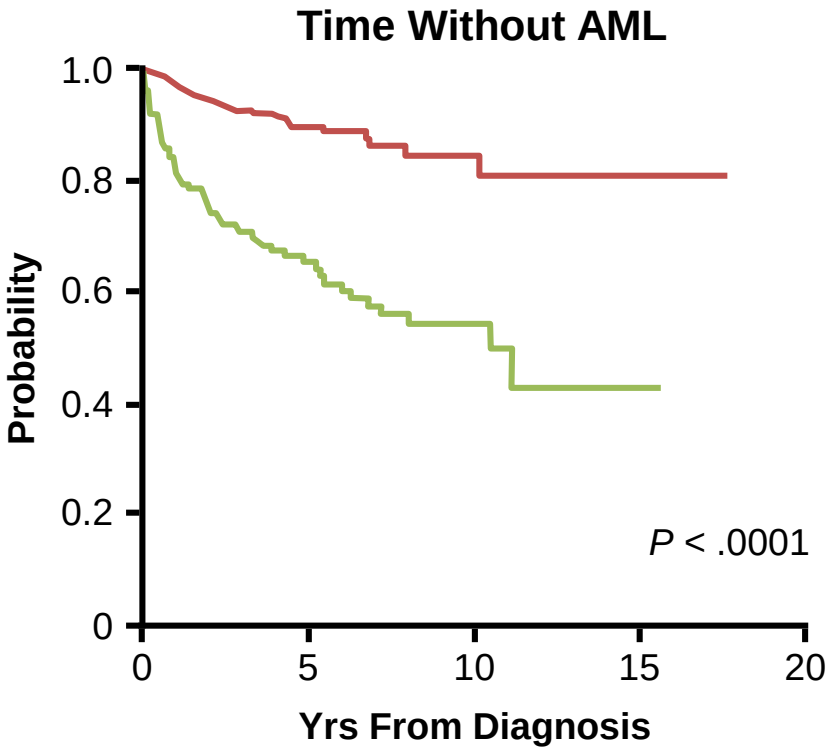


Malcovati L, et al. *Haematologica* 2006;91(12):1588-90

Serum Ferritin Is Predictive of Survival and Risk of AML in MDS

- Development of transfusional iron overload is a significant independent prognostic factor for overall survival and evolution to AML

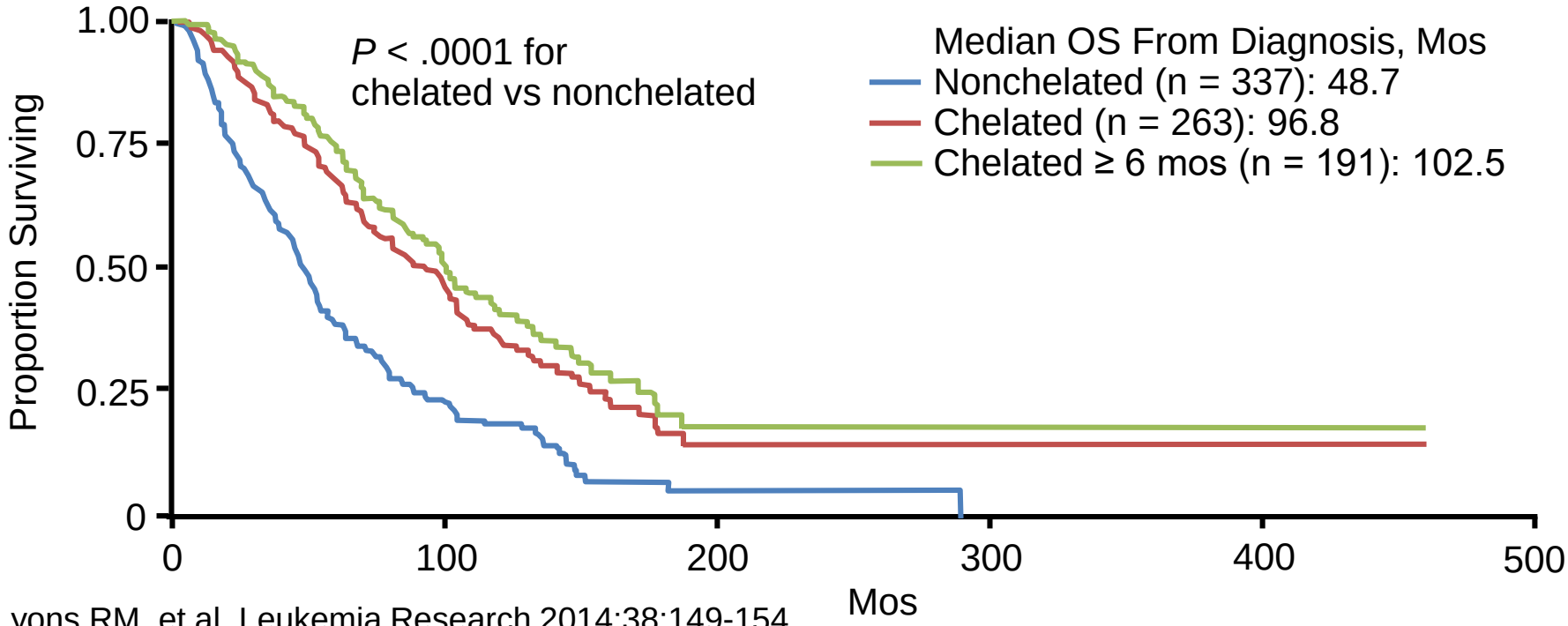




Sanz G, et al. 2008 ASH. Abstract 640.

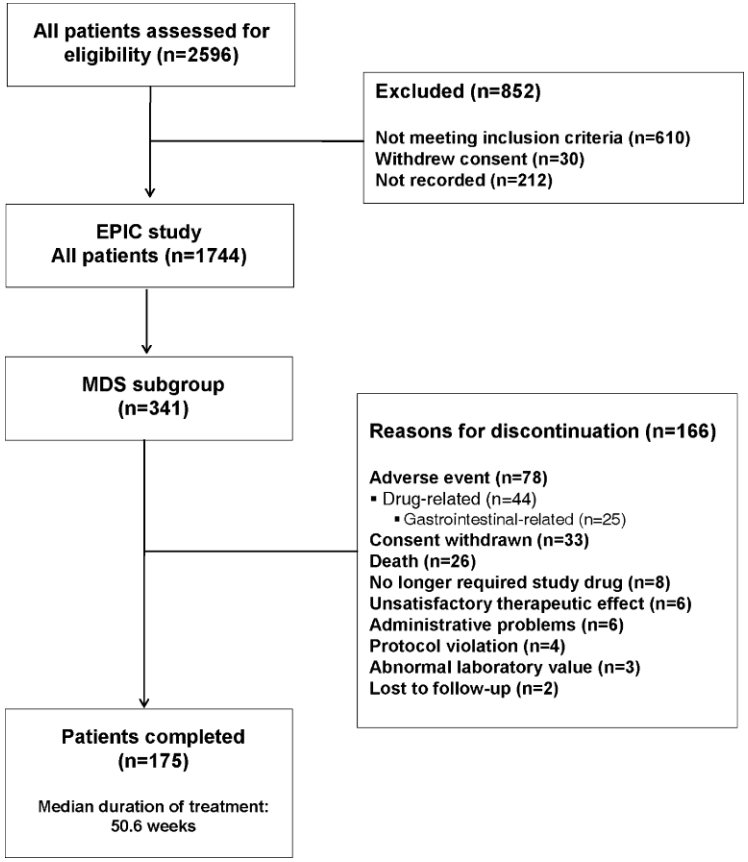
Prospective Chelation Study in Lower-Risk MDS: 48-Mo Update—OS

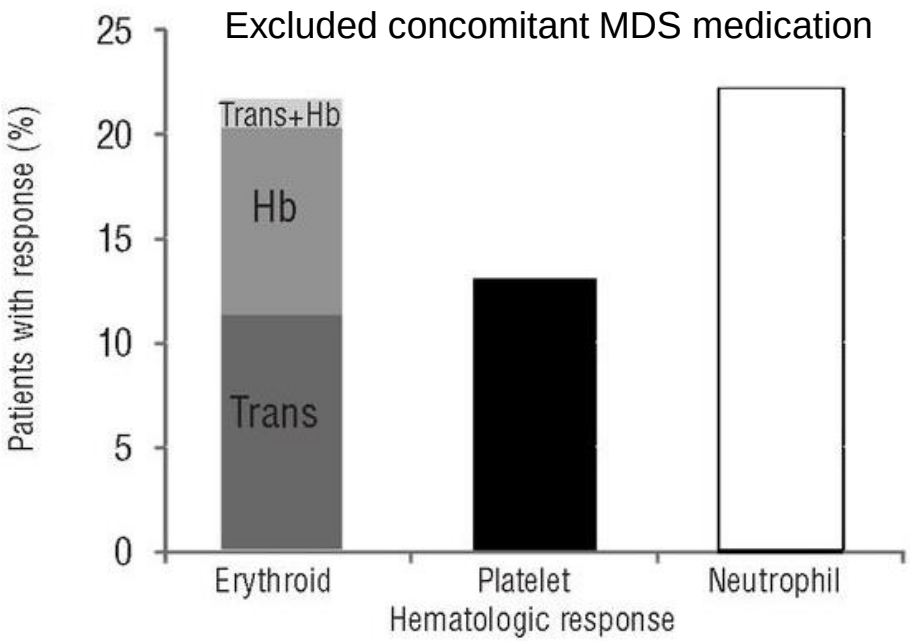
- 5-yr noninterventional registry study of 600 patients with lower-risk MDS and transfusional iron overload treated with or without chelation
- At 48 mos, chelated patients had significantly longer OS vs nonchelated



Lyons RM, et al. Leukemia Research 2014;38:149-154

EPIC Trial

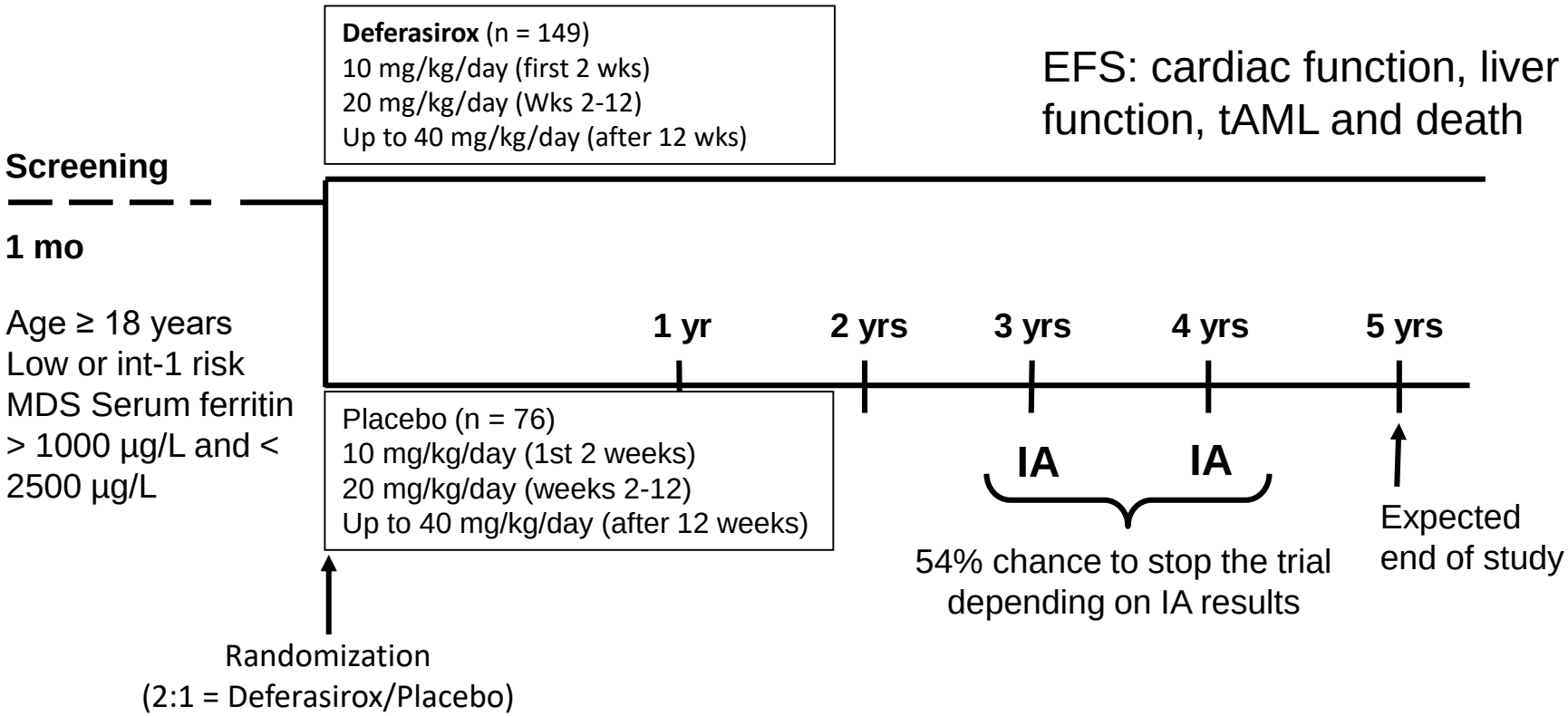




Prospective 1-year phase 2 trial with deferasirox
Primary endpoint reduction in serum ferritin

Gatterman et al. Leuk Res. 2010;34(9):1143-1150
Gatterman et al. Haematologica 2012;97(9):1364-1371

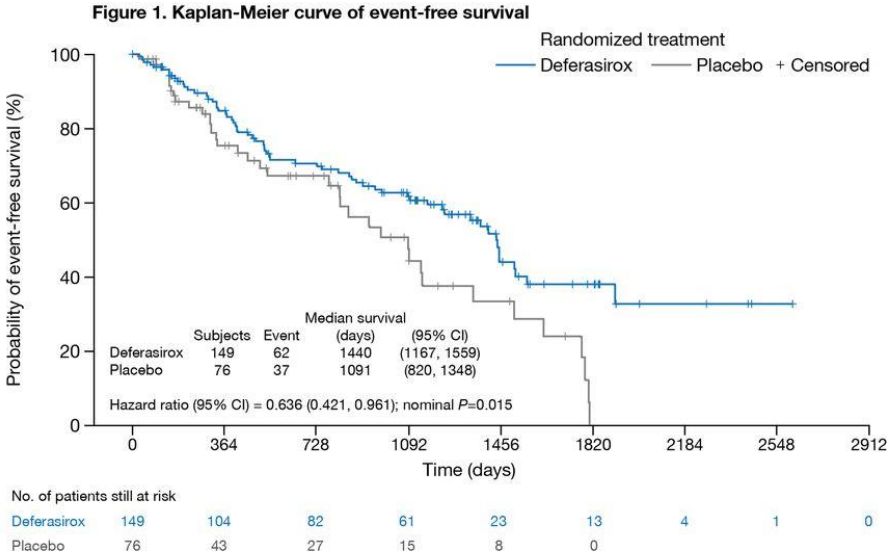
TELESTO Phase 2 Study Design

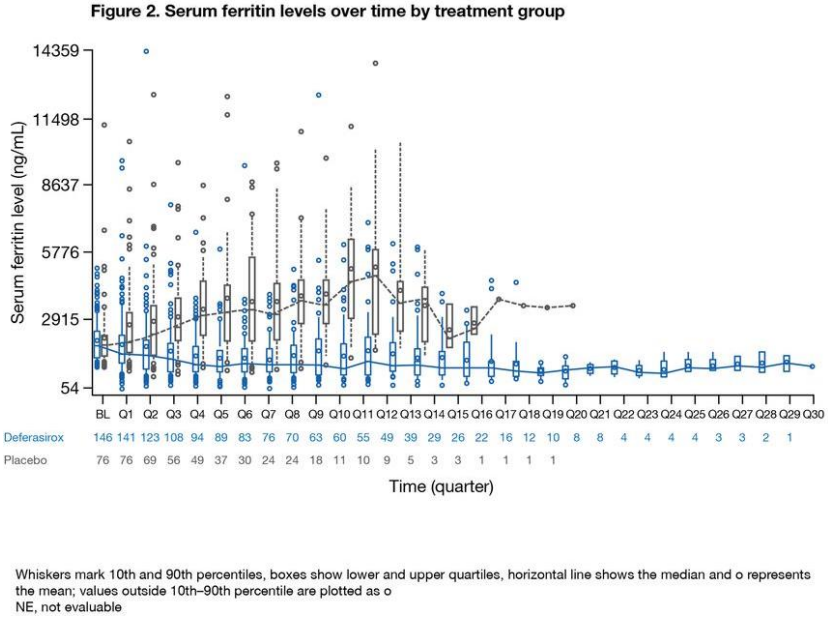


Interim analysis: at 50% of primary composite events (~ 3 yrs)
at 75% of primary composite events (~ 4 yrs)

Angelucci et al. *Blood* 2018;132:234

TELESTO Results





Angelucci et al. *Blood* 2018;132:234

MDS Patients Who Are Likely to Benefit Most From Management Iron Overload

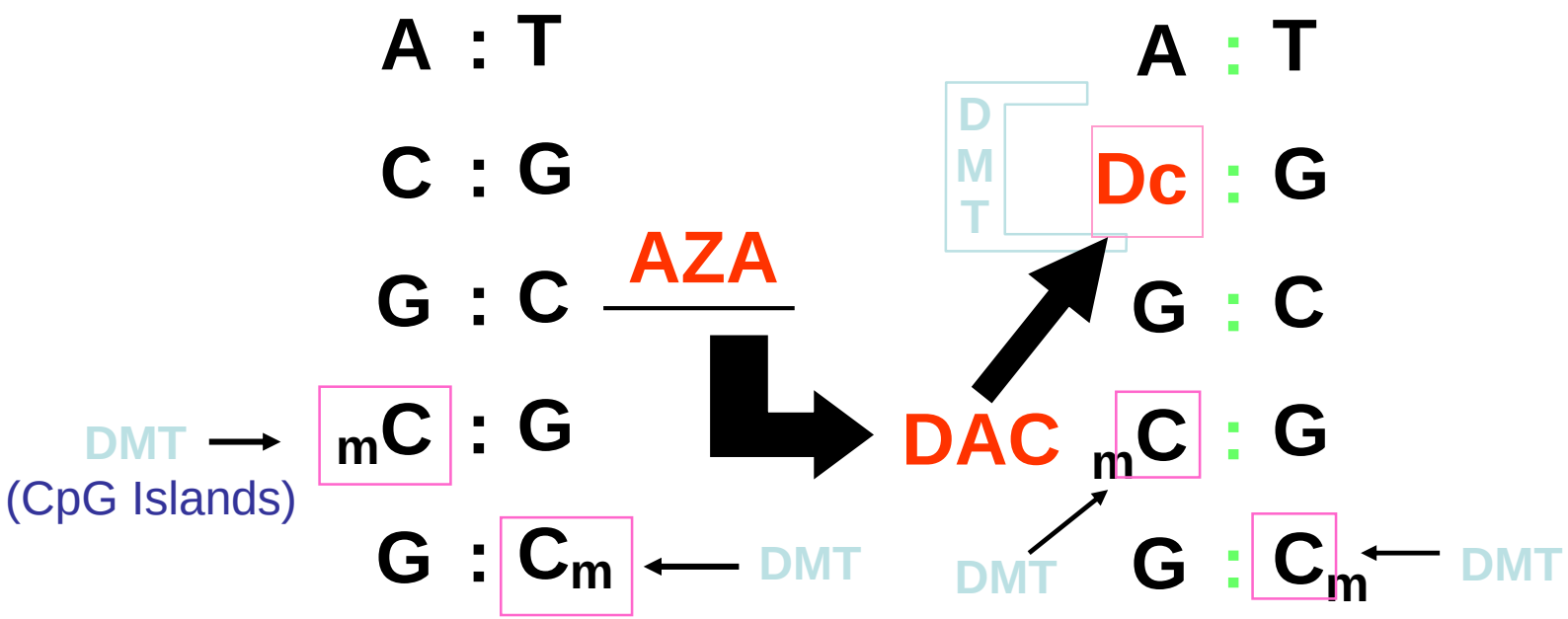
Characteristic	NCCN[1]	MDS Foundation[2]
Transfusion status	▪ Received > 20 RBC transfusions ▪ Continuing transfusions	▪ Transfusion dependent, requiring 2 units/mo for > 1 yr
Serum ferritin level	▪ > 2500 µg/L	▪ 1000 µg/L
MDS risk	▪ IPSS: low or intermediate-1 risk	▪ IPSS: Low- or Int-1 ▪ WHO: RA, RARS and 5q-
Patient profile	▪ Candidates for allografts	▪ Life expectancy > 1 yr and no comorbidities that limit progress ▪ A need to preserve organ function ▪ Candidates for allografts

1. NCCN. Clinical practice guidelines in oncology. MDS. v2.2015. 2. Bennett JM. J Hematol. 2008;83:858-861

Treatment Options for Higher-risk MDS

- Azacitidine/Vidaza
- Decitabine/Dacogen
- Clinical Trial

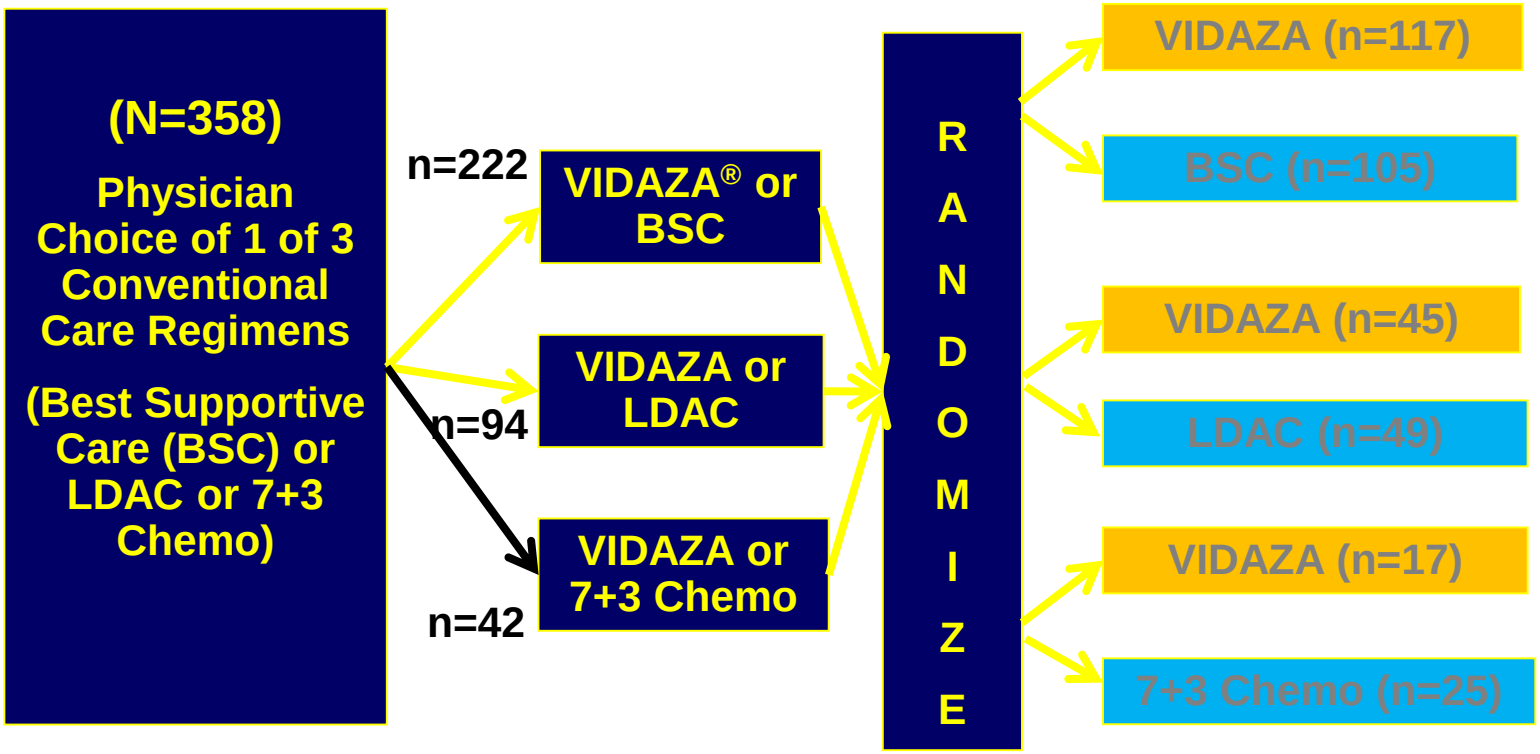
Methyltransferase Inhibitor (MTI) Induces DNA Hypomethylation and Gene Activation



- **Azacitidine (AZA) is incorporated into DNA *in lieu* of cytosine residue**
- **Inactivates DMT**
- **Leads to formation of newly synthesized DNA with unmethylated cytosine residues**
- **Results in hypomethylation and transcription of previously quiescent genes**

Silverman L. *The Oncologist.* 2001;6(S5):8-14.

AZA-001 Randomization Schema



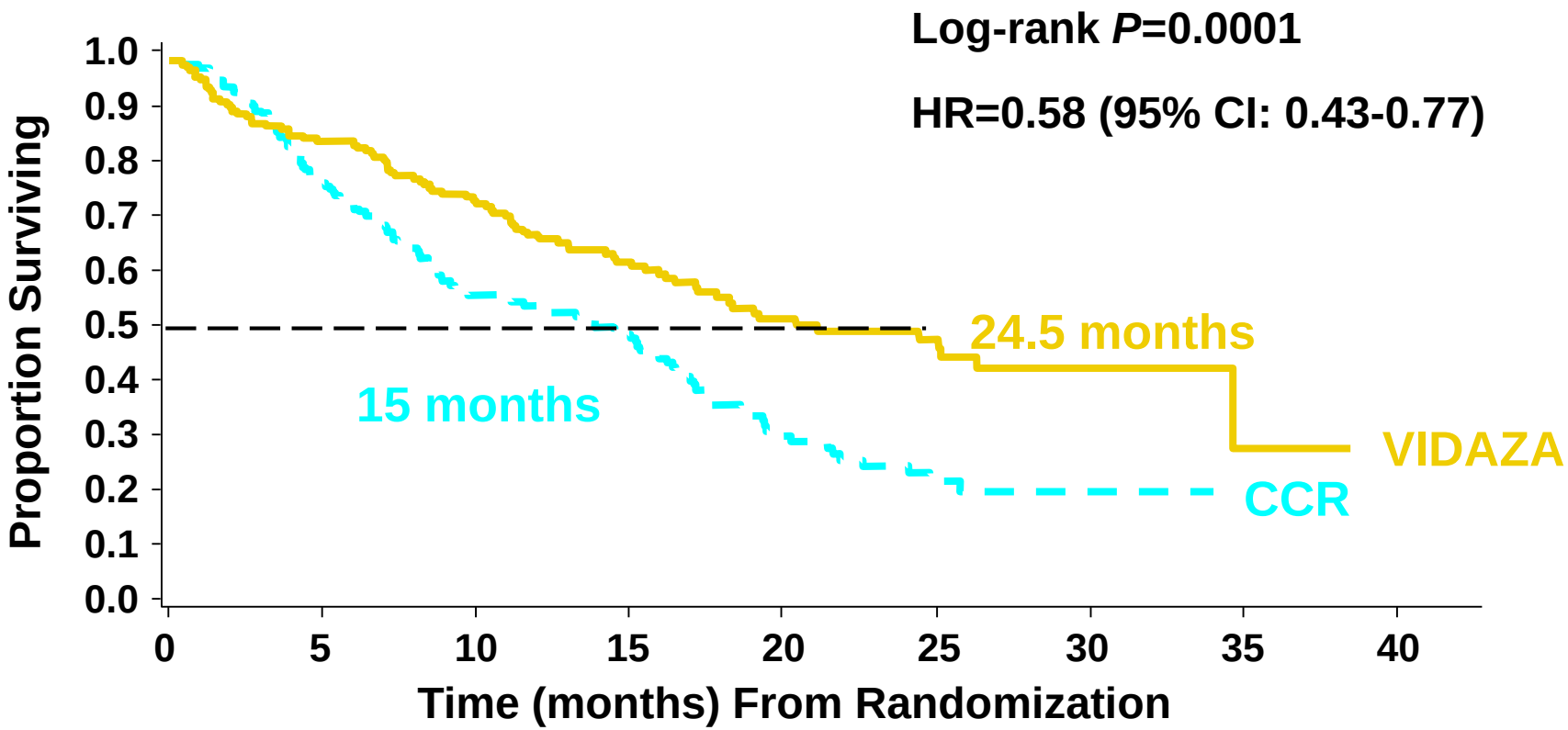
Fenaux et al. Lancet Oncol 2009;10:223-32

AZA-001 Trial: Baseline Clinical Characteristics*

			CCR Regimens N=179		
	VIDAZA® N=179	CCR N=179	BSC, Only N=105	LDAC N=49	7+3 Chemo N=25
Age					
Median (yrs)	69	70	70	71	65
≥65 (%)	68.1	76.0	77.1	85.7	52.0
FAB (%)					
RAEB	58.1	57.5	64.8	51.0	40.0
RAEB-T	34.1	34.6	28.6	38.8	52.0
CMMoL	3.4	2.8	3.8	2.0	0
IPSS (%)					
Int-1	2.8	7.3	8.6	4.1	8.0
Int-2	42.5	39.1	43.8	42.9	12.0
High	45.8	47.5	43.8	42.9	72.0
WHO (%)					
RAEB-1	7.8	9.5	12.4	6.1	4.0
RAEB-2	54.7	53.1	57.1	49.0	44.0
CMMoL-1	0.6	0	0	0	0
CMMoL-2	5.6	2.8	2.9	0	8.0
AML	30.7	32.4	25.7	40.8	44.0

*Numbers may not add up to 100%, some patient information unknown

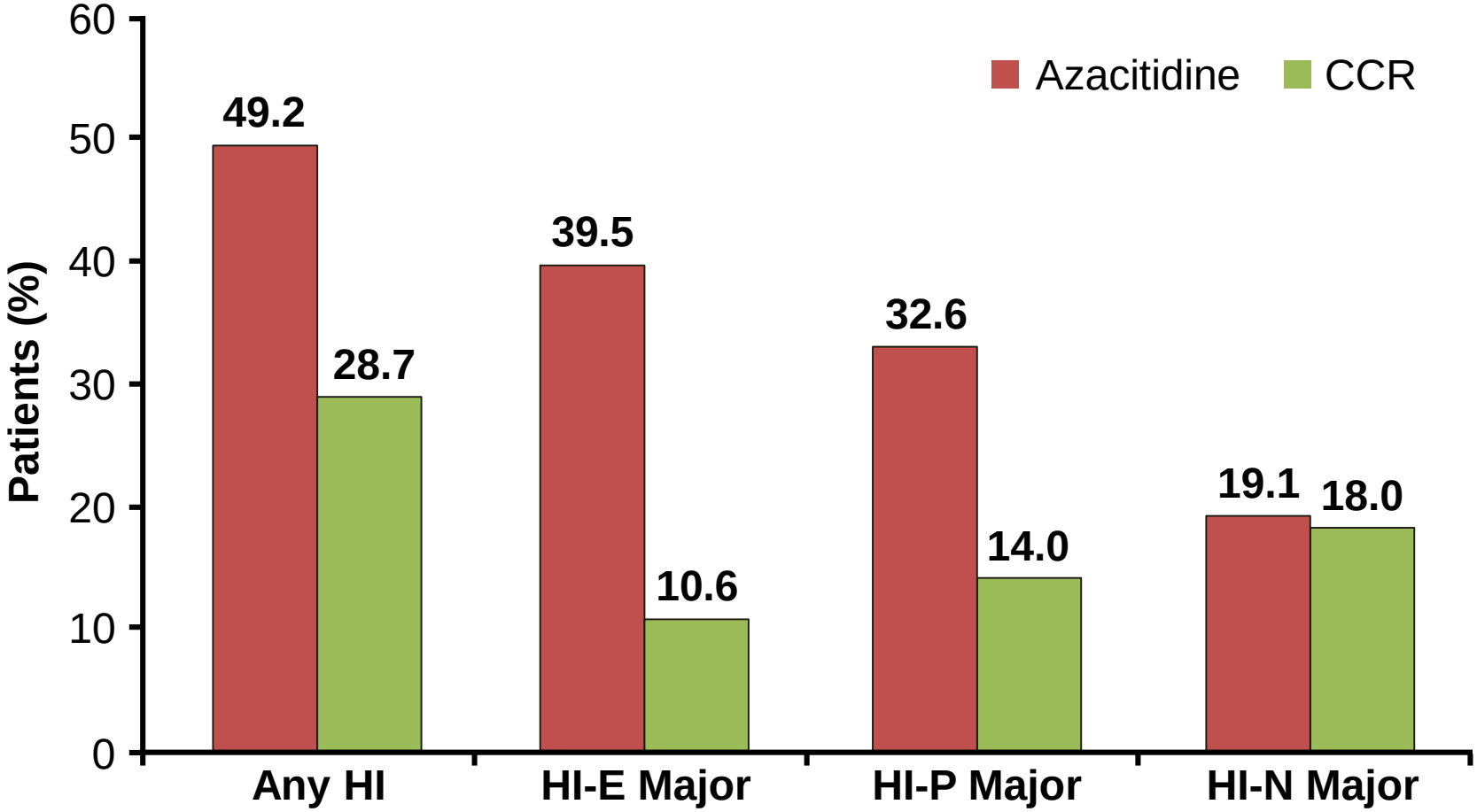
AZA-001 Trial: VIDAZA® Significantly Improves Overall Survival (OS)



Fenaux et al. Lancet Oncol 2009;10:223-32

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.

AZA-001: Hematologic Improvement (2000 IWG)



Fenaux P, et al. Lancet Oncol. 2009;10:223-232.

AZA-001: Grade 3/4 Adverse Events (≥ 2% of Patients)*

Adverse Events, n (%)	Azacitidine (n = 175)	BSC Only (n = 102)
Neutropenia	159 (91)	70 (69)
Thrombocytopenia	149 (85)	72 (71)
Leukopenia	26 (15)	1 (1)
Anemia	100 (57)	67 (66)
Febrile neutropenia	22 (13)	7 (7)
Pyrexia	8 (5)	1 (1)
Abdominal pain	7 (4)	0
Dyspnea	6 (3)	2 (2)
Fatigue	6 (3)	2 (2)
Hematuria	4 (2)	1 (1)
Hypertension	2 (1)	2 (2)

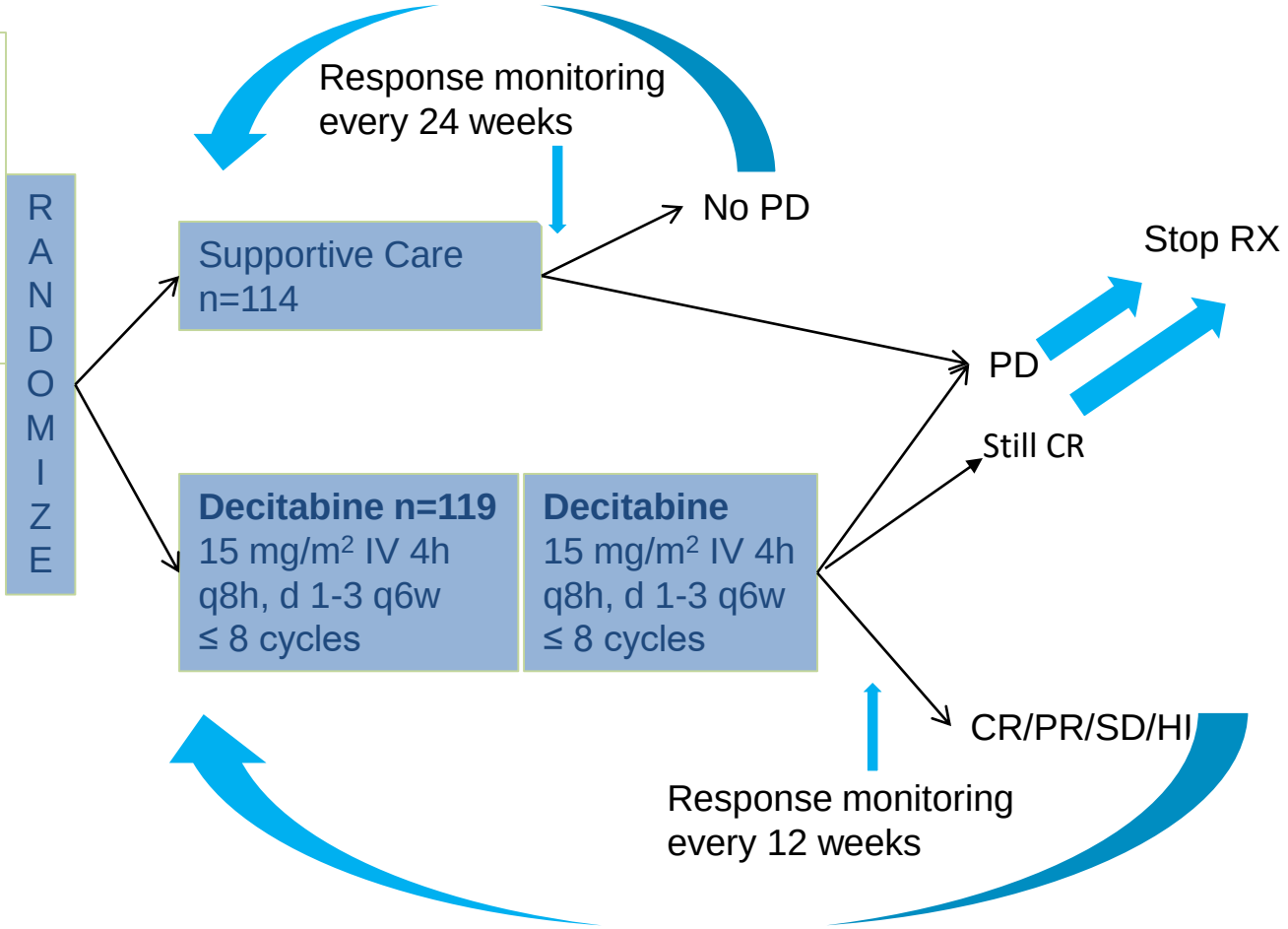
*When any grade of the reactions occurs in ≥ 5% of azacitidine-treated patients.

Fenaux P, et al. Lancet Oncol. 2009;10:223-232.

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

Eligibility criteria n=223:
- Intermediate- or high-risk MDS or CMML
- Age ≥ 60 years
- Blast cell count 11%-30% or ≤ 10% with poor cytogenetics

<u>Stratification</u>
- Cytogenics risk group
- IPSS
- Primary vs secondary
- Study center



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

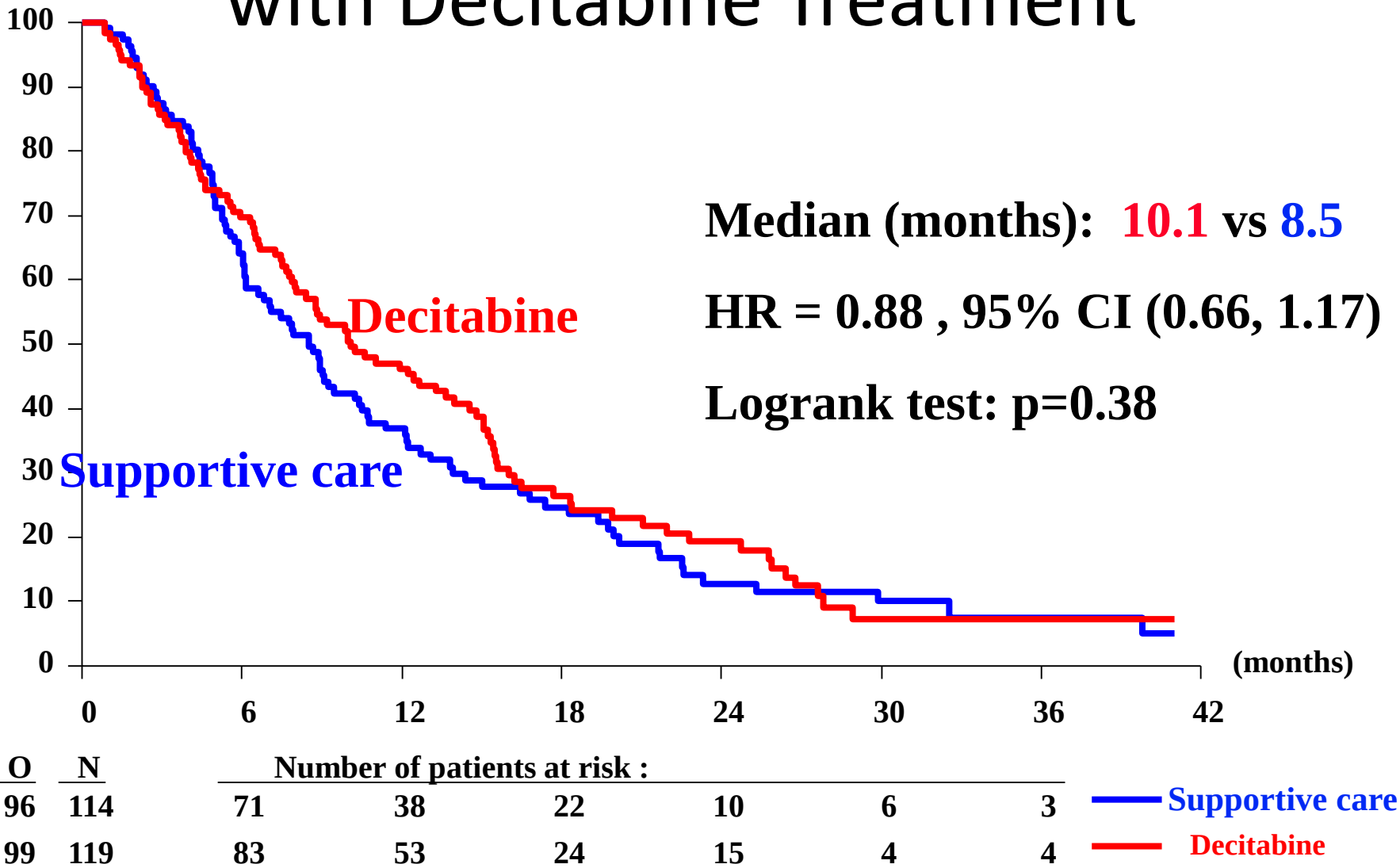
Reason for going off-protocol

	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 with Decitabine Treatment



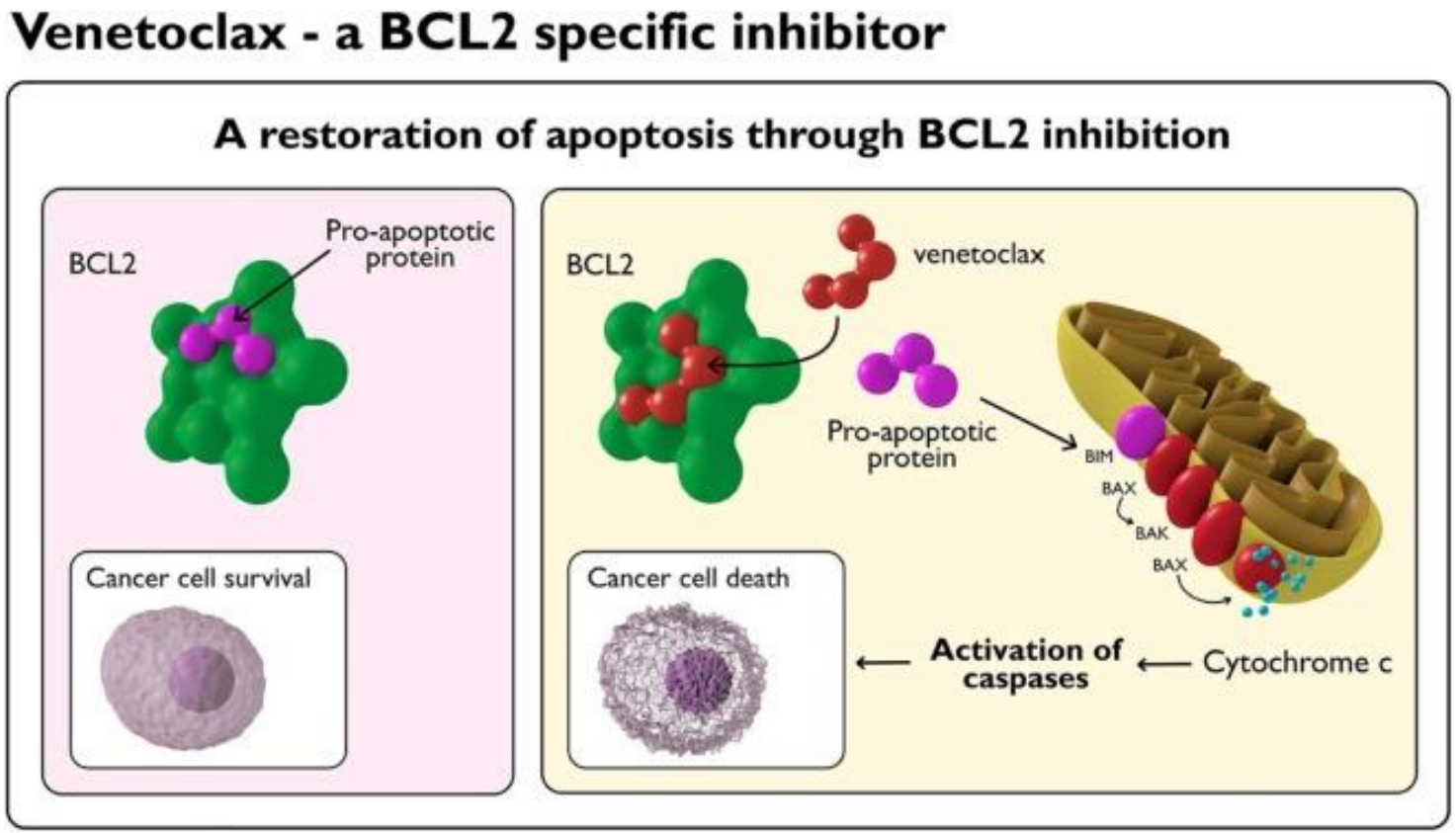
O	N	Number of patients at risk :					
96	114	71	38	22	10	6	3
99	119	83	53	24	15	4	4

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

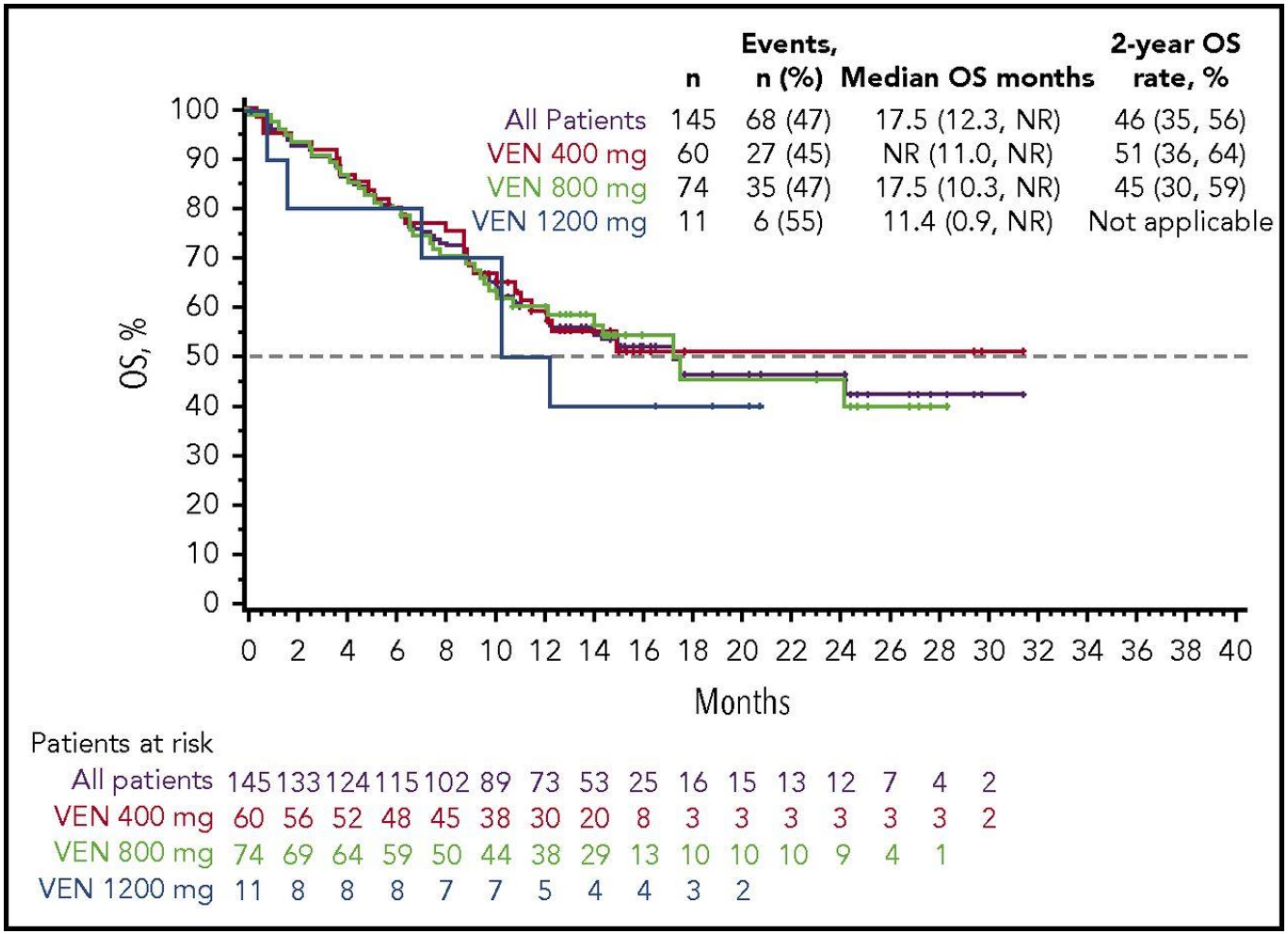
No survival advantage for DAC?

- 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

Venetoclax


Venetoclax - a BCL2 specific inhibitor
A restoration of apoptosis through BCL2 inhibition
BCL2
Pro-apoptotic protein
Cancer cell survival
BCL2
venetoclax
Pro-apoptotic protein
BIM
BAX
BAK
BAX
Cancer cell death
Activation of caspases
Cytochrome c

Venetoclax + HMA



DiNardo et al. *Blood* 2019;133:7-17

Clinical Trials

Overall Survival After AZA Failure (HR-MDS)

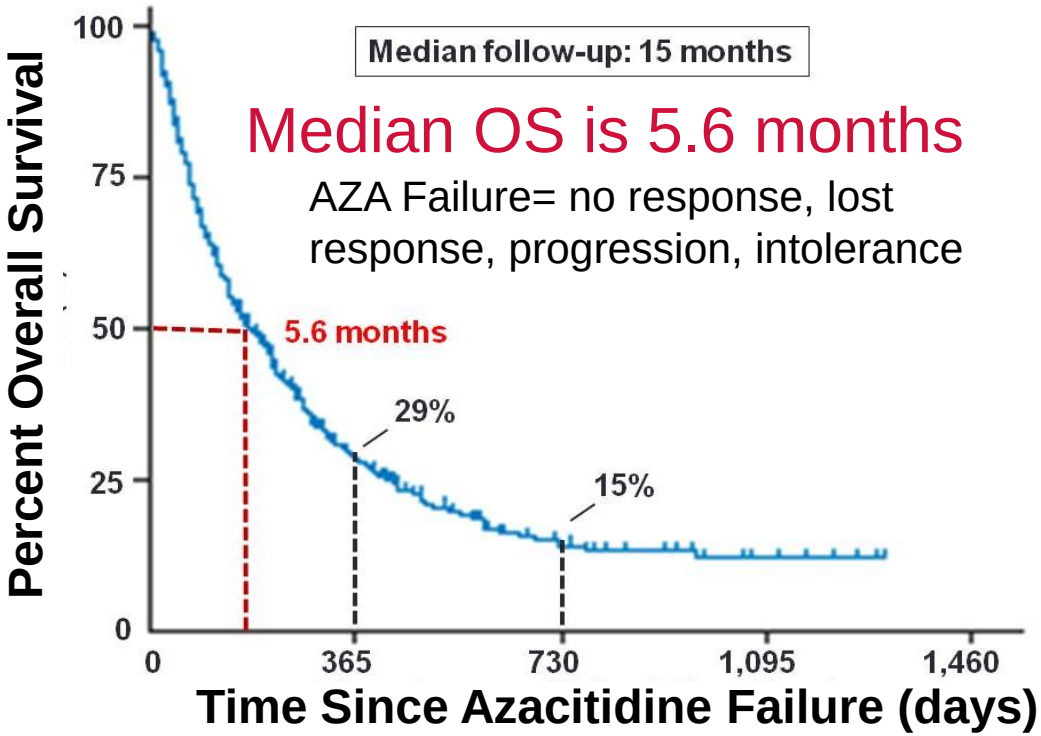
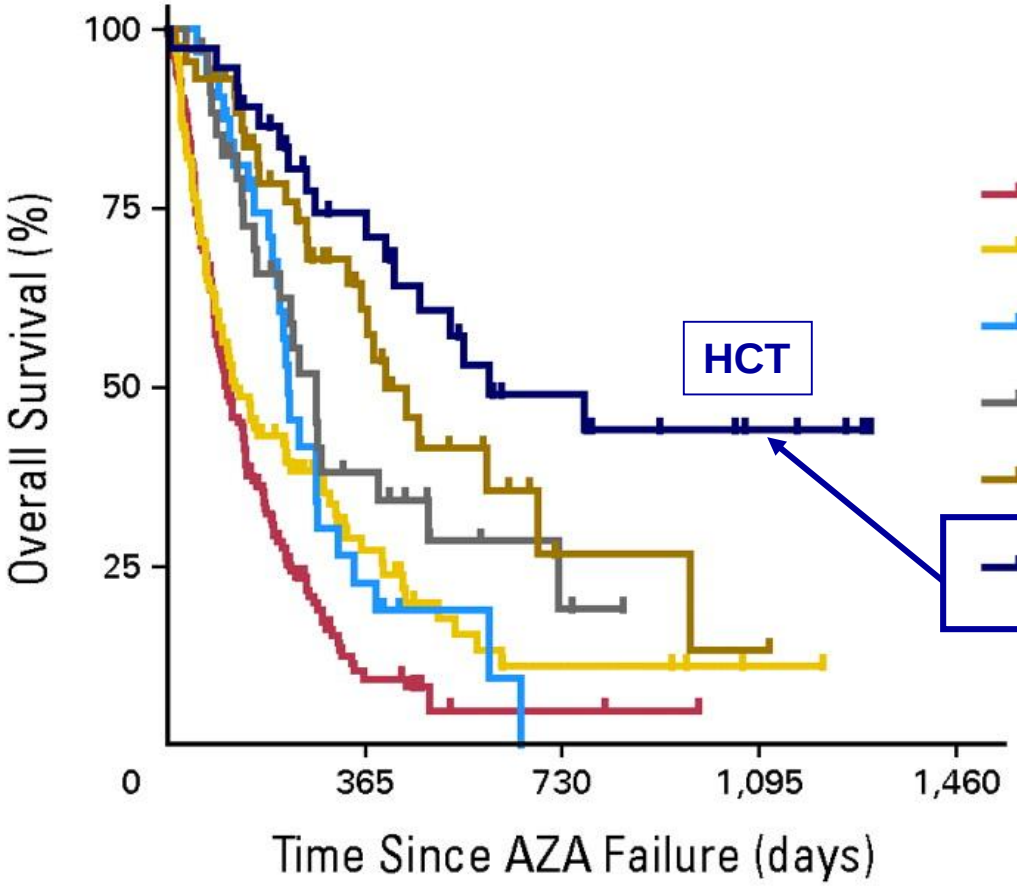


Table 2. Distribution of Patients According to the Type of Failure

Disease Status N=435	Patients No.	Patients %
Primary failure*	229	55
Stable disease	91	24
Progressive disease	138	31
Secondary failure†	164	36
Failure after CR	32	7
Failure after PR	12	2
Failure after HI	120	27
AZA intolerance	42	9
Without ongoing response	29	6
During response to AZA	13	3

Prébet et al. *J Clin Oncol* 2011;29:3322-3327

HR MDS post AZA failure OS by Salvage Therapy

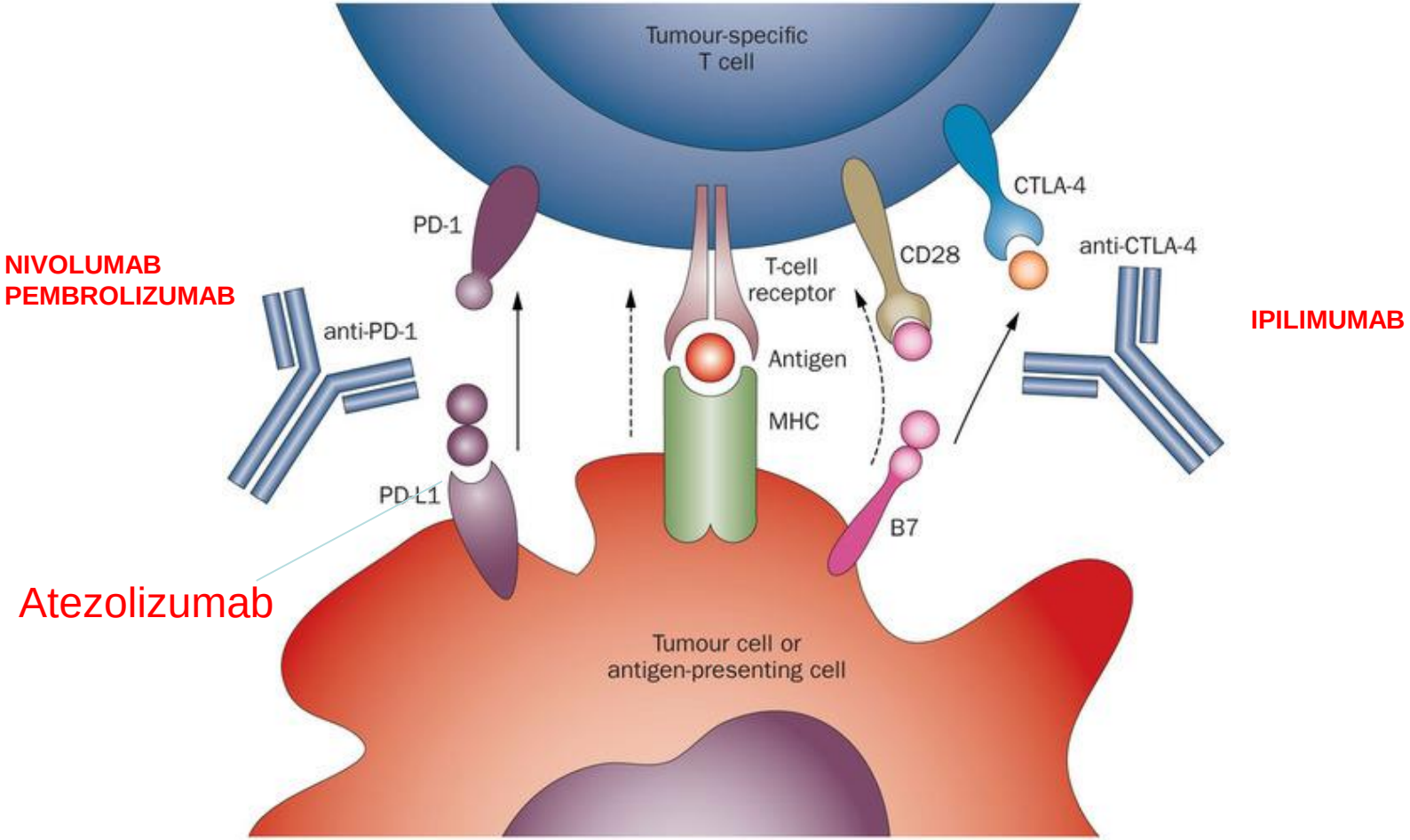


Type of salvage	N 435	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

†P<0.001

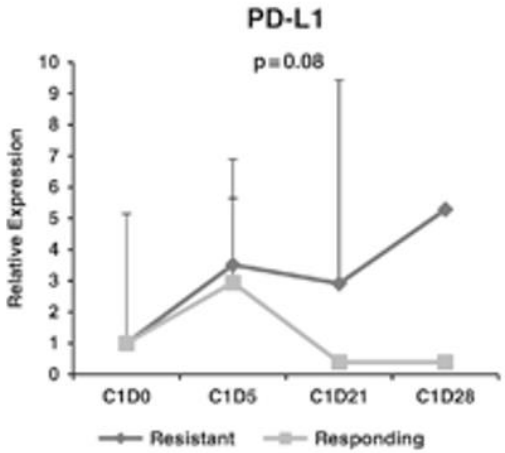
Prébet et al. *J Clin Oncol* 2011;29:3322-3327

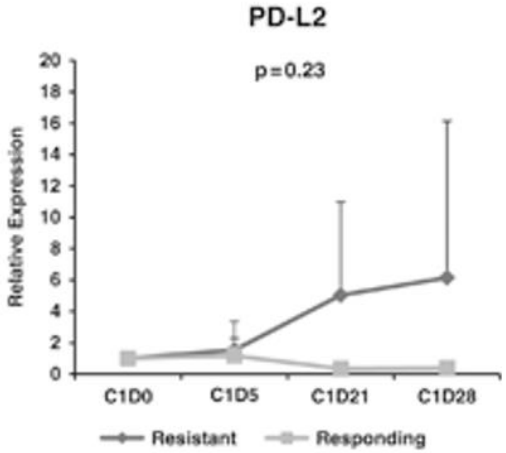
ICPI

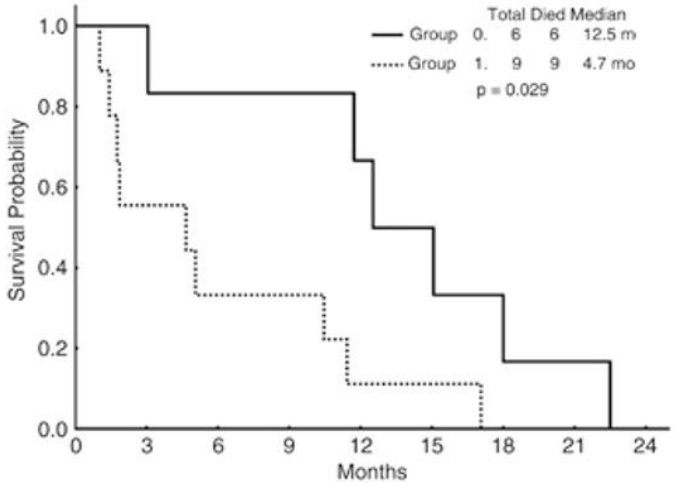

Tumour-specific
T cell
PD-1
CTLA-4
CD28
anti-CTLA-4
T-cell
receptor
Antigen
MHC
anti-PD-1
PD-L1
B7
Tumour cell or
antigen-presenting cell
NIVOLUMAB
PEMBROLIZUMAB
IPILIMUMAB
Atezolizumab

Increased PD-L1 Expression in HMA Failure

<u>Aza + Vorinostat</u>
Responders n=7
Resistance n=11





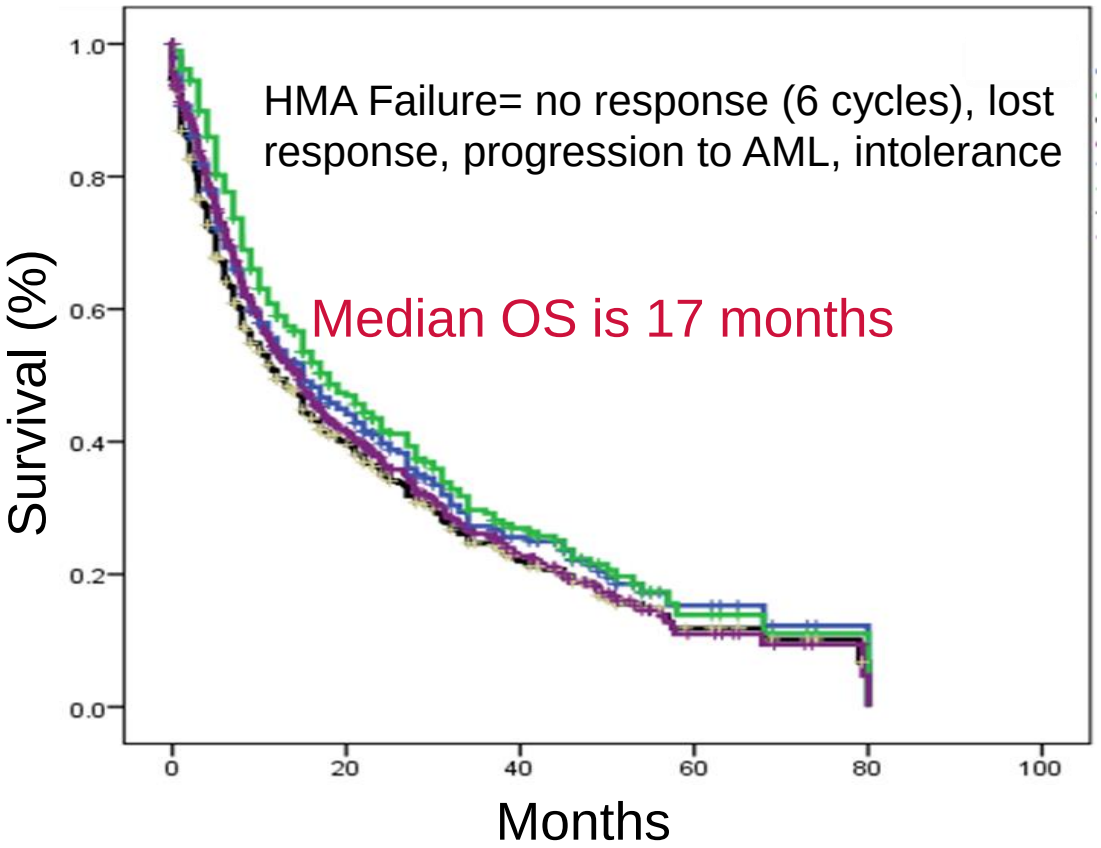


Group 0: no PDL-2 expression induction
Group 1: PDL-2 expression induction

mRNA from PBMNC

Yang et al. *Leukemia* 2014;28:1280-88

OS and TFS After HMA Failure (LR-MDS)



	N	Events	Months
OS*	290	204	17
TFS*	290	201	15
OS	438	315	15
TFS	438	318	12

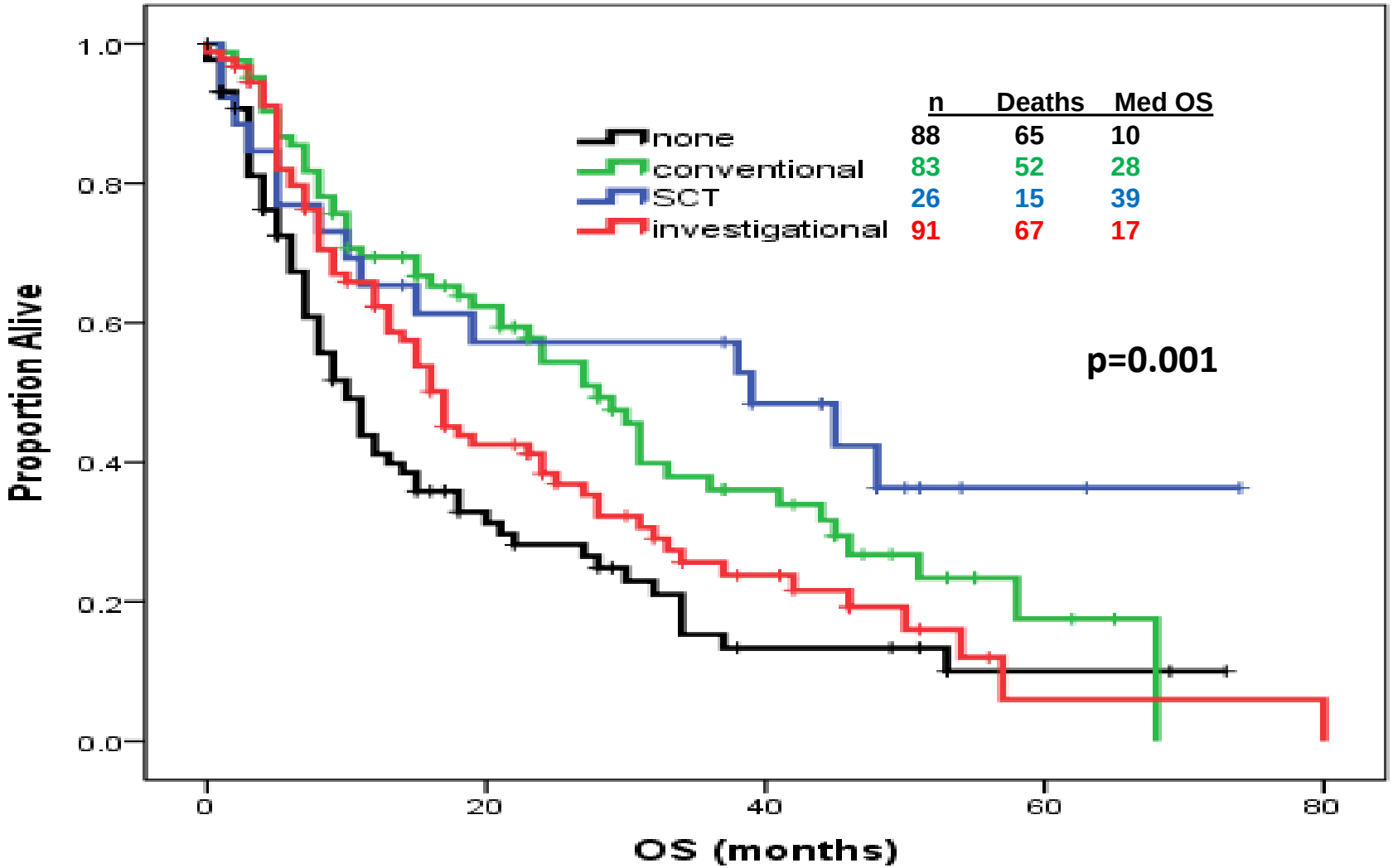
*Karyotype data available at time of failure

TABLE 2. Response to HMA Therapy and Reasons for Failure

	No. (%)
Best response	
Complete response	42 (10)
Partial response	19 (4)
Hematologic improvement	92 (21)
Stable disease	238 (54)
Progressive disease	36 (8)
Died while receiving therapy	11 (3)
Reason for stopping therapy	
Loss of response	133 (30)
Primary resistance	195 (45)
Transformation into AML	26 (6)
Side effects	13 (3)
Other	71 (16)

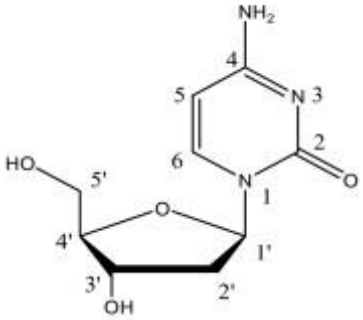
Jabbour et al, *Cancer* 2015;121:876-882.

LR MDS post HMA Failure. OS by Salvage Therapy

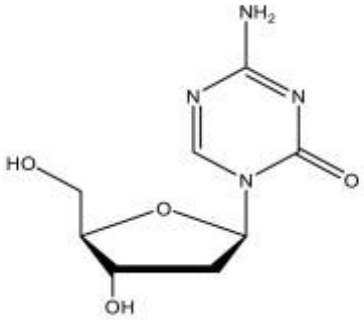


Jabbour et al, *Cancer* 2015;121:876-882.

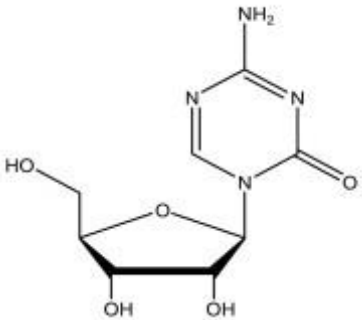
S110: Guadecitabine



cytidine

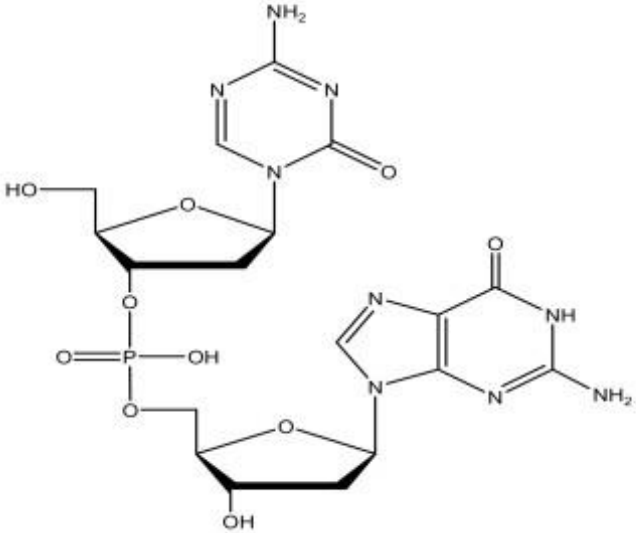


5-aza-2'-deoxycytidine (decitabine)



5-azacytidine

S110



Guanosine
Inhibits cytidine deaminase

347:SG-110 in MDS/CMML/AML after AZA failure

- GDAC 60 mg/m^2/day Day 1-5 q 28 days
  - Median 3 cycles
- N=56; 15 refractory and 41 relapsed
- 9 responded (16%)
  - 1 CR, 2CRp, 5 marrow CR, 1 HI
- Median duration of response 9 months
- Median OS 6.7 mos
  - 33 died: 14 progression,13 infection, 1 bleeding, 5 other

Sebert et al. *Blood* 2016;128:347

ASTRAL-2 Design

MDS or **CMML** Patients who failed or progressed on full course of prior **HMA** and any other prior active anticancer therapy
408 patients

Study treatment randomization **2:1**

Guadecitabine
(n=272)
60 mg/m2/d x5 Q28d
+ Best Supportive Care

****Requires 6 cycles of treatment*

Treatment Choice (TC)
(n=136)

Low dose Cytarabine (LDAC) **or**
- 20 mg/m2 SC or IV once daily for 14 days in 28 day cycles (other schedules are allowed per institutional and standard practices)

Intensive Chemotherapy (IC) 7+3 **or**
- Cytarabine 100-200 mg/m2/day (7 days) and an anthracycline per institutional standard practice (3 days)

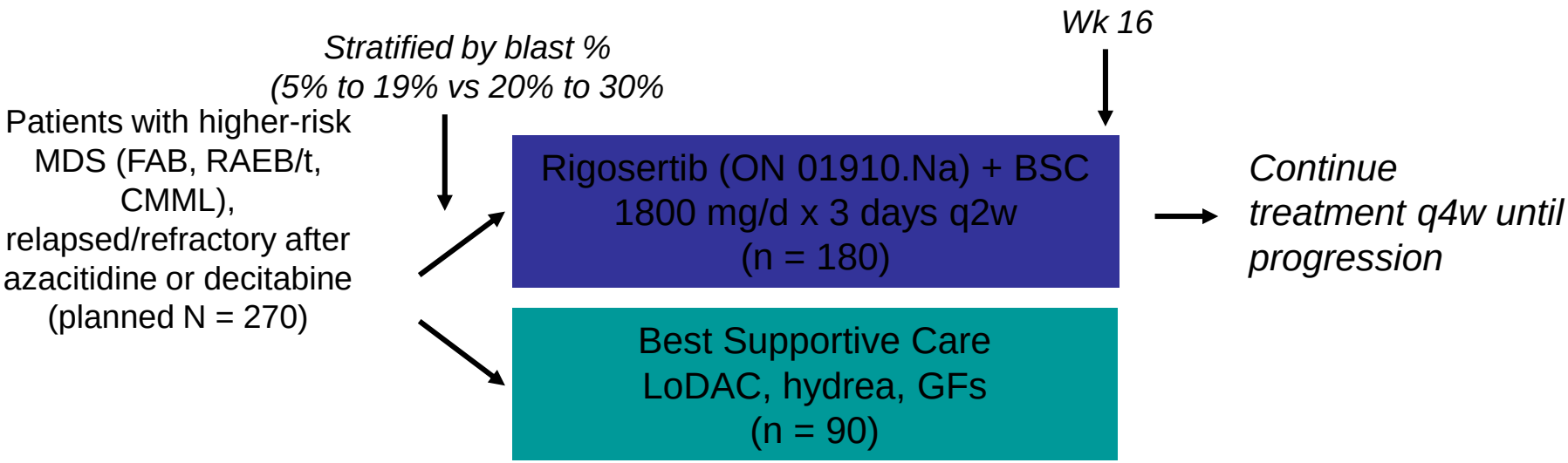
Best Supportive Care (BSC) only
- Per institution standard/practice

Primary Analyses (**OS**) after at least 316 death events have occurred

Note: All treatment options (guadecitabine and TC) may include BSC options

Phase III ONTIME: Rigosertib in Higher-Risk MDS After HMA Failure

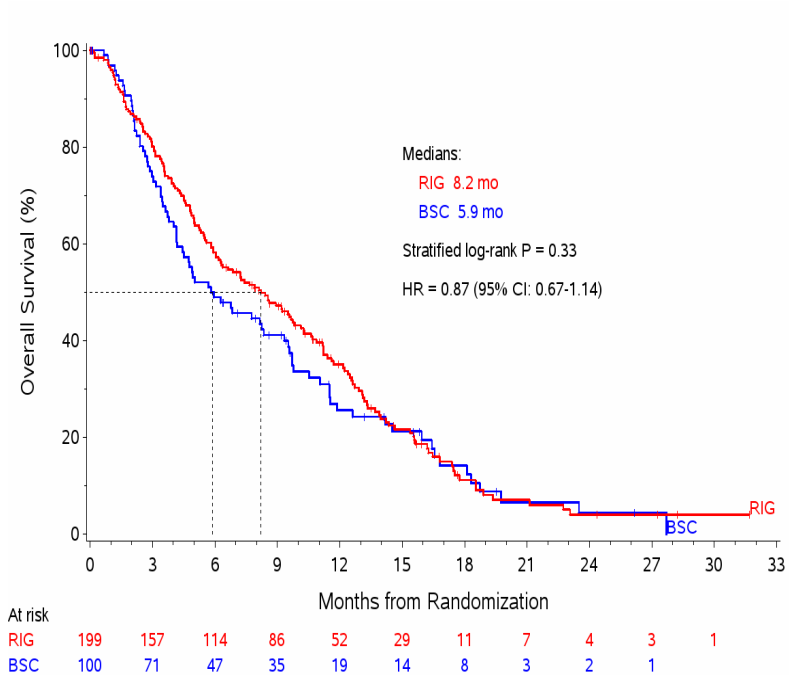
- Rigosertib: PLK and PI3K inhibitor; a novel synthetic benzyl styryl sulfone that is cytotoxic against a variety of human tumor cell lines

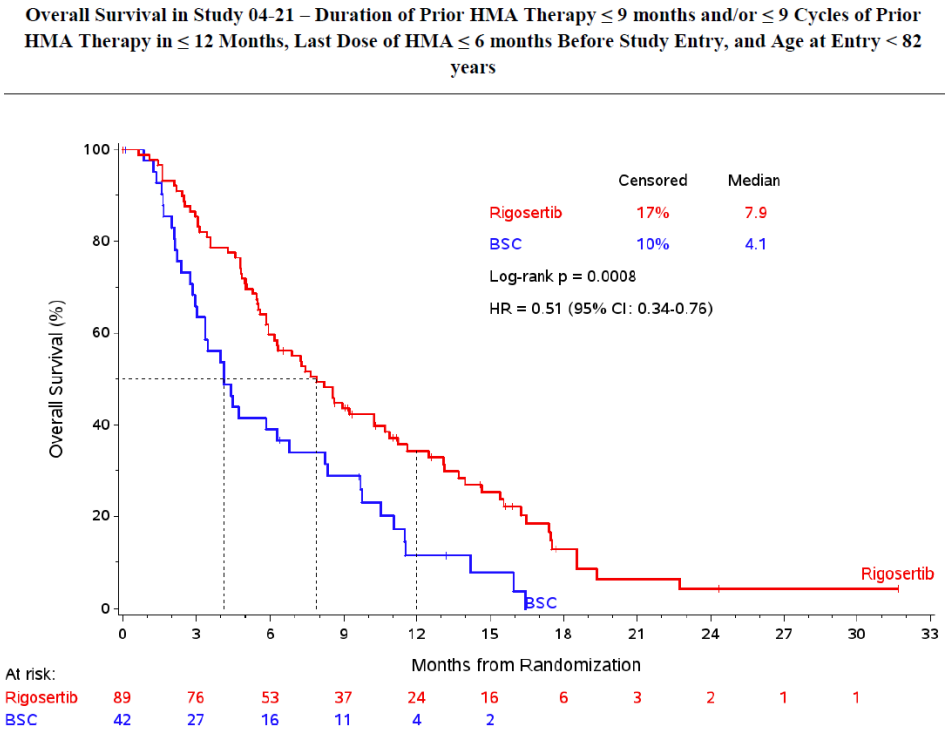


- Primary endpoint: OS (HR: 0.62)
- Secondary endpoints: IWG response, transformation to AML, infection, bleeding, QoL

Garcia-Manero et al. *Lancet Oncology*; 2016;17:496-508

Rigosertib vs. BSC

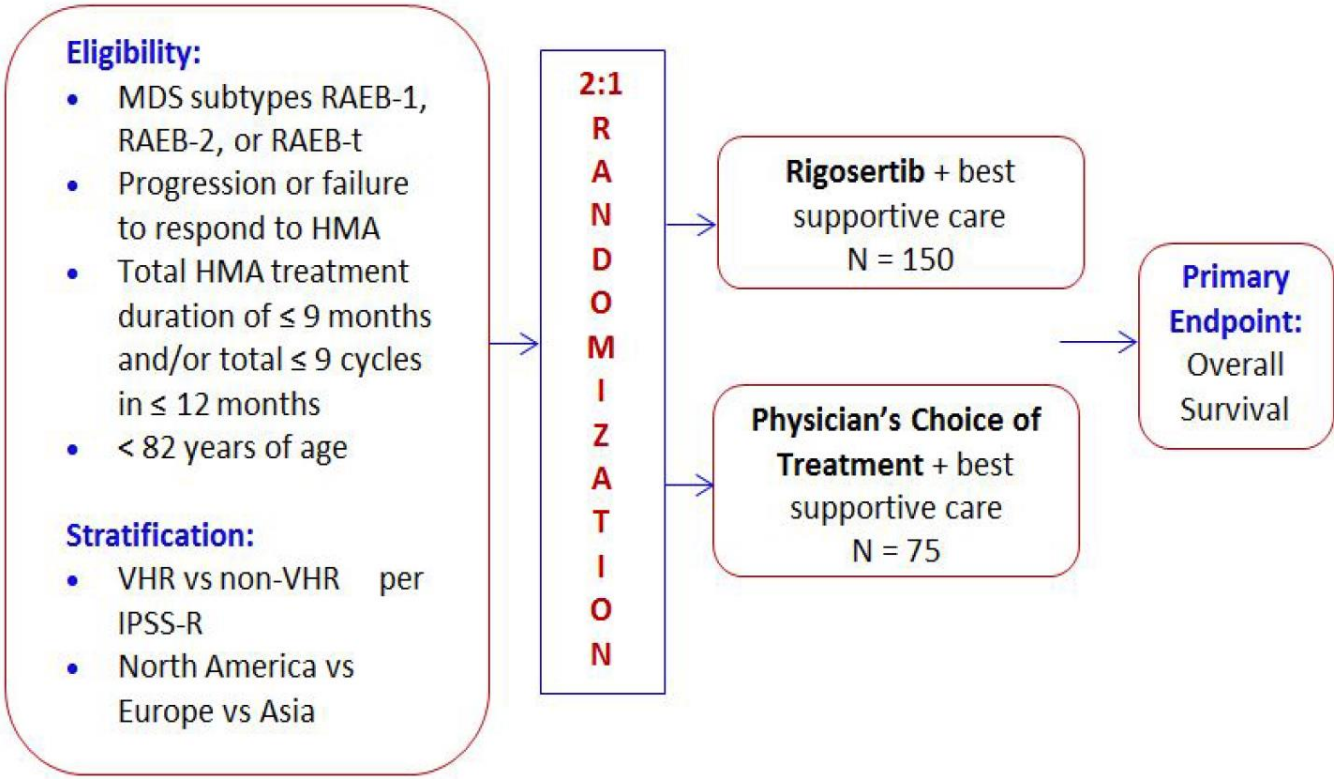




Subset analysis indicated improved responses with primary failure

Garcia-Manero et al. *Lancet Oncology*; 2016;17:496-508

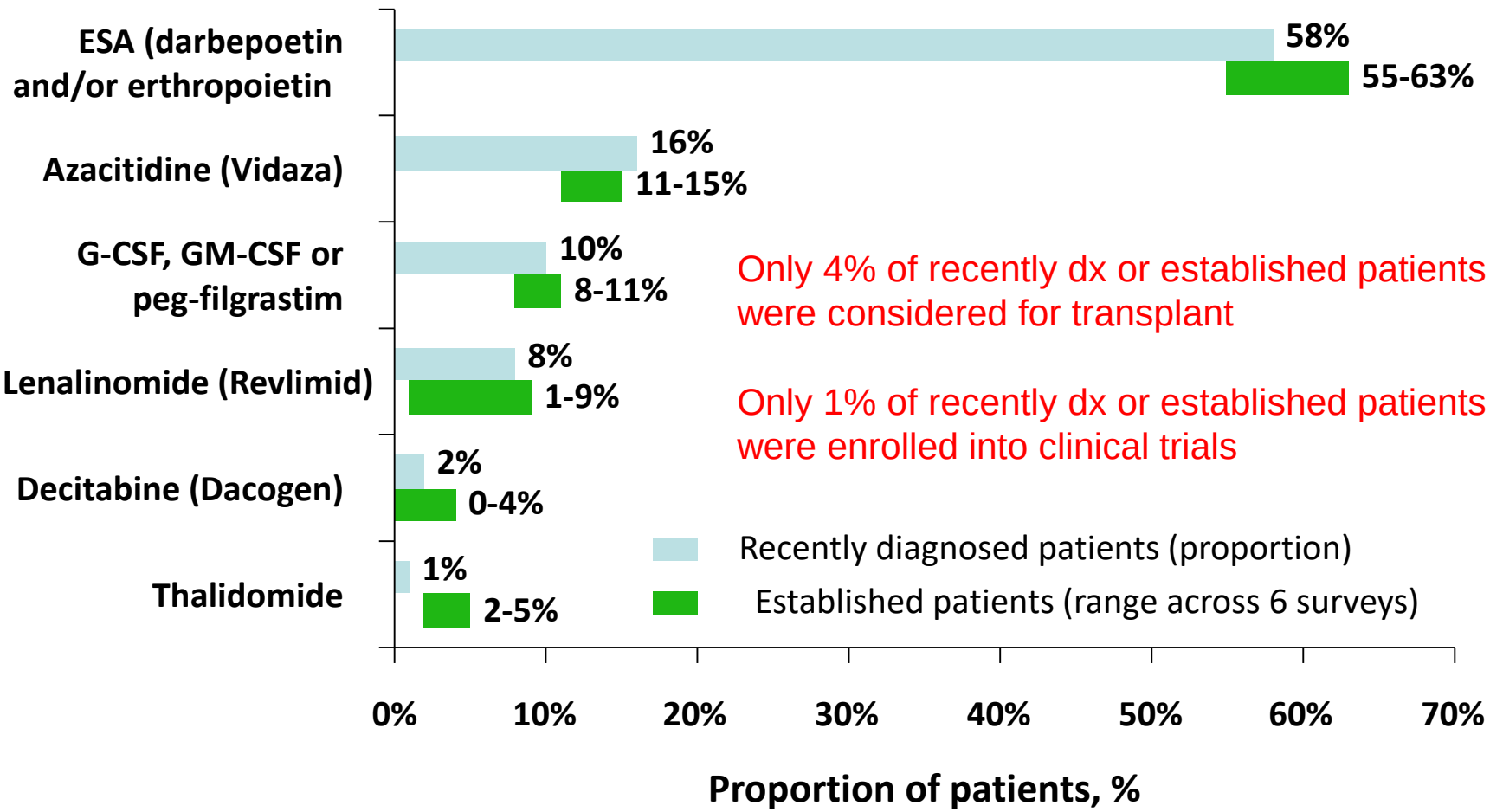
ONTIME 2



Best supportive care = red blood cell and platelet transfusions, and growth factors (growth factors, granulocyte colony-stimulating factor (G-CSF), erythropoietin, and thrombopoietin)

U.S. treatment approaches to MDS

Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapies at the time of the survey



Only 4% of recently dx or established patients were considered for transplant

Only 1% of recently dx or established patients were enrolled into clinical trials

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

Conclusions: Non-Transplant Therapy for MDS

- Transfusion support plus SC is an appropriate choice for some patients with MDS
- Growth factors remain the most common treatment choice for MDS
- IST is an appropriate choice for some patients with low/int-1 risk MDS
- Lenalidomide indicated for rec cell TD low/int-1 risk del (5q) MDS
- Aza has been shown to improve OS in patients with int-2/high risk MDS
- The role of iron-chelation remains controversial pending results of a RCT TELESTO

MDS Treatment Algorithm