Myelodysplastic Syndromes

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Disclosures

Research Support/PI	Astex, Celgene, Chroma Therapeutics, EntreMed, Roche
Employee	N/A
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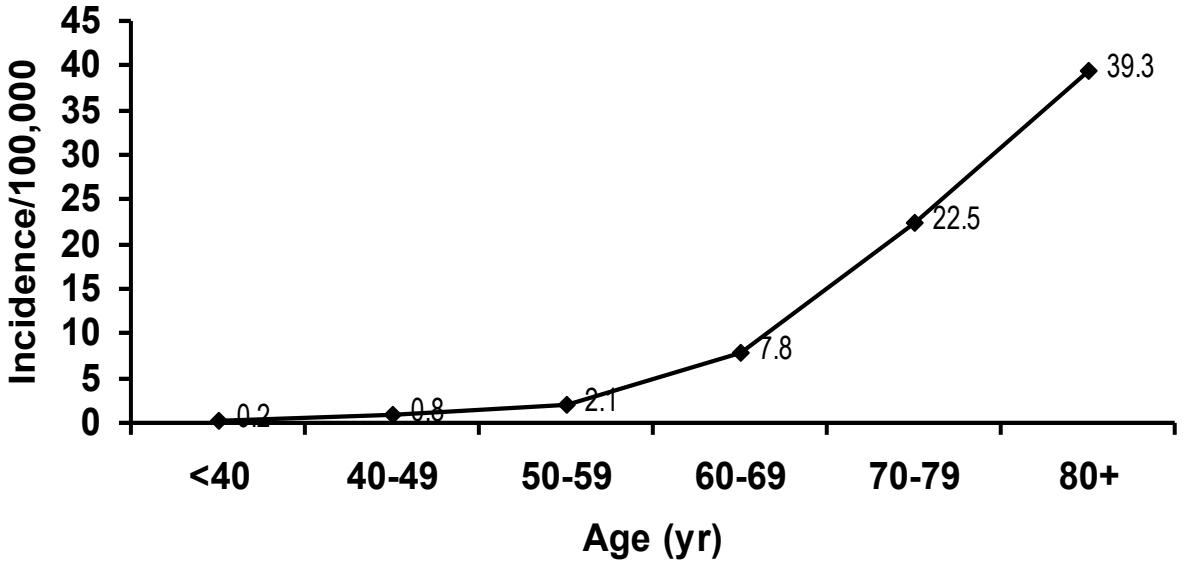
Overview

- Background
- Risk-Based Treatment Strategies:
  - Lower (Low & Int-1) Risk
    - Erythropoietin Stimulating Agents (ESAs)
    - Lenalidomide
    - (Iron Chelation)
  - Higher (Int-2 & High) Risk
    - Hypomethylating Agents
    - (Allogeneic Stem Cell Transplantation)

University Health Network

MDS Age-Specific Incidence Rates (2001-2004)



Statistics Canada 2006
NCI-SEER 2006
National Vital Stats 2006

Prognostic Indicators in MDS:

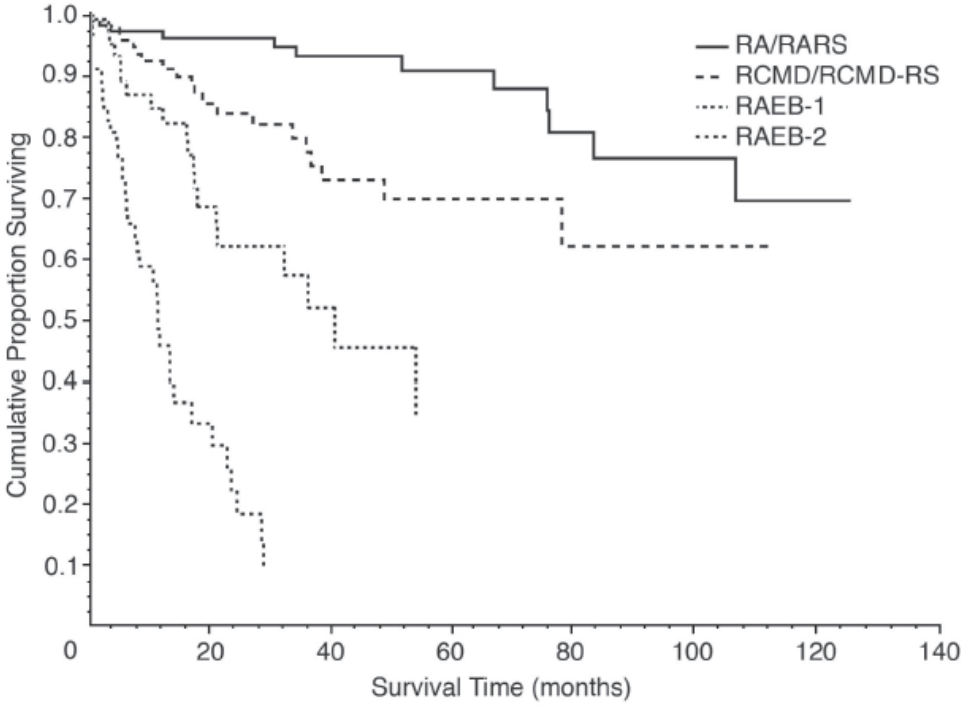
French-American-British (FAB) Classification (1992)
World Health Organization (WHO) Classification (2008)

International Prognostic Scoring System (IPSS; 1997)
IPSS-Revised (IPSS-R; 2012)

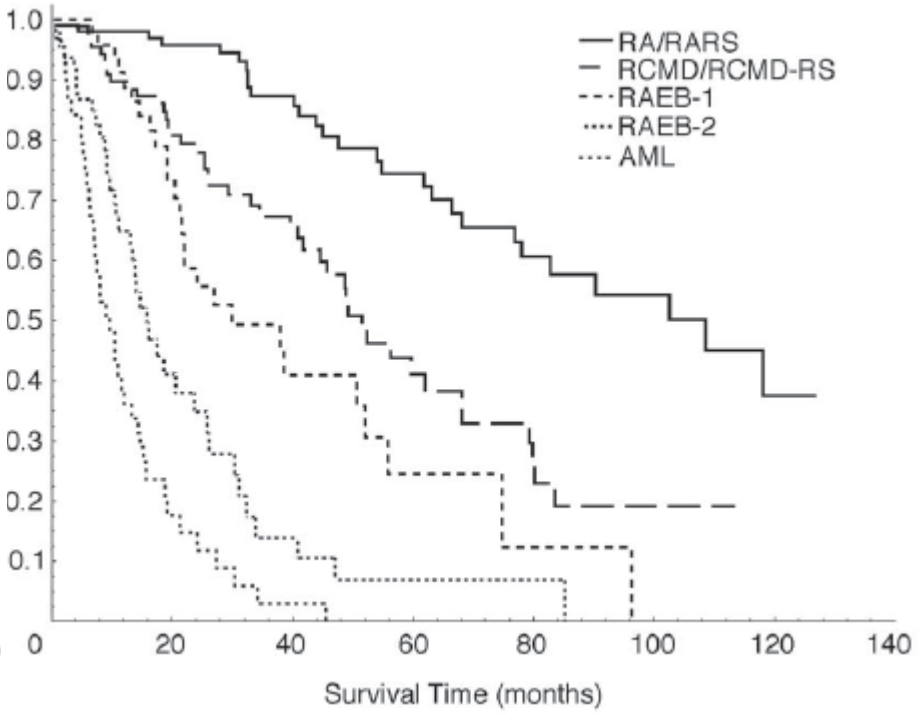
FAB Classification (1982)	WHO Classification (2008)
Refractory anemia (RA)	Refractory cytopenia with unilineage dysplasia (RCUD) *(RA; RT; RN)* Refractory cytopenia with multilineage dysplasia (RCMD)
Refractory anemia with ring sideroblasts (RARS)	Refractory anemia with ring sideroblasts (RARS)
Refractory anemia with excess blasts (RAEB)	Refractory anemia with excess blasts (RAEB-1) RAEB-2
Refractory anemia with excess blasts (RAEB-T)* Chronic myelomonocytic leukemia (CMML)*	MDS-unclassifiable (MDS-U) MDS with isolated del(5q)

WHO Classification: Survival & AML Evolution

Leukemia-Free Survival



Overall Survival



Malcovati et al. J Clin Oncol 2005

International Prognostic Scoring System (IPSS) Risk Classification

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

* Good, normal, −Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

Greenberg et al. Blood 1997

Survival & Risk of AML Evolution by IPSS Score

	IPSS Risk Group			
	Low	**Int-1**	**Int-2**	**High**
Score	0	0.5–1.0	1.5–2.0	≥ 2.5
Lifetime AML Evolution	19%	30%	33%	45%
Median Years to AML †	9.4	3.3	1.1	0.2
Median Survival (years)	5.7	3.5	1.2	0.4

† Time to 25% of patients evolving to AML

Greenberg et al. Blood 1997

Causes of Death in MDS by IPSS Risk Group

IPSS Risk Group	No. (%)	Died (%)	Died with Leukemia (%)	Died without Leukemia (%)
Low	235 (31)	113 (48)	22 (19)	91 (81)
Int-1	295 (39)	181 (61)	55 (30)	126 (70)
Int-2	171 (22)	147 (86)	49 (33)	98 (67)
High	58 (8)	51 (88)	23 (45)	28 (55)
Total	**759**	**492 (65)**	**149 (30)**	**343 (70)**

Greenberg et al. Blood 1997

IPSS-R Classification

Prognostic Variable	Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetics*	V good	-	Good		Int	Poor	V poor
BM blasts (%)	≤2%	-	>2–<5%		5–10%	>10%	-
Hb level (g/dL)	≥10	-	8-<10	<8	-	-	-
ANC ($x10^9$/L)	≥0.8	≤0.8	-		-	-	-
Platelets ($x10^9$/L)	≥100	50-<100	<50		-	-	-

* Schanz et al. J Clin Oncol 2012

Scores for risk groups are as follows: Very Low, ≤1.5; Low, >1.5-3; Intermediate, >3-4.5; High, >4.5-6; and Very High, >6

Greenberg et al. Blood 2012

Survival & Risk of AML Evolution by IPSS-R Score

	IPSS-R Risk Group				
	Very Low	**Low**	**Intermediate**	**High**	**Very High**
Score	≤1.5	>1.5-3	>3-4.5	>4.5-6	>6
Median Years to AML †	NR	10.8	3.2	1.4	0.7
Median Survival (years)	8.8	5.3	3.0	1.7	0.7

† Time to 25% of patients evolving to AML

Greenberg et al. Blood 2012

Goals of Therapy in MDS

- Based on age, functional status, other medical conditions, and IPSS risk group

- Decrease disease-related complications (improve blood counts)
- Improve quality of life
- Change the natural history of disease (increase survival; delay leukemic transformation; potential for cure)

Cheson et al. Blood 2000

Cheson et al. Blood 2006

Erythropoietin Stimulating Agents (ESAs)

Decision Model: EPO +/- G-CSF

Variable	Value	Score	Value	Score
Transfusion need*	< 2 U/month	0	≥ 2 U/month	1
Serum-Epo*	< 500 U/liter	0	≥ 500 U/liter	1

* Pre-treatment evaluation

Predicted response rate: Total score 0 = 74%, 1 = 23%, 2 = 7%

Predicted value of model $P < 0.001$ [14]

Patients with score 2 do not benefit from treatment with Epo + G-CSF

	Response
EPO ± G-CSF	35-40%

Hellstrom-Lindberg et al. Hematology 2005

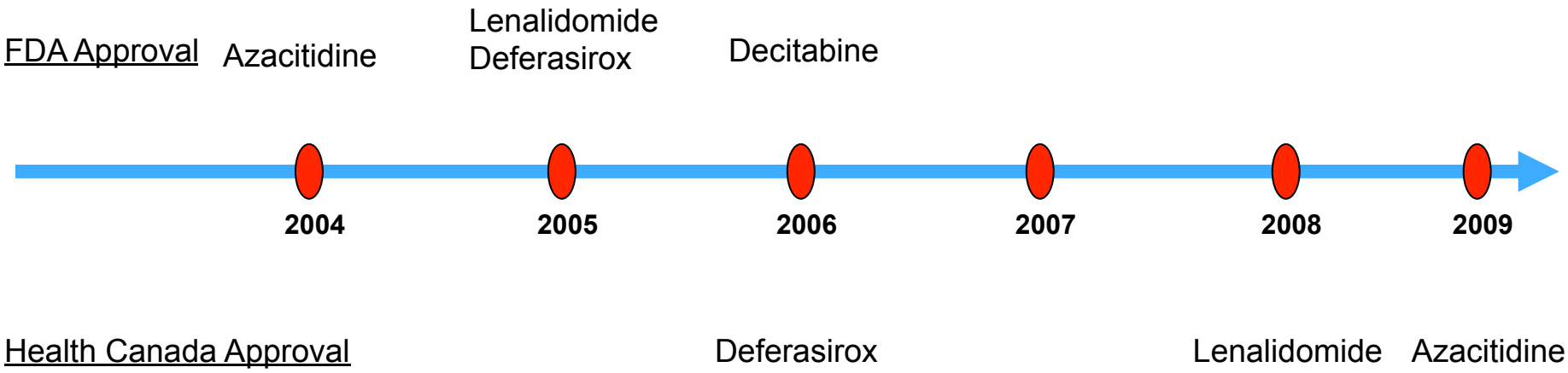
Effect of EPO on Disease Progression & Overall Survival in Lower-Risk MDS

Reference, y	Progression to AML	OS
Jädersten (GFM) 2008	No difference	OS_{5y} 40% *v* 20%[a]
Park (Nordic/Pavia) 2008	No difference*	OS_{5y} 64% *v* 39%[b]
Greenberg 2009	No difference	No difference[c]

[a] *P* = 0.002; [b] *P* < 0.001; [c] Improved OS in erythroid responders *v* nonresponders (median, 5.5y *v* 2.3y; *P* = 0.004)

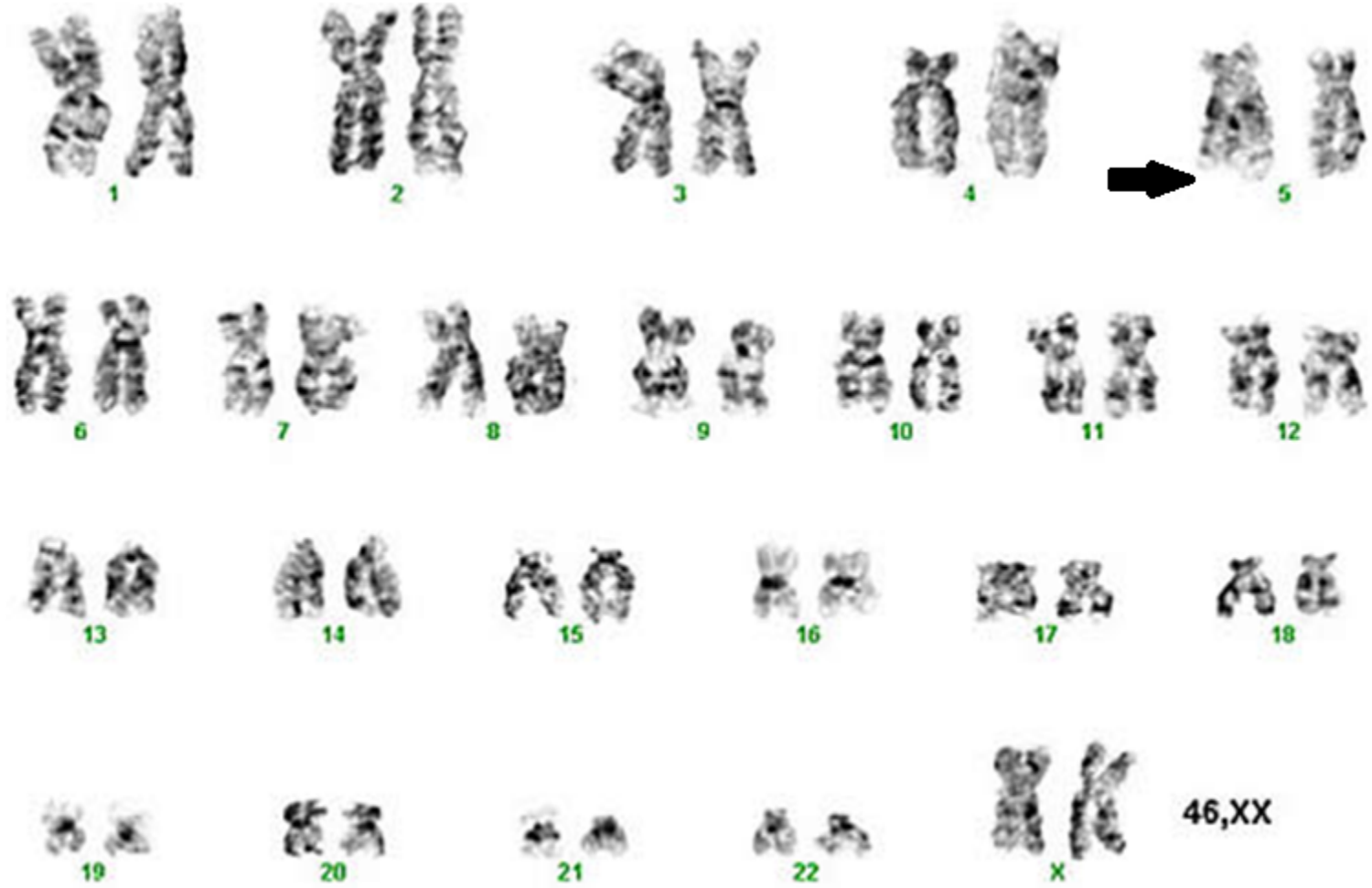
Jädersten et al. J Clin Oncol 2008; Park et al. Blood 2008; Greenberg et al. Blood 2009

New Drug Approval Timelines



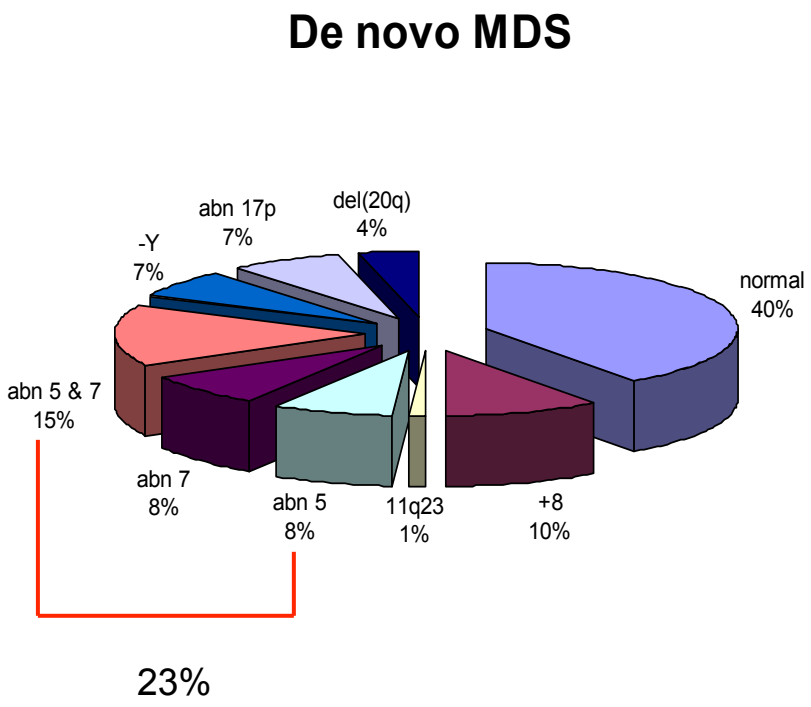
Lenalidomide in patients with lower-risk MDS & del(5q) abnormalities

Cytogenetics --



Cytogenetic analysis reveals loss of a portion of the long arm of chromosome 5.

Chromosomal Abnormalities



List et al. Hematology 2004

MDS-003:
Phase II Lenalidomide in del(5q) MDS

	Lenalidomide (n=148)
Transfusion-Independence	99 (67%)
Complete Remission	38 (36%)

Median time to response 4.6 wks; Median max. Hgb 134 g/L

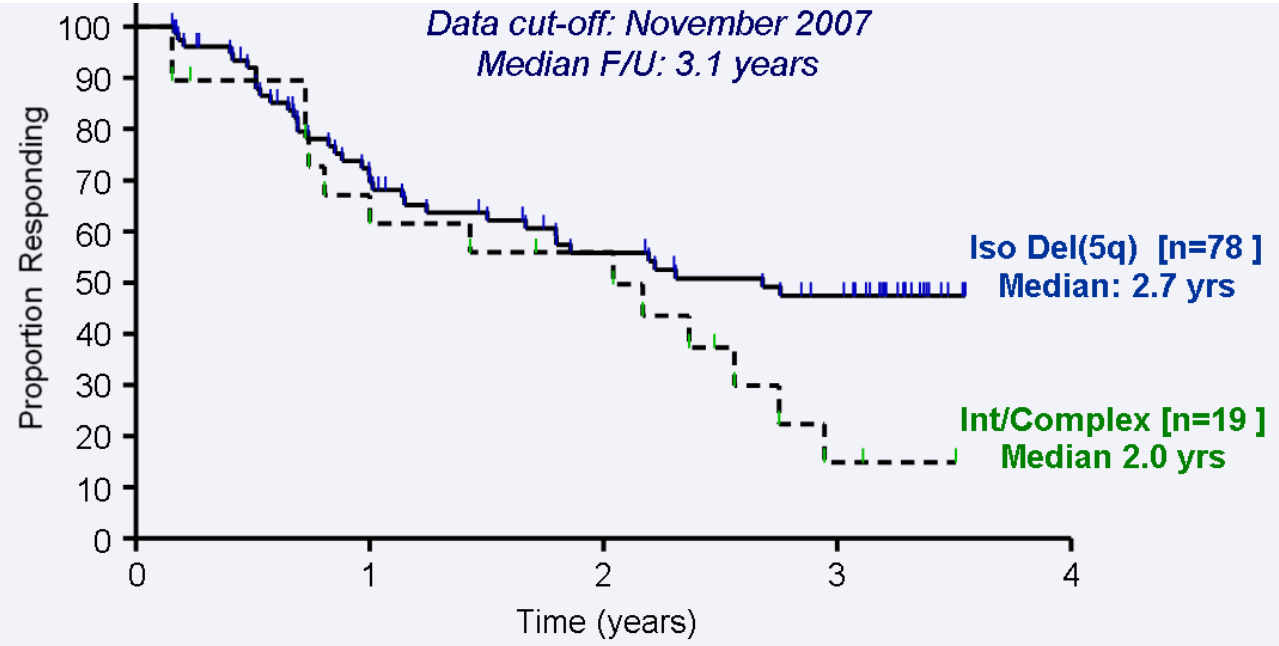
Median F/U >26 mos; Median response duration is not reached (> 104 wks)

Response adversely affected by baseline ↓plt & > 4U PRBCs/8 wks; Cytogenetic response correlated with transfusion-independence

List et al. N Engl J Med 2006

Duration of Major Erythroid Response

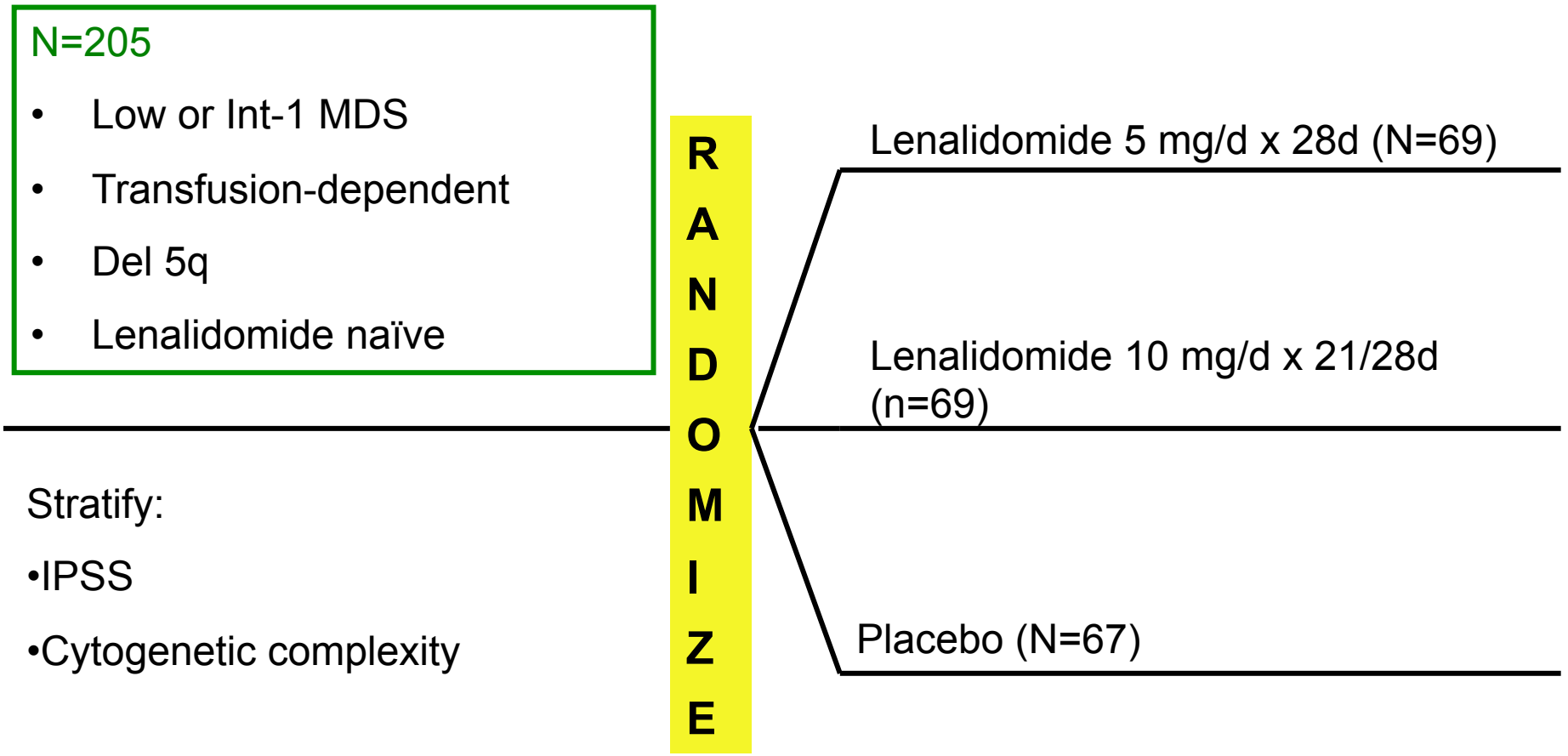
Isolated del(5q) *v* Int/Complex [N=97]



§Symbols are censored patients who remain TI at time of data cut-off or at time of study discontinuation.

List et al. EHA 2008

MDS-004: Phase III Lenalidomide in del(5q) MDS



Responders (after 16 wks of treatment) continued treatment until erythroid relapse or disease progression; Crossover permitted for nonrepsonders (after 16 wks of treatment) on placebo and lenalidomide 5 mg/d arms

Fenaux et al. ASH 2009

MDS-004: Response & Tolerance

	Placebo (N=51)	LEN 5 mg (N=46)	LEN 10 mg (N=41)
RBC Transfusion Independence (TI ≥ 26 wks)	3 (6%)	19 (41%)*	23 (56%)*
Hematologic AEs ≥ grade 3			
Neutropenia	15%	74%	75%
Thrombocytopenia	2%	33%	41%
Dose Reduction	0	52%	58%
Discontinuation due to AEs	5%	16%	9%

* *P* < 0.001 *v* placebo; *** *P* = 0.01 *v* placebo

Fenaux et al. ASH 2009

Long-Term Outcomes

- Median F/U 36 mos
- 22% (31/138) patients progressed to AML (median time to progression not reached)
- 48% (66/138) patients have died
  - Median OS 3.68 y
  - OS_{3y} 56%
- Achievement of RBC-TI for $\geq$ 26 weeks with lenalidomide was associated with ↓ risk of AML progression & death (*P* =0.021)

Fenaux et al. ASH 2010

Predictors of Response to Lenalidomide in del(5q) MDS Patients

	MDS-003 Study	
Variable	**Odds Ratio**	***P***
Decline in platelets (≥ 50% *v* < 50%)	4.68	0.008
Decline in ANC (≥ 75% *v* < 75%)†	4.56	0.056

† In patients with normal baseline ANC; ANC – absolute neutrophil count

Sekeres et al. J Clin Oncol 2008

MDS-002:
Phase II Lenalidomide in nondel(5q) MDS

	Lenalidomide (n=214)
Transfusion-Independence	56 (26%)
Complete Remission (n=105)	1 (1%)

*as defined by IWG criteria 2000

Median time to beginning of transfusion-independence 4.8 wks (range, 1-39 wks); Median max Hgb 116 g/L

Median F/U 19 mos (n=56 transfusion-independent responders);

Median response duration 10.2 mos [20 (36%) pts had response duration > 1 y]

Of the 56 patients who achieved TI: 45 (80%) good karyotype; 10 (18%) intermediate; 0 poor

Raza et al. Blood 2007

Comparison of Responses to Lenalidomide: del(5q) *vs* nondel(5q) MDS

	MDS-003: Del(5q) MDS (n=148)	**MDS-002: Nondel(5q) MDS** (n=214)
Transfusion Response	112 (76%)	93 (43%) ←
Transfusion-Independence (TI)	99 (67%)	56 (26%) ←
> 50% reduction in transfusion	13 (9%)	37 (17%)
Median time to response	4.6 wks	4.8 wks ←
Median response duration (TI)	26 mos	10.2 mos
Grade 3/4 neutropenia	81 (55%)	54 (25%)
Grade 3/4 thrombocytopenia	65 (44%)	43 (20%)

MDS-005: Phase III Lenalidomide in nondel(5q) MDS

N=375 (2:1 randomization in favor of lenalidomide)

- Low/Int-1 risk
- Non-del(5q)
- Not responsive to ESAs *or* EPO > 500 U/L
- RBC transfusion dependent

RANDOMIZE

Lenalidomide 10 mg daily

Placebo

Primary Outcomes:

- Proportion of subjects that become transfusion independent
- Proportion of subjects with an erythroid differentiation gene expression signature that become transfusion independent

Recommendations for Lenalidomide

- Low/Int-1 risk red cell transfusion-dependent *de novo* MDS with interstitial deletion involving 5q31
- Recent data suggest administering lenalidomide 10 mg as a starting dose, with dose reductions or discontinuations if needed
- Role in Low/Int-1 risk red cell transfusion-dependent *de novo* MDS without interstitial deletion involving 5q31 is currently being evaluated

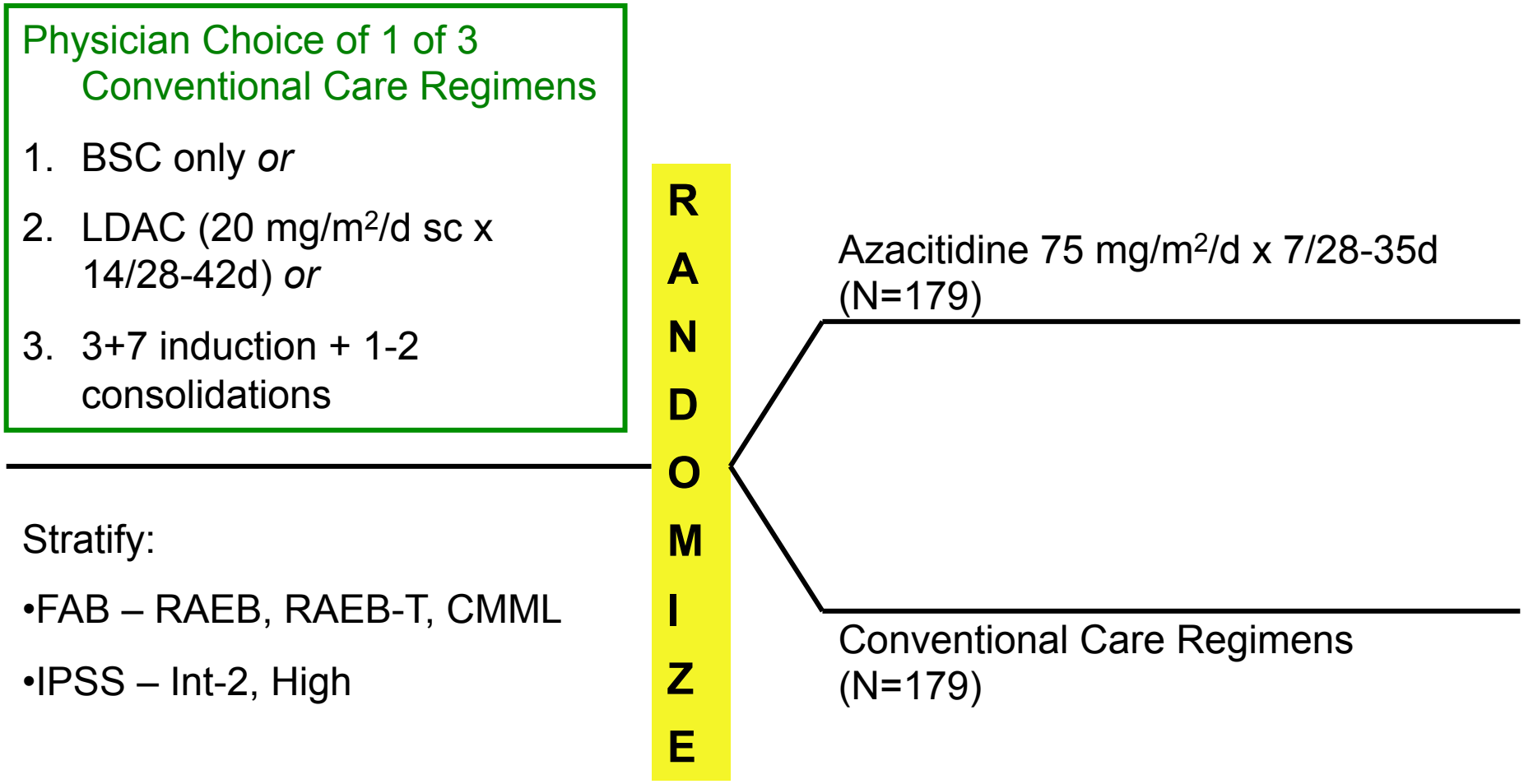
The role of hypomethylating agents in patients with MDS

Hypomethylating Agents:

(a) Azacitidine

(b) Decitabine

AZA-001: Phase III Azacitidine in Higher-risk MDS



Treatment continued until unacceptable toxicity or AML transformation or disease progression

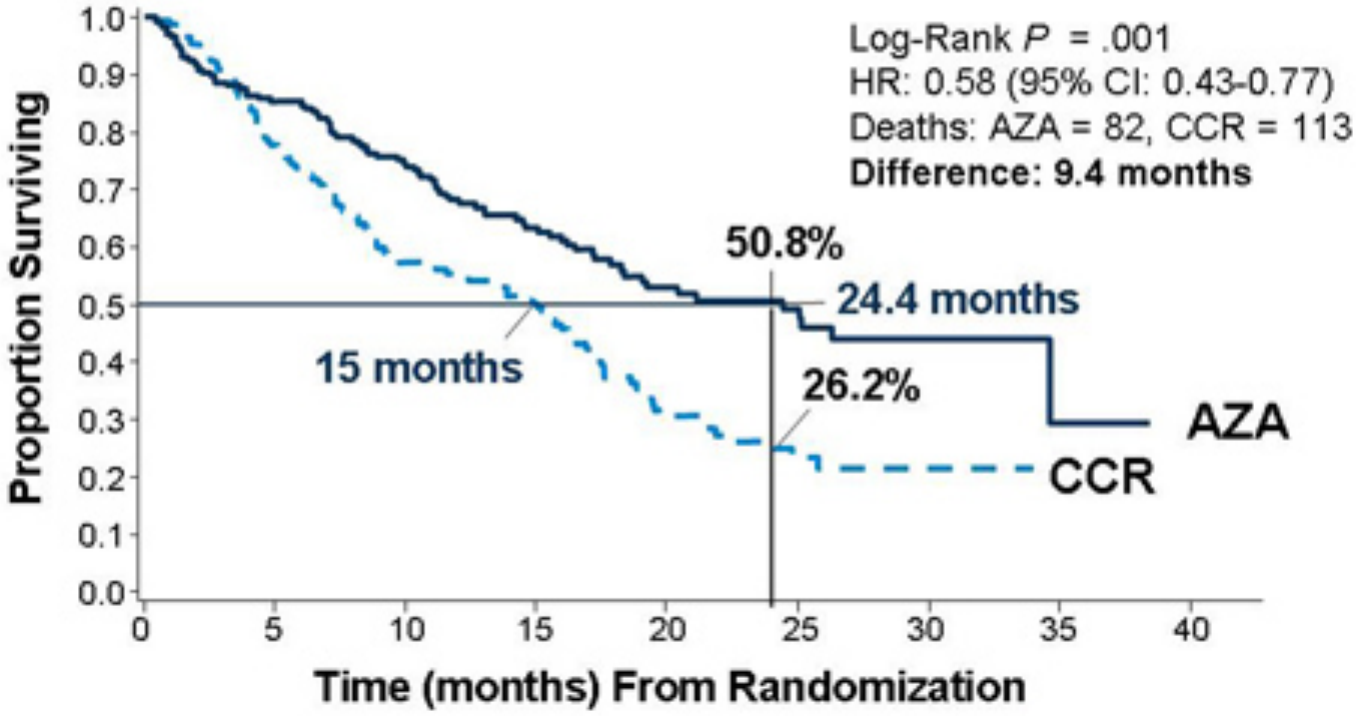
Fenaux et al. Lancet Oncol 2009

AZA-001: Response Rates

	Azacitidine (n=179)	CCR (n=179)
Overall Response (CR+PR, %)	**29**	**12**
CR	17	8
PR	12	4

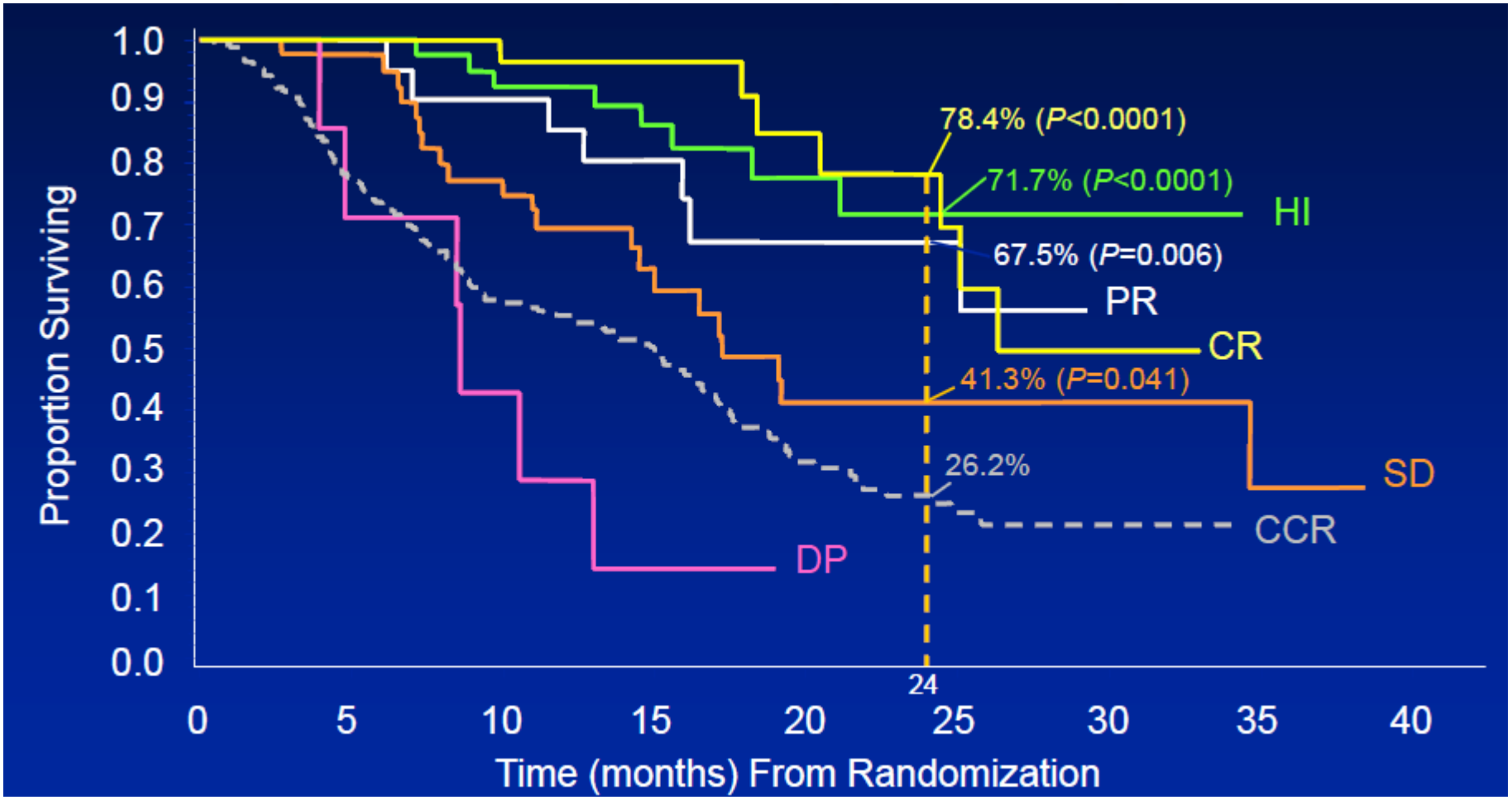
Azacitidine was administered for a median of 9 cycles; 81% achieved a first response by 6 cycles & 90% achieved a first response by 9 cycles

Overall Survival: Azacitidine vs CCR
ITT Population



Number at Risk								
AZA	179	152	130	85	52	30	10	1
CCR	179	132	95	69	32	14	5	0

Overall Survival with Azacitidine by Best Response (IWG 2000)

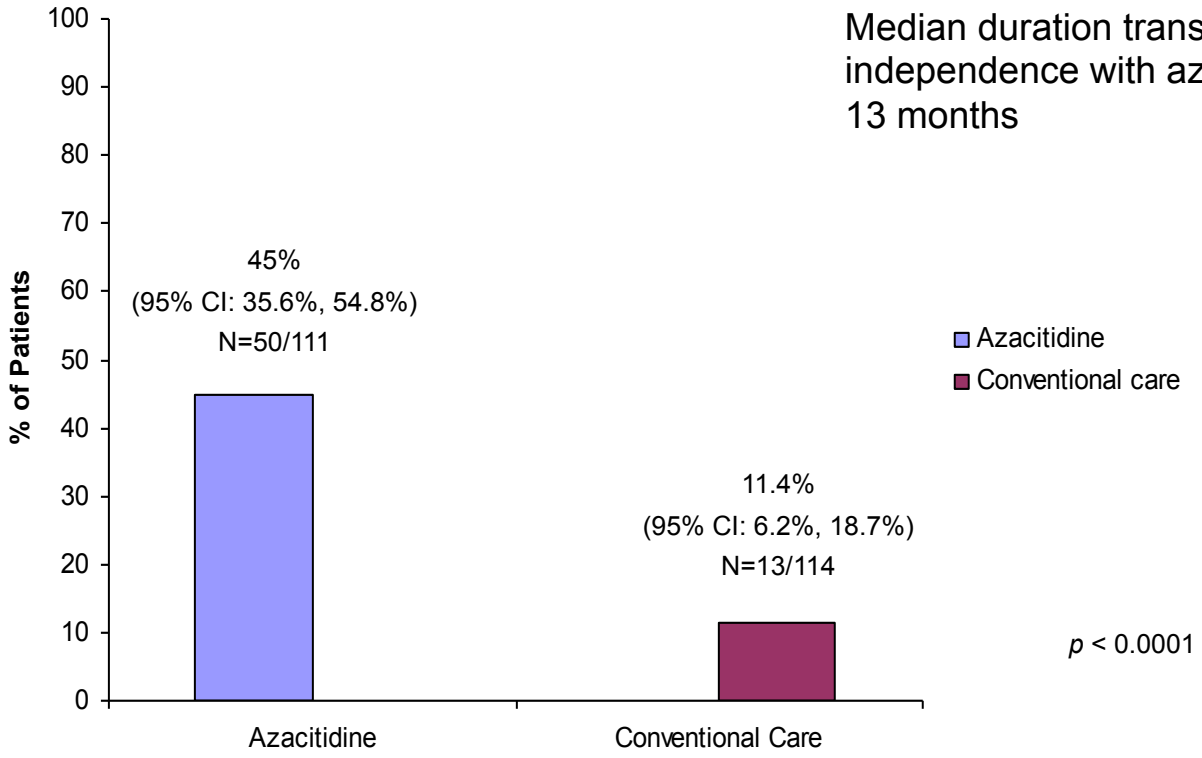


List et al. J Clin Oncol 2008

Azacitidine Prolongs Time to Development of AML or Death

	Azacitidine (n=179)	**CCR (n=179)**	***P* value**
Time to AML or Death (mos)	13	7.6	0.003
Time to AML (mos)	26.1	12.4	0.004

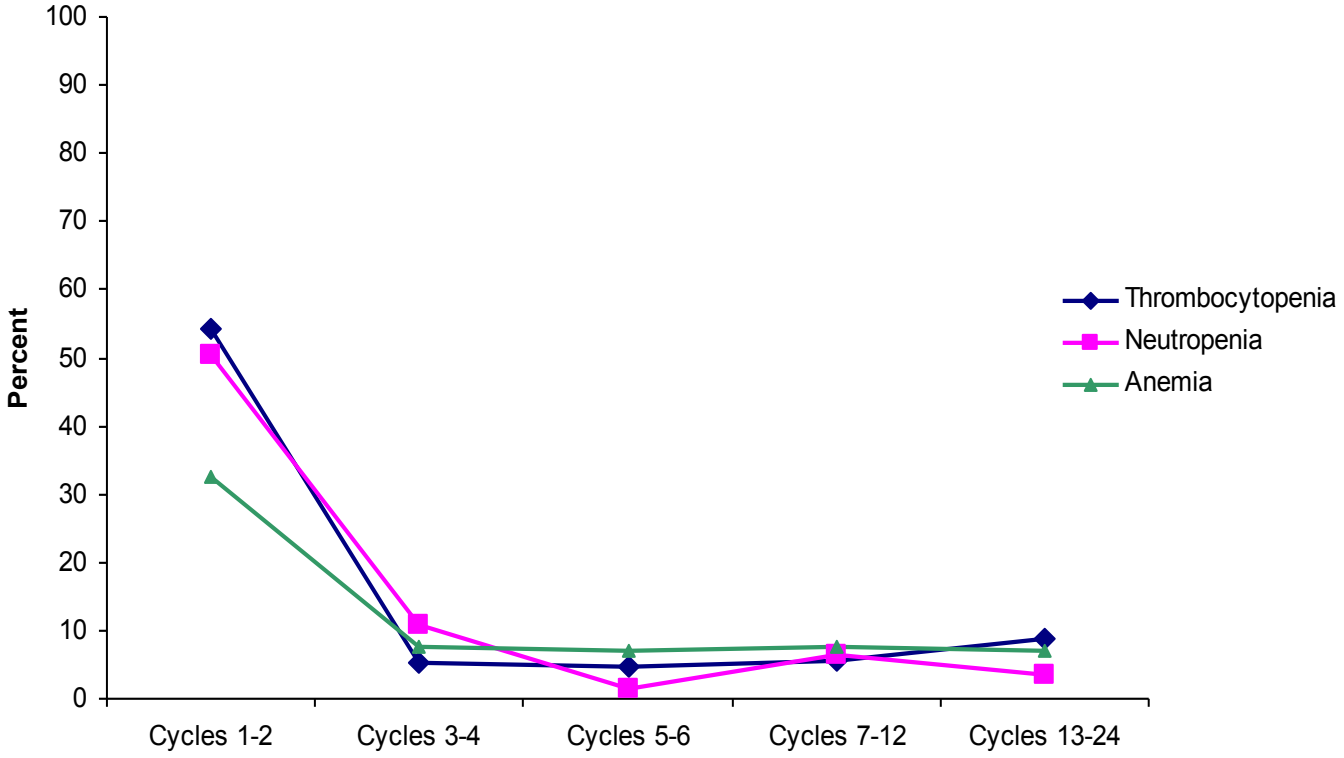
Azacitidine & Red Blood Cell Transfusion Independence



Azacitidine: Side Effects

- Cytopenias – low neutrophil counts, low platelets, & anemia
- Nausea & vomiting
- Injection site reactions
- Constipation (?due to anti-nausea medication)

Azacitidine: Incidence of Cytopenias



	Cycles 1-2	Cycles 3-4	Cycles 5-6	Cycles 7-12	Cycles 13-24
Thrombocytopenia	54.3%	5.4%	4.6%	5.6%	8.9%
Neutropenia	50.3%	10.9%	1.5%	6.5%	3.6%
Anemia	32.6%	7.5%	6.9%	7.5%	7.1%

32% lower annual risk of infections requiring IV antimicrobials compared to CCR

(p = 0.0032)

Scoring System Predicting Survival (with Azacitidine)

	Score Value		
	0	**1**	**2**
ECOG status	0/1	≥ 2	-
Presence of circulating blasts	N	Y	-
RBC transfusion dependency (Units/8 wks)	0-3	≥ 4	-
IPSS cytogenetic risk*	Good	Intermediate	Poor

Scores for risk groups are as follows: Low (0), Intermediate (1-3), and High (4-5)

* Good (normal, -Y, del(5q), or del(20q)); Poor (complex (≥ 3 abnormalities) or chr(7) anomalies); Intermediate (other abnormalities)

Itzykson et al. Blood 2010

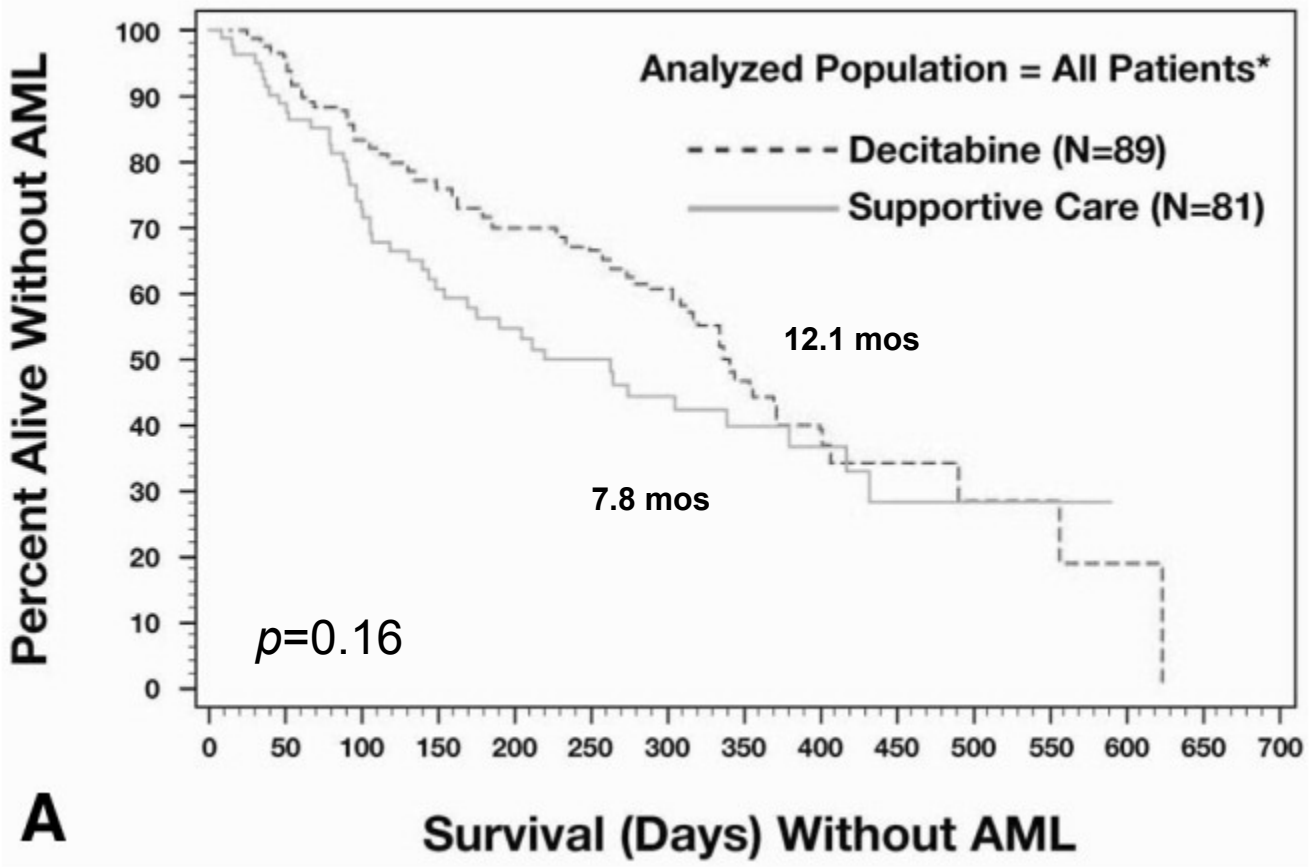
Survival (with Azacitidine) by Risk Group

	Risk Group		
	Low	**Intermediate**	**High**
Score	0	1-3	4-5
Median Survival (months)*	Not reached	15	6.1

* $P < 0.0001$

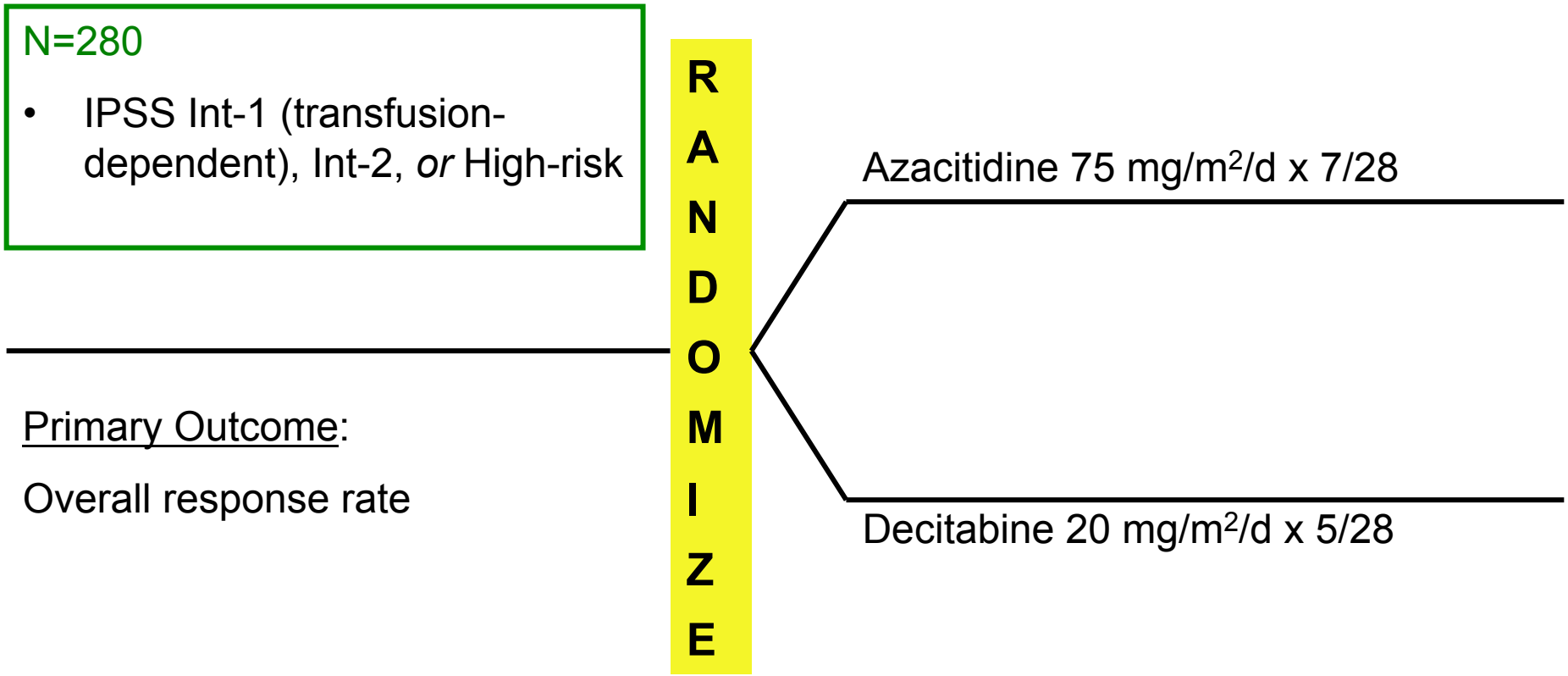
Itzykson et al. Blood 2010

Phase III Decitabine in MDS



Kantarjian et al. Cancer 2006

Phase III Azacitidine *v* Decitabine Higher-risk MDS



Recommendations for Hypomethylating Agents

- Azacitidine in patients with Int-2/High-risk MDS who are not transplant candidates
- Benefit of hypomethylating agents in patients with Low/ Int-1 risk MDS is unclear
- Phase III trial is currently underway to evaluate response rates in patients receiving azacitidine *vs* decitabine. However, not designed to assess differences, if any, in OS
- Role of hypomethylating agents as a bridge to allogeneic stem cell transplant is being evaluated

Phase I/II Azacitidine + Lenalidomide in Higher-risk MDS

	N=36
Overall Response (CR+HI)	**26 (72%)**
Complete Response (CR)	16 (44%)
Hematologic Improvement (HI)	10 (28%)
Median Time to Initial Response (mos)	**3.7 (1.4-7.4)**
Median CR Duration (mos)	**17+ (3-39+)**
Median Overall Survival (mos)	**13.6 (3-55)**

Sekeres et al. Blood 2012

Phase I Azacitidine + Vorinostat in MDS & AML

	N=28 (21 evaluable)
Overall Response (CR+CRi+HI)	**18 (86%)**
Complete Response (CR)	9 (43%)
CR with incomplete platelet recovery (CRi)	2 (10%)
Hematologic Improvement (HI)	7 (33%)
Median Time to Initial Response	**2 cycles**

53%

MDS (n=20); AML (n=8)

Mean no. cycles administered 5 (range 1-17)

Silverman et al. Blood 2008

Phase II Azacitidine +/- Lenalidomide or Vorinostat in Higher-risk MDS or CMML

N=240

- RAEB-1/2 or CMML-1/2
- Int-2 or High MDS (Int-1 if >5% blasts)
- No prior hypomethylating agents, HDAC inhibitors (vorinostat), or lenalidomide

RANDOMIZE

Azacitidine 75 mg/m2/d x 7/28d* + Lenalidomide 10 mg/d x 21/28d (n=80)

Azacitidine 75 mg/m2/d x 7/28d* (n=80)

Azacitidine 75 mg/m2/d x 7/28d* + Vorinostat 300 mg bid D3-9 q28d (n=80)

Primary Outcomes:

- Response rate (CR, PR, HI)
- Overall survival
- Relapse-free survival
- Toxicity
- Association of cytogenetics with outcome

Treatment continued until unacceptable toxicity or disease progression

Phase I Oral Azacitidine in MDS/CMML: Response Rates

	Treatment Schedule				Total (n=15)
	300 mg		200 mg		
	Daily for 14d (n=6)	**Daily for 21d** (n=3)	**Twice daily for 14d** (n=3)	**Twice daily for 21d** (n=3)	
Overall Response (CR + any HI + marrow CR)	**4 (67%)**	**3 (100%)**	**3 (100%)**	**0**	**10 (67%)**
Complete Response (CR)	0	2 (67%)	0	0	**2 (13%)**
Hematologic Improvement (HI)	2/5 (40%)	3 (100%)	1 (33%)	0	6/14 (43%)
Transfusion Independence	3/5 (60%)	2/2 (100%)	2/3 (67%)	0	7/10 (70%)
RBC	1/3 (33%)	1/1 (100%)	1/1 (100%)		3/5 (60%)
Platelets	2/2 (100%)	1/1 (100%)	1/2 (50%)		4/5 (80%)
Marrow CR	0	1/1 (100%)	1/2 (50%)	0	2/4 (50%)

77% Low/Int-1 risk MDS; No prior azacitidine or decitabine

Garcia-Manero et al. Blood 2010

AZA-MDS-003: Phase III Oral Azacitidine in Low-risk MDS

N=386

- Low risk
- RBC transfusion dependent
- Low platelets
- No prior hypomethylating agents or lenalidomide

RANDOMIZE

Azacitidine 300 mg/d x 21/28d

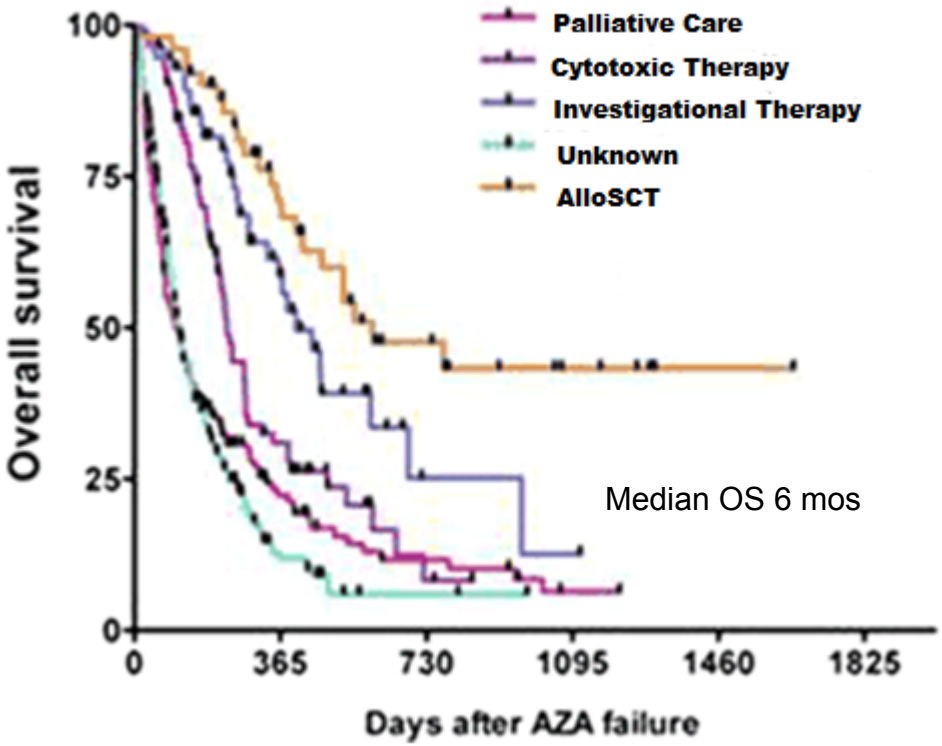
Placebo x 21/28d

Primary Outcome:

- RBC transfusion independence

Treatment options for patients with MDS who fail to respond to, lose response to, or are intolerant of hypomethylating agents

Overall Survival According to Salvage Therapy



Salvage Therapy	N (%)	Response Rate	Median OS (mos)[a]
AlloSCT	50 (9%)	17/25 (68%)	18.3
Investigational Therapy[b]	56 (10%)	4/39 (10%)	13.2
Cytotoxic Chemotherapy[c]	84 (15%)	1/25 (4%) & 5/33 (15%)[d]	7.6
Palliative Care	160 (28%)	N/A	3.3
Unknown	215 (38%)	N/A	3.6

[a] Survival was measured from the date of AZA failure; [b] Epigenetic drugs, immunomodulatory drugs, nonregistered compounds; [c] Induction chemotherapy, low dose chemotherapy (cytarabine, 6-mercaptopurine); [d] Induction chemotherapy

Prebet et al. ASH 2010

Overall Survival: Rigosertib (ON 01910.Na) in MDS

	FAB/WHO Classification (N=60)			
	RCMD (n=9)	**RAEB-1** (n=17)	**RAEB-2** (n-21)	**RAEB-t** (n=13)
Median OS (mos)[a]	24.5	20.5	8.8	5.2

	IPSS Risk Group (N=51 RAEB-1, RAEB-2, RAEB-t)		
	Intermediate-1 (n=10)	**Intermediate-2** (n=14)	**High** (n=27)
Median OS (mos)[b]	Not reached	9.2	7

	Bone Marrow (BM) Blast Response (N=38 RAEB-1, RAEB-2, RAEB-t Refractory to or Relapsing after Azacitidine/Decitabine)			
	≥ 50% Decrease in Blasts (n=13)	**Stable BM Blasts** (n=12)	**Progressive Disease** (n=3)	**Not Assessed** (n=10)
Median OS (mos)[c]	11	12.2	3.8	2.5

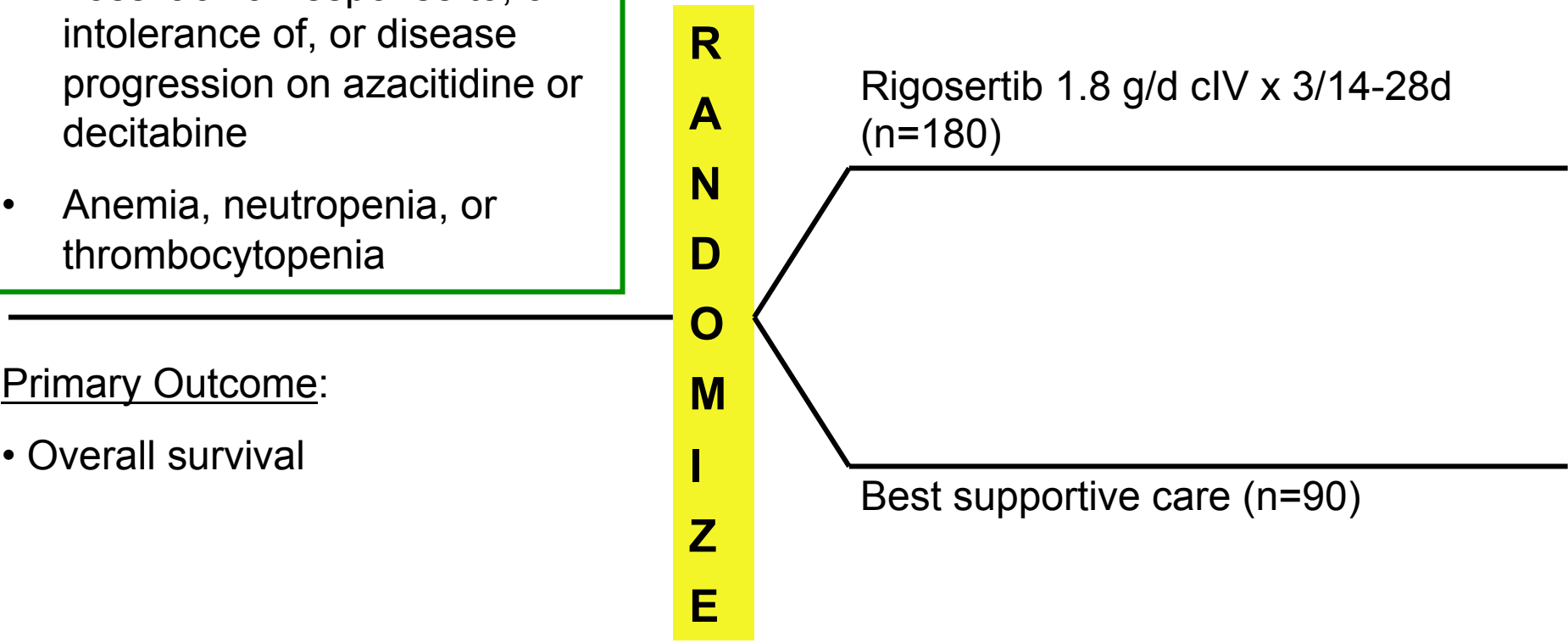
[a] P=0.04; [b] P=0.02; [c] P=0.001

Raza et al. Blood 2011

Phase III Rigosertib (ON 01910.Na) in MDS Patients Failing Hypomethylating Agents

N=270 (2:1 randomization in favor of rigosertib)

- RAEB-1/2, RAEB-t, or CMML
- Loss/lack of response to, or intolerance of, or disease progression on azacitidine or decitabine
- Anemia, neutropenia, or thrombocytopenia



Primary Outcome:

- Overall survival

Closing Comments

- Lenalidomide yields durable erythroid responses [i.e. RBC transfusion independency in patients with del(5q) MDS]
- Currently, azacitidine is the only hypomethylating agent that has shown an improved OS in patients with Int-2/High-risk MDS
- Need to improve outcomes for patients, especially those failing disease modifying treatments