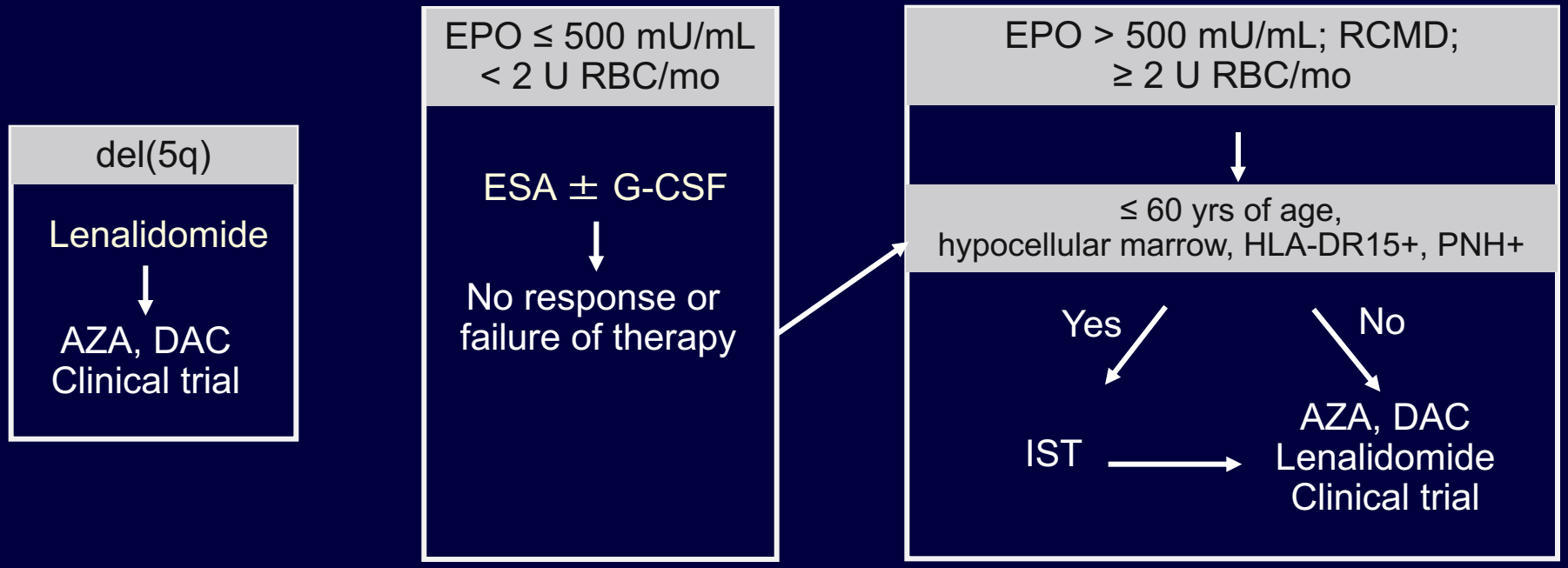
Treatment Options for Lower-Risk MDS

Anemia Management Algorithm 2016: Low- or Intermediate 1–Risk MDS

- Assess potential causes of anemia
- RBC transfusion support for symptomatic patients



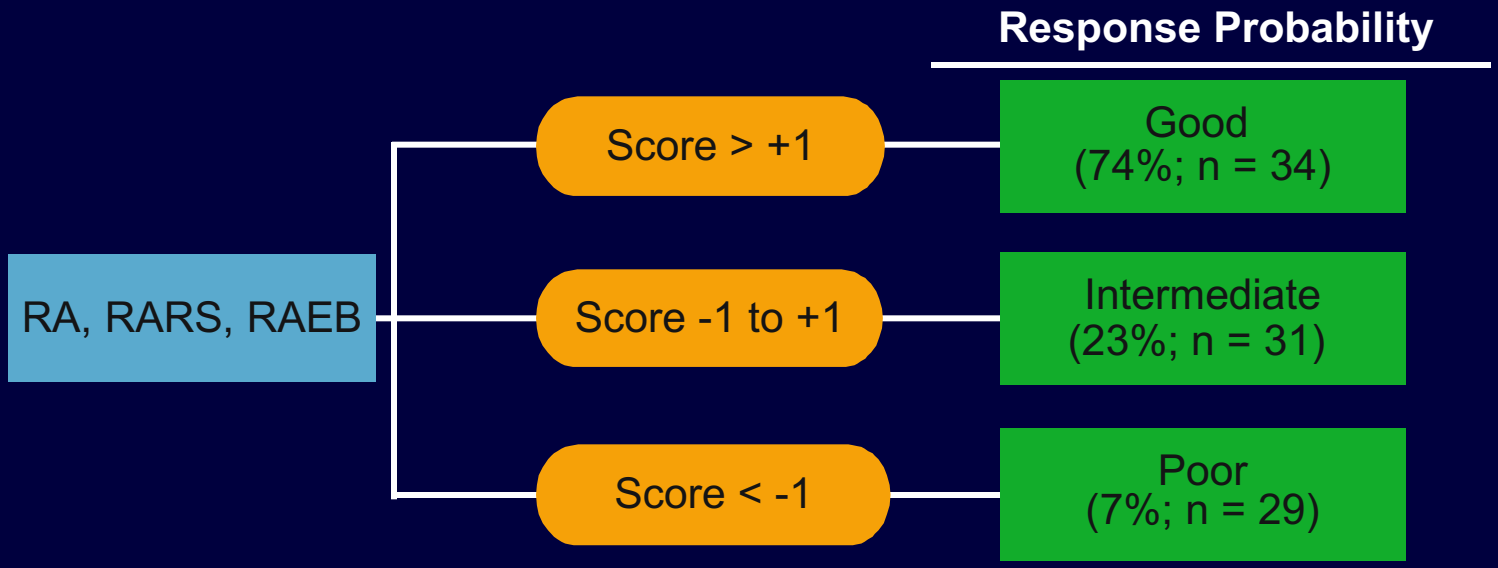
NCCN. Clinical practice guidelines in oncology: myelodysplastic syndromes. V1.2016

Erythropoietin in MDS

- Response rates to erythropoietin much lower in MDS than in other malignancies
  - Mean response rate: 16% to 20%
  - Predictors for good response were serum EPO level < 500 U/L, nonrefractory anemia with ring sideroblasts subtype, and lack of previous need for transfusion
- Response rates may improve when given in combination with G-CSF (> 40%)

Ludwig H. Semin Oncol. 2002;29(3 suppl 8):45-54. Hellström-Lindberg E. Br J Haematol. 1995;89:67-71. Casadevall N, et al. Blood. 2004;104:321-327.

Predictive Model for Response to Treatment With rhuEPO + G-CSF



Treatment Response Criteria

CR	Stable Hb > 11.5 g/dL
PR	Increase in Hb with > 1.5 g/dL or total stop in RBC transfusions

Treatment Response Score

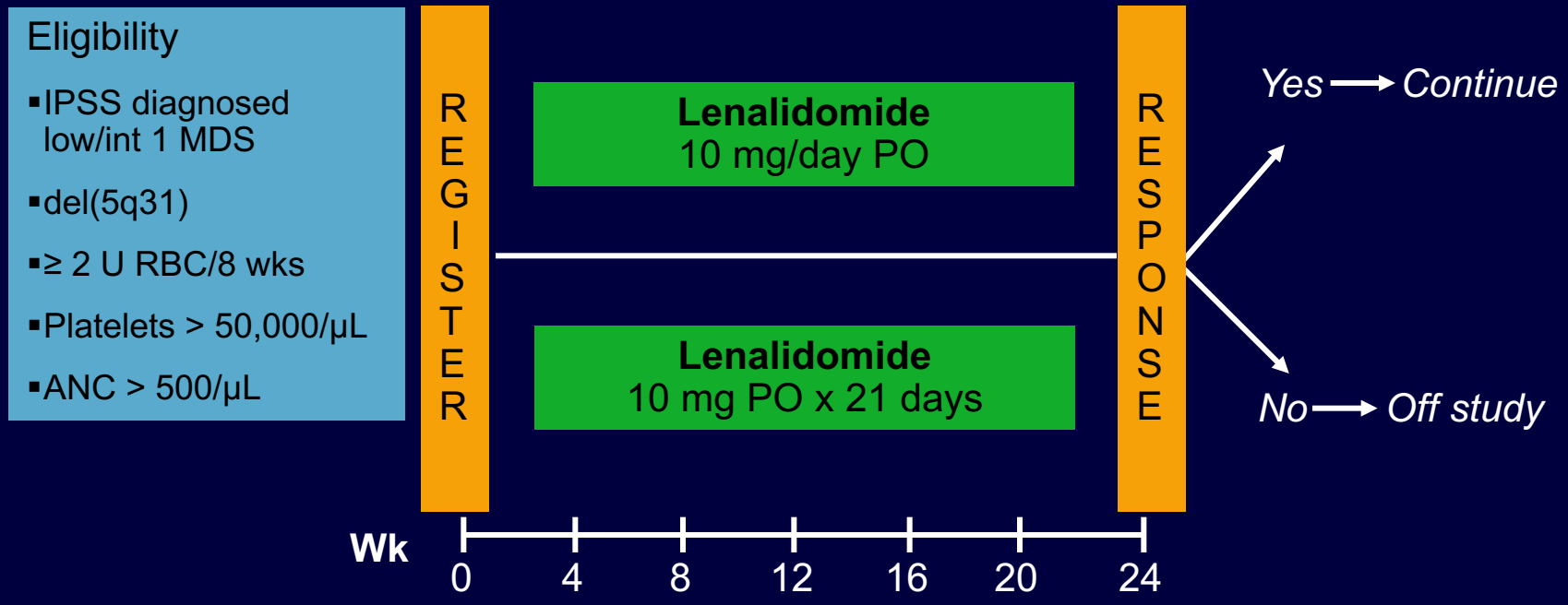
S-EPO U/L	< 100	+2
	100-500	+1
	> 500	-3
Transf U RBC/mos	< 2 units/mo	+2
	≥ 2 units/mo	-2

Hellström-Lindberg E, et al. Br J Hematol. 2003;120:1037-1046.

Lenalidomide

- Thalidomide analogue with immunomodulatory, antiangiogenic, and antineoplastic properties
- Approved for use
  - Transfusion-dependent anemia due to low- or intermediate 1–risk MDS associated with del(5q), with or without additional abnormalities
  - Multiple myeloma in combination with dexamethasone in patients who have received at least 1 previous therapy

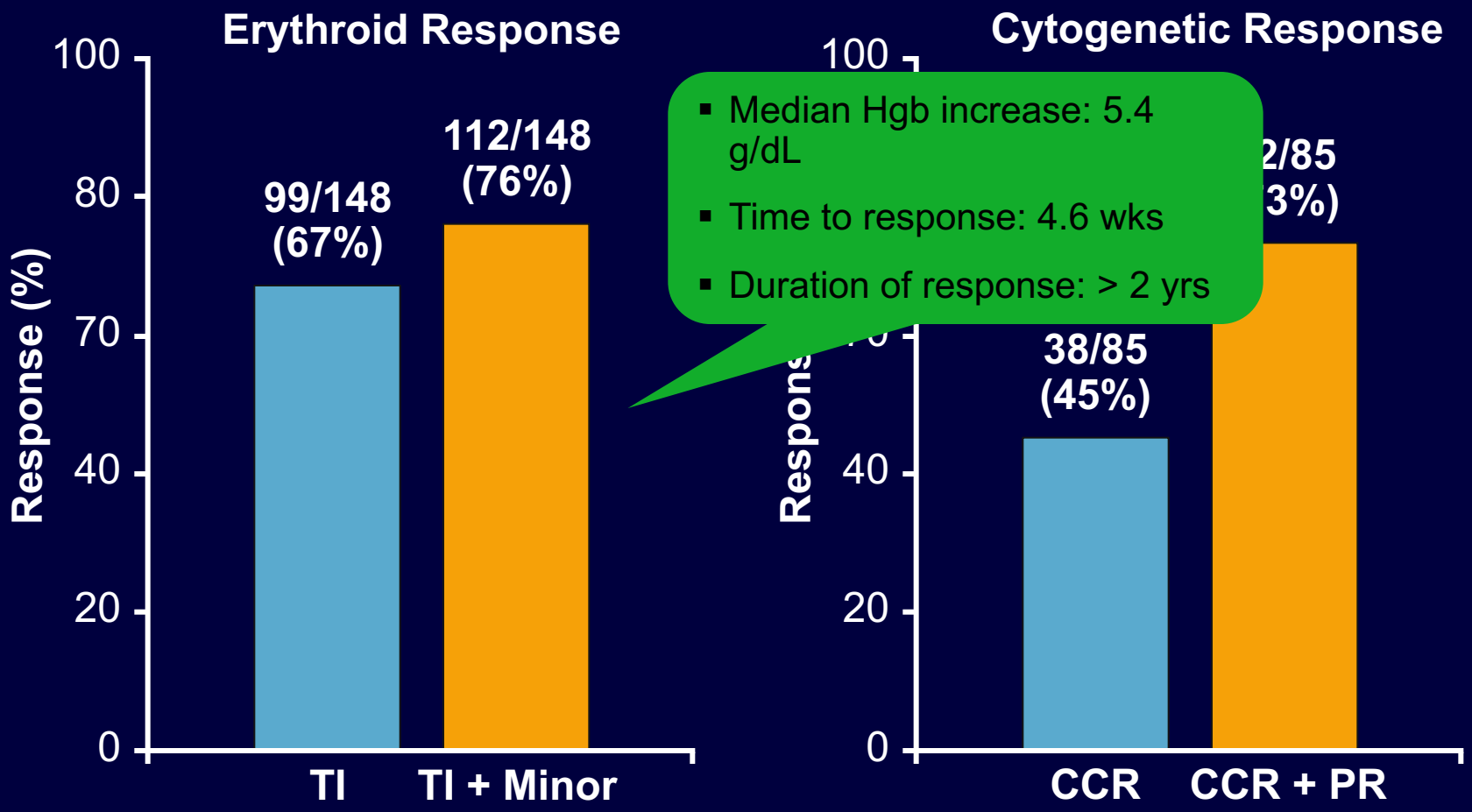
MDS-003: Lenalidomide in MDS With 5q Deletion



- Primary endpoint: transfusion independence
- Secondary endpoints: duration of TI, cytogenetic response, minor erythroid response, pathologic response, safety

List AF, et al. N Engl J Med. 2006;355:1456-1465.

MDS-003: Response to Lenalidomide Therapy

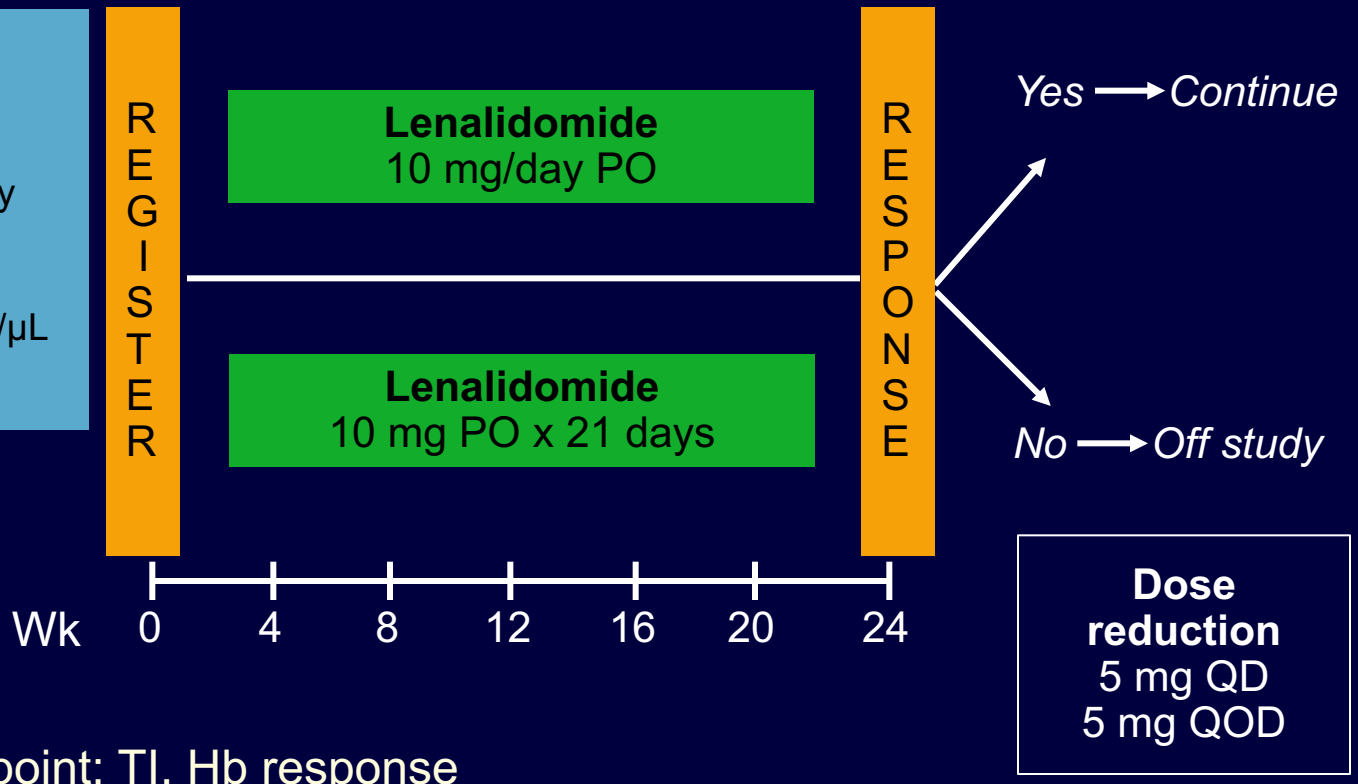


List AF, et al. N Engl J Med. 2006;355:1456-1465.

MDS-002: Phase II Study of Lenalidomide in RBC-Dependent Non-del(5q) MDS

Eligibility

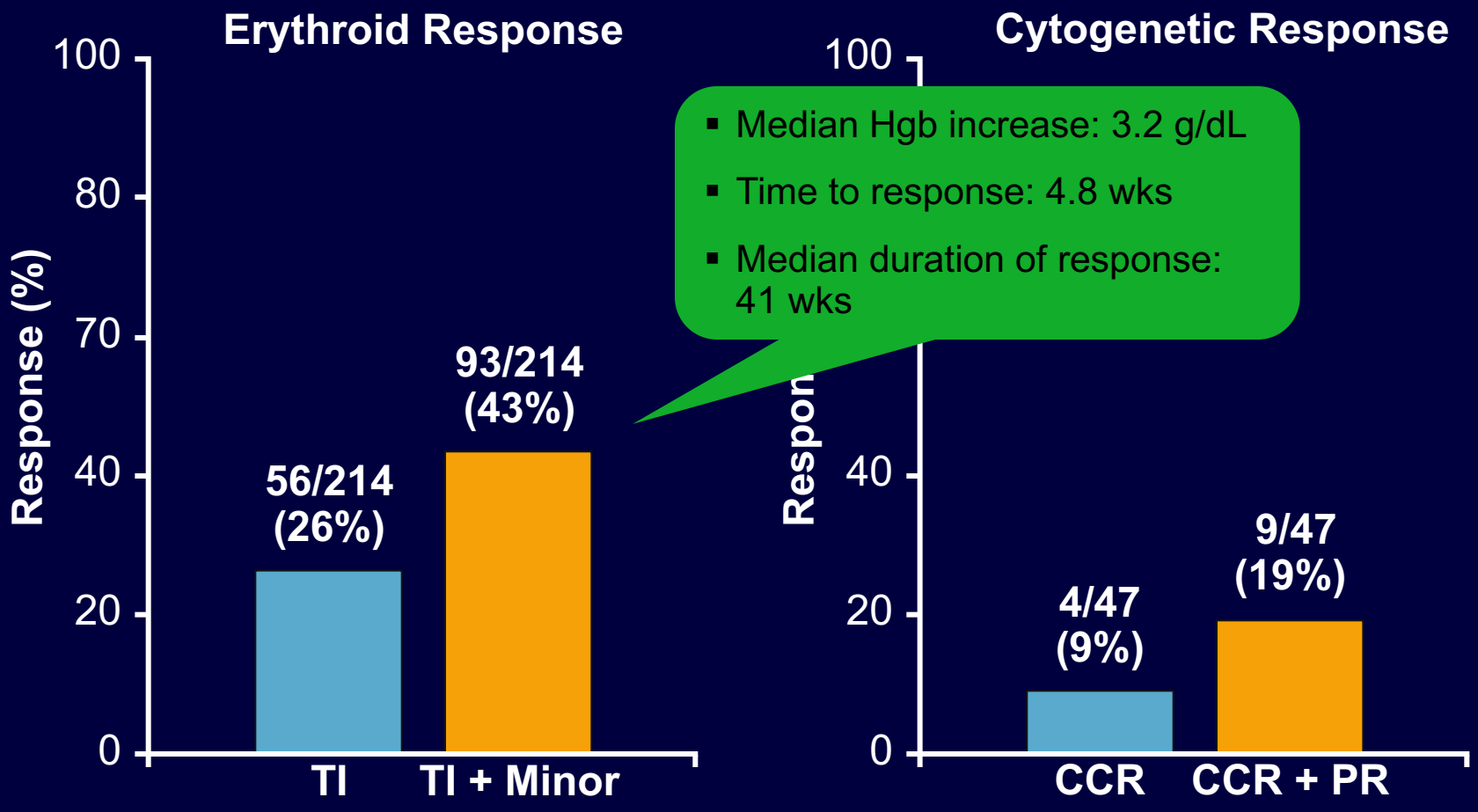
- IPSS diagnosed low/int-1 MDS w/o del(5q) abnormality
- ≥ 2 U RBC/8 wks
- Platelets > 50,000/μL
- ANC > 500/μL



- Primary endpoint: TI, Hb response
- Secondary endpoints: cytogenetic response, safety

Raza A, et al. Blood. 2008;111:86-93.

MDS-002: Response to Lenalidomide Therapy



Raza A, 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.

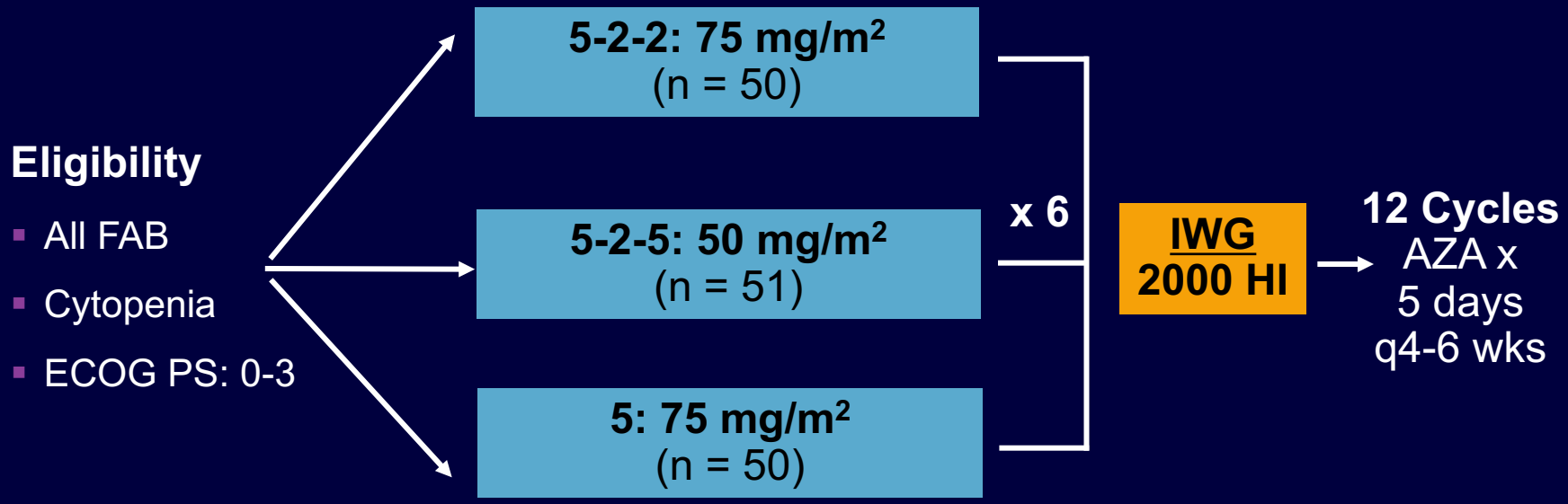
Azacitidine Treatment for Low- or Intermediate 1–Risk MDS

- Pyrimidine nucleoside analogue of cytidine
- Approved for use in MDS of the following subtypes
  - Refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions)
  - Refractory anemia with excess blasts
  - Refractory anemia with excess blasts in transformation
  - Chromic myelomonocytic leukemia
- Causes hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow

Silverman LR, et al. Nat Clin Pract Oncol. 2005;2(suppl 1):S12-S23. Azacitidine [package insert]. 2012.

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)



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

Alternate Azacitidine Dose Schedule Study: Frequency of Major HI

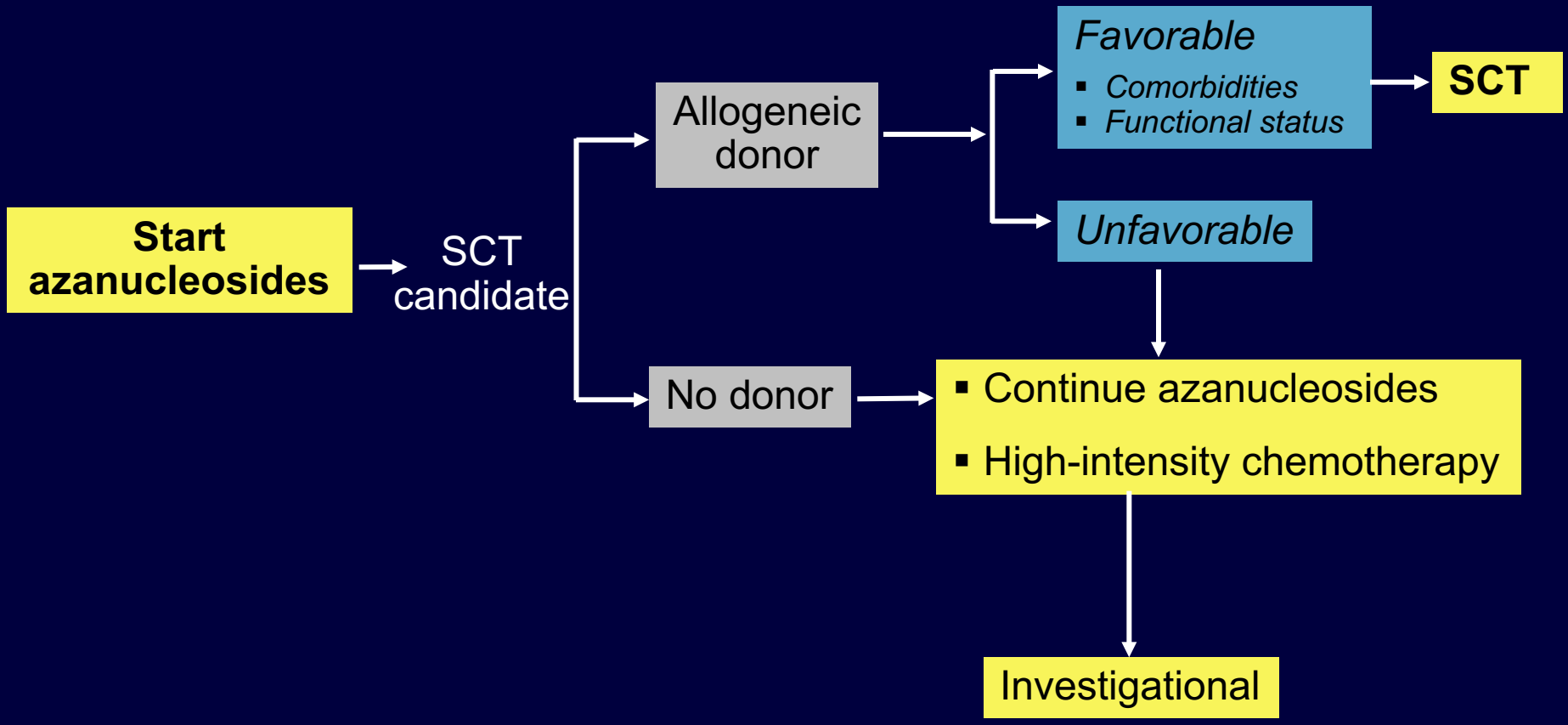
Parameters in Evaluable Pts,* n/N (%)	5-2-2 (n = 50)	5-2-5 (n = 51)	5d (n = 50)
$Erythroid_{Ma}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	**12/24 (50)**	**12/22 (55)**	**15/25 (64)**
$Platelet_{Ma}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
$Neutrophil_{Ma}$	4/23 (17)	4/23 (17)	9/24 (38)
Heme AEs > grade 3	**33/50 (66)**	**24/48 (50)**	**17/50 (34)**
AE Tx delay	**34/50 (68)**	**30/48 (63)**	**17/50 (34)**

*IWG 2000 criteria.

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

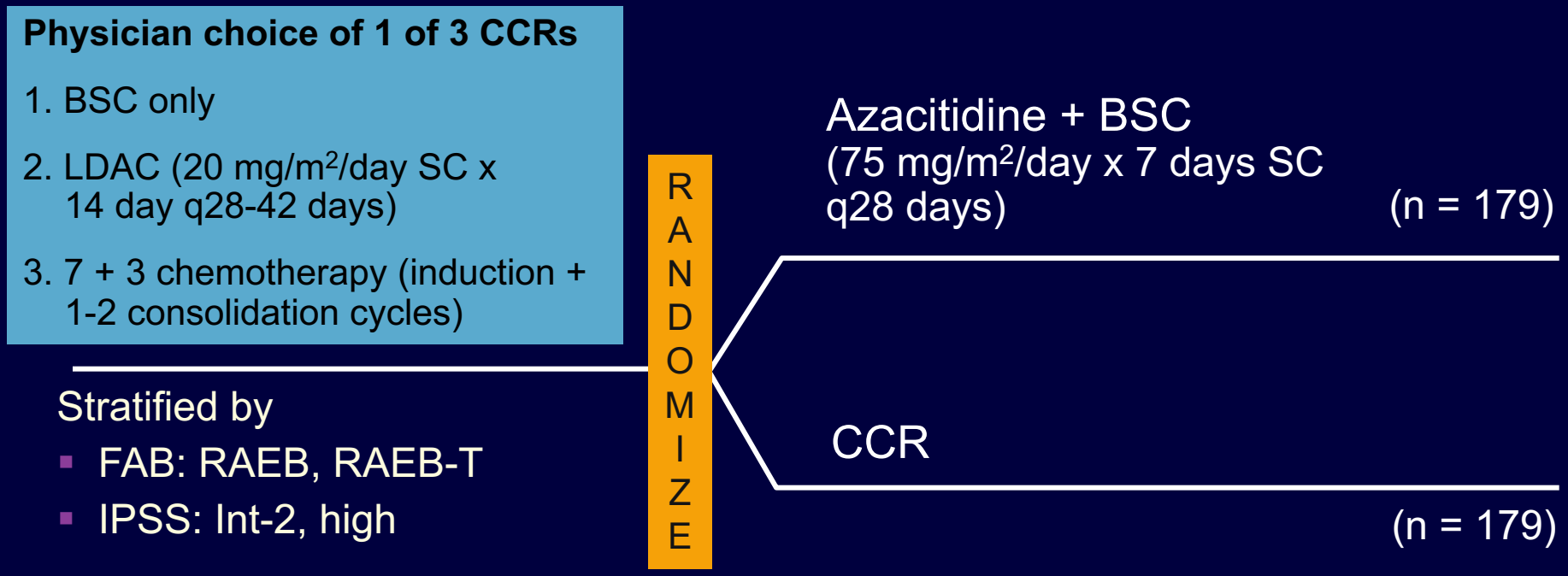
Treatment Options for High-Risk MDS

Treatment Algorithm 2016: Intermediate 2–Risk/High-Risk MDS



Adapted from NCCN. Clinical practice guidelines in oncology. MDS. V.1.2016.

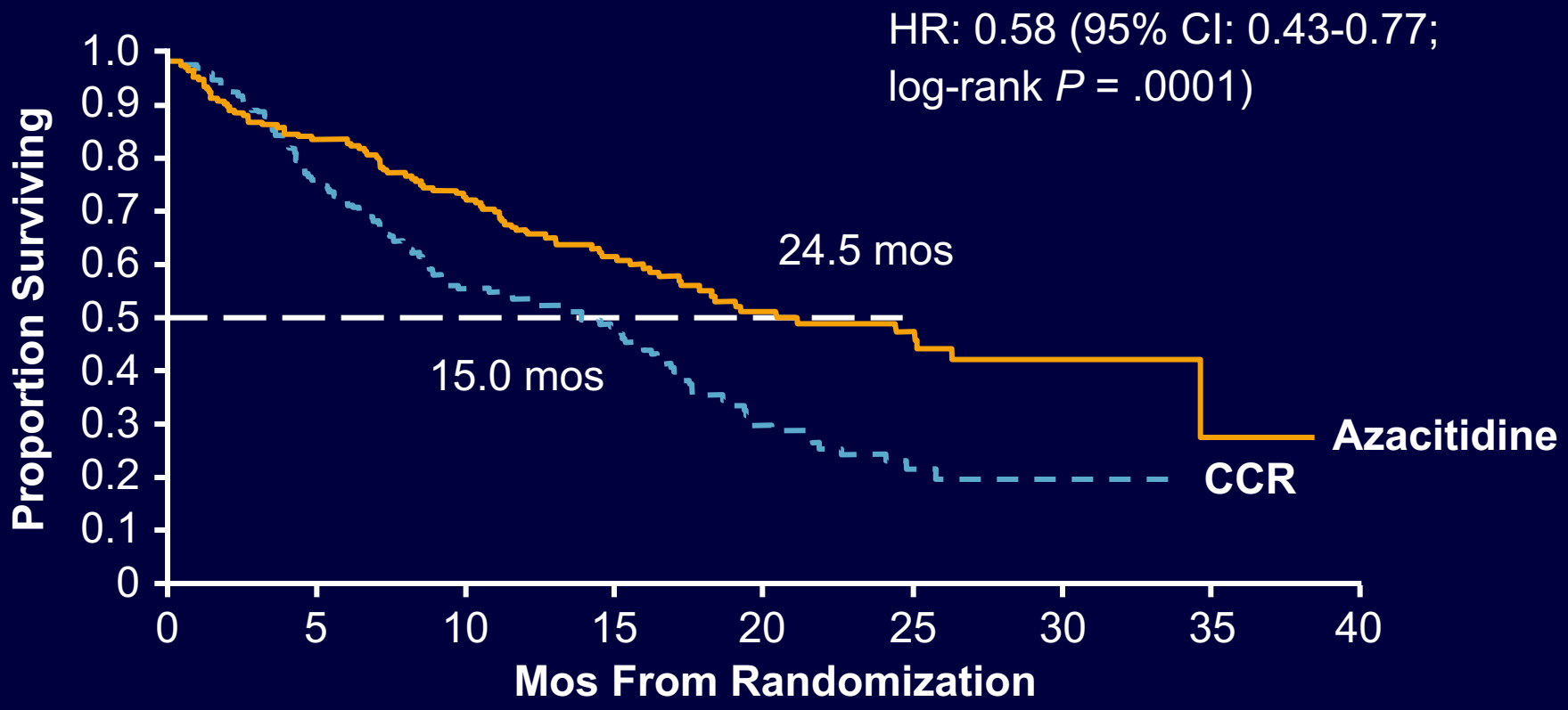
AZA-001: Trial Design



Treatment continued until unacceptable toxicity or AML transformation or disease progression

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

AZA-001 Trial: Azacitidine Significantly Improves OS



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.

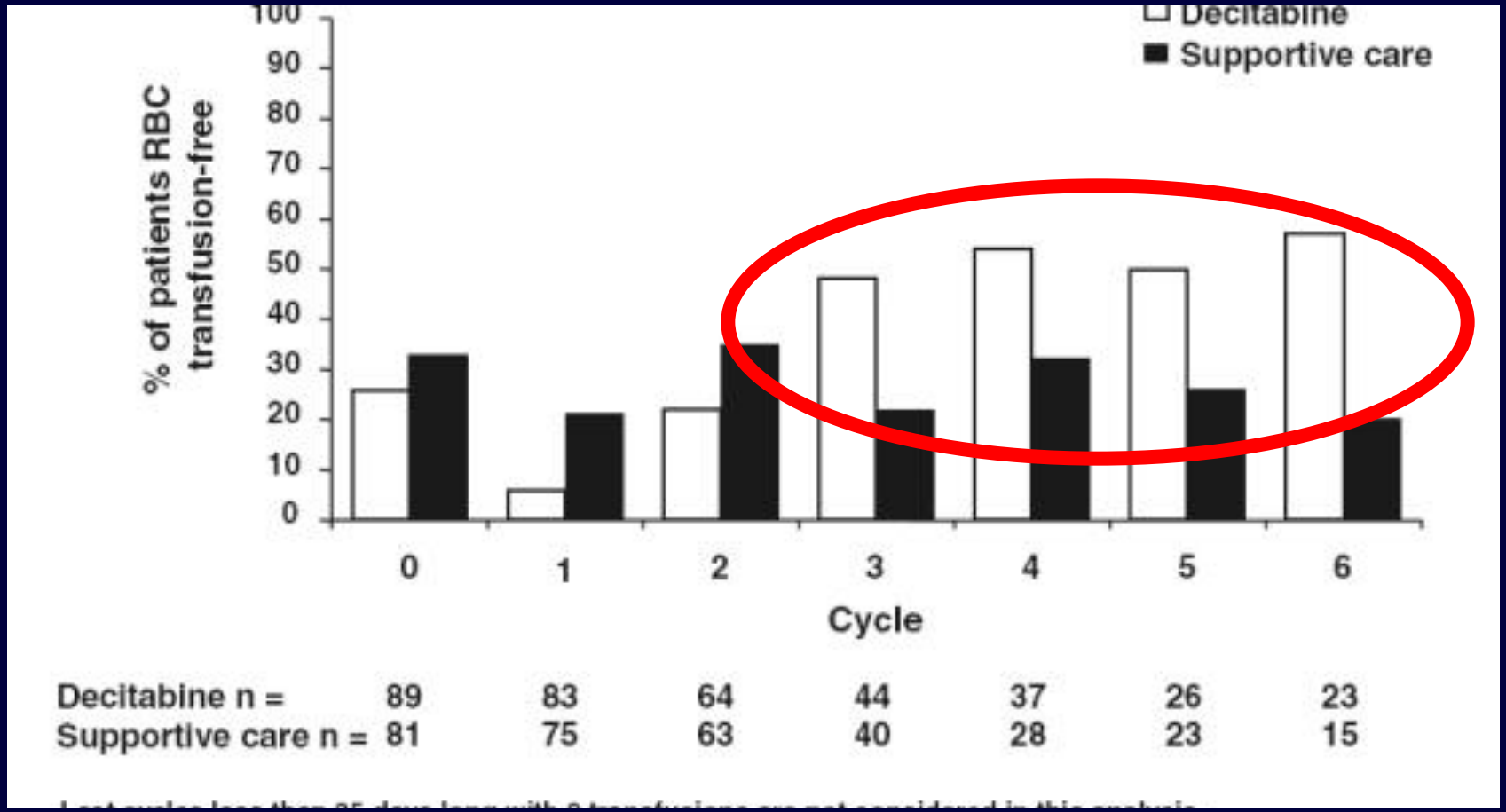
Fenaux P, et al. Lancet Oncol. 2009;10:223-232.

Decitabine for MDS

- Approved for the treatment of patients with MDS:
  - Previously treated or untreated
  - De novo or secondary MDS
  - FAB subtypes (RA, RARS, RAEB, RAEB-T, and CMMoL)
  - Intermediate-1, intermediate-2, and high-risk IPSS groups
- Decitabine 15 mg/m2 IV Q 8 hours Days 1, 2, 3 every 6 weeks
- Decitabine 20 mg/m2 IV QD Days 1-5 every 4 weeks

Kantarjian H, et al. Blood. 2007

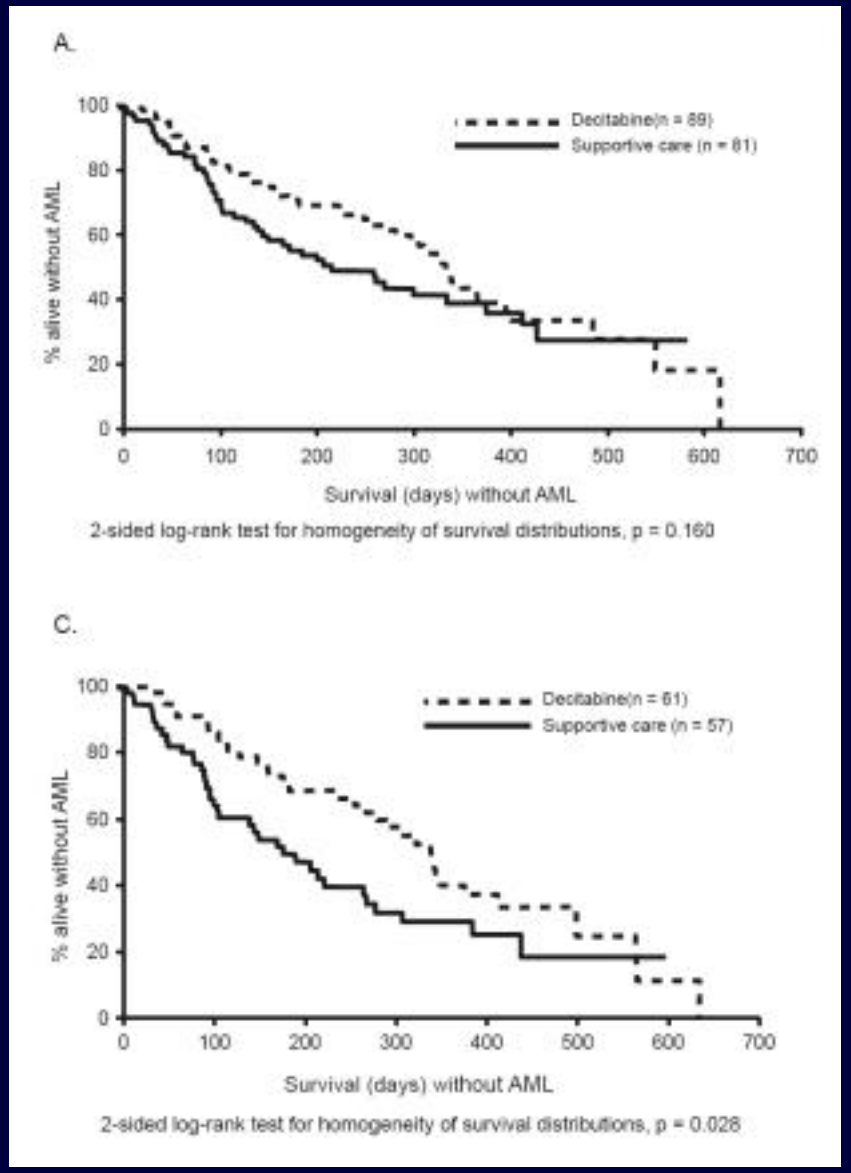
Decitabine for MDS



Kantarjian H, et al. Cancer. 2006;106:1794–803

Decitabine for MDS

- Phase III trial
- No PFS benefit for all comers
- But improved PFS in
  - INT-2 & High IPSS Risk
  - De novo disease



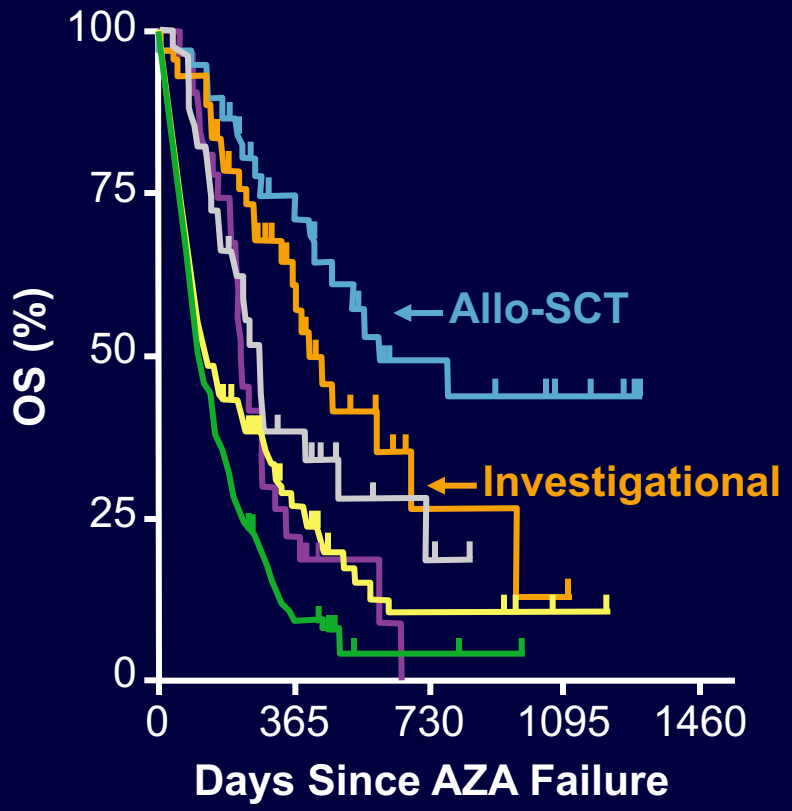
Kantarjian H, et al. Cancer 2006

Decitabine for MDS

- Most common side effects
  - Neutropenia 90%
  - Thrombocytopenia 89%
  - Anemia 82%
  - Fever 53%
  - Nausea 42%
  - Cough 40%
  - Petechiae 53%
  - …

Saba, et al. Ther Clin Risk Manag 2007

Salvage Therapy After Azacitidine Failure: GFM and AZA001 Studies



Type of Salvage	N	ORR	Median OS, Mos
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*†

*Log-rank comparison of BSC vs intensive CT ($P = .04$), investigational therapy ($P < .001$), or alloSCT ($P < .001$).
†Comparison of intensive CT vs investigational therapy ($P = .05$), intensive CT vs ASCT ($P = .008$), or IT vs ASCT ($P = .09$).

Prébet T, et al. J Clin Oncol. 2011;29:3332-3327.

Questions?