



# Case #4

## High-Risk Myelodysplastic Syndromes

**Aristoteles Giagounidis, MD, PhD**  
**St Johannes Hospital**  
**Duisburg, Germany**



# Treatment Options in Myelodysplastic Syndromes

Risk stratification according to WPSS

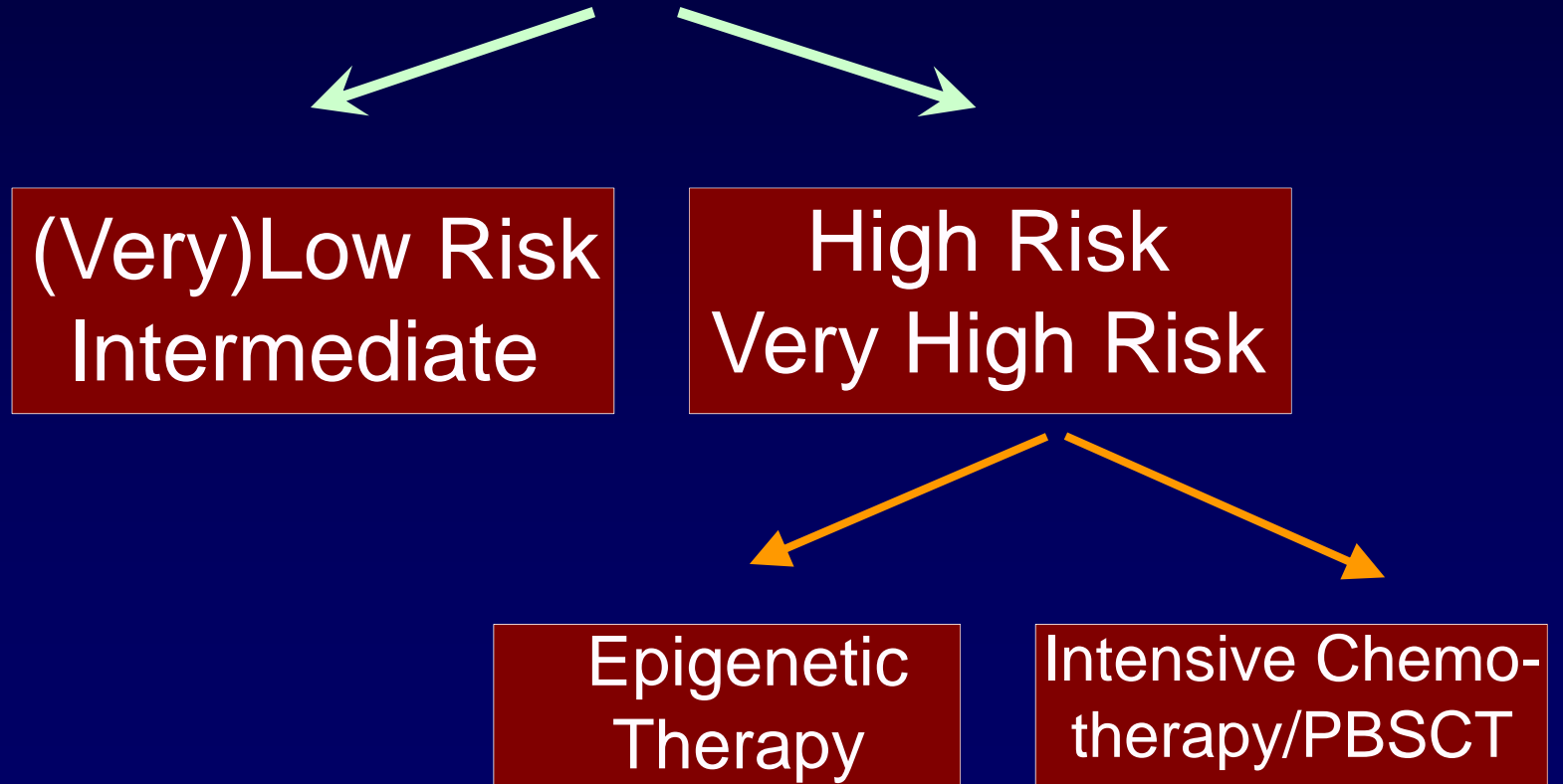


(Very) Low Risk  
Intermediate

High Risk  
Very High Risk

# Treatment Options in Myelodysplastic Syndromes

**Risk stratification according to WPSS**



# Results of Intensive Induction Regimens in Patients With MDS (Metaanalysis\*)

<i>No. of patients</i>	<i>910</i>
<i>Median age</i>	<i>54 yrs</i>
<i>Complete remission (CR)</i>	<i>51%</i>
<i>Non response (NR)</i>	<i>18%</i>
<i>Early death (ED)</i>	<i>11%</i>

\* Michels, 1989; De Witte, 1990; Estey, 1994; De Witte, 1995; Bernstein, 1996; Aul, 1996; Wattel, 1997; Ruutu, 1997; Parker, 1997; Verbeek, 1997; Beran, 1996; Ganser, 2000; Jackson, 2001; De Witte, 2001

# Factors Predictive of Successful Remission Induction in MDS

- Younger age
- Good performance score
- No previous cytotoxic therapy
- Short interval from diagnosis to treatment
- RAEB/T > RAEB subtype
- Presence of Auer rods
- Normal karyotype
- Low levels of MDR1 protein

# AZA-001 Phase III Survival Study

*AZA 75 mg/m<sup>2</sup>/d x 7 days  
Every 28 days* *N = 179*

**Stratify (FAB, IPSS)**

*N = 358*

**Eligibility**

- RAEB, RAEB-t, CMML
- 10% to 29% blasts
- IPSS: INT-2/High risk

*N = 179*

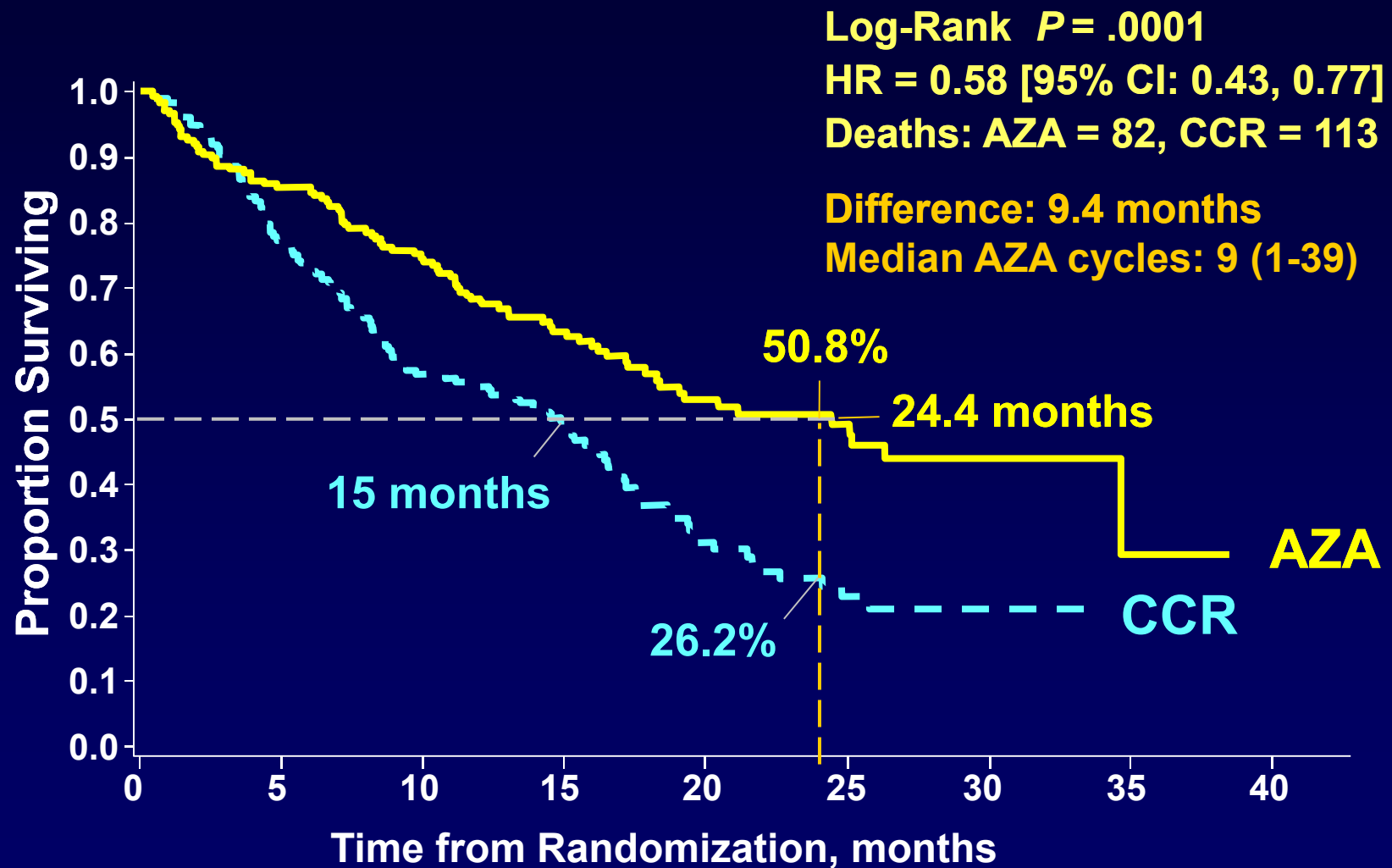
**Conventional Care Regimen (CCR):**

1. BSC only, *n = 105*
2. Low-dose ara-C, *n = 49*
3. Induction/consolidation, *n = 25*

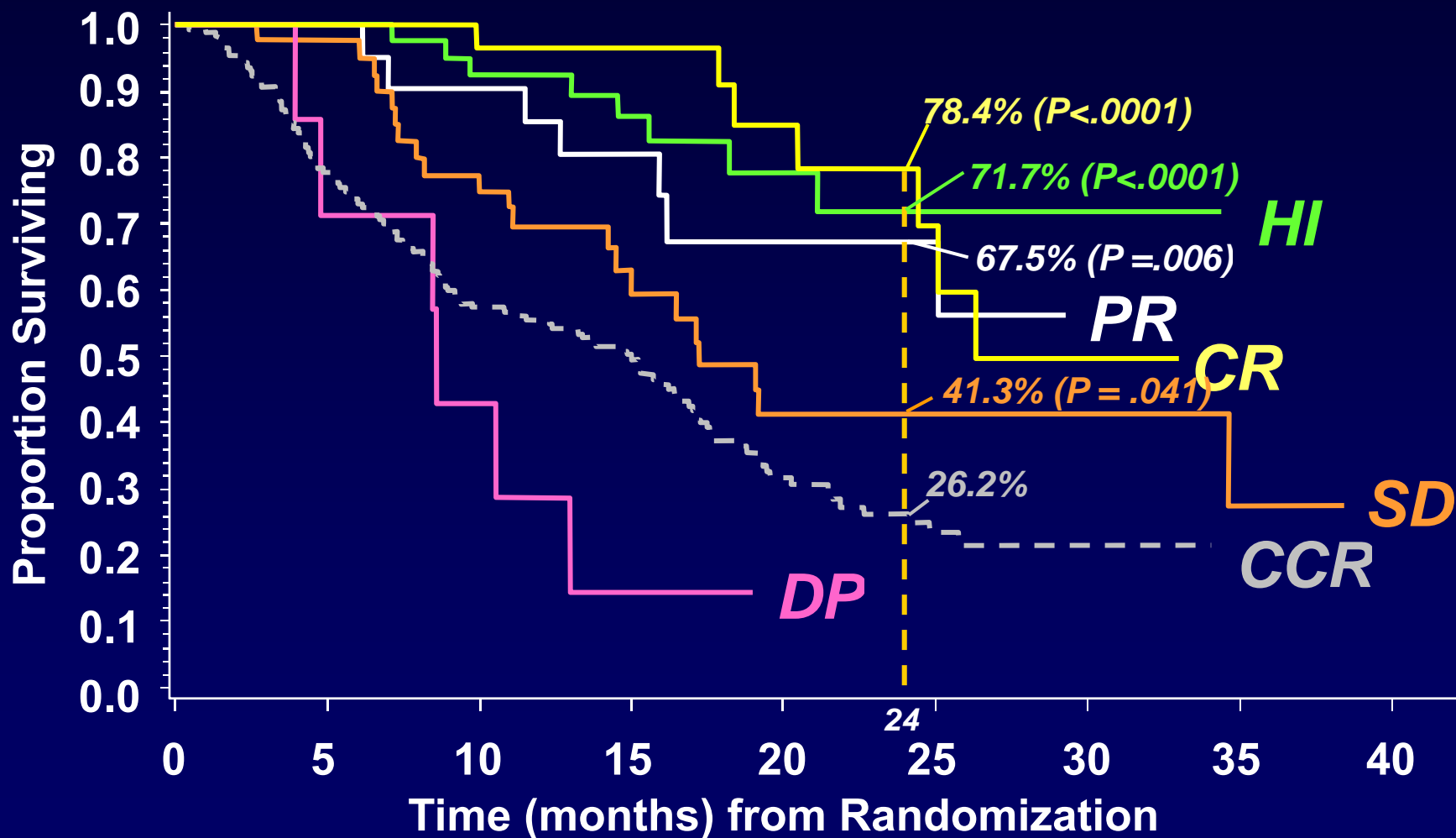
**Primary endpoint:** Overall survival

**Secondary endpoints:** Time to AML, RR, TI, infection, safety

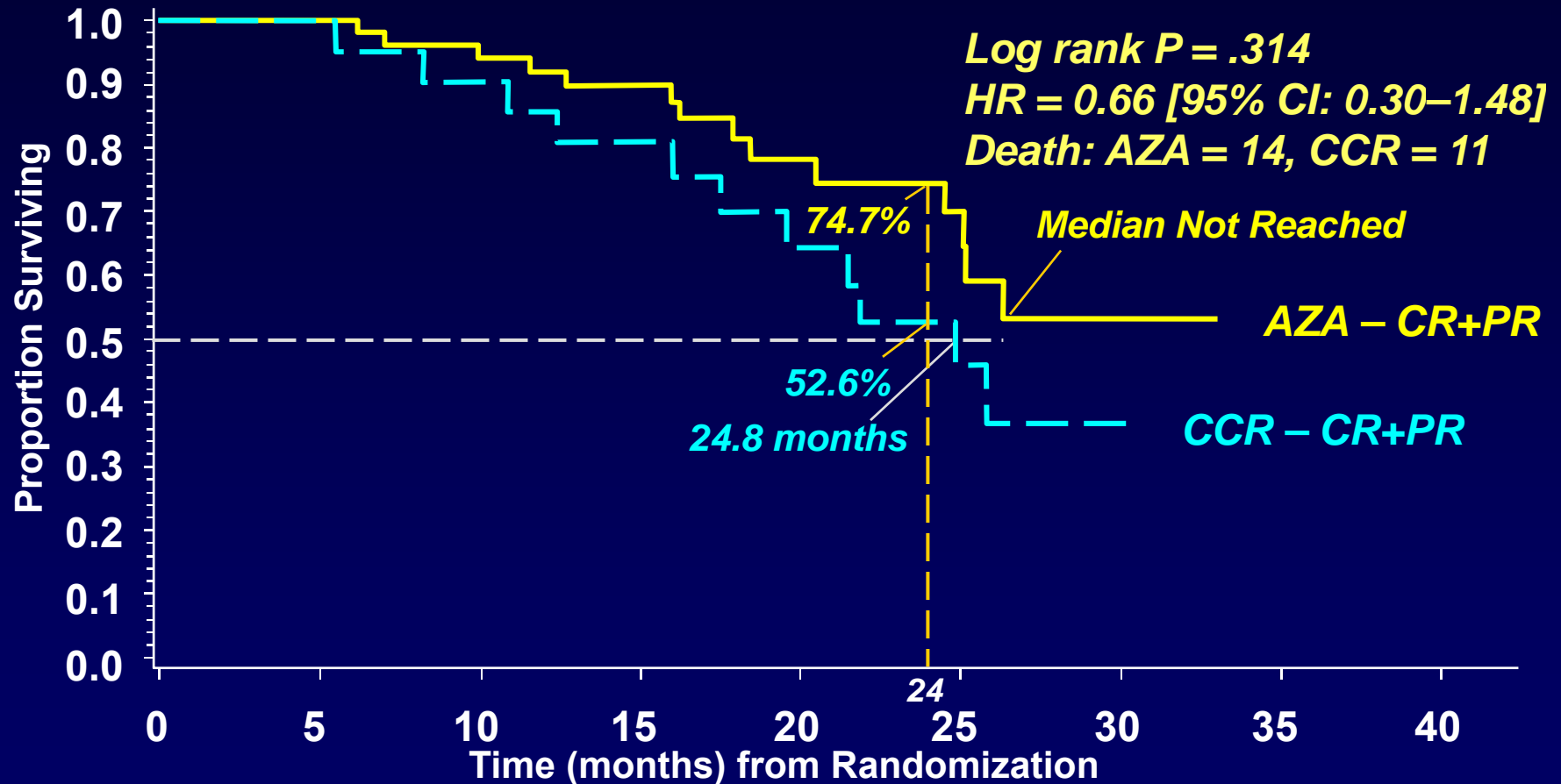
# Overall Survival: Azacitidine vs CCR ITT Population



# Overall Survival With AZA by Best Response (IWG 2000)



# AZA vs CCR: Overall Survival in Patients with Best Response of CR + PR



# at risk

AZA	51	51	48	37	23	13	3	0	0
CCR	21	21	19	16	11	6	1	0	0

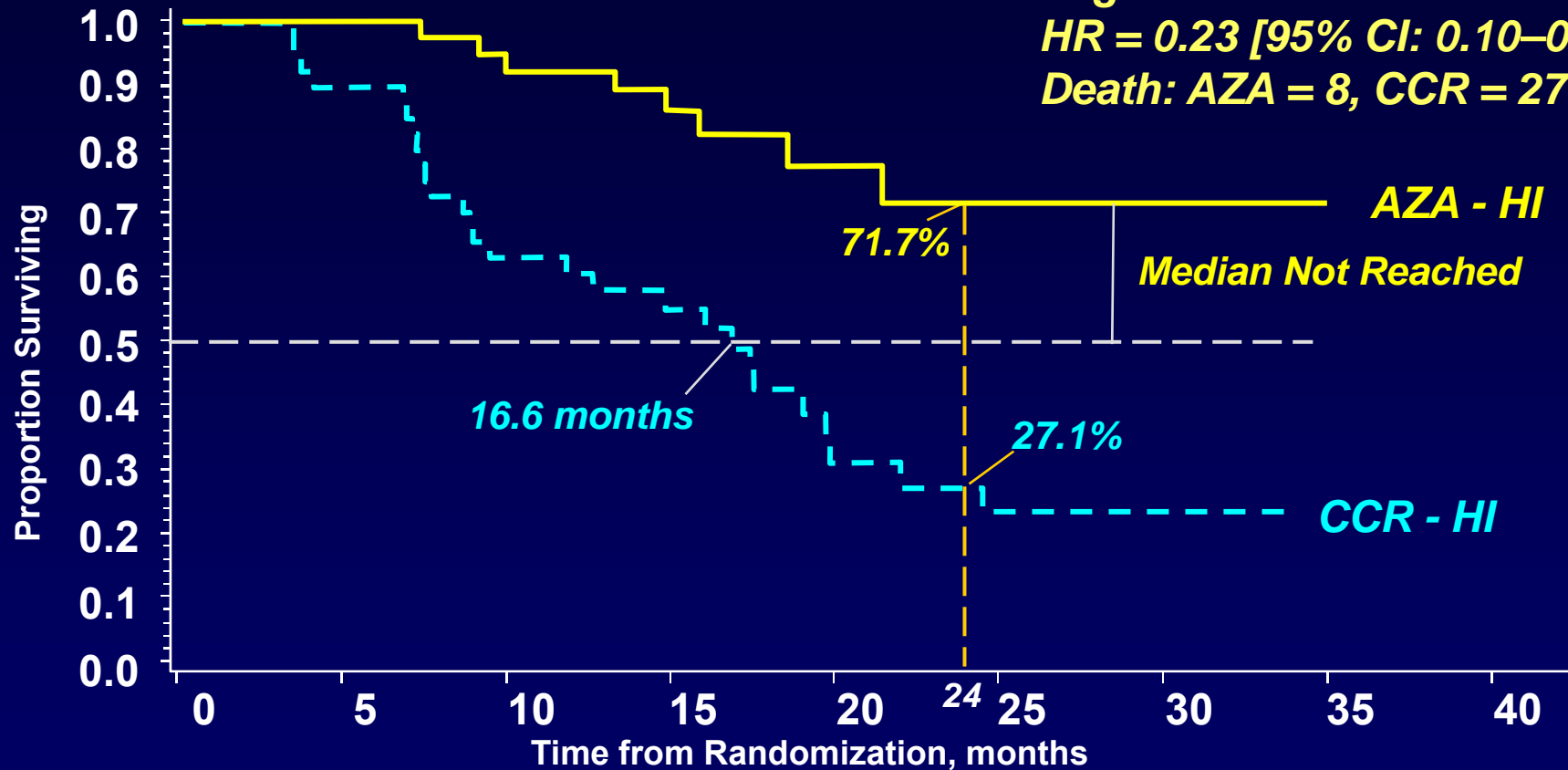
Fenaux P, et al. *Blood*. 2007;110: Abstract 817.

# AZA vs CCR: Overall Survival in Patients with Best Response of HI

Log rank  $P < .0001$

HR = 0.23 [95% CI: 0.10–0.51]

Death: AZA = 8, CCR = 27

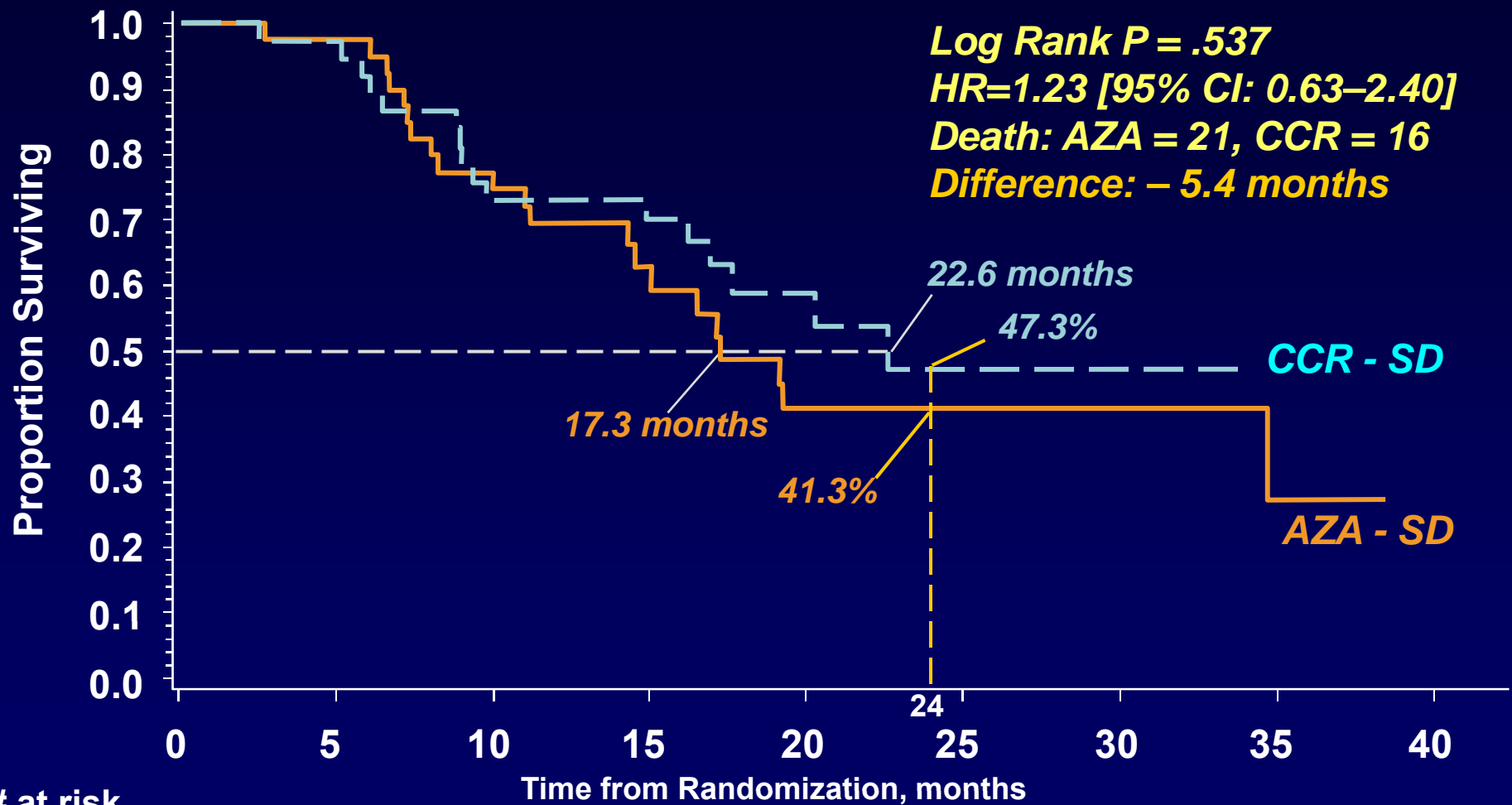


# at risk

AZA	40	40	36	25	15	7	2	0	0
CCR	41	37	26	18	8	5	3	0	0

Fenaux P, et al. *Blood*. 2007;110: Abstract 817.

# AZA vs CCR: OS in Patients with Best Response of SD



# at risk

AZA	40	39	30	18	11	8	4	1	0
CCR	38	37	27	23	12	3	1	0	0

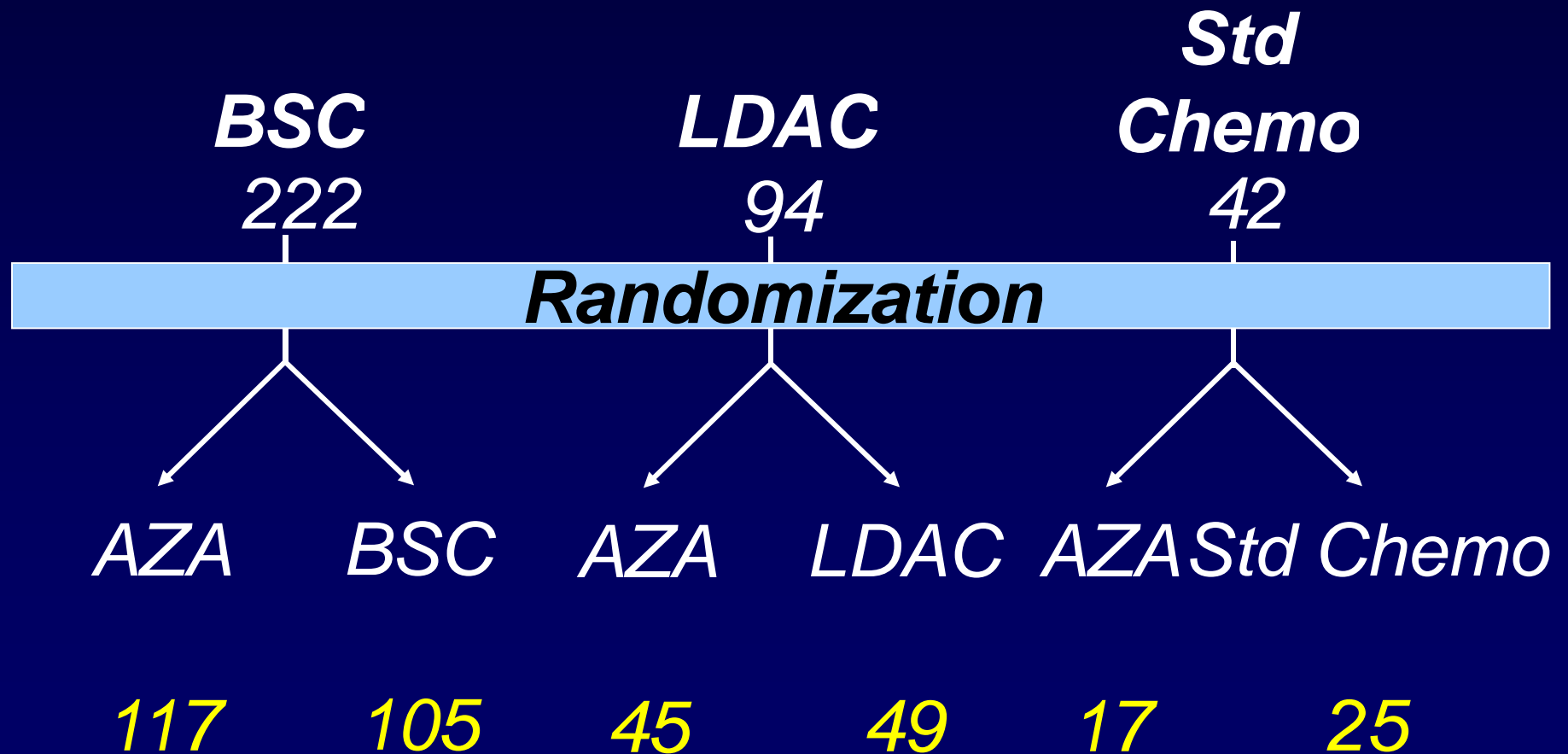
Fenaux P, et al. *Blood*. 2007;110: Abstract 817.

## Secondary Endpoints: IWG (2000) RR and HI

Response	CCR Regimens					P-Value AZA vs CCR
	AZA N=179 (%)	CCR N=179 (%)	BSC Only N=105 (%)	LDAC N=49 (%)	Std Chemo N=25 (%)	
Overall (CR+PR)	29	12	5	12	40	0.0001
CR	17	8	1	8	36	0.02
PR	12	4	4	4	4	0.009
IWG HI						
Major+Minor	49	29	31	25	28	<0.0001
HI-E Major	40	11	8	10	22	<0.0001
HI-P Major	33	14	10	19	20	0.0003
HI-N Major	19	18	20	11	24	0.87

# Additional Analysis: Investigator Treatment Selection of CCR

**N = 358**



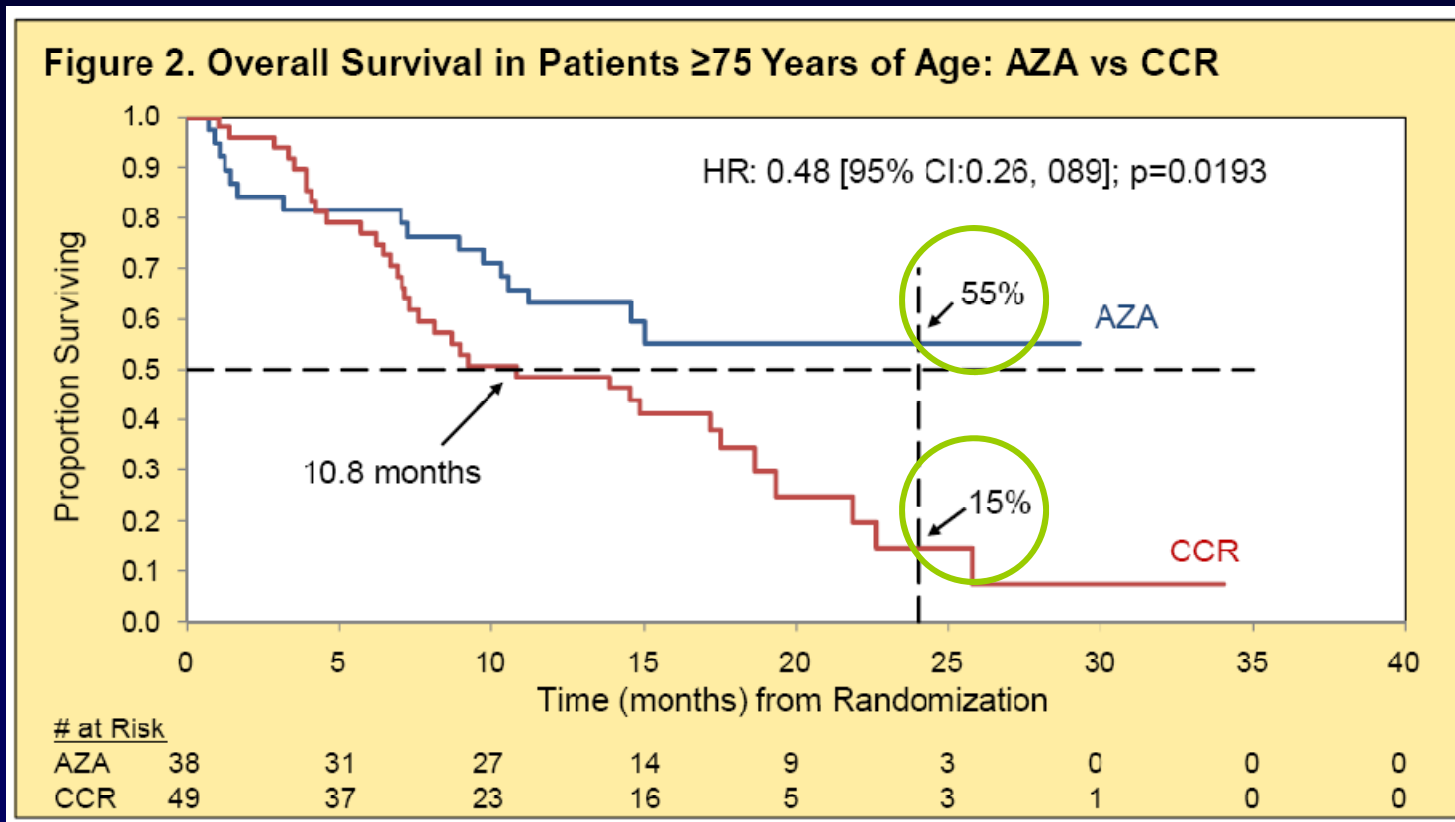
# Additional Analysis: Median OS by Investigator Selection

Treatment	K-M OS Time mos	Differences			
		K-M OS Time mos	Hazard Ratio	Log- rank P	
AZA (N = 117) vs BSC (N = 105)	21.1	11.5	9.6	0.56	0.002
AZA (N = 45) vs LDAC (N = 49)	24.5	15.3	9.2	0.58	0.075
AZA (N = 17) vs Stand Chemo (N = 25)	25.1	15.7	9.4	0.87	0.75

## Grade 3 and 4 Hematologic Toxicity

	% of Patients			
	AZA N=175	Conventional Care Regimens		
		BSC N=102	LDAC N=44	Std Chemo N=19
<b>Grade 3-4 Toxicity</b>				
Neutropenia	91	71	88	94
Thrombocytopenia	85	71	98	100
Anemia	56	67	76	61
<b>Pts with Baseline Grade 0-2 shifting to Grade 3-4 on Tx</b>				
Neutropenia	84	48	79	83
Thrombocytopenia	74	54	97	100
Anemia	54	61	79	50

# Azacitidine in MDS Patients (Aged $\geq 75$ Years)



Median follow-up: 17.7 months

Median OS: AZA, not reached vs CCR, 10.8 months,  $P = .0193$

2-year survival: **55% vs 15%,  $P = .0003$**

# Azacitidine in MDS Patients (Aged $\geq 75$ Years)

## Demographic and Disease Characteristics at Baseline

	Azacitidine (n = 38)	CCR (n = 49)
<b>Age, years</b>		
Median (range)	78.0 (75-83)	77.0 (75-88)
<b>Gender, n (%)</b>		
Male	27 (71.1)	31 (63.3)
<b>IPSS, n (%)</b>		
Intermediate-1	3 (7.9)	2 (4.1)
Intermediate-2	15 (39.5)	22 (44.9)
High	19 (50.0)	22 (44.9)
Indeterminable	0	2 (4.1)
Not applicable	1 (2.6)	1 (2.0)
<b>ECOG status, n (%)</b>		
Grade 0	8 (21.1)	21 (42.9)
Grade 1	27 (71.1)	22 (44.9)
Grade 2	3 (7.9)	6 (12.2)

# Azacitidine in MDS Patients (Aged $\geq 75$ Years)

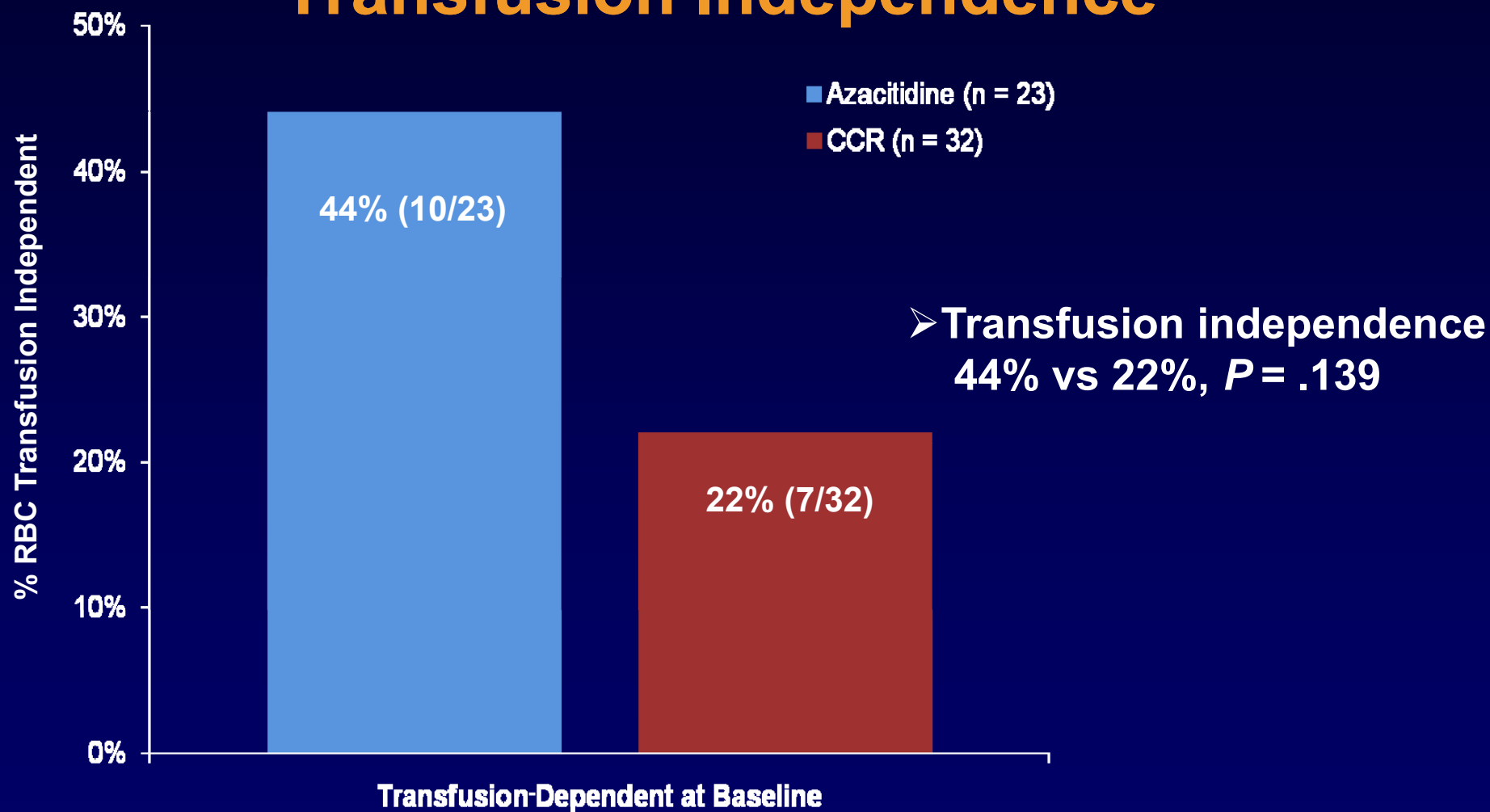
## Treatment Cycles

Cycle Length	Azacitidine (N = 299 cycles)	CCR (N = 64 cycles)
<b><math>\leq 28</math> days</b>		
N Cycles (%)	151 (51)	25 (39)
Median (Range)	28(21-28)	28 (27-28)
<b>29-35 days</b>		
N cycles (%)	79 (26)	26 (41)
Median (Range)	33 (29-35)	34 (29-35)
<b>&gt; 35 days</b>		
N cycles	69 (23)	13 (20)
Median (Range)	42 (36-106)	40 (36-65)

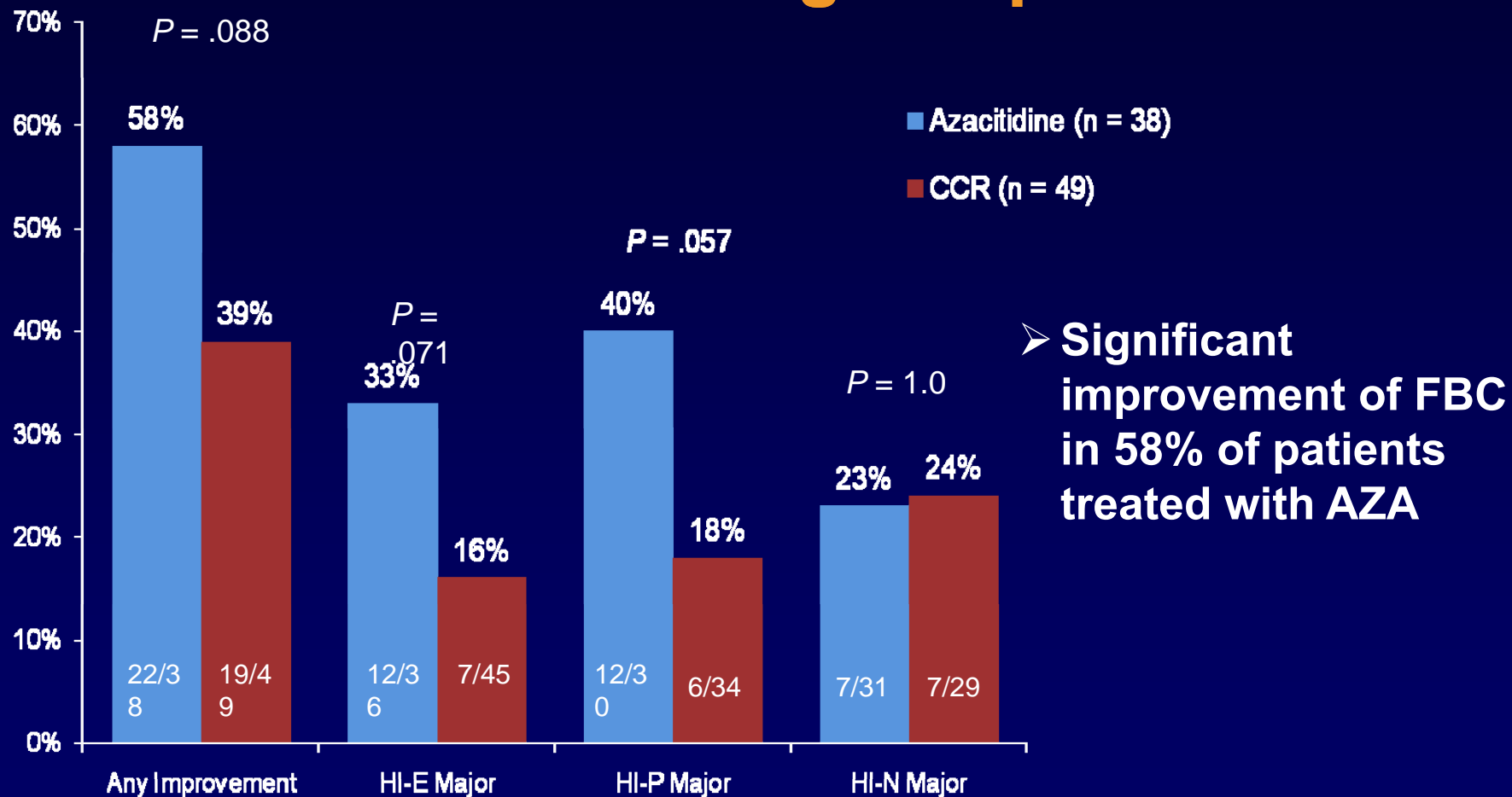
➤ More than  $\frac{3}{4}$  of elderly patients tolerated AZA in cycles of 4-5 weeks

➤ AZA well tolerated (Interruption for AEs 13% AZA vs. 8% CCR)

# Azacitidine in MDS Patients (Aged $\geq 75$ Years) Transfusion Independence



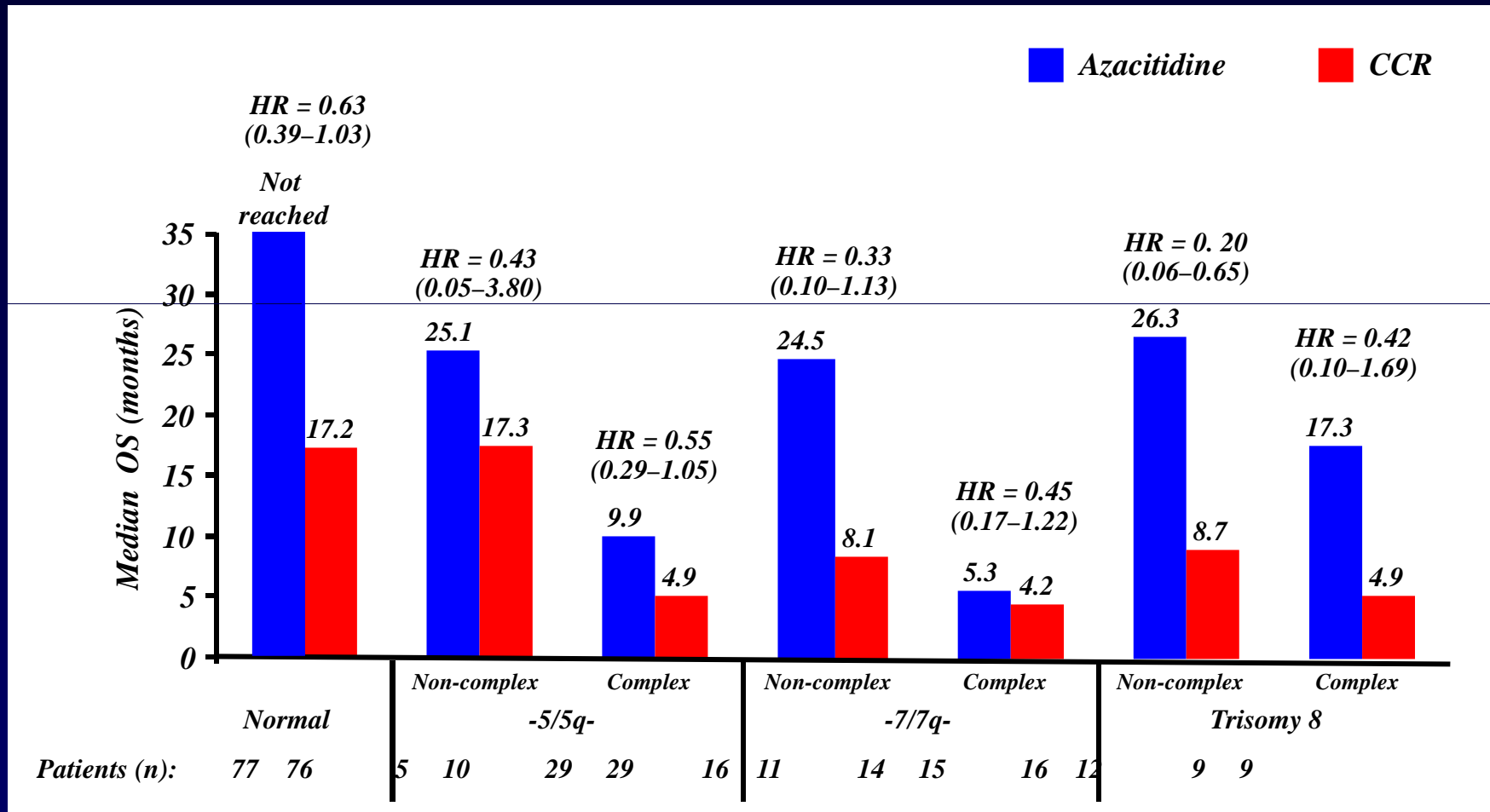
# Azacitidine in MDS Patients (Aged $\geq 75$ Years) IWG 2000 Hematologic Improvement



# Patients and Karyotype

- Of the 358 pts enrolled in AZA-001, 343 had cytogenetic data available:
  - 153 pts had normal karyotype (AZA 77, CCR 76)
  - 118 pts had non-complex karyotype (AZA 60, CCR 58)
  - 72 pts had complex karyotype (AZA 34, CCR 38)
- 136 pts had -5/5q-, -7/7q- and/or trisomy 8 as part of a non-complex or complex karyotype

# Survival With Respect to Karyotype



HR = Hazard Ratio

# *Therapeutic Options in MDS*

