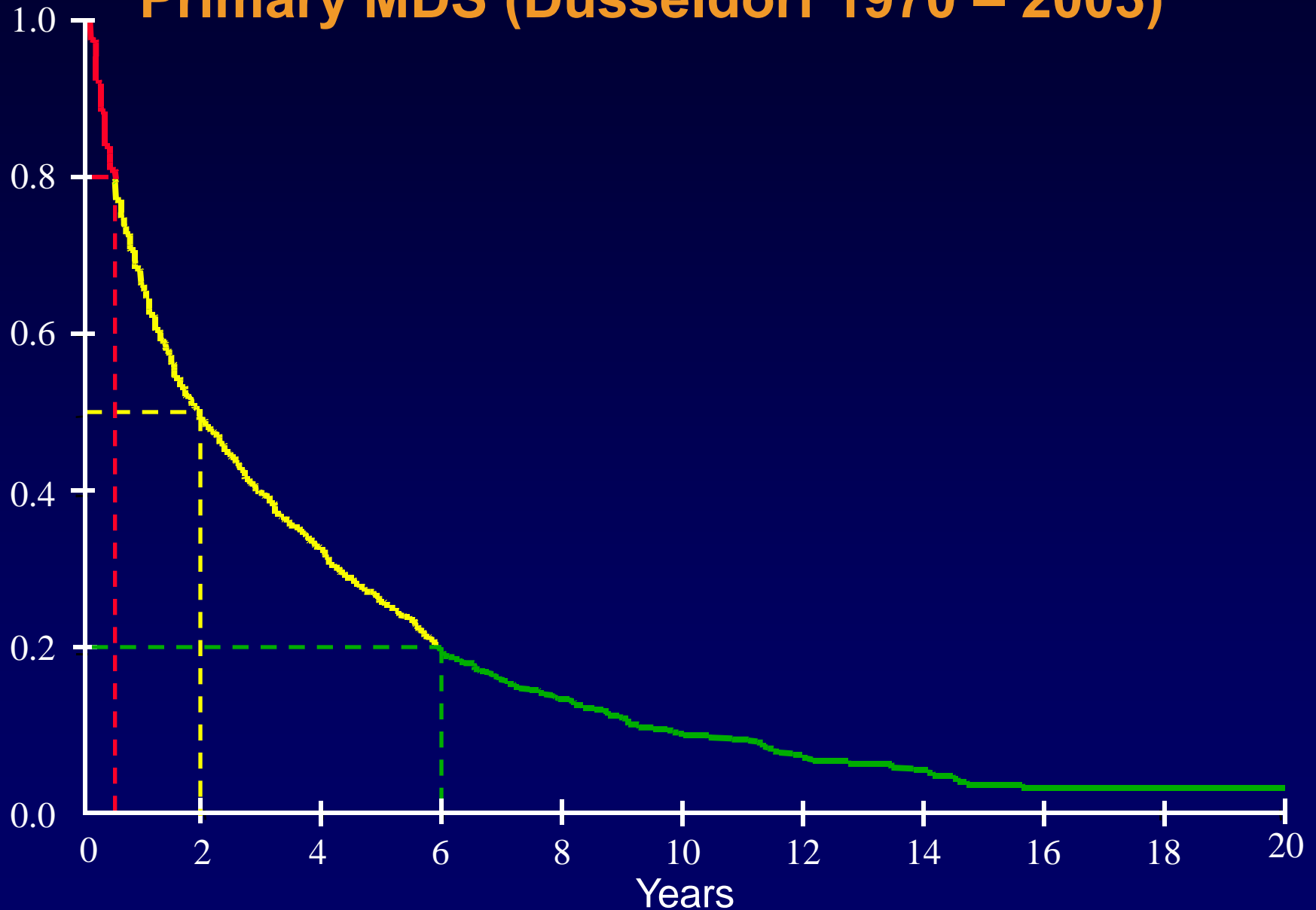


High-Risk Myelodysplastic Syndromes: Improved Survival with Epigenetic Therapy

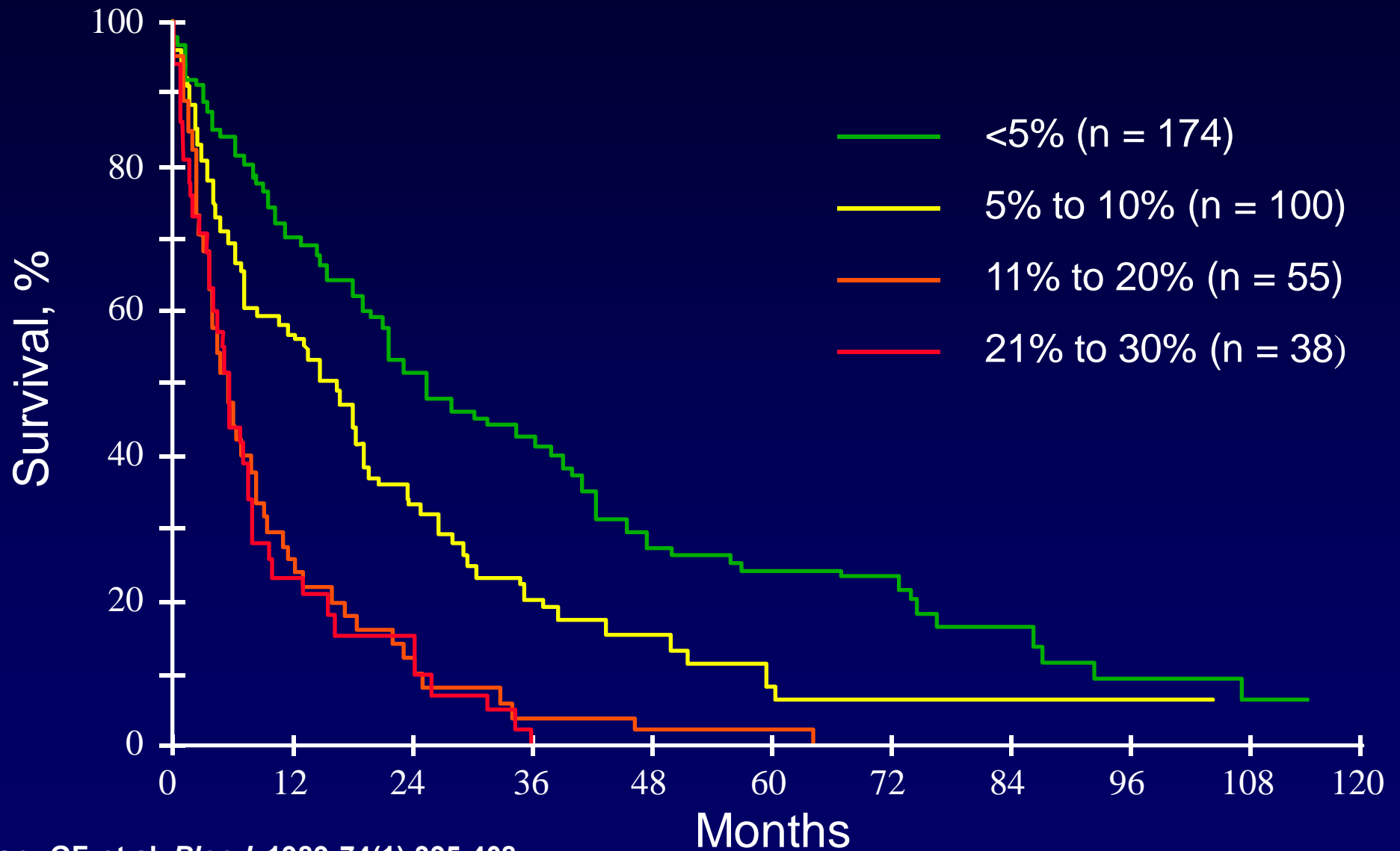
Aristoteles Giagounidis, MD, PhD
St. Johannes Hospital
Duisburg, Germany



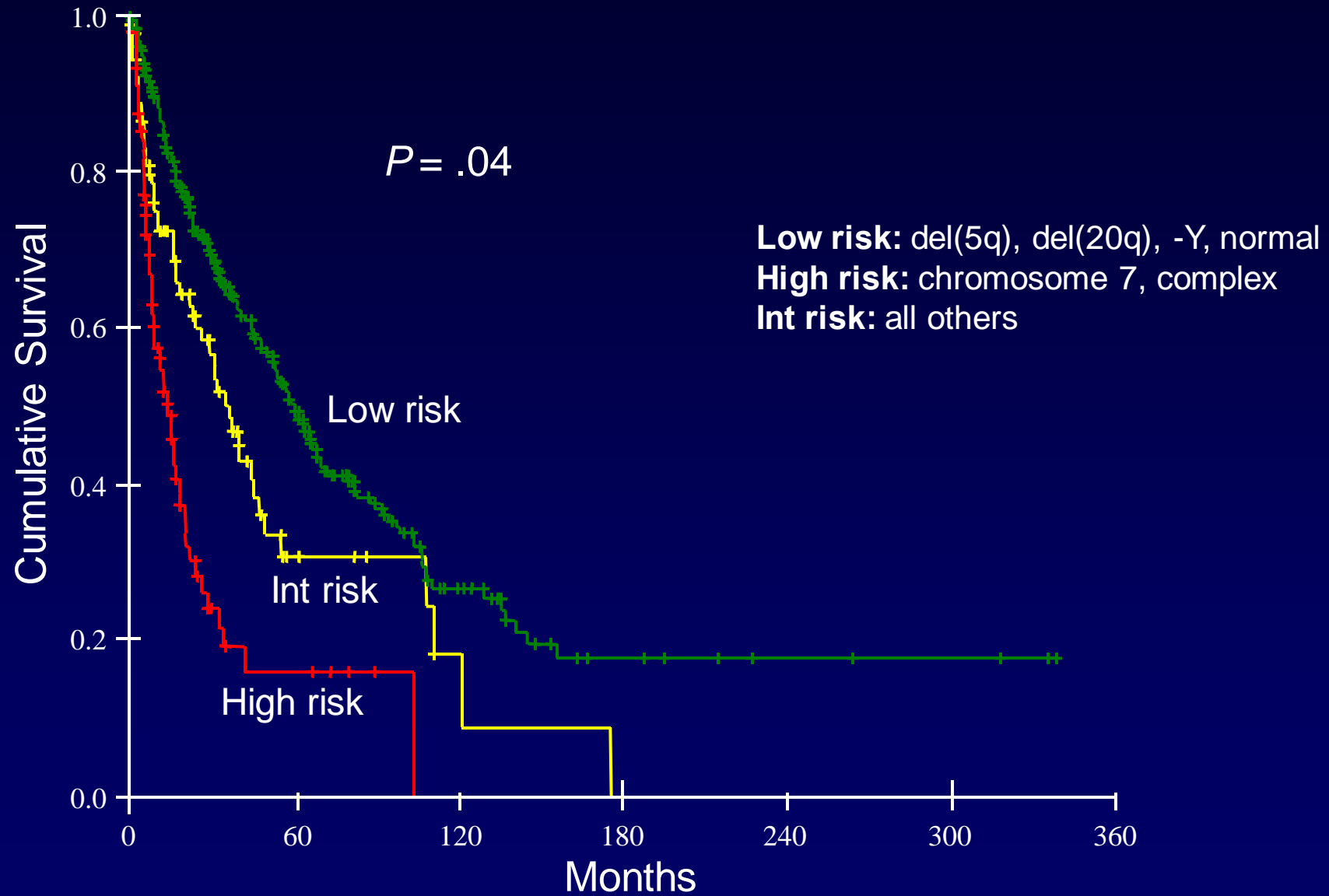
Cumulative Survival of 1806 Untreated Patients with Primary MDS (Düsseldorf 1970 – 2003)



Survival of MDS Patients According to Medullary Blast Percentage at Time of Diagnosis



Prognostic Value of Cytogenetic Findings in MDS



International Prognostic Scoring System

	Score				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Bone marrow blast percentage	< 5	5-10		11-20	21-30
Cytogenetics	Good	Intermed	Poor		
Cytopenias	0/1	2/3			

Risk Group	Score
Low	0
Intermediate I (INT-1)	0.5 – 1.0
Intermediate II (INT-2)	1.5 – 2.0
High	≥2.5

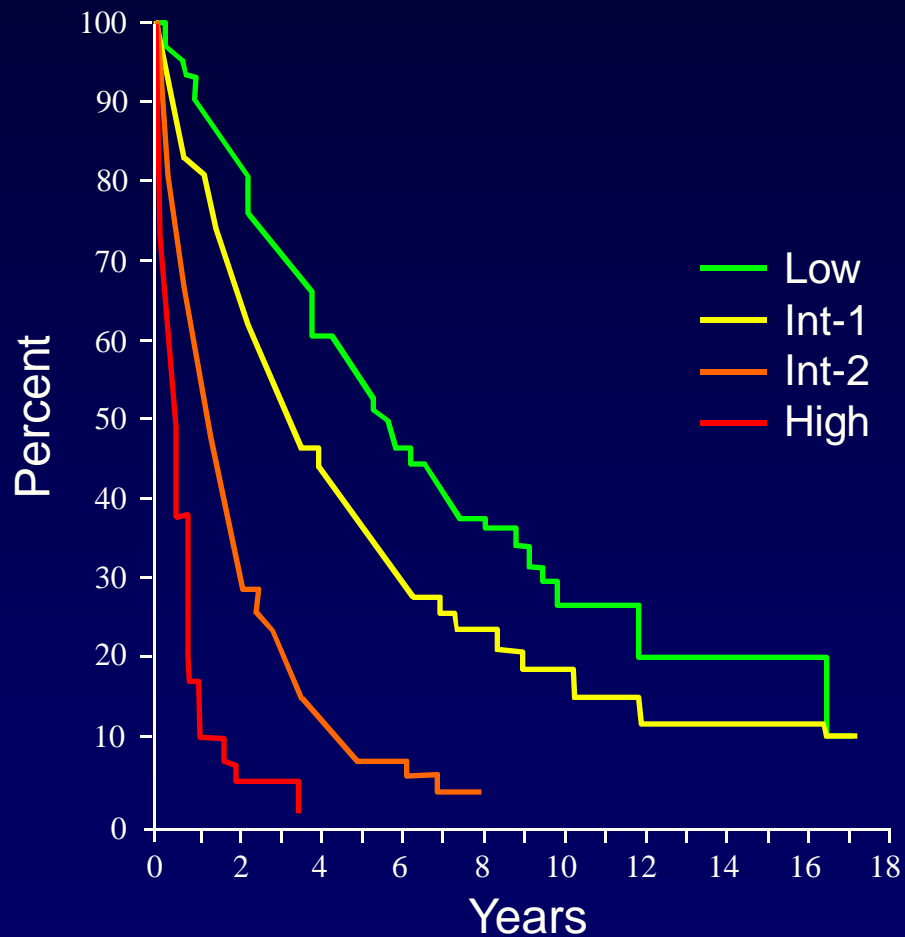
Cytopenias: ANC < 1.800/μL, HGB < 10.0 g/dL, PLT < 100,000/μL

Good Risk: [-Y,del(5q), del(20q),NI]; Intermediate Risk: [8+,other]; Poor Risk: [Chr. 7 abn, ≥3 abn]

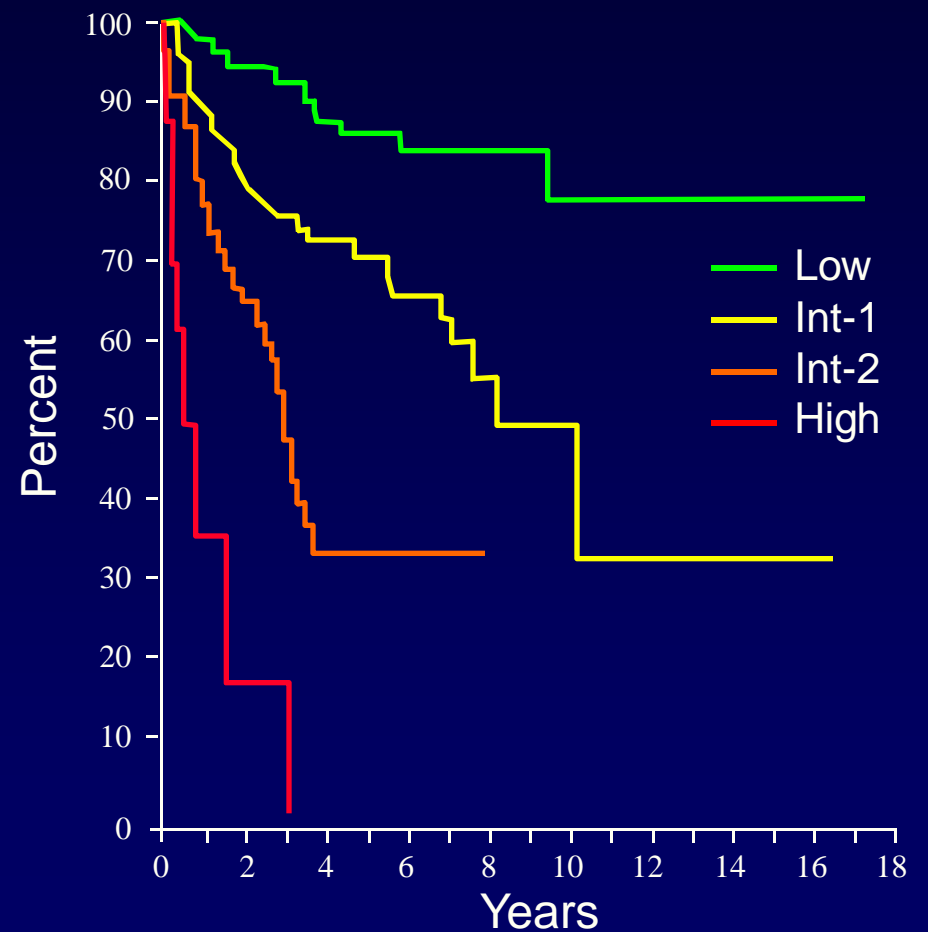
Greenberg P, et. al. *Blood*. 1997;89(6):2079-2088.

International MDS Risk Classification

Survival



Freedom from AML Evolution



Treatment Options in Myelodysplastic Syndromes

Risk stratification according to IPSS

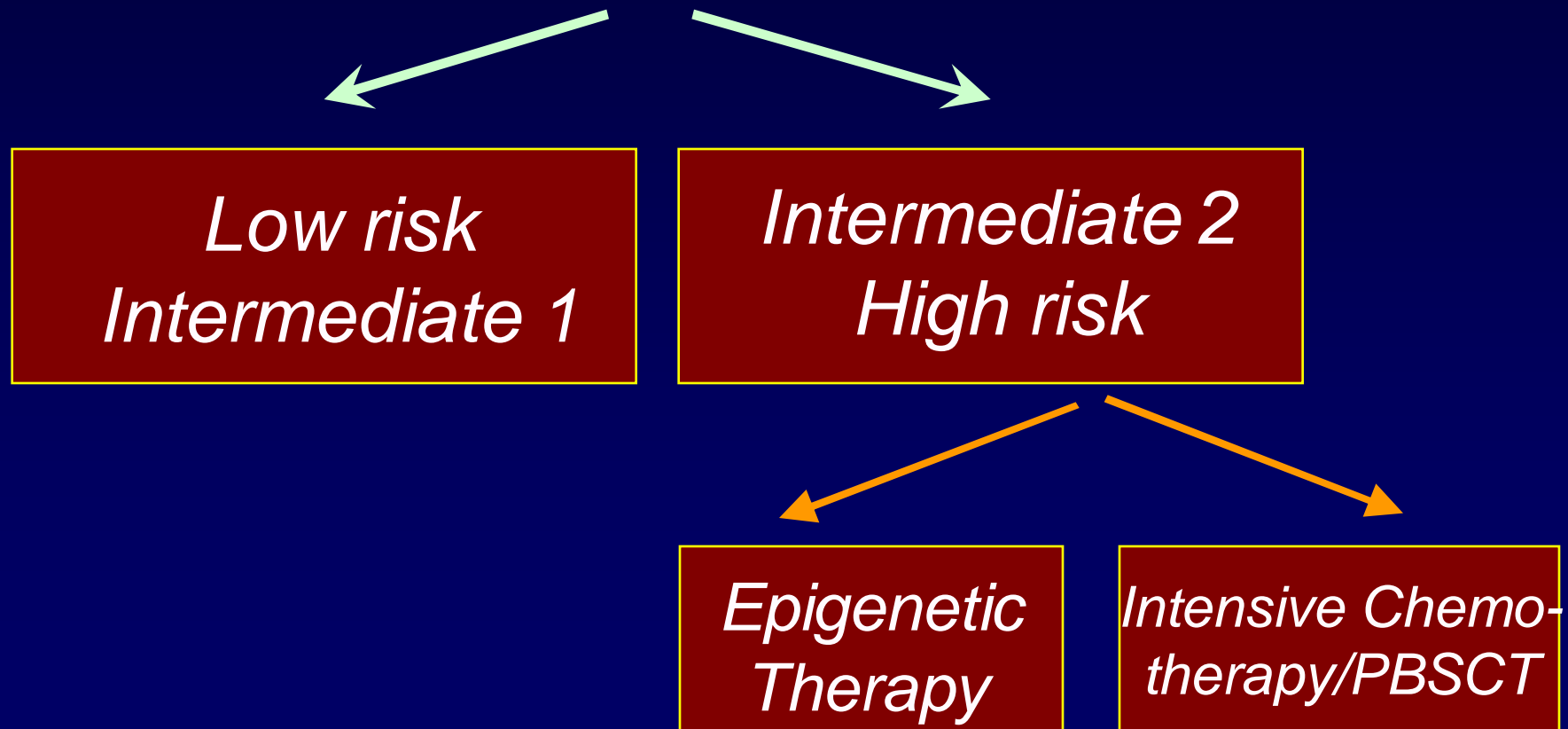
```
graph TD; A["Risk stratification according to IPSS"] --> B["Low risk  
Intermediate 1"]; A --> C["Intermediate 2  
High risk"]
```

*Low risk
Intermediate 1*

*Intermediate 2
High risk*

Treatment Options in Myelodysplastic Syndromes

Risk stratification according to IPSS

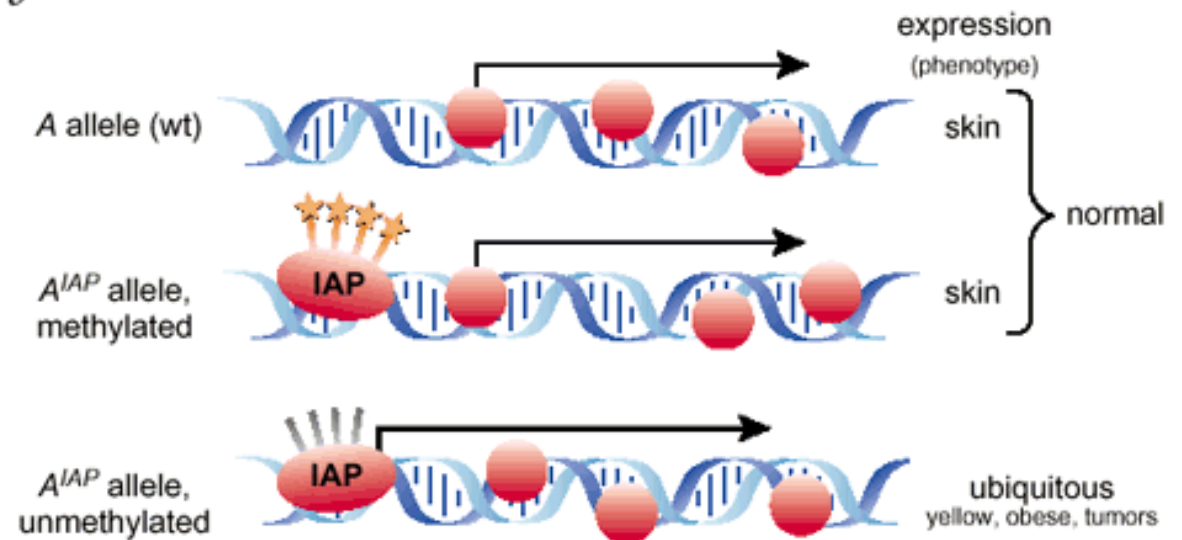


Epigenetic Modulation

a

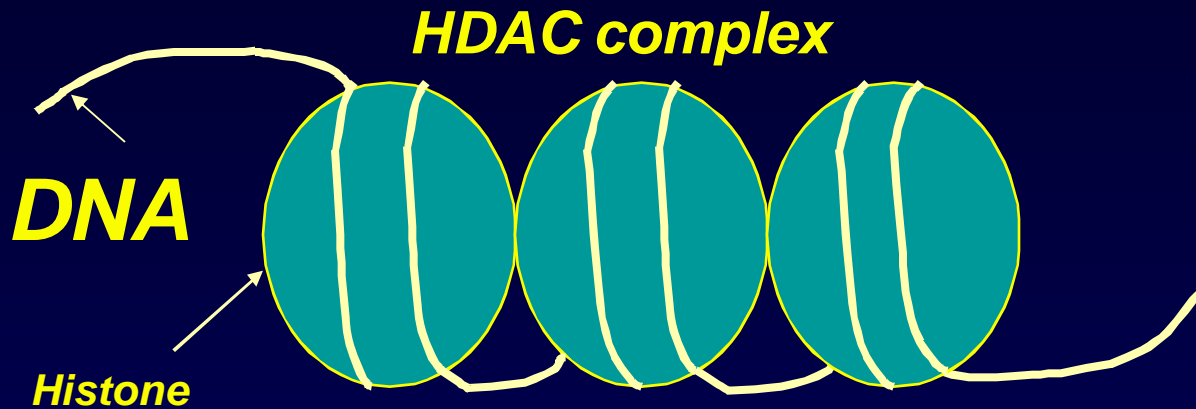


b

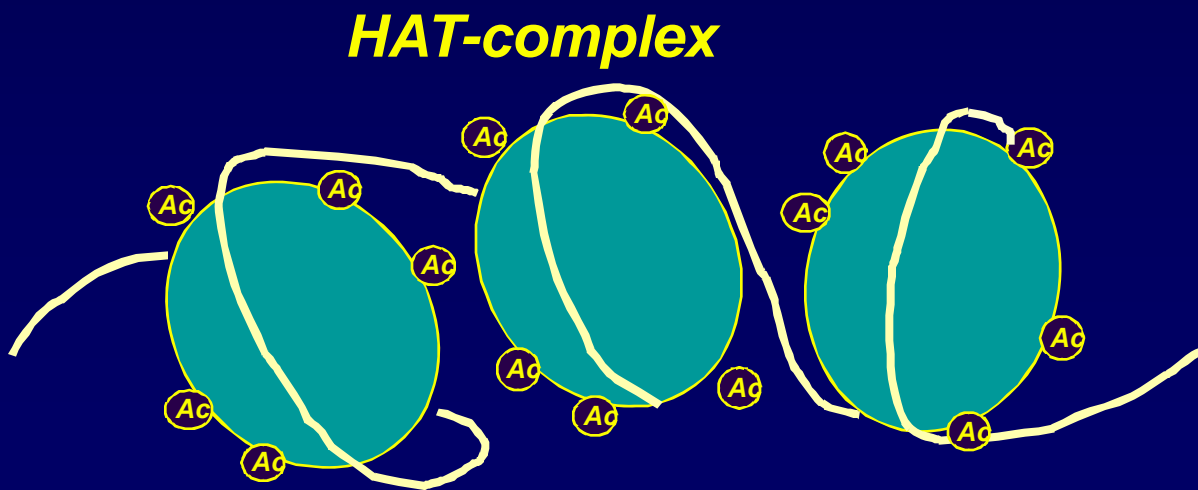


IAP: Intracisternal A Particle

Histone deacetylation → gene silencing



Histone acetylation → gene transcription



Acetylation



AZA-001 Phase III Survival Study

Stratify (FAB, IPSS)

Eligibility

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

AZA 75 mg/m²/d x 7 days
Every 28 days

N = 179

N = 358

N = 179

Conventional Care Regimen (CCR):

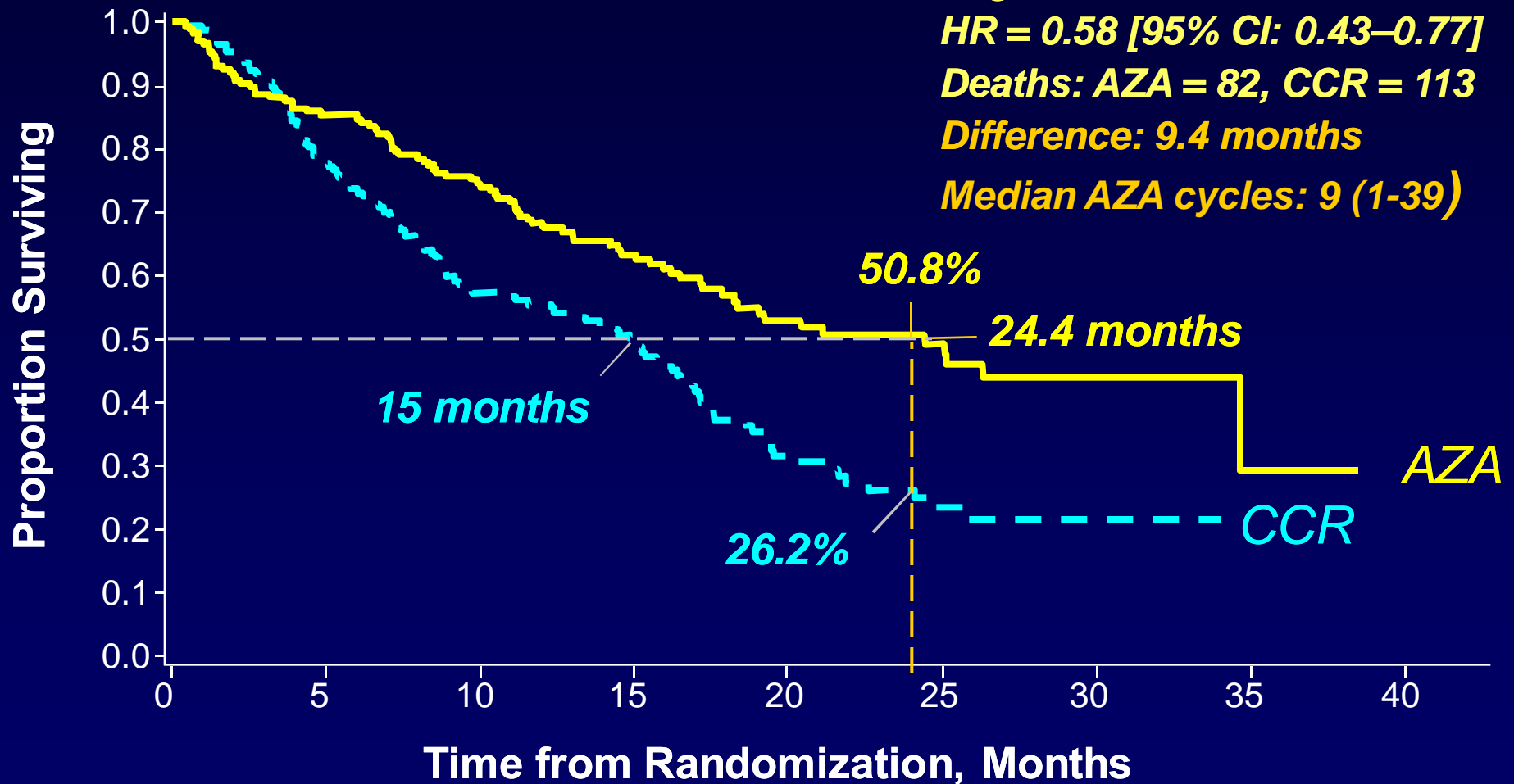
1. BSC only, **n = 105**
2. Low-dose ara-C, **n = 49**
3. Induction/consolidation, **n = 25**

Primary endpoint: Overall survival

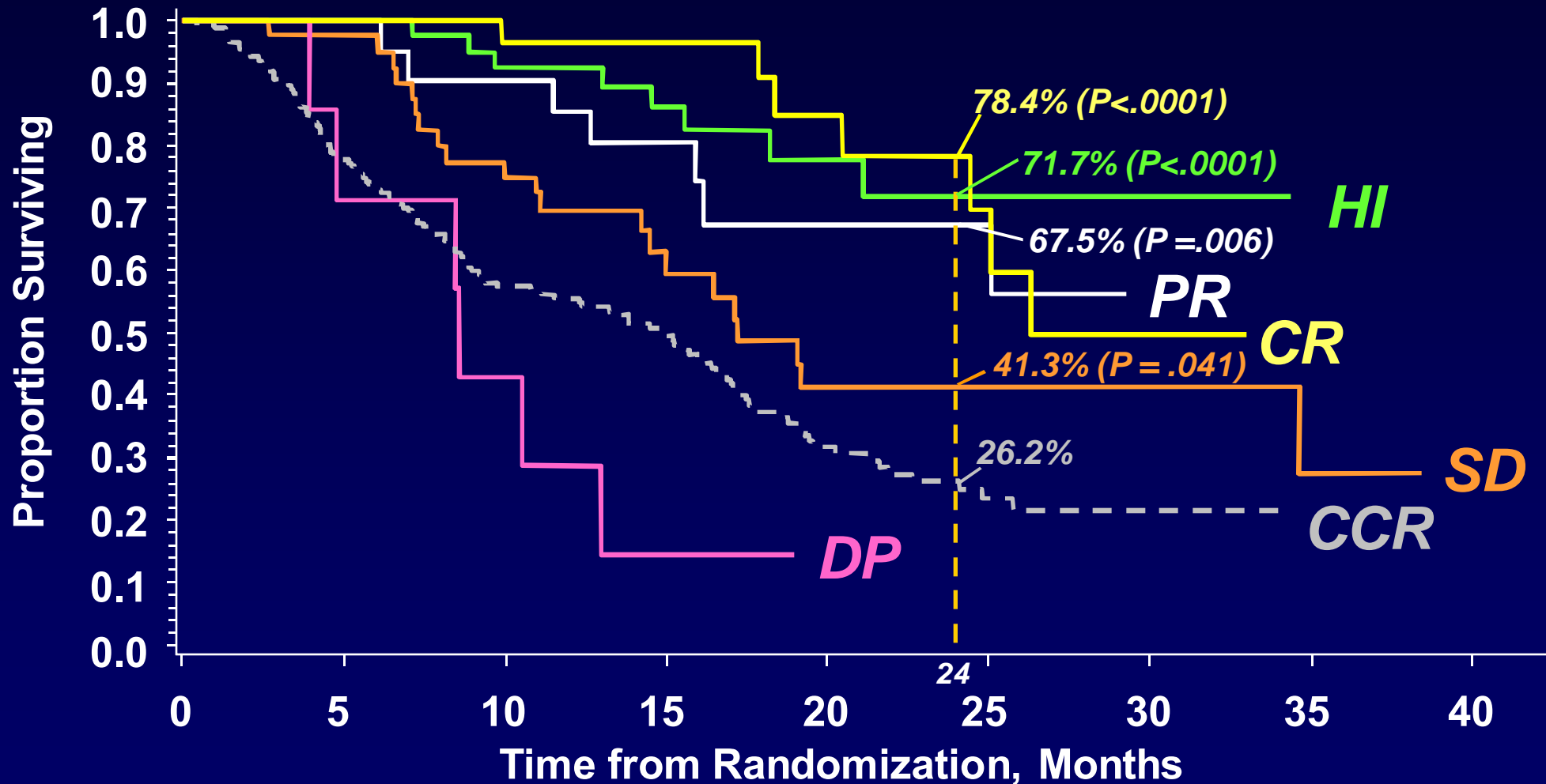
Secondary endpoints: Time to AML, RR, TI, infection, safety

Overall Survival: Azacitidine vs CCR Intent-to-Treat Population

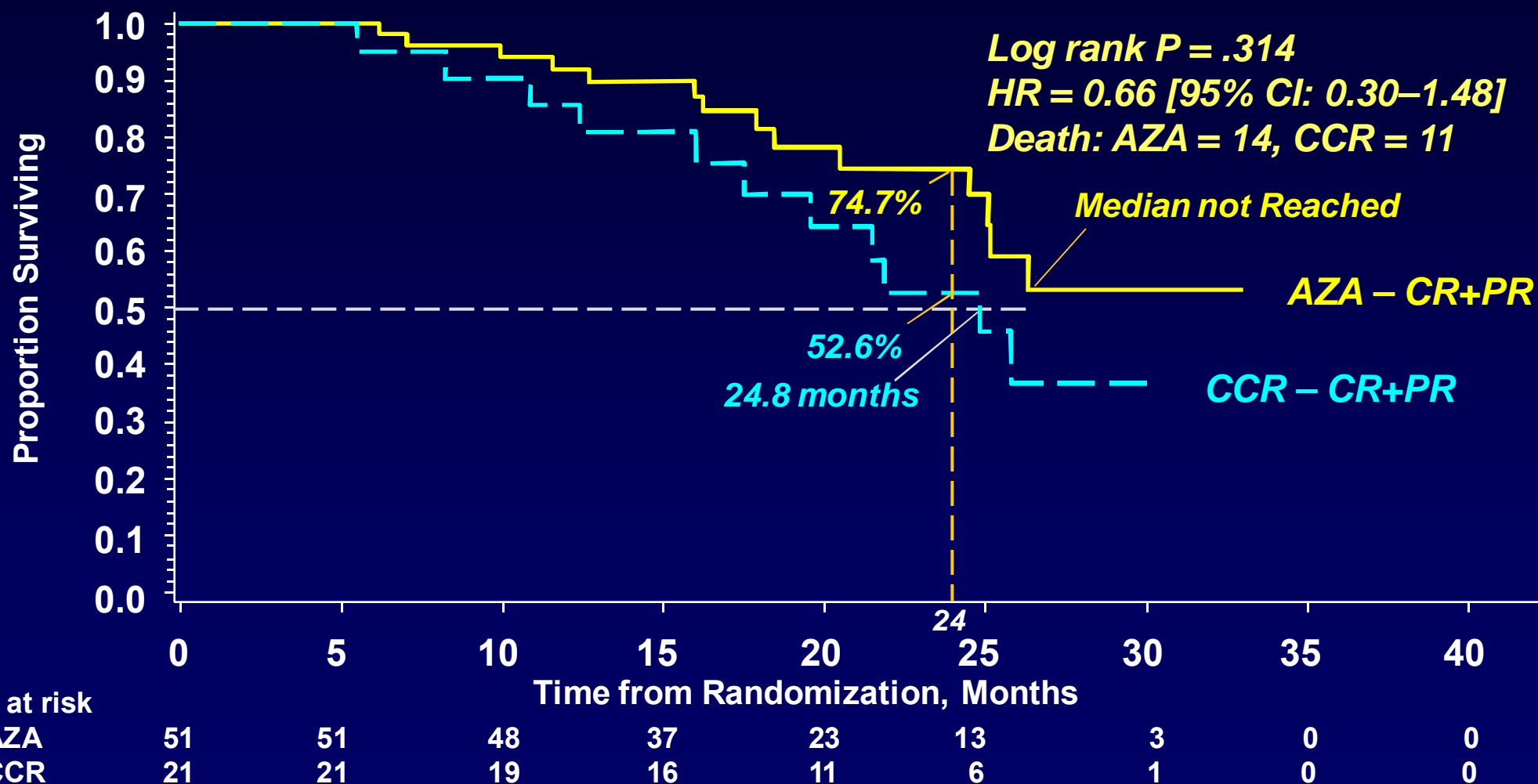
Log-Rank $P = .0001$
HR = 0.58 [95% CI: 0.43–0.77]
Deaths: AZA = 82, CCR = 113
Difference: 9.4 months
Median AZA cycles: 9 (1-39)



Overall Survival with AZA by Best Response (IWG 2000)

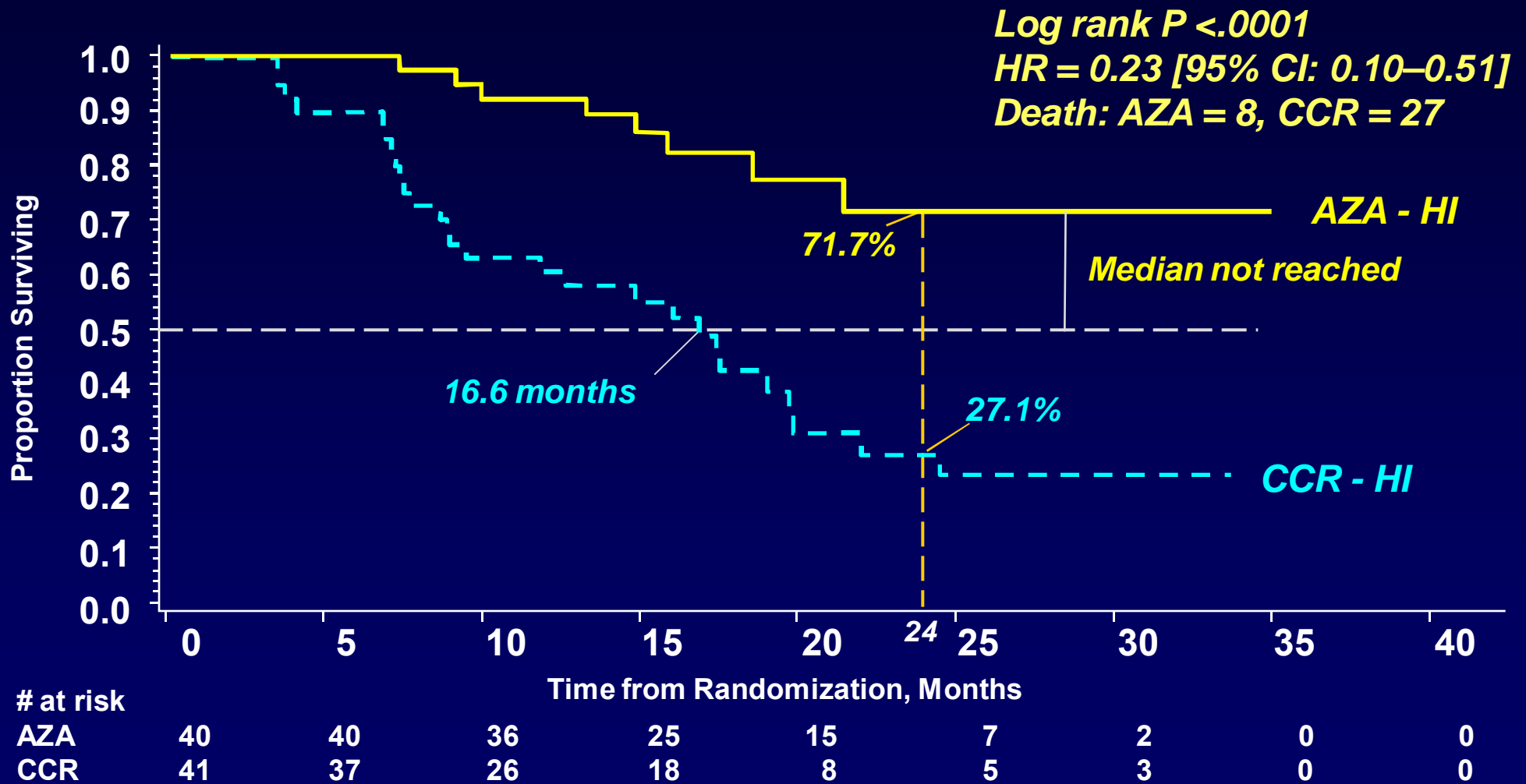


AZA vs CCR: Overall Survival in Patients with Best Response of CR + PR



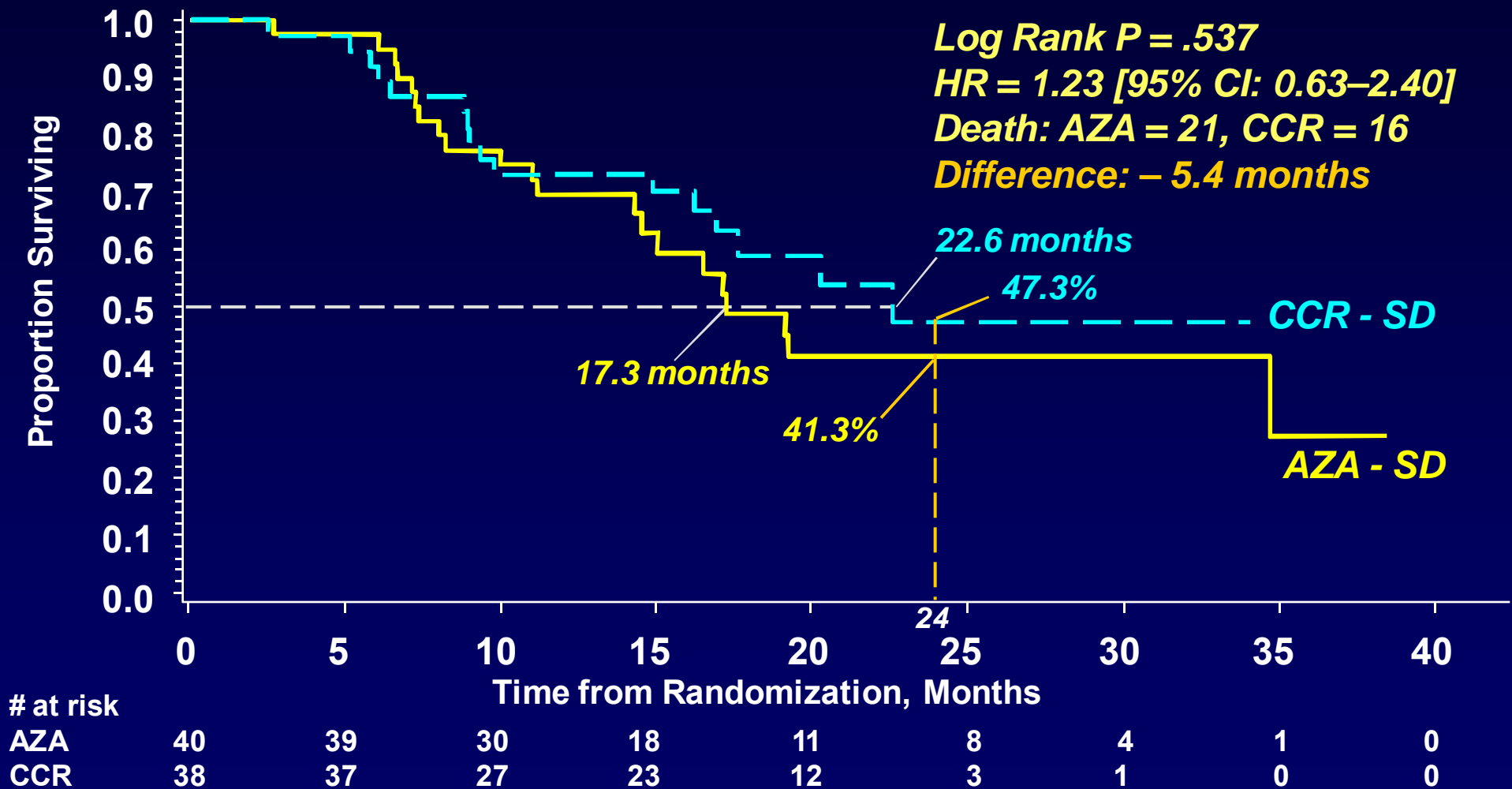
Fenaux P, et al. *Blood*. 2007;110: Abstract 817.

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

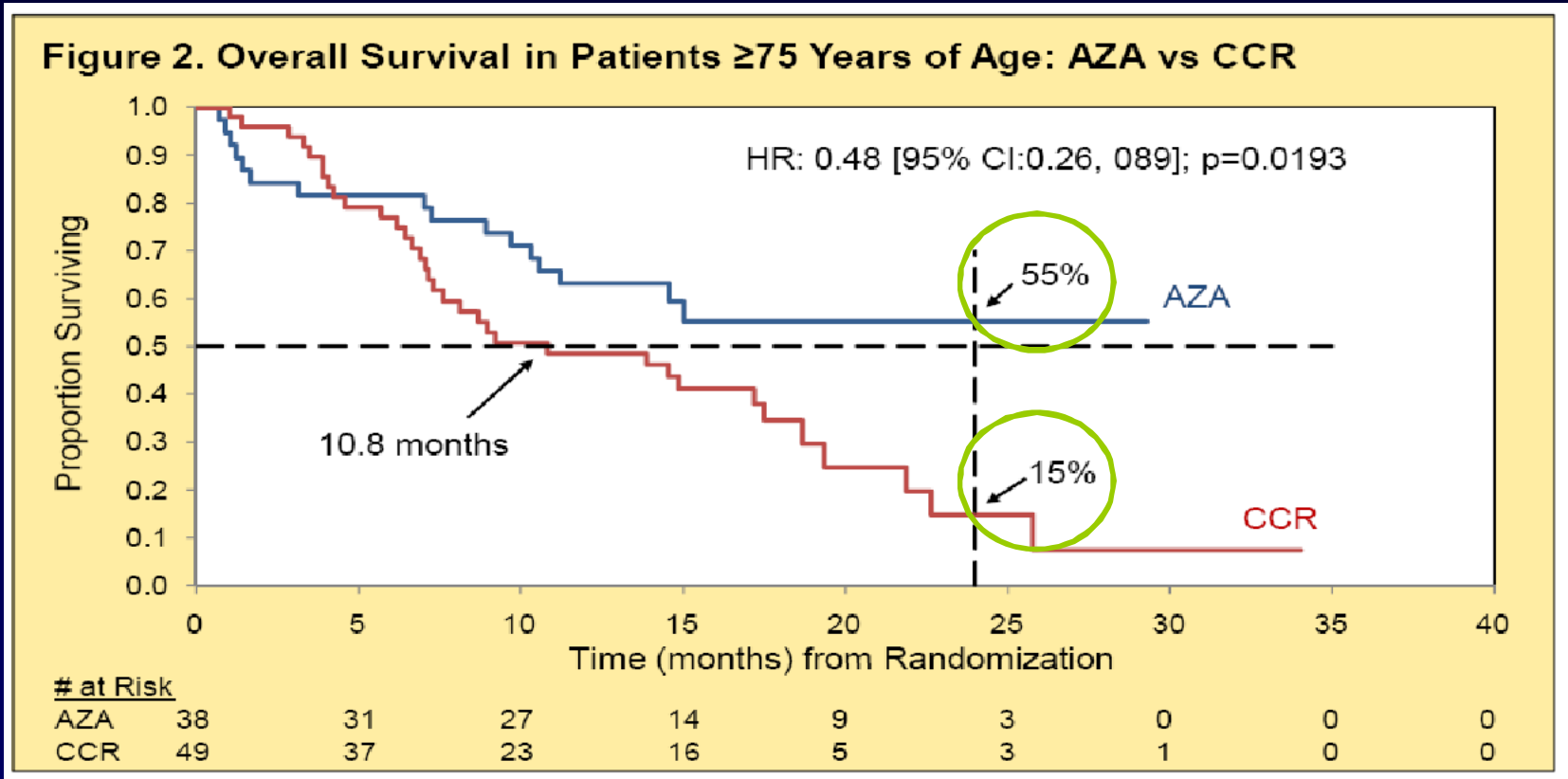


Fenaux P, et al. *Blood*. 2007;110: Abstract 817.

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



Azacitidine in MDS Patients (Aged ≥ 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%, $P = .0003$

Seymour JF, et al. *Blood*. 2008;112: Abstract 3629.

Azacitidine in MDS Patients (Aged ≥ 75 Years)

Demographic and Disease Characteristics at Baseline

	Azacitidine (n = 38)	CCR (n = 49)
Age, years		
Median (range)	78.0 (75-83)	77.0 (75-88)
Gender, n (%)		
Male	27 (71.1)	31 (63.3)
IPSS, n (%)		
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)
ECOG status, n (%)		
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 ≥ 75 Years)

Treatment Cycles

	Azacitidine (N = 299 cycles)	CCR (N = 64 cycles)
≤ 28 days		
N cycles (%)	151 (51)	25 (39)
Median (range)	28 (21-28)	28 (27-28)
29-35 days		
N cycles (%)	79 (26)	26 (41)
Median (range)	33 (29-35)	24 (29-35)
>35 days		
N cycles (%)	69 (23)	13 (20)
Median (range)	42 (36-100)	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 ≥75 Years)

Demographic and Disease Characteristics at Baseline

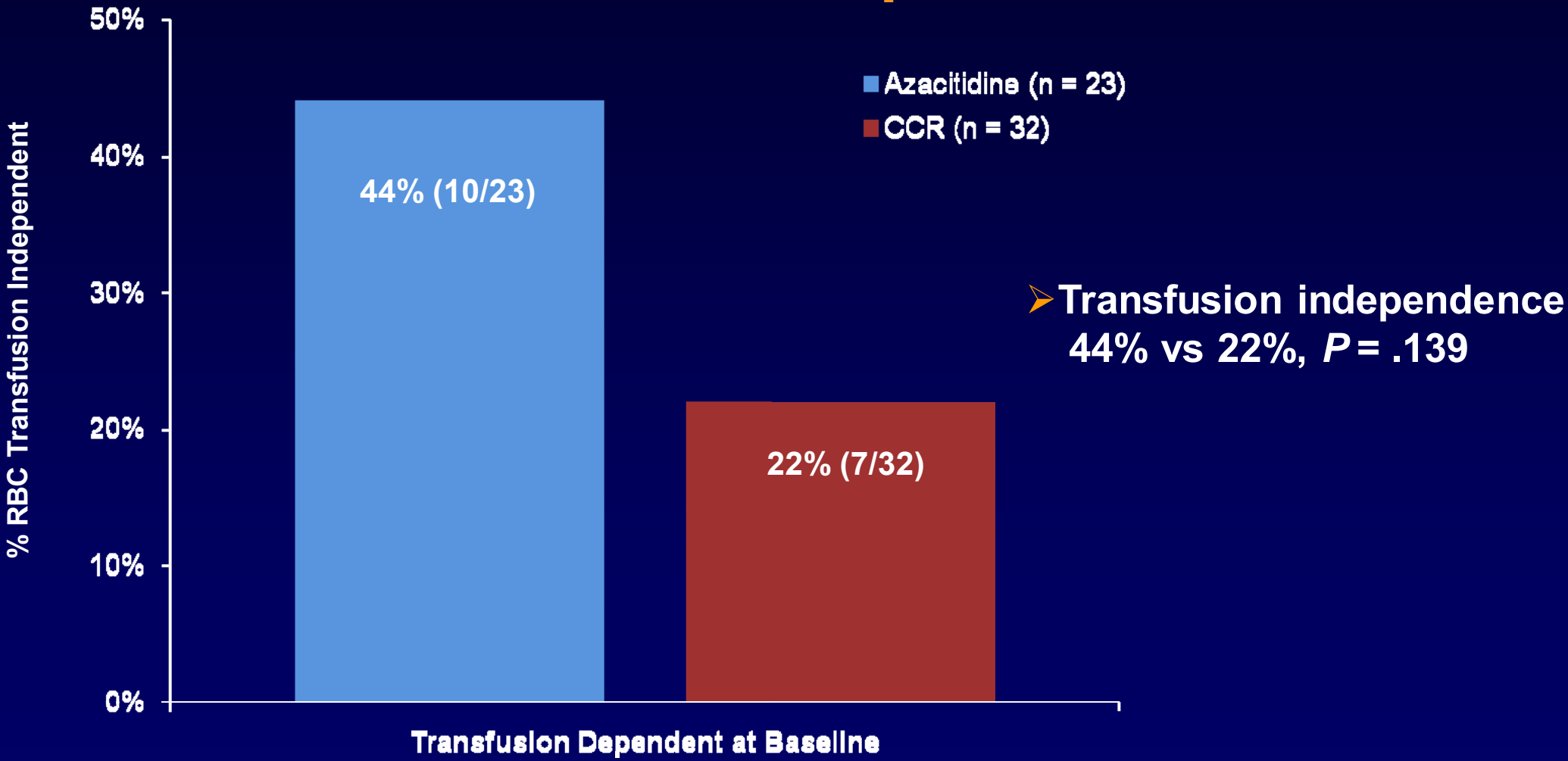
	Azacitidine (n = 38)	CCR (n = 49)
Age, years		
Median (range)	78.0 (75-83)	77.0 (75-88)
Gender, n (%)		
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Median (range)	42 (36-100)	40 (36-65)

- *More than ¾ of elderly patients tolerated AZA in cycles of 4-5 weeks*
- *AZA well tolerated (Interruption for AEs 13% AZA vs 8% CCR)*

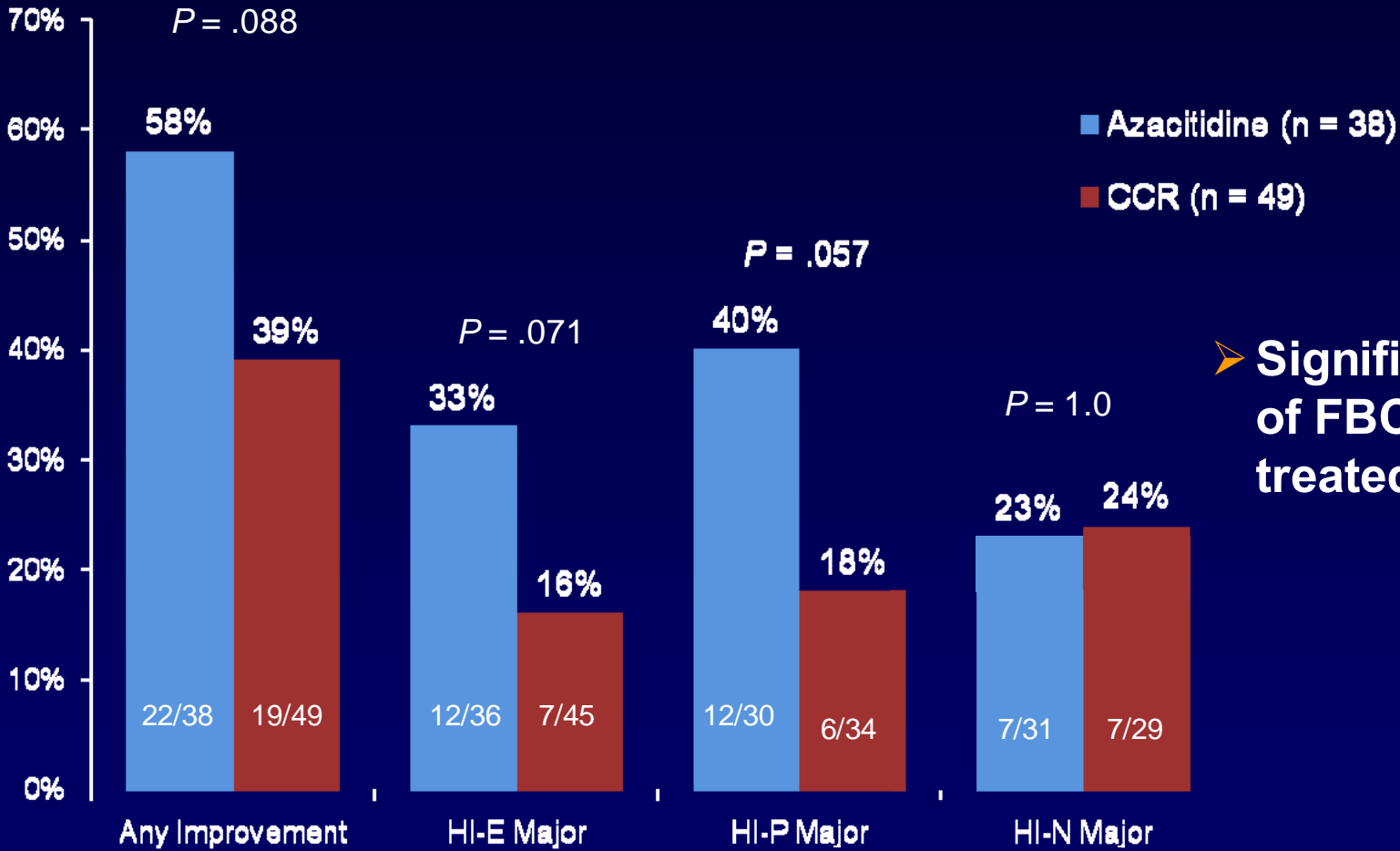
Azacitidine in MDS Patients (Aged ≥ 75 Years) Transfusion Independence



Seymour JF, et al. *Blood*. 2008;112: Abstract 3629.

Azacitidine in MDS Patients (Aged ≥ 75 Years)

IWG 2000 Hematologic Improvement

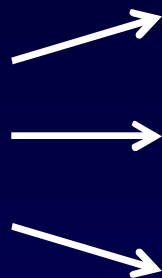


➤ Significant improvement of FBC in 58% of patients treated with AZA

Seymour JF, et al. *Blood*. 2008;112: Abstract 3629.

Low-Dose Decitabine in Intermediate Risk, High Risk, or Noncategorized MDS

IPSS INT-2 or high-risk MDS, secondary MDS, or CMML + leukocytosis (n = 124)



Decitabine 20 mg/m ² IV over 1 hour daily for 5 days q 4 weeks* (n = 93)
Decitabine 20 mg/m ² SQ daily for 5 days q 4 weeks* (n = 14)
Decitabine 10 mg/m ² IV over 1 hour daily for 10 days q 4 weeks* (n = 17)

* Or until progressive disease

Outcome	5-Day IV (n = 93)	10-Day IV (n = 17)	5-Day SQ (n = 14)
Overall response, %	72	78	70
CR, %	39	24	21
PR, %	1	0	7
mCR, %	14	18	7
mCR + HI, %	8	24	21
HI, %	10	12	14
Median overall survival, months	19	24	16

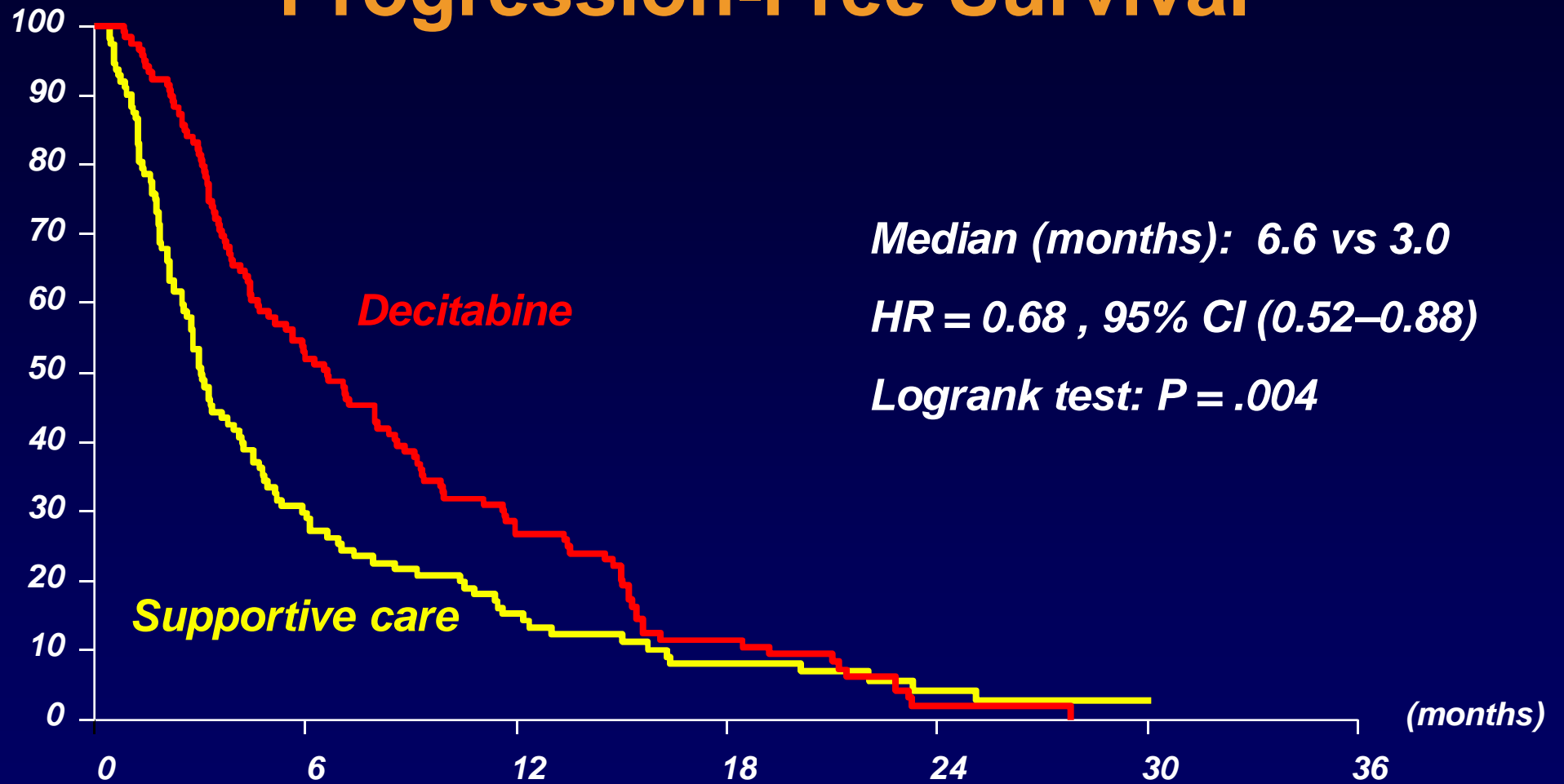
Phase II Study of Decitabine 20 mg/m² IV Administered Daily for 5 Days q 4 Weeks

ITT Preliminary Response Data (n = 99)

IWG 2006 Criteria	ITT (n=99), %
CR	17
mCR	15
PR	0
HI	18
SD	24

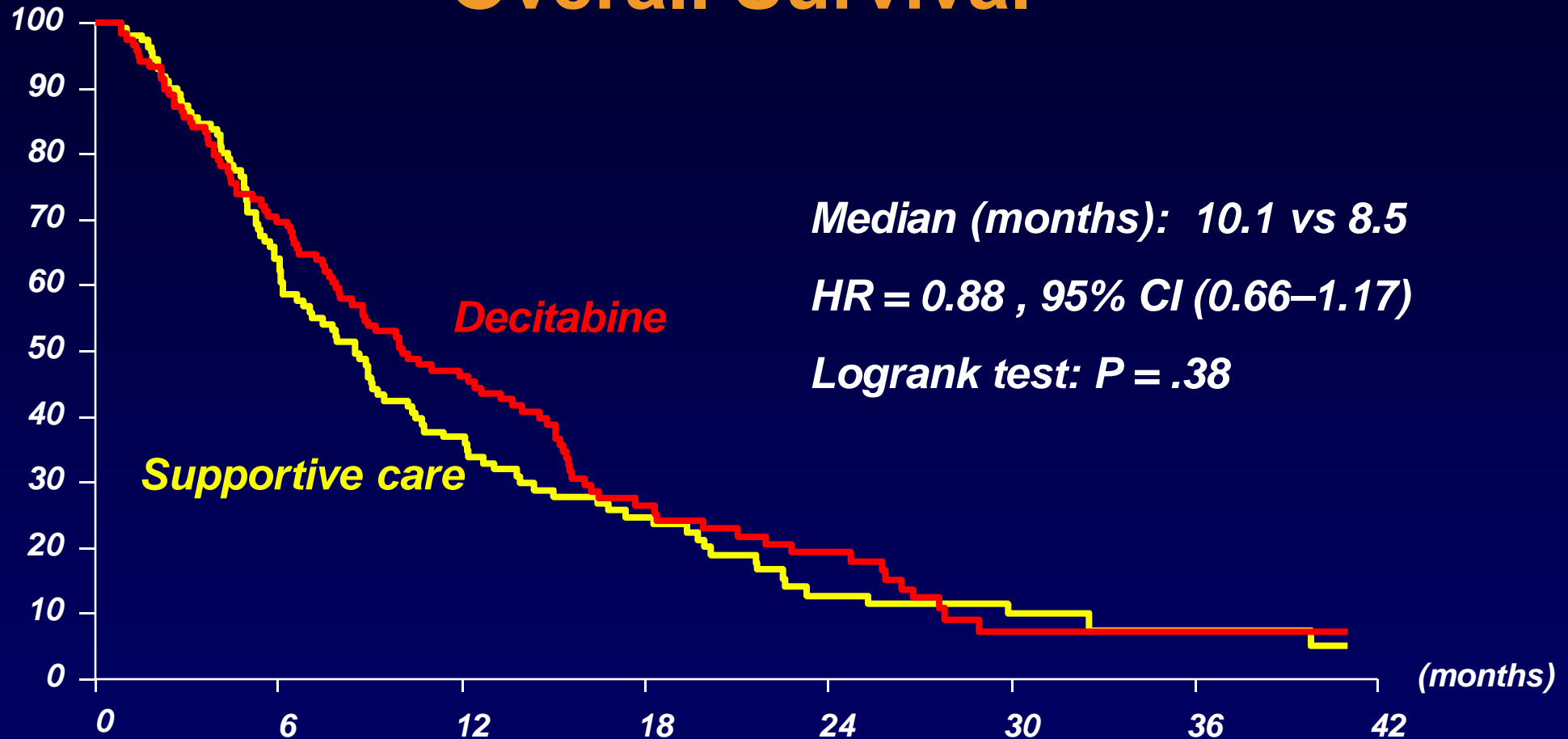
- Time to improvement in patients with clinical improvement (\geq HI) was rapid: 82% by cycle 2
- \geq Grade 3 adverse events: neutropenia 37%; thrombocytopenia 22%; anemia 21%; febrile neutropenia 17%; and pancytopenia 5%

Progression-Free Survival



O	N	Number of patients at risk :					
105	114	33	15	7	3	1	Supportive care
113	119	62	32	11	2	0	Decitabine

Overall Survival



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

Therapeutic Options in "MDS"

