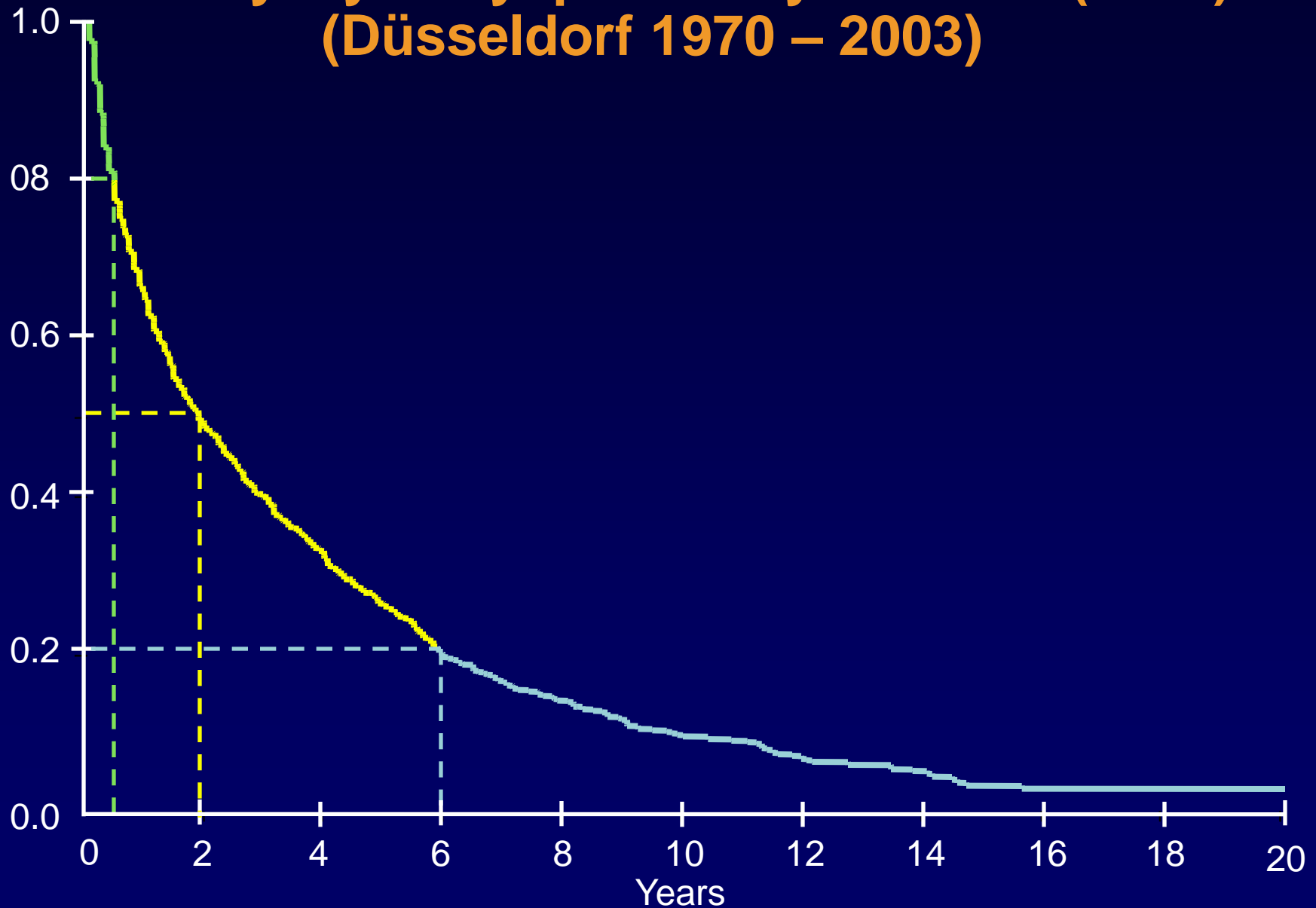


# Case #6 — Low-Risk Myelodysplastic Syndromes



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

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



# International Risk Score

	Points				
	0	0.5	1	1.5	2.0
BM blasts, %	0-4	5-10	-	11-20	21-29
No. of cytopenias <sup>1</sup>	0-1	2-3	-	-	-
Cytogenetic category <sup>2</sup>	Low	Int	High		

Risk Groups	Score
Low	0
Intermediate I	0.5 - 1
Intermediate II	1.5 - 2
High	≥2.5

<sup>1</sup>Platelets < 100,000/μL, hemoglobin <10 g/dL, neutrophils <1800/μL

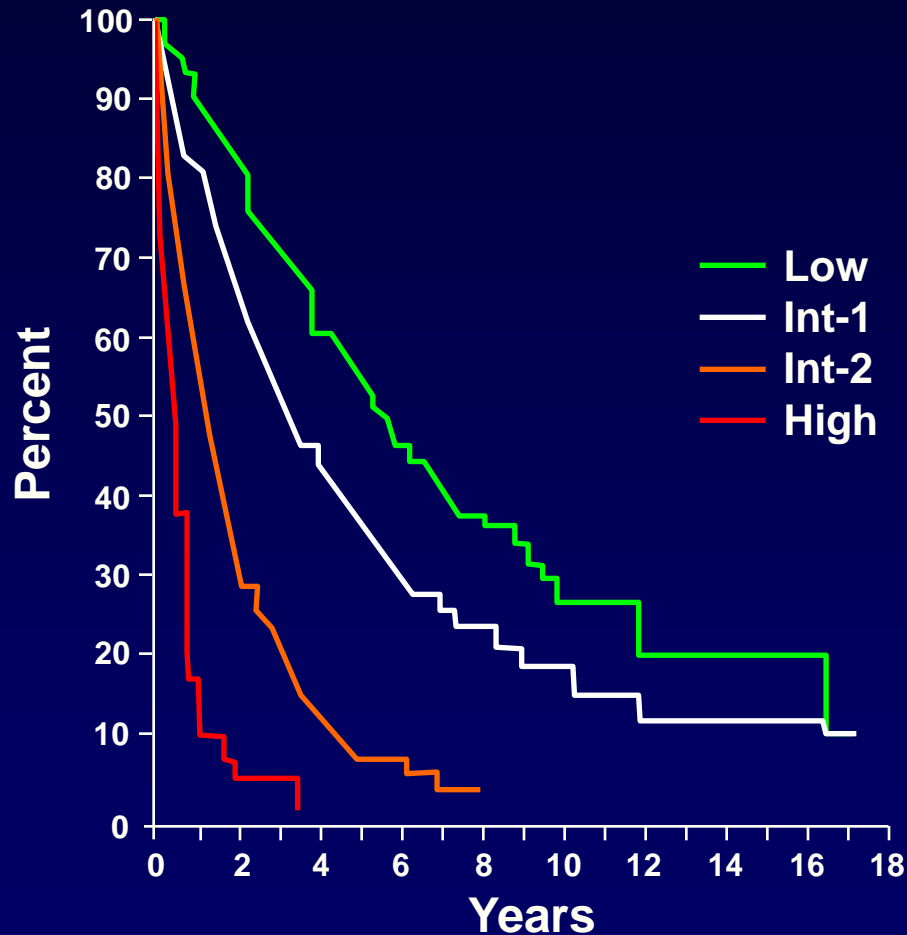
<sup>2</sup>Low = Normal, 5q-, 20q-, -Y

Intermediate = Other anomalies

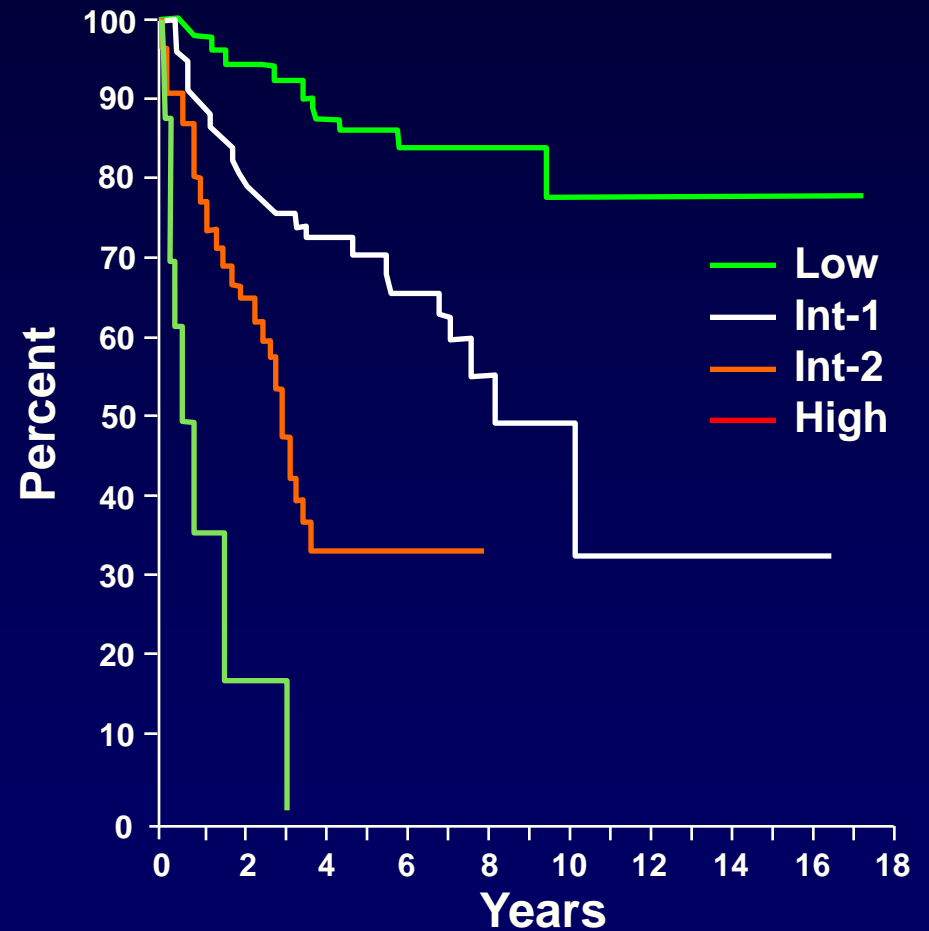
High = Complex (≥3 abnormalities), chromosome 7 anomalies

# International MDS Risk Classification

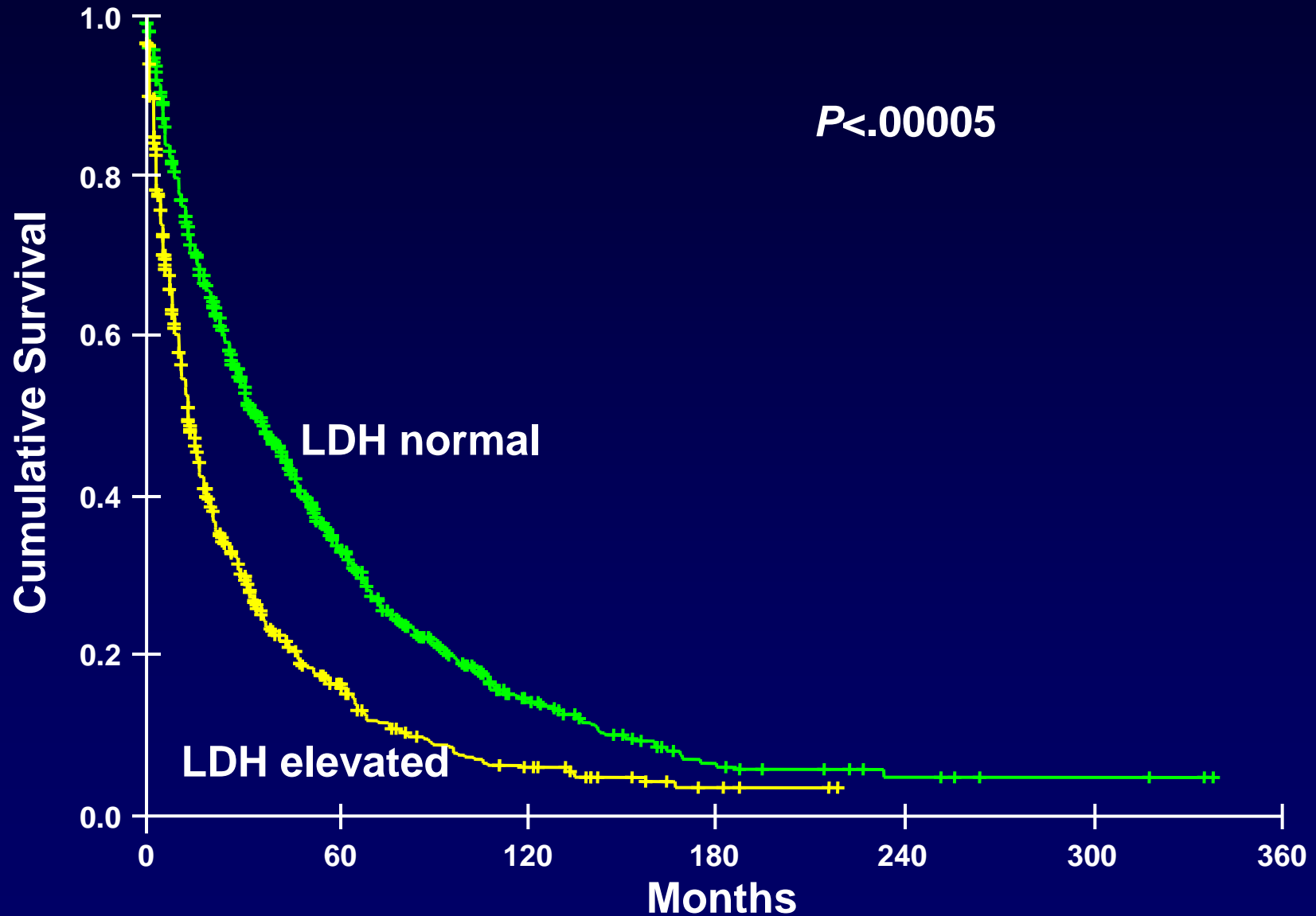
## Survival



## AML Evolution



# Prognostic Implications of LDH in MDS

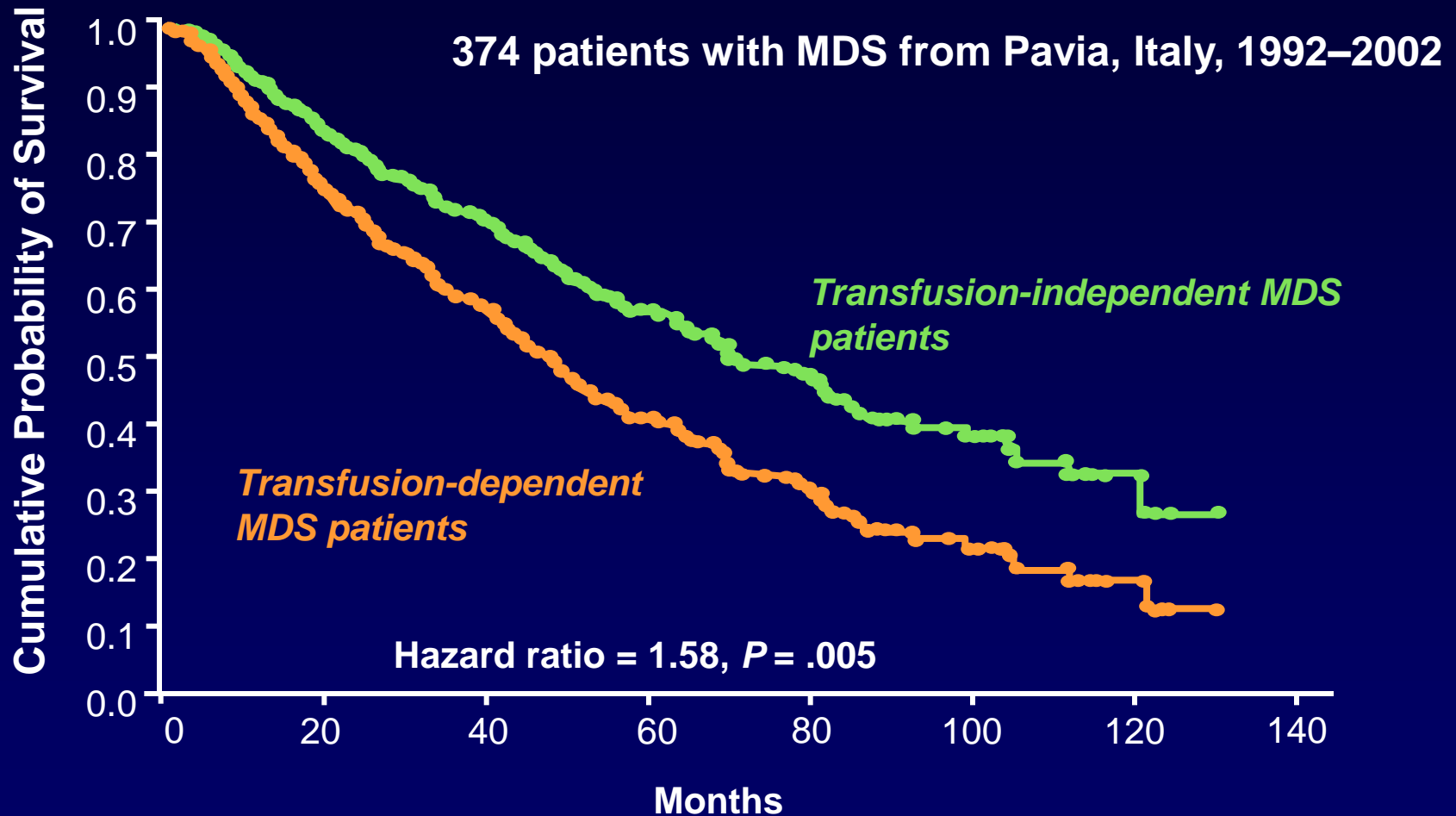


# Impact of Addition of LDH to the IPSS

IPSS	n	MS	LDH	n	MS	P Value
Low	263	88	Normal	209	107	.0011
			Elevated	52	63	
Int-1	295	55	Normal	180	66	.0006
			Elevated	108	36	
Int-2	153	23	Normal	92	26	.01
			Elevated	59	16	
High	181	13	Normal	92	16	.01
			Elevated	87	11	

MS, median survival

# Survival of MDS Patients According to Transfusion Dependence

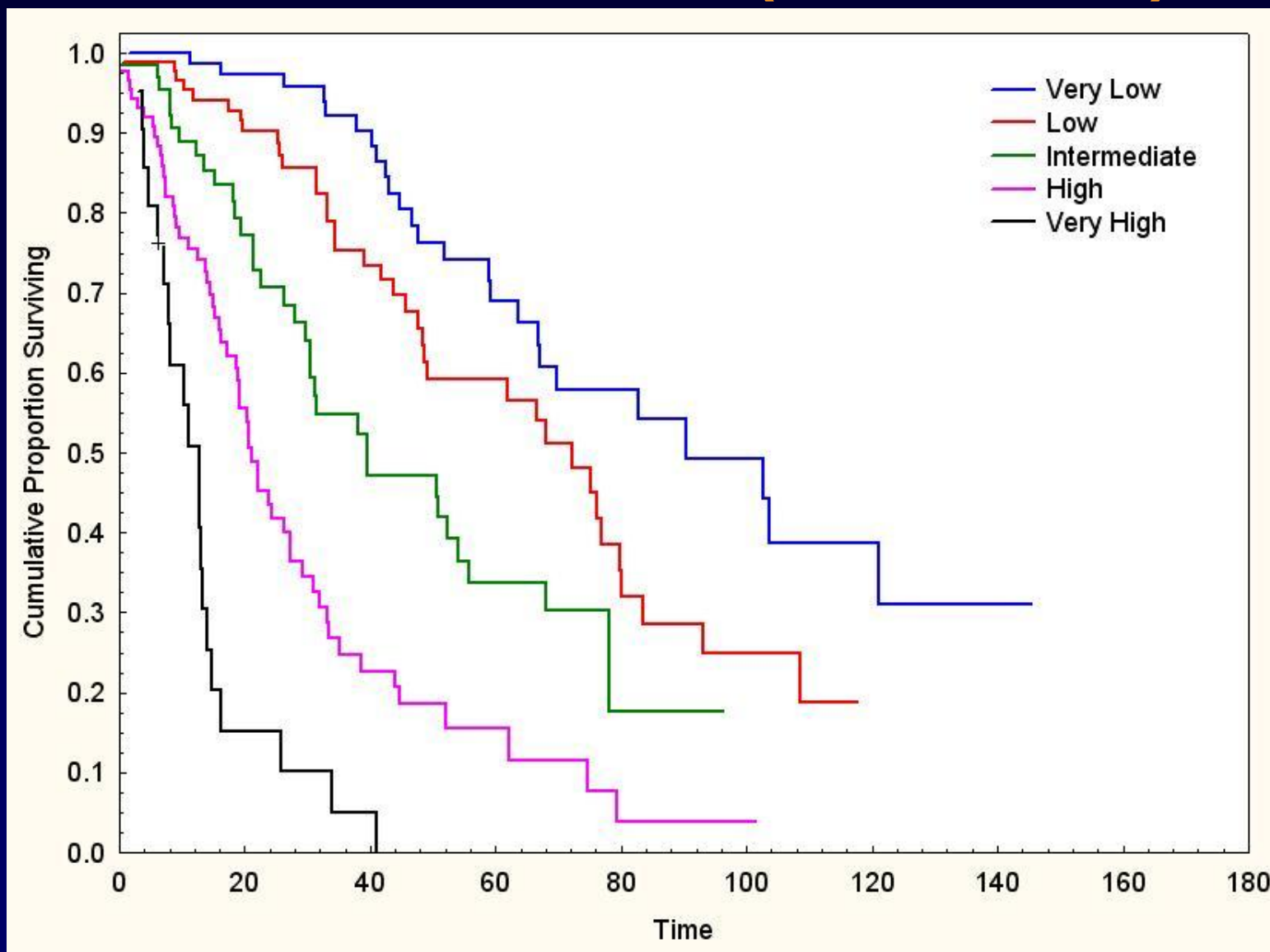


# A WHO-Based Prognostic Scoring System

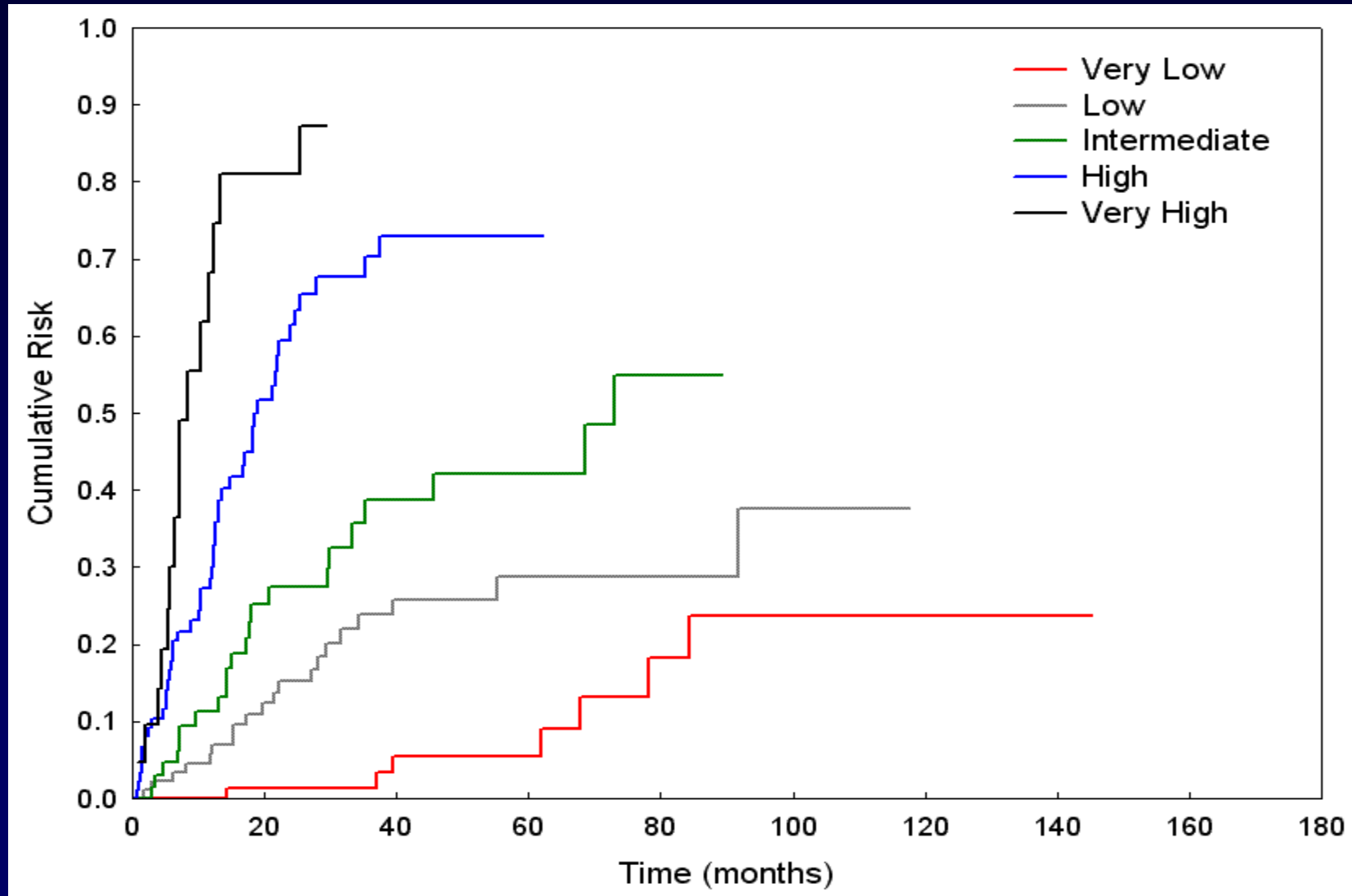
	Point			
	0	1	2	3
WHO subtype	RA, RARS 5q-	RCMD RCMD-RS	RAEB-I	RAEB-II
Transfusion requirement	None	Regular	-	-
Cytogenetic category	Low	Intermediate	High	

Risk Groups	Score
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

# A WHO-Based Prognostic Scoring System: Overall Survival (in Months)



# A WHO-Based Prognostic Scoring System: AML Evolution



# Treatment Options in Myelodysplastic Syndromes

Risk stratification according to IPSS

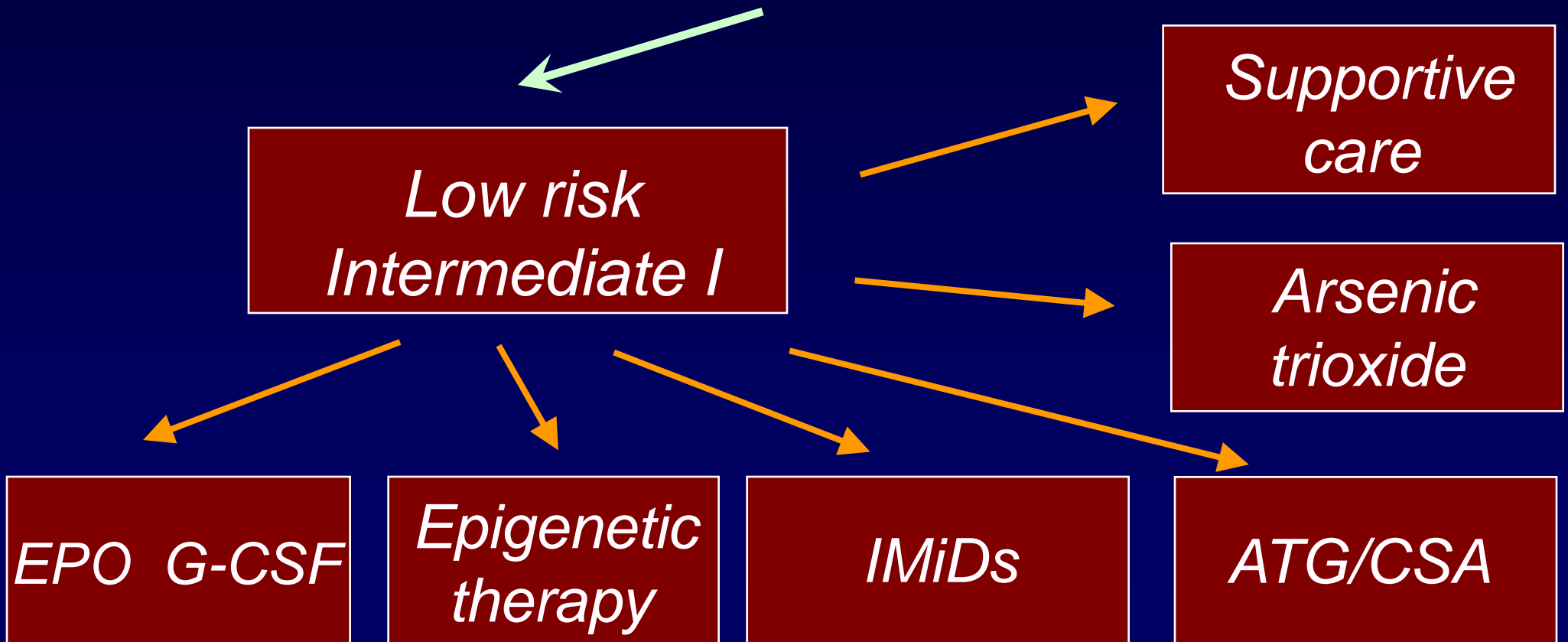
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graph TD; A[Risk stratification according to IPSS] --> B[Low risk Intermediate I]; A --> C[Intermediate II High risk];
```

Low risk  
Intermediate I

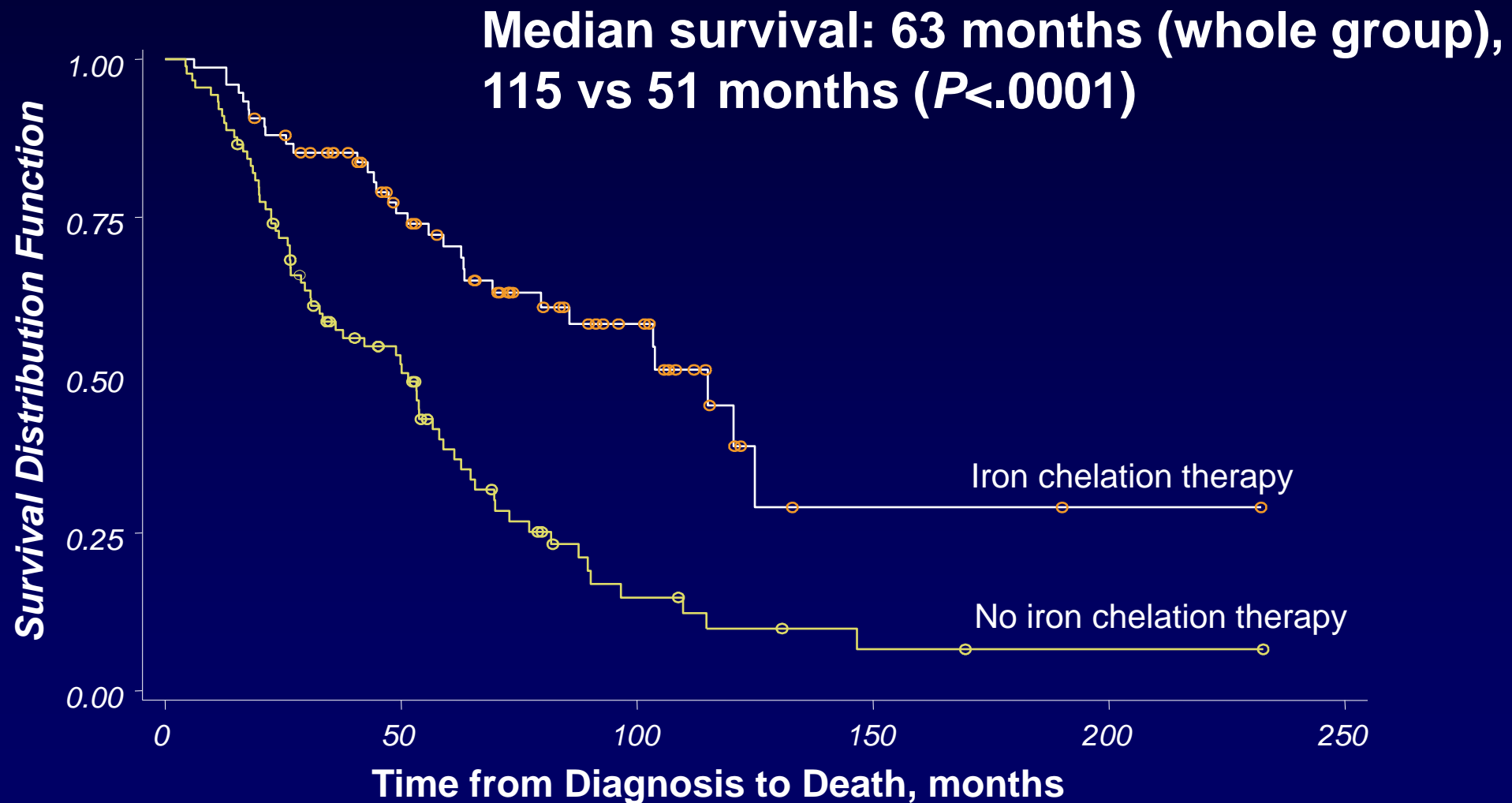
Intermediate II  
High risk

# Therapeutic Options for Myelodysplastic Syndromes

*Risk stratification according to IPSS*



# Results of Iron Chelation in Low-Risk MDS



# Prognostic Score for the Use of EPO + G-CSF in MDS

Variable	Value	Score	Value	Score
Transfusion requirement*	<2 U/month	0	≥2 U/month	1
Serum EPO*	< 500 U/L	0	≥500 U/L	1

\* Pretherapeutic levels

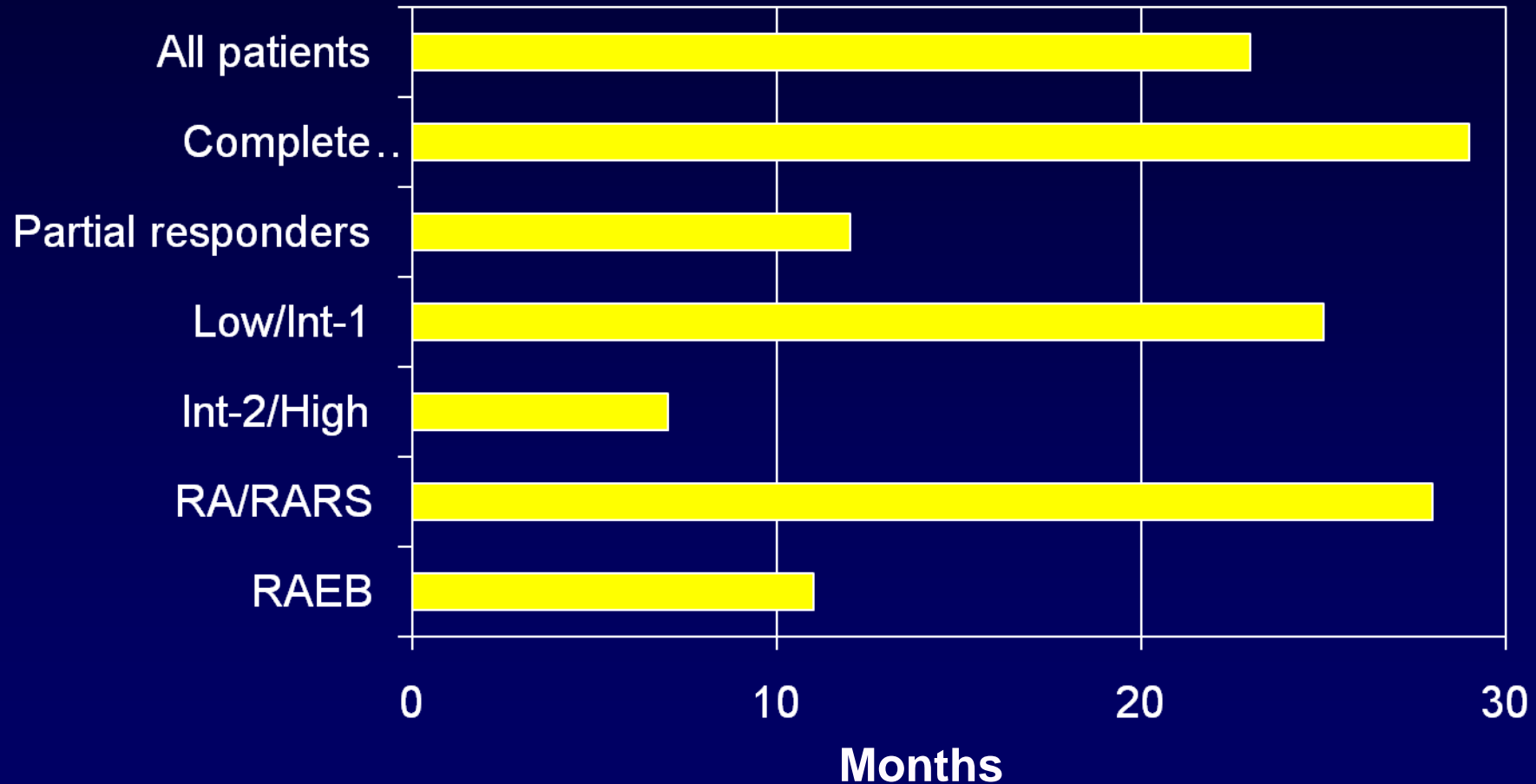
## Predicted Response

**Score = 0: 74%**

**Score 1: 23%**

**Score 2: 7%**

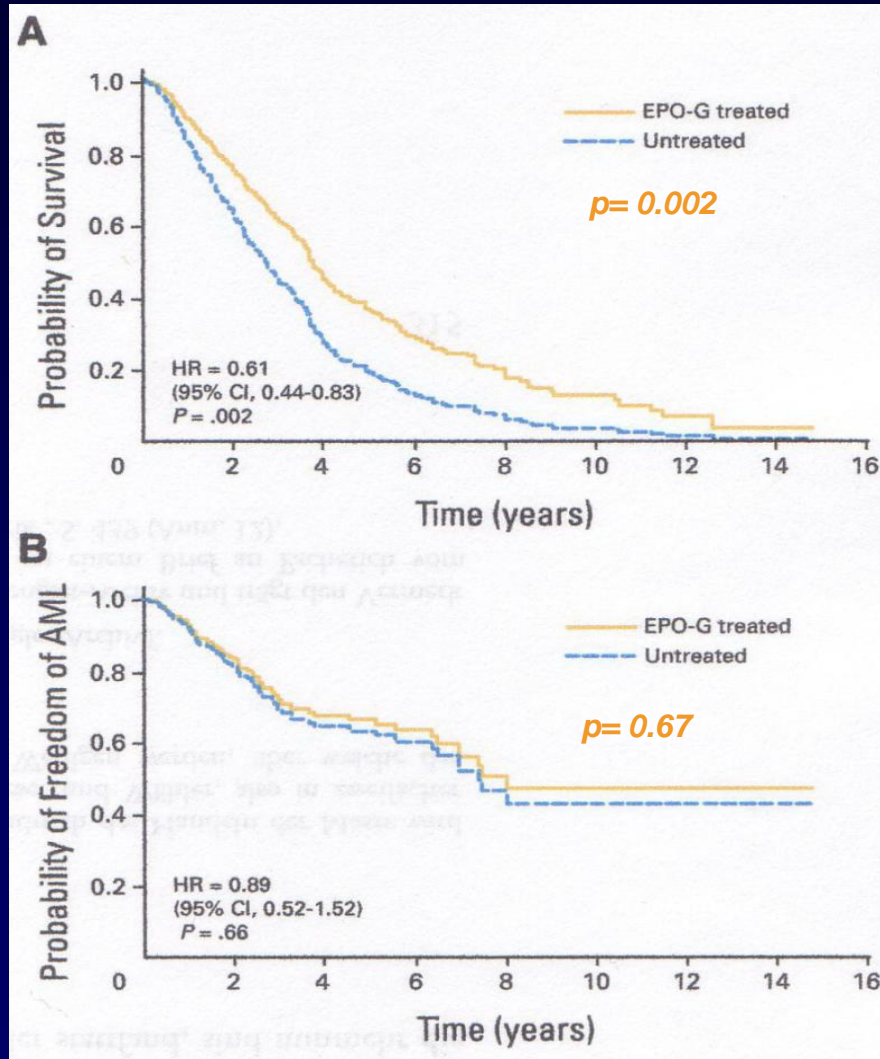
# Median Duration of Response to EPO plus G-CSF in 129 Patients with MDS



# Erythropoietin in MDS +/- G-CSF

	<b>French Patients n = 284</b>	<b>IPSS-Patients n = 225</b>	<b>P Value</b>
<b>5-year Overall survival</b>	<b>64%</b>	<b>39%</b>	<b>&lt;.001</b>
<b>5-year AML-transformation</b>	<b>12%</b>	<b>13%</b>	<b>.21</b>

# Erythropoietin in MDS + G-CSF

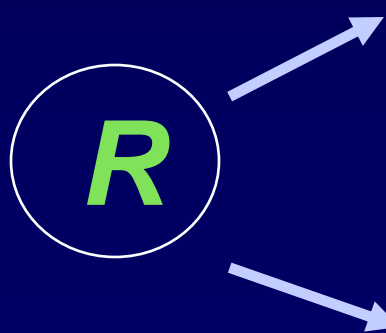


EPO + G-CSF, n= 121

Untreated patients, n = 237

# SAKK-Swiss Group for Clinical Cancer Research German MDS Study Group (SAKK 33/99)

- *Inclusion criteria:*
- *Hypoplastic MDS*
- *MDS subtype RA, RARS und RAEB with  $\leq 10\%$  blasts*
- *Transfusions dependence <24 months*
- *ECOG performance score  $\leq 2$*
- *Age >18 years*



*Arm A:*

*ATG 15 mg/kg/d IV days 1-5*

*CSA 2.5 mg/kg PO bid days 1-180*

*Arm B:*

*Best supportive care*

# ATG/CsA in MDS—Randomized Study Survival After 6 Months

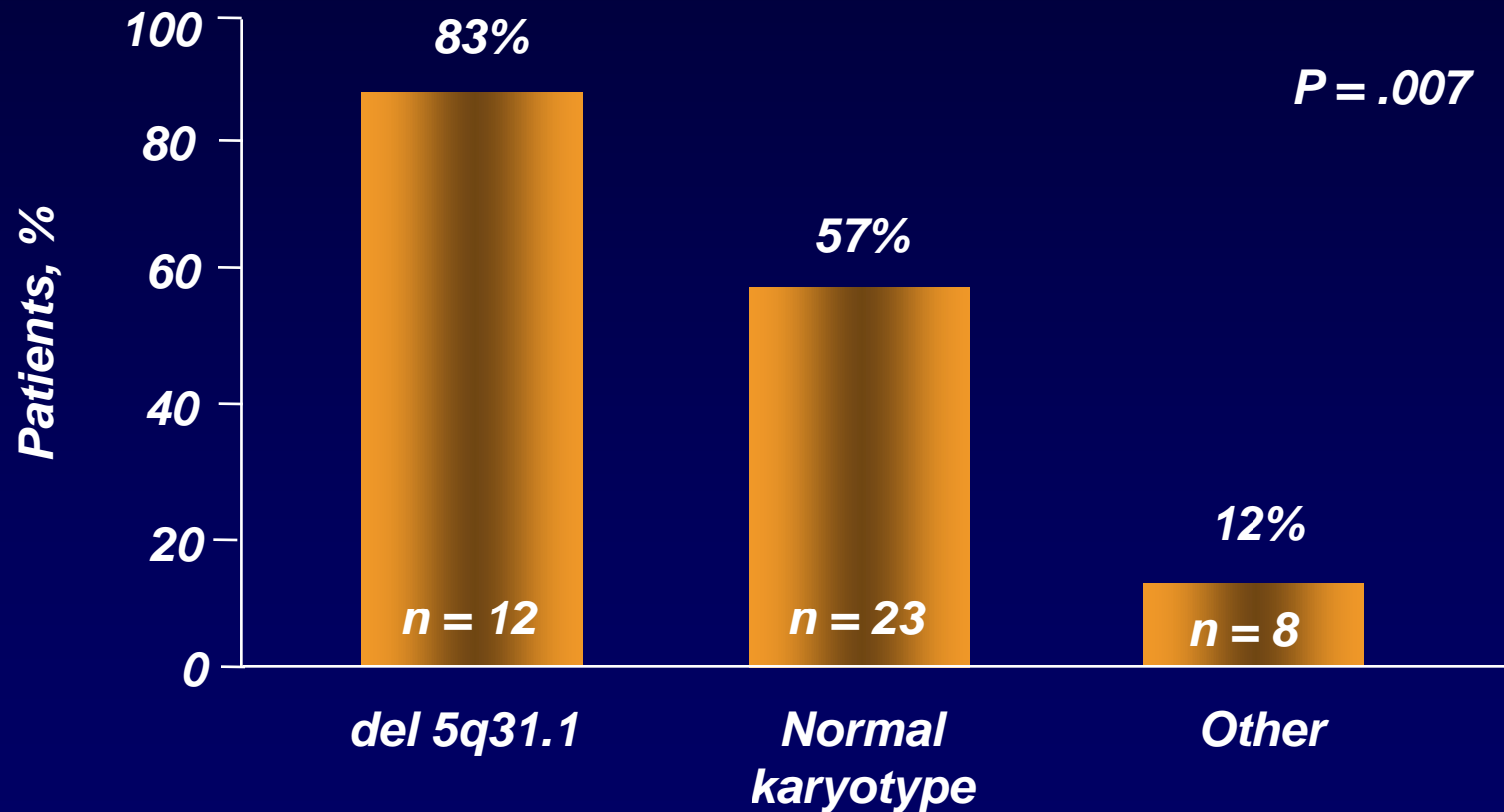
Parameter	ATG	BSC
Patient number	45	43
Hematologic response		
CR + PR (%)	13 (29)	4 (9) ( <i>P</i> = .016)
Median duration of response	16.4 months	
Transformation-free survival	46%	55% ( <i>P</i> = .73)
Overall survival (2 years)	49%	63% ( <i>P</i> = .83)

# Predictive Factors for ATG

- Low-risk MDS
- Hypoplastic MDS, pancytopenia
- Age < 60 years
- Duration of transfusion dependence < 2 years
- HLA-DR15
- Normal karyotype

Age (years) + Duration of Transfusions (months)		
DR 15-	DR15+	Probability
>57	>71	Low (0% to 40%)
≤57	≤71	High (87% to 100%)

# Erythroid Response to Lenalidomide by Karyotype



# Erythroid Response (ITT) in del 5q MDS

Feature	Total
<b>N</b>	<b>148</b>
<b>Erythroid response, n (%) [CI]</b>	
<b>TI</b>	<b>99 (67) [58-74]</b>
<b>Minor (&gt;50% ↓)</b>	<b>14 (9)</b>
<b>TI + minor</b>	<b>113 (76) [68-83]</b>
<b>Time to response, weeks</b>	
<b>Median</b>	<b>4.6</b>
<b>Range</b>	<b>3.6–5.3</b>

*TI = transfusion independent*

# Lenalidomide in del(5q) Response (TI) Characterization

<b>Variable</b>	<b>Median Value [range]</b>
<b>Maximum Hgb (g/dL)</b>	
Baseline	7.8 [5.3-10.4]
Lenalidomide	13.4 [9.2-18.6]
<b>Median Hgb↑</b>	5.3 g/dl [1.1-11.4]
<b>Transfusion-Indep.</b>	
Week 24	97
Sustained (3-31-05)	71 (73%)

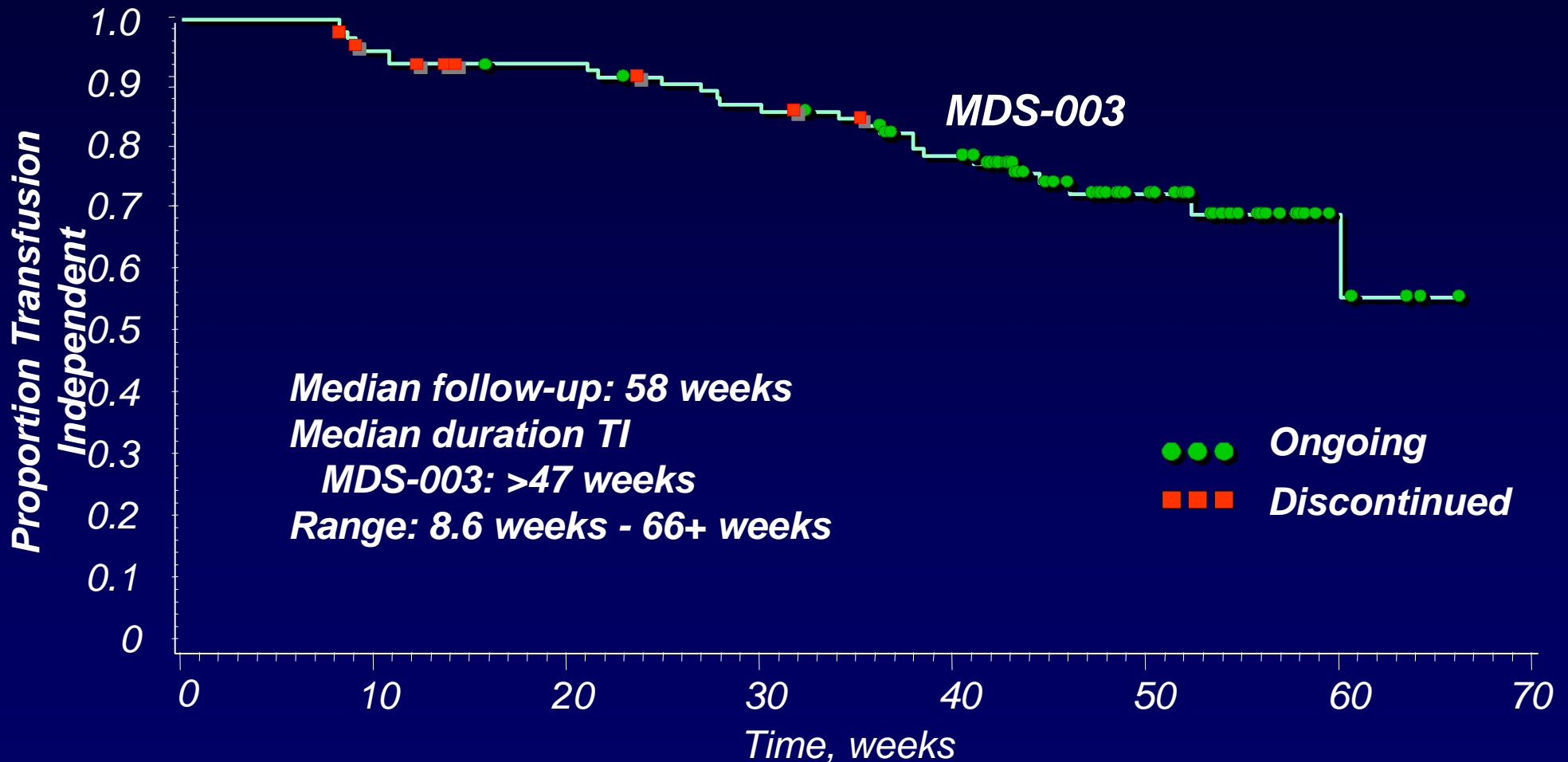
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# Cytogenetic Response in del5q MDS

	Patients, N*	Patients, n (%)	
		CR + PR	CR
Eligible patients	85	62 (73)	38 (44)
Baseline cytogenetics			
Isolated del 5q	64	49 (77)	29 (45)
5q- syndrome	28	22 (79)	14 (50)
del 5q + 1	15	10 (67)	6 (40)
Complex ( $\geq 3$ )	6	3 (50)	3 (50)

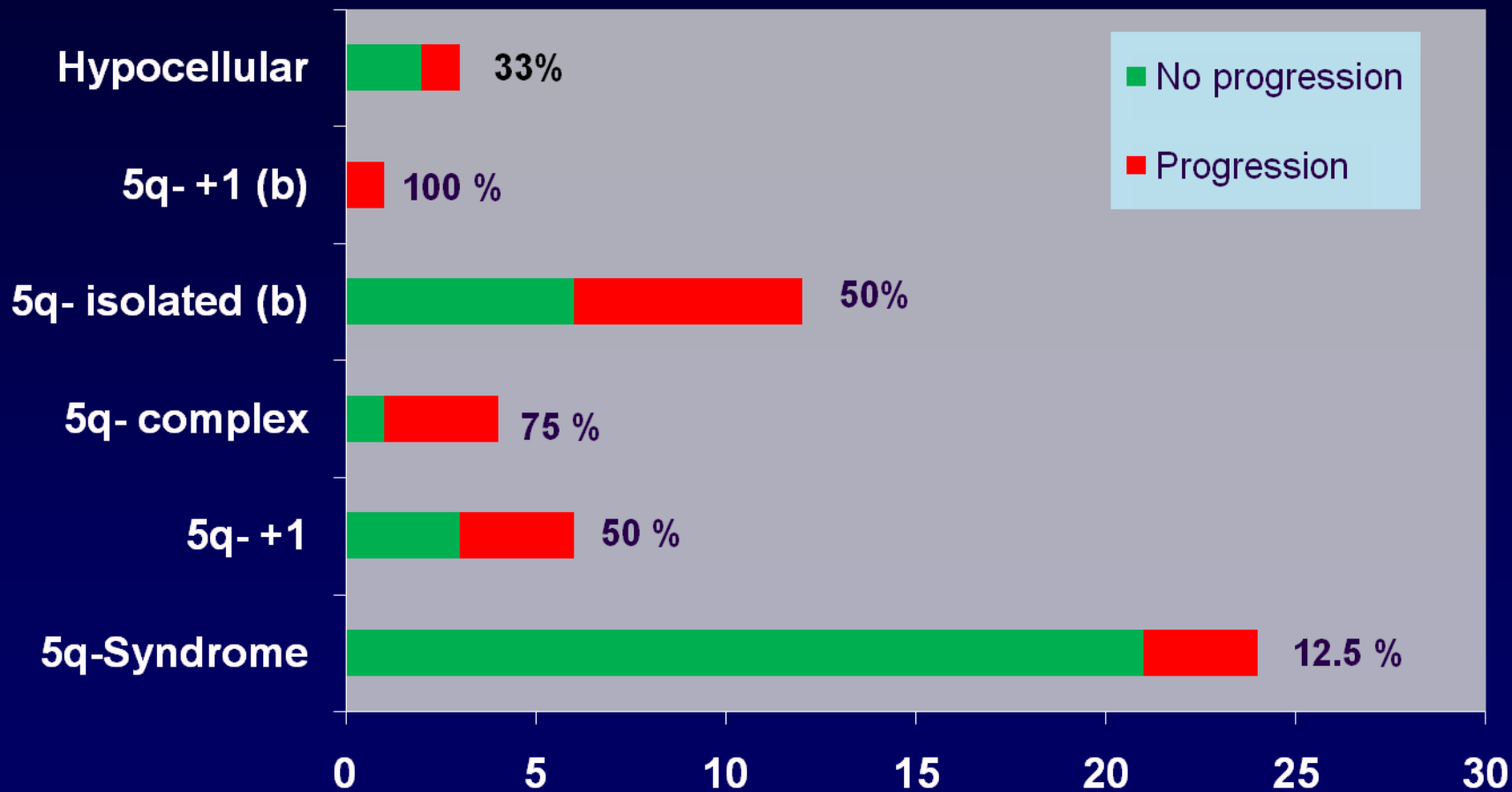
\* Evaluated patients on 20 or more metaphases at baseline and follow-up based on International Working Group (IWG) guidelines.

# Duration Transfusion-Free n = 97



Kaplan-Meier curves.

# Lenalidomide: Disease Progression

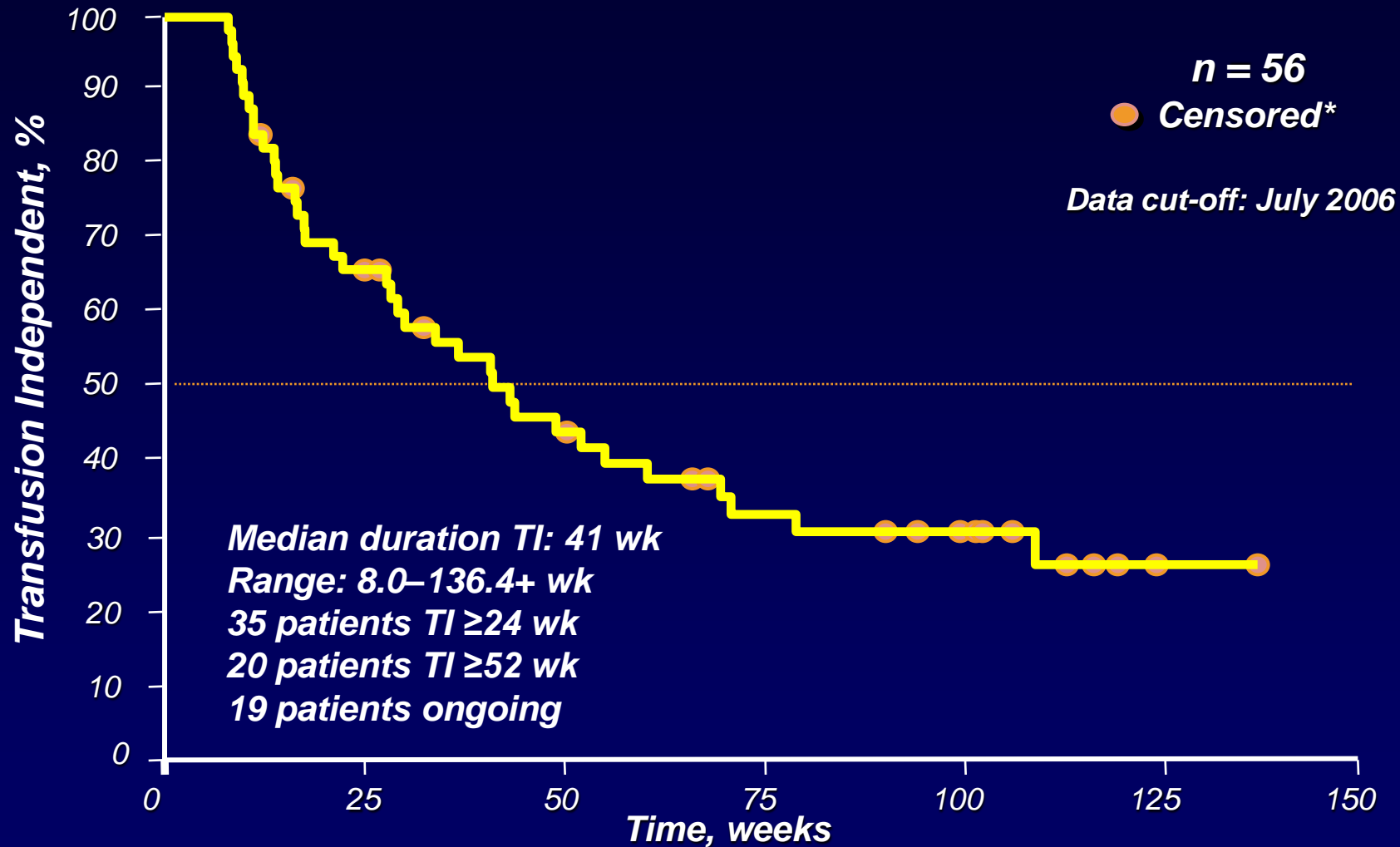


*n = 50, St. John's Hospital Duisburg; (b; patients with blasts > 5%; +1, 1 additional chromosomal abnormality to del(5q))*

# Erythroid Response (ITT) in non del 5q MDS (MDS-002)

Feature	Total
N	215
Erythroid response, n (%)	
TI	57 (27)
Minor (> 50% ↓)	36 (17)
TI + minor	93 (43)
Time to response, weeks	
Median	4.6
Range	2.9–6.7

# MDS-002: Duration of Transfusion Independence



**\*Censored patients who remain TI at time of data cut-off or at time of study discontinuation**

# Drug-Related Adverse Events

Adverse Event	All Grades, %		≥Grade 3, %	
	003	002	003	002
Thrombocytopenia	58	25	54	19
Neutropenia	57	27	55	24
Pruritus	32	21	2	1
Rash	28	22	7	4
Diarrhea	24	12	2	1
Fatigue	12	13	3	2

---

# Therapeutic Options in Low-Risk MDS

## Anemia

Transfusions  
± iron chelation  
(Ferritin  $\geq 1000\mu\text{g/l}$ )

del 5q: Lenalidomide  
Epo < 500: Epo ± G-CSF  
Epo < 500+ RS > 15%: Epo + G-CSF  
Epo > 500 { Valproic acid  
Lenalidomide  
ATG/CSA  
Clinical studies

## Thrombocytopenia

Transfusions  
± protease inhibitors

ATG/CSA  
Danazol  
Valproic acid  
Clinical studies:  
Romiplostim  
Eltrombopag

## Neutropenia

Early antimicrobial intervention  
Pneumovax-/HiB  
G-CSF