

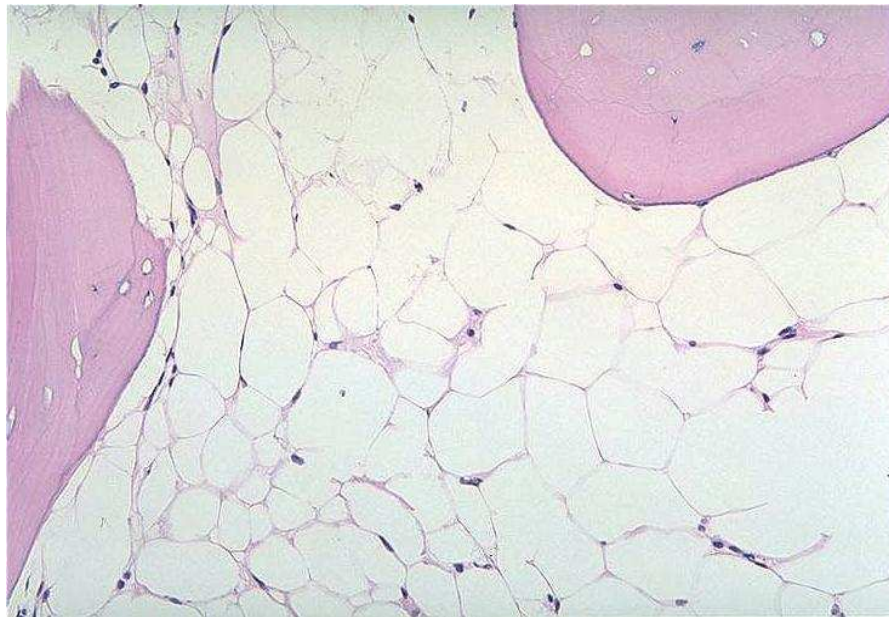
# Therapy in patients with Severe Aplastic Anemia

André Tichelli

# Definition of aplastic anemia and severity of the disease

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- Pancytopenia
- Persistent and unexplained marrow aplasia
- Hematopoiesis replaced by fat cells



## **SAA**

at least 2/3 criteria:

ANC	< $0.5 \times 10^9/L$
Platelets	< $20 \times 10^9/L$
Reticulocytes (microsc.)	< $20 \times 10^9/L$
Reticulocytes (auto)	< $60 \times 10^9/L$

## **vSAA**

ANC	< $0.2 \times 10^9/L$
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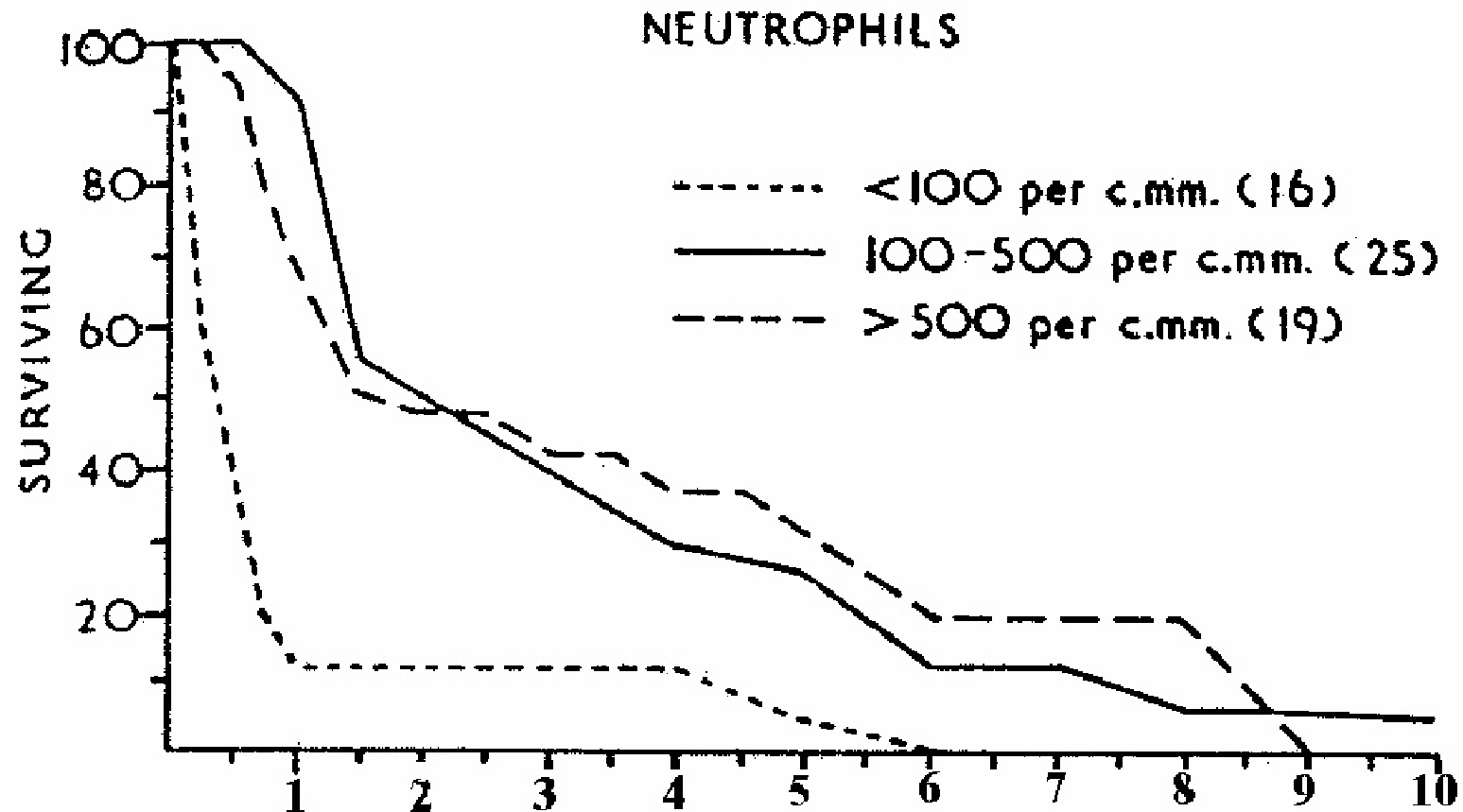
## **moderate AA**

not fulfilling criteria of SAA

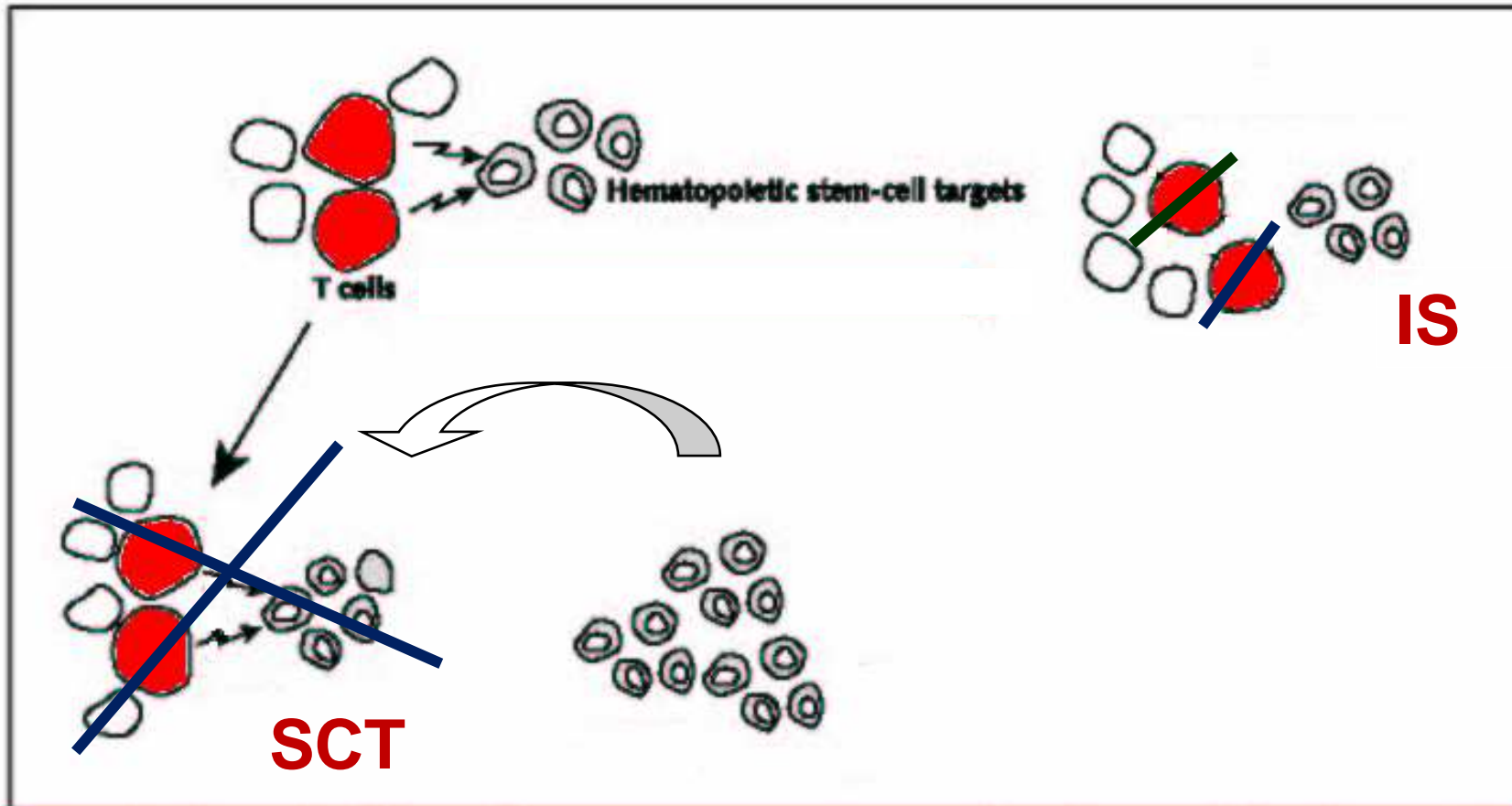
ANC	> $0.5 \times 10^9/L$
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## Untreated SAA has a poor prognosis: historical data published in 1956

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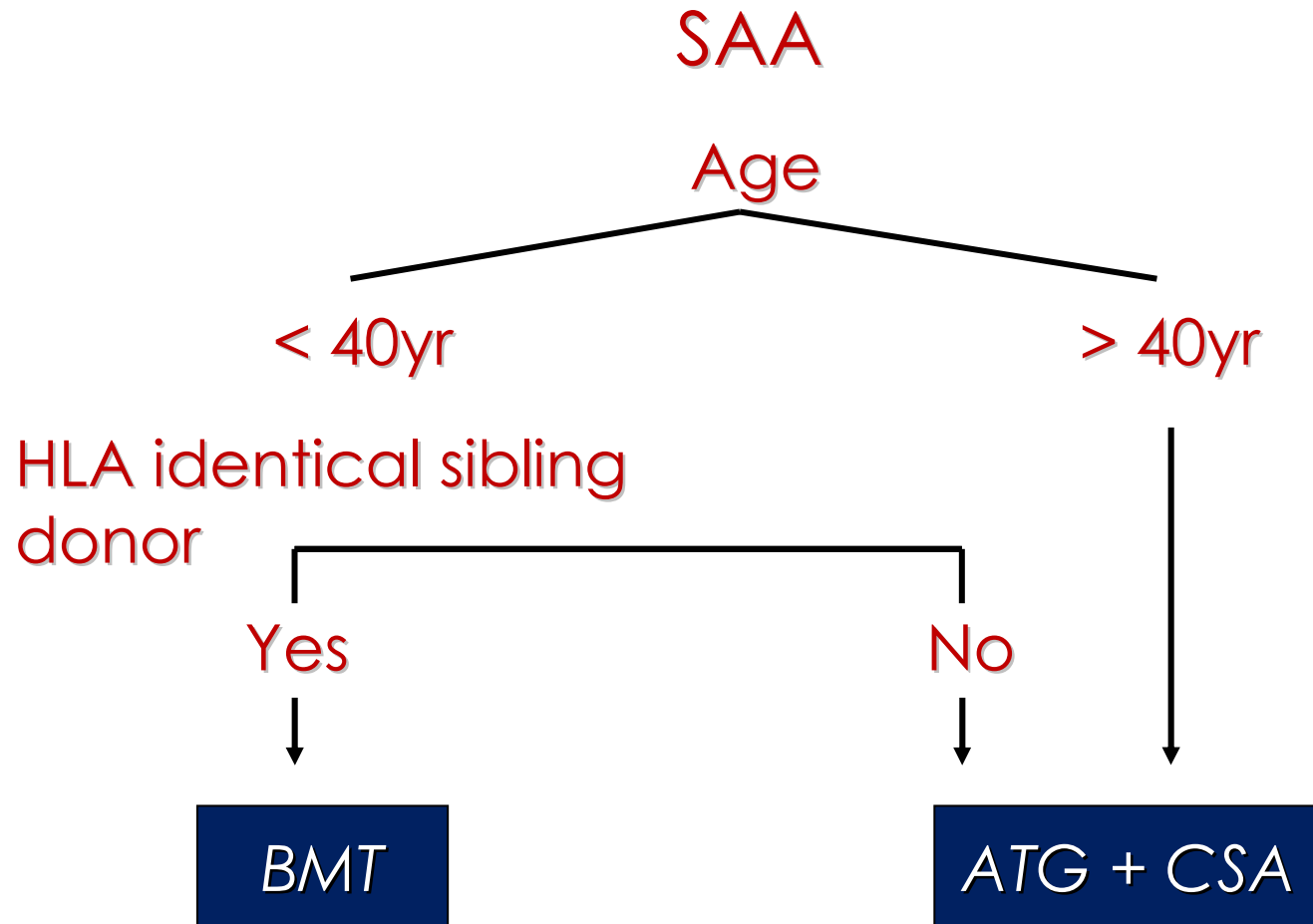


# Treatment options in aplastic anemia

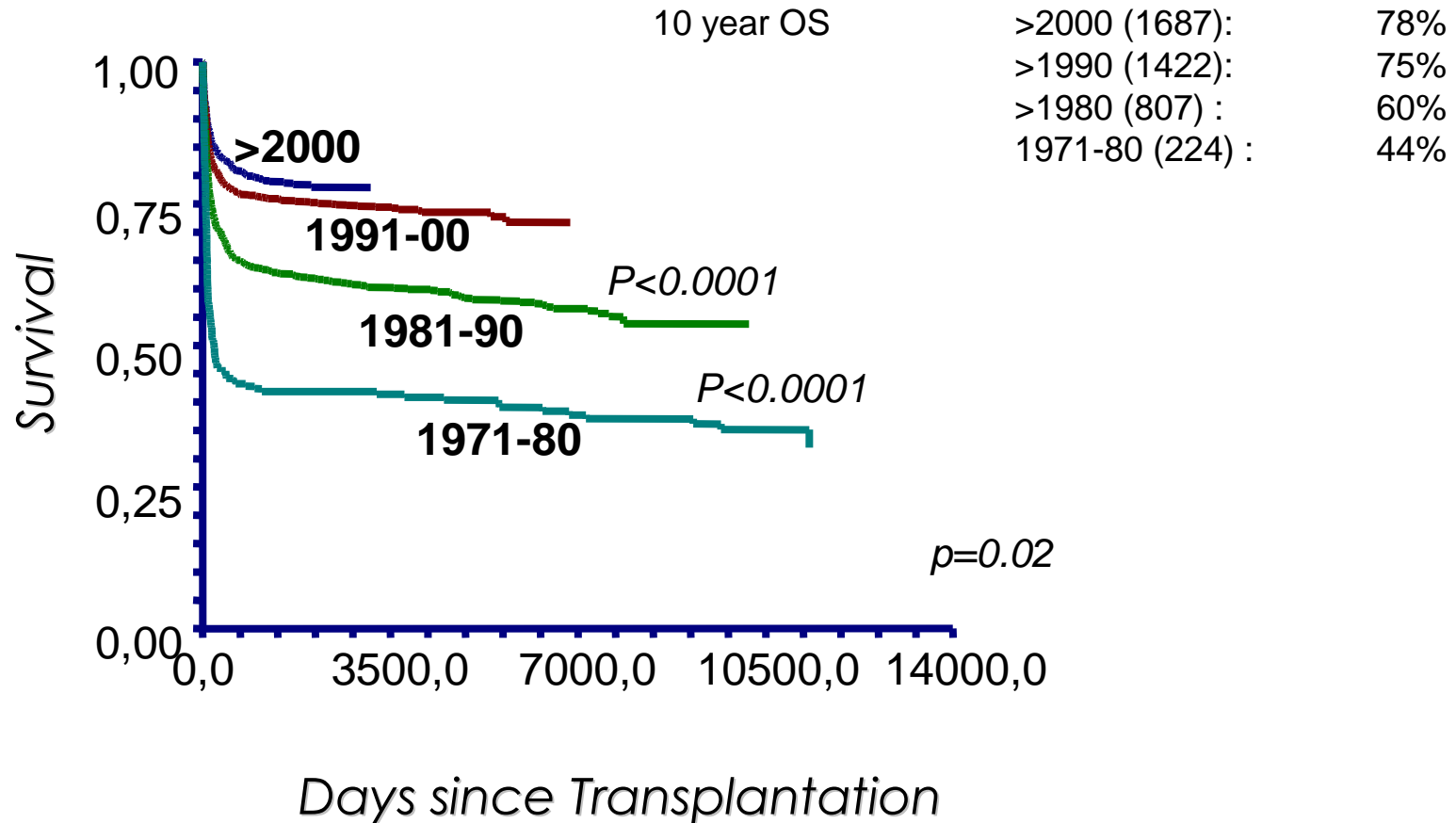


# Initial therapeutic decision

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# Improvement of survival in SAA treated with HLA-identical sibling BMT



# HLA identical sibling BMT

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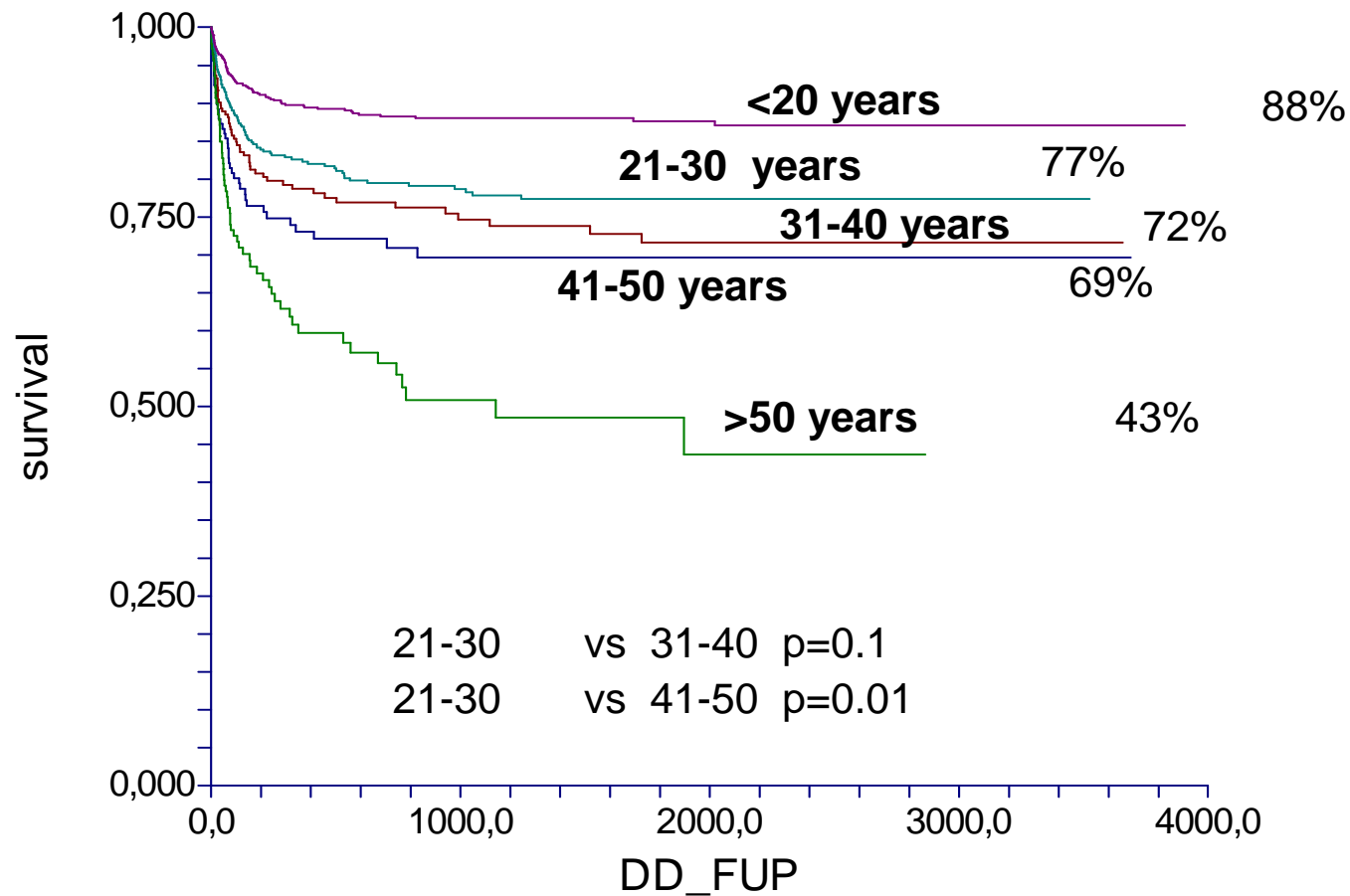
Cyclophosphamide 200mg/kg  $\pm$  ATG

Overall survival 80-90%

## *Critical barriers to improved outcome*

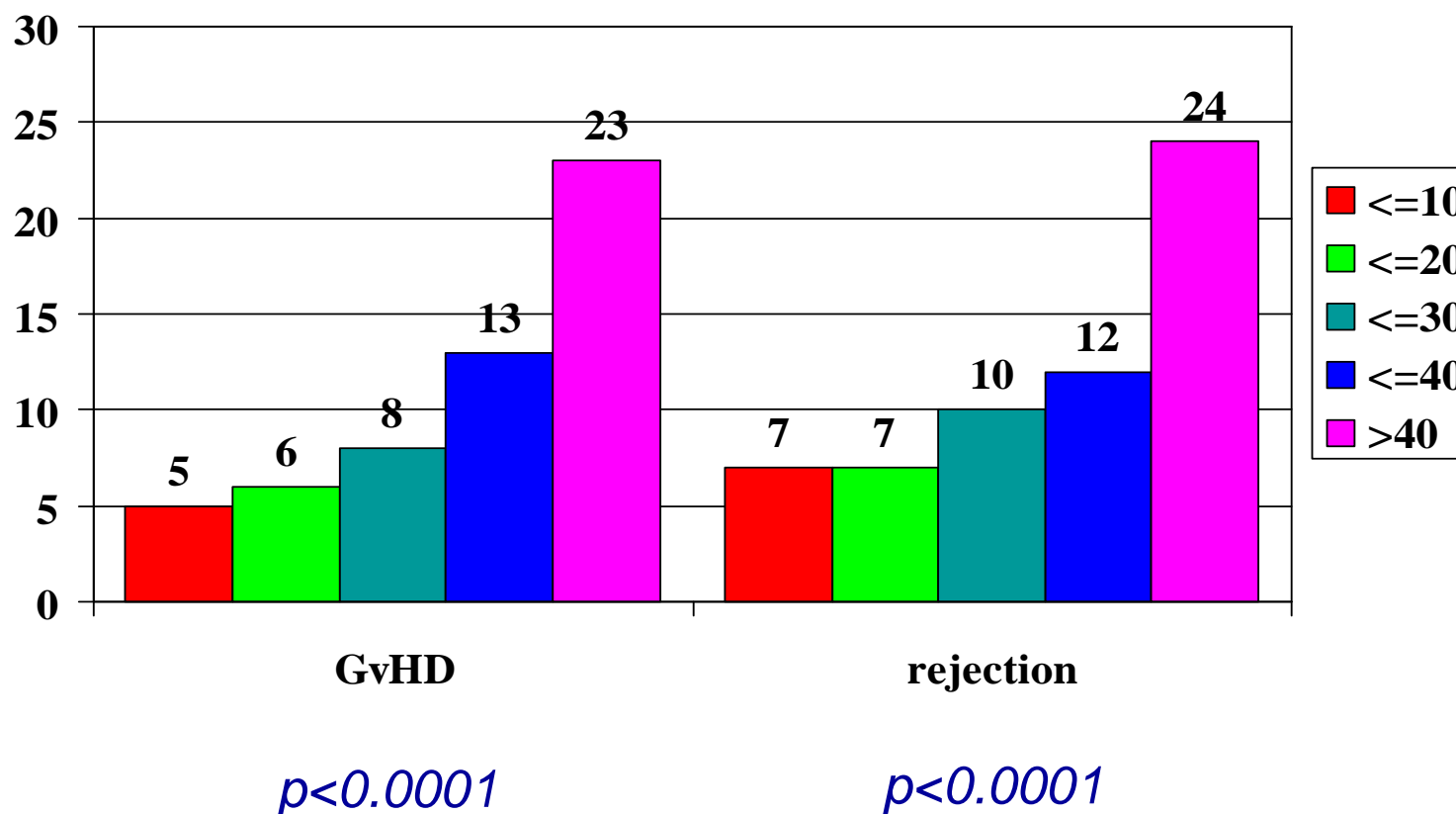
- Graft failure: 4-14%
- Acute GVHD: 12-30%
- Chronic GVHD: 30-40%

# Influence of age on 10-year overall survival in HLA identical siblings grafted 1999-2009



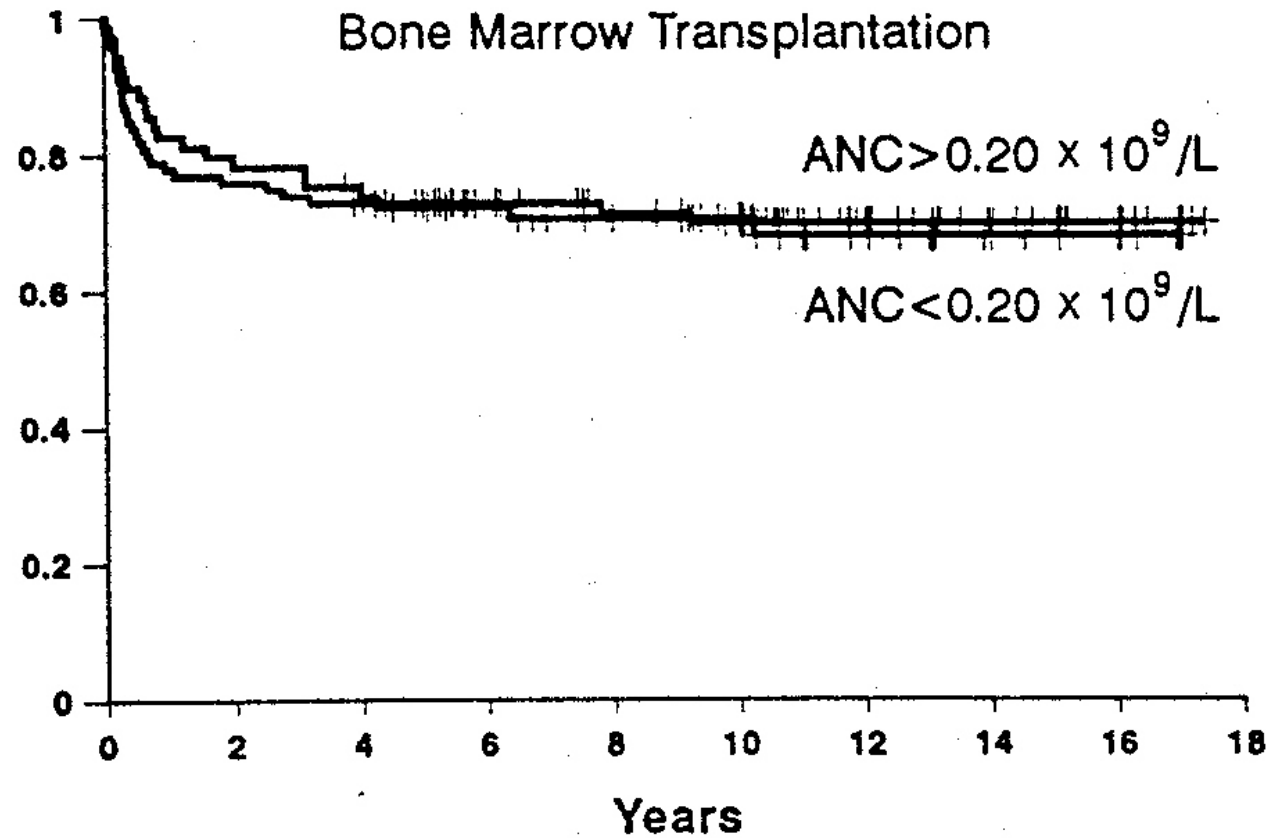


# Cause of death in relation to patient's age in HLA identical sibling transplants

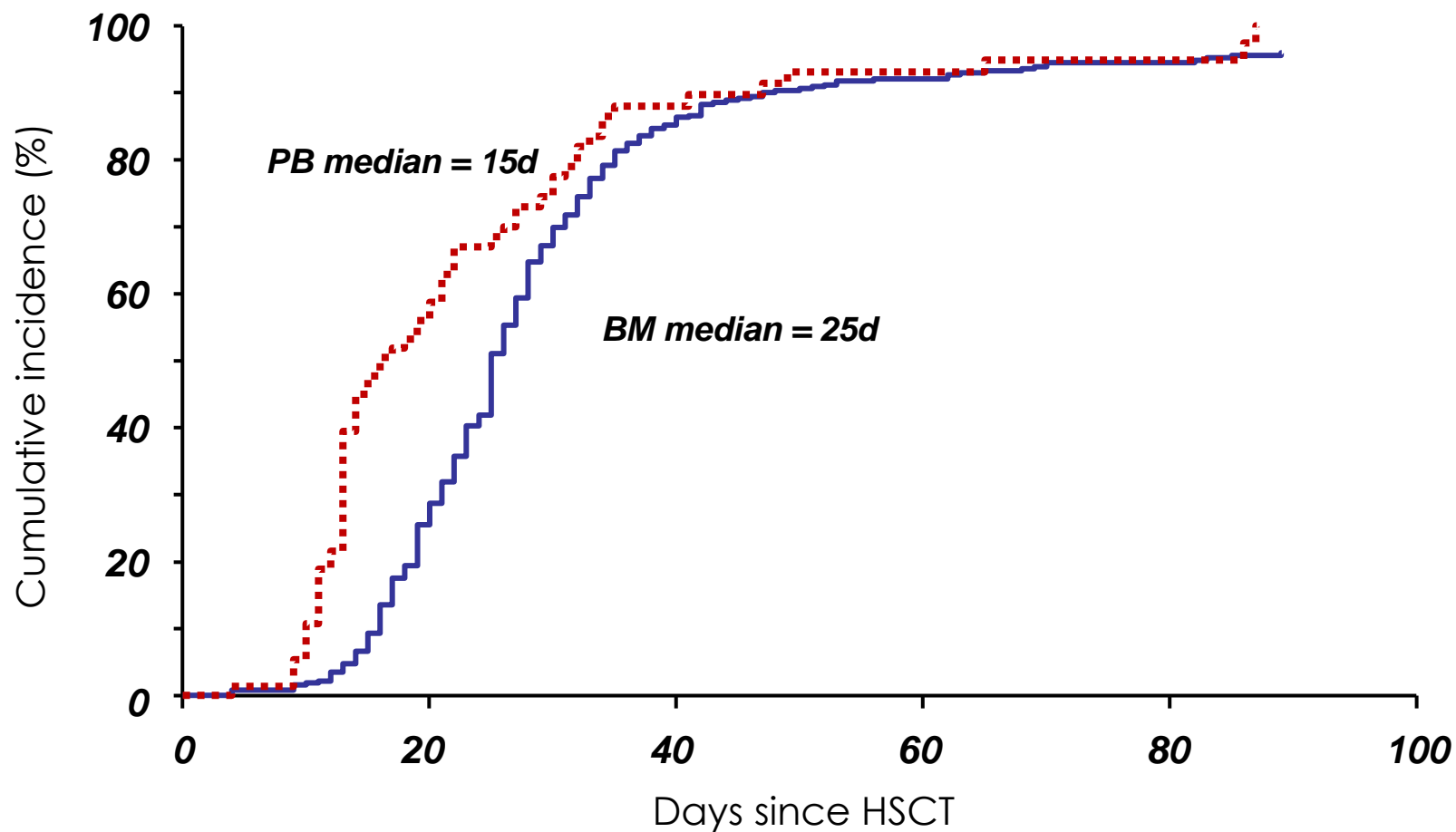


# Severity of the disease does not influence outcome in HSCT

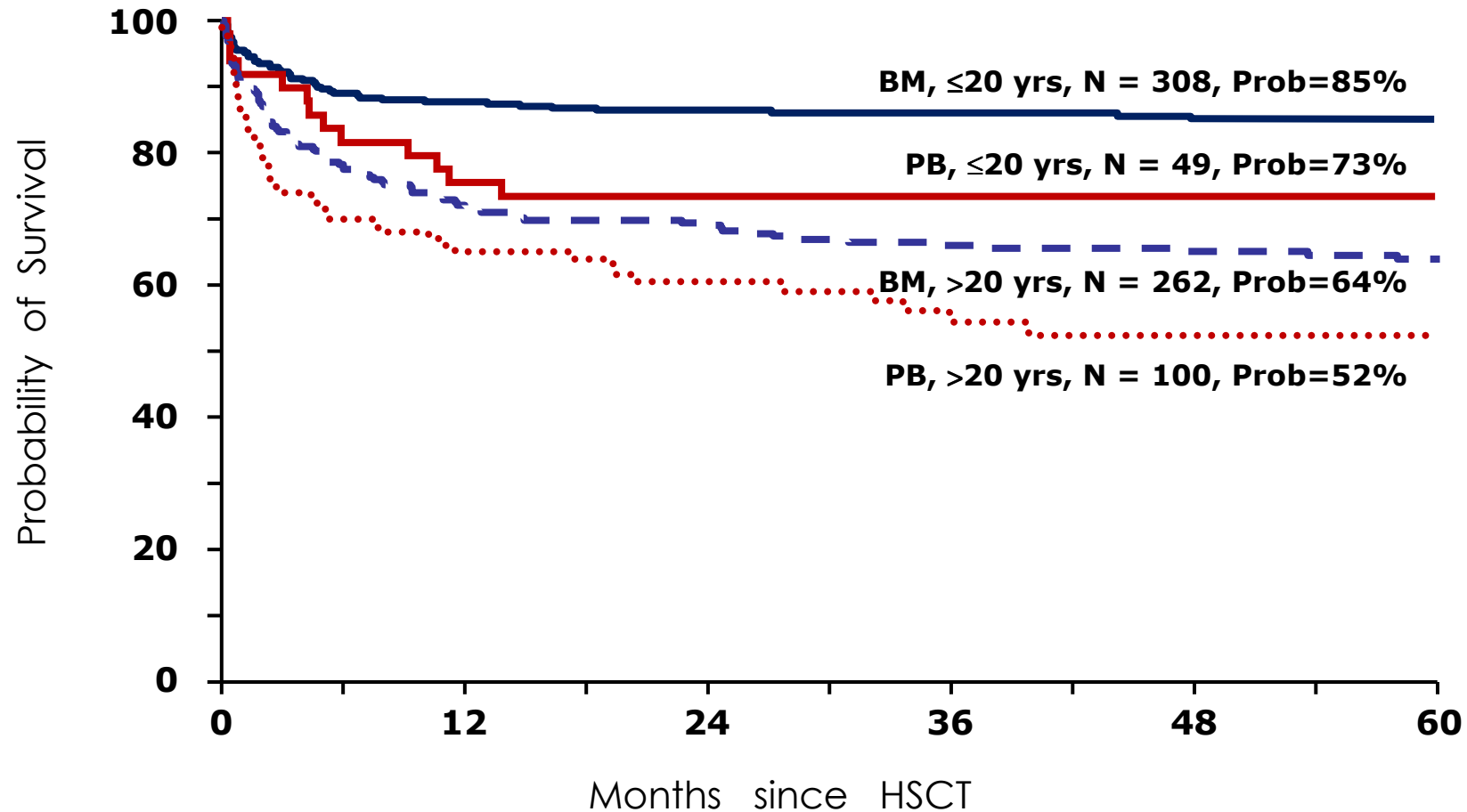
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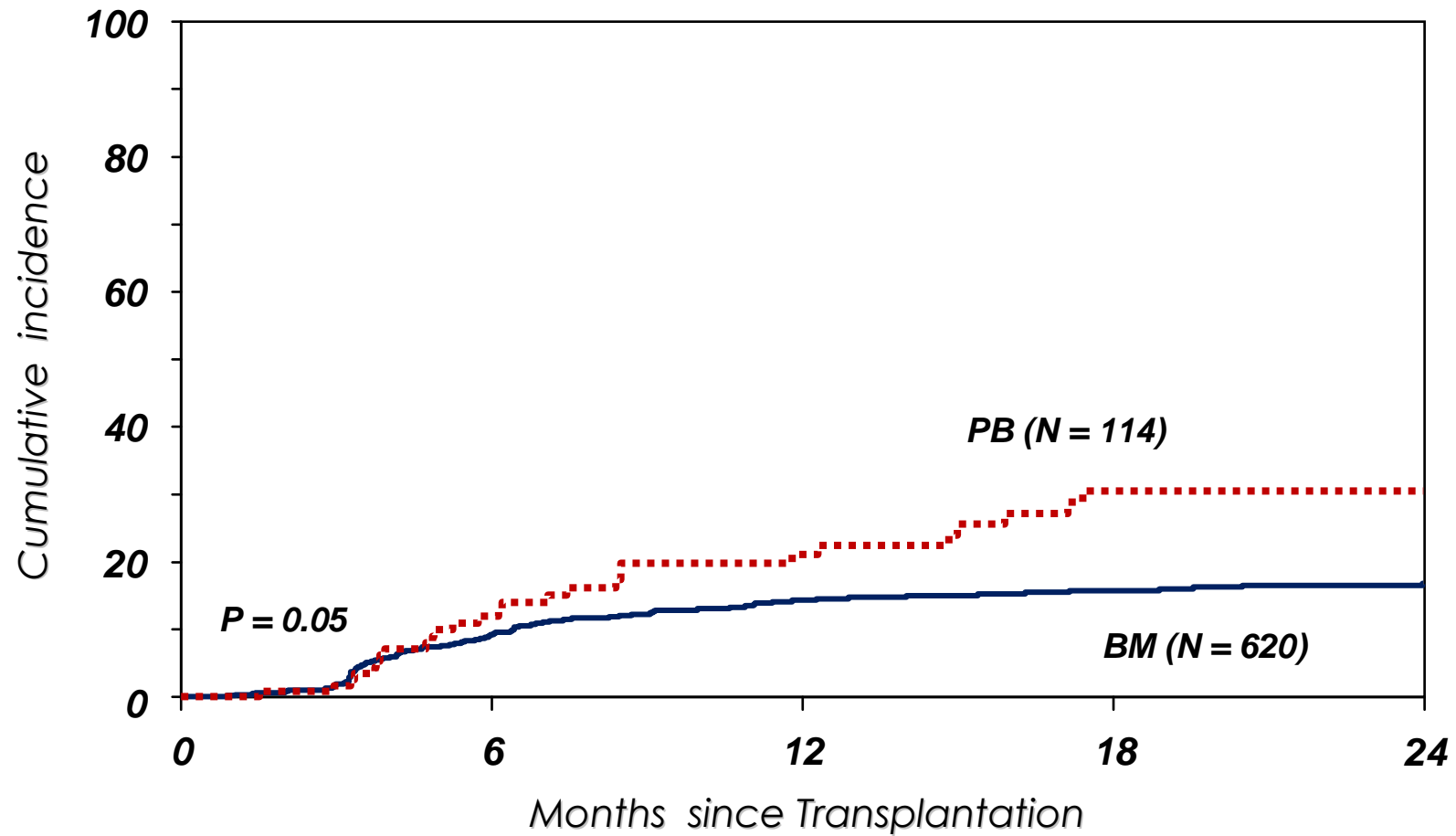
# Platelet recovery according to the stem cell source: Peripheral blood (PB) versus bone marrow (BM)



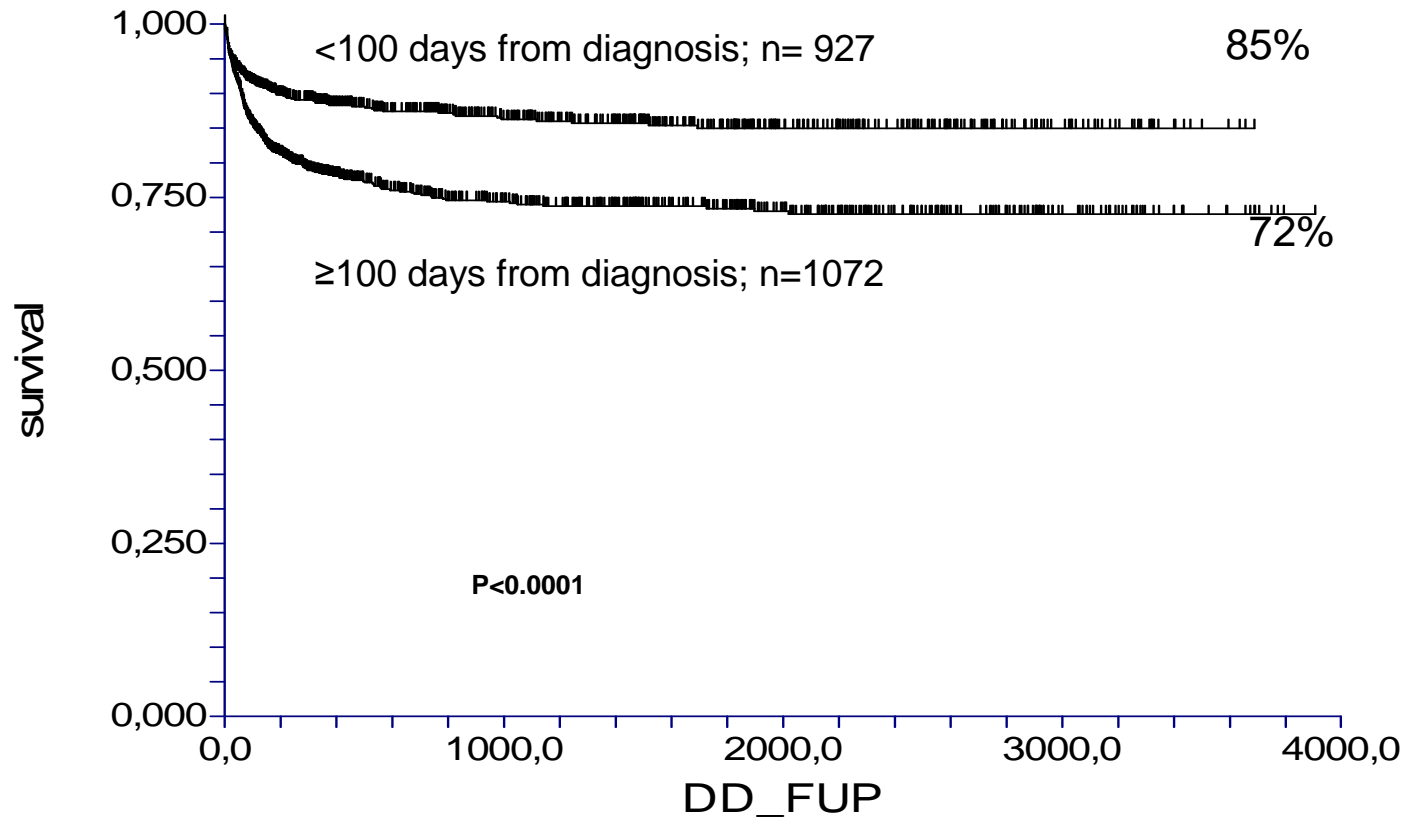
# Survival according to stem cell source: SAA does not need an antileukemic effect



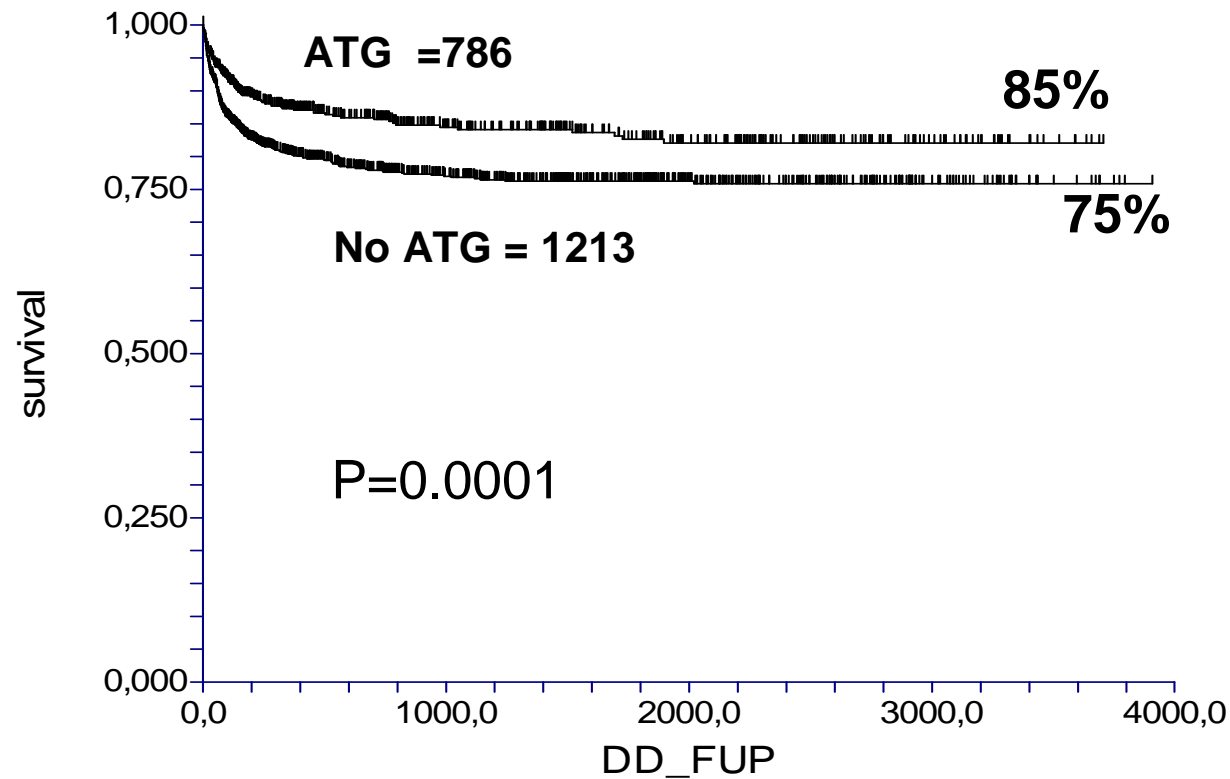
# Cumulative incidence of chronic GVHD according to stem cell source



# Influence of time interval between diagnosis and HSCT



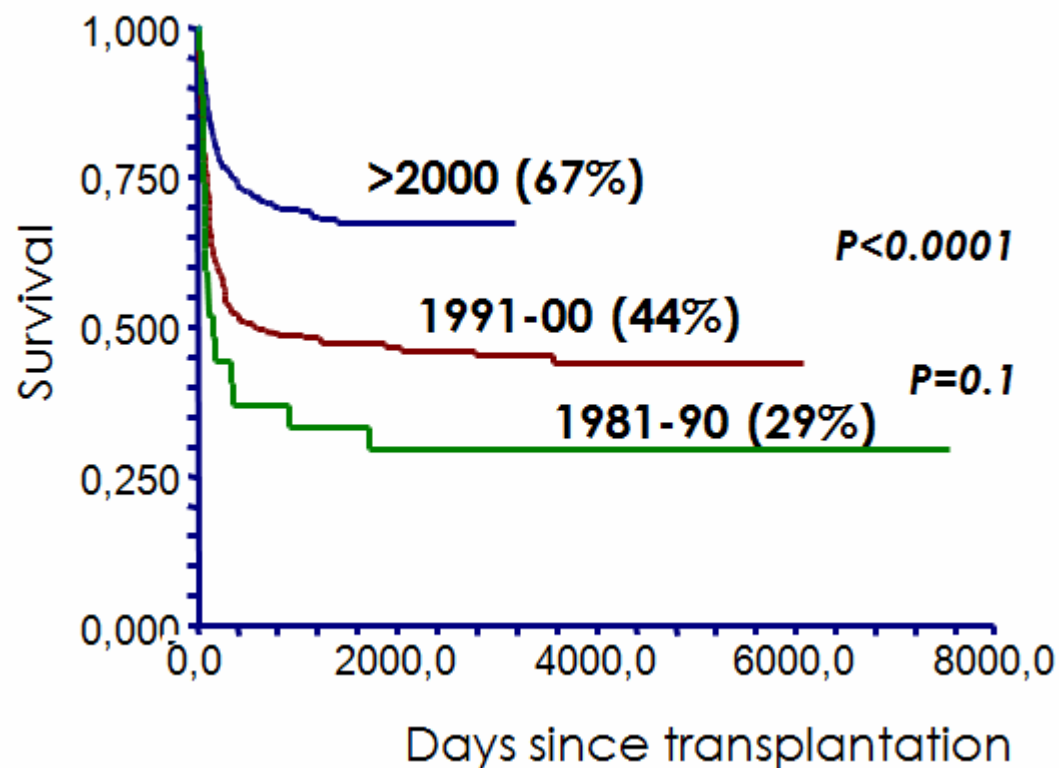
# ATG used as conditioning improves survival and reduces the risk of GVHD



*ATG is a favorable predictor of outcome*

- For BMT and PBPC
- Especially in patients > 20 years

# Alternative donor when a matched sibling donor is not available



## Alternative donor

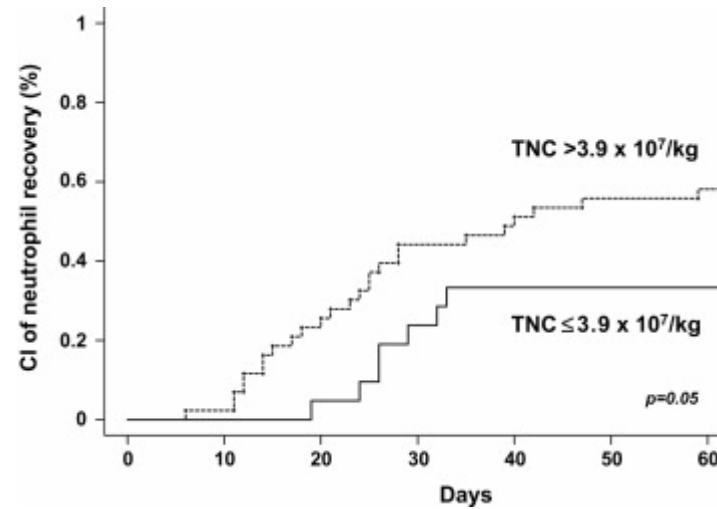
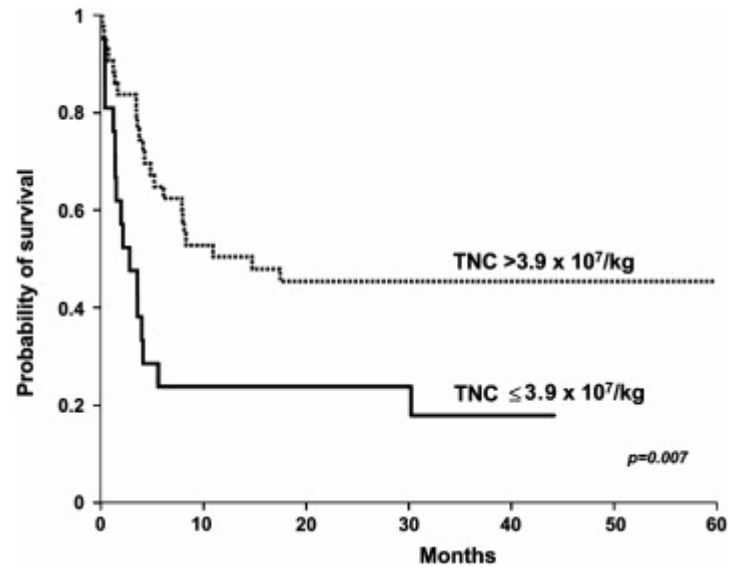
- Matched unrelated
- Cord-blood (double cord)
- Haplo-transplantation

## Improvement of outcome due to

- Less graft failure
- Less acute and chronic GvHD
- high resolution of HLA-typing and better donor selection

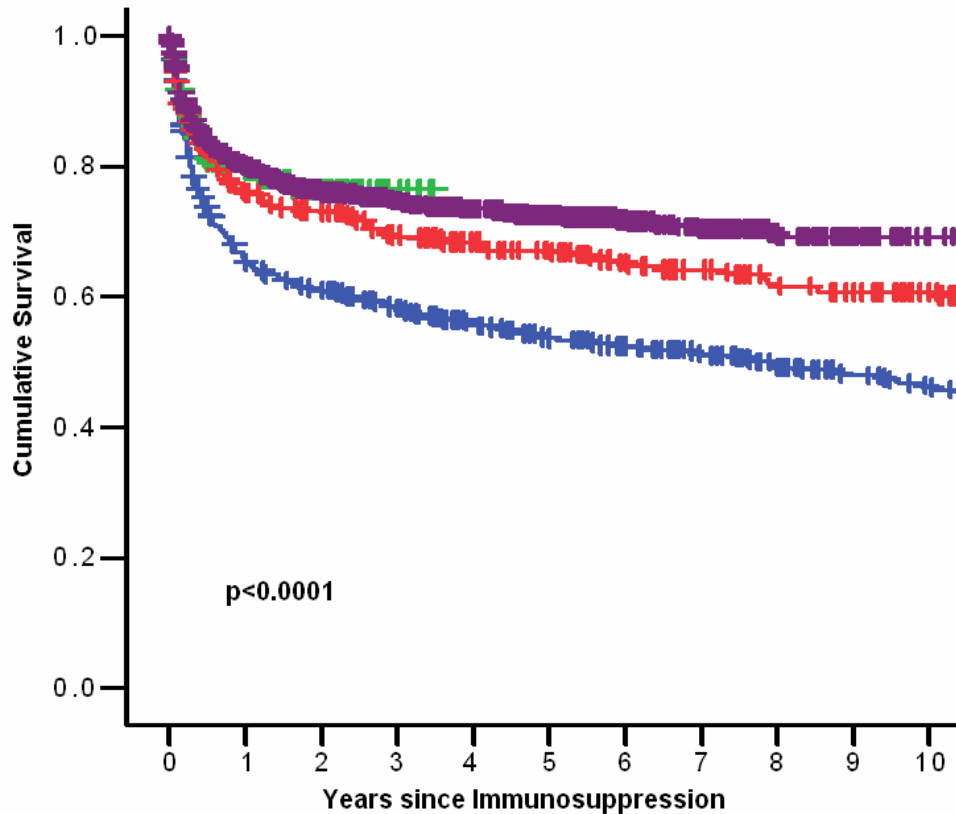


# Influence of nucleated cell dose on survival of unrelated cord blood transplantation in SAA



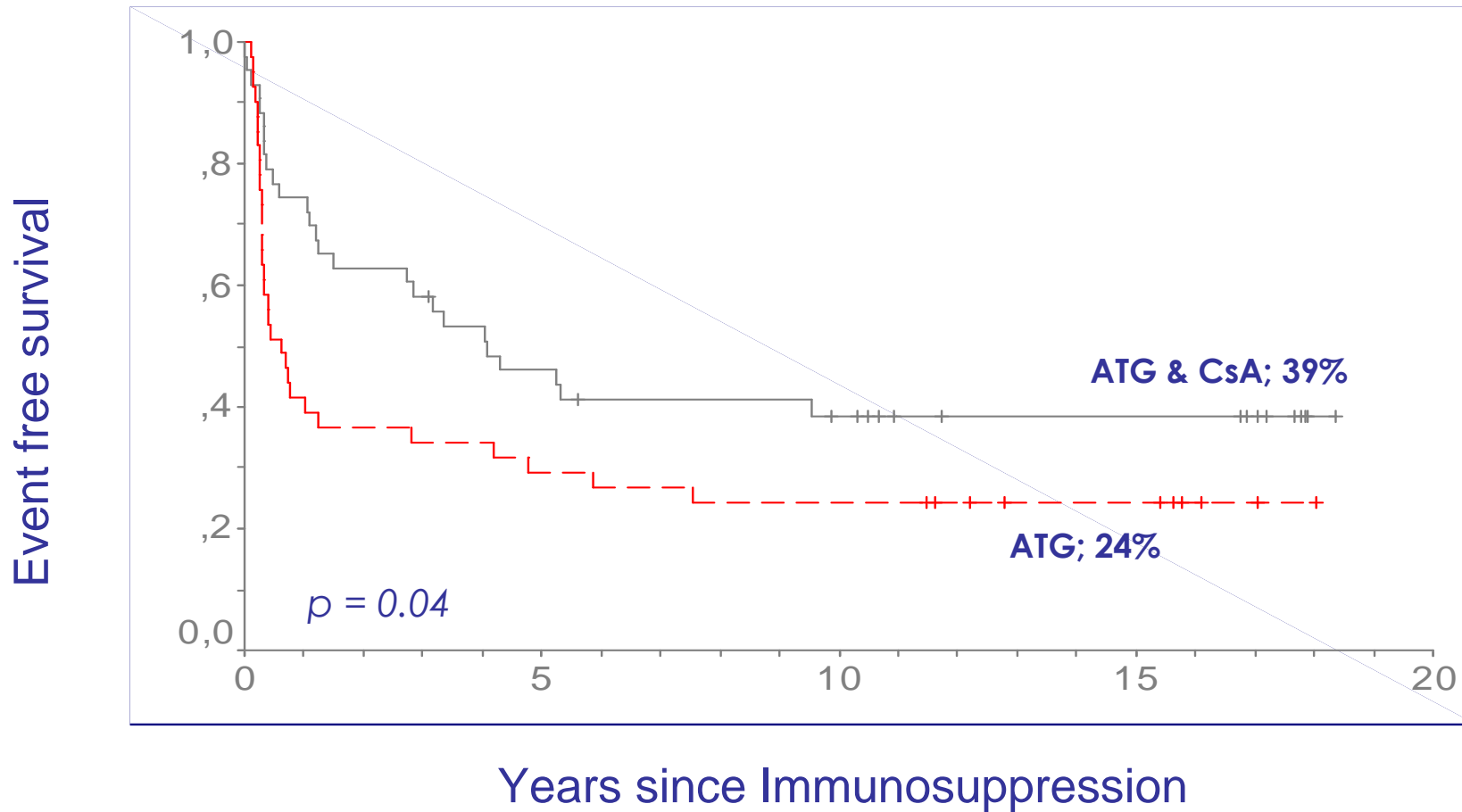
Retrospective analysis from the EUROCORD on 71 patients with SAA

# Improvement of survival of AA treated with immunosuppression



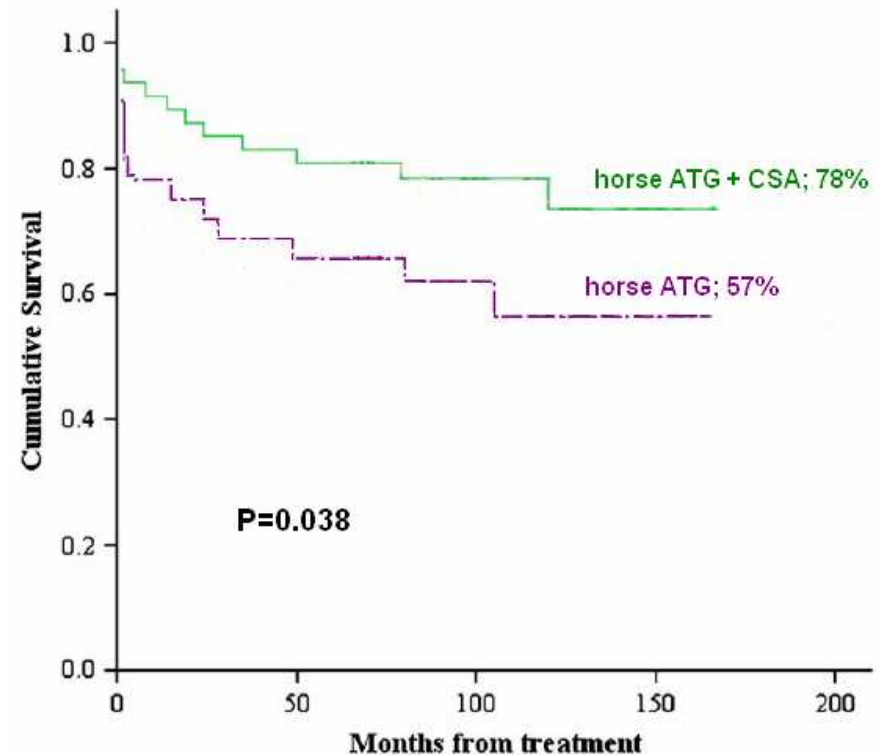
Time period	N	Survival	
		5 years	10 years
>2000	160	77±8%	
1990-2000	1114	73±3%	69±4%
1980-1990	413	67±5%	61±5%
<1980	577	54±4%	46±4%

# What is the best immunosuppressive treatment for aplastic anemia?



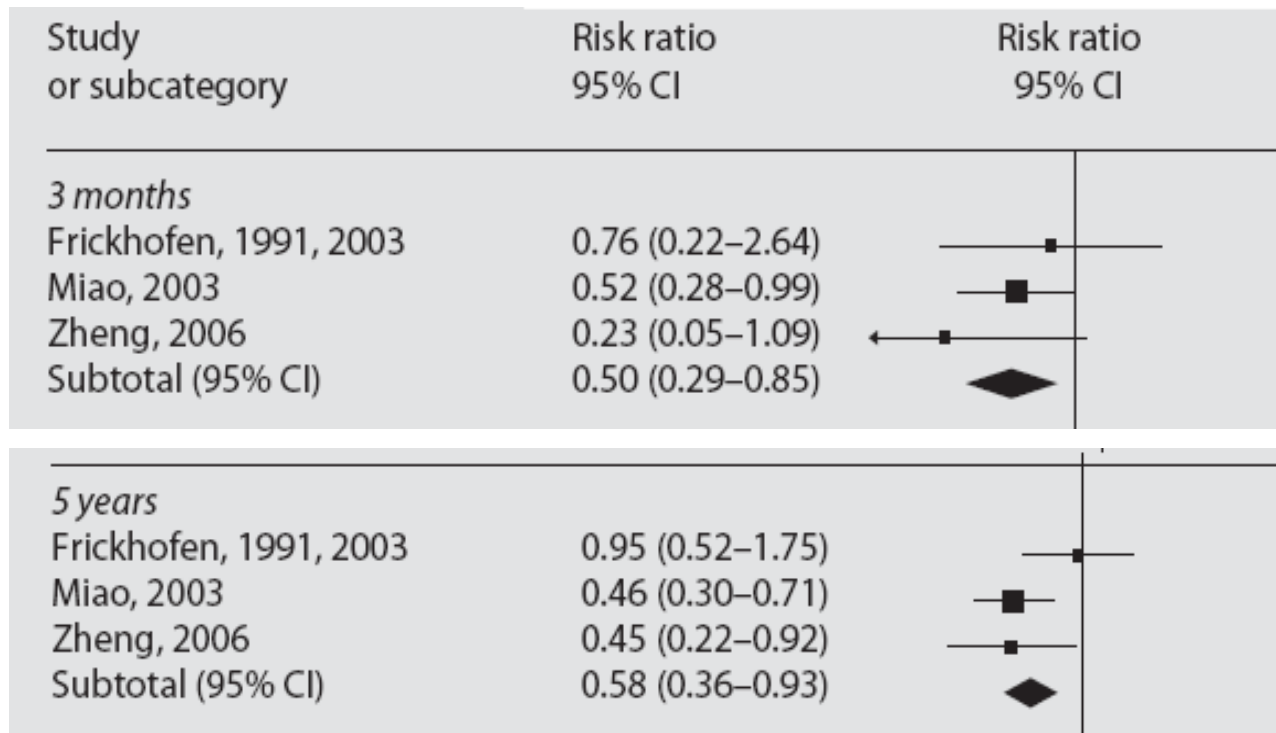
# Comparison of survival between ATG and CSA and ATG alone

- Randomized prospective study on immunosuppressive therapy in acquired SAA
- Unique course of IS applied
- Horse ATG and CSA improves overall survival compared to ATG alone



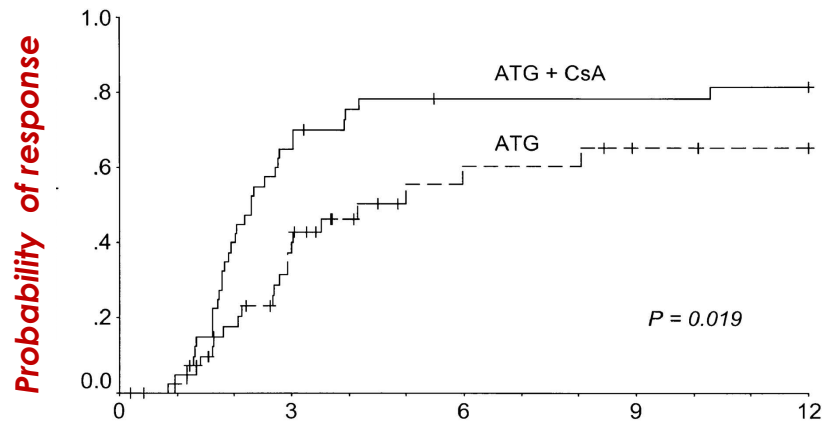
# Meta-analysis comparing ATG combined with CSA with ATG alone

Favors ATG&CSA      Favors ATG



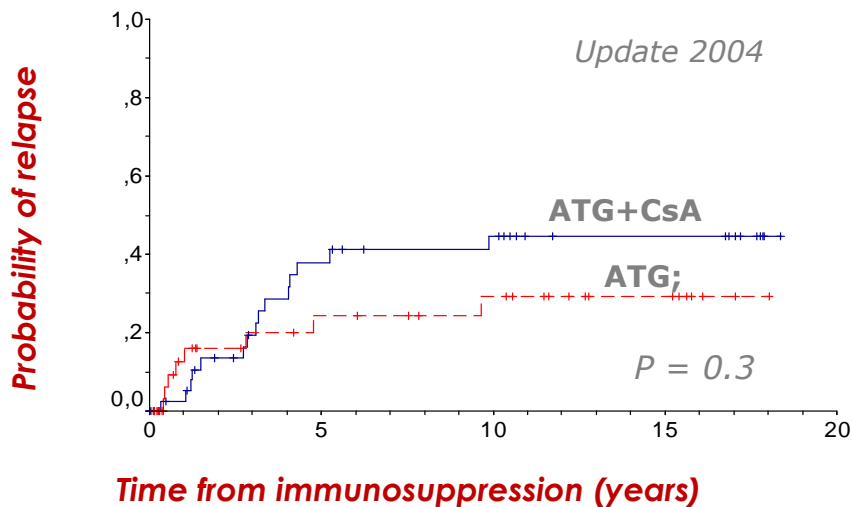
1. ATG & CSA significantly reduces
  - all-cause mortality by 50% at 3 months, 1 and 5 years
  - non response
2. No difference for risk of relapse and clonal evolution

# ATG combined with CSA improves and fastens recovery, but does not prevent relapse



## Kinetics of remission

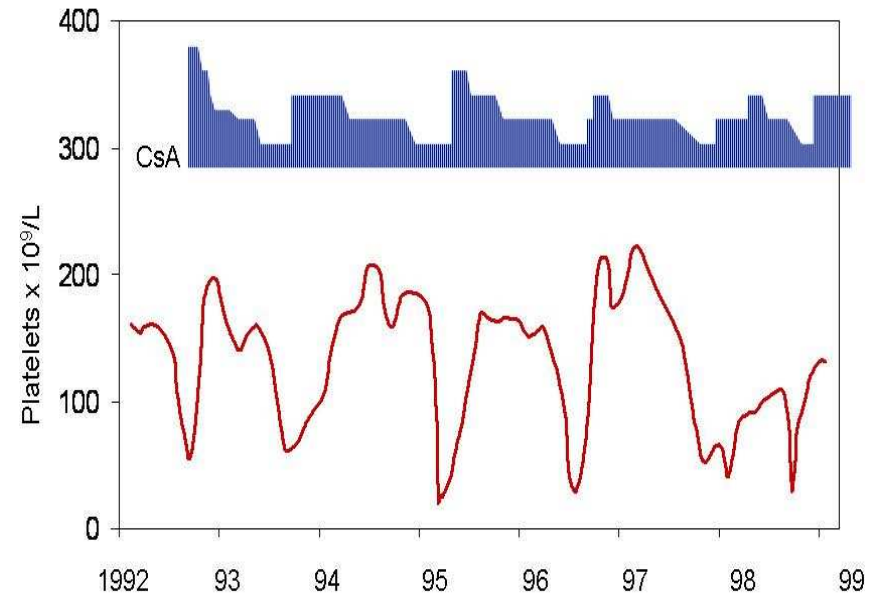
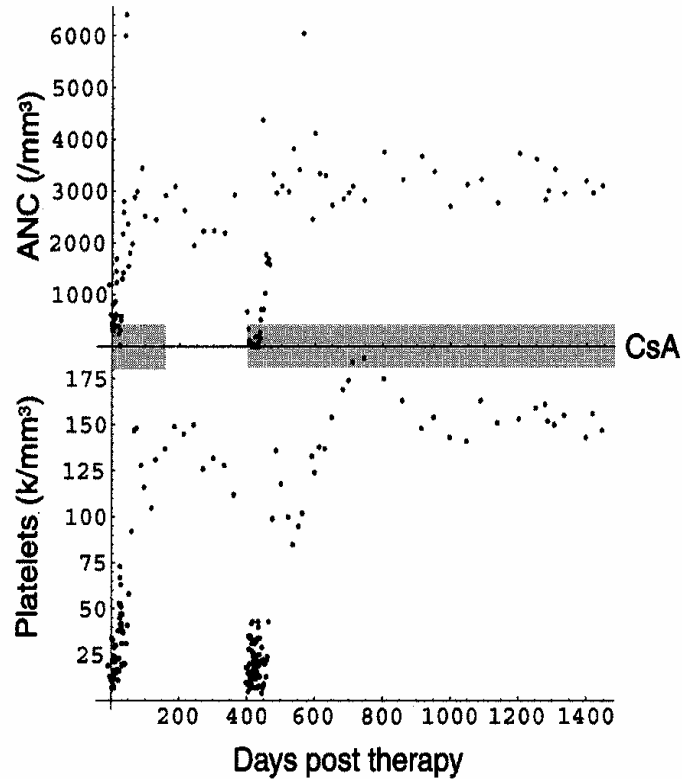
- Late improvement of blood values
  - 12/84
  - 4 months – 3.5 years
  - 6/12 stable remissions at 9-12 years



## Quality of remission

- 47 surviving responders
- Normal counts in
  - 47 (100%) for neutrophils
  - 40 (85%) for hemoglobin
  - 30 (64%) for platelets
  - 27 (57%) in CR

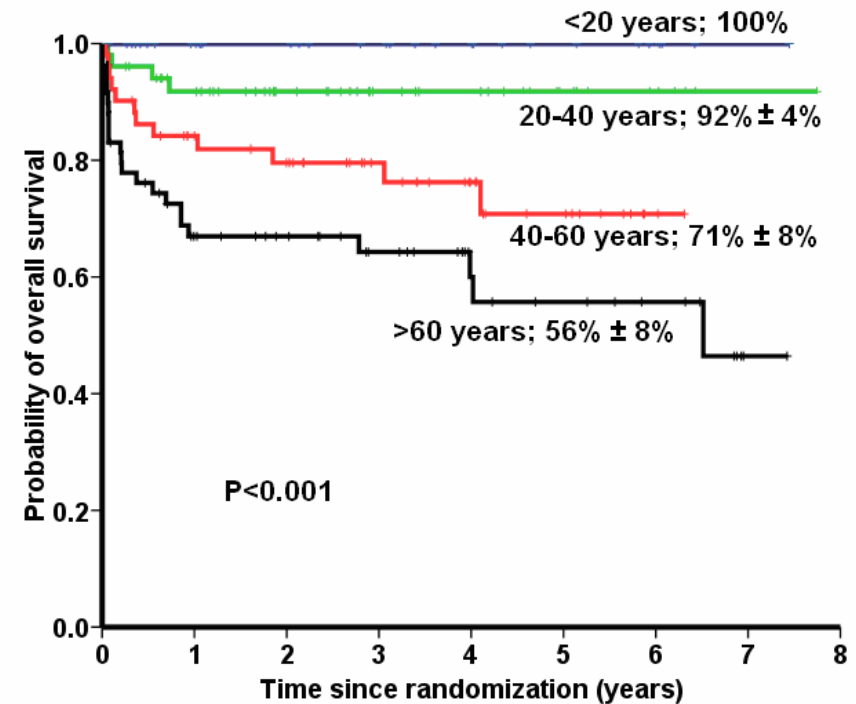
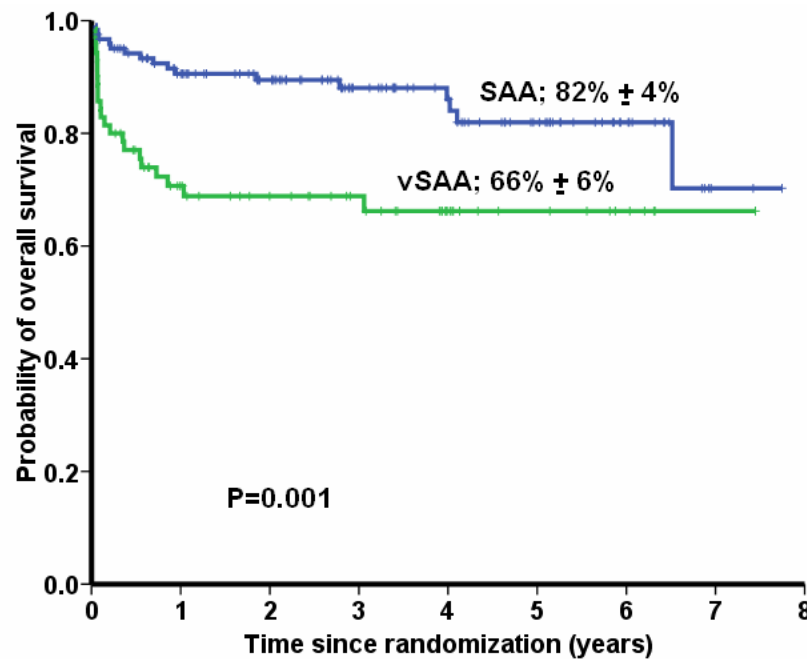
# Some of the patients are cyclosporine dependent of years



- 11/43 (26%) needed CsA >6 months
- 6 patients on continuous CSA for 9-12 years

Frickhofen N. Sem Hematol. 2000 (37). 56-68

# Survival according to severity of the disease and patients' age

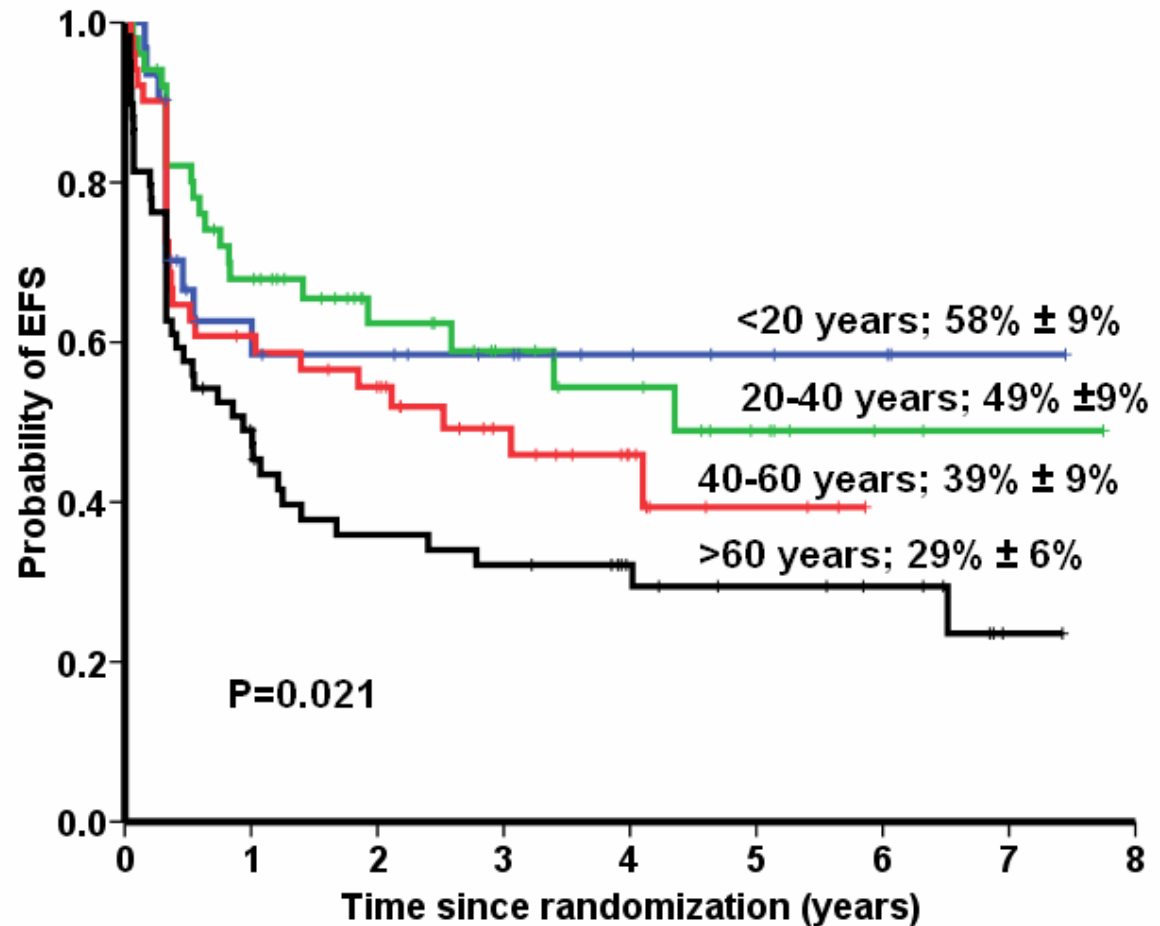




# EFS according to age groups: Even young patients present events in SAA

Definitions of an event

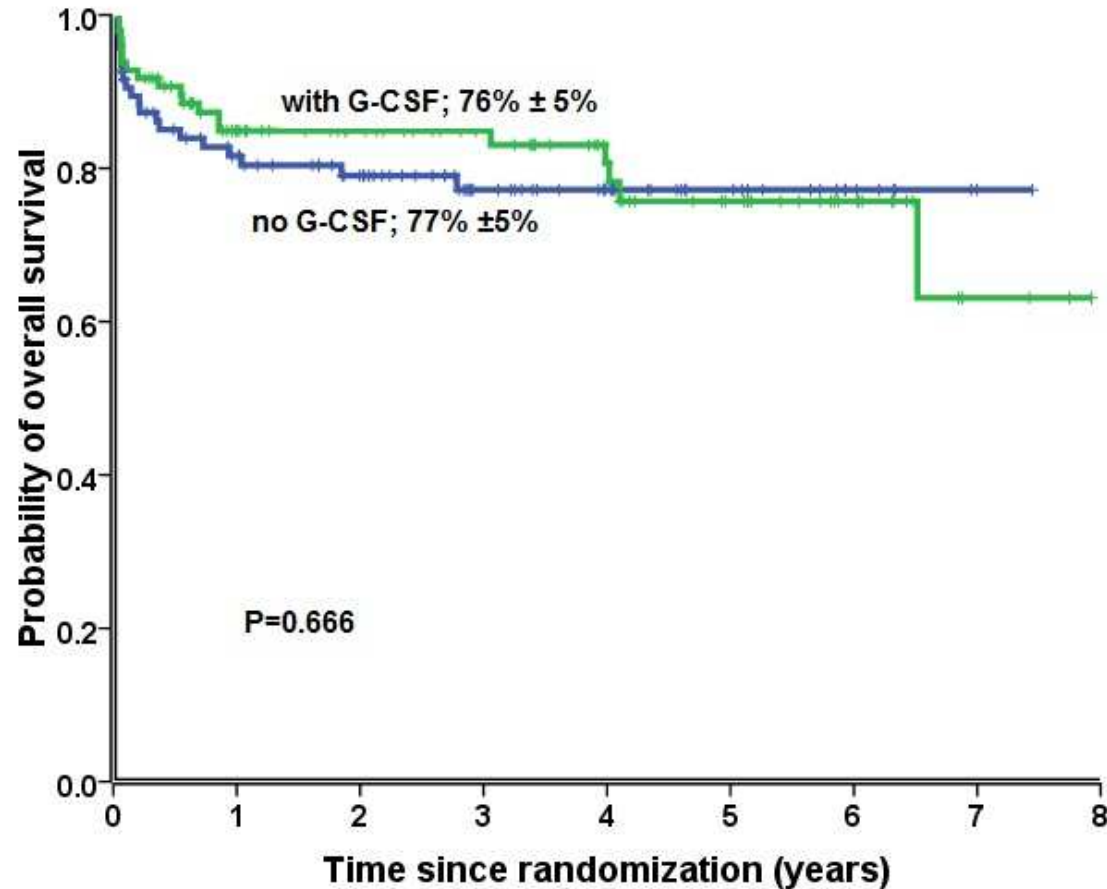
- Death
- Relapse
- Clonal complication
- Non-response at day 120



# Randomized studies on growth factors in aplastic anemia patients treated with immunosuppression

Study	Growth factor	Severity AA / SAA/ vSAA	G-CSF no/with
Teramura, Japan, 2007	G-CSF	0 / 65 / 30	48 / 47
Zheng, China, 2006	GM-CSF +EPO	0 / 52 / 25	47 / 30
Gluckman, EBMT, 2002	G-CSF	0 / 57 / 45	49 / 53
Kojima, Japan, 2000	G-CSF	28 / 36 / 0	33 / 31
Shao, China, 1998	GM-CSF +EPO	NA	18 / 18
Gordon-Smith, EBMT, 1991	GM-CSF	NA	14 / 13

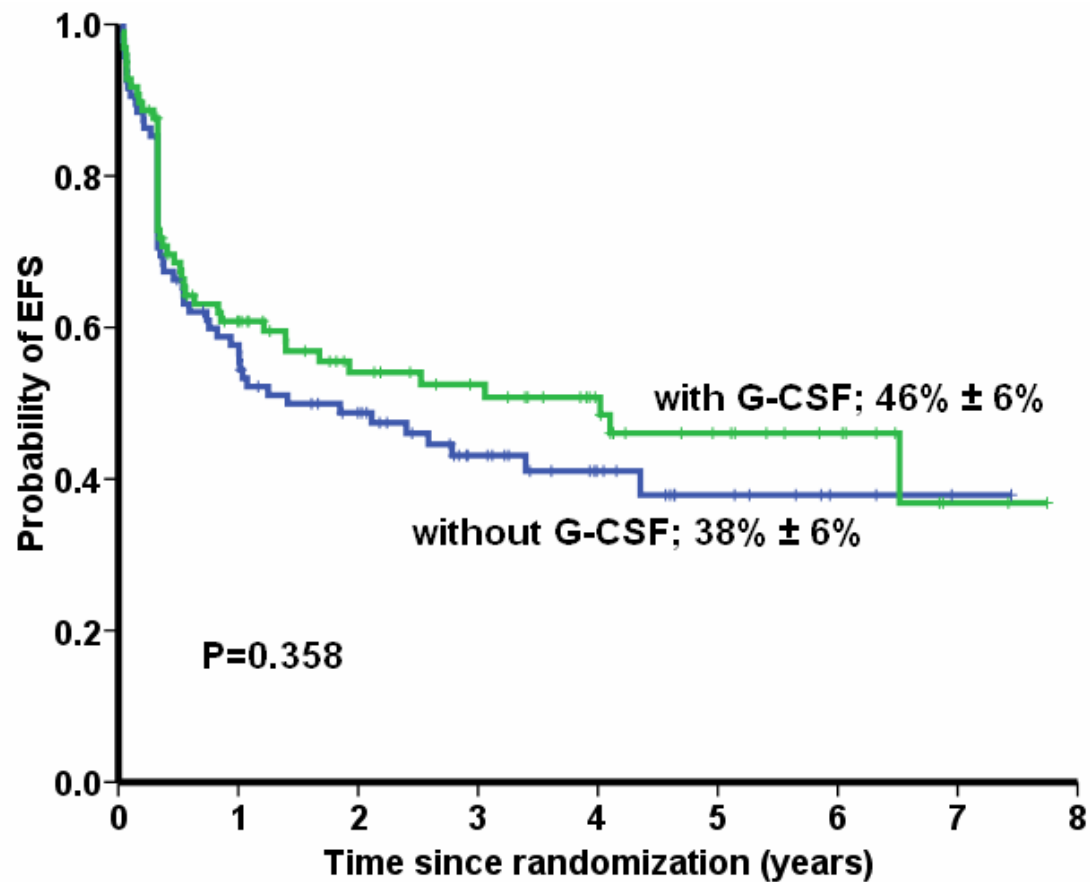
# Overall survival according to randomization with G-CSF versus no G-CSF



# Event free survival according to randomization with G-CSF versus no G-CSF

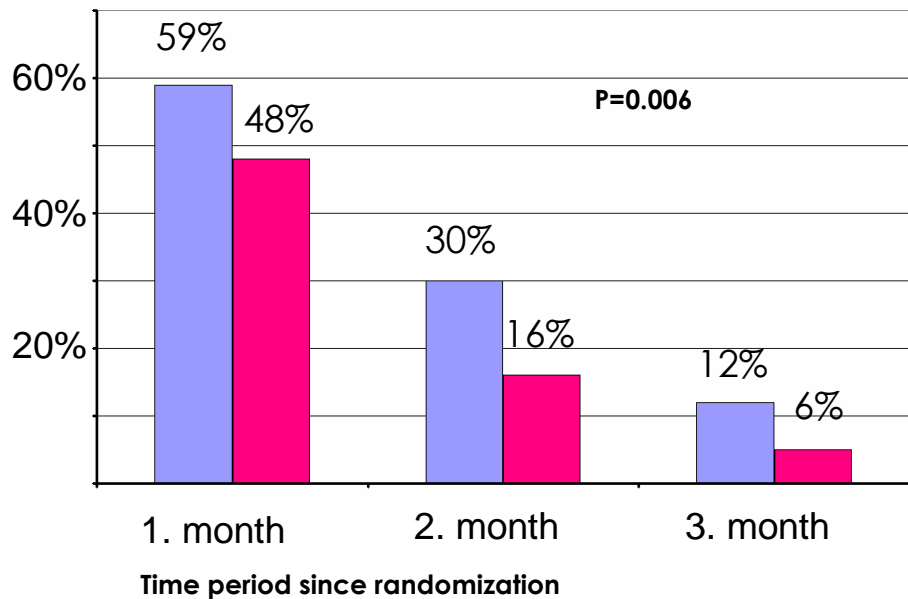
Definitions of an event

- Death
- Relapse
- Clonal complication
- Non-response at day 120

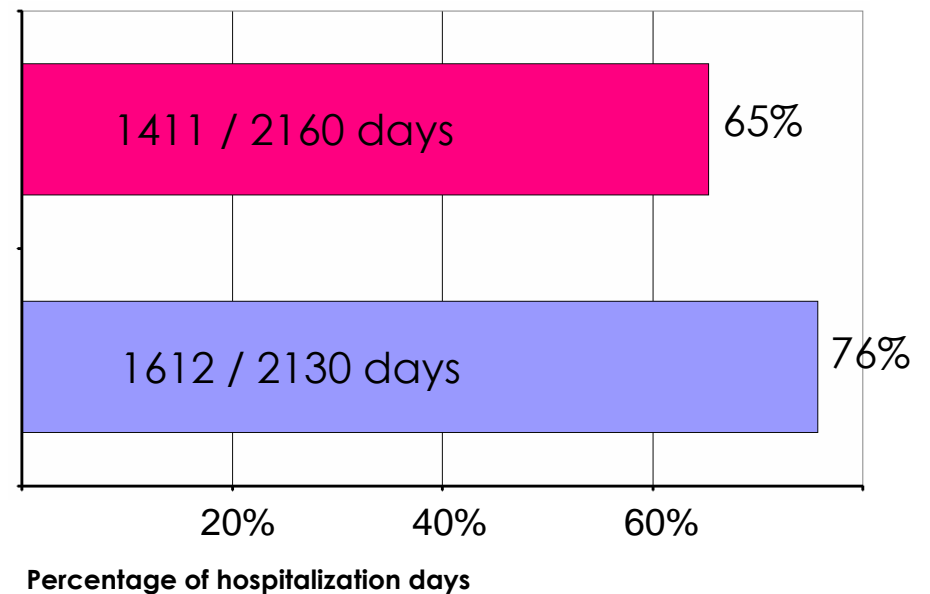


# Episodes of infection and days of hospitalization

*% of episodes of infections*

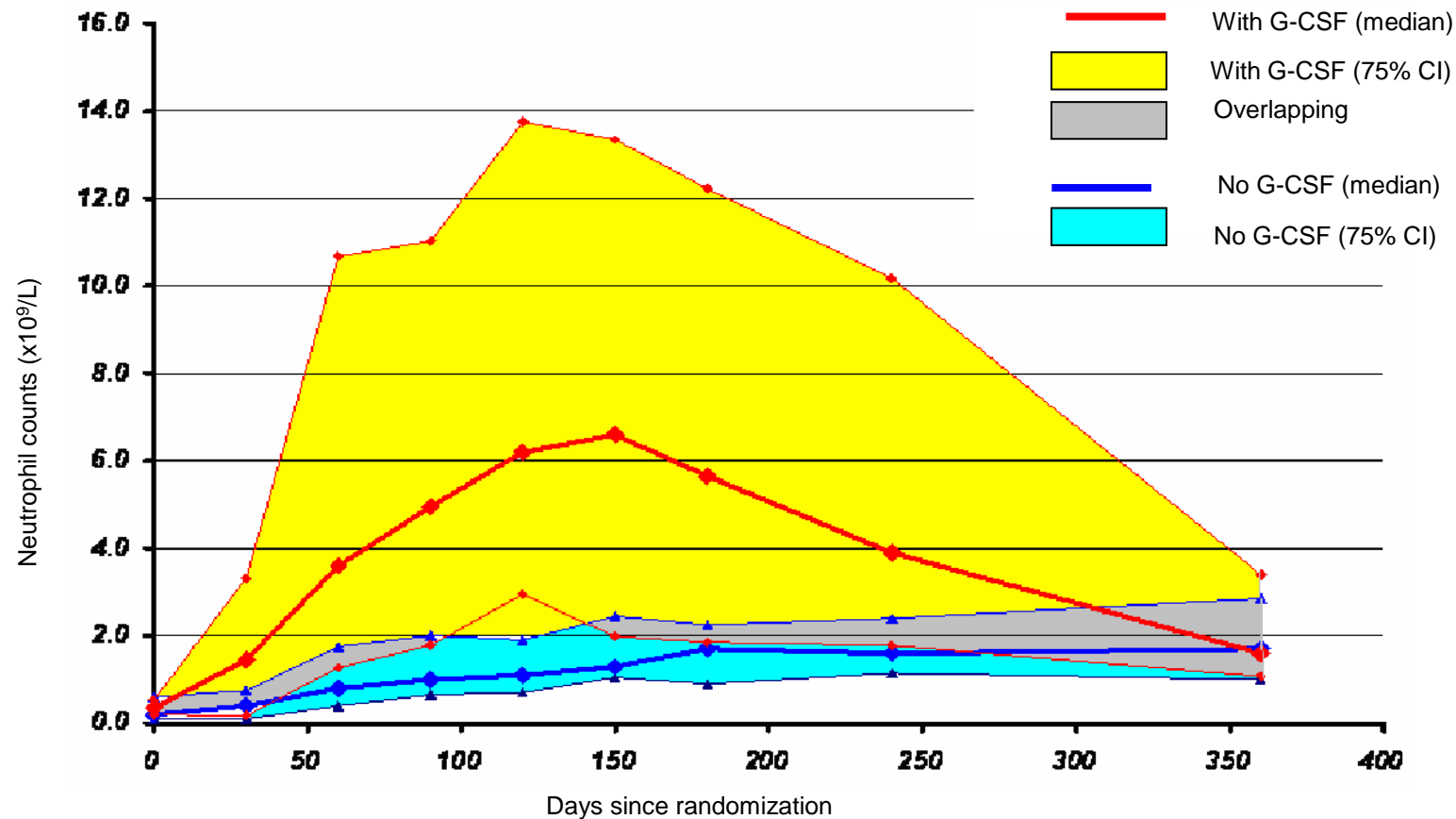


*% of days of hospitalization during the first 30 days*

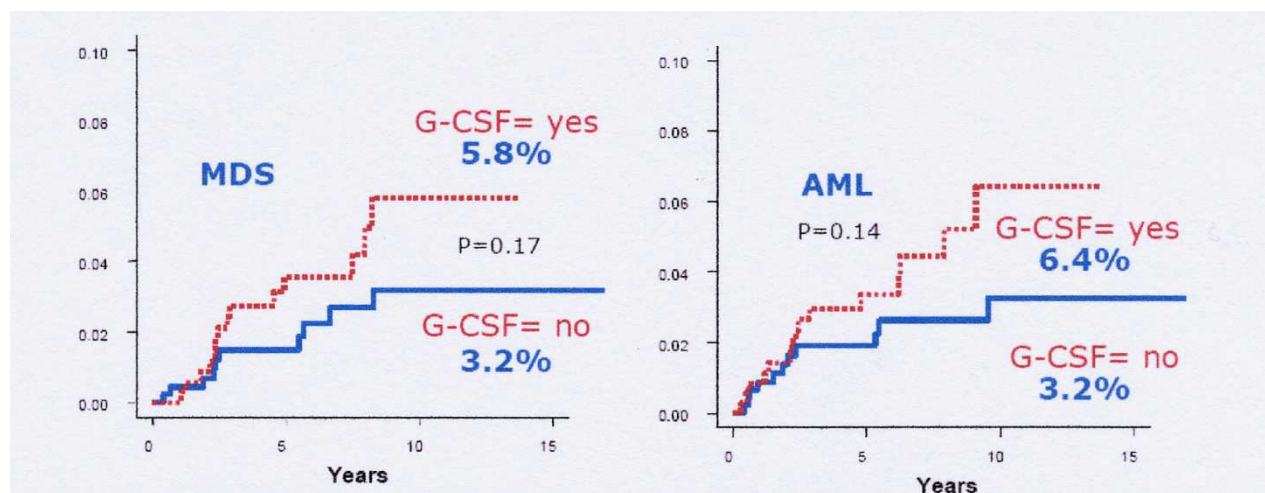


No G-CSF  
 With G-CSF

# Neutrophil counts in patients randomized to be treated with G-CSF versus no G-CSF



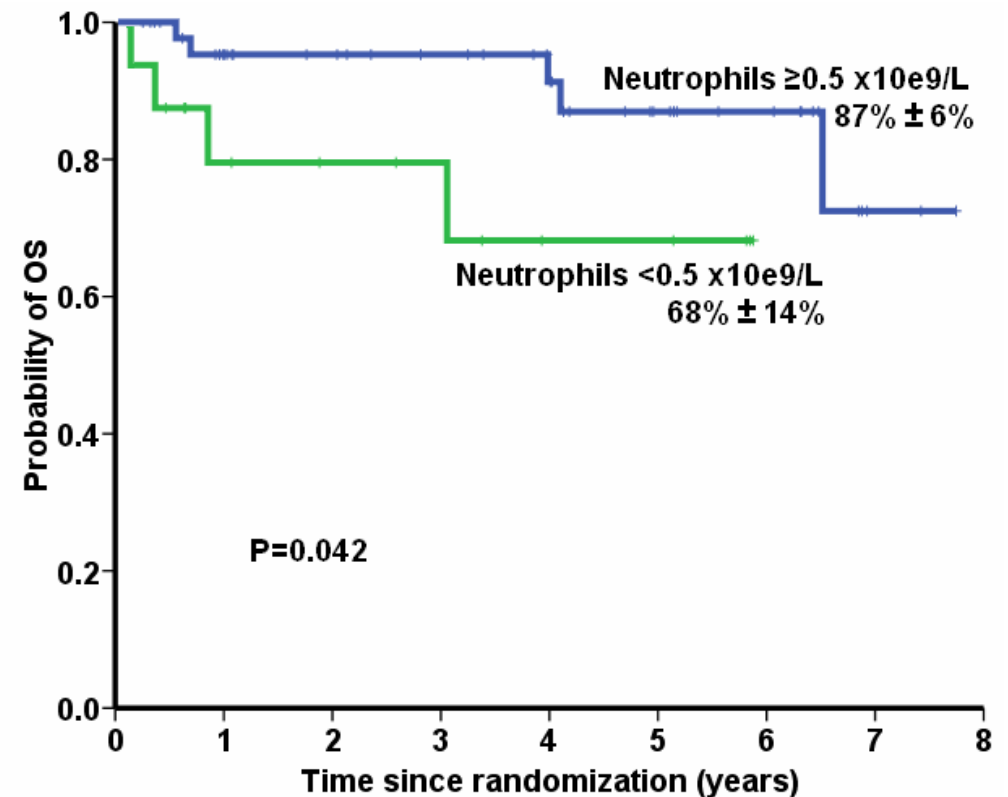
# G-CSF and risk of MDS/AML after immunosuppressive therapy



	Risk factors	HR	p
MDS	Age > 45yr	2.9	0.01
AML	Age > 45yr	4.1	0.002
	G-CSF	2.5	0.003
MDS/AML	Age > 45yr	2.9	0.001
	G-CSF	1.9	0.04

# Response to G-CSF at day 30 predicts response rate and overall survival

Neutrophils at day 30	Response (%)	P-value
$\geq 0.5 \times 10^9/L$	38/47 (81%)	0.048
$< 0.5 \times 10^9/L$	10/18 (56%)	





# SAA

Age <18 years

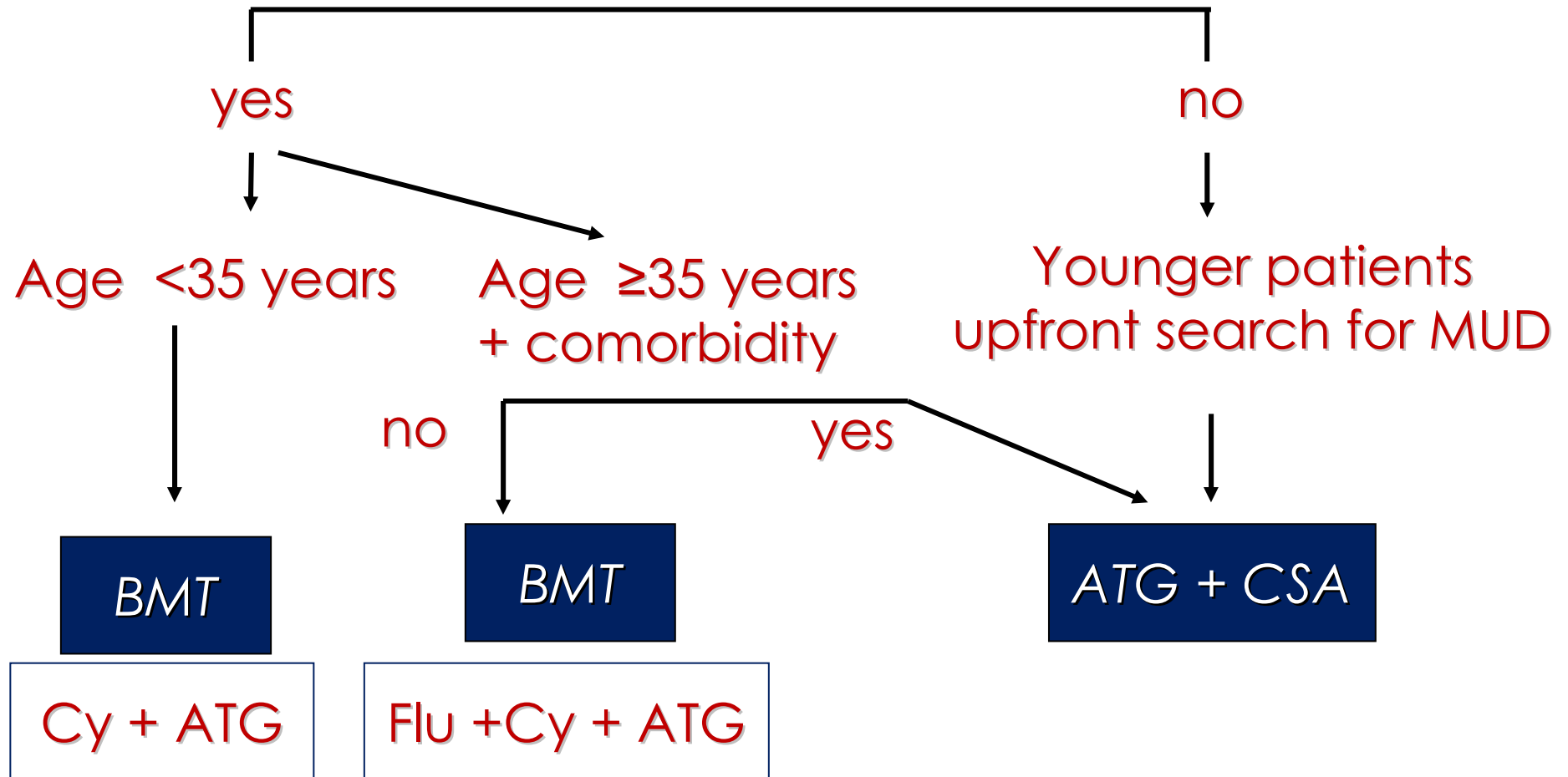
HLA identical  
sibling donor



# SAA

Age 18 - 60 years

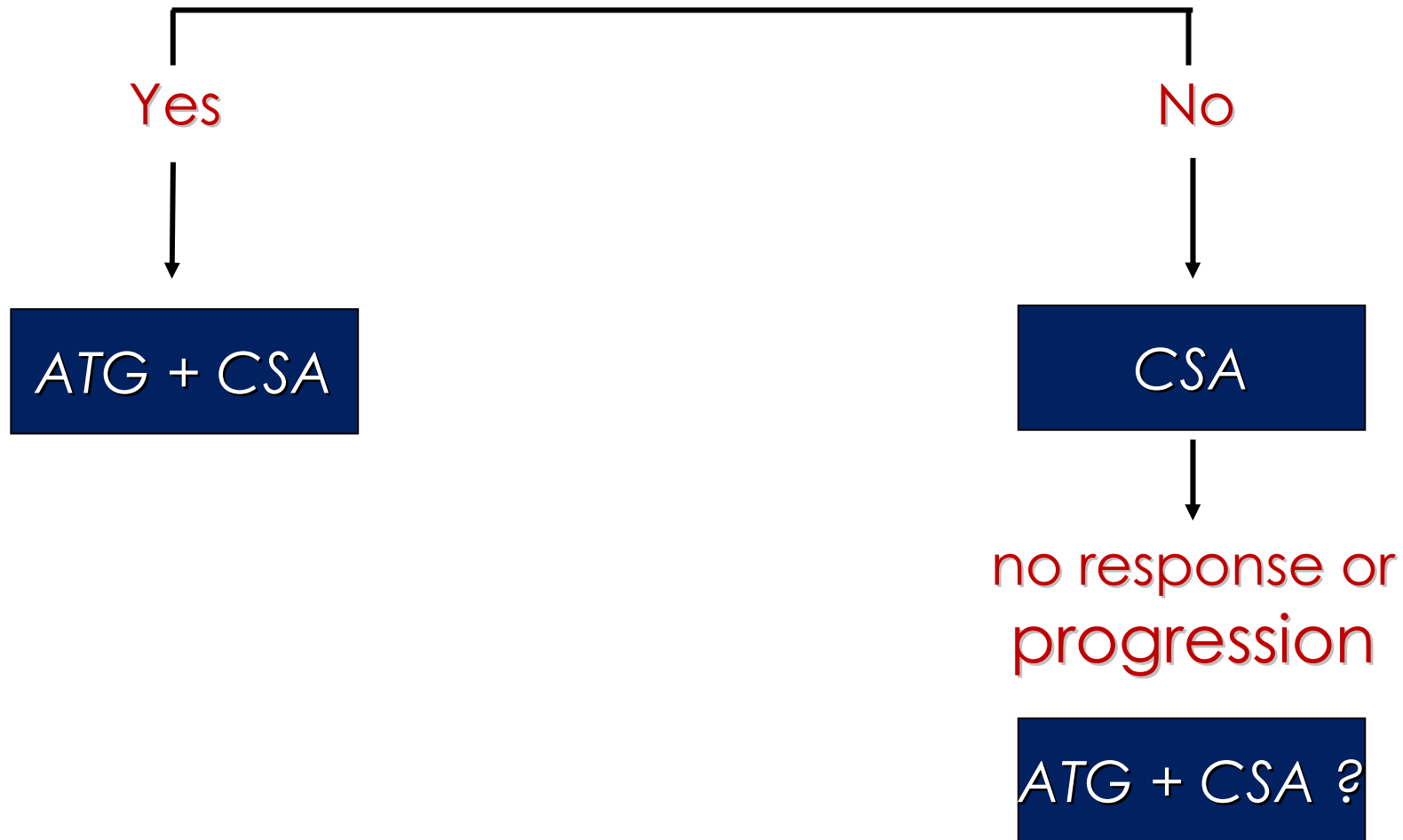
HLA identical  
sibling donor



SAA

Age  $\geq 60$  years

vSAA or  
hospitalization for infection



# Conclusions

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- Age has a major impact on outcome in SAA. Decision making is strongly related to age and comorbidity
- Matched related HSCT is the treatment of choice in patients younger patients
- At any age immunosuppressive therapy should be started immediately in patients without a matched sibling donor
- Upfront search for an alternative donor in children and young adults without a matched sibling donor
- No absolute upper age-limit for HSCT in refractory patients