Oxford University Hospitals NHS
NHS Trust

eurocord

Graft Failure After HSCT

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BSBMT

UNIVERSITY OF OXFORD
The MRC Weatherall Institute of Molecular Medicine is a strategic alliance between the Medical Research Council and the University of Oxford
MRC Medical Research Council

Clinical cases

- 35 y old male with CML transplanted with a HLA matched unrelated BMT after ivBU+CY+ATG .Engraftment at day+20 and graft failure at day +25.

- 2 y old boy with JMML, transplanted with a cord blood (5 x107/kg) 4/6 after ivBU+FLU+MEL+ATG. Non engraftment at day +28

- 8 y old boy with VSAA (no response to 2 courses of ATG); transplanted with Haplo (mother BM cells) CY+FLU+TBI and CY after. Engraftment at day+17 and graft failure at day+24.

- 52 y female with secondary AML, transplanted with 9/10 unrelated PBSC after RIC (FLU+MEL+Campath). Engraftment at day 18 and graft failure at day +26. Diagnosis of Aspergillus infection at day +30

Clinical cases

- 35 y old male with CML transplanted with a HLA matched unrelated BMT after ivBU+CY+ATG Engraftment at day+20 and graft failure at day +25. Decision for a second transplant: double UCBT after TBI2CY + ATG done at day +50. Engraftement at day +20 . CNS and Lung PTLD, responded to mini-CHOP and intrathecal Rituximab. Alive 7 years after HSCT
- 2 y old boy with JMML, transplanted with a cord blood (5 x107/kg) 4/6 after ivBU+FLU+MEL+ATG; Non engraftment at day +28. Decision for Haplo identical using BM mother cells and post HSCT CY. Conditioning regimen CY+FLU+TBI. Infusion at day + 38. Engraftment at day+15. Alive and well 2 years after HSCT
- 8 years old boy with VSAA (no response to 2 courses of ATG); transplanted with Haplo (mother BM cells) CY+FLU+TBI and CY after. Engraftment at day+17 and graft failure at day+24. Decision for Haplo identical using PBSC father cells and post HSCT CY. Conditioning regimen FLU+ATG. Infusion at day + 40. Engraftment at day+15. Alive and well 1,3 years after HSCT
- 52 y female with secondary AML, transplanted with 9/10 unrelated PBSC after FLU+MEL+Campath. Engraftment at day 18 and graft failure at day +26. Diagnosis of Aspergillus infection at day +30. Decision for Haplo identical hsct using brother PBSC cells and post HSCT CY. Engraftment at day 12. Alive and well at 6 months after HSCT

Introduction

- Graft Failure or non-engraftment is a complication after HSCT that occurs between 5% to 20%
- Conventionally described as primary or secondary, depending on temporal relation to transplant
- Multiple mechanisms underlying graft failure have been proposed
- Outcomes after graft failure have been dismal

Second transplants for graft failure

Study	N	PGF	SGF	Median Age	Donor Source	Engraftment	TRM	OS	DFS
Chewning et al, 2007	16	11	5	22y	BM / PBSC	100%	-	35% - 3y	18% - 3y
Guardiola et al, 2000	82	28	54	25y	BM / PBSC	73%	53%	30% - 3y	26% - 3y
Stucki et al, 1998	44 (3 groups)	-	-	-	BM	27-66%	-	5-83% - 10y	-
Chan et al, 2008	10	-	-	6,5y	CB	100%	-	60% - 3y	-
Grandage et al, 1998	12	5	7	8,5y	BM	90%	42%	41%	17%
de Medeiros et al, 2001	34	9	25	18y	BM	-	-	50% -13y 22%(PGF)	-

Schriber et al (BBMT 2010) in 120 patients given a second allograft for primary graft failure 11% 1yr OS

How and when to make the diagnosis?

Screen for infection: exclude viral causes of failed engraftment such as CMV, HHV6 and Parvo-virus. Appropriate samples should be sent to Microbiology for PCR, serology and cell culture.

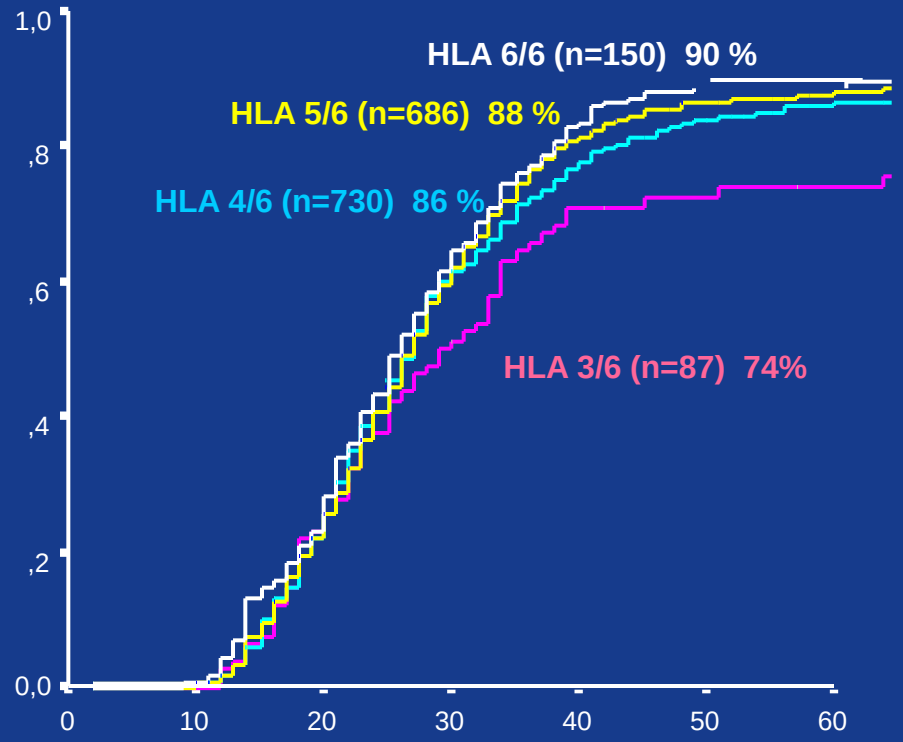
Review patient's drug therapy and minimise the use of myelosuppressive drugs such as Cotrimoxazole and Ganciclovir .

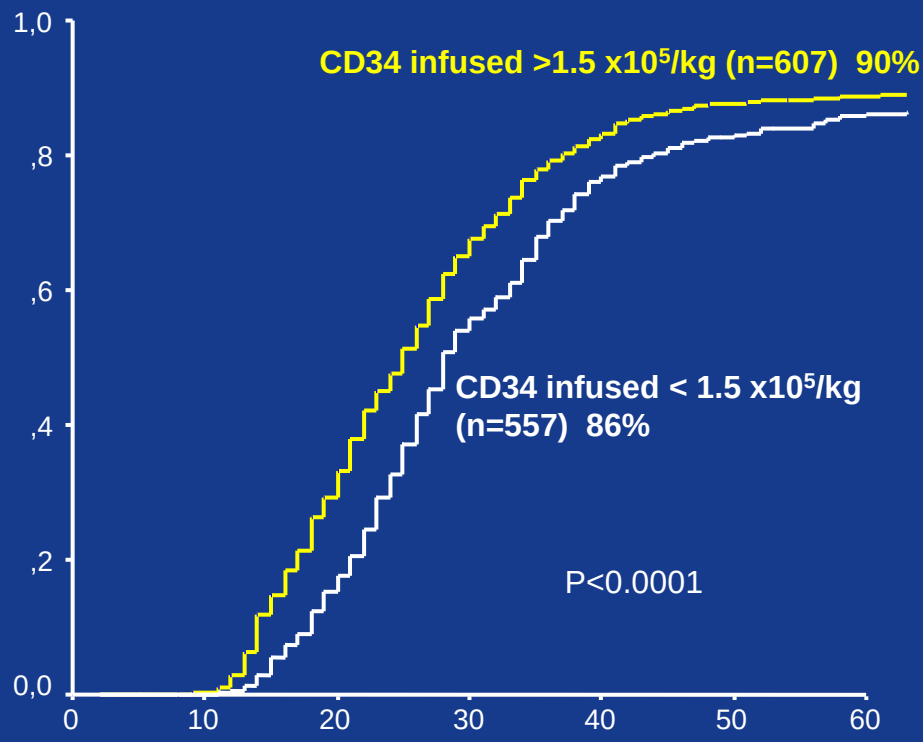
Further management will be based on chimeric status.

Some questions

- Can we predict a graft failure?
- Which are the outcomes and risk factors after a second transplant?
- When to decide for a second transplant?
- Should we use a conditioning regimen before 2nd transplant?
- Should we wait for a patient better clinical condition?

DETERMINANTS OF ENGRAFTMENT: HLA MATCHING AND CELL DOSE





Neutrophil recovery after single UCBT for patients with malignant disorders after myeloablative conditioning regimen

SECOND ALLOGENEIC TRANSPLANTS FOR GRAFT FAILURE

Robert Lown, Paul Veys, Mary Slatter, Rob Wynn, Adrian Bloor, Julia Perry, Rachel Pearce, Keiren Kirkland, Bronwen Shaw

On behalf of the British Society of Bone Marrow Transplantation (BSBMT)

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Objectives and methods

- Assess patient outcomes following second allograft for graft failure, and identify factors influencing:
  - Engraftment
  - Overall survival
- Aim of the study not to investigate incidence/risk factors for graft failure
- 130 UK patients, identified from ProMISe data registry 2000-2010 (interim analysis)
- Transplant centres approached to provide follow-up data for all subjects

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Results

- Mean time between transplants 173 days (8-4102d)
- Median age 9 years (4 months – 69 years)
- 40% adults (>18)
- 39/130 primary graft failure
- 47% malignant
- 68% re-conditioned for second allograft
  - Majority (69% of conditioned) used serotherapy (Alemtuzumab or ATG)
  - 30% MA, 38% RIC (compared to 56%, 43% at first allo)

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Diseases

Disease	n (%)
ALL	8 (6%)
AML	17 (13%)
Biphenotypic	3 (2%)
Secondary	2 (1%)
MDS/MPN	13 (9%)
CLL	4 (4%)
CML	4 (3%)
Myeloma	2 (1%)
Histiocytic disorders	1 (1%)
BM failure	12 (9%)
Haemoglobinopathy	3 (2%)
Lymphoma	10 (7%)
Inherited disorder	53 (40%)

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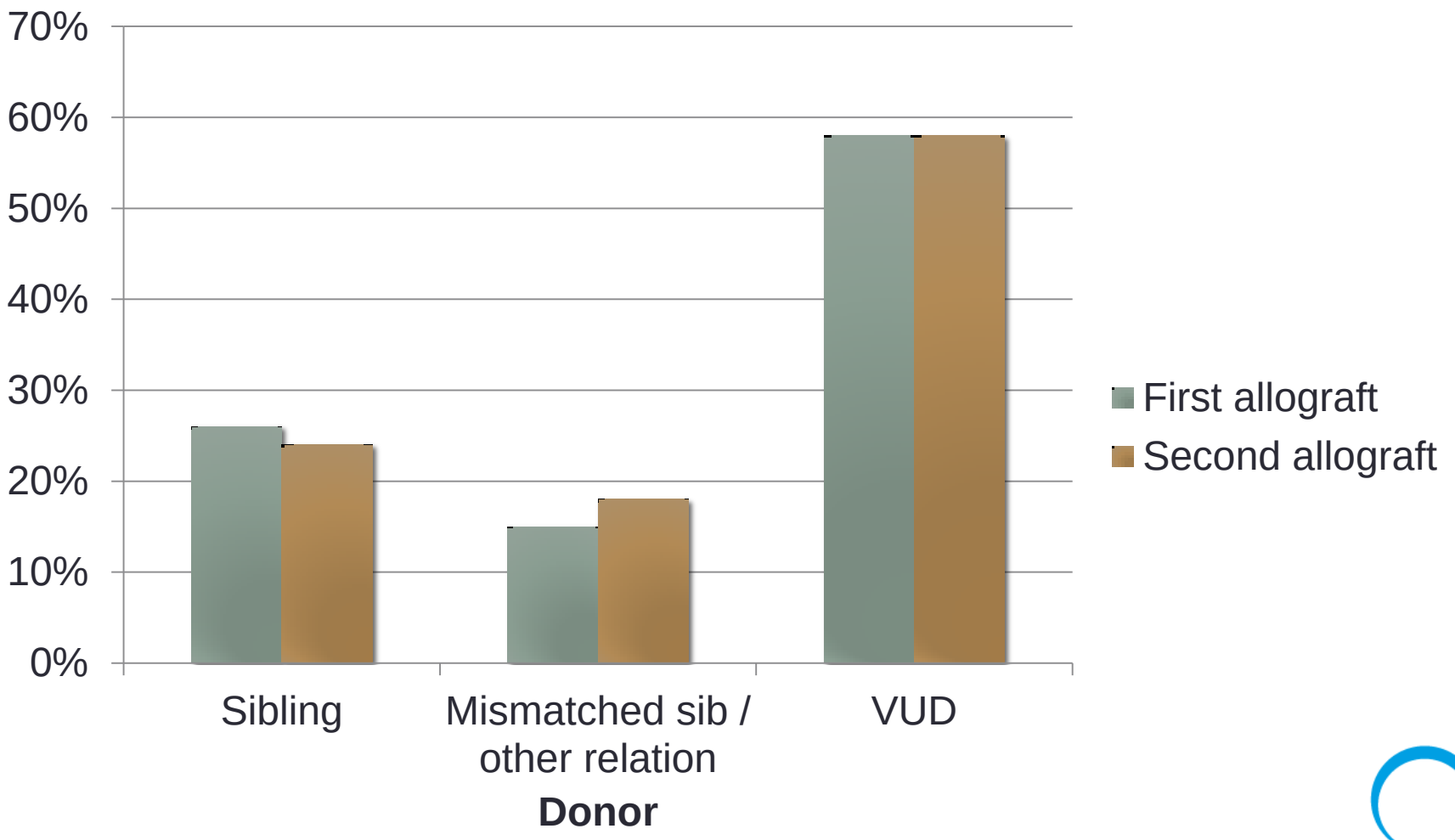
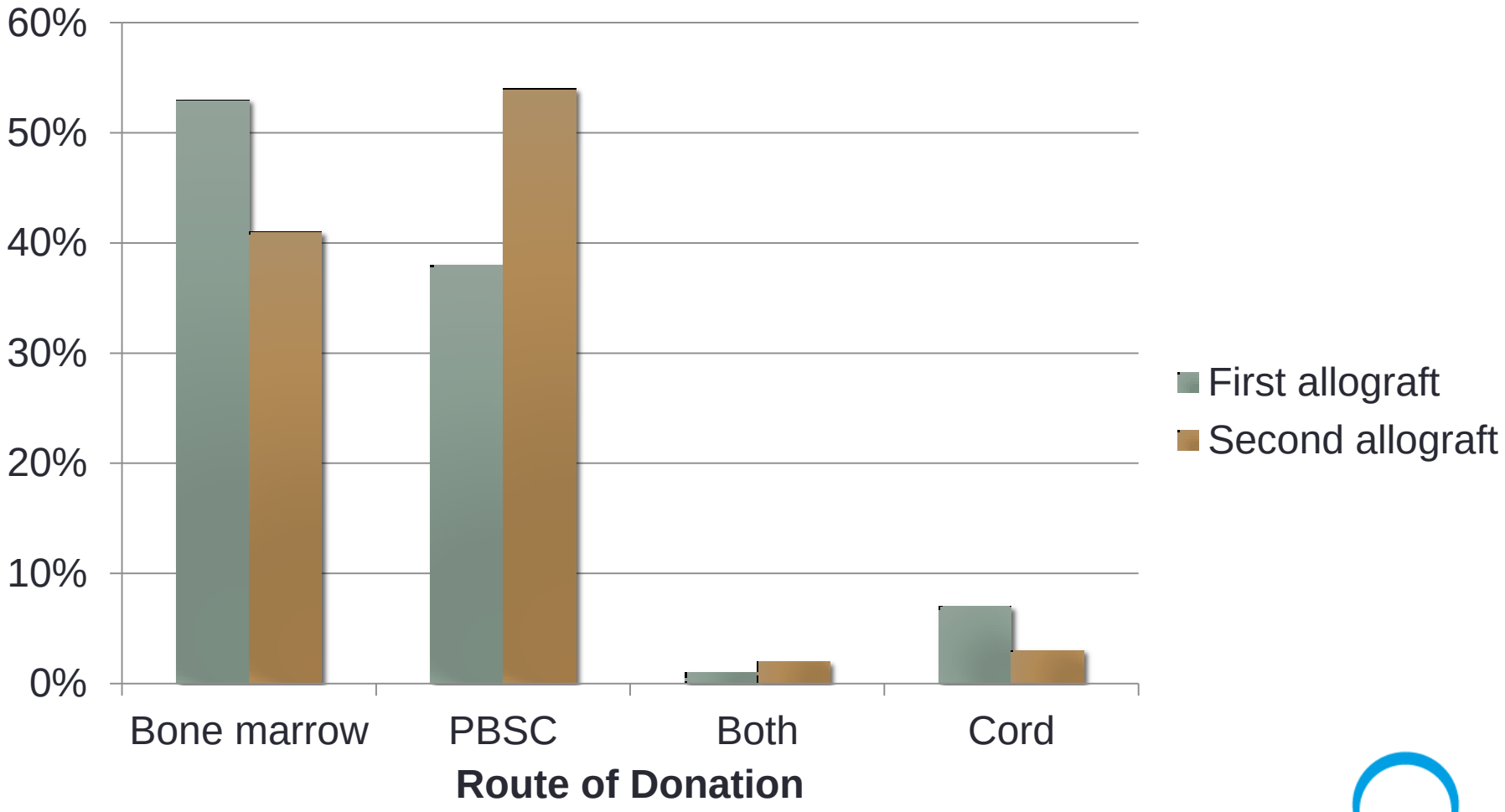
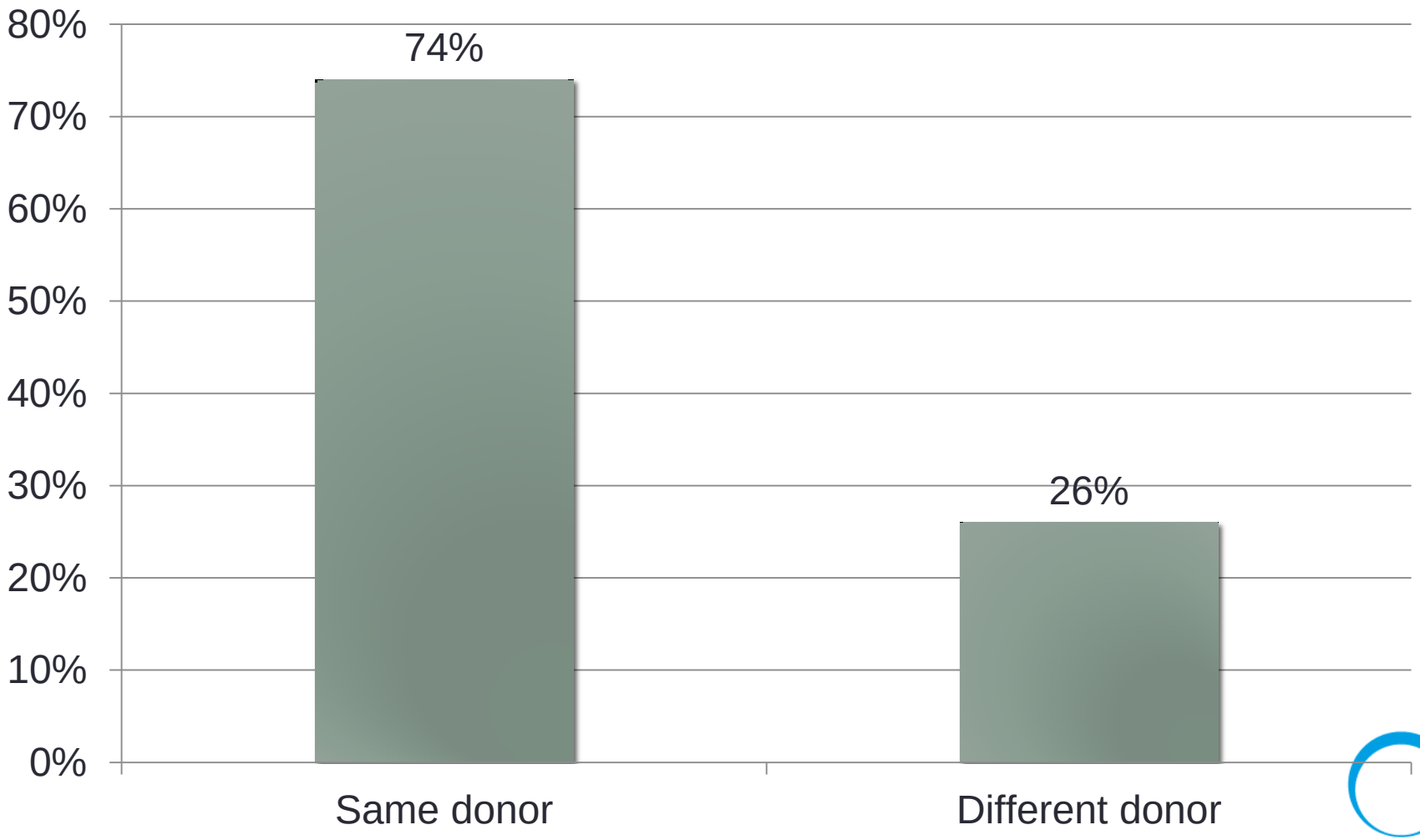
Results


70%
60%
50%
40%
30%
20%
10%
0%
Sibling
Mismatched sib / other relation
VUD
Donor
First allograft
Second allograft

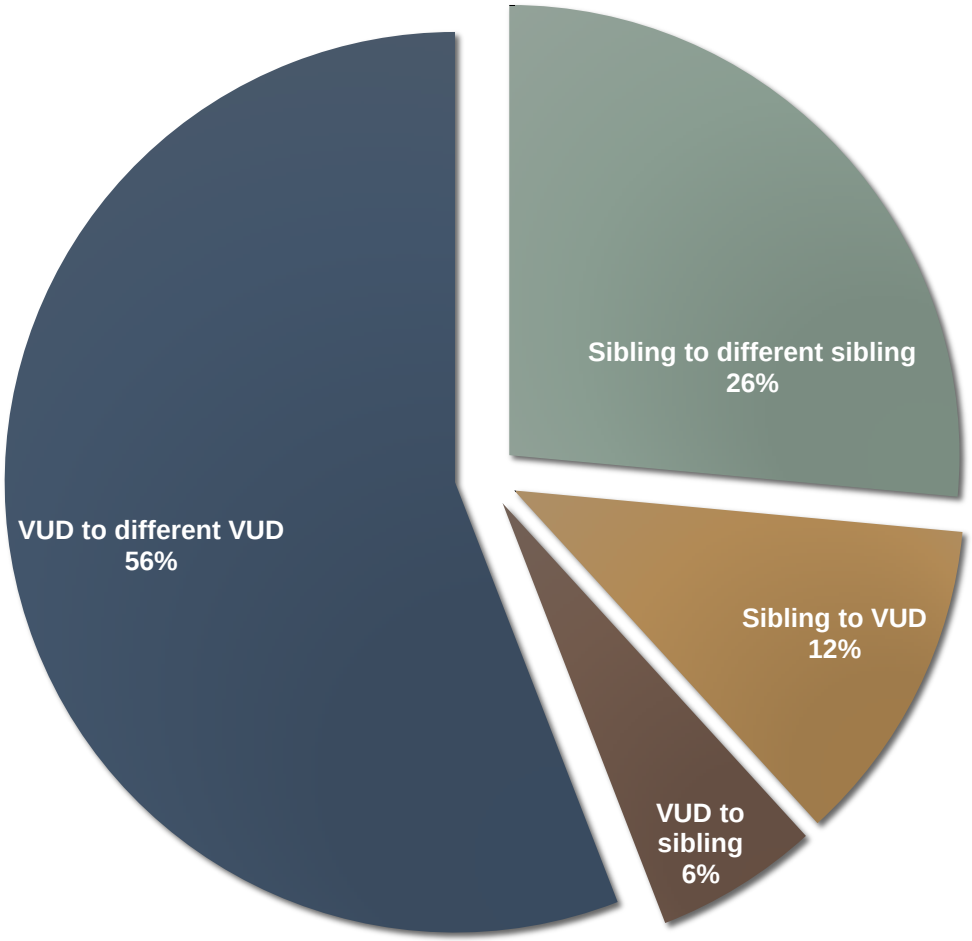
Results


60%
50%
40%
30%
20%
10%
0%
Bone marrow
PBSC
Both
Cord
Route of Donation
First allograft
Second allograft

Results



Results – different donor



Engraftment

- Engraftment in 88% of patients following second allograft

- Factors associated with engraftment failure post 2nd allograft
  - Primary graft failure, p=0.038
  - Older age (>18y), p=0.003
  - Male recipient, p=0.025
  - Reduced intensity conditioning, p=0.031
  - Use of different donor, p=0.026
- No effect of
  - Stem cell source
  - Time between transplants (</>90 days)
  - TNC/CD34+ infused
  - Use of serotherapy

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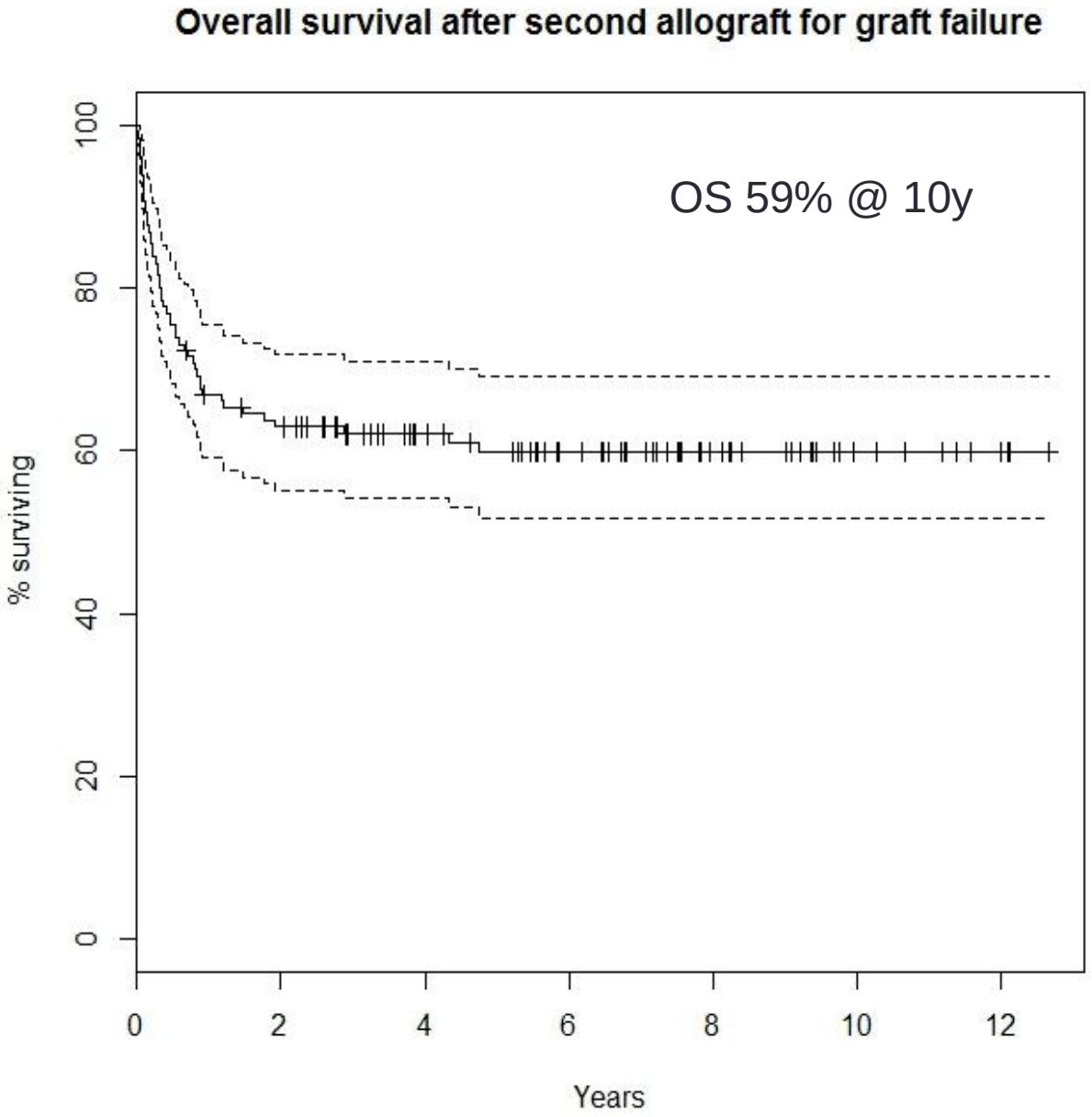
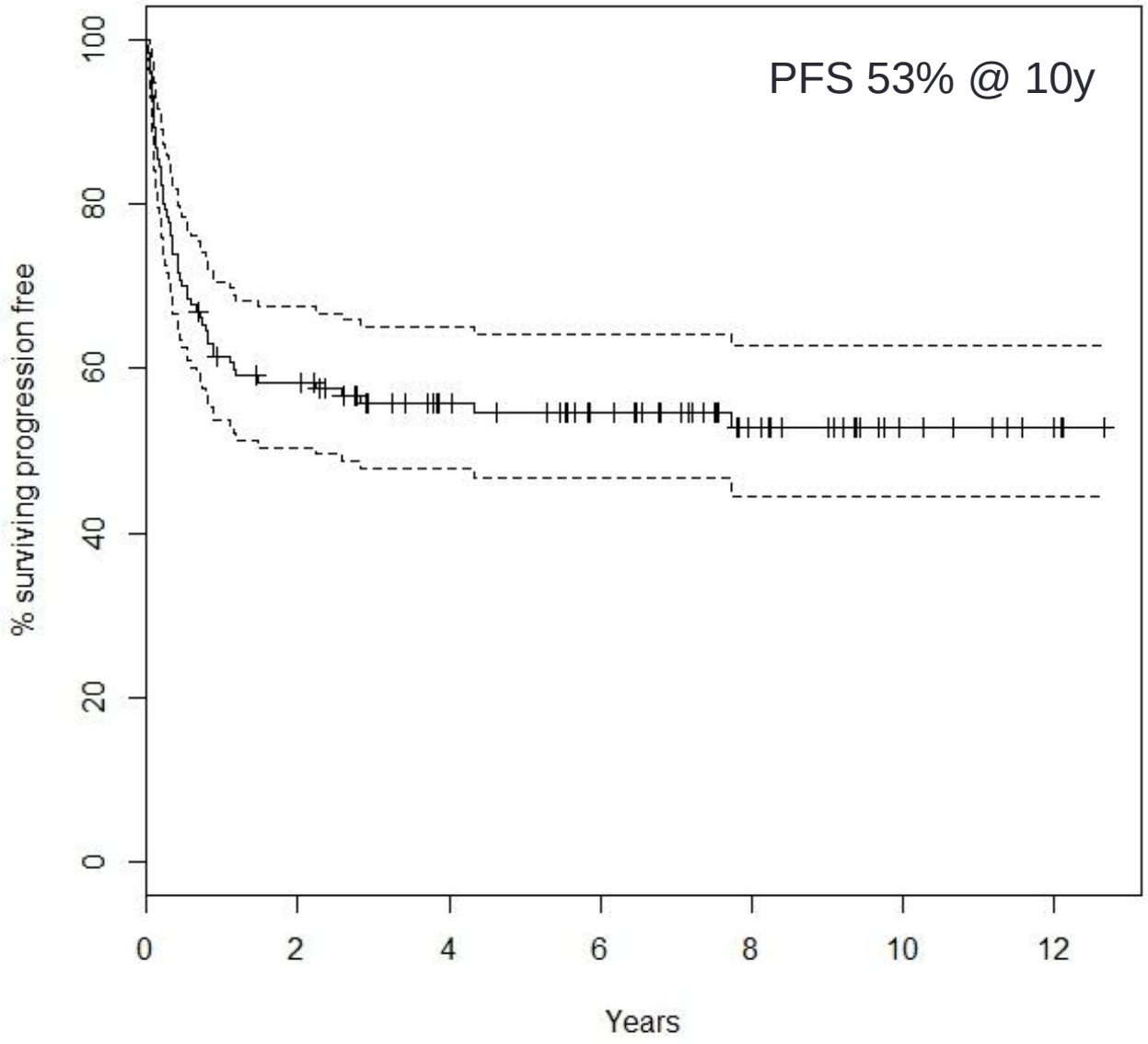
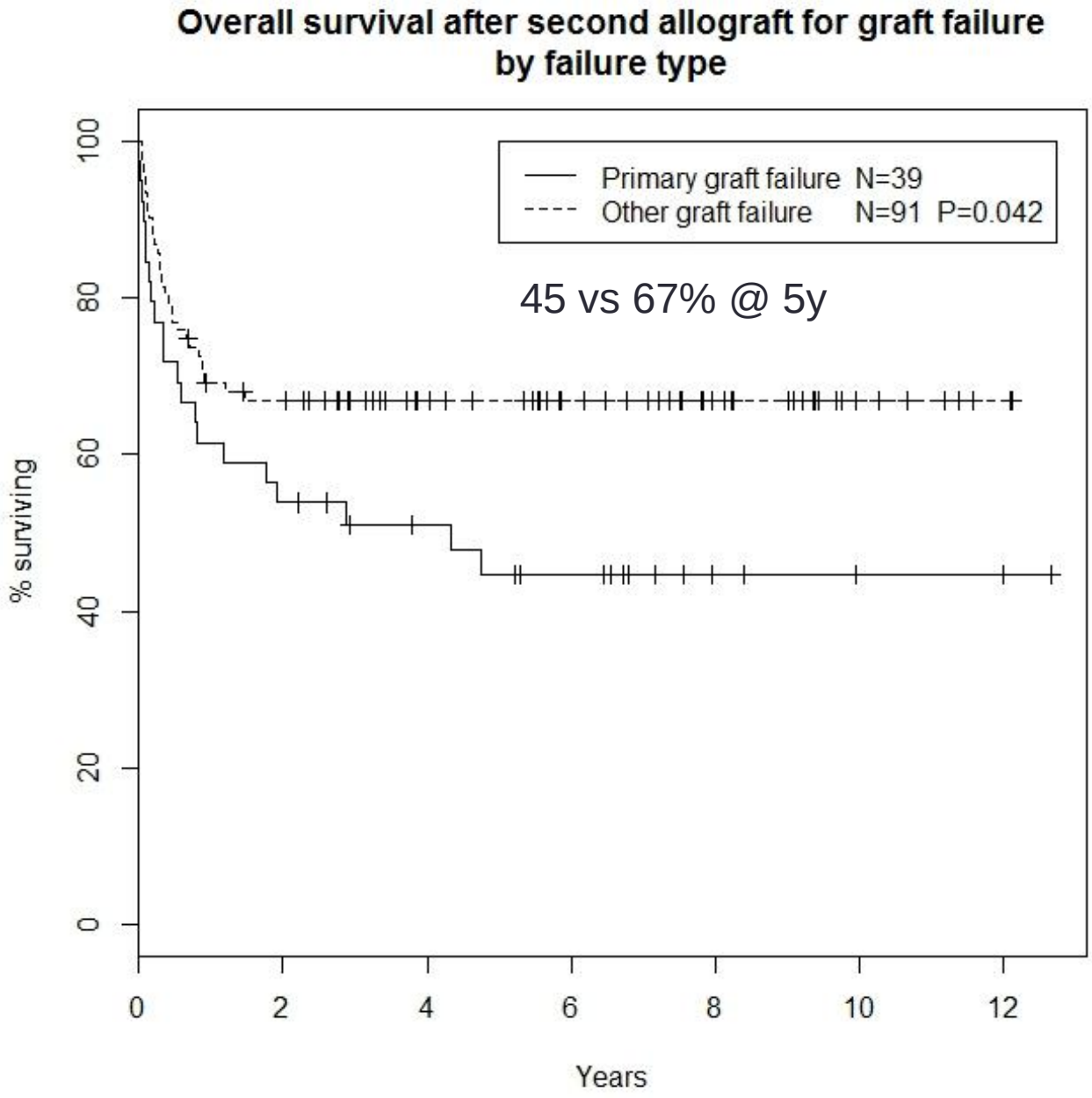
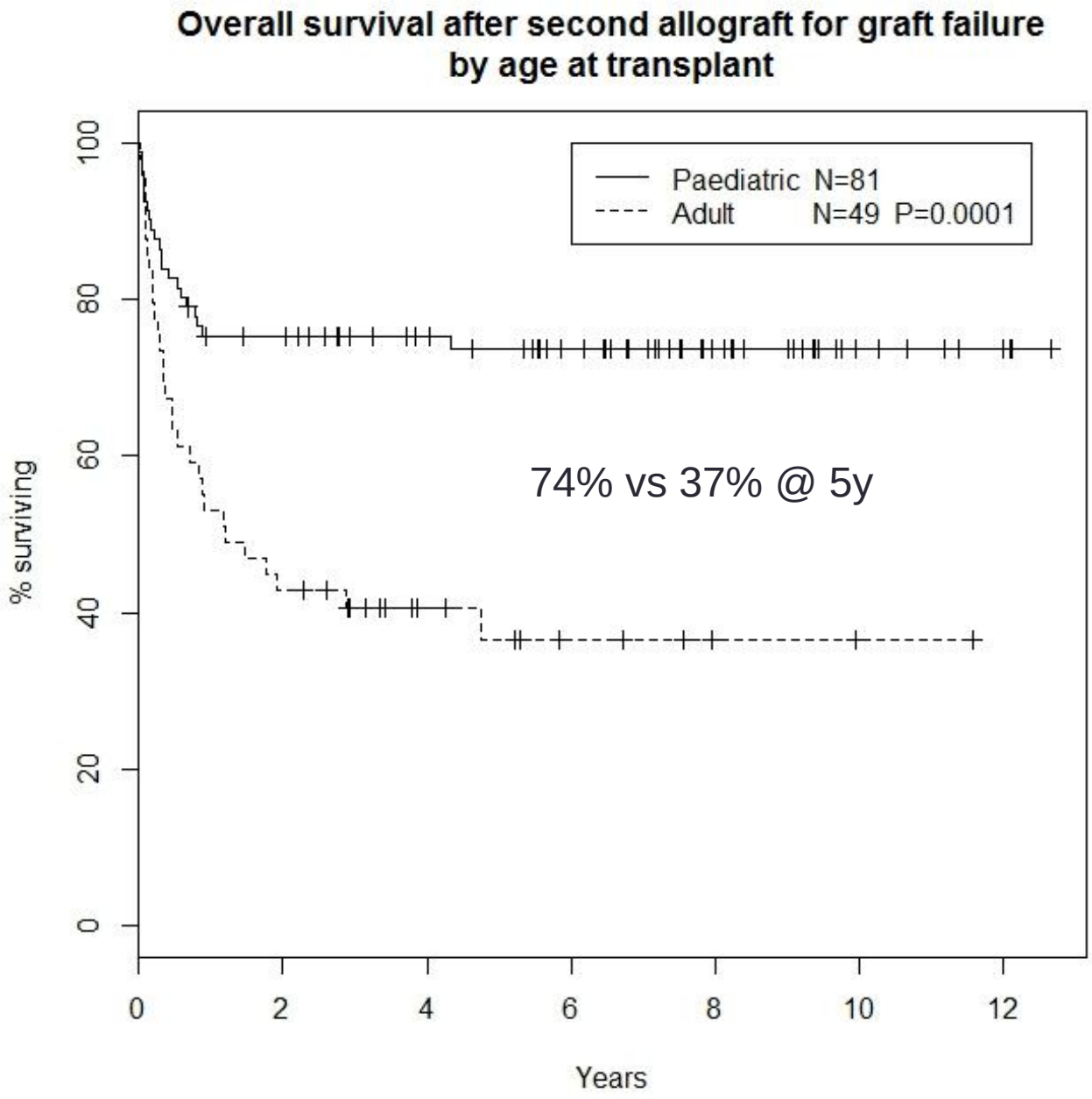
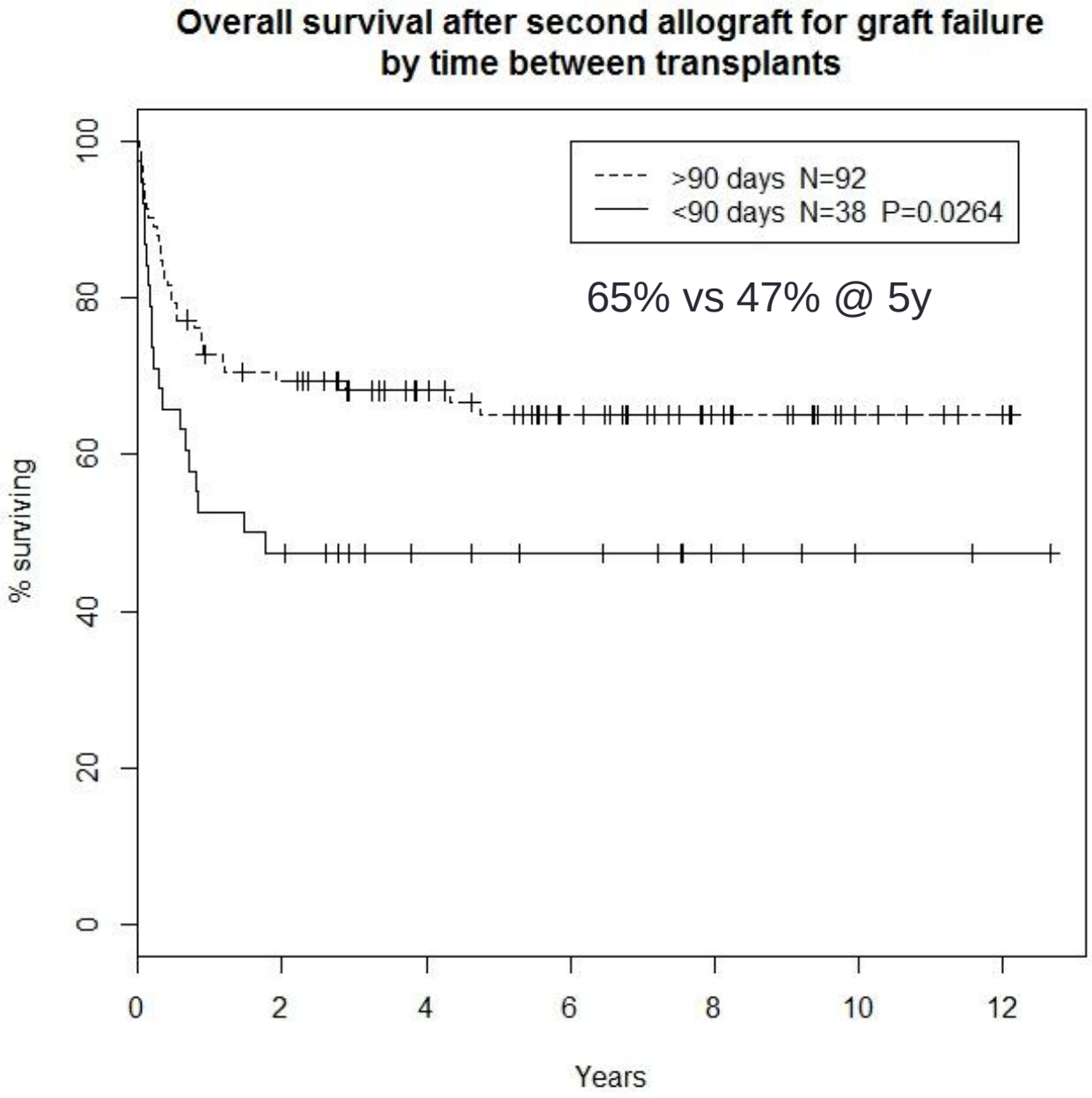

Overall survival after second allograft for graft failure
OS 59% @ 10y
% surviving
0
20
40
60
80
100
0
2
4
6
8
10
12
Years

Progression free survival after second allograft for graft failure




Overall survival after second allograft for graft failure by failure type
Primary graft failure N=39
Other graft failure N=91 P=0.042
45 vs 67% @ 5y
% surviving
0
20
40
60
80
100
0
2
4
6
8
10
12
Years


Overall survival after second allograft for graft failure
by age at transplant
Paediatric N=81
Adult N=49 P=0.0001
74% vs 37% @ 5y
% surviving
0
20
40
60
80
100
0
2
4
6
8
10
12
Years


Overall survival after second allograft for graft failure
by time between transplants
>90 days N=92
<90 days N=38 P=0.0264
65% vs 47% @ 5y
% surviving
0
20
40
60
80
100
0
2
4
6
8
10
12
Years

Other factors in univariate analysis

- None of the following were found do have significant impact on OS or PFS
  - Graft source (BM vs PBSC vs Cord)
  - Donor type (Sib vs other relative vs VUD)
  - Same donor or different donor
  - TNC/CD34+ dose
  - Use of serotherapy

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Multivariate analysis - Engraftment

Multivariate	HR for engraftment	P value
Primary graft failure	2.19	0.245
Sex (Male)	2.11	0.389
Conditioning (None v. RIC v. MA)	1.90	0.237
Non malignant v. malignant	1.53	0.703
Age (paediatric v. adult)	7.31	**0.063**
Same donor	8.99	**0.010**

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Multivariate analysis – OS/PFS

	HR for mortality	P value	HR for progression free survival	P value
Primary graft failure vs other	1.22	0.525	1.45	0.538
Age (adult v. paediatric)	1.46	0.298	2.59	**0.013**
Time between transplants <90d	1.43	0.224	1.22	0.468
Malignant	2.53	**0.018**	1.46	0.325

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Limitations

- Retrospective dataset
- Interim analysis
- Data ambiguous on whether primary or secondary graft failure
- Numbers small for primary graft failure limiting formal analysis of this population
- Wide variation in clinical practice, e.g. conditioning regimens

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Conclusions

- Encouraging results
- Successful engraftment and long-term survival possible following a second allograft for graft failure
- Outcomes superior in children and those with non-malignant disease
- However, over a third of adult patients and those with malignant disease can also achieve long-term survival

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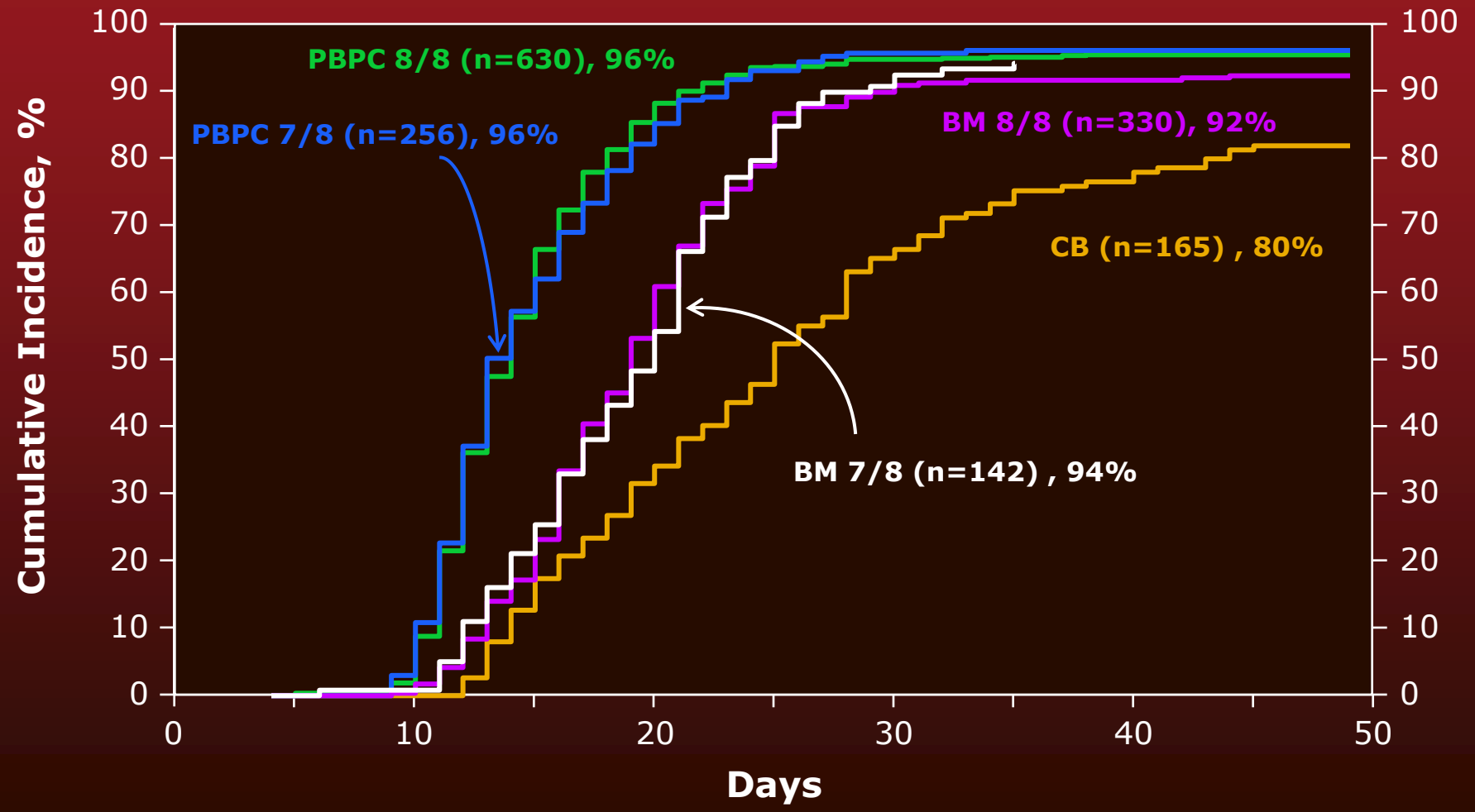
Graft failure after UCBT

Neutrophil Recovery after single UCBT compared to HLA allele typing BM or PB in Adults with Acute Leukemia



M Eapen, V Rocha, E Gluckman and J Wagner on behalf of CIBMTR and Eurocord EBMT 2009

Possible reasons for delayed engraftment and higher incidence of graft failure

Biological reasons (quantity and quality reasons)
- Cell dose (stem cells, progenitors and lymphocytes)
- Immature progenitors cells and lymphocytes
- Accessory cells (?)
- Homing?

Clinical reasons
- Influence of HLA
- Other genetic factors ?
- Disease related factors
- ABO incompatibility
- Transplantation related factors
- Banking and procedures related factors

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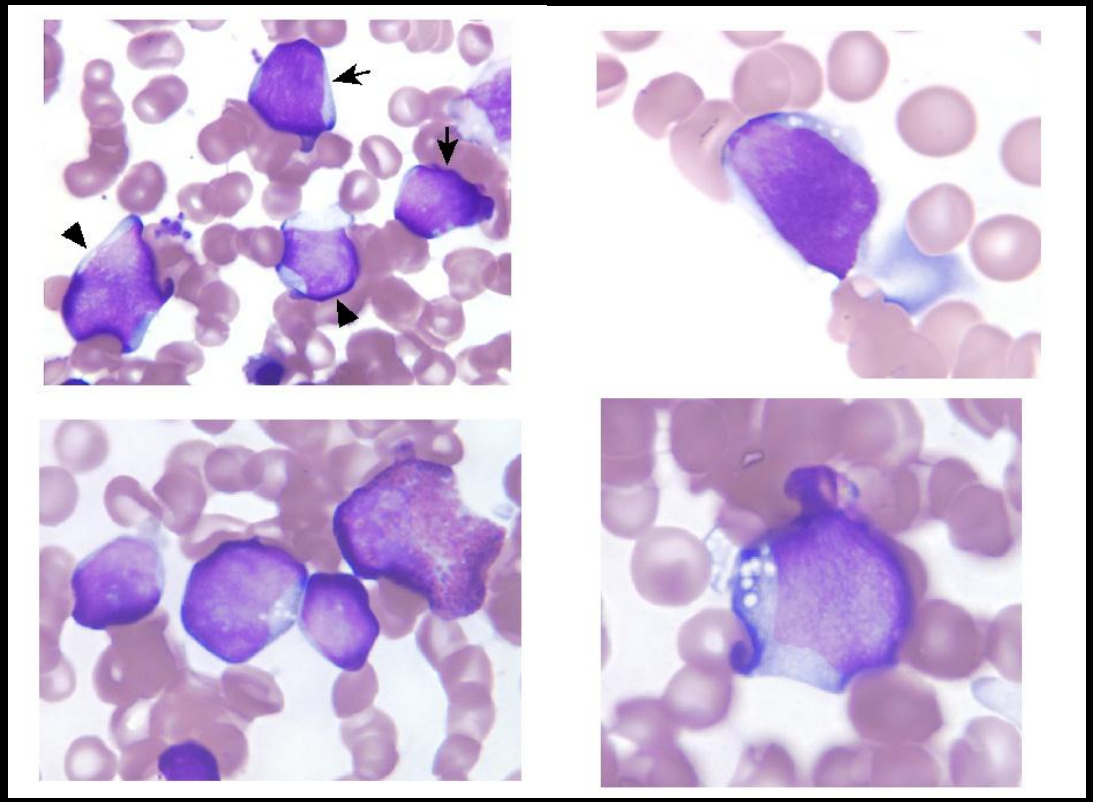
Is the problem too few stem cells or too few committed progenitors?

Day 21 marrow



McKenna D et al, Leukemia 2002; 16: 2171

Courtesy of J Wagner

79 UCBT patients evaluated

- **14 (17.7%) with 3-50% TdT+ lymphoblast like cells**
- **persist as long as 23 months after UCBT**
- **observed in 1/79 BMT patients (2.2%)**

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Multivariate analysis for neutrophil recovery

- Number of CD34+ cells >1.5
- HLA compatibility (6/6, 5/6 , 4/6 versus 3/6)
- Use of Fludarabine
- Use of prophylactic HGF
- Remission status of the disease

Multivariate analysis for platelets recovery

- Number of CD34+ cells >1.5
- Use of Fludarabine
- Use of prophylactic HGF
- Transplant year >2004

DETERMINING TIME OF LATE ENGRAFTMENT AFTER SINGLE CORD, UNRELATED TRANSPLANTATION: AN ANALYSIS OF THE EUROCORD REGISTRY

R. Saccardi, M. Labopin, A. Ruggeri, C. Kenzey, W. Chavez, R. Cunha, E. Gluckman and V. Rocha

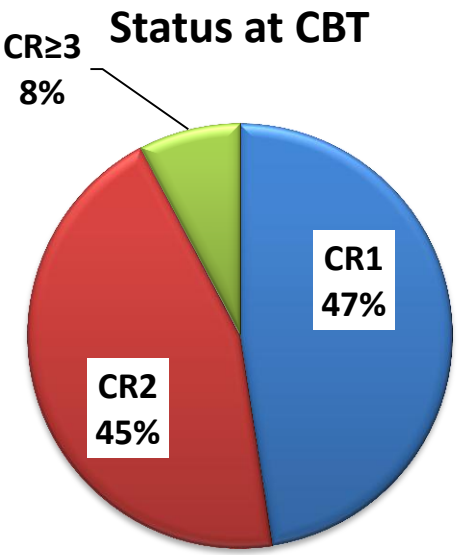
Eurocord, Paris

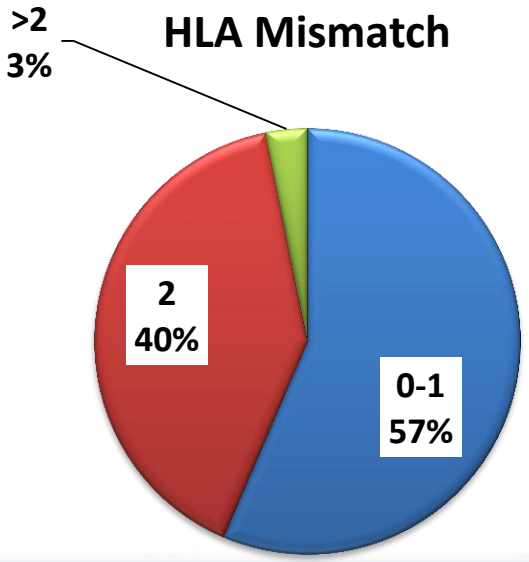
GRAFT FAILURE AFTER UCBT

- Graft failure is reported in about 10-20% of clinical reports.
- Procurement of an alternative SC source for a 2nd transplant is time-consuming and need to be adequately planned
- Time definitions of late engraftments and graft failure are not universally accepted
- We investigated the kinetics engraftment in UCBT to develop an evidence-based strategy supporting the decision of a 2nd transplant

PATIENTS SELECTION

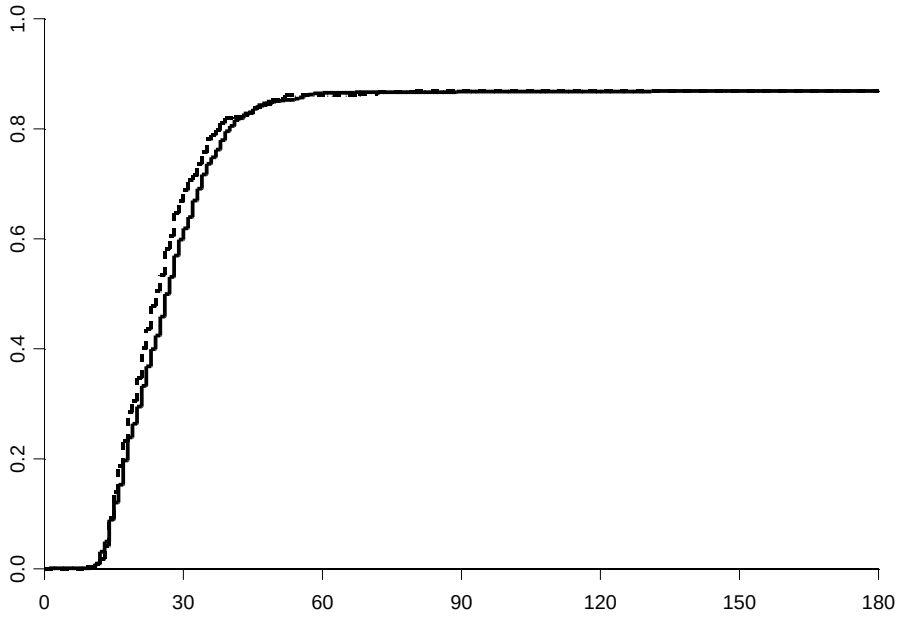
- 1268 single, unrelated
- Acute Leukemia
  - AML 455
  - ALL 813
- Ped/adult = 929/338
- Weight = 33 Kg (5-112)
- Myeloablative Cond.
  - TBI 49.6%
  - ATG/ALG 77.1%
  - MoAb 0.9%
- TNCx10^7/Kg= 5.1 (1.1-41.8)





ENGRAFTMENT

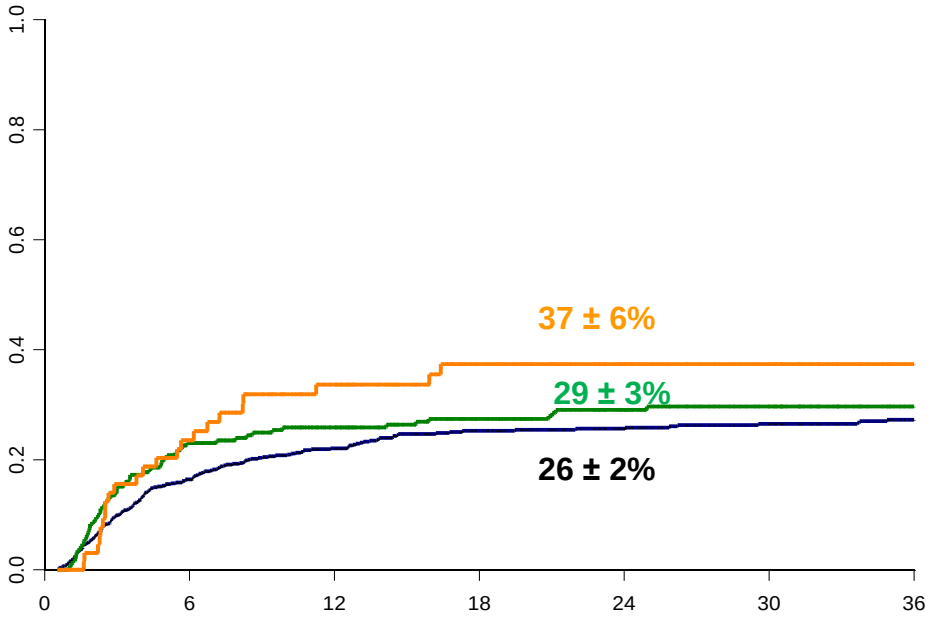
- Cumulative incidence of engraftment was 86% at +60 d
- Median time to engraft was:
  - Children 25 (11-108)
  - Adults 23 (11-116)
- The two subsets were analyzed together in the engraftment study



Adult vs Ped ns

Impact of engraftment time on TRM

- 1102 pts engrafted @24 d (10-131)
- Cumulative incidence of NRM was 29% @ 36 months
- Main causes of NRM were GVHD (25.3%), Viral (16.5%), fungal and bacterial infections (11.9)%
- Engraftment beyond +42 has a detrimental effect on non-relapse mortality

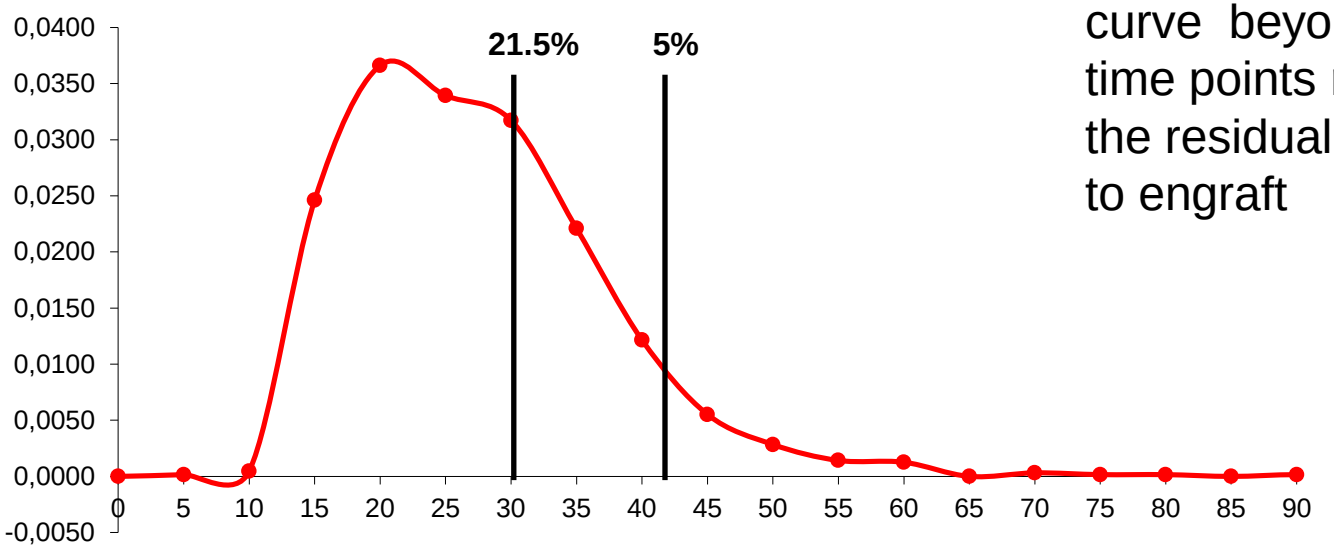


Engraftment time

> 42
30-42 d
<30

PROBABILITY OF ENGRAFTMENT

- The **Probability Density** to engraft describes the probability to engraft at each time point from CBT, also considering competing events (ie early deaths)
- The engraft probability peaks at +21, the median halves at +31 (21.5%) and drops to 5% at day 42



The area under the curve beyond each time points represents the residual probability to engraft

Outcomes of Second Allogeneic Transplants for Early Graft Failure after Unrelated Cord Blood Transplantation

Juliana F Fernandes, Daniela Setubal, Marc Bierings, Martin A Champagne, Ricardo Pasquini, Gérard Socié and Eliane Gluckman, Vanderson Rocha
on behalf of Eurocord

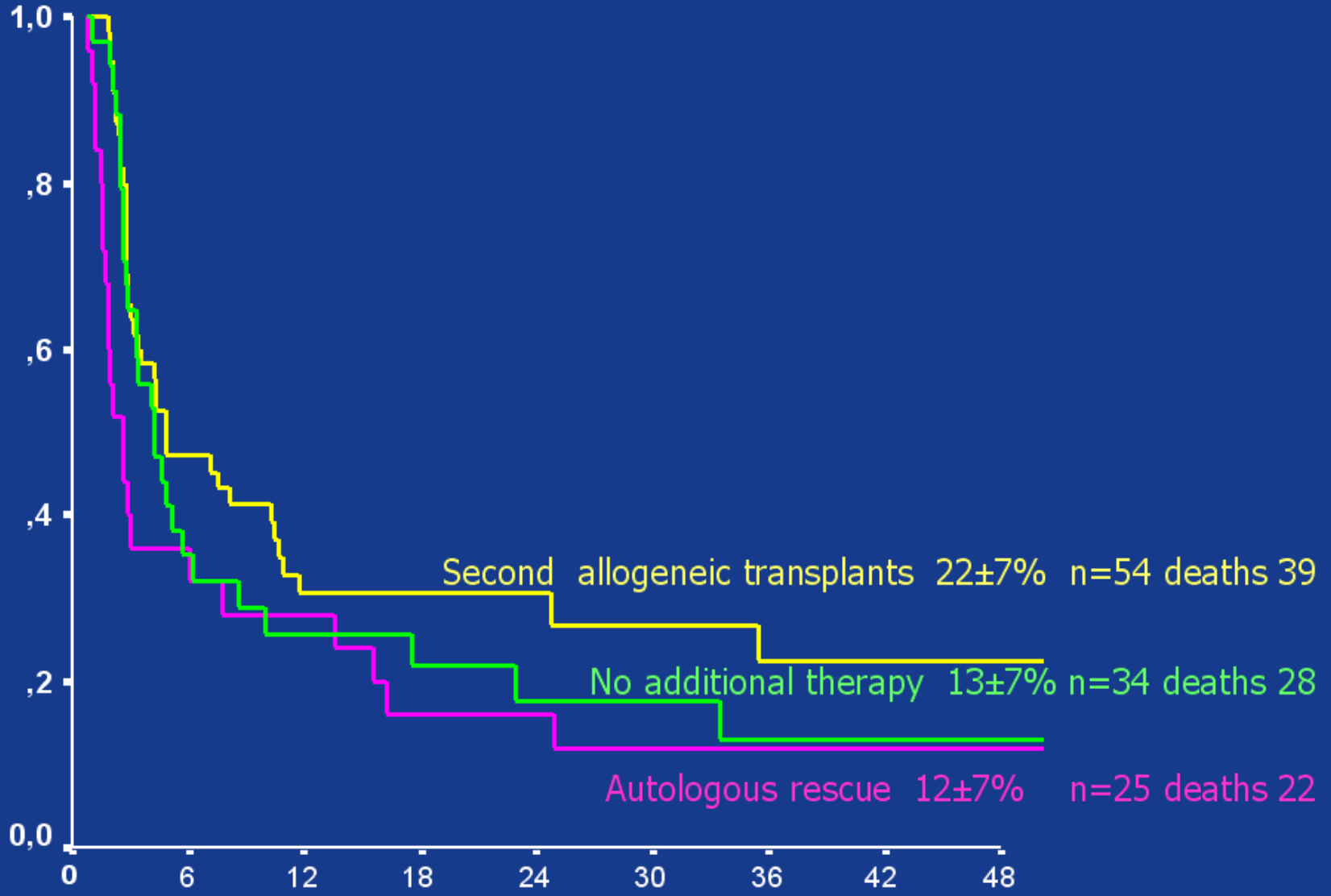
Eligibility

- Inclusion criteria
  - Unrelated cord blood transplantation for malignant and non-malignant hematological diseases
  - Primary Graft Failure
    - Failure to achieve a stable peripheral blood neutrophil count > $500x10^6$/L for 3 consecutive days until 60 days after UCBT or having received a treatment for graft failure in this period defined by the transplant center
- Exclusion criteria
  - Relapse within 100 days from the transplant
  - Previous allogeneic transplant
  - Survival inferior to 28 days

Patients Selection

- Retrospective study
- 57 participating centers in 18 countries
- 1115 Unrelated Cord Blood Transplants for hematological diseases reported to Eurocord / EBMT
- 113 patients met the eligibility criteria of the study

3 years Event-free survival after graft failure in UCBT recipients



Patients Characteristics n=54

- Diagnosis
  - Hematological malignancies (n=34) – 63%
    - ALL = 16
    - AML = 9
    - MDS = 8
    - NHL =1
  - Bone Marrow Failures (n=20) – 37%
    - Fanconi Anemia = 14
    - Idiopathic AA = 5
    - Congenital Amegakaryocytosis = 1

First transplants:

- Single cord n=50 (93%)
- Myeloablative conditioning n=44 (81%)

At second transplants

- Median age = 12 yrs (1-51)
- Median weight = 40kg (9-90)
- 31 males ; 23 females
- Active infectious disease at 2nd transplants= 21 (42%)
- Performance status (Karnofsky/Lansky) ≤ 80 = 15/38 (40%)
- Median follow-up time for survivors = 24 months (5-92)

Second Transplants – Graft Characteristics

Cell Source	n	HLA mismatches (n)	TNC infused/kg (median)	CD34+ cells infused/kg (median)
Unrelated Bone Marrow	5	1 - 3 / 10	$4,4 \times 10^8$	$4,2 \times 10^6$
Haploidentical related PBSC	13	1 - 3 / 6	-	$7,38 \times 10^6$
Unrelated Single Cord Blood	26	1 - 4 / 6 0-1 (8) / 2-4 (15)	3×10^7	$1,3 \times 10^5$
Unrelated Double Cord Blood	10	1 - 3 / 6	5×10^7	3×10^5

Second Transplants Characteristics

- Median time between first and second transplants = 56 days (33-116)

  UBMT= 86 (64-98)
  Haplo = 55 (36-105)
  Cord Blood = 56 (33-116)

- Conditioning regimen
  - No conditioning n=5
  - Myeloablative n=5
    - BU + CY + ATG = 2
    - FLU + MELPH ± TBI = 2
    - FLU + CY + BU + MOAB = 1
  - Non-Myeloablative n=39
    - FLU + CY ± ATG ± TBI = 14
    - FLU ± ATG ± TBI = 8
    - ATG = 5
    - CY ± ATG ± TBI = 5
    - FLU + MELPH ±TBI ± ATG = 4
    - OTHERS = 3

- GVHD prophylaxis
  - CsA + steroids = 9
  - CsA + MMF = 7
  - CsA + MTX = 5
  - CsA = 6
  - MMF + steroids = 2
  - Others = 7

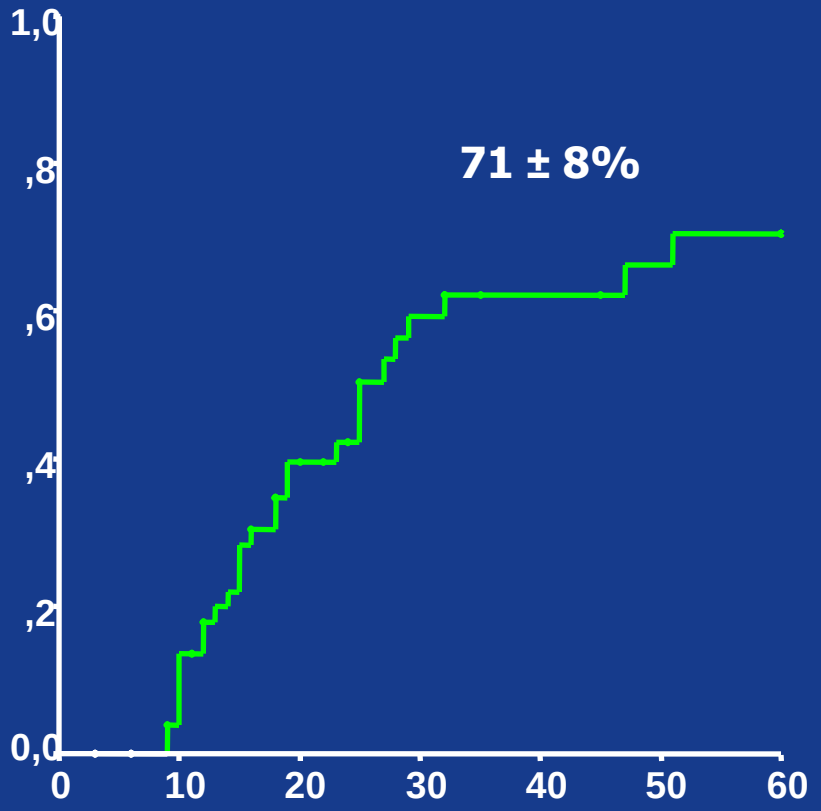
- T-cell depletion – 12 (24%)
  - Haplo (n=11)
  - UBMT (n=1)

Results

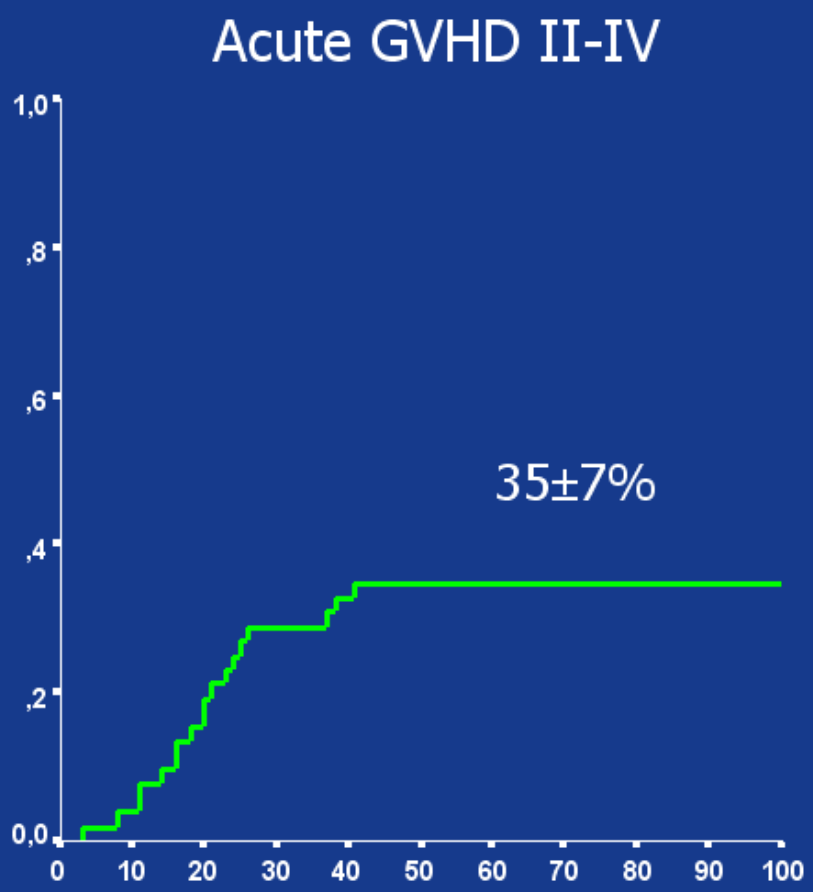
- Median time for neutrophil engraftment (days) = 16 (9-51)

UBM	n = 5	engrafted = 5
PBSC	n = 13	engrafted = 11
SCB	n = 26	engrafted = 5
DCB	n = 10	engrafted = 8

60 Day – Probability of engraftment



Results



- Acute GVHD by stem cell source

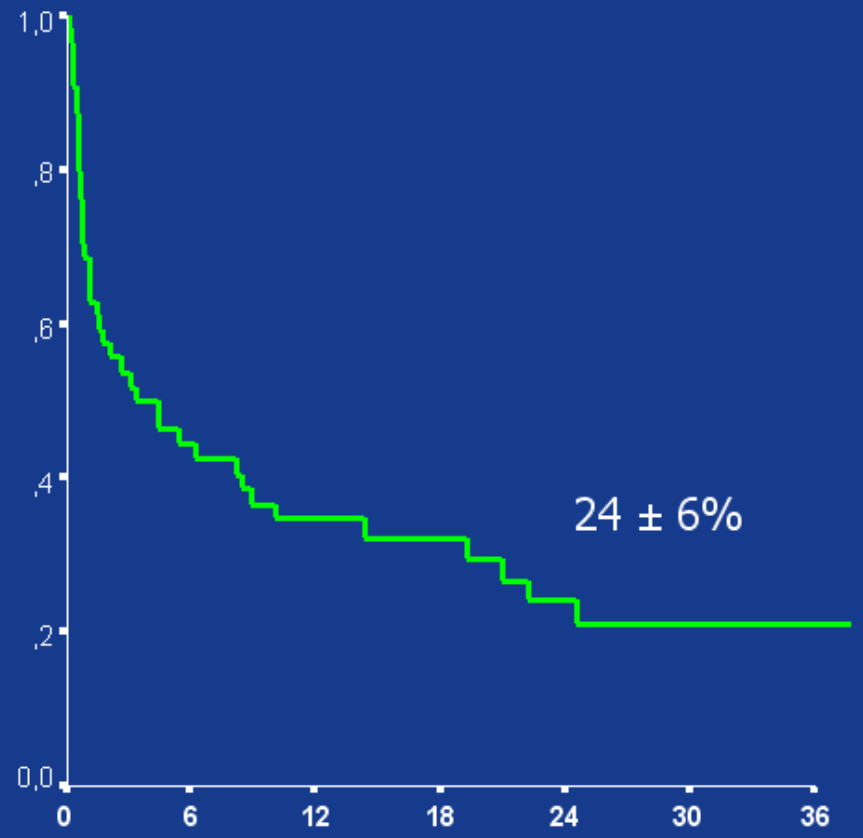
  UBM n = 5 ev = 4
  PBSC n = 13 ev = 3
  SCB n = 26 ev = 4
  DCB n = 10 ev= 7

- Acute GVHD III-IV ev = 12

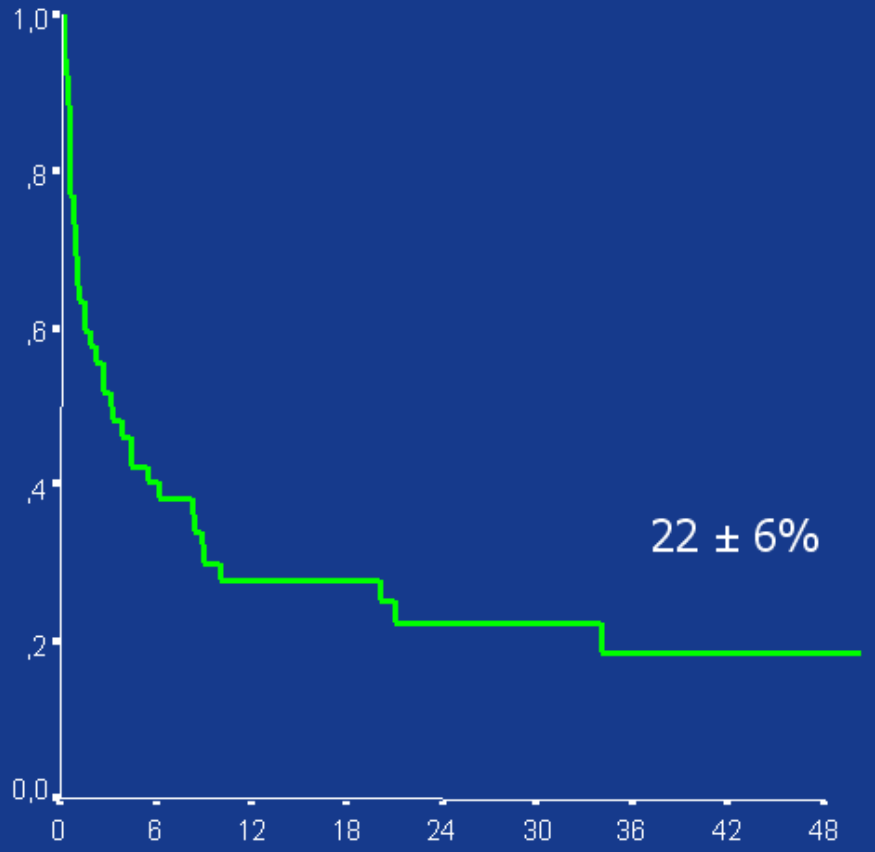
- Chronic GvHD
  - 8 / 24 (33%)
    - Limited – 3
    - Extensive – 5

Results

2 years – Overall Survival

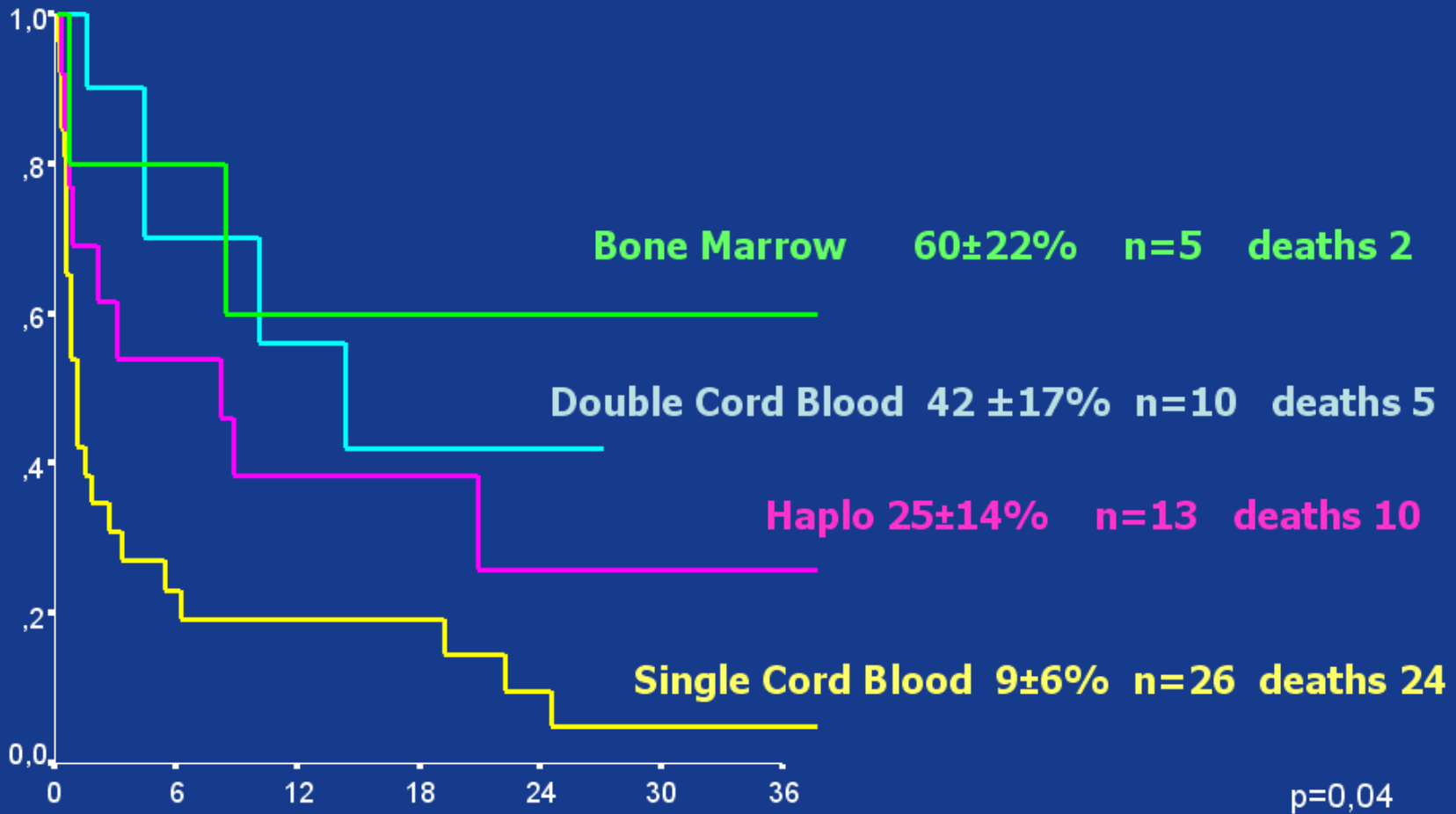


2 years – Event-Free Survival



Results

2 years event-free survival after second transplants according to the source of cells



Conclusion

- With an overall survival of 24%, second transplants may be considered as a salvage therapy for primary graft failure after unrelated cord blood transplantation
- Choice of conditioning regimen and best cell source are open questions
- Double cord blood units, haploidentical PBSC donors and non-myeloablative conditioning regimens seem to be more suitable choices

Avoiding graft failure after UCBT

Following recommendations

If after thawing nucleated cell dose $<1x10^7$/kg and CD34 lower than $1x10^5$/kg ask urgently for another cord blood, preference of double cord and communicate to the CB bank.

If cell dose after thawing between 1 to 2 $x10^7$/kg, look at CD34 and other risk factors and importantly look for CFU-GM results

If at day 28 no sign of neutrophil recovery, perform bone marrow aspirate and chimerism. If no sign of engraftment , discussion of second transplant (median time of 10 to 15 days to have another graft available)