Oxford University Hospitals NHS
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Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

Update on Unrelated Cord Blood Transplantation

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eurocord

State of the art: UCBT

- Eurocord Registry update
- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen
- Complications (engraftment and infections)

UCBT

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Eurocord Registry Update

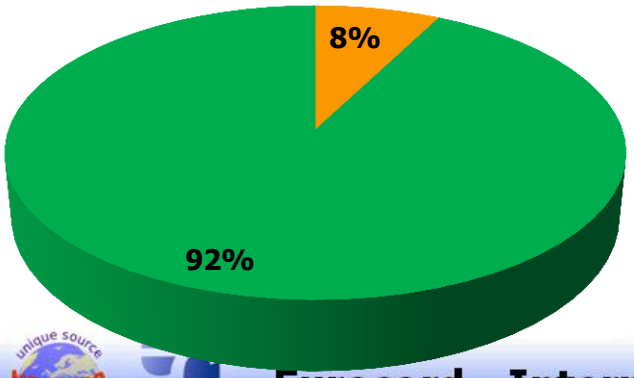
- **12.066 CBU shipped for transplantation (283, 2%, not used):**

11.783 CBU used for:

- **9.883 CBT from 1988 to 2012 in 51 countries and 577 centres**

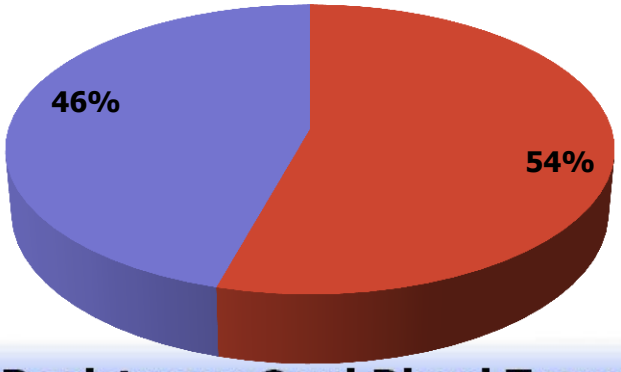
293 EBMT
267 Non-EBMT

- **Related n=708 (8%)**
- **Unrelated n=8618 (92%)**



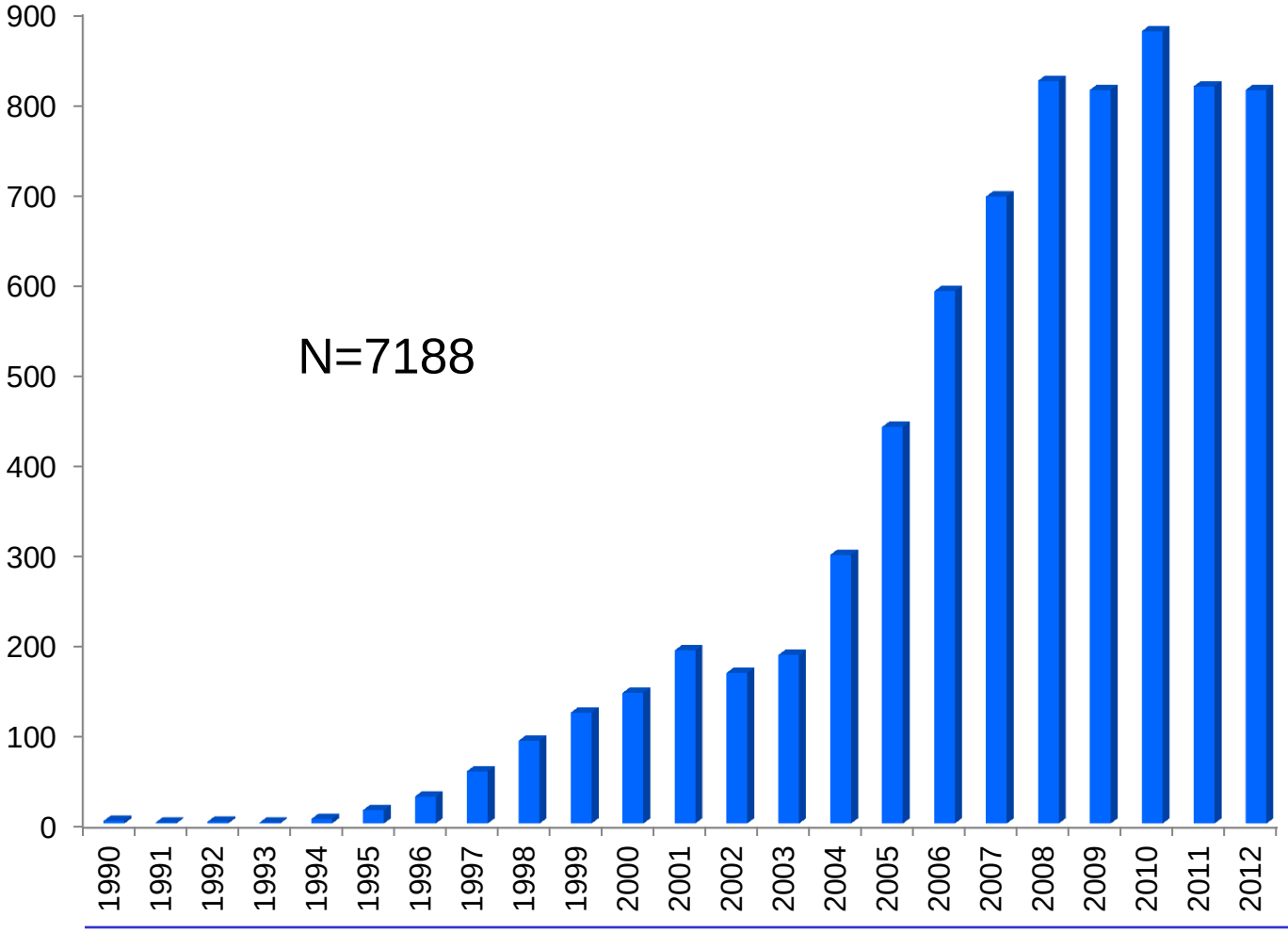
6958 cases (75%)
2379 cases (25%)

- **Children n=5071 (54%)**
- **Adult n=4265 (46%)**



Eurocord Registry

N° of European CBUs shipped by year*



Year of shipment	N of CBUs
1990	3
1991	1
1992	2
1993	1
1994	5
1995	15
1996	30
1997	58
1998	92
1999	123
2000	145
2001	192
2002	167
2003	187
2004	298
2005	440
2006	590
2007	695
2008	823
2009	813
2010	878
2011	817
2012	813

agence de la biomédecine

* 215 CBUs not infused are included in the bar chart

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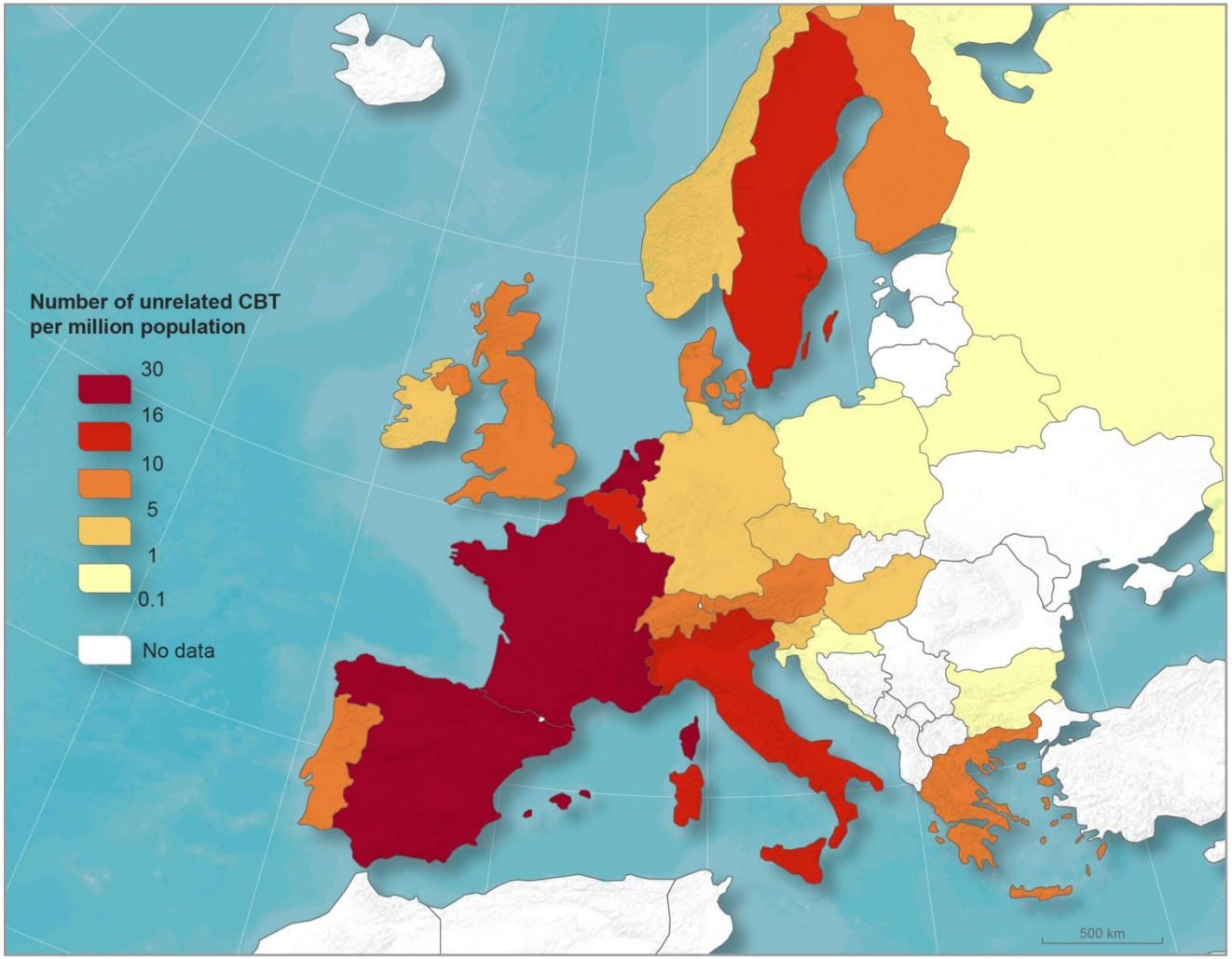
Eurocord Registry - European CBT

Unrelated Cord Blood Transplantations performed in Europe until December, 31st, 2012, data from Eurocord registry



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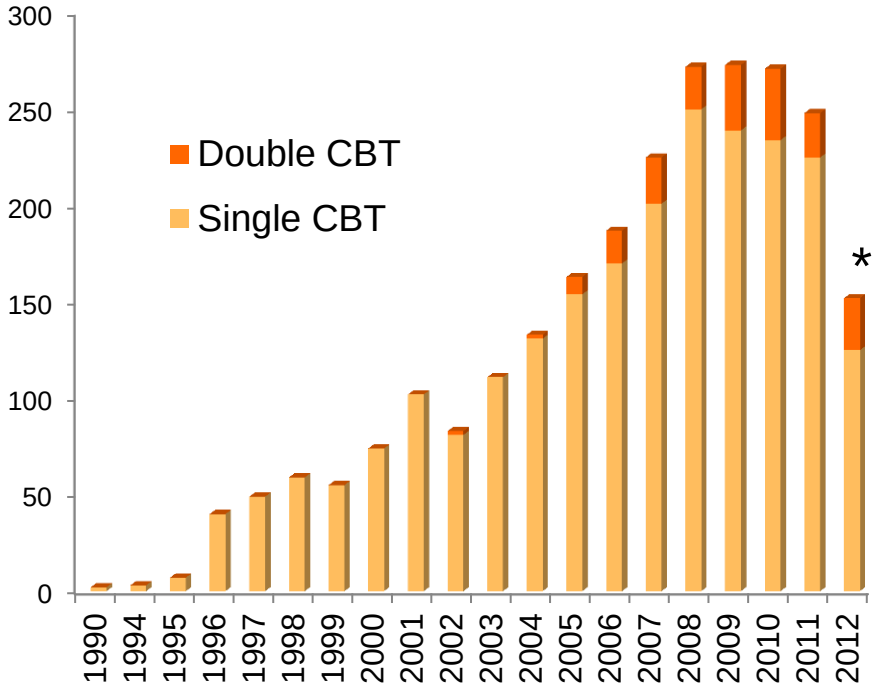
Eurocord Registry

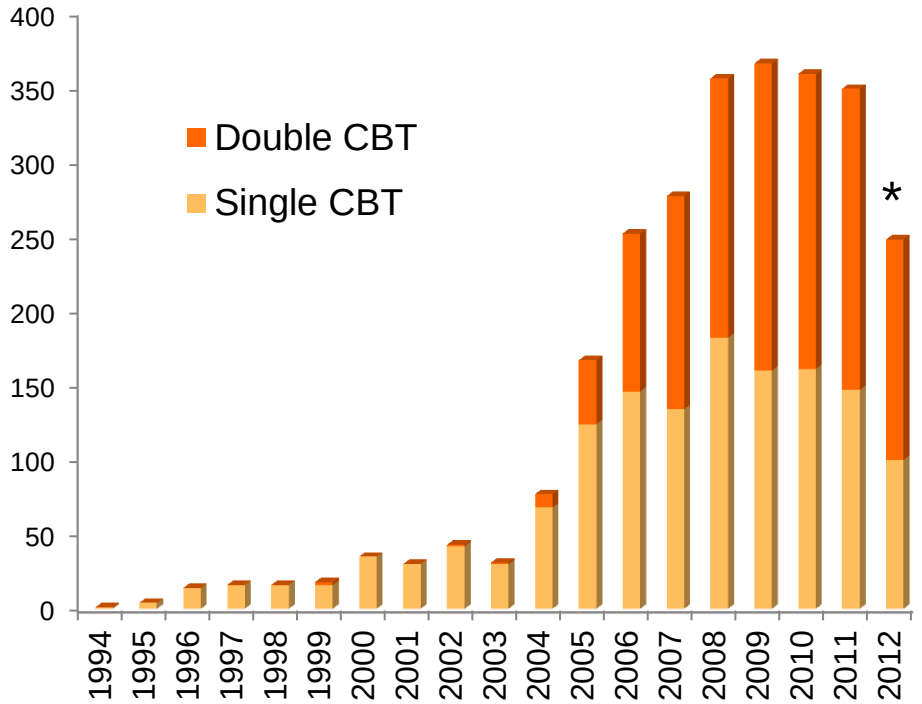
Unrelated European CBT by recipient's age and graft type

Children



In children: 92% single CBT

Adults



In adults: 47% double CBT

agence de la biomédecine

* Still collecting 2012 data

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UCBT

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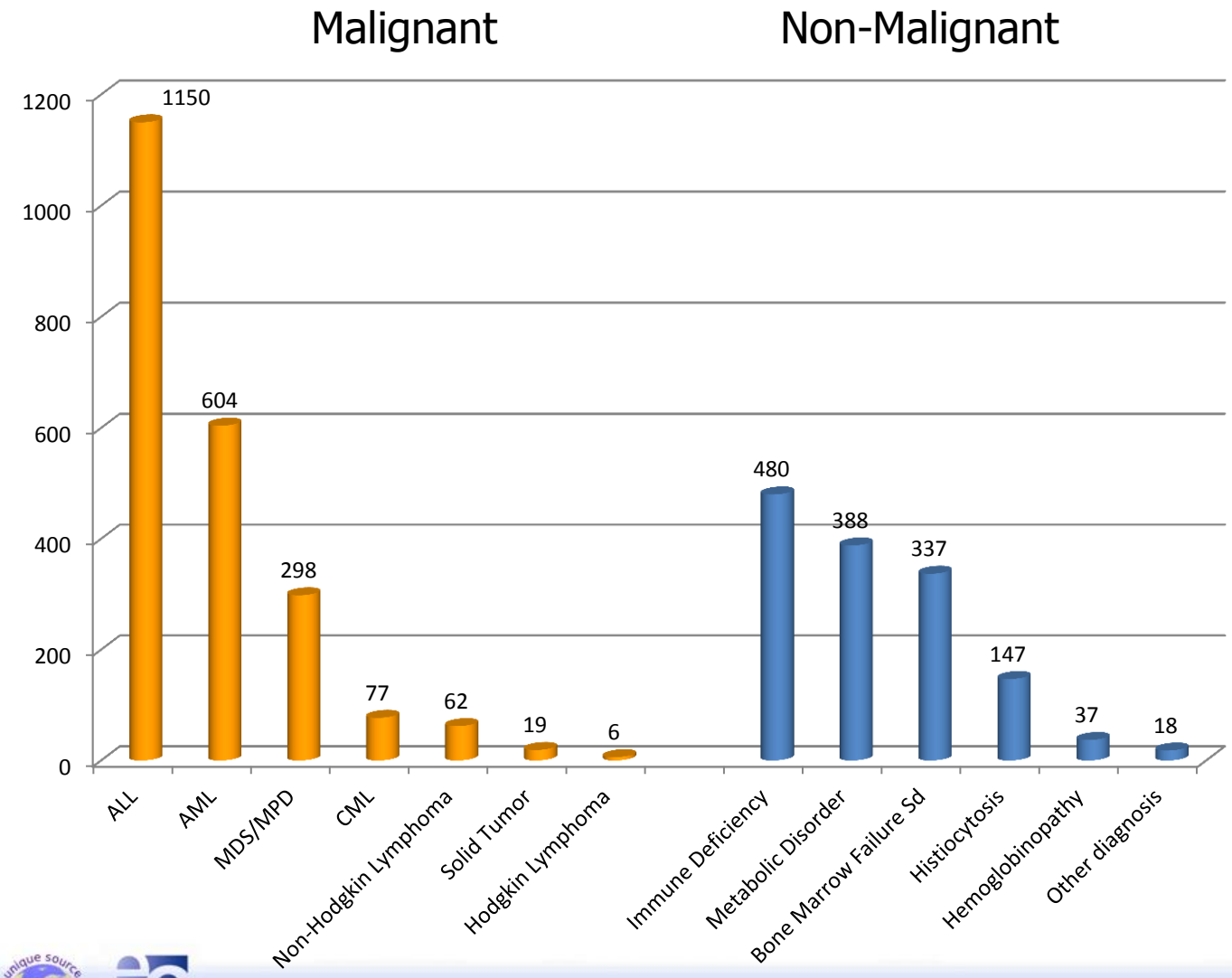
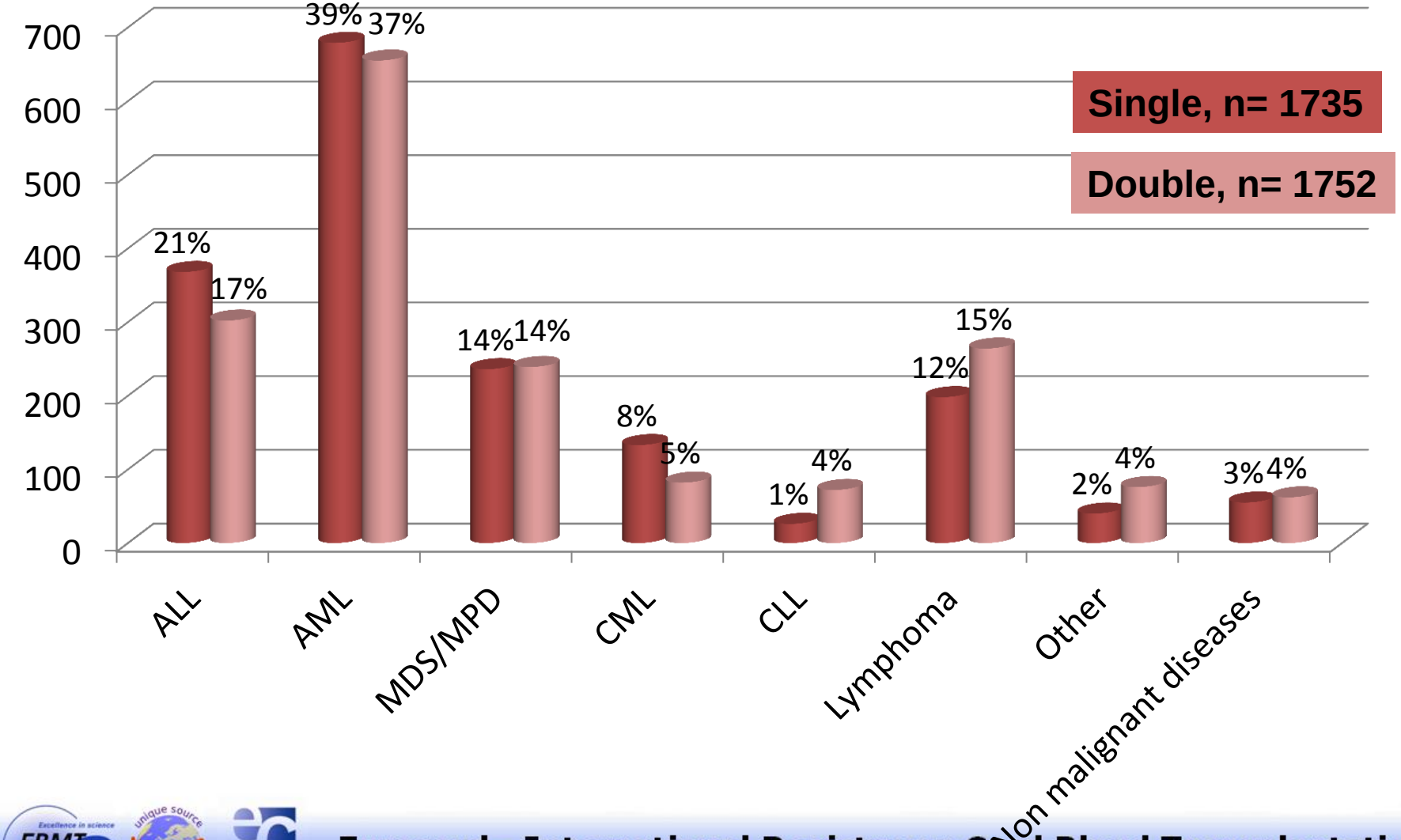
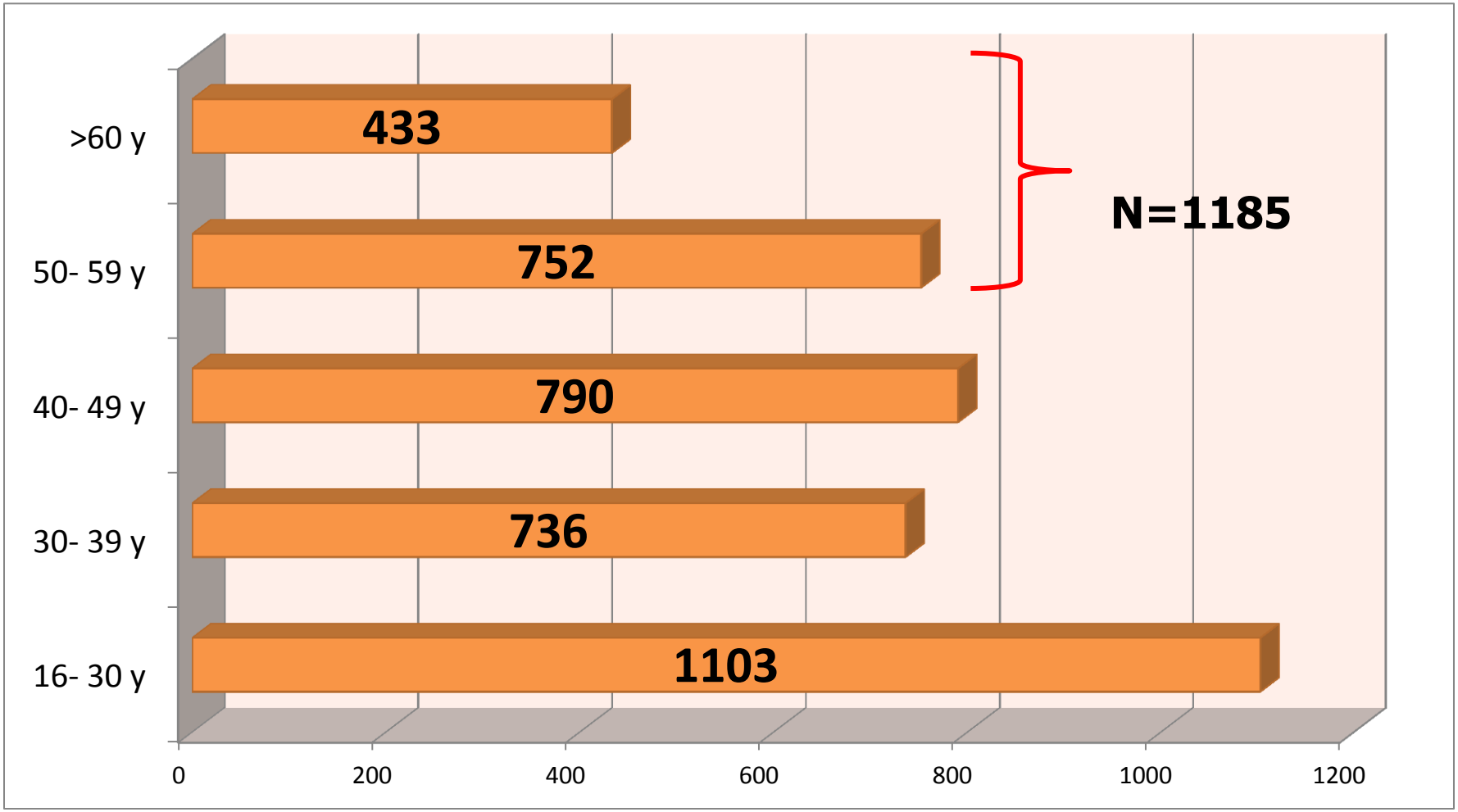
Indications of Unrelated UCBT in Children



Indication for Unrelated UCBT in adults



Age distribution for adult patients



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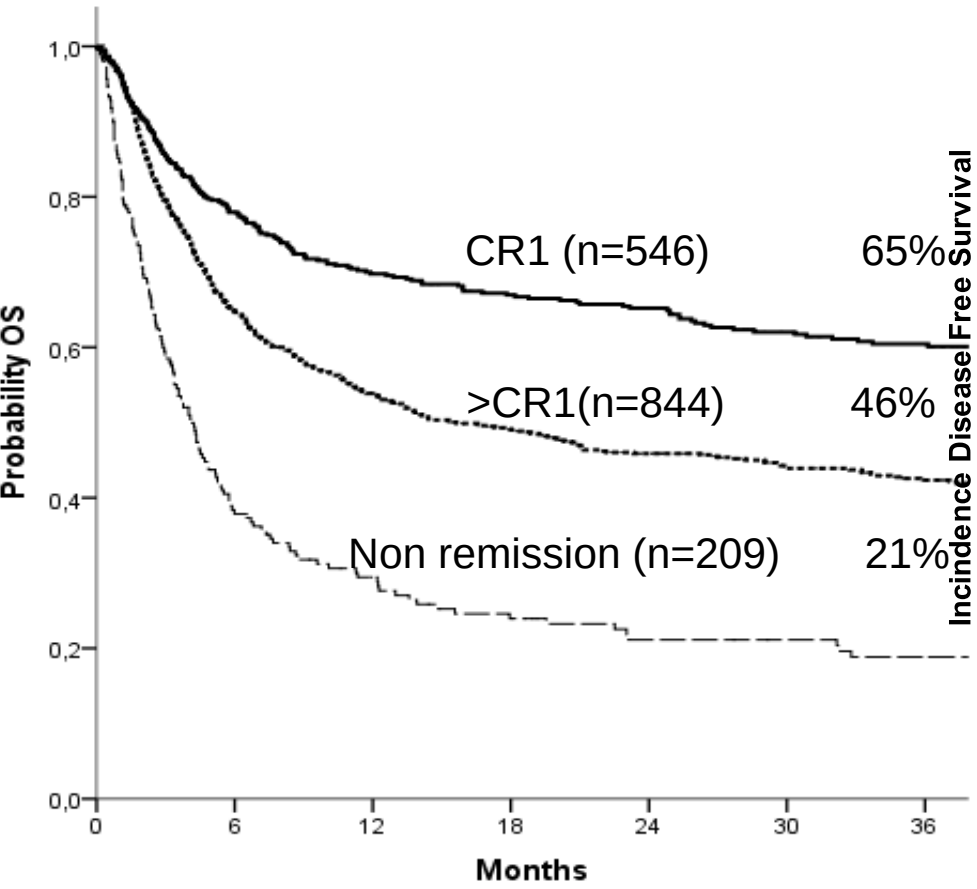
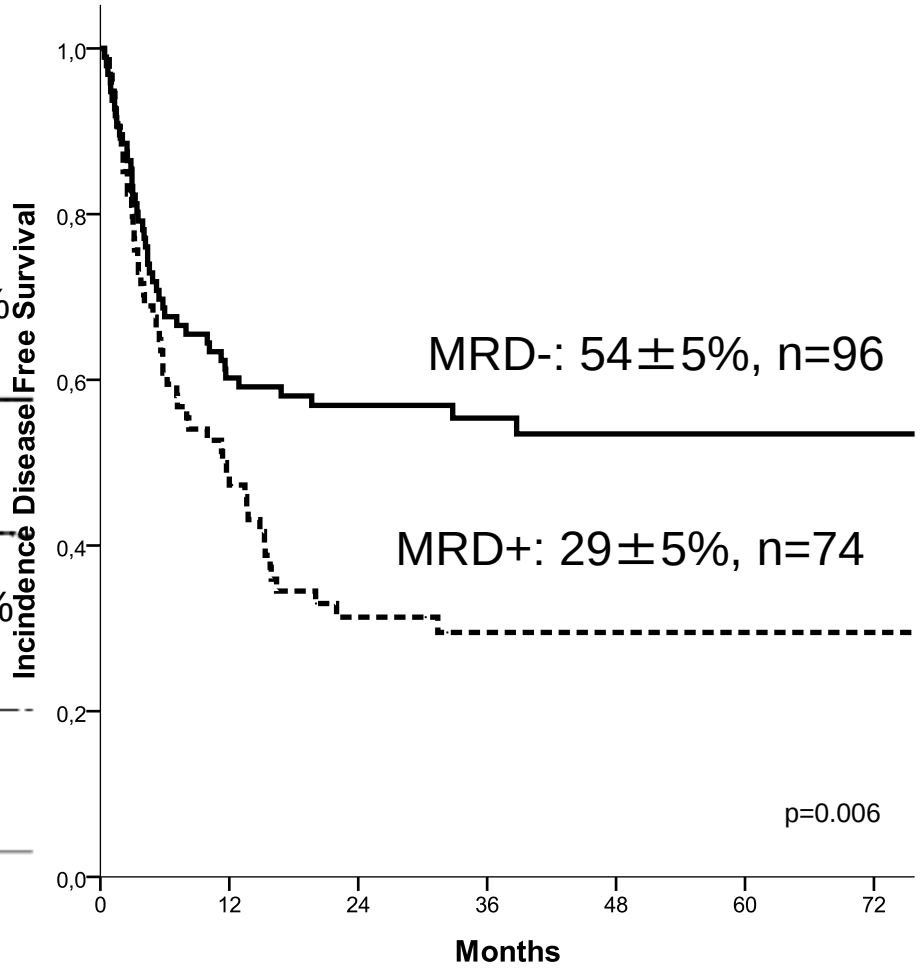
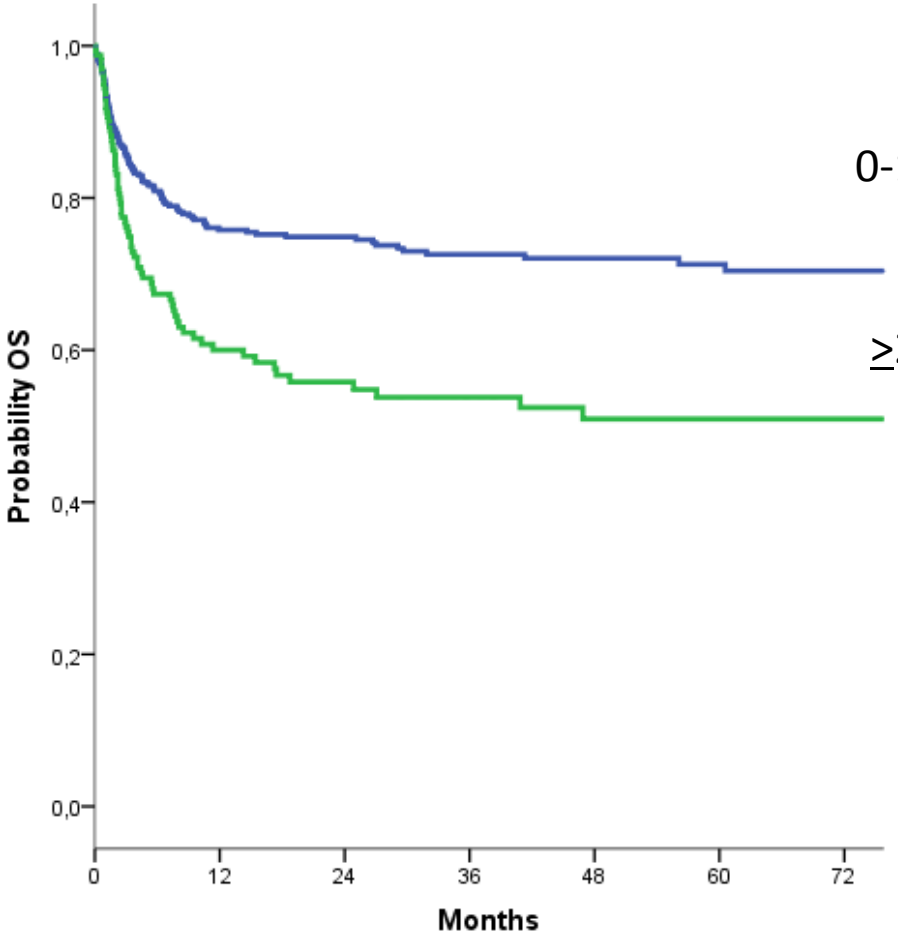
Survival after UCBT for children with malignant (n=1055) and in Children with ALL (n=170)





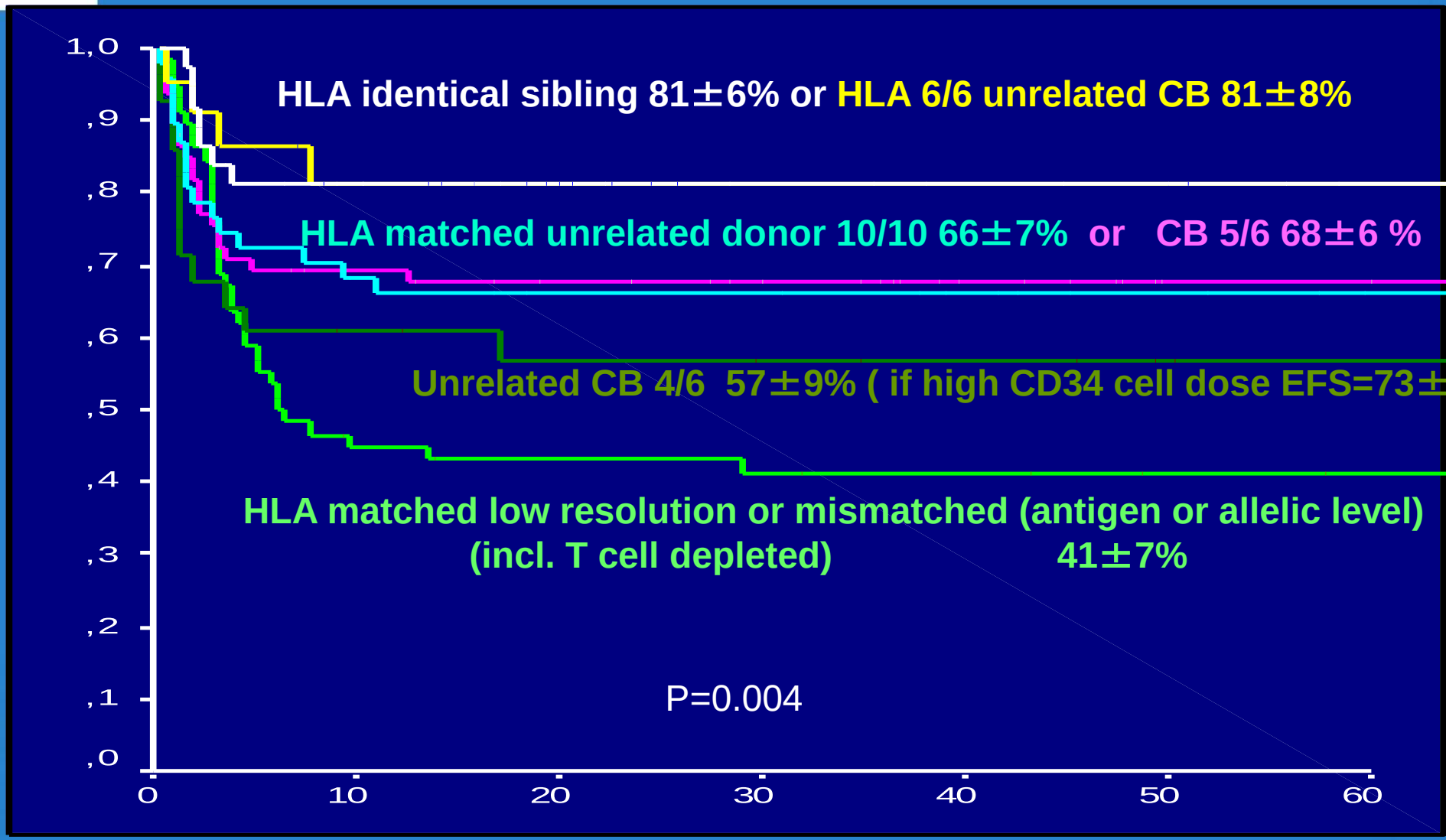
Survival after UCBT for children with non malignant disorders (n=681)



0-1 HLA MM: 72±4%

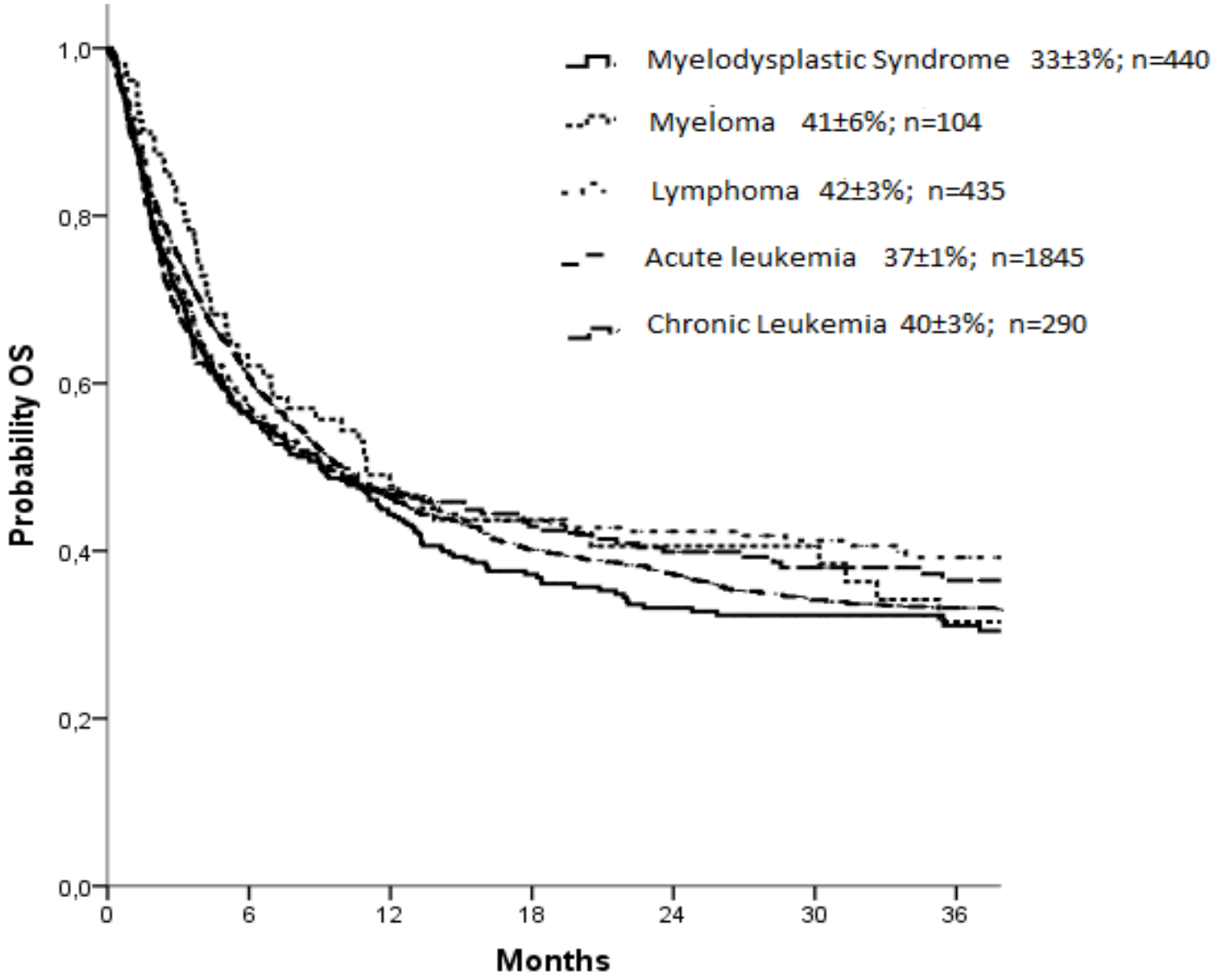
≥2 HLA MM: 52±4%

Children with Hurler disease
Disease Free Survival by type of donor and HLA

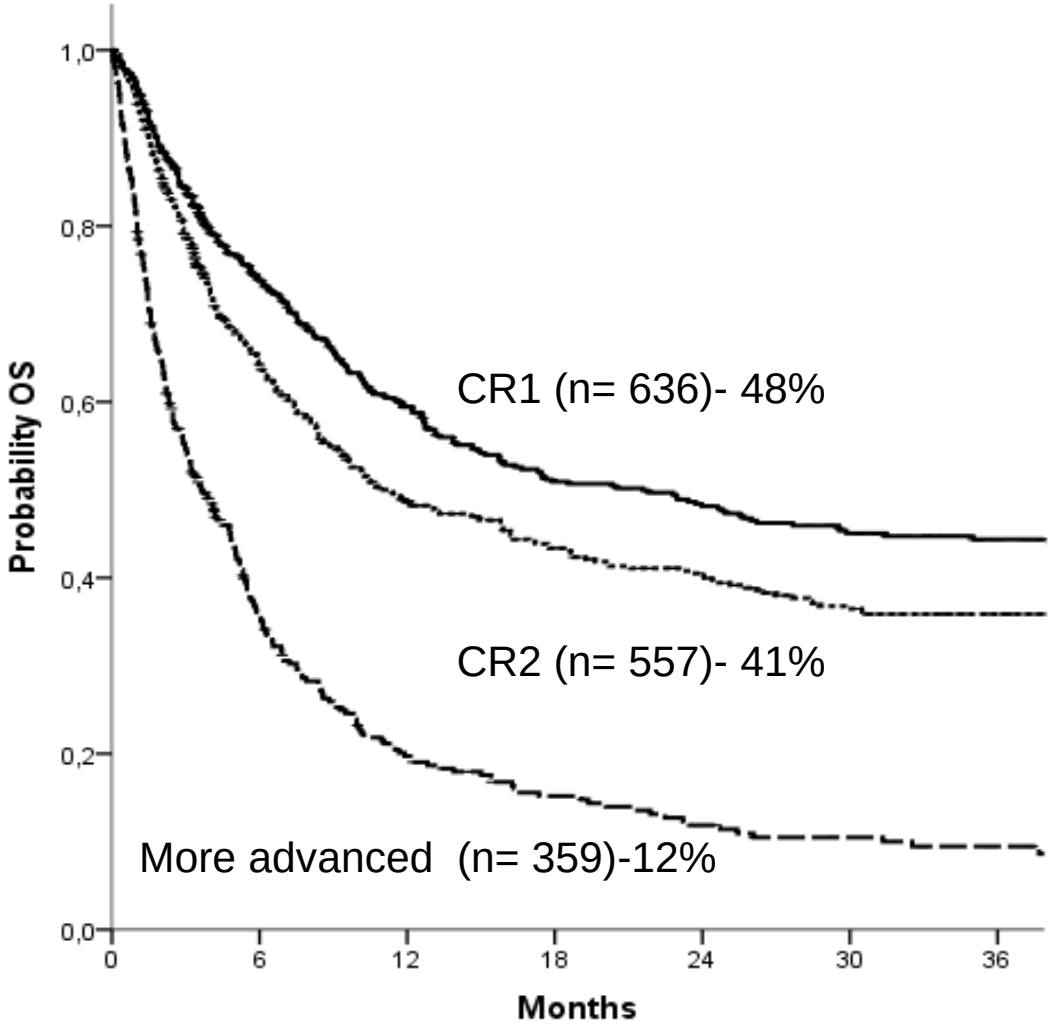


Boelens J on behalf of Eurocord-EBMT, Minneapolis and Duke University , Blood 2013

2 Years Survival in Adults (single and double unrelated CBT)



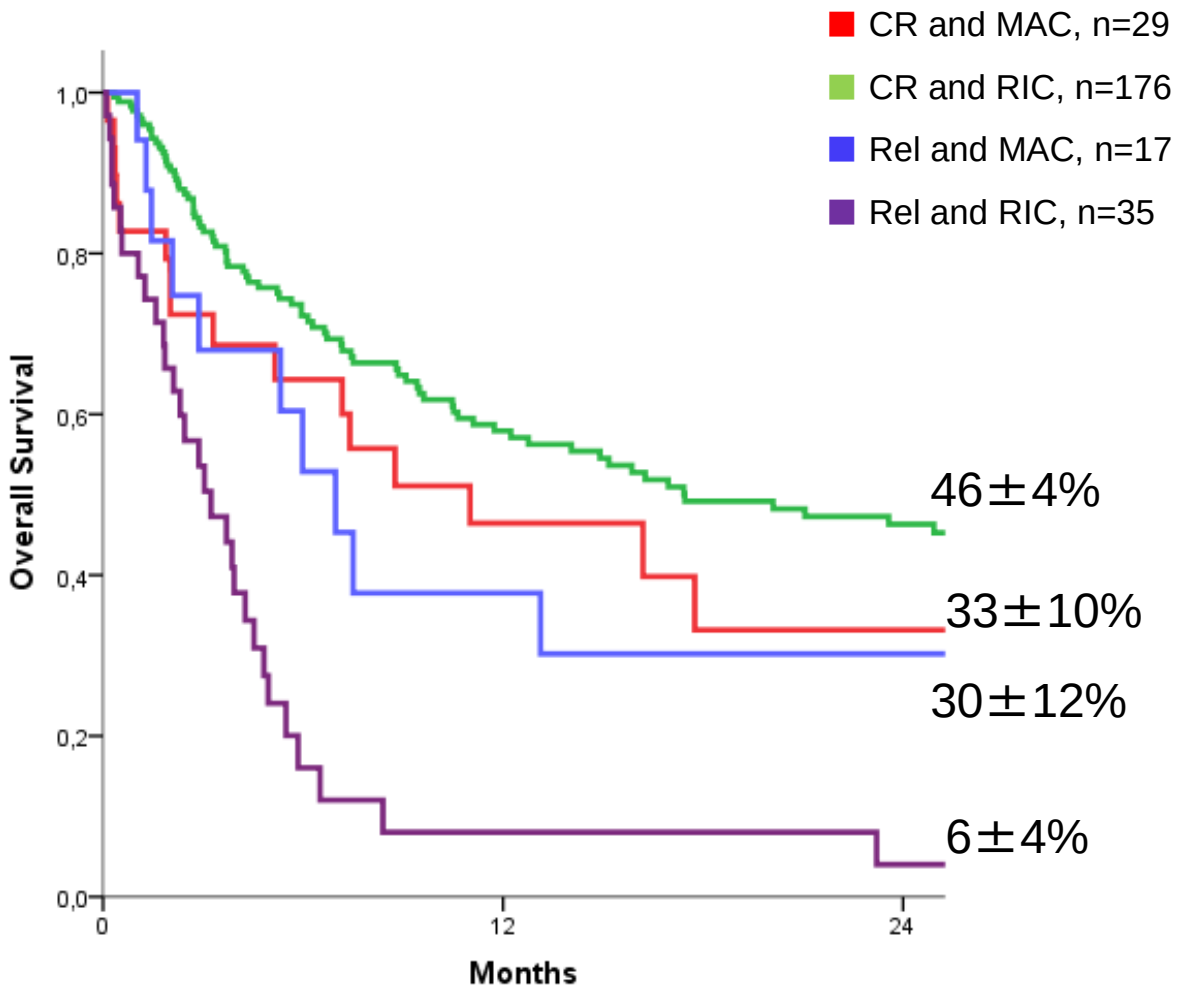
2 Years Survival in Adults (single and double unrelated CBT) with Acute Leukemia (n=1552) by disease status



Overall Survival

AML by disease status and conditioning

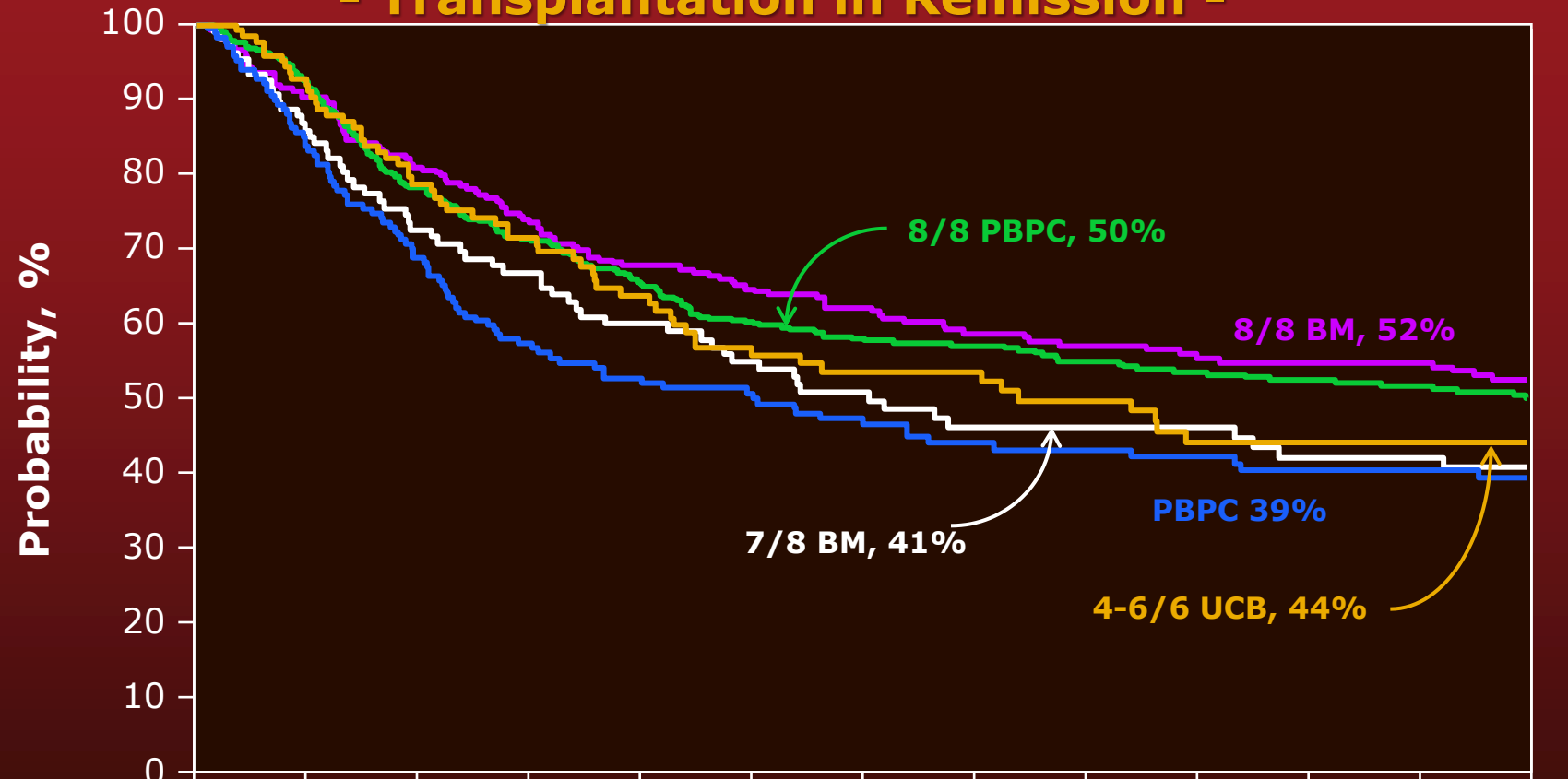
adults >50 years- (n=257)



Ruggeri A et al

Leukemia-free Survival after Single UCBT – MAC in adults with leukemias

- Transplantation in Remission -



Months	0	6	12	18	24
8/8 matched BM	246	177	139	99	82
7/8 matched BM	106	69	46	35	31
8/8 matched PBPC	452	316	220	143	112
7/8 matched PBPC	166	89	66	45	36
4/6-6/6 matched UCB	123	77	47	30	24

Eapen et al; Lancet Oncol 2010

Survey on Double UCBT for adults

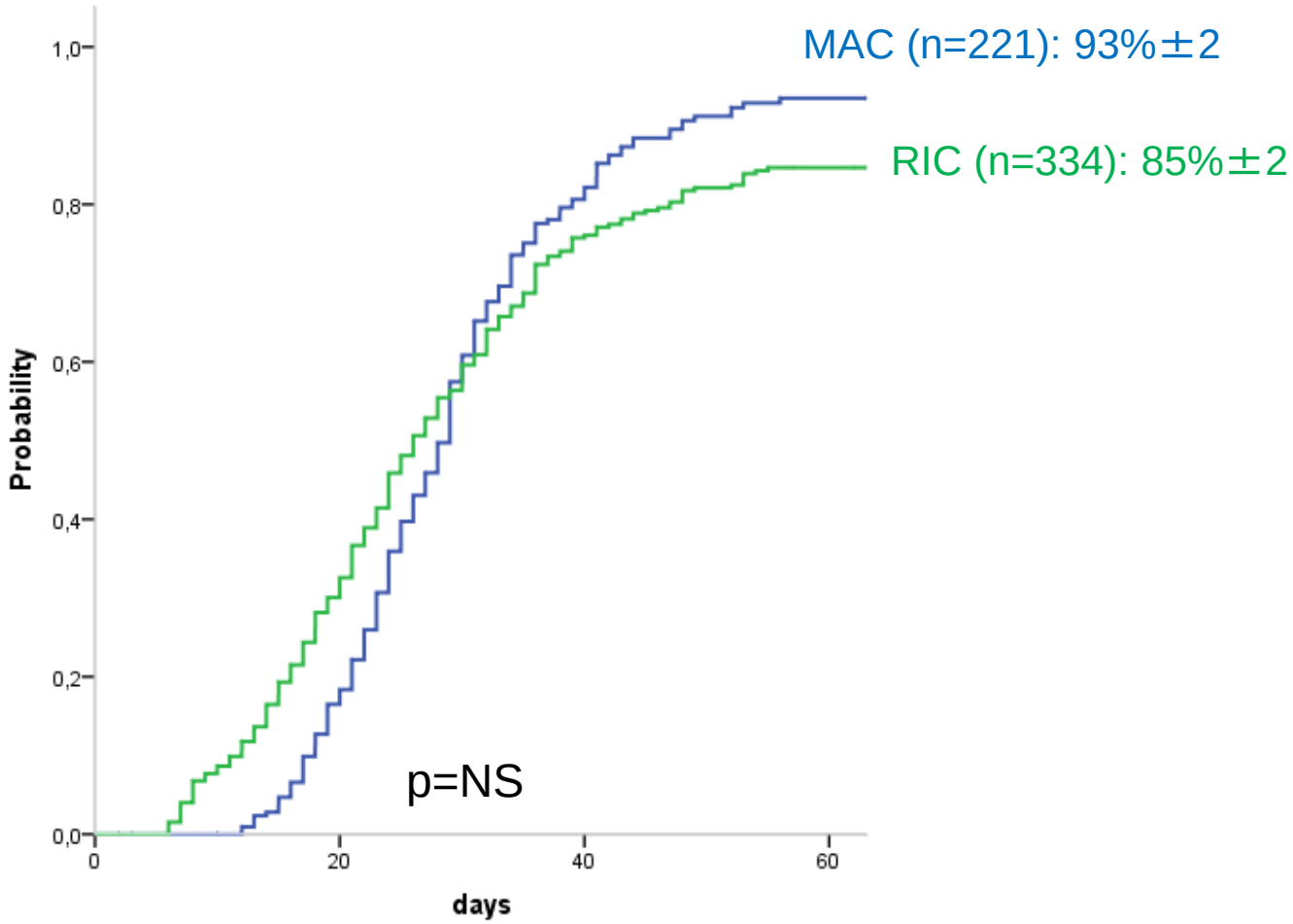
Double UCBT in adults (n=1055)

- Median age at transplant: 45 years (18-76)
- Median weight: 71 kg (40-151)
- Median follow-up: 14 months (1-85)
- Median number of collected nucleated cells
  $4.9x10^7$/kg (2.1-14.8)

- HLA compatibility (n=855)
  6/6: 1% (n=12)
  5/6: 26% (n=222)
  4/6: 73% (n=598)

Double UCBT in adults with AL (n=578)

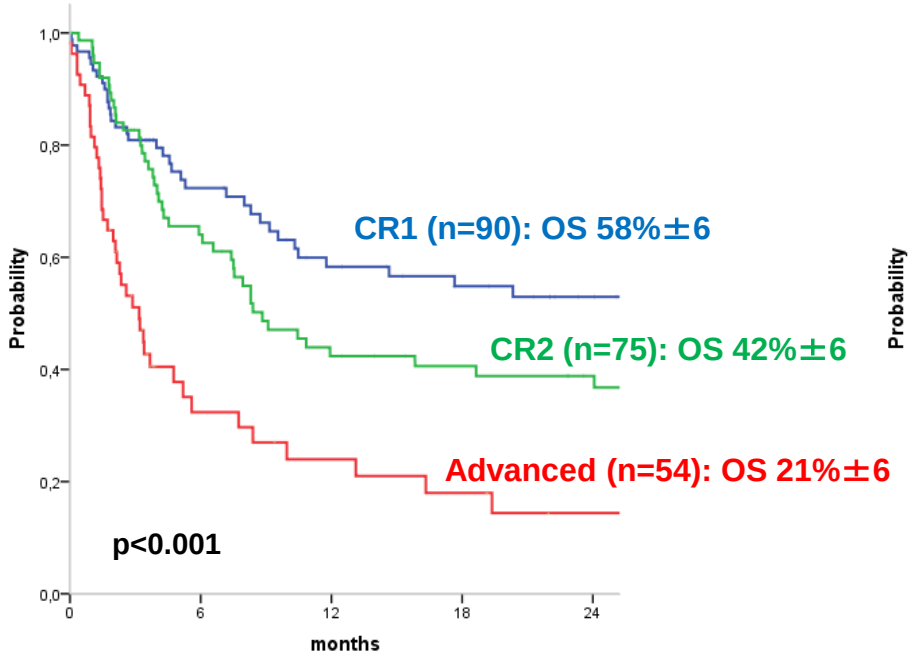
Neutrophil recovery



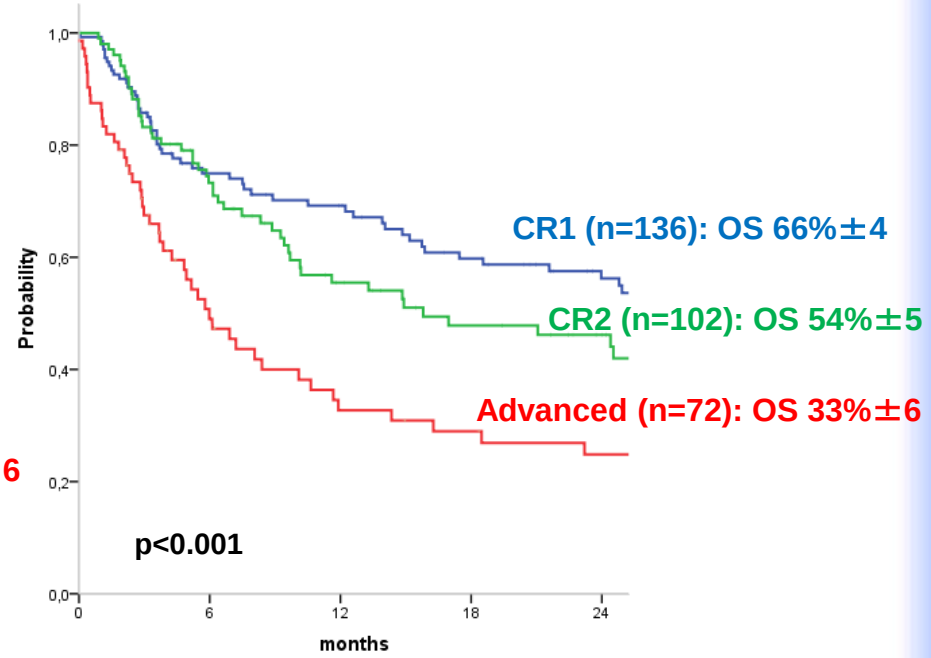
Double UCBT in adult with AL (n=578)

Survival by disease status at dUCBT

MAC



RIC



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Recomendations for CB unit choice 2012

Search for antibodies against HLA antigens of the cord blood unit (

Cord Blood Bank accreditation and location)

1. Look at the number of TNC and/or CD34+ cells in MAC, RIC:

$\geq$2.5-3.0 x10^7 NC/kg and/ or $\geq$1x10^5 CD34+/kg

2. Second look at HLA matches:

- 0-1 mm better than 2 avoid 3-4 mm
- Prefer class I mismatches than class II
- Include HLA C typing low resolution, avoiding mismatches C +DRB1

3. Then adapt to graft indication:

- Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
- Non malignant diseases: increase cell dose ($\geq$4.0x10^7 NC/kg) and find the best HLA match (avoid CB 4/6)
- If the criterion for the minimum number of cells for a single CBU transplantation is not achieved, a double CBT should be considered

4. Other considerations, if several CBU are available consider:

- Cord Blood Bank accreditation and location
- ABO compatibility
- NIMA status

Is Allele-Level HLA-Matching Relevant for Single Umbilical Cord Blood Transplants?

Eurocord and Center for International Blood and Marrow Transplant Research

M Eapen, JP Klein, A Ruggeri, S Spellman, W Arcese, LA Baxter-Lowe, M Fernandez-Vina, MM Horowitz, SJ Lee, F Locatelli, A Paolo Lori, S Marino, G Michel, GF Sanz, E Gluckman and V Rocha

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Lesser vs. Allele-level HLA-match (n=1500)

	3/8	4/8	5/8	6/8	7/8	8/8
4/6	11%	31%	49%	10%	—	—
5/6	1%	8%	22%	44%	25%	—
6/6	—	—	4%	18%	24%	54%

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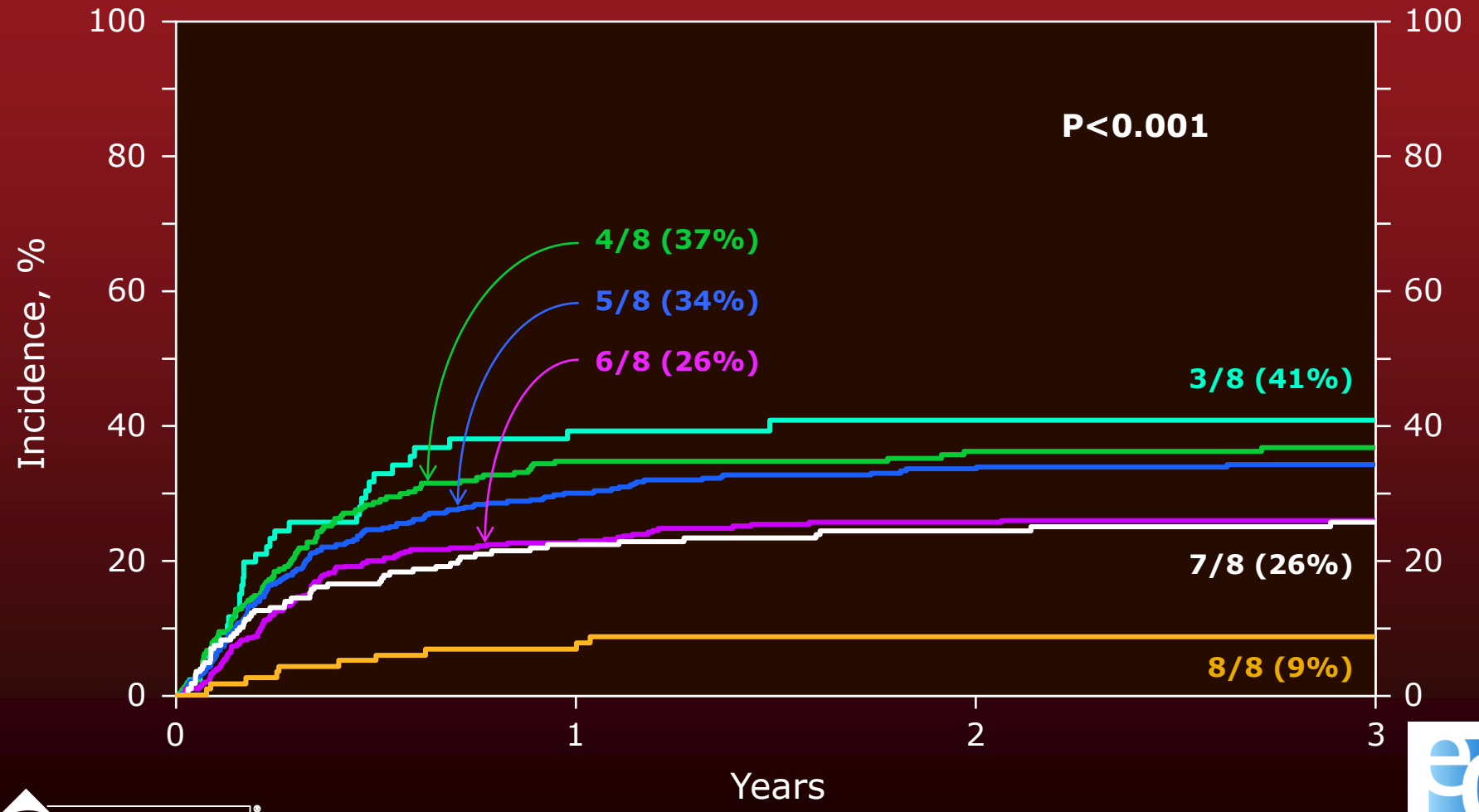
Non-Relapse Mortality

- Allele-level Matched at A, B, C, DRB1 -



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NRM at 1-year by pre-cryopreserved TNC and HLA-match

	HLA-match			
	4/8	5/8	6/8	7/8
TNC ≤3.0	43% (28-58)	44% (33-57)	36% (24-49)	45% (29-62)
TNC >3.0 – 5.0	*39% (30-49)	31% (24-38)	21% (14-30)	15% (7-26)
TNC >5.0	*25% (17-33)	25% (20-31)	20% (15-25)	19% (13-26)

*Significant difference: p=0.02 testing TNC >3.0 – 5.0 vs. >5.0.
Other groups testing TNC >3.0 – 5.0 vs. >5.0: p-value=NS
The multivariate model tested TNC ≤3.0 vs. >3.0 (optimal cut point determined statistically in the model for mortality). In the univariate analysis there is a significant difference between TNC ≤3.0 vs. >3.0

Select units with TNC ≥ 3 x 10^7/kg

Best HLA-match
Allele-level match at HLA-A, -B, -C and –DRB1

Avoid 3/8 HLA-matched transplants

Absence of HLA-C typing
match at HLA-B
HLA-C at confirmatory typing

7/8 and 6/8 are better tolerated than 5/8 or 4/8 HLA-matched transplants

TNC in excess of minimum required does not lower NRM

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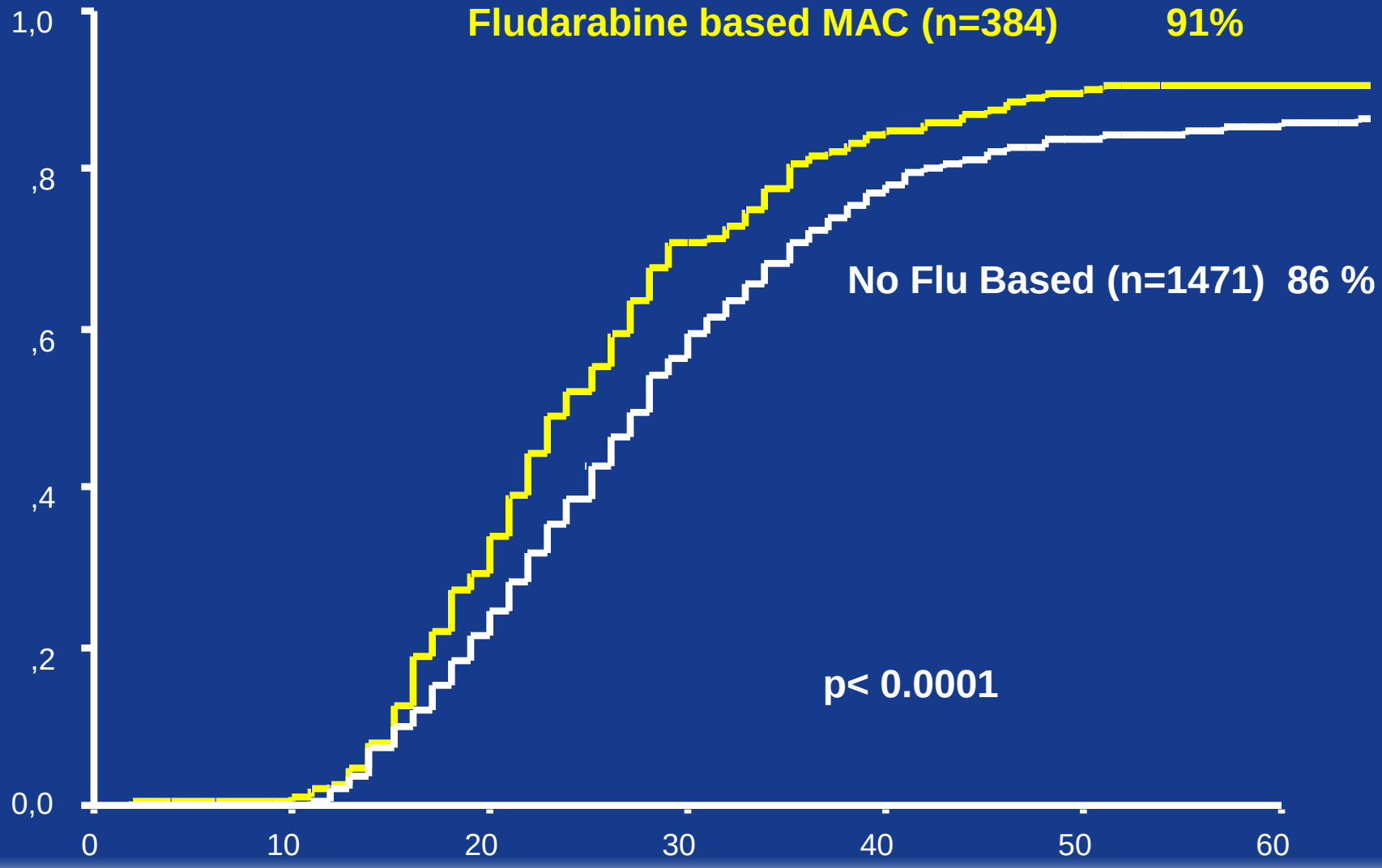
Neutrophil recovery after single UCBT for patients with malignant disorders after myeloablative conditioning regimen (n=1946)



Conditioning regimen
Myeloablative

Analyze the impact of TT, iv BU, F+ATG (TBF-ATG) on long term outcomes after single unit UCBT compared to other MAC regimens in adults with leukemias in remission

H Bittencourt et al. # 377, Oral session EBMT

Thiotepa-Busulfan-Fludarabine versus Cyclophosphamide-based Myeloablative Conditioning Regimen

In Remission

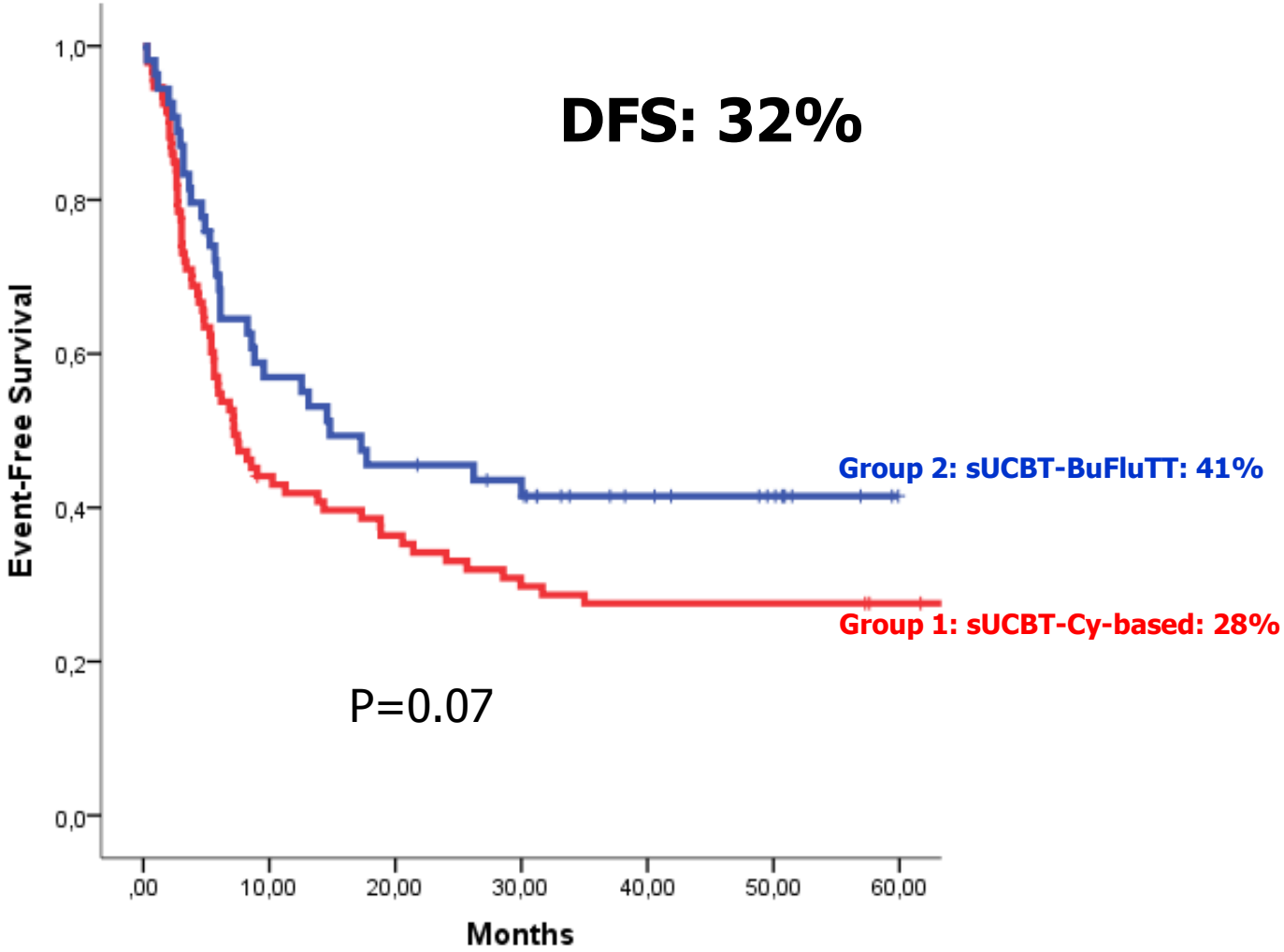
Early Stage (n=147)

Characteristics	Group 1, sUCBT Cy-based n=93	Group 2, sUCBT Bu+Flu+TT n=54
Age (years)	33(18-54)	32 (19-51)
HLA match – 4/6	51(56%)	28(53%)
Acute Leukemia*	79(85%)	52 (96%)
Median TNC after thawing (10^7Kg)	2.5 (0.6-7.6)	2.3 (1.4-4.9)
GVHD Prophylaxis: CSA+Steroids ATG	 78(84%) 83(89%)	 38 (70%) 48(89%)
Year of UCBT*	2003 (2000-2007)	2006 (2005-2008)

* P<0.05

Besides ABO major incompatibility (P=0.02), there was no other differences among the 2 groups for patients disease and UCBT characteristics (gender, weight, CMV status, previous autologous HSCT, CD34+ infused cells)

EFS at 5 years
Early Stage



BuFluTT associated with better event-free survival in multivariate analysis
HR 0.64 (CI95%:0.41-0.99 – P=0.04)

TBF Single UCBT

vs

other MAC single UCBT

vs

TBI+CY+Flu double UCBT

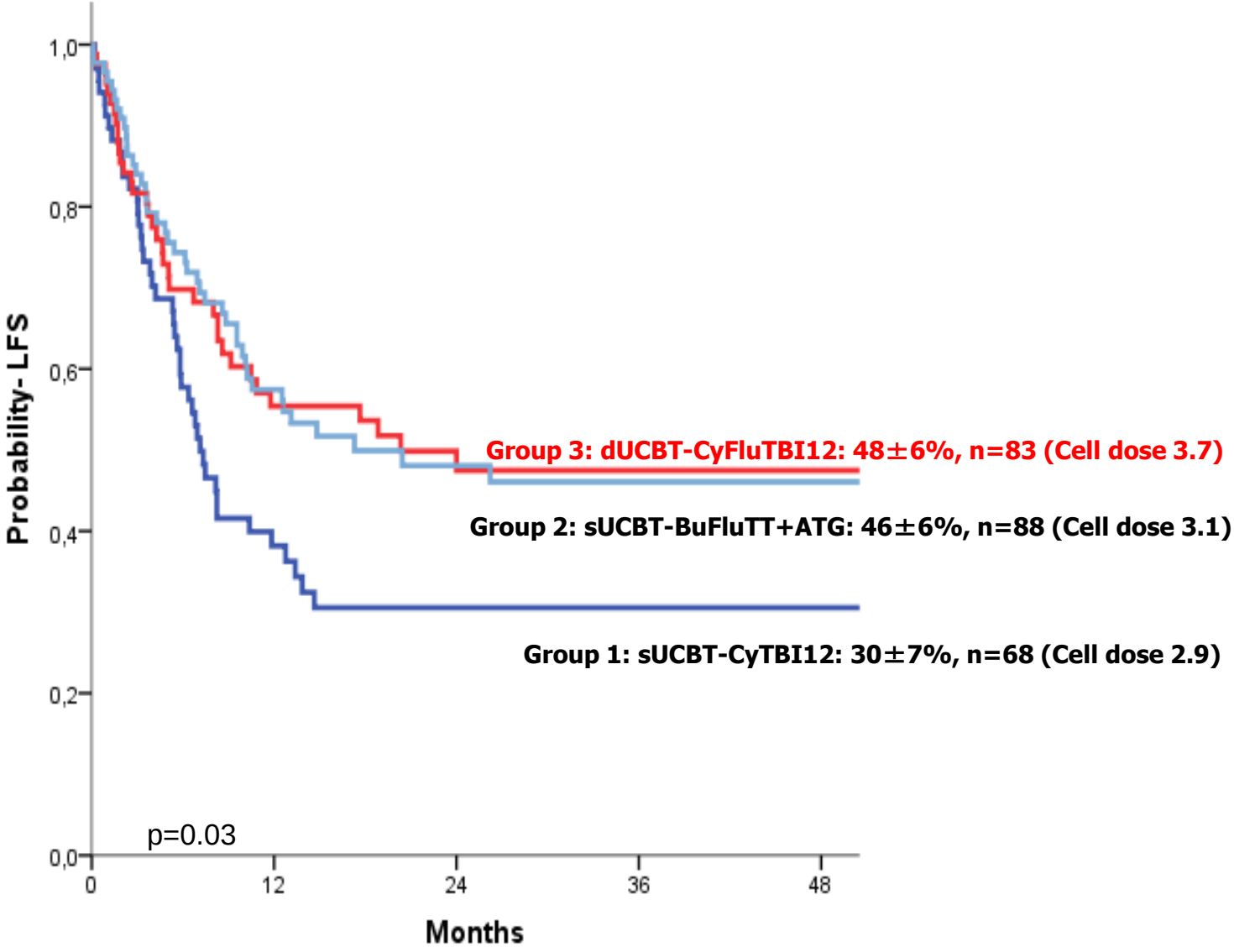
What are the results ?

Are outcomes after myeloablative conditioning regimen in double cord blood transplantation (UCBT) better than single UCBT for adults with acute leukemia in remission? Eurocord-EBMT analysis

Annalisa Ruggeri et al

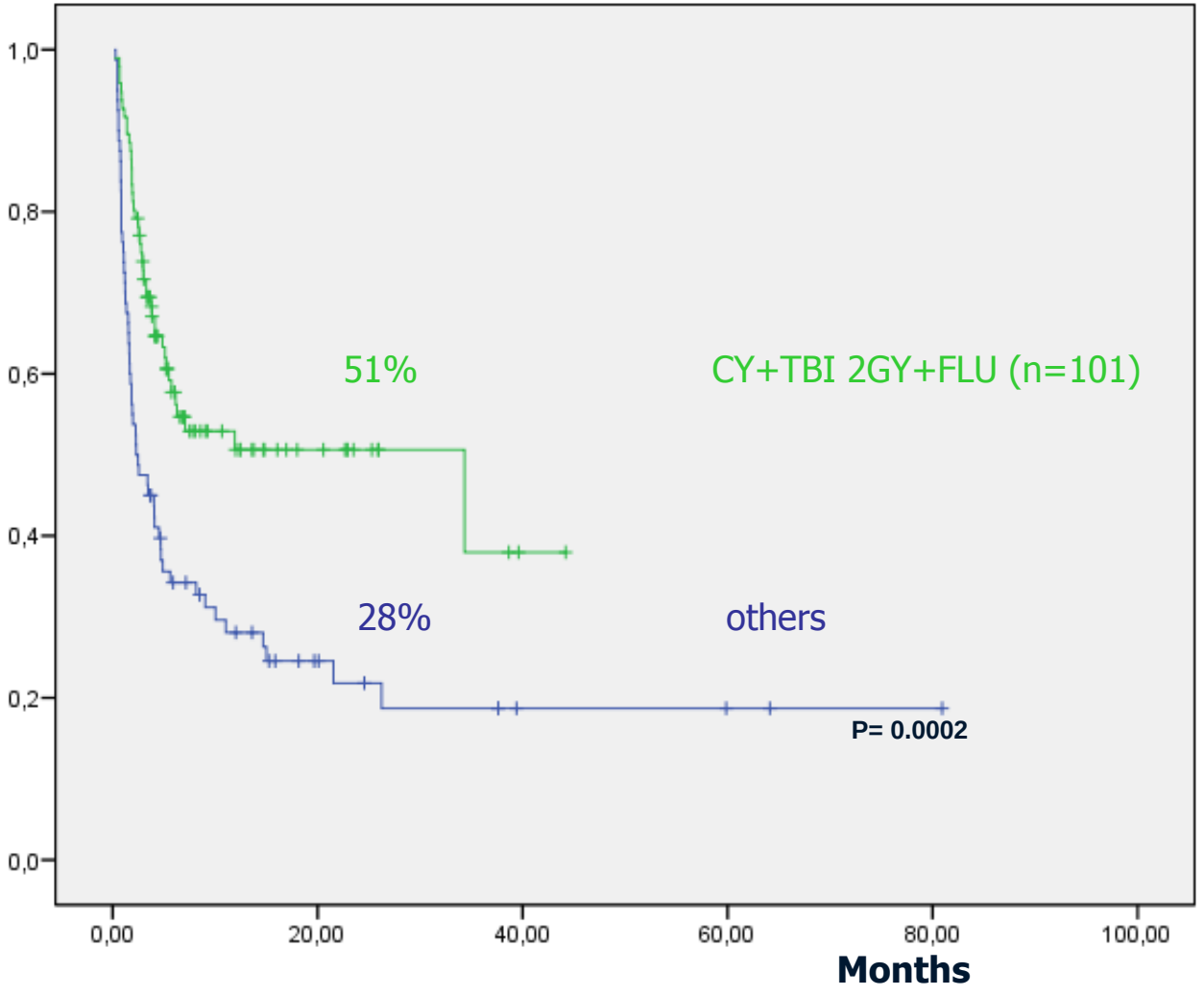
No conflict of interest to disclose

LFS at 2 years
MAC sUCBT and dUCBT in adults with AL in CR1

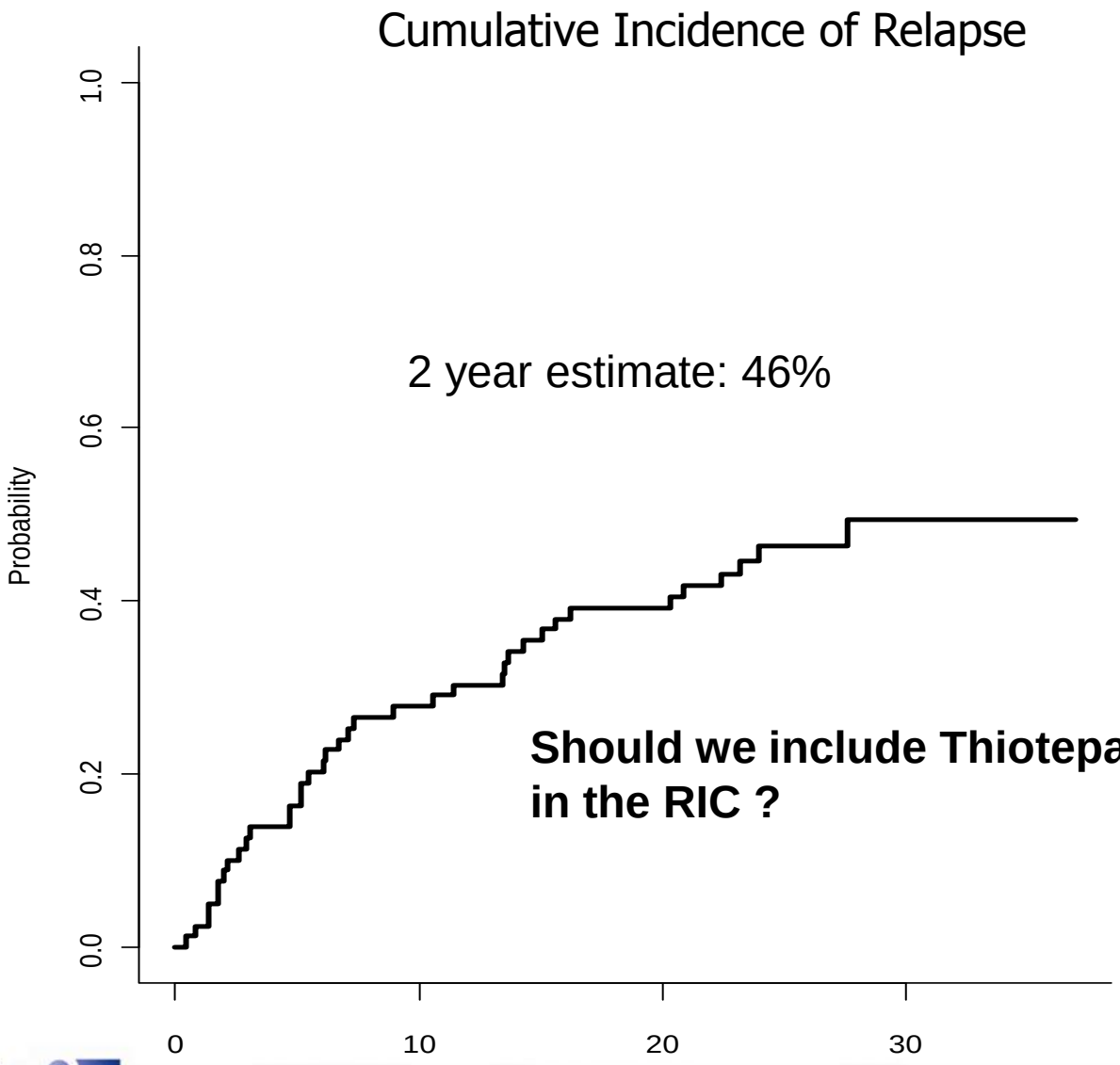


Which is the “best” RIC for UCBT?

Disease Free Survival according to conditioning after single and double UCBT for malignancies in adults (n=155)



Phase II trial in France on the use of TCF–RIC in UCBT for AML (n=79)



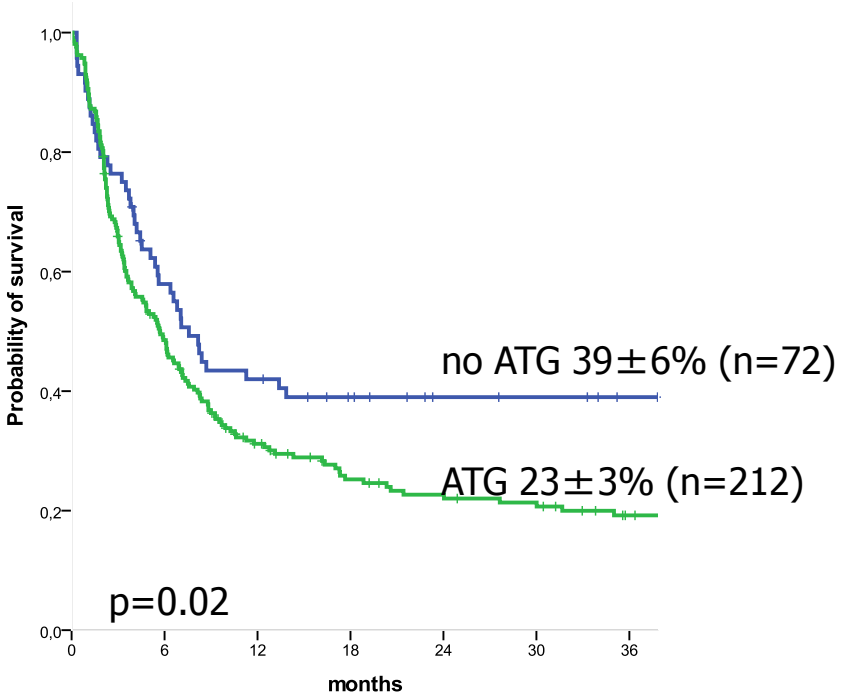
Should we include Thiotepa or increase TBI in the RIC ?

Rio B et al

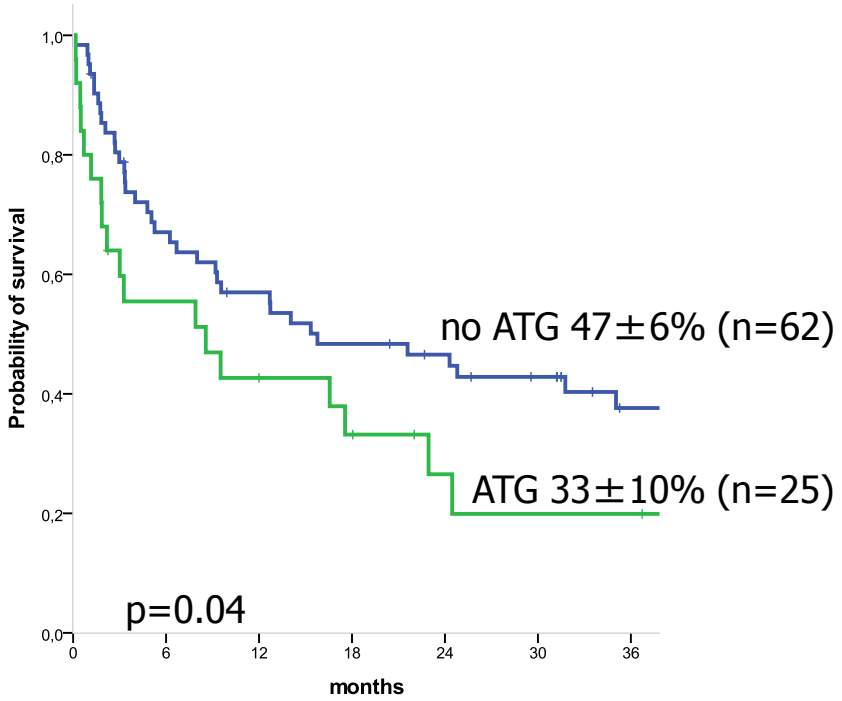
Should we include ATG in the conditioning regimen in MAC and RIC?

Results - 2y LFS after UCBT for adults with ALL

MAC



RIC



Tucunduva L et al

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Risk factor associated with decreased cumulative hazard of severe **bacterial** infections

Multivariate analysis

	HR	p
Longer time to neutrophil recovery (time dependent)	4.54	<0.0001

Risk factor associated with decreased cumulative hazard of severe **viral** infections

Multivariate analysis

	HR	p
Positive CMV serology	3.54	0.0005
Number of HLA disparities > 2	4.76	0.02
Longer time to engraftment (time dependent)	2.5	0.0007
Infections before transplant	2.18	0.05

Risk factor associated with decreased cumulative hazard of severe **fungal** infections

Multivariable analysis

	HR	p
Recipient's age >15 years	9.65	<0.01
Diagnosis of Inborn and BMF	7.69	0.04
Longer time to engraftment (time dependent)	5.88	0.02
Acute GVHD III-IV (time dependent)	4.24	0.03

UCBT

Summary

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- New criteria for Cord Blood Unit Choice
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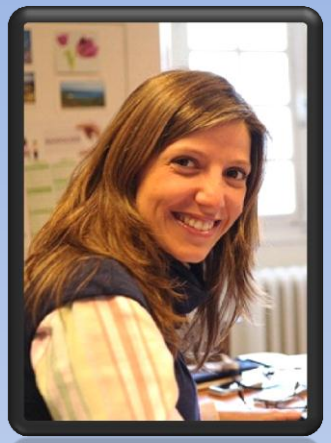
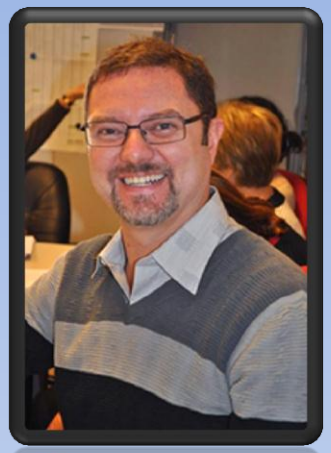
- Complications (engraftment and infections)

EUROCORD TEAM 2012-2013



Annalisa Ruggeri, MD



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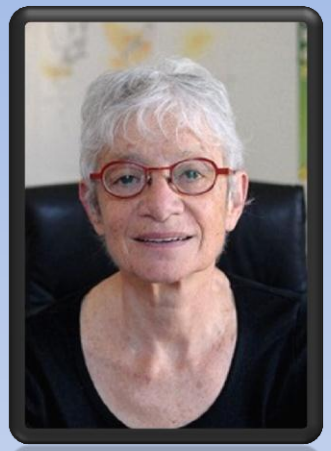

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