

Blood vs. Bone Marrow Grafts for HCT: What's the difference?

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Background

Higher CD34 cell dose limits transplant-related mortality

- cord
- sibling marrow
- unrelated marrow

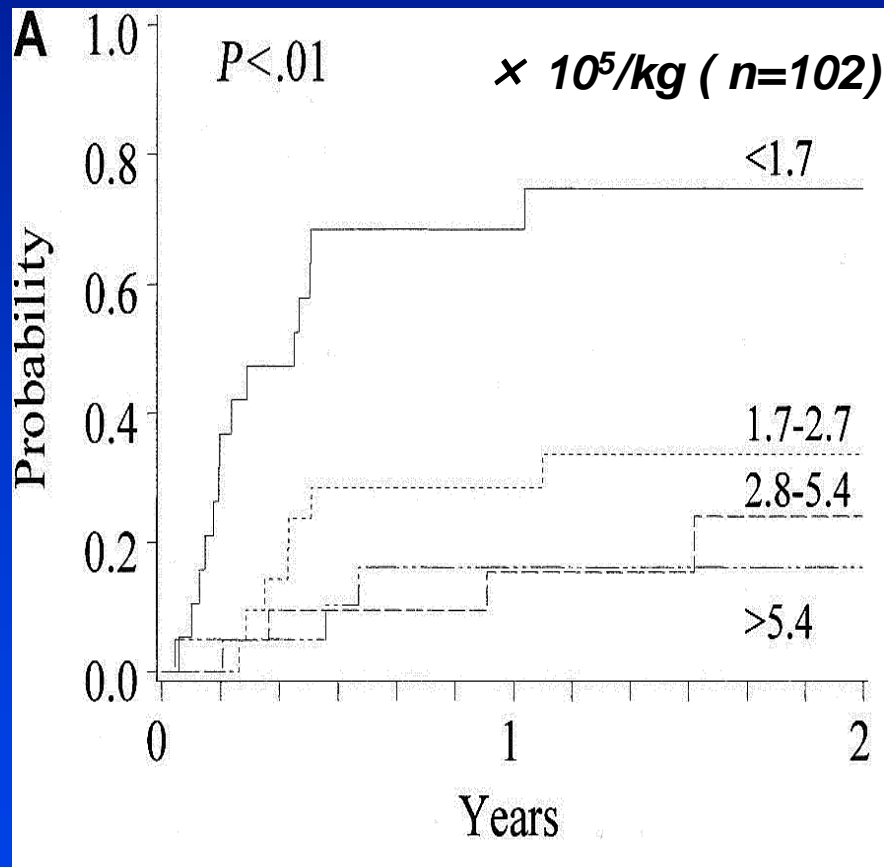
PBSC contain higher numbers of CD34 cells

Is outcome improved using PBSC?

- sibling phase III trials
- unrelated phase II trials
- NMDP/CTN phase III trial

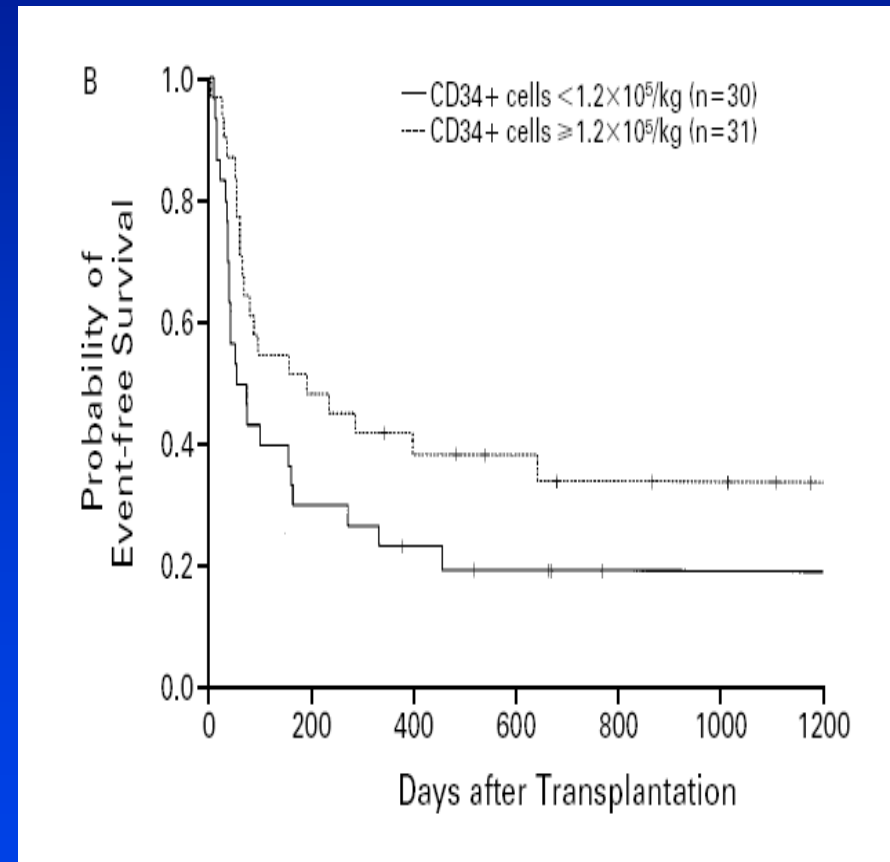
Effect of CD34 cell dose on outcome of unrelated UCB transplants

Mortality



Wagner et al. Blood 2002; 100:1611

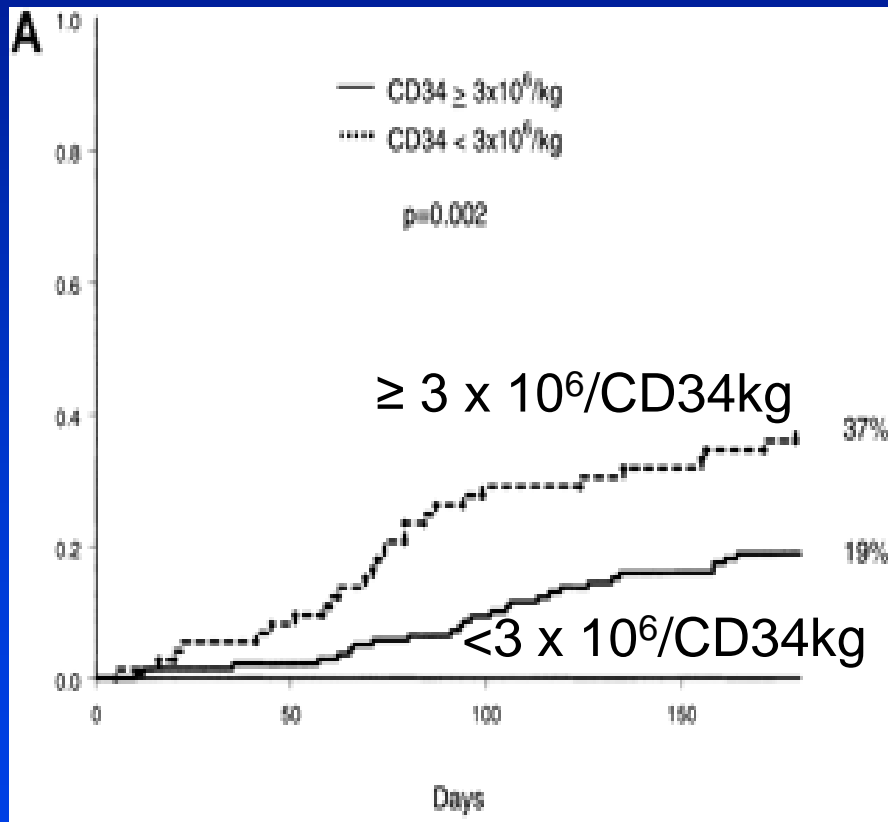
Event-Free Survival



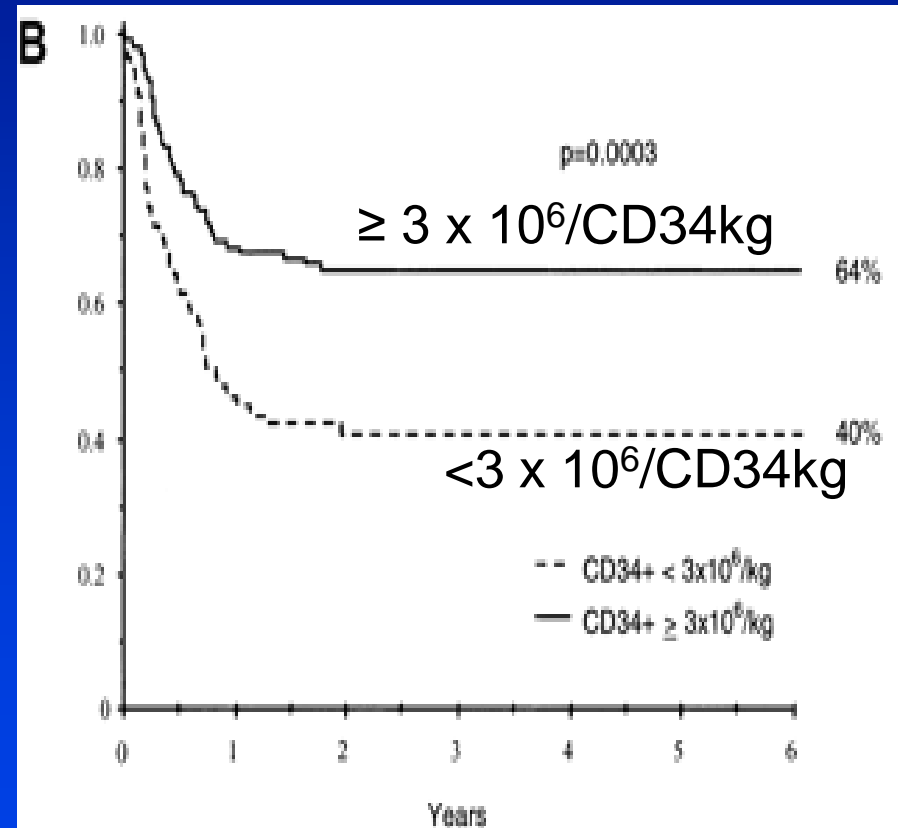
Laughlin et al. NEJM 2001; 344:1815

CD34 cell dose on outcome of sibling marrow transplants

Mortality



Survival



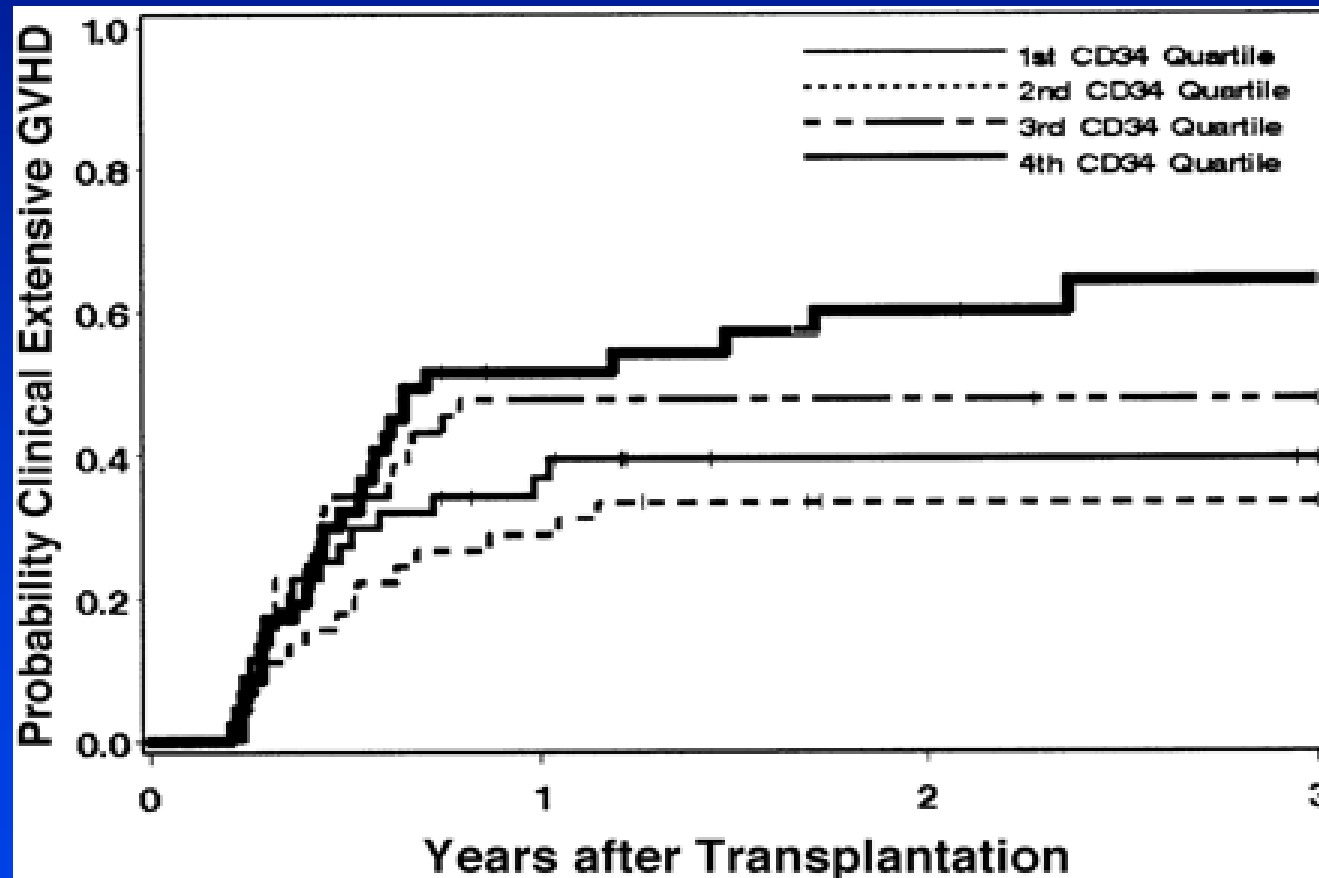
European Prospective Randomized Study Allogeneic Marrow vs. Blood Stem Cells

siblings with standard-risk leukemia, n=350

- No survival difference
- CD34 cell dose correlated with survival after marrow, but not after PBSC
- Increased acute GVHD with PBSC
- Increased chronic GVHD with PBSC
- T cell dose correlated with chronic GVHD

Larger CD34 cell dose: more chronic GVHD

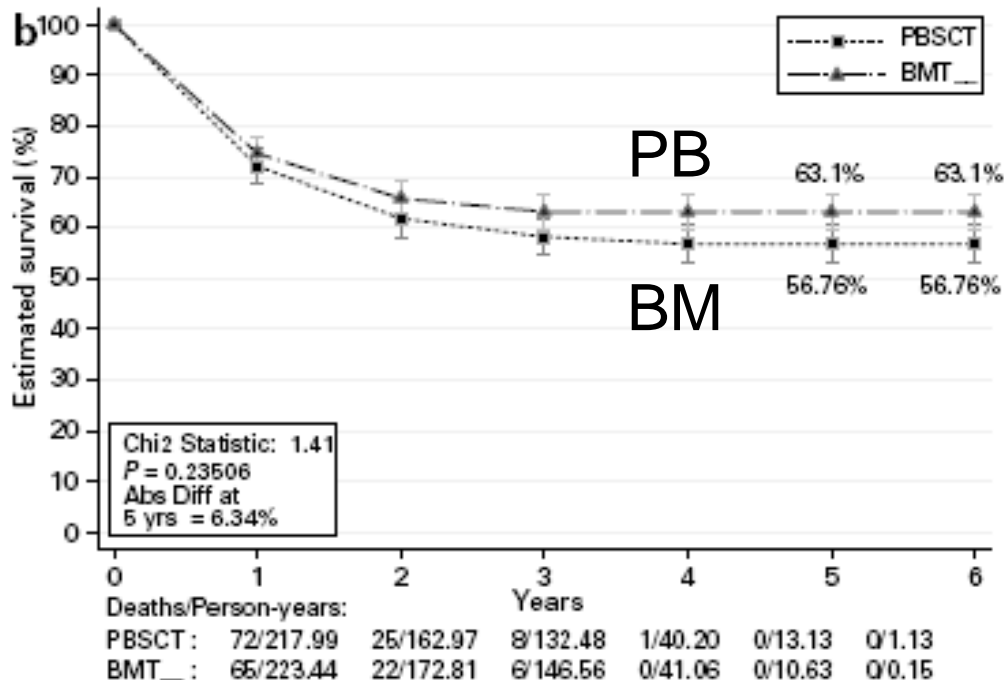
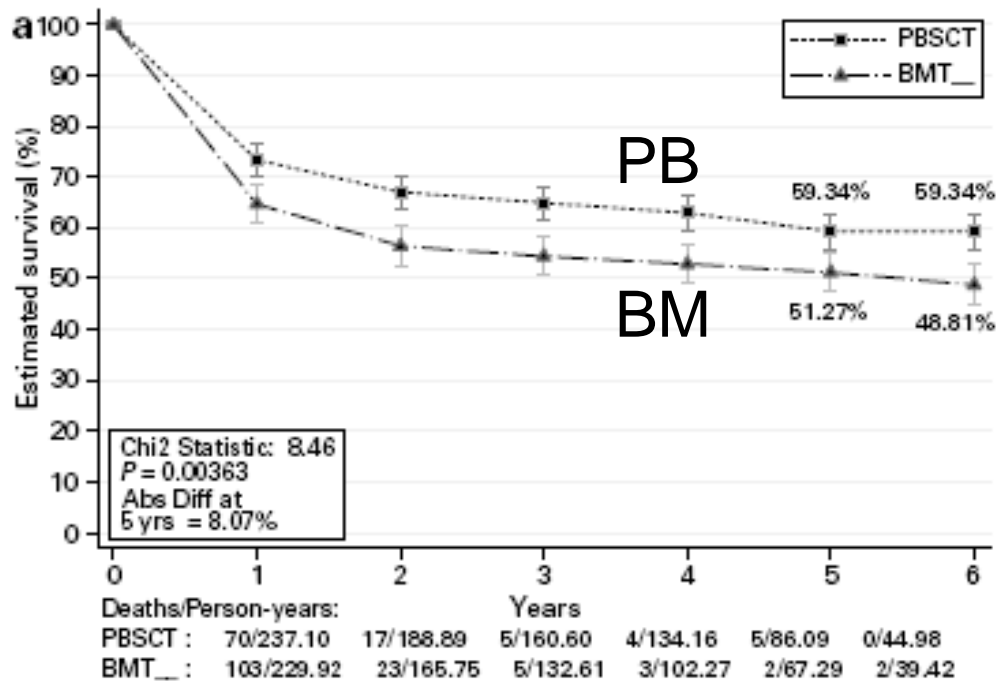
T-replete PBSC



Survival: PBSC vs BM

9 Randomized trials (n=1107)

4 doses methotrexate
8.07% advantage @ 6 years
p=0.004

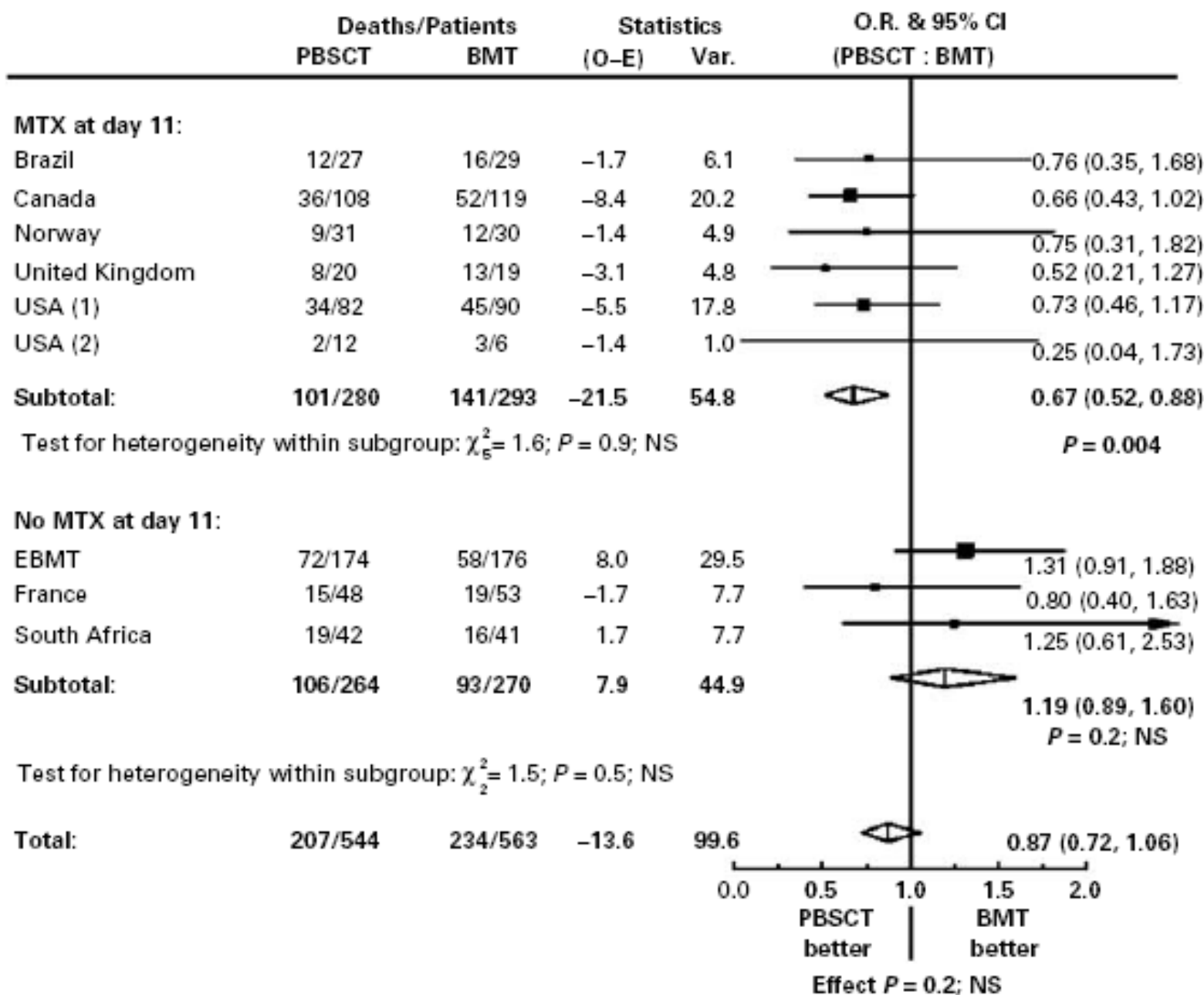


3 doses methotrexate
6.34% advantage @ 6 years
p=0.24

Influence of
Mtx for GVHD prophylaxis

Stem cell transplant: PBSCT vs BMT

Survival (all trials): Effect of MTX use at day 11



**Survival after
PBSC vs BM
Sibling grafts**

**PBSC ++
4 dose Mtx**

**BM slightly +
3 dose Mtx**

Net equivalent

Bensinger, 2006

URD Graft composition

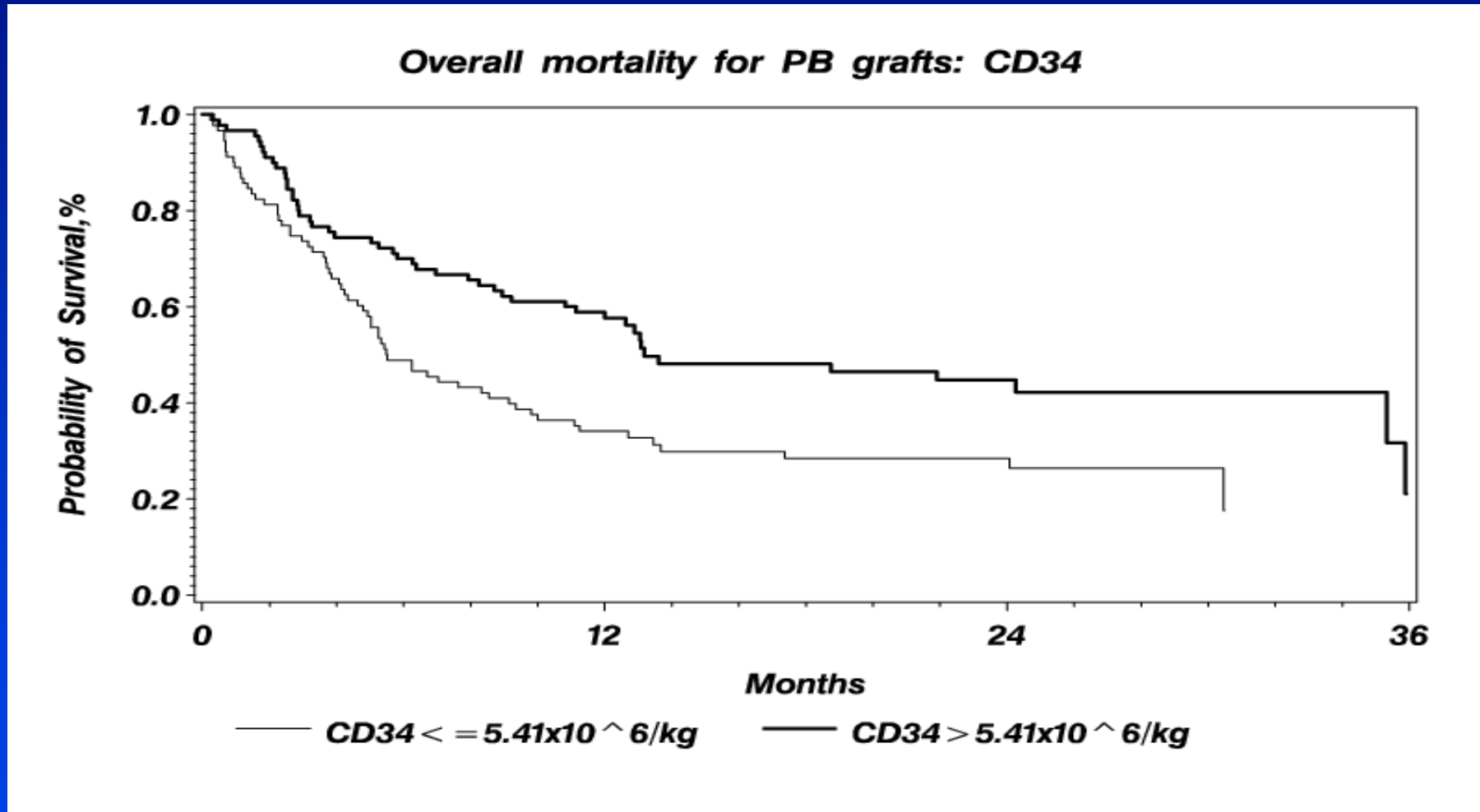
PBSC has	<u>PBSC (n=181)</u>	<u>BM (94)</u>
More Nucleated cells	7.23	$2.34 \times 10^8/\text{kg}$
More CD34	5.41	$3.62 \times 10^6/\text{kg}$
More CD34+38+	15.4	$9.44 \times 10^4/\text{kg}$
More CD3	2.37	$0.25 \times 10^8/\text{kg}$

But No graft composition subset predicted GVHD.

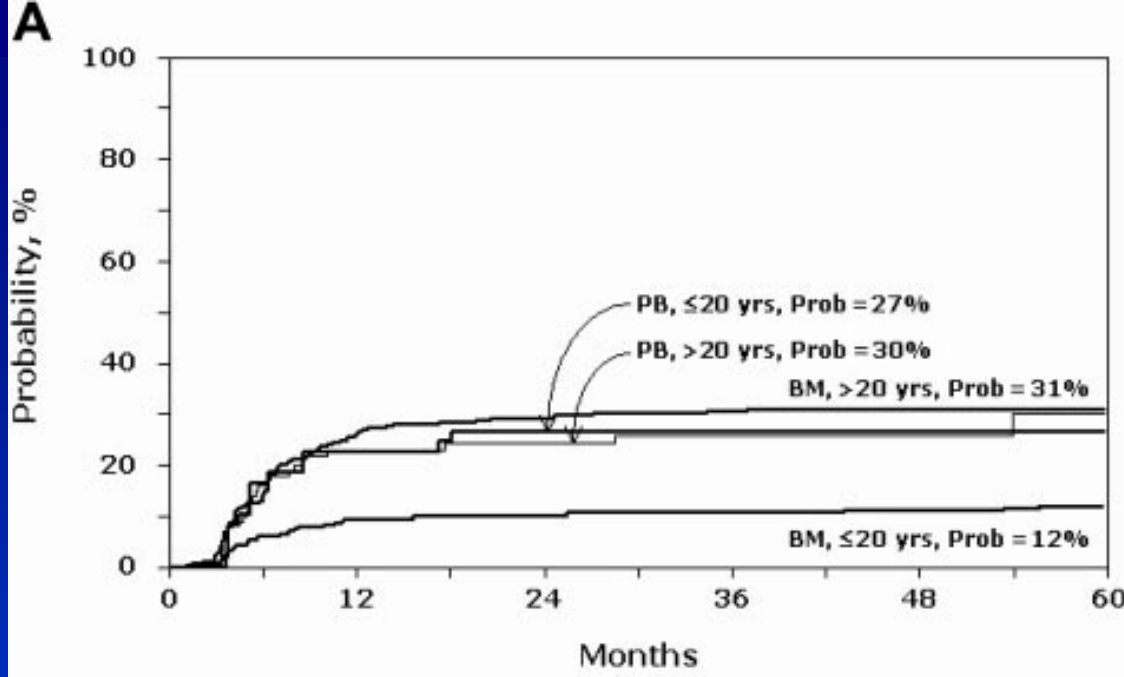
Better survival with PB CD34 $> 5 \times 10^6/\text{kg}$; not with BM

PB: 1 year survival 56% vs 34%

Better survival with larger PB CD34+ grafts



cGVHD



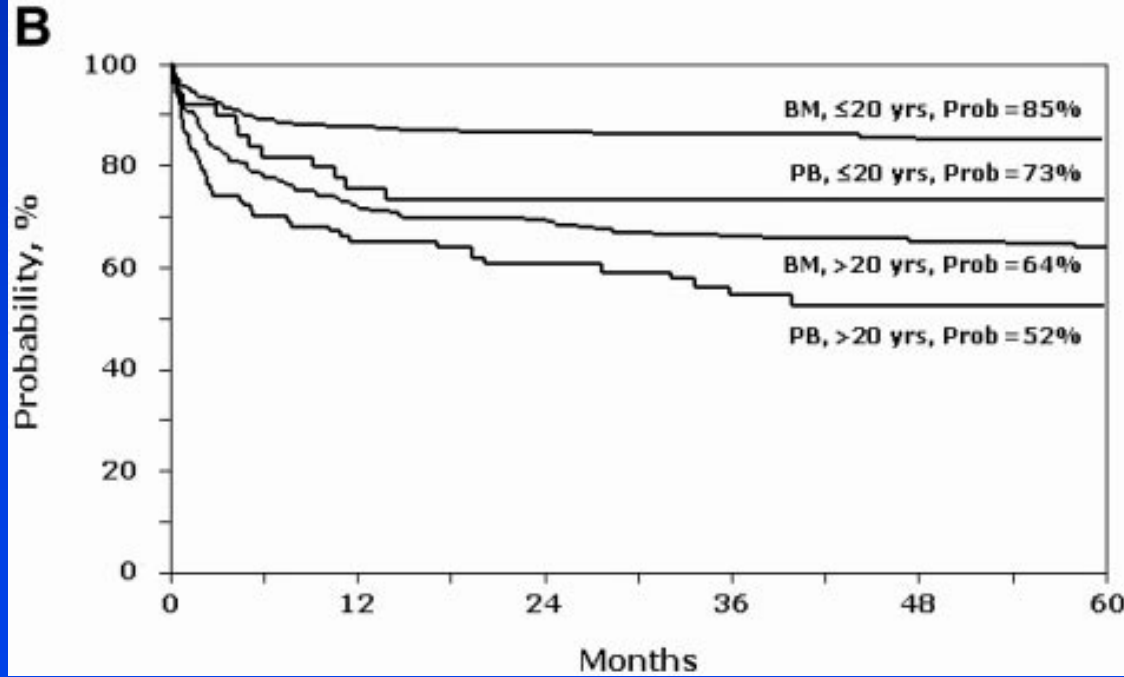
Young patients with Aplastic Anemia

More cGVHD and poorer Survival using PBSC

Other

BM <age 20

Survival



BM ≤ 20

PB ≤ 20

BM >20

PB >20

Schrezenmeier Blood 2007

BM vs G-BM vs G-PB in Severe Aplastic Anemia

Outcome	Odds Ratio (95% Confidence Interval)	P Value
Neutrophil recovery at day 30		
BM versus G-BM	1.07 (0.46-2.47)	.877
PBPC versus G-BM	1.30 (0.46-3.67)	.626
PBPC versus BM	1.21 (0.57-2.57)	.614
Platelet recovery at day 100		
BM versus G-BM	0.97 (0.47-2.03)	.943
PBPC versus G-BM	0.91 (0.40-2.08)	.821
PBPC versus BM	0.93 (0.53-1.65)	.813

**Equivalent
engraftment**

BM vs G-BM vs G-PB in Severe Aplastic Anemia

Variable	Relative Risk (95% Confidence Interval)	P Value
Grade 2-4 aGVHD		
BM versus G-BM	0.82 (0.43-1.55)	.539
FBPC versus G-BM	2.37 (1.21-4.64)	.012
FBPC versus BM	2.90 (1.95-4.31)	< .001
Grade 3-4 aGVHD		
BM versus G-BM	0.74 (0.29-1.91)	.535
FBPC versus G-BM	1.66 (0.61-4.56)	.323
FBPC versus BM	2.24 (1.23-4.10)	.009
Chronic GVHD		
BM versus G-BM	1.56 (0.76-3.24)	.229
FBPC versus G-BM	5.09 (2.42-10.69)	< .001
FBPC versus BM	3.26 (2.31-4.60)	< .001
Overall mortality		
BM versus G-BM	0.63 (0.40-1.00)	.050
FBPC versus G-BM	0.80 (0.47-1.37)	.424
FBPC versus BM	1.28 (0.87-1.88)	.212

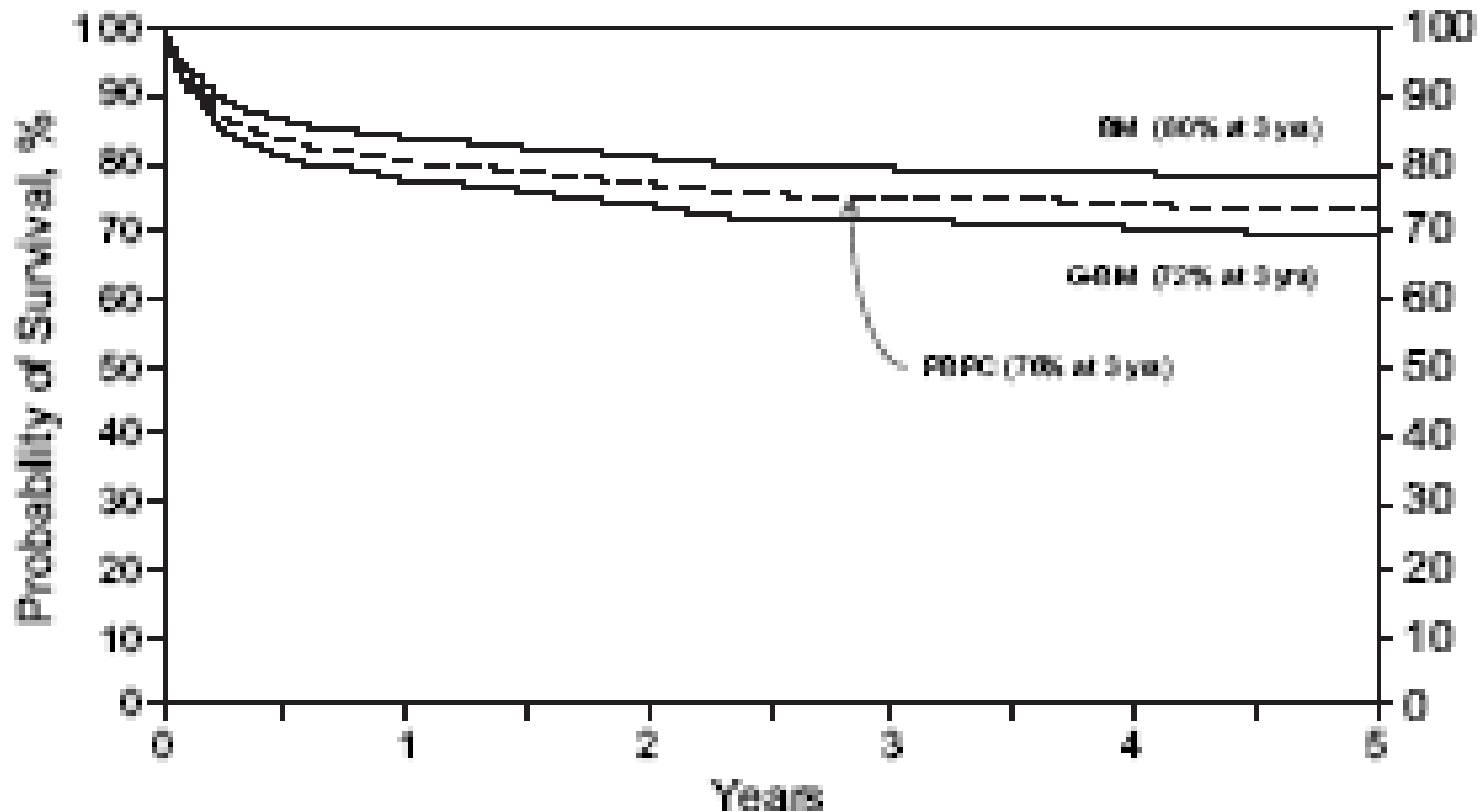
**More acute GVHD
G-BM or PB**

**More chronic GVHD
G-BM or PB**

**Survival better
with BM vs G-BM**

**Survival similar with
PBSC or BM**

BM vs G-BM vs G-PB in Severe Aplastic Anemia



BM
G-PB
G-BM

Retrospective URD comparative Study PBSC vs BM

- **Evaluate collection of PBSC from NMDP unrelated donors (URD)**
- **Assess safety of G-CSF administration and leukapheresis graft collection**
- **Assess safety and efficacy of PBSC vs. BM grafting in URD recipients**

Mobilization and Collection Protocols

- G-CSF 10 $\mu\text{g}/\text{kg}$ sq daily x 4 or 5
- One or two apheresis collections based upon recipient weight:
 - ≤ 35 kg, one collection ≥ 12 liters
 - >35 and ≤ 70 kg, 1 or 2: 18-20 liters total
 - >70 kg, 2: 24 liters total

PBSC Collection Characteristics (preliminary cohort)

	<u>1st, 222</u>	<u>2nd, 175 (79%)</u>
Liters processed	12	12
range	6-24	4-21
CD34 cells ($10^6/L$)	23	21
range	0.1-111	0.7-95
CD34 cells ($10^6/kg$)	4.0	3.2
range	0.02-79	0.1-16
Transit time (hrs)	37	16
range	7-66	9-41

Patients and Donors

	<u>PBSC n=331</u>	<u>BMT n=586</u>	<u>P-value</u>
Age > 40, years	50%	46%*	0.14
CML	20%	29%	0.007
Karnofsky > 80	34%	66%	0.005
HLA 8/8 allele M	58%	58%	0.97
Female Donor	42%	36%	0.33
CMV+ recipient	48%	49%	0.1
Cell dose x10 ⁸ /kg	6.7 (2-25.2)	2.9 (<1-21.8)	<0.001
2001+	63%	34%	<0.01

****favorable***

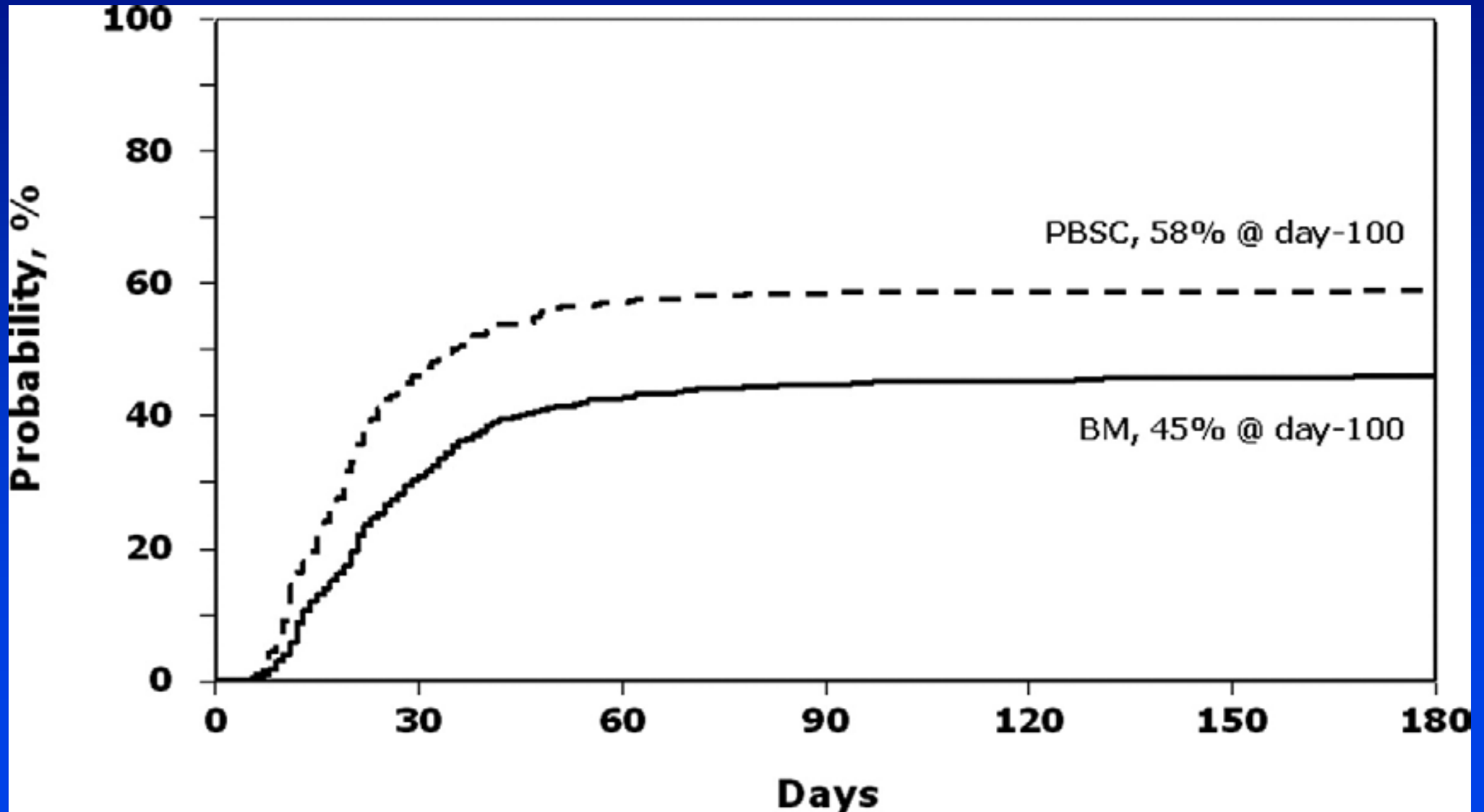
Eapen, et al BBMT 2007

Engraftment PBSC vs. Marrow

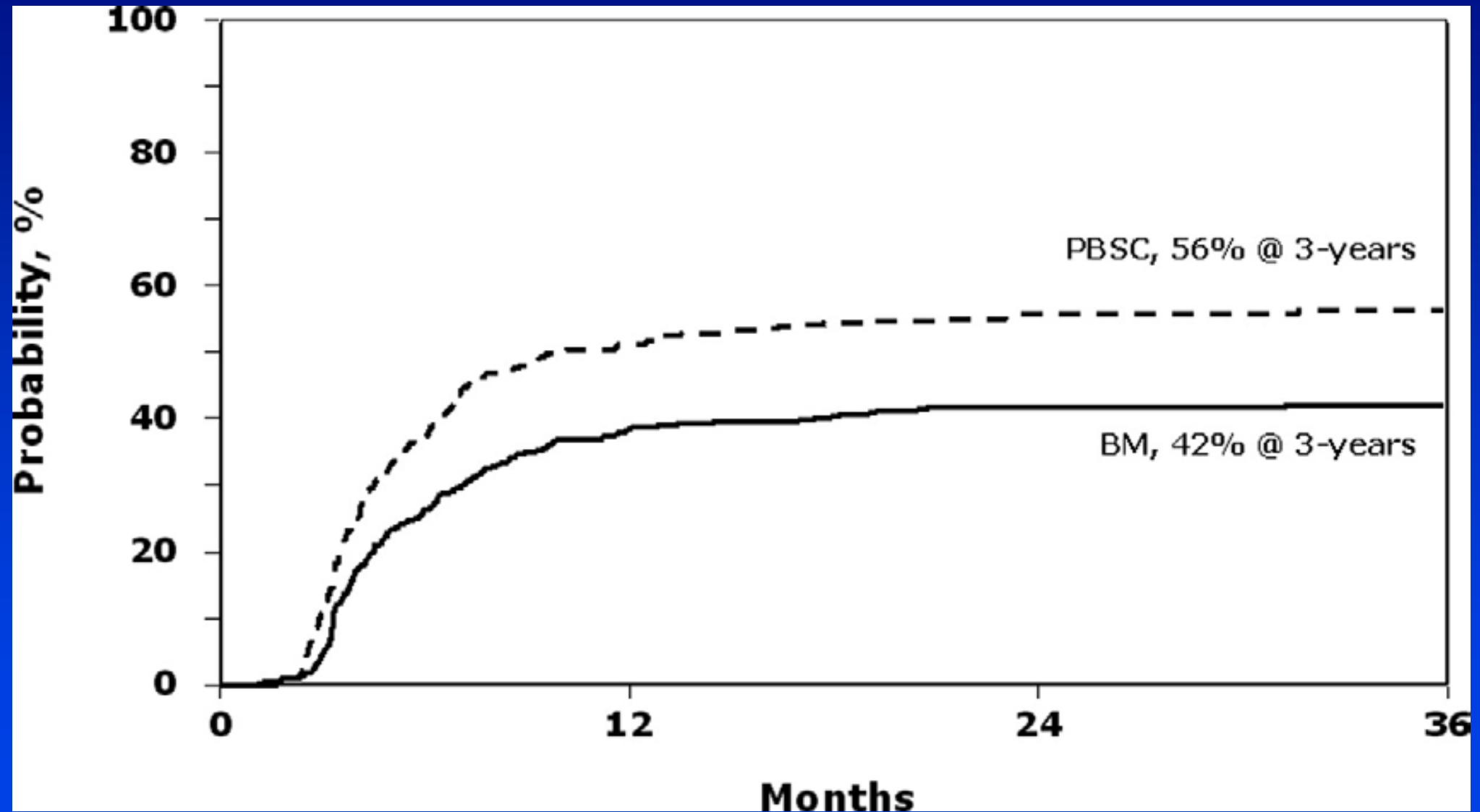
	<u>PBSC</u>		<u>BM</u>	<u>P value</u>
Day 28 ANC	94	vs	87%	<0.001
Day 100 Platelet	80	vs	69%	<0.0001

Faster engraftment with PBSC

Grades II-IV Acute GvHD: more with PBSC



More chronic GvHD with PBSC



Retrospective PB vs BM Cohort Chronic GVHD

	<u>OR [RR]</u>	<u>95% CI</u>	<u>P value</u>
CD34 cell dose x 10⁶/kg			
9.3 - 25.6	1	*	*
5.9 - 9.3	0	(0.0-0.0)	<0.0001
4.1-5.9	.19	(0.0-1.4)	0.11
0.7-4.1	.28	(0.1-1.3)	0.10

Suggestion of more cGVHD with larger CD34 dose

GVHD

PBSC vs. Marrow: multivariate analysis

	<u>PBSC</u>	<u>P value</u>
Acute GvHD (II-IV)	1.50 (1.27-18.1)	<0.01
Acute GvHD (III-IV)	1.17 (0.90-1.51)	0.249
Chronic GvHD	1.72 (1.41-2.10)	<0.001

More GVHD with PBSC

No improved relapse protection despite more cGVHD

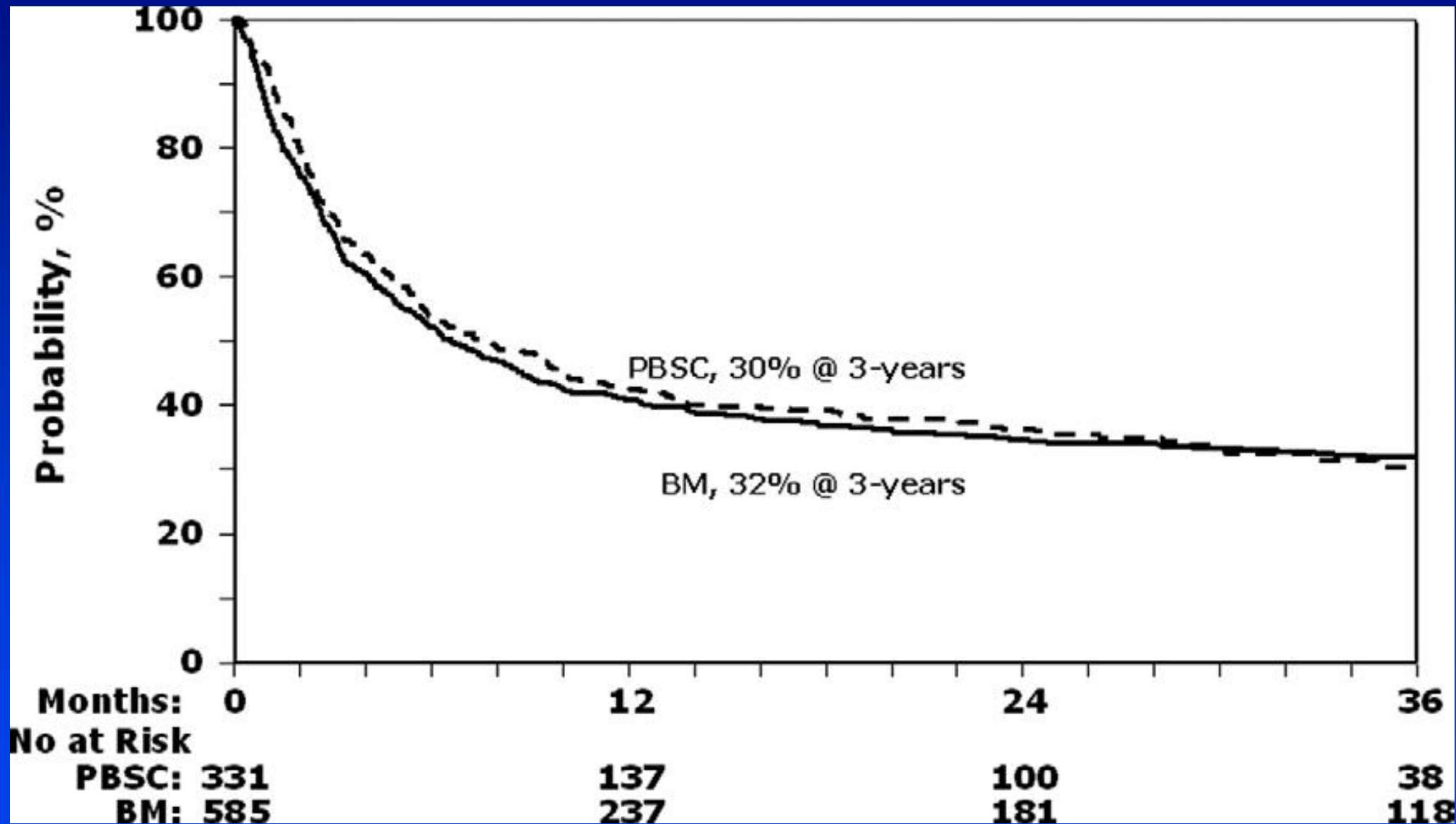
Multivariate Analyses PBSC vs. Marrow

	<u>PBSC</u>	<u>BM</u>
TRM to day 100	22%	26%
TRM @ 3 years	44%	44%
Relapse @ 3 years	26%	24%
Relapse or Death	30%	32%

Equivalent TRM, relapse

Equivalent survival and relapse-free survival with PBSC

Leukemia-Free Survival



Retrospective Summary

- Collection of PBSC from unrelated donors is feasible
- G-CSF toxicity to the donors is tolerable
- PMN and Platelet recovery is faster with PBSC
- PBSC might lead to more GVHD
- There is no sustained survival advantage with PBSC

Leading to

Prospective, randomized, controlled trial

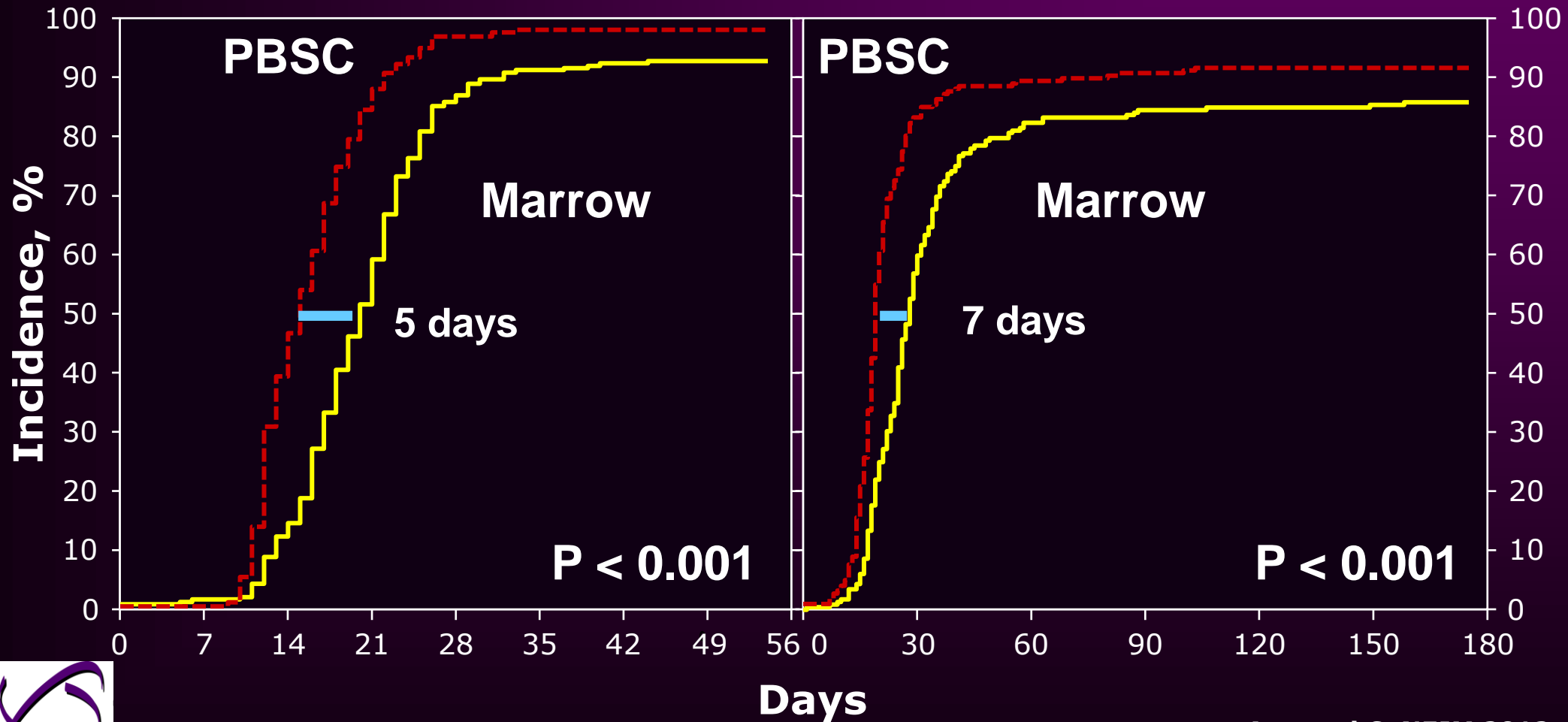
BMT CTN 0201 N=550 completed accrual 2009

Anasetti et al, NEJM 2012

Engraftment after Transplantation

Neutrophils

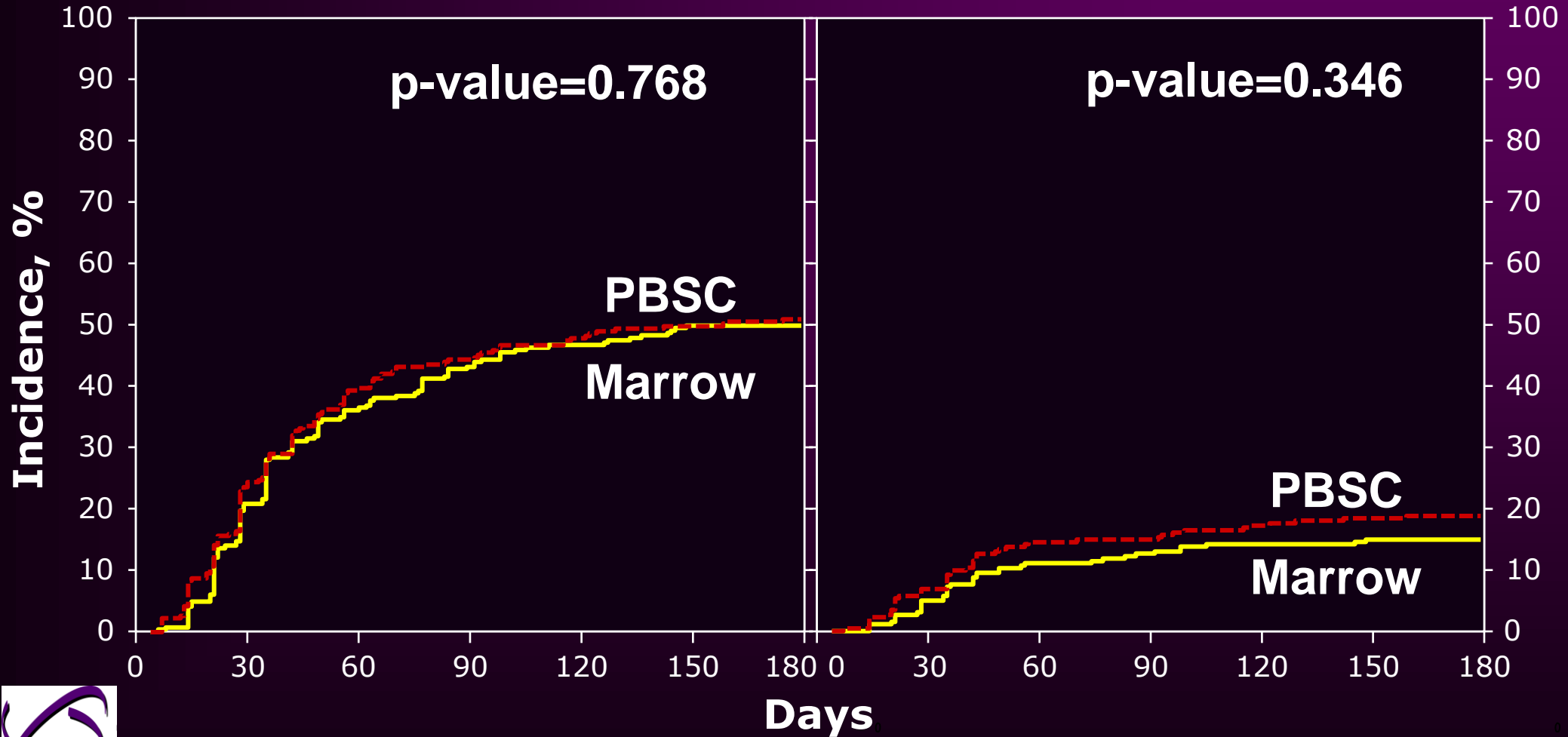
Platelets > 20k



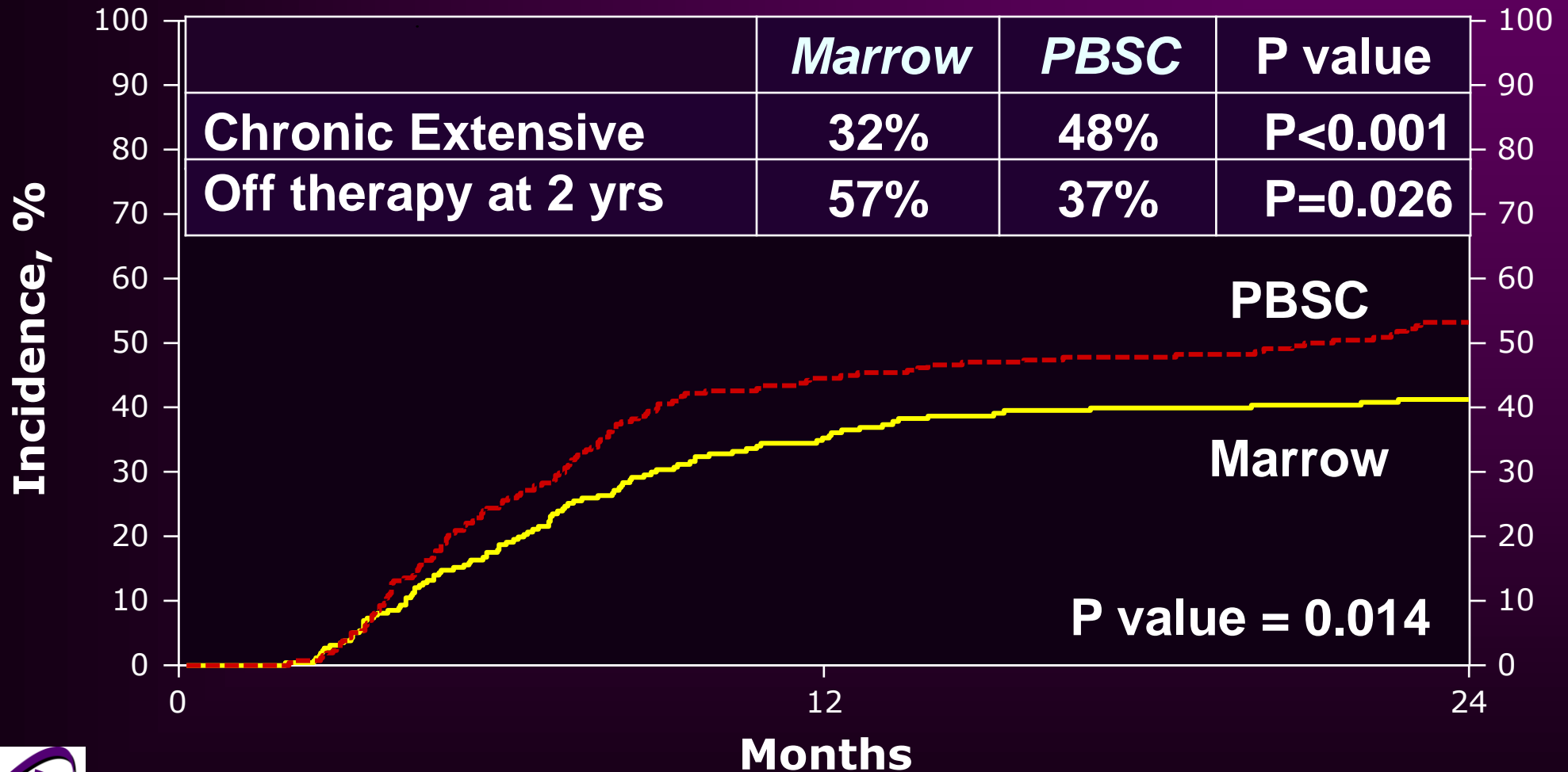
Acute Graft-versus-Host Disease

Grades 2-4

Grades 3-4

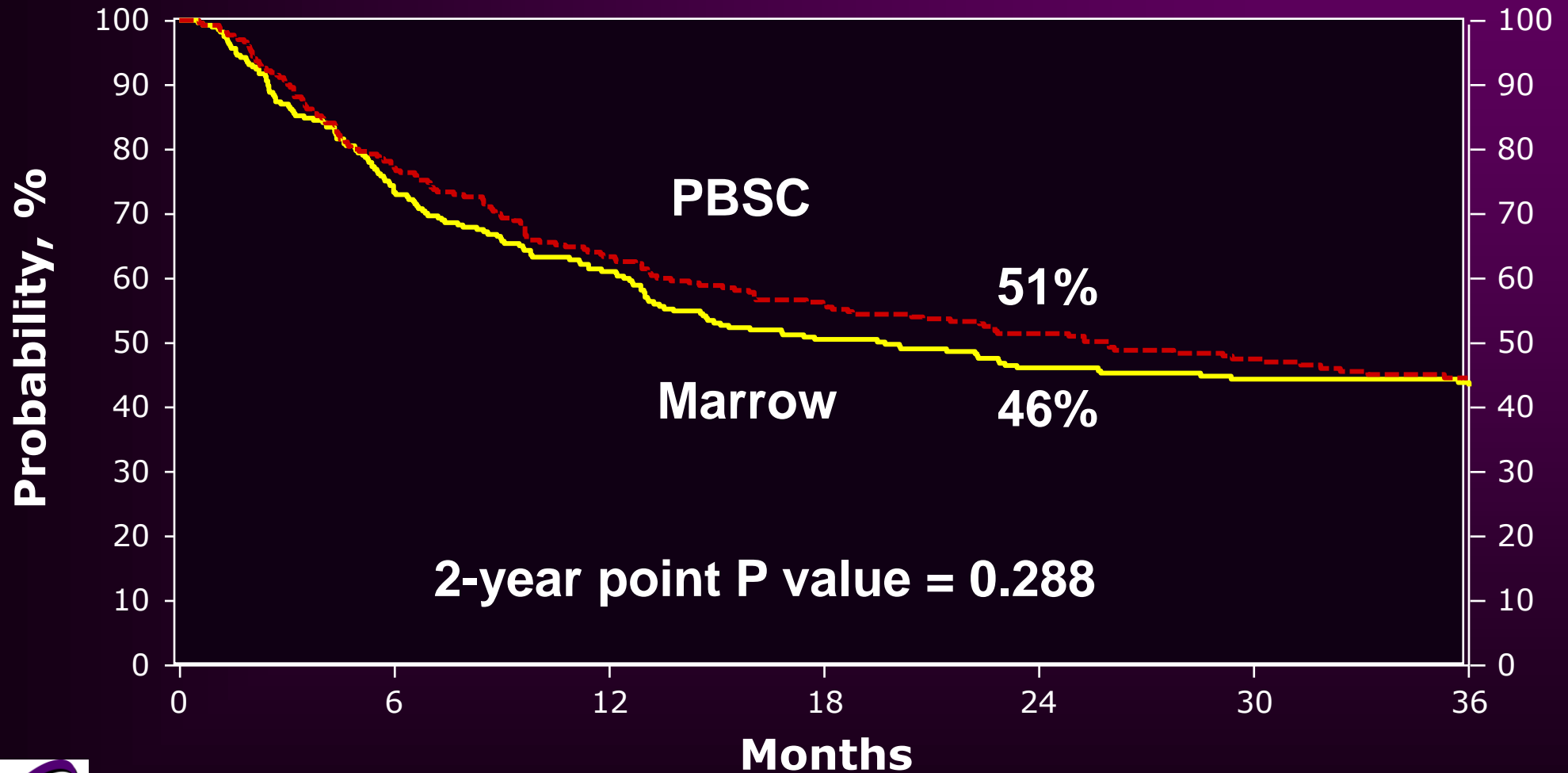


Overall Chronic GVHD

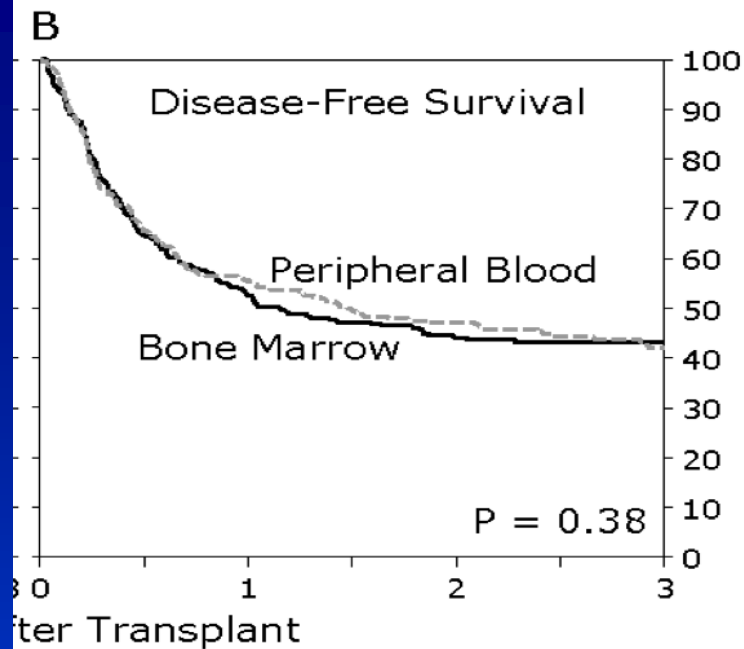


Overall Survival from Randomization

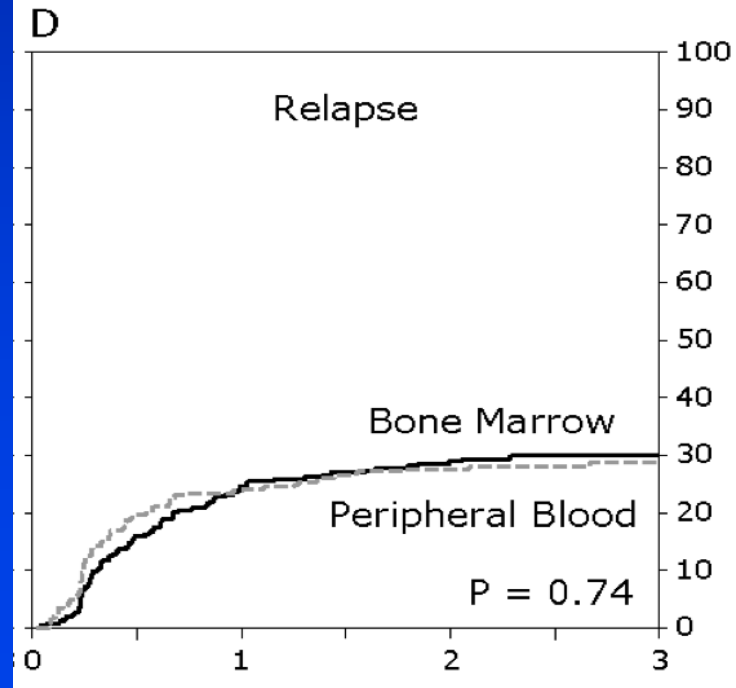
Intent-to-treat analysis



DFS



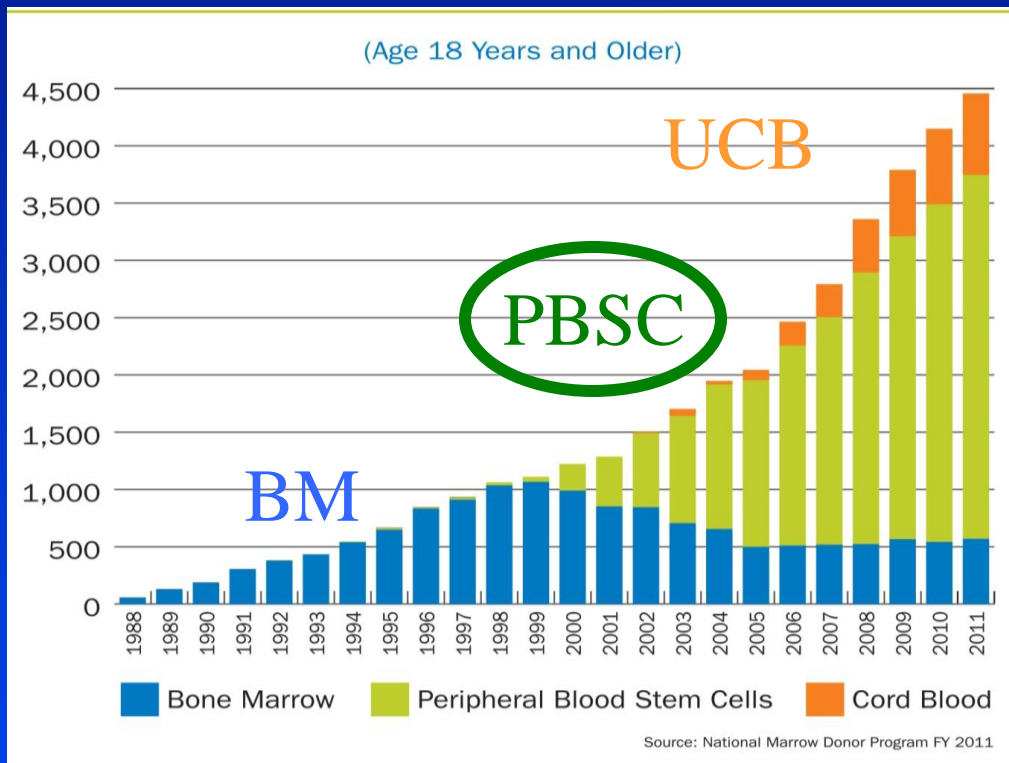
DFS and Relapse are identical after URD PBSC or BM transplants



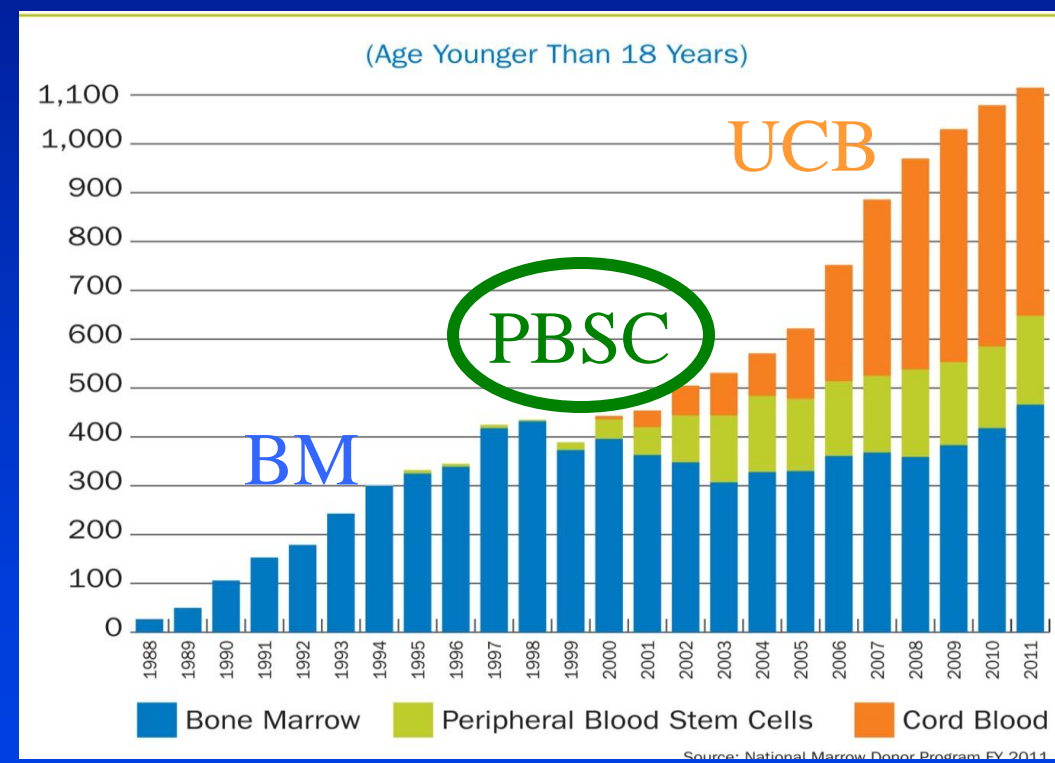
Relapse

NMDP Graft types thru 2011

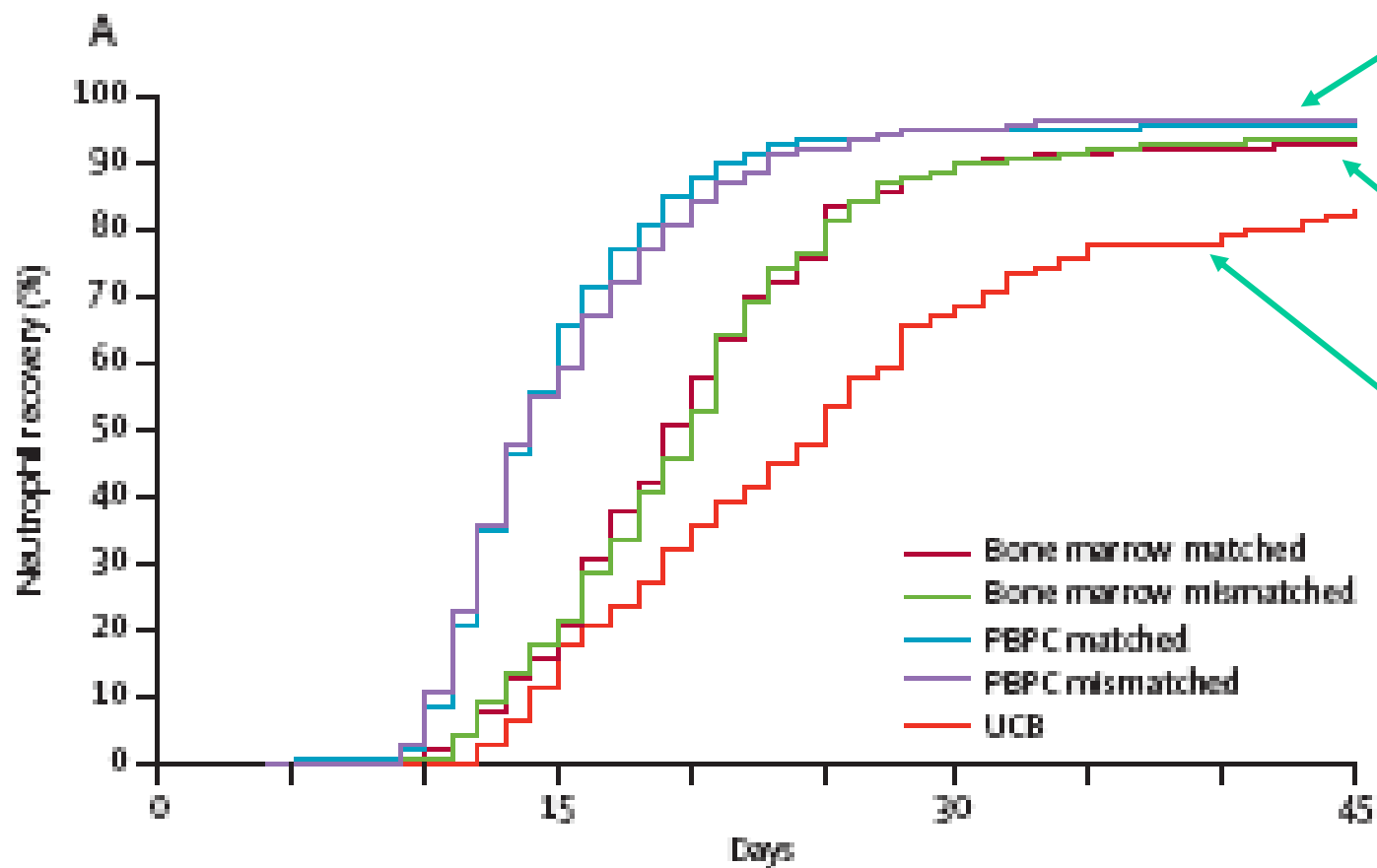
Adults 18+ years



Pediatrics

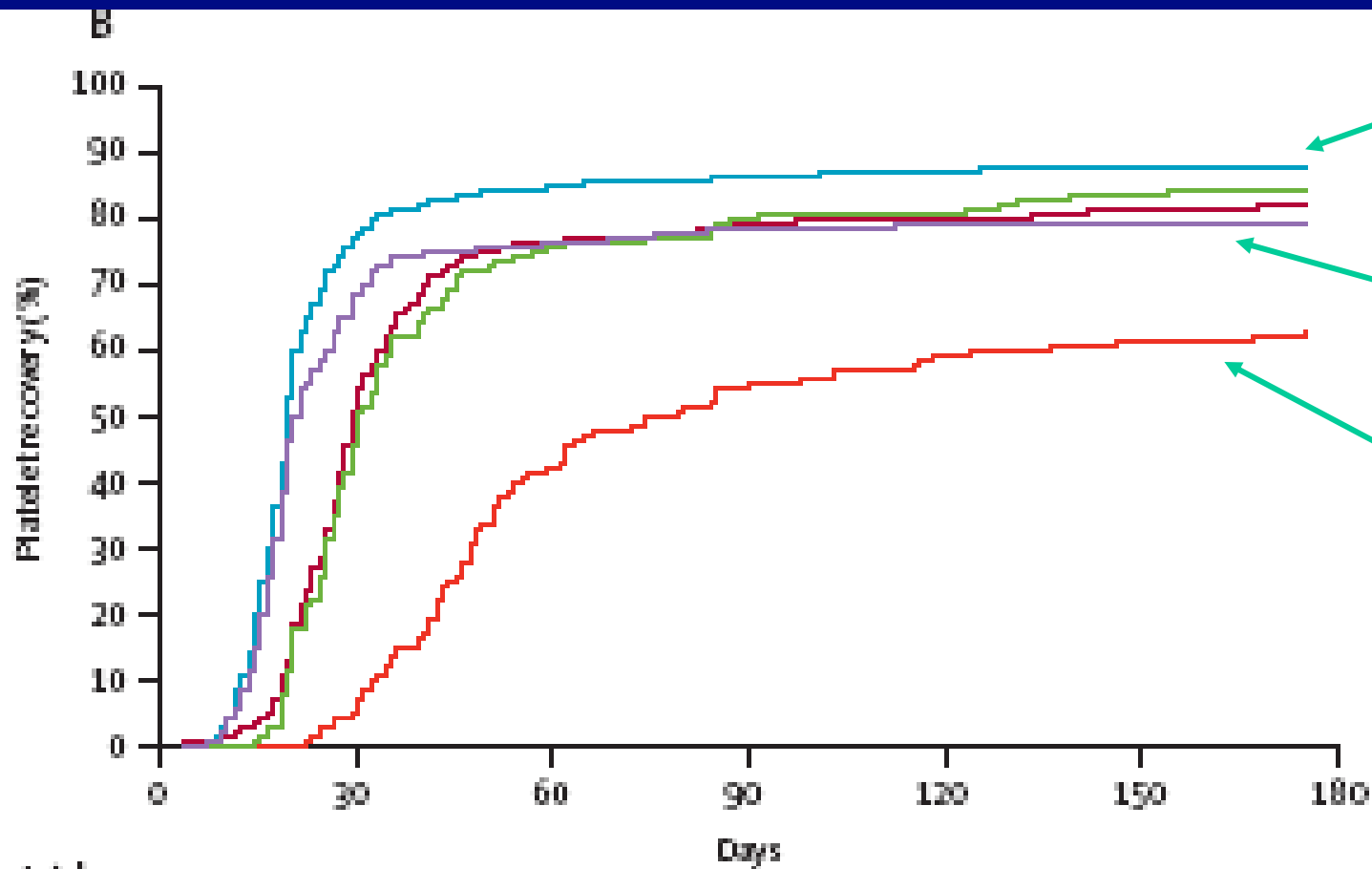


Neutrophil recovery: Graft source UCB vs PB vs BM



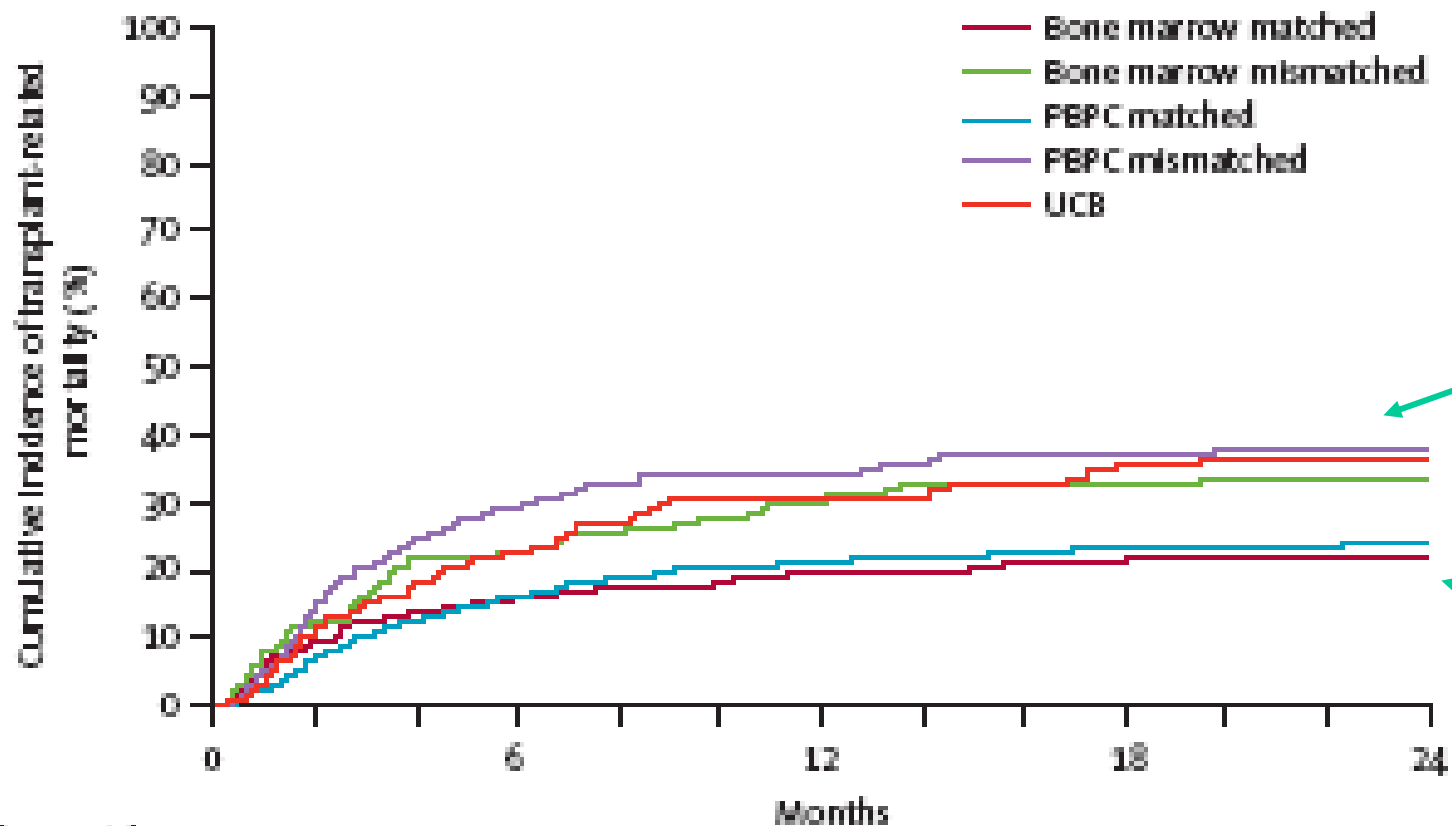
Number at risk		0	15	30	45
8/8 matched bone marrow	332			20	2
7/8 matched bone marrow	140			8	1
8/8 matched PBPC	632			11	2
7/8 matched PBPC	256			5	0
4/6-6/6 matched UCB	165			47	13

Platelet recovery: Graft source



PB M
PB mm
BM M
BM mm
UCB

Treatment related mortality: Graft source



PB mm

UCB

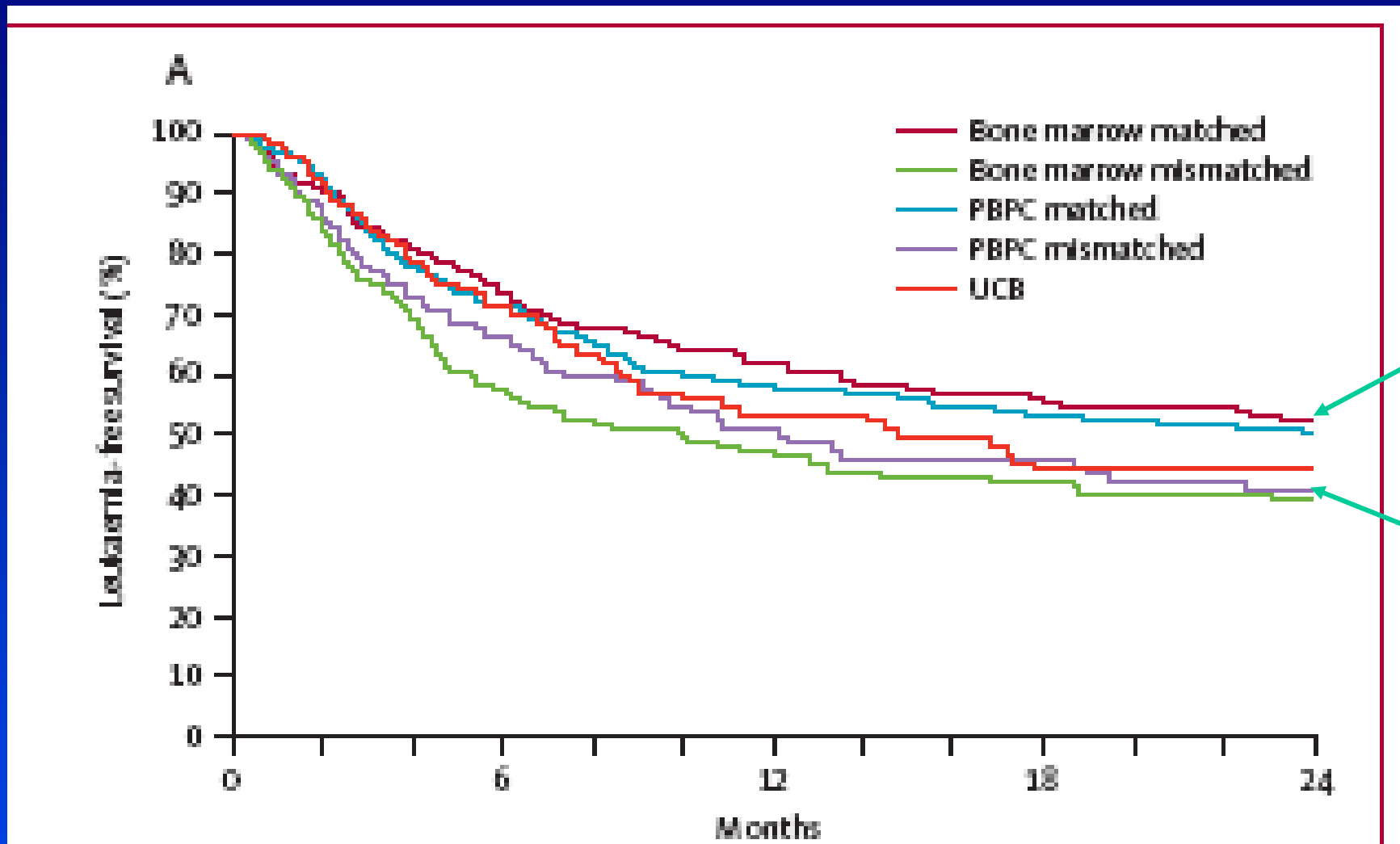
BM mm

PB M

BM M

	Number at risk				
	0	6	12	18	24
8/8 matched bone marrow	332	208	156	112	92
7/8 matched bone marrow	140	81	51	38	34
8/8 matched PBPC	632	379	259	162	126
7/8 matched PBPC	256	123	85	57	44
4/6-6/6 matched UCB	165	94	57	39	30

LFS Patients in remission: Graft source



PBSC vs. BM

Similar outcomes overall

Likely more GVHD with PBSC

No evidence of more GVL; *could be modified*

Still appealing to consider an engineered graft

Avoid PBSC in non-malignant disease

Tailor to specific:

Situation; donor; GVHD prophylaxis

Comparison with UCB