



Therapy of relapsed ALL

Review UK data

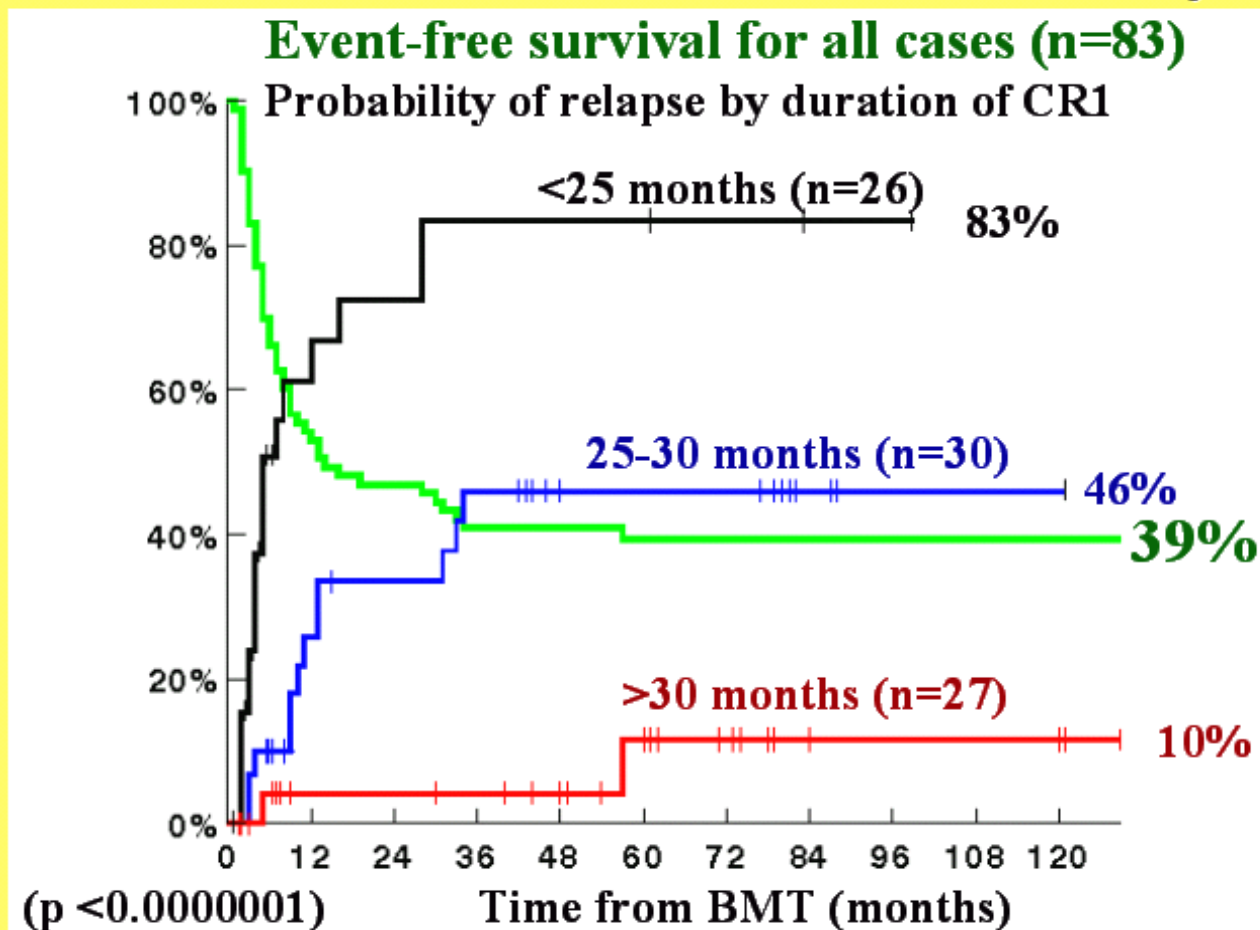
IBFM data and indication

R3 trial and outcomes

Future directions



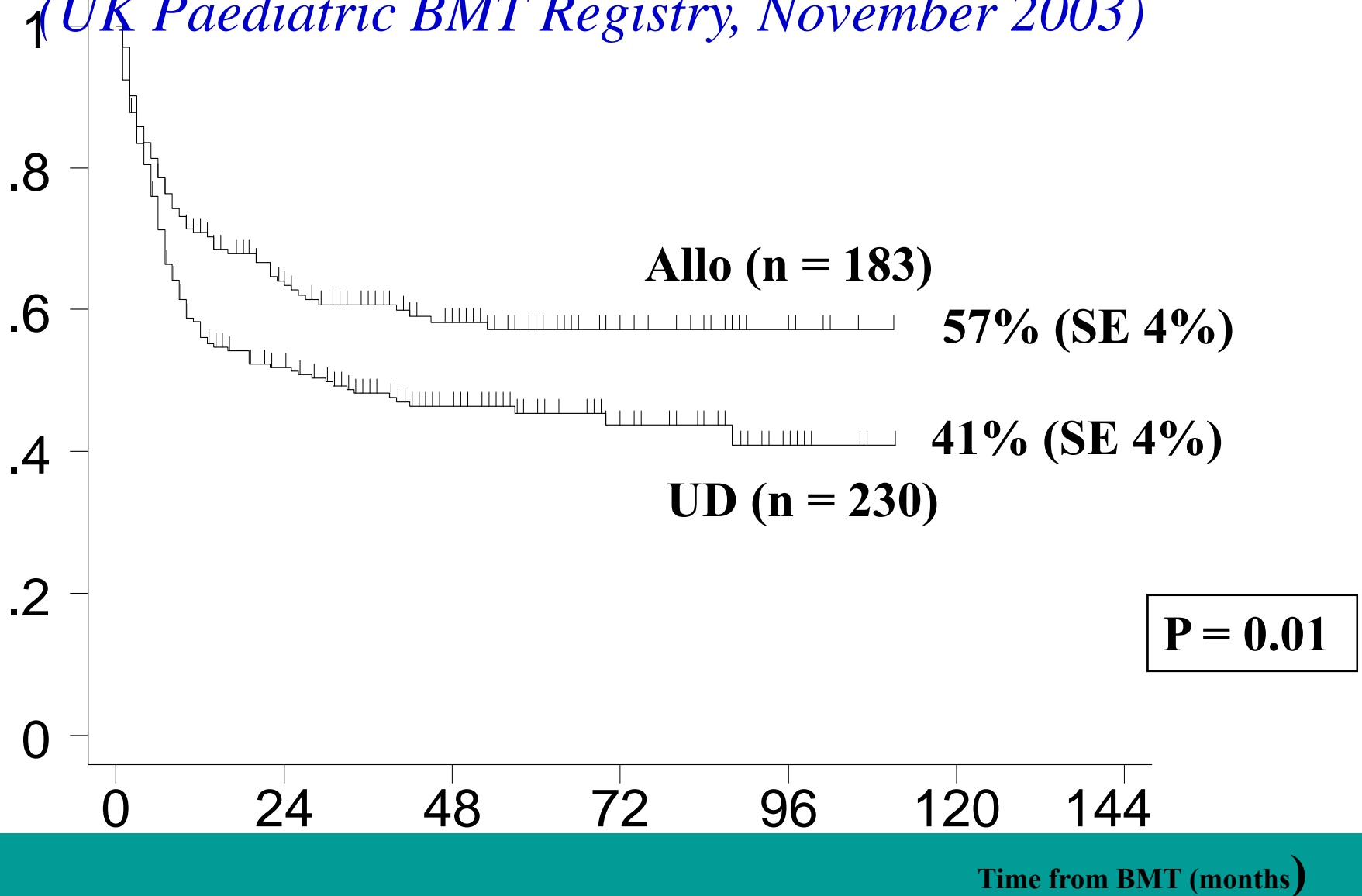
UD BMT for A.L.L. in 2CR with BM +/- Extramedullary Relapse



(Bristol BMTs, February 2003)

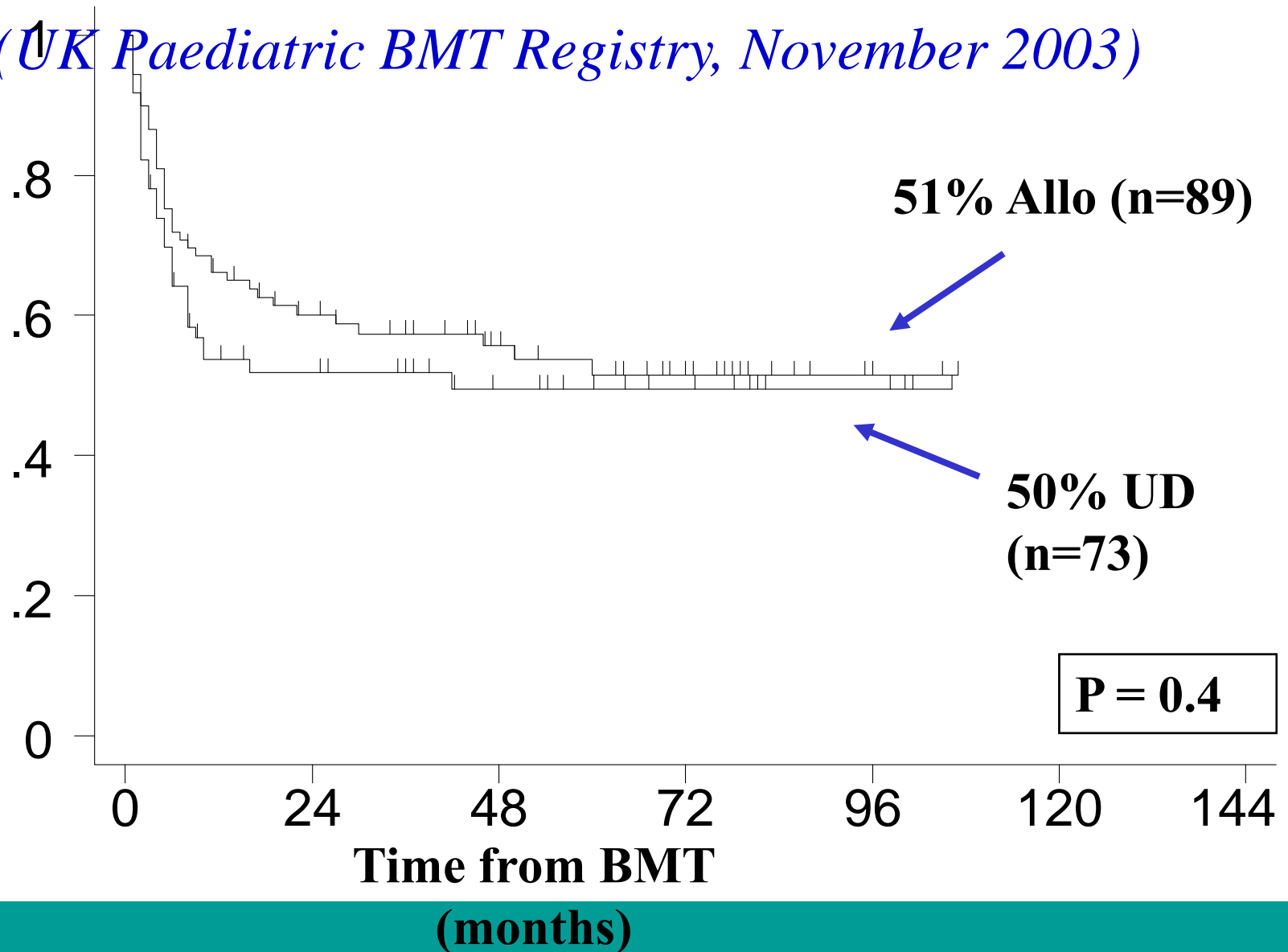
Event-Free Survival after BMT - ALL in 2CR, UD v Allo

(UK Paediatric BMT Registry, November 2003)



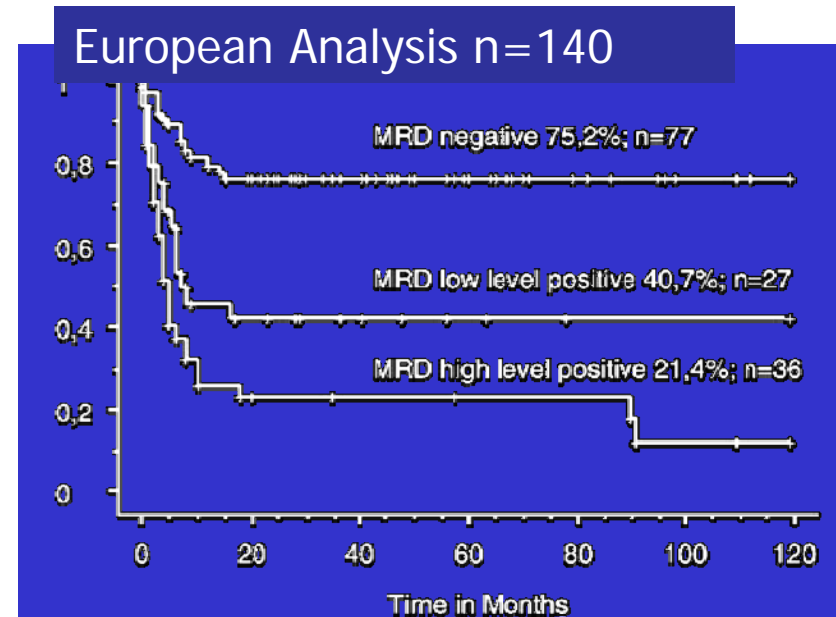
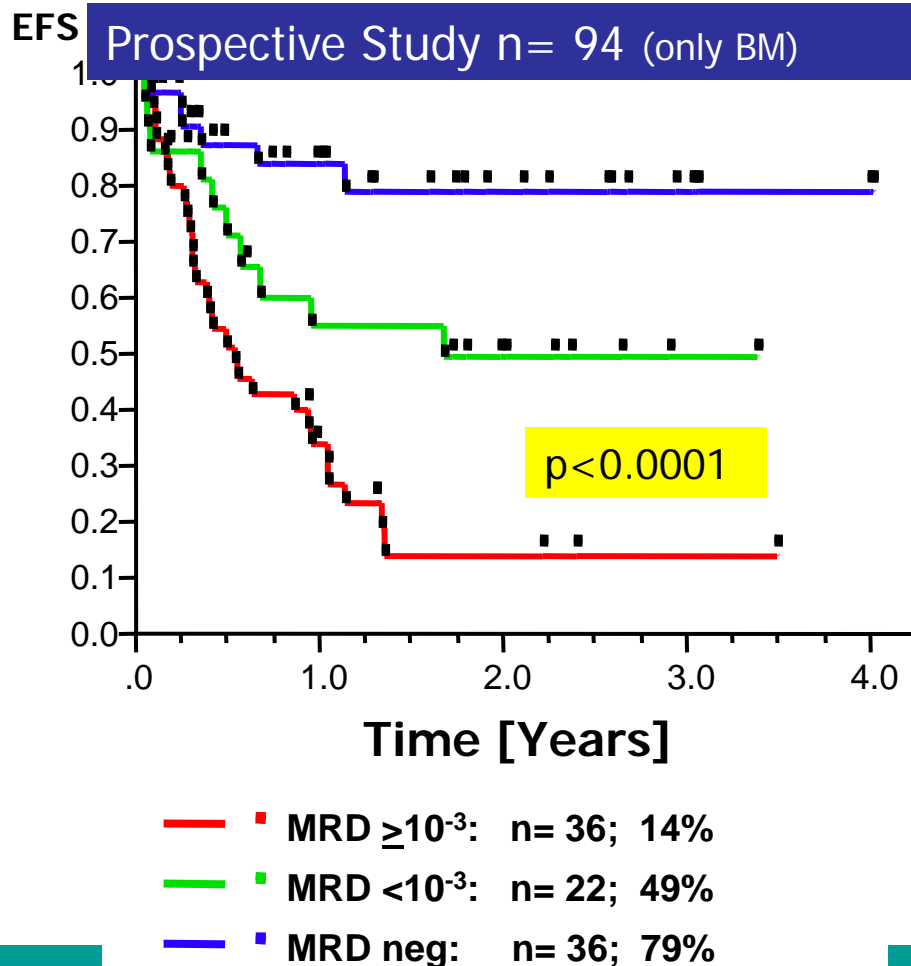
Event-Free Survival after BMT - ALL in 1 CR, UD v Allo

(UK Paediatric BMT Registry, November 2003)



Impact of MRD Load Prior to allo-SCT

Loses significance if controlled for duration of CR1



Results of previous studies



Allo SCT from MSD



**superior to CT
in high risk patients**

Allo SCT from UD



high TRM

T-cell depletion



**high relapse rate
in poor remission**

Pre TX factors

-MRD

-Time of relapse

-Site of relapse



**influence post
SCT course**

ALL SCT BFM 2003 – Aims:



Improve results from alternative donors (MD/MMD)

precise HLA-typing, homogeneous donor selection
established conditioning regimen: TBI/ETP
sufficient T-cell depletion if indicated

Reduce relapse incidence

short GVHD-prophylaxis
monitoring of MRD and chimerism

Reduce toxicity and infections

homogenous supportive care
monitoring of viral and fungal infections



Donor selection: conclusion

HLA identity donor/recipient	sibling donor	family donor	unrelated donor
10/10	MSD	MFD	MUD
9/10	1MMFD		1MMUD
< 9/10	MMFD		MMUD

MSD

MD

MMD

Cord blood: current stratification

HLA-identical sibling = MSD

5/6 or higher = MD

Less than 5/6 = MMD

Indications for CR2, > CR2



Very high risk:

*all T-phenotypes except **

non T: very early BM
 early combined

(*> CR 2*)

MSD

MD

MMD

High risk:

t (9;22)

Isolated extramedullar: bilateral testes

BM isolated: initial BCC > 10.000/ μ l PBC

MRD $\geq 10^{-3}$

non T:

late BM without MRD

late combined without MRD

„Standard risk“:

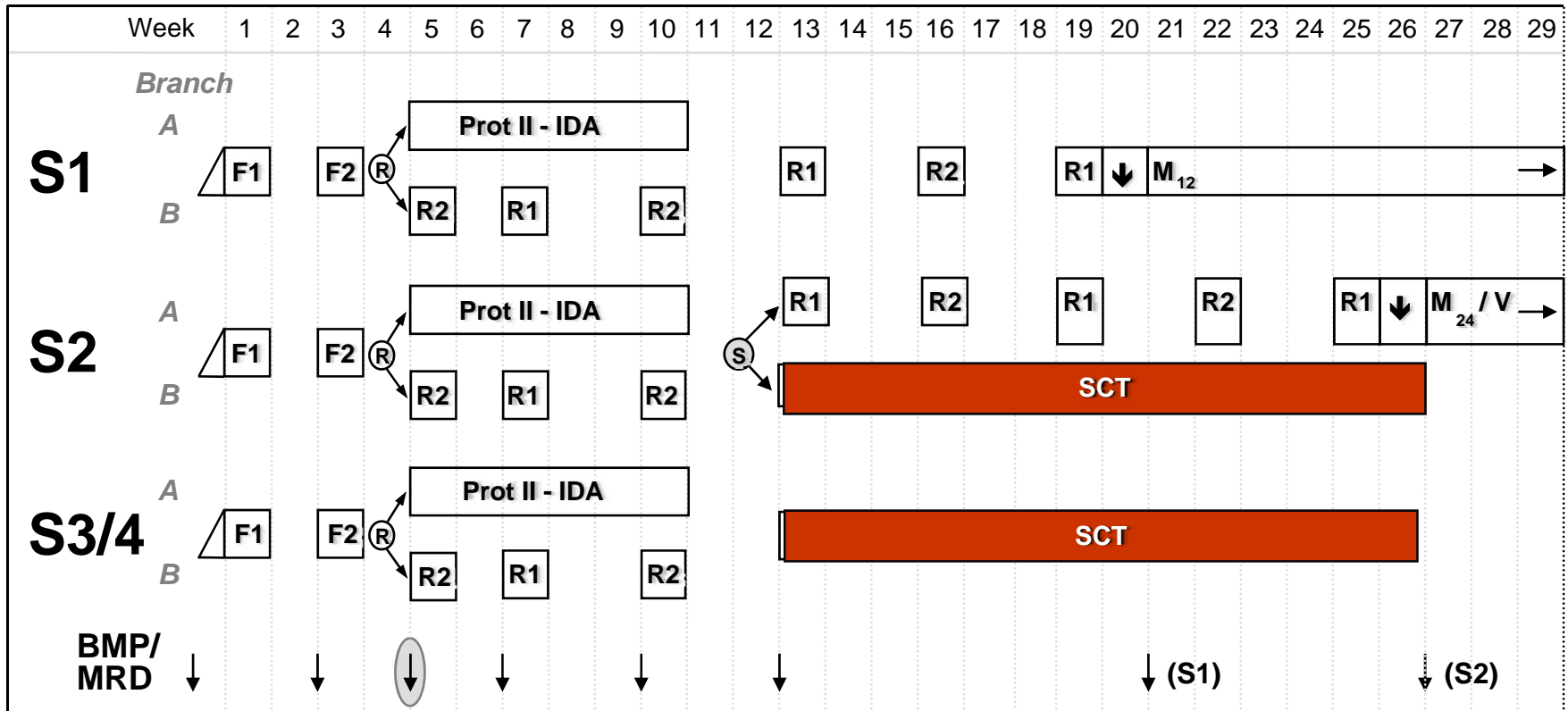
non T: late BM, late comb: MRD < 10^3

early combined: without MRD

*isolated
extramedullar
very early and
early T & non T

	Non -T			Pre - T		
	Extramed	Combined	Marrow	Extramed	Combined	Marrow
Very early Diag <18m Treat < 6m	I	H	H	I	H	H
Early Diag >18m Treat < 6m	I	I	H	I	H	H
Late Treat > 6m	S	I	I	S	H	H

Treatment Schedule ALL - REZ BFM 2002



D12/D24, 12/24 month maintenance tx; (R), randomization; (S), stratification; V, VP16-reinduction pulses; ↓, local radiotherapy; (↓), BMP-time-point for post-remission stratification in S2; SCT, stemcelltransplantation; BMP, bone-marrow puncture; MRD, minimal residual disease; chemotherapy courses: F1, F2, R2, R1, Protocol II-IDA.

Conditioning Regimen & GVHD-prophylaxis > 24 mts



MSD

FTBI (12 Gy)
-6, -5, -4
VP16 60 mg/kg
-3

CSA iv 2 x 1,5mg/kg
-1 until oral intake

CSA po 2 x 3mg/kg
until day 60

FTBI (12 Gy)
-6, -5, -4
VP16 60 mg/kg
-3

ATG Fresenius 20 mg/kg
-3, -2, -1

CSA iv 2 x 1,5mg/kg
-1 until oral intake
MTX 10 mg/m²/Leukovorin
+1, +3, +6

CSA po 2 x 3 mg/kg
until day 100

MMUD/FD

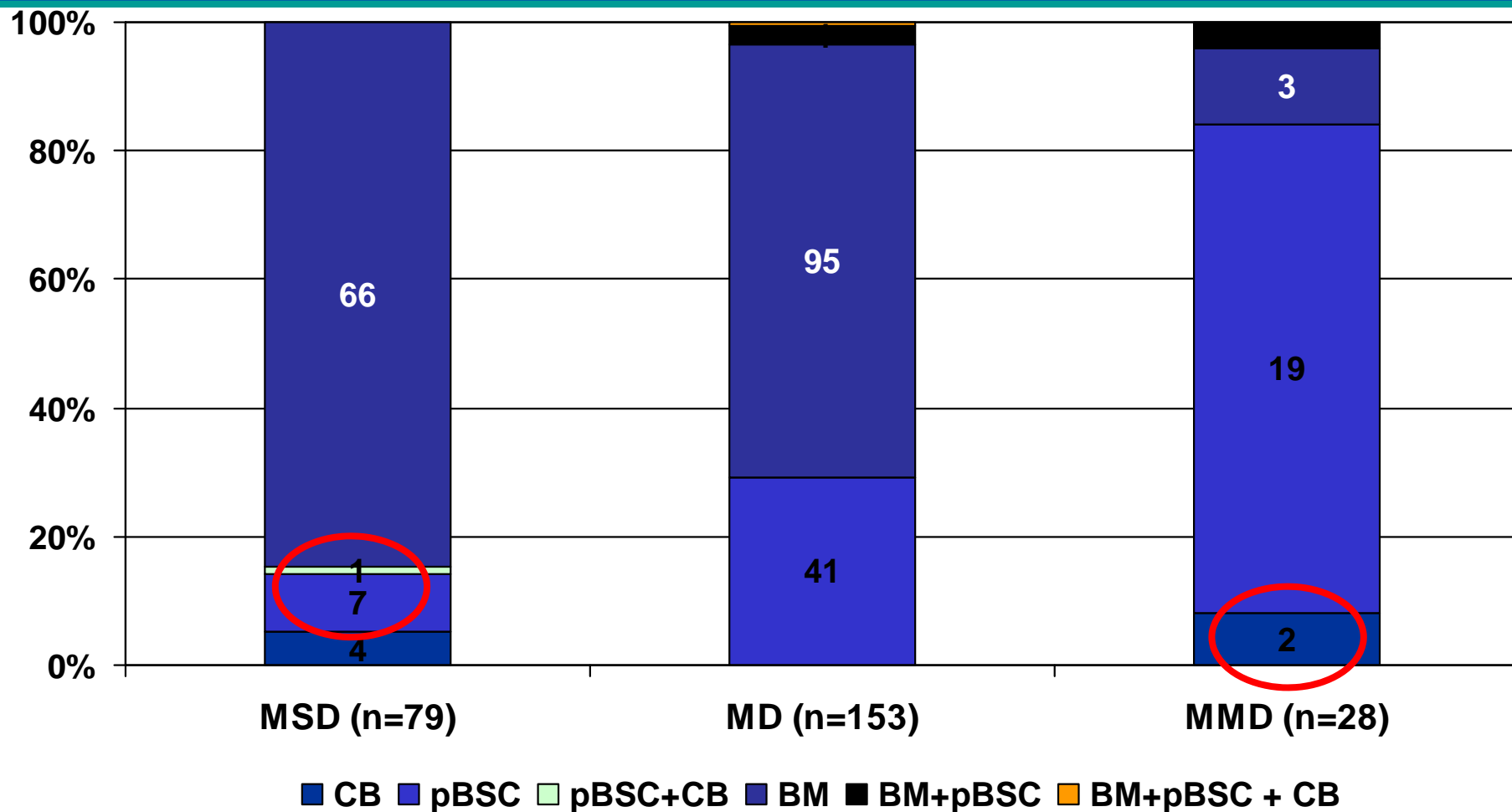
FTBI (12 Gy)
-10, -9, -8
Fludara 40 mg/m²
-7, -6, -5, -4
VP16 40 mg/kg
-3

ATG Fresenius 20 mg/kg
-3, -2, -1

CD3/19 depletion
> 10 x 10⁶/kg CD34
< 3 x 10⁴/kg CD3+



Stem Cell Source/Donor



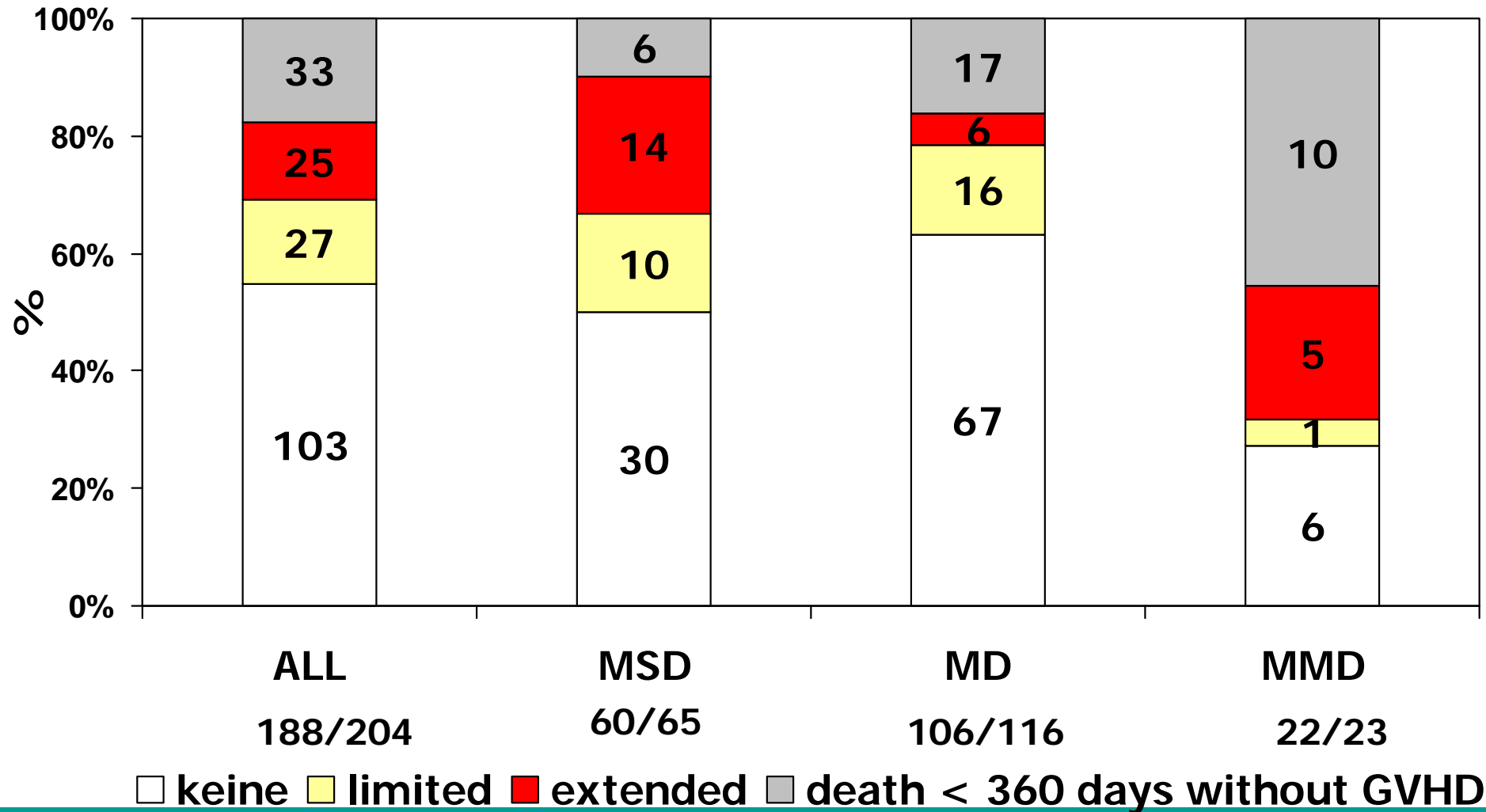
unbekannt

n=1

n=12

n=3

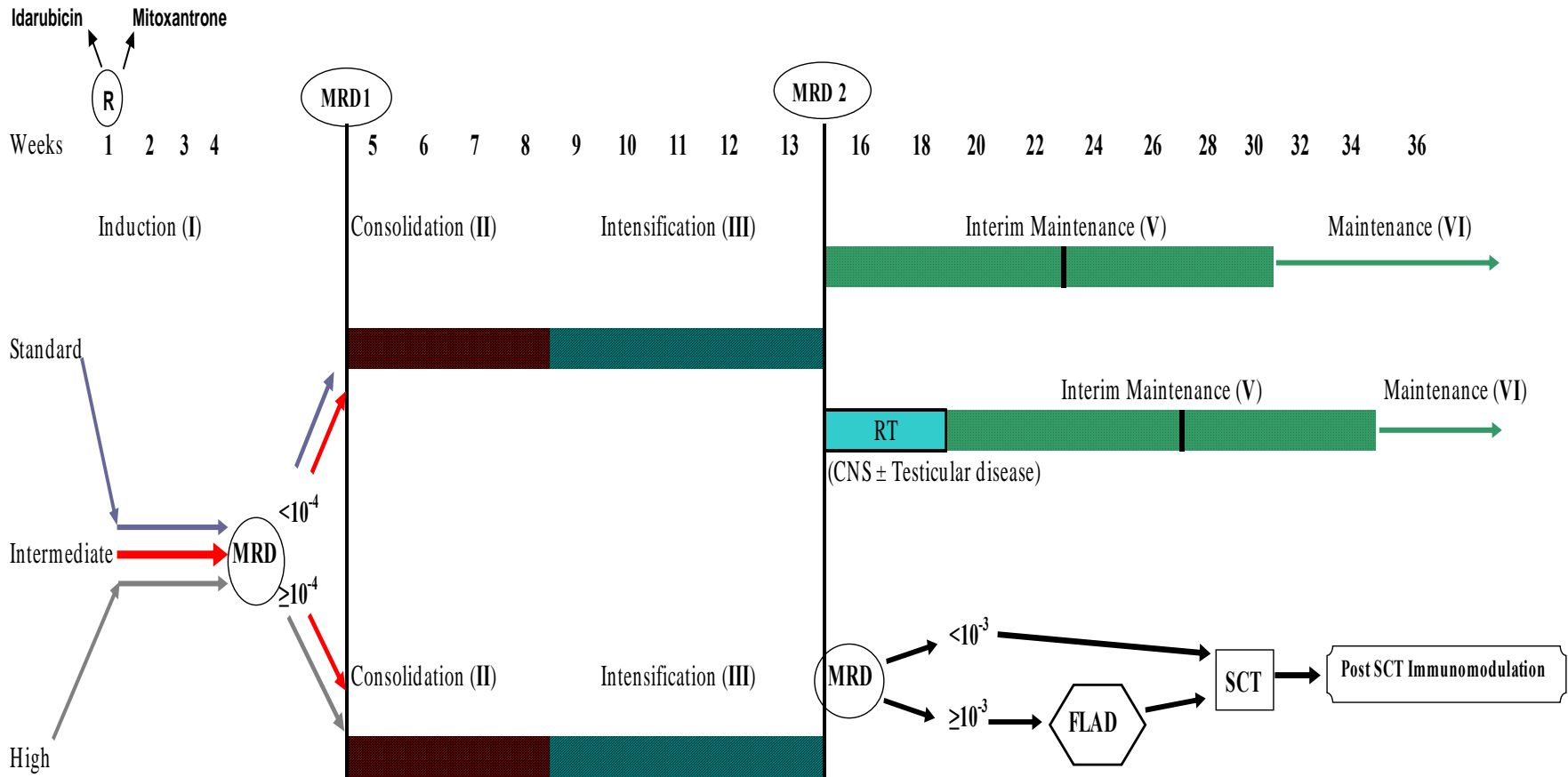
Chronic GvHD (SCT before April 2007)



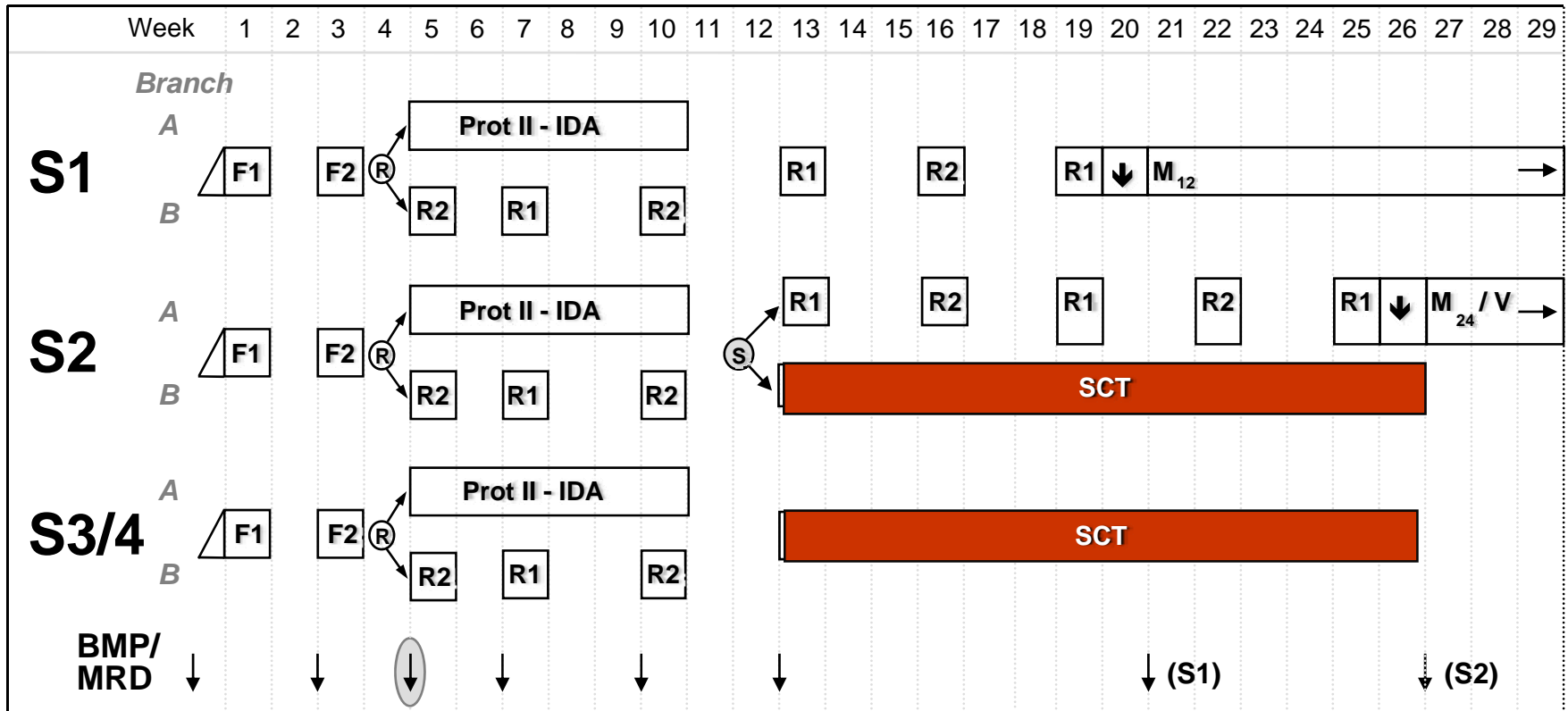


- Standardization of treatment for primary refractory and relapsing ALL patients
- Heterogeneous group of patients
- R1 – First U.K. Trial had very favorable results but on back of suboptimal primary treatment (Lawson et al, B.J. Haematology 2000; 108 (3) : 531-43)
- R2 – Attempt to randomize allogeneic BMT/MUDBHT poor uptake.
- We have been unable to conduct a randomized trial for any form of B.M.T. in relapsed ALL due to parental and physician prejudice but trend for benefit in Early Relapse (MRC) and T cell disease (BFM)

Study Design



Treatment Schedule ALL - REZ BFM 2002



D12/D24, 12/24 month maintenance tx; (R), randomization; (S), stratification; V, VP16-reinduction pulses; ↓, local radiotherapy; (↓), BMP-time-point for post-remission stratification in S2; SCT, stemcelltransplantation; BMP, bone-marrow puncture; MRD, minimal residual disease; chemotherapy courses: F1, F2, R2, R1, Protocol II-IDA.



Treatment for Risk Groups

High Risk

Results from R1 suggest benefit for BMT over chemo only

(Harrison G. et al, Ann. Oncol. 2000 11(8) 999 – 1006.

Therefore induction/consolidation → BMT (any donor)

(v. early comb. + BM, Early BM, ALL Tcell Comb. + BM)

Standard Risk

R1 – 70% E.F.S. (Lawson et al 2000)

Therefore Chemotherapy ± local radiotherapy

(Late Extramedullary relapses)



Intermediate Risk

- EBMT data suggests BMT may not benefit isolated extramedullary relapses (Dini et al BMT 1996) but it may for BM relapse.

Nos. too small in U.K. +failure of randomisations on R1/R2

- Induction, consolidation; if MRD + ve at week 5, at $\geq 10^{-4}$ will be transplanted if have a donor.

If MRD negative (2 targets) chemotherapy only.

Shared UkALL and 1 – BFM approach



- MRD by Real – Time PCR for 1g H and TCR rearrangements (Pan European Guidelines – 5 U.K. labs – coordinated Nick Goulden)
- Time points for MRD end of week 5 (results by week 8) and at week 13/14 (results by week 14/15 after treatment on either protocol).



Uni- and multivariate significance of parameter for EFS in childhood isolated CNS relapse of ALL by study group

	<u>ALL</u>		<u>BFM</u>		<u>FRA</u>		<u>NET</u>		<u>NOP</u>		<u>NO/IS/CZ</u>	
	univ	cox	univ	cox	univ	cox	univ	cox	univ	cox	univ	cox
Sex			+									
Immun; T vs B-prec	+		+	+								
Initial age; < vs ≥ 6y	+	+	+	+	+	+			+			
Timepoint; ve/e/l	+	+	+	+	+		+	+			+	



EFS and size of subgroups defined by parameters age at initial diagnosis and timepoint of relapse

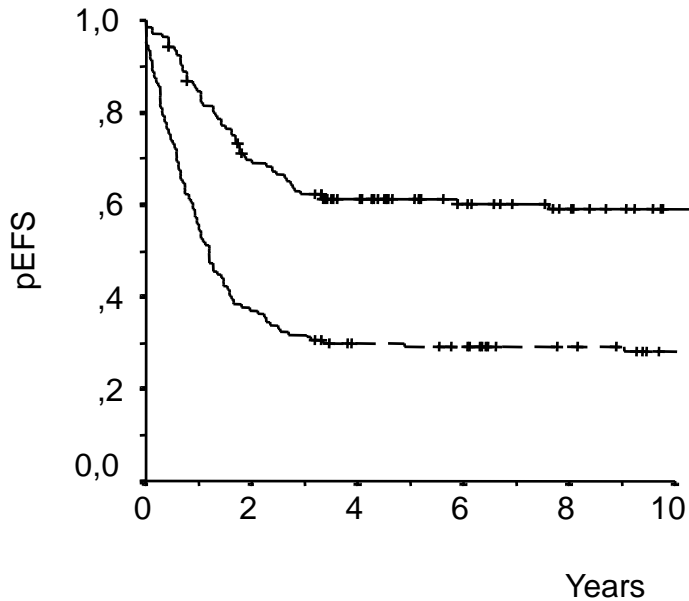
Timepoint	Age at initial diagnosis	
	< 6 years	≥ 6 years
very early	n = 56; pEFS = .36 ± .06	n = 55; pEFS = .24 ± .06
early	n = 86; pEFS = .57 ± .05	n = 43; pEFS = .27 ± .07
late	n = 34; pEFS = .64 ± .08	n = 17; pEFS = .76 ± .11

■ = High risk group; ■ = standard risk group



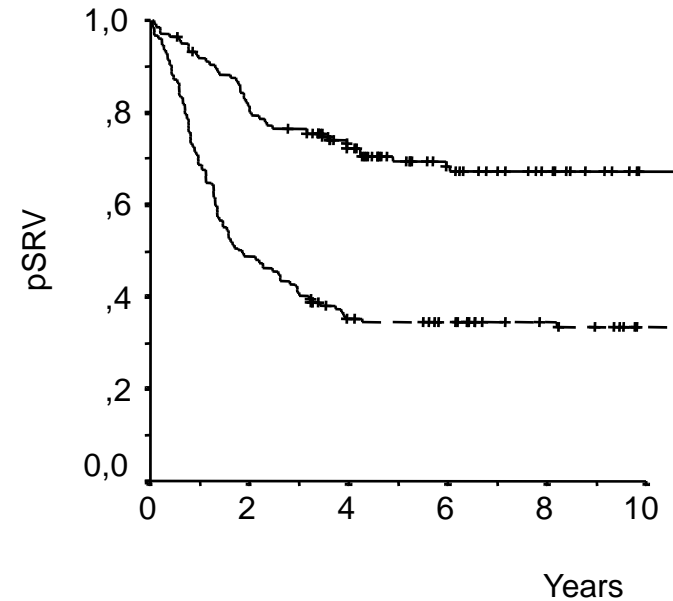
ALL groups: EFS by new CNS risk criteria

EFS by new CNS risk criteria, ALL data



----- SR: n = 137; cens. = 82; pEFS = $.61 \pm .04$
 ——— HR: n = 154; cens. = 44; pEFS = $.29 \pm .04$
 p < 0.001

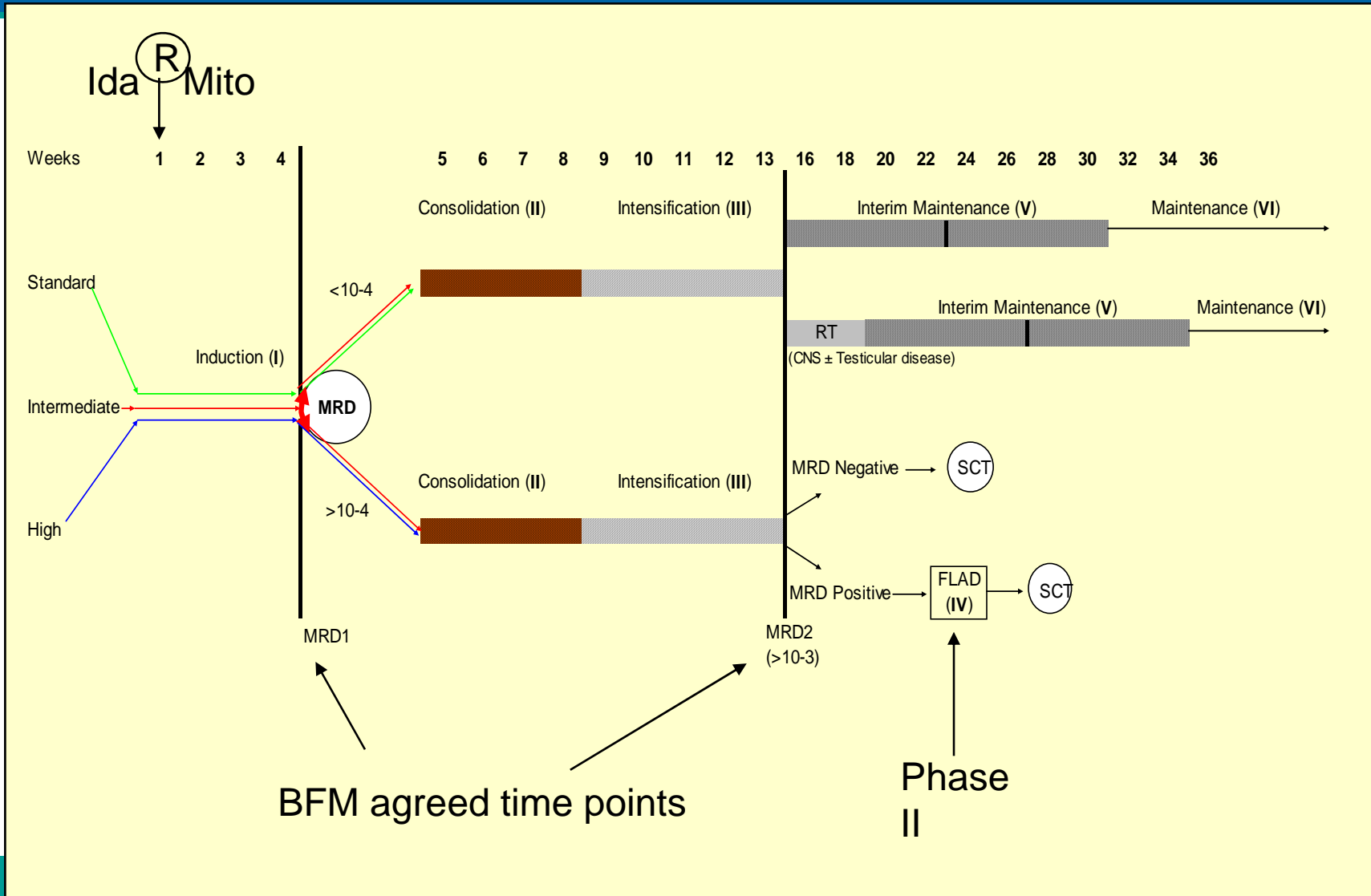
Survival by new CNS risk group, ALL data



n = 137; zens. = 95; pSRV = $.70 \pm .04$
 n = 154; zens. = 53; pSRV = $.35 \pm .04$
 p < 0.001

	Non -T			Pre - T		
	Extramed	Combined	Marrow	Extramed	Combined	Marrow
Very early Diag <18m Treat < 6m	H	H	H	H	H	H
Early Diag >18m Treat < 6m	I	I	H	I	H	H
Late Treat > 6m	S	I	I	S	H	H

Study Design



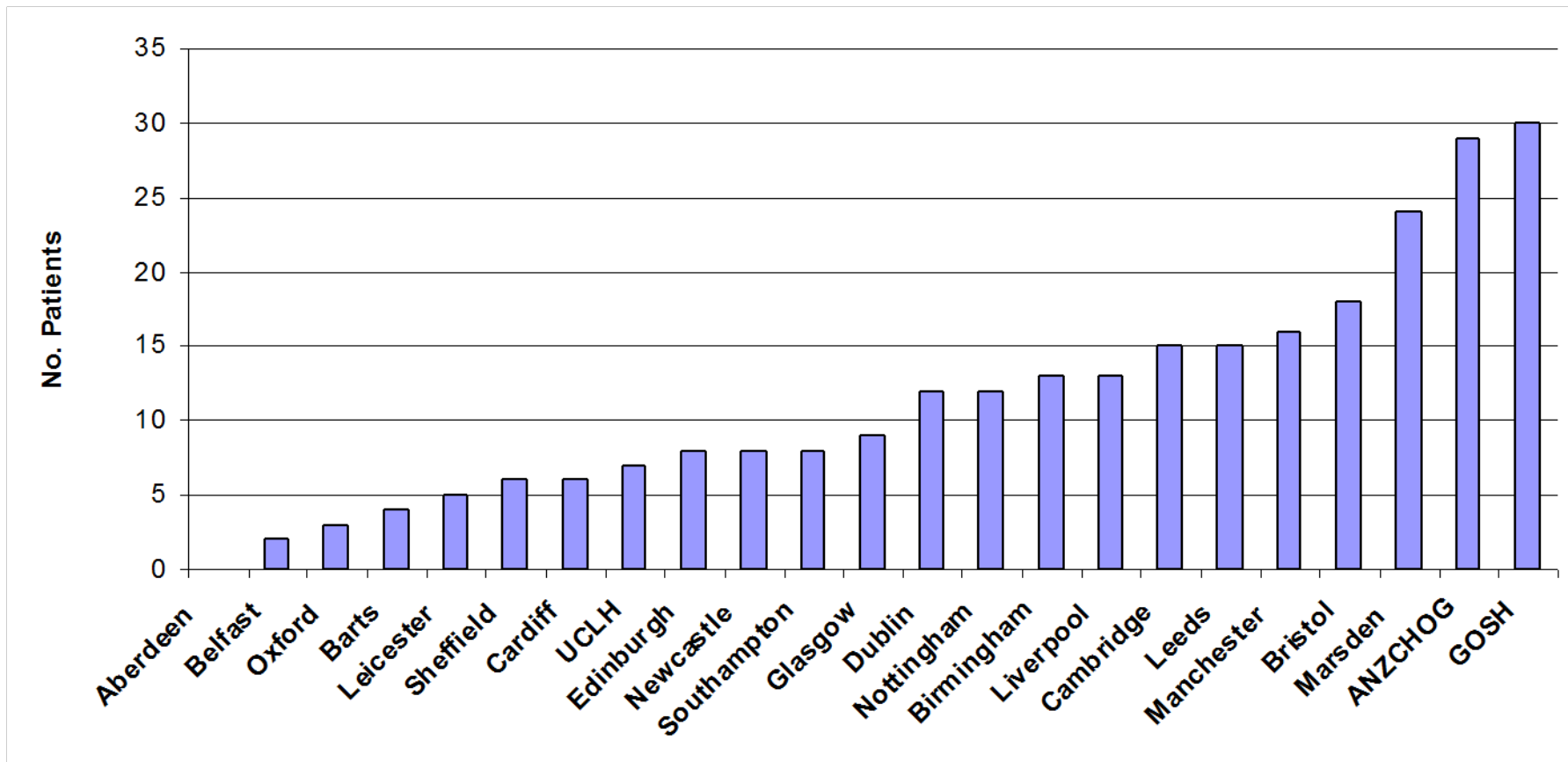


Current status of trial

- Opened to recruitment January 2003
- 21 UK & 10 ANZ centres approved to participate
- Randomisation closed 21st December 2007
- Randomised n= 212 (91%)
 - Mitoxantrone 102
 - Idarubicin 110
- Detailed transplant data collected on 51 patients to date (104 patients HR & IR MRD^{hi} at wk 5 - 13 not transplanted & 40 outstanding)



Recruitment by centre





Demographics

January 2003 - August 2008

No. Recruited:	263	
Not Eligible	4	
Risk Group:	HR	64
	IR	186
	SR	13
Relapse Site:	BM	155
	BM + CNS	30
	Other	78
Gender:	Male 158	Female 105
Mean Age:	9.88 years	



Treatment Response

- Primary Refractory 20 (8%)
- Death in CR 34 (13%)
- 2nd Relapse 46 (17%)



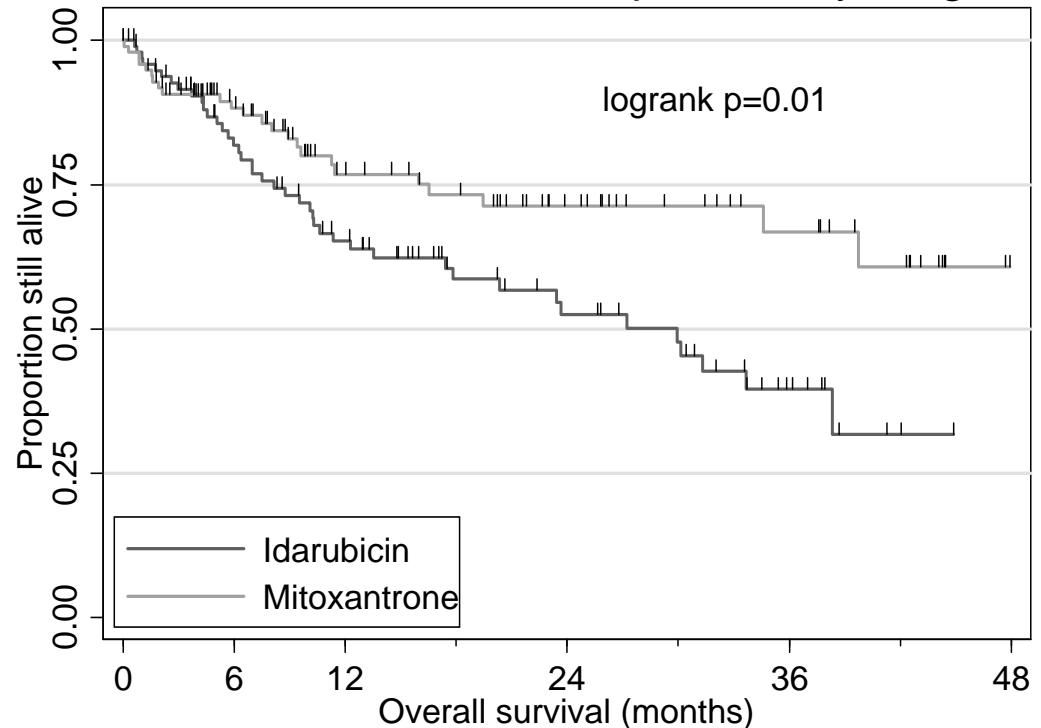
	<u>I darubicin</u>	<u>Mitoxantrone</u>
n	120	168
Randomised	109	103
Male:Female	1.7: 1	1.4:1
Mean Age (range)	9.7 (1.3-17.5)	10.3 (1.1-18)
Risk Stratification		
High	24	25
Intermediate	80	75
Standard	5	3
T cell (%)	13	11
Isolated Extramedullary (%)	33 (30)	19 (18)
Cytogenetics		
High Hyperdiploid	24%	33%
TEL-AML1	18%	15%
T-cell	16%	11%
*High Risk	14%	16%

*MLL, Ph+, Haploid, E2A

Randomisation results

- Interim analysis revealed survival benefit in Mitoxantrone arm (3yr OS 40% in Ida vs 67% in Mito)
- DMC recommended closure of randomisation and all subsequent patients to receive Mitoxantrone
- Randomisation ended 21st December 2007.

OS for all randomised patients by drug

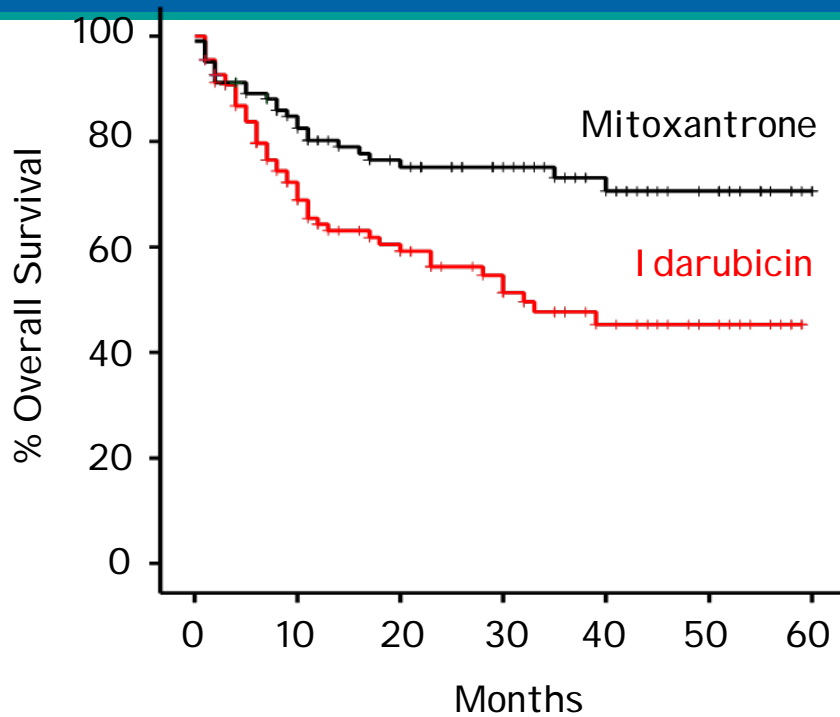


	0	6	12	18	24	30	36	42	48
Number at risk									
Idarubicin	101(18)	66 (13)	48	(8)	25	(5)	9	(1)	0
Mitoxantrone	102(11)	72 (10)	47	(3)	28	(1)	15	(1)	0

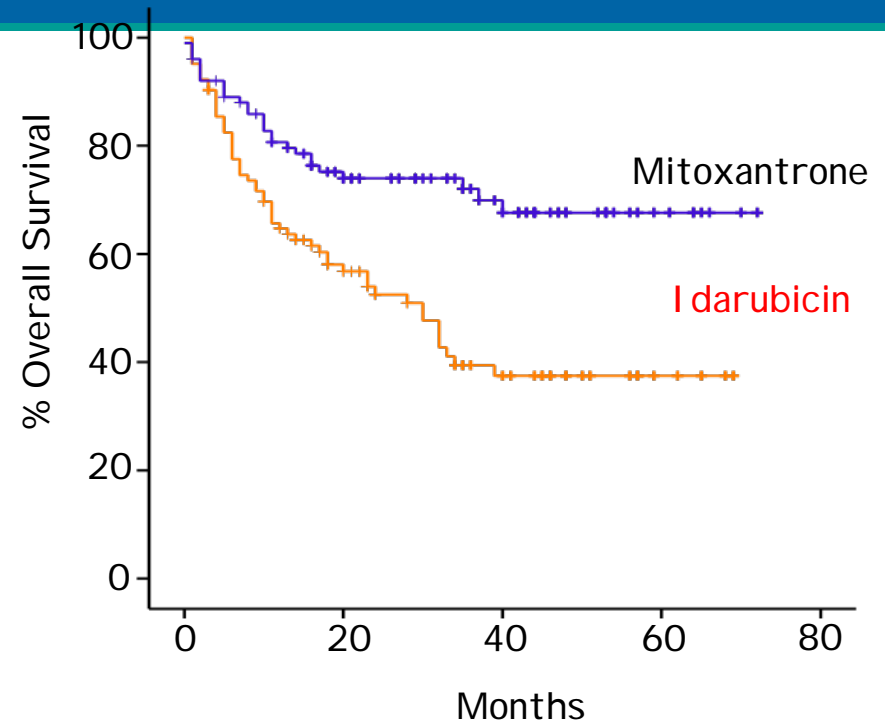
Outcome of I darubicin vs Mitoxantrone randomisation in ALL R3



2003-2007



2003-2008

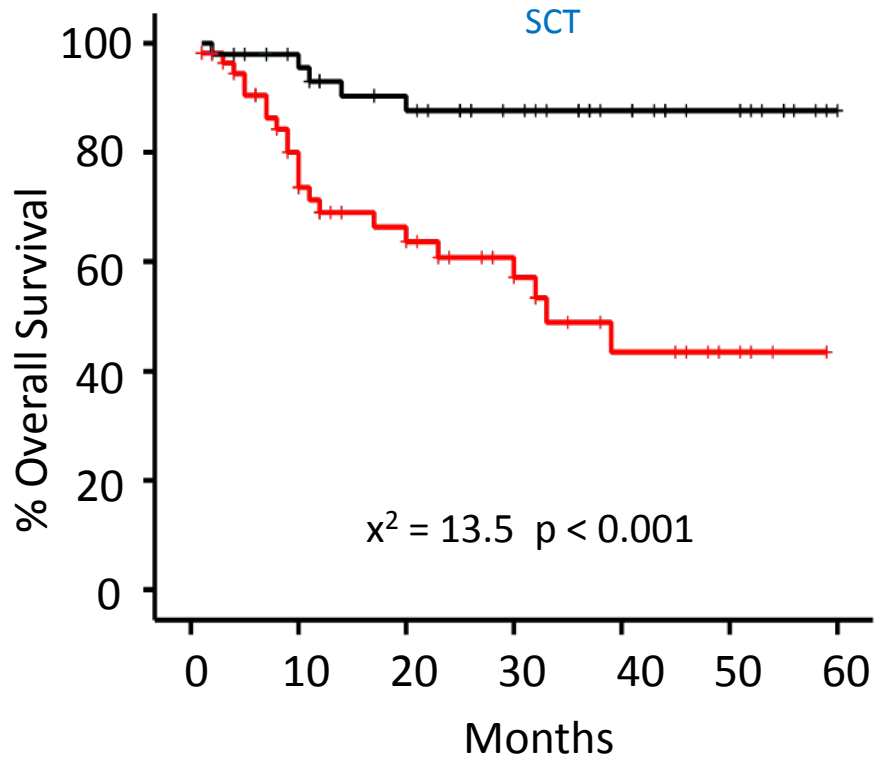
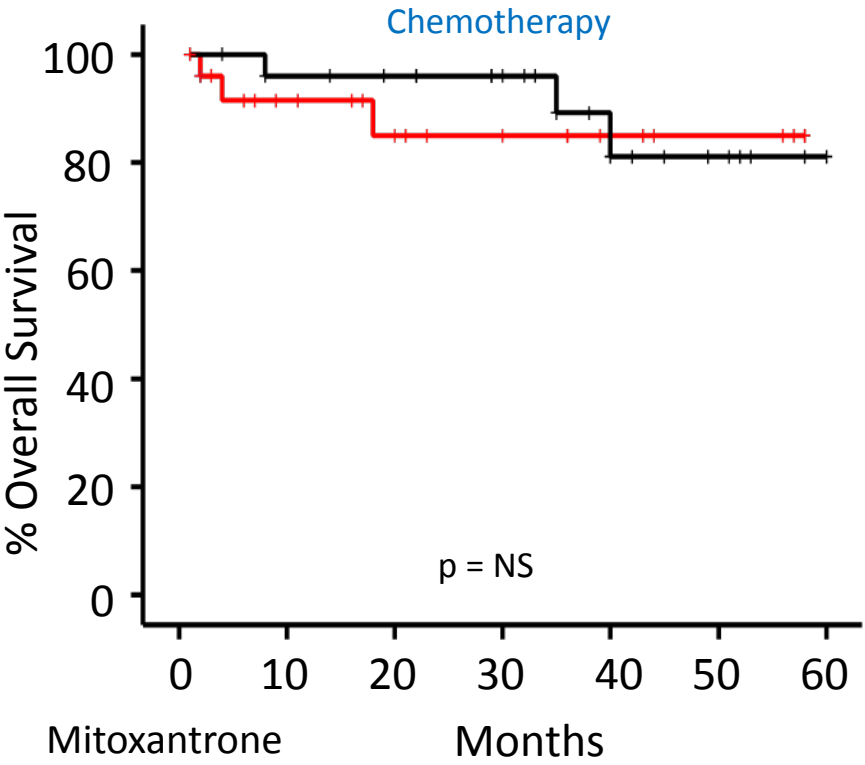


Difference in outcome between I darubicin and Mitoxantrone is widening as events continue in the I darubicin group

Outcome of Idarubicin vs Mitoxantrone randomisation in ALL R3



Intermediate and Standard Risk Patients – Intended Treatment

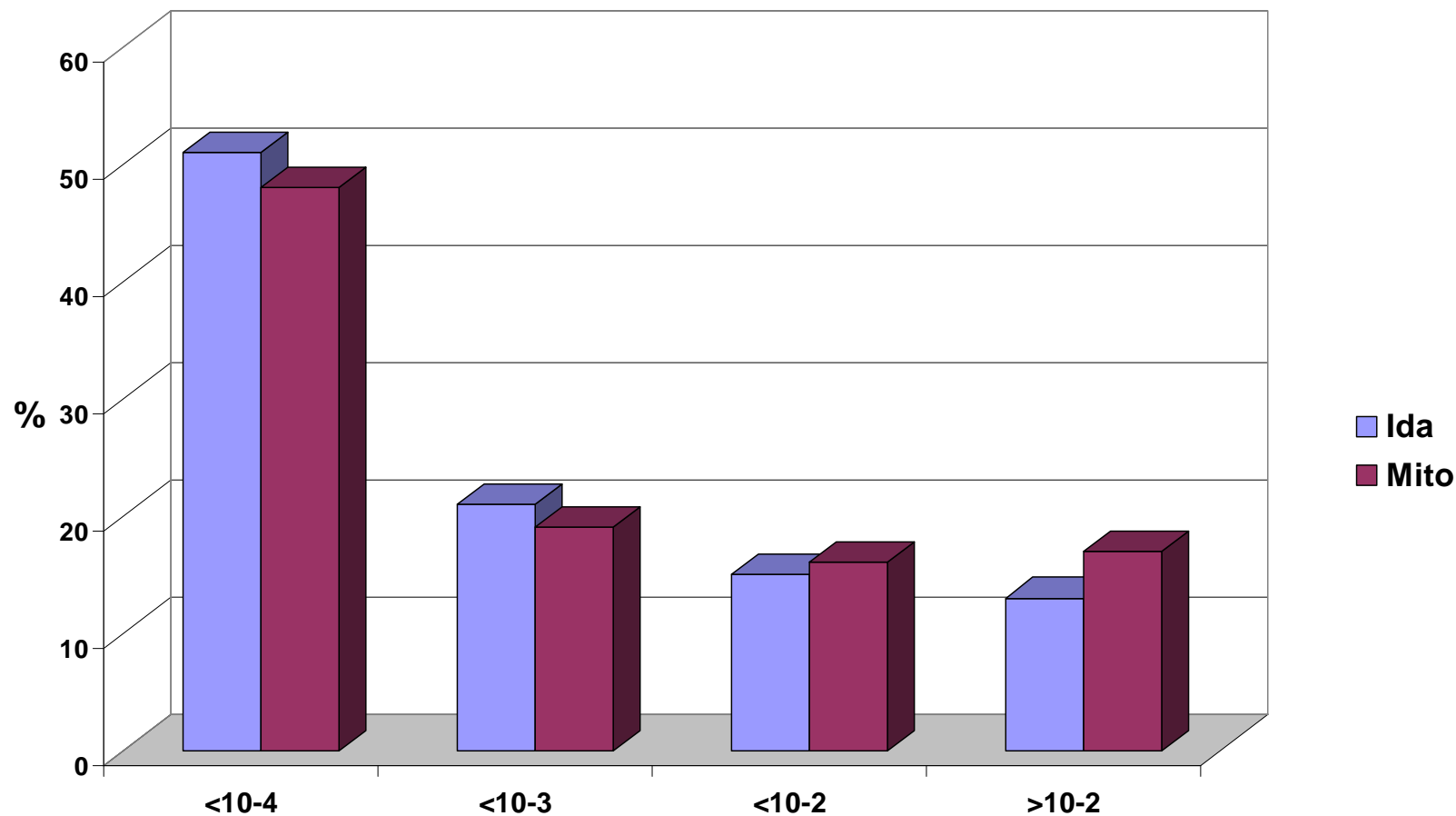


Idarubicin

In the IR/SR group, the benefit of Mitoxantrone is seen primarily in those at a higher risk and who are transplanted. The effect is related to both the numbers reaching SCT and maintaining CR2 post SCT

% patients experiencing > Grade 3 toxicities		
	Idarubicin	Mitoxantrone
Induction	36	16
Consolidation	12	7
Intensification	5	6

MRD (all evaluable) at week 5



(UK data only n = 116)

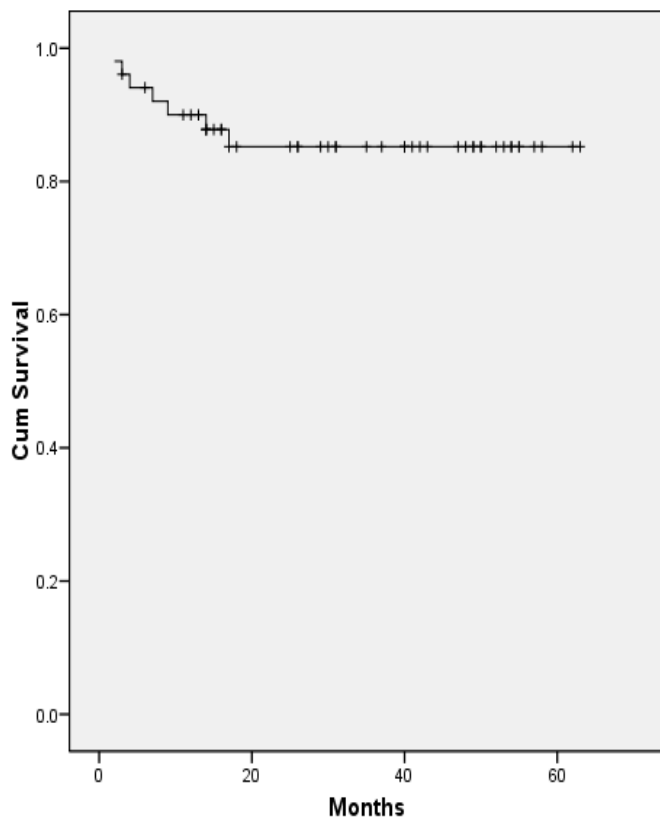


Demographics

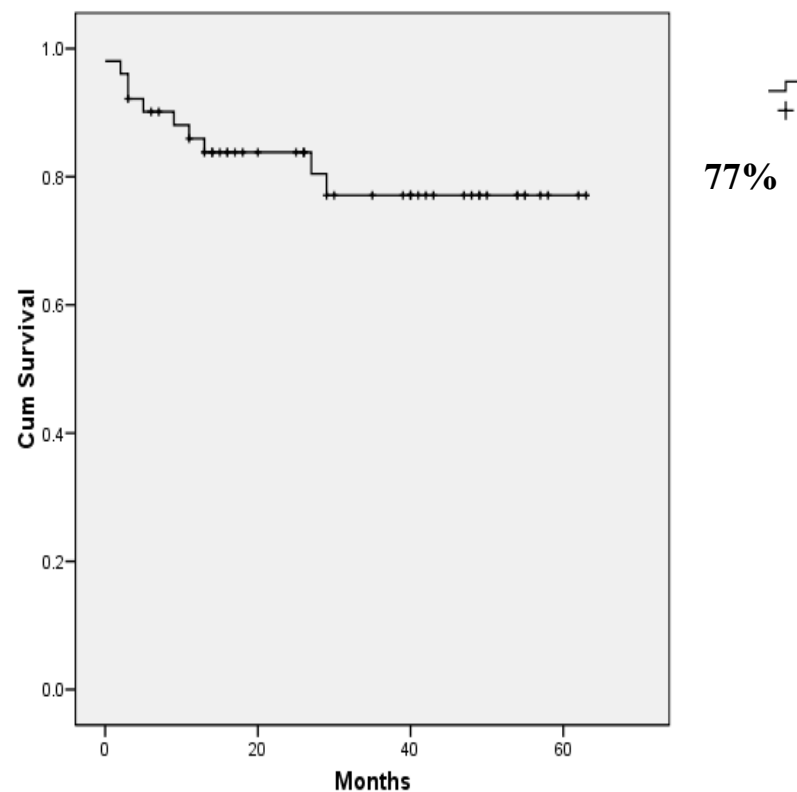
- Mean age = 9 years (range 2.8 to 17.6 years)
- Median time to transplant = 155 days (range 112 to 622)
- High risk = 9
- Intermediate risk = 42
- Idarubicin = 23
- Mitoxantrone = 28

OS & EFS - All BMT patients

OS



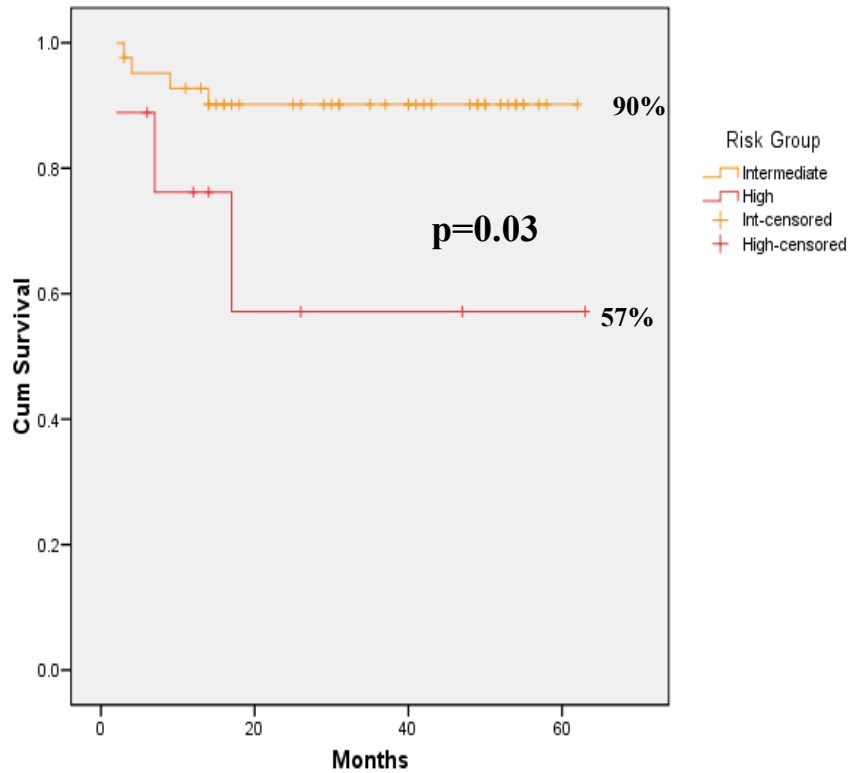
EFS



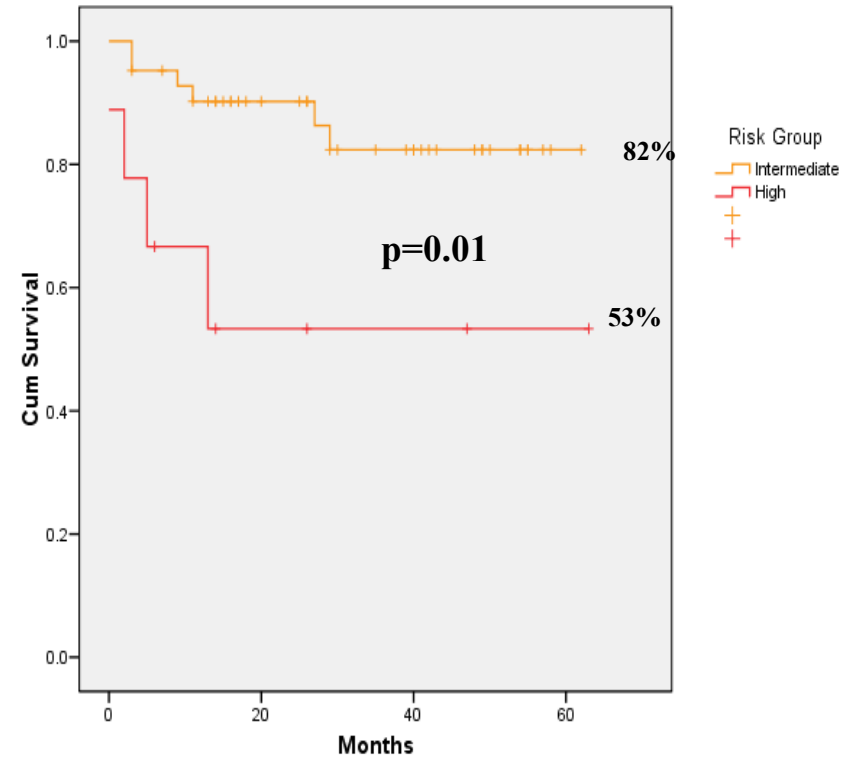
OS & EFS – from time of transplant. Censored 31/10/08

OS & EFS - Risk Status

OS

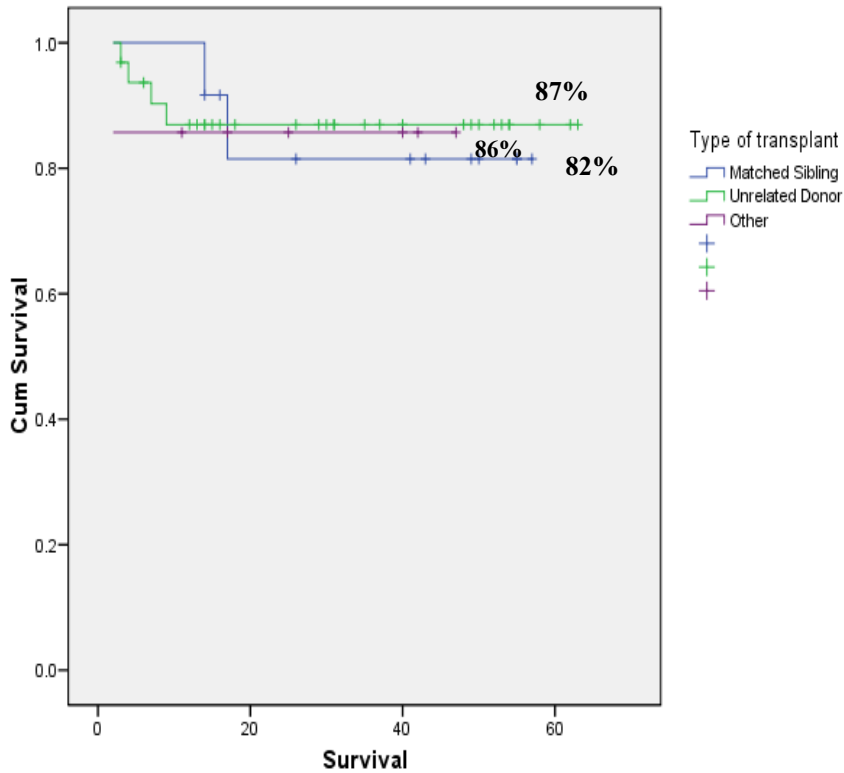


EFS

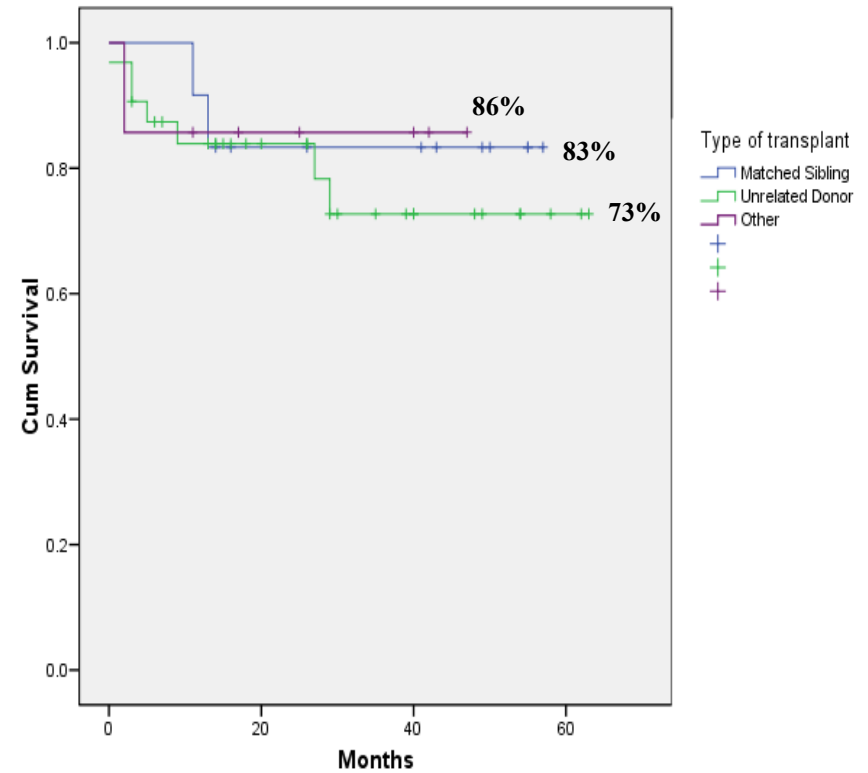


OS & EFS – Donor Type

OS



EFS

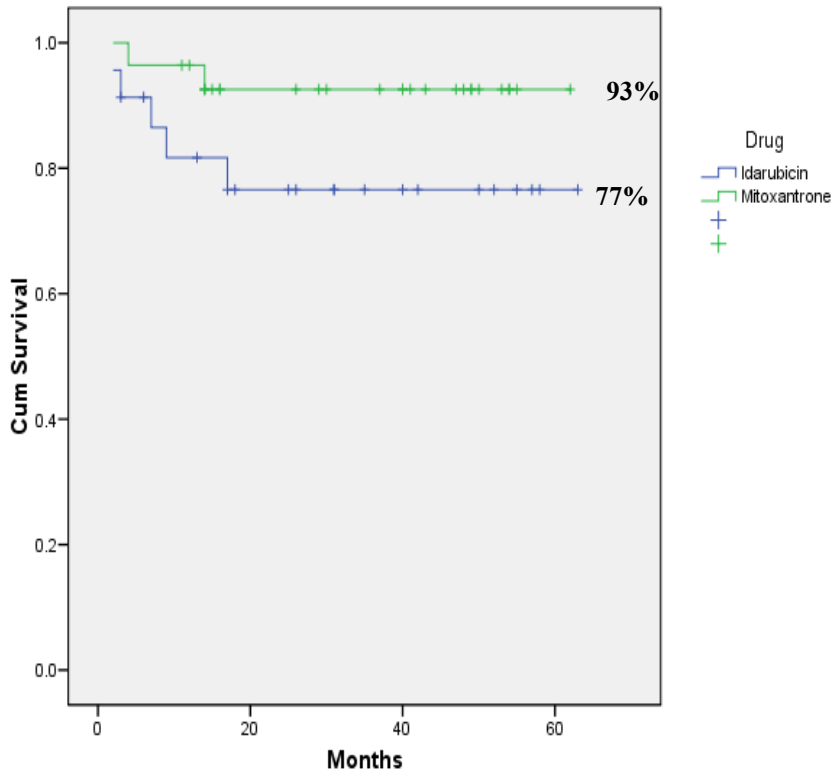


No cord donors in this cohort of patients

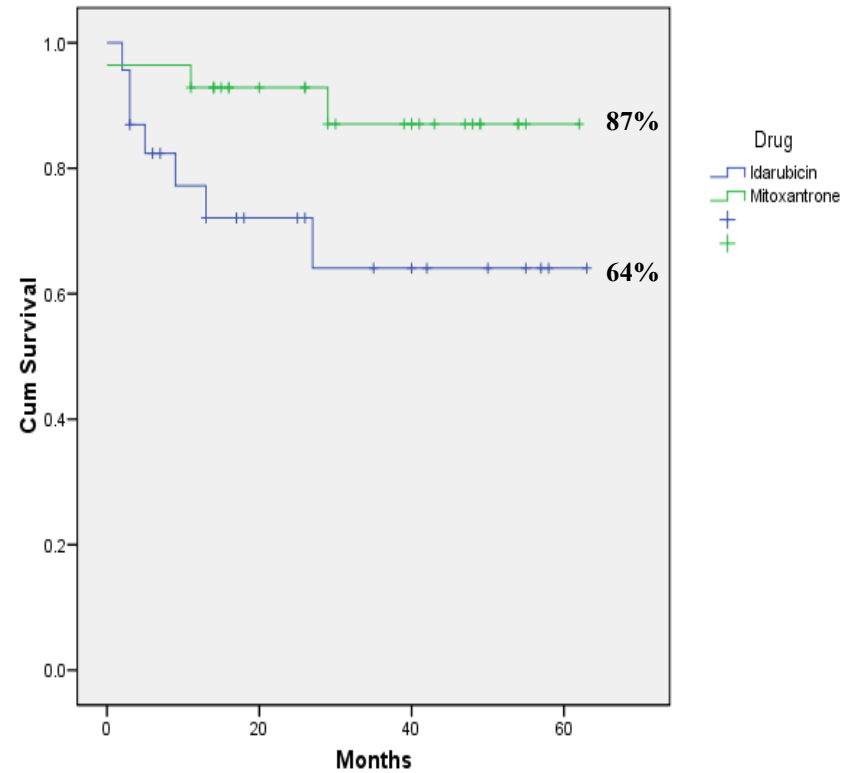


OS & PFS – Randomised Drug

OS



EFS





Relapse Rates

	No. Relapses	%
Overall	7/51	14
Randomised Group		
Idarubicin	5/23	22
Mitoxantrone	2/28	7
Risk Group		
High	4/9	44
Intermediate	3/42	7
MRD @ Week 5		
Positive	3/19	16
EM	1/11	9
Unknown	3/16	19



Transplant Related Mortality

- 3 TRM (6%)
- 2 due to infection (1 fungal) & 1 due to severe GvHD
- 1 HR patient, 2 IR
- 2/3 on Idarubicin arm
- All received unrelated PBSC
- 2/3 MRD –ve at week 13



Summary

- Low data return (56%), so initial results
- Overall relapse rate in this cohort 14% - trial overall relapse rate is around 20%
- Patients treated with Idarubicin prior to transplant have reduced OS & EFS and are more likely to relapse compared to those treated with Mitoxantrone



Summary

- Improved outcome in comparison to previous trials
- Significant improvement for those on Mitoxantrone
- No other trial is providing comparable results
 - (i) BFM OS similar in both arms ~ 46%
 - (ii) CCG reported 68% CR after induction (BFM and R3 >80%) 3-year EFS <40%
- This is in the face of continuing improvement with ALL 2003
- Key to the improvement with R3 was the use of Mitoxantrone
 - CR rates are same – so we assume equal efficacy
 - MTZ less toxic than Ida
 - Effect seen primarily in the IR group
 - Protects against marrow relapse
 - No difference in MRD between Ida and MTZ at week 5



R4 & EuReALL

- Modification for HR patients – new induction regime planned for early 2009
- form part of Pan European protocol for relapsed ALL (EuReALL).
- BFM relapse trial due to close 2010 and will then join high risk arm. EuReALL scheduled start 2011.



High Risk Modification

- CCED induction:
 - **Clofarabine**
 - Cyclophosphamide
 - Etoposide
 - Dexamethasone
- Sibling, unrelated or haploidentical donors
- PEG-asparaginase started on day 14 to avoid potential interaction with clofarabine



CCED Treatment Schedule

	Day – 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Allopurinol	◆	◆	◆	◆	◆	◆		
Clofarabine 40mg/m²/day		◆	◆	◆	◆	◆		
Etoposide 150mg/m²/day		◆	◆	◆	◆	◆		
Cyclophosphamide 300mg/m²/day		◆	◆	◆	◆	◆		
Dexamethasone 10mg/m²/day		◆	◆	◆	◆	◆	◆	◆
IT MTX*		◆						

	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
PEG-Asparaginase 1000 u/m² IM	◆						
Dexamethasone 10mg/m²/day	◆	◆	◆	◆	◆	◆	◆
IT MTX*							

Indication for CR1 „new“



NR day 33

PPR & t (9;22)

MRD day 77: $\geq 10^{-2}$

MRD day 77: $\geq 10^{-3}$

PPR & t(4;11)

Without MRD:

PPR & proB-ALL

T

M3 BM day 15

initial WBC \geq
100.000/ μ l

PGR & t (9;22)

Hopefully benefit:

PGR & t (4;11)

MSD

MD

MMD



Future studies

- European collaboration
- MRD guided therapy
- Novel high risk induction
- Possibly randomise antibody
- Align BMT protocols



High Risk

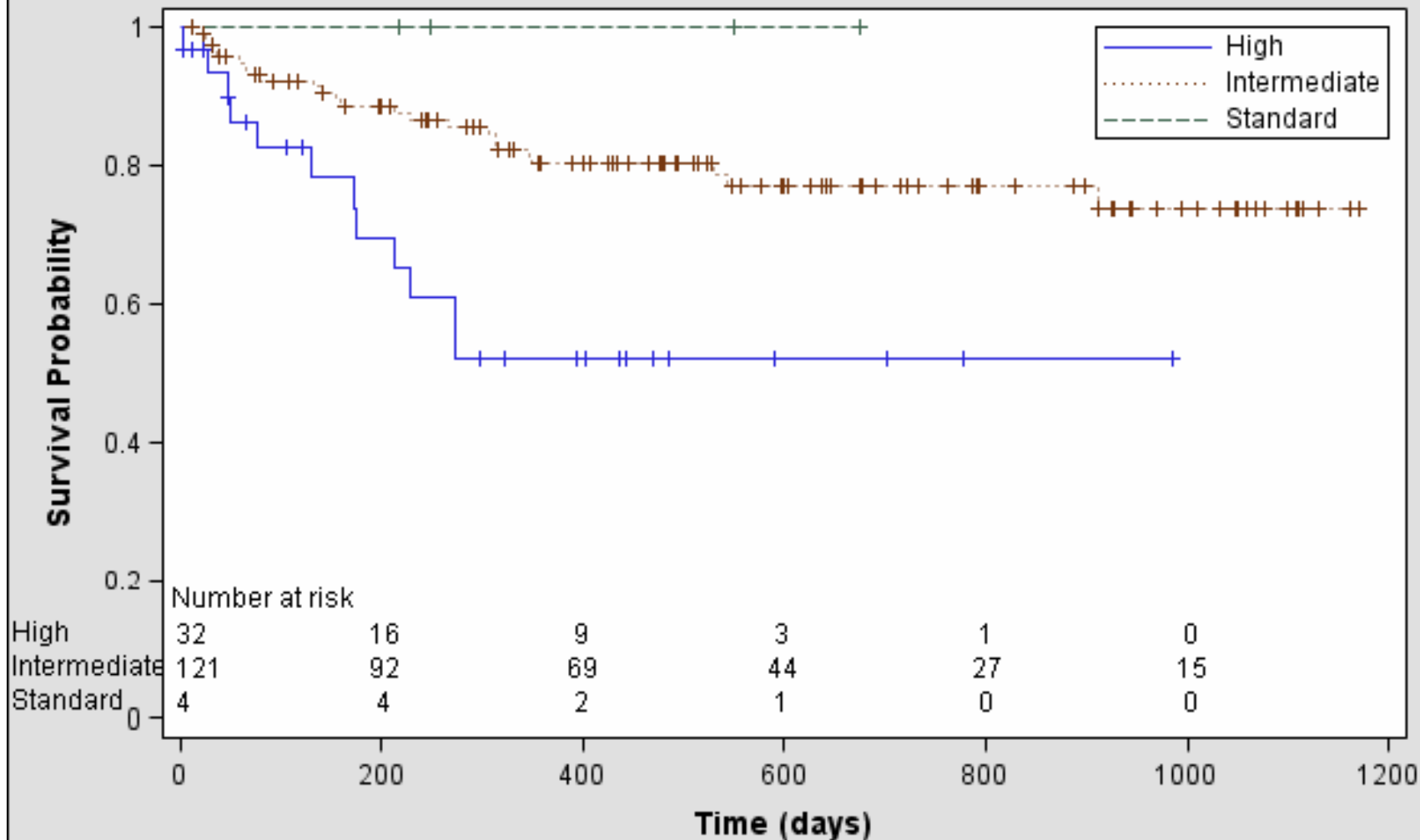
Results from R1 suggest benefit for BMT over chemo only (Harrison G. et al, Ann. Oncol. 2000 11(8) 999 – 1006.
Therefore induction/consolidation → BMT (any donor)
(v. early comb. + BM, Early BM, ALL Tcell Comb. + BM)

Standard Risk

R1 – 70% E.F.S. (Lawson et al 2000)
Therefore Chemotherapy ± local radiotherapy

(Late Extramedullary relapses)

Overall survival by risk group

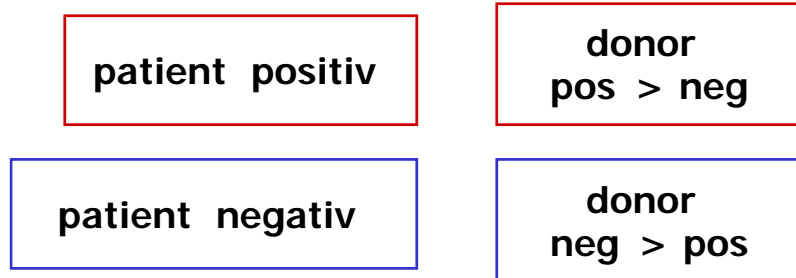


	No. of Subjects	Event	Censored	Median Survival (95% CL)
High	32	38% (12)	63% (20)	NA (213.0 NA)
Intermediate	121	20% (24)	80% (97)	NA (NA NA)
Standard	4	0% (0)	100% (4)	NA (NA NA)



- HLA -match :
10/10 > Allel -mismatch > AG -mismatch

- CMV -match :



- gender :

f

donor m or f

m

donor m > f

- age:

donor j > o

- stem cell source :

id

BM > PBSCT > CB

mm

PBSCT + CD3/19 depletion



ALLR3 BMT

Speaker

Phil Darbyshire