Who and When to Transplant in Adult ALL

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EXCELLENCE INNOVATION COMPASSION

Problems

- ALL is not one disease
- Wide differences exist between elderly, adults and children/ adolescents
- Majority of patients achieving CR relapse
- The most effective regimens are the most toxic

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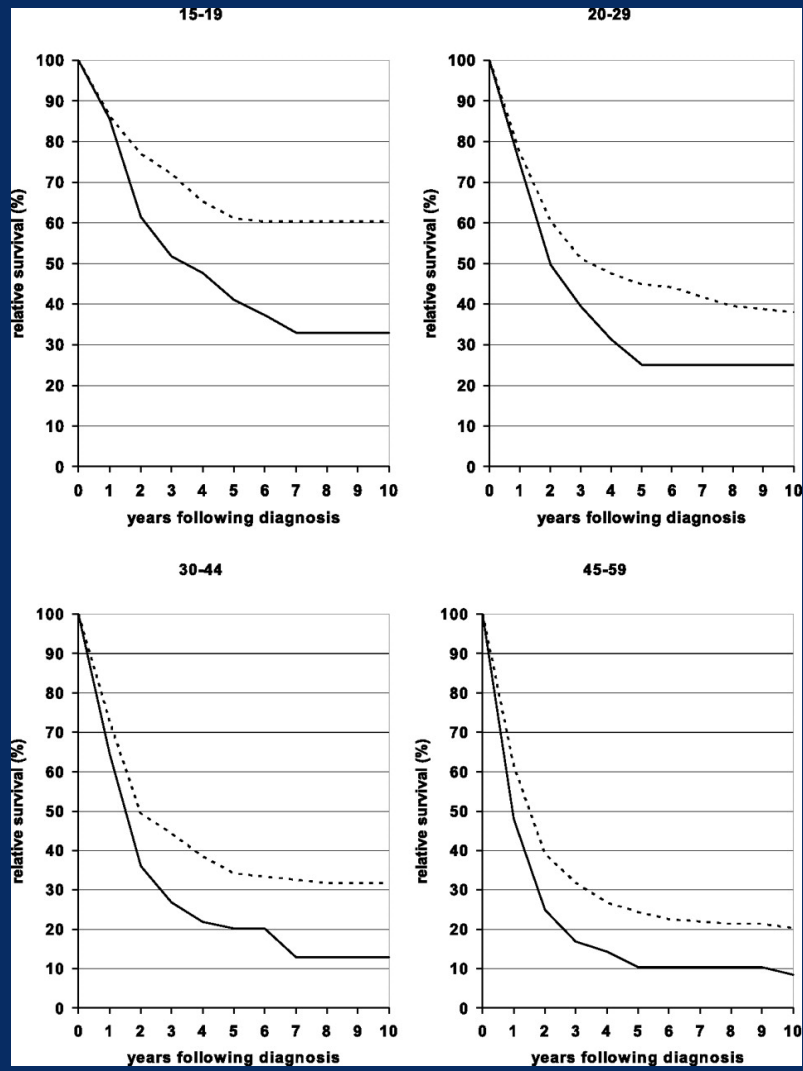
Figure 1 Ten-year relative survival curves of patients with ALL by major age groups

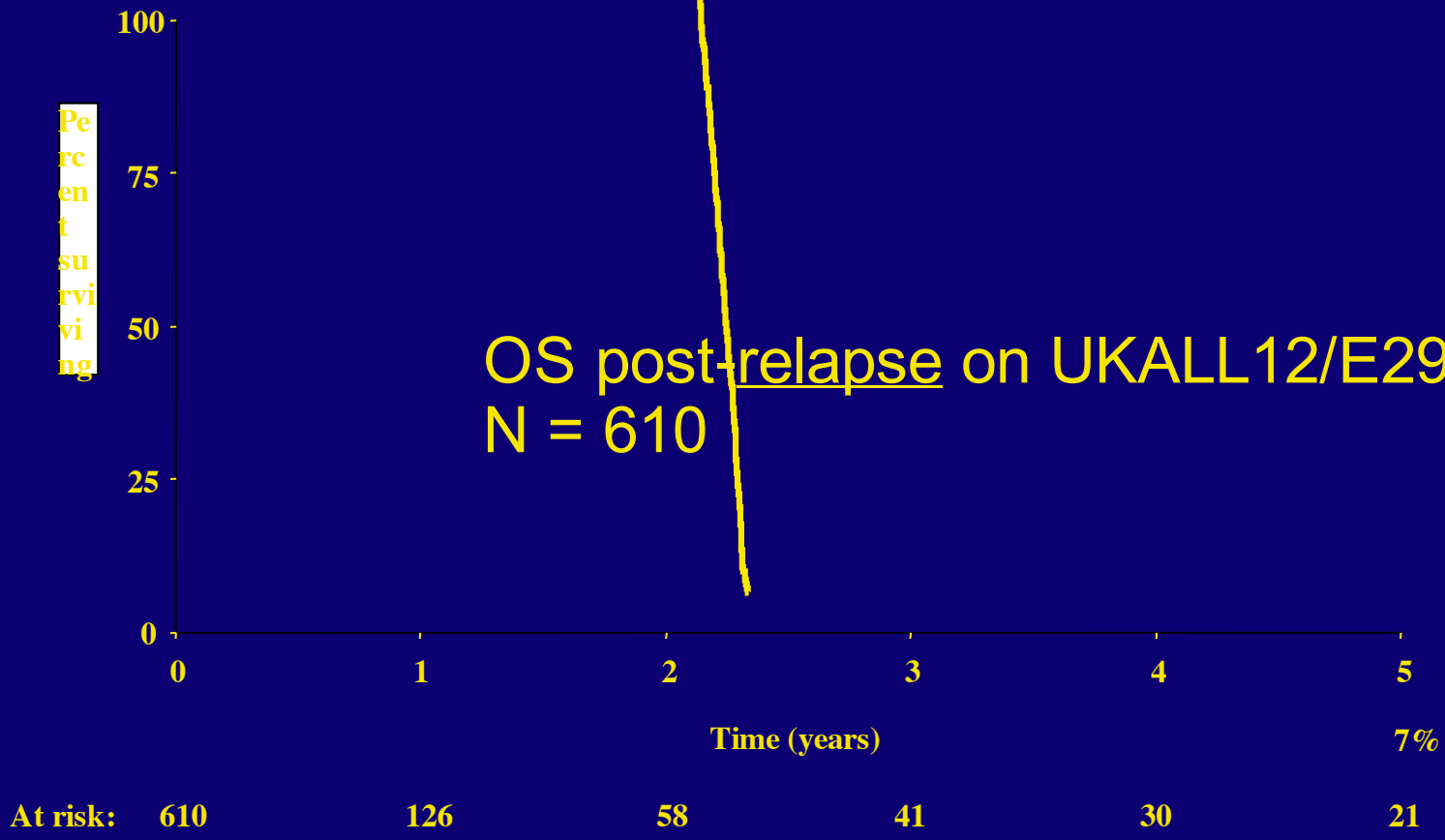


2000-04

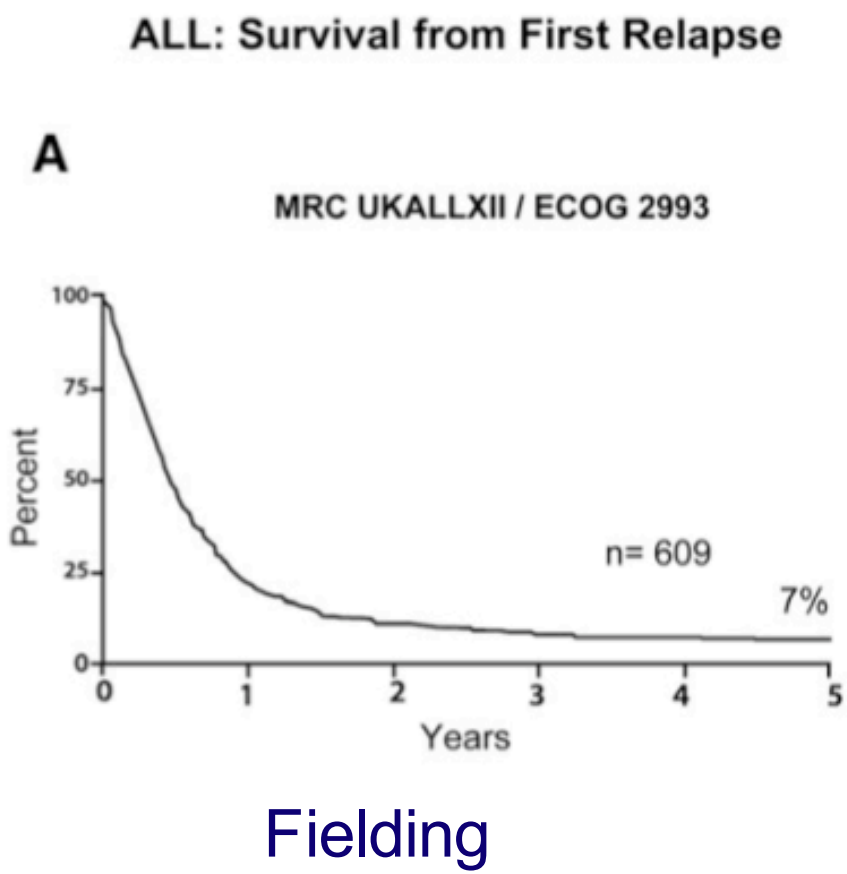
1980-84

Pulte, D. et al. Blood 2009;113:1408-1411

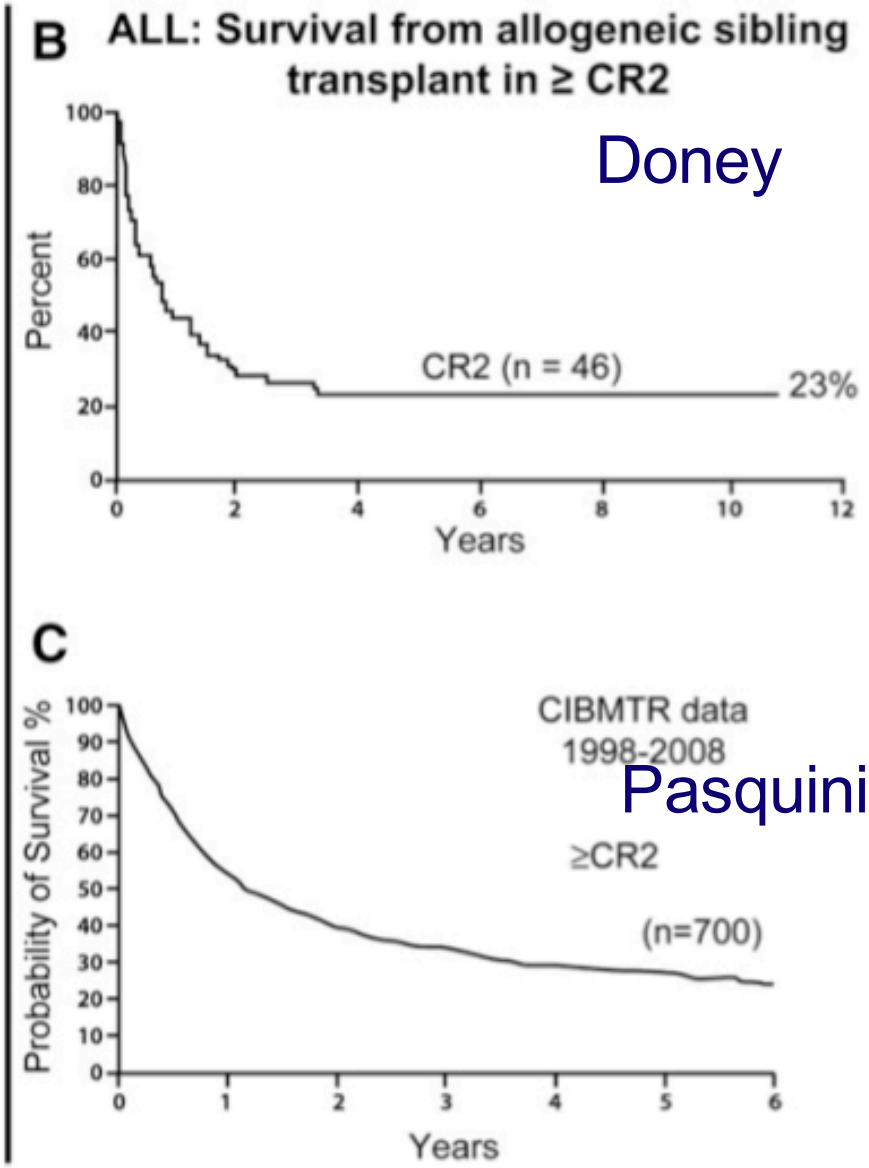
What happens to those that relapse?



Fielding et al, Blood 2007UKALL12/ECOG2993 Tavernier, Leukaemia 2007 LALA94


ALL: Survival from First Relapse
A
MRC UKALLXII / ECOG 2993
Percent
100
75
50
25
0
n= 609
7%
0
1
2
3
4
5
Years

Fielding


B
ALL: Survival from allogeneic sibling transplant in ≥ CR2
Doney
Percent
100
80
60
40
20
0
CR2 (n = 46)
23%
0
2
4
6
8
10
12
Years
C
CIBMTR data
1998-2008
Pasquini
≥CR2
(n=700)
Probability of Survival %
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Years

What should our best expectations be in newly diagnosed ALL?

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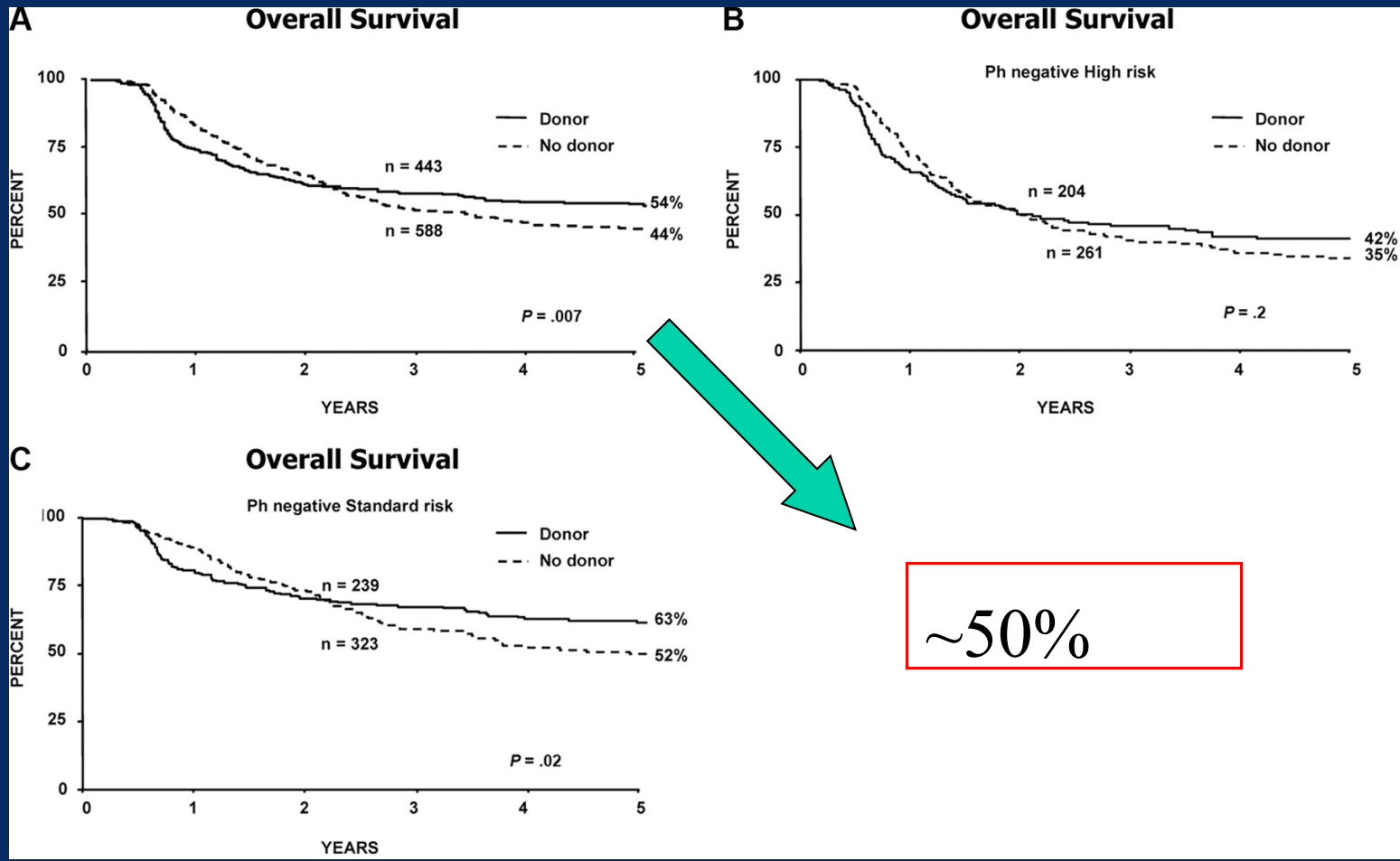
Overall survival from diagnosis for donor versus no-donor for Ph-negative patients



~50%

Goldstone, A. H. et al. Blood 2008;111:1827-1833

LALA 94 – High risk ALL

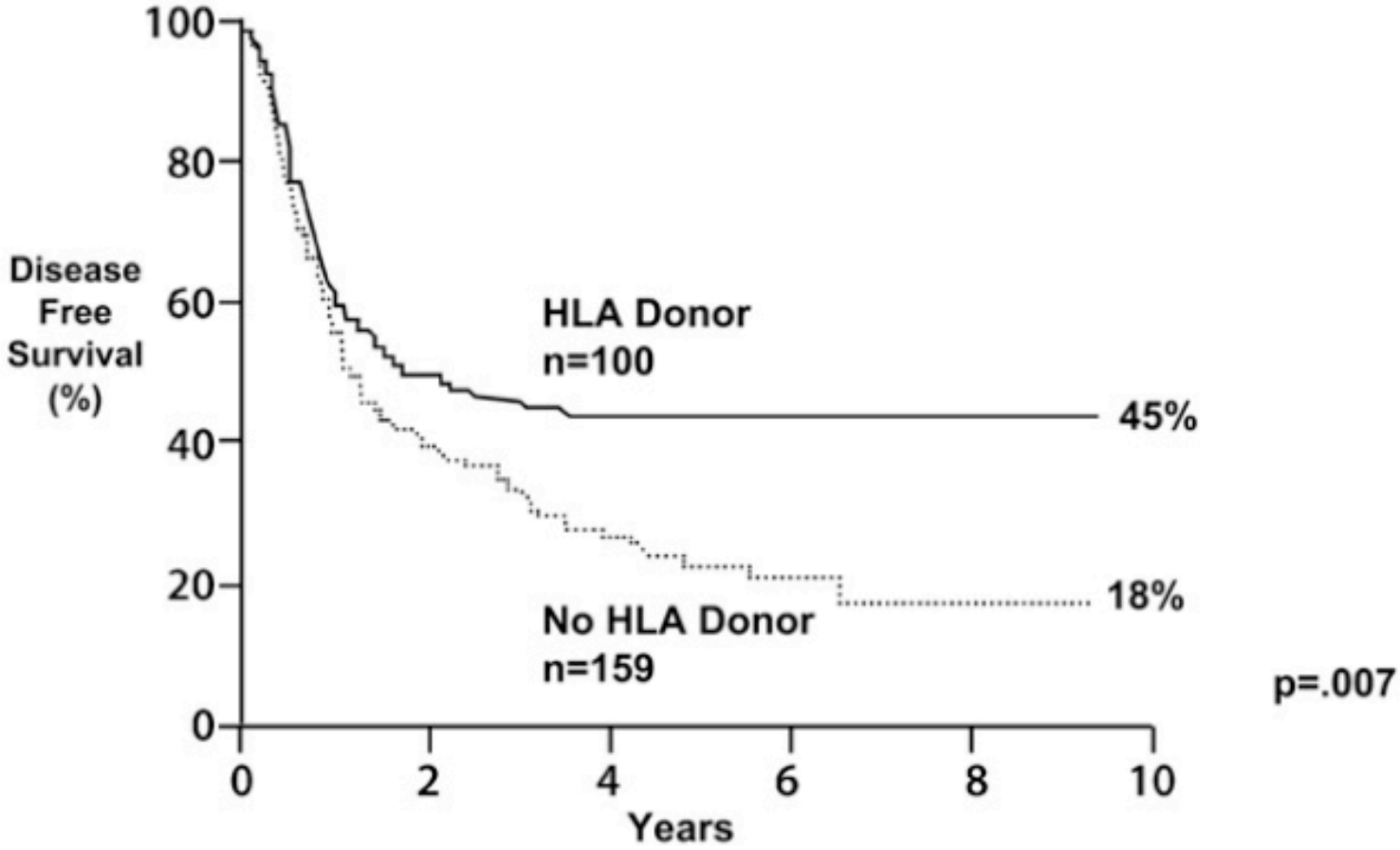
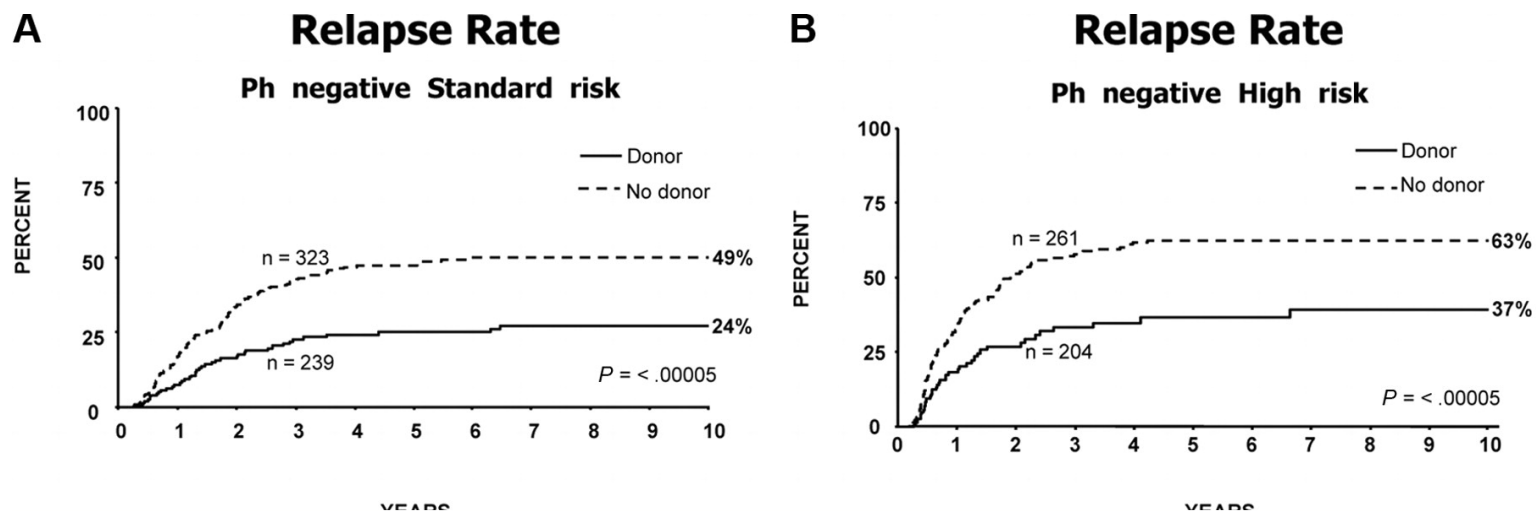


Figure 3. Donor versus no-donor analysis for high-risk patients in the LALA 94 study.Reproduced with permission from Thomas et al. [12].

Goldstone et al, Blood 2008 (UKALLXII/ECOG2993)



There was still a donor-attributable reduction in relapse risk for both groups but this did not translate into survival benefit due to increased TRM

Primary Question

- Is Not “CR1 vs beyond CR1”
  but should be
- “CR1 vs no *planned* transplant”

Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 10

http://www.thecochranelibrary.com

Adult
CR1

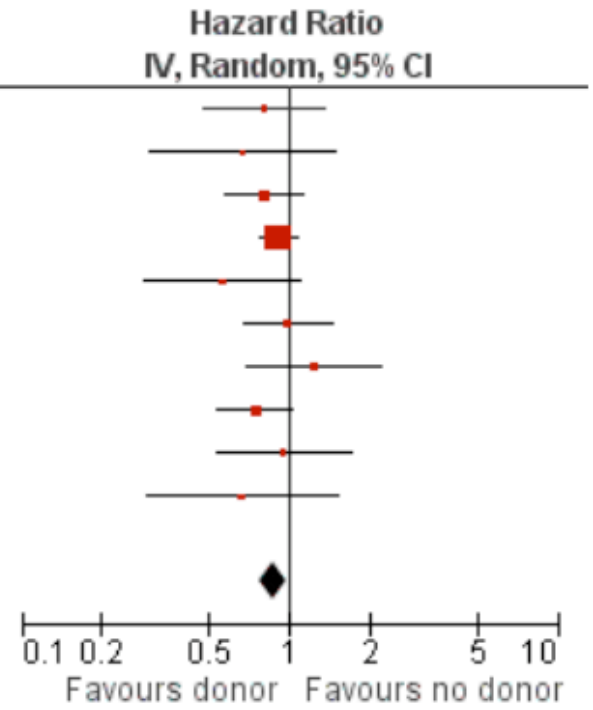
Mainly
TBI
MSD

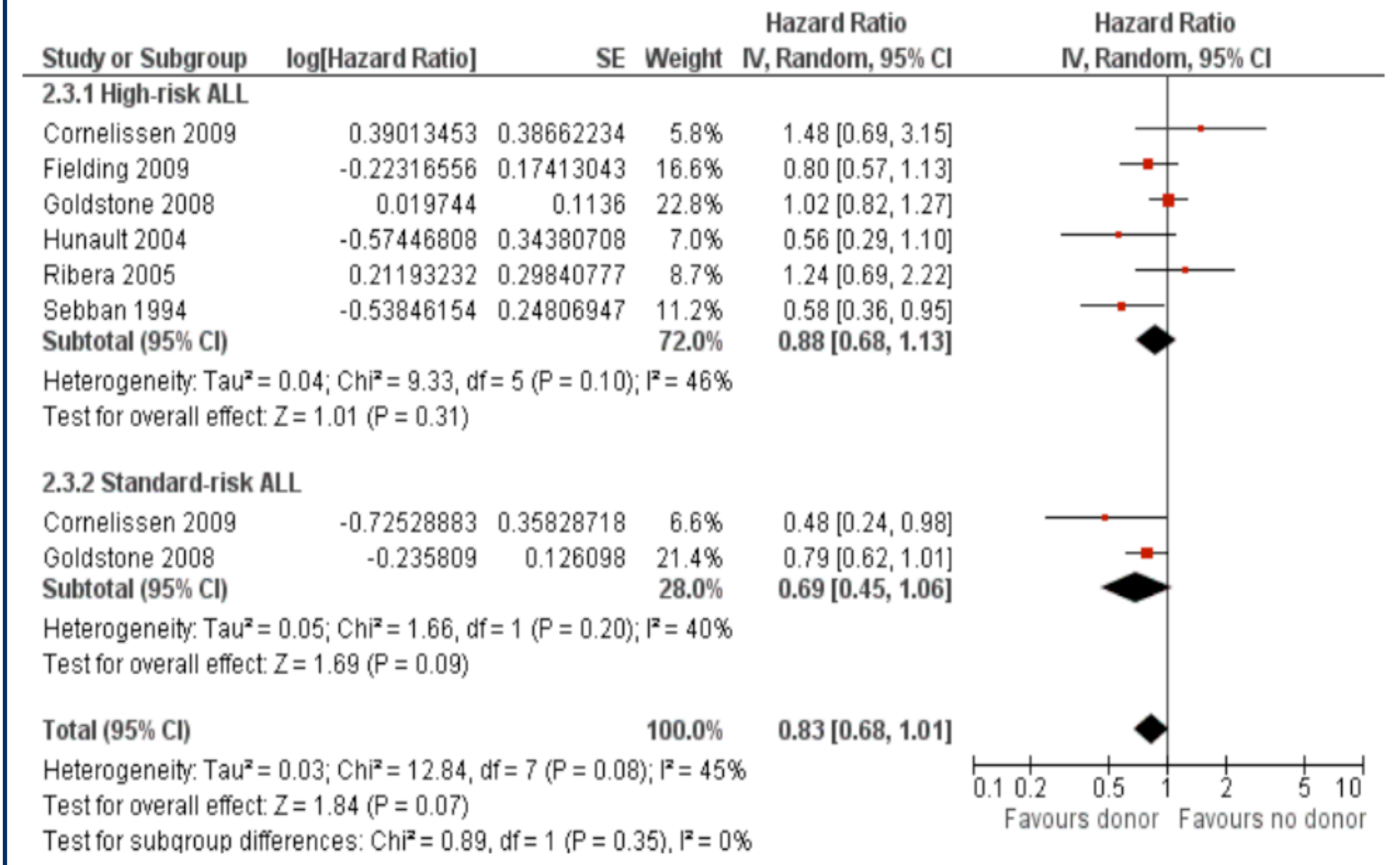
Figure 2. Forest plot of comparison: 1 Donor versus no donor, outcome: 1.1 Overall survival (overall sample).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Cornelissen 2009	-0.21453287	0.26306682	5.0%	0.81 [0.48, 1.35]
De Witte 1994	-0.40677966	0.41169348	2.1%	0.67 [0.30, 1.49]
Fielding 2009	-0.22316556	0.17413043	11.5%	0.80 [0.57, 1.13]
Goldstone 2008	-0.094302	0.086306	46.7%	0.91 [0.77, 1.08]
Hunault 2004	-0.57446808	0.34380708	2.9%	0.56 [0.29, 1.10]
Labar 2004	-0.02020202	0.19341962	9.3%	0.98 [0.67, 1.43]
Ribera 2005	0.21193232	0.29840777	3.9%	1.24 [0.69, 2.22]
Sebban 1994	-0.28986301	0.16552118	12.7%	0.75 [0.54, 1.04]
Takeuchi 2002	-0.05008944	0.2990743	3.9%	0.95 [0.53, 1.71]
Ueda 1998	-0.41186736	0.41775599	2.0%	0.66 [0.29, 1.50]
Total (95% CI)			**100.0%**	**0.86 [0.77, 0.97]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.70$, df = 9 (P = 0.77); $I^2 = 0\%$

Test for overall effect: Z = 2.48 (P = 0.01)



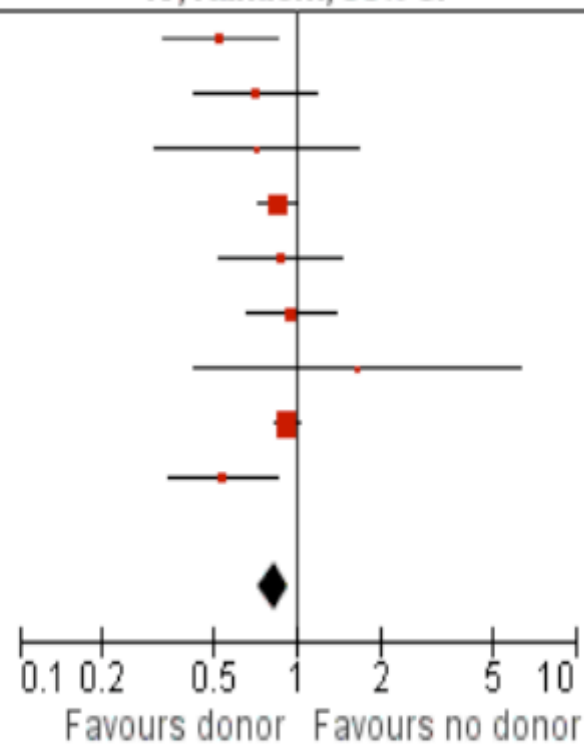


DFS

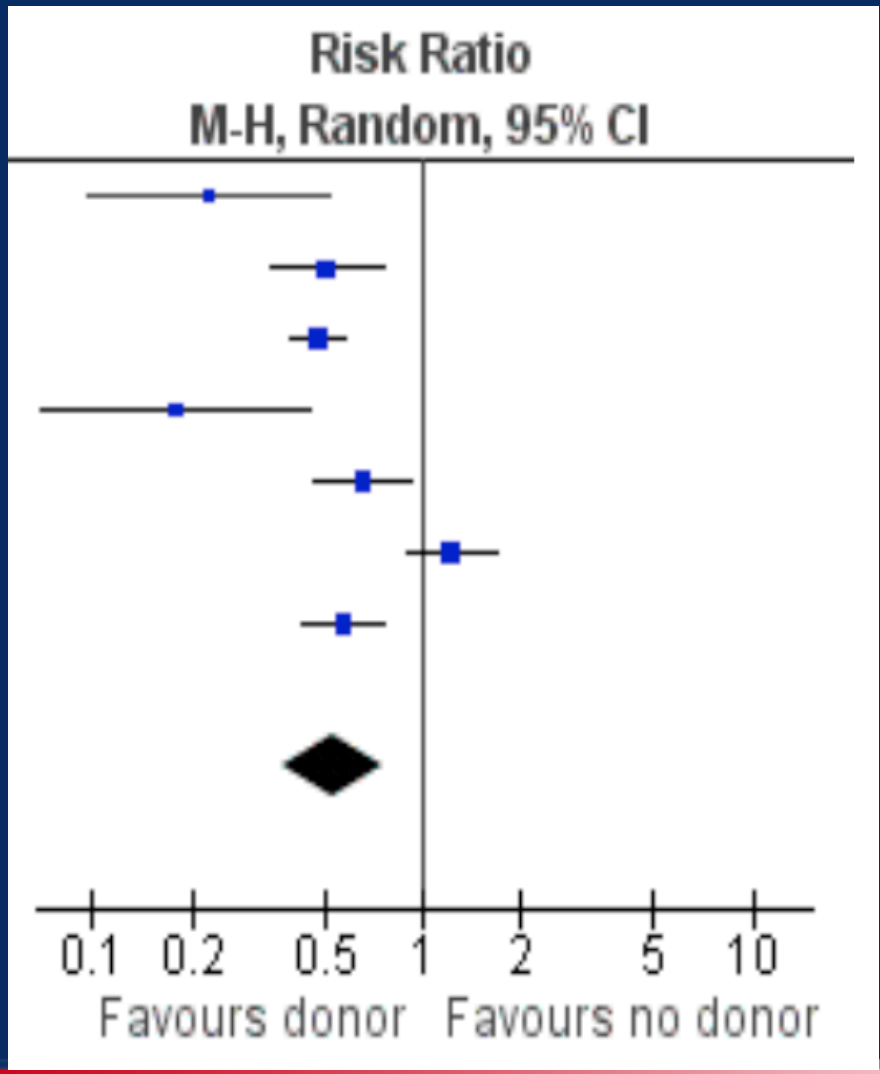
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Attal 1995	-0.64281	0.244193	6.4%	0.53 [0.33, 0.85]
Cornelissen 2009	-0.35037	0.25932508	5.7%	0.70 [0.42, 1.17]
De Witte 1994	-0.32649	0.431934	2.3%	0.72 [0.31, 1.68]
Goldstone 2008	-0.154567	0.081239	26.9%	0.86 [0.73, 1.00]
Ifrah 1999	-0.13528	0.257513	5.8%	0.87 [0.53, 1.45]
Labar 2004	-0.05135	0.188177	9.8%	0.95 [0.66, 1.37]
Ribera 2005	0.5	0.690066	0.9%	1.65 [0.43, 6.38]
Sebban 1994	-0.087	0.052899	35.0%	0.92 [0.83, 1.02]
Thomas 2004	-0.61785	0.229114	7.1%	0.54 [0.34, 0.84]
Total (95% CI)			**100.0%**	**0.82 [0.72, 0.94]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.55$, $df = 8$ ($P = 0.17$); $I^2 = 31\%$

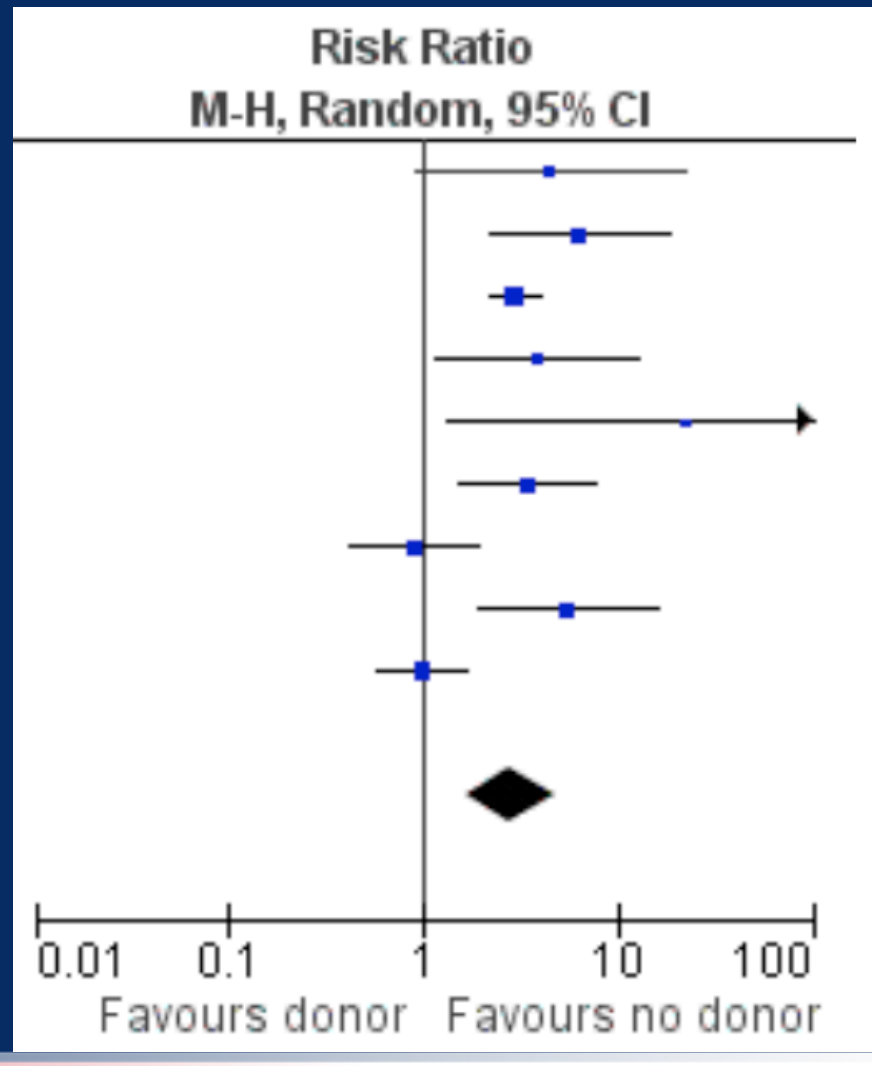
Test for overall effect: $Z = 2.90$ ($P = 0.004$)



Relapse


Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours donor
Favours no donor

NRM


Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours donor
Favours no donor

MRC UKALL XII / ECOG 2993
Non-Relapse Mortality (%)

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9

Who should (or shouldn't) get a transplant in CR1?…

Risk Stratification

Factor	High risk	Std Risk
Age	>55	<25
WCC	B> 30 T > 100	other
Cytogenetics	Near-Hyperdip +21; t(1:19); Ph+, (4:11), -7	Diploid Hyperdiploid
Immuno-phenotype	CD10 neg CD1a neg ?CD20 Cytoplasmic u chain	CD10 pos
Molecular	Hox11L2; ERG	TLX1 + low ERG/BAALC FBXW73-17 Notch-1

Outcome by risk stratification

Variation between study groups
Age >35
WCC >30/100
Cytogenetics
CR delayed >4w

0-1 ~25-35%
3-4 ~10%

Unclear if MRD replaces or adds to current risk stratification?

Study	Year	Patient No.	Definition of Risk Group*	OS/DFS by Risk Group
PETHEMA[9]	2005	222	SR: 0; HR: ≥ 1	5-year DFS: 35% in HR SR, not reported
MRC-ECOG[10]	2008	1,913	SR: 0; HR: ≥ 1	5-year OS by donor *v* no donor analysis in Ph-negative: 62% *v* 52% in SR ($P = .02$), 41% *v* 35% in HR ($P = .2$)
GRAALL[13]	2008	225	SR: 0; HR: ≥ 1	3.5-year DFS: 68% in SR *v* 52% in HR ($P = .05$)
HOVON[14]	2009	433	SR: 0; HR: ≥ 1	5-year OS: 50% in SR *v* 30% in HR ($P < .001$)
GMALL[15,16]	2006, 2007	713	SR: 0, MRD-HR: ≥ 1, MRD+ VHR: Ph+	5-year survival of CR patients: 59% in SR *v* 55% in HR *v* 49% in VHR; 3-year DFS in SR by MRD: 100% in MRD- *v* 53% in MRD± *v* 6% in MRD+ ($P < .001$)
NILG[17]	2009	280	SR: MRD-HR: MRD+VHR: Ph+, t(4;11)+	5-year OS: 49% in SR *v* 27% in HR *v* 24% in VHR ($P = .0005$); 5-year DFS by MRD: 72% in MRD- *v* 14% in MRD+ ($P = .001$)

MRD

Primary determinant of outcome= sensitivity to chemo

CR with first induction
Rapid blood or marrow clearance
Prednisolone sensitivity
Well accepted treatment determinant in paediatric ALL.
van Dongen; Lancet 1998
Two post-induction MRD time points
MRD- negative low-risk (43% of all patients) 5y 2% relapse MRD
high-risk group with MRD levels >103 at both time points (15% of patients) 84% relapse rate
MRD intermediate-risk group (patients) 24% relapse rate years.

Leukemia **24**, 521-535 (March 2010) | doi:10.1038/leu.2009.268

Standardized MRD quantification in European ALL trials: Proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18–20 September 2008

M Brüggemann, A Schrauder, T Raff, H Pfeifer, M Dworzak, O G Ottmann, V Asnafi, A Baruchel, R Bassan, Y Benoit, A Biondi, H Cavé, H Dombret, A K Fielding, R Foà, N Gökbuget, A H Goldstone, N Goulden, G Henze, D Hoelzer, G E Janka-Schaub, E A Macintyre, R Pieters, A Rambaldi, J-M Ribera, K Schmiegelow, O Spinelli, J Stary, A von Stackelberg, M Kneba, M Schrappe and J J M van Dongen

Table 1. Characteristics of the Techniques Currently Employed for MRD Detection in ALL

Characteristic	PCR Analysis of Ig and TCR Gene Rearrangements	PCR Analysis of BCR-ABL Transcripts	Multiparameter Flow Cytometry
Sensitivity	RQ-PCR: 10^{-4}–10^{-5}	10^{-4}–10^{-6}	3- to 4-color: 10^{-3}–10^{-4} 6- to 9-color: 10^{-4}–10^{-5} Depends also on cell input
Quantitative range	RQ-PCR: 10^{-2}–10^{-4}	Not yet defined	Not yet defined
Applicability	Precursor-B-ALL: 90%–95% T-ALL: 90–95%	Ph^+-ALL (5%–8% of children with precursor-B-ALL, 30%–35% of adults with precursor-B-ALL)	Precursor-B-ALL: 80%–95% T-ALL: 90%–95% Depends also on number of colors
Advantages	• High sensitivity • High degree of standardization reached • Well-established stratification tool in various clinical protocols • Most published data for evidence based treatment decisions • Applicable for almost all ALL patients • Stability of DNA (multicenter setting)	• High sensitivity • Stability of target during course of treatment • Fast • Relatively cheap	• Applicable for almost all ALL patients • Rapid • Quantitative • Additional information on benign cells • Additional information on malignant cells • Growing standardization throughout Europe

Risk stratification
MRC UKALL14

- Presenting WBC >30 x109/l B-cell (>100 x109/l T-cell) (Rowe et al, Blood 2005)
- Age >40 (Rowe et al, Blood 2005)

Age >40 is a risk for treatment failure and high TRM w myeloablative alloHSCT

- High-risk cytogenetic abnormalities (Moorman et al 2007)
- Standard-risk but MRD positive at end phase 2

(Patel et al, BJH 2010)

bjh research paper

Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993

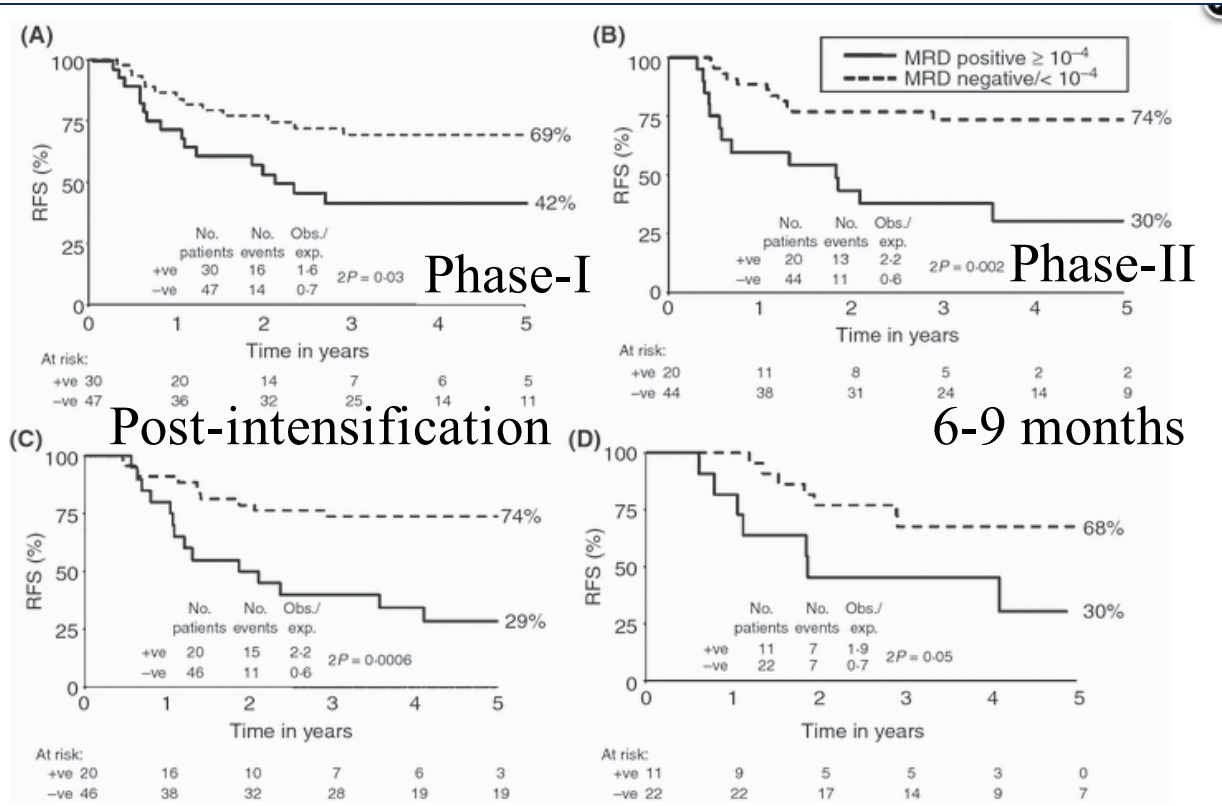


Figure 2. Kaplan–Meier estimates of RFS according to MRD results at four time-points in auto-SCT/chemotherapy treated patients. (A) End of phase 1 induction, (B) end of phase 2 induction, (C) post-intensification therapy, (D) 6–9 months. Obs, observed; Exp, expected.

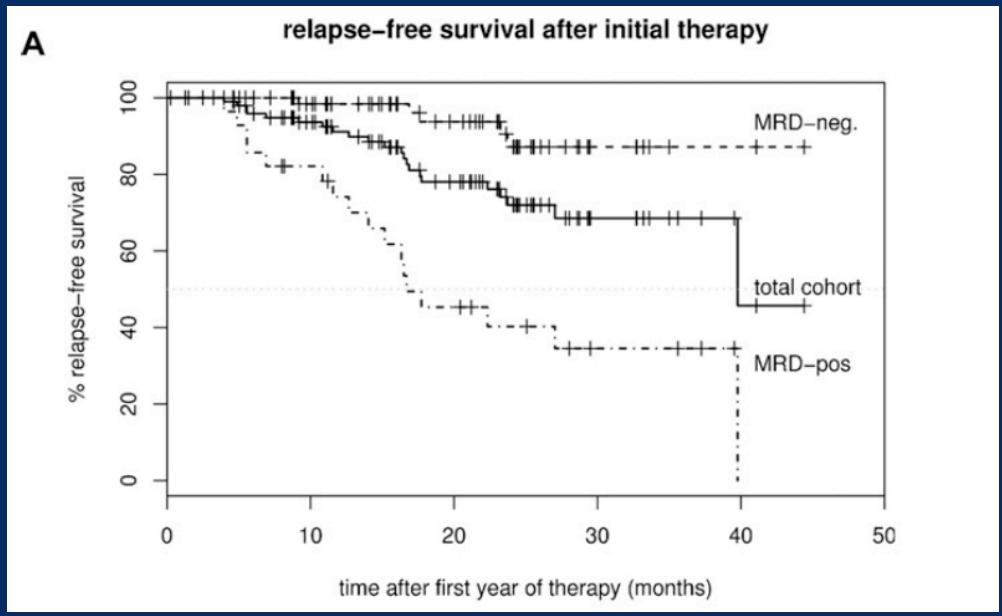
Pre-consolidation MRD studies

- Brüggemann; Blood 2006
  GMALL MRD n=196; MRD >104; DFS=12%
- Mortuza; JCO 2002
  n=85;
  MRD+ at 3 months; DFS=11%
  MRD- at 3 months; DFS=74%
- Vidriales; Blood 2003
  n= 102
  MRD by FC at 35d; even those with <0.05% had relapse rate of 50%

MRD kinetics- earlier is better

- Those becoming MRD neg at day 11 or 15 have an excellent out come with DFS reports of 90-92%

Continuous monitoring



Raff and Gokbuget
Blood 2007

Does MRD directed intervention improve outcome?

Risk adaptive vs unrestricted transplant approach

SR + MRD neg = no transplant
IR + MRD neg = no transplant
HR or MRD pos = transplant

vs

Transplant all adults with HLA-matched donor

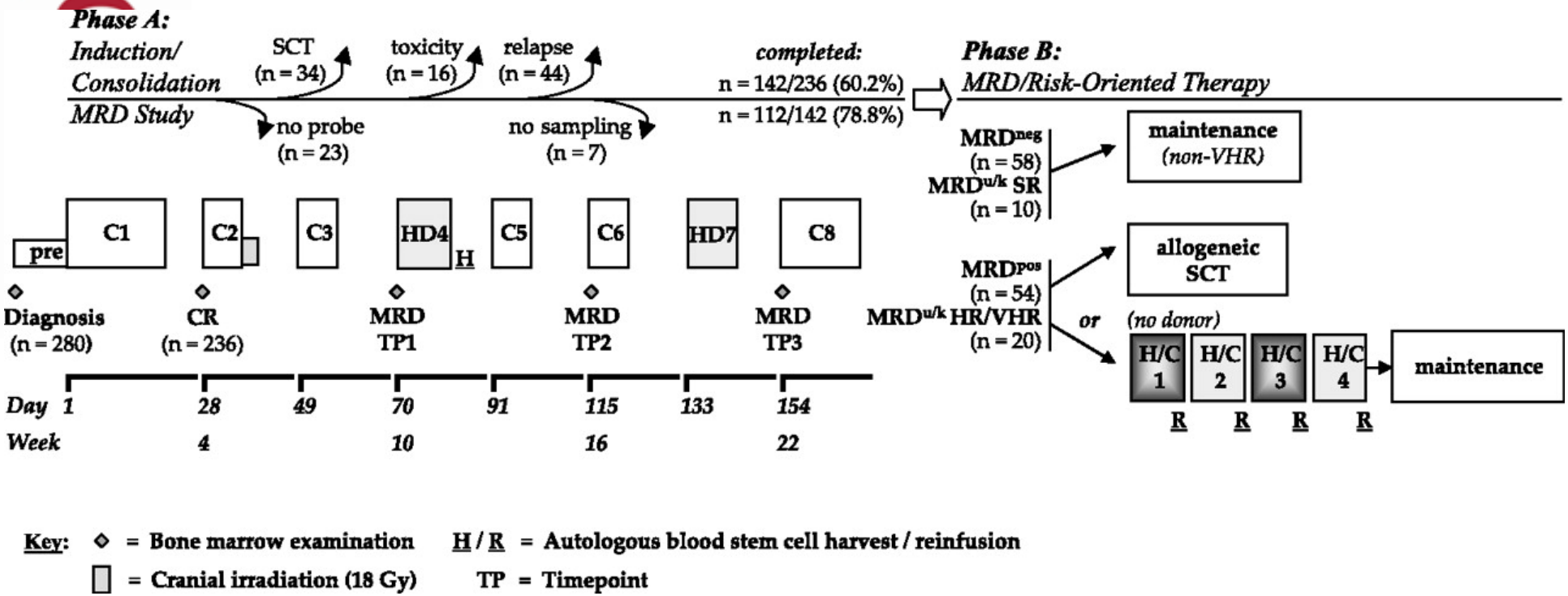
GMALL 07/03 trial

- patients with MRD levels consistently <104 = MRD-LR group
- patients with persistent MRD levels >104 MRD-HR group
- Maintenance treatment after the first year of therapy was omitted in MRD-LR patients.
- MRD-HR group were allografted.

PETHEMA ALL-AR-03

- High risk Ph(neg) ALL
- If MRD neg post-consolidation AlloSCT is deferred
- If MRD pos then AlloSCT is offered.
- Preliminary data suggests no detriment of deferring allo.

Outline of protocol NILG-ALL 09/00, MRD study, and treatment realization.

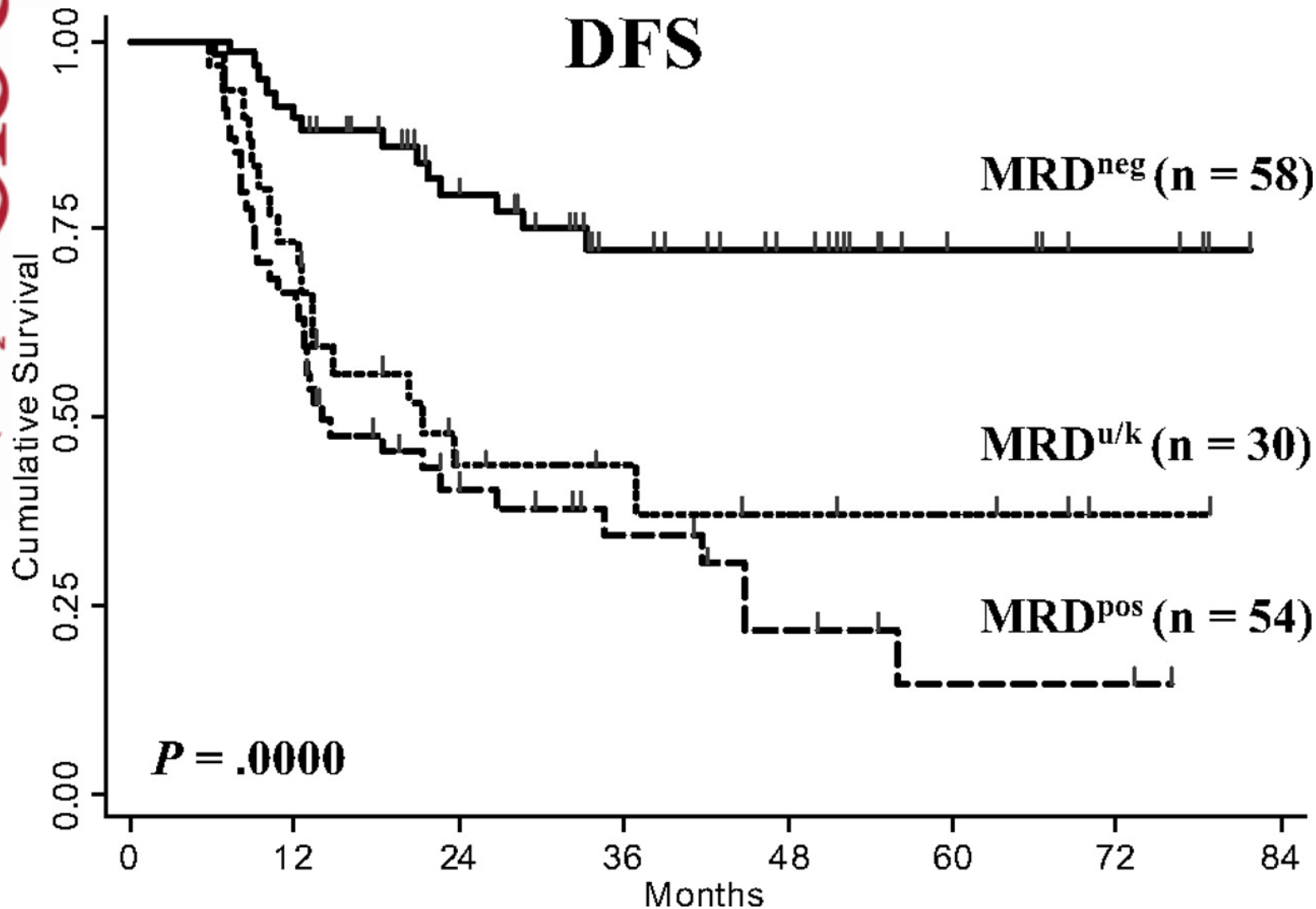


Key: ◇ = Bone marrow examination H / R = Autologous blood stem cell harvest / reinfusion
▯ = Cranial irradiation (18 Gy) TP = Timepoint

Bassan R et al. Blood 2009;113:4153-4162

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

DFS according to MRD study results.



Bassan R et al. Blood 2009;113:4153-4162

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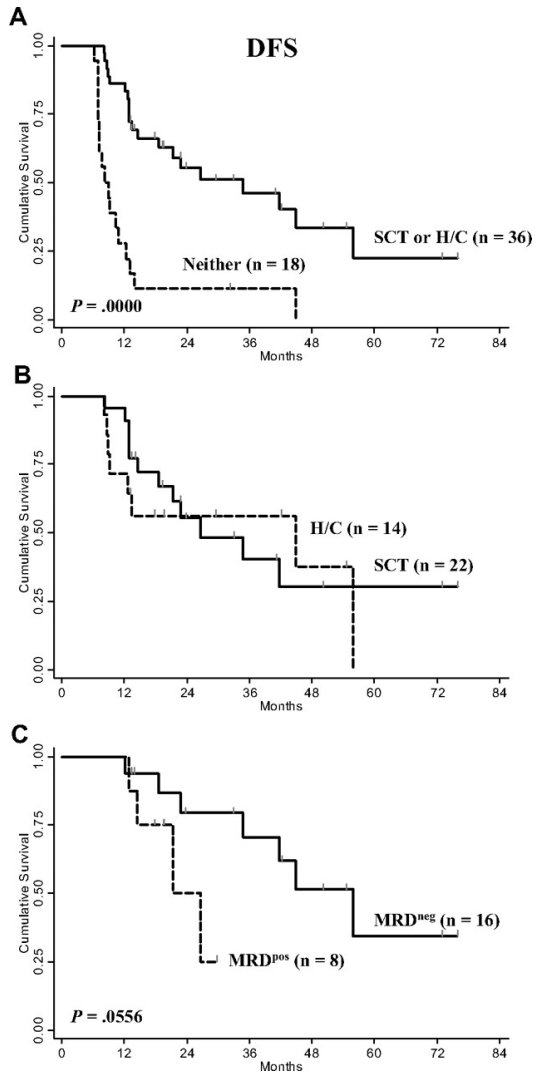
DFS of MRDpos group.



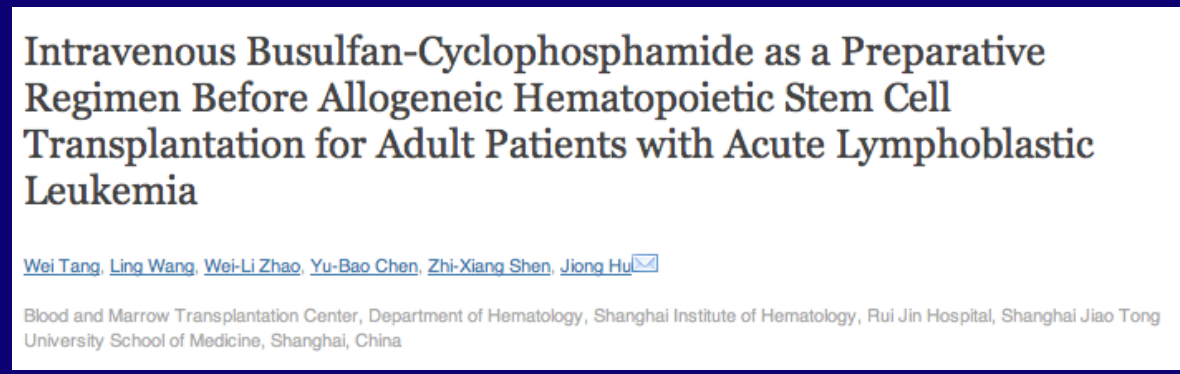
Bassan R et al. Blood 2009;113:4153-4162

Myeloablative HSCT - how ?

Conditioning regimen:

TBI 13.2 Gy

Etoposide or cyclophosphamide



Intravenous Busulfan-Cyclophosphamide as a Preparative Regimen Before Allogeneic Hematopoietic Stem Cell Transplantation for Adult Patients with Acute Lymphoblastic Leukemia

Wei Tang, Ling Wang, Wei-Li Zhao, Yu-Bao Chen, Zhi-Xiang Shen, Jiong Hu

Blood and Marrow Transplantation Center, Department of Hematology, Shanghai Institute of Hematology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Marks 2006 Biol Blood Marrow Transpl IBMTR

Myeloablative allogeneic HSCT

Non-Relapse Mortality (%)

	3 m	6 m	1 yr	2 yr
High Risk				
Donor	1.2	5.7	29	39
No Donor	1.3	2.3	10	12
Std Risk				
Donor	0.5	3.4	18	20
No Donor	0.4	1.4	6	7

Goldstone et al, Blood 2008 (UKALLXII/ECOG2993)

Reduced Intensity Conditioned AlloHSCT for ALL

Retrospective EBMT study N=97

Mohty et al, Haematologica 2008 (EBMT)

2yr outcome for those in CR1 (N=28)

OS 52+/-9%

LFS 42+/-10

NRM 18+/-7%

Update: Blood 2010.

Brief report

Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation

Mohamad Mohty,[1] Myriam Labopin,[2] Liisa Volin,[3] Alois Gratwohl,[4] Gérard Socié,[5] Jordi Esteve,[6] Reza Tabrizi,[7] Arnon Nagler,[8] and Vanderson Rocha,[5] on behalf of the Acute Leukemia Working Party of EBMT

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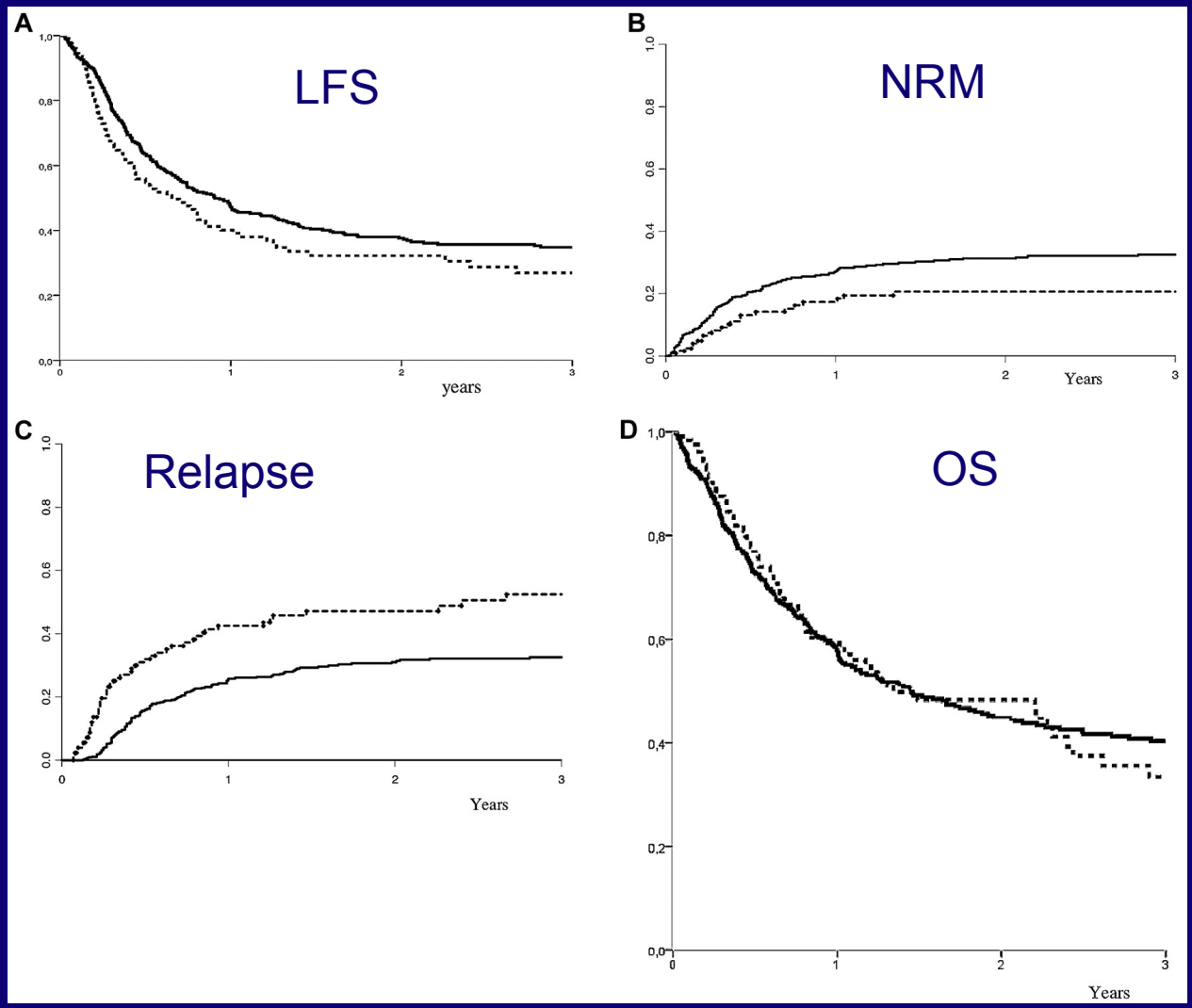
Survival probabilities



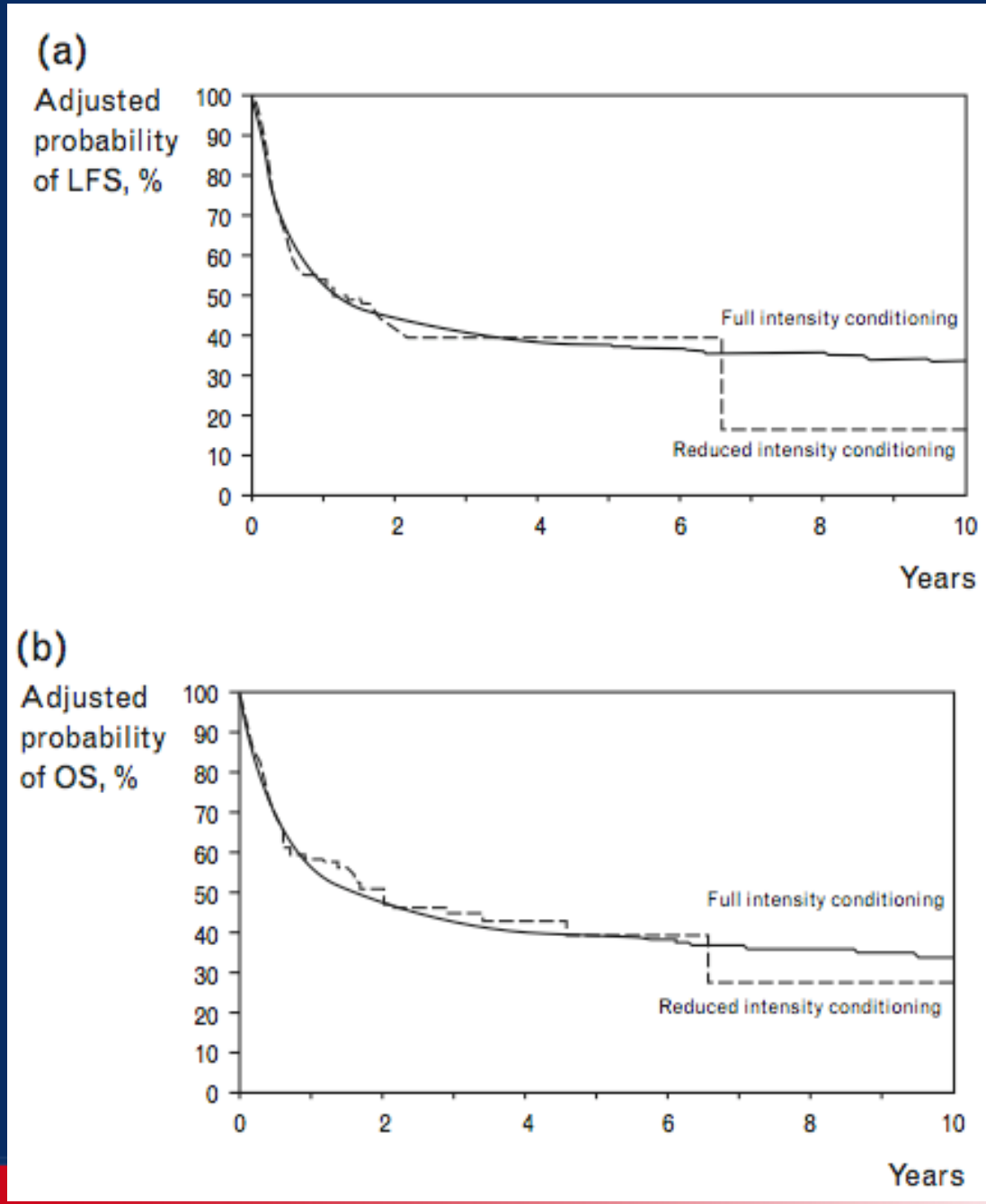
MAC= 449
RIC= 127

Mohty, M. et al. Blood 2010;116:4439-4443

Table 2. Studies of RIC alloHSCT regimens in patients with ALL

Study	Center/ registry/ multicenter	Median age (total population)	Ph^+, N	Ph^+ CR1, N	Conditioning regimen	TKI after alloHSCT?	TRM, % (total population)	CGVHD, % (total population)	OS Ph^+ subgroup
Arnold[42]	M	38	11	3	Flu/Bu ± ATG	No	45	46	N/S
Martino[43]	M	50	11	3	Various	N/S	23	72	N/S
Mohty[44]	R	38	37	N/S	Various	N/S	28	37	N/S
Stein[41]	S	47.5	9	6	Flu/Mel	Various	21.5	86	N/A
Bachanova[45]	S	49	14	10	Flu/Cy/TBI 2 Gy	Only for morphological or to relapse	27	45	N/A
Ram[24]	S	57	25	19	Flu/TBI 2 Gy	4–600 mg daily, upon count recovery, for 1 year	28	44	62% 3 y

N/A indicates numbers too small/status at transplantation too various to give a single figure; N/S, not specified; TBI, total body irradiation; Flu, fludarabine; Bu, bulsuphan; Mel, melphalan; Cy, cyclophosphamide; ATG, anti-thymocyte globulin; S, single; R, registry; and M, multicenter.



Marks; Blood 2010
CIBMTR
MAC=1428
RIC=93

Ph+ ALL

- Historically associated with the poorest prognosis
- Long term OS with CT ~10%
- Long term OS with AlloSCT ~30%
- TKI + chemo
- TKI monotherapy

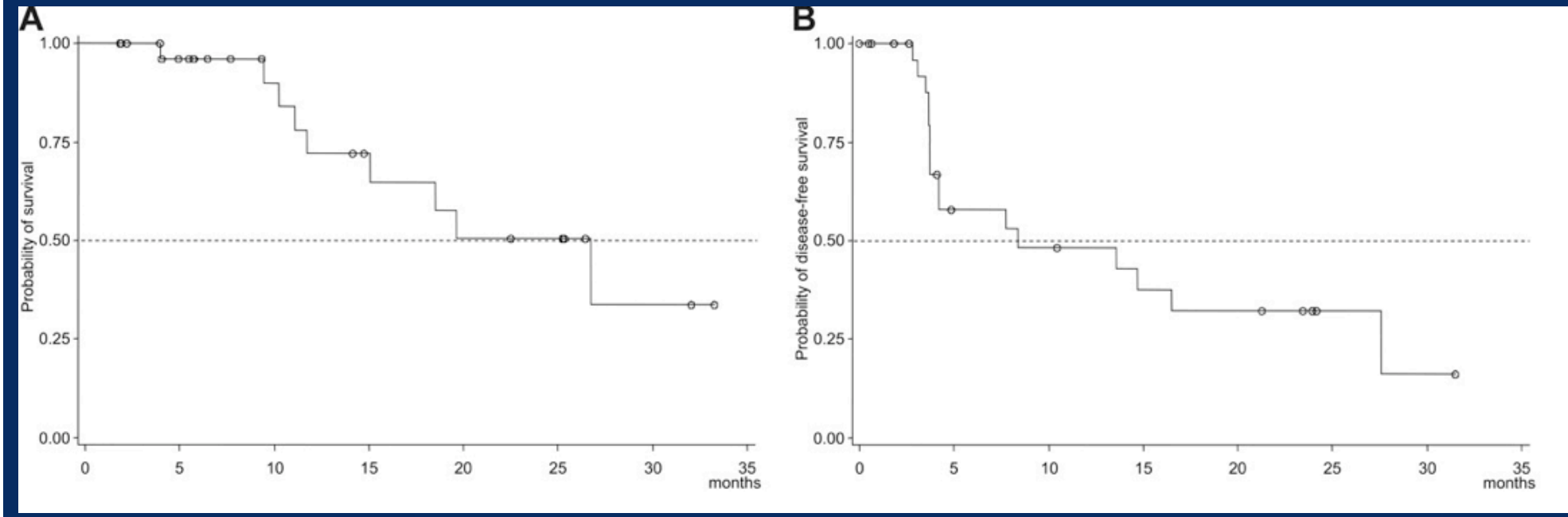
Imatinib + chemo in Ph+ ALL

Parameter	MDACC[63] (n = 20)	GMALL[65] (n = 92)	JALSG[66] (n = 80)	GRAALL[67] (n = 45)	PETHEMA[68] (n = 32)
Induction regimen	Hyper-CVAD	DEX, CY, VCR, DNR, ASP, Ara-C, MP	CY, DNR, VCR, PDN	DNR, CY, VCR, ASP, PDN, MT, Ara-C, DEX	VCR, DNR, PDN
Imatinib, mg/d	600	400	600	600	400
CR	93	95	96	96	90
HSCT	50	77	71	48	78
Induction mortality	NR	7	2.5	5	7
Death in CR	16	5	27 (by HSCT)	11 (9 by HSCT)	35 (by HSCT)
OS	75, at 20 months	36-43, at 2 years	61, at 1 year	65, at 1.5 years	30, at 4 years
PCR negative	59	52	71	38	86

Imatinib +/-corticosteroids CR rates of 90% to 100%.

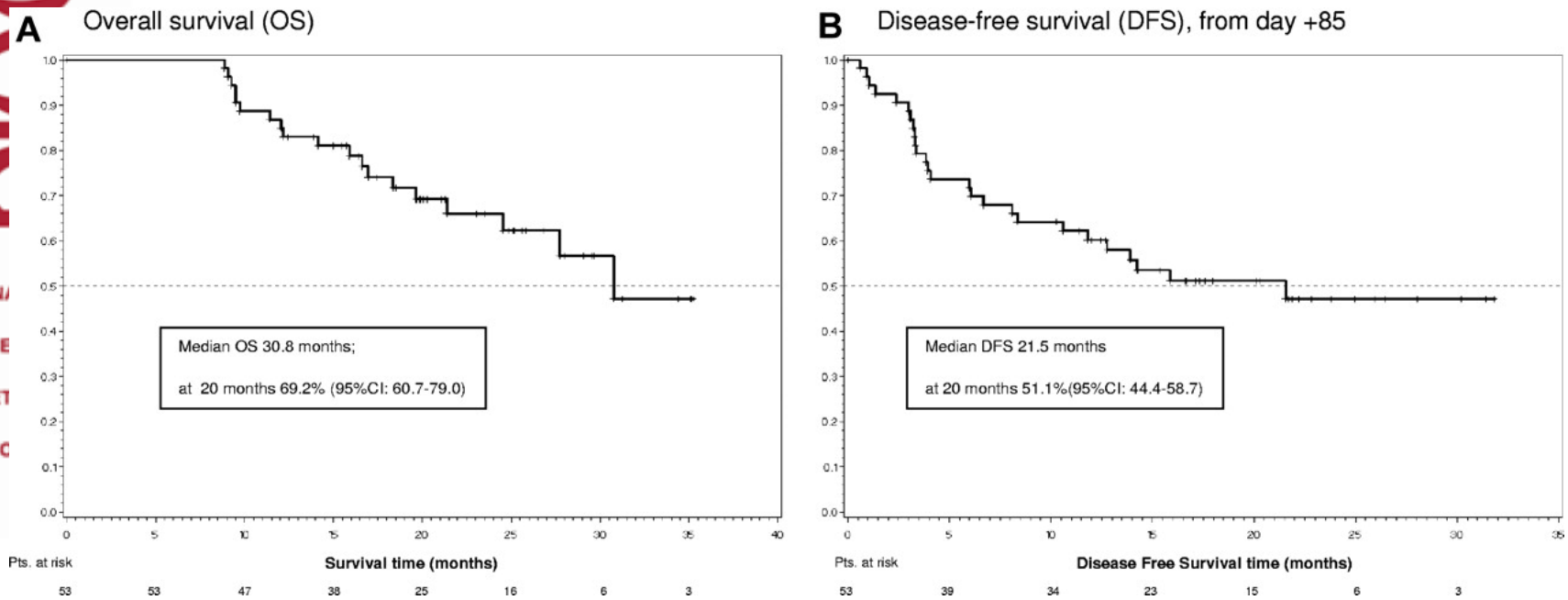
Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome–positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol

Marco Vignetti,[1] Paola Fazi,[2] Giuseppe Cimino,[1] Giovanni Martinelli,[3] Francesco Di Raimondo,[4] Felicetto Ferrara,[5] Giovanna Meloni,[1] Achille Ambrosetti,[6] Giovanni Quarta,[7] Livio Pagano,[8] Giovanna Rege-Cambrin,[9] Loredana Elia,[1] Raffaello Bertieri,[10] Luciana Annino,[11] Robin Foà,[1] Michele Baccarani,[3] and Franco Mandelli[1]



Dasatinib + Corticosteroids

Survival curves.



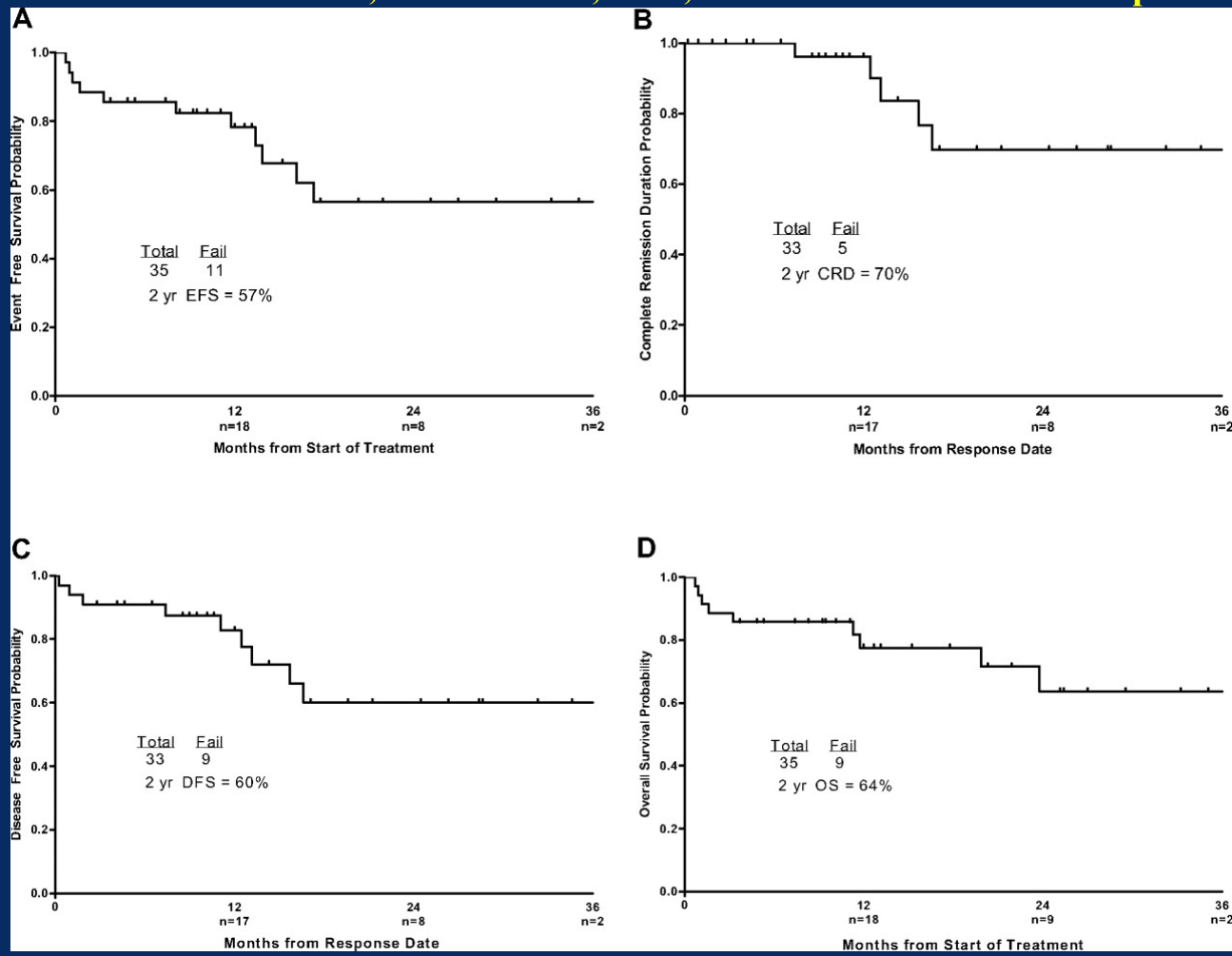
No further treatment, (2)
TKI alone, 19 patients (16 dasatinib, 2 imatinib, and 1 imatinib-dasatinib);
TKI plus chemotherapy (10)
autografting (4),
allografting, 18 patients.

Foà R et al. Blood 2011;118:6521-6528

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

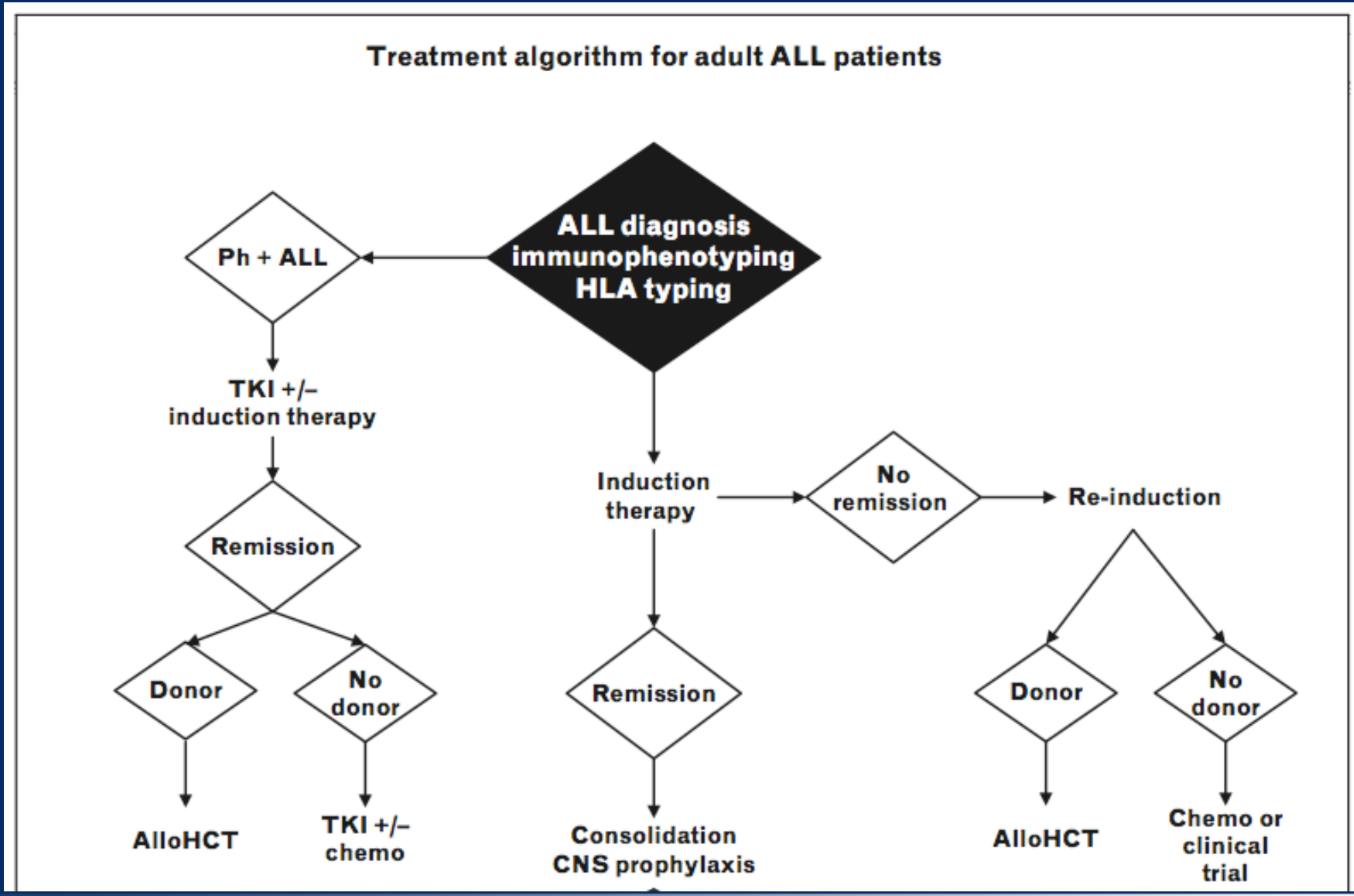
Dasatinib + Hyper-CVAD

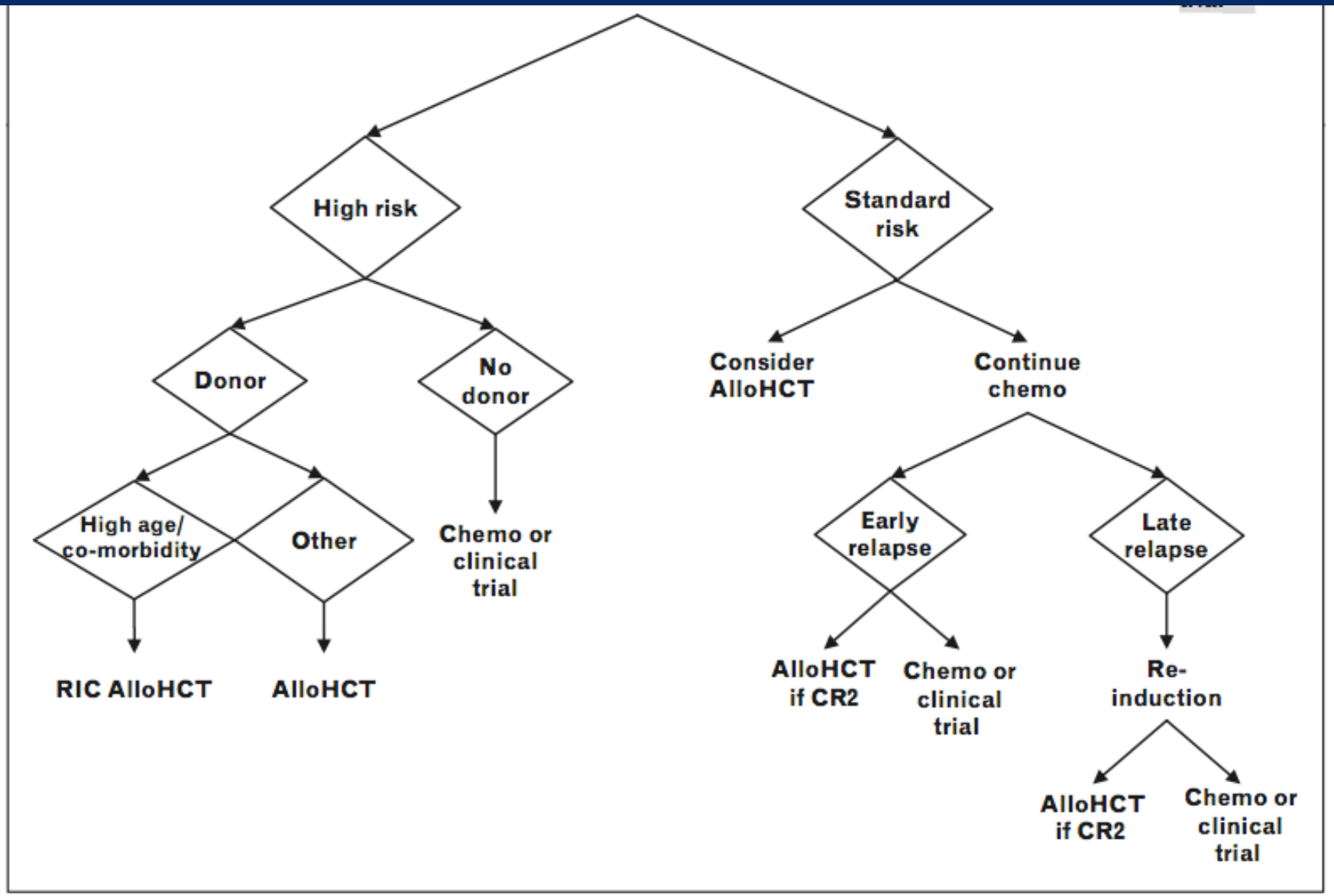
Event-free survival, CR duration, DFS, and overall survival of the patients



Ravandi, F. et al. Blood 2010;116:2070-2077

Khaled, Thomas, Forman; Curr Op Onc 2012





Summary

- ALL is a bad disease
- MRD is the best guide to outcome and may help avoid unnecessary intensification
- Transplantation delivers the best disease control
- Patients remain at considerable risk of TRM even with RIC.
- In Ph+ disease, non-chemo based induction may lessen alloSCT toxicity.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