Jornadas de Hematología y Medicina Transfusional
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Tratamiento de la leucemia aguda linfoblástica

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La LAL es una enfermedad de predominio en la infancia

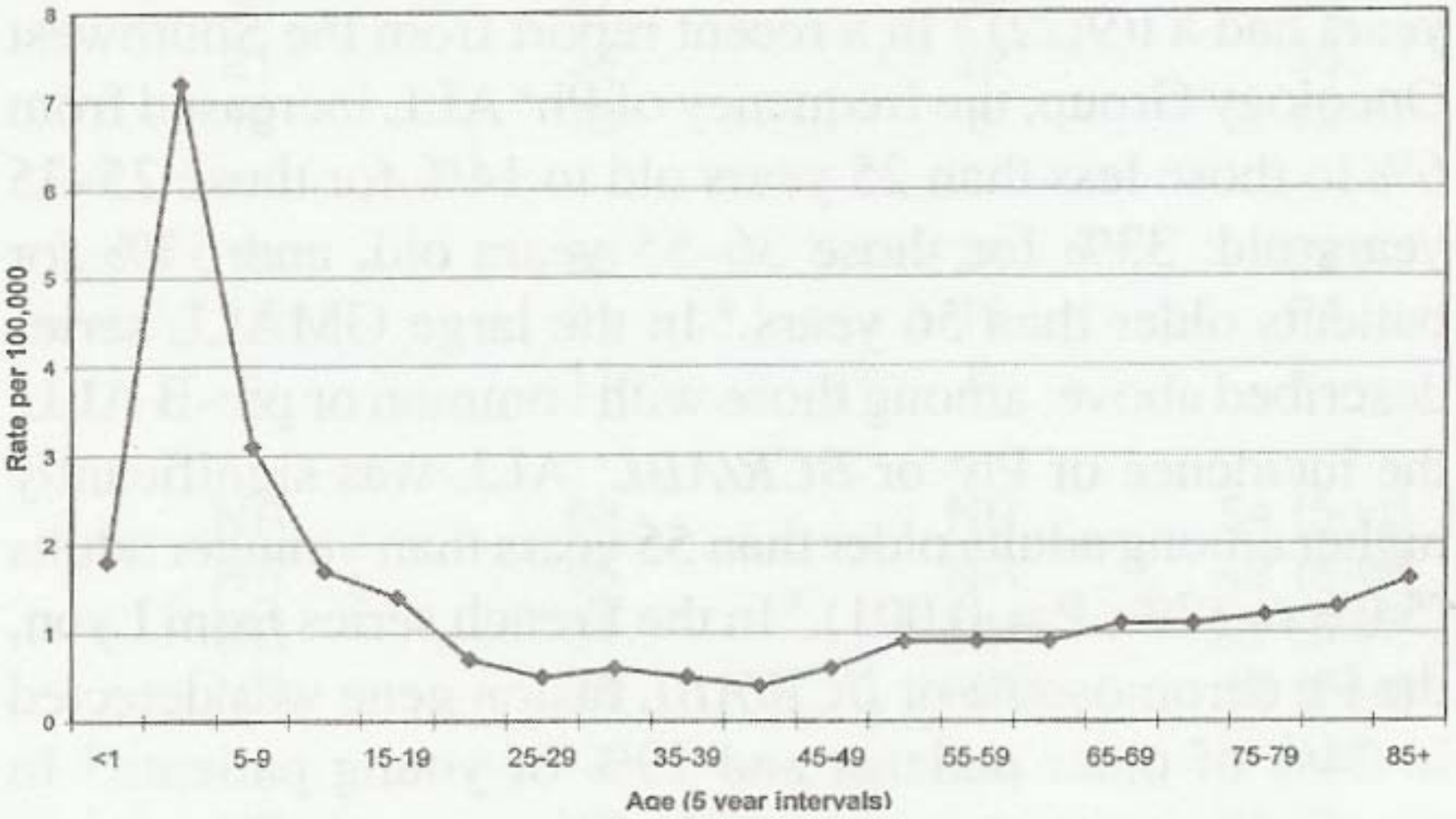


Figure 1. Age-specific annual incidence of acute lymphoblastic leukemia (US-SEER data, 1998–2002).

LAL infantil. Factores pronósticos

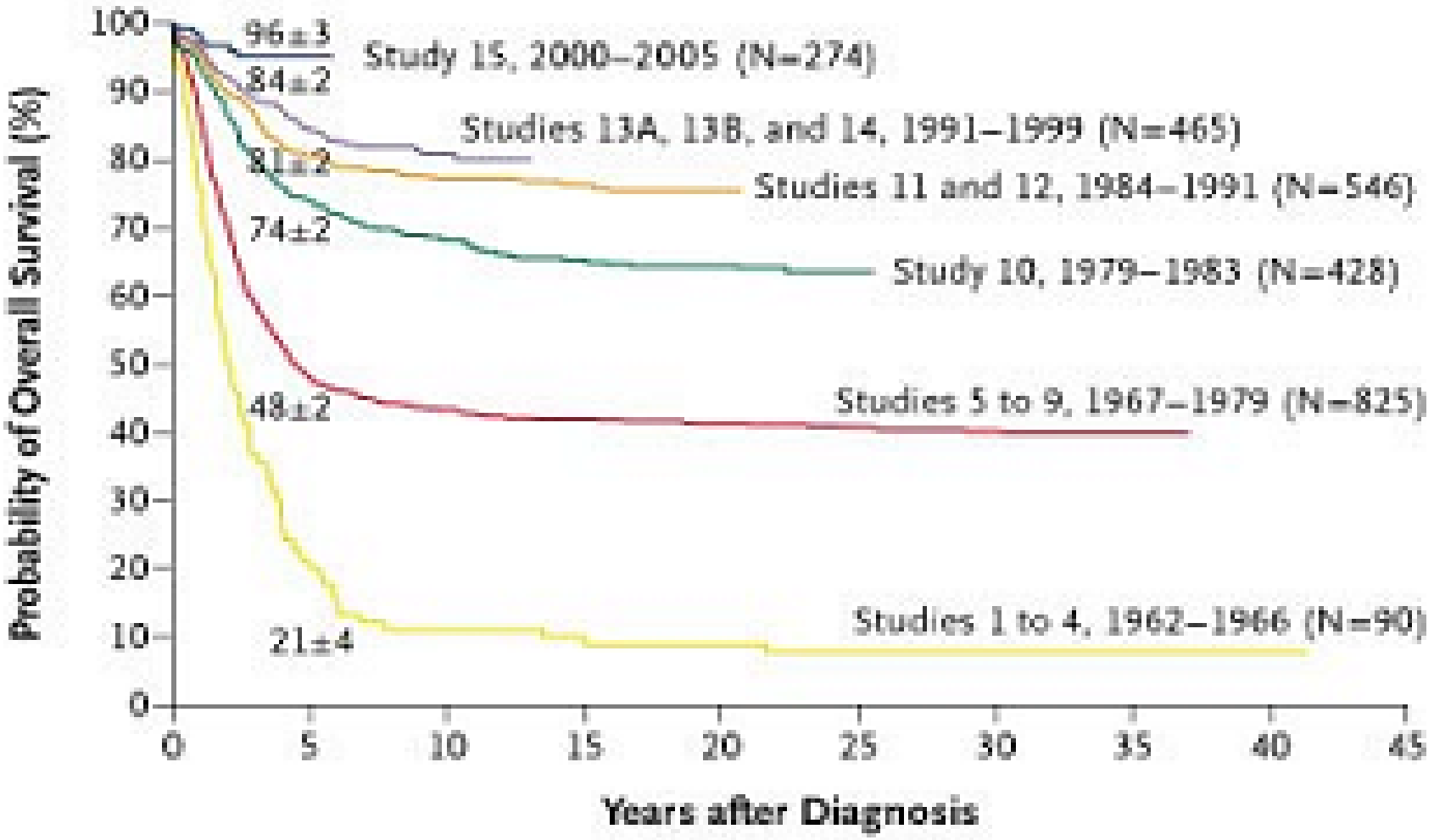
- Edad
- Leucocitos
- Fenotipo (B frente a T)
- Citogenética/genética molecular
- Rapidez respuesta al tratamiento
  - Respuesta a PDN
  - % blastos MO d14
  - Respuesta al final inducción (4-5 semanas)
- Enfermedad residual

Grupos de riesgo
LAL de precursores B. NCI-Roma, 1996

- Riesgo estándar
  - Edad 1-10 años
  - Leucocitos < $50x10^9/L$
- Alto riesgo
  - Edad <1 año o >10 años
  - Leucocitos > $50x10^9/L$

Smith M, Arthur D, Camitta B, et al. J Clin Oncol 1996; 14: 18-24

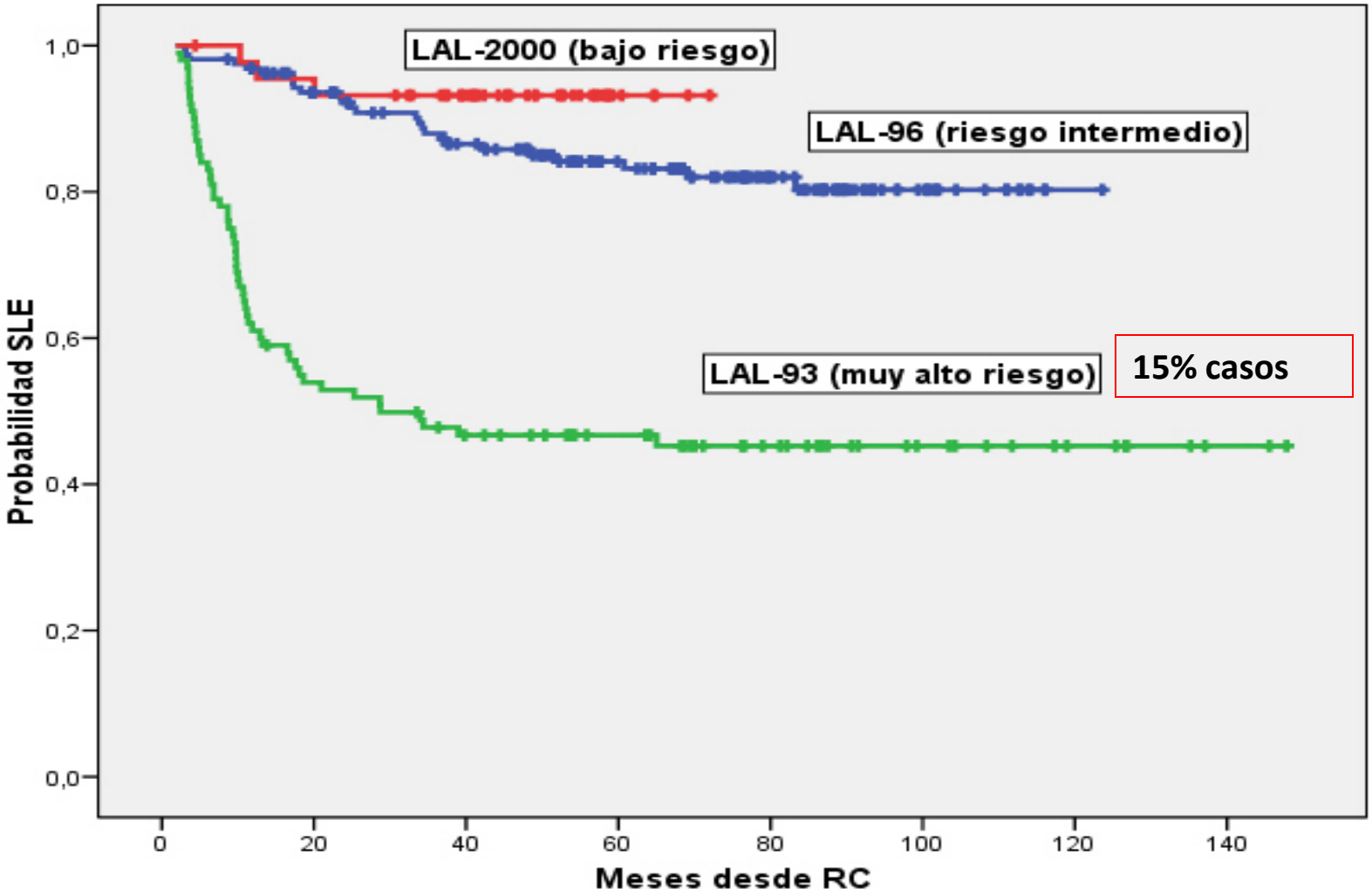
Childhood ALL. Overall survival



Pui CH, NEJM 2006

LAL . Resultados protocolos PETHEMA

LAL infantil



Resultados tratamiento LAL infantil (NCI BR, B-lin)(1990-2000)
Grupos cooperativos europeos

Group	Protocol	N	CR	10-yr EFS	10-yr OS
BFM	BFM 90/ 95	1262/1257	99/99	84/86	91/92
AIEOP	AIEOP 91/95	765/1110	97/98	77/76	85/88
MRC	UKALL XI/ ALL 97	257/1134	99/99	67/80	- / -
NOPHO	NOPHO 92/2000	1093/645	98/97	81/85*	91/95*
COALL	COALL 92/97	307/396	99/99	71/81	85/91
DCOG	ALL8/ ALL9	290/469	99/99	77/82	87/85
Czech Republic	90/95	195/198	98/99	81/81	86/90
Israel	98	174	97	84	91
PETHEMA	**LAL-BR-01**	**176**	**98**	**87***	**97***

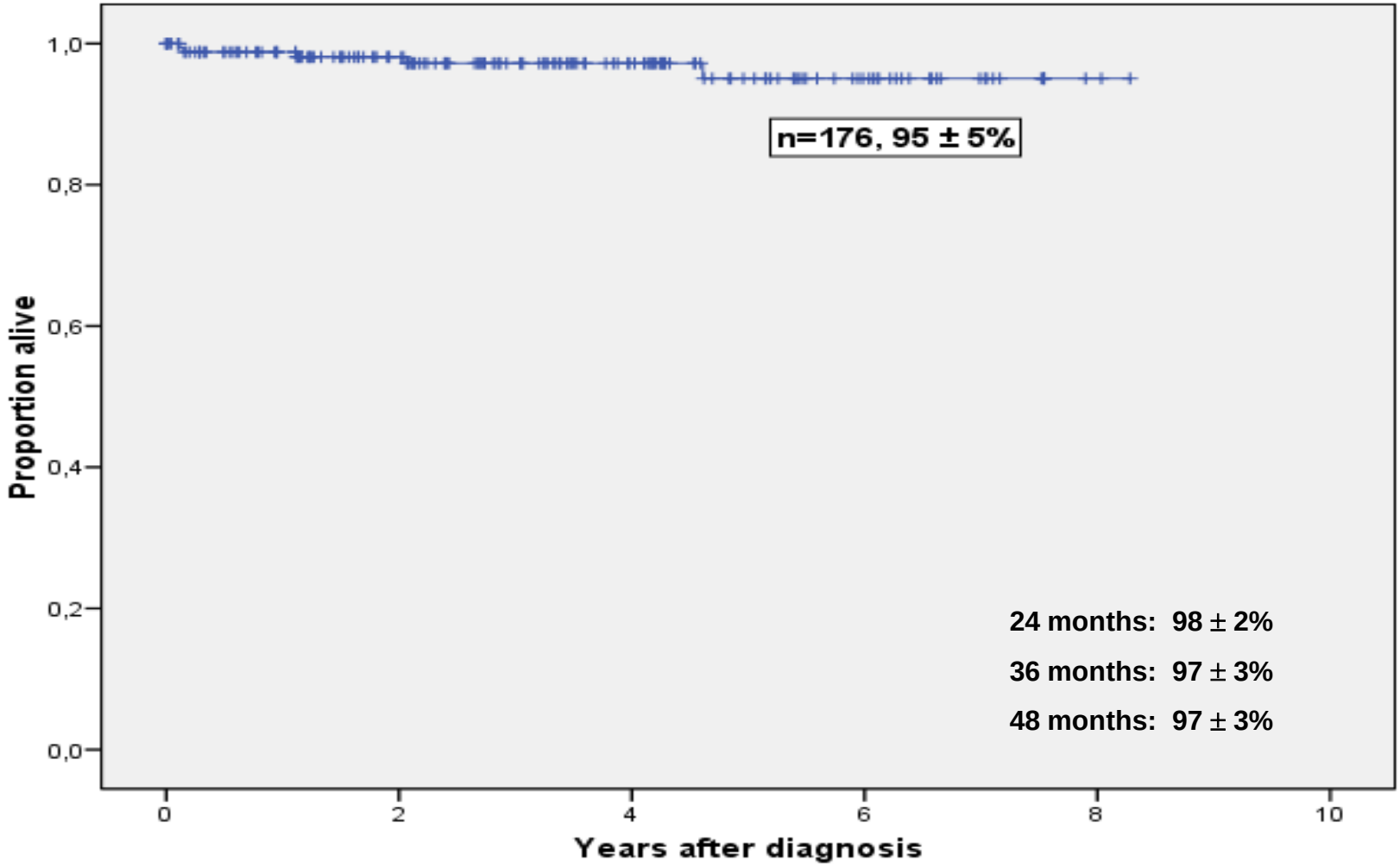
*Datos a 5 años

Resultados tratamiento LAL infantil (NCI BR, B-lin)(1990-2000)
Grupos cooperativos de EEUU y Extremo Oriente

Group	Protocol	N	CR	10-yr EFS	10-yr OS
St. Jude	Study 13A/13B	84/113	98/98	83/85	86/89
Dana Farber	91-01/ 95-01	239/303	98/98	82/83	87/93
CCSG	L92-13/L95-14	206/373	96/95	64/81	86/91
COG	ALinC15/ALinC16	4468	99,8	76	88
CCG	CCG 1900 series	1242	100	78	89
JCCLSG	ALL911	139	99	71	81
Taiwan	TPOG 97/2002	326/435	96/97	80/84*	88/94*
PETHEMA	**LAL-BR-01**	**176**	**98**	**87***	**97***

*Datos a 5 años

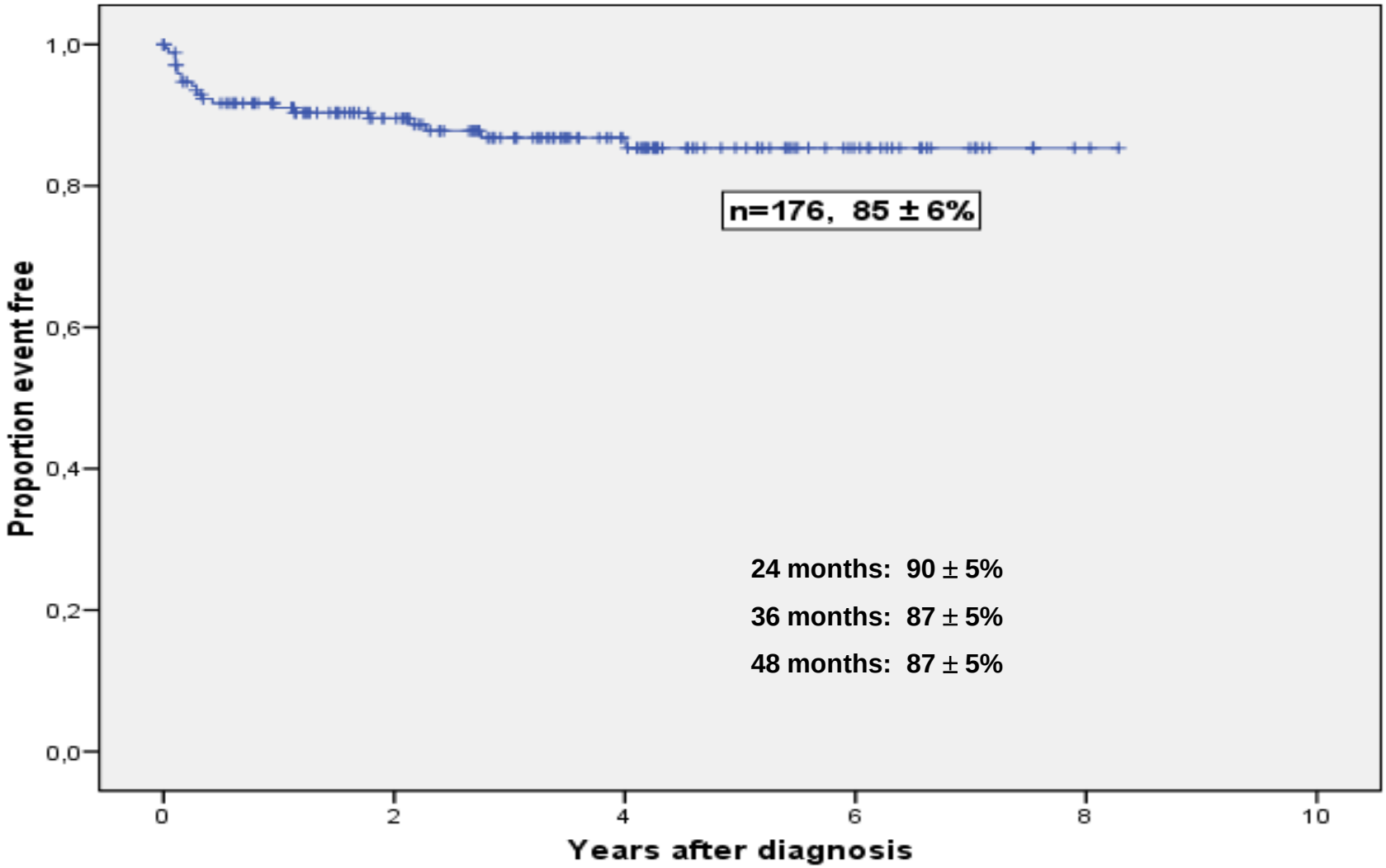
PETHEMA LAL-BR-01
Supervivencia global



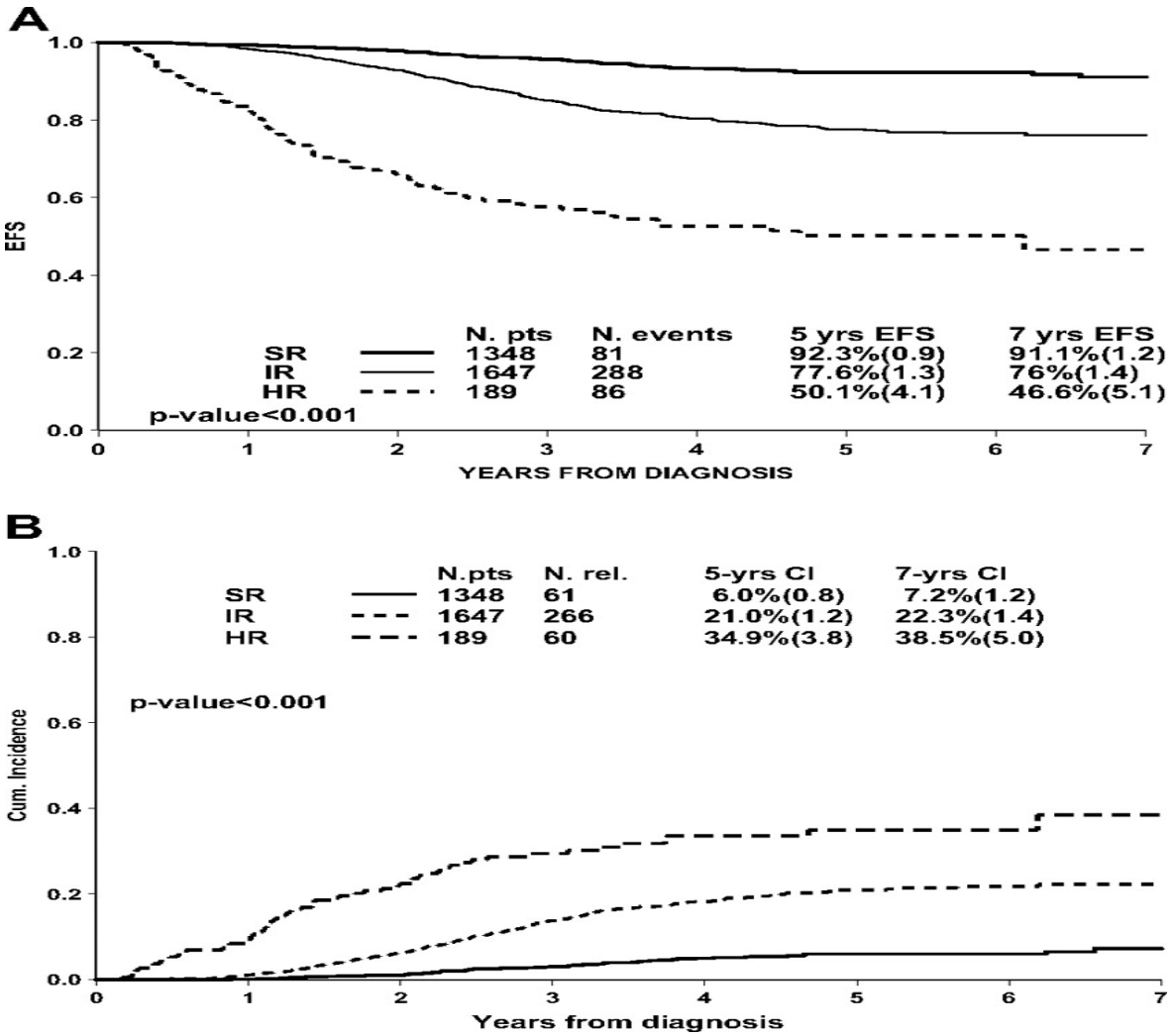
Mediana de seguimiento: 3,2 [0,1-8,3] años

NOTA: El evento tardío (4,2 a) es la muerte por recaída de paciente con respuesta lenta d14.

PETHEMA LAL-BR-01.
Supervivencia libre de evento

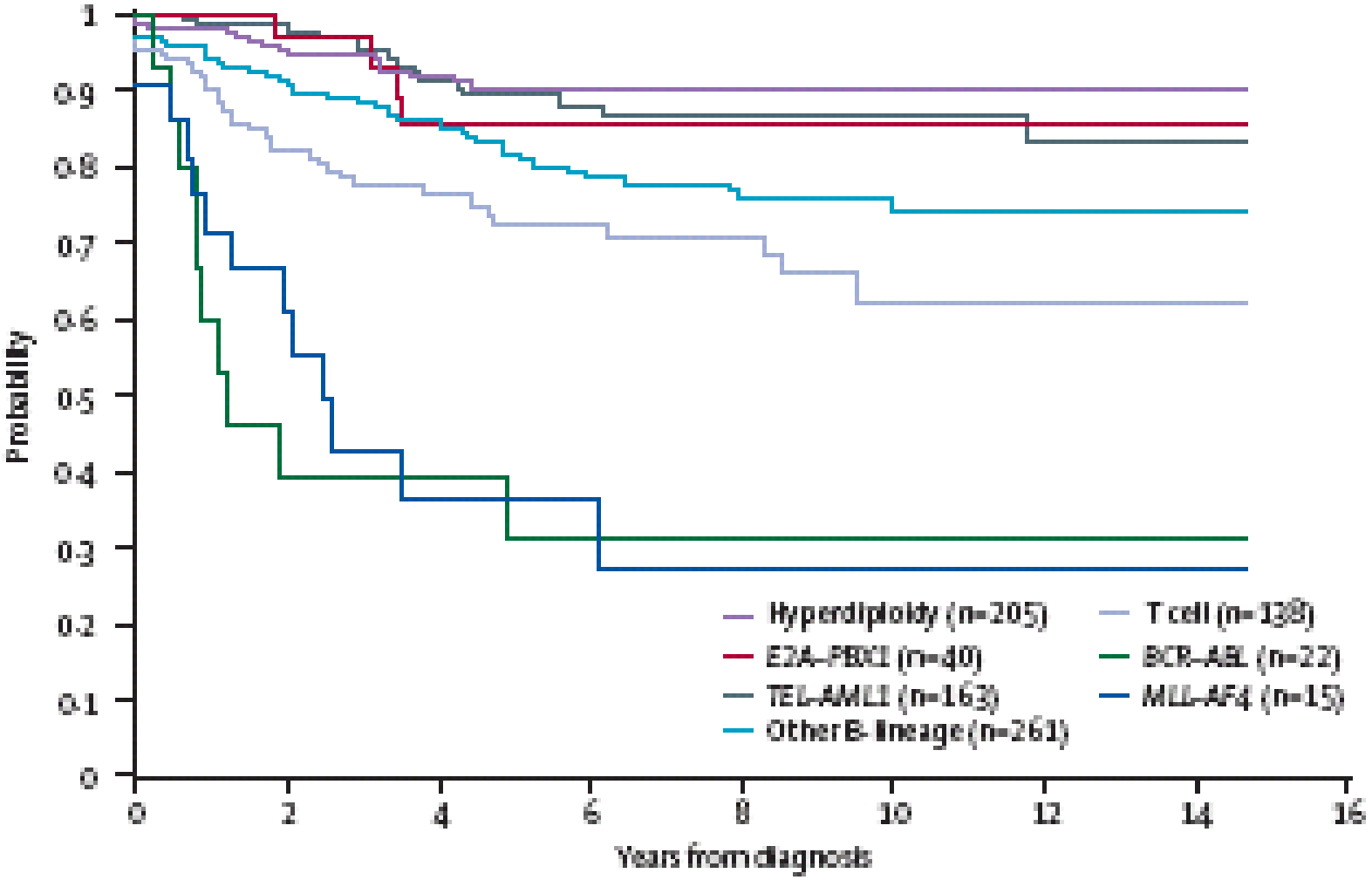


Prognostic value of MRD AIEOP-BFM ALL 2000 study (3184 pB-ALL patients)



Conter, V. et al. Blood 2010;115:3206-3214

Prognostic impact of genetic and molecular classification of childhood ALL



Pui C-H. Lancet 2008;371:1030

Late MRD response determines relapse risk of childhood T-cell ALL. AIEOP-BFM-ALL 2000 study (n=464)

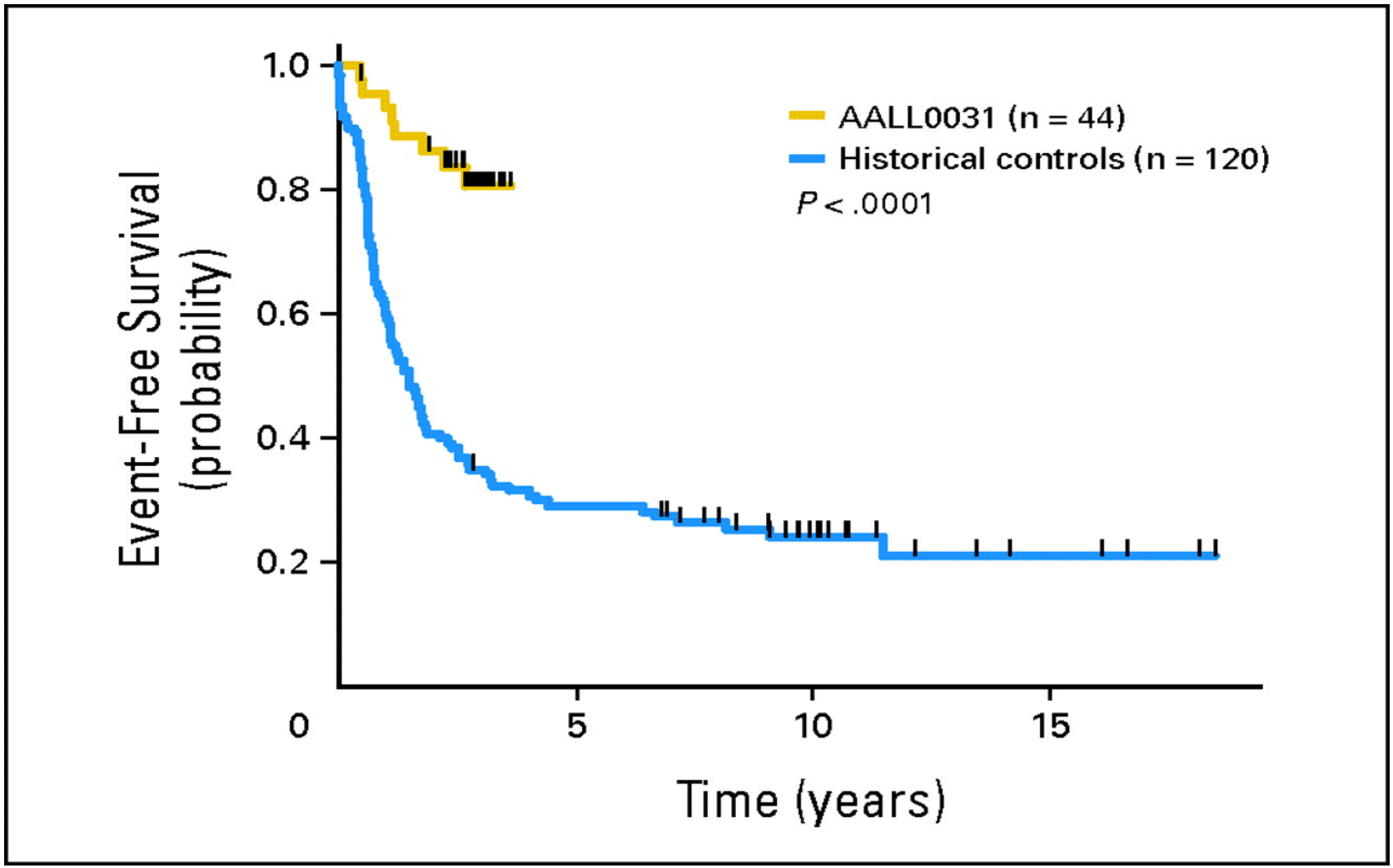
- MRD-SR: MRD-neg at d33 (TP1) and d78 (TP2)
- MRD-IR if pos at d33 or d78 and $<10^{-3}$ at d78
- MRD-HR if $\geq 10^{-3}$ at d78

	Frequency (%)	7-yr EFS (%)
MRD-SR	16	91,1
MRD-IR	63	80,6
MRD-HR	21	41,8

MRD $\geq 10^{-3}$ at TP2: the most important predictive factor for relapse in childhood T-ALL

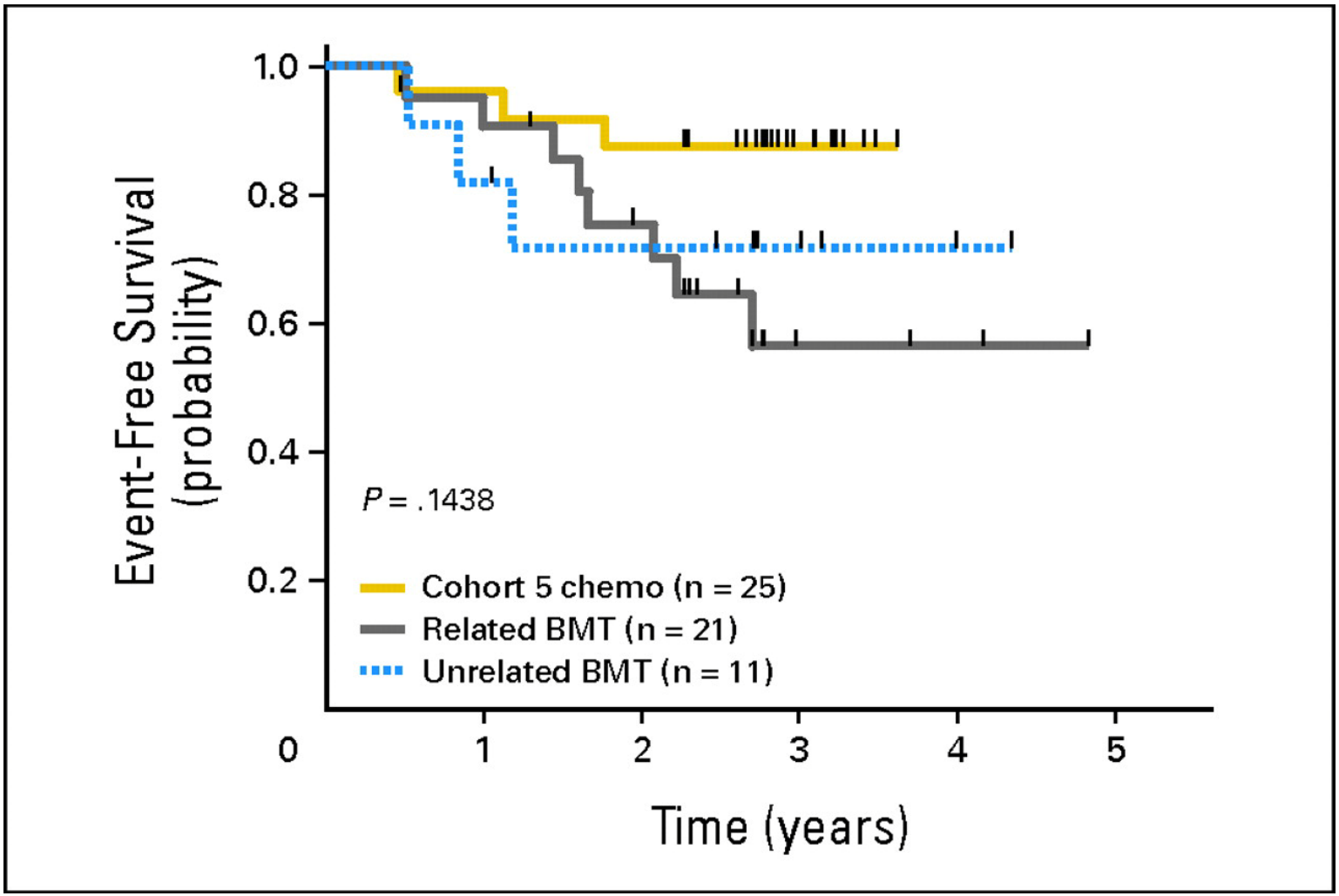
Schrappe M, et al. Blood. 2011 Jun 30. [Epub ahead of print]

EFS in Ph+ ALL patients treated with imatinib



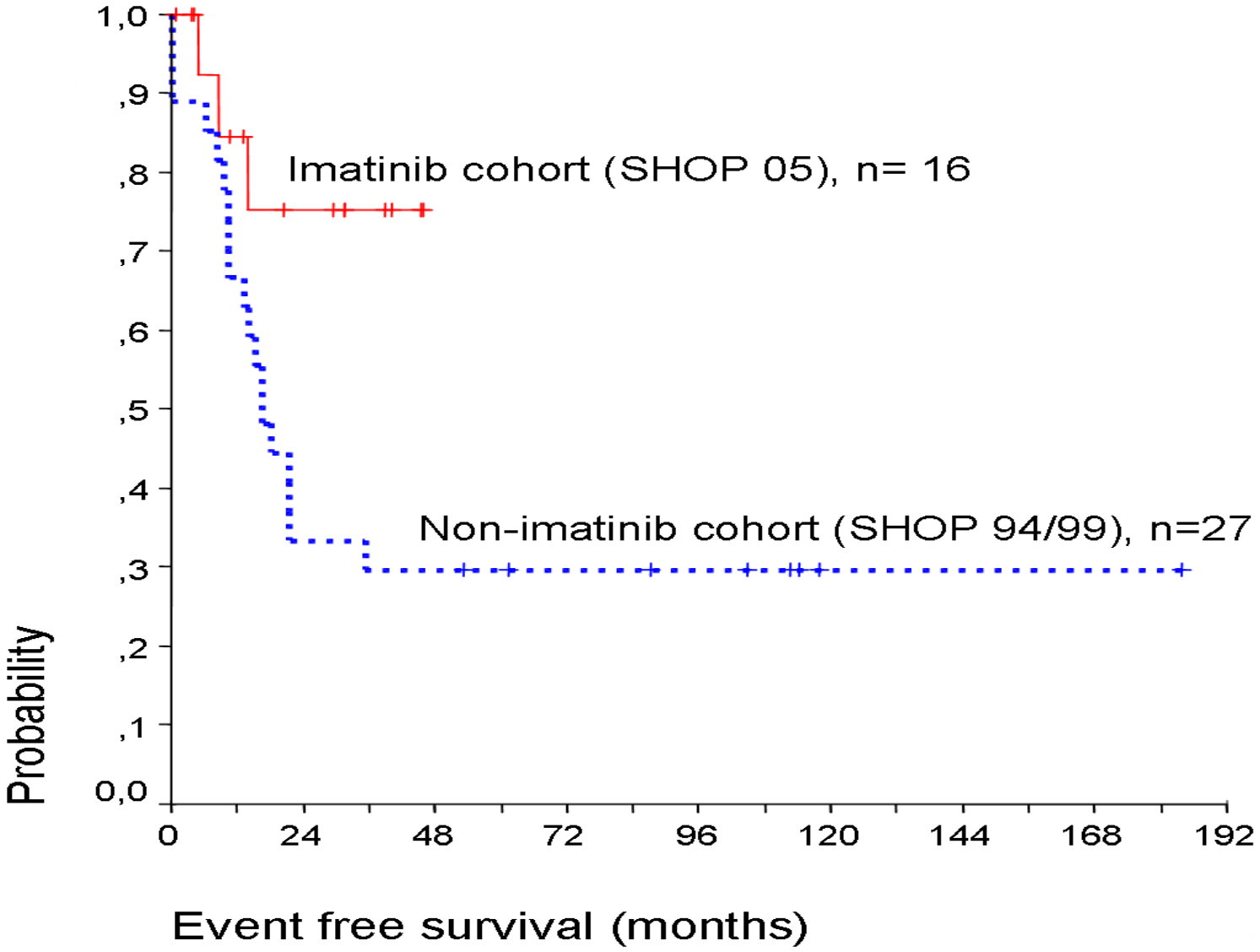
Schultz, K. R. et al. J Clin Oncol 2009; 27:5175-5181

EFS for Cohort 5 chemotherapy only vs. related-donor BMT vs. unrelated-donor BMT



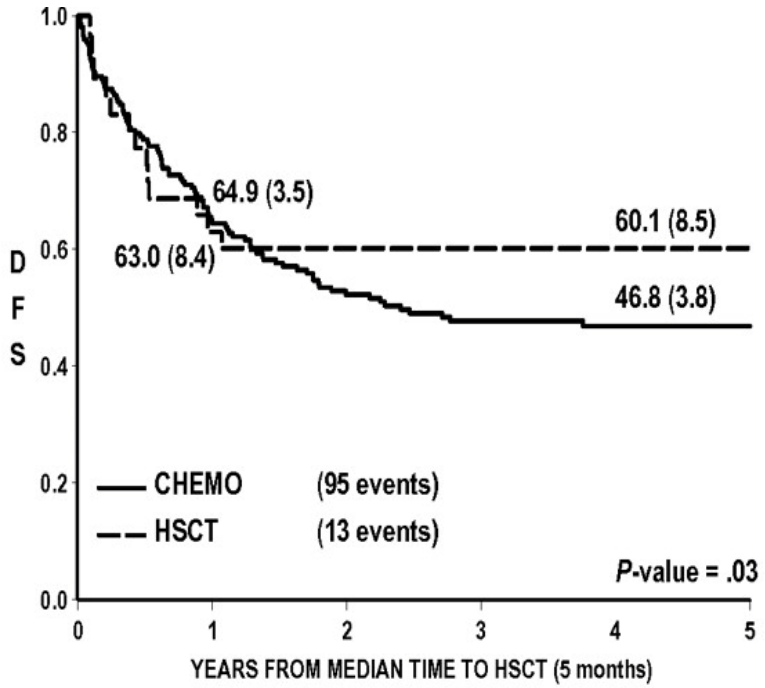
Schultz, K. R. et al. J Clin Oncol 2009; 27:5175-5181

Datos del grupo SHOP

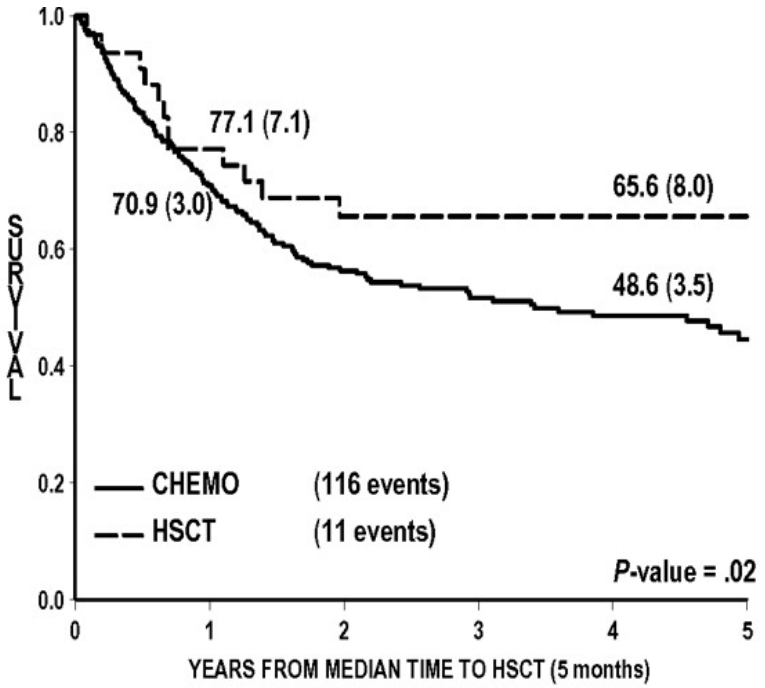


Rives S, et al. Br J Haematol 2011

DFS and OS of 274 MLL+ infant ALL patients by treatment performed, adjusted by waiting time to HSCT.



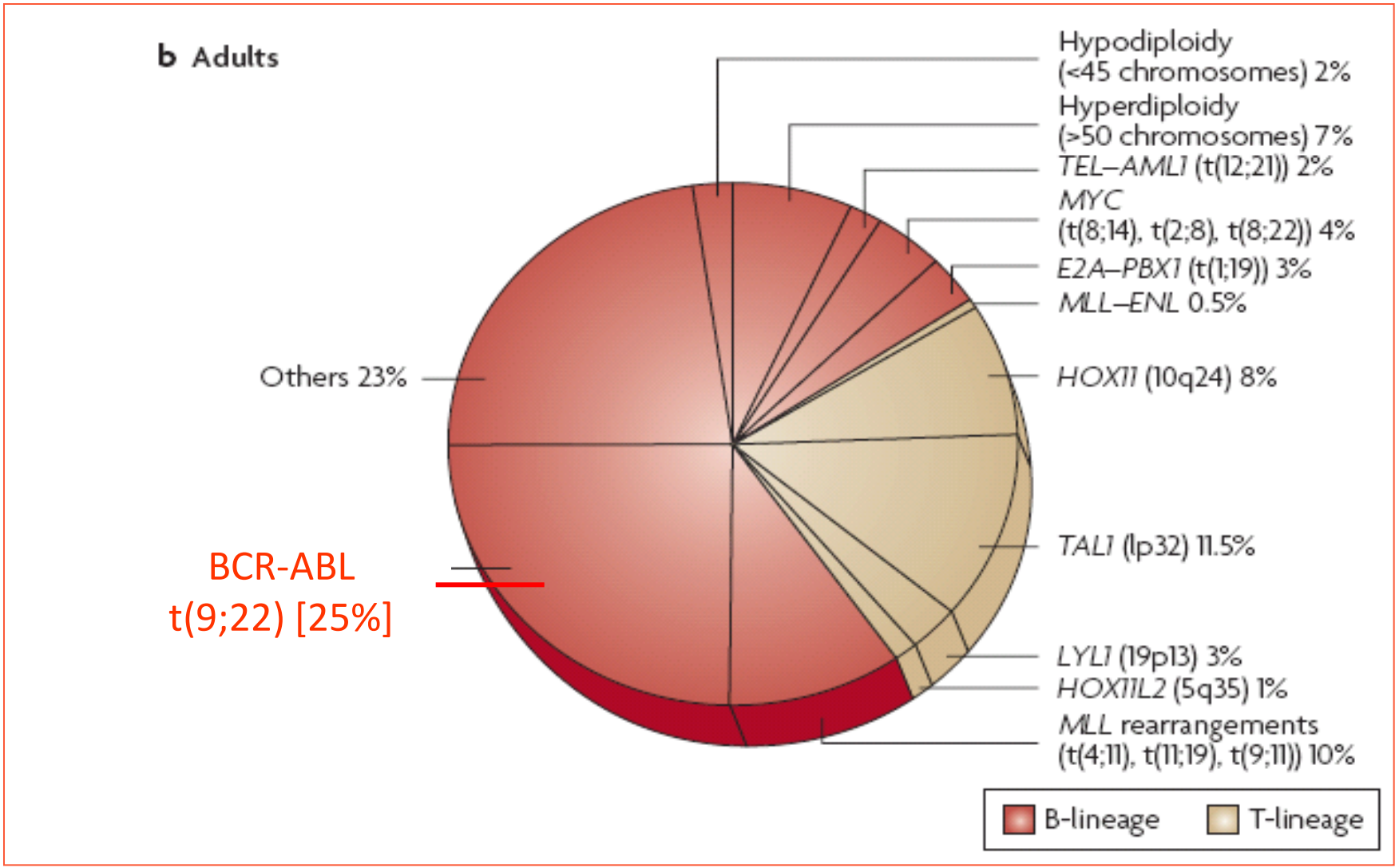
At risk						
CHEMO	199	116	84	68	48	29
HSCT	19	23	17	13	11	6



At risk						
CHEMO	241	158	118	92	67	37
HSCT	21	30	20	17	14	8

Mann G et al. Blood 2010;116:2644-2650

La LAL del adulto es una enfermedad heterogénea



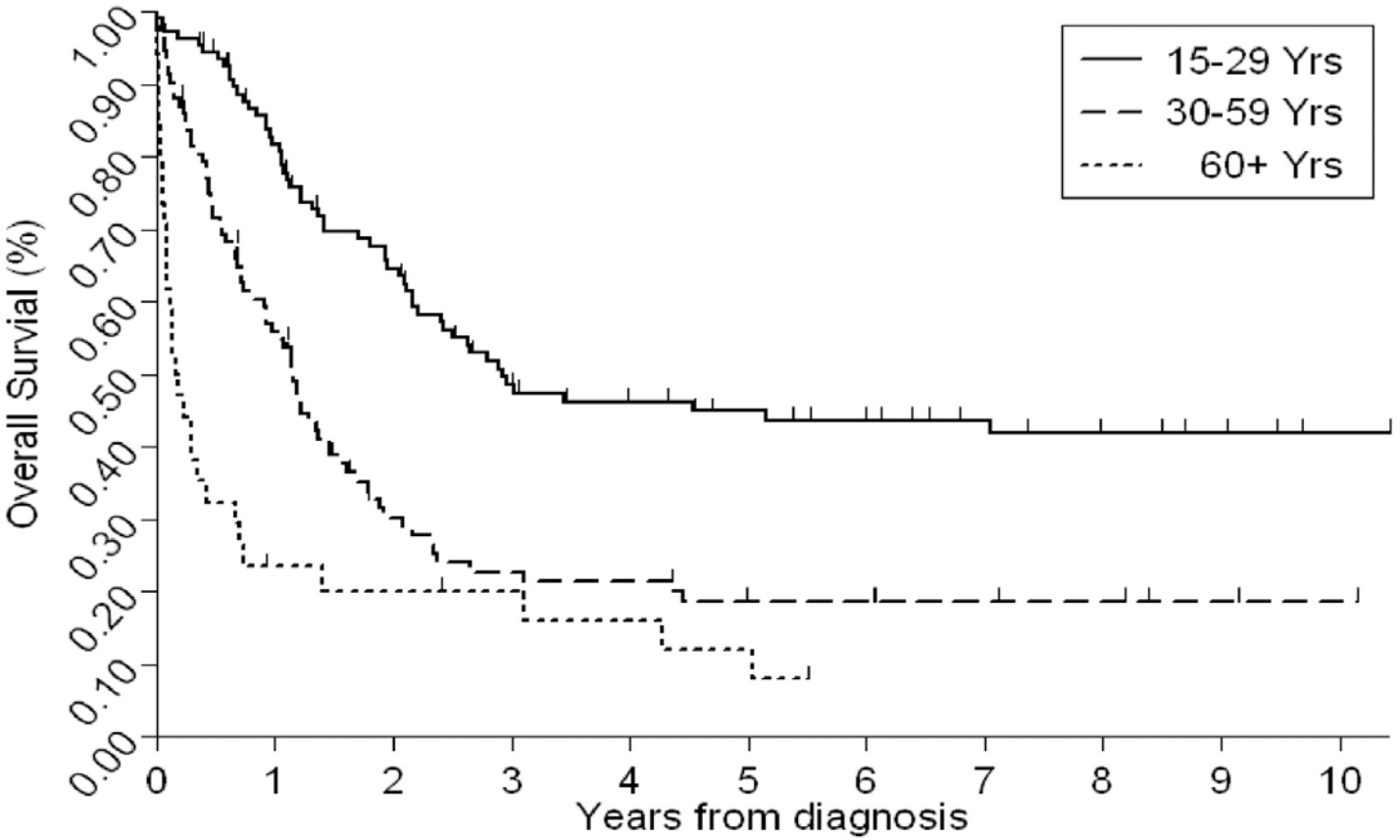
Pui C.-H., Jeha S. Nature Rev Drug Discovery 2007; 6:149-165

Factores pronósticos

- **Bien establecidos**
  - **Edad** (>30a, >55a)
  - **Leucocitos**
    - >$30x10^9$/L (línea B)
    - >$100x10^9$/L (línea T)
  - **Alteraciones citogenéticas**
    - t(9;22)(*BCR-ABL*)
    - t(4;11)(*MLL-AF4*)
  - **Respuesta lenta al tratamiento**
    - Mala respuesta citológica precoz
    - Lentitud obtención RC
- "**Nuevos**"

  Fenotipo inmunológico Pro-B, Pre-T, tímica madura
  Cariotipo complejo
  CD20+ en LAL Ph-
  Enfermedad residual

OS of adults with ALL by age at diagnosis



Number at risk

15-29 Yrs	108	83	63	44	38	34	30	26	23	21	18
30-59 Yrs	92	50	24	18	17	13	13	11	10	8	7
60+ Yrs	34	7	6	5	4	3	1	1	1	1	1

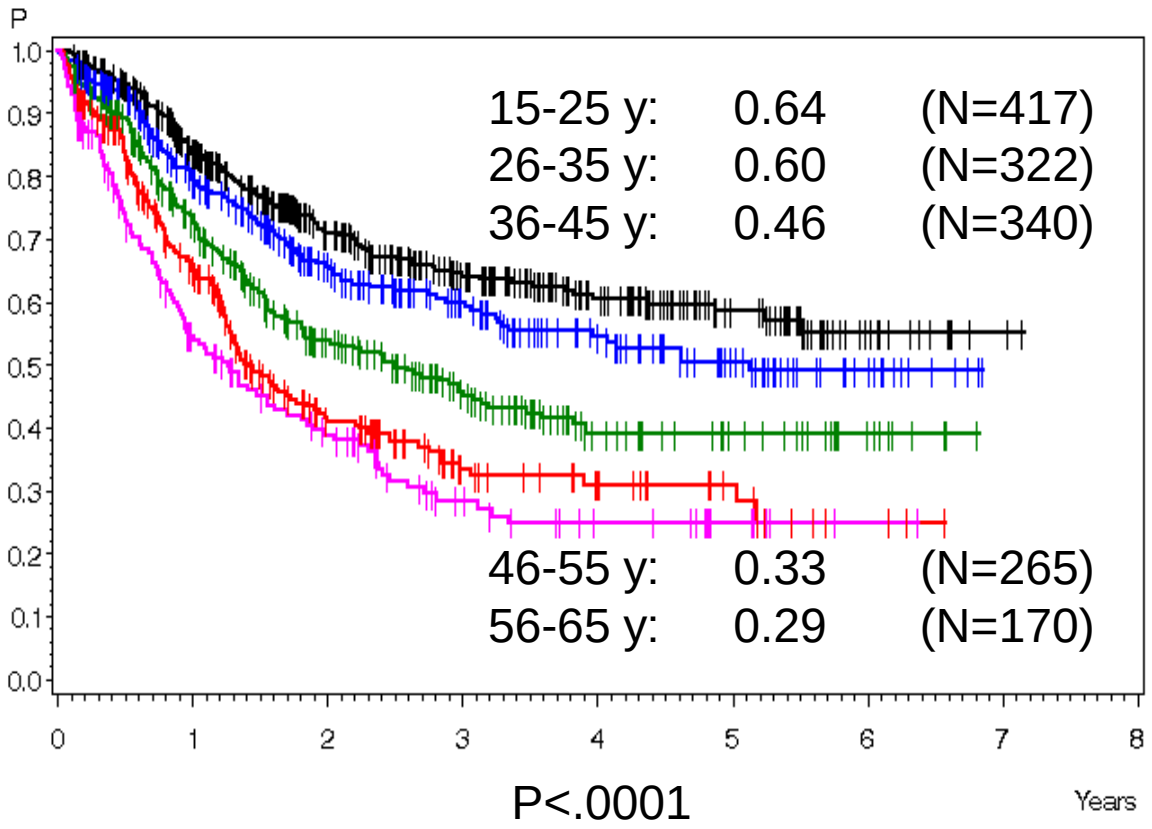
Moorman, A. V. et al. Blood 2010;115:206-214

Age is the Strongest Prognostic Factor in ALL

Results of Induction

Age	CR	ED
26-35	86%	4%
36-45	84%	6%
46-55	78%	9%
56-65	76%	14%
P<.0001		

Overall Survival

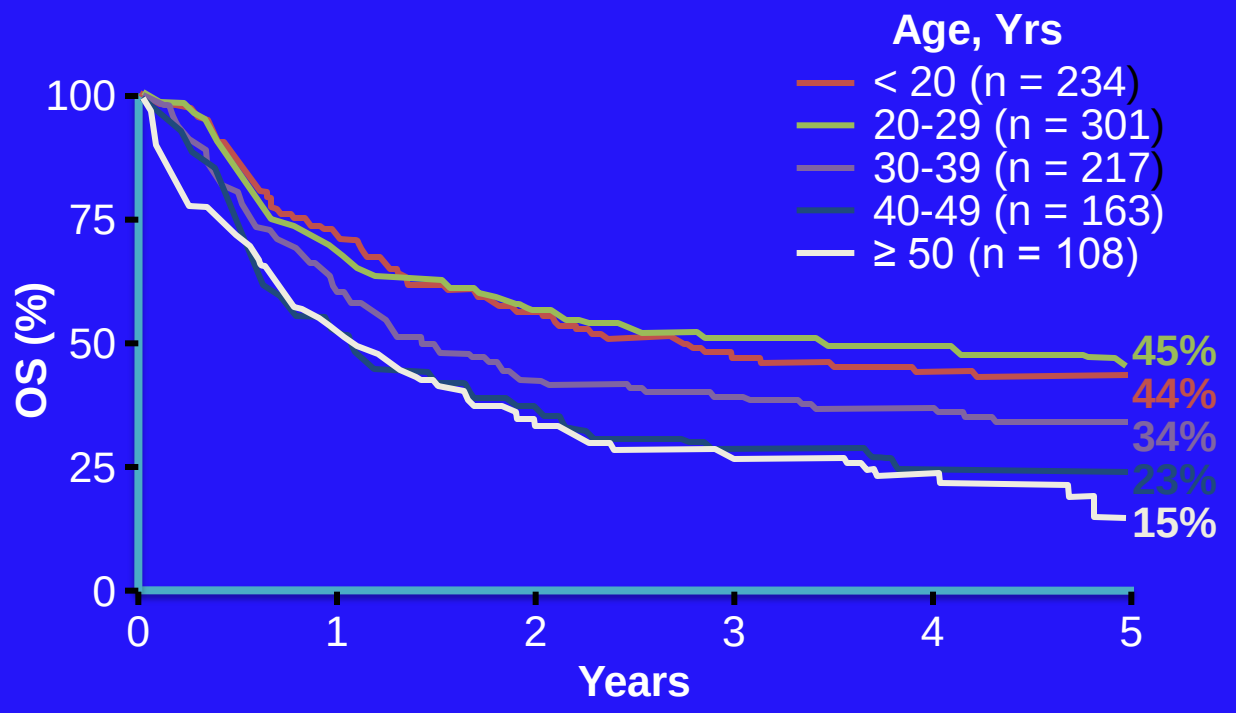


P<.0001

Courtesy of N Gökbuget

Impact of age in ALL patients when treated on standard adult protocols

- UKALLXII/ ECOG2993 study (N = 1521)
  - Survival decreases with age; 35 years identified as significant cutoff point ($P < .001$)



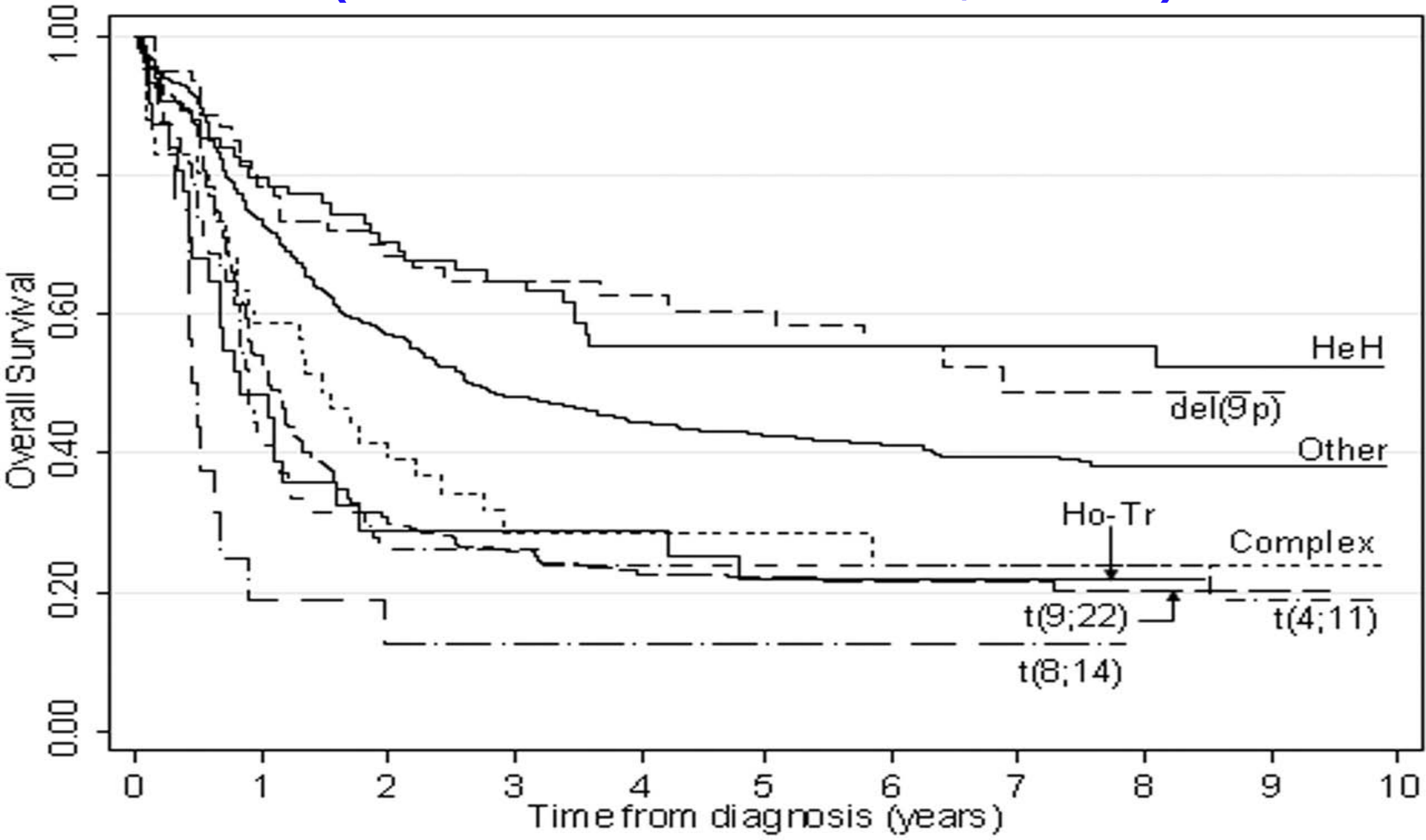
Rowe JM, et al. Blood. 2005;106:3760-3767

Survival in adult ALL Has Improved in All Age Groups Except the Oldest Patients

5-Yr Relative Survival*				
Age Range,% ± SE	1980-1984	2000-2004	Increase, %	*P* Value
15-29 yrs	33.7 ± 3.5	53.6 ± 3.2	19.9	< .0001
30-44 yrs	20.2 ± 4.8	34.3 ± 3.9	14.1	.002
45-59 yrs	10.3 ± 4.9	24.3 ± 3.4	14.0	.0002
> 60 yrs	8.4 ± 3.4	12.7 ± 2.9	4.3	.48

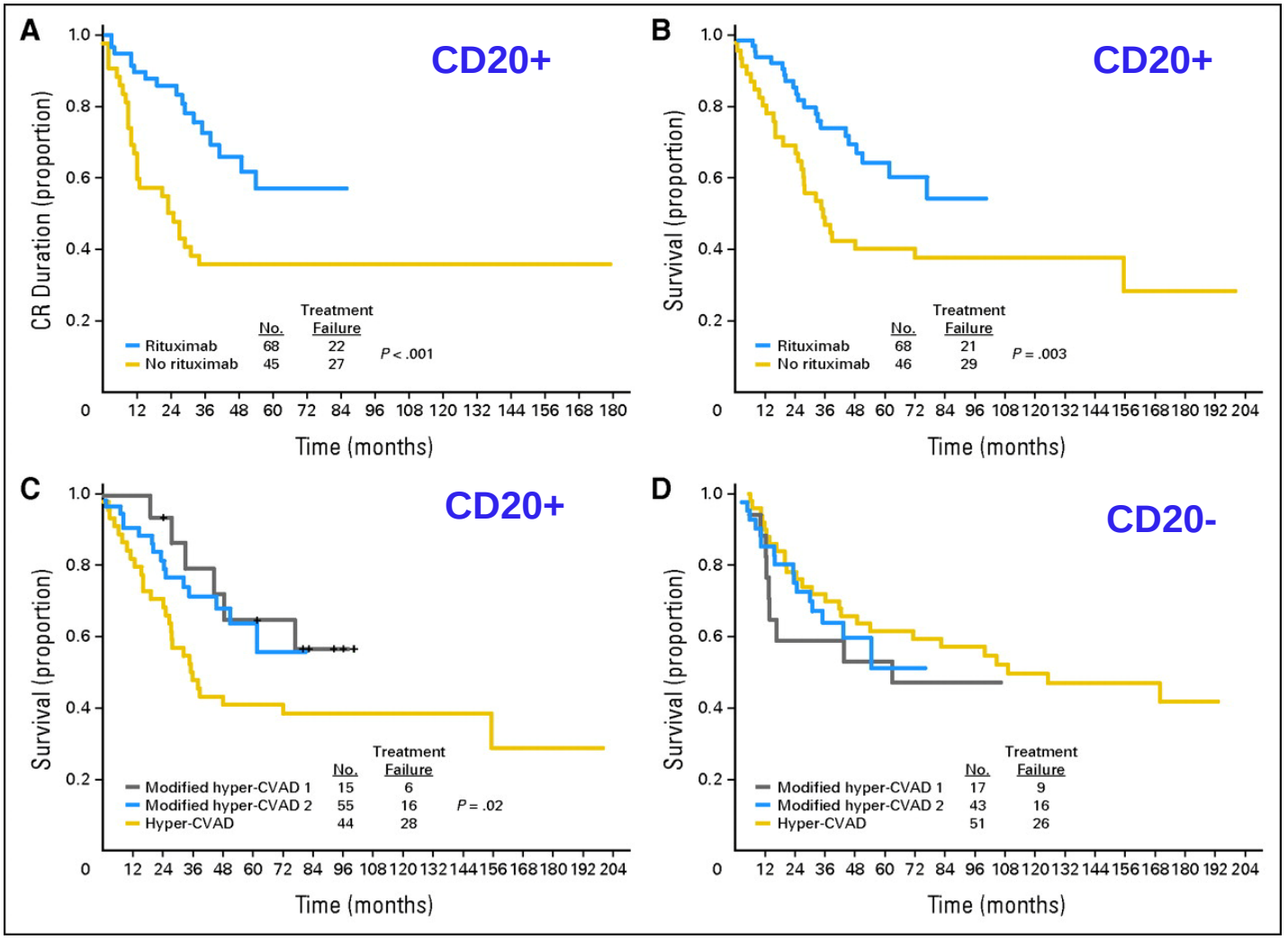
Pulte D, et al. Blood. 2009;113:1408-1411.

Genetics and prognosis in adult ALL.
(MRC UKALLXII/ECOG 2993, n= 1522)



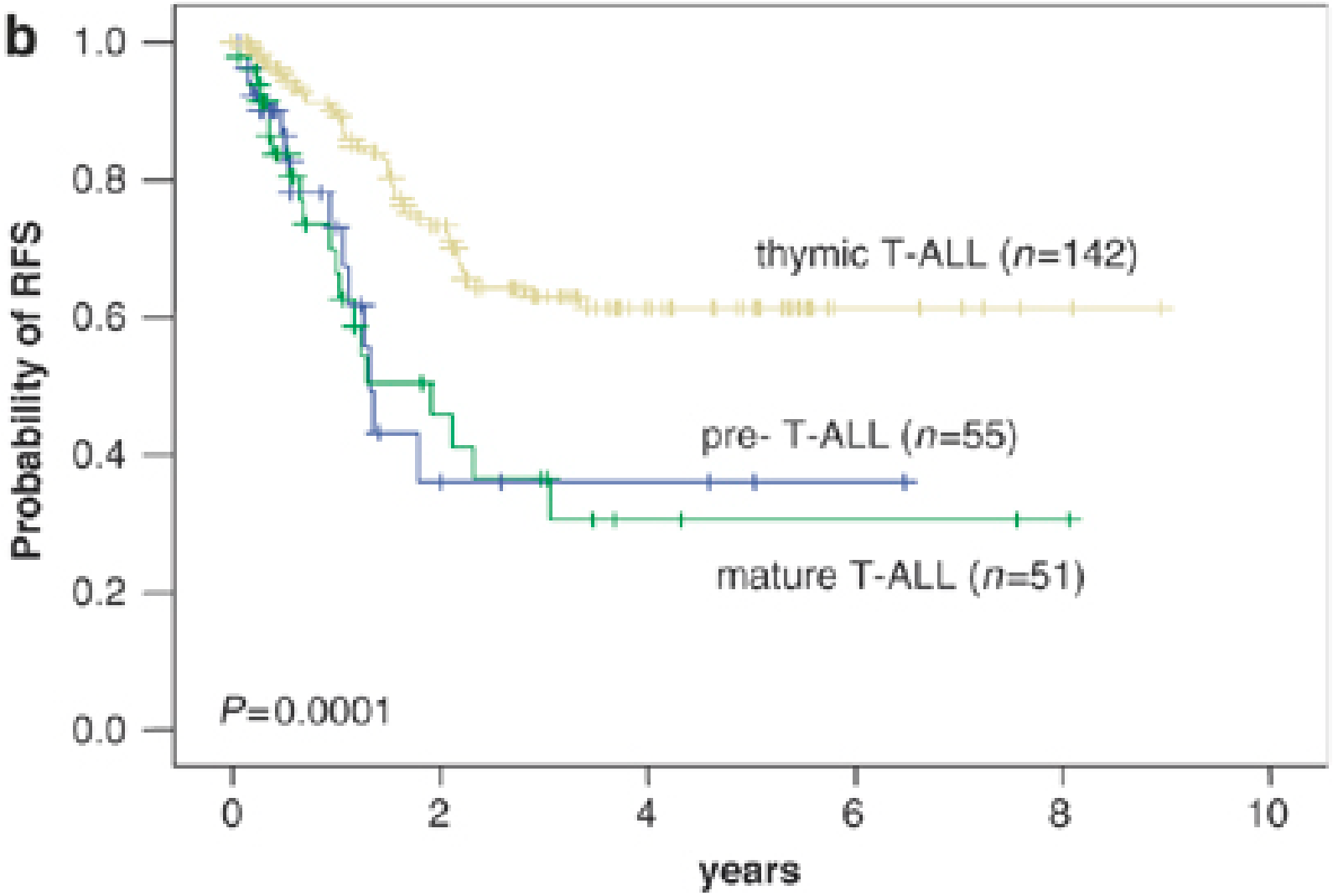
Moorman, AV. et al. Blood 2007; 109:3189-97

Prognostic value of CD20 expression in Ph- ALL



Thomas, D. A. et al. J Clin Oncol 2010; 28:3880-3889

T-ALL: prognostic value of differentiation stage/phenotype

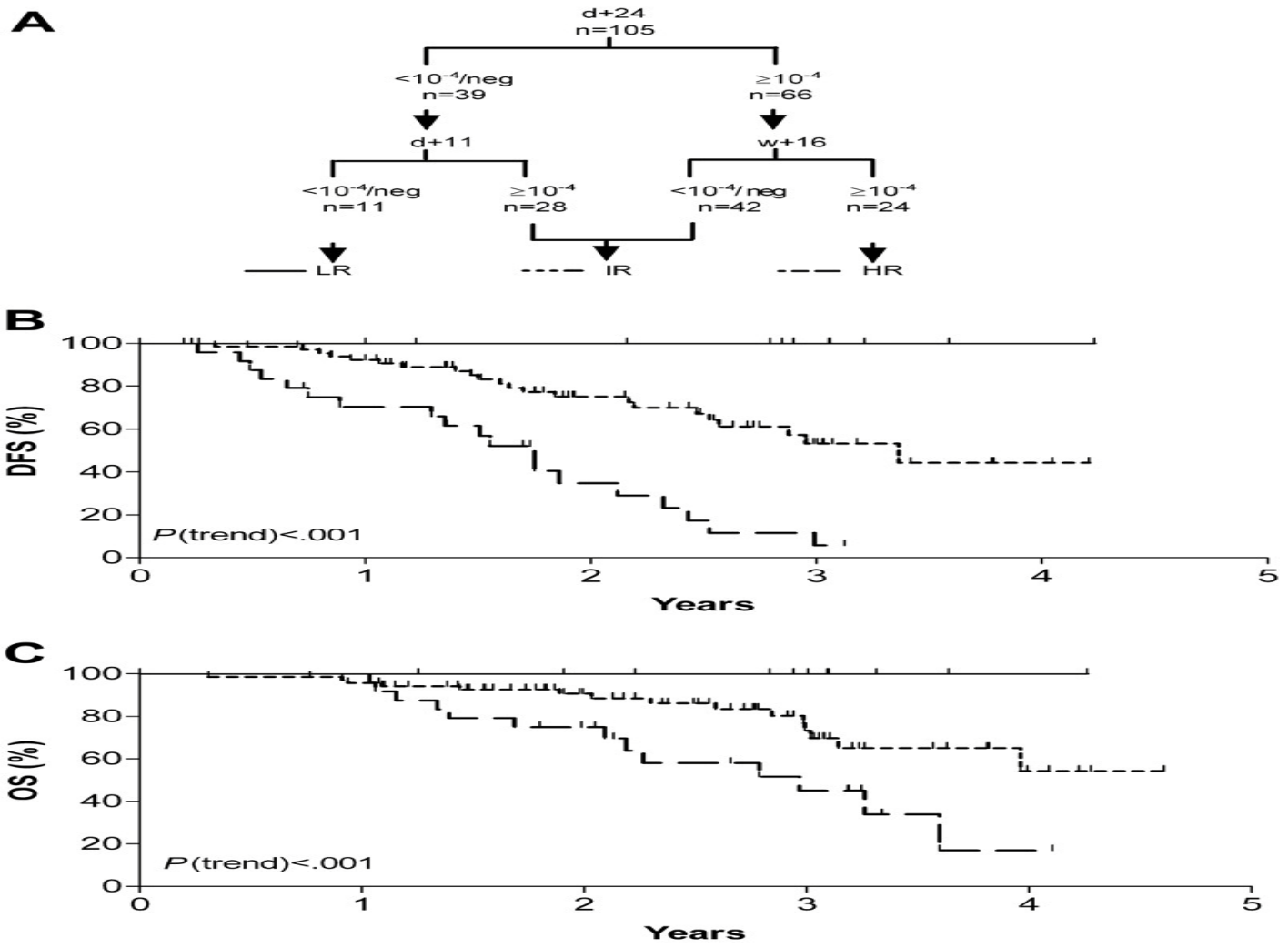


GMALL protocols

Baak U et al, Leukemia 2008

MRD and Prognosis in Adult ALL

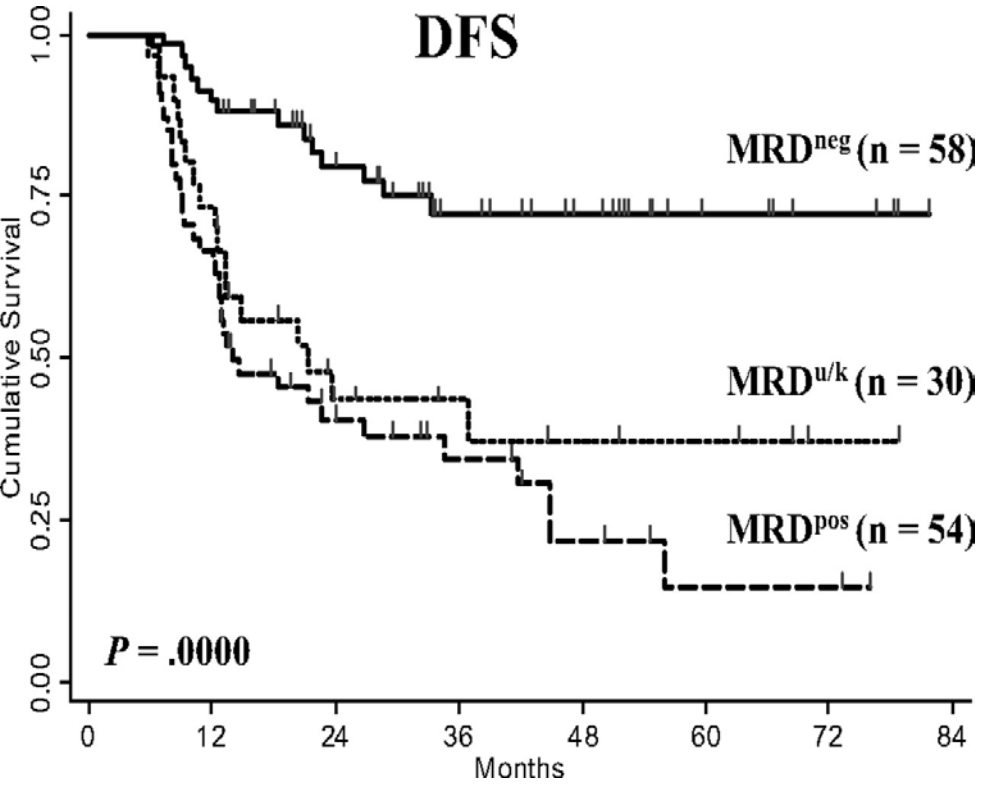
GMALL 07/03. Standard-risk ALL



Bruggemann, M. et al. Blood 2006;107:1116-1123

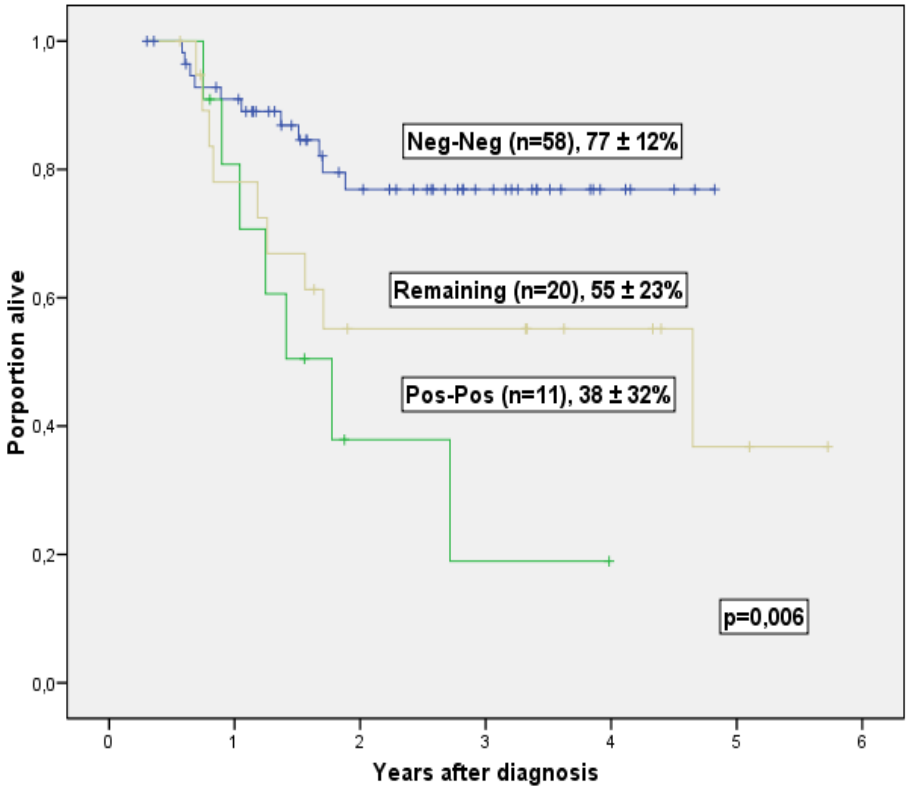
Aclaramiento ER y pronóstico en LAL adulto

RE y AR



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

Solo AR

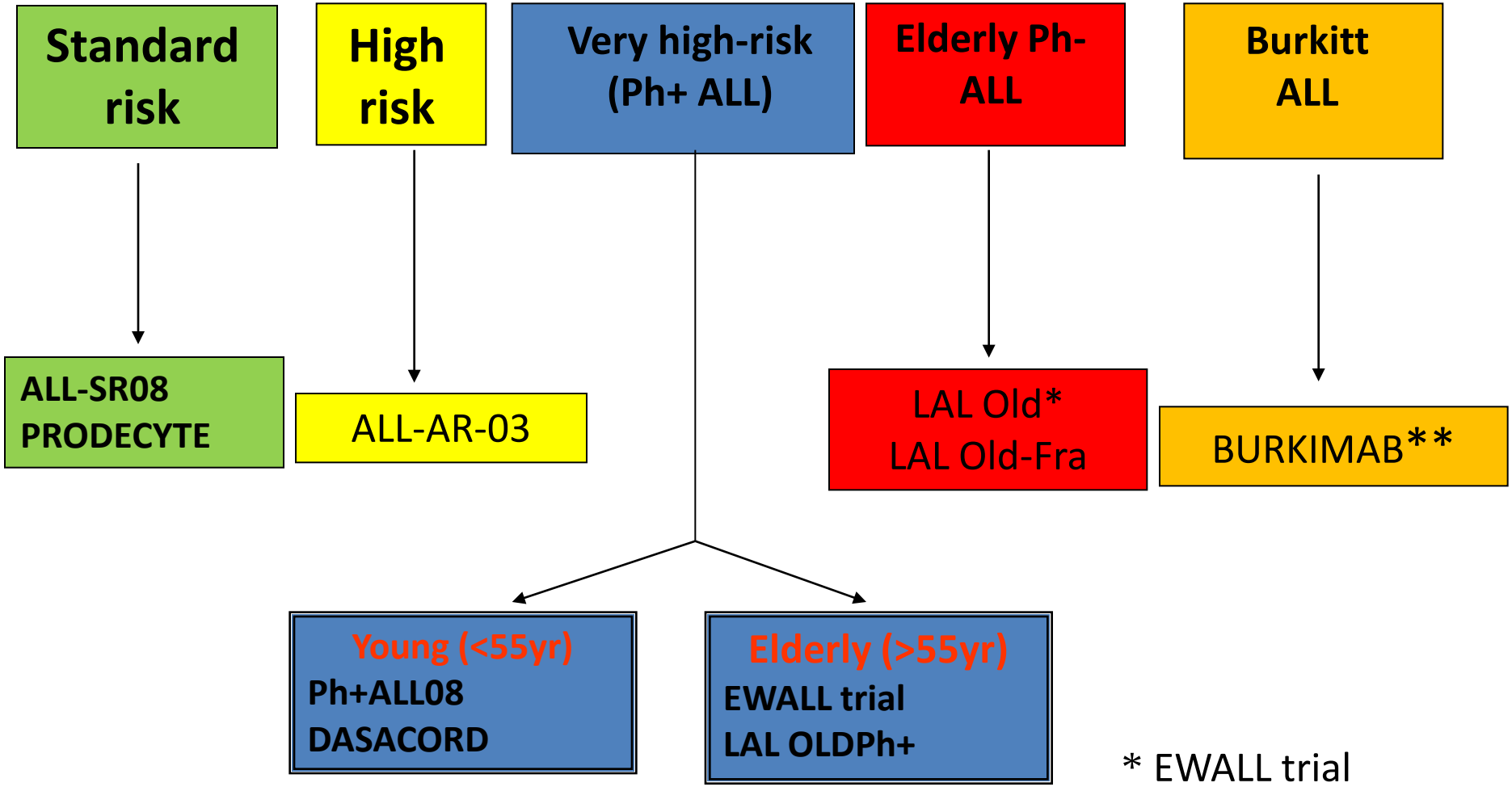


JM Ribera et al, ASH 2009, oral presentation

LAL adulto. Tratamiento

- **Tratamiento adaptado al riesgo**
  - Estándar
  - Alto
- **Tratamiento en subtipos específicos**
  - LAL Ph+
  - LAL Burkitt-*like*
- **Tratamiento en poblaciones seleccionadas**
  - Adolescentes y adultos jóvenes
  - Edad avanzada
- **Nuevos agentes terapéuticos**

Spanish PETHEMA protocols in adult ALL
Front line

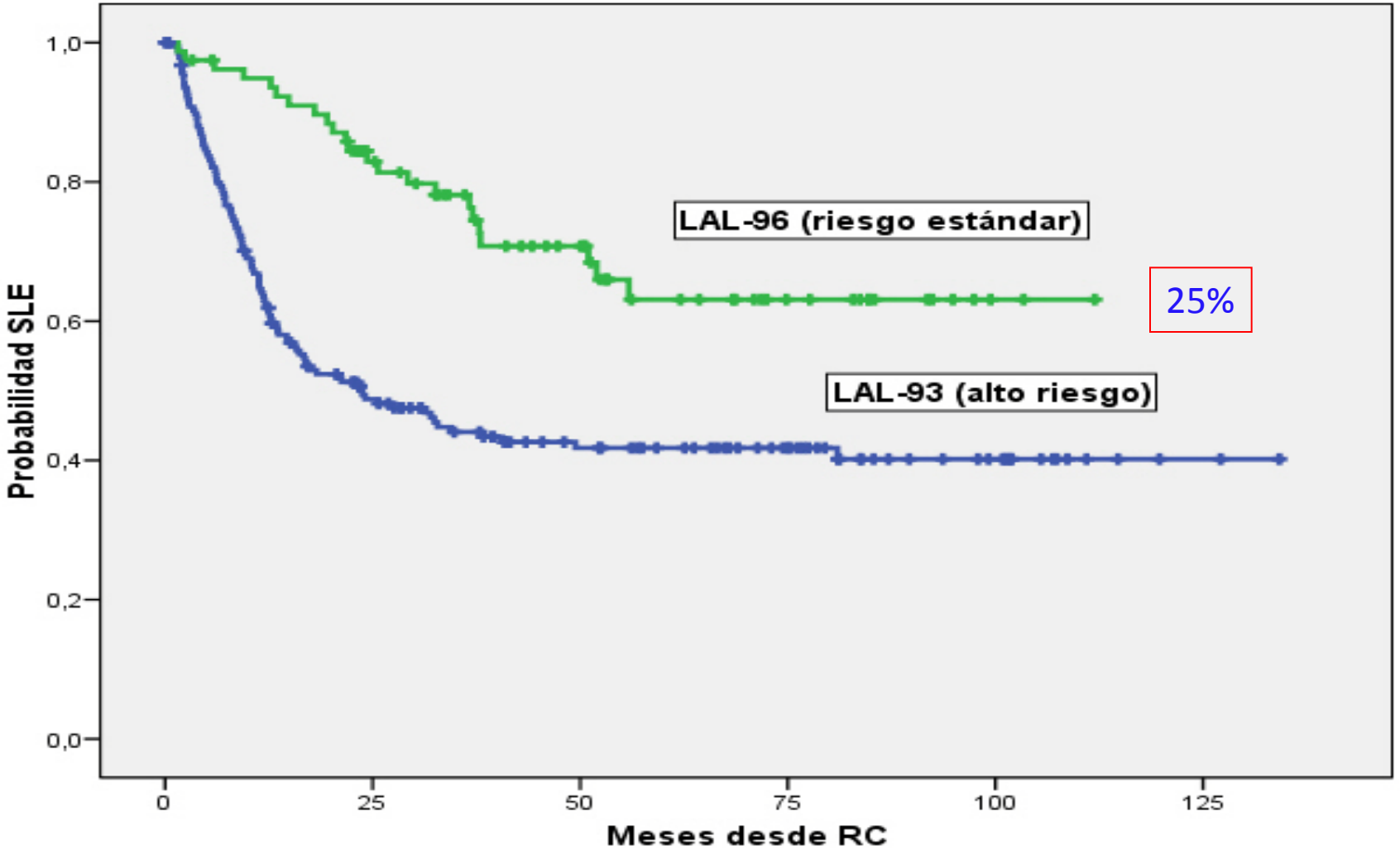


* EWALL trial

**Joined with GMALL

LAL del adulto. Tratamiento adaptado al riesgo

Protocolos PETHEMA



LAL riesgo estándar

Edad <30 a, leucocitos <30x10^9/L, no t(9;22), no t(4;11)

Respuesta estándar al tratamiento

↓

Protocolos de base pediátrica

AL in AYA. Retrospective comparative studies "Pediatric" vs "adult" treatments

Country	Protocol	Age	N	CR(%)	5yr.EFS(%)
USA	CCG(P)	16-21	197	96	64
	CALGB(A)	16-21	124	93	38
France	FRALLE93(P)	15-20	77	94	67
	LALA94 (A)	15-20	100	83	41
Holland	DCOG (P)	15-18	47	98	69
	HOVON (A)	15-20	44	91	34
UK	ALL97 (P)	15-17	61	98	66
	UKALLXII(A)		67	94	49
Italy	AIEOP (P)	14-18	150	94	80
	GIMEMA (A)		95	89	71(2yr)
Sweden	NOPHO-92(P)	10-18	144	99	66
	Adult (A)	15-25	99	90	42
Finland	NOPHO (P)	10-25	128	96	67
	ALL (A)		97	97	60

Reviewed in: Ribera JM. Hematol Oncol Clin North Am 2009; 23:1033-42

Major differences in pediatric vs. adult protocols

- **Higher dose of essential drugs**
  - Up to 3x vinca alkaloids
  - Up to 5x prednisolone
  - Up to 20x asparaginase
- **Less use of myelosuppressive drugs**
  - eg, anthracyclines, cyclophosphamide, cytarabine
- **Less use of BMT**
  - BMT only recommended by pediatricians for very high-risk ALL
- **Less delays between therapy elements**
  - Time to treatment following initial CR was 2 days in pediatric practice vs. 7 days in adult practice (P = .002)

Prospective studies on therapy of ALL in AYA

Group-Protocol	Age	N	CR(%)	EFS (%)
DFCI 91-01,95-01	15-18	51	94	78
GRAALL-03*	15-45	172	95	58
PETHEMA ALL96**	15-18	35	94	60
	19-30	46	100	63
DFCI	18-50	74	82	72
Toronto-Modified DFCI	18-60	85	89	71
FRALLE 93 HR-derived***	18-55	40	90	72 (OS)
Toronto-Modified DFCI****	17-64	32	84	83 (OS)

*Increase of 8.6-fold, 3.7-fold and 16-fold in cumulated doses of PDN, VCR and L-ASP compared to ALL-94 protocol. Better results in patients up to 45 yr

** No differences between adolescents and young adults

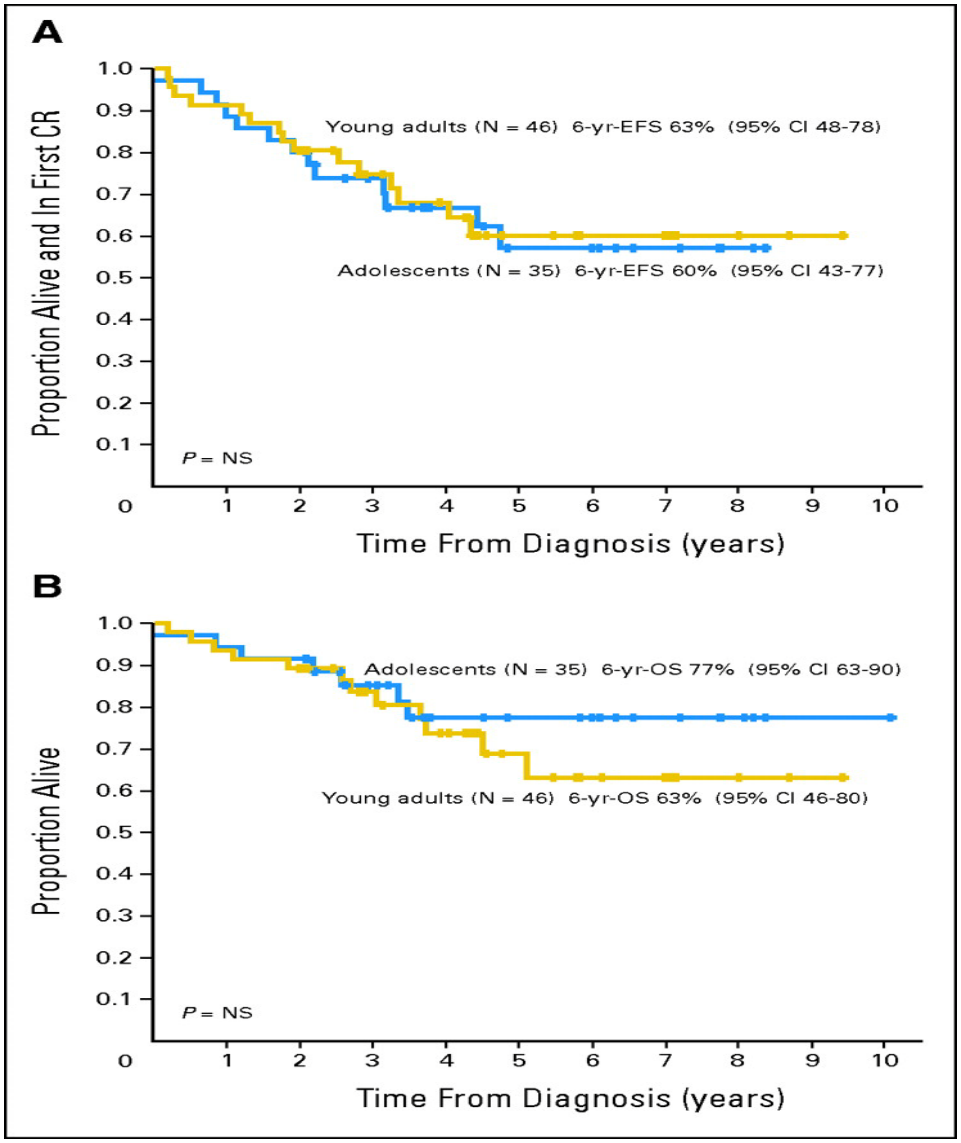
***Better results in patients up to 40 yr

**** Only T-ALL

Reviewed in: Ribera JM. Hematol Oncol Clin North Am 2009; 23:1033-42

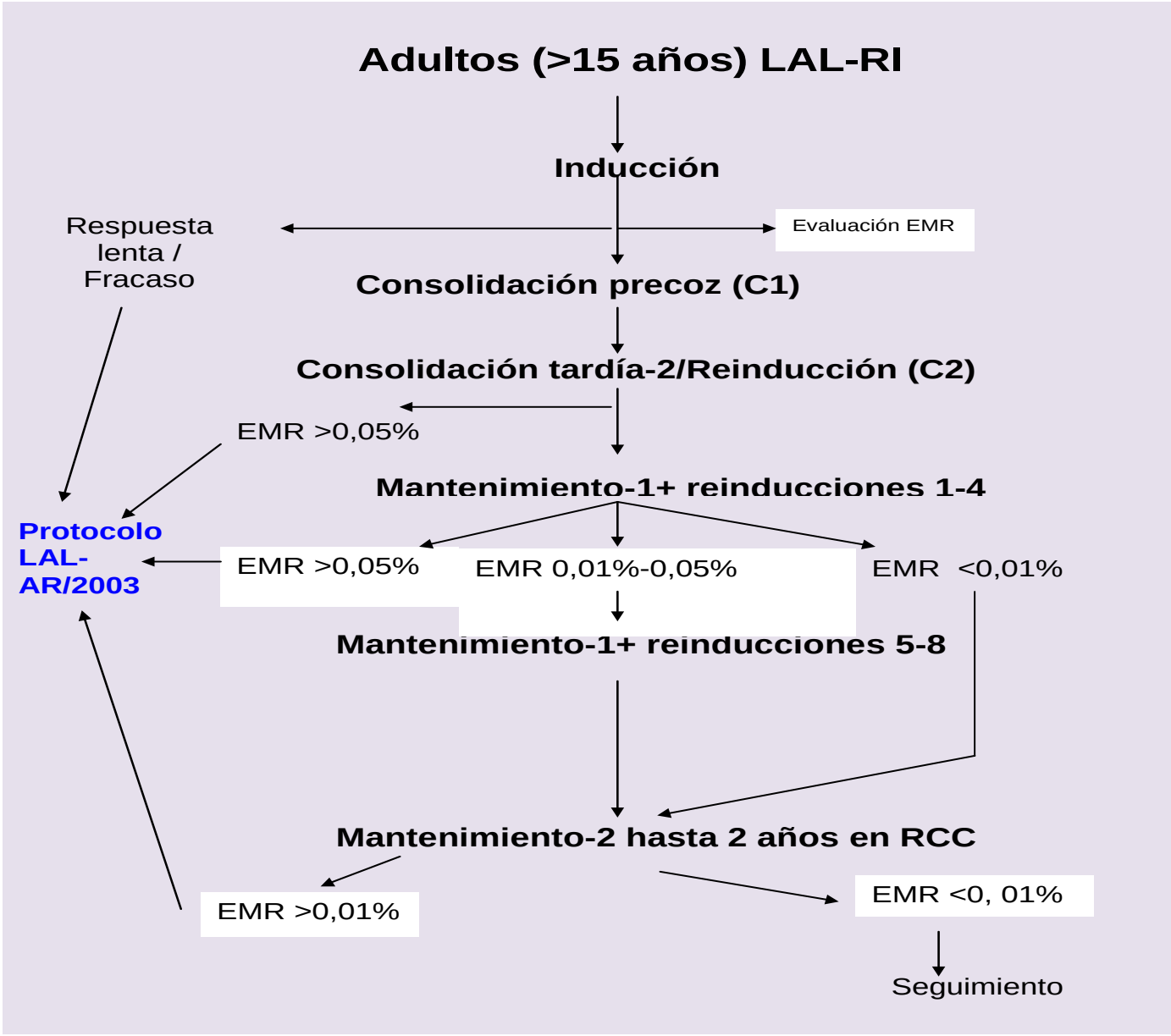
PETHEMA ALL-96

Adolescents 15-18 yr.
Young adults: 19-30 yr.

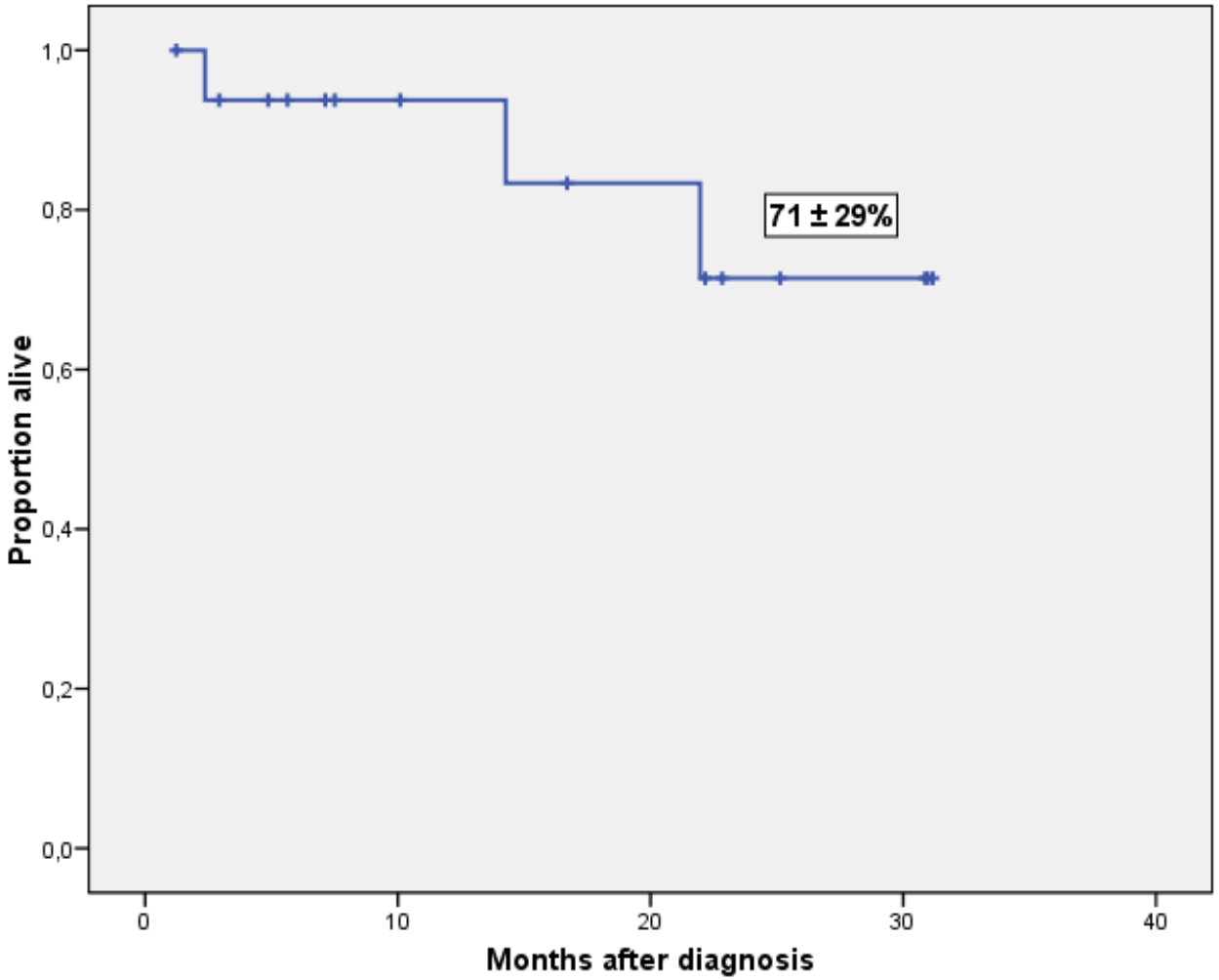


Ribera, JM. et al. J Clin Oncol 2008; 26:1843-1849

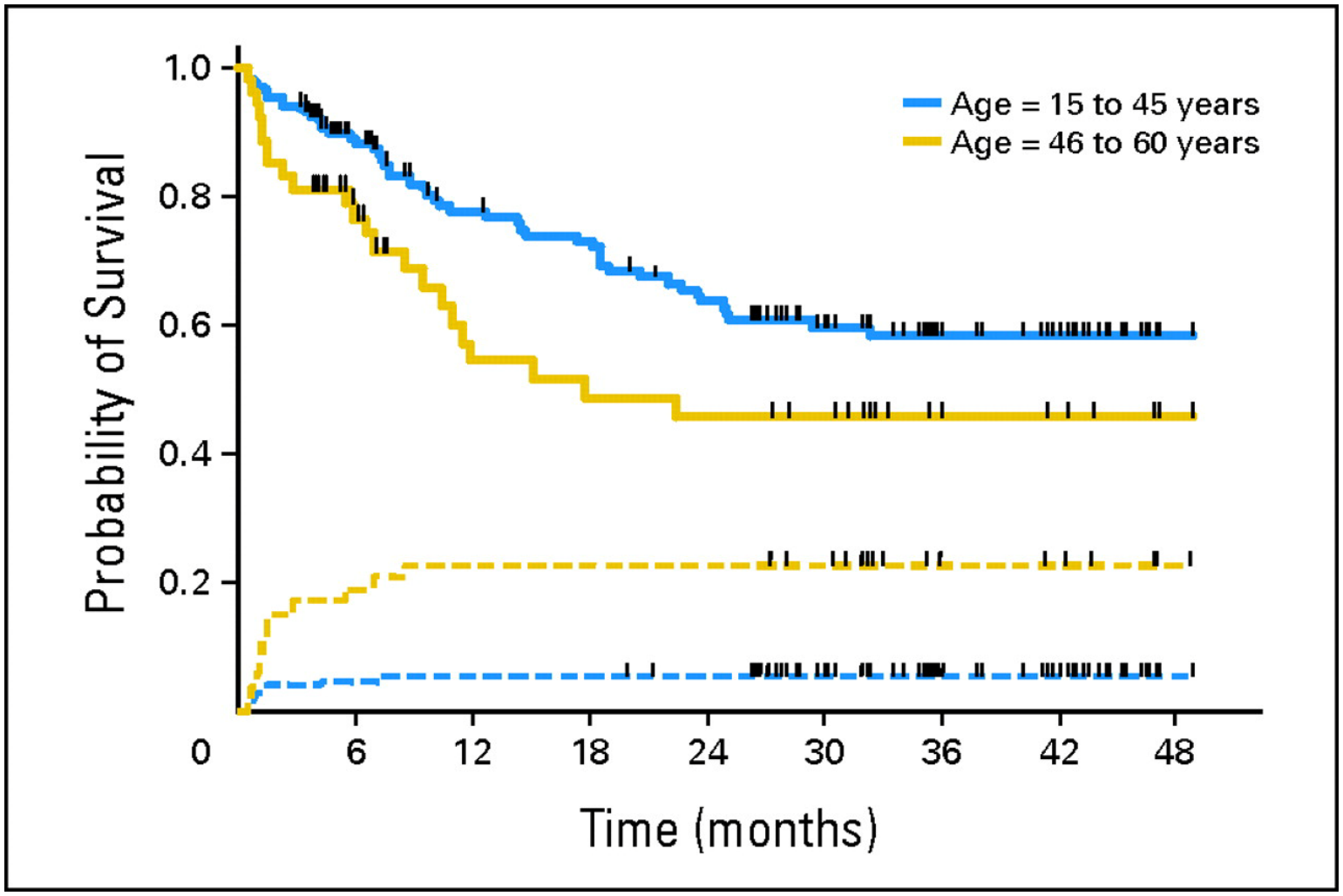
LAL riesgo estándar. PETHEMA RI-08



SG (n=17)


1,0
0,8
0,6
0,4
0,2
0,0
Proportion alive
71 ± 29%
0
10
20
30
40
Months after diagnosis

How far can we go with pediatric protocols?

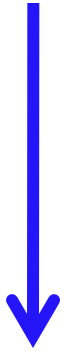


Huguet, F. et al. J Clin Oncol; 27:911-918 2009

LAL riesgo elevado, Ph-negativa

Edad >30 a, leucocitos >30x10^9/L, t(4;11)

Respuesta lenta al tratamiento



Quimioterapia

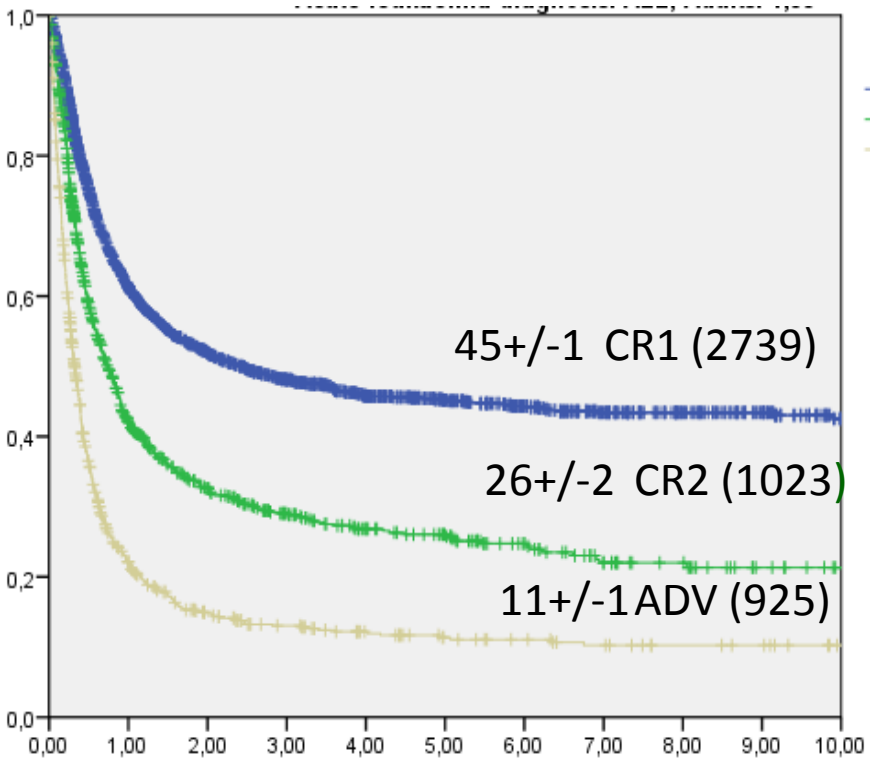
Trasplante progenitores hematopoyéticos

Results of adult ALL trials: induction therapy

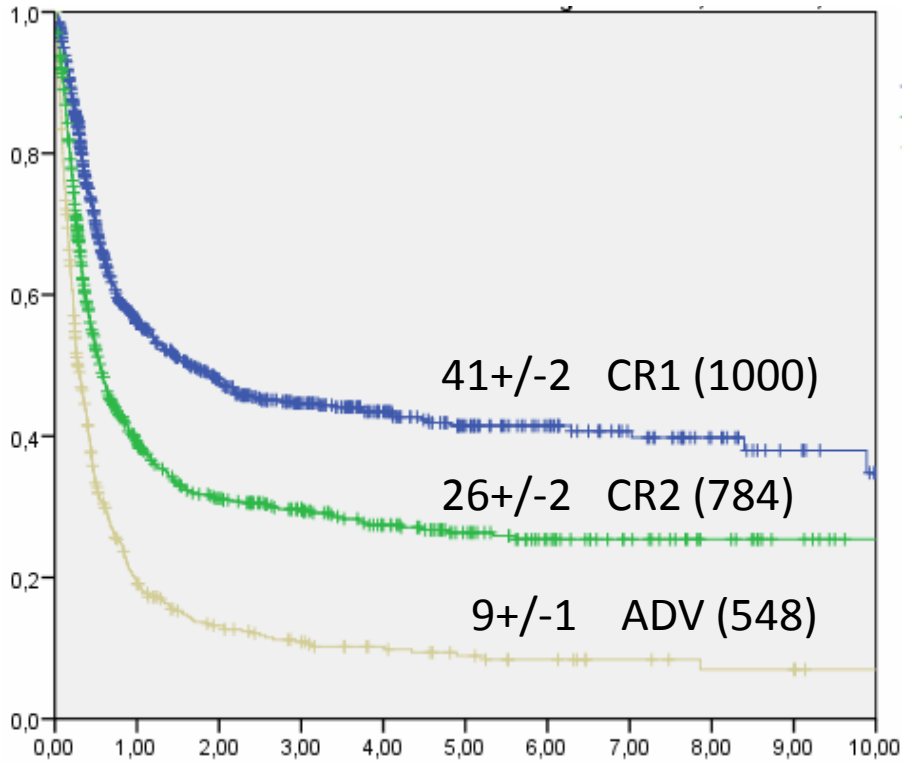
Study	*Year*	*n*	*Age*	*Drugs*	*CR rate*
GMALL 02/84	1993	562	28	V,P,A,D,C, AC,M,MP	75%
FGTALL	1993	572	n.r.	V,P,D/R,C, [AM,AC]	76%
MRC XA	1997	618	>15	V,P,A,D	82%
PETHEMA	1998	108	20	V,P,D,A,C	86%
CALGB	1998	198	35	V,P,D,A,C	85%
MDACC	2000	204	39	V,DX,A,D,C	91%
GMALL 05/93	2001	1163	35	V,P,D,A,C,AC,MP	83%
Lombardia	2001	121	35	V,P,A,[C]	84%
Sweden	2002	153	42	V,BX, HDAC,C,D,AM	86%
GIMEMA	2002	794	28	V,P,A,D,C [HDAC,Mi]	82%
PETHEMA/ALL-93	2005	222	27	V,P,D,A,C	82%
MRC/ECOG	2005	1521	<35	V,P,A,D,C,AC,MP	91%
		6236			**84%**

Outcome after alloHSCT from for ALL: ALWP registry 1994 - 2008

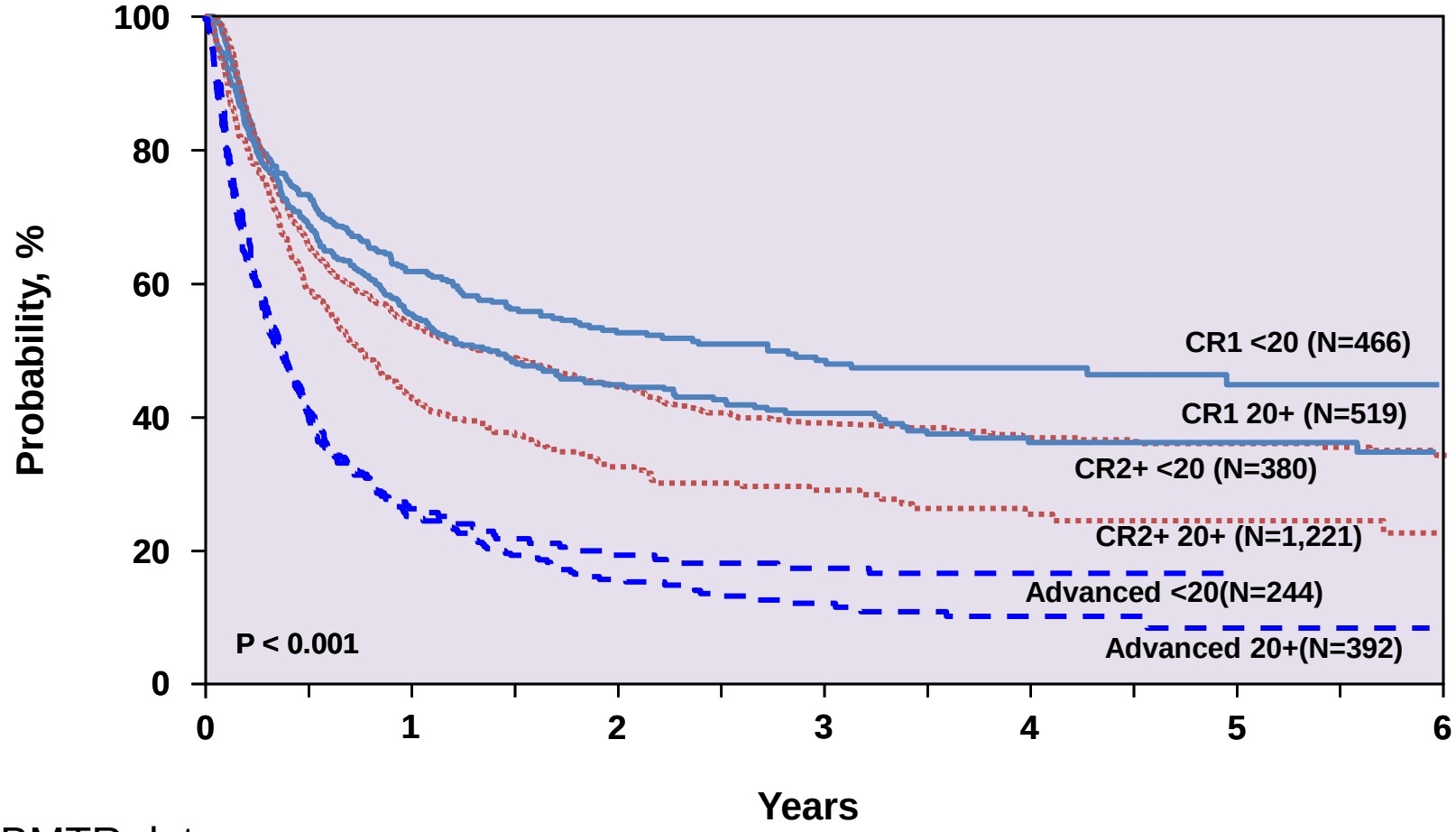
HLA-identical sibling (N=4687)



Matched unrelated donor (N=2332)

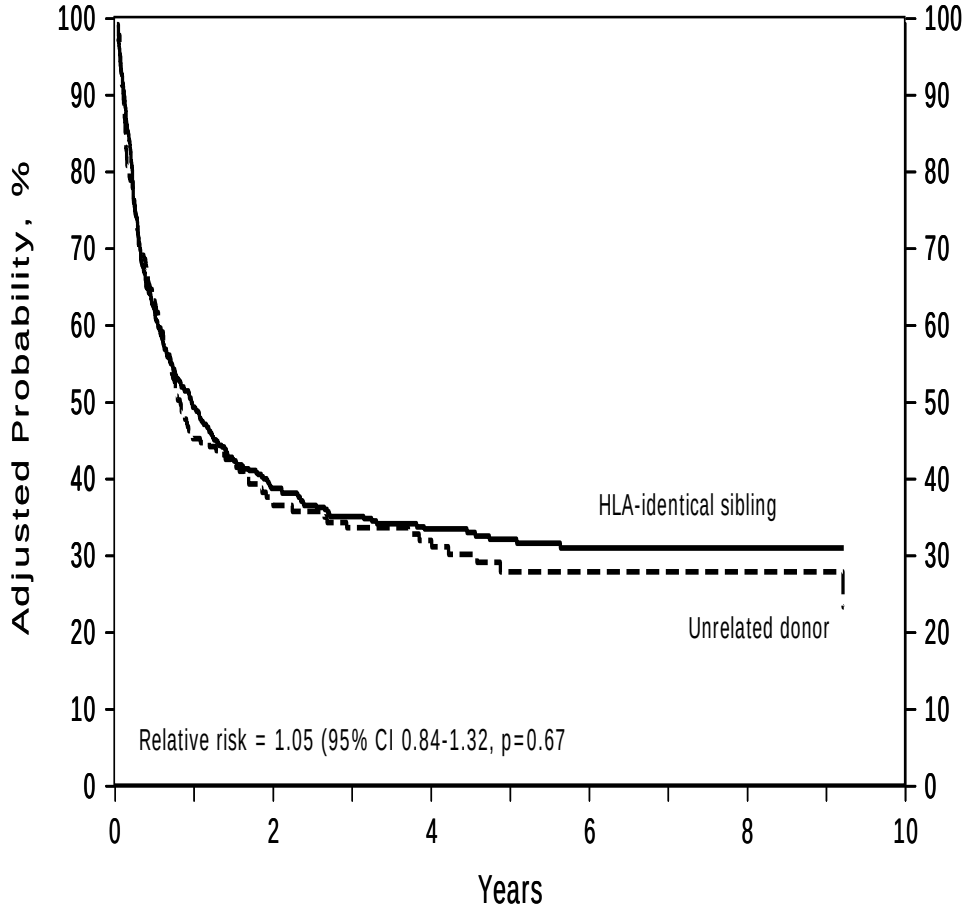


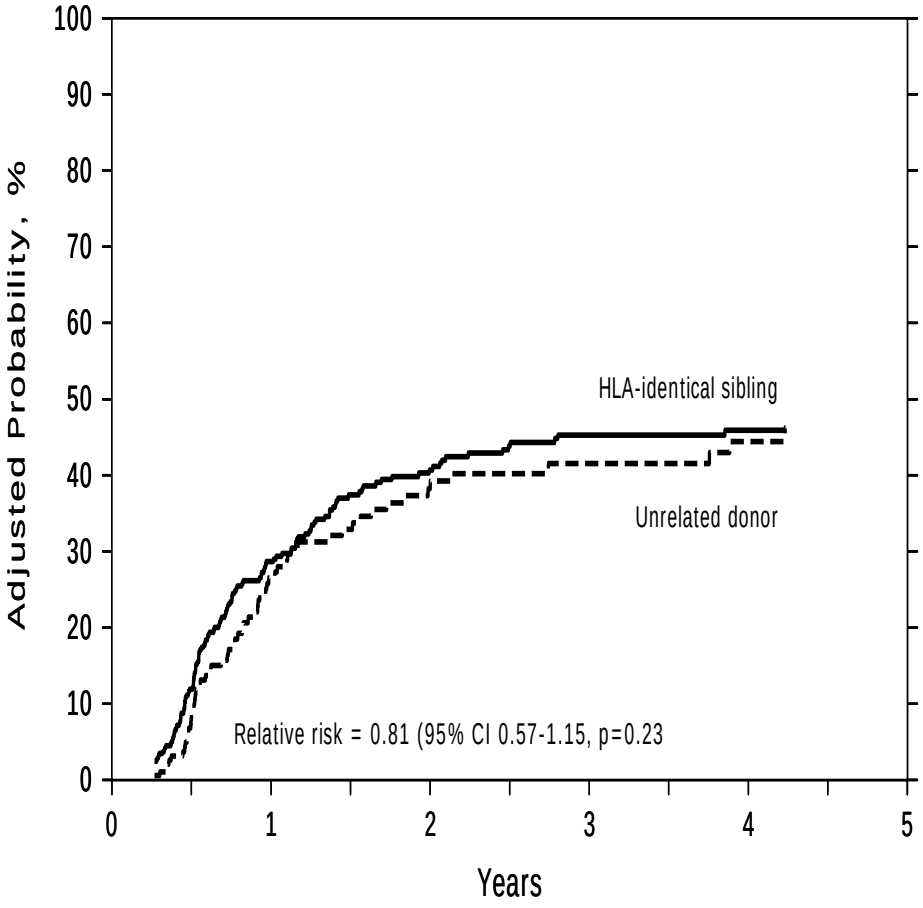
Probability of Survival after Unrelated Donor Transplants for ALL, 1998-2004
- by Age and Disease Status -



CIBMTR data

Adjusted Leukemia-Free Survival and relapse in ALL





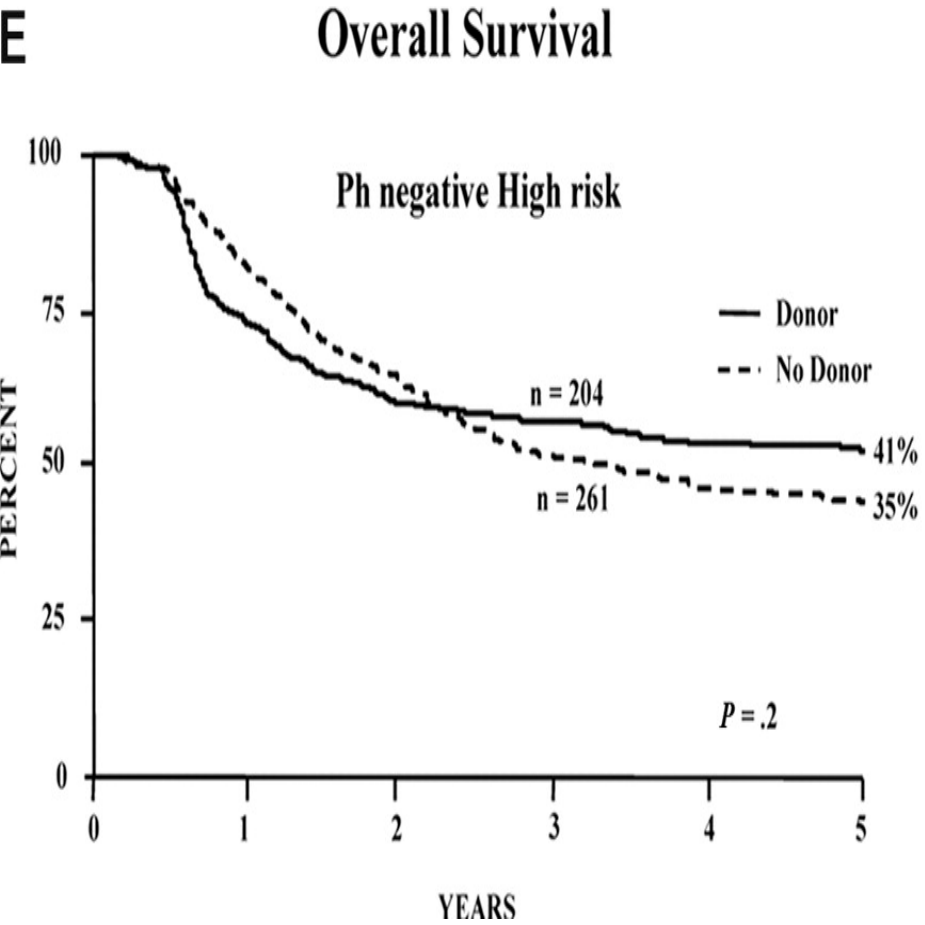
Ringden O, et al. Blood. 2009;113:3110-3118

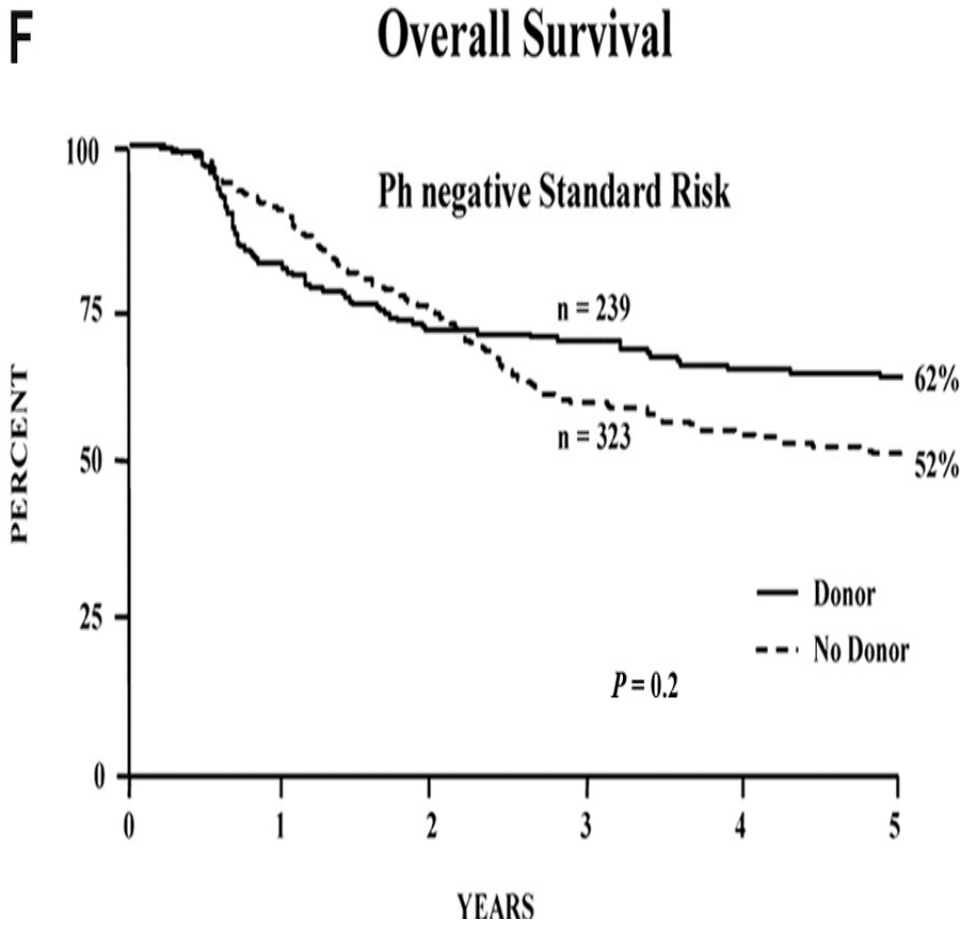
Role of alloHSCT for adult ALL in CR1: comparative prospective studies (donor vs. no donor)

Study	*n*	*Population*	*DFS*	*Surv*
LALA-87	116 vs 141	Adult ALL	45 vs 31%	48 vs 35%
		in high-risk ALL	39 vs 14%	44 vs. 11%
JALSG-93	34 vs 108	Adult ALL	NR	46 vs 40%
LALA-94	100 vs 159	High-risk ALL	45 vs 23%	51 vs 33%
GOELAL02	41 vs 106	High-risk ALL	75 vs 40%	75 vs 33%
EORTC	68 vs 116	Adult ALL	38 vs 36%	41 vs 39%
PETHEMA	84 vs 98	High-risk ALL	40 vs 49%	37 vs 46%
MRC/ECOG	443 vs 558	Adult ALL	50 vs 41%	53 vs 45%
		in high-risk ALL	38 vs 32%	41 vs. 35%

—— *: allo > control*

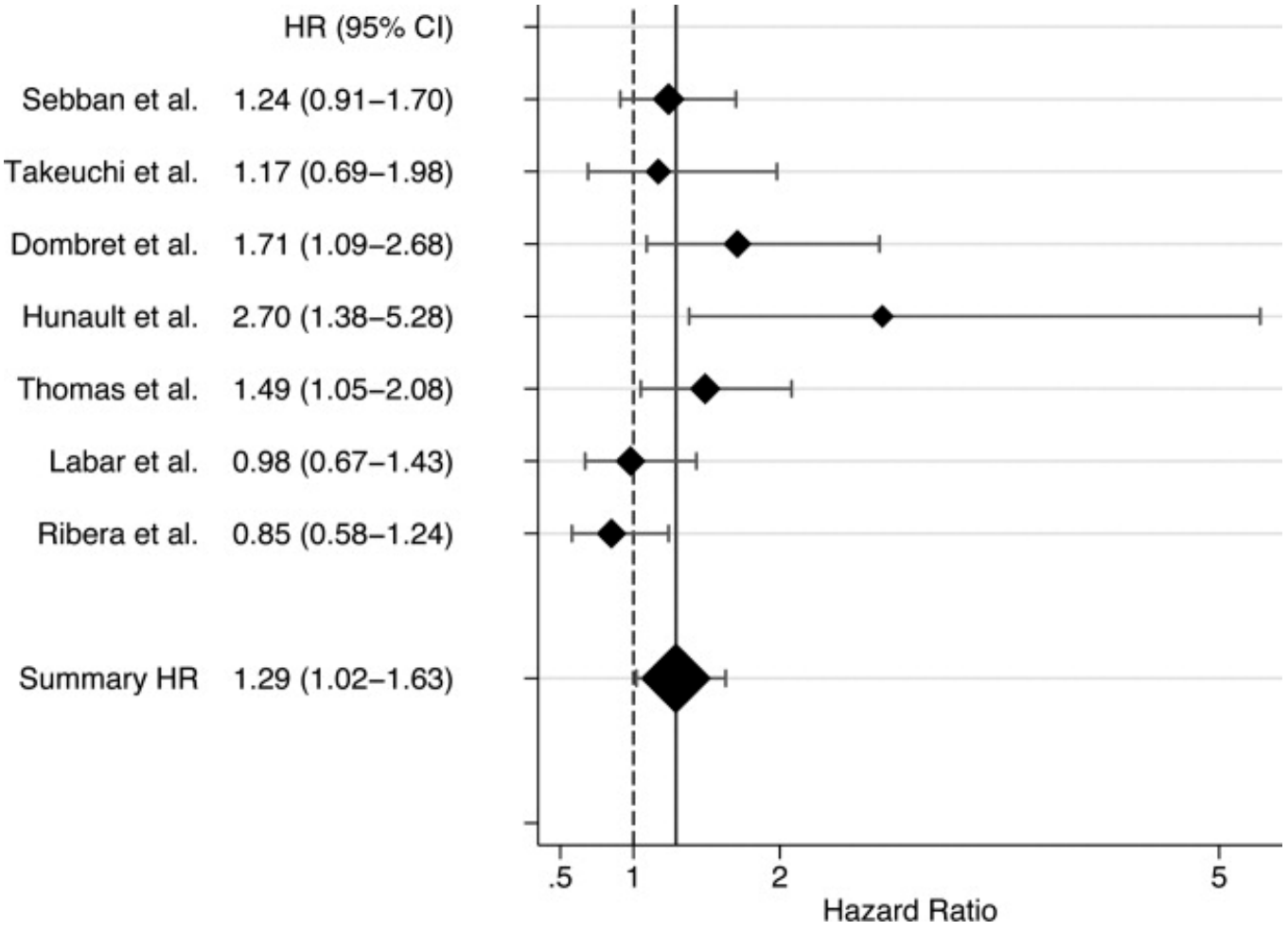
Role of alloHSCT in adult ALL (CR1): better outcome in patients with a matched-related donor (MRC UKALL XII/ECOG E2993)





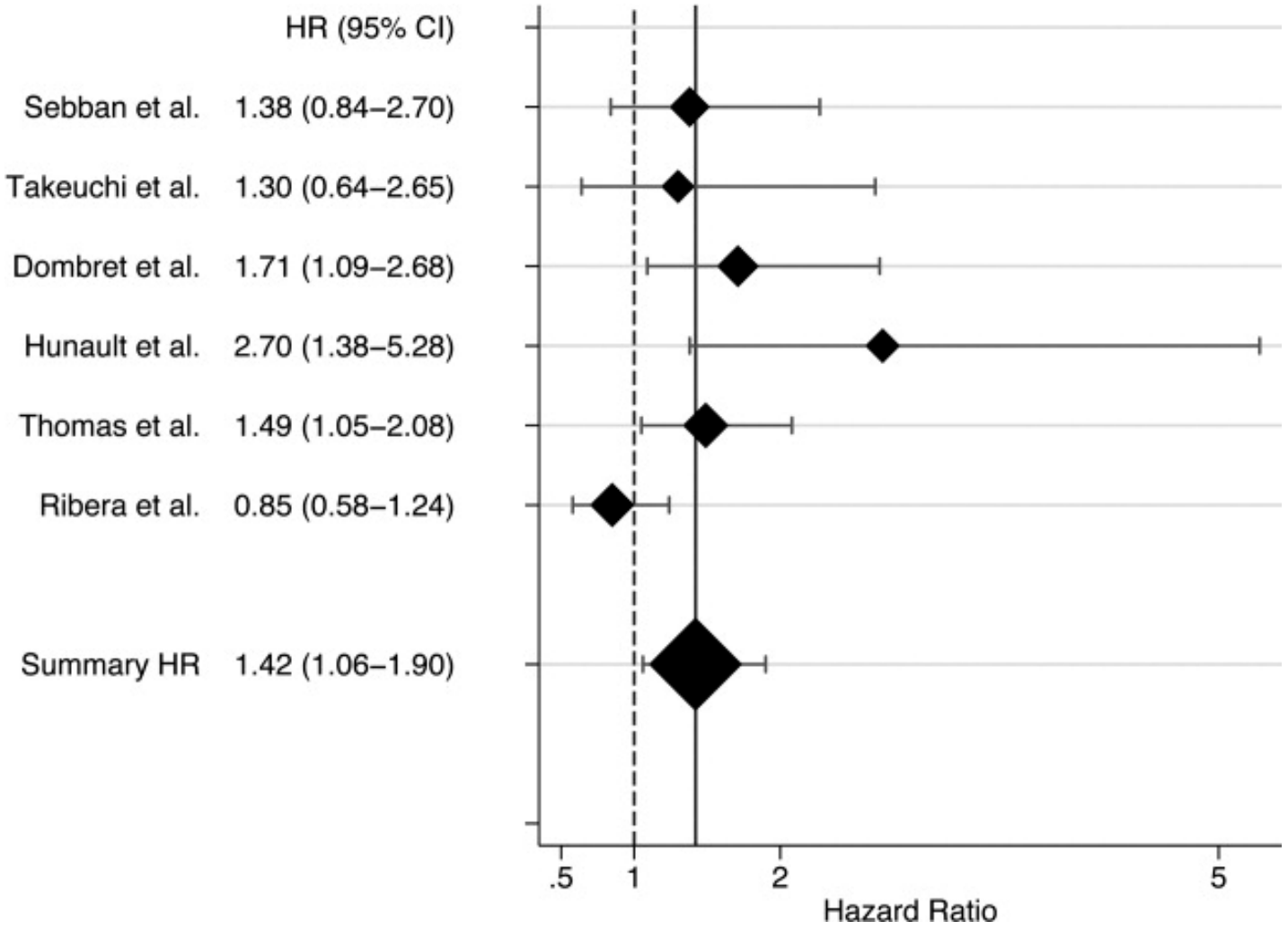
Goldstone et al, Blood 2008

Role of alloHSCT for adult ALL in CR1: a meta-analysis of prospective trials



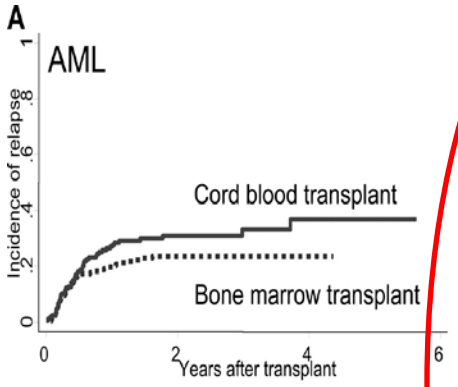
Yanada et al, Cancer 2006

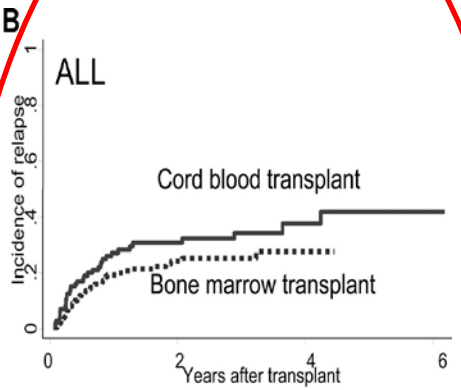
Role of alloHSCT for adult ALL in CR1: high-risk patients

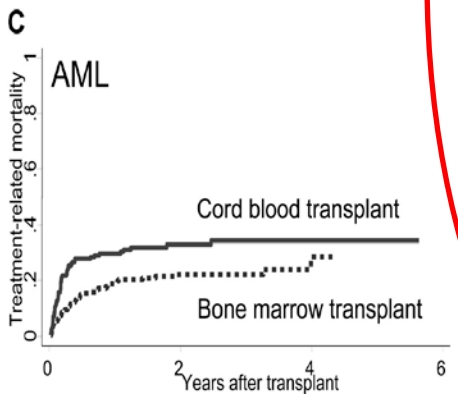


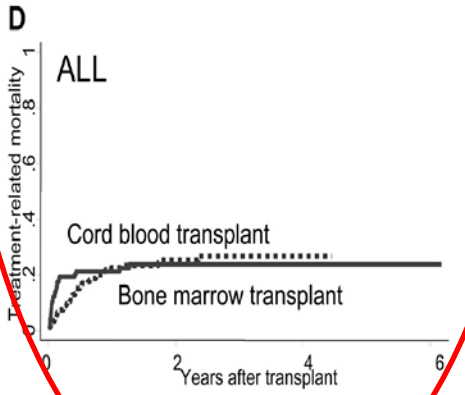
Yanada et al, 2006

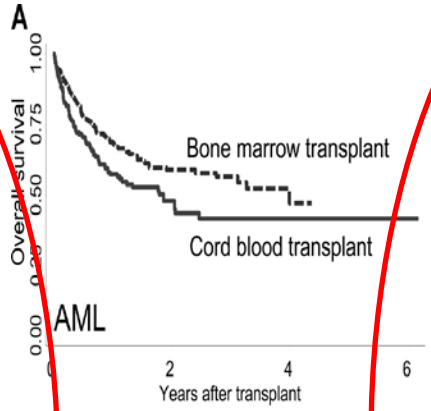
Unrelated SCT. Cord blood vs. bone marrow

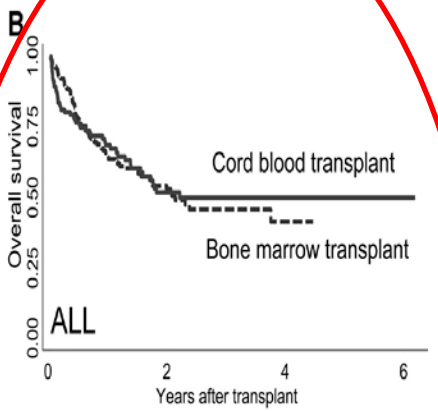


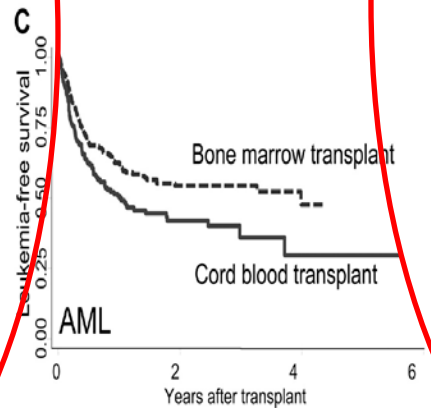


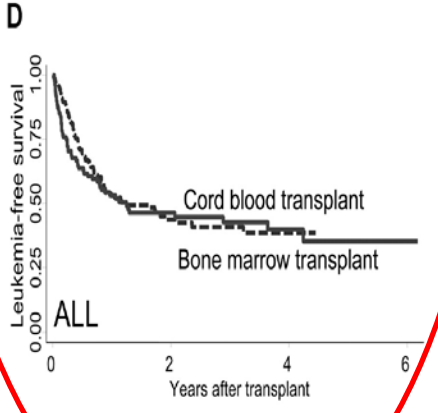












Atsuta et al. Blood 2009

Results of non-myeloablative SCT in adult ALL

Author	Year	Age (med)	N ALL	OS	REL *CCR*	TRM
Martino et al	2003	50	27	31%	49%	23%
Arnold et al	2002	38	22	18%	36%	41%
Gutierrez et al	2007	19	43CR2	30%	nr	21%
Hamaki et al	2005	55	43	40%1y	50%	30%
Mohty et al (EBMT)	2008	38	97	31%2y	51%	28%
TOTAL			**232**	**31%**	**49%**	**28%**

RIC vs. Myeloablative SCT
(patients >45 yr, EBMT registry)

	RIC	Mieloabl.	P
N	97	601	
Edad mediana	56	50	0,0001
SP	88%	58%	0,001
EICHa II-IV	35%	28%	NS
EICHa III-IV	14%	10%	NS
NRM a 2a.	22%	32%	0,04
Prob. Recaída 2a.	42%	30%	0,0007
Prob. SLE 2a*	37%	38%	0,42

*Prognositc facto: ALL status at SCT

Mothy M, 2008

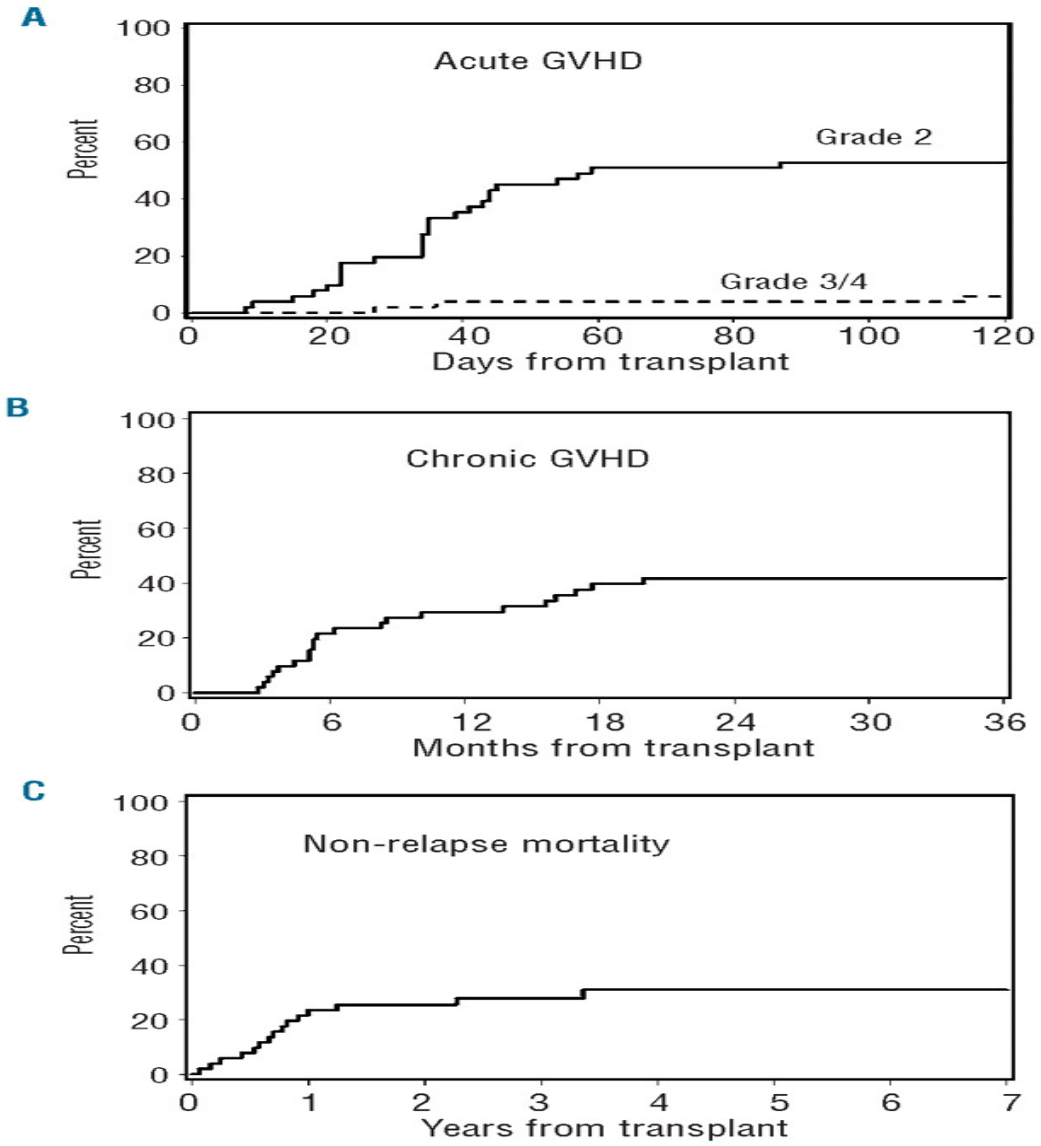
RIC in adult ALL. Seattle experience

Characteristics	Ph⁻ ALL (*n*=26)	Ph⁺ ALL (*n*=25)
Median age: years (range)	56 (8-65)	57 (38-69)
Disease status at time of HCT: *n*, (%)		
CR1 without MRD	12 (46%)	13 (52%)
CR1 with MRD	1 (4%)	6 (24%)
>CR1 (CR2/CR3)	13 (50%)	5 (20%)
Persistent disease	0	1 (4%)
Months from diagnosis to HCT: median, (range)		
CR1	7.7 (4-10.7)	7.6 (4.4-10.9)
Beyond CR1	30.6 (10.7-90.7)	38.7 (8.9-126.1)
History of myeloablative HCT (%)	4 (15%)	2 (8%)
HCT-CI[1] (%)		
0-1	9/17 (53%)	14/18 (78%)
≥2	8/17 (47%)	4/18 (22%)
Recipient gender (male/female)	11/15	16/9
Female donor to male recipient: (%)	5 (19%)	6 (24%)
Donor type: (%)		
HLA-identical sibling	4 (15%)	5 (20%)
Unrelated HLA matched	14 (54%)	17 (68%)
1 HLA allele mismatched	3 (12%)	3 (12%)
1 HLA antigen mismatched	5 (19%)	0
Cell dose × 10^6 CD34⁺ cells/kg: median, (range)	8.8 (2-20.2)	8.2 (0.9-24.4)
Cell source (marrow/PBSC)	0/26	1/25

ALL: acute lymphoblastic leukemia, CR1: first complete remission, HCT-CI: hematopoietic cell transplantation comorbidity index, MRD: minimal residual disease, PBSC: peripheral blood stem cells, Ph: Philadelphia chromosome. [1]Data were available for 17 Ph– ALL patients and for 18 Ph⁺ ALL patients.

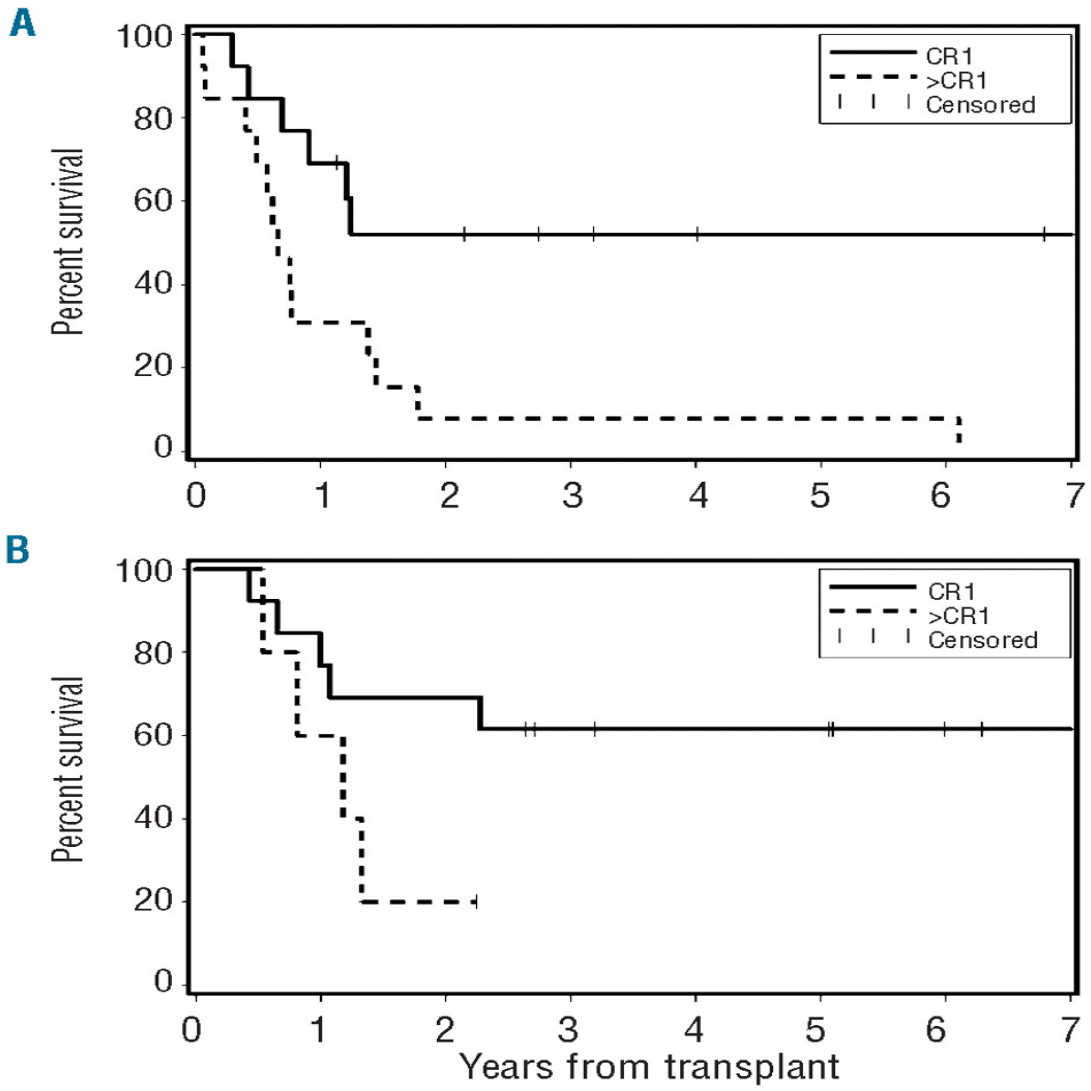
Ram, R. et al. Haematologica 2011;96:1113-1120

Cumulative incidences (n=51) of (A) AGVHD (B) cGVHD (C) NRM



Ram, R. et al. Haematologica 2011;96:1113-1120

OS for (A) Ph- ALL, CR1 (n=13) vs. beyond CR1 (n=13) (B) Ph+ ALL CR1 with imatinib after SCT(n=13) vs. beyond CR1 (n=5)



Ram, R. et al. Haematologica 2011;96:1113-1120

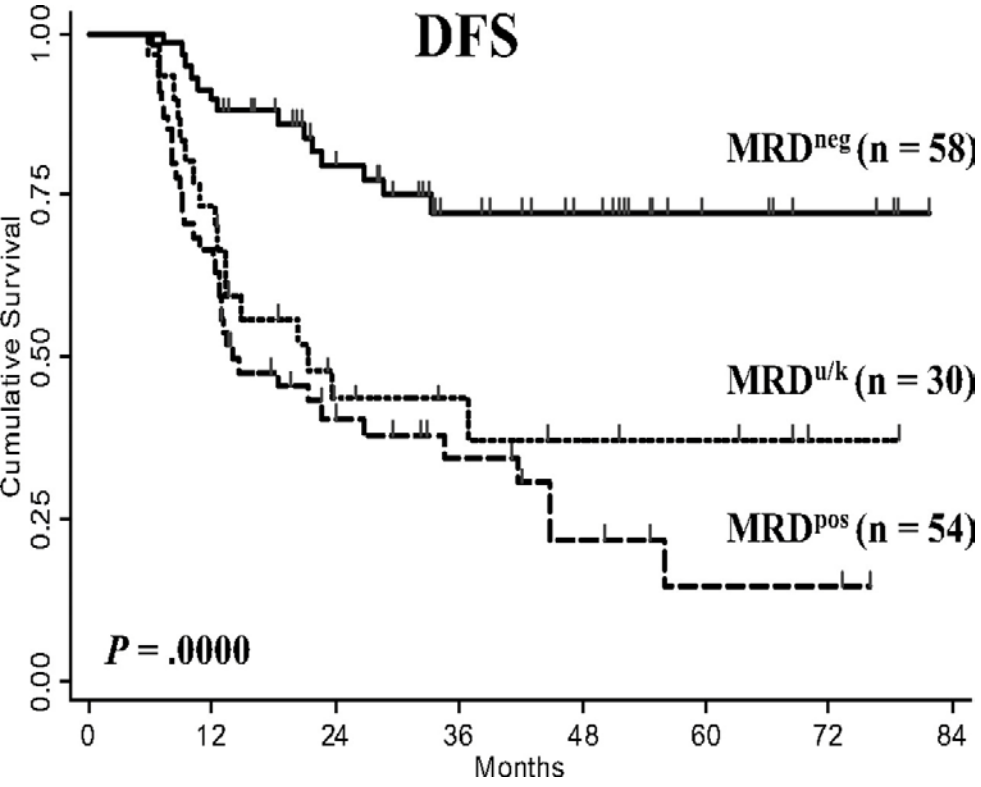
TPH LAL adulto. Indicaciones actuales

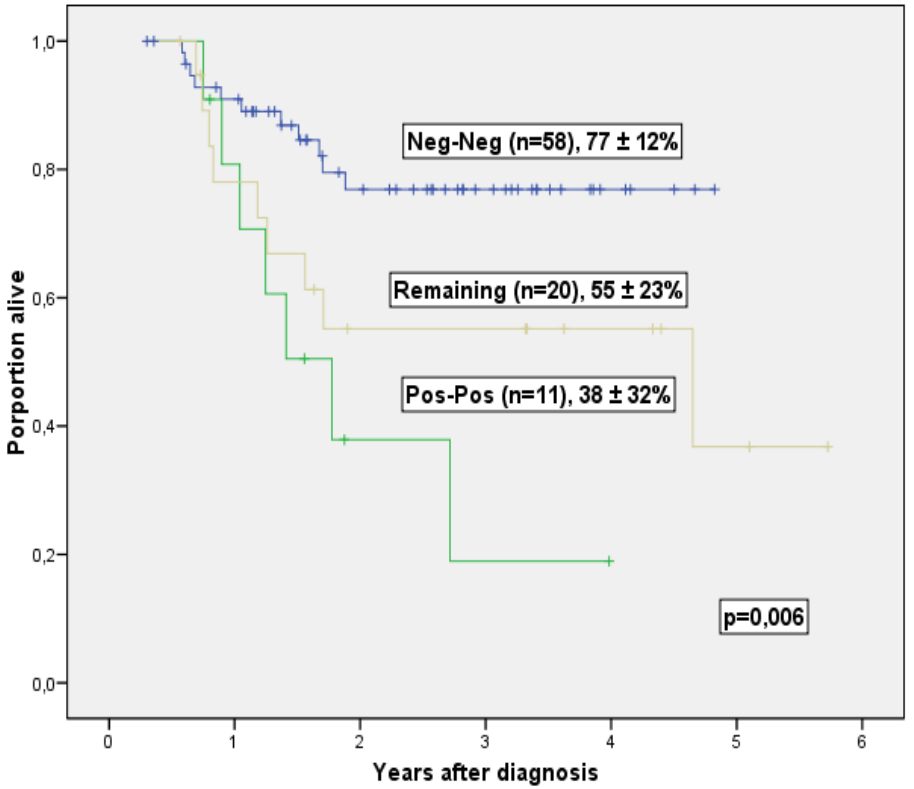
Fase y subtipo	Alo DE	Alo DNE	Auto
RC-1			
- Adultos jóvenes RE	No	No	No
- Riesgo elevado	Si	Si	No
- LAL Ph+	Si*	Si*	No
- LAL-B (Burkitt)	No	No	No
- LAL edad avanzada	¿AIR?	¿AIR?	No
RC>1	Si	Si	No

Risk-adapted therapy in T-ALL: proposed strategy according to molecularly defined subgroups

Risk group	*Post-remission tx*
Thymic T-ALL with favorable markers • Absence of HOX11L2 (TLX3) expression • Low BAALC/ERG expression • HOX11 (TLX1) high	CT-based
Thymic T-ALL with unfavorable markers • HOX11L2 (TLX3) expression • High BAALC or ERG expression **Early T-ALL** **Mature T – ALL**	AlloHCT in CR1

Will MRD negativity stop more allografts?





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

JM Ribera et al, ASH 2009, oral presentation

LAL Ph+

LAL Ph (BCR-ABL) en pacientes jóvenes

Quimioterapia

+

Inhibidores de tirosincinasa de ABL

+

Trasplante alogénico de progenitores hematopoyéticos

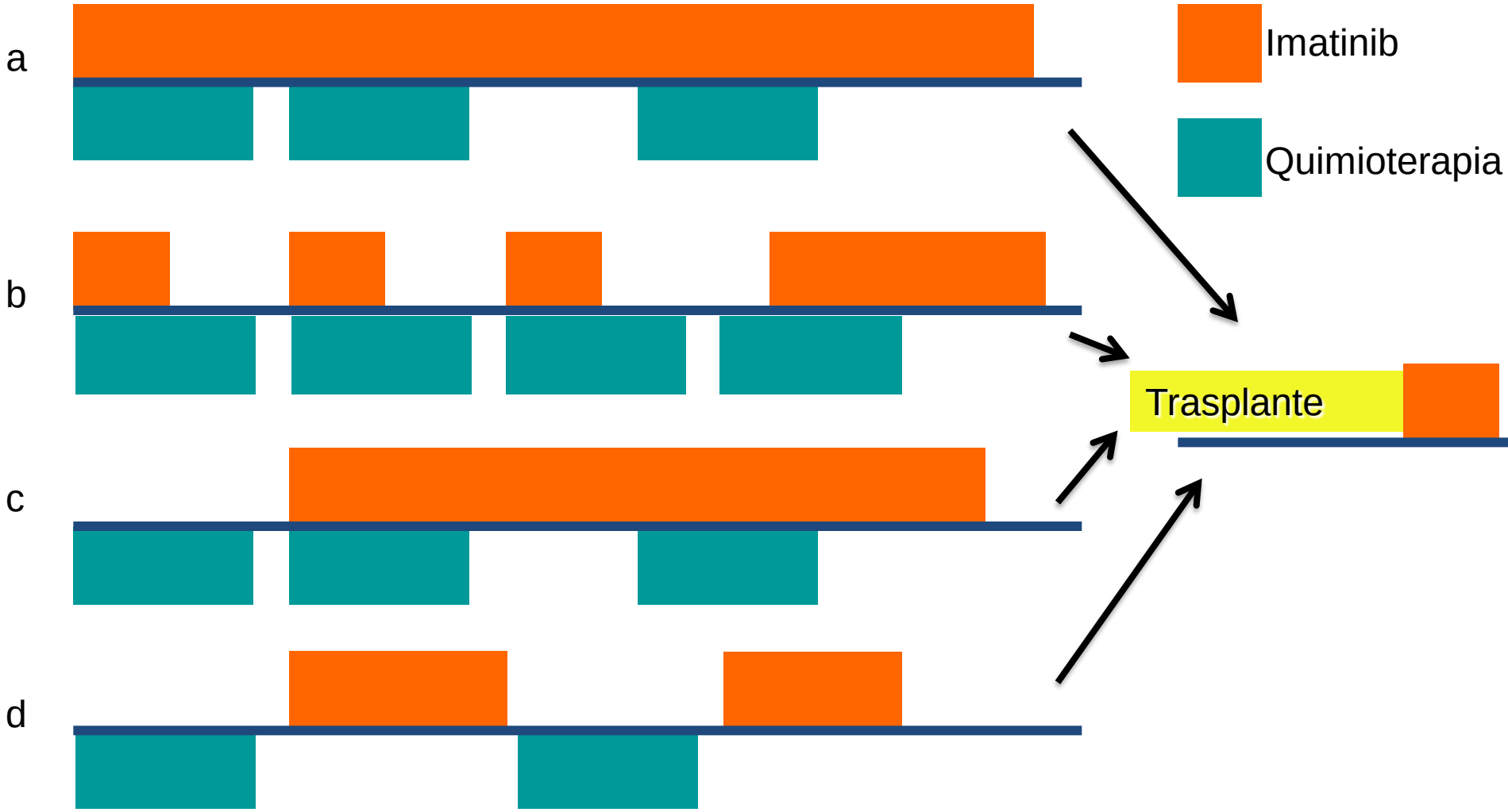
Approved substances and pipeline

ATP-Binding			Nonkinase
Bcr-Abl	Abl & Src	T315I-Active	Inhibition
Imatinib	Dasatinib	MK-0457	17-AAG
Nilotinib	Bosutinib	KW-2449	HDAC
	INNO-406	XL228	DAC
		AT9283	HHT
		PHA-739358	

Imatinib plus Intensive Chemoinduction in Adult Ph+ ALL

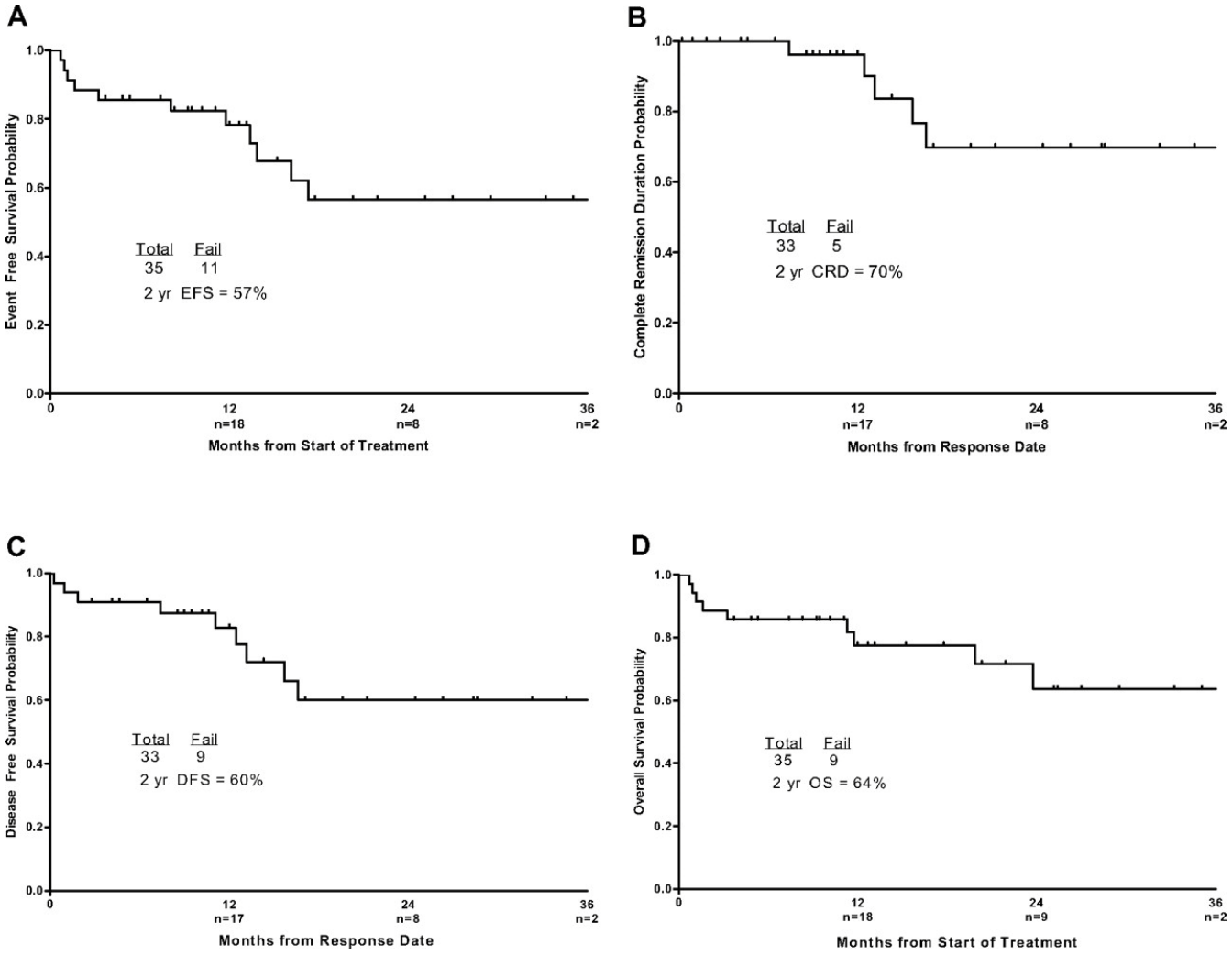
	Lee[57] (n = 20) KOREA	Wassmann[58] (n=92) GMALL	Yanada[59] (n = 80) JALSG	De Labarthe[60] (n=45) GRAALL	Thomas[56] (n = 54) MD Anderson	Ribera[62] (n=32) PETHEMA
	2005	2006	2006	2007	2008	2009
Induction regimen	DNR, VCR, PDN, ASP	DEX, CYP, VCR, DNR, ASP, ARAC, MP, MTX	CYP, DNR, VCR, PDN	DNR, CYP, VCR, ASP, MD-AC	Hyper-CVAD	VCR, DNR, PDN
Imatinib [mg/day]	600	400	600	600	600	400
CR	95%	95%	96%	96%	93%	90%
Transplant rate	75%	77%	71%	48%	33%	78%
Induction mortality	5%	7%	2.5%	5%	2%	7%
Death in remission	10% (10% TRM)	5%	(27% TRM)	11% (9%TRM)	NR	(35% TRM)
OS	60% 2,5 years	36-43% 2 years	61% 1 year	65% 1.5 year	49-66% 3 years	30% 4 years
PCR neg	72%	52%	71%	38%	52%	86%

Modalidades de combinaciones



Aprobación de imatinib para el tratamiento de pacientes adultos con LAL Ph+ de diagnóstico reciente, integrado con quimioterapia

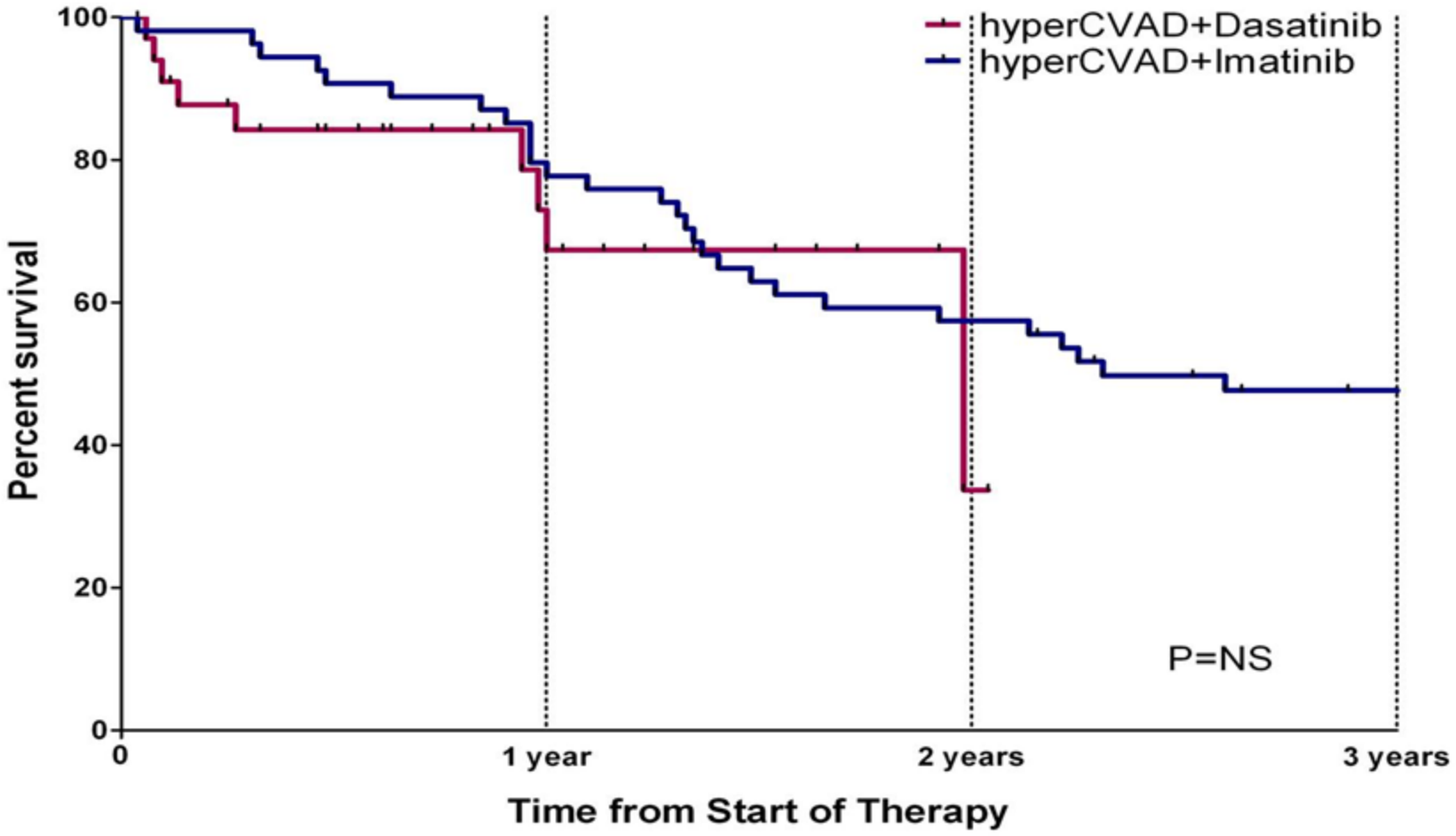
Dasatinib +HyperCVAD
EFS, CR duration, DFS, and OS.



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

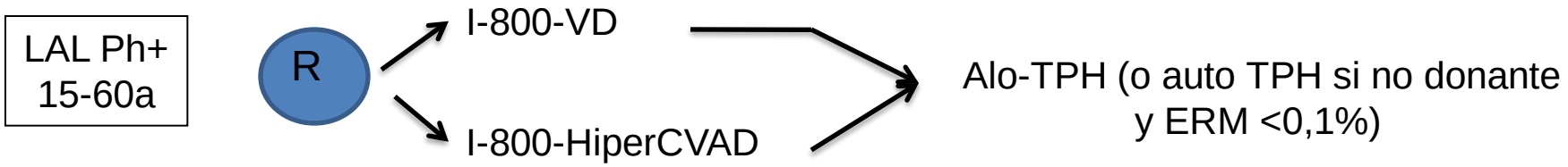
Dasatinib + Hyper-CVAD in *de novo* Ph+ ALL (n=33)

Overall Survival



Ravandi et al, ASH 2008, abstract 2921

Estudio aleatorizado GRAAPH-2005

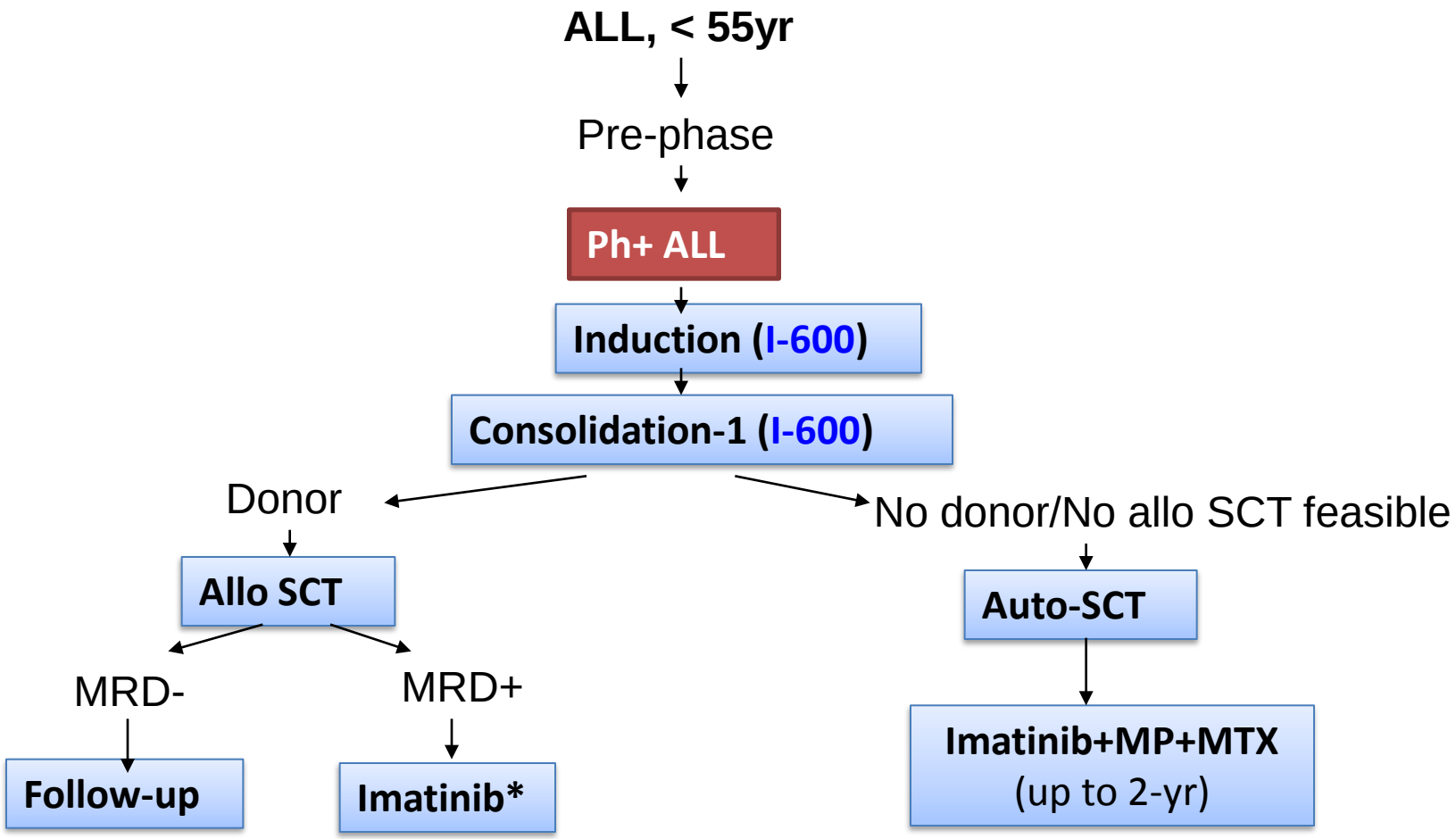


	I-VD	I-HiperCVAD	p
N	42	41	n.s.
RC (%)	100	95	n.s
ERM <0,1% fin inducc (%)	35	45	n.s
ERM <0.1% fin consol (%)	48	72	0,05
SG 2 a (%)	68	54	n.s.
SLE 2 a (%)	54	32	n.s.

Mensaje: Intensificación QT asociada a imatinib mejora la ERM pero no tiene influencia en duración RC. La toxicidad pre-TPH es alta en brazo de QT intensiva

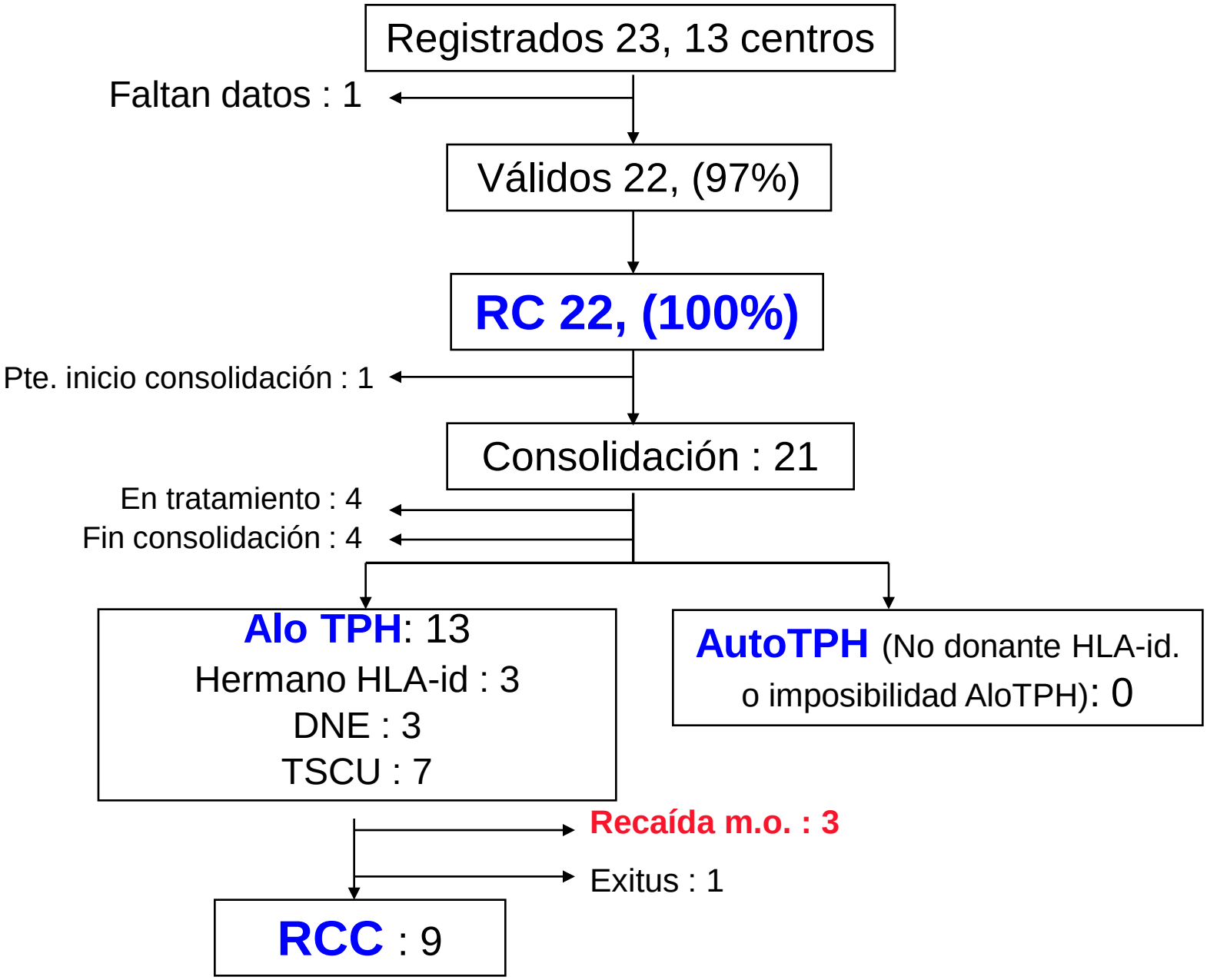
#12. Chalandon Y, et al. First Results of the GRAAPH-2005 Study in younger Adult Patients with De Novo Philadelphia Positive Acute Lymphoblastic Leukemia. ASH 2008

Ph+ ALL < 55 yr. ALL Ph-08

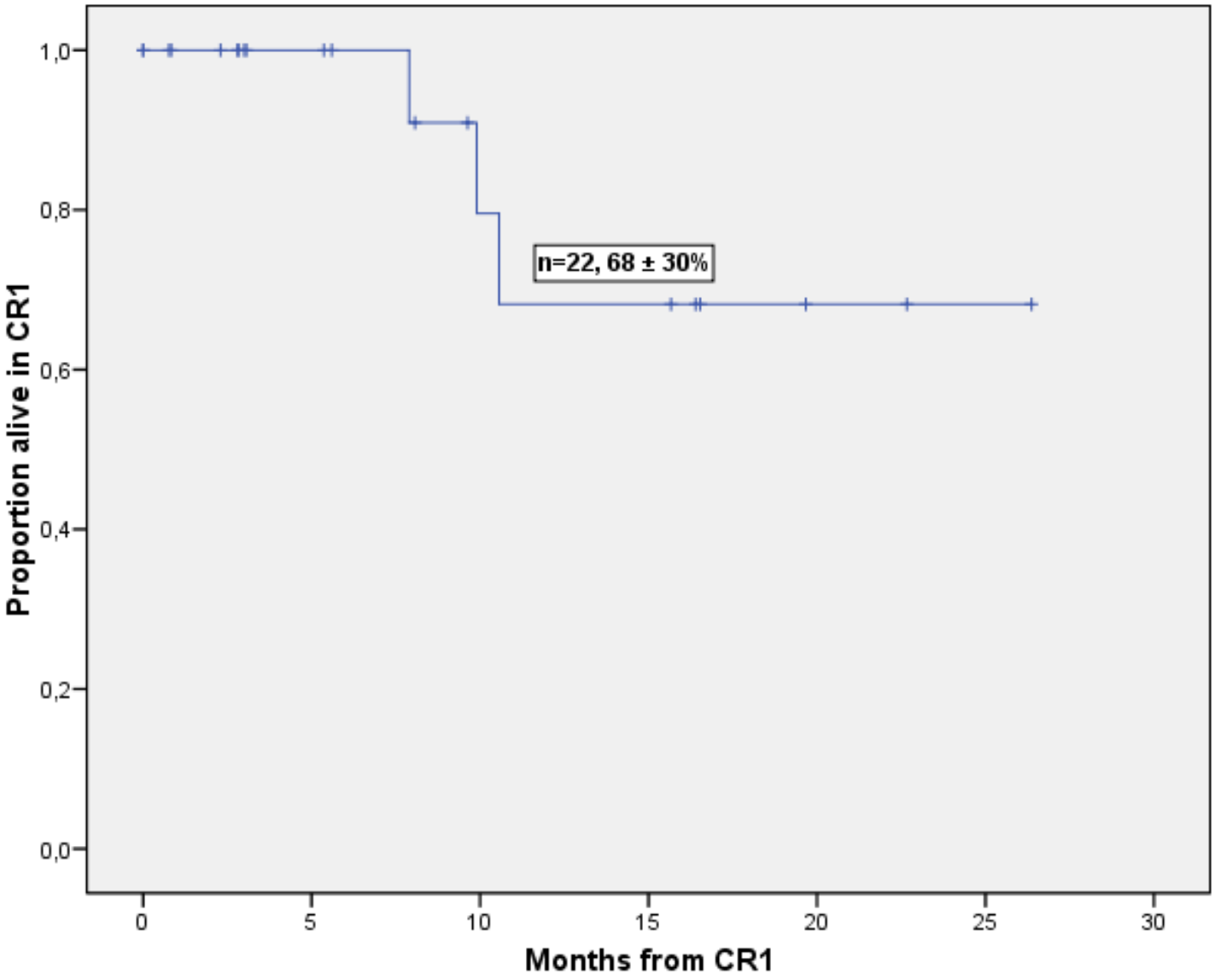


*Except T315I mutation

LAL-PH-08


Registrados 23, 13 centros
Faltan datos : 1
Válidos 22, (97%)
RC 22, (100%)
Pte. inicio consolidación : 1
Consolidación : 21
En tratamiento : 4
Fin consolidación : 4
Alo TPH: 13
Hermano HLA-id : 3
DNE : 3
TSCU : 7
AutoTPH (No donante HLA-id. o imposibilidad AloTPH): 0
Recaída m.o. : 3
Exitus : 1
RCC : 9

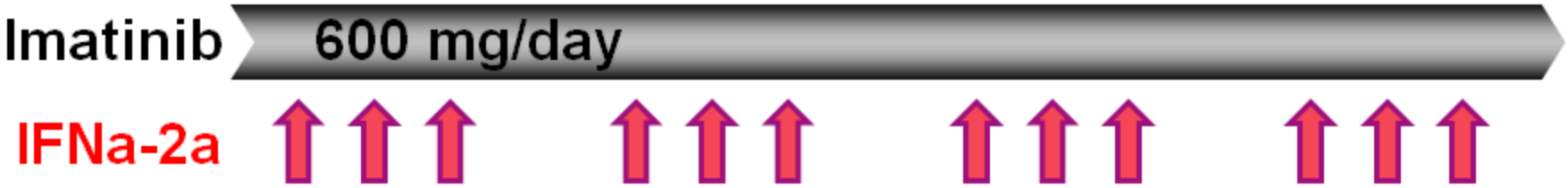
DURACIÓN DE LA RC



CSTI BES02 vs. ALL Ph08

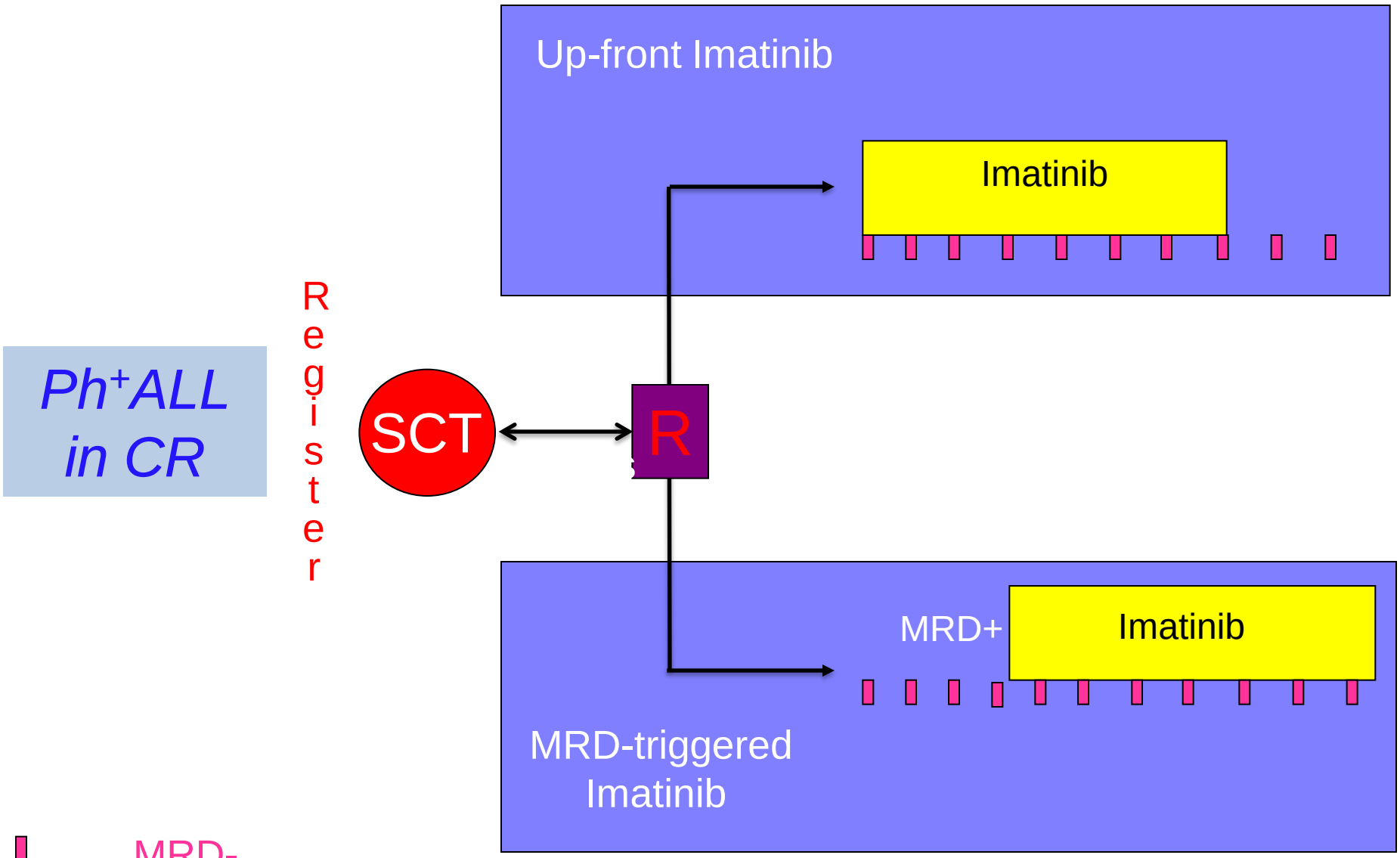
	CSTIBES02	ALL Ph-08
Evaluable patients	30	24
Early death	2	0
Resistance	1	0
CR (%)	90	96
Molecular remission (%)	50	59
Relapse before SCT	1	0
Allo/Auto SCT	16/5	14/0
TRM allo	6/14	1/14
Relapse after SCT	5	3

Approaches to Maintenance Therapy



Imatinib 600 mg/day
Interferon-alfa-2a (Roferon®) 3x/week 3 MIU/day

Randomized Study of Pre-emptive *versus* MRD-Triggered Imatinib after SCT for Ph+ALL



Courtesy of O Ottmann

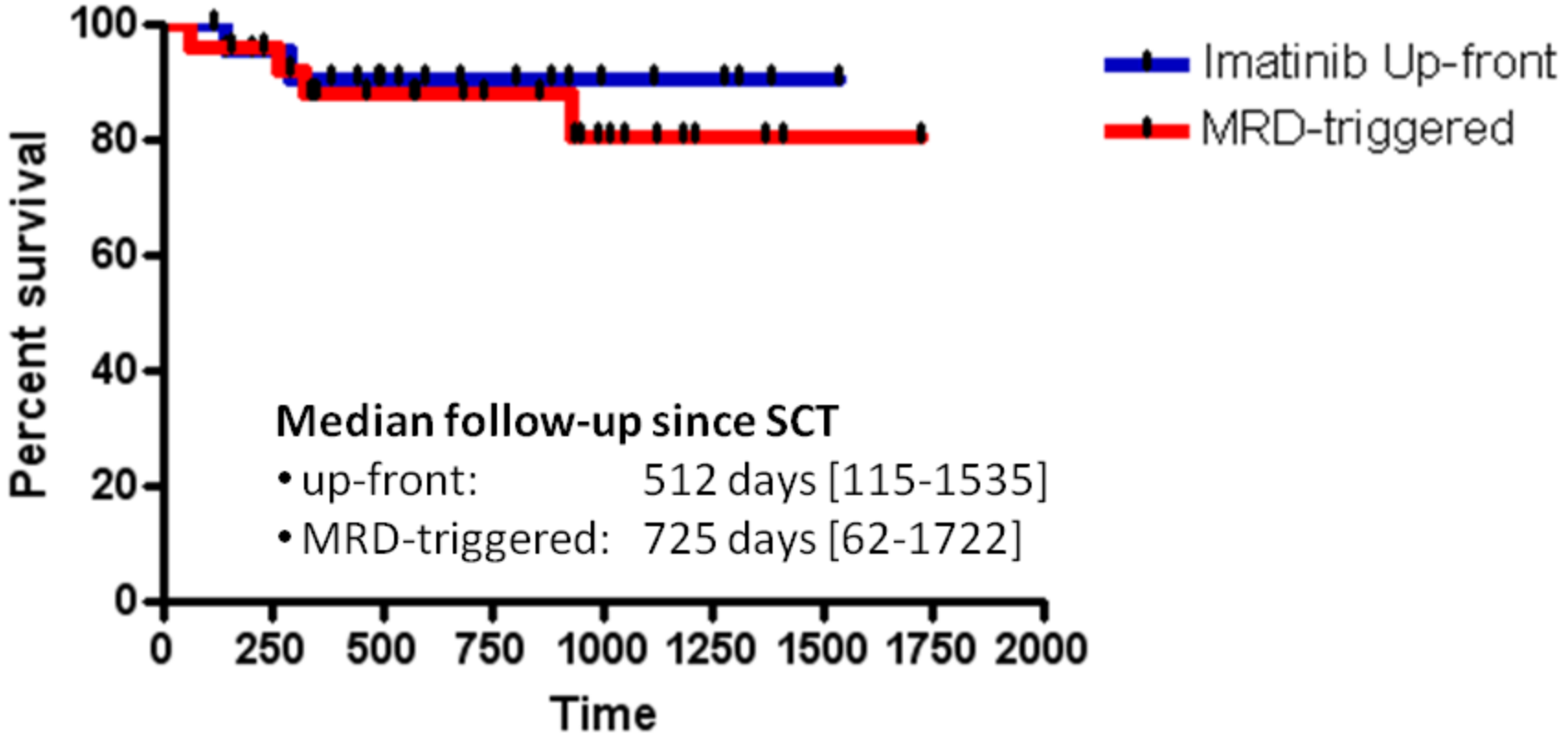
Pre-emptive *vs* MRD-Triggered Imatinib after SCT

Status of Imatinib Administration

	Imatinib cohort	
	up-front	MRD-triggered
N	25	28
Imatinib started	23	13
- regular EOS	5	5
- discontinued early	13	7
- ongoing / na	5 / 2	1
Duration of IM		
median	87 days	237 days
[range]	[0-408 d]	[23-876 d]

Pre-emptive *vs* MRD-Triggered Imatinib after SCT

Remission Duration since SCT



LAL Ph (BCR-ABL) en pacientes edad avanzada

Quimioterapia de moderada intensidad

+

Inhibidores de tirosincinasa de ABL

+

¿? ¿alo-TIR± ITK?

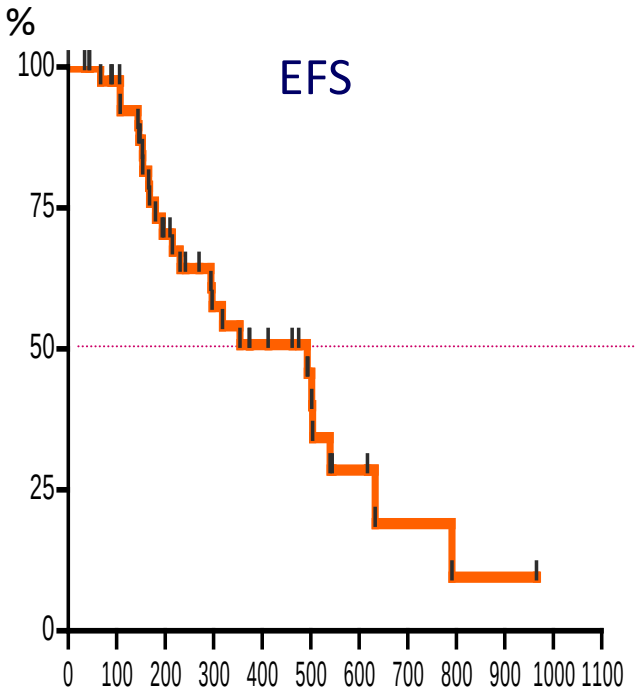
LAL Ph+ edad avanzada
Imatinib o dasatinib +PDN/DXM

Autor	N	RC	SLE (%)	SG (%)
Ottmann	55	96	-	42 (2a)
Delannoy	30	72	58	76(1a)
Vignetti	30	100	48	74(1a)
Foa*	55	100	**	65(20m)

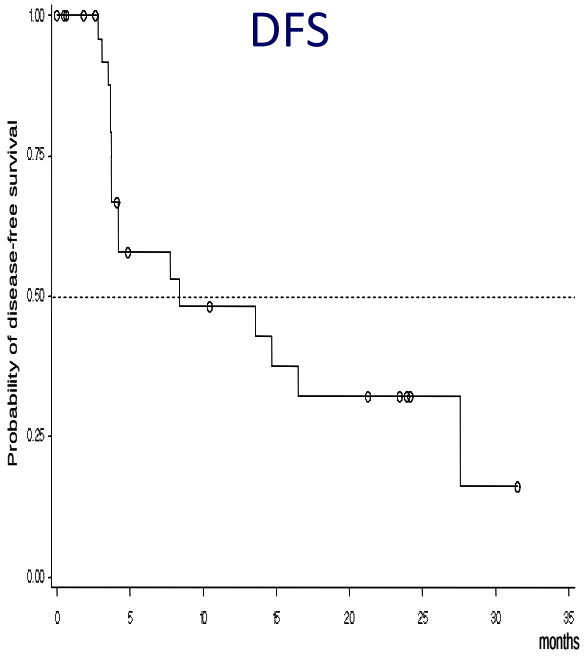
* Dasatinib **14 relapses.

Imatinib-Based Therapy in Elderly Ph(+) ALL: Comparison of Outcome

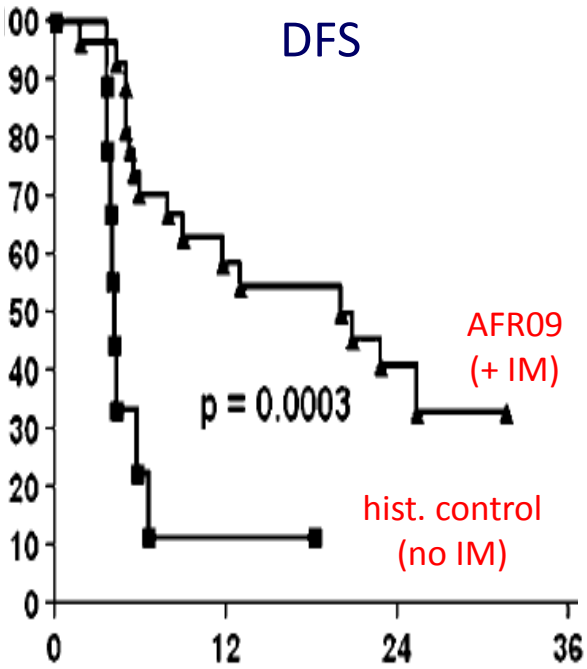
GMALL[1]



GIMEMA[2]



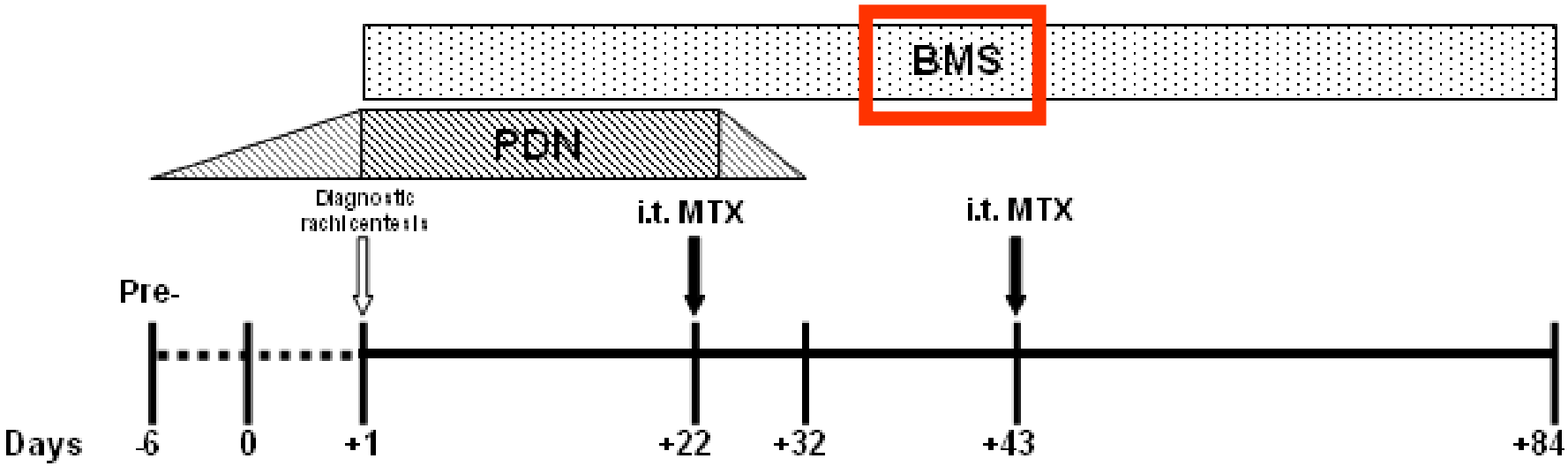
GRAALL[3]



[1]Ottman et al, *Cancer* 2007;109:2068-76; [2] Vignetti et al. *Blood*. 2007;109(9):3676-8; [3]Delannoy et al., *Leukemia*. 2006; 20:1526-32

Dasatinib-based therapy in elderly Ph+ ALL. GIMEMA LAL1205 Protocol

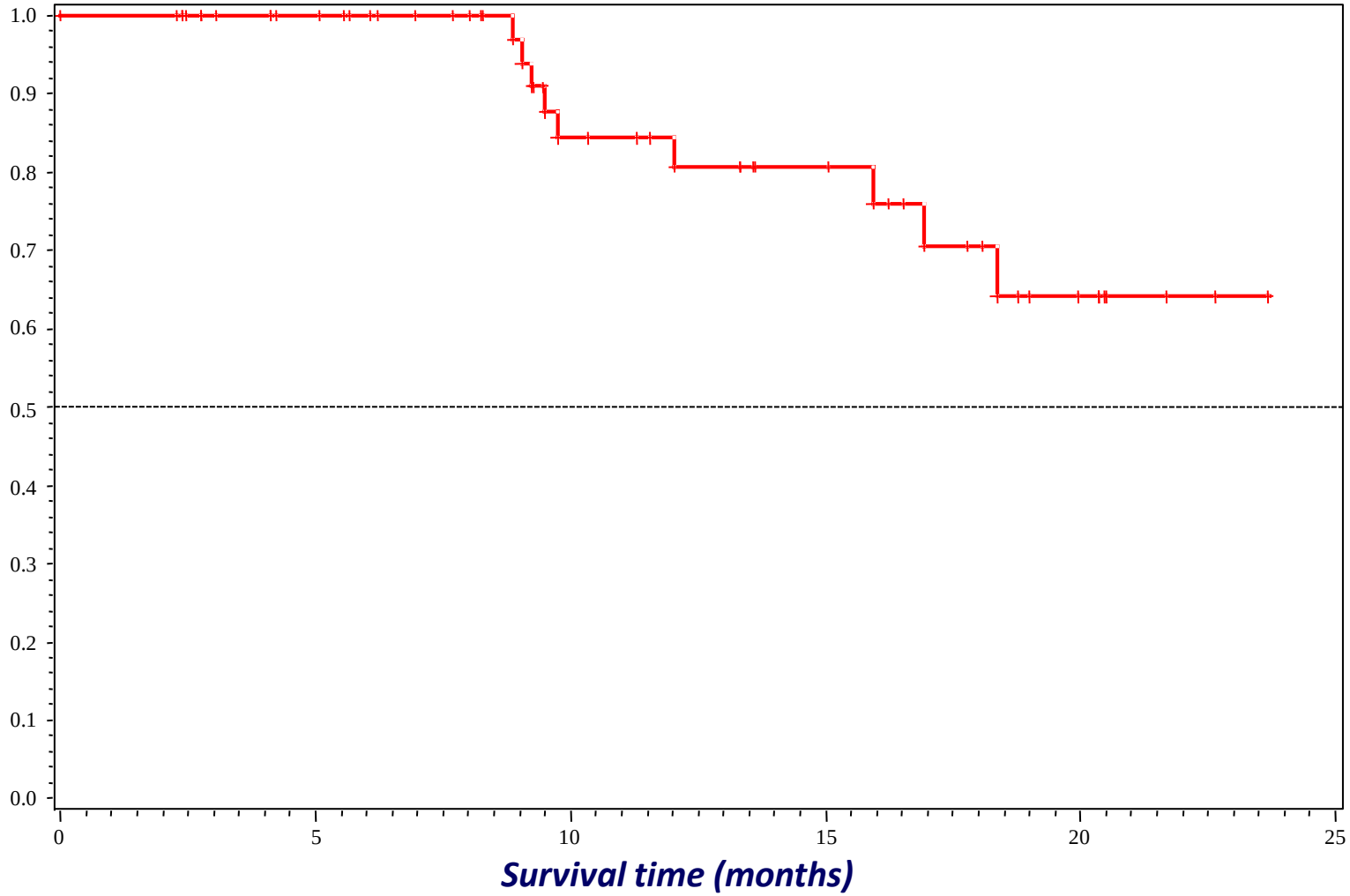
Treatment scheme



Dasatinib ***70 mg twice a day (total planned treatment is 12 weeks, i.e. 84 days)***

★ ***Diagnostic work-up (within 7 d) and monitoring of MRD carried out centrally in Rome***

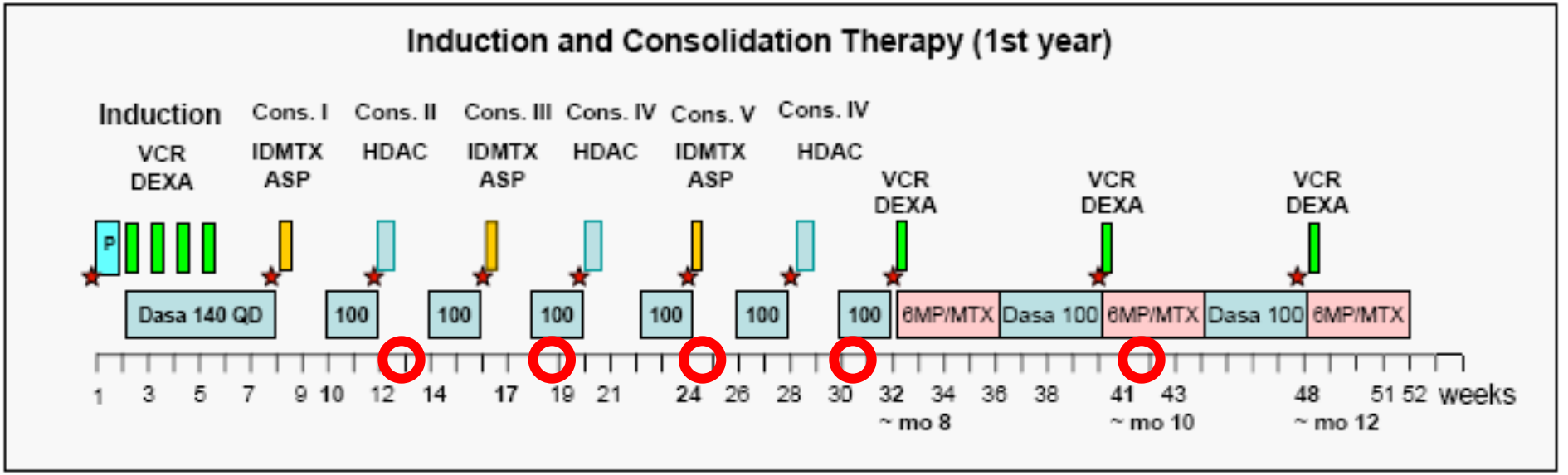
Overall survival

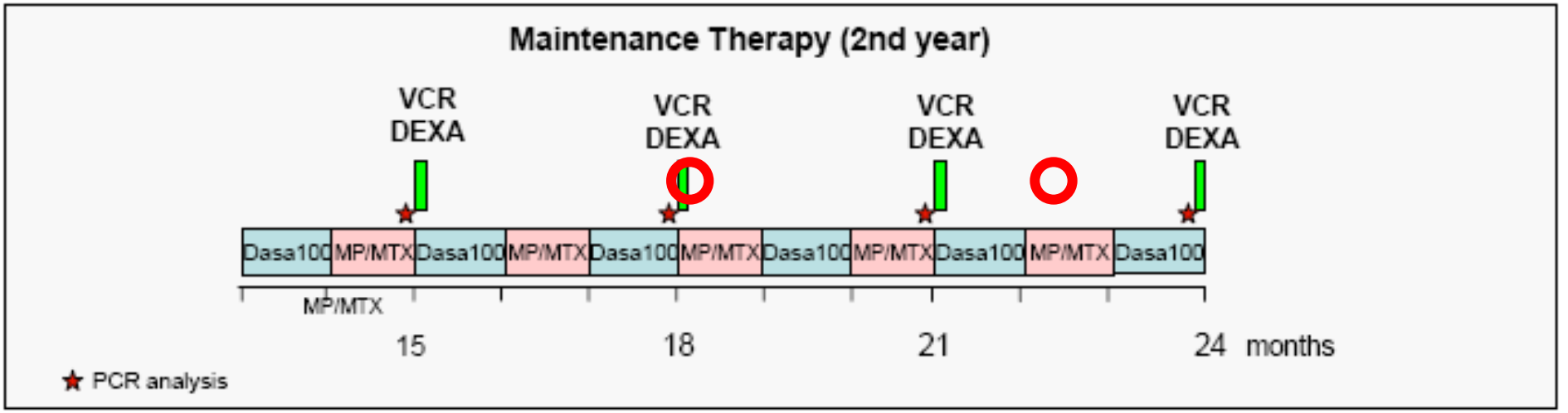


Median OS not reached

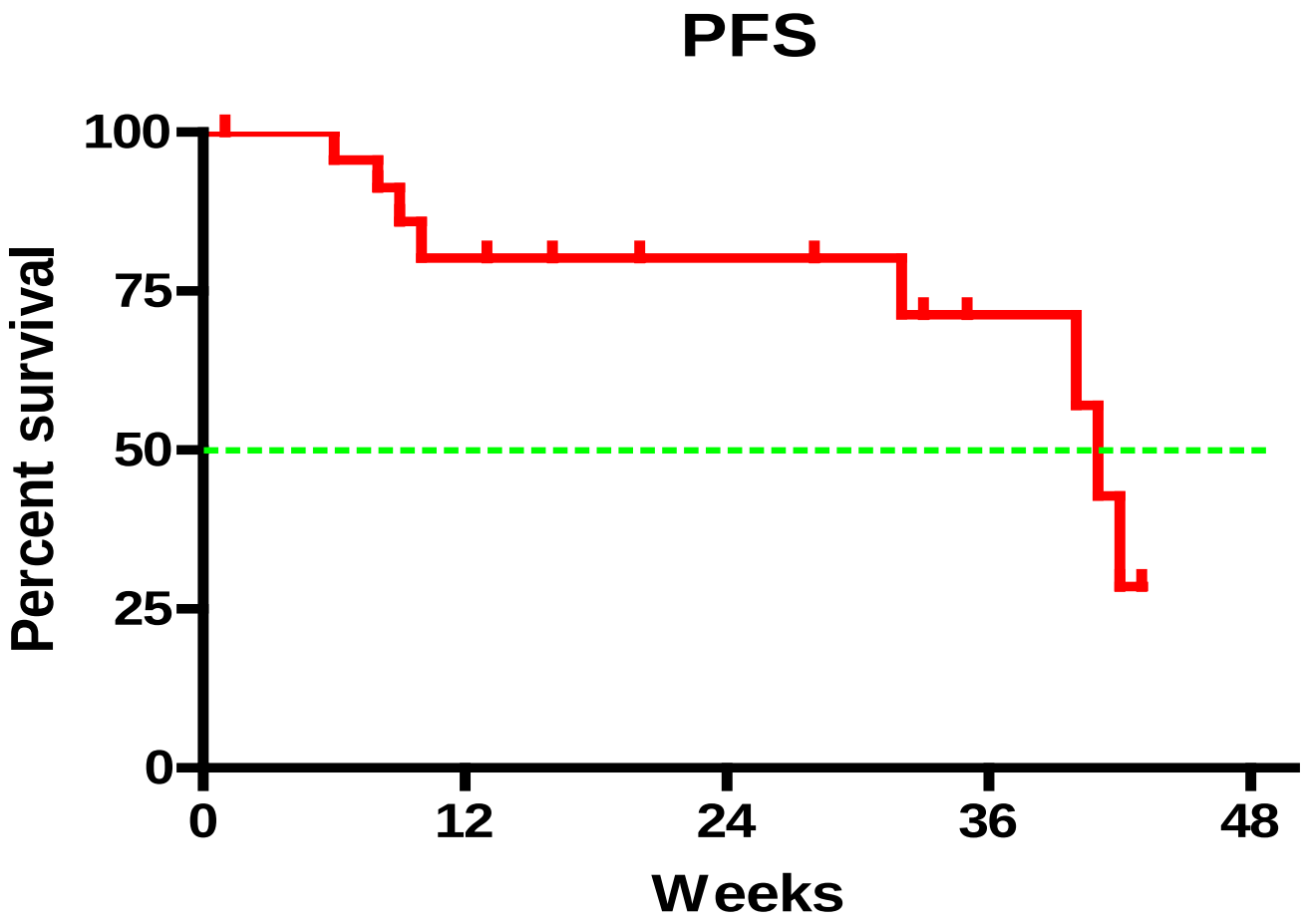
OS at 14 months: 80.7% (CI 95%)

Dasatinib + non-genotoxic chemotherapy
Elderly Ph+ ALL. EWALL-PH-01 overview





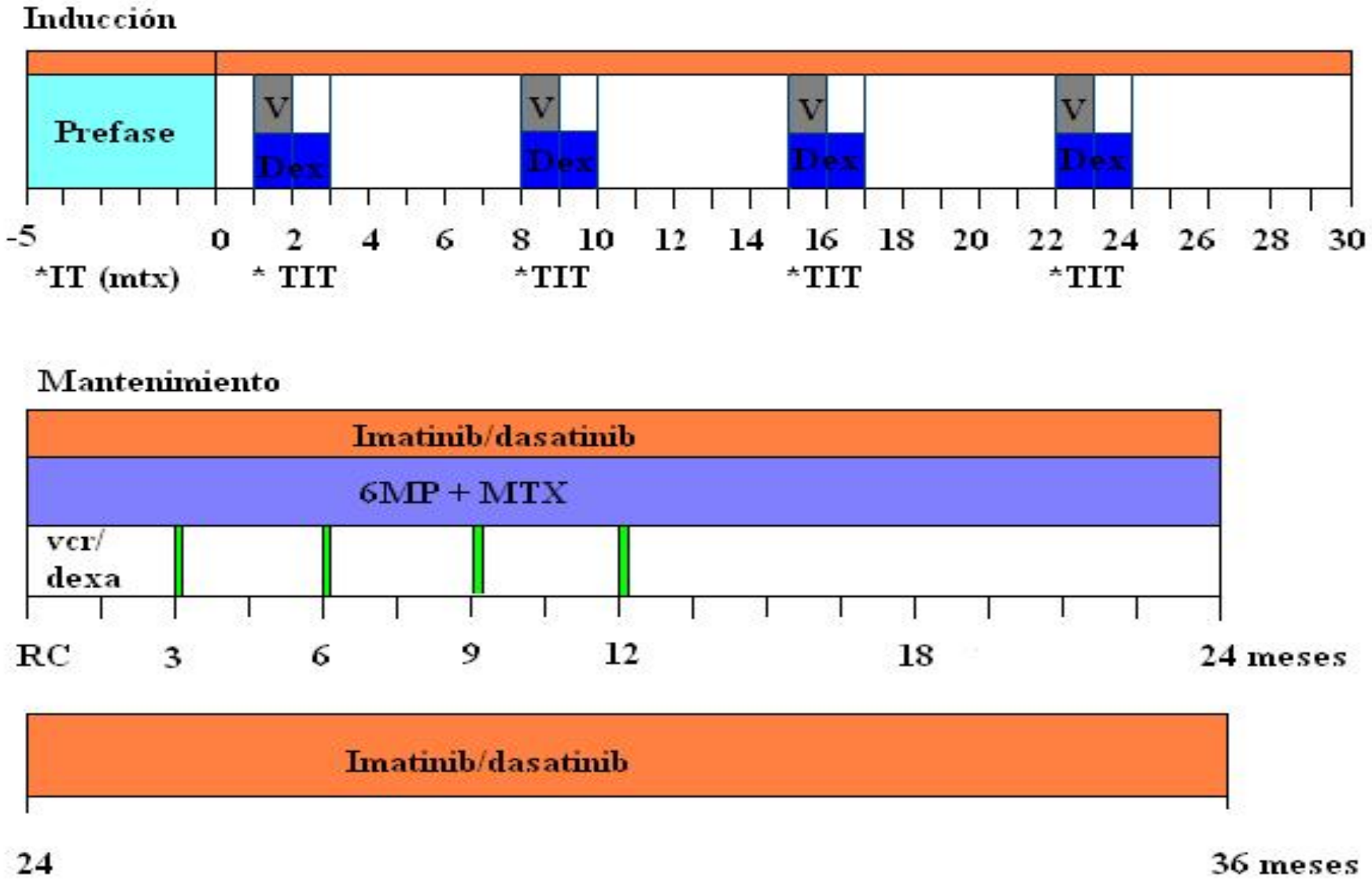
Efficacy

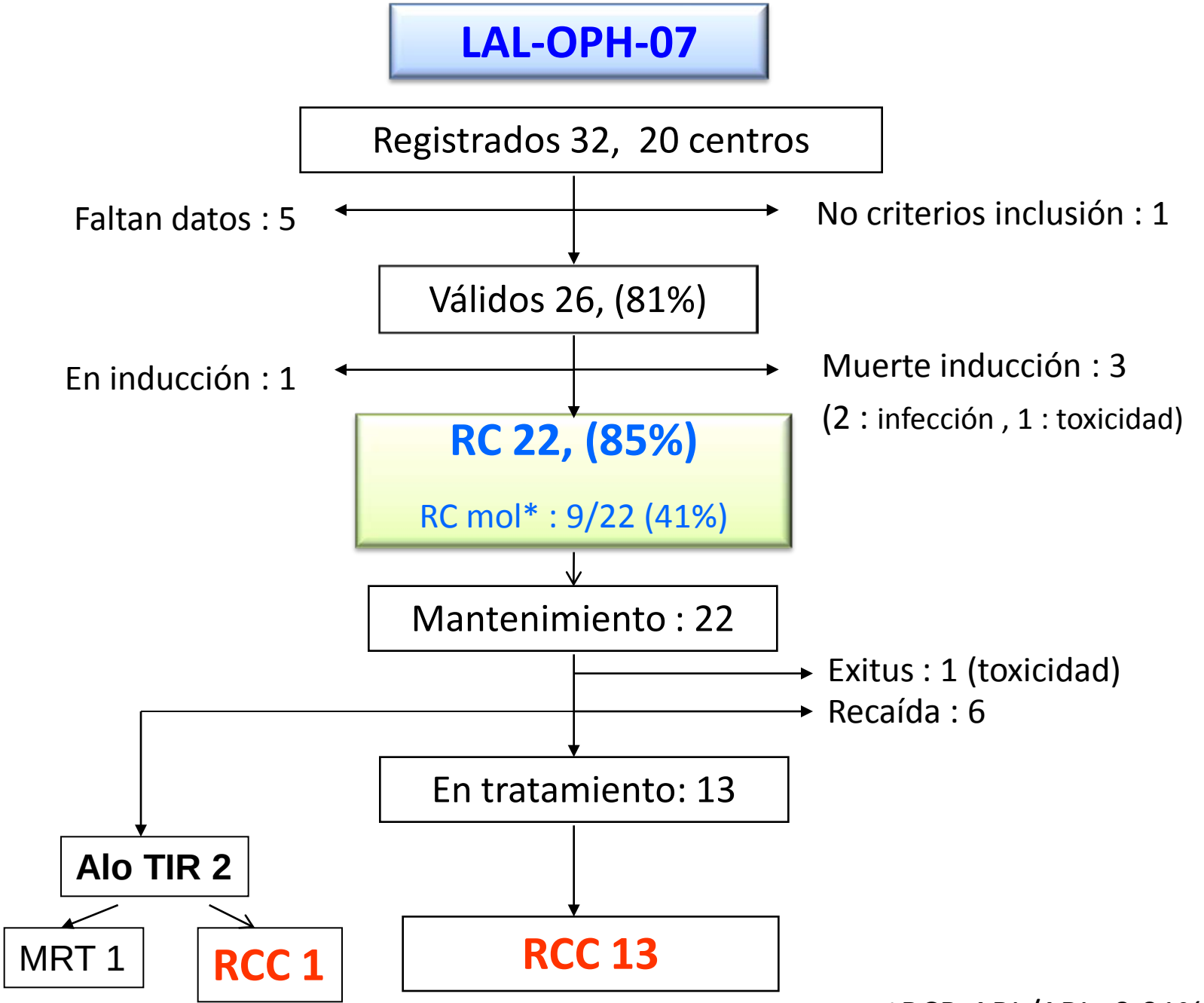


Courtesy of Ph. Rousselot

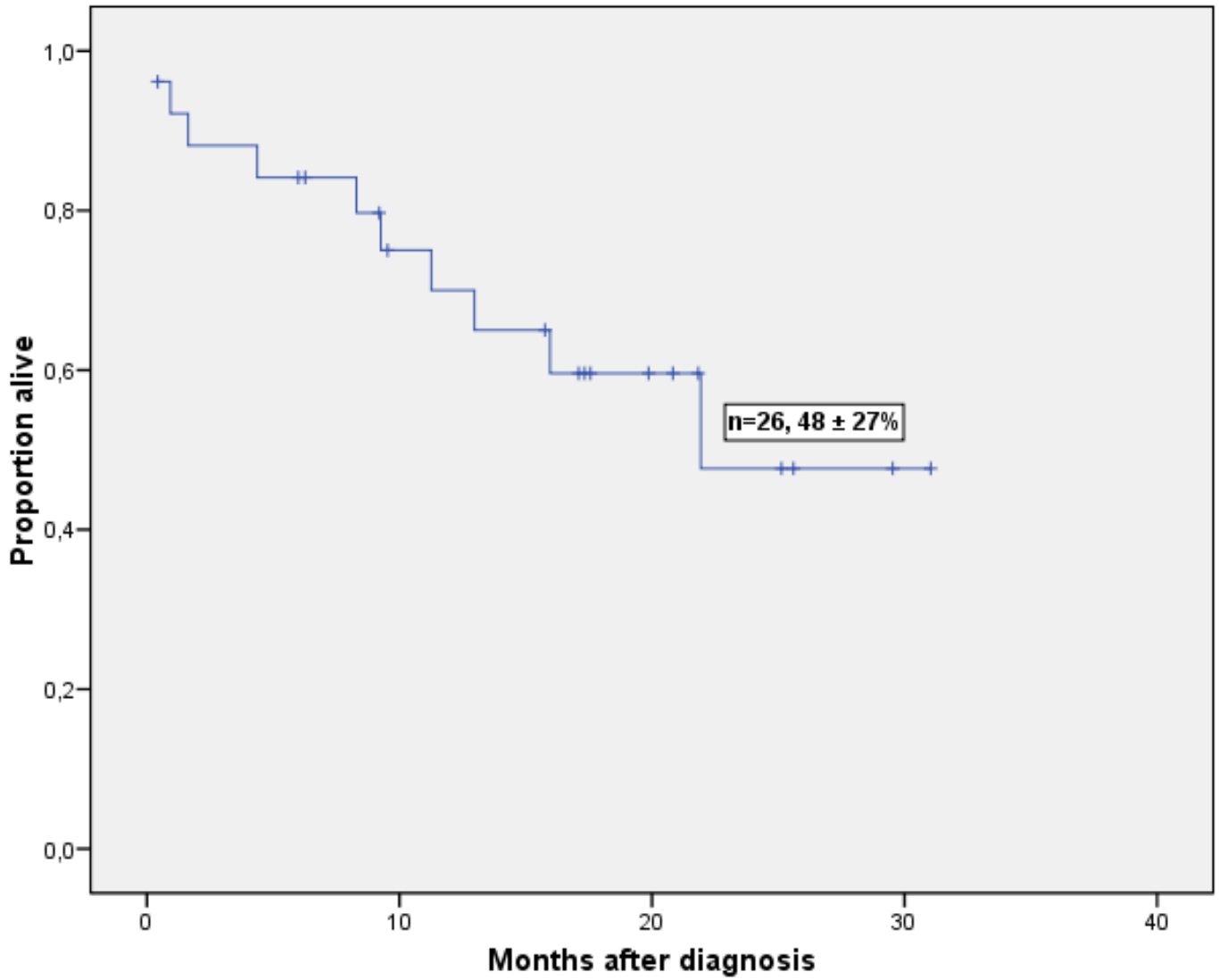
Ph+ All >55 yr. LAL OLDPh

Assistential trial




LAL-OPH-07
Registrados 32, 20 centros
Faltan datos : 5
No criterios inclusión : 1
Válidos 26, (81%)
En inducción : 1
Muerte inducción : 3
(2 : infección , 1 : toxicidad)
RC 22, (85%)
RC mol* : 9/22 (41%)
Mantenimiento : 22
Exitus : 1 (toxicidad)
Recaída : 6
En tratamiento: 13
Alo TIR 2
MRT 1
RCC 1
RCC 13
*BCR-ABL/ABL<0,01%

Supervivencia global (n=26)



Mediana de seguimiento: 18 meses

LAL en pacientes de edad avanzada (>55/>60 a) y BCR-ABL negativo

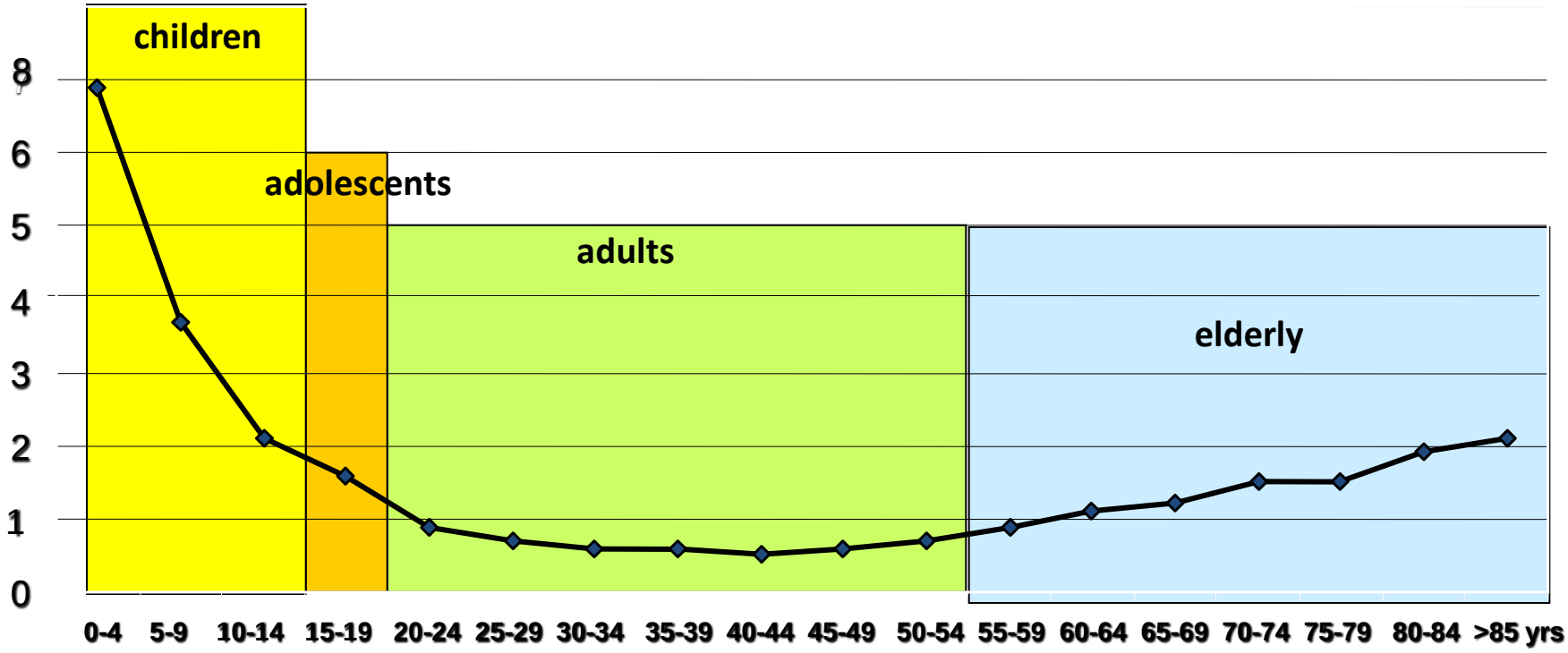
↓

Tratamiento semiintensivo

+

Nuevos fármacos

Incidence of ALL



SEER Program (www.seer.cancer.gov)
Public-Use, Nov 2003 (incidences 1992-2001)

Outcome in Older Patients with ALL

(pooled published data)

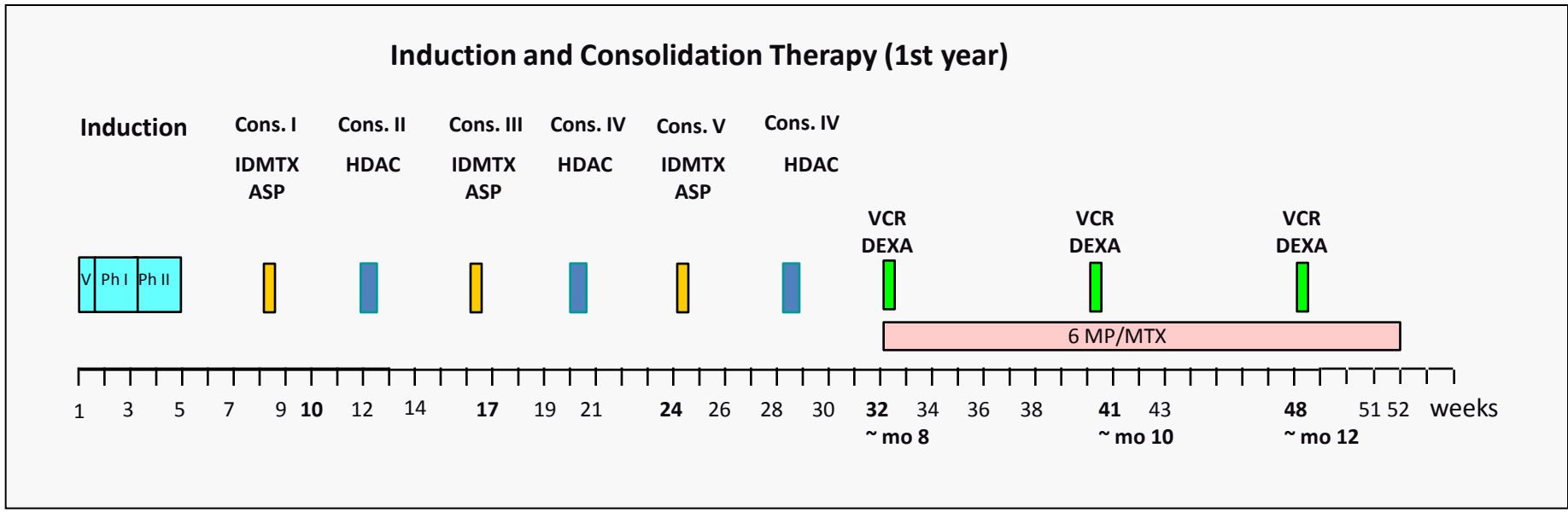
	Age (range)	N Studies	N Pts	CR	ED	OS (mo/prob.)
Supportive tx	67-91y	1	9	0	n.a.	< 1
Palliative Chemo	60-91y	4	94	43%	24%	7
Intensive Chemo	60-92y	15	519	56%	23%	14%
Age specific tx	55-86y	5	187	58%	16%	22%

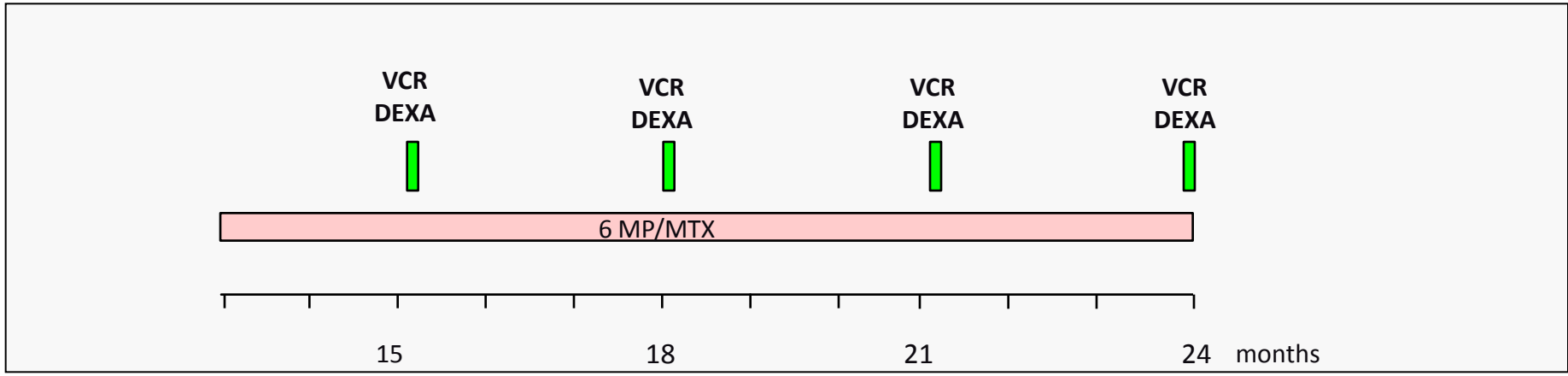
Best results with age specific moderately intensive chemo
- **Lower rate of ED**
- **Better survival**

Final European Proposal for Standard Chemotherapy of Elderly Patients with *de novo* Ph-negative ALL

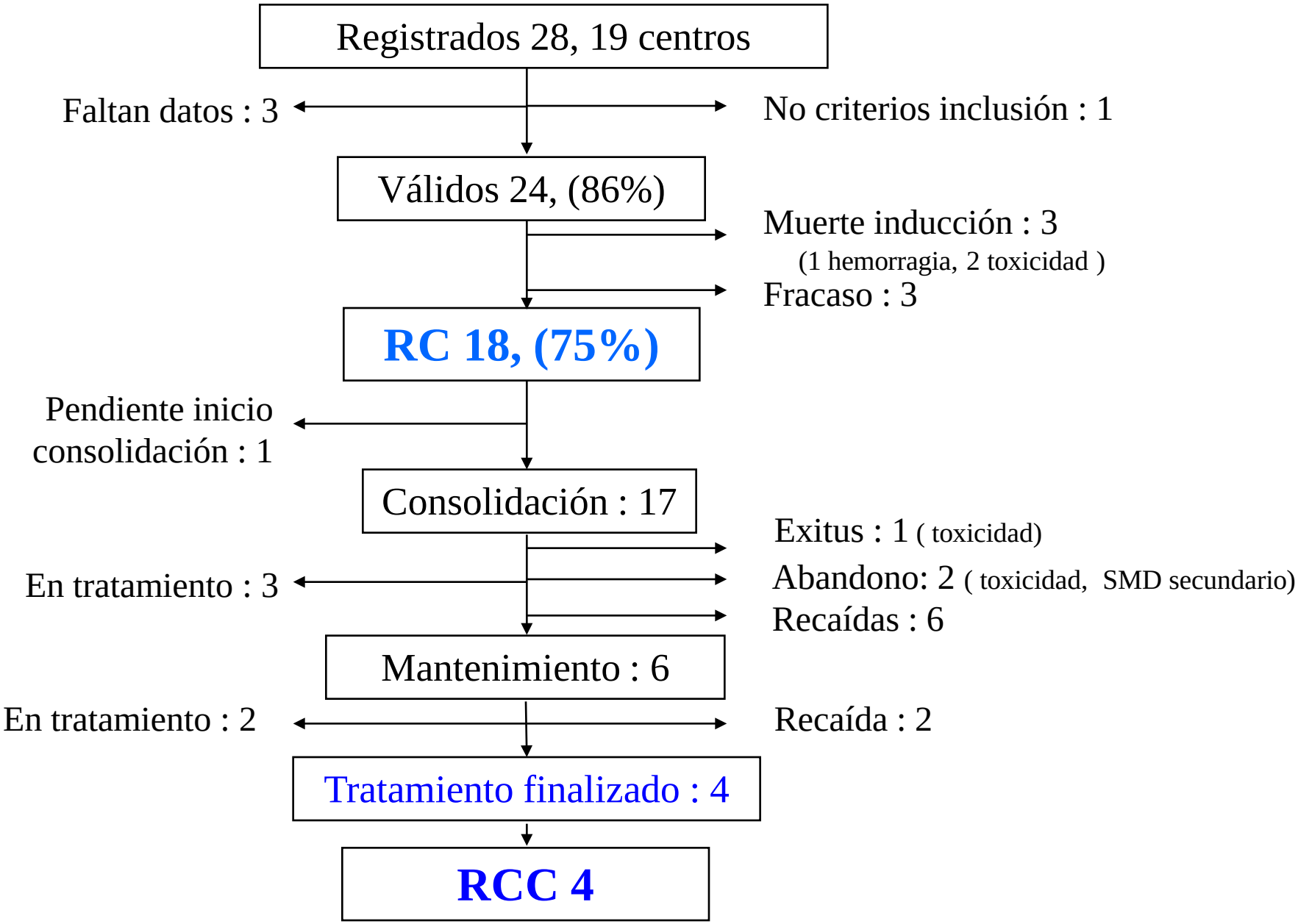
Cooperative Study by GMALL, GIMEMA, GRAALL, NILG, PETHEMA and PALG

OVERVIEW

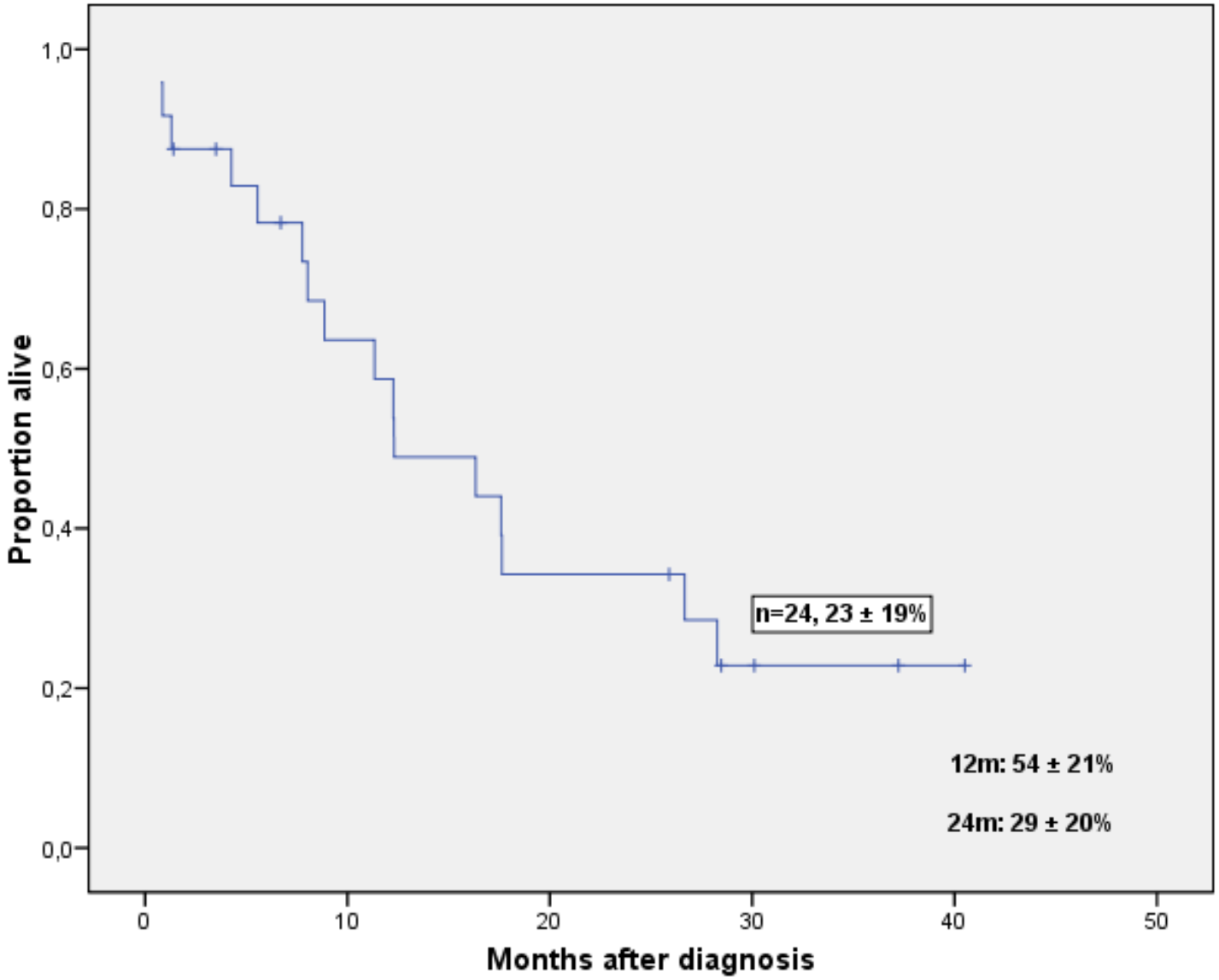




LAL-OLD-07


Registrados 28, 19 centros
Faltan datos : 3
No criterios inclusión : 1
Válidos 24, (86%)
Muerte inducción : 3
(1 hemorragia, 2 toxicidad)
Fracaso : 3
RC 18, (75%)
Pendiente inicio consolidación : 1
Consolidación : 17
Exitus : 1 (toxicidad)
En tratamiento : 3
Abandono: 2 (toxicidad, SMD secundario)
Recaídas : 6
Mantenimiento : 6
En tratamiento : 2
Recaída : 2
Tratamiento finalizado : 4
RCC 4

Supervivencia global

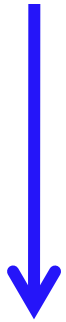


ALL in Older Patients: Summary

- Outcomes often poor
- Treatment with “palliative” intent may paradoxically produce equally good OS due to very high rates of treatment-related mortality
- CR rates and survival in older Ph+ ALL have improved dramatically with tyrosine kinase inhibitors
- Clinical trials specifically designed for older individuals are vital

LAL Burkitt-like

t(;14), t(2;8), o t(8;22), reordenamiento C-MYC

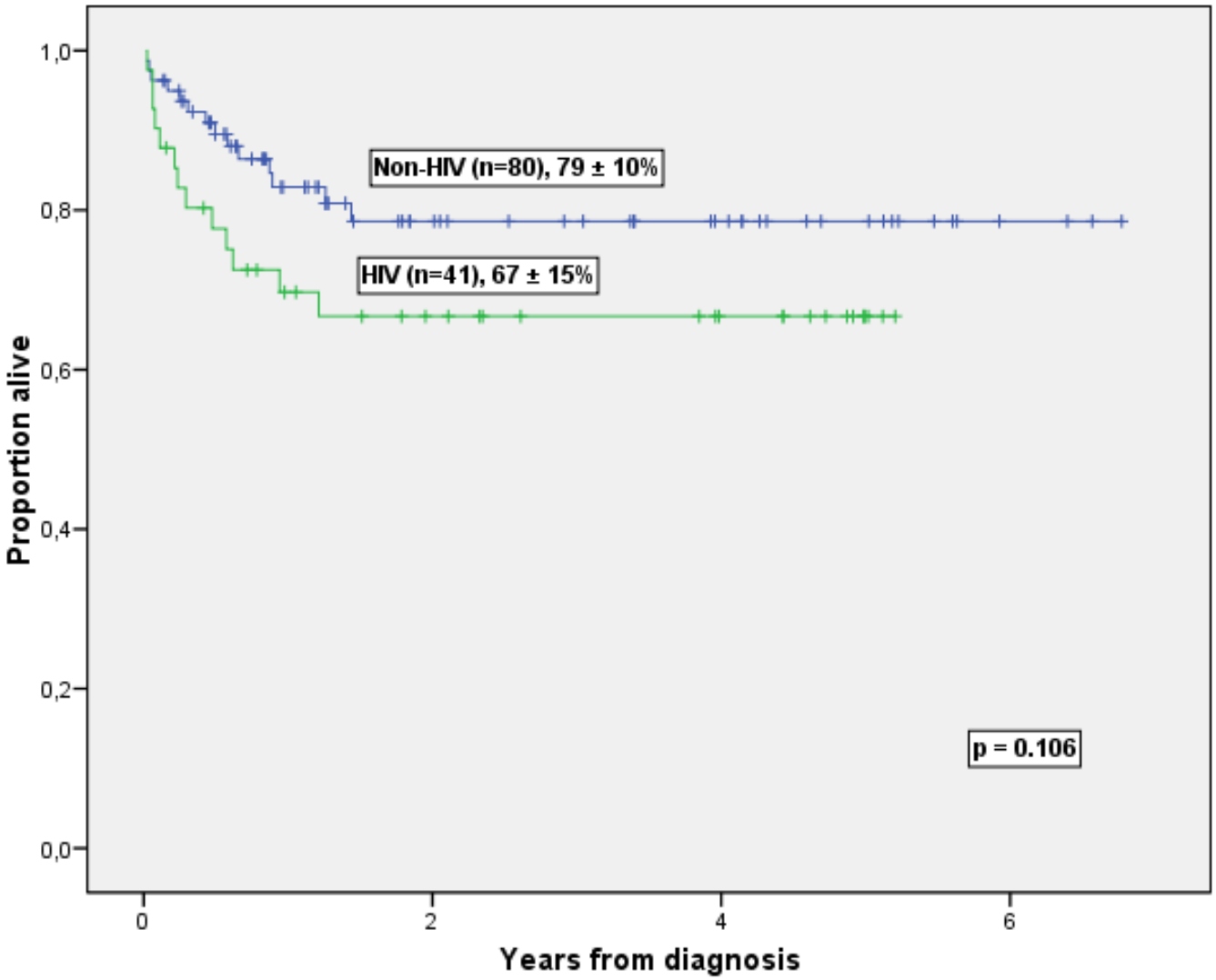


Quimioterapia específica

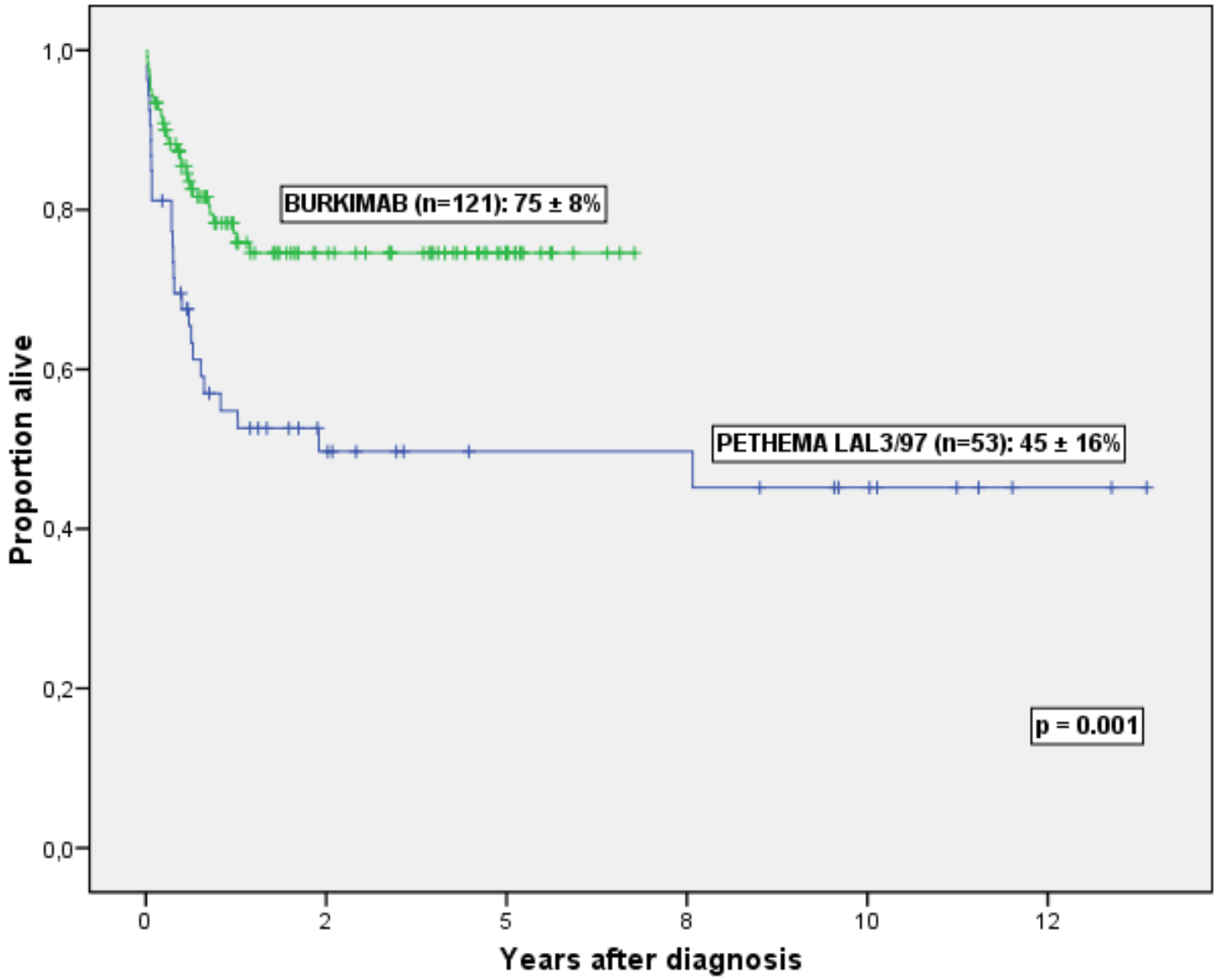
+

Rituximab

Overall Survival (OS)



Comparison between PETHEMA LAL3/97 and BURKIMAB protocols



Nuevos agentes en el tratamiento de la LAL

Dianas moleculares en LLA

Grupo terapéutico	Fármaco	Tipo LAL
Inhibidores de tirosincinasas I	imatinib dasatinib nilotinib Otros	*BCR-ABL*, *NUP214-ABL1*
Inhibidores de *FLT3*	Lestaurtinib	*MLL*, hiperdiploidia>50?
Inhibidores farnesiltransferasa	Tipifarnib Lonafarnib	*BCR-ABL*?, LAL-T?
Agentes hipometilantes	Azacitidina	
Inhibidores histona desacetilasa	Vorinostat Panobinostat	LAL Burkitt?
Inhibidores de m-TOR	Temsirolimus	
Inhibidores del proteasoma	Bortezomib	
Inhibidores de gamma secretasa	MK0752	LAL T

T-ALL. Nucleoside analogs

Cell death

DNA degradation

dGuo

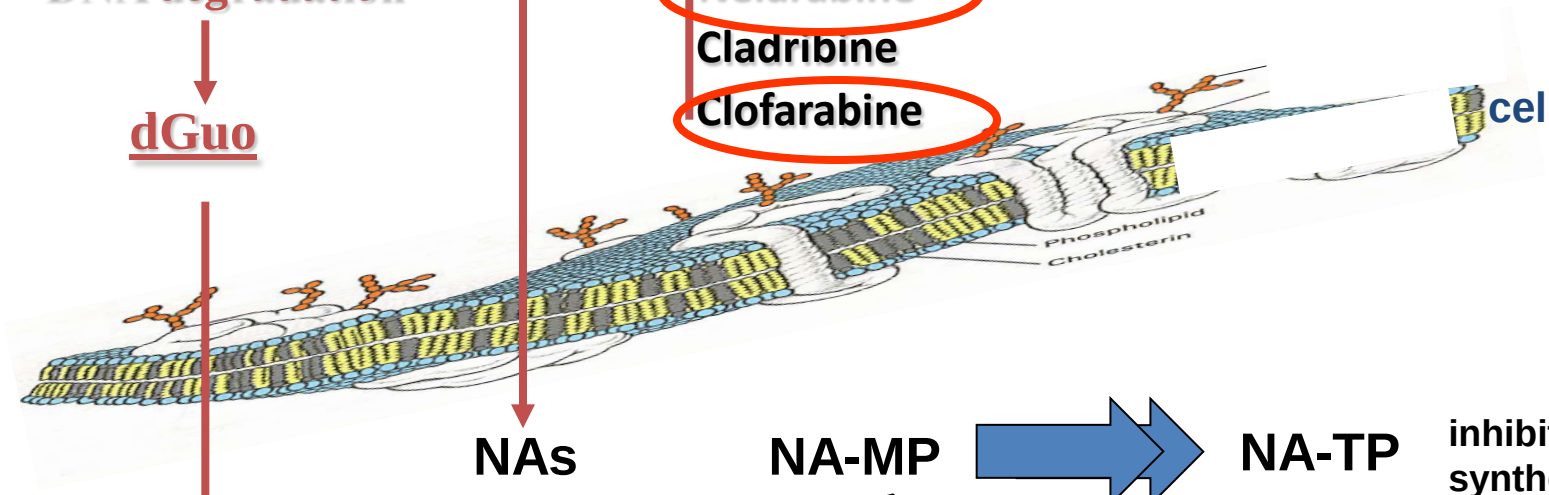
Fludarabine

Cytarabine

Nelarabine

Cladribine

Clofarabine



NAs → NA-MP → NA-TP

dCK

dGuo ⇄ dGMP → dGTP

PNP

Forodesine

5-Nucleotidase

inhibition of DNA synthesis/repair

DNA strand breaks

inhibition of ribonucleotide reductase

dNTP imbalance

endonuclease activation

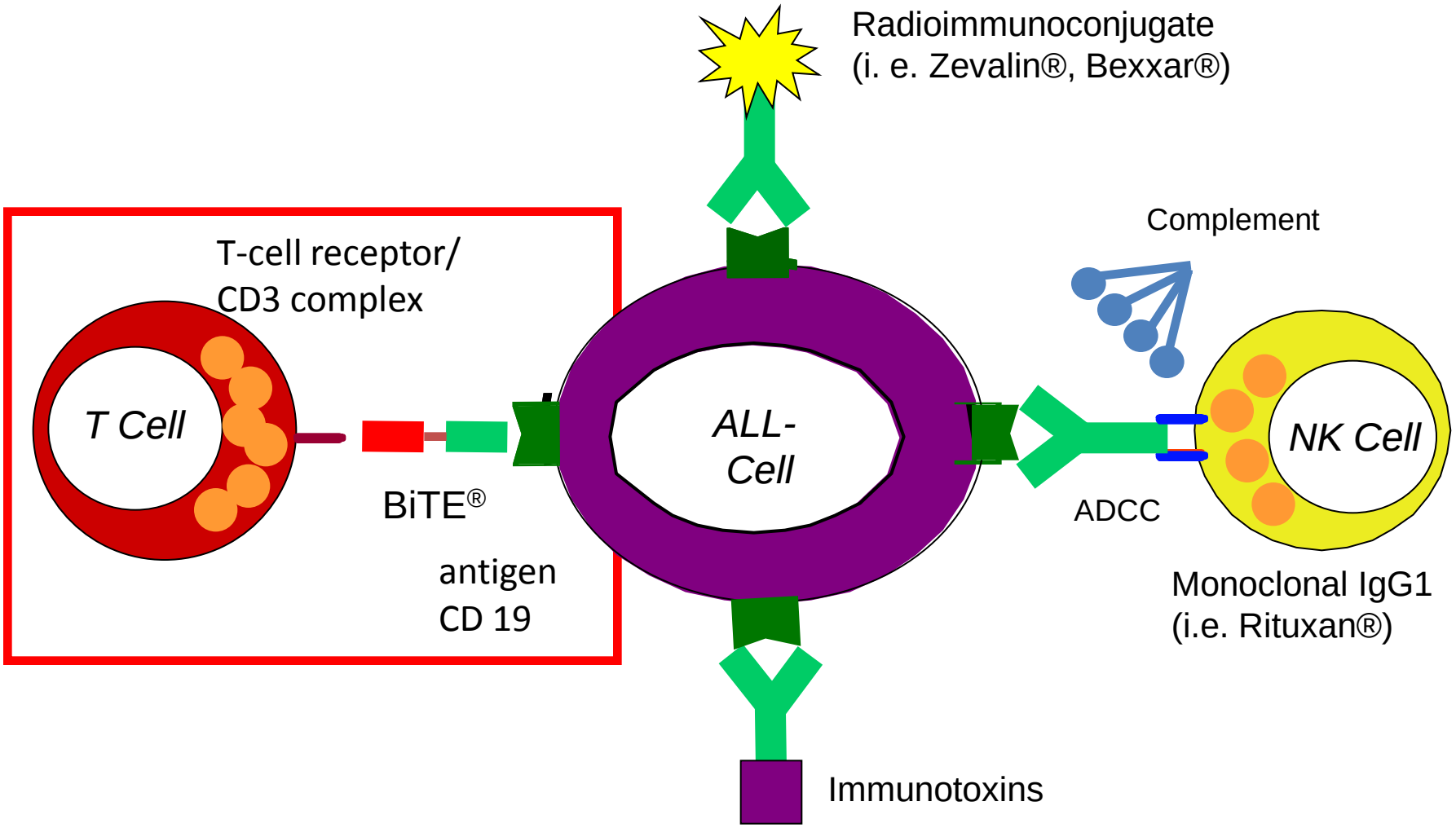
apoptosis

Nelarabina en LAL-T/LL-T adulto refractaria/recaída
Estudio Fase II. GMALL

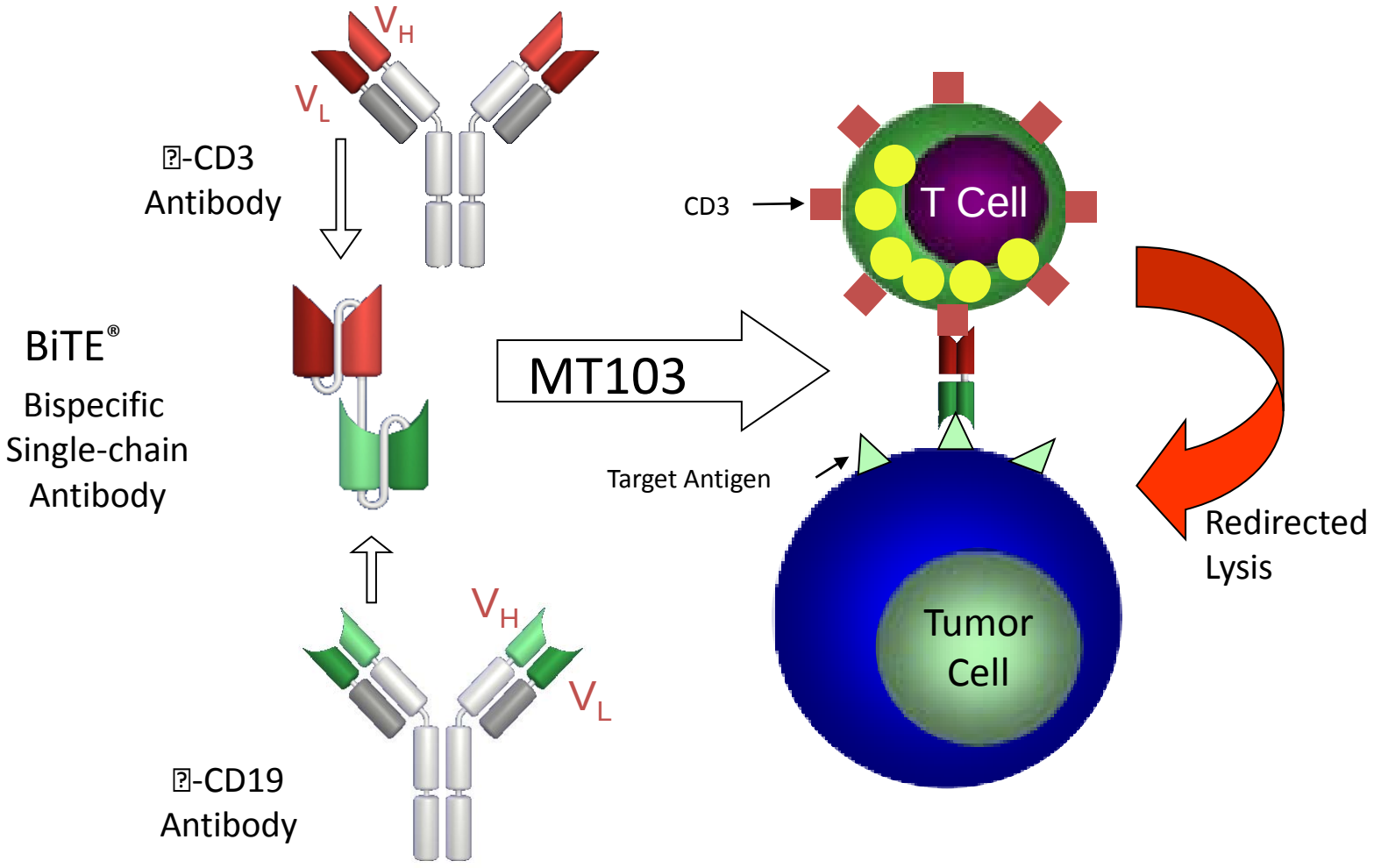
- N=126 (18-81 a.)
- RC tras 1-2 ciclos: 45/126 (36%)
- RP: 12 (10%)
- SG: 24% (1 a.), 11% (6 a.)
- TPH en 80% pacientes en RC
- SG pacientes TPH: 31% (3a.)
- Toxicidad
  - Neurológica III-IV: 4% ciclos, 7% pacientes

Gokbuget N. Blood 2011, E-pub, june 28

Bispecific T Cell Engagers (BiTEs) Redirect Any Cytotoxic T Cell to Tumor Cells



Blinatumomab. Mode of Action

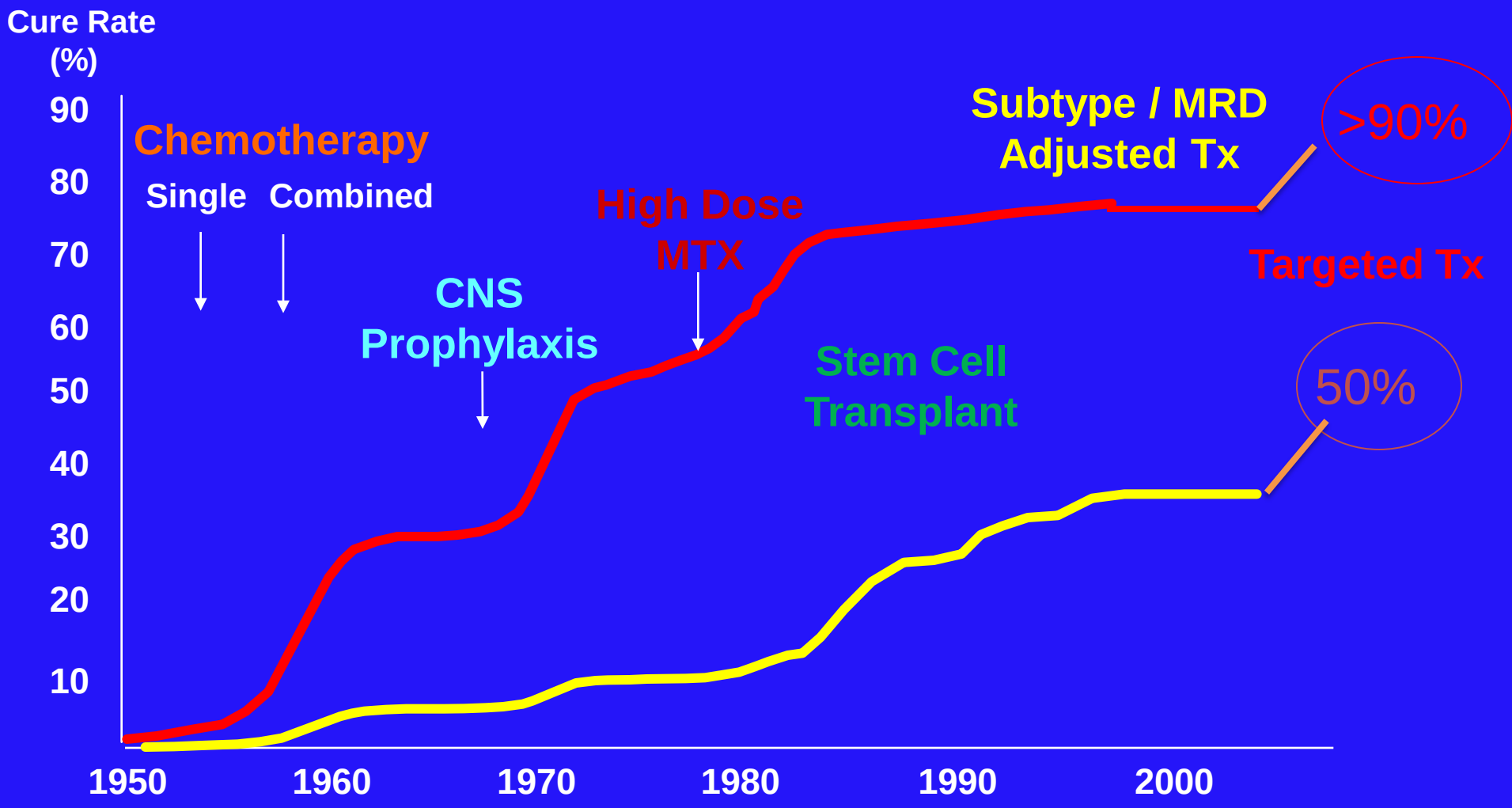


Blinatumomab in chemotherapy-refractory minimal residual disease in B-lineage ALL

- 21 patients with MRD persistence or relapse after induction and consolidation therapy.
- 4-week continuous intravenous infusion 15 μg/m^2/24 h
- 16/21 patients became MRD negative (12 patients had been molecularly refractory to previous chemotherapy)
- Probability for RFS is 78% at a median follow-up of 405 days
- Most frequent grade 3 and 4 adverse event was lymphopenia, which was completely reversible like most other adverse events

Topp MS, et al. J Clin Oncol. 2011 Jun 20;29(18):2493-8.

History of Treatment in Acute Lymphoblastic Leukemia



Agradecimientos

- Investigadores grupos PETHEMA y GETH
- Fundación PETHEMA
- Deutsche José Carreras Leukämie-Stiftung
- EWALL Group
- Acute Leukemia Working Party EBMT

jribera@iconcologia.net

White blood cells from a patient with acute lymphoblastic leukaemia

Lancet Oncology 2009