Risk-adapted stratification and treatment of childhood ALL

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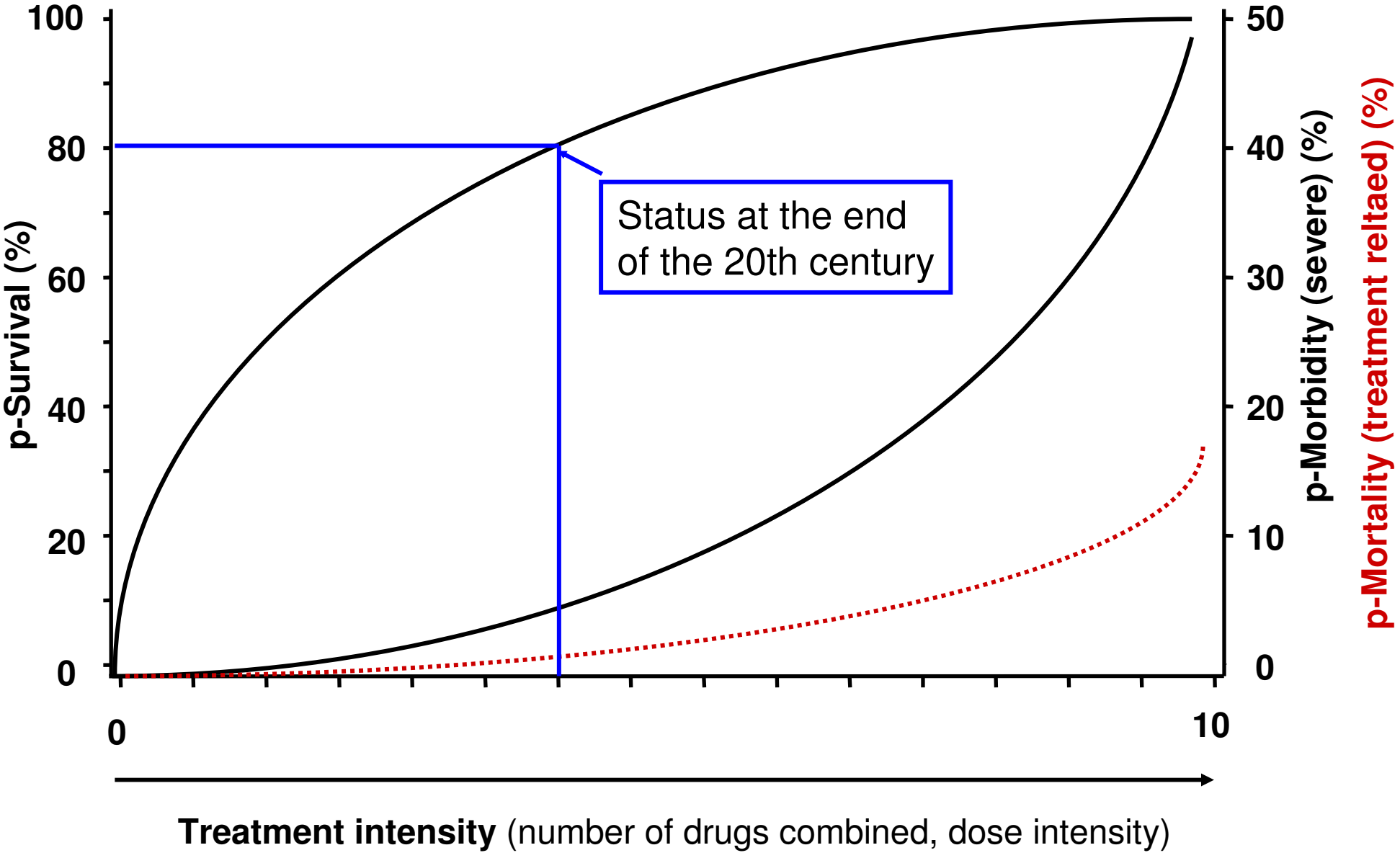
Childhood ALL: The Treatment Dilemma



Current issues addressed in pediatric ALL

- To identify and to target the remaining 20% of patients who do not survive ALL
- To determine the essential elements of therapy
- To identify the patients at very low risk to relapse to prevent further intensification for them
- To adapt therapy to limit toxicity
- To eliminate treatment elements with potential long-term toxicity

Results of international clinical trials in ALL of children and adults

Table 1. Results of Selected Clinical Trials in Patients with ALL.*

Patients and Study Group	Years of Study	No. of Patients	Age Range	5-Yr Event-free Survival	Reference
			yr	%	
Children					
ALL–BFM 90	1990–1995	2178	0–18	78±1.0	Schrappe et al.[1]
CCG-1800	1989–1995	5121	0–21	75±1.0	Gaynon et al.[2]
COALL-92	1992–1997	538	1–18	76.9±1.9	Harms and Janka-Schaub[3]
DFC protocol 91-01	1991–1995	377	0–18	83±2	Silverman et al.[4]
NOPHO ALL-92	1992–1998	1143	0–15	77.6±1.4	Gustafsson et al.[5]
SJCRH XIII	1991–1998	412	0–18	79.4±2.3	Pui et al.[6]
Adults					
GMALL 02/84	1983–1987	562	15–65	39 (at 7 yr)†	Gökbuget and Hoelzer[7]
MDACC	1992–1998	204	16–79	38†	Kantarjian et al.[8]
UCSF 8707	1987–1998	84	16–59	48±13	Linker et al.[9]

* Plus–minus values are means ±SE. BFM denotes Berlin–Frankfurt–Münster, CCG Children's Cancer Group, COALL Cooperative Study Group of Childhood Acute Lymphoblastic Leukemia, DFC Dana–Farber Consortium, NOPHO Nordic Society of Pediatric Haematology and Oncology, SJCRH St. Jude Children's Research Hospital, GMALL German Acute Lymphoblastic Leukemia Study Group, MDACC M.D. Anderson Cancer Center, and UCSF University of California, San Francisco.

† The rate of continuous complete remission is shown; patients in whom induction therapy failed and those who died were excluded from the analysis.

Pui CH et al. (2004) NEJM 350: 1535-48

Results of international clinical trials in ALL of children and adults

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Can differences be explained by differences in biology and aetiology?

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Or is different treatment outcome due to better ALL treatment protocols in Pediatric Hematology / Oncology?

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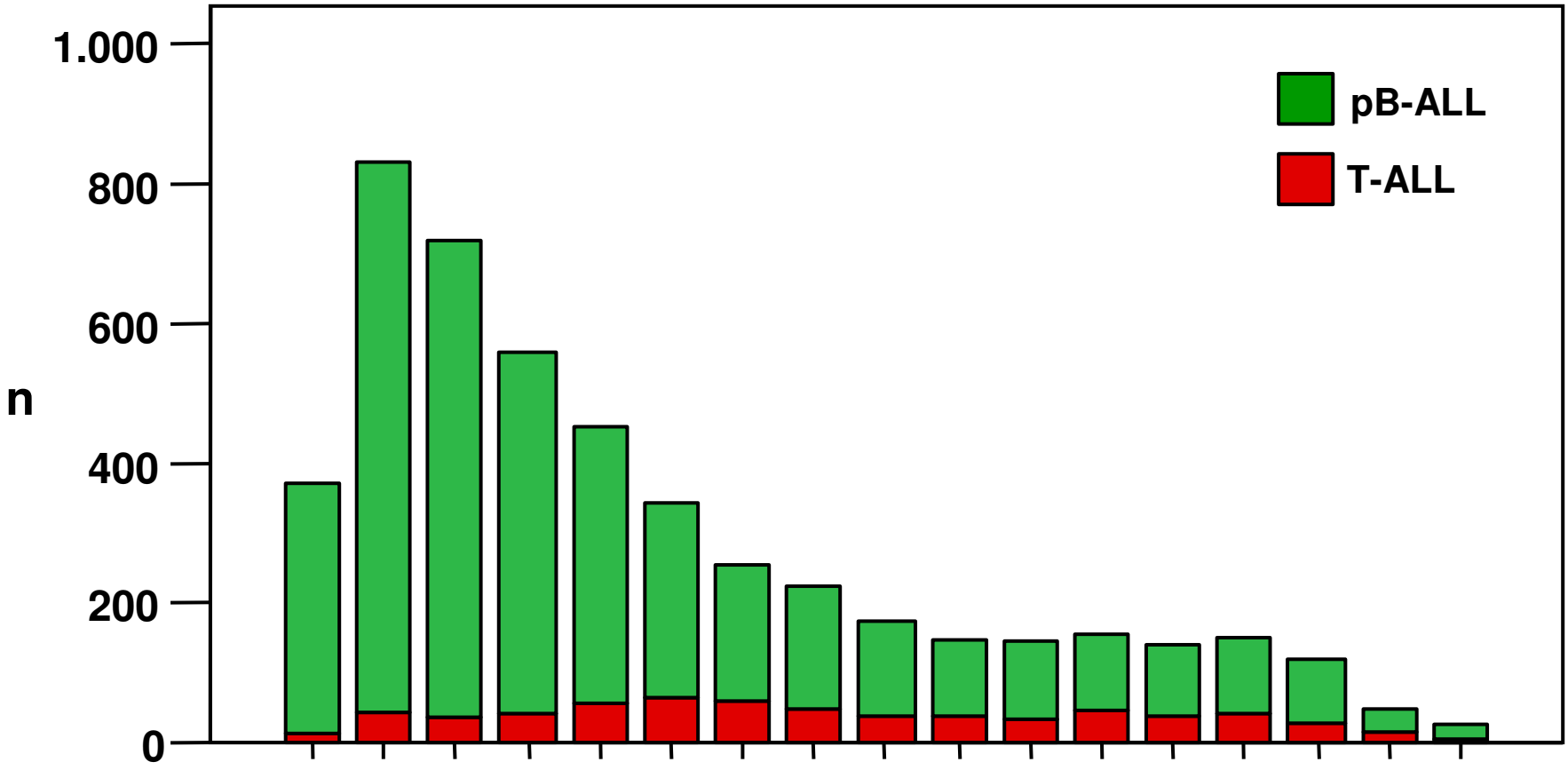
Pui CH et al. (2004) NEJM 350: 1535-48

Trials ALL-BFM 86, 90 and 95 (n = 4988)

Age distribution by immunologic subtype

Cases per age group (year of diagnosis)

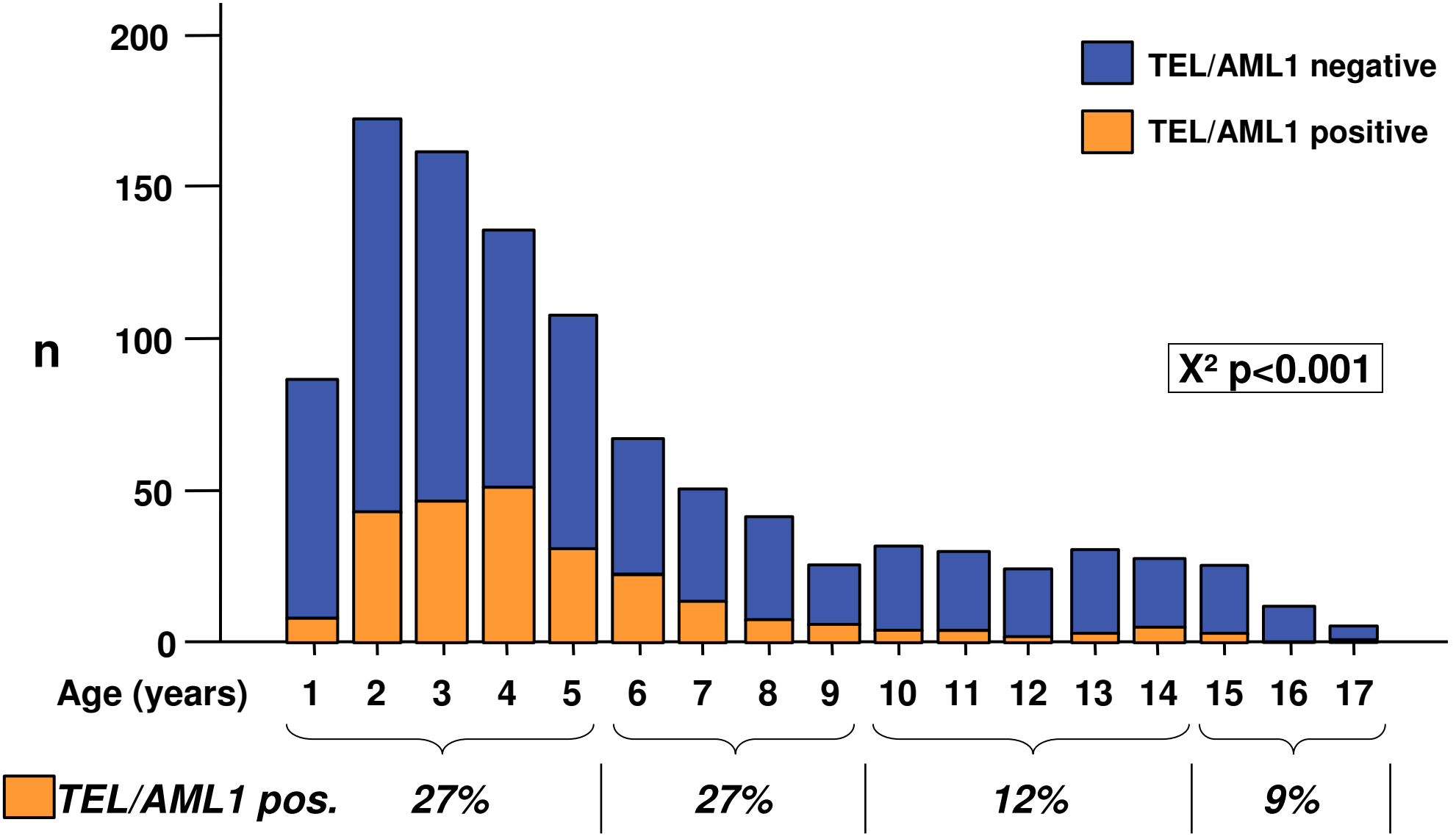
age 1-17
infants excl.



Age at dx (yrs)	1 2 3 4 5	6 7 8 9	10 11 12 13 14	15 16 17
pB-ALL	93%	79%	73%	75%
T-ALL	7%	21%	27%	25%

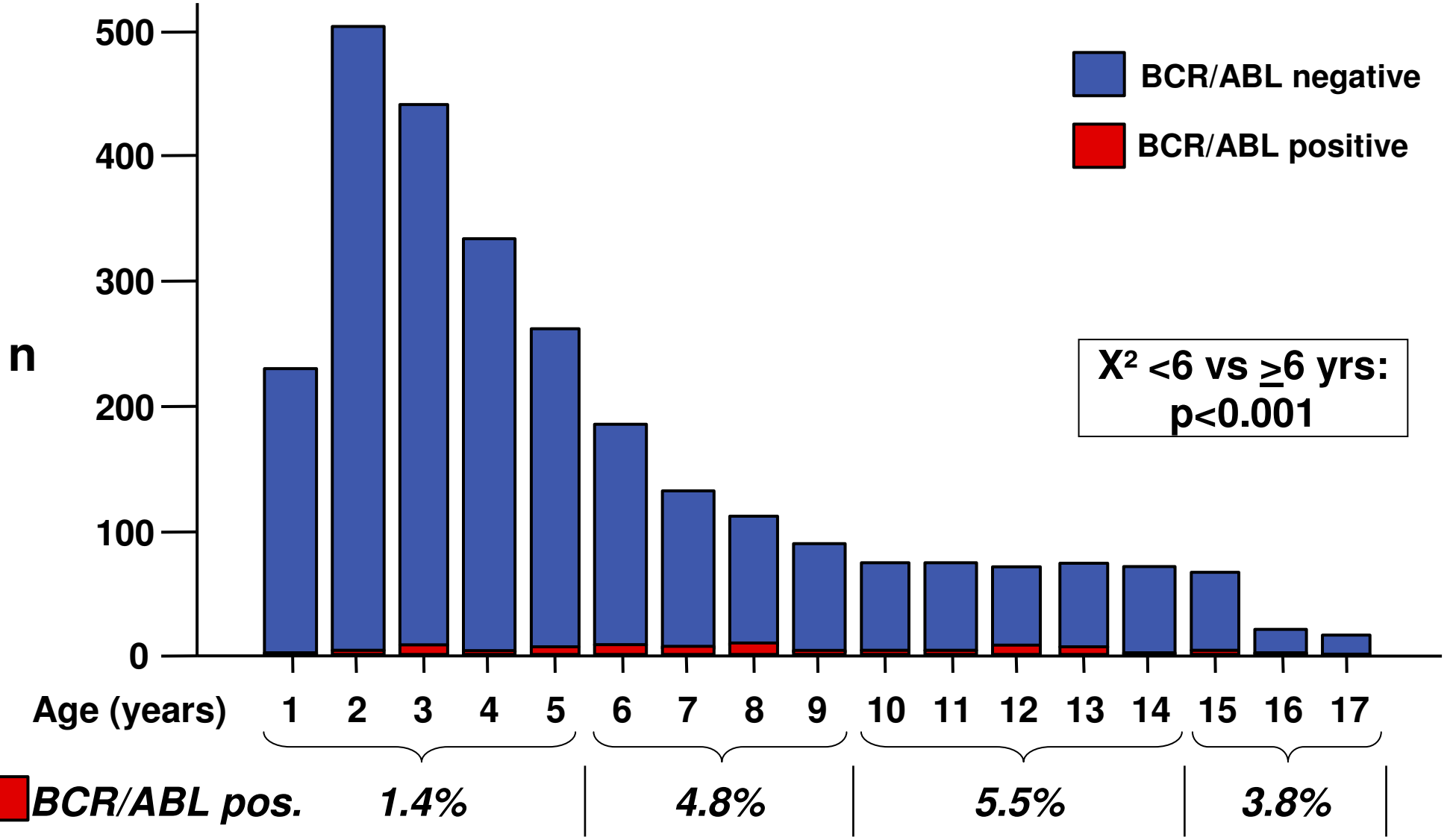
Trials ALL-BFM 86, 90 and 95 (n=1063)

Age distribution in pB-ALL by presence of TEL/AML1



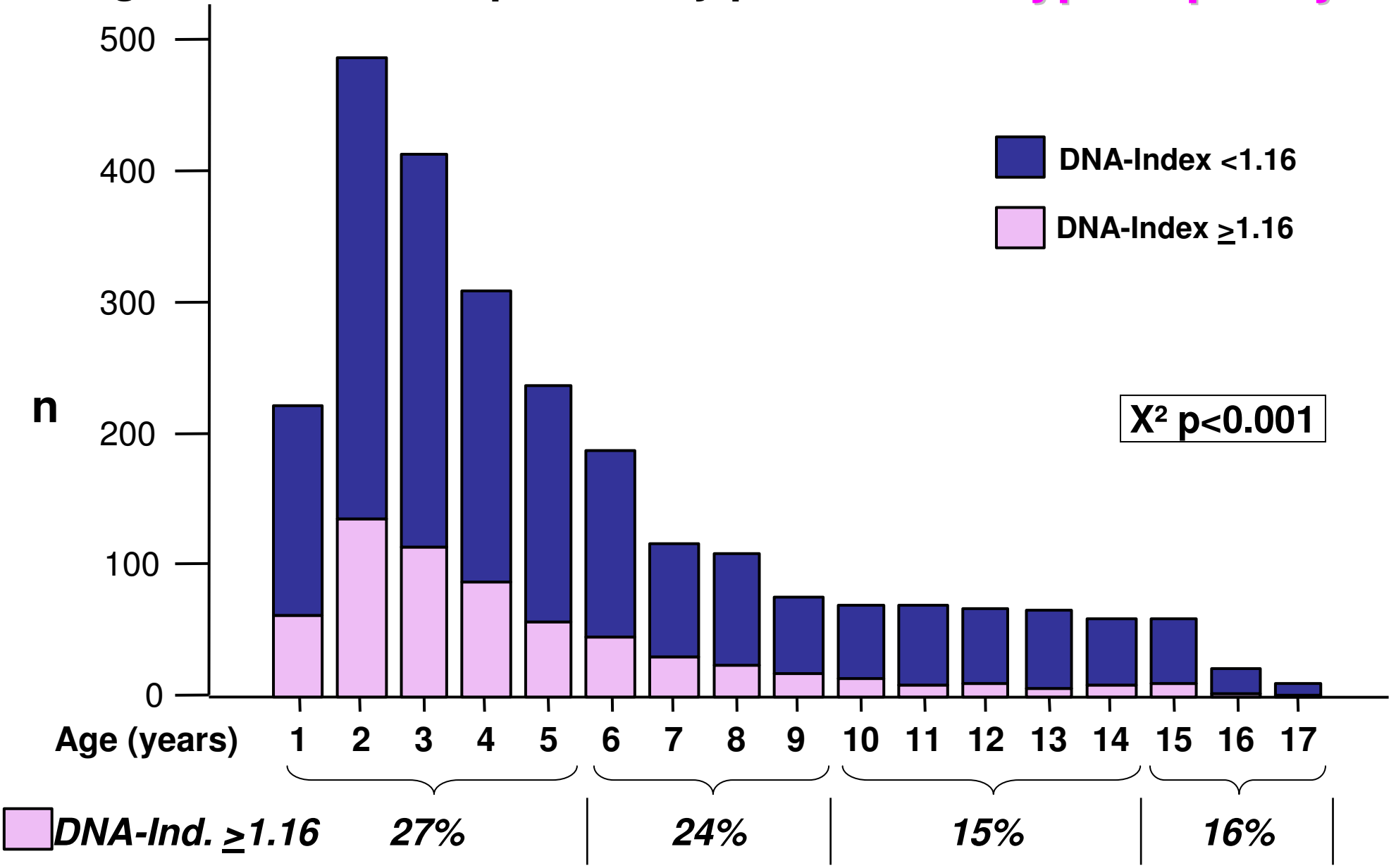
Trials ALL-BFM 86, 90 and 95 (n=2845)

Age distribution in pB-ALL by presence of BCR/ABL



Trials ALL-BFM 86, 90 and 95 (n = 2654)

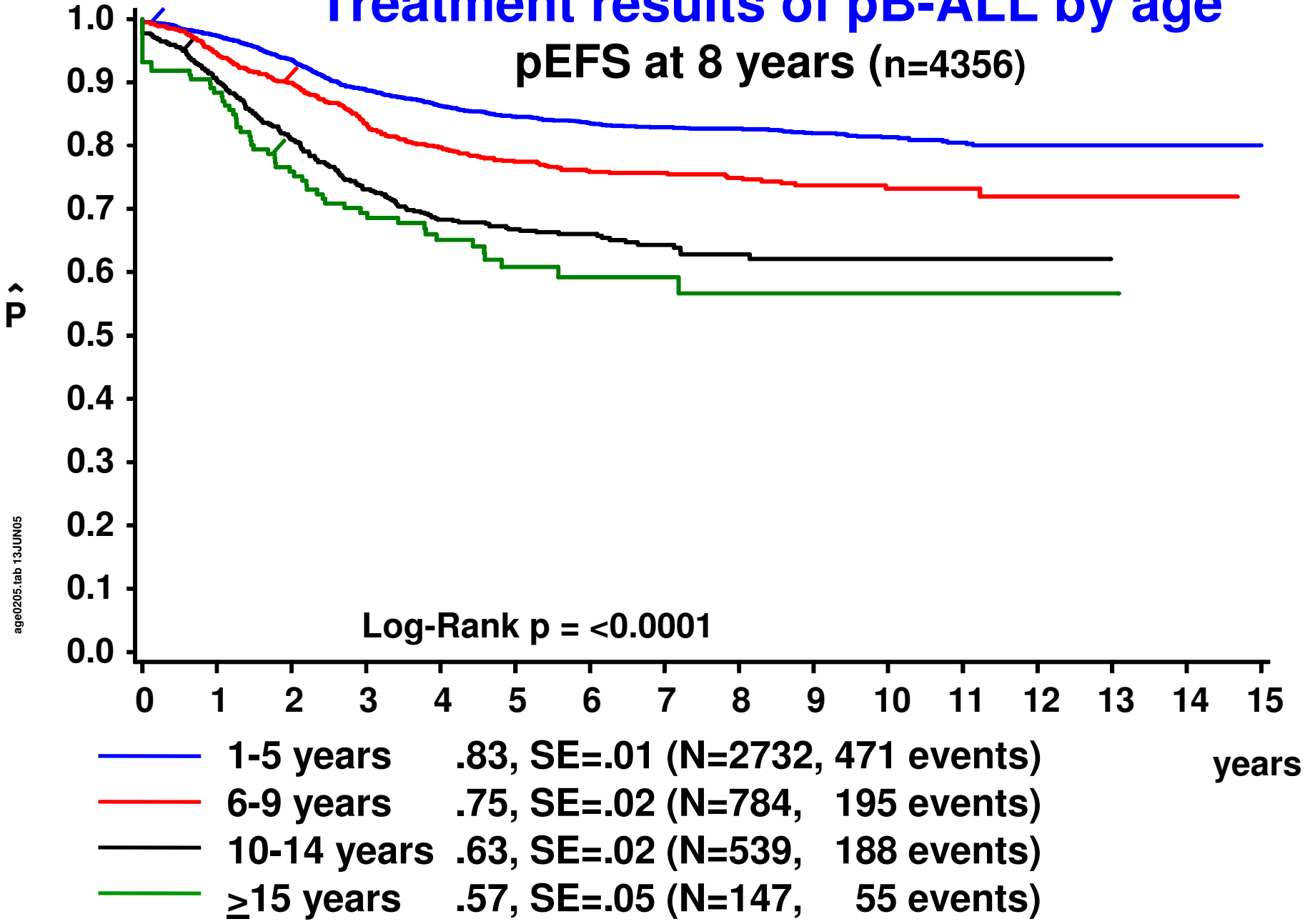
Age distribution in pB-ALL by presence of hyperdiploidy



Trials ALL-BFM 86, 90 and 95

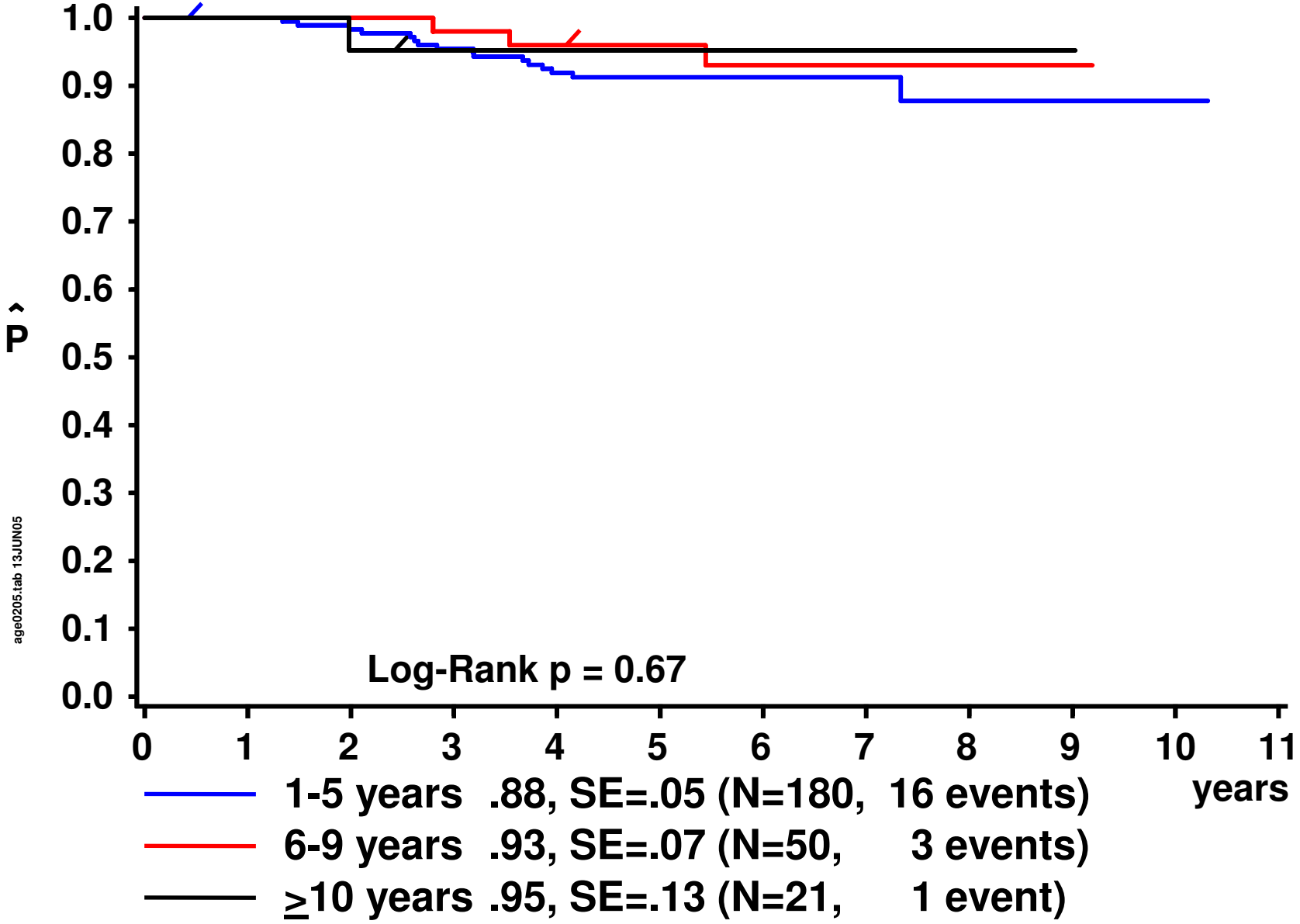
Treatment results of pB-ALL by age

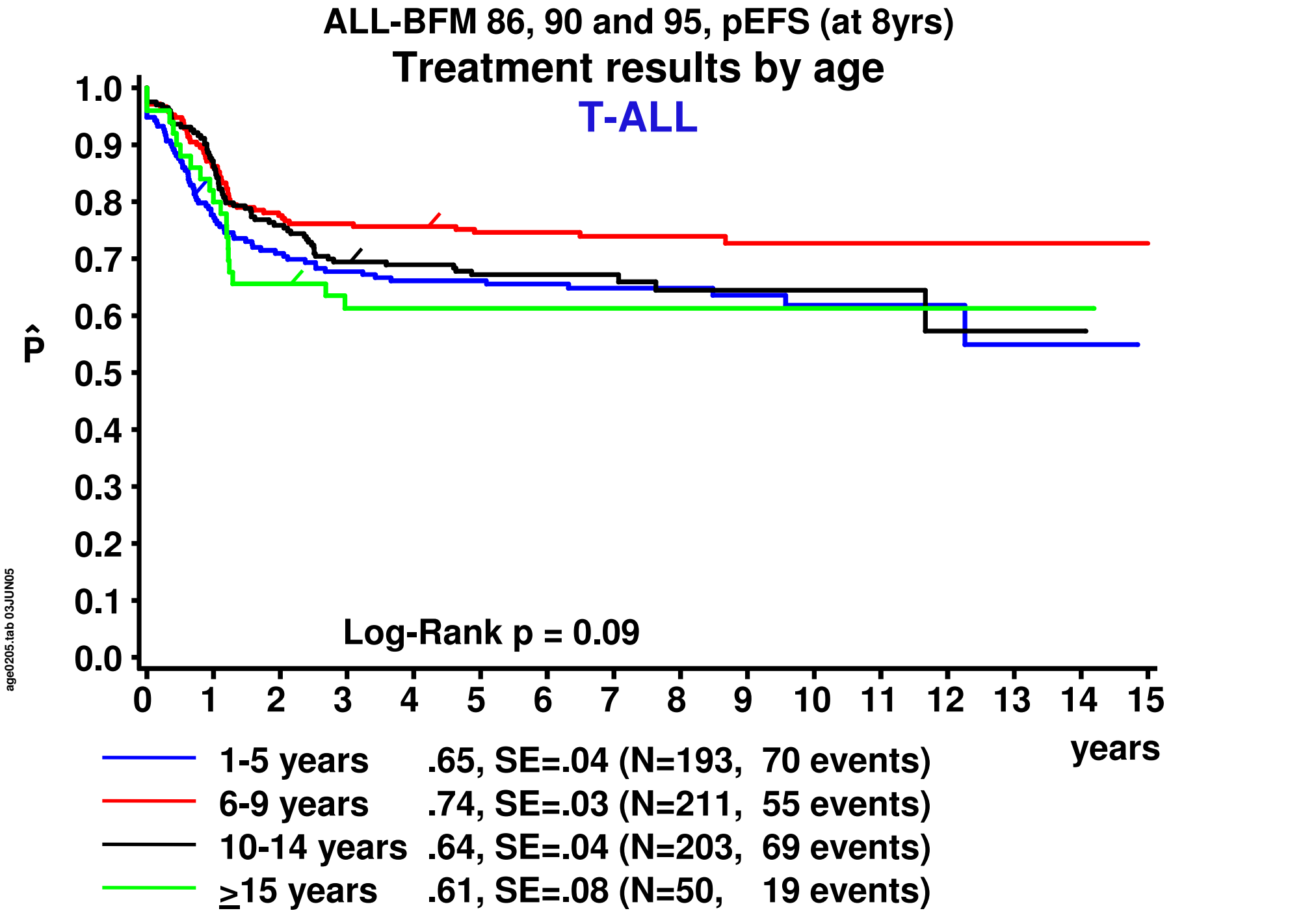
pEFS at 8 years (n=4356)



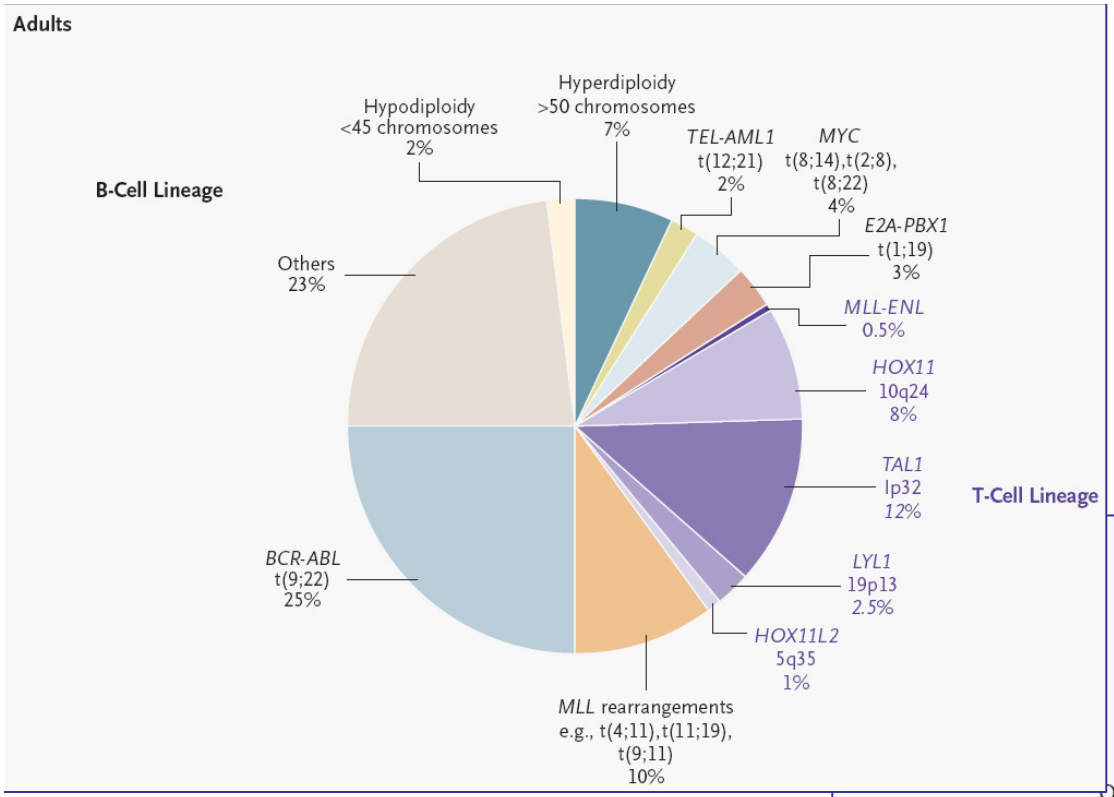
Trials ALL-BFM 86, 90 and 95

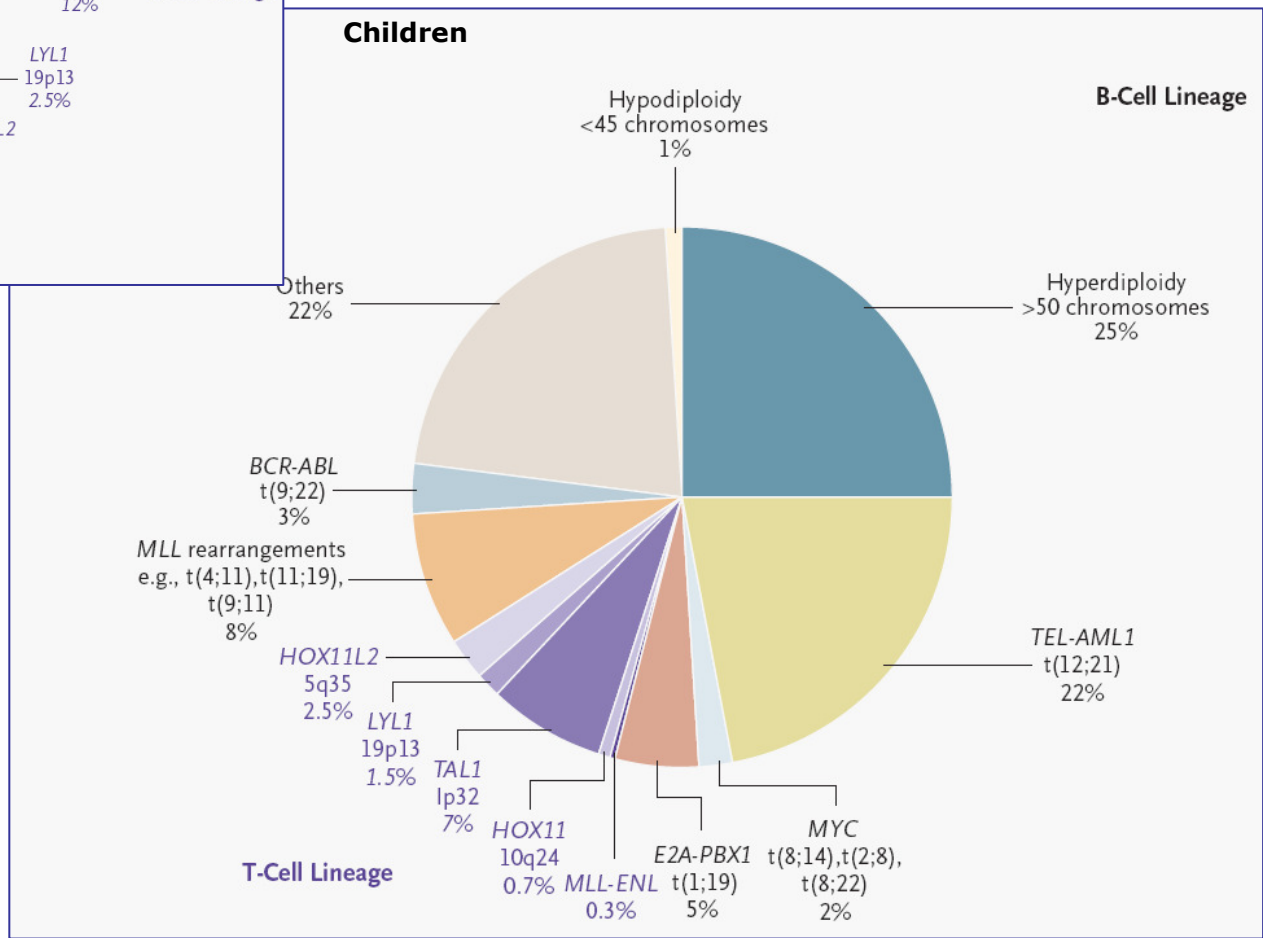
Treatment results of TEL/AML1 pos pB-ALL by age




ALL-BFM 86, 90 and 95, pEFS (at 8yrs)
Treatment results by age
T-ALL
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P̂
Log-Rank p = 0.09
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
years
1-5 years .65, SE=.04 (N=193, 70 events)
6-9 years .74, SE=.03 (N=211, 55 events)
10-14 years .64, SE=.04 (N=203, 69 events)
≥15 years .61, SE=.08 (N=50, 19 events)
age0205.tab 03JUN05

Comparison of genetic subgroups in ALL of children and adults





Pui CH et al. (2004) NEJM 350: 1535-48

Clinical challenge

- in childhood ALL, high risk (HR) subsets are small:

  = data analysis per study group is limited, intergroup metaanalysis may serve as substitute.

- most intermediate risk (IR, 5y-EFS ~80%) or low risk (LR, 5y-EFS >90%) subsets are large:
  - **The contribution of any additional therapeutic element will only be proven if large patient numbers are available for such trial.**
  - **The dilemma: any additional therapeutic intervention (*if not clearly less toxic and replacing previously used elements*) will be unnecessary for most patients as they are already cured with existing treatment.**

ALL: Stratification (1)

Based on initial clinical and diagnostic parameters:

- **age**
- **WBC**
- **extramedullary involvement**
- **immunphenotype**
- **cyto- and molecular genetics**

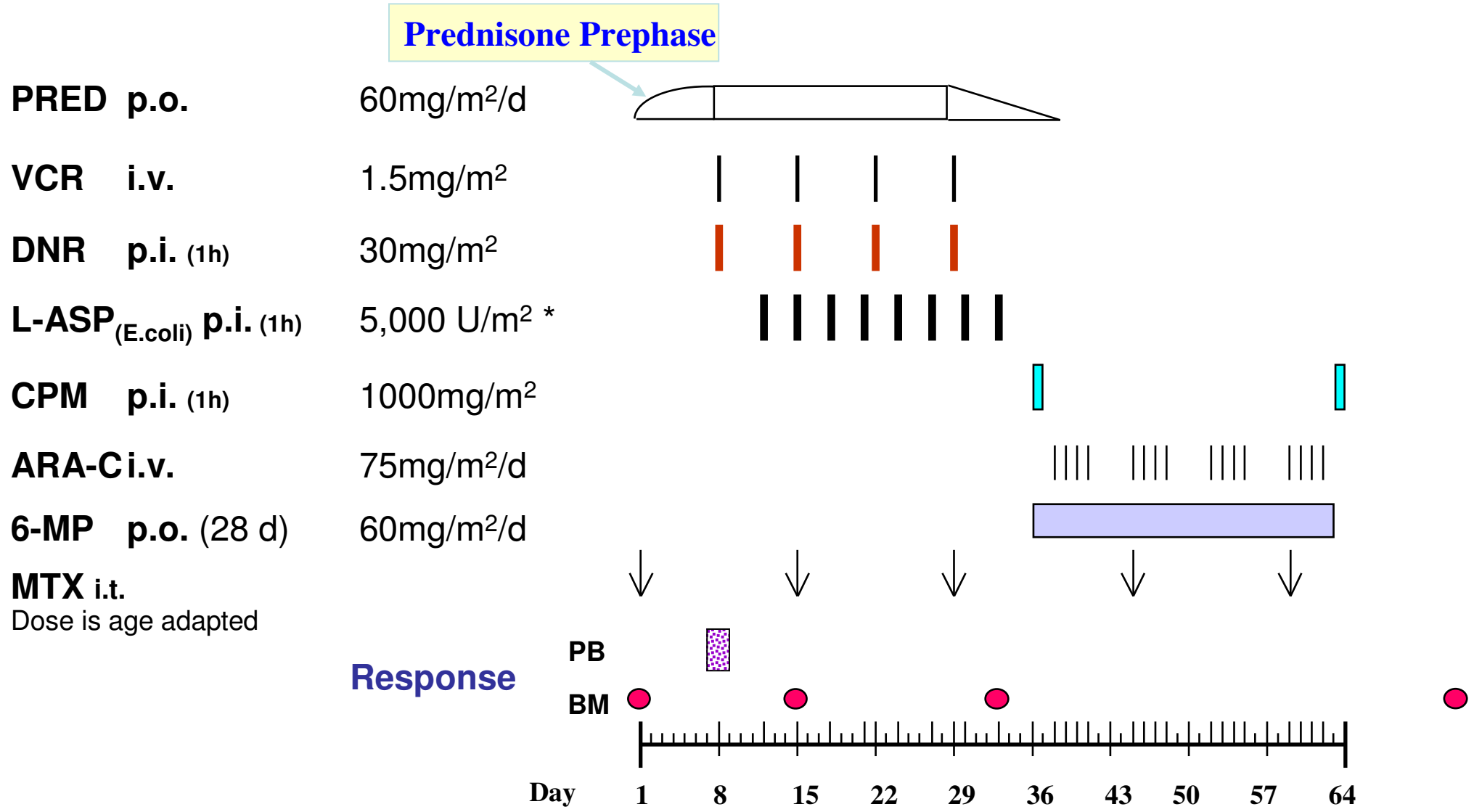
Stratification (2)

Based on initial clinical and diagnostic parameters:

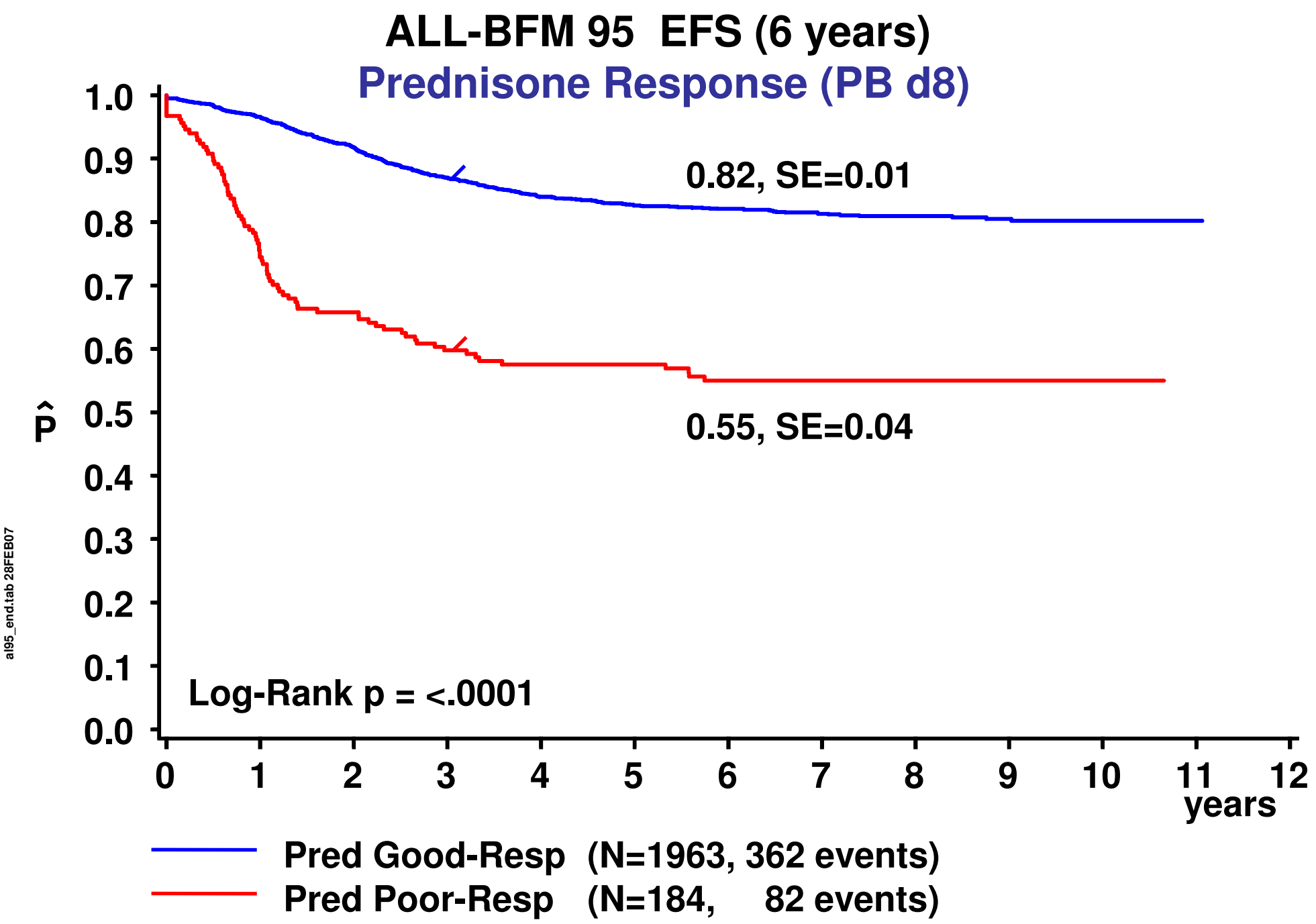
- age
- WBC
- extramedullary involvement (e.g. CNS-3, TLP+)
- immunphenotype
- cyto- and molecular genetics:
  - **relevant high risk (HR) subsets:**
    - t(9;22) (BCR-ABL)
    - t(4;11) (MLL-AF4)
    - hypodiploidy (<46 [<44] chromosomes)
    - [other MLL rearrangements]
  - **relevant low risk (LR) subsets:**
    - t(12;21) (TEL-AML1)
    - hyperdiploidy
    - [t(1;19) (E2A-PBX1)]

Individual Treatment Response as additional tool for risk assessment

ALL-BFM 90, 95 and AIEOP-BFM ALL 2000:
Induction and induction-consolidation ("Protocol I-A/B")



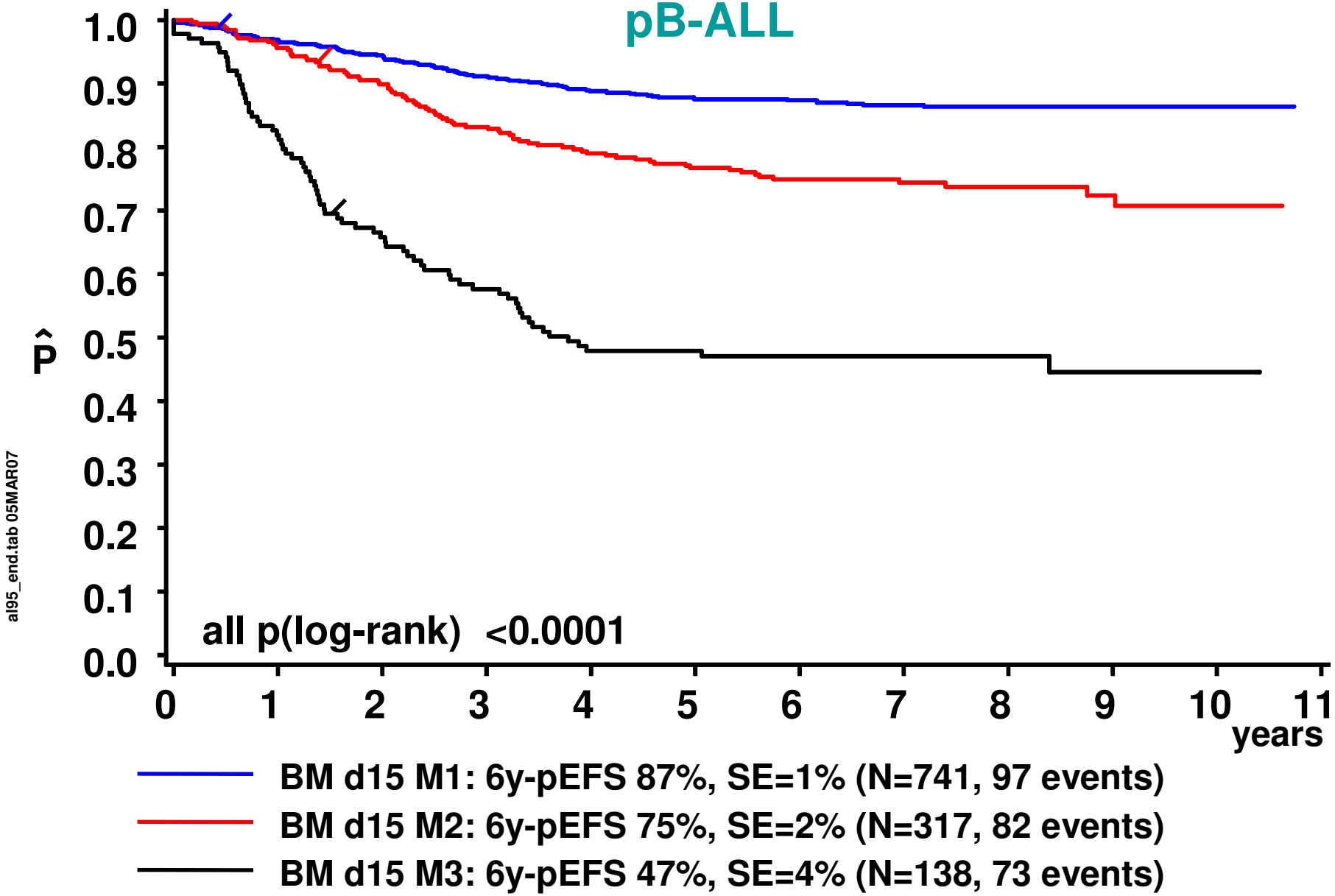
*** In previous ALL-BFM trials dose and product was different**


ALL-BFM 95 EFS (6 years)
Prednisone Response (PB d8)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P̂
0.82, SE=0.01
0.55, SE=0.04
Log-Rank p = <.0001
0
1
2
3
4
5
6
7
8
9
10
11
12
years
Pred Good-Resp (N=1963, 362 events)
Pred Poor-Resp (N=184, 82 events)
al95_end.tab 28FEB07

ALL-BFM 95

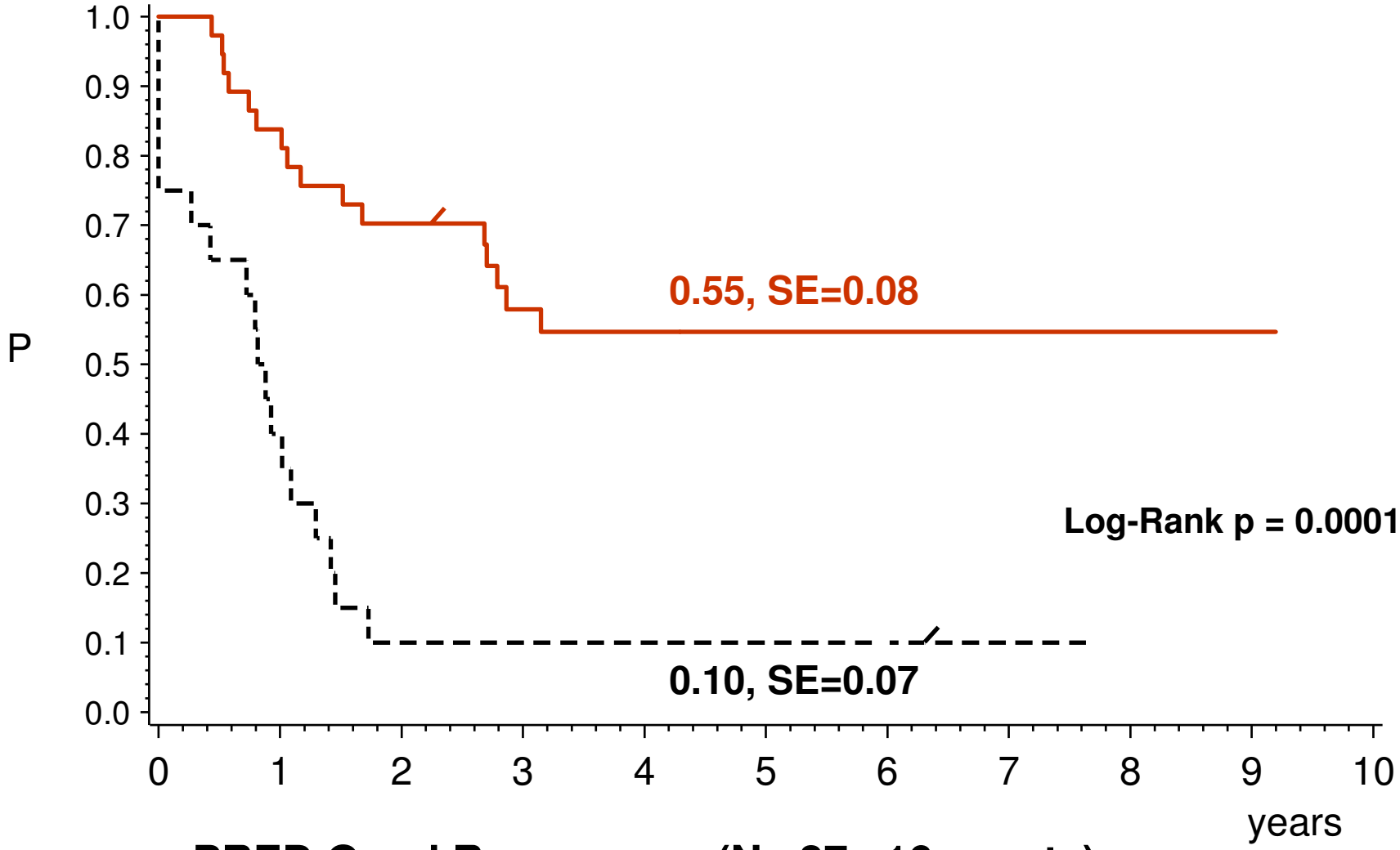
Prognostic Impact of BM Response on Day 15

pB-ALL



EFS in Ph+ ALL according to Prednisone Response

Results from BFM and AIEOP (1986-95)



Schrappe M, Arico M, Harbott J, et al.
BLOOD 92 (1998): 2730

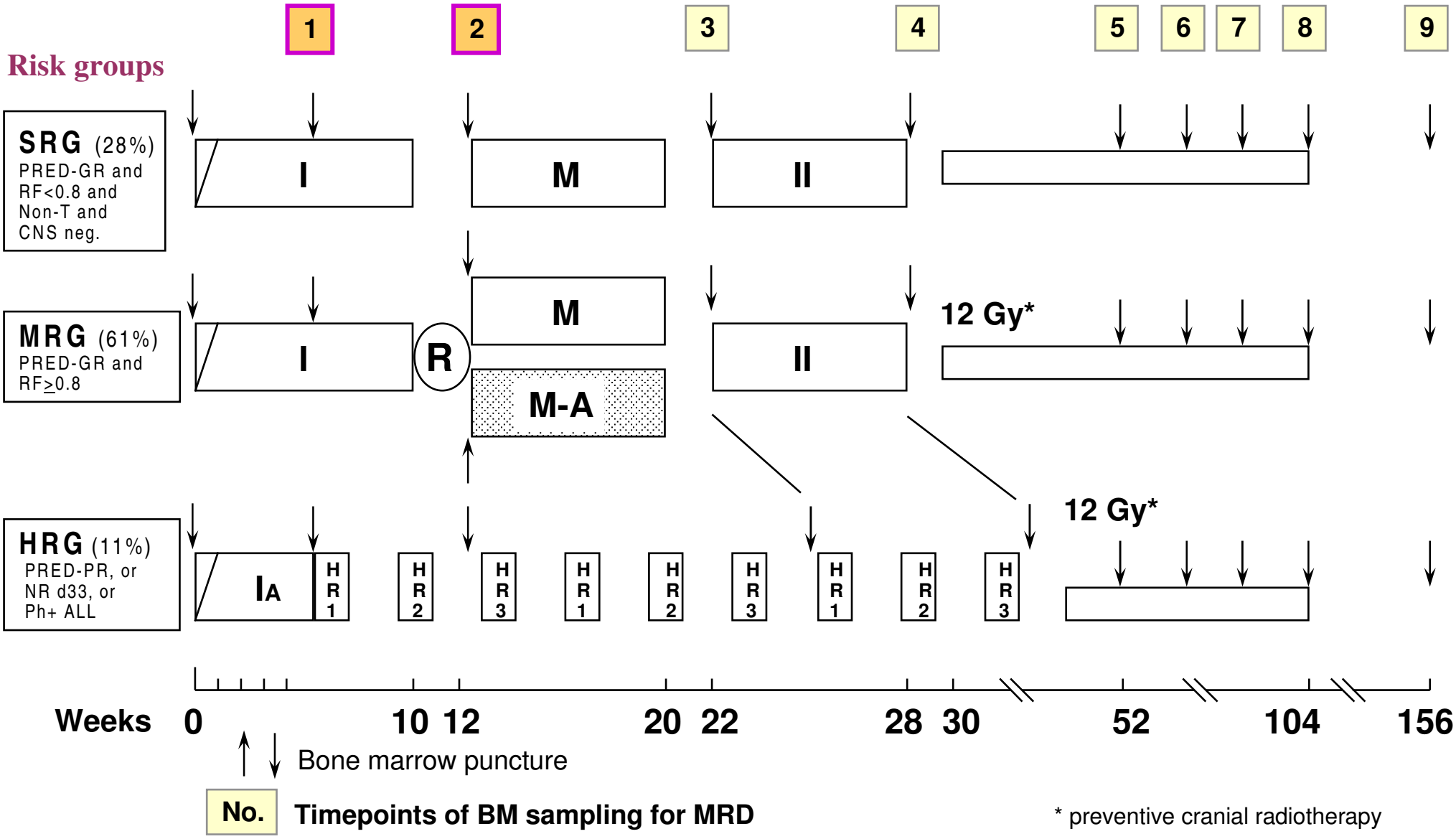
Improve risk group definition through detection of MRD

I-BFM-SG MRD Study (1991-95)

BFM-G, BFM-A, DCOG, AIEOP

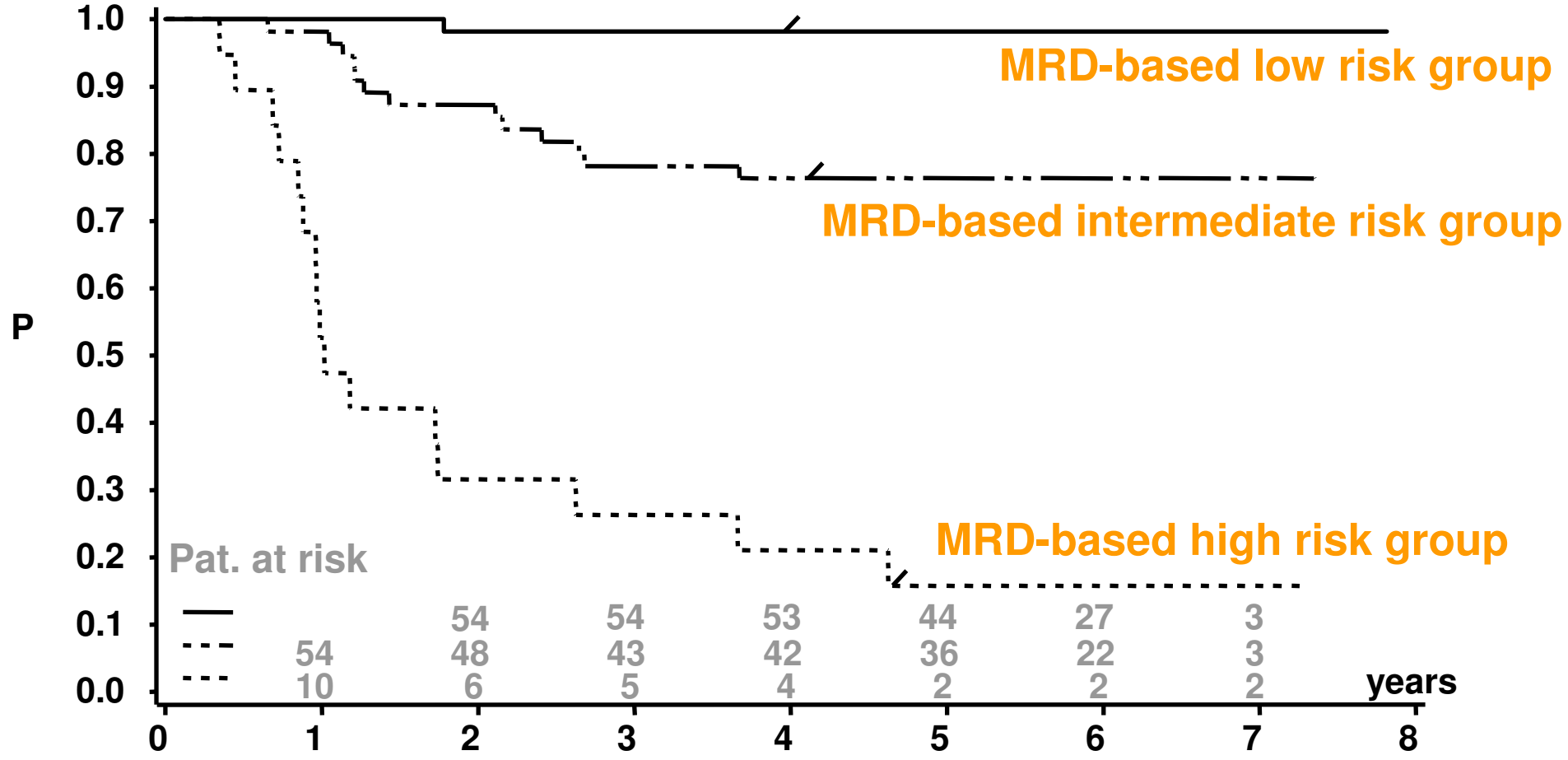
JJM van Dongen et al., Lancet 352 (1998): 1731

I-BFM-SG MRD Study (1991-95): Monitoring of minimal residual disease (MRD) in the course of treatment



I-BFM-SG MRD-Study: Relapse free survival *

Risk groups by MRD at 5 weeks (Tp 1) and 12 weeks (Tp 2)



Tp 1+2 neg.: RFS .98, SE=.02; n= 55 (43%), 1 relapse (3%)

Tp 2 < 10^{-3}: RFS .76, SE=.06; n= 55 (43%), 13 relapses (43%)

Tp 2 >=10^{-3}: RFS .16, SE=.08; n= 19 (14%), 16 relapses (54%)

Distribution of relapses

MRD0599h.tab 23MAY99

* Update 2002, see JJM van Dongen et al., Lancet 352 (1998): 1731

Use of a MRD based risk group definition for stratification to improve risk-adapted therapy

AIEOP-BFM ALL 2000

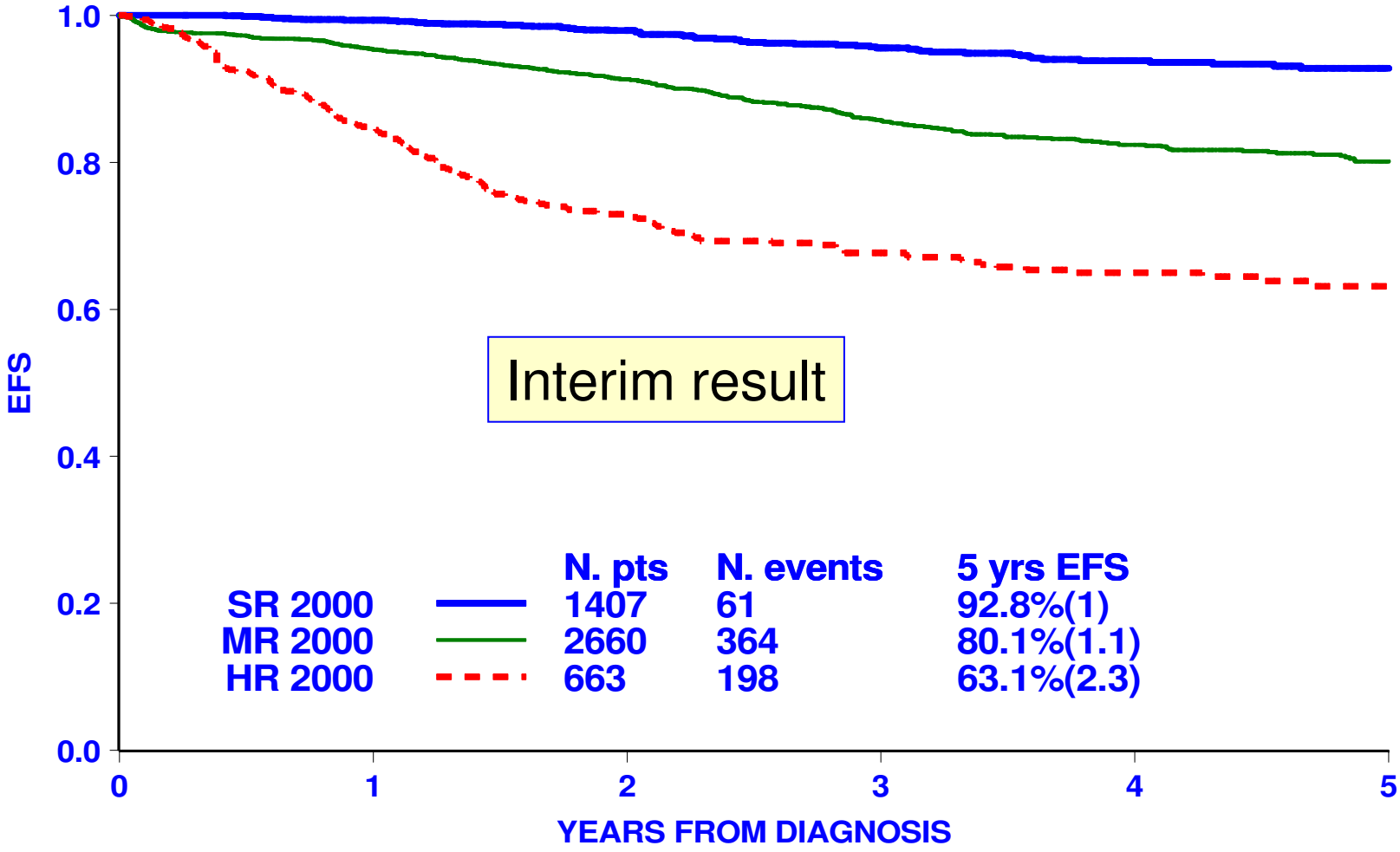
Trial Steering Committee:

M. Schrappe, Kiel

G. Masera, Monza

H. Gadner, Wien

AIEOP-BFM 2000
by risk group
4730 patients



CORS/Hannover - Apr 2007

no Ph+

Risk adapted stratification: Combination of upfront and response derived criteria

- **Based on initial parameters:**
  - **age**
  - **WBC**
  - **extramedullary involvement**
  - **immunphenotype**
  - **cyto- and molecular genetics**
- **Based on early response:**
  - **prednisone response: blast count d8 in PB**
  - **BM response: blast count at d15**
  - **BM response: blast count at d33 (end of induction)**
  - **MRD response:**

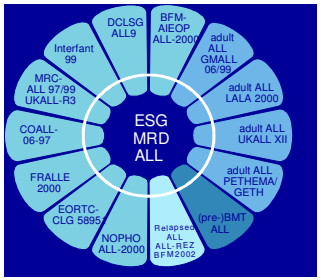
Organization of Treatment

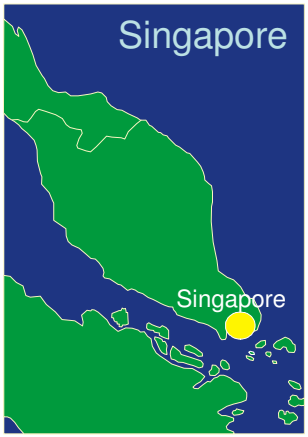
- **well-controlled clinical trials comprising**
  - **registry and follow-up,**
  - **diagnostics and sample banking,**
  - **prospective treatment questions.**

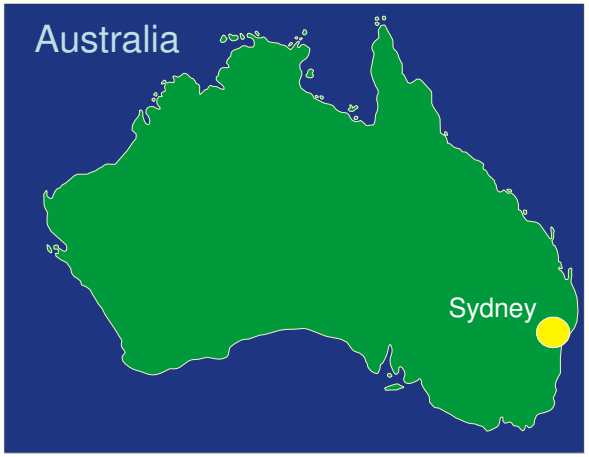
European Study Group on MRD detection in ALL

Quality control and further refinement

(ESG-MRD-ALL; 30 labs in 15 countries)







by courtesy of J.J.M. van Dongen

Organization of Treatment

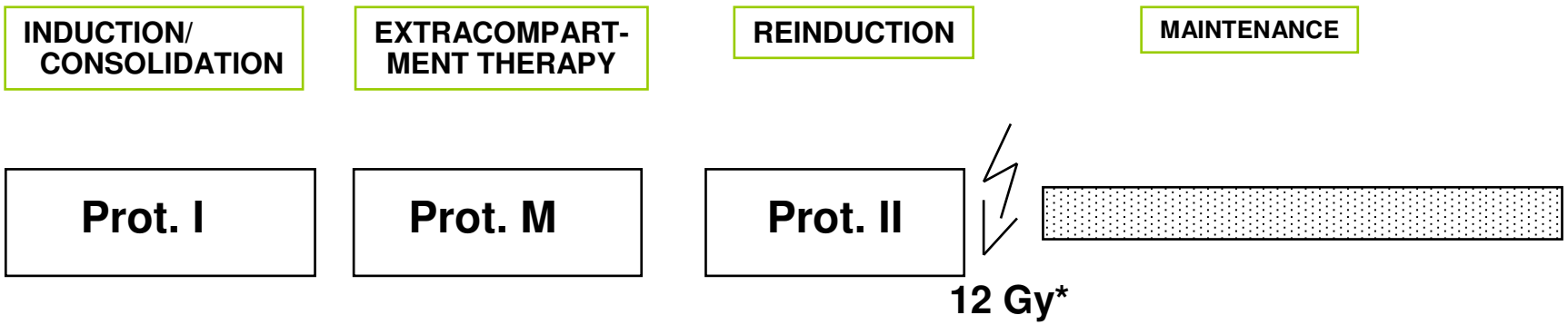
- well-controlled clinical trials comprising
  - registry and follow-up,
  - diagnostics and sample banking,
  - prospective treatment questions
- population-based patient entry
- internal and external data and safety monitoring
- funding through public research grants or foundations

Pediatric ALL: Coverage through clinical trials in Europe

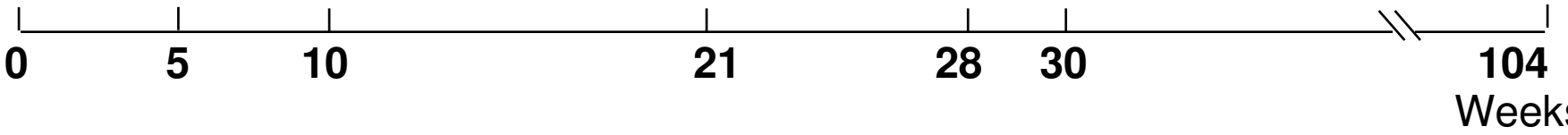
Country	Study Group	Patients (est., p.a.)	Population based
A	BFM-A	50	yes
B/F/P	EORTC-CLG	200	(yes)
CH	BFM, others	50	n.k.
D	BFM-G; COALL	550	yes
F	FRALLE	370	(yes)
I	AIEOP	340	yes
Scand.	NOPHO	180	yes
U.K.	CCG-LWP	350	yes

Treatment

ALL-BFM "Backbone": Platform for prospective evaluation of treatment variants



Studies on:	PDN	MD/HD-MTX	ASP	DEX/VCR pulses
	DEX	ASP		
	ASP	ARA-C		
		CPM	*pCRT*	
		allo SCT	*DDI*	



- no prophylactic cranial radiotherapy (pCRT) if age <1y;
- since ALL-BFM 95, pCRT only in T-ALL and HR-group
- CNS positive: 0 Gy <1y, 18 Gy >=1y

Relevant treatment components

Approaches and open questions

- **Induction/consolidation**
  - **Corticosteroid: DEX (dose?) replacing PRED?**
  - **Asparaginase: Timing, type, dose?**
  - **role of anthracyclines?**
- **Extracompartment therapy: HD-MTX, IT therapy?**
- **Preventive cranial radiotherapy (for which pts?)**
- **Delayed intensification (x1, or x2?)**
- **Allogeneic hematopoetic stem cell transplantation?**
- **Maintenance therapy: components?**

Example of a large subset of ALL in which the result of a prospective clinical trial may allow to avoid treatment burden in the future

Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial

Valentino Conter, Maria Grazia Valsecchi, Daniela Silvestri, Myriam Campbell, Eduardo Dibar, Edina Magyarosy, Helmut Gadner, Jan Stary, Yves Benoit, Martin Zimmermann, Alfred Reiter, Hansjörg Riehm, Giuseppe Masera, Martin Schrappe

Lancet 2007; 369: 123–31

Randomized cases: n=2618

IR pts treated between 1995 and 2001 from:

Argentina (GATLA), Austria (BFM-A), Chile (PINDA), Czech Republic (CPH), Belgium/France (EORTC-CLG), Germany (BFM-G), Hungary (HPOG), Italy (AIEOP)

I-BFM-SG study on pulses in maintenance

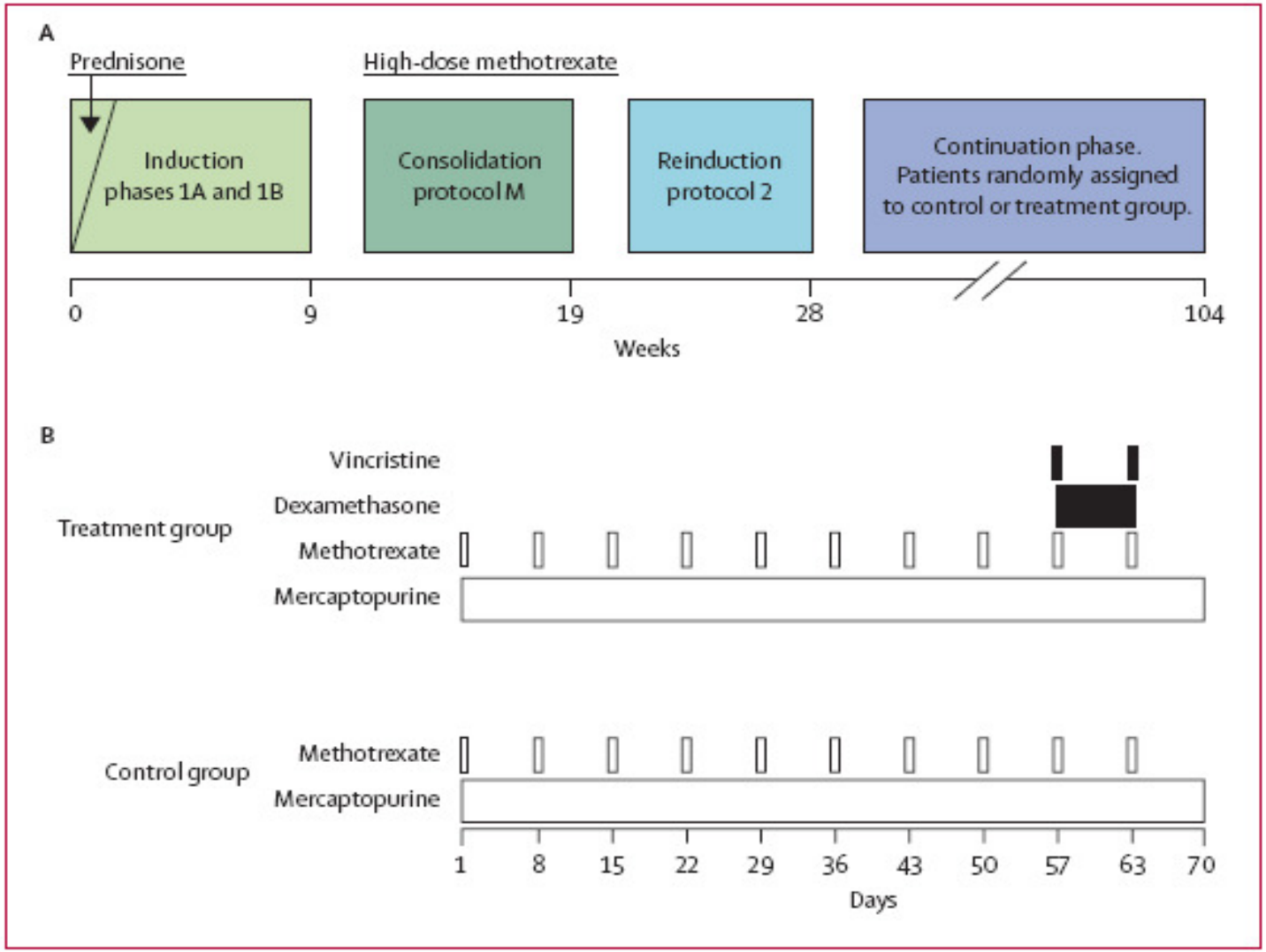


Figure 1: **Schematic of trial protocol based on BFM treatment strategy**
(A) Trial phases by week. (B) Different schedules for control and treatment groups during continuation phase.

IR-ALL: Impact of DEX/VCR during Maintenance Therapy (I-BFM-SG)

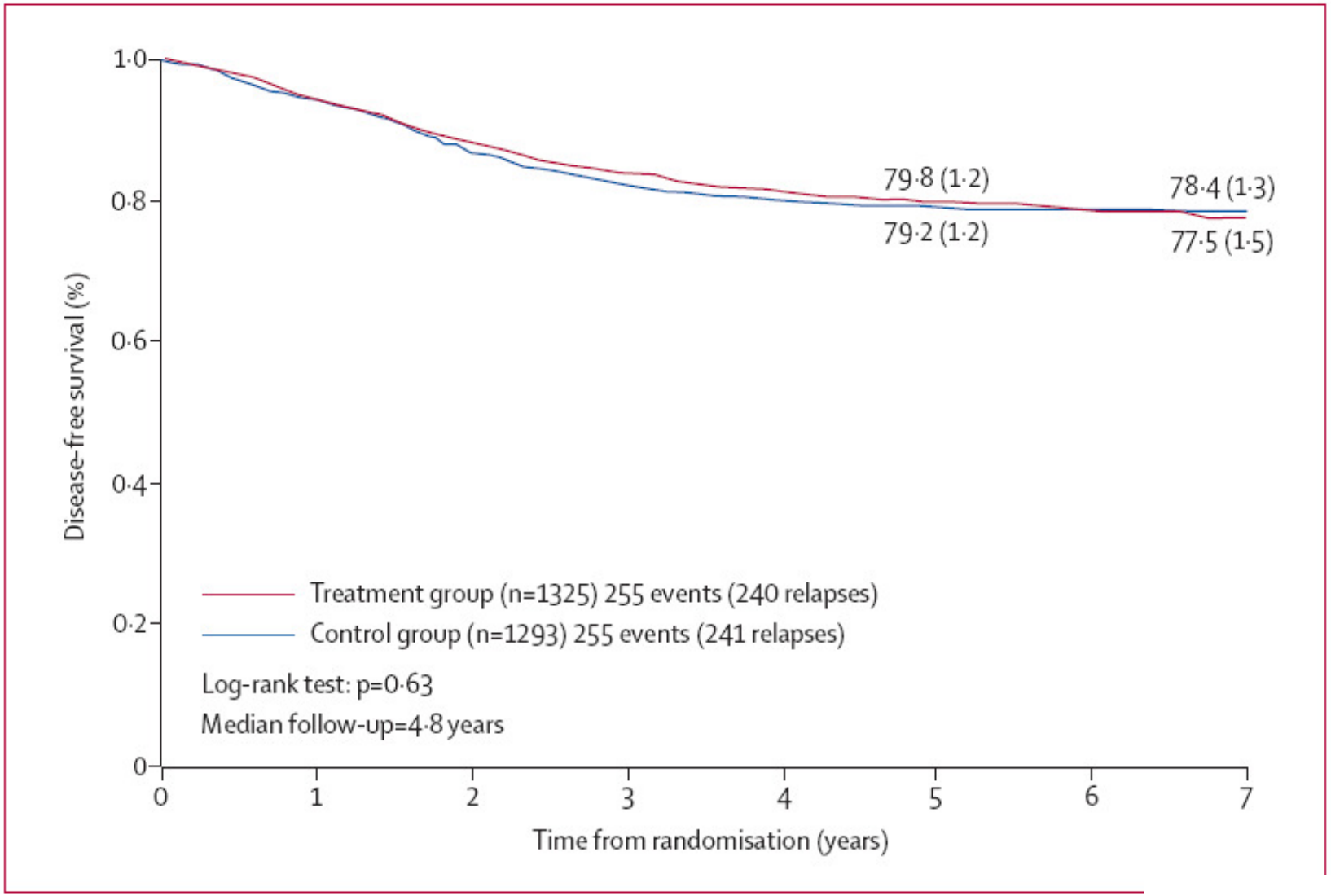


Figure 3: Disease-free survival curves in treatment and control groups

Lancet 2007; 369: 123–31

IR-ALL: Impact of DEX/VCR during M.T. (I-BFM-SG)

Participating organisation	Events (patients) Control group	Treatment group	Hazard ratio (CI)
AIEOP	79 (391)	75 (376)	0·94 (0·62–1·43)
BFM–A	6 (53)	12 (60)	1·78 (0·49–6·47)
BFM–G	90 (480)	87 (526)	0·87 (0·59–1·28)
CPH	11 (43)	6 (43)	0·52 (0·14–1·91)
EORTC–CLG	5 (42)	5 (39)	1·07 (0·21–5·47)
GATLA	18 (102)	24 (95)	1·53 (0·69–3·42)
HPOG	13 (57)	13 (63)	0·89 (0·32–2·43)
PINDA	33 (125)	33 (123)	1·02 (0·54–1·93)
Total	255 (1293)	255 (1325)	0·97 (0·81–1·15)

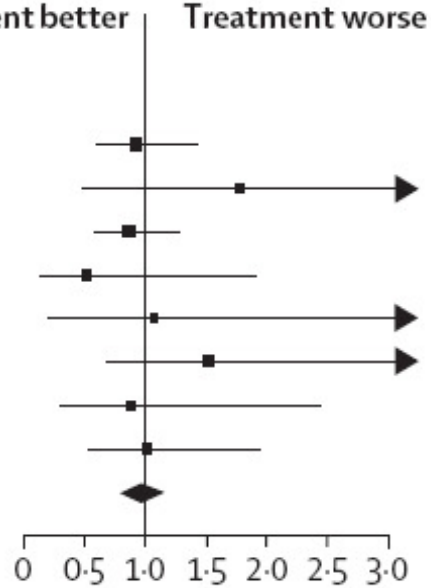


Figure 4: **Estimated effect on disease-free survival of the addition of vincristine and dexamethasone pulses to the continuation phase of intensive chemotherapy, by participating organisation**

Squares indicate the hazard ratio estimate for each participating organisation; horizontal lines show 99% CI; and the diamond shows the hazard ratio and 95% CI for pooled data from all organisations.

Lancet 2007; 369: 123–31

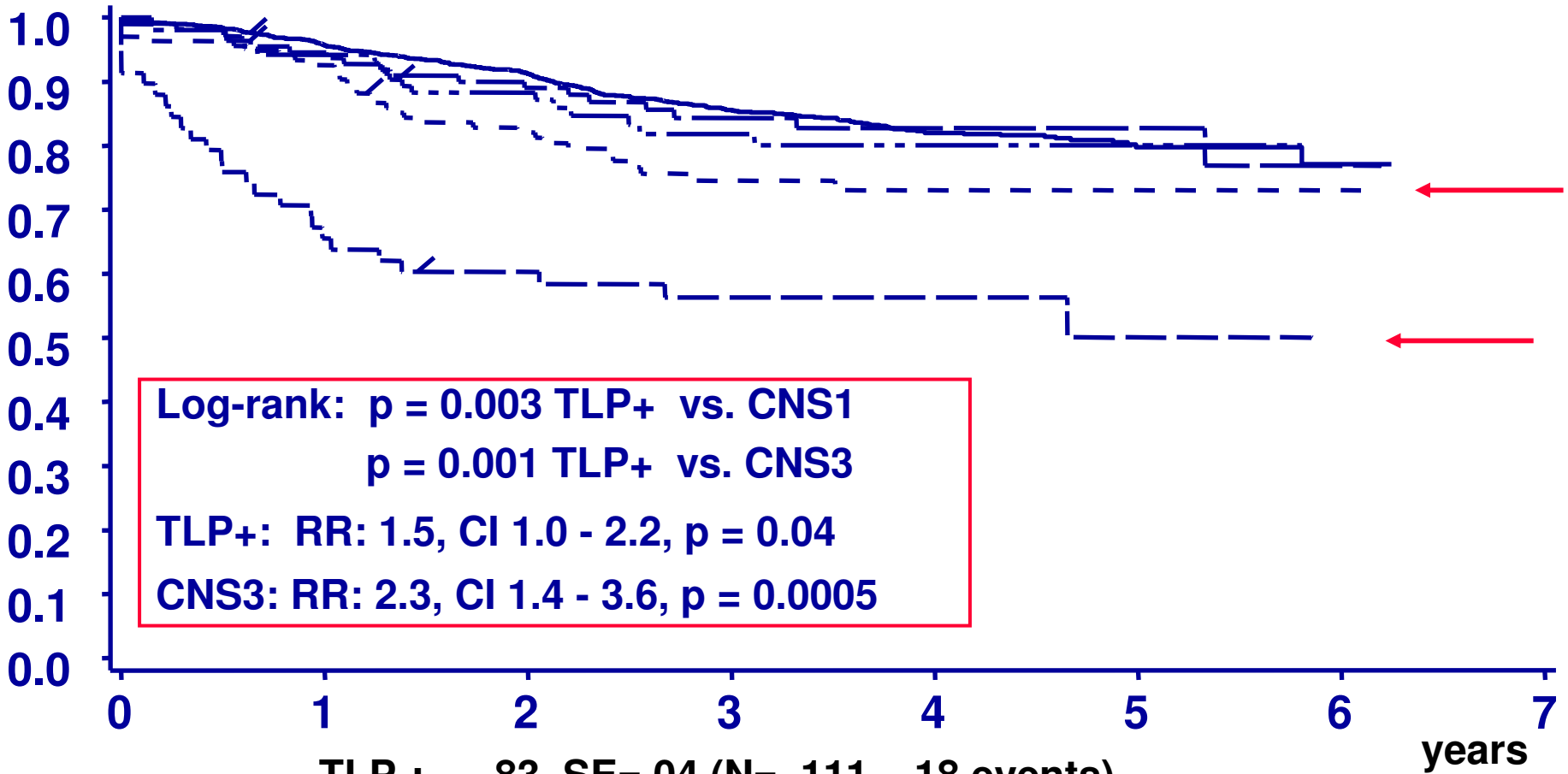
Examples for small and unfavorable subsets of ALL

(published)

- **CNS involvement: BFM (2003, 2007)**
- **intergroup analysis for**
  - **Ph+ ALL (2000)**
  - **11q23 rearrangements (2002)**
  - **Hypodiploidy (2007)**
- **inadequate early response: I-BFM study on HR ALL (2006)**

5y-pEFS according to CNS status

Trial ALL-BFM 95 (-6/99); n=2012, 295 events



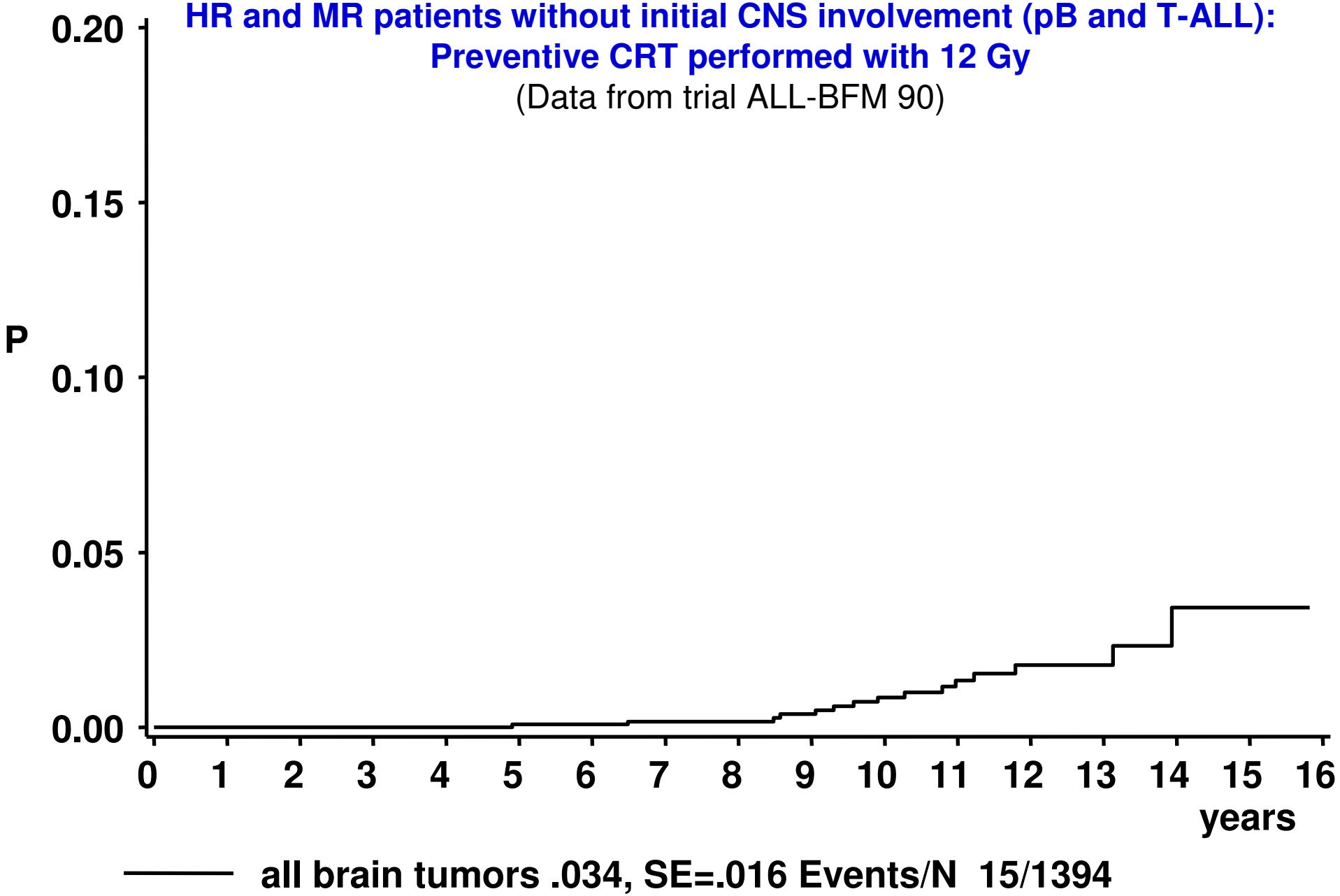
TLP-: .83, SE=.04 (N= 111, 18 events)
CNS1: .80, SE=.01 (N=1605, 250 events)
CNS2: .80, SE=.04 (N= 103, 18 events)
TLP+: .73, SE=.04 (N= 135, 33 events)
CNS3: .50, SE=.08 (N= 58, 26 events)

Bürger, B. et al. J Clin Oncol, *21:* 184-188, 2003

Cumul. incidence of secondary brain tumors (CI at 16 years)

HR and MR patients without initial CNS involvement (pB and T-ALL):
Preventive CRT performed with 12 Gy

(Data from trial ALL-BFM 90)



CNS Disease in Childhood ALL

Problems:

- **Comprehensive characterization of CNS status at diagnosis is difficult.**
- **Adequate adaptation of CNS-directed therapy is still missing**

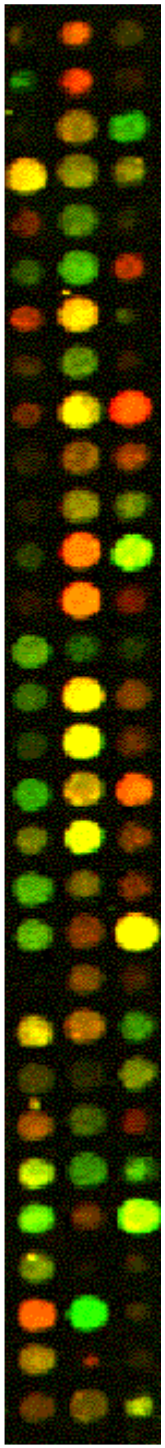
Hypothesis:

- **Leukemic cells migrating into the CNS display specific biological characteristics that can be uncovered by genome-wide gene expression profiling.**

Characteristics of 43 childhood ALL patients from trial ALL-BFM 2000 analyzed by gene expression profiling of initial BM samples:

Results of frequency matching

		Number of subjects and prevalence (%)		
		CNS1	CNS3	*P*
Age (years)	1 - < 10	18 (69.2)	11 (64.7)	
	≥ 10	8 (30.8)	6 (35.3)	0.757
Sex	male	18 (69.2)	12 (70.6)	
	female	8 (30.8)	5 (29.4)	0.925
Presenting	< 10,000	6 (23.1)	3 (17.6)	
WBC count/µl	10,000 - < 50,000	7 (26.9)	4 (23.5)	
	50,000 - < 100,000	3 (11.5)	2 (11.8)	
	≥ 100,000	10 (38.5)	8 (47.1)	0.946
Immunopheno-	B-precursor	18 (69.2)	9 (52.9)	
type	T-ALL	8 (30.8)	8 (47.1)	0.280
BCR/ABL positive		-	-	-
MLL/AF4 positive		-	-	-
TEL/AML1 positive		-	2 (11.8)	0.151



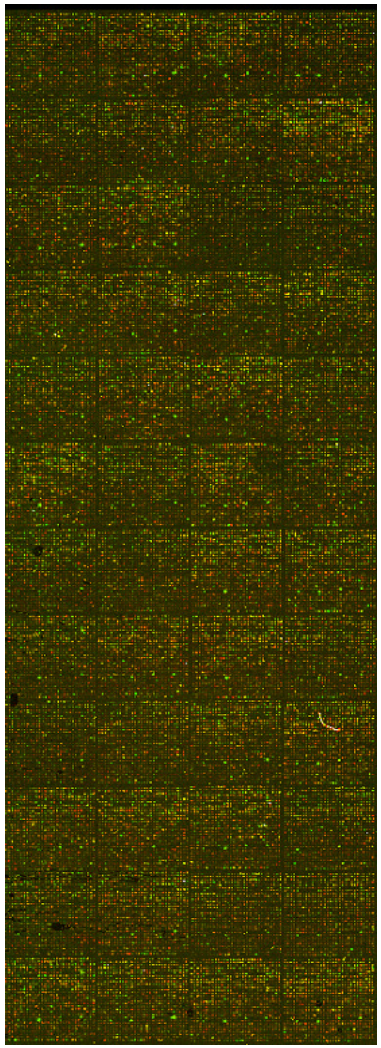
Methods

Spotted cDNA Arrays > 42,000 spots (~30,000 genes)
(Stanford Functional Genomics Facility)

Analysis

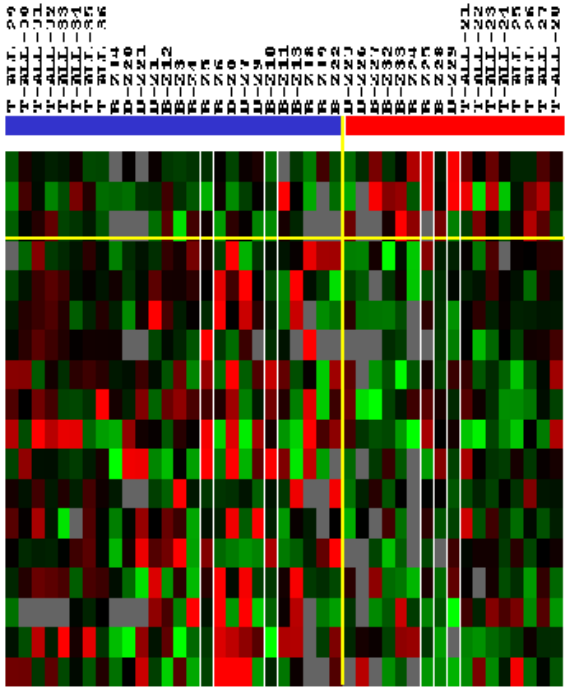
1. Unsupervised Clustering Analysis

2. Analysis of differentially expressed genes using SAM
   (Significance Analysis of Microarrays, PNAS, 2001)



SAM identified 18 candidate genes differentially expressed in initial BM samples (with >70 % blasts) comparing CNS-positive and -negative ALL

(SAM: 1000 permutations, FC ≥ 2, FDR 61%)



CNS negative
CNS positive

FC (1)	Gene symbol	Accession-No.
2.24	IL15	N59270
2.79	PFKFB2	W52085
2.14	PDE4A	AA975441
0.43	HDHD1A	AA278240
0.47	CLTC	N30042
0.40	GLDC	N58494
0.48	IRX2	H88050
0.48	TGFB1I4	AA664389
0.45	CD9	AA412053
0.35	ARHGEF10	N53385
0.47	GPR109A	AA903016
0.50	ZNF300	AA994690
0.50	CHC1L	AI015999
0.46	SGCB	W81562
0.47	PHYH	N91990
0.41	RIMS3	H41394
0.44	AKAP12	AA478542
0.45	PTPRS	AA137144

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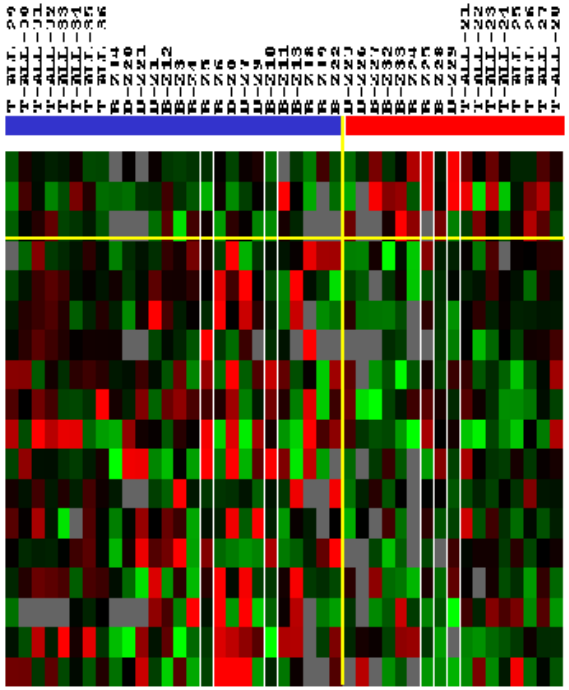

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0.47	PHYH	N91990
0.41	RIMS3	H41394
0.44	AKAP12	AA478542
0.45	PTPRS	AA137144

Can this result adversely be influenced through contaminating normal cells ?

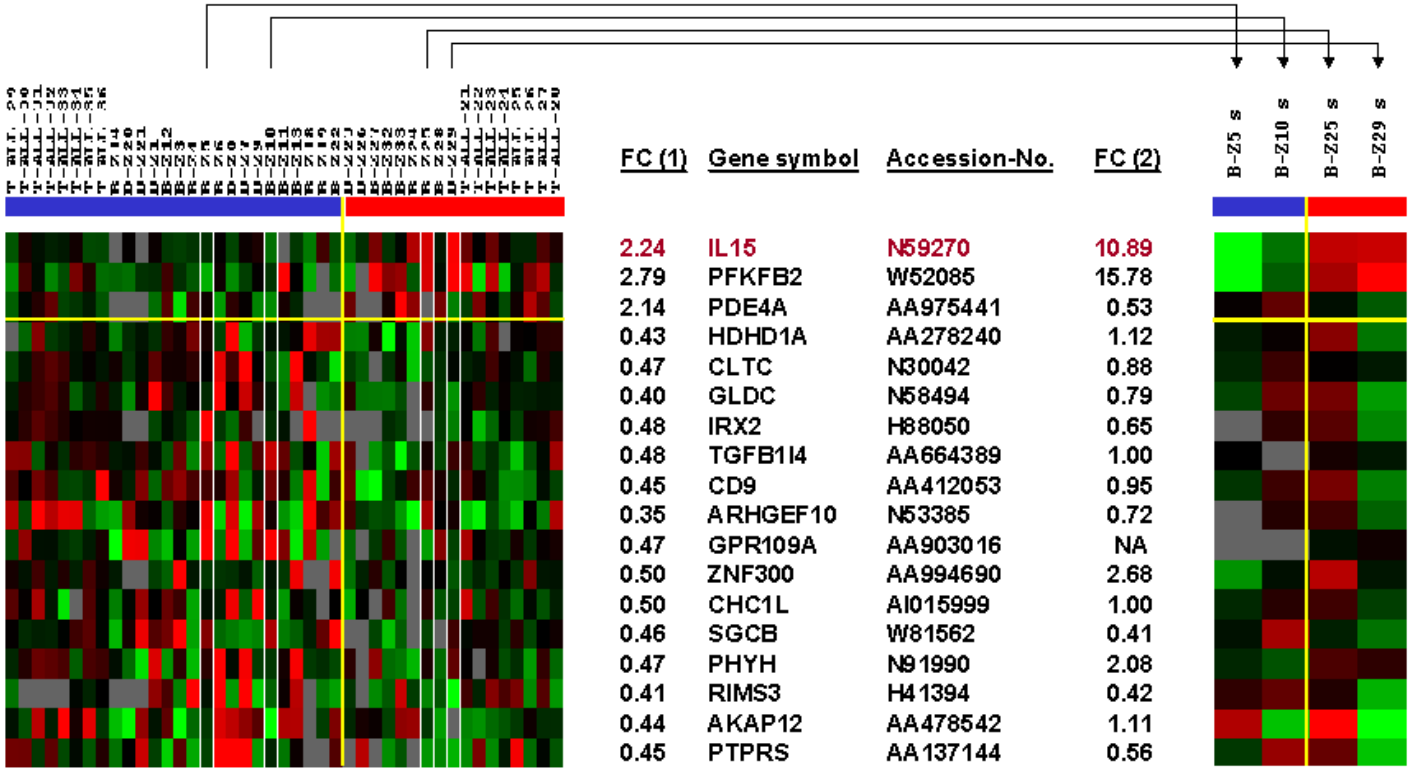
Analysis of the expression of candidate genes after purification of blasts in four B-pc-ALL samples

[Purification: Cell sorter: FACSVantage BD, anti-CD19/anti-CD10 antibody]

NAME	CNS-neg_B-Z5_s	CNS-neg_B-Z10_s	CNS-pos_B-Z25_s	CNS-pos_B-Z29_s	FC pos/neg
IL15 || Interleukin 15	-2.07	-0.65	2.05	2.12	10.89
PDE4A || Phosphodiesterase 4A	-1.3	-0.51	-1.49	-2.14	0.53
PFKFB2 || 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	-2.88	-0.52	1.75	2.81	15.78
CD9 || CD9 antigen	2.01	2.99	3.5	1.36	0.95
ARHGEF10 || Rho guanine nucleotide exchange factor (GEF) 10	NA	2.37	2.59	1.19	0.72
TGFB1I4 || TSC22 domain family, member 1	0.18	NA	0.37	-0.02	1.00
GLDC || Glycine dehydrogenase	-2.62	-1.1	-1.01	-3.39	0.79
CLTC || Clathrin, heavy polypeptide (Hc)	-2.66	-1.84	-2.32	-2.56	0.88
IRX2 || Iroquois homeobox protein 2	NA	-1.31	-0.96	-2.9	0.65
HDHD1A || Haloacid dehalogenase-like hydrolase domain containing 1A	-0.06	0.24	1.36	-0.86	1.12
ZNF300 || Zinc finger protein 300	-3.97	-2.82	-1.08	-2.87	2.68
PTPRS || Protein tyrosine phosphatase, receptor type, S	-4.62	-2.82	-3.25	-5.86	0.56
PHYH || Phytanoyl-CoA hydroxylase (Refsum disease)	-0.22	-0.61	0.77	0.51	2.08
AKAP12 || A kinase (PRKA) anchor protein (gravin) 12	-1.25	-4.49	-0.19	-5.24	1.11
SGCB || Sarcoglycan, beta	-0.51	1.08	-0.63	-1.36	0.41
CHC1L || Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 2	-0.91	-0.21	-0.01	-1.1	1.00
RIMS3 || Regulating synaptic membrane exocytosis 3	-0.51	-0.07	-0.63	-2.48	0.42
GPR109A || G protein-coupled receptor 109A	NA	NA	1.42	1.7	NA

SAM identified 18 candidate genes differentially expressed in initial BM samples (with >70 % blasts) comparing CNS-positive and -negative ALL

(SAM: 1000 permutations, FC ≥ 2, FDR 61%)



FC (1)	Gene symbol	Accession-No.	FC (2)
2.24	IL15	N59270	10.89
2.79	PFKFB2	W52085	15.78
2.14	PDE4A	AA975441	0.53
0.43	HDHD1A	AA278240	1.12
0.47	CLTC	N30042	0.88
0.40	GLDC	N58494	0.79
0.48	IRX2	H88050	0.65
0.48	TGFB1I4	AA664389	1.00
0.45	CD9	AA412053	0.95
0.35	ARHGEF10	N53385	0.72
0.47	GPR109A	AA903016	NA
0.50	ZNF300	AA994690	2.68
0.50	CHC1L	AI015999	1.00
0.46	SGCB	W81562	0.41
0.47	PHYH	N91990	2.08
0.41	RIMS3	H41394	0.42
0.44	AKAP12	AA478542	1.11
0.45	PTPRS	AA137144	0.56

CNS negative
CNS positive

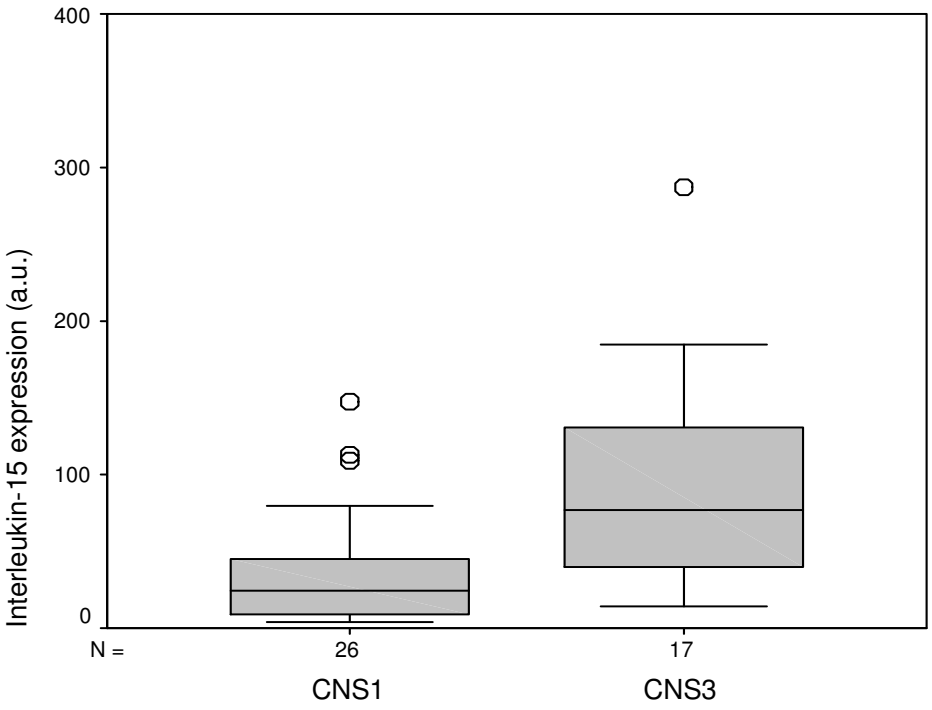
Interleukin 15 (IL-15)

- **chromosome 4q21**
- **proinflammatory cytokine sharing many biological functions of IL-2**
- **expressed by multiple tissues and cell types including leukemic blasts**
- **regulates T and natural killer cell activation and proliferation**
- **activates proinflammatory functions of PMN cells (as opposed to IL-2)**
- **RNA and protein expression is upregulated in PBMNC in patients with chronic progressive Multiple Sclerosis**

Leukemic IL-15 expression in diagnostic BM of ALL patients without (CNS1) and with (CNS3) leukemic CNS involvement

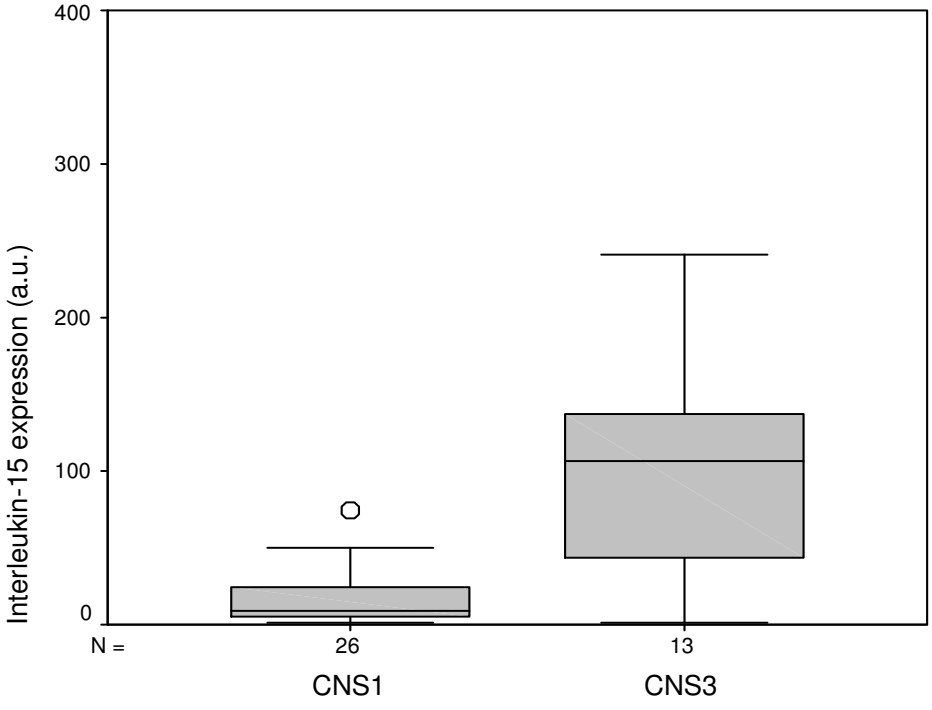
Validation analysis by RQ-PCR

Patients included in microarray analysis



$P < 0.001$

Independent set of patients



$P < 0.001$

Uni- and multivariate associations and likelihood ratios for IL-15 expression quartiles and CNS status in 82 childhood ALL patients

IL-15 quartiles	Number of subjects and prevalence (%)		Univariate odds ratio (95% CI)	*P*	Multivariate odds ratio (95% CI)	*P*	Likelihood ratio (95% CI)
	CNS1 n=52	CNS3 n=30					
I	19 (36.5)	1 (3.3)	1.00		1.00		0.09 (0.01-0.65)
II	17 (32.7)	4 (13.3)	4.46 (0.45-4.39)	0.200	6.39 (0.51-59.17)	0.130	0.41 (0.15-1.10)
III	12 (23.1)	9 (30.0)	14.22 (1.60-126.58)	0.017	22.03 (1.57-153.85)	0.011	1.30 (0.62-2.72)
IV	4 (7.7)	16 (53.3)	75.76 (7.69-769.23)	<0.001	153.25 (10.37-2264.69)	<0.001	6.93 (2.55-18.83)

CNS Disease in Childhood ALL

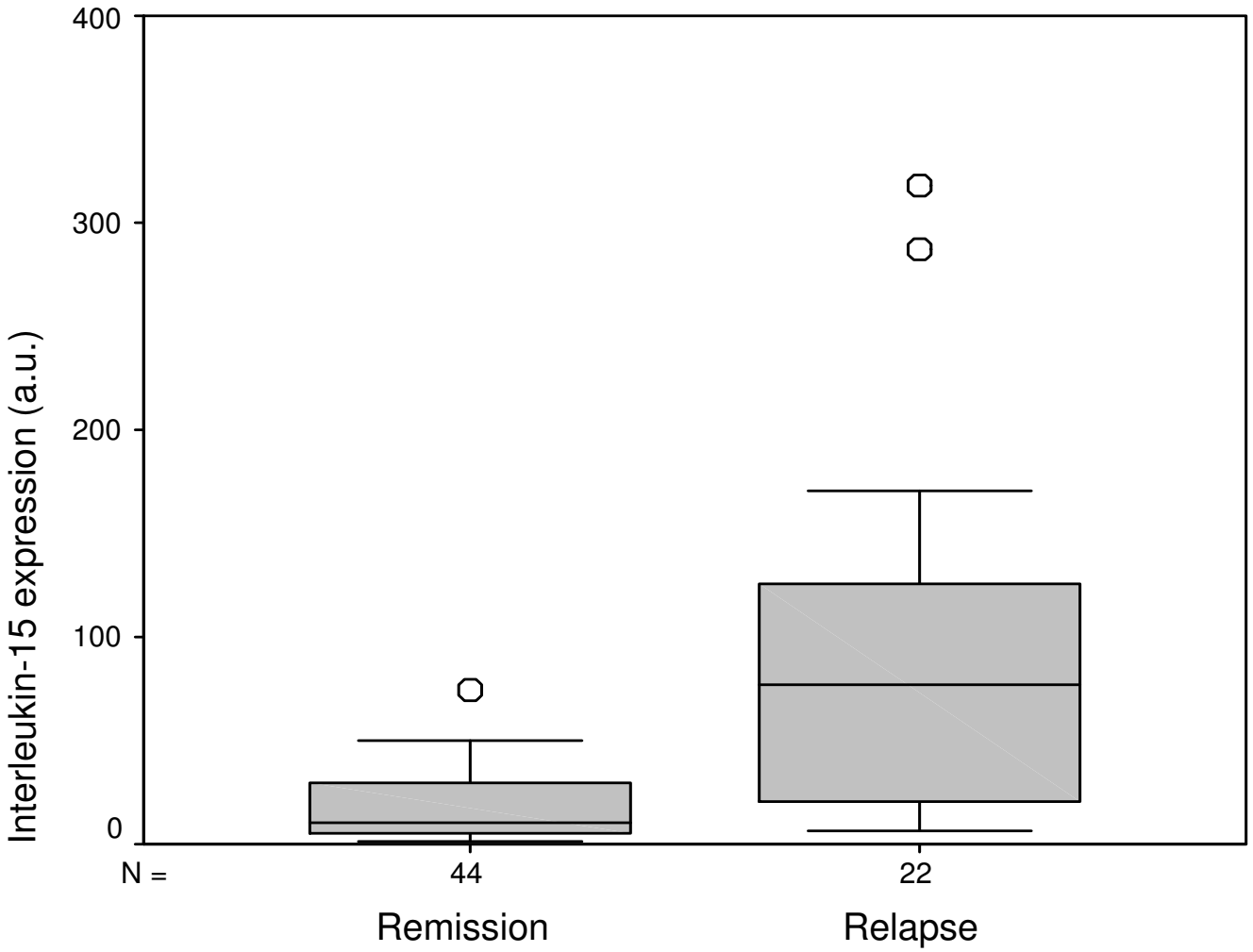
Is IL-15 expression relevant for CNS relapse?

Patients from trial ALL-BFM 2000 that were initially CNS-negative (CNS1) with subsequent isolated or combined CNS relapse were compared to CNS1 patients with a minimum follow-up of three years.

Characteristics at initial diagnosis of 44 CNS1 patients in longterm remission and 22 CNS1 patients relapsing with CNS involvement

		Number of subjects and prevalence (%)		*P*
		Remission	Relapse	
Age (years)	1 - < 10	27 (61.4)	15 (68.2)	
	≥ 10	17 (38.6)	7 (31.8)	0.587
Sex	male	26 (59.1)	17 (77.3)	
	female	18 (40.9)	5 (22.7)	0.144
Presenting	< 10,000	7 (15.9)	6 (27.3)	
WBC count/µl	10,000 - < 50,000	16 (36.4)	4 (18.2)	
	50,000 - < 100,000	9 (20.5)	5 (22.7)	
	≥ 100,000	12 (27.3)	7 (31.8)	0.440
Immunopheno-	B-precursor	37 (84.1)	19 (86.4)	
Type	T-ALL	7 (15.9)	3 (13.6)	0.808
BCR/ABL positive		-	2 (9.1)	0.108
TEL/AML1 positive			2 (9.1)	0.108
Treatment group	standard risk	18 (40.9)	3 (13.6)	
	intermediate risk	11 (25.0)	14 (63.6)	
	high risk	15 (34.1)	5 (22.7)	0.007

IL-15 expression in leukemic blasts at initial diagnosis predicts subsequent relapse with involvement of the CNS



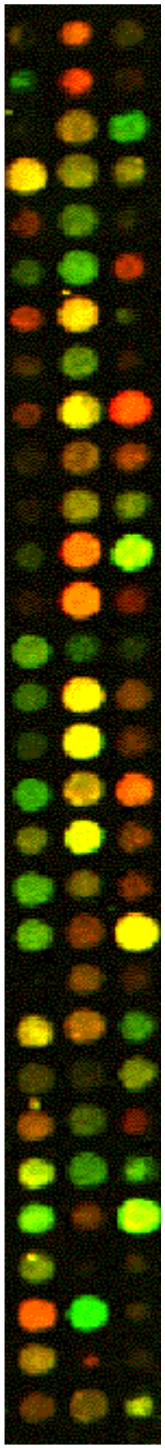
***P* < 0.001**

Odds ratio* for IL-15 expression levels above the median = 13.80, 95% CI 3.38-56.31, *P* < 0.001

***controlling for gender, age and WBC at diagnosis, immunophenotype, presence of BCR/ABL or TEL/AML1 fusion transcripts (yes/no), and treatment group**

Conclusions from the CNS/IL-15 study

- **IL-15 expression characterizes CNS involvement at initial diagnosis of childhood ALL.**
- **IL-15 predicts CNS relapse in patients classified as CNS1 at initial diagnosis by morphological criteria.**
- **IL-15 has excellent diagnostic potential for assessing CNS status in ALL.**
- **Analysis of IL-15 expression opens new perspectives for adaptation of CNS-directed therapy in childhood ALL.**
- **Our data suggest a role for IL-15 in the pathogenesis of leukemic CNS involvement.**
- **IL-15 may serve as a potential therapeutic target in ALL.**



Cario G, Izraeli S, Teichert A, Rhein P, Skokowa J, Moricke A, Zimmermann M, Schrauder A, Karawajew L, Ludwig WD, Welte K, Schunemann HJ, Schlegelberger B, Schrappe M, Stanulla M (2007)

High interleukin-15 expression characterizes childhood acute lymphoblastic leukemia with involvement of the CNS.

***J Clin Oncol* 25: 4813-4820**

Funding from BMBF (Bonn), Young Investigator Faculty Grant (Kiel), M. Schickedanz Foundation (Fuerth)

Examples for small and unfavorable subsets of ALL
(published)

- **CNS involvement: BFM (2003, 2007)**
- **intergroup analysis for**
  - **Ph+ ALL (2000)**
  - **11q23 rearrangements (2002)**
  - **Hypodiploidy (2007)**
- **inadequate early response: I-BFM (2006)**

OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

MAURIZIO ARICÒ, M.D., MARIA GRAZIA VALSECCHI, PH.D., BRUCE CAMITTA, M.D., MARTIN SCHRAPPE, M.D., JUDITH CHESSELLS, M.D., ANDRÉ BARUCHEL, M.D., PAUL GAYNON, M.D., LEWIS SILVERMAN, M.D., GRITTA JANKA-SCHAUB, M.D., WILLEM KAMPS, M.D., CHING-HON PUI, M.D., AND GIUSEPPE MASERA, M.D.

N Engl J Med 2000;342:998-1006

N = 326

Pts recruited within 10y from 10 study groups

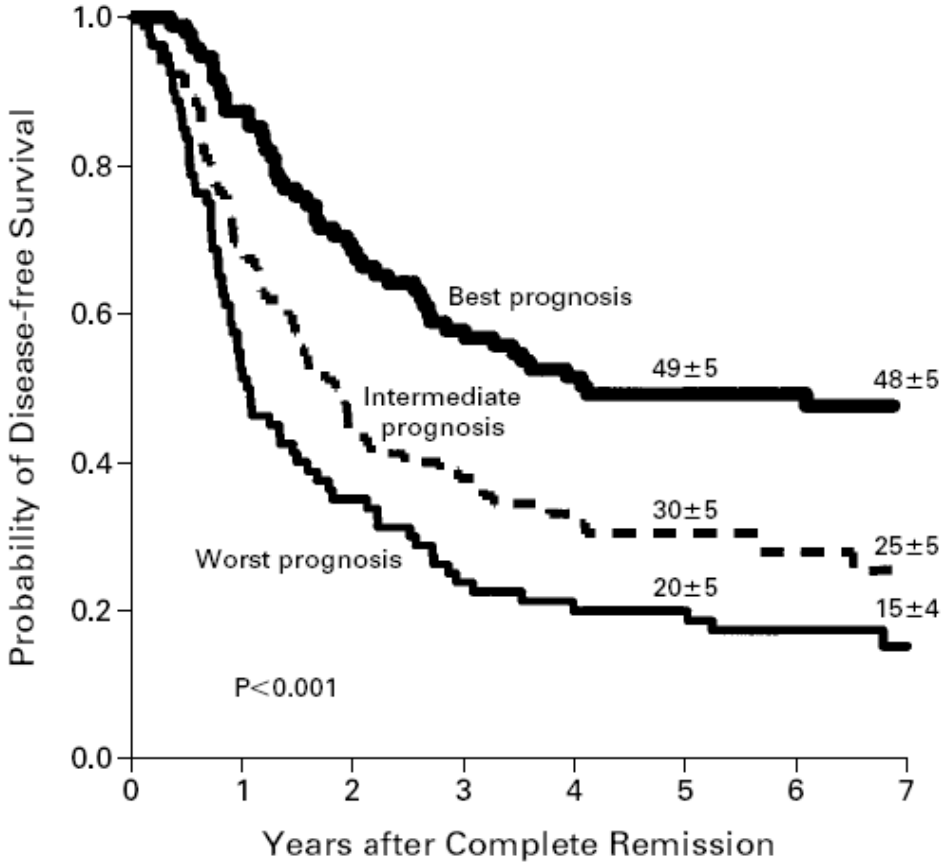
OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

N Engl J Med 2000;342:998-1006

CHARACTERISTIC	5-YR EVENT-FREE SURVIVAL	P VALUE
	%	
0–2 yr	38±8	
3–5 yr	32±5	
6–9 yr	33±5	
10–14 yr	18±4	
≥15 yr	21±8	
White-cell count at diagnosis (per mm³)		<0.001
<10,000	40±6	
10,000 to <25,000	42±6	
25,000 to <50,000	30±8	
50,000 to <100,000	25±7	
≥100,000	14±3	
Response to glucocorticoid plus intrathecal methotrexate		<0.001
Poor (at 1 yr)‡	9±6	
Good (at 1 yr)§	74±6	

OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

N Engl J Med 2000;342:998-1006

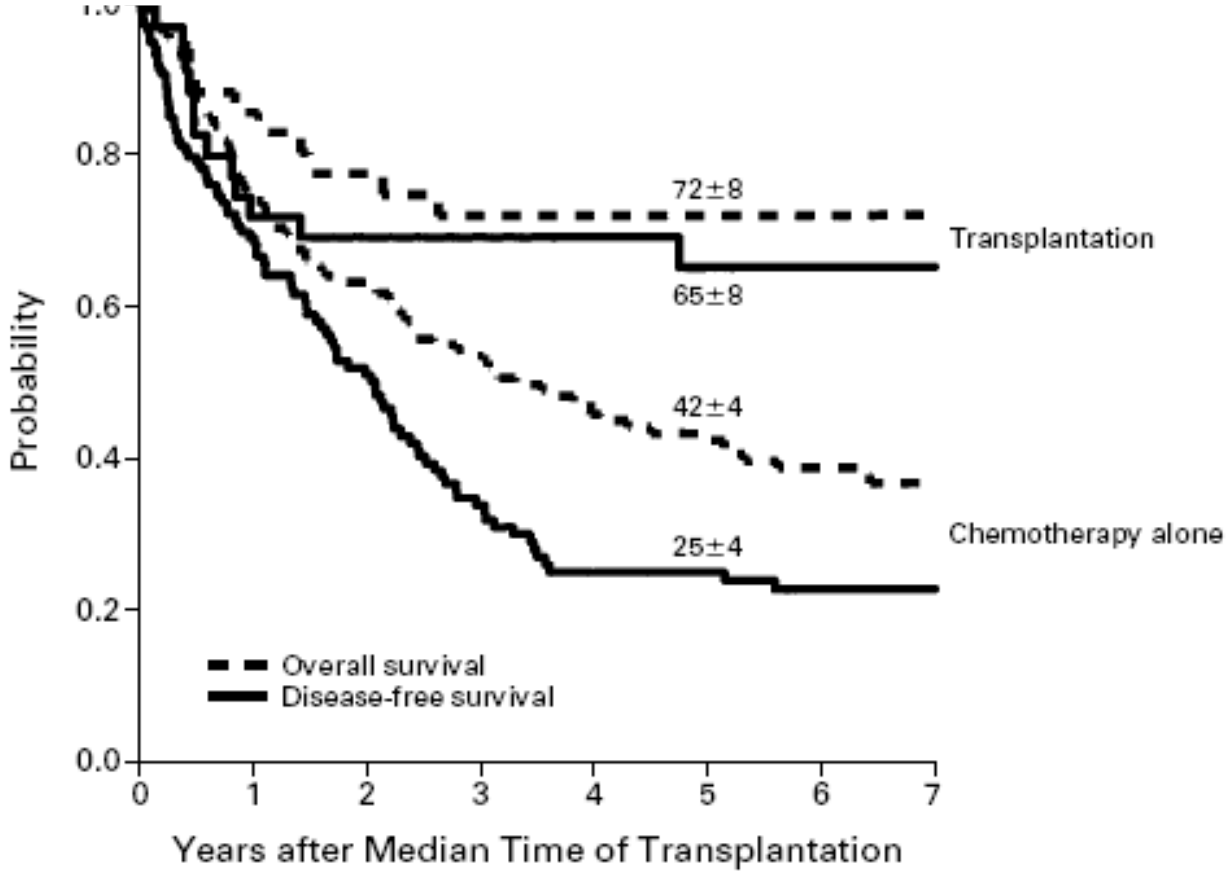


PATIENTS AT RISK								
Best prognosis	95	83	65	55	46	39	32	22
Intermediate prognosis	92	64	40	33	25	14	11	9
Worst prognosis	80	42	28	19	16	15	10	5

Best prognosis: age <= 10y, and WBC < 50,000
Intermediate prognosis: age >10y, or WBC 50-100,000
Worst prognosis: any age but WBC >100,000

OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

N Engl J Med 2000;342:998-1006



PATIENTS AT RISK

Chemotherapy alone	198	84	57	36	24	22	18	14
Transplantation from matched related donor	18	28	25	26	23	17	9	6

Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region

*Ching-Hon Pui, Paul S Gaynon, James M Boyett, Judith M Chessells, André Baruchel, Willem Kamps, Lewis B Silverman, Andrea Biondi, Dörthe O Harms, Etienne Vilmer, Martin Schrappe, Bruce Camitta**

Lancet 2002; **359:** 1909–15

N = 497

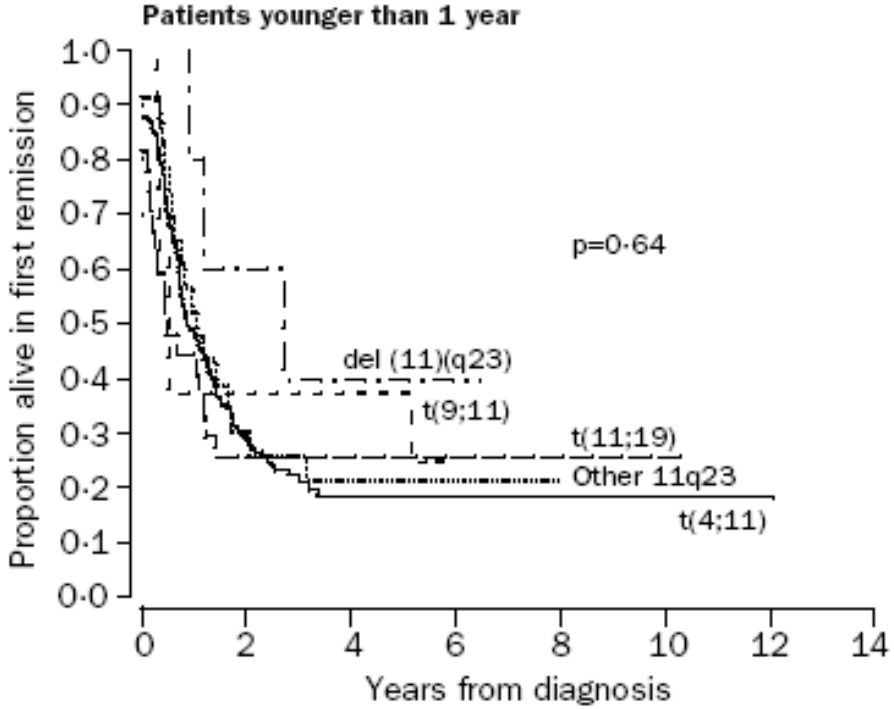
Patients enrolled in participating centers of one of the 13 study groups and institutions between 1983 and 1995.

Patient population (11q23)

	t(4;11)	t(11;19)	t(9;11)	Other 11q23	del(11) (q23)
Age (years)					
<1	151	27	8	23	5
1–9	59	12	10	44	64
⩾10	45	10	1	10	25
Leucocyte count ($\times 10^9$/L)					
<50	47	11	10	44	66
⩾50	208	38	10	33	29
National Cancer Institute-Rome risk criteria					
Standard	13	3	5	23	43
High	243	46	15	54	52
Lineage					
B	239	39	18	54	69
T	2	8	0	17	13

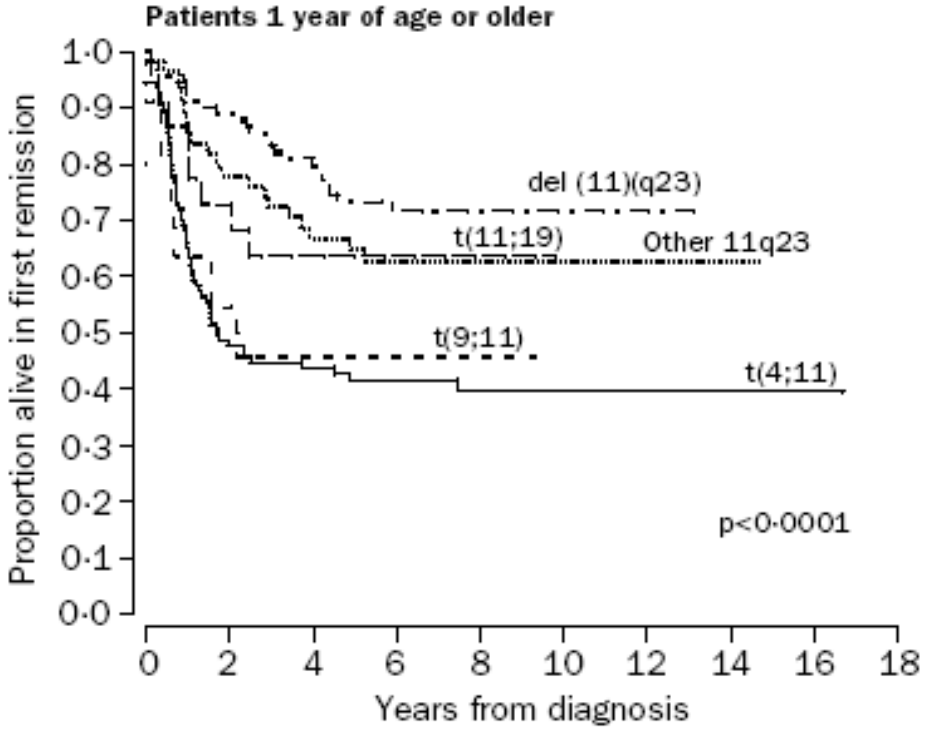
Lancet 2002; **359:** 1909–15

Outcome by age (11q23)



Patients at risk

del (11)(q23)	5	3	2	1	0	0
t(9;11)	8	3	3	0	0	0
t(11;19)	27	7	6	5	4	1
Other 11q23	23	7	5	4	0	0
t(4;11)	149	44	27	23	11	4

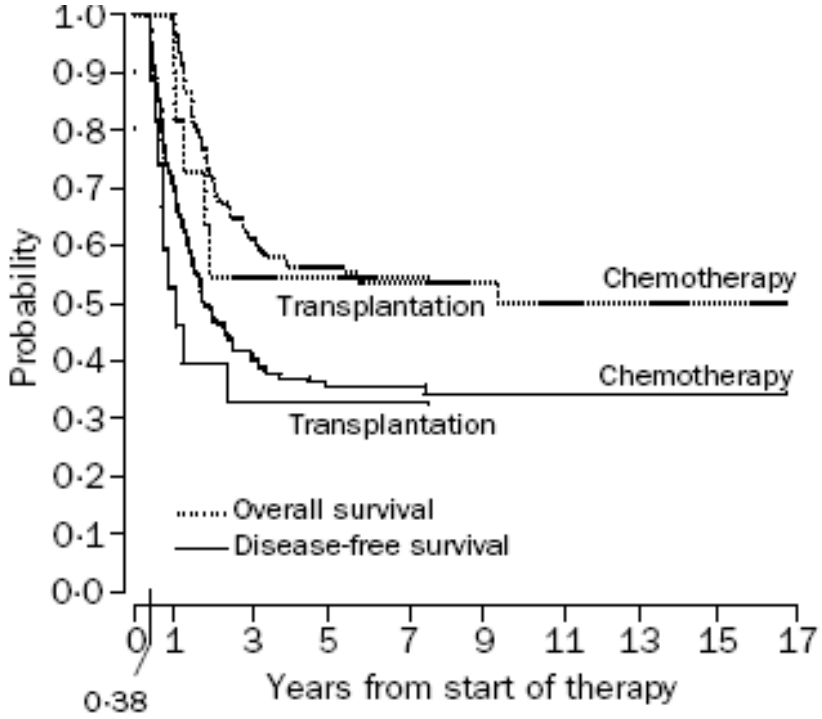


Patients at risk

del (11)(q23)	89	78	65	40	15	6	6	0
t(11;19)	22	16	13	9	4	0	0	0
Other 11q23	54	42	35	28	16	9	6	1
t(9;11)	11	6	5	4	2	0	0	0
t(4;11)	103	49	43	30	14	7	5	3

Lancet 2002; **359:** 1909–15

11q23: Outcome by regimen: Chemo vs SCT



Patients at risk

Overall survival							
Chemotherapy		134	80	70	44	18	11
Transplantation		11	6	3	2	0	0
Disease-free survival							
Chemotherapy	183	109	63	50	35	15	10
Transplantation	14	8	5	2	2	0	0

Figure 2: **Mantel-Byar estimates of disease-free survival with a landmark of 0·38 years, and Kaplan-Meier estimates of survival with a landmark of 1 year in patients with t(4;11)**

Lancet 2002; **359:** 1909–15

Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia

James B. Nachman,[1] Nyla A. Heerema,[2] Harland Sather,[3] Bruce Camitta,[4] Erik Forestier,[5] Christine J. Harrison,[6] Nicole Dastugue,[7] Martin Schrappe,[8] Ching-Hon Pui,[9] Giuseppe Basso,[10] Lewis B. Silverman,[11] and Gritta E. Janka-Schaub[12]

BLOOD 110 (2007): 1112-1115

N = 139 (less than 45 chromosomes)
= 130 (Ph neg. ALL)

Pts recruited in 10y from 10 study groups

Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia

James B. Nachman,[1] Nyla A. Heerema,[2] Harland Sather,[3] Bruce Camitta,[4] Erik Forestier,[5] Christine J. Harrison,[6] Nicole Dastugue,[7] Martin Schrappe,[8] Ching-Hon Pui,[9] Giuseppe Basso,[10] Lewis B. Silverman,[11] and Gritta E. Janka-Schaub[12]

BLOOD 110 (2007): 1112-1115

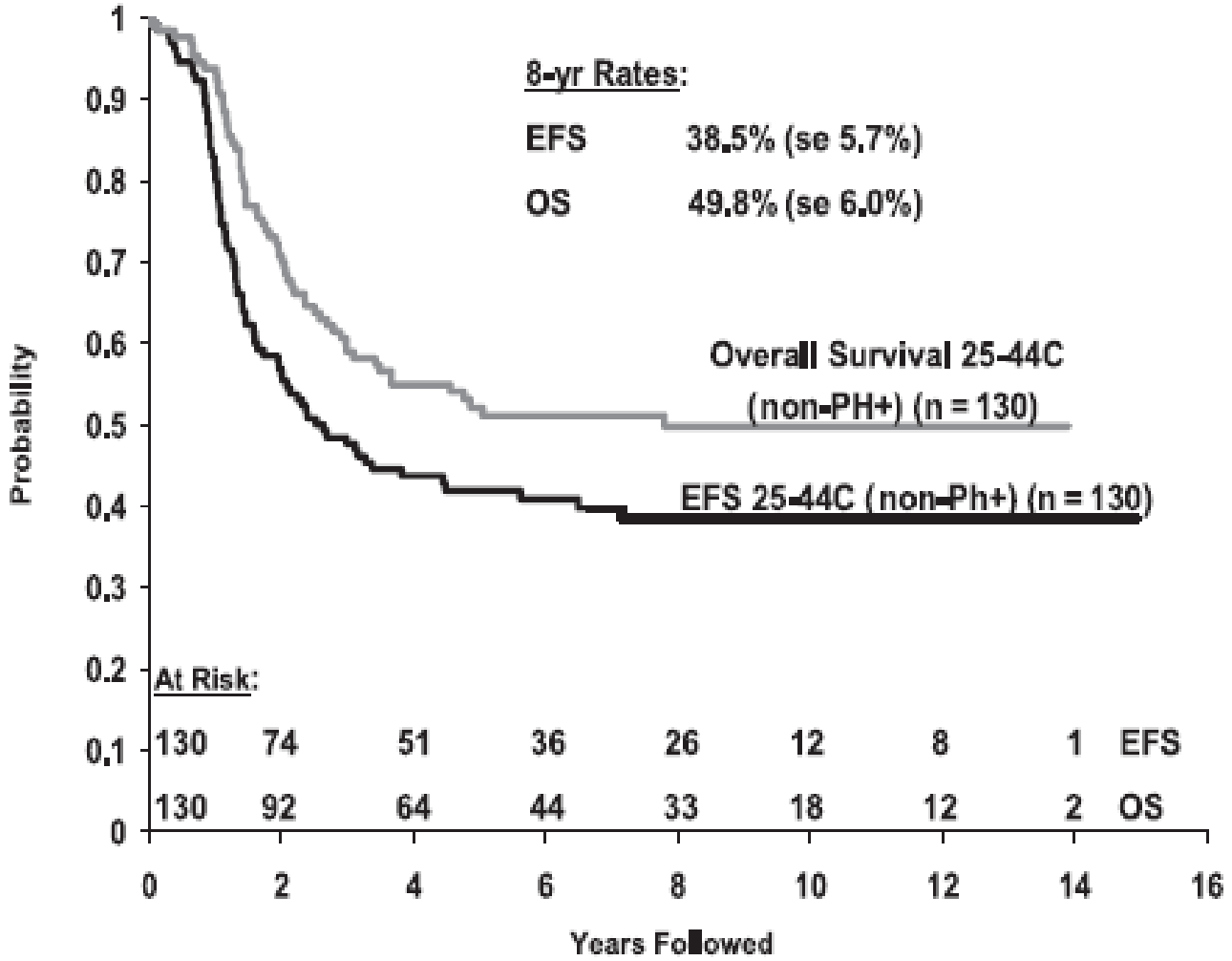


Figure 2. EFS and OS for non-Ph$^+$ hypodiploid patients.

Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia

James B. Nachman,[1] Nyla A. Heerema,[2] Harland Sather,[3] Bruce Camitta,[4] Erik Forestier,[5] Christine J. Harrison,[6] Nicole Dastugue,[7] Martin Schrappe,[8] Ching-Hon Pui,[9] Giuseppe Basso,[10] Lewis B. Silverman,[11] and Gritta E. Janka-Schaub[12]

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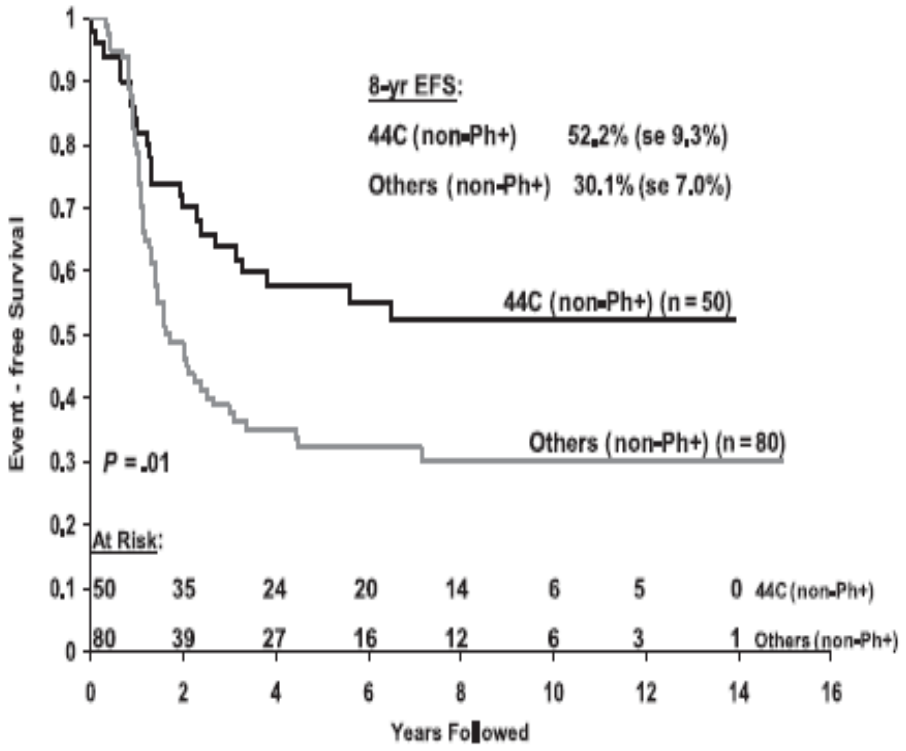

Figure 3. Comparison of EFS for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

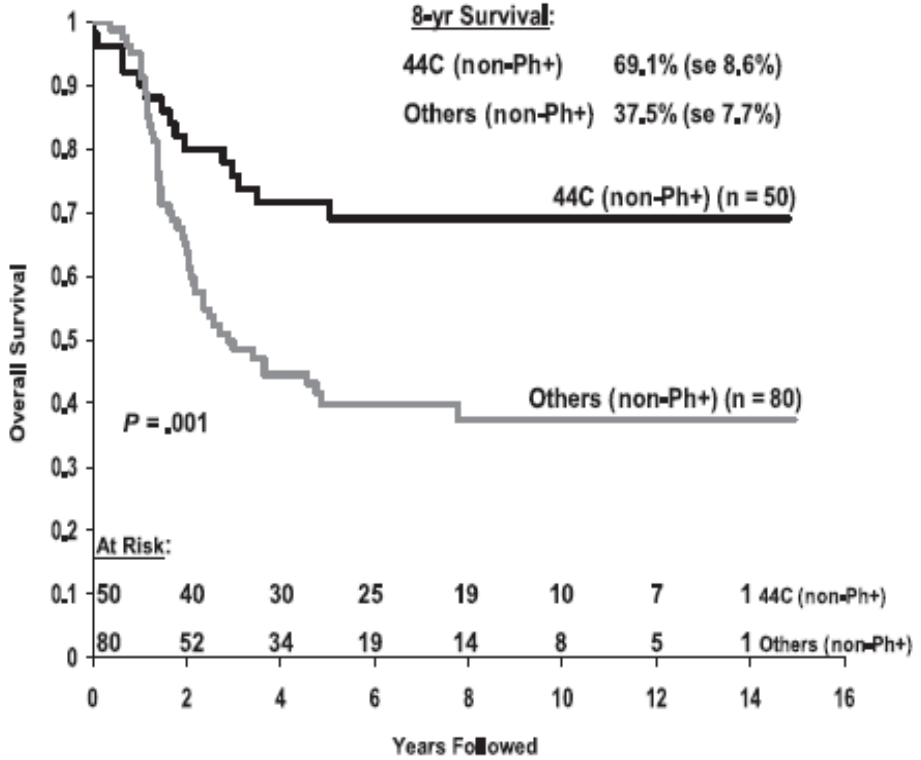

Figure 4. Comparison of survival for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia

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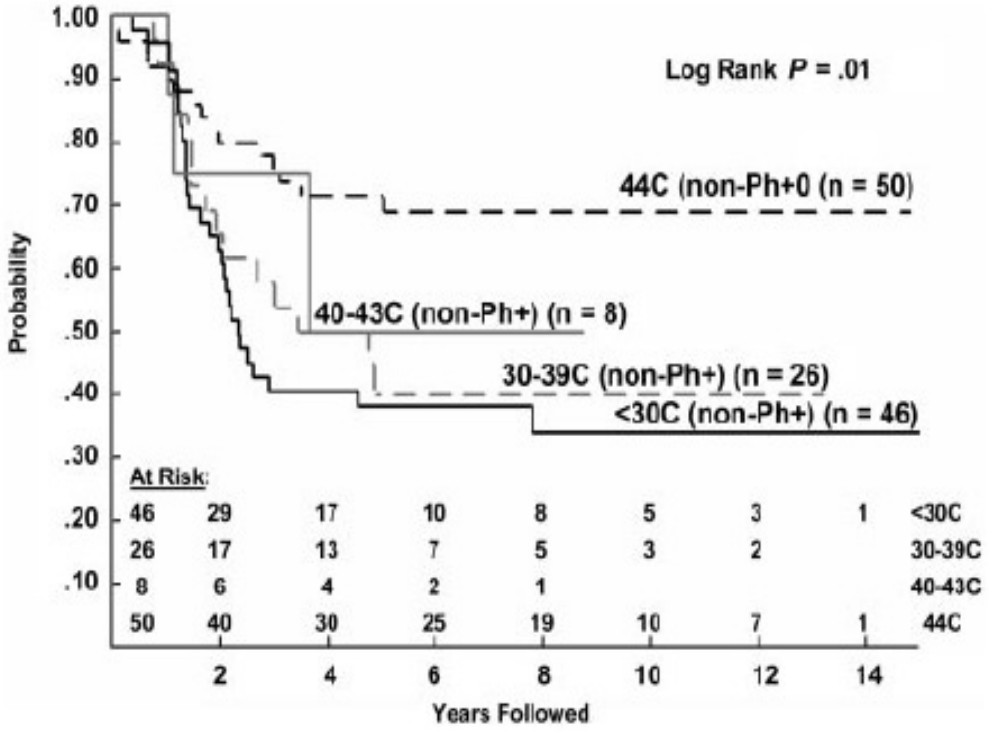

Figure 6. OS for 130 evaluable, non-Ph+ patients by modal chromosome number: 44 chromosomes, 40 to 43 chromosomes, 30 to 39 chromosomes, and 24 to 29 chromosomes.

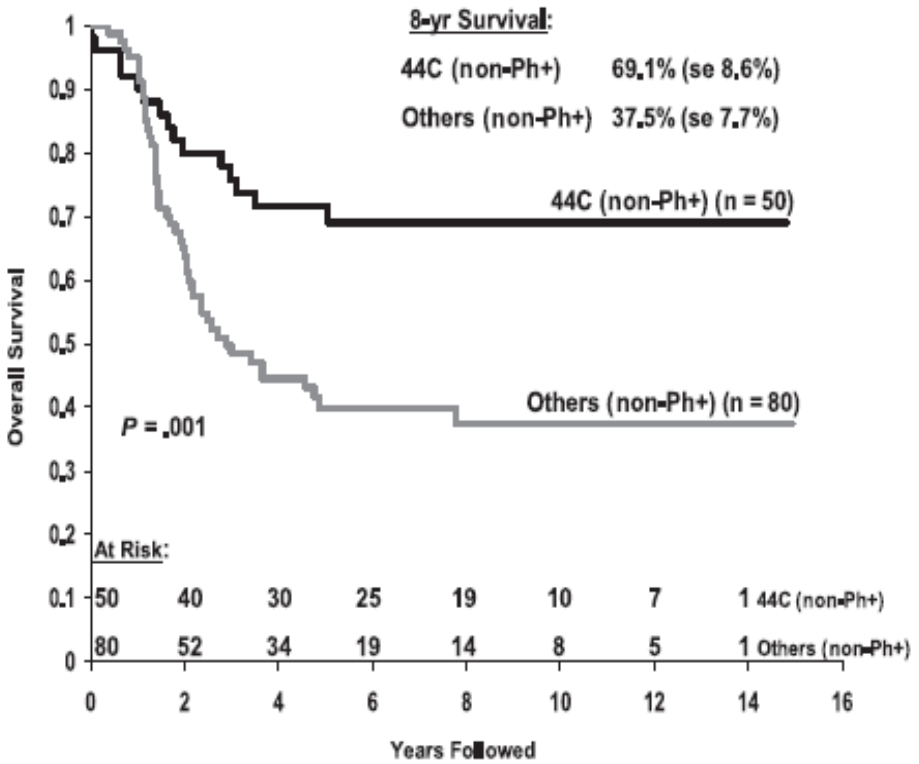

Figure 4. Comparison of survival for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

Examples for small and unfavorable subsets of ALL
(published)

- CNS involvement: BFM (2003, 2007)
- intergroup analysis for
  - Ph+ ALL (2000)
  - 11q23 rearrangements (2002)
  - Hypodiploidy (2007)
- **inadequate early response: I-BFM (2006)**

Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study

Adriana Balduzzi, Maria Grazia Valsecchi, Cornelio Uderzo, Paola De Lorenzo, Thomas Klingebiel, Christina Peters, Jan Stary, Maria S Felice, Edina Magyarosy, Valentino Conter, Alfred Reiter, Chiara Messina, Helmut Gadner, Martin Schrappe

Lancet 2005; 366: 635–42

Argentina (GATLA), Austria (BFM-A), Czech Republic (CPH), Germany (BFM-G), Hungary (HPOG), Italy (AIEOP)

Patients enrolled from 4/95 to 12/2000.

VHR-ALL: Patient characteristics by treatment

	Allocated treatment		
	Chemotherapy (n=280)	Related donor transplantation (n=77)	Total (n=357)
Boys	179 (64%)	53 (69%)	232 (65%)
Median (IQR) age at diagnosis (years)	7 (3–11)	7 (4–12)	7 (3–11)
Median (IQR) white-blood-cell count at diagnosis ($\times 10^9$/L)	101 (27–249)	114 (20–249)	102 (26–249)
T immunophenotype	126 (45%)	30 (39%)	156 (44%)
Clonal translocations			
Absent	21 (7%)	17 (22%)	38 (11%)
t(9;22)	75 (27%)	8 (10%)	83 (23%)
t(4;11)	27 (10%)	8 (10%)	35 (10%)
Other abnormalities	35 (12%)	10 (13%)	45 (12%)
Not known	122 (44%)	34 (45%)	156 (44%)
Induction failure			
No	210 (75%)	49 (64%)	259 (73%)
Yes	58 (21%)	25 (32%)	83 (23%)
Not known	12 (4%)	3 (4%)	15 (4%)
Response to prednisone			
Poor	176 (63%)	56 (73%)	232 (65%)
Good	102 (36%)	21 (27%)	123 (34%)
Not known	2 (1%)	0	2 (1%)

	Allocated treatment		
	Chemotherapy (n=280)	Related donor transplantation (n=77)	Total (n=357)
Eligibility criteria*			
Induction failure	58 (21%)	25 (33%)	83 (23%)
t(9;22)	67 (24%)	7 (9%)	74 (21%)
t(4;11)	25 (9%)	7 (9%)	32 (9%)
PPR+T	36 (13%)	8 (10%)	44 (12%)
PPR+WBC	24 (9%)	14 (18%)	38 (11%)
PPR+T+WBC	70 (24%)	16 (21%)	86 (24%)

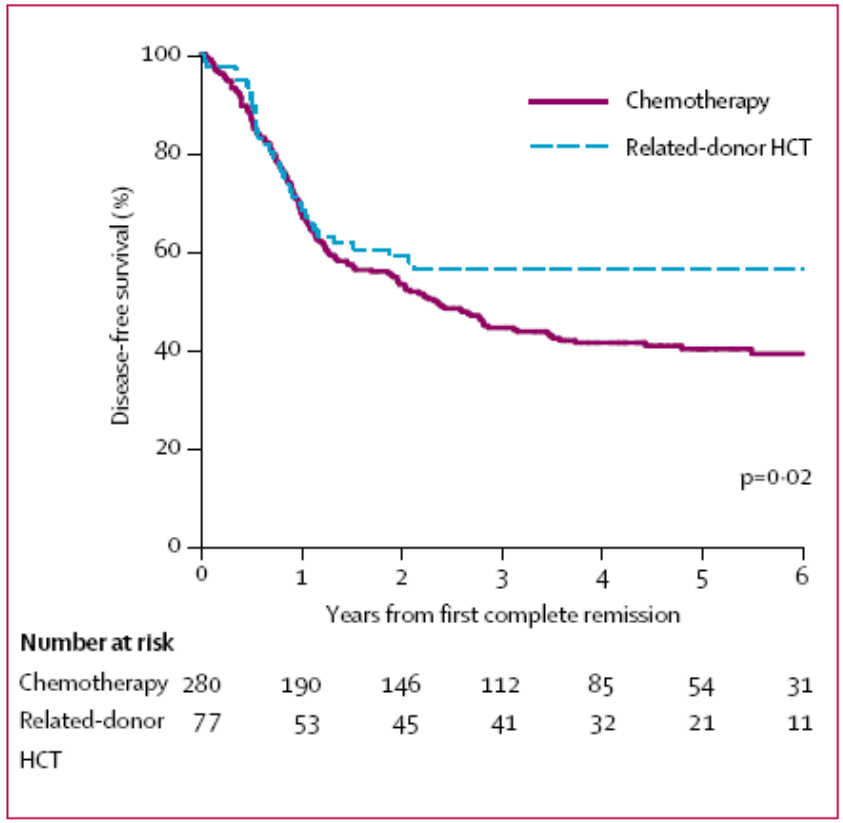

Figure 2: **Estimates of disease-free survival, by treatment assigned**
HCT=haemopoietic-cell transplantation.

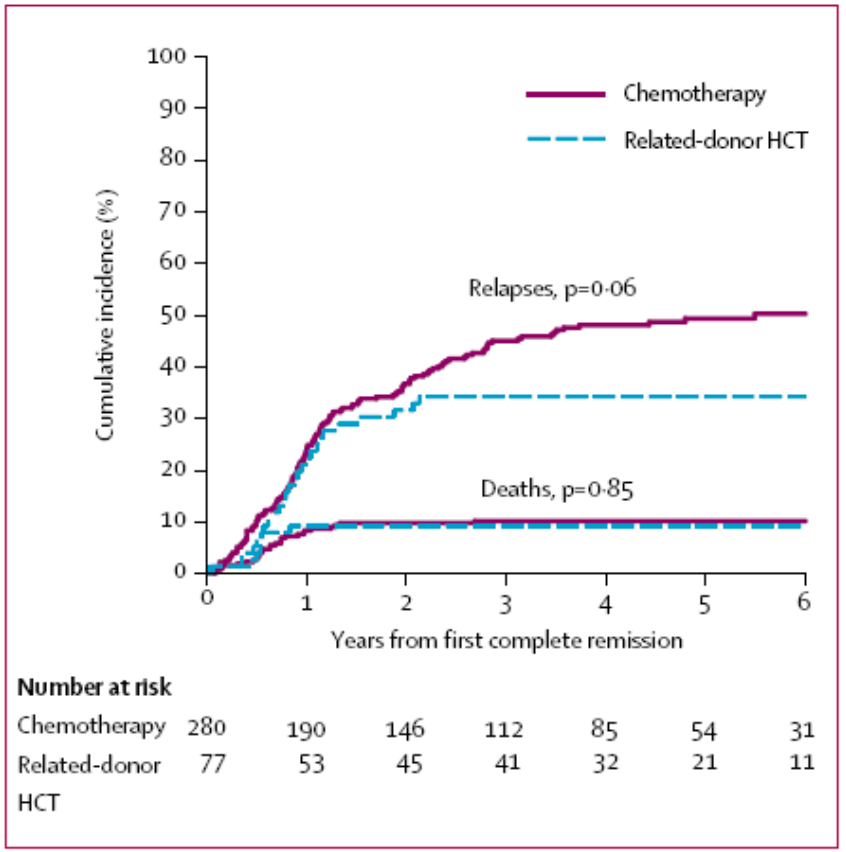

Figure 3: **Estimates of cumulative incidence of relapse and death, by treatment assigned**
HCT=haemopoietic-cell transplantation.

	Hazard ratio (95% CI)
At 6 months	0·77 (0·21–1·16)
At 1 year	0·61 (0·41–0·93)
At 2 years	0·48 (0·32–0·72)
At 3 years	0·41 (0·27–0·63)

Hazard ratios are for related donor transplantation versus chemotherapy (p=0·03 for overall analysis).

Table 2: **Estimated hazard ratios (95% CI) associated with assigned treatment, by time from first complete remission**

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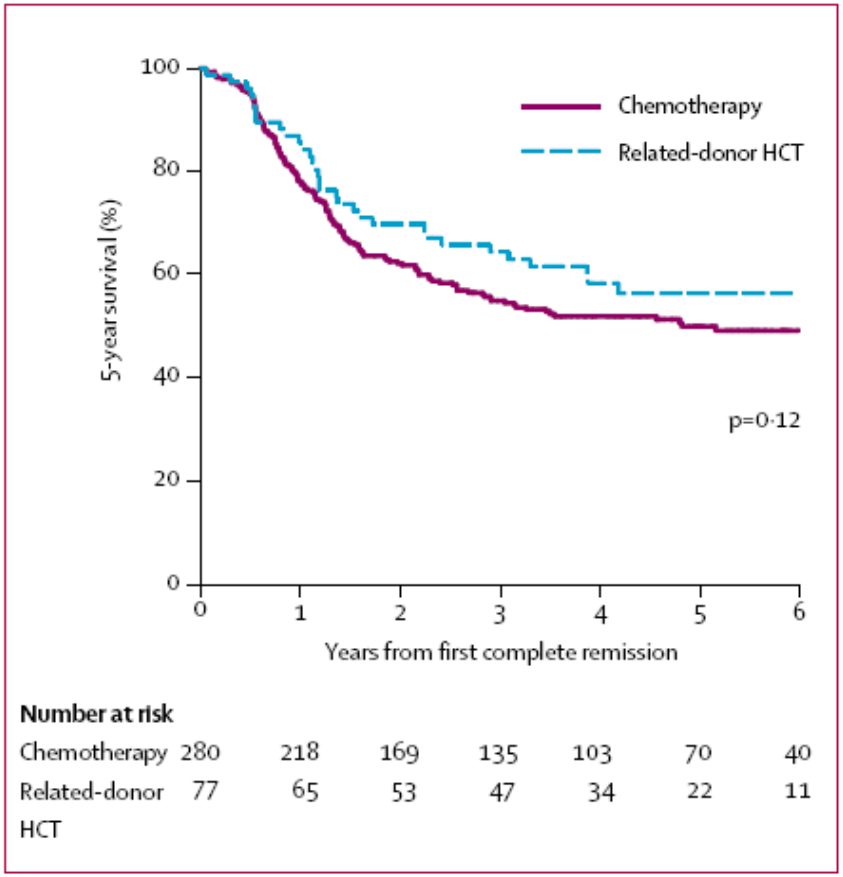

Figure 4: **Estimates of survival, by treatment assigned**
HCT=haemopoietic-cell transplantation. One death after relapse occurred after 6 years.

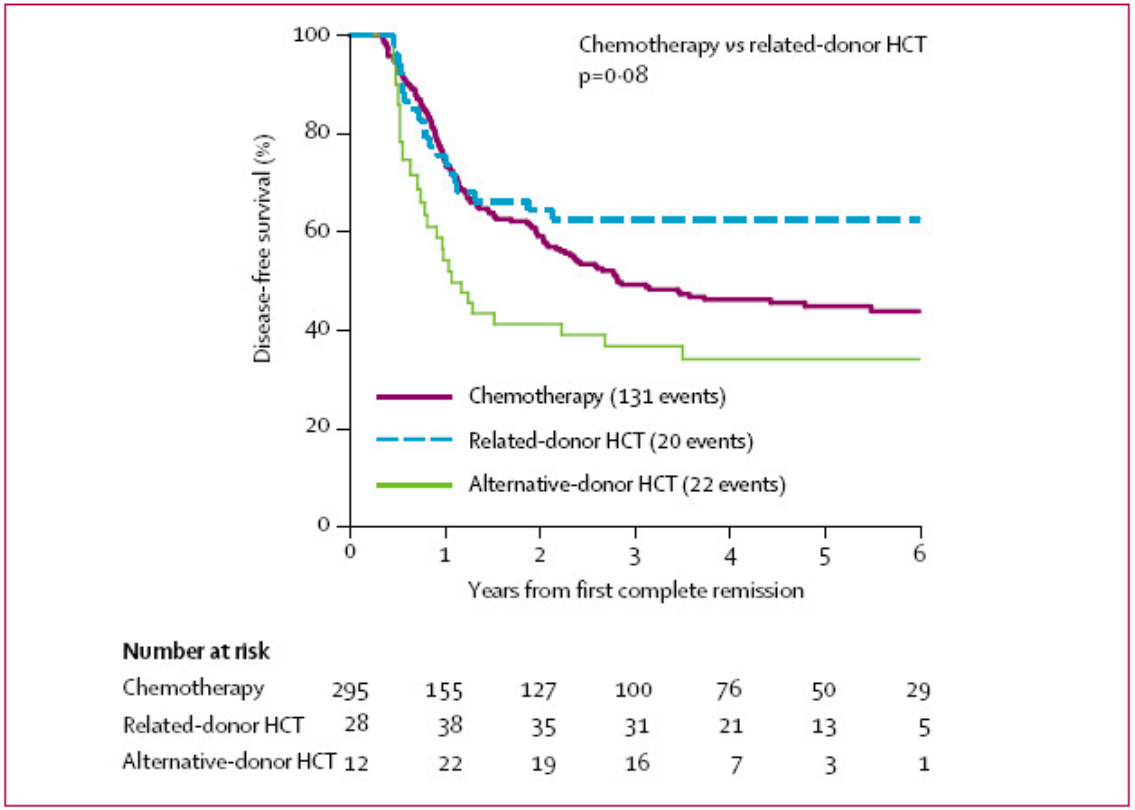

Figure 5: **Estimates of disease-free survival, by treatment received (adjusted by waiting time to transplantation)**
HCT=haemopoietic-cell transplantation.

Lancet 2005; 366: 635–42

Conclusions

- Currently, initial patient characteristics are of limited value for risk assessment as response to treatment is heterogenous in all subgroups, even in well-defined subsets of ALL (e.g. in Ph+ ALL).
- Thus, even more-refined ways to determine the patient at (increased) risk to relapse are needed
  - to save others from (unnecessary) therapy
  - to identify those HR patients who may need alternative therapy (e.g. hSCT).
- Treatment is effective but too toxic (and no change in sight!).
- Relapsed patients are at high risk to (eventually) die of the disease.
- Thus, effective prevention is a most relevant issue.

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