La leucemia linfoblastica acuta del bambino: storia di un successo terapeutico

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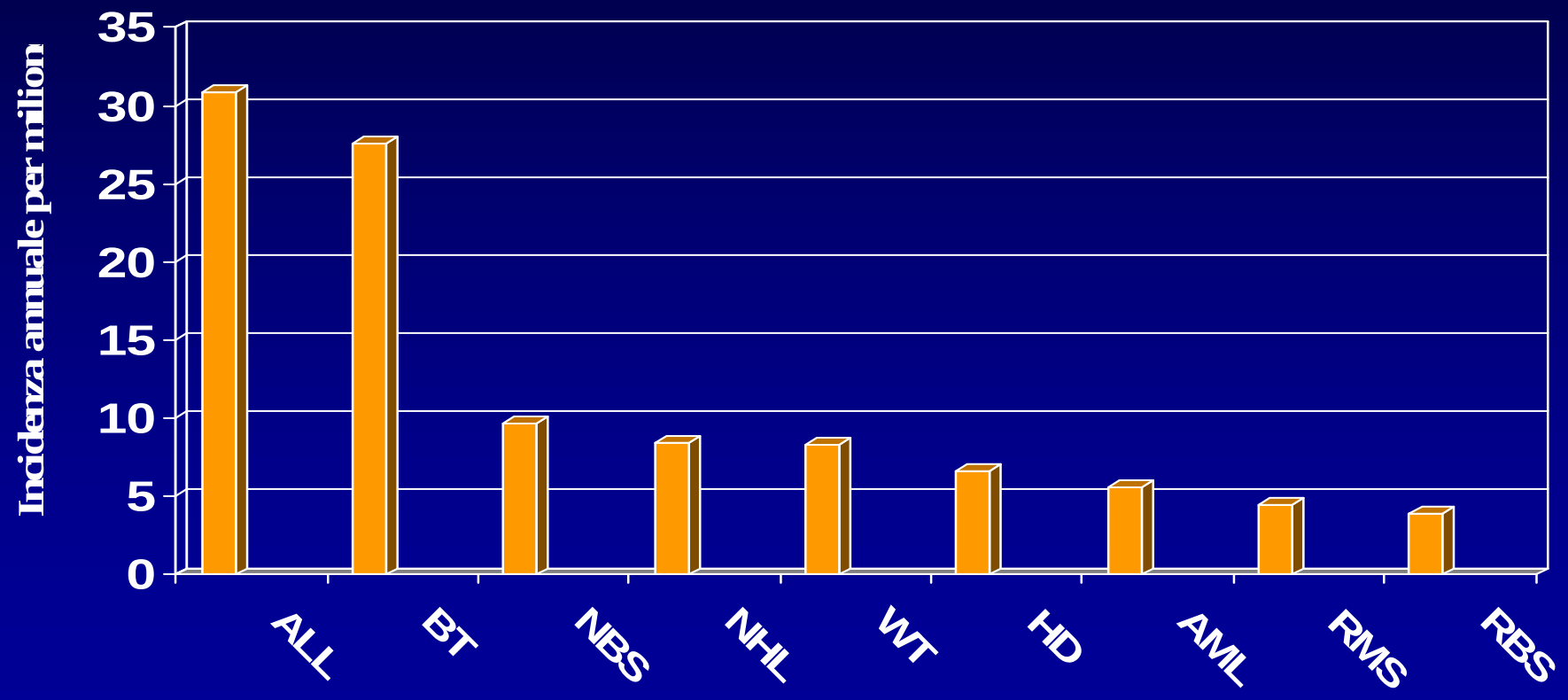
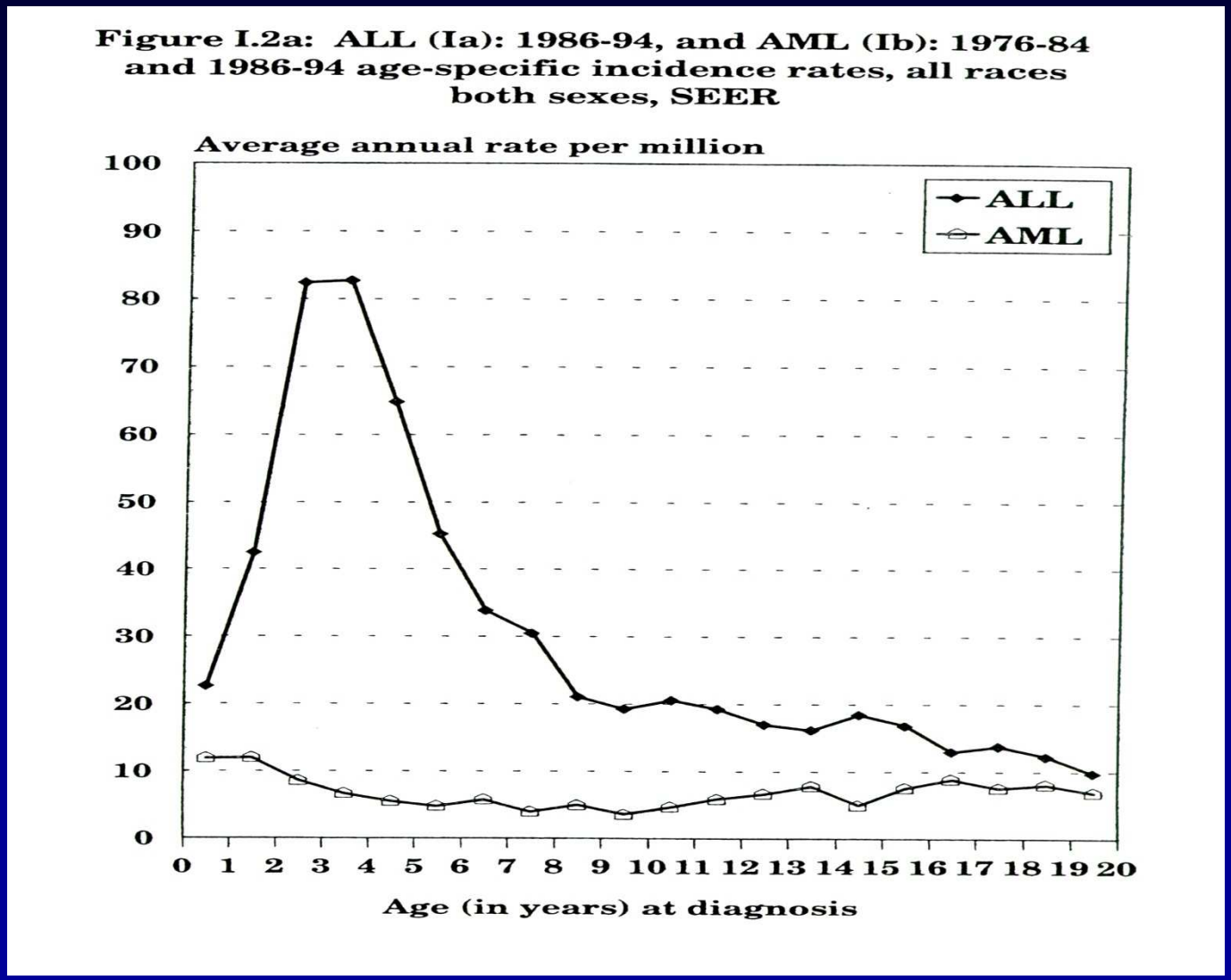
Incidenza annuale dei tumori dell'età pediatrica



CHILDHOOD ACUTE LEUKEMIA

- ALL accounts for 80% of all childhood acute leukemia;
- Among childhood ALL, 80-85% of patients have BCP ALL, 15-20% T-ALL and 2-3% mature B-ALL;
- With the remarkable exception of Down-Syndrome patients, there is no genetic predisposition to develop acute leukemia.

Leucemie acute-Distribuzione per età



Picco

2-4 anni

Predominanza dei maschi

Presentation of childhood leukemia

- Hyperleukocytosis and huge organomegaly;
- Pseudoaplastic/single-bilinear cytopenia;
- «Rheumatic disease»;
- Bone pain/swelling;
- Mediastinal involvement;
- Chloroma/granulocytic sarcoma;

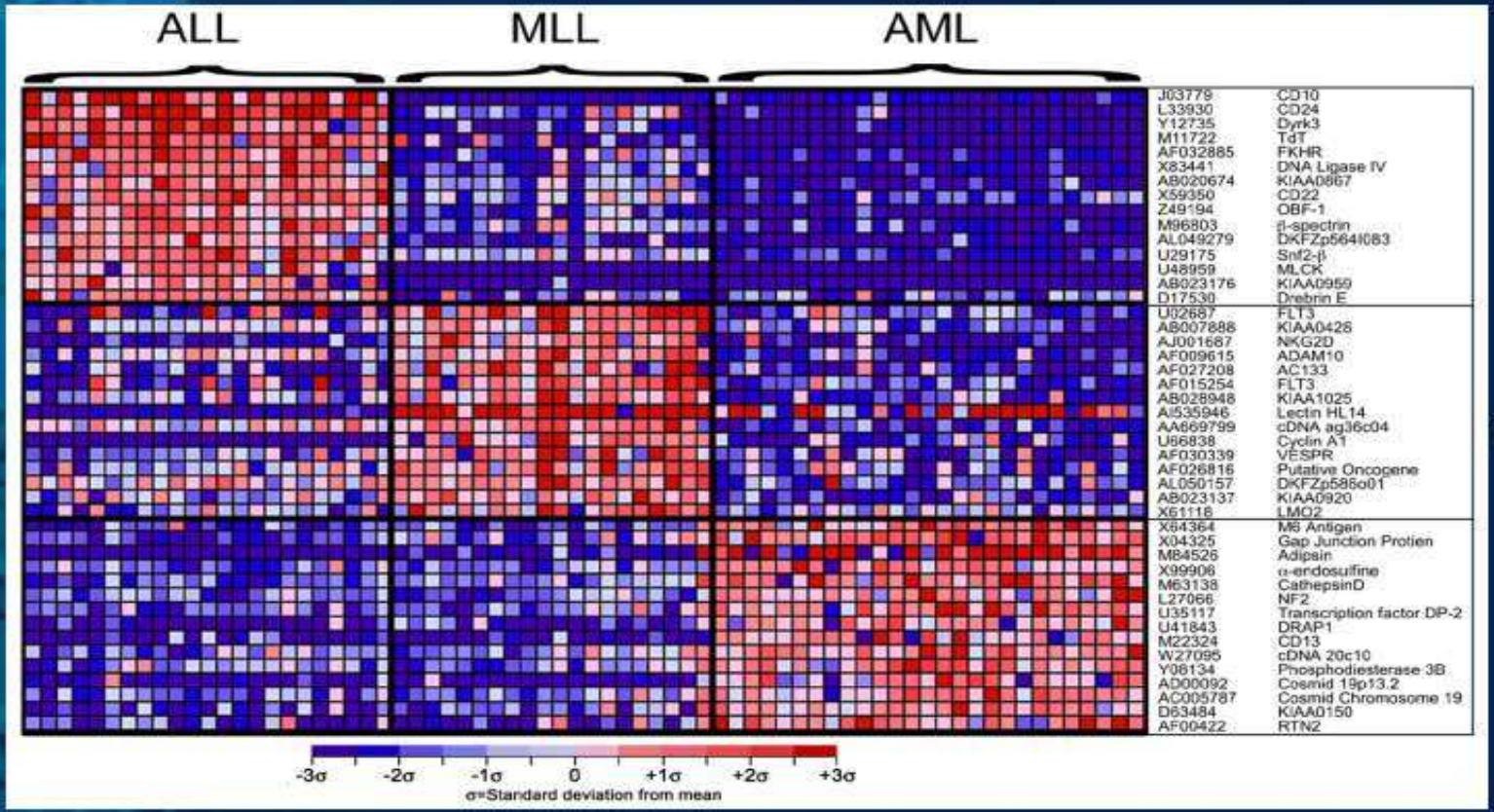
LLA-Caratteristiche cliniche alla diagnosi

Caratteristica	Percentuale di casi
Febbre	61
Petecchie/Porpora	48
Dolori osteo-articolari	25
Linfadenopatia	50
Splenomegalia	63
Epatomegalia	68

LLA-Caratteristiche di laboratorio alla diagnosi

Caratteristica	Percentuale di casi
Conta leucocitaria	
< 10,000	53
10,000-49,000	30
> 50,000	17
Emoglobina (g/dl)	
< 7	43
7 – 11	45
> 11	12
Conta piastrinica (mm^3)	
< 20K	28
20 - < 100K	47
> 100K	25

Classifying AML, ALL and MLL

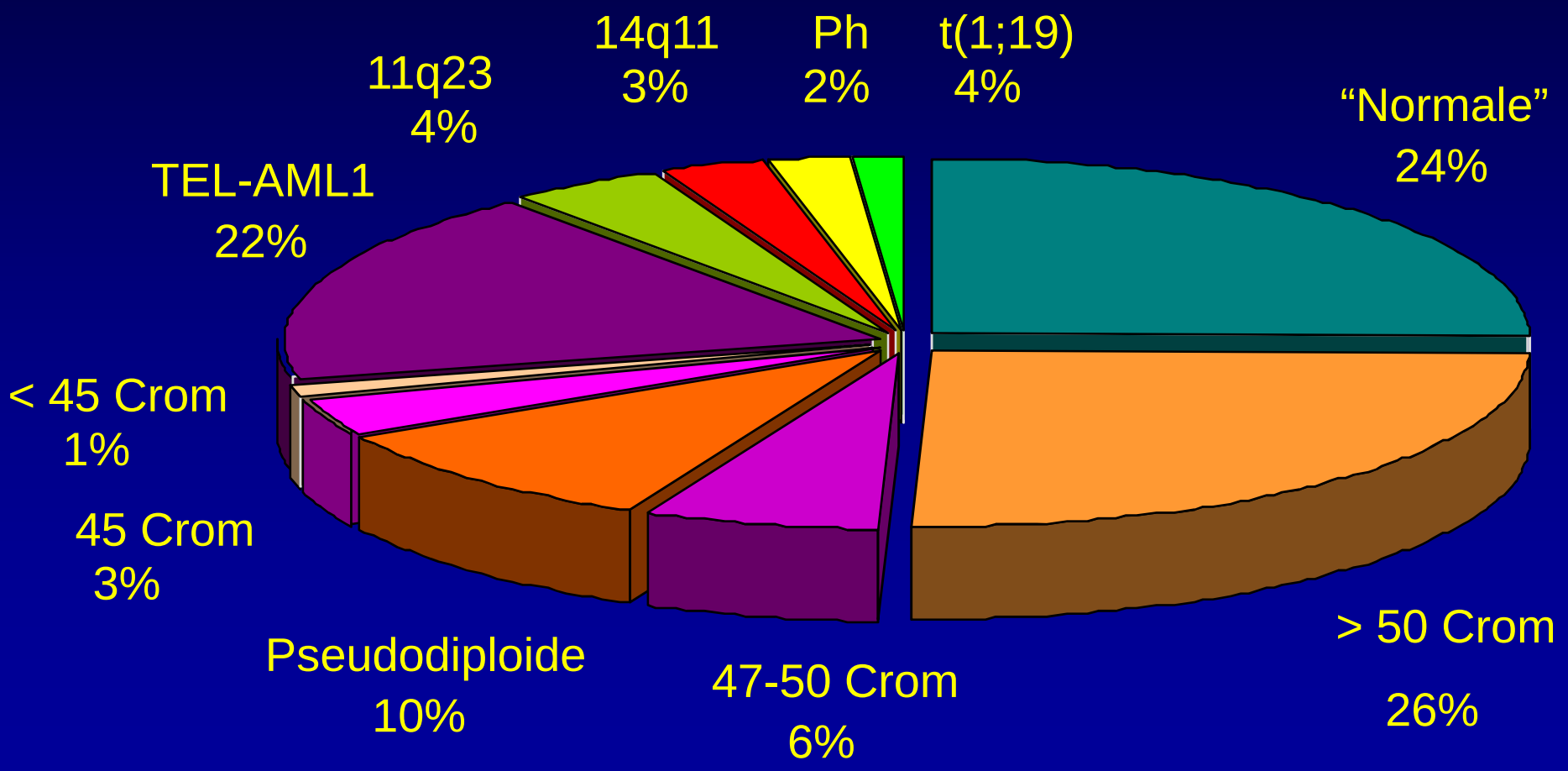


> 95% correct diagnoses

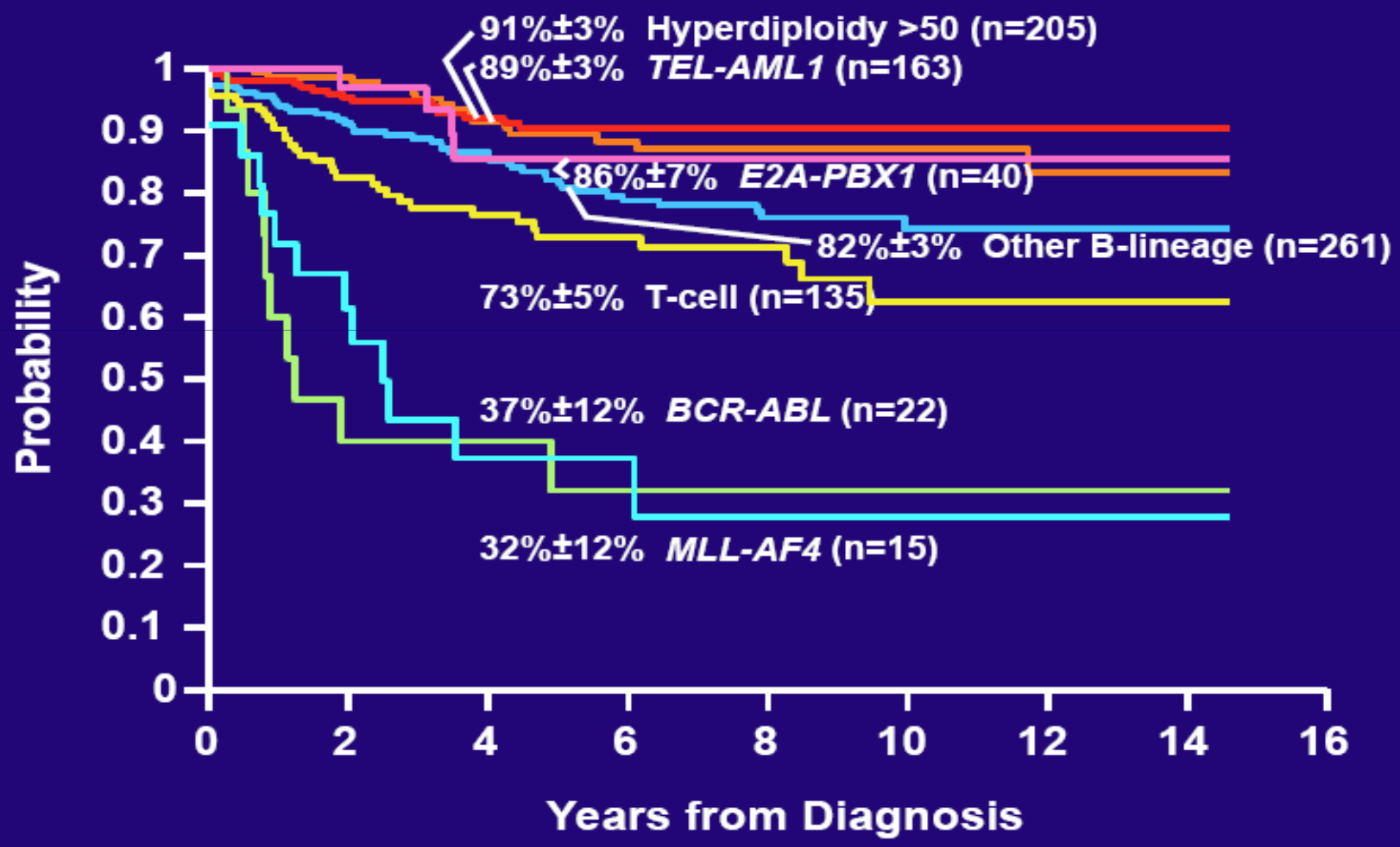
Armstrong, S.A., et al. **Nature Genetics** 30: 41-47, 2002

AFFYMETRIX

Eterogeneità genetica nella LLA dell'infanzia

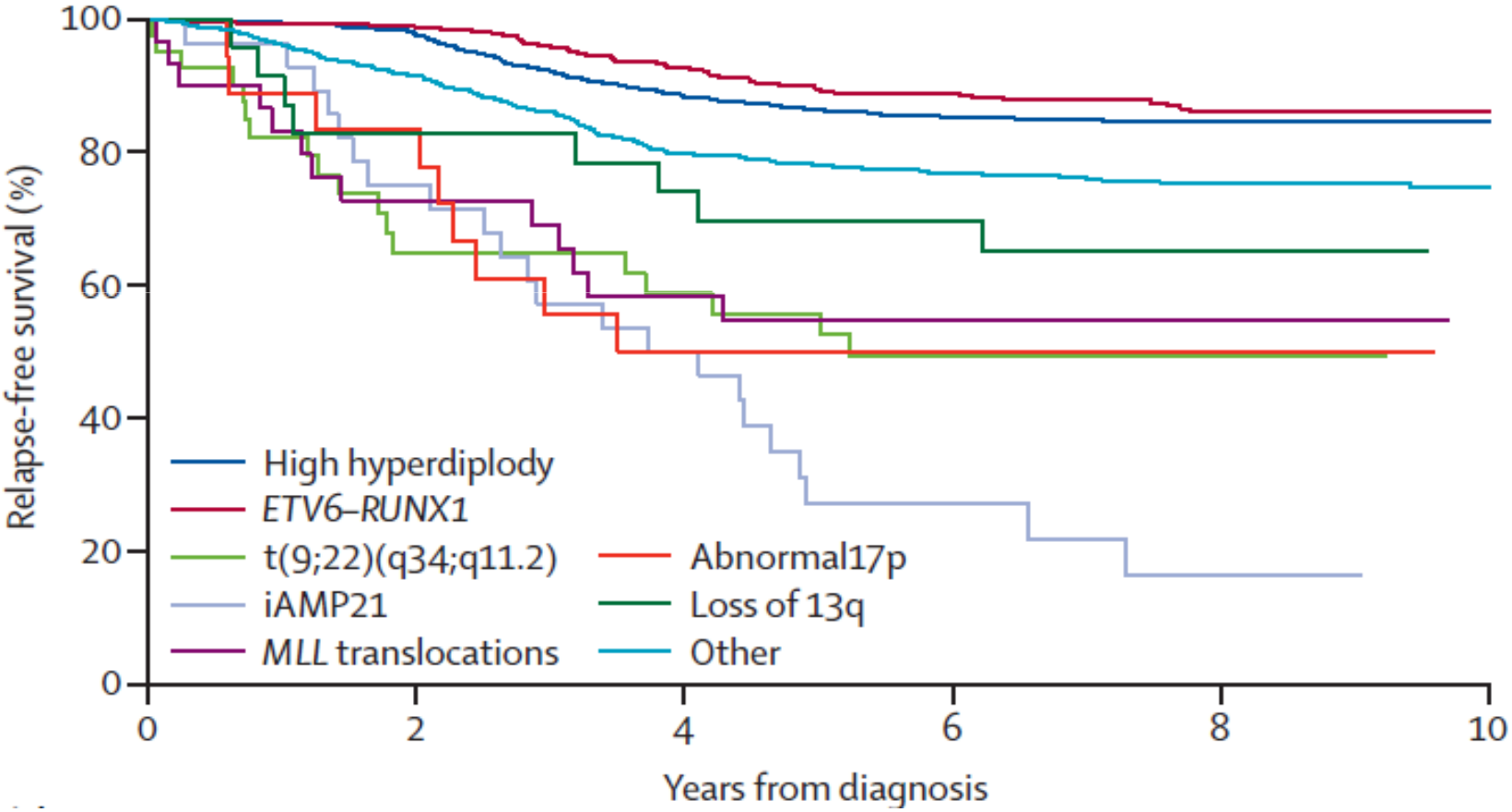


EFS According to Genotype and Phenotype



Pui et al. Lancet 2008;371:1030-43.

The impact of a more sophisticated cytogenetic classification



Moorman AV et al. Lancet Oncology 2010;11:429-438

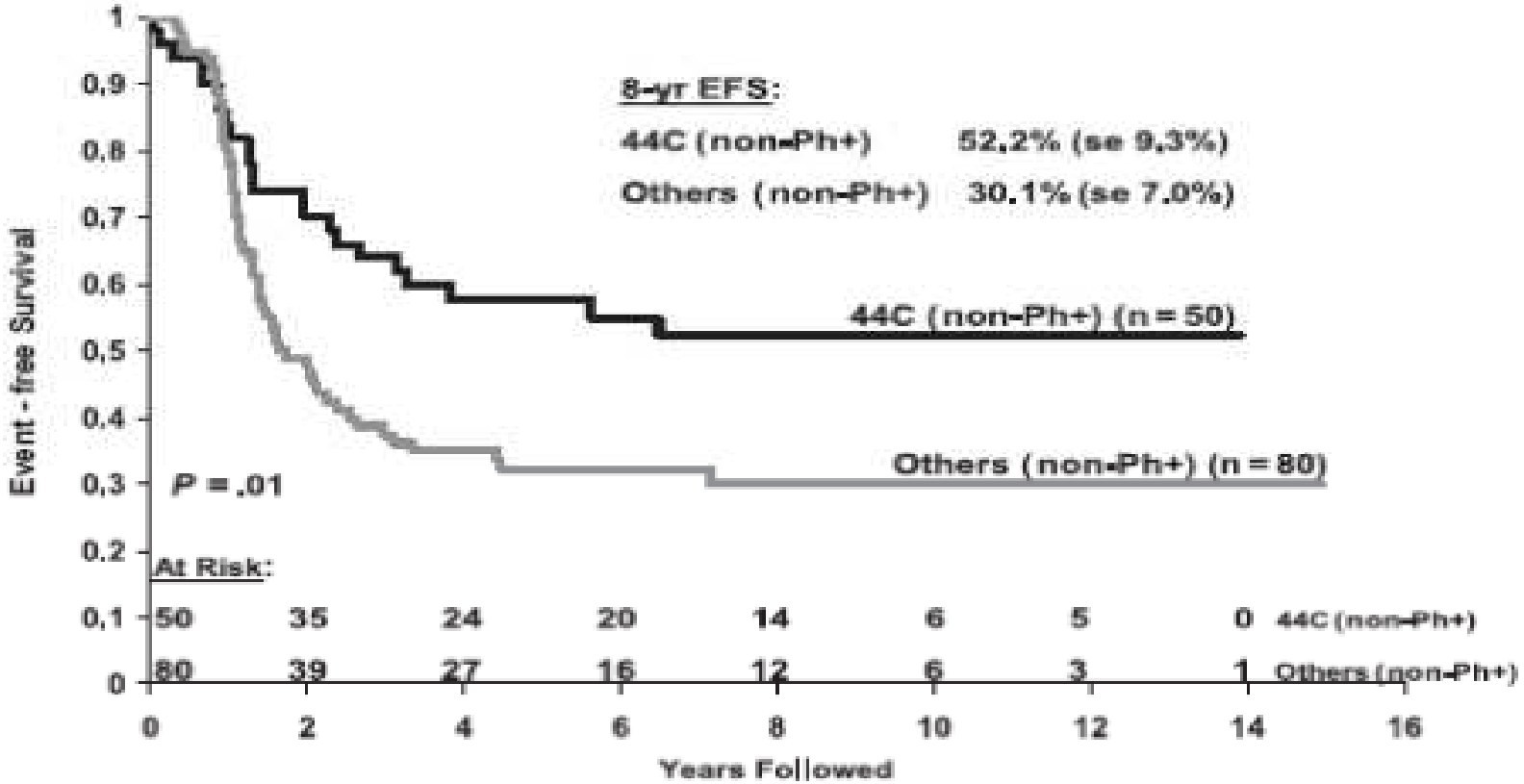
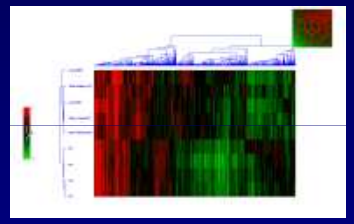


Figure 3. Comparison of EFS for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

Concepts of *Today* for the *Future*: Optimizing Therapy

Define the molecular specific response profile

Dx expression analysis

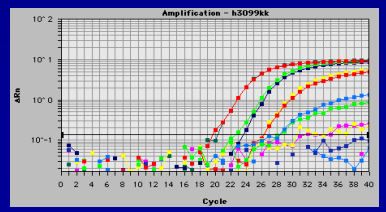


Responsive genotype → "Conservative" therapy

Unresponsive genotype → "Aggressive" therapy

MRD monitoring

"Hi-risk"



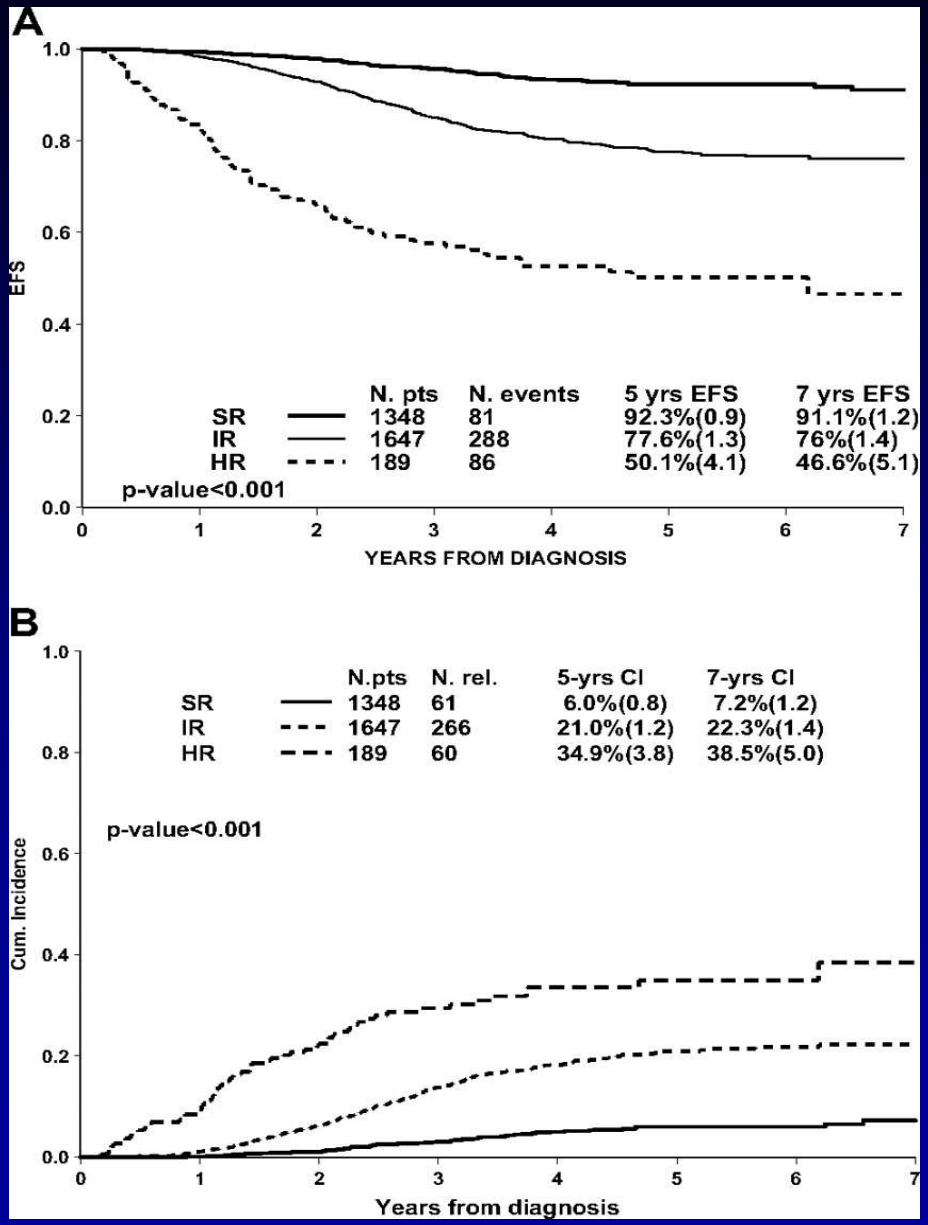
Courtesy of Jerry Radich, FHCRC

Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study

*Valentino Conter,[1,2] *Claus R. Bartram,[3] Maria Grazia Valsecchi,[4] André Schrauder,[5] Renate Panzer-Grümayer,[6] Anja Möricke,[5] Maurizio Aricò,[7] Martin Zimmermann,[8] Georg Mann,[6] Giulio De Rossi,[9] Martin Stanulla,[5] Franco Locatelli,[10] Giuseppe Basso,[11] Felix Niggli,[12] Elena Barisone,[13] Günter Henze,[14] Wolf-Dieter Ludwig,[15] Oskar A. Haas,[6] Giovanni Cazzaniga,[16] Rolf Koehler,[3] Daniela Silvestri,[4] Jutta Bradtke,[17] Rosanna Parasole,[18] Rita Beier,[8] Jacques J. M. van Dongen,[19] Andrea Biondi,[1,16] and Martin Schrappe[5]

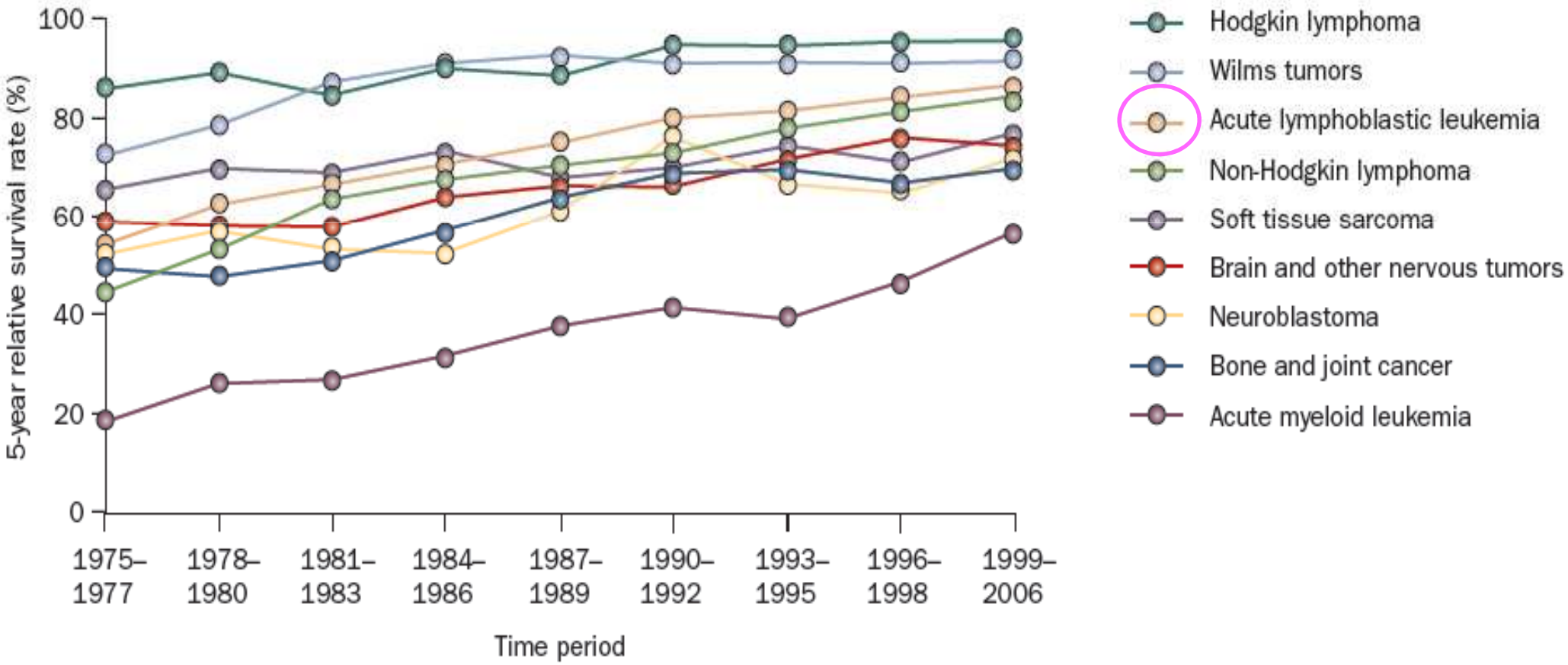
BLOOD, 22 APRIL 2010 • VOLUME 115, NUMBER 16

Event-free survival (A) and cumulative incidence of relapse (B) according to PCR-MRD classification in 3184 pB-ALL patients



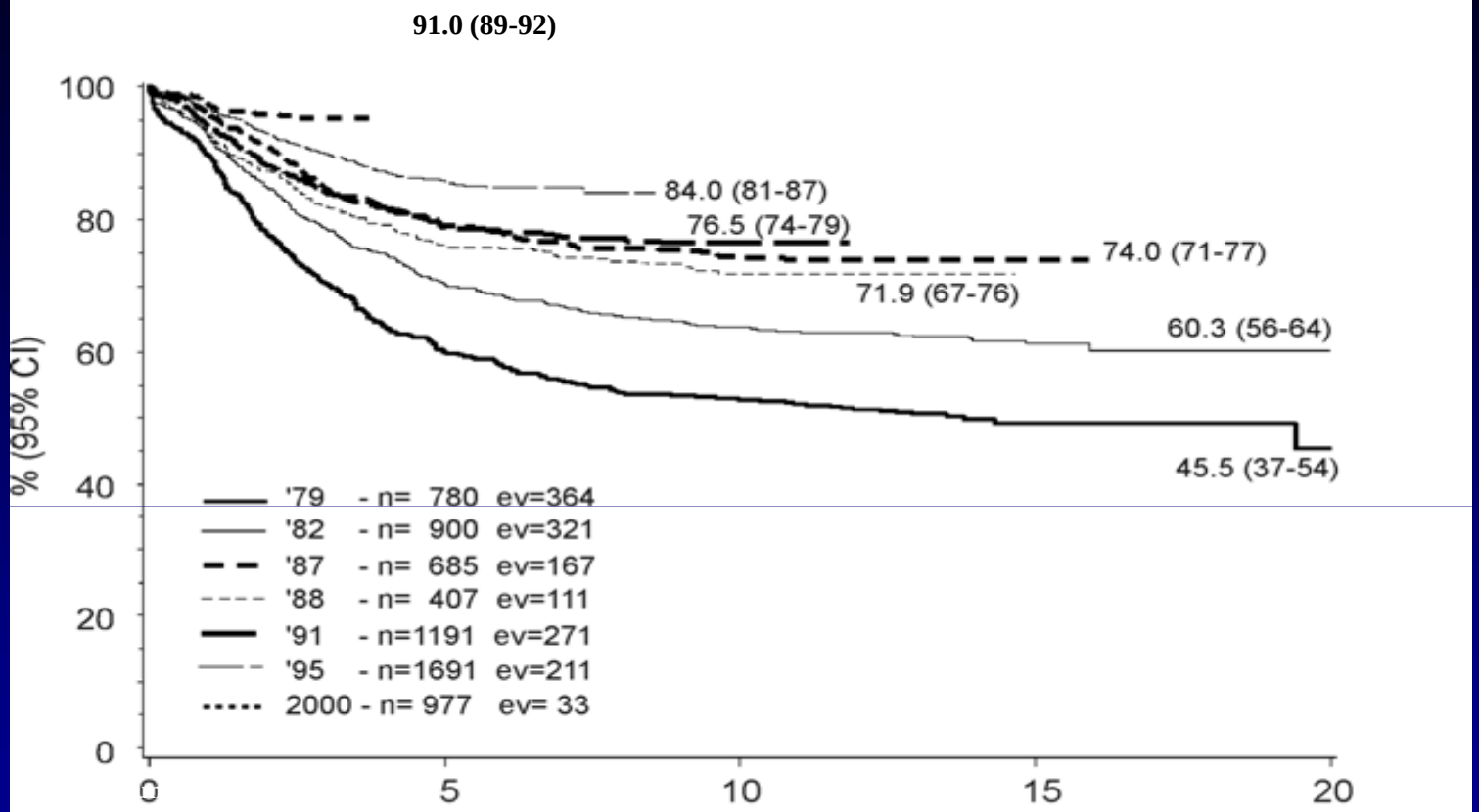
Conter V. et al. Blood 2010;115:3206-3214

Five-year relative survival rates for selected primary cancers according to year of diagnosis (1975–2006) among children younger than 20 years of age



Pui, C.-H. et al. Nat. Rev. Clin. Oncol. 2011;28;8:540-549

PROTOCOLLI AIEOP PER LEUCEMIE LINFOBLASTICHE ACUTE



780	438	323	54	- '79
900	589	466	126	- '82
687	506	351	17	- '87
407	304	189	0	- '88
1191	911	105	0	- '91
1691	604	0	0	- '95
977	0	0	0	- 2000

TRATTAMENTO MULTIDISCIPLINARE ARMONICO e INTEGRATO

Supporto organizzativo

Supporto sociale

Supporto psicologico

Supporto anti-infettivo

CHIRURGIA

RADIO TERAPIA

LENI TERAPIA

CHEMIO TERAPIA

IMMUNO TERAPIA

Supporto metabolico

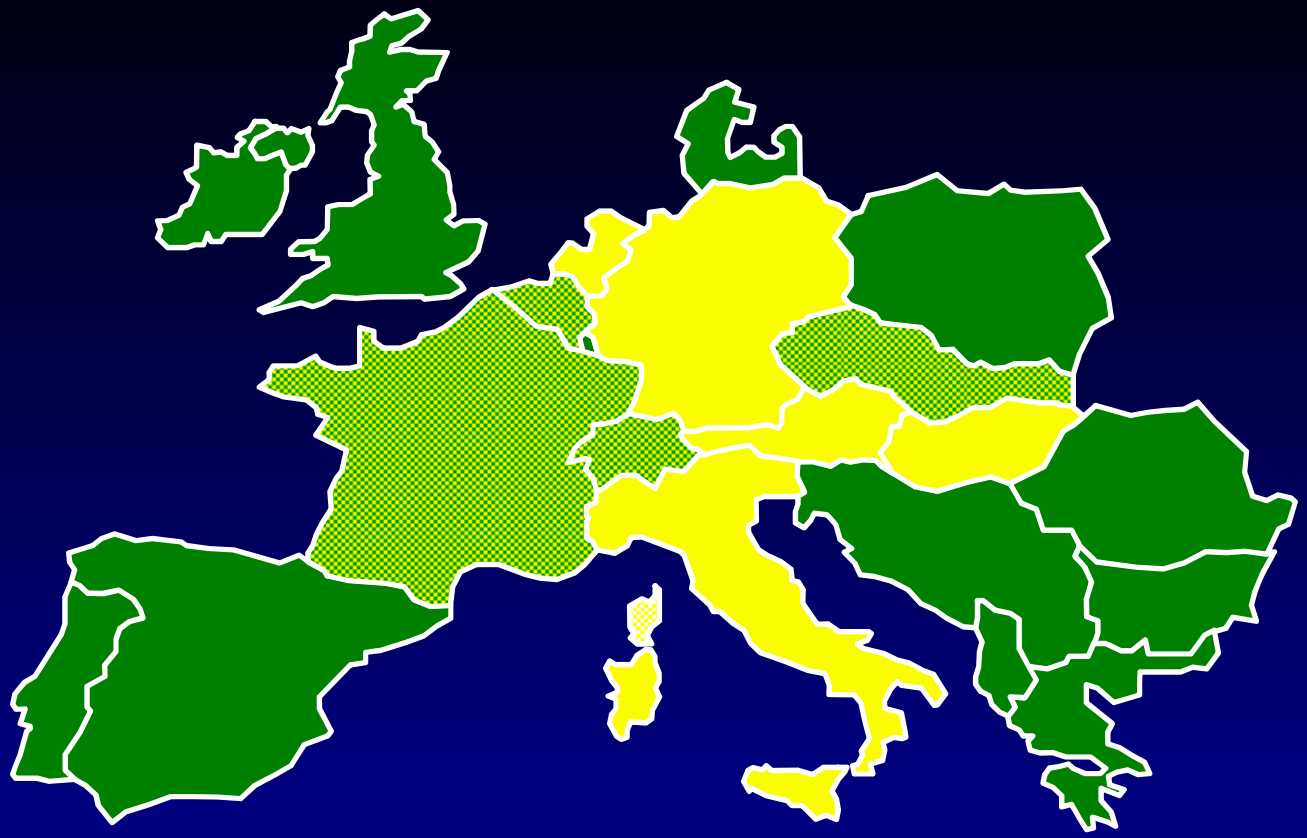
Supporto Spec.Org.

Supporto trasfusionale

Supporto immunologico

LLA: elementi del trattamento polichemioterapico

- Fase citoriduttiva e di induzione della remissione
- Necessità di consolidare il risultato ottenuto con la fase di Induzione.
- Reinduzione
- Trattamento specifico sul Sistema Nervoso Centrale
- Mantenimento



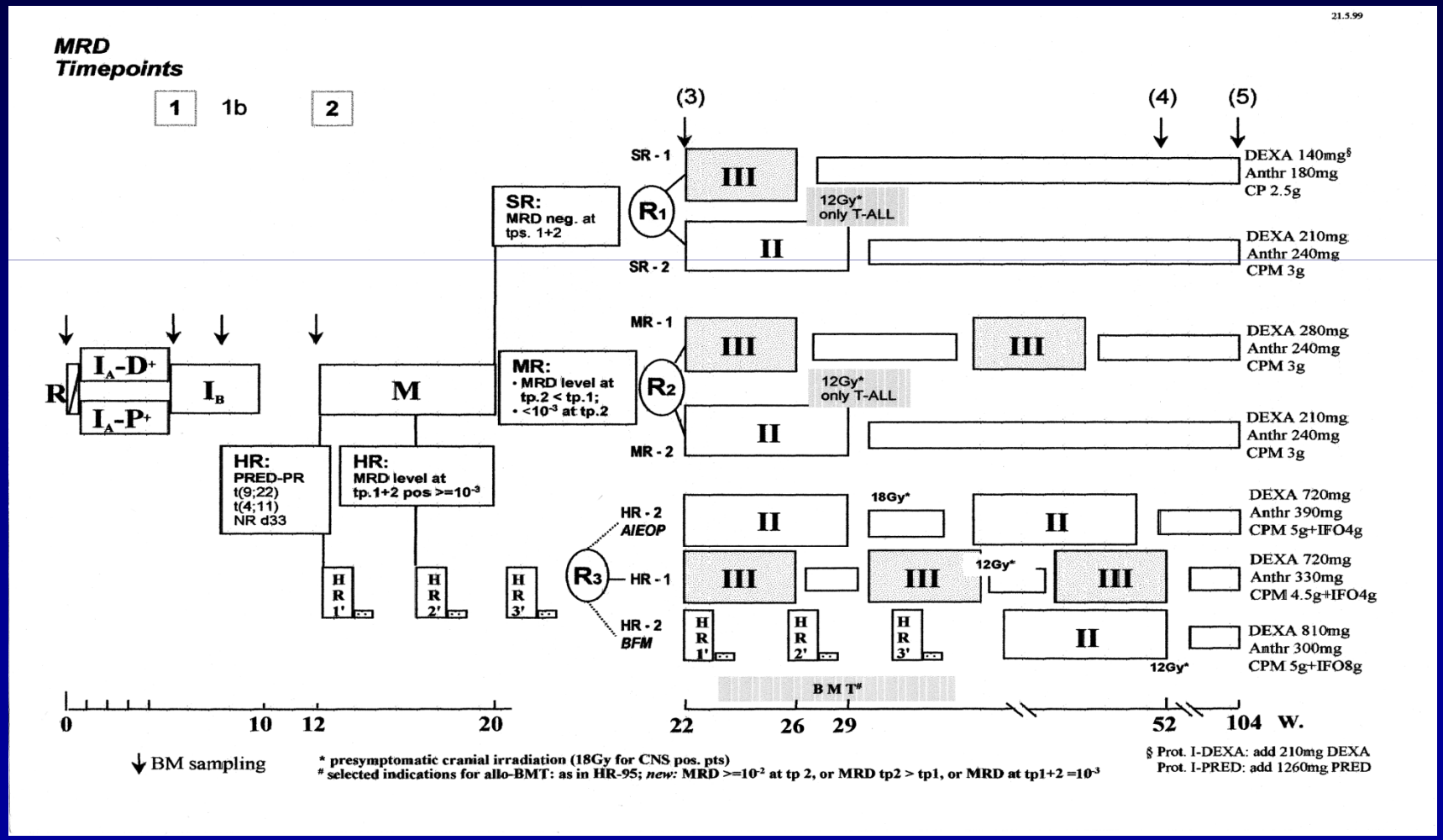
International BFM Study Group

Belgio
Francia
Germania
Ungheria
Italia
Svizzera
Olanda

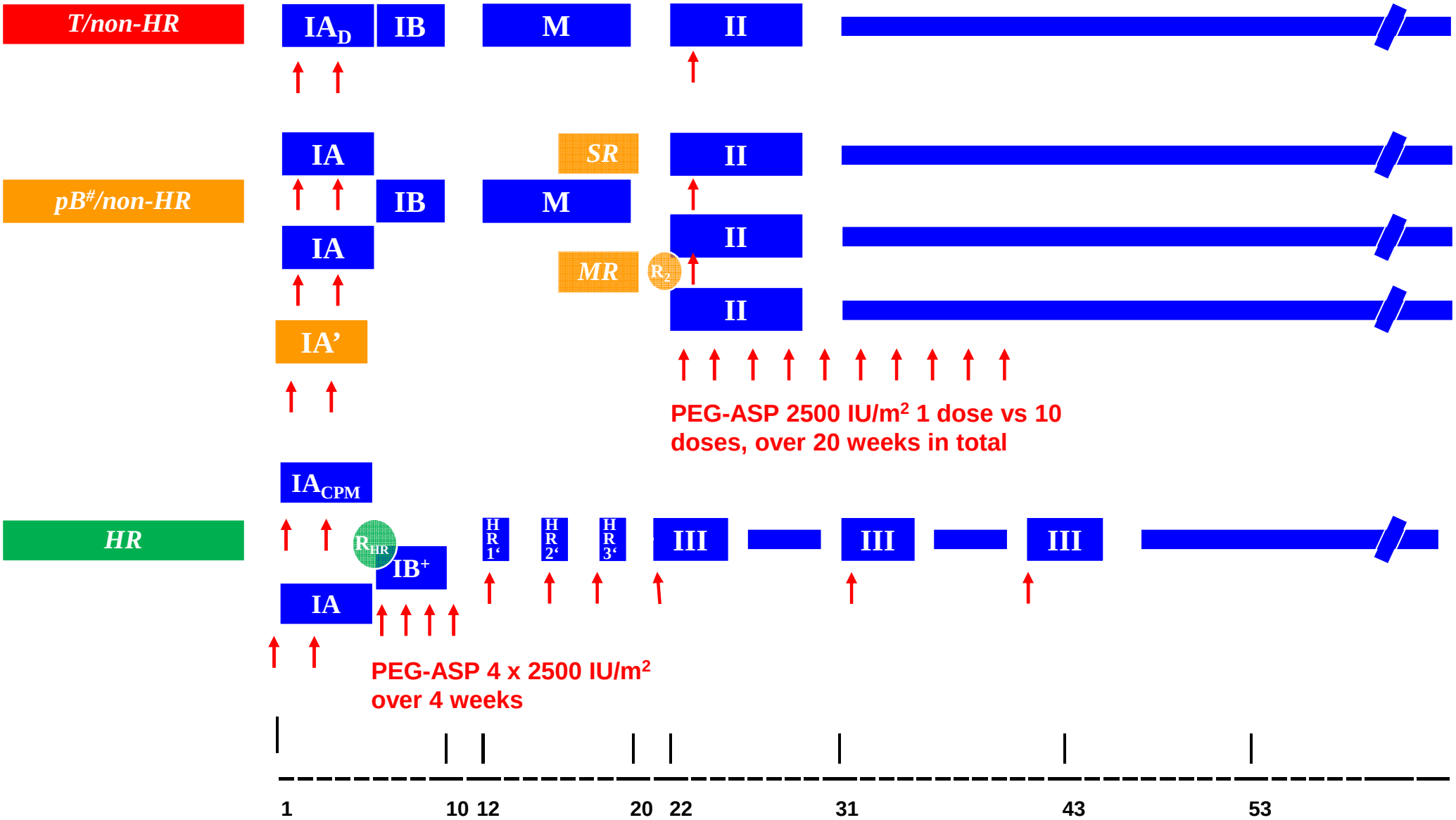
Argentina
Cile
Repubblica Ceca
Hong Kong

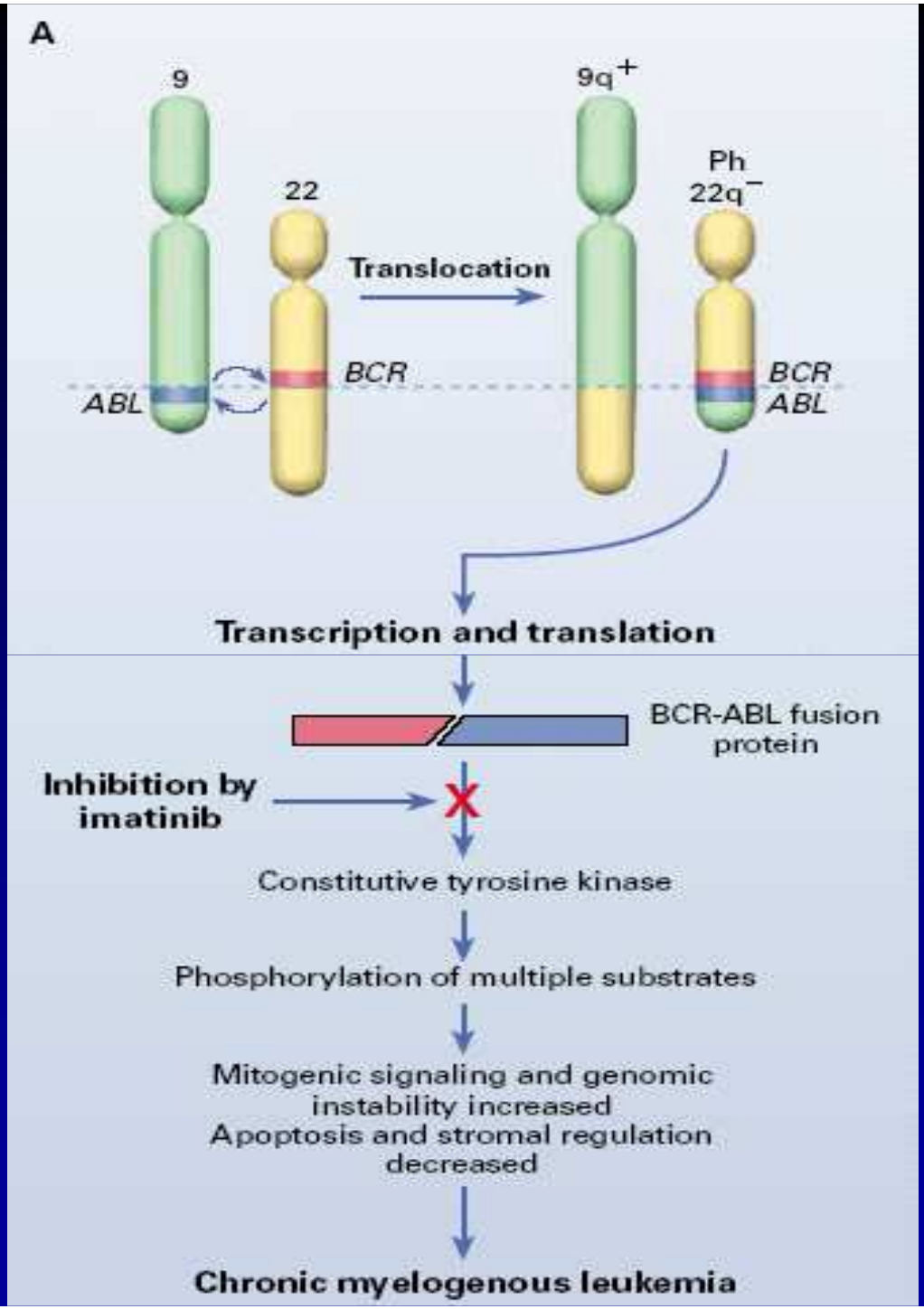
- Tutti i centri
- Alcuni centri

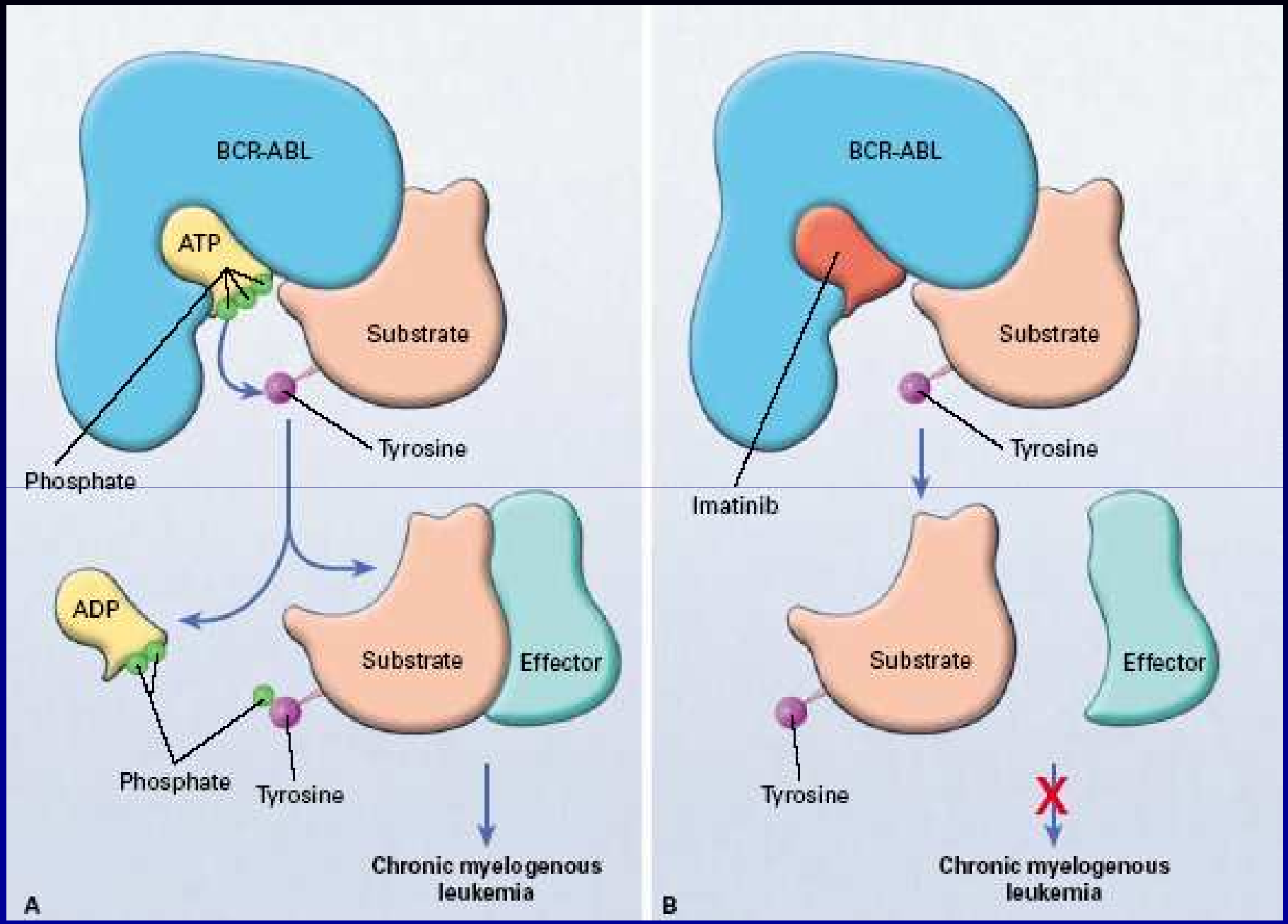
Protocollo AIEOP/BFM-ALL 2000



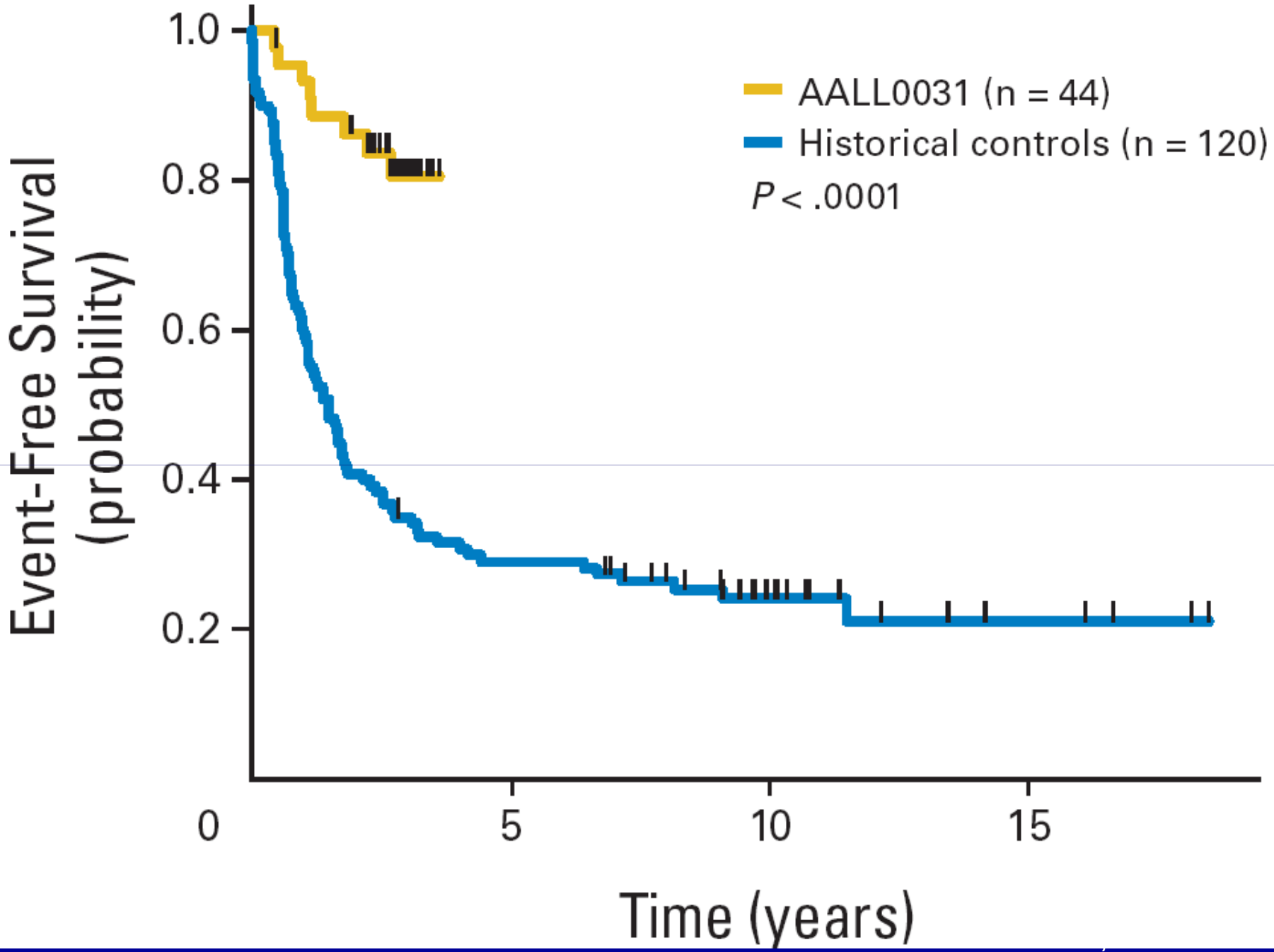
AIEOP-BFM ALL 2009 outline with randomized studies



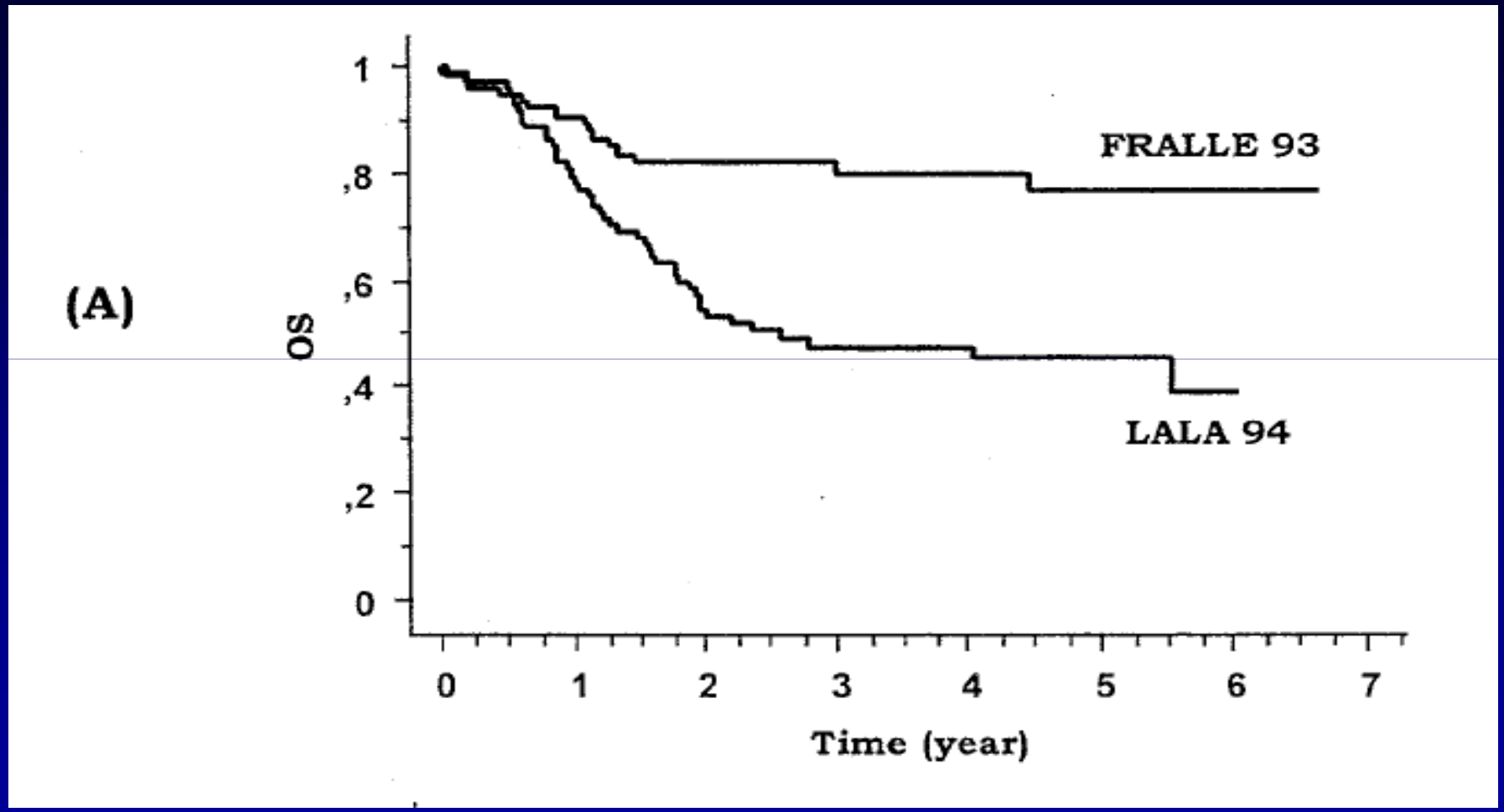

A
9
22
9q+
Ph
22q−
Translocation
BCR
ABL
BCR
ABL
Transcription and translation
BCR-ABL fusion protein
Inhibition by imatinib
Constitutive tyrosine kinase
Phosphorylation of multiple substrates
Mitogenic signaling and genomic instability increased
Apoptosis and stromal regulation decreased
Chronic myelogenous leukemia



Savage DG and Antman KH, N Engl J Med, 2002


Event-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
5
10
15
Time (years)
AALL0031 (n = 44)
Historical controls (n = 120)
P < .0001

Probability of OS in adolescents treated in pediatric Institutions with pediatric protocols or in adult Institutions with adult protocols



Boissel N, et al. J Clin Oncol 2003

Quel che rimane ancora da superare……

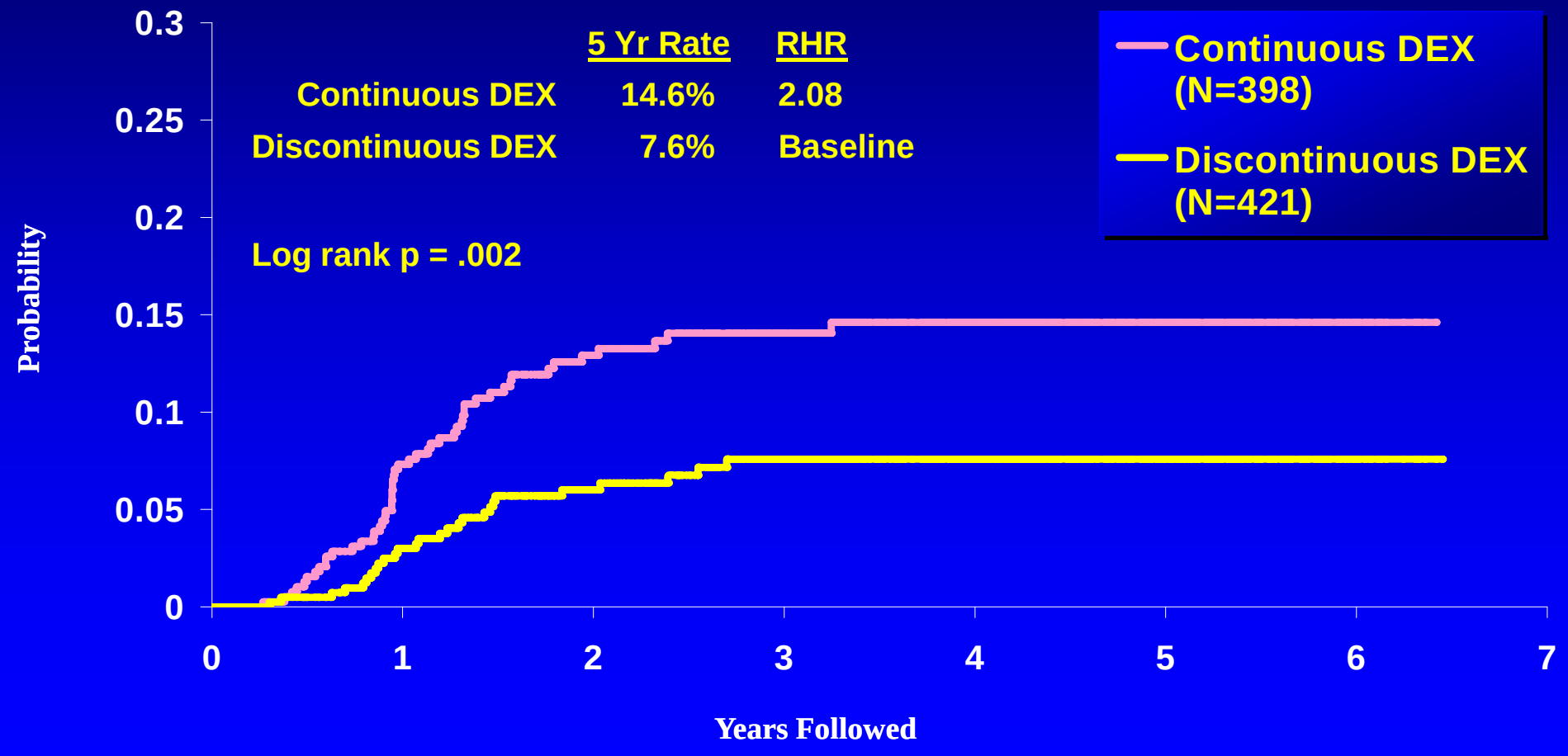
AVN – CCG 1961

- 7/769 Patients < 10 Years Developed AVN – 1%

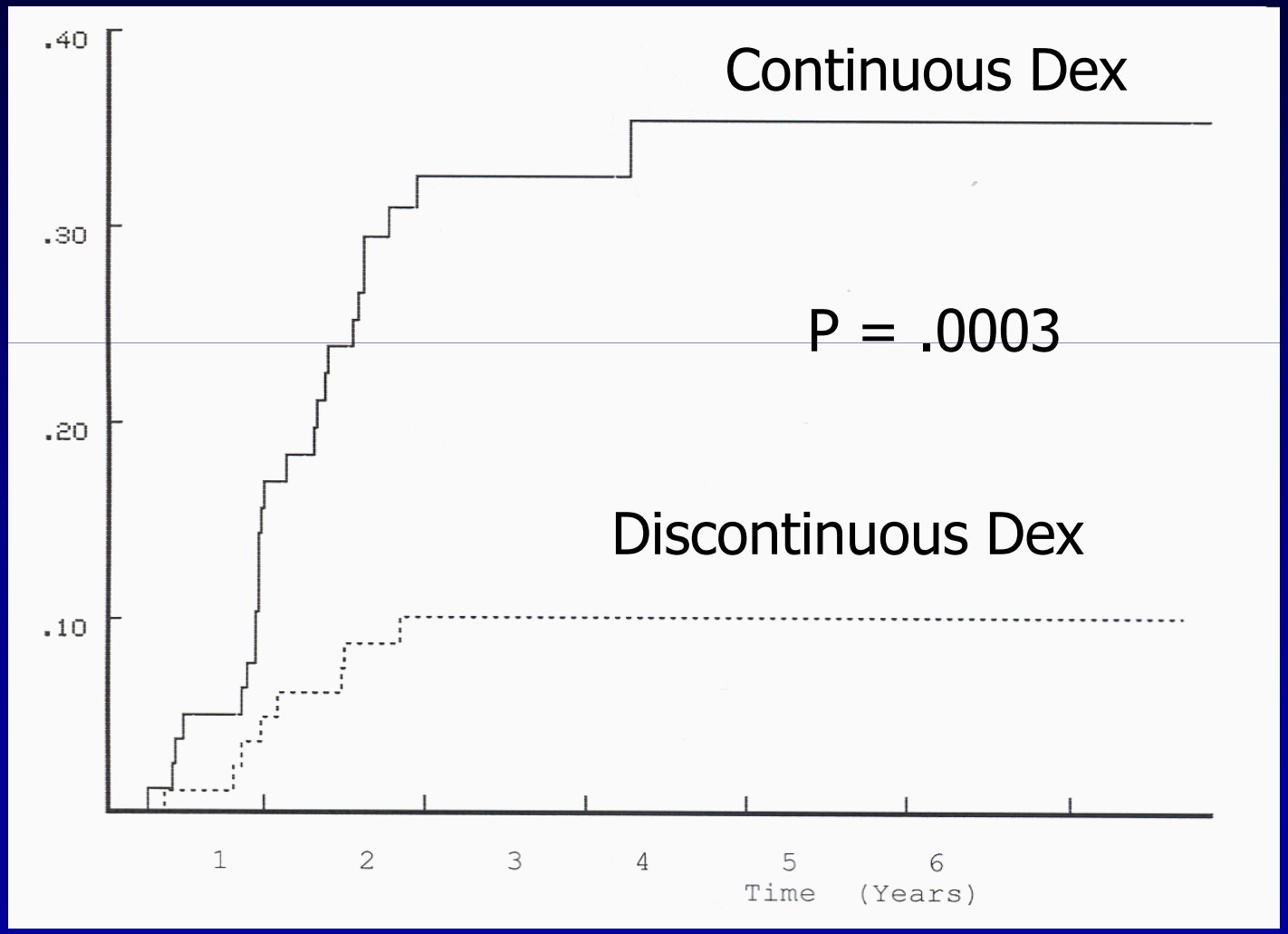
- 126/1287 Patients ≥ 10 Years Developed AVN – 9.8%
  - 10-12 Years 32/505 7%
  - 13-15 Years 53/520 12.6%
  - 16+ Years 41/262 18.5%

- Incidence of AVN Twice As High In Females

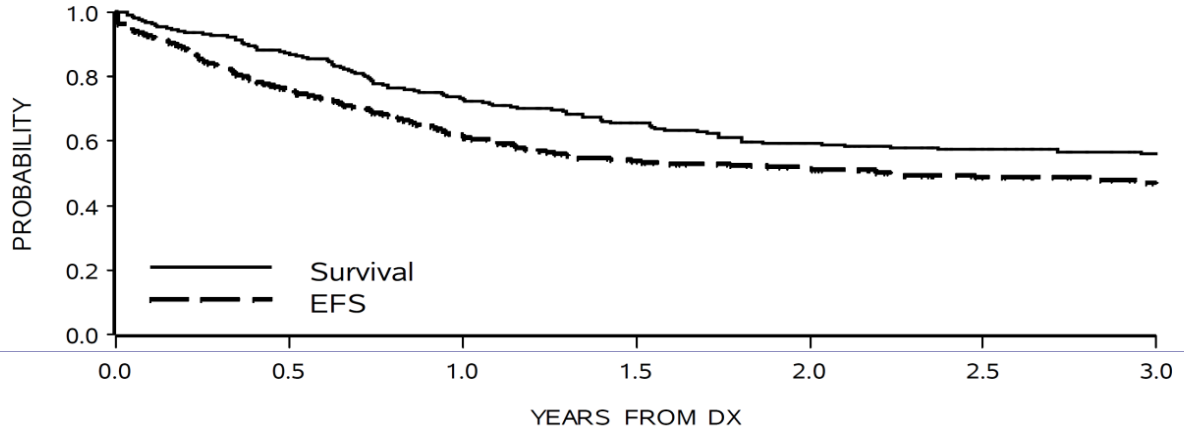
CCG-1961 AVN by RER Groups
(Age 10+ Yrs)



AVN Incidence In 16+ Patients
Continuous vs. Discontinuous Dexamethasone



Interfant-06
Overall outcome



N. pts.	N. events (relapses)	EFS (SE)		N. deaths	Survival (SE)	
		3-year	4-year		3-year	4-year
385	168 (102)	47.3 (3.0)	47.3 (3.0)	131	56.0 (3.1)	56.0 (3.1)

Median follow-up (min-max) month: 26 (1 - 81)

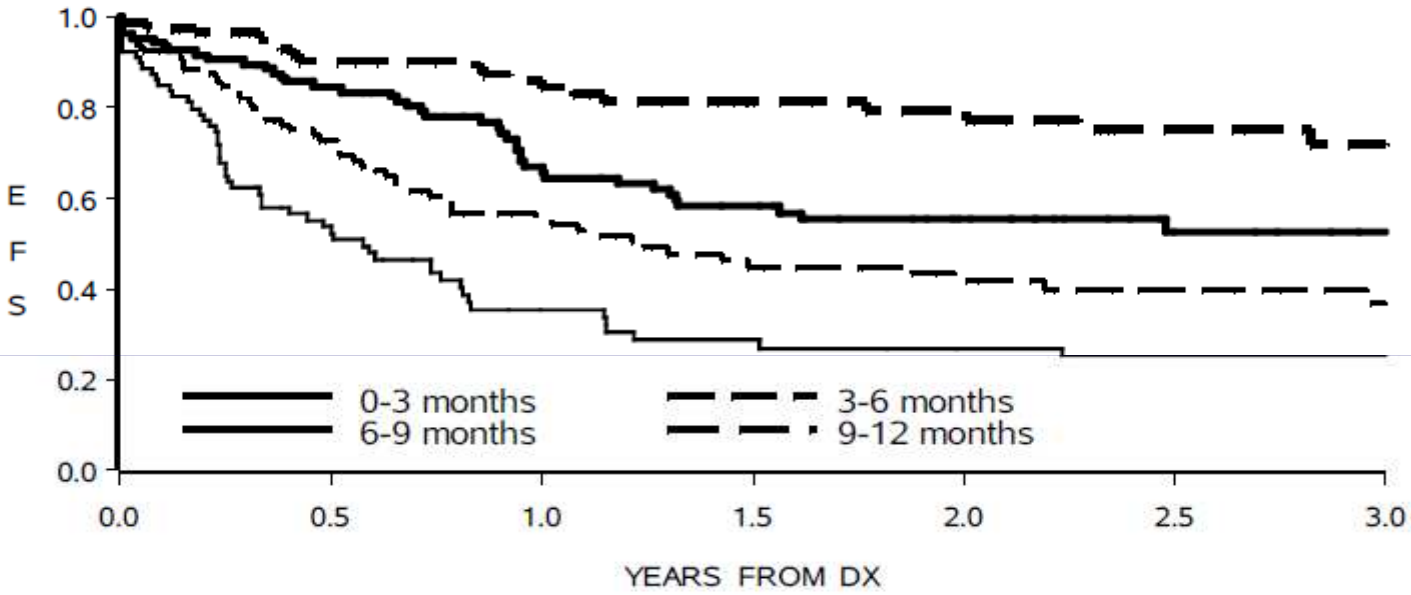
NOTE: The EFS curve do not show 1 relapse in BM that occurred at 4.3 years (is alive in CR at last follow-up)

Outcome in Interfant99

Update at Dec 2007, median follow-up (min-max) month: 58 (1 - 102)

N. pts.	N. events (relapses)	EFS (SE)		N. deaths	Survival (SE)	
		3-year	*6-year*		3-year	*6-year*
478	249 (193)	47.9 (2.3)	*46.5 (2.3)*	206	59.3 (2.3)	*53.8 (2.5)*

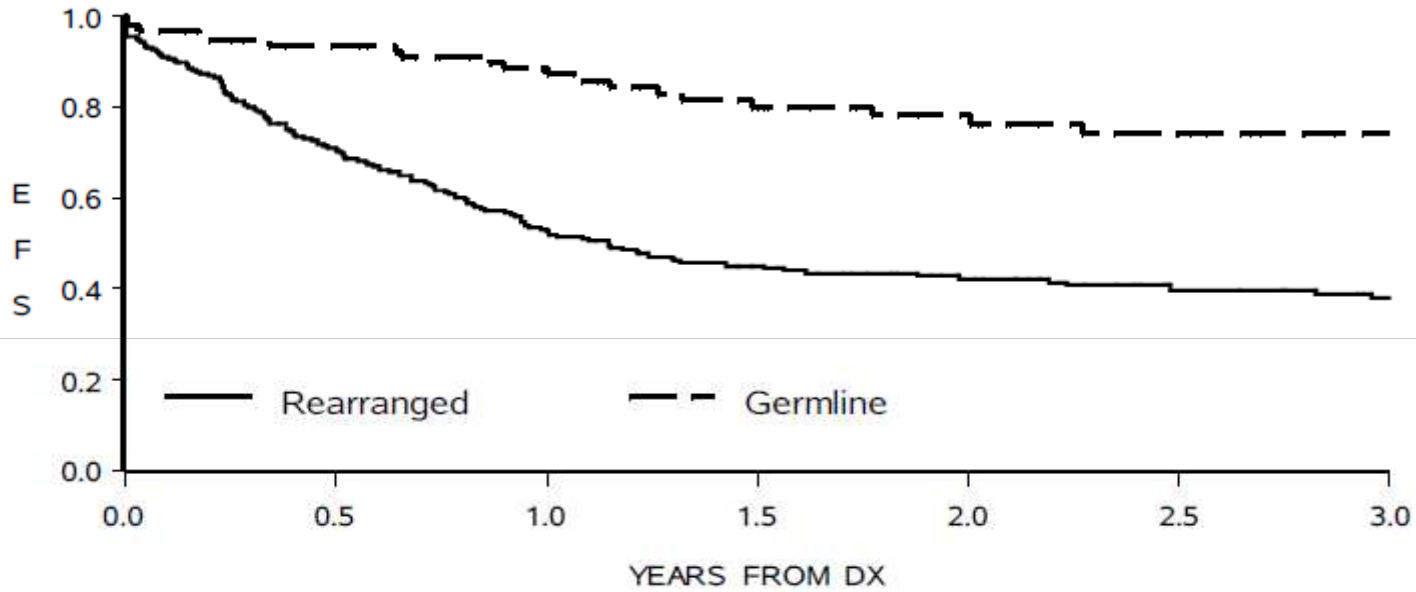
Interfant-06
EFS by age at diagnosis



Age at diagnosis	N. pts.	N. events	3-year EFS (SE)	p-value	Interfant99 3-year EFS (SE)
< 3 months	80	53	25.3 (5.5)	<0.0001	27.9 (4.4)
3 - 6 months	108	55	37.6 (5.8)		38.3 (4.6)
6 - 9 months*	108	42	53.0 (5.7)		53.2 (4.6)
9-12 months	89	18	72.1 (6.0)		68.5 (4.1)

* The curve do not show 1 event that occurred at 4.3 years (1 relapse in BM).

Interfant-06
EFS by MLL Status



MLL Status	N. pts.	N. events	3-year EFS (SE)	p-value	Interfant99 3-year EFS (SE)
Rearranged	285	145	38.0 (3.5)	<0.0001	37.3 (2.8)
Germline*	96	20	74.6 (5.2)		76.6 (4.7)
Not evaluable	4	3	-		-

* The curve do not show 1 event that occurred at 4.3 years (1 relapse in BM).

Factors influencing the prognosis of children with relapsed ALL

Major variables

- Duration of first CR
- Site of relapse
- Immunophenotype

Minor variables

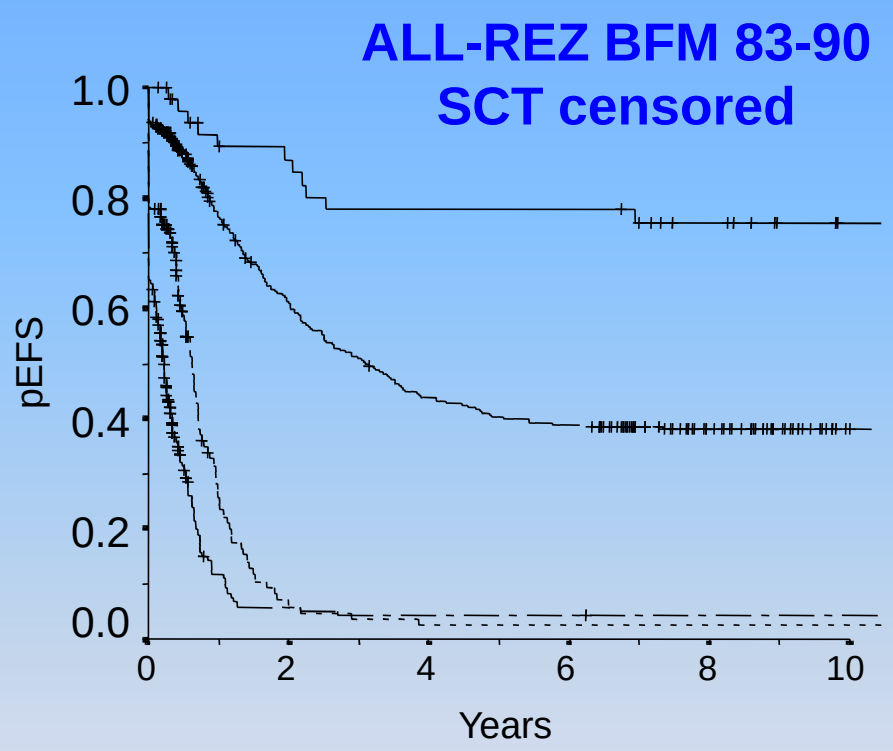
- Sex
- Age
- PB blast count at time of relapse

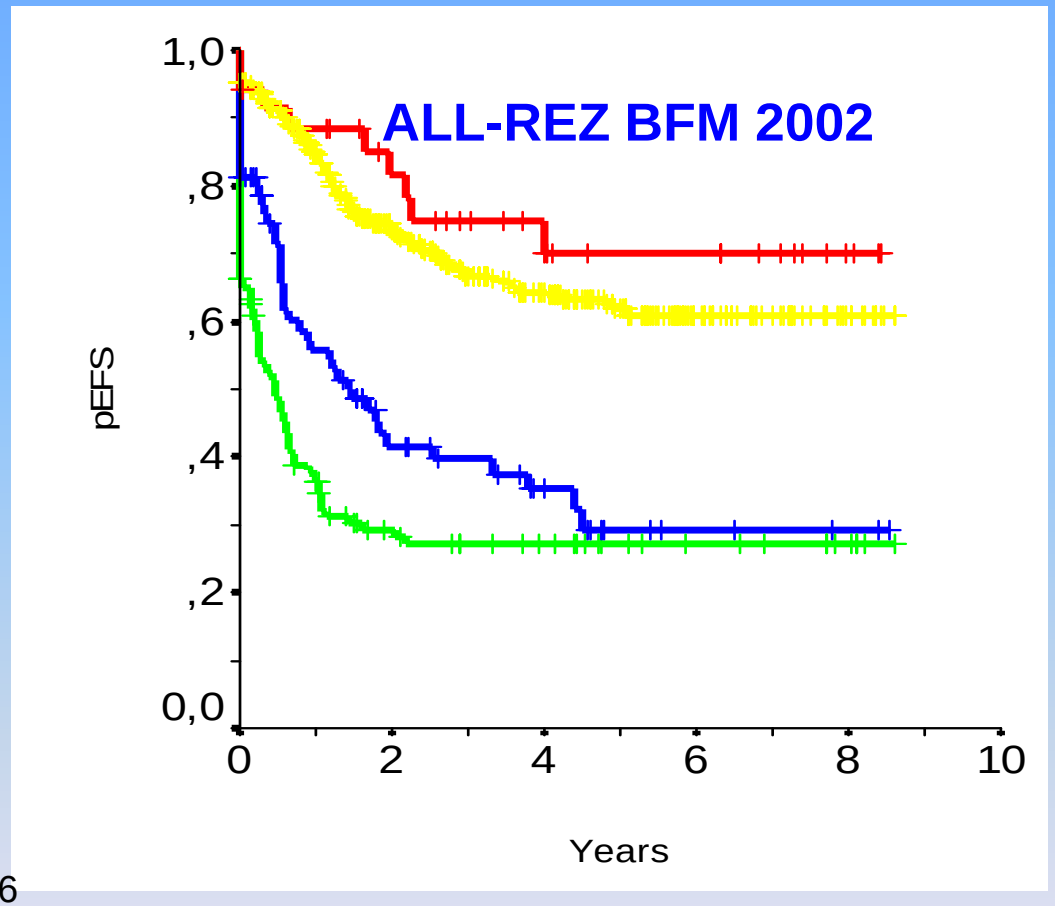
BFM Classification of Relapsed Childhood ALL

S1	1. Late extramedullary relapses.
S2	1. Early extramedullary relapses; 2. Very early extramedullary relapses; 3. Non-T late bone marrow relapses; 4. Non-T combined early / late relapses.
S3	1. Non-T early bone marrow relapses.
S4	1. Very early bone marrow relapses; 2. Very early combined relapses; 3. T phenotype bone marrow relapses.

- **Very early relapse:** < 18 months from diagnosis.
- **Early relapse:** ≥ 18 months from diagnosis, but < 6 months from treatment discontinuation.
- **Late relapse:** ≥ 6 months from treatment discontinuation.

EFS of childhood relapsed ALL
ALL-REZ BFM 83-90 (SCT censored) versus 2002



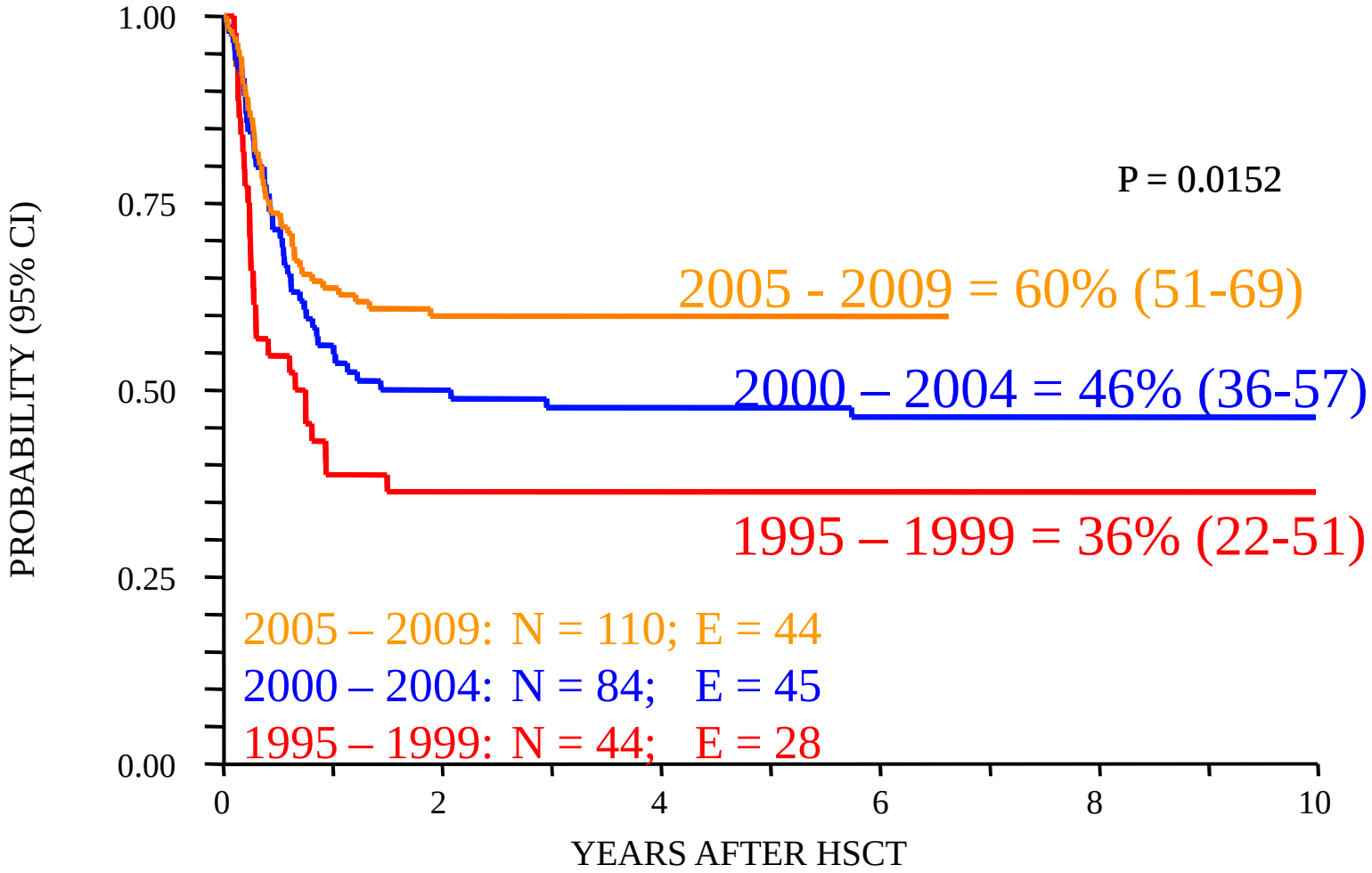


____	S1:	n = 51; zens. = 40; pEFS = .75	± .06
__	S2:	n = 577; zens. = 277; pEFS = .38	± .02
_ _ _	S3:	n = 153; zens. = 46; pEFS = .02	± .02
__ _	S4:	n = 252; zens. = 60; pEFS = .04	± .02
		p < 0.001	

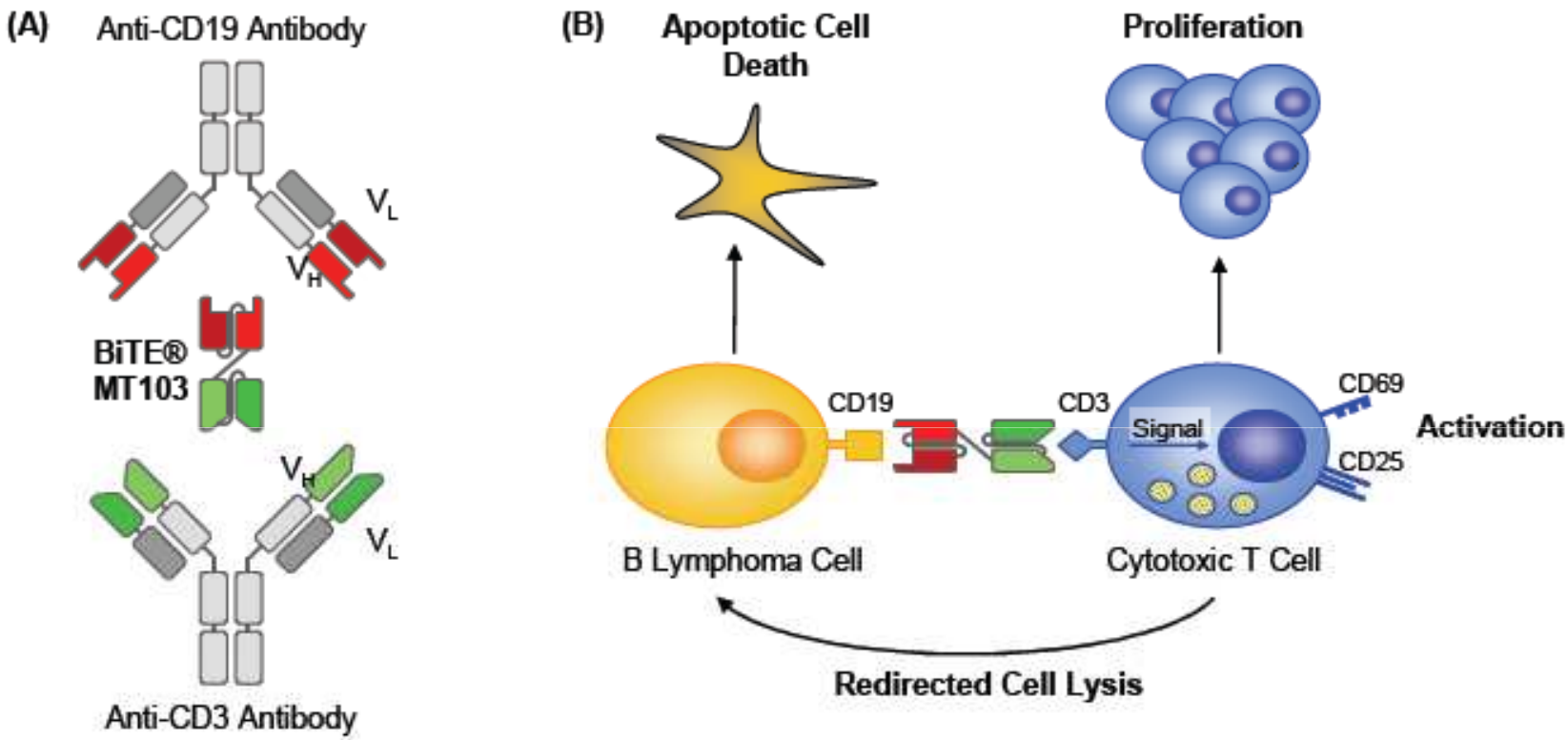
S1:	n = 35; cens = 26; pEFS = .70 ± .09	
S2:	n = 390; cens = 271; pEFS = .61 ± .03	
S3:	n = 80; cens = 33; pEFS = .29 ± .06	
S4:	n = 134; cens = 41; pEFS = .27± .04	
	P < 0.001	

IntReALL 2010
ALL-REZ BFM 03/11

ALL in 2nd CR – MUD HSCT
Disease-free survival by year of HSCT



Blinatumomab (MT103), a T Cell-engaging BiTE® Antibody



(A) BiTE antibody blinatumomab is derived by linking the variable regions (V_H and V_L) of two parental murine antibodies via short linker sequences

(B) The mode of action of blinatumomab involves polyclonal activation and proliferation of T cells and redirected lysis of B lymphoma cells, resulting in apoptotic B lymphoma cell death

Hematologic and Molecular Remission Rate within 2 Cycles of Treatment

	15 µg/m²/d Cohort 1 (n = 7), n (%)	5-15-30 µg/m²/d Cohort 2b (n = 6), n (%)	5-15 µg/m²/d Cohorts 2a + 3 (n = 12), n (%)
CR/CRh*	5 (71)	3 (50)	9 (75)
CR	2 (29)	3 (50)	7 (58)
CRh*	3 (43)	0	2 (17)
Nonresponder	1 (14)	3 (50)	3 (25)
Not evaluable	1 (14)	0	0

- All patients with CR/CRh* achieved MRD-response (defined as MRD $<10^{-4}$ measured by PCR evaluation of individual rearrangements of immunoglobulin or TCR genes in a central laboratory)
- High response rate in all patient subgroups (including Ph+ ALL and t(4,11) translocation)

Clinical Trial MT103-205

A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Pediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)

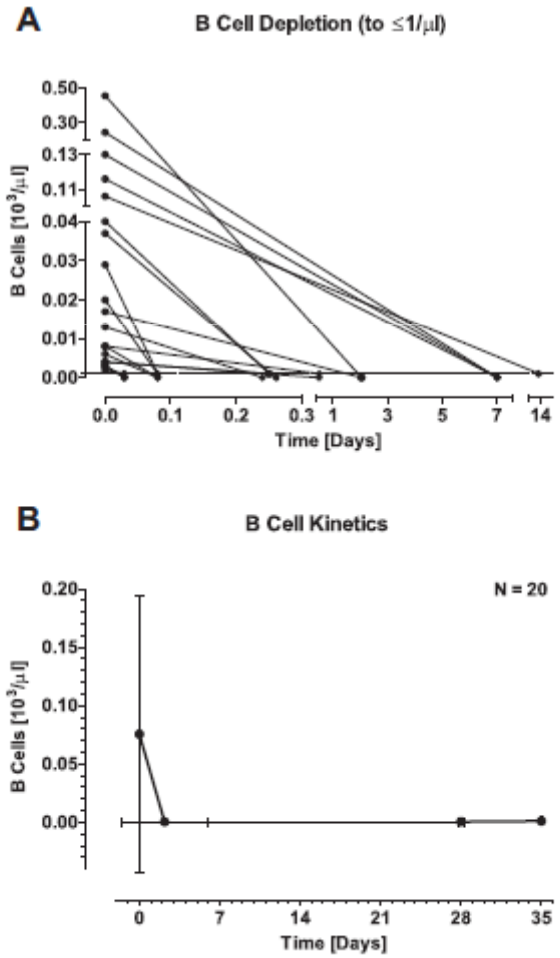
micromet

Coordinating Investigators

- I-BFM: Arend von Stackelberg
- COG: Lia Gore
- Country Coordinating Investigators:
  - Christina Peters, Austria
  - James Whitlock, Canada
  - Pierre-Simon Rohrlich, France
  - Arend von Stackelberg, Germany
  - Franco Locatelli, Italy
  - Michel Zwaan, The Netherlands
  - Lia Gore, USA

Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell–engaging CD19/CD3-bispecific BiTE antibody blinatumomab

Matthias Klinger,[1] Christian Brandl,[1] Gerhard Zugmaier,[1] Youssef Hijazi,[1] Ralf C. Bargou,[2] Max S. Topp,[2] Nicola Gökbuget,[3] Svenja Neumann,[4] Mariele Goebeler,[2] Andreas Viardot,[5] Matthias Stelljes,[6] Monika Brüggemann,[4] Dieter Hoelzer,[3] Evelyn Degenhard,[1] Dirk Nagorsen,[1] Patrick A. Baeuerle,[1] Andreas Wolf,[1] and Peter Kufer[1]



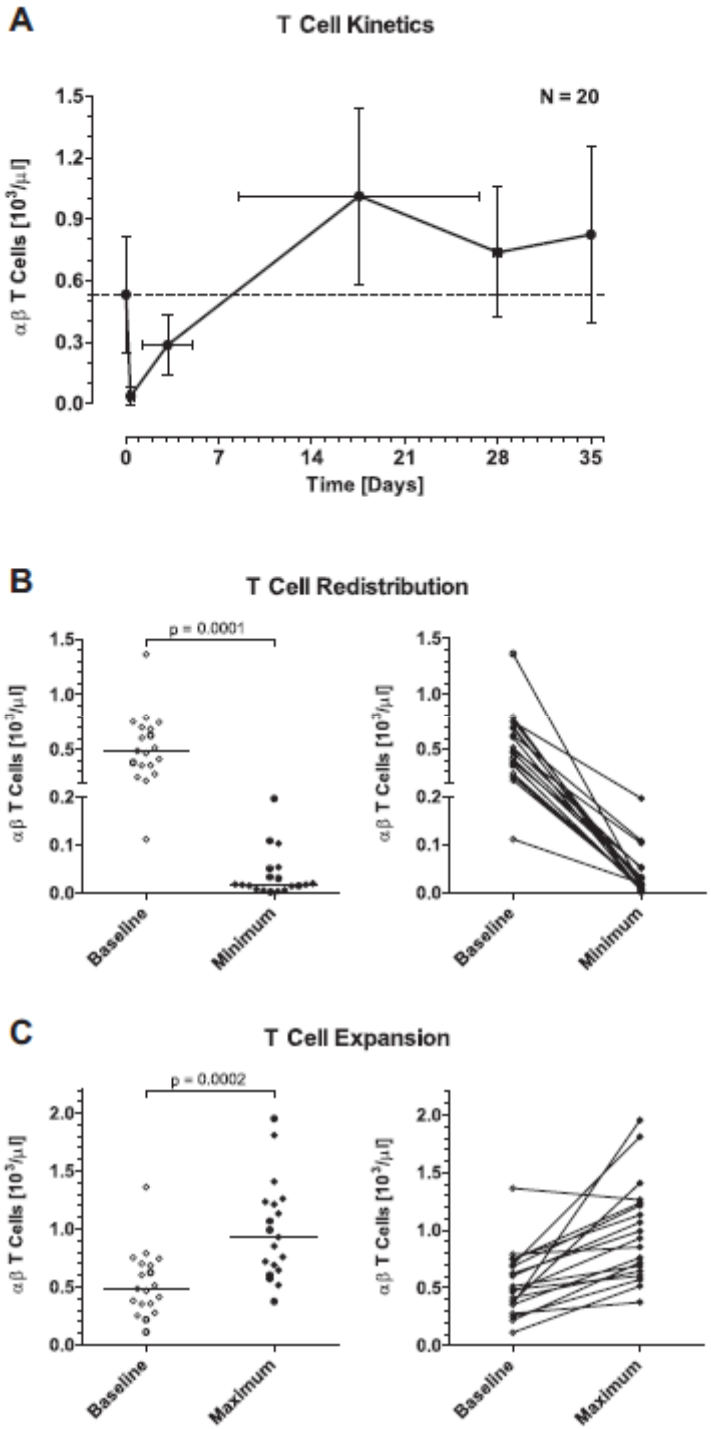

A
T Cell Kinetics
N = 20
αβ T Cells [10³/μl]
1.5
1.2
0.9
0.6
0.3
0.0
0
7
14
21
28
35
Time [Days]
B
T Cell Redistribution
p = 0.0001
αβ T Cells [10³/μl]
1.5
1.0
0.5
0.2
0.1
0.0
Baseline
Minimum
C
T Cell Expansion
p = 0.0002
αβ T Cells [10³/μl]
2.0
1.5
1.0
0.5
0.0
Baseline
Maximum

Table: Summary of Dose Cohorts and Outcomes (Jan 2013)

Cohort	Dose level µg/m²/day	Patients Treated, n	No of SAEs regardless of causality	No of DLTs	Cytological complete remission (CR) / molecular remission (MR) in bone marrow
1	5	5	4	0	2 CR and 2 MR
2	15	7	2	1	4 CR and 4 MR
3	30	5	3	2	2 CR and 2 MR
Total		17	9	3	8 CR and 8 MR