Bambino Gesù
OSPEDALE PEDIATRICO

Leucemia linfoblastica acuta

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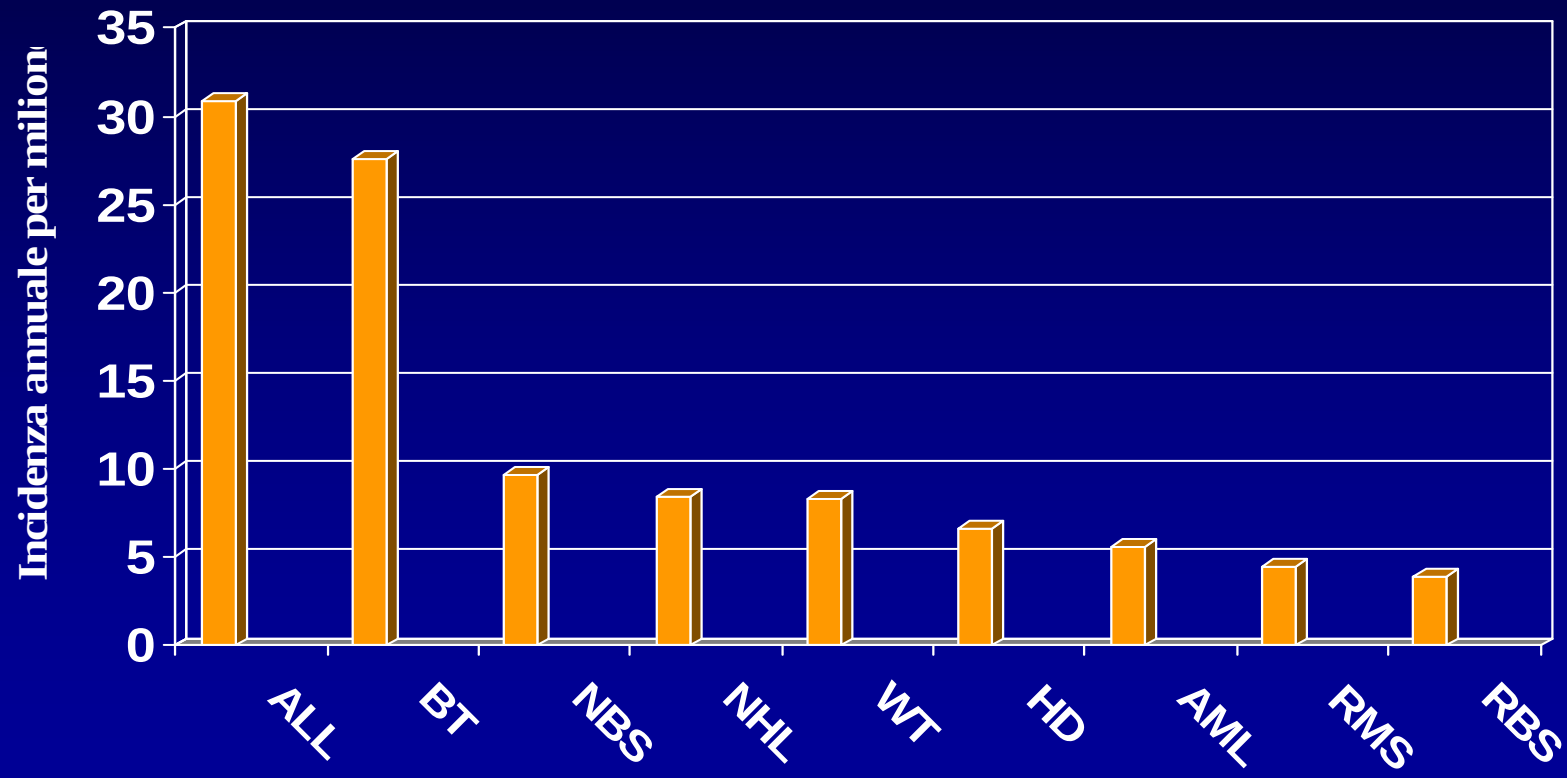
Incidenza annuale dei tumori dell'età pediatrica

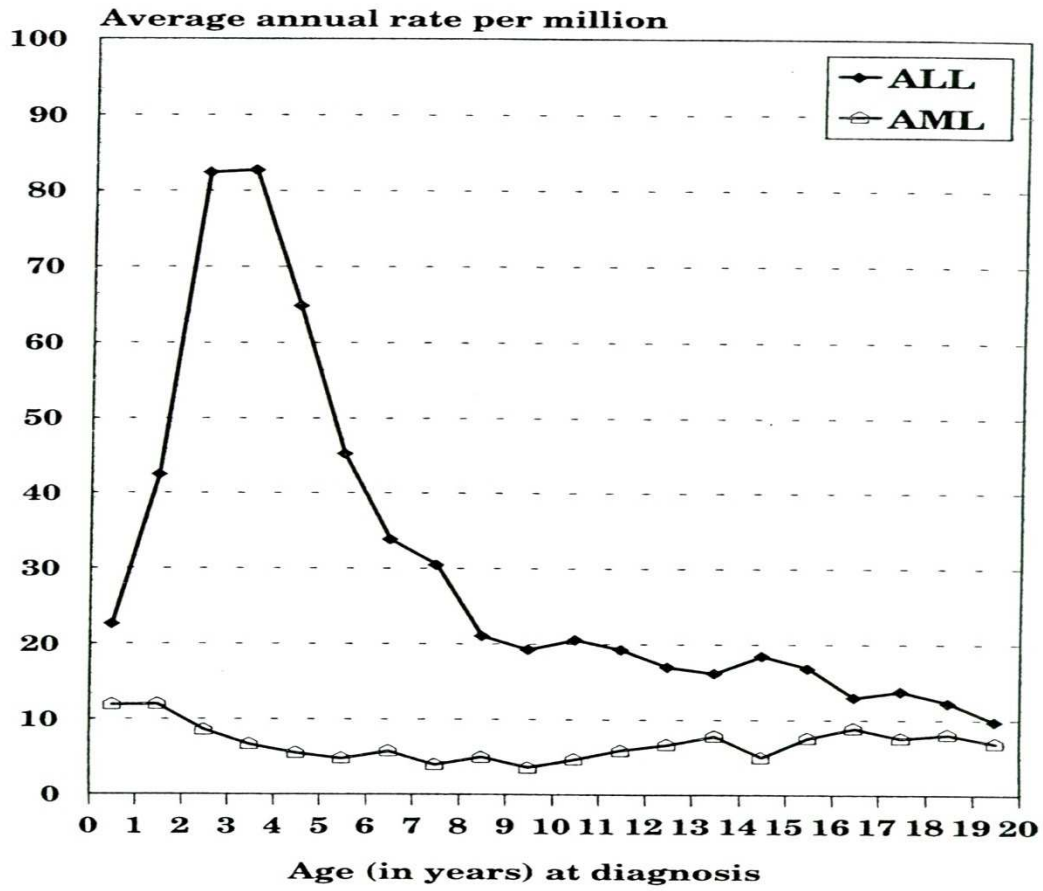


CHILDHOOD ACUTE LEUKEMIA

- 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;
- AML accounts for 20% of childhood acute leukemia;
- With the remarkable exception of Down-Syndrome patients, there is no genetic predisposition to develop acute leukemia;
- There is an heterogeneous distribution of childhood ALL according to patient's age.

Leucemie acute-Distribuzione per età

Figure I.2a: ALL (Ia): 1986-94, and AML (Ib): 1976-84 and 1986-94 age-specific incidence rates, all races both sexes, SEER



Picco

2-6 anni

Lieve predominanza dei maschi

Presentation of childhood acute lymphoblastic leukemia

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

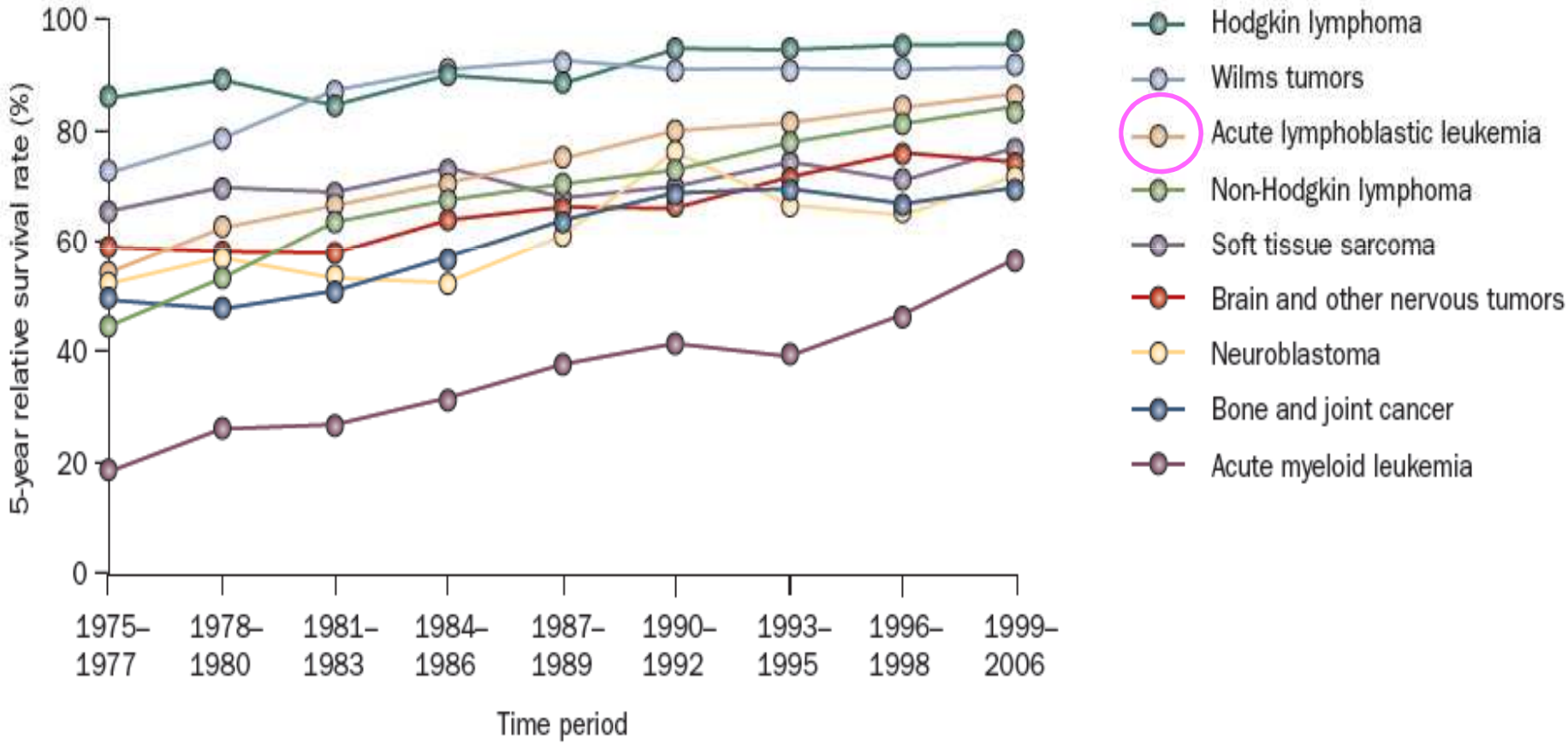
LLA-Caratteristiche cliniche alla diagnosi

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

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

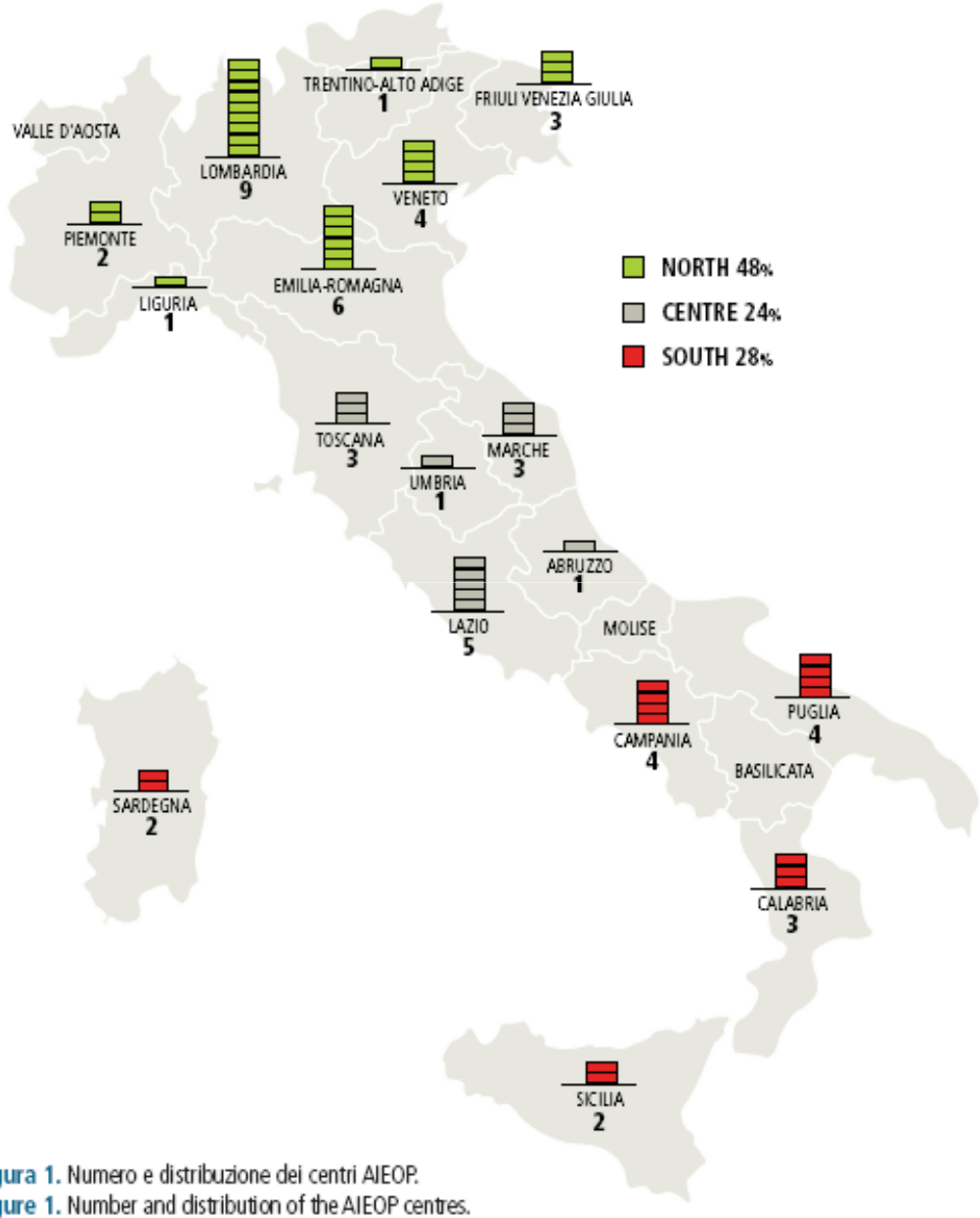


Figura 1. Numero e distribuzione dei centri AIEOP.
Figure 1. Number and distribution of the AIEOP centres.

Struttura delle Banche Dati AIEOP

A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

Portale AIEOP
Centri AIEOP
Schede malattia
Gruppi di lavoro

FUP

MOD 1.01
Registro
44.024 casi

TCSE
Registro
7774 casi, **9543** TCSE

Protocolli non AIEOP
33% casi

Protocolli AIEOP
175 protocolli
67% casi

LAB
Analisi e diagnosi centralizzate

LAL	LAM	SE	LH	ID	ICL	DBA	RTB	MDS
10244	1340	301	2148	1916	877	189	15	52

Altri dati:
BD centri,
BD pubblicazioni,
ecc…

AIEOP CLINICAL DATA WAREHOUSE

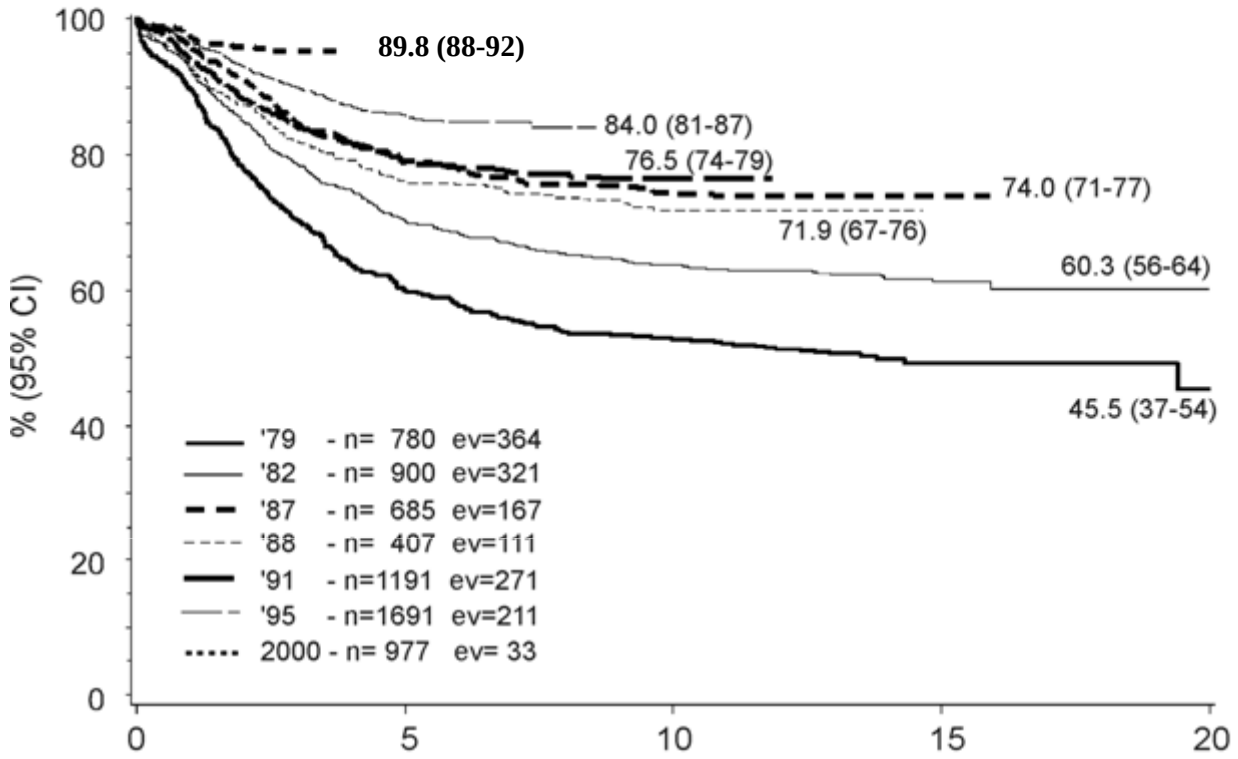
WCA
Area documentale
Forum di discussione
Agenda/riunioni

Coordinatori | Data managers | Centri | Laboratori | Statistici | …

Dati aggiornati al 10 Marzo 2013

PROTOCOLLI AIEOP PER LEUCEMIE LINFOBLASTICHE ACUTE

Sopravvivenza per generazione di protocollo



Anni dalla diagnosi

Numero di pazienti a rischio

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

A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

A I E O P

Centro Operativo

Registro AIEOP Mod.1.01

Rapporto tra casi osservati e casi attesi per anno

29650 casi (0-19 anni) residenti in Italia nel periodo 1989-2010
(Attesi: AIRTUM 2008)

Diagnosi	*0-14 anni*	*15-19 anni*
LAL	0.94	0.27
LAM	0.90	0.22
LH	0.65	0.11
LnH	1.18	0.15
T.SNC	0.64	0.19
Osteo	0.96	0.35
SE	1.13	0.47
RMS	1.17	0.36
TCG	0.70	0.05
Carcinomi	0.24	0.02
Totale	***0.81***	***0.12***

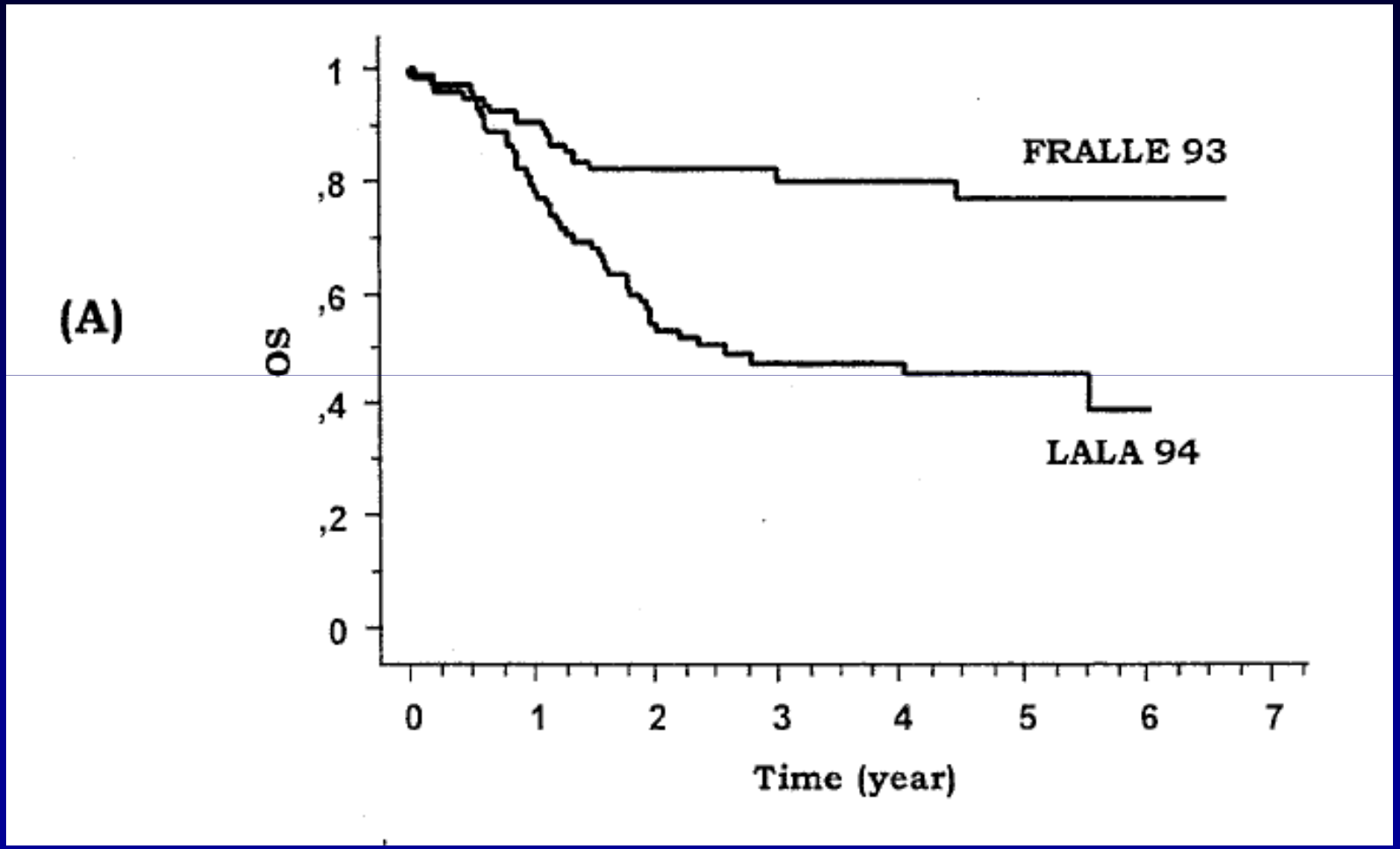
0-14 anni
0.73
(89-99)
vs
0.88
(00-10)

M: 0.92 (08-10)

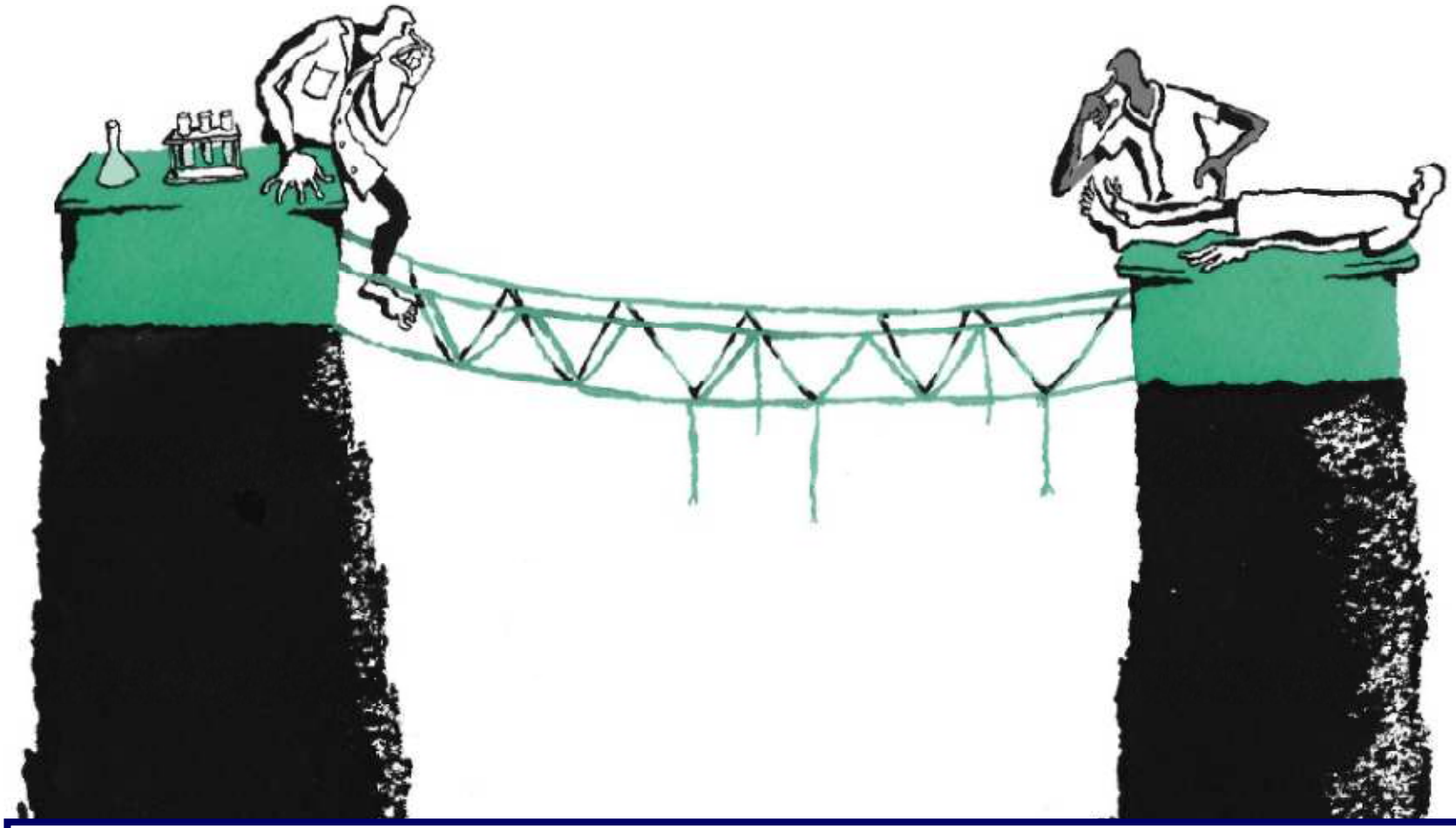
15-19 anni
0.07
(89-99)
vs
0.18
(00-10)

M: 0.25 (08-10)

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 200



From bench to bedside, and back!

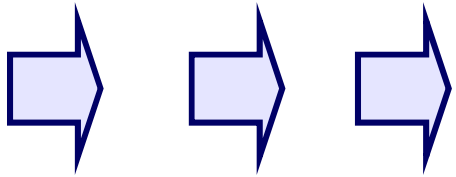
Translational Research
Current Definition

T1

- **Translation from basic science to human studies**

T2

- **Translation from human studies to clinical practice healthcare decisions**



Basic Biomedical

Clinical Science Research

Improved Health

Dall'oncologia *organizzata* .....

all'oncologia *personalizzata:*

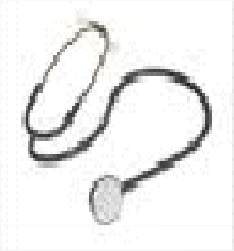
la sfida dell'oggi che si proietta nel domani

How Do We Achieve Personalized Medicine?

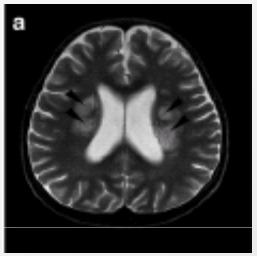
- **Increase knowledge in the role of individuals' genetic and biological characteristics in disease.**
- **Use more informed selection and dosing for medication to improve efficacy and reduce side effects.**
- **Develop more focused and targeted drugs.**

Adequate Tumor Staging

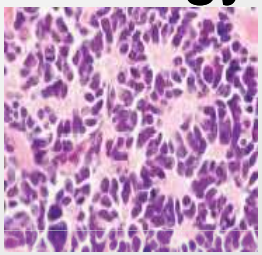
Clinic



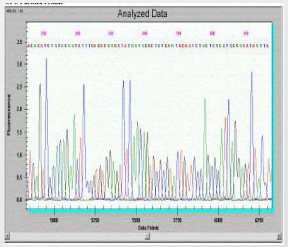
Imaging



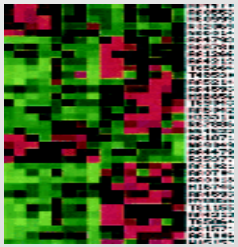
Histology



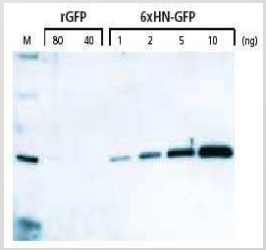
DNA



RNA



Protein



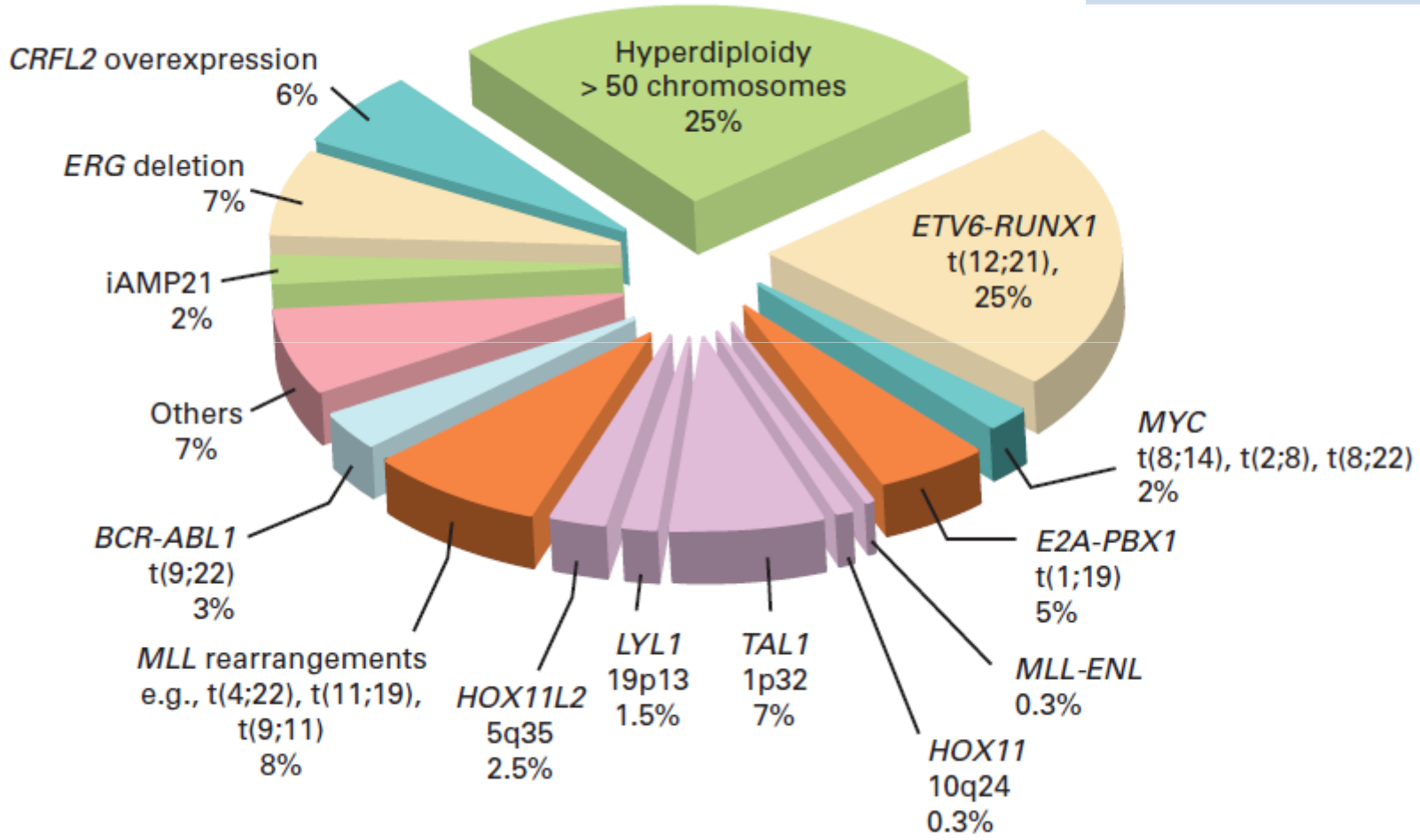
- ✓ Diagnosis
- ✓ Risk Definition - Prognosis
- ✓ Risk Adapted Therapy / MRD
- ✓ Molecular Target Therapy
- ✓ Personalized Medicine

Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update

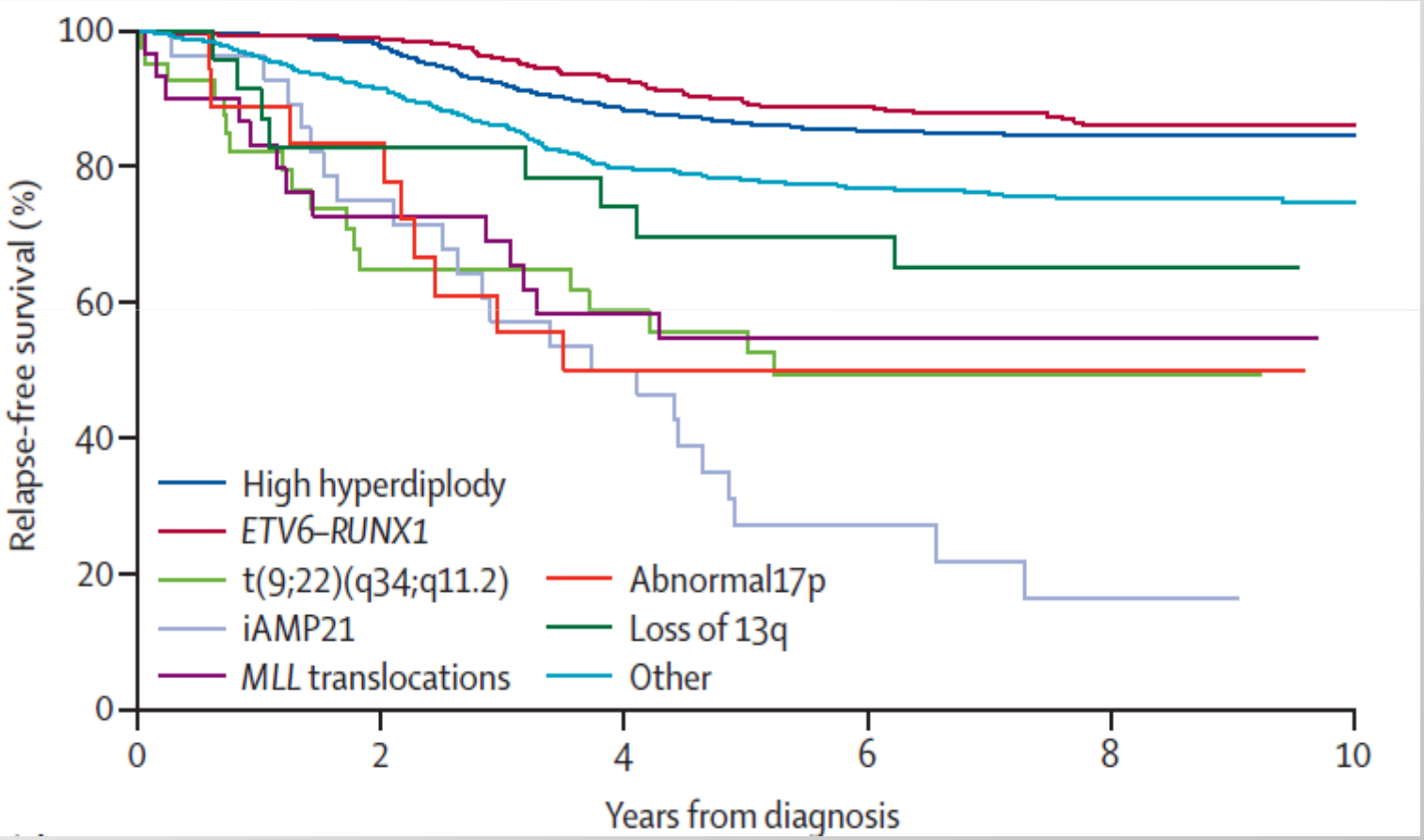
Ching-Hon Pui, William L. Carroll, Soheil Meshinchi, and Robert J. Arceci

VOLUME 29 · NUMBER 5 · FEBRUARY 10 2011

JOURNAL OF CLINICAL ONCOLOGY



The impact of a more sophisticated cytogenetic classification



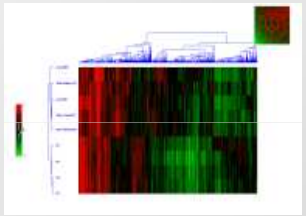
Moorman, Lancet Oncology 2010

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

Define the molecular specific response profile

Dx expression analysis

Responsive genotype



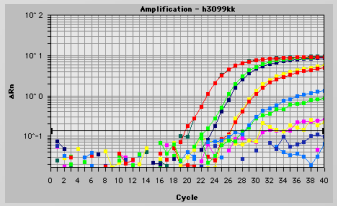
Unresponsive genotype

“Conservative” therapy

MRD monitoring

“High-risk”

“Aggressive” therapy



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]

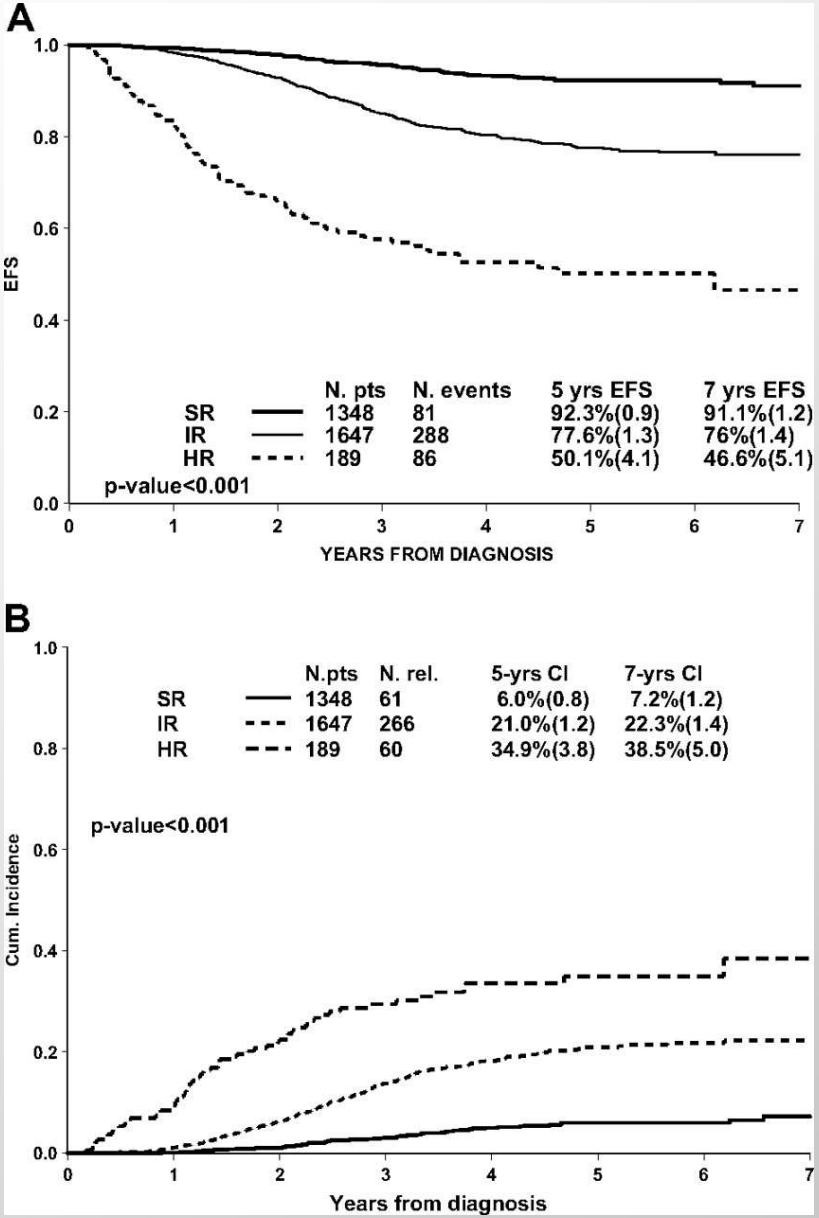
BLOOD, 22 APRIL 2010 • VOLUME 115, NUMBER 16

Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study

*Martin Schrappe,[1] *Maria Grazia Valsecchi,[2] Claus R. Bartram,[3] André Schrauder,[1] Renate Panzer-Grümayer,[4] Anja Möricke,[1] Rosanna Parasole,[5] Martin Zimmermann,[6] Michael Dworzak,[4] Barbara Buldini,[7] Alfred Reiter,[8] Giuseppe Basso,[7] Thomas Klingebiel,[9] Chiara Messina,[7] Richard Ratei,[10] Giovanni Cazzaniga,[11] Rolf Koehler,[3] Franco Locatelli,[12] Beat W. Schäfer,[13] Maurizio Aricò,[14] Karl Welte,[6] Jacques J.M. van Dongen,[15] Helmut Gadner,[4] †Andrea Biondi,[11,16] and †Valentino Conter[16,17]

BLOOD, 25 AUGUST 2011 • VOLUME 118, NUMBER 8

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



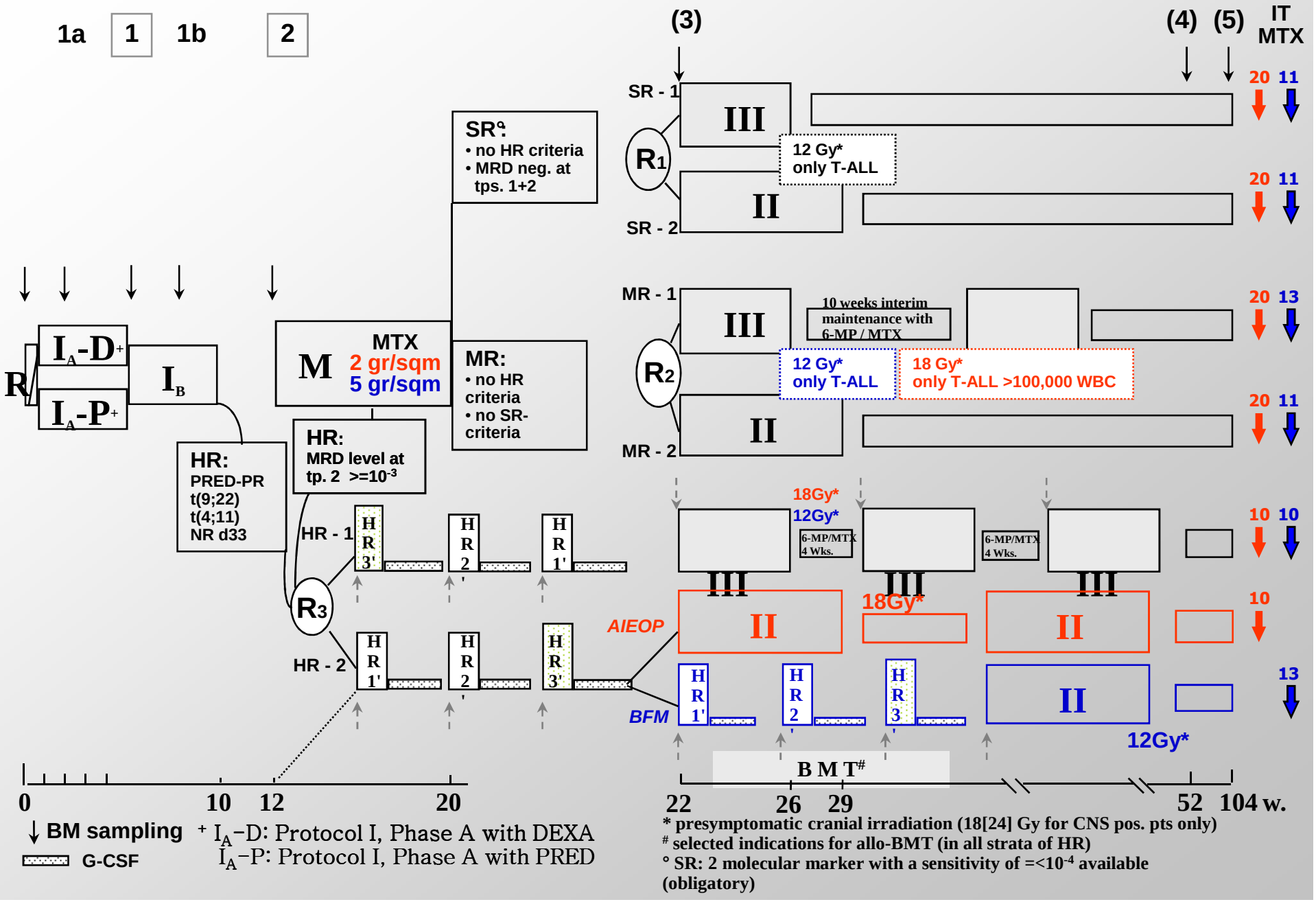
Conter V. et al. Blood 2010;115:3206-3214

AIEOP-BFM ALL 2000

30/7/2000

MRD Timepoints

1a | 1 | 1b | 2



How Do We Achieve Personalized Medicine?

- Increase knowledge in the role of individuals' genetic and biological characteristics in disease.
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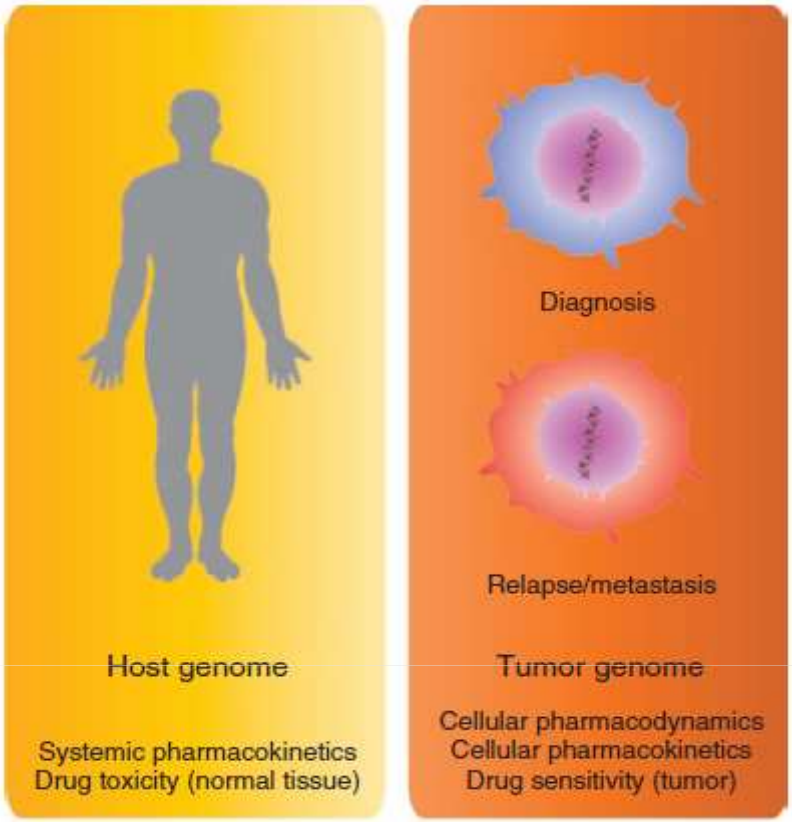

Diagnosis
Relapse/metastasis
Host genome
Tumor genome
Systemic pharmacokinetics
Drug toxicity (normal tissue)
Cellular pharmacodynamics
Cellular pharmacokinetics
Drug sensitivity (tumor)
DNA
Candidate genes
GWAS
Whole-genome sequencing
Epigenetics
RNA
mRNA
microRNA
Transcriptome sequencing
Clinical treatment outcome
Event-free survival
Overall survival
Toxicity risk (OR)
Target inhibition

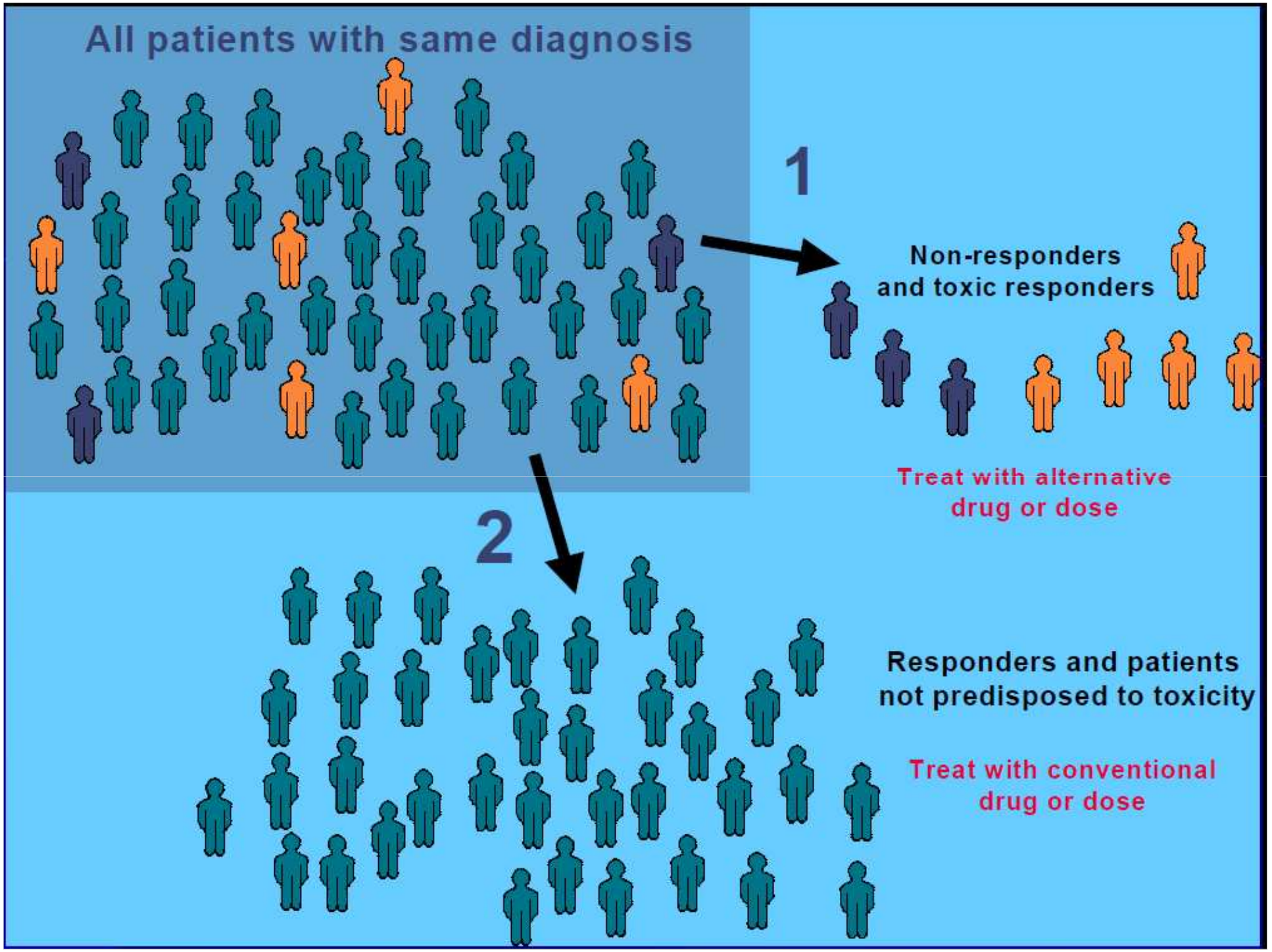
The next revolution…

Pharmacogenetics and Pharmacogenomics

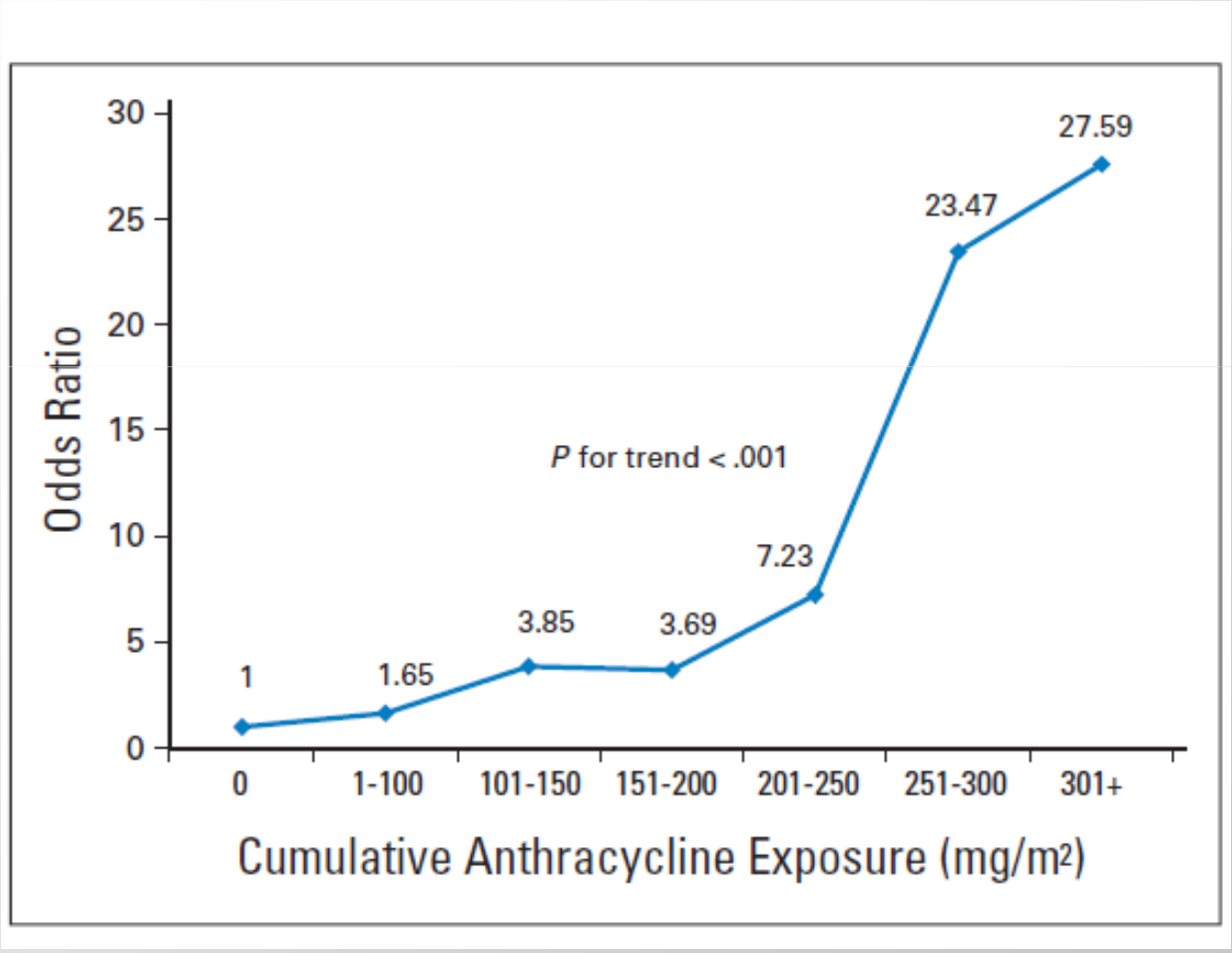
The study of genetic variation that gives rise to differing response to drugs.

Traditional method for drug development

Treat all patients with the same diagnosis with the same medications

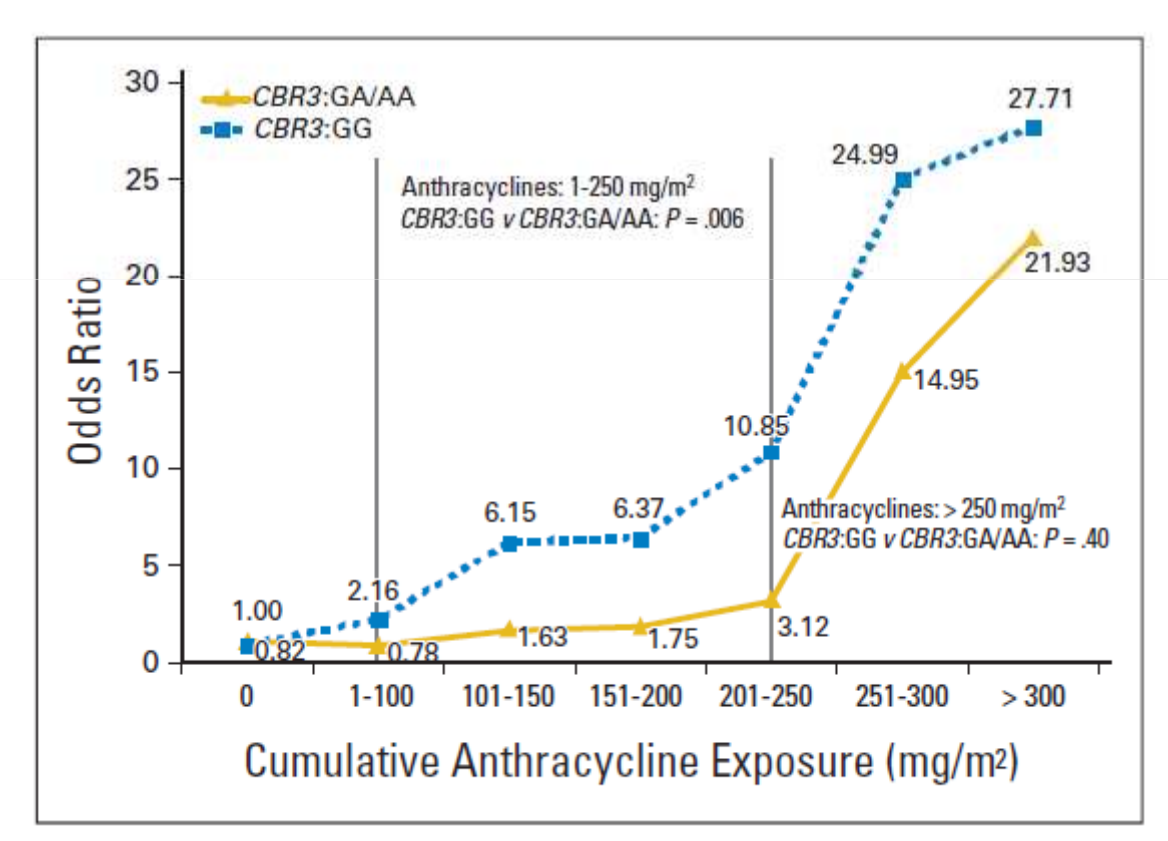

All patients with same diagnosis
1
Non-responders
and toxic responders
Treat with alternative
drug or dose
2
Responders and patients
not predisposed to toxicity
Treat with conventional
drug or dose

Cardiac toxicity and anthracyclines



Blanco JG, et al. J Clin Oncol May 2012

The role of carbonyl reductase polymorphisms

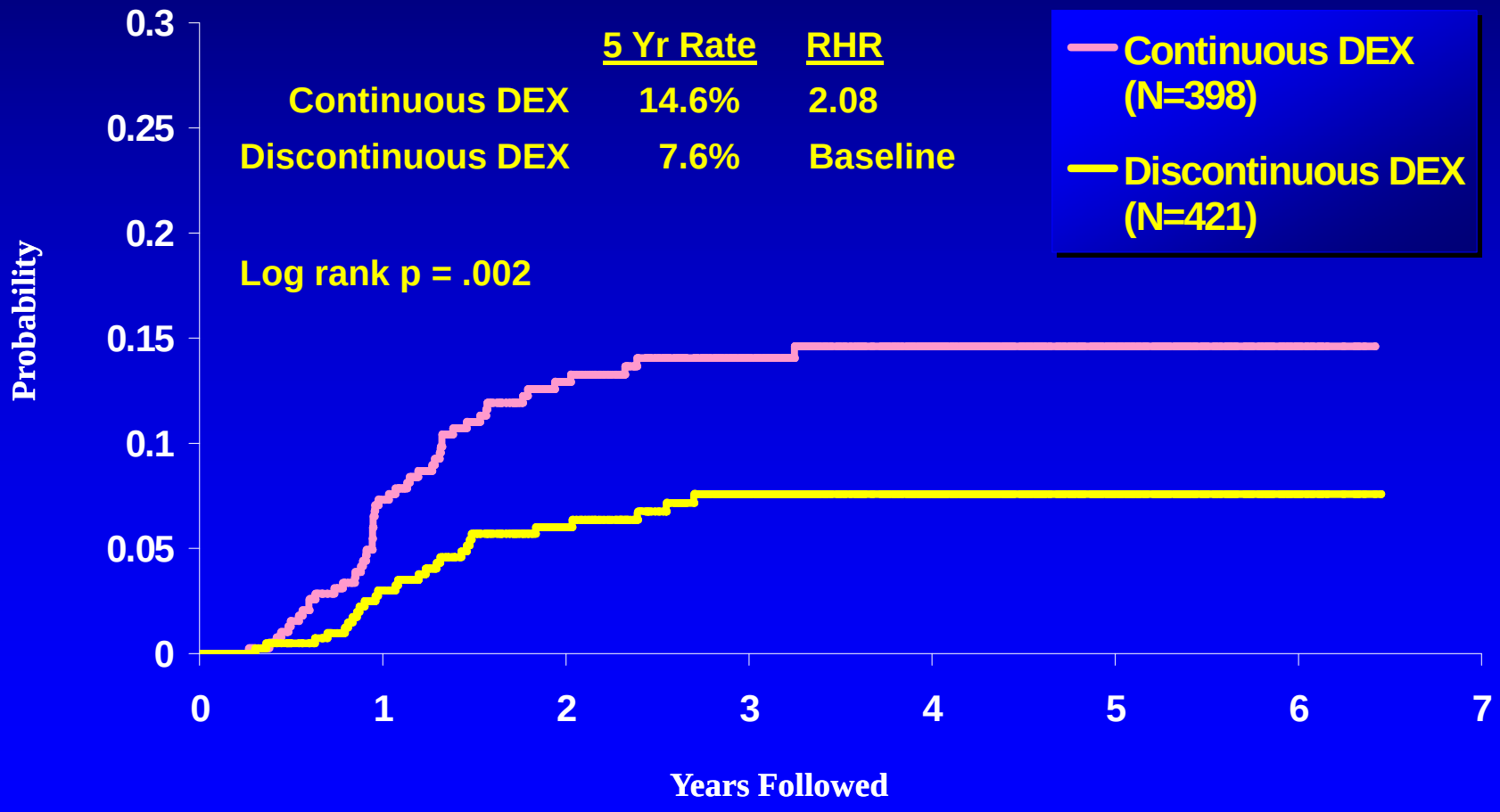


Blanco JG, et al. J Clin Oncol May 2012

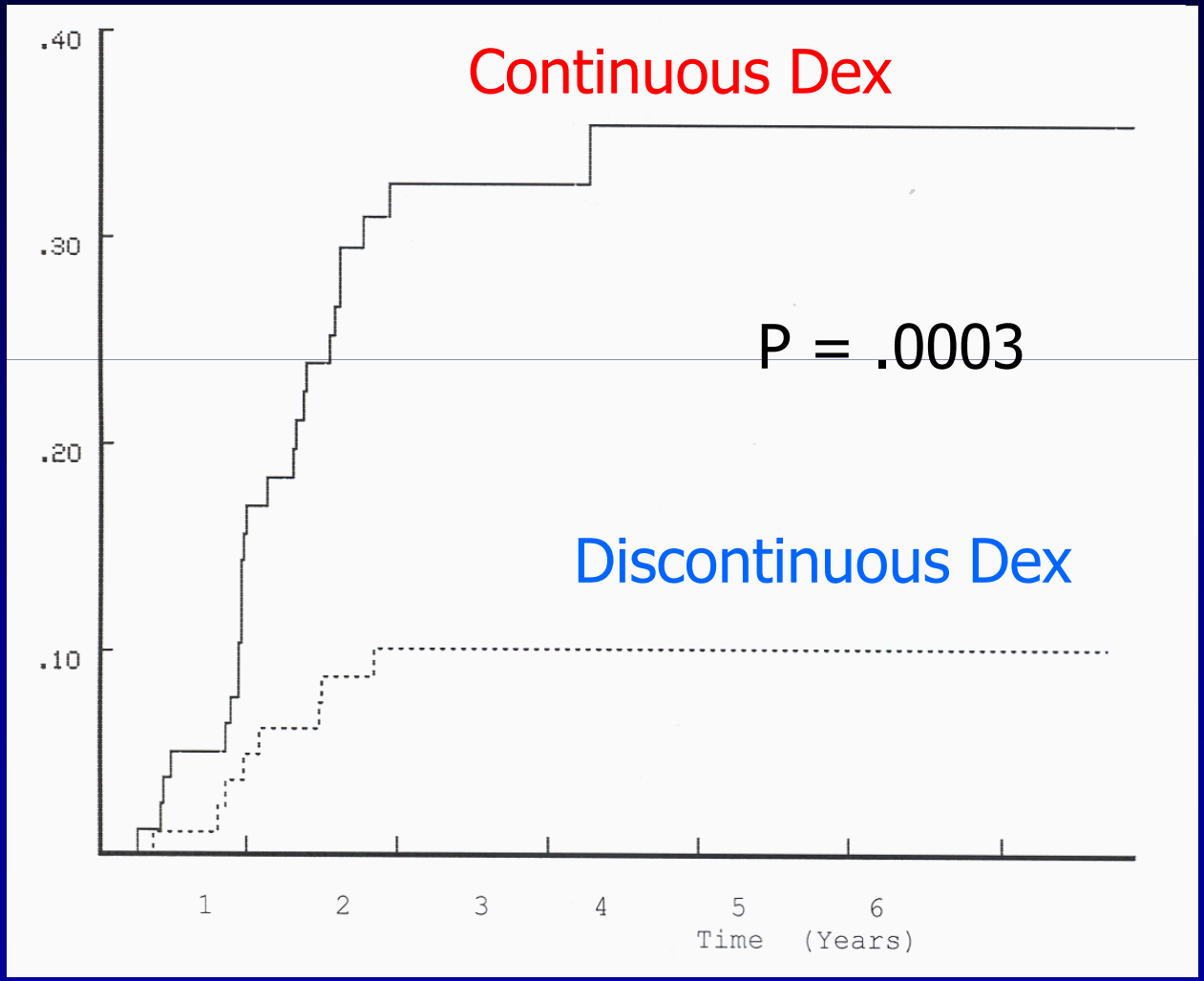
AVN – CCG 1961

- 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



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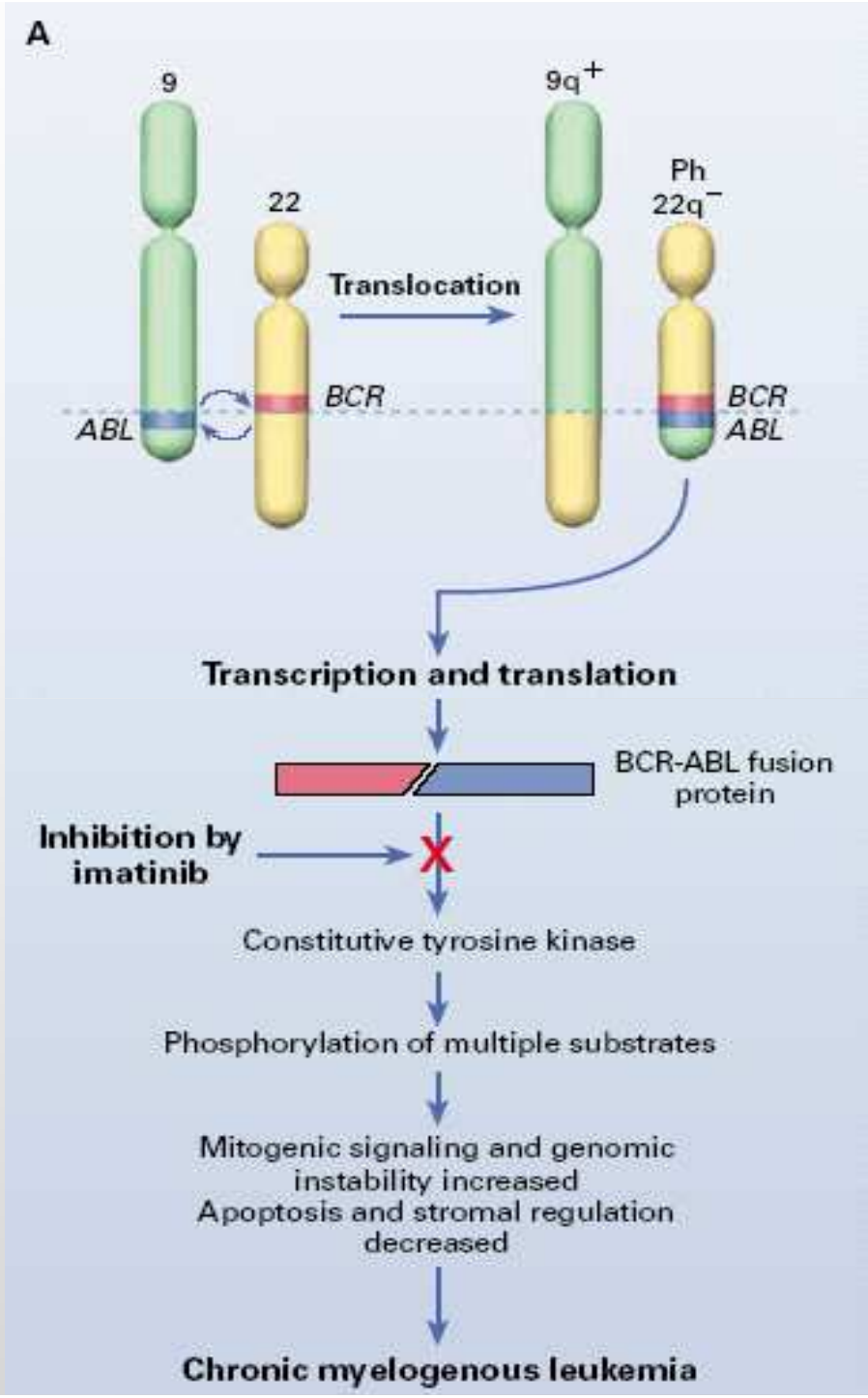
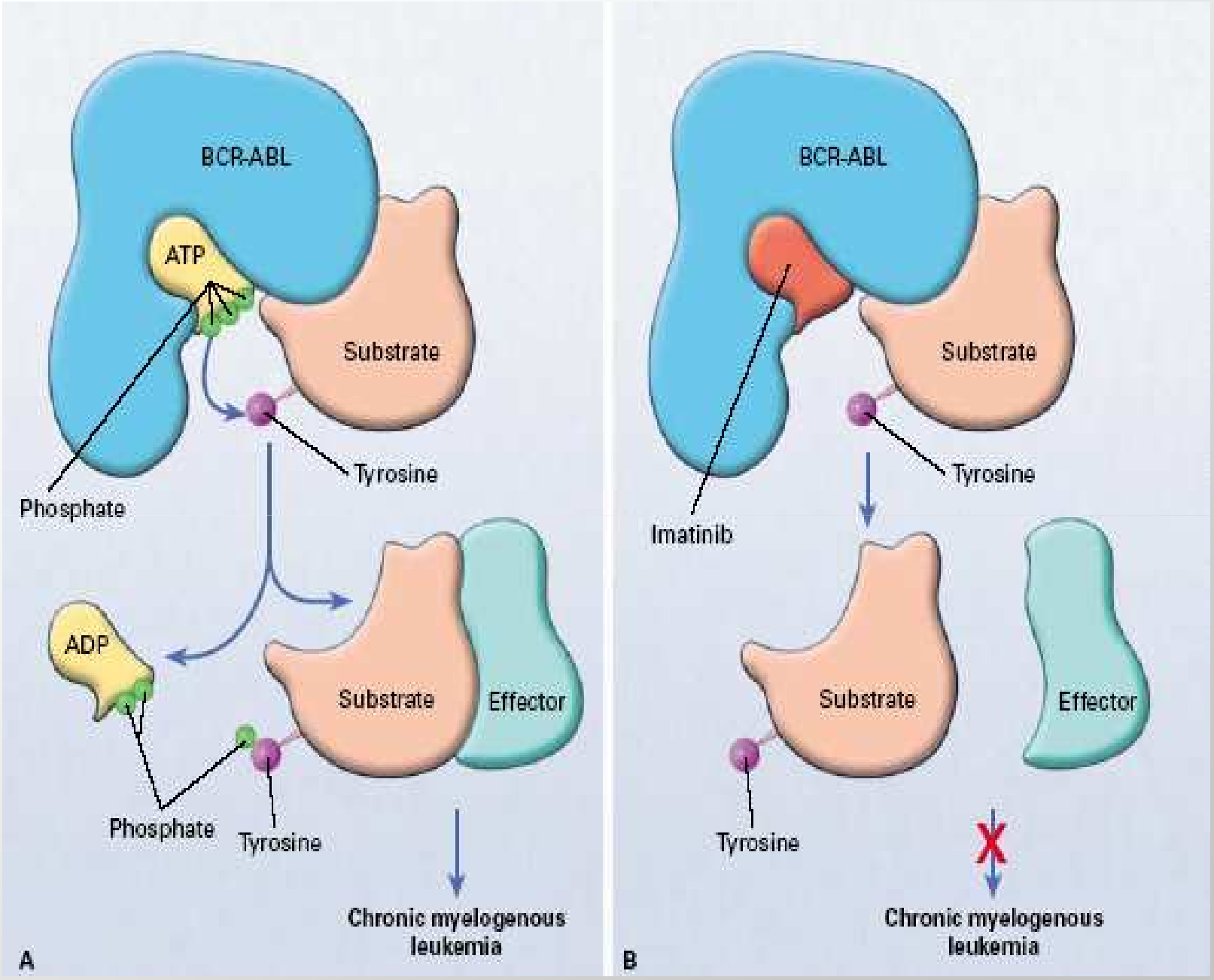
Molecularly Targeted Therapy (MTT)

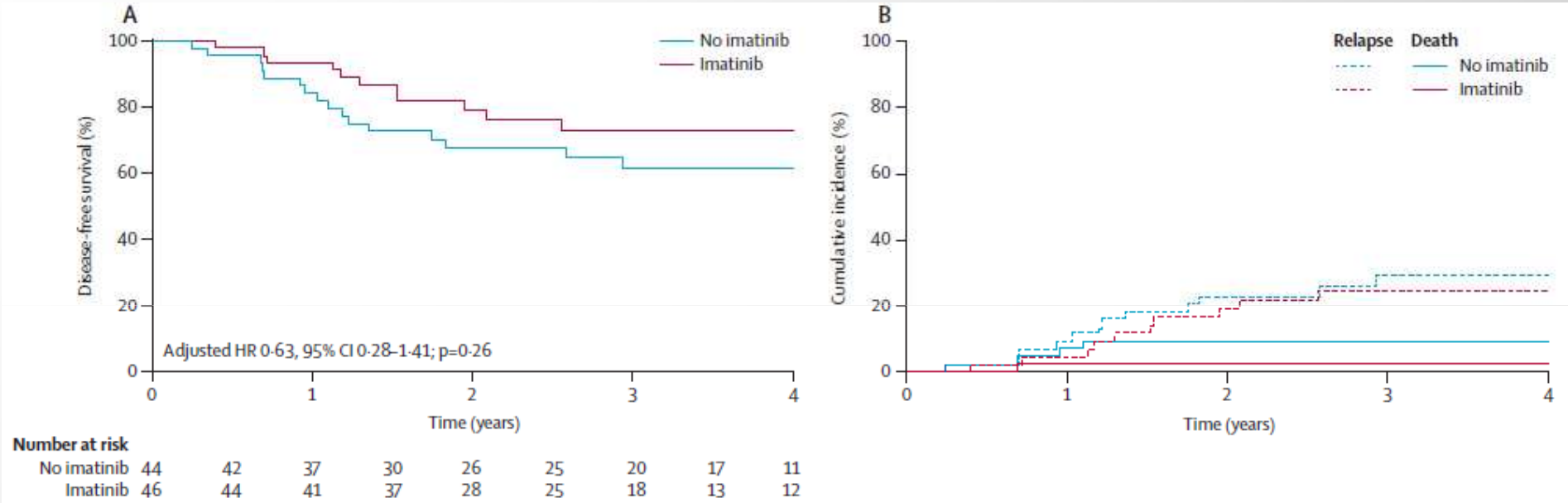
- **Therapeutic approaches that target molecular alterations or pathways that are specifically (or at least selectively) important in the function/survival of cancer vs. normal cells**
- **Holds the promise of increased effectiveness and decreased toxicity compared to standard cytotoxic approaches (which affect global cellular processes)**


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

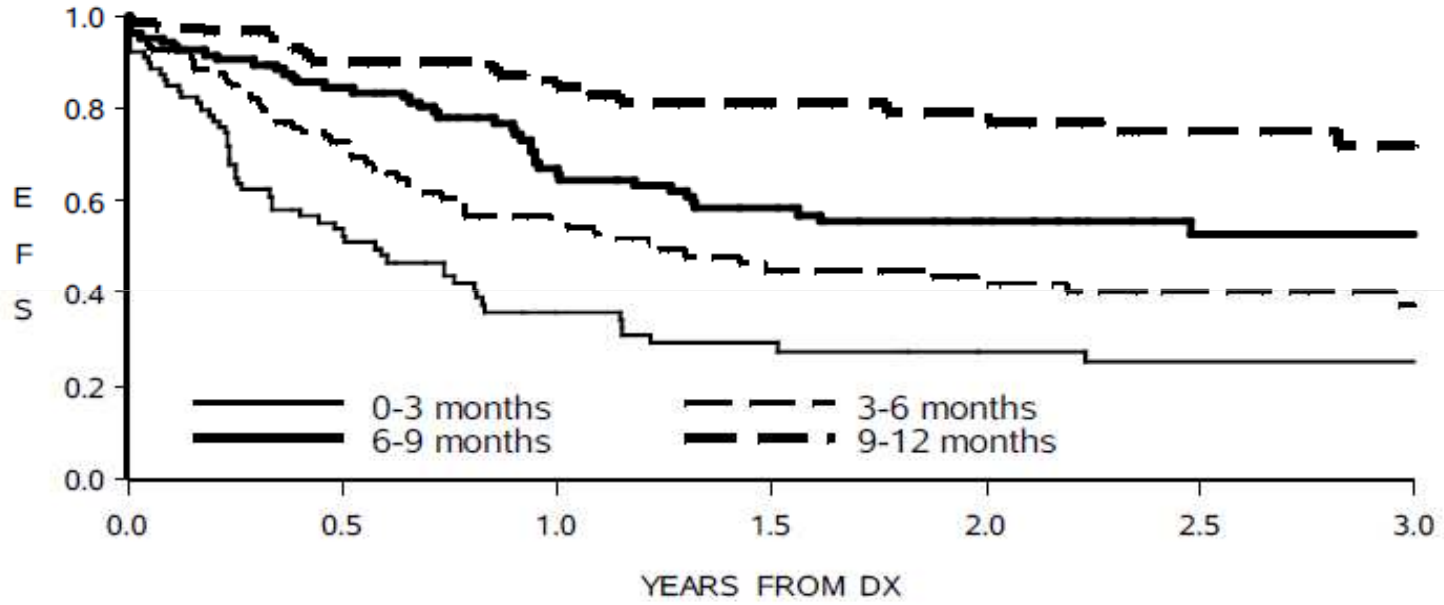
Role of imatinib mesylate in good-risk Ph+ ALL



igure 3: Disease-free survival and cumulative incidence of relapse and of death in continuous complete remission in good risk patients, analysed by intention to treat

A) Disease-free survival. (B) Cumulative incidence of relapse and death continuous complete remission for patients in the good-risk group. One event in a patient in the imatinib group at 6 years after ndomisation is omitted (died in continuous complete remission of pulmonary graft-versus-host disease after transplantation).

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)

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 (5%)	1.	Late extramedullary relapses.	(CR 99%)
S2 (55%)	1.	Early extramedullary relapses;	
	2.	Very early extramedullary relapses;	(CR 97%)
	3.	Non-T late bone marrow relapses;	
	4.	Non-T combined early / late relapses.	
S3	1.	Non-T early bone marrow relapses.	(CR 80-85%)
S4	1.	Very early bone marrow relapses;	
	2.	Very early combined relapses;	(CR 70-75%)
	3.	T phenotype bone marrow relapses.	

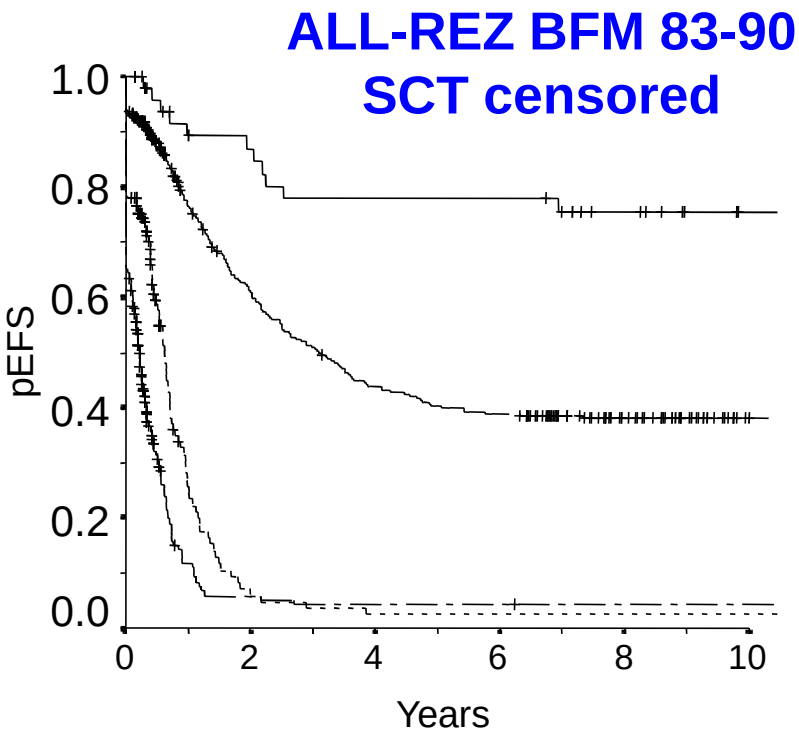
40%

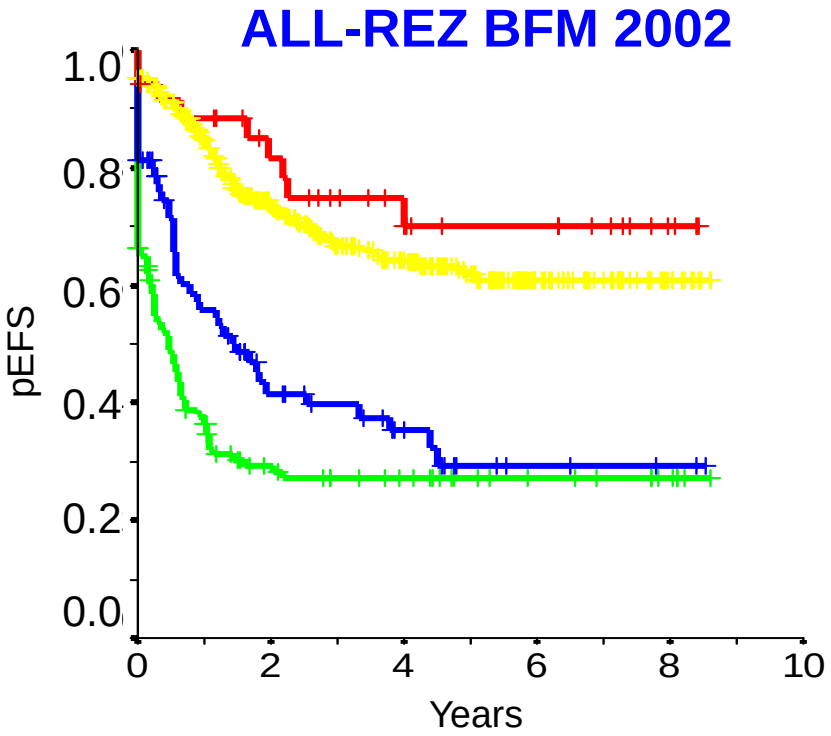
- **Very early relapse:** < 18 months from diagnosis.
- **Early relapse:** ≥ 18 months from diagnosis, but < 6 months from treatment discontinuation.
- **Late relapse:** ≥ 6 months from treatment discontinuation.

Locatelli F et al. How I treat relapsed childhood ALL Blood 2012

EFS of childhood relapsed ALL

ALL-REZ BFM 83-90 (SCT censored) versus 2002





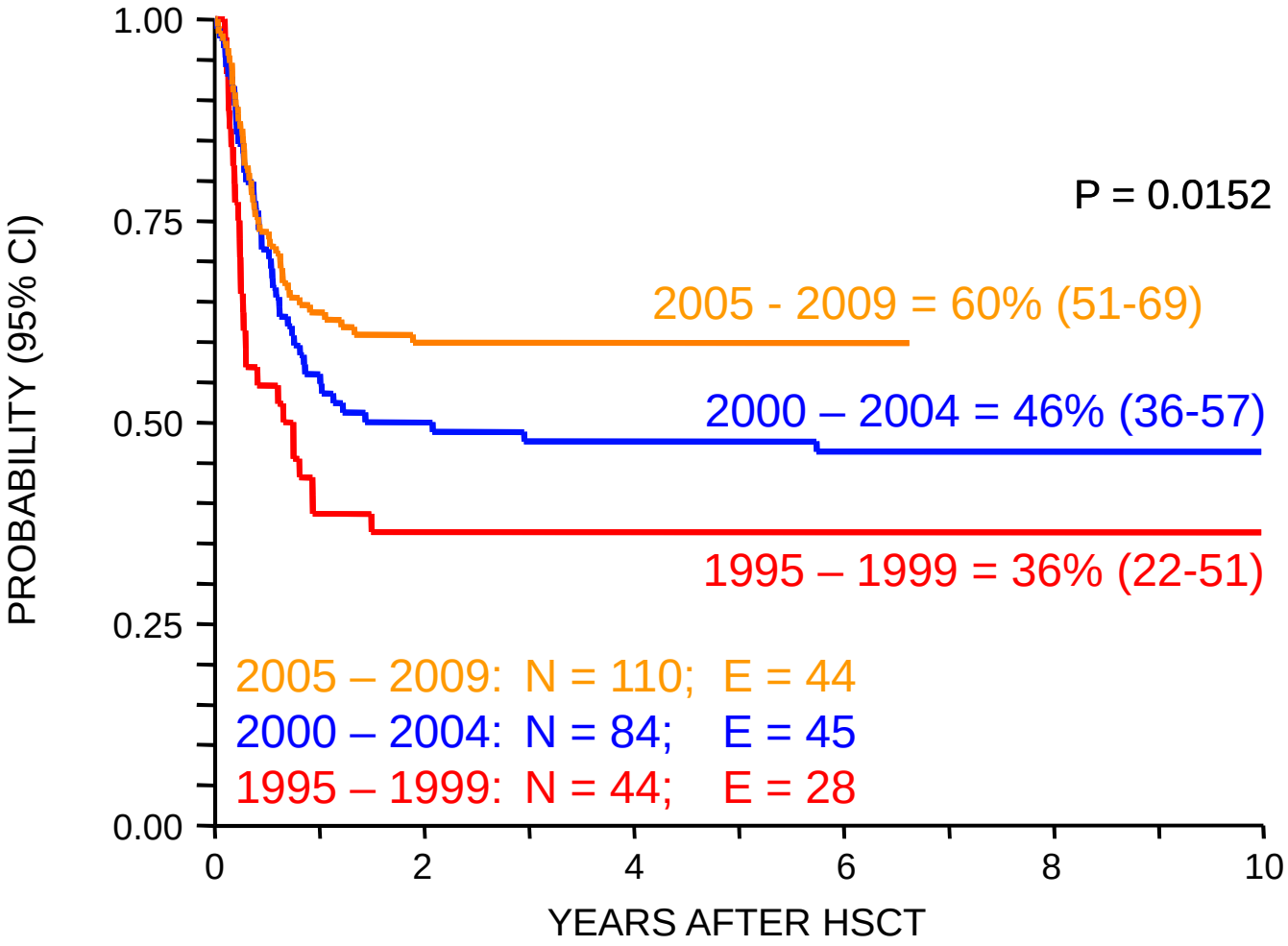
S1: n = 51; zens. = 40; pEFS = .75 ± .06
S2: n = 577; zens. = 277; pEFS = .38 ± .02
S3: n = 153; zens. = 46; pEFS = .02 ± .02
S4: n = 252; zens.= 60; pEFS = .04 ± .02
p < 0.001

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

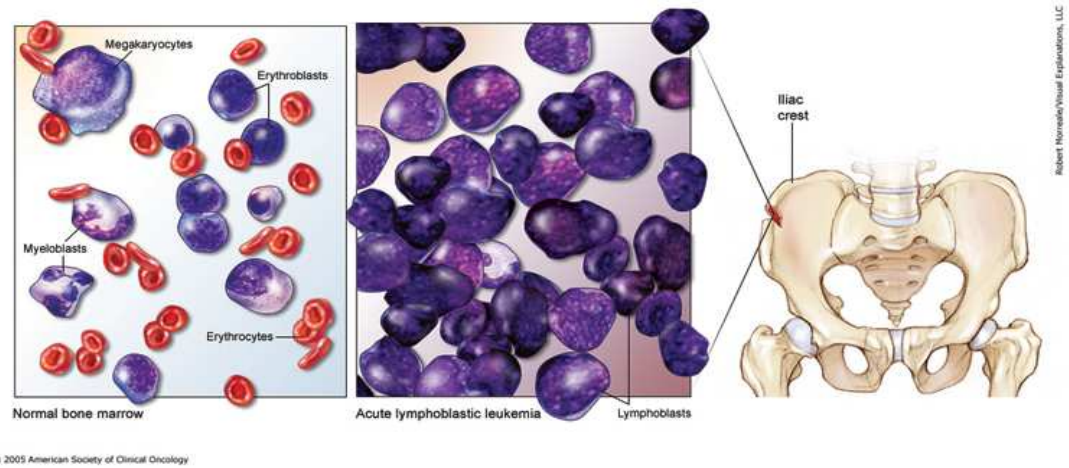
IntReALL 2010
ALL-REZ BFM 03/11

ALL in 2nd CR – MUD HSCT

Disease-free survival by year of HSCT



Antibody-Based Therapy for ALL



Advantages of mAbs

- Greater specificity in targeting tumour cells

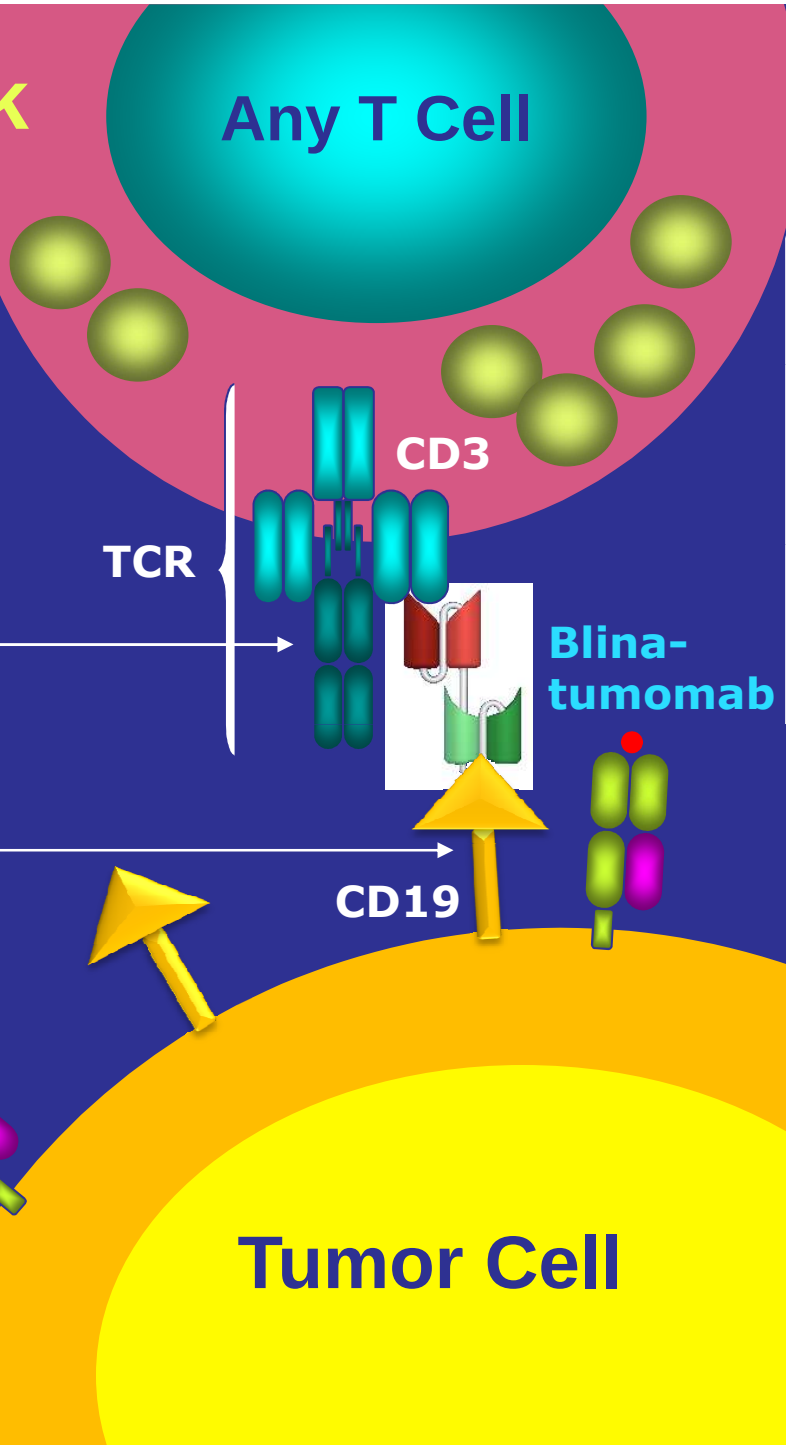
- Mechanisms of action that are distinct from conventional chemotherapy

- Their generally favourable safety profile

Barth M et al. Br J Haematol 2012

How BiTE® Antibodies Work

(BiTE® = Bi-specific T-Cell Engager)

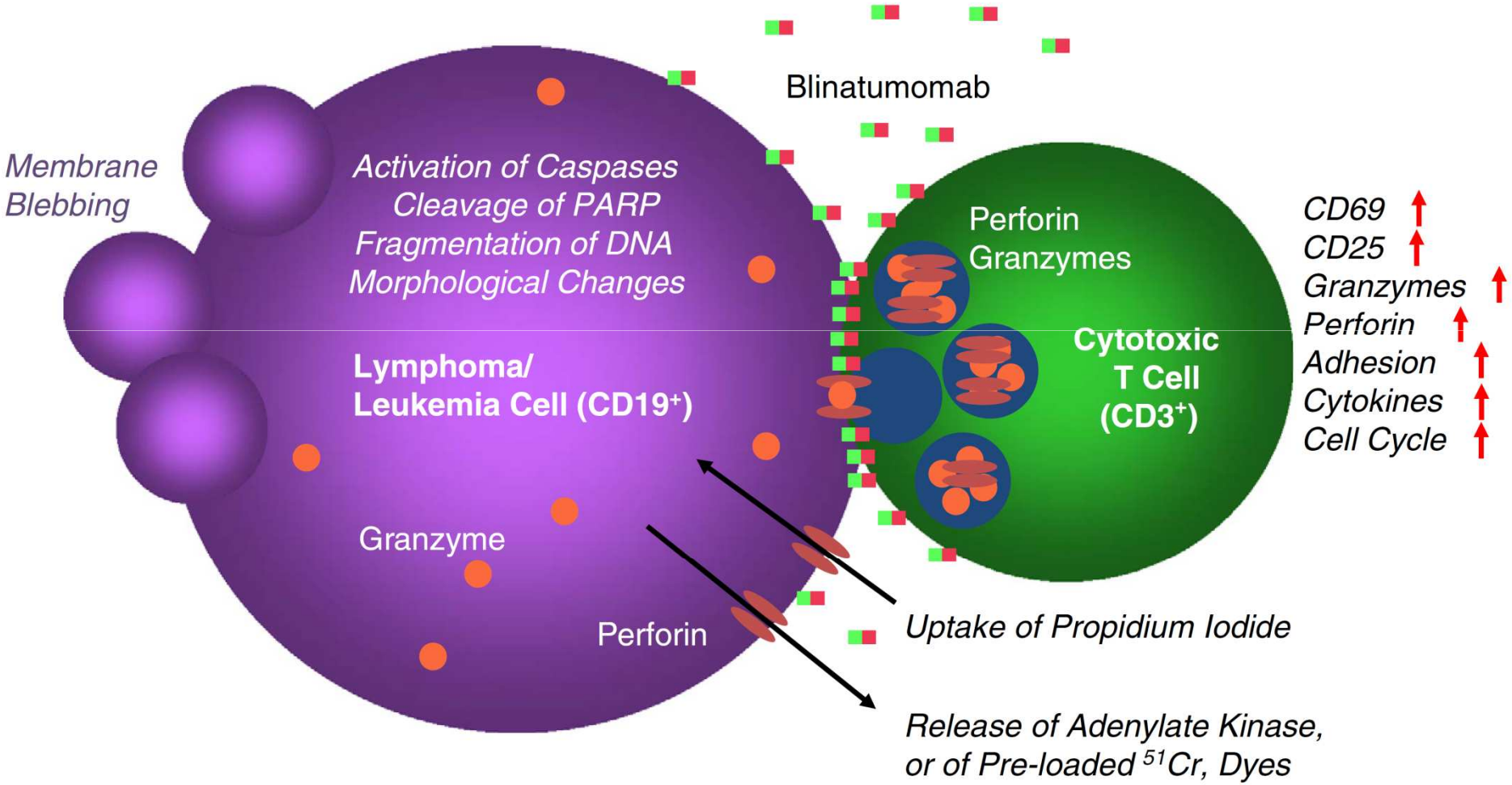


Act independently of specificity of T Cell Receptor (TCR)

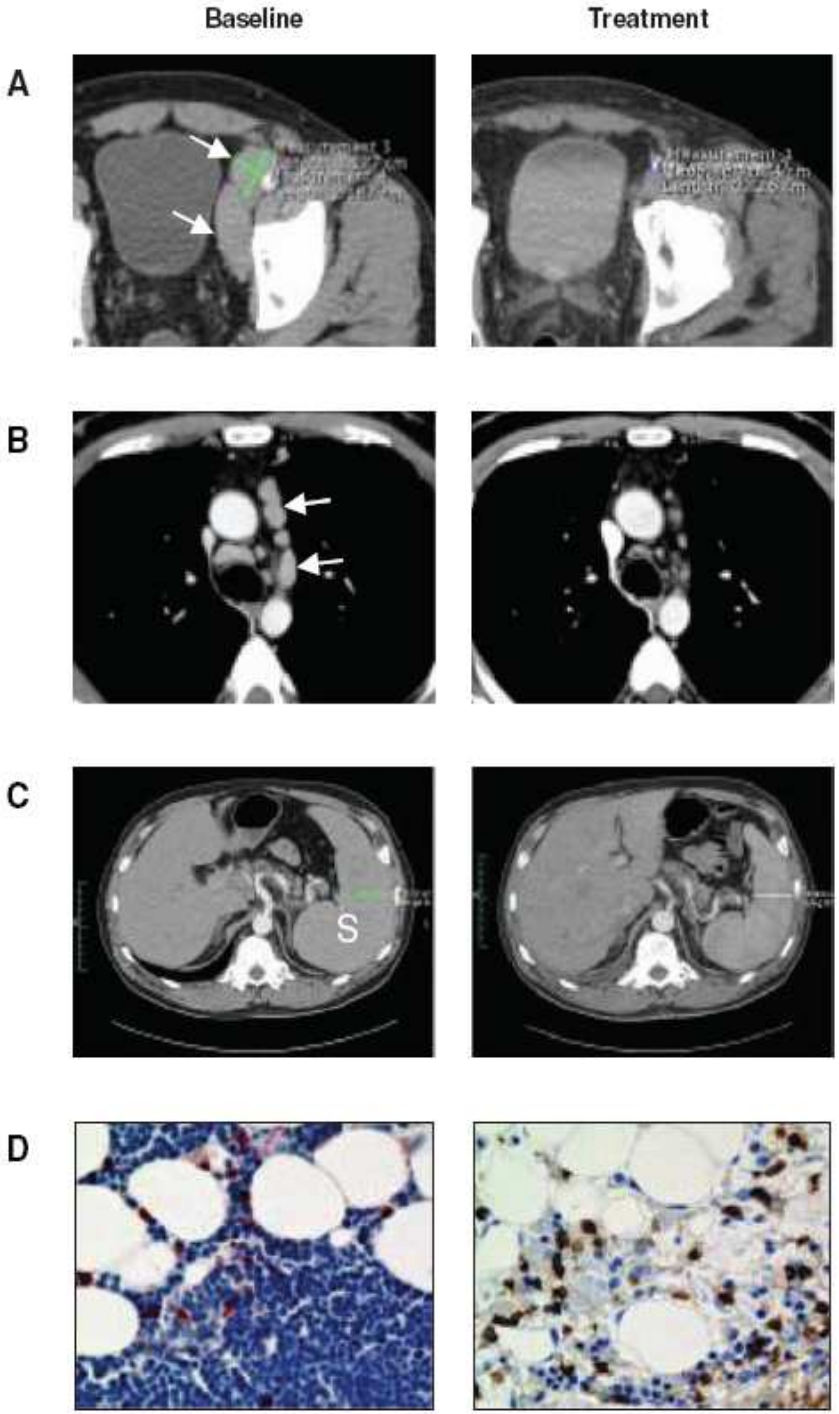
Allow T cells recognition of tumor-associated surface antigen (TAA)

Do not require MHC Class I and/or peptide antigen

Modes of action



Nagorsen D, et al. Pharm Ther 2012; 136:334-342.



Bargou R, et al.
Science 2008

Response Data

Number of Patients Included in Study	Number of Patients Evaluable for Response Assessment	Number of Patients Reaching MRD Negativity (N)	MRD Response Rate
21	20*	16	80%

*One patient not evaluable due to less than one treatment cycle and lack of response assessment

- **Responders include**
  - Three out of 5 patients with Philadelphia (bcr/abl) positive ALL including one patient with T315I mutated ALL
  - One out of 2 patients with t(4/11) ALL
- **Transplantation after blinatumomab treatment**
  - Five responders
  - Two non-responders

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)

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

Cytological and molecular remissions with blinatumomab treatment in second or later bone marrow relapse in pediatric acute lymphoblastic leukemia (ALL)

Lia Gore, Gerhard Zugmaier, Rupert Handgretinger, Franco Locatelli, Tanya M. Trippett, Susan R. Rheingold, Peter Bader, Arndt Borkhardt, Todd Michael Cooper, Maureen Megan O'Brien, Christian M. Zwaan, Anja Fischer, James Whitlock, Arend von Stackelberg

Presented at the 2013 ASCO Annual Meeting.

ASCO Annual '13 Meeting

Best Response Within 2 Cycles

Response (n)	Dose Cohort (μg/m²/day) 5 (n=5)	15 (n=7)	30 (n=5)	15 / 30 (n=6)	Total (N=23)
CR / CRi	3	3	2	1	9 (39%)
MRD(–)	3	3	2	1	9 (39%)
PR	1	—	—	—	1 (4%)
SD	1	3	—	2	6 (26%)
PD	0	0	2	1	3 (13%)
Aplastic	0	0	0	1	1 (4%)
Not available*	0	1	1	1	3 (13%)

CR/Cri, complete remission/complete remission with incomplete hematological recovery
MRD(–), MRD $<10^{-4}$ by PCR testing of individual rearrangements of Ig or TCR genes (central lab)
PD, progressive disease; PR, partial remission; SD, stable disease

*Data missing due to lacking bone marrow assessment (patient discontinued study after serious adverse event)

Now this is not the end. It is not even the beginning of the end, but it is, perhaps, the end of the beginning……