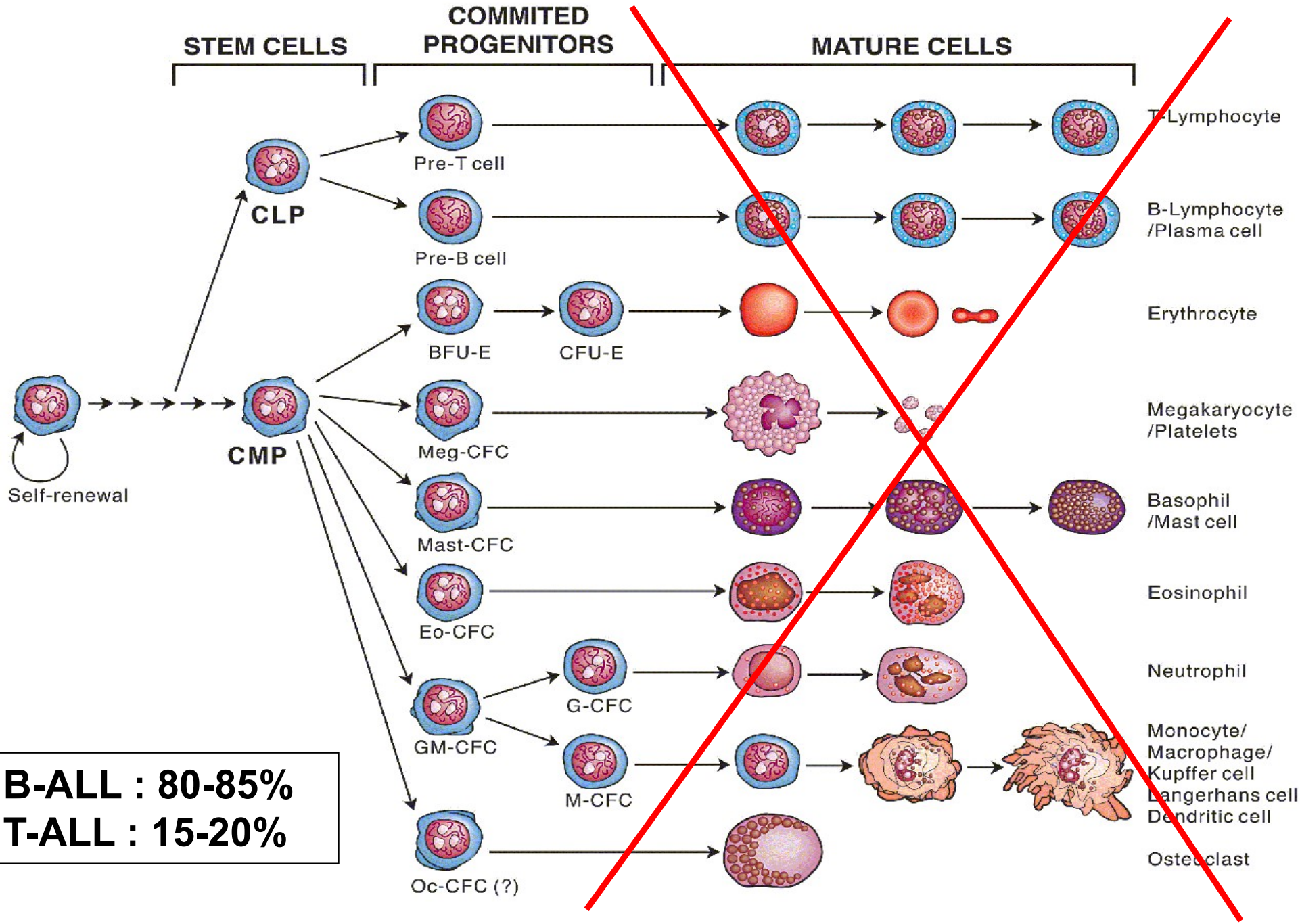
Acute Lymphoblastic Leukemia in Adults

BHS Training Course
on
Acute Leukemia

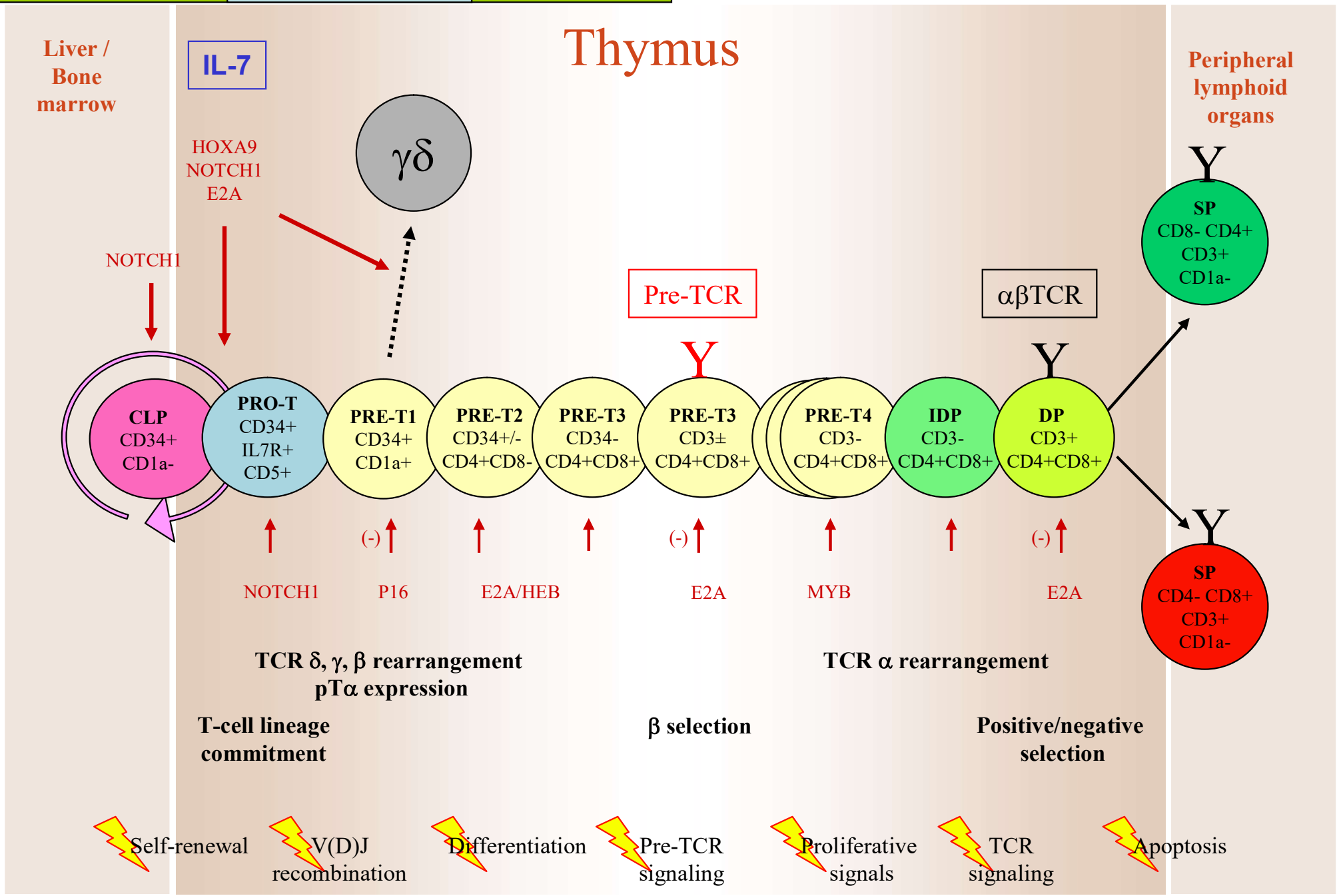
Pr Carlos Graux
CHU UCL Namur -Godinne

Saturday december 16th, 2023

8h30	8h45	Introduction	Chairman
8h45	9h30	AML : WHO classification, biology and prognosis	Dimitri BREEMS (ZiekenhuisNetwerk Antwerpen)
09h30	10h15	AML - treatment for fit and unfit patients	Koen Theunissen (Jessa Ziekenhuis)
10h15	10h30	Brief discussion for infectious prophylaxis in the setting of VenAZA	Adrien DE VOEGHT (CHU Liège)
10h30	10h45	Break	
10h45	11h30	APL treatment	Wittnebel Sebastian (HUB Institute Jules Bordert)
11h30	12h15	ALL from Biology to the treatment	Carlos Graux (CHU UCL Namur- Godinne)
12h15	13h	Acute leukemia and agressive lymphoma in children	Barbara De Moerloose (UZ Ghent)
13h	13h15	End of the session	chairman



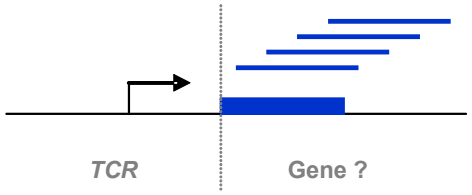
B-ALL : 80-85%
T-ALL : 15-20%



Graux C. et al Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: from thymocyte to lymphoblast Leukemia 2006

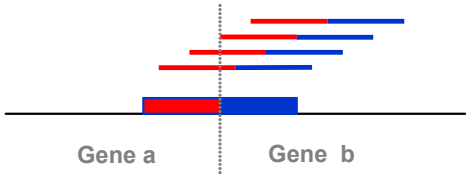
Chromosomal rearrangements involving *TCR* → activation of transcription factors (TCRαδ/14q11 or TCRβ/7q34)

- t(7;10)(q34;q24), t(10;14)(q24;q11) → ***TLX1 (HOX11)*** (7%/31%)
- * t(5;14)(q35;q32) (cryptic) → ***TLX3*** **(HOX11L2)** (20%/13%) * *BCL11B* /14q32
- inv(7)(p15q34) (cryptic) → ***HOXA*** (3%)
- t(1;14)(p32;q11) → ***TAL1*** (3%)
- t(7;19)(q34;p13) → ***LYL1*** (<1%)
- t(11;14)(p15;q11) → ***LMO1*** (2%)
- t(11;14)(p13;q11) and t(7;11)(q35;p13) → ***LMO2*** (3%)
- t(7;9)(q34;q34.3) → ***NOTCH1*** (<1%)
- t(6;7)(q23;q24) → ***MYB*** (<1%)
- …



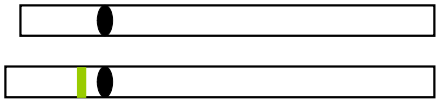
Formation of fusion genes

- 1p32 deletion → ***SIL-TAL1*** (9-30%)
- t(10;11)(p13;q14) (often cryptic) → ***CALM-AF10*** (10%)
- t(11;?)(q23;?) → ***MLL-?*** (4-8%)
- t(9;9)(q34;q34) (most often on amplified episomes) → ***NUP214-ABL1*** (6%)
- …



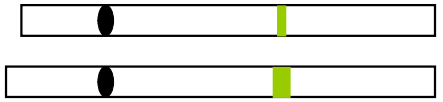
(Cryptic) deletions

- 9p21 → loss of ***P16 (CDKN2A)*** (65%)
- del(6q) → **?**
- …



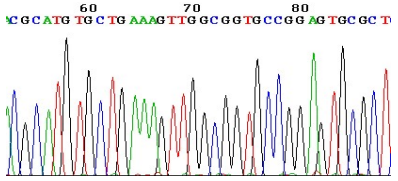
Duplications

- 6q23.3 → ***MYB***
- 9q34 → ***ABL1, VAV2, TRAF2, NOTCH1*** **?**
- …

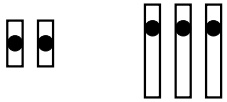


(Activating or inactivating) mutations

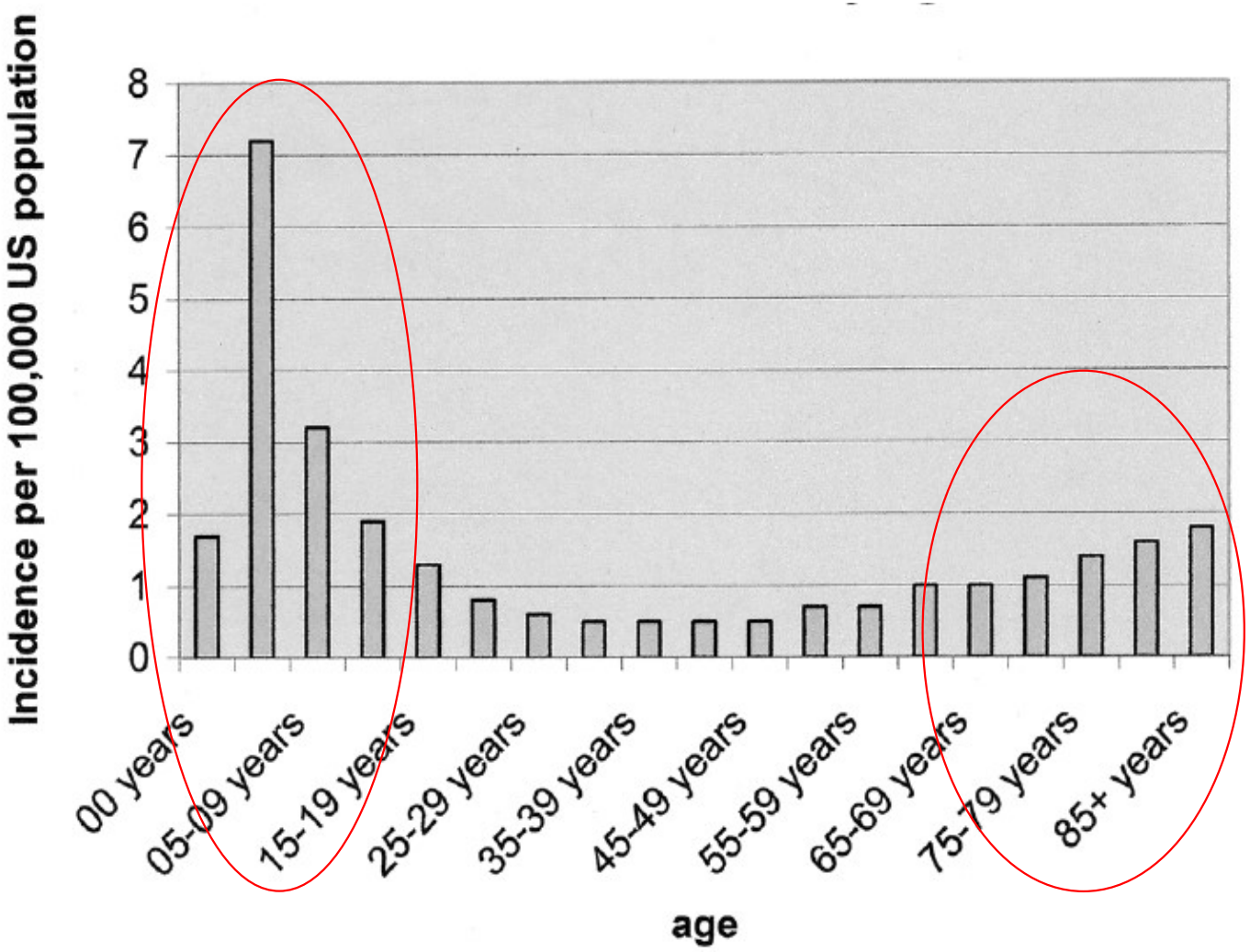
- ***NOTCH1, PTEN, FBXW1, FLT3, N -RAS, JAK1***
- …



Aneuploidy

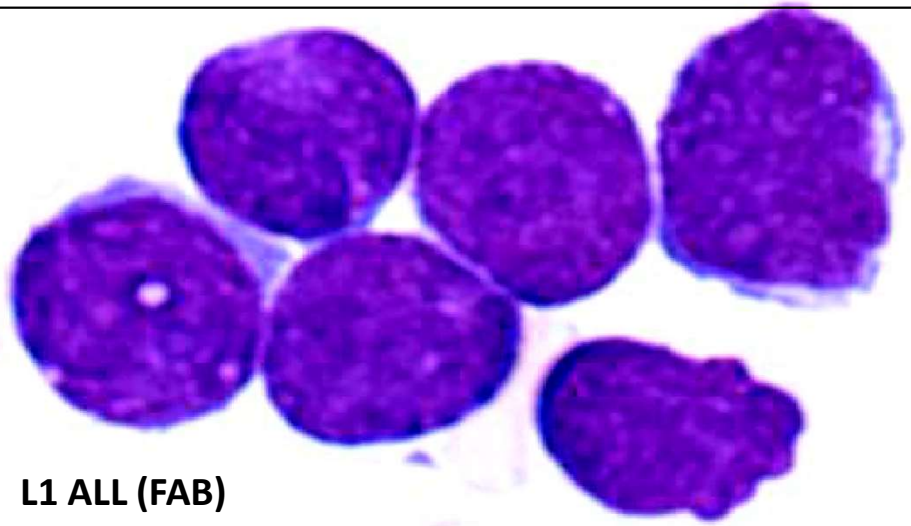


Age-specific incidence of ALL

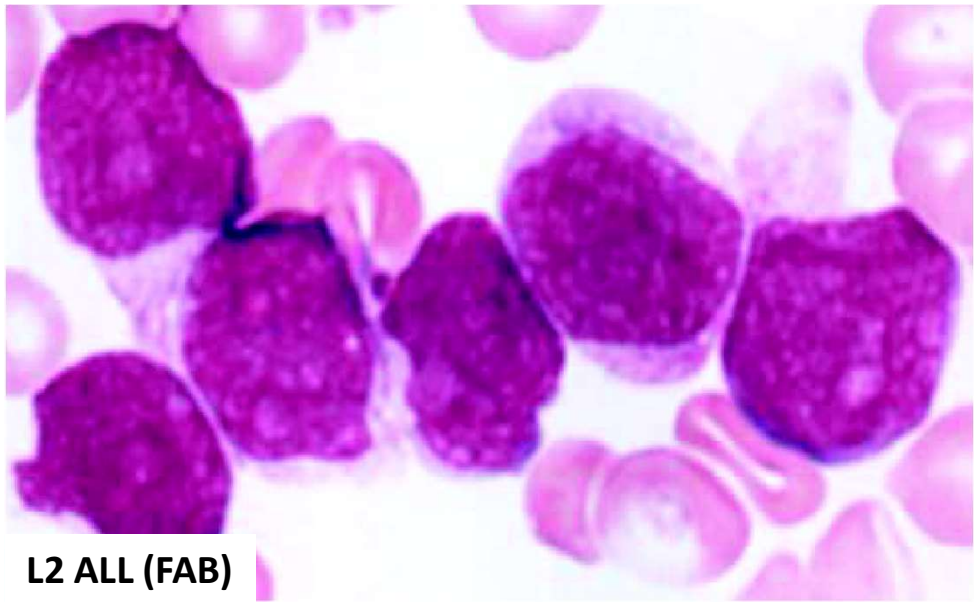


SE Sallan. Hematology 2006

Common type lymphoblasts from Precursor B or T-cell acute lymphoblastic leukemia (WHO)

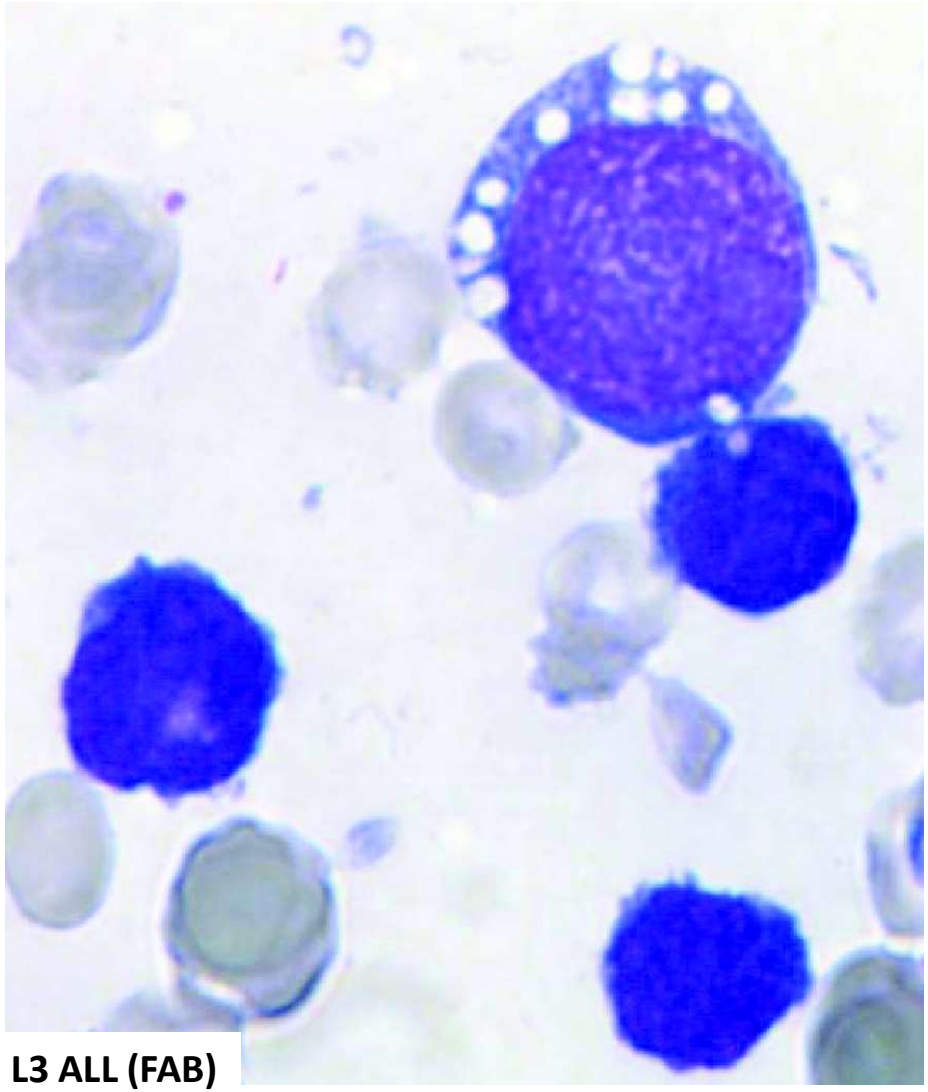


L1 ALL (FAB)



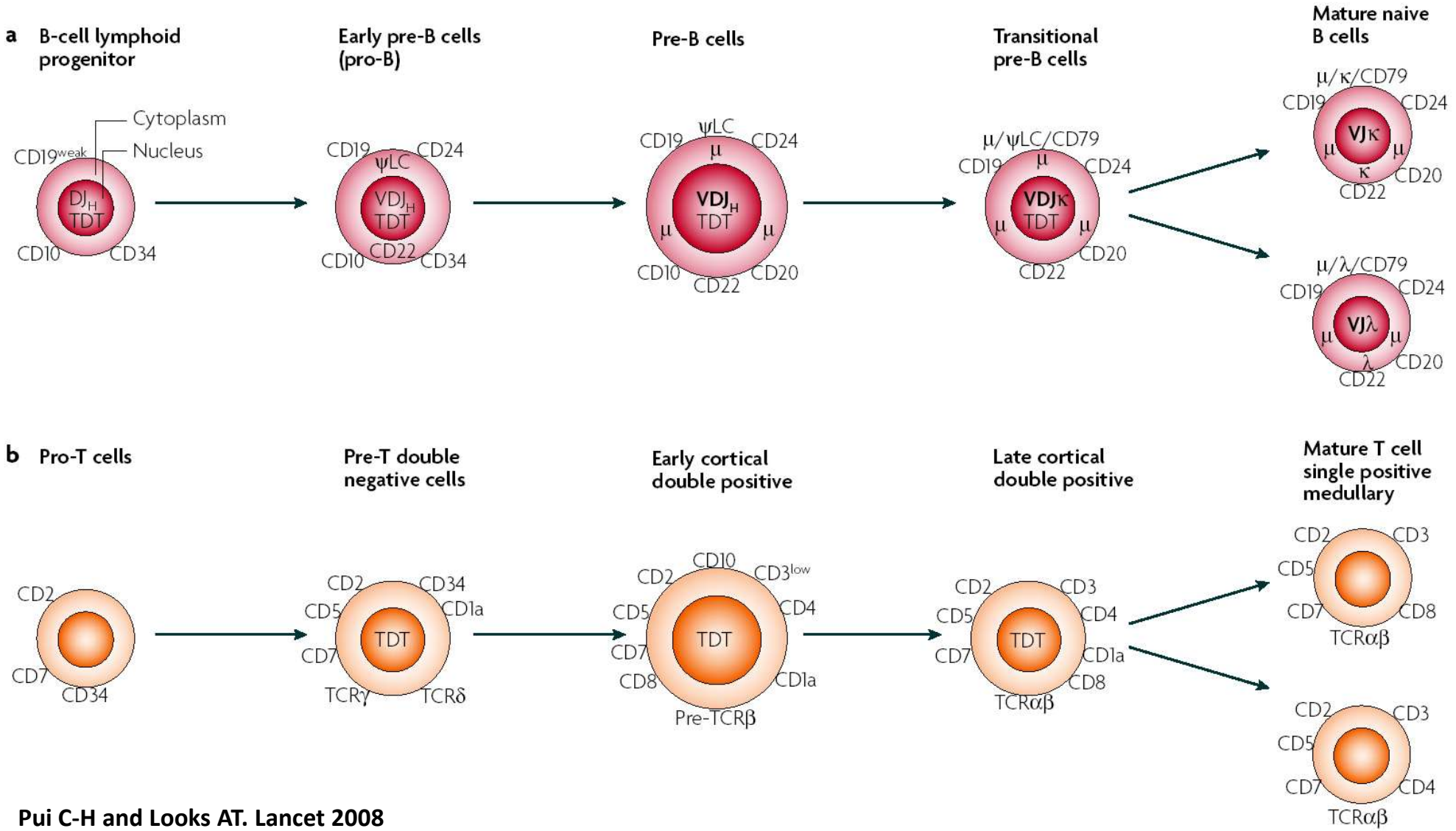
L2 ALL (FAB)

Burkitt's lymphoblasts from Burkitt's lymphoma (WHO)



L3 ALL (FAB)

Immunophenotyping



Pui C-H and Looks AT. Lancet 2008

GEIL/EGIL Scoring system

Points	B lineage	T lineage	Myeloid lineage
2	CD79 cμ cCD22	CD3 TCR	MPO (lysozyme)
1	CD19 CD10 CD20	CD2 CD5 CD8 CD10	CD13 CD33 CD65 CD117
0.5	TdT CD24	TdT CD7 CD1a	CD14 CD15 CD64

Biphenotypic AL: > 2 points for myeloid antigens and one of the lymphoid lineage

GEIL/EGIL classification of B-cell ALL

	cCD79/CD19/CD22 (s ou c)	CD10	C-μ	sIg
B1	+	-	-	-
B2	+	+	-	-
B3	+	+/-	+	-
B4 *	+	+/-	+/-	+

B1 = pro-B-ALL, B2 = Common B-ALL, B3 = pre-B-ALL, B4 = mature B-ALL

* *B4 = Burkitt's leukemia/lymphoma*

GEIL/EGIL classification of T-cell ALL

	cCD3	CD7	CD2/CD5/ CD8	CD1a	sCD3/CD1a-
T1 *	+	+	-	-	-
T2 *	+	+	+	-	-
T3	+	+	+	+	-
T4	+	+	+	-	+

T1= Pro-T-ALL, T2= Pre-T-ALL, T3= cortical T-ALL, T4= mature T-ALL

* *T1 and T2 = ETP ALL (early T cell precursor ALL)*

Relevance of immunophenotyping

- **Diagnosis** of B-ALL/T-ALL/bi-phenotypic AL

- **Specific therapy**
  - Identifying mature B-cell ALL (Burkitt's ALL)
  - Some surface markers are potential targets for antibody therapy and for other innovative therapies (CD19, CD20, CD22, CD52, …)

- In most cases **minimal residual disease** can be assessed by flow cytometry (especially when leukemic lymphoblast express aberrant antigens)

Risk assessment

Balance between the risk of relapse and the risk related to the toxicity of the treatment

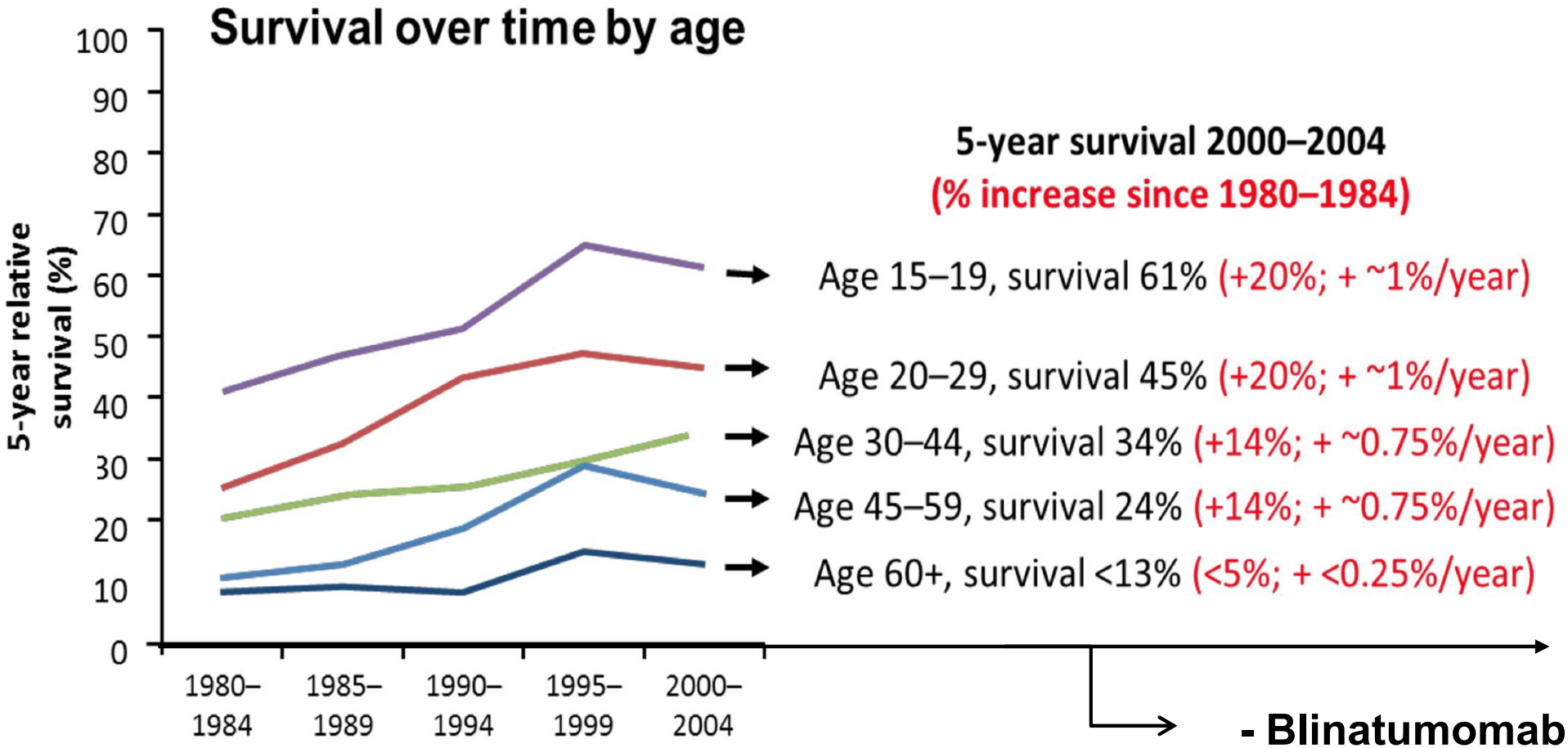
Takes into account:

- patient (host) characteristics
  - age (comorbidity), social situation (compliance), general condition,…
  - Specific pharmacodynamics, pharmacogenetics

- disease characteristics
  - clinical prognostic features
  - genetics (chromosomal/gene abnormalities, MDR genes expression, gene expression profiling, …)

→ selecting therapy that will avoid excessive toxicity but maintain a high cure rate

Age



Exception: infant ALL with t(4;11) (MLL-AF4)

Pulte et al. Blood 2009

Pharmacodynamics/genetics

Polymorphisms in genes that encode drug-metabolizing enzymes, transporters, receptors, and drug targets

→ wide differences in terms of drug disposition and pharmacologic effects

→ influence toxicity and efficacy of chemotherapy

- Drug interactions !

Phenytoin, phenobarbital, carbamazepine

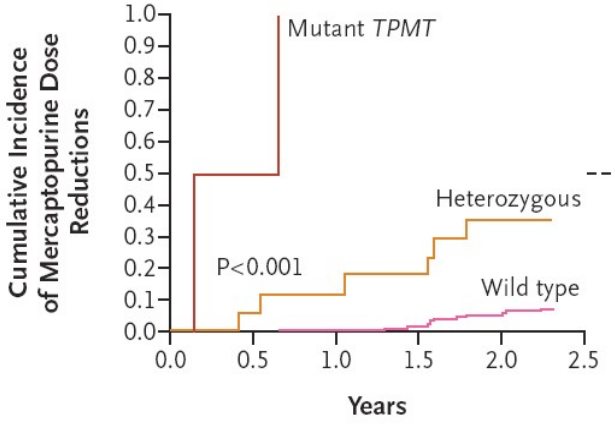
→ induce the production of cytochrome P-450 enzymes

→ increase the systemic clearance of antileukemic agents

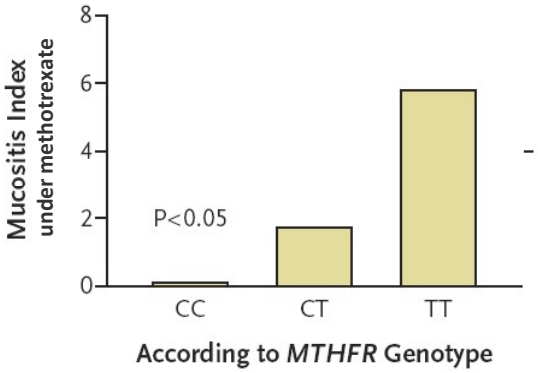
→ adversely affect treatment outcome

!!! Azole antifungal drugs (V-Fend®, Noxafil®, ….) and vinca alkaloids, corticoids

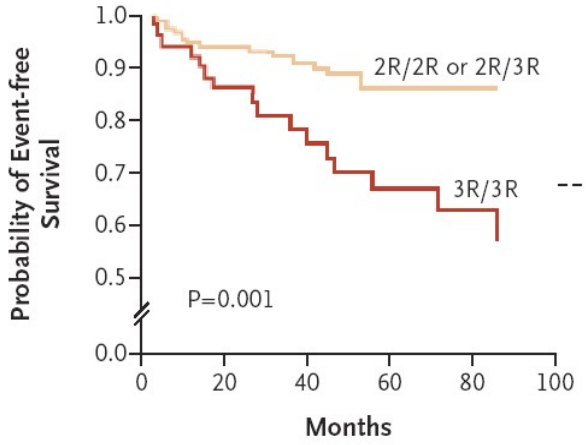
Homozygous or heterozygous deficiency of thiopurine methyltransferase

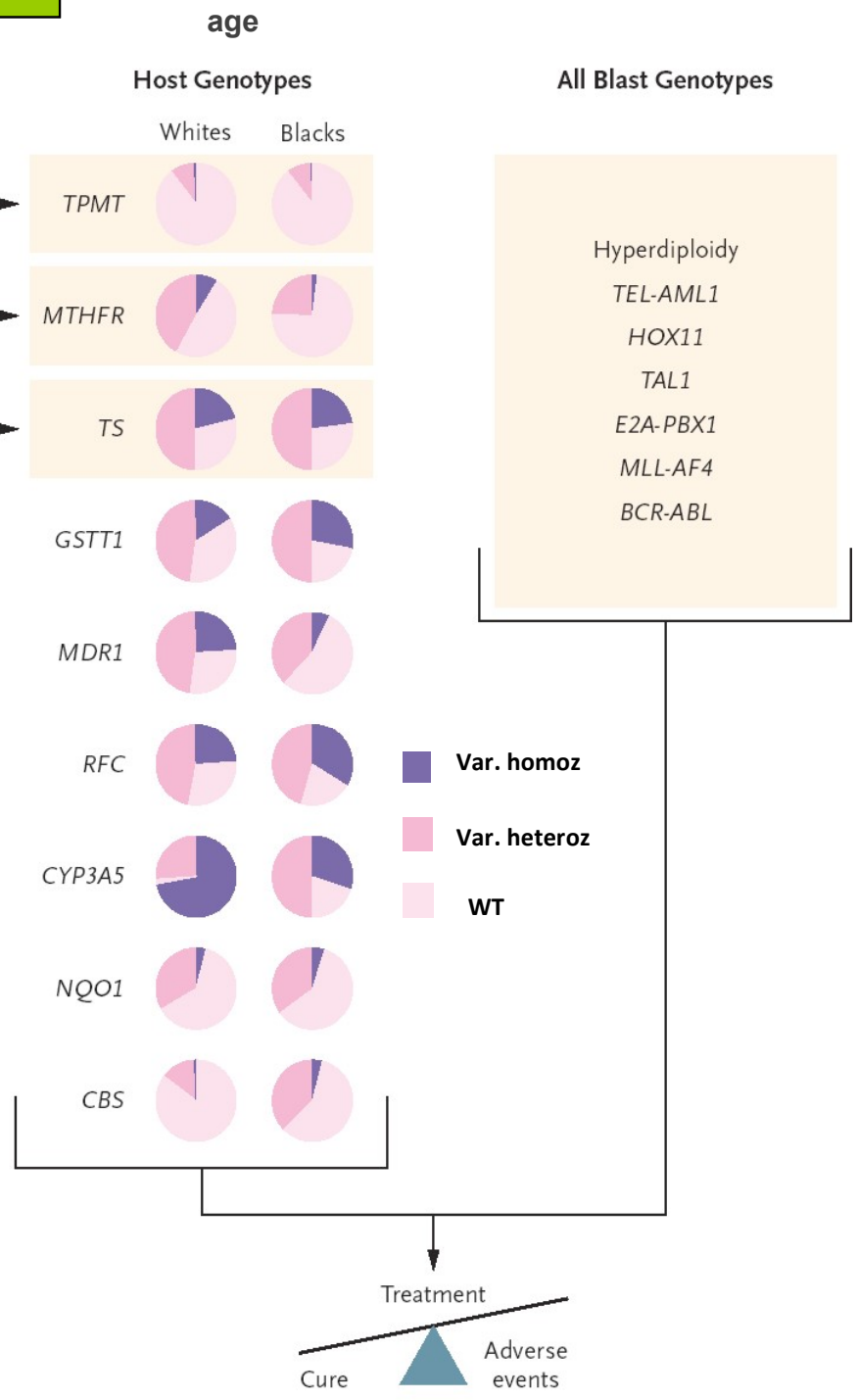


C→T polymorphism at position 677 in the methylenetetrahydrofolate reductase (*MTHFR*) gene



Tandem-repeat polymorphism within the enhancer region of the thymidylate synthase gene one of the major targets of methotrexate





Pui CH. NEJM 2004

Clinical features

- **Leukocyte count**
  - **> 30.000/µL (B-ALL)**
  - **> 100.000/µL (T-ALL)**
- Extramedullary disease
- High LDH level,
- Low Hgb level, low platelet count
- CNS involvement

Negatively impact on prognostic

Cytogenetics

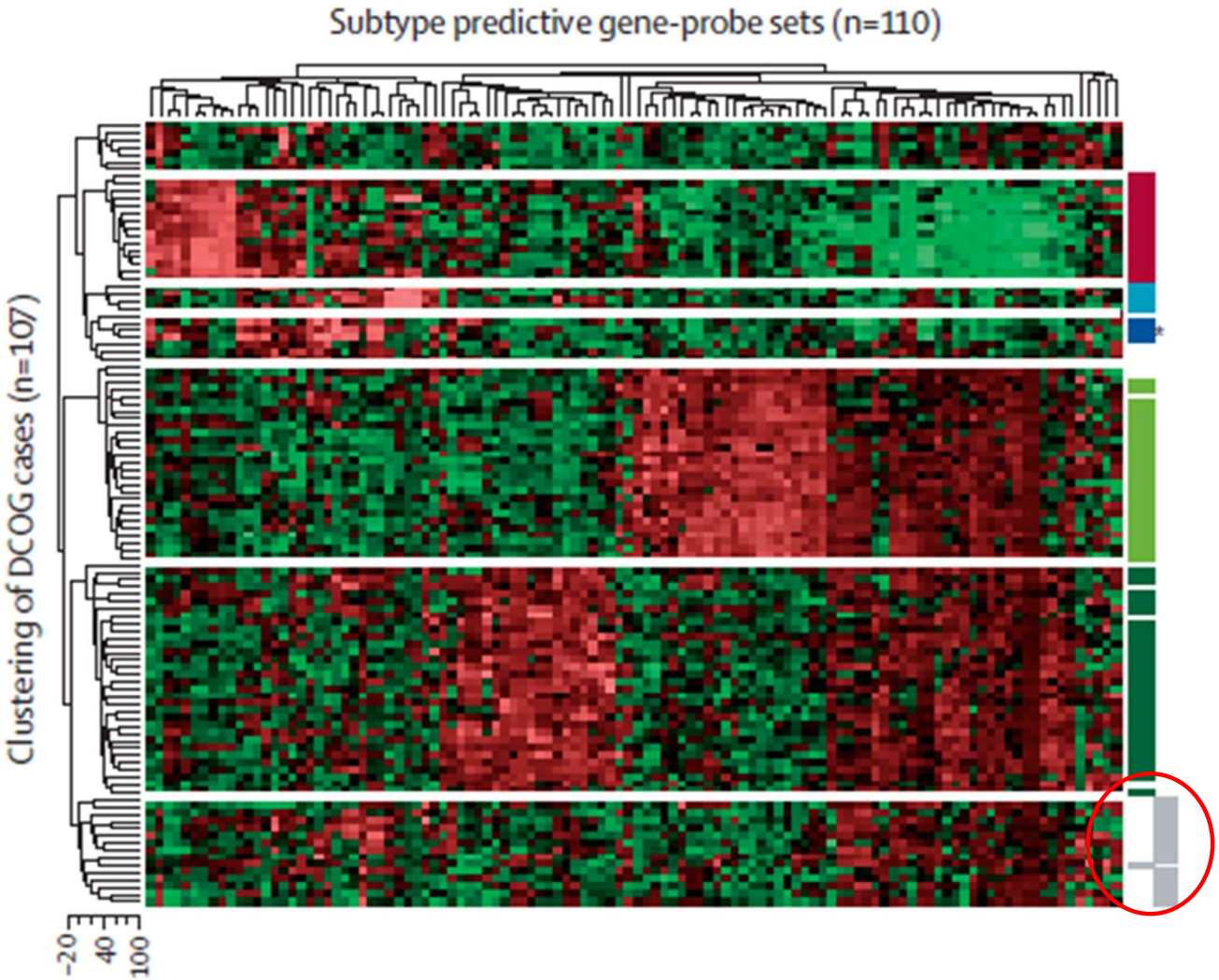
B-cell precursor ALL		
Favorable features		
- **hyperdiploidy** (> 50 chromosomes)		HD MTX
- **t(12;21) → *TEL-AML1***	in 30 % of childhood cases in 5 % of adult cases	Intensive- Asparaginase
- **t(1;19) → E2A-PBX1** (CD34-, CD20-)	outcome depends on treatment used	Intensive
- **trisomy 4, 10, 17**	in children	
Unfavorable features:		
- **hypodiploidy** (< 45 chromosomes)	< 2 % of pediatric or adult cases	
- **t(4;11) → *MLL-AF4*** (CD10-, CD19+, CD15+)	+/- 50 % of cases in infants 2 % of cases in children 5 to 6 % of cases in adults	HD Ara-C
- **t(9;22) → *BCR-ABL1*** (p190 or p210) (CD34+, myeloid antigens, CD25)	3 % in children 20 % in adults 50 % in patients older than 50 years	Glivec/ new TKI
T-cell precursor ALL		HD MTX, Ara-C, cyclophosphamide
Favorable features:		
- **t(7;10) and t(10;14) → *HOX11 (TLX1)*** (CD10+/-, CD1a+)		
- **t(11;19) → *MLL-ENL***		
Unfavorable features:		
- **t(5;14) (cryptic) → *HOX11L2***		Controversial Impact of NUP214-ABL1 expression?

Large scale genome analysis : GEP/CNA/WES, WTS, WGS

- Reveals new subtypes of ALL
  - ex: the BCR-ABL1 like subtype (Ph-like subtype)
    → poor prognostic sub-group
    → targetable underlying ”mutations”
    ex: EBF1-PDGFRB
- Identifies genes
  - whose expression/deletion may have prognostic significance
    - IKZF1 deletions, CRLF2 rearrangements, TP53 mutations in B-ALL
      → poor prognosis
    - ERG-deregulations in B-ALL → favorable
    - NOTCH1 signaling mutated in T-ALL → good prognosis

    (used to stratify the risk in the current therapeutic GRAALL protocol)

Dutch study: non-selected cohort, n=507



Gene expression profile similar to

Ph+ ALL

No Ph chromosome

no BCR-ABL1

« Pro-B » signature

*IKZF1 a*lterations (70-80%)

Negative for most recurrent genetic abnormalities

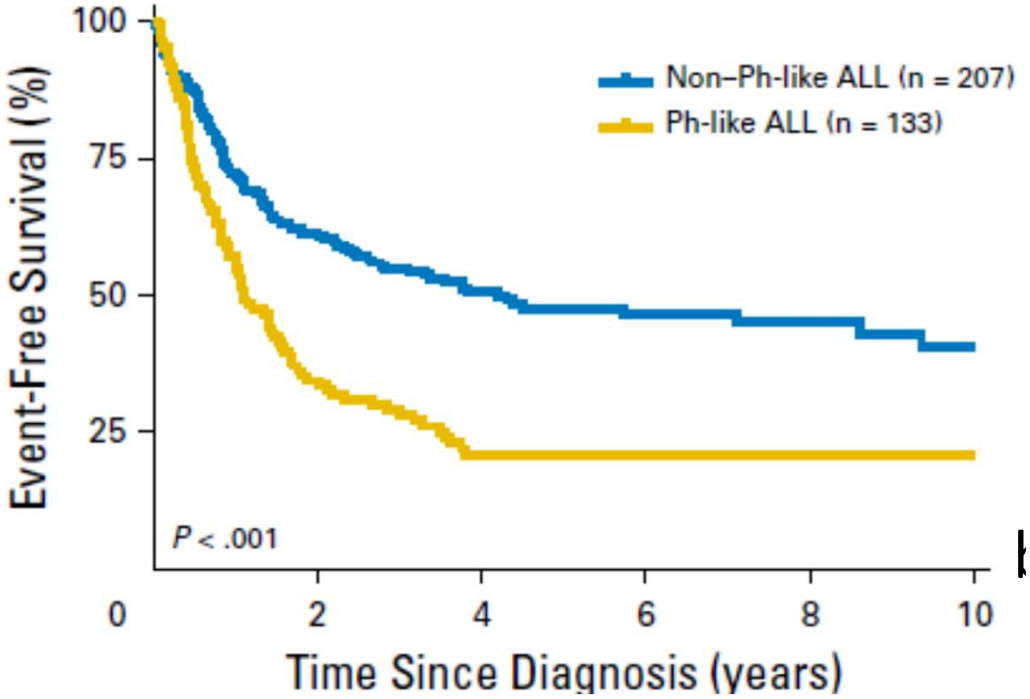
=

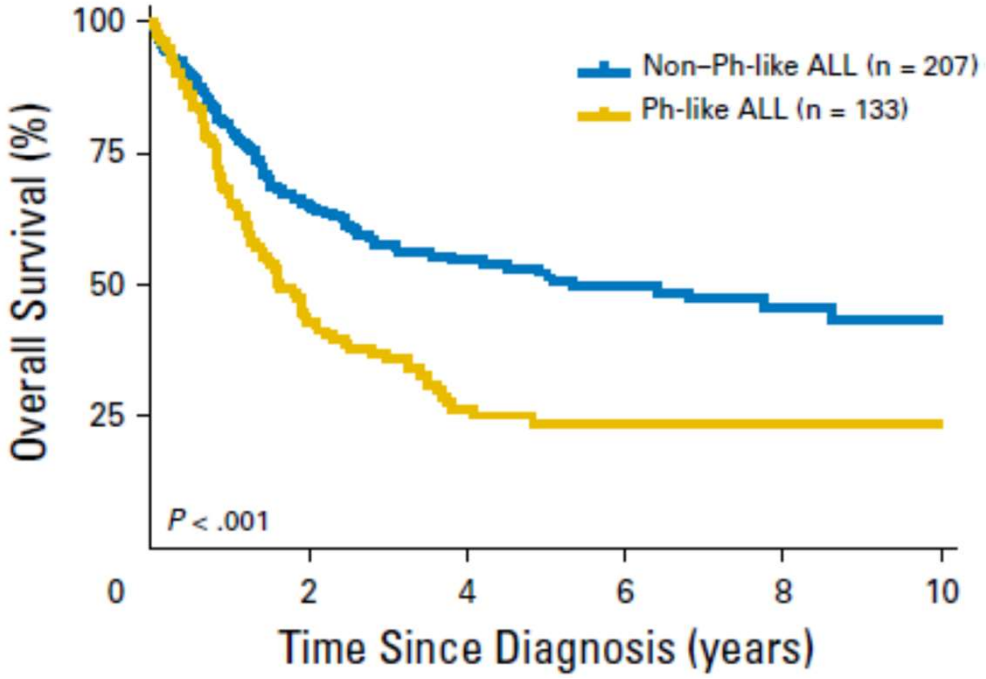
« Ph-like » ALL

(+/- 15% of B-ALL)

Den Boer et al. A subtype of childhood ALL with poor treatment outcome: genome-wide classification study. Lancet Oncol. 2009

« Ph-like » ALL

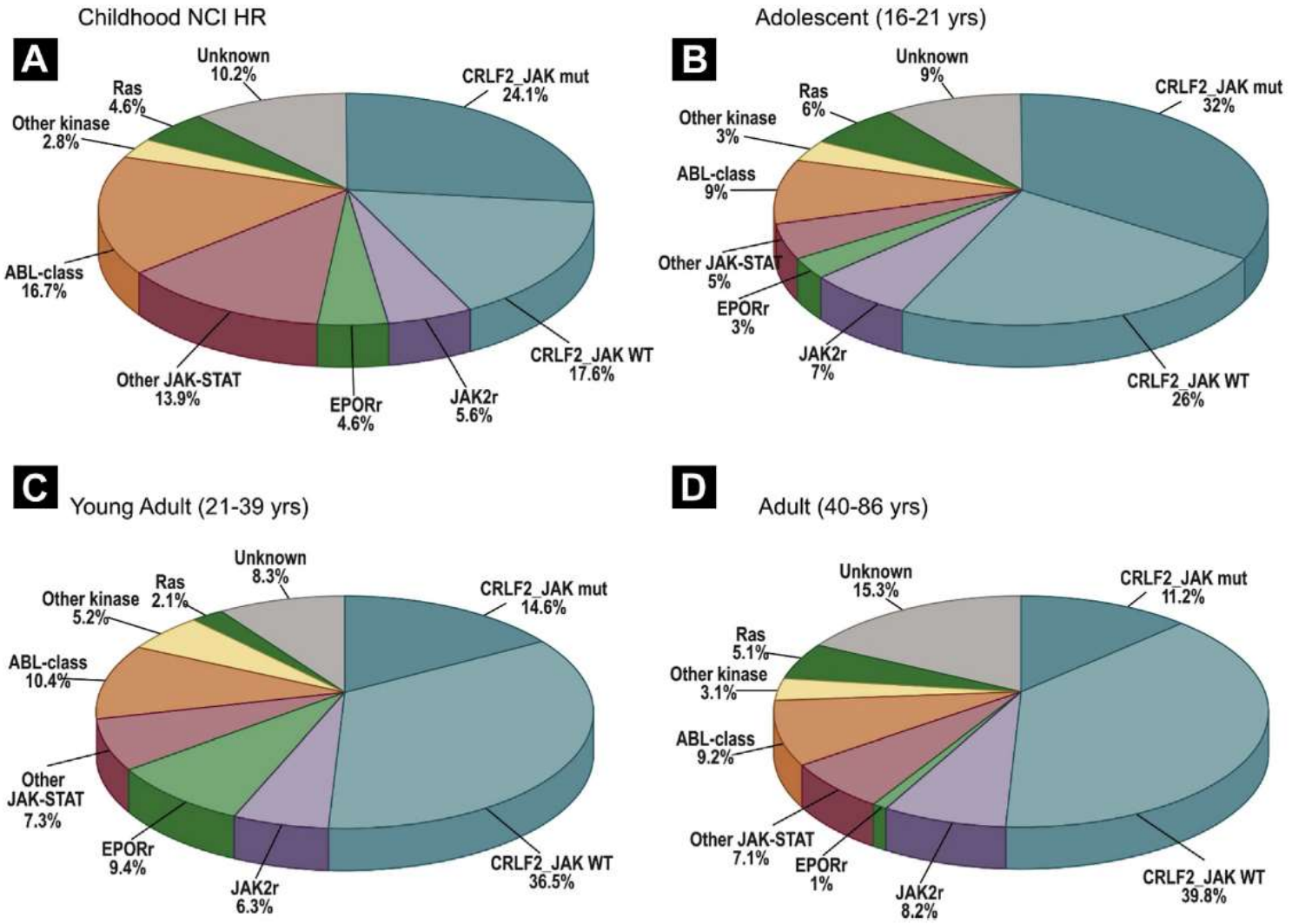




Less MRD < 0,01% (47% vs 94%; *P = .002)*

Roberts KG et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like ALL in Adults. J Clin Oncol. 2017

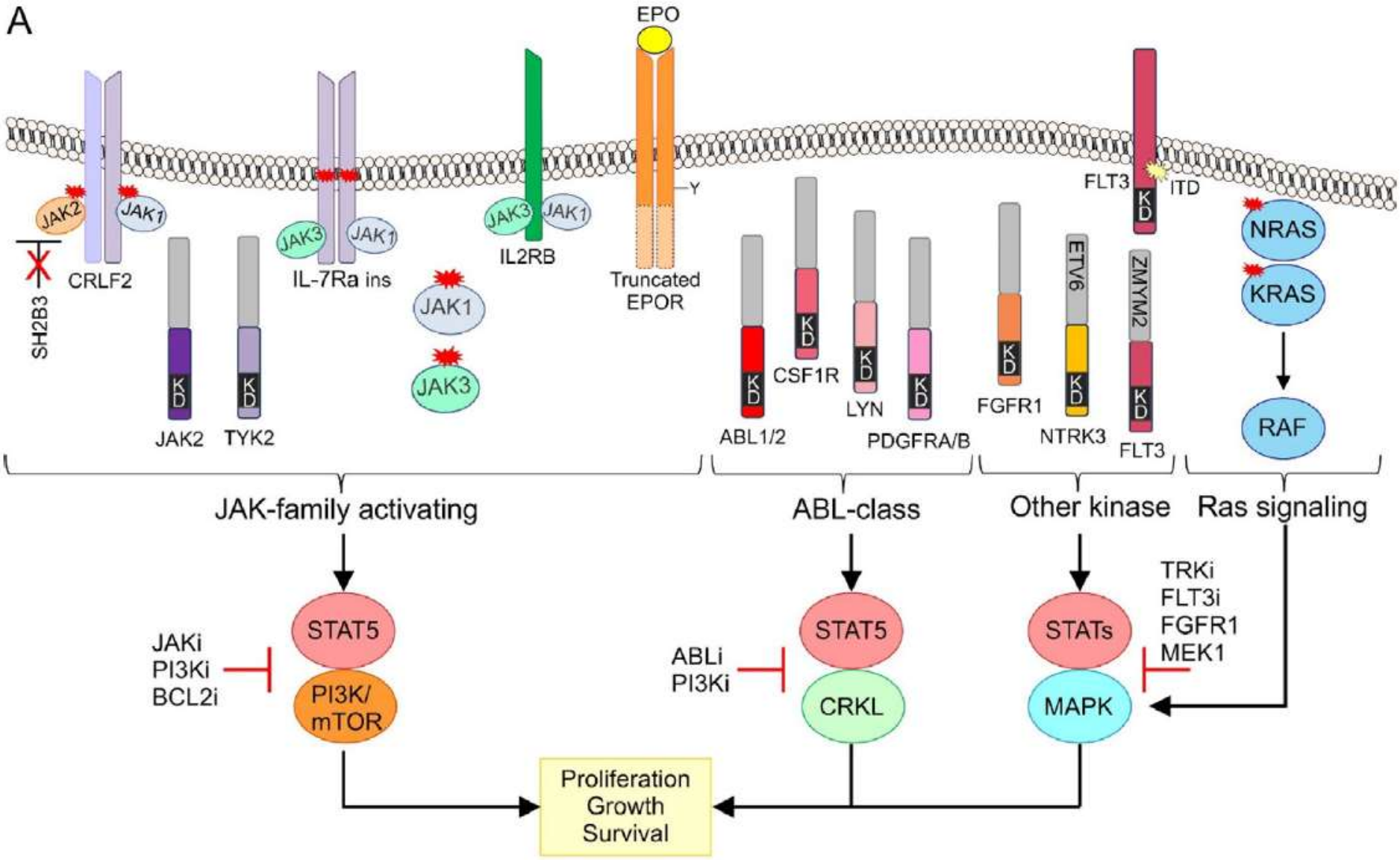
« Ph-like » ALL



→ **Multiple cytokine receptor and kinase activating lesions**

Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia Chromosome-like ALL. Clin Lymphoma Myeloma Leuk. 2017

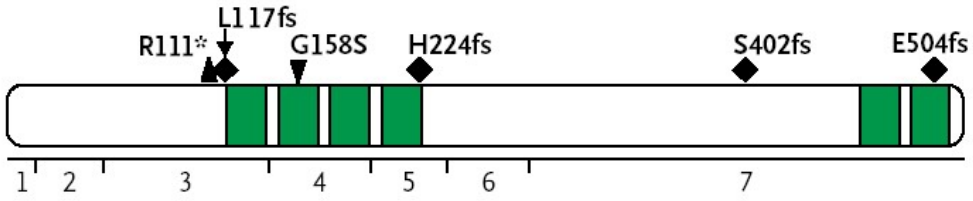
Kinase alterations and signaling pathways dysregulated in Ph-like ALL



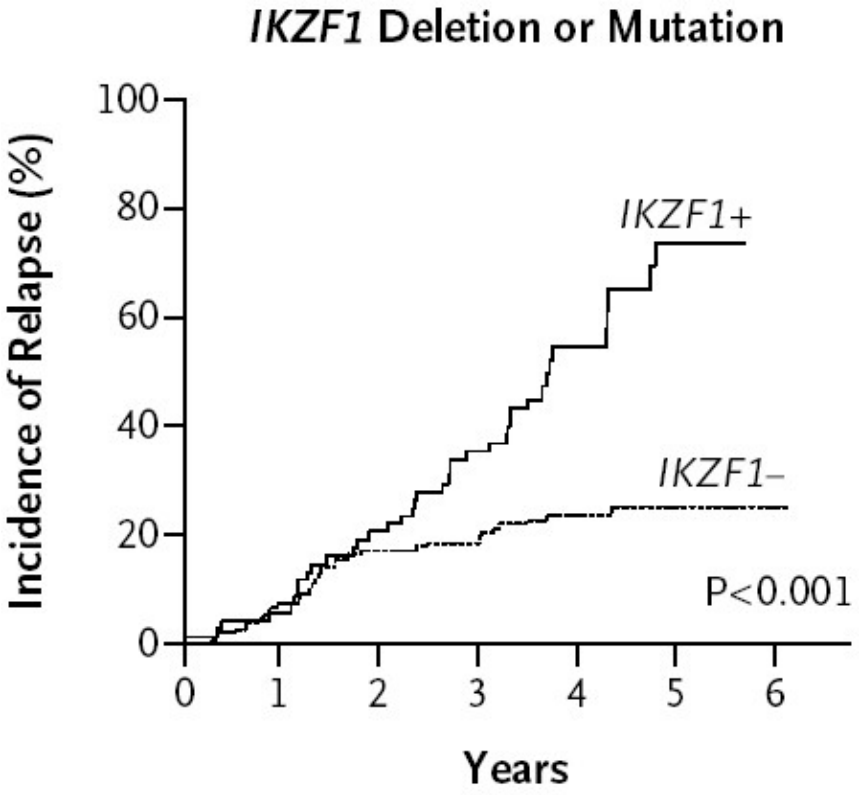
Charles G. Mullighan. Best practice & research clinical heamatology 2019

The majority of kinase and cytokine receptor alterations converge on two pathways that activate JAK-family member signaling or ABL-signaling:
- alterations that activate JAK-STAT signaling can be targeted with JAK and PI3K inhibitors.
- ABL-class alterations can be targeted with ABL-inhibitors such as dasatinib.
- other kinase alterations and those that activate Ras signaling can be targeted with specific inhibitors including those that inactivate TRK, FLT3, FGFR1, and MEK for the MAPK pathway.

IKZF1



Missense mutations
Frameshift mutations
Splice-site mutations
Intragenic deletion



High risk based on:
CNS or testicular disease,
***MLL* gene rearrangement, or**
age, sex, leukocyte count
Excluded: BCR-ABL1+, infant, hypodiploid ALL

Mullighan CG et al. NEJM 2009; 360(5): 470-480

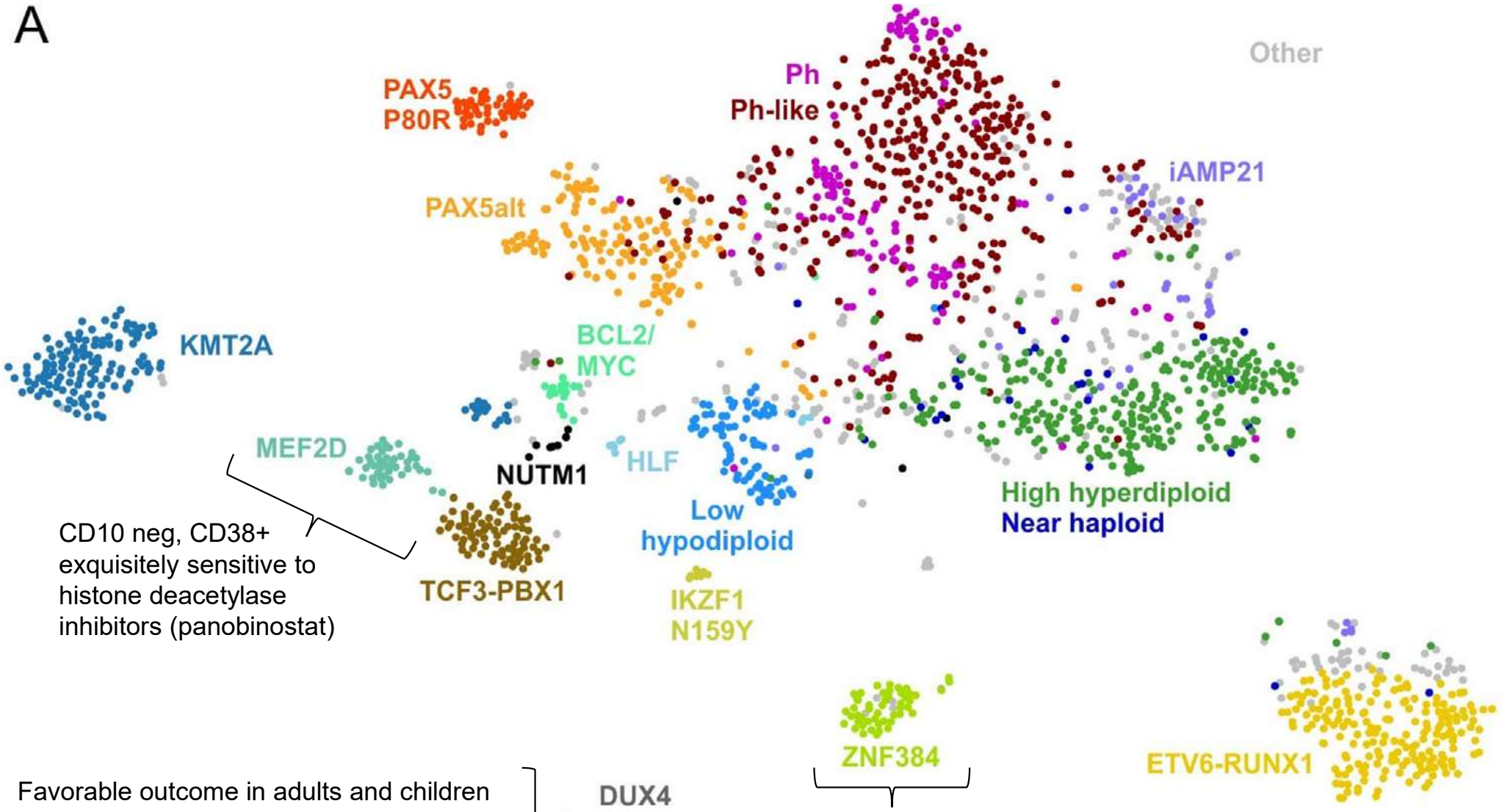
Prevalence and prognosis of subtypes in B-ALL based on WTS analysis of 1988 ALL cases

ALL subtype	Category	Median age (yrs)	Peak prevalence	Genomic alterations	Clinical features	Therapy
Hyperdiploid (> 50 chromosomes)	Aneuploid	4	Children (25%)	Ras pathway, epigenetic modifiers	Excellent prognosis	Reduce intensity
Low hypodiploid (31–39 chromosomes)	Aneuploid	47	Adults (10–15%)	*IKZF2* deletion, *TP53* mutation (commonly inherited)	Poor prognosis	BCL2 inhibitors
Near haploid (24–30 chromosomes)	Aneuploid	5.4	< 3% in all ages	Ras pathway, *IKZF3* deletion	Intermediate prognosis	BCL2 inhibitors
iAMP21	Copy number gain	10	~3% in children and AYA	Complex structural alterations of chromosome 21	Good prognosis with intensive therapy, low WBC	
ETV6-RUNX1 t (12; 21) (p13; q22)	TF rearrangement	4	Children (25%)	*PAX5* deletion, *WHSC1* mutation	Excellent prognosis	Reduce intensity
ETV6-RUNX1-like	TF rearrangement	3	Children (3%)	*ETV6* fusions and deletion, *IKZF1* fusions and deletion	Unknown	Reduce intensity
DUX4-rearranged	TF rearrangement	14.3	AYA (~8%)	*ERG* deletion, *IKZF1* deletion, Ras pathway	Excellent prognosis	Reduce intensity
KMT2A-rearranged	TF rearrangement	40	Infants (~90%) and adults (~15%)	Ras pathway (commonly subclonal)	Poor prognosis	Bortezomib, DOT1L inhibitors, Menin inhibition
TCF3-PBX1 t (1; 19) (q23; p13)	TF rearrangement	8	Children (5%)		Good prognosis, CNS relapse	
ZNF384-rearranged	TF rearrangement	15	AYA (~5%)	Epigenetic modifiers, Ras pathway	Intermediate prognosis	FLT3 inhibition
MEF2D-rearranged	TF rearrangement	14	AYA (~7%)	Ras pathway	Intermediate prognosis,	HDAC inhibition
NUTM1-rearranged	TF rearrangement	3	Children (1%)	Unknown	Excellent prognosis	Bromodomain inhibitors
TCF3-HLF t (17; 19) (q22; p13)	TF rearrangement	15	Rare rare in all ages (< 1%)	*TCF3* mutation, *PAX5* deletion, Ras pathway	Very poor prognosis,	BCL2 inhibitors
PAX5alt	Other TF driven	10	Children (~11%)	*PAX5* fusion, mutation, amplification	Intermediate prognosis	
PAX5 P80R	Other TF driven	22	Adults (~4%)	Ras pathway	Intermediate prognosis	
IKZF1 N159Y	Other TF driven		Rare in all ages (< 1%)	Unknown	Unknown	FAK inhibitors, rexinoids
BCL2/MYC-rearranged	Other TF driven	48	AYA and adults (~3%)	Unknown	Poor prognosis	
Ph-like	Kinase driven	21	AYA (25–30%)	Multiple kinase alterations, *IKZF1* deletion and mutation, *CDKN2A/B* deletion	Poor prognosis, amenable to TKI therapy	TKI, PI3Ki, BCL2 inhibitors
BCR-ABL1 t (9; 22) (q34; q11.2)	Kinase driven	40–45	Adults (40–50%)	*IKZF1* deletion and mutation, *CDKN2A/B* deletion	Prognosis improved with TKI	TKI, FAK inhibitors, rexinoids
Other		16	~5% children, ~10% AYA and adults	Unknown	Intermediate prognosis	

Gu Z, et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat Genet 2019

Charles G. Mullighan. How advanced are we in targeting novel subtypes of ALL? Best practice & resaerch clinical heamatology 2019

Major B-ALL subtypes based on gene expression profiling of 1988 cases



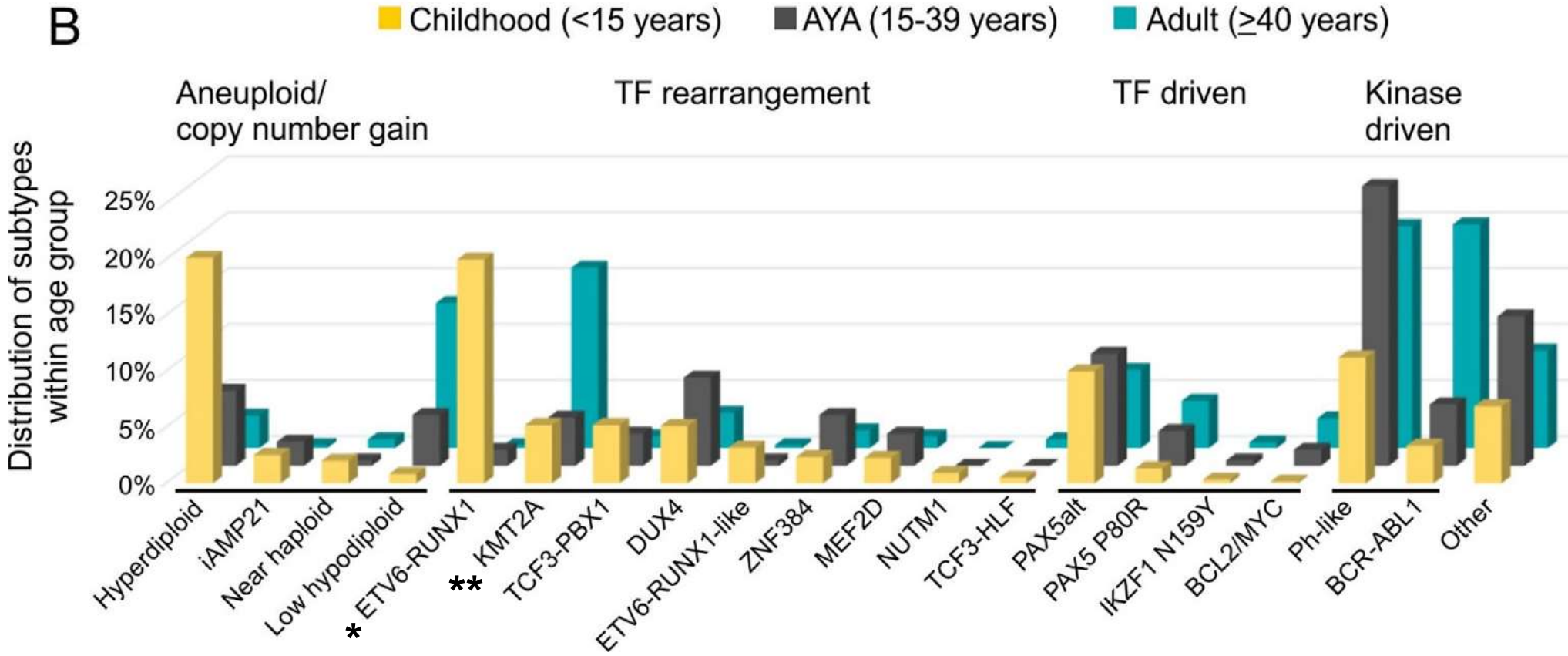
CD10 neg, CD38+
exquisitely sensitive to
histone deacetylase
inhibitors (panobinostat)

Favorable outcome in adults and children
CD2+, CD371+
ERG deletion in 50% of cases
Associated to IKZF1 deletions (but remains favorable!!!)

Associated
- to B/myeloid mixed phenotype acute leukemia
- to immunophenotypic multiclonality

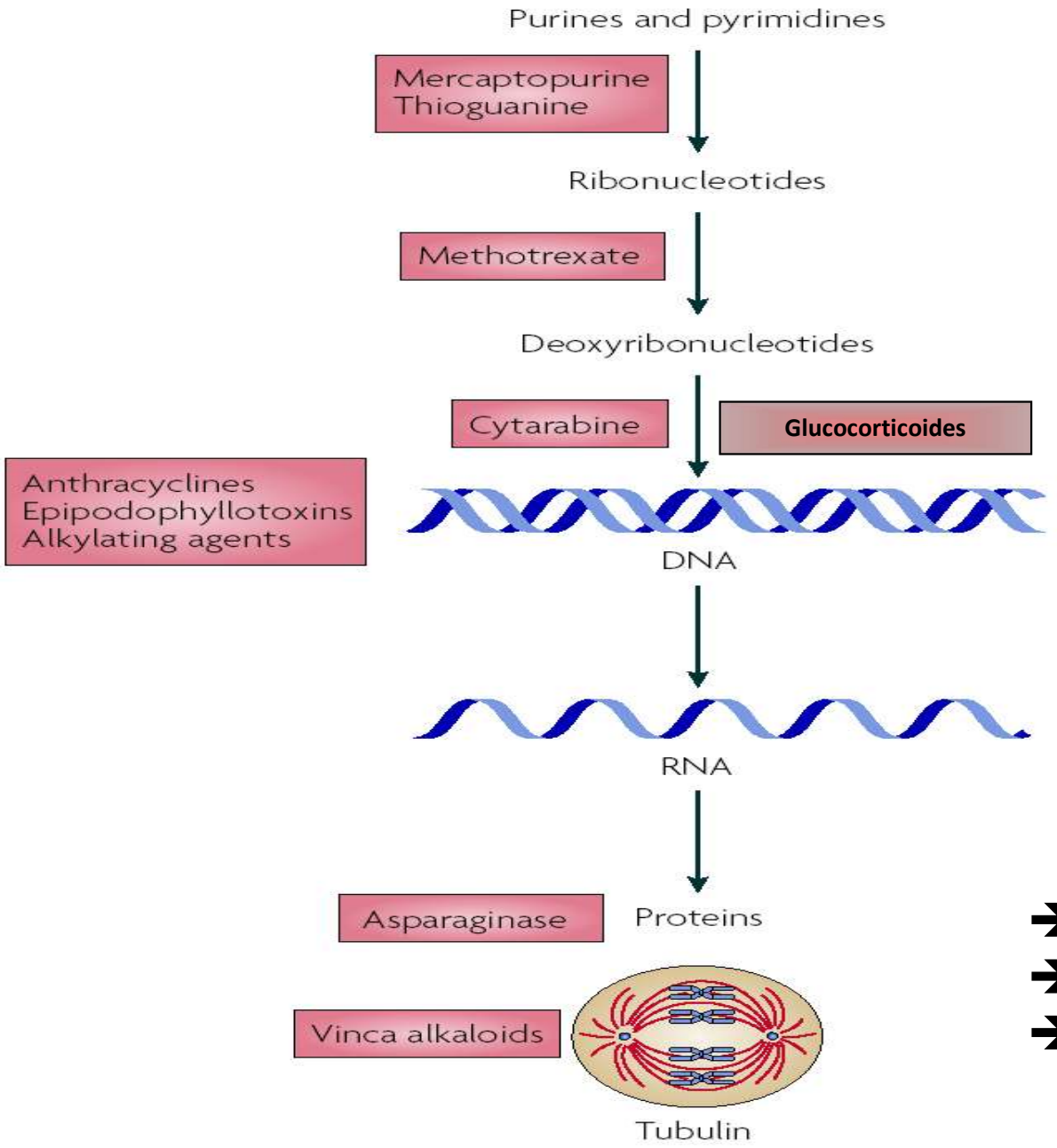
→ Lymphoid disease may recur as myeloid disease and vice versa

Distribution of B-ALL subtypes within each age group



* ETV6 - RUNX1 = TEL - AML1
** KMT2A = MLL

Treatment



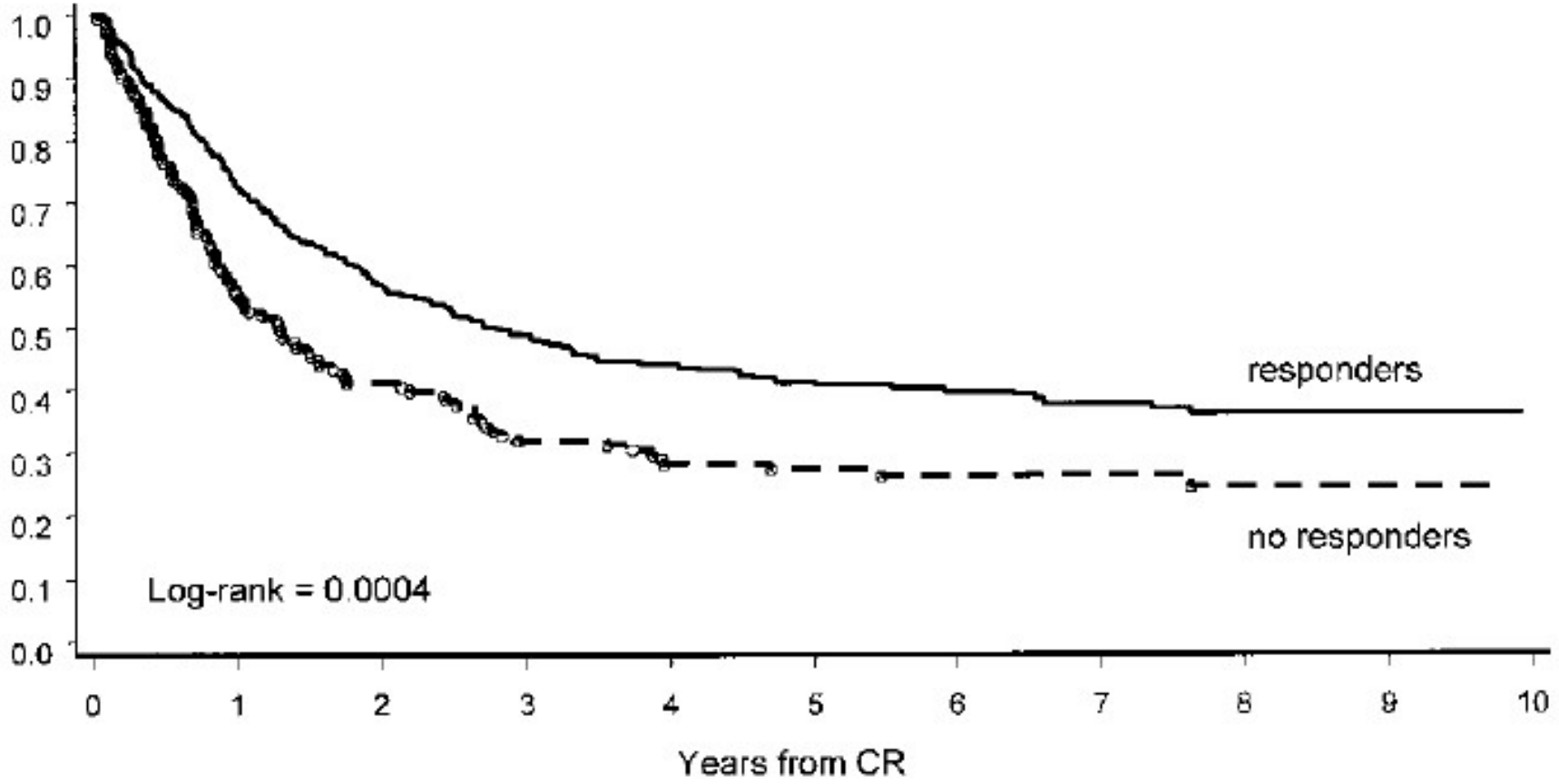
Chemotherapy

- non specific
- narrow therapeutic index

Optimal use
of the same antileukemic agents

➔ Better associations
➔ Better dosages
➔ Better schedules

Prephase with corticoïds



Steroid sensitivity (prednisone 60 mg daily for 7 days: blast cells should be less than 1000/µL in peripheral blood by day 8)

Annini L. et al. Blood 2002

Remission induction therapy

- Goal
  - to eradicate > 99 % of the initial burden of cells
    - to restore a normal hematopoiesis
    - to restore a normal performance status

- Always includes the administration of:
  - a glucocorticoid (prednisone, prednisolone, or **dexamethasone**),
  - vincristine,
  - and at least one other agent (usually **asparaginase**, an anthracycline, or both). Interest of cyclophosphamide in T-ALL.

→ complete remission rates of 96-99 % for children and 78-93 % for adults

Response to the induction

It **depends on** interconnected variables:

- the ability of individual patients to metabolize anti-leukemic drugs
- clinico-biological features of the disease
- chemotherapy dosages, schedule of administration & interactions

It is **evaluated by** the rate of clearance of leukemic cells (leukemia cytoreduction)

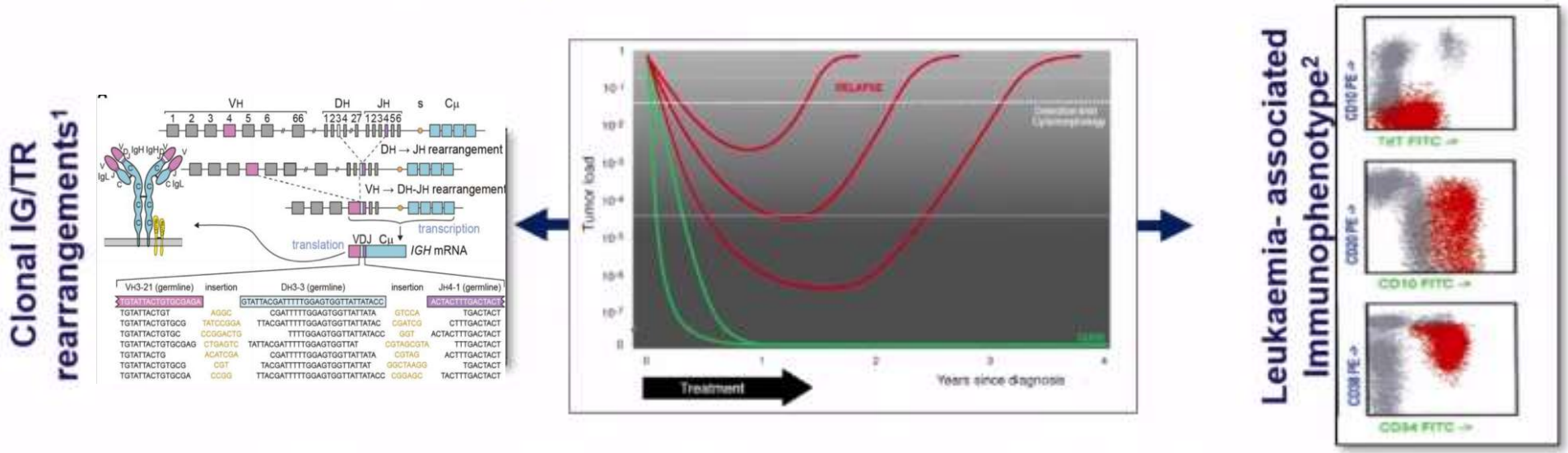
- that reflects the collective impact of the different variables
- evaluated by **morphology** at day 15 (insensitive)
- Better evaluated by the measure of the **minimal (mesurable) residual disease** (MRD) by molecular and flow cytometric methods at the end of induction (>100-fold more sensitivity)

MRD = most useful prognostic indicator → adaptation of the R/
= independent from the presence of conventional risk factors (Bassan R et al Blood 2009)

< 0.01 % (10-4) during or on completion of initial induction therapy
→ good treatment outcome

> 1 % at the end of remission-induction therapy or ≥ 0.1 % at later times
→ very high risk of relapse

Techniques to measure MRD in ALL



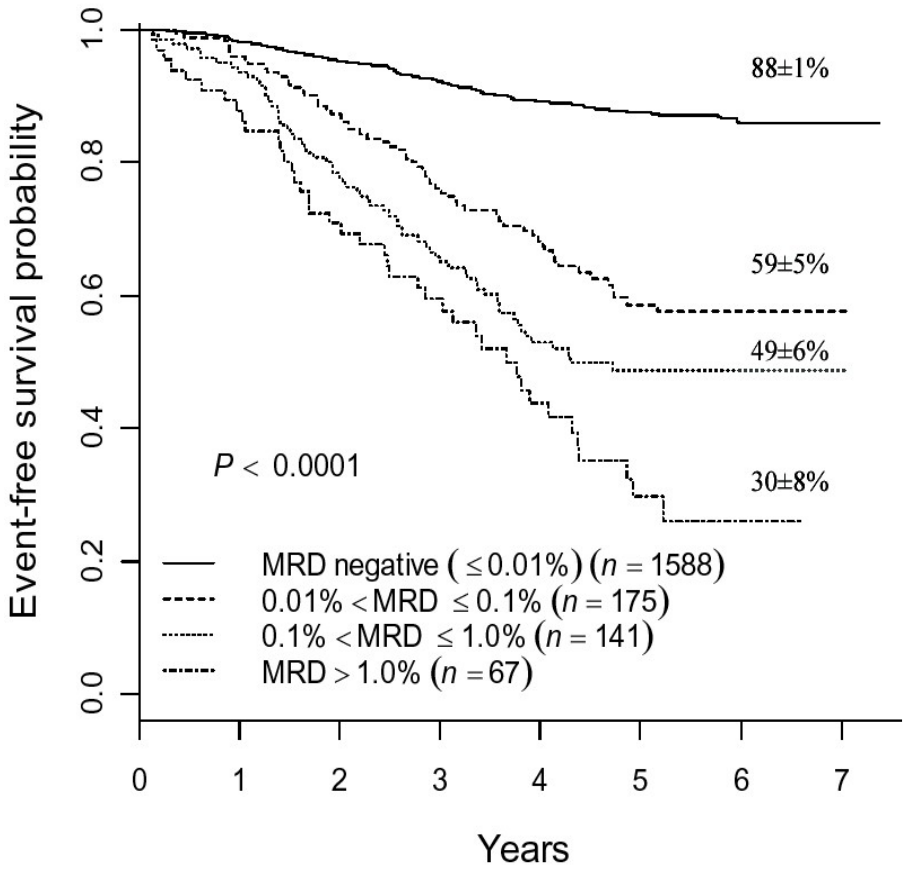
	Molecular IG/TR analysis (ASO RQ-PCR)	Multicolor Flow cytometry
PROS	+ Sensitivity + DNA based method (stability, shipment time) + **high degree of standardisation, published experience**	+ Fast + **Additional information on** background cells and **leukemia characteristics**
CONS	– Time consuming – Clonal evolution phenomena – need for patient specific reagents	– Sensitivity – Need for fresh material (max 48 hours) – Standardisation ('medical art') – Instability of markers

Extracted and adapted from 1. van Dongen JJM *et al. Blood* 2015;125:3996-4009
2. Lucio P *et al. Leukemia*. 2001;15:1185-92

Adapted from Bruggmann, EHA 2021

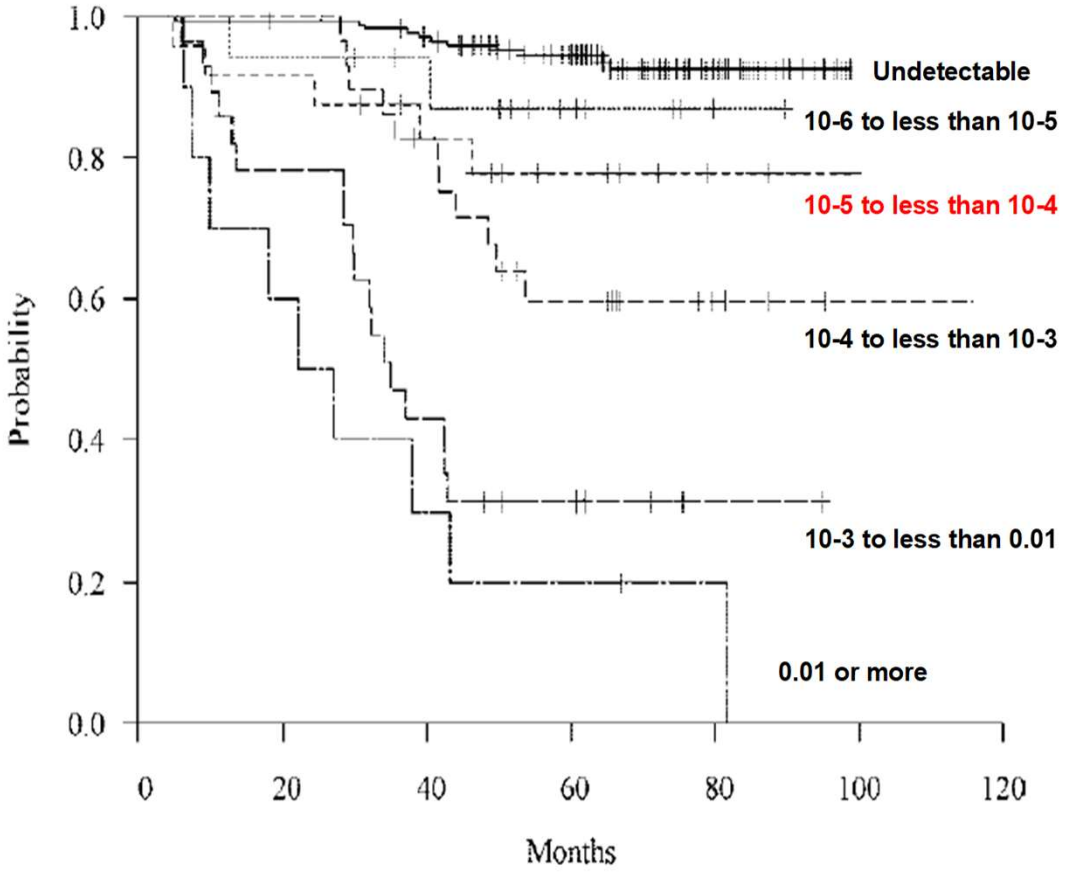
Minimal residual disease

MRD at day 29 by immunophenotyping



Borowitz MJ et al. Blood 2008

MRD at day 30 by RQ-PCR for IgH/TCR rearrangement



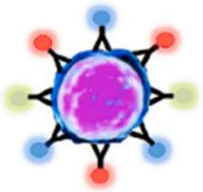
Zhou J. et al. Blood 2007

→ identify patients predicted to have superior outcome (**prognostic indicator**) who might be candidates for trials testing less intensive therapies (**individualization of the treatment**)

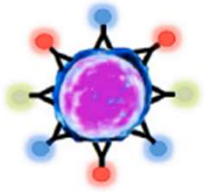
MRD

Consensus around 10-4 as the treshold for prognostication value

Flow Cytometry



Leukemia associated immunophenotype



Aberrancy from normal

NGS (ClonoSEQ)

Ig/TCR clonotype (Genetic barcode)

Sensitivity of MRD by MPFC depends :

- on the presence of a LAIP or aberrant phenotype

- on the numbers of cells analysed (10-50 events with the same IT to define a unique population)

→ 100000-500000 cells for 10-4 sensitivity

→ 1-5 x 10exp6 cells to reach 10-5 sensitivity

! time to run the assay

- 8-color tubes

→ next-generation flow cytometry (NGF) for 10-5 sensitivity

NGS can be used to monitor the Ig/TCR clonotype instead of ASO RQ-PCR

Sensitivity of 10-6 or more

It challenges the pertinence of the 10-4 treshold

Opportunity to quantify MRD in the peripheral blood

Minimal residual disease : limitations

- MRD after immunotherapy has not the same value as the MRD after chemotherapy
    - immunoprivileged sites
    - mesure extrinsec factors more than intrinsec factors

- MRD by MPFC can be difficult under immunotherapy (masked antigens)

- Lymphoblastic lymphoma without morphological invasion or minimal disseminated disease (MDD) in the bone marrow at the time of diagnosis

Consolidation (intensification) / re-induction

- Goal
  - eradicate drug-resistant residual leukaemic cells
  - reduce risk of relapse

- No consensus on the best regimen and duration

  - **Intensification** :
    - high dose methotrexate (→ 5 gr/m2) + mercaptopurine
    - High dosis of cytarabine

  - **Reinduction treatment** :
    - essentially a repetition of the initial induction therapy :
      - frequent pulses of vincristine and corticosteroids
      - prolonged high doses of asparaginase
      - cytarabine, cyclophosphamide, anthracyclines (in adults)

Intensification - Allogeneic HSCT

- Ultimate form of treatment intensification
- TBI = standard backbone for myeloablative conditioning in adults with ALL
- 12 (8?) Gy TBI applied in 6 fractions in combination with cyclophosphamide (Cy) 2x 60 mg/kg/d
- Risk of relapse decreases with allogeneic HSCT but the concomitant TRMortality decreases the potential survival benefit

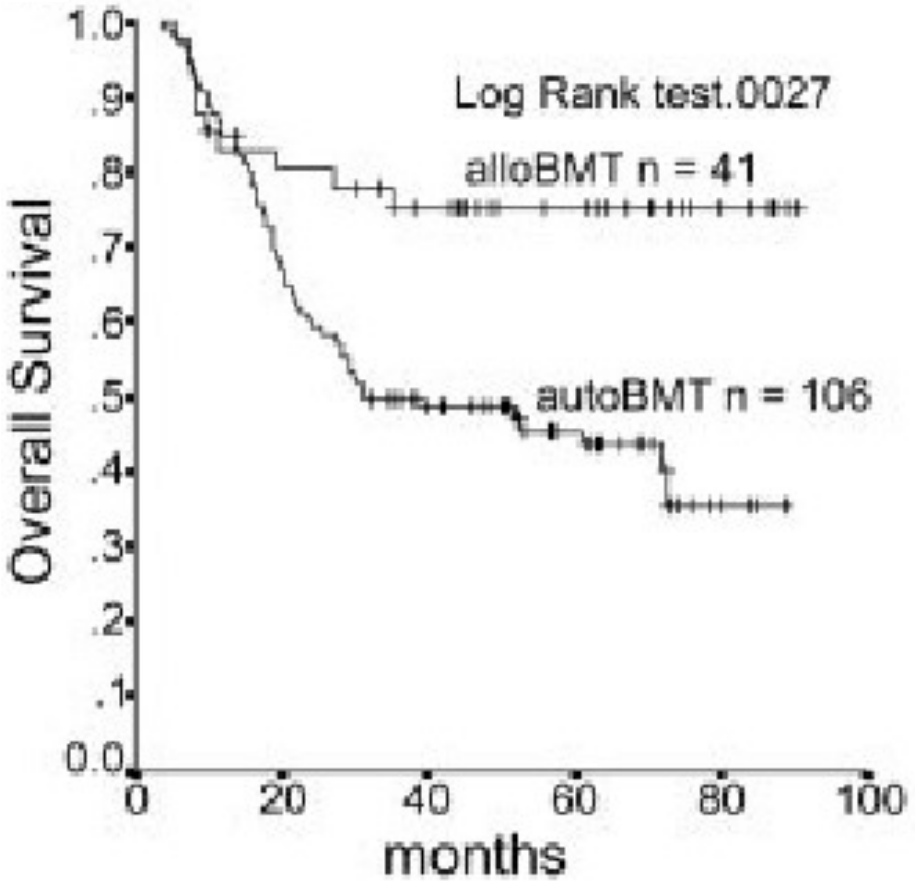
  ! Also to long term TRMorbidity
- > 35 y, in Ph- ALL, improved outcome seen in patients who undergo a MUD allogeneic HST is progressively lost when using myeloablative regimen
- Reduced intensity conditionning (RIC) are more frequently based on chemotherapy than irradiation

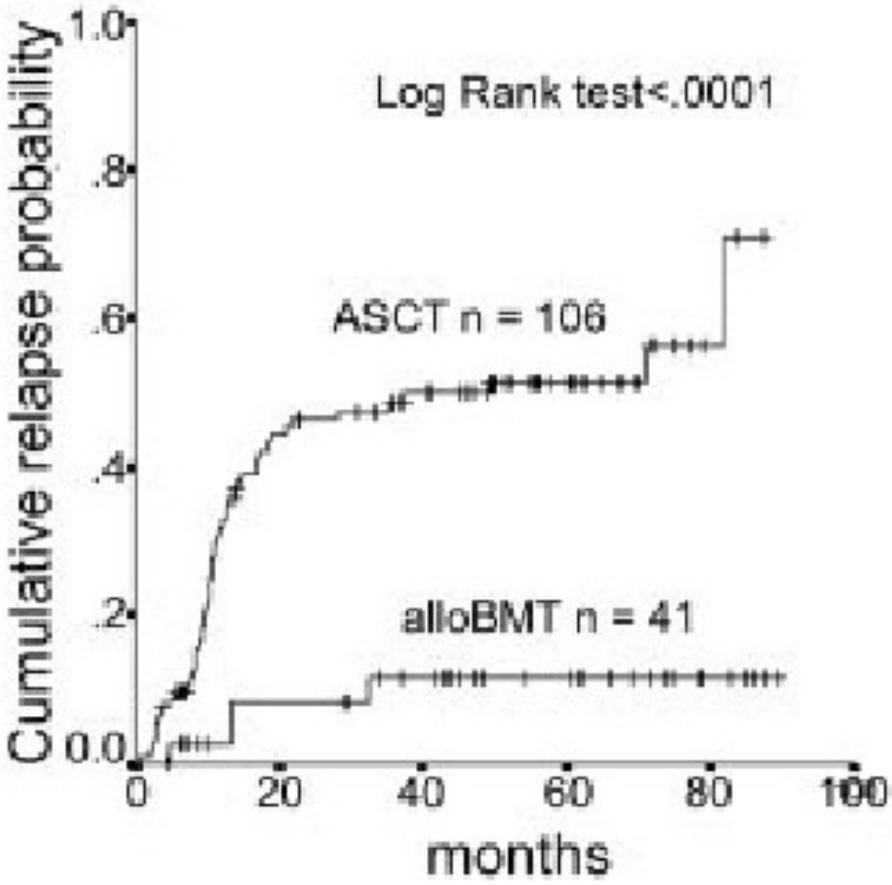
When to propose allogeneic HSCT?

- Inadequate MRD response is the most commonly accepted factor for alloHSCT
  = persistent MRD after induction (>10-3) or after the firsts blocs of consolidation (>10-4) or recurrent MRD at any time

- Allogeneic transplantation benefits some very-high-risk pediatric and adult patients
  - Clearly
    - Second remission (CR2)
  - Probably
    - *BCR-ABL+* ALL (a least in adults)
    - t(4;11) ALL
    - IKZF1 deleted B-ALL
    - Low hypodiploïdy, near triploïdy, complex karyotype (≥ 5 abnormalities)
    - ETP-ALL
    - NOTCH1/FBXW7 unmutated T-ALL
    - NRAS/KRAS mutated T-ALL, PTEN altereted T-ALL?
  - Less clear
    - WBC > 30.000? >100.000 in T-ALL?
    - Refractory ALL?
    - CNS ALL?

- Among adults with high risk ALL,
  - long-term DFS of 30 to 40 % have been obtained with **chemotherapy**,
  - as compared with 45 to 75 % with **allogeneic HCST**
    - » Hunault M. et al. Blood 2004
    - » Thomas X. et al. J. Clin. Oncol.





Patient characteristics:

at least one of the following features

- **> 35 y or**
- **B-ALL or**
- **WBC > 30000 or**
- **t(9;22) or t(4;11) or t(1;19) or**
- **failure to achieve CR**

if HLA identical sibling
→ Allo HSCT
If no HLA identical sibling or age > 50 Y
→ auto BMT

Hunault M. et al. Blood 2004

Maintenance treatment

- Non transplanted ALL patients generally require prolonged maintenance
  - for two years or more

- The base of most continuation regimens is a combination of
  - mercaptopurine given daily
  - methotrexate administered weekly
  - Vinca alcaloïds (once) + corticoïds (1 week) given monthly (during the 1ste year)

- Accumulation of increased intracellular concentrations of the active metabolites of methotrexate and mercaptopurine, and administration of this combination to the limits of tolerance, have been associated with improved clinical outcome

- The identification of inherited deficiency of **thiopurine-*S*-methyltransferase** among patients with hematopoietic toxic effects allows the clinician to lower the dose of mercaptopurine selectively without modifying the dose of methotrexate

CNS prevention treatment

- CNS = sanctuary site → CNS relapses

- Factors associated with an increased risk of CNS relapse include:
  - high risk genetic features,
  - T-cell immunophenotype,
  - a large leukemia-cell burden: hyperleukocytosis, extramedullary disease
  - presence of leukemia cells in the cerebrospinal fluid (even from iatrogenic introduction through a traumatic lumbar puncture)

- Based on:
  - cranial irradiation (second cancers, late neurocognitive deficits, and endocrinopathy, …) … now avoided in most pediatric protocols
  - largely been replaced by
    - intrathecal therapy: methotrexate, cytarabine, corticoïds

      ! traumatic lumbar punctures
    - systemic chemotherapy: HD methotrexate, HD cytarabine, dexamethasone

CNS+ ALL

- **At diagnosis**
  - **> 5 WBC/µL with typical morphology (FCM)**
  - **Incidence: +/- 7%**
  - **Treatment (not standardized):**
    - **intrathecal drug(s) twice weekly until clearance of blast cells**
    - **+"intensive" systemic (HD methotrexate, …, TBI before alloHSCT)**
    - **CNS irradiation**

- 2-10% of **relapses** restricted to the CNS
  - outcome depends on the duration of remission,
  - T-cell ALL or prior cranial irradiation are bad factors

Ph+ ALL

Before imatinib

- Allogeneic HSCT conferred similar OS and relapse rates for Ph+ patients compared with those with normal cytogenetics supporting a graft-versus-leukemia (GVL) effect
  - » **Doney K, Biol Blood Marrow Transplant. 2003;9:472-481**
- **but**
  - The incidence of Ph+ ALL increases with age (+/- 50% at 50 y, …)
  - Availability of a donor
  - Low rate of remission
  - Relapse before transplantation

With imatinib

- Given during induction → CR rate increase from approximately 60% to >90% → more HSCT
- Given after transplantion (preemptive or preventive)→ decreases relapse rate

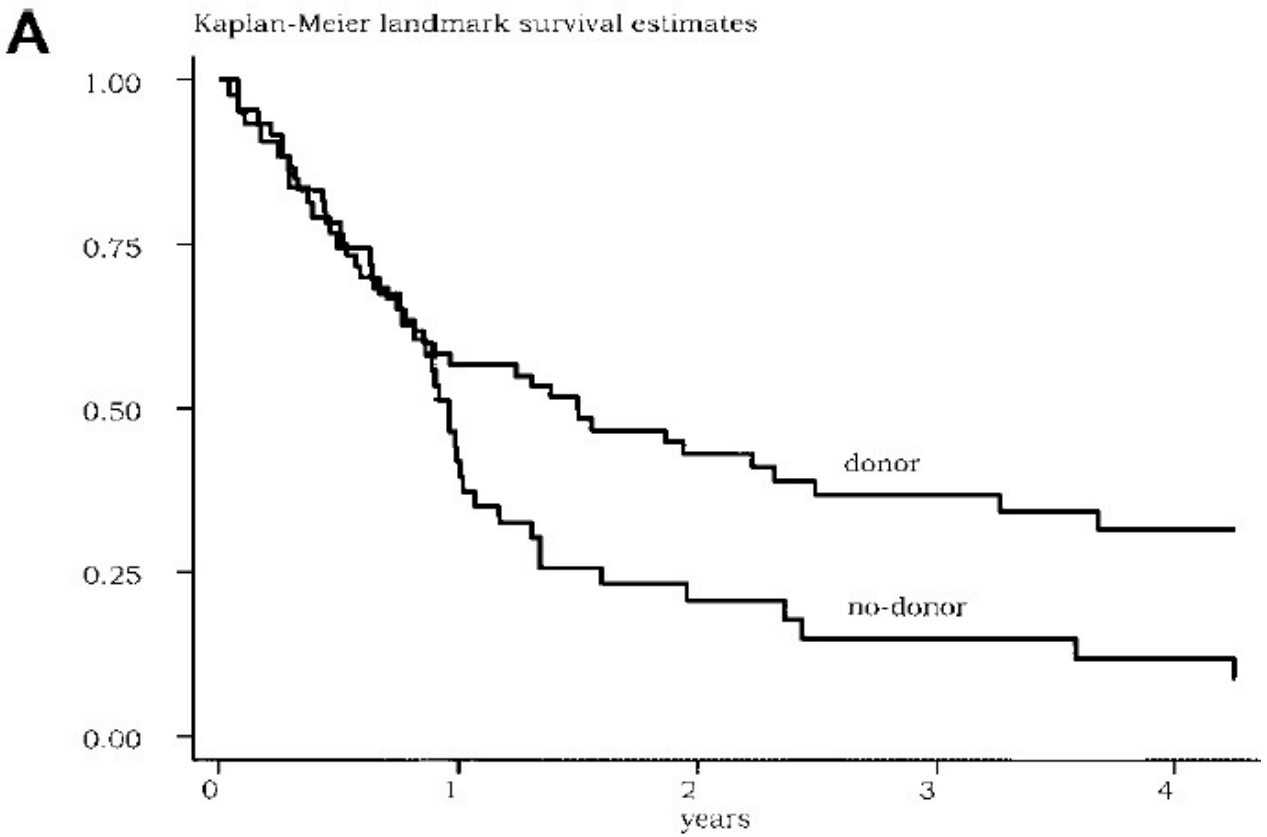
→ Imatinib + conventional chemotherapy provided results comparable with allogeneic HSCT
- » **de Labarthe A, Blood 2007**

- but clinical resistance to imatinib develops
- kinase domain mutations of BCR-ABL1 give rise to relapse (! T315I BCR-ABL1 mutation)
  - » **Pfeifer H, Blood 2007**

→ **Still recommended to proceed to HSCT in adults Ph+ ALL whenever possible**

New TKI : dasatinib, ponatinib (active against the T315I BCR-ABL1 mutation)

Ph+ ALL

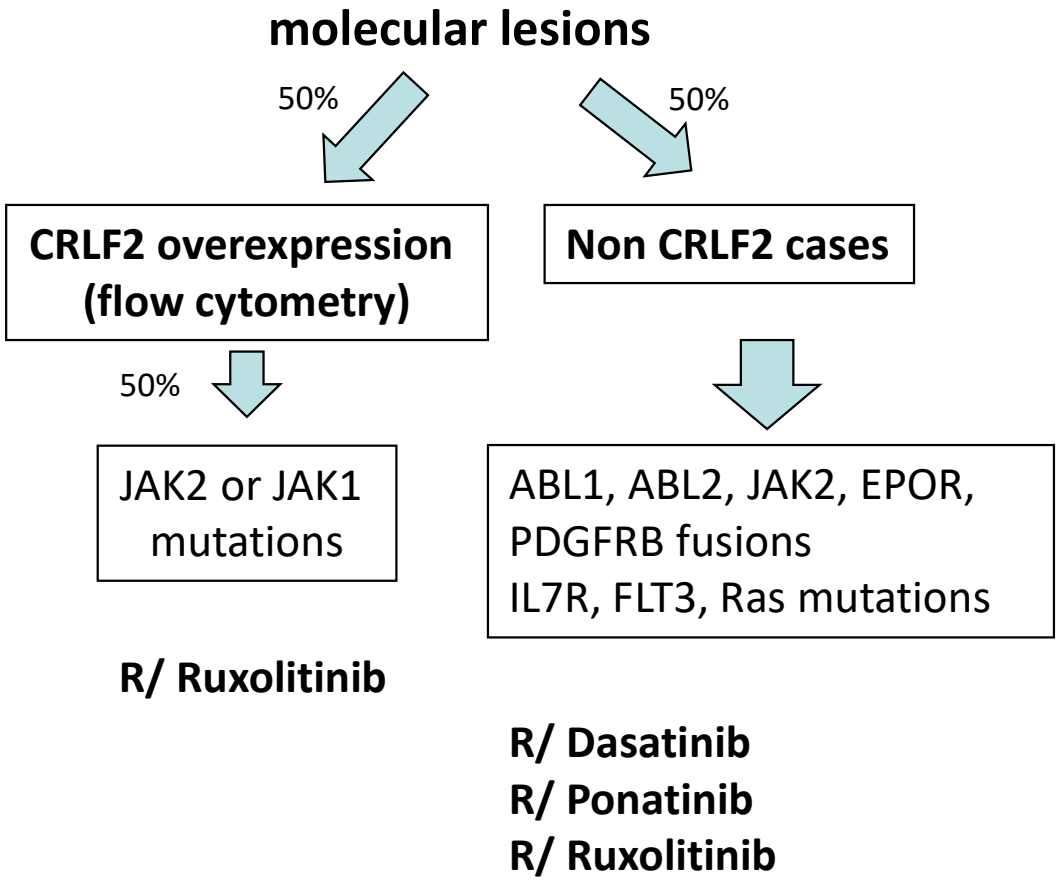


Dombret et al. Blood 100 p2357, 2002

Table 4 Published frontline trials of TKI-based regimens in adult Ph-positive ALL

TKI	*N*	Median age, years [range]	CR rate, %	Induction mortality, %	Overall CMR rate, %	HSCT rate, %	RFS rate, %	OS rate, %
Intensive chemotherapy + TKI								
Imatinib	54	51 [17-84]	93	2	45	30	43 (5-year)	43 (5-year)
Imatinib	169	42 [16-64]	92	5	NR	72	50 (4-year)	38 (4-year)
Dasatinib	72	55 [21-80]	96	4	60	17	44 (5-year)	46 (5-year)
Nilotinib	90	47 [17-71]	91	9	86	70	72 (2-year)	72 (2-year)
Ponatinib	86	46 [21-80]	100	0	86	21	84 (3-year)	78 (3-year)
Lower-intensity chemotherapy + TKI								
Imatinib	135	49 [18-59]	98	9	28	62	EFS 37 (5-year)	46 (5-year)
Dasatinib	71	69 [59-83]	96	4	24	10	EFS 28 (5-year)	36 (5-year)
Dasatinib	60	42 [19-60]	100	0	19	42	49 (3-year)	58 (3-year)
Nilotinib	79	65 [55-85]	94	2	58	16	42 (4-year)	47 (4-year)
Nilotinib	60	47 [18-59]	98	2	NR; MMR 80	52	85 (1-year)	96 (1-year)
Steroids + TKI								
Imatinib	30	69 [61-83]	100	0	4	NR	48 (1-year)	74 (1-year)
Dasatinib	53	54 [24-77]	100	0	15	34	51 (2-year)	69 (2-year)
Ponatinib	42	69 [27-85]	95	0	46	NR	NR	88 (1-year)
Blinatumomab + TKI								
Dasatinib	63	55 [24-82]	97	2	36	19	88 (1-year)	95 (1-year)

Ph-like ALL

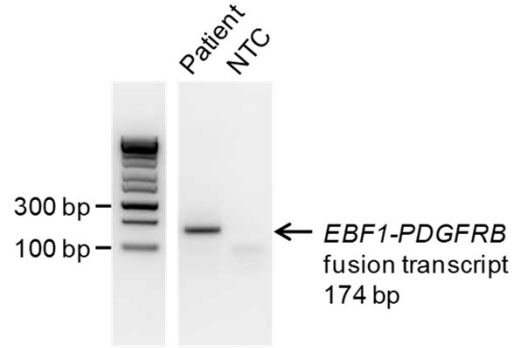


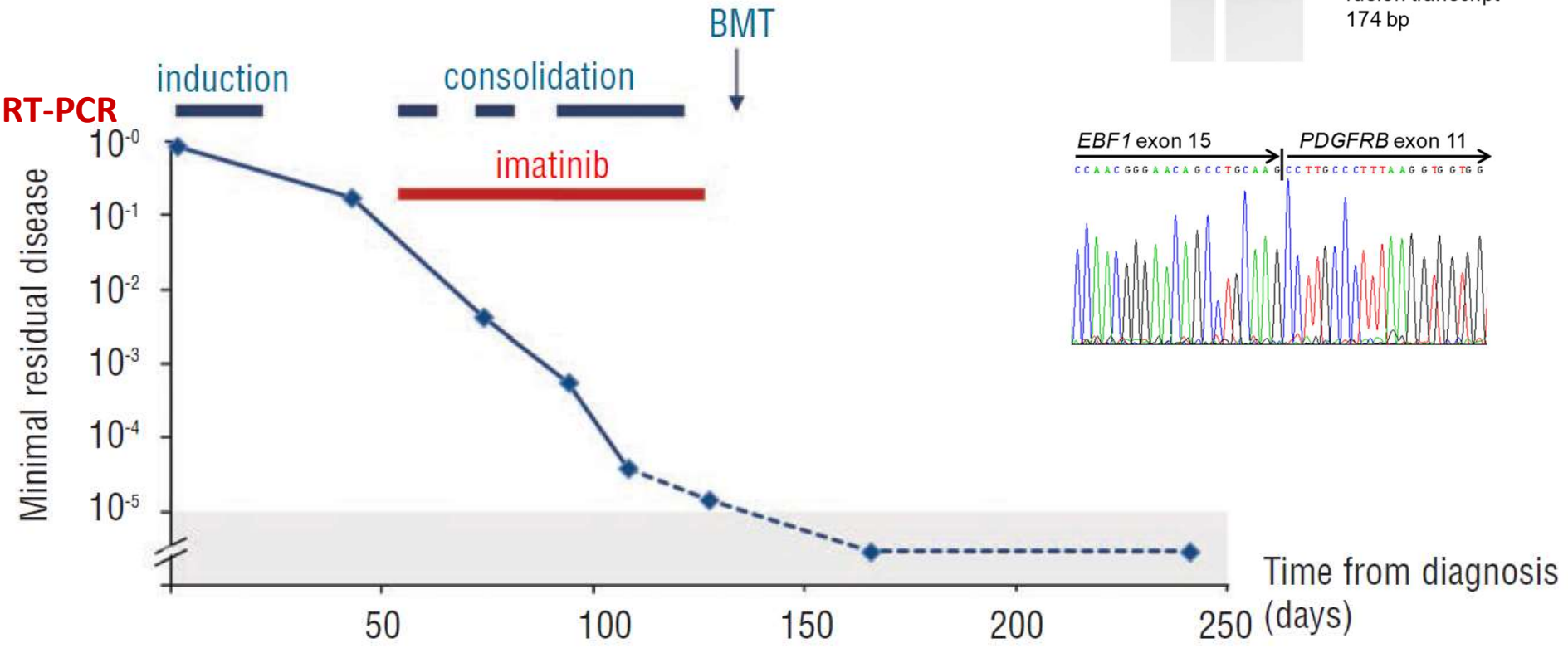
Kinase	Tyrosine Kinase Inhibitor	Number of Gene Partners	Fusion Partner Genes
ABL1	Dasatinib	12	*CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1*
ABL2	Dasatinib	3	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Dasatinib	3	*SSBP2, MEF2D, TBL1XR1*
PDGFRB	Dasatinib	7	*ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8*
PDGFRA	Dasatinib	1	*FIP1L1*
CRLF2	JAK2 inhibitor	2	*IGH, P2RY8*
JAK2	JAK2 inhibitor	19	*ATF7IP, BCR, EBF1, ETV6, PAX5, PCM1, PPFIBP1, RFX3, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, GOLGA5, SMU1, HMBOX1, SNX29, ZNF340*
EPOR	JAK2 inhibitor	4	*IGH, IGK, LAIR1, THADA*
TSLP	JAK2 inhibitor	1	*IQGAP2*
DGKH	Unknown	1	*ZFAND3*
IL2RB	JAK1/JAK3 inhibitor	1	*MYH9*
NTRK3	TRK inhibitor	1	*ETV6*
PTK2B	FAK inhibitor	3	*KDM6A, STAG2, TMEM2*
TYK2	TYK2 inhibitor	3	*MYB, SMARCA4, ZNF340*
FLT3	FLT3 inhibitor	1	*ZMYM2*
FGFR1	Sorafenib/dasatinib	1	*BCR*
BLNK	?SYK/MEKi	1	*DNTT*

Pui CH et al. Philadelphia chromosome-like ALL. Clinical Lymphome, Myeloma & Leukemia, 2017

Ph-like ALL

Fusion *EBF1-PDGFRB*



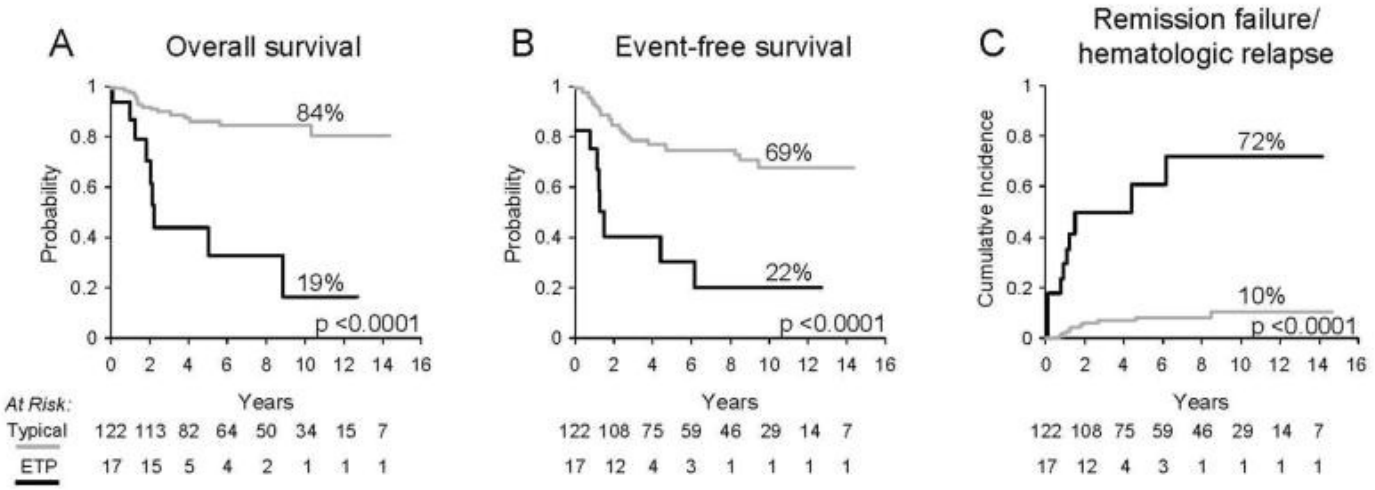


Lengline E et al. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor ALL with EBF1-PDGFRB fusion. Haematologica. 2013

ETP ALL (early T-cell precursor ALL)

A subset of very high-risk ALL : less NOTCH1 mut, more MRD+

More prevalent in adults



- CD1a negative (<5%)
- CD8 negative (< 5%)
- No or weak CD5 (<75%)
- Presence of one or more of myeloïd/ stem cell marker (> 25%)
  - CD117, CD34, HLA-DR, CD13, CD33, CD11b, CD65
- Unrearranged TCRγ

→ allo-SCT in CR1

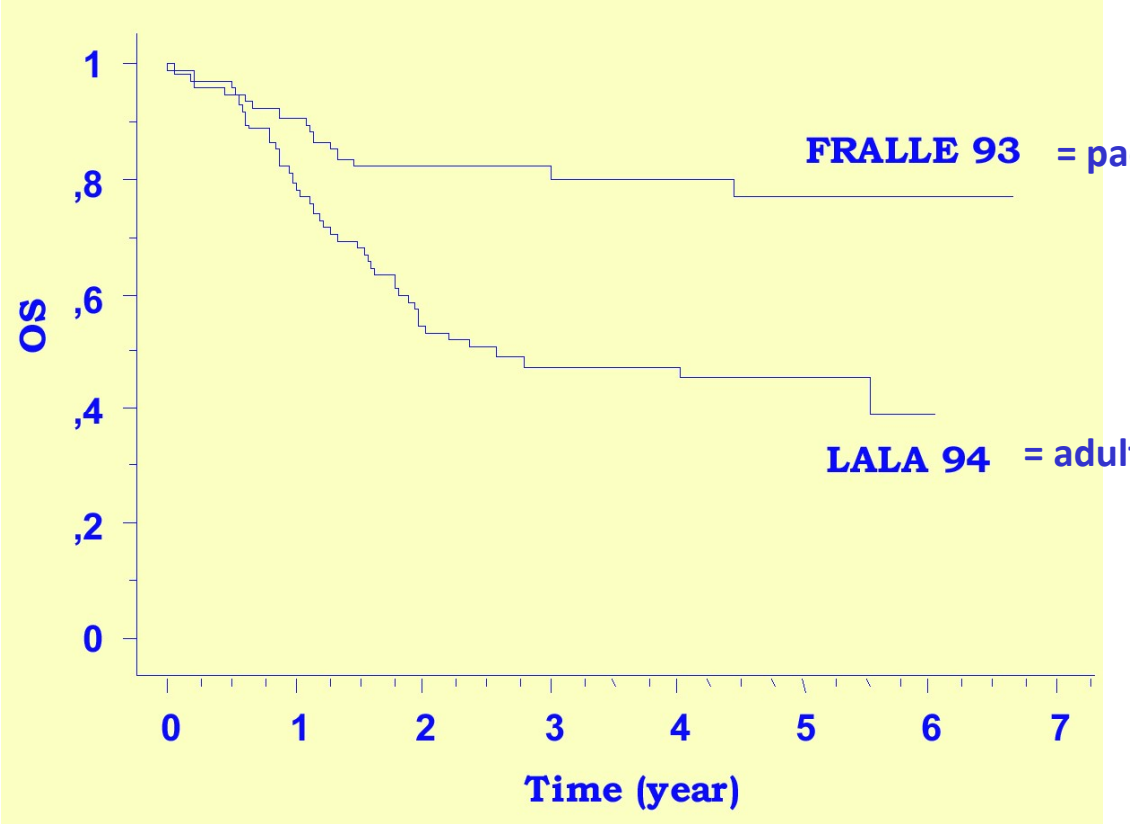
Myeloid based regimen?

Targetable mutations:

- FLT3 (35%)
- IDH1/2 (+/- 15%)
- NRAS
- Hyperactivation of JAK-STAT pathway → ruxolitinib?
- preferentially sensitive to the BCL-2 inhibitor, venetoclax

Coustan-Smith E et al. Lancet Oncol 2009; 10(2): 147-156

Young adult ALL (15-20 y)



Nicolas Boissel et al. JCO. 2003

Paediatric treatments are more effective
Better adherence by patients, parents, and doctors in a paediatric environment

→ nowadays, (young) adult protocols are “paediatric inspired” (more asparaginase, vincristine, corticoïds)

Elderly patient ALL (> 55 y → > 65 y)

- Biological differences in the spectrum of ALL (more Ph+ ALL, less T-ALL, less favorable cytogenetic features)
- Coexisting medical disorders → decreased tolerance for chemotherapy

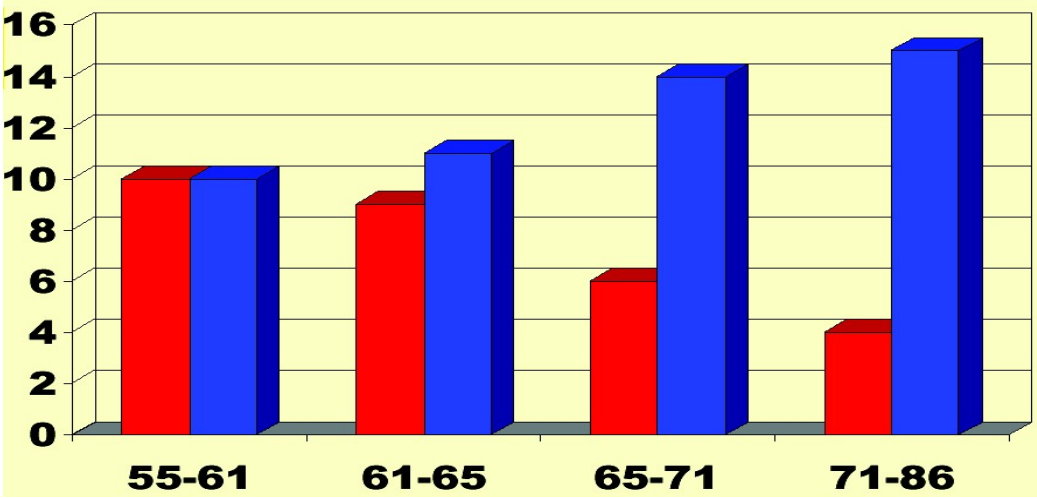
  High mortality rate during induction if treated according to young adult programs (corticoides- vincristine, **l-asparaginase**,…)
- Since TKI therapy area → Ph+ ALL is “a good prognostic factor” in the elderly
  - TKI + minimal chemotherapy (vincristine, corticoïds)
  - Chemo free regimens (ponatinib + blinatumomab)
- New formulations of old-drugs (*PEG-asparaginase, liposomal cytarabine, vincristine, liposomal and PEGylated anthracyclines, …)* : not really less toxic
- Introduction in first line of the new very active drugs : blinatumomab and inotuzumab

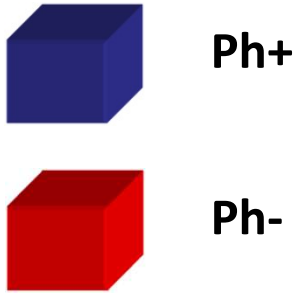
Elderly patient ALL (> 55 y → > 65 y)

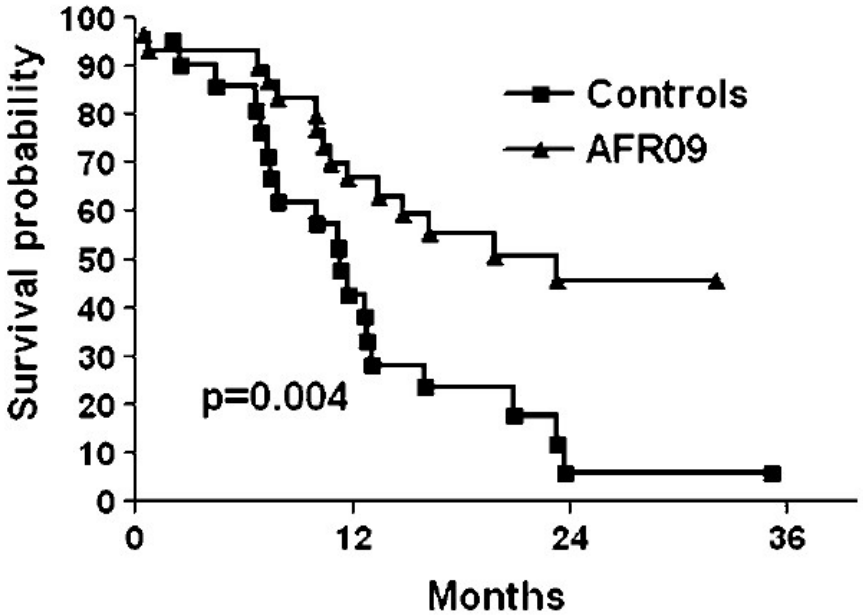
Table 3 Challenges in treating older patients with ALL

Clinical factors
Decreased performance status
Increased number of comorbidities
Decreased organ function
Polypharmacy
Frequent dose reductions, delays, or omission
Higher risk of adverse events (infections, neurotoxicity, secondary malignancies)
Biological factors
Increased incidence of adverse-risk karyotype (e.g., low hypodiploidy/near-triploidy, t(9;22), t(4;11), complex cytogenetics)
Lower incidence of favorable-risk karyotype (hyperdiploidy, t(12;21), ETV6-RUNX1)
Higher incidence of adverse risk molecular signatures (Philadelphia chromosome-like, TP53 mutation)
Social factors
Inadequate caregiver and/or social support
Transportation/travel difficulties to tertiary centers
Other factors
Perceived lack of benefit of receiving anti-leukemia therapy rather than supportive/hospice care

The elderly patient (> 55 y → > 65 y)







Delannoy et al. Leukemia 2006

The relapsing patient

The length from first CR (> vs < 2 years) has a major impact on outcome

No standard rescue therapy (Hyper-CVAD, clofarabine based, …)

CR rates with various regimens ± 50%

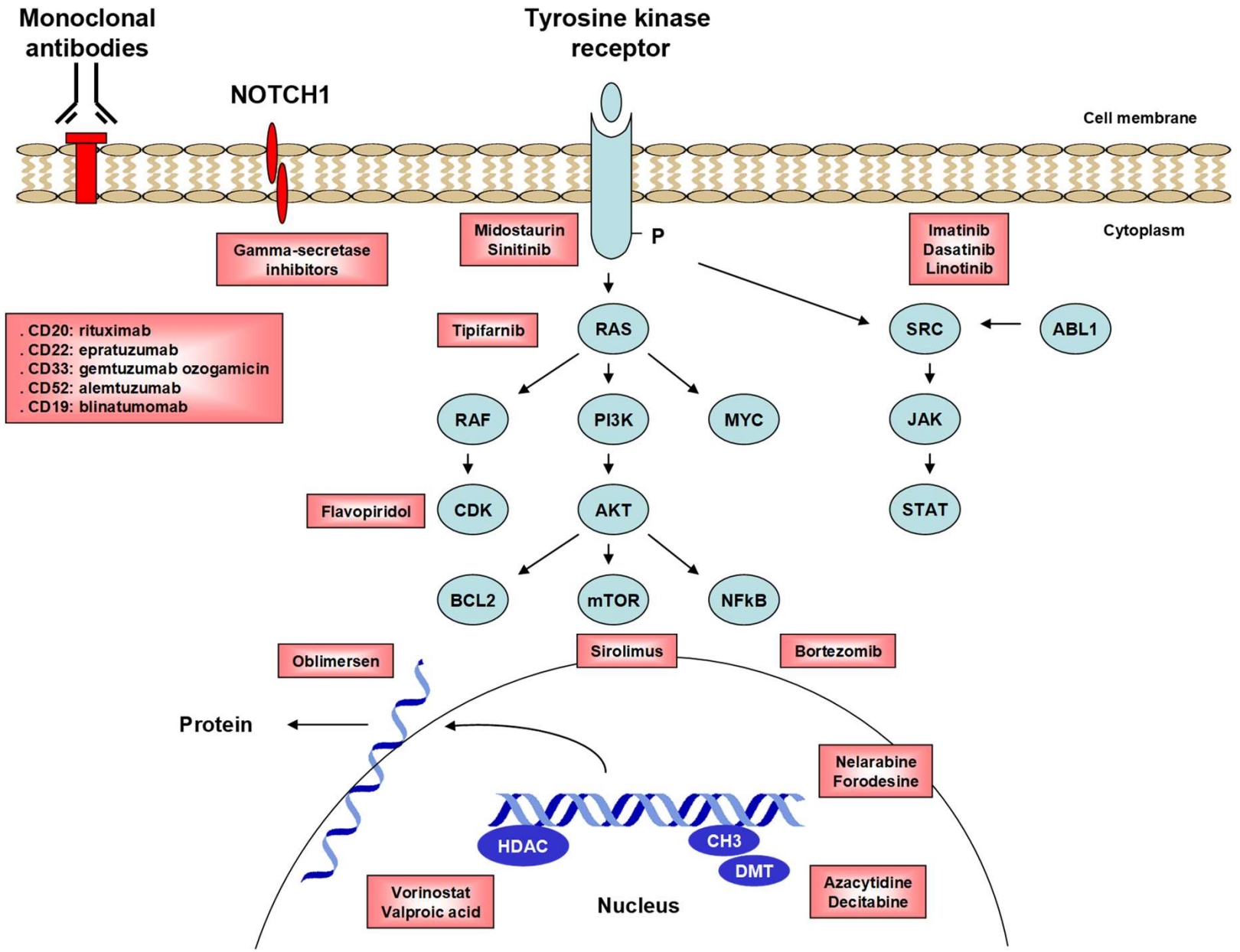
CR duration ± 2-5 months

Allogeneic transplantation: whenever feasible (± 20-30% long-term DFS)

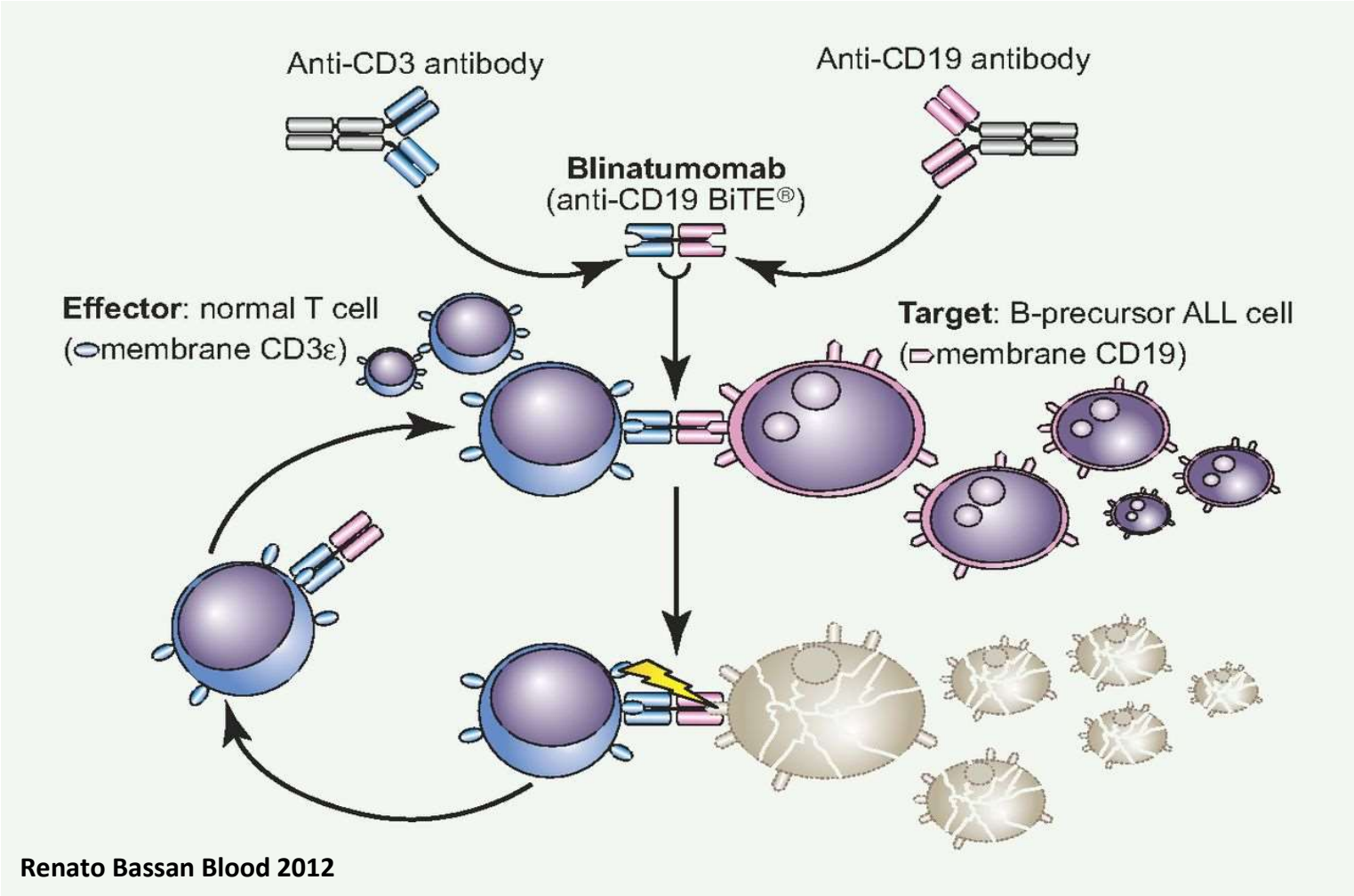
New drugs: blinatumomab, inotuzumab, CART-cells

!!!!! T-ALL →venetoclax, HDAC & HMA, ruxolitinib

New drugs

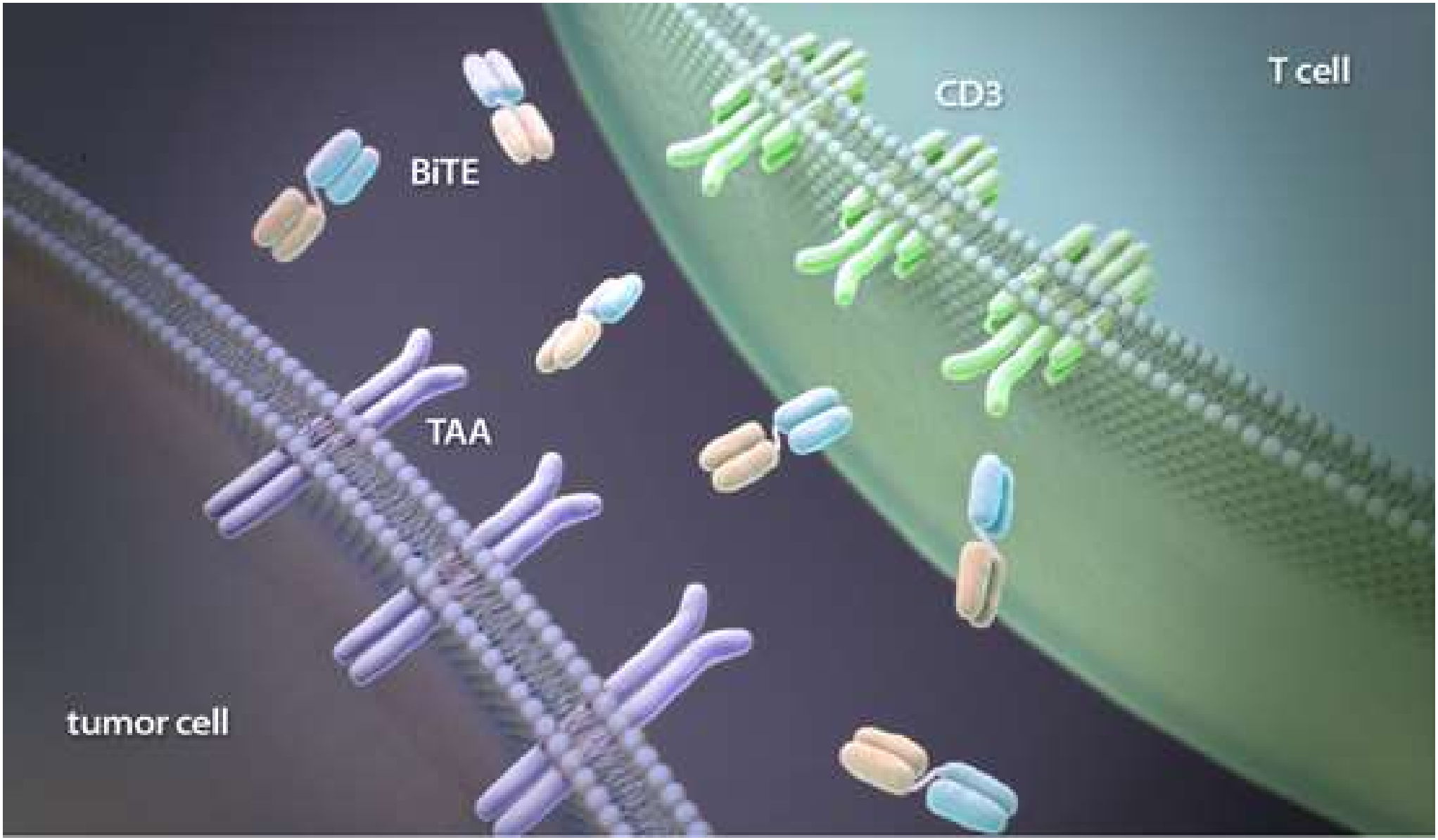

Monoclonal antibodies
NOTCH1
Tyrosine kinase receptor
Cell membrane
Cytoplasm
Gamma-secretase inhibitors
Midostaurin
Sinitinib
P
Imatinib
Dasatinib
Linotinib
. CD20: rituximab
. CD22: epratuzumab
. CD33: gemtuzumab ozogamicin
. CD52: alemtuzumab
. CD19: blinatumomab
Tipifarnib
RAS
SRC
ABL1
RAF
PI3K
MYC
JAK
Flavopiridol
CDK
AKT
STAT
BCL2
mTOR
NFkB
Oblimersen
Sirolimus
Bortezomib
Protein
Nelarabine
Forodesine
HDAC
CH3
DMT
Azacytidine
Decitabine
Vorinostat
Valproic acid
Nucleus

Blinatumomab: mode of action

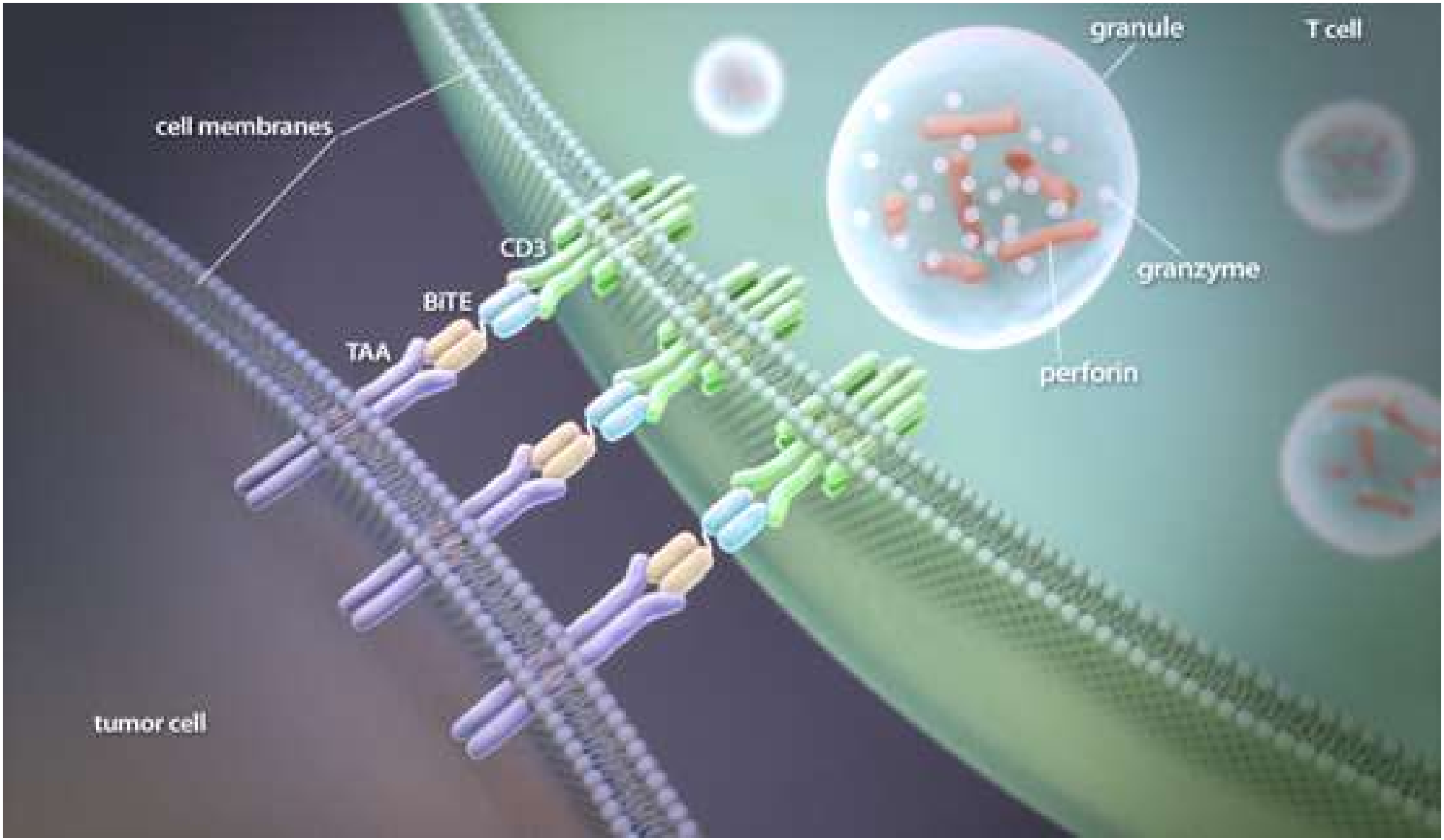


Blinatumomab (MT103) is a Bispecific T-cell Engager (BiTE®) antibody designed to direct cytotoxic T-cells to CD19 expressing cancer cell

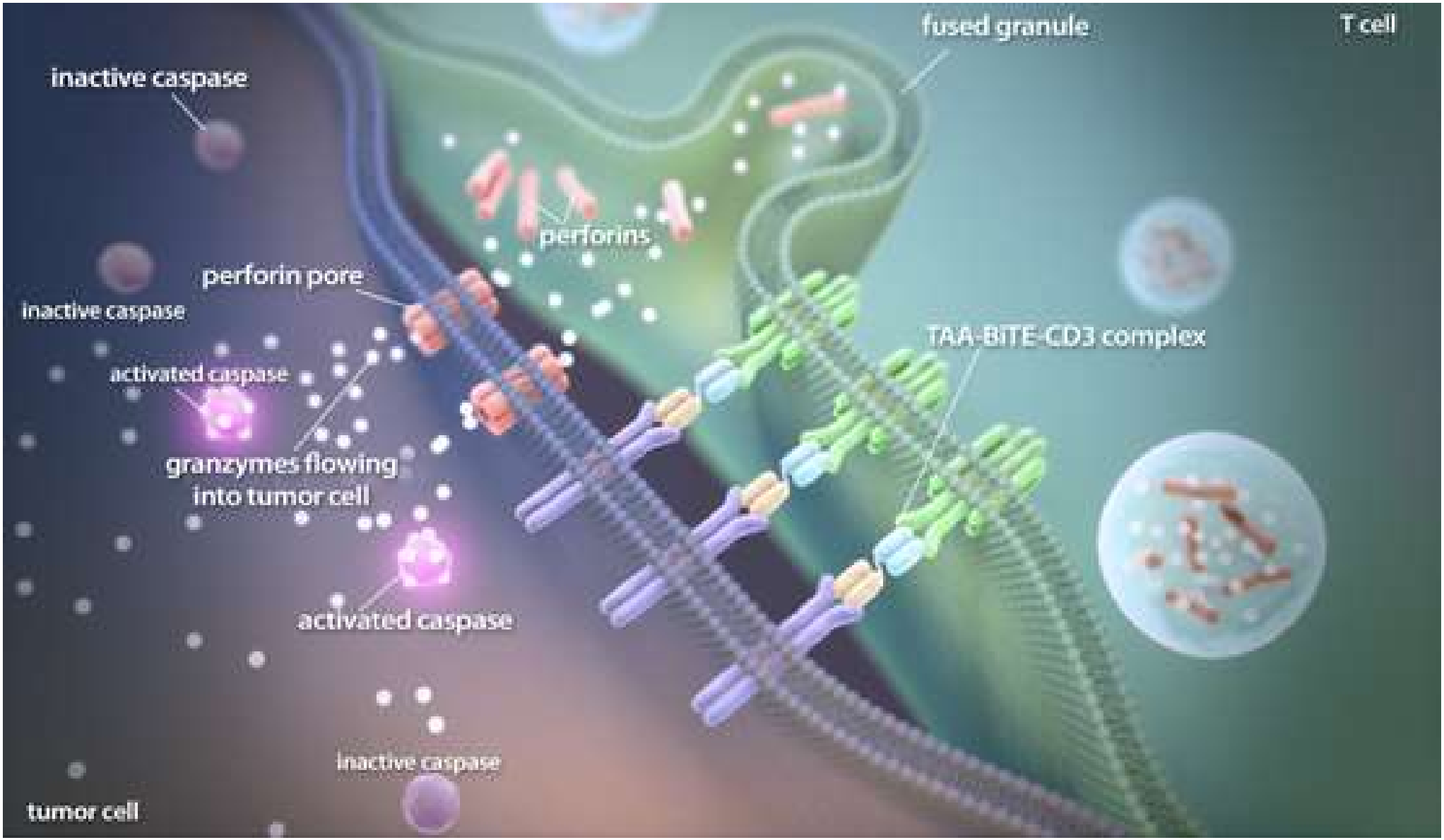
Blinatumomab: mode of action



Blinatumomab: mode of action



Blinatumomab: mode of action



Blinatumomab: mode of action

- 80% of MRD eradication (BLAST study)
- +/- 40% of CR rate as single agent in R/R ALL (TOWER)
- Blinatumomab is a **non genotoxic**, immunotherapeutic, **mutation agnostic**, well tolerated, **very active drug** opening a large spectrum of applications :

  ➔bridge to allo

  ➔consolidation post-allo

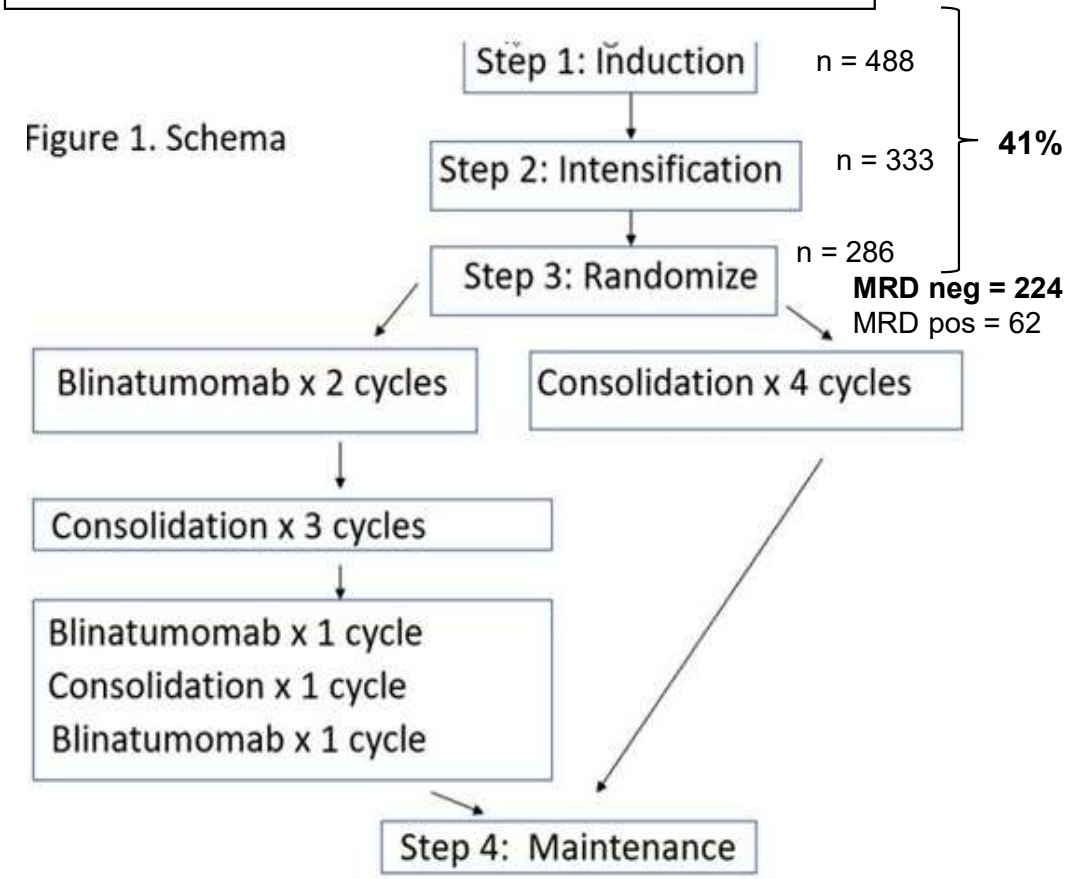
  ➔association to first line strategy as post remission therapy (ECOG-ACRIN E1910 study)

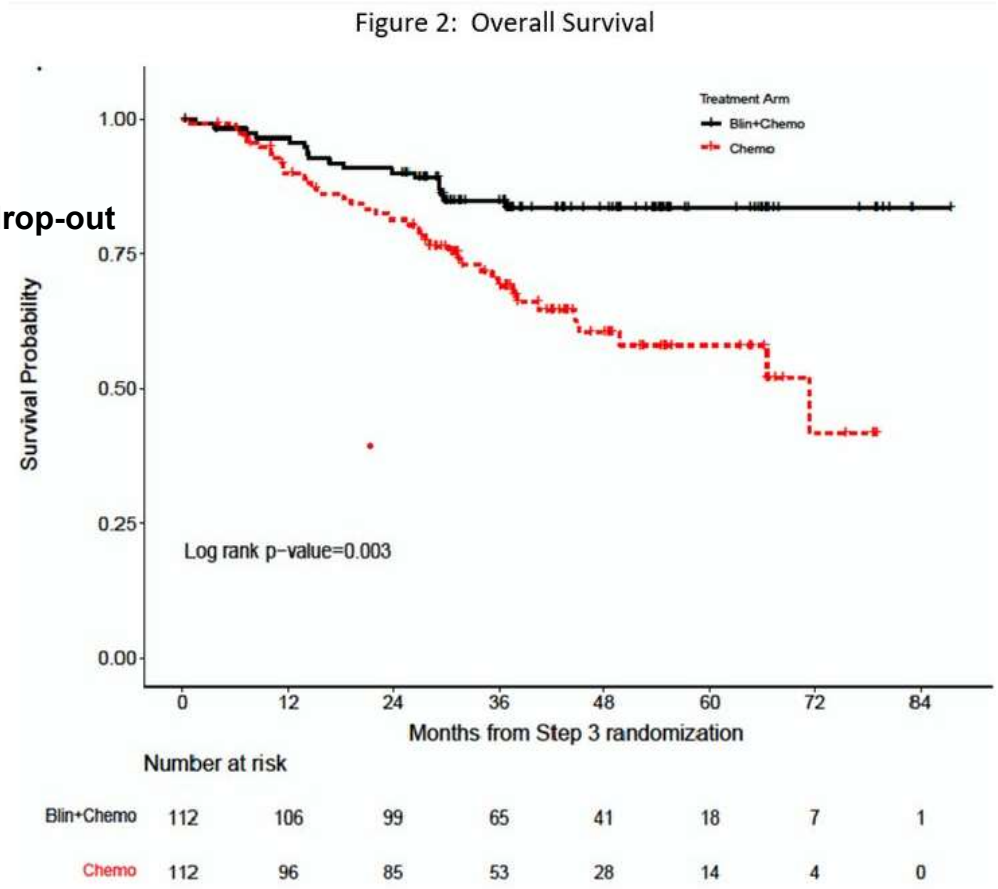
  ➔ incorporation into the induction course to decrease toxicity in elderly patients (Goldengate study)

ECOG-ACRIN E1910 study : association of blinatumomab to first the line strategy as post remission therapy

Age : 30-70 years
Primary endpoint : OS among MRD neg pt

Figure 1. Schema

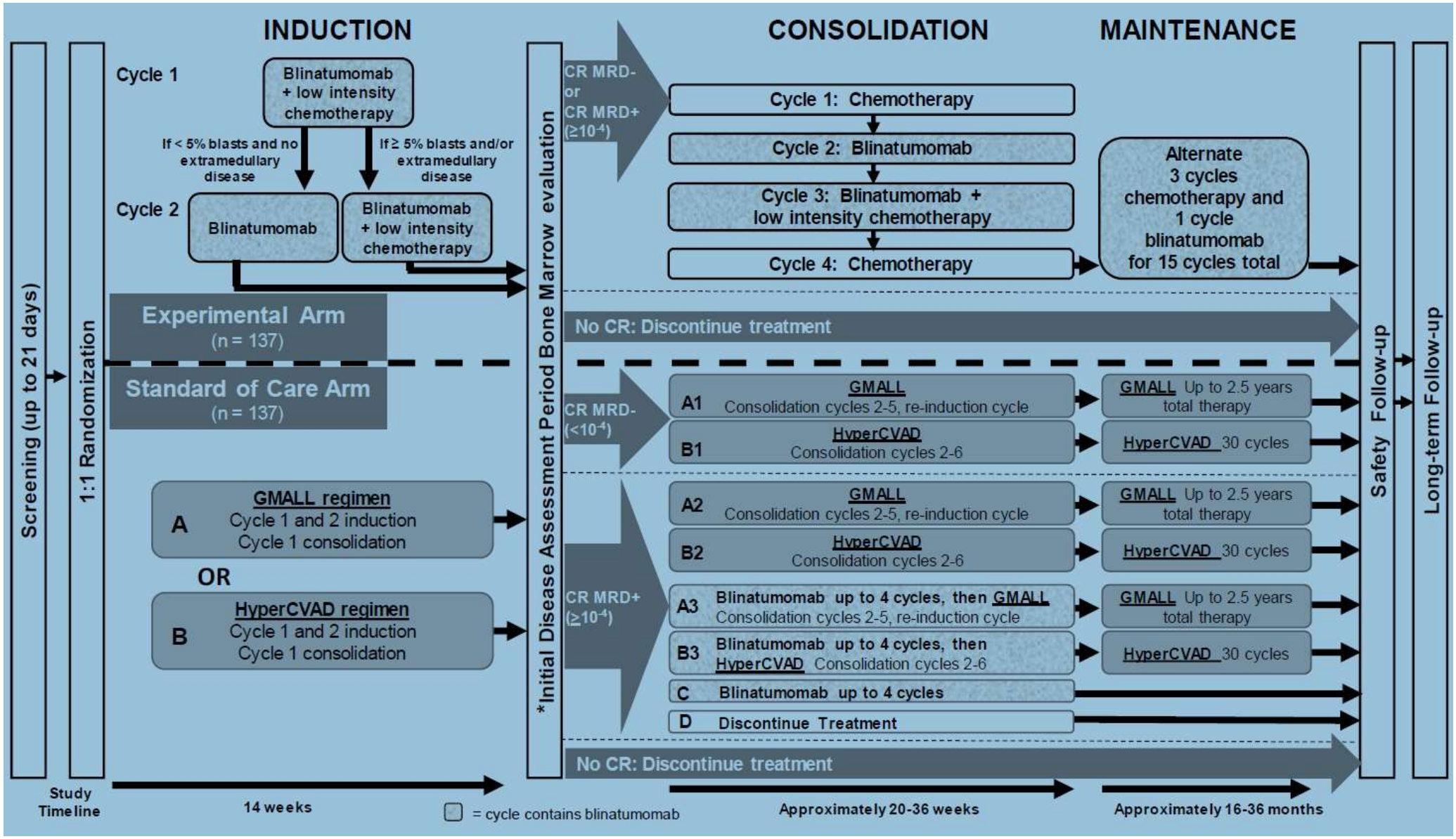




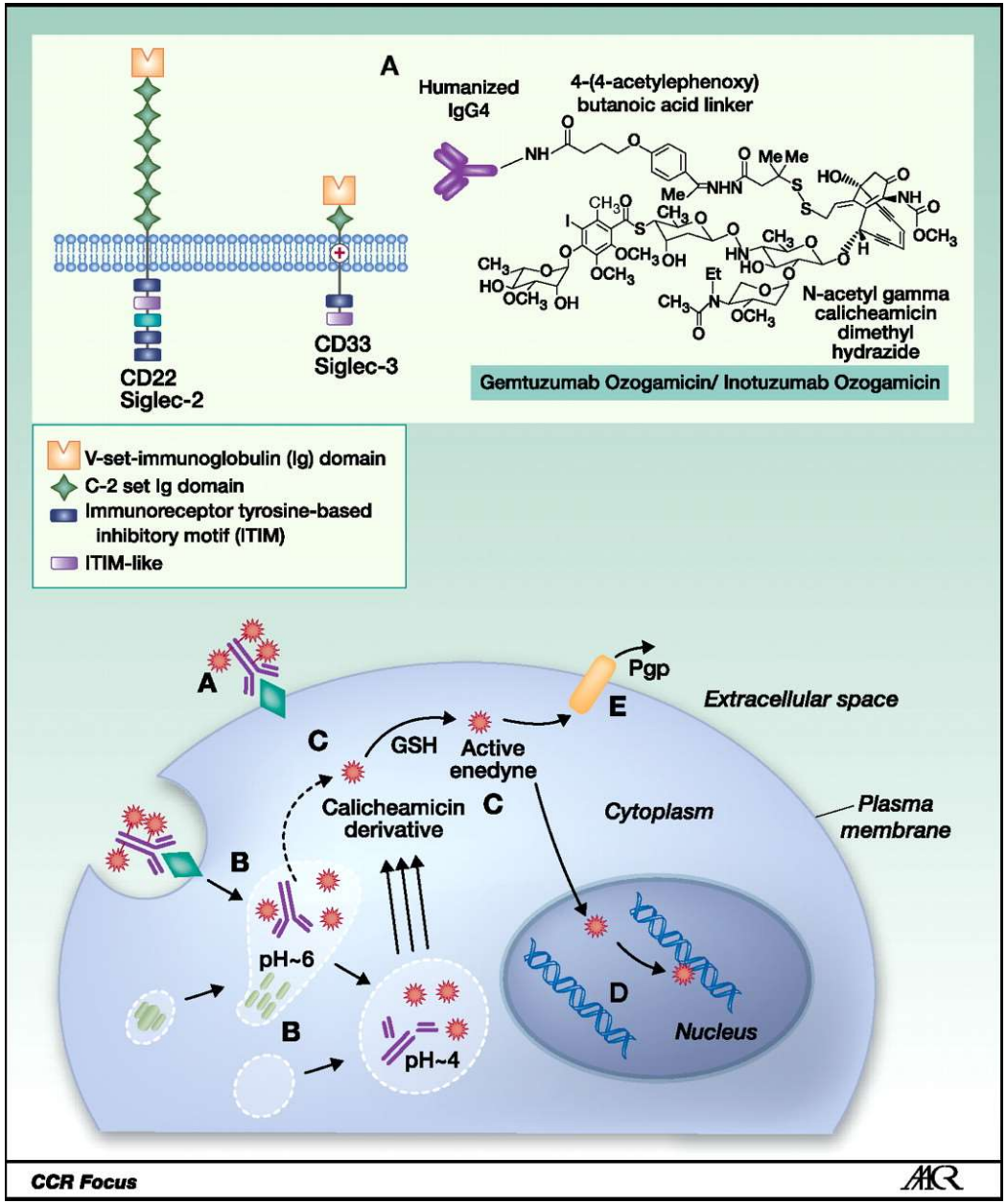
Mark R Litzow et al ASH 2022

Consolidation therapy with blinatumomab improves OS in newly diagnosed adult patients with B-lineage acute lymphoblastic leukemia in MRD negative remission

Goldengate study : blinatumomab alternating with low-intensity chemo vs standard of care for older adults with newly diagnosed ALL



Inotuzumab: mode of action



Alejandro D. Ricart Clin Cancer Res 2011;17:6417-6427

The antibody-drug conjugate is internalized upon binding to CD22

Calicheamicin is released inside the tumor cell

Calicheamicin binds to DNA, inducing double-stranded DNA breaks

Development of DNA breaks is followed by apoptosis of the tumor cell

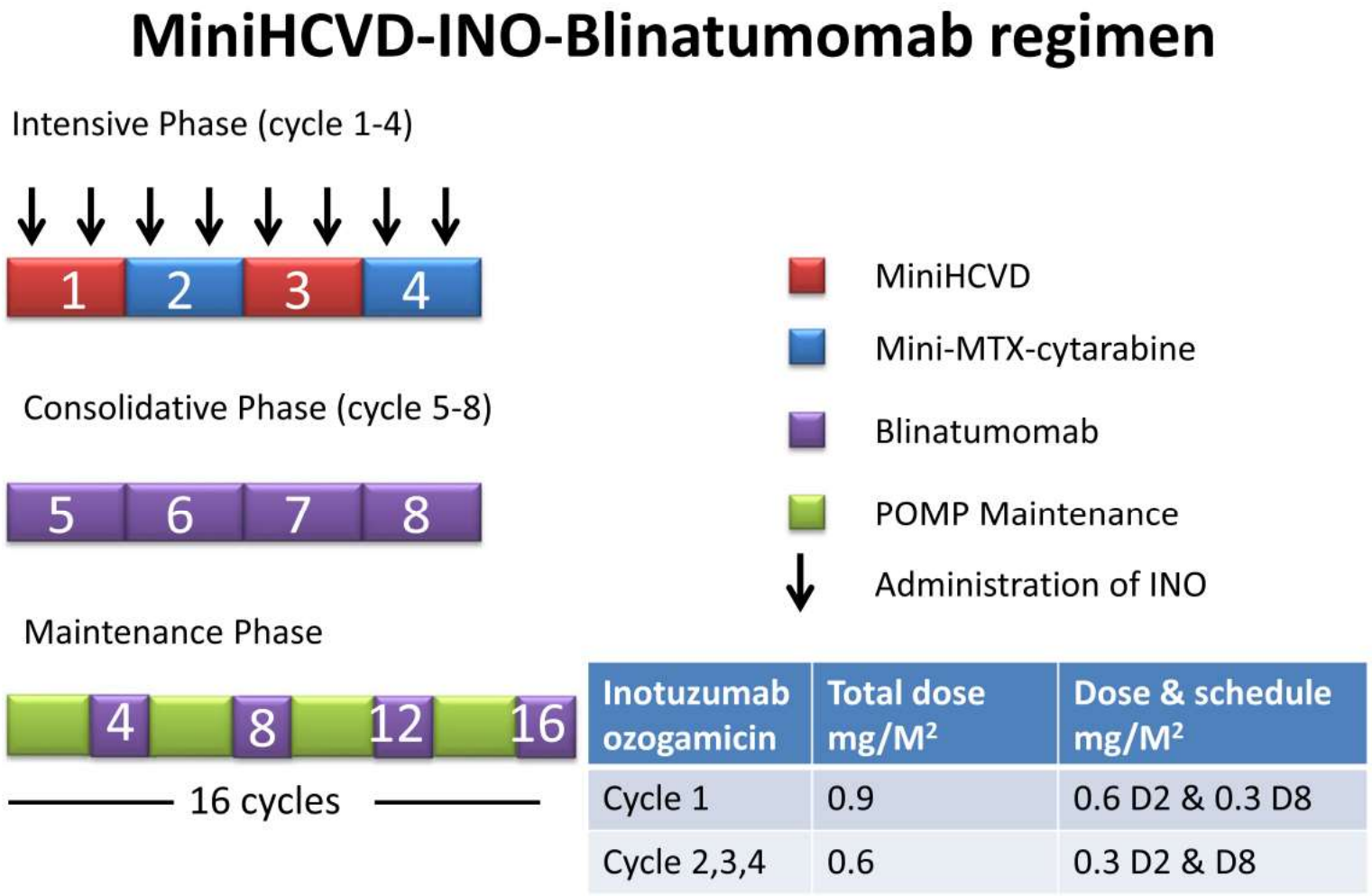
Very active drug in monotherapy in R/R B-ALL: +/- 80% CR

→ Ongoing trials incorporeting inotuzumab to less intensive chemo schedules in first line setting

! Veno-occlusive disease

Table 2 Published trials of combination of novel agents in adult Ph-negative ALL

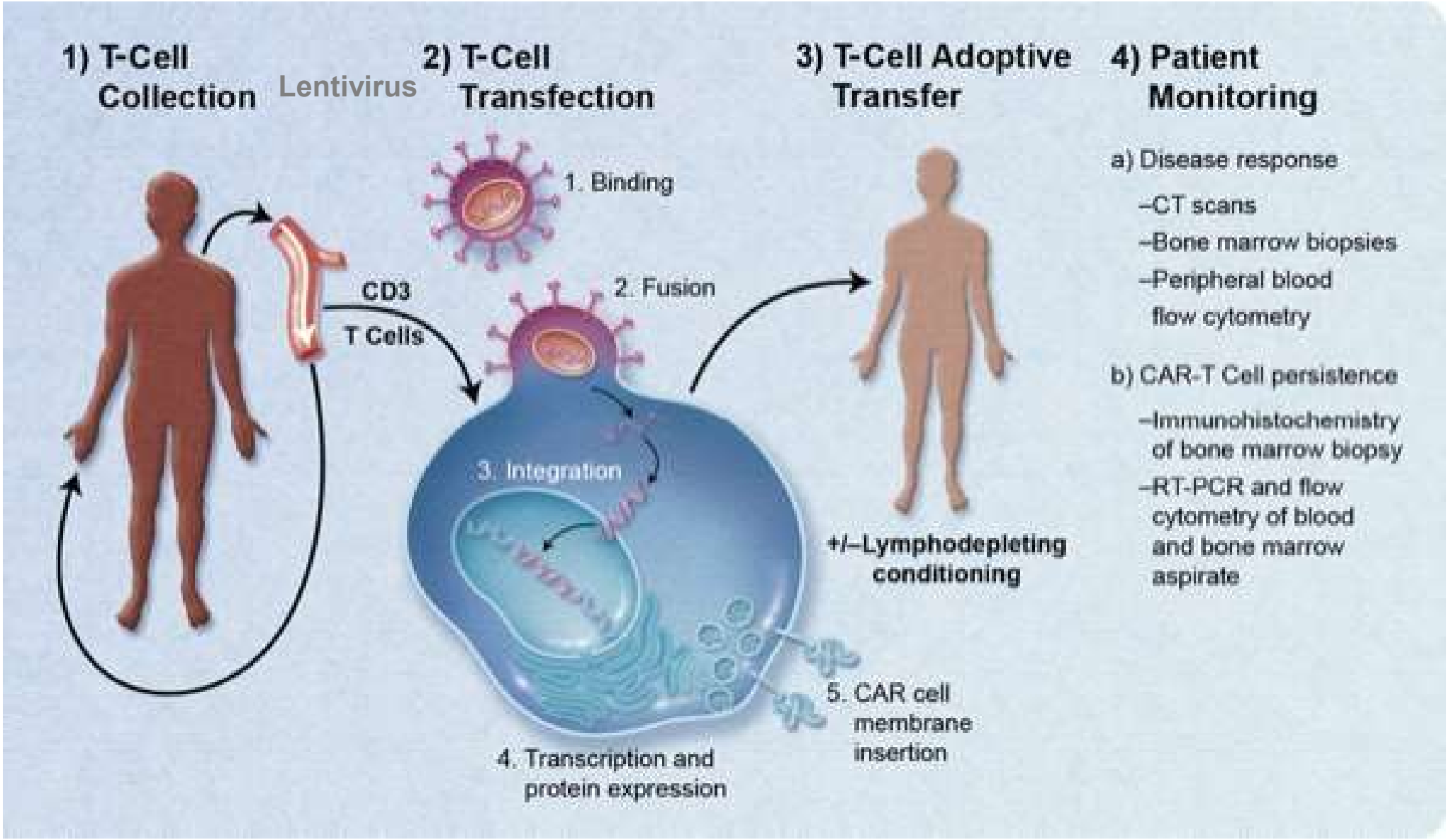
Regimen	Patient population	*N*	Median age [range], years	Induction mortality, %	CR/CRi rate, %	MRD negativity, %	HSCT rate, %	CR duration, %	OS rate, %
			R/R Ph-negative ALL						
Mini-HCVD + InO ± blinatumomab	Primary refractory 13% CR1 duration < 1 year 40% Prior HSCT 23%	84	35 [9-87]	2	80	80	40	52% (2-year)	39 (2-year)
CVP + InO (SWOG 1312)	Salvage 1: 44% Prior blinatumomab 38% Prior HSCT 19%	48	43 [20-79]	2	61	NR	30	NR	Median 10.9 months
Venetoclax + navitoclax	B cell ALL 50% T cell ALL 50% Median prior therapies: 4 Prior HSCT 14% Prior CAR T cells 17%	36	29 [6-72]	8	56	56	25	44% (6-month)	NR
			Frontline Ph-negative older ALL						
Mini-HCVD + InO ± blinatumomab	Age ≥ 60 years	64	68 [60-81]	0	98	95	5	76% (3-year)	54 (3-year)
Blinatumomab + POMP (SWOG 1318)	Age > 60 years	31	73 [66-84]	0	66	92	3	DFS 56 (1-year)	65 (1-year)
			Frontline Ph-negative younger ALL						
Sequential HCVAD + blinatumomab	Age < 60 years	27	38 [18-59]	0	100	96	30	RFS 76 (1-year)	89 (1-year)



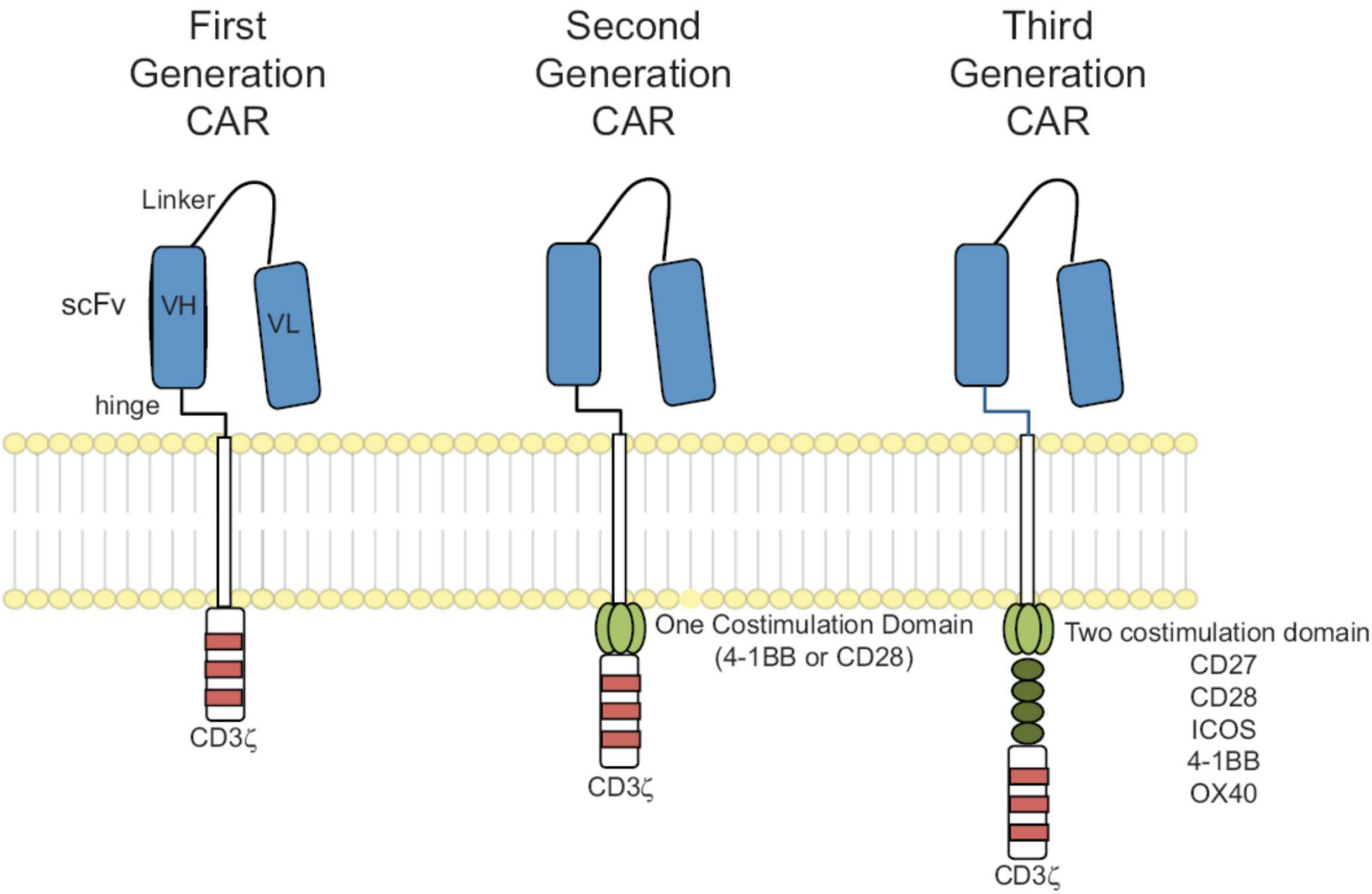
Inotuzumab ozogamicin	Total dose mg/M²	Dose & schedule mg/M²
Cycle 1	0.9	0.6 D2 & 0.3 D8
Cycle 2,3,4	0.6	0.3 D2 & D8

Fig. 1 The diagrammatic schema of miniHCVD-inotuzumab ozogamicin-blinatumomab regimen. This was adapted from Jabbour et al. (2018) and Short et al. (2018). Detailed dosages and schedules are summarized in Table 4. miniHCVD low-dose hyper-fractionated cyclophosphamide, vincristine, dexamethasone. MTX methotrexate. INO inotuzumab ozogamicin; POMP prednisone, vincristine, methotrexate, mercaptopurine; D day

Anti-CD19 chimeric antigen receptor (CAR) T cells



Chimeric antigen receptors (CARs)



M. Maus et al. Antibody modified T cells: CARs take the front seat for hematologic malignancies. Blood 2014

Challenges with CAR T cells

Toxicity

- Cytokine release syndrome
- Neurotoxicity (CD19)
- B-cell aplasia (CD19)

Loss of CAR-T cells → relapses

Security/efficacy of retrovirals

Potential insertionnal mutagenesis → T-cell malignancy

Latency, replication

Transgene variegation → exhaustion of the clone → impact on efficacy

Immuno-editing → CD19 relapses

Manufactoring time process

Cost

M. Maus et al. Antibody modified T cells: CARs take the front seat for hematologic malignancies. Blood 2014

Conclusion

- Cure rate of **childhood** ALL > 80%

  → Still serious acute and late complications due to treatments (osteonecrosis, hyperglycemia, anthracycline-induced myocardial injury, neurologic defects, …)

  → Shift toward the reduction of deleterious acute and **late** effects of treatment

- Cure rate in **adults** decline sharply to less than 50% in adults
- over the age of 40
  → The future resides in defining the molecular pathways underlying the pathogenesis of ALL in order to find proteins suitable for less toxic targeted therapy
  → Room +++ for immunotherapy (also in first line)

- Further elucidating the underlying pharmacogenetic factors of the host
- When comparing different treatment trials, remember that slightly different median ages can translate into relatively large differences in outcome

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