

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen



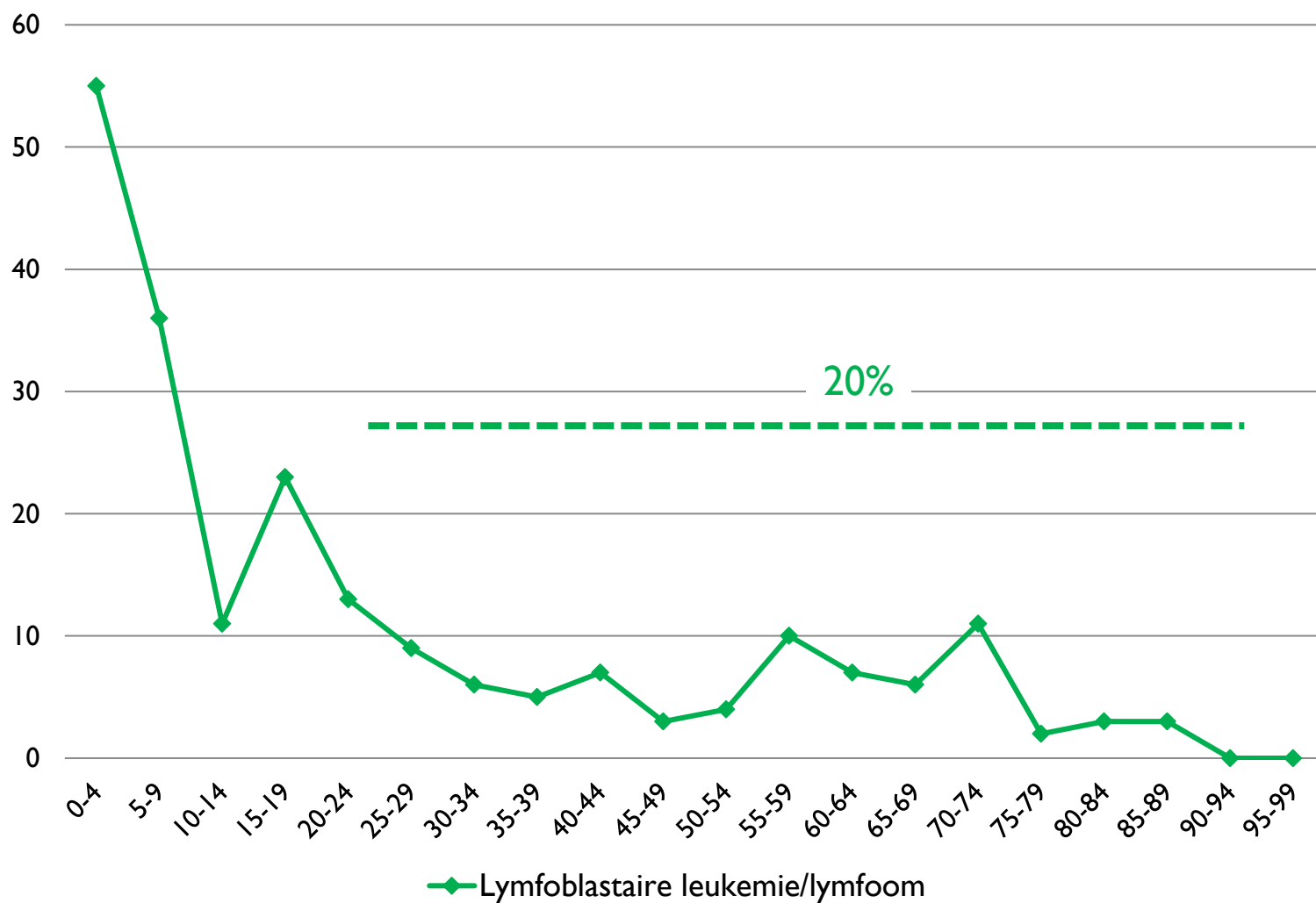


Acute Lymfatische Leukemie

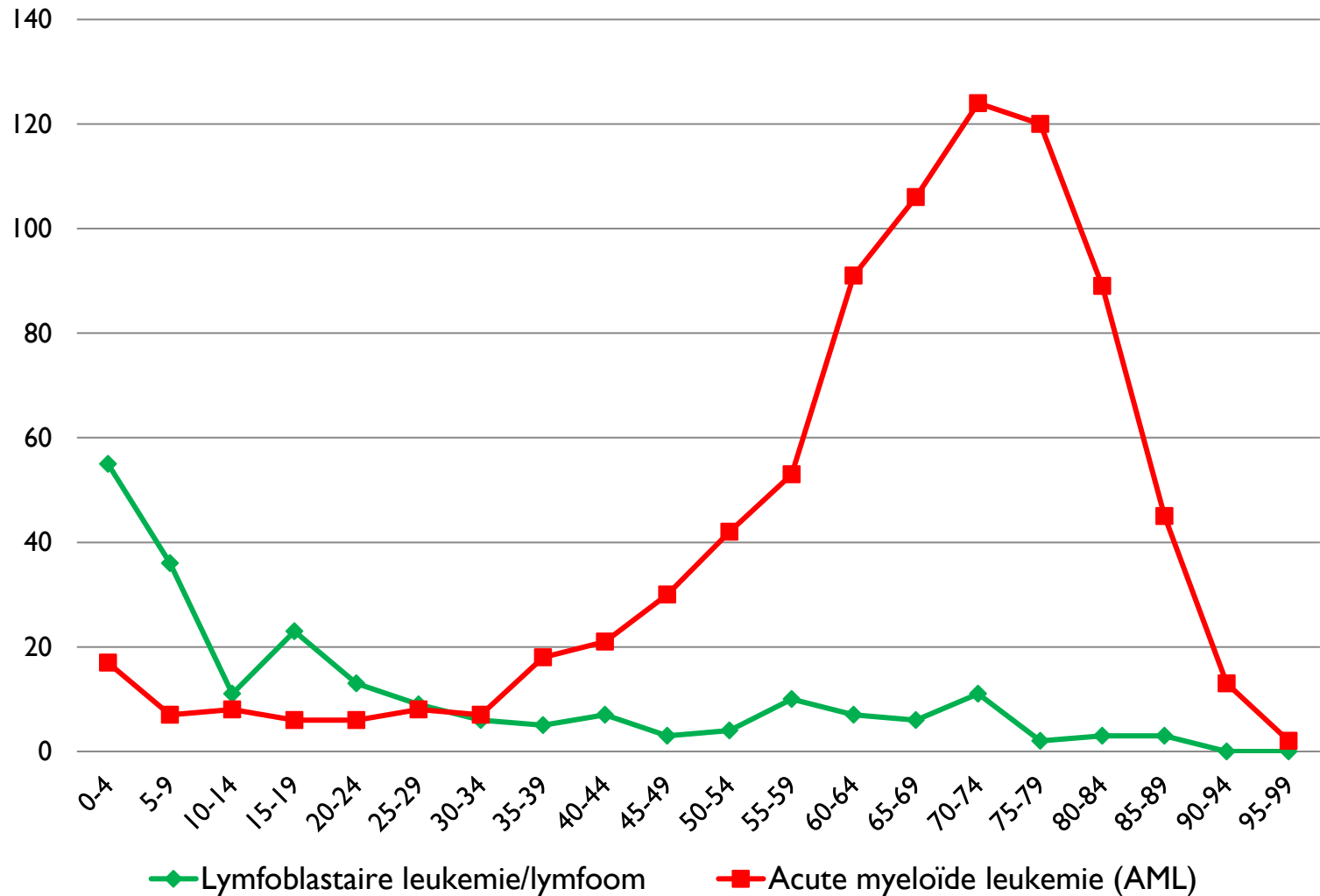
Classificatie, Cytologie en Flow Cytometrie



Incidentie ALL in Nederland 2023

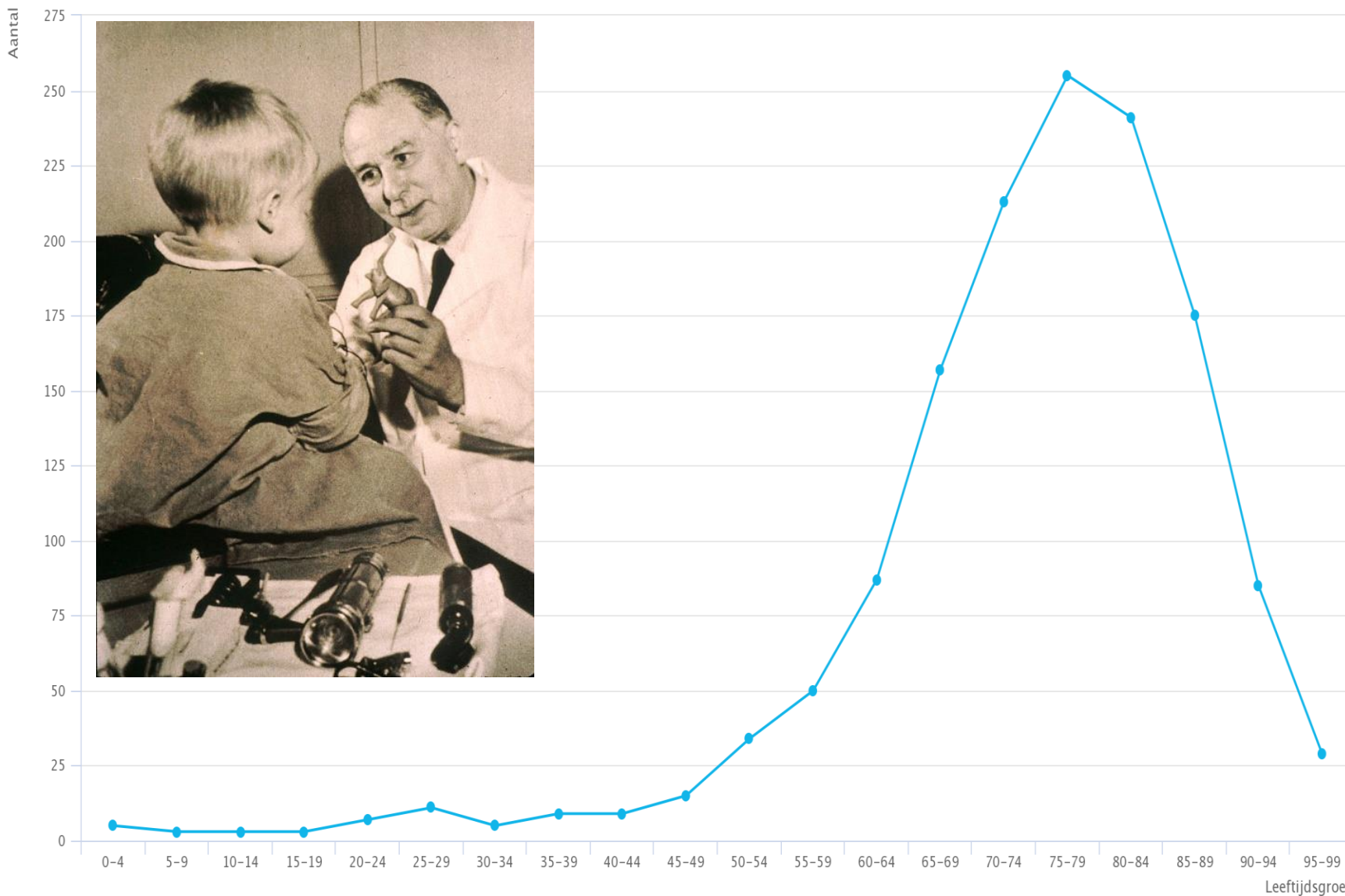


Incidentie ALL/AML 2023



Sterfte, Leukemie, 2017, Aantal

Totaal 1396

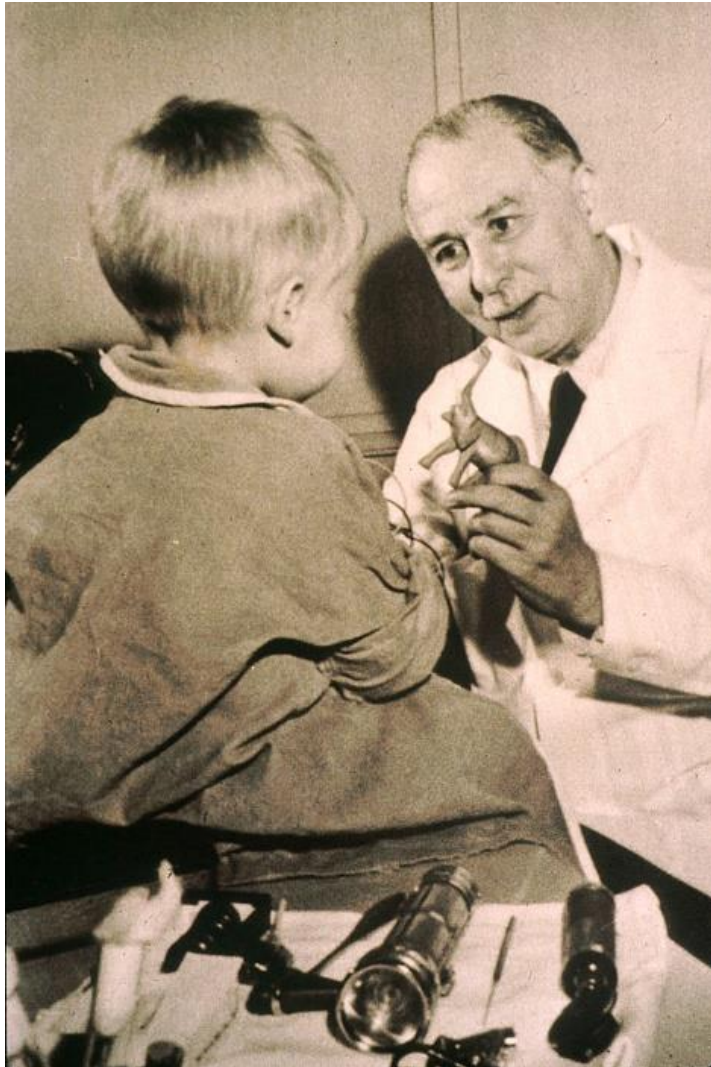


◆ Sterfte

Leeftijdsgroep

NKR
Bron: CBS

Sydney Farber



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TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.||

BOSTON

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to the time of this writing (April 15, 1948) we have made studies on 16 children with acute leukemia to whom the most powerful folic antagonist we have yet encountered, 4-aminopteroyl-glutamic acid (aminopterin††) was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic and pathological evidences of improvement of important

DE
KEIZER
ALLER
ZIEKTES



EEN BIOGRAFIE VAN KANKER

SIDDHARTHA
MUKHERJEE

'Magistrale, gedurfde en aangrijpende geschiedenis.'

— NRC HANDELSBLAD



ALL behandelning

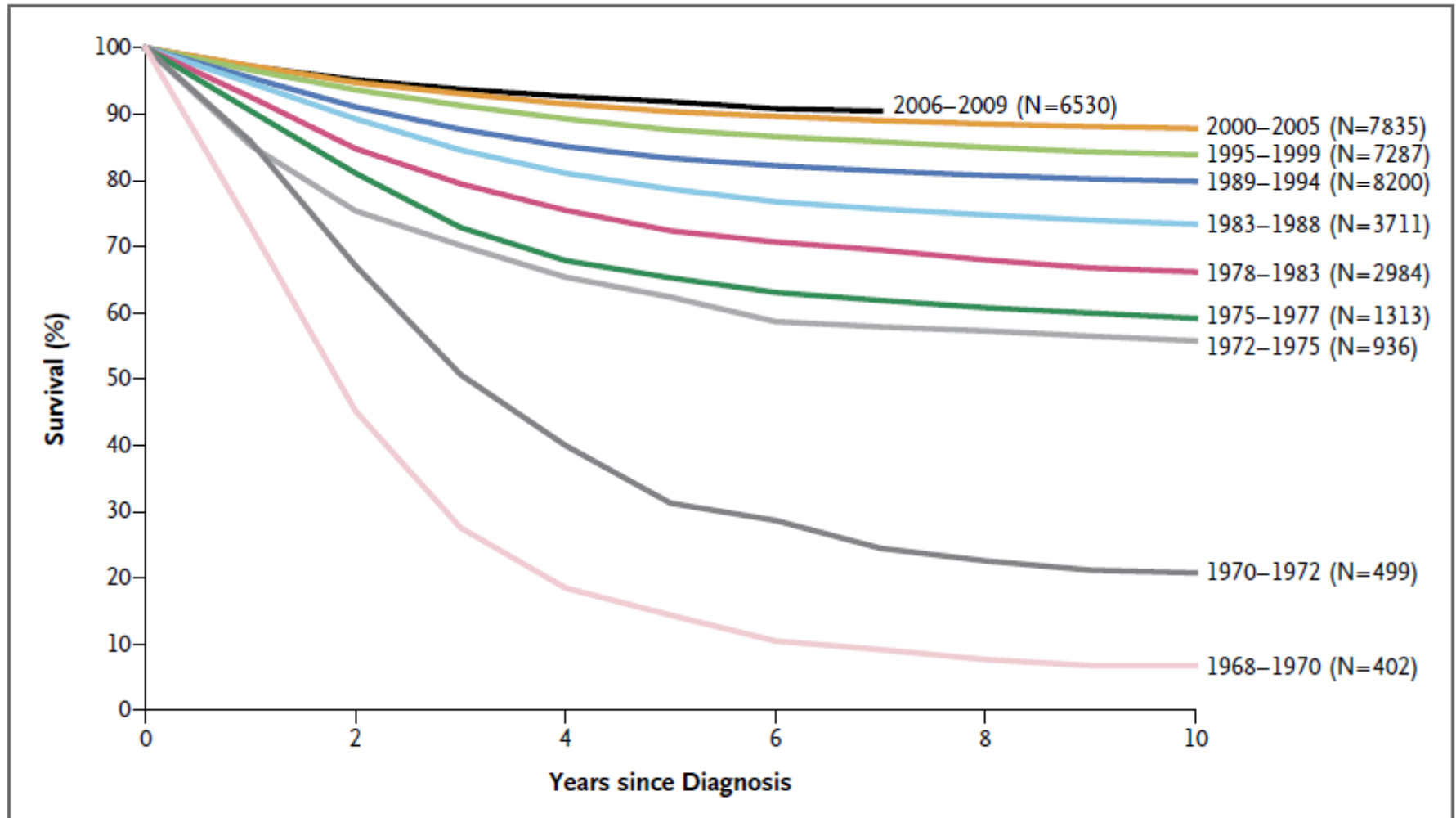
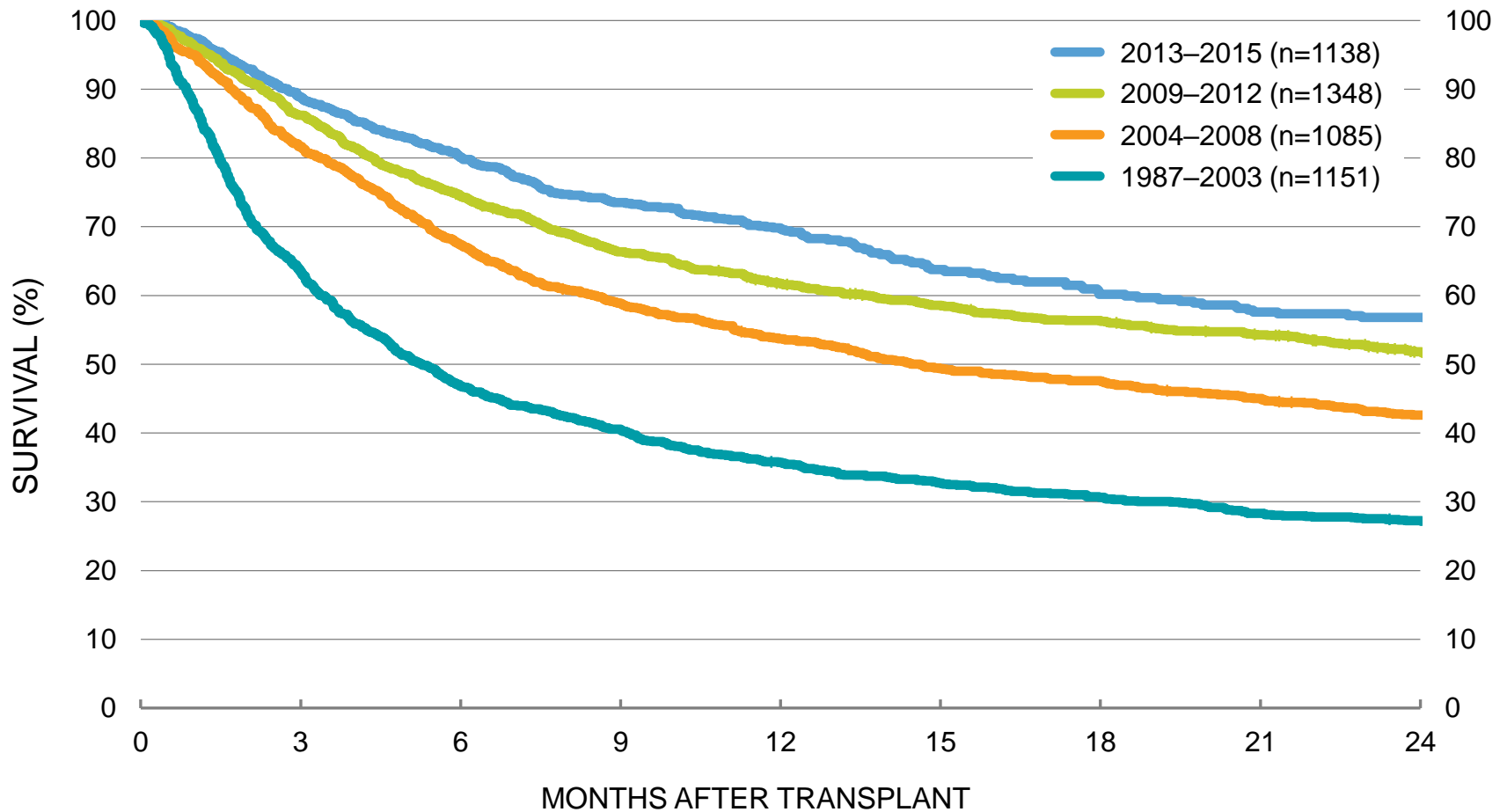
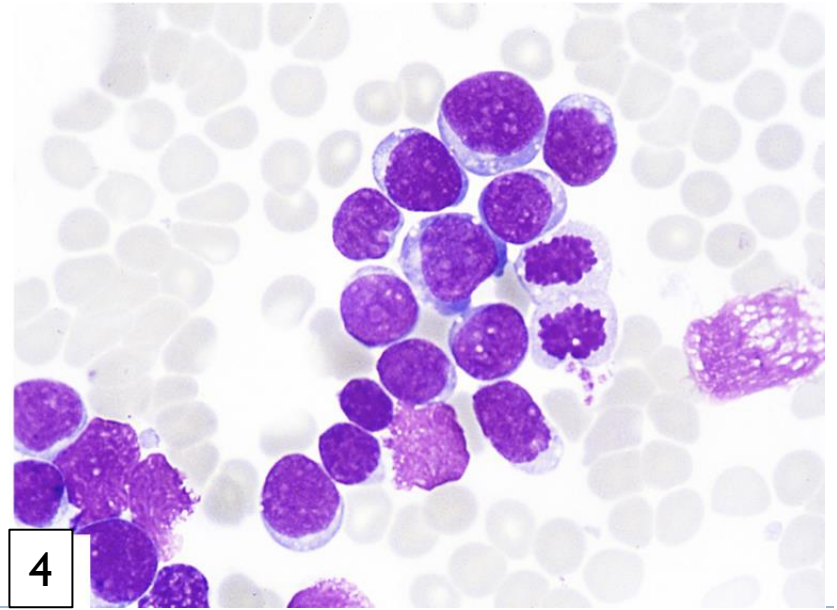
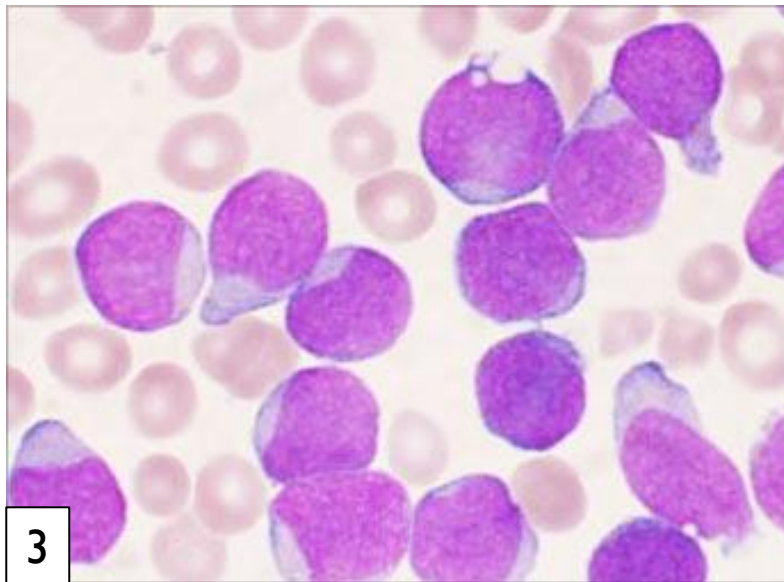
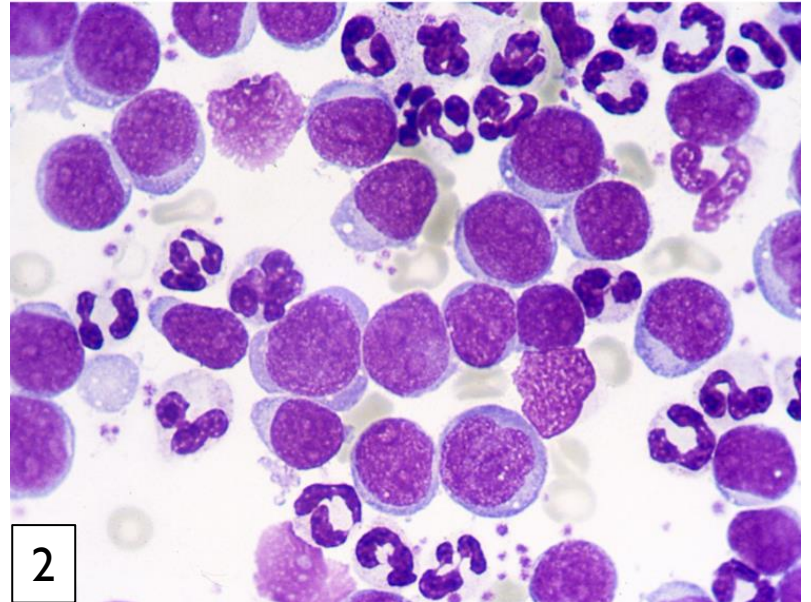
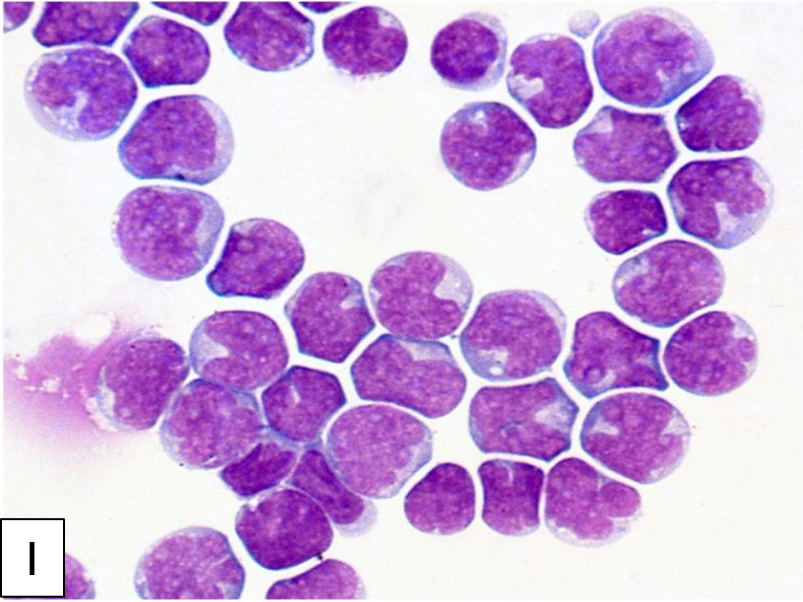


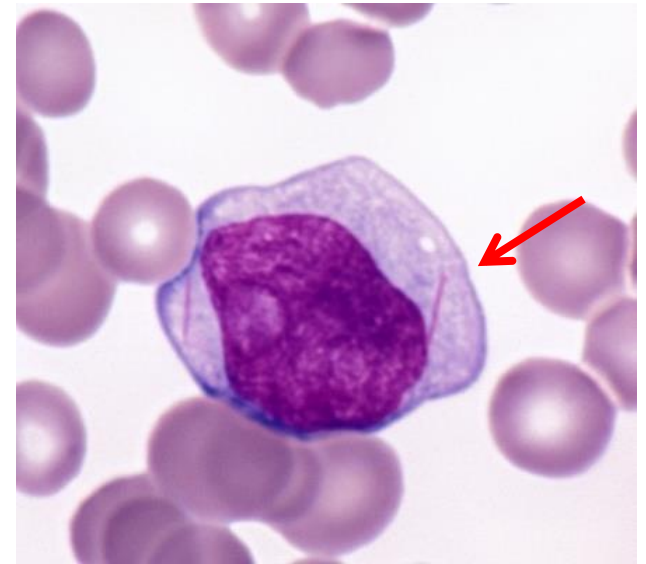
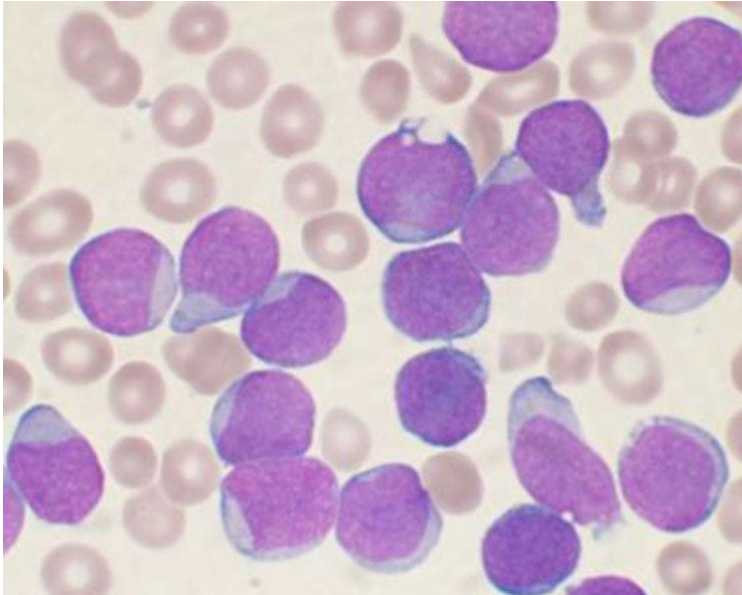
Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968-2009.

ALL survival volwassenen





Morfologie lymfatisch vs myeloid



Kenmerken van blasten

- Auerse staaf
- Korreling
- Nucleolus
- Grote
- Cytoplasma
- Hand-mirror cel
- Chromatine



Cytochemische kleuringen

- ▶ **Peroxidase**
 - ▶ Kleuring van Myeloperoxidase

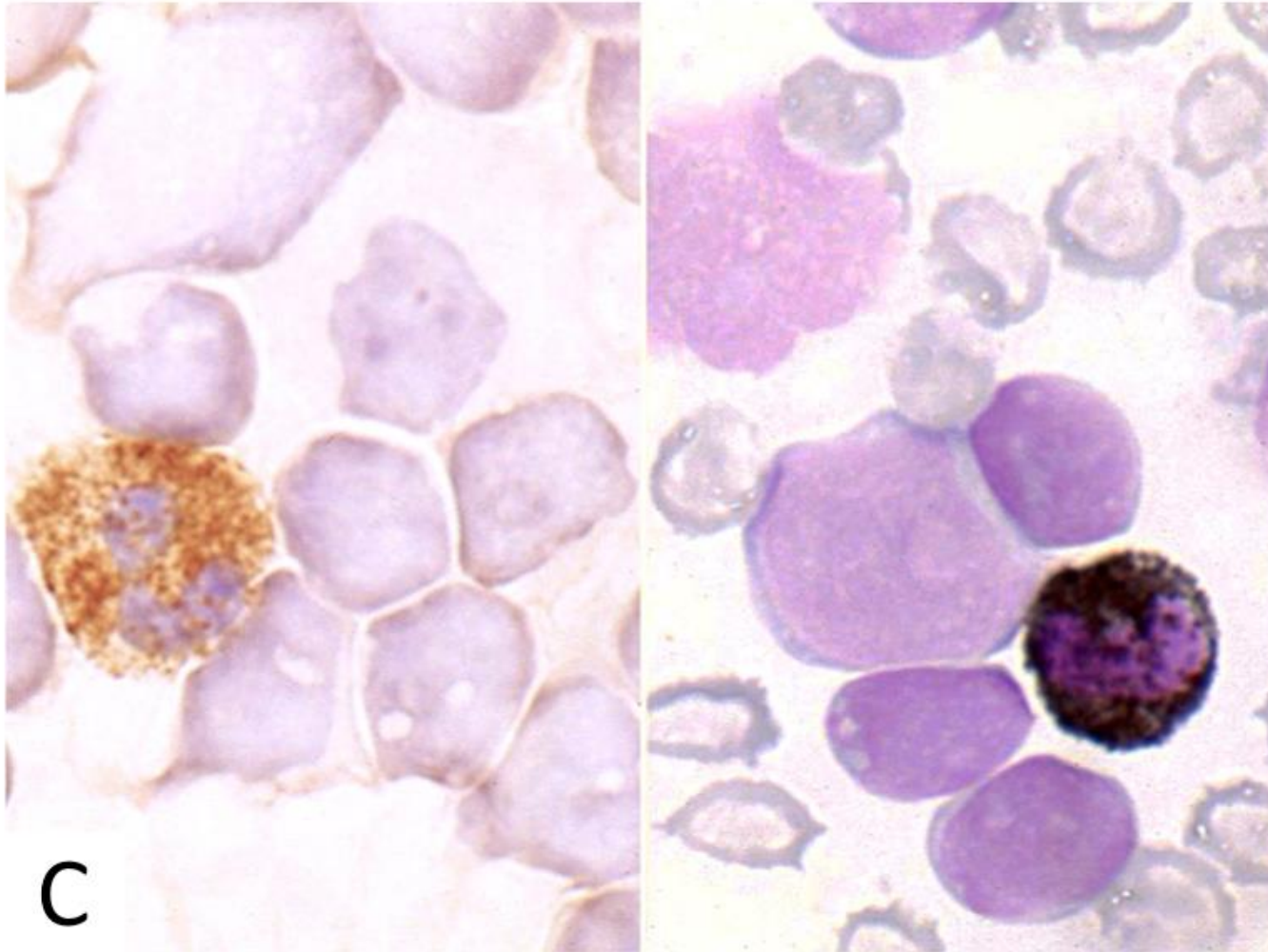
- ▶ **Sudan-Black**
 - ▶ Kleurstof voor fosfolipiden van primaire en secundaire granules myelo en monocyttaire cellen

- ▶ **Periodic acid-Schiff**
 - ▶ Polysaccharides zoals glycogeen en glycolipiden

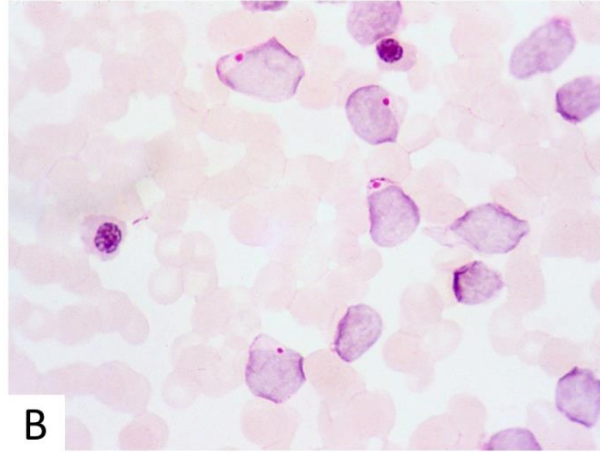
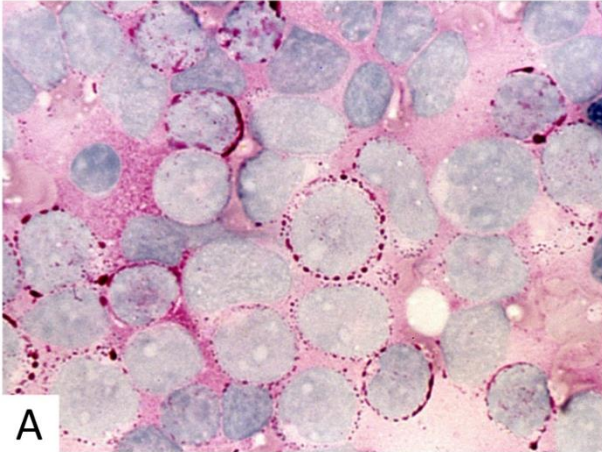
- ▶ **Acid phosphatase stain**
 - ▶ Aankleuring enzymen die organisch fosfaat-esters hydrolyseren



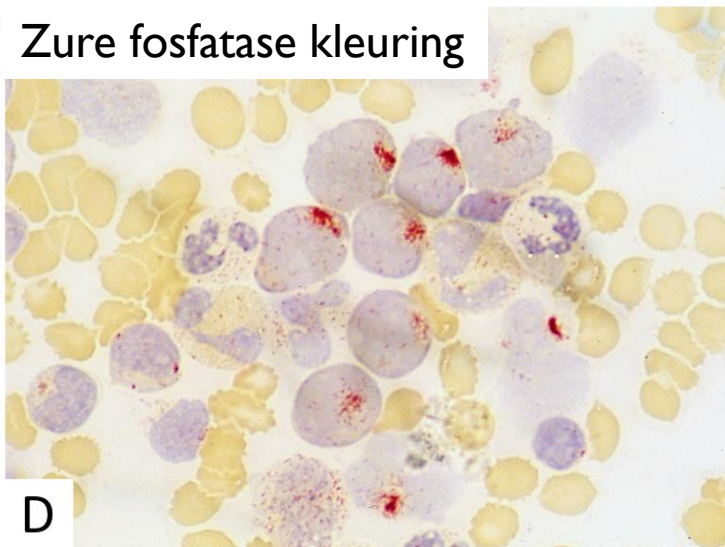
MPO en Sudan Black



Periodic Acid Schiff (PAS)



Zure fosfatase kleuring



Proposals for the Classification of the Acute Leukaemias

FRENCH-AMERICAN-BRITISH (FAB) CO-OPERATIVE GROUP

J. M. BENNETT,* D. CATOVSKY,† MARIE-THERÈSE DANIEL,‡ G. FLANDRIN,‡
D. A. G. GALTON,† H. R. GRALNICK§ AND C. SULTAN¶

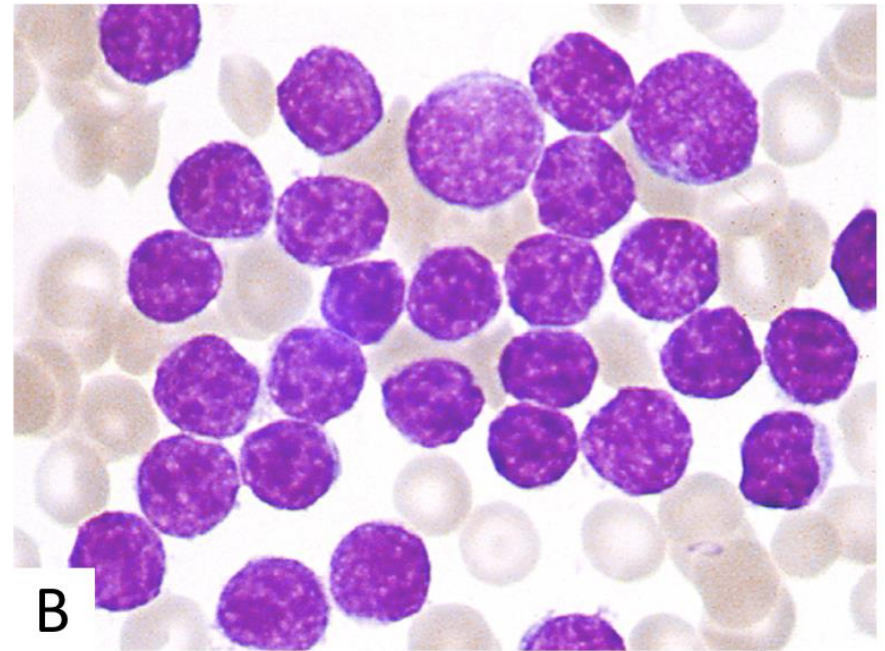
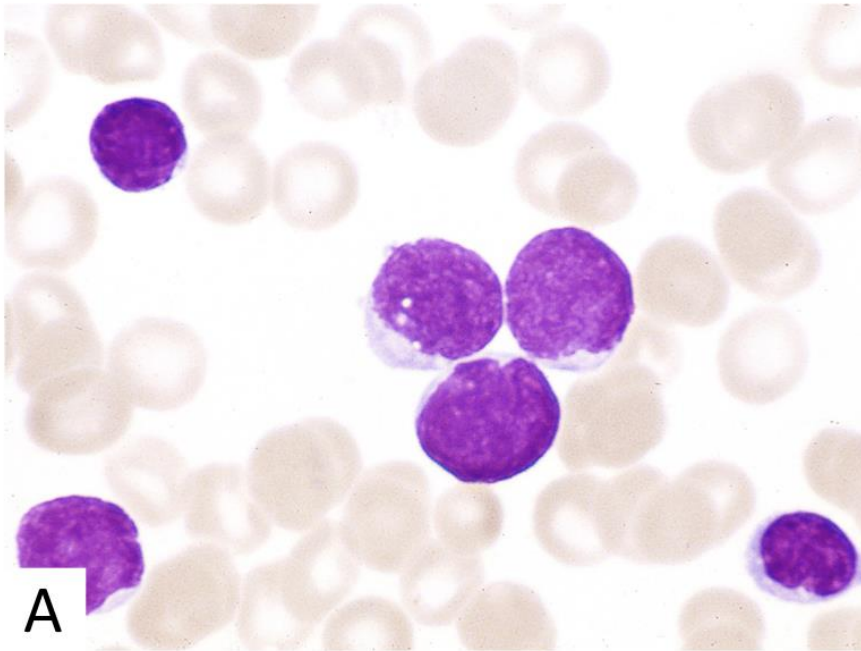
FAB classification of acute lymphoblastic leukaemia.

Criterion	Classification
High nucleus:cytoplasm ratio > 75% of cells	+
Low nucleus:cytoplasm ratio > 25% of cells	-
Nucleoli: 0-1 (small) > 75% of cells	+
Nucleoli: 1 or more (prominent) > 25% of cells	-
Irregular nuclear membrane > 25% of cells	-
Megaloblasts > 50% of cells	-

Obtain 1 classification in each category, sum total of signs.

Total classification (-4 to +2): 0 to +2 L1 acute lymphoblastic leukaemia; -1 to -4 L2 acute lymphoblastic leukaemia.





L1 Lymphoblastic leukaemia with
 homogeneous structure

Frequency:

Between 25% and 30% of cases in adults,
and 85% of cases in children.

Morphology:

Blasts are homogeneous, nucleus is regular,
chromatin is homogeneous,
small or no nucleoli, scanty cytoplasm,
and mild to moderate basophilia.

Immunophenotype

B:

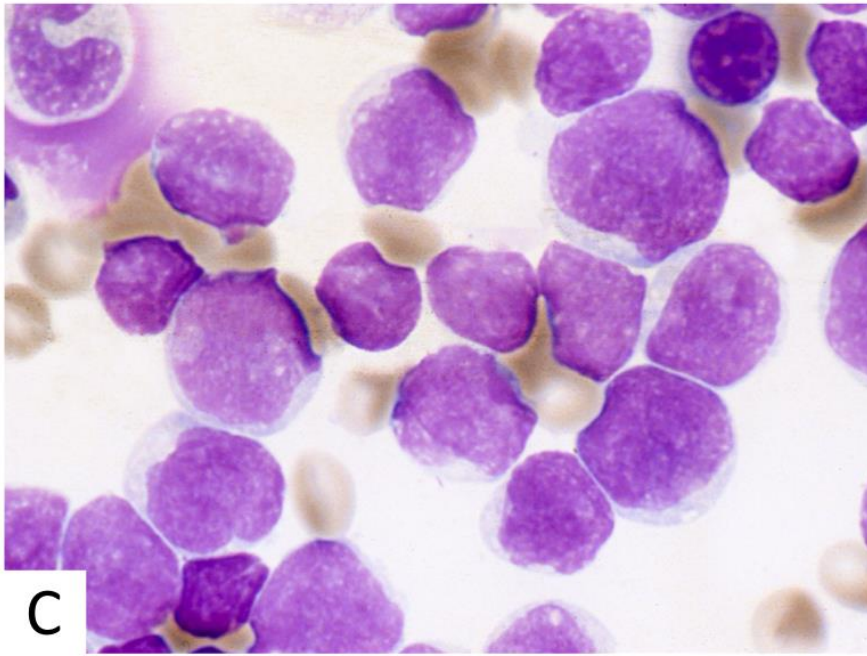
- CD19
- CD22
- CD79a
- CD10
- CD20

T:

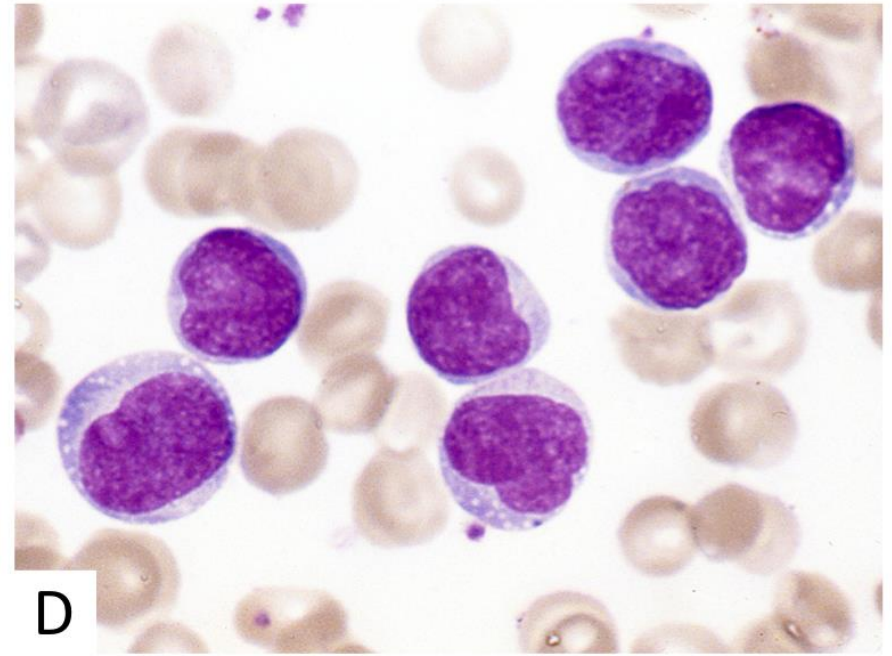
- CD3
- CD7
- CD5
- CD2
- CD4

• Cytoplasmic or superficial immunoglobulin





C



D

L2 Lymphoblastic leukaemia with varied structure

Frequency:

Accounts for 70% of cases in adults, and 14% in children.

Morphology:

Nucleus is irregular, heterogeneous chromatin structure, large nucleoli.

Immunophenotype

B:

- CD19
- CD22
- CD79a
- CD10
- CD20

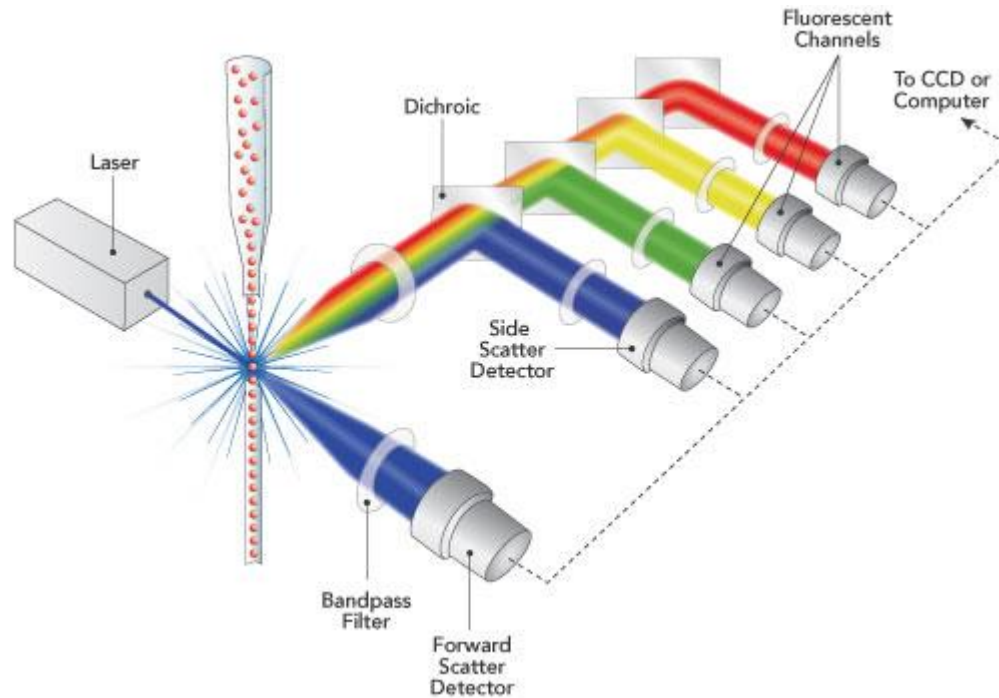
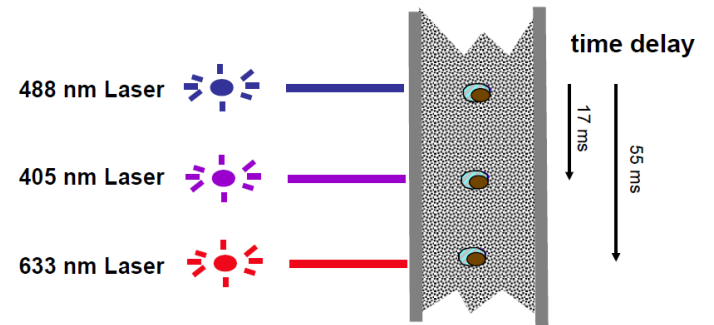
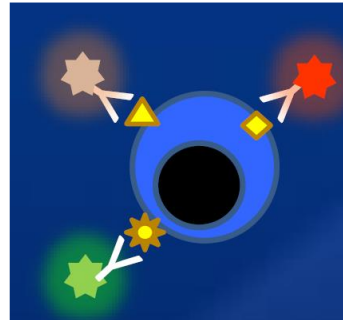
T:

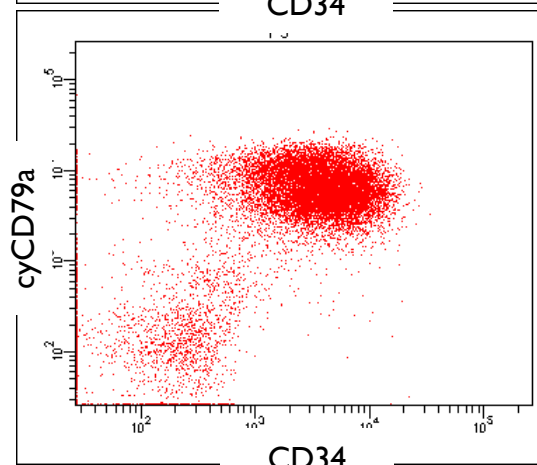
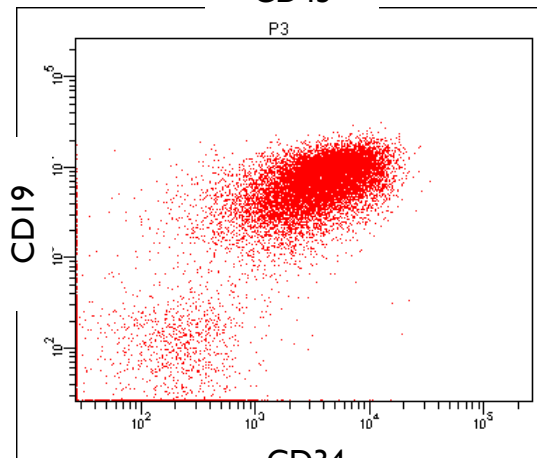
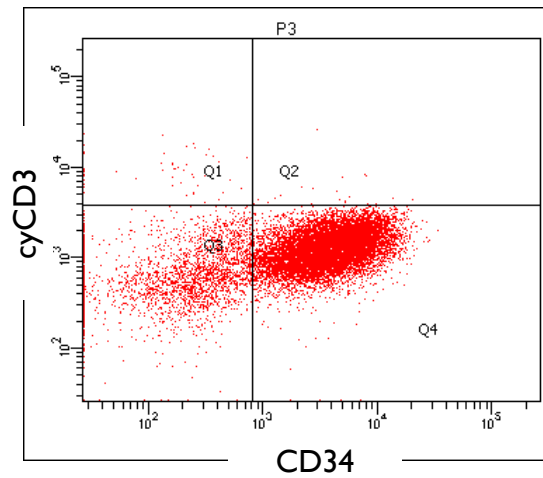
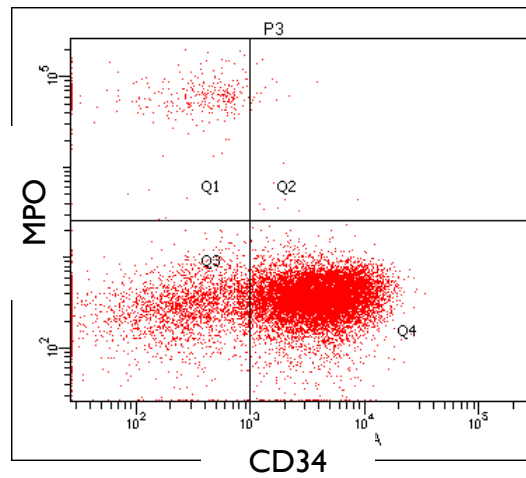
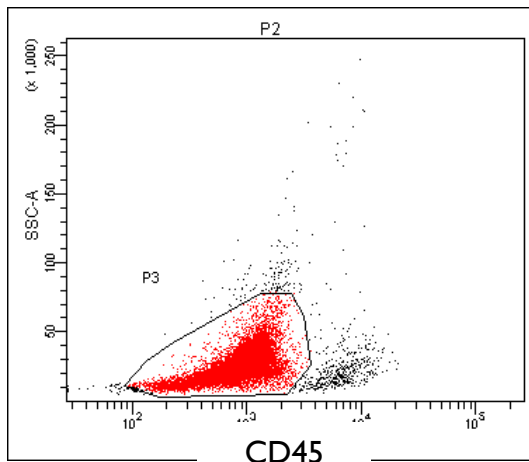
- CD3
- CD7
- CD5
- CD2
- CD4

•Cytoplasmic or superficial immunoglobulin

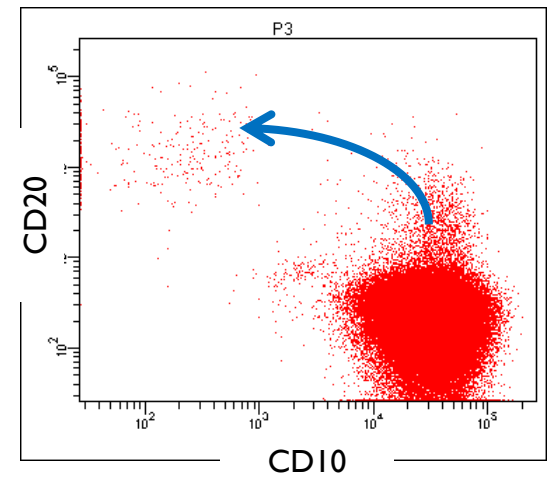
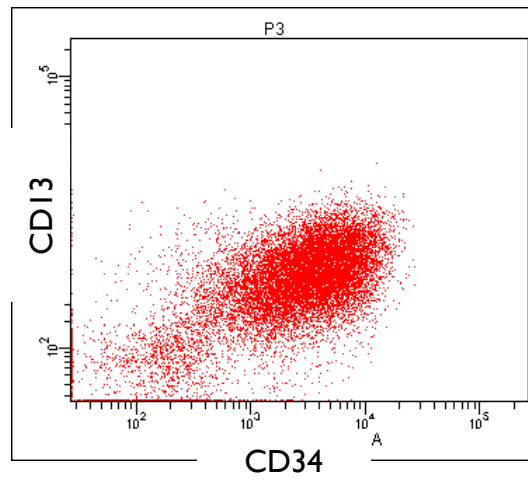
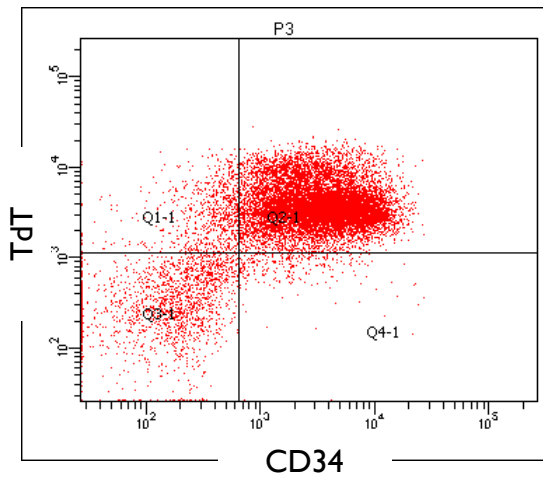
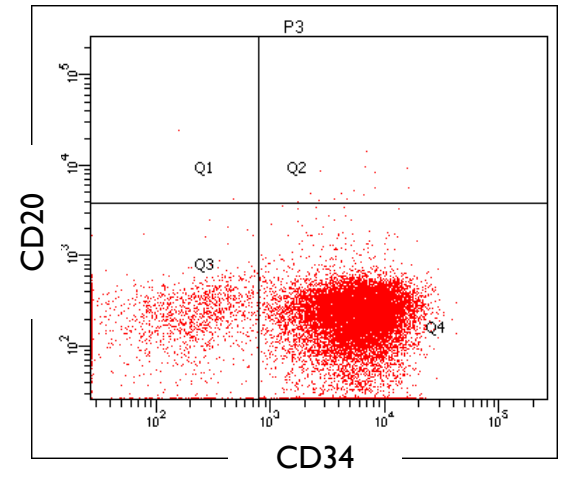
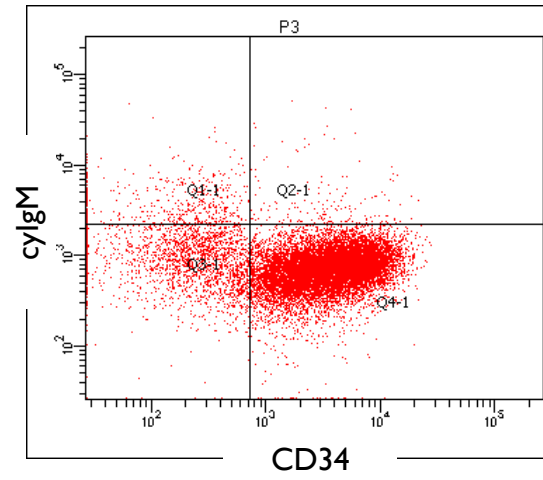
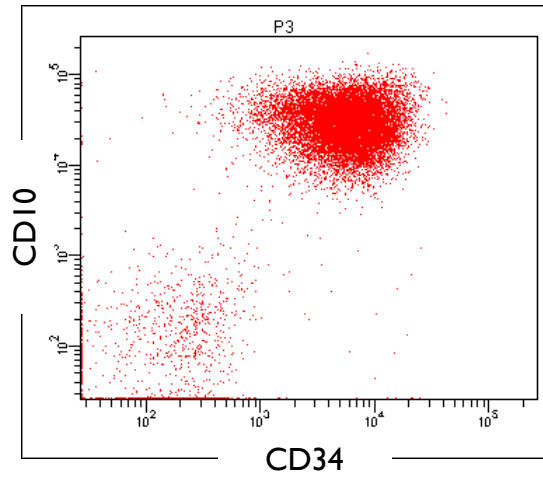


Flow cytometrie

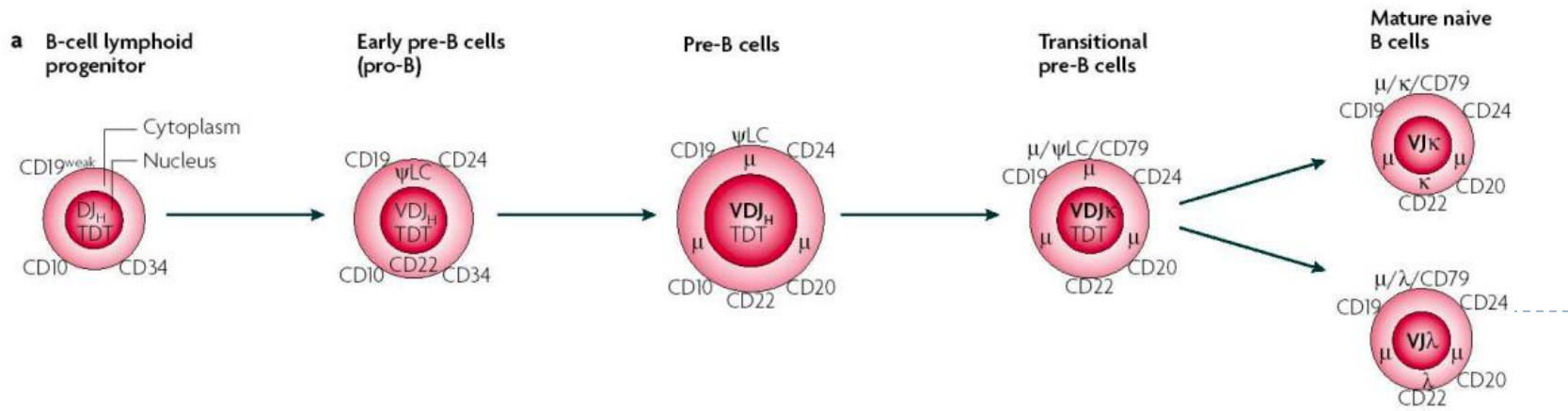




Lijn	Markers
Myeloid	MPO
	2x (CD11c, CD14, CD64)
T lineage	Cytoplasmatisch CD3
	Oppervlakte CD3
B lineage	CD19 sterk + (CD79a, CD22 of CD10)
	CD19 zwak + 2x (CD79a, CD22 of CD10)



Markers	pro-B-ALL (EGIL B-I)	common ALL (EGIL B-II)	pre-B-ALL (EGIL B-III)
TdT	+++**	++	++
CD10	-	++	++
CD19	++	++	++
CD20	-	+	+
CD22	++	++	++
CyCD79	++	++	++
CyI μ	-	-	+++***
SmVpre-B/ λ 5	-	-	-
Smlg-CD79	-	-	-
CD34	+	+	+



WHO 2022 ALL Classificatie

▶ WHO-HAEM5

- ▶ Genetisch & moleculair onderzoek belangrijker
- ▶ Alle technieken niet overal beschikbaar
- ▶ “Essential” versus “desirable” diagnostische criteria

▶ B-ALL

- ▶ Morfologie & flow cytometrie -> B-ALL not further classified
- ▶ Classificatie volgt de WHO2016
- ▶ Naamgeving van cytogenetisch naar moleculair



WHO 2022 ALL Classificatie

Precursor B-cell neoplasms	
<i>B-cell lymphoblastic leukaemias/lymphomas</i>	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with <i>BCR::ABL1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); <i>BCR-ABL1</i>
B-lymphoblastic leukaemia/lymphoma with <i>BCR::ABL1</i> -like features	B-lymphoblastic leukaemia/lymphoma, <i>BCR-ABL1</i> -like
B-lymphoblastic leukaemia/lymphoma with <i>KMT2A</i> rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); <i>KMT2A</i> -rearranged
B-lymphoblastic leukaemia/lymphoma with <i>ETV6::RUNX1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); <i>ETV6-RUNX1</i>
B-lymphoblastic leukaemia/lymphoma with <i>ETV6::RUNX1</i> -like features	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with <i>TCF3::PBX1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); <i>TCF3-PBX1</i>
B-lymphoblastic leukaemia/lymphoma with <i>IGH::IL3</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); <i>IGH/IL3</i>
B-lymphoblastic leukaemia/lymphoma with <i>TCF3::HLF</i> fusion	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)

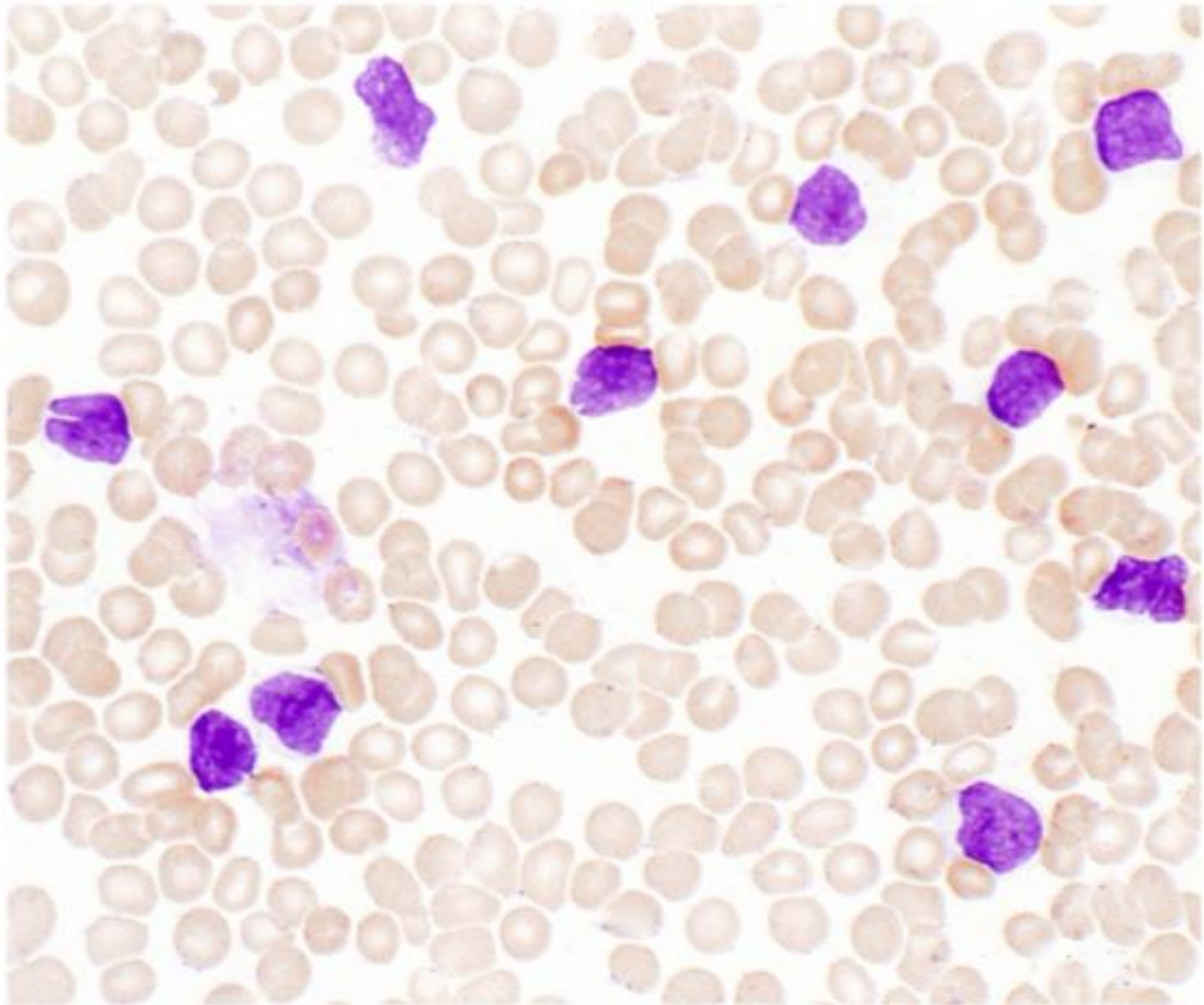


B-ALL Not Otherwise Specified

- ▶ **Definitie B-ALL/LBL**
 - ▶ Neoplasm van precursor B-cellen
 - ▶ B-LBL
 - ▶ Nodale massa
 - ▶ Minimaal bloed en beenmerg
 - ▶ B-ALL
 - ▶ Extensieve bloed en beenmerg betrokkenheid
 - ▶ WHO geen vast grens % blasten (>20%)

- ▶ Geen genetische verandering van de andere categorieën





B-ALL met BCR::ABL1 fusion

▶ Prevalentie

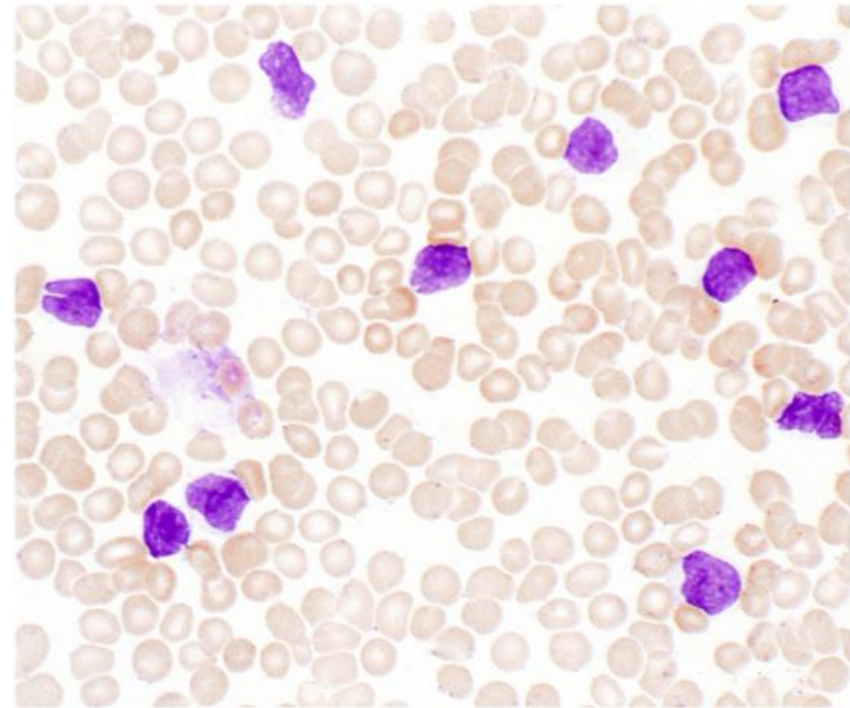
- ▶ c.a. 25% van de volwassenen
- ▶ c.a. 2-4% kinderen

▶ Immunofenotype

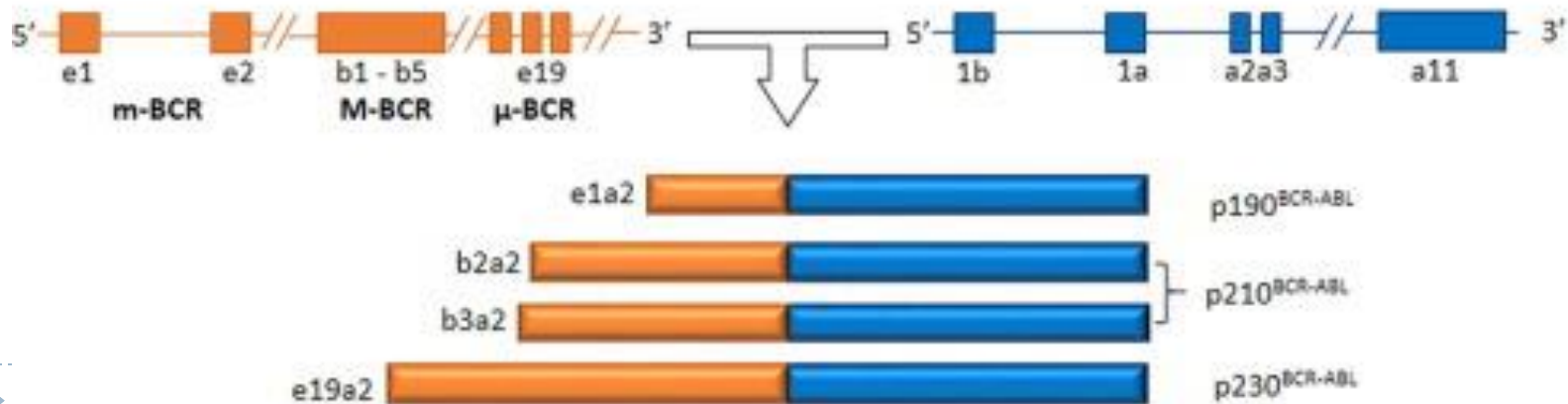
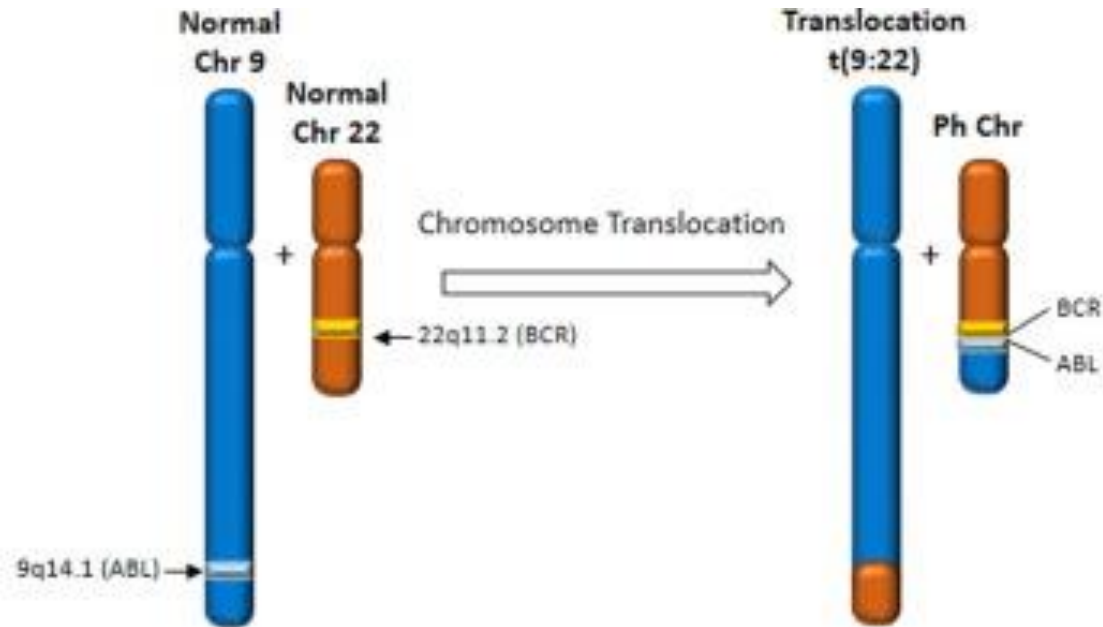
- ▶ Common B-ALL (CD10, CD19)
- ▶ Expressie van myeloïde markers
CD13 CD33

▶ Moleculair t(9;22); BCR-ABL1

- ▶ e1a2 breukpunt
- ▶ e13a2 e14a2 breukpunt

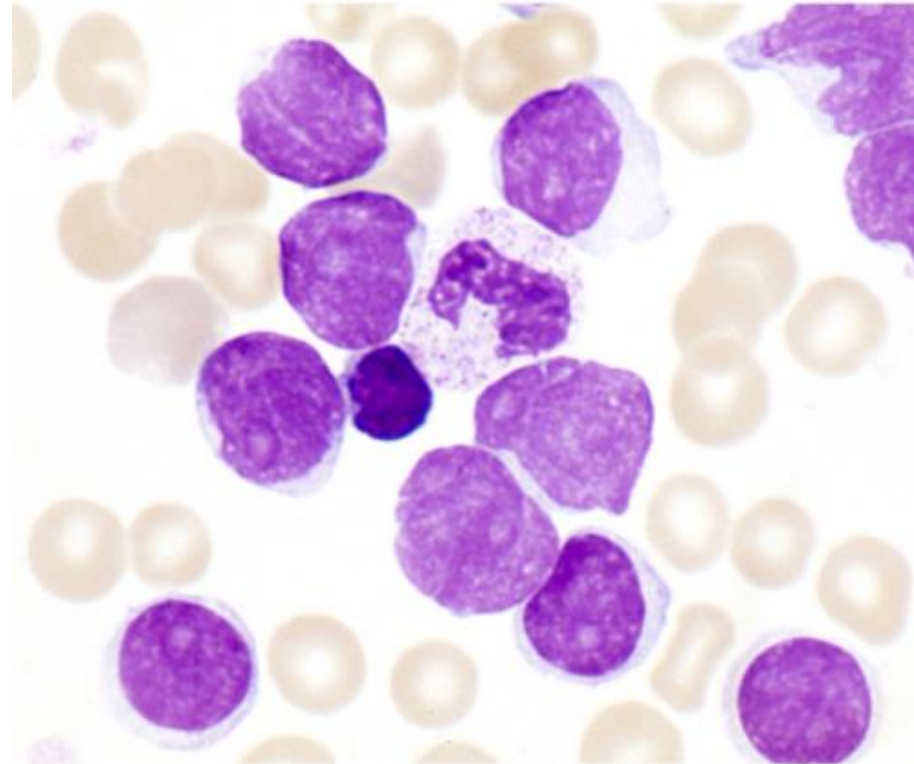


B-ALL met BCR::ABL1 fusion



B-ALL met KMT2A rearranged

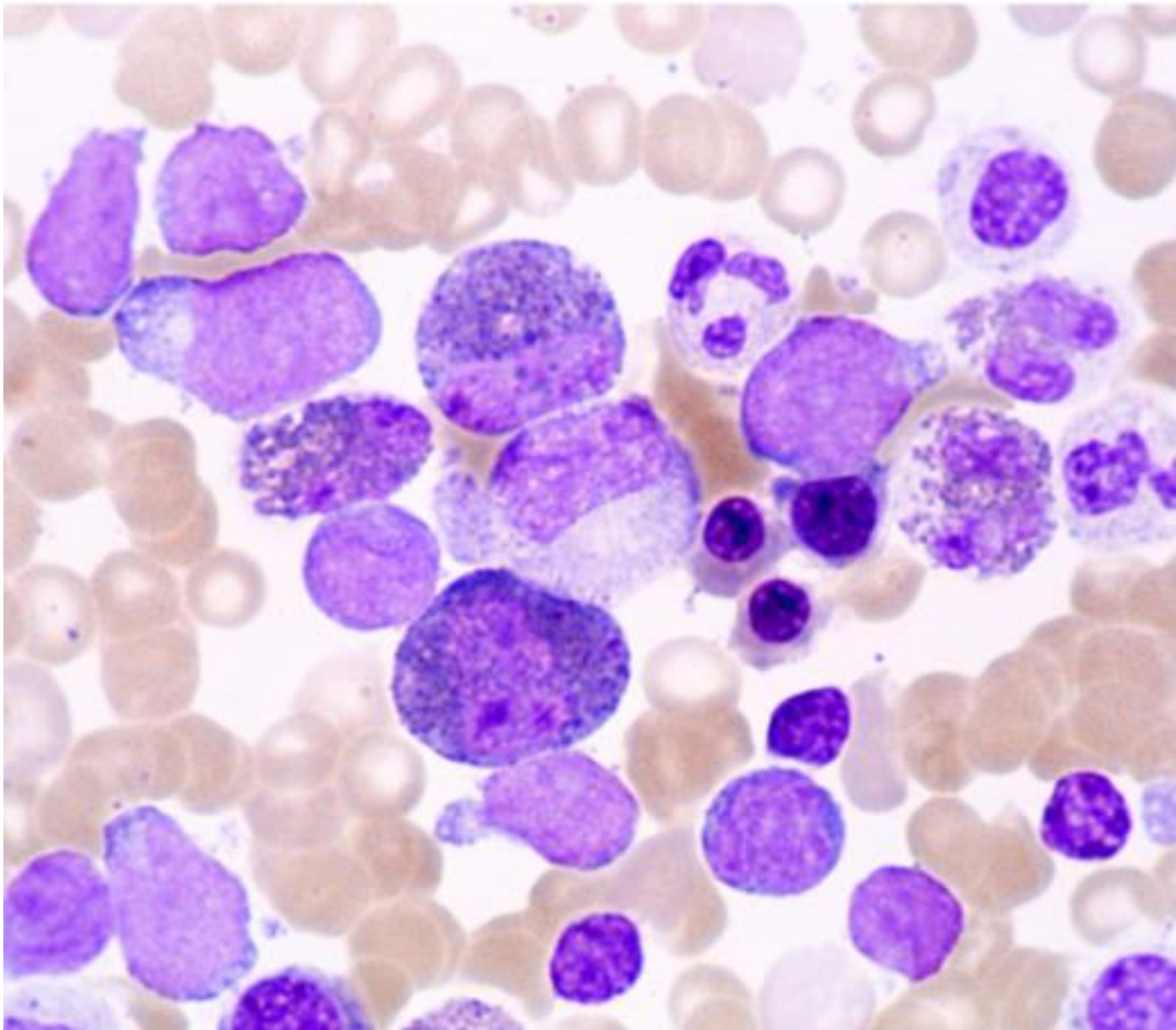
- ▶ **Prevalentie**
 - ▶ Frequent bij kinderen <1 jaar
- ▶ **Overige**
 - ▶ Hoge WBC bij presentatie
 - ▶ CNS lokalisatie
- ▶ **Moleculair t(v;11q23,3);**
 - ▶ KMT2A ook wel MLL genoemd
 - ▶ >100 fusiepartners
 - ▶ Aanwezig in utero?



Overige B-ALL

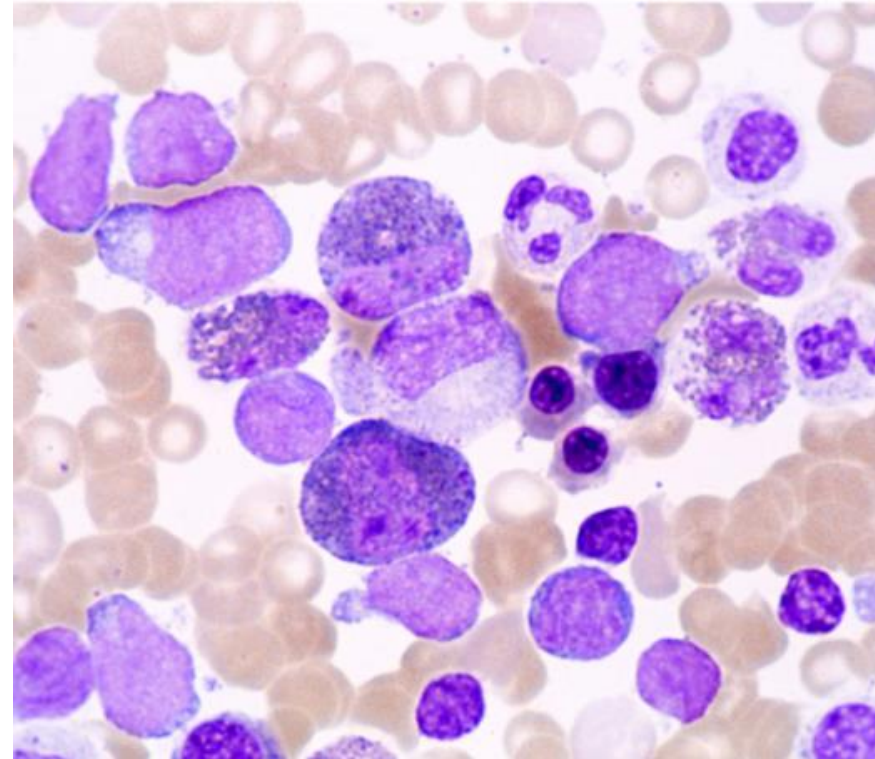
- ▶ **B-ALL met ETV6::RUNX1 fusie**
 - ▶ Synoniem TEL;AML1
 - ▶ Vnl bij kinderen (25%), zeldzaam bij volwassenen
- ▶ **B-ALL met hyperdiploidie**
 - ▶ Blasten bevatten >50 chromosomen
 - ▶ Geen translocaties of andere structurele veranderingen
- ▶ **B-ALL met hypodiploidie**
 - ▶ Blasten bevatten <46 chromosomen





Overige B-ALL

- ▶ **B-ALL met IGH::IL3 fusion**
 - ▶ Overexpressie IL-3 en vaak reactieve eosinofilie,
 - ▶ Zeldzaam



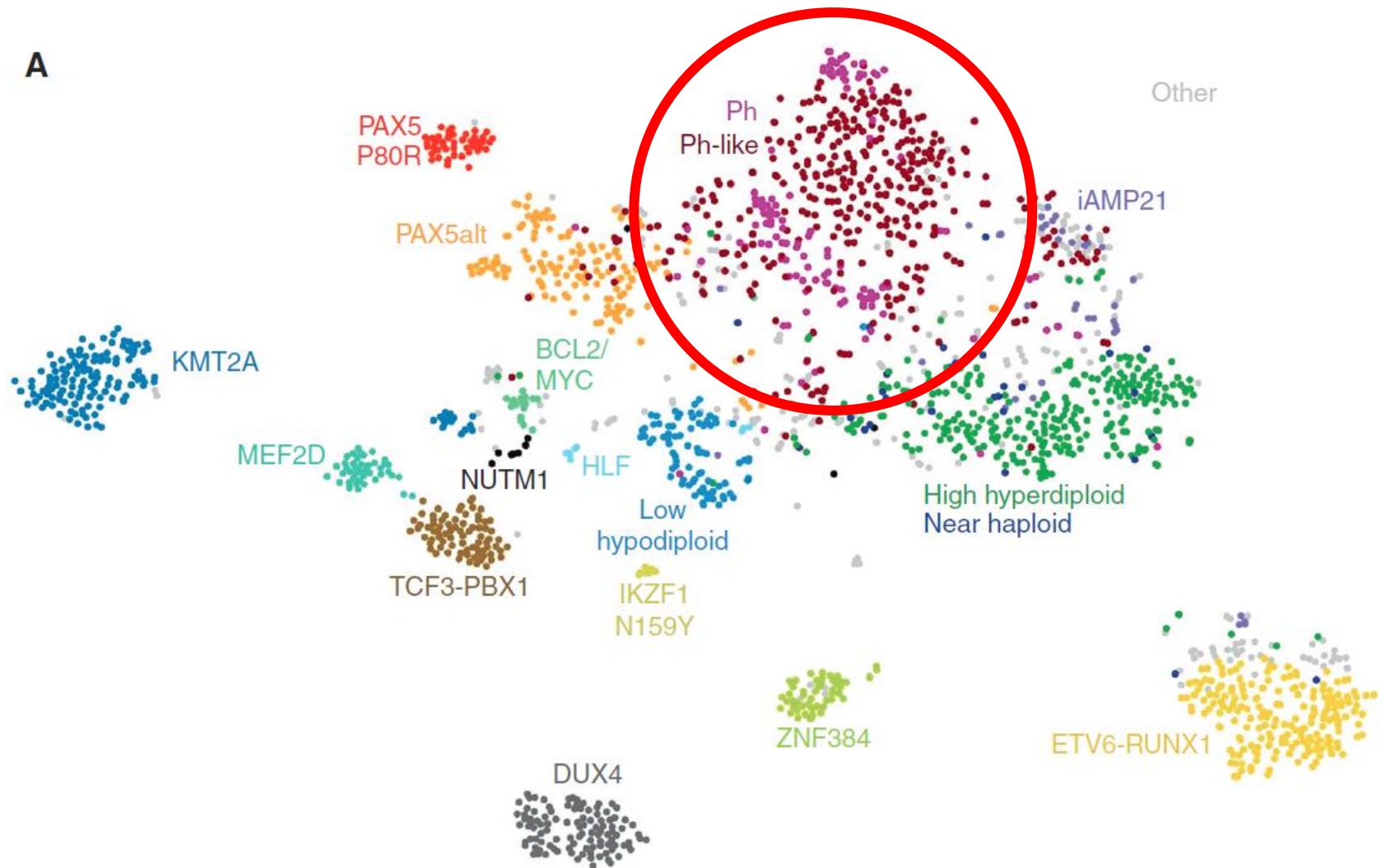


Figure 1. (A) tSNE plot showing B-progenitor acute lymphoblastic leukemia (B-ALL) subtypes based on RNA-seq gene expression profiling of 1988 cases. (B) Distribution of B-ALL subtypes within each age group. Subtypes

B-ALL BCR::ABL1 like features

▶ Prevalentie

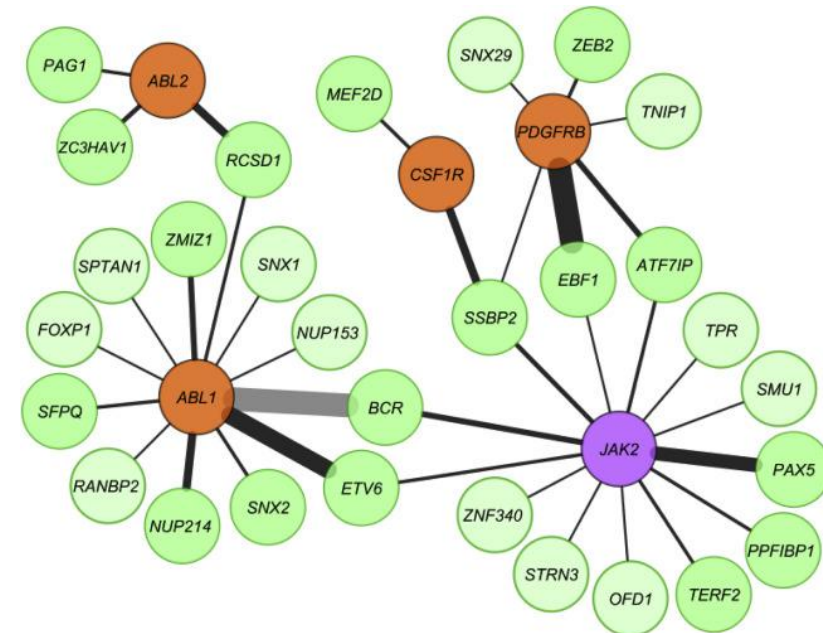
- ▶ 10-20% van de ALL

▶ Overige

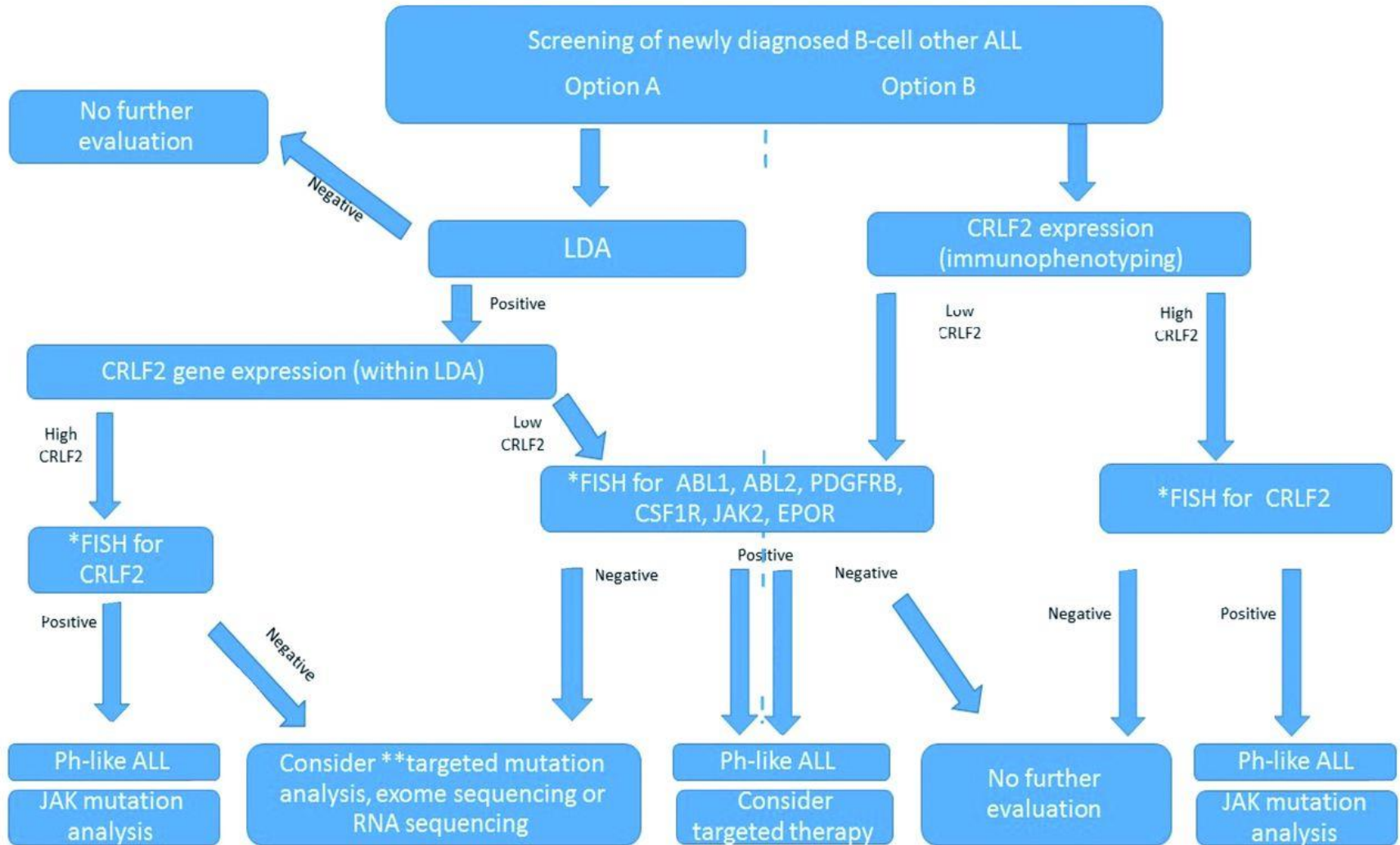
- ▶ Geen specifieke morfologie of flow cytometrie
- ▶ CLRF2 expressie!!!

▶ Genetisch

- ▶ Expressie profiel van BCR-ABL1
- ▶ Geen translocatie BCR-ABL1

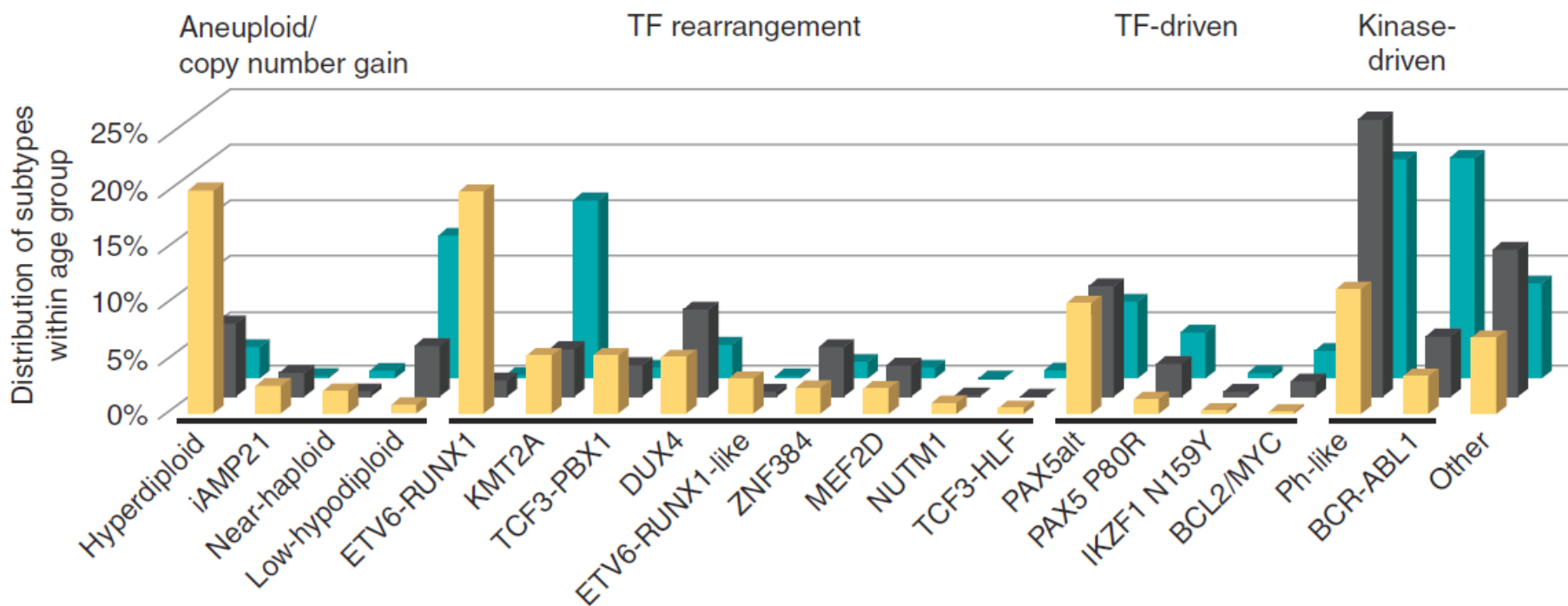


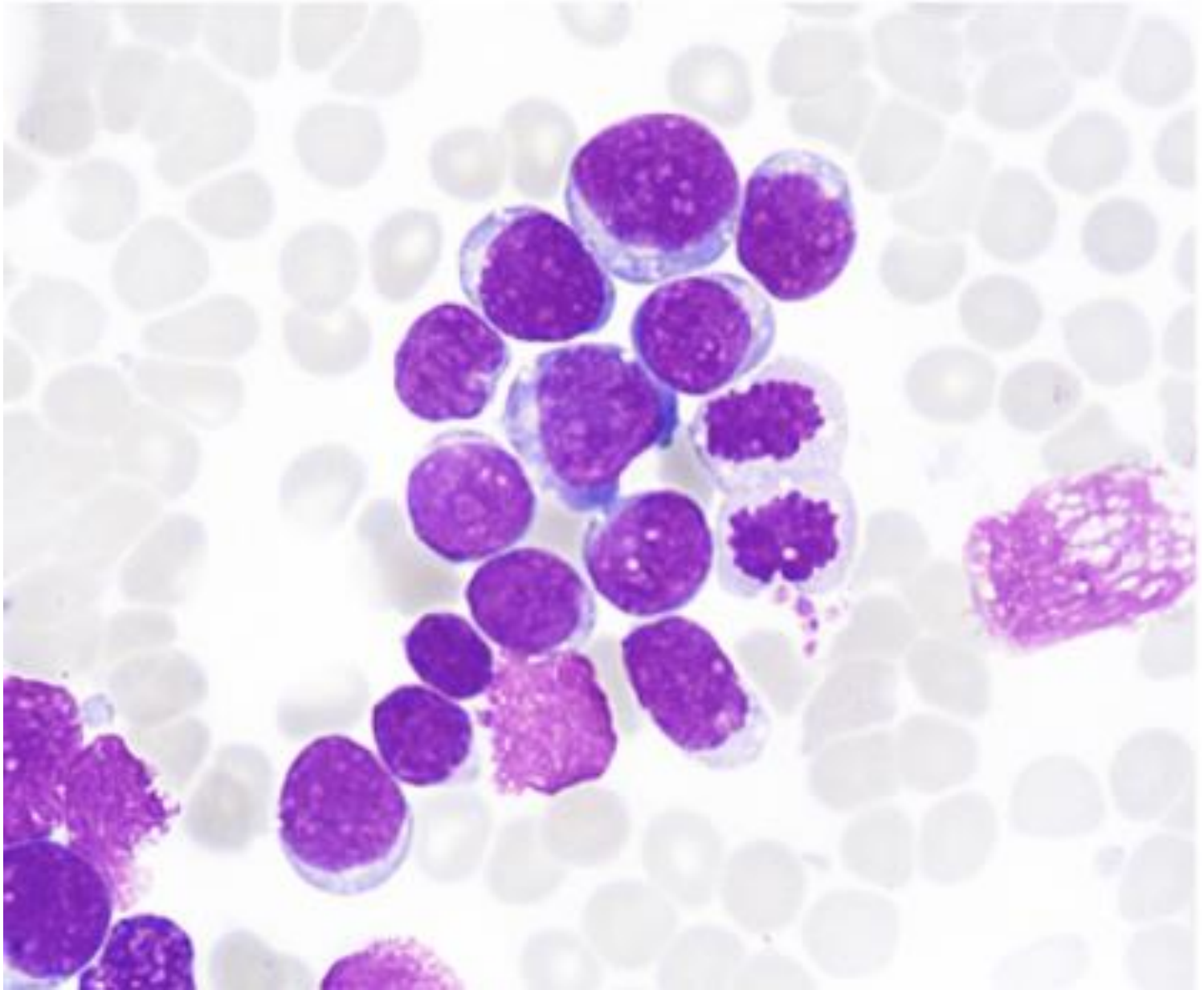
Flowchart diagnostiek



B

Childhood (<15 years) AYA (15–39 years) Adult (≥40 years)





T-ALL Not Otherwise Specified

▶ Prevalentie

- ▶ c.a. 15% van de volwassenen met ALL
- ▶ c.a. 80-90 LBL is T-LBL

▶ Presentatie

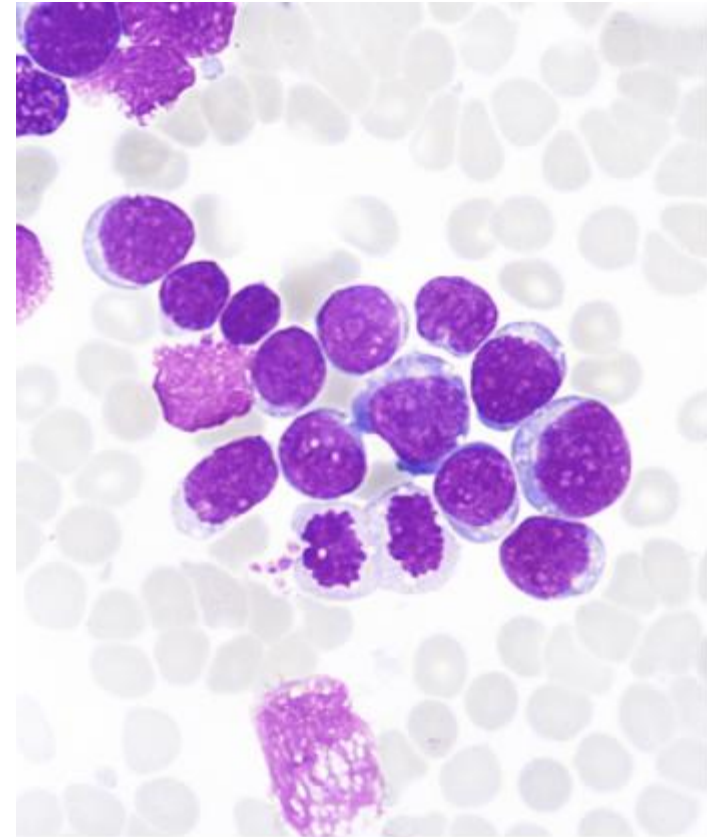
- ▶ Leukocytose, mediastinale massa
- ▶ Rest hematopoëse relatief gespaard

▶ Morfologie

- ▶ Geen goed onderscheid met B-ALL

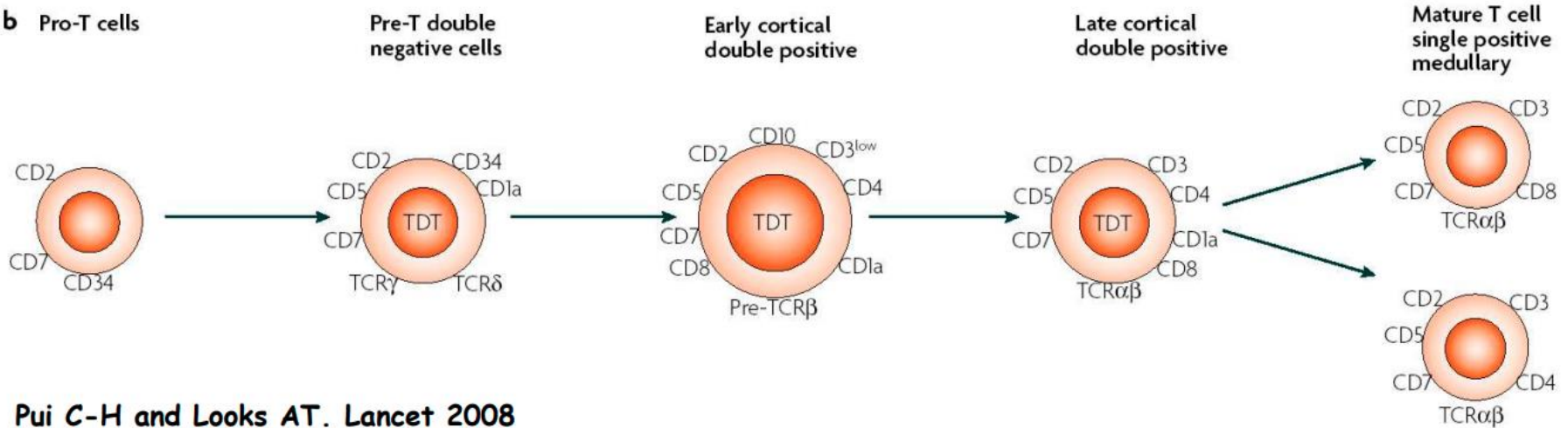
▶ Flowcytometrie

- ▶ cyCD3, meestal TdT en CD7
- ▶ Soms cyCD79a (10%), CD13 en CD33 (30%)



Flowcytometrie

b Pro-T cells



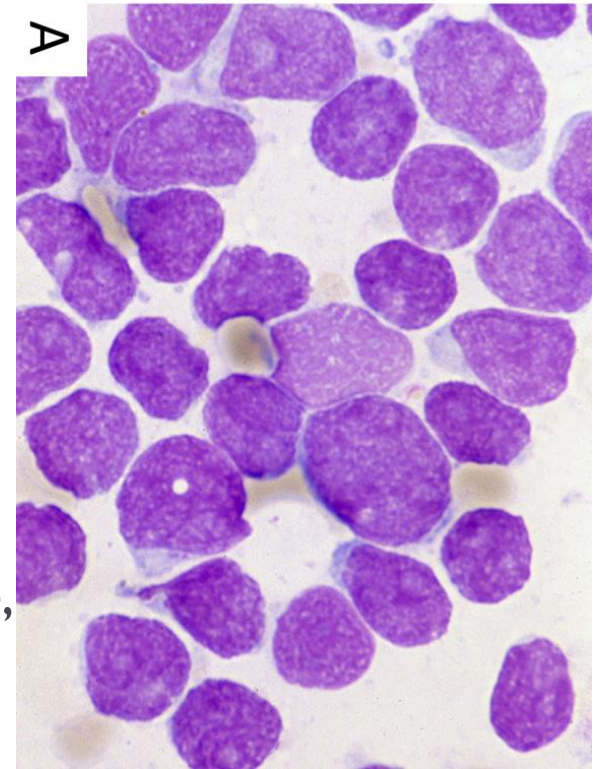
Pui C-H and Looks AT. Lancet 2008

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

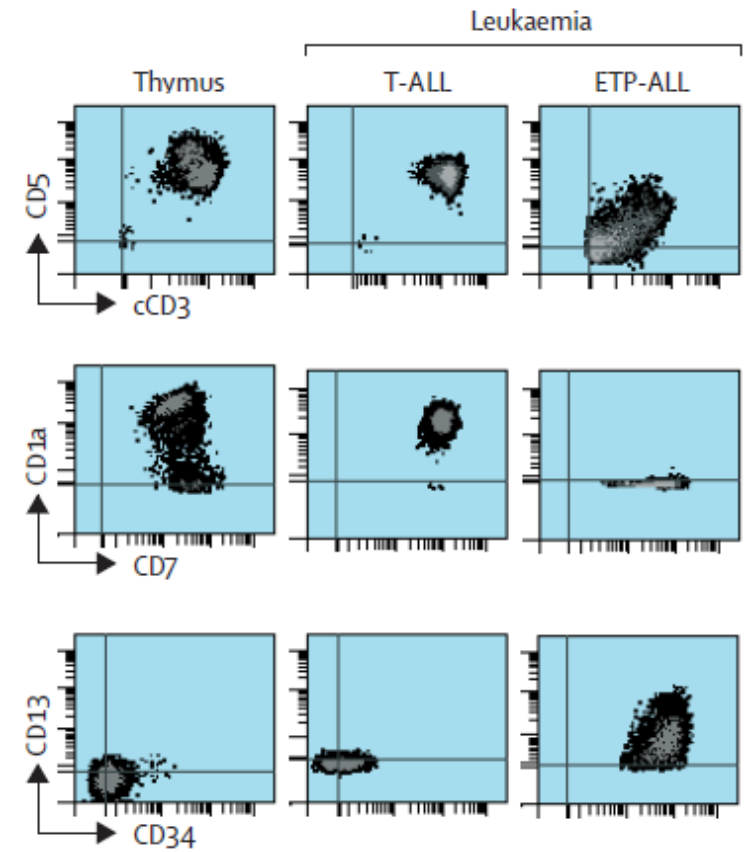
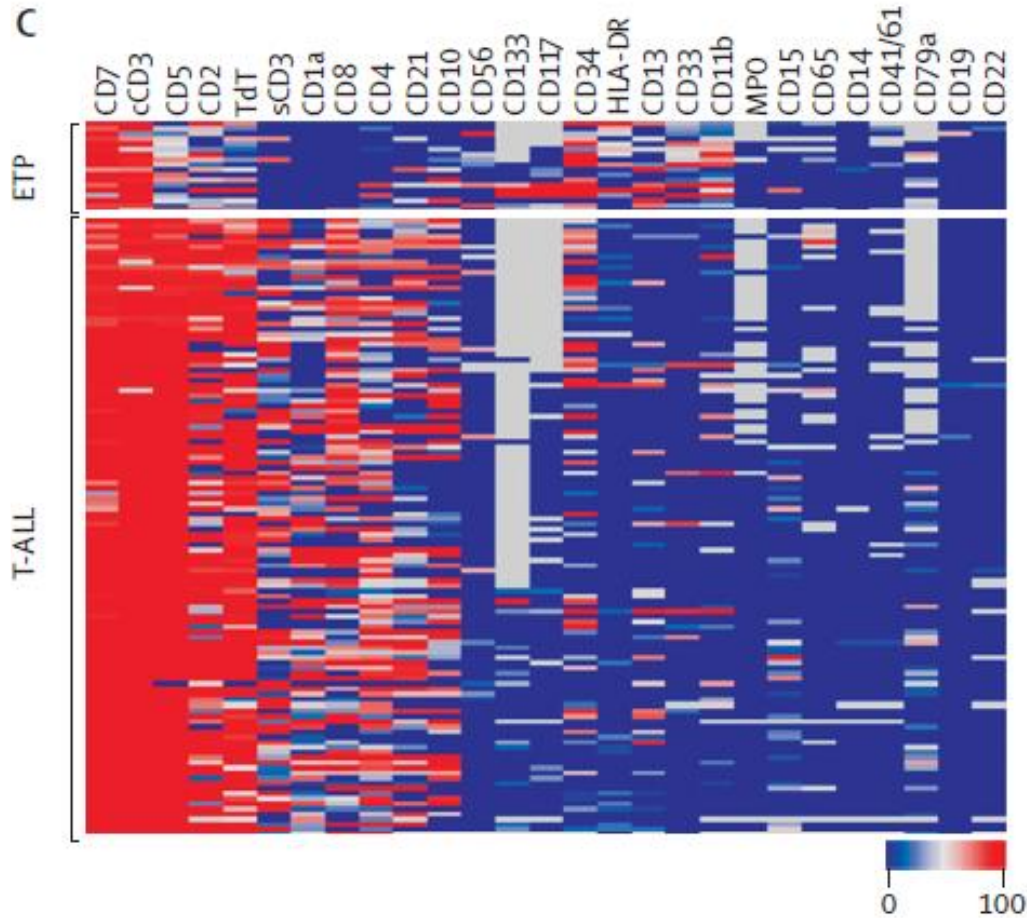
T1= Pro-T-ALL, T2= Pre-T-ALL, T3= cortical T-ALL, T4= mature T-ALL

Early T-cel precursor ALL

- ▶ **Prevalentie**
 - ▶ c.a. 5-10% van de volwassenen
- ▶ **Blast met minimale T cel differentiatie met myeloïde/stamcel kenmerken**
- ▶ **Immunofenotype**
 - ▶ Positief CD7 en cyCD3
 - ▶ Negatief CD8 en CD1a
 - ▶ Positief voor stamcel/myeloïde markers CD34, CD117, CD13, CD33
- ▶ **Genetisch myeloïde mutaties**
 - ▶ FLT3, NRAS/KRAS, DNMT3A, IDH1 en IDH2



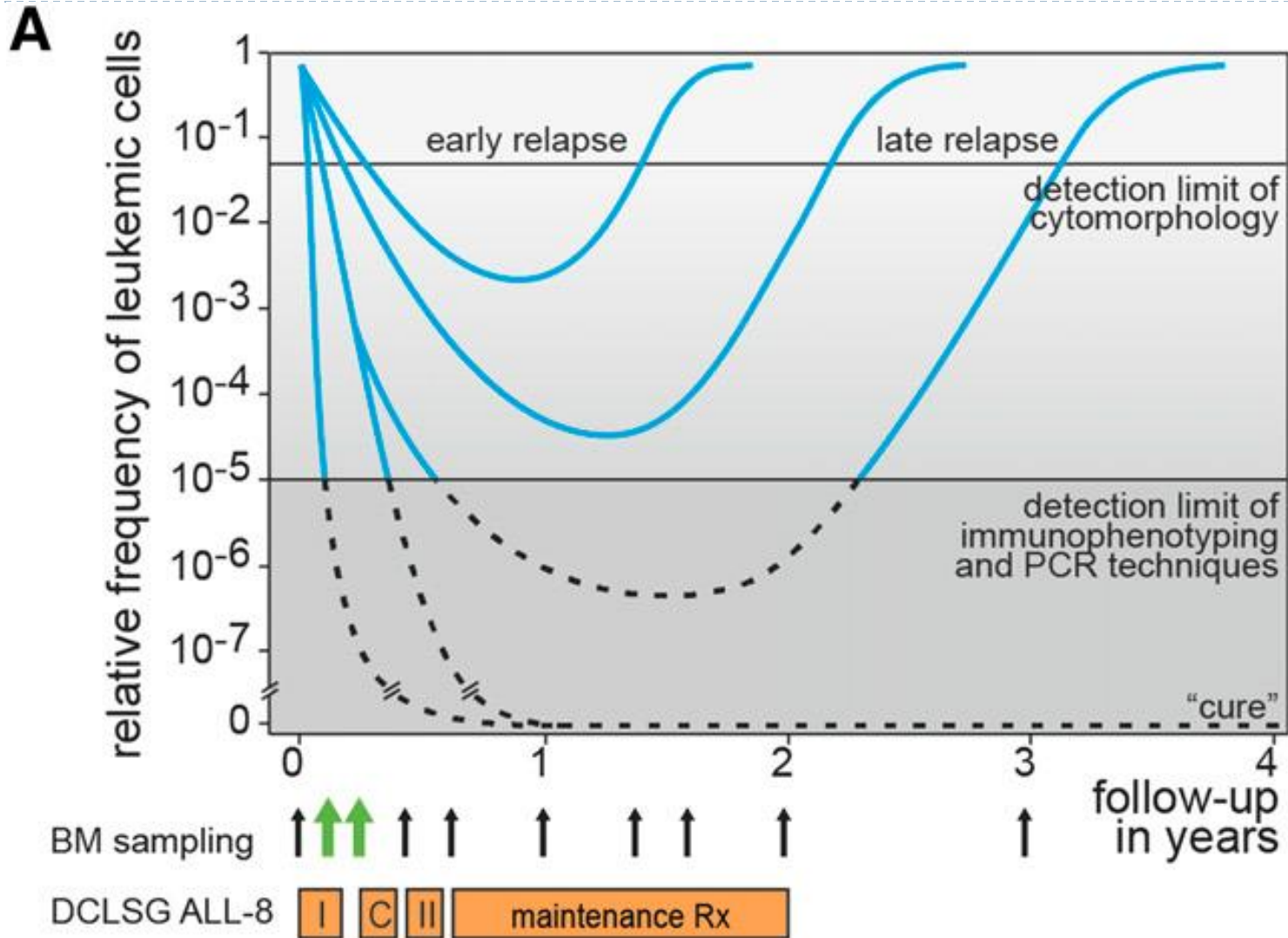
ETP-ALL



Risicogroepen in precursor B- en T-ALL

	Hoog risico	Intermediair risico	Laag risico
Leucocytenaantal bij diagnose B-ALL: > 30x10 ⁹ /L T-ALL: > 100x10 ⁹ /L	+	-	-
Cytogenetische afwijkingen	a. Philadelphia chromosoom t(9;22)(q34;q11)/BCR-ABL1 b. MLL of 11q23 afwijkingen c. lage hypodiploidie/near-triploidie d. complexe structurele en numerieke chromosoom afwijkingen (≥ 5), geen hyperdiploidie	-	-
Moleculaire afwijkingen	BCR-ABL/MLL fusie	-	-
CR na remissie inductie kuur 1	Geen CR na 1ste RI	CR na 1ste RI	CR na 1ste RI
Flowcytometrische MRD na 1ste consolidatie 1b of remissie inductie kuur 2 ^a	≥ 10 ⁻⁴	<10 ⁻⁴	<10 ⁻⁴
Leeftijd (geen parameter)	18-70 jaar	40-70 jaar	≤40 jaar

Minimale restziekte (MRD)



MRD meting



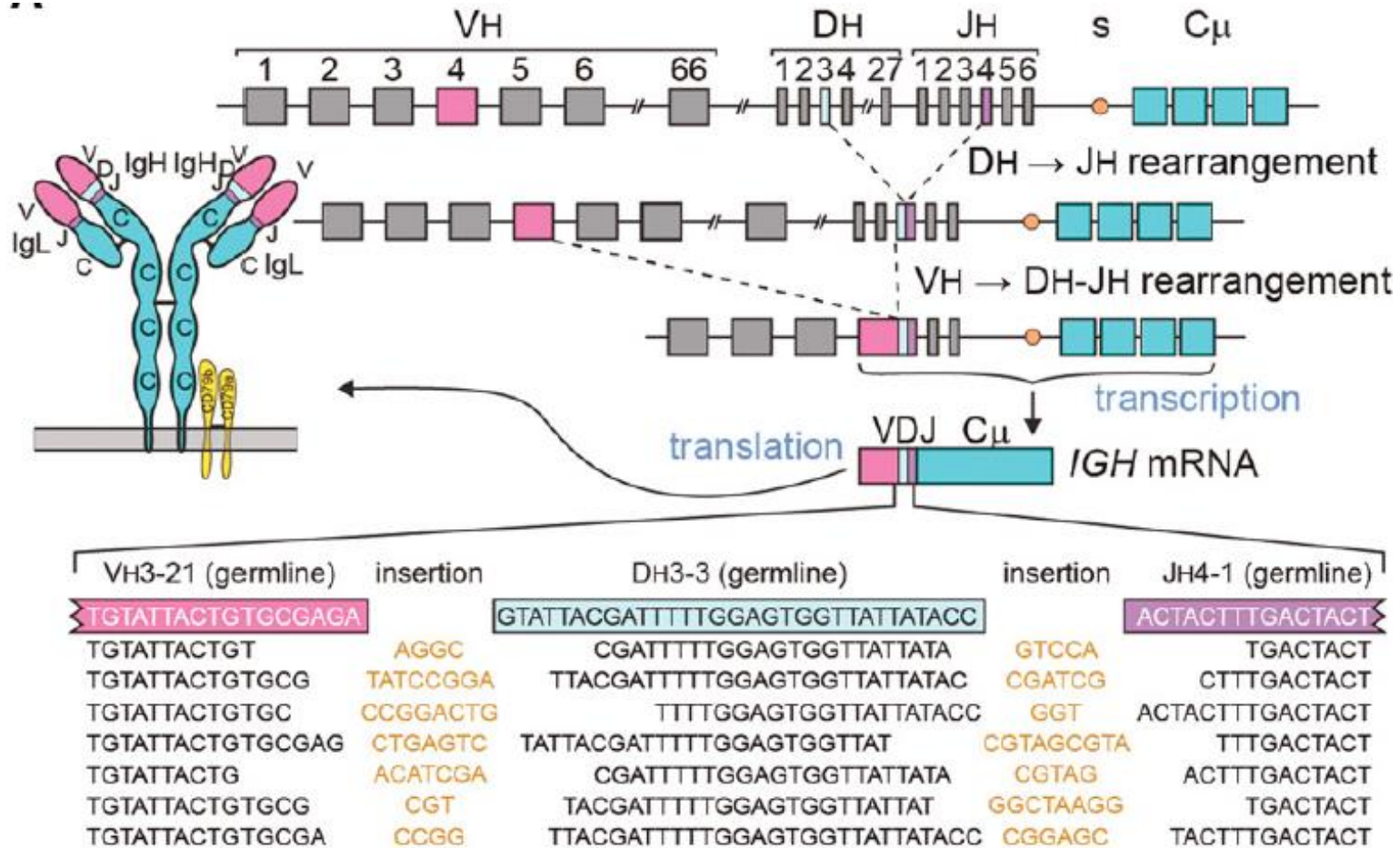
Ig/Tr rearrangements (PCR)



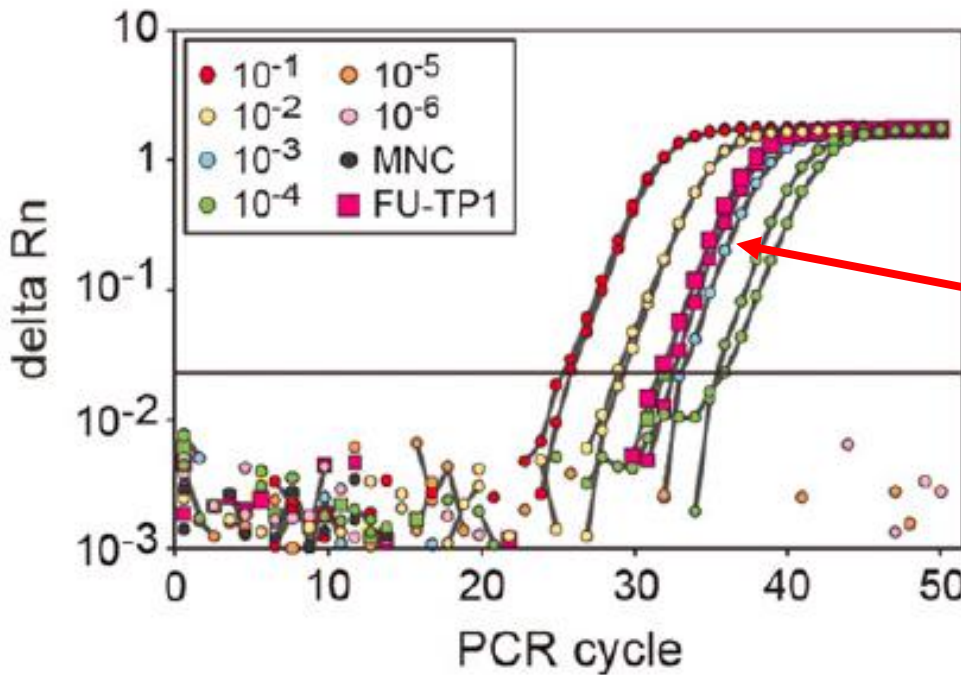
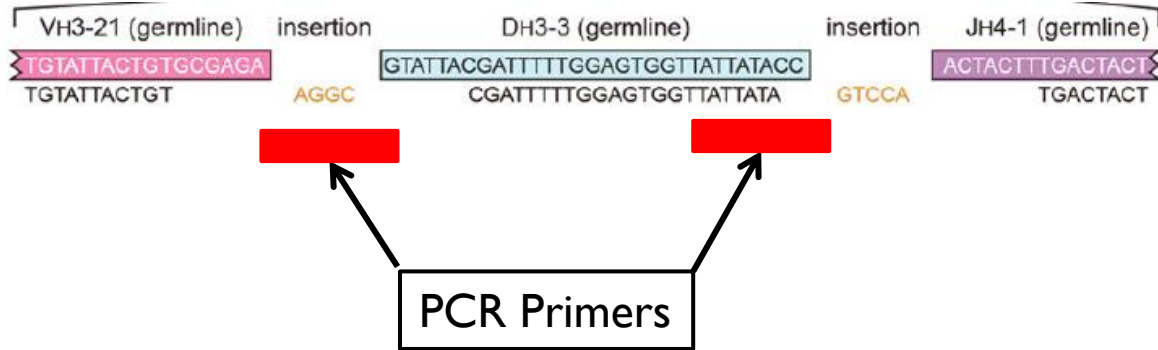
Flow cytometrie



PCR IG/TR MRD



PCR IG/TR MRD



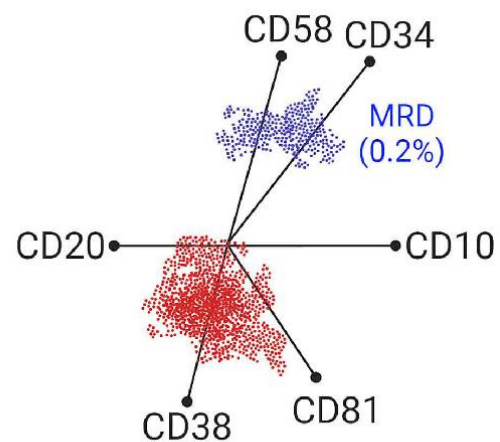
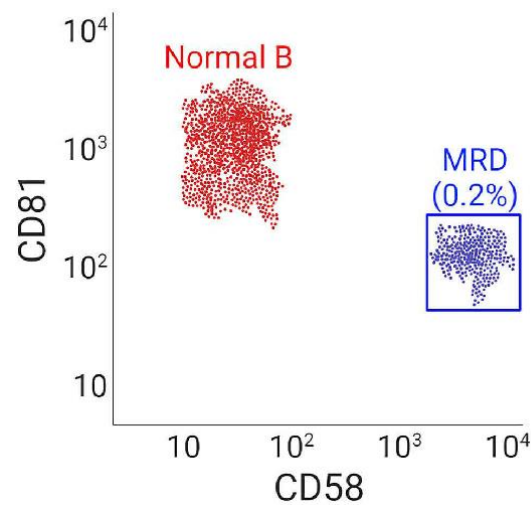
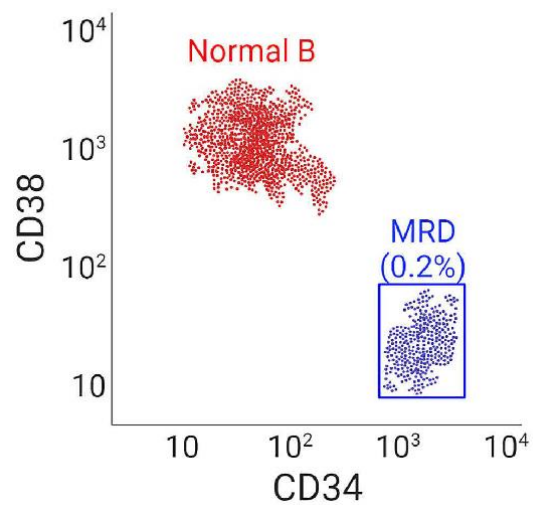
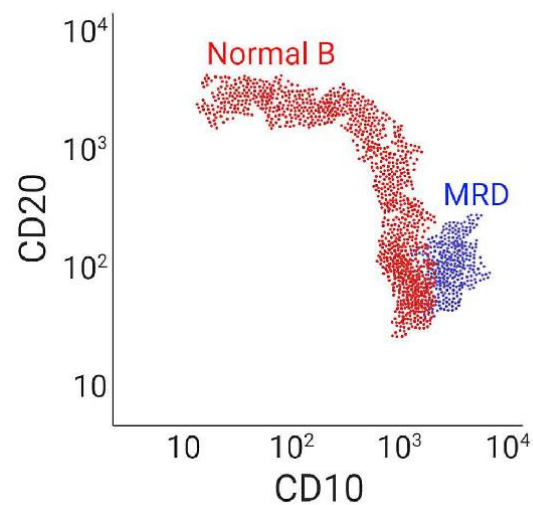
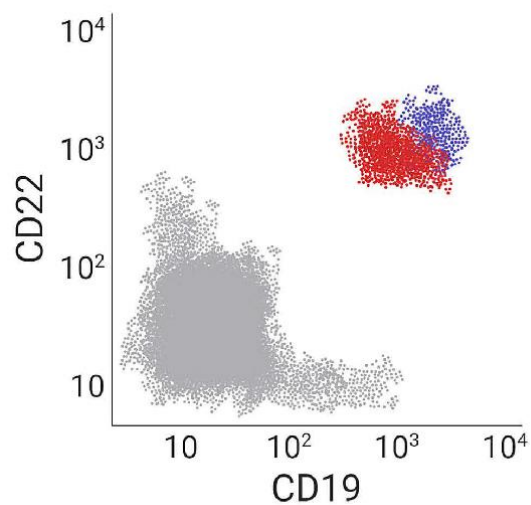
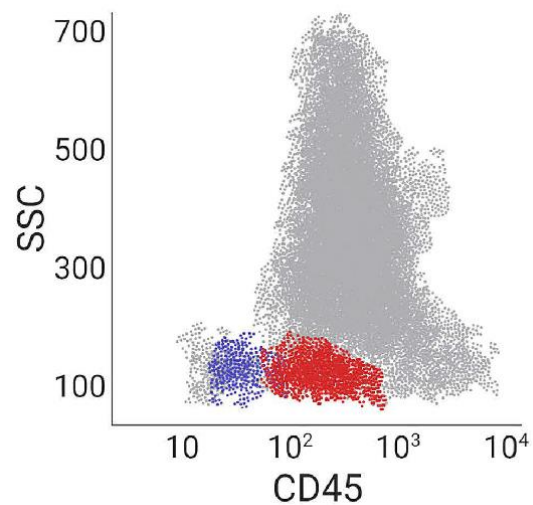
Gevoeligheid 10^{e-4}

Flowcytometrie MRD

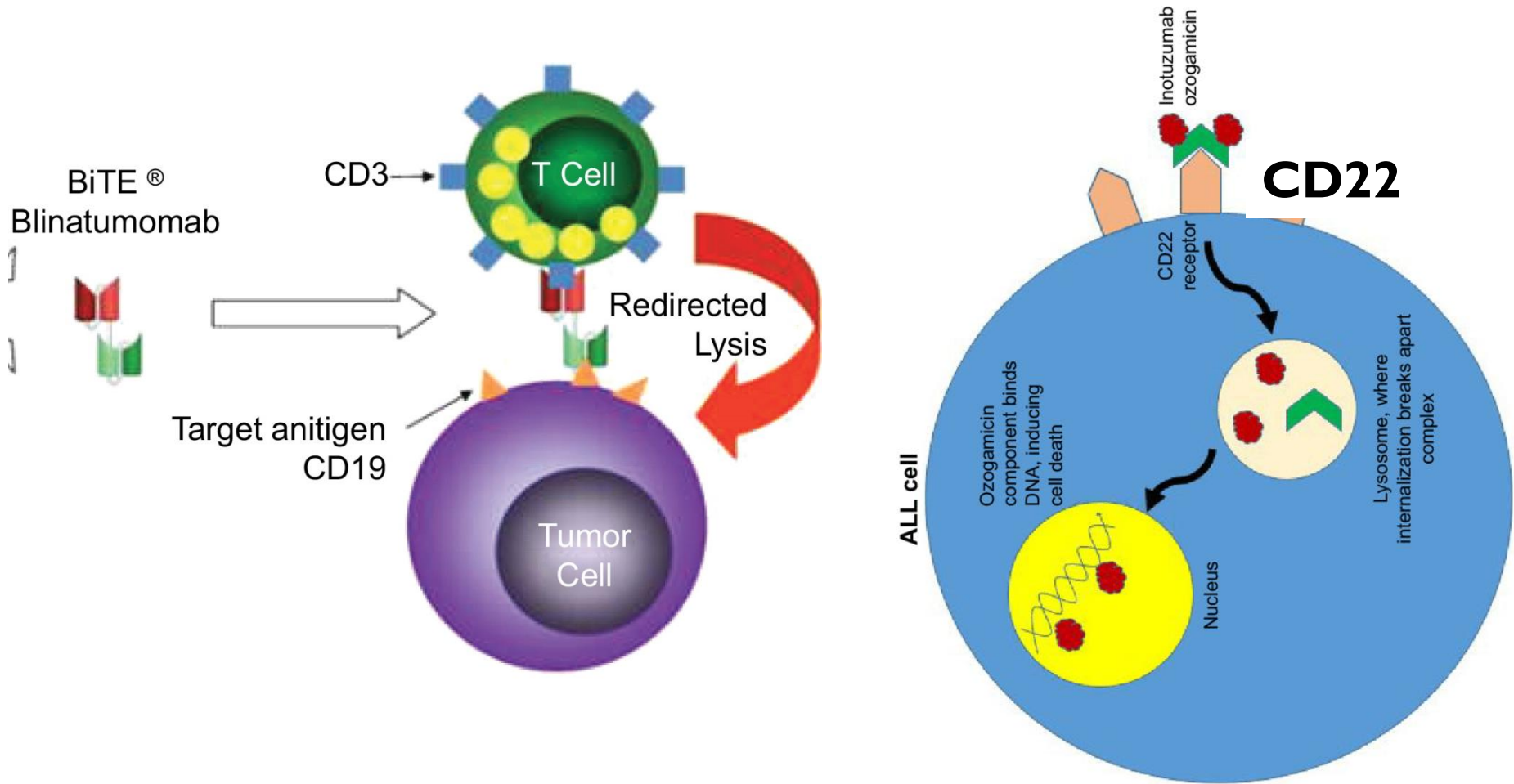
Table 11. Utility of BCP-ALL markers

Tube	Target antigen	Identification of blasts	Additional markers, 1st level			Additional markers, 2nd level		Aim per tube
			Positive diagnosis	Differential diagnosis ^a	Classification (e.g. maturation stage)	Classification (molecular aberrancy)	LAP identification	
Backbone Markers	CD34	X	X			X	Identification of blasts	
	CD19	X	X					
	CD45	X		X				
Tube 1	CD20		X				X	Diagnosis Classification LAP markers Molecular subtypes
	CD58						X	
	CD66c				X	X	X	
	CD10		X		X		X	
	CD38				X	X	X	
Tube 2	Smlgκ				X			Diagnosis Classification
	CyIgμ		X		X			
	CD33				X			
	CD117				X			
	SmlgM				X	X		
	Smlgλ				X	X		
Tube 3	CD9					X	X	Diagnosis Classification LAP markers Molecular subtypes
	NuTdT		X					
	CD13				X			
	CD22		X				X	
	CD24		X			X	X	
Tube 4	CD21						X	Classification LAP markers Molecular subtypes
	CD15				X	X		
	CDw65				X	X		
	NG2					X		
	CD123				X		X	
	CD81						X	

Abbreviations: ALL, acute lymphoblastic leukemia; AUL, acute undifferentiated leukemia. BCP, B-cell precursor; Cy, cytoplasmic; LAP, leukemia-associated phenotypes; MPAL, mixed phenotype acute leukemia; Nu, nuclear; Sm, surface membrane. ^aMain differential diagnoses considered: mature B-cell malignancies, normal immature B-cells (hematogones), other acute leukemias with B-cell marker expression, MPAL/AUL.



B-ALL MRD Flowcytometrie



Post CD19 therapy relapse

