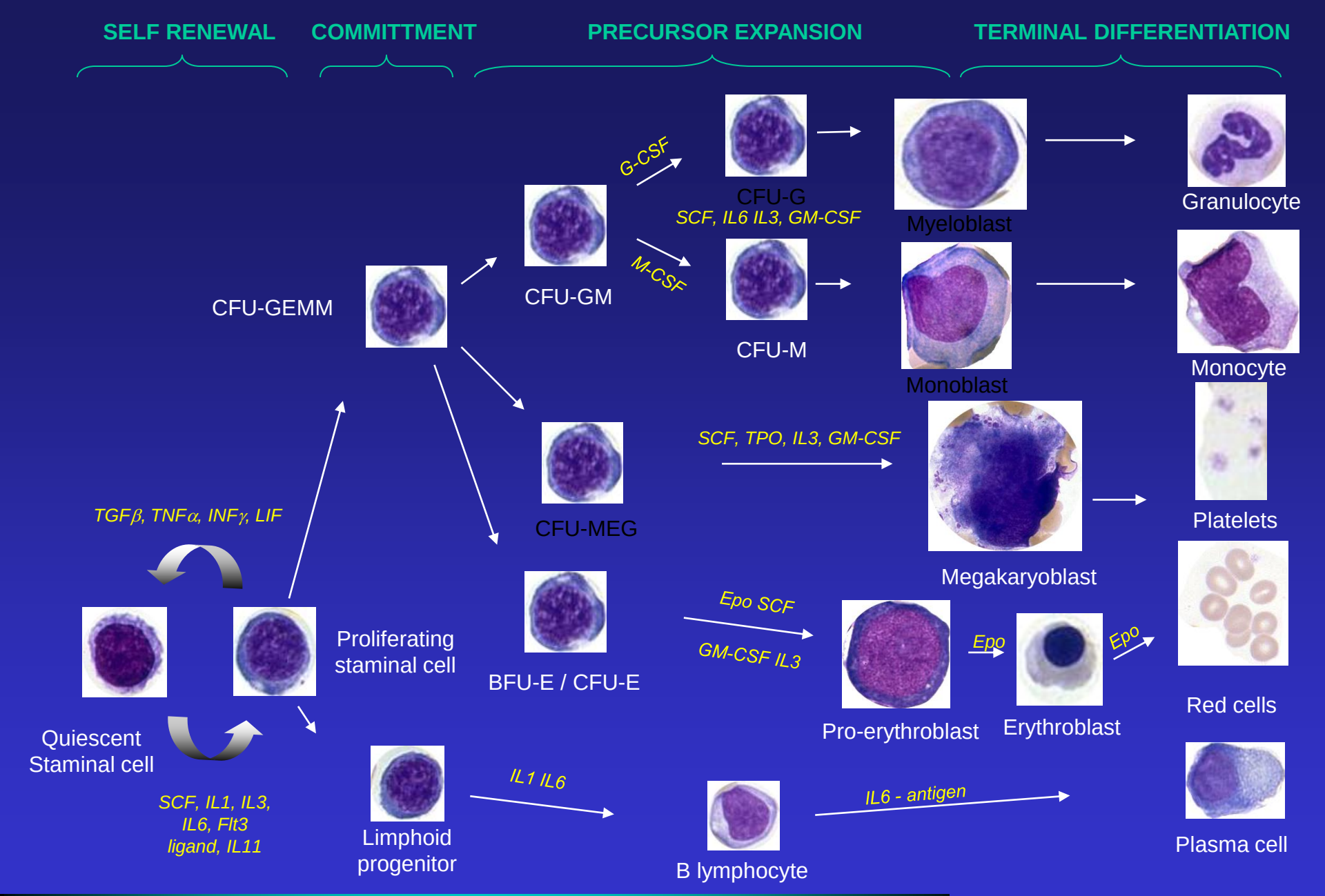
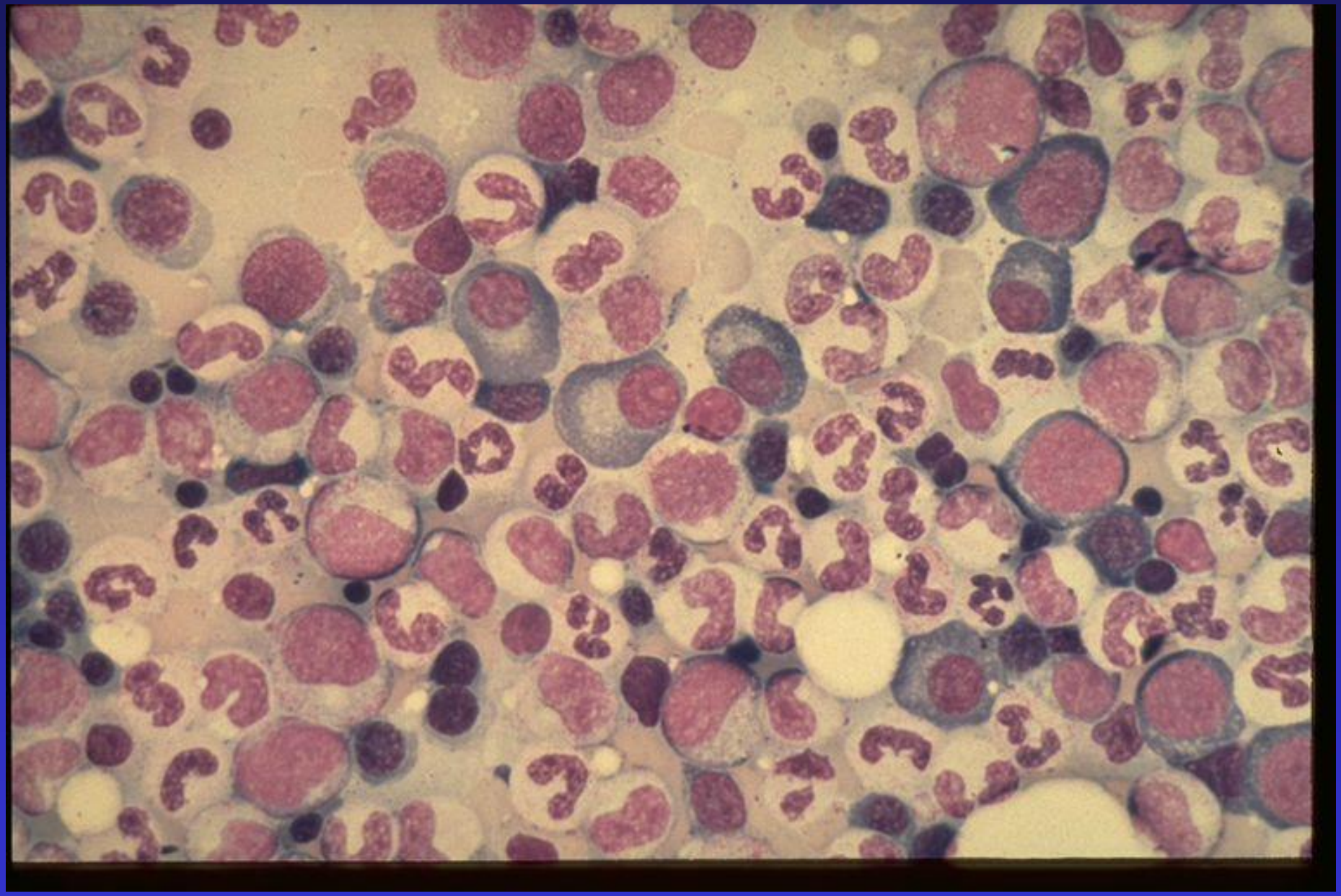
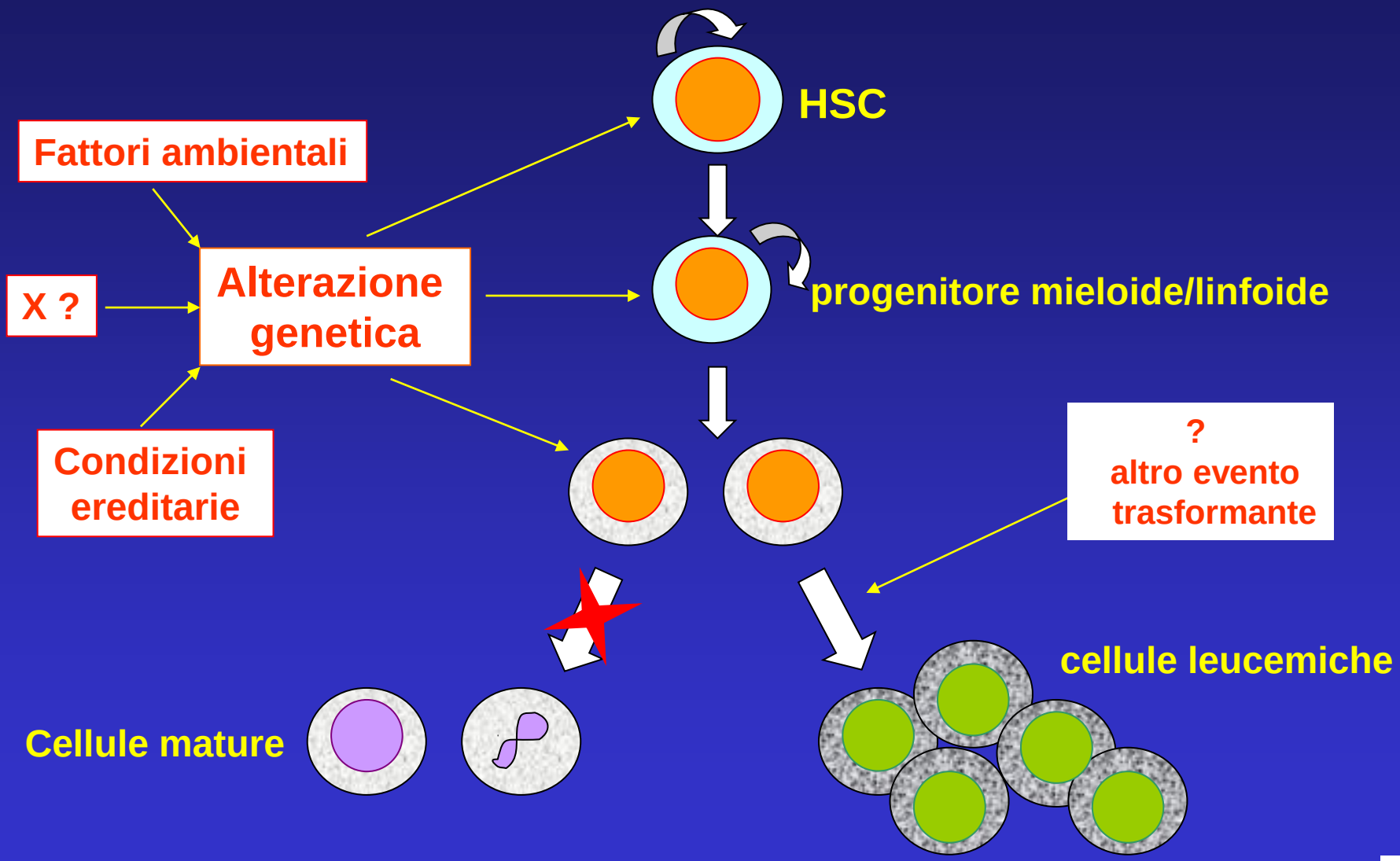


Normal hematopoiesis



EZIOPATOGENESI DELLE LEUCEMIE ACUTE



CONDIZIONI EREDITARIE

Sindromi ereditarie

- Sindrome Down (trisomia 21)
- Sindromi con deficit del "DNA-repair" (S. Bloom, Anemia di Fanconi)
- Sindromi da immunodeficienza (S. Wiskott Aldrich)

Alto rischio familiare di LA

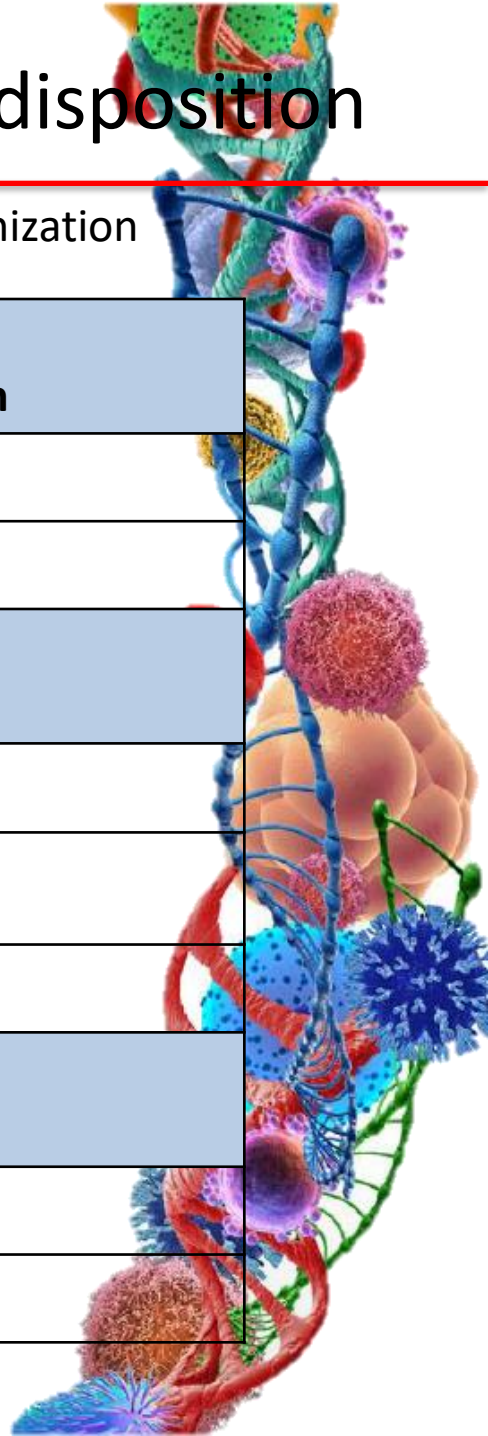
- Monosomia del 7 (SMD)
- Mutazione AML-1

Myeloid Neoplasm with Germline Predisposition

A New Provisional Entity Within the World Health Organization

Myeloid neoplasm with germline predisposition without preexisting disorder or organ dysfunction
• CEBPA mutation
• DDX41 mutation*
Myeloid neoplasm with germline predisposition and preexisting platelet disorders
• RUNX1 mutation*
• ANKRD26 mutation*
• ETV6 mutation*
Myeloid neoplasm with germline predisposition and other organ dysfunction
• GATA2 mutations
• BMF syndromes , Noon sd, Down sd*, TBDs

*Lymphoid neoplasms also reported



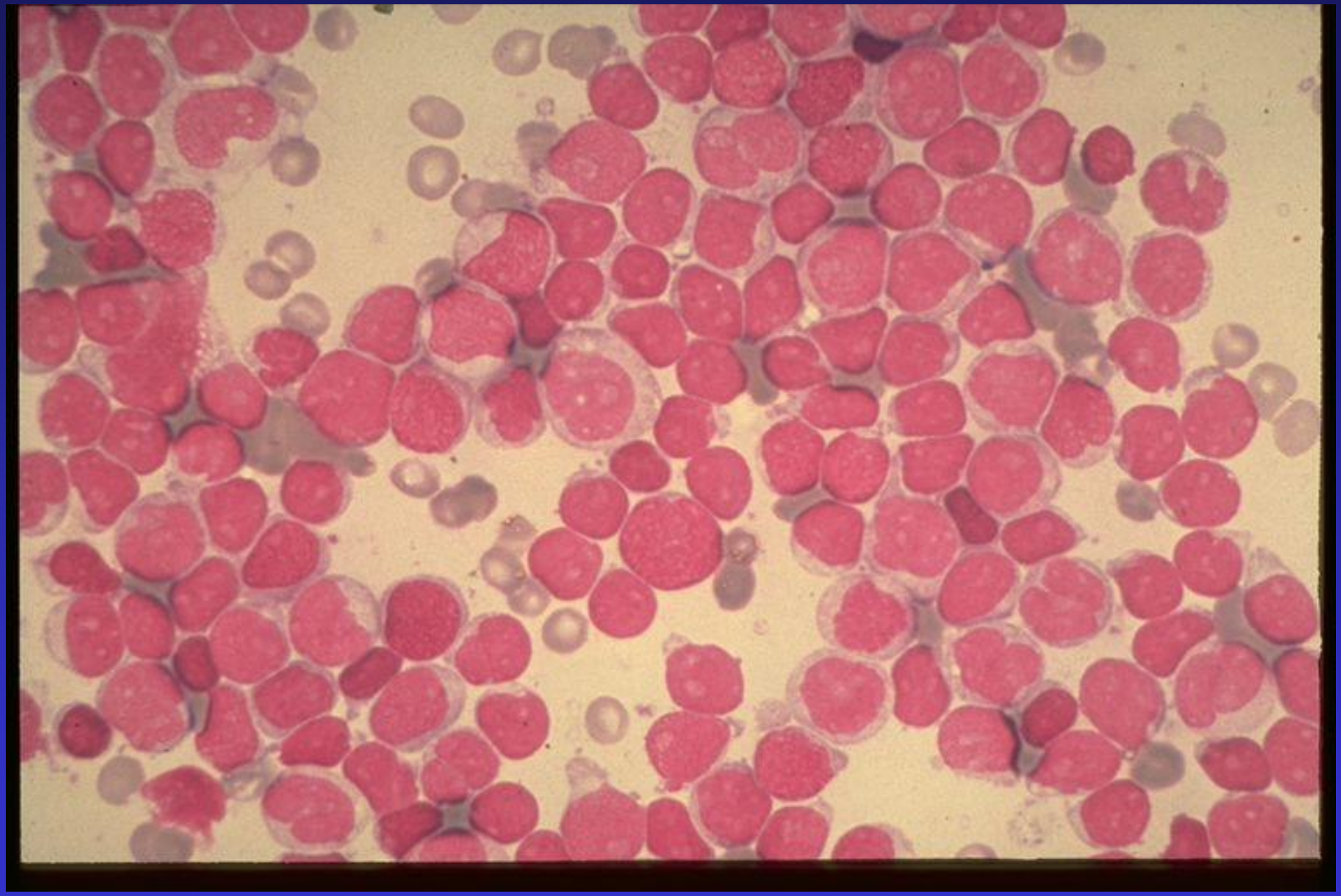
Epidemiologia

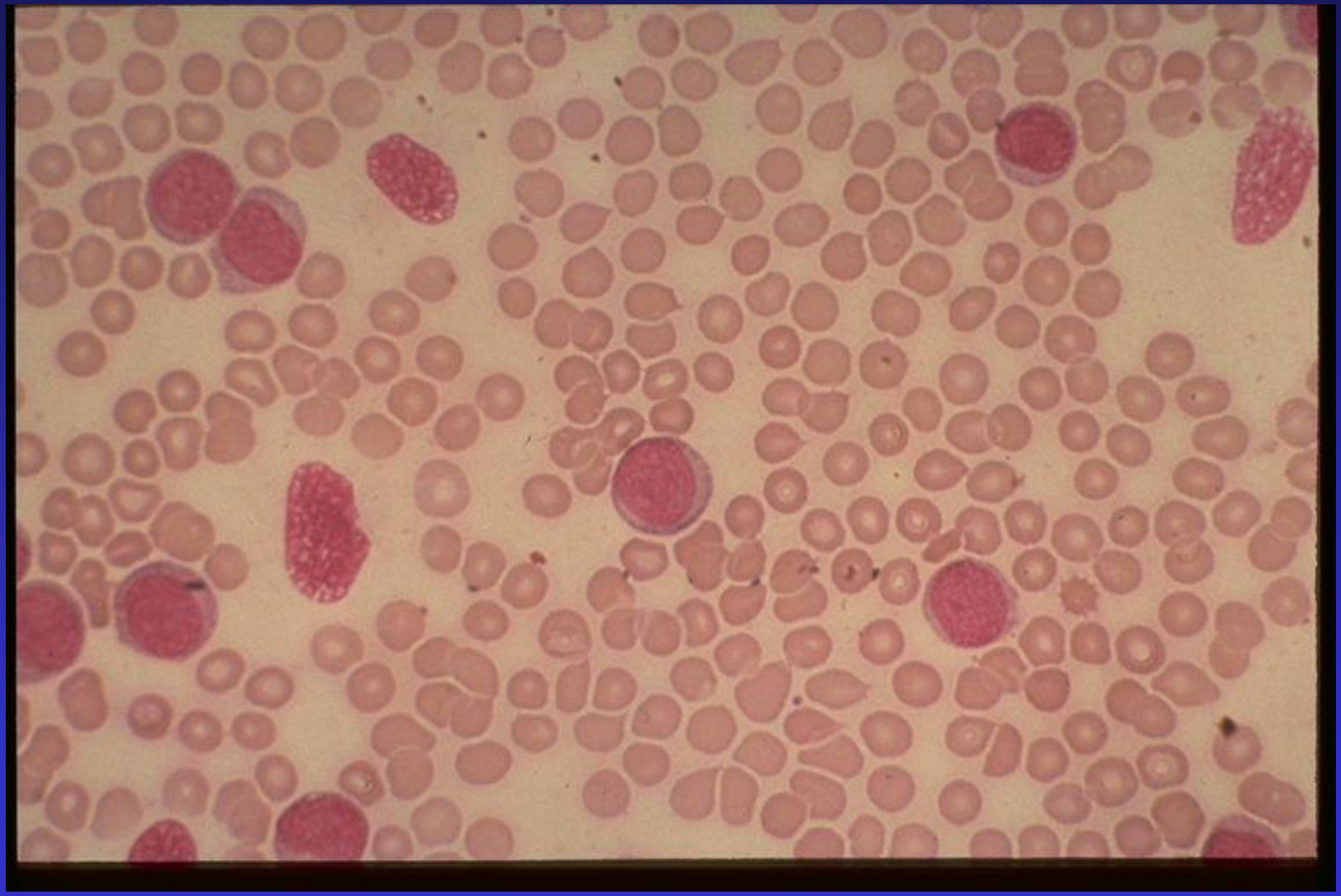
80% delle LA nell'adulto

(10% delle LA prima dei 10 aa)

Incidenza: 3-5 :100.000 , aumenta con l'età

(30-34 aa 1:100.000 → 65-69 aa 11:100.000)





LEUCEMIE ACUTE

FISIOPATOLOGIA

1) **INSUFFICIENTE E DIFETTIVA PRODUZIONE DI LEUCOCITI (infezioni); ERITROCITI (anemie) E PIASTRINE (emorragie);**

2) **INFILTRAZIONE DI TESSUTI E ORGANI NON EMOPOIETICI DA PARTE DELLE CELLULE BLASTICHE (organomegalia; danno funzionale)**

3) **LIBERAZIONE DI CITOCHINE (febbre, algie, calo ponderale, sudorazioni);**

SINTOMI E SEGNI CLINICI DI ESORDIO IN 466 CASI DI LAM «DE NOVO» O PRIMARIE

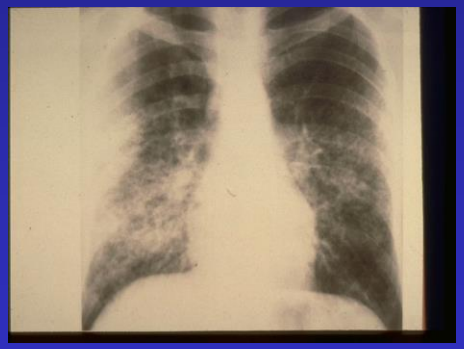
Astenia	93 (%)
Cardiopalmo, dispnea	55 (%)
Febbre	62 (%)
Febbricola	25 (%)
Emorragie	61 (%)
Dolori ossei o muscolari	23 (%)
Sudorazioni profuse	8 (%)
Splenomegalia	18 (%)
Epatomegalia	11 (%)
Linfoadenomegalia	9 (%)
Ipertrofia gengivale	11 (%)
Interessamento cutaneo	5 (%)
Sintomi e segni neurologici	1 (%)

Leucemia Acuta

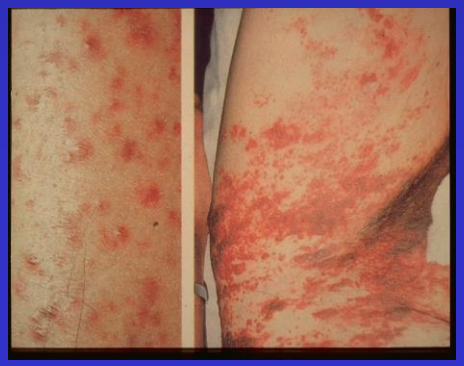
Quadro Clinico - Obiettivo

- Anemia

- Infezioni



- S. Emorragica



Laboratorio

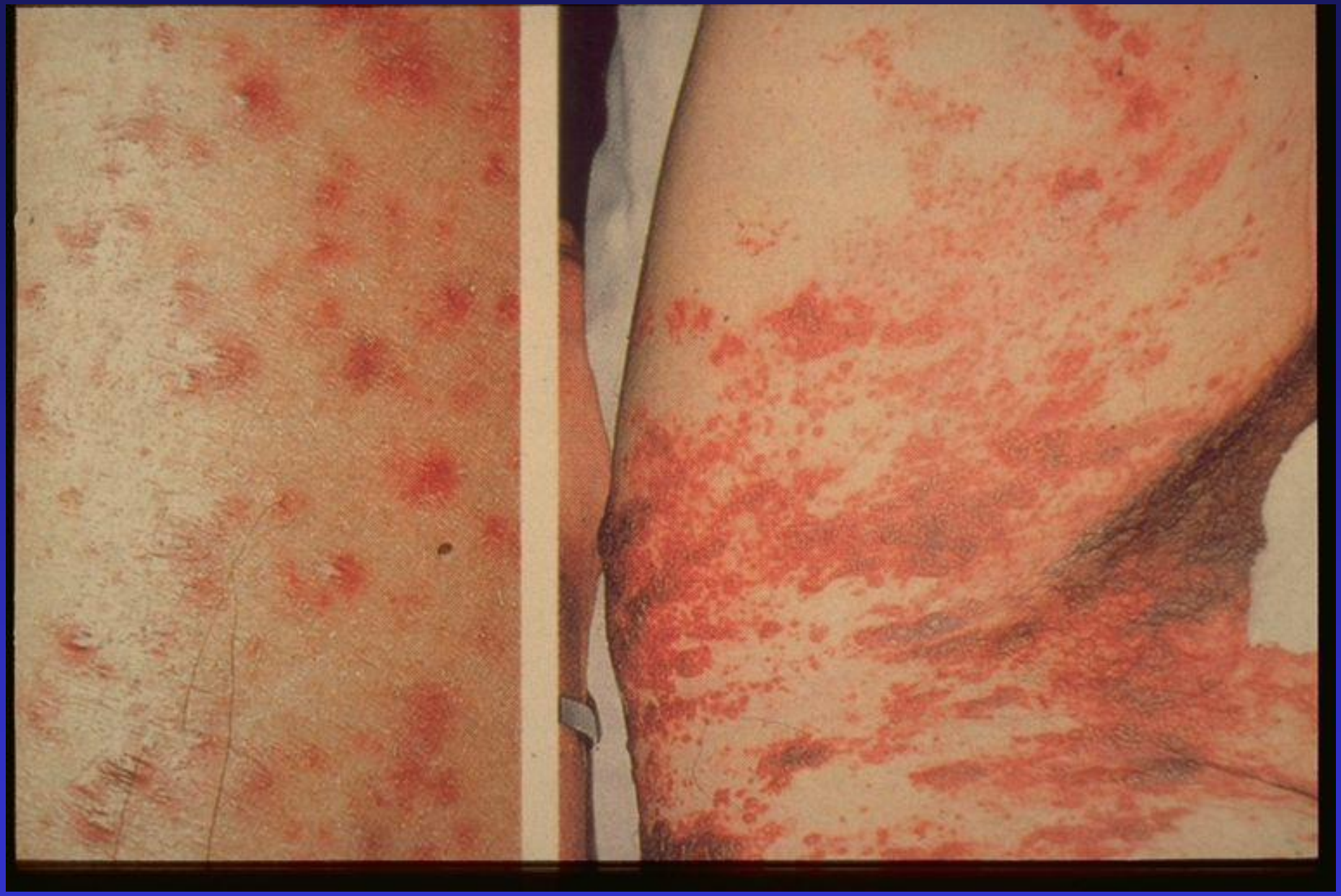
Hb < 12.5 g/dl uomo
Hb < 11.5 g/dl donna

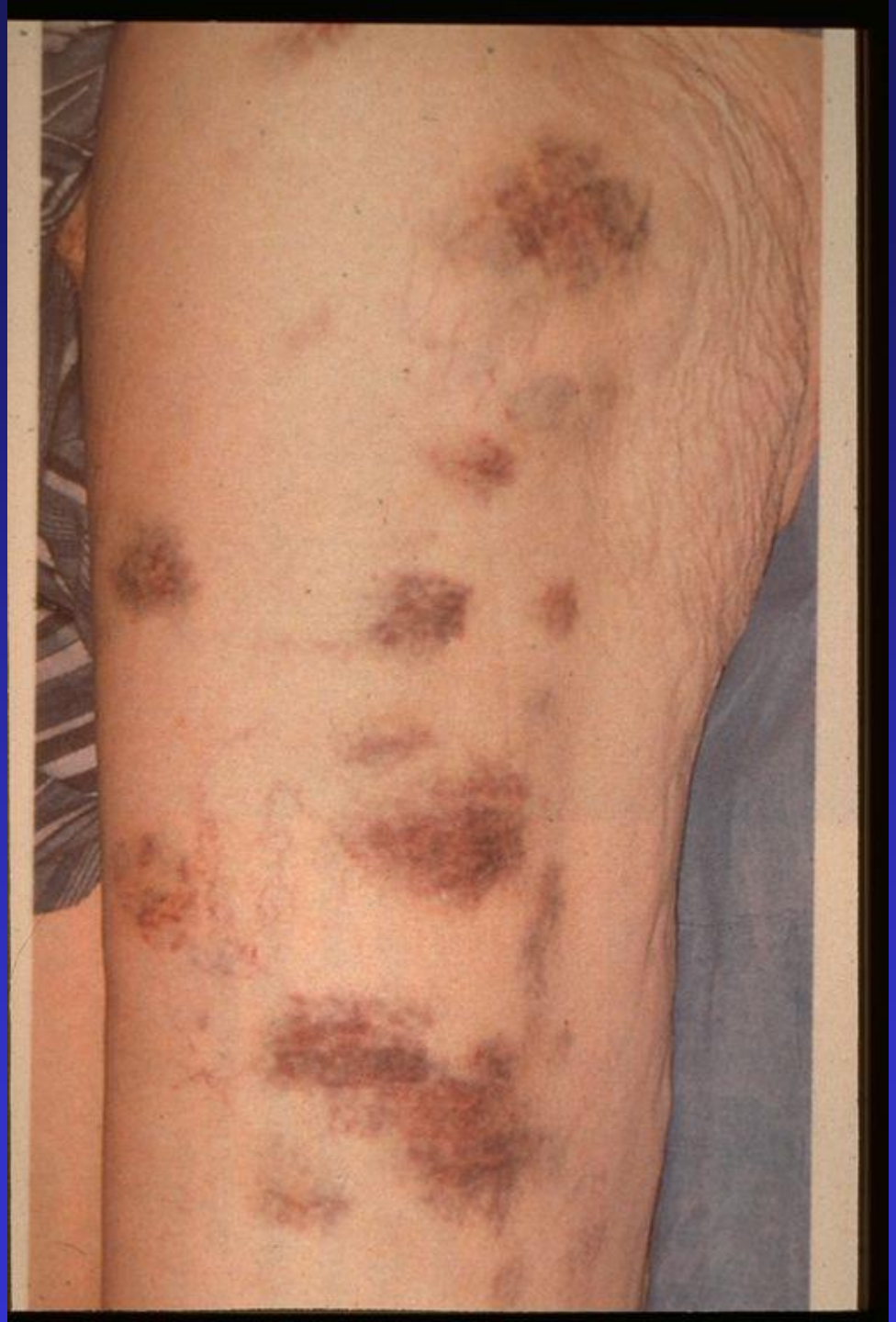
Neutropenia
< 1000/mm3

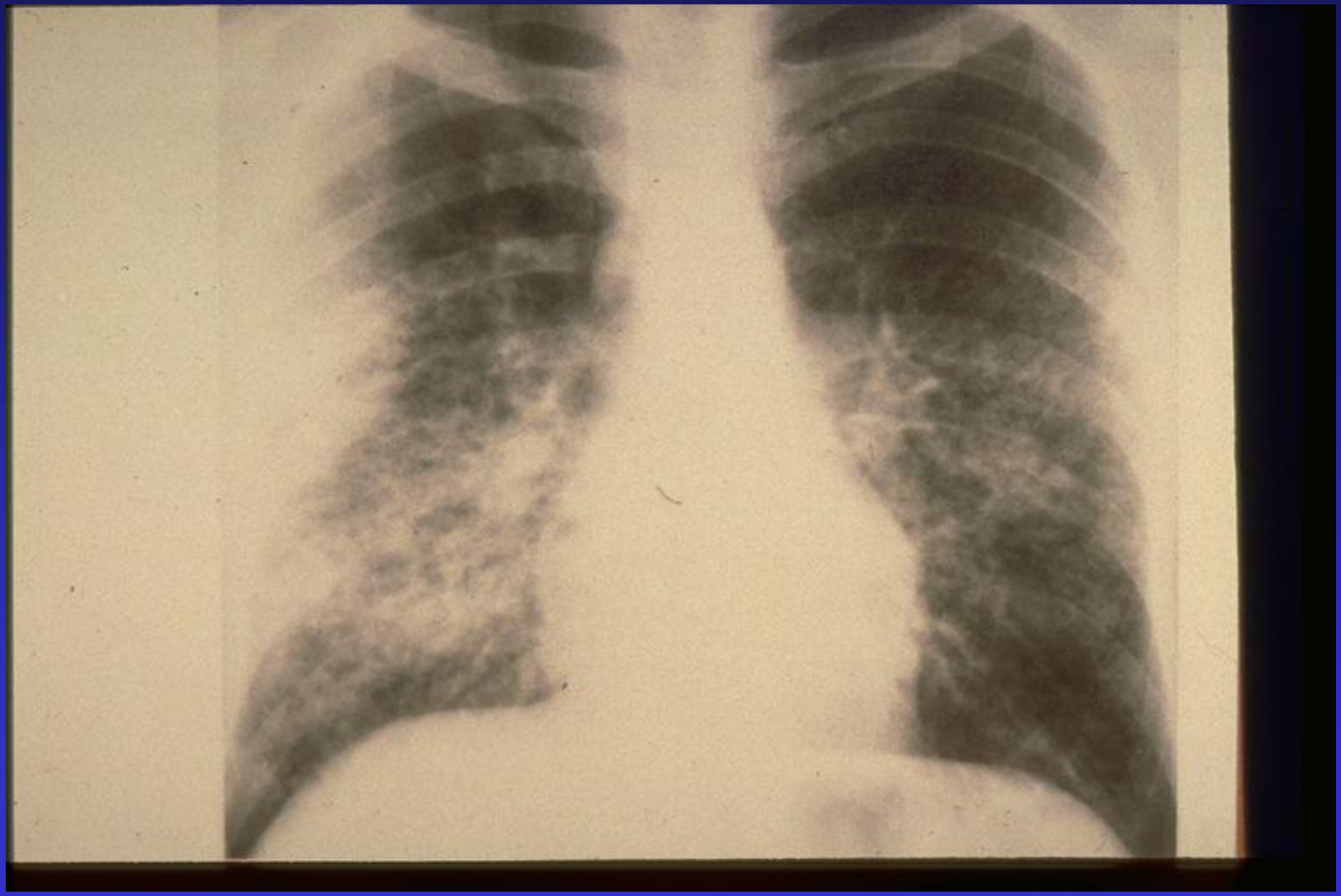
Blastosi Leucemica

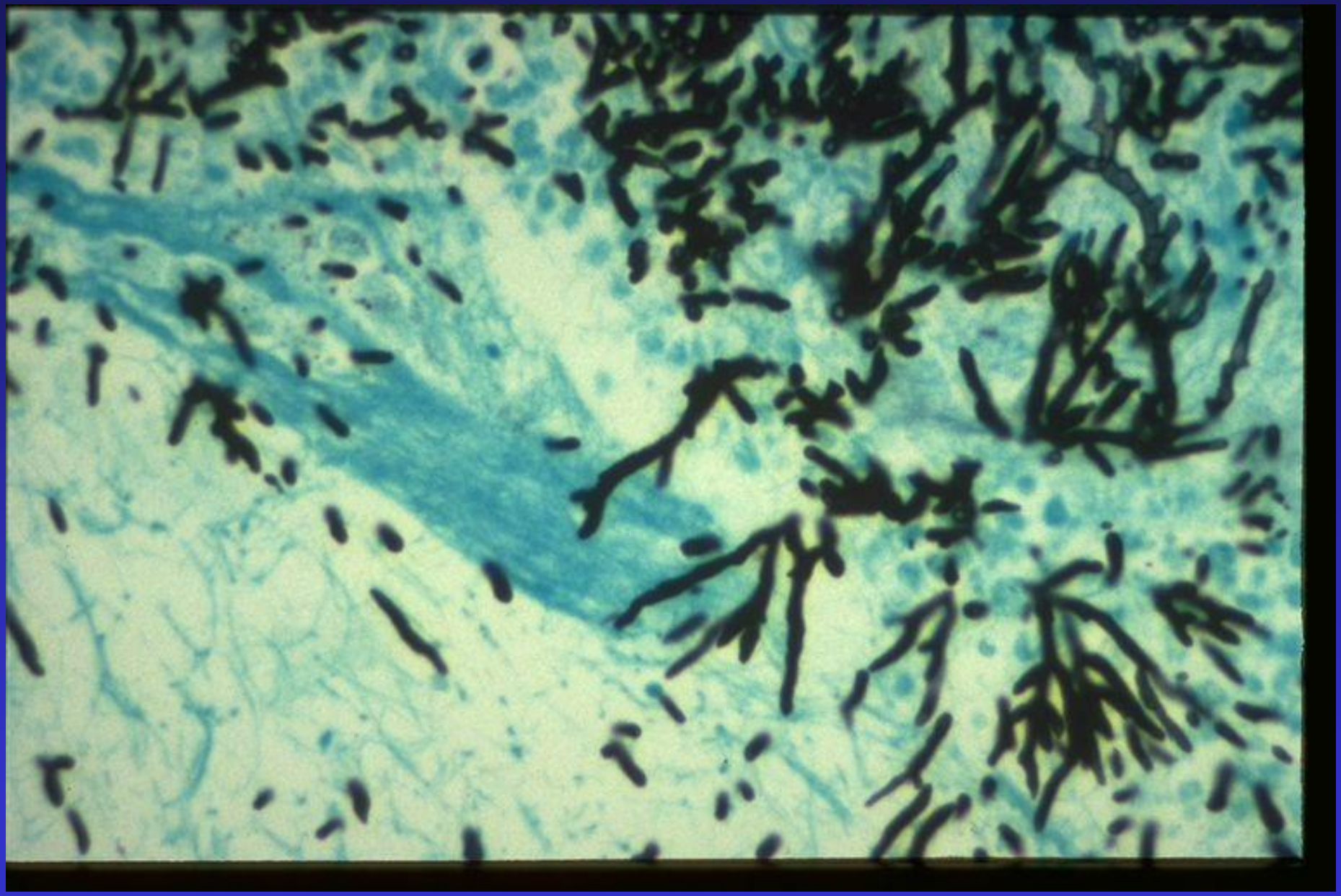
PLT < 150 x 10^9/L

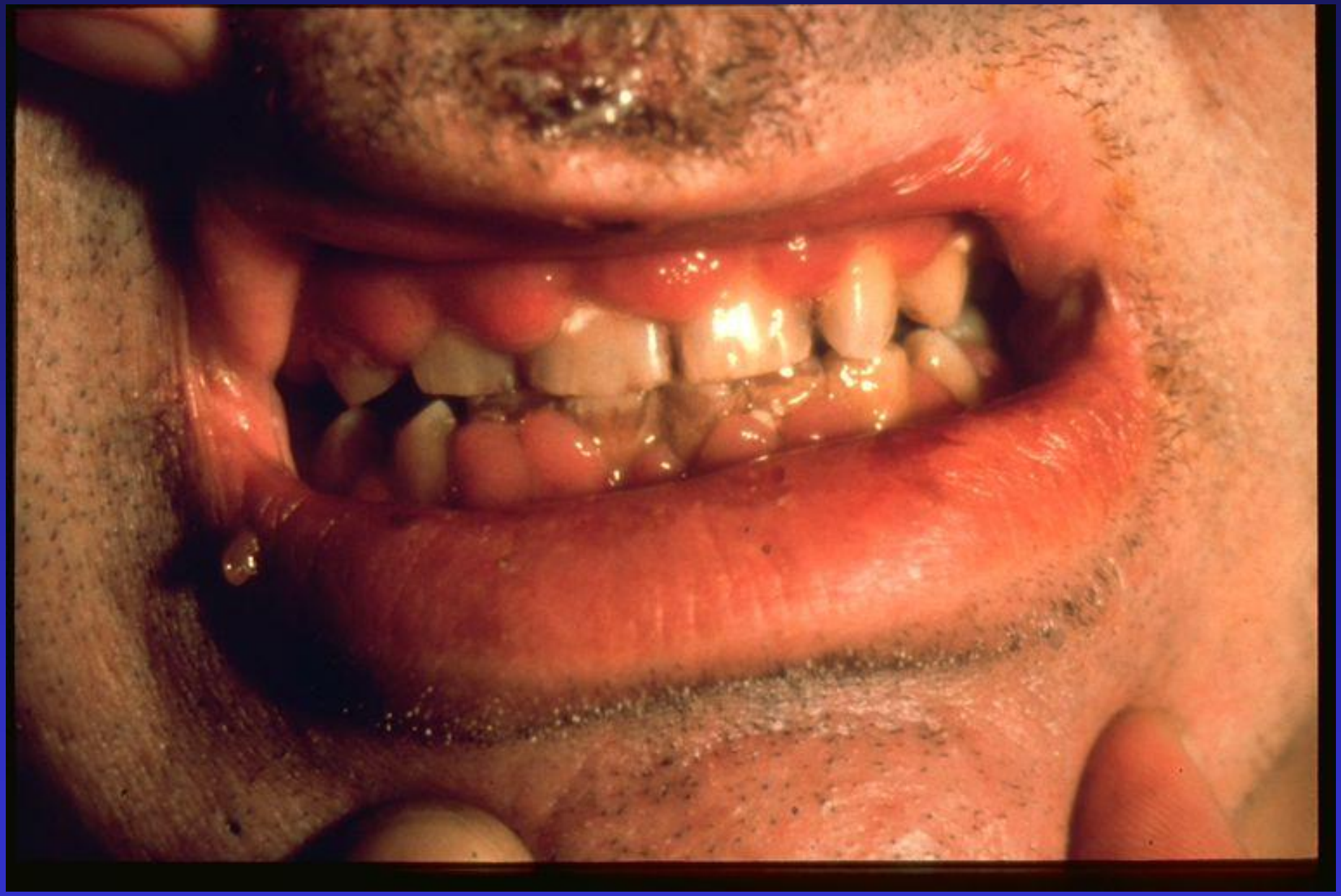
(CID)











Leucemia Acuta - Esordio

Terapia di Supporto

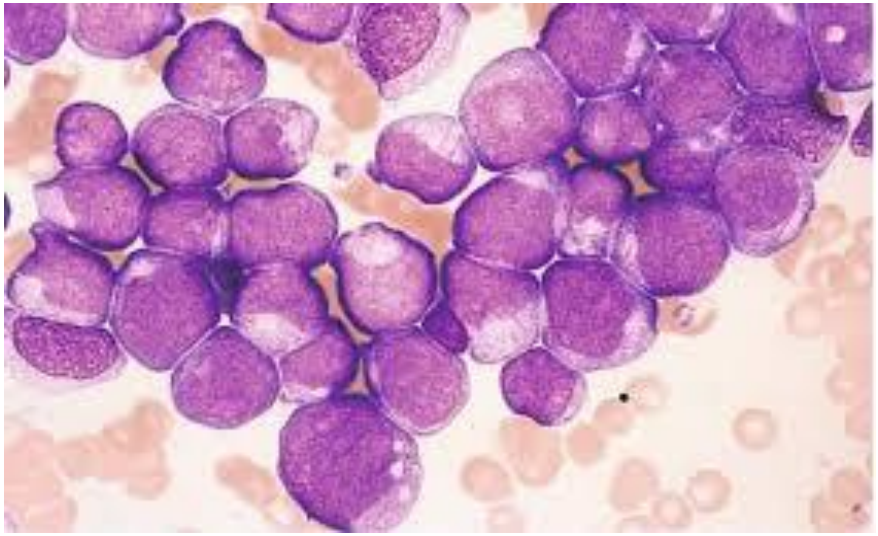
- **Globuli Rossi Concentrati**
- **Piastrine**
- Plasma
- Leucociti

Caratterizzazione

- **Citomorfologica**
- **Immunofenotipica**
- **Citogenetica**
- **Molecolare**

LE LEUCEMIE ACUTE MIELOIDI (LAM)

Neoplasie del tessuto emopoietico caratterizzate da una proliferazione incontrollata di cellule immature della linea mieloide, chiamate *blasti.* Originano dalla trasformazione leucemica di una cellula staminale emopoietica che acquisisce plurime mutazioni geniche e riarrangiamenti cromosomici.

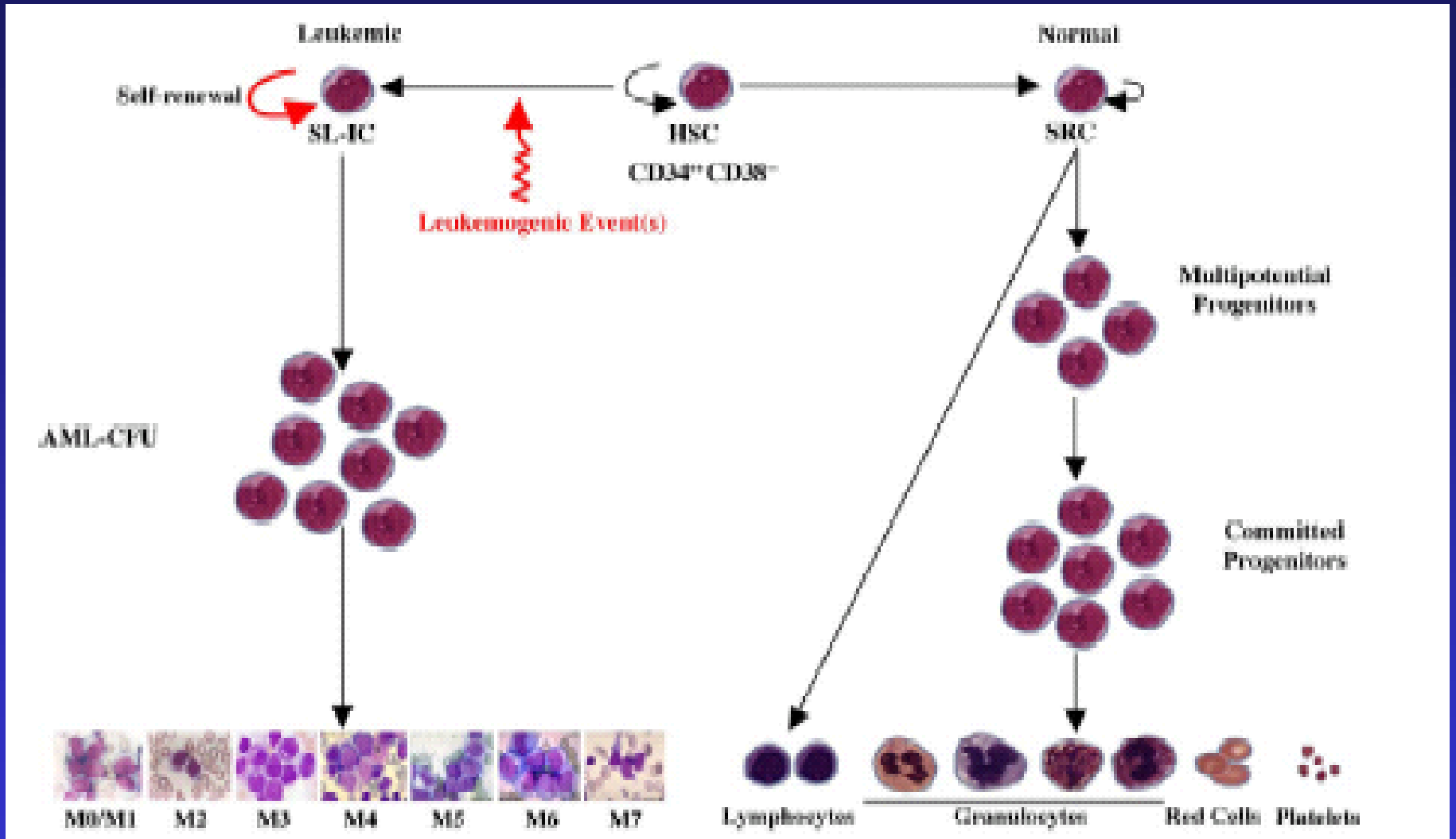


Striscio di sangue midollare in paziente con LAM

DIAGNOSI ATTUALE:

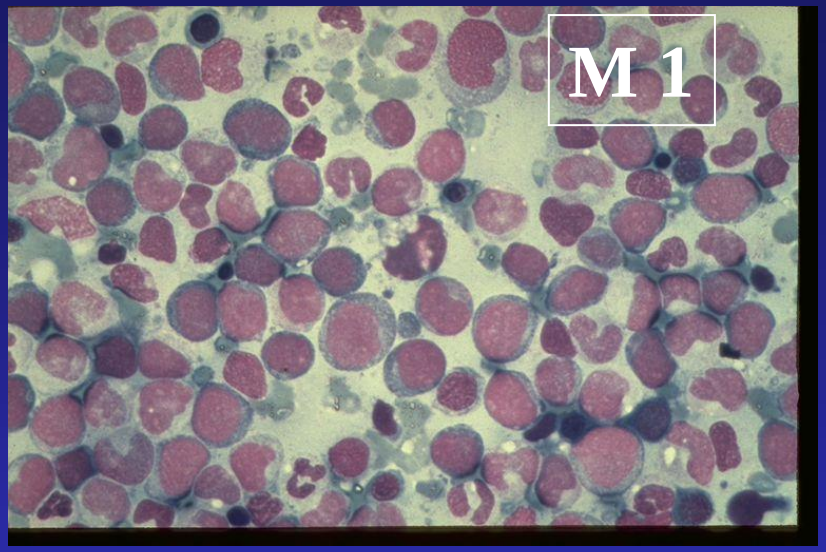
- CITOMORFOLOGIA
- IMMUNOFENOTIPO
- CITOGENETICA
- BIOLOGIA MOLECOLARE: FLT3, NPM1, CEBPα con metodica di Sanger

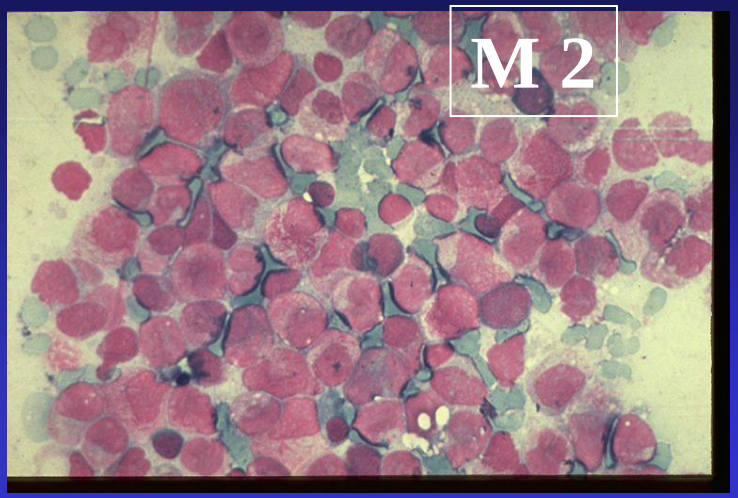
LEUCEMOGNESI

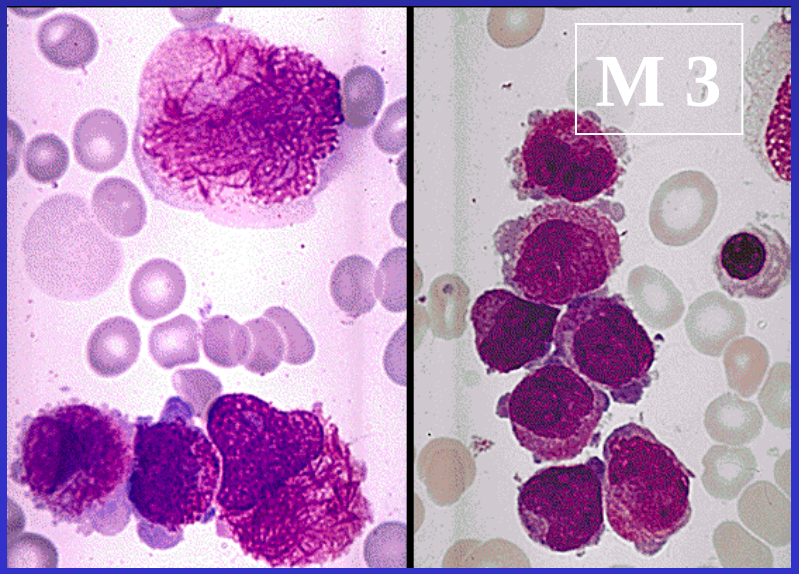


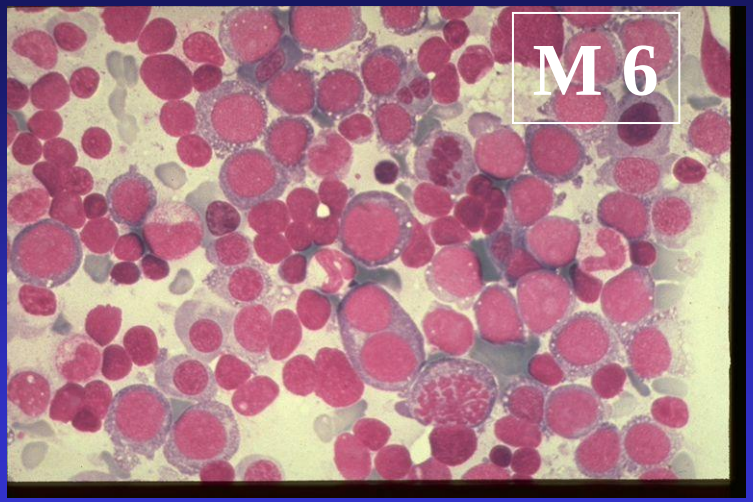
1. A model of AML heterogeneity that postulates leukemogenic events occurring in primitive stem cells resulting in increased self-renewal, abrogation of nal differentiation, and the creation of a leukemic stem cell that originates a leukemic hierarchy.

LA - Citomorfologia









Acute Leukaemia: Morphological Classification

Myeloid (AML)

M_0: minimally differentiated
M_1: without maturation
M_2: with maturation
M_3: hypergranular promyelocytic
M_4: myelomonocytic
M_5: a) monoblastic b) monocytic
M_6: erythroleukaemia
M_7: megakaryoblastic
Rare types, e.g. eosinophilic

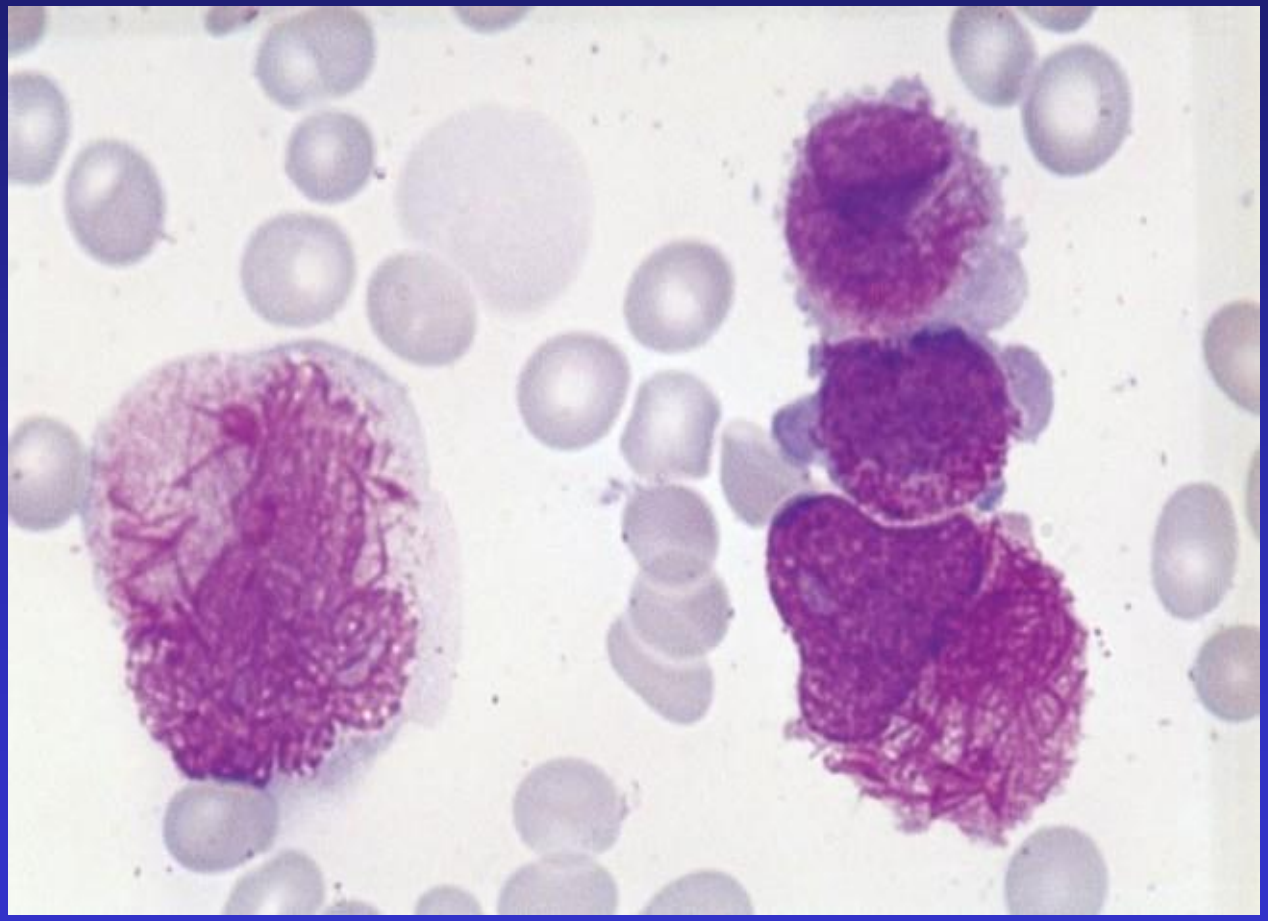
Lymphoblastic (ALL)

L_1: small, monomorphic
L_2: large, heterogeneous
L_3: Burkitt cell-type

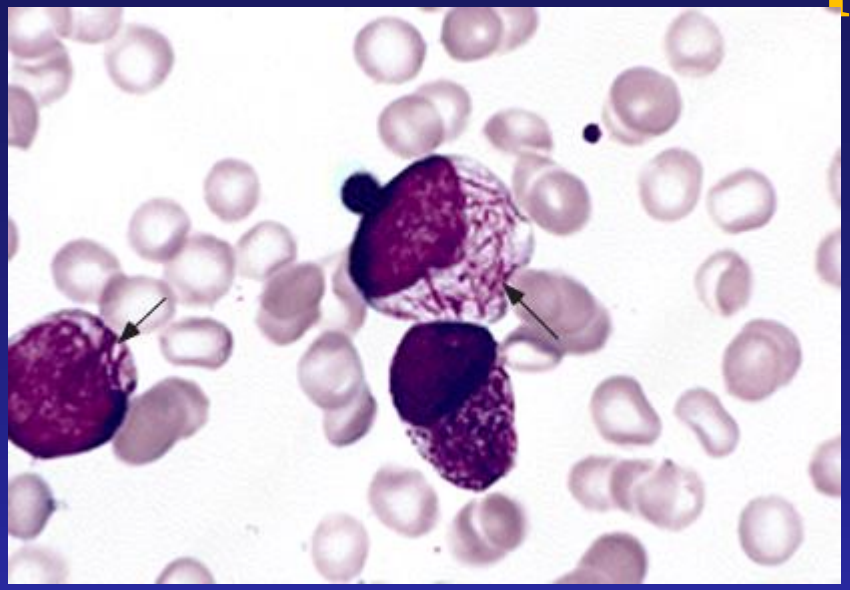
L'immunofenotipo delle LA

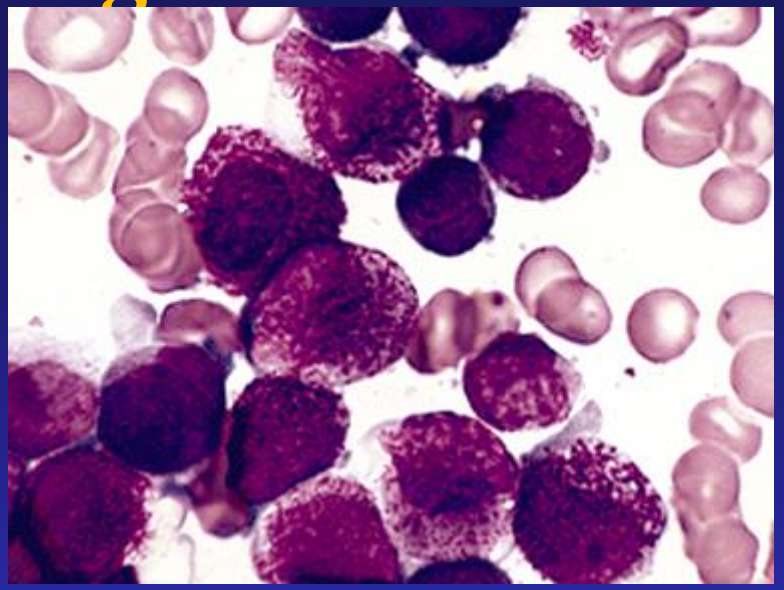
- **Definizione diagnostica**
- **Identificazione di sottotipi a diversa prognosi**
- **Identificazione di combinazioni di marcatori da utilizzare nel monitoraggio della malattia minima residua**

LAM M3

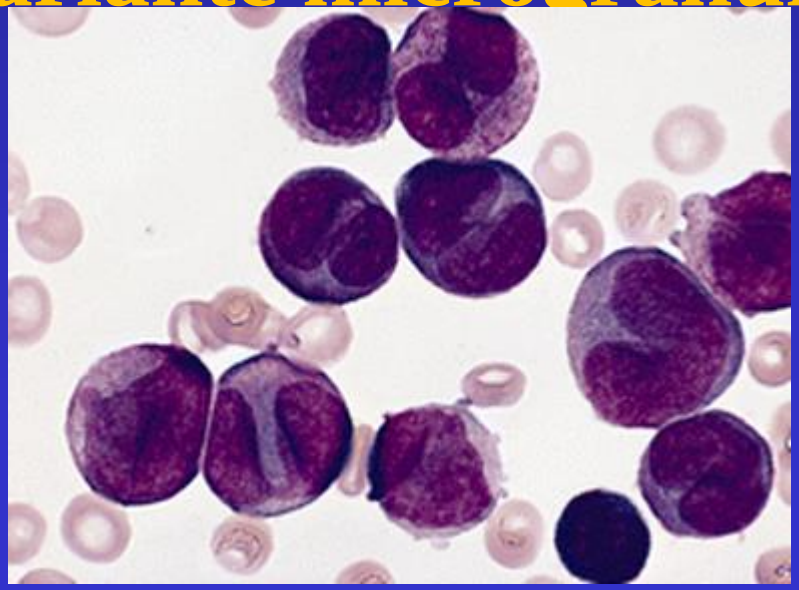


Variante ipergranulare





Variante microgranulare



Leucemia acuta promielocitica

5-8% dei casi di AML

Importante inizio precoce del trattamento (ATRA)

PRESENTAZIONE CLINICA

- Complicanze della pancitopenia (anemia, trombocitopenia, leucopenia)
- DIC: EMERGENZA EMATOLOGICA!

Se non trattata → emorragie fatali nel 10-20% dei casi

MORFOLOGIA

VARIANTE IPERGRANULARE: 75% casi

-Promielociti atipici con citoplasma stipato di granuli blu-rossastri o viola, talora corpi di Auer raggruppati in fasci, nucleo spesso indentato, ripiegato

-MPO++, NSE+ nel 25% dei casi

VARIANTE MICROGRANULARE: 25% casi

-Nucleo bilobato o reniforme, citoplasma apparentemente privo di granuli (non visibili alla microscopia ottica)

-MPO++, NSE – o debole

IMMUNOFENOTIPO

- CD13+, CD33+, HLA-DR- e CD11b-
- CD34 - o debole, CD15 – o neg, CD17 – /variabile
- Variante microgranulare: coespressione di CD2 e talora CD34
- alcune forme CD56+ (prognosi peggiore)

ALTERAZIONI GENETICHE

t(15;17)(q22;q12) - PML-RARA

TECNICHE DIAGNOSTICHE:

- analisi del cariotipo
- FISH
- RT-PCR

Altre anomalie:

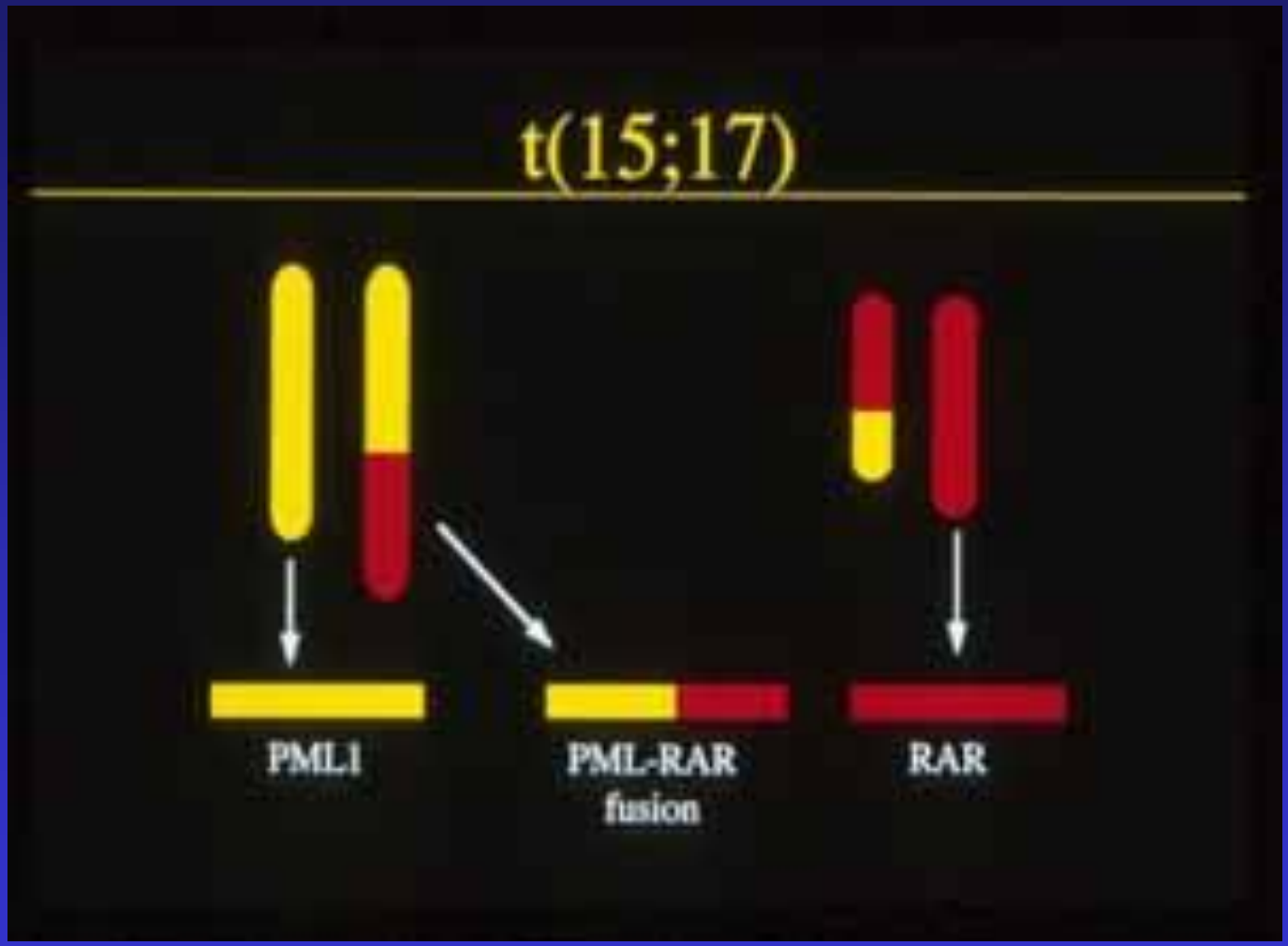
t(11;17)(q23;q21) — PLZF/RARa, spesso CD13+, CD56+ (1%) RESISTENTE AD ATRA
t(5;17)(q35;q21) — NPM1/RARa, spesso CD13-, CD56- (0,5%) RESPONSIVA AD ATRA
t(11;17)(q13;q21) — NuMA/RARa RESPONSIVA AD ATRA

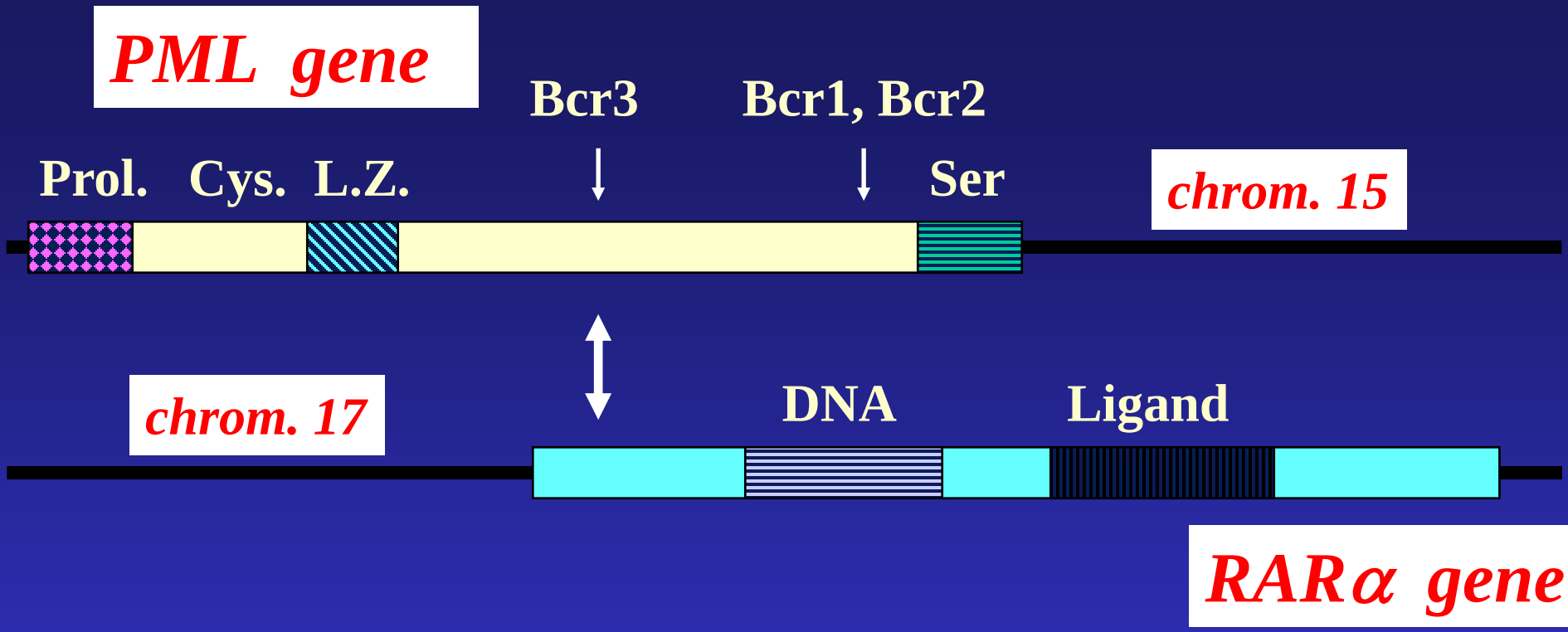
- in ca. 40% sono presenti anomalie citogenetiche aggiuntive
- nel 35-40% sono presenti mutazioni di FLT3

L'immunofenotipo delle LA

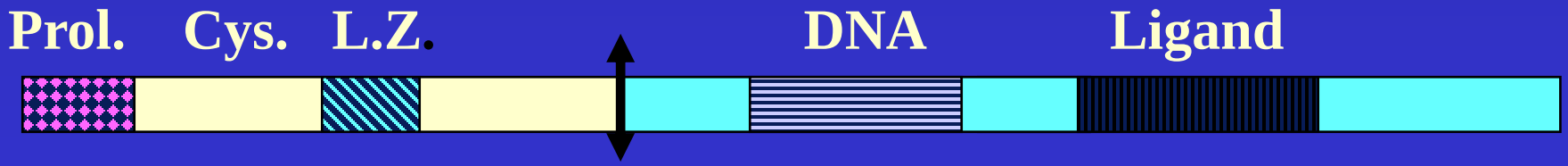
M0, M1, M2, M4	MPO7$^+$, CD13$^+$,CD33$^+$,CD117$^+$,	CD34$^+$, HLADR$^+$
M3	MPO7$^+$, CD13$^+$, CD33$^+$,CD117$^+$,	CD34+/-, HLADR$^-$
M5	MPO7$^+$, CD13$^+$, CD33$^+$,CD117$^+$,	CD34$^-$, HLADR$^+$, CD14$^+$
M6	MPO7$^+$, CD13$^+$, CD33$^+$,CD117$^+$,	CD34$^-$, HLADR$^+$, CD71$^+$, glicoforina$^+$
M7	MPO7$^+$,CD13$^+$,CD33$^+$,CD117$^+$,	CD34$^-$, HLADR$^+$, CD41$^+$

Leucemia acuta a promielociti

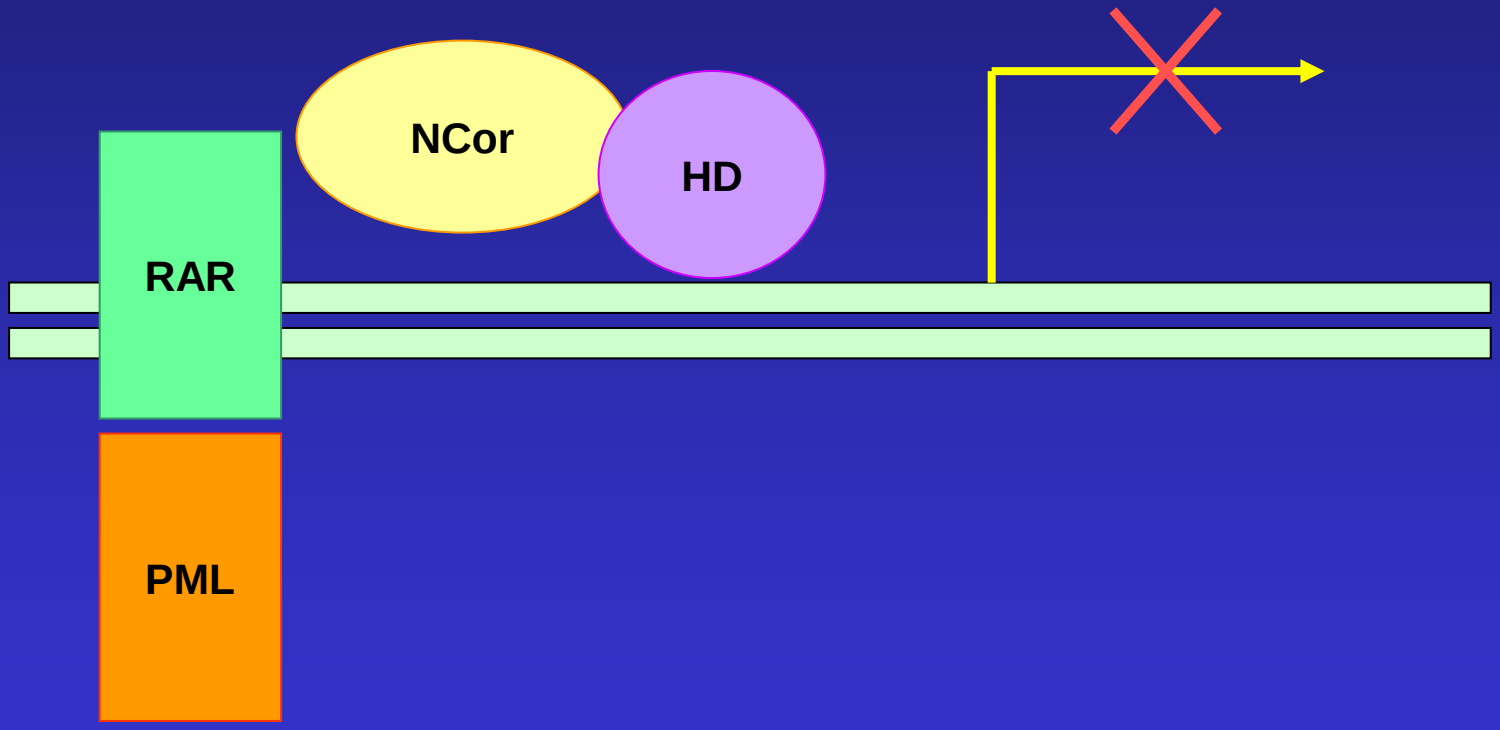




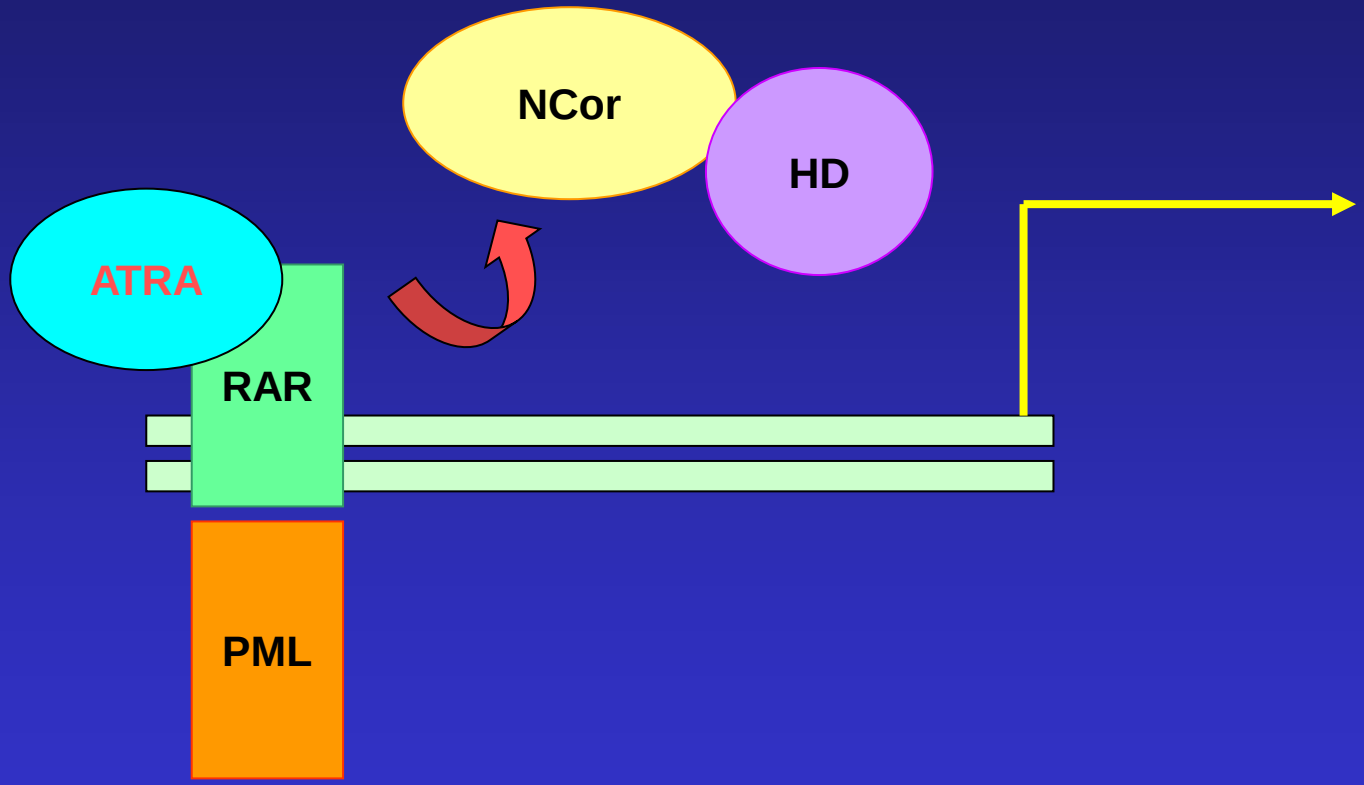
PML/RARα fusion gene



PML-RARα



PML-RARα



t(15;17) (q22;q21)
PML-RARα
responsiva ad
ATRA

Fattore pro-
apoptosi

t(11;17) (q23;q21)
PLZF-RARα
resistente ad ATRA

Repressore della
trascrizione

t(5;17) (q32;q21)
NPM-RARα
responsiva ad
ATRA

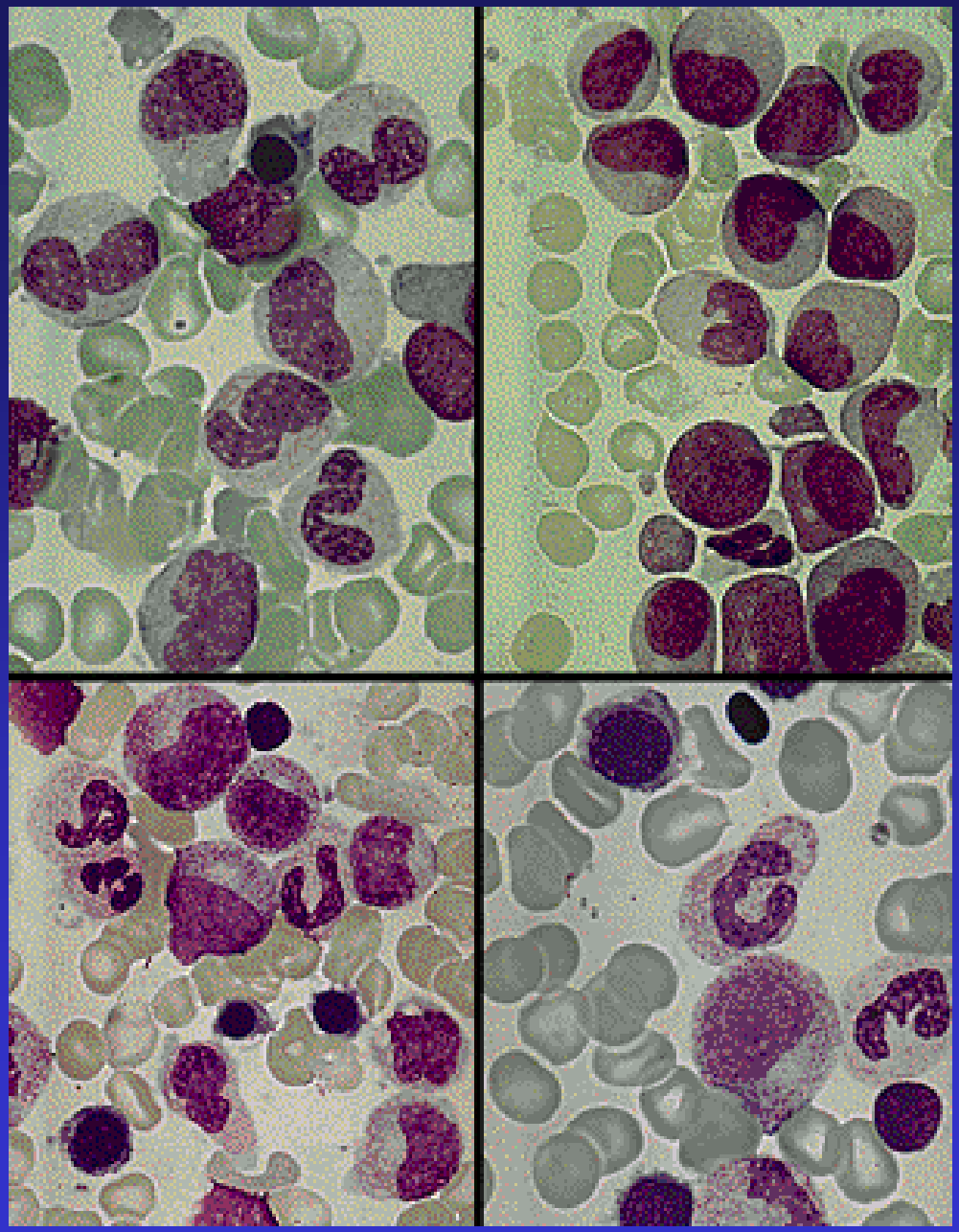
Fosfoproteina
nucleare

t(11;17) (q13;q21)
NuMA-RARα
responsiva ad
ATRA

Apparato mitotico
nucleare

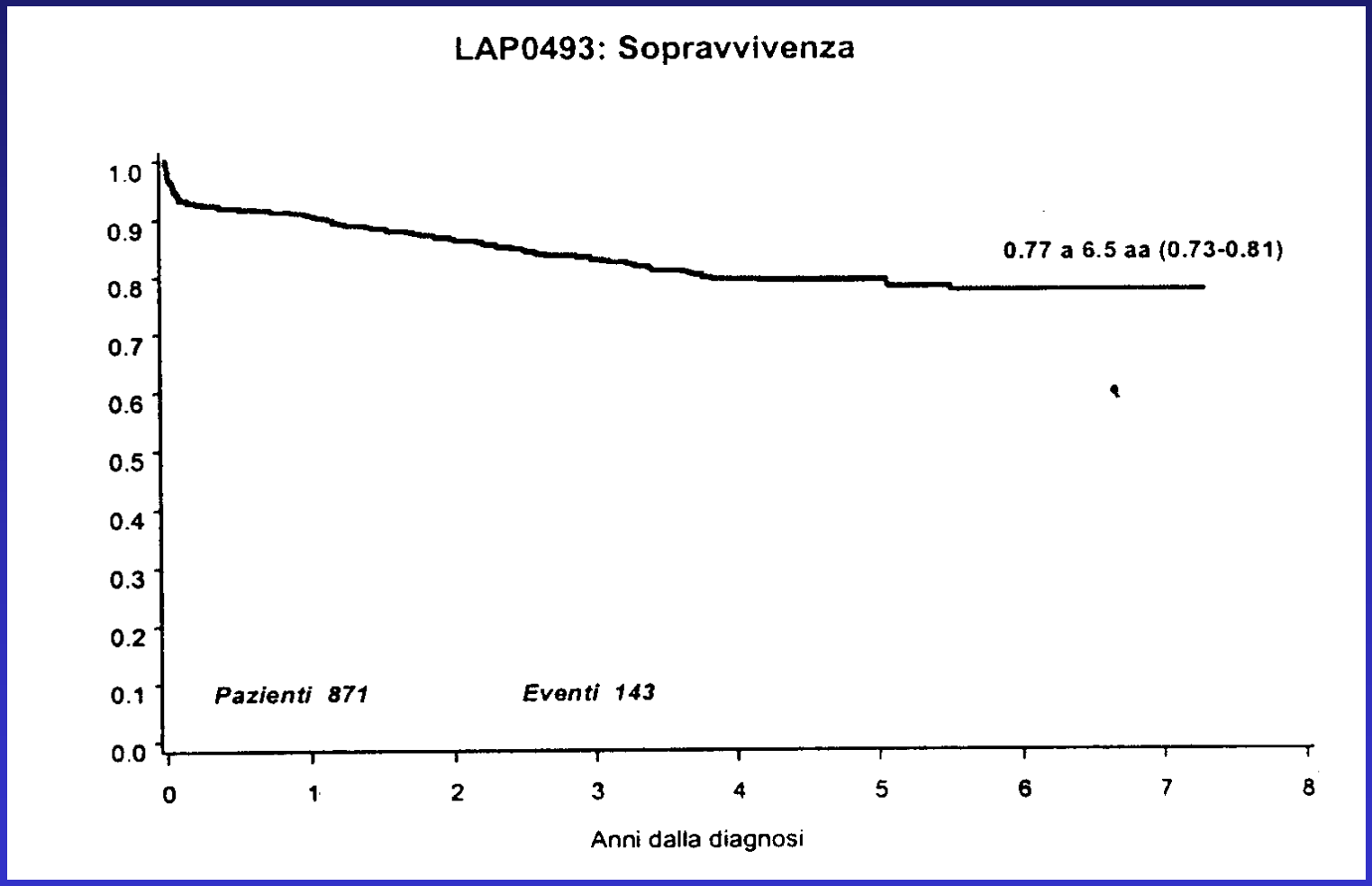
Delezione
interstiziale
cromosoma 17q21
Stat5b-RAR α
non responsiva ad
ATRA

Trasduttore di
segnale e
attivatore della
trascrizione



AML- M3
ATRA- differentiation

OVERALL SURVIVAL
IN ALP PATIENTS TREATED WITH ATRA + CHT



GIMEMA Report, luglio 2001

STRATIFICAZIONE DEL RISCHIO

- **BASSO:**

GB ≤ 10.000/uL e piastrine >40.000/uL; RFS 98%

- **INTERMEDIO:**

GB ≤ 10.000/uL e piastrine ≤40.000/uL; RFS 89%

- **ALTO RISCHIO:**

GB > 10.000/uL; RFS 70%

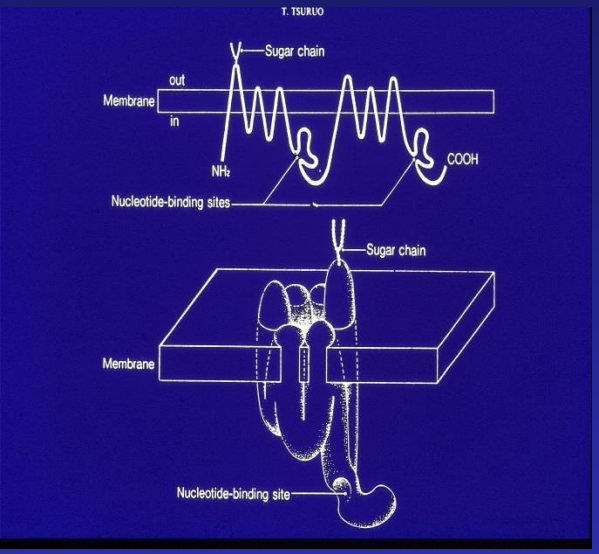
L'immunofenotipo delle LAM: aspetti prognostici

Antigeni con significato prognostico negativo nelle LAM

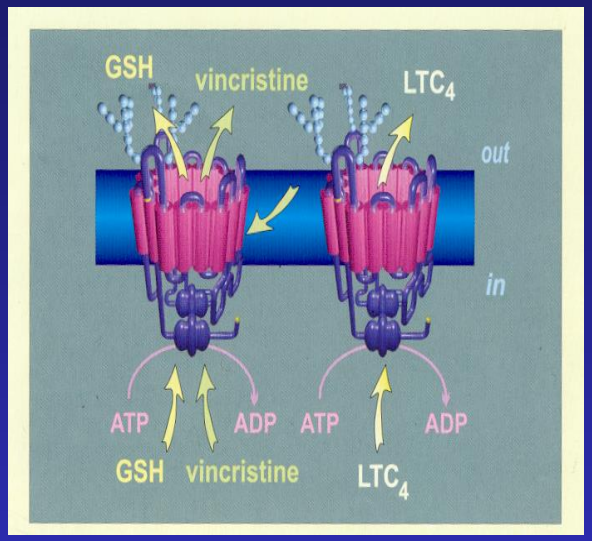
TdT	bcl-2
CD7	PgP
CD34	CD56
	HLADR

Multidrug resistance - MDR

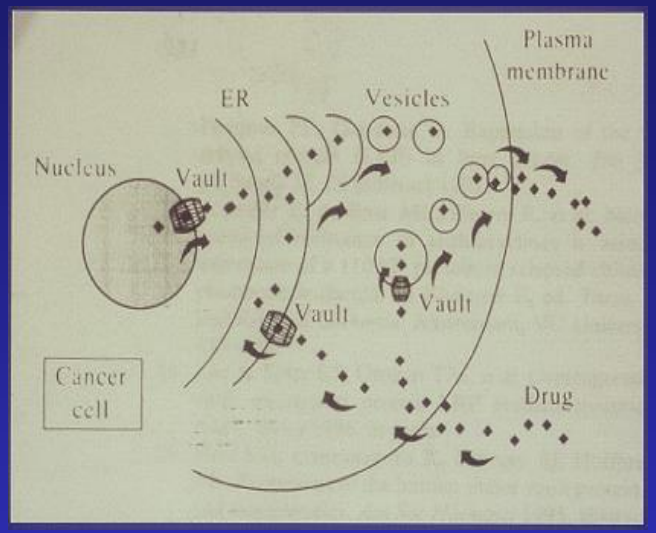
Pgp



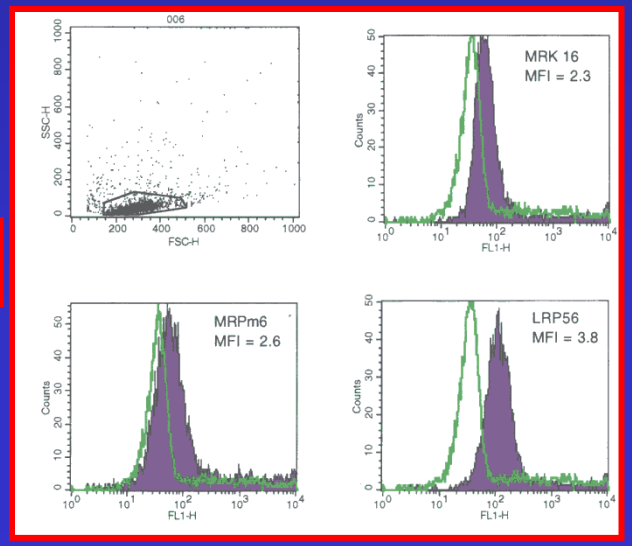
MRP



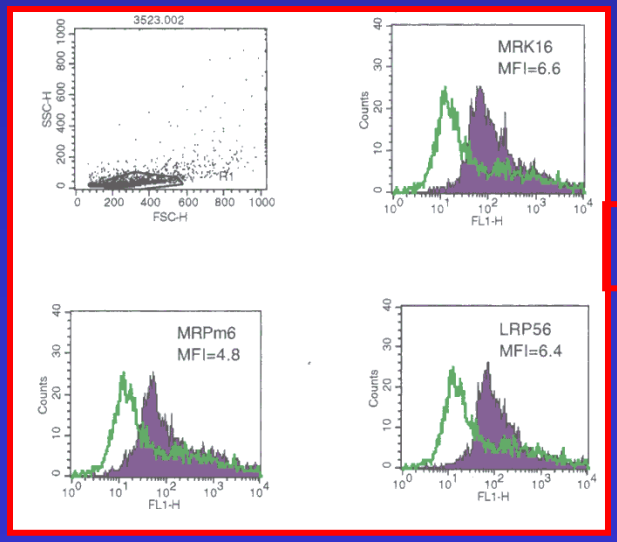
LRP



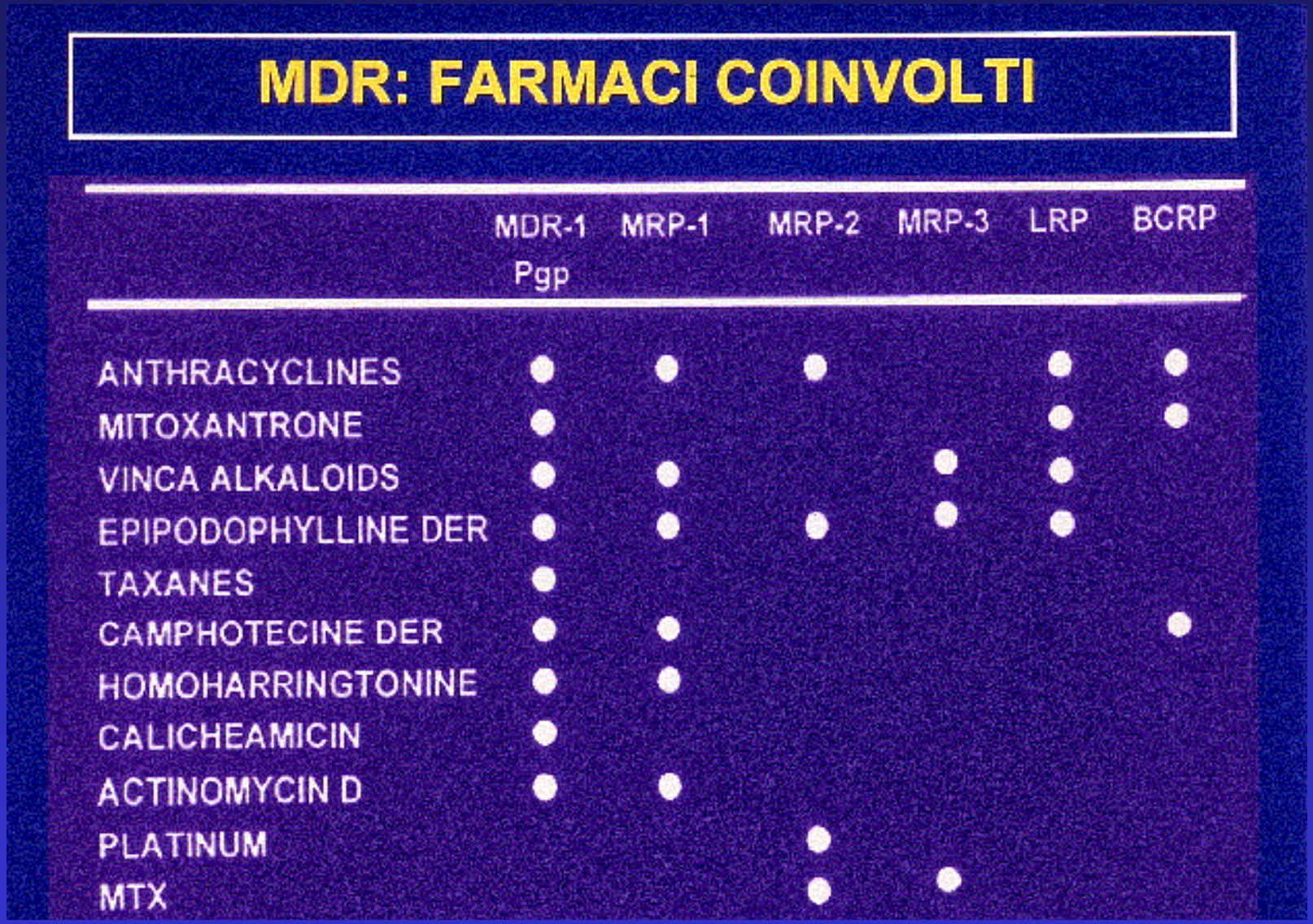
MDR -



MDR +

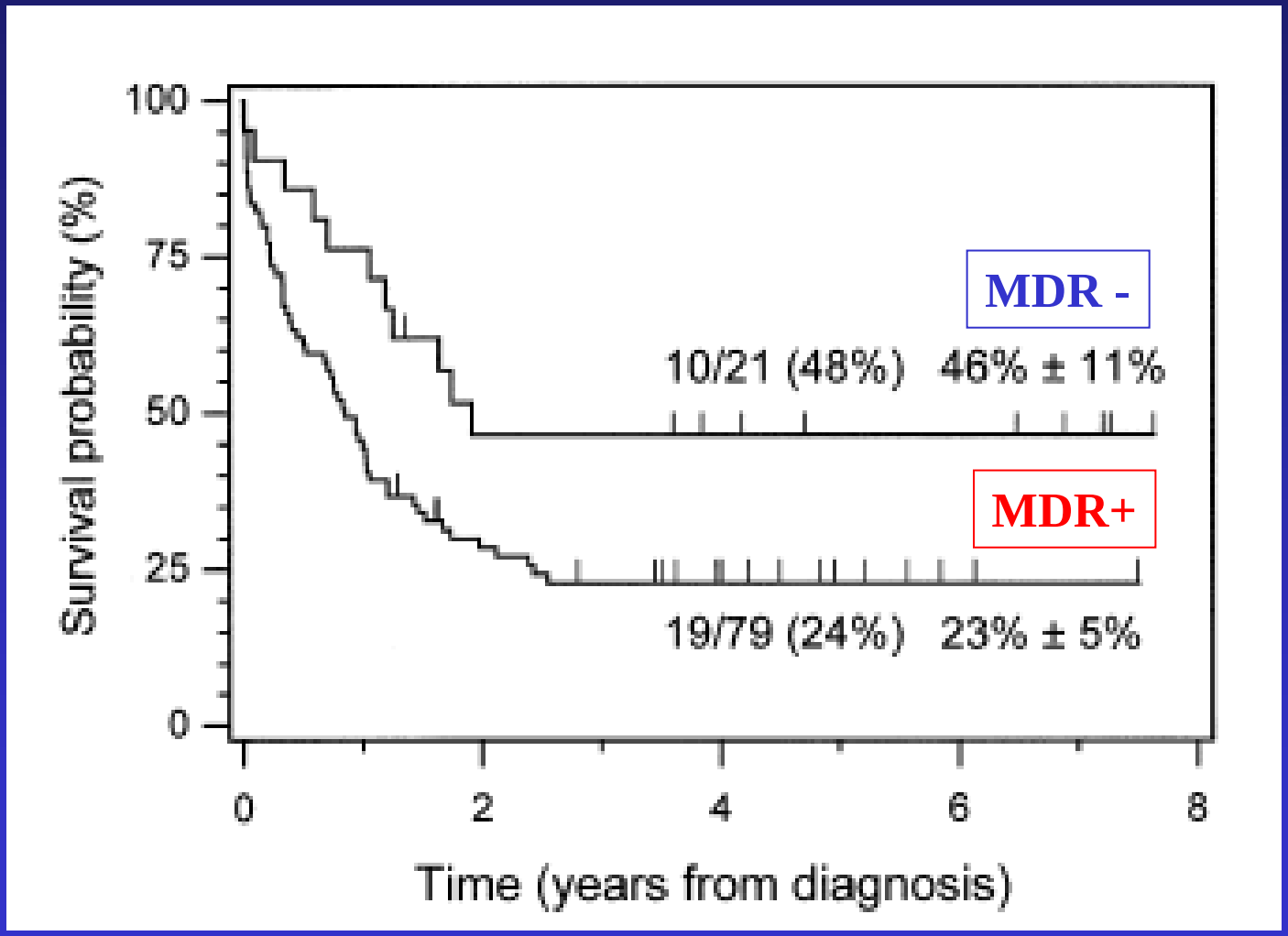


Multidrug resistance - MDR



Multidrug resistance - MDR

OS



Kasimir-Bauer et al, Exp Hematol 2002

Immunofenotipo

Antigene panleucocitario (DD cellule non ematologiche) esclusi eritrociti e piastrine	**CD45 (pos)**
DD ALL	**cMPO, CD117 (pos) vs. cCD3, cCD79a, cCD22 (neg)**

DIAGNOSI AML	
Precursori	CD34, CD38, CD117, CD133, HLA-DR
Markers granulocitari	CD13, CD15, CD16, CD33, CD65, cMPO
Markers monocitari	CD11c, CD14, CD64, lisozima, CD4, CD11b, CD36, ANAE, NG2 omologo
Markers megacariocitari	CD41 (gp IIb/IIIa), CD61 (gp IIIa), CD42 (gp Ib)
Markers eritroidi	CD235a (glicoforina A)

Acute leukemia of ambiguous lineage

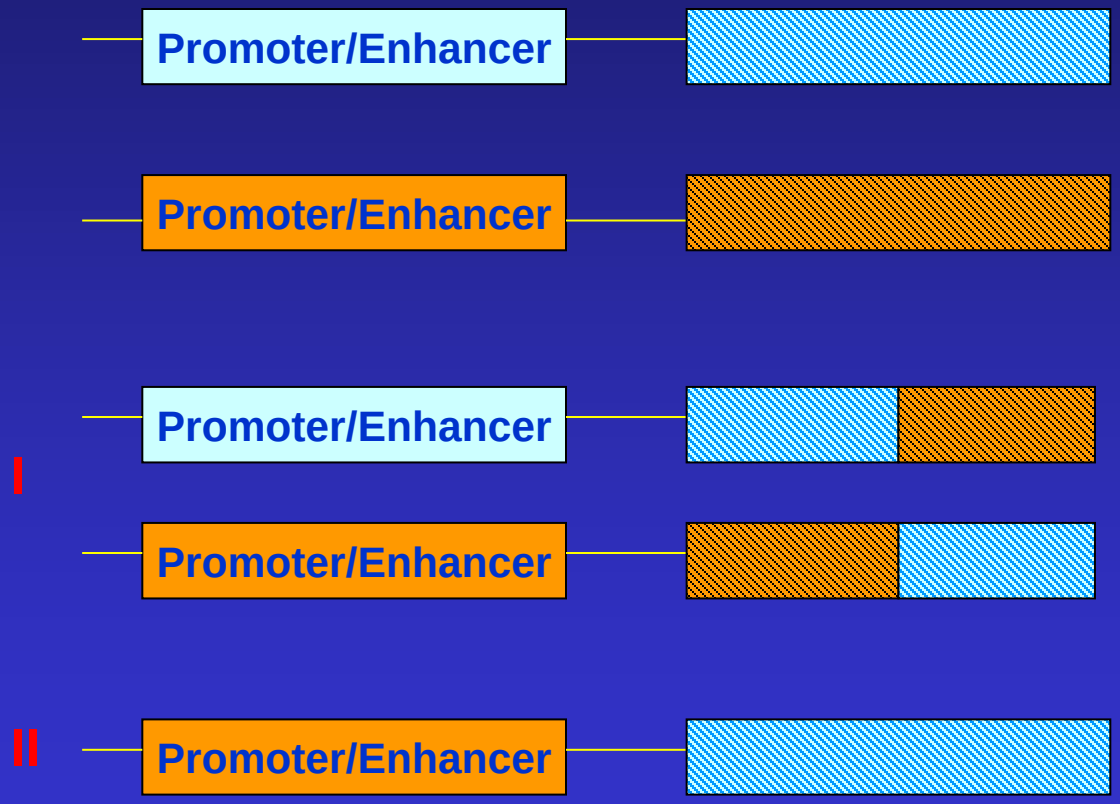
Acute leukemias of ambiguous lineage

- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*||
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B/myeloid, NOS
- Mixed phenotype acute leukemia, T/myeloid, NOS

DIAGNOSI DI MPAL (mixed phenotype acute leukemia)	
Linea mieloide	MPO (citometria a flusso, immunoistochimica o citochimica) o Evidenza di differenzazione monocitaria (almeno 2 tra i seguenti markers: NSE, CD11c, CD14, CD64, lisozima)
Linea B	CD19 forte + almeno 1 tra: CD79a, cCD22, CD10 (forte) o CD19 debole + almeno 2 tra: CD79a, cCD22, CD10 (forte)
Linea T	cCD3 o CD3 di superficie

LEUCEMIE ACUTE: ALTERAZIONI GENETICHE

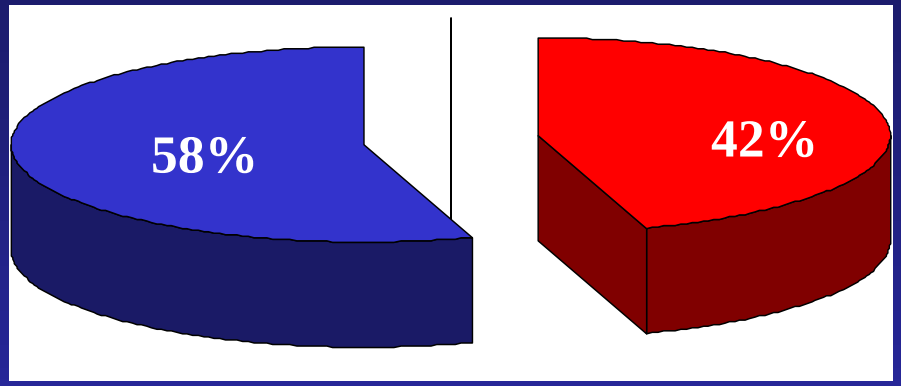
TRASLOCAZIONI CROMOSOMICHE

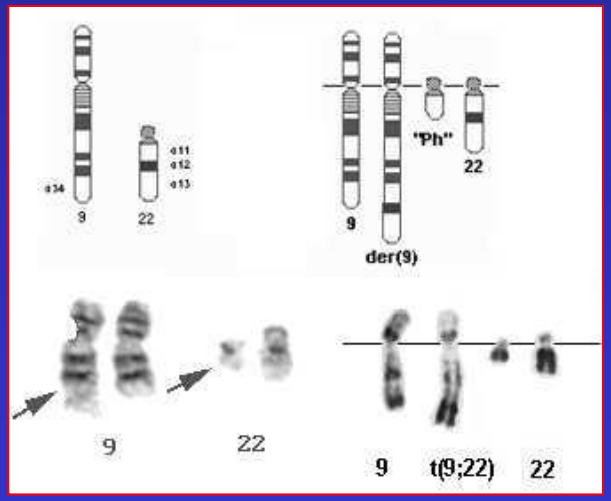


LA - Citogenetica

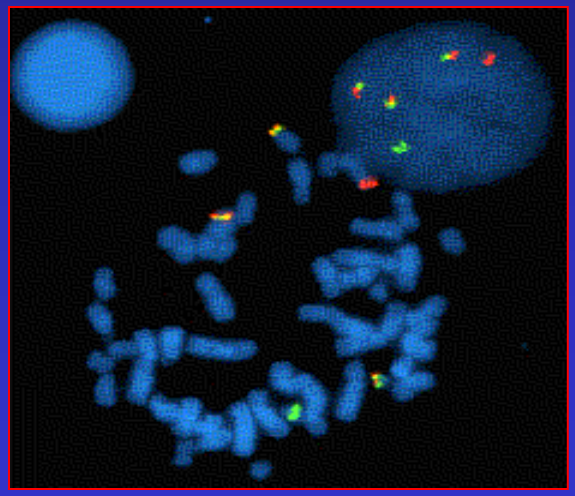
1612 casi LAM diagnosi

Grimwade, Blood 1998





Citogenetica Convenzionale



Citogenetica Molecolare (FISH)

Biologia Molecolare

ALTERAZIONI CITOGENETICHE BILANCIATE

ALTERAZIONI	FAB	FREQUENZA	GENI COINVOLTI	PROGNOSI
t(8;21)(q22;q22)	M2/M1	9-12%	AML/ETO	FAV
inv(16)(p13q22) t(16;16)(p13;q22)	M4 (eos)	8%	MYH11/CBFB	FAV
t(15;17)(q22;q21)	M3/M3v	8-10%	PML/RARα	FAV
alt(11)(q23)	M4 M5	8-10%	MLL	SFAV
inv(3)(q21q26) t(3;3)(q21;q26)		0,5-2%	EVI1/MDS/RPN	SFAV
t(9;22)(q34;q11)	M1 M2 M4	1-2%	BCR/ABL	SFAV
t(6;9)(q23;q34)	M1 M2	rara	DEK/KAN	SFAV
t(8;16)(p11;p13)	M5b	1%	MOZ/CPB	SFAV

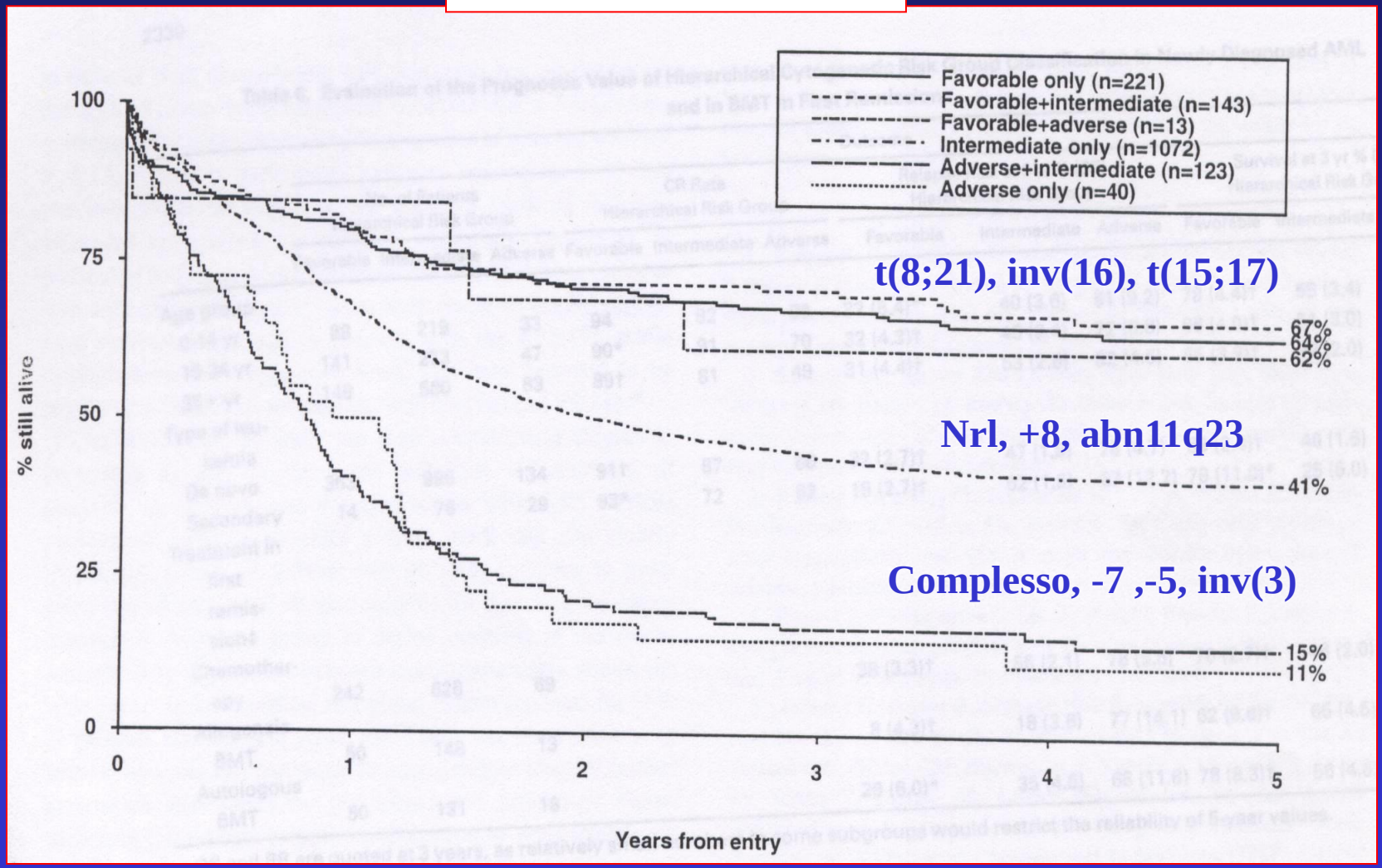
ALTERAZIONI CITOGENETICHE NON BILANCIATE

ALTERAZIONI	FAB	FREQUENZA	PREC TERAPIA	PROGNOSI
+8, -5, -7	M1-7 SMD	15-20%	Si	**SFAV**
del(5q) del(7q) del(29q)	M1-7 SMD	10 – 30%	Sì	**SFAV**
Cariotipo complesso	M1-7 SMD	5 – 15%	Sì	**SFAV**
del(12p) del(17p), del(9q)	M1-7 SMD	1 - 5%	Sì	**SFAV**
+4, +11, +13, +21	M1-7 SMD	1 – 3 %	No	**SFAV**

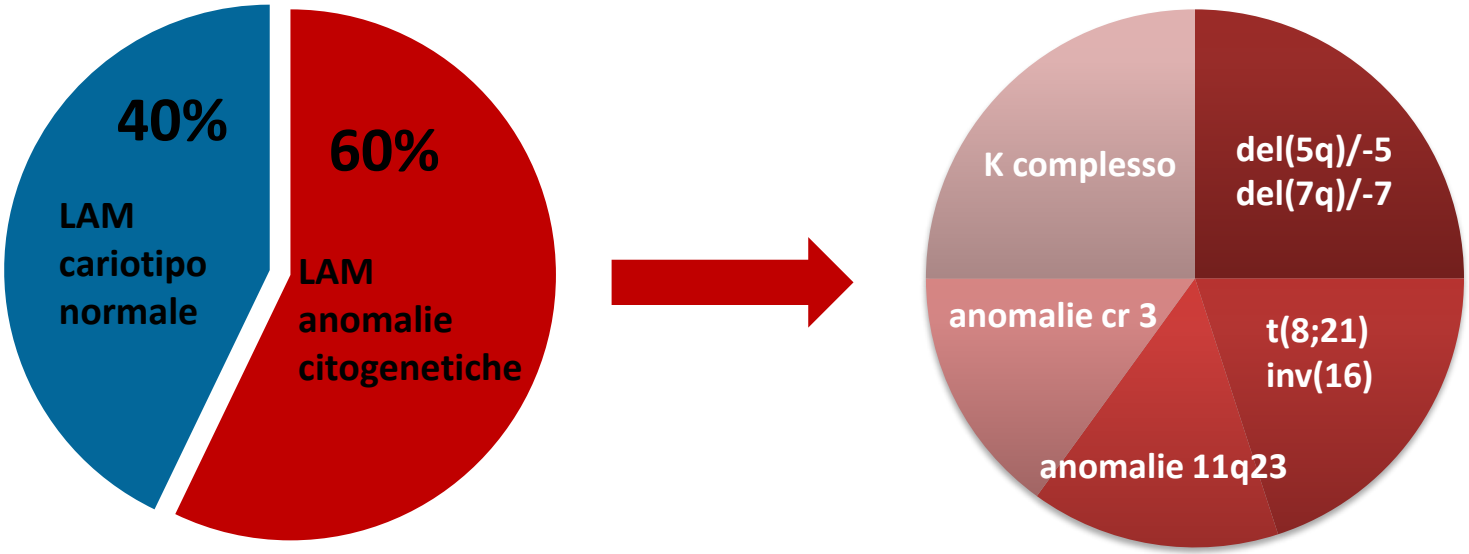
I parametri biologici e la prognosi delle LA

OS 1612 pz < 55 aa

Grimwade et al. Blood 1998



INCIDENZA E RILEVANZA PROGNOSTICA DELLE ALTERAZIONI CITOGENETICHE NELLE LAM



FAVOREVOLE	t(8;21) inv(16) del(16q) t(15;17)
INTERMEDIA	K normale t(9;11)(p22;q23) +8
SFAVOREVOLE	del(5q)/-5 del(7q)/-7 t(9;22) 3q, 9q, 11q, 20q, 21q, 17p t(6;9) K complesso/monosomico

Cariotipo normale-anomalie genetiche

- Flt3 (ITD) → prognosi sfavorevole
- Flt3 mutazione D835 → ?
- NPM1→ prognosi favorevole (40% associato a Flt3(ITD))
- CEBPA (mutazione biallelica) → prognosi favorevole

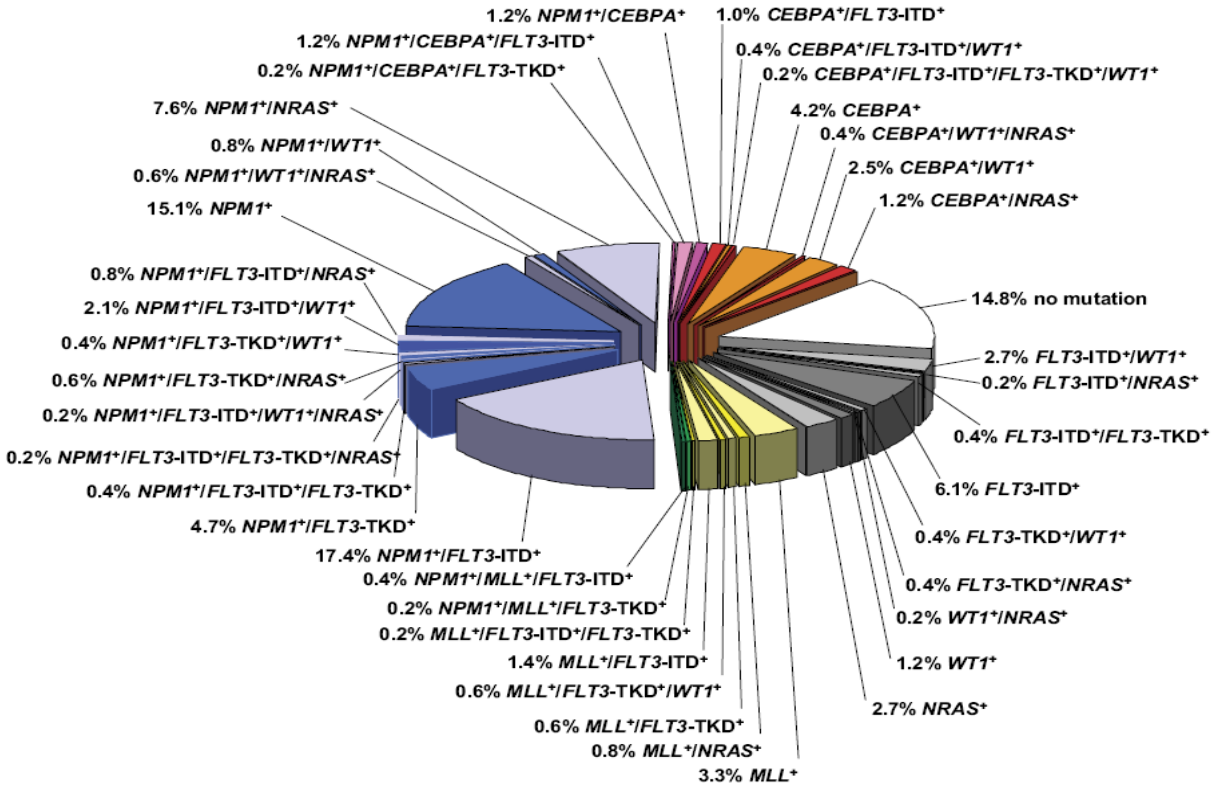
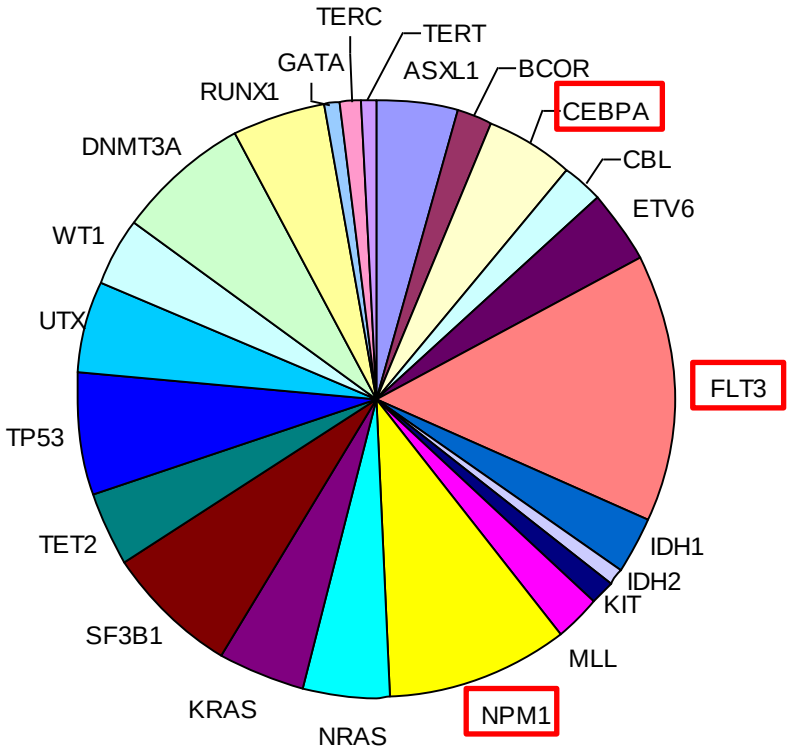


Figure 1. Pie chart illustrating the molecular heterogeneity of cytogenetically normal AML based on mutations in the *NPM1*, *CEBPA*, *MLL*, *FLT3* (ITD and TKD mutations at codons D835 and I836), *NRAS*, and *WT1* genes. The bluish colors denote *NPM1*-mutated subsets, the orange/red colors *CEBPA*-mutated subsets, and the yellow/green colors *MLL*-mutated subsets. The gray colors depict subsets without hypothetical class II mutations, and the white sector shows the subset without any mutation in the above-mentioned genes. Data are derived from mutational analysis of 485 younger adult patients with cytogenetically normal AML from AMLSG.

INCIDENZA E RILEVANZA PROGNOSTICA DELLE ALTERAZIONI MOLECOLARI NELLE LAM



Modificato da Dohner et al, Blood 2010

FAVOREVOLE	NPM1 mutato senza FLT3-ITD (cariotipo normale) CEBPα mutato (cariotipo normale)
INTERMEDIA	NPM1 mutato e FLT3-ITD (cariotipo normale) NPM1 *wild type* e FLT3-ITD (cariotipo normale)
SFAVOREVOLE	NPM1 *wild type* senza FLT3-ITD (cariotipo normale)

Citogenetica e alterazioni molecolari

Table 4. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

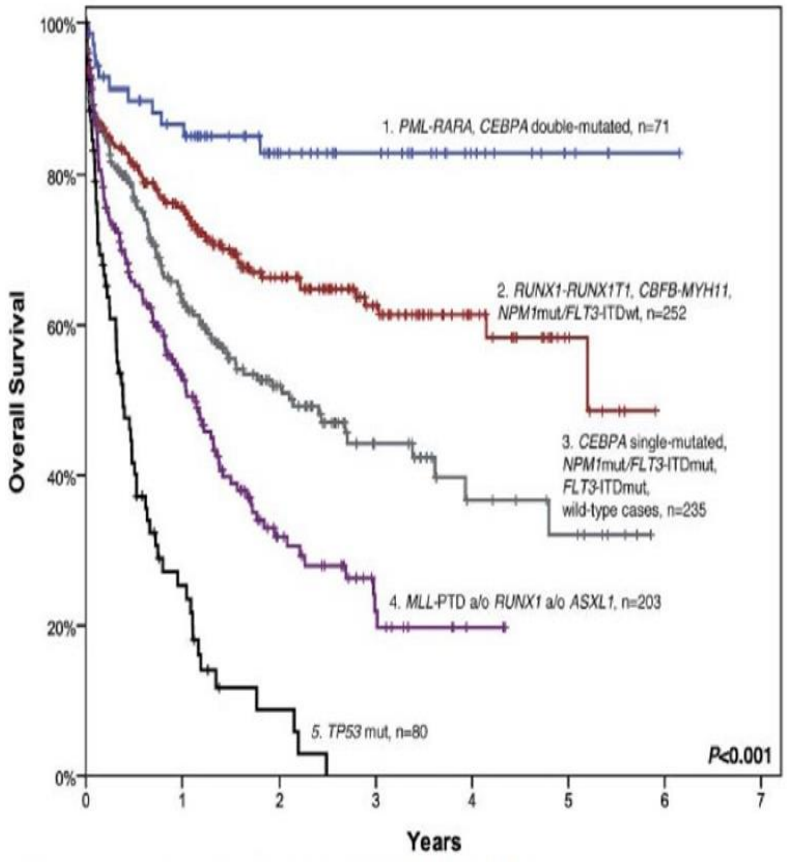
Döhner, Blood 2010; 115:453

Genetic group	Subsets
Favorable 16%	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I* 39%	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II 20%	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse†
Adverse 25%	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype‡

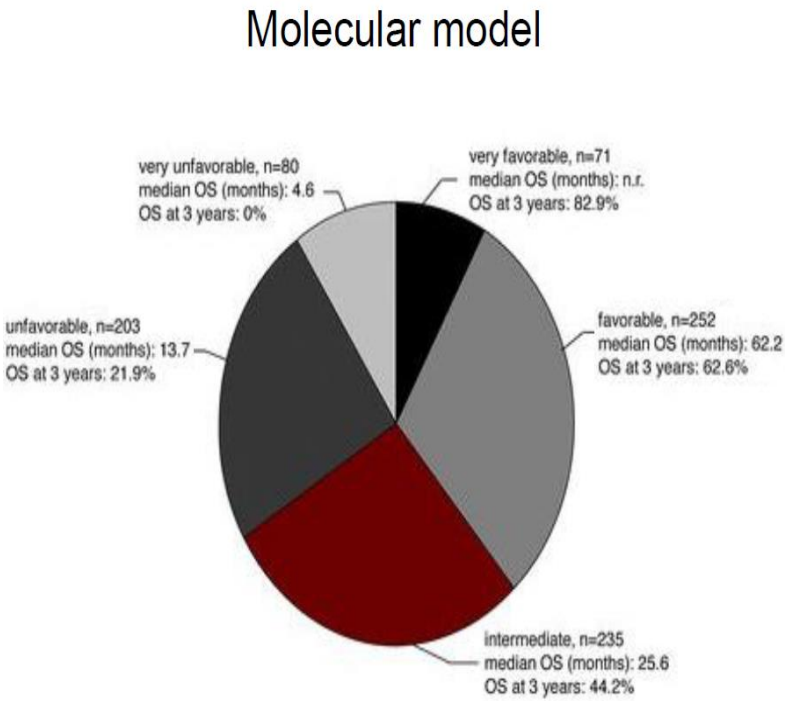
Cariotipo complesso: 3 o più anomalie cromosomiche in assenza do t(15;17), inv(16) o t(16;16), t(8;21)

Cariotipo monosomiale: ≥2 monosomie (escluse –X e –Y) o 1 monosomia associata ad un'altra anomalia cromosomica strutturale

STRATIFICAZIONE DEL RISCHIO MOLECOLARE



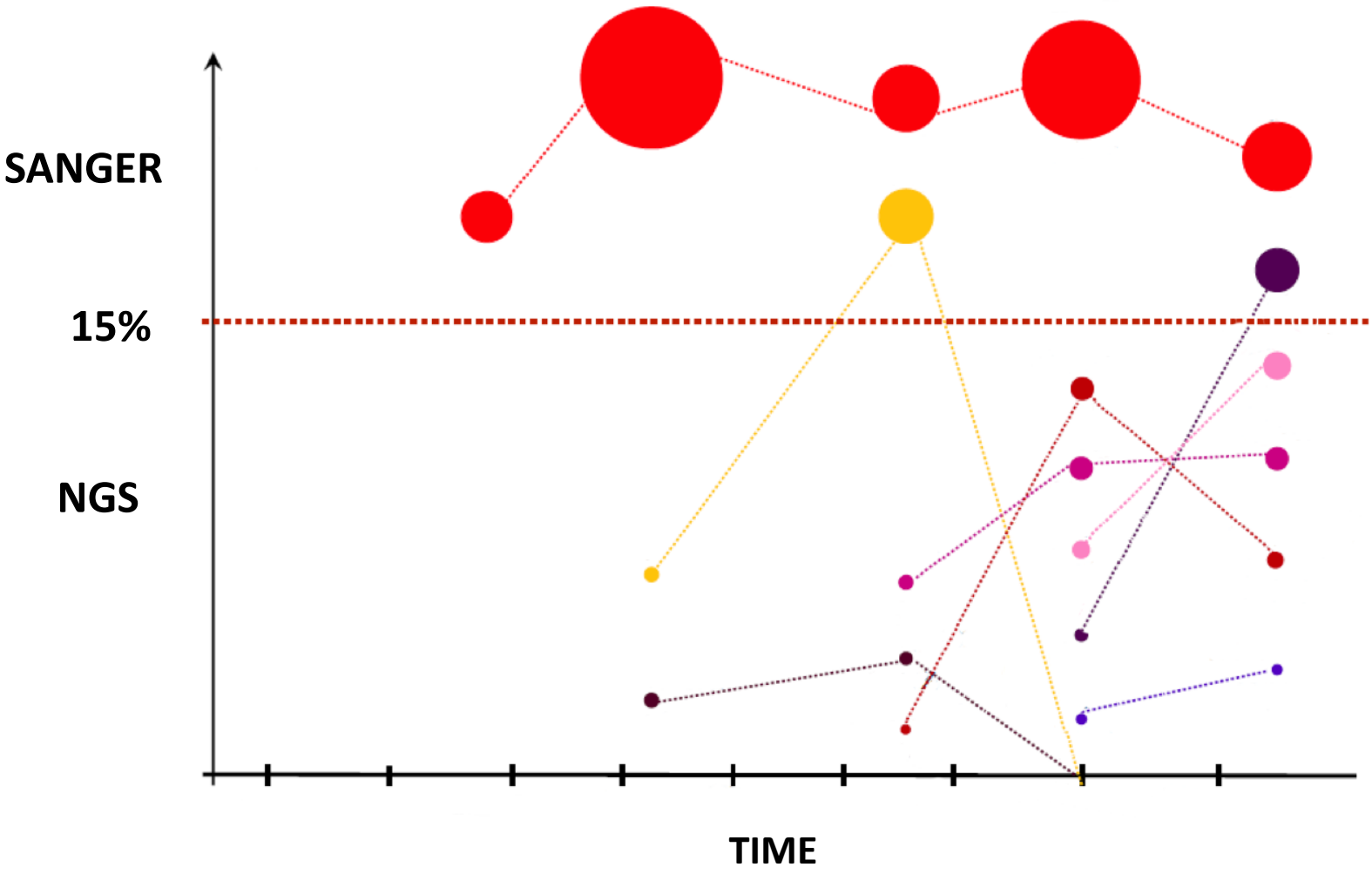
Model
1. very favorable (n=71): *PML-RARA*, *CEBPA* double-mutated
2. favorable (n=252): *RUNX1-RUNX1T1*, *CBFB-MYH11*, *NPM1*mut/*FLT3*-ITD-
3. intermediate (n=235): *CEBPA* single-mutated, *FLT3*-ITD+, *NPM1*mut/*FLT3*-ITD+, wild-type cases
4. unfavorable (n=203): *MLL*-PTD a/o *RUNX1* a/o *ASXL1* mutated
5. very unfavorable (n=80): *TP53* mutated



SENSIBILITÀ DELLE TECNICHE DIAGNOSTICHE CONVENZIONALI

Limite di sensibilità della metodica Sanger →

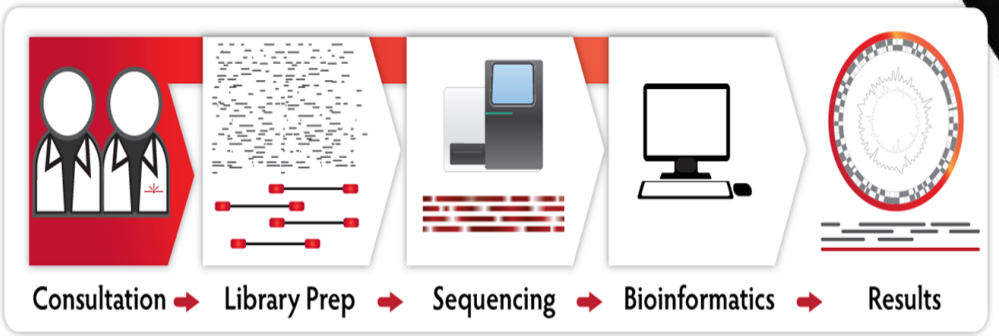
IL PROBLEMA DELLA SENSIBILITÀ



NEXT GENERATION SEQUENCING (NGS)

Tecnologia che consente di sequenziare milioni di frammenti di DNA in parallelo e in modo rapido (high-throughput).

- Sensibilità elevata (2%)
- Analisi di ampie regioni dei geni target
- Detection contemporanea di più mutazioni
- Capacità di discovery di nuove mutazioni

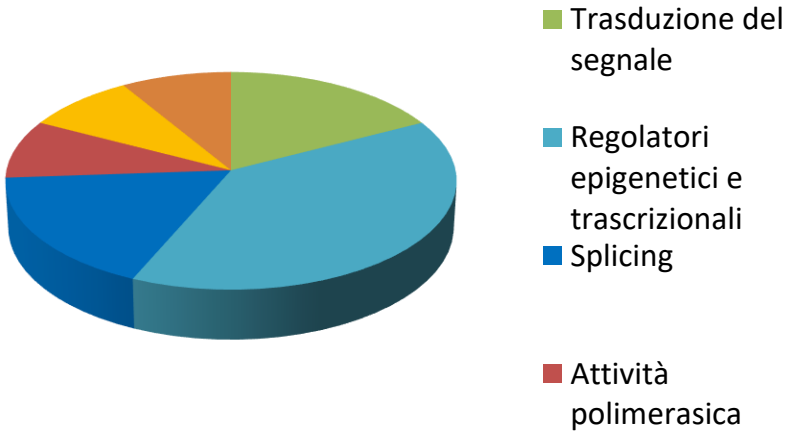


GENE PANEL DEEP SEQUENCING (GPDS)

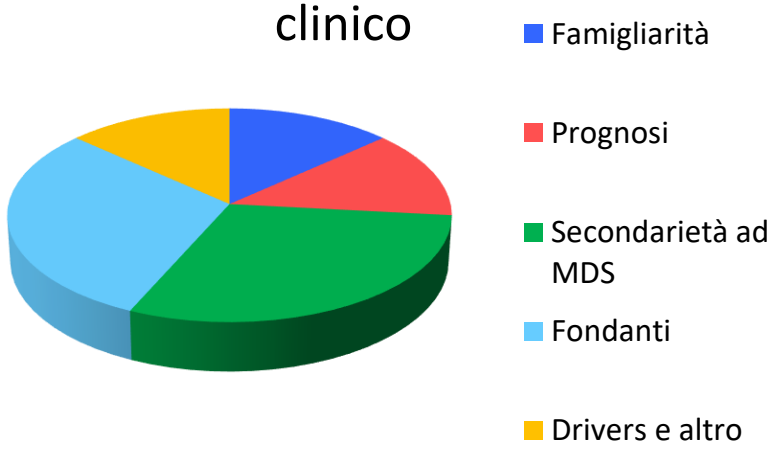
I geni inclusi
nell'analisi erano:

FLT3	TET2	RUNX1	TP53	ASXL1	BCOR	EZH2	DNMT3A	SF3B1
KRAS	NRAS	SRSF2	IDH1	IDH2	KMT2A	DDX41	ZRSR2	ETV6
CBL	NPM1	GATA2	TERT	TERC	CEBPA	U2AF1	ANKRD26	SRP72

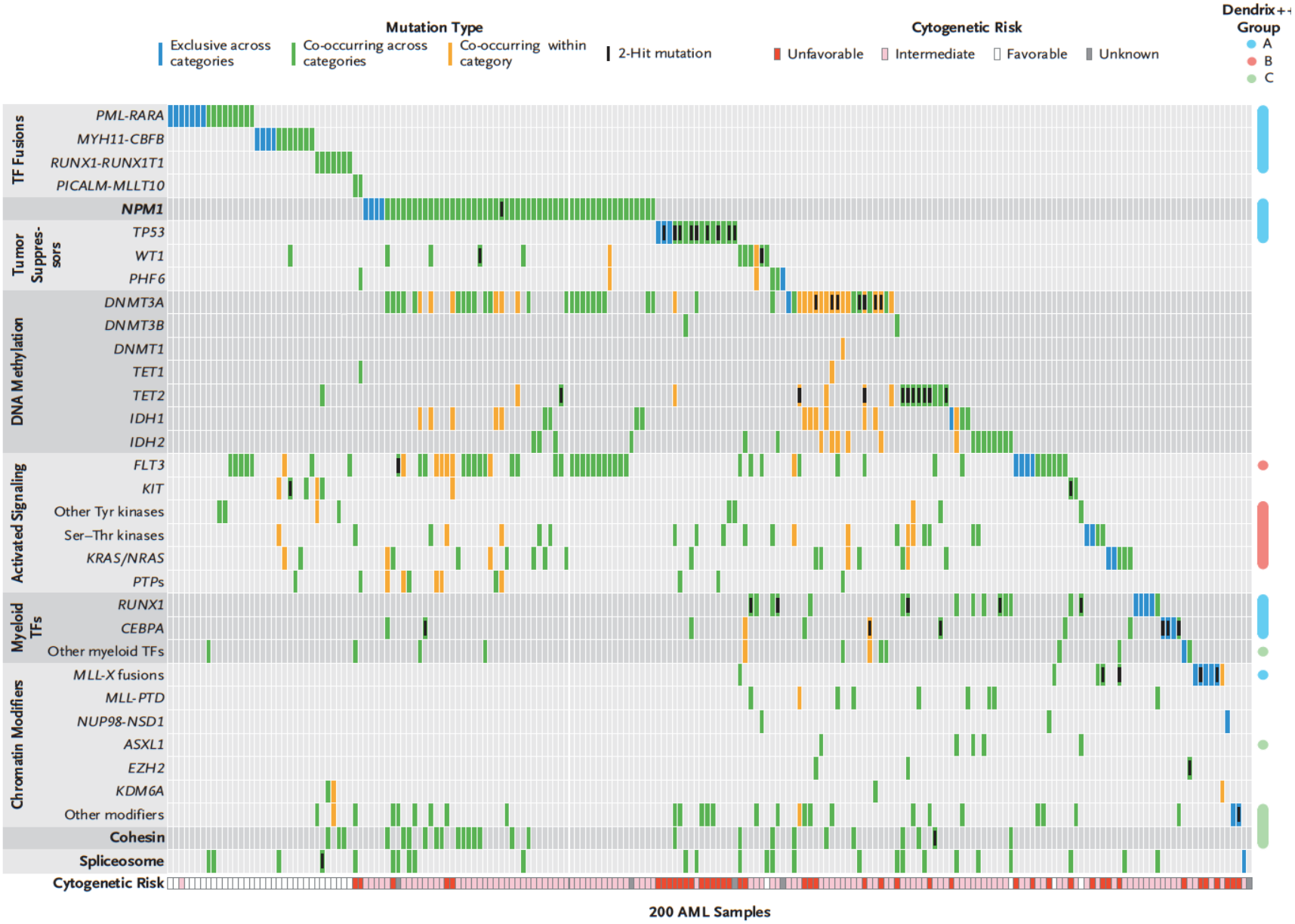
Geni suddivisi in base alla funzione biologica



Geni suddivisi in base all'impatto clinico



COMPLESSITÀ GENOMICA DELLE LAM



Cancer Genome Atlas Research Network. NEJM 2013; 368 (22): 2059

Acute myeloid leukemia and related precursor neoplasms, and acute leukemias of ambiguous lineage (WHO 2008)

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA**
- AML with t(9;11)(p22;q23); *MLLT3-MLL*†
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes‡

Therapy-related myeloid neoplasms§

Acute myeloid leukemia, not otherwise specified (NOS)
- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)

Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)

Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

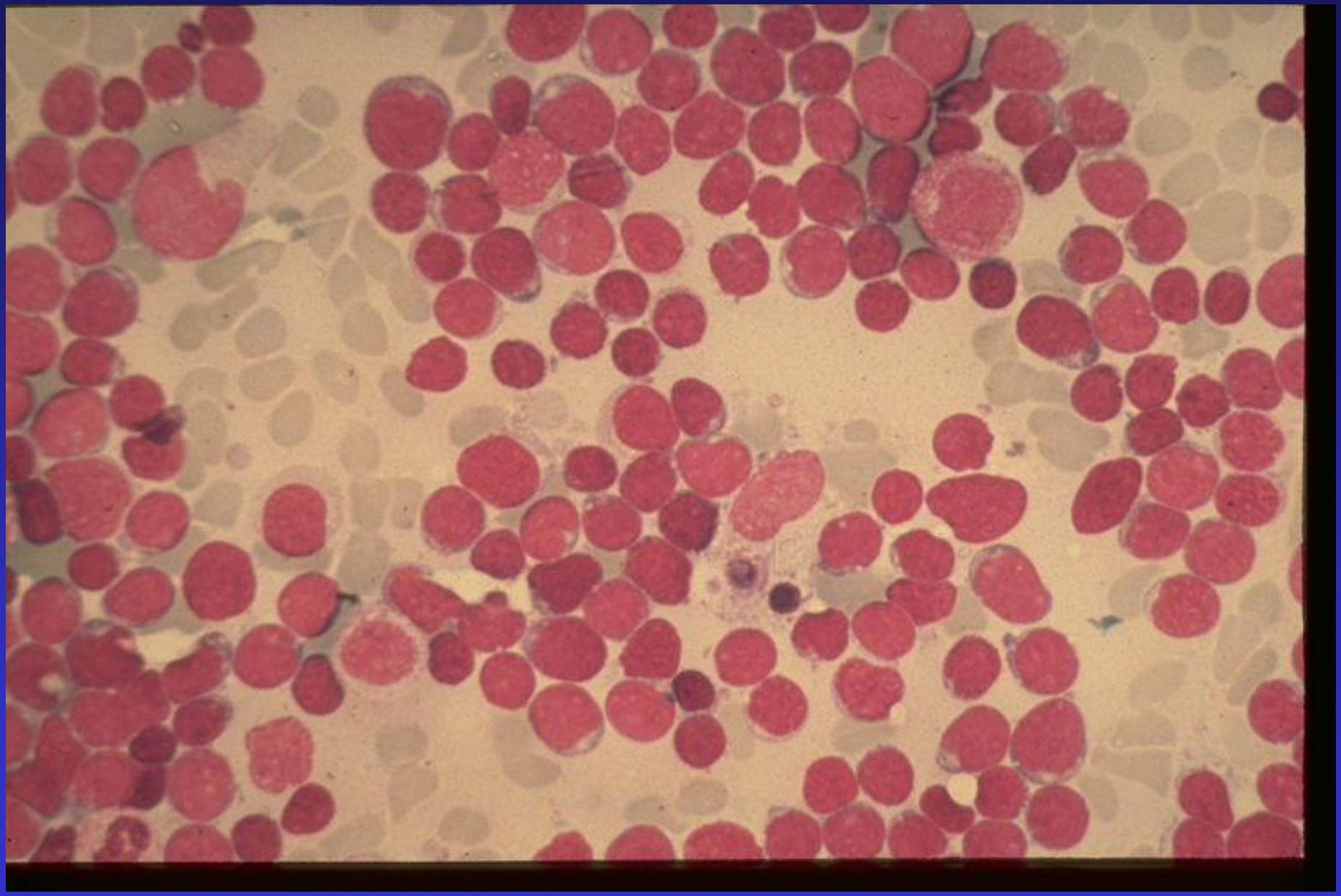
Acute leukemias of ambiguous lineage
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*‖
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B/myeloid, NOS
- Mixed phenotype acute leukemia, T/myeloid, NOS
- *Provisional entity: Natural killer (NK)–cell lymphoblastic leukemia/lymphoma*

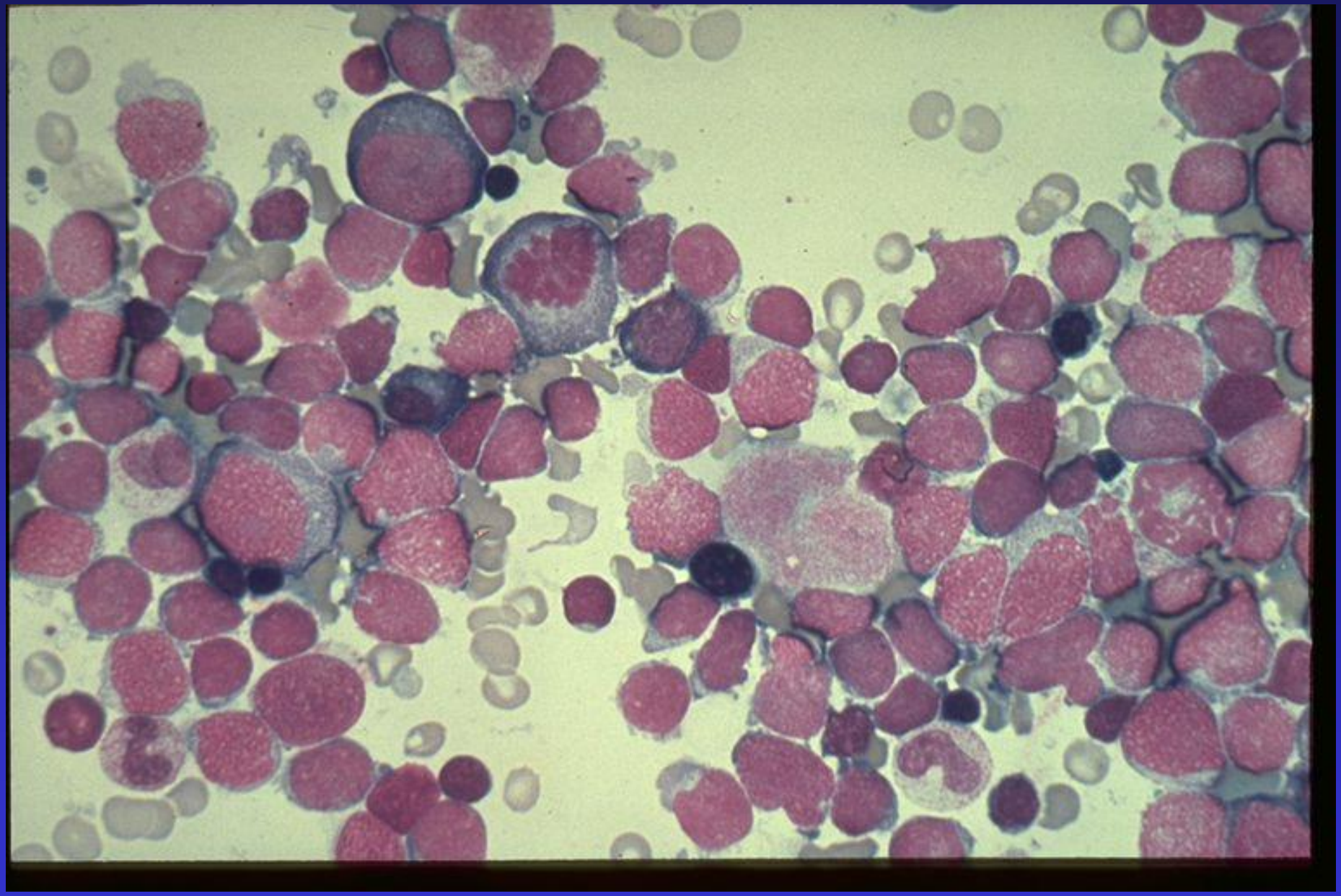
Leucemia Acuta Mieloide – Fattori di Rischio

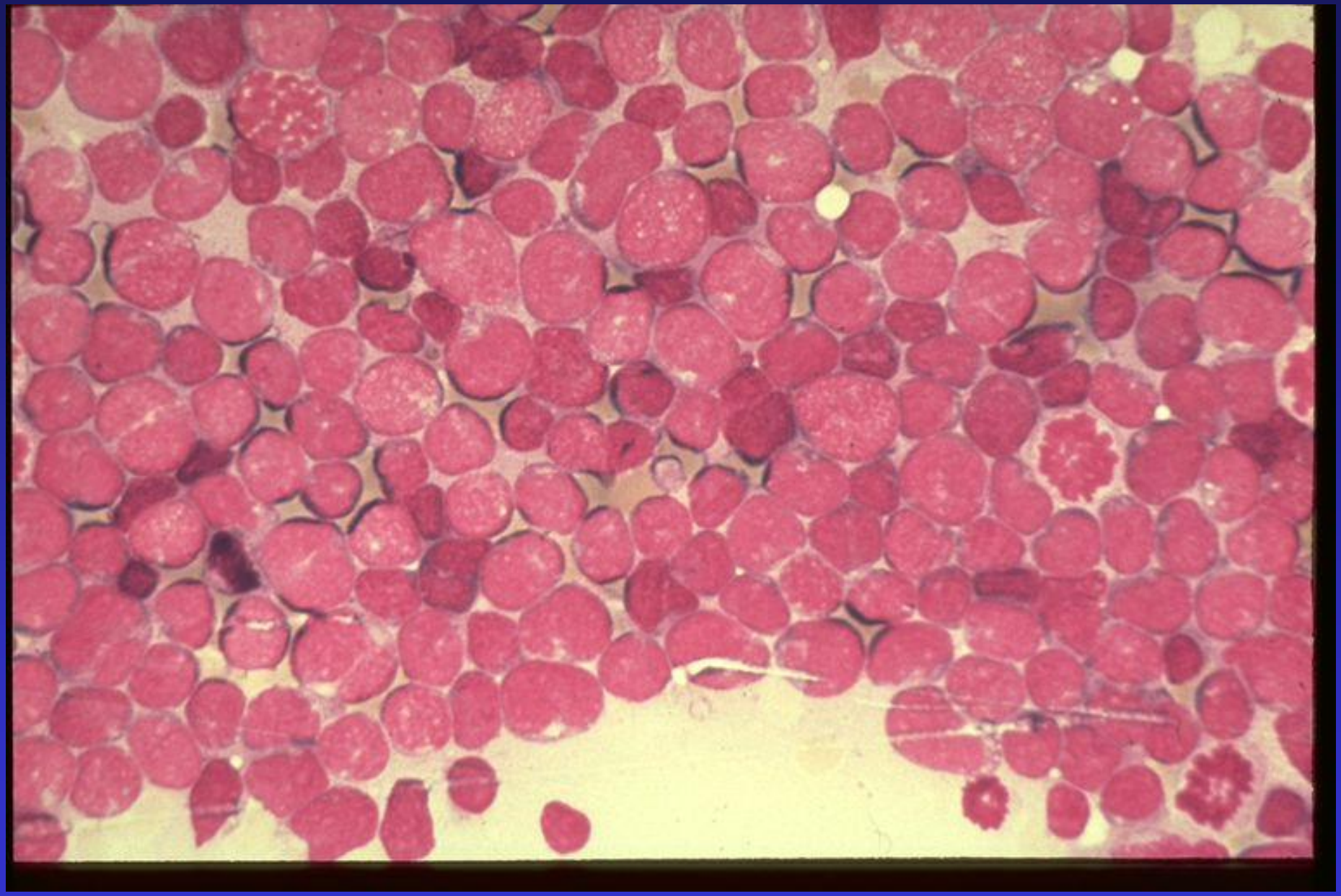
- **Età > 60 aa**
- **LAM sec. a Mielodisplasia**
- **Anomalie del Cariotipo**:
  - ad eccezione di:
    - -t(15;17)
    - -inv(16) (?)
    - -t(8;21) (?)
- **MDR + (Pgp)**
- **Leucocitosi > 30 x 10^9/L**

ALTO RISCHIO

nUOVA who 206 E NUOVA eln 2022







CASO AP, 3/8/1983

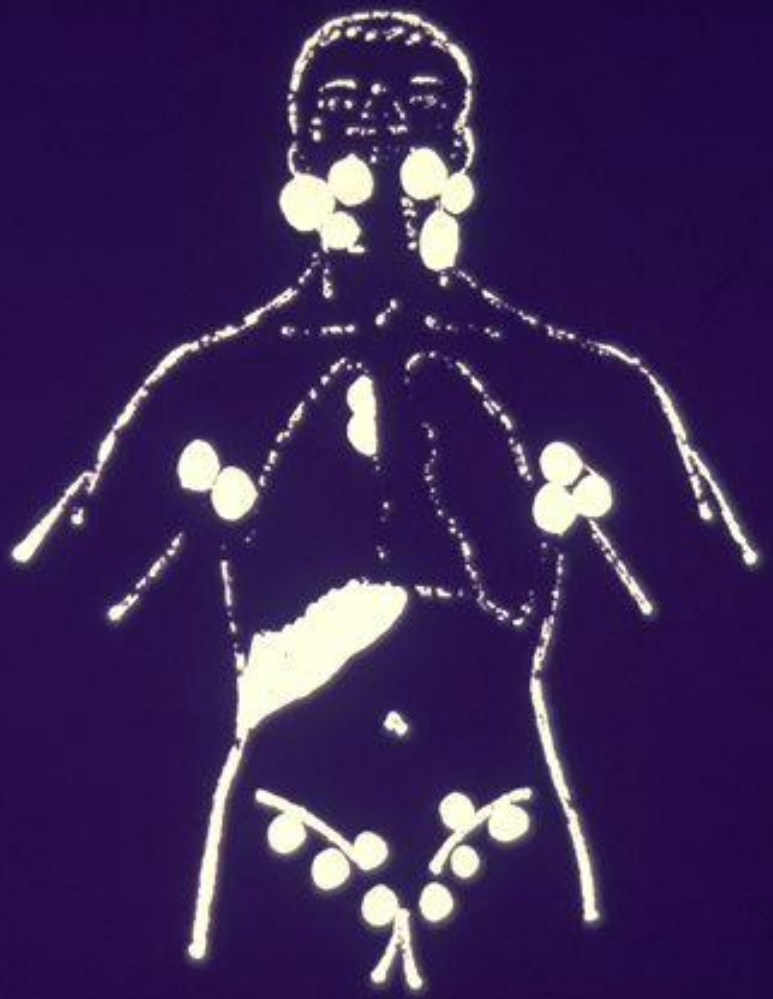
LEUCOCITI 11500/μL

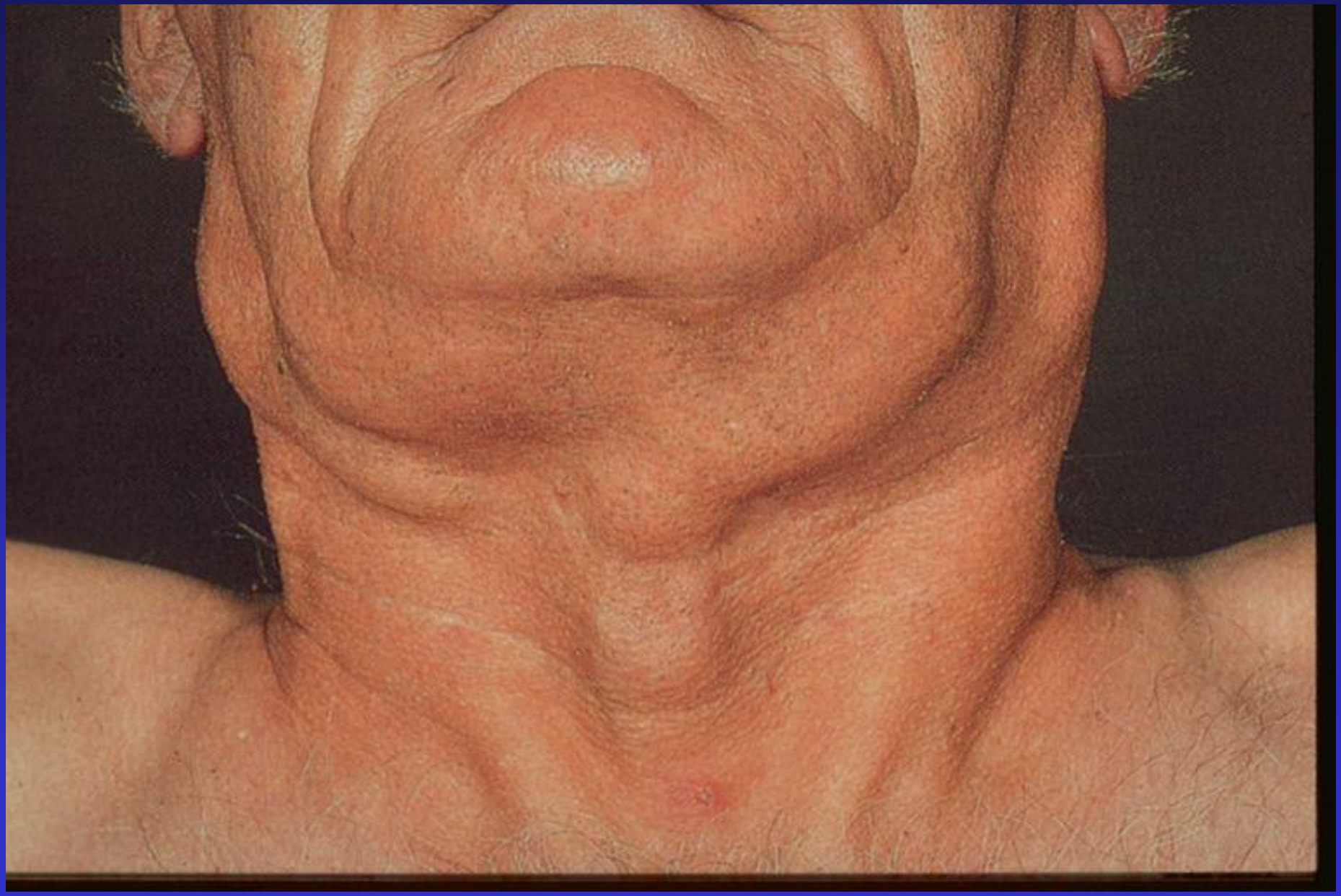
CON 33 % BLASTI

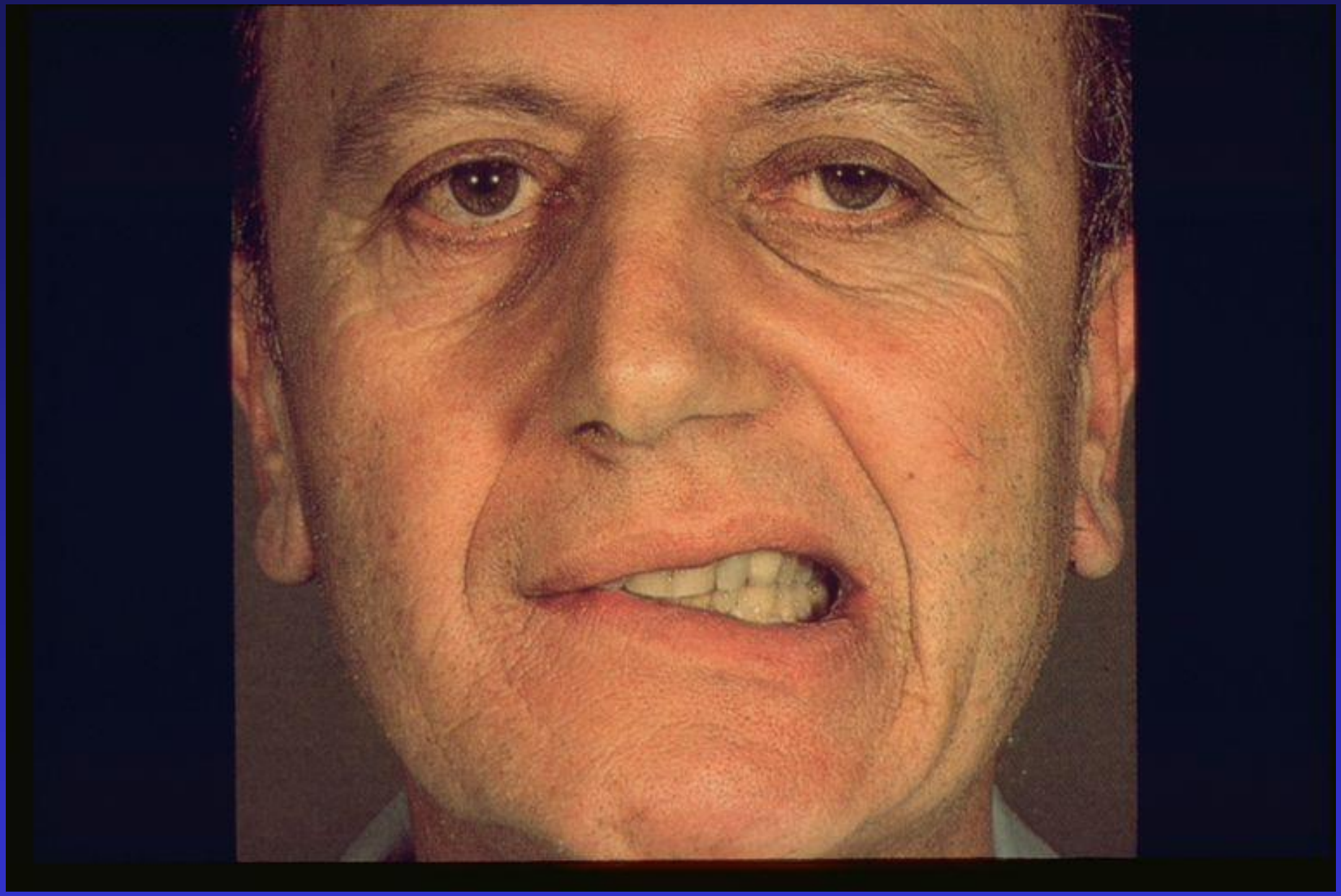
LINFOIDI

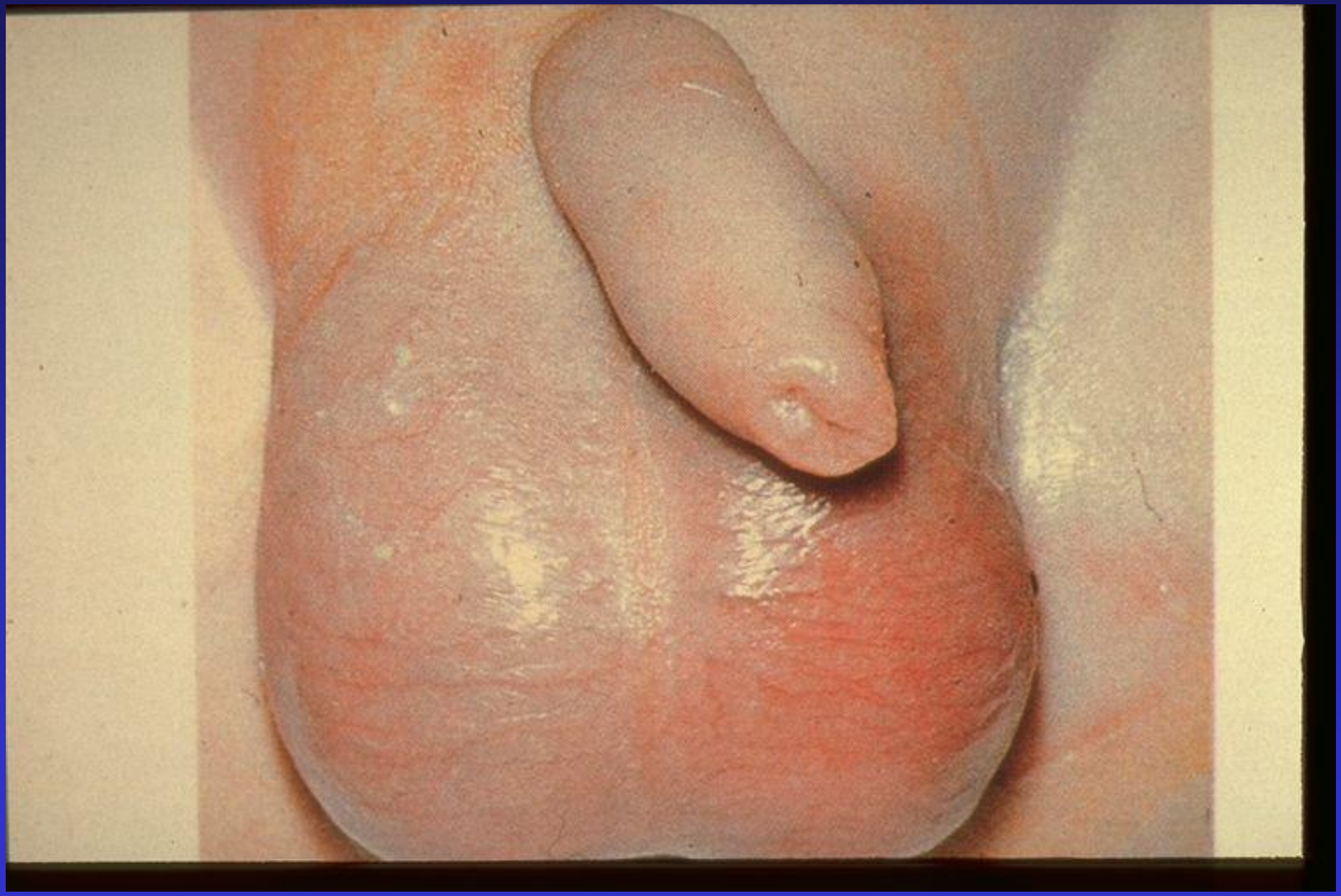
VES 81 MM

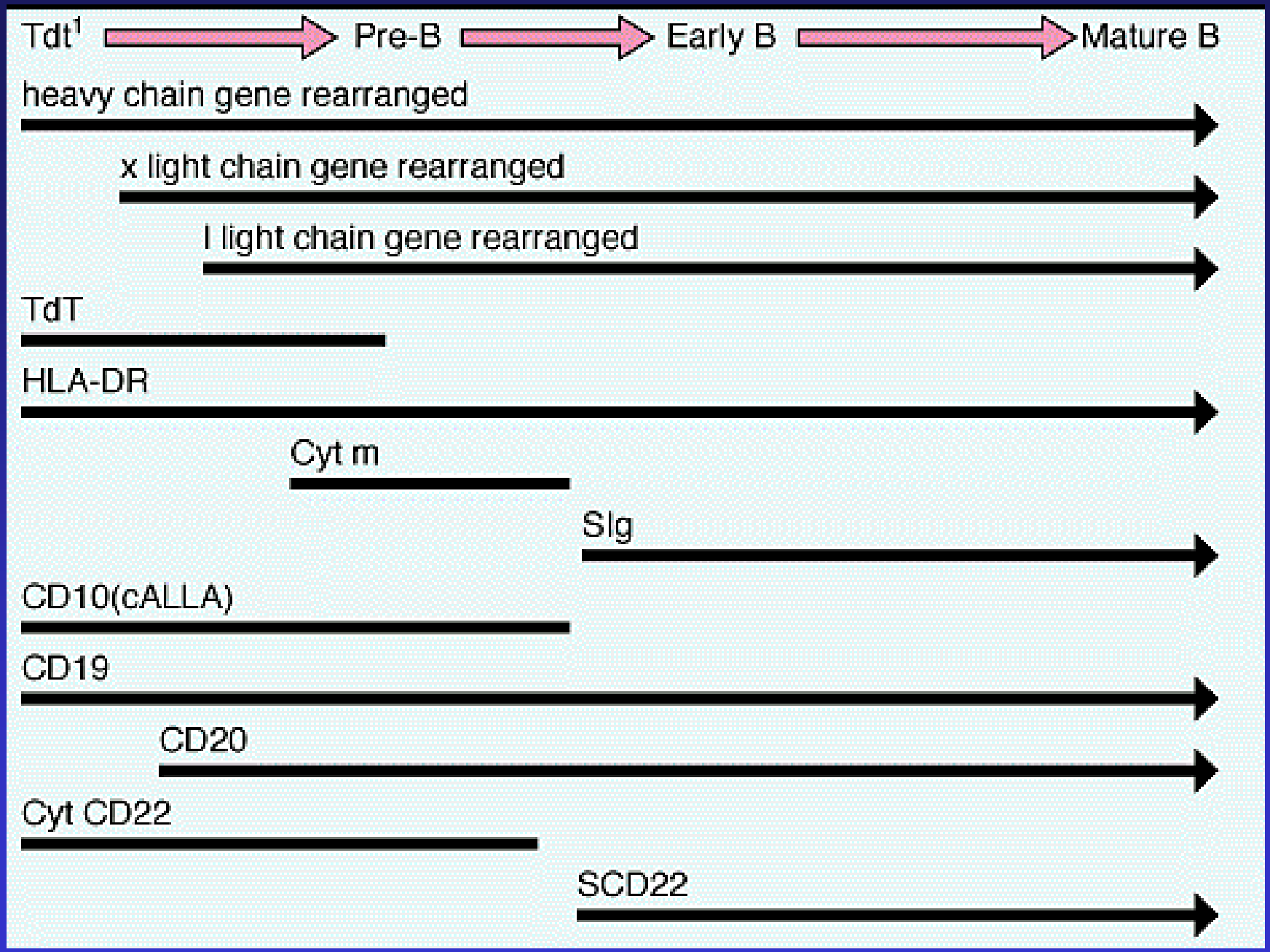
LDH 833





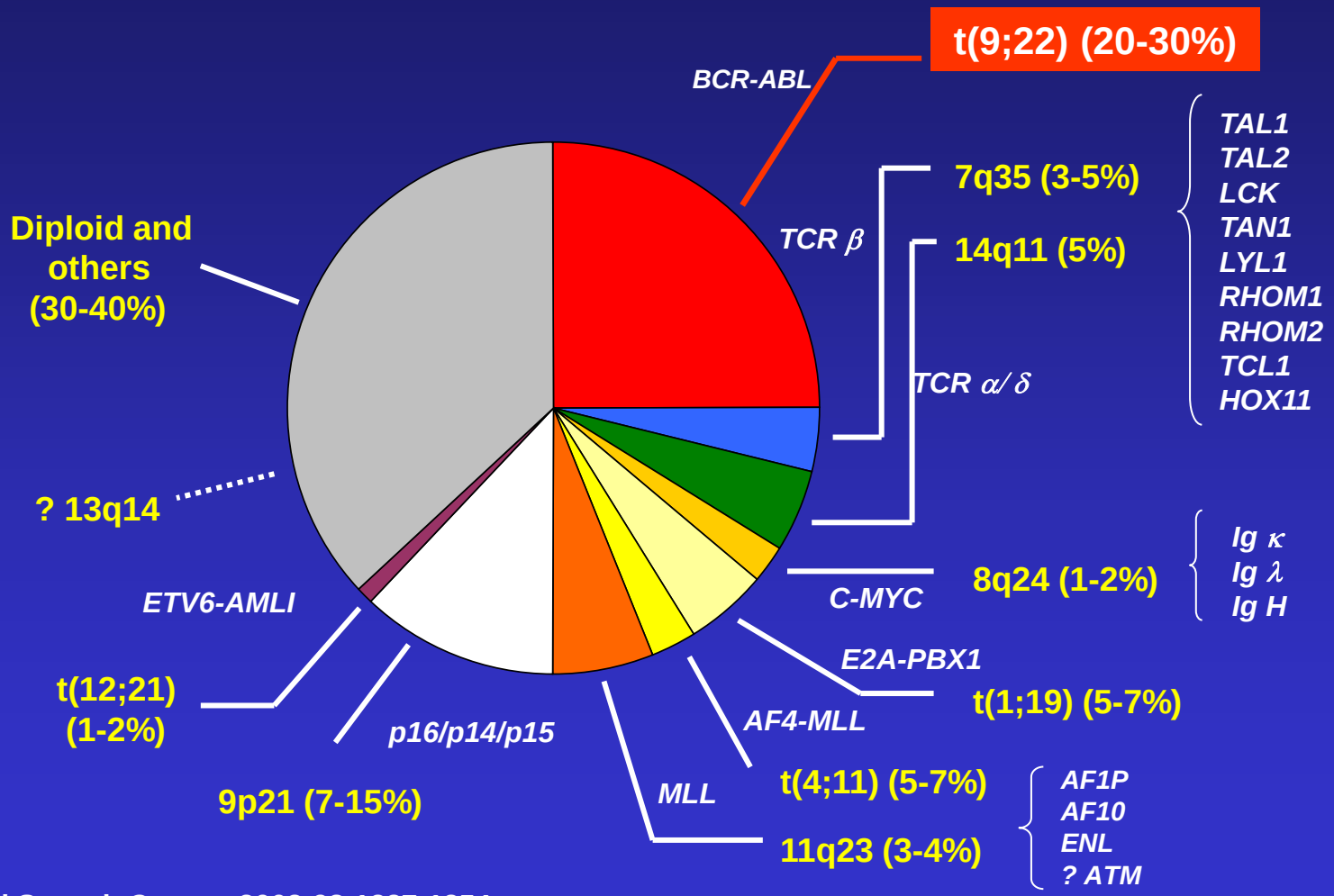





Tdt[1]
Pre-B
Early B
Mature B
heavy chain gene rearranged
x light chain gene rearranged
l light chain gene rearranged
TdT
HLA-DR
Cyt m
Slg
CD10(cALLA)
CD19
CD20
Cyt CD22
SCD22

Marcatori immunologici e riarrangiamenti genici nella leucemia acuta				
	LAL Linea B	**LAL-B**	**LAL-T**	**LAM**
Cellula staminale				
Deossinucleotidil transferasi terminale (TdT)	+	-	+	-
HLA-DR	+	+	-	±
CD34	±	-	-	±
Associati alla cellule B				
CD10	+ (in pro-B)	±	-	-
CD19 (**m**)	+	+	-	-
CD20	+	+	-	-
cCD22	+	+	-	-
CD79a (cit)	+	+	-	-
catena μ… (cit)	+ (pro-B)	+	-	-
Smlg	-	+	-	-
Associati alla cellula T				
CD2	-	-	+ (- in met)	-
cCD3	-	-	+	-
CD5	-	-	+	-
CD7	-	-	+	-
Associati alla linea mieloide/monocitica				
Anti-MPO	-	-	-	+
CD11	-	-	-	+
CD13	-	-	-	+
CD14	-	-	-	+ (soprattutto M_4, M_5)
CD33	-	-	-	+
Megacarioblastico (gpIIb/IIIa piastrinico)	-	-	-	+ (M_7)
CD41				
CD42		-		
CD61	-	-	-	+ (M_6)
Glicoforina A (gp 41)		-		
Geni delle immunoglobuline Geni per il recettore T	Riarrangiato Linea germinale o riarrangiato	Riarrangiato Linea germinale	Linea germinale o riarrangiato Riarrangiato	Linea germinale Linea germinale

Cytogeneic Abnormalities in Adult ALL



Faderl S, et al. *Cancer.* 2003;98:1337-1354.

CONFRONTI FRA BAMBINI E ADULTI

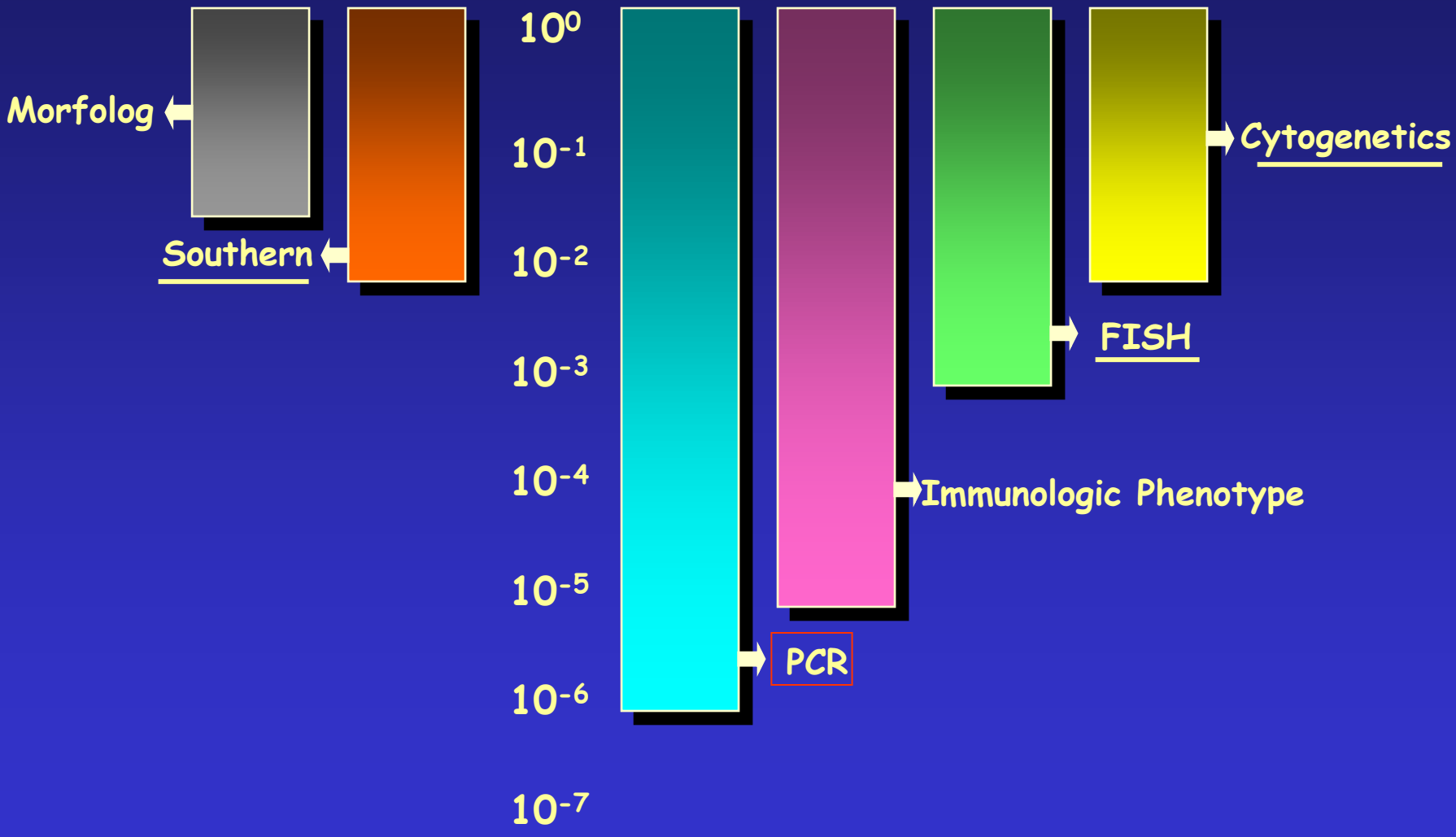
	Bambini	*Adulti*
Remissioni complete	95%	80%
Lunghi sopravviventi	> 70-80%	20%
Citotipi prevalenti	L1	L2
Immunofenotipi prevalenti	pre-B-comune	nessuno
Immunofenotipi ibridi	rari	frequenti
Cariotipo t(9.;22) (Ph+)	raro	frequente

Leucemia Acuta Linfoide – Fattori di Rischio

- **Età > 15 aa var. continua**
- **Interessamento SNC**
- **Anomalie del Cariotipo:**
- **Fenotipo T / B maturo**
- **MDR + (Pgp)**
- **Leucocitosi > 30 x 10^9/L**

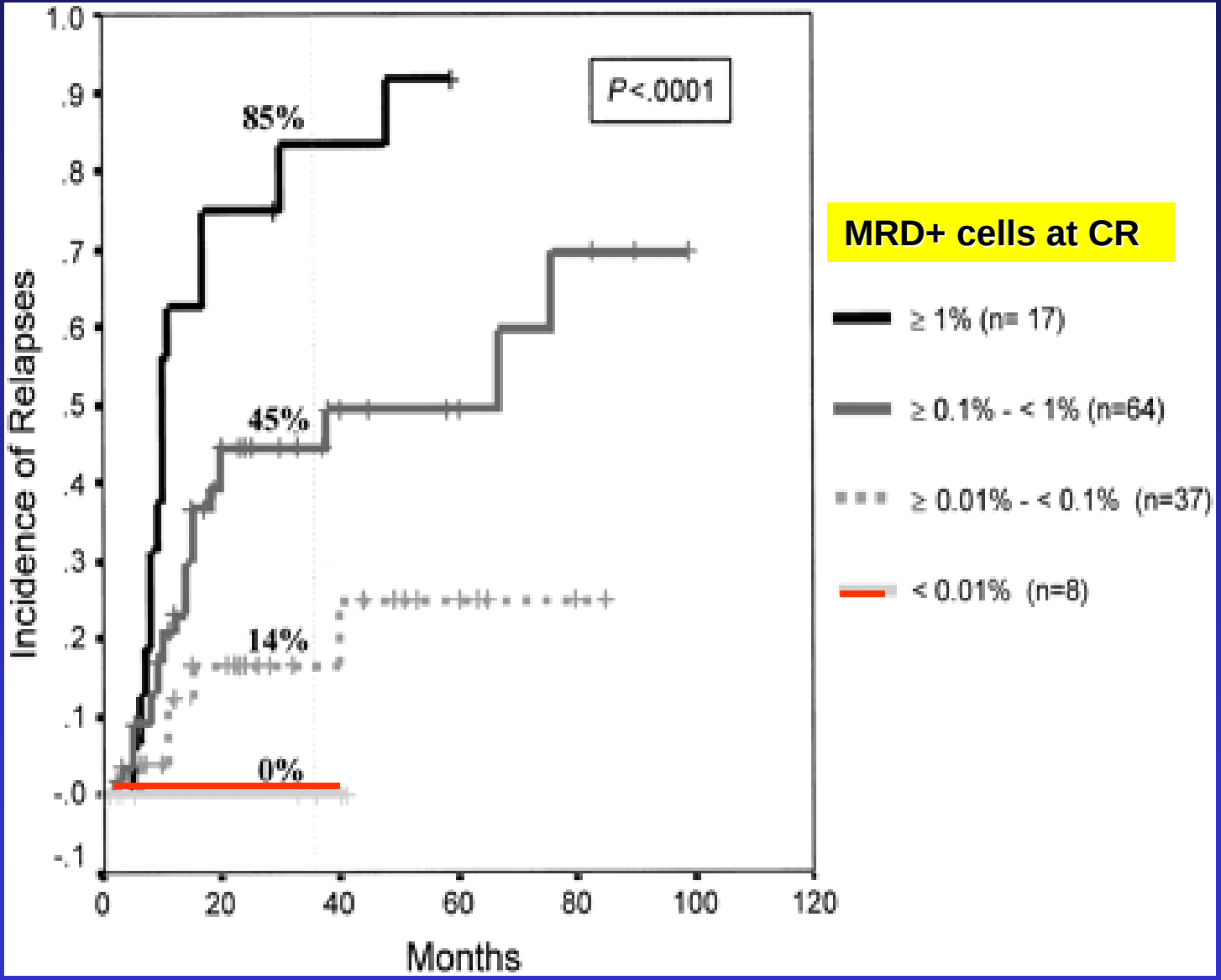
ALTO RISCHIO

METHODS TO DETECT MRD.



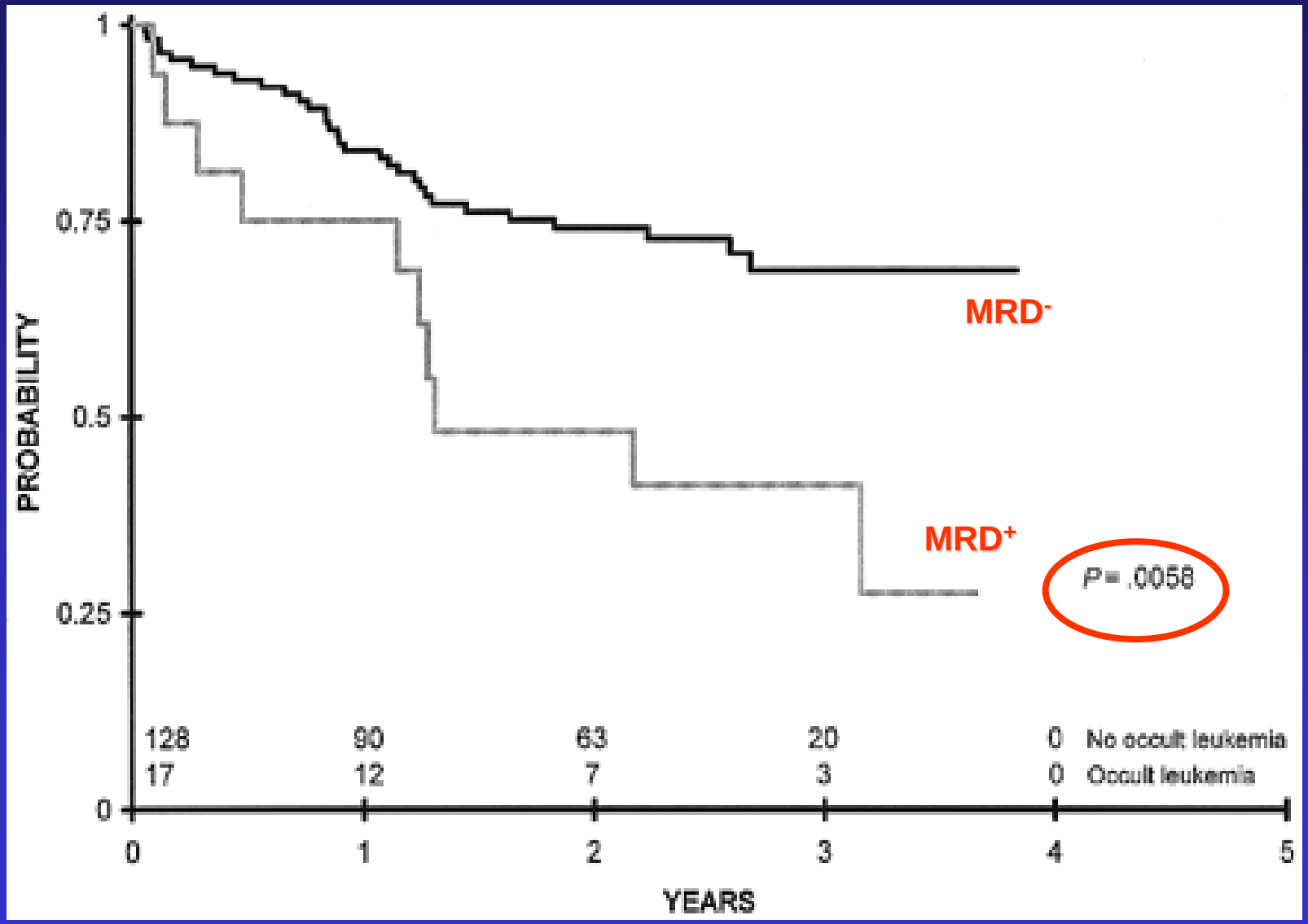
LAM: MMR ed incidenza di ricaduta

San Miguel, Blood 2001



LAM: MMR e sopravvivenza

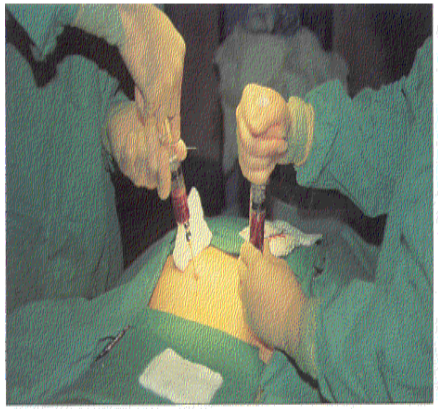
Sievers Blood 2003



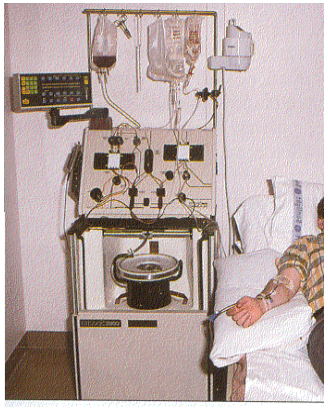
Trapianto di CS Autologhe

RC

RACCOLTA DI CELLULE STAMINALI DA MIDOLLO OSSEO



RACCOLTA DI CELLULE STAMINALI DA SANGUE PERIFERICO

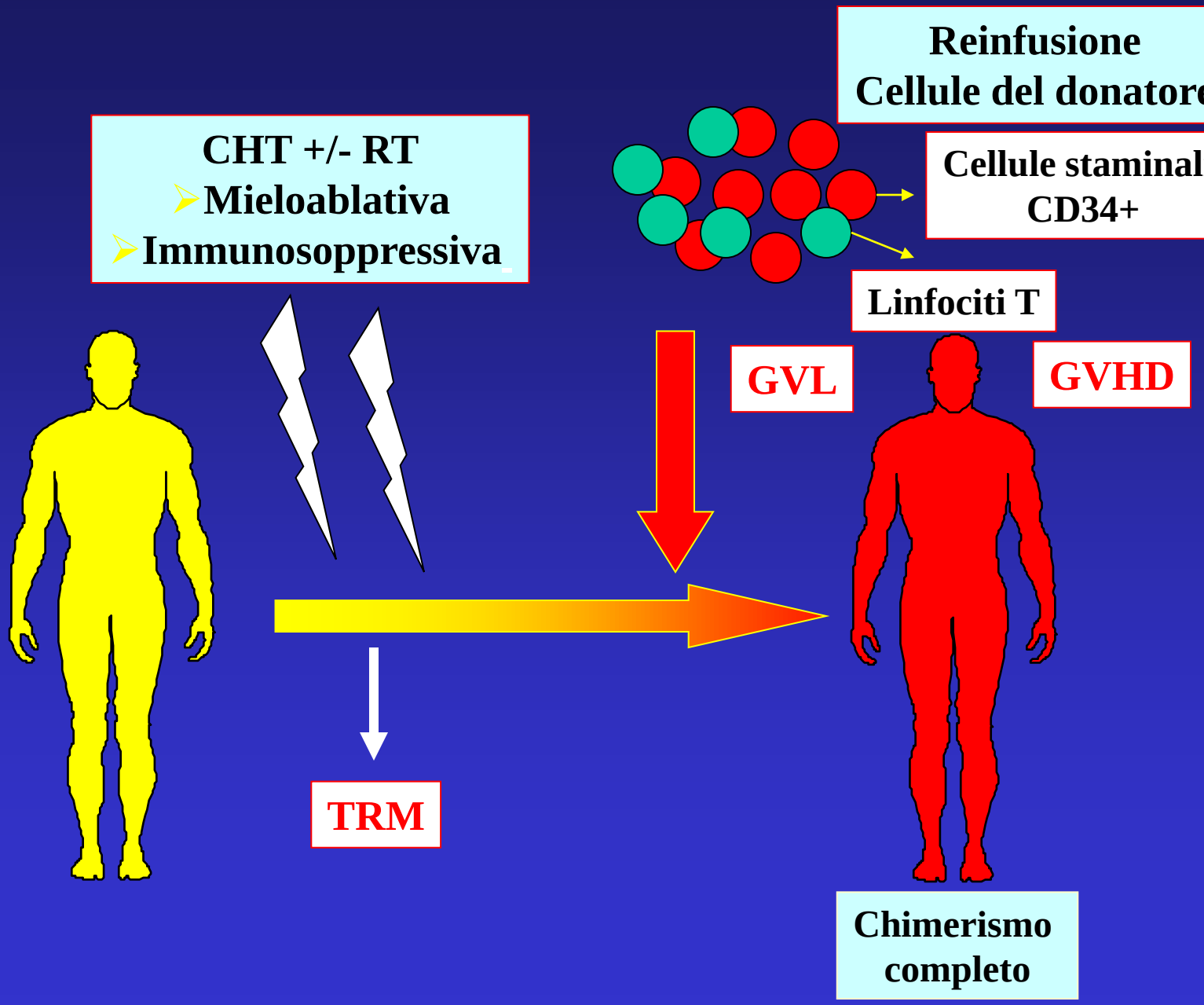


Condizionamento Tx

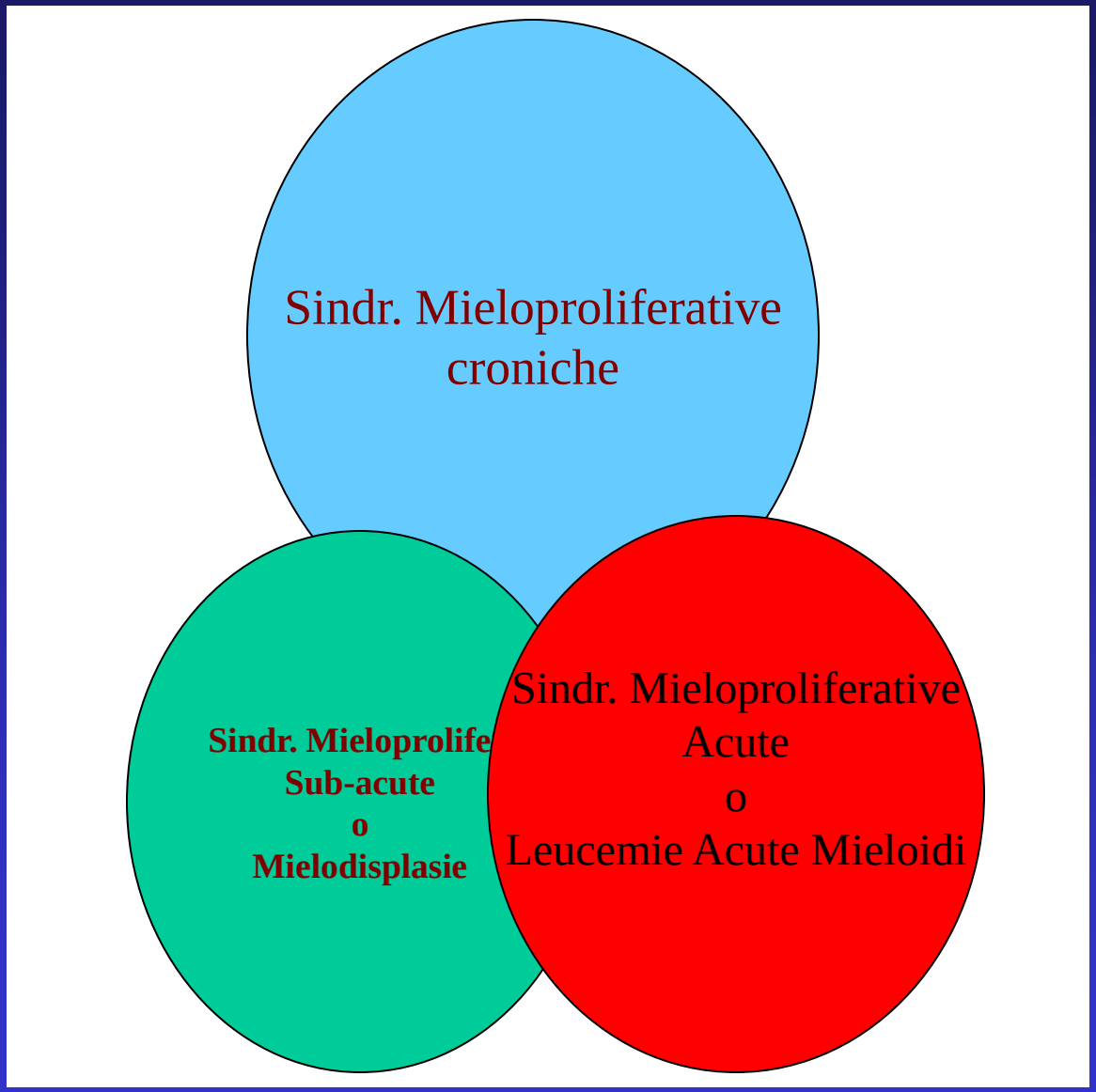
Reinfusione CD34+

Schema della terapia delle leucemie acute e della sua azione sulla proliferazione cellulare leucemica

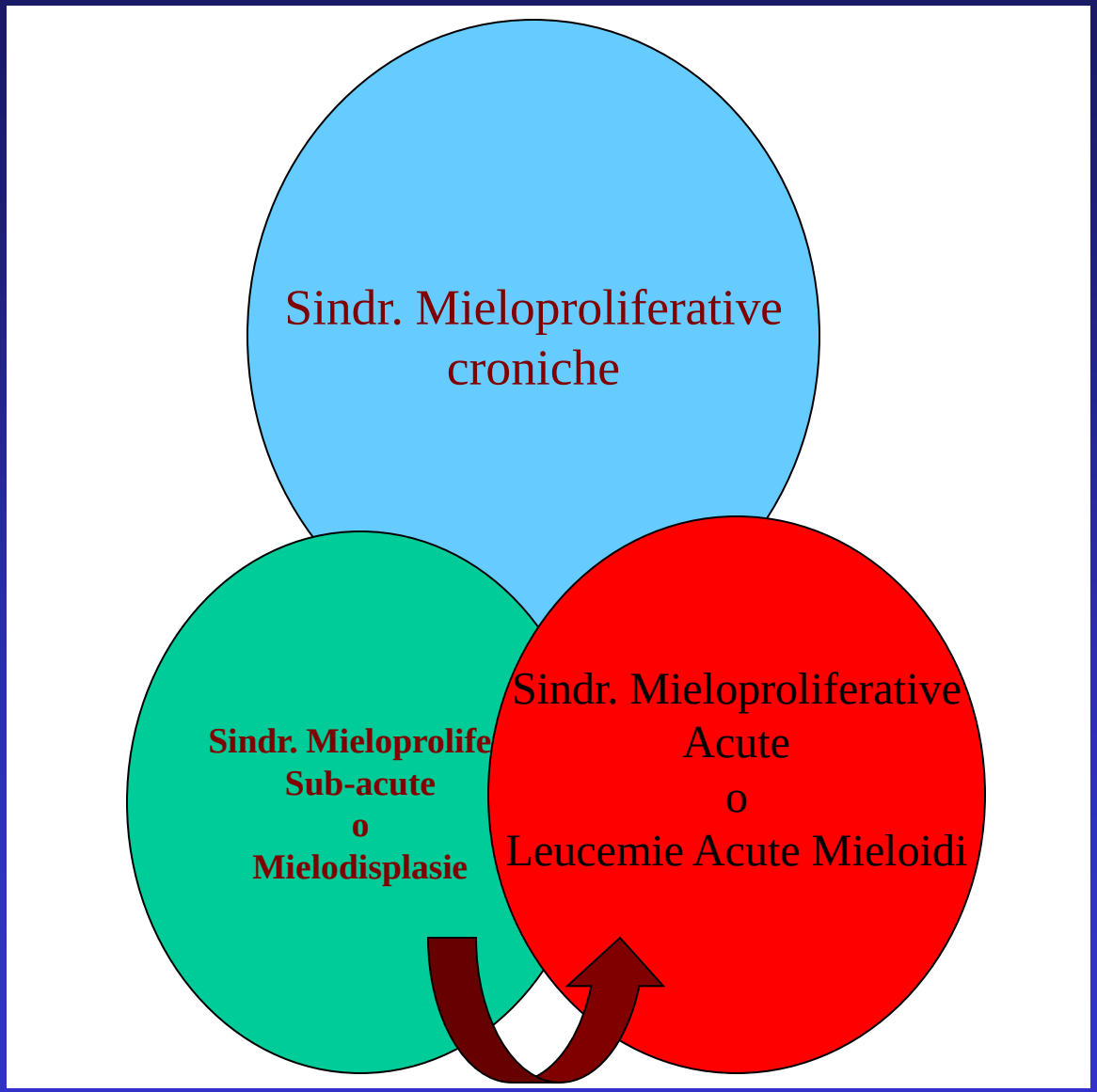
Trapianto di CS Allogeniche



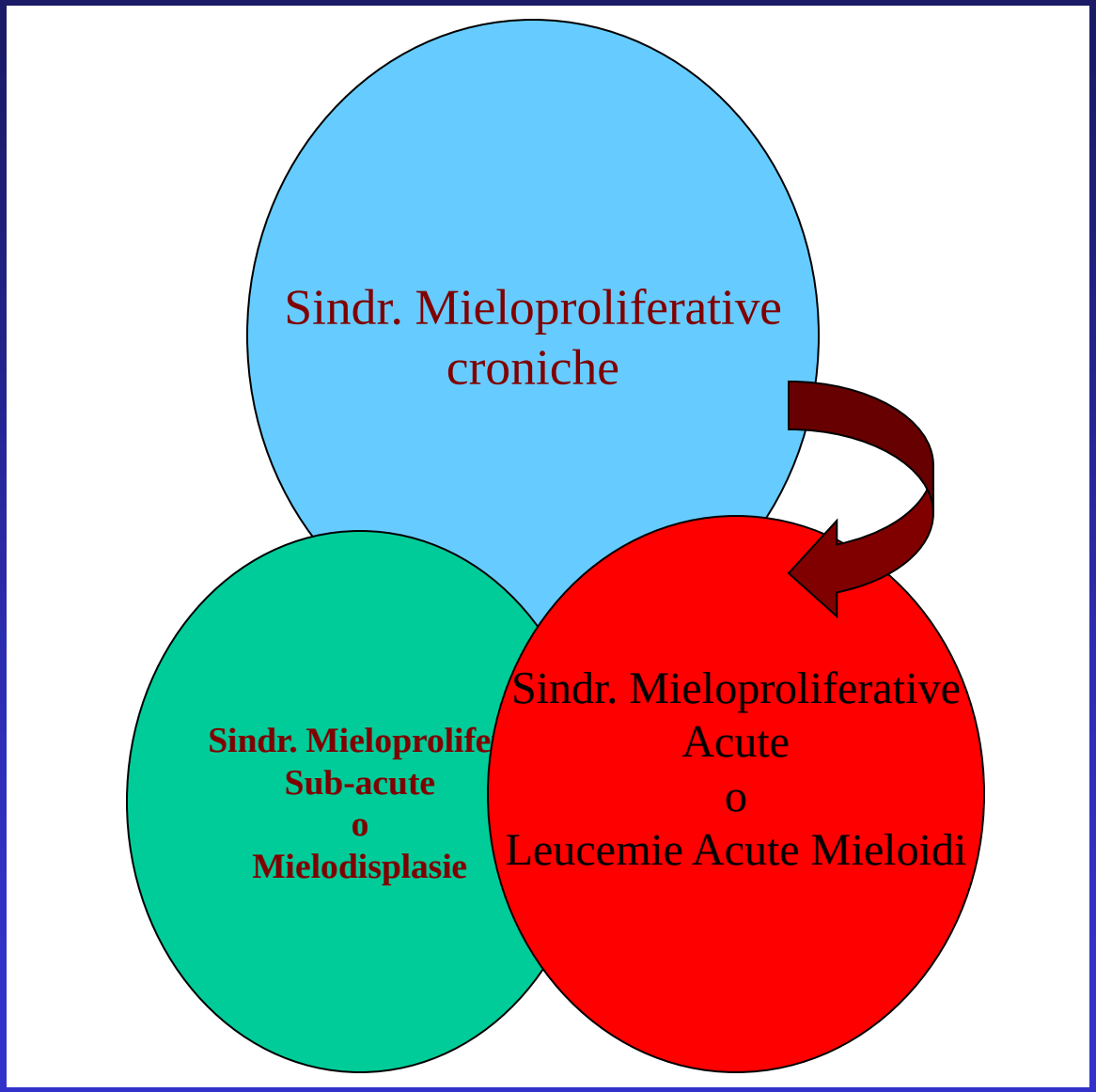
Sindromi Mieloproliferative



Sindromi Mieloproliferative



Sindromi Mieloproliferative



SCHEMA DI CLASSIFICAZIONE DELLE LEUCEMIE MIELOIDI O SINDROMI MIELOPROLIFERATIVE

ACUTE	SUBACUTE	CRONICHE
Leucemie acute mieloidi	**Sindromi mielodisplastiche**	**Leucemia mieloide cronica**
M1 (mieloblastica senza maturazione)	Anemia refrattaria (AR) con sideroblasti a corolla	**Mielofibrosi con metaplasia mieloide splenoepatica**
M2 (mieloblastica con maturazione)	AR senza sideroblasti a corolla	**Trombocitemia primitiva**
M3 (promielocitica)	AR con blastosi midollare	**Policitemia vera**
M4 (mielomonoblastica)	AR con blastosi midollare in trasformazione	
M5 (monoblastica)	Leucemia mielomonocitica cronica	
M6 (eritroblastica)		
M7 (megacarioblastica)		
Leucemie acute ibride		

Tabella 3.3

PRINCIPALI CARATTERI BIOLOGICI E PATOGENETICI DELLE LEUCEMIE MIELOIDI O SINDROMI MIELOPROLIFERATIVE

	ACUTE	SUBACUTE	CRONICHE
Proliferazione	Incontrollata, autonoma senza differenziazione	Parzialmente controllata con parziale differenziazione	Parzialmente controllata con differenziazione
Maturazione	Molto ridotta o assente	Ridotta e inefficace	Normale
Accumulo di blasti	Elevato	Modesto	Irrilevante
Produzione di: eritrociti, granulociti, piastrine	Fortemente difettosa	Difettosa	Aumentata
Clinica	Anemia, infezioni, emorragie	Anemia, più raramente infezioni e emorragie	Secondaria all'espansione del tessuto mieloide (splenomegalia, epatomegalia) e delle cellule mature (eritrocitosi, trombocitosi e leucocitosi)

Tabella 3.4.