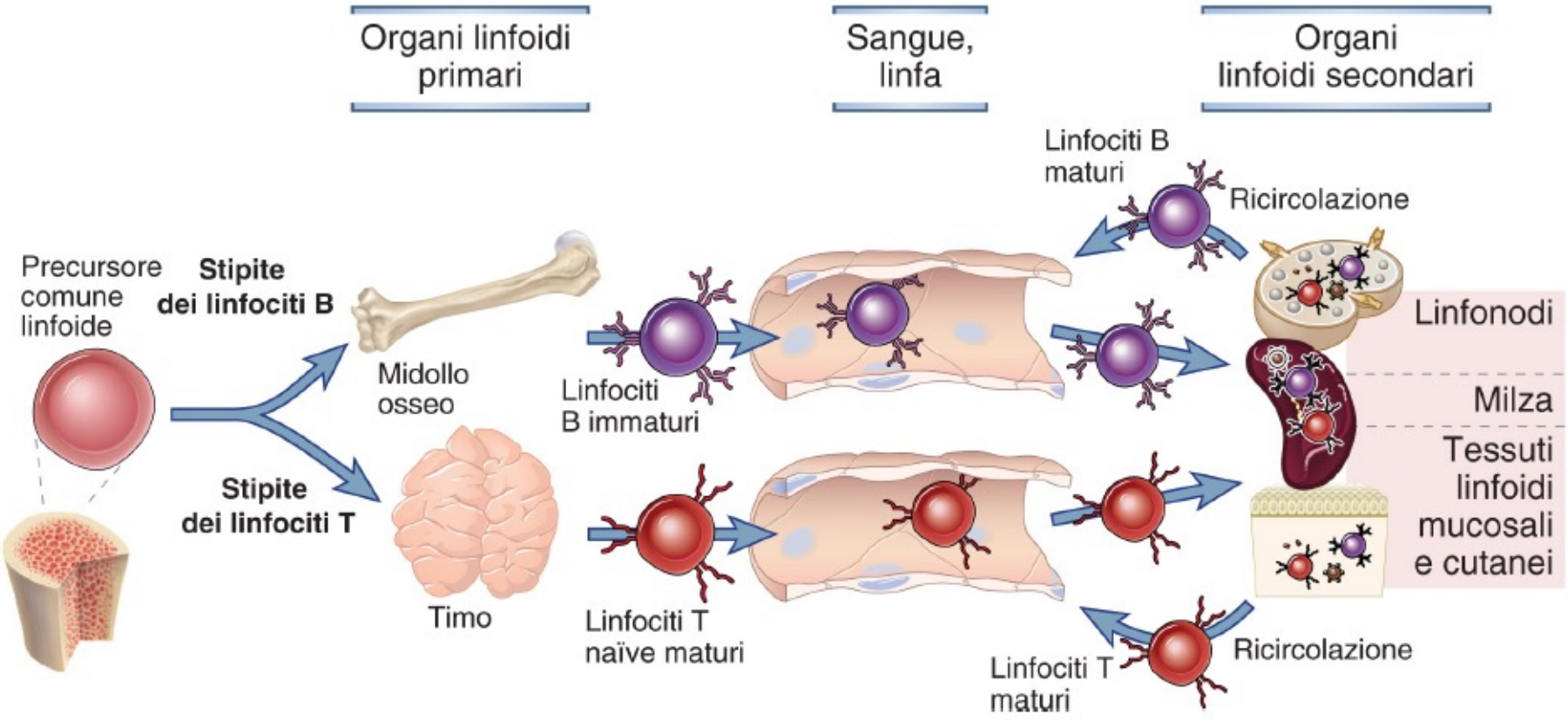
Il percorso di maturazione dei linfociti



Linfomi: definizione

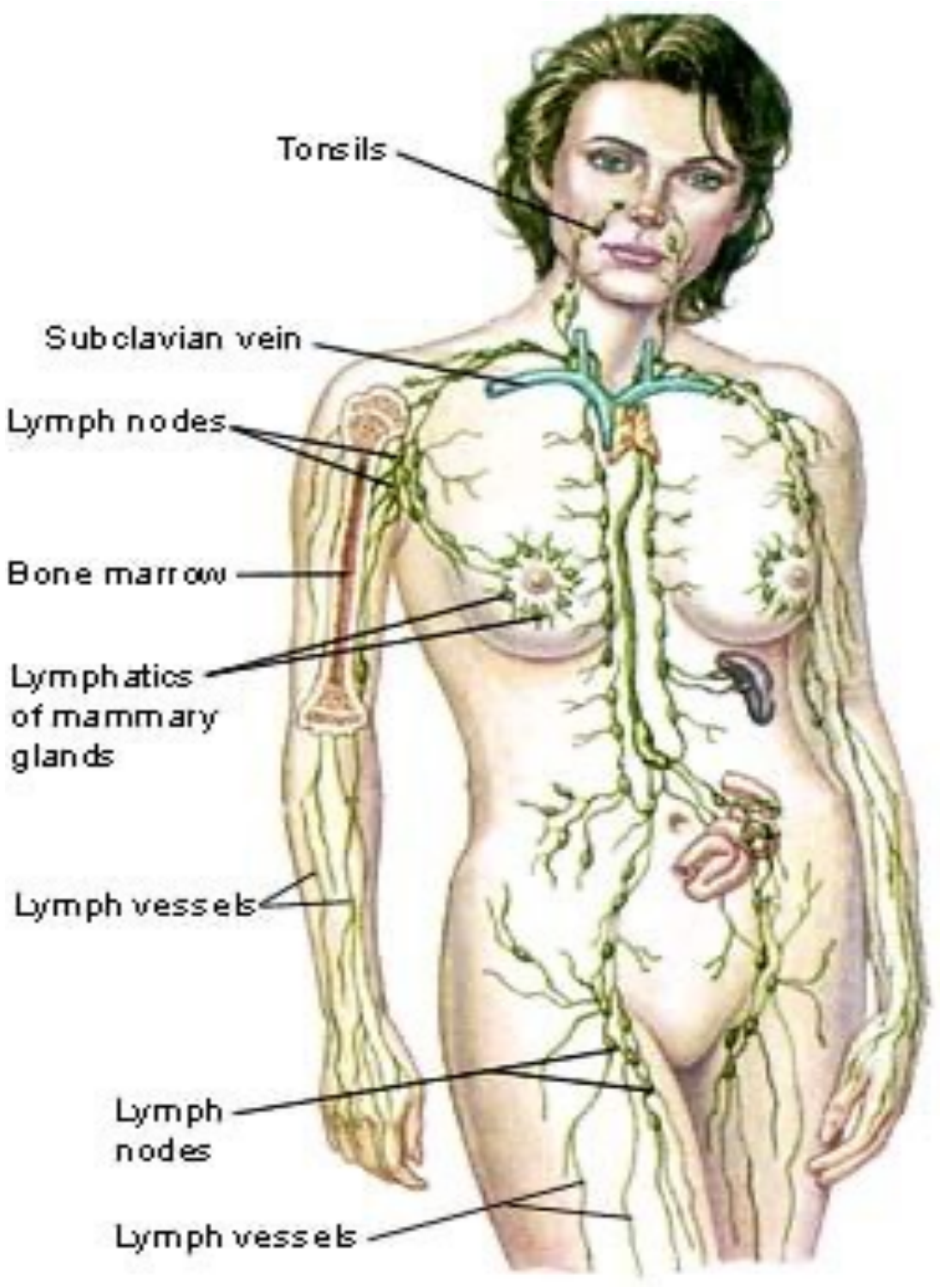
Tumori del sistema linfatico

Gruppo eterogeneo di malattie che si differenziano per:

- Epidemiologia
- Eziologia
- Biologia
- Aggressività
- Presentazione clinica
- Risposta alle terapie
- Prognosi

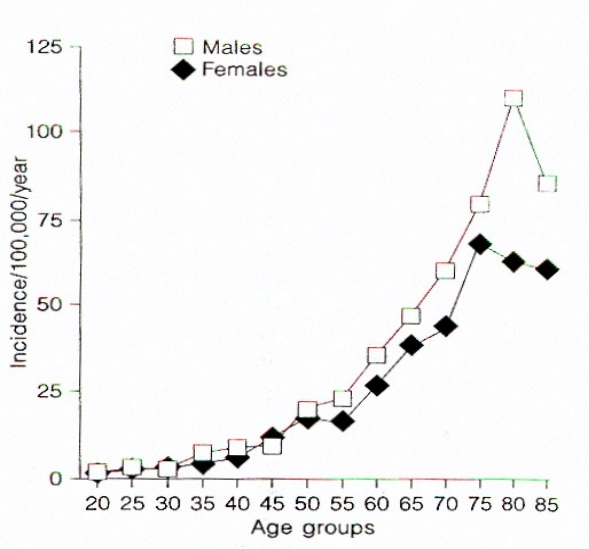
Sistema Immunitario Primario
- Midollo osseo
- Timo

Sistema Immunitario Secondario
- Linfonodi
- Milza
- Tessuto linfatico cute
- Tessuto linfatico intestino
- Tessuto linfatico faringe



Linfomi: epidemiologia

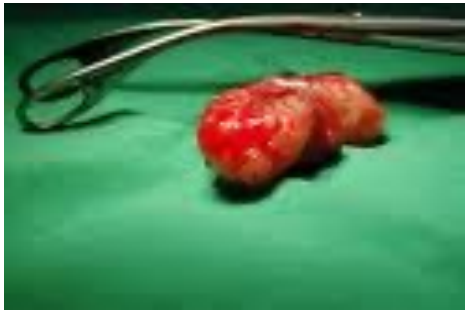
- 4% delle nuove diagnosi di tumore maligno;
- Incidenza: circa 30 nuovi casi su 100.000 abitanti anno;
- Incidenza in incremento;

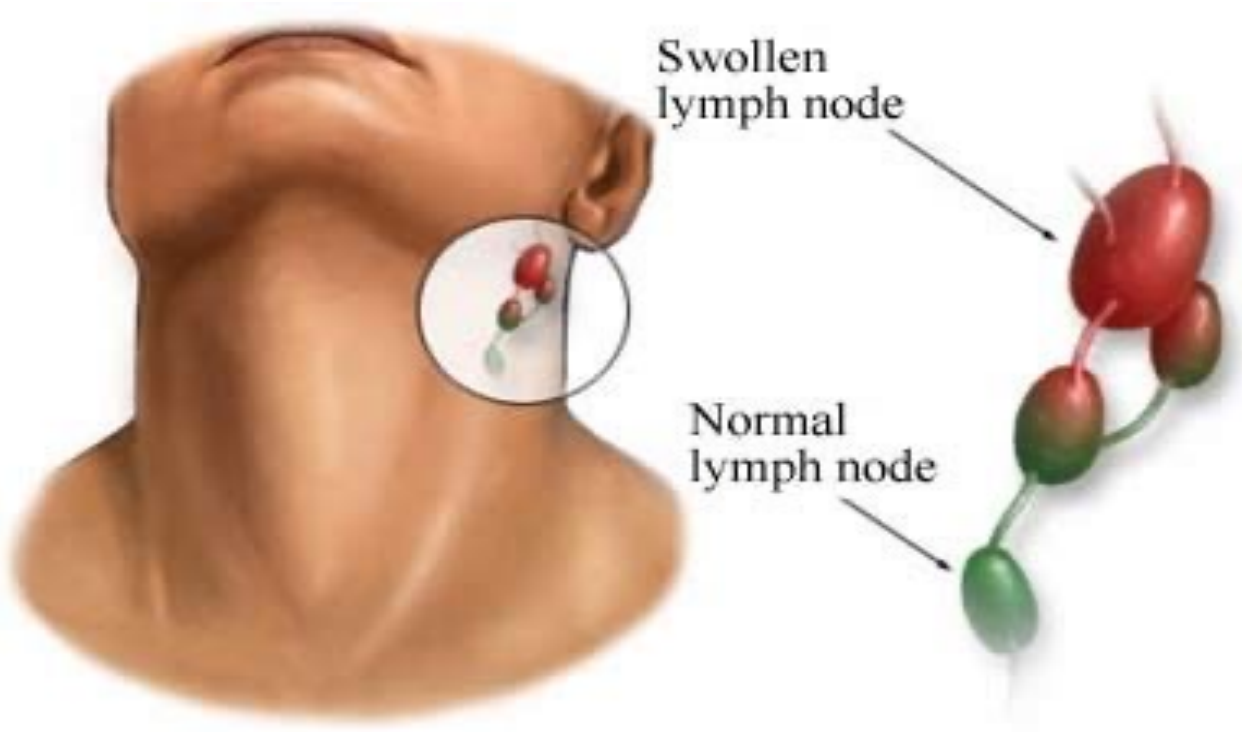


- Età di insorgenza: variabile a seconda del tipo di linfoma; età media intorno ai 60-70 anni;
- Lieve prevalenza nel sesso maschile;
- Categorie a rischio: pazienti con stato di immunosoppressione o affetti da patologie del sistema immunitario (malattie autoimmuni);

Linfomi: presentazione

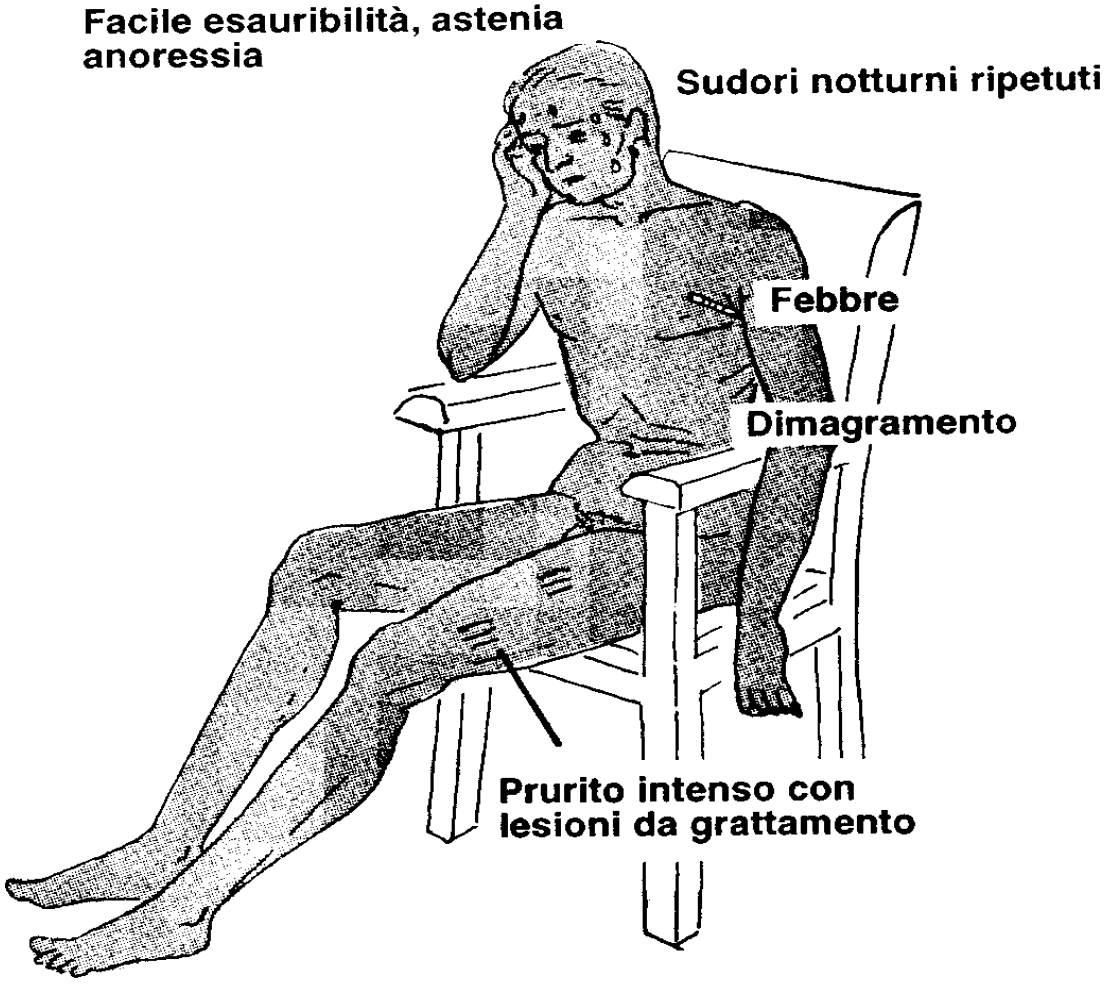
1. Tumefazione delle sedi linfatiche coinvolte





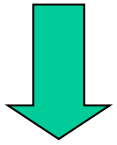
Linfomi: presentazione

2. Sintomi generali



Linfomi: presentazione

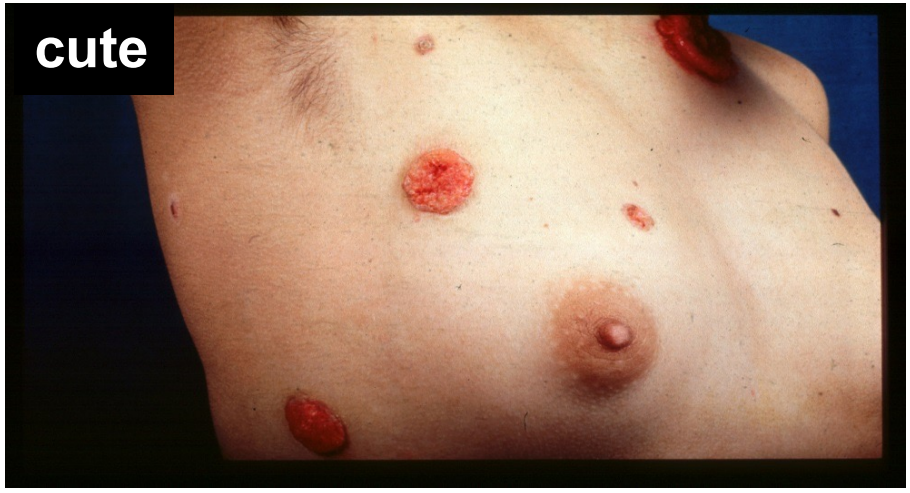
3. Stato di immunosoppressione

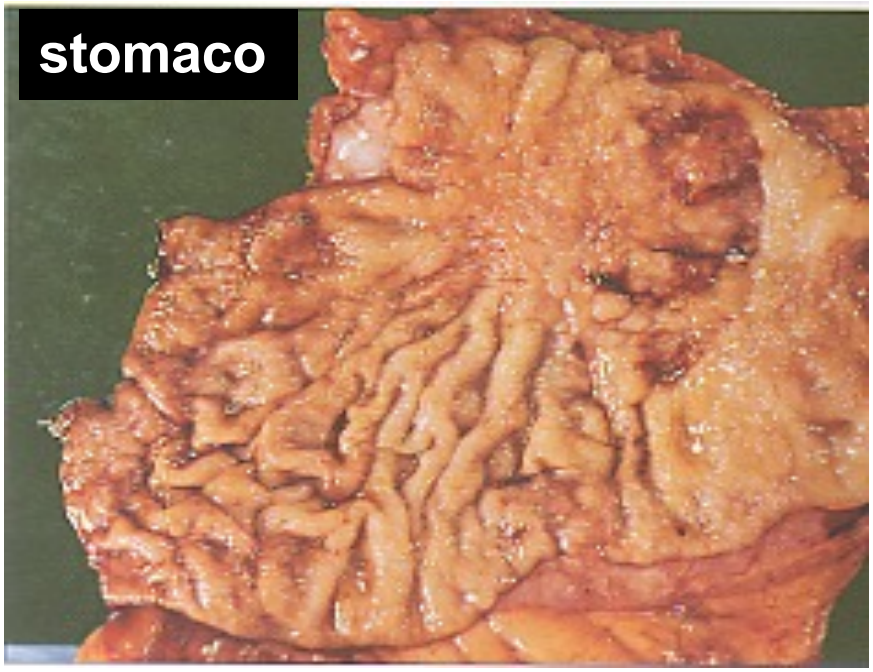


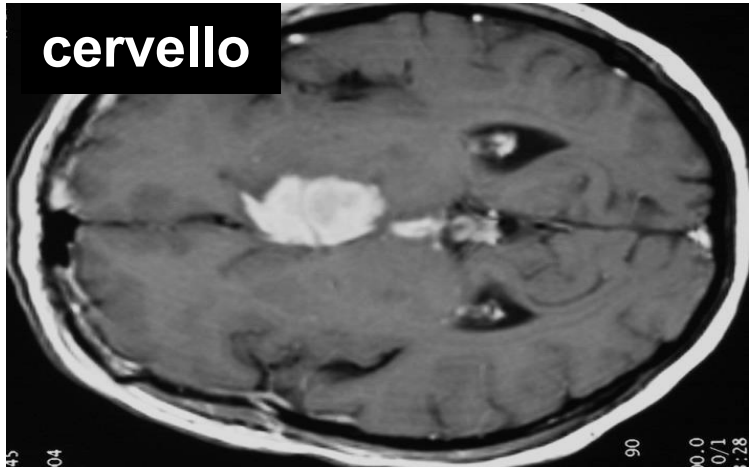
Maggiore ricettività alle infezioni

Linfomi: presentazione

4. Possibile interessamento anche di organi non linfatici

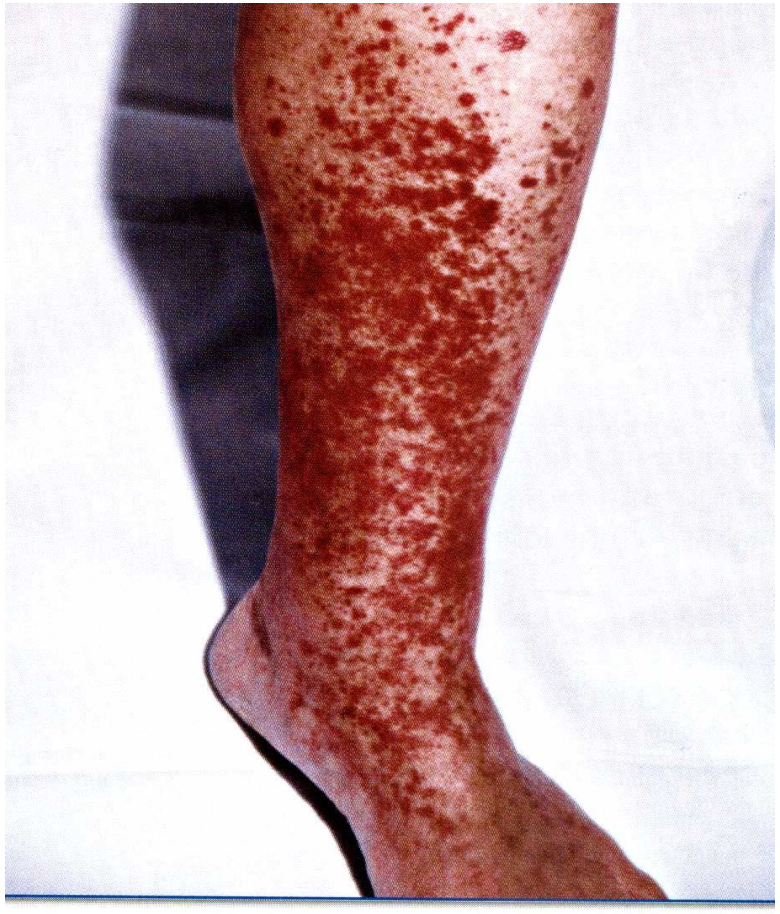


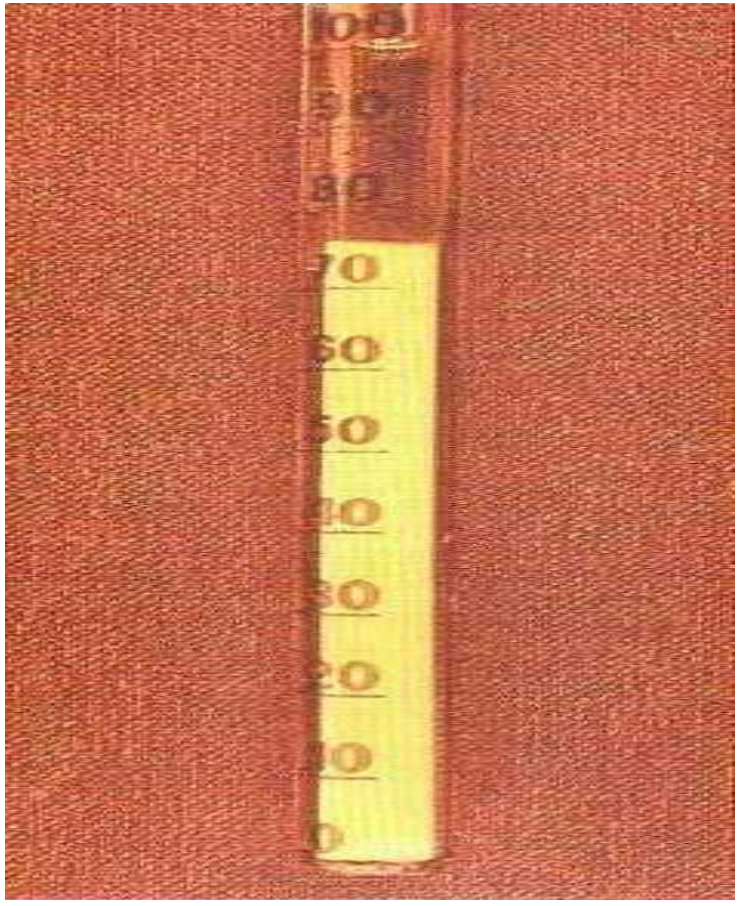




Linfomi: presentazione

5. Fenomeni particolari





Linfomi: eziologia

1. Sconosciuta nella maggior parte dei casi
2. Agenti “inquinanti” in genere (fumo, pesticidi, radiazioni)
3. Alcuni farmaci (chemioterapici, farmaci immunosoppressori)
4. Agenti infettivi:
   - Virus (HCV, EBV, HIV, …)
   - Batteri (Helicobacter Pilori, Clamidia Psittaci, …)

DIAGNOSI

La diagnosi di linfoma deve essere

SEMPRE

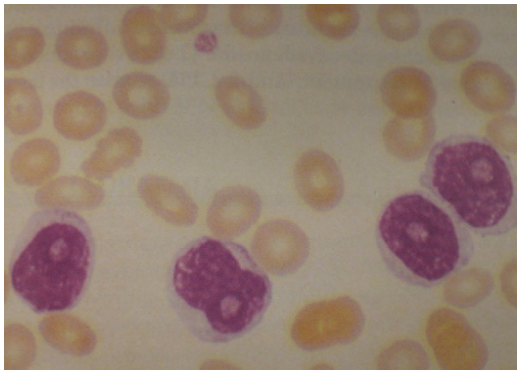
documentata istologicamente

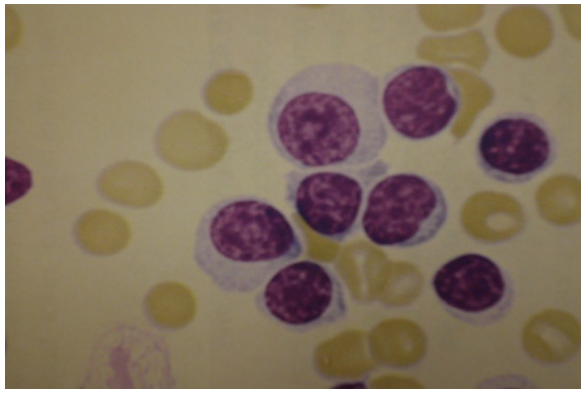
~~AGOASPIRATO LINFONODALE~~

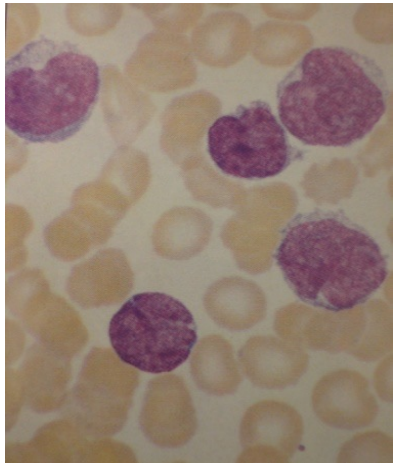
- insufficiente per iniziare una chemioterapia antitumorale
- può alterare l'architettura strutturale del linfonodo e rendere quindi problematica la diagnosi sulla successiva biopsia
- elevata percentuale di falsi positivi o negativi
- inadeguato ai fini della precisazione classificativa del linfoma
- quanto tempo ci fa perdere?

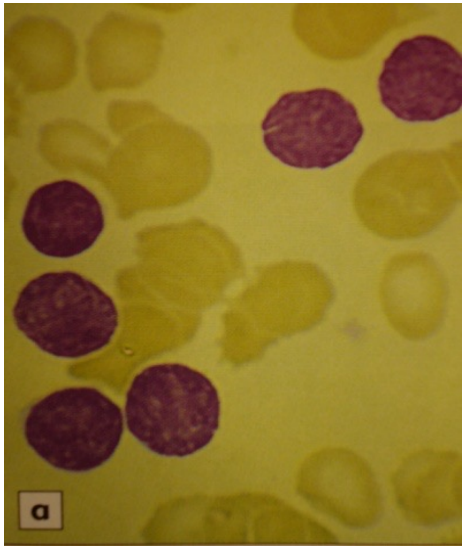
ACCERTAMENTI DI LABORATORIO

- esame emocromocitometrico completo, con formula ed osservazione dello striscio al microscopio
- tests sierologici (mononucleosi, toxoplasmosi, HIV, CMV)
- LDH
- β_2 microglobulina
- protidemia con elettroforesi, immunodiffusione e immunofissazione





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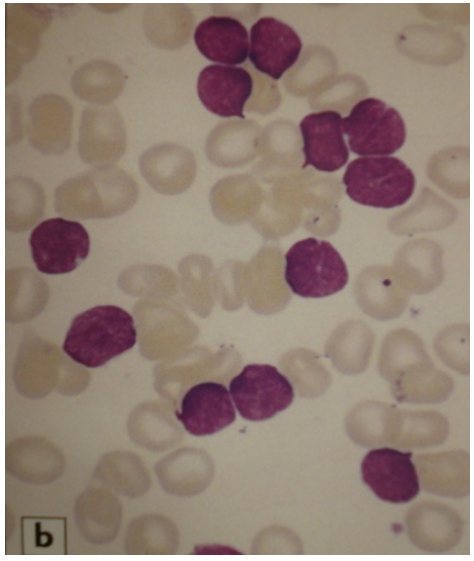
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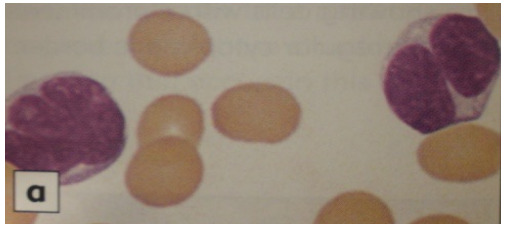
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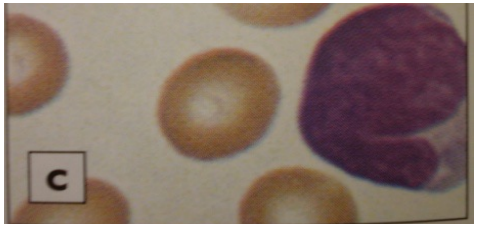

c

Linfomi: diagnosi e inquadramento

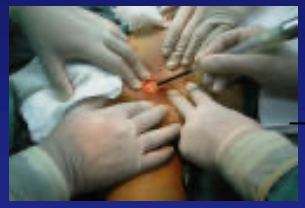
- Biopsia: linfonodo e midollo osseo, altri organi
- Esame clinico
- Esami di laboratorio
- Indagini radiologiche:
  - TAC collo-torace-addome
  - Risonanza Magnetica
  - PET (TC-PET)

Indagini particolari:

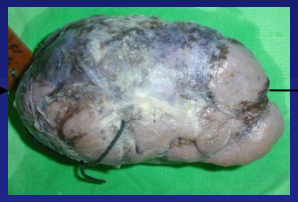
  - Puntura lombare
  - Endoscopia (stomaco, intestino)
  - Diagnostica molecolare

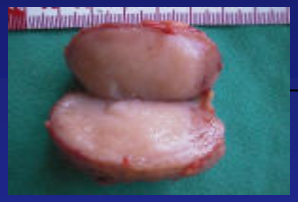
Ottimizzare:

- diagnosi
- prognosi
- terapia



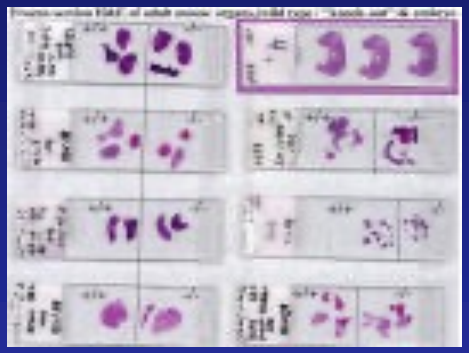
Biopsy



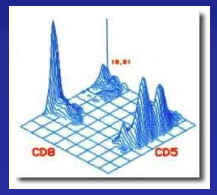


Lymph node

Laboratory



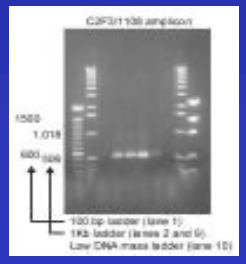
Histology



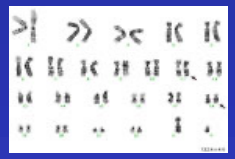
Flow Cytometry

fresco

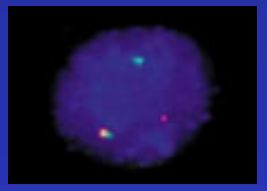
inclusione



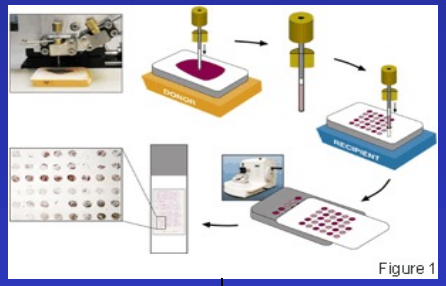
Molecular diagnosis

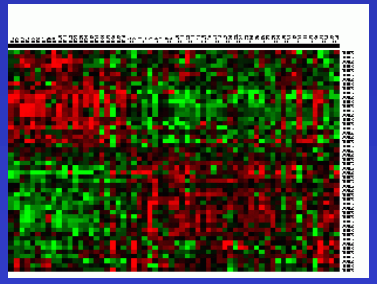


Citogenetics



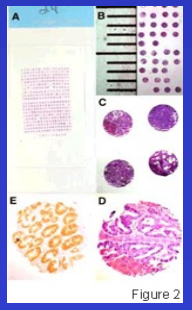
FISH





Gene profiling

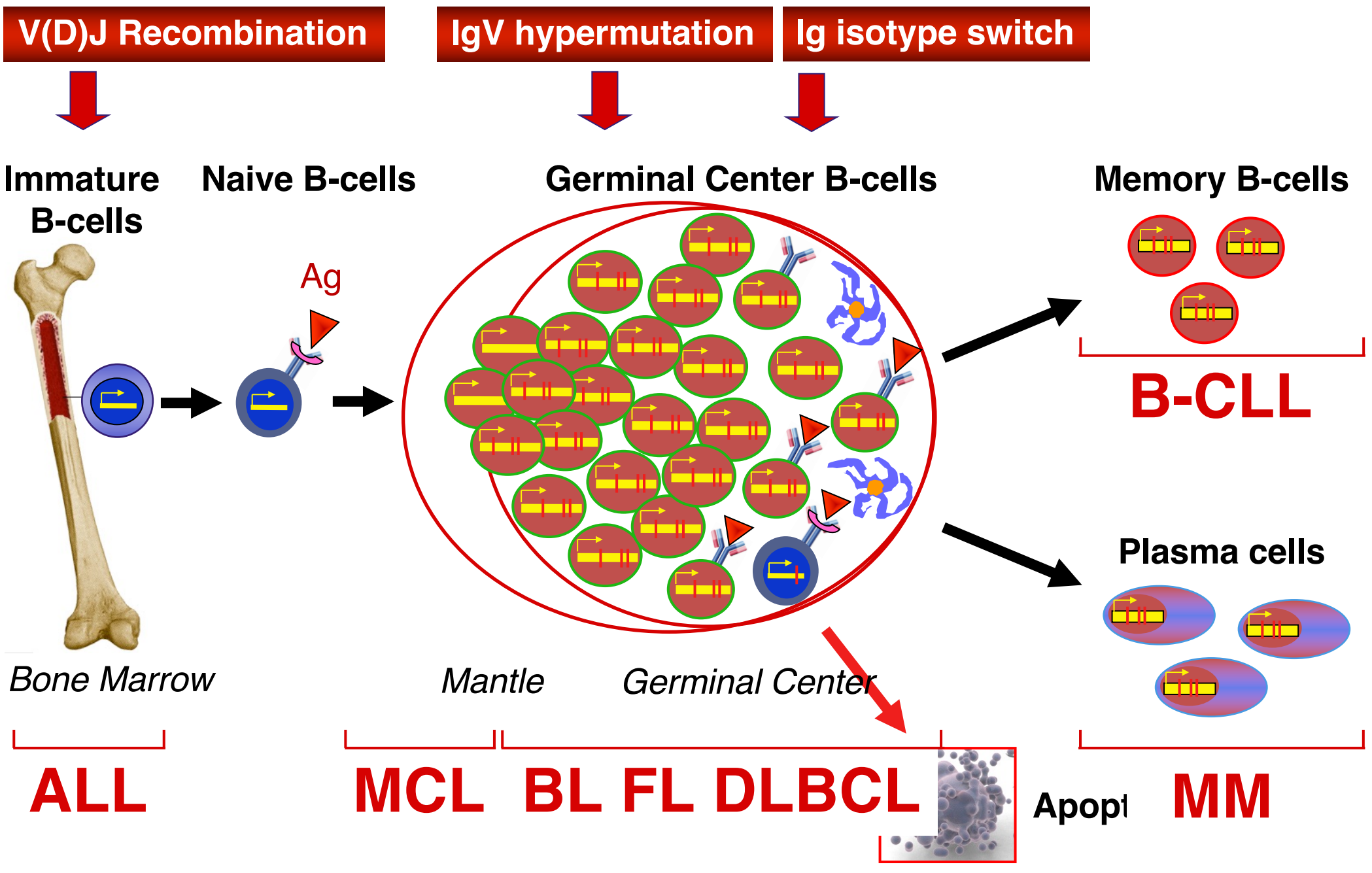
Antibodies

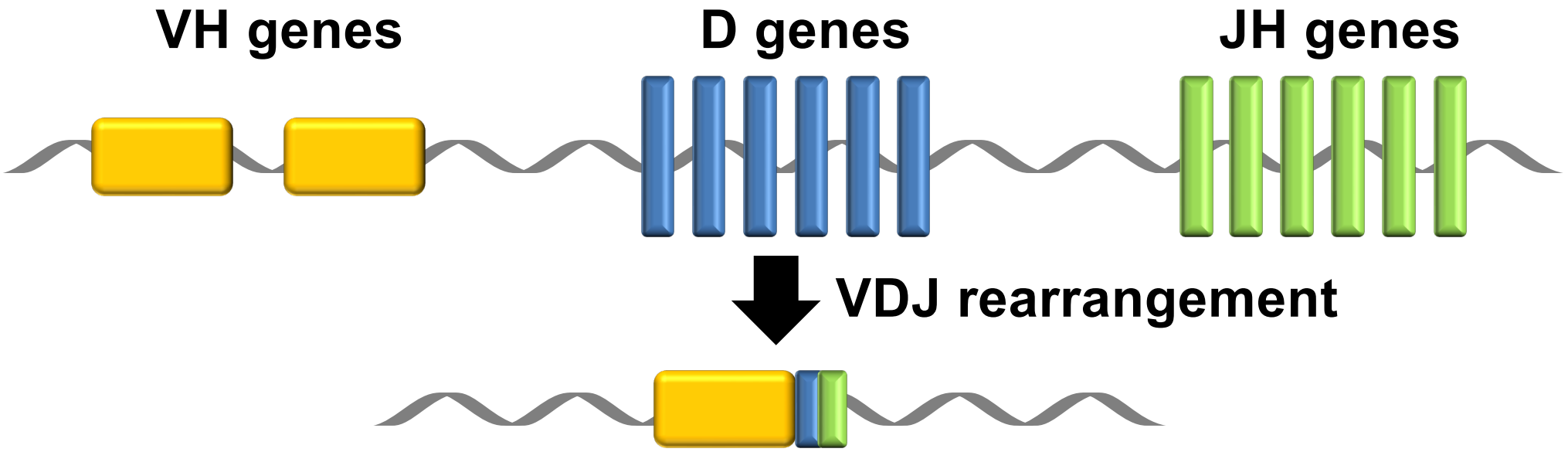


Tissue microarray

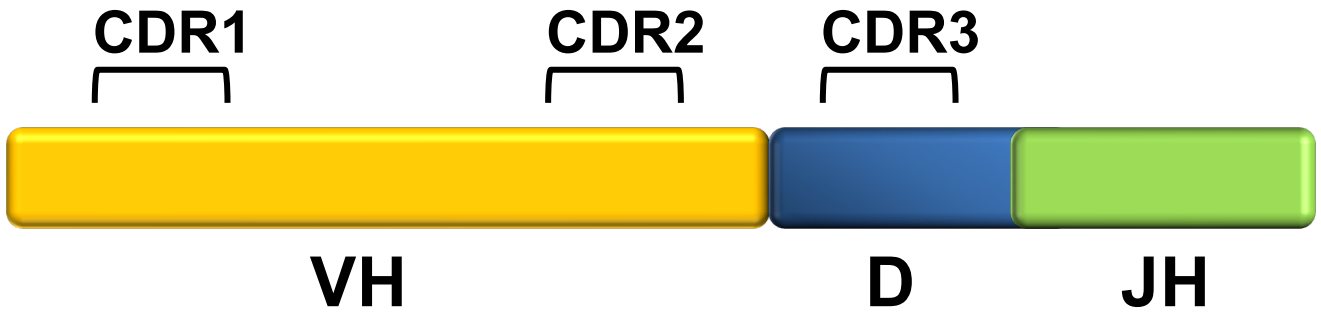
Proteomics

Germinal Centers and Lymphomagenesis





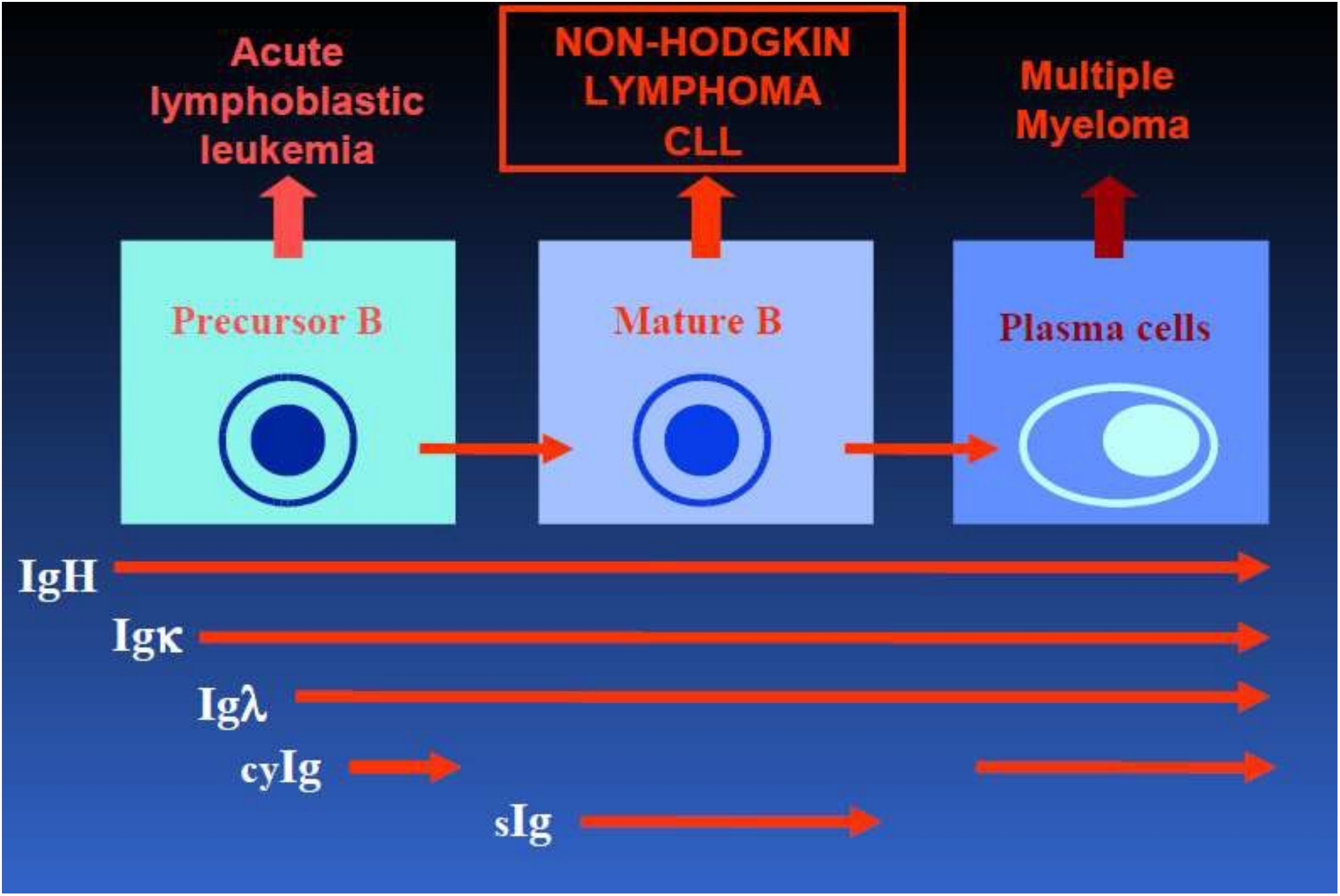
IGH 51 V genes x 27 D genes x 6 J genes = 8262 possible combinations
+
IG light chain VJ rearrangements
=
~4.7 x 10^{6} possible combinations



Nucleotide addition and/or deletion + somatic hypermutation =
> 10^{12} possible combinations

Sindromi linfoproliferative croniche

	Clinica	Morfologia	Fenotipo	Cariotipo
LLC	↑ ly- lfn- M-F	linfociti maturi	CD5+ CD23+ Sig -/+ FMC7-	13q14, 11q- +12, 17p13
aLLC	↑ ly- lfn- M-F	PLL 10-50%	CD5+ CD23+ Sig -/+ FMC7-	
PLL	↑↑ ly-M	PLL > 50%	Sig+ FMC7+ CD5-/+ CD22+	
HCL	Citopenia, ↑ M	tricoleucociti	CD103+ FMC7+ CD22+	
HCL-v	↑ ly-lfn-M	tricoleucociti at.	CD103+ FMC7+ CD22+	
SLVL	↑ ly-M	linfociti villosi	CD22+	
Marginale	LNH	Cc.	CD5- CD10-	+3, +18, 1
Immunoc.	CM,↑ M	Ly + ly plc + plc	CD5- CD23-	t(9;14)
Follicolare	LNH	CB-cc	CD10+/- Sig+ bcl-2+	t(14;18)
Mantellare	LNH	Cc	CD5+ CD23- Sig + FMC7+	t(11;14)
LGL-L	↑ ly, ↓ N	ly granulare	CD3+ CD8+ CD16+	
MF/SS	Cute, ↑ ly	nucleo cerebrif.	CD 4 +	


Acute lymphoblastic leukemia
NON-HODGKIN LYMPHOMA CLL
Multiple Myeloma
Precursor B
Mature B
Plasma cells
IgH
Igκ
Igλ
cyIg
sIg

Sindromi linfoproliferative croniche

Caratteristiche comuni

Espansione della malattia più per accumulo che per attiva replicazione

Cellule arrestate in fase G0 del ciclo cellulare per meccanismo di inibizione dell'apoptosi

Decorso spesso indolente

Difficile eradicazione

Possibilità di trasformazione verso una forma più aggressiva

LEUCEMIA LINFATICA CRONICA

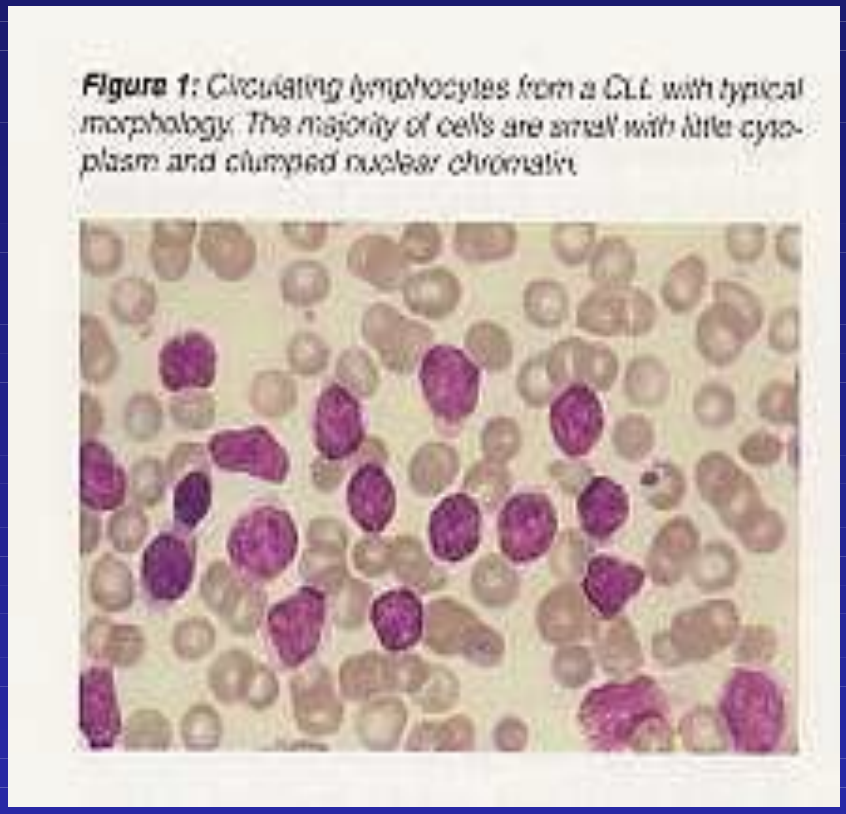
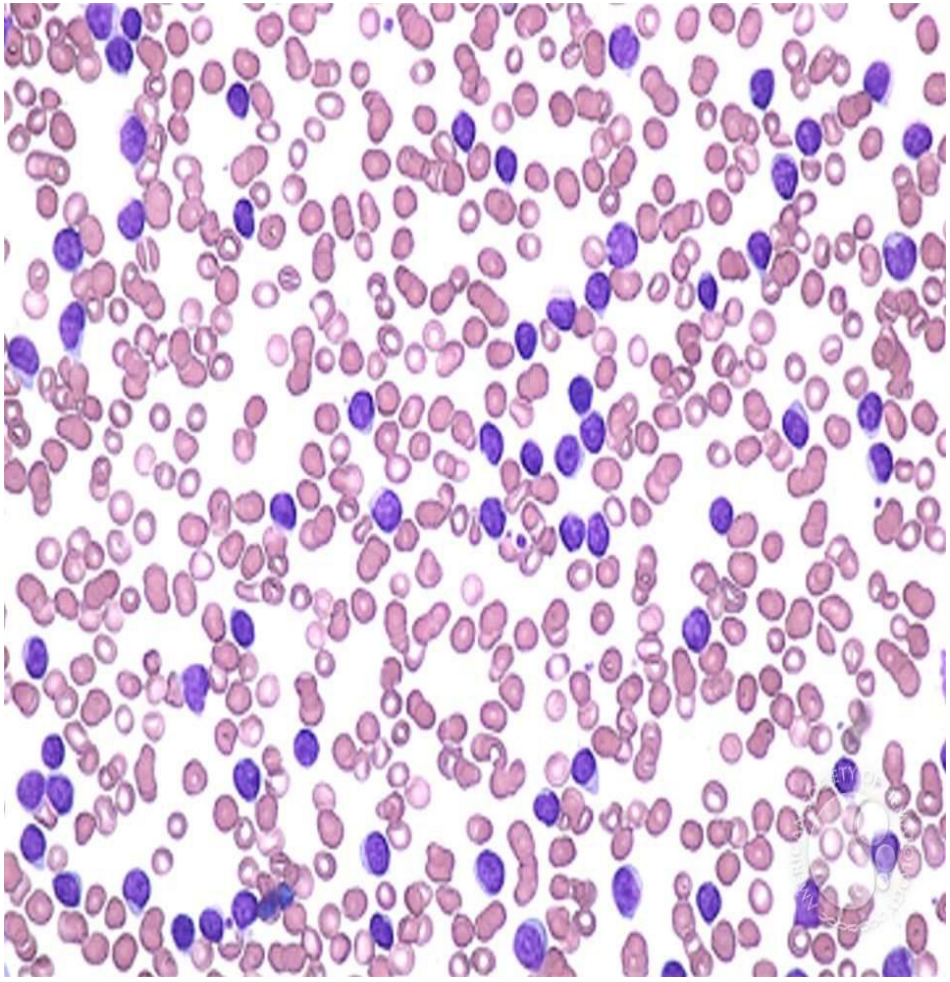


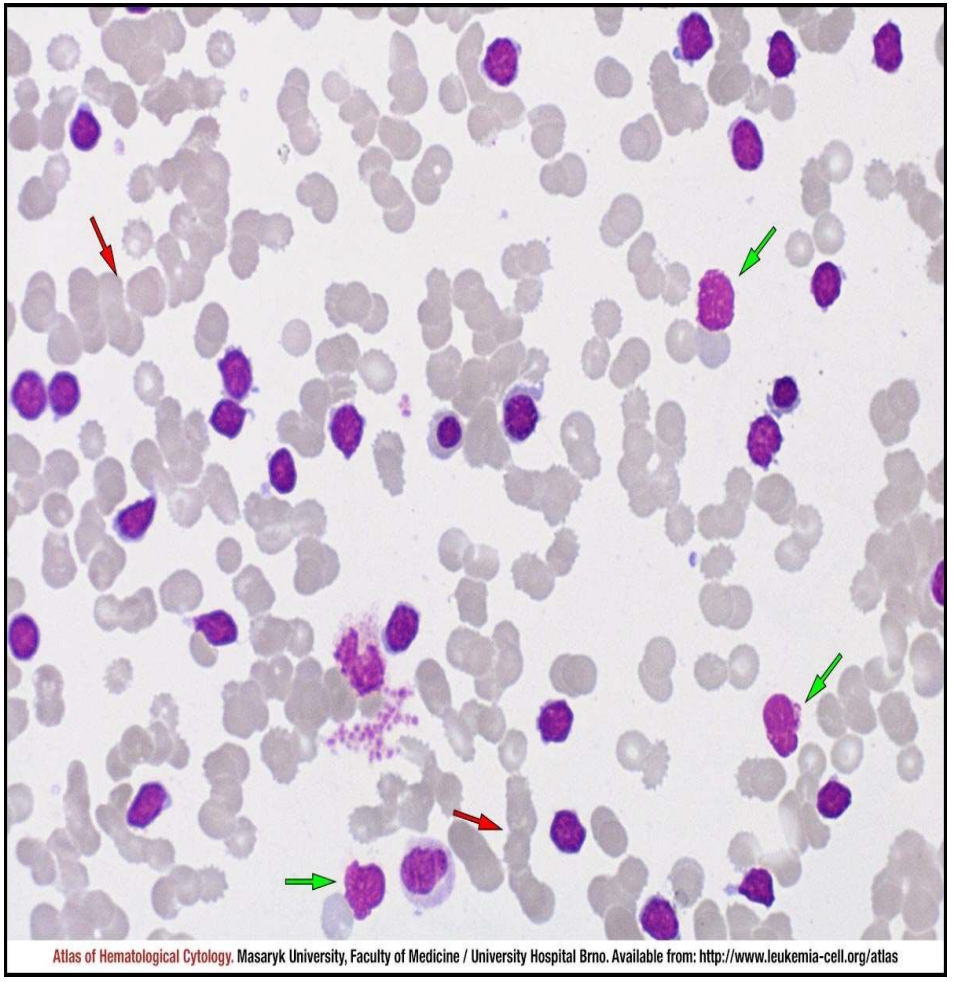
Figure 1: *Circulating lymphocytes from a CLL with typical morphology. The majority of cells are small with little cytoplasm and clumped nuclear chromatin.*

Definizione

La LLC è una neoplasia ematologica caratterizzata dalla proliferazione ed accumulo nel sangue, midollo e tessuti linfatici, di piccoli linfociti apparentemente maturi di origine B-linfocitaria.

CLL: blood smear





In blood smear an high percentage of **small**, mature **lymphocytes can be detected,** as well as, **Gumprecht** shadows

CLL EPIDEMIOLOGY

At diagnosis

Median Age 72 years

Incidence 4/100.000/year

M:F = 2:1

White:Black:Asian = 4.5:3.3:0.9

CLL – ETIOLOGY

The cause of CLL is unknown

There is increased incidence in farmers, rubber manufacturing workers, asbestos workers, and tire repair workers

Genetic factors have been postulated to play a role in high incidence of CLL in some families

Cytogenetics

- clonal chromosomal abnormalities are detected in approximately 50% of CLL patients
- the most common clonal abnormalities are:
  - trisomy 12

    structural abnormalities of chromosomes 13, 14 and 11

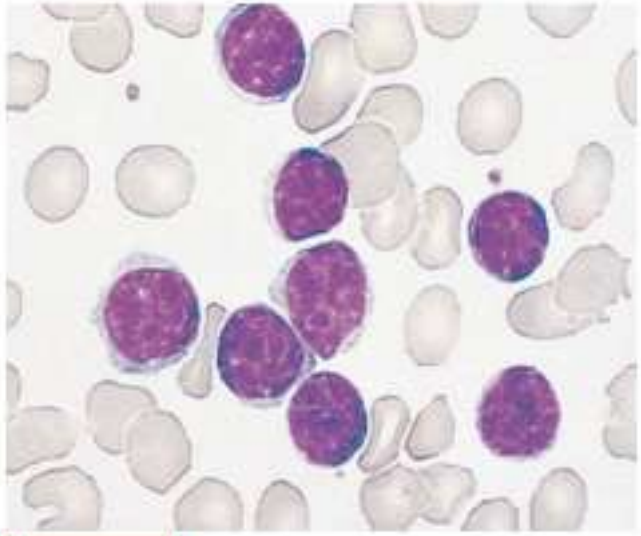
  patients with abnormal karyotypes have a worse prognosis

Oncogenes

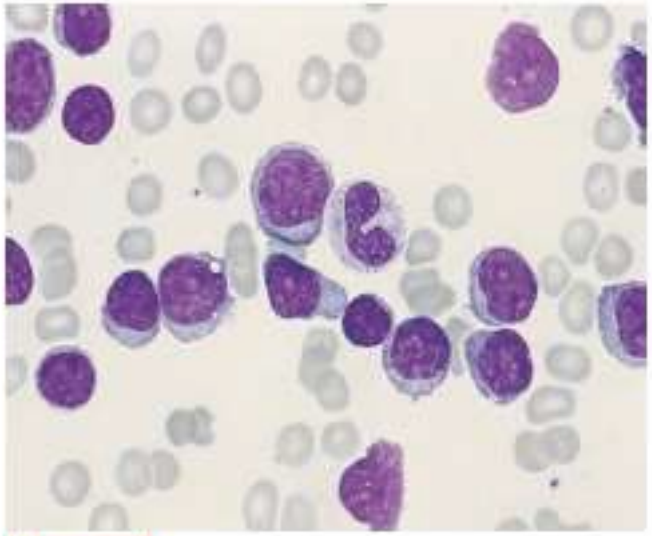
- in most cases of CLL is overexpressed the proto-oncogene c-fgr 9a member of the src gene family of tyrosine kinases

CRITERI DIAGNOSTICI PER LA DIAGNOSI DI B-LLC

- Linfociti B clonali > 5.000/mcL (se <5000/mcL in assenza di adenopatie o organomegalie: MBL)
- Presenza variabile di prolinfociti e/o di linfociti polimorfi fino al 55% e delle cosiddette "ombre di Gumprecht"
- Immunofenotipo caratteristico (CD5+/CD19+, CD23+, SmIg clonali a bassa intensità)



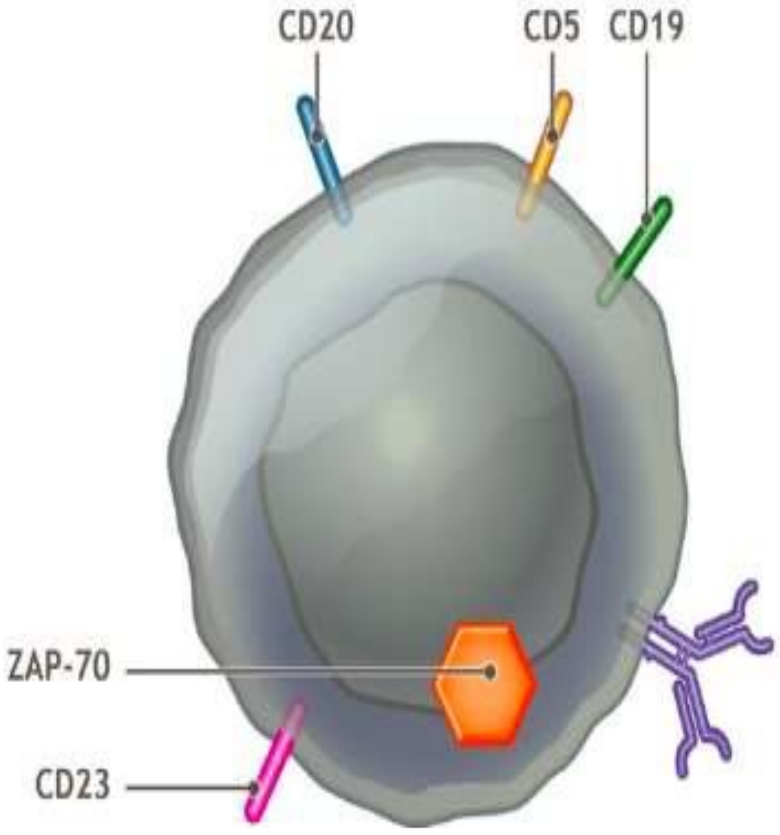
Classica



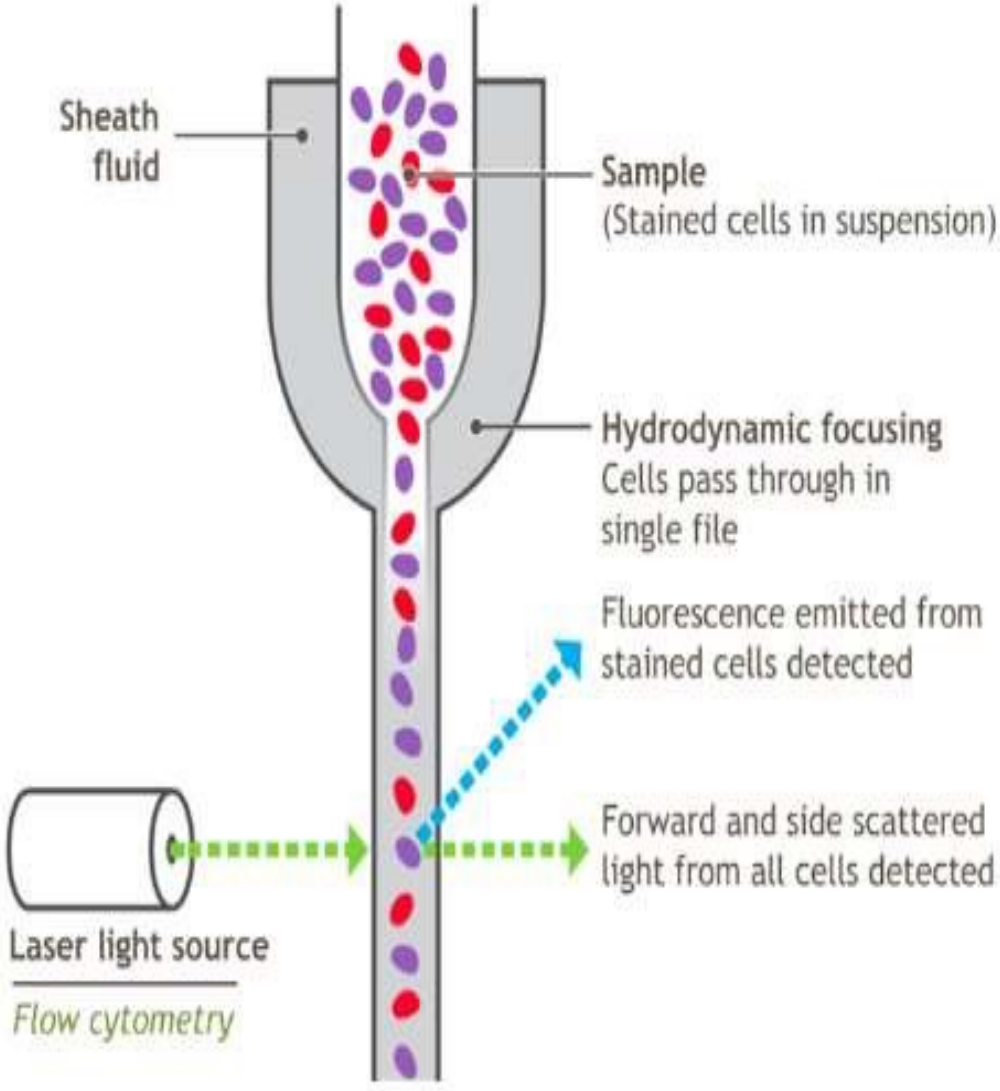
Mista

Immunophenotyping and flow-cytometry

CLL cells express the surface T-cell antigen **CD5** as well as othe B-cell antigens, including **CD19**, **CD20**, **CD23**, **ZAP70**.
Immunophenotyping allows the identification of the antigens expressed by cells

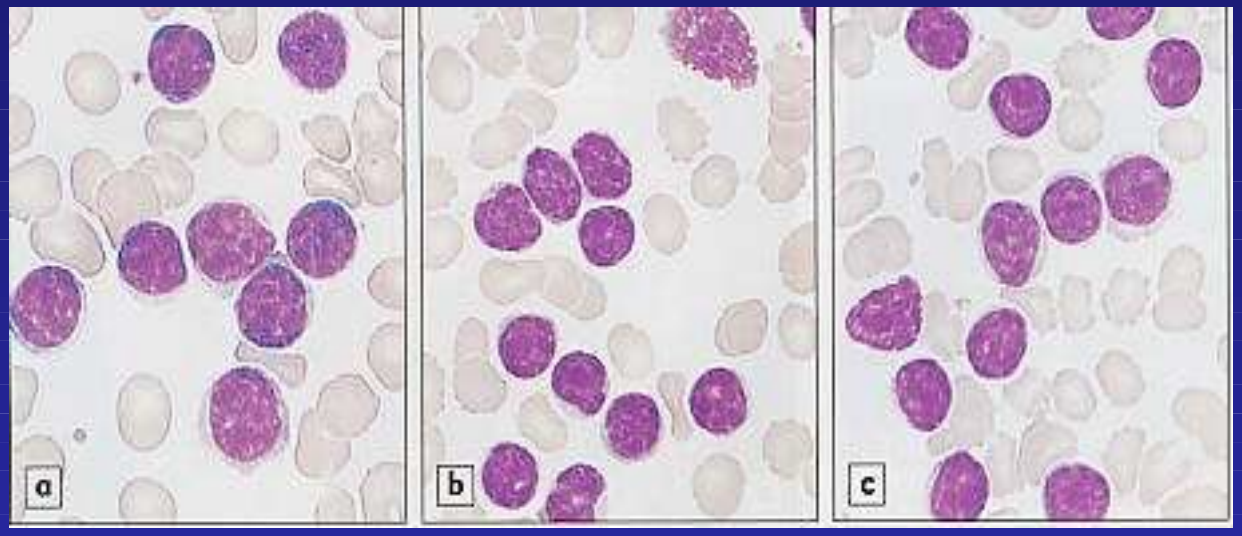


Flow-cytometry allows confirmation of the **clonality** of the B cells in peripheral blood and represent the most useful test for a definitive diagnosis of CLL

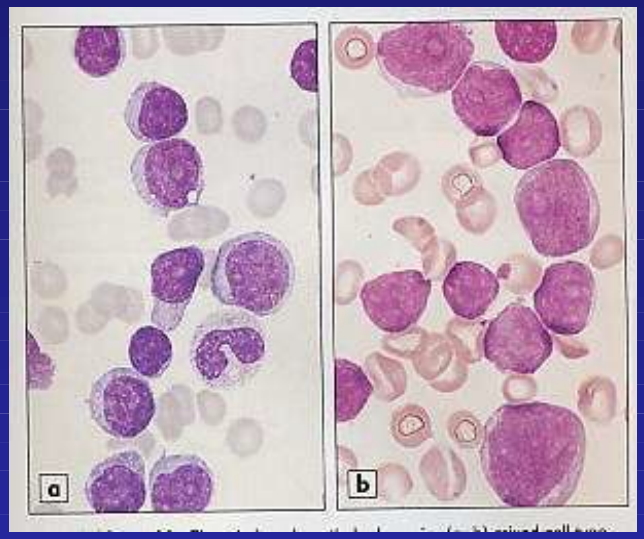


LEUCEMIA LINFATICA CRONICA

Laboratorio:sangue periferico



Morfologia tipica



Morf. atipica (PLL 10-50%)

	SIg	CD 5	CD 23	FMC7	CD 22	CD 79b
LLC	weak	+CD19 ++	++	-/+	weak/-	weak/-
aLLC	weak	++	++	-/+	weak/-	weak/-

CLL – LAB FINDINGS

a) Blood test lymphocytosis ≥ 5G/l (4 weeks)

b) Morphology monoconal population of small mature lymphocyte

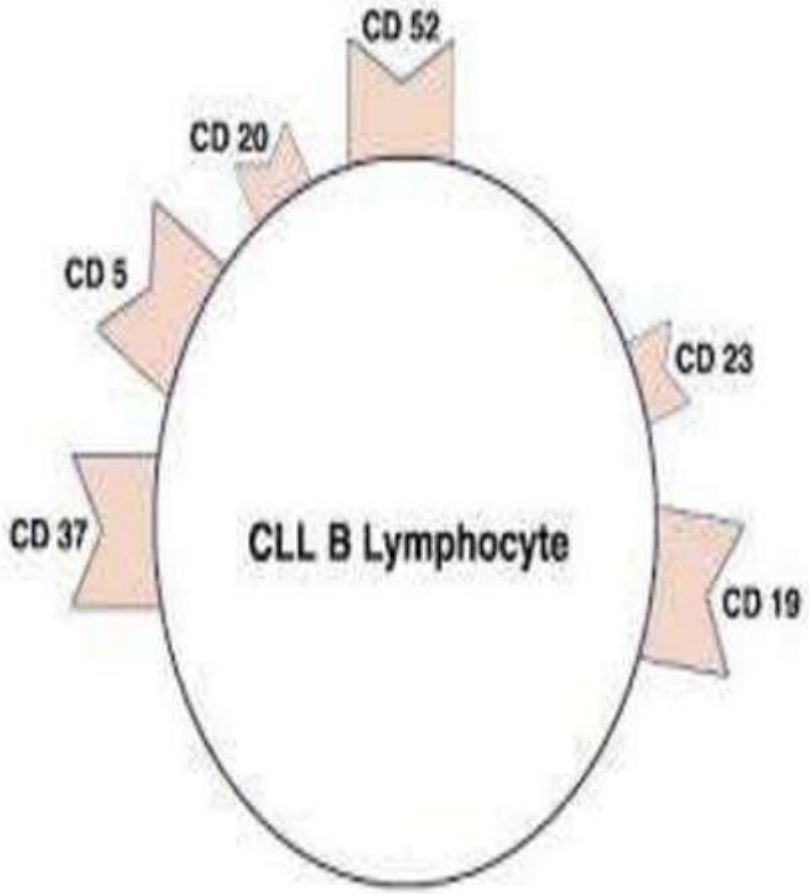
c) B-cell CLL phenotype clonal CD5+/CD19+ population

of lymphocyte

d) Markers of clonality κ/λ light chain restriction; cytogenetical abnormalities

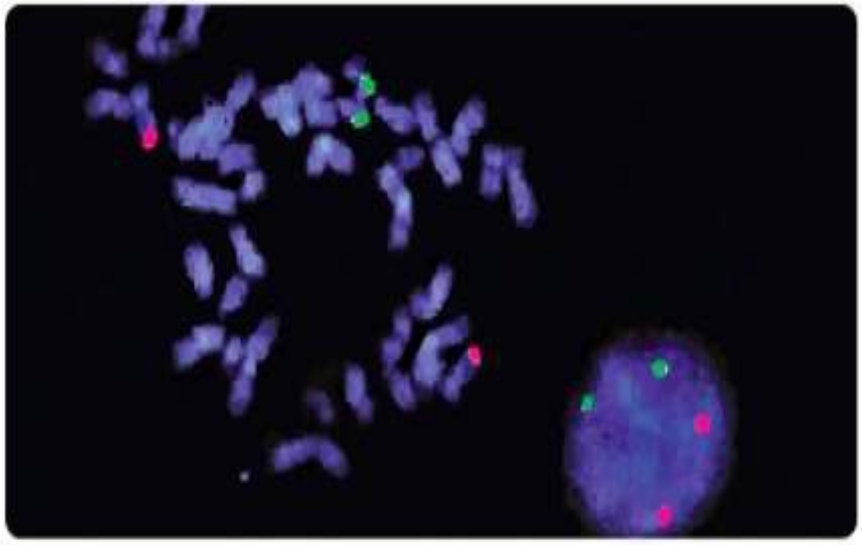
e) Bone marrow infiltrate > 30% of nuceated cells on aspirate

f) Lymph node diffuse infiltrate of small lymphocye

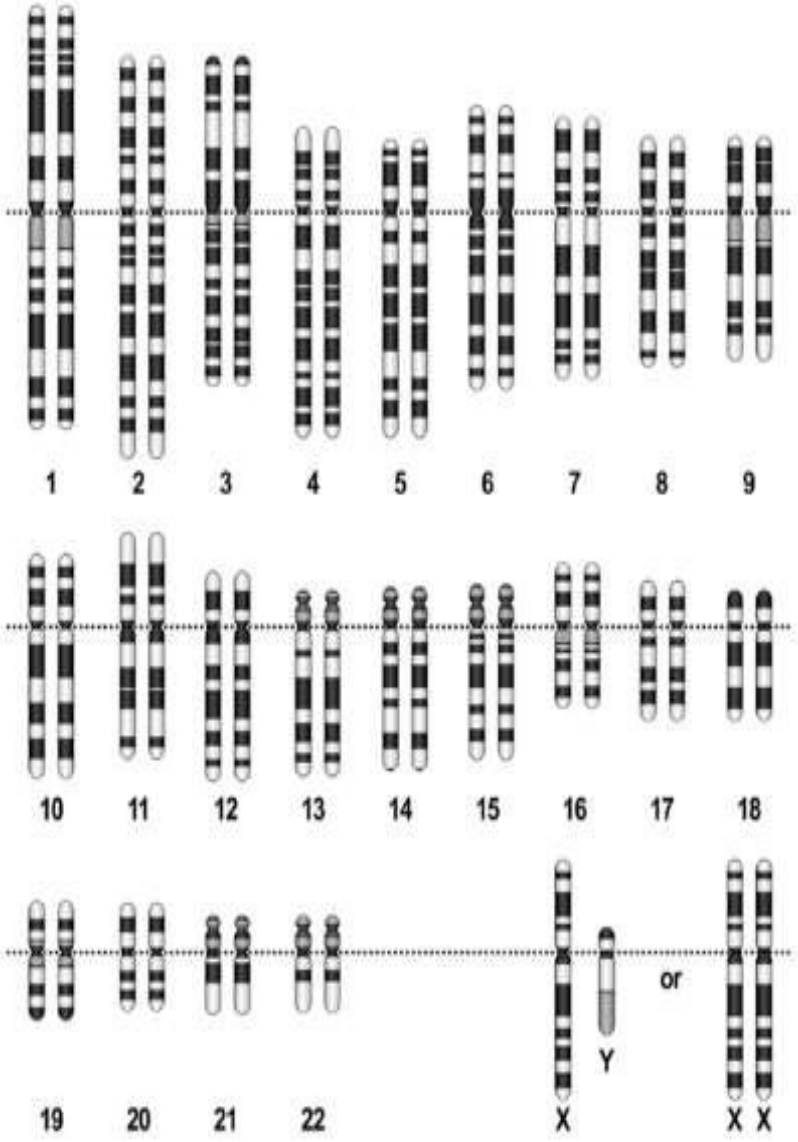


Fluorescence in situ Hybridization

FISH is a **cytogenetic technique** that uses microscopy and relies on fluorescent probes to detect the presence of specific DNA sequences on chromosome.
It does **not require** the cells to be **dividing**. This allows a more sensitive technice than chromosomal banding. **Chromosomal translocation** and **deletions** can be therefore easily identified and monitored during the course of a disease



FISH



Chromosomal banding

Incidence of cytogenetical abnormalities

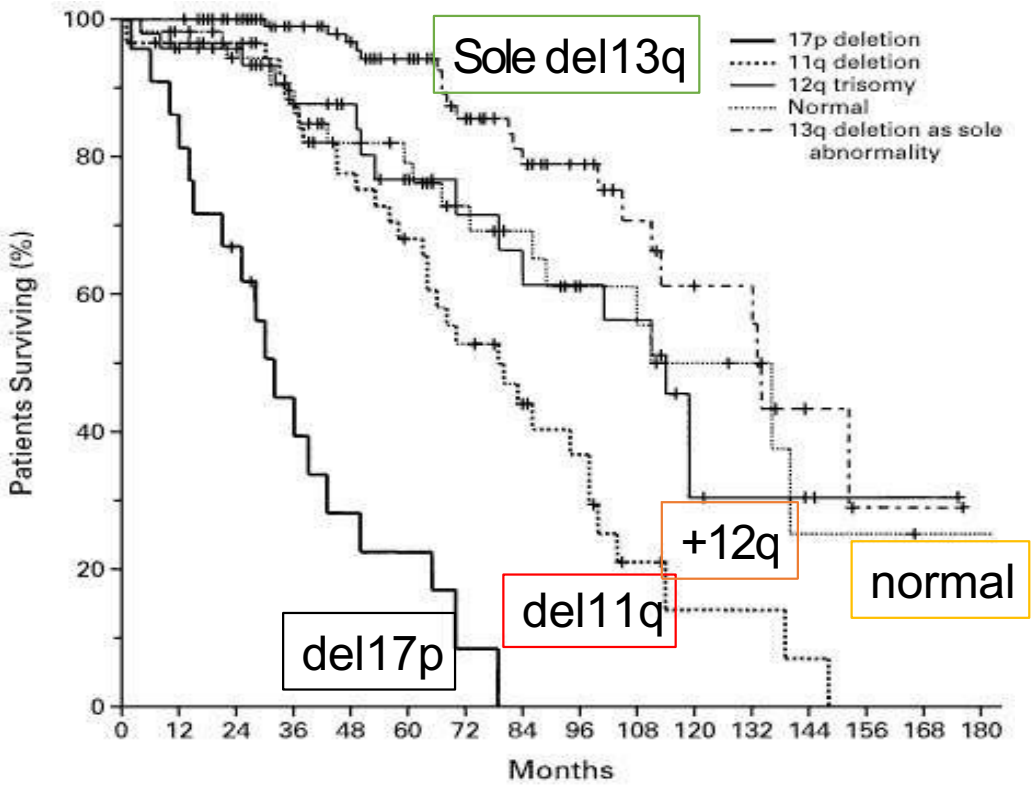
TABLE 1. INCIDENCE OF CHROMOSOMAL ABNORMALITIES IN 325 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

ABERRATION	NO. OF PATIENTS (%)*
13q deletion	178 (55)
11q deletion	58 (18)
12q trisomy	53 (16)
17p deletion	23 (7)
6q deletion	21 (6)
8q trisomy	16 (5)
t(14q32)	12 (4)
3q trisomy	9 (3)
Clonal abnormalities	268 (82)
Normal karyotype	57 (18)

*One hundred seventy-five patients had one aberration, 67 had two aberrations, and 26 had more than two aberrations.

82% Clonal chromosomal abnormalities

35% >1 clonal alteration

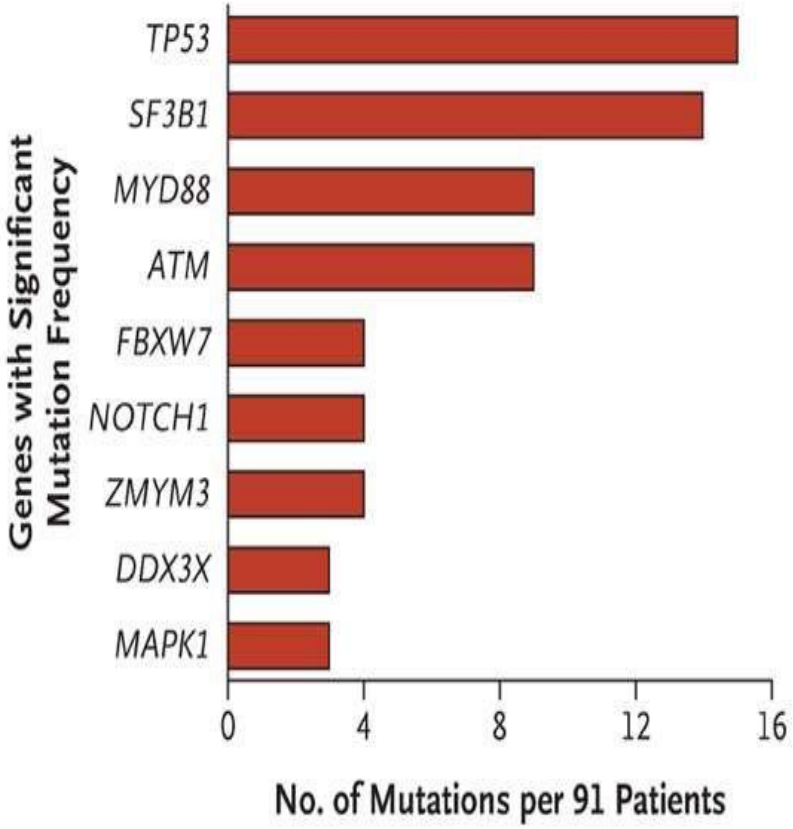


NO. AT RISK

17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

Dohner H et al. ***N Engl J Med 2000***; 343:1910-1916

Molecular landscape in CLL



	No. of Mutations (%)	No. of Base Pairs	P Value	Q Value
TP53	15 (15)	119,041	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
SF3B1	14 (15)	359,856	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
MYD88	9 (10)	73,805	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
ATM	9 (9)	837,986	2.4×10^{-9}	1.1×10^{-5}
FBXW7	4 (4)	225,671	2.0×10^{-6}	7.4×10^{-3}
NOTCH1	4 (4)	306,968	3.3×10^{-6}	1.0×10^{-2}
ZMYM3	4 (4)	314,226	3.5×10^{-5}	7.4×10^{-2}
DDX3X	3 (3)	181,343	1.6×10^{-5}	4.3×10^{-2}
MAPK1	3 (3)	89,405	1.9×10^{-5}	4.4×10^{-2}

Wang L et al. ***N Engl J Med 2011***;365:2497-2506

The NEW ENGLAND JOURNAL of MEDICINE

LEUCEMIA LINFATICA CRONICA

Aspetti clinici

- Linfocitosi in presenza o meno di linfoadenomegalie, epato-splenomegalia; sviluppo di anemia, piastrinopenia, ipogamma-globulinemia
- Diagnosi spesso occasionale
- Decorso spesso indolente ma progressivo
- Morbidità legata allo sviluppo di insufficienza midollare ed immunodeficit
- Principale causa di mortalità: infezioni

LEUCEMIA LINFATICA CRONICA

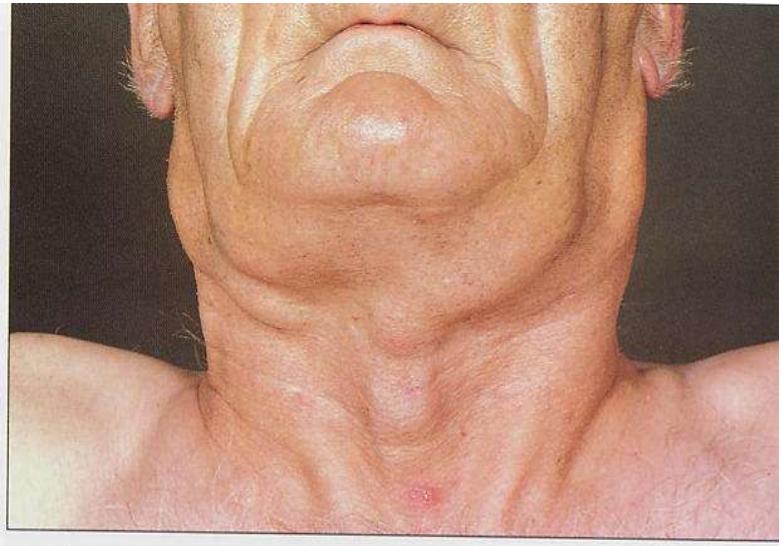
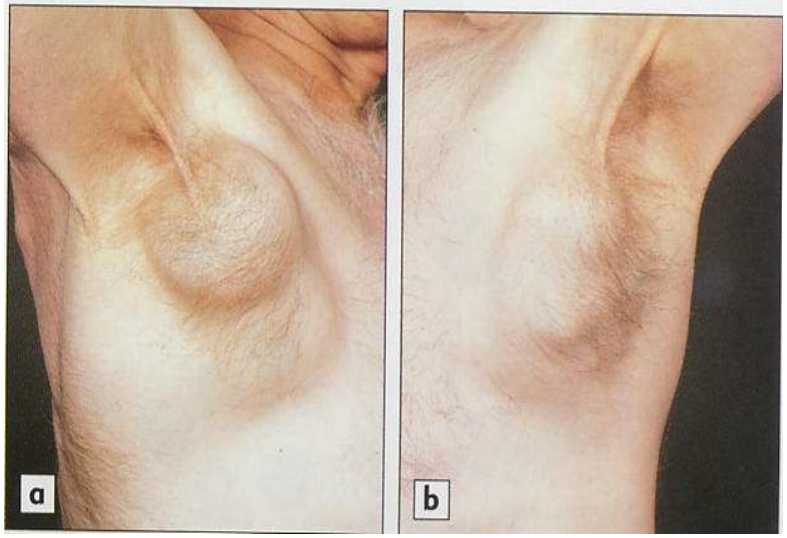
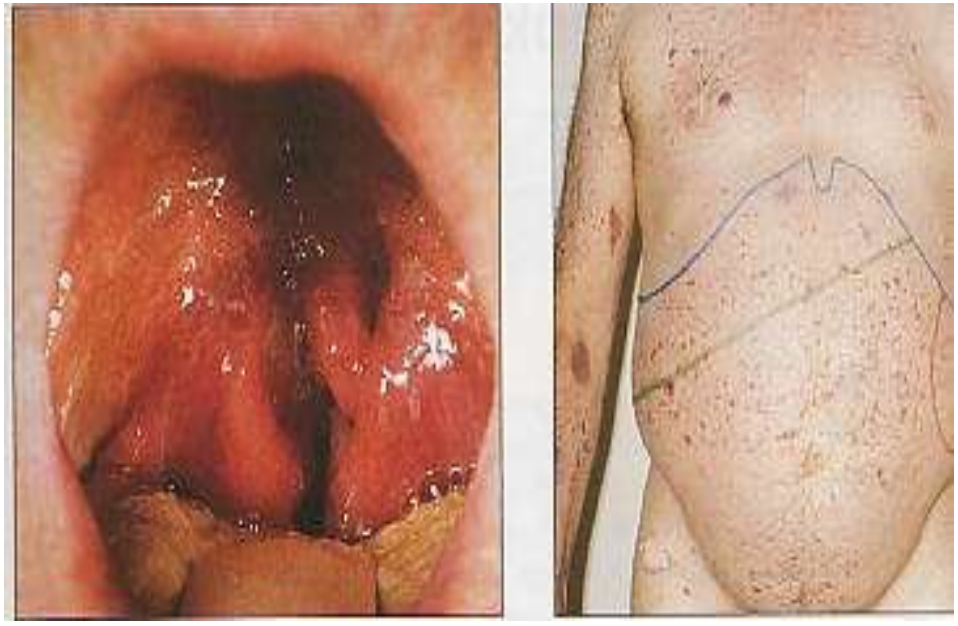
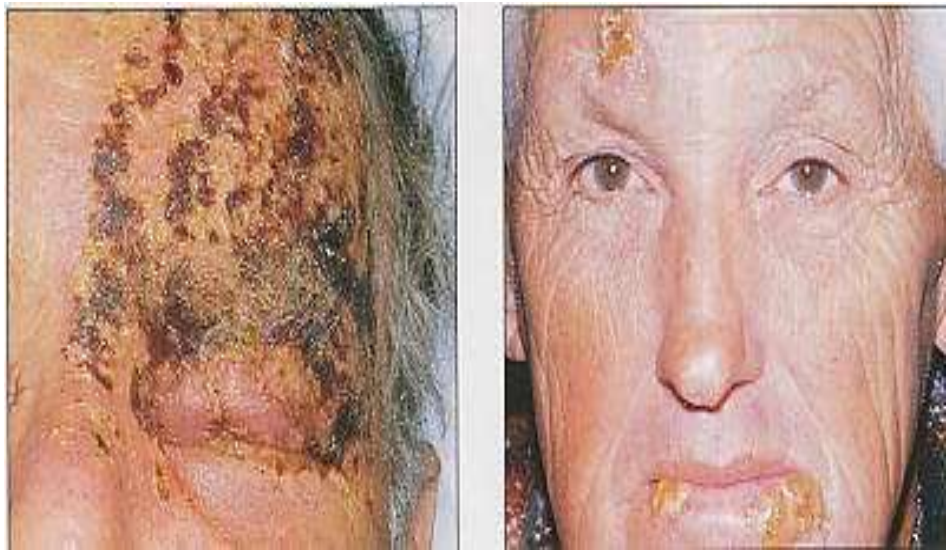


Fig. 10.2 Chronic lymphocytic leukaemia: bilateral cervical lymphadenopathy in a 65-year-old man. [Hb, 12.5 g/dl; WBC, 150 × 10^9/l (lymphocytes, 140 × 10^9/l); platelets, 120 × 10^9/l.]







CLL - COMPLICATIONS

Severe systemic infections

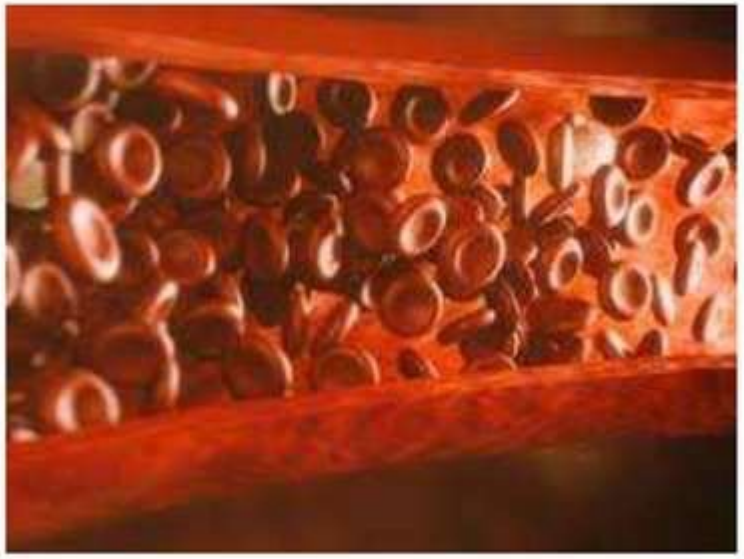
Bleeding

Richter's transformation

Prolymphocytoid transformation

Secondary malignancies

Acute myeloid leukemia



CLL

- Richter's synd. (5 %) :-
  - DLBCL (3 %), HD (O.5 %),
  - Occur in both Mut. & Unmut. variant,
  - a/w del 11q, overexpression of C-MYC gene, p53 mut,
  - Median survival 5 - 8 months,
  - MC seen in pts t/t with Purine Nucleotide Analogue

LEUCEMIA LINFATICA CRONICA

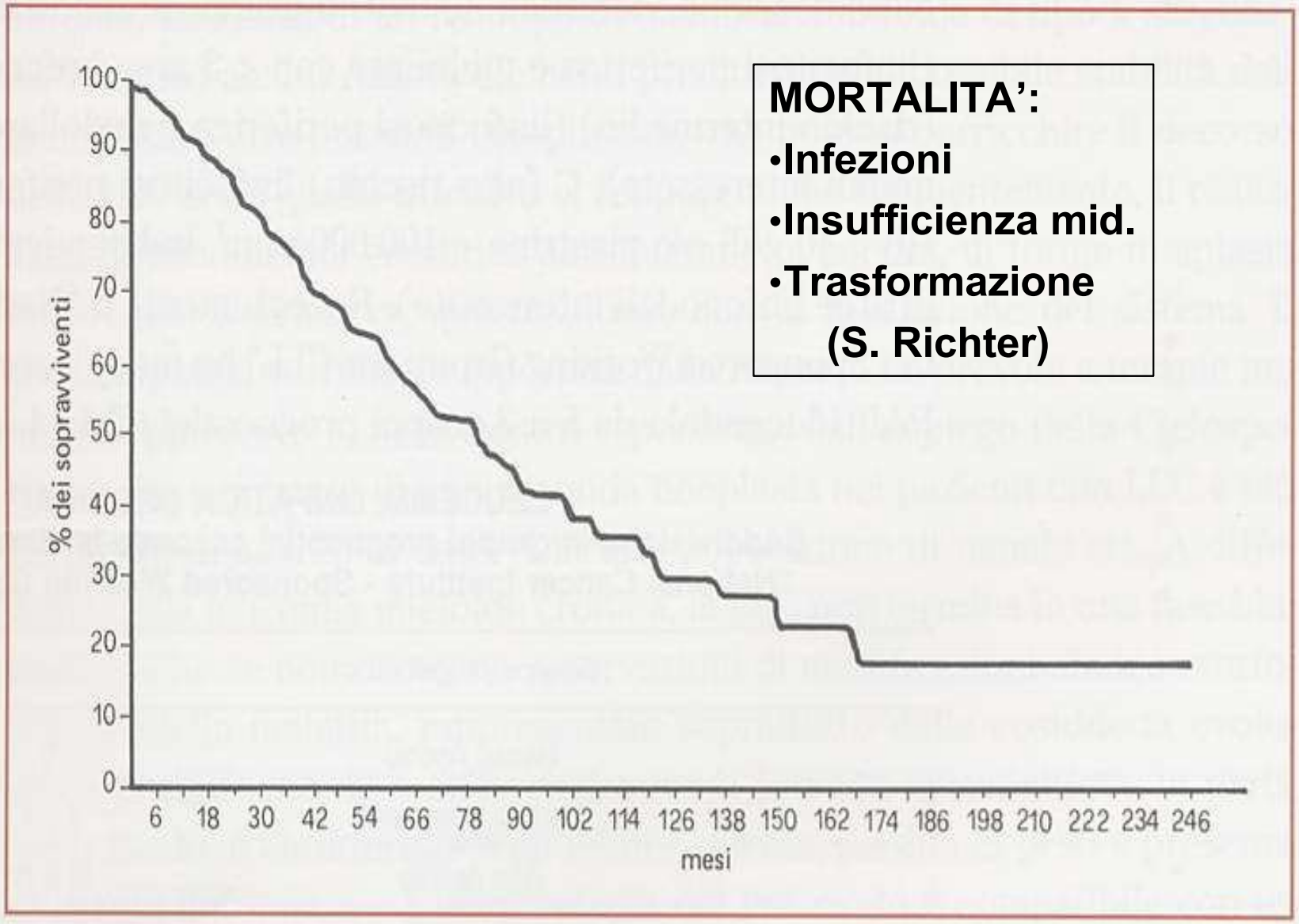


Figura 4.12 - Curva di sopravvivenza globale dei 180 pazienti con leucemia linfatica cronica.

Rai Clinical Stage (original)

Adapted from Rai et al, 1975

Stage	Clinical features
0	Lymphocytes >15 x 10s/L
I	As 0 + lymphadenopathy
II	As 0 + hepato- or splenomegaly
III	As 0 + anemia (Hb < 11 g/dL)
IV	As 0 + thrombocytopenia (platelets < 100 x10s/L)

Modified Rai Clinical Stage

Adapted from Rai et al, 1987

Risk category	Clinical features	Median Survival (y)
Low	Lymphocytes > 15 x 10s/L	>10
Inter mediate	As 0 + lymphadenopathy or hepato- or splenomegaly	7
High	Anemia (Hb ≤ 11 g/dL) or thrombocyto penia (platelets ≤ 100 x10s/L)	1.5-4

Binet Clinical Stage

* The four lymphadenopathy areas are: cervical, axillary, inguinal, spleen/liver

Adapted from Binet et al, 1981

Stage	Clinical features	Median Survival (y)
A	Lymphocytosis, does not meet criteria for stages B or C	12
B	≥ 3 areas of lymphadenopathy*, does not meet criteria for stage C	7
C	Anemia (Hb < 10 g/dL) or thrombocytopenia (platelets < 100 x10s/L)	2-4

LEUCEMIA LINFATICA CRONICA

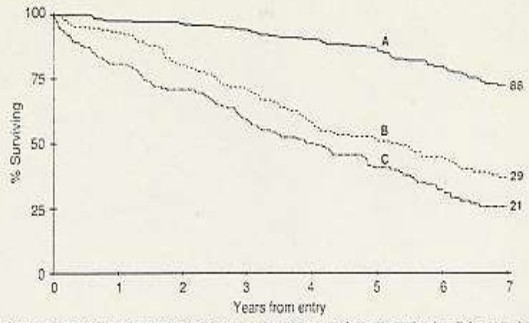


Fig 2. Outcome by International stage. Only CLL related deaths (censored at non-CLL death) were considered in all the survival curves (Figs 2–7). Numbers shown indicate number of patients alive at 7 years from entry.

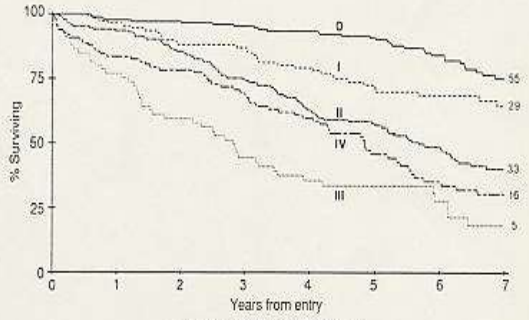


Fig 3. Outcome by Rai staging system.

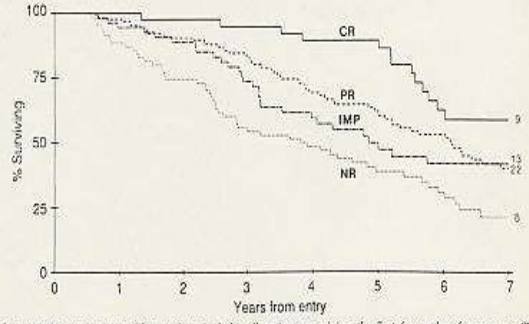


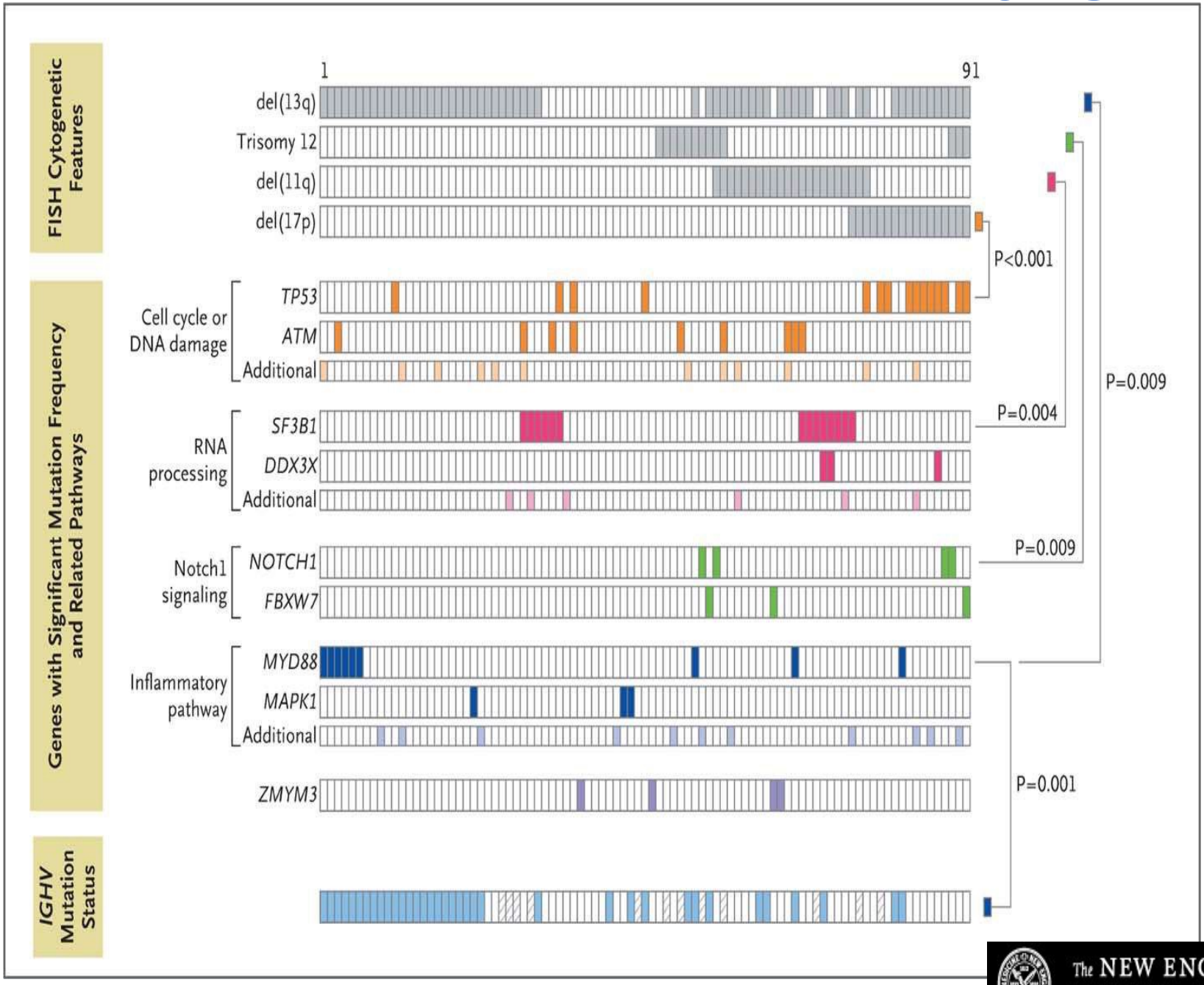
Fig 4. Outcome by response to treatment. This analysis includes all patients surviving the first 6 months of treatment. CR = complete and PR = partial response; IMP = improvement; NR = no response.

POOR PROGNOSTIC FACTORS IN CLL

Advance stage at diagnosis
Male sex
Diffuse pattern of bone marrow infiltration
Short lymphocyte doubling time
High expression of Ki67, p27, NOTCH1mut, SF3B1mut, BIRC3mut
High serum levels of B2-microglobulin, Thymidine kinase, soluble CD23, TNFa
Poor-risk cytogenetics: 17p, 11q deletions, and complex cytogenetic abnormalities
TP53 mutations
IgHV unmutated mutational status
High level of CD38
High level of zap70 expression
High expression of lipoprotein lipase
Altered microRNA
Poor response to therapy or short duration of response

Gribben. Blood, 2010

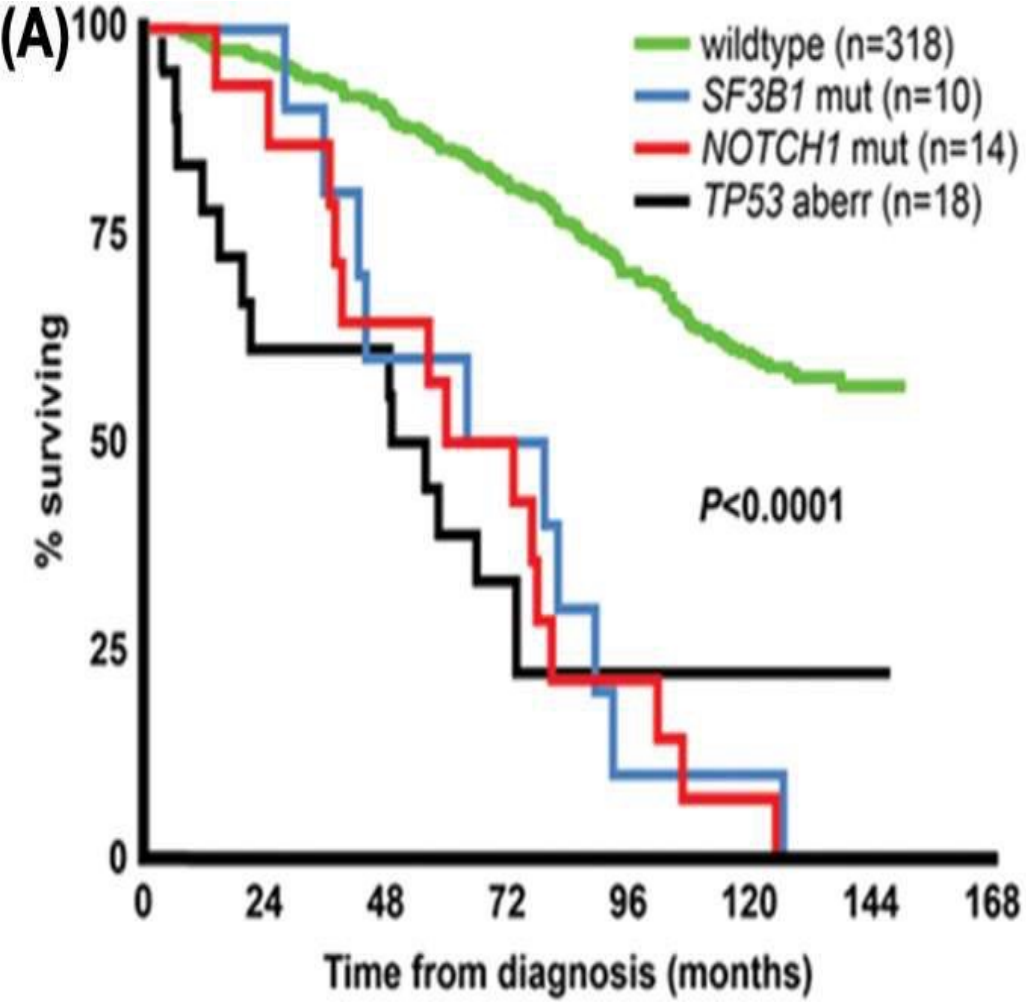
Association between molecular data and cytogenetics

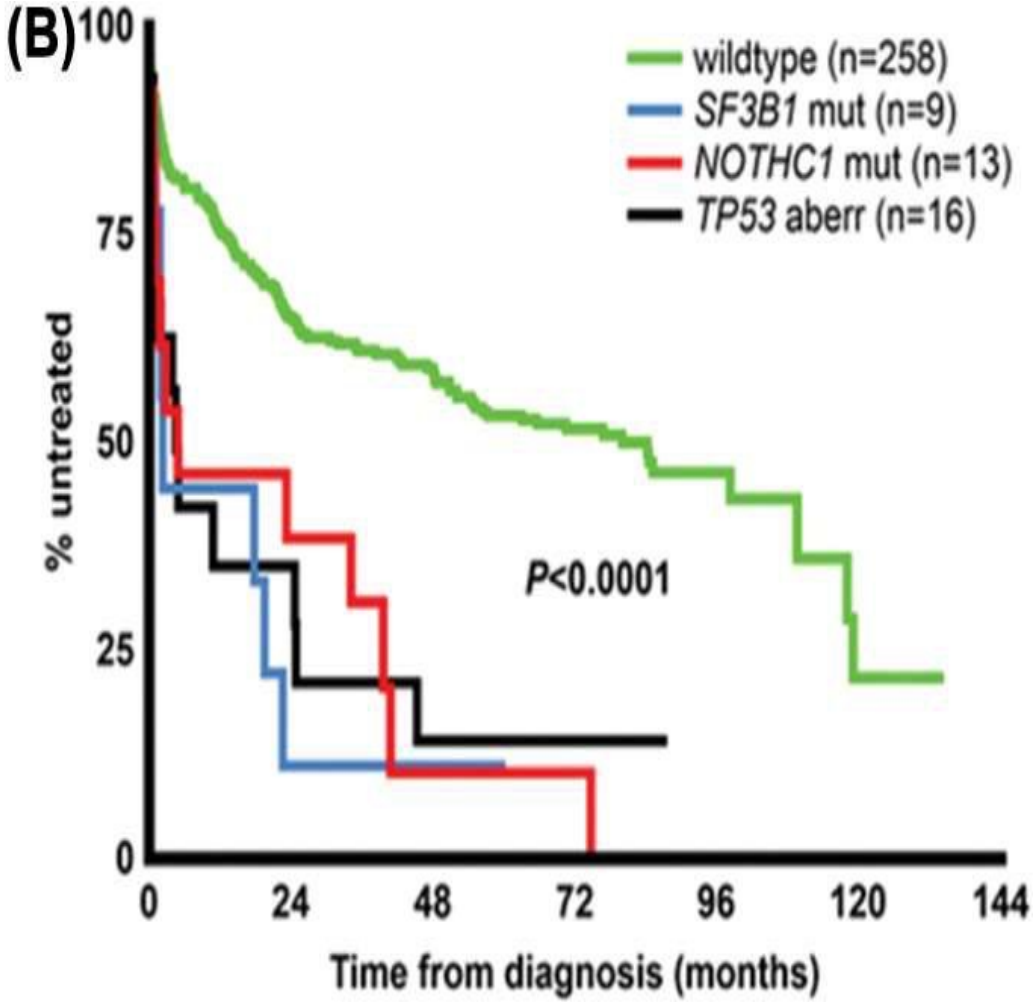


Wang L et al. ***N Engl J Med 2011***;365:2497-2506

The NEW ENGLAND JOURNAL of MEDICINE

Prognostic significance of molecular data





Pre-novel agents era

Rosenqvist R et al. ***Leuk Lymphoma2013*** Nov;54(11):2351-64.

CLL IPI

	Adverse factor	Assigned risk
TP53 status	Deleted or mutated	4
IGHV mutational status	Unmutated	2
B2microglobulin concentration	>3.5 mg/L	2
Clinical stage	Rai I-IV or Binet B-C	1
Age	>65 aa	1

The International CLL-IPI working group. *Lancet Oncol*, 2016; 17:779-90.

CLL IPI

CLL-IPI category	Score	OS at 5 years (%)	Potential clinical consequence
Low risk	0-1	93.2	Do not treat
Intermediate risk	2-3	79.3	Do not treat except if disease is really symptomatic
High risk	4-6	63.3	Traetment indicated except if the disease is asymptomatic
Very high risk	7-10	23.3	If you need to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials

The International CLL-IPI working group. *Lancet Oncol*, 2016; 17:779-90.

INICATIONS FOR TREATMENT

- IWCLL/NCI-WG Guidelines
- Monitoring for low risk
- Initiation of treatment for intermediate and high risk

Hallek M. et al. *Blood*, 2008. 111, 12

ACTIVE DISEASE*

- Evidence of bone marrow failure
- Massive (i.e., >6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., >10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with LDT of less than 6 months
- Autoimmune anemia/thrombocytopenia poorly responsive to corticosteroids or other standard therapy
- Disease related symptoms

* At least one of the following criteria should be met

Hallek M. et al. *Blood*, 2008. 111, 12

PRE-TREATMENT EVALUATION OF CLL PATIENTS

Table 1. Pretreatment evaluation of patients with CLL

Diagnostic test	Section of guidelines	General practice*	Clinical trial
Tests to establish the diagnosis	1		
Complete blood count and differential count	1.1	Always	Always
Immunophenotyping of lymphocytes	1.2	Always	Always
Assessment before treatment	3.5.1		
History and physical, performance status	3.5.1.1, 3.5.1.2	Always	Always
Complete blood count and differential	3.5.1.3	Always	Always
Marrow aspirate and biopsy	3.5.1.4	Desirable	Desirable
Serum chemistry, serum immunoglobulin, direct antiglobulin test	3.5.1.5, 3.5.1.6, 3.5.1.7	Always	Always
Chest radiograph	3.5.1.8	Always	Always
Infectious disease status	3.3	Always	Always
Additional tests before treatment	3.5.2		
Cytogenetics (FISH) for del(13q), del(11q), del(17p), trisomy 12, del(6q) in the peripheral blood lymphocytes	3.5.2.1	Desirable	Always
IgVH mutational status, ZAP-70, and CD38	1.2	NGI	Always
CT scan of chest, abdomen, and pelvis	3.5.2.2	NGI	Desirable
MRI, lymphangiogram, gallium scan, PET scans	3.5.2.3	NGI	NGI
Abdominal ultrasound*	3.5.2.4	Possible	NGI

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.

mutTP53

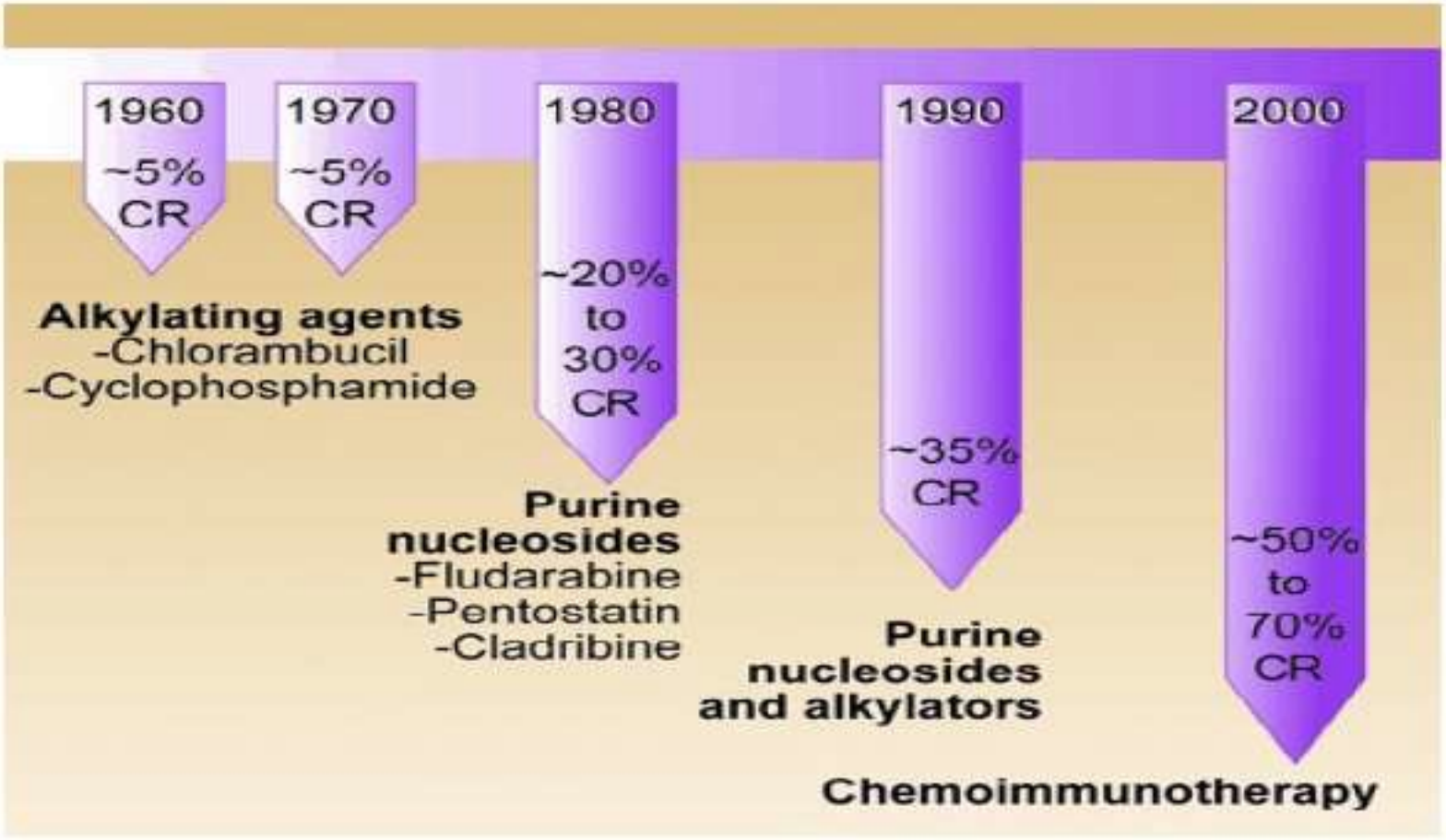
Hallek M. et al. *Blood*, 2008. 111, 12

CUMULATIVE ILLNESS RATING SCALE (CIRS)

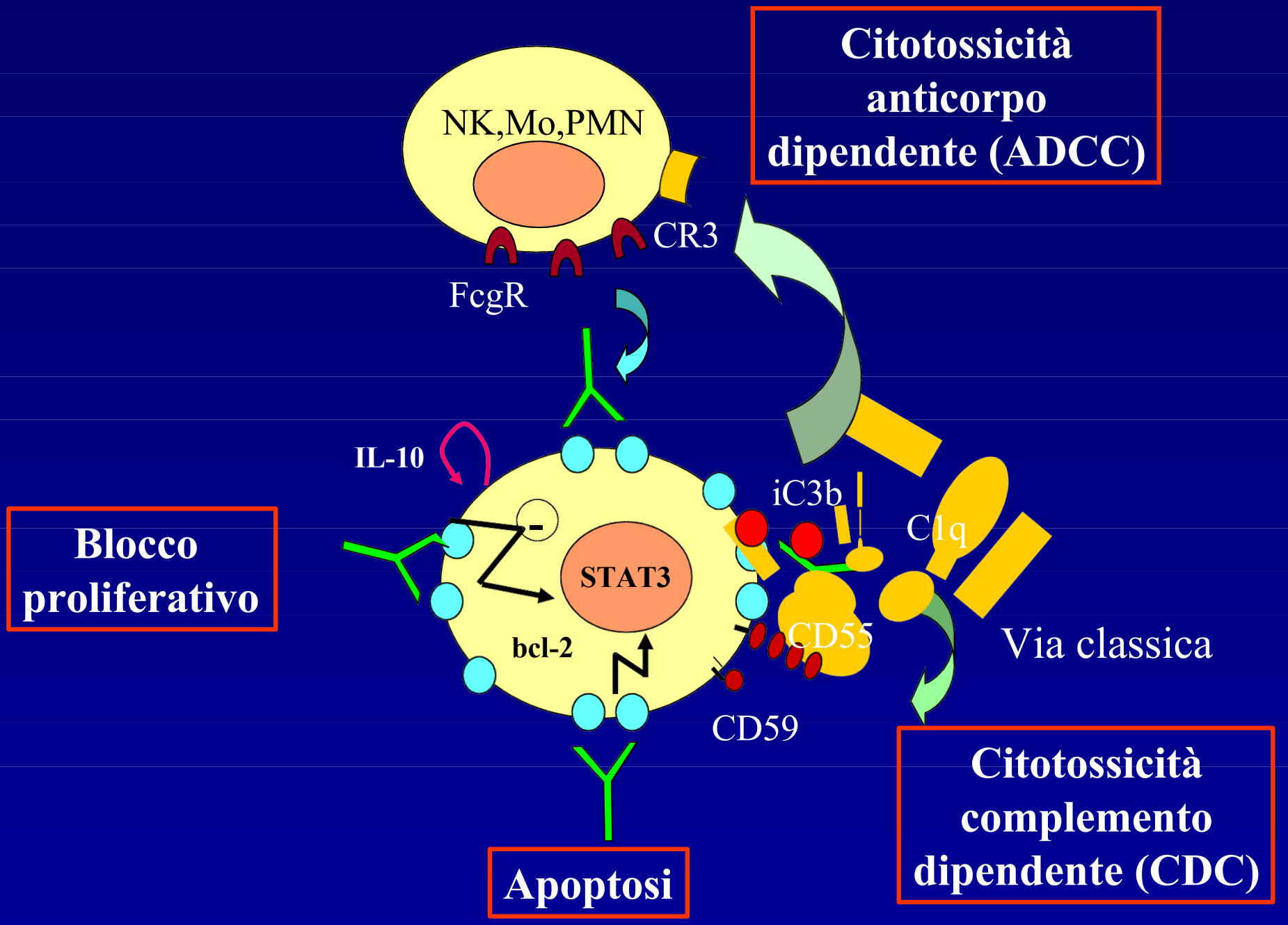
		SEVERITY				
1)	**heart diseases** (heart only)	0	1	2	3	4
2)	**hypertension** (severity should be evaluated. Involved organs should be considered separately)	0	1	2	3	4
3)	**vascular diseases** (blood, vessels, bone marrow, spleen, lymphatic system)	0	1	2	3	4
4)	**respiratory diseases** (lungs, bronchi, trachea under larynx)	0	1	2	3	4
5)	**EENT** (eyes, ear, nose throat, larynx)	0	1	2	3	4
6)	**Upper GI tract** (esophagus, stomach, duodenum, biliary tract, pancreas)	0	1	2	3	4
7)	**Lower GI tract** (bowel, hernia)	0	1	2	3	4
8)	**Liver diseases** (liver only)	0	1	2	3	4
9)	**Renal diseases** (kidney only)	0	1	2	3	4
10)	**Other genito-urinary diseases** (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11)	**Musculo-skeletal system and skin** (muscles, bones, teguments)	0	1	2	3	4
12)	**Nervous system diseases** (central and peripheral nervous system not including dementia)	0	1	2	3	4
13)	**Endocrine-metabolic diseases** (diabetes, infections, sepsis, toxic state)	0	1	2	3	4
14)	**Psychiatric-behavioural diseases** (dementia, depression, anxiety, agitation, psychosis)	0	1	2	3	4

FIT PATIENTS: CIRS<6, CREATININE CLEARANCE >70 ml/min

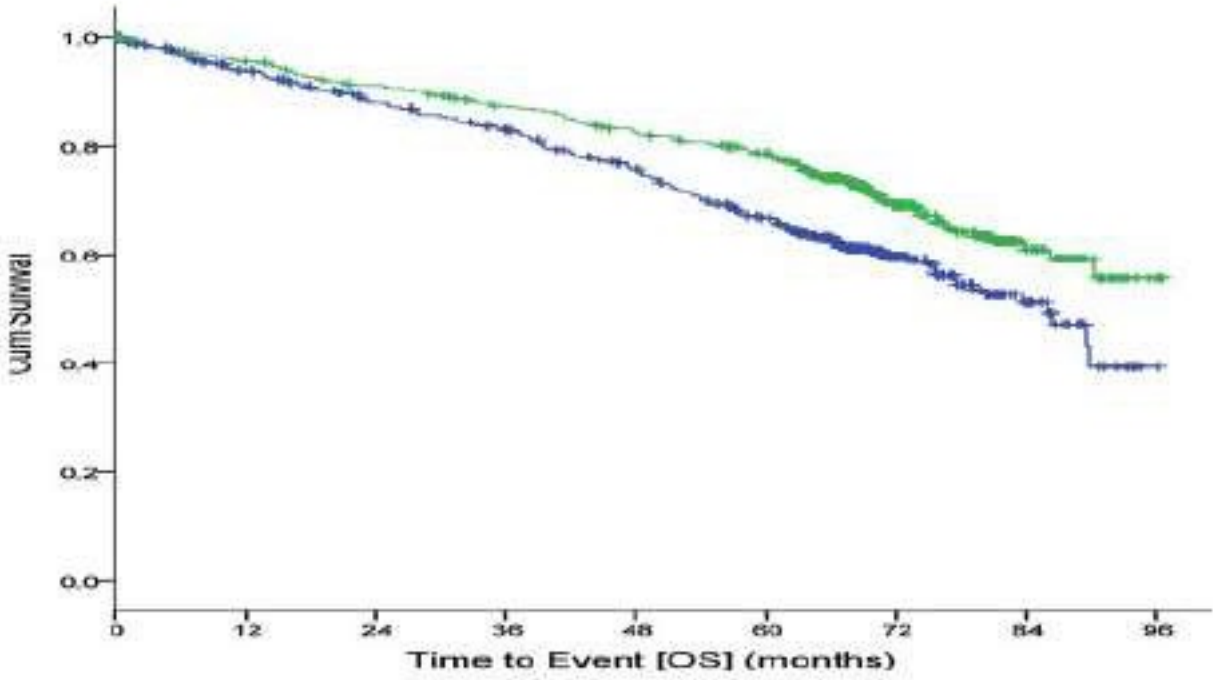
EVOLUTION TREATMENT IN B-CLL



Meccanismo di azione del Rituximab



FCR IS ESTABLISHED AS FRONTLINE TREATMENT OF CHOICE FOR FIT CLL PATIENTS AND NO del17p



Time to event [OS] months

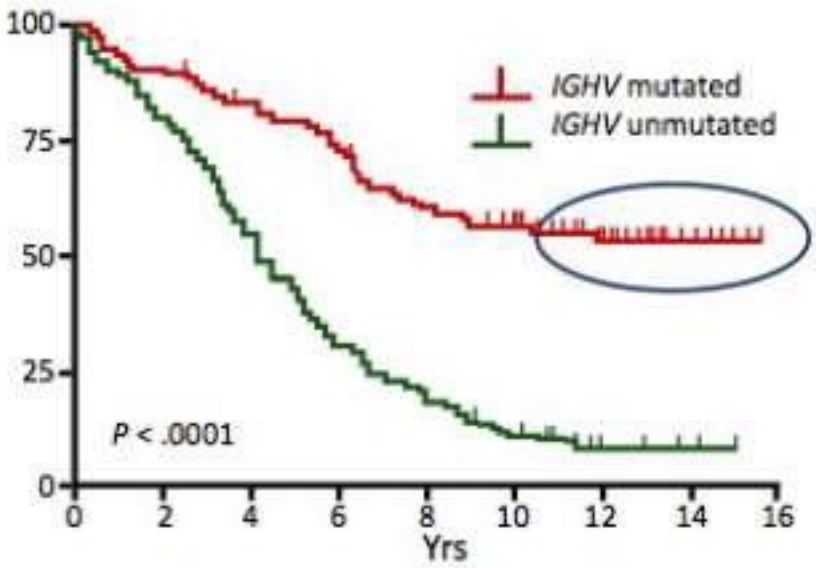
Median observation time 5.9 years

FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

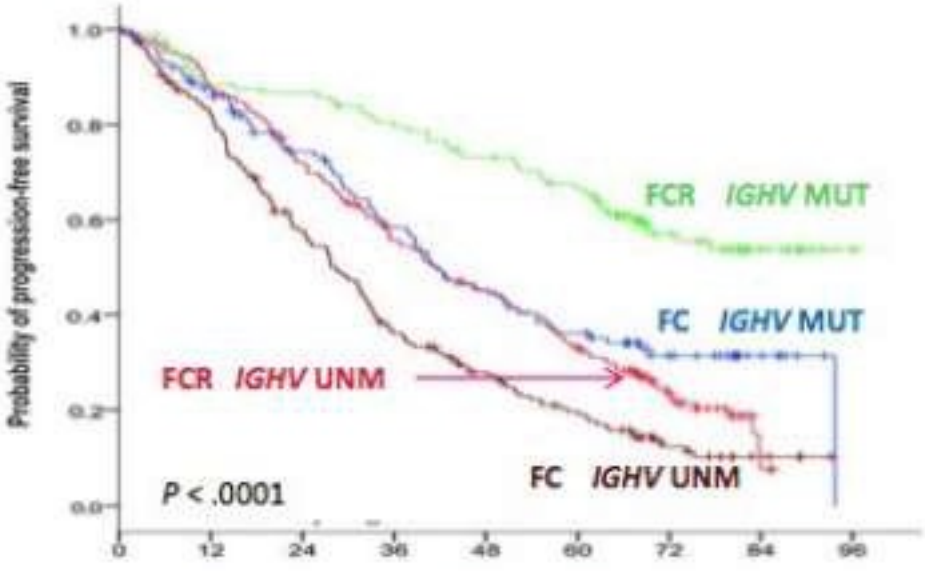
HR 0.68,
95% CI 0.535-0.858
p=0.001

Hallek et al. Lancet 2010; 376(9747):1164-74;
Fischer K et al. iwCLL 2013

IGHV mut AND del13p PATIENTS GAIN THE GREATEST BENEFIT FROM FCR

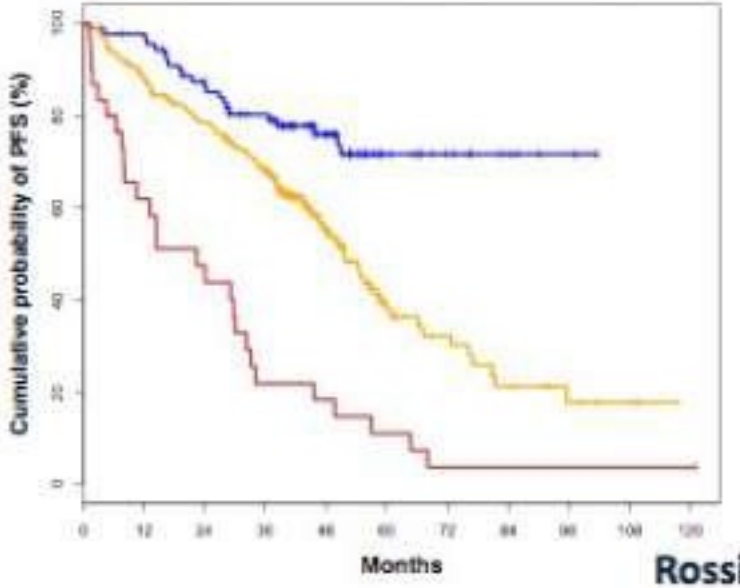


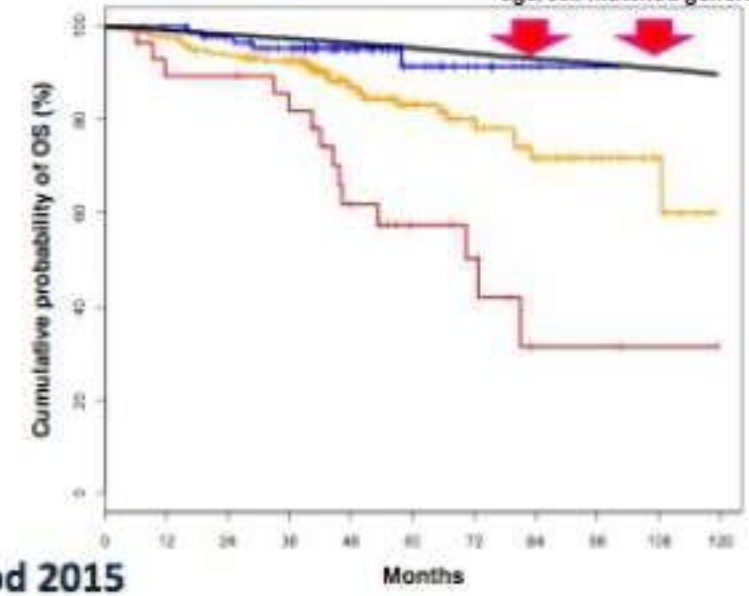
Thompson et al, Blood 2015



Fischer et al, Blood 2016

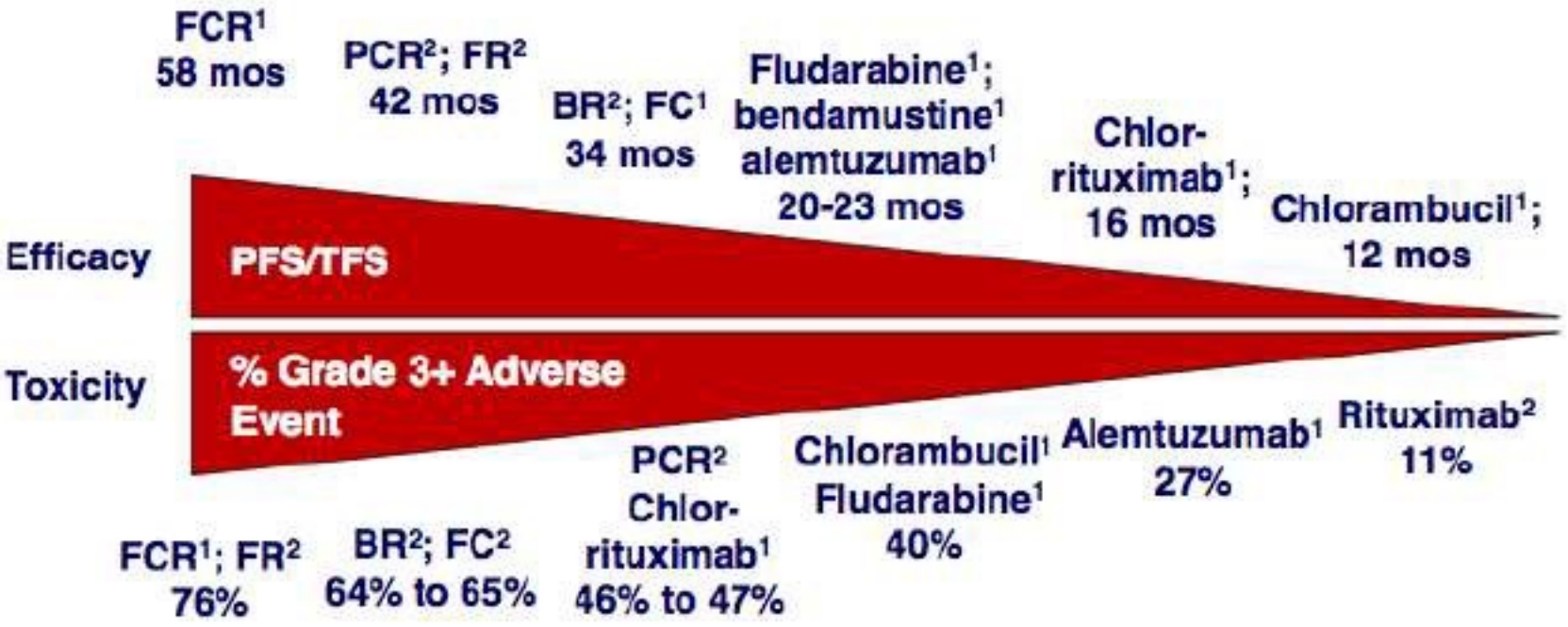
- Low-risk group (*IGHV* mutated)
- Intermediate-risk group (*IGHV* unmutated and/or 11q deletion)
- High-risk group (17p deletion)





Rossi et al, Blood 2015

EFFICACY vs TOXICITY



[1] **Phase III data.**

[2] **Phase II data.**

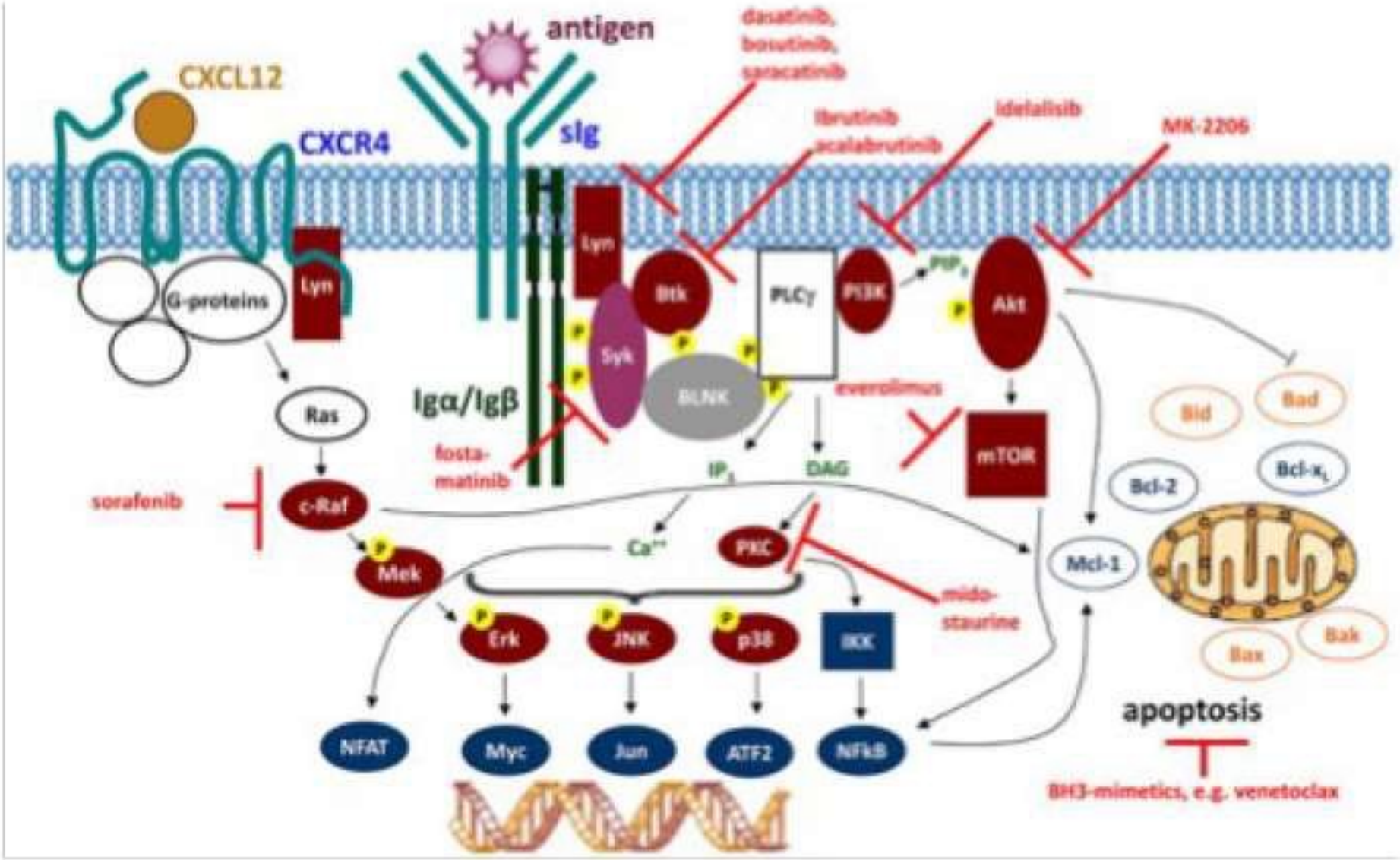
Shanafelt T. Hematology 2013;2013:158-167.

WHAT WILL THE ROLE OF CHEMOIMMUNOTHERAPY BE IN CLL PATIENTS WITH 17pDELETION OR TP53 MUTATION?

No Role
FIT/UNFIT

Novel Agents

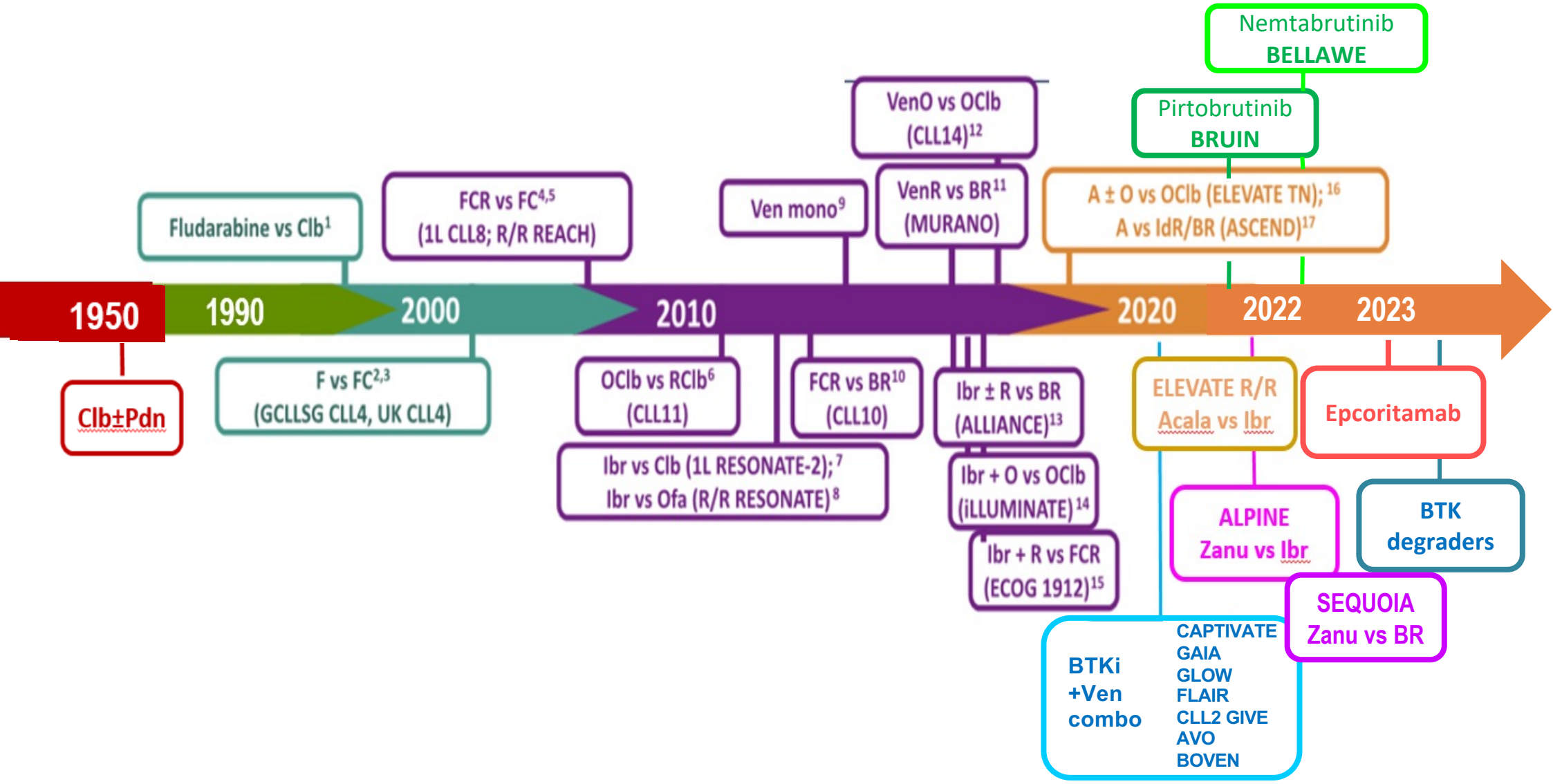
SURVIVAL SIGNALING IN CLL: TARGETS OF NOVEL AGENTS



NEW AGENTS

- Monoclonal Antibodies
- BTK Inhibitors
- PI3K Inhibitors
- BCL-2 Inhibitors
- Immunomodulatory Agents

TREATMENT EVOLUTION IN CLL



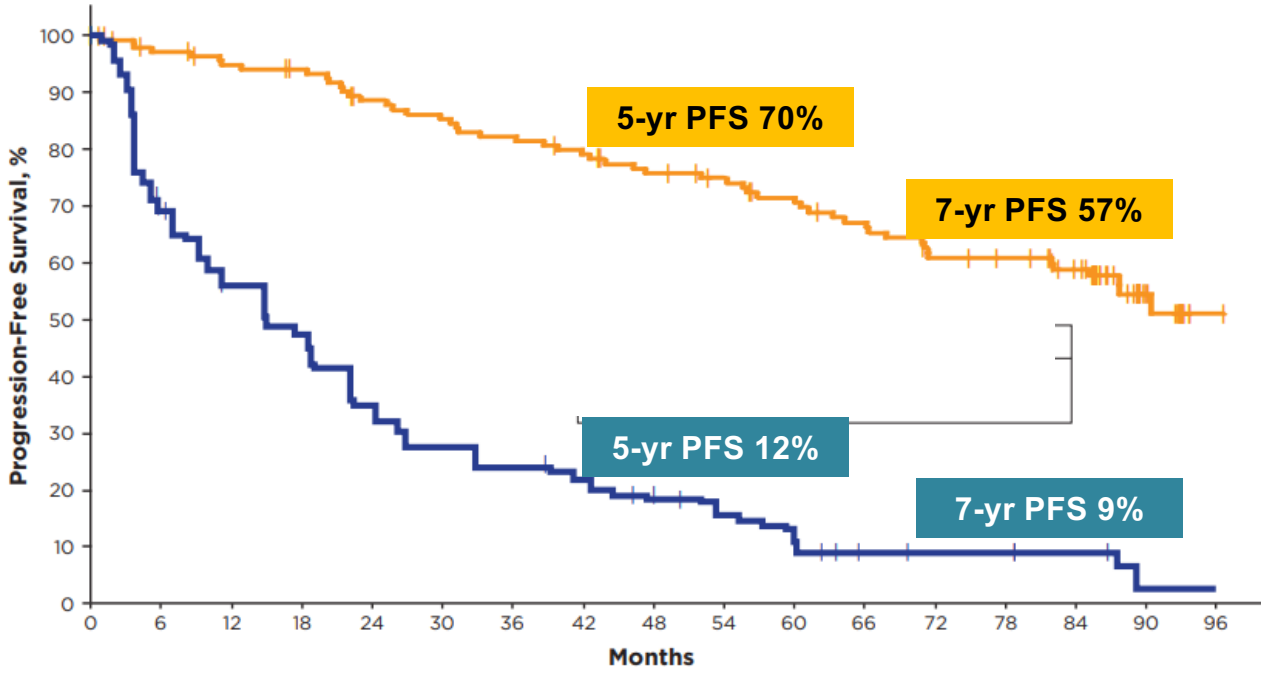
1L IBRUTINIB: PROLONGED PFS IN TN PATIENTS WITH CLL

RESONATE 2
Median FU: 8 years

N=269
Key eligibility criteria
- Previously untreated CLL/SLL requiring therapy
- Age ≥65 years
- Age 65–69 years with comorbidities
- del(17p) excluded

RANDOMIZE 1:1

- Ibrutinib 420 mg once daily until disease progression (PD) or unacceptable toxicity **n=136**
- Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 + 15 of 28-day cycle, up to 12 cycles **n=133**



Patients at Risk

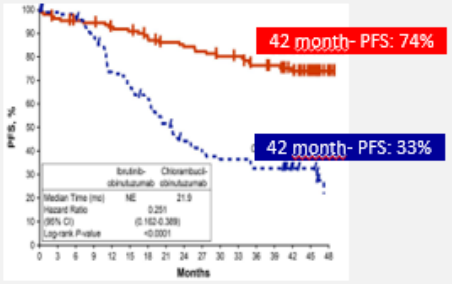
Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	76	67	65	57	17	1
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	4	1	0

Barr et al., Blood Adv, 2022

1L IBRUTINIB: SUPERIOR PFS vs. CHEMOIMMUNOTHERAPY

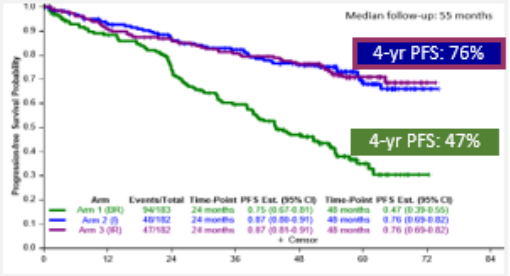
Illuminate
Moreno et al. Haematologica 2022

mFUP 45 months



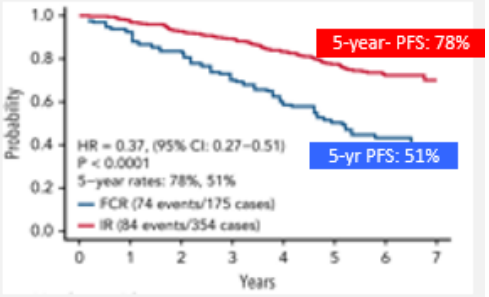
Alliance
Woyach et al. 2021 ASH meeting

mFUP 55 months



ECOG1912
Shanafeltet al. Blood 2022

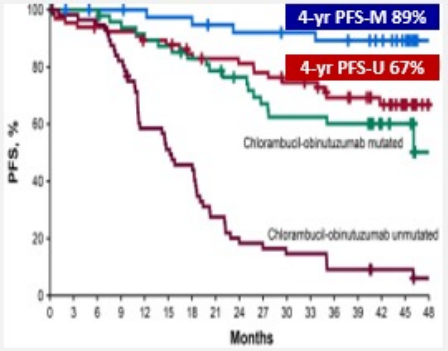
mFUP 69.6 months



1L IBRUTINIB IN UNMUTATED PATIENTS

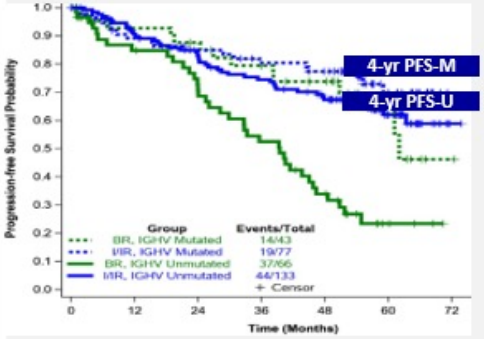
Illuminate
Moreno et al. Haematologica 2022

mFUP 48 months

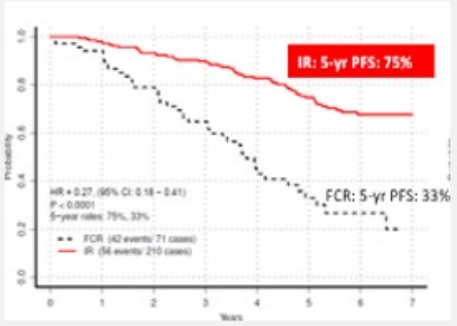


Alliance
Woyach et al. 2021 ASH meeting

mFUP 55 months

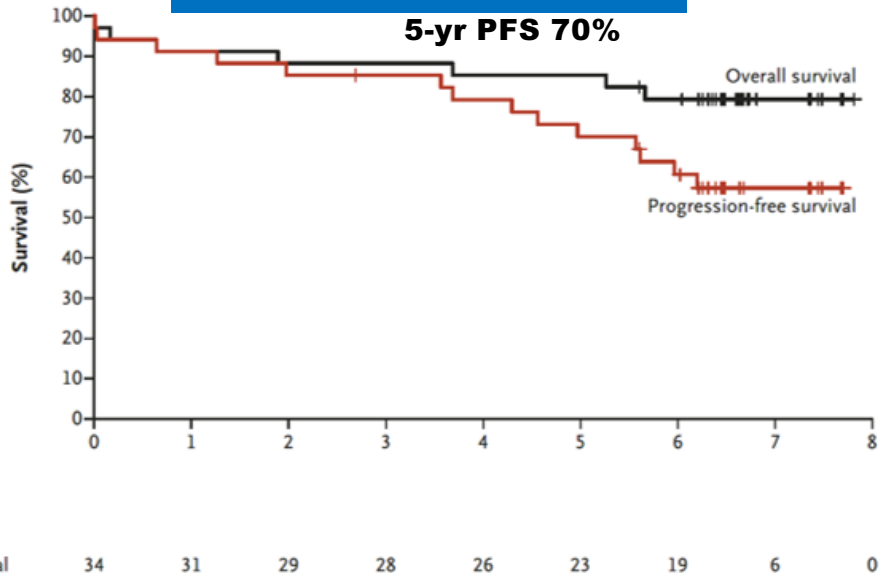


ECOG1912
Shanafelt, et al. Blood. 2022



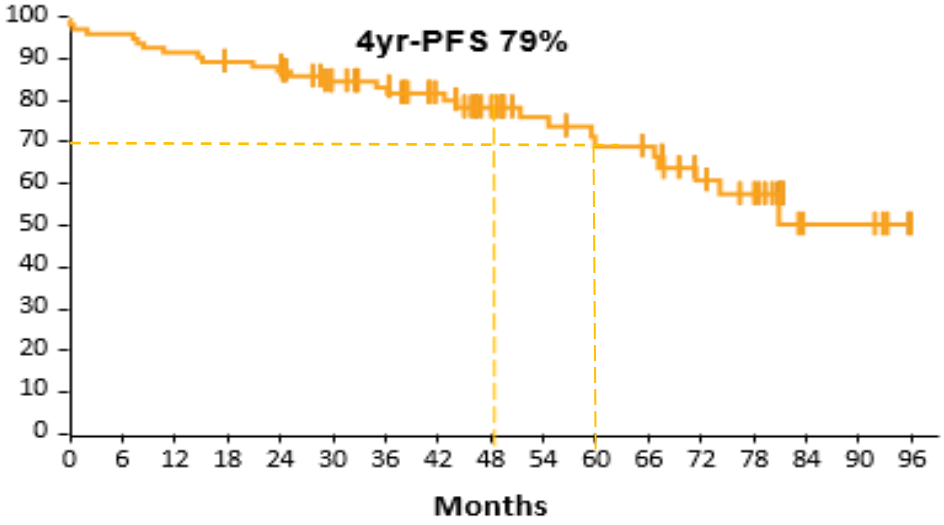
1L IBRUTINIB: PROLONGED PFS IN PATIENTS WITH *TP53* DISRUPTION

Ahn et al. NEJM, 2020



% (95% CI)	2-Year	3-Year	4-Year	5-Year	6-Year
OS	88 (78-100)	88 (78-100)	85 (74-98)	85 (74-98)	79 (67-94)
PFS	85 (74-98)	85 (74-98)	79 (67-94)	70 (56-88)	61 (46-80)

Allan et al. BJH2021



	PCYC-1122e (NIH study)	RESONATE-2	iLLUMINATE	ECOG1912
N = 89	34	11	18	26
Regimen	Ibr	Ibr	Ibr + Obinu	Ibr + Ritux
Patients	del(17p)/ *TP53*mut	*TP53*mut	del(17p)/ *TP53*mut	*TP53*mut

Caso Clinico: M.R. 68 anni

M.R. è una **uomo** di 68 anni che si reca dal medico curante per controllo di routine

Anamnesi
Pensiato, ex Operaio metalmeccanico; fuma 1 pacchetto/giorno, alcol saltuario ai pasti.
Iperteso in trattamento da circa 5 anni

Esame obiettivo: nella norma

Emocromo

Esame	*Risultato*	*Valori riferimento*
Globuli bianchi	**14.500**	4.000-10.000/mmc
- Neutrofili	**28%**	*40-74%*
- Linfociti	**69%**	*20-45%*
- Monociti	3%	*3-9%*
Globuli rossi	3.800.000	3.800.000-4.800.000/mmc
Emoglobina	14,5	12-16 g/dL
MCV	90	82-99 fL
MCH	29	27-31 pg
RDW	15%	12-17%
Piastrine	219.000	150-400.000/mmc

Che cosa presenta?

LEUCOCITOSI

Di che tipo?

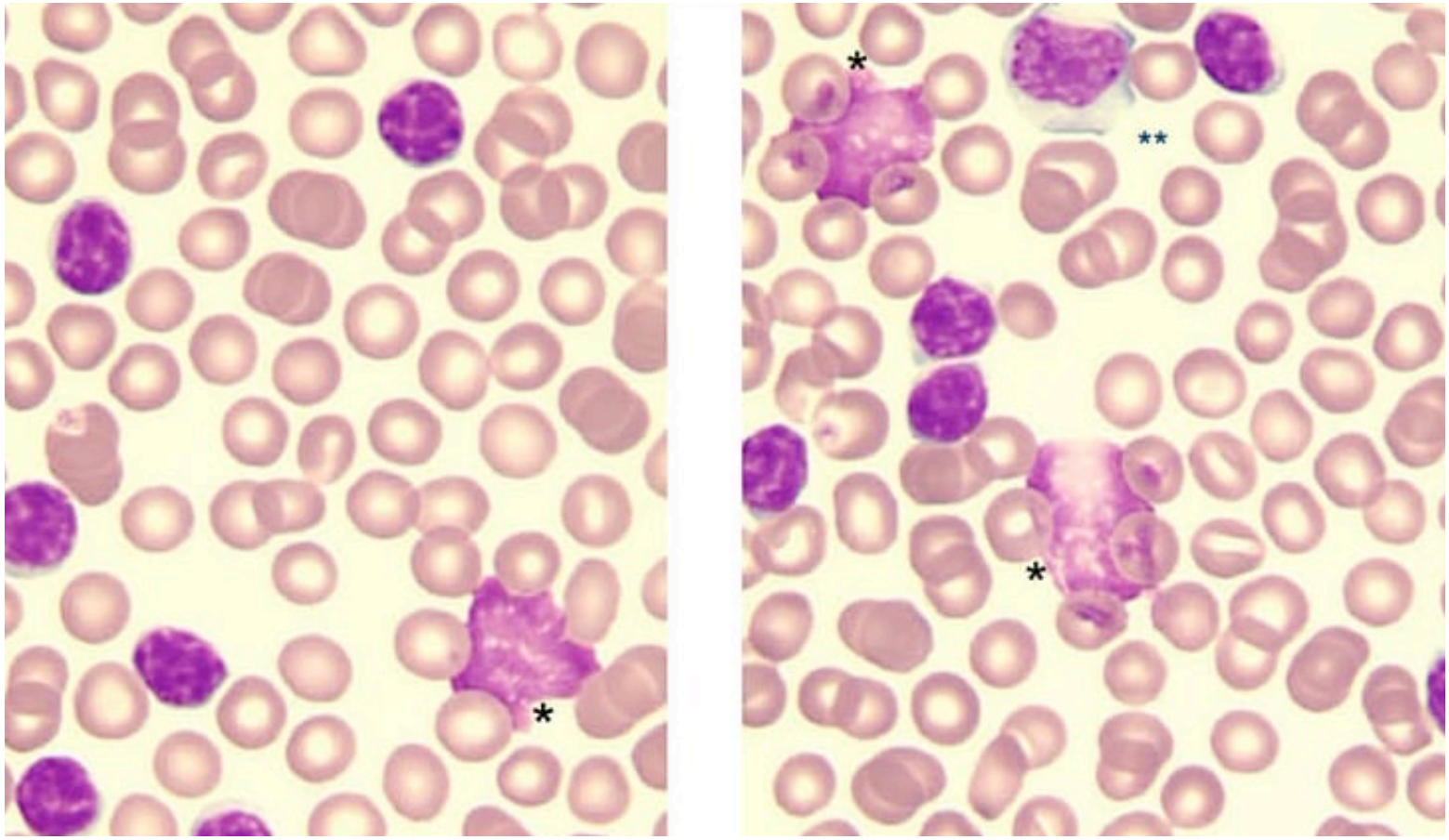
1) Linfocitosi 2) Neutrofilia 3) Monocitosi

Il paziente presenta neutropenia?

Relativa, ma non assoluta
(legata alla linfocitosi)

Chiedereste altri esami per inquadrare linfocitosi?

Striscio di sangue periferico



Che cosa sospettate?

LLC

Chiedereste altri esami?

1) Esame citofluorimetrico

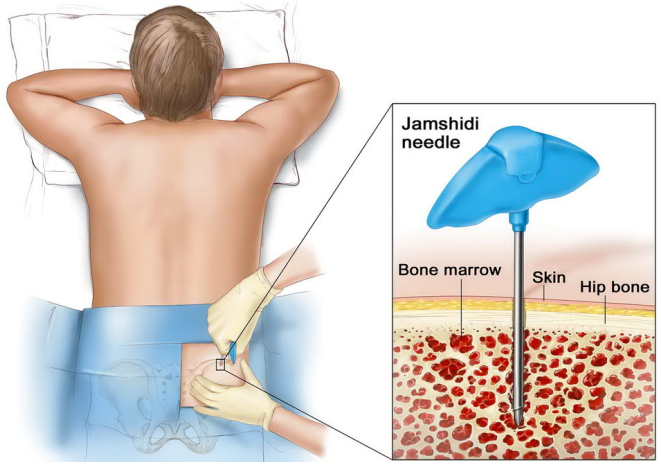
2) Stato marziale

3) Acido folico e folati

*Immunofenotipo SP: 62% linfociti clonali per catena leggera kappa, che esprimono CD20 (bassa intensità), CD19, **CD5, CD23 e CD200**; negativi CD38 e ZAP70.*

Quale altro esame a completamento?

Valutazione midollare con BIOPSIA OSTEO MIDOLLARE



- *normale cellularità,*
- *infiltrato linfoide clonale patologico CD5+ del 5%*

Completamento inquadramento prognostico

- ***Stato mutazionale delle immunoglobuline: non produttivo per mutazioni***

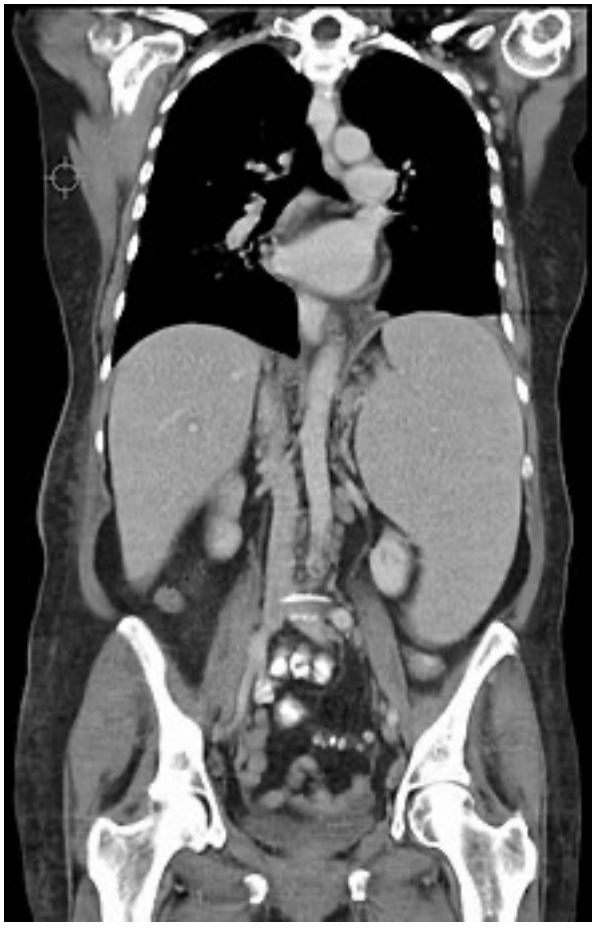
- ***FISH: non lesioni a carico dei cromosomi 11, 12, 13, 17***

- ***Esclusa mutazione di p53***

- ***IGHV non mutato***

Quale altro esame a completamento?

TAC total body con e senza MDC



- *linfadenopatie sovra- e sotto diaframmatiche di massimo 1.5 cm di diametro*

- *organi addominali di dimensioni conservate*

Leucemia linfatica cronica, stadio RAI 0, Binet A

CLL-IPI Intermedio (IGHV unmut)

Che tipo di trattamento?

- Sintomi sistemici riferibili alla malattia
  - perdita di peso non giustificata (≥10% di peso corporeo negli ultimi 6 mesi)
  - febbre ≥38 °C per almeno 2 settimane in assenza di infezione
  - sudorazione notturna per più di 1 mese in assenza di infezioni
  - astenia che limita le normali attività o che determina performance status ECOG ≥2

- Progressione di malattia
  - linfoadenopatie ≥10 cm; linfoadenopatie progressive o sintomatiche
  - splenomegalia >6 cm dall'arcata costale; splenomegalia progressiva o sintomatica
  - anemia con Hb <10 gr/dl non causata da anemia emolitica autoimmune
  - piastrinopenia con livelli di Pst <100.000/microlitro, non causata da piastrinopenia autoimmune**.
  - aumento della linfocitosi con aumento della conta ≥50% in due mesi o raddoppio della conta in meno di 6 mesi (si consideri valore di partenza >30.000 se questo è l'unico criterio che indica il trattamento)

- Complicanze
  - anemia emolitica o piastrinopenia autoimmune poco responsiva agli steroidi
  - coinvolgimento extra-nodale sintomatico e/o manifestazioni paraneoplastiche riferibili alla malattia non responsive ad altre terapie

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** Da iniziare in presenza di almeno 1 delle condizioni;*

*** In alcuni pazienti le piastrine possono essere <100.000/microlitro e rimanere stabili; la piastrinopenia isolata pertanto non determina automaticamente la necessità di iniziare terapia se questo rappresenta l'unico criterio.*

Watch and Wait

Dopo 4 anni di monitoraggio

- ***Progressiva linfocitosi****, comparsa di* ***linfadenopatie*** *e* ***calo ponderale,*** *che conduce a una ristadiazione:*

• *EEC: GB 64.1 x109/L, Ly 61.3 x109/L, Hb 101 g/L, PLT 92 x109/L*

• *TC total body: comparsa di linfadenopatia in sede giugulo-digastrica (25x18 mm), mediastinica (22x15 mm), ascellare (dx 31x25 mm), interportocavale (45x30x60 mm) e paravescicale (55x28 mm), milza di 17.5 cm.*

• *Confermata FISH negativa, IGHV unproductive. CD38 neg. ZAP70 neg. TP53 wt, BIRC3 wt, NOTCH1 wt, SF3B1 wt.*

• *Karyotype: 45,XY,15,der(19)t(15;19)(q15;q13)[22]/46,XY,t(10;13)(q23;q14)[2]*

Trattamento

Avviato a terapia con ***ibrutinib (non comorbidità cardiologiche significative)****:*

Dopo 6 mesi di trattamento:

- *EEC: persistenza di linfocitosi (Ly 63.6 x109/L),*
- *TC: regredite le linfadenopatie*

Prosegue trattamento e monitoraggio