Chronic lymphocytic leukemia

Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma and Monoclonal B-cell Lymphocytosis: Concept

- • Disorders of “mature” CD5+ B lymphocytes
- • SLL and CLL = counterparts (lymph nodes and blood) of the same tumor
- • MBL: Clinical situation not fulfilling CLL criteria that may or (more frequently) may not evolve to CLL

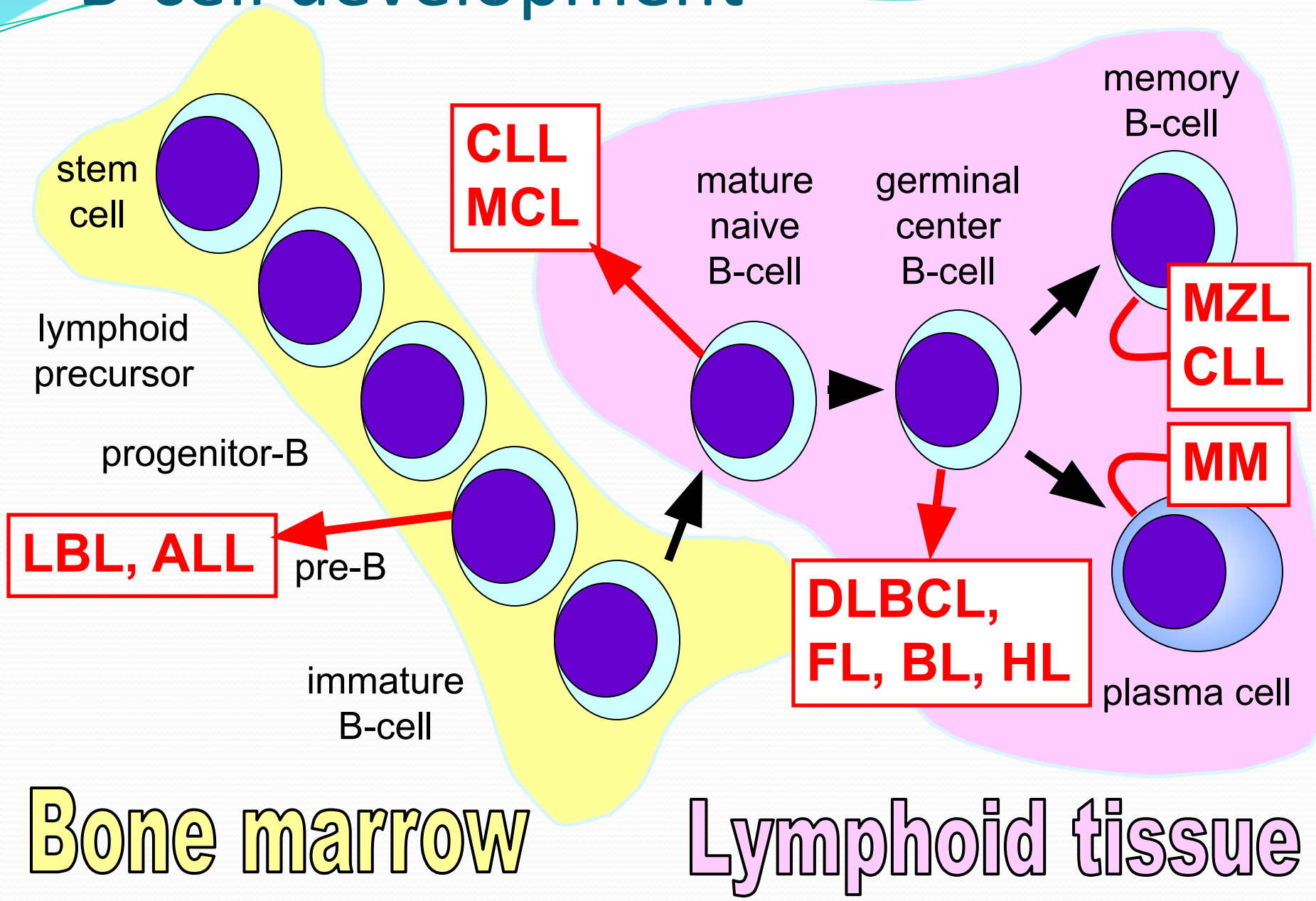
CLL

- Most frequent leukemia in adults – 30% of all adult leukemias
- Incidence in western world: 4-5 new cases/ 100000/year, **10** times lower in Asia - around 0.48/100000/year
- Median age at presentation 72; 9% diagnosed between ages 45 – 54, 20% - 55-64 years old, 27% - 65-74 years old, 29% - 75-84 years old, 13% - above 85 years old
- Median age of CLL patients in clinical trials is 60!!
- Male : Female 1.3-1.5:1

Aetiology

- 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

B-cell development



Differential diagnosis

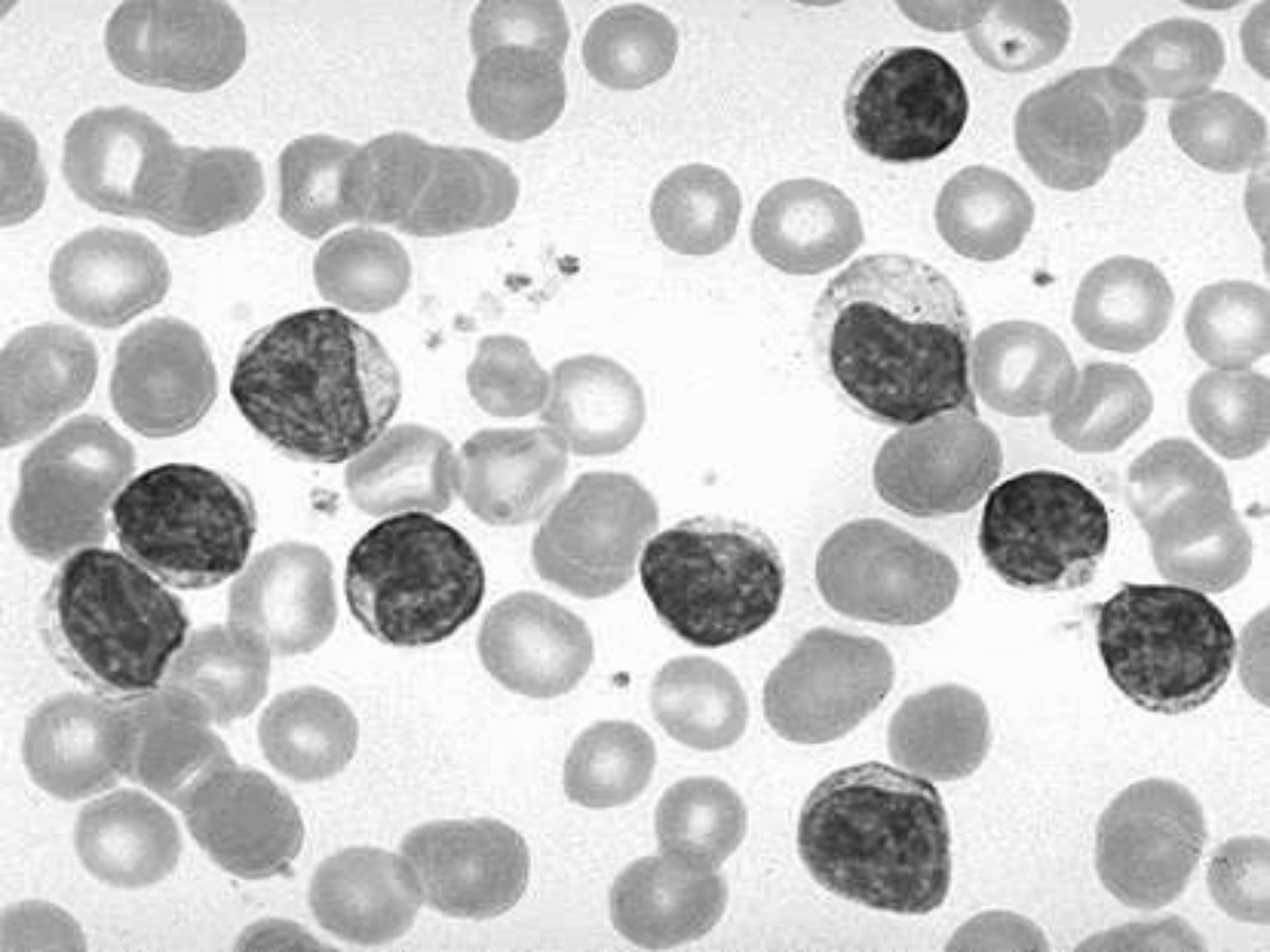
- Infectious causes
  - bacterial (tuberculosis)
  - viral (mononucleosis)
- Malignant causes
  - B-cell
  - T-cell
    - leukemic phase of non-Hodgkin lymphomas
    - Hairy-cell leukemia
    - Waldenstrom macroglobulinemia
    - Large granular lymphocytic leukemia

Clinical findings (1)

- Approximately 40% of CLL patients are asymptomatic at diagnosis
- In symptomatic cases the most common complaint is fatigue
- Less often the initial complaint are enlarged nodes, the development of an infection (bacterial) or bleeding diathesis (thrombocytopenia)

Clinical findings (2)

- Most symptomatic patients have enlarged lymph nodes (more commonly cervical and supraclavicular) and splenomegaly, hepatomegaly may occur
- The lymph nodes are usually discrete, freely movable, and non tender
- Less common manifestation are infiltration of tonsils, mesenteric or retroperitoneal lymphadenopathy, and skin infiltration
- Patients may present with features of anaemia, and bruising or bleeding



Investigations

- Pre-treatment studies of patients with CLL should include examination of:
  - complete blood count
  - peripheral blood smear
  - reticulocyte count
  - Coomb's test
  - renal and liver function tests - LDH
  - serum protein electrophoresis
  - immunoglobulin levels
  - plasma β2 micro globulin level
- If available immunophenotyping should be carried out to confirm the diagnosis
- Bone marrow biopsy and cytogenetic analysis is not routinely performed at diagnosis of CLL
- BM or blood cytogenetics (FISH)

Laboratory findings (1)

- The blood lymphocyte count above 5,0 G/L
- In most patients the leukemic cells have the morphologic appearance of normal small lymphocytes
- In the blood smears are commonly seen ruptured lymphocytes (“basket” or “smudge” cells)
- Careful examination of the blood smear can usually differentiate CLL, and the diagnosis can be confirmed by immunophenotyping

Laboratory findings (2)

- Clonal expansion of B Lymphocytes
  - In B-cell CLL clonality is confirmed by
    - the expression of either κ or λ light chains on the cell surface membrane
    - the presence of unique idiotypic specificities on the immunoglobulin produced by CLL cells
    - by immunoglobulin gene rearrangements
    - typical B-cell CLL are unique in being CD19+ and CD5+
- Hypogammaglobulinemia or agammaglobulinemia are often observed
- 10 - 25% of patients with CLL develop autoimmune haemolytic anaemia, with a positive direct Coombs' test or immune thrombocytopenia
- The marrow aspirates shows greater than 30% of the nucleated cells as being lymphoid

Immunophenotyping

MCL	FL	SLVL	HCL-V	HCL	PLL	CLL	Marker
++	++	++	+++	+++	++	++	CD19
++	++	++	+++	+++	+++	Dim	CD20
++	++	++	+++	+++	+++	Dim	sIg
++	+/-	+/-	-	-	+/-	++	CD5
-	+/-	+/-	-	-	+/-	-	CD10
++	++	++	+++	+++	++	dim-/+	CD22
-	-	+/-	-	-	+/-	++	CD23
-	-	-/+	-	+++	-/+	+/-	CD25
-	-	-/+	+++	+++	-	-	CD103

Staging

Rai

- 0 – lymphocytosis.
- I – lymphocytosis + lymph nodes.
- II – lymphocytosis + spleen or liver ± LN.
- III – lymphocytosis + Hb<10, ± LN, spleen, liver.
- IV – lymphocytosis + PLT<100000, ± LN, spleen, liver

Binet

- Stage A – lymph node areas ≤2 ; Hb>10; PLT≥100000.
- Stage B – lymph node areas ≥3; Hb>10; PLT>100000.
- Stage C – Hb<10; PLT<100000.
- ***LN areas – cervical, axillary, inguinofemoral, spleen, liver***

Prognosis according to stage

- Rai classification (1975)

stage	median survival (years)
0	>10
I	> 8
II	6
III	2
IV	< 2

- Binet classification (1981)

stage	median survival (years)
A	> 10
B	7
C	2

Genomic aberrations

- Have pathogenetic and clinical relevance.
- Identifiable by FISH in 80% of CLL cases.
- Provide insights into the pathogenesis, they point to loci of candidate genes (17p13: P53; 11q22-q23: ATM).
- Identify subgroups with distinct clinical features – marked lymphadenopathy (11q-), resistance to treatment (17p-).
- Define specific subgroups that differ in the rate of disease progression (time from diagnosis to treatment) and overall survival.

Genomic aberrations by FISH

VH mutated	VH unmutated	-6q	-17p	12q+	11q-	13q-single	13q-	Study
44%	56%	7%	7%	16%	18%	36%	55%	Single center
59%	41%	2%	4%	13%	10%	40%	59%	CLL1
31%	69%	9%	3%	11%	21%	34%	53%	CLL4
32%	68%	6%	3%	12%	22%	27%	52%	CLL3
19%	81%	9%	27%	18%	32%	14%	48%	CLL2H

Markers of poor prognosis in CLL

- Advanced Rai or Binet stage
- Functional capacity, age , gender
- Peripheral lymphocyte doubling time <6 months
- Diffuse marrow histology
- Increased number of prolymphocytes or cleaved cells
- Poor response to chemotherapy
- High β2- microglobulin level
- Abnormal karyotyping
- Molecular – IgVH mutation, ZAP-70, CD38
- New markers under investigation

Risk Stratification

Diagnosis
TP53 anal
Age, gender,

TP53 intac
IgVH mutat

FISH•
Molecular•

TP53 defe
Very High

Risk factors – multivariate analysis

- VH unmutated & VH3-21 usage
- 17p deletion
- 11q deletion
- Age
- Lymphocyte count
- LDH
- ***When the model included cytogenetics and IgVH mutation status, the clinical stage lost it's significance***.

Surrogate markers for IgVH mutation status

- CD38 expression (Damle et al, Blood, 1999), correlation with unmutated IgVH and adverse prognosis.
- ZAP-70 – a tyrosine kinase expressed in B-CLL cells, correlates with unmutated IgVH and adverse prognosis (Crespo et al, NEJM,2003).
- **BUT –** subsequent studies yielded controversial results. (1) Differences between laboratories; (2) the expression levels may change over time (CD38); (3) careful separation of T-cells is necessary (ZAP-70); (4)different cut-off values for "+" and "-" (CD-38 and ZAP-70); (5)10-30% discordance with mutation status (both).

Genomic aberrations and IgVH mutation status

P-value	unmutated	Mutated	Aberration
	homology ≥98% n=168(56%)	homology <98% n=132(44%)	
.37	84%	80%	Clonal aberrations
.004	48%	65%	13q deletion
<.001	26%	50%	13q del single
.44	19%	15%	Trisomy 12
<.001	27%	4%	11q deletion
.03	10%	3%	17p deletion
<.001	35%	7%	17p or 11q del

Risk for progression in early stage CLL

Risk factors:

- Doubling time <12 months;
- Diffuse BM infiltration pattern;
- High tyrosine kinase (>7U/l);
- High β2μG (>3.5mg/l)
- Those patients have high incidence of “bad” cytogenetics (17p-; 11q-) and unmutated IgVH.

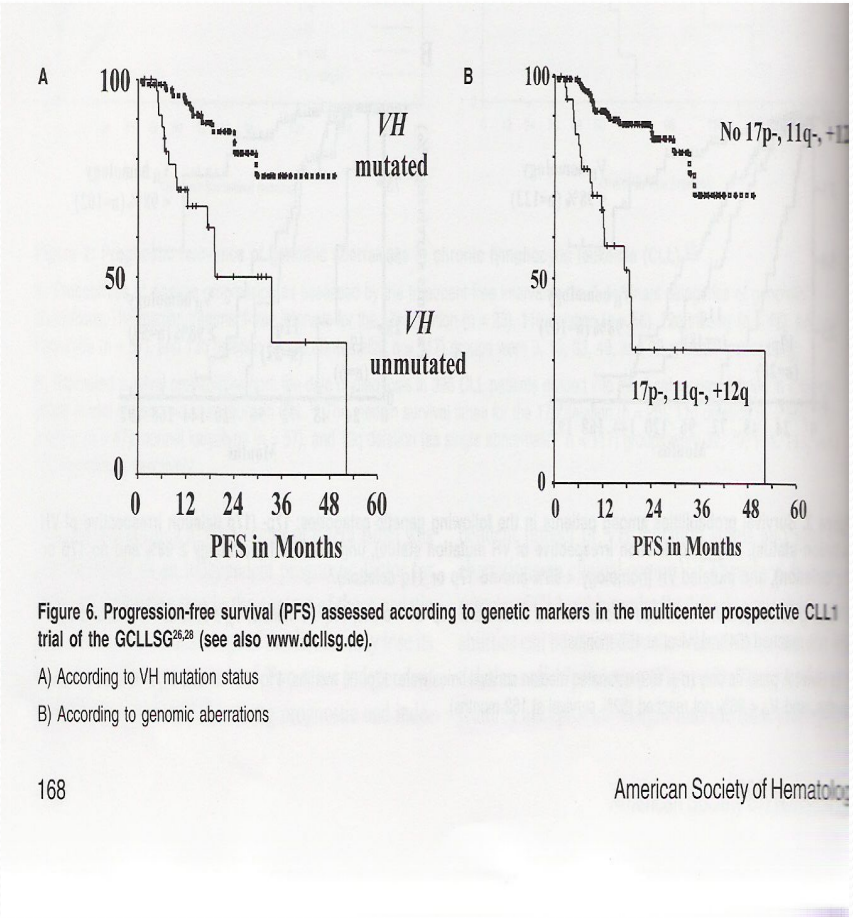


Figure 6. Progression-free survival (PFS) assessed according to genetic markers in the multicenter prospective CLL1 trial of the GCLLSG[26,28] (see also www.dcllsg.de).

A) According to VH mutation status

B) According to genomic aberrations

Genomic aberrations – prognostic relevance

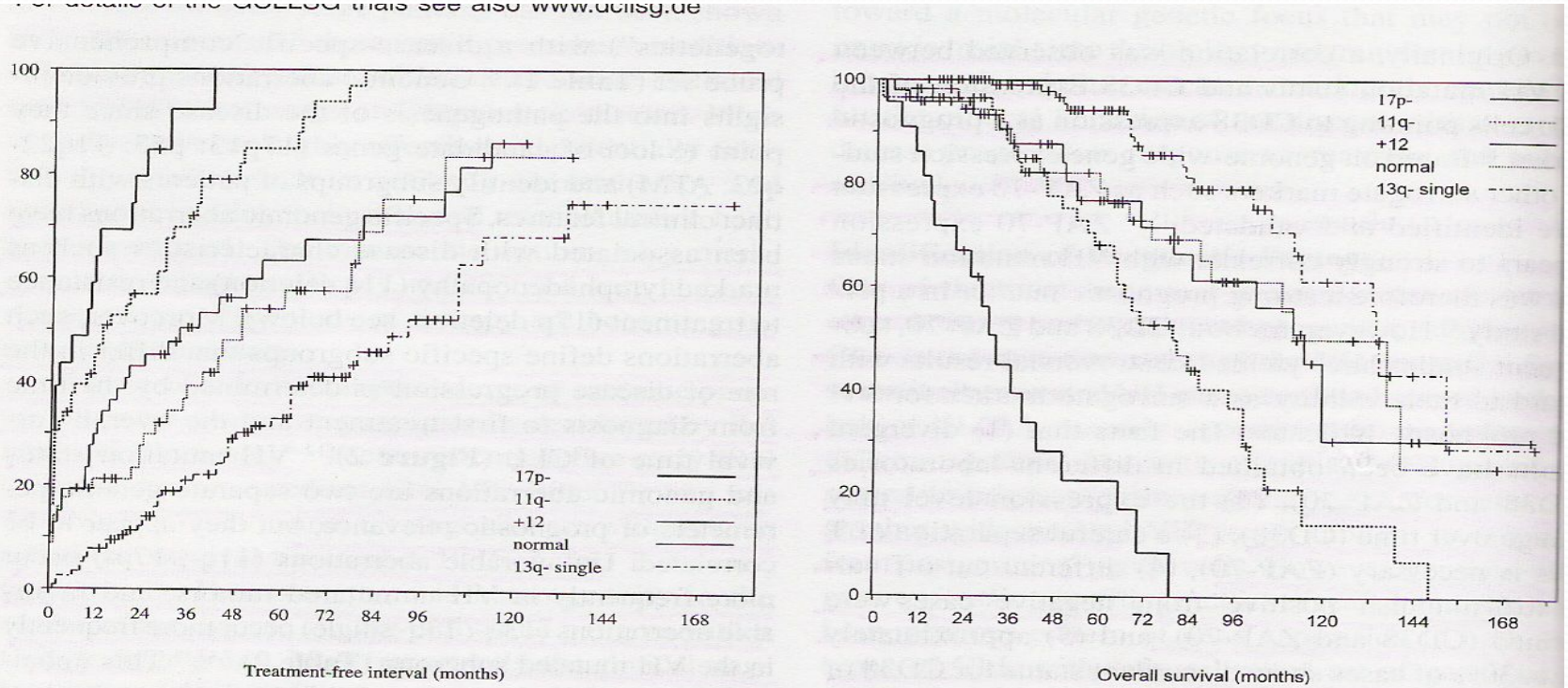
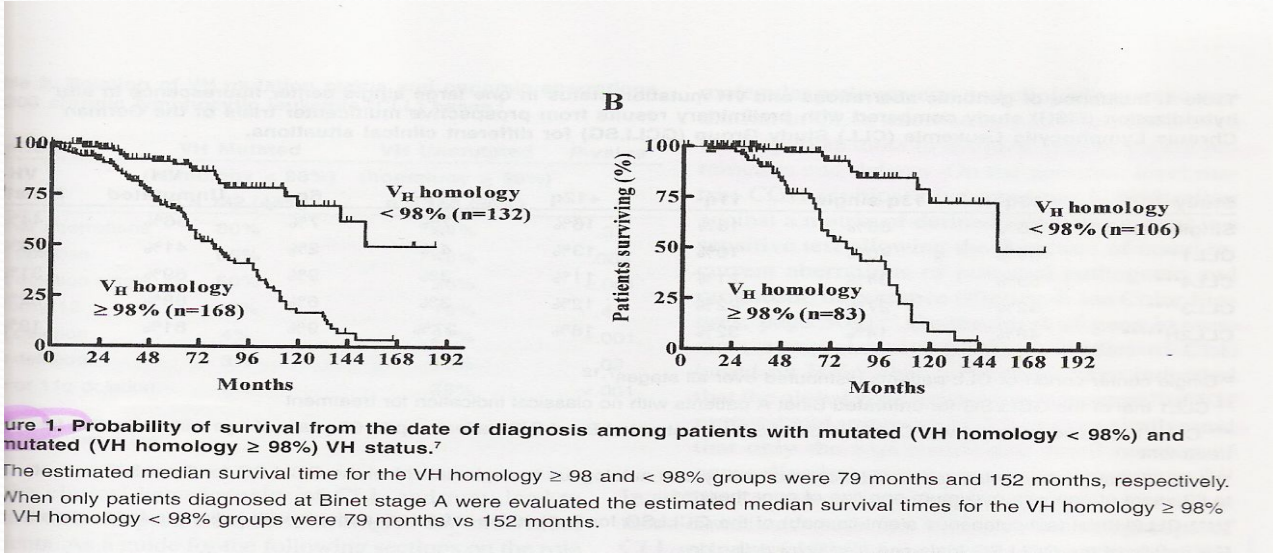


Figure 2: Prognostic relevance of genomic aberrations in chronic lymphocytic leukemia (CLL).[12]

A) Probabilities of disease progression as assessed by the treatment-free interval in the 5 dominant categories of genomic aberrations. The median treatment-free intervals for the 17p deletion (n = 23), 11q deletion (n = 56), 12q trisomy (n = 47), normal karyotype (n = 57), and 13q deletion (single abnormality; n = 117) groups were 9, 13, 33, 49, and 92 months, respectively.

B) Estimated survival probabilities from the date of diagnosis in 325 CLL patients divided into the 5 categories defined in a hierarchical model of genomic aberrations in CLL.[12] The median survival times for the 17p deletion (n = 23), 11q deletion (n = 56), 12q trisomy (n = 47), normal karyotype (n = 57), and 13q deletion (as single abnormality; n = 117) groups were 32, 79, 114, 111, and 133 months, respectively.

Prognostic factors



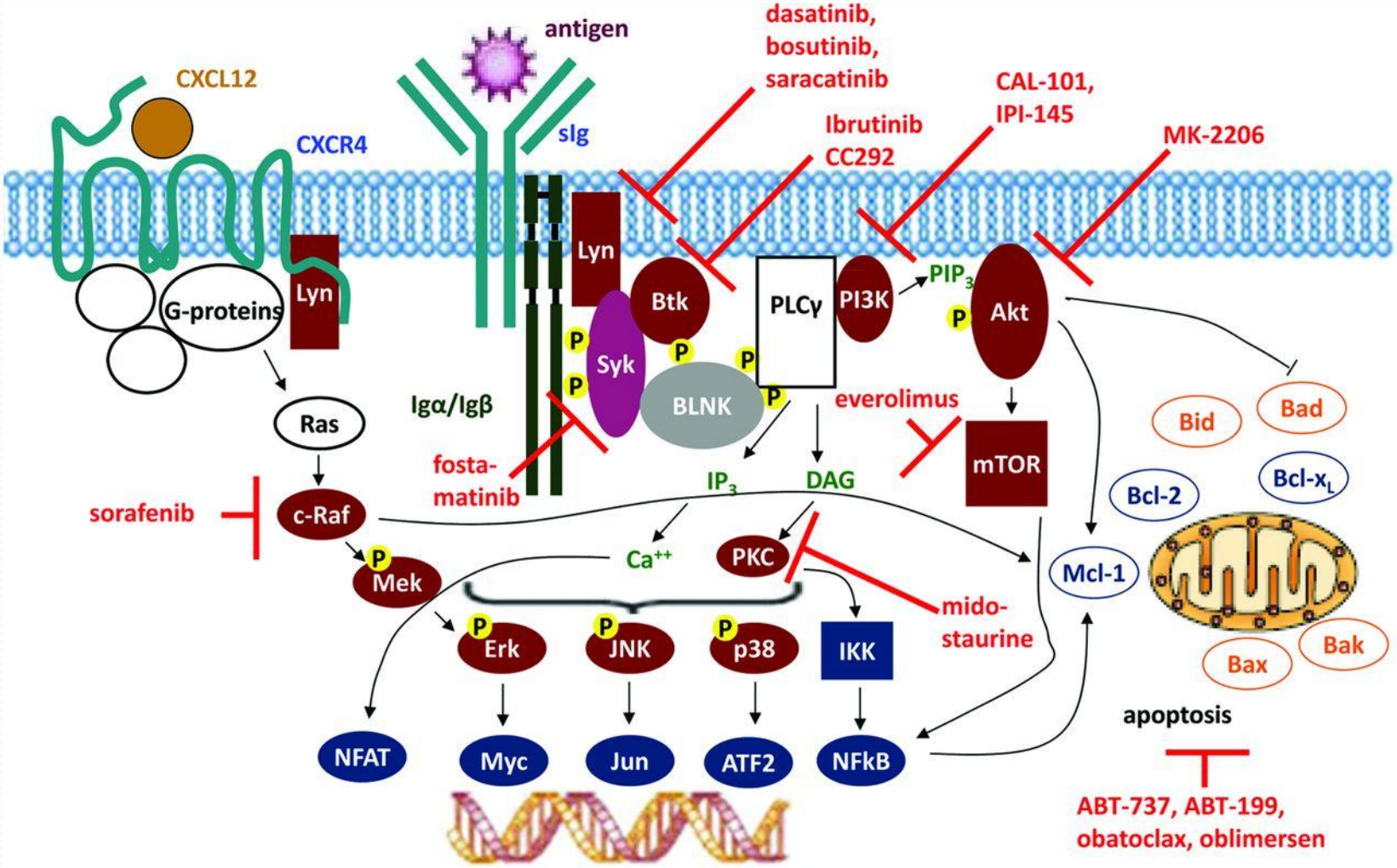
ure 1. Probability of survival from the date of diagnosis among patients with mutated (VH homology < 98%) and nutated (VH homology ≥ 98%) VH status.[7]

The estimated median survival time for the VH homology ≥ 98 and < 98% groups were 79 months and 152 months, respectively.

When only patients diagnosed at Binet stage A were evaluated the estimated median survival times for the VH homology ≥ 98% VH homology < 98% groups were 79 months vs 152 months.

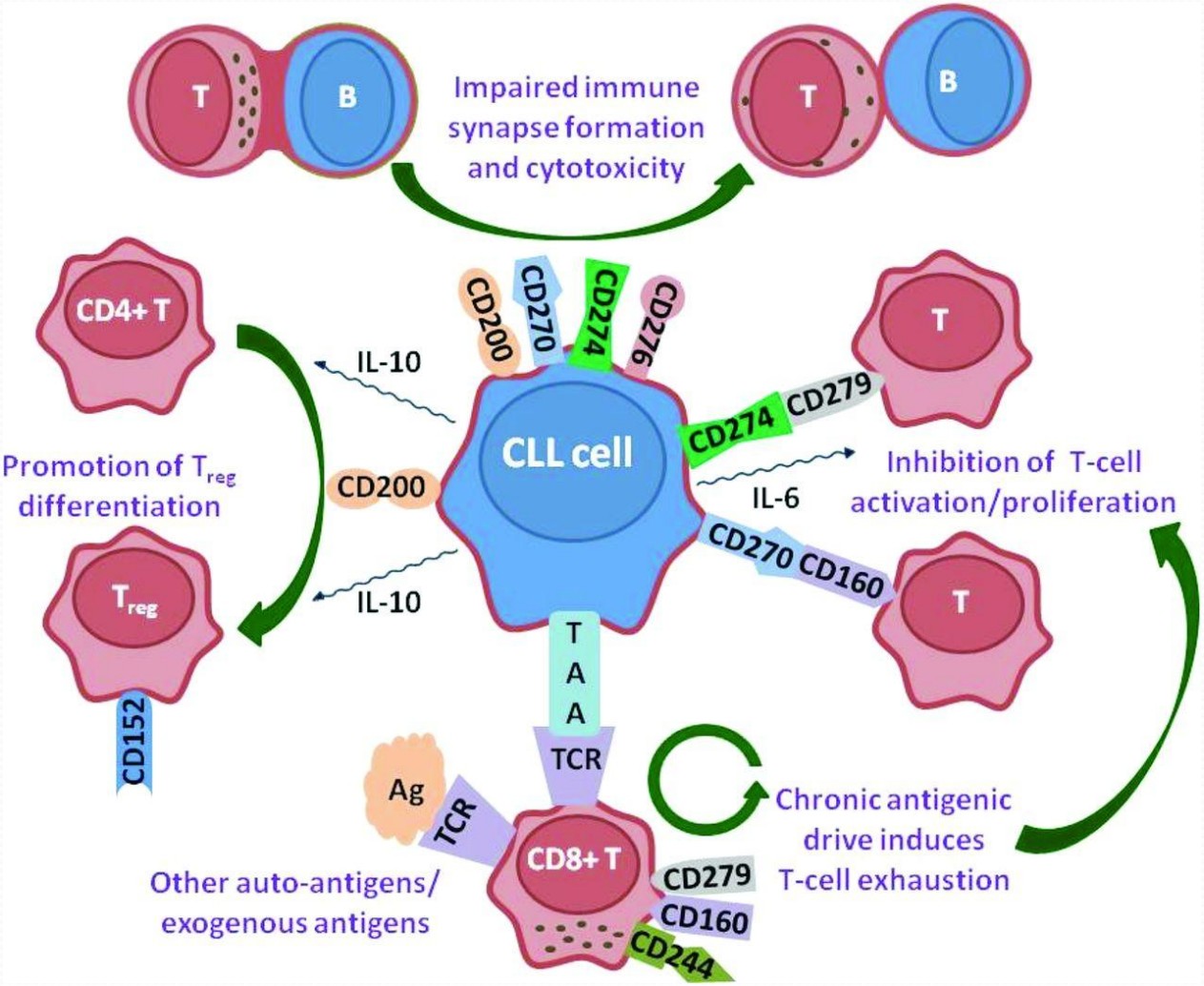
- Mutation status of IgVH gene – 50% mutated.
- Unmutated IgVH gene – pregerminal center B-lymphocytes, unfavorable.
- Mutated IgVH gene – post germinal center B-lymphocytes, favorable.
- Independent risk factor for all stages at diagnosis.

Targeting of BCR signaling as a therapeutic strategy in CLL. Red symbols and letters indicate .new therapeutics as discussed in the text



Hallek M Hematology 2013;2013:138-150

Inhibitory signaling axes in CLL. Up-regulation of CD200, CD270, CD274, and CD276 induces impaired actin polymerization and immunological synapse formation in CLL T cells



Gribben J G , and Riches J C Hematology 2013;2013:151-157

Treatment

- Alkylating agents (chlorambucil, cyclophosphamide)
- Nucleoside analogs (cladribine, fludarabine)
- Biological response modifiers, immunomodulators
- Monoclonal antibodies – antiCD20, antiCD52, antiCD23, antiCD37 etc.
- Chemoimmunotherapy (CIT)
- Bone marrow transplantation
- Systemic complications requiring therapy
  - antibiotics
  - immunoglobulin
  - steroids
  - blood products

CLL -Treatment

- Rai st. 0-2 or Binet st. A-B ⇒ observe every 3-6 months, treat if disease progress, short doubling time, symptomatic, recurrent infections, ITP, AIHA
- Advanced stage, symptomatic patient needs treatment at diagnosis (5-10% of the patients)
- *High and very high risk early asymptomatic patients should **not** be treated outside of a clinical trial*
- Low and intermediate-low risk symptomatic patients – B symptoms (weight loss, fever, night swetts), progressive lymphadenopathy, fatigue – need treatment

Categories of patients - CLL treatment

- "Go-Go" – fit, functionally independent with no or mild comorbidities and normal life expectancy should receive the most effective treatment – CIT: FCR or investigational alternative BR, FR with aim to prolong PFS and possibly OS
- "Slow Go" – medically less-fit patients – should be recruited into clinical trials. Can receive clorambucil±Rituximab, Bendamustine, clorambucil+ofatumomab or GA101, dose-reduced FCR, Pentostatin+Rituximab±CTX (PR or PCR)
- "No Go" – unfit, with >3 comorbidities, dependent with short life expectancy – palliative treatment only

Cll treatment

- No known defect in TP53, “Go Go” – FCR or clinical trial
- Defective TP53 – no standard of care. CIT provide low RR, rare durable responses. Therapies with TP53-independent action: high dose steroids, Alemtuzumab, combinations FLU-CAM, HD steroids+monoclonal Ab’s, provide short term responses, severe immune suppression.
- Novel agents – BCR pathway inhibitors
- Early Allogeneic transplantation for fit younger patients with a suitable donor

Relapsed/refractory disease

- If response duration > 1 year retreatment with CIT (FCR, etc.)
- Bendamustine + Rituximab
- Ofatumomab
- Investigational combinations
- Novel agents
- Allogeneic SCT – Reduced Intensity Conditioning

Novel drugs for CLL

- Ibrutinib – BTK inhibitor
- Idelalisib – PI3K inhibitor
- Lenalidomide – immune modulator (IMID)
- Alvocidib (flavopiridol) – CDK inhibitor
- Ofatumomab – human anti-CD20 monoclonal Ab
- Veltuzumab – humanized anti-CD20 monoclonal Ab
- HCD-122 – human anti-CD40 monoclonal Ab
- TRU-016 – anti-CD37 IgG fusion protein
- Obatoclax – BCL-2 inhibitor

Novel drugs for CLL

- Fostamatinib – SYK inhibitor
- Everolimus – mTOR inhibitor
- AiX – AKT inhibitor
- PGG β-glucan – Complement receptor 3 agonist
- 17-DMAG – HSP90 inhibitor
- Dasatinib – tyrosine kinase inhibitor
- Plerixafor – CXCL12 inhibitor
- ABT-263/ABT-737 – BCL2 and BCLXL inhibitors
- CAL-101 – PI3K inhibitor

Richter's Syndrome

- In 3-5% the disease undergoes a transformation into aggressive lymphoma - diffuse large cell or immunoblastic, rare Hodgkin lymphoma or T-cell lymphoma
- Severe B-symptoms, increased LDH, progressive lymphadenopathy
- The prognosis is poor, median survival <6 months

Second Malignancies

- Incidence of 8.9% (28% increased risk) of second malignancy
- Most frequent cancers associated with CLL are - skin, lung, gastrointestinal tumors (carcinoma of colon)
- There is no relationship between the course of CLL, it's treatment and the incidence of second cancers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