Chronic Lymphocytic Leukemia Overview

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1 CLL Overview and Classification

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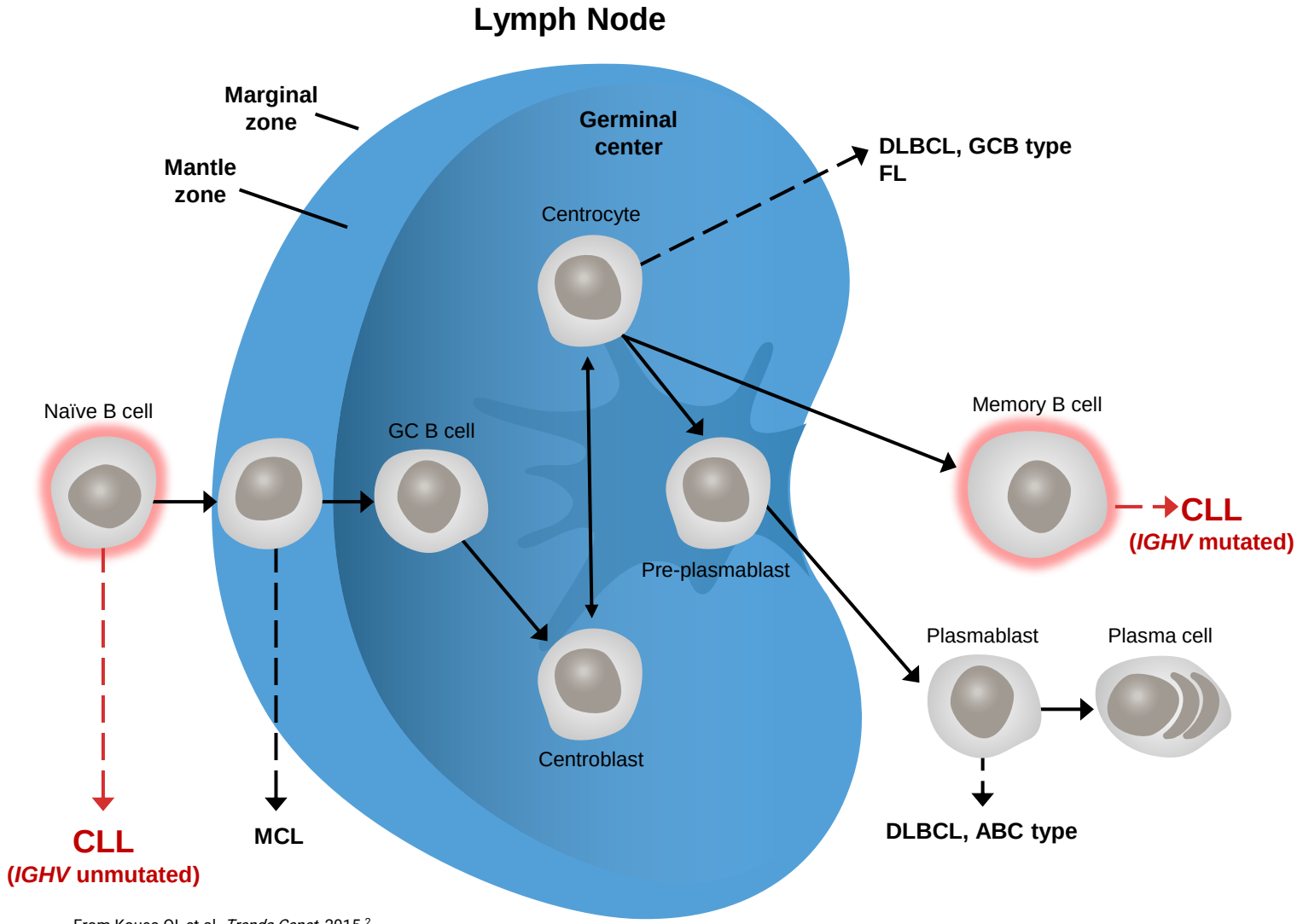
Introduction to CLL

Overview of CLL and Cellular Origins[1-3]

- CLL is a largely indolent lymphoproliferative disease characterized by the proliferation and accumulation of morphologically mature, but immunologically dysfunctional B lymphocytes[1]
- CLL is highly heterogeneous and mutational patterns and gene expression profiles divide CLL into two clinically and pathologically distinct groups corresponding with cellular origins of[2,3]
  - Naïve B cells (no antigen exposure)
  - Post-GC B cells (memory B cell)
- Mutated-*IGHV* CLL is thought to derive from post-GC B cells, whereas unmutated-IGHV CLL is thought to derive from pre-GC naïve B cells or a separate lineage of precursors[3]
- Primary disease sites include peripheral blood, spleen, lymph nodes, and bone marrow[1]



From Koues OI, et al. *Trends Genet.* 2015.[2]

CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; GC=germinal center; NHL=non-Hodgkin lymphoma.

1. Mukkamalla SKR, et al. *StatPearls Publishing;* 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/. 2. Koues OI, et al. *Trends Genet.* 2015 Dec;31(12):*720-731. 3.* Fabbri G, Dalla-Favera R.. *Nat Rev Cancer.* 2016;16(3):145-162.

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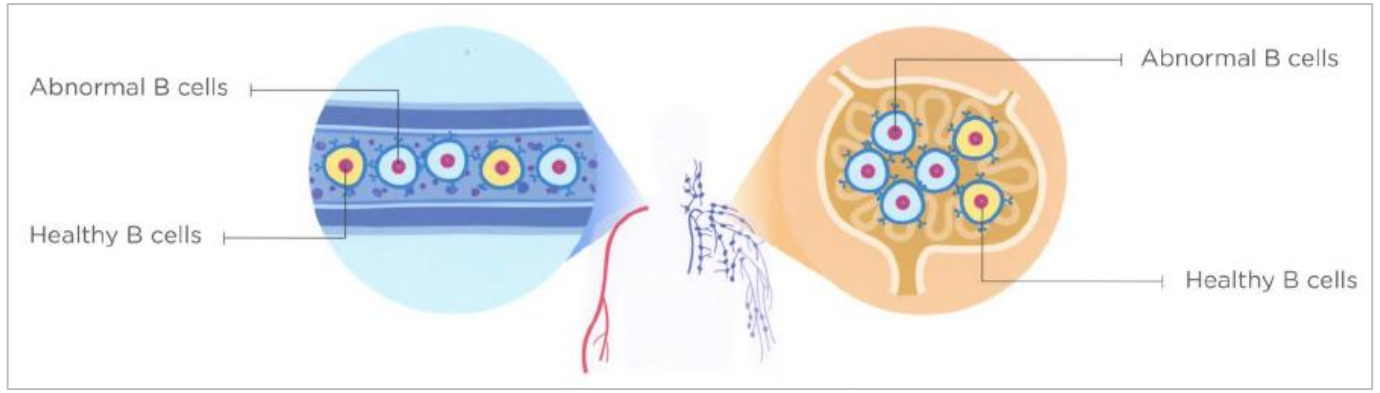
Understanding CLL and SLL

Different Manifestations of the Same Disease

CLL and SLL are denoted as "CLL/SLL" because they are different manifestations of the same disease, both originating from B lymphocytes with identical pathological and immunophenotypic characteristics[1]

In CLL, accumulation predominately in blood, bone marrow

In SLL, accumulation in lymph nodes



- CLL represents the leukemic form in which malformed B lymphocytes accumulate in the **blood and bone marrow**[1,2]
- SLL represents the lymphoproliferative form in which malformed B lymphocytes accumulate in the **lymph nodes**[1,2]

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

1. Mukkamalla SKR, et al. *StatPearls Publishing;* 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/.
2. Lymphoma Action. Accessed September 29, 2022. https://lymphoma-action.org.uk/types-lymphoma/chronic-lymphocytic-leukaemia-cll-and-small-lymphocytic-lymphoma-sll#what-is

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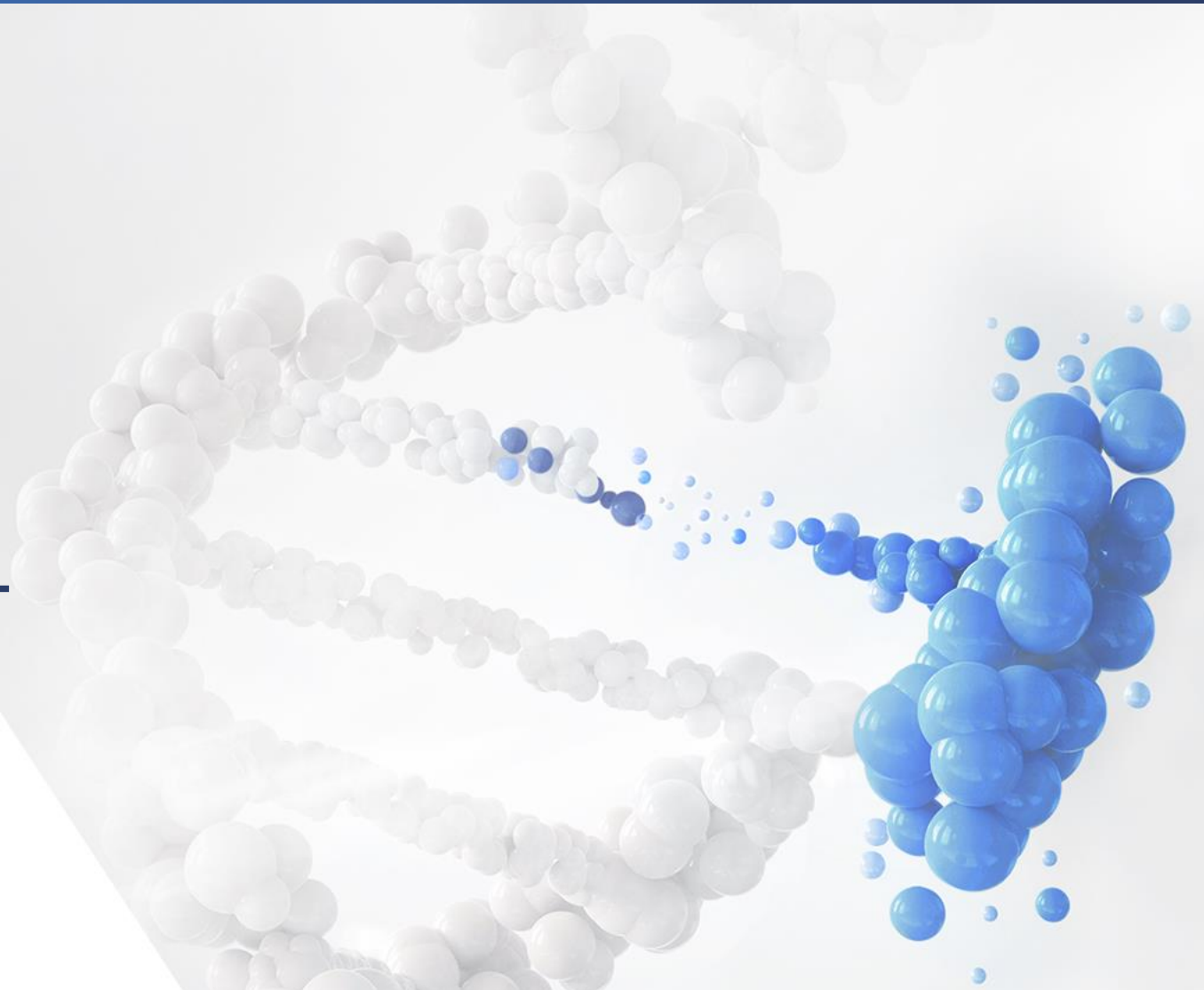
2 Epidemiology of CLL



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CLL Incidence, Prevalence, and Overall Survival

Incidence

Recently reported age-adjusted incidence of 4.7 per 100,000 per year in the US population[1]

- CLL represents 1.1% of all new cancer cases in the US[1]
- Approximately 0.6% of men and women will be diagnosed with CLL at some point during their lifetime[1]

Prevalence

In 2019, there were an estimated 200,766 people living with CLL in the US[1]

Overall Survival and Mortality

While the incidence of CLL has been stable over the last two decades, mortality has been declining[1,2]

- CLL is estimated to cause 4,410 deaths in 2022, representing 0.7% of all cancer deaths
  - From 2016-2020, the CLL mortality rate was 1.1 per 100,000 persons/year
- The 5-year relative survival has steadily increased[2]
  - In 1975, the 5-year relative survival was 65.1%, and it is now 87.9% based on data from 2012-2018[1,2]

Similar epidemiology of CLL has been reported in Europe, while lower incidences have been reported in Asian countries[2]

1. SEER. Cancer Stat Facts: Leukemia – Chronic lymphocytic Leukemia (CLL) Accessed September 30, 2022. https://seer.cancer.gov/statfacts/html/clyl.html 2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705.

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Risk Factors Associated with Development of CLL

Age

The median age at diagnosis is 70 years and incidence has been shown to rapidly increase with age[1,2]

- Only 9.1% of patients with CLL are younger than 45 years[1]
- CLL is extremely rare in children[2]

Gender

CLL is more common in men (1.9:1 male-to-female ratio)[1]

- However, studies have shown that women more commonly have a more aggressive form of CLL than men[2]

Race

The incidence of CLL varies by geographic location and race[2]

- The incidence of CLL is highest among the Caucasian population and Western countries[2]
- East Asians, Asian Indians, and Amerindians have a 5- to 10-fold *lower* age-adjusted incidence rate of CLL compared to persons of predominately European descent[3]

Genetics

CLL has a genetic basis and is known to develop in families[2]

- Age at diagnosis in second-generation offspring is nearly 20 years younger compared to the parent
- First-degree relatives of CLL patients have double the risk for CLL

Other

- Systemic exposure to medical radiation, petroleum, pesticides/chemical fertilizers, metals, and detergents[4]
- Pneumonia[4]
- Tobacco use and cigarette smoke [2]
- Agent Orange or herbicides used during military service (recognized by the Veterans Affairs)[2]

Correlative studies have shown associations between certain risk factors (specific exposures) and CLL-specific chromosomal aberrations[4]

1. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 2. Mukkamalla SKR, et al. *StatPearls Publishing;* 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/ 3. Yang S, Varghese AM, Sood N, et al. *Leukemia.* 2021;35(2):433-439. 4. Karakosta M, et al. *Arch Environ Occup Health.* 2016;71(6):317-329.

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Pathophysiology of CLL

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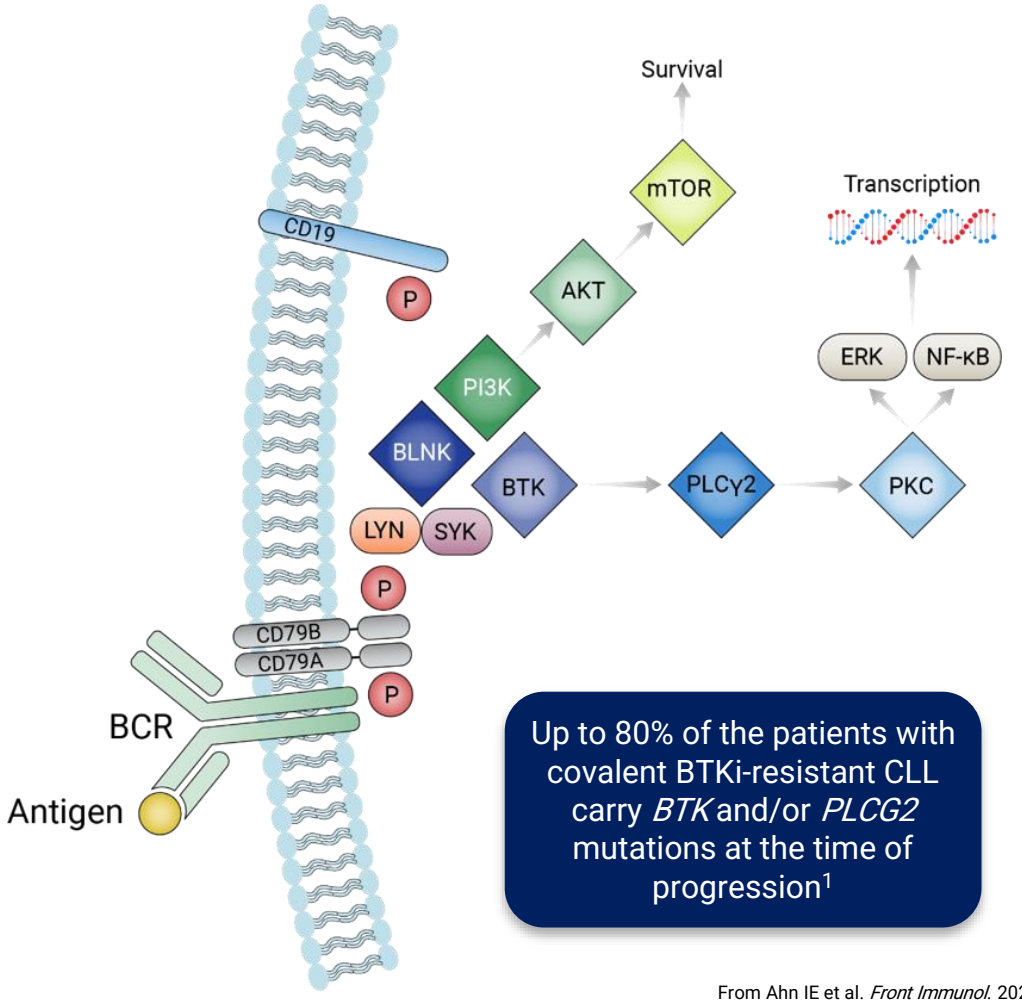
BCR Signaling in the Pathogenesis of CLL

- BCR signaling is an essential component of normal B-cell development as well as malignant B-cell survival[1]
- CLL cell survival is associated with continuous or repetitive BCR signaling[2]
  - Activated BCR signaling is an antigen-dependent process utilizing the canonical NF-kB pathway[1]
  - Antigen binding by surface immunoglobulin initiates BCR signaling, resulting in coupling and autophosphorylation of the CD79A/CD79B heterodimer[1]
  - This recruits a signaling cascade including LYN, SYK, BTK, PLCγ2, and PKC, which lead to activation of NF-κB, PI3K, and ERK[1]
- Acquisition of *BTK* and/or *PLCG2* mutations can occur any time during the disease course, leading to covalent BTKi resistance[1]
  - BTK mutations most commonly substitute the C481 residue with serine, leading to loss of covalent BTKi binding
  - Most PLCG2 mutations affect the N-terminal autoinhibitory SH2 domain



Up to 80% of the patients with covalent BTKi-resistant CLL carry *BTK* and/or *PLCG2* mutations at the time of progression[1]

From Ahn IE et al. *Front Immunol.* 2021.[1]

BCR=B-cell receptor; BTKi=Bruton's tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia; NF-kB, nuclear factor-κB; PI3K=phosphatidylinositol 3-kinase; PLCγ2=phospholipase C γ2; PKC=protein kinase C.

1. Ahn IE, Brown JR. *Front Immunol.* 2021;12:687458. 2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705.

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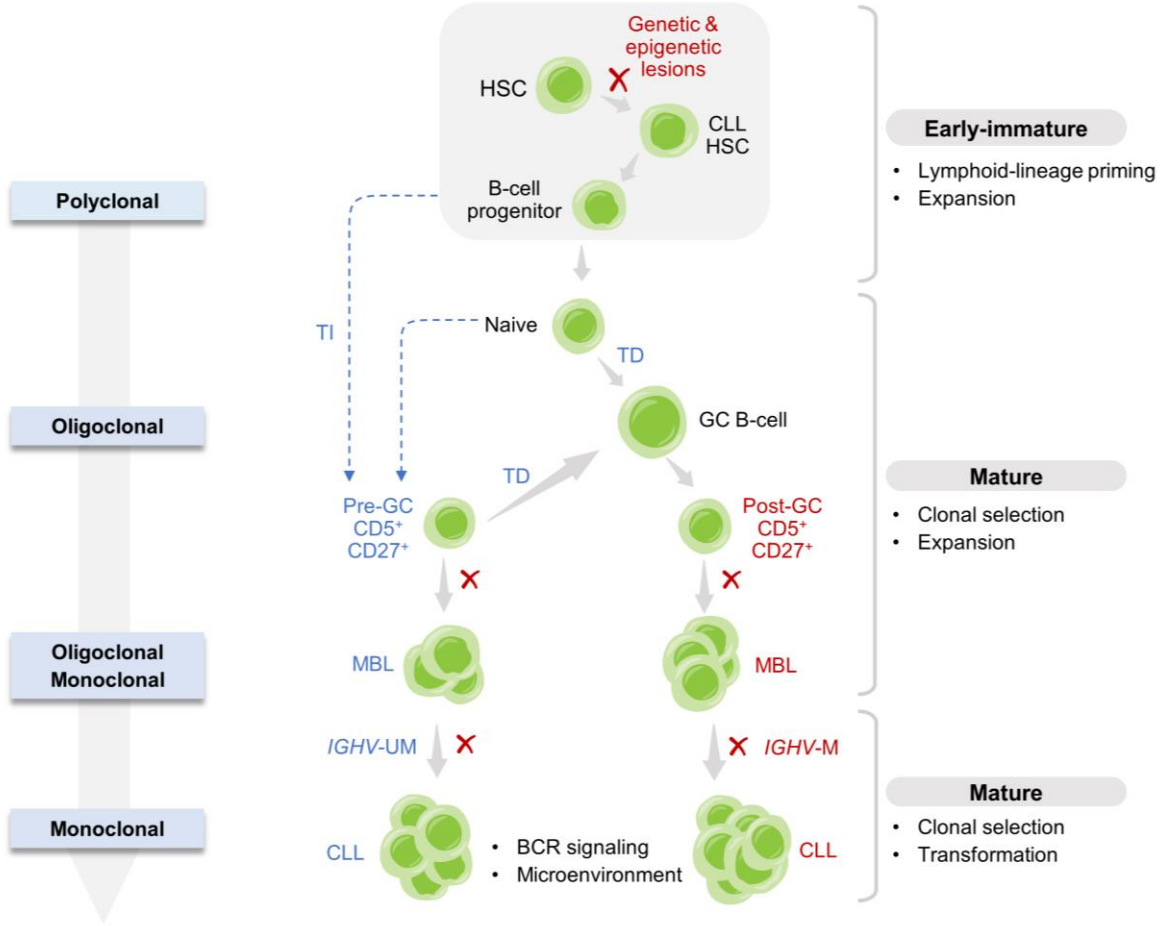
Pathophysiology of CLL

Molecular Pathogenesis in Development and Progression of CLL[1-3]



From Fabbri G, Dalla-Favera R. *Nat Rev Cancer.* 2016.[1]

- CLL may originate from post-germinal center B cells (*IGHV-M*) or pre-germinal center naive B cells (*IGHV-UM*) or a separate lineage of precursor B cells[1]
- The pathogenesis of CLL begins with an asymptomatic precursor state referred to as MBL, defined as the presence of a clonal B-cell population in the peripheral blood[1,2]
  - MBL results from genetic mutations, antigenic stimulation, and cytogenetic abnormalities[2]
- Overt leukemic transformation of these B cells due to either genetic or microenvironmental changes results in progression to CLL[2]
  - MBL progresses to overt CLL at a rate of ~1-2% per year[3]

BCR=B-cell antigen receptor; GC=germinal center; HSC=hematopoietic stem cell; *IGHV*-M=*IGHV* mutated; *IGHV*-UN=*IGHV* unmutated; MBL=monoclonal B-cell lymphocytosis.

1. Fabbri G, Dalla-Favera R. *Nat Rev Cancer.* 2016;16(3):145-162. 2. Mukkamalla SKR, et al. *StatPearls Publishing;* 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/. 3. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705.

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CLL *IGHV* Mutational Status

CLL can be classified into two subgroups based on the presence or absence of mutations in *IGHV* genes which reflect the stage of normal B-cell differentiation from which they originate[1,2]

- *IGHV*-UM CLL arising from naive B cells, is associated with high-risk genetic lesions and a dismal outcome
- *IGHV*-M CLL arising from post-GC B cells, is associated with low-risk genetic lesions and a favorable outcome

The high level of mutations that arise in *IGHV* in the germinal center are part of normal maturation of antibodies and unlike mutations in certain genes, are *not pathological*[2]

IGHV-Unmutated CLL (~40%)	*IGHV-Mutated CLL (~60%)*
• Poor prognosis	• Good prognosis
• Biased slg repertoire	• Biased sig repertoire
• More often stereotyped BCR	• Less frequently stereotyped BCR
• Low-affinity poly- or self-reactive BCR	• Oligo- or – mono-reactive BCR
• High-risk genetic lesions	• Low-risk genetic lesions
• Higher degree of clonal evolution	• Lower degree of clonal evolution

From Fabbri G, Dalla-Favera R. *Nat Rev Cancer.* 2016.[1]

IGHV-M=Ig heavy chain variable region mutated; *IGHV*-UN=Ig heavy chain variable region unmutated; MBL=monoclonal B-cell lymphocytosis.

1. Fabbri G, Dalla-Favera R. *Nat Rev Cancer.* 2016;16(3):145-162. 2. Kipps TJ et al. *Nat Rev Dis Primers.* 2017;3:16096.

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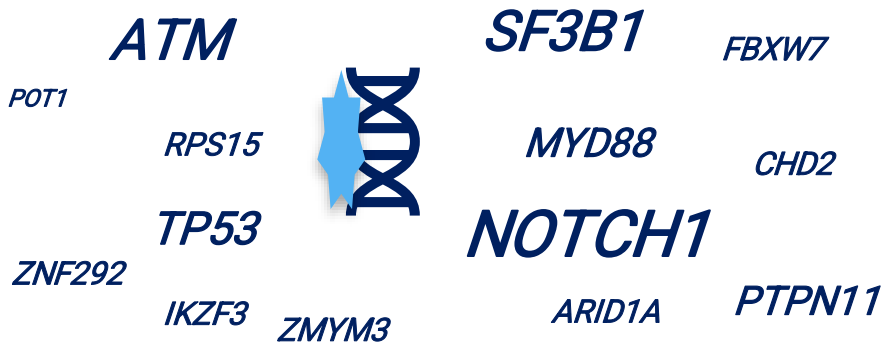
Overview of Chromosomal Abnormalities in CLL

Approximately 80% of patients with CLL carry at least one of four chromosomal alterations: del(13q), del(11q), trisomy 12, or del(17p)

Abnormality	Description	Frequency	Associated Risk
Del(13q)	Deletions of the long arm of chromosome 13; the critical region of del(13q14) contains miRNAs that regulate apoptosis and cell cycle progression	55% of patients with CLL	Isolated del(13q14) is characterized by a benign disease course
Del(11q)	Deletions of the long arm of chromosome 11; frequently encompasses 11q23 which harbors the *ATM* gene	25% of advanced disease[a] 10% of early disease	Typically associated with bulky lymphadenopathy, rapid progression, and reduced OS
Trisomy 12	Three copies of chromosome 12; the genes involved in the pathogenesis of CLL carrying trisomy 12 are largely unknown	10-20% of patients with CLL	Associated with an intermediate prognosis
Del(17p)	Deletions of the short arm of chromosome 17; the 17p13 harbors the *TP53* gene which encodes tumor suppressor protein P53	5-8% of chemotherapy-naïve patients with CLL	Patients with CLL carrying a del(17p) have a poor prognosis and marked resistance to genotoxic chemotherapies

[a] Chemotherapy-naïve disease.

There are also 44 recurrently mutated genes and 11 recurrent somatic copy number variations identified in CLL, involved in RNA processing and export, MYC activity, and MAPK signaling including:



Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705.

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TP53 Aberrations and Cytogenetic Testing in CLL

- *TP53* encodes the tumor suppressor protein p53 which regulates the cell cycle and apoptosis[1]
- Aberrations in *TP53* can arise through deletion of the *TP53* locus on chromosome 17 (17p13.1) or via mutations[1]
- Del(17p) is found in 5–8% of chemotherapy-naïve patients, and more commonly in those with unmutated *IGHV* status[2,3]
  - Del(17p) almost always leads to loss of functional p53 protein, with 80% of patients with del(17p) harboring TP53 mutations on the second allele[1]

Del(17p)/*TP53* mutations lead to increased genomic instability, poor prognosis, and marked resistance to genotoxic chemotherapies[2,3]

CLL=chronic lymphocytic leukemia; del(17p)=deletions of the short arm of chromosome 17.

1. Campo E, et al. *Haematologica.* 2018;103(12):1956-1968. 2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 3. Fabbri G, Dalla-Favera R. *Nat Rev Cancer.* 2016;16(3):145-162. 4. Hallek M, et al. *Blood.* 2018;131(25):2745-2760.

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4

Clinical Presentation and Diagnosis of CLL

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Clinical Presentation and Symptoms of CLL

- CLL is usually asymptomatic and discovered via routine blood tests that reveal abnormal lymphocytosis[1]
- Approximately 5-10% of CLL cases will present with B symptoms such as[1]

Unexplained fevers (>100.5°)

Unintentional weight loss (≥10% of body weight over a period of 6 months or less)

Drenching night sweats with no evidence of infection

- Additional symptoms include:

Early satiety

Extreme fatigue

- Lymphadenopathy is a frequent abnormal physical finding with common sites including cervical, supraclavicular, and axillary lymph nodes (50-90% of cases)[1]
- Additional signs and symptoms include[1]
  - Splenomegaly: 25-55% of cases
  - Hepatomegaly: 15-25% of cases

Extranodal Involvement

- Extranodal involvement may be a manifestation of advanced stage CLL, occurring in 0.3 per 100,000 person-years[2]
- Cutaneous manifestations are relatively common in CLL (25%) and include purpura, infections, non-melanoma skin cancers, vasculitis, and Sweet's syndrome[2,a]
- Less common involvement includes the liver, kidneys, GI tract, CNS, and cardio-pulmonary[1]

[a] Direct seeding of leukemic cells in the skin, is relatively rare in CLL, occurring in around 4% of patients.

1. Mukkamalla SKR, et al. StatPearls Publishing; 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/. 2. Gordon MJ, Ferrajoli A. *Am J Hematol.* 2022;97 Suppl 2:S26-S34.

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Initial Clinical Evaluation of CLL[1-5]

History and Physical Examination

- Measurement of liver, spleen, and palpable lymph nodes
- Assessment of B symptoms and evaluation of performance status
- Additional imaging if extranodal or bulky disease is suspected

Histopathology

- Hematopathology review of peripheral blood smear
- Bone marrow aspiration/biopsy and lymph node biopsy may be done as part of diagnostic workup

Laboratory Tests

- CBC with differential, comprehensive metabolic panel, and LDH
- Uric acid, β2M, and hepatitis testing
- FISH CLL panel to detect +12, del11q, del13q, del17p
- p53 sequencing and IGHV mutation status

Immunophenotyping

- An adequate panel for flow cytometry includes kappa/lambda, CD5, CD10, CD19, CD20 (dim), CD23, and CD200
- Cytospin for cyclin D1 or FISH for t(11;14); t(11q;v) aids in differential diagnosis to exclude other CD5+ B-cell malignancies

Additional Workup

- Quantitative immunoglobulins, reticulocyte count, haptoglobin, or Coombs test

β2M=β2 microglobulin; CBC=complete blood count; FISH=fluorescence in situ hybridization. LDH=lactate dehydrogenase.

1. Hallek M. Am J Hematol. 2019;94(11):1266-1287. 2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 3. Kay NE, et al. *Blood Rev.* 2022;54:100930. 4. Lynch DT, et al. Rotator cuff tendonitis. In: StatPearls. NCBI Bookshelf version. StatPearls Publishing: 2023. Accessed November 28, 2023. https://www.ncbi.nlm.nih.gov/books/NBK536985/. 5. Mukkamalla SKR, et al. StatPearls Publishing; 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/.

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Establishing a Diagnosis of CLL

Diagnosis of CLL is established by blood counts, blood smears, and immunophenotyping of circulating B lymphocytes[1]

Diagnostic Test	Finding Necessary for Establishing a Diagnosis of CLL[1,2]
Complete Blood Count	≥5000 B lymphocytes/μL in the peripheral blood for at least 3 months
Blood Smear	Leukemic cells in blood smear are typically small, mature lymphocytes and have a narrow border of cytoplasm, a dense nucleus without discernible nuclei, and partially aggregated chromatin
Flow Cytometry	Confirms clonality of circulating B lymphocytes; usually positive for CD5 antigen and the B-cell markers, CD23 and CD19; weak expression of surface membrane immunoglobulin (CD20 and CD79b)

FISH with peripheral blood lymphocytes can identify cytogenetic lesions known to influence prognosis and response to treatment and can aid differential diagnosis[3]

1. Hallek M. Am *J Hematol.* 2019;94(11):1266-1287. 2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 3. Hallek M, et al. *Blood.* 2018;131(25):2745-2760.

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Complications of CLL

Complication	Description	Frequency	Risk Factors
Richter's Transformation[1]	Occurrence of an aggressive lymphoma (most commonly DLBCL) in patients with a previous or concomitant diagnosis of CLL	2-10%	Bulky lymphadenopathy, hepato-splenomegaly, advanced stage disease, elevated β2M, and genetic aberrations (eg, del(17p), unmutated *IGHV*)
Autoimmune Cytopenias[2]	Immune-mediated destruction of immune cells including lymphocytes, red blood cells, and platelets	AIHA: 5-10% ITP: 1-5% PRCA: <1%	Hypogammaglobulinemia can exacerbate AIHA and ITP
Tumor Flare Reactions[3]	Manifests painful enlargement of the lymph nodes, sometimes accompanied by an elevated lymphocyte count, enlarged spleen, low-grade fever, rashes, and bone pain	Ranges from 28-58%	Associated with the use of several anti-cancer drugs including immunomodulatory agents and immune checkpoint inhibitors
Tumor Lysis Syndrome[4]	Acute, life-threatening disorder as a result of massive release of intracellular components into circulation from cytoreductive therapy	Not well defined	Bulky disease and malignancies highly sensitive to cytoreductive therapy; high LDH
Infection[5]	Symptomatic CLL and/or CLL treatment increases susceptibility to infection	Variable	Hypogammaglobulinemia; CLL treatments such as chemoimmunotherapy

AIHA=autoimmune hemolytic anemia; B2M=beta-2 microglobulin; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B cell lymphoma; ITP=immune thrombocytopenia; LDH=lactate dehydrogenase; PRCA=pure red cell aplasia.

1. Tadmor T, Levy I. *Cancers (Basel)*. 2021;13(20):5141. 2. Gordon MJ, Ferrajoli A.. *Am J Hematol*. 2022;97 Suppl 2:S26-S34. 3. Taleb B A.*Anticancer Drugs*. 2019;30(9):953-958. 4. Williams SM, Killeen AA. *Arch Pathol Lab Med*. 2019;143(3):386-393. 5. Mukkamalla SKR, et al. StatPearls Publishing; 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/.

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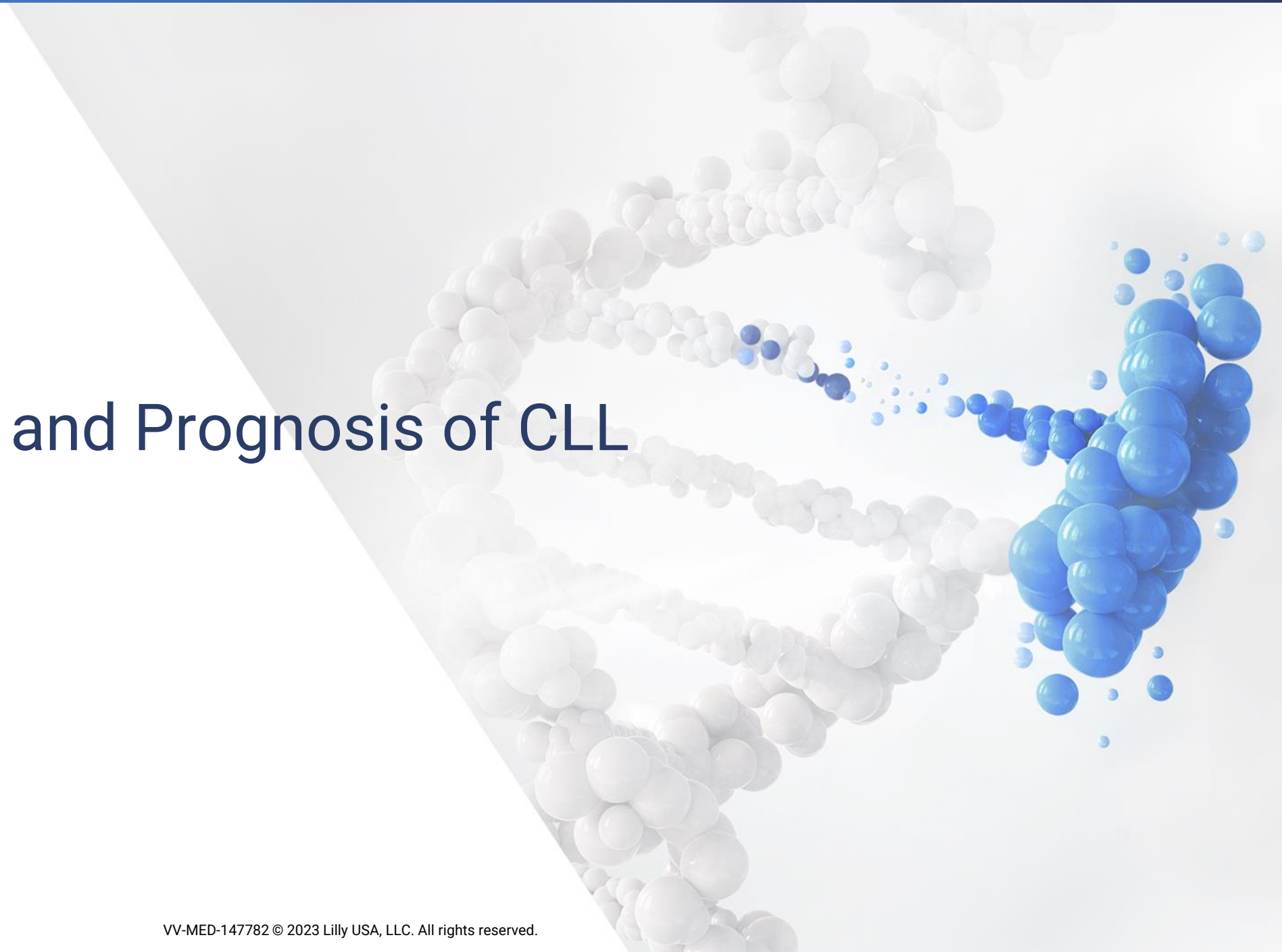
5

Staging and Prognosis of CLL



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Clinical Staging Systems for CLL

The Rai system and the Binet system have become the backbone of prognostication in both clinical practice and clinical trials relying on physician examination and standard lab tests[1,2,a]

Binet System (Primarily Europe)[1]	
Stage	**Characteristics**
A	<3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia
B	≥3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia
C	Anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/μL) are present, with any number of enlarged areas

Rai System (Primarily United States)[2]	
Stage/Risk	**Characteristics**
0 (Low)	Lymphocytosis, lymphocytes in blood >5 x 10^9/L clonal B cells and/or >40% lymphocytes in the bone marrow
I (Intermediate)	Lymphocytosis with enlarged node(s)
II (Intermediate)	Lymphocytosis with splenomegaly, hepatomegaly, or both
III (High)	Lymphocytosis with anemia (hemoglobin <11.0 g/dL or hematocrit <33%)
IV (High)	Lymphocytosis with thrombocytopenia (platelets <100,000/uL)

[a]The Lugano Modification of the Ann Arbor Staging System is used for SLL staging.[3]

1. Eichhorst B, et al. Ann Oncol. 2021;32(1):23-33. 2. Leukemia &Lymphoma Society. Chronic lymphocytic leukemia. Accessed March 30, 2023. https://www.lls.org/sites/default/files/file_assets/PS34_CLL_Booklet_2019_FINAL.pdf.
3. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.

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CLL International Prognostic Index

CLL-IPI Risk Group Criteria and Scoring[1]

Criteria	Scoring Basis	Points
Age	≤65 years	0
	>65 years	1
Clinical stage	Binet A or Rai 0	0
	Binet B-C or Rai I-IV	1
Serum β2M (mg/L or μ/mL)	≤3.5	0
	>3.5	2
IGHV mutational status	Mutated	0
	Unmutated	2
TP53 status	No abnormality	0
	Deletion 17p (FISH) and/or *TP53* mutation (sequencing)	4

5-year Survival by CLL-IPI Risk Group[1,2]

CLL-IPI Score	Risk	5-Year Survival
0-1	Low	93.2%
2-3	Intermediate	79.3%
4-6	High	63.3%
7-10	Very high	23.3%

CLL-IPI provides additional prognostic information regarding overall survival compared with conventional clinical staging[1]

The CLL-IPI combines genetic, biochemical, and clinical parameters into a prognostic model that categorizes patients into four subgroups: low, intermediate, high, and very high risk each with different survival at 5 years [1,2]

CLL-IPI=international prognostic index for chronic lymphocytic leukaemia; FISH=fluorescence in situ hybridization.

1. International CLL-IPI Working Group. *Lancet Oncol.* 2016;17(6):779-790. 2. Hallek M, Al-Sawaf O. Am J Hematol. 2021;96(12):1679-1705.

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Prognostic Biomarkers for CLL

Genetic Marker[1,2]	Frequency[1-3]	Importance[1,2]
Del(13q)	• **55%** of patients with CLL have **13q** deletion	• Solitary **deletion of 13q** linked with historically **favorable prognosis** • **Most common** cytogenetic abnormality in CLL
Trisomy 12	• **16%** of patients with CLL have **trisomy 12**	• Associated with intermediate-risk CLL if appearing alone • **Associated with higher-risk CLL if appearing in conjunction with other abnormalities**
Del(17p)	• **1 in 10** patients with CLL have the **17p** deletion • **Up to 30%** in R/R cases	• Critical *TP53* gene in the region is deleted • Poor response and rapid disease progression • **Does not respond well to chemotherapy or chemoimmunotherapy**
Del(11q)	• **1 in 5** patients with CLL have **11q** deletion	• Often associated with extensive lymph node involvement • Implies clinically progressive disease • Prognosis significantly improved with **chemoimmunotherapy**
Unmutated *IGHV*	• Nearly **40%** of patients with CLL have unmutated *IGHV*	• **Stable marker** (does not tend to change over time), should only need to be checked once • Linked to more **aggressive disease** • **More likely to benefit from newer agents**
Altered *TP53*	• **80%** of patients with CLL and del(17p) carry a *TP53* mutation	• **Gatekeeper** that protects cell DNA from damage • Associated with **poor prognosis** • Resistance to traditional therapy; newer therapies are used to treat patients with del(17p) or *TP53* mutation

CLL=chronic lymphocytic leukemia; del=deletion; FISH= fluorescence in situ hybridization; IGHV=immunoglobulin heavy chain gene; R/R= relapsed/refractory; TP53= tumor protein p53.

1. https://www.lls.org/sites/default/files/file_assets/PS34_CLL_Booklet_2019_FINAL.pdf (Accessed March 30, 2023). 2. Yun X et al. *Biomark Res.* 2020; 8:40. 3. Campo E, et al. *Haematologica.* 2018;103(12):1956-1968.

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Chronic Lymphocytic Leukemia Overview

- CLL is a largely indolent, heterogenous, lymphoproliferative disease characterized by the proliferation and accumulation of morphologically mature, but immunologically dysfunctional B lymphocytes[1,2,3]
- BCR signaling is an essential component of normal B-cell development and CLL cell survival is associated with continuous or repetitive BCR signaling[4,5]
- Diagnosis of CLL is established by blood counts, blood smears, and immunophenotyping of circulating B lymphocytes[6]
  - FISH with peripheral blood lymphocytes can identify cytogenetic lesions known to influence prognosis and response to treatment and can aid differential diagnosis[7]
  - Approximately 80% of patients with CLL carry at least one of four chromosomal alterations: del(13q), del(11q), trisomy 12, or del(17p)[5]
- CLL-IPI provides additional prognostic information regarding overall survival compared with conventional clinical staging[8]

CLL=chronic lymphocytic leukemia; BCR=B-cell receptor; FISH=fluorescence in situ hybridization; CLL-IPI=international prognostic index for chronic lymphocytic leukemia

1. Mukkamalla SKR, et al. *StatPearls Publishing;* 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/. 2. Koues OI, et al. *Trends Genet.* 2015 Dec;31(12):*720-731.*
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LOXO@Lilly