APSHO Regional Lecture Series

Accredited Educational Activities for Advanced Practitioners in Oncology

Collaborative Practice in the Management of Patients With Cancer

Management of Newly Diagnosed Chronic Lymphocytic Leukemia Patients

Program Chair

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Disclosures

Faculty

Ms. Kurtin has served as consultant for Amgen, BMS, Celgene, Genentech, Incyte, Janssen, Novartis, Takeda, and Pharmacyclics.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

Learning Objectives

- Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease-specific attributes
- Manage toxicities associated with newer agents used to treat CLL
- Describe the role of oral therapies in treating patients with CLL

CHRONIC LYMPHOCYTIC LEUKEMIA OVERVIEW

CLL Epidemiology

New Cases (US 2016)	Deaths (US 2016)	Mean Age at Diagnosis	5-yr Overall Survival 2016
18,960	4,660	71 yr	82.6%

Risk factors

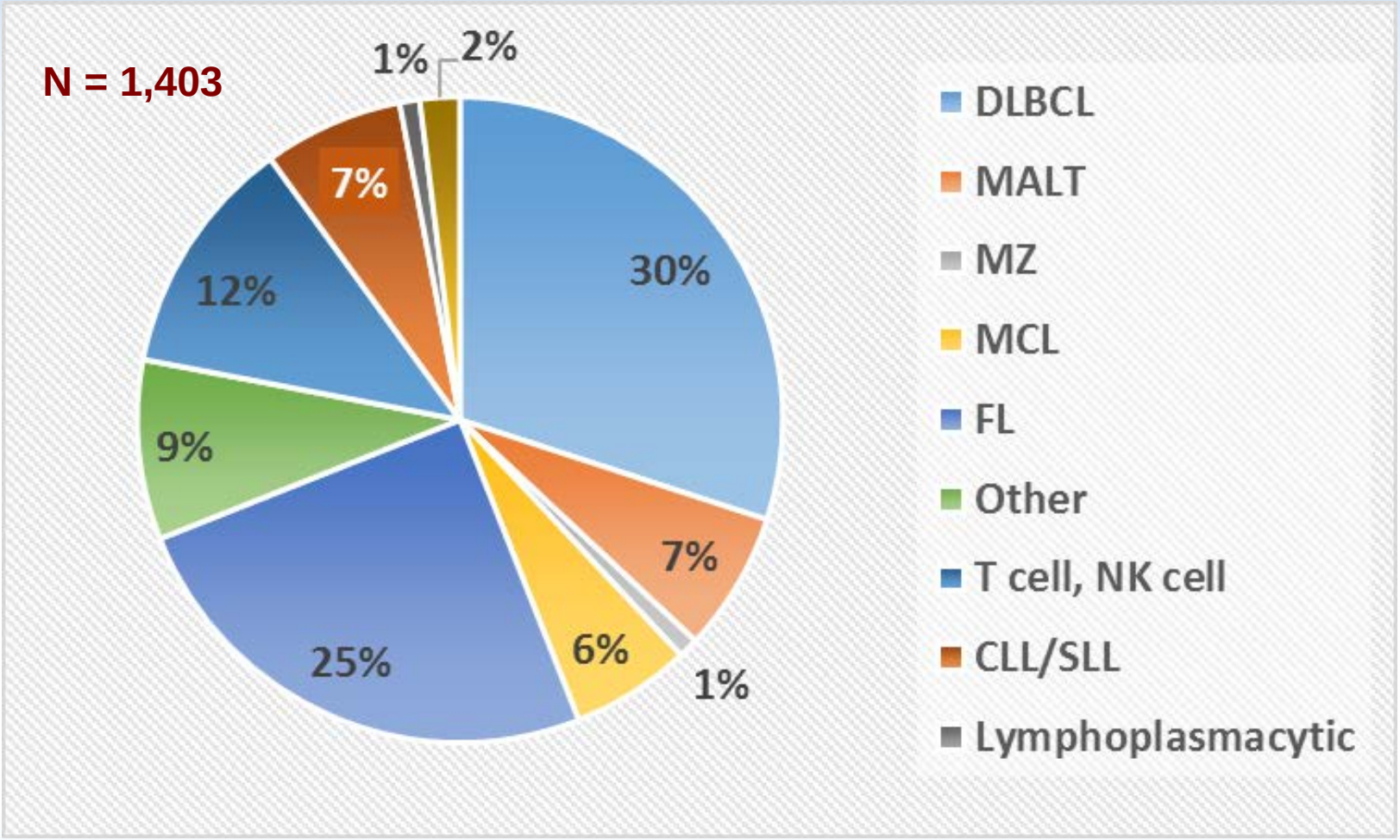
- Age: CLL is extremely rare < 20 years of age
- White > Black >>> Asian
- Monoclonal B-cell lymphocytosis with elevated absolute lymphocyte count
- Rare familial cases
- No association with environmental or external factors, although association with Agent Orange exposure

Survival

- 5-year relative survival rate has increased from 67.5% (1975-1977) to 81.7% (2005-2011)
- Deaths associated with CLL are highest in patients aged 75-84
- Variable response to treatment and variation in survival
- Absolute survival has increased during past 2 decades

http://seer.cancer.gov/statfacts/html/clyl.html;
http://www.publichealth.va.gov/exposures/agentorange/

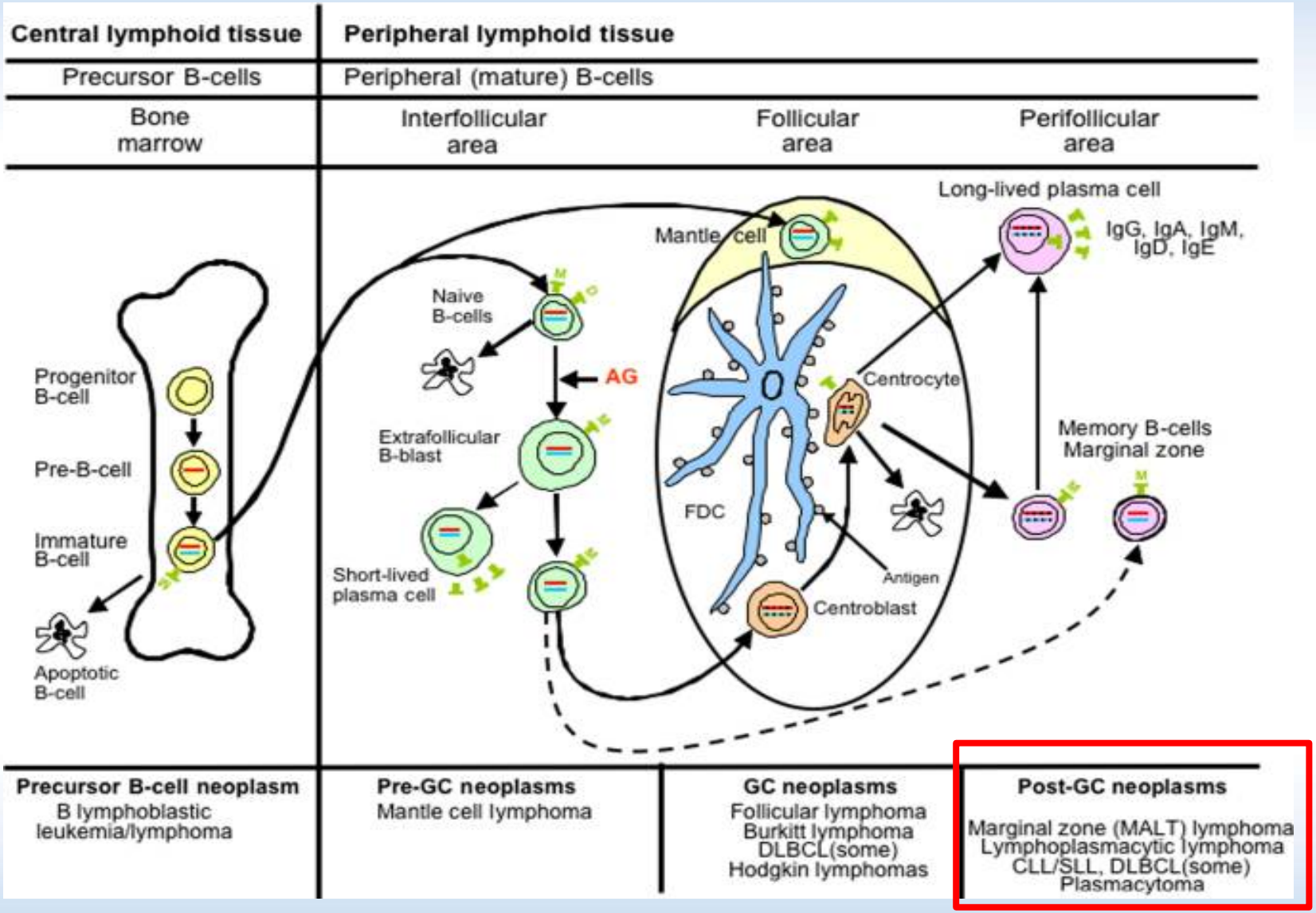
NHL Subtypes



DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; SLL = small lymphocytic lymphoma.

Kipps TJ & Wang HY. Chapter 92. Classification of malignant lymphoid disorders. In: Lichtman M, Beutler E, Kaushansky K, eds. *Williams Hematology*. 7th ed. New York, NY: McGraw Hill. 2006;1408.

Where Do B-Cell Lymphomas Originate?



CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MALT = mucosa-associated lymphoid tissue.

Jaffe E, et al., *Blood* 2008;112:4384-4399

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Clinical Behavior of NHL Subtypes

Indolent

- **CLL/SLL**
- Lymphoplasmacytic/ WM
- MZL
- Follicle center lymphoma, follicular, grade 1/2
- Most are incurable
- Goal is control and minimize symptoms

Aggressive

- MCL
- Follicle center lymphoma, follicular, grade 3
- DLBCL
- Primary mediastinal large B-cell lymphoma
- Require immediate therapy
- Variable treatment goals
- Cure rates vary

Very Aggressive

- Precursor B-lymphoblastic lymphoma/leukemia
- B-cell acute leukemia
- Therapy undertaken with curative intent
- Cure rates vary

WM = Waldenström's macroglobulinemia.

Ansell SM & Armitage J (2005). *Mayo Clin Proc* 80(8);1087-1097.

Presenting Signs and Symptoms

- Incidental finding in 70%–80% of cases
  - Up from 30%–40% in the 1970s
- Signs and symptoms
  - Fatigue/malaise
  - Dyspnea on exertion
  - Lymphadenopathy
  - LUQ discomfort/early satiety
  - Infection
  - B symptoms uncommon (15%)

LUQ = left upper quadrant.

Byrd JC & Flynn JM (2013). Chronic lymphocytic leukemia, in *Abeloff's Clinical Oncology*, Fifth Edition. J Niederhuber et al. (Eds.) Churchill Livingstone, an imprint of Elsevier Inc.,

General Diagnostic Workup for Lymphoma

- History and physical
  - Physical exam
    - Particular attention to node-bearing areas, including Waldeyer's ring, hepatomegaly, splenomegaly, abdominal masses, skin nodules
    - Presence of distal swelling or lymphedema
  - Performance status: Fit vs frail
  - B symptoms
- Laboratory analysis
- Tissue biopsy
- Bone marrow biopsy and aspirate
- Imaging studies for completion of staging in patients with bulky adenopathy

Byrd JC & Flynn JM (2013). Chronic lymphocytic leukemia, in *Abeloff's Clinical Oncology*, Fifth Edition. J Niederhuber et al. (Eds.) Churchill Livingstone, an imprint of Elsevier Inc.; NCCN, 2012b

Diagnostic Evaluation: Blood and Marrow

Diagnostic Study	Clinical Significance
CBC + differential + platelets reticulocyte count	Evaluate presence of cytopenias, lymphocytosis, morphological abnormalities, and bone marrow response to anemia
LDH, haptoglobin, coombs, and reticulocyte count	Evaluate for underlying hemolysis, particularly important in CLL
LDH	Necessary for risk stratification, risk for TLS, and hemolysis ULN may vary by institution
Serum β_2m	Prognostic relevance, reflects WBC membrane turnover Levels are affected by renal function
Renal and hepatic profiles	Dose modification may be required for elevated bilirubin levels or CRI
Hepatitis B testing if CD20 MoAb	Surface antigen and core antibody for patients with no risk factors Add e-antigen and if history of hepatitis B Check viral load and consult with gastroenterology if positive

Kurtin S. Leukemia and myelodysplatic syndromes, in Gobel BH, Yarbro C, Wujcik D, Eds. *Cancer Nursing, Principles and Practice*, 7th Ed, 2010. Updated for 8th Ed, currently in production.
NCCN Guidelines Version 2.2016 CLL/SLL

Diagnostic Evaluation: Blood and Marrow

Diagnostic Study	Clinical Significance
Morphology	Review of cytology using low-power microscope to define basic architecture of the lymphatic tissue
Immunohistochemistry	Excisional biopsy of adenopathy is the standard for initial diagnosis of NHL (fine needle aspirates are inadequate) Used to isolate cellular proteins which correlate with phases of B-cell differentiation
Flow cytometry	Immunophenotyping used to describe antigen expression on B-cells using peripheral blood and bone marrow Flow cytometry or immunohistochemistry for CD38 and/or ZAP-70 expression
Molecular testing	Molecular genetic analysis to establish IgV_h mutational status
Cytogenetics and fluorescent in situ hybridization (FISH)	Cytogenetics or FISH to detect: t(11;14), deletions of chromosomes 11q, 13q, 17p, or trisomy 12

Kurtin S. Leukemia and myelodysplatic syndromes, in Gobel BH, Yarbro C, Wujcik D, Eds. *Cancer Nursing, Principles and Practice*, 7th Ed, 2010. Updated for 8th Ed, currently in production.

Diagnostic Evaluation: Blood and Marrow

Diagnostic Study	Clinical Significance
Aspirate Should include spicules and be cellular enough to assess at least 500 cells	– Evaluation of morphologic abnormalities of hematopoietic precursors to allow WHO classification – Used for flow cytometry, FISH analysis, and cytogenetics
Biopsy Should be of adequate size for evaluation (1–2 cm)	Evaluate cellularity, topography, presence of lymphocytic infiltrates, exclusion of other bone marrow disorders or infiltration by solid tumors
Cytogenetics	– Evaluate for possible non-random chromosomal abnormalities – Based on evaluation of 20 metaphases – Greater than 2 metaphases is considered non-random
Molecular testing	Newer molecular profiling has identified key prognostic markers as well as potential targets for new therapies

FISH = fluorescent in situ hybridization.

Kurtin S. Leukemia and myelodysplatic syndromes, in Gobel BH, Yarbro C, Wujcik D, Eds. *Cancer Nursing, Principles and Practice*, 7th Ed, 2010. Updated for 8th Ed, currently in production.

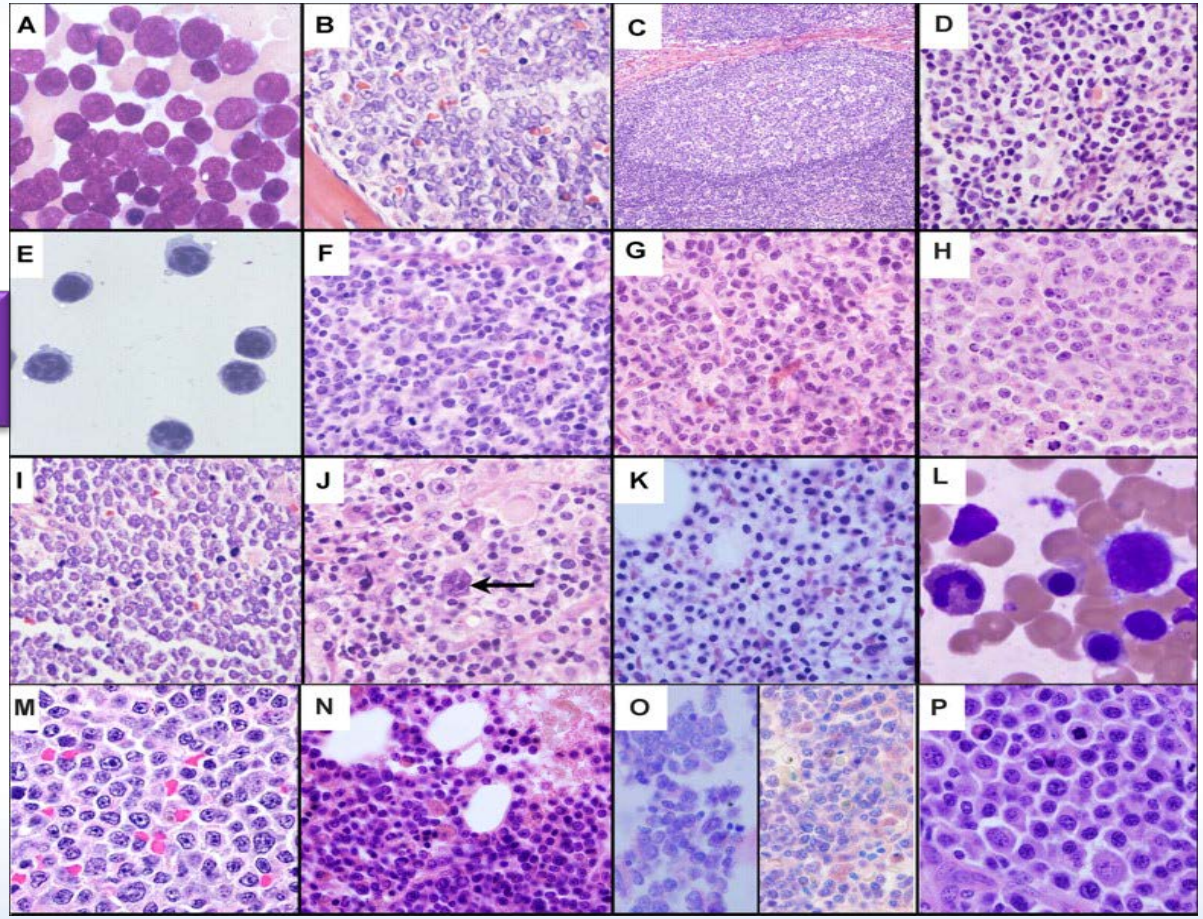
Immunohistochemistry: Unraveling the Patchwork of B-Cell Malignancies

Normal LN With Germinal Center and Surrounding MZL (C) Normal Germinal Center (F)

MCL (D)

ALL – Peripheral Blood (A) and BM (B)

Growth Pattern May Be Diffuse, Nodular, or Blastoid



FL (G)

CLL in Peripheral Blood (E)

DLBCL (H)

Hodgkin Disease (J)

HCL in Peripheral Blood (L) and BM (K)

BL (I)

MZL (M)

PL (P)

WM (N) **MM (O)**

ALL = acute lymphoblastic leukemia; HCL = hairy cell leukemia; PL = plasmablastic lymphoma; MM = multiple myeloma.

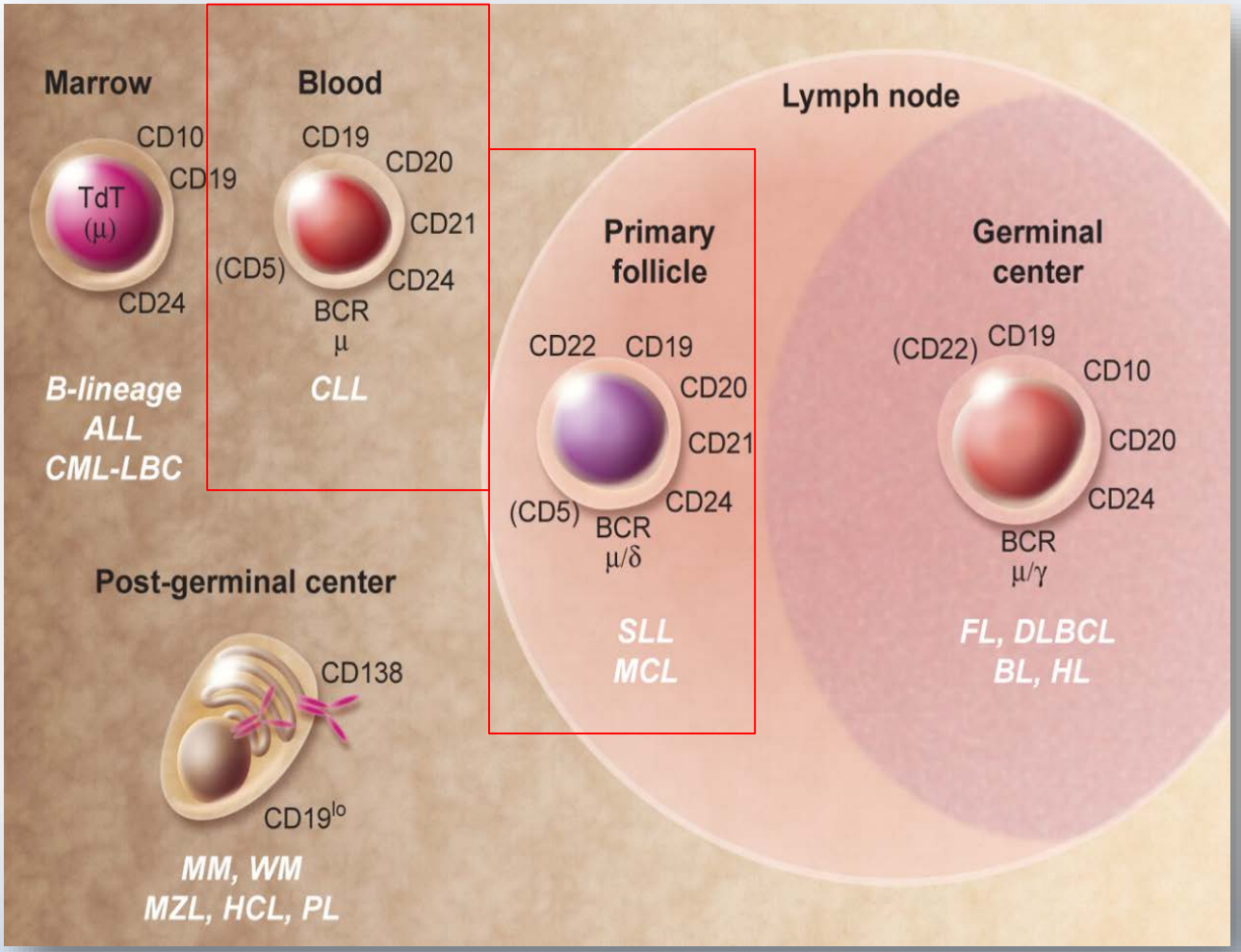
Lebien T & Tedder T (2008). *Blood*. 2008;112:157-580

Flow Cytometry: The Zip Code for Primary Cell Type of B-Cell Neoplasms

CLL/SLL Immunophenotyping

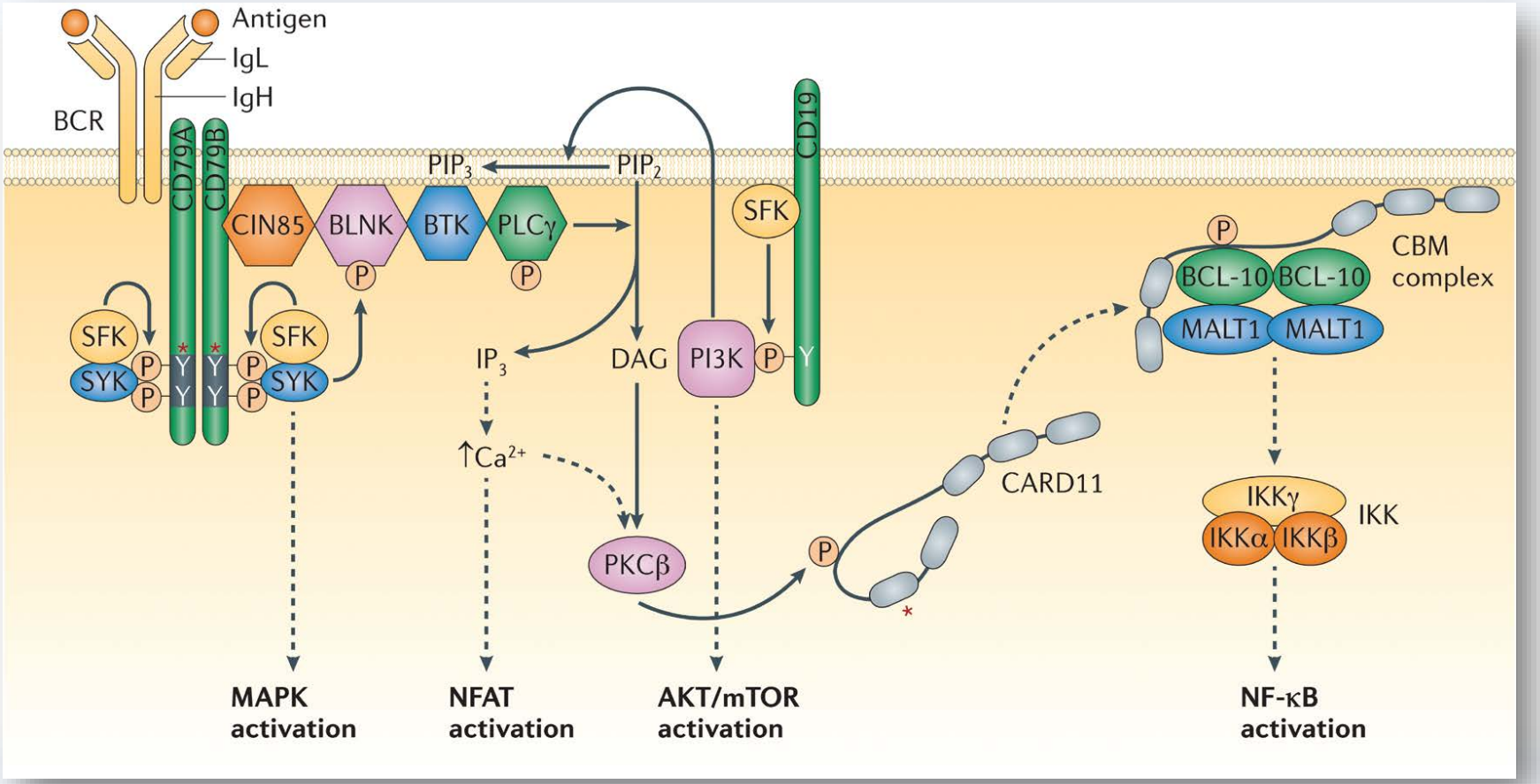
- CD19+
- CD20+
- CD5+
- CD23+
- Surface immunoglobulin (sIg)-positive cells

CLL = Blood
SLL = Nodal



Lebien T & Tedder T (2008). *Blood*. 2008;112:157-580

B-Cell Receptor Signaling



Young RM & Staudt LM (2013). *Nat Rev Drug Discov* 12:229-243

Clinical Characteristics of Monoclonal B-Cell Lymphocytosis (MBL), Chronic Lymphocytic Leukemia (CLL), and Small Lymphocytic Leukemia (SLL)

	MBL	CLL	SLL
Clonal B cells > 5×10^9/L	No	Yes	No
Lymph nodes > 1.5 cm	No	Yes/No	Yes
Enlarged spleen/liver	No	Yes/No	Yes/No
Anemia	No	Yes/No	Yes/No
Thrombocytopenia	No	Yes/No	Yes/No
Bone marrow involvement ≥ 30%	Yes/No	Yes	No
Molecular prognostic factors predictive of outcome	No	Yes	Yes
Higher risk of infection	No	Yes	Yes
Higher risk of autoimmune problems	No	Yes	Yes

Rawstron , A. C., et al. (2008). *N Engl J Med* 359(6):575-583; Byrd JC & Flynn JM. Chronic Lymphocytic Leukemia, in Abeloff's Clinical Oncology, Fifth Ed, 2013. Churchill Livingstone, an imprint of Elsevier Inc.

Clinical Staging Predicts Outcome

Staging system		Clinical features	Median survival
Rai stage	**0** (low risk)	Lymphocytosis in blood and marrow only	>150 mo (12.5 yr)
	I and II (intermediate risk)	Lymphadenopathy, splenomegaly ± hepatomegaly	71-101 mo (5.9-8.4yr)
	III and IV (high risk)	Anemia (Hb < 11.0 g/dL) thrombocytopenia (Plt < 100 × 10^9/L) ± Lymphadenopathy and Splenomegaly	19 mo
Binet group	**A**	Lymphocytosis < 3 areas of lymphadenopathy; no anemia or thrombocytopenia	Similar to age matched controls
	B	Lymphocytosis ≥ 3 areas of lymphadenopathy; no anemia or thrombocytopenia	7 yr
	C	Lymphocytosis Anemia (Hb < 10 g/dL) or thrombocytopenia (Plt < 100 × 10^9/L) ± ≥ 3 areas of lymphadenopathy	2 yr

Rai KR, et al. (1975) *Blood* 46:219-234;
Binet J, et al. (1981) *Cancer* 148:198-206

CLL International Prognostic Index

Prognostic Factor	Results	Points
FISH	Del17p/TP53 mutation	4
Serum β2	>3.5 mg/dL	2
Rai Stage	I-IV	1
IGHV	Unmutated	2
Age, years	>65	1

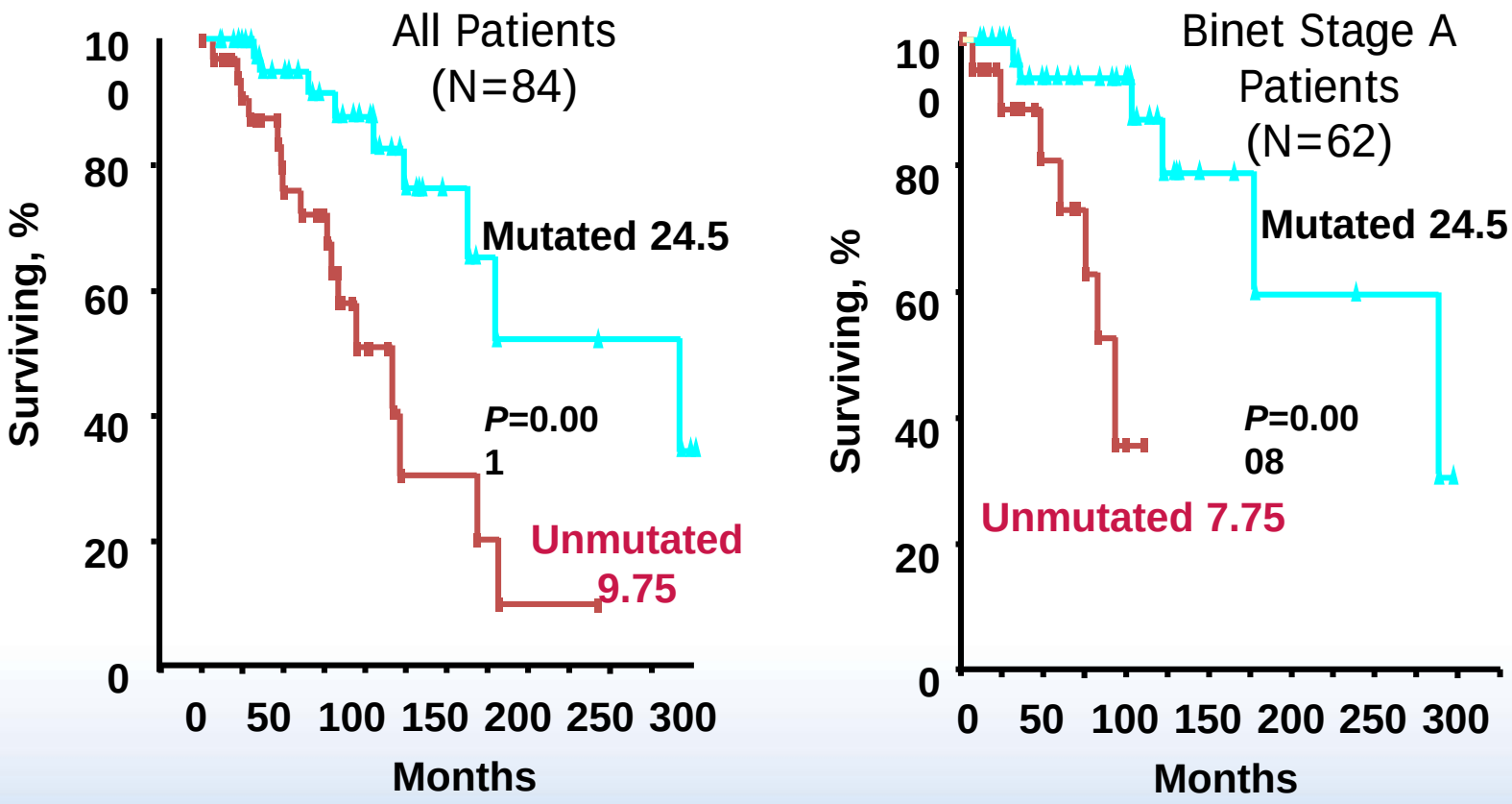
Risk Category	Composite Risk Score	5-year OS
Minimal risk	0-1	93%
Low risk	2-3	79%
Intermediate risk	4-6	64%
High risk	7-10	23%

(Parikh and Shanafelt 2016)

Prognosis Is Also Influenced by Cellular, Genetic, and Non-Disease Factors

Prognostic Factors		Parameter
Clinical	Evaluation	Staging (Rai or Binet) Response to prior therapy (CR/PR or no response)
	Serum Markers	β_2 microglobulin Thymidine kinase
	Investigations	Lymphocyte doubling time
Cellular	Chromosomal aberrations	**del17p** **del11q**
	Mutations	**IGV_h gene mutation status** **TP53 mutation**
	Protein expression	CD38 ZAP-70[1]
Patient-specific	Demographics	**Age** Gender
	Health status	**Fit vs. Frail** **Comorbidities**

CLL Prognostic Markers
Mutated vs. Unmutated IgV_H Genes



Overall Survival

Hamblin TJ, et al. (1999) *Blood* 94:1848-1854.

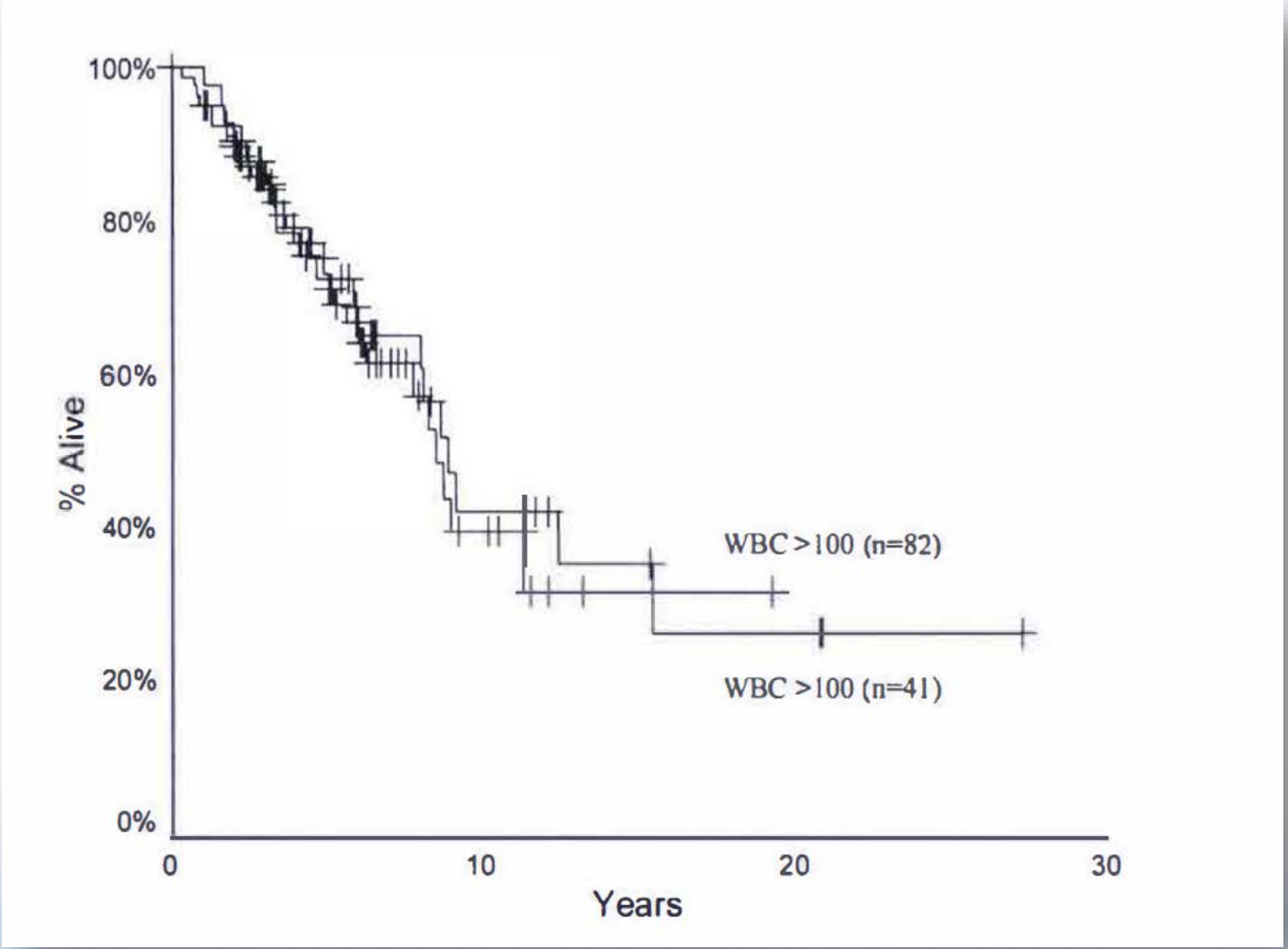
Genomic Alterations in CLL

Alteration	Risk (with sole abnormality)	Median Survival	Median TFS
13q deletion	Favorable	133 mo (11 yr)	92 mo (7.6 yr)
Normal	Neutral	111 mo (9.25 yr)	49 mo (4.1 yr)
Trisomy 12	Neutral	114 mo (9.5 yr)	33 mo (2.75 yr)
11q deletion	Unfavorable	79 mo (6.5 yr)	13 mo
17p deletion	Unfavorable	32 mo (2.6 yr)	9 mo

TFS = treatment-free survival

Cramer P, Hallek M (2011). *Nat Rev Clin Oncol* 8(1):38-47

Elevated WBC Alone Is Not a Significant Adverse Prognostic Factor



Silverman JA, et al. (2002) *Leuk Lymphoma* 43(6):1245-1251

Clinical Management of Newly Diagnosed CLL

To Treat or Not to Treat CLL

1. The clinical stage of the disease
2. The symptoms of the patient
3. The fitness of the patient
4. The genetic risk of the leukemia
5. The treatment situation (first vs second line, response vs non-response of the last treatment)

Hallek, M. (2015). *Am J Hematol* 90(5):446-460.

Case Study 1: Newly Diagnosed CLL/SLL

- 79-year-old female presenting with a left chest wall mass, progressive fatigue and a 10-pound weight loss over the past 4 months (BMI 18.65)
  - Biopsy shows CLL/SLL by immunohistochemistry
- She is a widow and lives alone, works as a tour guide in an art museum
- She has developed drenching night sweats and has had a 10% weight loss over the last 6 months
- PMH: hypothyroidism
- Peripheral blood flow cytometry:
  - Positive for CD19, CD20, CD23, BCL

    Note: typical CLL is CD5+

Case Study 1: Newly Diagnosed CLL/SLL (cont)

- Bone marrow biopsy confirms the diagnosis of CLL/SLL with 85% involvement; no 11q or 17p
- Physical exam shows peripheral adenopathy with the largest node measuring 3 x 2.5 cm
- CT chest, abdomen and pelvis shows multistation adenopathy with the largest nodal conglomerate measuring 5.6 x 3.5 cm in the gastrohepatic region, no organomegaly
- Peripheral blood shows a WBC 7.4 x 10 mm^3 with 65% lymphs, Hgb of 12.4/dL, platelets of 120,000

Does this patient require treatment?

Indications for Therapy Include the Extent and Severity of Disease Manifestations

Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (e.g., night sweats, fever without infection, severe fatigue, unintentional weight loss)
Tumor burden	• Massive nodes (i.e.,10 cm in longest diameter) or progressive or symptomatic lymphadenopathy • Massive (i.e., 6 cm below the left costal margin) or progressive or symptomatic splenomegaly • Progressive lymphocytosis with an increase of >50% over a 2-month period • Lymphocyte doubling time < 6 mo (if ALC > 30 x 10^9/L) • Threatened end-organ function (e.g., enlarged lymph node obstructing bowel) • Richter's transformation
Bone marrow failure	• Progressive anemia (Hgb < 11 mg/dL) • Progressive thrombocytopenia (platelets < 100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

Hallek M (2015). *Am J Hematol* 90(5):446-460; Hallek M, et al. (2008). *Blood* 111(12):5446-5456

Case Study 1: Newly Diagnosed CLL/SLL (cont)

- You determine based on her diagnostic workup that this 79-year-old female has intermediate-risk disease and does require treatment due to the size and extent of adenopathy with associated B symptoms.
- What other treatment considerations might you have?
- What would your treatment recommendation be for this patient?

CLL Front-Line Treatment

Stage	Fitness	Del(17p)/p53 mutation	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Fit and low Co-morbidity index (Go-Go)	No	FCR (age <70) BR (age >65) Chemoimmunotherapy
		Yes	Ibrutinib* Alemtuzumab
	Unfit and/or Complex co-morbidities (Slow-Go)	No	Chlorambucil *+ MoAb Obinutuzumab*; Rituximab; Ofatumumab Ibrutinib*
		Yes	Ibrutinib* Rituximab Ofatumumab

*NCCN category 1

Hallek, M. (2015). *Am J Hematol* 90(5): 446-460; NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas (v.3.2016)

Fludarabine in CLL

- "Gold standard" for younger and fit patients
- Nucleotide analog
- Response rate 80% in untreated patients
- FDA approved in 1991 for use in CLL
- Common single-cytotoxic dosing 25 mg/m^2 IV on days 1–5 of 28-day cycles x 6
- Hematologic toxicity common
  - ANC ≤ 500 in 59%
  - Long-term depletion of CD4+ T lymphocytes
  - ≥ 2-g drop in Hgb in 60%
  - ≥ 50% drop in platelets in 55%

NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.1.2016; Fludara (fludarabine) package insert

Fludarabine-Based Chemoimmunotherapy

- Fludarabine + R
- Fludarabine + cyclophosphamide + R
  - Increased incidence of hematologic and non-hematologic toxicity
  - Modified dosing for elderly or frail
- Pentostatin-based regimens
  - Some studies suggest reduced hematologic toxicity but no significant difference in a randomized trial of PCR vs FCR

NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.1.2016

Bendamustine in CLL

- FDA-approved for front-line treatment in 2008
- Hybrid agent: Nitrogen mustard with purine analog properties
- 90 mg/m^2 IV on days 1, 2
- 28-day cycles
- Administered over 30–60 min
- Antiemetic premedication
- Lower doses being utilized in many ongoing clinical trials using combination regimens

Fischer K, et al. (2012). *J Clin Oncol* 30(26):3209-3216.

CLL10: Ph3 FCR vs. BR in Frontline *Response*

Response, %	FCR (n = 284)	BR (n = 280)
CR	39.7%	30.8%
ORR	95.4	95.7

- Median observation time: 36 mo
- Median PFS
  - ***FCR: 55.2 mo vs BR: 41.7 mo (p < .001)***
- 3-yr OS
  - ***FCR: 90.6% vs BR: 92.2% (p = .89)***

FCR = fludarabine, cyclophosphamide and rituximab
BR = bendamustine, rituximab

Eichhorst B, et al. ASH 2013, Abstract 526

CLL10: Ph 3 FCR vs. BR in Frontline *Toxicity*

Adverse Events, %	FCR	BR	*P* Value
All	**90.8**	**78.5**	**< .001**
Hematologic	**90.0**	**66.9**	**< .001**
Neutropenia	**81.7**	**56.8**	**< .001**
Anemia	12.9	9.7	.28
Thrombocytopenia	**21.5**	**14.4**	**.03**
Infection	**39.0**	**25.4**	**.001**

Eichhorst B, et al. ASH 2014, Abstract 19

Alemtuzumab

- Anti-CD52 humanized monoclonal antibody
- FDA approved for use in B-cell CLL in 2001
- Stepped-up dosing (3 mg, 10 mg, 30 mg)
- 3 x per wk x 12 wk
- Premedicate with antihistamines and acetaminophen

Untreated CLL	Previously Treated CLL
83% ORR	21%–31% ORR
24% complete remission	0%–2% complete remission

Campath (alemtuzumab) prescribing information, 2009.

Alemtuzumab

Black Box Warnings

- Cytopenias: Severe/fatal pancytopenia, ITP, AIHA; do not administer > 30 mg daily or > 90 mg wkly
- Infusion reactions: Serious/fatal, hold for grade 3 or 4 infusion reactions
- Infections: Serious/fatal bacterial, viral, fungal and protozoan infections, PCP, and herpes prophylaxis

ITP = immune thrombocytopenic purpura; AIHA = autoimmune hemolytic anemia; PCP = pneumocystis pneumonia.

Campath (alemtuzumab) prescribing information, 2009.

Recently Approved Agents for the Treatment of CLL

Agent	Type of molecule	FDA indication for CLL	Schedule	Warnings and Precautions
Ibrutinib	BTK inhibitor	Frontline in CLL with or without del 17p Frail patients with significant co-morbidities All R/R CLL without 17p	420 mg (140×3) daily by mouth	A Fib Bleeding
Idelalisib	PI 3 kinase inhibitor	Relapse CLL, in combination with rituximab, in whom rituximab alone would be considered appropriate due to comorbidities	150 mg by mouth twice daily	Fatal and/or severe hepatotoxicity, diarrhea or colitis pneumonitis Intestinal perforation
Venetoclax	BCL-2 inhibitor	CLL with 17p deletion in patients who have received at least 1 prior therapy	20 mg by mouth daily for the first 7 days with weekly dose titration up to a maximum dose of 400 mg	Tumor lysis Syndrome Neutropenia Embryo-fetal toxicity

Jain N and O'Brien S (2015). *Blood* 126(4):463-470
Prescribing information for ibrutinib, idelalisib, venclexta

Monoclonal Antibodies Used to Treat CLL

Agent	Type of molecule	FDA indication for CLL	Schedule	Warnings and Precautions
Obinutuzumab	Type II anti-CD20 monoclonal antibody	In combination with chlorambucil in previously untreated CLL	300mg IV C1D1 1000 mg C1D8 1000 mg C2-6, D1 (28 days cycles)	Hepatitis B reactivation, PML
Ofatumumab	Type I anti-CD20 monoclonal antibody	Monotherapy in patients refractory to Fludarabine and Alemtuzumab	300 mg IV day 1 2000 mg doses 2-8 (weekly), then 2000 mg monthly ×4	Hepatitis B reactivation, PML
Rituximab	Type I anti-CD20 monoclonal antibody		375mg/m2 monthly every 3-4 weeks with chemotherapy; other regimens with variable dosing schedule	Hepatitis B reactivation, PML Tumor lysis

Jain N and O'Brien S (2015). *Blood* 126(4):463-470.