Diffuse Large B-Cell Lymphoma and CLL/SLL

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Disclosure

- Consultant, ADC Therapeutics

Non-Hodgkin's Lymphoma

- Cause is unknown
- Increased incidence in certain populations:
  - Organ transplants receiving immune suppressants
  - Autoimmune conditions
  - Human immunodeficiency virus (HIV)
  - Human T-cell leukemia/lymphoma virus-l (HTLV-I)
  - Hepatitis C virus (HCV)
  - Epstein-Barr virus (EBV)
  - H. pylori infection
  - Occupation exposure
    - Chlorinated organic compounds
    - Certain other chemicals

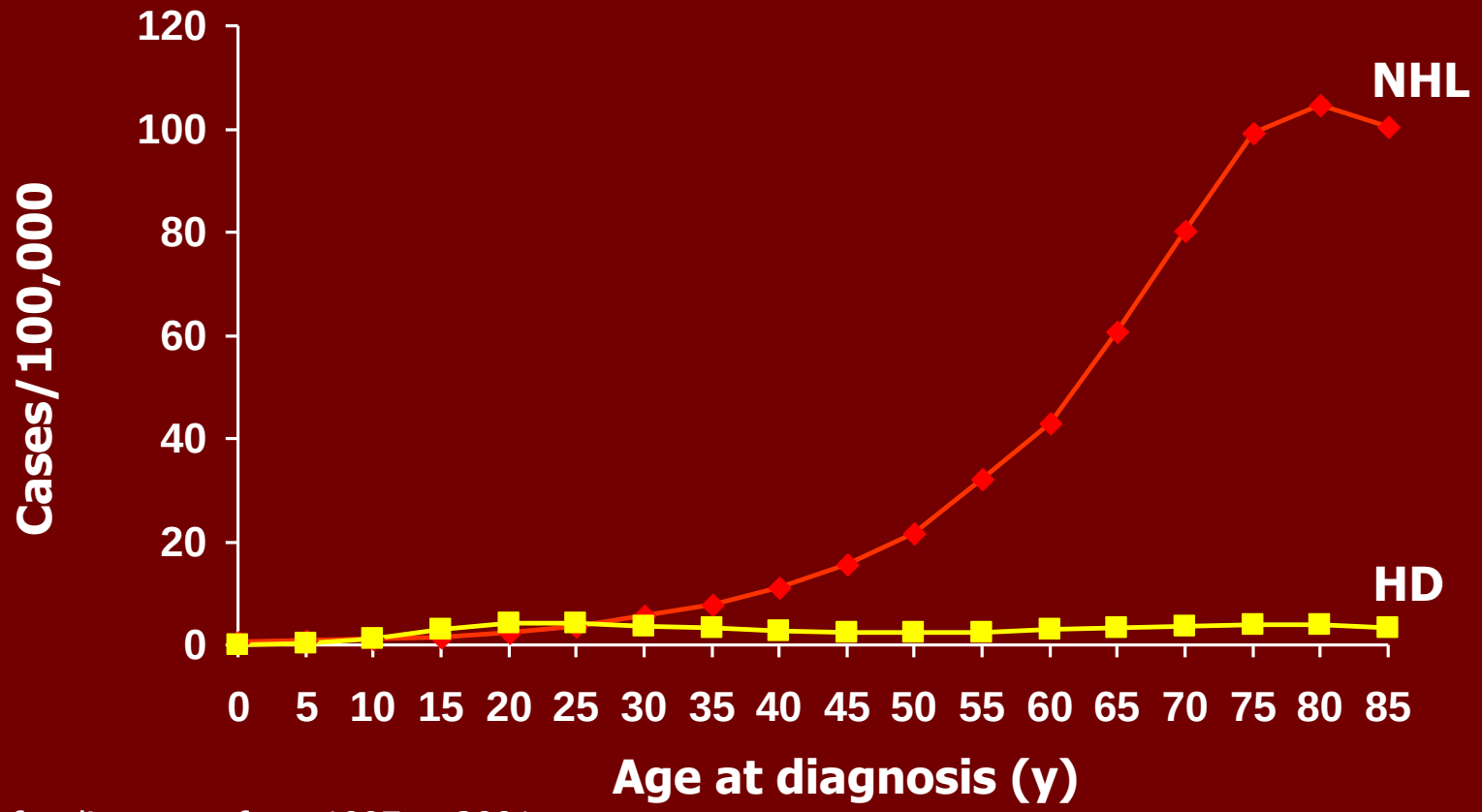
Non-Hodgkin's Lymphoma Epidemiology

- 2022
  - Estimated 81,470 new cases
  - Estimated 20,250 deaths

- Median age at diagnosis, 67 years

American Cancer Society. Cancer Facts & Figures 2022.

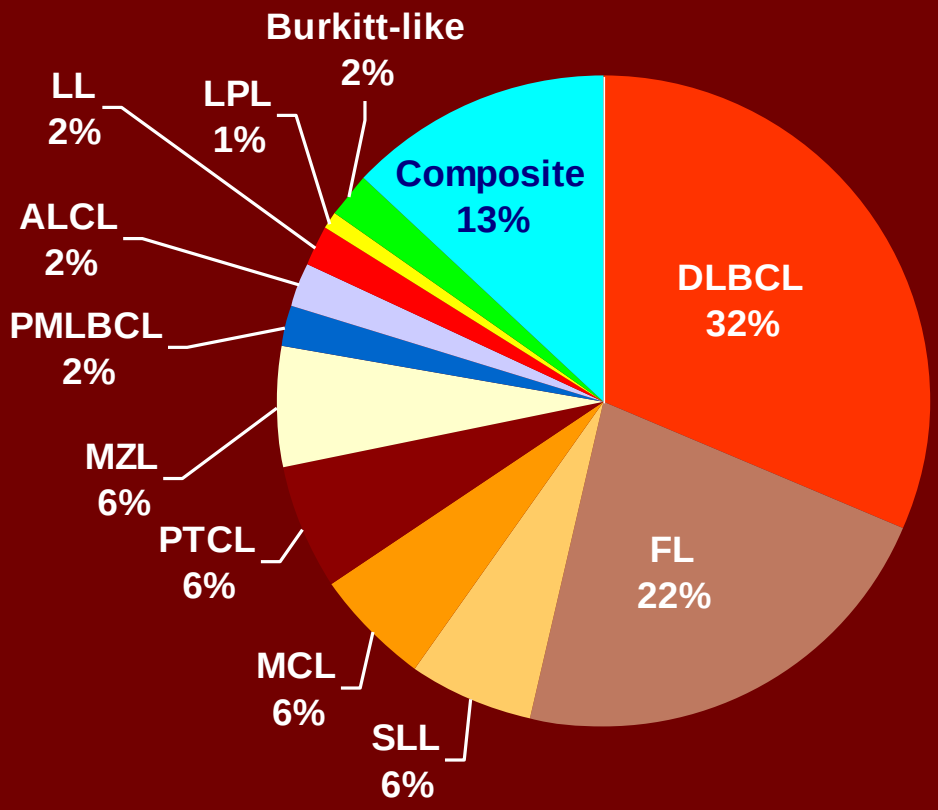
Age at Diagnosis for Hodgkin's and Non-Hodgkin's Lymphoma



Data for diagnoses from 1997 to 2001.

Jemal et al. *CA Cancer J Clin*. 2006;56:106.
At: http://seer.cancer.gov. Accessed March 23, 2005.

Relative Incidence of NHL Subtypes



Armitage and Weisenburger. *J Clin Oncol.* 1998;16:2780.
Adapted from Jemal et al. *CA Cancer J Clin*. 2006;56:106.

Diagnosis of non-Hodgkin's lymphoma:

(a) Morphology: Is essential that pathologists/haematologists involved in this process have the necessary additional training and experience to undertake this work.

(b) Immunophenotyping. All marker studies should be carried out using panels that are designed to test the validity of the morphological diagnosis. Immunological marker studies can be carried out using flow cytometry or immunohistochemistry.

(c) *Molecular techniques*. The main current techniques are polymerase chain reaction (PCR) to detect monoclonality and some translocations, and fluorescence *in situ* hybridisation (FISH) techniques for the detection of translocation and numerical chromosomal abnormalities

Almost all lymphoid cells are reactive for CD45 (leukocyte common antigen, or LCA).

B-lymphocytes

Almost all B-cells are reactive for CD19, CD20 and CD22.

Certain low-grade B-cell lymphomas are reactive for two markers otherwise usually found on T-cells: CD5 and CD43.

Follicular center cell lymphomas (as well as lymphoblastic lymphomas) are frequently CD10(+).

Almost all lymphoid cells are reactive for CD45 (leukocyte common antigen, or LCA).

T-lymphocytes

Pan T-cell markers (present on almost all T-cells) include CD2, CD3, CD5, and CD7.

Most T-cells mark with either CD4 (helper cells) or CD8 (suppressor cells or cytotoxic cells).

Immunophenotype of lymphoma subtypes

Diffuse large B-cell CD20+, CD3-, CD5-, CD45+

Mediastinal large B-cell CD20+, CD3-, **CD45+**

Follicular CD20+, CD3-, **CD10+**, CD5-

Burkitt CD20+, CD3-, **CD10+**, CD5-, Tdt-

Small lymphocytic/CLL CD 20+, CD3-, CD10-, **CD5+**, **CD23+**

Mantle cell CD20+, CD3-, CD10-, **CD5+, CD23-**, CD 43+, PRAD1+

MALT CD20+, CD3-, CD 10-, CD5-, CD23-

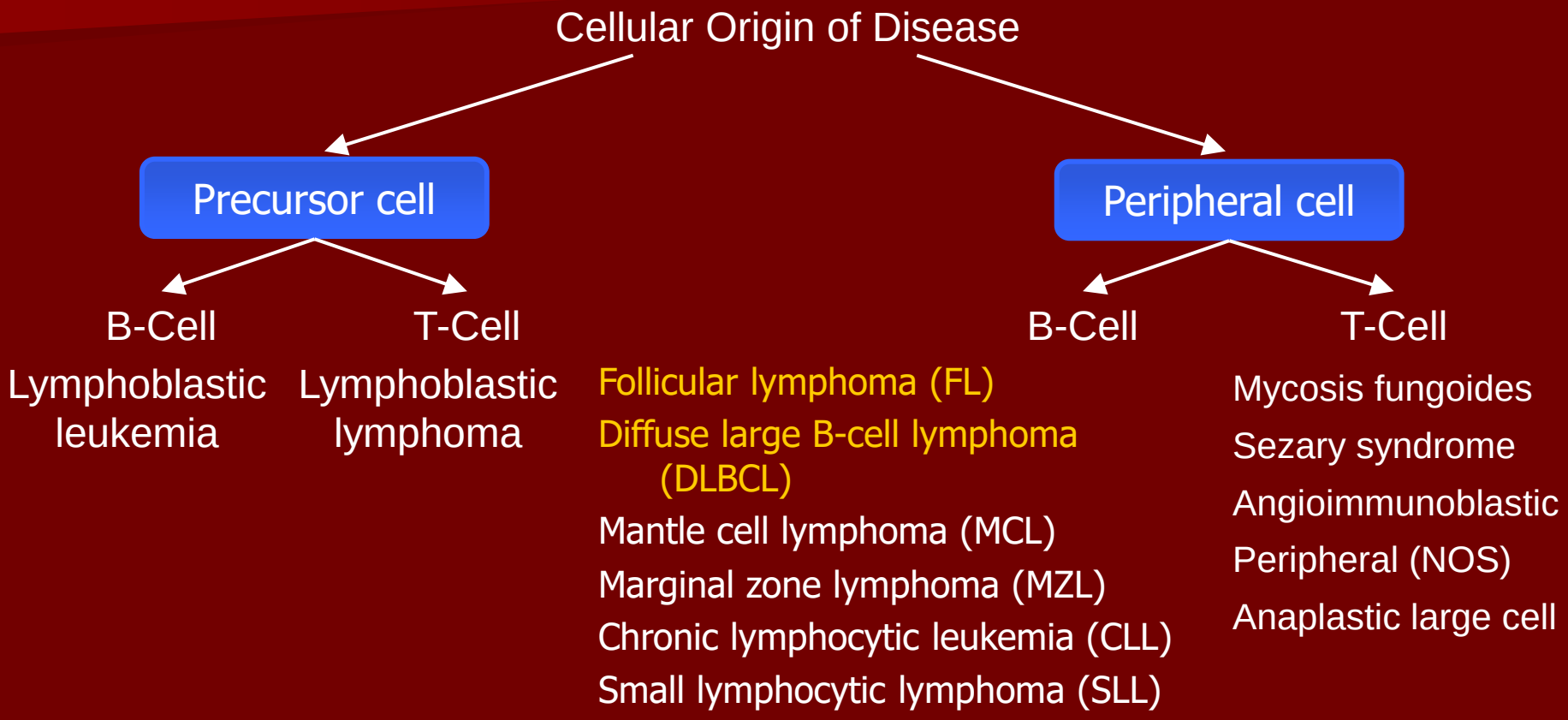
Marginal zone CD20+, CD3-, CD 10-, CD5-, CD23-

Immunophenotype of T cell lymphoma subtypes

Peripheral T-cell **CD20-, CD3+**

Anaplastic large cell **CD20-, CD3+**, **CD30+, CD15-**, EMA+, ALK+

World Health Organization Classification of B-Cell and T-Cell Neoplasms



Gordon. ASCO, 2005. Educational book.
Pileri et al. *Haematologica*. 2000;85:1291.

The Indolent lymphomas

B-cell neoplasms

- Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma (± Waldenstrom's macroglobulinemia)
- Plasma cell myeloma/plasmacytoma
- Hairy cell leukemia
- **Follicular lymphoma (grade I and II)**
- Marginal zone B-cell lymphoma
- Mantle cell lymphoma

T-cell neoplasms

- T-cell large granular lymphocyte leukemia
- Mycosis fungoides
- T-cell prolymphocytic leukemia

Natural Killer neoplasms

- Natural killer cell large granular lymphocyte leukemia

The aggressive lymphomas

B-cell neoplasms	T-cell neoplasms
• Follicular lymphoma (grade III)	• Peripheral T-cell lymphoma
• **Diffuse large B-cell lymphoma**	• Anaplastic large cell lymphoma, T/null cell
• Mantle cell lymphoma	

The highly aggressive lymphomas

B-cell neoplasms	T-cell neoplasms
• Burkitt's lymphoma	• Adult T-cell lymphoma/leukemia
• Precursor B lymphoblastic leukemia/lymphoma	• Precursor T lymphoblastic leukemia/lymphoma

Evaluation of NHL

- History and complete physical examination
- Laboratory evaluation
  - Standard blood tests
    - Complete blood count, differential blood count, blood smear examination
    - LDH
    - Liver function tests
    - Renal function tests
    - Serum electrolyte, calcium, and uric acid levels
- Clinical staging work up

Case #1

- 75 year-old female presents with fatigue, drenching night sweats and persistent palpable left axillary lymphadenopathy despite multiple courses of antibiotics

Hgb 13.5
WBC 11,000/uL
Platelets 300,000/uL

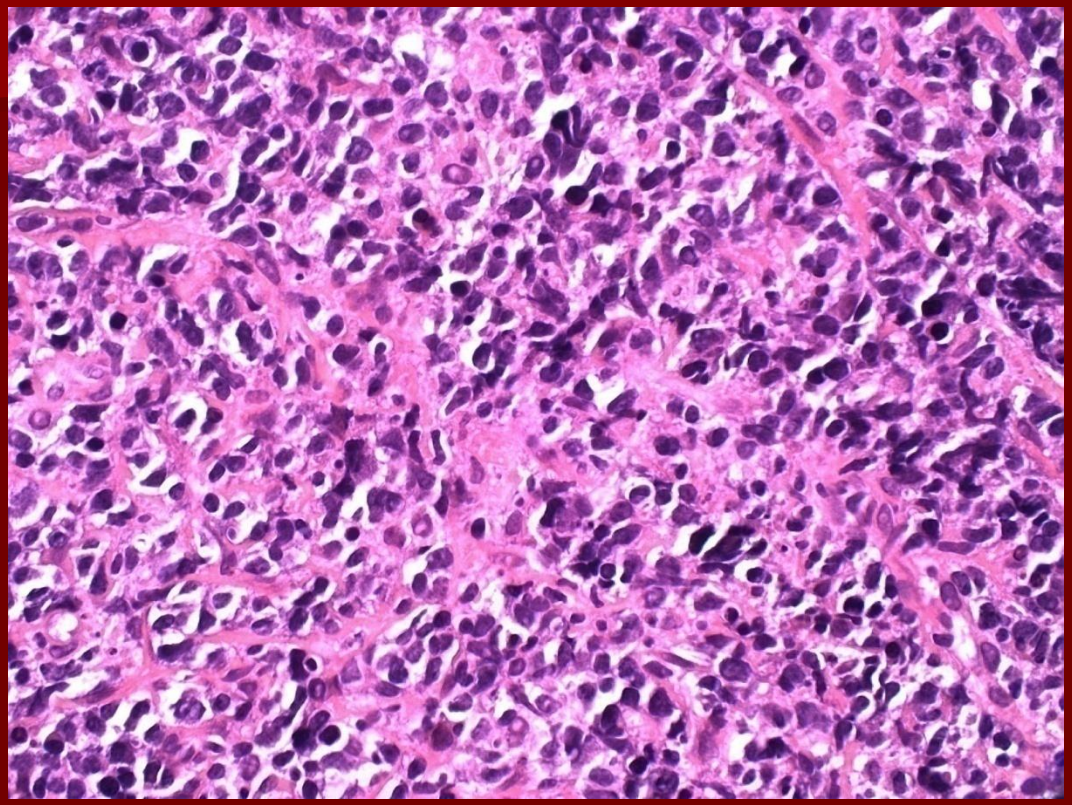
CMP normal

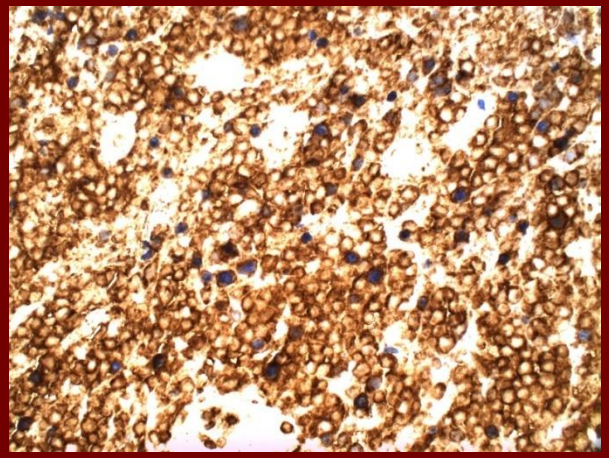
Case #1

What do you do next?

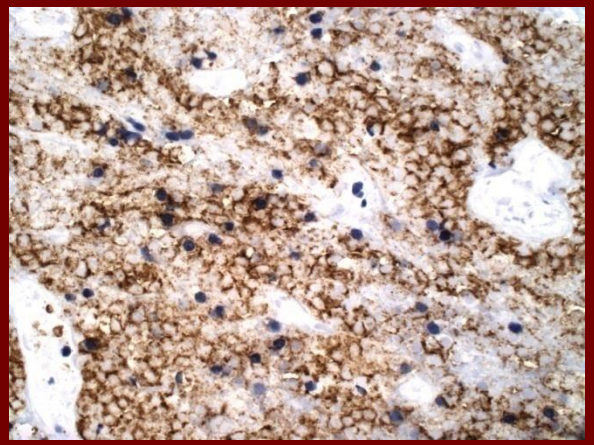
- A) Flow cytometry of peripheral blood
- B) PET-CT skull base to mid-thigh
- C) FNA of a left axillary lymph node
- D) Surgical Excision of left axillary node
- E) Bone Marrow Biopsy

Case #1





CD 45 +



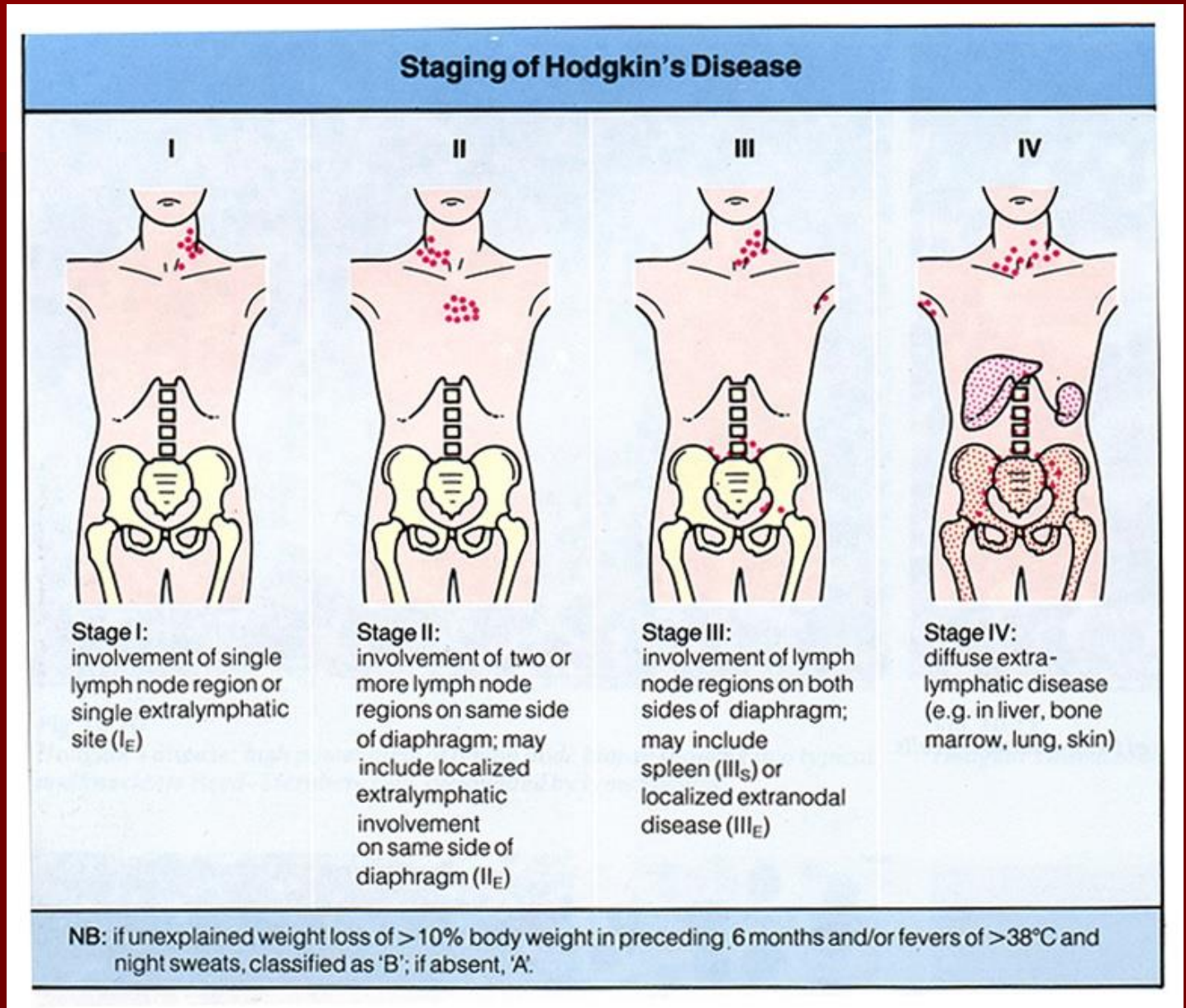
CD20 +

- Diffuse Large B-Cell Lymphoma (DLBCL);
  Positive CD 45 (CLA), CD20 (B cells)

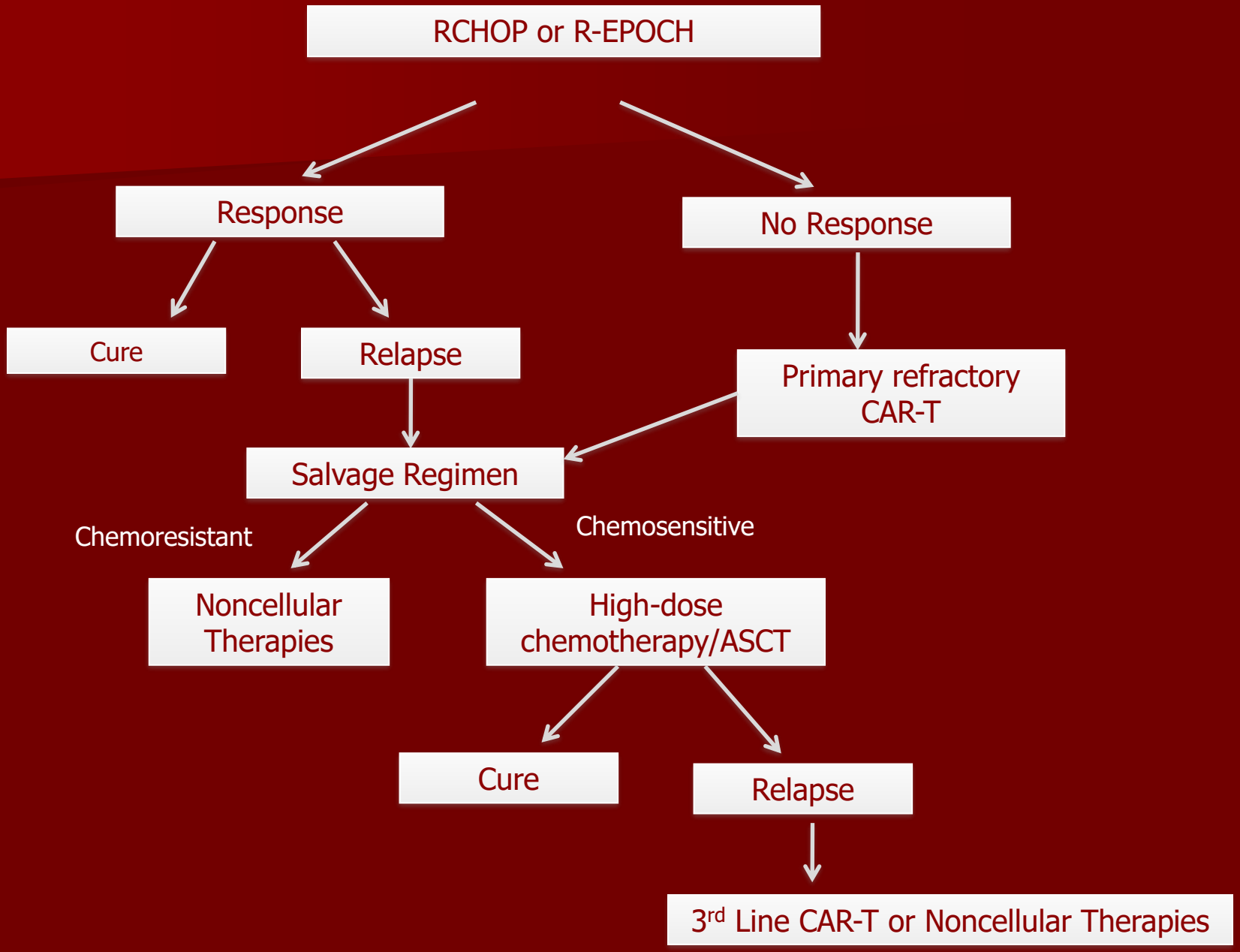
Staging Work Up

- H&P
- PET scan
- Bone Marrow Biopsy?
- Brain imaging and CSF exam in selected cases:
  - AIDS-Related Lymphoma
  - Highly aggressive (Burkitt's, Lymphoblastic)
  - Specific extranodal disease
  - Symptoms

Ann Arbor Staging System



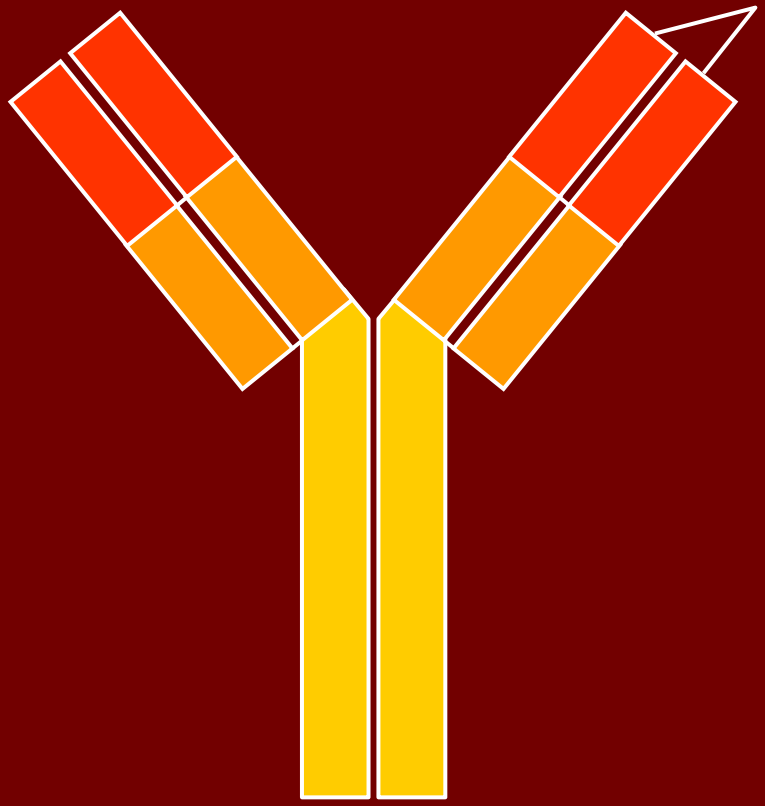
General approach to diffuse large B-cell lymphoma



RCHOP

- Rituximab
  - Baseline viral Hepatitis serology
- Cyclophosphamide
- Hydroxy-Adriamycin
  - Anthracycline
    - Potent Vesicant, needs to be administered through a central line
    - Cardiotoxic, need baseline 2-D Echocardiogram or MUGA scan to evaluate LVEF
- Oncovin (Vincristine)
- Prednisone

Design of Rituximab



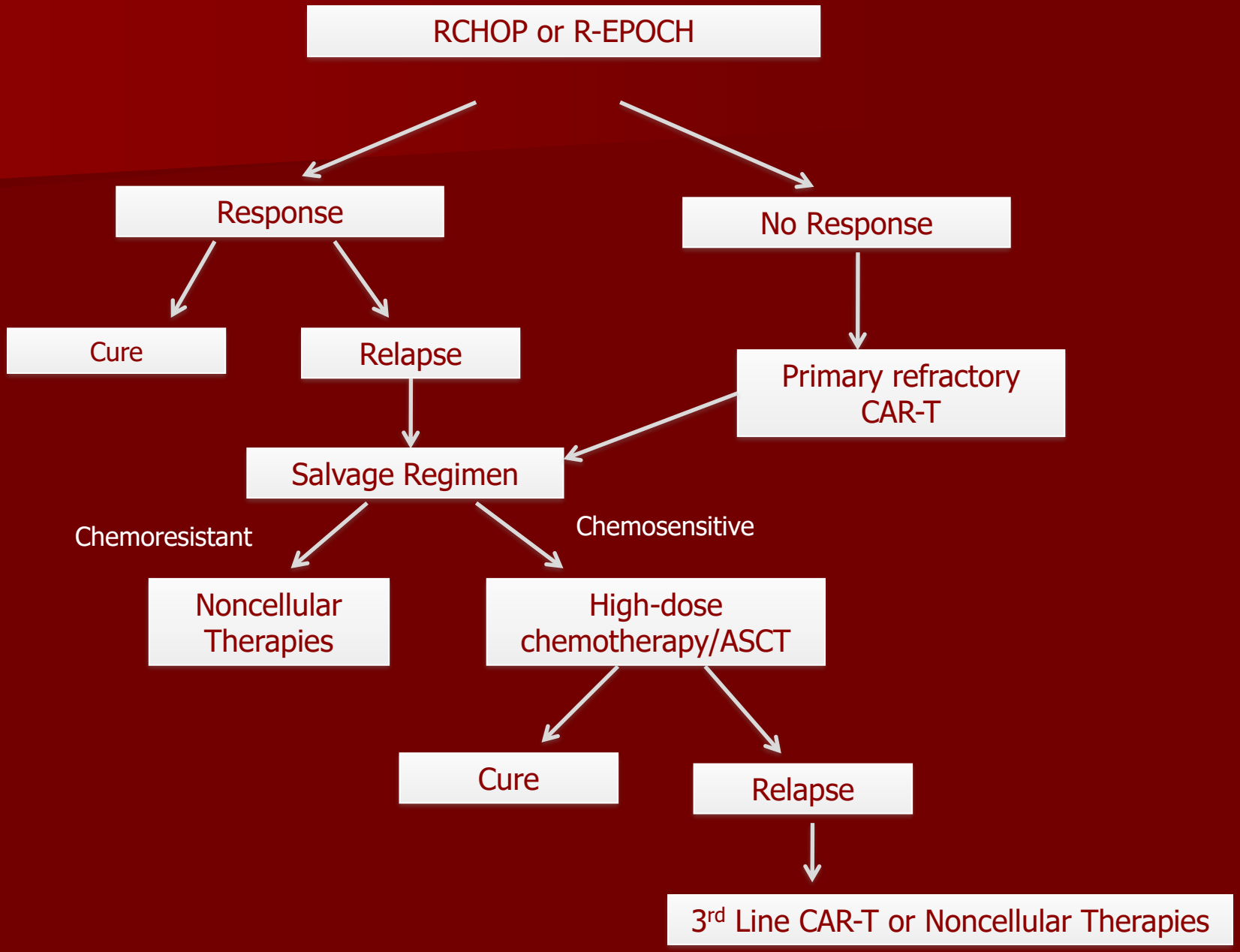
Murine variable regions bind specifically to CD20 on B cells

Adapted from Rybak et al. *Proc Natl Acad Sci U S A*. 1992;89:3165.

Rituxmab: Potential MOA's

- ADCC: Antibody-dependent cellular cytotoxicity
- Downregulates BCL-2 (Apoptosis)
- Increases Cytotoxicity of Chemotherapy
  - Anthracyclines
  - Cyclophosphamide
  - Platinums
  - Fludarabine

General approach to diffuse large B-cell lymphoma



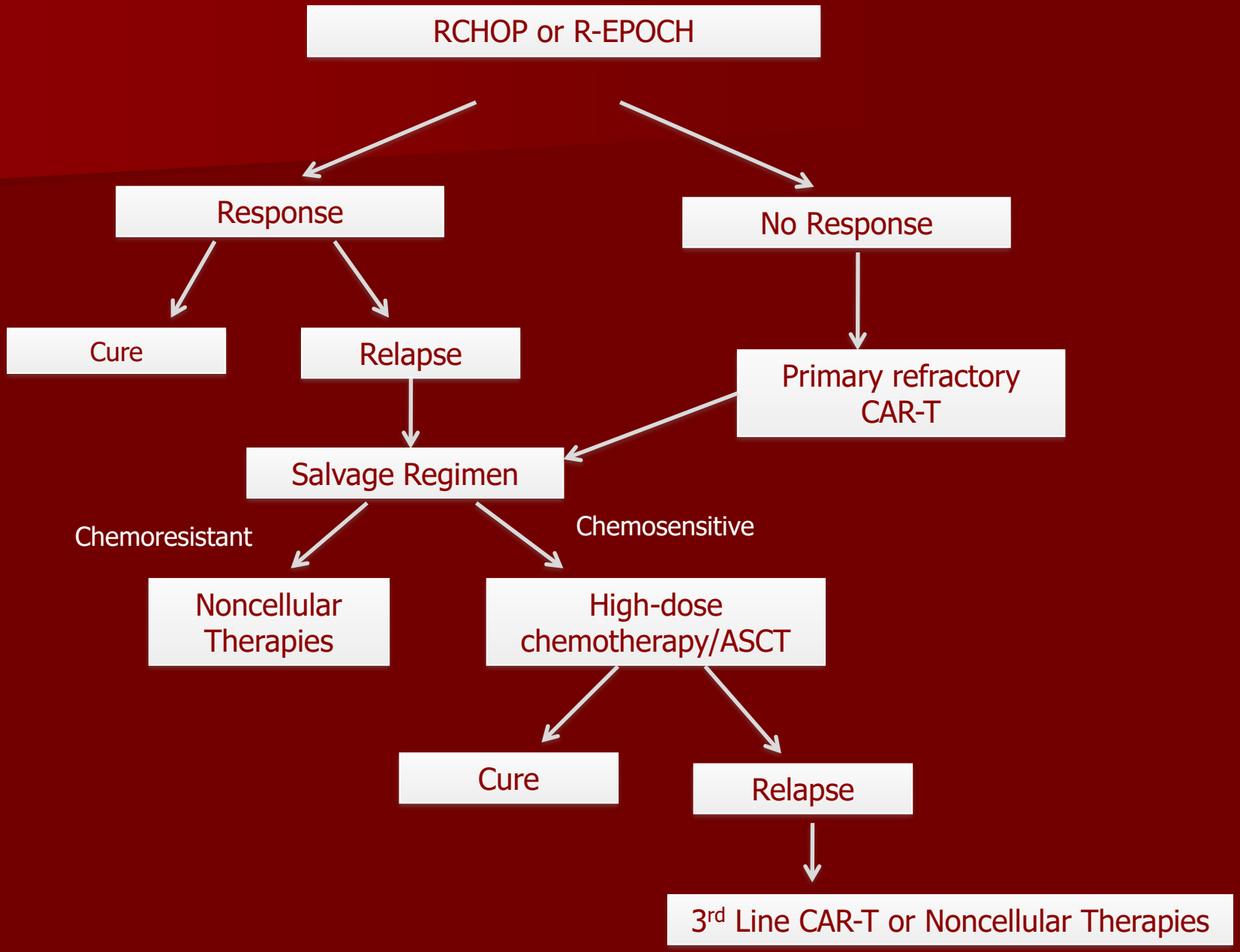
Importance of FISH

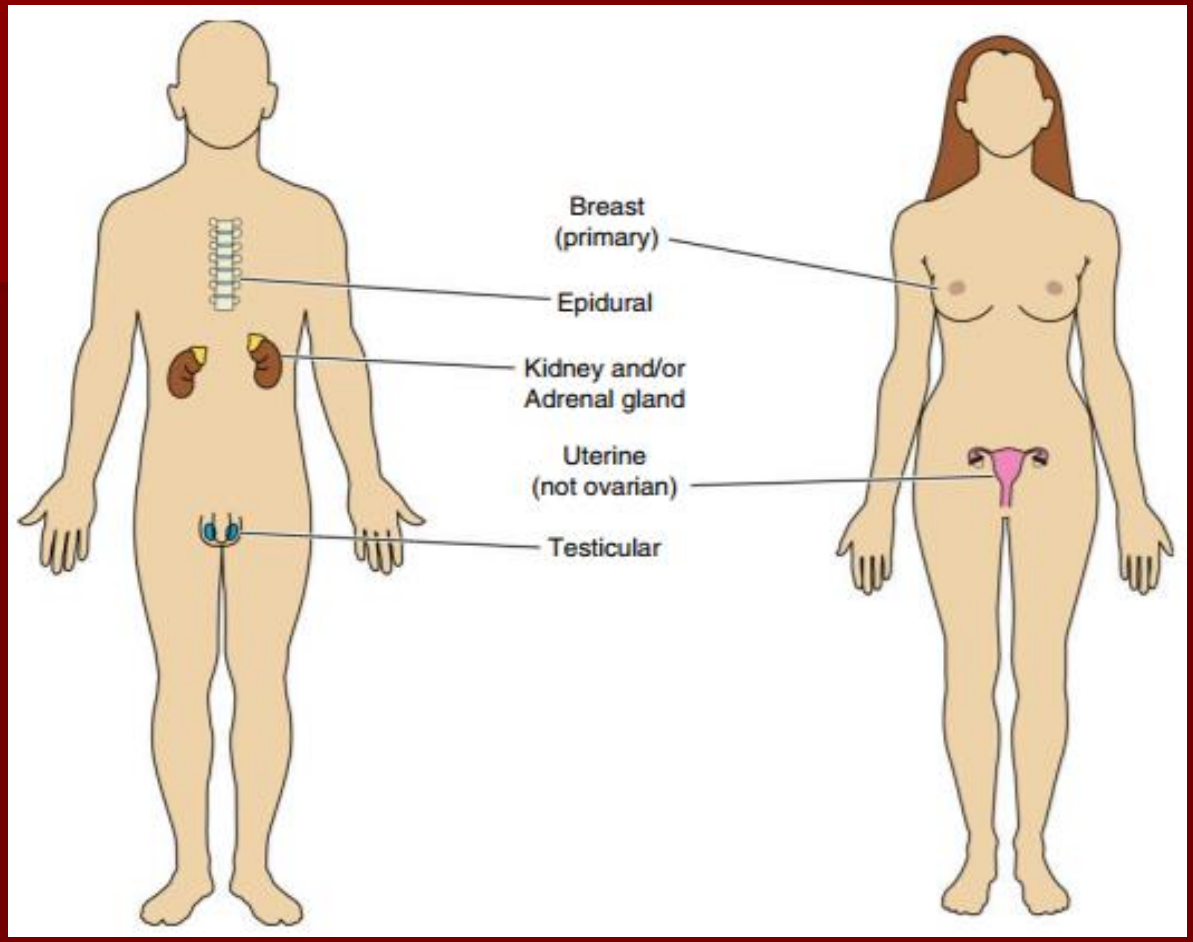
- "Double Hit" or "Triple Hit"
  - Rearragement in Myc plus:
    - Rearrangement in BCL-2 and/or BCL-6
  - Treated with inpatient R-EPOCH
    - Retrospective data

Age greater than 60 y, %
PS greater than 2, %
Elevated LDH, %
More than 1 extranodal site, %
Stage III/IV, %

Risk group	No. of IPI factors	% Patients	4-year PFS, %	4-year OS, %
Standard IPI				
Low	0, 1	28	85	82
Low-intermediate	2	27	80	81
High-intermediate	3	21	57	49
High	4, 5	24	51	59
Revised IPI				
Very good	0	10	94	94
Good	1, 2	45	80	79
Poor	3, 4, 5	45	53	55

General approach to diffuse large B-cell lymphoma





Specific extra nodal sites associated with increased risk of CNS relapse

Chin and Cheah. Blood. August 17, 2017;130(7):867-874

Case #2

- 65 year-old male presents with painless inguinal lymphadenopathy. Treated with antibiotics without improvement.
- Pathology of excisional lymph node biopsy showed Large B-cell Lymphoma. Not double or triple hit by FISH
- PET-CT: Lymphadenopathy above and below diaphragm (Stage IIIA)

Case #2

What tests do you order next?

- A) CBC w diff, CMP, LDH, uric acid
- B) Port Placement
- C) Echocardiogram or MUGA
- D) HIV and Hepatitis Serology
- E) All of the above

Case #3

- A 70 year-old female without any significant history is found to have progressively increasing lymphocyte-predominant leukocytosis
- Otherwise Asymptomatic

Hgb 14 g/dL
Platelet count 350,000/uL
WBC 90,000/uL
ALC 75,000/uL

Case #3

What do you do next?

- A) PET-CT
- B) Bone Marrow Biopsy
- C) Flow cytometry of peripheral blood
- D) COVID tests
- E) Do nothing

CLL and SLL

- Chronic Lymphocytic Leukemia
  - Disease in the Blood or Bone Marrow
- Small Lymphocytic Lymphoma
  - Disease in the Lymph Nodes

CLL

Most common leukemia in adults in Western countries.

Estimated 20,160 new cases

Estimated 4,410 deaths

Median age at diagnosis 70 years

M:F 2:1

Common: N America & Europe. Less common: People of African & Asian origin

American Cancer Society, Cancer Facts & Figures 2022

CLL/SLL

Usually diagnosed with incidental finding of asymptomatic lymphocytosis or Lymphadenopathy/splenomegaly

Only around 20% of patients have symptomatic disease at diagnosis:

- Symptomatic anemia
- Bleeding due to thrombocytopenia
- Symptomatic adenopathy or splenomegaly
- Constitutional symptoms

DIAGNOSIS of CLL:

CLL is a mature B cell neoplasm characterized by a progressive accumulation of monoclonal B lymphocytes.

Requires a peripheral B-Cell count of at least 5,000 cells/uL persistent for 3 months

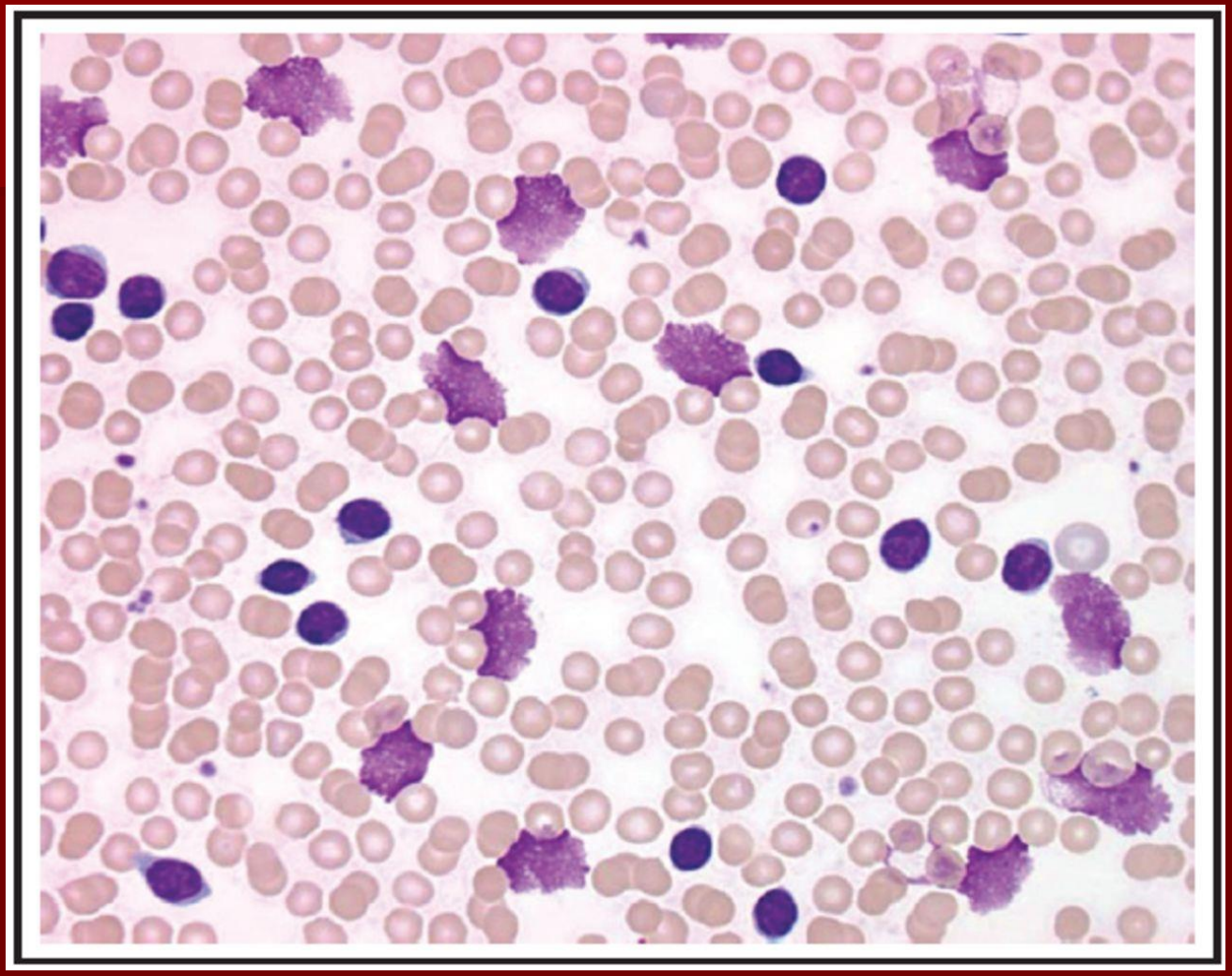
Peripheral Blood flow cytometry: Presence of clonal B-cells (light chain restriction) with co-expression of CD5, CD19, CD23, and low expression of CD20.

Molecular: t14:18 (bcl2 gene on c14, IgH gene on c18). Over expression of bcl-2, blocks apoptosis

BM exam: rarely required

PET-CT in certain situations

A peripheral blood smear of a patient with CLL (Giemsa stain; magnification ×400) shows small lymphocytes and numerous smudge cells.



Clive S. Zent, and Timothy G. Call ASH 2016;2016:617-637

Table II. Staging systems in CLL.

BINET Stage		Features
A		<3 Lymphoid areas*
B		≥ 3 Lymphoid areas
C		Haemoglobin < 100 g/l or platelet count < 100×10^9/l
RAI Stage	Risk group	
0	Low	Lymphocytosis only
I		Lymphadenopathy
II	Intermediate	Hepatomegaly or splenomegaly + lymphocytosis
III/IV	High	Haemoglobin < 110 g/l or platelet count < 100×10^9/l

*The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

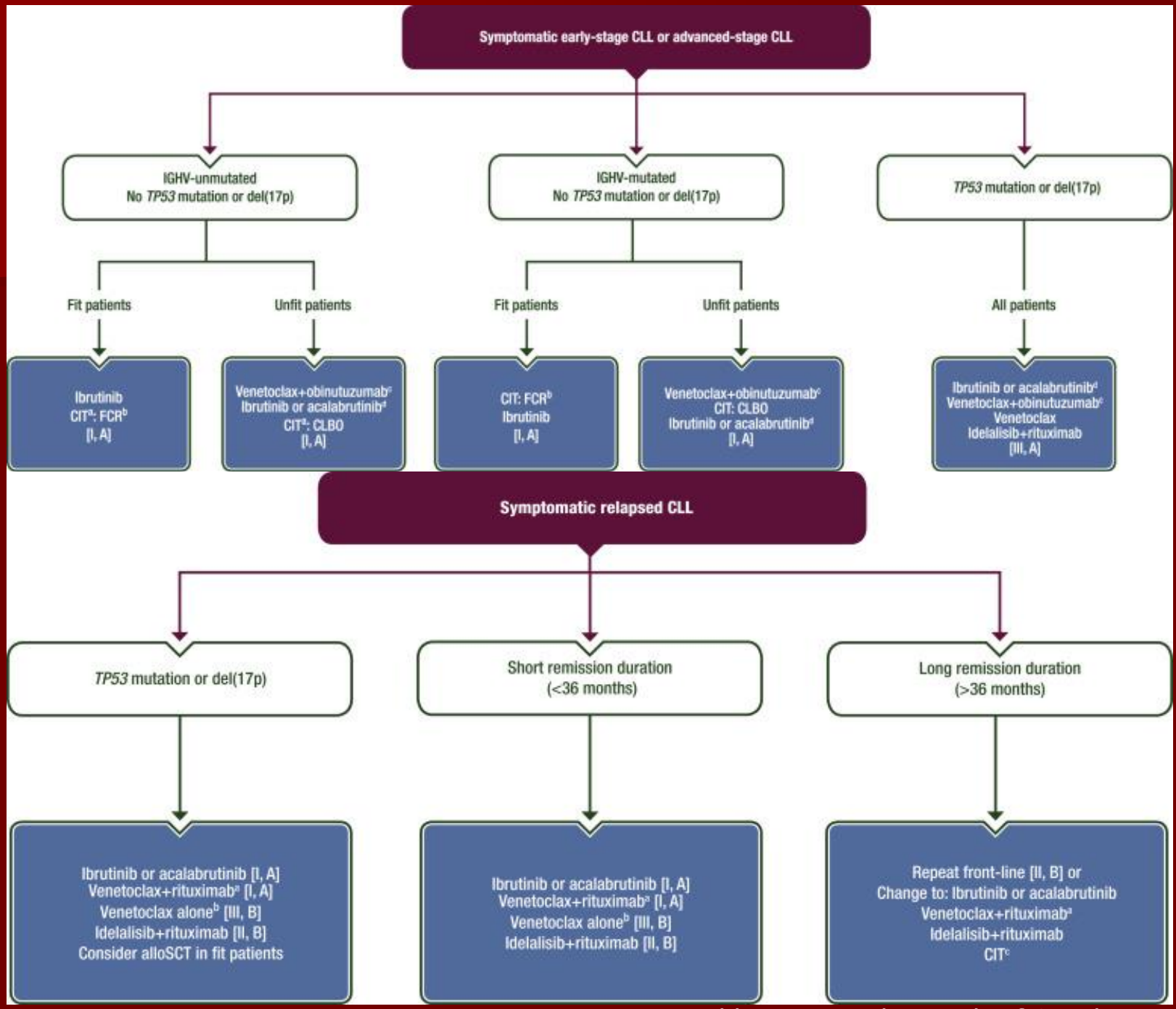
Table 24-4 General indications for initiation of treatment in CLL (IWCLL 2018)

Indication	Description	Precautions
Bone marrow failure	Anemia (eg, Hb <10 g/dL) and/or thrombocytopenia (eg, $<100 \times 10^9$/L and dropping)	Require bone marrow study to confirm bone marrow failure
Symptomatic disease	Unintentional weight loss >10% during the past 6 months Fatigue*: ECOG performance status ≥2; cannot work or perform usual activities Fevers >38°C for ≥2 weeks without evidence of infection Night sweats for >1 month without evidence of infection	Exclude other causative pathologies, eg, sleep disorder, depression, hypothyroidism, chronic infection/inflammation
Splenomegaly	Massive (>6 cm below the left costal margin) or symptomatic (abdominal distention, early satiety, pain) or progressive	
Lymphadenopathy	Massive (>10 cm in longest diameter) or symptomatic or progressive	Exclude infectious lymphadenitis and transformation to diffuse large B-cell lymphoma
Progressive lymphocytosis	Increase in absolute lymphocyte count (ALC) of >50% in 2 months or lymphocyte doubling time (LDT) of <6 months	Baseline ALC for calculation of LDT must be $>30 \times 10^9$/L. LDT needs to be determined by using multiple serial ALC counts (2 weekly ALC for >3 months) to perform linear regression analysis. All other potential causes of changes in ALC (eg, infection, recent use of corticosteroids) need to be excluded. ALC alone should not be used as an indication for treatment.
Autoimmune complications	Anemia or thrombocytopenia poorly responsive to corticosteroids	
Extranodal involvement	Symptomatic or functional, eg, skin, kidney, lung, spine	

*Use of fatigue as a sole indication for treatment of patients with CLL requires a careful evaluation and exclusion of all alternative etiologies.

CLL/SLL

- Complications
  - Autoimmune
    - Coomb's Positive Hemolytic Anemia
    - ITP
    - Treat with steroids
  - Hypogammaglobulinemia
    - Treat with IVIG
    - Not an indication to treat CLL/SLL
  - Richter's Transformation to DLBCL
    - Poor prognosis



Eichhorst B, et al. Annals of Oncology. Jan 2021

CLL/SLL

- My Approach to Treatment:
  - Fixed duration therapy
    - Obinutuzumab and Venetoclax for one year
  - Indefinite therapy
    - Ibrutinib
    - Acalabrutinib and Obinutuzumab
    - Zanubrutinib
- Many options, all expensive!

Case #3

- Flow cytometry shows an abnormal lymphocyte population positive for CD5 and CD23 consistent with CLL/SLL
- PET-CT shows mildly FDG-Avid cervical lymph nodes without bulky disease or splenomegaly

Case #3

What do you do next?

- A- Start Observation
- B- Obtain an excisional LN biopsy
- C- Obtain a bone marrow biopsy
- D- Start Ibrutinib
- E- Refer to Hospice

Case #3

You observe her for 5 years but she develops recurrent infections. What do you do?

- A- Start treatment for CLL
- B- Continue observation and refer to ID
- C- Check serum immunoglobulins
- D- Order a PET-CT
- E- Start prophylactic antimicrobials

Table 24-1 Chronic B-cell lymphoproliferative disorders: immunophenotype

Disease	sIg	CD20	CD5	CD23	CD10	CD103
Chronic lymphocytic leukemia	dim	dim	+	+	–	–
Lymphoplasmacytic lymphoma	+	+	–/+	–/+	–	–
Mantle cell lymphoma	+	+	+	–/dim	–	–
Nodal marginal zone lymphoma	+	+	–	–/+	–	–
Splenic marginal zone lymphoma	+	+	–/+	–/+	–	–/+
Follicular lymphoma	+	+	–	–/+	+/–	–
Hairy cell leukemia	+	+	–	–	–	+
B cell prolymphocytic leukemia	+	+	–/+	–	–	–

Review Question 1

CLL versus SLL

- A) CLL is in the lymph nodes
- B) SLL is in the lymph nodes
- C) CLL is in the blood and bone marrow
- D) SLL is in the blood and bone marrow
- E) A and D
- F) B and C

Review Question 2

Indications to treat CLL

- A) Symptomatic Disease
- B) Rai Stage 3 or 4 disease (cytopenias)
- C) Hypogammaglobulinemia
- E) A and B
- F) All of the above

Review Question 3

Upfront treatment of DLBCL

- A) Rituximab alone
- B) A) with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
- C) CAR-T cell therapy
- D) Autologous Stem Cell Transplant

Review Question 4

Double or Triple Hit in DLBCL refers to:

- A) Rearrangements in IGH, Myc and BCL6
- B) Rearrangements in Myc, BCL2 and BCL6
- C) Multiple sites of lymph node involvement
- D) Lymph node and Bone marrow involvement

Bonus Question!

Steroids can be cytotoxic to:

- A) Eosinophils
- B) Neutrophils
- C) Lymphocytes
- D) A and C
- E) All of the above

Thank you!

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