CancerCare Manitoba
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CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

UPCON
Uniting Primary Care and Oncology

Blood Disorders Day 2016

FOR Health Professionals

What do *you* need to know about Chronic Lymphocytic Leukemia (CLL)?

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University of Manitoba

Disclosures

FINANCIAL DISCLOSURE

Grants/Research Support: TFRI/NCIC Post MD Research Award, Manitoba Medical Services Foundation, Thorlakson Foundation, University Research Grants Program, CancerCare Manitoba Foundation, Lady Tata International Leukemia Research Award, Shastri Indo-Canadian Research Grant, Research Manitoba CLL Cluster Grant

Consultant: Lundbeck, Roche, Gilead, Jannsen, Abbvie

Objectives

1. Understand the difference between monoclonal B cell lymphocytosis, chronic Lymphocytic Leukemia and small lymphocytic lymphoma

2. Understand the complications of CLL/SLL, the indications to treat and the treatment landscape

Resources:

CCMB CLL Guideline for Primary Care

http://www.cancercare.mb.ca/resource/File/CPG/Lymphoproliferative_Disorders/CG-Consensus_Recommendations_for_Mgmt_Chronic_Lymphocytic_Leukemia-Primary_Care_Guideline-posted_2016-03-01.pdf

CCMB CLL Management Guideline

http://www.cancercare.mb.ca/resource/File/CPG/Lymphoproliferative_Disorders/DM_LYMP-Consensus_Recommendations_for_Mgmt_Chronic_Lymphocytic_Leukemia_2015-10-30.pdf

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Outpatient Referral Form

Chronic lymphocytic Leukemia (CLL)
Small lymphocytic lymphoma (SLL)
Monoclonal B-cell lymphocytosis (MBL)

Label: _____ Reason for Referral: _____

Please include the following documentation and this check list to expedite the referral process for your patient:
Referral letter with complete History, Physical, Medication and Laboratory Investigations.
Please Fax to 204-786- 0621, Attention Lymphoma DSG

Required Investigations for suspected or biopsy proven CLL/SLL/MBL:

- ☐ CBC, Chemistry including Cr, LDH, uric acid, calcium
- ☐ B2 microglobulin
- ☐ Immunoglobulins, SPEP
- ☐ Flow Cytometery: Rule out lymphoproliferative disorder
- ☐ Pathology Report if any
- ☐ CT reports if any
- ☐ Haptoglobin
- ☐ HBsAg, HCV, HIV

Case 1

- 65 year old male
- WBC 12
- Absolute Lymphocyte count 4.0
- No Clinical findings

Case 1

- What is the diagnosis?

Case 2

- 91 year old male
- WBC 150
- Absolute lymphocyte count 145
- Asymptomatic

Case 2

- Should he be treated?

Work up of Lymphocytosis

- History and Full Physical Exam
  - Rule out secondary causes: inflammatory or infectious
  - Laboratory: CBC, Smear, Full chemistries, LFTs, LDH, Uric Acid, HIV, HEPB, HEPC (other serologies if indicated/exposed)
- If persistent or patient unwell and has concerning features
- Flow Cytometery (Specialized Laboratory testing) (no approval required): https://apps.sbgh.mb.ca/labmanual/test/loadDocumentPdf?documentId=55

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PLEASE COMPLETE ALL INFORMATION BELOW, PRINT CLEARLY

PRIMARY REPORT TO:

NAME OF PHYSICIAN ORDERING TEST: ..... (LAST) ..... (FIRST)

EMERGENCY CONTACT NUMBER: .....

REFERRING INSTITUTION NAME AND ADDRESS OR CODE:

INPATIENT LOCATION (WARD):

OUTPATIENT LOCATION (ADDRESS):

PATIENT NAME: LAST, FIRST

DATE OF BIRTH: DD/MM/YYYY

OUTPATIENT TELEPHONE NUMBER

SEX: ☐ F ☐ M

HISTORY AND CLINICAL IMPRESSION REQUIRED:

Age, Gender, Persistent Lymphocytosis Rule out Lymphoproliferative disorder

FLOW CYTOMETRY

HEALTH SCIENCES CENTRE

REASON FOR TESTING MUST BE PROVIDED ABOVE (EXCEPTION PB48)

- ☐ CD4/CD8 subsets (EDTA) PB48
- ☐ Enumeration Panel (T, B & NK cells) (EDTA) ..... PBEN
- ☐ Paroxysmal Nocturnal Hemoglobinuria (EDTA) ..... PNH
- ☐ Oxidative Burst (HSC only) (EDTA)* ..... OBRT
- ☐ Hereditary Spherocytosis (EDTA) ..... HSFC
- ☒ Immunophenotyping Peripheral Blood (EDTA) ..... PBFC
- ☐ Immunophenotyping Bone Marrow (Heparin) ..... BMFC
- ☐ Immunophenotyping Lymph Node ..... LNFC
- ☐ Immunophenotyping Fluid ..... FLFC
- ☐ Immunophenotyping Fine Needle Aspirate ..... FNFC
- ☐ Immunophenotyping Tissue ..... TSFC

***PRIOR ARRANGEMENT WITH LABORATORY REQUIRED**

☐ JO-1 ..... JO1 ☐ Scl-70 ..... SCL
☐ Sm ..... SM ☐ Sm/RNP ..... RNP

☐ Centromere B ..... CENB ☐ Hep2 ..... HEP2

Rheumatoid Arthritis
☐ Cyclic Citrullinated Peptide ..... CCP

Celiac Disease
☐ CELIAC Panel (includes Tissue Transglutaminase IgA & IgG and Endomysial IgA as required) ..... GLUG
☐ ONLY Tissue Transglutaminase IgG ..... TTG

Inflammatory Bowel Disease
☐ Saccharomyces Cerevisiae (IgG & IgA) ..... ASCA
☐ IFA Neutrophil Cytoplasmic Ab (does not include MPO and PR3) ..... IFNC

Phospholipid Syndrome
☐ Antiphospholipid (includes Ab to Cardiolipin IgG, Cardiolipin IgM, beta 2 glycoprotein 1 IgG, and beta 2 glycoprotein 1 IgM) ... APHL

Autoimmune Vasculitis
☐ Myeloperoxidase ..... MPO ☐ Proteinase 3 ..... PR3

Organ Specific Autoantibodies
☐ Mitochondrial ..... AMA ☐ Adrenal ..... ADA
☐ Smooth Muscle ..... SMA ☐ Pemphigus ..... PGUS
☐ Liver/Kidney Microsomal ..... LKM ☐ Pemphigoid ..... PGOD
☐ Parietal Cell ..... PCA ☐ Striated Muscle ..... STR
☐ Glomerular Basement Membrane ..... GBM ☐ Acetylcholine Receptor ..... ACHR
☐ Endomysial IgA ..... AEMA

☐ Complement C3 ..... C3
☐ Complement C4 ..... C4
☐ Rheumatoid Factor (RF) ..... RF
☐ Free Light Chain Ratio ..... FLCH
☐ C1 Esterase Inhibitor ..... CEI

Monoclonal Gammopathy Investigation
(includes M peak and immunoglobulin levels when applicable)
☐ SERUM ..... PE ☐ Initial ☐ Follow-up
☐ URINE ..... PEU ☐ Initial ☐ Follow-up

☐ **Total Complement Activity** CH50
(Aliquot and freeze within 1 hour of collection)

☐ **Serum Viscosity** ..... VIS
(Minimum 20 mL RED TOP/NO GEL required; clot at 37°C and aliquot)

☐ **Serum Cryoglobulin** ..... CRYO
(Minumum 15 mL RED TOP/NO GEL; clot at 37°C and aliquot)

Additional Tests

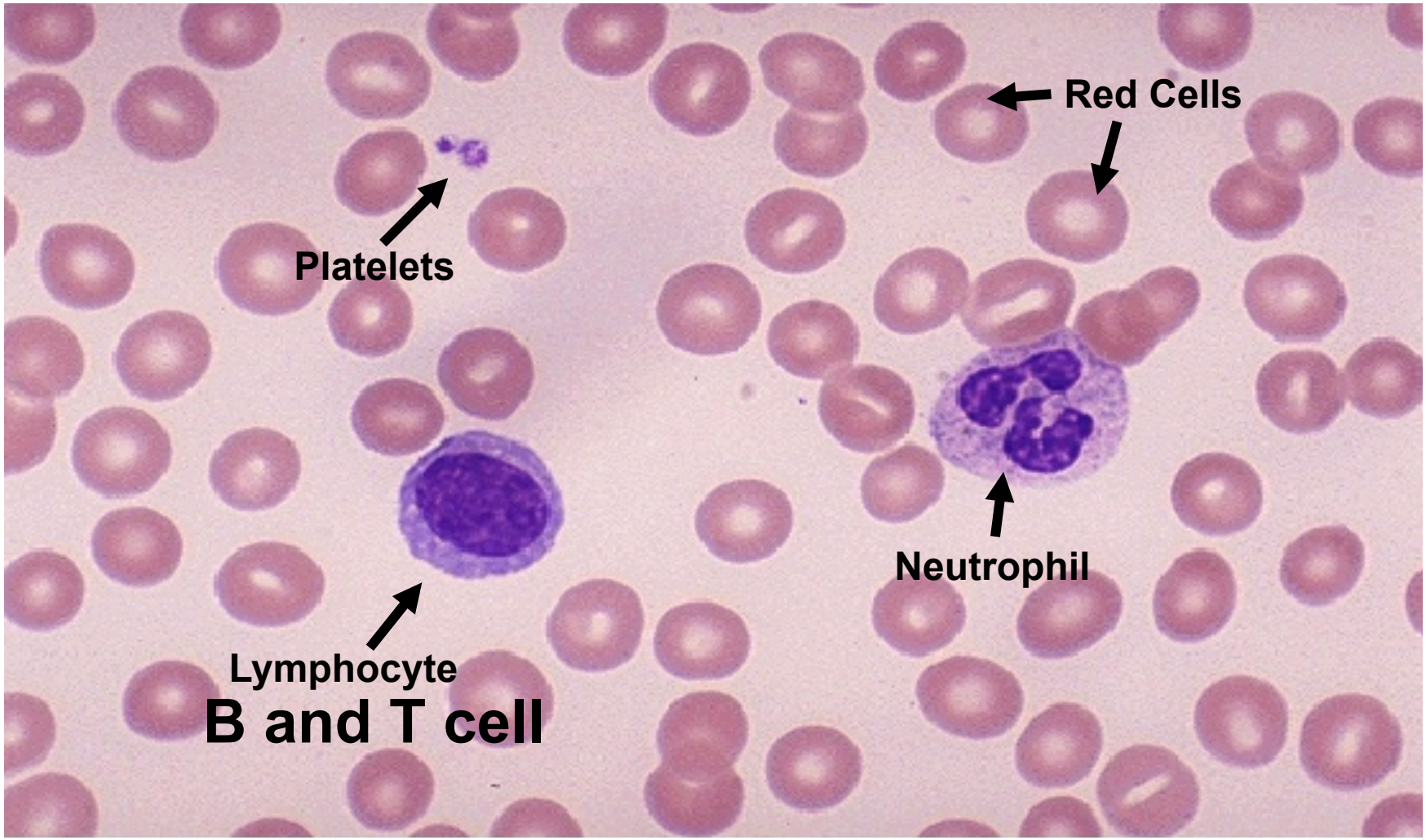
St. Boniface Hospital
Immunology Laboratory L1011
409 Tache Avenue
Winnipeg, Manitoba R2H 2A6
Phone: (204) 237-2026 Fax: (204) 233-0826

DIAGNOSTIC SERVICES MANITOBA
IMMUNOLOGY TEST REQUISITION

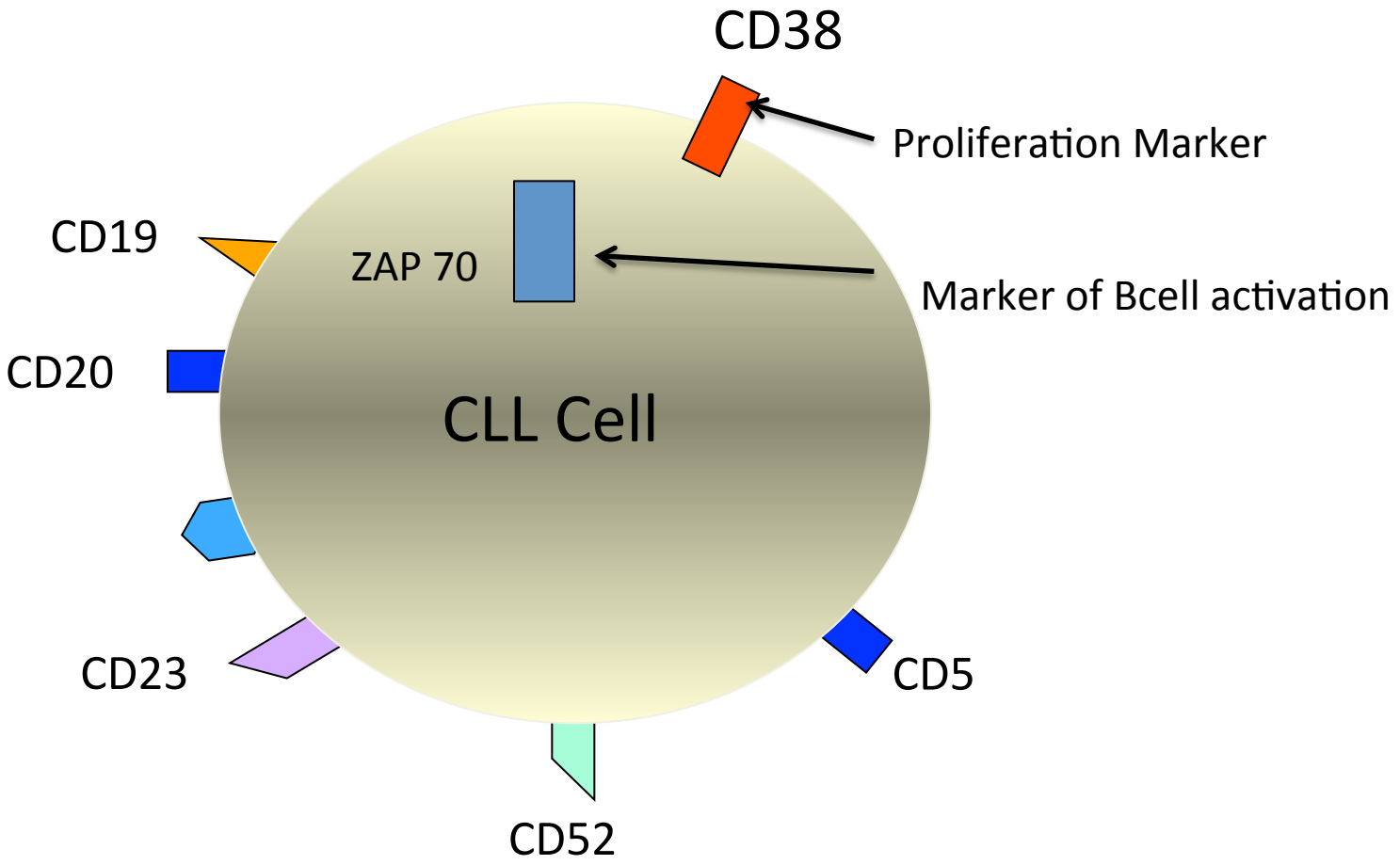
Health Sciences Centre
Immunology Laboratory
MS5 - 820 Sherbrook Street
Winnipeg, Manitoba R3A 1R9
Phone: (204) 787-2156 Fax: (204) 787-2058

FORM # NS01719 12/15

Normal Blood



The monoclonal B cell

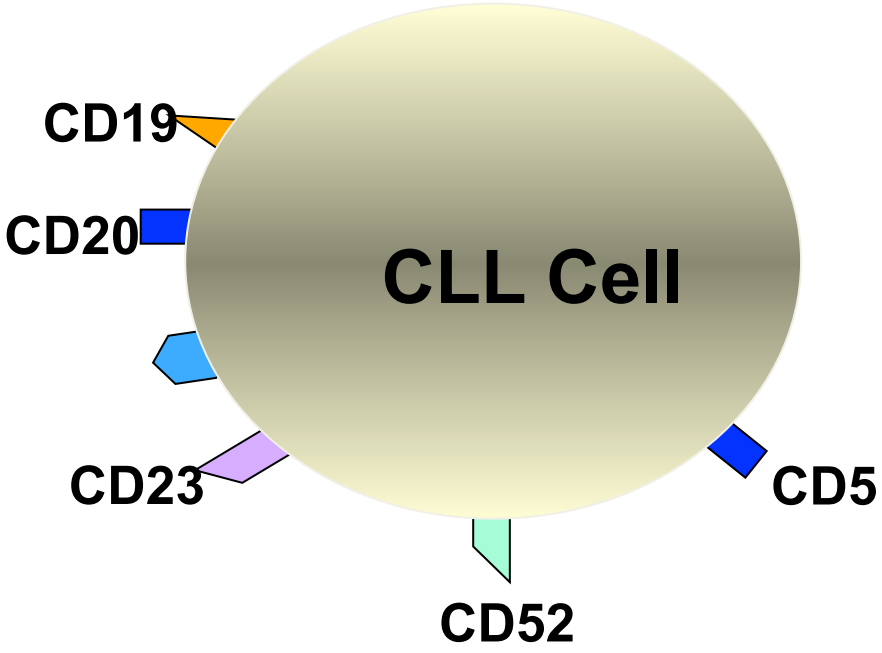


CD38 > 20% and or Zap70 >20% adverse prognosticators

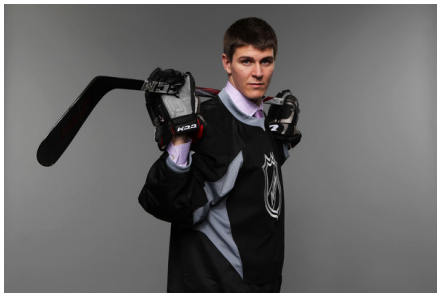
Calculating the absolute monoclonal B cell count

- CBC will list a lymphocyte count – This is a combination of B and T cells (e.g. 7 x 10^9/L)
- Flow report of the lymphocytes: 3% are T cells, 2% are NK cells and the rest are monoclonal B cells, Kappa restricted, CD 19, 20(dim), 5, 23 positive cells consistent with MBL, CLL, SLL
- Therefore, 95% of 7 x 10^9/L = ~ 5 x 10^9/L

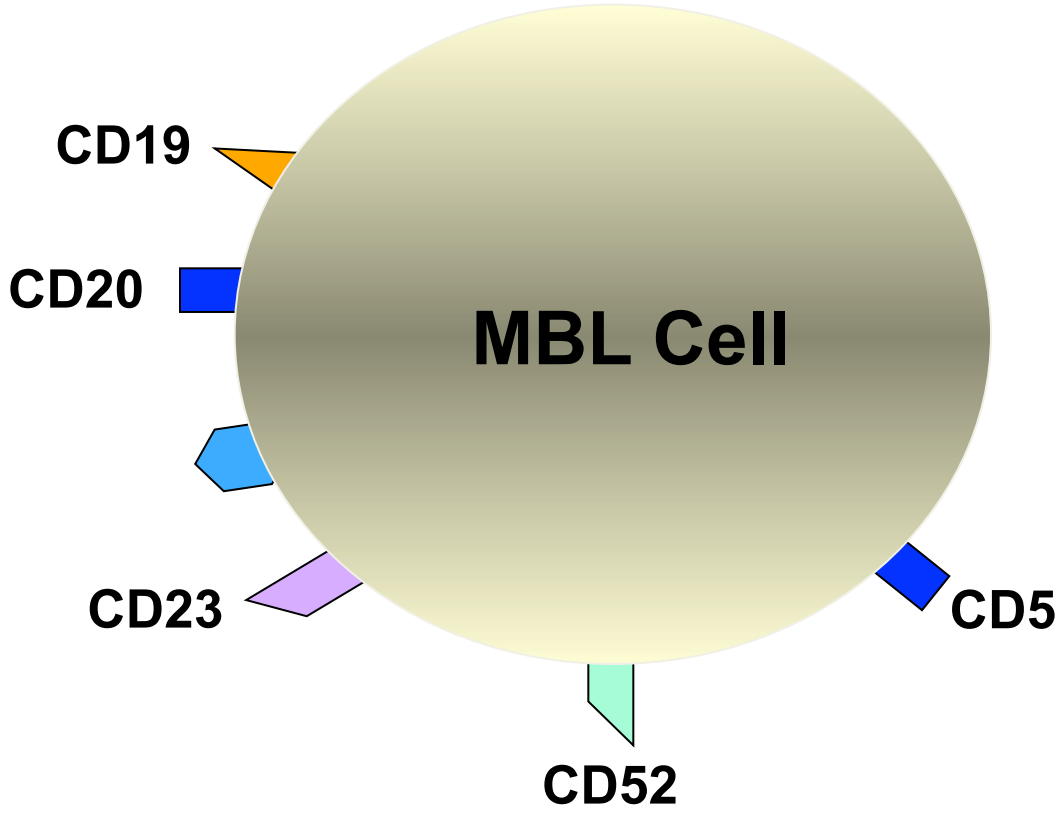
MBL	CLL	SLL
Monoclonal B cell Lymphocytosis	Chronic Lymphocytic Leukemia	Small Lymphocytic Lymphoma
< 5 x10^9 cell/L	> 5 x10^9 cell/L	< 5 x10^9 cell/L
NOT Cancer		Positive lymph node/ Bone marrow biopsy



In the blood:
Less than 5 x10^9/L

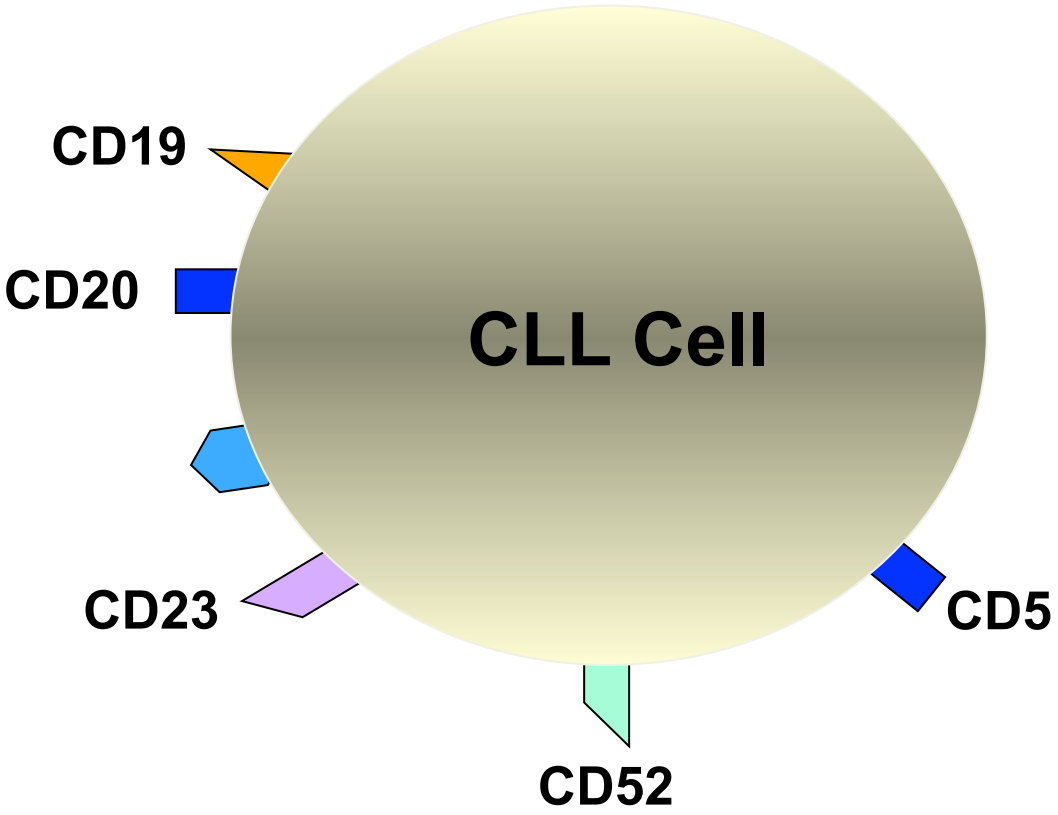


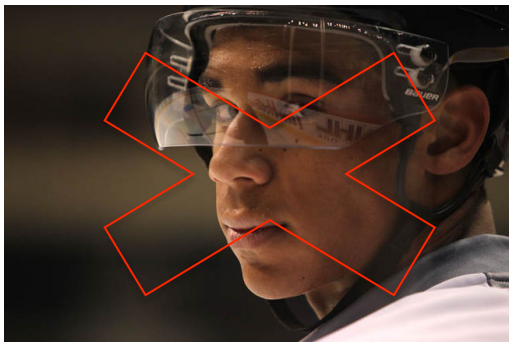
Drafted Player



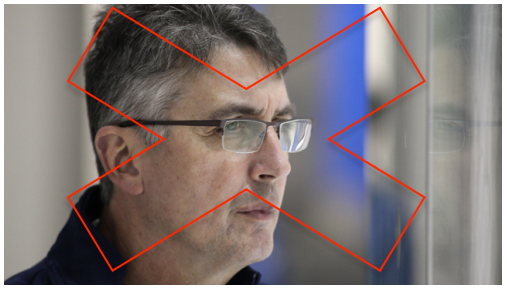
In the blood:
5 x10^9/L or more

Seasoned Player

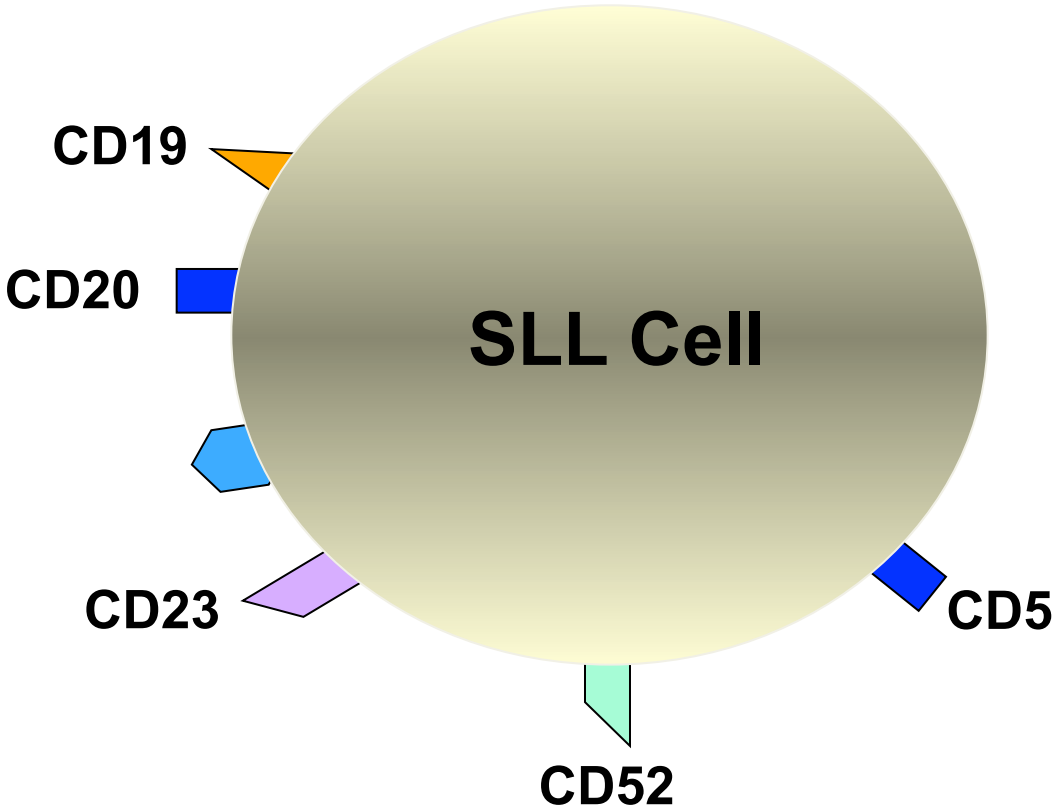




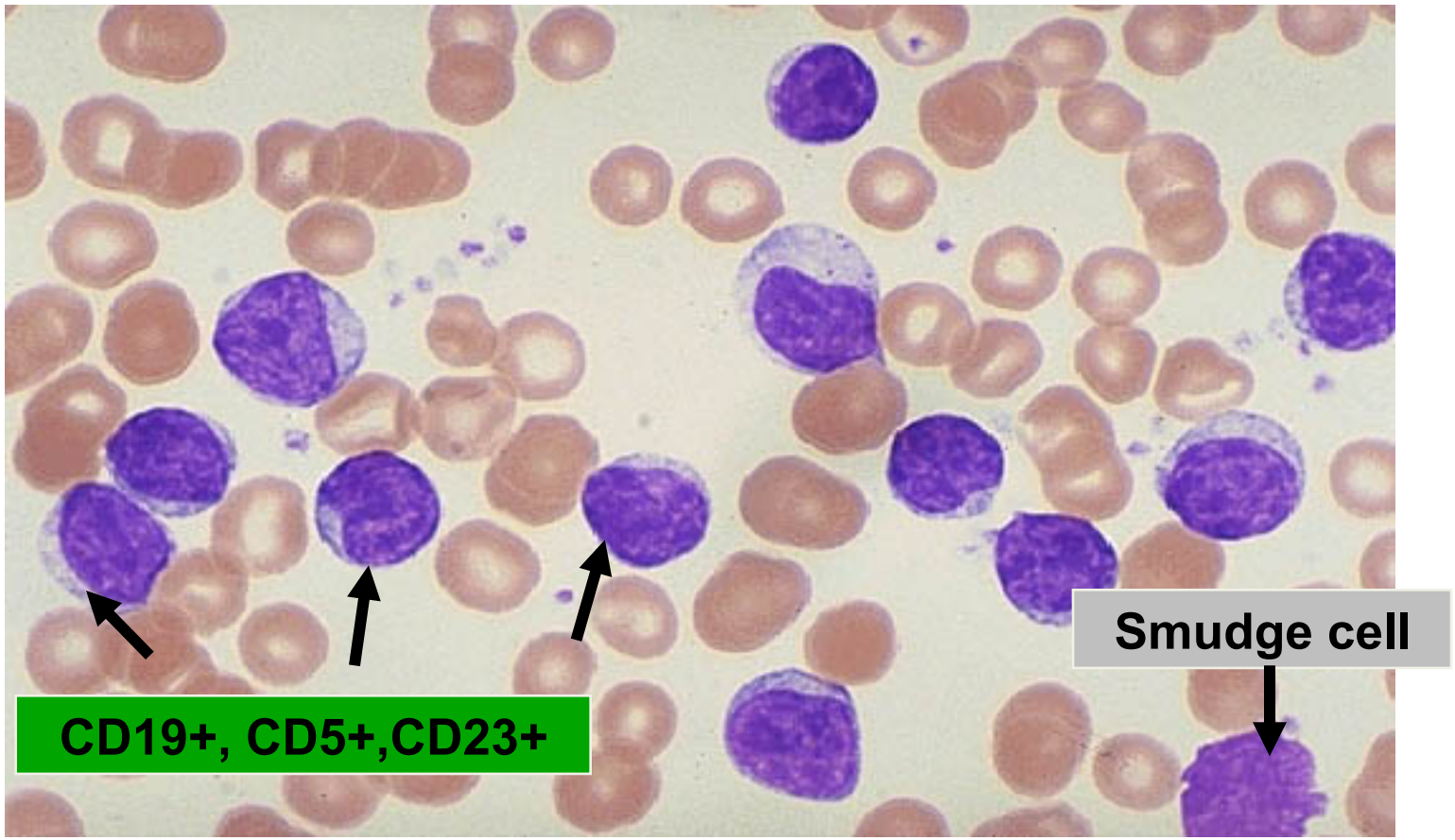
Not in the Blood



Coach



CLL Blood Smear



CLL / SLL

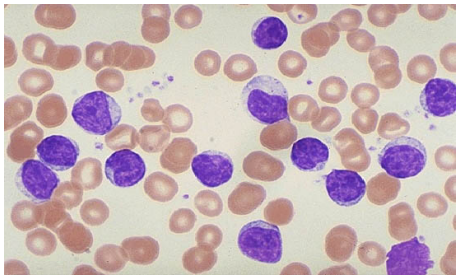
- Proliferation and accumulation of abnormal monoclonal lymphocytes in blood, bone marrow, lymph nodes and spleen

- Treatable but not curable

Who does it affect?

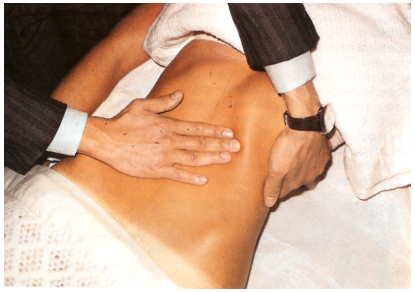
- ~100 new patients in Manitoba each year
- Average age at diagnosis is 72 years
- More common in men (1.3 to 1)
- No known cause
- 10% family history of CLL/lymphoma

Rai Clinical Staging System for CLL

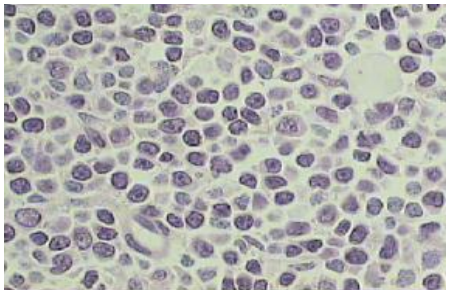


Rai 0

Rai I



Rai II



Rai III/IV

Complete Blood Count

CBC w/ Auto & Manual D 1

Comment: note that the hgb and all rbc indices have been corrected for high WBC

WBC	H	108.6	10^9/L	(4.5 - 11.0)	
RBC		4.44	10^12/L	(4.4 - 5.9)	
Hgb		142.0	g / L	(130.0 - 180.0)	
Hct		0.412	L/L	(0.4 - 0.52)	
MCV		92.8	fl	(80.0 - 96.0)	
MCH		31.9	pg	(26.0 - 34.0)	
MCHC		344.0	g / L	(320.0 - 365.0)	
RDW		13.2	absolute value	(11.5 - 14.5)	
Platelets		111.0	10^9/L	(140.0 - 440.0)	

Comment: checked

MPV		8.9	fL	(7.4 - 10.4)	
Platelet Dist. Width		15.7	absolute value		
Neutrophils		4.9	10^9/L	(0.7 - 7.8)	4.51 %
Lymphocytes	H	95.3	10^9/L	(1.0 - 3.3)	87.75 %
Monocytes	H	7.8	10^9/L	(0.1 - 0.9)	7.18 %
Eosinophils		0.2	10^9/L	(0.0 - 0.4)	0.18 %
Basophils	H	0.4	10^9/L	(0.0 - 0.1)	0.37 %
Manual Neutrophil Segs Abs.		7.802	10^9/L		
Manual Neutrophil Bands Abs.			10^9/L		
Toxic Granules					

WBC

Hgb <110

PLT < 100

Rai Clinical Staging

Rai Stage	Characteristic	Median survival: Original Report (n = 125)[15]	Median survival: Mayo Clinic CLL Database* (n = 2397)
0	Lymphocytosis only	150 months	130 months
I	Lymphadenopathy	101	106
II	Organomegaly	71	88
III	Anemia**	19	58
IV	Thrombocytopenia†	19	69

*All individuals with CLL seen in the Mayo Clinic Division of Hematology since 1995.
**Hg < 11 g/dL
†Platelet count $<100 \times 10^9$/L

Poor Prognosticators

ZAP 70 protein

- BCR signaling

CD38

- Proliferation marker

Beta 2 Microglobulin

- Elevated, > 4x risk of second cancers

IGH Mutational Status

- Unmutated (often correlates w/Zap70 status)

Recurrent cytogenetic abnormalities-FISH

- del11q/ATM, trisomy 12, del17p/p53

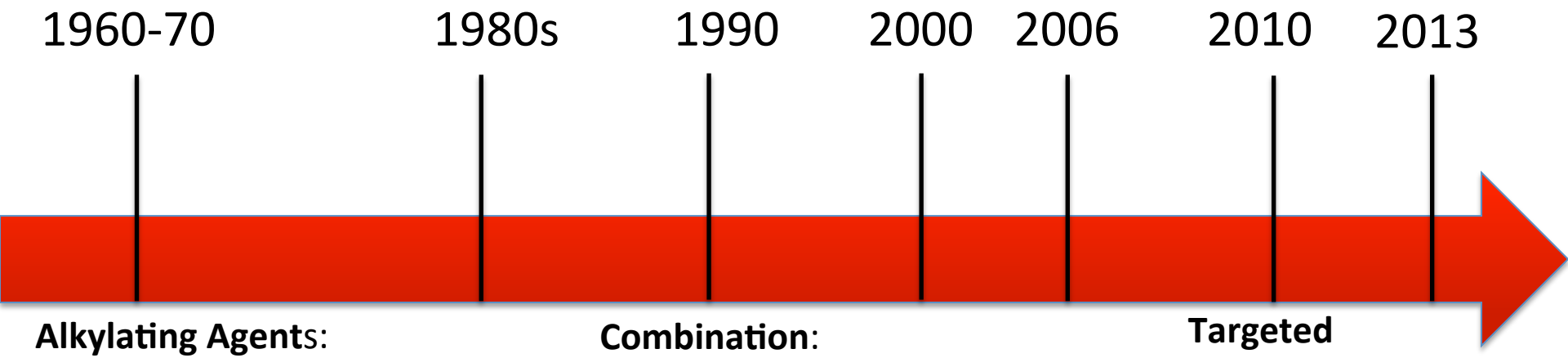
Approach to the Patient with CLL

- DO NO HARM
- Incurable disease for patients > 65 years of age
  - Quality of Life
- "Active observation"
- Indications to treat:
  - Traditional Chemotherapy / Tyrosine Kinase inhibitors
    - Infection
    - Symptoms
    - Rai Stage IV
    - Rapidly progressive disease
- Bone Marrow Transplant (< 65 years of age)

Counseling

- Decreased immunity, flu and pneumococcal vaccinations, no live vaccines
- Second cancer risk, higher than the general population and other indolent lymphomas
  - Dermatology referral, Age appropriate screening
- Active observation
- Treatment counseling

Treatment Evolution



Alkylating Agents:
Chlorambucil
Cyclophosphamide (C)

Nucleoside analogues:
Fludarabine (F)
Pentostatin
Cladrabine

Combination:
FC

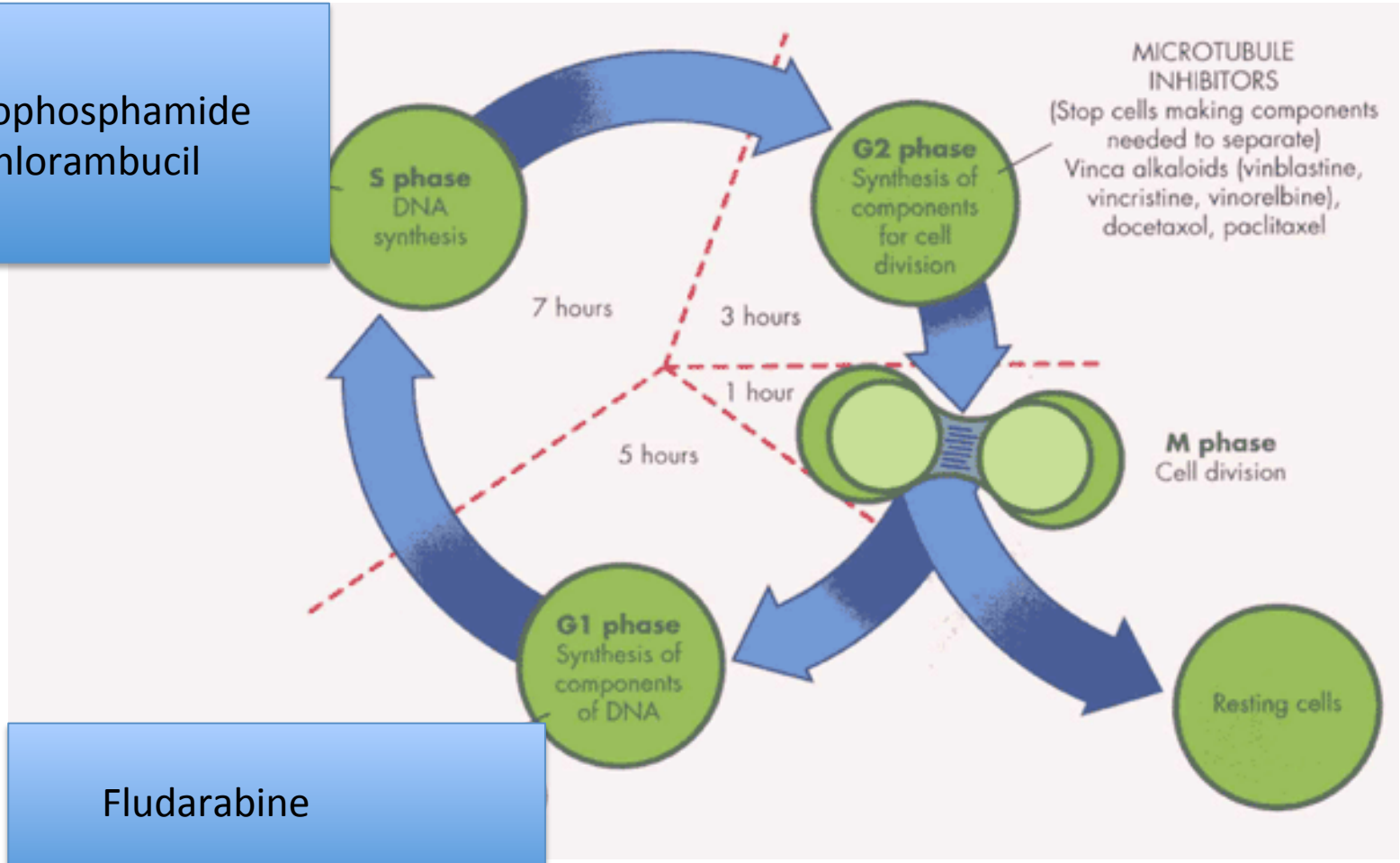
Monoclonal Antibodies:
Rituximab (CD 20)
Alemtuzumab (CD52)

Targeted agents
Ibrutinib
Fostamatinib
Idelalisib
ABT-199

Novel anti-CD 20 agents
Obinotuzi-mab

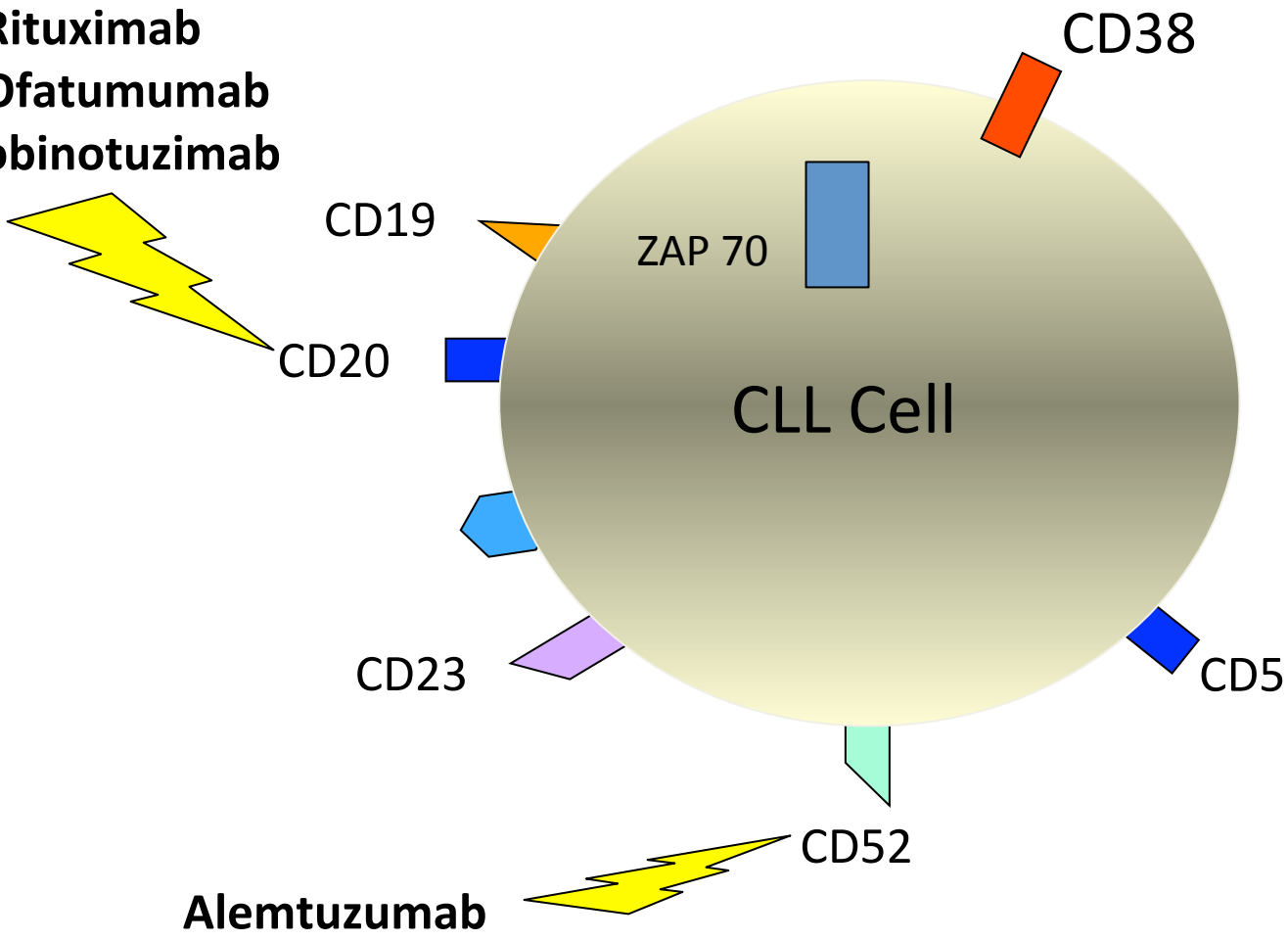
Cell Cycle

Cyclophosphamide
Chlorambucil



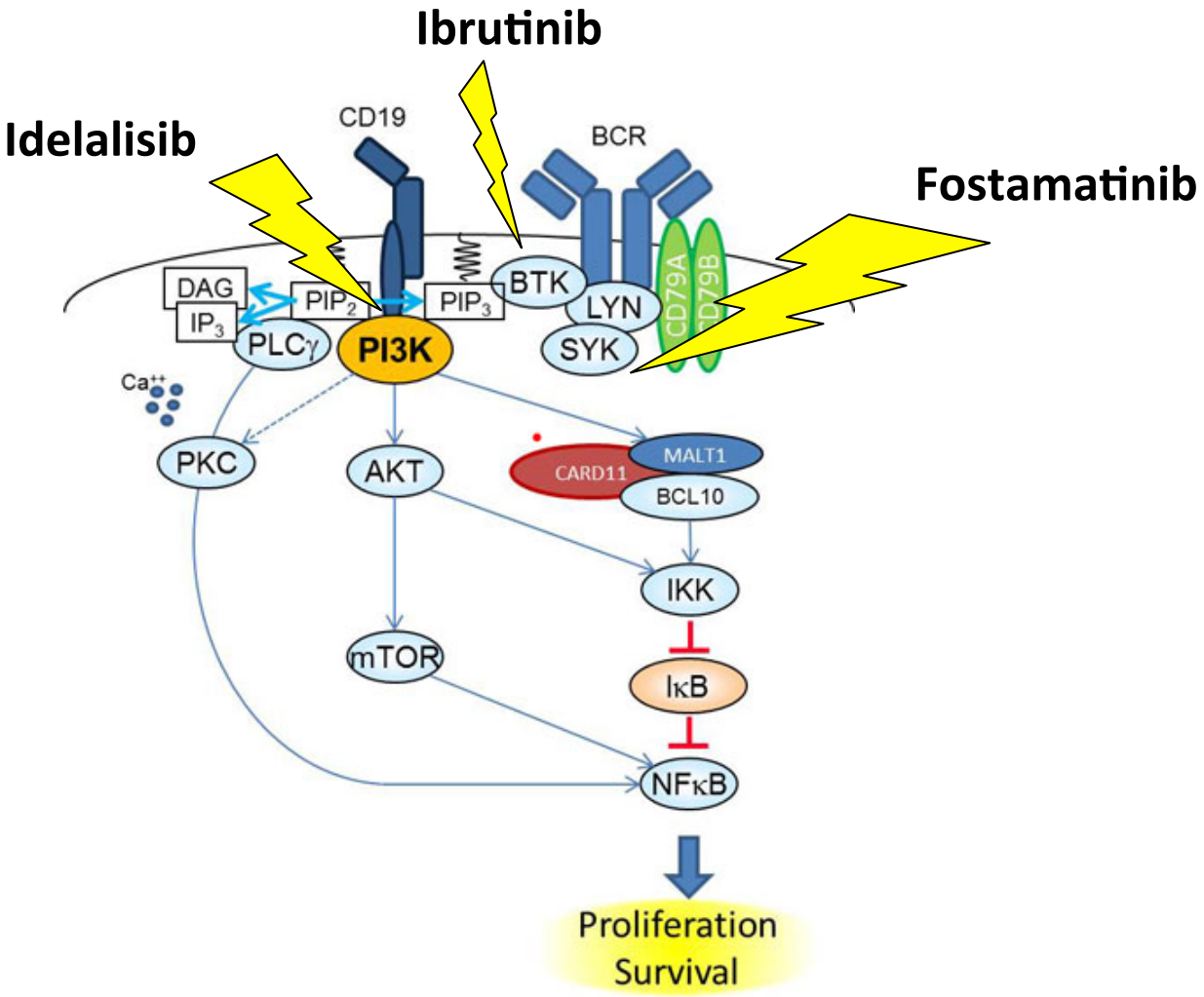
Fludarabine

Designer Drugs- monoclonal antibodies



Proposed mechanism of action AD cellular mediated lysis

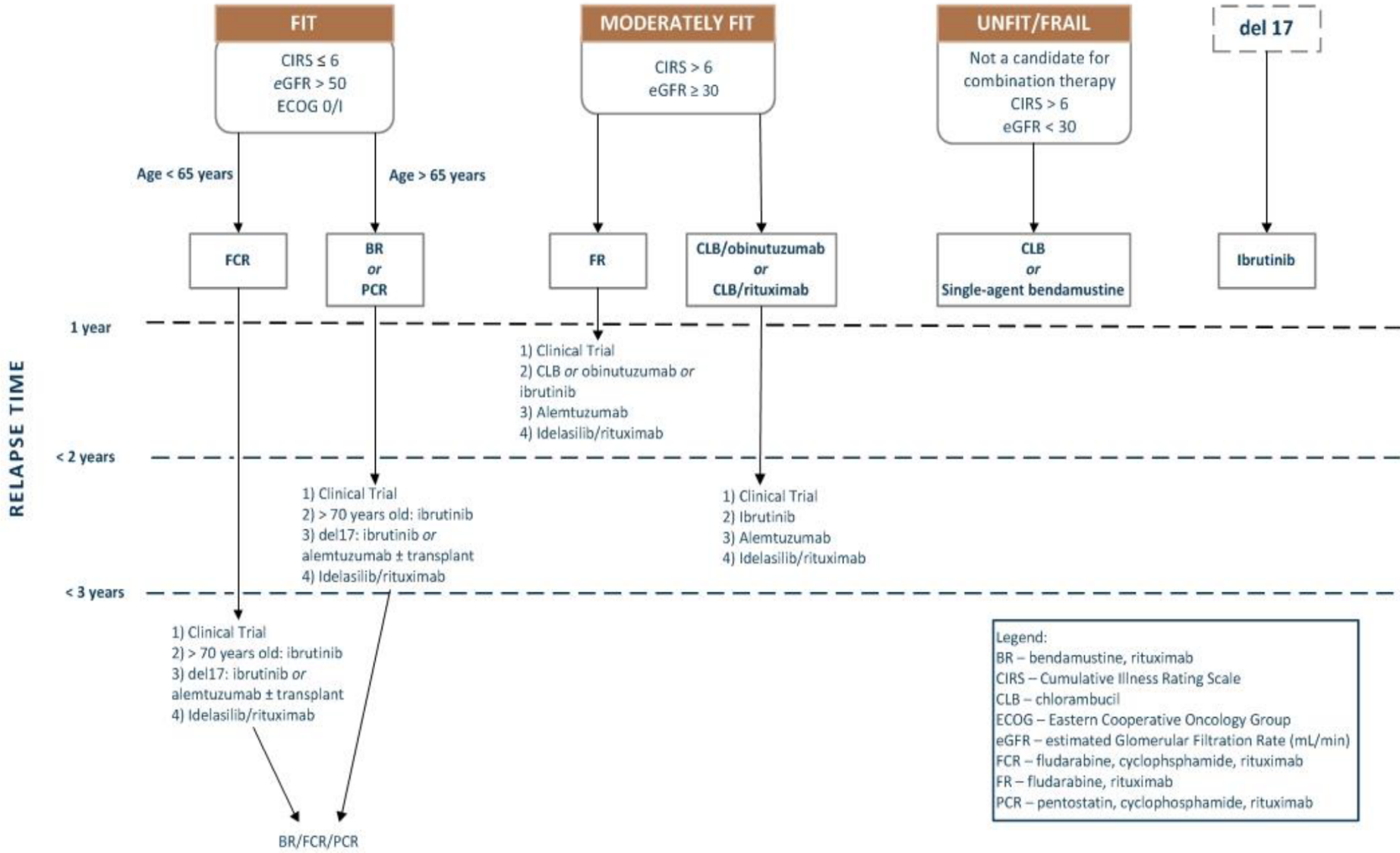
Novel targeted agents-Precision Medicine



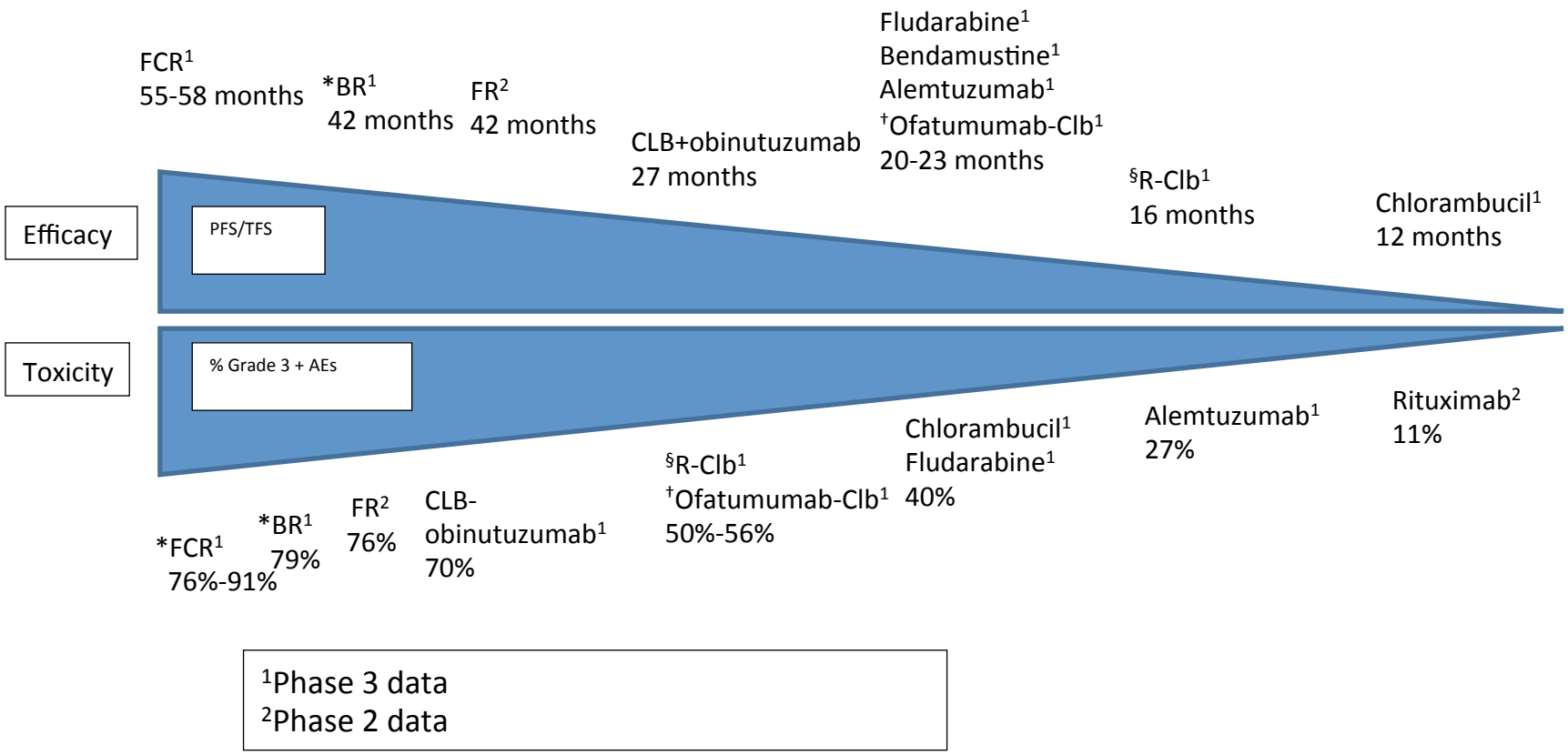
Treatment Stratification

- > 65 or < 65 years of age
- Comorbidity index rating system (CIRS)
  - > 6 or < 6
- Renal Function

Treatment Options for Chronic Lymphocytic Leukemia



Balancing Efficacy and Toxicity



[1]Phase 3 data
[2]Phase 2 data

Owen CJ et al. Clin Lymphoma Myeloma Leuk 2015

Case 1

- 65 year old male
- WBC 12
- Absolute Lymphocyte count 4.0
- No Clinical findings

Case 1

- What is the diagnosis?
- **MBL**
- CLL
- SLL

Case 2

- 91 year old male
- WBC 150
- Absolute lymphocyte count 145
- Asymptomatic

Case 2

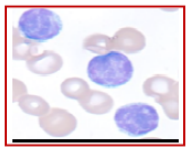
- Should he be treated ?
- Yes, if he has severe cytopenias, hemoglobin <110 and PLTs <100
- No, no other symptoms and normal hemoglobin and PLTs
- **Both of the Above**

Work-Up of LYMPHOCYTOSIS

Lymphocytes >5 (peristent, >2CBCs over 3 months)

Blood Smear AND History & Physical Exam
include nodes and spleen

Any of these Concerning Features
- Lymphocytes >30
- Hgb <110, PLT <100
- Night sweats/ weight loss
- Splenomegaly
- Lymphadenopathy



Flow Cytometry[1] AND

REFER TO LYMPHOMA DSG

Asymptomatic

Flow Cytometry[1]

Clonal?

NO

Normal / Polyclonal

Rule out secondary causes

IF Persistent Lymphocytosis AND Assistance required to interpret flow cytometry

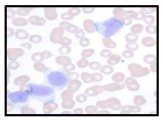
CALL CANCER QUESTION HELPLINE 204-226-2262

YES

REFER TO LYMPHOMA DSG

Refer to Supplemental Clonal Pathway

"Reactive" Lymphocytes
Patient symptoms of infection or acute illness



IF Persistent

Work-up for secondary causes
- Immunization
- Viral (eg. Hepatitis, CMV, EBV, adeno)
- Bacteria
- Drugs (eg. Steroids)
- Autoimmune
- Smoking
- Endocrine (eg. Myxedema, Addison's, hypopituitarism)
- Splenectomy
- Stress

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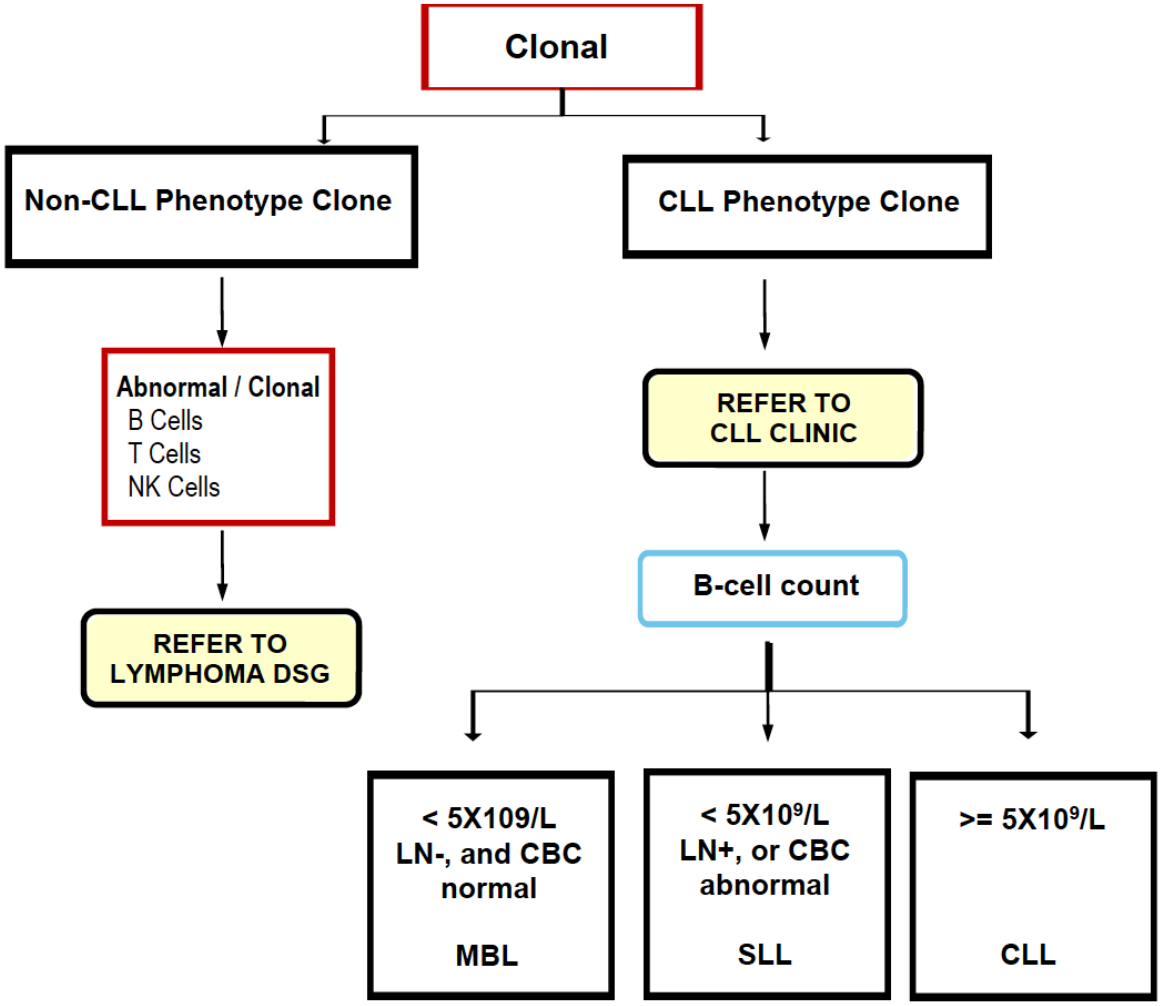
Strati and Shanafelt. Blood, 454-462, 2015 (Adapted) June.6, 2016: ©Hematology DSG FINAL (Johnston & Banerji)

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.

[1]**DSM-LIM>Immunology> Immunophenotyping (Peripheral Blood)** https://apps.sbgh.mb.ca/labmanual/test/loadDocumentPdf?documentId=55

Work-Up of CLONAL LYMPHOCYTES



Take Home Messages

- There is no such thing as a “good leukemia” in the eyes of the patient
- MBL carries the same risk of immunosuppression as a CLL or SLL patient
- Management is a balance in timing therapy when appropriate
- Tailored therapies based on age and comorbidities aim to decrease toxicities

Take Home Messages

- If patients are symptomatic or have severely abnormal counts
  - REFER to Lymphoma DSG and Order FLOW
- Persistent monoclonal lymphocytosis should be referred to Lymphoma DSG

http://www.cancercare.mb.ca/resource/File/CPG/Lymphoproliferative_Disorders/DM_LYMP-Consensus_Recommendations_for_Mgmt_Chronic_Lymphocytic_Leukemia_2015-10-30.pdf

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Questions?

vbanerji1@cancercare.mb.ca

University of Manitoba

8. A 91 year old male with WBC of 150 x10^9/L. Absolute lymphocyte count is 145 x10^9/L. Other than HTN and BPH he has no other medical comorbidities. He feels well with no constitutional symptoms. Flow cytometry is consistent with CLL HGB is 123 g/L. PLTs are 123 x10^9/L.
Does this patient require treatment for CLL?

A. Yes

B. No

C. Maybe

8. A 91 year old male with WBC of 150 x10^9/L. Absolute lymphocyte count is 145 x10^9/L. Other than HTN and BPH he has no other medical comorbidities. He feels well with no constitutional symptoms. Flow cytometry is consistent with CLL HGB is 123 g/L. PLTs are 123 x10^9/L.
Does this patient require treatment for CLL?

A. Yes

B. No

C. Maybe