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FOR Health Professionals

The Price of Progress: An update on the management of Chronic Lymphocytic Leukemia (CLL)

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Presenter Disclosure

- **Faculty : Dr. Versha Banerji**

- **Relationships with commercial interests:**
- **Grants/Research Support:** Canadian Institutes of Health Research, Leukemia Lymphoma Society of Canada, CancerCare Manitoba Foundation, University of Manitoba, Research Manitoba, Janssen, Abbvie
- **Speakers Bureau/Honoraria:** Medplan, MediCom
- **Consulting Fees:** Lundbeck, Abbvie, Janssen, Gilead, Roche, Astra Zeneca
- **Patents and Liscencing Fees:** BIOGEN

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Mitigating Potential Bias

- Guideline based discussion on treatments that are approved by Health Canada will be discussed

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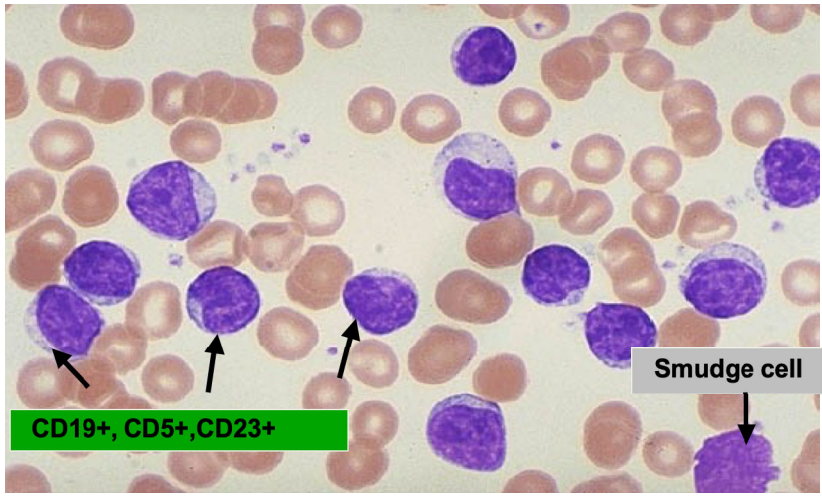
Learning Objectives

1. Referral Process and overview of CLL and similar lympho-proliferative disorders
2. Risk stratification and Treatment decisions
3. Where we can use your help: drug induced toxicities and their management

Referral to Hematology

- Approach to the elevated Lymphocyte count
- Often asymptomatic but could have short and long term sequela



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Lymphocytosis

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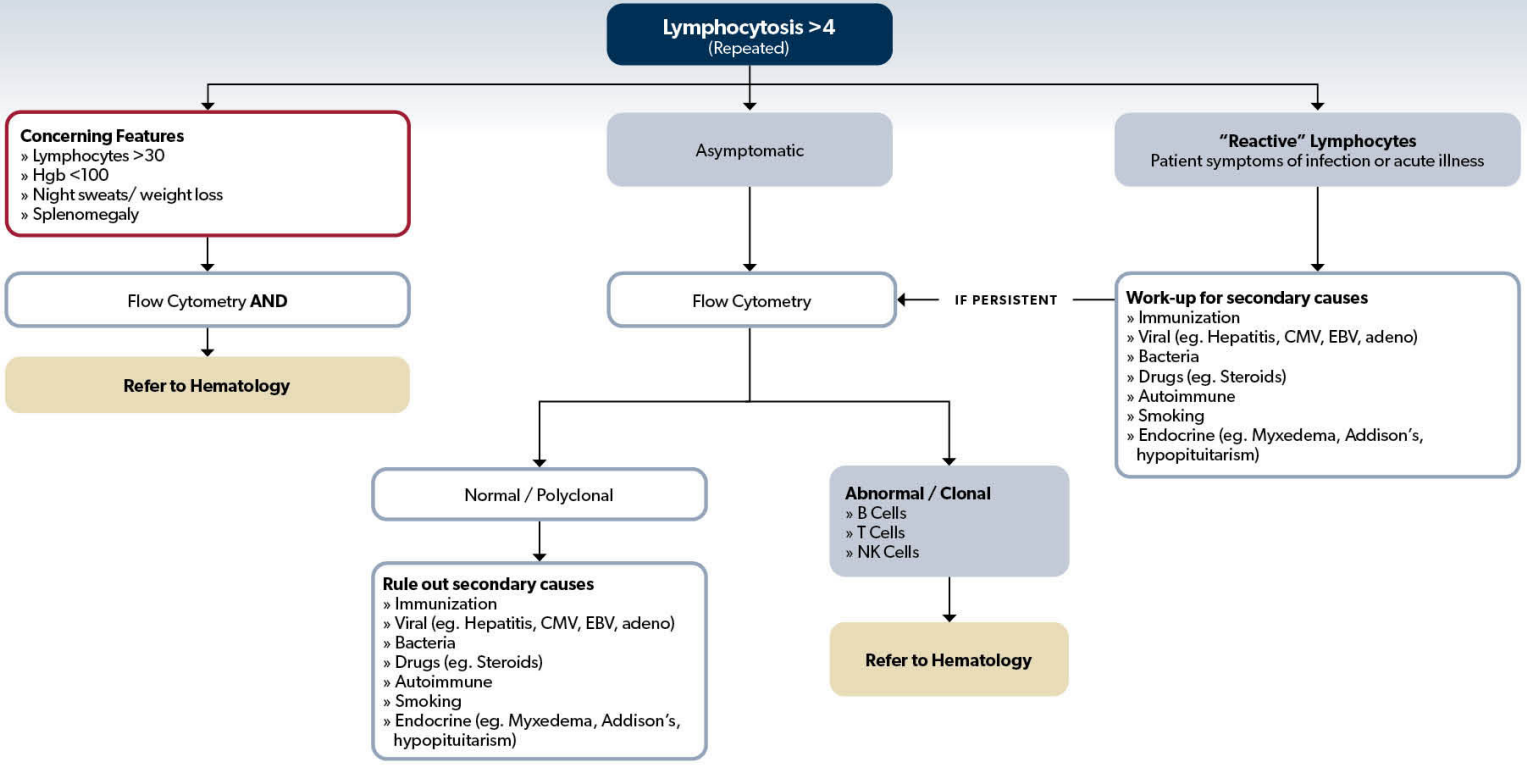

Pathways are subject to clinical judgement and actual practice patterns may not always follow the proposed steps in this pathway.

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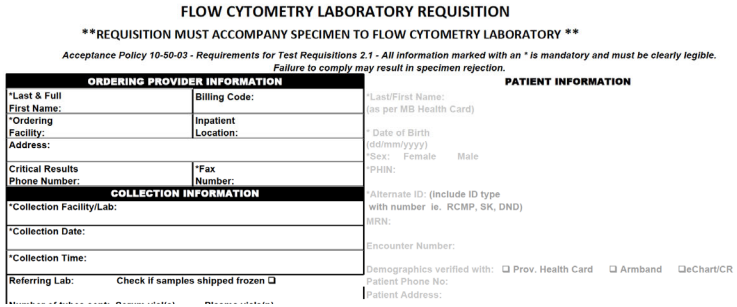
Please Order FLOW CYTOMETRY



FLOW CYTOMETRY LABORATORY REQUISITION

****REQUISITION MUST ACCOMPANY SPECIMEN TO FLOW CYTOMETRY LABORATORY ****

*Acceptance Policy 10-50-03 - Requirements for Test Requisitions 2.1 - All information marked with an * is mandatory and must be clearly legible. Failure to comply may result in specimen rejection.*

ORDERING PROVIDER INFORMATION	
*Last & Full First Name:	Billing Code:
*Ordering Facility:	Inpatient Location:
Address:	
Critical Results Phone Number:	*Fax Number:

COLLECTION INFORMATION
*Collection Facility/Lab:
*Collection Date:
*Collection Time:
Referring Lab: Check if samples shipped frozen ❑

PATIENT INFORMATION

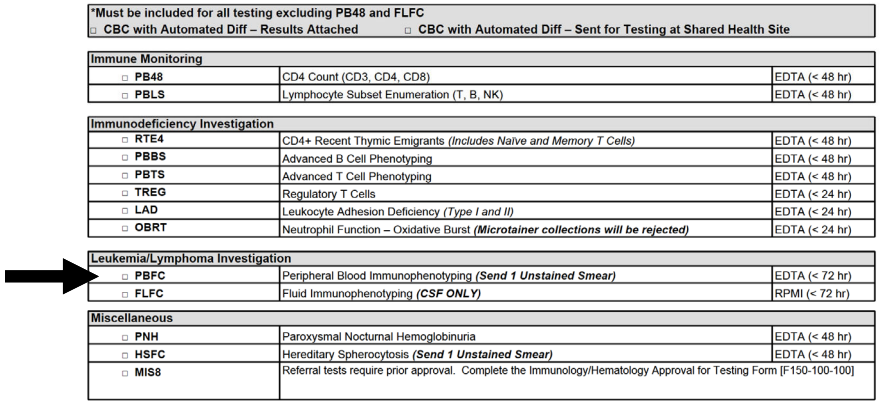
*Last/First Name:
(as per MB Health Card)

* Date of Birth
(dd/mm/yyyy)
*Sex: Female Male
*PHIN:

*Alternate ID: (include ID type with number ie. RCMP, SK, DND)
MRN:

Encounter Number:

Demographics verified with: ❑ Prov. Health Card ❑ Armband ❑eChart/CR
Patient Phone No:
Patient Address:



*Must be included for all testing excluding PB48 and FLFC
□ CBC with Automated Diff – Results Attached □ CBC with Automated Diff – Sent for Testing at Shared Health Site

Immune Monitoring		
□ PB48	CD4 Count (CD3, CD4, CD8)	EDTA (< 48 hr)
□ PBLS	Lymphocyte Subset Enumeration (T, B, NK)	EDTA (< 48 hr)

Immunodeficiency Investigation		
□ RTE4	CD4+ Recent Thymic Emigrants *(Includes Naïve and Memory T Cells)*	EDTA (< 48 hr)
□ PBBS	Advanced B Cell Phenotyping	EDTA (< 48 hr)
□ PBTS	Advanced T Cell Phenotyping	EDTA (< 48 hr)
□ TREG	Regulatory T Cells	EDTA (< 24 hr)
□ LAD	Leukocyte Adhesion Deficiency *(Type I and II)*	EDTA (< 24 hr)
□ OBRT	Neutrophil Function – Oxidative Burst ***(Microtainer collections will be rejected)***	EDTA (< 24 hr)

Leukemia/Lymphoma Investigation		
□ PBFC	Peripheral Blood Immunophenotyping ***(Send 1 Unstained Smear)***	EDTA (< 72 hr)
□ FLFC	Fluid Immunophenotyping ***(CSF ONLY)***	RPMI (< 72 hr)

Miscellaneous		
□ PNH	Paroxysmal Nocturnal Hemoglobinuria	EDTA (< 48 hr)
□ HSFC	Hereditary Spherocytosis ***(Send 1 Unstained Smear)***	EDTA (< 48 hr)
□ MIS8	Referral tests require prior approval. Complete the Immunology/Hematology Approval for Testing Form [F150-100-100]	

- https://sharedhealthmb.ca/wpfd_file/flow-cytometry-requisition/

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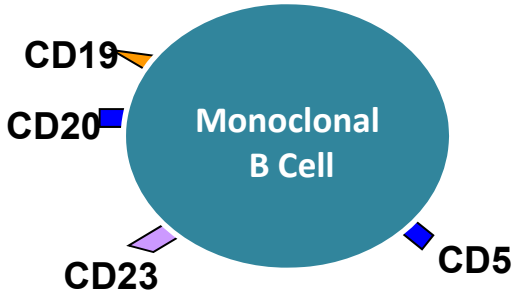
MBL	CLL	SLL
Monoclonal B cell Lymphocytosis	**Chronic Lymphocytic Leukemia**	**Small Lymphocytic Lymphoma**
<5 X10^9 cell/L	**>5 X10^9 cell/L**	<5 X10^9 cell/L
Uniformed cells circulating	Uniformed cells circulating	Uniformed cells circulating
NOT Cancer but may progress to one		Positive lymph node/ Bone marrow biopsy



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Epidemiology

- ~2600 new patients diagnosed in Canada each year (population based)
  - 100 new cases in Manitoba every year, many live with it
- Average age at diagnosis is 72 years
- More common in men (1.3 to 1)
- No known cause
- Chronic cancer which is actively observed
- Incurable cancer but **highly treatable despite advanced age and comorbidities**

Indications for treatment

- Progressive cancer symptoms
- Recurrent Infections
- A Hemoglobin <110, or Platelet count < 100
- Bulky lymphadenopathy
- Auto immune complication associated with the disease
  - Hemolysis
  - Immune mediated Thrombocytopenia
  - Pure red cell aplasia

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Then- Treatment was chemotherapy based

- Could the patient tolerate chemo?
- Can their bodies process the metabolites?

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NOW- Treatment decisions and what we consider

- Age is irrelevant to access treatment, but prognostic

- Fitness/overall health status is also less important due to paradigm shift in available treatments

- **Molecular testing**

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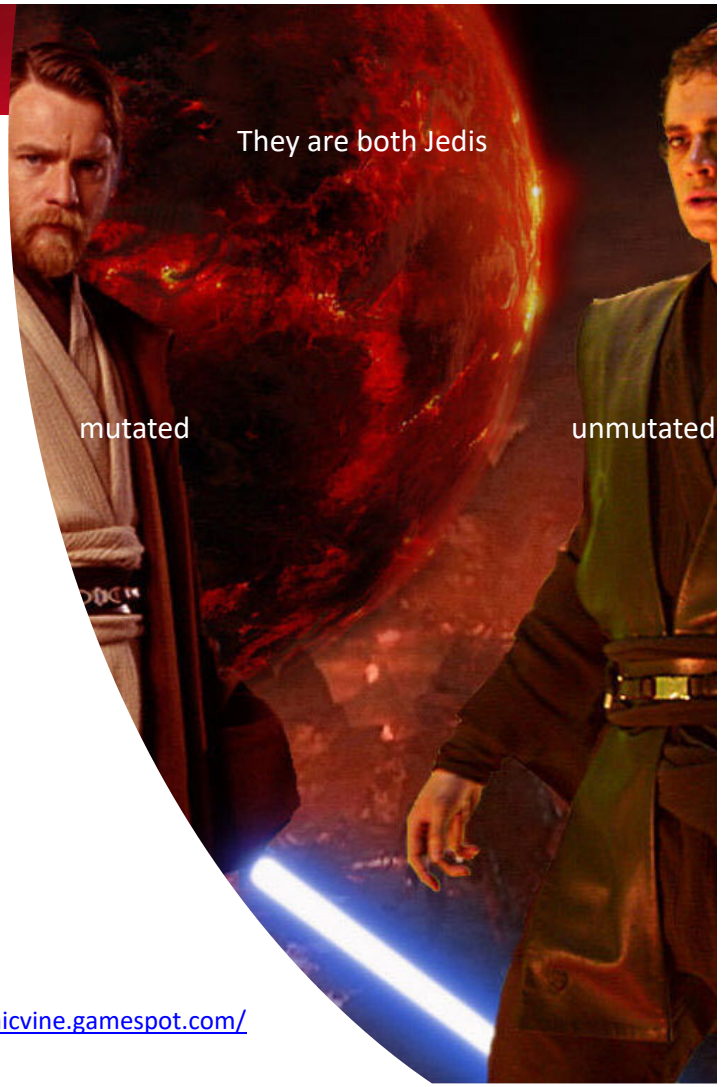
IGVH Mutation status

- A Patient may have A mutated (low risk) or unmutated (IGVH) (high risk)

- The unmutated IGVH CLL represents a less mature CLL cell
  - more aggressive trajectory likely needing treatment repeatedly

- A mutated CLL cell represents a more mature CLL cell
  - Less aggressive disease course
  - Delayed treatment course
  - Often Durable remissions



https://comicvine.gamespot.com/

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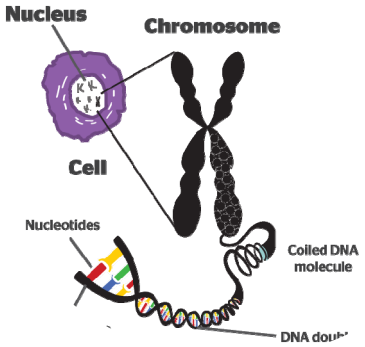
Hello Dolly, I mean FISH

Florescent in Situ Hybridization

Looking for chromosomal breaks

Identify chromosomal breaks that define High Risk Disease based on loss of tumour suppressor genes
P53*, also look at gene level sequences
ATM



Nature **volume 534**, pages604–608(2016), Disney's Finding Nemo

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Why does this matter?

Risk Category	CLL-IPI Risk Score	5 yr OS	10 yr OS	Hazard Ratio (95% CI)
Low	0-1	93.2%	79%	-
Intermediate	2-3	79.3	39.2	3.5 (2.5-4.8)
High	4-6	63.3	21.9	1.9 (1.5-2.3)
Very High	7-10	23.3	3.5	3.6 (2.6-4.8)

CLL-IPI : International Prognostic Index

- **del17p/TP53 status (4), IGHV status (2), ß$_2$M (2), Stage (1), Age (1)**
- **Chemotherapy based outcomes**

Bye Bye Chemotherapy ?

Low risk

- <65 – Fludarabine Cyclophosphamide or BTKi
- >65- Chlorambucil Obinutuzumab
  - BTKi
  - BCL2 inhibitor

High Risk

- BTKi
- BCL2 inhibitors

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BTKi- Ibrutinib, acalabrutinib, Zanzibrutinib…

- Phase 3 clinical trials have demonstrated long term efficacy in disease control and progression free survival benefits especially in high-risk patients in the relapsed and frontline setting

- In young (<65) and fit patients there is also an overall survival advantage

- Most are designed as Continuous therapies

Shanafelt TD, et al. ASH 2019 Meeting: Abstract 33, NEJIM 2019

Sharman JP, Banerji V et al. ASH 2019 Meeting: Abstract 31, Lancet 2020

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What is the price we pay?

Toxicities in patients

- Skin rashes
- Infections
- Cardiovascular
- Musculoskeletal

Toxicities to the health system

- Longer duration of treatment
- Longer sequela of toxicity management
- Increased cost of treatment
  - $10,000/per month

Adverse event	Management
Diarrhea	• Typically resolves quickly without need for dose modification[40] • Antidiarrheals such as loperamide can be used to manage symptoms[40] • Some situations (for example, fever, abdominal discomfort) should be evaluated for infection[41] • For grade 3 cases, therapy can be held until reduced to grade 2 or lower, followed by re-initiation of same dose, with option of dose reduction if severe diarrhea recurs[40]
Rash	• No dose modifications needed, can recover spontaneously without specific treatment[40,42] • Palpable, pruritic rash may require topical corticosteroids and oral antihistamines[40,42]
Arthralgia	• Generally, no dose modification needed[40] • Acetaminophen or short pulses of prednisone can be given[40] • Anti-inflammatories (for example, ibuprofen) may be used with caution (because of bleeding risk) if not resolved after 6 months[40] • If persistent and significantly affecting quality of life, dose can be delayed for up to 1 week and reduced upon re-initiating BTK inhibitor[40]
Headache (acalabrutinib)	• Managed with acetaminophen or caffeine, or both, without the need for dose alteration[40,41]

Atrial fibrillation	• Inquire about symptoms of arrhythmias and have a low threshold for cardiac workup[43]
	• Delaying ibrutinib dose is not recommended in the event of atrial fibrillation because it does not affect the resolution rate[44]
	• Management should involve consultation with a cardiologist and assessment of stroke (CHA_2DS_2-VASc score) and bleeding (HAS-BLED score) risk[40]
	  • CHA_2DS_2-VASc score 0–1: no anticoagulation required[42]
	  • CHA_2DS_2-VASc score > 2: anticoagulation needed, consider alternative CLL treatment or anticoagulation with newer agent (for example, apixaban, enoxaparin) if HAS-BLED score is low[40–42]
	• Rate or rhythm control (or both) should be achieved, with preference for beta-blockers (diltiazem, verapamil, and amiodarone are inhibitors of CYP3A4 and might increase ibrutinib toxicity; serum amiodarone might increase because of inhibition of P-glycoprotein by ibrutinib)[40]
	• Discontinue therapy if unprovoked initial atrial fibrillation occurs within first 3 months of treatment or is

Ventricular tachycardia (ibrutinib)	• Discontinue therapy if unprovoked significant ventricular tachycardia occurs within first 3 months or is recurrent at any point[40] • Inquire about symptoms of arrhythmias and have a low threshold for cardiac work-up[43]
Hypertension	• Monitor blood pressure regularly[45] • Upon diagnosis, start antihypertensive therapy without modifying BTK inhibitor dose[40]
Major bleeding	*Prevention* • Concurrent warfarin not recommended; vitamin K antagonist, DOAC, and anti-platelet therapy should be avoided[41] • If anticoagulation required, alternative CLL therapy or use of a newer anticoagulant (for example, apixaban, enoxaparin) might be practical[41,45] • Hold BTK therapy 3–4 days before and after minor surgery, or 1 week after major surgery[41] *Management* • Upon major bleeding event, discontinue BTK inhibitor treatment and transfuse with platelets until bleeding is resolved[45]
Infection	*Prevention* • Consider prophylactic acyclovir or valacyclovir because of increased risk of varicella zoster[45] • Prophylaxis against *Pneumocystis jirovecii* pneumonia could be considered; however, evidence is weak and further study is needed[46] • Live-attenuated virus vaccine should be avoided[47] *Management* • Discontinuation not required for grades 1–3 infections[45] • With grade 4 infection, delay BTK inhibitor dose until resolved to grade 3 or less[45] • Thoroughly evaluate suspected fungal infections, with high suspicion for aspergillosis[45] • Evaluate potential drug interactions between BTK inhibitors and anti-infective agents[45] • If strong CYP3A4 inhibitors are required, reduced BTK inhibitor dose and careful monitoring for toxicity is recommended[45]

Banerji V et al Current Oncology 2020

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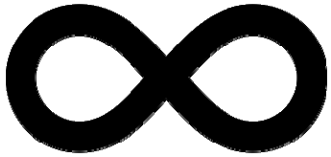
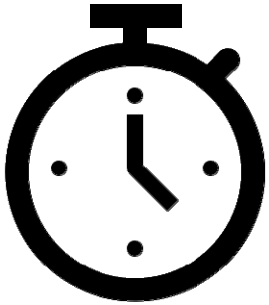
Moving to time limited therapy





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BCL-2 Inhibitors- Venetoclax

- High risk of tumour lysis
- Lots of initial blood monitoring
- Easily tolerated
- Overall survival advantage over chemotherapy in the front and second-line setting
- Being combined with Anti CD 20 antibodies to deliver time limited treatment options or as a single continuous agent where appropriate

Fischer K, *et al. N Engl J Med* 2019; DOI: 10.1056/NEJMoa1815281.

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Barriers to Practice Change

- Geography
- Transportation
- Language
  - Most exacerbated by COVID 19
  - Working with CCMB to have all treatments accessible

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Take home message(s)

- If your stable patient has developed a new cardiac toxicity (a fib, or hypertension), rash, bleeding withing the first 3-6 months on therapy with Ibrutinib, acalabrutinib, please let us know. This may be drug induced.

- So many options for people that are accessible and equitable.

- Many drugs being used in other lymphomas and elderly AML and MDS

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Thank you

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