



AAPA 2023

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# OPTIMIZING CARE OF PATIENTS WITH CLL

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Nashville, TN



OPTIMIZING CARE OF PATIENTS WITH CLL

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## **DISCLOSURES**

- Advisory Boards: AbbVie, TG Therapeutics, Pharmacyclics, Astra Zeneca, Janssen

OPTIMIZING CARE OF PATIENTS WITH CLL

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## LEARNING OBJECTIVES

At the conclusion of this session, participants should be able to:

1. List medications commonly utilized in their practice that interact with oral targeted therapies in patients with CLL
2. Identify possible side effects of oral targeted therapies in patients with CLL relevant to their daily practice
3. Educate patients with CLL on the importance of age-appropriate cancer screenings and routine vaccinations

OPTIMIZING CARE OF PATIENTS WITH CLL

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## TEST YOUR KNOWLEDGE

- CLL is associated with a 6-8x higher risk of which of the following:
  - A. Colorectal Cancer
  - B. Non-melanoma Skin Cancer
  - C. Melanoma Skin Cancer
  - D. Breast Cancer

OPTIMIZING CARE OF PATIENTS WITH CLL

## TEST YOUR KNOWLEDGE

- True or false: live vaccines are contraindicated in patients with CLL
  - A. True
  - B. False

## TEST YOUR KNOWLEDGE

- Which of the following therapies for COVID-19 interacts with several oral therapies for CLL, including BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), and the BCL2 inhibitor venetoclax?
  - A. Paxlovid (nirmatrelvir + ritonavir)
  - B. Molnupiravir
  - C. Remdesivir
  - D. Convalescent Plasma

OPTIMIZING CARE OF PATIENTS WITH CLL

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## TEST YOUR KNOWLEDGE

- Which of the following side effects are not described with use of BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) in CLL?
  - A. Bleeding
  - B. Hypertension
  - C. Cardiac arrhythmias
  - D. QT prolongation

## TEST YOUR KNOWLEDGE

- Tumor Lysis Syndrome can be associated with which of the following oral therapies in CLL?
  - A. Ibrutinib
  - B. Acalabrutinib
  - C. Zanubrutinib
  - D. Venetoclax



## OPTIMIZING CARE OF PATIENTS WITH CLL

# OUTLINE

### VISION

Provide practical clinical pearls for taking care of patients with CLL outside of the Hematology clinic

### INTRODUCTION TO CLL

Pathophysiology & Epidemiology



### SUPPORTIVE CARES IN CLL

Routine health maintenance: second malignancies & vaccinations  
Covid considerations

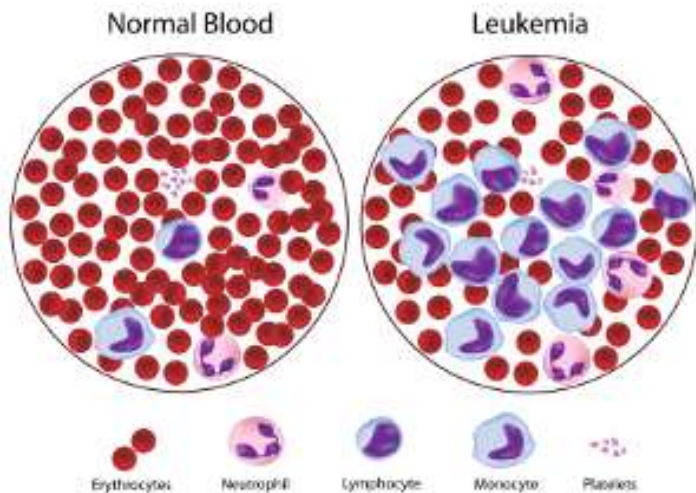
### CLL THERAPY: WHAT YOU NEED TO KNOW

BTK inhibitors: ibrutinib, acalabrutinib, zanubrutinib  
BCL2 inhibitor: venetoclax




OPTIMIZING CARE OF PATIENTS WITH CLL

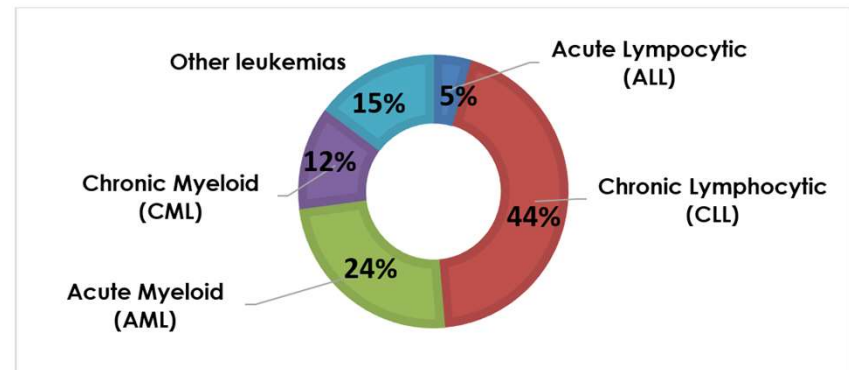
# LEUKEMIA BASICS



<http://www.physicianassistantexamreview.com/leukemia-lymphoma-multiple-myeloma/>

- Leukemia = “leukos” + “hamia”  
i.e. “white blood”

	Myeloid	Lymphoid
Acute	Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia
Chronic	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia 

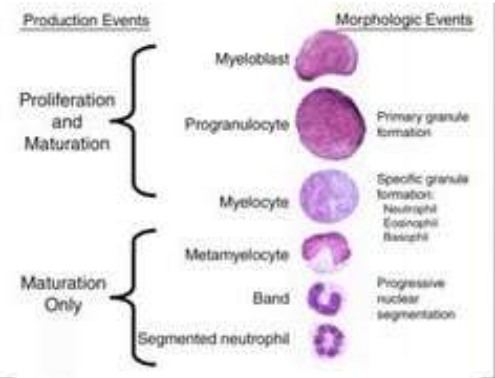


\*excluding Quebec ages 15-99 years

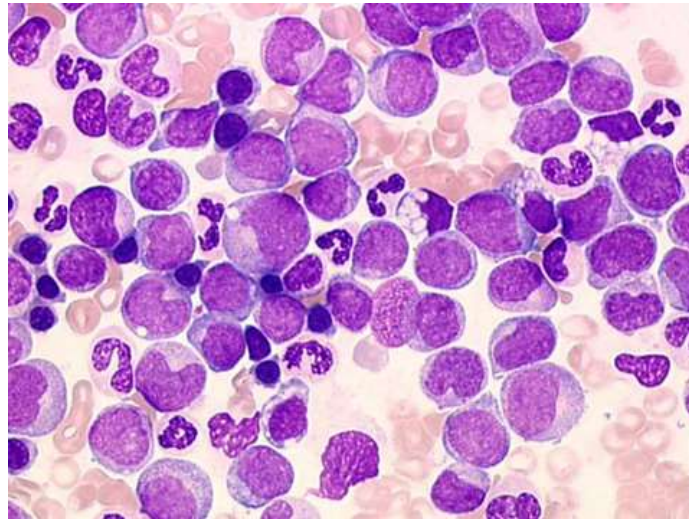
<http://www.llscanada.org/disease-information/facts-and-statistics#Leukemia>

OPTIMIZING CARE OF PATIENTS WITH CLL

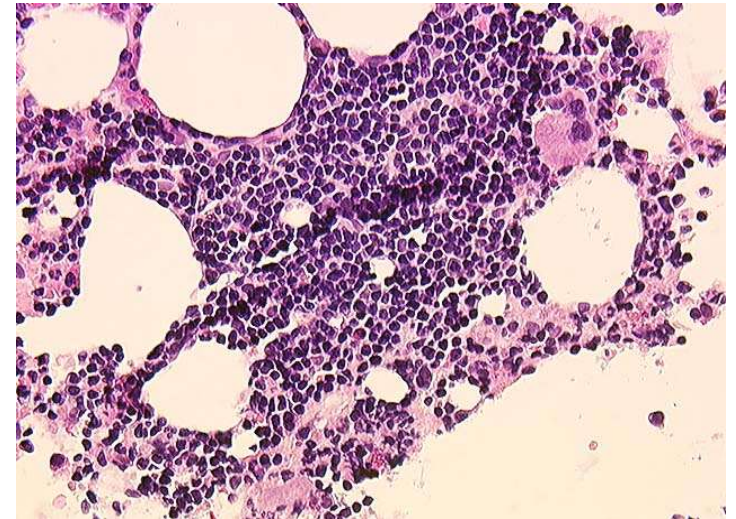
# LEUKEMIA BASICS: SIZE MATTERS!



<https://clinicalgate.com/neutrophil-maturation/>



<http://atlasgeneticsoncology.org/Reports/0219QuilichiniID100006.html>



<https://path.upmc.edu/cases/case141/images/micro3.jpg>

OPTIMIZING CARE OF PATIENTS  
WITH CLL

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## CLL: WHEN WE WATCH, WHEN WE TREAT

- Often an incidental diagnosis
  - Elevated WBC count
    - Predominately lymphocytes on differential
  - Diagnosis confirmed by flow cytometry
  - May also present as lymphadenopathy
    - Typically nontender, symmetric
    - Diagnosis confirmed with biopsy
- Indications for treatment<sup>15</sup>:
  - Large, symptomatic lymphadenopathy or splenomegaly
  - Cytopenias due to CLL
    - Hgb <10g/dL
    - PLT <100k
  - B symptoms

**CLINICAL PEARL:** if lymphoma is on your differential, cores or excisional biopsy are preferred

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Routine health maintenance: second malignancies & vaccinations  
Covid considerations

### CLL THERAPY: WHAT YOU NEED TO KNOW

BTK inhibitors: ibrutinib, acalabrutinib, zanubrutinib  
BCL2 inhibitor: venetoclax



## SUPPORTIVE CARES

### SECOND MALIGNANCIES

- Annual full body skin exam
  - 6-8x higher risk of NMSC
- Colorectal cancer screening
  - Mammogram
    - PSA?

### IMMUNIZATIONS

- No live vaccinations
- Pneumonia vaccinations
  - Shingrix series
  - Annual flu shot
- Covid-19 vaccines



## OPTIMIZING CARE OF PATIENTS WITH CLL

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# COVID CONSIDERATIONS

- Initial data (2020) demonstrated ~30% mortality rates for patients with CLL<sup>1,2</sup>
- Updates in 2021 weren't much better (~27-28%)<sup>3,4</sup>
  - Additional publications in 2023 show similar numbers<sup>5,6</sup>
- Patients with CLL have suboptimal response to vaccination, especially if on treatment<sup>7,8</sup>



## OPTIMIZING CARE OF PATIENTS WITH CLL

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# COVID CONSIDERATIONS

- Evusheld (tixagevimab + cilgavimab) no longer authorized for pre-exposure prophylaxis<sup>9</sup>
- Paxlovid (nirmatrelvir + ritonavir) interacts with CLL medications<sup>10</sup>
  - Often can be held – contact patient's hematologist
  - If cannot be held: remdesivir + convalescent plasma



## OPTIMIZING CARE OF PATIENTS WITH CLL

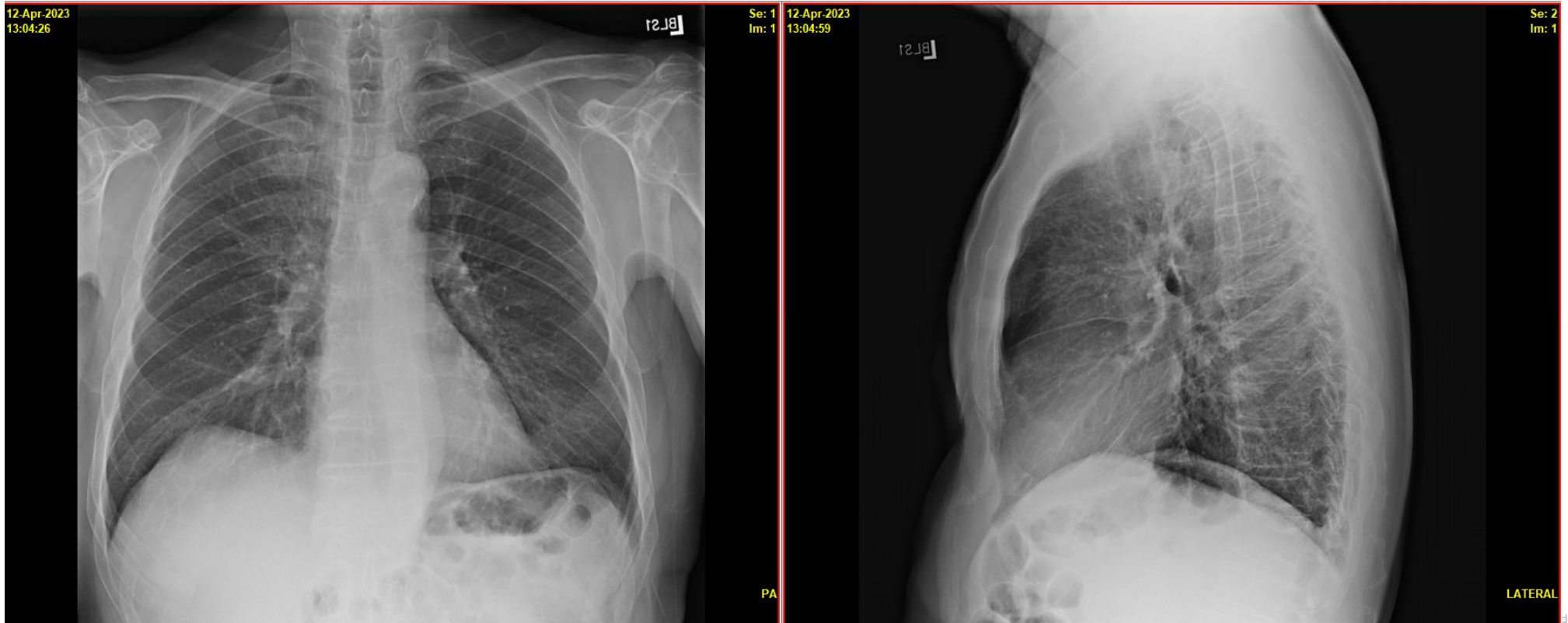
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# CASE STUDY

- 70M w/CLL in remission, off treatment for the past 6 months, and hyperlipidemia. He presents to clinic for routine CLL follow-up. He reports being diagnosed with COVID 4 months ago, treated with Paxlovid. He had what he describes as some minor residual “cold symptoms” but otherwise felt well. 1 month ago, he presented to the ED with shortness of breath; chest CT demonstrated multiple subsegmental pulmonary emboli and pneumonia. He was found to be COVID+ on PCR and admitted, where he was given remdesivir, Rocephin, and doxycycline, and started on anticoagulation with rivaroxaban.
- Today, he appears weak and fatigued. He has lost nearly 20 pounds since the initial diagnosis of Covid 4 months ago. He is tachycardic (pulse 109 bpm) and tachypneic (respiratory rate: 22/min); oxygen saturation is 99% on room air and he is afebrile.
- CXR is unremarkable. Repeat home Covid test in office is negative.

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**CASE STUDY**



## OPTIMIZING CARE OF PATIENTS WITH CLL

# CASE STUDY

- Labs demonstrate stable mild anemia (hemoglobin 10g/dL), normal WBC count, and lymphopenia ( $0.47 \times 10^9/L$ ). Creatinine is WNL but liver tests are abnormal:
  - Total bilirubin 0.7 mg/dL (WNL)
  - ALT 167 U/L (H) [reference range 7 - 55 U/L]
  - AST 130 U/L (H) [reference range 8 – 48 U/L]
  - Alkaline phosphatase 755 U/L (H) [reference range 40 – 129 U/L]
- IgG is low at 391 mg/dL [reference range 767 – 1590 mg/dL]

**CLINICAL PEARL:** Hypogammaglobulinemia is common in CLL – consider IVIG repletion if IgG is  $<400^*$  +  $\geq 3$  infections in the past 6 months

## OPTIMIZING CARE OF PATIENTS WITH CLL

# CASE STUDY

- The team elected to give him IVIG and arranges for this to be given same day. He receives pre-medications with acetaminophen & diphenhydramine but develops rigors and fever up to 38.4 degrees celsius and is directly admitted for further management and workup.
- Inpatient, he is treated with empiric cefepime for fevers & dyspnea and undergoes bronchoscopy, which demonstrates active COVID-19 infection. Additional infectious workup is negative. He was therefore treated with an additional 5 day course of remdesivir and convalescent plasma with improvement in symptoms. He also received a total of 5 days of cefepime and 3 of azithromycin as empiric antibiotic therapy.
- Liver biopsy was unremarkable; ultimately differential included drug-induced liver injury in light of multiple recent antibiotic and antiviral courses vs. infectious etiology. The liver biopsy was tested for COVID-19; results are pending.

**CLINICAL PEARL:** Consider persistent COVID infection and need for convalescent plasma in patients with CLL if symptoms are not improving – even if repeat home tests are negative

## OPTIMIZING CARE OF PATIENTS WITH CLL

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# OUTLINE

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### ~~INTRODUCTION TO CLL~~

~~Pathophysiology & Epidemiology~~

### ~~SUPPORTIVE CARES IN CLL~~

~~Routine health maintenance: second malignancies & vaccinations  
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### **CLL THERAPY: WHAT YOU NEED TO KNOW**

BTK inhibitors: ibrutinib, acalabrutinib, zanubrutinib  
BCL2 inhibitor: venetoclax



OPTIMIZING CARE OF PATIENTS WITH CLL

## ORAL THERAPY IN CLL

### Bruton's Tyrosine Kinase (BTK) Inhibitors

Ibrutinib (Imbruvica)  
Acalabrutinib (Calquence)  
Zanubrutinib (Brukinska)

Indefinite

### BCL2 Inhibitors

Venetoclax (Venclexta)

Fixed duration

OPTIMIZING CARE OF PATIENTS WITH CLL

## ORAL THERAPY IN CLL

- Which of the following medications do you see or use most commonly in your practice?
  - Azole antifungals  
(fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole)
  - Clarithromycin
  - Carbamazepine
  - Rifampin
  - St. John's Wort
  - Phenytoin
  - Diltiazem or Verapamil

OPTIMIZING CARE OF PATIENTS WITH CLL

## DRUG-DRUG INTERACTIONS WITH ORAL AGENTS IN CLL

- Both BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) and BCL2 inhibitor venetoclax are **major** CYP3A substrates
  - Moderate CYP3A inhibitors require dose reductions of CLL medications
    - *Fluconazole, clarithromycin, diltiazem, verapamil*
  - Strong CYP3A inhibitors should be avoided if possible
    - *St. John's wort, carbamazepine, rifampin, posaconazole, voriconazole*
- Both acalabrutinib and venetoclax are also *minor* p-gp substrates
- Always check for drug-drug interactions before starting a new medication in a patient with CLL
  - Can discuss with the patient's hematologist/oncologist to determine if CLL medications can be dose reduced to accommodate the medication

CLINICAL PEARL: ibrutinib has been associated with fungal infections, especially pulmonary aspergillosis - so avoiding azole antifungals may not always be possible<sup>11</sup>



OPTIMIZING CARE OF PATIENTS WITH CLL

## KEY CLASS EFFECTS: BTK INHIBITORS

ibrutinib, acalabrutinib, zanubrutinib



### **BLEEDING**

Reversible  
Impaired platelet  
function



### **HYPERTENSION**

Increases  
over time

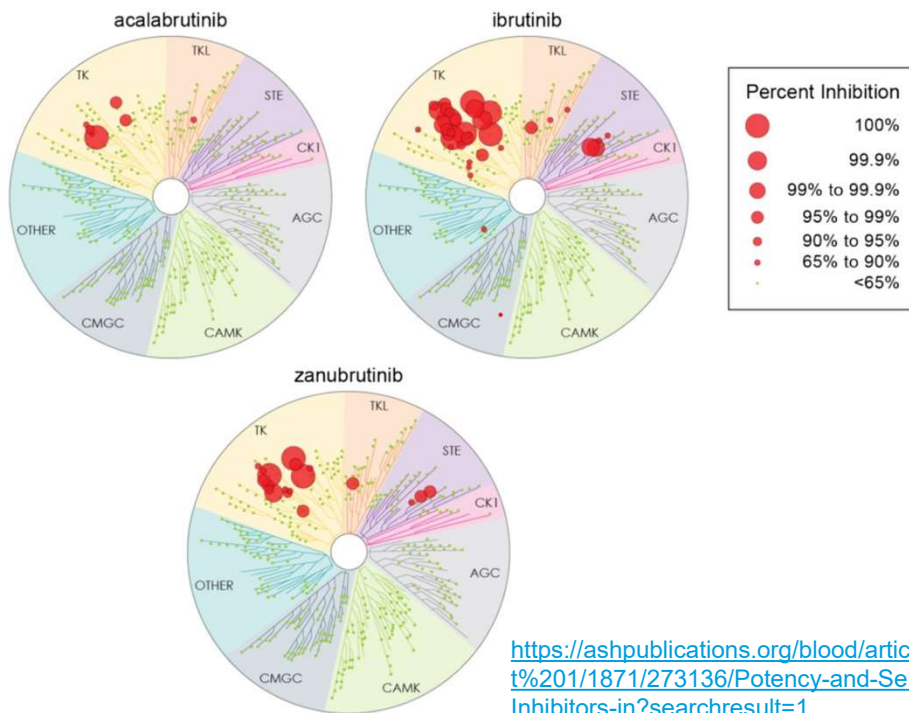


### **ARRHYTHMIAS**

Atrial fibrillation  
Ventricular  
arrhythmias

## OPTIMIZING CARE OF PATIENTS WITH CLL

# CAVEAT: RATES OF SIDE EFFECTS VARY BY BTK INHIBITOR



**A**

	Ibru	Acala	Zanu
Anemia	27	14	22
Neutropenia	23	10.6	53
Thrombocytopenia	16	7.3	32
Infection	83	79.4	75.8
Diarrhea	53	34.6	23.8
Fatigue	36	18.4	/
Upper respiratory infection	29	18.4	39
Arthralgia	22	15.6	17.4
Pneumonia	18	7.3	25
Hypertension	21	6.7	15.4
Headache	17	36.9	/
Atrial fibrillation	11	3.9	/
Rash	35	14	36
Bleeding/Bruising	55	39.1	28.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

■ ≥40  
■ ≥30  
■ ≥20  
■ ≥10

**B**

	Ibru	Acala	Zanu
Anemia	7	6.7	8
Neutropenia	18	9.5	15
Thrombocytopenia	6	2.8	5
Infection	31	14	10.8
Diarrhea	5	0.6	0.8
Fatigue	3	1.1	/
Upper respiratory infection	1	0	0
Arthralgia	2	0.6	3.4
Pneumonia	12	2.2	10
Hypertension	7	2.2	3.4
Headache	2	1.1	/
Atrial fibrillation	5	0	/
Rash	3	0.6	0
Bleeding/Bruising	6	1.7	3.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

■ ≥10  
■ ≥7.5  
■ ≥5  
■ ≥2.5

<https://www.nature.com/articles/s41375-020-01072-6>

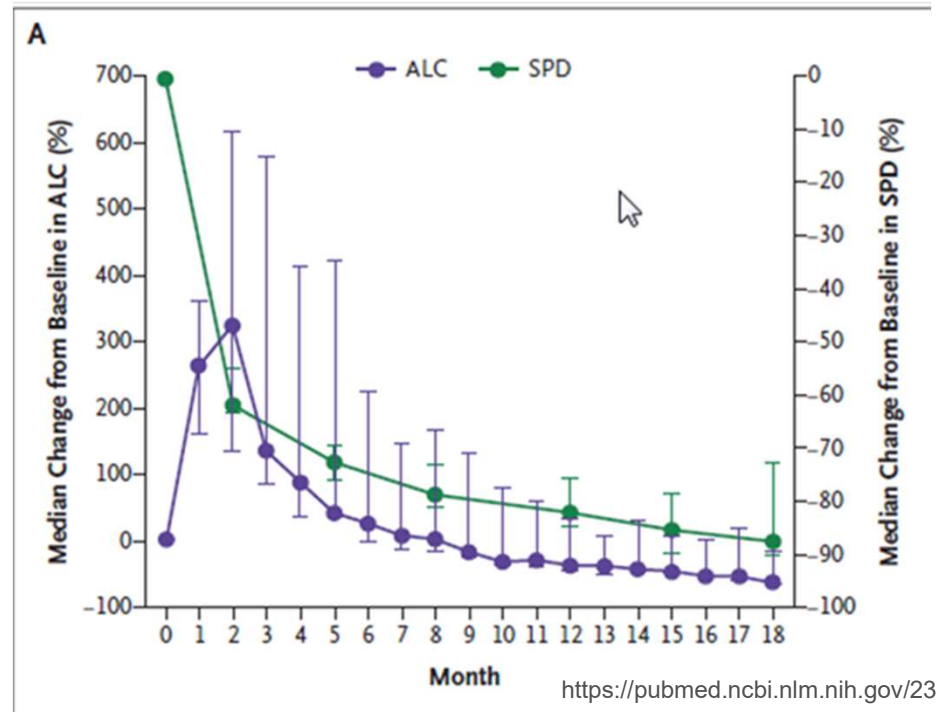
## **CLASS EFFECTS & CLINICAL PEARLS: BTK INHIBITORS**

- BRUISING & BLEEDING
  - Hold for 3-7 days pre- and post-procedures<sup>12,13,14</sup>
    - Examples: colonoscopy, total joints
    - No need to hold for routine dental cleaning
- HYPERTENSION<sup>12,13,14</sup>
  - Lifestyle modifications, consider dose reductions of BTKi
  - Drug-drug interactions with diltiazem and verapamil
- ARRHYTHMIAS<sup>12,13,14</sup>
  - Very low threshold for further workup of palpitations: EKG, Holter, etc
  - Rates of atrial fibrillation vary; highest with ibrutinib (10-15%)
  - Rare ventricular arrhythmias and sudden cardiac death have also been described

OPTIMIZING CARE OF PATIENTS WITH CLL

# CLASS EFFECTS & CLINICAL PEARLS: BTK INHIBITORS

- BTKi-related redistribution lymphocytosis



## OPTIMIZING CARE OF PATIENTS WITH CLL

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# CASE STUDY

- A 64 year old female with hypertension, obesity, type 2 diabetes, and CLL presents with newly diagnosed atrial fibrillation. Her medications are listed below. What is the most appropriate anticoagulation strategy in this patient?

### Med List

lisinopril

ibrutinib

acyclovir

metoprolol

- a. Warfarin
- b. Aspirin
- c. DOAC
- d. None – anticoagulation is contraindicated in CLL patients on ibrutinib

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ibrutinib  
acyclovir  
metoprolol

- Warfarin
- Aspirin
- DOAC**
- None – anticoagulation is contraindicated in CLL patients on ibrutinib

CLINICAL PEARL: discuss with hematologist, as dose reduction of ibrutinib and/or DOAC may be necessary

## OPTIMIZING CARE OF PATIENTS WITH CLL

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# CASE STUDY

- A 68 year old male presents for pre-operative evaluation for a planned total knee replacement. His PMH is significant for type 2 diabetes mellitus, well controlled on metformin, hypertension, well controlled on lisinopril, and CLL on therapy with acalabrutinib. How would you counsel the patient regarding his acalabrutinib for his upcoming surgery?
  - a. Acalabrutinib does not need to be held for the surgery
  - b. Acalabrutinib should be held for 3 days before & after surgery
  - c. Acalabrutinib should be held for 7 days before & after surgery
  - d. I have no idea – ask your hematologist!

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  - c. **Acalabrutinib should be held for 7 days before & after surgery**
  - d. I have no idea – ask your hematologist!

CLINICAL PEARL: add BTK inhibitors to your perioperative bleeding risk assessment in patients with CLL



## TAKE HOME POINTS: BTK INHIBITORS

ibrutinib, acalabrutinib, zanubrutinib

- The hematologist is your friend – we're here to help!
- **Drug-Drug Interactions** via CYP3A
- **Need to be held for 3-7 days pre- and post-procedurally** to minimize risk of bleeding
- Can be associated with atrial fibrillation (and, more rarely, ventricular arrhythmias)
  - **AVOID warfarin**; DOACs preferred
- White count often initially goes up after starting therapy
  - "Redistribution Lymphocytosis"
- Keep fungal infections on your differential

OPTIMIZING CARE OF PATIENTS WITH CLL

## ORAL THERAPY IN CLL

### Bruton's Tyrosine Kinase (BTK) Inhibitors

Ibrutinib (Imbruvica)  
Acalabrutinib (Calquence)  
Zanubrutinib (Brukinska)



### BCL2 Inhibitors

Venetoclax (Venclexta)



OPTIMIZING CARE OF PATIENTS WITH CLL

## BCL2 INHIBITOR: VENETOCLAX

- BCL2 protein impairs apoptosis, allowing unchecked cell division
  - i.e. the brakes are broken
  - Inhibiting BCL2 "fixes the brakes", restoring apoptosis



OPTIMIZING CARE OF PATIENTS WITH CLL

## KEY CLASS EFFECTS: BCL2 INHIBITOR

venetoclax



**TUMOR LYSIS  
SYNDROME**



**GI SIDE EFFECTS**

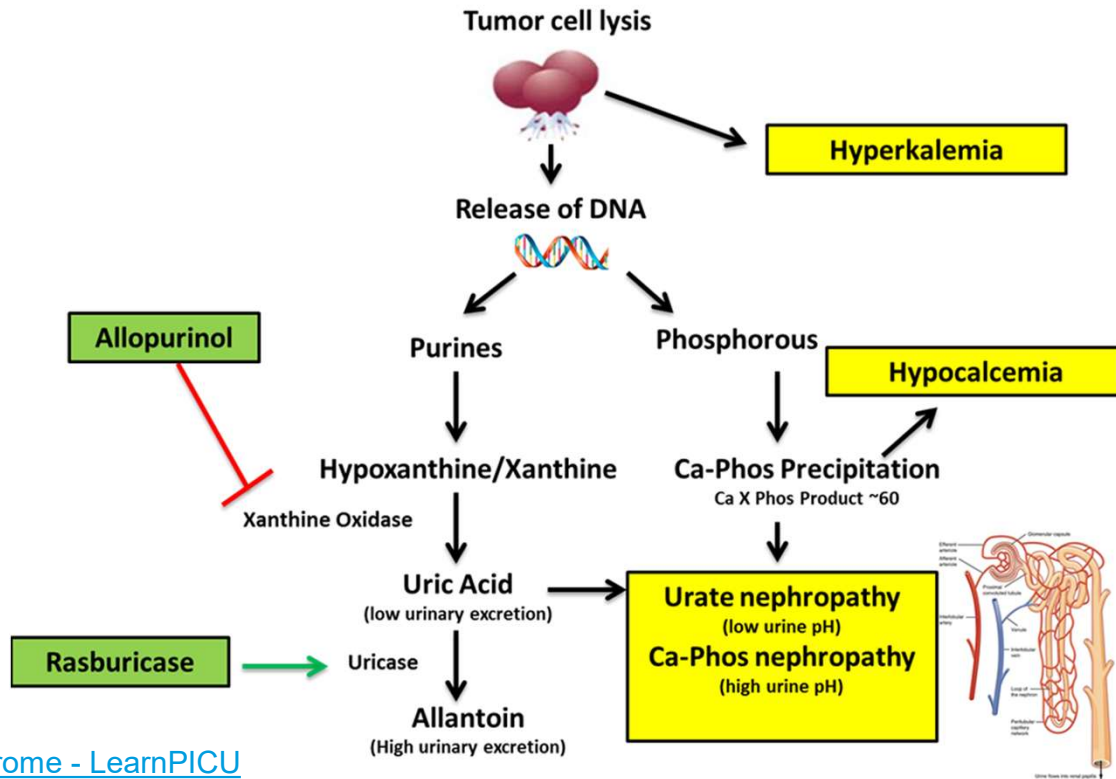
Nausea  
Diarrhea



**NEUTROPENIA**

OPTIMIZING CARE OF PATIENTS WITH CLL

# TUMOR LYSIS SYNDROME

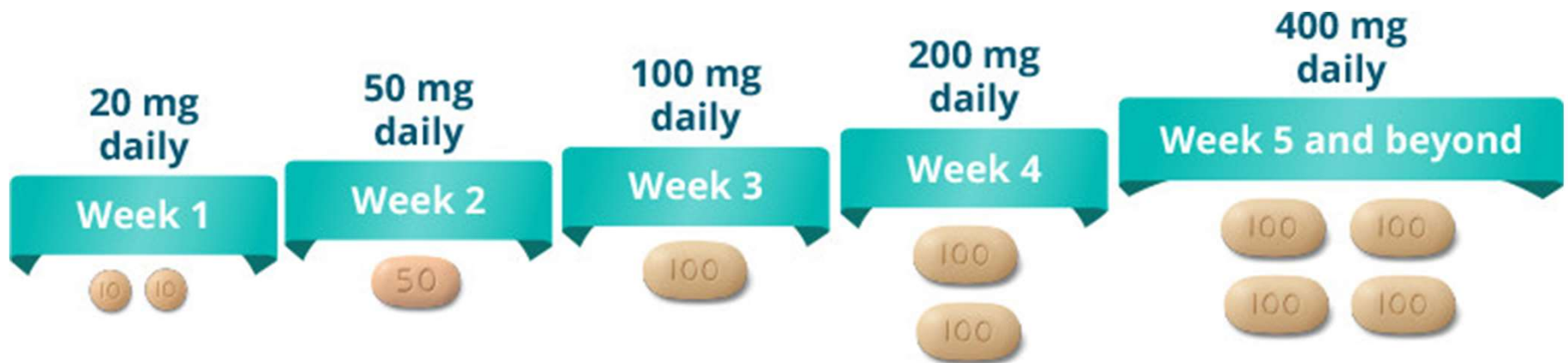


TLS Labs
Potassium
Phosphorous
Calcium
Uric Acid
Creatinine

OPTIMIZING CARE OF PATIENTS WITH CLL

## BCL2 INHIBITOR: VENETOCLAX

- Dose escalation protocols mitigate risk for tumor lysis syndrome (TLS)



Tablets not actual size.

Venclexta.com

## CLINICAL PEARLS: VENETOCLAX

- GI SIDE EFFECTS (nausea, diarrhea)
  - Take pills in evening instead of morning
  - Loperamide if infectious causes of diarrhea ruled out
  - Dietary changes
  - Patients can discuss dose reduction of venetoclax with hematologist
- TUMOR LYSIS SYNDROME
  - Hydrate, hydrate, hydrate!
  - Newer regimens help mitigate this risk
- NEUTROPENIA
  - GCSF +/- dose reductions of venetoclax (managed by hematology)

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# WHAT DID WE LEARN?

- CLL is associated with a 6-8x higher risk of which of the following:
  - A. Colorectal Cancer
  - B. Non-melanoma Skin Cancer
  - C. Melanoma Skin Cancer
  - D. Breast Cancer

OPTIMIZING CARE OF PATIENTS WITH CLL

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OPTIMIZING CARE OF PATIENTS WITH CLL

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## WHAT DID WE LEARN?

- True or false: live vaccines are contraindicated in patients with CLL
  - A. True
  - B. False

OPTIMIZING CARE OF PATIENTS WITH CLL

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  - D. Venetoclax

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  - C. Zanubrutinib
  - D. **Venetoclax**

## OPTIMIZING CARE OF PATIENTS WITH CLL

# REFERENCES

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3. [COVID-19 severity and mortality in patients with CLL: an update of the international ERIC and Campus CLL study - PubMed \(nih.gov\)](#)
4. [COVID-19 in patients with CLL: improved survival outcomes and update on management strategies - PubMed \(nih.gov\)](#)
5. [Improved outcomes in patients with chronic lymphocytic leukaemia infected during the omicron BA.5 subvariant surge - PubMed \(nih.gov\)](#)
6. [COVID-19 in patients with chronic lymphocytic leukemia: a multicenter analysis by the Czech CLL study group - PubMed \(nih.gov\)](#)
7. [Functional humoral and cellular response of monovalent COVID-19-vaccines against Omicron BA.2 variant of SARS-CoV-2 in patients with chronic lymphocytic leukemia - PubMed \(nih.gov\)](#)
8. [Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia - PubMed \(nih.gov\)](#)
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12. [Ibrutinib \(Imbruvica\) Prescribing Information: Microsoft Word - 208736.docx \(rxabbvie.com\)](#)
13. [Acalabrutinib \(Calquence\) Prescribing Information: Calquence Full Prescribing Information \(den8dhaj6zs0e.cloudfront.net\)](#)
14. [Zanubrutinib \(Brukinska\) Prescribing Information: prescribing-information.pdf \(brukinsa.com\)](#)
15. [iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL | Blood | American Society of Hematology \(ashpublications.org\)](#)



# THANK YOU





# THANK YOU

# QUESTIONS & ANSWERS

