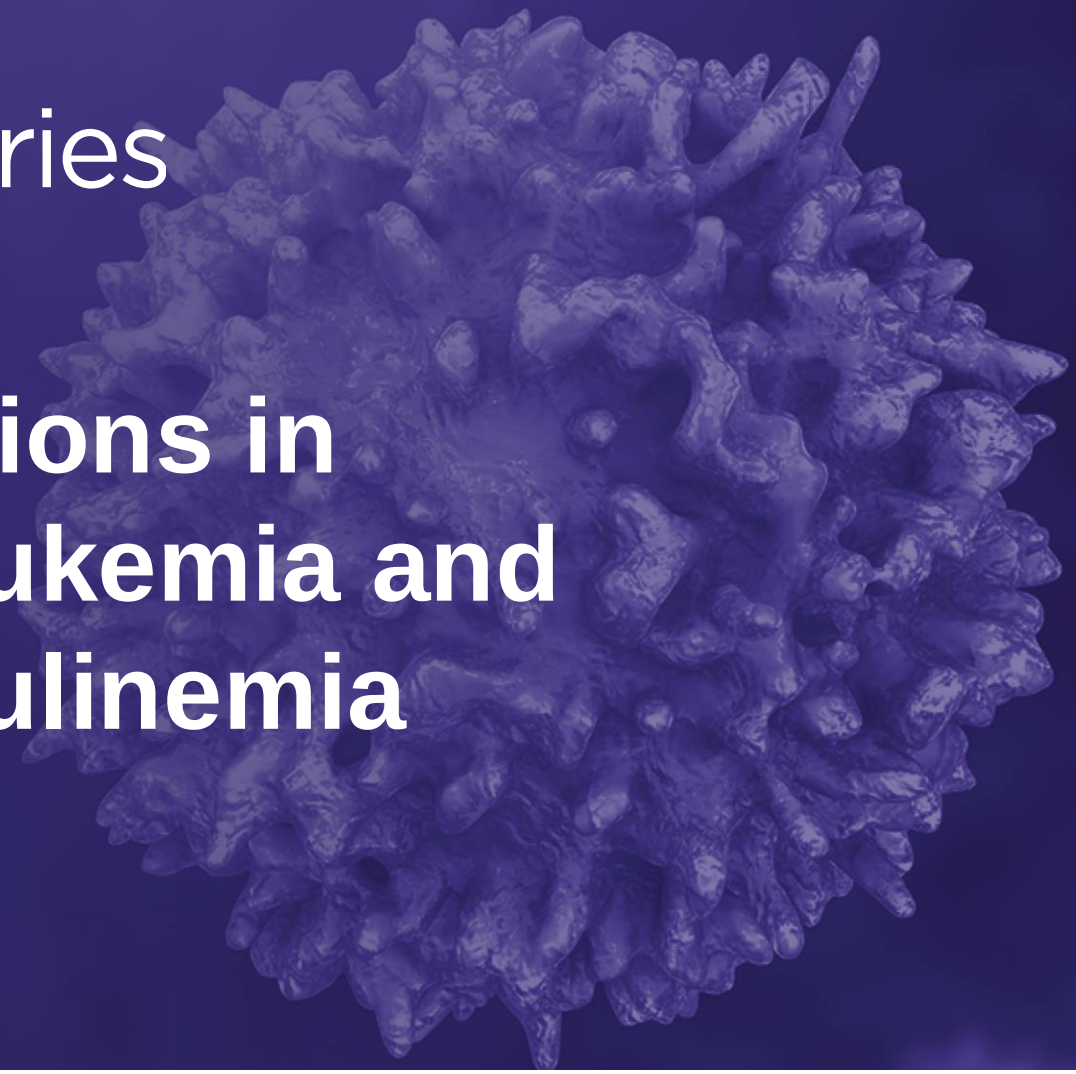
JADPRO Clinical Case Series

BTK Inhibitor Considerations in Chronic Lymphocytic Leukemia and Waldenström Macroglobulinemia Patient Populations



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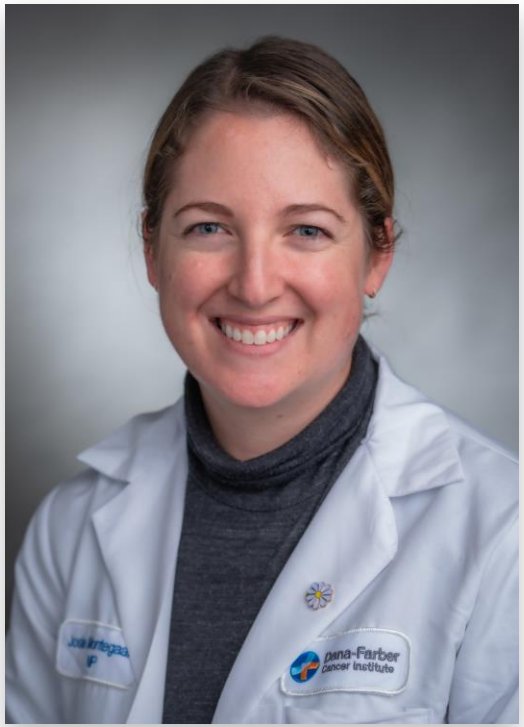

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Program Agenda

- Discuss FDA-approved indications for BTKis in CLL and WM, differences between generations, and progression/resistance on a BTKi
- Evaluate the use of BTKi dose modification to treat AEs in WM
- Review the management of swallowing difficulty/dysfunction among patients with CLL/WM receiving BTKi therapy
- Discuss the management of resistance mutations in CLL

AEs, adverse events; BTKis, Bruton tyrosine kinase inhibitors; CLL, chronic lymphocytic leukemia; WM, Waldenström macroglobulinemia.

Overview of BTKis

Highly effective novel targeted therapies used to treat patients with CLL/SLL and WM

- Inhibit BTK within the B-cell receptor signaling pathway, thus impairing B-cell proliferation and survival
- Multiple BTKis are FDA approved for CLL/SLL and WM in both the frontline and R/R settings

R/R, relapsed/refractory; SLL, small lymphocytic leukemia.

Overview of BTKis

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
Generation	First	Second	Second	Third
Mechanism of action	Covalent	Covalent	Covalent	Noncovalent
Dosing	420 mg QD	100 mg BID	160 mg BID or 320 mg QD	200 mg QD
FDA-Approved Indications				
CLL	First line, R/R	First line, R/R	First line, R/R	R/R, after 2 lines of prior treatment including prior BTKi and BCL2i
WM	First line, R/R	None; off label	First line, R/R	None; off label

Ibrutinib prescribing information. Janssen Biotech; 2022; Acalabrutinib prescribing information. AstraZeneca Pharmaceuticals; 2022; Zanubrutinib prescribing information. BeiGene USA; 2023; Pirtobrutinib prescribing information. Eli Lilly; 2023. BCL2i, B-cell lymphoma 2 inhibitor.

Differences Among BTKi Generations

Newer-generation BTKis are more selective for BTK, resulting in fewer “off-target” effects and better tolerability.

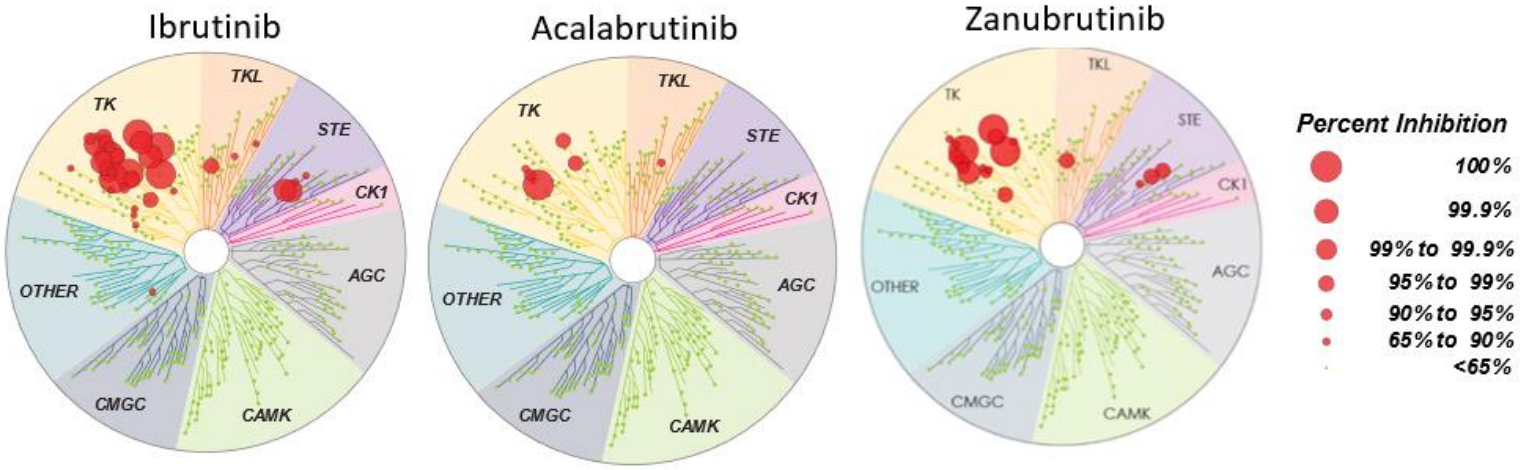


Figure 1. Kinome profiling at a single dose of 1 µM (KINOMEscan, Eurofins DiscoverX)

Kaptein A, et al. *Blood.* 2018;132(Suppl 1):1871; Mato AR, et al. *Lancet.* 2021;397:892-901; Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020(1):336-345.

Differences Among BTKi Generations (cont.)

- ELEVATE-RR[1]: Acalabrutinib arm less A-fib, hypertension, arthralgia, and bleeding vs ibrutinib arm
  - Headaches, a notable side effect of acalabrutinib, were reported more frequently on acalabrutinib arm vs ibrutinib arm
- ALPINE[2]: Zanubrutinib arm had less A-fib vs ibrutinib arm
  - Higher incidence of neutropenia noted on zanubrutinib arm vs ibrutinib arm
- **Having multiple generations of BTKis offers flexibility to switch if a patient can't tolerate one**

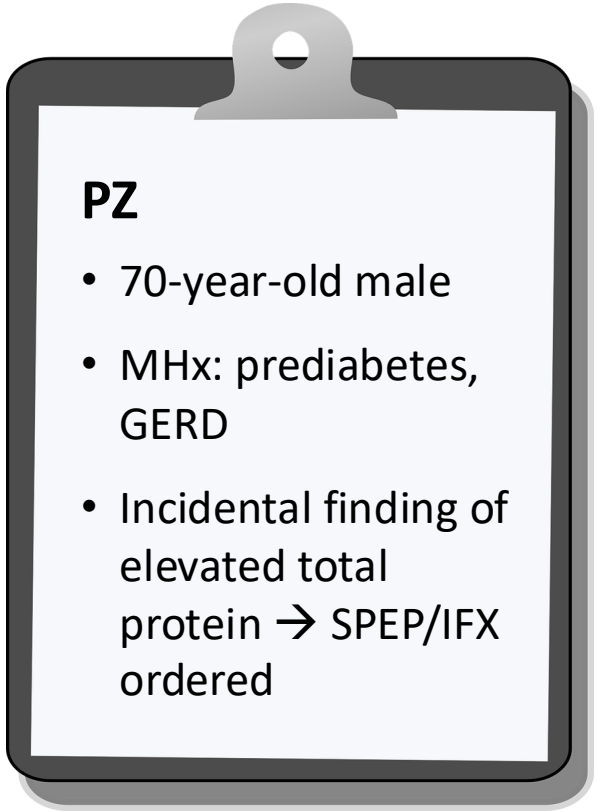
1. Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-3452; 2. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332. A-fib, atrial fibrillation.

BTKi Progression and Resistance

- Driven by acquisition of BTK resistance mutations, which impact function at BTK binding site
- Ibrutinib, acalabrutinib, and zanubrutinib covalently bind to BTK at the C481 amino acid
- Noncovalent BTKis (e.g., pirtobrutinib) do not require binding at the C481 site and therefore may still effectively inhibit BTK despite an acquired binding site mutation
- **BTK resistance mutations can be detected on NGS panels**

NGS, next-generation sequencing.

Case 1: BTKi Dose Modification to Treat AEs in WM



- Oncology consultation → WM diagnosis rendered → ibrutinib therapy initiated (420 mg PO QD)
  - **Serum IgM 6100 mg/dL; monoclonal protein**
  - Mild anemia (Hgb 11.2 g/dL)
  - BMBX: **30% involvement, lymphoplasmacytic cells; *MYD88* (L265P) mutation**
  - CT C/A/P: no extramedullary disease
  - ROS: negative
  - PE notable for *retinal hemorrhages*
- PZ continued ibrutinib 420 mg PO QD for 6 months, with close follow-up
  - Response to treatment was noted

BMBX, bone marrow biopsy; CT CAP, CT chest/abdomen/pelvis; GERD, gastroesophageal reflux disease; Hgb, hemoglobin; IFX, immunofixation; IgM, immunoglobulin M; MHx, medical history; PE, physical exam; ROS, review of systems; SPEP, serum protein electrophoresis.

Case 1: BTKi Dose Modification to Treat AEs in WM (cont.)

- PZ re-locates and establishes care with new oncology team; meets with the AP for 8-month follow-up
- Chief complaint: Myalgias and arthralgias
  - Mild, intermittent, tolerable over past 3 months; over past 3 weeks, newly severe, almost constant
  - Disrupting sleep, exercise routine
  - Using acetaminophen, topical heat, and stretching provides insufficient relief
- Last week PZ skipped ibrutinib dosing for 4 days
  - Symptoms resolved during this time
  - Severe symptoms promptly returned once he resumed

6-Month Progress Notes

- Vital signs stable; normotensive
- PE: unremarkable
- Hgb 13.5 g/dL, no cytopenias
- CMP: WNL
- Serum IgM 2400 mg/dL
- No retinal hemorrhages

AP, advanced practitioner; CMP, comprehensive metabolic panel; WNL, within normal limits.

Case 1: BTKi Dose Modification to Treat AEs in WM (cont.)

- AP reviews options:
  - Trial a reduced ibrutinib of dose
  - Discontinue ibrutinib (switch to another therapy, OR practice watchful waiting, off treatment, with close clinic follow-up)
- Shared decision-making → ibrutinib dose reduced to 280 mg PO QD
  - Plan to return to clinic in 1 month with repeat labs and trend IgM
  - If symptoms do not improve, can consider additional dose reduction(s) (140 mg, 70 mg)

Evaluating Patients With WM on Ibrutinib

Discontinue ibrutinib

- Close monitoring required
- Continuation of ibrutinib until next therapy should be considered (to maintain disease control)
- 37/51 (73%) patients with WM experienced IgM rebound after discontinuing ibrutinib[1]
  - 16% of those individuals developed symptomatic hyperviscosity (median time from ibrutinib discontinuation to hyperviscosity syndrome: 25 days)

Dose reduce ibrutinib

- ~25% of >350 patients with WM treated with ibrutinib required a dose reduction due to AEs[2]
- MSK/rheum symptoms: The most common AE category requiring dose reduction
  - 20/28 (71%) patients with had improvement or resolution in MSK/rheum symptoms
- Following dose reduction for any symptom:
  - Hematologic response was maintained or improved for most (79%)
  - PD in minority of cases (13%)

MSK, musculoskeletal; PD, progressive disease

1. Gustine JN, et al. *Am J Hematol.* 2018;93:511-517; 2. Sarosiek S, et al. *Br J Haematol.* 2023;201:897-904.

Case 1: BTKi Dose Modification to Treat AEs in WM (cont.)

At follow-up 1 month later, PZ's myalgias and arthralgias are mild and intermittent, with stability in IgM (2300 mg/dL; partial response to treatment maintained).

Case 1: Key Takeaways

1. For some patients with WM experiencing intolerable AEs on ibrutinib therapy, dose reduction leads to resolution or improvement of AEs without compromising disease control.

2. Shared decision-making regarding treatment options (including zanubrutinib, second-generation BTKi with FDA approval for use in WM) is important.

3. IgM rebound, and in some cases symptomatic hyperviscosity, can arise in the first weeks after discontinuation of BTKi therapy. Close monitoring and planning for next treatment, with or without temporary plasmapheresis, is prudent.

Case 1: Polling Question

When managing the care of a patient with Waldenström macroglobulinemia receiving a BTK inhibitor, for which side effects would you feel more comfortable discontinuing (rather than dose-reducing) therapy? (Select all that apply)

A. Musculoskeletal/rheumatologic **6%**

B. Hypertension and/or palpitations **16%**

C. Atrial fibrillation **23%**

D. Nail/skin/hair changes **2%**

E. Mucosal/gastrointestinal symptoms **1%**

F. Bruising/bleeding **8%**

G. Infection **8%**

H. Fatigue **2%**

I. Liver and renal dysfunction **17%**

J. Drug-drug interactions **16%**

Case 2: Managing Swallowing Difficulty/Dysfunction Among Patients With CLL/WM Receiving BTKi (cont.)

MB is a 68-year-old female experiencing homelessness who presents to the local emergency department (ED) following a choking event while eating dinner.

Case 2: Managing Swallowing Difficulty/Dysfunction Among Patients With CLL/WM Receiving BTKi (cont.)

- ED and subsequent inpatient oncology evaluations reveal:
  - Bulky lymphadenopathy throughout body, including large cervical nodes (7- to 8-cm lymph node [LN] conglomerates bilaterally)
  - Flow cytometry: Monoclonal B-cell population positive for CD5, CD19, and CD23 (consistent with diagnosis of CLL)
  - FISH and cytogenetic findings: Notable for del(17p) and del(11q)
  - IGHV testing: Unmutated IGHV
  - PET scan: Bulky adenopathy with low SUVs (lowered suspicion for Richter transformation)

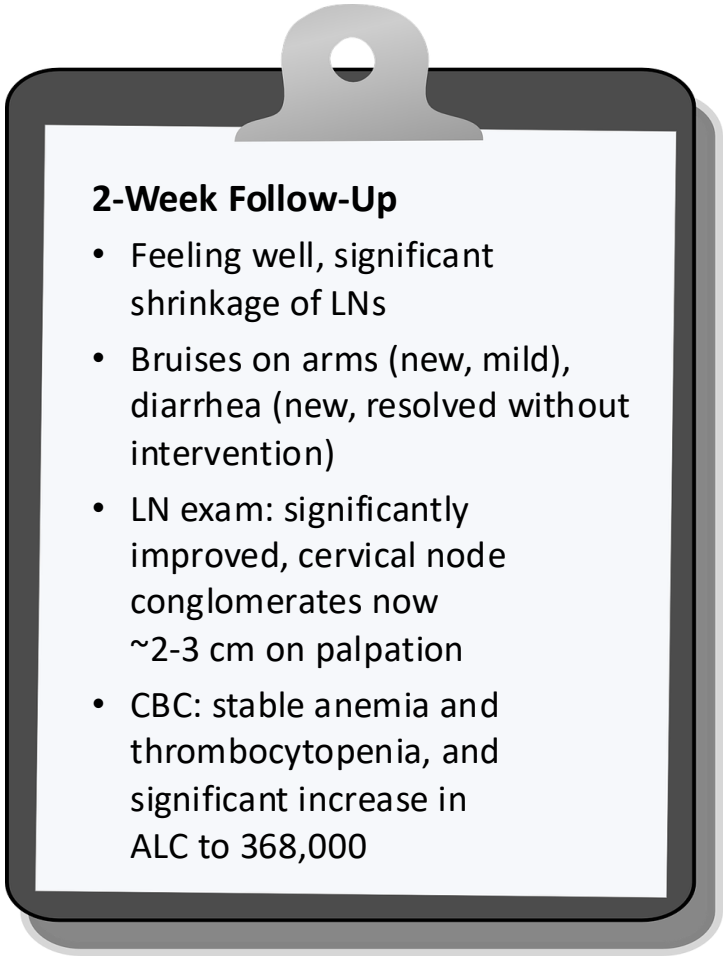
Lab	Value
WBC	224.0 K/µL
ALC	218.0 K/µL
Hgb	10.2 g/dL
Plt	132 K/µL
LDH	330 K/µL

ALC, absolute lymphocyte count; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; Plt, platelets; SUV, standardized uptake value; WBC, white blood cell count.

Case 2: Managing Swallowing Difficulty/Dysfunction Among Patients With CLL/WM Receiving BTKi (cont.)

- Treatment with BTKi was recommended for MB, based on aggressive cytogenetics and bulky lymphadenopathy.
- Considering MB's report of long-standing anxiety surrounding pills, plus current dysphagia with current cervical lymphadenopathy, ibrutinib liquid suspension is recommended and prescribed.

Case 2: Managing Swallowing Difficulty/Dysfunction Among Patients With CLL/WM Receiving BTKi (cont.)



- The AP reviews with MB that elevated ALC is due to lymphocyte redistribution, a normal phenomenon that occurs early in treatment with BTK inhibitors, and it should start to downtrend and normalize over the next weeks to months.
- Plan: Continue on ibrutinib oral suspension indefinitely moving forward for management of her CLL.

Case 2: Key Takeaways

1. The liquid suspension formulation of the novel covalent BTK inhibitor ibrutinib is a compelling option for use in patients with CLL or WM who have swallowing difficulty or dysfunction.

2. BTKis are very effective and durable treatment options for patients with CLL with high-risk features, including del(17p) and TP53 mutations.[1]

3. Adherence to treatment is essential to maximize efficacy and durability of BTKi treatment.[2]

1. Woyach JA, et al. *Blood.* 2024;143:1616-1627; 2. Barr PM, et al. *Blood.* 2017;129:2612-2615.

Case 2: Polling Question

What percentage of patients with CLL in your practice do you think would benefit from an oral liquid formulation of CLL treatment?

A. 0%-10% **52%**

B. 10%-25% **29%**

C. 25%-50% **19%**

D. >50% **0%**

Case 3: Management of Resistance Mutations in CLL

- DW is a 62-year-old male with unmutated IGHV and mutated *TP53* on ibrutinib 420 mg and tolerating treatment well.
- He returns to clinic after 5 years of being on ibrutinib.
  - He reports feeling very well
  - No missed doses of ibrutinib
  - No noticeable side effects, outside of minor
  - bruising
  - PE: New palpable axillary lymph nodes
  - The AP is concerned for disease progression

Lab	Value
WBC	36.0 K/µL
ALC	31.2 K/µL
ANC	3.5 K/µL
Hgb	13.0 g/dL
Plt	130 K/µL

Case 3: Management of Resistance Mutations in CLL (cont.)

- Next steps for DW
  - Repeat cytogenetic and FISH studies → no new cytogenetic nor FISH abnormalities
  - Perform NGS to evaluate for acquired BTK resistance mutations → NGS reveals new BTK^{C481S} mutation
  - Determine if and when additional treatment may be indicated
    - Given that DW continues to feel well without significant cytopenias, the AP feels he can continue on ibrutinib, with close monitoring of his blood counts for further CLL progression

Case 3: Management of Resistance Mutations in CLL (cont.)

- DW returns to clinic 3 months later
  - Continues to feel well overall
  - Rising ALC and new anemia
- AP recommends starting new CLL treatment
- Factors to consider:
  - DW has aggressive disease features (unmutated IGHV, *TP53* mutation) and young age
  - NGS results revealing a new *C481S* mutation
  - Other medical comorbidities
  - Logistical factors (visit schedule, social support, patient preference, cost)

Lab	Value
WBC	80.0 K/µL
ALC	76.2 K/µL
ANC	3.5 K/µL
Hgb	10.0 g/dL
Plt	111 K/µL

Case 3: Management of Resistance Mutations in CLL (cont.)

- Treatment decision: FDA-approved treatment for CLL in the R/R setting

SECOND-LINE OR THIRD-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Acalabrutinib[f,g,q,*] (category 1) • Venetoclax[f,h] + rituximab (category 1) • Venetoclax[f,h] • Zanubrutinib[f,g,q,*] (category 1)	• Ibrutinib[f,g,i,*] (category 1) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• For relapse after a period of remission (if previously used) ▸ Venetoclax[f,h] ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) • Resistance or intolerance to prior covalent BTKi therapy ▸ Pirtobrutinib[f,**]

  - After reviewing the treatment options, DW and the AP agree to proceed with venetoclax + rituximab treatment
    - Will reserve use of pirtobrutinib for a later line of therapy

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 3.2024. March 26, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

Case 3: Key Takeaways

1. Disease progression on covalent BTKis is typically due to an acquired BTK resistance mutation such as *C481S*.
2. Once a patient develops a BTK resistance mutation on a covalent BTK, they are resistant to all other covalent inhibitors.
3. It is recommended to repeat full cytogenetic testing and NSG prior to starting a patient on new treatment, as this will help sequence treatment appropriately.
4. Treatment options for patients who have developed BTK resistance mutations include venetoclax-based regimens and pirtobrutinib, a noncovalent BTKi that is still effective despite BTK resistance mutations.

Case 3: Polling Question

Which of the following BTK resistance mutations do you come across most often in your practice?

A. *C481S* **38%**

B. *PLCG-2* **10%**

C. *T474I* **14%**

D. I do not test for BTK resistance mutations **38%**

Clinical Pearls

- For some patients with WM experiencing intolerable AEs on ibrutinib therapy, dose reduction leads to resolution or improvement of AEs without compromising disease control.
- The liquid suspension formulation of ibrutinib is a compelling option for use in patients with swallowing difficulty or dysfunction.
- When a patient with CLL experiences disease progression while on a covalent BTKi, it is recommended to repeat cytogenetic and molecular testing, including NGS, to determine the presence of acquired BTK resistance mutations to guide next-line treatment selection.

Q & A

Please type your questions for Josie Montegaard and Catherine Flynn into the **question box**.

Thank You

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