# BTK Inhibitor Cardiac Side Effect Management for the Advanced Practice Provider

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## I. Learning Objectives

1. Define CLL/SLL as a hematologic malignancy and state treatment criteria.
2. Understand the historical landscape of BTK-inhibitors and their side effects.
3. Evaluate and manage side effects of hypertension, bleeding, and arrhythmias in patients on BTK inhibitors.
4. Identify available resources for guidance on BTK inhibitor toxicity management.

## II. Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)

CLL/SLL is a progressive accumulation of functionally incompetent lymphocytes that are usually monoclonal in nature. Chronic Lymphocytic Lymphoma (CLL) and Small Lymphocytic Leukemia (SLL) are two manifestations of the same disease.

- **CLL**: proliferation in the **bloodstream** and **bone marrow**
- **SLL**: proliferation in the **lymph nodes**

Median onset age is **~70 years** with ~23,690 new U.S. cases in 2025.

Diagnostic Factors:

- CLL: >5000 clonal lymphocytes in peripheral blood
- SLL: Presence of lymphadenopathy and/or splenomegaly and <5000 clonal lymphocytes in peripheral blood
- Peripheral blood flow cytometry: CD5+, CD23+, CD19+
- Peripheral blood flow cytometry can be enough to make the diagnosis; a biopsy is not necessary

Prognostic Factors:

- **Unfavorable**: TP53 mutation, **unmutated IGHV**, del(11q), **del(17p)**, CD38 (≥30%), ZAP-70 (≥20%)
- **Favorable**: **Mutated IGHV**, del(13q), CD49d (≥30%)
- Neutral: Normal cytogenetics, trisomy 12

## III. Treatment Indications & Landscape

Treatment is indicated per the **International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria** for the following:

- Progressive cytopenias: Hgb <10, or Plt <100k
- Splenomegaly >6cm below the costal margin, or progressive, symptomatic splenomegaly
- 10cm LN or progressive & symptomatic LAD
- Progressive lymphocytosis (>50% over a 2 month period)
- Autoimmune complications (ITP or AIHA) poorly responsive to corticosteroids
- Symptomatic or functional extranodal involvement
- Disease-related symptoms
    - Weight loss (>10% in 6 mos)
    - Fatigue (EOCG 2+)
    - Fevers (>100.5F for 2+ weeks without evidence of infection)
    - Night sweats (x 1 month without evidence of infection)

Main Drug Classes:

1. **BTK Inhibitors**: Ibrutinib, Acalabrutinib, Zanubrutinib, Pirtobrutinib
2. **Anti-CD20 mAbs**: Rituximab, Obinutuzumab
3. **BCL2 Antagonists**: Venetoclax

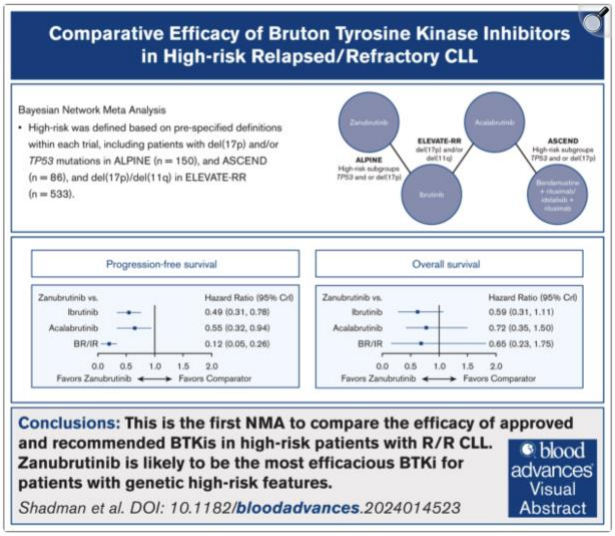
| Preferred Regimen | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| **WITHOUT del17p/TP53 mutation** | | |
| Venetoclax/Acalabrutinib +/- Obinutuzumab<br>Venetoclax + Obinutuzumab<br>Acalabrutinib + Obinutuzumab<br>Zanubrutinib | Venetoclax/Ibrutinib | Venetoclax/Zanubrutinib<br>Ibrutinib<br>Ibrutinib + anti-CD20 mAb<br>High-dose methylprednisolone + anti-CD20 mAb<br>Bendamustine + anti-CD20 mAb<br>Fludarabine/Cyclophosphamide + Rituximab<br>Chlorambucil + Obinutuzumab<br>Obinutuzumab |
| **WITH del17p/TP53 mutation** | | |
| Venetoclax + Obinutuzumab<br>Venetoclax/Acalabrutinib + Obinutuzumab<br>Venetoclax/Zanubrutinib<br>Acalabrutinib +/- Obinutuzumab<br>Zanubrutinib | Ventoclax/Ibrutinib | Ibrutinib<br>High-dose methylprednisolone + anti-CD20 mAb<br>Obinutuzumab |

## IV. Evolution of BTK Inhibitors

**First Generation** – **Ibrutinib (Imbruvica)**: Demonstrated progression-free survival (PFS) benefit in the RESONATE trial but associated with cardiac toxicities including atrial fibrillation and hypertension.

**Next Generation** – **Acalabrutinib (Calquence)**: Lower arrhythmia and bleeding risk. Acalabrutinib (Calquence) + obinutuzumab or acalabrutinib alone vs obintuzumab + chlorambucil in the ELEVATE TN trial demonstrated superior PFS in both Calquence groups. In the ASCEND trial, acalabrutinib (Calquence) vs idelalisib + Rituxan (IdR) or bendamustine + Rituxan (BR), demonstrated superior PFS, 62%, with Calquence vs 19% with standard-of-care (SOC). Calquence seemed to overcome poor prognosis of del17p/TP53 disease better than SOC IdR or BR.

**Next Generation** – **Zanubrutinib (Brukinsa)**: Lower arrhythmia and bleeding risk. SEQUOIA trial, zanubrutinib (Brukinsa) versus bendamustine + rituximab (BR) demonstrated PFS benefit. Non-del17p: 24-month PFS 85% (Brukinsa) vs 69% (BR); Median PFS: NR. Del17p: 24-month PFS: 89% (Brukinsa); Median PFS: NR. The ALPINE trial, ibrutinib (Imbruvica) vs zanubrutinib (Brukinsa) in relapsed/refractory CLL (at least 1 prior line of therapy), demonstrated 24-month PFS of 78.4% with zanubrutinib vs 65.9% with ibrutinib. PFS benefit held up in patients with del17p.




The ALPINE + ELEVATE + ASCEND network meta-analysis suggests that zanubrutinib and acalabrutinib (second generation BTKi) offer advantages for patients with high-risk disease features, with zanubrutinib emerging as the most efficacious BTK inhibitor for those with genetic high-risk profiles.

**Next Generation** – **Pirtobrutinib (Jaypirca)**: A non-covalent BTKi approved for CLL patients who have failed another BTK-inhibitor and a Bcl2 antagonist. Its non-covalent feature can overcome BTKi resistance.

## V. Management of Cardiac Adverse Events

1. **Hypertension**:
   - Monitor BP at each visit - encourage home monitoring
   - Follow AHA hypertension guidelines
   - Titrate antihypertensives as needed
2. **Atrial Fibrillation/Flutter:**
   - BTKis are not contraindicated in stable atrial fibrillation (AF)
   - For new-onset AF, hold BTKi, consult cardiology, start beta-blocker ± anticoagulation
   - Poorly controlled – BTKi may not be the best treatment (e.g., ibrutinib is not recommended due to increased cardiac arrythmias). Consider time-limited therapy with venetoclax/Bcl2 antagonist if appropriate.
3. **Bleeding**:
   - Minor procedures: Hold 3 days prior, 24–72h post
   - Major surgery: Hold 7 days prior, 48–72h post
   - Hold for acute bleeding, resume after stabilization
   - Colonoscopies: Recommend holding for 7 days prior
     - Hold for 24h post-procedure if NO polyps removed
     - Hold for 48-72h post-procedure if polyps removed
   - Permanently discontinue for life-threatening bleeds

## VI. Drug-Drug Interactions

BTK inhibitors are **CYP3A4 substrates**. **Moderate inhibitors** (e.g., amiodarone, verapamil, diltiazem) increase exposure—**reduce dose**. Other inhibitors to educate patients on: grapefruit, colchicine, most –azole antifungals, tacrolimus, cyclosporine. Avoid strong inducers (e.g., rifampin, St. John's wort). Favor metoprolol (or other beta-blockade) for atrial fibrillation.

## VII. Resources & Decision Tools

• BTKi Package Inserts: Prescribing and dose-modification guidance
• Clinical Care Options (CCO) Interactive Tool: Managing BTKi-associated adverse events (AE)

## VII. Key Takeaways

• CLL is chronic and indolent; treat only when iwCLL criteria are met.
• Second-generation BTK inhibitors have much lower rates of grade 3 arrhythmias, bleeding, and hypertension.
• Atrial fibrillation, hypertension, and bleeding are not indications to stop BTK-inhibitors unless life-threatening. All can be medically managed.
• Avoid/adjust dose for CYP3A4 interactions.

## References


- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed [November 14, 2025]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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