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# Tools for Understanding BTK Inhibitor Resistance in CLL/SLL and MCL[1-9]

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| | Notes | Relevant Mutations |
|---|---|---|
| **CLL/SLL** | • Resistance to ibrutinib contributes to discontinuation and progression; similar patterns observed with other covalent BTK inhibitors (BTKi) | • Mutations in *BTK* at C481 binding site<br>• Mutations in *PLCγ2* at multiple hotspots (R665, L845, and S707)<br>• Rare mutations: *BRAF*, *CARD11*, etc |
| **MCL** | • Resistance is not well characterized compared with CLL, though it appears to contribute to progression | • Primary resistance via cell cycle, *ERB4*, *PIM*, *SMARCA2, SMARCA4, TRAF2, BIRC2*, and other mutations that activate NF-Kb<br>• Secondary resistance via uncommon mutations in C481S, *PLCγ2, CARD11*, and *SMARCA4*, among others |

| | |
|---|---|
| **Why Resistance Is Relevant for Practice & Key Clinical Points** | • Progression in CLL after therapy with covalent BTK inhibitors is mainly driven by *BTK* C481 mutations<br>• In MCL, resistance to BTK inhibitor therapy is also a driver of disease progression/poor clinical outcomes |
| | • The presence of resistance mutations curtails the efficacy of covalent BTKi (ibrutinib, acalabrutinib, and zanubrutinib) and should prompt a different approach to therapy |
| | • Non-covalent BTK inhibitors, such as pirtobrutinib, do not require C481 to bind to the kinase domain, and thus can overcome the presence of *BTK* resistance mutations |

1. Woyach J et al. *N Engl J Med*. 2014;70:2286-2294. 2. Ahn IE et al. *Blood*. 2017;129:1469-1479. 3. Sharma S et al. *Oncotarget*. 2016;7:68833-68841. 4. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 5. Kanagal-Shamanna R et al. *Cancer*. 2019;125:559-574.
6. Martin P et al. *Blood*. 2016;127:1559-1563. 7. Agarwal R et al. *Nature Med*. 2019;25:119-129. 8. Jain P et al. *Br J Haematol*. 2019;183:578-587. 9. Mohanty A et al. *Oncotarget*. 2018;7:73558-73572.

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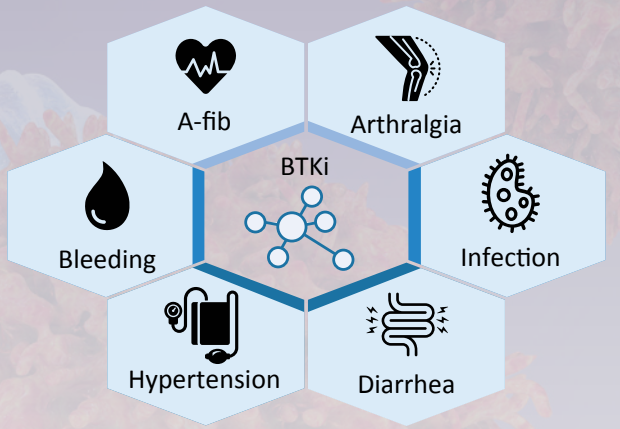
Understanding the spectrum of treatment-emergent AEs with BTK inhibitors is an important first-step toward effective toxicity management

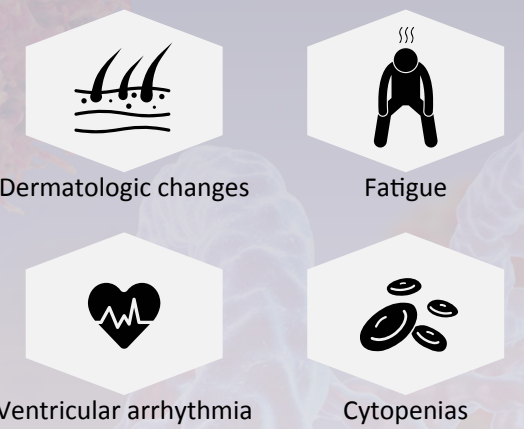
Management approaches for BTKi AEs are available for all currently approved agents used in B-cell cancer settings

## Common Toxicities




- ❑ Don't give BTKi concomitantly with warfarin
- ❑ For new onset a-fib, consider non-warfarin anticoagulation + monitoring
- ❑ Hypertension: manage with antihypertensives
- ❑ Monitor for and manage cardiac arrhythmia/a-fib; treat appropriately
- ❑ Monitor patients for signs of bleeding

## Additional Important Toxicities




- ❑ Headaches commonly occur early in therapy with acalabrutinib and typically resolved in 1-2 months (manage with acetaminophen + caffeine)
- ❑ Monitor for neutropenia **(particularly with zanubrutinib)**
- ❑ Monitor for infections and secondary malignancies

**In real-world settings, BTKi toxicity appears to be the most common reason for treatment discontinuation in the frontline and relapsed/refractory settings**


1. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. 2. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program*. 2020;1:336-345. 3. Byrd JC et al. ASCO 2021. Abstract 7500. 4. Hillmen P et al. EHA 2021. Abstract LB1900. 5. Mato AR et al. *Lancet*. 2021;397:892-901. 6. Mato AR et al. *Blood*. 2016.28:2199-2205. 7. Mato AR et al. *Haematologica*. 2018;103:874-879.

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# Tools for Understanding BTK Inhibitor Resistance in CLL/SLL and MCL[1-7]

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More selective covalent BTK inhibitors appear to have few off-target effects leading to AEs vs ibrutinib

Non-covalent BTK inhibitors are associated with low rates of BTK-mediated toxicities

## Acalabrutinib and Zanubrutinib

In head-to-head trials, there was significantly less a-fib/atrial flutter compared with ibrutinib

**Clinical note:** More selective BTKi can be used in the setting of ibrutinib intolerance (based on published evidence in CLL and current NCCN guidelines)

## Pirtobrutinib

In published studies on B-cell cancers no grade 3/4 a-fib/flutter has been reported

**Clinical note:** Non-covalent agents, such as pirtobrutinib, are effective in the setting of BTKi intolerance (based on evidence to date)

1. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. 2. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program*. 2020;1:336-345. 3. Byrd JC et al. ASCO 2021. Abstract 7500. 4. Hillmen P et al. EHA 2021. Abstract LB1900. 5. Mato AR et al. *Lancet*. 2021;397:892-901. 6. Mato AR et al. *Blood*. 2016.28:2199-2205. 7. Mato AR et al. *Haematologica*. 2018;103:874-879.

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# Tools for Planning Therapy in the Setting of BTK Inhibitor Resistance/Intolerance[1-6]

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| If a patient with CLL/SLL | | … then consider |
|---|---|---|
| **Progresses on a BTKi ± resistance mutation** | ▶ | • Venetoclax[1] (PI3K inhibitors may work but are less tested)<br>• Clinical trial: options include non-covalent BTKi (eg, pirtobrutinib)[1,2,a] |
| **Is unable to tolerate ibrutinib but has responded to therapy** | ▶ | • Sequencing to acalabrutinib (and possibly zanubrutinib)[3,4,b]<br>• Non-covalent agents, such as pirtobrutinib, which are effective in this setting (via a clinical trial) |

| If a patient with MCL | | … then consider |
|---|---|---|
| **Progresses after upfront therapy** | ▶ | • BTKi options (acalabrutinib, ibrutinib, and zanubrutinib) based on comorbidities and toxicity profiles |
| **Progresses on second-line BTKi therapy** | ▶ | • Using CAR-T therapy as an approved option for eligible patients<br>• Sequencing to other agent classes (venetoclax) or non-covalent BTKi (pirtobrutinib) |
| **Is therapeutically intolerant to ibrutinib** | ▶ | • Use of similar algorithms developed for CLL |

[a] Pirtobrutinib is experimental and only available as part of a clinical trial. [b] Zanubrutinib is off label for CLL but is included in the NCCN guidelines exactly for these circumstances.

1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75. 2. Mato AR et al. ASH 2020. Abstract 542. 3. Rogers K et al. *Haematologica*. 2021 Mar 18 [Online ahead of print]. 4. Shadman M et al. ASH 2020. Abstract 2947. 5. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. 6. NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.