The Impact of Progression vs Intolerance on Treatment Decisions in CLL

This presentation was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

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CLL, chronic lymphocytic leukemia.

Learning Objectives

- Apply current clinical guidelines to evaluate how disease progression and treatment intolerance impact treatment decisions in CLL
- Provide examples of how treatment sequencing considerations can impact clinical decision making for patients with CLL after treatment intolerance and/or disease progression

CLL, chronic lymphocytic leukemia.

1 Introduction

Advent of Targeted Therapies Has Revolutionized the Therapeutic Landscape of CLL[1]

CLL/SLL treatment regimens based on the National Comprehensive Cancer Network Guidelines In Oncology (NCCN Guidelines®)[2,*]

Preferred 1L therapy NCCN Guidelines†

Without del(17p)/*TP53* mutations

- BCL-2i-containing regimens
  - Venetoclax/acalabrutinib ± obinutuzumab (fixed duration) (category 1)
  - Venetoclax + obinutuzumab (fixed duration) (category 1)
- cBTKi-based regimens
  - Acalabrutinib (continuous) ± obinutuzumab (category 1)
  - Zanubrutinib (category 1)

With del(17p)/*TP53* mutations

- BCL-2i-containing regimens
  - Venetoclax + obinutuzumab (fixed duration)
  - Venetoclax/acalabrutinib + obinutuzumab (MRD-guided)
  - Venetoclax/zanubrutinib (MRD-guided)
- cBTKi-based regimens
  - Acalabrutinib (continuous) ± obinutuzumab
  - Zanubrutinib (continuous)

Preferred 2L therapy NCCN Guidelines†

With or without del(17p)/*TP53* mutations

- BCL-2i-containing regimens
  - Venetoclax + obinutuzumab
- cBTKi-based regimens
  - Acalabrutinib (continuous) (category 1)
  - Zanubrutinib (continuous) (category 1)
- ncBTKi-based regimen
  - Pirtobrutinib (continuous) (category 1) (resistance or intolerance to prior cBTKi-based regimens)

Treatment should be initiated in patients with advanced or active, symptomatic disease according to iwCLL 2018 criteria[3]

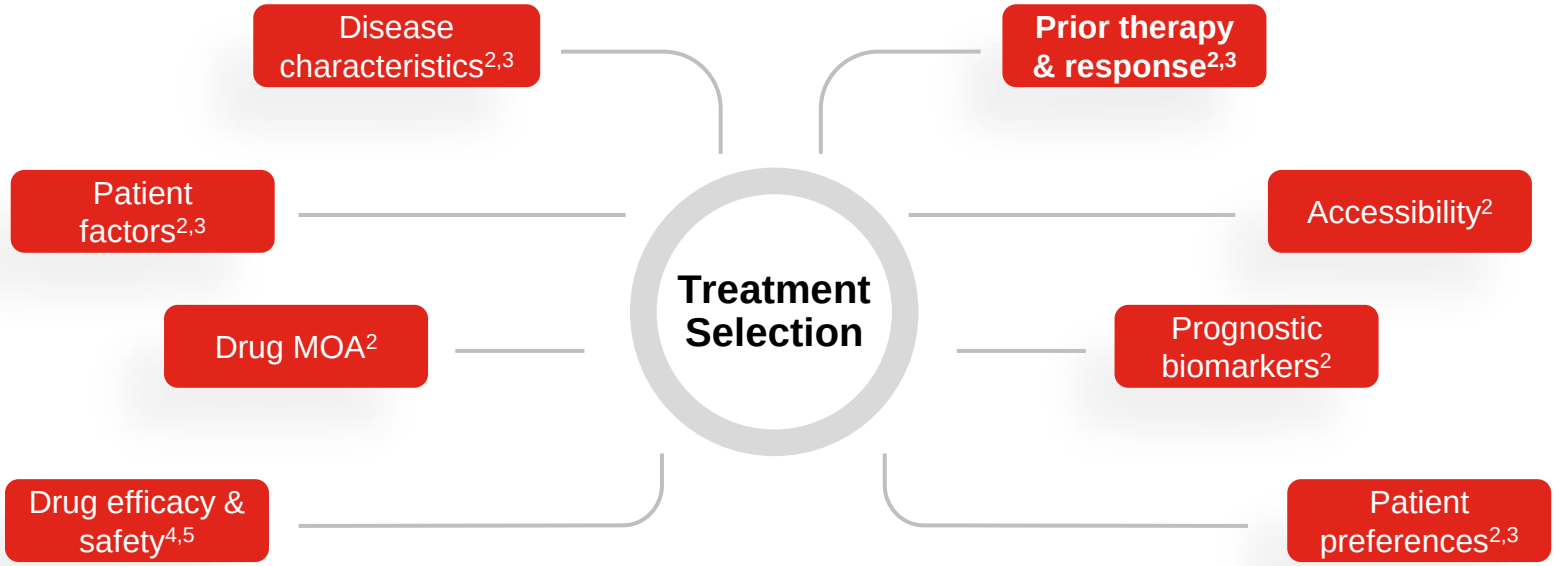
*See the NCCN Guidelines for a full list of preferred therapies and other recommended regimens. †CIT is no longer considered appropriate treatment in the R/R CLL setting. Progression after 1L CIT warrants consideration of treatment with a BTK inhibitor or BCL-2i.[4,5]

1L, first line; 2L, second line; BCL-2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; NCCN, National Comprehensive Cancer Network; SLL, small lymphocytic lymphoma; R/R, relapsed/refractory; *TP53*, tumor protein 53.

1. Molica S. *Expert Rev Hematol*. 2025;18(3):195-200. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed December 22, 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. 3. Hallek M. *Am J Hematol.* 2025;100(3):450-480. 4. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 5. Shadman M. *JAMA*. 2023;329(11):918-932.

Multiple Factors Impact the Selection and Sequencing of Drugs for CLL Treatment[1-5]

Once criteria from the iwCLL guidelines are met for initiating treatment in patients with CLL (frontline or R/R setting), various clinical factors and patient characteristics should be considered when selecting therapy[1-3,*]



A holistic approach to patient care involving the multidisciplinary team which considers the patient's comorbidities/other medications is necessary for optimal management and to ensure that potential AEs are not being interpreted as a new medical condition[6-8]

*Observation without treatment is the standard of care for asymptomatic patients without anemia, neutropenia, or thrombocytopenia; most patients do not require treatment at the time of diagnosis.
AE, adverse event; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MOA, mechanism of action; R/R, relapsed/refractory.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Odetola O, Ma S. *Curr Hematol Malig Rep*. 2023;18(5):130-143. 3. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 4. Ahn IE, Brown JR. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):323-328. 5. Laurenti L, et al. *Hemasphere*. 2022;6(9):e771. 6. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 7. Lymphoma Research Foundation. Accessed July 1, 2025. https://lymphoma.org/wp-content/uploads/2018/03/6609-LRF-Oral-Therapies-White-Paper-Final2-Web-03_14.pdf 8. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996.

Treatment Intolerance and Disease Progression Have Different Clinical Implications

Distinguishing between **treatment intolerance** and **disease progression** can be challenging as they may present with similar symptoms (eg, cytopenia)[1-4]

It's essential to differentiate **treatment intolerance** from **disease progression** as they result in different clinical implications[5-7]

Intolerance
Inability of the patient to endure adverse events associated with a treatment[8]

Progression
Worsening of disease as it continues to spread in the body[9]

Clinical decision making regarding subsequent therapy:

If a patient is intolerant to a given therapy, a drug with a **similar** MOA can be an option at a later time[5,7]

When progression occurs on treatment, a switch to a therapy with a **different** MOA is recommended[5,7]

To distinguish between **treatment intolerance** and **disease progression**, it's important to utilize diagnostic tools and to consider the anticipated side effect profile of therapy, the patient's comorbidities, and DDIs[1-3]

AE, adverse event; DDI, drug-drug interaction; MOA, mechanism of action.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Hallek M. *Am J Hematol.* 2025;100(3):450-480. 3. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996. 4. Upchurch MD, et al *Expert Rev Clin Pharmacol.* 2024;17(5-6):467-475. 5. CGTlive. Accessed May 2, 2025. https://www.cgtlive.com/view/new-agents-and-optimal-patient-selection-in-cll-comprise-modern-paradigm 6. Shadman M. *JAMA*. 2023;329(11):918-932. 7. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 8. Flannery MA, et al. *J Clin Oncol.* 2021;39(19):2150-2163. 9. National Cancer Institute. Accessed December 15, 2025. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/progression

2

The Impact of Treatment Intolerance on Treatment Decisions in Patients With CLL

Considerations of Disease Manifestations and Anticipated Adverse Reaction Profile Are Necessary for Effective AE Management

- Before choosing treatment, evaluation of a patient's clinical factors, disease symptoms, and anticipated AE profile is recommended[1-4]
  - Clinical factors to assess include preexisting comorbidities, such as CV conditions, need for anticoagulation, bleeding risk, and renal function[1,2]
  - Evaluation should also include concomitant medications that may impact efficacy due to DDIs[1,2]
- Despite impressive efficacy, targeted therapies have specific AE profiles that should be considered when selecting appropriate treatment[1]
  - Some AEs can manifest as class effect toxicities—for example, CV toxicity with BTKi, TLS with BCL-2i, and CRS with cellular therapy[1,6]

Principal factors in treatment selection and development of AEs[1]

Available drugs and combinations

Age

DDIs

Notable factors to consider in management of AEs

Baseline CV health

Renal function

TLS prevention

AEs must be monitored regularly, identified promptly, and managed effectively to maximize anticancer treatment efficacy and maintain quality of life for patients[1,5]

AE, adverse event; BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; CV, cardiovascular; DDI, drug-drug interaction; TLS, tumor lysis syndrome.

1. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996. 2. Hallek M. *Hematol Oncol.* 2023;419suppl1):129-135. 3. Hallek M. *Am J Hematol.* 2025;100(3):450-480. 4. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 5. Muñoz JL, et al. *Interdisciplinary Cancer Research.* Cham, Switzerland: Springer International Publishing; 2023. 6. Shadman M. *JAMA.* 2023;329(11):918-932.

Anticipated Adverse Reactions Vary Among the Agents Used in the Treatment of CLL

Time-limited therapies
(eg, BCL-2i containing regimens)

Continuous therapies
(eg, covalent BTKi-based regimens)

Anticipated AE profile:

For patients treated with BCL-2i: AEs may include cytopenia, GI events, infections, and TLS[1]

For patients on covalent BTKis: AEs may include cytopenia, arthralgias, myalgias, diarrhea, dermatologic complications, headaches, infections, and CV events[1]

Considerations for patients with comorbidities:

Reduced renal function is a risk factor for development of TLS with BCL-2i treatment[2,3]

- For treatment with BCL-2i, initial dose ramp-up protocol with TLS prophylaxis and monitoring is recommended

Treatment with BTKis may elevate the risk of CV events, specifically in patients with preexisting **CV comorbidities**[4-6]

- For patients with **hypertension**, BTKis can be appropriate for those with well-managed CV risk[4]
- For patients with **AF history**, more selective BTKis can be appropriate with multidisciplinary team involvement[4]

AE, adverse event; AF, atrial fibrillation; BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; GI; gastrointestinal; TLS, tumor lysis syndrome.

1. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996. 2. Wanchoo R, et al. *Clin Kidney J*. 2018;11(5):670-680. 3. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 4. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 5. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996. 6. Molica S, et al. *Cancers (Basel).* 2025;17(1):119.

The Type of Therapy Impacts Timing of Discontinuation in Responding Patients[1-3]

	Time-limited therapies[4]	Continuous therapies[4]
Grade 1/2	**Continue** unless patient is unable to cope	**Continue** unless patient is unable to cope
Grade 3/4	**Interrupt or lower dose** unless the AE persists and/or patient is unable to cope (ie, **intolerance**), then **stop therapy**	**Interrupt or lower dose** unless the AE persists and/or patient is unable to cope (ie, **intolerance**), then **stop therapy** (therapy can be stopped for an **extended period of time**)

Both **time-limited** and **continuous therapies** can be interrupted, dose adjusted, or discontinued due to an AE; to avoid early discontinuation, dose adjustment based on the PI should be performed along with prescribing symptom-targeted measures[4]

AE, adverse event; PI, prescribing information.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 3. Jain N, et al. Lancet. 2024;404(10453):694-706. 4. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996.

Intolerance to BCL-2i Therapy: Switching Drug Classes May Be Necessary

Patient meeting the iwCLL criteria for treatment initiation[1]

→ **BCL-2i-based therapy** (eg, venetoclax + obinutuzumab) → **Treatment intolerance**

Patient has active disease, defined by the iwCLL criteria[2-5]

After discontinuation of BCL-2i-based regimen due to treatment intolerance, the next recommended therapy is a cBTKi

- Subsequent options include R/R therapies after prior cBTKi-based and BCL-2i-containing regimens

cBTKi

- Acalabrutinib
- Zanubrutinib

R/R after prior cBTKi-based and BCL-2i-containing regimens

- ncBTKi pirtobrutinib*
- Clinical trial
- CAR T-cell therapy lisocabtagene maraleucel
- Consider allo-HCT in fit patients

Patient does not have symptomatic disease/is in remission[5-7]

Discuss patient goals and priorities, including preferences for treatment-free remissions

- In the CLL14 study of patients treated with 1L venetoclax + obinutuzumab for 1 year, the 3-year PFS rate was 81.9% after 40 months of follow-up[7]
- In the MURANO trial of patients with R/R CLL treated with venetoclax + rituximab† for up to 2 years, after 48 months of follow-up, the PFS rate was 57%[7]

The approach after time-limited BCL-2i treatment is discontinued due to intolerance depends on response and the type of prior therapy[4]

*If not previously given in 2L. Pirtobrutinib is approved for R/R CLL/SLL after prior cBTKi treatment.[8] †Patients received rituximab for the first 6 months plus venetoclax for up to 2 years.[6]

1L, first line; 2L, second line; allo-HCT, allogeneic hematopoietic cell transplant; BCL-2i, B-cell lymphoma 2 inhibitor; CAR, chimeric antigen receptor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 3. Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. 4. Shadman M. *JAMA.* 2023;329(11):918-932. 5. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 6. Bennett R, et al. *Blood Cancer J.* 2024;14(1):33. 7. Molica S. *Int J Hematol Oncol*. 2020;9(4):IJH31. 8. FDA. Accessed December 15, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

Intolerance to cBTKi Therapy: When Is Rechallenge Appropriate?

Patient meeting the iwCLL criteria for treatment initiation[1]

→

cBTKi-based therapy
(eg, ibrutinib, acalabrutinib, zanubrutinib)

→

Treatment intolerance

Patient has active disease, defined by the iwCLL criteria[2-6]

In patients who discontinue cBTKi due to toxicity, a rechallenge with another cBTKi is possible, depending on the type of toxicity and its severity

- For example, cBTKi rechallenge can be an option for a patient with myalgias, rash, diarrhea, or hypertension
- A different MOA may need to be considered in case of major/recurrent cardiotoxicity or major bleeding

Treatment options
- Alternative cBTKi
- ncBTKi pirtobrutinib*
- BCL-2i-based regimen

Patient does not have symptomatic disease/ is in remission[4-7]

Discuss patient goals and priorities, including preferences for treatment-free remissions

- Some patients with CLL whose disease is responding to treatment and who discontinue therapy due to intolerance have durable treatment-free remissions
- In a long-term follow-up of patients who discontinued ibrutinib due to toxicity, the median time to disease progression was 23 months, suggesting that many patients may have a prolonged treatment-free interval before needing additional therapy[7]

In patients discontinuing cBTKi due to intolerance, it is important to assess if subsequent therapy is needed according to the iwCLL criteria[4,6,7]

*ncBTKi is indicated after cBTKi in R/R CLL. NCCN guidelines recommend to sequence ncBTKi after either progression or intolerance to cBTKi.[8]

BCL-2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MOA, mechanism of action; ncBTKi, NCCN, National Comprehensive Cancer Network; noncovalent Bruton's tyrosine kinase inhibitor; R/R, relapsed/refractory.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. 3. Shadman M. *JAMA.* 2023;329(11):918-932. 4. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 5. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 6. Bennett R, et al. *Blood Cancer J.* 2024;14(1):33. 7. Simon F, et al. *Curr Oncol Rep*. 2023;25(10):1181-1189. 8. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed December 22, 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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The Impact of Disease Progression on Treatment Decisions in Patients With CLL

Assessment of Progressive Disease in Patients With CLL Receiving Treatment

PD during or after therapy is characterized by **at least 1 of the parameters below**

Parameter	Definition of progressive disease
Lymphadenopathy	• A new lesion such as enlarged lymph nodes (≥1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates • An increase by ≥50% in greatest determined diameter of any previous site (≥1.5 cm) ❖ **Transient increases during treatment with novel agents should not be counted as PD**
Splenomegaly	• An increase in spleen size by ≥50% of its prior increase beyond baseline or new appearance of splenomegaly
Hepatomegaly	• An increase in the liver size of ≥50% of the extent of enlargement of the liver below the costal margin defined by palpation, or new appearance of hepatomegaly ❖ **Hepatomegaly must be attributable to lymphoid involvement to count as PD**
Lymphocytosis	• An increase in the number of blood lymphocytes by ≥50% with ≥5 x 10^9/L B lymphocytes ❖ **Certain therapies may cause lymphocytosis, and, in these cases, lymphocytosis alone is not a sign of PD**
Aggressive histology	• Transformation to a more aggressive histology (Richter syndrome or Richter transformation) diagnosed by lymph node or tissue biopsy
Cytopenia	• Cytopenia (neutropenia, anemia, or thrombocytopenia) ❖ **Not attributable to autoimmune cytopenia (eg, ITP and AIHA)** ❖ **Cytopenia is a side effect of many therapies and cannot be used to define PD in patients during treatment. Progression of cytopenia at least 3 months after treatment defines PD**

AIHA, autoimmune hemolytic anemia; ITP, autoimmune thrombocytopenia; PD, progressive disease.

Hallek M, et al. *Blood.* 2018;131(25):2745-2760.

Clinical Approach to CLL Disease Progression Depends on the Outcome of Prior Therapy

If a patient exhibits symptoms of active/progressive disease during treatment with:

Time-limited therapies[1-3]

For patients on BCL-2i:
determine whether rechallenge is an option

- If a patient's disease progresses during a treatment-free period, re-treatment may be an option, depending on the **length of remission***

Continuous therapies[1-3]

For patients on covalent BTKis:
switching to a drug with a different MOA may be necessary

- Patients who experience disease progression often develop **BTK resistance mutations**
  - C481 mutation is a common mechanism of acquired resistance to cBTKi; rechallenge with another cBTKi is not recommended
  - ncBTKi binding is independent of C481 status

The decision whether to rechallenge or switch to another drug class after disease progression depends on the specific response and type of therapy (time-limited vs continuous)[3-6]

*BCL-2i retreatment is recommended for patients with ≥1 year DOR off treatment after prior BCL-2i.[1,3]

BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase; cBTKi, covalent Bruton's tyrosine kinase inhibitor; DOR, duration of response; MOA, mechanism of action; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor.

1. Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. 2. Shadman M. *JAMA*. 2023;329(11):918-932. 3. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 4. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 5. Jain N, et al. *Lancet*. 2024;404(10453):694-706. 6. Bennett R, et al. *Blood Cancer J*. 2024;14(1):33.

Progression After Time-Limited BCL-2i Therapy: When Is Retreatment With BCL-2i Appropriate?

Patient meeting iwCLL criteria for treatment initiation[1]

→ **BCL-2i-based therapy** (eg, venetoclax + obinutuzumab) →

Disease progression

Progression on treatment[2-5]

When patient experiences disease progression while on venetoclax, the next recommended line of therapy is a second-generation cBTKi or one of the R/R treatment options

cBTKi

- Acalabrutinib
- Zanubrutinib

R/R after prior cBTKi-based and BCL-2i-containing regimens

- ncBTKi pirtobrutinib*
- Clinical trial
- CAR T-cell therapy lisocabtagene maraleucel
- Consider allo-HCT in fit patients

Progression during treatment-free interval[2-5]

Although no prospective data exist to guide retreatment, venetoclax tolerability and length of time from completion of prior venetoclax are important factors

Progression after short (<1 year) remission

A cBTKi therapy is recommended for patients who experienced progression after <1 year since completing prior venetoclax treatment

Progression after long (≥1 year) remission

Retreatment with venetoclax can be considered for patients who tolerated venetoclax well and if their disease progressed after ≥1 year since completion of prior treatment

When BCL-2i ± anti-CD20 mAb retreatment is recommended, addition of anti-CD20 mAb and optimal treatment duration should be individualized to each patient[5]

*If not previously given in 2L. Pirtobrutinib is approved for R/R CLL/SLL after prior cBTKi treatment.[6]

2L, second line; allo-HCT, allogeneic hematopoietic cell transplant; BCL-2i, B-cell lymphoma 2 inhibitor; CAR, chimeric antigen receptor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 3. Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. 4. Shadman M. *JAMA.* 2023;329(11):918-932. 5. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 6. FDA. Accessed December 15, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

Progression on a cBTKi: A Drug Class Switch Is Recommended

Patient meeting iwCLL criteria for treatment initiation[1]

cBTKi-based therapy
(eg, ibrutinib, acalabrutinib, zanubrutinib)

Disease progression

Considerations for patients with disease progression on a cBTKi therapy[2-5]

- Acquired resistance mutations in the *BTK* binding pocket and *PLCG2* gain-of-function mutations occurred in 57%-87% of patients who progressed on ibrutinib
  - A *BTK* C481 mutation is the most common resistance mechanism in patients whose disease progressed on a cBTKi

Treatment options[3,6]
- ncBTKi pirtobrutinib
- BCL-2i-based regimen

Switching drug classes after progression on a cBTKi

ncBTKi[3,7,8]
- Pirtobrutinib is a highly selective, ncBTKi with substantial clinical activity in patients with disease progression on a cBTKi, including patients with a *BTK* C481 mutation
- Similar to cBTKis, pirtobrutinib is administered orally and taken until progression or intolerance

BCL-2i[2,3,8,9]
- There is limited clinical trial evidence regarding efficacy/safety of BCL-2i in patients with prior cBTKi exposure
- It is recommended to continue cBTKi until the target dose of venetoclax is reached during initial ramp-up to reduce the risk of potential disease flare/rapid disease progression that may occur with prompt cBTKi discontinuation

When a patient experiences disease progression on a cBTKi-based regimen, switching to a therapy with a different MOA is recommended[3,8]

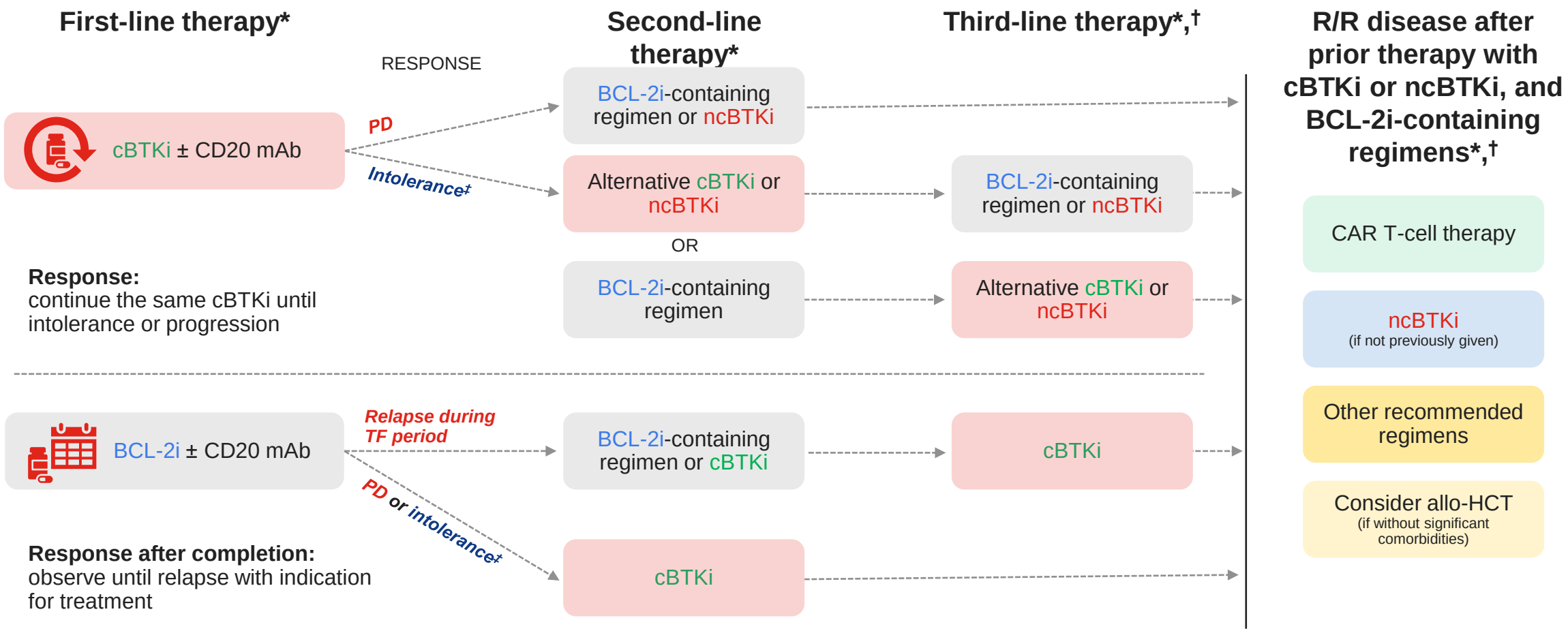
BCL-2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; cBTKi, covalent Bruton's tyrosine kinase inhibitor; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MOA, mechanism of action; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Simon F, et al. *Curr Oncol Rep*. 2023;25(10):1181-1189. 3. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 4. Naeem A, et al. *Blood Adv*. 2023;7(9):1929-1943. 5. Thompson PA, et al. *Blood*. 2023;141(26):3137-3142. 6. FDA. Accessed December 15, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic 7. Mato AR, et al. *N Engl J Med.* 2023;389(1):33-44. 8. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 9. Hampel PJ, et al. *Am J Hematol*. 2020;95(3):E57-E60.

4

Considerations for Treatment Sequencing in Patients With CLL After Treatment Intolerance and Disease Progression

CLL Treatment Sequencing Can Be Complex[1,2]



*Treatment should be initiated in patients meeting the iwCLL criteria. In case of intolerance, a TF period may be considered for patients without active disease.[1,3,4] †Treatment options for patients with CLL/SLL who discontinued previous therapy due to intolerance or PD. ‡Intolerance followed by PD.

allo-HCT, allogeneic hematopoietic cell transplant; BCL-2i, B-cell lymphoma 2 inhibitor; CAR, chimeric antigen receptor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TF, treatment-free.

1. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed December 22, 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. 3. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 4. Bennett R, et al. *Blood Cancer J.* 2024;14(1):33.

Representative CLL Treatment Journey: Hypothetical Patient Case 1

Patient 1

Clinical factors
A 63-year-old man, initially diagnosed with Rai stage I CLL

- Mutated *IGHV* and del(17p)

Comorbidities
Well-controlled hypertension

Patient factors/preferences
As the patient lives in a rural area, he prefers treatment with limited visits/monitoring

Watch and wait The patient is initially under active surveillance[1,2]

3 years later, the patient is not exhibiting any new or bothersome symptoms that would warrant treatment discussion[1]

After 4 years, the patient begins exhibiting symptoms of disease progression, including fatigue, new swollen lymph nodes, lymphocytosis, and cytopenia. The patient needs treatment based on iwCLL criteria[1,2]

1L

Second-generation cBTKi is selected due to efficacy reported in clinical trials and subgroup analyses of patients with del(17p).

Based on patient's well-controlled hypertension, the potential AE profile of cBTKi aligned with fewer clinic visits for monitoring[3]

6 months later, the patient is responding and tolerating treatment

5 years into the treatment, the patient is exhibiting disease symptoms, including enlarged lymph nodes, fatigue, and cytopenia[1]

2L

ncBTKi is selected based on patient's preference for oral medication, comorbidities (well-controlled hypertension), and duration of response to previous cBTKi therapy. The patient can continue with familiar dosing and side effect profile[4,5]

This is a hypothetical patient case scenario.

1L, first line; 2L, second line; AE, adverse event; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; *IGHV*, immunoglobulin heavy chain variable region genes; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Leukemia and Lymphoma Society. Accessed November 11, 2025. https://bloodcancerunited.org/blood-cancer/leukemia/chronic-lymphocytic-leukemia-cll/treatment 3. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 4. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011 2025;9(5):1213-1229. 5. FDA. Accessed December 15, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

Representative CLL Treatment Journey: Hypothetical Patient Case 2

Patient 2

Clinical factors
A 71-year-old woman diagnosed with Rai stage III CLL, *IGHV*-mutated, *TP53* wild-type CLL

Comorbidities
Well-controlled hypertension, type 2 diabetes, and treatment-refractory AIHA. The patient has history of AF

Preferences
Patient prioritizes efficacious therapy that allows for potential time off-treatment

The decision is made to initiate therapy based on iwCLL criteria[1,2]

1L

BCL-2i + anti-CD20 mAb is selected based on efficacy and patient's comorbidities (well-controlled hypertension and history of AF). It aligns with patient preference for potential for treatment-free periods[2]

6 months later, the patient is responding and tolerating treatment

8 months into the treatment, the patient is experiencing repetitive grade 3-4 infections. Treatment interruption and dose reduction did not resolve the AE. When treatment is discontinued due to infectious AEs, the patient exhibits symptoms of disease progression. During SDM, the patient and HCP agree to switch treatment[3]

2L

Second-generation cBTKi is selected based on the patient's comorbidities (well-controlled hypertension and history of AF). After SDM discussion, the patient is open to continuous therapy based on efficacy and safety demonstrated in clinical trials[2,4]

6 months later, the patient is responding and tolerating treatment[1,2]

6 years later, the patient is exhibiting symptoms of disease progression, including enlarged lymph nodes, night sweats, fatigue, and fever[1]

3L

ncBTKi is selected based on duration of response to and tolerance of previous cBTKi, as well as the patient's comorbidities (well-controlled hypertension, history of AF)[4,5]

This is a hypothetical patient case scenario.
1L, first line; 2L, second line; 3L, third line; AE, adverse event; AF, atrial fibrillation; AIHA, autoimmune hemolytic anemia; BCL-2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; GI, gastrointestinal; HCP, healthcare provider; *IGHV*, immunoglobulin heavy chain variable region genes; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; SDM, shared decision making.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 3. Galitzia A, et al. *Cancers (Basel).* 2024;16(11):1996. 4. FDA. Accessed December 15, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

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Key Takeaways

Key Takeaways

Treatment intolerance and disease progression have different clinical implications on subsequent therapy selection[1-3]

- In case of intolerance, it's possible to try a different agent from the same drug class
- In contrast, when a patient experiences disease progression, a new MOA is recommended

When patients discontinue CLL therapy due to intolerance, it’s important to assess the need for direct **subsequent therapy** according to iwCLL 2018 criteria and whether treatment-free remission may be an option[4-6]

The choice of **subsequent line of therapy** in patients with **active disease** after progression or intolerance depends on **careful consideration of numerous factors**, including depth and duration of response to previous lines of therapy, acquired resistance, and patient factors and preferences[6-9]

Treatment sequencing in CLL can be complex due to the number of different options and factors to consider following **frontline therapy,** but following recommendations from **clinical treatment guidelines** can help[3,6-8]

BCL-2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton’s tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MOA, mechanism of action.

1. CGTlive. Accessed December 15, 2025. https://www.cgtlive.com/view/new-agents-and-optimal-patient-selection-in-cll-comprise-modern-paradigm 2. Shadman M. *JAMA*. 2023;329(11):918-932. 3. Fresa A, et al. *Cancers (Basel).* 2024;16(11):2011. 4. Bennett R, et al. *Blood Cancer J*. 2024;14(1):33. 5. Simon F, et al. *Curr Oncol Rep*. 2023;25(10):1181-1189. 6. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 7. Odetola O, Ma S. *Curr Hematol Malig Rep.* 2023;18(5):130-143. 8. Hallek M, et al. *Am J Hematol.* 2021;96(12):1679-1705. 9. Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161.