Identifying Disease Progression Versus Treatment Intolerance in CLL

In CLL, **disease progression** and **treatment intolerance** are the primary reasons for treatment discontinuation but may be challenging to differentiate as they could present with similar symptoms (eg, cytopenia).[1-4]

When assessing **treatment response** and **PD, physical examination** and evaluation of **blood** and **bone marrow** should be performed[4,5]

Timing of response assessment[4,5]

- Fixed-duration therapies: at least **2 months** after completing therapy
- Continuous therapies: at least **2 months** after **maximum response**

Assessment of CLL disease progression or treatment intolerance

PD during or after therapy is characterized by at least one of the parameters below[4]

1. Lymphadenopathy[4]

Increase ≥50% from BL or from response

- Transient increases during treatment can occur with novel agents and may not be PD

2. Hepatomegaly/splenomegaly[4]

Increase ≥50% from BL or from response

- Hepatomegaly must be attributable to lymphoid involvement to count as PD

3. Constitutional symptoms[2,4,6]

Any (eg, unexplained weight loss, fatigue, recurrent fever, drenching night sweats)

- ▶ Some can also be an AE of CLL therapies

4. Cytopenia[4,*]

Decrease in platelet count of ≥50% from BL, or in hemoglobin of ≥2 g/dL from BL*

- ▶ Can be an AE of many CLL therapies

5. Lymphocytosis[4]

Increase ≥50% over BL†

- ▶ Can be an AE of certain therapies

6. Marrow infiltration[4]

Increase of CLL cells by ≥50% on successive biopsies

Treatment Sequencing Considerations for PD and Intolerance

- If a patient experiences **intolerance**, it may be possible to try a different agent from the **same drug class**[7,8]
- In contrast, when **disease progression** occurs, a therapy with a **new MOA** is recommended[7,8,¶]

Treatment	Outcome	Subsequent therapy
cBTKi	Intolerance‡	Alternative cBTKi or ncBTKi§
cBTKi	Progression	BCL-2i or ncBTKi§

Differentiating between **disease progression** and **treatment intolerance** is essential to ensure patients maximize adherence to therapy and overall treatment journey to optimize outcomes, as each has distinct implications for subsequent therapy selection.[3,7,8]

*Secondary to CLL. To define PD, cytopenia cannot be attributable to AIC and must progress at least 3 months after treatment.[4] †A temporary increase in lymphocyte count can also be associated with certain therapies so lymphocytosis alone may not be a sign of treatment failure or PD.[4] ‡Intolerance with active disease. §Noncovalent BTKi therapy is indicated after at least two prior lines of therapy, including a BTKi and a BCL-2i.[9] ¶If disease progression occurs during a treatment-free interval after completion of fixed-duration therapy (eg, BCL-2i), a re-challenge with the same MOA is an option.[7]

AE, adverse event; AIC, autoimmune cytopenia; BCL-2i, B-cell lymphoma 2 inhibitor; BL, baseline; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MOA, mechanism of action; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; PD, progressive disease.

1. Shadman M, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23(7):515-526. 2. Hallek M. *Am J Hematol*. 2025;100(3):450-480. 3. Galitzia A, et al. *Cancers (Basel)*. 2024;16(11):1996. 4. Hallek M, et al. *Blood*. 2018;131(25):2745-2760. 5. Del Giudice I, et al. *Cancers (Basel)*. 2024;16(11):2049. 6. CLL Society. https://cllsociety.org/cll-sll-patient-education-toolkit/cancer-related-fatigue/ 7. Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. 8. Hampel PJ, Parikh SA. *Blood Cancer J*. 2022;12(11):161. 9. Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229.