How Is CLL Treated?

WHEN TO TREAT

- Many patients are **asymptomatic** at diagnosis, during which **observation** is the standard of care[1]
- Therapy is often necessary once disease is **symptomatic**[1,2]

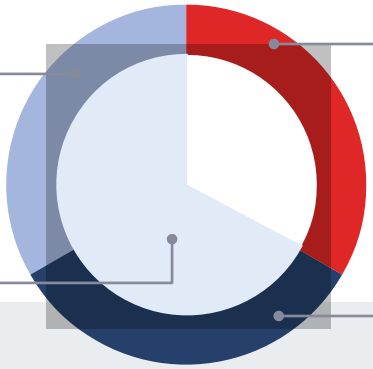
Among patients with CLL[1,3]

≈1/3
Will not need immediate treatment, but will need it at some point

≈1/3
Need immediate treatment

≈1/3
May never need treatment

Watch and wait



iwCLL 2018 criteria for therapy initiation[2,4,*]

Lymph nodes, liver and/or spleen size
Massive, progressive, or symptomatic[†]

Constitutional symptoms
Disease related[‡]

Circulating lymphocyte count
Progressive ≥50% over a 2-month period, or lymphocyte doubling time <6 months[§]

Worsening anemia and/or thrombocytopenia
Due to progressive marrow failure[¶]

Bone marrow
Progressive marrow failure as per above

Extranodal symptoms
(eg, skin, kidney, lung, spine)

Patients meeting **one or more** of the criteria above **should be treated**[1,2,4,5]

FIRST-LINE THERAPY

Approach to management of previously untreated CLL[1,4-6]

Presence or absence of ***TP53* mutation** is one of the most important **prognostic/predictive biomarkers** in CLL[4]

In addition, choice of frontline therapy may depend on patient **age, fitness,** and presence of additional **molecular and cytogenetic markers** (eg, *IGHV* mutation)[5]

Potential therapies include:
- Covalent BTKi ± anti-CD20 mAb
- BCL-2i + anti-CD20 mAb

Prognostic modeling with the **CLL-IPI**, along with consideration for **functional status, comorbidities**, and **patient preference**, may guide treatment options[1,2,4,5]

*Autoimmune complications (including autoimmune cytopenias) poorly responsive to corticosteroids or current treatment may represent an additional indication for change in treatment. [†]Lymph nodes ≥10 cm, liver and/or spleen size ≥6 cm below the left costal margin. [‡]Unintentional weight loss ≥10% within the previous 6 months; significant fatigue (ECOG PS ≥2), fevers (38.0 °C) for ≥2 weeks without evidence of infection; night sweats for ≥1 month without evidence of infection. [§]Non-CLL factors that may contribute to lymphocytosis (e.g., infections and corticosteroids) should be excluded. [¶]Thrombocytopenia <100 x 10^9/L, anemia <10 g/dL. Hemoglobin and platelet count cutoffs require consideration of the rate of decline. In certain patients, counts slightly below these levels may remain stable for an extended period and not require treatment initiation.[4]

BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, immunoglobulin heavy chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; *TP53*; tumor protein 53.

References: 1. Shadman M. *JAMA*. 2023;329(11):918-932. **2.** Hallek M, et al. *Blood*. 2018;131(25):2745-2760. **3.** HealthTree Foundation for Chronic Lymphocytic Leukemia. https://healthtree.org/cll/community/articles/what-is-watch-and-wait-for-cll. **4.** Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J*. 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. **5.** Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. **6.** Al-Sawaf O, et al. [published correction appears in *Nat Commun*. 2023;14(1):6724]. *Nat Commun*. 2023;14(1):2147.

How Is CLL Treated?

Identifying disease progression[1-3]

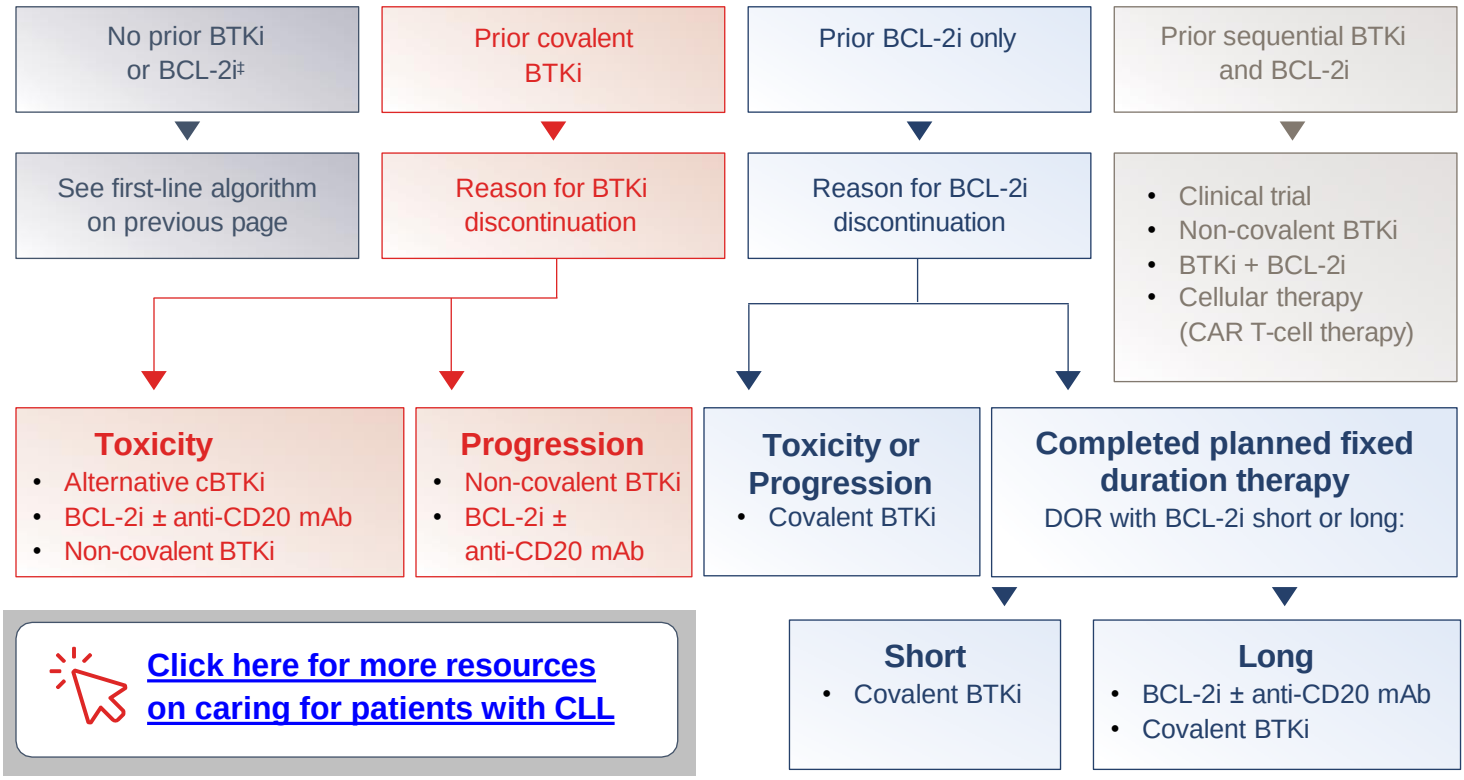
Symptoms of CLL progression include:

- Unexplained weight loss (>10% in 6 months)
- Extreme fatigue
- Fever (>2 weeks without signs of infection)
- Night sweats (>1 month)
- Increasing number of CLL cells in bone marrow*
- Enlarged spleen†
- Additional enlarged lymph nodes and/or enlarged liver
- Increase in lymphocytes (>50% in 2 months or rapid doubling time)

R/R THERAPY

- Therapy options for R/R CLL are based on the **patient's response** to previous line(s) of therapy, including **timing of progression, tolerance** to prior therapy, and **patient goals**[4-6]
- Repeat testing of **del(17p)/*TP53*** may also help guide later lines of therapy[4,5]

Approach to management of previously treated CLL[6-11]



Click here for more resources on caring for patients with CLL

*Leading to anemia and/or thrombocytopenia.[3] †Resulting in abdominal pain/fullness or early satiety.[2,3] ‡CIT consisting of fludarabine-cyclophosphamide + rituximab, bendamustine-rituximab, and chlorambucil-obinutuzumab was previously the first-line therapy for CLL before the introduction of novel agents.[4]

BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; DOR, duration of response; mAb, monoclonal antibody; R/R, relapsed/refractory; *TP53*; tumor protein 53.

References: 1. HealthTree Foundation for Chronic Lymphocytic Leukemia. Accessed September 6, 2024. https://healthtree.org/cll/community/articles/cll-progressing. **2.** Medical News Today. Accessed September 6, 2024. https://www.medicalnewstoday.com/articles/cll-symptom-progression. **3.** Canadian Cancer Society. Accessed September 6, 2024. https://cancer.ca/en/cancer-information/cancer-types/chronic-lymphocytic-leukemia-cll/disease-progression. **4.** Shadman M. *JAMA*. 2023;329(11):918-932. **5.** Hallek M, et al. *Blood*. 2018;131(25):2745-2760. **6.** Hampel PJ, Parikh SA. [published correction appears in *Blood Cancer J.* 2022;12(12):172]. *Blood Cancer J.* 2022;12(11):161. **7.** Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. **8.** FDA. Accessed August 20, 2024. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel. **9.** Thompson MC, et al. *Blood Adv.* 2022;6(15):4553-4557. **10.** Sharman JP et al. *J Clin Oncol.* 2025;43(22):2538-2549. **11.** Hallek M. *Am J* Hematol. 2025;100:450-480.