CLL Clinical Decision Making: Patient Case Study

Patient characteristics*

Clinical and prognostic factors

- A 78-year-old man, diagnosed with Rai stage III CLL
- Unmutated *IGHV*

Comorbidities

- History of AF
- Treatment refractory AIHA
- Frequent respiratory infections

Additional considerations

- Lives with an elderly spouse and travel to clinic is challenging

The patient needs CLL therapy based on treatment refractory cytopenia and additional symptoms of active disease according to iwCLL criteria[1,2]

Treatment options[3-5]

- Continuous
  - cBTKi ± anti-CD20 mAb

OR

- Time limited
  - BCL-2i ± anti-CD20 mAb
  - BCL-2i + cBTKi[†]

Patients with CV risk factors can often be safely treated with BTKi therapy; a full CV pretreatment workup can help evaluate the level of CV risk[6,7]

Pretreatment workup[6-10]

For all patients

COMPREHENSIVE PATIENT HISTORY

- Blood pressure measurement
- ECG
- Concomitant medications

CV RISK FACTOR ASSESSMENT

- Presence of diabetes, obesity, hypertension, dyslipidemia, CRD
- History of VHD, arrhythmias, HF, or LV dysfunction/reduced ejection fraction

For patients with high CV risk or established CV disease

ADDITIONAL CV WORKUP

- Echocardiogram, baseline cardiac biomarkers (eg, cTn or NP)
- Evaluate risk of stroke/systemic embolism (CHA_2DS_2-VASc score); consider FRS-CVD score for stratification

*This is a fictional case study to illustrate concepts and considerations for CLL decision making. Individual results may vary.
[†]The phase 3 AMPLIFY clinical trial included cBTKi + BCL-2i + anti-CD20 mAb study arm.[11]

AF, atrial fibrillation; AIHA, autoimmune hemolytic anemia; BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]; CLL, chronic lymphocytic leukemia; CRD, chronic renal disease; cTn, cardiac troponin; ECG, electrocardiogram; FRS-CVD, Framingham risk score-cardiovascular disease; HF, heart failure; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; CV, cardiovascular; LV, left ventricular; mAb, monoclonal antibody; NP, natriuretic peptide; VHD, valvular heart disease.

1. Hallek M, et al. *Blood*. 2018;131(25):2745-2760. 2. Hallek M, Al-Sawaf O. *Am J Hematol*. 2021;96(12):1679-1705. 3. Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229. 4. Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. 5. FDA. Accessed April 23, 2026. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-acalabrutinib-veneto-clax-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma. 6. Awan FT, et al. *Blood Adv*. 2022;6(18):5516-5525. 7. Quartermaine C, et al. *JCC CardioOncol*. 2023;5(5):570-590. 8. Munir T, et al. Acta Haematol. Published online July 18, 2025. doi:10.1159/000547426. 9. Lyon AR, et al. *Eur Heart J*. 2022;43(41):4229-4361. 10. Hindricks G, et al. *Eur Heart J*. 2021;42(5):373-498. 11. Brown JR, et al. *N Engl J Med*. 2025;392(8):748-762.

CLL Clinical Decision Making: Patient Case Study

Treatment decision

- Based on the patient's comorbidities, second-generation cBTKi or BCL-2i–based therapy can be considered[1]
  - –Pretreatment workup, including baseline biomarkers and FRS-CVD score, did not identify additional CV risk factors aside from history of AF[2]
  - –Treatment with DOAC is recommended based on patient's CHA_2DS_2-VASc score of >2. Second-generation cBTKi is preferred over first-generation cBTKi for patients with established CV disease[2-5]
- During SDM, the patient expressed that travel to clinic is challenging; thus, oral dosing of cBTKi with limited visits/clinical monitoring aligns with the patient's preferences[1]

Second-generation cBTKi was chosen as therapy

CV monitoring during treatment[4]

The patient has key risk factors for development of BTKi-induced CV toxicity including history of AF, male sex, and age >65 years

- Regular screening is important to detect asymptomatic AF with ECG recommended every 3 to 6 months at clinic visits for the first year
- For patients with CHA2DS2-VASc score of ≥2, 24-h Holter monitoring may help identify asymptomatic AF
- Advise patients to self-monitor for palpitations, dyspnea, and fatigue (smart watches or phone applications can be used to detect AF)

Treatment outcome

- After 5 months of treatment the patient experienced grade 2 AF, which resolved with a treatment interruption. He was able to continue with cBTKi therapy[2-4]
- **After 5 years of cBTKi treatment the patient developed symptoms of disease progression according to iwCLL criteria[6,7]**

R/R treatment options[1,8]

Progression on a cBTKi →
- Noncovalent BTKi
- BCL-2i ± anti-CD20 mAb

R/R treatment decision

- Noncovalent BTKi or BCL-2i–based therapy can be considered after progressing on a cBTKi[8,9]
  - –Clinical studies show that the majority of patients who discontinued a prior BTKi due to cardiac AE, did not experience recurrence with a noncovalent BTKi[10]
- The patient prefers oral medication. With a noncovalent BTKi the patient can continue with familiar dosing and types of side effects[8,11]
- Clinical data show that patients previously treated with a cBTKi can respond to noncovalent BTKi[1,8,12]

Noncovalent BTKi was chosen as the next line of therapy

This is a fictional case study to illustrate concepts and considerations for CLL decision making. Individual results may vary. AE, adverse event; AF, atrial fibrillation; BCL-2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]; CLL, chronic lymphocytic leukemia; CV, cardiovascular; DOAC, direct-acting oral anticoagulant; ECG, electrocardiogram; SDM, shared decision making.

1. Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229. 2. Awan FT, et al. *Blood Adv*. 2022;6(18):5516-5525. 3. Quartermaine C, et al. *JCC CardioOncol*;5(5):570-590.4. Munir T, et al. *Acta Haematol*. Published online July 18, 2025. doi:10.1159/000547426. 5. Hindricks G, et al. *Eur Heart J*. 2021;42(5):373-498. 6. Tam CS, et al. *Blood Adv*. 2025 Aug 19:bloodadvances.2025015986. 7. Hallek M, et al. *Blood*. 2018;131(25):2745-2760. 8. Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. 9. FDA. Accessed April 23, 2026. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic. 10. Shah NN, et al. *Haematologica*. 2025;110(1):92-102. 11. Lewis KL, et al. *J Pers Med*. 2021;11(8):764. 12. Mato AR, et al. *N Engl J Med*. 2023;389(1):33-44.