

# CLL Clinical Decision Making: Patient Focused

*Patients with active, high-risk CLL*

## Identifying high-risk CLL

- High-risk CLL is defined by the presence of adverse genomic, cytogenetic, or clinical features that predict poorer outcomes or earlier disease progression<sup>1</sup>
- High-risk disease can be assessed using prognostic indexes such as CLL-IPI that combines age, biomarkers, and disease stage<sup>1</sup>

## Key high-risk biomarkers

- **Del(17p) and TP53 mutations** are recommended to be tested before each new line of therapy<sup>2,3</sup>
- **Unmutated IGHV** testing is recommended only before the first line of therapy<sup>3,4</sup>
- **Complex karyotype** is defined as  $\geq 3$  aberrations and is recommended to be tested before each new line of therapy<sup>5,6</sup>

## Consider: Disease background



- What symptoms is the patient presenting with, and how would you classify their disease?
- Are high-risk features present (del[17p]/TP53 mutation, IGHV mutational status, cytogenetics), and is the disease behaving indolently or aggressively for the risk group?

## Consider: Patient background



- What is the patient's current medication burden ( $\geq 5$  medications), and are any likely to interact with CLL therapy?
- What comorbidities does the patient present with, and how severe are they? (Consider cardiac, renal, and hepatic function)
- Is the patient up to date on vaccinations, and are there concerns about infection risk?

## Consider: Patient preference



- How does the patient define a successful treatment? Improved/sustained QOL? Minimal side effects? Treatment-free periods?
- How far away does the patient live from the clinic and do they have easy access to transportation and caregiver support?
- What is their preference for drug administration (eg, no IV)?

## Consider: Key aspects of 1L treatment options

### BCL-2i features and considerations<sup>6,7</sup>



- Time-limited therapy (treatment-free periods)
- May include intravenous multidrug therapy
- Frequent visits/labs in the first 8 weeks
- Additional surveillance for TLS in patients with kidney disease or substantial disease burden along with TLS prevention (eg, hydration)

### BTKi features and considerations<sup>6</sup>



- Continuous oral therapy
- Limited visits/laboratory monitoring
- Additional pretreatment workup recommended for patients with CV risk factors

1L, first-line; BCL-2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CLL-IPI, Chronic Lymphocytic Leukemia-International Prognostic Index; CV, cardiovascular; IGHV, immunoglobulin heavy-chain variable region; IV, intravenous; QOL, quality of life; TLS, tumor lysis syndrome; TP53, tumor protein 53 gene.

1. International CLL-IPI working group. *Lancet Oncol.* 2016;17(6):779-790. 2. Eichhorst B, et al. *Ann Oncol.* 2024;35(9):762-768. 3. Campo E, et al. *Haematologica.* 2018;103(12):1956-1968. 4. Heerema NA, et al. *Haematologica.* 2021;106(6):1608-1615. 5. Baliakas P, et al. *Blood.* 2019;133(11):1205-1216. 6. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 7. Anderson MA, et al. *Cancers (Basel).* 2024;16(5):980.

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1

## Biomarker testing



### **TP53 aberrations**

incidence including del(17p)/TP53 mutations increase from 10% when starting treatment to 40% with R/R CLL<sup>1</sup>

### **IGHV mutational status**

remains unchanged throughout the treatment course; unmutated IGHV is present in approximately 40% of patients with untreated CLL<sup>2</sup>

### **Complex karyotype**

is found in 14%-34% of patients with treatment-naïve CLL and in up to 25%-35% of patients with R/R CLL<sup>3</sup>

2

## Treatment initiation



**Regardless of biomarker test results**, guidelines recommend only initiating treatment if there are signs of active disease defined by iwCLL criteria<sup>4-6</sup>

3

## Treatment considerations



Guidelines recommend **targeted therapies** for patients with CLL especially high-risk patients since patients with TP53 aberrations, unmutated IGHV, or complex karyotype are associated with better outcomes and favorable safety profiles when treated with a targeted treatment<sup>4-6</sup>

## Consider: For subsequent treatment

- Is the patient presenting with active CLL symptoms (considering subsequent treatment), or are they under surveillance (considering a treatment holiday)?
- What were the prior lines of therapy, respective outcomes, reasons for discontinuation, and any notable adverse reactions?
- What is the current del(17p)/TP53 mutation status, and has it been reassessed since prior therapy?
- Have there been any changes in the patient's health status, comorbidities, or treatment goals since initiating prior therapy?



**For patients with CLL high-risk features**, including TP53 aberrations, unmutated IGHV, and complex karyotype, consider targeted therapy options and careful treatment sequencing planning that incorporates biomarker retesting when needed<sup>4-6</sup>



CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy-chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; R/R, relapsed/refractory; TP53, tumor protein 53 gene.

1. Stefaniuk P, et al. *Cancer Manag Res*. 2021;13:1459-1476. 2. Lee J, et al. *J Mol Diagn*.

2020;22(9):1114-1125. 3. Cavallari M, et al. *Oncotarget*. 2018;9(76):34398-34412.

4. Hallek M, et al. *Am J Hematol*. 2025;100(3):450-480. 5. Eichhorst B, et al. *Hemasphere*. 2026;10(6):e70403. 6. Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229.