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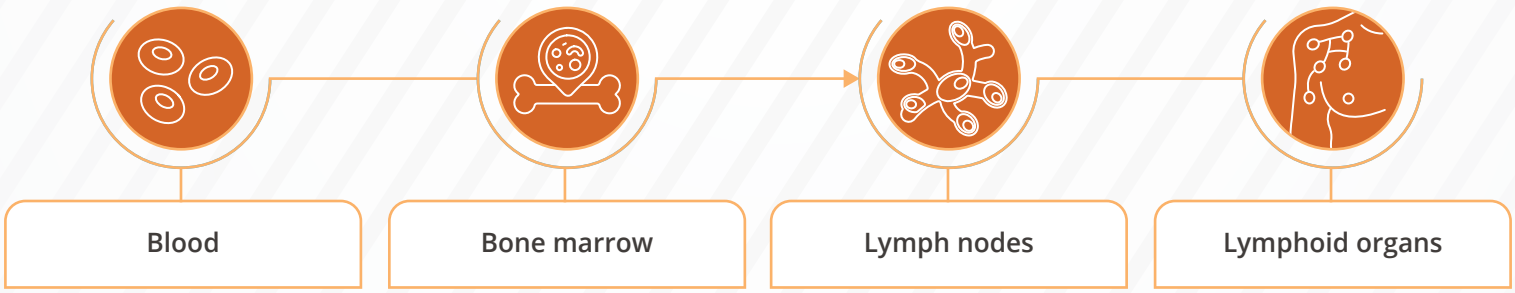
Recent Advances in Chronic Lymphocytic Leukemia Treatment

Key Insights from the American Society of Hematology 2024 Conference

Chronic lymphocytic leukemia (CLL) is a type of blood cancer characterized by the uncontrollable growth of CD5+ B-cells in[1,2,3]:



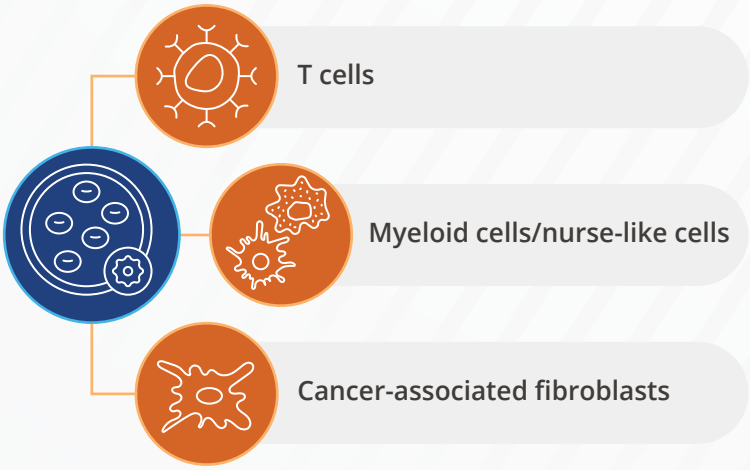
CLL is highly variable in clinical presentation and progression[1]

- Indolent or symptomatic disease
- Rapid progression or progression after several years

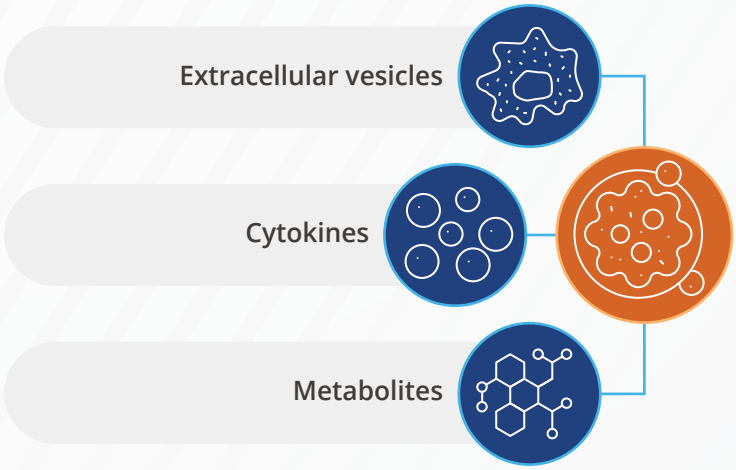
CLL treatment success depends on molecular genetic alterations, in particular immunoglobulin heavy variable gene somatic hypermutation status and 17p deletion/*TP53* mutation

Interaction of CLL cells with tumor microenvironment (TME)[4,5]

CLL cells



CLL cells interact with the TME via:



Predictive markers in CLL[2]

- *TP53* gene disruption
- Unmutated immunoglobulin heavy chain variable (*IGHV*) gene mutational status

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Richter syndrome (RS)–an aggressive transformation of CLL[4,6,7]

RS is a phase of CLL that sometimes follows drug resistance and disease relapse

- Resistance to existing therapies
- Poor prognosis
- Promising future treatment modalities:
  - Immune checkpoint blockade
  - Bispecific antibodies

Novel insights into molecular triggers in RS[6]

- Loss of function mutations in *TP53*
- Deletion of cyclin-dependent kinase (CDK) inhibitors, CDKN2A and CDKN2B

→ Cells bypass B-cell receptor (BCR)-associated blocking of cell cycle progression → Development of RS phenotype

Factors influencing treatment response in RS[8]

- Changes in the tumor microenvironment
- Clonal hematopoiesis of indeterminate potential mutations

BCR signaling as a target in CLL treatment strategies[1,2,3]

BCR signaling involved:
- → B-cell survival
- → B-cell proliferation

Bruton tyrosine kinase (BTK) → Crucial enzyme for BCR signaling

BTK inhibitor (BTKi)[1,3] → Enzyme inhibitor used in any line of therapy for CLL

Approximately, 10%–15% of patients with CLL develop resistance to treatment with the selective BTKi ibrutinib, which is widely used as a front-line therapy for CLL, or experience disease relapse due to minimal residual disease (MRD) cells remaining in the blood[1]

Emerging treatment approach in the case of MRD[9]

Evasion of BTK inhibition in CLL cells with BCR^{low}/ERK^{high} phenotype → Inhibition of Ras/Raf/MEK/ERK signaling → Delayed tumor growth

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Benefits of venetoclax in CLL treatment

B-cell lymphoma 2 (BCL-2) is a protein that regulates apoptosis

Venetoclax is a selective BCL-2 antagonist that induces apoptosis of CLL cells

- Enhances activation and function of immune cells[10]
- Exerts immunomodulatory effects on T-cell features[11]
- Prevents T-cell exhaustion[11]

Combination therapies that prevent T cell exhaustion

Venetoclax and epcoritamab, a bispecific CD3 and CD20 targeted monoclonal antibody[12]

Targeting S100A9 protein in TME during chimeric antigen receptor T-cell therapy[5]

Venetoclax and chemoimmunotherapy[13]

Recent studies on the efficacy of BTK and BCL2 inhibitors

Fixed duration triplet therapy with:
- Acalabrutinib (second generation BTKi)
- Venetoclax
- Obinutuzumab (anti-CD20 antibody)

vs

Monotherapy with one agent (acalabrutinib, venetoclax, or obinutuzumab)

Improved progression-free survival (PFS) in previously untreated CLL patients[14]

Randomized phase III trial

Pirtobrutinib (non-covalent BTKi)

vs

Chemotherapy Idelalisib + rituximab or bendamustine + rituximab

Improved PFS in heavily pretreated high-risk patients with a more favorable safety profile[15]

Examination of safety profile

Pirtobrutinib + venetoclax + obinutuzumab

High rate of undetectable bone marrow MRD[16]

Sonrotoclax:
Higher potency than venetoclax

Emerging alternatives for venetoclax and ibrutinib—next-generation BCL-2 inhibitor with reduced toxicity[17]

Zanubrutinib:
Higher potency than ibrutinib

Emerging alternatives for BTKi—BTK degraders[18,19]

BTK degraders NX-5948 and BGB-16673 have demonstrated safety and efficacy in treating heavily pretreated relapsed or refractory CLL with poor prognosis[18,20]

Improving quality of life of patients with CLL

Therapies that demonstrated significant improvement in health-related quality of life (HRQoL):

Venetoclax and ibrutinib
- Patients with relapsed and refractory CLL[19]
- Older patients with comorbidities[21]

Venetoclax and obinutuzumab with or without ibrutinib (GAIA/CLL13 trial data)
- First-line therapy[22]

Key message

Future innovations for CLL treatment should strive to balance treatment efficacy with safety, HRQoL, and long-term disease control

References:

1. Lee, J., & Wang, Y. L. (2020). Prognostic and predictive molecular biomarkers in chronic lymphocytic leukemia. *The Journal of Molecular Diagnostics, 22*(9), 1114–1125.
2. Cohen, J. A., Bomben, R., Pozzo, F., Tissino, E., Härzschel, A., Hartmann, T. N., Zucchetto, A., & Gattei, V. (2020). An updated perspective on current prognostic and predictive biomarkers in chronic lymphocytic leukemia in the context of chemoimmunotherapy and novel targeted therapy. *Cancers, 12*(4), 894.
3. Hallek, M., & Al-Sawaf, O. (2021). Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *American Journal of Hematology, 96*(12), 1679–1705.
4. https://cll.knowledgehub.wiley.com/conference-coverage/ash-2024/
5. Palma, A. U., Varela, M. M., Marquez, M. E., Gamal, W., Oppezzo, P., Sahakian, E., & Pinilla-Ibarz, J. (2024). Enhancing CAR-T therapy in CLL by modulating the immunosuppressive tumor microenvironment: A novel approach with significant therapeutic potential. *Blood, 144*, 4607.
6. Martines, C., Chakraborty, S., Felician, G., Hofmann, K., Blasutig, S., Negara, I., ... & Efremov, D. G. (2024). Richter Syndrome-associated genetic lesions in *TP53* and the cell cycle inhibitors CDKN2A and CDKN2B induce transformation of a CD5+ B cell subset characterized by a restricted *IGHV* repertoire, autoreactivity and BCR dependence. *Blood, 144*, 759.
7. Ten Hacken, E., Gustafsson, J., Tomasoni, C., Hoffmann, G. B., Cruz, K., Lu, W. S., ... & Wu, C. J. (2024). Polyfunctional effector PD-1+ CD8+ T Cells and M1 macrophages promote immune checkpoint blockade response in Richter syndrome mouse models. *Blood, 144*, 761.
8. Cosentino, C., Mouhssine, S., Almasri, M., Romano, I., Di Bergamo, L. T., Nabki, J., ... & Moia, R. (2024). Prevalence and clinical impact of clonal hematopoiesis of indeterminate potential (CHIP) in chronic lymphocytic leukemia and Richter transformation. *Blood, 144*, 762.
9. Forestieri, G., Loh, J. W., Singh, A., Spina, V., Zucchetto, A., Condoluci, A., ... & Rossi, D. (2021). CLL-358: Adaptation of chronic lymphocytic leukemia to ibrutinib is mediated by epigenetic plasticity of residual disease and bypass signaling via the MAPK pathway. *Clinical Lymphoma Myeloma and Leukemia, 21*, S323–S324.
10. Cortese, M. J., Wright, J. P., Mavis, C., Mandeville, T. K., Niu, A., Kim, D. K., ... & Hernandez-Ilizaliturri, F. (2024). Multiomic evaluation of immunologic changes in chronic lymphocytic leukemia with venetoclax treatment. *Blood, 144*, 78.
11. Griggio, V., Vitale, C., Jones, R., Mancin, G., Bondielli, G., Visentin, A., ... & Coscia, M. (2024). Treatment with venetoclax positively modulates immunological parameters and T-cell features in patients with chronic lymphocytic leukemia. *Blood, 144*, 1854.
12. Saleh, L. M., Mhibik, M., Playà-Albinyana, H., Sun, C., Pleyer, C., & Wiestner, A. (2024). T cells from CLL patients on venetoclax mount potent cytotoxic responses in combination with epcoritamab, a CD20/CD3 bispecific antibody. *Blood, 144*, 3231.
13. Jacobs, C. F., D'Hargues, Y., Robrecht, S., Fürstenau, M., Fischer, K., Fink, A. M., ... & Peters, F. S. (2024). In-depth immune and metabolic profiling of GAIA/CLL13 patients to uncover treatment-specific changes to the T-cell compartment. *Blood, 144*, 1846.
14. Brown, J. R., Seymour, J. F., Jurczak, W., Aw, A., Wach, M., Illes, A., ... & Ghia, P. (2024). Fixed-duration acalabrutinib plus venetoclax with or without obinutuzumab versus chemoimmunotherapy for first-line treatment of chronic lymphocytic leukemia: Interim analysis of the multicenter, open-label, randomized, phase 3 AMPLIFY trial. *Blood, 144*, 1009.
15. Sharman, J. P., Munir, T., Grosicki, S., Roeker, L., Burke, J. M., Chen, C. I., ... & Barr, P. M. (2024). BRUIN CLL-321: Randomized phase III trial of pirtobrutinib versus idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma. *Blood, 144*, 886.
16. Jain, N., Ferrajoli, A., Swaminathan, M., Reville, P. K., Burger, J. A., Bharathi, V., ... & Wierda, W. G. (2024). Combined pirtobrutinib, venetoclax, and obinutuzumab as first-line treatment of patients with chronic lymphocytic leukemia (CLL). *Blood, 144*, 1011.
17. Soumerai, J. D., Cheah, C. Y., Anderson, M. A., Lasica, M., Verner, E., Opat, S. S., ... & Tam, C. S. (2024). Sonrotoclax and zanubrutinib as frontline treatment for CLL demonstrates high MRD clearance rates with good tolerability: Data from an ongoing phase 1/1b study BGB-11417–101. *Blood, 144*, 1012.
18. Thompson, M. C., Parrondo, R. D., Frustaci, A. M., Allan, J. N., Ghia, P., Mocanu, I., ... & Seymour, J. F. (2024). Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Results from the phase 1 CaDAnCe-101 study. *Blood, 144*, 885.
19. Eurelings, L. E. M., Rotbain, E. C., Kersting, S., Van Der Straten, L., Enggaard, L., Veldhuis, G. J., ... & Levin, M. D. (2024). Quality of life in patients with relapsed/refractory chronic lymphocytic leukemia improves after minimal residual disease-guided treatment with ibrutinib plus venetoclax. *Blood, 144*, 888.
20. Shah, N. N., Omer, Z., Collins, G. P., Forconi, F., Danilov, A., Byrd, J. C., ... & Munir, T. (2024). Efficacy and Safety of the Bruton's Tyrosine kinase (BTK) degrader NX-5948 in patients with relapsed/Refractory (R/R) chronic lymphocytic leukemia (CLL): Updated results from an ongoing phase 1a/b study. *Blood, 144*, 884.
21. Niemann, C. U., Munir, T., Owen, C., Follows, G., Rivas, J. A. H., Benjamini, O., ... & Kater, A. P. (2024). First-line ibrutinib plus venetoclax vs chlorambucil plus obinutuzumab in elderly or comorbid patients (Pts) with chronic lymphocytic leukemia (CLL): Glow study 64-month follow-up (FU) and adverse event (AE)-free progression-free survival (PFS) analysis. *Blood, 144*, 1871.
22. Fürstenau, M., Rotbain, E. C., Eurelings, L., Robrecht, S., Von Tresckow, J., Giza, A., ... & Eichhorst, B. F. (2024). Patient-reported quality of life outcomes with venetoclax-based first-line combinations in CLL: An analysis from the phase 3 GAIA/CLL13 trial. *Blood, 144*, 3238.

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