Leukemia insights

MARCH 2025

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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In this month's Leukemia Insights newsletter, written by Mahesh Swaminathan, M.D., Nitin Jain, M.D., and William Wierda, M.D., Ph.D., we provide a summary of ongoing clinical trials in patients with chronic lymphocytic leukemia (CLL). Learn more about our Leukemia program.

New therapies and combinations for chronic lymphocytic leukemia (CLL)

The development of oral small molecule inhibitor targeted therapies against key proteins of the B-cell receptor signaling pathway, such as Bruton tyrosine kinase (BTK), and against the anti-apoptotic protein BCL-2 fundamentally changed the treatment landscape of CLL. These agents are effective in both first-line and relapsed CLL, including in patients with high-risk features such as del(17p) and mutated TP53 . The BTK inhibitors (BTKi) ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib, and the BCL2 inhibitor venetoclax are currently approved for patients with CLL and have replaced chemoimmunotherapy for the treatment of first line and relapsed disease. Our current therapeutic objectives include optimizing the depth of remission with first-line treatment through combined targeted therapy, gaining understanding of optimal sequencing of targeted therapies and combinations to improve outcomes, delay and avoidance of resistance to targeted therapy and progression to Richter transformation, and improving outcomes for patients who develop Richter transformation. We continue to identify new therapeutic targets to achieve these objectives and to develop novel agents that work by different mechanisms of action.

Continuous treatment with B-cell receptor signaling pathway inhibitors yields highly effective debulking and durable disease control, while BCL2i-based treatment produces deep remissions with time-limited treatment. Combinations of targeted therapies with complementary clinical activity, non-overlapping toxicities, and in vitro data demonstrating synergy are well-tolerated and produce deep and durable remissions with fixed-duration treatment. Therapeutic sequencing is also an important consideration for long-term disease management owing to the chronicity of CLL and the fact that the use of these agents is not

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mutually exclusive. The preferred strategy at our center is to begin with time-limited treatment to achieve deep remission. Therefore, efforts at therapeutic development have focused on optimizing targeted combinations. Decisions about retreatment at the time of relapse/progression are based on remission duration.

Clinical trials in first-line CLL

BTK and BCL2 are established therapeutic targets for highly effective small molecule inhibitors. In first-line CLL, indefinite therapy with BTKi (ibrutinib, acalabrutinib +/- obinutuzumab, zanubrutinib) and time-limited treatment with venetoclax + obinutuzumab are FDA approved. The time-limited treatment with acalabrutinib + venetoclax ± obinutuzumab is expected to receive FDA approval soon. The following clinical trials are currently accruing previously untreated patients with CLL/SLL:

1. Pirtobrutinib + venetoclax + obinutuzumab (NCT05536349). In this trial, patients meeting iwCLL treatment indication who have no prior treatment for CLL receive the time-limited triplet of pirtobrutinib + venetoclax + obinutuzumab. Pirtobrutinib is a non-covalent BTKi with a favorable safety profile. Pirtobrutinib is supplied at no cost.
2. Atezolizumab + venetoclax + obinutuzumab (NCT02846623). In this trial, patients meeting iwCLL treatment indication who have no prior treatment for CLL can receive the time-limited triplet of atezolizumab + venetoclax + obinutuzumab. Atezolizumab is a PD-L1 checkpoint inhibitor. All 3 drugs are supplied at no cost.
3. Acalabrutinib (time-limited) + obinutuzumab (NCT04505254). In this trial, patients receive time-limited treatment with acalabrutinib for 24 cycles along with 6 cycles of obinutuzumab. Re-treatment is allowed for patients progressing in the off-therapy phase. Acalabrutinib is supplied at no cost.

Clinical trials for consolidation and measurable residual disease

Consolidation is a term used to describe additional treatment that deepens remission in responding patients as a strategy to improve time-to-event outcomes. In this case, it refers to the addition of agents to deepen remission for patients on BTKi-based treatment, potentially as a strategy to convert to time-limited treatment, or simply to deepen remission and enhance outcomes with maintenance therapy. Patients with CLL are eligible for consolidation with BCL2 inhibitor therapy if they have residual disease (less than CR) after treatment with a BTKi. The following clinical trials are currently accruing:

1. Venetoclax consolidation (NCT03128879). This trial allows patients with high-risk CLL on ibrutinib or acalabrutinib (for at least 12 months) and residual disease. The maximum duration of protocol treatment is 24 cycles (2 years). Venetoclax is supplied at no cost.
2. Lisaftoclax (APG2575), a novel BCL2 inhibitor (NCT06104566). This is a randomized phase 3 trial (GLORA study) of acalabrutinib + lisaftoclax vs. acalabrutinib in patients with residual CLL while on acalabrutinib (for at least 12 months). The protocol is being amended to allow patients on other covalent inhibitors such as ibrutinib and zanubrutinib. The protocol treatment is continued until disease progression. Lisaftoclax is supplied at no cost.

Clinical trials in relapsed and/or refractory CLL

Treatment for relapsed/refractory (R/R) CLL depends on the type of therapy the patient has previously received, development of resistance to targeted treatment, and comorbidities. Covalent BTKi's irreversibly bind to BTK at the C481 amino acid and inhibit function; recovery of functional BTK requires synthesis of new BTK in the CLL cells in the absence of the inhibitor. Patients who develop resistance to a covalent BTKi typically acquire an associated mutation in the BTK C481 amino acid, which prevents covalent binding of the inhibitor and maintained BTK kinase activity. Pirtobrutinib is a BTKi that binds reversibly to BTK, independent of C481, and has therapeutic activity in patients who progress on a covalent BTKi (ibrutinib, acalabrutinib or zanubrutinib). Venetoclax binds to BCL2, blocking function and favoring a pro-apoptotic balance in the BCL2 protein family, hurling the CLL cells into cell death. Resistance to venetoclax can involve mutation of BCL2 that causes conformational change preventing venetoclax binding, but various other resistance mechanisms also have been reported.

The following clinical trials are currently accruing patients with R/R CLL/SLL:

1. AS-1763, a novel noncovalent BTKi (NCT05602363). This is a phase 1b trial of AS-1763 in patients with R/R CLL who have had at least ≥2 prior lines of treatment. Prior use of BTKi's such as ibrutinib, acalabrutinib, zanubrutinib and pirtobrutinib is allowed. Prior use of a BCL2 inhibitor is allowed. AS-1763 is supplied at no cost.
2. Liso-cel (lisocabtagene maraleucel; CD19 CAR-T cells) (NCT03331198). This is a phase 2 study in patients with R/R CLL previously treated with BTKi and BCL2i-based therapy. This trial is with liso-cel monotherapy . Liso-cel is supplied at no cost.
3. ABBV-101 is an oral BTK degrader under development for patients with CLL in this phase I/II trial (NCT05753501). Patients with R/R CLL who have had at least 2 prior lines of treatment are eligible. ABBV-101 is supplied at no cost.
4. NX-5948, is an oral BTK degrader in phase I/II trial (NCT05131022). This degrades both wild-type and mutated BTK. Patients with R/R CLL and 2 prior lines of therapy are eligible. NX-5948 is supplied at no cost.
5. ABBV-525 is an oral mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT-1) inhibitor currently in phase I/II trial. MALT-1 is a downstream signaling molecule in the NF-kB pathway (NCT05618028). ABBV-525, a new oral kinase inhibitor, was developed to overcome BTKi resistance. Any patient with R/R CLL, who has had at least 2 prior lines of treatment is allowed. ABBV-525 is supplied at no cost.
6. Epcoritamab +/- venetoclax (NCT04623541). Phase 1/2b study. In this phase 1/2b study, epcoritamab, a bi-specific antibody that binds CD20 and CD3 to activate T-cell mediated killing of CLL cells, is administered as a subcutaneous injection. Epcoritamab is supplied at no cost.

Acalabrutinib + obinutuzumab + venetoclax (NCT04169737). This trial allows patients with R/R CLL, including those who may have received prior covalent BTKi's or BCL2i. All 3 drugs are supplied at no cost.