Leukemia insights

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Making Cancer History®

In this month's Leukemia Insights newsletter, written by Nitin Jain, M.D., and William Wierda, M.D., Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we provide a summary of the progress made in the last ten years in the treatment of patients with chronic lymphocytic leukemia (CLL). Learn more about our Leukemia program.

Chronic Lymphocytic Leukemia – Next Steps

Remarkable progress has been made in the last decade in the treatment of patients with CLL. More patients than ever are achieving remission, and treatments are improving overall survival. This is due to 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. These agents are highly effective in both first-line and relapsed CLL, even in patients with high-risk features such as del(17p) and mutated *TP53*. The BTK inhibitors (BTKi) ibrutinib, acalabrutinib and zanubrutinib, and the BCL2 inhibitor venetoclax, have proved most effective. Chemoimmunotherapy no longer has much, if any role in the management of patients with CLL.

Highly effective disease burden reduction and durable disease control are achieved with continuous treatment with B-cell receptor signaling pathway inhibitors, while BCL2i-based treatment produces deep remissions with fixed-duration treatment. Complimentary clinical activity, non-overlapping toxicities, and in vitro data demonstrating synergy were the basis for combined targeted therapy, which is well-tolerated and produces deep and durable remissions with fixed-duration treatment. Owing to the chronicity of CLL and the fact that the use of these agents is not mutually exclusive, therapeutic sequencing is also an important consideration for long-term disease management. The preferred strategy at our center is to begin with fixed-duration treatment to achieve deep remission. Therefore, efforts at therapeutic development have been directed to optimize targeted therapy combinations. Decisions about retreatment at the time of relapse/progression are based on remission duration.

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It's the easiest way to stay current with information on the latest leukemia news, research, and resources. View archived issues.

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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 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 provided free of charge.
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 provided free of charge.
3) Acalabrutinib + obinutuzumab (NCT04505254). In this trial, patients receive time-limited treatment with acalabrutinib for 24 cycles along with obinutuzumab. Re-treatment is allowed for patients progressing in the off-therapy phase. Acalabrutinib is provided free of charge.
4) Zanubrutinib + rituximab (NCT04458610). In this trial, patients receive time-limited treatment with zanubrutinib and rituximab. Re-treatment is allowed for patients progressing in the off-therapy phase. Zanubrutinib is provided free of charge.

Clinical Trials in Relapsed and/or Refractory CLL

Treatment choice for R/R CLL depends on the type of previous therapy the patient has received, presence of resistance mutations, and comorbidities. Currently available BTKi's covalently bind to BTK at the C481 amino acid and irreversibly inhibit function. One major mechanism of resistance to covalent BTKi's is a mutation in C481, preventing covalent binding. Work is ongoing to develop BTKi's that bind reversibly to BTK, independent of C481, to enable continued treatment with a BTKi for patients who are developing resistance. Venetoclax binds BCL2, blocking function and favoring a pro-apoptotic balance in BCL2 family proteins, hurling the CLL cells into cell death. Resistance to venetoclax can involve mutation of BCL2 that causes conformational change that does not allow venetoclax binding, but other resistance mechanisms are involved.

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

1) Acalabrutinib + obinutuzumab + venetoclax (NCT04169737). This trial allows patients with R/R CLL, including those who may have received prior covalent BTKi's. All 3 drugs are provided free.
2) AS-1763, a novel noncovalent BTKi (NCT05602363). This is a phase 1 dose escalation trial of AS-1763. Prior use of covalent BTKi's such as ibrutinib, acalabrutinib, and zanubrutinib is allowed. Prior use of a BCL2 inhibitor is allowed. AS-1763 is provided free of charge.
3) MS-553, an oral PKC-B inhibitor (NCT03492125). PKC-B is a downstream signaling molecule from BTK. This trial allows patients with R/R CLL. MS-553 is provided free of charge.

4. SC291, an allogeneic CAR-T product (NCT05878184). This CAR-T product has genetic modifications to prevent rejection. Patients with R/R CLL are allowed. Because the cells are allogeneic, or premade, there is no need for leukapheresis or wait time for cell manufacturing. Cells are provided free of charge.
5. LP-118, an oral dual BCL2/XL inhibitor (NCT04771572). Any patient with R/R CLL is allowed. LP-118 is provided free of charge.
6. BGB-11417, a novel BCL2 antagonist (NCT04277637). In this trial, BGB-11417 is given in combination with the approved BTKi zanubrutinib for R/R CLL and front-line CLL (front-line cohort currently filled). Both drugs provided free of charge.
7. ABBV-525, novel MALT1 inhibitor (NCT05618028). This phase 1 study is for patients with relapsed/refractory CLL. ABBV-525, a new oral kinase inhibitor, was developed to overcome BTKi resistance. The drug is provided free of charge.
8. Epcoritamab +/- venetoclax (NCT04623541). Phase 1/2b study. In this phase 1/2b study, epcoritamab, a bi-specific antibody that binds simultaneously to CD3 and CD20 to activate the T-cell mediated killing of CLL cells is administered as a subcutaneous injection. It is provided free of charge.

Announcements

SOHO 2023 Annual Meeting-Hybrid

The Eleventh Annual Meeting of the **Society of Hematologic Oncology** (SOHO 2023) is scheduled for **September 6–9, 2023** at the George R. Brown Convention Center in Houston, Texas. As a hybrid event, SOHO 2023 offers in-person and virtual attendance options. Organized by its founders and world class committees, SOHO is the only worldwide society specific to the field of hematologic malignancies. The 2023 meeting promises to be a dynamic and informative event. SOHO is the premier meeting that focuses specifically on new advances and practical clinical applications in the field of hematologic malignancies. The speakers are a multidisciplinary group of internationally recognized experts that represent the spectrum of these diseases. Click here to register.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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Leukemia Faculty Contacts (continued)

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