



• CHRONIC LYMPHOCYTIC LEUKEMIA •

CLL RESEARCH

2022 Year In Review

CLL Global Research Foundation has provided over \$33 million in research funding (2005-2022)

Greetings!

As we come upon the end of another remarkable year for CLL research, I am reminded yet again that the days may be long, but the years fly by! Having retired from the clinic, I am focused full-time on the next steps in curing CLL, ensuring we address unmet needs for all patients, especially those who have high-risk features, have relapsed on, or are refractory to current therapies, and those who develop Richter's transformation. Embracing my role as thought leader – or should I say instigator? – I find myself full of ideas on how to make the world better for patients. We've made extraordinary progress in advancing CLL therapeutics over the last decade, with the possibility of long-term remission (dare we say cure?) achievable with oral, fixed-duration combination therapies for a majority of patients. What is missing? A majority is not all.



We need to think outside-the-box to develop options for patients whose CLL proves a match for the current weapons of choice. Bi-specific antibodies, novel cellular therapies, and identifying new, druggable targets are options being explored at this very moment. I also think it is imperative that we create avenues to disseminate these rapidly evolving best practices to providers and patients outside the academic medical community. A vast majority of CLL patients will be treated in a community clinic, and I aim to make sure they have access to the same treatment options and information as my patients did. Stay tuned as CLL Global Research Foundation helps to make these dreams become a reality!

Sincerely,
Dr. Michael Keating

Good News for CLL Patients

Advances in the treatment of CLL have occurred at a dizzying pace over the last several years, and calling CLL an incurable disease may no longer be accurate. In the 1990s, younger, fit patients with good prognostic factors treated with FCR (fludarabine, cyclophosphamide, and rituximab) had a 10-year disease-free survival rate of 55-60%, and it was the first therapy to show a survival improvement. Fast-forward to today and the development of targeted small molecule inhibitors that disrupt CLL cell survival signals, including BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), BCL2 inhibitors (venetoclax), and anti-CD20 monoclonal antibodies (obinutuzumab, rituximab), have significantly increased the survival rate for the vast majority of patients. Recent updates from clinical trials using fixed-duration combinations of these targeted therapies are showing three-year progression-free survival rates of >80%, including in patients with high-risk features, making CLL potentially functionally curable for many patients. The focus now is to maintain the momentum in developing new therapeutics to make CLL a curable disease for all patients. CLL Global Research Foundation is front and center in this crusade, ensuring that the financial and scientific resources are available to advance the next generation of therapies. *Kantarjian, HM, et al. Cancer 2022;128:240-259



Good News

REGARDING DRUG COSTS

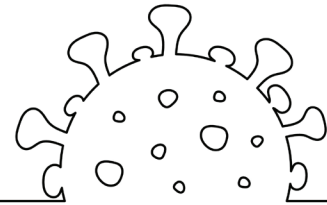
Many CLL patients are covered by Medicare with a supplemental drug plan (Part A, B, and D) or a Medicare Advantage Plan. As some of you know all too well, this means that when it comes to targeted oral anti-cancer drugs, the out-of-pocket costs can be over \$10,000 a year. These high out-of-pocket expenses mean roughly one-third of patients struggle with following their recommended treatment plan.

The Inflation Reduction Act, passed this year, will greatly improve access to care and lower the financial burden for cancer patients. Starting in 2024, CLL patients covered by Medicare Part D will no longer have to pay 5% of oral drug costs after reaching catastrophic coverage (\$7,050). Starting in 2025, the out-of-pocket cap will be reduced to \$2,000 with no added financial responsibility once reached. Further, the act allows Medicare to negotiate directly with manufacturers for certain brand name drugs starting in 2023, with ibrutinib likely on the list as one of the first drug prices negotiated. Over time, this should reduce oral anti-cancer drug costs not only for those on Medicare, but for people covered under other health plans as well.

GOOD NEWS ON COVID-19

In the Omicron era, CLL patients who test positive for COVID-19 generally have milder disease and lower fatality rates, with hospital admissions declining significantly, compared with earlier in the pandemic*. In contrast to two years ago, we have far more weapons in our arsenal to fight COVID-19, including for those who are immunocompromised.

CORONAVIRUS



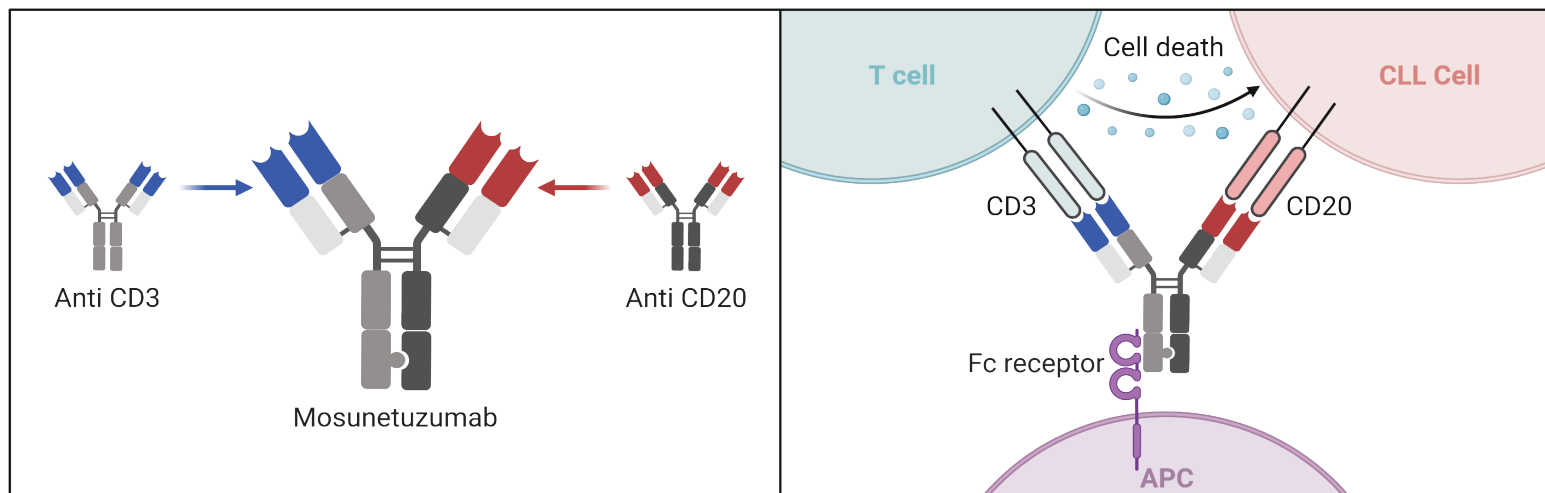
We now have vaccines, and CLL patients should be fully vaccinated, even though vaccine efficacy may be reduced due to immune dysfunction and/or treatment with a BTK inhibitor or anti-CD20 antibody. We also have Evusheld, the first pre-exposure prophylaxis available to people who are immunocompromised. It is recommended that CLL patients talk with their physicians about receiving Evusheld to lower their risk of infection. Repeat dosing is recommended every 6 months to ensure ongoing protection. For patients who do get infected with COVID-19, there are many treatment options now available, including a variety of monoclonal antibodies, remdesivir, and Paxlovid. With these preventative measures and early intervention strategies in place, along with taking sensible, daily precautions, the risk of severe COVID-19 and mortality are greatly reduced. As the SARS-CoV-2 virus continues to mutate, additional information and recommendations will be forthcoming. *Niemann, CU, et al. Blood 2022;140(5): 445-450

NEW ON THE SCENE: BI-SPECIFIC ANTIBODIES

You have probably heard of rituximab and obinutuzumab as therapies used to treat CLL. These are monoclonal antibodies that recognize a target exclusively found on normal and cancerous B cells called CD20. Monoclonal antibody binding to CD20 identifies the B cell as abnormal and tells the immune system to destroy it. In CLL, however, the immune system doesn't work as it should, and the T-cell component of the immune system is "exhausted" so not all cancerous cells are destroyed.



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Adapted from "Bispecific Antibody Design", by BioRender, August 2020, retrieved from <https://app.biorender.com/biorender-templates/figures/all/t-5fb3ddff0b3b2e00a6435389-bispecific-antibody-design> Copyright 2022 by BioRender.

How do we give those exhausted T cells a boost? One way is with bi-specific antibodies. Bi-specific antibodies recognize two different targets. In the case of mosunetuzumab, the antibody recognizes CD20 on B cells and CD3 on T cells. This design allows the bi-specific antibody to bind both the cancerous B cell and the exhausted T cell, facilitating T-cell-mediated cancer cell death. Based on promising results from a clinical trial in follicular lymphoma*, a Phase I/II trial of mosunetuzumab has been initiated in CLL patients. The future of bi-specific antibodies in treating CLL is promising, in part because it allows a patient's own immune system to help control the disease.

*Budde LE, et al. Lancet Oncology 2022; published online July 5. [https://doi.org/10.1016/S1470-2045\(22\)00335-7](https://doi.org/10.1016/S1470-2045(22)00335-7)

Upcoming Events

American Society of Hematology (ASH)

The 64th annual American Society of Hematology (ASH) Meeting is scheduled for December 10-13, 2022, in New Orleans, LA. This is the premiere malignant hematology event of the year where the latest developments in CLL, including new therapies, updated clinical trial findings, and improved practice methods, are presented and discussed. CLL Global Research Foundation looks forward to sharing updates with you on the hottest topics in CLL presented at this year's conference.

CLL Global Research Foundation Virtual Town Hall

Please join us on Friday, January 13, 2023, from 12 to 1 PM CT for our first Town Hall of 2023. Panelists will include our founder, Dr. Michael Keating, CLL Global Research Foundation president

and CEO, Dr. William Wierda, and Dr. Nitin Jain, Associate Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. The event will be moderated by CLL patient advocate, Jeff Folloder. Hear the latest news on emerging CLL research and clinical trials presented at the 64th annual ASH conference and learn how support from CLL Global Research Foundation is helping Dr. Jain to make fixed-duration ibrutinib plus venetoclax the standard of care in the treatment of CLL. Our favorite part of these events is hearing from you—our audience—so for this town hall we are dedicating extra time to answering your questions. Please click the Upcoming Events tab on our website at cllglobal.org to register and submit your questions for our expert panel. Registration is free!

Are You Up To Date?



This year's flu season has started off fast and furious, proving to be more severe than the previous 13 years. It is recommended that everyone who is eligible receive this year's trivalent influenza vaccine. The shot form of the vaccine, as opposed to the nasal mist form, is safe for cancer patients and survivors as it is made with inactivated virus. While you are at it, you can get your flu shot and your COVID-19 bivalent booster at the same time. While vaccination may not prevent all infections, the trivalent flu and bivalent COVID-19 vaccines are proving to be very effective at preventing severe infection and death. The best way to protect yourself and those you love is by getting both vaccines as soon as possible.

Evusheld UPDATE



On October 3, 2022, the Food and Drug Administration released an update regarding Evusheld, informing patients and healthcare providers of an increased risk for developing COVID-19 when exposed to variants of the SARS-CoV-2 virus that are not neutralized by Evusheld. The use of Evusheld for pre-exposure prophylaxis continues to be recommended, along with receiving the bivalent COVID-19 booster, as it still offers protection against a majority of the currently circulating

variants. For patients who do develop COVID-19 symptoms, it is recommended to be tested and talk with your healthcare provider right away as timely treatment can reduce the risk of severe disease, hospitalization and death.

Happy New Year!

As we emerge from the past 2 years of the pandemic, I reflect to focus on important lessons and blessings from this experience. Despite the adversity and challenges, research and treatment progress have flourished. Virtual communication with FaceTime and Zoom kept us in contact, but cannot replace face-to-face conversations, in person interactions, meetings, or hugs. There has never been a more optimistic time for cure of CLL and we are energized to push past the finish line. We are all in this together.

Sincerely,
Dr. William Wierda



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**Our mission is to abolish CLL as a threat to the life and health of patients
by accelerating CLL research.**

Please consider making a donation today and help us turn our passion for finding a cure for CLL into a reality for patients around the world. To donate online, visit our website at cllglobal.org/donate. Donations may also be mailed to CLL Global Research Foundation, P.O. Box 301402, Unit 428, Houston, Texas 77230.