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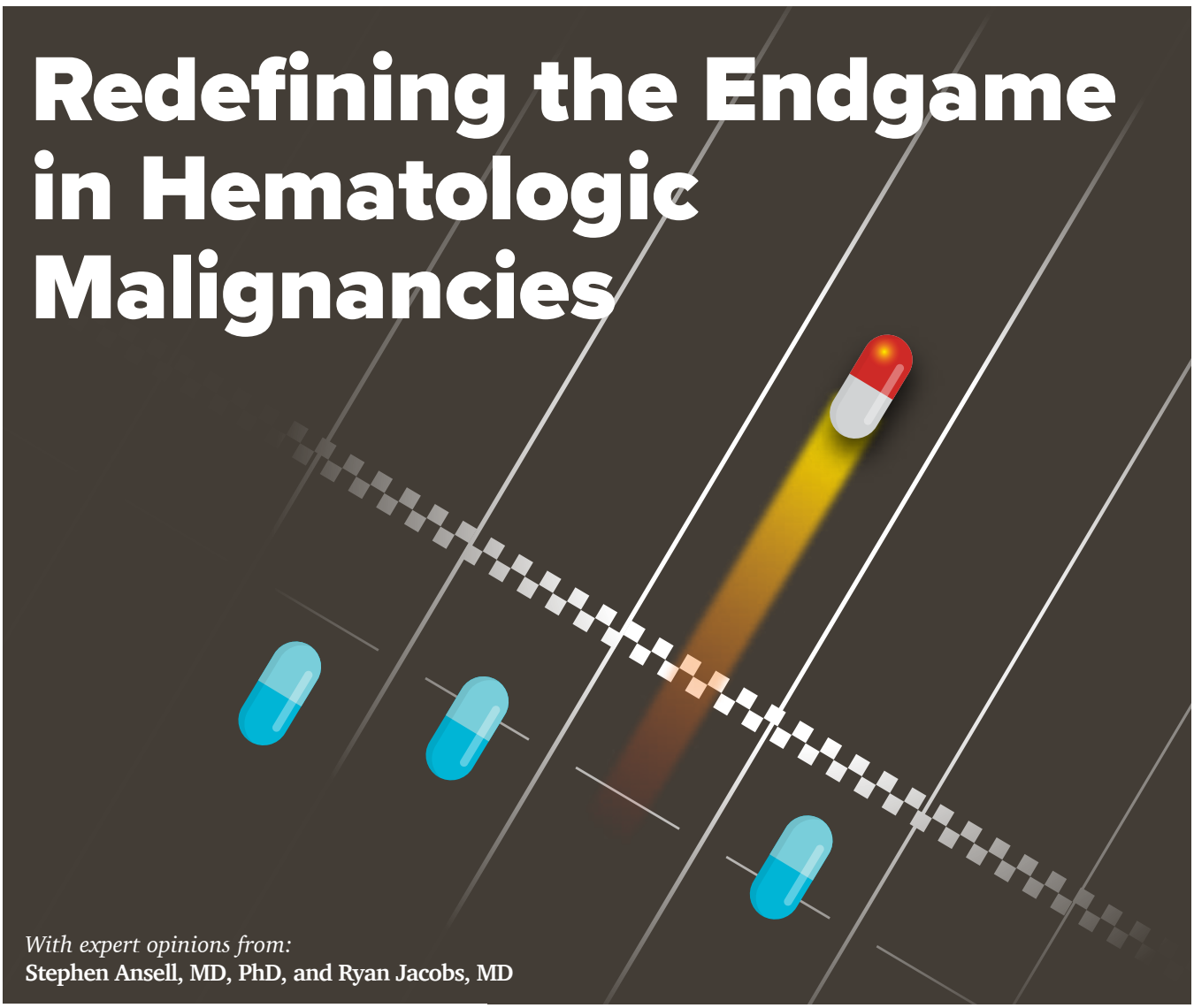

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PHYSICIAN'S WEEKLY

TURNING MEDICAL MISINFORMATION INTO MEANINGFUL PATIENT CONVERSATION

Alex McDonald, MD, explains how physicians can navigate polarized health conversations by replacing sound bites with nuance, curiosity, and trust—turning disagreement into connection with practical strategies that strengthen patient relationships and improve outcomes.

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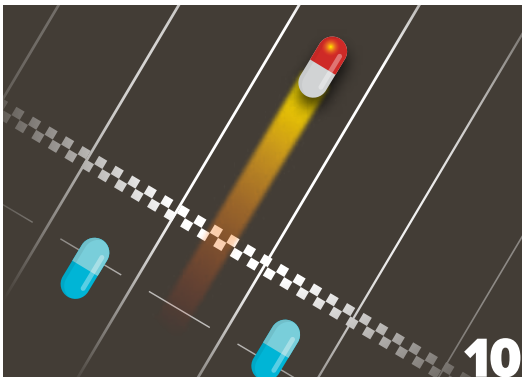

Redefining the Endgame in Hematologic Malignancies

For decades, the management of indolent hematologic malignancies centered on disease control rather than eradication. The assumption that these diseases were not curable outside of allogeneic transplant is now being challenged.

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What Real-World Data Are Teaching Us That Trials Cannot

Mehdi Hamadani, MD
Associate Editor

For the past two decades, I have watched real-world evidence evolve from a supplementary data source to an essential component of how we understand and deliver care to patients with hematologic malignancies. But the relationship between randomized controlled trials and real-world data is often misunderstood.

Randomized trials remain the gold standard, and there are several reasons for that. Their design, randomization, and rigor help minimize imbalances in patient populations. But patients who make it into clinical trials are not always representative of the patients we see in our clinics. Trial participants often have resources to travel to academic centers. They are generally fitter, more educated, and frequently from higher socioeconomic backgrounds. When we take clinical trial results and apply them in real-world clinical practice, we need to keep these limitations in mind.

This is where high-quality, real-world data become invaluable. Notice I said *high-quality*—not all real-world data carry the same weight. I am talking about prospectively maintained databases such as the Center for International Blood and Marrow Transplant Research (CIBMTR) in the United States and the European Bone Marrow Transplant (EBMT) registry. These registries collect data on consecutive patients using prespecified case report forms, with trained statisticians and data managers ensuring consistency in data collection. The Surveillance, Epidemiology, and End Results (SEER) program offers similar rigor. Compare this with multicenter retrospective studies in which data collection and training vary across sites; consecutive patient capture may be incomplete, and recall bias can skew results in either direction.

Real-world data can be used to validate whether observations made in trials translate to actual practice. They can also answer questions that prospective trials simply cannot address. Take chimeric antigen receptor (CAR) T-cell therapy for lymphomas, for instance. The pivotal trials established CAR T-cell therapy as the standard of care for large cell lymphomas, but large cell lymphoma is not one disease. It is a heterogeneous group. What about T-cell/histiocyte-rich large B-cell lymphoma? What about high-grade B-cell lymphoma, not otherwise specified? These rare subtypes are underrepresented in trials, yet real-world databases have allowed us to

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assess CAR T-cell efficacy in these populations and inform treatment decisions.

Sometimes, real-world evidence challenges trial conclusions. The TRANSFORM and ZUMA-7 trials showed that for patients with large cell lymphoma whose disease relapses early, CAR T-cell therapy outperforms traditional chemotherapy followed by autologous transplant. But those trials treated all early-relapsing patients as one population—a one-size-fits-all approach. Using CIBMTR data, we analyzed patients who responded to bridging therapy before receiving either transplant or CAR T-cell therapy. In those chemotherapy-sensitive, responding patients, transplant actually outperformed CAR T-cell therapy. This remains somewhat controversial, but it illustrates how real-world data can identify subsets when trial results may not apply uniformly.

Real-world data can also drive changes in how we deliver care. When CAR T-cell therapy first received approval, the FDA required patients to remain at transplant centers for observation for 4 weeks after infusion. The American Society for Transplantation and Cellular Therapy used real-world data to demonstrate that most clinically significant complications occur in the first 2 weeks. Why keep patients away from home for a month? The FDA changed its recommendation to 2 weeks based on this evidence. That is a tangible improvement in patient quality of life informed by observational research.

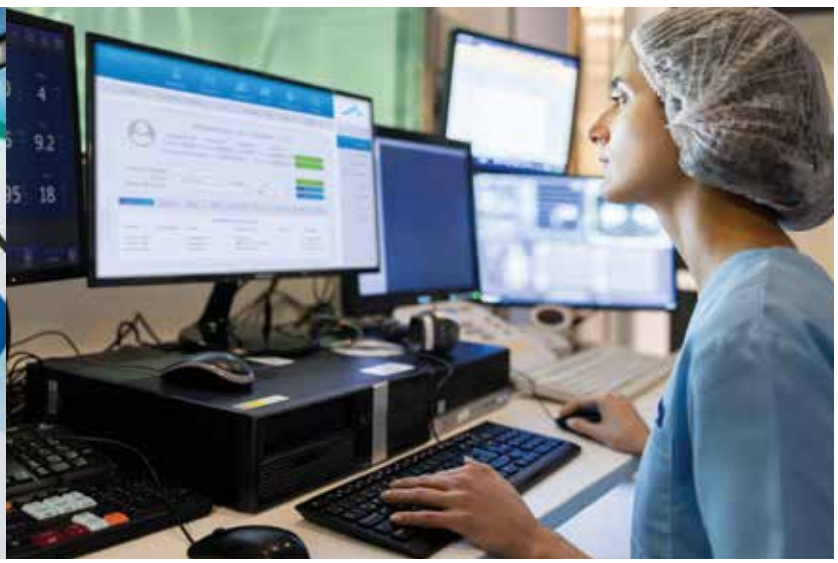
The FDA has also begun using real-world data for drug approvals. Tafasitamab received full approval for diffuse large B-cell lymphoma based partly on comparison against a retrospective real-world dataset. This represents a shift in how regulatory bodies view high-quality observational data.

But real-world data come with pitfalls. You must assess data quality before drawing conclusions. You need consecutive patient capture to avoid recall bias, as physicians tend to remember patients who did well or did poorly, and selective recall skews results. Data collection must include uniform definitions and be conducted by equally trained personnel across sites. Many retrospective studies lack central audits to catch collection errors. These limitations need to be taken into account when evaluating real-world results.

My advice is to keep an open mind but be critical when evaluating real-world evidence. Real-world datasets are important for understanding treatment efficacy across diverse patient populations, studying rare diseases, assessing access to care, and validating trial results in practice. They complement randomized trials rather than replace them. When you encounter real-world evidence, ask about the data source, the patient selection method, and the quality controls. Good observational research does not often generate practice-changing evidence but rather provides practice-validating evidence, and that validation matters, especially for patients who would not qualify for a clinical trial but still need our best care.

"Real-world datasets are important for understanding treatment efficacy across diverse patient populations, studying rare diseases, assessing access to care, and validating trial results in practice."

—Mehdi Hamadani, MD, Professor of Medicine and Chief of Hematologic Malignancies, Medical College of Wisconsin



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The Sunset of 7+3 and the Sunrise of Hypomethylating Agents With BCL-2-Inhibition in AML

By ***Moaath Mustafa Ali, MD, MPH***

Today's "7+3" induction chemotherapy—the current standard-of-care regimen for newly diagnosed fit patients with acute myeloid leukemia (AML)—emerged from a long series of scientific discoveries and clinical trials. Early reports on treatment with cytarabine demonstrated response rates approaching 50% in AML.[1,2] Later, in the 1970s, after a series of foundational experiments, Yates and colleagues at Roswell Park combined cytarabine with daunorubicin and confirmed its efficacy in AML, with response rates exceeding 60%.[3] Several subsequent trials were conducted to determine the optimal doses of anthracyclines and cytarabine.[4,5] Because of the proven efficacy of this regimen, additional agents were incorporated over time, including gemtuzumab ozogamicin, midostaurin, and, more recently, quizartinib for specific AML subtypes.[6-8]

Therapy for AML remained largely static until 2020, when azacitidine in combination with venetoclax (AZA+VEN), administered to unfit patients with previously untreated AML, was shown to be superior to single-agent azacitidine.[9] Venetoclax, a BCL-2 inhibitor, promotes apoptosis in leukemia cells. Today, several new B-cell lymphoma 2 (BCL-2) inhibitors are under development and in clinical trials, including lisaftoclax, sonrotoclax, and ZN-d5.

Initially, these regimens were primarily used in treatment of older adult or unfit patients with newly diagnosed or relapsed AML. However, in recent years, both observational and interventional studies have shown that hypomethylating agents (HMAs) combined with VEN provide response rates and survival outcomes comparable with those of intensive chemotherapy regimens such as 7+3.[10] In a propensity score–adjusted study of 172 patients treated with 7+3 and 74 patients treated with HMA+VEN, our team (Albliwi and colleagues) demonstrated that HMA+VEN achieved complete composite remission (CCR), overall survival (OS), and event-free survival (EFS) comparable with those achieved with 7+3.[11] Initially, we were skeptical of these findings; however, multiple analytical approaches consistently yielded the same results.

The first randomized trial demonstrating that HMA+VEN was noninferior to 7+3 was conducted by Lu and colleagues[12] in China. In this randomized study of 188 treatment-naive, fit patients with AML aged 18 to 59 years, VEN plus decitabine (VEN+DEC) achieved a higher CCR rate than standard idarubicin plus cytarabine (89% vs 79%), meeting criteria for noninferiority, with similar measurable residual disease negativity rates. VEN+DEC was associated with significantly fewer severe infections and shorter duration of thrombocytopenia. At a median follow-up of 12.1 months, overall and progression-free survival were similar between groups, supporting VEN+DEC as an effective and safer alternative induction strategy for younger, fit patients with AML.[12]

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More recently, at the Plenary Session of the American Society of Hematology 2025 meeting, Fathi and colleagues reported results from the randomized phase 2 PARADIGM trial involving 172 fit patients with newly diagnosed AML. AZA+VEN significantly improved EFS compared with intensive chemotherapy (hazard ratio, 0.61; P=0.017), with higher overall response (88% vs 62%) and CCR (81% vs 55%). A greater proportion of patients receiving AZA+VEN proceeded to transplant (61% vs 40%), and the early mortality rate was lower (0% vs 3.5%-4.7%), with numerically fewer severe infections. AZA+VEN also resulted in improved early quality of life, fewer ICU admissions, and significantly fewer hospital days, supporting it as a potentially superior frontline alternative to intensive chemotherapy in fit patients with AML, although OS data were immature.[13] Some arguments arose after this study presentation as to whether outcomes differ depending on whether transplant was planned for a patient. However, this argument may be less compelling, given that randomization occurred at treatment initiation and analyses were conducted on an intention-to-treat basis.

Based on accumulating evidence, the combination of an HMA and BCL-2 inhibition appears to provide efficacy comparable with intensive chemotherapy, but with fewer cytopenias, better tolerability, and reduced hospitalization. Another important feature of the HMA+VEN regimen is that duration of VEN administration can be safely reduced without compromising efficacy, thereby allowing the integration of additional targeted therapies.[14] However, nearly all randomized trials combining AZA+VEN with novel agents have maintained a fixed 28-day VEN schedule. This approach has frequently resulted in substantial hematologic toxicity and increased early toxicity-related mortality. A classic example is the ENHANCE-3 trial. Earlier phase 1 and 2 studies suggested promising activity when magrolimab, a monoclonal antibody targeting CD47, was combined with AZA+VEN. However, in the phase 3 study, the combination did not improve OS compared with AZA+VEN alone. One critical concern is that the VEN dose intensity and duration were not meaningfully adjusted when magrolimab was layered onto the backbone, potentially amplifying myelosuppression and offsetting any incremental therapeutic benefit.[15]

The remaining question for the leukemia community is whether we require a large randomized controlled trial to definitively establish this shift. Would the leukemia community in the United States be able to conduct such a trial, given the funding challenge, or will we depend on international trials from colleagues in Europe or elsewhere?

We are witnessing a transformation in AML therapy. The 1970s marked the birth of 7+3. The 2020s may represent the birth of HMA+VEN as a new standard. Every empire has its peak and its sunset. The question for the leukemia community is whether we are ready to turn the page—or continue clinging to the ways of our predecessors.

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Get to Know

Learn more about the leaders, innovators, and educators in hematologic oncology

Joshua Richter, MD

Dr. Richter's personal and professional interests are encapsulated by three M's: medicine, music, and myeloma.

*By **Melissa Badamo***

From One Borough to Another

Joshua Richter, MD, grew up in Forest Hills, Queens, just a borough away from the Big Apple where he works as an associate professor of medicine at Mount Sinai's Tisch Cancer Institute on the Upper East Side of Manhattan.

"I always knew that I wanted to pursue hematology oncology," Dr. Richter said. "I was interested in science, philosophy, and end-of-life care. In undergrad, I majored in psychology and minored in philosophy. Then, I realized hematology oncology is a good place to think about science and life on a grand scale."

Dr. Richter completed his internal medical residency at St. Vincent's Hospital and Medical Center in Greenwich Village, which housed one of the largest multiple myeloma programs before its 2010 closure. The program was led by **Sundar Jagannath, MBBS,** one of Dr. Richter's many mentors.

"I started learning about the background of myeloma, the research being done, and the headway we were on the cusp of making," Dr. Richter reflected. "There is an amazing connection you can develop with patients that you can follow for years or decades, help them through the good times, help them through the bad times. I really got enamored with myeloma as a disease."

After residency, he completed a fellowship in hematology oncology at Yale New Haven Hospital under the mentorship of **Madhav Dhodapkar, MBBS,** which solidified his decision to pursue myeloma as a specialization.

Coming full circle, Dr. Richter joined Mount Sinai in 2018, working directly with Dr. Jagannath. There, he treats patients with multiple myeloma and related diseases such as AL amyloidosis, plasma cell leukemia, and Waldenström's macroglobulinemia and serves as the director of Multiple Myeloma at the Blavatnik Family–Chelsea Medical Center. Having coauthored more than 100 publications, he also leads clinical trials on novel immunotherapies with a focus on precision medicine.

> **"There is an amazing connection you can develop with patients that you can follow for years or decades, help them through the good times, help them through the bad times."** *—Joshua Richter, MD*

Bispecific Antibodies: A Universal Myeloma Therapy

Dr. Richter is the senior investigator of the LINKER-MM trial, which established the durable efficacy and safety of linvoseltamab, a bispecific antibody, in patients with relapsed or refractory multiple myeloma.[1] He is drawn to the universality and equity of bispecific antibodies compared with chimeric antigen receptor (CAR) T-cell therapy, which, despite its benefits, has limited access nationally and globally due to infrastructure and specialty training requirements.

"Success in cancer treatment is that everyone, everywhere, has access to top-quality healthcare, no matter who they are."
—Joshua Richter, MD

"I'm all about equity in healthcare," he said. "Some of the work that's being done all over the world is amazing. But if you cure or provide optimal treatment strategies for a select few groups of people, that's not success in cancer treatment. Success in cancer treatment is that everyone, everywhere, has access to top-quality healthcare, no matter who they are."

"With a little bit of push, you can give a bispecific antibody anywhere," Dr. Richter added. "You don't need the same type of cellular infusion infrastructure required for CAR-Ts. Bispecific antibodies are already part of later relapse, but they're on the cusp of being a part of early relapse and upfront therapy, which is going to change things. We're starting to construct functional cure approaches for many of our patients, and bispecific antibodies can get us there."

Dr. Richter is taking a page from the playbook of **Bart Barlogie, MD, PhD,** who pioneered the concept of Total Therapy and the notion that if you hit the disease hard enough, you can cure myeloma. However, one major question remains.

"As we get more therapies, do we combine them upfront or do we sequence them along the way?" Dr. Richter posed.

With the goal of hitting multiple targets, his research team embarked on the RedirecTT-1 study combining teclistamab, an anti-BCMA bispecific antibody, with talquetamab, an anti-GPRC5D bispecific antibody.[2] The combination yielded "unreal response rates" for hard-to-treat patients with extramedullary disease, according to Dr. Richter.

"Their disease disappeared with this regimen, but it's a harder regimen to keep people on," he said.

Trispecific Antibodies: The Next Step in Myeloma Care

Rather than combining two bispecific antibodies, trispecific antibodies offer a novel, all-in-one approach to myeloma treatment. Mount Sinai is leading several clinical trials on trispecific antibodies in relapsed or refractory myeloma, including ramantamig. This T-cell–engaging trispecific antibody simultaneously targets BCMA, GPRC5D, and CD3 and has shown a response rate of 100% in previous studies.[3]

"When you tell someone it has a 100% response rate, that has a very specific impact on patients," Dr. Richter said. "If that's where we're headed, not just in the upfront setting but in the relapse setting, that means we have several chances to either cure or functionally cure myeloma."

According to Dr. Richter, myeloma is on the precipice of reflecting the diverse treatment landscape of lymphoma as new options become available.

"Follicular and large cell [lymphoma] are all treated differently," he explained. "Some patients get pills every day; some get high-dose therapy; some get transplants; some get CAR-T. We don't have that granularity with myeloma just yet. As we get the granularity of the disease and combine our amazing therapies, the most exciting thing is taking this incurable disease and transporting it to curability."

The Three M's: Medicine, Music, Myeloma

When he's not treating patients or researching the latest therapies, Dr. Richter is also an avid music fan, often posting electric guitar covers on his X account (@JoshuaRichterMD). He has an ever-growing guitar pedal collection, and his passion for the six-string began at age 13.

"My weakness is that I need to be surrounded by guitars at all times," he quipped. "I speak all over the world, and the first thing I do is go online between lectures and find out where the guitar stores are."

"We're starting to construct functional cure approaches for many of our patients, and bispecific antibodies can get us there.
—Joshua Richter, MD

Dr. Richter even plays in a house band called *The Plasma Cells* at the International Myeloma Working Group Summit, which takes place 3 days before the European Hematology Association Congress each year in mid-June. From playing in a band with his colleagues to pushing for a cure for myeloma, the highlight of Dr. Richter's career is translating the latest research directly into the clinic to offer patients the best care.

"I'm at this phase in my life where I just try to be a good physician, try to be a good husband and father, and wake up every day and try to do some good," he concluded.

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Fox Chase Cancer Center's Outpatient Pilot Program Transforms Care for Patients Receiving T-Cell Redirecting Therapies

How home-based monitoring can improve patient experiences while saving hospital resources

*By **Melissa Badamo***

Fox Chase Cancer Center in Philadelphia has developed an outpatient, home-based monitoring system for patients with relapsed or refractory lymphoma and multiple myeloma receiving T-cell redirecting therapies—a population historically plagued by long hospital stays due to the risk of significant toxicities.[1]

This pilot outpatient T-cell redirecting therapy (TCR) program successfully monitors for cytokine release syndrome (CRS) and immune factor cell-associated neurotoxicity (ICANS), two major toxicities associated with chimeric antigen receptor (CAR) T-cell therapy, without the need for inpatient hospitalization.[1]

"CAR-T has traditionally been done with fully inpatient observation during the risk period," explained **Asya Varshavsky-Yanovsky, MD, PhD**, an associate professor in the Blood Cancer and Cellular Therapy Institute at Fox Chase. "That leads to patients being in the hospital for monitoring admissions rather than acute care admissions, which leads to occupying acute care beds with patients who don't really need them, patients not being home with their families, and patients being exposed to inherent risks associated with hospitalization. We felt that our patients will be happier and our beds will be available for other patients who need them if we try keep some of our patients outpatient while they're doing well."

Asya Varshavsky-Yanovsky, MD, PhD

Since its inception in 2020, the outpatient pilot program significantly reduced the length of hospitalization with no negative outcomes, according to a study presented at the 67th American Society of Hematology (ASH) Annual Meeting & Exposition. Dr. Varshavsky-Yanovsky and her team treated 63 patients with outpatient CAR-T and 104 patients with inpatient CAR-T such as idecabtagene vicleucel (ide-cel), lisocabtagene maraleucel (liso-cel), ciltacabtagene autoleucel (cilta-cel), axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and brexucabtagene autoleucel (brexu-cel).[2]

"There was significant difference in the length of inpatient stay within the first 30 days," Dr. Varshavsky-Yanovsky explained.

For liso-cel, there was a median of 1 inpatient day among patients initially treated in the outpatient setting, compared with 6 days for those treated in the inpatient setting. The respective difference was 3 days versus 8.5 days for cilta-cel and 5 days versus 10 days for axi-cel. The research team did not observe notable differences for brexu-cel, while ide-cel and tisa-cel showed a nonsignificant decrease in inpatient days.[2]

"Importantly, 47% of patients treated with liso-cel and 20% of patients treated with cilta-cel did not require hospitalization at all," Dr. Varshavsky-Yanovsky added. "The biggest factor probably contributing to this difference is median time to onset of these toxicities."

Most patients treated with cilta-cel did not develop toxicities and did not require admission until day 6. The percentage of outpatient patients who did not require hospitalization in the first 30 days was 47% for liso-cel, 20% for cilta-cel, and 45% for tisa-cel. Grade 3 CRS occurred in only one outpatient patient.[2]

How Home-Based Monitoring Works

Home-based monitoring relies on education, collaboration, and participation from both the patient and caregiver.

To be eligible for outpatient monitoring, patients must have a dedicated caregiver available during the first month of therapy, and they must be located close enough to the treatment center to quickly address any safety concerns.

"We needed to establish the system where patients can get to our centers quickly if any concerns arise, and a system of rapid response within our center for all the providers involved to be able to manage them appropriately," Dr. Varshavsky-Yanovsky explained.

After Dr. Varshavsky-Yanovsky and her team rapidly detect toxicities like CRS and ICANS, the next step is educating patients and caregivers to respond to and manage them. Caregivers also are instructed to perform simple, nonformal assessments such as monitoring vital signs three times per day and assessing patients' handwriting for signs of neurotoxicity. In addition to the crucial role of caregivers, a cellular therapy physician is on call 24/7 to safely guide patients.

"To make it happen safely, we needed to create an infrastructure to appropriately take care of those patients, and we also needed to make sure that patients who are going through it are actually able to go through it safely," Dr. Varshavsky-Yanovsky added. "What really is required is to be able to rapidly detect and manage potential toxicities of those therapies as they arise."

"Our system is something that many institutions and hospital systems could adopt right now in real time. That's the future of delivery of these therapies."

Bispecific T-Cell Engagers Program

Fox Chase built its outpatient bispecific T-cell engagers program on the infrastructure of the CAR-T program. Of the 48 patients who received a bispecific T-cell engager, such as teclistamab, talquetamab, or elranatamab, more than half (54%) did not require hospitalization after step-up dosing or develop CRS or ICANS, showing that this program follows the same success as the CAR-T program. All 48 patients had a cumulative total of 72 inpatient stays, averaging to 1.5 days per patient, compared with an estimated 282 days of drug-specific monitoring periods.[2]

"We had a 75% reduction in the inpatient stay, which is again a big deal for the patients who were able to stay home and a big savings of hospital resources," Dr. Varshavsky-Yanovsky stated.

Although 46% of patients experienced toxicities, CRS was limited to grade 1-2 and ICANS was limited to grade 1.[2]

Home-Based Monitoring Challenges

Despite the ongoing success of the TCR program, the main challenges revolve around a lack of outpatient support. Certain patient characteristics, such as fitness, also can affect a patient's eligibility for home-based monitoring. Therefore, some patients may benefit most from inpatient versus outpatient monitoring.

"There are situations when someone in dire need of cardiotherapy would not have the social setup that is required," Dr. Varshavsky-Yanovsky explained. "In that case, those patients would benefit from being monitored inpatient."

Similarly, patients who are candidates for bispecific T-cell engagers may not have the same social support as CAR-T patients. As Dr. Varshavsky-Yanovsky described, these patients may present as frailer and more symptomatic than CAR-T patients.

"To make someone a candidate for cardiotherapy, they need to be fit enough, and they need to meet certain social support requirements," she explained. "Patients who are evaluated for bispecific T-cell engagers may have very limited social support and they may be very sick from the underlying disease. Not all patients were good candidates."

One Program, Big Impact

Following the success of Fox Chase's outpatient TCR program, Dr. Varshavsky-Yanovsky hopes other hospital systems can adopt their model to safely monitor patients who receive CAR-T or bispecifics without the need for hospitalization. Fox Chase also leads several clinical trials, including trispecific engagers in patients with relapsed or refractory multiple myeloma.

"Based on our analysis presented at ASH, we concluded that this program is a success," Dr. Varshavsky-Yanovsky said. "We are continuing to treat patients in this model. One of the big advantages of our program is that it's very simple. Our system is something that many institutions and hospital systems could adopt right now in real time. That's the future of delivery of these therapies."

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Redefining the Endgame in Hematologic Malignancies

By ***Leslie Feldman***

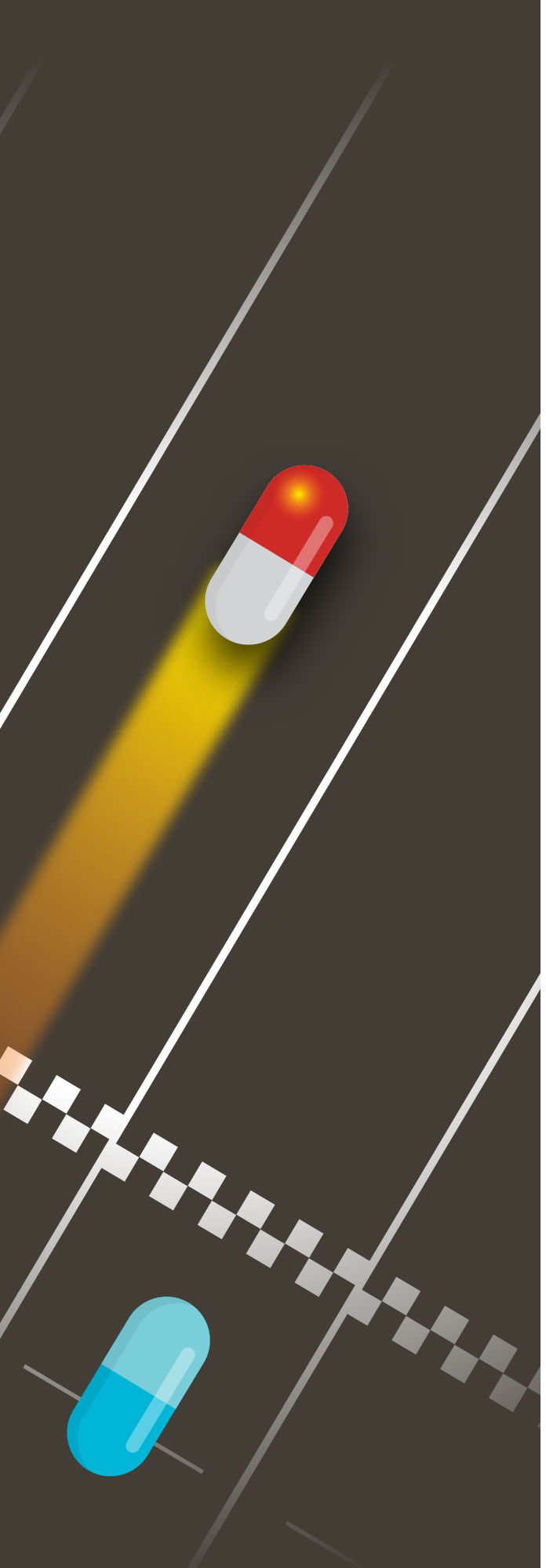

Illustration by John Salesi

For decades, the management of chronic lymphocytic leukemia (CLL) and other indolent hematologic malignancies centered on disease control rather than eradication. Continuous therapy with chemoimmunotherapy and, more recently, covalent Bruton's tyrosine kinase (BTK) inhibitors, defined a "treat-to-progression" paradigm aimed at suppression, not cure. The prevailing assumption was that these diseases, while treatable, were not curable outside of allogeneic transplant.

That assumption is now being challenged.

Emerging data suggest that time-limited strategies, deeper remissions, measurable residual disease (MRD)–guided approaches, and prolonged treatment-free intervals are reshaping expectations for clinicians and patients alike. Increasingly, the therapeutic goal is not simply disease control, but durable remission and, in some cases, what many experts describe as a functional cure.

Disease-Specific Perspectives on Cure

Historically, cure in hematologic malignancies implied complete eradication of detectable malignant cells.

"This is particularly true in acute myeloid leukemia," **Stephen Ansell, MD, PhD,** chair, Division of Hematology, Department of Internal Medicine, Mayo Clinic, noted, where MRD often predicts relapse and long-term survival is closely linked to complete molecular remission.

In contrast, indolent diseases such as CLL and low-grade lymphomas behave differently. Patients may achieve profound remissions and remain treatment-free for years and even decades despite the persistence of small numbers of malignant cells.

"In that setting, a functional cure, meaning patients live a normal lifespan without ongoing therapy, is a meaningful and satisfactory end point for many," Dr. Ansell said.

Multiple myeloma represents an intermediate case. Modern triplet and quadruplet regimens, along with cellular therapies and bispecific antibodies, can induce deep and durable responses. Yet many patients require intermittent maintenance or re-treatment to sustain disease control. As MRD-guided strategies evolve, the definition of cure in myeloma may continue to shift.

Challenging the Chronic Management Model in CLL

"Initially, CLL-14 gave us the frontline option of chemo-free, time-defined treatment with venetoclax and obinutuzumab," said **Ryan Jacobs, MD,** director, Section of Lymphoma, associate professor of Cancer Medicine, Wake Forest University School of Medicine, Division of Hematology, Atrium Health Levine Cancer Institute. "Broad uptake of this regimen

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as an initial treatment approach has been challenging for numerous reasons, including patient apprehension about infusional therapies and concerns regarding the necessary ramp-up to avoid tumor lysis syndrome with venetoclax."

The phase 3 CLL14 trial[1] established fixed-duration venetoclax plus obinutuzumab as a frontline standard for previously untreated CLL. The study demonstrated high rates of deep remission, including undetectable MRD, with a defined 12-month treatment course.

Despite these encouraging data, infusion requirements and the complexity of venetoclax dose ramp-up initially limited enthusiasm in some practice settings. However, evolving combinations may reduce those barriers.

"All-oral, time-defined treatments involving combinations of BTK inhibitors and BCL-2 inhibitors appear likely to open the door to more patients for time-defined treatment," Dr. Jacobs said.

Earlier phase 2 data from the CAPTIVATE[2] study further reinforced the concept that deep remissions, including high rates of undetectable MRD, are achievable with time-limited combination therapy. Importantly, early follow-up suggests that many patients maintain remission well after therapy discontinuation.

Taken together, these studies suggest that for a growing subset of patients, CLL may increasingly resemble a disease that can be managed in defined intervals rather than continuously suppressed.

Cellular Therapy and the Heavily Pretreated Patient

While time-limited targeted therapy is reshaping frontline management, advances in cellular therapy are redefining expectations for heavily pretreated patients.

"For selective patients who have progressed after multiple prior lines of therapy, encouraging data with [the] use of liso-cel [lisocabtagene maraleucel] as a one-time intervention leading to sustained, treatment-free durable remissions were presented at ASH 2026," Dr. Jacobs said.

> **"All-oral, time-defined treatments involving combinations of BTK inhibitors and BCL-2 inhibitors appear likely to open the door to more patients for time-defined treatment."**
>
> *—Ryan Jacobs, MD, Atrium Health Levine Cancer Institute*

The CLL17 trial[1] compared continuous ibrutinib therapy with fixed-duration regimens combining venetoclax or BTK inhibitors with a CD20 antibody. Initial follow-up presented at the 2025 American Society of Hematology (ASH) Annual Meeting & Exposition suggested that time-defined approaches, including venetoclax plus obinutuzumab and the all-oral combination of ibrutinib plus venetoclax, produced outcomes comparable with continuous ibrutinib.

"This result ultimately supports the notion that we can shift away from the treat-to-progression chronic management model to a time-defined approach with less financial toxicity," Dr. Jacobs noted.

Financial toxicity remains a significant consideration in chronic therapy. Continuous BTK inhibition may require years, sometimes indefinitely, of daily treatment. Time-limited strategies offer not only clinical durability but potential economic relief and improved quality of life.

Similarly, the AMPLIFY[1] study demonstrated that the all-oral combination of acalabrutinib plus venetoclax can be safely administered as a defined-duration regimen. This approach has since earned a Category 1 recommendation in the National Comprehensive Cancer Network guidelines.

Liso-cel is a CD19-directed chimeric antigen receptor (CAR) T-cell therapy evaluated in the TRANSFORM study,[1] which supported regulatory advancement. Real-world data analyses presented subsequently suggest that outcomes may be further improved by optimizing sequencing strategies.

"Availability of pirtobrutinib as a bridge to liso-cel appears to have improved overall outcomes beyond what was seen in the original TRANSFORM CLL study," Dr. Jacobs added.

The emergence of noncovalent BTK inhibitors such as pirtobrutinib offers new therapeutic options for patients who develop resistance to earlier-generation agents. Used strategically as bridging therapy, these agents may help control disease while patients prepare for cellular therapy, potentially improving response durability.

Importantly, CAR T-cell therapy represents a fundamentally different therapeutic model: a one-time immune-based intervention with the potential for prolonged, treatment-free remission. For some patients with multiply relapsed disease, this approach raises the possibility of sustained control without ongoing therapy. This is a concept that was nearly inconceivable a decade ago.

Defining Deep Remission and Functional Cure

The growing ability to achieve deep remissions has reframed the definition of success in indolent malignancies. Dr. Jacobs described functional cure as a state in which a patient can live out a normal life expectancy while only periodically addressing their CLL.

"In the case of time-defined treatment with treatment-free intervals, it appears that we can rechallenge select patients who require retreatment and still obtain effective responses," he explained.

Mutation analyses from CAPTIVATE indicate that many patients relapsing after fixed-duration ibrutinib plus venetoclax do not harbor resistant BTK or *BCL-2* mutations. This suggests that retreatment with similar agents may remain effective, reinforcing the viability of an intermittent treatment model.

Dr. Ansell offered a broader conceptual framework. "I do believe that we are redefining the end goal in many blood-related cancers," he said. "But these goals vary by histology, the patient's clinical condition and the natural history of the disease."

He emphasized that time-limited therapy, deeper remissions, and longer disease-free intervals are increasingly attainable, particularly in indolent hematologic malignancies, but these gains must be balanced against overtreatment risks in asymptomatic patients.

Implications for Trial Design and Patient Conversations

These evolving therapeutic goals are transforming clinical trial design.

"In the past, achieving a good overall response rate in a clinical trial was considered [a] success," Dr. Ansell said. "Now, success often means complete metabolic response on PET imaging and/or MRD negativity."

MRD assessment has become a central end point in many modern trials, reflecting its strong prognostic significance. Increasingly, studies are designed not only to measure response but to determine whether therapy can be safely discontinued once deep remission is achieved.

This shift also affects how clinicians counsel patients. Dr. Jacobs noted that conversations are increasingly centered on treatment-free intervals rather than indefinite therapy. Patients frequently ask, "Will this control my disease?" and "How long will I need to take this?"

Time-defined therapy offers a tangible answer, and for many, psychological relief. At the same time, clinicians must navigate complex decisions around sequencing, toxicity management, and long-term surveillance. As more options become available, personalization becomes paramount.

A Shift in the Therapeutic Horizon

The cumulative impact of BTK and BCL-2 inhibitor combinations, noncovalent BTK inhibitors, cellular therapies, and MRD-guided treatment strategies signals a broader transformation. The era of chronic, indefinite suppression may gradually give way to personalized, time-limited approaches designed to achieve deep remission, minimize toxicity, and maximize quality of life. For patients with CLL and other indolent hematologic malignancies, the therapeutic horizon has expanded. Achieving durable remission and, in select cases, functional cure, is no longer an aspirational concept. It is an increasingly realistic clinical objective.

As data mature and follow-up extends, the field will continue to refine what cure truly means. But one thing is increasingly clear: the endgame in hematologic malignancies is being rewritten.

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Point | Counterpoint

Two experts take opposing sides on clinical and controversial topics in hematologic oncology

Can 7+3 Intensive Chemotherapy Be Discontinued in AML?

Ioannis Mantzaris, MD, MS, an associate professor in the department of oncology at Albert Einstein College of Medicine, and **Jesus Gonzalez Lugo, MD,** an assistant professor of hematologic malignancies and cellular therapeutics at the University of Kansas Medical Center, participated in a head-to-head debate on whether the use of 7+3 intensive chemotherapy can be discontinued in the treatment of acute myeloid leukemia (AML).

Dr. Mantzaris argued that 7+3 has a crucial role in the treatment of patients with AML, especially those with *NPM1* mutations or *KMT2A* rearrangements. He also explained how novel combinations, such as addition of venetoclax or bleximenib to 7+3 intensive chemotherapy, can address treatment gaps for these difficult-to-treat patients.

On the opposing side, Dr. Gonzalez Lugo recognized the benefits of 7+3 intensive chemotherapy while describing a study of venetoclax-azacitidine versus 7+3. For Dr. Gonzalez Lugo, the results look promising, especially among high-risk patient populations.

The following transcript has been edited for clarity.

Dr. Mantzaris: My stance is that we're not yet ready to abandon 7+3 in the newly diagnosed AML population that is still fit for intensive chemotherapy. The backbone of 7+3 has been long lasting, about 5 decades now, and data have shown that it's an intensive regimen with a lot of consistency associated with it. There is an urge to abandon chemotherapy to mitigate toxicities associated with it, but those toxicities have been improved over the years with supportive care and tweaks in the dosing of the different compounds of the 7+3 regimen.

There are certain subsets of acute myeloid leukemia that are tough to treat, and we know that the 7+3 does not do a great job. CPX-351 came to address this gap in treatment for acute myeloid leukemia patients with secondary disease, myelodysplastic-related changes, and that led to another option for those patients. Whether that's the final solution for this very difficult-to-treat AML subgroup is not clear, but [it] certainly was an advancement in the field. Altogether, there is still a role for intensive chemotherapy, whether that's 7+3 or CPX-351, in the treatment of this patient population.

"I'm not ready to quit intensive chemotherapy, even with the promise of targeted agents."

—Ioannis Mantzaris, MD, MS, Associate Professor in the Department of Oncology, Albert Einstein College of Medicine

Ioannis Mantzaris, MD, MS

The most modern question, truthfully, is whether we want to keep them not as a standalone therapy, but more as a backbone to other modern approaches such as the addition of bleximenib to 7+3 for a certain molecular subgroup of patients with *NPM1* mutations and *KMT2A* rearrangements. That shows a lot of promise in early-phase trials now being moved to the randomized setting. Those trials are eagerly awaited to see what the winner is going to be. This is built on the promise that 7+3 still remains the main backbone, and we ask the questions of whether we will improve the efficacy of the 7+3 backbone.

Similarly, the addition of venetoclax to 7+3, and other intensive chemotherapy backbones, has recently been shown to come with a lot of promise. It shows high response rates, high quality of responses, [and] deep MRD [measurable residual disease] eradication; and that creates questions of whether that's going to be the new standard compared with 7+3 alone.

With that mindset, I think sticking with intensive chemotherapy, at least for now, for the patients … who can take intensive chemotherapy, is the right thing to do. It might

be a little premature to abandon the intensive chemotherapy for the intensified approaches, even in combination with targeted agents.

Dr. Gonzalez Lugo: I do agree with many of the points that Dr. Mantzaris mentioned. I agree that intensive chemotherapy is something that we have been doing for decades, and we are very comfortable doing [it]. We have a track record of managing toxicities better. However, there's a study of venetoclax-azacitidine versus intensive chemotherapy presented at ASH. Looking at the data, it's something that is very promising and might change the field, specifically in high-risk patient populations. We know those patients don't do as well with 7+3. When giving these patients venetoclax-azacitidine, they have lower toxicity, lower ICU admissions, better quality of life, and improved depression.

I do agree that right now, intensive chemotherapy is the mainstay of treatment, but that might change in a subset of patients, especially higher-risk populations. This study showed that [an] HMA [hypomethylating agent] plus venetoclax at least was better or comparable with 7+3 with lower toxicity.

"Intensive chemotherapy is the mainstay of treatment, but that might change in a subset of patients, especially higher-risk populations."

Jesus Gonzalez Lugo, MD

—Jesus Gonzalez Lugo, MD, Assistant Professor of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center

What is the potential for novel less intensive alternatives to 7+3 in AML such as venetoclax plus HMAs, ASTX727 plus venetoclax and revumenib, or ivosidenib plus azacitidine?

Dr. Gonzalez Lugo: We're still exploring these regimens in clinical trials for a subset of patients, specifically with menin inhibitors, for patients with *NPM1* or *KMT2A* rearrangements. ASTX727 plus venetoclax and revumenib is an all-oral regimen, which is very good, since there's less time at the clinic and less trips to the infusion center. In this patient population, if it ends up having better overall survival, it would be very good for patients who are not fit for intensive chemotherapy.

Dr. Mantzaris: I do think this is the key point that although those trials look very promising, the majority are targeting that 'not-fit-for-intensive-chemotherapy' patient population. The provocative thought is whether the right approach is to move even in the fit-for-intensive-chemotherapy population. To that [end], I'm not in full agreement as of yet. The current paradigm so far has followed the route of keeping intensive chemotherapy for fit patients and low-intensity HMA-venetoclax for unfit patients, and we add the third targeted agent, whether that's a menin inhibitor or an IDH [isocitrate dehydrogenase] inhibitor. We still separate the patient population by fitness for intensive chemotherapy. I'm not sure we're ready to abandon that, although it's very provocative to start considering alternative therapy for this very high-risk population that Dr. Gonzalez Lugo mentioned.

Transplantation is the goal; and less intensive, less toxic regimens could bridge … [patients] to transplantation. We need more robust data to truly tease out who are those patients who can get away with less as opposed to a general categorization of high-risk AML or intermediate-risk AML. There are different flavors even within this big group of adverse-risk AML that can have different behavior when treated with intensive chemotherapy versus low intensive chemotherapy. I'm not ready to quit intensive chemotherapy, even with the promise of targeted agents.

Is there a particular approach that's best for a particular patient population?

Dr. Gonzalez Lugo: If the patients are higher risk and have a *TP53* mutation, I tend to not give them intensive chemotherapy. I usually give them [an] HMA or HMA-venetoclax. There's a lot of data regarding if they do well or not. If they have *FLIT3* mutations, you put them with a FLIT3 inhibitor.

Dr. Mantzaris: The question of whether there is a scenario that we have a perfect solution is unfortunately hard to find. Even in situations where we thought we did, in the favorable-risk subgroups in AML where there is a high cure rate with intensive chemotherapy, there are still unmet needs within that small niche of favorable-risk AML that are still being challenged, such as the addition of third agents. I would say that there is no setting for which we have the perfect treatment. There are definitely some scenarios that we feel more comfortable with and some scenarios that … have huge unmet needs in certain subgroups that we don't have good therapies for, such as *TP53*-mutated disease or MECOM rearrangements, which are notorious for poor outcomes, and yet another area of unmet need. We're still constantly striving to improve outcomes in AML.

Regulatory Actions

Regulatory approvals, designations, and guidance in the field of hematologic oncology

Scan to learn more.

February 6, 2026

FDA Approves Label Update for Axicabtagene Ciloleucel for Relapsed or Refractory Primary Central Nervous System Lymphoma

This label update removes the prior *Limitations of Use* based on a manageable safety profile with no new safety signals, according to a press release from Kite Pharma. In a phase 1 study, 85% of patients had any grade neurologic toxicities. Grade 3 or 4 adverse events included hypotension (23%), encephalopathy (15%), seizure (15%), gait disturbance (8%), headache (8%), hypoxia (8%), muscular weakness (8%), nausea (8%), pyrexia (8%), thrombosis (8%), and tremor (8%).

February 17, 2026

TuHURA Submits Investigational New Drug Application for TBS-2025 for the Treatment of Relapsed or Refractory AML

The bioscience company TuHURA has submitted an investigational New Drug Application to the FDA for the study of TBS-2025, a novel VISTA inhibiting antibody, in combination with a menin inhibitor for patients with *NPM1*-mutated, relapsed or refractory acute myeloid leukemia (AML). If accepted, TuHURA hopes to initiate a phase 2 study in patients who are menin inhibitor naive in the second quarter of 2026.

February 19, 2026

FDA Approves Venetoclax Plus Acalabrutinib for Previously Untreated Chronic Lymphocytic Leukemia

The FDA has approved fixed-duration venetoclax plus acalabrutinib as a frontline treatment for chronic lymphocytic leukemia based on results of the phase 3 AMPLIFY trial. The combination had a consistent safety profile and showed superior efficacy to chemotherapy, with a median progression-free survival of not reached versus 47.6 months, respectively.

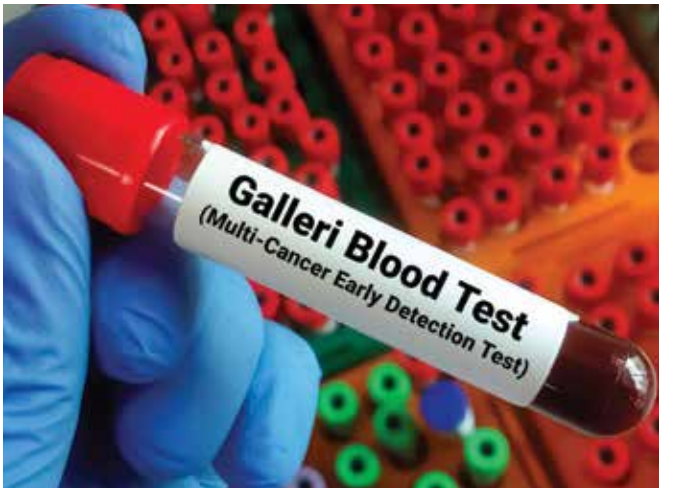
February 23, 2026

FDA Issues Guidance for Accelerating Development of Individualized Therapies for Ultra-Rare Diseases

The FDA has provided new framework to guide sponsors developing individual therapies for ultra-rare diseases. This framework includes guidance on generating evidence that therapies are safe and effective when small patient populations make randomized controlled trials unfeasible. In a press release, FDA Commissioner Marty Makary, MD, MPH, described the guidance as a “critical step” for the FDA to “tailor our regulatory approach to patients with ultra-rare conditions.”

Grail's Multi-Cancer Early Detection Test Fails to Reduce Late-Stage Cancer Diagnoses

*By **Melissa Badamo***



Grail's Galleri multi-cancer early detection test has failed to show a statistically significant reduction in the number of cancers diagnosed at stage III or IV, according to updated results from the randomized controlled NHS-Galleri trial. The goal of the test is to detect cancer early when a cure is possible, the healthcare company shared in a press release.[1]

In partnership with England's National Health Service (NHS), the NHS-Galleri study enrolled 142,000 asymptomatic participants aged 50 to 77 years. Participants were followed up for 3 years and provided three blood samples, approximately one per year. Half of the participants received standard-of-care screening, and the other half received standard-of-care screening plus the Galleri test.[1,2]

The primary end point, a statistically significant reduction of stage III or IV cancers in participants who received the Galleri test versus those who did not, was not met. However, the study demonstrated a favorable trend toward detection of fewer stage III and IV cancers, a "substantial and clinically meaningful" reduction in stage IV cancer diagnoses compared with standard-of-care screening alone, and an increased detection of stage I and II cancers.[1]

"The [NHS-Galleri] study was powered and designed to answer this question of stage III and IV cancers lumped together. Certainly, it's a real finding and needs to be taken seriously," said **Nima Nabavizadeh, MD,** an associate professor of radiation medicine at Oregon Health and Science University, in an interview. Dr. Nabavizadeh is also the lead investigator of the US-based PATHFINDER-2 study, a single-arm, prospective, multicenter, interventional study on the safety and performance of the Galleri test.


Nima Nabavizadeh, MD

"There are still a lot of nuances and caveats that it's going to take time for us to interpret, largely because the data hasn't been presented or released yet," he added. "It's important for researchers such as myself and policy makers to look at the full data before making any determinations on the validity or utility of the test. But again, missing the primary end point is an important thing that's taken seriously."

Dr. Nabavizadeh also noted the difference between stage III and IV cancers, especially when it comes to cure rates.

"Many folks in the field, myself included as a radiation oncologist, understand that stage III cancers are not quite the same thing as stage IV cancers and have been discouraged that the primary end point had these two cancers lumped together," he said. "I think it was an ambitious goal to try to meet the primary end point of stage III and IV cancers lumped together."


Elizabeth O'Donnell, MD

Similarly, **Elizabeth O'Donnell, MD,** director of the multi-cancer early detection clinic at the Dana-Farber Cancer Institute, believes the study design was an "ambitious goal."

"What the press release offers is very limited," Dr. O'Donnell said. "There is still a lot to be learned."

"As cancer clinicians, we are all hopeful for a test that can detect cancers earlier and ease the burden of cancer therapy on patients," added **Chaely Medley, MSN, AGNP-C,** a nurse practitioner at Novant Health Cancer Institute. For Medley, it is "disappointing" that the study did not meet its primary end point. She also commented on the study design and how the tests were drawn yearly for 3 years.


Chaely Medley, MSN, AGNP-C

"Many cancers can establish and grow significantly in 1 year, so I'd be interested to see the types of cancers detected in more advanced stages," she said.

Other oncology experts, such as **Amanda Brink, DNP, APRN, FNP-BC, AOCNP,** an oncology nurse practitioner at the Sarah Cannon Research Institute, are optimistic about the study's results.


Amanda Brink, DNP, APRN, FNP-BC, AOCNP

"As an oncology nurse, I was encouraged by the results of the NHS-Galleri trial. These findings suggest that multi-cancer early detection testing may help identify cancers earlier, which for oncology nurses could mean caring for more

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PHOTO CREDIT: istock.com/Md Saiful Islam Khan

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patients receiving curative therapies, such as surgery, rather than managing complications of metastatic disease, such as uncontrolled pain," Dr. Brink said. "I also appreciate that the study added the Galleri test to standard screening rather than replacing it, maintaining current recommendations while exploring new ways to detect cancer earlier."

The Galleri test works by detecting cancer signals from cell-free DNA in the blood and predicts cancer signal origin using a machine learning algorithm.[1,3] The test aims to detect 12 cancer types: anus, bladder, colorectal, esophagus, head and neck, liver/bile duct, lung, lymphoma, myeloma/plasma cell neoplasm, ovary, pancreas, and stomach cancers.[1] The Galleri test's premarket approval application, submitted on January 29, 2026, is currently pending review by the FDA.[4]

"What makes this test unique is that it's taking advantage of common features that all cancers have in regard to shedding of the circulating free DNA within the bloodstream, allowing us to screen for multiple cancers at the same time by analyzing their shared genomic features," Dr. Nabavizadeh said. "This test specifically looks at the methylation profile of this circulating DNA, and methylation is a way of silencing different parts of the genome … this test is quite novel in its approach of not only telling you that there is a cancer signal, but also where that cancer signal could be coming from to help guide diagnostic evaluation."

Predating the NHS-Galleri study, PATHFINDER-2 found that the Galleri test increased the number of screen-detected cancers by seven times when added to standard-of-care screening, with a positive predictive value of 61.6% and a specificity of 99.6%. Based on data from 25,114 safety evaluable patients, the test also showed a favorable safety profile. Findings were presented at the European Society for Medical Oncology Congress 2025.[3]

However, there was a lack of a comparable arm in PATHFINDER-2, Dr. Nabavizadeh noted, as all 23,161 evaluable patients received the Galleri blood test.[3]

Considering the mixed results of the NHS-Galleri study, experts agree that additional data are needed.

"I look forward to the release of their full research results and hope this can pave the path for additional studies with revised end points and, ultimately, a more specific test," Medley said. "While we await an advanced test such as this, I find health maintenance and age- or lifestyle-appropriate cancer screening tests even more important. Knowing family history, avoiding risk factors, and seeking early medical advice for new symptoms continue to be the best way to detect cancers earlier."

"Future research should examine outcomes including survival, quality of life, psychosocial impact, and integration into routine care to ensure multi-cancer screening can be used safely and effectively," Dr. Brink added.

In addition, there is no clear evidence on whether early detection can improve patient outcomes in cancers such as follicular lymphoma (FL), according to **Suheil Albert Atallah-Yunes, MD,** a lymphoma specialist and cellular therapist at the Memorial Sloan Kettering Cancer Center. Dr. Atallah-Yunes and colleagues evaluated the role of multi-cancer early detection tests in relation to outcomes for patients with FL and found no association between diagnosis type (incidental vs symptomatic) and survival outcomes.[5]

Suheil Albert Atallah-Yunes, MD

"In FL, early detection doesn't automatically translate into improved outcomes under current treatment paradigms, as a watch-and-wait strategy remains appropriate for many patients," Dr. Atallah-Yunes previously told *Blood Cancers Today*. "The ultimate value of MCEDs [multi-cancer early detection tests] in FL will depend on whether early intervention can meaningfully improve outcomes. Until such data emerge, clinical decision-making must continue to balance early identification with the principles of patient-centered care."

Detailed results of the NHS-Galleri study will be presented at the American Society of Clinical Oncology Annual Meeting, May 29 to June 2, 2026, in Chicago, Illinois. Additional analyses are currently ongoing, and Grail intends to increase the follow-up period of the NHS-Galleri study by 6 months to 1 year.

The currently enrolling REACH trial is a comparative study of participants with Medicare who received the Galleri test versus a synthetically generated population of people who did not receive the blood test, according to Dr. Nabavizadeh. He described the comparative study as a "tier below" randomized controlled trials.

"The end point for the REACH study is not a stage III and IV shift, but just a stage IV shift," he said. "In many ways, I wish the NHS-Galleri end point would have mimicked these similar end points."

Laura Litwin and Cecilia Brown contributed to the reporting of this article.

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Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, section editor* ***Matthew Davids, MD,*** *director of clinical research for the lymphoma division at Dana-Farber Cancer Institute and an associate professor at Harvard Medical School, highlights recent research in chronic lymphocytic leukemia.*

Visit bloodcancerstoday.com to stay up to date on the latest news in each area of hematologic oncology.

Matthew Davids, MD

CHRONIC LYMPHOCYTIC LEUKEMIA

Epcoritamab Extends Its Reach Into Richter Transformation in EPCORE CLL-1 Analysis

By Nichole Tucker

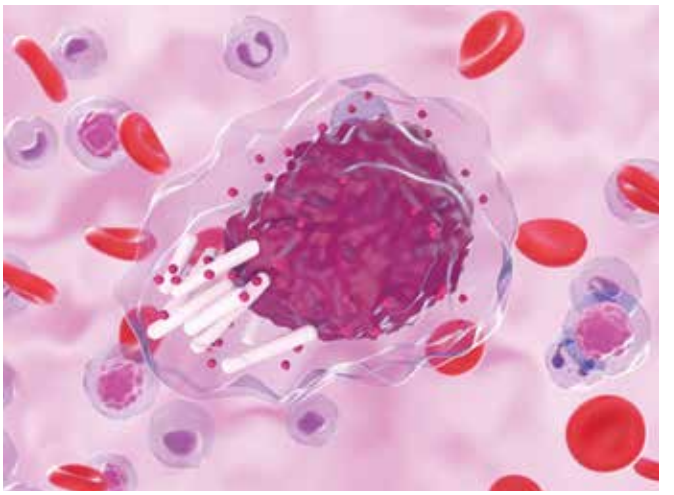
Treatment with epcoritamab monotherapy continues to show activity across the chronic lymphocytic leukemia (CLL) disease spectrum, with new data extending its potential into Richter transformation (RT). In a subgroup analysis of patients with RT, epcoritamab produced meaningful responses and a safety profile consistent with prior studies, reinforcing signals first seen in the primary analysis of EPCORE CLL-1 in heavily pretreated patients with relapsed or refractory (R/R) CLL.

"The promising activity of epcoritamab is particularly relevant for patients who are not candidates for chimeric antigen receptor [CAR] T-cell therapy. CAR T-cell therapy faces several limitations that are often exacerbated in the RT and R/R CLL populations. These include suboptimal T-cell fitness, a higher-risk clinical profile, and significant logistical challenges, such as geographic distance from treatment centers, need for intensive monitoring and need for caregiver support," **Jose Sandoval Sus, MD,** of Moffitt Cancer Center, told *Blood Cancers Today*.

Jose Sandoval Sus, MD

Results from the subgroup analysis show an objective response rate (ORR) of 47.6% (95% CI, 32.0%-63.6%) after a 22.9-month median follow-up (range 0.5–39.9). Despite not meeting the prespecified 50% benchmark, it was notable that responses were observed in both early and later-line patient populations. Specifically, the ORR observed among first-line patients was 57.1% (95% CI, 34.0%–78.2%) and in the later-line population, the ORR was 38.1% (95% CI, 18.1%–61.6%).

Dr. Sandoval Sus said, "Despite their biological differences, RT and R/R CLL share common vulnerabilities, including variable CD20 expression, underlying T-cell dysfunction, and similar resistance mechanisms, particularly in 'double-resistant' disease with prior BTK [Bruton's tyrosine kinase] and BCL-2 inhibitor exposure. These shared features often include unmutated IGHV status and *TP53* aberrations. The CD3xCD20 bispecific T-cell engager antibody epcoritamab is designed to exploit these vulnerabilities, demonstrating clinically meaningful activity independent of classic CLL/RT resistance pathways. Clinical trials support the breadth of epcoritamab's efficacy."



The EPCORE CLL-1 subgroup analysis adds to the breadth of knowledge around the efficacy of epcoritamab for CLL and RT. Safety results were consistent with the profiles of most bispecific antibodies. The most common grade 3 and 4 adverse events (AEs) among the 42 patients were neutropenia (45%), anemia (38%), thrombocytopenia (38%), infection (21%), pneumonia (10%), and COVID-19 (5%).

Notably, cytokine release syndrome (CRS) occurred in 86% of patients, of whom 75% experienced grade 3 CRS. Twelve percent of patients had immune effector cell–associated neurotoxicity syndrome, and 5% had clinical tumor lysis syndrome. Three patients died during the study as a result of AEs, namely, progressive disease, sepsis, and cerebrovascular accident. These fatal events did not result from study treatment. According to the study investigators, the safety findings in this analysis were also favorable.

Further evaluation of epcoritamab for the treatment of RT is warranted based on these subanalysis findings.

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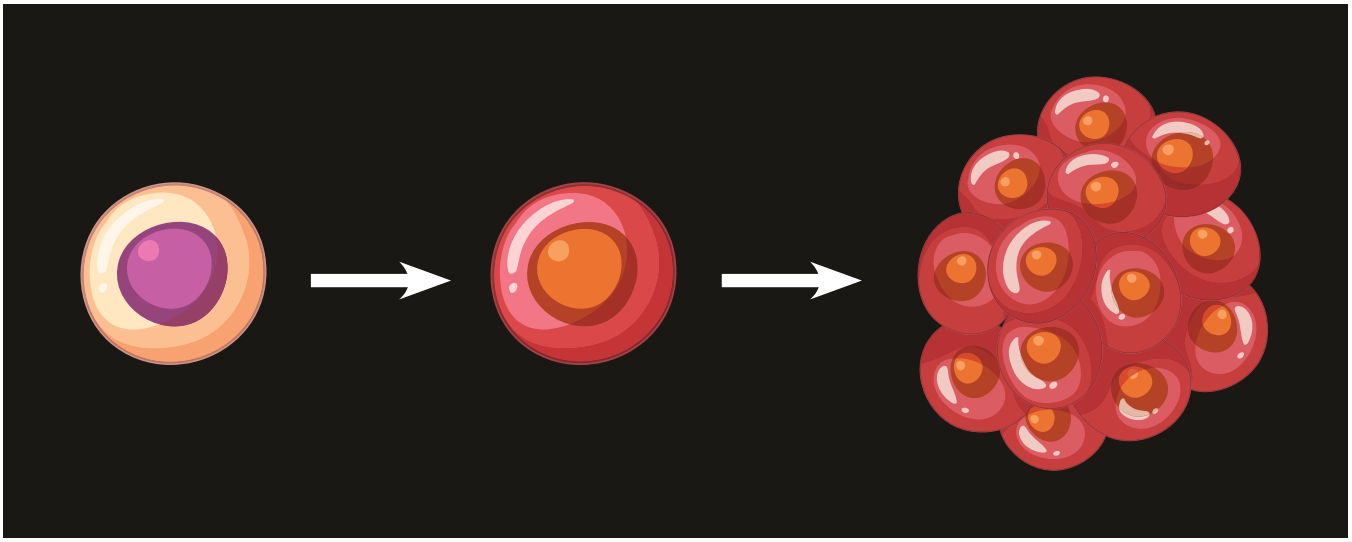

Clonal Evolution and BTK Resistance Under Pirtobrutinib in CLL

By ***Dean Patterson***

Sequencing data from the phase 1/2 BRUIN trial are offering one of the clearest views yet of how chronic lymphocytic leukemia (CLL) adapts to noncovalent Bruton's tyrosine kinase (BTK) inhibition. In a study recently published in *Blood,* investigators profiled genomic changes in heavily pretreated, covalent BTK inhibitor–exposed patients receiving pirtobrutinib, focusing on how baseline clones behave under therapeutic pressure and what ultimately accompanies disease progression.

The analysis included 245 patients with relapsed or refractory CLL previously treated with covalent BTK inhibitors, most commonly ibrutinib. The median number of prior therapies was four. At the May 2023 cutoff, the overall response rate to pirtobrutinib was 82%, the median treatment duration was just over 20 months, and about one-third of patients continued to receive therapy. Baseline targeted next-generation sequencing of peripheral blood cells revealed a high-risk genomic landscape. *BTK* mutations were present in 43% of patients, *TP53* in 38%, *SF3B1* in 25%, *NOTCH1* in 23%, *ATM* in 19%, and *PLCG2* in 9%. Cytogenetic abnormalities were common, including deletion 17p and deletion 11q, often paired with tumor suppressor mutations consistent with biallelic loss.

Most *BTK* alterations reflected prior covalent inhibitor exposure. Among patients with *BTK* mutations, substitutions at C481 dominated, particularly C481S, which carried the highest variant allele frequencies. Less common non-C481 variants included T474I and L528W, mutations previously linked to resistance to acalabrutinib or zanubrutinib. Longer exposure to earlier BTK inhibitors correlated with both the presence of *BTK* mutations and higher allele burden. Patients who discontinued prior therapy because of progression, rather than intolerance, were more likely to harbor *BTK* mutations and unmutated *IGHV*.

Despite this adverse genomic background, pirtobrutinib activity appeared largely preserved. Rates of baseline *BTK* and *TP53* mutations were similar in responders and nonresponders, and no single genomic feature clearly predicted primary resistance after statistical correction. *PLCG2* mutations were somewhat enriched in nonresponders and, along with elevated lactate dehydrogenase and prior targeted therapies, were associated with shorter progression-free survival in exploratory analyses.

Mechanisms of resistance were examined in 88 patients with paired baseline and progression samples. More than half of the overall cohort experienced disease progression, with follow-up approaching 29 months. Pirtobrutinib exerted strong selective pressure on classic C481 clones. Most patients with baseline C481 mutations showed reduction or clearance of those variants at progression. At the same time, new mutations emerged in about two-thirds of patients experiencing disease progression, most

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often in *BTK, TP53, PLCG2,* or *PIK3CA.* Gatekeeper T474 substitutions and kinase-impaired L528W variants were the dominant acquired BTK events.

As senior author **Jennifer R. Brown, MD, PhD,** explained in an interview with *Blood Cancers Today,* "We identified that different *BTK* mutations were the most common cause of acquired resistance, T474 gatekeeper mutations and L528W kinase dead mutations." These findings reinforce that resistance under noncovalent inhibition follows a biologically distinct trajectory compared with classic C481 escape, reshaping how clonal fitness is maintained."

Jennifer R. Brown, MD, PhD

High-sensitivity sequencing revealed that more than one-third of acquired *BTK* mutations were already present at very low levels before treatment, suggesting clonal selection rather than de novo mutation. In some patients, these subclones were detectable months before clinical progression. Functional assays showed that several BTK variants reduced pirtobrutinib binding yet preserved downstream signaling, supporting alternative mechanisms that maintain B-cell receptor activity.

Long-term responders demonstrated a different pattern. Clearance of C481 and *TP53* mutations was observed without emergence of BTK resistance variants at intermediate time points, although other low-level mutations accumulated, consistent with ongoing clonal evolution during therapy.

The mutational spectrum also has implications for therapeutic sequencing. Dr. Brown noted that "the results suggest that there is likely some cross-resistance between some covalent BTK inhibitors (ibru, acala, zanu) and pirtobrutinib. This could affect sequencing choices with these drugs." The presence of shared resistance pathways highlights the need to anticipate clonal selection when transitioning between covalent and noncovalent inhibitors.

Deeper sequencing further showed that standard clinical assays underestimate resistance complexity. Many patients experiencing disease progression who appeared mutation negative with routine testing harbored subclonal *BTK, PLCG2,* or *BCL2* alterations of uncertain clinical significance. These observations raise practical clinical questions about whether more sensitive genomic monitoring should guide earlier intervention.

Looking ahead, Dr. Brown emphasized that the breadth of *BTK* resistance mutations supports alternative strategies. "The frequency of a wide range of *BTK* mutations has suggested that BTK degraders, that can attack most or all mutations, might be a good approach," she said. She also pointed to parallel signaling adaptations, adding, "We are all working on other pathways to target. For example, I am starting a trial with a MEK inhibitor due to the constitutive ERK activation we see in these CLLs." Together, these approaches reflect a shift toward targeting adaptive signaling networks rather than single resistance nodes.

The evolving genomic architecture observed in this cohort underscores that CLL under BTK inhibition remains highly dynamic. Integrating sensitive molecular surveillance with rational sequencing and pathway targeting may ultimately be required to outpace clonal evolution.

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Clinical Trial Data Support Earlier Use of Zanubrutinib for Patients With CLL or SLL Regardless of Mutation Status

*By **Melissa Badamo***

The Bruton's tyrosine kinase inhibitor (BTKi) zanubrutinib is safe and effective in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) with del(17p) or *TP53* mutations, according to a clinical trial analysis published in *Blood*.

Constantine S. Tam, MD

Patients with these mutations are a high-risk population with a historically poor prognosis, according to first author **Constantine S. Tam, MD,** of Alfred Hospital and Monash University in Melbourne, Australia, and colleagues. To assess efficacy and safety outcomes of patients harboring del(17p) or *TP53* mutations, the study authors synthesized data from three clinical trials of zanubrutinib in patients with CLL and SLL: the phase 3 SEQUOIA trial, the phase 3 ALPINE trial, and the phase 1/2 AU-003 trial. Of the 301 patients with del(17p) or *TP53* mutations across all three trials, 132 were treatment-naive, and 169 had relapsed or refractory disease.

"We have known for some time now that BTKi are good options for treatment of del(17p)/*TP53* mutant CLL, based on relatively small groups of patients," Dr. Tam told *Blood Cancers Today.* "The current analysis from randomized clinical trials with mature follow-up confirms that when patients with

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del(17p)/*TP53* mutant CLL are treated with zanubrutinib either in the firstline or for relapsed disease, that their outcomes are largely similar to those of patients without del(17p)/*TP53*. In the relapsed setting, the superior pharmacokinetics of zanubrutinib appear to confer a particular advantage over ibrutinib in patients with del(17p)/*TP53* mutant CLL."

SEQUOIA

Cohort 2 of the SEQUOIA trial included patients with del(17p) and/or *TP53* mutations treated with zanubrutinib. At a median follow-up of 64.8 months, the efficacy data looked promising: the median progression-free survival (PFS) was not reached, and the estimated 60-month PFS rate was 70.7. Similarly, the median overall survival (OS) rate was not reached, with an estimated 60-month OS rate of 82.3%.

Zanubrutinib also maintained a high PFS rate among patients without these mutations, with an estimated 60-month PFS rate of 76.5%. The median PFS and OS were not reached, and the estimated 60-month OS rate was 86.9%. These comparable PFS and OS rates among patients with mutations versus without mutations [suggest] that long-term efficacy with zanubrutinib in treatment-naïve CLL/SLL was independent of del(17p) and/or *TP53*-mutation status," the authors noted.

Zanubrutinib maintained high response rates, with an investigator-assessed response rate of 96.9% for treatment-naïve patients with del(17p) or *TP53* alterations. The complete response (CR)/CR with incomplete hematologic recovery rate was 17.3%.

ALPINE

Stratified by del(17p) or *TP53* mutation status, 150 patients in the ALPINE trial were randomized 1:1 to receive zanubrutinib (n=75) or ibrutinib (n=75). All subgroups favored zanubrutinib over ibrutinib for PFS. At a median follow-up of 38.9 months, the investigator-assessed PFS was 62.5% with zanubrutinib versus 39.9% with ibrutinib.

The study also included a breakdown of PFS by previous lines of therapy. Respectively, the estimated 36-month PFS rates for zanubrutinib and ibrutinib were 61.9% and 49.9% among patients who received one prior line of therapy and 53.8% and 27.8% among patients who received two or more prior lines of therapy.

To reduce bias, the investigators also assessed PFS by Independent Review Committee (IRC). IRC PFS also favored zanubrutinib versus ibrutinib, with a median PFS of 50.2 months versus 28.0 months, respectively. Meanwhile, the 36-month OS rates were comparable between the zanubrutinib and ibrutinib groups (73.6% vs 72.5%, respectively).

Investigators also observed high response rates with zanubrutinib: among those with del(17p) or *TP53* mutations, the investigator-assessed response rate rates were 89.3% with zanubrutinib versus 76.0% with ibrutinib. IRC-assessed response rates were 90.7% and 80.0%, respectively. In both SEQUOIA and ALPINE, response rates increased over the first year of treatment and leveled off after 18 months.

AU-003

In the AU-003 trial, 24 patients with del(17p) or *TP53*-mutated CLL or SLL received full-dose zanubrutinib starting at 60 mg twice daily for 15 patients and 320 mg daily for 9 patients. With a median follow-up of 69.6 months and a median treatment duration of 50.76 months, 10 patients had disease progression, and the median OS was not reached.

Four of five treatment-naïve patients remained progression free at 60 months. Among 19 patients with relapsed or refractory disease, the median PFS was 61.4 months, the estimated 60-month PFS rate was 50.6%, and the median OS was not reached.

The safety profile was generally consistent across the three trials. The most common treatment-emergent adverse events (TEAEs) were COVID-19, upper respiratory tract infection, arthralgia, diarrhea, and contusion. Grade 3 or higher TEAEs occurred in 66.9% of patients in SEQUOIA and 78.4% of patients in ALPINE, while serious TEAEs occurred in 55.9% and 52.7% of patients, respectively. Cumulatively in these two trials, 42 patients experienced AEs leading to treatment discontinuation and 22 died due to AEs.

Together, these three trials illustrate zanubrutinib's high efficacy, high PFS rates, and deep, sustained responses in patients with CLL and SLL, regardless of mutational status.

"These PFS data from ALPINE and SEQUOIA, in conjunction with longer-term follow-up and high rates of PFS seen in patients treated on the AU-003 study, demonstrate that zanubrutinib has strong and clear efficacy in this high-risk population and should be considered for use early in the CLL treatment paradigm," the authors wrote.

Despite these promising results, Dr. Tam noted, unmet needs remain.

"These patients continue to relapse and are at a higher lifetime risk of Richter transformation. Further work is needed to overcome the genomic instability inherent in this disease that leads to treatment resistance and large cell transformation," Dr. Tam told *Blood Cancers Today*.

REFERENCE

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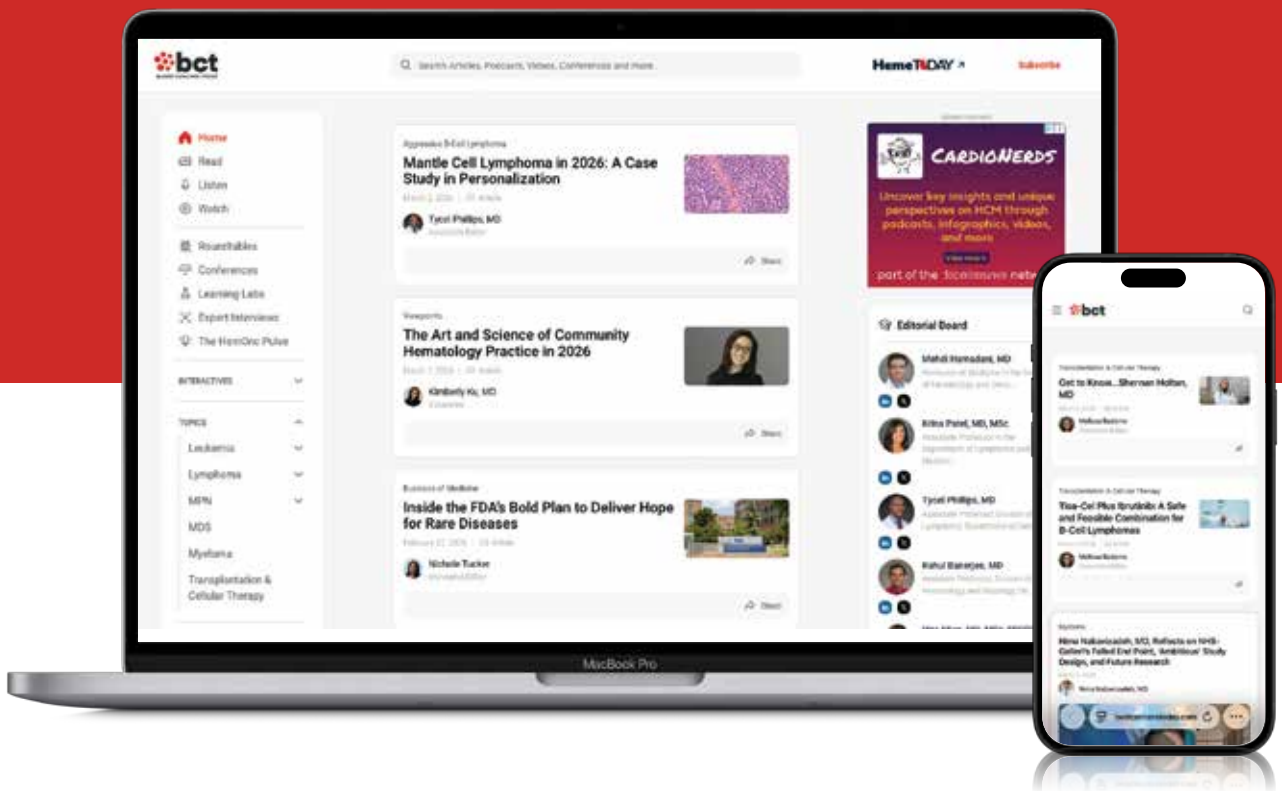

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Calendar

April 10–11
The International Ultmann Chicago Lymphoma Symposium
Chicago, Illinois

April 17–19
Clinical Multidisciplinary Hematology & Oncology: The 20th Annual Review – 2026
Scottsdale, AZ

April 17–22
American Association for Cancer Research (AACR) Annual Meeting 2026
San Diego, CA

April 29–May 2
2026 American Society of Pediatric Hematology/ Oncology (ASPHO) Conference
Minneapolis, MN

May 29–June 2
2026 American Society of Clinical Oncology (ASCO) Annual Meeting
Chicago, IL

June 8–9
22nd Global Summit on Hematology and Blood Disorders
Dubai, UAE

June 11–14
European Hematology Association (EHA) 2026 Congress
Stockholm, Sweden

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HemOnc Happenings

Reporting on recent announcements, awards, and appointments in the hematology/oncology sphere

Pediatric Oncology Pioneer Receives Top ASCO Honor

*By **Katie Kosko***

Louis S. Constine, MD

For decades, **Louis (Sandy) Constine, MD,** has remained dedicated to curing children with lymphomas and understanding and preventing the long-term late effects of the treatments that save their lives.

His commitment has been recognized with the 2026 American Society of Clinical Oncology (ASCO) Pediatric Oncology Award, which will be presented at the ASCO Annual Meeting's Opening Session in Chicago, Illinois, on Saturday, May 30, 2026. He is the first radiation oncologist to receive this award.

"This is a great honor, and I was humbled to have learned I was a recipient," said Dr. Constine, a professor of radiation oncology and pediatrics and vice chair of Radiation Oncology at the University of Rochester's Wilmot Cancer Institute in Rochester, New York. "Gratifyingly, it affirms my personal journey, and my good fortune in having colleagues who share with me a passion for advancing the treatment of children with cancer while also striving to understand and ameliorate the delayed consequences of chemotherapy and radiation."

"My work is a gift. I come to the hospital each day and gain perspective and inspiration by caring for families whose children are threatened."

Driven by Mission, Guided by Teamwork

A passion for helping children started early on for Dr. Constine, who worked as a diabetic youth camp counselor as a teenager. During medical school at Johns Hopkins University School of Medicine, it became clear that pediatrics alone would not define his career. "As I was learning pediatrics, I realized that having a child with cancer was the most tragic event for a family," he said in an interview with *Blood Cancers Today*.

Dr. Constine has studied and conducted research involving Hodgkin lymphoma and other malignancies for more than 50 years, guided by mentors like **Sarah Donaldson, MD,** and **Philip Rubin, MD,** a colleague turned friend who encouraged his move from Stanford University Medical Center to the University of Rochester in 1981.

A decade ago, he founded the Pediatric Normal Tissue Effects in the Clinic, an international consortium that investigates and has now made seminal contributions to elucidating normal tissue radiation dose-volume-response relationships in children with cancer. He continues to lead the initiative today. An outgrowth is biweekly Zoom meetings to mentor young investigators internationally in both high- and low-resource countries in the design of research into the long-term effects of radiation.

Dr. Constine has authored, coauthored, or edited more than 300 original and invited reports throughout his career. He also served as an editor and author of the "bible" of his field, *Pediatric Radiation Oncology,* which has six editions and has been translated into several languages.

Embrace the Extraordinary

Despite Dr. Constine's many accolades, he has no plans to slow down. "I'd rather die of exhaustion than boredom," he said.

Dr. Constine is currently involved in studying the toxic effects of a second course of radiation therapy on children who have cancer recurrences. He also remains committed to his work with the International Lymphoma Radiation Oncology Group, the Children's Oncology Group, and the International Guidelines for Late Effects Harmonization Group. Dr. Constine hopes to become more involved with the Adapted Resource and Implementation Application Guide, an international collaboration between St. Jude Global and the International Society of Paediatric Oncology designed to improve childhood cancer survival in low-resource settings.

"My work is a gift. I come to the hospital each day and gain perspective and inspiration by caring for families whose children are threatened," said Dr. Constine. Yet his most precious titles are husband, father, and grandfather. "I am blessed."

That perspective, he said, reminds him that the extraordinary is all around us; we just need to be mindful enough to appreciate it and always remain curious.

figure1

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