TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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BLOOD CANCERS TODAY

January 2026

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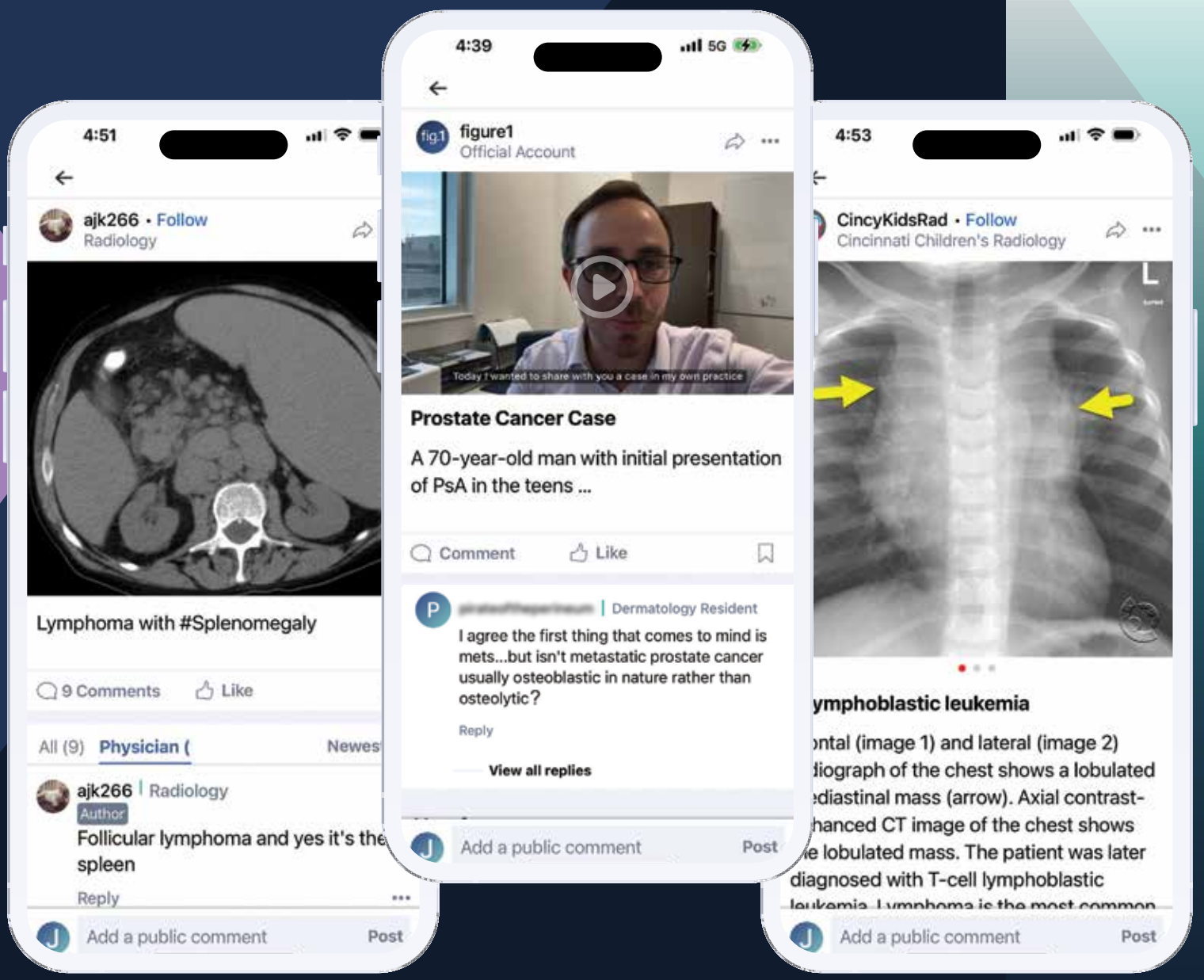

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Calendar

February 12–14
EHA-EBMT 8th European CAR T-Cell Meeting
Palma de Mallorca, Spain

February 26–28
30th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
Miami Beach, FL

March 14
Tri-State Blood Cancer Conference
New York, NY

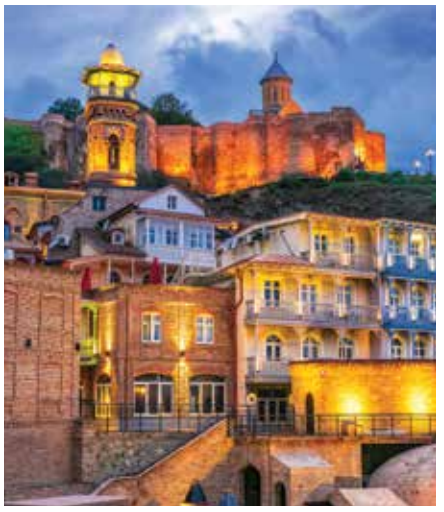
March 23–25
Society for Immunotherapy of Cancer (SITC) Sparkathon 2026: Next-Generation Cellular Therapies, T-Cell Engagers, and Combinations
Tucson, AZ

March 27–29
National Comprehensive Cancer Network (NCCN) 2026 Annual Conference
Orlando, Florida

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 19–21
24th CML Horizons Conference
Tbilisi, Georgia

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 Annual Meeting
Chicago, IL

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

A New Era in Follicular Lymphoma: Bispecific Antibodies in the First Line

*By **Charles J. Gaulin, MD***

The first-line treatment of follicular lymphoma (FL) is on the cusp of a paradigm shift. For patients with high-tumor burden FL, chemoimmunotherapy has long been the standard first-line treatment.[1] However, data presented at the 67th American Society of Hematology Annual Meeting & Exposition suggest that chemotherapy-free, bispecific antibody (BsAb)–based regimens are highly effective, potentially offering more tolerable and durable options in the first-line setting.

Charles J. Gaulin, MD

Recent findings from the EPCORE NHL-2 trial (arms 6 and 7)[2] underscore the potential of epcoritamab combinations. EPCORE NHL-2 investigated fixed-duration epcoritamab plus lenalidomide and rituximab (R2) in first-line FL (arm 6) or epcoritamab monotherapy maintenance following standard-of-care induction (arm 7).

In arm 6 (epcoritamab + R2, n=41), at a median follow-up of 35.9 months, this chemotherapy-free regimen yielded a best overall response rate (ORR) of 95% and a complete response (CR) rate of 88%. The estimated 33-month duration of CR (DOCR) was 93%, and the 36-month estimated progression-free survival (PFS) was 86%. All patients (n=26) evaluable for measurable residual disease (MRD) were MRD negative by clonoSEQ. Cytokine release syndrome (CRS) occurred in 61% of patients and was all grade 1-2. Grade 3 or higher infections occurred in 13 patients (32%), two of which were grade 5 events.

In arm 7 (epcoritamab maintenance for 2 years, n=19), all eight patients who started in a partial response converted to a CR during treatment, and all 10 who completed treatment remained in CR post treatment. At 33 months, an estimated 84% of patients remained in response, suggesting that epcoritamab maintenance can deepen and consolidate the initial treatment response. CRS occurred in 53% of patients and was grade 1 or 2 in all cases. Grade 3 or higher infections occurred in eight patients (42%), most commonly due to COVID-19.

Complementing these findings, a multicenter phase 2 trial[3] investigated fixed-duration therapy with rituximab plus epcoritamab in patients with high-tumor burden FL (n=35). The study hypothesized that a debulking course of rituximab before full-dose epcoritamab could lower the risk of CRS and deepen responses.

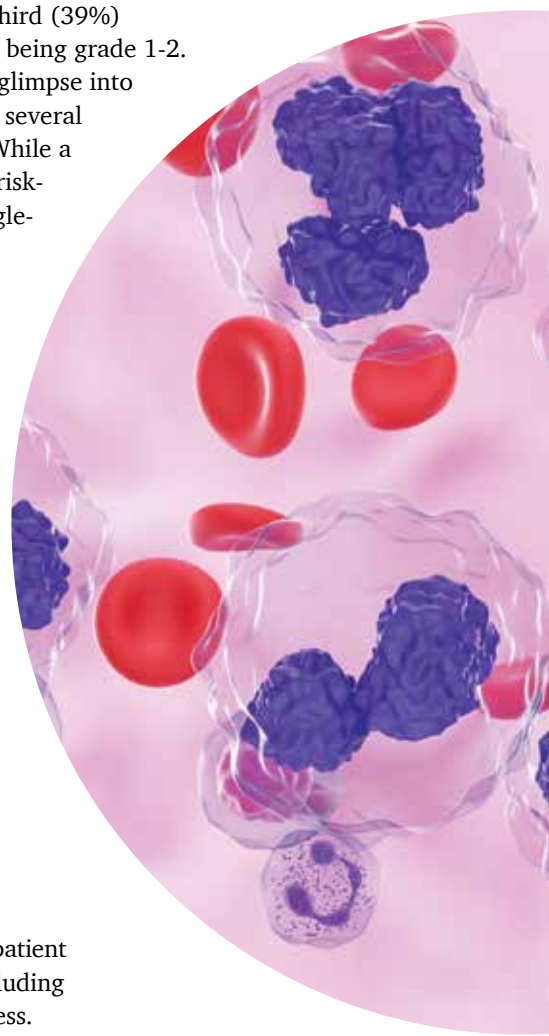
The best ORR was 97%, with a CR rate of 91%. Responses were rapid, with nearly all patients (n=34/35) responding after just two cycles. The pre-treatment with rituximab seemed to achieve its goal, as it appeared to lower the risk of CRS. All-grade CRS occurred in 43% of patients, but only 6% were grade 2, and none were higher. Notably, the nine patients who received a third epcoritamab step-up dose had a lower CRS rate (11%) than those who received only two step-up doses (54%). Infections occurred in 60% of patients (n=21), most of which were grade 1-2.

Two mosunetuzumab trials provided further evidence of the efficacy and flexibility of BsAbs. The phase 2 MorningSun trial[4] evaluated subcutaneous mosunetuzumab as a fixed-duration treatment with optional maintenance in previously untreated high-tumor burden FL (n=103). The ORR was 88.3%, with a CR rate of 65%. The 12-month DOCR was 90.9%. At a median follow-up of 22.3 months, the 12-month PFS rate was 86.7%. After 17 cycles, 46 patients (44.7%) received maintenance. Exploratory circulating tumor DNA (ctDNA) analysis by AOA-NHL assay in a subset of patients who achieved a CR at cycle 8 day 1 showed MRD negativity in 85.3% (n=29/34).

CRS occurred in 34% of patients (all grade 1-2) during initial treatment, and no CRS events occurred during the maintenance phase. There was only one neurotoxicity event (grade 4). Infections occurred in most patients (81%), with 19.4% being grade 3 or higher.

In addition, the phase 2 MITHIC-FL2 trial[5] evaluated the combination of mosunetuzumab and zanubrutinib in previously untreated high-burden FL (n=51). Early efficacy results showed an ORR of 92% and a CR rate of 82% among evaluable patients. CRS occurred in 61% of patients and was predominantly grade 1. There was no neurotoxicity. The hospitalization rate was 3%. Over one-third (39%) experienced infection, with most events being grade 1-2.

The data from these abstracts offer a glimpse into the future of first-line FL treatment, but several critical questions remain unanswered. While a fixed duration is desirable, the optimal risk-adapted strategy for BsAb use—as a single-line fixed treatment, fixed induction followed by maintenance, or even multiple-line use (like rituximab)—and the ideal combination remain to be defined to balance efficacy and safety.



Although more data are needed, the use of MRD may allow us to determine when a patient can stop treatment, providing more flexibility and reducing the risks associated with continuous treatment, such as infection. Additional studies are also needed to identify the ideal risk-adapted combination to enhance T-cell function, deepen responses, and minimize toxicity.

From a logistical perspective, subcutaneous mosunetuzumab and epcoritamab with a three step-up dosing schedule are anticipated to facilitate outpatient delivery in diverse practice locations, including community sites, broadening patient access.

The fundamental challenges in FL remain: its heterogeneity, the ability to predict early progression, and the risk of histologic transformation. It is yet unknown how earlier use of BsAbs will affect the subsequent treatment landscape, particularly given epcoritamab's recent approval in the second-line setting.[6] Whether BsAbs can prevent histologic transformation by effectively eradicating the common clonal progenitor cell before it evolves also remains to be seen.

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Blood Cancers Today *spotlights the latest research from medical residents and fellows in the field of hematologic malignancies.*

Award–Winning ASH Research Highlights Real-World Gains With Pola-R-CHP in DLBCL

By ***Nichole Tucker***

In the clinical setting, treatment for diffuse large B-cell lymphoma (DLBCL) is undergoing a period of transformation. Emerging immunotherapy-based regimens are prompting clinicians to reassess long-standing frontline and sequential treatment strategies.

"We are in a really exciting era where we have a lot of options in DLBCL treatment, but now we need to move beyond approval trials and start doing real-world, head-to-head comparisons to make sure we're truly best serving our patients," said American Society of Hematology (ASH) Abstract Achievement Award recipient, **Danielle C. Thor, DO,** resident physician, Jefferson Health, in an interview.

Danielle C. Thor, DO

At the 67th ASH Annual Meeting & Exposition, Dr. Thor presented real-world data that compared clinical outcomes of patients with DLBCL treated with polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHP; Pola-R-CHP) or the standard of care, which is the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The retrospective, real-world analysis aimed to build on data from the pivotal POLARIX trial and revealed that efficacy with Pola-R-CHP was superior compared with R-CHOP.

"What's most exciting is that we observed a survival benefit and longer time to next treatment with Pola-R-CHP compared with R-CHOP in a large real-world population. Even though this wasn't at the same level as the original POLARIX trial, the survival benefit continues to demonstrate itself in large-scale population studies," said Dr. Thor. "These findings encourage us to revisit frontline therapy and consider whether we can strip away more chemotherapy and add immunotherapy, which is often better tolerated by patients."

"We are in a really exciting era where we have a lot of options in DLBCL treatment, but now we need to move beyond approval trials and start doing real-world, head-to-head comparisons ..."

—Danielle C. Thor, DO

The results were derived from a dataset of 108,907 patients in the TriNetX United States Research Database, including 753 patients exposed to Pola-R-CHP and 16,664 exposed to R-CHOP. The median overall survival was 153.8 months with R-CHOP versus not met with Pola-R-CHP, resulting in a hazard ratio (HR) for overall survival favoring Pola-R-CHP of 0.653 (95% CI, 0.512-0.832; $P<0.006$). It was noted, however, that median follow-up differed substantially between the cohorts: 11.9 months in patients exposed to Pola-R-CHP and 47.8 months in those exposed to R-CHOP.

At data cutoff, the HR for time to next treatment was 0.560 (95% CI, 0.440-0.714; $P<0.001$). Both efficacy findings were statistically significant based on a prespecified threshold ($P<0.01$).

Investigators also explored secondary outcomes, including the risk of hospitalization and admission to an intensive care unit (ICU); for both endpoints, Pola-R-CHP was associated with a lower need compared with R-CHOP. The risk ratio (RR) for lower rates of hospitalization was 0.654 (95% CI, 0.582-0.735), and for lower ICU admission, the RR was 0.582 (95% CI, 0.449-0.755).

Pola-R-CHP also performed better versus R-CHOP in the occurrences of thrombocytopenia (RR, 0.741, 95% CI, 0.620-0.885), all-cause heart failure (RR, 0.699, 95% CI, 0.535-0.803), all-cause acute hypoxic respiratory failure (RR, 0.605, 95% CI, 0.460-0.796), acute kidney injury (RR, 0.621, 95% CI, 0.424-0.756), and all-cause encephalopathy (RR, 0.547, 95% CI, 0.396-0.756).

Dr. Thor explained in her presentation and reiterated during the interview that, as more novel agents emerge in the DLBCL paradigm, real-world, retrospective multi-cohort analyses will be fundamental.

"Access to advanced analytics allows real-time reanalysis of trials to ensure benefits persist in real-world populations—not just ideal study cohorts," Dr. Thor explained. "This helps ensure our work continues to hold up over time, even as diseases evolve and change."

The ASH Abstract Achievement Award is a merit-based award given to trainee investigators, such as Dr. Thor. This accomplishment was a full-circle moment, she said.

"Clinical research influenced my path long before medical school—it helped me appreciate hematology and made the science more accessible. Receiving this award felt like a capstone to my residency and was incredibly meaningful, especially knowing how excited my mentors were," said Dr. Thor.

Dr. Thor is a third-year internal medicine resident at Jefferson Health–New Jersey with clinical interests in malignant hematology and cellular therapy. She earned her DO from Touro College of Osteopathic Medicine–New York and an MA in Urban Bioethics from the Lewis Katz School of Medicine at Temple University. She has authored several peer-reviewed publications and presented nationally on transplant outcomes, cancer disparities, and early-onset cancers. She serves as Chair of the Jefferson Health-New Jersey Housestaff Quality & Safety Leadership Council and is active in ethics, diversity, and LGBTQ+ health advocacy.

The Fellowship Forging Tomorrow's Hematology Experts

*By **Nichole Tucker***

Advances in molecular profiling, biomarker-driven stratification, and novel therapies are reshaping the clinical management of hematologic malignancies, requiring hematology fellows to make complex, real-time decisions for increasingly nuanced patient populations.

At Mayo Clinic in Rochester, Minnesota, the Advanced Hematology Fellowship reflects this shift through disease-focused training tracks designed to meet the realities of modern practice. On the lymphoma and myeloma tracks specifically, fellows are immersed in high-acuity clinical care while being guided by a shared educational philosophy: meaningful autonomy, data-driven decision-making, and excellent mentorship.

In interviews with *Blood Cancers Today,* **Urshila Durani, MD, MPH,** leader of the lymphoma track, and **Wilson I. Gonsalves, MD,** leader of the myeloma track, shared details about their programs, making clear that although the diseases differ, the training principles that define excellence in blood cancer care and shape the next generation of hematologists-oncologists, are remarkably aligned.

Urshila Durani, MD

Wilson I. Gonsalves, MD

Taking the Lead in Patient Care

Dr. Durani explained, "Our fellows essentially run their own clinic—with supervision—but the patients are truly theirs. That level of autonomy changes how deeply you engage with diagnostics and treatment decisions."

This structure places fellows in the role of primary decision-maker early in training, reinforcing clinical accountability while maintaining close faculty oversight. This approach is designed to accelerate clinical judgment and confidence. "When it's your patient, you go further," Dr. Durani asserted.

She explained that this model is particularly critical in lymphoma because diagnoses for these patients can be interpreted in different ways, and the treatment landscapes for these diseases are rapidly expanding. The same can be said of the treatment of multiple myeloma.

Dr. Gonsalves shared, "We have one of the largest dysproteinemia practices in the country, and the clinical volumes far exceed what a traditional fellowship can cover, especially given how nuanced the field has become. This was a ripe era to design a myeloma dysproteinemia fellowship."

Secondary to the autonomy that clearly makes this fellowship unique compared with others across the United States, the programs allow fellows to integrate diagnostic insights they acquire early on with emerging therapies through close collaboration with multidisciplinary teams. Dr. Durani described it as "an approach echoed across both the lymphoma and myeloma tracks."

Collaboration at the Heart of Care

Dr. Gonsalves said, "Everything really revolves around teams and team science. Fellows learn by working across disciplines and building collaborative approaches that reflect how myeloma care is actually delivered."

For fellows on the myeloma track, this team-based model is embedded in daily clinical practice, where complex plasma disorders require managing patients through multiple lines of therapy. Fellows work alongside other clinicians, as well as researchers and data scientists, to understand the intersection of diagnostic data, outcomes research, and therapeutic sequencing, according to Dr. Gonsalves. Rather than viewing collaboration as ancillary, the program positions it as essential to delivering high-quality myeloma care.

Dr. Gonsalves said, "Myeloma care doesn't happen in silos, and we train fellows the same way: by bringing all the expertise to the table and teaching them how to synthesize it for each patient."

A similar structure supports trainees on the lymphoma track, where multidisciplinary tumor boards provide a critical learning environment, according to Dr. Durani. Through tumor board discussions, fellows engage directly with pathologists and radiologists to contextualize molecular and imaging findings in a way that improves patient care.

"Those tumor board discussions are where fellows really learn how to connect the dots—how pathology, imaging, and molecular data translate into treatment decisions for individual patients," Dr. Durani stated.

That emphasis on clinical reasoning and collaboration, of which Drs. Gonsalves and Durani spoke, is reinforced by a mentorship model designed to support fellows as they define their professional identities and select long-term career paths.

Guided Independence for the Next Generation of Hematologists

Mentorship at Mayo Clinic is not step-by-step guidance. Dr. Durani explained, "Mentorship is really about helping fellows see where they want to go and giving them the support and opportunities to get there."

Fellows are encouraged to build a diverse mentorship team, drawing on faculty with varying expertise and at various career stages to ensure they gain both the big-picture perspective and the practical tools needed for their success. This approach allows trainees to receive guidance that is tailored to their individual aspirations, whether they are aiming to lead clinical trials, develop specialized clinics, or take on academic leadership roles. By embedding mentorship in the day-to-day workflow, the program ensures alignment with real-world clinical responsibilities. It also fosters independence among fellows.

"The goal isn't a fixed curriculum: it's tailoring the fellowship to what fellows need to build when they move into their faculty careers," Dr. Gonsalves said. "When they leave that year, they're not going with just a fixed curriculum of 'this is what you need to know,' but really tailoring and adapting it to what they would need, what they want to build when they go into their next stages of their faculty careers."

Commencement of the Advanced Hematology Fellowship at Mayo Clinic is often the precursor to brilliance in medicine. Drs. Gonsalves and Durani shared that after the year is over, many fellows become independent faculty, clinical investigators, and leaders in the treatment of hematologic malignancies and plasma disorders.

"Watching fellows grow into independent clinicians and investigators is one of the most rewarding parts of this work," Dr. Gonsalves concluded.

Get to Know

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

Elizabeth Brem, MD

Dr. Brem, an associate clinical professor at the University of California, Irvine Health, shares her latest leukemia and lymphoma research, her greatest mentors, and how she balances her love for medicine with the art of ballet.

By Melissa Badamo

When Dr. Elizabeth Brem grew up in Buffalo, New York, she trained in the art of ballet dancing. She danced in a production of The Nutcracker every Christmas and even spent a summer alongside the New York City Ballet in Saratoga Springs, New York.

Yet, she always knew her heart was in medicine. She also participated in high school and community theatre, but eventually went on to major in biochemistry in college with a minor in musical theatre.

"I knew I wanted to be a doctor very young," she said. "When I was 6 or 7, I started telling people that's what I wanted to do. But, oncology came a lot later."

At Roswell Park Cancer Institute's (RPCI) summer research program for college students, she worked in the lab of **Myron Czuczman, MD,** who was instrumental in the clinical development of rituximab. She also credits **Francisco Hernandez, MD,** a junior faculty member at Roswell Park at the time and now director of lymphoma at RPCI, as an important mentor and close friend.

"They were nice enough to let me go to [the] clinic with them and shadow them. I got an early look at the bench-to-bedside aspect of medicine," Dr. Brem recalled. "That shaped my career, because I got to see all the different things you can do in the field, whether it's in the lab, in the clinic, or writing a clinical trial. It's hard to spend time with Dr. Czuczman and not want to be a lymphoma doctor! Academic lymphoma was the path from that moment forward."

Afterwards, Dr. Brem went on to complete her internal medicine residency and hematology-oncology fellowship at the Beth Israel Deaconess Medical Center in Boston. There, she learned functional medicine concepts, such as BH3 profiling, and interpersonal skills, including how to interact with and care for patients with lymphoma, from a mentorship team of Drs. Robin Joyce, Anthony Litai, and Matthew Davids.

Now, Dr. Brem resides in Southern California and works as an associate clinical professor at the University of California, Irvine (UCI) Health. She leads clinical trials in lymphoma and leukemia, focusing on resistance mechanisms and the BCL-2 family as a therapeutic target in B-cell and T-cell lymphomas.

"We know that BCL-2 is a fabulous target in CLL [chronic lymphocytic leukemia]," said Dr. Brem. "Venetoclax has changed how we treat that disease. Turns out it's also great for mantle cell lymphoma, but it's not the key switch in every disease. Those keys are probably different in T-cell lymphomas."

However, this concept was difficult to translate into clinical trials, she noted.

"Part of the reason venetoclax works so well is because it targets BCL-2 really well and doesn't have many off-target side effects. Some of the inhibitors for the other BCL-2 family members are more complicated to develop," Dr. Brem explained.

Dr. Brem and her co-collaborator, **David Furman, MD**, are studying the potential for statins to attenuate expression of BCL-2 family members and how they affect patients who respond to drugs like venetoclax.

"It's a cool concept. We could maybe make a standard drug work even better by adding a statin, which are commonly used drugs for cholesterol," she added.

A phase 1 trial (NCT04512105) added the statin drug pitavastatin to venetoclax in patients with acute myeloid leukemia (AML) and CLL and found that the statin did not result in additional toxicity.

"Our collaborators at the University of Pennsylvania demonstrated another pathway by which they think that *TP53*-mutated AML might benefit from the addition of a statin," Dr. Brem added. "We have that concept fleshed out, and we're trying to figure out exactly how to practically move it forward."

Although Dr. Brem mainly focuses on leukemia and lymphoma, she is also an investigator of an ongoing phase 1/2 trial on the bispecific antibody linvoseltamab in untreated multiple myeloma.

"There is a paradigm in oncology that myeloma is incurable. That we have all these great treatments, but you're not going to get rid of it. As the toolkit expands, it's interesting and fun to watch people try to challenge some of those beliefs," Dr. Brem said.

Another trial, Olympia-1 (NCT06091254), studied the bispecific antibody odronextamab in patients with high-risk, untreated follicular lymphoma. Odronextamab demonstrated an overall response rate and complete remission rate of 100% in 13 patients at 12 weeks, with no dose-limiting toxicities or cytokine release syndrome greater than grade 2.

"We have all these drugs that engage T cells, but a lot of times we're not pulling them out until patients have had three or four lines of chemotherapy. If we use these drugs before we've beat up the T-cells, maybe they work better," Dr. Brem said. "We know they work second- and third-line, which is great, but what if we use them from the beginning? Maybe we can train the immune system against the malignancy in the early stages. It will be interesting to see if that changes the natural history of these diseases that we otherwise haven't challenged."

"There is a paradigm in oncology that myeloma is incurable ... As the toolkit expands, it's interesting and fun to watch people try to challenge some of those beliefs."

According to Dr. Brem, one key takeaway from the trial is the feasibility to change the sequencing of effective therapies.

"We have a lot of amazing drugs in myeloma and slow-growing lymphomas, but we don't know the optimal order to use them in," she added. "We often save certain drugs that work great for later lines. We can learn from this study that it's okay to use these effective drugs upfront and change the sequencing of the drugs."

Aside from leading clinical trials, Dr. Brem recently accepted the role of vice chief for clinical affairs at UCI Health. This role involves managing schedules, organizing staff, resolving conflicts, and more.

Outside of work, Dr. Elizabeth Brem enjoys traveling, practicing ballet, and spending time with her husband and two children.

(Photos courtesy of Elizabeth Brem, MD)

"We've tripled in size in the 8 or 9 years that I've been here," Dr. Brem said. "We've grown as a faculty, and we're about to open a new hospital. That means a lot more people who need to be scheduled and coordinated with. This is the first time we've ever had a role like this."

At this point in her career, Dr. Brem has transitioned from the role of mentee to mentor. She shared her best advice for younger physicians or trainees in the field, including finding multiple mentors—whether that be lab research mentors, clinical research mentors, or even peer mentors.

"One of the things I tell the young people I'm working with is that you need a team of mentors. You can't get everything you need from one person. You're not going to be a carbon copy of somebody else's practice or career, so that's why you need multiple mentors."

Reflecting on her own career timeline, she also recommends getting involved with the American Society of Hematology (ASH) early in one's career. She was part of the ASH trainee council during her last 2 years of fellowship, served on several ASH committees, including the communications committee, and was a part of the ASH clinical news editorial team.

Together, her mentorship and involvement with ASH carved Dr. Brem into the clinician she is today. "I learned so much from that experience," she reflected. "In that time when I was learning how to take care of multiple myeloma, even though that wasn't necessarily something I planned to do, I reached out to people I had met through ASH for help. Everybody was so nice, helpful, and supportive."

For oncologists, the field is forever changing. However, there are still many constants in Dr. Brem's life—her love for medicine, and, of course, the art of ballet. After all, ballet dancing is like being an oncologist. Both require precision, focus, and determination.

Today, Dr. Brem is still part of an adult dance community in Southern California, nurturing her creative side alongside her scientific pursuits. She's even learning new things, like practicing Taekwondo with her husband and two children. Eventually, she wants to travel to Central America, Australia, and Asia.

"There is a lot of traveling in the job, but I don't do a lot of traveling outside the job," she said. "There are huge parts of the world I've never been to. When life slows down, there's a lot of places and cultures I want to experience."

RIGHT ON TARGET

Novel Protein Degradation Strategies in Blood Cancers

By Melissa Badamo

Developing targeted protein degraders for blood cancers is like practicing archery. It starts with recognizing a cancer-promoting protein, carefully locking in on the target, and finally hitting it with an effective drug.

This method of targeted protein degradation uses the ubiquitin-proteasome system to break down cancer-promoting proteins rather than merely inhibiting them.[1] As a result, targeted protein degraders (TPDs) can overcome challenges of small-molecule kinase inhibitors and monoclonal antibodies, such as resistance due to mutations.[2]

Currently, two major classes of TPDs have joined the fight against blood cancers: proteolysis-targeting chimeras (PROTACs), including Bruton's tyrosine kinase (BTK) degraders, and molecular glue degraders, including cereblon E3 ligase modulators (CELMoDs).

BTK Degraders

By utilizing differences in E3 ligase expression, PROTACs such as BTK degraders improve tissue specificity and mitigate toxicity.[3] They are composed of three parts: a ligand that binds the E3 ligases, a ligand that binds the point of interest, and a linker that connects the two ligands.[2]

According to **Alexey Danilov, MD, PhD,** a professor in early clinical therapeutics at the City of Hope National Medical Center, two BTK degraders currently stand out in B-cell malignancies: NX-5948 (bexobrutideg) and BGB-16673.

"Both of these agents are safe and efficacious, and both have been tested in highly refractory patient populations with CLL [chronic lymphocytic leukemia] who had a median of three to four prior therapies," he said. "In this heavily pre-treated patient population with high-risk genetic characteristics, the overall response rates were over 80% for both of these drugs."

BTK degraders aim to overcome BTK inhibitor resistance by linking a BTK ligand to the cereblon E3-ligase recruiting ligand, therefore inducing BTK degradation.[4] Compared with BTK inhibitors (BTKis), PROTACS do not rely on active site binding or sustained occupancy.[3]

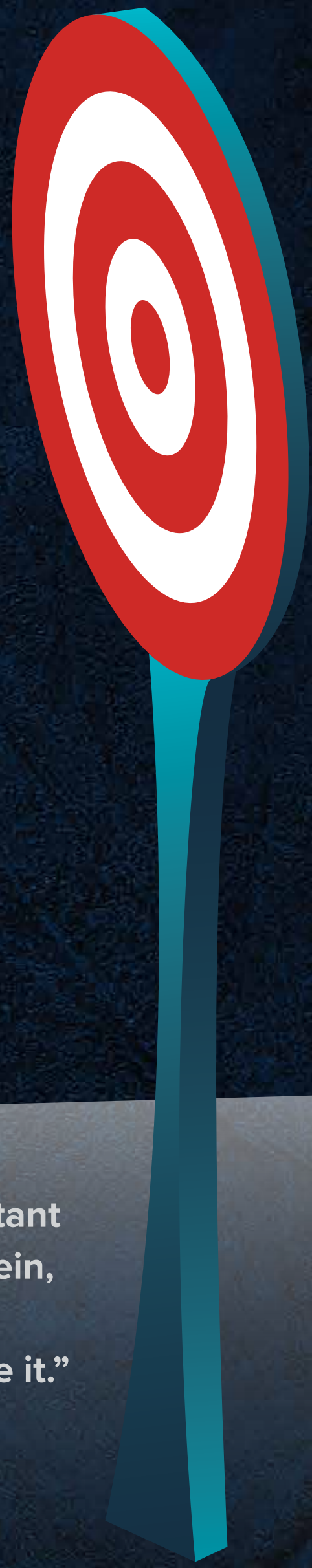
"They [bexobrutideg and BGB-16673] have a very similar mechanism of action where the compound binds both the BTK and E3 ligase at the same time," Dr. Danilov explained. "E3 ligase is an enzyme responsible for processing and destruction of proteins of interest, so in this case, BTK. When the compound binds BTK and links it to the E3 ligase, the whole complex is then degraded through the proteasome. In contrast to kinase inhibitors such as ibrutinib, BTK degraders completely eradicate the BTK molecule as opposed to simply inhibiting the BTK function or its kinase activity."

Updated results on bexobrutideg were presented at the 67th American Society of Hematology Annual Meeting & Exposition in December 2025.[5] In this ongoing phase 1a/b trial, one patient achieved a complete response, and the median progression-free survival was 22 months, Dr. Danilov explained. Adverse events included low-grade bleeding events, purpura/contusion, fatigue, infections, and diarrhea, and high-grade neutropenia.

"The safety of both compounds, BGB-16673 and bexobrutideg, is also very impressive considering that these patients can be exposed to multiple treatments in the past," Dr. Danilov added. "Most of the side effects are consistent with what we see with BTK inhibition."

According to Dr. Danilov, novel BTK degraders are needed for two reasons. First, BTK can undergo mutations that confer resistance to kinase inhibitors in CLL.

"The most commonly detected mutation is C481S. BTK degraders overcome this resistance mechanism for patients who carry these mutations, because the disease is still sensitive to BTK degraders," he explained. "Covalent BTK inhibitors



"If you find a protein or pathway that's important in a certain cancer, you either inhibit the protein, or you can get rid of the protein. When you degrade the protein, you permanently remove it."

—Daniel J. DeAngelo, MD, PhD, Harvard Medical School.

are unable to fully inhibit the function of mutant BTK. Degraders, by completely destroying BTK, are able to inhibit its function."

The second reason is that kinase-dead mutations confer resistance to both covalent and noncovalent BTK inhibitors, explained Dr. Danilov.

"The kinase activity of BTK is also reduced or completely eliminated when this mutation occurs," he said. "However, BTK has a scaffold function where BTK can contribute to signaling through [the] B-cell receptor by engaging other kinases. Kinase inhibitors are unable to eliminate the BTK scaffold function, but BTK degraders can. Not only are BTK degraders able to overcome most mutations occurring with covalent and noncovalent BTK inhibitors, but BTK degraders also eliminate the scaffold function of BTK. It is a twofold mechanism why BTK degraders are important."

"Not only are BTK degraders able to overcome most mutations occurring with covalent and noncovalent BTK inhibitors, but BTK degraders also eliminate the scaffold function of BTK. It is a twofold mechanism why BTK degraders are important."

—Alexey Danilov, MD, PhD, City of Hope National Medical Center.

CELMoDs

CELMoDs are a type of molecular glue degrader that targets the E3 ligase cereblon.[6] These include the approved drugs lenalidomide and pomalidomide, but novel CELMoDs are needed due to patient relapse.[7]

GSPT1 Degraders

GSPT1 is a small GTPase that promotes the progression of cancer cells.[8] As a result, GSPT1 degraders like CC-90009 bind to the cereblon protein to trigger the destruction of cancer-promoting proteins in multiple myeloma, acute myeloid leukemia (AML), and other blood cancers.

"Cereblon E3 ligase modulators are very important in the treatment of myeloma and a specific subtype of MDS, specifically del5q," said **Daniel J. DeAngelo, MD, PhD**, professor of medicine at Harvard Medical School and chief of the division of leukemia at the Dana-Farber Cancer Institute. "Patients with low-risk del5q MDS treated with lenalidomide have disease-modifying ability through CK1α degradation. In leukemia, targeting the GSPT1 protein helps transition cells from the G1 to [the] S phase during the cell cycle. By degrading GSPT1 through the cereblon E3 ligase, the hope was to have some antileukemic activity."

To test this theory, Dr. DeAngelo led a multicenter, open-label, phase 1, dose-escalation study of CC-90009 in patients with AML, with most having relapsed or refractory disease. Of 72 enrolled patients, 11 (15%) achieved an overall response. All responses were observed at higher dose levels of CC-90009 (3 mg or higher) administered on 5 or more consecutive days, and 14% of responding patients achieved complete remission or complete remission with incomplete count recovery.

"That's important because these are patients who are chemotherapy refractory," Dr. DeAngelo explained. "Single-agent therapies are often not associated with remission. CC-90009 had modest single-agent activity as monotherapy, and it seemed to have a very acceptable safety profile."

GSPT1 degradation can interfere with the inflammasome, Dr. DeAngelo explained, therefore leading to inflammatory side effects such as hypotension.

"That may be inherent of all GSTP CELMoDs because of the inflammatory or cytokine cascade observed," he said. Other common treatment-emergent adverse events (TEAEs) included sepsis and hypocalcemia.

"We were able to demonstrate that this agent is at least hitting the target, which is a successful phase 1 study in my book," Dr. DeAngelo said. "We saw greater than 90% degradation in GSPT1 that was associated with these inflammatory cytokine events, which seemed to be controlled with dexamethasone. The next phase is going to be combining it with chemotherapy, because an overall response rate of 14% is not enough."

CK1a Degraders

Dr. DeAngelo and colleagues are also investigating CC-91663, a CK1α degrader, in *p53* wild-type patients with relapsed or refractory AML and high-risk MDS.

"CK1α is important in stabilizing and activating the p53 cell cycle arrest," he explained. "*p53* is often mutated in a lot of cancers, which leads to unbridled proliferation."

In this dose escalation trial, CC-91663 was well tolerated, with TEAEs consisting of cytopenias, GI toxicity, and mild transaminitis. However, as with CC-90009, this agent exhibited only modest single-agent activity, with an overall response rate of 12%.

"Interestingly, there were more responses in the high-risk MDS group with a higher overall response rate. The question is whether this should be translated or combined with another agent in myelodysplastic syndromes," Dr. DeAngelo said.

Challenges, Limitations, and Future Research

The field is continuing its search for novel degradation targets to improve patient outcomes and overcome challenges. As Dr. DeAngelo explained: it's not about the drug itself, it's about finding the right target.

"Is the target feasible?" he questioned. "If you find a protein or pathway that's important in a certain cancer, you either inhibit the protein or you can get rid of the protein. When you degrade the protein, you permanently remove it."

Developing novel combinations is the next step to overcome challenges with both CELMoDs and BTK degraders. As Dr. DeAngelo mentioned, adding chemotherapy to CC-90009 and CC-91663 could potentially boost their clinical activity and improve overall response rates, but further studies are needed.

As for BTK degraders, one challenge is that resistance mechanisms are currently unknown, according to Dr. Danilov.

"One mutation has been described resulting from BTK degradation, which potentially impacts the binding of BTK degrader to the kinase," he explained. "It is also possible that other resistance mechanisms will emerge, including activation of collateral pathways and mutation in [the] E3 ligase. Resistance will occur invariably."

Another challenge, Dr. Danilov mentioned, is that these agents need to be administered continuously to maintain efficacy.

"The way of the future would be to combine BTK degraders with other compounds such as venetoclax, other BCL-2 inhibitors, or bispecific antibodies to allow for time-limited administration of BTK degraders and to potentially mitigate some resistance that might occur with continuous administration," he concluded.

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Regulatory Actions

Recent therapy approvals, updates, and clinical trial results in the field of hematologic oncology

FDA Approves Daratumumab and Hyaluronidase-fihj for Smoldering Multiple Myeloma

*By **Lauren Evoy Davis***

The FDA has approved daratumumab and hyaluronidase-fihj for patients with high-risk smoldering multiple myeloma (SMM) for prevention of disease progression to active MM. The approval was announced by Johnson & Johnson, which develops and markets this therapy as DARZALEX FASPRO, and by Halozyme Therapeutics, Inc, which produced the drug delivery technology that this commercial agent features.[1,2]

The first-of-its-kind FDA approval was based on the findings from the phase 3 AQUILA study, which evaluated the effectiveness and safety of the single-injection drug compared with a "watch and wait" approach, which up to now, was the standard of care.[3] In this trial, researchers enrolled 390 patients; 194 were assigned to the daratumumab arm and 196 to the active monitoring (watchful waiting) arm. Patients in the daratumumab group received 39 treatment cycles for 36 months, or until the disease progressed to MM.[4]

At the median follow-up at 65.2 months, the risk of disease progression or death was decreased by 51% with daratumumab versus watchful waiting,[4] although 15 deaths occurred in the daratumumab arm and 26 deaths occurred in the active monitoring arm.[4] At 5 years, the overall survival rate was 93% in the daratumumab arm and 86.9% in the active monitoring arm. Adverse effects included grade 3 or grade 4 hypertension, which was experienced by 5.7% of the patients in the daratumumab arm and 4.6% of patients in the active monitoring arm.[4] In a pooled safety population, 24% of patients had serious infections, the most common being pneumonia at 8.5%.[2]

"Until now, patients diagnosed with smoldering multiple myeloma only have the option to watch and wait for any active signs of progression to active disease," said **Peter Voorhees, MD,** of the Atrium Health/Levine Cancer Institute, Charlotte, North Carolina, in the Johnson & Johnson news release. "Results from AQUILA demonstrated *DARZALEX FASPRO* significantly delayed disease progression, underscoring the role of early disease intervention for patients with high-risk smoldering multiple myeloma," he added.[2]

High-risk SMM does not have obvious symptoms, and the aim of the study was to treat it before the disease progressed to active MM.[2] As explained by the Cleveland Clinic, conversion of SMM into active MM can be a years-long process, or it may not progress to active disease at all. Hematologists are investigating genetic mutations in oncogenes and obesity as possible drivers of the conversion of SMM to active MM.[3]

Overall, the combination of daratumumab and hyaluronidase-fihj appears to be safe and effective for people with SMM who want to prevent disease progression.

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FDA Approves Ziftomenib for *NPM1*-Mutated Relapsed or Refractory AML

*By **Lauren Evoy Davis***

The FDA has approved ziftomenib, a once-daily oral menin inhibitor, to treat relapsed or refractory acute myeloid leukemia (AML) with *NPM1* mutation. The approval is specifically for use in adults with disease that cannot be feasibly managed with any other treatment.[1]

Ziftomenib is co-developed and marketed by the multinational biopharmaceutical companies Kura Oncology, Inc, and Kyowa Kirin Co, Ltd, as KOMZIFTI. Kura Oncology issued a press release announcing the new FDA approval.[2]

"KOMZIFTI addresses a critical need for adult patients with R/R [relapsed or refractory] *NPM1*-m [*NPM1*-mutated] AML, many of whom are older and unable to tolerate intensive chemotherapy or transplant," remarked **Eunice Wang, MD,** chief of the Leukemia Service at Roswell Park Comprehensive Cancer Center in Buffalo, New York, in the Kura news release. "This approval equips physicians with a new oral therapy to integrate into care and improve outcomes for this vulnerable patient population."[2]

The FDA's approval was based on the results of the KO-MEN-001 clinical trial, which had a cohort of 112 patients with AML and diverse *NPM1* mutations and a median follow-up of 4.2 months. Efficacy, measured by complete remission (CR) plus CR with partial hematologic recovery (CRh), was 21.4%, with an exact CR rate of 17.0% and a CRh rate of 4.5%, and lasted for 5 months. Of the 66 patients who required red blood cell or platelet transfusions at baseline, 14 receiving study treatment no longer required transfusions during any 56-day period after baseline.[1]

In the KO-MEN-001 trial, the types of adverse reactions that affected 20% or more of the cohort were diarrhea, fatigue, febrile neutropenia, hemorrhage, infections, itching, musculoskeletal pain, nausea, and swelling, along with laboratory marker fluctuations. In the cohort, there was also a 26% prevalence of differentiation syndrome, a potentially lethal set of complications for which KOMZIFTI carries a Boxed Warning.[2]

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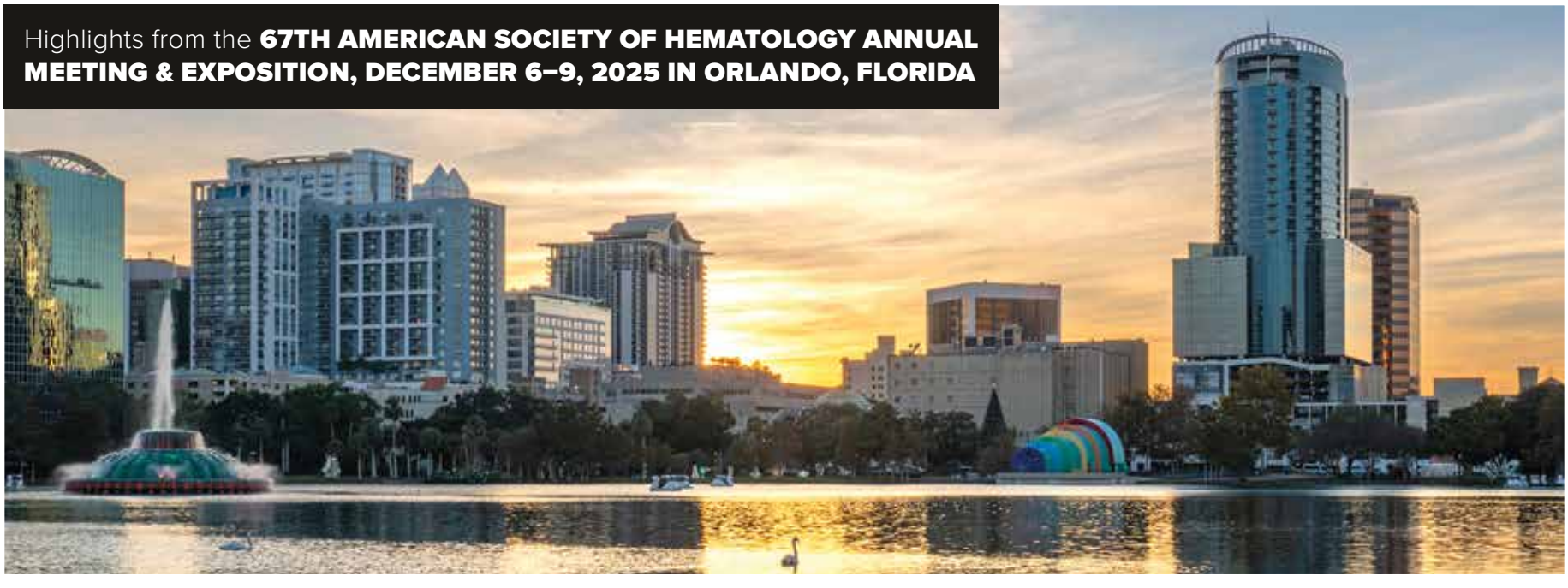
Highlights from the **67TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING & EXPOSITION, DECEMBER 6–9, 2025 IN ORLANDO, FLORIDA**



Earlier Cilta-cel Use Linked to Stronger Immune Fitness in Multiple Myeloma

By ***Dean Patterson***

New correlative data from the CARTITUDE program suggest that ciltacabtagene autoleucel (cilta-cel) works differently depending on how many prior lines of therapy a patient has received. Findings were presented at the 67th American Society of Hematology (ASH) Annual Meeting & Exposition by **Samir Parekh, MD.**

Samir Parekh, MD

The study investigators looked at immune fitness in both peripheral blood and the marrow microenvironment, trying to understand why patients treated earlier in the relapse course tend to see stronger and more durable outcomes.

"It was important to conduct this study to understand the biology behind improved outcomes with CAR-T [chimeric antigen receptor T-cell therapy] in earlier lines of treatment, specifically whether T-cell fitness and a supportive immune microenvironment is seen in patients with better outcomes," Dr. Parekh, professor of medicine, hematology, and medical oncology at Icahn School of Medicine told *Blood Cancers Today.*

Cilta-cel is already used for lenalidomide-refractory myeloma after at least one prior regimen. CARTITUDE-1 showed meaningful activity in heavily treated patients, and CARTITUDE-4 moved that benefit earlier by demonstrating a survival advantage in patients with one to three prior lines. The new analysis drew on both trials, pairing apheresis samples with bone marrow aspirates to observe how the immune system evolves before and after infusion and whether that trajectory explains the clinical gap between early and late use.

Across 248 apheresis samples, one signal kept resurfacing: patients who received CAR T-cell therapy after one or two prior lines of treatment had a greater proportion of CD4-naive T cells. By the time patients reached their third regimen, those levels had already dropped and tended not to decline much further. That pattern lined up with clinical outcomes. Individuals with more naive CD4 cells at baseline simply remained progression free longer, which adds some biological support to the idea that the starting T-cell pool matters as much as the CAR T-cell construct itself.

The marrow data told a parallel story. Investigators analyzed 148 samples from CARTITUDE-4 spanning screening, day 28, and the 6-month mark. Day 28 was a busy period immunologically. B cells and antibody-producing pathways were clearly depleted, which matched what was seen in flow cytometry and immunoglobulin measurements. At the same time, there was an uptick in M1-leaning macrophage signatures and gene expression linked to cytotoxic T-cell activity. Some of this early activity persisted. Pathways tied to T-cell differentiation and cytokine signaling remained elevated through 6 months.

Patients who remained progression free for more than 18 months showed strong M1 macrophage signatures at day 28. Those who experienced relapse sooner showed movement in the opposite direction. Their 6-month marrow samples had higher levels of regulatory T cells and showed more suppression of genes in interferon-related pathways. In other words, the environment appeared to be drifting toward immunosuppression before clinical relapse occurred.

Prior treatment exposure also shaped these signals. Patients with fewer prior lines had more pronounced B-cell depletion early on and a cleaner recovery by 6 months. They also displayed stronger activation of B-cell receptor pathways, and their macrophage activity at day 28 resembled what was seen in the longer responders.

Dr. Parekh said the clinical interpretation is becoming clearer: "CAR-T therapy in earlier lines is associated with better patient outcomes, due to better T-cell fitness and [a] more immunocompetent/supportive microenvironment. This is clinically relevant, as there are multiple options in early relapse, and for the young and fit patients, giving CAR-T earlier would be supported, given the clinical and correlative data."

The group concluded that immune fitness seems strongest in the first two treatment lines and then levels off. Although features within the marrow microenvironment may help stabilize responses in more heavily treated patients, they may not fully counterbalance the weaker T-cell starting point.

The analysis leaves clinicians with a few important questions. How far forward in the treatment sequence should cilta-cel realistically move for patients who are immunologically poised to benefit the most? Should immune fitness markers, especially CD4+-naive T-cell levels, start to play a role in determining which patients are referred early for CAR T-cell therapy?

These data do not settle those questions, but they add weight to a simple idea: earlier may be a better time to intervene, according to Dr. Parekh and colleagues.

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Promising Phase 1b Results Set Stage for Phase 3 Development of Bleximenib Plus 7+3 in AML

*By **Nichole Tucker***

Backbone 7+3 intensive chemotherapy (IC) may have more competition in the challenge of treating patients with IC-eligible newly diagnosed acute myeloid leukemia (AML) who harbor *KMT2A* rearrangements or *NPM1* mutations. Findings from a phase 1b dose-finding study (ALE1002) of bleximenib combined with 7+3 IC have demonstrated a safety profile consistent with the standard and showed preliminary efficacy.

Now in phase 3 development in other settings of AML, investigators of ALE1002 are planning a phase 3 study of the menin inhibitor, bleximenib, combined with 7+3 IC.

Hartmut Döhner, MD

"Menin inhibitors are one of the most promising and interesting classes of compounds currently in AML development, particularly for *NPM1*-mutated and *KMT2A*-rearranged disease, where there is strong preclinical rationale that menin inhibition works especially well in these genotypes," **Hartmut Döhner, MD,** of Ulm University Hospital told *Blood Cancers Today,* in an interview at the 67th American Society Hematology Annual Meeting & Exposition.

Further exploration of bleximenib plus 7+3 IC has been rationalized by achievement of a 95.8% overall response rate among the 24 patients from the intention-to-treat data set in ALE1002. In addition, the confirmed complete remission (CR) rate was 87.5%, and the CR with partial hematologic recovery (CRh) rate was 75%.

Among patients treated with bleximenib 100 mg bid, the median time to CR was 28 days (range, 21-36), which was similar to the time to first response. Treatment with bleximenib plus 7+3 IC was followed by allogeneic transplant in four patients.

The safety analysis set included 44 patients, and all of them experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs observed in the study were thrombocytopenia (79.5%), neutropenia (72.7%), diarrhea (70.5%), nausea (68.2%), and anemia and febrile neutropenia (63.6% each).

"The safety profile looks very good, with no safety signal beyond what we would expect from standard intensive chemotherapy alone," Dr. Döhner explained. Specifically, results showed that cytopenias were mid-grade, QT prolongation events were resolved quickly, and platelet count recovery (50×10^9/L) was rapid among those with a CR/CRh (32 days; range, 22.0-82.0). Moreover, neutrophil count recovery (0.5×10^9/L) was 30.0 days (range, 21.0-71.0).

"While we only have initial response data so far, these results are really very interesting and appear, at least, to be superior to what we know from conventional 3+7 induction chemotherapy," Dr. Döhner stated.

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Nemtabrutinib Shows Antitumor Activity, Manageable Safety Profile in MZL

*By **Sara Karlovitch***

Nemtabrutinib demonstrated sustained antitumor activity as well as a manageable safety profile in heavily pretreated patients with marginal zone lymphoma (MZL), according to data presented at the 67th American Society of Hematology (ASH) Annual Meeting & Exposition.

Alessandra Tucci, MD

Few therapeutic alternatives are available for patients with relapsed or refractory (R/R) MZL who experience disease progression or are unable to tolerate covalent Bruton's tyrosine kinase inhibitors (BTKis), according to lead author **Alessandra Tucci, MD,** of UOC Ematologia, and colleagues.

Nemtabrutinib, a noncovalent reversible BTKi taken orally once a day, has displayed encouraging antitumor activity in B-cell malignancies. In the BELLWAVE-003 phase 2 study, researchers evaluated treatment with nemtabrutinib in patients with hematologic malignancies, including R/R chronic lymphocytic leukemia or small lymphocytic lymphoma, follicular lymphoma, mantle cell lymphoma, MZL, Richter transformation, and Waldenström macroglobulinemia. Cohort F included patients with R/R MZL. In order to qualify for participation, patients with R/R MZL must have been unresponsive to treatment with a covalent BTKi or chemoimmunotherapy. Nemtabrutinib was administered until disease progression, withdrawal, or unacceptable toxicity levels occurred. The primary end point was objective response rate (ORR), and secondary end points included duration of response (DOR) and safety.

The median follow-up for this cohort was 9.2 months, and the recommended phase 2 dose (RP2D) of 65 mg/d was found to have both antitumor activity and a manageable safety profile in patients with MZL that was refractory to two or more lines of therapy, including a covalent BTKi.

In total, 23 patients with R/R MZL received nemtabrutinib at the RP2D. The median age was 68 years, 43% were male, 65% had Lugano stage IV disease, and the median number of prior therapies was three. At the RP2D level, the median time from first dose to cutoff was 10.3 months, and the median treatment duration was 4.7 months. More than half of patients (55%) are continuing treatment. The ORR was 52% based on blinded independent central review and 28% based on investigator review. The median DOR was 7.4 months.

In terms of safety, 87% of patients experienced all-cause adverse events (AEs) of any grade. The most common AEs in this category include pneumonia (30%), pyrexia (30%), anemia (26%), and diarrhea (26%). Grade 3 or 4 all-cause AEs were observed in 52% of patients. Dose reduction as a result of AEs was reported for 13% of patients, and discontinuation was reported for the same number. No AE-related deaths were reported.

"Not all patients with marginal zone lymphoma follow an indolent clinical course. Some of them present with symptomatic disease and subsequent progression phases requiring different lines of treatment," Dr. Tucci told *Blood Cancers Today.* "Nemtabrutinib offers an opportunity to this group of patients demonstrating antitumor activity in patients who had progressed on both chemoimmunotherapy and covalent BTKi treatment. At the same time, its safety profile, with no unexpected AEs identified, allow a manageable use in heavily pretreated patients."

According to Dr. Tucci, future analyses will focus on long-term follow-up regarding progression-free survival, overall survival, and potential late adverse events.

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TKI and Inotuzumab Drive Rapid Molecular Responses in Ph-Positive ALL

*By **Nichole Tucker***


Wendy Stock, MD

Nearly 10 years ago, investigators aimed to define the factors that influence the achievement of complete molecular responses (CMRs) in patients with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL).[1] This research laid the groundwork for explorations of tyrosine kinase inhibitors (TKIs) combined with antibody-based or immune-targeted therapies, according to **Wendy Stock, MD,** of UChicago Medicine, who presented results of a novel TKI/antibody drug conjugate (ADC) combination at the 67th American Society of Hematology (ASH) Annual Meeting & Exposition (ASH 2025).[2]

"What's driving this shift is not only the impressive efficacy we've seen with TKI-antibody combinations, but also the ability to deliver these regimens in the outpatient setting," said Dr. Stock in an interview with *Blood Cancers Today*.

At ASH 2025, Dr. Stock reported that the ADC, inotuzumab ozogamicin, demonstrated excellent molecular responses in newly diagnosed patients when combined with TKI therapy. The study specifically looked at achievement of aBCR::ABL1 qRT-PCR of <0.1% (MR3) or aBCR::ABL1 qRT-PCR of <0.01% (MR4) in 21 patients.

Results showed that by the end of course 2, which consisted of treatment with inotuzumab ozogamicin 0.5 mg/m^2 on days 1, 8, and 15, the MR4 rate was 62% and the MR3 rate was 19%. Notably, four patients achieved a complete response without MR3 or MR4. By the end of the third course, the MR4 rate climbed to 90%. In the subgroup of patients with *IKZF1* plus Ph-positive ALL, the MR4 rate was 67% by the end of course 2, which climbed to 100% by the end of course 3.

"Because we achieved a 100% combined molecular response rate within 3 months, we didn't feel any of our patients needed allogeneic transplant in first remission, and we're hopeful this approach may ultimately lead to long-term survival—or even cure—with relatively minimal therapy," Dr. Stock said.

They also evaluated measurable residual disease (MRD) via next-generation sequencing, which showed a MRD negativity rate of 62% by the end of course 2 and 90% by the end of the third course.

At a median follow-up of 1.66 years (range, 0.19-3.85), results showed an estimated 2-year overall survival rate of 79% (95% CI, 62%-100%). Of those in remission, there was one patient death, which resulted from respiratory failure during the fifth course of treatment. Three patients in remission died of either sepsis or a gastrointestinal bleed. There was one patient who relapsed with acquisition of an *ABL1 T315I* mutation after study treatment.

Patients in the study had a median age of 60 years (range, 21-79), were largely female (57%), and identified as non-Hispanic White (53%). Twenty-four percent of the population identified as Black, 14% were Hispanic, and 10% did not report.

The findings overall warrant further development of induction therapy consisting of inotuzumab ozogamicin and a TKI, especially to explore potential risks like that of post-protocol relapse.

"If these results continue to hold up long term, we may be looking at a future where Ph-positive ALL can be controlled—or even cured—with minimal therapy and without chemotherapy or transplant," said Dr. Stock in the interview.

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Ide-cel Shows Strong Results in Older Patients With Myeloma

*By **Dean Patterson***

The KarMMa-3 subgroup readout on older adults with relapsed or refractory myeloma provides a clearer view of how idecabtagene vicleucel (ide-cel) performs in the age group most oncologists see every day. Myeloma is primarily a disease of aging, yet trial rosters rarely reflect that. The gap has been evident for years, and this analysis tries to close at least part of it.


Sikander Ailawadhi, MD

"It was important to do this analysis, as clinical trials frequently do not represent the real-world population," **Sikander Ailawadhi, MD,** of Mayo Clinic, told *Blood Cancers Today*. "The average age at the time of diagnosis of multiple myeloma is around 70 years. Yet, clinical trial populations are frequently younger. Assessing the benefit and safety in the older patients is extremely important, so that the applicability of clinical trial results in the real-world setting can be better assessed."

KarMMa-3 enrolled adults who had already cycled through multiple treatments. Patients were randomized 2:1 to either a single ide-cel infusion or one of five standard regimens. The investigators split outcomes into two groups: those aged 70 years or older and those less than 70 years. That division alone creates some noise, since the younger ide-cel group came in with more high-risk disease, more cytogenetic risk, and more triple-class refractory disease than the older patients. So, the cleaner profiles of the older group must be kept in mind as the numbers roll out.

In patients 70 and up, the overall response rate with ide-cel reached 81.6%. The standard therapy group landed at 48.1%. Progression-free survival spread even further apart: 18.9 months with ide-cel compared with 5.7 months on standard regimens. Younger patients showed similar trends, but the older group results were sharper than expected.

"Quality-of-life studies were also better in older patients treated with ide-cel as compared to those who received standard treatments," Dr. Ailawadhi said. "No new safety signals were seen for ide-cel in the older patients. These observations reinforce the potential for durable benefit with a single ide-cel infusion in a real-world context without additional adverse safety signals, supporting its use across age groups."

Cytokine release syndrome, neurotoxicity, and infection rates were closely matched between the younger and older groups. Overall survival was not mature for the older cohort, so that piece will take more time to shake out.

One issue that hangs over the analysis, according to the investigators, is selection bias. The older patients who make it into a trial like this often look quite different from the older adults oncologists treat every week. Real-world data suggest that clinics are using ide-cel in a broader, more complicated population.

Whether these results will stretch to those patients is still unclear, setting the stage for the next round of questions clinicians seek to answer: How far can these outcomes be pushed into a more representative older population? And at what point does age stop being a meaningful dividing line when deciding whether to pursue chimeric antigen receptor T-cell therapy in late-line myeloma?

Those answers are still coming, but this slice of KarMMa-3 is likely to push more clinicians to rethink how they approach older candidates for ide-cel.

Reference

Ailawadhi S, et al. 67th American Society of Hematology Annual Meeting & Exposition. Abstract No. 2297.

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 (CLL).*

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Matthew Davids, MD

CHRONIC LYMPHOCYTIC LEUKEMIA

Real-World Cost Data Compare Acalabrutinib Versus Ibrutinib in First-Line CLL

By ***Dean Patterson***

A new paper in the *Journal of Comparative Effectiveness Research* takes a close look at how real-world costs compare for the Bruton's tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib when used as a first-line therapy for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Lindsey Fitzgerald, MD

Using the US Veterans Health Administration (VHA) database, **Lindsey Fitzgerald, MD,** of Huntsman Cancer Institute at University of Utah in Salt Lake City, and colleagues examined what patients and payers actually spend once treatment begins, including hospital care, outpatient visits, and pharmacy expenses.

The team found that patients treated with ibrutinib tended to have slightly lower, though comparable, total healthcare costs than those who started on acalabrutinib. Specifically, there were higher pharmacy costs in the acalabrutinib group, the primary cause of the slight cost difference found between the two groups, while the combined medical costs of inpatient, outpatient, and emergency department care were higher in the ibrutinib group.

The analysis focused on adults who initiated first-line monotherapy with either agent for CLL or SLL for at least 12 months. Follow-up extended long enough to capture treatment patterns and healthcare use after initiation, though the abstract does not state the median duration. The investigators acknowledged that because of the type of data used for analysis, their study could not address disease-specific measures such as response or progression-free survival.

While randomized trials have shown comparable efficacy between BTK inhibitors, real-world differences in toxicity and persistence on therapy can affect overall costs. Dr. Fitzgerald's team noted that this type of economic data may help inform formulary and payer decisions, especially with the multiple BTK inhibitor agent options now available.

As with any retrospective claims study, the findings come with caveats. The analysis lacked details on disease stage, cytogenetics, and treatment intent, and cost structures vary widely across health systems. The researchers also acknowledge that, in particular, in the context of the VHA, contracting agreements may have effects on the apparent cost advantage of different treatments.

Even so, the study fits a growing trend in oncology toward evaluating value beyond response rates. For clinicians, it offers a practical look at how two widely used CLL therapies play out in everyday practice, where adverse-event management, adherence, and patient comorbidities can drive costs as much as drug pricing itself.

The authors conclude that, based on these real-world economic data, acalabrutinib and ibrutinib deliver largely similar total healthcare costs in first-line CLL and SLL care, though these may be slightly lower with ibrutinib due to the pharmacy costs aspect. Whether that translates to better long-term value will depend on future studies that combine cost metrics with clinical outcomes such as duration of therapy and quality of life.

Reference

Fitzgerald T, et al. *J Comp Eff Res.* 2025;14(11). doi:10.57264/cer-2025-0084

Bexobrutideg Shows Safety and Durable Activity in Early Relapsed/ Refractory CLL Study

By ***Jill Elaine Hughes***

Bexobrutideg, a novel Bruton's tyrosine kinase inhibitor (BTKi), was well tolerated at all doses as treatment for relapsed or refractory chronic lymphocytic leukemia (CLL) in the first-in-human, phase 1a trial.

This study is the latest in a series of early-stage clinical trials of novel genetic oncology inhibition agents with **Alexey Danilov, MD, PhD,** as lead investigator. Updated findings were presented at the 2025 Lymphoma, Leukemia & Myeloma Congress.

Alexey Danilov, MD, PhD

Dr. Danilov and colleagues evaluated use of bexobrutideg in the context of emerging BTKi-resistant mutations that result in independent tumor signaling via BTK scaffolding function. "Bexobrutideg is a novel, orally administered small molecule degrader that induces removal of wild-type and mutant BTK through ubiquitination by the cereblon E3 ligase complex and subsequent proteasomal degradation," the authors explained.

The multicenter trial established bexobrutideg's wide tolerability and strong efficacy for patients with CLL that had proven refractory to two or more prior lines of treatment. The study's primary objectives were assessment of safety and tolerability and determination of the recommended dose for phase 2.

Enrolled patients received treatment at six daily oral dose levels: 50 mg (n=3), 100 mg (n=5), 200 mg (n=9), 300 mg (n=8), 450 mg (n=7), and 600 mg (n=16). Median age was 68.5 years (range, 35-88 years); 66.7% of patients were male.

Forty-seven patients were response evaluable for CLL, with an overall response rate of 80.9% (1 complete response and 37 partial responses). Observed responses were rapid (median time to first response, 1.9 months; range, 1.6-11.1 months). Of note, 47 of 48 patients had genetic testing information available, with the following represented mutations: *TP53* (44.7%), *BTK* (38.3%), *PLCG2* (14.9%), and *BCL2* (12.8%).

No dose-limiting toxicities were observed. One treatment-emergent adverse event (TEAE) unrelated to bexobrutideg (pulmonary embolism in a patient with a history of atrial fibrillation) resulted in a single discontinuation.

The most common TEAEs included purpura/contusion, diarrhea, fatigue, neutropenia, rash, petechiae, and headache, with no systemic fungal infections or new-onset atrial fibrillation observed.

"Bexobrutideg showed rapid and durable responses independent of prior treatment or high-risk features," Dr. Danilov and colleagues reported. "Phase 1b dose-expansion cohort enrollment is complete; enrollment is ongoing in additional phase 1b sub-population cohorts and pivotal trial(s) initiation is planned later in 2025."

Reference

Danilov A, et al. 2025 Lymphoma, Leukemia & Myeloma Congress. Abstract No. PO48.

Phase 1 Results Advance Study of Oral BTK Degrader for CLL and SLL

*By **Andrew Moreno***

CaDAnCe-101 is an international phase 1/2, open-label study to assess oral monotherapy of the Bruton's tyrosine kinase (BTK) degrader BGB-16673 for relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

The study is conducted by a team of researchers led by **Inhye Ahn, MD,** of the Dana-Farber Cancer Institute in Boston, Massachusetts. The phase 1 efficacy and safety results from this ongoing study were presented at the 2025 American Society of Hematology (ASH) Annual Meeting & Exposition in Orlando, Florida.

Inhye Ahn, MD

Based on their presented data, Dr. Ahn and coauthors concluded that "BGB-16673 has a tolerable safety profile and shows robust and deepening responses in patients with heavily pretreated R/R [relapsed or refractory] CLL/SLL, including those with prior BTK inhibitor treatment and *BTK* mutations."

The 67 patients enrolled for the study with confirmed relapsed or refractory CLL/SLL had a median age of 70 years. In 65.7% of the patients, the disease featured a *del(17p)* and/or *TP53* mutation, in 77.6% *IGHV* was unmutated, in 38.1% a *BTK* mutation was present, and 15.9% of patients had a *PLCG2* mutation.

The patients enrolled for the study had undergone at least two prior interventions, and the cohort had a median of four prior treatment lines. Of these patients, 94.0% of the cohort had received prior covalent BTK inhibitors (BTKis) and 20.9% had received non-covalent BTKis. For this study, the patients received once-daily 50 mg, 100 mg, 200 mg, 350 mg, or 500 mg oral BGB-16673.

The cohort's median study follow-up was 18.0 months. Response was evaluable in 66 patients, and the median time to first response was 2.8 months. The overall response rate (ORR), defined as a partial response with lymphocytosis, was 86.4%, and the team reported that responses deepened over time.

The ORR at 200 mg of BGB-16673 was 93.8%. The team highlighted that this would be the dose level used as the study proceeds into phase 2 and phase 3.

The response specifically among patients with *BTK* mutations was 75.0%, among patients without *BTK* mutations was 92.3%, among patients with a *del(17p)* and/or *TP53* mutation was 81.4%, and among patients with a *PLCG2* mutation was 90.0%. In patients previously treated with a covalent BTKi, the response was 85.5%, and with a noncovalent BTKi, it was 71.4%.

Regarding safety and tolerability results, 95.5% of the cohort experienced treatment-emergent adverse events (TEAEs) of any grade. The types of these TEAEs that affected at least 25% of the cohort were fatigue, contusion or bruising, diarrhea, and neutropenia, with prevalences of 37.3%, 31.3%, 28.4%, and 28.4%, respectively. Grade 3 or higher TEAEs affected 62.7% of the cohort, and the specific TEAE types that occurred in at least 5% of patients were neutropenia, pneumonia, and thrombocytopenia, with prevalences of 23.9%, 10.4%, and 6.0%, respectively. TEAEs that were attributed to the study treatment affected 4.5% of the cohort and were in the form of disseminated aspergillosis, maculopapular rash, and subdural hemorrhage.

At the phase 1 data cutoff, 58.2% of the cohort continued treatment. In 17.9% of the cohort, TEAEs led to treatment discontinuation. Death due to TEAEs occurred in 6.0% of the cohort, all of which were due to infection and none considered to be related to the study treatment.

Reference

Ahn I, et al. 67th American Society of Hematology Annual Meeting & Exposition. Abstract No. abs25-8349.

Head-to-Head Phase 3 Study: ORR Data Favor Pirtobrutinib Over Ibrutinib in CLL, SLL

*By **Andrew Moreno***

In a phase 3 study, investigators carried out a head-to-head comparison of the noncovalent Bruton's tyrosine kinase inhibitor (BTKi) pirtobrutinib with the covalent BTKi ibrutinib in management of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The overall response rate (ORR) data they report favor the noncovalent agent, pirtobrutinib.

This first-of-its-kind randomized study was conducted by an international team of clinical investigators led by **Jennifer Woyach, MD,** of the Ohio State University Comprehensive Cancer Center in Columbus. The findings were published online for the 2025 American Society of Hematology (ASH) Annual Meeting and Exposition in Orlando, Florida.

Jennifer Woyach, MD

In this study, the total population was 662 patients with CLL or SLL: 225 had untreated disease and 437 had covalent BTKi-naive relapsed or refractory disease. After randomization of the intent-to-treat population of 662 patients, 331 were administered pirtobrutinib 200 mg once daily and 331 were administered ibrutinib 420 mg once daily. In both cohorts, the median patient age was 67 years, and the median number of prior therapies was 1. Enrolled patients underwent treatment until unacceptable toxicity or disease progression occurred.

The primary end point in the study was for pirtobrutinib to show statistically significant noninferiority in ORR relative to ibrutinib. The primary end point was accomplished in the intent-to-treat population, with pirtobrutinib (the noncovalent BTKi) having produced an ORR of 87.0%, versus 78.6% with ibrutinib (the covalent BTKi), and an ORR ratio of 1.11 (2-sided $P<0.001$).

Pirtobrutinib demonstrated this ORR noninferiority again in the subcohort of patients who had covalent BTKi-naive relapsed or refractory disease, having produced in this group an ORR of 84.0% versus 74.8% with ibrutinib and an ORR ratio of 1.12 (2-sided $P<0.001$). For patients with untreated disease, ORR was higher with pirtobrutinib therapy than with ibrutinib at 92.9% versus 85.8%, respectively.

The investigators indicated that progression-free survival data in the study, although not yet mature, have also favored pirtobrutinib over ibrutinib. They calculated a hazard ratio of 0.57 in the intent-to-treat population over a median follow-up of 21.8 months, 0.24 in patients with untreated disease over a median follow-up of 22.5 months, and 0.73 in patients with covalent BTKi-naive relapsed or refractory disease over a median follow-up of 18.2 months. Pirtobrutinib recipients had to discontinue treatment due to progressive disease less frequently than ibrutinib recipients, at 4.5% versus 10.9%, respectively.

The investigators described the two BTKi agent cohorts as resembling each other in terms of treatment-emergent adverse events (AEs). However, incidence of certain AEs was lower in the pirtobrutinib cohort than in the ibrutinib cohort, with atrial fibrillation or flutter experienced by 2.4% of pirtobrutinib recipients versus 13.5% of ibrutinib recipients, and hypertension, by 10.6% of pirtobrutinib recipients versus 15.1% of ibrutinib recipients. Moreover, AE-related dose reductions were less common with pirtobrutinib than with ibrutinib at 7.9% versus 18.2%, respectively, and 81.3% of pirtobrutinib recipients are still receiving their treatment versus 69.5% of ibrutinib recipients.

Reference

Woyach J, et al. 67th American Society of Hematology Annual Meeting & Exposition. Abstract No. abs25-2587.

HemOnc Happenings

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

Esteemed Hematologist-Oncologists Elected to National Academy of Medicine

*By **Melissa Badamo***

Michel W. Sadelain, MD, PhD, and **Omar Abdel-Wahab, MD,** were recently elected to the National Academy of Medicine (NAM) for their excellence in the field of health and medicine and commitment to leading major blood cancer discoveries. The election is considered one of the highest honors in health and medicine.[1-3]

Michel W. Sadelain, MD, PhD

Omar Abdel-Wahab, MD

Dr. Sadelain, a pioneer in chimeric antigen receptor (CAR) T-cell therapy, serves as director of the Columbia Initiative in Cell Engineering and Therapy. He identified CD19 as a CAR target, leading to novel therapeutic breakthroughs for patients with relapsed or refractory leukemias. At the Sadelain lab, he is continuing to develop and advance novel cell-based therapies for blood cancers.[2]

"I am elated to see that cell therapies, which were viewed by some as mere academic exercises, are now recognized as pillars of contemporary medicine. I am humbled by the honor bestowed upon me by this eminent academy," Dr. Sadelain told *Blood Cancers Today*.

Dr. Abdel-Wahab serves as chair of the Molecular Pharmacology Program at Sloan Kettering Institute and an attending physician on the leukemia service at Memorial Sloan Kettering Cancer Center. At the Omar Abdel-Wahab lab, he leads clinical research on the role of genomic alterations that drive hematopoietic malignancies, including spliceosomal protein mutations in myelodysplastic syndromes and chronic lymphocytic leukemia.[1]

"It is a true honor to be inducted into the National Academy of Medicine and to represent the interests of blood cancer patients and the physicians and researchers working towards curing these cancers," Dr. Abdel-Wahab told *Blood Cancers Today*. "I would like to express my deepest gratitude to Drs. Deb Schrag, Joan Massage, and Ross Levine at Memorial Sloan Kettering Cancer Center who have supported my career development and promotion."

The NAM is a nonprofit organization that inspires positive action to address issues in health, science, medicine, and related policy. Each year, the NAM elects 100 health and medicine leaders during its annual meeting in October.[3]

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Immunology Researcher Robert Negrin, MD, Elected ASH 2026 President

*By **Melissa Badamo***

Robert S. Negrin, MD, a professor of medicine and former chief of the Division of Blood and Marrow Transplantation at Stanford University, has been elected 2026 president of the American Society of Hematology (ASH) during the Society's 67th annual meeting in December 2025.[1]

Robert S. Negrin, MD

With nearly 40 years as a hematologist-oncologist, Dr. Negrin has focused his research on cellular immunology, blood and marrow transplants, and graft-versus-host disease (GVHD) treatment and prevention.[2] He is currently studying natural killer T-cell therapy and is an investigator on the phase 3 PRECISION-T trial, presented at the ASH meeting, which showed that Orca-T improved GVHD outcomes compared with allogeneic transplant.[3]

Belinda Avalos, MD, a professor of medicine and a senior advisor to the president of Atrium Health Levine Cancer, passed the ASH gavel to Dr. Negrin during the meeting.[1]

"On behalf of the American Society of Hematology … I want to thank you [Dr. Avalos] for your extraordinary leadership during a very challenging time," Dr. Negrin remarked.[1] "We also have to recognize Belinda's incredible leadership skills, her resolve, her commitment to ASH over many decades, especially in this last year. I've learned a tremendous amount from Belinda, and I take this on with great enthusiasm as we continue the fight for hematology."

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Mount Sinai Tisch Cancer Center Receives NCI Comprehensive Cancer Center Designation

*By **Melissa Badamo***

The Mount Sinai Tisch Cancer Center in New York has received Comprehensive Cancer Center Designation from the National Cancer Institute (NCI) in recognition of its commitment to developing novel prognostic, diagnostic, and therapeutic approaches to cancer through state-of-the art research.[1,2] As part of this designation, the NCI will provide $3 million in annual funding to support and advance cancer research at Mount Sinai.

"This designation is a testament to the dedication and brilliance of our faculty, staff, students, and patients," **Ramon E. Parsons, MD, PhD,** director of The Tisch Cancer Institute and dean for Cancer Research at the Icahn School of Medicine at Mount Sinai, said in a press release.[1] "It affirms Mount Sinai's role not only as a place of scientific discovery but as a leader in bringing those discoveries to our patients."

Ramon E. Parsons, MD, PhD

Hematologist-oncologists at the Tisch Cancer Center have led numerous practice-changing clinical trials in blood cancer research, including the phase 1b/2 CARTITUDE-1 trial of ciltacabtagene autoleucel (cilta-cel) for relapsed or refractory multiple myeloma, which led to FDA approval of cilta-cel; the phase 3 MANIFEST-2 trial of ruxolitinib plus pelabresib for treatment-naive myelofibrosis; and a phase 2 trial of itacitinib for acute graft-versus-host disease.[1]

According to the NCI, Comprehensive Cancer Center Designation is attributed to centers that "meet rigorous standards for transdisciplinary, state-of-the-art research focused on developing new and better approaches to preventing, diagnosing, and treating cancer." There are currently 73 NCI-designated Comprehensive Cancer Centers in 37 states and the District of Columbia, and about 400,000 patients with cancer receive their diagnoses at an NCI-designated center.[2]

Mount Sinai will begin construction of the Mount Sinai Tisch Cancer Hospital in early 2026 to expand the center's cancer care and research, with a targeted opening date of early 2027.[1,3]

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