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With expert opinions from:
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and more

MAIL TO:

ASSOCIATE EDITOR
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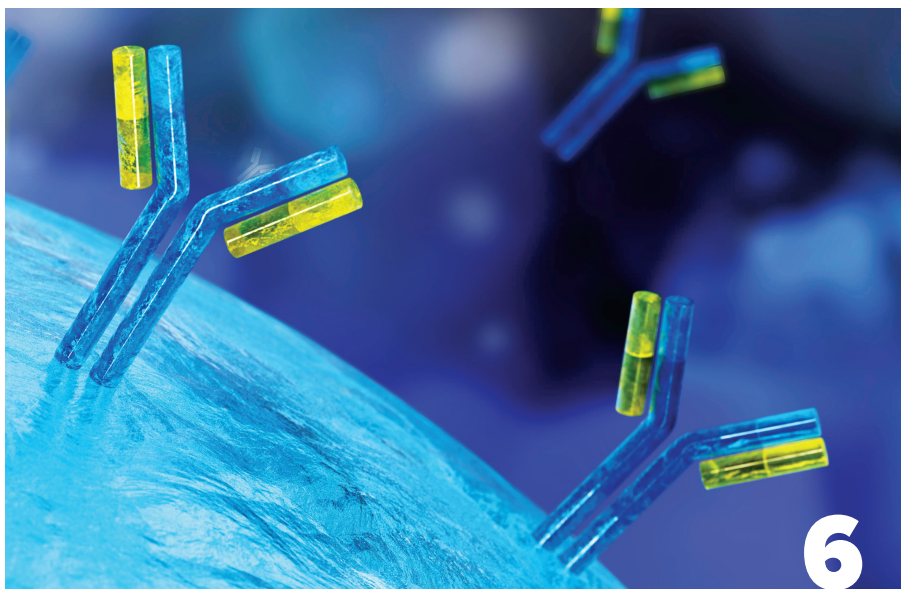

What's Old Is New

Old Technology Finds New Application in Plasma Cell Disorder Management

Early evidence has shown that mass spectrometry (MS) is likely more sensitive and specific at detecting the M protein in patients with myeloma than traditionally used methods such as protein electrophoresis and a serum free light chain assay. Now, researchers are working to refine the use of MS in plasma cell disorders and define and validate the ways in which it can aid in diagnosis and monitoring.

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About the Society of Hematologic Oncology
The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders. The Society's global network supports and is supported by members from more than 110 countries, who are leading the vital efforts to further treatments for those afflicted by these diseases.

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Calendar

March 1–2
Advanced Practice Providers Oncology Summit (APPOS) Charlotte 2024
Charlotte, North Carolina

March 4–6
American Association for Cancer Research (AACR) Blood Cancer Discovery Symposium
Boston, Massachusetts

March 8–9
Annual Meeting of the International Extranodal Lymphoma Study Group
Stresa, Italy

March 15–16
APPOS Boston
Boston, Massachusetts

March 18–21
European Hematology Association Research Conference 2024
Borovets, Bulgaria

April 3–6
2024 American Society of Pediatric Hematology/Oncology Conference
Seattle, Washington

April 3–6
Hematology/Oncology Pharmacy Association Annual Conference 2024
Tampa, Florida

April 5–7
National Comprehensive Cancer Network 2024 Annual Conference
Orlando, Florida

April 5–10
AACR Annual Meeting 2024
San Diego, California

April 12–13
7th Annual Hematology/Oncology Challenges and Advances in Patient Care for NPs, PAs, and Nurses
Fernandina Beach, Florida

April 12–14
9th Translational Research Conference
Budapest, Hungary

April 28–30
British Society for Haematology 64th Annual Scientific Meeting
Liverpool, United Kingdom

MARK YOUR CALENDARS
SEPTEMBER 4–7
2024 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas
https://soho.click/2024

Associate Editor's Message

Our 2024 Mission: Embrace Kindness, Share Knowledge, Be Part of SOHO

Thomas Martin, MD
Associate Editor

As we forge ahead into 2024 with excitement and optimism, I'd like to first take the time to reflect upon 2023 and how far we've come in the last three to five years regarding the treatment of blood cancers, including plasma cell disorders, lymphomas, and leukemias. The novel therapeutics and their use in specific patient populations and along various aspects of the treatment paradigm have led to proven benefits in progression-free survival (PFS) and overall survival (OS).

As a physician practicing at an academic center in the United States, I can't help but recognize how lucky "I" am and the collective "we" are to be practicing in a country that invests a significant percentage of our gross domestic product in health care, with a regulatory body like the US Food and Drug Administration that allows early access to breakthrough therapies. Because of those things, we're able to bring these therapies to patients who need them the most.

In the United States in 2022, two chimeric antigen receptor (CAR) T-cell products were approved for use after two independent, single-arm, phase II trials showed impressive responses in heavily pretreated patients with multiple myeloma (MM). Since then, close to 10,000 patients have received CAR-T therapy, the vast majority of whom were treated in the United States.

In 2023, an international group of researchers surveyed physicians from 33 countries to assess global access to novel therapies for MM. The results, published in *Blood*,[1] showed only three of the 33 countries had adequate access to ide-cel or cilta-cel and just seven of the 33 had access to teclistamab.

It was with this fact in mind that **Guillermo Garcia-Manero, MD,** the 2024 President of the Society of Hematologic Oncology (SOHO), selected "Translating Knowledge Worldwide" as the theme of the 2024 meeting. The plan is to have representation from all countries, including underserved countries, and to discuss the latest advances and best treatments for all patients, including those who may not have access to the novel and more expensive therapeutics.

I encourage everyone to participate in the SOHO Annual Meeting and, outside of the meeting, to help translate and transmit the knowledge you have cultivated to your peers.

In January 2024, we will be hosting a group of physicians from Latin America at the University of California, San Francisco (UCSF). One of the goals of this meeting is for us to provide real-world experience using novel therapeutics. The other goals are for us to understand the treatment landscape in Latin America and help deliver an optimized blueprint for implementing novel therapies locally.

We are very excited for this meeting (just as we are excited for SOHO 2024!) and look forward to the exchange of ideas.

The success of novel therapies in patients with MM cannot be overstated. My friend and colleague **Ajai Chari, MD,** often provides the historical context that prior to these novel therapies, when patients had exhausted or were refractory to our standard classes/agents, we generally began to consider supportive care options and hospice. Now, patients can receive CAR-T or bispecific antibody therapy (after the fourth line) and generally have the potential to live an additional two to three years or longer. What I'm really excited about is all the novel combinations that will soon be tested: CAR plus bispecific, bispecific plus CELMoD, and CAR plus CELMoD. These therapies will be evaluated earlier in the myeloma treatment paradigm, including in the frontline setting.

In 2023, we heard results from two phase III trials investigating CAR-T therapy versus standard triplet or doublet therapy in patients with early relapsed MM. Both studies reported improvements in PFS for patients in the CAR-T arms. However, in both studies there was also an early dip in OS in the CAR-T arms, which was worrisome due to the potential of early "harm."

These findings need to be further explained and interrogated, and it will be interesting to see how the regulators interpret the results. That said, it is inevitable that these therapies will be used throughout the myeloma treatment paradigm, and the next four to five years will help define and optimize the best timing and sequence of novel agents.

Lastly, upon return from the 65th American Society of Hematology Annual Meeting & Exposition, and following the many hematology meetings throughout the year, I'm always impressed by the collegial nature of our community. It makes such a big difference. We all need to support each other and especially our junior faculty. In this world filled with misinformation and turmoil, it is amazing to be working as good friends and peers.

Reference

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***Thomas Martin, MD,** is the Clinical Research Director of Hematologic Malignancies at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.*

Get to Know

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

Ching-Hon Pui, MD

Dr. Pui, Co-Leader of the Hematological Malignancies Program at the St. Jude Children's Research Hospital in Memphis, Tennessee; Director of the China Program at St. Jude Global; and an American Cancer Society professor, discusses his lifelong commitment to being a pediatric oncologist.

Where did you grow up, and when did you know you wanted to be a physician-scientist?
When I was in middle school, I saw a movie about the touching story of a young boy who was exposed to radiation from an atomic bomb explosion and later died of leukemia. This narrative left an indelible impression on me. I have always wanted to help children with leukemia. However, I had no idea what I wanted to be when I was growing up in Hong Kong. As my senior year of high school drew to a close, I approached my favorite biology teacher for advice. He encouraged me to become a medical doctor. My parents, who had not been afforded the opportunity to go to school, always emphasized the importance of education to me and my two brothers and three sisters. They dreamed that at least one of us would become a doctor one day.

Since we could not afford tuition at the medical school of the Hong Kong university, I went to study at the National Taiwan University, where I was granted a full scholarship. After I graduated from medical school, my brother, who was studying at the University of Minnesota, encouraged me to join him in the United States. After a year as an intern in St. Louis, I was granted a residency at St. Jude. It was during my time at St. Jude that I encountered the same movie that had profoundly affected me in middle school. Recognizing St. Jude as the ideal environment for fulfilling my passion for aiding children with leukemia, I decided to make it my lifelong commitment. Thus, I have dedicated my entire career to St. Jude, a place where my aspirations align seamlessly with the impactful work being done.

Were there any particular mentors who shaped your career path?
I was lucky that **Joseph Simone, MD,** who was the Chief Medical Officer and later became the third director of St. Jude, took an interest in me. When I was a junior faculty member, he assigned me to report the results of the TOTAL Therapy Study IX, the flagship protocol of St. Jude. St. Jude has always had a strong acute lymphoblastic leukemia (ALL) study team, which generates and builds up a rich database. Joe would encourage me and others to take advantage of it to publish and share the results with colleagues around the world. He provided me with the inspiration to do the same for junior faculty who came after me.

I also was very fortunate that **William Evans, PharmD,** who is one of the smartest people I have ever met, joined St. Jude one year before I did, and became the institution's fifth director. We share the same research interest and regularly brainstorm with each other to come up with projects and develop new protocols. We have collaborated on a lot of research, merging his basic science and laboratory expertise and my clinical and translational experience. We have co-authored over 200 publications.

"The observations by epidemiologists that children who attended day care or had microbial exposure early in life have a lower risk of developing ALL suggest that some preventive measures could be developed."

I have also been blessed by the strong support of St. Jude's other directors, **Arthur Nienhuis, MD,** and now **James Downing, MD,** who provided resources and promoted me academically.

All my interactions with these incredible mentors and colleagues made me the person I am today. I am not a particularly vocal person, partly because of my upbringing in Asia more than half a century ago, where students were discouraged from speaking up. Therefore, I teach and mentor people by example.

How do you approach patient care?
Patient care is my priority, and I treat my patients as if they were my children. I make sure we offer them the best treatment at the earliest possible time. I am very grateful to numerous colleagues who helped me achieve this goal over all these years. Being a pediatric oncologist is very rewarding, and my patients have taught me how to be courageous and resilient.

What still needs to be done in pediatric ALL?
Although we have raised the cure rate to more than 90%, we still have a lot of work to do. We need to push the cure rate toward 100% and, of equal importance, improve the quality of life for patients and their families. We need to replace toxic chemotherapies with novel molecular therapeutics, immunotherapies, and cellular and genetic treatments. We also need to find ways to identify patients so we can safely shorten the current treatment duration of two to two-and-a-half years.

Surviving patients suffer from many side effects, and many of them die earlier than their siblings due to the treatment-induced complications or development of second cancer. In this regard, at least 5% of patients have a cancer susceptibility gene. We need to identify not only these patients but also their family members who carry the gene for monitoring and intervention to reduce the risk and provide early treatment of second cancer. We also need to develop cost-effective treatments or other mechanisms to make curative treatments available for patients who reside in low- and middle-income countries. Finally, the observations by epidemiologists that children who attended day care or had microbial exposure early in life have a lower risk of developing ALL suggest that some preventive measures could be developed.

What would people be surprised to learn about you?
I like action movies, such as *Mission Impossible.* Also, I wake up at 4 AM to start answering the more than 200 emails a day I receive from individuals who live all over the world, including Asia and the Middle East. Anything related to a patient, I always answer. It is my weakness.

***Ching-Hon Pui, MD,** is Co-Leader of the Hematological Malignancies Program at the St. Jude Children's Research Hospital in Memphis, Tennessee; Director of the China Program at St. Jude Global; and an American Cancer Society Professor. He is also the 2024 recipient of the Society of Hematologic Oncology Emil Freireich Distinguished Pioneer Award.*

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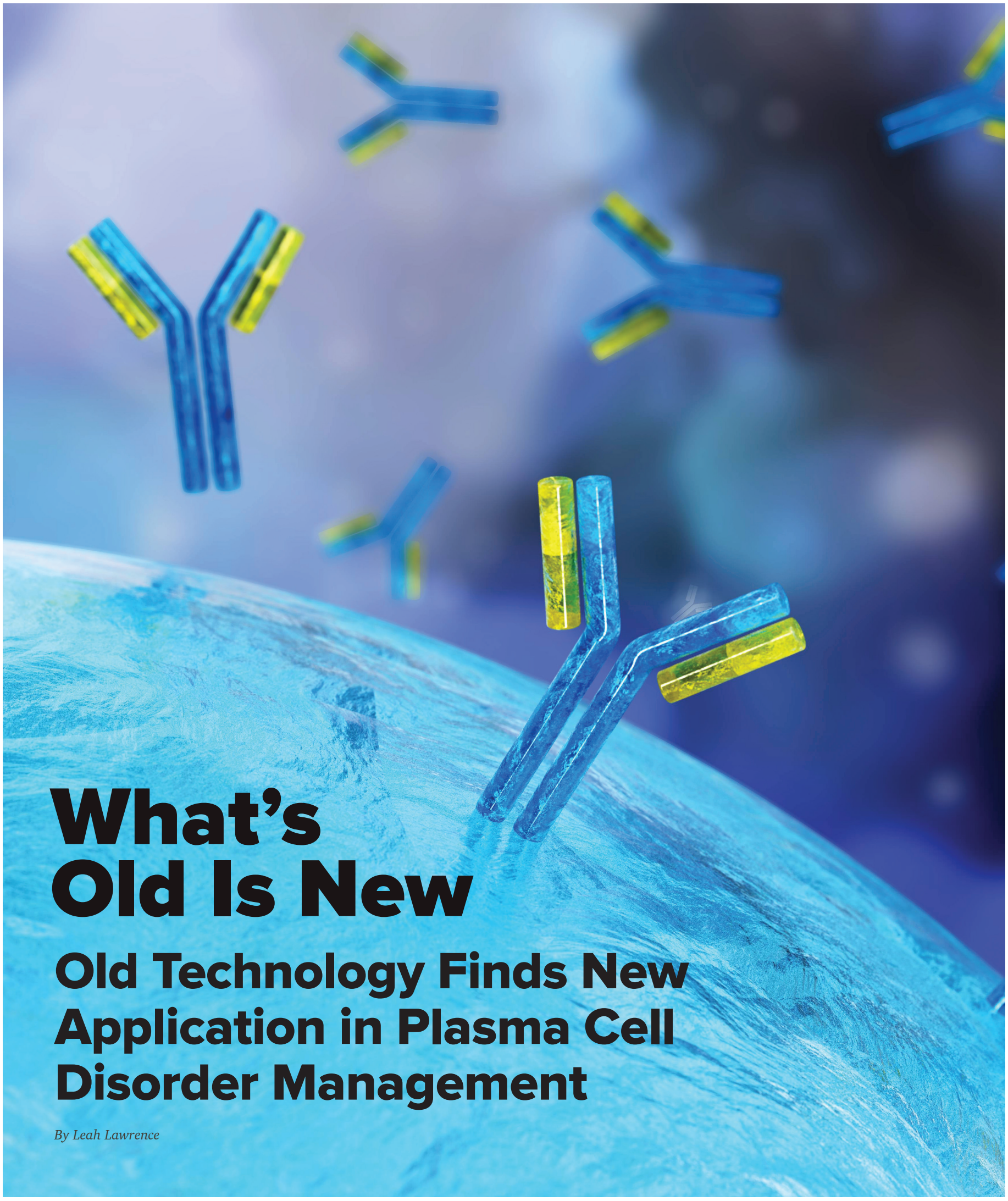

What's Old Is New

Old Technology Finds New Application in Plasma Cell Disorder Management

By Leah Lawrence

Every patient diagnosed with multiple myeloma (MM) has a unique monoclonal protein (M-protein), the abnormal protein produced by plasma cells. In the current management of MM, the M-protein is typically measured in the blood or urine using protein electrophoresis and a serum free light chain (FLC) assay. However, researchers and some medical institutions have begun to apply an age-old technology—mass spectrometry (MS)—to the diagnosis and monitoring of patients with plasma cell disorders.

"MS can be used to evaluate any complex chemical protein or subprotein in liquid samples, but the main focus of this methodology in MM is evaluating for the presence of M-protein," explained **Andrzej Jakubowiak, MD, PhD,** a Professor of Medicine and Director of the Myeloma Program at the University of Chicago.

Early evidence has shown that the technique is likely more sensitive and specific than serum or urine electrophoresis or a serum FLC assay and may yield advantages for clinicians and patients. Now, researchers are working to refine the use of MS in plasma cell disorders and define and validate the ways in which it can aid in diagnosis and monitoring. *Blood Cancers Today* recently spoke with Dr. Jakubowiak and other experts in the field to get their insight into MS-based proteomics and its potential role in the future of MM.

Finding a New Way

For more than 50 years, gel electrophoresis has been a standard for detecting M-protein, explained **Hannah Giles, MD,** of the University Hospitals Birmingham NHS Foundation Trust in the United Kingdom. This technology puts a patient's serum on an agarose gel and subjects it to an electrical current, which causes the proteins to migrate based on their electrical charge. The gel is stained with a dye and run through a light scanner. An M-protein is identified by the presence of a sharp, well-defined band with a single heavy chain. A similar band is seen with a kappa or lambda light chain.[1]

Serum FLC assays measure free light chains—a small part of the immunoglobulin or M-protein—and rely on evaluating the levels of the light chains and the ratio between two light chains. If there is a clonal disorder, the ratio will skew in one direction.

"Serum protein electrophoresis [SPEP] tests are not too expensive, are widely available, and have established criteria on how to monitor patients, but they have a limited degree of sensitivity," Dr. Giles explained.

For example, in a small proportion of patients, the myeloma cells produce very small amounts of monoclonal protein. These patients are more of a diagnostic challenge, and clinicians must rely on other diagnostic tests, such as serial bone marrow tests or imaging scans, which can be painful and invasive.

Additionally, SPEP lacks specificity. A restricted gamma band can be due to causes other than M-protein, such as fibrinogen, various levels of hemolysis, or high rheumatoid factor.[2] If an abnormality is detected, that sample is then sent for immunofixation (IFE), which can identify the abnormal protein.

"This method takes a while and is labor intensive," said **David L. Murray, MD, PhD,** an Assistant Professor of Laboratory Medicine and Pathology in the Division of Clinical Biochemistry at the Mayo Clinic. "When I joined the lab at Mayo, we set out to try to do something new and ended up ... with this MS method for detecting M-protein."

MS Methods

MS takes samples, ionizes them into charged molecules, and measures their mass-to-charge ratio. Multiple MS methods have been developed, and researchers hope to adapt these methods for multiple uses within the diagnosis and management of plasma cell disorders.

One MS method employs immunoglobulin trypsin digestion to break proteins into peptides and detect peptides specific to the M-protein complementarity determining region (CDR); this process is sometimes called the clonotypic peptide approach, Dr. Murray said.

"We started with this method at Mayo, but it uses really expensive mass spectrometers," Dr. Murray noted. "Ninety-five percent of these [machines] are used for research purposes and not in the clinic. I thought this was a difficult and unreliable method that required a lot of knowledge."

Instead of using trypsin digestion, a simpler approach uses reagents and washes to isolate the immunoglobulins and remove nonimmunoglobulin proteins. The immunoglobulins are then treated to separate the light chains and spotted onto specialized plates, which are analyzed by MS. Referred to as intact light chain assays, this method can be done using liquid-chromatography mass spectrometry (LC-MS), and the assay is known as monoclonal immunoglobulin rapid accurate mass measurements, or miRAMM.[2,3] Later, this method was for use with higher-throughput mass spectrometers using a form of MS called matrix-assisted laser desorption ionization time of flight (MALDI-TOF) MS.

"Instead of migrating through a gel, they migrate through a vacuum," Dr. Murray said. "They acquire a charge and fly from the bottom of the tube to the top, and we time how long it takes to get there. That is what happens when we measure mass."

The MALDI-TOF MS assay developed by the Mayo Clinic is often referred to as MASS-FIX in the literature, and it replaced SPEP and IFE at the Mayo Clinic in 2018. Mayo patented miRAMM and MALDI-TOF MS and licensed the methodology to Thermo Fisher under its Binding Site Division. Thermo Fisher has developed a commercialized MALDI-TOF MS assay (the brand name is EXENT, but it is also sometimes referred to in the literature as QIP-MS).

Why Better?

The MALDI-TOF MS assays are simpler and faster than traditional electrophoresis methods and appear to be more sensitive and specific.

Among the evidence in support of this approach is an early study from Mayo, which compared serum and urine MASS-FIX with SPEP, IFE, and FLC and identified 18 patients with negative results on SPEP/IFE and serum FLC who had positive M-proteins on MASS-FIX. Of the 18 patients, 10 had MM or amyloid light chain (AL) amyloidosis but were thought to have had complete hematologic response by serum/urine PEP/IFE and serum FLC.[4] A larger subsequent study showed that MASS-FIX was able to identify M-protein in patients with a wide variety of plasma cell disorders.[5]

One validation study of the method showed that MALDI-TOF MS detected M-protein in 100% of samples that were positive by SPEP and IFE and the majority of samples that were positive by IFE but negative by SPEP. MALDI-TOF MS identified one additional positive sample among those that tested negative by both SPEP and IFE.[6]

"MASS-FIX is a very powerful alternative to IFE," Dr. Jakubowiak said. "It is able to pick up an additional 20% of patients negative by IFE for presence of M-protein."

Another advantage of MS is its ability to distinguish between a patient's M-protein and a therapeutic monoclonal antibody.

"These days, a lot of patients will receive a monoclonal antibody, and patients with immunoglobulin G kappa monoclonal protein given a monoclonal antibody can get interference," Dr. Giles said. "With MS you get a specific mass-to-charge ratio, allowing you to differentiate between residual disease and the therapeutic monoclonal antibody in most patients just using the standard MS assay."

Finally, **Faith E. Davies, MD,** Director of the Clinical Myeloma Program at Perlmutter Cancer Center at New York University, pointed out that there is still a small percentage of patients with MM, low-grade monoclonal gammopathy of undetermined significance (MGUS), or AL amyloidosis who have a clone that cannot be detected on SPEP or serum FLC, but it can be detected on MS.

Drs. Davies, Giles, and colleagues conducted a small study in patients with nonmeasurable MM and showed that 91% of patients had detectable M-protein by MS at presentation, indicating that these patients with "nonmeasurable" disease do have low-level secretion.[7] The ability to measure M-protein in these patients should allow for better monitoring of their disease.

Other Potential Uses

The International Myeloma Working Group has approved MS methodologies in lieu of IFE, and Thermo Fisher launched its EXENT Solution technology commercially in Europe in August 2023. The package includes a preparation instrument, a MALDI-TOF mass spectrometer, and software for data review.[8]

Additional data out of the 65th American Society of Hematology Annual Meeting & Exposition supported the use of EXENT for the diagnosis and monitoring of MM and other plasma cell disorders. One study of 460 patients showed a diagnostic sensitivity of MS of 95.0% with a diagnostic specificity of 68.2%, which the researchers said was impacted by detection of minor M-proteins not detectable on SPEP.[9] MS demonstrated similar, if not superior, sensitivity compared with SPEP and a high concordance with IFE for the M-protein isotype.

In addition to its possible role of more widely replacing SPEP and IFE, MALDI-TOF is also being used to measure M-protein as a way of measuring response via measurable residual disease (MRD), Dr. Jakubowiak said.

In Focus

"At the moment we usually use SPEP to monitor for response, and when we get below the detection limit for SPEP we switch to doing bone marrow tests and start using next-generation sequencing [NGS] or flow cytometry for evidence of myeloma in the bone," said Dr. Davies. "Everyone is keen to have a blood-based marker of MRD."

Dr. Davies said it is possible that blood-based MS techniques may be able to serve as a "bridge" between SPEP and 10^{-6} MRD bone marrow testing.

"We have found that certain more advanced MS techniques can be comparable [with] MRD evaluation by bone marrow-based techniques," Dr. Jakubowiak said.

A study comparing MALDI-TOF MS in peripheral blood with next-generation flow (NGF) cytometry in bone marrow in 71 patients with MM found concordance between methods for 62% of patients (44/71); eight patients were positive using both methods and 36 were negative for both. An additional 17 patients were detectable only by MALDI-TOF, and 10 patients were detectable only by NGF.[10] The samples studied were not paired samples.

Dr. Jakubowiak and colleagues also published the results of a phase II analysis where they compared MS—both LC-MS and MALDI-TOF MS—in the peripheral blood with SPEP/IFE, positron emission tomography/computed tomography imaging, multiparametric flow cytometry, and NGS in the bone marrow in 76 patients with newly diagnosed MM enrolled in a study of KRd. MALDI-TOF MS was at least as sensitive as MRD by NGS, with limit of detection of less than 10^{-5} in the bone marrow.[11]

MRD assessment using LC-MS increased sensitivity. For some paired samples LC-MS was superior to the current standard of MRD negativity, with limit of detection less than 10^{-5}, and was at least as sensitive as MRD by NGS, with limit of detection less than 10^{-6}.

A more recent analysis comparing MRD assessment with MALDI-TOF MS and MS-LC in peripheral blood and NGS again showed that LC-MS could possibly exceed the sensitivity of MRD by NGS in the marrow, with a sensitivity threshold of 10^{-6}.[12]

"MS with or without liquid chromatography has limitations," Dr. Jakubowiak said. "With this technique, at least at the moment, there is a requirement to have earlier samples where the M-protein is still present in reasonable abundance so you can identify the mass of M-protein. You have to have that original sample to know that the original M-protein is not detectable or substantially reduced."

In addition, Dr. Giles said that bone marrow-based tests still appear to be the very best, but they are also more expensive and invasive for the patient, and the high negative predictive value of the MS assays is encouraging.

"There are studies looking at the sensitivity of MS compared with a bone marrow-based assay," Dr. Giles said. "It could be that MS will become a supplement to bone marrow testing. We may wait until the patient tests negative in the blood before doing a bone marrow test."

Remaining Questions

One question related to MS that remains is whether the method is too sensitive in certain situations.

"Anyone who presents and is suspected of MM is screened with the gel method and FLC assay, and if MGUS is picked up you have to monitor it," Dr. Giles said. "If you are using MS and pick up something tiny, but the patient doesn't have any suggestive symptoms, when do clinicians assign them as having this precursor condition? What are the required concentrations? Is persistence needed for a certain period of time before you label it as MGUS?"

To illustrate this point, Dr. Murray discussed a screening study of the population of Olmstead County in Minnesota that originally found that 3.2% of people aged 50 or older had MGUS.[13] Subsequently, using the MALDI-TOF and miRAMM, Dr. Murray and colleagues identified a prevalence of 5.1% for MGUS among persons 50 or older.[14] Most recently, using data from a clinical biobank, MASS-FIX identified MGUS in 10.8% of European American and 16.5% of Black individuals aged 50 or older.[15]

Whether that low-level detection of M-protein is important to each patient, and how these patients should be managed clinically, will take time to figure out.

Another pending question relates to how widely MS will be adopted.

Up until now, a main barrier to wider use has been availability, Dr. Giles said. In the United States, Mayo Clinic has MASS-FIX and would perform testing for outside institutions, but the technology is not yet commercially available.

"Now that we have the approval in Europe, people are becoming more aware of the technologies and how much they cost," Dr. Giles said. "Moving forward, people will have to balance out how much they cost with how much information they provide."

Another potential barrier to more widespread adoption will relate to training of laboratory staff and education of physicians who have been using SPEP for many years, according to Dr. Davies.

Ultimately, each institution is likely to weigh the learning curve and associated costs of doing MS in-house against the cost of sending samples out for testing, Dr. Jakubowiak said. "Some places, including our own high-volume lab, have felt that it would be less expensive to send out samples to the Mayo Clinic lab," he continued. "We still get results very quickly…faster than FLC from our own lab."

For his part, Dr. Murray is excited to see wider adoption of MS techniques for plasma cell disorders.

"I think it will be similar to what happened with microbacteria. They switched to MALDI-TOF for identifying microbacteria and that slowly progressed to be the standard," said Dr. Murray, who admitted that he is biased in favor of the technology after seeing what it can do day in and day out.

__Leah Lawrence__ is a freelance health writer and editor based in Delaware.

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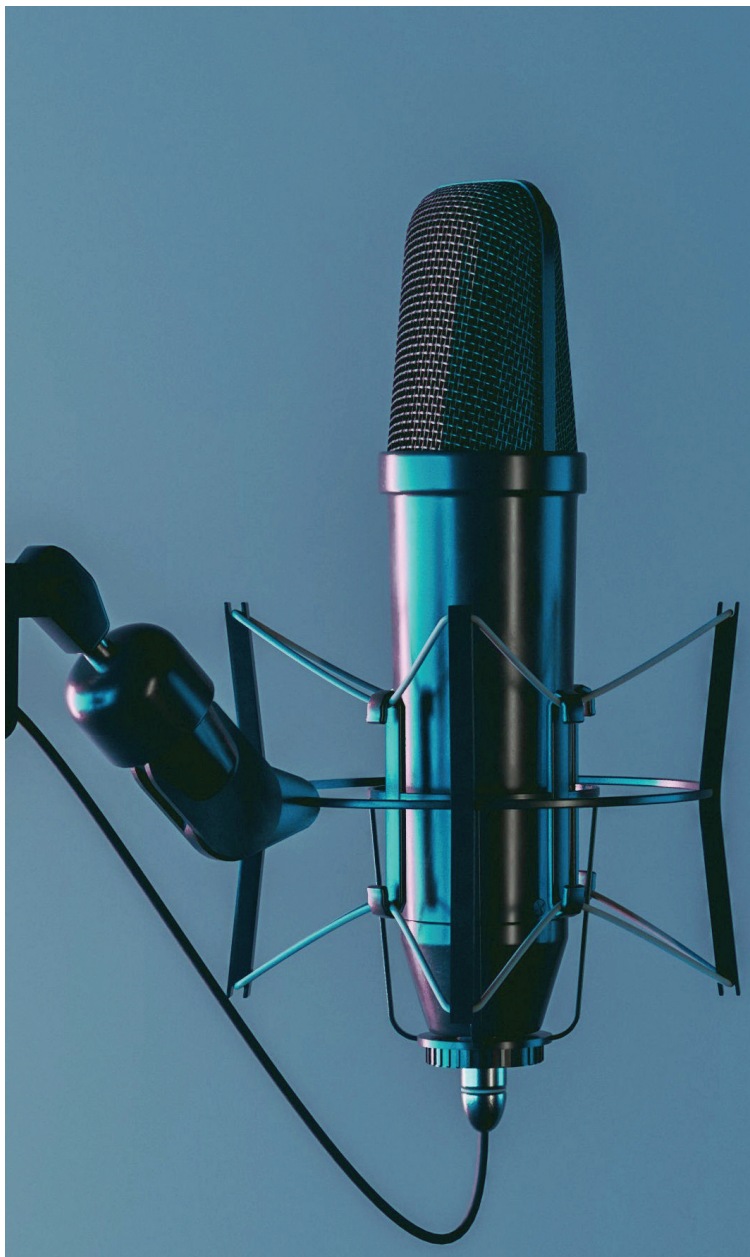


Clinician-Researcher by Day … Podcaster/ Social Media Guru by Night?

Hematologist-oncologists are increasingly turning to podcasts and social media to learn about new data and to share research findings with their peers.

Many might picture a hematologist-oncologist sporting a white lab coat and surgical mask inside a treatment center or research lab—not behind a microphone or a webcam. However, there are some who do both. Like two sides of a coin, they're clinicians by trade, podcast hosts on the side.

In fact, many of these podcasters are highly active on social media platforms like X, where they not only promote their own content but share clinical research and even post medical memes.

How do these clinicians balance their day jobs with social media posting and podcasting? **Chadi Nabhan, MD, MBA, FACP; Ronak Mistry, DO;** and **Edward Cliff, MBBS, MPH,** offered some tips for health care professionals looking to tread the social media waters.

Find a Niche

Those looking to build an online presence should focus on their specialty or area of expertise, according to Dr. Nabhan, host of "The HemOnc Pulse," a podcast sponsored by *Blood Cancers Today* and the Society of Hematologic Oncology.

"The HemOnc Pulse" covers a breadth of topics in the hematologic oncology space. Recently, Dr. Nabhan hosted a series on the 65th American Society of Hematology Annual Meeting & Exposition, in which expert guests such as **Jerald Radich, MD; Sangeetha Venugopal, MD;** and **Saad Usmani, MD, MBA, FACP,** discussed various meeting abstracts in acute myeloid leukemia, myelodysplastic syndromes, multiple myeloma, and more.

"We wanted to create a podcast dedicated to the world of hematologic oncology, which has become increasingly complex when it comes to the type of diseases that physicians are dealing with and the therapeutics that are required to be used or that physicians need to be aware of, especially as we have had many newer approved therapies recently," said Dr. Nabhan in an earlier interview with *Blood Cancers Today*. "This podcast is for folks who really prefer to consume information by listening."

"The HemOnc Pulse" covers crucial, thought-provoking topics such as coordinating care with complex therapies like chimeric antigen receptor T-cell therapy, navigating drug prices, and making care more affordable to patients.

Dr. Mistry, co-host of "The Fellow on Call: The Heme/Onc Podcast" along with **Vivek Patel, MD,** and **Dan Hausrath, MD,** also recommends finding a specific niche to define and drive your brand.

"Once you find a niche you would like to fill, work to figure out a very concrete vision and mission for your platform," he suggested. "What are you hoping to achieve? What is the audience experience supposed to be?" Before landing on a specific niche, Dr. Mistry recommends scoping out the type of content already being created.

"If you think you want to get into being more active on social media or in podcasting, spend

Field Dispatch

some time seeing what is already out there," he said. "Once you have an understanding of what is currently available, then you can figure out what is missing or how you can do something differently that would be beneficial for your audience."

With the ever-growing amount of multimedia and podcasting content getting pushed online daily, how do you make your content stand out?

"The key question is, does the type of podcast you're looking for exist already? There has been a proliferation of podcasts in oncology, hematology, and hematological oncology in the past couple of years," Dr. Cliff said.

Dr. Cliff hosts "Blood Cancer Talks" with **Rajshekhar Chakraborty, MD,** and **Ashwin Kishtagari, MD.** Their podcast draws in a wide range of experts, such as **Alexander Perle, MD; Nancy Bartlett, MD;** and **Michael Dickinson, MD,** to discuss the latest advances in blood cancers.

Shortly after the podcast's launch in 2022, Dr. Cliff jumped on board as the trio's designated lymphoma expert.

"Raj leads the plasma cell dyscrasias and myeloma side of things. Ashwin runs the myeloid side of things, and I lead the lymphoma episodes," he said. "We complement each other nicely in that sense."

Aside from blending perspectives from three corners of the hematology world, Dr. Cliff outlined the formula that helps their podcast thrive.

"The type of podcast we do is similar to a "How I Treat" article in *Blood*," he said. "We invite a world expert in an area, start with a case, and then go through that topic with the expert over the course of 45 minutes to an hour. I'm not sure anyone else is doing that in the same way as we are, and so I hope we have a unique value proposition."

Other than finding a niche topic and including field experts, there's another key ingredient to hosting a successful podcast—knowing your target audience.

"We have a reasonably good understanding of what our audience wants, because we are our target audience," Dr. Cliff said. "Our podcast is targeted to people with a strong interest in blood cancers—typically fellows, hematologists, and oncologists. It's very clinically focused, and we try to host the best people."

Be Yourself

Dr. Cliff has just over 4,000 followers on X, a platform he uses to share infographics, retweet clinical studies, and, of course, highlight the latest "Blood Cancer Talks" episodes.

"I get a lot of the scientific papers I read from Twitter (now X)," he explained. "I try to follow some of the best people in the field who are reading, sharing, and commenting on the most important articles."

Dr. Cliff mentioned another main reason he keeps coming back to X—it's faster and more accessible than email for gaining access to expert information.

"There aren't that many other forums that enable you to interact with world experts in such a straightforward, rapid, and easy way," he said.

Similarly, Dr. Nabhan shared a core reason he is drawn to platforms like X.

"Social media really started as a hobby," he said. "Then, I realized there are a lot of people on social media who are like-minded and who I could learn from and have a conversation with about medical topics."

However, while X is a convenient hub for knowledge sharing, Dr. Cliff highlighted the main reason the platform stands out—the sense of community it provides.

"The professional communities we build on X have been really powerful," he said. "That exists a little bit on other social media, but nowhere really as much as X."

Dr. Nabhan, who has over 18,000 followers on X, shared a similar sentiment on the value of online community building.

"I started enjoying the community I was building around me and getting to meet people I otherwise wouldn't have met. You're always limited by where you work and geography, but social media crosses and expands on these limits," he said.

"Social media really breaks all these barriers, and suddenly you could be communicating with someone who lives in Japan and collaborating with someone who lives in Europe."

This sense of friendship and community is ultimately what drives engagement in the form of likes, comments, shares, and follows. In fact, Dr. Nabhan highly encourages users to prioritize authenticity on social media. "Be authentic. Simply be who you are," he urged. "This is important for connecting with your audience and those who follow your work."

In order to build an audience, it's also crucial to let your real-world personality shine online.

"Keep it exciting, and it is okay to be silly every so often," reassured Dr. Nabhan. "This shows the human element of who we are and helps us connect easier with others."

This sense of connection is also ingrained in the foundation of "Blood Cancer Talks." Rather than merely lecturing their audience on a specific topic, Dr. Cliff and his colleagues engage in a didactic, interactive conversation with one another. "We go back and forth," he said. "If someone says something we're not sure about, we can delve deeper and go down tangents in a way that you don't get in a lecture."

Dr. Nabhan also encourages a conversational approach to facilitate stimulating discussions.

"Use social media to stay current and also to share current events in the areas you're interested in," he said. "Be polite and respectful to those who disagree with your opinion and leverage social media for civil debates and discussions that can benefit the general public who are interested in health care."

Push Past the Growing Pains

Many users should expect to experience some growing pains when first starting out, Dr. Mistry said.

"In the beginning, there will be growing pains," he said. "It's okay to take several attempts to create your first post or podcast episode. Be open to feedback and commit to wanting to be your very best."

It might be tough to build a following, but Dr. Mistry believes the hard work is worth it.

"Once you find your rhythm, the process can be incredibly gratifying, especially when you get your first email or message from a follower stating how helpful your content is," he said. "Let that be your motivation to keep wanting to be better, not a message to become complacent."

***Melissa Badamo** is an Assistant Editor for* Blood Cancers Today.

Regulatory Actions

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

FDA Requests Boxed Warning Label on CAR-T Therapies Used to Treat Blood Cancers

The US Food and Drug Administration (FDA) has notified drug manufacturers of chimeric antigen receptor (CAR) T-cell therapies indicated to treat blood cancers to make safety-related labeling changes following potential serious risks identified by the FDA Adverse Event Reporting System.

On January 19, the agency specifically asked manufacturers to update the prescribing information of the therapies with a boxed warning label, the strictest warning issued by the FDA, to indicate that T-cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies.

The FDA notifications were sent to the following drug manufacturers:

- Celgene Corporation, a subsidiary of Bristol Myers Squibb (idecabtagene vicleucel [ide-cel]; Abecma)
- Janssen/Legend Biotech, of Johnson & Johnson (ciltacabtagene autoleucel [cilta-cel]; Carvykti)
- Novartis (tisagenlecleucel; Kymriah)
- Kite Pharma, a Gilead company (axicabtagene ciloleucel [axi-cell]; Yescarta)
- Juno Therapeutics, a Bristol Myers Squibb company (lisocabtagene maraleucel [liso-cel]; Breyanzi)

The agency's request follows its November 2023 statement on the possible risk of CAR-T treatment resulting in secondary T-cell malignancies.

"The FDA has received reports of T-cell malignancies, including CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T-cell immunotherapies," the agency said in a statement in November. "Reports were received from clinical trials and/or postmarketing adverse event data sources."

In that same statement, the agency acknowledged that the overall benefits of the therapies continue to outweigh the potential risks for their approved uses.

Response From Drug Manufacturers

In an email to *Blood Cancers Today,* a spokesperson for Johnson & Johnson wrote that the company would work with the FDA to update the prescribing information for cilta-cel.

Tada Images: Shutterstock

"With the FDA's determination that the risk of T-cell malignancy is applicable to all currently approved BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, we will work with the agency to update the Carvykti prescribing information," Brian Kenney, of Johnson & Johnson, said in the statement.

Novartis also confirmed it would work with the FDA to update the Kymriah prescribing information "appropriately in the interest of patients" and noted that the company "has not found sufficient evidence to support the causal relationship between Kymriah and secondary T-cell malignancies to date and remains confident in the favorable benefit/risk profile" of the therapy.

The Novartis spokesperson added that the company has treated over 10,000 patients globally since the therapy was approved in August 2017 in the United States.

Bristol Myers Squibb was "evaluating next steps on the labels for Abecma and Breyanzi," according to the news agency Reuters.

Drug manufacturers now have 30 days to respond to the FDA.

FDA Lifts Partial Hold on Lacutamab Clinical Trial Program After Investigation

The FDA has lifted the partial clinical hold on the investigational new drug (IND) application for lacutamab following its analysis of a mortality in the TELLOMAK trial, according to Innate Pharma, the manufacturer of the drug.

Lacutamab is an anti-KIR3DL2 antibody developed to treat patients with cutaneous T-cell lymphoma (CTCL) and peripheral T-cell disease, rare lymphomas that carry a poor prognosis and lack effective therapies. KIR3DL2 is an inhibitory receptor expressed by approximately 65% of all patients with CTCL subtypes, and by up 90% of patients with aggressive CTCL subtypes, especially Sézary syndrome.

The open-label, phase II TELLOMAK trial enrolled patients with Sézary syndrome and mycosis fungoides across the United States and Europe. The primary endpoint is objective global response rate, and secondary endpoints include progression-free survival (PFS), duration of response, overall survival (OS), quality of life, pharmacokinetics, immunogenicity, and adverse events.

The partial clinical hold was placed on the lacutamab clinical trial program after the death of a patient with Sézary syndrome was initially attributed to hemophagocytic lymphohistiocytosis. After further investigation, the FDA, alongside the program's steering committee of independent experts, judged the death was not related to lacutamab therapy and lifted the hold.

"We have worked closely with the FDA to diligently resolve the partial clinical hold on the lacutamab IND, which included an in-depth analysis of the fatal case, which was due to progression of an aggressive form of the disease," said **Sonia Quaratino, MD, PhD,** Chief Medical Officer at Innate Pharma.

One arm of the study enrolled approximately 60 patients with Sézary syndrome who previously received two lines of systemic therapy, including mogamulizumab. Outcomes with lacutamab monotherapy in this arm could support a dedicated indication for lacutamab, according to Innate Pharma.

"The lacutamab program continues to plan following the publication of the positive Sézary syndrome results at the recent [American Society of Hematology] Annual Meeting [& Exposition]. We now look forward to sharing final data in mycosis fungoides," Dr. Quaratino added.

Regulatory Actions

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

FDA Approves Label Update for Zanubrutinib for CLL

The FDA has approved a label update for zanubrutinib for the treatment of chronic lymphocytic leukemia (CLL) to include PFS results from the ALPINE trial.

ALPINE is a phase III trial that compared zanubrutinib with ibrutinib in patients with pretreated relapsed or refractory CLL. The Bruton's tyrosine kinase inhibitor was approved in the United States in January 2023 based on superior overall response rates (ORRs) compared with ibrutinib (80.4% vs 72.9%; *P*=.0264).

The label update includes results from a median follow-up of 31 months, in which zanubrutinib demonstrated superior PFS compared with ibrutinib (hazard ratio, 0.65; 95% CI, 0.49-0.86; *P*=.0024). Zanubrutinib also demonstrated a favorable cardiac safety profile, with significantly lower rates of atrial fibrillation and flutter (5.2% vs 13.3%) and zero deaths from cardiac disorders versus six with ibrutinib (0.0% vs 1.9%).

"The ALPINE trial is the first and only study to demonstrate PFS superiority in a head-to-head comparison versus ibrutinib in CLL," said **Mehrdad Mobasher, MD, MPH,** Chief Medical Officer of Hematology at BeiGene, the manufacturer of the drug. "When making treatment decisions, it is critical that physicians and patients understand the totality of data supporting the robust efficacy and differentiated safety [of zanubrutinib] in CLL."

Label Update for Axi-Cel Approved by US FDA After ZUMA-7

The FDA has approved a label update for axi-cel (Yescarta) based on results from the phase III ZUMA-7 study that showed axi-cel significantly improved OS compared with standard of care in patients with relapsed or refractory large B-cell lymphoma (LBCL).

Axi-cel, sold under the trade name Yescarta, is an autologous CAR T-cell therapy used as a potentially curative second-line treatment for LBCL within 12 months of first-line therapy completion.

"Our ZUMA-7 overall survival analysis proves that when given as second-line therapy, Yescarta is even more effective in improving patient survival than standard-of-care treatment. Coupled with our rapid and reliable manufacturing, it is our hope to provide patients a chance to live longer lives," said **Frank Neumann, MD, PhD,** the Senior Vice President and Global Head of Clinical Development at Kite Pharma, the manufacturer of the drug.

Standard-of-care therapy for relapsed or refractory LBCL conventionally includes chemoimmunotherapy that, if successful, is followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).

Less than 40% of patients who begin the process actually undergo HSCT, according to a press release from Kite, whereas 94% of patients who received a one-time infusion of axi-cel in ZUMA-7 went on to complete transplantation.

Axi-cel is the "first and only treatment in nearly 30 years" to yield improved survival in patients with relapsed or refractory LBCL in the second-line setting, the release concluded.

Selinexor Added to China's National Reimbursement Drug List

Selinexor (Xpovio®) has been added to China's National Reimbursement Drug List (2023 Version; NRDL) for the treatment of adult patients with relapsed or refractory multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The updated NRDL took effect on January 1, 2024, according to a press release from the manufacturer of the drug, Antengene Corporation Limited.

"Antengene is committed to ensuring that our innovative treatments are delivered swiftly to myeloma patients across China, with improved affordability and accessibility, as a result of [the inclusion of Xpovio in the] NRDL," said **Jay Mei, MD, PhD,** Antengene's founder, Chairman, and Chief Executive Officer. "Moving forward, Antengene remains steadfast and focused on our vision of 'treating patients beyond borders.' We are determined to expand the use of Xpovio to additional indications, fully realizing its therapeutic potential and contributing to the continuous improvement of health outcomes for patients in China."

China's NMPA Accepts sBLA for Relma-Cel Injection

The National Medical Products Administration (NMPA) of China accepted the supplemental Biological License Application (sBLA) for the anti-CD19 autologous CAR T-cell immunotherapy product relmacabtagene autoleucel injection (Carteyva®; relma-cel) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

The sBLA is supported by data from a single-arm, multicenter, pivotal study on relma-cel in adult patients with relapsed or refractory MCL in China. As of October 25, 2023, a total of 59 participants received a relma-cel infusion. Of 56 efficacy-evaluable participants, relma-cel demonstrated a three-month best ORR of 81.36% and a three-month best complete response rate of 66.10%, according to JW Therapeutics, the manufacturer of the drug.

"We are delighted to have a product that can deliver meaningful efficacy in this disease. Nearly 70% of participants with [relapsed or refractory] MCL have achieved complete remission after treatment with relma-cel, and the overall safety data demonstrated that the treatment was generally well [tolerated]," **Mark Gilbert, MD,** the Chief Medical Officer of JW Therapeutics, said in a press release.

FDA Grants Breakthrough Device Designation for Multicancer Early Detection Solution

The FDA has granted Breakthrough Device Designation to CanScan, a multicancer early detection solution.

CanScan uses low-depth whole-genome sequencing on circulating cell-free DNA from a single tube of peripheral blood. It is able to detect early cancer signals with 99% specificity and predict the tissue of origin of cancers to help guide next steps for cancer diagnosis, according to Geneseeq, the manufacturer of the device.

The device detects cancer types currently without effective standard-of-care screening methods, including the blood cancer lymphoma.

The performance of CanScan has been validated in a large-scale clinical study series in over 13 cancer types, according to Geneseeq. CanScan is currently under real-world evaluation in the Jinling Cohort, a large-scale, prospective, multicenter trial.

This article discusses the current state of the art in the treatment of acute lymphoblastic leukemia (ALL). The following material is reproduced from "SOHO State of the Art Updates and Next Questions: Acute Lymphoblastic Leukemia," published on January 8, 2024, in Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Jayastu Senapati, MBBS, MD; Hagop Kantarjian, MD; Fadi Haddad, MD; Nicholas Short, MD; Mary Alma Welch, MD; Nitin Jain, MD; and Elias Jabbour, MD.*

New Agent-Based Regimens Rapidly Replace Old Intensive Chemotherapy Paradigm in ALL

The past two decades have witnessed a rapid change in the treatment of ALL. The incorporation of the more potent targeted BCR-ABL1 tyrosine kinase inhibitors (TKIs) into the treatment of Philadelphia chromosome (Ph)-positive ALL, and of targeted and immune therapies in pre-B-cell ALL and Ph+ ALL have improved outcomes drastically. The old treatment paradigm of intensive chemotherapy, which prevailed for 50 years, is being rapidly replaced by regimens that incorporate the new agents, and that may omit chemotherapy completely or significantly reduce its intensity and duration.

Importance of Measuring Residual Disease by Newer, More Sensitive Methodologies

Next-generation sequencing (NGS)-based measurable residual disease (MRD) assays track leukemia-associated immunoglobulin (IG) or T-cell receptor (TR) rearrangements through deep sequencing and MRD detection sensitivity of 10^{-6}. NGS MRD is superior to multiparameter flow cytometry methods, both in terms of sensitivity and discrimination of relapse risk. Patients who achieve rapid NGS MRD clearance have very low rates of relapse. Thus, patients with early NGS MRD clearance might be suitable candidates for treatment de-escalation in future investigational trials. In patients with high-risk cytomolecular features (eg, adverse cytogenetics, Ph-like genotype, etc) where allogeneic hematopoietic stem cell transplantation (HSCT) in first remission is still a standard of care, NGS-based response assessment might enable clinicians to select patients in whom allogeneic HSCT could be safely avoided. Patients with very low-level MRD by high-sensitivity NGS assay may also be candidates for chimeric antigen receptor (CAR) T-cell consolidation as an alternative to allogeneic HSCT, a strategy that is being investigated in prospective clinical trials.

Persistence of MRD in remission is associated with a higher risk of relapse and worse survival across subtypes of ALL. In patients with Ph+ ALL, MRD monitoring is routinely done using reverse-transcription polymerase chain reaction (RT-PCR) for BCR-ABL1 transcripts. However, a recent analysis evaluating the correlation between RT-PCR for BCR-ABL1 and NGS for IG/TR in Ph+ ALL showed that approximately 15% to 30% of patients who achieve NGS MRD negativity at a sensitivity of 1×10^{-6} may still have detectable BCR-ABL1 transcripts by RT-PCR. Among patients who achieved NGS MRD negativity, the presence or absence of BCR-ABL1 by RT-PCR did not carry a prognostic impact, suggesting that the persistent BCR-ABL1 transcripts in these patients did not represent true ALL blastic MRD. Thus, NGS-based MRD may be a better tool than RT-PCR for BCR-ABL1 in monitoring patients with Ph+ ALL and making MRD-guided treatment decisions.

"Great strides have been made in the past two decades in the treatment of adult ALL, but challenges remain."

Frontline Therapy for B-Cell ALL

The integration of the immunotherapy agents inotuzumab ozogamicin (InO), a CD22 antibody-drug conjugate, and blinatumomab, a CD19 bispecific T-cell engager, into the frontline treatment of adults with pre-B-cell ALL has significantly improved survival outcomes. The phase III ECOG-ACRIN E1910 trial showed that even in patients with negative MRD (<0.01%), the addition of blinatumomab to consolidation therapy led to a survival benefit (five-year overall survival [OS] rates, 80% vs 55%).

Other studies showing similar OS benefits raise questions about the value of the established intensive chemotherapy treatment paradigms in ALL and whether these newer regimens incorporating targeted immunotherapy could be deintensified and shortened. The availability of NGS methods that detect residual disease in a million cells may allow finessing of strategies in relation to the intensity duration of therapy, as well as the need to change therapy and consider HSCT or CAR-T in first or later complete remissions (CRs) based of the sequential NGS MRD results.

However, treatment of older patients (≥60 years of age) remains challenging due to aggressive disease biology and inability to tolerate intensive chemotherapy or to proceed to allogeneic HSCT. With these traditional forms of therapy, the five-year OS rates are below 20%.

At the University of Texas MD Anderson Cancer Center, Dr. Senapati and colleagues started using less intensive chemotherapy that incorporated initial InO simultaneously with attenuated chemotherapy, and later added sequential blinatumomab. This new mini-hyper-CVD-InO regimen with or without blinatumomab as frontline therapy in older adults with newly diagnosed B-cell ALL resulted in a promising five-year progression-free survival (PFS) rate of 44% and an OS rate of 46%.

Treatment of Ph+ ALL

Ph+ ALL is another ALL subset where chemotherapy-free regimens are gaining traction. Historically, Ph+ ALL was associated with a very poor outcome, but the discovery and addition of BCR-ABL1 TKIs to intensive chemotherapy changed the outcome drastically. For example, the long-term survival of patients with newly diagnosed Ph+ ALL improved from less than 10% with intensive chemotherapy, to 40% with hyper-CVAD and imatinib, and to 65% with hyper-CVAD and dasatinib. Despite the survival benefit observed with first- and second-generation TKIs, outcomes remained suboptimal due to the low rate of complete molecular response (CMR; undetectable BCR-ABL1 transcripts by RT-PCR) and the development of the *T315I* mutations in up to 75% of relapsing patients.

To deepen molecular responses and prevent the emergence of *T315I*-mutated clonal ALL relapse, the third-generation TKI ponatinib was combined with hyper-CVAD in the frontline setting, which improved the CMR rate to 84% and the six-year OS rate to 75%. In another study, a simultaneous combination of blinatumomab and ponatinib resulted in a CMR rate of 84% and an NGS MRD rate of 91%. In this

particular study, only one (2%) patient received an allogeneic HSCT in first remission due to persistently detectable BCR-ABL1 transcripts, highlighting that this chemotherapy-free regimen could mitigate the need for transplant in the frontline setting.

Improving Treatment Options in T-Cell ALL

The development of newer therapeutics in T-cell ALL has lagged behind pre-B-cell ALL. Subsets of T-cell ALL such as early T-cell precursor (ETP) ALL in adults continue to have poor outcomes. Knowledge of the dependence of T-lymphoblasts on BCL-2 and BCL-xL has led to the initiation of clinical trials with venetoclax and navitoclax along with chemotherapy in the relapsed or refractory setting and in frontline patients with the ETP phenotype. T-lymphoblasts are sensitive to asparaginase, and the combination of hyper-CVAD, pegylated asparaginase, and nelarabine has produced five-year PFS and OS rates of 60%. Clinical trials have also been initiated using ponatinib with chemotherapy in relapsed or refractory T-cell ALL. The development of CAR T-cell therapies in T-cell ALL has been stymied by concerns about fratricide, but new manufacturing techniques to develop CAR-T products against CD5 and CD7 that are resistant to fratricide are demonstrating promising early results.

Treatment, Sequence of Therapies in Relapsed or Refractory B-Cell ALL

Both InO and blinatumomab are approved as monotherapy in the relapsed or refractory setting, but in the registration trials, the median OS with either of these agents as monotherapy is seven to eight months, and the three-year OS rates are approximately 20% to 25%, which indicates that these treatments as approved by the regulatory agencies offer a poor treatment value (high cost and modest benefit). Combining these agents with mini-hyper-CVD improved median OS to 17 months and the three-year OS rate to 40%.

A dose-dense strategy combining the administration of InO and blinatumomab (rather than sequential blinatumomab) with mini-hyper-CVD is promising. The anti-CD19 CAR T-cell product brexucabtagene autoleucel was approved for the treatment of adults with relapsed or refractory B-cell ALL and resulted in a median OS of 18 months among evaluable patients. Though each of these individual approaches can be used in sequence as patients relapse, a complementary approach of consolidative CAR T-cell therapy after the best possible response on salvage chemoimmunotherapy might lead to better outcomes, and such clinical trials are ongoing.

One approach might be CAR-T consolidation after remission induction with chemoimmunotherapy salvage regimens, but concerns about optimal CAR T-cell expansion with slow-burden disease need to be assessed. This strategy can then be used in the frontline setting for high-risk B-cell ALL and could possibly replace allogeneic HSCT.

New CAR T-cell products, such as obecabtagene autoleucel (obe-cel), a CD19-directed autologous CAR T-cell therapy that uses the fast-off approach, are under development, with the goal of reducing immunotoxicity and improving CAR-T persistence. An interim analysis of the FELIX trial, which is investigating obe-cel, showed that the infusion of obe-cel resulted in low rates of grade 3 or higher cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.

"In the future, simplified chemoimmunotherapy regimens that include subcutaneous blinatumomab, and/or tri-specific or tetra-specific T-cell engagers in place of the continuous blinatumomab infusion formulation, might improve patients' outcomes and quality of life and reduce in-hospital durations," Dr. Senapati and colleagues wrote.

Ensuring Patients Have Access to Best Therapies

Better disease prognostication, genomic assessment, and wider accessibility to newer agents are important to ensure all patients with ALL have access to the best available therapy.

Highly effective targeted drugs and CAR T-cell therapies have revolutionized the outcomes in adult B-cell ALL. Yet, beyond some positive studies with nelarabine, no new agent has yet shown similar promise in T-cell ALL.

"Great strides have been made in the past two decades in the treatment of adult ALL, but challenges remain," the authors concluded. "Ongoing trials will answer some of these questions, but the challenges related to high-risk B-cell ALL and relapsed or refractory T-cell ALL need enhanced focus."

Sylvester Research Group Develops New Tool for Predicting Myeloma Risk

Researchers have developed the first individual risk prediction model for newly diagnosed multiple myeloma (MM), according to a study published in the *Journal of Clinical Oncology*.

Led by **Francesco Maura, MD,** an Assistant Professor at the University of Miami Sylvester Comprehensive Cancer Center, the study also identified 12 distinct subtypes of the blood cancer, expanding on previous classifications.

Our model is based on the idea of predicting the risk of the individual patient rather than that of the group," Dr. Maura said.

The Individualized Risk Model for Myeloma (IRMMa), which predicts an individual's prognosis based on their tumor genomics and treatments, was developed in collaboration with scientists at Memorial Sloan Kettering Cancer Center, NYU Langone Health, Moffitt Cancer Center, and Heidelberg University Hospital.

The IRMMa was significantly more accurate than all comparator prognostic models, with a concordance index for OS of 0.726, compared with the International Staging System (ISS; 0.610), revised-ISS (0.572), and the second revision of the ISS (0.625), according to the study.

To build the computational model, researchers used genetic, treatment, and clinical data from almost 2,000 patients with newly diagnosed MM. They first identified 90 driver genes from patients' DNA sequences, which bear mutations in the cancer cells that drive tumor growth. Next, they looked at the treatments each patient received, matching treatment outcome to tumor genetic sequences for individual patients.

The original method for classifying the disease in the 1970s consisted of staging for solid tumors and relied on the amount of cancer present. Now, with newly developed treatments such as immunotherapies, the amount of cancer is less significant than the nature of the cancerous cells.

According to Dr. Maura, the field still lacked precise prediction ability despite advancements in prognostic tools over the years, such as tumor genomic features. However, there have since been new findings on genomic risk factors, which had not yet been included in a prediction model.

Additionally, preexisting prognostic tools relied on population averages, sorting patients into "standard risk" and "high risk" categories and providing prognoses for overall groups. In contrast, the IRMMa considers individualized risk and how it can be tailored by personalized treatments. The model can also update a patient's prognosis under specific circumstances, such as if a patient received a transplant.

Dr. Maura and colleagues aim to improve the model by including more patient data.

"This model can only grow with the help of the research community," Dr. Maura said in a press release. "The next challenge is to keep feeding it with the right datasets so at a certain point it will be usable for clinical purposes."

Reference

Maura F, Rajanna AR, Ziccheddu B, et al. Genomic classification and individualized prognosis in multiple myeloma. *J Clin Oncol.* 2024. doi.org/10.1200/JCO.23.01277

STIMULUS-MDS1 Trial Compares Sabatolimab Plus HMAs Versus Placebo in Higher-Risk MDS

While sabatolimab showed a manageable safety profile in patients with higher-risk myelodysplastic syndromes (MDS), combining sabatolimab with a hypomethylating agent (HMA) did not significantly improve complete response rates (CRRs) or progression-free survival (PFS), according to a phase II study published in *The Lancet Haematology*.

Led by **Amer Zeidan, MBBS, MHS,** of the Yale University Cancer Center, the randomized, double-blind, placebo-controlled trial compared the efficacy and safety of sabatolimab plus an HMA versus placebo plus an HMA in patients with untreated, higher-risk MDS. Dr. Zeidan and colleagues conducted the study because "patients with higher-risk [MDS] are in need of better treatment options that provide durable clinical responses with good tolerability."

Amer Zeidan, MBBS, MHS

A total of 127 patients from 54 investigational sites were randomized into two groups: the intravenous sabatolimab group (n=65) or the placebo plus an HMA group (n=62). The former group received intravenous sabatolimab 400 mg on days eight and 22, while the latter group received either intravenous decitabine 20 mg/m^2 on days one to five or intravenous or subcutaneous azacitidine 75 mg/m^2 on days one to seven or days one to five and eight and nine. The median treatment exposure was 9.1 months in the sabatolimab group and 8.6 months in the placebo group.

The primary endpoints included CRR and PFS. A complete response (CR) was achieved in 14 (22%) patients in the sabatolimab group versus 11 (18%) patients in the placebo group (P=.77). The median PFS was 11.1 months in the sabatolimab group versus 8.5 months in the placebo group (P=.1022).

The secondary endpoints were OS, event-free survival (EFS), leukemia-free survival (LFS), overall response rate (ORR), duration of CR, time to CR, improvement in red blood cell or platelet transfusion independence, safety, pharmacokinetics, and immunogenicity.

The median OS was 19.0 months in the sabatolimab group and 18.0 months in the placebo group, while the median LFS was 16.8 months in the sabatolimab group and 13.6 months in the placebo group. The ORR was 68% in the sabatolimab group versus 61% in the placebo group.

Patients in the sabatolimab group had a longer median CR duration than patients in the placebo group (18.0 months vs 9.2 months, respectively). Of the patients who received sabatolimab, 22% reached a CR by six months, compared with 17% of patients who received placebo.

EFS, improvement in transfusion independence, pharmacokinetics, and immunogenicity will be reported in the final trial analysis. The researchers noted that because most patients did not reach a CR within six months, the EFS data are difficult to interpret.

Patients were followed up for safety evaluations for up to 30 days after HMA discontinuation, and for 150 days after sabatolimab or placebo discontinuation. The safety profile was comparable with that of monotherapy plus HMA. The most common adverse events (AEs) in either group included neutropenia, thrombocytopenia, constipation, diarrhea, anemia, febrile neutropenia, and leukopenia. One patient in the sabatolimab group developed a serious potential treatment-related, immune-mediated AE, and a second patient died due to pneumonitis.

"Clinical benefit of treatment might be mainly restricted to patients who achieve restoration of hematopoiesis … since it has been reported that response rates differentially correlate with OS," the researchers wrote. "A randomized, phase III trial is ongoing to assess the potential benefit of sabatolimab plus azacitidine on overall survival in this setting."

Reference

Zeidan AM, Ando K, Rauzy O, et al. Sabatolimab plus hypomethylating agents in previously untreated patients with higher-risk myelodysplastic syndromes (STIMULUS-MDS1): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Haematol.* 2023. doi.org/10.1016/S2352-3026(23)00333-2

Is Early Intervention for Smoldering MM Beneficial?

The majority of patients with high-risk smoldering MM (SMM) will eventually progress to MM, as predicted by their baseline risk assessment, according to clinical trial data that support early intervention in high-risk patients.

The study also found that clinically significant end-organ damage may not be preventable and that progression to MM is not always detected by routine interval surveillance testing.

Led by **Nadine Abdallah, MD,** of the Mayo Clinic in Rochester, Minnesota, the study aimed to describe the myeloma-defining events (MDEs) and clinical presentations leading to MM diagnosis among patients with SMM.

Dr. Abdallah and colleagues conducted the study because despite clinical trial data suggesting benefit from early intervention, most patients with SMM are observed.

The study included 406 patients seen at the Mayo Clinic between 2013 and 2022. Twenty-four percent of patients met MM criteria based on marrow plasmacytosis (≥60%) or free light chain ratio (>100), while 45% had clinically significant MDEs (hypercalcemia, renal insufficiency, or bone lesions).

Of 90 patients with high-risk SMM, 21% received early intervention and 79% were observed. At a median follow-up of 3.9 years, two (11%) patients who received early treatment progressed to MM, compared with 51 (72%) patients who were observed.

The MDEs for high-risk patients included bone lesions (37%), anemia (35%), hypercalcemia (8%), and renal failure (6%). Among high-risk patients who were observed and progressed by last follow-up, the presentations leading to MM diagnosis included surveillance labs or surveillance imaging (44%), workup due to laboratory changes (14%), bone pain (19%), workup for an unrelated symptom (2%), and hospitalization due to MM complications or symptoms (4%).

Of 226 non-high-risk patients, 35 (15%) received treatment for SMM after a median of four months after diagnosis, and 191 (85%) were observed. Three (9%) patients who received treatment progressed, compared with 59 (31%) patients who were observed.

The MDEs for non-high-risk patients included bone lesions (51%), anemia (36%), hypercalcemia (7%), renal insufficiency (8%), and bone marrow plasma cells or free light chain ratio criteria (14%). For non-high-risk patients, the presentations leading to MM diagnosis included surveillance labs or surveillance imaging (32%), workup due to laboratory changes (17%), bone pain (20%), workup for an unrelated medical condition/symptom (7%), unknown presentation (14%), and hospitalization due to MM complications or symptoms (10%).

Approximately half of patients who progressed to MM had clinically significant end-organ damage, including one patient who progressed to end-stage renal disease.

According to Dr. Abdallah and colleagues, early intervention in patients with high-risk SMM is justified by the morbidity associated with progression to MM reported in this study; the benefit in delaying progression reported in prior trials, including the QuiRedex study and the E3A06 ECOG-ACRIN phase III trial; and the lack of evidence for the emergence of resistant clones.

"These findings may provide support for early intervention in high-risk patients," the researchers concluded. "Efforts to further refine the current risk stratification systems will better delineate the subset of patients who would benefit from early intervention in the future."

Reference

Abdallah NH, Lakshman A, Kumar SK, et al. Mode of progression in smoldering multiple myeloma: a study of 406 patients. *Blood Cancer J.* 2024. doi.org/10.1038/s41408-024-00980-5

How Do Coping Strategies Impact Patients Prior to HSCT?

Patients' coping strategies prior to hematopoietic stem cell transplantation (HSCT) had significant effects on their psychological distress and quality of life (QOL), with approach-oriented coping strategies yielding improved outcomes compared with avoidant coping strategies, concluded an analysis of baseline patient data published in *Blood Advances*.

"[The] study findings highlight the ongoing need for supportive care providers with expertise in facilitating adaptive coping, including social workers, chaplains, psychologists, and palliative care clinicians to be available and involved during early hospitalization," suggested the authors, led by **Richard Newcomb, MD,** from the Harvard Medical School in Boston, Massachusetts.

The analysis included 360 patients with hematological malignancies and a mean age of 55.4 years who were admitted to a hospital prior to allogeneic or autologous (49.7%) HSCT.

Participants' QOL, psychological distress, and coping strategies were assessed via the Functional Assessment of Cancer Therapy-Bone Marrow Transplant, Hospital Anxiety and Depression Scale and PTSD-Civilian Version, and Brief-COPE (creativity, optimism, problem solving, and expert information) tools, respectively, within 72 hours of admission.

According to the study, 43.5% of patients used approach-oriented coping and 31.3% used avoidant coping. Common examples included emotional support (60.9%), acceptance (51.2%), self-blame (33.0%), and denial (31.3%). Notably, avoidant coping strategies were less common in patients aged 65 years or older (odds ratio, 0.5; P=.01).

Overall, approach-oriented coping was associated with improvements in baseline QOL (B, 6.7; P=.001), depression (B, −1.1; P=.001), and anxiety (B, −0.9; P=.02) measures, while avoidant coping was associated with reductions in baseline QOL (B, −13.3; P<.001), depression (B, 1.9; P<.001), anxiety (B, 3.1; P<.001), and post-traumatic stress disorder (B, 8.1; P<.001) measures.

"These data support the need for interventions to address coping during [HSCT] hospitalization," concluded Dr. Newcomb and colleagues.

Reference

Newcomb RA, Amonoo HL, Nelson AM, et al. Coping in patients with hematologic malignancies undergoing hematopoietic cell transplantation. *Blood Adv.* 2024. doi:10.1182/bloodadvances.2023011081

Highlights from the **65TH AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING & EXPOSITION**

Baseline Immunologic State Affects CAR T-Cell Response in LBCL

The baseline immunologic state of a patient with large B-cell lymphoma (LBCL) could affect response to chimeric antigen receptor (CAR) T-cell therapy, according to an abstract presented at the 65th ASH Annual Meeting & Exposition. This process could be affected through modulation of the T-cell apheresis product composition and promotion of a more favorable circulating immune compartment prior to therapy.

Katie Maurer, MD, PhD, of the Dana-Farber Cancer Institute in Boston, Massachusetts, and colleagues collected serial peripheral blood mononuclear cell samples from patients with relapsed or refractory LBCL treated with axicabtagene ciloleucel (axi-cel). Samples were taken from day –30 to +28 relative to receipt of the CAR T-cell infusion. In addition, the researchers collected bag washings from infusion products (IPs).

There was no difference in postinfusion circulating immune subsets among patients who did or did not respond to CAR T-cell therapy. However, the researchers did find that the proportion of B cells was increased in patients who had responded (P=.012). Additionally, circulating B cells were highest among complete responders. When the responders were separated into complete responders and those who did not have complete response, complete responders had significantly increased frequency of circulating B cells (P=.0057).

Responders also had a higher lymphocyte-to-monocyte ratio compared with nonresponders (P=.22). This finding was confirmed in a larger flow cytometry cohort of patients and validated in a cohort of patients treated with commercial axi-cel at the Dana-Farber Cancer Institute from 2019 to 2022.

Using single-cell RNA sequencing analysis, the researchers found that IP cells demonstrated an increased proportion of CD8 T cells in responders compared with nonresponders (P=.024) and showed a trend toward an increased effector memory T-cell expression profile (P=.079). The researchers also observed greater clonal expansion of CD8 effector memory T cells in responders compared with nonresponders.

"These data implicate clonal expansion and T-cell activation at infusion as key indicators of CAR-T response," the researchers wrote. "These features, detectable by highly accessible clinical measures, could be leveraged for improved patient selection and enhanced CAR-T manufacturing."

Reference

Maurer K, Grabski IN, Houot R, et al. Baseline immune state and T cell clonal kinetics are associated with response to CAR-T therapy in large B-cell lymphoma. Abstract #223. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Momelotinib Improves 'Quality of Survival' in Myelofibrosis

In addition to its activity against anemia, symptoms, and splenomegaly related to myelofibrosis, the JAK1/JAK2/activin A receptor type 1 inhibitor momelotinib provided certain additional anemia benefits that led to improved "quality of survival," according to a pooled analysis of data from the Simplify-1 and Simplify-2 trials.

Ruben Mesa, MD

At the 65th ASH Annual Meeting & Exposition, **Ruben Mesa, MD,** of the Atrium Health Wake Forest Baptist Comprehensive Cancer Center in Winston-Salem, North Carolina, discussed the results of the study, which showed that treatment with momelotinib resulted in less time reliant on red blood cell transfusion and more time free from transfusions and anemia events.

"Patients treated with [momelotinib] spent less time reliant on [red blood cell] transfusions and more time free from transfusions and anemia events, without the cost of increased [adverse events (AEs)], compared with those treated with [ruxolitinib] or [best available therapy]," the authors wrote.

Dr. Mesa and colleagues examined these outcomes in patients from the safety populations of the Simplify-1 (JAK inhibitor naïve) and Simplify-2 (JAK inhibitor exposed) trials.

In Simplify-1, patients treated with momelotinib spent less time in a transfusion-dependent (TD) state compared with patients assigned to ruxolitinib (mean duration of transfusion dependence, 28.3 days vs 62.7 days). Additionally, patients treated with momelotinib had more time without transfusion reliance (TWiTR) compared with those on ruxolitinib (163.4 days vs 131.1 days).

This decrease in transfusion dependence and increase in time free from transfusions came without an increase in anemia AEs, according to the researchers. Overall, there were fewer treatment-emergent anemia AEs among patients receiving momelotinib. When anemia events were incorporated into the analysis, the mean time spent in the TD-anemia state—having any-grade anemia event in the TD state—was increased among all patients, but the increase was smaller in the momelotinib arm.

The mean duration of TWiTR or anemia-worsening TWiTR (TWiTR-An) was 159.7 days with momelotinib compared with 119.0 days with ruxolitinib.

In Simplify-2, incorporation of anemia AEs had less of an effect than in Simplify-1, according to the researchers. The mean duration of transfusion dependence was 69.4 days with momelotinib compared with 89.9 days with ruxolitinib. Mean duration of the TD-anemia state was 69.6 days for momelotinib compared with 89.9 days for ruxolitinib.

The mean duration of TWiTR-An was slightly longer with momelotinib at 118.3 days compared with 95.9 days with ruxolitinib.

According to the researchers, "These analyses suggest that the anemia benefits of momelotinib led to improved quality of survival for patients with myelofibrosis."

Reference

Mesa RA, Talpaz M, Mazerolle F, et al. Time without transfusion reliance or anemia worsening: a novel method for integrating transfusion dependence, anemia, and survival with myelofibrosis therapies based on the phase 3 Simplify-1 and Simplify-2 trials. Abstract #1826. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Combining Triplet With Molecularly Targeted Therapy Could Enhance MM Response

The MyDRUG trial successfully identified patients with functional high-risk multiple myeloma (MM) who would benefit from molecularly targeted therapies used in combination with standard triplet regimens, according to **Joshua Richter, MD,** of the Icahn School of Medicine at Mount Sinai in New York, who presented results from one of the trial's arms.

MyDRUG is a genomically guided umbrella trial that includes patients with functional high-risk disease defined as early relapse after primary therapy. All included patients had specific genetic abnormalities, and those without actionable abnormalities were enrolled in a "nonactionable" arm.

Dr. Richter presented data from the Y3 arm of the trial, which tested selinexor, ixazomib, pomalidomide, and dexamethasone (Seli-IPd), an all-oral regimen given on a 28-day cycle.

Seventeen patients were in the Y3 arm. They had a median of two prior lines of therapy and were a median of 29 months from diagnosis.

More than half of patients responded to Seli-IPd, with an overall response rate of 52.9% and a clinical benefit rate of 58.8%. Median progression-free survival was 10.2 months, and median overall survival has not yet been reached. As of the data cutoff, all patients were still alive.

About half (47.1%) of patients experienced a serious AE. Two patients required treatment discontinuation due to AEs, and two patients required dose reduction.

Overall, results from the Y3 arm showed that the molecularly targeted therapy Seli-IPd had "significant efficacy and a manageable adverse event profile," the authors wrote. The all-oral regimen could minimize patient office visits and reduce parenteral therapy administrations.

Reference

Richter J, Zonder JA, Nathwani N, et al. Selinexor, ixazomib, pomalidomide, and dexamethasone in functionally high-risk multiple myeloma: results from the Myeloma Developing Regimens Using Genomics (MyDRUG) Sub-Protocol Y3. Abstract #3387. Presented at the 65th ASH Annual Meeting & Exposition; December 9–12, 2023; San Diego, California.

Real-World Data Show High Rate of Second Cancers After PV Diagnosis

More than one-third of patients with polycythemia vera (PV) reported at least one second primary cancer after PV diagnosis, according to a retrospective analysis.

The most common second cancer was skin cancer, driven by nonmelanoma skin cancers, noted study presenter **Naveen Pemmaraju, MD,** of the University of Texas MD Anderson Cancer Center.

Dr. Pemmaraju and colleagues conducted their retrospective study using electronic health record (EHR) data on 105 million US patients with linked medical and prescription claims from 2007 to 2019. Of those patients, more than 82,000 had one or more PV diagnoses at any time.

For this retrospective study, the researchers included 20,089 patients with PV who had two or more PV diagnosis codes with 60 days or more between the first and last diagnosis code. Patients were indexed at the first diagnosis code of PV preceded by ≥1 year of EHR data and required ≥1 year of postindex data or death prior to the end of the data period.

With a median duration of follow-up of 4.3 years, the researchers found that 35.7% of patients had at least one second cancer during the postindex period. The rate of second cancer during that period was 109.7 events per 1,000 patient years.

Skin cancer comprised the majority of second cancers, accounting for 22.1 events per 1,000 person-years. It was followed by prostate cancer and breast cancer.

Of the patients with a second cancer, 9.1% reported at least one skin cancer, 8.3% with a nonmelanoma skin cancer. Nonmelanoma skin cancer diagnosis was sixfold more prevalent than melanoma.

Of the more than 20,000 patients included in the study, 17,402 had preindex medication data available. About one-fifth (20.2%) were treated with at least four weeks of hydroxyurea at any time, and about one-fifth (19.0%) were treated with phlebotomy.

Second cancer after hydroxyurea was 2.5 times more common than after phlebotomy (140.4 events vs 55.3 events per 1,000 person-years; $P<.0001$). Rates of second skin cancers were twofold greater in the patients exposed to hydroxyurea compared with phlebotomy for any skin cancer ($P<.0001$), nonmelanoma skin cancers ($P<.0001$), and melanoma ($P=.0219$).

Reference

Pemmaraju N, Markova A, Masarova L, et al. Prevalence of second cancers in patients with polycythemia vera (PV): a retrospective analysis of US real-world claims data. Abstract #3190. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Luspatercept Is Effective for ESA-Naïve, Transfusion-Dependent, Lower-Risk MDS

Patients with erythropoiesis-stimulating agent (ESA)-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (LR-MDS) had improved red blood cell transfusion independence (RBC-TI) and erythroid responses when treated with luspatercept compared with ESAs, indicating that luspatercept could be a new standard of care for these patients, according to full results from the COMMANDS trial.

The COMMANDS trial enrolled 182 patients with Revised International Prognostic Scoring System-defined LR-MDS with <5% bone marrow blasts and serum erythropoietin (sEPO) <500 U/L. Patients were randomly assigned to luspatercept or epoetin alfa. The primary endpoint was RBC-TI of 12 weeks or longer, with a concurrent mean hemoglobin increase of at least 1.5 g/dL.

The primary endpoint was achieved by 60.4% of patients assigned to luspatercept compared with 34.8% of patients assigned to epoetin alfa ($P<.0001$).

Response rates with luspatercept versus epoetin alfa were greater for patients with *SF3B1*-mutated and nonmutated disease, with baseline sEPO ≤200 U/L and with baseline sEPO >200 to <500 U/L, and greater for ring sideroblast-positive patients. There was no significant difference in response for ring sideroblast-negative patients.

Median duration of RBC-TI of 12 weeks or longer with luspatercept was 128.1 weeks compared with 89.7 weeks with epoetin alfa (hazard ratio, 0.534).

Five patients in both arms progressed to acute myeloid leukemia. The majority of patients in both treatment arms experienced treatment-emergent AEs (TEAEs) of any grade. Grade 3 or 4 TEAEs occurred in 58.8% of patients assigned to luspatercept and 49.2% of patients assigned to epoetin alfa.

The rates of on-therapy and post-therapy deaths were similar for all patients.

Reference

Garcia-Manero G, Platzbecker U, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent (ESA)-naïve patients (pts) with transfusion-dependent (TD) lower-risk myelodysplastic syndromes (LR-MDS): full analysis of the COMMANDS trial. Abstract #193. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Knowledge Hubs

In each issue of Blood Cancers Today*, we will take a closer look at a particular topic in hematologic malignancies. This month, Associate Editor Laurie Sehn, MD, chooses three abstracts from the 65th American Society of Hematology (ASH) Annual Meeting & Exposition to highlight the indolent B-cell lymphoma Knowledge Hub. Visit* BloodCancersToday.com *to view all of our Knowledge Hubs and stay up to date on the latest news in each area of hematologic oncology.*

INDOLENT B-CELL LYMPHOMA

Laurie Sehn, MD
Associate Editor

Dr. Sehn writes: "This year at ASH, we saw more data demonstrating the remarkable efficacy of CD20/CD3 bispecifics in follicular lymphoma. The pivotal phase II trial of epcoritamab in relapsed or refractory follicular lymphoma after at least two prior lines of therapy demonstrated a high rate of durable responses. These agents may be even more effective earlier in the course of therapy, as suggested in the phase II trials exploring the use of mosunetuzumab monotherapy and the combination of mosunetuzumab and lenalidomide in previously untreated patients with follicular lymphoma, in which complete response rates of >80% were observed."

Mosunetuzumab Treatment Achieves 'Highly Encouraging Efficacy' for Follicular Lymphoma in Phase II Study

Subcutaneous mosunetuzumab treatment attained a promising safety and efficacy profile in patients with untreated, high-burden follicular lymphoma (FL), according to a phase II study.

Led by **Lorenzo Falchi, MD,** of the Memorial Sloan Kettering Cancer Center in New York, the multicenter study included 43 patients with stage II-IV FL. Subcutaneous mosunetuzumab was administered at 5 mg on day one, 45 mg on days eight and 15 of cycle one, and 45 mg on day one of each subsequent 21-day cycle. Before each dose of mosunetuzumab, patients were premedicated with dexamethasone, diphenhydramine, and acetaminophen during cycle one and on day one of cycle two if cytokine release syndrome (CRS) was observed.

Treatment continued for eight cycles in patients who achieved complete response (CR) and up to 17 cycles in patients who achieved partial response.

Why I chose this research:

"This phase II study reported by Dr. Falchi and colleagues demonstrates that the CD20/CD3 bispecific antibody mosunetuzumab may be even more effective earlier in the course of therapy for patients with follicular lymphoma. Administered as monotherapy in patients with high tumor burden, previously untreated follicular lymphoma, a best ORR of 96% and a CR rate of 81% were observed."

Among 26 response-evaluable patients, the best overall response rate (ORR) was 96% and the CR rate was 81%. Two patients experienced disease progression at a median follow-up of six months.

Among 39 safety-evaluable patients, the most common treatment-emergent adverse events (TEAEs) were all grade 1 and included injection site reaction (71%), CRS (51%), fatigue (33%), dry skin (33%), skin rash (26%), alanine aminotransferase elevation (23%), and aspartate aminotransferase elevation (21%). CRS occurred most often after day one of cycle one.

Overall, Dr. Falchi and colleagues concluded that mosunetuzumab treatment presents a manageable safety profile and "highly encouraging efficacy," though a follow-up assessment of durability of response is needed.

Reference

Falchi L, Okwali M, Ghione P, et al. Subcutaneous (SC) mosunetuzumab (mosun) as first-line therapy for patients (pts) with high tumor-burden follicular lymphoma (FL): first results of a multicenter phase 2 study. Abstract #604. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Dual Treatment Shows Promising Efficacy in Untreated Follicular Lymphoma

Mosunetuzumab combined with lenalidomide showed a manageable safety profile and promising efficacy in patients with untreated FL, according to a phase Ib/II trial.

The trial, led by **Franck Morschhauser, MD, PhD,** of the University of Lille in France, studied a fixed-duration regimen of mosunetuzumab plus lenalidomide throughout 12 cycles. A total of 37 patients received subcutaneous mosunetuzumab 5 mg on day one and a target dose of 45 mg on days eight and 15 of cycle one and day one of cycles two to 12. Meanwhile, patients received oral lenalidomide 20 mg on days one to 32 of cycles two to 12.

Why I chose this research:

"Dr. Morschhauser and colleagues have presented preliminary results from a phase Ib/II trial of mosunetuzumab and lenalidomide in patients with previously untreated follicular lymphoma. Results further support the efficacy and tolerability of this combination that is being evaluated in ongoing phase III trials."

All patients reported at least one TEAE, with 26 patients experiencing TEAEs related to mosunetuzumab and 29 experiencing TEAEs related to lenalidomide. Two patients discontinued treatment, one due to uveitis and one due to tumor flare. Sixteen (43.2%) patients experienced at least one grade 3-4 TEAE, most commonly neutropenia. CRS was observed in 20 (54.1%) patients.

Of 27 efficacy-evaluable patients, 22 (81.5%) reached a complete metabolic response, and two (7.4%) reached a partial metabolic response.

Blood sample analysis showed increased CD69 and sustained human leukocyte antigen-DR expression in CD8 T cells, modulation of CD8 subsets favoring central and effector memory phenotypes, sustained activity of natural killer cells, and minimal effects on CD4 T cells.

"This fixed-duration, chemotherapy-free [mosunetuzumab plus lenalidomide] regimen offers a convenient means for outpatient [subcutaneous] administration," the researchers concluded. "Advancing [this regimen] into the first-line setting offers potential benefits in chemotherapy-naïve [patients]."

Reference

Morschhauser F, Patel K, Bobillo S, et al. Preliminary findings of a phase Ib/II trial indicate manageable safety and promising efficacy for mosunetuzumab in combination with lenalidomide (M+Len) in previously untreated (1L) follicular lymphoma (FL). Abstract #605. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

Phase I Dose Expansion Readout for Epcoritamab in High-Risk Follicular Lymphoma

Monotherapy with subcutaneous epcoritamab yielded "deep and durable responses" with a promising ORR and CR rate among hard-to-treat patients with high-risk relapsed or refractory FL, according to data from a phase I, dose-expansion trial.

The safety profile of epcoritamab was manageable, the development of CRS was predictable, and the incidence and severity of CRS was reduced with optimized step-up dosing, reported lead author, **Kim Linton, MD, PhD,** of the Christie NHS Foundation and Trust and Manchester Cancer Researcher Centre in the United Kingdom. Dr. Linton and colleagues also noted that responses were comparable between subgroups and that measurable residual disease negativity was correlated with improved progression-free survival (PFS).

The study enrolled 128 patients with grade 1-3a relapsed or refractory FL between September 2020 and Octoboer 2022. The cohort had a median age of 65 years, 61% had Follicular Lymphoma International Prognostic Index scores of three to five, and 85% had stage III-IV disease. Participants had a median of three prior lines of therapy (range, 2-9 lines), and 31% had four or more.

Common prior lines of therapy included anthracyclines in 77%, lenalidomide in 31%, and autologous stem cell transplant in 19%. The majority of patients were primary refractory (54%), double refractory (70%), or refractory (69%) to their most recent line of therapy. By the data cutoff of April 21, 2023, the median follow-up was 17.4 months, and the ORR and CR rate were 82% and 63%, respectively. The median time to response and to CR was 1.4 months and 1.5 months, respectively. Researchers reported that the ORR and CR rate trended higher in patients with fewer prior lines of therapy. Additionally, the median PFS was 15.4 months, while median duration of response, duration of CR, and overall survival were not reached.

Patients with fewer prior lines of therapy trended toward higher ORRs and CR rates at 89% and 72% with two prior lines, 88% and 68% with three prior lines, and 68% and 45% with four or more prior lines, respectively. Of patients who achieved a CR, an estimated 85% maintained CR at 12 months and 74% maintained CR at 18 months.

The most common any-grade TEAEs were CRS in 66% of patients, injection-site reaction in 57%, COVID-19 in 40%, fatigue in 30%, neutropenia in 28%, diarrhea in 27%, and pyrexia in 25%. CRS events were 40% grade 1, 25% grade 2, and 2% grade 3 and primarily developed after the first full dose. Authors noted no CRS led to treatment discontinuation.

Why I chose this research:

"In this study, Dr. Linton and colleagues further demonstrated the remarkable efficacy of CD20/CD3 bispecifics in follicular lymphoma. In this pivotal trial in patients with relapsed or refractory follicular lymphoma after at least two prior lines of therapy, epcoritamab was associated with a high rate of durable responses."

TEAEs that led to treatment discontinuation were reported in 19% of patients, of which COVID-19 was the most common. Immune effector cell-associated neurotoxicity syndrome developed in eight (6%) patients and was resolved without treatment discontinuation in all. Fatal TEAEs were reported in 13 patients.

Overall, researchers reported that no new safety signals were detected and added that epcoritamab was being evaluated in an ongoing phase III trial on relapsed or refractory FL.

Reference

Linton K, Jurczak W, Lugtenburg P, et al. Epcoritamab SC monotherapy leads to deep and durable responses in patients with relapsed or refractory follicular lymphoma: first data disclosure from the Epcore NHL-1 follicular lymphoma dose-expansion cohort. Abstract #1655. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

HemOnc Happenings

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

2024 ASH President Begins Term for Society

Mohandas Narla, DSc, a Distinguished Scientist at New York Blood Center Enterprises, began a year-long term as President of the American Society of Hematology (ASH), succeeding **Robert Brodsky, MD.** Dr. Narla will serve as ASH President through December 2024.

Mohandas Narla, DSc

Dr. Narla's research interests include red cell physiology and pathology, and he currently serves as Head of the Laboratory of Red Cell Physiology at New York Blood Center Enterprises. His research focuses on advanced understanding of the molecular and structural basis for red cell membrane disorders, as well as insights into the pathophysiology of thalassemia and sickle cell anemia.

During his tenure, Dr. Narla will focus on global efforts such as overseeing the selection of the Editor-in-Chief of *Blood Global Hematology;* continuing collaborative programs like the Consortium on Newborn Screening in Africa, which screens children for sickle cell disease in sub-Saharan Africa; and supporting training programs in Latin America.

"ASH has become a global influence in hematology, both in practice and research. I'm looking forward to showing how ASH can help improve patient care and equity around the world," Dr. Narla said in a press release. "We at ASH are committed to addressing health care inequalities."

Dr. Narla also plans to strengthen the hematology workforce by sustaining mentorship initiatives such as the Hematology-Focused Fellowship Training Program.

Dr. Narla has been a member of ASH for 34 years and has served on four different committees, including the ASH Research Collaborative. He has served as Associate Editor for *Blood*, the flagship journal of ASH. He also received the Wallace H. Coulter Award for Lifetime Achievement in Hematology in 2020, which recognizes hematologists who demonstrate a lasting commitment to the field.

"Hematology has always been at the forefront of biomedical research, and global research has only grown in the 50 years I've been in hematology," Dr. Narla said in the release. "ASH has been my professional home, and I am honored to serve as ASH President."

Hematologist-in-Training Receives ASH Abstract Achievement Award

Mariia Mikhaleva, MD, a Research Fellow at the Dana-Farber Cancer Institute, received an Abstract Achievement Award at the 65th ASH Annual Meeting & Exposition for her study on mutational burden in patients with treatment-naïve chronic lymphocytic leukemia (CLL).

This merit-based award honors the accomplishments of hematologists-in-training with high-scoring abstracts of which they are the first or senior author and presenter.

Mariia Mikhaleva, MD

"It was a little bit unexpected," Dr. Mikhaleva said of the award. "This is the first ASH award that we have, and I heard this year was really competitive. We are really honored to get this award, and I would like to thank the research team for the greatest help with this project."

A first-generation graduate student, Dr. Mikhaleva earned her doctor of medicine degree in St. Petersburg, Russia, and joined the CLL laboratory of **Jennifer Brown, MD, PhD,** at Dana-Farber in September 2022 as a Fullbright Scholar to continue her doctoral research. Her award-winning abstract, "Higher Mutational Burden Is an Independent Predictor of Shorter Time to First Treatment in Untreated Chronic Lymphocytic Leukemia Patients," identified patterns of co-occurrence and mutual exclusivity among mutations in CLL and their impact on time to first treatment.

Dr. Mikhaleva described the proudest moment so far in her career as being able to combine "the research and the patient." She added, "It is a great feeling that you are involved in the research … that could have an impact in the clinical setting, and a couple of years later, you can use those methods or drugs directly with your patients."

In the future, she plans to continue research in CLL and to study clonal evolution in myelodysplastic syndromes.

"I'm really interested in those clonal evolution patterns in a cell," she said. "I think it could be my next little project."

Lifetime Achievement Award Recognizes Lymphoma Researcher

John Leonard, MD, Senior Associate Dean for Innovation and Initiatives, Interim Chair of the Weill Department of Medicine, and the Richard T. Silver Distinguished Professor of Hematology and Medical Oncology at Weil Cornell Medicine in Ithaca, New York, was given the Lifetime Achievement Award from the Cancer Research & Treatment Fund (CR&T) during the organization's 2023 Cancer Survivor Hall of Fame Dinner.

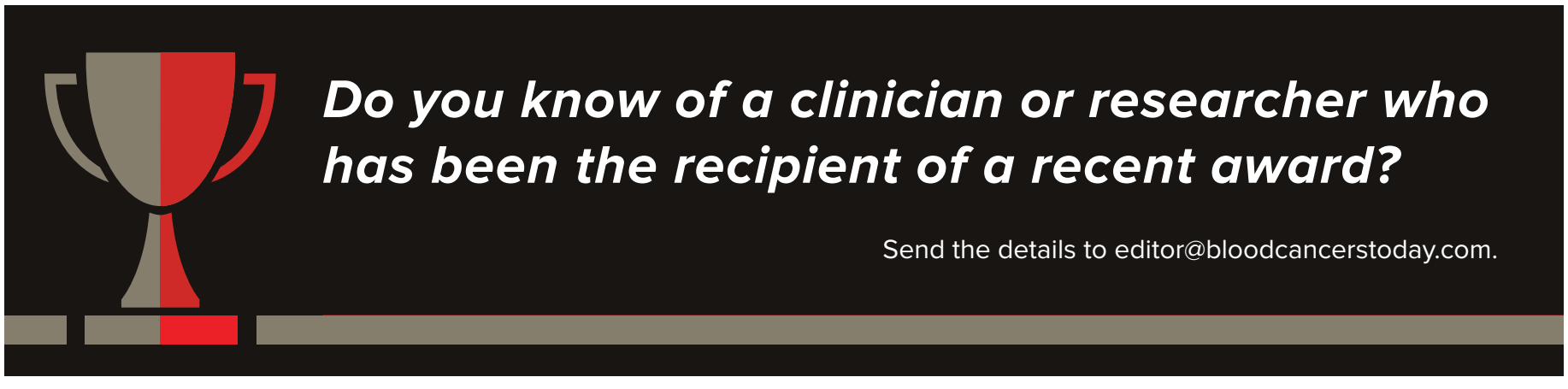
Dr. Leonard received his medical degree from the University of Virginia School of Medicine and was an editorial board member for both *Blood* and the *Journal of Clinical Oncology*. He served as Chair of the Lymphoma Research Foundation from 2012 to 2015.

The CR&T invests in research related to the cause, prevention, treatment, and cure of myeloproliferative neoplasms and other blood and solid tumor cancers, according to a press release from Weil Cornell Medicine.

At left, Dr. Leonard receives the Lifetime Achievement Award from Morton Coleman, MD. Image courtesy of John Munson/CR&T.

"I am honored to be included among the CR&T awardees this year," Dr. Leonard said. "CR&T is a wonderful organization whose work funding vital research directly impacts patients."

The Lifetime Achievement Award recognizes "distinguished researchers and clinicians whose discoveries and commitment to patient care have helped prolong and save lives," according to CR&T.



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HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

Over the course of the last decade, it has been recognized by hematologists and hematologist oncologists that the amount of research and interest in the field of hematologic oncology has increased to the point that the exchange of information could not be accomplished at the other major scientific societies. It was clear that this specialized group needed an opportunity to focus on these malignancies, and to have a meeting where outstanding leaders, innovators and budding young investigators, could interact to stimulate progress in this important field. In 2012, the decision was made to form a new society, the **Society of Hematologic Oncology** (SOHO), which would sponsor an annual meeting to bring together leading investigators and practitioners in the field.

Today, SOHO is a non-profit association committed to promoting worldwide research, education, prevention, clinical studies and optimal patient care in all aspects of hematologic malignancies and related disorders.

GLOBAL REACH

SOHO represents physicians and other health care professionals from all corners of the world. The SOHO global network supports and is supported by nearly 8,000 members from 122 countries, who are leading vital efforts to further treatments for patients with hematologic malignancies. The society is an organization that focuses on learning and educational excellence, and promotes diversity and inclusion.