TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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BLOOD CANCERS TODAY

September/October 2024

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Unpacking CHIP: Recent Updates, Remaining Questions

While research on CHIP has gained momentum in recent years, treating the premalignant condition remains in debate.

With expert opinions from:
Sanam Loghavi, MD;
Catherine Coombs, MD;
and more.

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Translating Modern Care of Blood Cancers Beyond the Academic Walls

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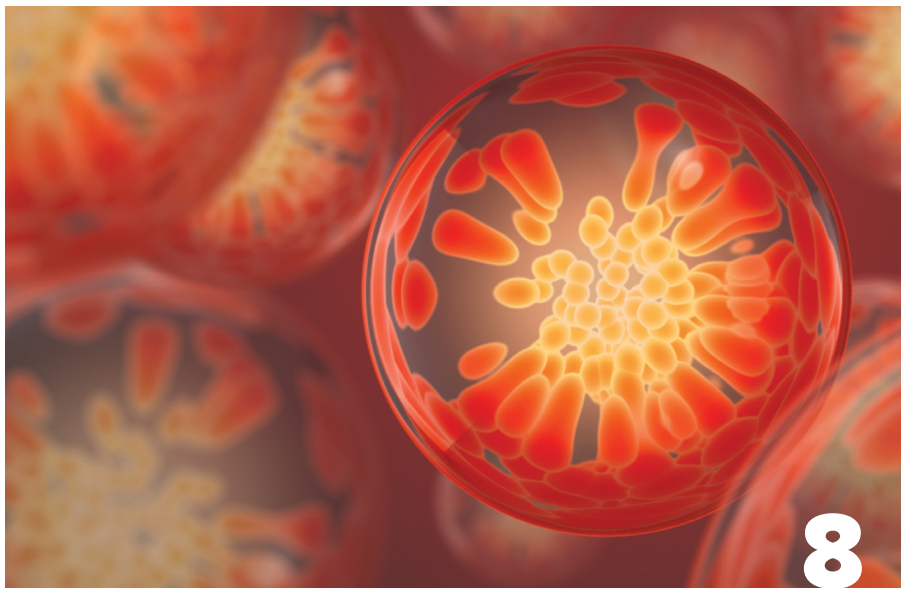

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While research on CHIP has gained momentum in recent years, treating the premalignant condition remains in debate. However, clinicians are focusing on optimizing patient health, monitoring for disease progression, and managing the comorbidities associated with CHIP.

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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

November 6–10, 2024
Society for Immunotherapy of Cancer 39th Annual Meeting
Houston, Texas

November 14–17, 2024
JADPRO Live
Grapevine, Texas

November 15–16, 2024
13th Annual New Therapeutics in Hematology and Oncology: The Road to Personalized Medicine
Los Angeles, California

November 22, 2024
2024 SOHO State of the Art Updates and Next Questions
Virtual

December 6–8, 2024
European Society for Medical Oncology (ESMO) Asia Congress 2024
Singapore, Republic of Singapore

December 7–10, 2024
66th American Society of Hematology (ASH) Annual Meeting & Exposition
San Diego, California

December 11–13, 2024
ESMO Immuno-Oncology Congress 2024
Geneva, Switzerland

January 10–11, 2025
Highlights of ASH North America New York, New York
Seattle, Washington

February 1, 2025
The Leukemia & Lymphoma Society Blood Cancer Conference
San Francisco, California

February 6–8, 2025
EHA-EBMT 7th European CAR T-Cell Meeting
Strasbourg, France

February 12–15, 2025
2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®
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Editor's Message

Translating Modern Care of Blood Cancers Beyond the Academic Walls

Sagar Lonial, MD, FACP
Editor-in-Chief

As I sit here at the beginning of a new academic year, a time when we renew and recharge, welcome new learners, and set the agenda for the coming year, I am struck by a few reflections.

Life as an oncologist in 2024 is a conundrum. On one hand, we rejoice in the success of modern drug development, new molecular testing and diagnostics, and our newfound ability to detect the smallest hints of disease that went undetected just a decade ago. The breakthroughs have been nothing short of spectacular, and patients are clearly benefiting.

Balance this excitement with the patients we see in clinic who have exhausted all these options. We look them in the eye and talk about comfort and the best ways to spend their remaining time. It is impossible to live in both moments; yet they inform each other, drive each other, and drive me in my quest to leave no patient behind.

This is the Yin and Yang of clinical oncology. We see and experience firsthand the joy of remission or cure, with the struggle of discussions that often bring an abrupt end to cherished relationships with patients. New trainees with no long-term way to assess success are hungry for knowledge that can help them surpass the gains of our current generation. However, they haven't yet seen that not every patient benefits from all these new advances due to social, financial, and access-related reasons. At a time when the optimal way to deliver the highest level of care is politically, socially, and financially in flux, we are no closer to tangible solutions that help provide complex care for patients in rural or urban deserts of cancer care.

As we put together this issue of *Blood Cancers Today,* our readers and authors are confronted with the same set of challenges. Don't get me wrong; I would not for a moment go back two decades when therapeutic nihilism prevailed in cancer care; a time when we knew more than we could actually do. But the sting that not all patients can see these benefits remains and should drive our approach to democratize cancer care.

In high school, I was a big fan of Carl Sagan, who proclaimed, "We live in an extraordinary age. These are times of stunning changes…" He was just a few years early for cancer care. That time is now, and it is exciting to see that these developments have significant impacts on our practices and the patients we serve. At the same time, we must strive to improve access and ensure that high quality, state-of-the-art care is available for more than a select few who can travel to tertiary referral centers. If we can create ways to bring these "real world" solutions to the places where most cancer patients are treated, we will have successfully raised the tide of cancer care for all.

Sagar Lonial, MD, FACP, *is Chair and Professor in the Department of Hematology and Medical Oncology, the Anne and Bernard Gray Family Chair in Cancer, and Chief Medical Officer of Winship Cancer Institute at Emory University School of Medicine in Atlanta, Georgia.*

"We must strive to improve access and ensure that high quality, state of the art care is available for more than a select few that can travel to tertiary referral centers."

—Sagar Lonial, MD, FACP

Marlise Luskin, MD, MSCE

Marlise Luskin, MD, MSCE, Educational Director of the Adult Leukemia Program at the Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School, discusses why she pursued hematology-oncology, how she overcomes career challenges, and more.

Where did you grow up, and how did you know you wanted to be a hematologist-oncologist?
I grew up in Minneapolis, Minnesota, in the Midwest of the United States. When I was growing up, I did not know I wanted to be a hematologist. There are some people who have their path set out from an early age and know they want to be a physician. For me, it was more of a journey getting closer to hematology at different steps along the way.

I love reading and writing. When I was younger, I thought I might be an English teacher. As I made my way through high school and college, I realized that science was where I was headed. I was motivated by interactions with patients and their families, which led me to medical school as opposed to graduate school for a PhD in biology. I wanted to combine my interest in science and my interest in people. It was the right decision. I've never regretted it or looked back, even when there were challenges in this career.

I became interested in hematology-oncology during my medical school rotations, but I didn't decide on that until I was partway through my internal medicine training. Hematology-oncology blended all the things I liked most about medicine. I liked being able to see things with my own eyes, looking at blood smears, and making diagnoses on my own without having to rely on fancy tests or other people (although we certainly do those things now). I could interact with patients and see the results of my interventions right away. I got to be both a specialist and the generalist. I didn't have to choose if I wanted to be a primary care doctor or a specialist because, for our patients with blood disorders and leukemias, we're often managing all aspects of their care, which is really rewarding as well.

How did you get started with clinical research?
Sometimes, your focus develops based on interests and opportunities. When I took the job here at the Dana-Farber, I was interested in caring for patients with leukemia. I had been trained by my mentors at the University of Pennsylvania, and I took a gut training in leukemia and bone marrow transplant. When I came here to Dana-Farber, I was given an opportunity by my current boss, **Daniel DeAngelo, MD, PhD,** to participate in acute lymphoblastic leukemia (ALL) research. As a junior faculty, I took a deeper dive into this disease, which I had been exposed to but hadn't necessarily focused on. The opportunity arose and I said, "Hey, this is really interesting."

Over the last eight years, I have gotten involved in clinical research related to ALL with a combination of learning how to do clinical trials. I've found a blend of both clinical trials and retrospective clinical research focusing on ALL, which is something that I've really enjoyed. It takes time to build expertise and learn how to do research. It's something I'm still learning. It adds a dimension of depth and satisfaction to my career.

What are some challenges you face in your career?
No job worth doing isn't without challenges. I think there are different types of challenges. First, there are the administrative and logistical hurdles of getting patients medication, fusions, and tests in the complex health care environment. Sometimes it's related to the institution where you're providing care, and sometimes it's related to the patient's support system or financial or insurance coverage. Learning how to navigate those hurdles and get your patients the care they need is a set of challenges we face every day.

Another challenge is balancing all the competing demands, particularly for those of us who are lucky enough to be in academic medicine, which is wonderful and exciting. We get to use different parts of our brains; we have days where we see patients in clinic, either in the outpatient setting or in the hospital where there's more acuity. But then we're switching gears and working on teaching, mentoring, lecturing, advising, and doing research and administrative tasks for managing a program. It's a challenge trying to balance all those competing demands, which don't always recognize the other. But it's a good challenge to have. It means I get to do different things on different days and feel rewarded in different ways.

"The most profound challenge is taking care of patients and bearing witness to the impact that diseases have on their lives... Caring for patients during those difficult journeys certainly has an emotional impact. And it *should,* because we're taking care of our fellow human beings."

—Marlise Luskin, MD, MSCE

The most profound challenge is taking care of patients and bearing witness to the impact that diseases have on their lives. In some cases, we're able to get them through a challenging period successfully, cure or control their disease, and allow them to continue pursuing their lives in the way they hoped to before. In other cases, the success of our treatments is not as good as we would hope. Caring for patients during those difficult journeys certainly has an emotional impact. And it *should,* because we're taking care of our fellow human beings.

Were there any mentors who shaped your career path? In medical school or your fellowships or beyond?
The people that stick out in my mind who inspired

me to be the doctor that I am today have been at both the Dana-Farber Cancer Institute and Brigham and Women's Hospital here in Boston, where I work and did my internal medicine residency. **Robert Soifer, MD,** Chief of the Division of Hematologic Malignancies at Dana-Farber, was very inspiring when I was a medical resident. Leaders of our leukemia group, **Richard Stone, MD,** and **Martha Wadleigh, MD,** also inspired me when I was a "Baby Doc." I left Dana-Farber, completed my fellowship at the University of Pennsylvania, then had the opportunity to come back. Joining the faculty here with so many people I admire is truly something I never thought would be possible.

I did my clinical training under **Alison Loren, MD, MSCE,** Chief of the Division of Hematology Oncology and Director of Bone Marrow Transplantation at Penn Medicine. Her approach to patient care, mentoring, and lifting up those around her is something I really found inspirational.

What advice do you give to your own mentees?

We're lucky that in medicine, there's so many different careers that provide lots of different opportunities. However, it can feel daunting to figure out the right path. So, remember to take lots of advice and ask your mentors how they care for patients, how they have been successful in their research careers, how they got to where they are today, what challenges they face, and which strategies helped them be successful.

I always tell my mentees to get exposure to and find many different role models and mentors, because no two human beings are the same. When we give advice to mentees, we're often modeling it on our own experiences. That mentee has different strengths, different skill sets, and often joined the workforce at a different time.

Blend the experiences of people who have had different journeys and apply the lessons that are most applicable to the challenges you might be facing. You probably won't be able to take everybody's advice, but be open to course correction when you do get advice.

Try to keep an open mind about redirection or advice, because course correction earlier on might save you time, effort, blood, sweat, and tears down the road. Consider evaluating your own experience. You might think that you enjoy a particular field, or a particular type of research or clinical environment, and decide to pursue that. But if you find that it's not the right fit, do that course correction early on.

Based on your own personal circumstances and the realities of the job market, you may need to calibrate your strategy. Are you restricted to a geographic area, or are you flexible to relocate for your ideal job? It's important to find the balance between idealism and realism to help you feel fulfilled in your career.

What do you hope to see in the field over the next 10 years?

There have been a number of new drug approvals, and outcomes are improving for patients with ALL of different subtypes. However, it's still a challenging disease. There are high-risk subtypes, chemotherapy-resistant ALL, and patients with other comorbidities who don't tolerate current treatments. I'm looking forward to improving the range of options for our patients and understanding how to best tailor treatment in terms of intensity and drug choice for patients regardless of their situation. It's a rare disease, so it requires a lot of international cooperation. I look forward to building on our knowledge base and moving the needle forward year by year for our patients.

What hobbies or activities do you enjoy outside of work?

I will be honest—I spend a lot of time working. The nine-to-five is filled with clinical work and immediate needs. A lot of research, reading, and thinking goes on after hours, and that's something I do by choice. You will find me in the evenings and some weekends reading papers from my colleagues and continuing to develop that expertise. This is important when you're in the patient's room the following week with the specific problem. You want to make sure that your research is up to date. Work-life balance is important, but developing a passion and a career is okay too.

However, we all need to take a break. It's important to let your brain have some diastole. I enjoy spending time with friends outside of work, trying new restaurants, being outdoors, and going for hikes. I also enjoy reading novels and catching up on my favorite Netflix shows.

First SOHO-ABHH Joint Symposium to Kick Off at HEMO 2024

By ***Melissa Badamo***

For the first time, the Society of Hematologic Oncology (SOHO) is teaming up with the Brazilian Society of Hematology (ABHH) for a joint session at the 2024 Brazilian Congress of Hematology, Hemotherapy and Cellular Therapy (HEMO) Meeting. The third largest hematology congress in the world, this annual event will take place October 23-26 at the Transamerica Expo Center in São Paulo, Brazil, drawing an anticipated 7,000 attendees.

Leaders from SOHO and ABHH spoke with *Blood Cancers Today* to discuss the goals and initiatives of the joint symposium, how the meeting came about, and what they hope to accomplish in future meetings.

Joint Symposium Origins

Phillip Scheinberg, MD, PhD, President of SOHO and Chief of Hematology at the Hospital A Beneficência Portuguesa de São Paulo in Brazil, first described how the SOHO and ABHH leaders came together to prepare the joint symposium for takeoff.

Phil Scheinberg, MD, PhD

After SINTOMA 2018, the Brazilian edition of SOHO and the first SOHO meeting outside of Houston, Dr. Scheinberg and his team began looking for opportunities to increase engagement of SOHO with a Brazilian audience.

Silvia Magalhães, MD, PhD

"It became about bringing SOHO closer to the things that were happening in Brazil," he elaborated. After proposing the idea, the SOHO team met with HEMO leaders in February 2024. After a successful meeting, the idea crystallized into an opportunity for the two societies to unite to promote the exchange of research and information on blood cancers.

Angelo Maiolino, MD, PhD

"We have a great team trying to organize the symposium," said **Silvia Magalhães, MD, PhD,** President of HEMO, Director of ABHH, and Professor of Clinical Medicine at the Walter Cantídio University Hospital. "I am very honored to be President of HEMO this year. SOHO makes us very happy, and we expect to have a great partnership this year and in future years."

Besides SOHO, ABHH also has partnerships with the American Society of Hematology and the European Hematology Association, Dr. Magalhães said. In addition, HEMO 2024 will feature joint sessions with the two societies.

"It's tradition to have joint symposiums at our meeting," added **Angelo Maiolino, MD, PhD,** President of ABHH and Professor of Hematology at the Federal University of Rio de Janeiro. "We are excited to have the first joint symposium with SOHO. It is a great opportunity for us, and we hope to have another one in our upcoming meetings and at the SOHO meetings."

Goals and Initiatives

The joint symposium will feature expert speakers and include two sessions: a morning session focusing on acute myeloid leukemia (AML), and an afternoon session focusing on myelodysplastic syndromes (MDS). Specifically, the symposium will include updates on higher-risk MDS with **Amy Dezern, MD, MHS,** Professor of Oncology and Director of the Bone Marrow Failure and MDS Program at Johns Hopkins University; updates in lower-risk MDS with **Rami Komrokji, MD,** Vice Chair of the Malignant Hematology Department at the Moffitt Cancer Center; and recent progress in cellular therapy in acute lymphoblastic leukemia and AML with **Jae Park, MD,** Chief of Cellular Therapy Service at Memorial Sloan Kettering Cancer.

"We want to bring perspectives and innovation," Dr. Scheinberg said. "The sessions will bring different perspectives of the data, how these experts see this information, and how they apply it to their practice. We're also doing something really forward looking, [chimeric antigen receptor T-cell therapy] for AML, which is not something that's been approved and is in early stages of development. We thought about balancing the present and the future to give perspective about what's coming in the field."

Furthermore, Dr. Scheinberg hopes to ensure that each speaker engages with the local audience so that attendees can apply the information to their own practices.

"It's a different audience, so we always like to brief the speaker so they can understand the local reality of things," he said. "Otherwise, the speaker may come across as being too distant from the audience's reality and speak in terms and in ways that are not applicable to what we have here. We're looking for this proximity for this engagement, and we're looking for engagement from the audience."

This applies to geographical aspects such as regulatory access to drugs, Dr. Scheinberg explained, which varies in different parts of the world.

"We're looking forward to bringing value to the HEMO meeting," Dr. Scheinberg concluded. "SOHO will learn from it, because they will learn from different physicians from different markets and different parts of the world. That has always been the SOHO mission since its inception in 2012."

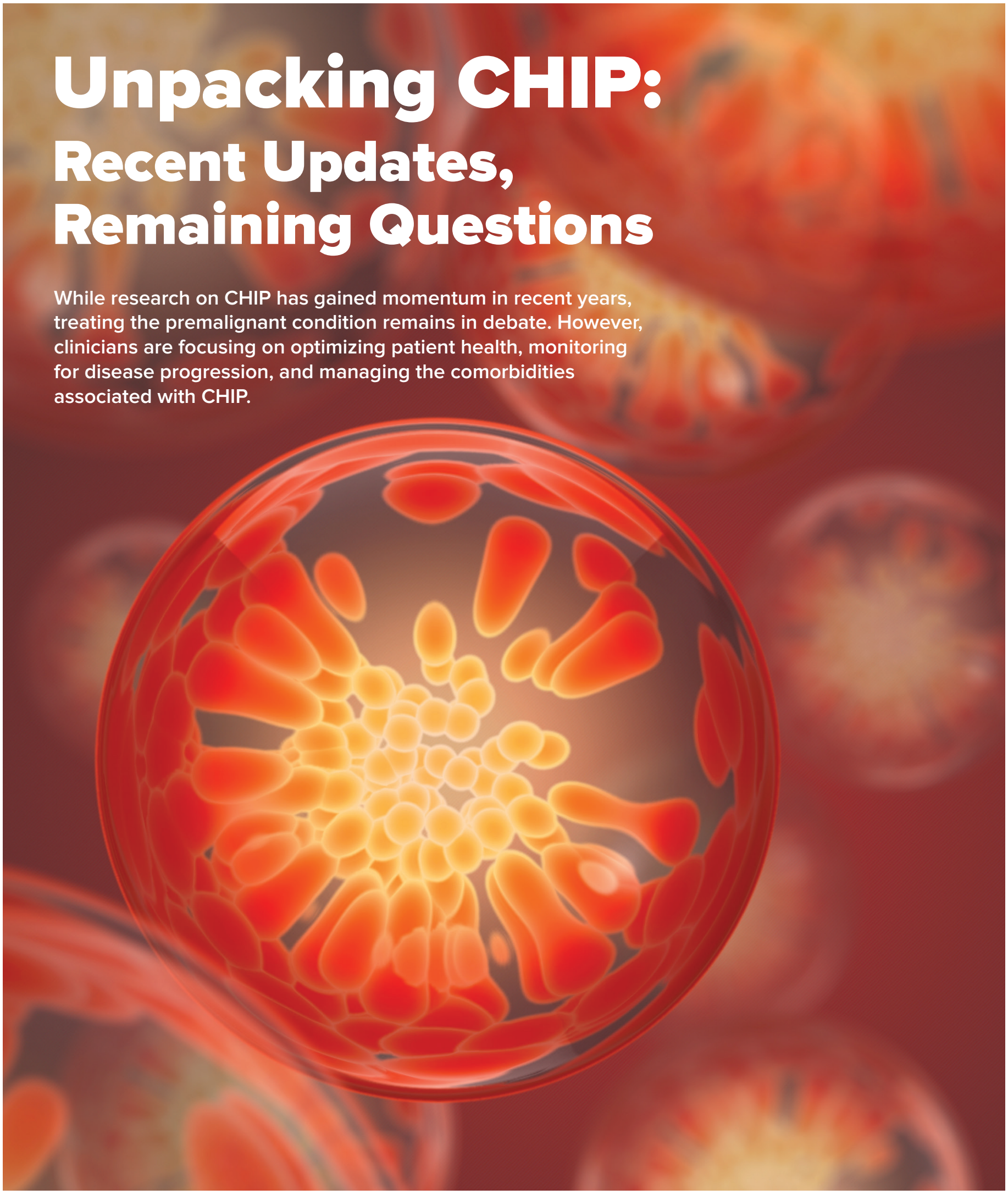
***Melissa Badamo** is an Assistant Editor for* Blood Cancers Today.

In Focus

Blood Cancers Today *takes an in-depth look at hot topics in hematologic oncology*

Unpacking CHIP: Recent Updates, Remaining Questions

While research on CHIP has gained momentum in recent years, treating the premalignant condition remains in debate. However, clinicians are focusing on optimizing patient health, monitoring for disease progression, and managing the comorbidities associated with CHIP.



Clonal hematopoiesis of indeterminate potential (CHIP) refers to a biological process when a hematopoietic stem cell gains clonal potential from a mutation, providing it with a growth advantage over normal healthy cells.

"CHIP is considered preclinical, in that those who have CHIP may go on to develop a malignant condition in the future," said **Yael Kusne, MD, PhD,** an Assistant Professor of Medicine at Mayo Clinic Arizona. "It is akin to monoclonal B cell lymphocytosis prior to development of chronic lymphocytic leukemia or monoclonal gammopathy of undetermined significance prior to development of multiple myeloma."

Research on CHIP has gained momentum in recent years with the advancement of technology and has linked the preclinical condition to a variety of comorbidities. *Blood Cancers Today* spoke with several physicians and researchers about CHIP, research into the condition, recent developments, and remaining questions.

CHIP Gains Notice

As it is understood today, CHIP was first described in two large-scale clinical studies published on Christmas Day 2014 in the *New England Journal of Medicine*.

One study used whole-exome sequencing on data from more than 17,000 unselected individuals to look for somatic mutations in 160 genes that are mutated in hematologic cancers. They found that the presence of these mutations increased with age and was associated with an increased risk for hematologic cancer, all-cause mortality, incident coronary heart disease (CHD), and ischemic stroke.[1]

The second study used whole-exome sequencing of DNA from more than 12,000 individuals and found an increase in somatic mutations with age and increased risk for hematologic cancer.[2]

"It has been more than a decade now since CHIP was formally described, but it has not been well-described in the clinical literature until recently," said **Shyam Patel, MD, PhD,** an Assistant Professor at UMass Chan Medical School.

CHIP became "well-described" in 2022 when researchers from the Wellcome-MRC Cambridge Stem Cell Institute and colleagues published the results of genome-wide analyses from more than 200,000 individuals in the United Kingdom (UK) Biobank that increased the number of germline associations with CHIP from four to 14, and again confirmed the association of CHIP with increased risk for myeloproliferative neoplasia, nonhematologic malignancies, and atrial fibrillation.[3]

"It took about eight years for CHIP to go from a pathophysiologic process to a clinically defined disease," Dr. Patel said. "Now, we are seeing patients with CHIP on a regular basis because it is a recognized disease entity."

In 2022, CHIP was included in both the 5th edition World Health Organization Classification (WHO-HAEM5) and the International Consensus Classification as a myeloid precursor lesion.[4,5]

How Is CHIP Diagnosed?

The definition of CHIP has evolved as technologies have advanced, explained **Sanam Loghavi, MD,** an Associate Professor of Pathology and Lab Medicine at The University of Texas MD Anderson Cancer Center.

"Age-related clonal hematopoiesis is defined as having a somatic mutation in a gene that is recurrently mutated in myeloid malignancies, but occurs in healthy individuals with no cytopenia, with a variant allele frequency (VAF) of ≥2%," Dr. Loghavi said.

The most commonly mutated genes are *DNMT3A, TET2,* and *ASXL1*.[6]

"Somatic mosaicism is often age-related, but there are some data that shows that it can happen very early on in age,"[7] Dr. Loghavi said. "If you look with very sensitive methods at individuals older than 40, almost everybody has clonal hematopoiesis. Some people might argue that it is an evolutionary mechanism to conserve hematopoiesis."

> **"If you look with very sensitive methods at individuals older than 40, almost everybody has clonal hematopoiesis. Some people might argue that it is an evolutionary mechanism to conserve hematopoiesis."**
>
> *—Sanam Loghavi, MD, Associate Professor of Pathology and Lab Medicine, The University of Texas MD Anderson Cancer Center.*

CHIP was first recognized in healthy individuals because researchers were looking for these mutations in large-scale cohorts. In the real-world setting, people are often diagnosed with CHIP because their blood is getting sequenced for other reasons, Dr. Loghavi explained.

"The field of CHIP has evolved to include two broad categories; one is truly age-related clonal hematopoiesis or CHIP in a healthy individual who will probably go on to live life without ever developing myeloid neoplasms," Dr. Loghavi said. "The other is referred to as context-dependent CHIP. These are often discovered in someone with another type of cancer who may get exposed to chemotherapy or have other predisposing conditions that may 'fuel the fire' and increase the risk for developing myeloid neoplasms."

Comorbidity Risk

Studies have shown CHIP to be linked with a plethora of other comorbid conditions. "There are at least six different nonhematologic diseases for which CHIP is an independent risk factor," Dr. Patel said.

In 2017, **Siddhartha Jaiswal, MD, PhD,** of Stanford University School of Medicine, and colleagues published the results of their whole-exome sequencing analysis looking for associations between CHIP in peripheral blood cells and CHD. Using samples from four case-control studies including more than 4,000 individuals, they found that CHIP was associated with an almost twofold increased risk for CHD compared to noncarriers of CHIP. Mutations in *DNMT3A, TET2, ASXL1,* and *JAK2* were individually associated with CHD.[8]

More recently, a study of individuals from the Jackson Heart Study and the Women's Health Initiative showed a more than twofold higher risk for incident heart failure with preserved ejection fraction among those with *TET2* CHIP.[9]

In 2023, researchers from the TOPMed Diabetes Working Group and National Heart, Lung, and Blood Institute TOPMed Consortium published results of a whole-genome sequencing study of blood DNA taken from more than 17,500 individuals without prior type 2 diabetes, cardiovascular disease, or cancer. Baseline CHIP was associated with a 23% higher risk for type 2 diabetes. Specifically, risk was higher in those with *TET2* (hazard ratio [HR]=1.48), and *ASXL1* (HR=1.76) mutations.[10]

Because CHIP was linked with cardiovascular disease, researchers also looked at the association between CHIP and another age-related inflammatory process: chronic obstructive pulmonary disease (COPD). After analyzing data from almost 50,000 individuals, the researchers established associations between CHIP and the presence and severity of COPD.[11]

A recently published study using data from the UK Biobank established a link between CHIP and the risk for neurodegenerative diseases such as vascular neurodegenerative diseases (HR=1.31) and amyotrophic lateral sclerosis (ALS; HR=1.50). This increased risk was mainly seen with *DNMT3A, ASXL1,* or *SRSF2* mutations.[12]

Other studies have linked CHIP to increased incident osteoporosis diagnosis and decreased bone

mineral density,[13] gout,[14] chronic kidney disease,[15] and acute kidney injury.[16]

Now What?

For individuals with CHIP, nothing can be done to change the natural history of the identified mutation, said **Catherine C. Coombs, MD,** an Associate Clinical Professor at the University of California, Irvine.

"When I see a patient referred for [CHIP], I explain the common nature of having such mutations but note that there are no proven strategies to reduce or eliminate these clones," Dr. Coombs said. "However, CHIP does have other health implications, such as increased risk for CVD mortality, and we can optimize health from a cardiac standpoint."

oncologist, we made the recommendation that continuing the PARP inhibitor may be of more harm than good."

If a patient has CHIP and is getting chemotherapy, there is a higher risk of therapy-related myeloid neoplasms, Dr. Coombs said. This should help inform the risk-benefit discussion, but "in the end, you have to deal with the cancer you know you have as opposed to one you might get," Dr. Coombs said.

For healthy individuals with CHIP, monitoring for progression to a hematologic malignancy is a watchful waiting strategy, Dr. Coombs said.

However, there are tools that allow clinicians to estimate risk for development of a myeloid neoplasm.

"When I see a patient referred for [CHIP], I explain the common nature of having such mutations but note that there are no proven strategies to reduce or eliminate these clones. However, CHIP does have other health implications...and we can optimize health from a cardiac standpoint."

—Catherine C. Coombs, MD, Associate Clinical Professor, University of California, Irvine.

This optimization of modifiable risk factors typically involves working with a cardiologist or a primary care provider to help patients optimize blood pressure and lipids and to adopt healthy lifestyle behaviors such as increasing exercise or losing weight if needed.

When referred to a patient with CHIP who also has a solid tumor, Dr. Coombs said that the CHIP diagnosis only occasionally changes her recommendations for cancer treatment.

"This will depend on the strength of evidence for the treatment they are getting, if they have active disease, if the therapy is being given adjuvantly, and how high of a risk mutation they have," Dr. Coombs said.

For example, Dr. Coombs was referred a patient with CHIP who had a *TP53* mutation with VAF of 20%. This patient was on a PARP inhibitor to treat ovarian cancer, but did not have a *BRCA* mutation.

"Because there was no *BRCA* mutation, the benefit of adjuvant therapy with a PARP inhibitor is low, but we do know that a PARP inhibitor can lead to increased risk of therapy-related myeloid neoplasms," Dr. Coombs said. "In conjunction with the patient's gynecological

Establishing Risk

"The clonal hematopoiesis risk score [CHRS] takes information about the patient and uses a computational algorithm to stratify patients into low-, intermediate-, or high-risk," said Dr. Kusne. "This allows us to provide patients with a general idea of their risk for developing blood cancers in the future."

In 2023, **Lachelle Weeks, MD, PhD,** of the Dana-Farber Cancer Institute, and colleagues performed an analysis on sequenced exomes of more than 400,000 healthy individuals from the UK Biobank to develop the CHRS, which was then validated in cohorts of patients with CHIP or clonal cytopenia of undetermined significance (CCUS)—CHIP in the presence of unexplained cytopenia. The risk score used factors such as single *DNMT3A* mutations, high-risk mutations, having two or more mutations, a VAF ≥20%, age ≥65, red blood cell indices, and more.[17]

The majority (88.4%) of individuals were defined as low-risk. Most myeloid neoplasms eventually developed in those considered high-risk.

"This was based on samples in the UK Biobank from healthy individuals, and retrospectively looked at people who developed myeloid neoplasm to construct the risk score," Dr. Loghavi said. "This does not necessarily apply in the context-dependent setting."

Dr. Patel acknowledged that in a real-world setting, most cases of clonal hematopoiesis are diagnosed in the presence of cytopenias. To address this, Dr. Patel and colleagues conducted a study attempting to characterize the clinical trajectories of patients with clonal hematopoiesis who had a clinical indication for CHIP testing in the first place.[18]

"We found slightly different results," Dr. Patel said. "In our analysis, the predictors of progression were presence of non*DNMT3A/TET2/ASXL1* mutations, high VAF, and presence of *RUNX1* mutation. These factors conferred high relative risk for progression."

In this analysis, *RUNX1* mutations had the strongest risk for progression to myeloid neoplasm (odds ratio=10.27), and mean VAF across all genes was higher in those who progressed than in those who did not.[18]

Another real-world study published in *Blood* earlier this year developed a three-parameter Clonal Cytopenia Risk Score (CCRS)—the presence of splicing mutation(s) (score=2 points), platelet count <100×109/L (score=2.5), and ≥2 mutations (score=3)—and stratified patients into low- (score<2.5 points), intermediate- (score 2.5-<5), and high-risk (score≥5) groups.[19] This CCRS predicted the two-year cumulative incidence of development of myeloid neoplasms, with high-risk groups having a 37.2% risk.

"The utility of risk assessment is knowledge for the clinician and the patient," Dr. Patel said. "It can help them plan accordingly."

Dr. Coombs agreed, "If you have a detail-oriented patient, you can do these models in front of them to help them understand what their risk is."

What Can Be Done?

"Whether patients with high-risk CHIP who also have blood count abnormalities—CCUS—should be treated prior to hematologic malignancy remains in debate," Dr. Kusne said. "There are clinical trials for this currently."

The IMPACT study is investigating canakinumab, a monoclonal antibody targeting interleukin-1β, for CCUS.[20] Memorial Sloan Kettering has a pilot study of the IDH2 inhibitor enasidenib in patients with CCUS and *IDH2* mutations.[21] Similarly, researchers at Washington University School of Medicine have launched a trial of the IDH1 inhibitor ivosidenib in patients with CCUS and mutations in *IDH1*.[22]

At the CHIP Clinic at Stanford Medicine, **Tian Yi Zhang, MD, PhD,** an Assistant Professor of Medicine, is hoping to launch a clinical trial investigating whether magrolimab can prevent the development of acute myeloid leukemia in patients with therapy-related *TP53* CHIP mutation.[23]

Data presented at the European Hematology Association 2024 Hybrid Congress detailed a randomized study on the use of vitamin C supplementation in patients with low-risk myeloid malignancies or CCUS, with preliminary results showing "significantly longer overall survival" in the vitamin C supplementation group.[24]

"With a small study, sometimes you get lucky with your results and find something significant even when it is not the primary endpoint," Dr. Coombs said. "The full paper on this is not out yet, but there could be something to the vitamin C story."

Unanswered Questions

Despite recent progress, many unanswered questions remain.

Dr. Patel said one area of interest is whether artificial intelligence could identify patterns of specific mutations that predict the development of myeloid neoplasms.

"There are so much raw clinical data in terms of genomics, but it is hard to analyze manually," Dr. Patel said. "It would be interesting to see if there was a way to use an automated pipeline to analyze this genetic information to predict the likelihood and timeframe of myeloid neoplasms development."

Another important question is whether there are effective interventions to change the natural history, specifically as it relates to hematologic malignancies and cardiovascular disease, Dr. Coombs said.

"I am aware of these studies for CHIP, but another big question is who should we be checking to identify patients to enroll in these studies," Dr. Coombs said. "We don't want to check everyone because that would be a huge financial cost and a lot of unnecessary anxiety."

Dr. Patel also said that he would like to see the development of evidence-based or expert-consensus guidelines for the management of patients with CHIP, and the hematologic and nonhematologic conditions associated with CHIP.

"Implementation of formalized clinical guidelines on CHIP would help patients and might be a big step forward in terms of large-scale population health," Dr. Patel said. "Guidelines may also help determine whether to screen stem cell transplant donors for CHIP, which affects population health in large-scale."

In fact, a recent meta-analysis examined a series of studies looking at the effects of donor-engrafted clonal hematopoiesis in patients undergoing allogeneic and autologous hematopoietic stem cell transplantation (HSCT).

Using data from five allogeneic HSCT studies and nine autologous HSCT studies, Dr. Patel and colleagues found that pretransplant clonal hematopoiesis among patients undergoing autologous HSCT was associated with worse overall survival (hazard ratio [HR]=1.30), progression-free survival (HR=1.35), and higher risk for therapy-related myeloid neoplasms (HR=4.85).

"When using stem cell donor in the allogeneic setting, there was no adverse impact imparted by donor-derived clonal hematopoiesis upon the recipient," Dr. Patel said.

Clonal hematopoiesis after HSCT decreased risk of relapse, but had no effect on survival outcomes.

"With this meta-analysis, there were clearly inferior outcomes in autologous [HSCT] setting," Dr. Patel said. "Our study suggests that it is probably worth screening autologous [HSCT] recipients for clonal hematopoiesis."

Lastly, as Dr. Kusne pointed out, the biology of CHIP has not been completely elucidated.

"While we know why some clones grow over others—for instance, clones with DNA damage repair pathway mutations gain growth advantage from chemotherapy and radiation—the mechanisms behind how these clones interact and impact their environment is not yet clear," Dr. Kusne said. "In time, with the continual improvement of our technologies, we will be able to answer more of these questions and perhaps determine when and how to intervene."

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

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Highlights From the **2024 PAN PACIFIC LYMPHOMA CONFERENCE**

NX-5948 Shows Early Promise in CLL After BTKi Failure

Treatment with NX-5948 demonstrated tolerable safety and induced promising responses in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), according to data from a phase Ia study presented at the 2024 Pan Pacific Lymphoma Conference. The study was led by **Nirav Shah, MD,** of the Medical College of Wisconsin.

Nirav Shah, MD

"Deep clinical responses were observed in a heavily pretreated population of patients with CLL and NHL, some with Bruton's tyrosine kinase inhibitor (BTKi) resistance mutations, high-risk molecular features, and central nervous system [(CNS)] involvement," wrote the study's authors.

NX-5948 in Treatment of CLL After BTKi

This first-in-human, dose-escalation trial enrolled patients with two or more prior lines of therapy, evaluable disease, and Eastern Cooperative Oncology Group performance scores of zero or one. The primary objectives were to evaluate the safety and efficacy of NX-5948, establish a maximum tolerated dose, and identify a recommended phase II dose.

The study enrolled 46 patients, of whom 16 had CLL and 30 had NHL, including six with CNS involvement. The median age was 64 years (range, 42-88 years), and 67.4% were male. Participants received once-daily doses of 50 mg, 100 mg, 200 mg, 300 mg, 450 mg, or 600 mg.

After an overall median duration of follow-up of 3.4 months (range, 0.2-20.1 months), NX-5948 was reportedly well tolerated at all doses, with no treatment-related serious adverse events (AEs) and no patients discontinuing due to treatment-emergent AEs (TEAEs). The most common TEAEs were purpura or contusion, thrombocytopenia, and neutropenia.

Among 10 patients with evaluable CLL, seven had a partial response at doses of 50 mg to 200 mg. Among 24 patients with evaluable NHL, eight patients responded at doses of 50 mg to 600 mg. Notably, all four patients who received the 450-mg dose had a response, including three complete responses and one partial response.

"These data suggest a role for NX-5948 in the CLL treatment landscape and warrant its continued investigation in NHL, including subtypes where BTKi may not be sufficient," the researchers concluded.

Reference

Shah N, Linton K, Collins P. Latest results from an ongoing first-in-human phase 1a/b study of NX-5948, a selective Bruton's tyrosine kinase (BTK) degrader, in patients with relapsed/refractory CLL and other B-cell malignancies. 2024 Pan Pacific Lymphoma Conference; July 15-19, 2024; Lahaina, Hawaii.

Bispecific Antibody Produces Response in CLL With Richter Transformation

Epcoritamab monotherapy produces noteworthy response rates with manageable safety in patients who have Richter transformation (RT), according to updated results from the phase Ib/II EPCORE CLL-1 trial presented at the 2024 Pan Pacific Lymphoma Conference in Lahaina, Hawaii. The study was led by **Arnon Kater, MD,** of the Cancer Center Amsterdam.

Initial trial findings on the use of this subcutaneous bispecific antibody to treat CLL and RT were promising, and trial investigators presented results at the conference from a larger patient cohort with longer follow-up.

Arnon Kater, MD

"These highly encouraging data support further evaluation of epcoritamab as a chemotherapy-free treatment option for [patients] with RT," the investigators wrote.

The cohort included 35 adult patients with a median age of 69 years. Among them, 91% had received at least one prior treatment for CLL or RT, and 49% had prior treatment specifically for RT. The cohort received epcoritamab 48 mg in 28-day cycles until disease progression and had a median follow up of 8.1 months.

In the 26 patients for whom response could be evaluated, the overall response rate was 50% and 35% of patients achieved complete response (CR). Among those patients who achieved CR, the investigators estimated that 53% were still in CR at nine months, and that this rate specifically among patients with untreated RT was higher still at 75%.

"Safety was tolerable and consistent with prior reports. Most cytokine release syndrome [CRS] was low grade, and no new safety signals were observed," the investigators wrote regarding treatment-emergent adverse events (TEAEs).

CRS was the most common nonhematologic TEAE and occurred in 80% of the cohort. Four patients experienced immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical tumor lysis syndrome (CTLS) occurred in three patients. However, no instances of CRS, ICANS, or CTLS led to epcoritamab discontinuation. There were three mortalities in the trial, two from general physical health deterioration and one due to sepsis. Efforts to further mitigate CRS with C1 optimization, including an additional step-up dose of epcoritamab, are ongoing," the investigators concluded.

Reference

Kater AP, Janssens A, Eradat H, et al. Single-agent epcoritamab leads to deep responses in patients (pts) with Richter's transformation (RT): primary results from the EPCORE CLL-1 trial. Presented at the 2024 Pan Pacific Lymphoma Conference; July 15-19, 2024; Lahaina, Hawaii.

Luspatercept Use in MDS Associated With Fewer Patient Visits, Less Resource Use

Compared to erythropoiesis-stimulating agents (ESAs), treatment with luspatercept led to significantly less health care resource utilization (HRU) by patients with myelodysplastic syndromes (MDS), according to a study of real-world data.

The study was led by **Brian Ball, MD,** of the City of Hope National Medical Center, and presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology in Houston, Texas.

Brian Ball, MD

The research team utilized patient data from January 1, 2015, through December 29, 2022, in the Symphony Health database. Data were collected on patients with MDS who filed a first luspatercept or ESA claim, with no other MDS treatments at baseline. The primary outcome was the number of annual inpatient and outpatient visits. The researchers estimated HRU rates after adjusting for age, sex, region, Charlson Comorbidity Index (CCI), transfusion burden, and baseline HRU.

The analysis included 243 patients treated with luspatercept and 3,515 treated with ESAs. At index, the median age was similar between groups (77 years in the luspatercept group vs 78 years in the ESA group). Compared to the ESA group, patients who received luspatercept had lower baseline CCI (3.3 vs 4.2) and were more likely to have had four or more transfusion dates in the eight weeks preceding the first treatment claim (6.6% vs 1.2%). Roughly half of the luspatercept cohort had other MDS treatments before baseline, compared to 1.6% of the ESA cohort.

"HRU rates after treatment initiation were significantly lower among patients treated with luspatercept," the study authors reported. Treatment with luspatercept was associated with a 26% lower rate of inpatient visits compared with ESAs (incidence rate ratio [IRR], 0.74; 95% CI, 0.58–0.93). For the number of outpatient visits, the luspatercept group had a 31% lower rate than the ESA group (IRR, 0.69; 95% CI, 0.61–0.79). In addition, follow-up inpatient visits were significantly lower in the luspatercept cohort (IRR, 0.75; 95% CI, 0.56–0.99).

In summary, the investigators wrote, "This study found luspatercept was associated with a statistically significant reduction in HRU compared with ESA treatments."

Reference

Ball B, Song R, Zanardo E, et al. Real-world impact of luspatercept versus erythropoiesis-stimulating agents on the healthcare resource utilization of patients with myelodysplastic syndromes in the United States. Abstract #MDS-059. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology; September 4-7, 2024; Houston, Texas.

How Has the B-ALL Patient Journey Evolved Following Tisa-Cel Therapy?

Patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) are receiving tisagenlecleucel (tisa-cel) earlier in their treatment regimens, therefore prolonging relapse-free survival (RFS) and reducing the use of hematopoietic stem cell transplantation (HSCT), according to a recent study.

The study was led by **Rayne H. Rouce, MD,** of Baylor College of Medicine, and presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology in Houston, Texas. Dr. Rouce and colleagues aimed to examine the impact of tisa-cel on the patient treatment journey following its 2017 approval by the US Food and Drug Administration.

Rayne H. Rouce, MD

The researchers collected data for the noninterventional, prospective, longitudinal study using the Center for International Blood & Marrow Transplant Research (CIBMTR) registry. They gathered data on 974 patients who received the chimeric antigen receptor T-cell therapy.

Disease burden before infusion decreased from 18% in 2018 to 4% in 2022. The percentage of patients receiving tisa-cel while in morphologic complete remission increased from 34% in 2018 to 51% in 2022. Fewer patients were in third or greater relapse (14% in 2018 vs 2% in 2022).

The percentage of patients undergoing HSCT prior to tisa-cel infusion also decreased from 37% in 2018 to 15% in 2022. However, the rate of post-infusion HSCT remained unchanged at 34.5%. Reasons for post-infusion HSCT included relapse, persistent or progressive disease, or measurable residual disease positivity.

HSCT frequency decreased in patients with high-risk cytogenetics. Despite 72% of patients harboring a *KMT2A* rearrangement, only 16% received a prior HSCT and 43% received a post-infusion HSCT in 2017.

Censoring for HSCT increased the median RFS from 18 months in 2018 to 27 months in 2020. Without censoring, overall survival probabilities were 66 (95% CI, 61–71) and 62 (95% CI, 57–66), respectively.

"The use of HSCT in this setting should be carefully evaluated," the researchers noted.

Reference

Rouce RH, Baumeister SHC, Curran KJ, et al. Evolution of tisagenlecleucel use for the treatment of pediatric and young adult relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL): Center for International Blood & Marrow Transplant Research (CIBMTR) registry results. Abstract #ALL-173. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology; September 4-7, 2024; Houston, Texas.

Triplet Use at First Relapse Provides Better Survival Outcomes, Tolerance in MM

Researchers who conducted a study to evaluate daratumumab plus carfilzomib plus dexamethasone (DKD) in patients with early relapsed multiple myeloma (MM) have determined the triplet to be effective in this population.

"DKD is effective in treating relapsed or refractory MM, with better survival and good tolerance among patients [who] received DKD at first relapse," the researchers concluded. The study was led by **Rasha Ghonema, MD,** of the Kuwait Cancer Control Center, and presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology in Houston, Texas.

The retrospective database study included 29 patients with MM who received DKD at relapse after at least one prior line of treatment. The total cohort had a median age of 60 years and 17 patients were female. In addition, 26 patients were transplant eligible and 21 had undergone autologous stem cell transplantation prior to receiving DKD.

The cohort included 25 patients who had anemia, 23 with comorbidities, 10 who presented with infection, eight with extramedullary disease, four with plasma cells in peripheral blood, four with hyperdiploidy, and four with *Tp53* deletion. Furthermore, 10 patients had International Staging System stage 3 disease, 11 had stage 2 disease, and three had stage 1 disease.

The median follow-up for the total cohort was 14.7 months. Among the 13 patients who received DKD at first relapse, the objective response rate was 89%, progression-free survival was 55.17%, and overall survival at 12 months was 65.51%. The investigators wrote that these outcome measurements were all higher than in the 12 patients who received DKD as third-line therapy or later.

Grade 1 or 2 infection occurred in 22 patients when immunoglobulin G fell below 4 g/L and they received intravenous immunoglobulin, and five patients experienced life-threatening infections. One patient had a symptomatic decrease in left ventricular ejection fraction from a baseline of 65% to 43%.

The investigators underscored that therapy selection for relapsed MM is complex and that a "triplet regimen containing at least two novel drugs to which the patient is sensitive should be considered."

Reference

Ghonema R, Hasaneen M, Alshemmari S, et al. Retrospective analysis of a group of early relapsed multiple myeloma (MM) patients treated by daratumumab carfilzomib dexamethasone (DKD). Abstract #MM-285. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology; September 4-7, 2024; Houston, Texas.

Treatment Combination Significantly Reduces Spleen Size, Improves Anemia in Myelofibrosis

The MANIFEST-2 trial (NCT04603495) is a global, double-blind, phase III study evaluating the efficacy and safety of pelabresib combined with ruxolitinib versus placebo with ruxolitinib in Janus kinase inhibitor (JAKi)-naïve patients with myelofibrosis. Pelabresib, an investigational BET inhibitor, aims to reduce the expression of myelofibrosis target genes.

The study was led by **John Mascarenhas, MD,** of the Icahn School of Medicine at Mount Sinai, and presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology.

John Mascarenhas, MD

The trial involved 430 patients with intermediate-1 or higher-risk myelofibrosis, meeting specific criteria such as spleen volume, symptom severity, and performance status. Patients were randomized to receive either pelabresib or placebo, along with ruxolitinib, over 21-day cycles. The primary endpoint was a ≥35% reduction in spleen volume (SVR35) at week 24. Secondary endpoints included changes in total symptom score (TSS) and a ≥50% reduction in TSS (TSS50), as well as hemoglobin response and safety.

At week 24, the pelabresib+ruxolitinib group showed a significantly higher SVR35 response rate (65.9%) compared to the placebo+ruxolitinib group (35.2%) ($P<0.001$). Although the mean reduction in TSS was greater in the pelabresib group, it was not statistically significant ($P=0.055$). The TSS50 response was similar between the two groups (52.3% vs.46.3%, $P=0.22$). A hemoglobin response was observed in 10.7% of patients in the pelabresib group versus 6.0% in the placebo group, with sustained differences in hemoglobin levels up to week 48.

In terms of safety, common treatment-emergent adverse events included anemia (43.9% vs 54.7%), thrombocytopenia (52.8% vs 37.4%), and diarrhea (23.1% vs 18.7%) in the pelabresib+ruxolitinib and placebo+ruxolitinib groups, respectively.

The study concluded that pelabresib combined with ruxolitinib significantly reduces spleen size, improves anemia, and shows a trend toward better symptom management in JAKi-naïve myelofibrosis patients.

"Pelabresib+ruxolitinib significantly reduced splenomegaly, with numerically smaller TSS at week 24, and improved anemia at week 24 and week 48 compared with placebo+ruxolitinib in JAKi-naïve patients with myelofibrosis, addressing key hallmarks of myelofibrosis," the study authors concluded. "Results support a potential paradigm shift to combination therapy for myelofibrosis."

Reference

Mascarenhas J, Rampal RK, Grosicki S, et al. Safety and efficacy of pelabresib in combination with ruxolitinib for myelofibrosis: latest data from the phase III MANIFEST-2 study. Abstract #MPN-135. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology; September 4-7, 2024; Houston, Texas

Regulatory Actions

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

Daratumumab-Based Quadruplet Approved in United States for Treatment of MM

The US Food and Drug Administration (FDA) has approved daratumumab and hyaluronidase-fihj plus VRd (D-VRd) as induction and consolidation therapy for transplant-eligible patients with newly diagnosed multiple myeloma (MM), according to a press release from Johnson & Johnson, the manufacturer of the drug.

The approval is based on results from the phase III PERSEUS trial, in which D-VRd achieved deeper responses after consolidation compared to VRd. D-VRd also reduced the risk of disease progression or death by 60% compared with VRd (hazard ratio, 0.40; 95% CI, 0.29-0.57; $P<.0001$).

The daratumumab-based regimen demonstrated higher measurable residual disease negativity rates than VRd alone (57.5% vs 32.5%, respectively).

"The efficacy data supporting this new quadruplet regimen, combined with its established safety and tolerability profile, provide compelling evidence that adding D-VRd upon initial diagnosis as compared [with] VRd can deepen responses and prolong remissions in the context of autologous [hematopoietic] stem cell transplantation," said **Amrita Y. Krishnan, MD,** Professor and Director of the Judy and Bernard Briskin Multiple Myeloma Center at the City of Hope, in the press release.

FDA Grants Fast Track Designation to DSP-5336 for AML

DSP-5336 has received Fast Track Designation from the FDA for relapsed or refractory acute myeloid leukemia (AML) with *KMT2A* rearrangement, according to a press release from Sumitomo Pharma America, Inc., the manufacturer of the drug.

In an ongoing, phase I/II study presented at the European Hematology Association 2024 Hybrid Congress in Madrid, Spain, the investigational small-molecule inhibitor achieved an objective response rate of 57% and a complete remission or complete remission with partial hematologic recovery rate of 24%.

No dose-limiting toxicities, significant cardiac signals, or treatment-related discontinuations or deaths were observed.

"We are excited by these early results and FDA Fast Track Designation and look forward to working closely with the agency and our collaborators to rapidly advance this program, with the goal of providing a well-tolerated and effective targeted treatment option for patients with relapsed or refractory [AML]," said **Jatin Shah, MD,** Chief Medical Officer of Oncology at Sumitomo Pharma, in the press release.

EC Grants Conditional Approval to Epcoritamab for Relapsed or Refractory Follicular Lymphoma

The European Commission (EC) has granted conditional marketing authorization to epcoritamab (TEPKINLY) as monotherapy for adult patients with relapsed or refractory follicular lymphoma (FL) after at least two lines of systemic therapy. This approval was announced in press releases from AbbVie and Genmab, who are co-developing the agent.

Epcoritamab is a subcutaneous, IgG1-bispecific antibody that binds to CD3 on T cells and CD20 on B cells, thereby directing cytotoxic T cells to target CD20+ cells. It is the first, and currently only, agent with approval as monotherapy in the European Union, Iceland, Liechtenstein, Northern Ireland, and Norway for treating both relapsed or refractory FL and relapsed or refractory diffuse large B-cell lymphoma after at least two lines of prior systemic therapy.

Conditional authorization from the EC for epcoritamab in this setting was supported by data from the Phase I/II EPCORE® NHL-1 clinical trial, the results of which were published in *The Lancet Haematology.* In the trial, patients with relapsed or refractory FL after two or more lines of prior systemic therapy who received this agent had an overall response rate of 83%, a complete response rate of 63%, and a median duration of response of 21.4 months.

The most common adverse reactions with epcoritamab in the trial were cytokine release syndrome, diarrhea, fatigue, injection site reactions, musculoskeletal pain, neutropenia, pyrexia, and viral infection.

Epcoritamab is approved in the United States and Japan under the brand name EPKINLY and has also received regulatory approval for use in certain lymphomas across multiple countries.

FDA Approves Axatilimab-csfr for Chronic GVHD

The FDA has approved axatilimab-csfr for the treatment of chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy, according to a press release from the federal agency.

Axatilimab-csfr, sold under the brand name Niktimvo, is a colony-stimulating factor-1 receptor-blocking antibody co-developed by Incyte Corporation and Syndax Pharmaceuticals.

The approval is based on results of the randomized, open-label, multicenter AGAVE-201 trial investigating three doses of the drug: 0.3 mg/kg every two weeks, 1.0 mg/kg every two weeks, or 3.0 mg/kg every four weeks. The study included adult and pediatric patients with recurrent or refractory chronic GVHD, a complication of hematopoietic stem cell transplantation.

The overall response rate was 75% (95% CI, 64-84) in 79 patients treated with the recommended dose of 0.3 mg/kg. The median time to first response was 1.5 months, and the median duration of response was 1.9 months. For at least 12 months, 60% of patients who achieved a response did not experience death or new systemic therapy initiation.

Serious adverse events (AEs) occurred in 44% of patients, according to a press release from Incyte and Syndax. AEs leading to dose interruption in more than two patients included viral infection, infection (pathogen unspecified), bacterial infection, musculoskeletal pain, and pyrexia.

"Advanced chronic GVHD is characterized by the development of fibrotic tissue across multiple organ systems, including, most commonly, the skin and mucosa, and can be extremely difficult to treat, leading to high rates of morbidity and mortality," **Daniel Wolff, MD, PhD,** Head of the GVHD Center at the University Hospital Regensburg and lead investigator of the AGAVE-201 trial, said in the press release. "I am highly encouraged by the robust responses observed across all organs and patient subgroups within the heavily pretreated population enrolled in the AGAVE-201 trial. I look forward to having a new and differentiated treatment option for my patients who need additional therapies to address this very difficult to manage, debilitating disease."

EC Approves Odronextamab for Follicular Lymphoma, DLBCL

The EC has approved odronextamab (Ordspono) for the treatment of relapsed or refractory FL or diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, according to a press release from Regeneron, the manufacturer of the drug.

The approval is based on results from the phase I ELM-1 and phase II ELM-2 trials published in *Annals of Oncology.* Patients with FL achieved an objective response rate (ORR) of 80% and a complete response (CR) rate of 73%. Among patients with DLBCL who had not received prior chimeric antigen receptor (CAR) T-cell therapy, 52% achieved an ORR and 31% achieved a CR. Among patients with DLBCL who progressed after CAR-T therapy, 48% achieved an ORR and 32% achieved a CR.

The most common AEs included cytokine release syndrome (54%), neutropenia (41%), pyrexia (39%), anemia (38%), thrombocytopenia (27%), diarrhea (24%), and COVID-19 (22%).

Editor's Picks

In each issue of Blood Cancers Today, *our guest editors will take a closer look at a particular topic in hematologic malignancies. This month,* ***Kristen Pettit, MD,*** *Clinical Associate Professor in Hematology, Medical Oncology, and Internal Medicine at the University of Michigan Rogel Cancer Center, highlights recent research in myelodysplastic syndromes. Visit bloodcancerstoday.com to stay up to date on the latest news in each area of hematologic oncology.*

Kristen Pettit, MD

MDS

TP53 Mutations Affect Outcomes in MDS With Chromosome 5q Deletion

A subtype of MDS features isolated deletion of chromosome 5q, or MDS-del(5q). Outcomes in patients with this disease subtype are influenced by TP53 gene mutations and the allelic status of those mutations, a study published in *Blood* determined.

"Mutations in the TP53 gene, particularly multihit alterations, have been associated with unfavorable clinical features and prognosis in patients diagnosed with MDS," explained lead study author **Maria Julia Montoro, MD, PhD,** of Vall d'Hebron University Hospital in Barcelona, Spain.

The study assessed how *TP53* mutations affect outcomes, specifically in MDS-del(5q) subtype disease. In a cohort of 682 patients with this diagnosis, investigators searched for *TP53* mutations and examined allelic imbalances. Among the patients with *TP53* mutations in this cohort, 24% had multihit alterations and 76% had monoallelic mutations.

In patients with *TP53* multihit alterations, the alterations were predictive of an increased risk of leukemic transformation.

Among the patients with *TP53* monoallelic alterations, the study found that the effect of those alterations varied by variant allele frequency (VAF). In patients with VAF of less than 20%, the disease behaved like *TP53* wild-type disease. In patients with VAF of 20% or greater, outcomes matched those seen in patients with *TP53* multihit alterations.

Why I chose this research:

"Not all TP53 *mutations confer the same risk in MDS. This study demonstrates differences in disease behavior depending on* TP53 *monoallelic or multihit alterations, as well as VAF, specifically in MDS with isolated del5q."*

"This study underscores the importance of considering *TP53* allelic state and VAF in the risk stratification and treatment decision-making process for patients with MDS-del(5q)," Dr. Montoro concluded.

Reference

Montoro MJ, Palomo L, Haferlach C, et al. Influence of TP53 gene mutations and its allelic status in myelodysplastic syndromes with isolated 5q deletion. *Blood*. 2024. doi:10.1182/blood.2024023840

Luspatercept as New Standard of Care in Lower-Risk MDS

Compared to epoetin alfa, treatment with luspatercept improved rates of transfusion independence and hematological improvement in significantly more patients with transfusion-dependent lower-risk MDS, according to primary analysis of the phase III COMMANDS trial.

Matteo Giovanni Della Porta, MD, of the Humanitas Research Hospital Cancer Center in Milan, Italy, and lead author of the study, and colleagues published the data in *The Lancet Haematology*.

From January 2019 to September 2022, the COMMANDS trial randomized 363 erythropoiesis-stimulating agent (ESA)-naïve patients to luspatercept (n=182) or epoetin alfa (n=181). The cohort had a median age of 74 years (interquartile range [IQR], 69-80) and was 55% male.

The primary endpoint was red blood cell transfusion independence lasting at least 12 weeks plus a mean hemoglobin increase of at least 1.5 g/dL from weeks one to 24.

After a median follow-up of 17.2 months (IQR, 10.4-27.7) in the luspatercept group and 16.9 months (IQR, 10.1-26.6) in the epoetin alfa group, 60% (n=110) of patients treated with luspatercept achieved the primary endpoint compared to 35% (n=63) of patients treated with epoetin alfa.

The safety analysis covered a median follow-up of 21.4 months (IQR, 24.1-32.4) in the luspatercept group and 20.3 months (IQR, 12.7-30.9) in the epoetin alfa group.

Why I chose this research:

"The primary analysis of the COMMANDS trial demonstrated that those treated with luspatercept had greater rates of transfusion independence compared with those treated with epoetin alfa. This study supports the use of luspatercept in select groups with MDS, though some caveats exist (for example, the ESA formulation studied differs from what is standardly used in the United States)."

The most common grade 3 to 4 treatment-emergent adverse events (TEAEs) in the luspatercept group included hypertension (n=19), anemia (n=18), pneumonia (n=10), syncope (n=10), neutropenia (n=9), dyspnea (n=8), and MDS (n=6).

The most common grade 3 to 4 TEAEs in the epoetin alfa group were anemia (n=14), pneumonia (n=14), neutropenia (n=11), MDS (n=10), hypertension (n=8), iron overload (n=7), and COVID-19 pneumonia (n=6).

"Luspatercept represents a new standard of care for ESA-naive patients with transfusion-dependent, lower-risk MDS," Dr. Della Porta and colleagues summarized.

Reference

Porta MGD, Garcia-Manero G, Santini V, et al. Luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): primary analysis of a phase 3, open-label, randomised, controlled trial. *Lancet Haematol.* 2024. doi:10.1016/S2352-3026(24)00203-5

HemOnc Happenings

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

SOHO Presents Named Awards at the Twelfth Annual Meeting

Live from Houston, Texas, the Society of Hematologic Oncology (SOHO) presented two named awards during the plenary sessions at the Twelfth Annual Meeting on September 4-7.

Emil J Freireich Distinguished Pioneer Award

Ching-Hon Pui, MD, Co-Leader of the Hematological Malignancies Program at St. Jude Children's Research Hospital, received the Emil J Freireich Distinguished Pioneer Award during the first plenary session on September 4. The award recognizes SOHO members who have advanced the society's mission by promoting "worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders," according to SOHO's website.

Ching-Hon Pui, MD

After receiving the award, Dr. Pui, who specializes in pediatric acute lymphoblastic leukemia (ALL), gave the plenary talk on precision treatment for childhood ALL. The award was introduced by **Hagop Kantarjian, MD,** Session Chair, Professor, and Chair of the Department of Leukemia at The University of Texas MD Anderson Cancer Center.

"Dr. Pui is admired by many of us and is a hero to many of us. He is very well known for his work in childhood ALL and has made many discoveries which have advanced the cure rate in childhood ALL," said Dr. Kantarjian. Dr. Pui is also credited with organizing research in China and bringing essential medications to the country.

"It is a great privilege to be here to honor my hero," Dr Pui said. "Dr. Freireich was a trailblazer in our field and developed pioneering work which we are still using today as a guide to help manage our patients."

Emil J. Freireich, MD, was the first person to develop curative regimens for adult and pediatric ALL, Dr. Kantarjian noted. He also designed apheresis machines used to separate platelets.

Michael J. Keating Outstanding Achievement Award

John Seymour, MBBS, FRACP, PhD, Director of the Hematology Department at the Peter MacCallum Cancer Centre and the Royal Melbourne Hospital, received the Michael J. Keating Outstanding Achievement Award at the second plenary session on September 5 for his contributions to the field of chronic lymphocytic leukemia (CLL).

John Seymour, MBBS, FRACP, PhD

"Our recipient is very appropriate for this award, particularly because he was brought to the MD Anderson Cancer Center in 1986 from Australia by Dr. Keating," said session chair **Susan O'Brien, MD,** of UCI Health.

Dr. O'Brien described Dr. Keating as a "pioneer in the treatment of CLL" and an "excellent physician." He also began the CLL global foundation, a charitable foundation funding CLL research.

"It's a huge privilege and one of the greatest honors of my career to receive an award named after Michael Keating, a giant in the field of CLL and hematologic research," Dr. Seymour said before accepting the award.

Following the award, Dr. Seymour gave the plenary talk on BCL2 inhibition in CLL and described the journey to understanding apoptosis.

"When I first met Michael when I entered medical school, the evasion of apoptosis as a mechanism of leukemogenesis was not recognized," he explained. "Now, it's seen as standard routine. We are now able to succinctly and directly target that therapeutically, and CLL is the paradigm that does it most successfully."

Phil Scheinberg, MD, PhD, Elected SOHO President

Dr. Scheinberg, Chief of Hematology at the Hospital A Beneficência Portuguesa de São Paulo in Brazil, was elected President of the Society of Hematologic Oncology (SOHO).

Dr. Scheinberg succeeds **Guillermo Garcia-Manero, MD,** Chief of the Section of Myelodysplastic Syndromes, Deputy Chair of Translational Research, and a Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center.

"I am deeply honored and humbled to step into the role of President of [SOHO], succeeding the exceptional Dr. [Garcia-Manero], who led with excellence the society in 2023-2024," Dr. Scheinberg wrote on X (formerly Twitter). "I have big shoes to fill!"

Dr. Garcia-Manero passed the SOHO torch during the closing remarks at the Twelfth Annual Meeting on September 7 in Houston, Texas.

Photo courtesy of Phillip Scheinberg, MD, on X (@scheinbp)

Guillermo Garcia-Manero, MD and Phil Scheinberg, MD, PhD

"I have known Dr. Phillip Scheinberg for many years," Dr. Garcia-Manero began. "He trained in the United States but went back to Brazil, helping transform care for leukemia patients there. He has been tremendously involved with the society and I cannot think of a better leader for this year than Dr. Scheinberg."

Dr. Scheinberg's clinical interests include myelodysplastic syndromes, bone marrow transplantation, and marrow failure syndromes such as aplastic anemia. After graduating with a medical degree from the University of Santo Amaro in Brazil, he secured an internship and residency at Mount Sinai Medical Center in Miami, Florida. He then became a staff clinician at the National Institutes of Health and National Heart, Lung, and Blood Institute before returning to Brazil in 2012 for his current role at the Hospital A Beneficência Portuguesa de São Paulo.

SOHO-ABHH Joint Session in Brazil

October 25

The Society of Hematologic Oncology is holding a joint session with the Brazilian Association of Hematology, Hemotherapy, and Cell Therapy (ABHH).

This meeting will take place on October 25, 2024, at the HEMO 2024 congress, in São Paulo, Brazil.

The session will feature lectures in higher- and lower-risk myelodysplatic syndromes (MDS) and acute myeloid leukemia (AML).

The MDS section will be from 8:30 am to 10 am BRT, and the AML section will be held from 11:30 am and 13 BRT.

To register for the SOHO-ABHH event, visit hemo.org.br/2024/.

Amy DeZern, MD

Rami Komrokji, MD

Sylvia Magalhães, MD, PhD

Jae Park, MD

Eduardo Rego, MD, PhD

Phil Scheinberg, MD, PhD

SOHO-SEHH/SETH Joint Session in Mallorca

October 26

SOHO is excited to announce a joint session with the Spanish Society of Hematology and Hemotherapy (SEHH) and the Spanish Society of Thrombosis and Hemostasis (SETH) during the 2024 SEHH-SETH National Congress.

The SOHO-SEHH/SETH joint session will be held from 16:15-17:15 CEST on October 26, 2024.

The speakers will include Guillermo Garcia-Manero MD; Adolfo de la Fuente Burguera, MD; and Maria Victoria Mateos Manteca, MD, PhD.

To register for the SEHH/SETH National Congress, visit hemato2024.com/inscripcion

Dr. De la Fuente Burguera

Dr. Garcia-Manero

Dra. Mateos