TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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Improving Identification of Intolerance or Resistance to Ph+ CML-CP TKIs for Better Patient Experience

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Introduction

Philadelphia chromosome—positive chronic myeloid leukemia (Ph+ CML) is a myeloproliferative neoplasm characterized by a balanced genetic translocation involving a fusion of the Abelson gene *(ABL1)* with the breakpoint cluster region (*BCR*) gene, otherwise known as the Philadelphia chromosome (Ph) rearrangement. Chronic myeloid leukemia (CML) is relatively uncommon, with an incidence of 1 to 2 cases per 100,000, accounting for nearly 15% of newly diagnosed leukemia cases in adults, of which over 90% are Ph+.[1,2] Treatment of patients with CML in the chronic phase (CML-CP) was revolutionized by the discovery and development of tyrosine kinase inhibitors (TKIs).[3] Implementation of TKI therapy changed the course of CML-CP, leading to an improvement in 8-year survival rates (from 6% to 80%-90%).[2,3] However, patients treated with TKIs may eventually develop resistance (a lack of a significant or appropriate response despite optimal adherence to prescribing recommendations) or intolerance (the presence of adverse reactions [ARs] that cannot be managed by dose reduction or treatment of symptoms).[4-6] While adjusting doses and switching therapies are both options to manage the patient experience, there are still unmet needs in identifying when it is appropriate to switch TKI therapy.[7,8] This could be partly due to differing expectations for and perceptions of TKI therapy between oncologists and their patients.[8]

This report aims to shed light on the complexities in managing resistance or intolerance in patients receiving TKI therapy to develop more personalized and patient-centric therapeutic strategies in this clinical setting. While healthcare professionals (HCPs) may not recognize a significant unmet need because they are satisfied with the efficacy of current treatments and their ability to manage associated side effects, there may be a disconnect with patients' experiences relating to the impact of TKI-related side effects on their quality of life (QOL). This disconnect could lead to suboptimal patient care and necessitates further investigation. Moreover, a lack of knowledge among HCPs regarding the benefit vs risk profiles of other TKI options may hinder their consideration.

Educational Objectives:

- Identify and analyze the unmet needs of patients with Ph+ CML-CP receiving TKIs, focusing on challenges related to efficacy, resistance, intolerance, side effects, and QOL
- Evaluate the impact of unmet needs on patient satisfaction and overall outcomes in the management of Ph+ CML-CP with TKIs
- Highlight key areas in which HCPs can play a pivotal role in addressing the unmet needs of patients with Ph+ CML-CP on TKIs to improve treatment outcomes

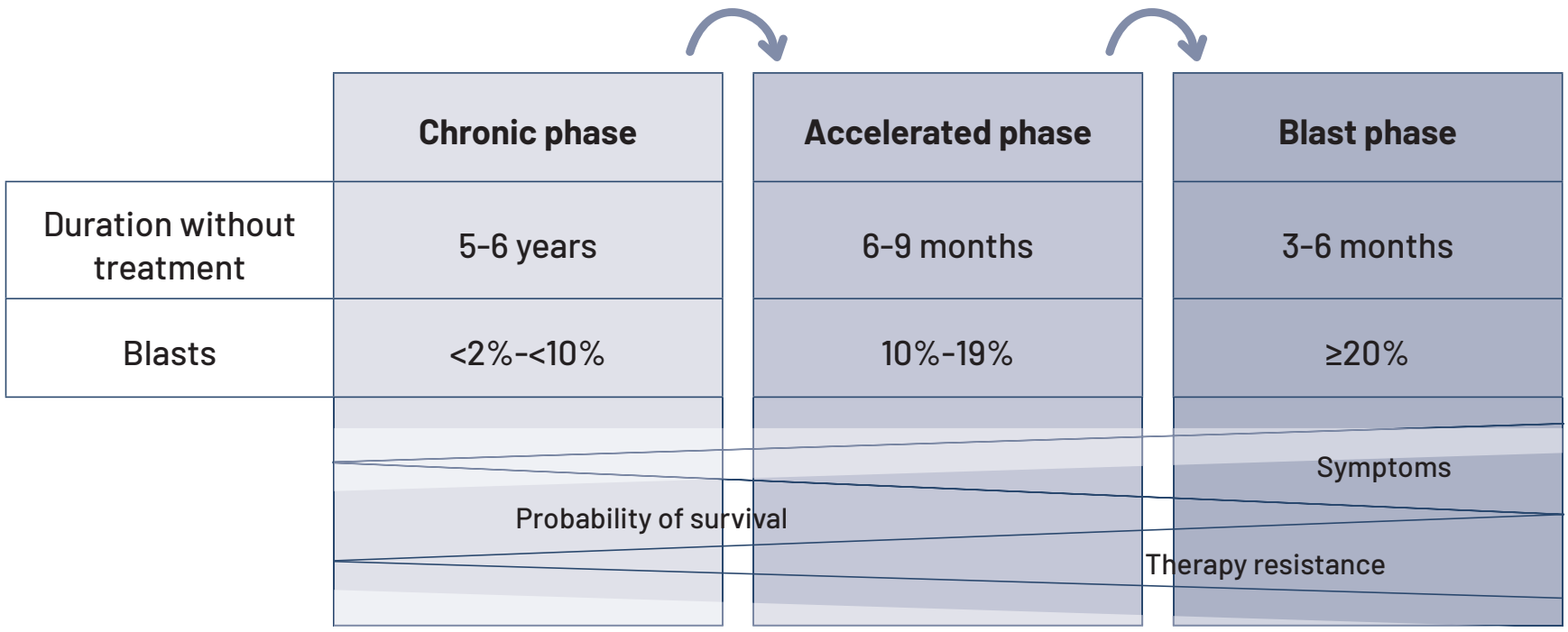

Figure 1. Correlations of CML progression with symptoms, survival, and resistance.[2]

CML and TKIs

Pathophysiology of CML

CML is characterized by the presence of the Philadelphia chromosome, which is the result of a balanced translocation between chromosome 9 (*ABL* gene) and chromosome 22 (*BCR* gene).[9] The subsequent BCR::ABL fusion oncoprotein is a constitutively active tyrosine kinase involved in several pro-growth and survival signaling pathways.[10,11] There are 3 distinct phases of CML: chronic phase (<2%-<10% blast cells in peripheral blood/bone marrow), accelerated phase (10%-19% blast cells in peripheral blood/bone marrow), and blast phase (≥20% blast cells in peripheral blood/bone marrow) **(Figure 1)**.[2]

24% **of patients discontinue their CML TKI treatment due to ARs[19]**

TKIs for the Treatment of Ph+ CML-CP and Problems That May Lead to Discontinuation

Treatment of CML was revolutionized by the discovery and development of TKIs, which have contributed to remarkable increases in 10-year survival rates.[2] TKIs dramatically improved the survival of patients with Ph+ CML-CP compared with existing therapies.[3,6] TKIs were developed and initially approved for patients with resistance or intolerance to prior therapies.[12,13] Second-generation TKIs have since expanded to patients with newly diagnosed (ND) Ph+ CML-CP.[12,13] Most TKIs are adenosine triphosphate (ATP)–competitive, meaning they target the ATP-binding site on the ABL1 portion of BCR::ABL **(Figure 2)** and inhibit the phosphorylation and activation of proteins involved in regulating downstream signaling pathways and preventing subsequent leukemic cell proliferation.[12-14] The myristoyl pocket of BCR::ABL is an additional target for inhibition.[15] Allosteric binding of the myristoyl pocket can also change the conformation of BCR::ABL from an active to an inactive state.[16]

> “The biggest cause of failure is subtherapeutic drug levels due to poor adherence.” **— Dr Bradley**

> “Because there is some structural conversation between kinases that results in similar binding sites, there will be limitations with TKIs in CML. This is why other kinases are being inhibited, including BCR::ABL.” **— Dr Levy**

A challenge associated with TKIs is the inability to selectively inhibit kinases, even those specific to CML.[17] It is believed that this lack of selectivity can result in off-target effects leading to ARs.[17,18] For CML, these highly conserved and structurally similar binding sites on different kinases can make it difficult to mitigate off-target toxicities while still targeting the BCR::ABL kinase.[17,18] These off-target effects of TKIs can lead to long-term safety issues and intolerance, with up to 24% of patients discontinuing treatment.[19] Although treatment-related ARs can sometimes be managed with dose modifications or interruptions, and/or concomitant medications, many patients treated previously with 2 or more TKIs may experience TKI intolerance.[12,13,15,20] It is important that patients tolerate their treatment in order to achieve molecular milestones as depicted in **Figure 3**.[7,21]

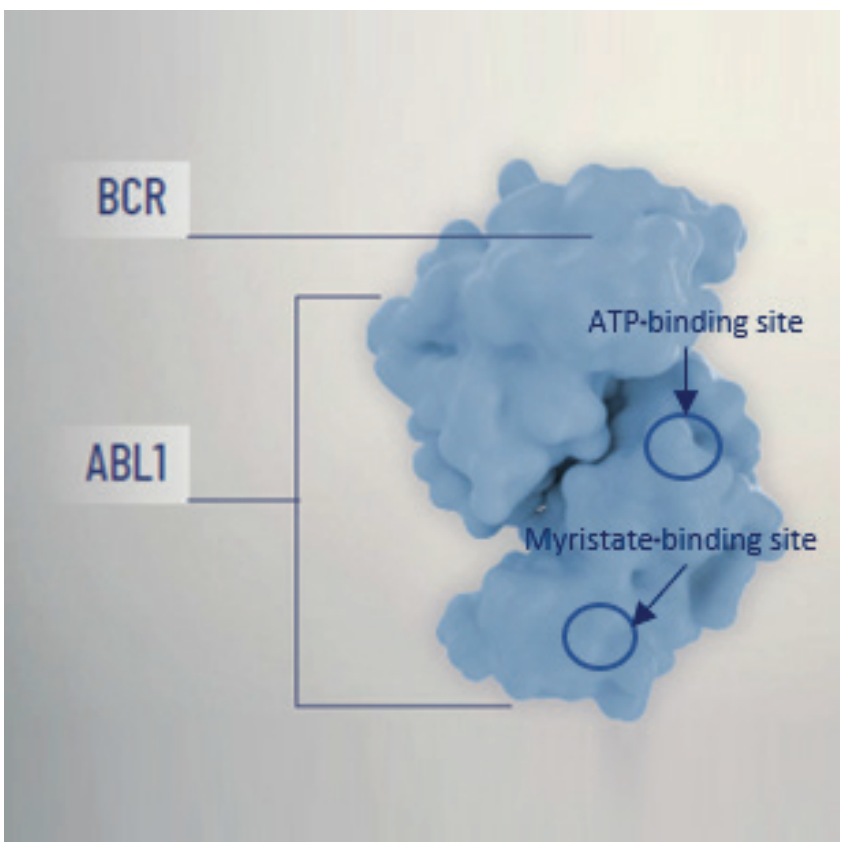

Figure 2. TKI-binding sites on BCR::ABL protein.[12-14]

Unmet Needs in Patients Receiving TKIs

Issues With Intolerance, Resistance, and Adherence

Although TKIs targeting the BCR::ABL1 kinase fusion protein have drastically improved the outcomes of patients with Ph+ CML-CP,[3] the impact of long-term TKI use can be affected by several factors. Patients may experience suboptimal response, intolerance, and/or resistance to TKIs.[7,19,22-27] In fact, 30% to 50% and 63% to 72% of patients receiving first- and second-line therapy, respectively, eventually develop resistance.[19,22-26] Intolerance to TKIs can also result in adherence issues from mismanaged and/or uncontrolled ARs.[7,27] Furthermore, overall survival (OS) rates are significantly lower in later lines of therapy **(Figure 4)**,[28] and patients who are resistant and/or intolerant to 2 or more TKIs have very few treatment options.

QOL and Psychosocial Impact

QOL is another factor that is important to consider in patients treated with TKIs.[8,18] Each TKI is associated with a particular AR profile. However, not all patients experience the same ARs.[12,13,15] The severity of ARs can range from mild to severe and can also be transient (likely to lessen or resolve over time), but the chronicity of these ARs should also be considered.[12,13,15] For example, grade 2 diarrhea can be considered manageable by physicians, but if it becomes chronic, it may begin to negatively impact patients' QOL if not managed properly.[8] Additionally, patients report feeling physically and emotionally fatigued, are unable to exercise as much as before, and that their personal and social life are impacted by their current TKI.[8]

Switching TKI therapies may impact patients' long-term QOL and is a major concern for oncologists.[8] While oncologists believe their patients are grateful for potential treatment options to switch to, they also believe that stress, physical/emotional fatigue, and patients' mental health are among the most concerning negative impacts of 2L and 3L treatment.[8]

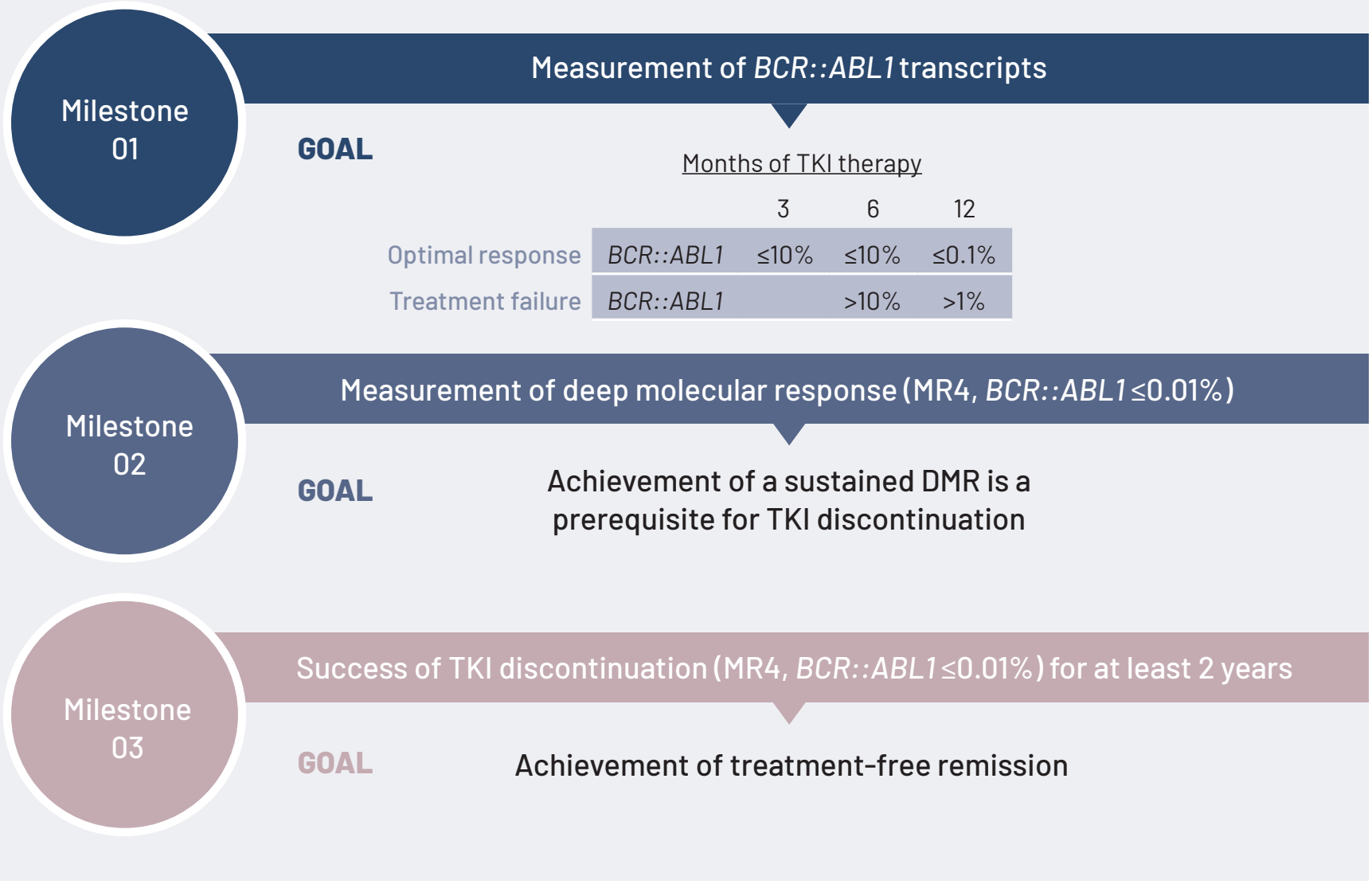

Figure 3. Milestones following treatment of CML.[7]
MR4, molecular response, 4-log reduction.

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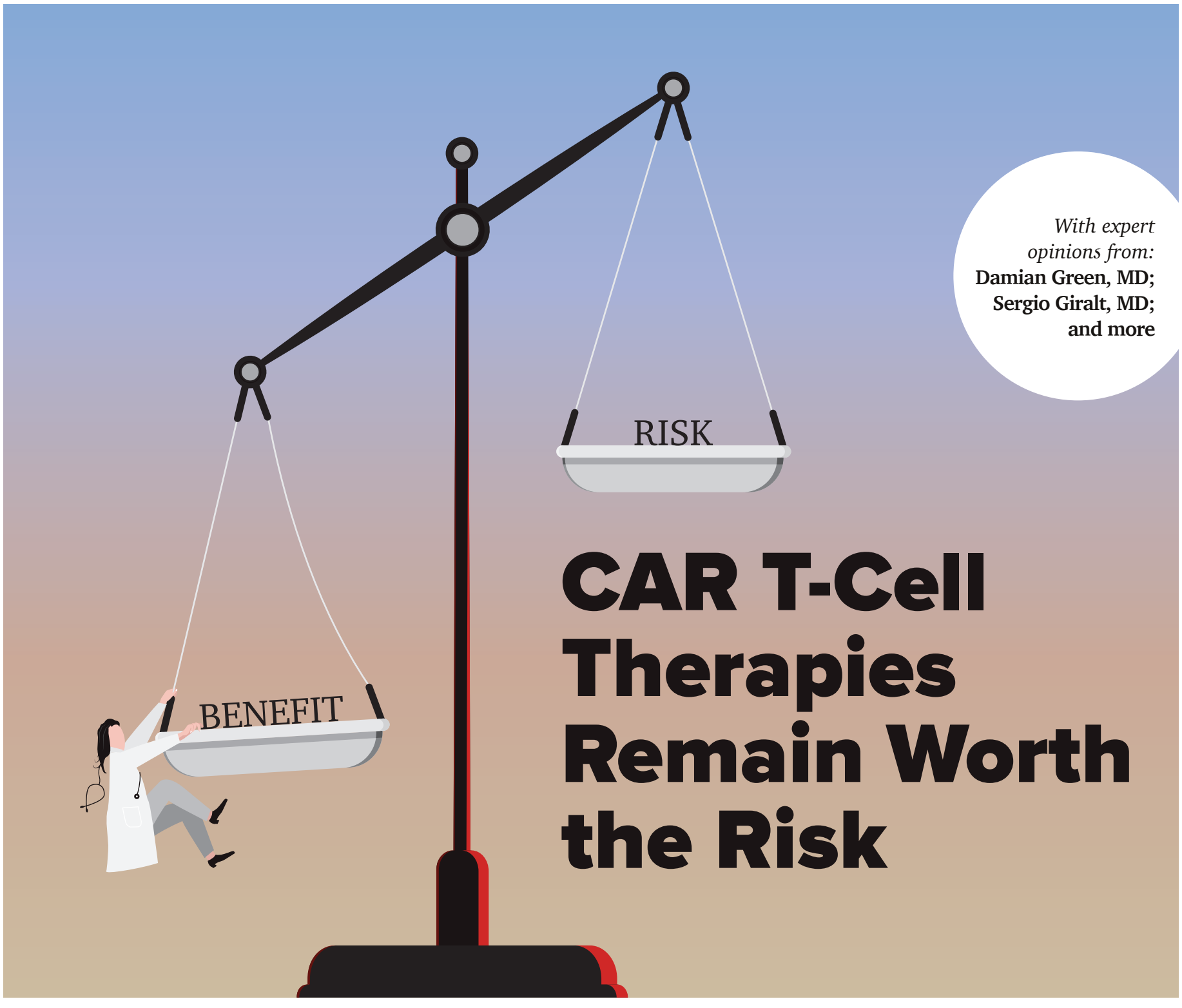

With expert opinions from:
Damian Green, MD; Sergio Giralt, MD; and more

CAR T-Cell Therapies Remain Worth the Risk

MAIL TO:

EXECUTIVE EDITOR
ELIAS JABBOUR, MD

The Journey of an Optimistic Oncologist

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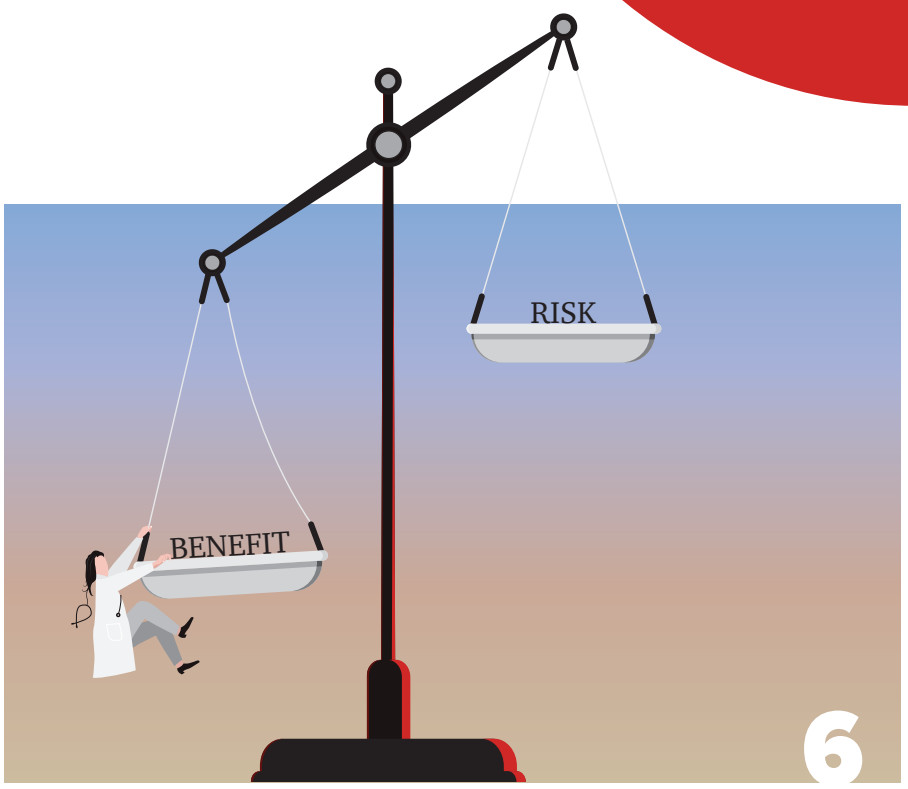

CAR T-Cell Therapies Remain Worth the Risk

Despite the addition of a "Black Box" warning, the benefits of chimeric antigen receptor (CAR) T-cell therapies outweigh the hypothetical future risk of secondary malignancies. Experts agree that the new warnings are unlikely to have a significant effect on treating patients with CAR-T therapies moving forward, but some changes are possible.

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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

July 25–28
2024 Debates and Didactics in Hematology and Oncology Conference
Sea Island, Georgia

August 16–17
2024 Seattle Cellular Therapy Summit: Updates and Focus on Accessibility
Seattle, Washington

September 20–21
National Comprehensive Cancer Network Annual Congress: Hematologic Malignancies
New York, New York

September 25–27
EHA-SfPM Precision Medicine Meeting
Copenhagen, Denmark

September 25–28
21st International Myeloma Society Annual Meeting
Rio de Janeiro, Brazil

October 11–13
2024 Summit on Hematological Cancers
Nashville, Tennessee

October 24–25
16th International Congress on Myeloproliferative Neoplasms
Brooklyn, New York

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

November 22
2024 SOHO Highlights: State of the Art and Next Questions
Virtual

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

February 12–15, 2025
2025 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR
Honolulu, HI

April 25–30, 2025
American Association for Cancer Research Annual Meeting
Chicago, Illinois

Executive Editor's Message

The Journey of an Optimistic Oncologist

Elias Jabbour, MD
Executive Editor

As a hematologist-oncologist, I can relate to former President Barack Obama's sentiment in a 2016 editorial he wrote for *Wired*: Despite all we face, now is the greatest time to be alive. Some might find that perspective bold, but the belief in our readiness to confront challenges deeply resonates with me as a clinician who treats patients with blood cancers. There are no better days in oncology than today—except, of course, for tomorrow, which holds even more promise for our patients.

We are fortunate to practice medicine at a time when we're discovering the cure for diseases that were once fatal. Today, we can offer our patients hope that what was completely unachievable only a few years ago is now achievable.

I want to redefine leukemias as curable or less curable—a reflection of my optimism in how this cancer is being managed—instead of how they are currently characterized: acute, chronic, early stage, or late stage.

Currently, hairy cell leukemia is one of two cancers with a very high cure rate (90%-95%). It can be cured with minimal intervention, essentially with chemotherapy, a drug called cladribine, and rituximab. The second is acute promyelocytic leukemia. Even with no chemotherapy, by giving all-trans-retinoic acid and arsenic trioxide, the cure rate in adult patients is 90% and above.

Chronic lymphocytic leukemia (CLL) also falls into the curable category. Today, patients with CLL can live a normal lifespan and receive a finite therapy, instead of being treated for life, by combining Bruton's tyrosine kinase and B-cell lymphoma 2 inhibitors and eventually novel CD20 antibodies. The remission rate is quite good with one or two years of therapy, and patients can be expected to have a normal lifespan without continuing therapy.

Chronic myeloid leukemia (CML) is another form of leukemia that is curable. Until 2000, only a few patients were cured, and those were young patients who had a potential donor and transplantation. Today, with the availability of tyrosine kinase inhibitors (TKIs), a patient with CML who is responsive to treatment can expect to live a normal lifespan.

After we redefine leukemias, the next step is to ask, "In treating CML, even if we achieve a good response, can we stop therapy?" Today, with our treatment aimed at inducing deep and durable remissions, we're looking not only to extend patients' lifespans to normal, but also to free them from a lifetime of medication. We're working toward inducing a deep remission that can be maintained for three to five years, offering a real chance at stopping therapy.

"Today is the best day to practice medicine in leukemia. I'm optimistic that the cure of this disease will happen in our lifetime."

I want to highlight other curable leukemias that were incurable not too long ago.

The cure rate of Philadelphia-positive acute lymphoblastic leukemia (ALL) used to be 10%. Then we were able to offer transplant to these patients, improving the cure rate to 30% to 40%. Next, we added TKI to chemotherapy, which improved the survival rate to 50% to 60% but also resulted in a plateau of the cure rate. Today, with upfront immunotherapy and the combination of TKIs, we're witnessing a survival rate of 90% in these patients, which is amazing.

ALL in younger patients was traditionally incurable, with cure rates that plateaued at 60%, regardless of the treatment regimen (pediatric or hyper-CVAD). Today, these patients are doing well with the integration of immunotherapy upfront, with cure rates of 80% to 85%.

Continued on next page

Executive Editor's Message

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For older patients with ALL, survival was very poor until 2010. Medicare data showed a survival rate of six to eight months, which was driven by poor biology, inducing resistance to chemotherapy and comorbidities and leading to poor tolerance to treatment intensity. The integration of immunotherapy upfront in these patients led to universal responses and a five-year survival rate of 50%.

Today, we are moving away from intensive chemotherapy and exploring chemotherapy-free approaches for more improved outcomes.

A notoriously challenging disease, acute myeloid leukemia (AML) used to have a survival rate of 10% to 20%. Today, younger patients with AML have improved outcomes, with a survival rate of approximately 60%, which can be attributed to better understanding of the disease biology, improved diagnoses, targeted therapies that are added to the treatment upfront, and better transplant techniques.

The management of older patients with AML remains challenging. Although we have a new standard of care—venetoclax and hypomethylating agents (HMAs)—improvement remains modest. We're building on that regimen to further improve outcomes by treating patients with a triplet of cladribine, low-dose cytarabine, and venetoclax, alternating with an HMA and venetoclax. Overall, we have improved the cure rate to 50% to 60%. These patients are getting to transplant, and we have targeted therapies available to further improve outcomes.

Alongside our significant progress, several subtypes remain difficult to treat. Patients with MECOM AML have very poor outcomes, and we're exploring new agents for this target. The AML subtype with KMT2Ar- or 11q23-rearranged disease is also challenging to treat. We are exploring a plethora of menin inhibitors in these patients, with very promising early results.

The evaluation of menin inhibitors in combination with intensive chemotherapy or targeted therapy with an HMA and venetoclax to further improve outcomes in frontline treatment is ongoing, and results will be reported soon.

Finally, in *TP53*-positive AML, none of the drugs explored thus far has succeeded, but additional agents are being investigated.

Other tough-to-treat leukemias include high-risk myelodysplastic syndromes (MDS), where we are eagerly awaiting the combination of an HMA and venetoclax. Once a patient fails frontline therapy, there are few treatment options available outside of clinical trials. However, I would again like to highlight my optimism. Several drugs are now approved in low-risk MDS, including luspatercept and oral decitabine. Imetelstat, a telomerase inhibitor, will hopefully receive approval soon.

We are making progress in developing effective therapies for myelofibrosis and myeloproliferative neoplasms. Treatment advances began with Janus kinase 2 (JAK2) inhibitors. Now, we are witnessing progress in several randomized trials exploring combinations of JAK2 inhibitors plus other agents, such as MDM2 inhibitors, BCLXL inhibitors, and other therapies, to further improve outcomes.

Today is the best day to practice medicine in leukemia. I'm optimistic that the cure of this disease will happen in our lifetime. We have everything we need. Trials are ongoing, and in the next few years, perhaps we will witness measured improvements in outcomes across all types of leukemia.

Elias Jabbour, MD, *is a Professor in the Department of Leukemia at the MD Anderson Cancer Center.*

Get to Know

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

Julie Vose, MD, MBA

Dr. Vose, Chief of the Division of Oncology and Hematology at the University of Nebraska Medical Center, discusses how she followed in her family's footsteps to become a hematologist, why it's important to choose a compatible mentor, and how she nurtures her artistic side outside of work.

Where did you grow up, and when did you know you wanted to be a hematologist?
I grew up in Mitchell, South Dakota, which is a small town. My father was a pathologist, and I worked in his lab during the summers while I was in high school and college. I worked with blood smears and pathology specimens and decided I wanted to go into medicine by doing that. When I went to medical school, I became interested in cancer and decided to go into hematology-oncology. I started doing research, and here I am today!

Are there any specific mentors who shaped your career path?
I had some very good mentors early on who shaped my career. I started doing research with lymphoma expert **James Armitage, MD,** when I was in medical school, and that's how I became interested in taking care of patients and doing research in lymphoma. I started doing some retrospective chart reviews way back when I was a medical student. Later, I went into hematology-oncology and specialized in clinical research in lymphoma, as well as transplantation.

Can you speak about your current research?
Over the years, I've mostly done research on new drugs, therapies, antibodies for lymphoma, chimeric antigen receptor T-cell transplantation, and monoclonal antibodies for non-Hodgkin lymphoma. Things have evolved and changed over the years, and we have a lot of treatments now that we didn't have just a few years ago. Clinical trials are great because they always feature new and exciting areas of research, and, of course, the result is to help our patients.

What do you hope to see in the field over the next 10 years?
As lymphoma research advances, we're understanding that it's many different types of diseases, many more subtypes than we ever knew were possible. All of them need to be treated differently. We're learning more about therapies that are less toxic for the patient and more directed at the lymphoma itself, minimizing impact on normal tissues and organs, and therefore have fewer side effects. We're also combining different regimens and therapies to try to improve patient outcomes. The desired result is to have less toxic therapy, and less therapy overall that patients have to go through, yet a higher cure rate. That's our ultimate goal.

What advice would you give to younger physicians or trainees in the field?
Try to get involved with a mentor very early. Try to choose some projects to work on. It's hard when you're first starting out because you don't really know what you're interested in. As early as possible, choose someone to work with who can give you some good direction and advice. Someone who's accessible and with whom you can relate. Someone who will give you tips along the way in your short- and long-term career.

Are there any moments in your career that stand out to you?
In oncology, unfortunately, a lot of our patients pass away over time. But, as I've been practicing several years now, I am still seeing patients who I took care of way back when I was a fellow. A lot of those patients are thriving, surviving, and have families of their own. That's really nice to see.

I think it's important to remember that we're here to help patients, make discoveries, and pass things on to the next generation. It's important that we continue to teach in a positive direction, and to make sure that the doctors of tomorrow are there to help us when we need it.

What hobbies or activities do you enjoy in your free time?
I am an artist; I like to paint watercolors or acrylic paintings. I'm more of an impressionistic artist, so I mostly paint landscapes. I also like to work out. I like running, lifting weights, and playing pickleball. It's so important to stay active and do things that you like outside of work.

Julie Vose, MD, MBA, *is the Chief of the Division of Oncology and Hematology at the University of Nebraska Medical Center.*

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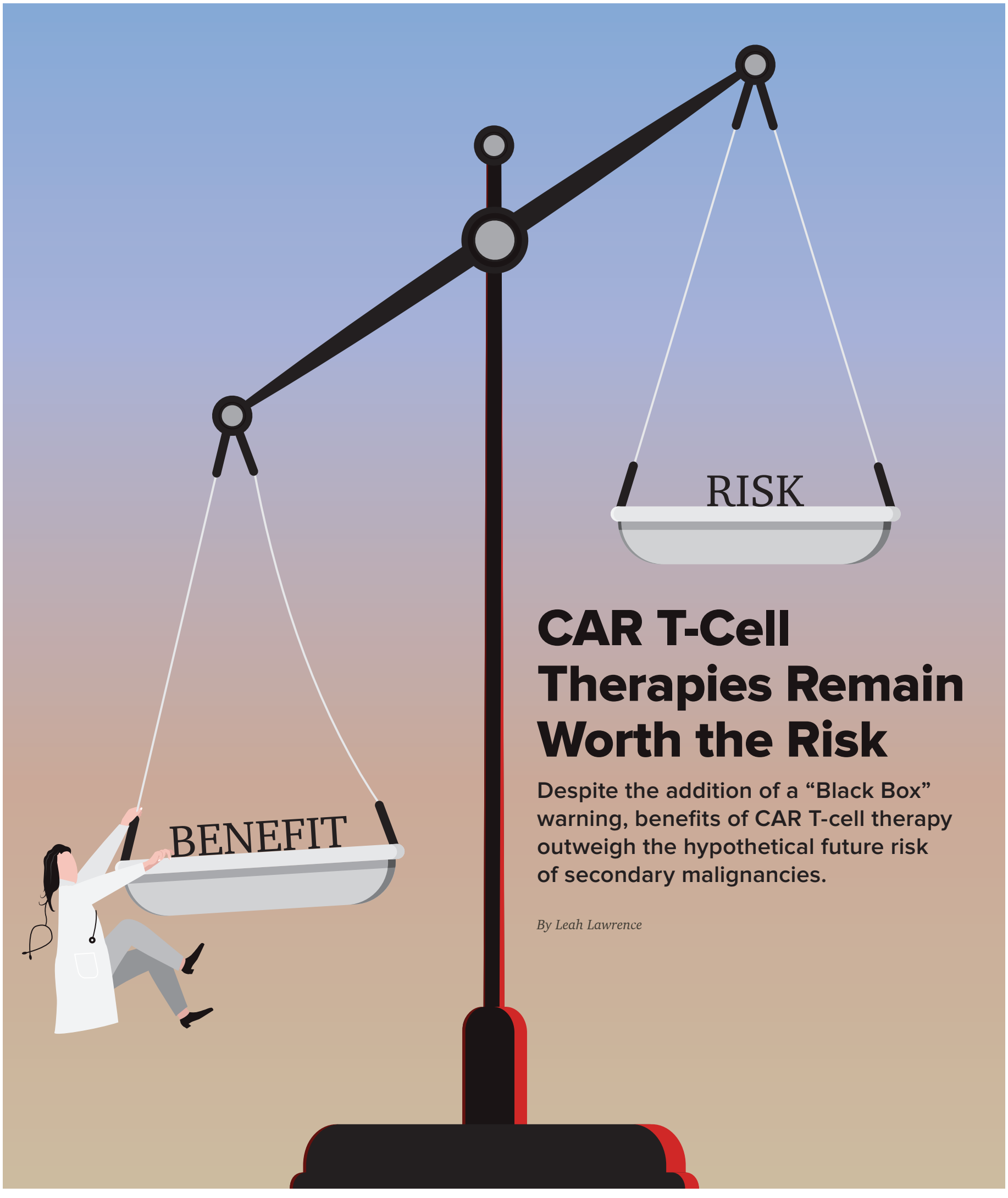

CAR T-Cell Therapies Remain Worth the Risk

Despite the addition of a "Black Box" warning, benefits of CAR T-cell therapy outweigh the hypothetical future risk of secondary malignancies.

By Leah Lawrence

In January, the US Food and Drug Administration (FDA) notified manufacturers of both BCMA- and CD19-directed chimeric antigen receptor (CAR) T-cell therapies that it would require product safety information to include a boxed warning for T-cell malignancies.[1]

In a series of letters sent to the manufacturers, the FDA said it had "become aware of the risk of T-cell malignancies, with serious outcomes, including hospitalization and death, following treatment with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies." Based on this "new safety information," the product must henceforth carry a boxed warning reading, "T-cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies."[2]

This action followed a November 2023 announcement that the FDA was investigating serious risk of T-cell malignancy in these CAR T-cell immunotherapies.[3] Products affected include brexucabtagene autoleucel (Tecartus, Kite), idecabtagene vicleucel (ide-cel; Abecma, Bristol Myers Squibb), lisocabtagene maraleucel (Breyanzi, Bristol Myers Squibb), ciltacabtagene autoleucel (cilta-cel; Carvykti, Janssen Oncology and Legend Biotech), tisagenlecleucel (Kymriah, Novartis), and axicabtagene ciloleucel (Yescarta, Kite).[1]

"I am not surprised that the 'Black Box' warning came out based on what was reported in November," said **Damian Green, MD,** Chief of the University of Miami's Sylvester Comprehensive Cancer Center's Division of Transplantation and Cellular Therapy, "but there are many other factors that must also be considered when we think about approaching CAR T-cell therapy in patients."

What Are the Details?

In November 2023, the FDA issued a summary stating that it had received reports of T-cell malignancies, including a CAR-positive lymphoma, in patients who had received BCMA- or CD19-directed autologous CAR T-cell therapy. The statement revealed that the reports were from clinical trial and postmarketing adverse event data sources but did not provide more specifics.

Only limited information on these cases was available. In late 2023, news outlets reported that the FDA had received approximately 20 reports of T-cell malignancies.[4,5] This report was confirmed in a *New England Journal of Medicine* Perspective published in February in which **Nicole Verdun, MD,** and **Peter Marks, MD, PhD,** of the FDA's Center for Biologics Evaluation and Research, wrote that as of December 31, 2023, the FDA was aware of 22 cases of T-cell malignancies that occurred after receipt of CAR T-cell therapies.[6]

The cases included T-cell lymphoma, T-cell large granular lymphocytosis, peripheral T-cell lymphoma, and cutaneous T-cell lymphoma. Fourteen of the 22 cases have adequate data available; all of them occurred within two years of administration, with about half occurring within the first year.

"In three cases for which genetic sequencing has been performed to date, the CAR transgene has been detected in the malignant clone, which indicates that the CAR-T product was most likely involved in the development of the T-cell cancer," Drs. Verdun and Marks wrote.

Simon Harrison, MBBS, PhD, Director of the Centre of Excellence for Cellular Immunotherapy and a hematologist at Peter MacCallum Cancer Centre in Victoria, Australia, told *Blood Cancers Today* that, as far as he is aware, his team has published details on the only CAR-positive T-cell malignancy in multiple myeloma (MM).[7]

An online-only abstract from the 2023 American Society of Hematology (ASH) Annual Meeting & Exposition detailed a patient enrolled in the CARTITUDE-4 study who was diagnosed with a CAR-positive T-cell lymphoma after receipt of cilta-cel, an anti-BCMA CAR-T therapy. The 51-year-old male patient achieved stringent complete response and measurable residual disease negativity. Five months after infusion, "a relatively rapidly growing erythematous nasofacial plaque developed" and a T-cell lymphoma was subsequently diagnosed, with analysis revealing that 90% to 100% of lymph node biopsy cells were CAR-positive.[7]

"In this case, the patient had many other things going on genetically that put him at high predisposition at the time," Dr. Harrison said, including a germline mutation seen in T-cell malignancies.

"This rare malignancy was potentially driven by genetic mutations (eg, *TET2, NFKB2, PTPRB,* or *JAK3*), some of which may have existed in the form of a clone with malignant potential before cilta-cel manufacturing (eg, *TET2* p.H1416R and *JAK3* p.V722I variants)," Dr. Harrison and colleagues wrote in the abstract. "A potential contributory role of the CAR insertion in the three-inch untranslated region of *PBX2* to [T-cell lymphoma] development remains unclear and cannot be excluded at this time."

In another 2023 ASH abstract, researchers from China detailed outcomes from 48 patients with relapsed or refractory B-cell non-Hodgkin lymphoma treated with C-CAR039, an autologous anti-CD20/CD19 bispecific CAR T-cell therapy. Researchers observed secondary primary malignancies in three patients, one of which was an Epstein-Barr virus–positive, cytotoxic T-cell lymphoma at eight months after C-CAR039 infusion. None was related to C-CAR039.[8]

In January, researchers from the University of Pennsylvania published details of a retrospective study of 449 patients treated with CAR T-cell therapy at Penn Medicine and found with a median follow-up of 10.3 months that only 3.6% of patients had a secondary primary malignancy. They found only a single case of an incidental T-cell lymphoma that did not express the CAR gene; this lymphoma was found in a patient who had developed a secondary lung tumor after CAR T-cell therapy.[9]

More Information Needed

The recognition of a possible risk for T-cell malignancies related to gene therapy has long been recognized, according to **Sergio Giralt, MD,** Chief of Adult Bone Marrow Transplant at Memorial Sloan Kettering Cancer Center.

"We all recognize that with all genetically modified treatments, or with genetically modified cells, there is a possibility that you could potentially introduce oncogenic stimuli into normal cells and potentially make malignant cells more malignant," Dr. Giralt said. "That is why these cellular therapies like CAR T-cell therapy undergo rigorous and extensive clinical trials before they become commercially available."

"If the patient succumbs to their current cancer, it is a moot point if there is a risk for secondary cancer." *—Damian Green, MD*

Dr. Green said that he recognized the FDA is requiring these warnings in an attempt to protect the public, but he added that there is currently no quantification of the risk.

Dr. Giralt agreed. "Is the risk one in a million? Is it one in 1,000? We don't know." The FDA has still not provided much information on the exact characteristics of each of these cases. He said that his institution's dataset reveals second primary malignancies after CAR T-cell therapy but no T-cell malignancies.

"As clinicians and the people involved in the development of these products, the real-world incidence [of T-cell malignancies] has been very low based on available data up to this juncture," Dr. Green said. "These warnings don't substantially change how we think about approaching CAR T-cell therapy in our patients."

Clinicians are still trying to understand the cause of the T-cell malignancies. Is it CAR-T or something else?

"One question that someone posed (where T-cell malignancies are concerned) is whether they are related to the CAR T-cell therapy or to significant immune deficiency that patients have because they are extensively pretreated with therapies that inhibit their immune system," Dr. Giralt said.

Dr. Harrison echoed this possibility, pointing out that therapies such as fludarabine, which modulate the composition and function of T cells, also have signals for myeloid malignancies.[10]

"People are looking at this more carefully, particularly in relation to cilta-cell," Dr. Harrison said. The original LEGEND-2 trial of cilta-cell used lymphodepleting chemotherapy with

cyclophosphamide only, but "fludarabine was added because it became the standard in the field," he noted.

The addition of fludarabine to cyclophosphamide improved outcomes related to CD19 CAR T-cell therapy.[11] However, fludarabine was found to be associated with increased toxicities in patients with relapsed or refractory MM treated with ide-cel,[12] and national shortages of the drug have led to analysis of alternative lymphodepletion regimens that may be equally effective.[13]

"Fludarabine made a difference in CD19 land, but does it still need to be there in cilta-cel land?" Dr. Harrison said. "That study probably needs to be done in terms of changing lymphodepletion and asking if we still need [fludarabine]."

Patient Conversations

Patients are aware of these FDA warnings, according to Dr. Harrison, especially the ones who are more informed.

"Conversations typically revolve more around the acute toxicities," he said. "In myeloma, long-term survivors get second malignancies. We know that."

These patients get melphalan, immunomodulatory agents, cyclophosphamide … they get [secondary] malignancies, Dr. Harrison noted. That is not new information.

Dr. Giralt said that with increased awareness of this guidance from the FDA, he informs patients that there have been cases of T-cell malignancies reported after CAR T-cell therapies.

"I tell them that the potential benefit still far outweighs the risk," he said. "The main reason that people die after CAR T-cell therapy is their malignancy. People don't respond to treatment or have rare toxicities related to infections or because their immune system is affected."

In an editorial in *Blood Advances* last year, **Rahul Banerjee, MD,** of the University of Washington, and colleagues suggested the use of a three-pronged approach when addressing patient concerns about the possibility of T-cell malignancies.[14]

First, emphasize that the benefits of CAR T-cell therapy far outweigh the risks, a statement backed up by the FDA.

"As clinicians and research scientists, our job is to do what we feel is most likely to be in the patient's best interest with respect to both quantity and quality of life," Dr. Green said. "We weigh the risks for second cancers in many settings, including stem cell transplant, chemotherapeutic and radiation therapies."

Second, explain that several factors other than the CAR T-cell therapy itself could explain why certain patients developed second primary malignancies, including treatments undertaken prior to CAR-T.

"Patients can only develop second primary malignancies if they do not first die of their primary malignancies; as such, patients who receive effective cancer therapies will have higher rates of second primary malignancies compared [with] patients who do not," Dr. Banerjee and colleagues wrote.

Third, the active cancer is a greater risk than the hypothetical risk of a future cancer.

"If the patient succumbs to their current cancer, it is a moot point if there is a risk for secondary cancer," Dr. Green said. "I don't want to minimize the risk, but you would be hard-pressed to find a patient who would say 'Don't give me a therapy that is likely to prolong my life' out of concern that at some point in the future it might, perhaps slightly, increase risk for a second cancer."

Future Effects

Experts agreed that these new "Black Box" warnings are unlikely to have a significant effect on these therapies going forward, but some changes are possible. One possible effect is delaying CAR T-cell therapy until later lines of treatment where possible, Dr. Giralt said.

"Patients may have an alternative treatment with the use of bispecific antibodies, particularly in myeloma," he noted. "That may lead to some patients choosing a bispecific before the CAR-T because of risk of cancer." However, he added that bispecifics are not without their own risks.

Dr. Green said that previously there was a mandate to follow patients undergoing CAR T-cell therapy for 15 years. Now, patients should likely be followed for the rest of their lives.

"When patients enroll in clinical trials, it is their prerogative to decide how long they want to participate in follow-up," Dr. Green said. "We should emphasize the importance of working in partnership with patients to hopefully encourage them to stay involved and allow us to follow them over the arc of their experience so we can identify any problems arising."

Despite the FDA's action, the Australia Therapeutic Goods Administration has not yet issued a response; CAR T-cell therapy is not approved in Australia and only administered as part of clinical trials. In January, the European Medicines Agency announced it would begin to review data on secondary malignancies seen after CAR T-cell therapies.[15] In the end, what is needed is time, Dr. Harrison said.

"Accumulating numbers is the only way to be clear one way or another if there is an excess of T-cell malignancies or not," he noted. "There is an inherent bias in positive reporting at the moment, and time will help determine if this is just background noise or if it is the real thing."

Once it is determined if the risk is real, Dr. Harrison said, the field can look at the numbers and decide if the amount of risk is acceptable.

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Regulatory Actions

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

Cilta-Cel Approved for Expanded Use in Patients With Relapsed or Refractory MM

The US Food and Drug Administration (FDA) has approved ciltacabtagene autoleucel (cilta-cel; Carvykti) for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

The approval was based on positive results from the phase III CARTITUDE-4 study, which demonstrated that the earlier use of cilta-cel reduced the risk of disease progression or death by 59% compared with standard therapies in adults with relapsed and lenalidomide-refractory MM who received one to three prior lines of therapy.

Cilta-cel was previously approved by the FDA for the treatment of patients with relapsed or refractory MM after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This approval was supported by the earlier CARTITUDE-1 study.

Ide-Cel Approved for Triple-Class Exposed Myeloma After Two Prior Lines in United States

The FDA has approved idecabtagene vicleucel (ide-cel) in adult patients with relapsed or refractory MM after two or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, according to a press release from Bristol Myers Squibb and 2seventy bio, Inc.

The FDA approval updated the indication for ide-cel to allow its use in earlier lines of therapy among triple-class exposed patients with MM.

The expansion was supported by positive data from the KarMMa-3 study. "The results of the KarMMa-3 study are remarkable," stated **Al-Ola Abdallah, MD,** of the University of Kansas. "With this approval, these patients now have an opportunity to be treated at an earlier line of therapy with a potentially transformative therapy that offers significantly improved progression-free survival for this difficult-to-treat disease that has had no established treatment approach."

Ide-cel is also approved after two or more prior lines of therapy for triple-class exposed adult patients with relapsed or refractory MM in Japan, Switzerland, and the European Union, and after three or more prior lines in Great Britain and Israel.

FDA Declines BLA for Odronextamab for Non-Hodgkin Lymphoma

The FDA has declined approval of the bispecific antibody odronextamab for the treatment of non-Hodgkin lymphoma, according to a press release from Regeneron, the manufacturer of the drug.

The Biologics License Application (BLA) for odronextamab for the treatment of relapsed or refractory follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy was previously accepted for Priority Review by the FDA in September 2023.

The approval was declined due to the enrollment status of the confirmatory trials, the FDA wrote in response letters to the company.

The regulatory agency requires that the phase III trials include both dose-finding and confirmatory portions. While Regeneron has been enrolling patients in the dose-finding portions, the confirmatory portions "should be underway," the company reported.

The complete response letters "did not identify any approvability issues with the odronextamab clinical efficacy or safety, trial design, labeling, or manufacturing," according to the press release.

The CD20×CD3 bispecific antibody is being reviewed by the European Medicines Agency and has been granted Orphan Drug Designation in the European Union.

"Regeneron is committed to working closely with the FDA and investigators to bring odronextamab to patients with [relapsed or refractory FL and DLBCL] as quickly as possible," the company wrote in the press release.

MRD Receives Support as a Biomarker for FDA Accelerated Approval in Myeloma Therapies

The 12 members of the FDA Oncology Advisory Drugs Committee (ODAC) unanimously voted in favor of the use of measurable residual disease (MRD)-negativity as an intermediate endpoint for FDA accelerated approval in MM clinical trials.

In addition to the voting question, ODAC also discussed whether the data support the use of MRD in newly diagnosed and relapsed or refractory MM subgroups; the assessment timepoints of nine-month, 12-month, and any-time MRD-negative complete response; and the requirement for durability assessments.

Matt Maurer, DMSc, MS, of the Mayo Clinic, said, "I echo everyone's comments here about the strength of the work that's been done over the last 10 years … to move endpoints forward. It shows that the accelerated approval process has been a big success in myeloma, and I think MRD continues to move that forward. [MRD] clearly met the criteria of an intermediate clinical endpoint."

Though several speakers did qualify some additional questions and uncertainties regarding the use of MRD as a marker in MM trials, none was opposed to the use of MRD in the context of the voting question.

"Because we live in the real world, the evidence for a trial-level association is less robust … the endpoint will not perfectly capture clinical benefit in all scenarios, and may sometimes mislead us, but that's why we are talking about accelerated approval," **Christopher Hourigan, MD,** of Fralin Biomedical Research Institute at Virginia Tech, commented during the meeting. "There is harm in inaction. We are not currently curing people of MM, and I'm not willing to make patients wait on principle for a theoretical perfect that may never come."

Ravi Madan, MD, of the National Cancer Institute and Chairperson of ODAC, said, "The FDA showed that MRD does fall short of true surrogacy, but that's a high bar and that wasn't the question today. I think our clinical experts and the FDA both agree that MRD does meet the criteria for accelerated approval, and that's why I voted yes."

Regulatory Actions

Cilta-Cel Approved for Myeloma Treatment in Europe

The European Commission has approved Cilta-cel for the treatment of relapsed or refractory multiple myeloma (MM), according to a press release from Legend Biotech Corporation.

Cilta-cel is now indicated for adult patients who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent; are refractory to lenalidomide; and have experienced disease progression on their most recent therapy.

The approval of cilta-cel was supported by positive findings in the CARTITUDE-4 study, in which cilta-cel exhibited statistically significant and clinically meaningful improvements in progression-free survival compared with PVd or DPd in adults with relapsed and lenalidomide-refractory MM with one to three prior lines of therapy.

Cilta-cel was also recently approved by the FDA for adult patients with relapsed or refractory MM with at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, who are refractory to lenalidomide.

FDA Grants Fast Track Designation to Tamibarotene for Newly Diagnosed AML

The FDA has granted Fast Track Designation to tamibarotene combined with azacitidine and venetoclax for the treatment of newly diagnosed acute myeloid leukemia (AML) with RARA overexpression, according to a press release from Syros Pharmaceuticals, the manufacturer of the drug.

The combination was approved for adults who are over 75 years of age or have comorbidities that preclude intensive induction chemotherapy.

The oral, first-in-class selective retinoic acid receptor alpha agonist is currently being evaluated in combination with azacitidine and venetoclax in the SELECT-AML-1 clinical trial. Randomized data from an interim analysis showed that the triplet achieved a 100% complete response/complete response with incomplete hematologic recovery (CR/CRi) rate compared with a 70% CR/CRi rate for venetoclax and azacitidine alone.

The safety profile indicated no new toxicities with tamibarotene in combination with azacitidine and venetoclax, and there was no evidence of increased myelosuppression compared with venetoclax and azacitidine alone.

FDA Grants Accelerated Approval to Ponatinib in Ph+ ALL

The FDA has granted accelerated approval to ponatinib with chemotherapy for adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Efficacy was evaluated in the phase III PhALLCON study, a randomized, active-controlled, multicenter, open-label trial of 245 adult patients with newly diagnosed Ph+ ALL. Patients were randomized to receive either ponatinib 30 mg orally once daily or imatinib 600 mg orally once daily with chemotherapy. Chemotherapy consisted of three cycles of induction with vincristine and dexamethasone, six cycles of consolidation alternating between methotrexate and cytarabine, and 11 cycles of maintenance with vincristine and prednisone. The ponatinib dose was reduced to 15 mg once daily after completion of the induction phase and achievement of measurable residual disease (MRD)-negative CR.

Efficacy was based on the MRD-negative CR rate at the end of induction, which was 30% in the ponatinib arm and 12% in the imatinib arm.

"The potential benefit to patients who achieve this early deep response may be important to improve long-term survival outcomes," said lead author **Elias Jabbour, MD,** of the University of Texas MD Anderson Cancer Center, in a 2023 press release. "The trial results indicate ponatinib as a potential standard of care for patients newly diagnosed with Ph+ ALL."

FDA Advisory Committee Supports Benefit of Imetelstat for Anemia in Lower-Risk MDS

The FDA ODAC held a vote on whether the benefits of treatment with imetelstat outweigh the risks during an advisory meeting on Thursday, March 14. The count was 12 in favor and two against, including a "no" vote from Committee Chair **Ravi Madan, MD,** of the National Cancer Institute's Center for Cancer Research.

Many of the panel members called for a clearer understanding of the subset of patients who are likely to benefit from the therapy.

Jacqueline Garcia, MD, of the Dana-Farber Cancer Institute, who was in favor of imetelstat, said, "I appreciate the access to details from both the FDA and company perspectives and the raw data beyond the published paper. The stories from the patients were extremely meaningful and impactful, and they really mimic what I hear from my own patients about what they want and what's important to them. ... I look forward to the correlates and biomarker data that might come out in the future."

Michael Sekeres, MD, of the Sylvester Comprehensive Cancer Center, who previously served as chair of ODAC, said, "I believe the benefits associated with the drug justify the risks. The benefits are real. When 40% of patients who previously depended on red blood cell transfusions no longer need transfusions, and this outcome lasts for an average of one year, I think that's a significant benefit."

The New Drug Application (NDA) for imetelstat, a first-in-class telomerase inhibitor developed by Geron Corporation, seeks an indication as an injectable therapy for transfusion-dependent anemia in adult patients with lower-risk myelodysplastic syndromes (MDS) who are not eligible for erythropoiesis-stimulating agents.

The NDA was supported by findings from the phase III IMerge trial.

The trial results, published in *The Lancet,* showed that imetelstat achieved significantly higher rates of red blood cell transfusion independence for at least eight consecutive weeks compared with placebo ($P<.001$).

Those who achieved transfusion independence had a median duration of transfusion independence approaching one year. Significant efficacy outcomes were observed across MDS subgroups regardless of ring sideroblast status.

"Based on the highly differentiated qualities of imetelstat reported in this study, we believe that, if approved by regulatory authorities, imetelstat could substantially improve the treatment paradigm in certain patients with lower-risk MDS," **Faye Feller, MD,** Executive Vice President and Chief Medical Officer at Geron, previously commented in a company release.

Additionally, the Marketing Authorization Application for imetelstat was validated by the European Medicines Agency and is undergoing regulatory review by the European Committee for Medicinal Products for Human Use.

Following this vote, ODAC will decide whether to provide a recommendation for the approval of imetelstat to the FDA. Although a positive recommendation from ODAC is nonbinding, the FDA typically follows advisory committee recommendations when making regulatory decisions.

State of the Art

Experts discuss how frailty status impacts treatment decisions in patients with multiple myeloma and why incorporating frailty scales into clinical care is important.

This article discusses the current state of the art in the treatment of prefibrotic myelofibrosis. The following material is reproduced from "SOHO State of the Art Updates and Next Questions: Acute Lymphoblastic Leukemia" published in January 2024 in Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Pankit Vachhani, MD; Sanam Loghavi, MD; and Prithviraj Bose, MD.*

How to Diagnose, Manage Prefibrotic Primary Myelofibrosis

Prefibrotic primary myelofibrosis (prefibrotic PMF) is a myeloproliferative neoplasm (MPN) with distinct characteristics comprising histopathological, clinical, and biological parameters. There are currently two distinct subtypes of PMF: early or prefibrotic PMF, the focus of this article, and overt fibrotic PMF.

Brief Diagnostic History

The earliest awareness of prefibrotic PMF came in 1976 when European pathologists recognized that a subtype of chronic myeloproliferative disorder was characterized by megakaryocytic and granulocytic hyperplasia, with atypical megakaryocyte morphology, but without any significant bone marrow fibrosis. Work in the 1990s led to a more mature understanding of histopathologic and clinical differences between various MPNs with thrombocythemia, culminating in the 2001 WHO classification of "chronic idiopathic myelofibrosis (CIMF), prefibrotic stage." The 2016 World Health Organization (WHO) classification was the first to recognize prefibrotic PMF as a distinct cinicopathological entity, and the 2022 WHO classification (5th edition) and the International Consensus Classification (ICC) continue to recognize early/prefibrotic PMF, without any changes to the diagnostic criteria, as a distinct subtype of PMF that is different from overt PMF.

Making the Diagnosis

In clinical practice, it is critical to correctly distinguish prefibrotic PMF from essential thrombocythemia (ET) especially, but also from overt PMF, besides other myeloid neoplasms. The three major ICC diagnostic criteria for prefibrotic PMF are as follows:

1. Bone marrow (BM) biopsy showing megakaryocytic proliferation and atypia, BM fibrosis grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
2. *JAK2, CALR,* or *MPL* mutation or the presence of another clonal marker or absence of reactive BM reticulin fibrosis
3. Diagnostic criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera (PV), ET, myelodysplastic syndromes, or other myeloid neoplasms are not met

The four minor criteria include the following characteristics: anemia not attributed to a comorbid condition, leukocytosis ≥11 × 109/L, palpable splenomegaly, and a lactate dehydrogenase level above the reference range.

Diagnosis requires confirmation of all three major criteria and at least one minor criterion confirmed in two consecutive determinations.

Importantly, although the fifth edition of the WHO classification includes leukoerythroblastosis as a minor criterion for both prefibrotic and overt PMF, in the authors' experience, this "feature is typically not seen in prefibrotic PMF."

"We should remain cognizant that prefibrotic PMF has an indolent course with relatively long survival."

Pankit Vachhani, MD, and colleagues recommend performing a BM aspiration and biopsy, reviewing the peripheral blood smear, and strictly adhering to the established diagnostic criteria.

"Hematologists and pathologists should realize the inherent subjectivity in some of the diagnostic criteria and the associated imperfect intra- and interprofessional reproducibility," the authors wrote.

Risk Stratification for Prefibrotic PMF

Risk stratification and survival outcomes for prefibrotic PMF are worse than ET but better than overt PMF. Rates of progression to overt PMF and blast phase disease are also higher for prefibrotic PMF than ET. Major bleeding episodes may be more common in prefibrotic PMF than ET, with one study finding that major bleeding associated with thrombocytosis might be relatively specific to PMF, and that low-dose aspirin exacerbates these hemorrhagic events. Overall, prefibrotic PMF is associated with worse outcomes for the combined endpoints of thrombosis, bleeding, and progression to overt PMF or acute myeloid leukemia (AML).

Risk stratification tools specifically designed for prefibrotic PMF are lacking. In clinical practice, the existing tools for overt PMF are often extended for prognostication and, therefore, management guidance, although the authors note caution must be exercised when applying these models to clinical decision-making because they are not well validated in prefibrotic PMF.

The use of the International Prognostic Score of Thrombosis (IPSET-T) or revised IPSET-T has been suggested until more dedicated risk tools are available. Recently, a validation study found that the IPSET-T score, and to a somewhat lesser extent (as indicated by the hazard ratios [HRs] of the individual risk categories) the revised IPSET-T, effectively discriminates patients with pre-PMF into low-, intermediate- (HR, 2.81 vs low-risk), and high-risk (HR, 4.14) categories of thrombotic risk. The rates of thrombosis in these categories were generally similar to those reported in patients with ET and approximately two- to threefold higher than expected in a normal population.

Managing Patients With Prefibrotic PMF

Neither the National Comprehensive Cancer Network guidelines nor the European LeukemiaNet 2018 recommendations specifically address the management of patients with prefibrotic PMF. Clinical trials have also not investigated outcomes in prefibrotic PMF specifically. As such, there is no specific management paradigm for those with prefibrotic PMF. Whether MF- or ET-like approaches should be taken continues to be debated, and practices vary. Given the generally indolent course of prefibrotic PMF, the day-to-day concerns in managing the disease lie more in preventing bleeding and thrombotic episodes.

As patients with prefibrotic PMF without prior thrombotic events have a thrombotic risk comparable with those with ET, one method is to adopt the IPSET-T-based approach to aspirin prophylaxis and cytoreduction in prefibrotic PMF patients. This approach translates to use of low-dose acetylsalicylic acid (ASA; 81-100 mg once or twice daily) in those with low-risk disease (aged under 60 years with JAK2 mutation) or worse and cytoreduction in those with intermediate- and especially high-risk disease.

In those patients with a history of thrombotic episodes, both ASA prophylaxis and cytoreduction should be performed—akin to management of PV and ET. On the other hand, in those with a previous major bleeding event or at high bleeding risk (eg, acquired von Willebrand disease secondary to "extreme" thrombocytosis), cytoreduction but not

ASA prophylaxis should be performed.

Several studies have compared the baseline characteristics, complications, and outcomes of patients with prefibrotic PMF to those of either ET or overt PMF. Although some of these studies have raised concerns about the reproducibility, interobserver reliability, and utility of the bone marrow histology-based subjective diagnostic criteria in differentiating ET from prefibrotic MF, several other studies have demonstrated that amongst experienced hematopathologists, WHO criteria were applicable, reliable, and reproducible, and there is a notably high proportion of patients with a change in diagnosis when the cases are reviewed by expert hematopathologists.

Hydroxyurea is the most used cytoreductive treatment, not because of well-established efficacy in prefibrotic PMF, but rather due to familiarity with its use across MPN and randomized, controlled trial data in ET. In those with hydroxyurea resistance or intolerance, recombinant interferons can be considered. Anagrelide use is generally discouraged because the drug may increase BM fibrosis. Ruxolitinib may possibly stabilize or improve fibrosis in those with overt PMF; such effects, if any, in prefibrotic PMF patients are unknown. Its use should be considered in those with spleen-related or other symptoms.

High-risk patients with prefibrotic PMF (approximately 12% of all prefibrotic PMF) according to the International Prognostic Scoring System have a median survival of less than 5 years. In such patients, and in those who are similarly risk-stratified by MIPSS70 score, aggressive management approaches, including allogeneic stem cell transplant, should be considered.

Critical Need in Prefibrotic PMF Research

Although algorithms and formulae exist for differentiating ET from prefibrotic PMF, these remain complex, abstract, and largely unvalidated externally. They are capable of confidently allocating only about half of patients with WHO-defined ET or prefibrotic PMF. Ultimately, diagnosis could be improved with expanded expertise in BM assessment and identification of novel biomarkers. The use of artificial intelligence also holds promise in distinguishing between PMF and ET. It should help with efficient and correct diagnosis, and even potentially inform therapy selection, both in routine practice and in clinical trials, as well as prediction of outcomes.

“Risk stratification tools specifically designed for prefibrotic PMF are lacking.”

At least two items are critically needed in prefibrotic PMF research. The first is prospectively collected data of confirmed prefibrotic PMF patients in registries as per the current diagnostic criteria. This would help elucidate the true natural course of prefibrotic PMF. The second is a risk-stratification schema based on clinical and molecular factors dedicated to prefibrotic PMF. Current practice is variable (eg, the choice of ET- or overt PMF-based models). Ideally, a dedicated risk-stratification model would help with prognostication and management decisions.

In the future, newer approaches that incorporate therapies that modify the disease course will emerge.

“Identifying those at highest risk for progression to overt PMF and AML would be important,” the authors wrote. “Other patients could then receive treatment primarily based on symptomatology and risk of thrombotic and hemorrhagic events. Until then, we should remain cognizant that prefibrotic PMF has an indolent course with relatively long survival. Therefore, it is important to not over-treat patients.”

Pankit Vachhani *is an Assistant Professor of Medicine at the University of Alabama at Birmingham and Associate Scientist of Experimental Therapeutics.* ***Sanam Loghavi, MD,*** *is an Assistant Professor in the Department of Hematopathology at the University of Texas MD Anderson Cancer Center.* ***Prithviraj Bose, MD,*** *is a Professor in the Department of Leukemia at the MD Anderson Cancer Center.*

Early Blinatumomab Findings Show Promising Outcomes in Pretreated B-Cell ALL

Therapy with subcutaneous blinatumomab demonstrated "high efficacy" and high rates of negative measurable residual disease (MRD) status with acceptable safety in heavily pretreated adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-cell ALL), suggested data from a phase Ib trial.

"These encouraging results could be practice-changing and warrant further exploration for patients with B-cell ALL," wrote the authors, led by **Elias Jabbour, MD,** of the University of Texas MD Anderson Cancer Center in Houston, in the report published in the *American Journal of Hematology*.

The phase Ib trial evaluated blinatumomab doses of either 250 µg once a day in week one followed by 500 µg three times weekly (n=14) or 500 µg once daily in week one followed by 1,000 µg three times weekly (n=13). The primary endpoint was complete remission or complete remission with partial hematologic recovery within two cycles. MRD negativity was defined as less than 10^{-4} leukemic blasts.

By the data cutoff of September 15, 2023, 12 out of 14 (85.7%) patients in the lower-dose group achieved the primary endpoint, including nine (75.0%) who had negative MRD status. In the higher-dose group, 12 out of 13 (92.3%) patients achieved the primary endpoint and all 12 had negative MRD status.

The cohort had no cases of treatment-related grade 4 cytokine release syndrome (CRS) or neurologic events, and all cases of treatment-related grade 3 CRS and neurologic events were resolved via standard care or treatment interruption or discontinuation. The blinatumomab injections were reportedly well tolerated.

The authors acknowledged the study was limited by a small sample size, though they stated pharmacokinetic evidence of a dose-dependent increase in exposure, early large reductions of tumor load, and the combination of complete remissions with high rates of MRD negativity all corroborated the clinical conclusions.

In closing, Dr. Jabbour and colleagues suggested that "randomized, controlled trials are warranted to test these hypotheses."

Reference

Jabbour E, Zugmaier G, Agrawal V, et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. *Am J Hematol.* 2024. doi:10.1002/ajh.27227

UM171 Induces Stem Cell Expansion in High-Risk Leukemias, Myelodysplasias

The proprietary small molecule UM171 has the potential to create improved hematopoietic stem cell (HSC) therapies through efficient HSC expansion in patients with high-risk leukemias and myelodysplasias, according to a study published in *Blood*.

The study further elucidated the mechanism of action of UM171, which promotes degradation of the CoREST1 complex, or ELM2 domain-containing proteins, and reduces levels of chromatin-bound MYC by activating the $CRL3^{KBTBD4}$ E3 ubiquitin ligase, according to the authors, led by **Jalila Chagraoui, PhD,** of Maisonneuve-Rosemont Hospital in Canada.

UM171 is a proprietary small molecule with a first-in-class mechanism of action that upregulates stem cell renewal and enhances graft compositions by selectively increasing primitive and immuno-modulatory cells while preserving cellular fitness and functionality, according to a release by ExCellThera, the developer of UM171.

"Our work emphasizes the importance of two interconnected determinants (epigenetic and metabolic) for achieving expansion of functional HSCs," Dr. Chagraoui and colleagues wrote. "UM171-mediated $CRL3^{KBTBD4}$ potentiation not only preserves the epigenetic signature of HSCs through CoREST1 degradation, but also limits division rate, CD71 clearance, and protein synthesis, potentially through MYC reduction, thus ensuring their full regenerative potential."

MYC reduction is critical for UM171-induced expansion and preservation of HSCs. While HSC expansion requires a shift from dormancy state to activation and cycling, excessive HSC activation results in reduced self-renewal and an increased propensity for myeloid-biased differentiation.

Dr. Chagraoui and colleagues evaluated UM171 in ex vivo human cell lines and in vivo NOD scid gamma mice. Due to high clonogenicity, they used OCI-AML1 cell lines to dissect the mode of action of UM171. At an optimal, nontoxic dose of 250 nM, most OCI-AML1 cells respond to UM171 treatment. The researchers determined that KBTBD4 is critical for both in vivo activity of UM171-expanded cells and UM171-induced MYC reduction.

The study also evaluated the effect of UM171 on RNA and protein synthesis and observed a "significant KBTBD4-dependent reduction" (30%) in 5-ethynyluridine labeling of nascent RNA in OCI-AML1 cells. UM171 also decreased the rate of protein synthesis in both OCIAML1 cells and CD34+ cells in a KBTBD4-dependent manner. Additionally, CD34+ cells exposed to UM171 showed an increase in lysosome content.

"A more comprehensive understanding of the molecular requirements for engineering healthy HSCs would greatly improve our ability to expand them without limiting their repopulating capacity and would be critical for future therapeutically relevant HSC manipulation," the authors wrote.

Expanding HSCs ex vivo while preserving their therapeutic potential poses a key challenge, especially for hematologic cancers, David Millette, Chief Executive Officer of ExCellThera, explained in a release.

"HSCs have significant therapeutic potential, especially for hematologic cancers, but a key challenge is being able to expand the number of cells ex vivo to the levels needed while also preserving their self-renewal and regenerative capacity for successful complication-free transplants," he said. "Building upon previous mechanism-of-action studies, these new data further validate the use of UM171 to create improved HSCs, including our UM171 Cell Therapy that has shown promise in treating patients with high-risk leukemias and myelodysplasias. We are excited to continue advancing the development of UM171 Cell Therapy and bring this potentially transformative therapy to patients."

Reference

Chagraoui J, Girard S, Mallinger L, Mayotte N, Tellechea MF, Sauvageau G. KBTBD4-mediated reduction of MYC is critical for hematopoietic stem cell expansion upon UM171 treatment. *Blood*. 2024. doi:10.1182/blood.2023021342

HIV-1 Infection Cured in Older Patient After Reduced-Intensity HSCT for AML

An older patient with acute myeloid leukemia (AML) who received reduced-intensity conditioning hematopoietic stem cell transplantation (HSCT) appeared to be cured of HIV-1 infection, according to a case report presented in *The New England Journal of Medicine*.

"At the time of this follow-up, the patient had been free of HIV-1 infection for 35 months after the discontinuation of antiretroviral therapy," reported lead author, **Jana Dickter, MD,** an Associate Clinical Professor in the Department of Medical Specialists in the Division of Infectious Disease at the City of Hope in Duarte, California.

The patient, a 63-year-old male, was diagnosed with HIV-1 infection 31 years before undergoing transplantation. He had a history of undetectable HIV-1 RNA levels while on antiretroviral therapy and had wild-type homozygous CCR5 receptors and predominantly R5 virus.

HSCT was recommended after he experienced AML remission on salvage chemotherapy.

The patient received reduced-intensity conditioning without T-cell depletion because of his age, "unlike other HCT recipients who have had prolonged HIV-1 control," the authors of the report stated.

The conditioning regimen included fludarabine and melphalan plus sirolimus and tacrolimus as prophylaxis for graft-versus-host disease.

The transplant donor was matched for human leukocyte antigens and had different genotypes of killer-cell immunoglobulinlike receptors compared with the patient. Notably, the donor had a Δ32 mutation that causes a CCR5-Δ32/Δ32 deletion that has been associated with resistance to HIV-1 infection, according to Dr. Dickter.

After undergoing HSCT, the patient was negative for AML and his blood, bone marrow, and reservoir sites were reported to have full chimerism with CCR5-Δ32/Δ32 donor cells. Immunity to hepatitis B virus was also achieved after the patient received vaccination.

Is HSCT a Cure for HIV?

Prior to transplant, the patient had HIV DNA present in peripheral blood mononuclear cells; after HSCT, HIV DNA was "mostly undetectable" in both peripheral blood mononuclear cells and gut tissues. Antiretroviral therapy was interrupted at 25 months post-HSCT to evaluate remission of HIV-1 infection.

At six months after interruption of antiretroviral therapy post-transplant, the patient's cells were resistant to in vitro infection by HIV-1 CCR5 strains but not by CXCR4 or dual-tropic virus strains. The study's authors contrasted this outcome with detectable levels of p24 antigens in CD8-depleted peripheral blood mononuclear cell samples from two healthy controls.

Further, at 12 months after antiretroviral interruption, the patient had T-cell activation in response to a CD3/CD28 beads and cytomegalovirus (CMV) peptide mix but no response to a HIV peptide mix, "which indicated the patient's T-cell exposure to CMV but not to HIV," the researchers stated.

Testing for intact proviral DNA showed a greater than two-log reduction in total proviruses after HSCT and no detectable intact or total proviruses after treatment interruption. The study noted that, since the time of treatment interruption, both HIV-1 RNA and cellular DNA or RNA have been undetectable, and CD4 counts ranged from 356 to 1271 cells per microliter.

"At the time of this report, the patient remains in remission from HIV and AML while receiving topical treatment for oral GVHD," Dr. Dickter and colleagues concluded. "This case has shown that older patients who are undergoing reduced-intensity conditioning HCT for the treatment of cancer may be cured of HIV-1 infection."

Reference

Dickter JK, Aribi A, Cardoso AA, et al. HIV-1 remission after allogeneic hematopoietic-cell transplantation. *N Engl J Med.* 2024;390(7):669-671. doi:10.1056/NEJMc2312556

Meeting News

Blood Cancers Today *reports from recent major medical meetings*

Highlights From the **2024 AMERICAN SOCIETY OF PEDIATRIC HEMATOLOGY/ONCOLOGY (ASPHO) CONFERENCE**

The 2024 ASPHO Conference was held April 3-6 at the Seattle Convention Center in Washington. *Blood Cancers Today* spoke with Caroline Hastings, MD, who completed her term as ASPHO President during the Society's annual conference, about which sessions she was excited about, why embracing humor is important for pediatric hematologists and oncologists, and what unanswered questions exist in leukemia treatment.

Caroline Hastings, MD

What are some unique sessions you are particularly interested in?

The conference has a lot of great sessions, including an untraditional keynote speaker, William "Dr. Glaucomflecken" Flanary, MD. He's a cancer survivor, so I think what this group of physicians is practicing is very relatable to him. He's a practicing physician, but he's also a patient.

His shtick is about embracing humor in work. We've done a lot of work in our subspecialty around humanism. We're pediatricians; we consider ourselves more closely engaged with our patients and their families. That kind of relationship is critical to developing trust and being fully engaged with the welfare of our patients.

But there's doctor humor, too. We're very careful about what we say in front of people because they may be offended, but doctor humor and trying to find humor in everything we do helps us get through very stressful times. It helps us, and it helps our patients.

The keynote adds some levity to the symposium where we're talking about complex and complicated diseases, many of which currently have poor outcomes.

One type of leukemia that's becoming more recognizable as we learn more about biology and how to classify and separate different types of leukemia is mixed-phenotype acute leukemia. It has features of two types of leukemia that are treated very differently from each other: acute lymphoid leukemia and acute myeloid leukemia.

When you've got something that appears mixed, it's always been a bit of a conundrum. How do we address it? What kind of therapy do we do? Is it a combination? Do you start with one and then add the other? We're looking at applying new updates and classifications in biology and how that will influence our treatment strategies.

There are also sessions that address cancer predisposition, the impact of genetics, and lymphoid malignancies that have an association with inborn errors of immunity but are genetic predispositions. There is something wrong with our immune surveillance that prevents the body from detecting cancer early enough and repairing the defects that may have occurred. It is important to understand how that is recognized and influences treatment. We know that not every type of lymphoid cancer is the same and that genetic influences actually impact our treatment decisions.

Caroline Hastings, MD, *ASPHO Immediate Past President and Chair of the Society's Leadership Development Committee, serves as a Professor of Pediatrics and the Director of the Fellowship Program at the University of California, San Francisco, Benioff Children's Hospital, Oakland.*

What Is the Role of HSCT in Pediatric, Young Adult Patients With BPDCN?

Jeremy Connors, MD

The role of hematopoietic stem cell transplant (HSCT) in pediatric, adolescent, and young adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) remains unclear, according to a recent study presented at the 2024 ASPHO Conference.

Jeremy Connors, MD, of the University of Texas MD Anderson Cancer Center, and colleagues studied HSCT as consolidative treatment in this patient population because "the prognostic indicators have not been established, hindering standardized treatment approaches and rendering the role and timing of HSCT ambiguous."

The investigators reviewed 21 case reports of patients 20 years old and younger who underwent therapy for BPDCN, including HSCT. The median age was nine years.

As initial therapy, 10 patients received acute lymphoblastic leukemia-based regimens, four received acute myeloid leukemia-based regimens, four received non-Hodgkin lymphoma-based regimens, two received CHOP-based regimens, and one received tagraxofusp monotherapy.

Eighteen (85.7%) patients were in complete remission at the time of HSCT, and three patients had persistent disease. Following first and second relapse, two patients underwent a second HSCT.

The median overall survival was 16 months. Three patients died, one from pulmonary toxicity after conditioning and two from therapy-related myeloid disease.

"While there is more success in the initial therapy of these patients, especially when an acute lymphoid leukemia-based regimen is utilized, definitive indicators of increased risk for relapse are illusive," Dr. Connors and colleagues wrote. "Further study is needed as to predictors of relapse, and thus those who would benefit most from early HSCT."

Reference

Connors J, Ramakrishnan R, Elgehiny A, et al. Hematopoietic stem cell transplant in the pediatric/AYA blastic plasmacytoid dendritic cell neoplasm. Poster #408. Presented at the 2024 American Society of Pediatric Hematology/Oncology Conference; April 3–6, 2024; Seattle, Washington.

How Can We Reduce Pediatric Cancer Treatment Abandonment in Low- and Middle-Income Regions?

Srinithya Gillipelli

Interventions that combined socioeconomic support, psychosocial support, and clinical care improvements yielded the greatest reductions in pediatric cancer treatment abandonment in low- and middle-income countries, according to a scoping literature review of 24 studies.

"Our scoping review describes interventions that were associated with reduced pediatric cancer treatment abandonment in [low- and middle-income countries]," described by **Srinithya Gillipelli,** of Baylor College of Medicine in Houston, Texas.

The researchers also found that survival outcomes "improved in many studies" with these interventions. Data were presented at the 2024 ASPHO Conference.

The meta-analysis reviewed the MEDLINE Ovid, Embase, Web of Science, CINAHL, and Cochrane databases for studies that included patients aged 18 years or younger, were conducted in World Bank income classification-defined low- or middle-income countries, and described both pre- and postintervention treatment abandonment outcomes.

The enrolled studies included nine from the Americas, eight from the Southeast Asian region, four from the African region, and three from the Western Pacific region. Six studies solely evaluated socioeconomic support, five solely evaluated improved clinical care, and five solely evaluated improved education or psychosocial support. Of the remaining studies, four each evaluated a mixture of either two or three categories.

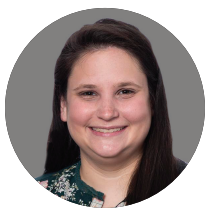
Reportedly, all 24 studies observed a decrease in pediatric cancer treatment abandonment after the intervention. The authors reported a median absolute risk reduction of 16% (range, 1%-55%) and a median relative risk reduction of 40% (range, 24%-100%). Survival "generally improved" in the 14 studies that reported survival data.

"These findings suggest that treatment abandonment can be effectively reduced and survival outcomes improved in [low- and middle-income countries] with targeted interventions aimed at augmenting clinical care and patient support," Dr. Gillipelli and colleagues concluded.

Reference

Gillipelli S, Schaeffer A, McAtee C, et al. Interventions to reduce pediatric cancer treatment abandonment in LMICs: a scoping review. Poster #623. Presented at the 2024 American Society of Pediatric Hematology/Oncology Conference; April 3–6, 2024; Seattle, Washington.

What Is the Role of Palliative Care in Pediatric Patients with Blood Cancers?



Meagan Vacek, DO

Early integration of consults with a palliative care team (PaCT) could decrease symptom burden and distress for pediatric patients with blood cancers receiving hematopoietic stem cell transplantation (HSCT), according to a study presented at the 2024 ASPHO meeting.

The study, led by **Meagan Vacek, DO,** of Children's Mercy Hospital, aimed to increase the number of PaCT consults for patients receiving HSCT for targeted diagnoses from 48% to 75% by December 2023. Targeted diagnoses included relapsed or refractory leukemias and lymphomas, myelodysplastic syndromes, high-risk myeloid leukemias, and metabolic disorders such as Hurler syndrome.

The researchers conducted a chart review for 48 patients who underwent HSCT from July 2020 to July 2022, then utilized a plan-do-study-act (PDSA) method. Of the 48 patients, 25 had a targeted diagnosis.

The first PDSA cycle consisted of increasing communication and education at division meetings about palliative care and its involvement in HSCT patients. The second cycle involved adding the question, "Is PaCT consulted?" to the HSCT referral form. The PaCT also attended weekly transplant team meetings to discuss current and upcoming patients.

"The American Academy of Pediatrics and American Society of Clinical Oncology encourage palliative care engagement and their involvement with [HSCT] patients," the authors wrote, continuing that the practice "has been shown to be beneficial as HSCT is associated with a high degree of morbidity and possible mortality."

Between July 2020 and July 2022, the PaCT met 12 of 25 patients (48%) who had a targeted diagnosis. Of 14 patients with a targeted diagnosis who underwent HSCT from January 2023 to November 2023, eight (57%) received a PaCT consult.

"Palliative care facilitates communication, helps with physical and psychological symptom management, and assists in goals of care and advance care planning discussions," Dr. Vacek and colleagues wrote. "Future PDSA cycles to further increase involvement include adding PaCT consultation to the transplant evaluation order set in the electronic medical record and review of the comments on the completed HSCT referral forms to identify possible barriers in the PaCT consultation process."

Reference

Vacek M, Tarbell L, List M, et al. Increasing palliative care team involvement in pediatric hematopoietic stem cell transplant patients. Poster #410. Presented at the 2024 American Society of Pediatric Hematology/Oncology Conference; April 3–6, 2024; Seattle, Washington.

Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, Executive Editor* ***Elias Jabbour, MD,*** *highlights four recent studies in acute myeloid leukemia (AML). 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.*

Elias Jabbour, MD
Executive Editor

ACUTE MYELOID LEUKEMIA

ASTX727 Plus Venetoclax Is a Safe Regimen in Older Patients With AML

When combined with venetoclax, oral decitabine and cedazuridine (ASTX727) is safe in older or unfit patients with AML, according to a recent study.

The single-center, phase II study was led by **Alexandre Bazinet, MD,** of the University of Texas MD Anderson Cancer Center, and published in *The Lancet Haematology*.

The study comprised two treatment groups: the frontline group (n=49), which included patients with newly diagnosed AML who were ineligible for chemotherapy, and the relapsed or refractory group (n=13), which included patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of two or less.

All 62 patients received cedazuridine 100 mg and decitabine 35 mg orally for five days plus venetoclax 400 mg orally for 21 to 28 days in 28-day cycles. The primary endpoint was overall response rate (ORR). Secondary endpoints included overall survival (OS), relapse-free survival (RFS), duration of response (DOR), rate of transition to stem cell transplantation, and safety.

Why I chose this research:

"ASTX727 plus venetoclax is an active, fully oral regimen that is safe in most older or unfit patients with AML. This combination might constitute a backbone to which additional targeted agents could be added."

At a median follow-up of 18.3 months, the ORR was 64% in the frontline cohort and 46% in the relapsed or refractory cohort. The median OS was 11.5 months (95% CI) in the frontline cohort and 7.2 months in the relapsed or refractory cohort.

Three deaths, potentially treatment related, occurred in patients in remission. The most common grade ≥3 treatment-emergent adverse events (AEs) included febrile neutropenia in 18% of patients, pneumonia in 13%, respiratory failure in 8%, bacteremia in 6%, and sepsis in 6%.

"The major limitation of our study was that it was performed at a single large academic center and patient numbers were relatively small," Dr. Bazinet and colleagues wrote. "Our findings should be confirmed in larger multicentric studies."

Funding for this study was provided by Taiho Oncology and Astex Pharmaceuticals.

Reference

Bazinet A, Garcia-Manero G, Short N, et al. Oral decitabine and cedazuridine plus venetoclax for older or unfit patients with acute myeloid leukaemia: a phase 2 study. *Lancet Haematol.* 2024. doi:10.1016/S2352-3026(24)00033-4

Novel AML Therapy Shows Promising Anticancer Activity

Monotherapy with pivekimab sunirine, a first-in-class antibody-drug conjugate of a high-affinity CD123 antibody, cleavable linker, and novel indolinobenzodiazepine pseudodimer payload, demonstrated activity in patients with relapsed or refractory CD123-positive AML, and researchers identified a recommended phase II dose of 0.045 mg/kg once every three weeks.

Findings from the study, led by **Naval Daver, MD,** of the MD Anderson Cancer Center, were published in *The Lancet Oncology*.

The phase I/II dose-escalation and -expansion trial enrolled 91 patients across nine hospitals in France, Italy, Spain, and the United States. Of these, 68 patients received a dosing schedule of day one of a three-week cycle, and 23 patients received a fractionated dosing schedule of days one, four, and eight of a three-week cycle.

The primary endpoints were the maximum tolerated dose and a recommended phase II dose, and the secondary endpoint was antileukemia activity based on overall response and a composite of complete remission outcomes. The fractionated dosing schedule was discontinued after the researchers compared safety and antileukemia activity outcomes with the single-day dosing schedule.

Why I chose this research:

"Pivekimab, a novel anti-CD123 antibody-drug conjugate, showed single-agent activity in relapsed or refractory AML, with a recommended phase II dose of 0.045 mg/kg once every three weeks. These findings led to a phase Ib/II study of pivekimab plus azacitidine and venetoclax in patients with CD123-positive AML."

Participants received six doses escalating from 0.015 mg/kg to 0.450 mg/kg. No maximum tolerated dose was identified, though three dose-limited toxicities were reported: two cases of reversible veno-occlusive disease at 0.180 mg/kg and 0.450 mg/kg and one case of neutropenia at 0.300 mg/kg.

In 29 patients treated with the recommended phase II dose of 0.045 mg/kg once every three weeks, the most common grade 3 or worse treatment-related AEs were febrile neutropenia (n=3), infusion-related reactions (n=2), and anemia (n=2). The ORR was 21% (n=6; 95% CI, 8-40), and the composite complete remission outcome rate was 17% (n=5; 95% CI, 6-36).

Treatment-related serious AEs in 5% or more of the 29 patients included two cases of febrile neutropenia and two infusion-related reactions. In the 68 patients on schedule A, one death with an unknown cause was deemed related to pivekimab sunirine at a dose of 0.300 mg/kg.

In closing, Dr. Daver and colleagues noted that the results of this study motivated a phase Ib/II trial on pivekimab sunirine plus azacitidine and venetoclax in patients with CD123-positive AML.

Reference

Daver NG, Montesinos P, DeAngelo DJ, et al. Pivekimab sunirine (IMGN632), a novel CD123-targeting antibody-drug conjugate, in relapsed or refractory acute myeloid leukaemia: a phase 1/2 study. *Lancet Oncol.* 2024;25(3):388-399. doi:10.1016/S1470-2045(23)00674-5

FLT3 Gene Cluster Expression, Not *FLT3* Mutation Status, Predicts Quizartinib Response in AML

Benefit from treatment with quizartinib, an FLT3 inhibitor, was accurately predicted by an "*FLT3*-like" gene expression signature identified in patients with AML both with and without *FLT3* mutations, according to a study presented at the 65th American Society of Hematology Annual Meeting & Exposition.

Notably, "patients without the *FLT3*-like signature did not demonstrate a benefit compared with placebo," stated the study's lead author, **Adrian Mosquera Orgueira, MD, PhD,** from the University Hospital of Santiago de Compostela in Spain.

Researchers reported these findings after conducting a preplanned correlative RNA-sequencing analysis of bone marrow and peripheral blood samples, including 161 samples from patients without *FLT3*-ITD mutations who were enrolled in QUIWI and 55 samples from patients with *FLT3*-ITD mutations who had failed screening.

Why I chose this research:

"The FLT3*-like gene expression signature in patients with wild-type FLT3 successfully identified a subset of patients who derived the most benefit from quizartinib, while patients without the* FLT3*-like signature did not demonstrate a benefit compared with placebo. These findings support the use of the* FLT3*-like signature as a potential biomarker to identify those wild-type FLT3 AML patients who may benefit from quizartinib."*

FLT3 Expression Signature Predicts Treatment Response

Based on their analysis, the authors reported the *FLT3*-like gene cluster was specifically enriched in *FLT3*-mutated AML at 71.1% of mutated samples, while it was present in 112 of the 206 (54.37%) total samples — including 80 of the 161 (49.67%) *FLT3* wild-type samples, which the authors termed "*FLT3*-like patients."

Comparing patients without the *FLT3*-like expression in the placebo and quizartinib groups, the investigators found no significant differences in the total number of deaths (Fisher's *P*-value=.63), event-free survival (EFS; hazard ratio [HR], 1.07; 95% CI, 0.56-2.06; *P*=.83), relapse-free survival (RFS; HR, 0.88; 95% CI, 0.38-2.01; *P*=.76), and overall survival (OS; HR, 1.22; 95% CI, 0.55-2.67; *P*=.62).

Conversely, between patients with *FLT3*-like expression in the placebo and quizartinib groups, there were significant differences in the total number of deaths (Fisher's *P*-value=.004), EFS (HR, 0.45; 95% CI, 0.25-0.82; *P*=.009;), RFS (HR, 0.37; 95% CI, 0.18-0.79; *P*=.01), and OS (HR, 0.41; 95% CI, 0.20-0.84; *P*=.01).

The report added that no statistically significant association was identified between the *FLT3*-like expression signature and European LeukemiaNet 2017 risk classifications, as the stratification in the *FLT3*-like subgroup was 30.4% low risk, 40.5% intermediate risk, and 29.1% high risk.

Ultimately, "these findings support the use of the *FLT3*-like signature as a potential biomarker to identify those wild-type *FLT3* AML patients who may benefit from [quizartinib], providing a valuable insight for personalized treatment in AML," Dr. Orgueira and colleagues concluded.

Reference

Orgueira AM, Encinas PM, Arias JAD, et al. The *FLT3*-like gene expression signature predicts response to quizartinib in wild-type *FLT3* acute myeloid leukemia: an analysis of the Pethema Quiwi trial. Abstract #974. Presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, California.

Is Gilteritinib Effective as Post-Transplant Maintenance in Patients With *FLT3*-ITD-Mutated AML?

Treatment with the FLT3 inhibitor gilteritinib improved relapse-free survival (RFS) after allogeneic hematopoietic stem cell transplantation (HSCT) in a subset of patients with *FLT3*-ITD-mutated AML, according to data published in the *Journal of Clinical Oncology*.

The authors, led by **Mark Levis, MD, PhD,** of Johns Hopkins University, said their results demonstrated that molecular measurable residual disease (MRD) might be used to guide treatment in patients with AML undergoing allogeneic HSCT.

Dr. Levis and colleagues wrote they conducted the study "to challenge the assumption that all patients with *FLT3*-ITD AML worldwide, regardless of those variations, should receive an FLT3 inhibitor post-[HSCT], and our results have indeed invalidated that assumption."

Why I chose this research:

"Gilteritinib given as post-HSCT maintenance does confer a benefit for patients with FLT3*-ITD AML with peri-HSCT,* FLT3*-ITD MRD only. These findings are practice-changing."*

In a randomized trial of post-allogeneic HSCT maintenance with gilteritinib, 356 adults with *FLT3*-ITD-mutated AML in first remission underwent allogeneic HSCT and were randomly assigned to placebo or gilteritinib 120 mg once daily for 24 months after transplant. The primary endpoint was RFS, and secondary endpoints included OS and the effect of detection of MRD pre- and post-allogeneic HSCT on RFS and OS.

Although RFS was higher in the gilteritinib arm, the difference was not statistically significant (HR, 0.679; 95% CI, 0.459-1.005; two-sided *P*=.0518).

"We found that post-[HSCT] maintenance with gilteritinib does confer a benefit for patients with *FLT3*-ITD AML, but only for those with peri-[HSCT] *FLT3*-ITD MRD," the authors wrote.

However, 50.5% of participants had MRD detectable pre- or post-allogeneic HSCT, and, in a prespecified subgroup analysis, gilteritinib was beneficial in this population (HR, 0.515; 95% CI, 0.316-0.838; *P*=.0065). Those without detectable MRD showed no benefit (HR, 1.213; 95% CI, 0.616-2.387; *P*=.575).

"Although the overall improvement in RFS was not statistically significant, RFS was higher for participants with detectable *FLT3*-ITD MRD pre- or post-[allogeneic HSCT] who received gilteritinib treatment," the authors wrote. "These prospective results establish *FLT3*-ITD mutations as essential markers of MRD and illustrate how molecular MRD can be used to guide the therapy of patients with AML undergoing [allogeneic HSCT]."

Dr. Levis and colleagues said the results were "practice-changing" in the article. "These findings are practice-changing, and further study of the data from this trial is likely to yield more insights into the biology and management of this disease," they concluded.

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Clinical Trial Updates

Blood Cancers Today *shares clinical trials currently enrolling patients*

Phase Ib Study on Iberdomide (CC-220) or CC-99282 Plus R-CHOP in Lymphoma

This phase Ib study has an estimated enrollment of 174 patients and comprises dose-escalation and dose-expansion phases. The escalation phase will evaluate iberdomide (CC-220) or CC-99282 added to R-CHOP-21 as first-line therapy in patients with B-cell lymphoma. The dose-expansion phase will evaluate the regimen at the recommended phase II dose. Additionally, researchers will evaluate CC-220 and CC-99282 in combination with pola-R-CHP.

The primary outcomes in the escalation phase are maximum tolerated dose and the recommended phase II dose. Primary outcomes in the expansion phase include the safety and tolerability of CC-220 and CC-99282 at the recommended dose, as well as the maximum tolerated and recommended doses for the CC-220 and CC-99282 plus pola-R-CHP regimens.

Principal investigator: **Grzegorz Nowakowski, MD, Mayo Clinic**
Treatment agents: CC-220; pola-R-CHP; CC-99282
NCT04884035

Phase I Trial on Venetoclax Plus Decitabine in Acute Myeloid Leukemia

This phase I study is evaluating venetoclax plus decitabine administered as a 10-day regimen in an estimated 26 patients with high-risk acute myeloid leukemia. Cycle one of the regimen consists of decitabine on days one to 10, with a venetoclax ramp-up on days one to three, followed by venetoclax at the target dose on days four to 21. Cycle two includes the same decitabine schedule and venetoclax at the target dose on all days.

The rate of dose-limiting toxicities over 24 months and the maximum tolerable dose are the study's primary endpoints. Additional endpoints include overall survival (OS) and levels of toxicity based on adverse events (AEs), dose-limiting toxicities, and other safety signals.

Principal investigator: **Olatoyosi Odenike, MD, University of Illinois College of Medicine**
Treatment agents: Decitabine; venetoclax
NCT03844815

R289 in Participants With Lower-Risk MDS

This open-label, phase Ib study is enrolling approximately 34 patients in several locations in the United States. The trial is evaluating the tolerability and preliminary efficacy of R289 in patients with relapsed or refractory lower-risk myelodysplastic syndromes (MDS) who are resistant, are intolerant, or have inadequate response to prior therapies such as erythropoietin, thrombopoietin, luspatercept, or hypomethylating agents.

The study's primary endpoints include the incidence of AEs, discontinuation or interruptions of R289 due to AEs, and dose-limiting toxicities.

Additional endpoints include red blood cell (RBC) transfusion independence at 24 weeks (the proportion of patients who achieve a ≥50% reduction in number of RBC transfusions compared with baseline and ≥24 weeks), maximum plasma concentration at eight weeks, and a change from baseline biomarker expression levels in plasma and bone marrow in one year.

Principal investigator: **Guillermo Garcia-Manero, MD, University of Texas MD Anderson Cancer Center**
Treatment agent: R289
NCT05308264

Epcoritamab in Relapsed or Refractory CLL, Richter Syndrome (EPCORE CLL-1)

This global, multicenter study of approximately 184 participants will evaluate the safety and efficacy of subcutaneous epcoritamab (EPKINLY) and GEN3013 (DuoBody-CD3×CD20) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and patients with Richter syndrome. The study will also determine the recommended phase II dose and the maximum tolerated dose of epcoritamab, if reached.

For patients with CLL or SLL, epcoritamab will be studied as monotherapy or in combination with venetoclax. For those with Richter syndrome, epcoritamab will be studied as monotherapy or in combination with lenalidomide or R-CHOP. The trial will consist of two phases: a phase Ib dose-escalation phase and a phase II dose-expansion phase. The latter phase will include only patients with Richter syndrome.

Primary endpoints for the dose-escalation phase (measured from the first dose until the end of the 60-day safety follow-up period) include the following:

- Dose-limiting toxicities
- Treatment-emergent AEs (TRAEs)
- Serious AEs
- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Clinical tumor lysis syndrome (CTLS)

The secondary endpoint for the escalation phase is overall response rate (ORR), defined as the percentage of patients who achieve a partial response or a complete response.

In the dose-expansion phase, the primary endpoint is ORR. Secondary endpoints for the expansion phase include the number of patients with the following:

- TRAEs
- Serious AEs
- CRS
- ICANS
- CTLS
- Measurable residual disease negativity
- Partial remission or nodular partial remission

Secondary outcomes for both phases include duration of response, number of patients with complete remission, time to response, progression-free survival, and OS.

Principal investigator: **Mazyar Shadman, MD, MPH, Fred Hutchinson Cancer Center**
Treatment agents: Epcoritamab; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; venetoclax; lenalidomide
NCT04623541

Phase III VERIFY Study of Rusfertide in PV

This phase III study will include an estimated 250 patients with polycythemia vera (PV) who require routine phlebotomy. It will evaluate the safety and efficacy of the experimental drug rusfertide, compared with a placebo, in maintaining hematocrit control and improving symptoms of PV. Thirty-two weeks of either rusfertide or placebo will be added to each patient's ongoing treatment for PV.

The study's primary endpoints include the proportion of patients who achieve a response (defined as the absence of phlebotomy eligibility) between weeks 20 to 32 receiving rusfertide versus placebo. The study's other endpoints include a comparison of the mean number of phlebotomies between rusfertide and placebo, the proportion of patients with hematocrit values <45% for rusfertide and placebo, a comparison of the mean change from baseline in total fatigue score based on the Patient-Reported Outcomes Measurement Information System Short Form between rusfertide and placebo, and a comparison of the mean change from baseline in Myelofibrosis Symptom Assessment Form total score.

Principal investigator: **Tamanna Haque, MD, Memorial Sloan Kettering Cancer Center**
Treatment agents: Rusfertide; placebo
NCT05210790

HemOnc Happenings

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

Nirali Shah, MD, MHSc, Receives Frank A. Oski Memorial Lectureship at ASPHO

Nirali Shah, MD, MHSc

Dr. Shah, Head of the Hematologic Malignancies Section of the Pediatric Oncology Branch at the National Cancer Institute (NCI), received the 2024 Frank A. Oski Memorial Lectureship for her accomplishments in pediatric hematologic oncology.

The lectureship is presented annually to an early- or mid-career clinical or laboratory investigator in the field of pediatric hematologic oncology "whose cutting-edge research is of the caliber of the investigations made by Dr. Oski," according to the American Society of Pediatric Hematology/Oncology (ASPHO).

Dr. Shah's areas of expertise include immunology and immunotherapy, rare tumors, chimeric antigen receptor (CAR) T-cell therapies, and blood and bone marrow transplantation. Specifically, her research focuses on the development of targeted immunotherapy approaches to treating high-risk leukemia and lymphoma in children, adolescents, and young adults.

Her clinical trials explore the use of CAR T-cell therapies to target the surface proteins of leukemia cells to improve outcomes for patients who do not respond to chemotherapy. She also studies the prevention and treatment of relapsed disease following allogeneic hematopoietic stem cell transplantation.

As the 2024 recipient of the Frank A. Oski Memorial Lectureship, Dr. Shah presented a state-of-the-art lecture at the 2024 ASPHO Conference in Seattle, Washington, April 3-6. The lecture highlighted her research, career accomplishments, and how mentorship played a role in her career trajectory.

"[Dr. Shah] is a tireless advocate for her patients, who are some of the most refractory and sickest patients in the field of pediatric hematologic malignancies," said Dr. Shah's nominator. "Her incessant efforts in obtaining Breakthrough Therapy designation by the US Food and Drug Administration for the CD22 CAR T-cell trial, based on the application she authored, is one of many examples of her grit and selfless dedication to her patients. There are very few who understand the clinical field of immunotherapy targeting cell surface receptors, in particular CD22, in pediatric [B-cell acute lymphoblastic leukemia] as well as Dr. Shah."

Franco Cavalli, MD, Honored for Cancer Research, Education Initiatives

Franco Cavalli, MD

Dr. Cavalli, President of the Foundation for the Institute of Oncology Research (IOR) in Bellinzona, Switzerland, received the 2024 American Association for Cancer Research (AACR) Distinguished Public Service Award for Lifetime Achievement in Cancer Research at the AACR Annual Meeting, which took place April 5-10 in San Diego, California.

Dr. Cavalli was honored for his accomplishments in the fields of leukemia, lymphoma, and breast cancer; his clinical investigations involving VP16; and his contributions to the development of therapeutics such as cisplatin, carboplatin, and paclitaxel, according to the AACR. Throughout his career, he has published more than 600 journal articles and contributed to the publication of several textbooks, including the *Textbook of Medical Oncology*.

The award also recognized Dr. Cavalli's commitment to improving global cancer research through the initiation and development of the International Conference on Malignant Lymphoma. Additionally, he helped establish several organizations to advance research and education in the field, including the IOR, the International Extranodal Lymphoma Study Group, the European School of Oncology, the Oncology Institute of Southern Switzerland, the Institute for Research in Biomedicine, the Bellinzona Institutes of Sciences, and the European Organization for Research and Treatment of Cancer Early Clinical Trials Group.

As the former president of the Union for International Cancer Control, he contributed to the launch of the My Child Matters initiative, which was formed in 2005 to improve the survival rate of children with cancer in low- and middle-income countries, and the World Cancer Declaration, which promotes equal access to cancer services and helps bring the global cancer crisis to the attention of government leaders and policymakers, according to their respective websites.

An AACR member since 1981, Dr. Cavalli has served on several AACR committees, including the AACR-Millennium Fellowship in Lymphoma Research Scientific Review Committee from 2013 to 2015 and the Pezcoller Foundation-AACR International Award for Extraordinary Achievement in Cancer Research Selection Committee from 1998 to 1999.

"Dr. Cavalli is an exceptional scientist and leader," said **Margaret Foti, PhD, MD (hc),** Chief Executive Officer of the AACR, in a press release. "His work both in the lab and as a tireless advocate for improved collaboration and communication among cancer researchers has led to crucial progress against this dreaded disease for the benefit of patients around the world. The AACR is so proud to honor him with this prestigious award."

Owen Witte, MD, Recognized for Leukemia Discoveries at AACR

Owen Witte, MD

Dr. Witte, University Professor of Microbiology, Immunology, and Molecular Genetics at the University of California, Los Angeles, received the AACR Award for Outstanding Achievement in Blood Cancer Research at the 2024 AACR Annual Meeting in San Diego, California, on April 9.

During his presentation, Dr. Witte highlighted his decades-long career trajectory and research, which has led to the development of kinase targeted therapy for leukemias and the co-discovery of Bruton's tyrosine kinase.

The session included opening remarks from **Matthew Schulz,** Assistant Scientific Director at AbbVie, and **Faith E. Davies, MD,** Chair of the Selection Committee for the award and Director of the Center for Blood Cancers at NYU Langone's Perlmutter Cancer Center.

"Dr. Witte's body of work offers a compelling example of target discovery and validation in human cancers and illustrates the critical importance of understanding basic disease mechanisms as a guide for the development of novel therapies," Dr. Davies said. "His discoveries have led to the development of targeted therapies that have revolutionized modern cancer treatment and changed the lives of countless patients with leukemia and lymphoma."

Dr. Witte's recent research focuses on finding immunological targets for both antibody and cell-mediated therapy.

"There's still lots of work to do to find good targets to treat cancer," Dr. Witte said. "Particularly, with the field of immunotherapy exploding, any single target we find that can match with an antibody, a CAR, or a T-cell receptor will be of real value to patients."

Do you know of a clinician or researcher who has been the recipient of a recent award?

Send the details to editor@bloodcancerstoday.com.

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Aligning Patient and Physician Perceptions on Whether to Switch

Patients' perceptions regarding TKI therapy can differ from those of their oncologists. Results from the CML SUN survey showed that oncologists cited resistance as the main reason for switching therapy; however, patients more often reported side effects as the main reason for the decision to switch to a different TKI therapy.[8] Additionally, the majority of patients who reported side effects felt their oncologist lacked empathy and oncologists often did not feel the side effects were serious enough to consider switching TKIs.[8] The survey also found that patients' top treatment goals differed with oncologists, even when switching therapies. In the 1L, patients reported inhibiting disease progression as the primary goal whereas oncologists reported QOL improvement as the most important goal of a 1L therapy.[8] In the 2L, these goals shift as patients view QOL as the primary treatment goal and oncologists are most concerned with achieving an major molecular response (MMR). By 3L, both patients and physicians are aligned to maintain or improve patient QOL.[8]

> "The goal is always the same for all patients to prevent progression to advanced-phase disease. You're going to want to match the therapy to the patient's characteristics as well as disease characteristics. Oncologists are going to pick and choose the TKI based on the efficacy and AR profiles, the patient's expected life span, and whether or not they're going for a treatment-free remission. They're looking at a lot more than just what TKI was used last." **— Dr Levy**

Determining When and How to Take Action for a Better Patient Treatment Journey

Identify TKI Management Goals and the Appropriate Time to Switch

In general, alignment of clearly defined management goals between the patient and oncologist is foundational to a positive patient experience with a TKI treatment. To manage the patient experience with TKIs, patients need to be routinely monitored not only for molecular response, but also for TKI-related toxicity.[7] The role of the oncologist includes determining how patients are responding to their current TKI therapy, what side effects the patient may be experiencing, and whether they need to consider adjusting the TKI dose or switching to an alternative TKI.[7] This involves proactively inquiring about the occurrence of any TKI-related side effects and their impact on QOL and continual monitoring for a molecular response to ensure treatment efficacy and that management goals are being met.[7,29] Additionally, failing to identify patients who are not adherent to therapy due to intolerance issues and/or not recognizing that a patient has developed resistance to a TKI therapy can negatively impact clinical responses.[7,29] If patients continue to have issues related to a treatment (eg, issues related to intolerance, safety, and/or achieving MMR), even after employing management strategies (eg, dose adjustment), it may be appropriate to consider switching to an alternative TKI.[7]

Maintain Open Communication Channels

Since perceptions on TKI therapy and goals for new treatment can differ between patients and their oncologists, open communication is important to improve the overall patient experience.[8] Open communication between multidisciplinary care team members (eg, physician, nurse practitioner, nurse, pharmacist) is also vital for optimal patient management. Even if CML in a patient is well controlled, it is important to ensure they are still able to communicate frequently with the care team.

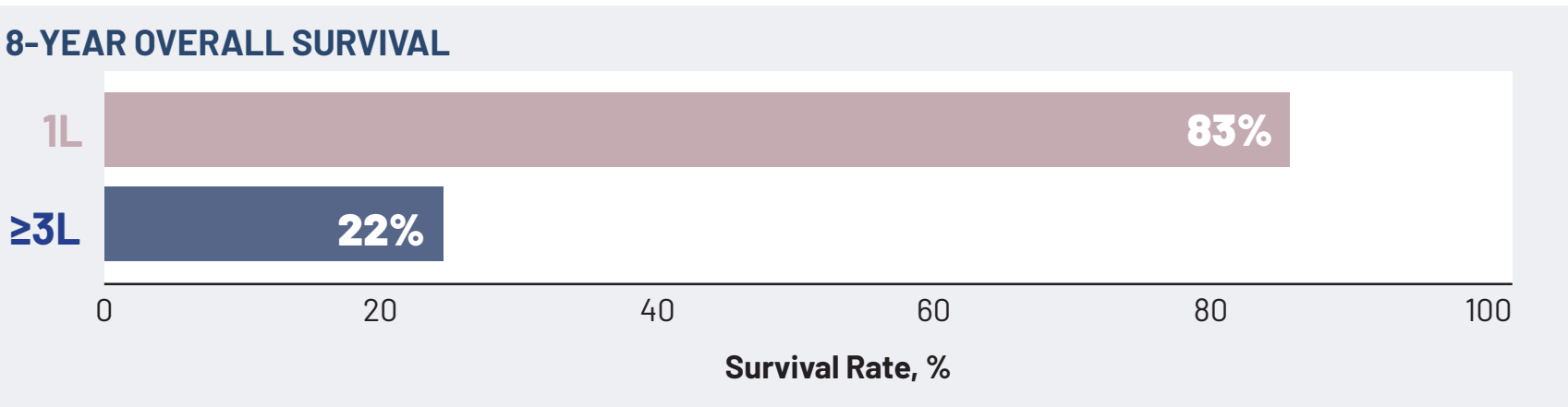

Figure 4. 8-Year OS in patients with CML who maintain TKI as 1L therapy and patients who received ≥3L of treatment.[28]
1L, first-line; 3L, third-line.

The following adapted patient cases illustrate how monitoring patients receiving TKIs can help identify intolerance or resistance issues that prompt a timely dose adjustment or a switch to a new therapy.

REAL-WORLD PATIENT CASES

Patient Case #1: Switching Due to Intolerance Issues

John, a 42-year-old male diagnosed with CML 1.5 years ago, experienced cytopenia (grade 3) and pleural effusion (revealed by a chest x-ray) while taking his first TKI. Due to intolerance issues, John found it difficult to remain adherent, and even though he responded well to the treatment (BCR::ABL1=0.7% at 6 months), he was switched to a second TKI. John was able to achieve adherence to the second TKI; however, even though the second TKI achieved a molecular response (BCR::ABL1=10% at 3 months), John was switched to a third TKI due to severe ARs. He has since been responding well to therapy.

In the above case, John was achieving a molecular response from his initial treatment, but intolerance issues resulted in a need to switch his therapy. Intolerance issues, whether they are mild or more severe, can impact patient QOL even though the patient is achieving molecular response.

Intolerance was again the issue with his second therapy, resulting in another switch. It is understandable that John has already gone through impactful events with these initial lines of therapy; therefore, it is important to continue to actively monitor him for any additional intolerance issues that could occur. Also, it may be important to consider the tolerability profile for later lines of therapy (eg, fourth-line therapy).

> "The goals of therapy can be disparate based on the age of the patient and their comorbidities, among other considerations." **— Dr Bradley**

Patient Case #2: Switching Due to Efficacy/Intolerance Issues

Mary, an 85-year-old female diagnosed with CML 16 years ago, responded well for years to her initial TKI but never achieved the MMR milestone. Over time, the response to the first TKI started declining, leading to a switch to a second TKI after mutation panels were examined. While the second TKI initially showed a response, Mary developed issues, such as pleural effusion and pericardial effusion (revealed by chest x-rays), requiring hospitalization. Consequently, Mary was switched to a third TKI but faced challenges with the initial high dose, resulting in discontinuation. The treatment plan now involves considering restarting the same third TKI at a lower dose or exploring alternative TKIs.

In the above case, Mary was achieving a molecular response for years from her initial TKI treatment; however, she never achieved complete molecular remission. Over time, response to the TKI diminished, resulting in a switch to another TKI therapy. Reduced efficacy can be a reason for switching TKIs since the main goal of therapy is to prevent progression to blast phase.

Intolerance was the issue with her second therapy, prompting another switch. Severe intolerance issues can greatly impact patient QOL, especially in older populations. Also, it is important to note that efficacy and intolerance issues are not mutually exclusive; they may occur independently or together, depending on the patient and treatment. It may be important to ensure that the ARs are not transient before switching TKIs.

Mary faced intolerance issues with the initial high dose of the third TKI and discontinued use. Restarting the TKI treatment at a lower dose is being considered; however, adherence may be an issue and could result in failure due to subtherapeutic drug levels if Mary continues to experience intolerance issues.

Summary

The treatment of CML with TKIs has greatly improved survival rates, but some patients may develop resistance or intolerance to these therapies, leading to suboptimal outcomes. Although TKIs are highly effective, their inability to selectively target kinases specific to CML can result in off-target effects leading to nonspecific ARs. An additional TKI strategy is to target the myristoyl pocket of BCR::ABL, which results in a conformational change from an active to an inactive state.

There exists a disconnect between oncologists' satisfaction with the efficacy of current treatments and patients' perceptions of the impact of TKI-related side effects and tolerability issues on their QOL. This disconnect may lead to suboptimal patient care and requires further investigation. Additionally, patients and oncologists also differ in their views on switching TKI therapies, with oncologists often prioritizing efficacy while patients prioritize reducing the burden of ARs.

To manage the patient experience with TKIs, routine monitoring for unmanageable side effects and toxicity is essential. Oncologists should proactively inquire about any TKI-related side effects and their impact on daily life to adjust treatment as needed. Open communication between patients, oncologists, and the multidisciplinary care team is vital for optimal patient management and improved survival outcomes.

In summary, addressing gaps in managing resistance or intolerance to TKI therapy in patients with CML requires better understanding of patients' treatment perceptions and the AR management practices of oncologists. Effective communication between patients and HCPs is crucial in making informed decisions about treatment options and achieving better outcomes for patients with CML.

> "Customizing therapy to an individual patient is important, as well as managing expectations of what the patients [on TKIs] should or might expect." **— Dr Bhatnagar**

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