TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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BLOOD CANCERS TODAY

October 2025

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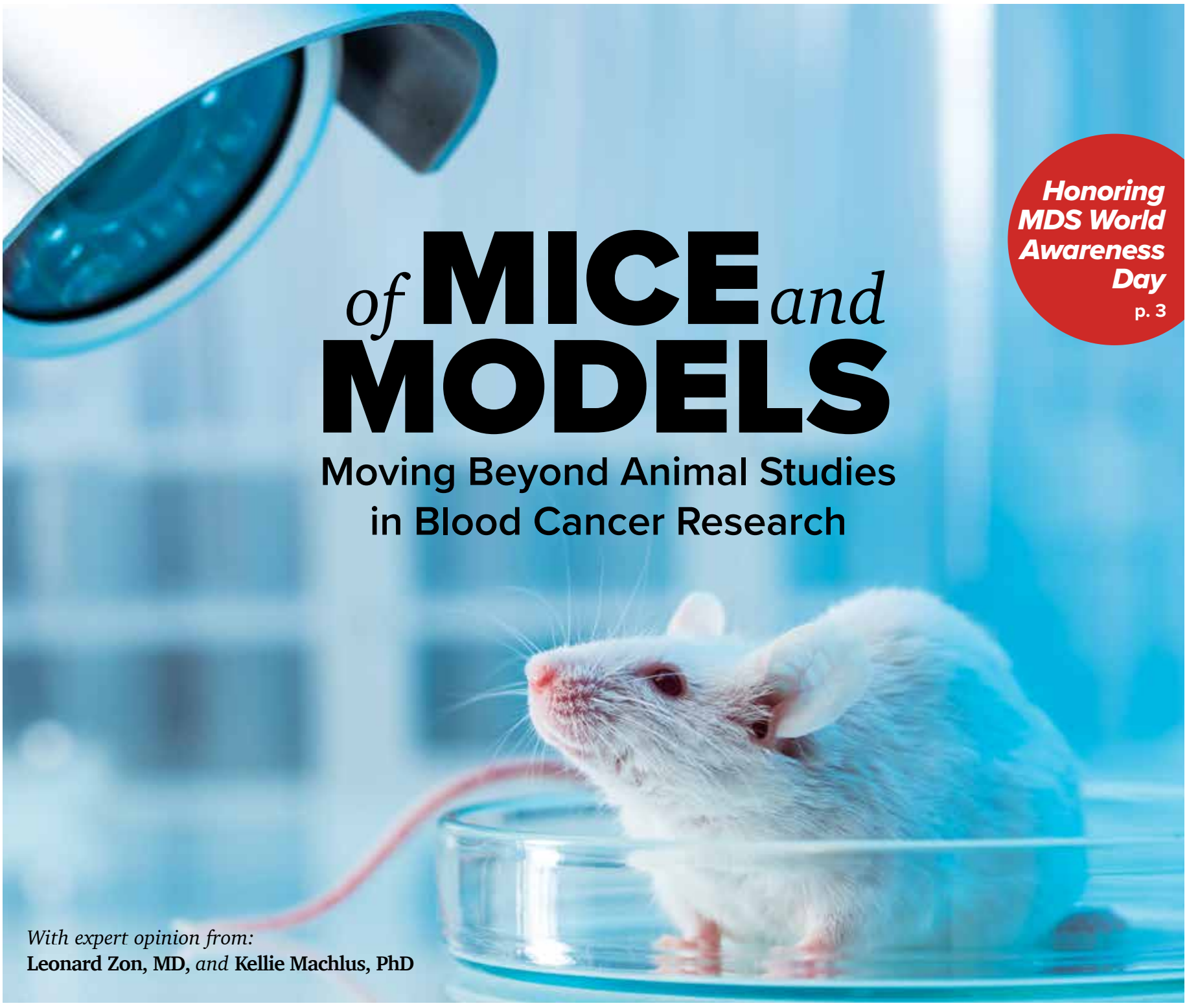
Thromboembolic Events Underreported in Cancer Clinical Trials
p. 12

Teclistamab Triplets Show "Unprecedented" Efficacy in Myeloma
p. 13

From Promise to Uncertainty in Venetoclax + Azacitidine for MDS
p. 16

Myeloma Researchers Honored at IMS Annual Meeting
p. 17



of MICE *and* MODELS

Moving Beyond Animal Studies in Blood Cancer Research

With expert opinion from:
Leonard Zon, MD, *and* **Kellie Machlus, PhD**

Honoring MDS World Awareness Day
p. 3

MAIL TO:

KIMBERLY KU, MD
Advancing Outpatient CAR-T in Local Oncology Practices

figure1

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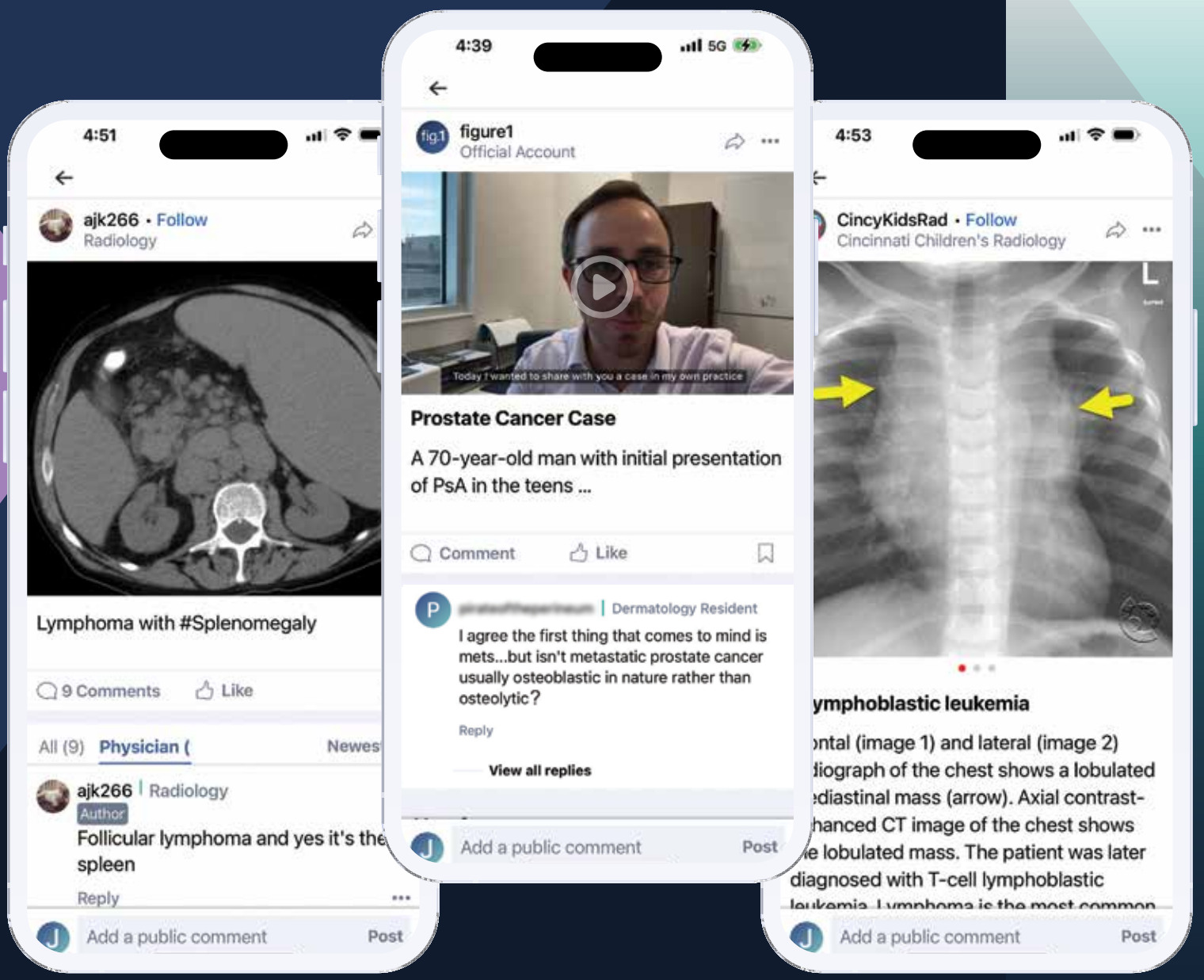

CONTENTS

Volume 4 | Number 10 | October 2025

Of Mice and Models
Moving Beyond Animal Studies in Blood Cancer Research

In light of the NIH's recent initiative to reduce funding for animal studies, computational models and organoids are offering new pathways for preclinical research in combination with animal models.

6

News

The HemOnc Pulse

Listen to new episodes of **"The HemOnc Pulse"** for all the latest news in hematologic oncology.

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CU Anschutz

Assistant professor **Mathew Angelos, MD, PhD,** is part of a research team pioneering a novel, homegrown CAR-T therapy approach for AML at CU Anschutz.
9

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Calendar

2025

November 1, 2025
Mid-Atlantic Blood Cancer Conference
Bethesda, MD

November 5-9
Society for Immunotherapy of Cancer (SITC) 40th Annual Meeting
National Harbor, MD

November 6-7, 2025
17th International Congress on Myeloproliferative Neoplasms
Brooklyn, NY

November 12-14, 2025
European Society for Medical Oncology (ESMO) AI & Digital Oncology Congress
Berlin, Germany

November 13-14, 2025
American Association for Cancer Research (AACR)–Korean Cancer Association (KCA) Joint Conference on Precision Medicine in Cancer
Busan, Korea

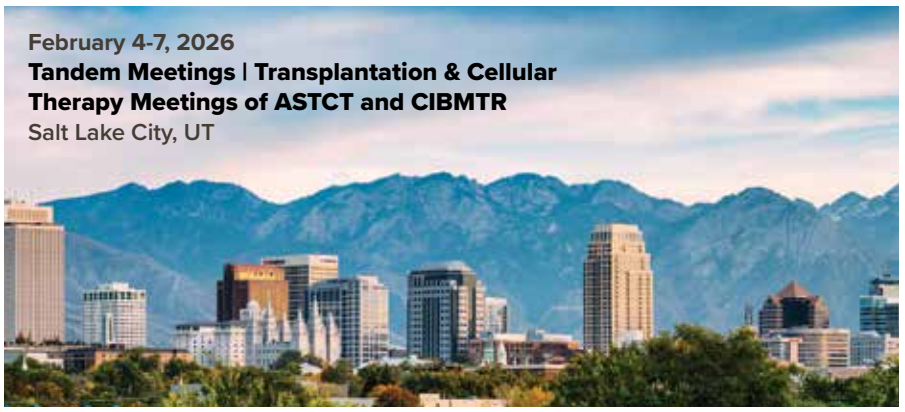
November 20, 2025
Society of Hematologic Oncology (SOHO) Breakthroughs in Blood Cancers 2025
Virtual

December 4-6, 2025
AACR Special Conference in Cancer Research: Cancer Evolution: The Dynamics of Progression and Persistence
Albuquerque, NM

December 6-9, 2025
67th American Society of Hematology (ASH) Annual Meeting and Exposition
Orlando, FL

2026

January 16-18, 2026
2nd Annual Cleveland Clinic Cancer Conference
Hollywood, FL



February 4-7, 2026
Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR
Salt Lake City, UT

February 12-14, 2026
EHA-EBMT 8th European CAR T-Cell Meeting
Palma de Mallorca, Spain

February 26-28, 2026
30th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
Miami Beach, FL

March 14, 2026
Tri-State Blood Cancer Conference
New York, NY

March 25-27, 2026
Society for Immunotherapy of Cancer (SITC) Sparkathon 2026: Next-Generation Cellular Therapies, T-Cell Engagers, and Combinations
Tucson, AZ

Perspectives

Guest contributors provide commentary from the field.

In honor of MDS World Awareness Day on October 25, experts in myelodysplastic syndromes (MDS) describe what this day means to them as a clinician researcher and outline remaining unmet needs in MDS.

Sangeetha Venugopal, MD, MS
Assistant Professor of Clinical Medicine
Division of Hematology
University of Miami Miller School of Medicine

What does MDS Awareness Day mean to you?
Myelodysplastic syndromes/neoplasms are rare blood disorders predominantly affecting people older than 70 years, or younger if exposed to treatment for other cancers. MDS World Awareness Day spotlights this rare blood cancer in which outcomes are still suboptimal.

What are the remaining unmet needs in MDS?
In the past two decades, hypomethylating agents have remained the standard of care in higher-risk MDS. Even though hematopoietic cell therapy is curative, not all patients can undergo curative intent therapy. Novel targeted and nontargeted therapies in higher-risk MDS remain a longstanding unmet need.

Andrew Brunner, MD
Medical Oncologist
Massachusetts General Hospital

What does MDS Awareness Day mean to you?
MDS is one of the most common myeloid blood cancers, but how it impacts a given patient can vary substantially, so it can be less well known or understood compared to other cancers. MDS World Awareness Day is a great way to recognize efforts to beat this cancer and also connect patients and caregivers to resources.

What are the remaining unmet needs in MDS?
In spite of advances in recent years, there is no curative therapy for MDS outside of transplant, and few drugs have prolonged life. We must prioritize ongoing development of new drugs in this space and support new approaches for this family of blood cancers.

Tiffany Tanaka, MD
Associate Professor
Division of Blood & Marrow Transplantation
UC San Diego Moores Cancer Center

What does MDS Awareness Day Mean to you?
MDS Awareness Day is an opportunity to raise awareness about a rare group of cancers, advocate for more resources to advance research discoveries, and most of all, to recognize the real and daily challenges that patients and families face when dealing with low blood counts and the associated symptom burden.

What are the remaining unmet needs in MDS?
With revolutionary advances in sequencing technology, my hope is that more effective and less toxic treatments continue to be developed. Most patients with MDS are elderly, so we have to balance treatment efficacy with toxicity (side effects) to not only help patients live longer, but with a good quality of life.

From Network to Impact: Advancing Outpatient CAR-T in Local Oncology Practices

*By **Kimberly Ku, MD***

In the community setting, despite most medical oncologists acknowledging chimeric antigen receptor (CAR) T-cell therapy as a potentially curative innovation, as much as one quarter of patients who are eligible for it are not receiving CAR T-cell therapy.[1,2]

Kimberly Ku, MD

With a great deal of highly rigorous scientific literature defining the term of *value* in cancer care,[3-8] it seems the literature becomes much more influential when it includes the authentic patient experience. How much cancer care is *worth* becomes a much more personal question when we consider someone in our immediate community. The following question remains: When and how will outpatient CAR T-cell therapy become accessible as a standard of care in every community?[10-12]

According to a registry search, 156 sites that are accredited by the Foundation for the Accreditation of Cellular Therapy in the United States provide CAR T-cell therapy. Although this search did not include the number or locations of outpatient CAR T-cell therapy centers, the interest in providing outpatient therapy is growing. Community oncologists may be particularly well positioned to offer complex, advanced therapeutics closer to home.[13]

Movement toward outpatient CAR T-cell delivery is further encouraged by increasing community collaboration models[14-16]; telehealth use[17]; increasing adoption of bispecific antibodies, which make community providers more familiar with side effect management protocols for cellular therapies; and the recent FDA elimination of Risk Evaluation and Mitigation Strategies for CAR T-cell therapies.[18] Moreover, there is forward-looking integration of artificial intelligence with CAR T-cell therapies at multiple points, from design and efficient manufacturing to patient selection, patient response predictions, and monitoring.[19,20]

Successful adoption and scale of new technologies in the field of oncology often follow a similar pattern, as seen with the initially slow uptake followed by rapid use of immune checkpoint inhibitors. In addition, there is an increasing trend of vertical integration not just in oncology, but also in healthcare in general. Beyond success, the consistent reminder and self-reflection of social responsibility and the upholding of future generations are more important.

Advancing the use of CAR T-cell therapy requires deliberate steps to build both expertise and infrastructure at the community level.[21-23] This first step is to identify a local champion who can serve as the resident expert and guide the initiative. The second step is to establish a partnership with a hospital and its designated champion that share the vision of expanding community access to CAR T-cell therapy and can collaborate in the event of patient admissions. The third step is to secure the infrastructure necessary to deliver CAR T-cell therapy safely in the outpatient setting. Once these critical success factors are in place, additional features that may further strengthen access and outcomes include patient support services, streamlined referral pathways, and enhanced monitoring programs.

Beyond implementation, the way we live out our mission is equally important. This echoes a warning often attributed to Albert Einstein: "I fear the day that technology will surpass our human interaction." To prevent this, we must integrate technology in ways that enhance, rather than replace, human engagement. Potential solutions include fostering open dialogue across teams, building intentional opportunities for collaboration, and using tools to support, not overshadow, our shared values. By aligning implementation with thoughtful, human-centered practices, we ensure that our mission advances both innovation and meaningful connection.

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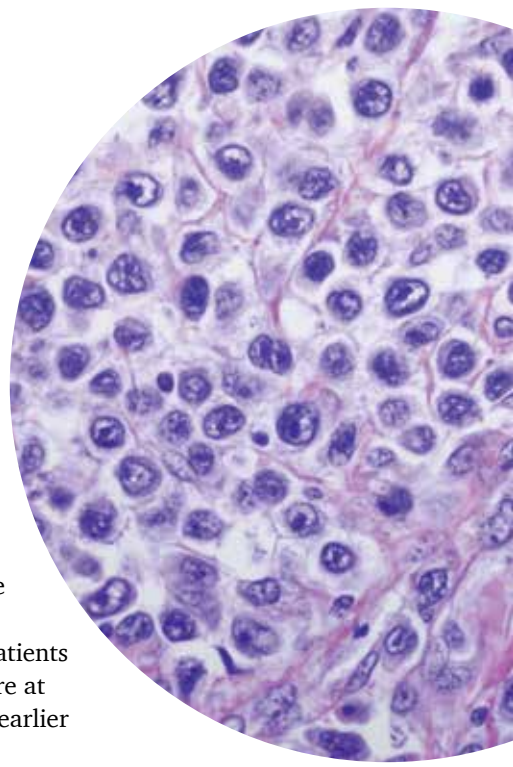
Redefining Remission for Patients With Large B-Cell Lymphoma Using ctDNA-Based MRD



*By **Charles Gaulin, MD***

The Lugano Classification established fluorodeoxyglucose–PET-CT as the standard for staging and response assessment for patients with large B-cell lymphoma (LBCL).[1] However, despite its superiority over traditional CT, PET-CT has notable limitations. A positive PET-CT scan at the end of treatment, although often indicative of residual disease, may produce false-positive results due to inflammatory or other nonmalignant uptake. These ambiguous findings can lead to additional, often invasive biopsies to confirm disease status and could lead to overtreatment. Conversely, even among those who achieve a complete metabolic response as determined by end-of-treatment PET-CT, a significant proportion will experience disease progression.

Charles Gaulin, MD

To address these diagnostic and prognostic limitations, circulating tumor DNA (ctDNA)–based measurable residual disease (MRD) testing has emerged as a complementary tool. By analyzing tumor-derived DNA fragments in the blood, ctDNA testing can provide a more sensitive and quantitative measure of residual disease burden than imaging alone.

Early studies demonstrated the prognostic value of ctDNA at baseline and during the initial cycles of chemotherapy, but a key challenge has been achieving the necessary sensitivity to detect the very low levels of residual disease present at the end of treatment.[2]

Several methods for ctDNA-based MRD testing have been studied in LBCL including immunoglobulin high-throughput sequencing (Ig-HTS), cancer personalized profiling by deep sequencing (CAPP-seq), and phased variant enrichment and detection sequencing (PhasED-seq).

The Ig-HTS method uses immunoglobulin sequencing to track variable, diversity, and joining (VDJ) rearrangements, which are unique to each B-cell clone. It is a highly sensitive method (analytical sensitivity of ~0.005%), but it can only track a limited number of loci (1-8) and requires VDJ identification in tumor tissue.[2-4]

CAPP-seq is a method that uses targeted high-throughput sequencing with hybrid capture enrichment to track a broader range of alterations, including single-nucleotide variants (SNVs), copy number variants, translocations, and VDJ rearrangements. CAPP-seq can track more than 100 loci and has an analytical sensitivity of approximately 0.002%.[2,5,6]

PhasED-seq, another method, leverages phased variants—DNA molecules with two or more SNVs located close together on a single DNA fragment—to improve the signal-to-noise ratio and increase the assay's sensitivity. PhasED-seq can track more than 100 loci and has an analytical sensitivity of approximately 0.00005%.[2,7,8]

These liquid biopsy technologies are poised to help resolve the uncertainty of indeterminate PET-CT scans and identify high-risk patients who might benefit from alternative therapeutic strategies. The former utility has been recognized in the National Comprehensive Cancer Network (NCCN) Guidelines (B-Cell Lymphomas, Version 2.2025) as an option for patients with LBCL and a positive end-of-treatment PET-CT scan.

In a recent study, Roschewski and colleagues[8] used PhasED-seq to assess the prognostic utility of MRD among 137 patients with LBCL receiving first-line therapy. The study found that ctDNA-based MRD status at the end of treatment was a much stronger prognostic indicator than conventional PET-CT scans. Patients with undetectable ctDNA at the end of treatment had a remarkable 2-year progression-free survival (PFS) of 97%, compared with just 29% for those with detectable ctDNA. In fact, MRD status was independently prognostic regardless of the PET-CT scan results. Among patients with a negative PET-CT scan, those who had detectable MRD had a 2-year PFS of only 31%, in stark contrast to the 98% PFS for those with undetectable MRD. This finding strongly suggests that ctDNA testing can identify a subgroup of patients with "false-negative" PET-CT results who are at high risk for relapse and may benefit from earlier treatment intensification.

The clinical implications of MRD at the end of treatment for LBCL are profound and potentially paradigm changing. An accurate, ultrasensitive MRD test could inform clinical decision-making across the board. Circulating tumor DNA–based MRD testing methods represent a major step forward in refining the definition of remission for patients with LBCL. Thus, achieving undetectable MRD, rather than just a negative PET-CT scan, should become the new benchmark of curative-intent therapy for LBCL.

Of course, challenges remain. Barriers, such as the need for optimized testing workflows, bioinformatics solutions, cost, and rapid turnaround times, must also be overcome to ensure clinical applicability.

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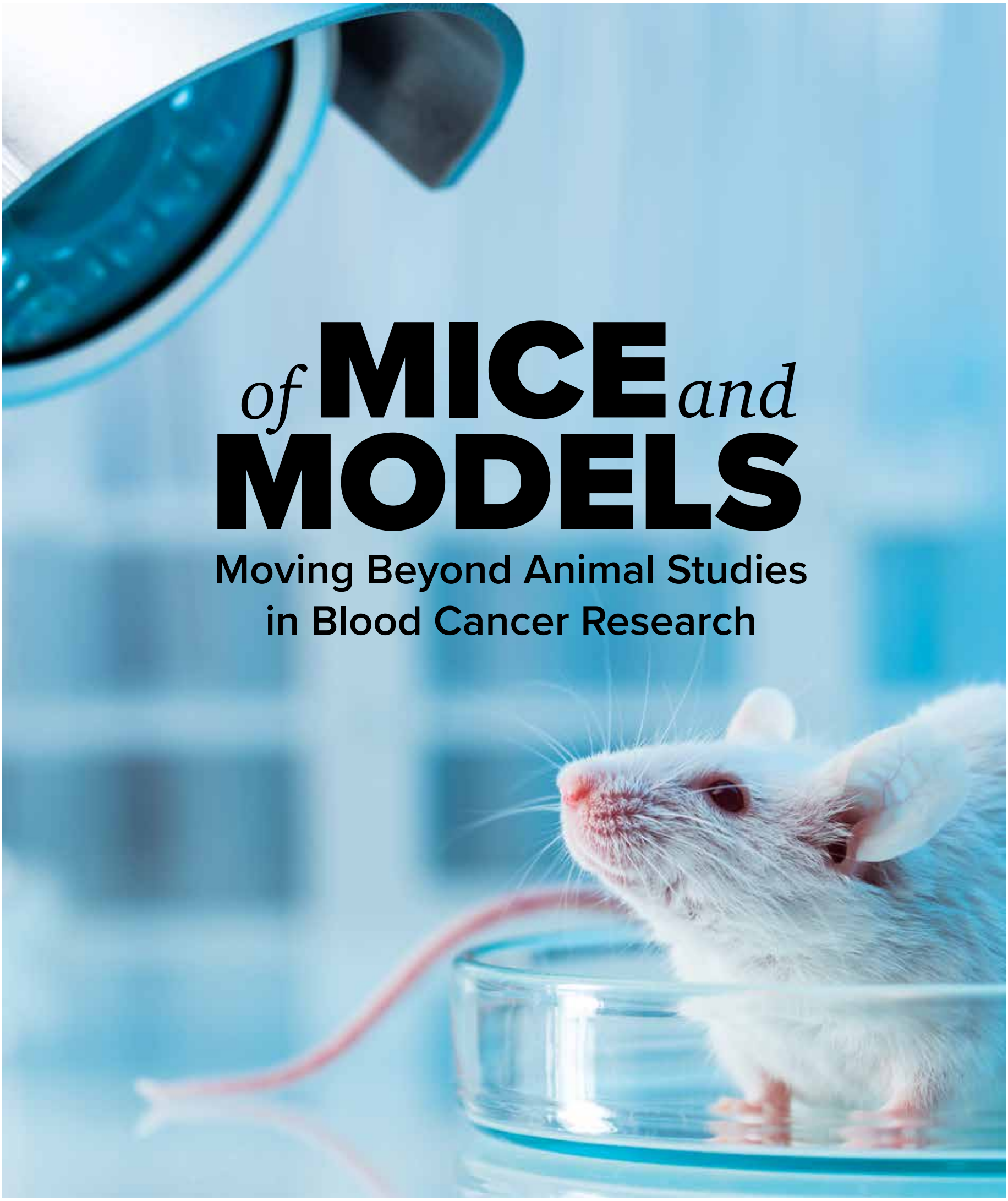
In Focus

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



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Moving Beyond Animal Studies in Blood Cancer Research

In light of the NIH's recent initiative to reduce funding for animal studies, computational models and organoids are offering new pathways for preclinical research in combination with animal models.

By ***Melissa Badamo***

Animal studies have been the backbone of cancer research for nearly a century. In the age of artificial intelligence (AI) and machine learning, that may be changing.

In July 2025, the NIH announced a new initiative to reduce the use of animals in NIH-funded research by expanding human and AI-based innovations such as computational modeling and human organoid testing.[1] As a result, the federal agency will no longer develop new funding opportunities focused exclusively on animal models.[2]

"Going forward, new funding opportunities will be designed more broadly with language that also encourages various approaches [to] be considered," the NIH wrote in a statement to *Blood Cancers Today*. "This means researchers may choose any model they deem appropriate—including a combination of approaches—to answer a research question when submitting applications seeking NIH support. This strategy is intended to open the possibilities of which types of models can be submitted in response to funding opportunities, not be restrictive or prescriptive."

This announcement rides on the heels of the FDA's new plan to phase out animal testing requirements for monoclonal antibodies and other drugs.[3] This approach aims to improve drug safety, expedite the FDA evaluation process, and reduce research and drug costs.[3]

"It is a win-win for public health and ethics," said FDA Commissioner **Martin A. Makary, MD, MPH,** in a press release.[3]

Blood Cancers Today spoke with several experts to gauge the ethics of animal studies, their role in blood cancer research, and emerging human-based research techniques that may reduce the need for animal studies.

Animal Studies in Blood Cancer Research

Mice are considered the "model organism" for studying human disease due to their genetic and physiologic similarities to humans, small size, reliable breeding, and short lifespan.[4] Patient-derived xenografts, for example, have allowed researchers to validate novel drugs, screen drug-sensitive patients, and explore drug resistance mechanisms by implanting tumor tissues from patients into humanized mice.[5]

A genetically engineered mouse model offered insight into mechanisms and evolution of chronic lymphocytic leukemia (CLL) and Richter's transformation. By modeling the genetic heterogeneity of CLL in mice through CRISPR-Cas9 B-cell editing of loss-of-function drivers, **Elisa ten Hacken, PhD,** an assistant professor at Weill Medical College of Cornell University, and colleagues uncovered key features that drive progression from CLL to Richter's transformation—including tonic PI3K signaling—while offering new insights into therapeutic avenues.[6]

Translating Zebrafish Models to Humans

Although mouse models have traditionally been the animal models of choice, zebrafish models have made a splash in cancer research due to their unique features such as small size, faster embryo development than mice, and large number of offspring.[7] Zebrafish also have transparent embryos, allowing researchers to view blood stem cells through a microscope.

The Zon Laboratory at Harvard University Stem Cell Institute is one of about 1,500 laboratories across the globe that conduct zebrafish research. Lead investigator **Leonard Zon, MD,** director of the Stem Cell Program at Boston Children's Hospital, uses zebrafish blood stem cell models to study genes associated with worse prognosis in several blood cancers. By recapitulating clonal expansion in zebrafish blood stem cell models, Dr. Zon's laboratory investigates the hematopoietic development and clonality of leukemias and lymphomas.[8]

"The zebrafish stands out as a tremendous system to model human blood disease," Dr. Zon said. "We've cloned five genes that predict new human diseases, and then we've also been able to use cellular barcoding techniques to resolve how clones of cells are differentiating or dividing in response to a blood cancer."

From identifying *c-MYB* gene overexpression as a leukemia driver in zebrafish[9] to discovering that prostaglandin E_2 (PGE_2) improves stem cell engraftment through mouse models,[10] Dr. Zon's animal studies have paved the way for new discoveries that could be translated to humans.

"We did a chemical screen in zebrafish, where we added chemicals to the water and found a chemical that could increase blood stem cells in vivo in the animal," he explained. "We showed that that drug worked in mice. We do what's called a 'competitive transplant'. We took marrow from a mouse, gave it the chemical, took untreated marrow from a different mouse, and mixed them together and gave them to another mouse. We showed that mice had much better engraftment of stem cells if they were pretreated with our chemical dimethyl prostaglandin E_2 for just 2 hours."

Dr. Zon and his team replicated this experiment in humans, in which 12 patients without a sibling match received one cord blood sample treated with dimethyl PGE_2 and one untreated cord blood sample. The treated cord blood showed better engraftment, and since then, about 150 patients have been treated with dimethyl PGE_2 before transplant.

Regarding the ethics of animal studies in cancer research, Dr. Zon explained that all of his zebrafish experiments are conducted under the care of a veterinarian. "We take everything very seriously and treat the animals with respect," he said. "We do everything we can to not use an animal if we can figure it out without it. Everything is done with respect for the organism."

A New Era of Innovation: Organoids and Computational Models

Organoids and Human-Based Lab Models

Novel technology has allowed scientists to grow "organoids," individualized collections of cells that resemble patient tissue.[11] Derived from human stem cells, these three-dimensional models can mimic the brain, kidney, lung, intestine, stomach, liver, and more, providing insight into how drugs interact with different organs.[11]

In a 2023 study published in *Cancer Discovery,* researchers tested a human organoid model that may reduce reliance on animal testing in blood cancer research. The researchers modeled bone marrow fibrosis using primary cells from patients with myeloid and lymphoid blood cancers—including multiple myeloma, acute lymphoblastic leukemia, and myeloid leukemias, which are traditionally challenging to maintain ex vivo.[12] The human cells successfully engrafted and survived within bone marrow organoids, and treating the organoids with transforming growth factor β (TGF-β)—a driver of myelofibrosis—induced organoid fibrosis.[12]

"We helped develop one of the first human bone marrow organoids that faithfully recapitulates the myeloid lineage," said study author **Kellie Machlus, PhD,** assistant professor at Harvard Medical School and principal investigator of Boston Children's Hospital Vascular Biology Program. "They have the benefit of being human. In our case, they're derived from human-induced pluripotent stem cells. They're not as complex as an animal because they don't have biofeedback from other organs, but they're more complex than one type of cell culture."

Although leukemia cells are difficult to study in vivo due to their short lifespan, adding them to organoids increases their lifespan, Dr. Machlus explained. Organoids can also be treated with investigational drugs to study their efficacy. In fact, early research is investigating bortezomib and selinexor combinations for multiple myeloma in organoids.

"We're excited about looking more towards personalized medicine now that we have a bone marrow that's fibrotic or has grafted AML [acute myeloid leukemia]," said Dr. Machlus. "We can now

In Focus

treat it with different chemotherapeutic agents and see which ones work best…It feels very magical."

Inside the organoids, cancer cells are labeled with fluorescent dye. After the organoid is treated, Dr. Machlus and her team can count the number of cancer cells remaining over time. "We can also see if megakaryocytes and red blood cells are dying, so we can also monitor side effects and whether the drug is going to cause thrombocytopenia or anemia," she said. "We're not just looking at one thing; we're looking at the dynamics."

Computational Models

By stimulating biological human systems, disease pathways, and drug interactions,[1] computational models can identify patterns in heterogeneous data and predict the best targets for therapy.[13] Like organoids, these early-stage models could "drastically" reduce the need for animal studies, according to the FDA.[3]

"The benefit of organoids is that it's made from human cells, but it's still just a bone marrow…In an animal, you have all the organ systems…the best way to use them is to combine the models and understand the limitations of each." *—Kellie Machlus, PhD, Harvard Medical School*

A computational model of chimeric antigen receptor (CAR) T-cell immunotherapy accurately predicted individualized treatment responses among patients with leukemia.[14] The researchers collected early-stage CAR T-cell and tumor burden data from 209 patients with B-cell acute lymphoblastic leukemia across 10 clinical trials, then assigned the data to virtual cohorts—continuous remission, nonresponse, CD19+ relapse, and CD19– relapse—before calibrating the model with clinical data. The model successfully identified patterns across heterogeneous data and predicted patterns of late response and CD19+ and CD19− relapse.[14]

Computational models also offer insight into how each patient's mutational burden and tumor microenvironment determine the response to treatment for aggressive B-cell lymphoma.[13] For example, researchers identified five target genes that could be used as potential binding sites against diffuse large B-cell lymphoma (*CTSL, NR1H2, PDPK1, MDM2,* and *JAK3*) using machine learning.[15]

The Future of Animal Models

Despite these recent developments, can novel technologies such as organoids and computational models completely replace mouse studies?

"I think there's no substitute for an in vivo model," Dr. Zon said. "We use AI all the time in our zebrafish and mouse work. You can model things pretty well, and it develops potential mechanisms and hypotheses to test, but using it [AI] as a proof that something is actually going to work is pretty difficult."

Although organoids are becoming a good standard for detecting the efficacy and activity of certain drugs, it is often difficult to test a drug's toxicity within a single organoid, Dr. Zon said.

"You can see some things in an organoid, but often, the organoid is specific to that particular organ," he added. "When you're going in from an FDA point of view to see if a drug is safe, we usually give it to a whole animal in vivo to see if it causes toxicity in other organs. So, I think that's a difficulty. When you give a drug to a whole zebrafish, and you see there's a toxicity, you know that it was something unexpected and you can score it. You can soak a chemical with zebrafish embryos and then see if a particular organ is affected because you can see it all in front of you under a light microscope. I think AI is hypothesis generating, but it's hard to prove a point using AI. Usually, you'd want to find out in a whole organism whether you're going to get a toxicity, even if that is in an animal model."

Dr. Machlus agrees. Although she doesn't think organoids can fully replace animal models, they may help limit the amount of animal studies needed. "The benefit of organoids is that it's made from human cells, but it's still just a bone marrow. You're not going to understand if it impacts the brain or kidneys. You're never going to understand toxicities that could impact other organs. In an animal, you have all the organ systems. You get different information from all the models, and I think the best way to use them is to combine the models and understand the limitations of each."

The NIH acknowledged that animal models are vital to advancing scientific knowledge and that using new technologies and alternative nonanimal research models in combination with traditional approaches can expand a researcher's toolbox to answer difficult research questions.[1] The NIH will also publicly report on annual research spending to measure their goal toward reducing funding for animal studies and increasing funding for human-based approaches.[1]

However, they will continue to support grants that use animal models if deemed scientifically appropriate, justifiable, and with appropriate animal welfare oversight to ensure the social, emotional, psychological, and physical care of animals.[16] For example, the Office of Laboratory Animal Welfare oversees all NIH-supported research involving live vertebrate animals.[16]

Dr. Zon said that although the NIH funding landscape is uncertain, he doesn't think the NIH fund cuts will drastically affect his research.

"We're unclear at the current moment, and I really don't know," he said. "It seems that if you are proposing animal research but also including human studies in your grants, that they would be funded. I think the important part is to be able to propose human experiments or AI experiments. There's always human experiments or human validation in all of our studies, so I'm not expecting us to have a reduction in our funding because we've always included human studies and related what we find in the zebrafish to what we find in humans."

Dr. Zon is continuing to develop new insights and innovations through his research with zebrafish models. He is currently studying the mechanism of macrophage stem cell interaction in zebrafish and teaching macrophages how to "eat" mutant stem cells, which will benefit patients with myelodysplasia and leukemia.

Although novel technology such as organoids and computational models may not completely replace animal studies just yet, it's a step toward a new era of innovation in blood cancer research.

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CARVYKTI®
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Give your adult patients with RRMM who have received a PI and an immunomodulatory agent, and are lenalidomide-refractory, a chance for

POWERFUL RESULTS AS EARLY AS 2L[1]

PRESCRIBED CAR-T CELL THERAPY FOR RRMM[2*] #1

CARVYKTI® demonstrated a

↓59% **Reduction in the risk of disease progression or death vs standard therapy (DPd or PVd)[1†]**
(HR=0.41; 95% CI: 0.30-0.56; *P*<0.0001)

CARTITUDE-4 STUDY DESIGN

CARTITUDE-4 is a randomized, open label, multicenter controlled study evaluating the efficacy and safety of CARVYKTI® for the treatment of adult patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a PI and an immunomodulatory agent. A total of 419 patients were randomized 1:1 to receive either CARVYKTI® (n=208) or standard therapy, which included daratumumab, pomalidomide, and dexamethasone (DPd) or pomalidomide, bortezomib, and dexamethasone (PVd) selected by physician prior to randomization based on patient's prior antimyeloma therapy (n=211). The primary efficacy measure was PFS analyzed based on the Intent-to-Treat Analysis Set.[1]

2L=second-line; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival; PI=proteasome inhibitor; RRMM=relapsed or refractory multiple myeloma.

*From January 2021 to November 2024.
†15.9 month median follow-up (Intent-To-Treat Analysis Set).

INDICATIONS AND USAGE

CARVYKTI® (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI®. Do not administer CARVYKTI® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI®, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI®. Provide supportive care and/or corticosteroids as needed.

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI®.

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI®. HLH/MAS can occur with CRS or neurologic toxicities.

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI®.

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI®. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®.

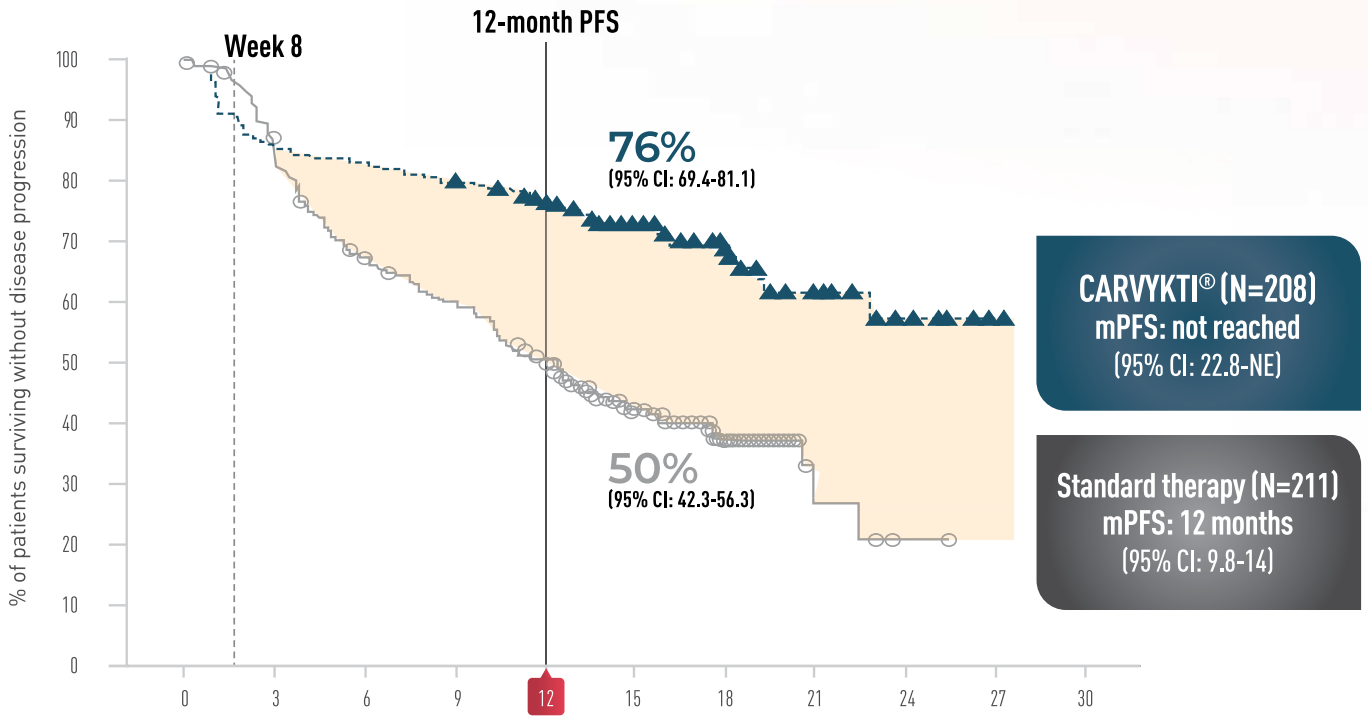
CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

POWERFUL RESULTS

CARTITUDE-4 median follow-up of 15.9 months

CARVYKTI® SIGNIFICANTLY PROLONGED PROGRESSION-FREE SURVIVAL (PRIMARY ENDPOINT) vs STANDARD THERAPY (DPd or PVd)

PROGRESSION-FREE SURVIVAL[1,3*]



15.9-month median follow-up (Intent-to-Treat Analysis Set)

CARVYKTI® arm	208	177	172	166	146	94	45	22	9	1	0
Standard therapy arm	211	176	133	116	88	46	20	4	1	0	0

CARVYKTI® arm — Standard therapy arm

CARVYKTI® demonstrated a

59%

Reduction in the risk of disease progression or death vs standard therapy (DPd or PVd)
(HR=0.41; 95% CI: 0.30-0.56; *P*<0.0001)[1*]

DEEP RESPONSES[2]

85% overall response rate was achieved with CARVYKTI®

81% of patients achieved a deep response with CARVYKTI®[1,3*]

- Deep response is defined as ≥VGPR
- **With CARVYKTI® (N=208): 85% ORR[†] (95% CI: 79.0-89.2), 74% ≥CR (95% CI: 67.5-79.9), 81% ≥VGPR** (66% sCR, 8% CR, 8% VGPR), and 3% PR
- With standard therapy (DPd or PVd) (N=211): 68% ORR[†] (95% CI: 61.0-74.0), 22% ≥CR (95% CI: 16.8-28.5), 46% ≥VGPR (18% sCR, 4% CR, 23% VGPR), and 22% PR

DURABLE RESPONSES

Median duration of response for CARVYKTI® was not reached[1*]

- **mDOR was not reached with CARVYKTI® in patients who achieved PR or better or in patients who achieved CR or better** vs 16.6 months with standard therapy (95% CI: 12.9-NE)[1*‡]

Percentages rounded to nearest whole number.

CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PFS=progression-free survival; PR=partial response; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent complete response; VGPR=very good partial response.

*Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
[†]Includes patients who achieved PR or better.
[‡]Estimated mDOR.

Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI®.

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OVERALL SURVIVAL

CARTITUDE-4 median follow-up of 15.9 months

MEDIAN OVERALL SURVIVAL WAS NOT REACHED WITH CARVYKTI® OR STANDARD THERAPY[1]

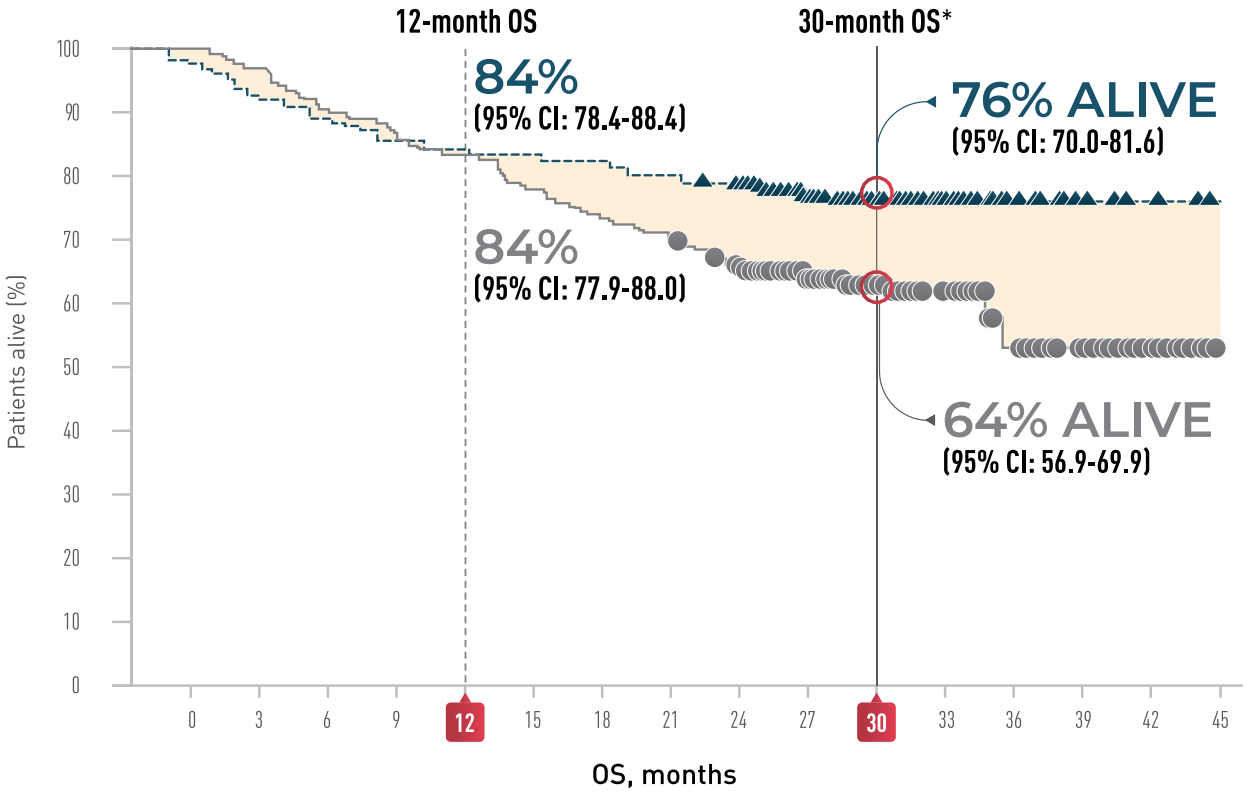
- 34% of the planned OS events have occurred
- Within the first 10 months of randomization, a higher proportion of patients in the CARVYKTI® arm died compared with the standard therapy arm

CARTITUDE-4 median follow-up of 33.6 months

OVERALL SURVIVAL FOR CARVYKTI® vs STANDARD THERAPY IN 2L+

You are now viewing a subsequent follow-up analysis of the CARTITUDE-4 trial. This information is not included in the current USPI and should be interpreted with caution. The data are presented here for descriptive purposes only.

OVERALL SURVIVAL[1-4*†]



CARVYKTI® (N=208)
mOS: not reached
(95% CI: NE-NE)

Standard therapy (N=211)
mOS: not reached
(95% CI: 37.75-NE)

CARVYKTI® arm	208	201	190	183	175	173	171	167	163	159	146	93	44	24	9	0
Standard therapy arm	211	207	196	184	173	163	154	147	137	133	127	71	35	13	4	0

CARVYKTI® arm — Standard therapy group

CARVYKTI® demonstrated a

↓45%

Reduction in the risk of death vs standard therapy (DPd or PVd) (HR=0.55; 95% CI: 0.39-0.79[4*†])

Percentages rounded to nearest whole number.
2L=second-line; CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mOS=median overall survival; NE=not estimable; OS=overall survival; PVd=pomalidomide, bortezomib, and dexamethasone; USPI=US Prescribing Information.
*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.
†HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

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CARVYKTI®
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WARNINGS AND PRECAUTIONS

Increased early mortality - In CARTITUDE-4, a (1:1) randomized controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI® treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI® arm compared to (25/211; 12%) in the control arm. Of the 29 deaths that occurred in the CARVYKTI® arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI® infusion, and 19 deaths occurred after CARVYKTI® infusion. Of the 10 deaths that occurred prior to CARVYKTI® infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI® infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI® Among patients receiving CARVYKTI® for RRMM in the CARTITUDE-1 & 4 studies (N=285), CRS occurred in 84% (238/285), including ≥Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. Median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). CRS resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia. CRS occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS.

Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI®.

Of the 285 patients who received CARVYKTI® in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 10 days following CARVYKTI® infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Neurologic toxicities, which may be severe, life-threatening, or fatal, occurred following treatment with CARVYKTI®. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies, and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies for RRMM, one or more neurologic toxicities occurred in 24% (69/285), including ≥Grade 3 cases in 7% (19/285) of patients. Median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS): Patients receiving CARVYKTI® may experience fatal or life-threatening ICANS following treatment with CARVYKTI®, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, ICANS occurred in 13% (36/285), including Grade ≥3 in 2% (6/285) of the patients. Median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1 to 143 days). Median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Of patients with ICANS 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients respectively.

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IMPORTANT SAFETY INFORMATION (cont'd)

Neurologic toxicities (cont'd)

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3). The most frequent ≥2% manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%) and sleep disorder (2%).

Monitor patients at least daily for 10 days following CARVYKTI® infusion at the REMS-certified healthcare facility for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 4 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed.

Parkinsonism: Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. Median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. Median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes. Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI® treatment.

Guillain-Barré syndrome: A fatal outcome following GBS occurred following treatment with CARVYKTI® despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune mediated myelitis: Grade 3 myelitis occurred 25 days following treatment with CARVYKTI® in CARTITUDE-4 in a patient who received CARVYKTI® as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause.

Peripheral neuropathy occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥3 in 1% (3/285) of the patients. Median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). Median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cut off.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4). Monitor patients for signs and symptoms of peripheral neuropathies. Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial nerve palsies occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥3 in 1% (1/285) of the patients. Median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). Median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Cranial nerve palsies occurred in 9% of patients in CARTITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

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IMPORTANT SAFETY INFORMATION (cont'd)

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS): Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI®, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI®.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

CARVYKTI® REMS: Because of the risk of CRS and neurologic toxicities, CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS.

Further information is available at https://www.carvyktirems.com/ or 1-844-672-0067.

Prolonged and Recurrent Cytopenias: Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, Grade 3 or higher cytopenias not resolved by day 30 following CARVYKTI® infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285) and anemia 2% (6/285). After Day 60 following CARVYKTI® infusion 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death.

Monitor blood counts prior to and after CARVYKTI® infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

Infections: CARVYKTI® should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, infections occurred in 57% (163/285), including ≥Grade 3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI® had an increased rate of fatal COVID-19 infections compared to the standard therapy arm.

Monitor patients for signs and symptoms of infection before and after CARVYKTI® infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI® infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia. Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing. Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Hypogammaglobulinemia: can occur in patients receiving treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500mg/dl after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500mg/dl, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI® for either an adverse reaction or prophylaxis.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (cont'd)

Hypogammaglobulinemia (cont'd)

Monitor immunoglobulin levels after treatment with CARVYKTI® and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines: The safety of immunization with live viral vaccines during or following CARVYKTI® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI® treatment, and until immune recovery following treatment with CARVYKTI®.

Hypersensitivity Reactions occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤Grade 2. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI®. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Secondary Malignancies: Patients treated with CARVYKTI® may develop secondary malignancies. Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI®. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes.

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status, seizures, neurocognitive decline or neuropathy, patients receiving CARVYKTI® are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurologic toxicities.

ADVERSE REACTIONS

The most common nonlaboratory adverse reactions (incidence greater than 20%) are pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common Grade 3 or 4 laboratory adverse reactions (incidence greater than or equal to 50%) include lymphopenia, neutropenia, white blood cell decreased, thrombocytopenia, and anemia.

Please read accompanying full Prescribing Information, including Boxed Warning, for CARVYKTI®.

cp-258862v9

References: 1. CARVYKTI®. Prescribing information. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.*2023;389(4):335-347. doi:10.1056/NEJMoa2303379 **4.** Mateos MV, San-Miguel J, Dhakal B, et al. Overall survival with ciltacabtagene autoleucel versus standard of care in lenalidomide-refractory multiple myeloma: phase 3 CARTITUDE-4 study update. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Oral Presentation. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.1.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed January 31, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

Give your adult patients with RRMM who have received a PI and an immunomodulatory agent, and are lenalidomide-refractory, a chance for results that are

POWERFUL. DEEP. DURABLE.
After a One-Time Infusion[1,2]*

CARTITUDE-4 primary analysis demonstrated†:

POWERFUL

mPFS not reached with CARVYKTI® (95% CI: 22.8-NE) **vs 12 months with standard therapy (DPd or PVd)** (95% CI: 9.8-14)

59% reduction in the risk of disease progression or death vs standard therapy‡
(HR=0.41; 95% CI: 0.30-0.56) *P*<0.0001

DEEP

85% ORR and **74% ≥CR** with **CARVYKTI®** vs 68% ORR and 22% ≥CR with standard therapy

81% of patients achieved a deep response of VGPR or better

DURABLE

mDOR not reached with CARVYKTI® in patients who achieved PR or better or in patients who achieved CR or better vs 16.6 months with standard therapy

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

NCCN CATEGORY 1

***THE FIRST AND ONLY* CAR-T CELL THERAPY TO BE DESIGNATED AS NCCN CATEGORY 1** in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for multiple myeloma after 1 prior therapy[5]

Listed under "Therapy for Previously Treated Multiple Myeloma Relapsed/Refractory Disease After 1-3 Prior Therapies" as an option after 1 prior line of therapy, including an IMID and a PI, and refractory to lenalidomide. Additionally, ciltacabtagene autoleucel is designated as Category 2A after 3 prior therapies.[5]

CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; IMID=immunomodulatory drug; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NCCN=National Comprehensive Cancer Network; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.

*As part of a 5-step process.
†Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
‡Based on a stratified Cox proportional hazards model. An HR <1 indicates an advantage for CARVYKTI® arm. For all stratified analyses, stratification was based on investigator's choice (DPd or PVd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized.

Johnson&Johnson

LEGEND BIOTECH

Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI®.

CARVYKTI® (ciltacabtagene autoleucel) suspension for intravenous infusion
Brief Summary of Full Prescribing Information

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].*

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI. Provide supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].*

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI *[see Warnings and Precautions].*

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI. HLH/MAS can occur with CRS or neurologic toxicities *[see Warnings and Precautions].*

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI *[see Warnings and Precautions].*

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI *[see Warnings and Precautions].*

CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS Program *[see Warnings and Precautions].*

INDICATIONS AND USAGE

CARVYKTI (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increased Early Mortality

In CARTITUDE-4, a randomized (1:1), controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI arm compared to (25/211; 12%) in the control arm *[see Clinical Studies (14) in Full Prescribing Information]*. Of the 29 deaths that occurred in the CARVYKTI arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI infusion, and 19 deaths occurred after CARVYKTI infusion. Of the 10 deaths that occurred prior to CARVYKTI infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

Cytokine Release Syndrome

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. Among patients receiving CARVYKTI for relapsed or refractory multiple myeloma in the CARTITUDE-1 and CARTITUDE-4 studies (N=285), CRS occurred in 84% (238/285), including ≥ Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. The median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). Cytokine release syndrome resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥ 10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia *[see Adverse Reactions]*.

Cytokine release syndrome occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS. Please see *Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)*.

Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI.

Of the 285 patients who received CARVYKTI in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 10 days following CARVYKTI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 in Full Prescribing Information *[see Dosing and Administration (2.3) in Full Prescribing Information]*.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling information]*.

Neurologic Toxicities

Neurologic toxicities, which may be severe, life-threatening or fatal, occurred following treatment with CARVYKTI. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time *[see Patient Counseling Information]*.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies for relapsed and refractory multiple myeloma, one or more neurologic toxicities occurred in 24% (69/285), including ≥ Grade 3 cases in 7% (19/285) of patients. The median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients *[see Adverse Reactions]*.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, ICANS occurred in 13% (36/285), including Grade ≥ 3 in 2% (6/285) of the patients. The median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1 to 143 days). The median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Of patients with ICANS 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients respectively.

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3).

The most frequent ≥2% manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%) and sleep disorder (2%) *[see Adverse Reactions]*.

Monitor patients at least daily for 10 days following CARVYKTI infusion at the REMS-certified healthcare facility for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 4 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Parkinsonism

Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. The median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. The median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

The manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI treatment.

Guillain-Barré Syndrome

A fatal outcome following GBS occurred following treatment with CARVYKTI despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune Mediated Myelitis

Grade 3 myelitis occurred 25 days following treatment with CARVYKTI in CARTITUDE-4 in a patient who received CARVYKTI as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause *[see Adverse Reactions]*.

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥ 3 in 1% (3/285) of the patients. The median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). The median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cut off *[see Adverse Reactions]*.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4).

Monitor patients for signs and symptoms of peripheral neuropathies.

Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥ 3 in 1% (1/285) of the patients. The median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). The median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients including those with ongoing neurologic events at the time of death or data cut off *[see Adverse Reactions]*.

Cranial nerve palsies occurred in 9% of patients in CARITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI *[see Adverse Reactions]*.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

CARVYKTI REMS

Because of the risk of CRS and neurologic toxicities, CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS *[see Boxed Warning, Warnings and Precautions]*. The required components of the CARVYKTI REMS are:

- Healthcare facilities that dispense and administer CARVYKTI must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after CARVYKTI infusion, if needed for treatment of CRS.

Further information is available at www.carvyktirems.com or 1-844-672-0067.

Prolonged and Recurrent Cytopenias

Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, Grade 3 or higher cytopenias not resolved by day 30 following CARVYKTI infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285) and anemia 2% (6/285). After Day 60 following CARVYKTI infusion 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death *[see Adverse Reactions]*.

Monitor blood counts prior to and after CARVYKTI infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

Infections

CARVYKTI should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, infections occurred in 57% (163/285), including ≥ Grade 3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI had an increased rate of fatal COVID-19 infections compared to the standard therapy arm *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection before and after CARVYKTI infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing.

Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500mg/dl after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500mg/dl, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI for either an adverse reaction or prophylaxis *[see Adverse Reactions]*.

Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

Hypersensitivity Reactions

Hypersensitivity reactions occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤ Grade 2. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting.

T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes *[see Boxed Warning, Adverse Reactions, Patient Counseling Information]*.

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status, seizures, neurocognitive decline or neuropathy, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurologic toxicities.

ADVERSE REACTIONS

The following clinically significant adverse reactions are also described elsewhere in the labeling:

- Increased Early Mortality *[see Warnings and Precautions, Clinical Studies (14) in Full Prescribing Information]*.
- Cytokine Release Syndrome *[see Warnings and Precautions]*.
- Neurologic Toxicities *[see Warnings and Precautions]*.
- Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) *[see Warnings and Precautions]*.
- Prolonged and Recurrent Cytopenias *[see Warnings and Precautions]*.
- Infections *[see Warnings and Precautions]*.
- Hypogammaglobulinemia *[see Warnings and Precautions]*.
- Hypersensitivity Reactions *[see Warnings and Precautions]*.
- Secondary Malignancies *[see Warnings and Precautions]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS and PRECAUTIONS section reflect exposure to CARVYKTI in 285 patients with relapsed or refractory multiple myeloma: one randomized, open label with 188 patients in CARTITUDE-4 and one single-arm, open label study with 97 patients in CARTITUDE-1.

CARTITUDE-4

The safety of CARVYKTI was evaluated in CARTITUDE-4, a randomized, open label multicenter study, in which patients with relapsed and lenalidomide refractory multiple myeloma received CARVYKTI meeting the product specifications (N=188) or standard therapy (N=211) *[see Clinical Studies (14) in Full Prescribing Information]*. Patients with known active or prior history of central nervous system involvement, patients who exhibit clinical signs of meningeal involvement of multiple myeloma and patients with a history of Parkinson's disease or other neurodegenerative disorder, were excluded from the trial. Patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.41 to 1.08×10^6 cells/kg). The median age of the 188 participants was 62 years (range: 27 to 78 years); 40% were 65 years or older, and 57% were male; 76% were White, were 9% Hispanic or Latino, 8% were Asian, and 3% were Black.

The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 56%, 1 in 44%. For the details about the study population, see *Clinical Studies (14) in Full Prescribing Information*.

The most common nonlaboratory adverse reactions (≥20%) included pyrexia, CRS, hypogammaglobulinemia, musculoskeletal pain, fatigue, diarrhea, upper respiratory tract infection, viral infections, headache, hypotension, and nausea.

Serious adverse reactions occurred in 34% of patients. The most common nonlaboratory serious adverse reactions (≥5%) were pneumonia (9%), viral infection (6%), CRS (6%), and cranial nerve palsies (5%).

Table 1 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

CARVYKTI® (ciltacabtagene autoleucel)

Table 1: Adverse reactions observed in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4

	CARVYKTI N=188		Standard Therapy N=208	
System Organ Class (SOC) Preferred term	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
Gastrointestinal disorders	-	-	-	-
Diarrhea[a]	27	3	27	2
Nausea	20	0	18	1
Constipation	10	0	21	1
General disorders and administrative site conditions	-	-	-	-
Pyrexia	79	5	16	1
Fatigue[b]	28	3	50	3
Edema[c]	11	1	20	1
Pain[d]	10	1	14	<1
Immune system disorders	-	-	-	-
Hypogammaglobulinemia[e]	94	9	72	<1
Cytokine release syndrome	78	3	<1	0
Infections and infestations	-	-	-	-
Upper respiratory tract infection[f]	25	1	40	5
Viral infection[g]	23	4	31	6
Bacterial infection[h]	15	6	17	4
Pneumonia[i]	14	9	18	11
Metabolism and nutrition disorders	-	-	-	-
Decreased appetite	10	0	5	0
Musculoskeletal and connective tissue disorders	-	-	-	-
Musculoskeletal pain[j]	34	2	47	4
Nervous system disorders	-	-	-	-
Headache[k]	23	0	13	0
Encephalopathy[l]	11	2	4	1
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Cough[m]	15	0	18	0
Hypoxia	12	3	1	1
Vascular disorders	-	-	-	-
Hypotension[n]	23	4	3	0

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.
[b] Fatigue includes Asthenia, Fatigue, and Malaise.
[c] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.
[d] Pain includes Anorectal discomfort, Catheter site pain, Flank pain, Inflammatory pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Rhinalgia, and Sacral pain.
[e] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion or standard therapy.
[f] Upper respiratory tract infection includes Bronchitis, Nasal congestion, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Rhinitis, Rhinorrhea, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral pharyngitis.
[g] Viral infection includes Adenovirus infection, Asymptomatic COVID-19, COVID-19, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viremia, Hepatitis B reactivation, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Human herpesvirus 6 infection, Influenza, Lymphadenitis viral, Metapneumovirus infection, Parainfluenza virus infection, Parvovirus B19 infection, Parvovirus infection, Respiratory syncytial virus infection, Respiratory tract infection viral, and Rotavirus infection.
[h] Bacterial infection includes Bordetella infection, Bronchitis bacterial, Campylobacter infection, Catheter site infection, Cellulitis, Chalazion, Citrobacter infection, Clostridium difficile colitis, Device related infection, Gingivitis, Perichondritis, Pyelonephritis acute, Salmonellosis, Skin infection, Staphylococcal infection, Superinfection bacterial, Vascular access site infection, and Vascular device infection.
[i] Pneumonia includes COVID-19 pneumonia, Lower respiratory tract infection, Metapneumovirus pneumonia, Pneumonia, Pneumonia moraxella, Pneumonia pseudomonal, and Pneumonia streptococcal.
[j] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Bursitis, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Myositis, Neck pain, Non-cardiac chest pain, Osteoarthritis, Pain in extremity, Plantar fasciitis, Rotator cuff syndrome, Spinal pain, and Tendonitis.
[k] Headache includes Headache and Tension headache.
[l] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Immune effector cell-associated neurotoxicity syndrome, Lethargy, and Psychomotor retardation.
[m] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.
[n] Hypotension includes Hypotension, and Orthostatic hypotension.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- *Blood and lymphatic system disorders:* coagulopathy[a] (5%), febrile neutropenia (2%), lymphocytosis (2%),
- *Cardiac disorders:* tachycardia[b] (5%), cardiac arrhythmias[c] (3%)
- *Gastrointestinal disorders:* abdominal pain[d] (6%), vomiting (5%)
- *General disorders and administration site conditions:* chills (6%)
- *Immune system disorders:* HLH (1%)
- *Infections and Infestations:* gastroenteritis[e] (7%), sepsis[f] (9%), urinary tract infection[g] (5%), fungal infection[h] (3%)
- *Investigations:* c-reactive protein increased (6%)
- *Metabolism and Nutrition Disorders:* hypophosphatemia (10%), hyperferritinemia (7%)
- *Neoplasms benign, malignant, and unspecified (incl cysts and polyps):* hematologic malignancy[i] (3%)
- *Nervous system disorders:* dizziness[j] (9%), cranial nerve palsies[k] (9%), motor dysfunction[l] (9%), peripheral neuropathy[m] (7%), sleep disorder[n] (6%), tremor (4%), aphasia[o] (3%), ataxia[p] (3%),
- *Psychiatric disorders:* delirium[q] (2%) personality changes[r] (2%)
- *Renal and urinary disorders:* renal failure[s] (5%)
- *Respiratory, thoracic and mediastinal disorders:* dyspnea[t] (10%)
- *Skin and subcutaneous tissues:* rash[u] (7%)
- *Vascular Disorders:* hemorrhage[v] (9%), hypertension (7%), thrombosis[w] (3%), capillary leak syndrome (1%)

[a] Coagulopathy includes Blood fibrinogen decreased, Coagulation test abnormal, Coagulopathy, Disseminated intravascular coagulation, and Hypofibrinogenemia.
[b] Tachycardia includes Sinus tachycardia, and Tachycardia.
[c] Cardiac arrhythmias includes Atrial fibrillation, and Atrioventricular block second degree.
[d] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Dyspepsia.
[e] Gastroenteritis includes Enterocolitis viral, Enterovirus infection, Gastroenteritis, Gastroenteritis rotavirus, Gastroenteritis salmonella, Gastrointestinal infection, and Large intestine infection.
[f] Sepsis includes Bacteremia, Candida sepsis, Device related bacteremia, Enterococcal bacteremia, Hemophilus sepsis, Neutropenic sepsis, Pseudomonal sepsis, Sepsis, Septic shock, Staphylococcal bacteremia, Systemic candida, and Urosepsis.
[g] Urinary tract infection includes Cystitis, Escherichia urinary tract infection, and Urinary tract infection.
[h] Fungal infection includes Candida infection, Oral candidiasis, Tongue fungal infection, and Vulvovaginal candidiasis.
[i] Hematologic malignancy includes Myelodysplastic syndrome, Acute myeloid leukemia, and T-cell lymphoma. Incidence based on cutoff date of 01 November 2022 (median follow-up time of 115.9 months).
[j] Dizziness includes Dizziness, Dizziness postural, Presyncope, Syncope, and Vertigo.

[k] Cranial nerve palsies includes Facial paralysis, Facial paresis, IIIrd nerve paralysis, and Trigeminal palsy.
[l] Motor dysfunction includes Bradykinesia, Coordination abnormal, Dysgraphia, Extrapyramidal disorder, Micrographia, Muscle spasms, Muscular weakness, and Parkinsonism.
[m] Neuropathy peripheral includes Peripheral motor neuropathy, Peripheral sensory neuropathy, and Polyneuropathy.
[n] Sleep disorder includes Insomnia, Sleep disorder, and Somnolence.
[o] Aphasia includes Aphasia, and Dysarthria.
[p] Ataxia includes Ataxia, Balance disorder, Dysmetria, and Gait disturbance.
[q] Delirium includes Agitation, Disorientation, and Hallucination.
[r] Personality changes includes Personality change, and Reduced facial expression.
[s] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, Renal failure, and Renal impairment.
[t] Dyspnea includes Dyspnea, Dyspnea exertional, Respiratory failure, Tachypnea, and Wheezing.
[u] Rash includes Dermatitis psoriasiform, Drug eruption, Erythema, Pityriasis lichenoides et varioliformis acuta, Rash, Rash erythematous, Rash maculo-papular, Rash papular, and Urticaria.
[v] Hemorrhage includes Catheter site hemorrhage, Conjunctival hemorrhage, Contusion, Epistaxis, Hematemesis, Hematoma, and Hematuria.
[w] Thrombosis includes Deep vein thrombosis, Pulmonary embolism, and Venous thrombosis limb.

Laboratory Abnormalities

Table 2 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

Table 2: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4

	CARVYKTI (N=188)	Standard Therapy (N=208)
Laboratory Abnormality	**Grade 3 or 4 (%)**	**Grade 3 or 4 (%)**
Lymphocyte count decreased	99	62
Neutrophil count decreased	95	88
White blood cell decreased	94	69
Platelet count decreased	47	20
Hemoglobin decreased	34	17

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0. Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include fibrinogen decreased, gamma glutamyl transferase increased, hypokalemia, alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, hypoalbuminemia, hyponatremia, hypertriglyceridemia, hypomagnesemia, hypocalcemia, and blood bilirubin increased.

CARTITUDE-1

The safety data described in this section reflect the exposure of 97 adult patients with relapsed/refractory multiple myeloma in the CARTITUDE-1 study (USA cohort) to CARVYKTI and includes 17 patients (18%) with manufacturing failures either because they received CARVYKTI that did not meet product release specifications or there were insufficient data to confirm product release specifications for CARVYKTI. Patients received CARVYKTI across a dose range of 0.51 to 0.95×10^6 CAR-positive viable T cells/kg body weight *[see Clinical Studies (14) in Full Prescribing Information]*. Patients with a history of CNS disease (such as seizure or cerebrovascular ischemia) or requiring ongoing treatment with chronic immunosuppression were excluded. The median duration of follow-up was 18 months. The median age of the study population was 61 years (range: 43 to 78 years); 36% were 65 years or older, and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 40%, 1 in 56%, and 2 in 4% of patients. Three of the patients treated with CARVYKTI had a creatinine clearance of <45 mL/min at baseline. For the details about the study population, see *Clinical Studies (14) in Full Prescribing Information*.

The most common (greater or equal to 10%) Grade 3 or higher nonlaboratory adverse reactions were infections-pathogen unspecified (19%), pneumonia (13%), hematologic malignancy (10%) and hypotension (10%).

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, CRS, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting.

Serious adverse reactions occurred in 55% of patients. The most common non-laboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (8%). Fatal adverse reactions occurred in 9% of patients.

Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

Table 3: Adverse reactions observed in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)

System Organ Class (SOC) Preferred term	Any Grade (%)	Grade 3 or higher (%)
Blood and lymphatic system disorders	-	-
Coagulopathy[a]	22	2
Febrile Neutropenia	10	9
Cardiac disorders	-	-
Tachycardia[b]	27	1
Gastrointestinal disorders	-	-
Diarrhea[c]	33	1
Nausea	31	1
Constipation	22	0
Vomiting	20	0
General disorders and administrative site conditions	-	-
Pyrexia	96	5
Fatigue[d]	47	7
Chills	33	0
Edema[e]	23	0
Immune system disorders	-	-
Cytokine release syndrome[f]	95	5
Hypogammaglobulinemia[g]	93	2
Infections and infestations[h]	-	-
Infections-pathogen unspecified[i]	41	19
Upper respiratory tract infection[j]	28	3
Viral infections[k]	23	7
Pneumonia[l]	14	13
Sepsis[m]	10	7
Metabolism and nutrition disorders	-	-
Decreased appetite	29	1
Musculoskeletal and connective tissue disorders	-	-
Musculoskeletal pain[n]	48	2
Nervous system disorders	-	-
Encephalopathy[o]	30	6
Headache	27	0
Dizziness[p]	23	1
Motor dysfunction[q]	16	3

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Table 3: Adverse reactions observed in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97) (continued)

System Organ Class (SOC) Preferred term	Any Grade (%)	Grade 3 or higher (%)
Psychiatric disorders	-	-
Insomnia	13	0
Respiratory, thoracic and mediastinal disorders	-	-
Cough[r]	39	0
Dyspnea[s]	23	3
Nasal congestion	15	0
Hypoxia	12	4
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)		
Hematologic malignancy[t]	10	10
Vascular disorders	-	-
Hypotension[u]	51	10
Hypertension	19	6
Hemorrhage[v]	16	4

Adverse reactions are reported using MedDRA version 23.0
[a] Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalized ratio increased, and Prothrombin time prolonged. Also includes terms reported under investigation SOC.
[b] Tachycardia includes Sinus tachycardia, and Tachycardia.
[c] Diarrhea includes Colitis, and Diarrhea.
[d] Fatigue includes Asthenia, Fatigue, and Malaise.
[e] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.
[f] Cytokine release syndrome includes CRS, and Systemic inflammatory response syndrome.
[g] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia (12%) and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion (92%).
[h] Infections and infestations System Organ Class Adverse Events are grouped by pathogen type and selected clinical syndromes.
[i] Infections - pathogen unspecified includes Abscess limb, Atypical pneumonia, Bacteremia, Bronchitis, Conjunctivitis, Enterocolitis infectious, Folliculitis, Gastroenteritis, Lung abscess, Lung opacity, Osteomyelitis, Otitis media, Parotitis, Perirectal abscess, Pneumonia, Rash pustular, Rhinitis, Sepsis, Septic shock, Sinusitis, Skin infection, Soft tissue infection, Upper respiratory tract infection, and Urinary tract infection.
[j] Upper respiratory tract infection includes Human rhinovirus test positive, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection. Also includes terms reported under investigation SOC. Upper respiratory tract infections may also be included under pathogen categories.
[k] Viral infection includes Adenovirus test positive, Coronavirus infection, Cytomegalovirus syndrome, Cytomegalovirus viremia, Enterovirus infection, Gastroenteritis viral, Herpes zoster, Herpes zoster disseminated, Influenza, Influenza like illness, Oral herpes, Parainfluenza virus infection, Rhinovirus infection, Urinary tract infection viral, and Viral upper respiratory tract infection.
[l] Pneumonia includes Atypical pneumonia, Lung abscess, Lung opacity, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.
[m] Sepsis includes Bacteremia, Bacterial sepsis, Pseudomonal bacteremia, Sepsis, Septic shock, and Staphylococcal bacteremia.
[n] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Joint stiffness, Muscle strain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, and Pain in extremity.
[o] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, and Somnolence.
[p] Dizziness includes Dizziness, Presyncope, and Syncope.
[q] Motor dysfunction includes Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, and Myoclonus.
[r] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.
[s] Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Tachypnea.
[t] Hematologic malignancy includes Myelodysplastic syndrome and Acute myeloid leukemia.
[u] Hypotension includes Hypotension, and Orthostatic hypotension.
[v] Hemorrhage includes Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eye contusion, Hematochezia, Hemoptysis, Infusion site hematoma, Oral contusion, Petechiae, Post procedural hemorrhage, Pulmonary hemorrhage, Retinal hemorrhage, and Subdural hematoma.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- *Cardiac disorders:* cardiac arrhythmias[a] (8%), chest pain[b] (7%)
- *Eye disorders:* diplopia (1%)
- *Gastrointestinal disorders:* dysphagia (1%)
- *Immune system disorders:* HLH (1%), hypersensitivity reaction (5%)
- *Infections and Infestations:* bacterial infections[c] (9%), urinary tract infection[d] (4.1%)
- *Injury, Poisoning and Procedural complications:* fall (3.1%)
- *Metabolism and Nutrition Disorders:* tumor lysis syndrome (1%)
- *Musculoskeletal and Connective tissue disorders:* posture abnormal (1%)
- *Nervous system disorders:* aphasia[e] (8%), ataxia[f] (8%), peripheral neuropathy[g] (7%), tremor (6%), parkinsonism (4.1%), micrographia (4.1%), dysgraphia (3.1%), reduced facial expression (3.1%), cranial nerve palsies (3.1%), bradykinesia (2.1%), paresis[h] (1%), cogwheel rigidity (1%), cerebrovascular accident (1%), seizure (1%), slow speech (1%), nystagmus (1%)
- *Psychiatric disorders:* delirium[i] (5%) depression[j] (4.1%), psychomotor retardation (1%)
- *Renal and urinary disorders:* renal failure[k] (7%)
- *Skin and subcutaneous tissues:* rash[l] (8%)
- *Vascular Disorders:* thrombosis[m] (5%)

[a] Cardiac arrhythmias includes atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia.
[b] Chest pain includes Angina pectoris, Chest discomfort, and Chest pain.
[c] Bacterial infection includes Abscess limb, Cholecystitis, Cholecystitis acute, Clostridium difficile colitis, Clostridium difficile infection, Enterocolitis bacterial, Osteomyelitis, Perirectal abscess, Soft tissue infection, Staphylococcal infection.
[d] Urinary tract infection includes Urinary tract infection, and Urinary tract infection viral.
[e] Aphasia includes Aphasia, Dysarthria, and Speech disorder.
[f] Ataxia includes Ataxia, Balance disorder, and Gait disturbance.
[g] Peripheral neuropathy includes Peripheral neuropathy, Peripheral motor neuropathy and Peripheral sensory neuropathy.
[h] Paresis includes Facial paralysis, and Peroneal nerve palsy.
[i] Delirium includes Agitation, Hallucination, Irritability, Personality change, and Restlessness.
[j] Depression includes Depression, and Flat affect.
[k] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, and Renal impairment.
[l] Rash includes Erythema, Rash, Rash maculo-papular, and Rash pustular.
[m] Thrombosis includes Deep vein thrombosis, and Device related thrombosis.

Laboratory Abnormalities

Table 4 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

Table 4: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)

Laboratory Abnormality	Grade 3 or 4 (%)
Lymphopenia	99
Neutropenia	98
White blood cell decreased	98
Anemia	72
Thrombocytopenia	63
Aspartate aminotransferase increased	21

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0.
Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include the following: fibrinogen decreased, hypoalbuminemia, alanine aminotransferase increased, hyponatremia, hypocalcemia, gamma glutamyl transferase increased, alkaline phosphatase increased, hypokalemia, blood bilirubin increased.

Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against the extracellular portion of the anti-BCMA CAR pre-dose, and at multiple timepoints post-infusion. In CARTITUDE-1, 19 of 97 (19.6%) patients were positive for anti-product antibodies. In CARTITUDE-4, 39 of 186 patients (21%) were positive for anti-CAR antibodies.

There was no clear evidence that the observed anti-product antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

Postmarketing Experience

Because adverse events to marketed products are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse event has been identified during postmarketing use of CARVYKTI.

Neoplasms: T cell malignancies

DRUG INTERACTIONS

HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with CARVYKTI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CARVYKTI has the potential to be transferred to the fetus and cause fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised that there may be risks to the fetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation

Risk Summary

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.

In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception and male patients with partners of childbearing potential or whose partners were pregnant were instructed to use a barrier method of contraception, until one year after the patient has received CARVYKTI infusion.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Infertility

There are no data on the effect of CARVYKTI on fertility.

Pediatric Use

Safety and effectiveness of CARVYKTI in pediatric patients have not been established.

Geriatric Use

Of the 97 patients in CARTITUDE-1 that received CARVYKTI, 28% were 65 to 75 years of age, and 8% were 75 years of age or older. CARTITUDE-1 did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. In 62 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 19% (12/62) and 6% (4/62), respectively. Of the 35 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 37% (13/35) and 20% (7/35), respectively.

Of the 188 patients in CARTITUDE-4 that received CARVYKTI, 38% were 65 to 75 years of age, and 2% were 75 years of age or older. In 112 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 16% (18/112) and 3% (3/112) respectively. Of the 76 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 34% (26/76) and 7% (5/76) respectively.

REFERENCES

1 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25: 625-638.
2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0; 2017.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of manufacturing failure [18%, (17/97 in the clinical study)]. In case of a manufacturing failure, a second manufacturing of CARVYKTI may be attempted. In addition, while the patient awaits the product, additional anticancer treatment (other than lymphodepletion) may be necessary and may increase the risk of adverse reactions during the pre-infusion period, which could delay or prevent the administration of CARVYKTI.

Advise patients that they will be monitored daily for the first 10 days following the infusion at a REMS-certified healthcare facility, and instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following the infusion.

Prior to infusion, advise patients of the following risks and to seek immediate medical attention in the event of the following signs or symptoms:

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

Inform patients of the risk of early mortality. In a clinical study, treatment in the CARVYKTI arm was associated with a higher rate of death (14%) compared to the control arm (12%) in the first 10 months from randomization. This higher rate of death was observed before receiving CARVYKTI and after treatment with CARVYKTI. The reasons for death were progression of multiple myeloma and adverse events *[see Warnings and Precautions, Clinical Studies (14) in Full Prescribing Information]*.

Cytokine Release Syndrome (CRS)

Signs or symptoms of CRS, including fever, chills, fatigue, headache, tachycardia, hypotension, hypoxia, dizziness/lightheadedness or organ toxicities *[see Warnings and Precautions, Adverse Reactions]*.

Neurologic Toxicities

Signs or symptoms associated with neurologic events, some of which occur days, weeks or months following the infusion including *[see Warnings and Precautions, Adverse Reactions]:*

ICANS: e.g., aphasia, encephalopathy, depressed level of consciousness, seizures, delirium, dysgraphia
Parkinsonism: e.g., tremor, micrographia, bradykinesia, rigidity, shuffling gait, stooped posture, masked facies, apathy, flat affect, lethargy, somnolence
Guillain Barré Syndrome: e.g., motor weakness and polyradiculoneuritis
Peripheral neuropathy: e.g., peripheral motor and/or sensory nerve dysfunction
Cranial Nerve Palsies: e.g., facial paralysis, facial numbness

Prolonged and Recurrent Cytopenias

Signs or symptoms associated with bone marrow suppression including neutropenia, thrombocytopenia, anemia, or febrile neutropenia for several weeks or months. Signs or symptoms associated with bone marrow suppression may recur *[see Warnings and Precautions, Adverse Reactions]*.

Infections

Signs or symptoms associated with infection *[see Warnings and Precautions, Adverse Reactions]*.

Hypersensitivity Reactions

Signs or symptoms associated with hypersensitivity reactions including flushing, chest tightness, tachycardia, and difficulty breathing *[see Warnings and Precautions]*.

Secondary Malignancies

Secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies have occurred *[see Boxed Warning, Warnings and Precautions, Adverse Reactions]*.

Advise patients of the need to:

- Have periodic monitoring of blood counts before and after CARVYKTI infusion *[see Warnings and Precautions]*.
- Contact Janssen Biotech, Inc. at 1-800-526-7736 if they are diagnosed with a secondary malignancy *[see Warnings and Precautions]*.
- Refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after treatment and in the event of any new onset of neurologic toxicities *[see Warnings and Precautions]*.
- Tell their physician about their treatment with CARVYKTI before receiving a live virus vaccine *[see Warnings and Precautions]*.

Manufactured/Marketed by:
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Horsham, PA 19044, USA
U.S. License Number 1864

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Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

cp-258863v5

Know the Practice

Blood Cancers Today *spotlights different specialties within the hematologic oncology discipline, focusing on a physician who is bringing the particular consideration to light.*

How Researchers at CU Anschutz Are Pioneering a Novel CAR-T Therapy Approach for AML

*By **Melissa Badamo***

Inside the research labs at the University of Colorado Anschutz Medical Campus (CU Anschutz), assistant professor **Mathew Angelos, MD,** is part of a team pioneering a novel, homegrown chimeric antigen receptor (CAR) T-cell therapy approach for the treatment of acute myeloid leukemia (AML). This approach utilizes CD64, a high-affinity Fc receptor expressed in subsets of leukemia stem and progenitor cells, as a therapeutic target.

Mathew Angelos, MD

"Our group has shown individuals that have a monocytic immunophenotype don't respond as well to venetoclax," Dr. Angelos explained. "Monocytic AML clones have a propensity to lose BCL-2 expression and render venetoclax-based therapies that we really rely on in the AML space to be less effective. Because CD64 tends to be enriched on those cells that are either monocytic or have failed venetoclax-based therapies, we think it makes it a nice target such that the CAR T-cell can find leukemic cells, engage with them, and then have cytotoxic activity against them."

CD64: A Missing Puzzle Piece for Relapsed or Refractory Patients

Treatment options are limited for patients who fail venetoclax-based therapies for AML, Dr. Angelos explained. Additionally, there's a large unmet need to identify other types of therapies that can effectively target a patient's individual disease.

"We're really excited about this approach because it adds a novel class of therapy to our armamentarium to treat AML for patients who have already failed the standard of care," Dr. Angelos explained. "For decades, treatment consisted of cytotoxic chemotherapy. "Now, over the past 10 years or so, we have lower intensity venetoclax-based combinations. We also have targeted therapies, but not all patients are candidates because their leukemia may not have a mutation that the drugs can target."

The average overall survival for patients who fail hypomethylating agents and venetoclax is around 2 to 3 months, according to Dr. Angelos. Additionally, other FDA-approved therapies only yield response rates of around 20% or less after failing chemotherapy or venetoclax-based treatments.

"By introducing a rationally designed cellular therapy like anti-CD64 CAR T-cells and strategically implementing their use in the right patient population, our hope is that we can minimize off-target toxicities that our field has identified as problematic with other CAR T-cell therapies against AML," Dr. Angelos explained. "If we start to see some good anti-leukemia activity signals, this could be a new type of therapy that we can introduce into the treatment paradigm for patients with myeloid diseases."

Preclinical In Vivo and In Vitro Studies

The preliminary science surrounding CD64 as a leukemic target originated from the research team of **Craig Jordan, PhD,** a professor of hematology at CU

Know the Practice

Anschutz. "Dr. Jordan's group did a lot of work validating that CD64 was a robustly expressed and universal protein on specific subsets of AML. It led it to be a natural target that could be used for immunotherapies and cellular therapies," Dr. Angelos explained.

From there, **Eric Kohler, MD, PhD,** an assistant professor in the Department of Pediatrics at Children's Hospital Colorado, and his research group engineered CD64 CAR T-cells and showed that they can effectively treat monocytic AML in preclinical models by eliminating CD64+ leukemia cell lines. Using lentiviral transduction, Dr. Kohler and colleagues expressed the CD64 CARs in healthy donor human T cells and tested the CARs in vitro and in vivo.[1]

In vitro, CD64 CAR-T eliminated 100% of Molm14 leukemia cells at 18 hours, compared with up to 10% in mock T-cell controls. All mice treated with CD64 CAR-T in vivo survived more than 50 days with no evidence of leukemia, while mock-treated mice survived less than 30 days and had high tumor burden ($P<0.01$).[1]

Upcoming Phase 1 Clinical Trial

These preliminary findings pave the way for an upcoming phase 1 clinical trial, which is slated to begin in the first quarter of 2026. To determine the safety and maximum tolerated dose of CD64 CAR-T, the trial will treat up to 18 adults at four different dose levels starting at 1×10^6 cells/kg and escalating to 1×10^7 cells/kg.

"We would like to introduce a good number of cells so that we can try to maximize potential efficacy while maintaining a relatively good safety profile for patients," Dr. Angelos explained. "There's a possibility to reduce the dose level should we see adverse safety signals once we start treating patients at the introductory dose level."

Eligible patients have a diagnosis of AML and have relapsed or are refractory to the standard of care combination of a hypomethylating agent with venetoclax. Patients with measurable residual disease (MRD+) and high-risk myelodysplastic syndromes will also be included.

"We have carefully selected inclusion criteria for patients," Dr. Angelos noted. "We're also trying to capture patients who have low-level disease burden that we know are at high risk for frank relapse in the future. Learning from other myeloid-directed CAR T-cell trials, we've seen that CAR T-cell products work better when patients don't have very high disease volumes."

The trial will also aim to optimize lymphodepleting chemotherapy regimens prior to CAR-T infusion.

> **"This could be a new type of therapy that we can introduce into the treatment paradigm for patients with myeloid diseases."**

From the Bench to the Trials

Dr. Angelos' interest in translational research stemmed from his experience conducting basic science research as an undergraduate student and working at the National Cancer Institute. "I was surrounded by physician scientists who were translating what they were seeing at the bench in the lab and moving it into clinical trials," he said. "From that experience, I wanted to be a physician scientist so I could bridge that gap between the basic science experiments that we were doing into direct results for patients."

During his MD/PhD program at the University of Minnesota, his graduate work focused on understanding how immune cells engineered in the lab could target specific types of blood cancers. From there, he completed a residency and fellowship program at the Hospital of the University of Pennsylvania.

"At that time, Penn was the epicenter of cellular therapy innovation, and it was where much of the initial CAR T-cell technology emerged," he said. "I was able to train from what I would consider to be the pioneers of cellular therapy, not only on the scientific side, but also on the clinical side. They gave me the toolkit to understand how we can engineer effective and novel cellular therapies and successfully put them into clinical trials."

Making Headway: Emerging Research at CU Anschutz

Dr. Angelos is working on additional trials that utilize other cellular and immunotherapies as a target against AML. "Our leukemia program has a particular emphasis on developing purposefully designed investigator-initiated trials that harnesses unique properties of leukemic stem cells that underlie the ineffectiveness of current therapies. This includes utilizing novel molecules and immunotherapies in the treatment for patients with AML," he said.

Other trials at CU Anschutz are focusing on generating novel, homegrown cellular therapy products for lymphoma and solid tumors to target specific proteins expressed on the surface of the cancer. Meanwhile, other trials are repurposing chemotherapies to treat patients with resistance to venetoclax-based therapies.

"Our group has done a lot of work to show what is driving people to be resistant to venetoclax-based treatments, and how we can use that information to better design clinical trials," he explained.

Dr. Angelos and his team are also focusing on optimizing the manufacturing of CD64 CAR-T cells at the Gates Biomanufacturing Facility, located adjacent to campus, to begin the phase 1 trial in early 2026.

"We're really excited to get this trial going," he said. "Cellular therapies for diseases like acute myeloid leukemia have traditionally not worked very well…We haven't found a suitable homogeneous target for cellular therapies against acute myeloid leukemia. We think CD64 is one piece to that puzzle to serve as a specific and robust CAR T-cell target that may yield deep and prolonged remissions where other treatments have fallen short."

Reference

1. Simpson HM, et al. *Blood* 2023:142(suppl 1):2064. doi10.1182/blood-2023-182123

> **"CD64 is one piece to that puzzle to serve as a specific and robust CAR T-cell target that may yield deep and prolonged remissions where other treatments have fallen short."**

Real-Time Reporting Marks Major Shift in FDA Drug Safety Oversight

*By **Nichole Tucker***

Pivoting toward more transparency regarding the adverse event profiles of pharmaceuticals, the FDA has begun real-time reporting of adverse events by way of the FDA Adverse Event Reporting System (FAERS).[1]

"Having real-time data more quickly is always helpful for researchers, so this news is good to hear," said *Blood Cancers Today* Editorial Board Member, **Rahul Banerjee, MD,** assistant professor, Clinical Research Division, Fred Hutch Cancer Center. "FAERS has many limitations as a source of data, most notably the lack of details or a denominator to calculate the incidence of toxicities. Nevertheless, it can be helpful for qualitative research or for toxicity comparisons between products. As such, real-time FAERS updates may be most helpful for researchers who are investigating emerging toxicities such as IEC-associated enterocolitis with chimeric antigen receptor [CAR] T-cell therapy."

CAR T-cell products may be especially important to monitor. In 2024, the FDA issued a class-wide box warning for B-cell maturation antigen-directed CAR T-cell therapies as well as CD19-directed CAR T-cell therapies due to the high potential for patients developing secondary T-cell malignancies.[2]

According to the latest report in FAERS[3], of the FDA-approved CAR T-cell therapies for the treatment of lymphoma (axicabtagene ciloleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel), there were 1,525 adverse event cases in 2025, accounting for 14.1% of all adverse events reported. Among the agents approved to treat multiple myeloma (ciltacabtagene autoleucel and idecabtagene vicleucel), FAERS shows 1,578 adverse event cases in 2025, representing 34.8% of all cases reported in this year. For tisagenlecleucel, the only approved CAR-T agent for leukemia, 337 cases were reported in 2025 (8.8% of all cases).

Aside from CAR-T, other drug classes can be concerning, including agents like chemotherapies and Bruton's tyrosine kinase (BTK) inhibitors. For example, in 2025, 3,359 adverse event cases (15.0%) were associated with ibrutinib, acalabrutinib, zanubrutinib, or pirtobrutinib.[3]

According to the FDA, this change is part of modernizations within the agency.[1] Their goals are to streamline the collection of adverse event data, which can identify serious errors with medicine and product quality. Experts question, however, if FAERS can do that efficiently.

"The FDA's move to publish adverse event data from the FAERS on a daily basis will hopefully improve faster access to these data, with potential for rapid identification of safety signals—critical for patient safety and public confidence," said **Mehdi Hamadani, MD,** professor of medicine and chief of Hematologic Malignancies at the Medical College of Wisconsin and co-editor-in-chief of *Blood Cancers Today*. "However, we will have to be careful that the mere presence of an adverse event (without appropriate clinical context) does not necessarily establish causality. This obviously carries the risk of potential misinterpretation of data, leading to undue alarm."

In a press release, FDA commissioner **Martin Makary, MD, MPH,** stated, "Adverse event reporting should be fast, seamless, and transparent. People who navigate the government's clunky adverse event reporting websites should not have to wait months for that information to become public. We're closing that waiting period and will continue to streamline the process from start to finish."

The daily reporting system is now available to the public with data contributions from healthcare professionals, consumers, and drug manufacturers.

References

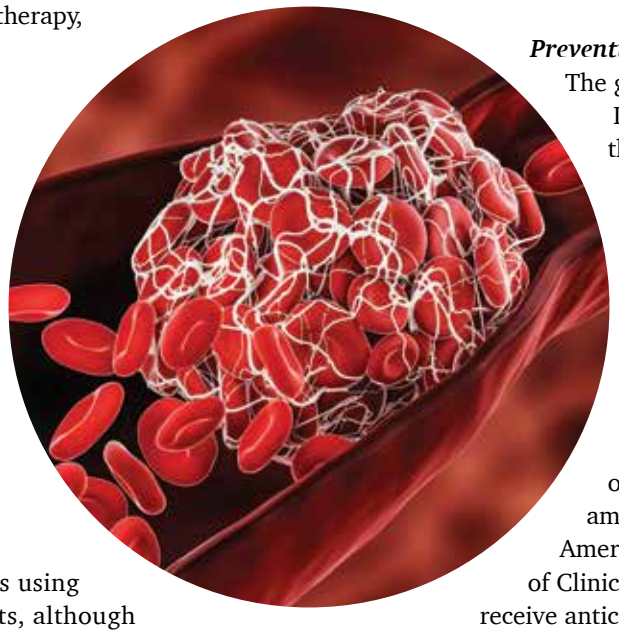
1. FDA. Accessed August 25, 2025. https://www.fda.gov/news-events/press-announcements/fda-begins-real-time-reporting-adverse-event-data
2. FDA. Accessed August 25, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-boxed-warning-t-cell-malignancies-following-treatment-bcma-directed-or-cd19-directed#:~:text=Therefore%2C%20in%20January%202024%2C%20FDA,@fda.hhs.gov
3. FDA Adverse Event Reporting System (FAERS). Accessed August 25, 2025. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

Thromboembolic Adverse Events Are Underreported in Cancer Clinical Trials

*By **Lauren Evoy Davis & Melissa Badamo***

Clinical trials are designed to evaluate the effectiveness of cancer therapies, but they come with a cost: adverse events (AEs).

New findings published in the *Journal of Clinical Oncology* showed that venous and arterial thromboembolic events (VTEs, ATEs) are inconsistently and inaccurately reported in cancer clinical trials. These events increase hospital admissions and can delay or interrupt cancer therapy, leading to poorer outcomes and increased death rates.



Underreporting or Misreporting Is Common

In a review of 18 real-world, retrospective studies, the cumulative VTE rate following treatment with immune checkpoint inhibitors was reported to be 5% to 8% at 6 months and more than 10% at 12 months. However, an earlier systematic review of 68 randomized controlled trials reported a lower VTE rate of 2.7% at 3-year follow-up. Similarly, ATE rates were inconsistently reported to be 1% to 5% at 12 months in the first review and 1.1% at 3 years in the second review. In fact, ATEs weren't reported at all in several randomized clinical trials.[1]

The authors attribute this discrepancy to the absence of standardized reporting protocols for thromboembolic events. Some clinicians report VTEs using the Common Terminology Criteria for Adverse Events, although physicians vary in their VTE reporting. Therefore, one solution is to incorporate International Society on Thrombosis and Haemostasis (ISTH) criteria and CONSORT Harms 2022 guidelines in clinical trials.

Moreover, clinicians may not recognize when symptoms are treatment-related, especially in cases where patients are taking multiple medications or have comorbidities. Clinicians may attribute symptoms such as nausea and fatigue to the underlying condition rather than the therapy. Patients may also be underreporting AEs.

Additionally, VTEs in clinical trials tend to occur more frequently in the first few months of a cancer diagnosis and decrease as time goes on. Patients often take part in clinical trials as the third or fourth line of treatment, which lessens the likelihood of thromboembolic events.

Prevention Is Possible

The good news: VTEs and ATEs are preventable.

In a large randomized controlled trial, primary thromboprophylaxis with 10 mg once-daily rivaroxaban anticoagulation reduced the risk for VTE or VTE-related death by 60% (hazard ratio, 0.62 [95% CI: 0.39-0.99]) as compared with placebo. The trial enrolled patients who were at high risk for VTEs.

Another type of VTE reporting is central venous catheter (CVC)-related thrombosis, which is asymptomatic in 14% to 18% of patients but presents with serious symptoms in approximately 5% of patients. This is a somewhat common complication among patients with cancer. Guidelines from the American College of Chest Physicians, the American Society of Clinical Oncology, and others recommend that patients receive anticoagulation for at least 3 months and for as long as CVC persists.

Going forward, standardization of reporting of AEs from both clinicians and patients, as well as using prevention strategies such as blood thinners like rivaroxaban, may help reduce the number of AEs.

Reference

1. Calverley DC, et al. *J Clin Oncol.* 2025;43(26):2851-2855. doi:10.1200/JCO-25-00489

Blood Cancers Today spoke with first author **David C. Calverley, MD,** of Portland VA Medical Center in Oregon, on how to standardize AE reporting in clinical trials.

What practical steps do you recommend for integrating ISTH criteria and CONSORT Harms guidelines into trial protocols so that investigators consistently capture both symptomatic and asymptomatic events?

ISTH criteria would be utilized as the framework for the CONSORT Harms guidelines related to VTE/ATE reporting. It's easy to integrate ISTH criteria into CONSORT guidelines, but it's not as straightforward to then facilitate uniform uptake of these guidelines among trial design teams, journal editors, and reviewers on a collective basis. We are still some distance away from applying uniform toxicity documentation to characterize and quantify harms associated with cancer treatment randomized controlled trials.

This commentary is intended to raise awareness among oncology professionals about the importance of reducing the second most common cause of death in cancer patients, other than the cancer itself. It's particularly timely because of the plethora of newer agents at our disposal for treating cancer that we collectively know comparatively little about with respect to incidence of venous and arterial thromboembolic events compared with traditional cytotoxic agents.

What criteria or risk assessment models do you see as most promising for identifying which cancer patients should receive prophylaxis in routine care without adding unnecessary bleeding risk?

In general, the Khorana score is the most widely utilized tool for assessing thromboembolic risk in cancer patients. There are caveats with respect to its predictability in certain circumstances, so it's not universally applicable in all settings. The answer to this question is somewhat nuanced as a result. It is primarily dependent on the primary tumor site, and this is among the five contributors to the Khorana score. Certain malignancies have well-established thrombosis risk assessment models that then inform the nature of appropriate anticoagulation prophylaxis, whether they be antiplatelet agents versus anticoagulation agents such as low-molecular-weight heparin or direct oral anticoagulants.

The more aggressive anticoagulation thromboprophylaxis measures that are seen to further reduce clot risk compared with less aggressive measures are, in turn, going to be associated with increased bleeding risk. There are agents currently being developed, such as factor XI/XIa inhibitors, that may be equally efficacious at preventing thrombosis as other anticoagulants while simultaneously carrying less of a bleeding risk. These characteristics would theoretically be very favorable in the cancer setting, since patients with cancer have a higher risk for clinically significant bleeding events associated with anticoagulation than patients without cancer.

Reference

1. Calverley DC, et al. *J Clin Oncol.* 2025;43(26):2851-2855. doi:10.1200/JCO-25-00489

Highlights From the **22ND INTERNATIONAL MYELOMA SOCIETY (IMS) ANNUAL MEETING & EXPOSITION SEPTEMBER 17–20, 2025, IN TORONTO, CANADA.**

Teclistamab-Daratumumab-Based Combinations Show "Unprecedented" Efficacy as Myeloma Induction Therapy

*By **Melissa Badamo***

Teclistamab combined with standard of care daratumumab-based regimens demonstrated clinical efficacy as induction therapy for patients with transplant-eligible, newly diagnosed multiple myeloma (MM), according to the phase 2 MajesTEC-5 trial. However, infections remain a risk for teclistamab-daratumumab-based combinations.


Marc Raab, MD

Results from the multicohort trial were presented at the 22nd IMS Annual Meeting by **Marc Raab, MD,** of the Heidelberg Myeloma Center in Germany. MajesTEC-5 is the first trial to study teclistamab-daratumumab-based regimens for MM.

Forty-nine patients aged 18 to 70 years received teclistamab combined with either daratumumab plus lenalidomide (Arm A/A1; n=10/20) or daratumumab plus bortezomib (Arm B; n=19) as induction therapy. Teclistamab was administered in six 28-day cycles, including two step-up doses in cycle 1. Dexamethasone maintenance (20 mg) was also added in the first four cycles in Arm A and the first two cycles in Arms A1/B. The median duration of treatment was 7.0 months, and two patients discontinued all treatments.

The primary end point was safety as measured by the rate of adverse events (AEs) and serious AEs. The secondary end point was measurable residual disease (MRD) negativity, assessed at 10^{-5} by next-generation flow cytometry and 10^{-6} by next-generation sequencing.

Forty-four (89.8%) patients had grade 3 to 4 treatment-emergent AEs (TEAEs), most commonly infections, and 26 (53.1%) patients experienced serious AEs. Almost all patients experienced hypogammaglobulinemia.

"When you combine a BCMA [B-cell maturation antigen] bispecific, especially in frontline, you have to keep a close eye on the infections," Dr. Raab explained during his presentation. Eighteen (36.7%) patients had grade 3 to 4 infection, most commonly upper respiratory tract infection, COVID-19, or pneumonia.

"Active infections are managed using appropriate antibacterial and antiviral therapies according to current guidelines," Dr. Raab told *Blood Cancers Today*. "To prevent high-grade infections, strict use of IVIG [[intravenous immunoglobulin] supplementation and PJP [pneumocystis jirovecii pneumonia] and VZV [varicella-zoster virus] prophylaxis was strongly recommended."

Any-grade hematologic TEAEs included neutropenia (63.3%), lymphopenia (61.2%), anemia (40.8%), thrombocytopenia (34.7%), and leukopenia (28.6%).

"Interestingly, the addition of bortezomib did not increase the rate of thrombocytopenia in this patient population," Dr. Raab said.

Thirty-two (65.3%) patients had grade 1 to 2 cytokine release syndrome. There were no immune effector cell–associated neurotoxicity syndrome events or TEAEs leading to full study treatment discontinuation or death.

All (100%) patients achieved an overall response, and all 46 (100%) MRD-evaluable patients achieved MRD negativity at both 10^{-5} and 10^{-6} sensitivity after cycle 6.

"MRD negativity is considered to be the best surrogate marker available for PFS [progression-free survival]. Achieving MRD negativity early in a line of therapy might be exceptionally beneficial," Dr. Raab told *Blood Cancers Today*. "This speaks to the unprecedented efficacy of this combination when used in first-line therapy."

Finally, all but one patient underwent successful stem cell mobilization, with a median stem cell yield of 8.1×10^{6}/kg.

"If the exceptional response rates will be translated into unprecedented sustained MRD negativity and finally PFS, and confirmed in large randomized trials, the next steps will be to evaluate options to limit treatment durations for certain subgroups of patients, aiming for treatment-free intervals or eventually even cure," Dr. Raab concluded.

Reference

Raab M, et al. 22nd International Myeloma Society Annual Meeting. Abstract OA-13

Imaging Substudy Results Back Utility of Whole-Body MRI to Assess Treatment Response in Multiple Myeloma

*By **Andrew Moreno***

Marina Hajiyianni, MD, of Heidelberg University Hospital in Germany, presented the results of an imaging substudy from the phase 3 German-speaking Myeloma Multicenter Group (GMMG)-HD7 clinical trial at an oral abstracts session of the 22nd IMS Annual Meeting and Exposition.


Marina Hajiyianni, MD

The GMMG-HD7 trial is a randomized, controlled study to evaluate isatuximab combined with bortezomib, lenalidomide, and dexamethasone for the treatment of patients with newly diagnosed, transplant-eligible multiple myeloma.

The substudy sought to determine the degree to which treatment response assessments made using whole-body MRI (WB-MRI), which apply Myeloma Response Assessment and Diagnosis System (MY-RADS) protocol reporting and scoring, correlate with postinduction bone marrow measurable residual disease (MRD) findings in the study population.

The substudy's cohort included 83 patients, was 66.3% male, and had a median age of 59 years. These patients underwent WB-MRI at baseline and after

receiving induction therapy, and researchers measured postinduction MRD using next-generation flow cytometry.

Following induction, there was a statistically significant association between the patients' MY-RADS diffuse infiltration scores and their MRD status for both whole-body and the pelvic region (Wilcoxon rank sum test, $P<0.001$ and $P=0.001$, respectively). Lower scores were associated with MRD negativity.

Patients who had a decrease in total whole-body or total pelvic MRI scores from baseline had a markedly greater likelihood of achieving MRD negativity, with odds ratios of 7.68 ($P=0.002$) and 7.09 ($P<0.001$), respectively. Baseline MRI scores on their own were not prognostic for patients' MRD status postinduction, but patients who had both a lower baseline burden and a decrease during induction were more likely to become MRD negative.

"I want to highlight here the role of dynamic monitoring, because if you see the baseline MRI scores are low, they are not predictive for MRD, but if you combine this information with the change of MY-RADS scores, then you get a very highly significant correlation," Dr. Hajiyianni emphasized.

In response to questions from the audience, Dr. Hajiyianni stated the MY-RADS-informed sequences her study team used in its MRIs. She mentioned that handling focal lesions that are unchanged after treatment is "not easy," but her team based its approach on b-values and the fat fraction map. To a question about how WB-MRI compares with PET-CT for measurement of bone marrow MRD, Dr. Hajiyianni answered that the sub-study had PET-CT findings that will be presented next year, but said that from what the team has observed in its limited sample size, WB-MRI is more sensitive.

"It's more sensitive, because what we've seen during the HD-7 with PET-CT is patients become PET-CT negative very, very early," Dr. Hajiyianni elaborated.

Reference

Hajiyianni M, et al. 22nd International Myeloma Society Annual Meeting. Presentation OA-17.

Dynamic Frailty Analysis Highlights Daratumumab Benefits in Transplant-Ineligible, Newly Diagnosed Multiple Myeloma

*By **Melissa Badamo***

Daratumumab plus standard of care improved treatment outcomes for both frail and nonfrail patients with transplant-ineligible, newly diagnosed multiple myeloma, according to a post-hoc subgroup analysis of the phase 3 MAIA and CEPHEUS trials. However, worsening frailty was associated with shorter progression-free survival (PFS) compared with improving or stable frailty.

Hira Mian, MD

Blood Cancers Today Associate Editor **Hira Mian, MD,** of McMaster University, presented the findings at the 22nd International Myeloma Society Annual Meeting. Dr. Mian and colleagues assessed safety and efficacy outcomes of daratumumab-based combinations based on dynamic frailty status.

"We know that frailty is a well-recognized, high-risk feature and predictor of survival outcomes in patients with multiple myeloma," Dr. Mian said during her presentation. "Frailty is not static, but a dynamic state. Dynamic frailty may be a better predictor of outcomes than a static one-time frailty measurement. Unfortunately, the data on dynamic frailty, particularly in phase 2 and 3 trials, is limited."

Frailty Status at Baseline Versus After Treatment

The MAIA and CEPHEUS trials evaluated daratumumab with lenalidomide-dexamethasone (DRd vs Rd) or bortezomib-Rd (DVRd vs VRd), respectively. The median follow-up was 64.5 months in the MAIA study and 58.7 months in the CEPHEUS study.

Patients were randomized 1:1 to receive DRd (n=368) or Rd (n=369) in the MAIA trial and DVRd (n=144) or VRd (n=145) in the CEPHEUS trial. In the MAIA trial, almost half of the patients were frail at baseline (47% assigned to DRd and 46% assigned to Rd). In the CEPHEUS trial, 33% of participants assigned to DVRd and 24% of those assigned to VRd were frail at baseline. In MAIA, 42% and 43% of frail patients in the DRd and Rd arms, respectively, were considered ultrafrail.

Frailty status was assessed at 1 year, 2 years, 3 years, and 4 years using the Intergroupe Francophone du Myélome (IFM) simplified frailty score. Patients were categorized as nonfrail if they had a Charlson Comorbidity Index score of 0-1, frail if they had a score of 2 or higher, and ultrafrail if they had a score of 3 or higher.

In both trials, frailty status changed at 1 year and 4 years of treatment. At 1 year of treatment, 21% of patients in the MAIA trial and 19% in the CEPHEUS trial saw a change in frailty status: 10% and 7% of patients improved in MAIA and CEPHEUS, respectively, while 10% and 12% of patients worsened. At 4 years of treatment, 25% and 34% of patients changed frailty status, with more patients worsening than improving.

"The reasons for deterioration in frailty were an increase in Eastern Cooperative Oncology Group (ECOG) performance status scale, particularly during year 1 and year 2," Dr. Mian explained.

Frailty Status and Efficacy/Safety

In both frail and nonfrail patients, daratumumab-based regimens improved PFS and measurable residual disease (MRD) negativity rates in both trials. However, frailty changes over the 4-year period influenced PFS. Patients were categorized as either improving frailty, worsening frailty, stable nonfrail, or stable frail.

"Looking at the 48-month PFS rate, there was a trend towards shorter PFS in those with worsening frailty status over the entire 4-year period," Dr. Mian explained during the presentation.

Patients in the daratumumab groups experienced fewer serious treatment-emergent adverse events, including those leading to treatment discontinuation, compared with patients who did not receive daratumumab. In the CEPHEUS trial, the rates of serious treatment-emergent adverse events were consistent across dynamic subgroups. However, in the MAIA trial, these rates were higher among patients with stable frailty or worsening frailty.

"I hope this highlights that we need additional prospective data looking at dynamic frailty in larger phase 3 trials," Dr. Main concluded.

Reference

Mian H, et al. 22nd International Myeloma Society Annual Meeting. Abstract OA-21

Editor's Picks

Blood Cancers Today *works with contributors to highlight recent thought-provoking and practice-changing articles in different specialties. This month,* Blood Cancers Today *associate editor* ***Uma Borate, MBBS,*** *associate professor in the Division of Hematology at The Ohio State University, highlights recent research in myelodysplastic syndromes in honor of MDS World Awareness Day on October 25.*

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

Uma Borate, MBBS

MDS

ELEMENT-MDS Trial: How Well Does Luspatercept Prevent or Delay RBC Transfusion Dependency Onset?

By ***Andrew Moreno***

In the wake of the COMMANDS study findings, clinical trials to evaluate luspatercept as treatment for anemia in patients with lower-risk myelodysplastic syndromes (MDS) continue. Among these is the actively enrolling ELEMENT-MDS trial, described in *Blood*.

Currently, efficacy and safety data for luspatercept in the management of anemia for patients who have erythropoiesis-stimulating agent (ESA)–naive lower-risk MDS but are not dependent on red blood cell (RBC) transfusions are lacking. The phase 3 randomized multicenter study addresses this lack by comparing luspatercept with epoetin alfa as treatment for MDS-associated anemia in this patient population. Key for the investigators conducting the study will be the degree to which luspatercept decreases progression to RBC transfusion dependency among these patients.

The investigators are seeking to enroll 360 adults with very low– to intermediate-risk MDS per the revised International Prognostic Scoring System (IPSS-R) who are experiencing MDS-associated anemia of moderate or worse severity. Participants in the study are to have baseline serum erythropoietin (sEPO) levels of no higher than 500 U/L, baseline hemoglobin no higher than 9.5 g/dL, and no RBC transfusions within 16 weeks of trial randomization.

The study period involves 5 weeks of screening and 96 weeks of treatment followed by an extension phase and a post-treatment follow-up period. Study participants will be randomized 1:1 to receive either luspatercept or epoetin alfa and will be stratified according to baseline sEPO level, ring sideroblast status, and IPSS-R risk category. Patients in the luspatercept arm will be administered the agent once every 3 weeks at a starting dose of 1.0 mg/kg, with escalation of up to 1.75 mg/kg permitted. Patients in the epoetin alfa arm will be administered the agent once a week at a starting dose of 450 IU/kg, with escalation of up to 1,050 IU/kg permitted.

To evaluate luspatercept's efficacy, the luspatercept and epoetin alfa arms will be compared in terms of proportions of patients who progress to transfusion dependency for 16 continuous weeks during weeks 1 through 96 of the study. The two arms will also be compared in terms of relative proportions of patients who have a hemoglobin increase of 1.5 g/dL or greater persisting for at least 16 weeks during weeks 1 through 48 of the study.

The luspatercept and epoetin alfa arms will also be compared in terms of respective proportions of patients who achieve transfusion independence lasting at least 24 weeks, as well as in rates of overall survival, transfusion-free survival, and progression to high-risk MDS or acute myeloid leukemia; time to progression to RBC transfusion dependence; and time to achievement of modified hematologic improvement-erythroid response. Quality-of-life measures will be included in the outcomes assessment, and adverse events will be logged and evaluated for any connections to the study agent.

Reference

Zeidan AM, et al. *Blood*. 2023;142(suppl 1):6503. doi: https://doi.org/10.1182/blood-2023-178635

Study of Durvalumab for HMA-Refractory MDS Terminated for Insufficient Responses

By ***Andrew Moreno***

An open-label, multicenter phase 1 study was launched to evaluate different approaches—including durvalumab, an immunoglobulin (IgG1) anti–PD-L1 (programmed cell death 1 ligand 1) monoclonal antibody—to treat adults with myelodysplastic syndromes (MDS) who have experienced disease progression despite treatment with a hypomethylating agent. However, the study's limited efficacy findings, published in *Annals of Hematology,* have led to its early termination.

"Additional studies are warranted to better understand the full potential of immune checkpoint therapies in the treatment of MDS, as single agents and in combination with other types of therapy, and to better identify subsets of patients who could potentially derive a clinical benefit from these types of therapies," wrote lead author **Guillermo Garcia-Manero, MD,** of the University of Texas MD Anderson Cancer Center in Houston, and colleagues.

The cohort for the two-part study included 40 patients in part 1 who received durvalumab monotherapy and 27 patients in part 2 who received durvalumab combined with tremelimumab, a cytotoxic T-lymphocyte–associated protein 4–blocking IgG2 monoclonal antibody, with or without azacitidine.

The efficacy outcomes data of the trial included the prevalence of hematologic improvement, which was 35% in the monotherapy group and 30% in the combinations group. A best overall response of marrow complete response, as defined by International Working Group criteria, occurred in 15% of patients in part 1 and 15% of patients in part 2. However, no patients in either part achieved a confirmed complete response or partial response, which led to the study's early termination.

"This is consistent with the final results of a phase 2 clinical trial of azacitidine with and without durvalumab in patients with high-risk MDS, in which no meaningful difference in efficacy was observed between treatments for either cohort," wrote Dr. Garcia-Manero and colleagues, citing a randomized phase 2 study published in *Blood*.

Regarding the study's safety results, dose-limiting toxicities affected no patients who received durvalumab monotherapy, but occurred in 11% of patients who received durvalumab combinations. Of the treatment-emergent adverse events (TEAEs) observed, in both part 1 and part 2 fatigue was one of the most common, affecting 40% and 44% of patients, respectively. Diarrhea was as prevalent as fatigue in the part 1 cohort at 40%, and the second most common TRAE among patients in part 2 was anemia at 37%.

Reference

Garcia-Manero G, et al. *Ann Hematol.* 2025;104(3):1577-1585. doi:10.1007/s00277-024-06081-4

From Promise to Uncertainty in Venetoclax Plus Azacitidine for MDS

*By **Andrew Moreno***

The combination of the B-cell lymphoma-2 inhibitor venetoclax with the chemotherapy agent azacitidine has been investigated for the management of untreated, newly diagnosed, high-risk myelodysplastic syndromes (MDS). This doublet has been used to treat newly diagnosed acute myeloid leukemia (AML) in older adult patients and those who cannot undergo standard chemotherapy.[1] However, it remains under clinical trial evaluation for utility in MDS, and recent findings have put its use into question.

Initial clues of potential usefulness of venetoclax plus azacitidine in MDS were observed in in-vitro study data published in *Experimental Hematology & Oncology*. That study presented promising evidence that this combination has a potential effect as an intervention for patients with MDS and secondary AML, including in patients for whom hypomethylating agent intervention (HMA) had been unsuccessful.[2]

"These patients have an extremely poor prognosis and new therapeutic strategies are urgently needed. Interestingly, in our in vitro setting even lower-dose 5-AZA [azacitidine] shows a valuable cytotoxicity on the malignant cell when combined with venetoclax. Toxicity on the non-malignant progenitors was significantly reduced," lead author for the study **Stefanie Jilg, MD,** of Technical University of Munich, wrote with colleagues about their findings.[2]

These data were followed by encouraging phase 1b study findings, published in *Blood,* on outcomes and safety of this combination specifically in patients with untreated, newly diagnosed, high-risk MDS. In this study, 107 patients were administered a recommended phase 2 dosing of venetoclax at 400 mg for 14 days per 28-day cycle, and azacitidine at 75 mg/m^2 for 7 days per 28-day cycle.[3]

In outcomes of this phase 1b study, the best response of complete remission (CR) occurred in 29.9% of the total cohort and of marrow CR in 50.5%, with a calculated modified overall response rate of 80.4%. The patients had an estimated survival at 1 year of 71.2% and at 2 years of 51.3%, and a calculated median overall survival (OS) of 26.0 months. Of 59 patients who at baseline had dependence on red blood cell or platelet transfusions, 40.7% became transfusion independent.[3]

Regarding tolerability, the prevalence in the cohort of constipation, diarrhea, febrile neutropenia, nausea, neutropenia, and thrombocytopenia was 53.3%, 41.1%, 42.1%, 49.5%, 48.6%, and 44.9%, respectively. These incidences were consistent with the expected safety profiles for venetoclax and azacitidine, the investigators noted.[3]

First author of the phase 1b study, **Jacqueline Garcia, MD,** of Dana-Farber Cancer Institute, and colleagues wrote that these results "provide evidence of tolerability and efficacy of venetoclax plus azacitidine treatment at the RP2D [recommended phase 2 dose] for patients with treatment-naive HR [higher-risk] MDS," and that the phase 3 VERONA clinical trial would assess patient survival benefit produced by this doublet.[3]

The most recently reported results from the ongoing randomized, controlled VERONA trial—which compared oral venetoclax plus azacitidine with placebo plus azacitidine in patients who have newly diagnosed, higher-risk MDS—found no new safety signals. However, the trial failed to meet its primary end point for OS outcomes, having produced a hazard ratio of 0.908 (stratified log-rank, P=0.377).[1]

Following these new data, AbbVie plans to present the VERONA results within a medical publication or at an upcoming medical conference. The trial results would not affect any of the currently approved indications for venetoclax, the company noted in a press release.[1]

References

1. AbbVie. Accessed August 27, 2025. https://news.abbvie.com/2025-06-16-AbbVie-Provides-Update-on-VERONA-Trial-for-Newly-Diagnosed-Higher-Risk-Myelodysplastic-Syndromes
2. Jilg S, et al. *Exp Hematol Oncol.* 2019;8:9. Published 2019 Apr 16. doi:1186/s40164-019-0133-1
3. Garcia JS, et al. *Blood.* 2025;145(11):1126-1135. doi:10.1182/blood.2024025464

HemOnc Happenings

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

More Than Half a Million in Funding Granted to Study the Impact of *RAS* Mutations in AML

*By **Sara Karlovitch***

Annabelle Anandappa, MD

More than $500,000 in funding has been granted to an investigator examining the role of *RAS* genes in acute myeloid leukemia (AML), according to an announcement from the University of Cincinnati. The research will focus on whether renin-angiotensin system (RAS) inhibitors can be an effective blood cancer treatment.

Annabelle Anandappa, MD, a physician-researcher and clinical instructor in the University of Cincinnati's College of Medicine, received both the American Society of Clinical Oncology (ASCO) Conquer Cancer Women Leaders in Oncology Endowed Young Investigator Award and a Damon Runyon Physician-Scientist Training Award.

The 1-year ASCO award is worth $50,000 and will support research on how RAS(ON) inhibitors affect AML. The 4-year Damon Runyon grant, which is worth $460,000, will fund the study of a second RAS(ON) inhibitor, as well as the interaction between the RAS and genes associated with inflammation. CRISPR technology will be used to screen a panel of inflammation-related genes to identify a potential target. The grant is designed to bridge the gap between completion of a fellowship and funding as an independent researcher.

RAS mutations are found in 15% to 20% of all AML cases at time of diagnosis, with recent data suggesting they are associated with treatment resistance to recently approved AML therapies. Although prior research exists on the impact of RAS-targeted treatments, most of it has been done in relation to solid tumors, including pancreatic cancer.

"We think this is a particularly timely project because we've known for a long time that *RAS* mutations are present in AML, but it wasn't always clear how significant they were in terms of driving outcomes," said Dr. Anandappa in a press release.

The projects will be mentored by **Linde Miles, PhD**, a member of the Cincinnati Children's Hospital Medical Center's Division of Experimental Hematology & Cancer Biology and an assistant professor in the University of Cincinnati's Department of Pediatrics, and **Daniel T. Starczynowski, PhD,** the Katherine Stewart Waters Endowed Chair of Hematologic Malignancies. Dr. Starczynowski also serves as the director at the Advanced Leukemia Therapies and Research Center and the Cincinnati Children's Hospital Medical Center.

Both mentors have previous relevant laboratory experience. AML mutations, including *RAS,* have been the focus of Dr. Miles's previous research. Dr. Starcynowski's research has focused on inflammatory signaling in myeloid malignancies.

Reference

Tedeschi T. Accessed August 21, 2025. https://www.uc.edu/news/articles/2025/08/two-prestigious-grants-allow-young-investigator-to-continue-blood-cancer-research.html

Myeloma Researchers Honored at IMS Annual Meeting

*By **Melissa Badamo***

Each year, the International Myeloma Society (IMS) recognizes three clinician researchers who have made major contributions to the field of myeloma. This year's award recipients, Drs. Elena Zamagni, Peter Leif Bergsagel, and María-Victoria Mateos, were honored at the 22nd IMS Annual Meeting in Toronto, Ontario, Canada, on September 18.

Bart Barlogie Clinical Investigator Award

Elena Zamagni, MD, PhD, director of the myeloma program and associate professor of hematology at the University of Bologna, received the Bart Barlogie Award for her pioneering research in myeloma imaging.

Elena Zamagni, MD, PhD

Dr. Zamagni's research focuses on the role of imaging in the treatment of newly diagnosed, transplant-eligible myeloma and the prognostic impact of measurable residual disease (MRD). In fact, she began her research career in imaging at the University of Arkansas under the mentorship of Bart Barlogie.

Dr. Zamagni was the first to demonstrate the prognostic value of positron emission tomography–computed tomography (PET-CT) in 2011. She also defined imaging and MRD as a category of responses, contributed to the recommendations in the imaging algorithm for all plasma cell disorders, helped standardize the use of PET-CT, and helped define extramedullary disease.

"It was not me who chose multiple myeloma when I was a young student and later a hematology trainee, but it was Professor Michele Cavo who assigned me a thesis titled 'Through the Cure of Multiple Myeloma,' said Dr. Zamagni as she accepted her award. "It was 1997, so [it was] quite an optimistic and visionary title…but now, as we hear in this meeting, it is close to reality for some of our patients."

Ken Anderson Basic and Translational Research Award

Peter Leif Bergsagel, MD, professor of medicine at the Mayo Clinic, received the Ken Anderson Basic and Translational Research Award for his breakthrough research in both mouse and human myeloma models.

Peter Leif Bergsagel, MD

Dr. Bergsagel was the first to identify recurrent immunoglobulin heavy chain (*IgH*) translocations and their partner genes in myeloma. He also laid the foundation for research in *MYC* translocations, including developing a transgenic mouse model to show that activation-induced deaminase-dependent activation of a *MYC* transgene induces myeloma in the germinal center.

He was commissioned as a lieutenant commander in the Public Health Service with Ronald Reagan as Commander in Chief in 1988, which sparked his interest in studying myeloma. After collecting 80 human myeloma cell lines from investigators around the world, he was able to identify genes expressed in mouse plasmacytomas in the early 1990s, replicate those studies in humans, and identify ectopic expression of *c-MAF.*

"After 35 years, I'm back to studying mouse myeloma cell lines and working with a great myeloma team in Calgary, Alberta," he concluded.

Waldenström Lifetime Achievement Award

María-Victoria Mateos, MD, PhD, associate professor of medicine at the University of Salamanca, received the Waldenström Lifetime Achievement Award for her research focusing on treatment for smoldering myeloma.

María-Victoria Mateos, MD, PhD

Dr. Mateos developed the concept of early intervention in high-risk smoldering myeloma with her 2013 study in the *New England Journal of Medicine* on lenalidomide-dexamethasone versus observation, proposing a curative strategy with carfilzomib, lenalidomide, and dexamethasone followed by high-dose therapy.

Dr. Mateos is also lead investigator of the ALCYONE trial, which evaluated bortezomib, melphalan, and prednisone with or without daratumumab for the treatment of patients with newly diagnosed myeloma.

"Myeloma is a very complex disease. Over the last 40 to 50 years, a great effort was made in basic and translational research in order to understand the pathophysiology of the disease," Dr. Mateos said, reflecting on her career journey and the evolution of myeloma research. "I was at the optimal timing because I completed my specialty in hematology and PhD at the end of the 1990s and beginning of the 2000s, when new compounds in myeloma were being introduced."

Reference

IMS Award Ceremony. Presented at the 22nd IMS Annual Meeting; September 17–20, Toronto, Ontario, Canada.

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