TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

BLOOD CANCERS TODAY

August 2025

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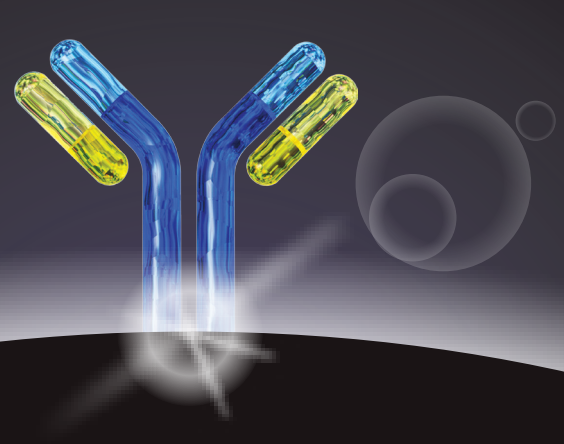

In an era of progress, one of the next goal posts is successful development of trispecifics.

With expert opinions from:
Joshua Richter, MD; Muhamed Baljevic, MD; and Hang Quach, MBBS

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Highlighting Recent MDS Research

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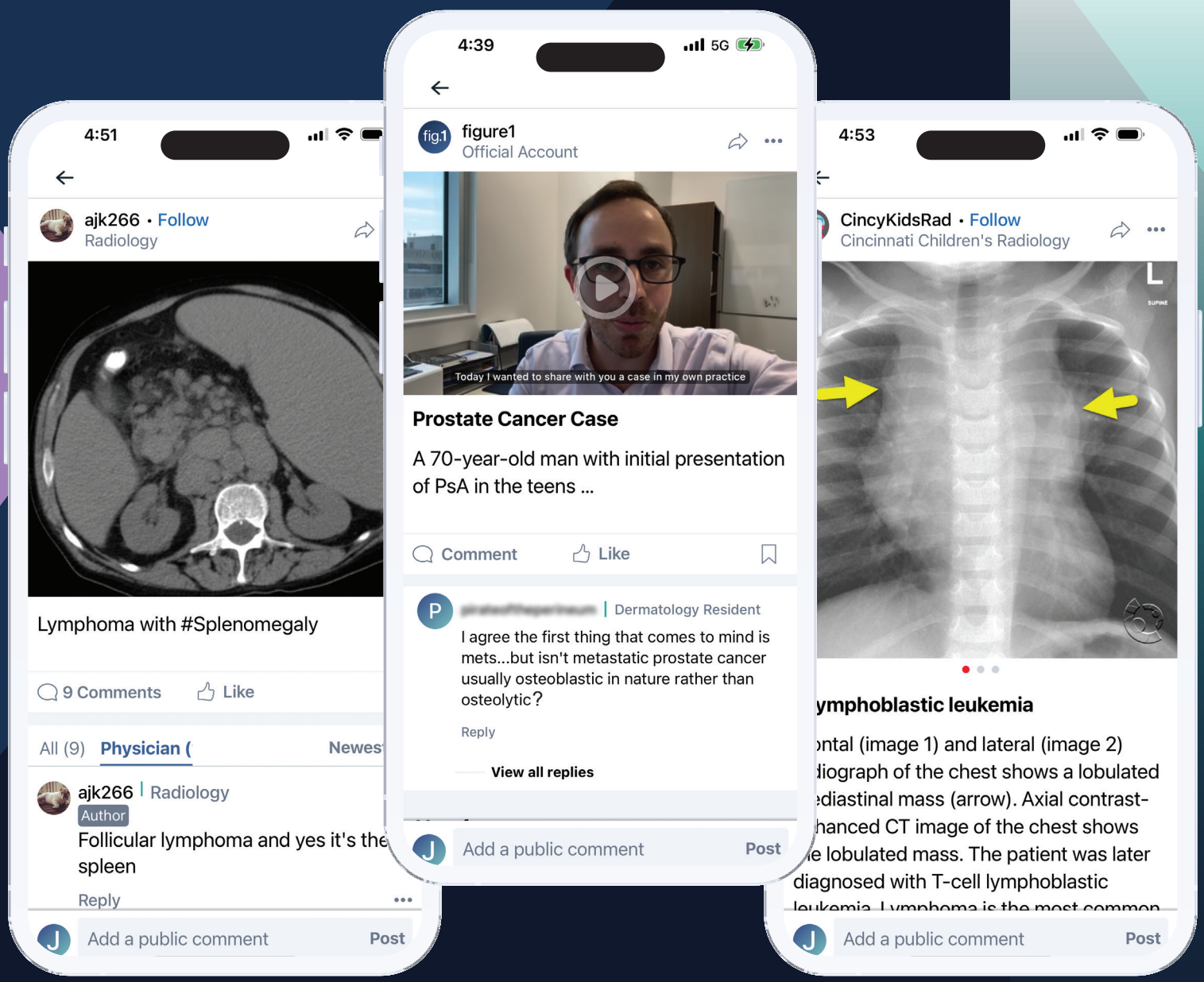

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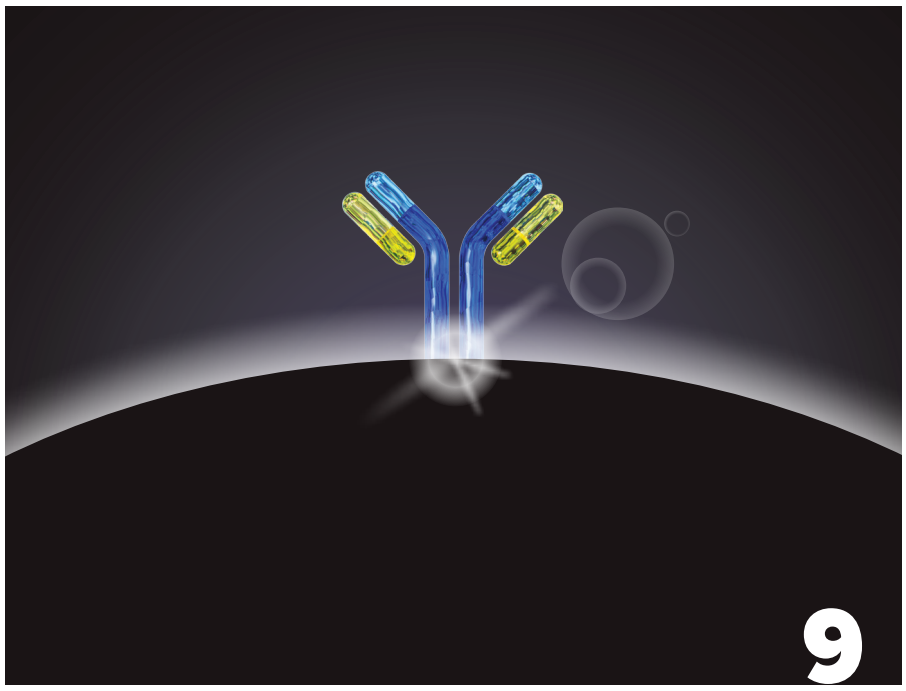

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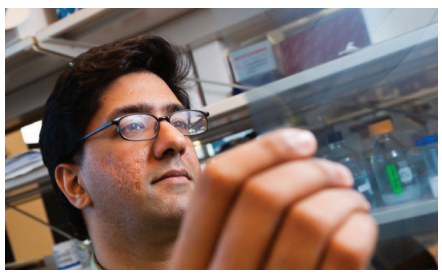

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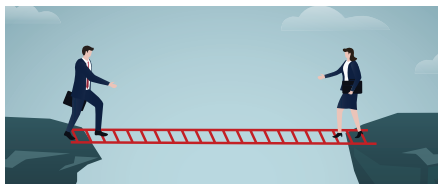

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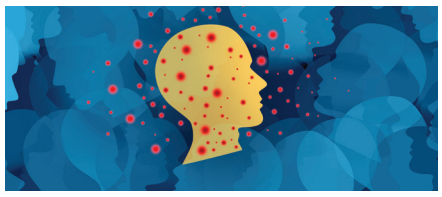

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Calendar

September 3-6
13th Annual Meeting of the Society of Hematologic Oncology (SOHO)
Houston, TX

September 13
Leukemia & Lymphoma Society National Blood Cancer Conference
Virtual

September 17-20
22nd Annual International Myeloma Society (IMS) Annual Meeting & Exposition
Toronto, Canada

September 24-27
American Association for Cancer Research (AACR) Conference on Mechanisms of Cancer Immunity and Cancer-Related Autoimmunity
Montreal, Canada

September 25-28
AACR Special Conference in Cancer Research: Discovery and Innovation in Pediatric Cancer—From Biology to Breakthrough Therapies
Boston, MA

September 25-28
10th Congress on Controversies in Stem Cell Transplantation and Cellular Therapies (COSTEM)
Berlin, Germany

September 26-27
7th Annual LEAD Conference: Enriching Experiences for Women in Hematology & Oncology
Scottsdale, AZ

October 6-10
16th Annual Comprehensive Hematology and Oncology Review Course
Seattle, WA

October 10-11
National Comprehensive Cancer Network (NCCN) Annual Congress: Hematologic Malignancies
San Diego, CA

October 10-12
ESH-iCMLf 27th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy
Estoril, Portugal

October 15-17
42nd Association of Cancer Care Centers National Oncology Conference
Denver, CO

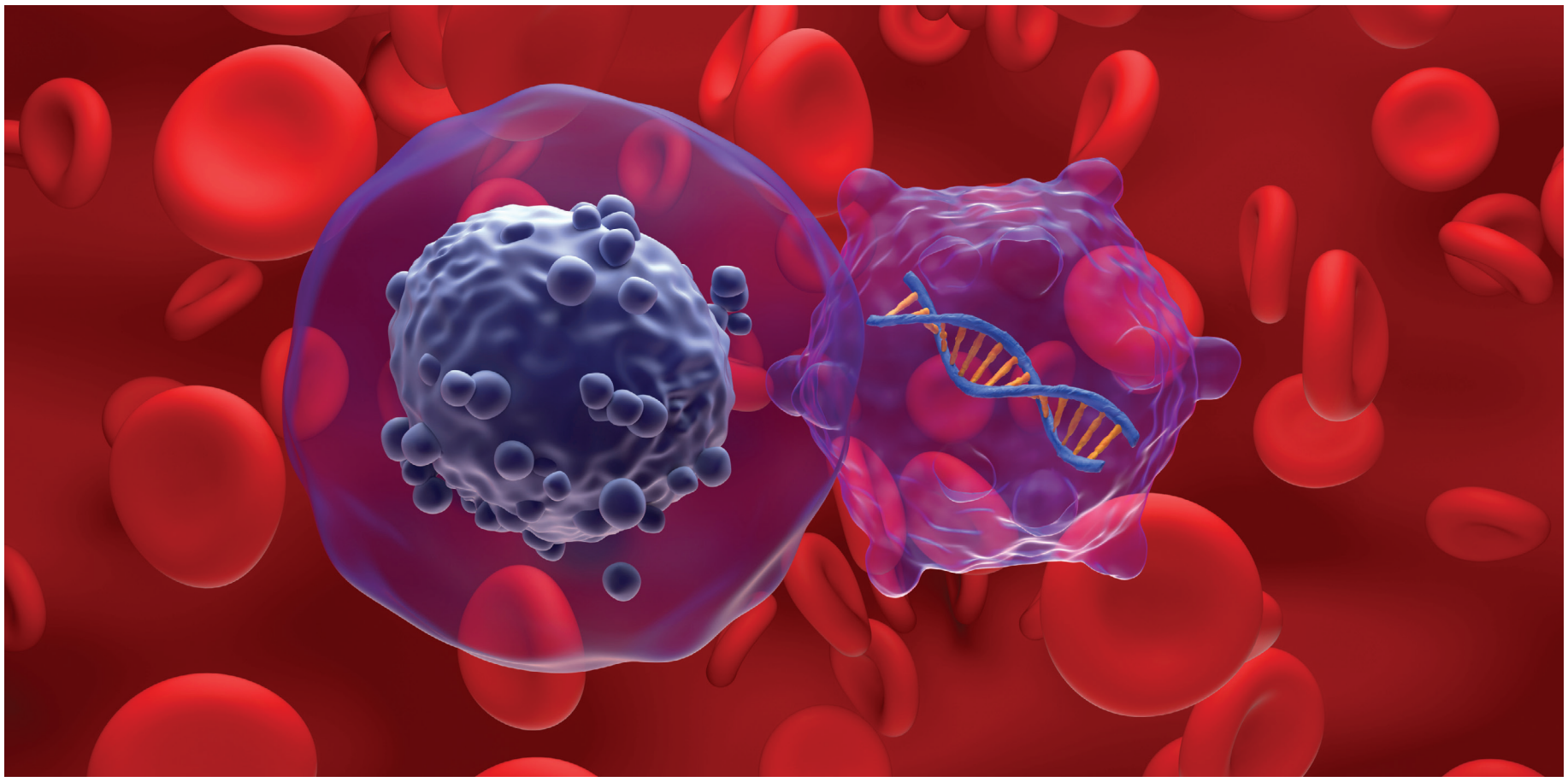
October 17-21
2025 European Society for Medical Oncology Congress
Berlin, Germany

October 23-26
JADPRO Live
National Harbor, MD

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

Get to Know

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



Raajit K. Rampal, MD, PhD

Science and medicine swirled in every corner of Dr. Raajit Rampal's upstate New York childhood home, from being quizzed by his scientist father about the chemical processes of cooking on the stove to spending a summer in high school conducting cancer research. From Buffalo to the Manhattan borough, the leukemia specialist shares his journey to becoming a hematologist-oncologist at Memorial Sloan Kettering Cancer Center in this exclusive *Get to Know* interview.

*By **Melissa Badamo***

Where did you grow up, and how did you know that you wanted to become a hematologist-oncologist?
I was born and raised in Buffalo, New York. My dad was a scientist, so science is in my blood. Since childhood, everything in our house [has] had some relation to science. When my mom was cooking eggs on the stove one day, my dad asked me, "Do you know why the eggs are turning white in the pan? Do you know what's happening here?" That's the type of conversations we used to have that influenced my thinking from a very early age.

Science led me to medicine. It was that sense of asking simple questions: "Why does this process happen?" During high school, I spent a summer in a chemistry lab at Roswell Park Cancer Institute. That was the first time I got exposed to cancer research. I worked on a very basic synthetic chemistry project, which got me interested in chemistry. From there, I went on to study biochemistry in college.

I was absolutely fascinated by it. I spent my summers doing research, but it wasn't necessarily all medically applicable. It was more basic science work. During one summer in college, I was working in a hematology research lab at the University of Rochester as an undergraduate, where I really began to understand the application of science to medicine. I worked in a lab that studied a clinically focused project. That was the moment I thought, "I want to do something that has a more practical application, and if I could do it in a way that merged with science, that would be perfect."

From there, I went into the MD/PhD program at Stony Brook University. I loved my basic science/PhD training and my clinical rotations as a medical student, but I hadn't figured out what I wanted to do. I went into internal medicine with an open mind.

"It was very evident that patient outcomes were not good…the only way forward is through research."

Get to Know

When I was a resident at the University of Chicago, I knew I wanted to pursue malignant hematology. I rotated there on the leukemia service and got to work with some of the giants in the field, like Drs. Richard Larson and Wendy Stock. That's when I knew I wanted to be a leukemia doctor.

It was very evident that patient outcomes were not good. They're better now, but they're still not good when we think about things like leukemia. It was obvious the only way forward is through research. That inspired me to aim my focus on both the basic biology and the clinical application of science to malignant hematology, particularly in the leukemia world.

I'm fortunate to be in a position where I can still carry on cutting-edge bench research and genomic research and take care of patients and run clinical trials.

You are the lead investigator of the MANIFEST-2 trial evaluating pelabresib plus ruxolitinib in first-line myelofibrosis. Can you please discuss this study?

This is a key example of something that went from the bench to the bedside, where that inhibition as a therapeutic strategy was developed in the lab and subsequently led through a long process to the MANIFEST-2 trial. The results recapitulate the preclinical observations, which is that the combination of ruxolitinib and pelabresib is better than ruxolitinib for many aspects of myelofibrosis, including shrinking the spleen and not adding toxicities that result in worsening symptoms for patients. The symptom benefits were more or less the same in both arms.

We also saw other improvements in terms of bone marrow fibrosis and hematologic parameters like anemia. All in all, there is absolutely clear evidence that the combination has effects that are beneficial for patients beyond those that we see with ruxolitinib alone. The interesting and important thing is that the data continue to mature. Updates of the initial data were presented subsequently at ASH [American Society of Hematology Annual Meeting & Exposition] and EHA [European Hematology Association Congress], showing that the difference continues to exist and that the durability of that initial response seems to be maintained. All of this is very encouraging, and I hope that pelabresib can find its way to approval.

"We have seen extraordinary development from the time I entered the field...There is still a huge unmet need and questions that pertain to developing better drugs that prevent patients from progressing."

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

I'm very optimistic. We have seen extraordinary development from the time I entered the field when we had one JAK [Janus kinase] inhibitor to where we are now talking about next-generation JAK inhibitors, targeting calreticulin, and drugs that are combination partners for JAK inhibitors. The field has moved forward tremendously.

That being said, there is still a huge unmet need and questions that pertain to developing better drugs that prevent patients from progressing and prevent bad outcomes in general. But, the other part of this is knowing the patients who are at risk. This is an area where we need to do a lot more. The biggest worry for patients and for physicians is whether this disease will progress and turn into AML [acute myeloid leukemia]. We don't have a lot of great tools to understand who is at risk, because we know there are patients who are going to do well overall. If we can figure out who is at risk, we can potentially intervene earlier with better drugs and prevent those outcomes without exposing patients who are likely going to do fine to additional therapies they don't need.

I'm proud to be a part of a major project launched by the MPN Research Foundation, which is a progression registry project to understand if we can identify which patients are at risk using large real-world datasets. Aside from advancing new drugs, that is another key thrust in moving the field forward.

What hobbies or activities do you enjoy outside of work?

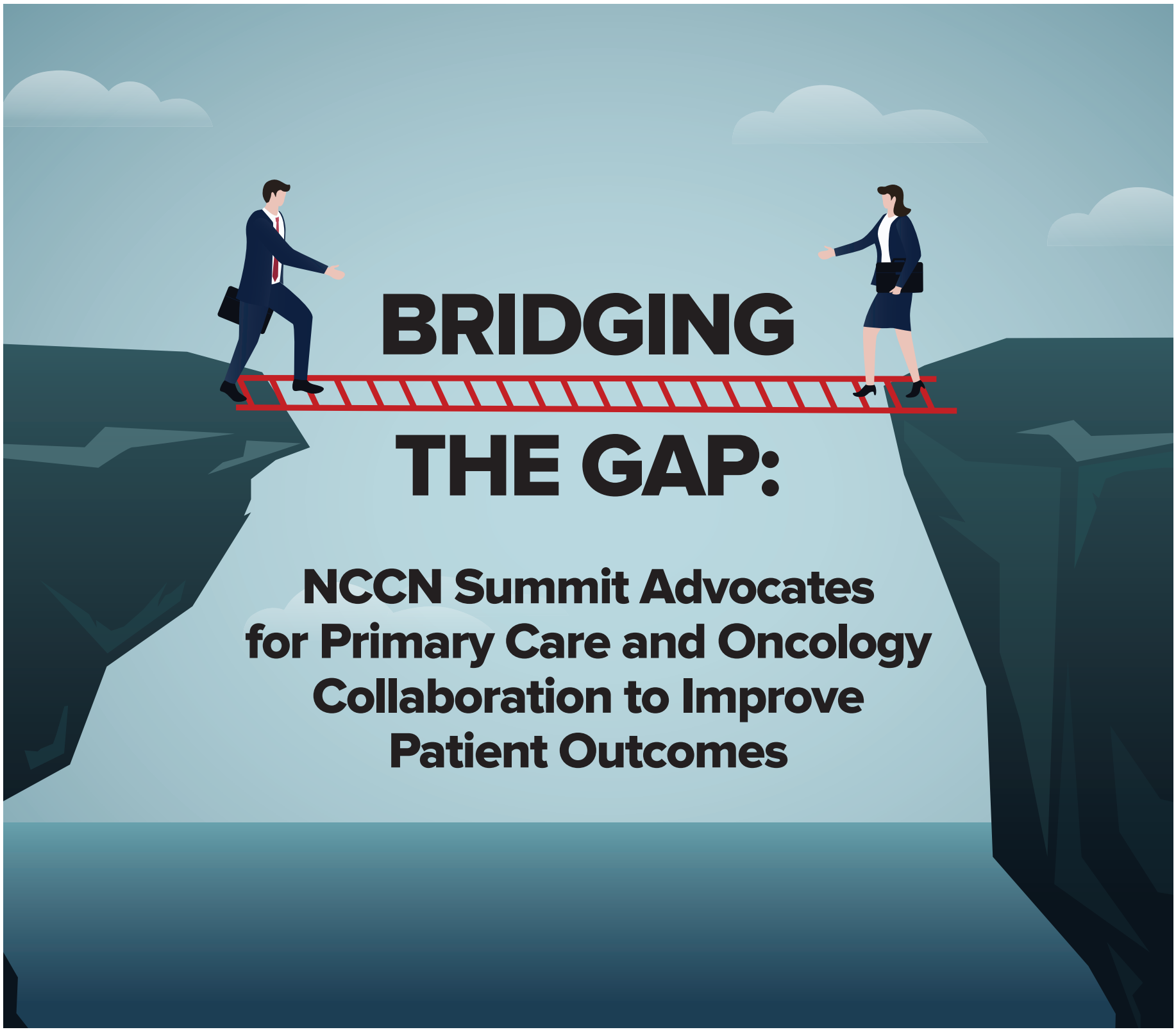
I'm somebody who very much loves music, photography, and art. From that perspective, living in New York City is absolute paradise. I'm an amateur guitarist and an amateur saxophonist, and my wife is a professional saxophonist. Music is a huge part of our household. For a wedding, most people have a first dance, which we did, but then we played dueling saxophones.

What is a fun fact that most people would be surprised to learn about you?

Some people are surprised to learn that I'm a diehard hockey fan and one of the people yelling in the stands. That's not my persona in professional meetings and professional settings, but put me into an NHL arena and it's a different thing!

What's on your bucket list?

Now that we have gotten to the point where there are commercial companies launching people into space, it's my hope that within our lifetime we can take trips around the low orbit of the Earth on a regular basis. That would be awesome.



By ***Melissa Badamo***

For patients with cancer, primary care professionals (PCPs) help promote cancer prevention, early detection, and survivorship care. However, gaps in coordination and collaboration between primary care and oncology may significantly impact long-term survival outcomes.

The National Comprehensive Cancer Network (NCCN) addressed these gaps in their Oncology Policy Summit on May 6, 2025, which facilitated a larger conversation on strengthening collaboration between primary care and oncology and the role of public health policy in advancing patient survival.

The Role of PCPs in Patient Survival

Primary care professionals may be the first to identify patients' symptoms, refer them to an oncologist, and ultimately facilitate early detection and diagnosis, **Veronika Panagiotou, PhD,** director of Advocacy and Programs at the National Coalition for Cancer Survivorship and panelist at the NCCN summit, told *Blood Cancers Today*.

"PCPs promote access to cancer-preventing vaccines like the HPV [human papillomavirus] and HBV [hepatitis B virus] vaccines, promote healthy lifestyles that may reduce cancer risk through diet and exercise, and also facilitate patient engagement with cancer screening," added **Alyssa Schatz, DrPH, MSW,** vice president of Policy & Advocacy at the NCCN.

In a 2022 study of 245,425 adult patients with metastatic cancer, some PCP visits—as compared with no previous visit—were associated with a 26% decreased odds of metastatic disease at diagnosis (odds ratio [OR], 0.74; 95% CI, 0.71-0.76; $P<0.001$) and a 12% reduced risk of cancer-specific mortality (subdistribution hazard ratio [SHR], 0.88; 95% CI, 0.86-0.89; $P<0.001$).

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Meanwhile, annual PCP visits were associated with a 39% decreased odds of metastatic disease (OR, 0.61; 95% CI, 0.59-0.63; $P < 0.001$) and a 21% reduced risk of cancer-specific mortality, suggesting that PCPs are vital for early cancer detection.[1]

However, the role of PCPs also extends to patients' long-term, post-treatment journey. "PCPs are also the professionals that patients return to when transitioning into survivorship care after cancer treatment; this requires management of a complex set of healthcare needs," Dr. Schatz said.

In a database study of 951 cancer survivors, 91.6% had at least one annual PCP visit, 54.6% had a PCP as their main healthcare provider, and 88% only saw a PCP, highlighting the "urgent need for smooth handoffs from oncology back to primary care."[2]

"Our primary care providers are best suited to help survivors get through the treatment process, and then more importantly, after the treatment process, to deal with all the other health issues that might be a direct result of that cancer diagnosis or they might have had before their cancer diagnosis," Dr. Panagiotou explained. "We need that comprehensive care to live long lives. Primary care is foundational to every human regardless of if they have a cancer diagnosis. They should be a part of every person's care team."

"Primary care is foundational to every human regardless of if they have a cancer diagnosis. They should be a part of every person's care team."

—Veronika Panagiotou, PhD, director of Advocacy and Programs at the National Coalition for Cancer Survivorship

Bridging the Gap Between Primary Care and Oncology

According to Dr. Panagiotou, the main gap in primary care and oncology is patient trust.

"Survivors have a real trust issue with primary care because they're worried about the physical, emotional, and financial costs of cancer. Some are worried that their primary care provider doesn't have enough information and training," she explained.

In a 2019 survey, 66% of PCPs reported patient preference to follow up with their oncologists as a barrier in caring for patients with hematologic malignancies. Other reported barriers included lack of resources to facilitate care (69%), lack of awareness of screening and prevention guidelines (55%) and psychosocial needs of survivors (65%), and inadequate time (65%).[3]

"[PCPs] are not trained in cancer, so [patients] have trouble leaving their oncologists because cancer is their focus," Dr. Panagiotou explained. "But oncologists can't do everything. And that's the burden on the other side of the equation. Oncologists cannot manage hypertension, diabetes, and other chronic conditions that are better suited for primary care."

Some cancer survivors also travel to different states or communities to receive specialized care, Dr. Panagiotou explained, creating a physical gap in cancer care. One model to overcome this barrier consists of merging primary care practices inside of cancer centers.

"That creates proximity," she said. "If PCPs see a big group of cancer survivors, they might be able to see trends. It creates an environment where there's more focus and collaboration. That's the kind of innovation that hopefully will bring us closer to getting better care for patients."

Drs. Panagiotou and Schatz also highlighted virtual gaps between primary care and oncology practices regarding medical record systems.

"They have a hard time communicating with each other. They're not in the same systems, and they don't have the same electronic health record [EHR] sometimes," Dr. Panagiotou said. "Oncologists use NCCN guidelines, but primary care has their own set of guidelines, so their guidelines don't quite match up."

"A key takeaway for me from the summit was the need to take action toward truly interoperable medical record systems," Dr. Schatz added. "This is challenging in the US, because we have so many different EHR/HIT [health information technology] vendors. Thankfully, the CMS [Centers for Medicare and Medicaid Services] has made this a priority and has made some progress toward the goal, but we still have a very long way to go."

Health Reimbursement Policies

As Dr. Schatz noted, improving primary care and oncology collaboration requires policy change.

"Coordination between specialties takes time and resources," she said. "We need to ensure that reimbursement systems are set up to recognize and reimburse this type of coordination. As we heard from Dr. Liz Fowler during the summit, value-based models of care may also play a key role in advancing better collaboration. The Center for Medicare and Medicaid Innovation recently announced new pillars, including embedding preventive care in all model designs. That may offer an opportunity for improving primary care and oncology collaboration."

"The federal government is the biggest insurer," added Dr. Panagiotou. "They take care of the Medicare and Medicaid populations. The rules in how they reimburse influence how private payers reimburse. If Medicare and Medicaid are not adequately paying physicians to provide survivorship care, then we're not going to get what we need, because we need providers to get the reimbursement they need to provide this service."

Dr. Panagiotou's organization, the National Coalition for Cancer Survivorship, advocates for survivorship care plans that provide roadmaps to help survivors navigate the next steps after treatment. With the goal of improving quality of life, these roadmaps include documented patient history as well as recommendations for future care, screening, and supportive services such as physical or occupational therapy.

"We advocate for reimbursement to create those plans because we know that they're tedious," she said. "It takes a physician or someone part of the team to create that document and have that conversation to move patients through their transition from treatment."

As Dr. Schatz noted, the NCCN Guidelines for Survivorship also provide recommendations on survivorship principles, late effects of cancer and cancer treatment, preventive health such as physical activity and nutrition, vaccinations, supplement use, and secondary cancers.[4]

"Survivorship care plans are super important in this space, and we need more reimbursement for supportive services so people can have access to get what they need within the healthcare system," said Dr. Panagiotou. "What our national centers do does have an impact on how we access healthcare. It starts there."

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As Measles Cases Reach a Record High, Oncologists Feel the Impact

By ***Sara Karlovitch***

Despite the elimination of measles in the US in the 2000s due to effective vaccination,[1] measles cases are the highest in 33 years, with more than 1,000 cases reported in 2025 as of July.[2]

"This outbreak has brought an acute awareness of the vulnerability of cancer patients to vaccine-preventable diseases, like measles, as well as highlighting how important community herd immunity is for protecting our most vulnerable patients," said **Amy Spallone, MD,** chief infection control officer at The University of Texas MD Anderson Cancer Center.

The highly contagious disease, which can be difficult to spot, can have profound impacts on oncology patients and lead to major complications.

A Vulnerable Population

A quarter of ambulatory patients with cancer lacked the antibodies needed to protect themselves against measles, and 38% lacked the antibodies needed for protection against mumps, according to a 2021 study published in *JAMA Network Open.* Research suggests that while rare, measles outbreaks in oncology wards can have a fatality rate of 70%.[3]

The cross-sectional study looked at outpatients who received care at the Fred Hutchinson Cancer Research Center's Seattle Cancer Care Alliance. All 959 patients included in the study had residual plasma samples available after routine clinical testing over a 5-day period in August 2019.[3]

Most patients (75%) had a positive measles antibody test, 17% had a negative test, and 8% had equivocal results. Immunity deficiencies were the most common in patients between the ages of 30 and 59 with hematologic malignant neoplasms who underwent hematopoietic stem cell transplant (HSCT).[3]

Other studies suggest that children are at a particular risk. Case fatalities for childhood leukemia

Field Dispatch

patients can range from 13% to 83%, according to a position statement published in *Transplantation and Cellular Therapy*.[4]

"Those who become infected while undergoing active cancer treatment or with hematologic malignancies are more susceptible to contracting measles and experiencing complications, like pneumonia, encephalitis, and other severe respiratory or neurological issues," said Dr. Spallone.

Additionally, immunosuppressed patients are more likely to experience complications related to the disease. It is estimated that approximately half of patients with hematological malignancies and a measles infection develop life-threatening complications, including pneumonia, liver failure, and encephalitis.[4]

However, protecting this population isn't as easy as administering a vaccine.

"Given that any immunity that you might have previously had is lost with an autologous transplant, you need to revaccinate after the transplant. With an allogeneic transplant, where you have to consistently suppress the immune system to prevent the graft from attacking the body, an infection such as measles could lead to unnecessary fatalities," said **Tycel Phillips, MD,** associate professor of medicine at the City of Hope National Medical Center.

The current measles, mumps, and rubella (MMR) vaccine uses a live attenuated strain—the Edmonston-Enders strain—and results in greater than 93% protective immunity in normal hosts. In 1989, it was recommended that two doses of the vaccine be administered to immunocompromised children. A third dose did not improve immune responses.[4]

For patients receiving exogenous immunosuppression, it isn't as simple. When it comes to vaccine administration, timing is vital. For patients with leukemia, the MMR vaccine should be administered at least 3 months after the conclusion of chemotherapy and 6 months after the administration of anti–B-cell antibodies, such as rituximab. Patients who have received autologous or allogeneic HSCT and are off immunosuppression and not receiving certain relapse prophylaxis or maintenance therapies can receive the vaccine 24 months post-transplantation.[4]

"This outbreak has brought an acute awareness of the vulnerability of cancer patients to vaccine-preventable diseases."

—Amy Spallone, MD, chief infection control officer at The University of Texas MD Anderson Cancer Center.

For patients who are more than 24 months post-allogeneic HSCT but require prolonged immunosuppressive therapy for chronic graft-versus-host disease, the vaccine can only be administered 8 to 11 months after ending immunosuppression therapy. The vaccine is not recommended for those receiving rituximab maintenance, but may be safe for those receiving bortezomib or lenalidomide.[4]

However, these guidelines were designed for situations in which there is no increased risk from community clusters or disease outbreaks. During large outbreaks, the benefits of vaccination may outweigh the associated risks. However, oncologists should take a case-by-case approach when deciding if vaccination is necessary and only after patients are at least 1 year post-transplantation.[4]

"For oncologists and healthcare providers, it is essential to discuss vaccinations with our patients, including revaccination during community outbreaks for those who are eligible to receive the vaccine. Immunocompromised patients who cannot receive the vaccine should avoid travel to areas known to have active measles cases," said Dr. Spallone.

Steps for Oncologists

Many US healthcare professionals have seen few—if any—measles cases during their practice, making it difficult to determine an appropriate response.[4] The evasive nature of the virus, which has an incubation period of 10 to 14 days, further complicates this. The period of contagiousness can be difficult to pin down, as RNA can appear for months after the appearance of the rash associated with the disease.[5] Additionally, before the appearance of the rash, measles symptoms are similar to those of most common respiratory viruses. This can make pinning down exposure in a timely manner incredibly difficult.[5]

"The measles virus can live for up to 2 hours in an airspace in which an infected person has coughed or sneezed. Therefore, when considering exposures, those who were in the same space (eg, playroom, household, clinic, waiting room) as the contagious patient for up to 2 hours, after that patient was present should be considered at risk for measles exposure," said **Heather Symons, MD, MHS,** clinical director of pediatric blood and marrow transplantation at Johns Hopkins Medicine.

In areas with active exposures, extra steps should be taken before the patient enters the facility. Those who screen positive should be isolated and undergo further testing. Additionally, transplant recipients should be fully educated on the impact of exposure and told to report any possible contact, along with limiting exposure to caregivers and family.[4]

If a patient tests positive or presents with concerning symptoms, they should be brought to a negative-pressure isolation room with airborne precautions. Portable rooms can be used if available. After the patient leaves the room, it should be left unoccupied for 2 hours then terminally disinfected. If negative-pressure rooms are not available, the patient should be put in a room by themselves with the door closed. All staff should use an N-95 mask or powered air purifying respirator along with standard measures.[4]

"Exposure to measles can lead to delays or changes in cancer treatment plans."

—Heather Symons, MD, MHS, clinical director of pediatric blood and marrow transplantation at Johns Hopkins Medicine

"The best measures to prevent an outbreak among our patients are to prevent possible measles-infected individuals from having contact with other patients on campus," said Dr. Spallone. "Specifically, we aim to quickly identify possible measles cases, place those patients on appropriate isolation precautions, and then alert hospital Infection Control so that additional investigations can begin in partnership with local public health authorities."

During times of widespread outbreak, cancer centers may need to take additional precautions, such as targeted screenings. After exposure, airborne isolation precautions should be maintained for 21 days, and 28 days for patients who receive postexposure prophylaxis with intravenous immunoglobulin.[4]

However, precautions can lead to care delays or interruptions, especially if isolation is needed. Additionally, outbreaks can have a financial impact on affected hospitals.

"In areas with outbreaks, or ongoing measles transmission, special screening and precaution measures that take time, money, and resources have had to be implemented. Some hospitals have needed to implement stricter isolation protocols, including designated areas for measles patients, enhanced hygiene practices, and increased surveillance for potential outbreaks," said Dr. Symons. "Exposure to measles can lead to delays or changes in cancer treatment plans, as patients may need to be isolated or their treatment schedule adjusted."

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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®.

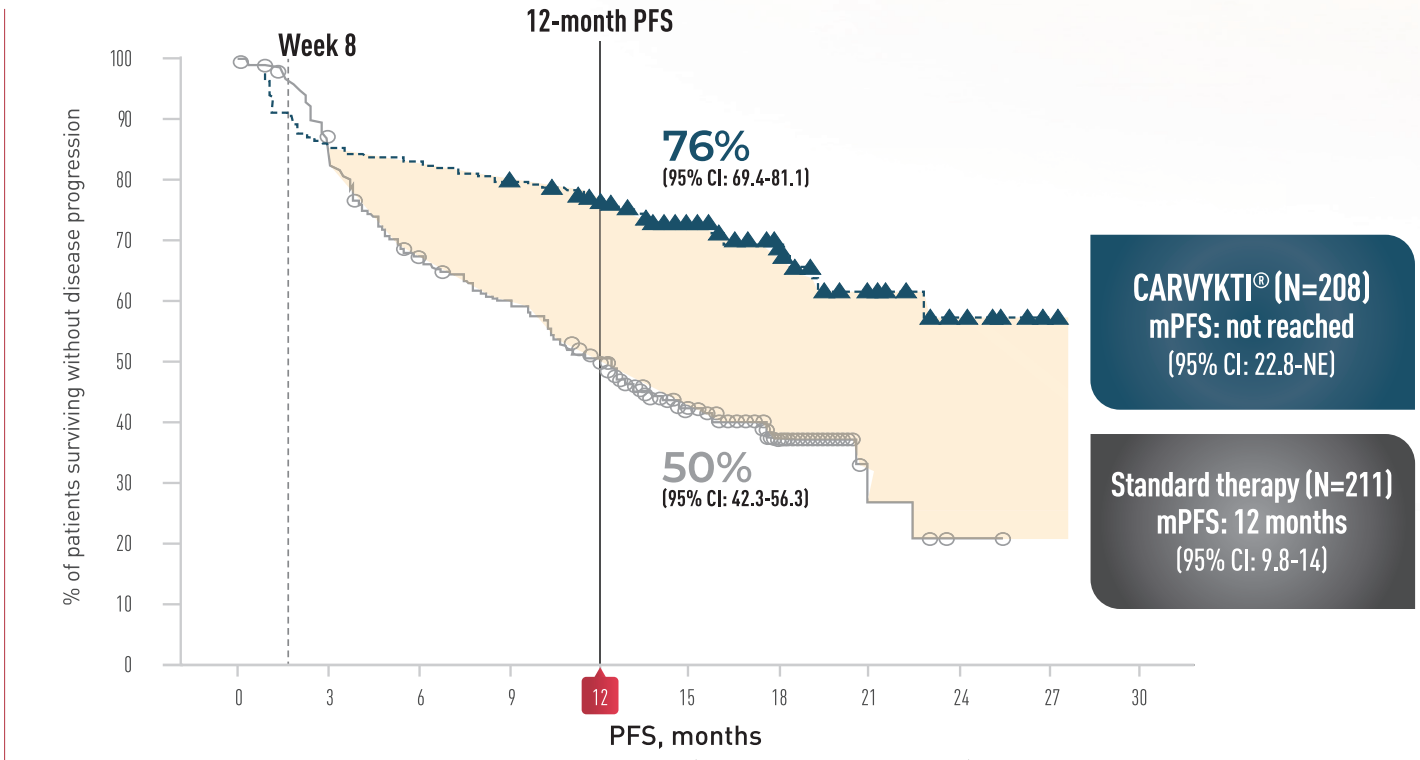
CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

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®.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

OVERALL SURVIVAL

CARTITUDE-4 median follow-up of 15.9 months

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

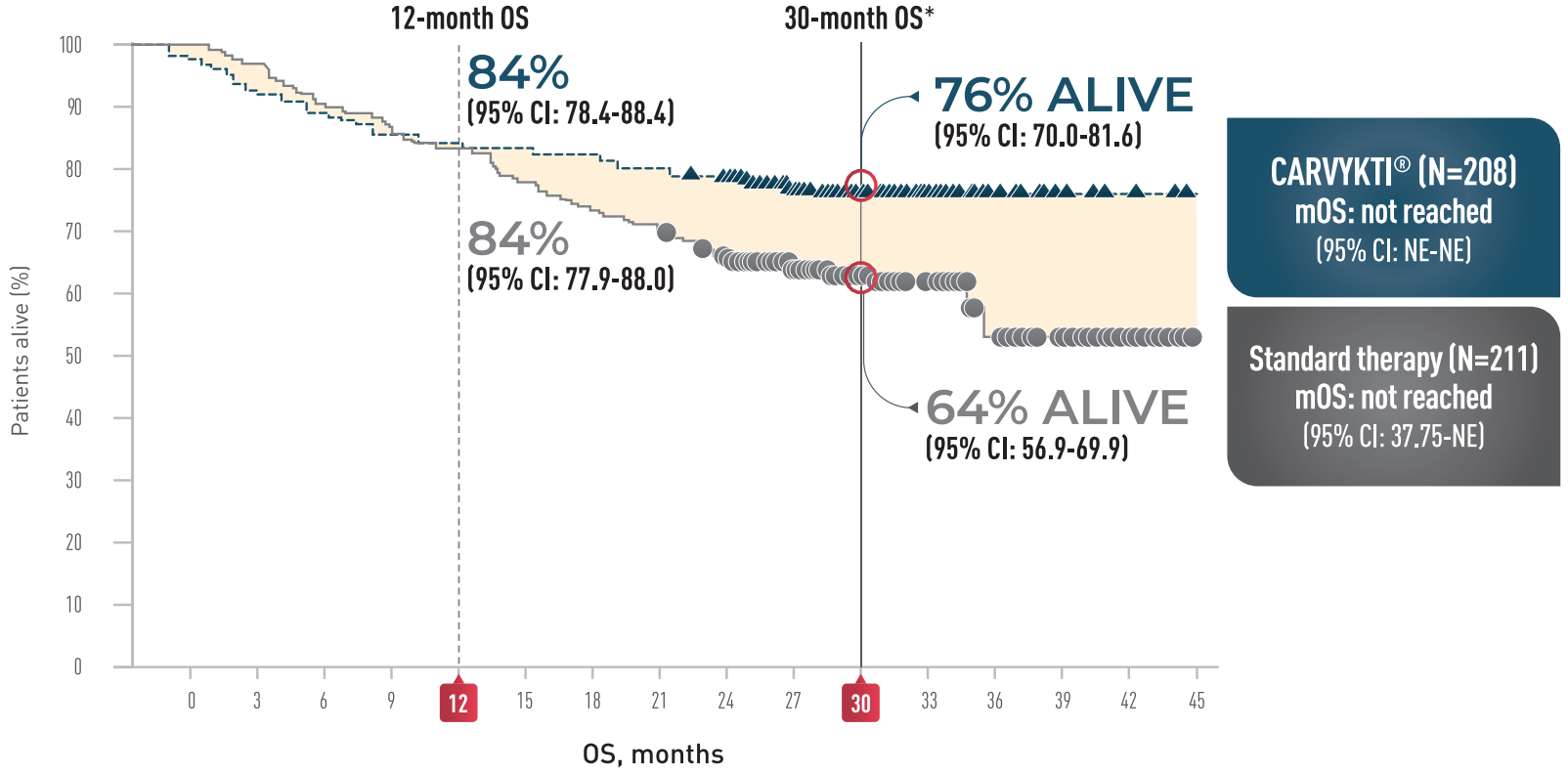
- 34% of the planned OS events have occurred
- Within the first 10 months of randomization, a higher proportion of patients in the CARVYKTI® arm died compared with the standard therapy arm

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® 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.

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

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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.

CARVYKTI®
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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

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:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

Marketed by:
Legend Biotech
Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

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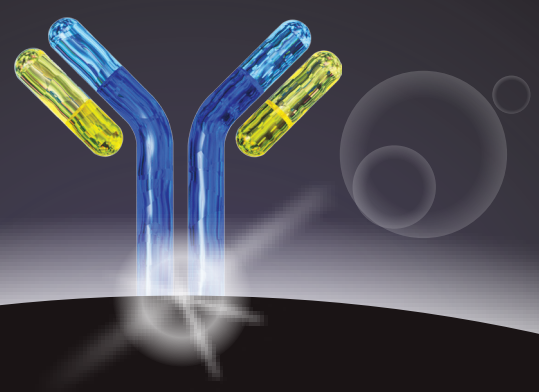
Multiple Myeloma Requires Multiple Targets



In an era of progress, one of the next goal posts is successful development of trispecifics.

*By **Leah Lawrence***

In the last year, results of several phase 1 clinical trials testing trispecific antibodies—proteins engineered to bind to 3 different targets—in the treatment of multiple myeloma (MM) have been presented at major medical meetings, generating excitement about this new class of therapy.

With different targets, each of these therapies is looking to take the concept of combination therapy and make it available through a single drug.

For example, recent results of the RedirecTT-1 trial showed that combining the G protein–coupled receptor, class C, group 5, member D (GPRC5D)–targeting talquetamab and the B-cell maturation antigen (BCMA)–targeting teclistamab yielded a 78.9% response rate in patients with relapsed MM with extramedullary disease.[1]

"Trispecifics ask, 'Can we avoid the use of two drugs and use just one drug? Can we improve the tolerability of this?'" said **Joshua Richter, MD,** associate professor of medicine at The Tisch Cancer Institute at Icahn School of Medicine at Mount Sinai. "We are really excited to see where that is going."

Recent Progress

The first well-documented case of MM occurred almost 200 years ago, with the patient receiving treatment with a rhubarb pill and an infusion of orange peel.[2]

"We have come a long way since then," said **Muhamed Baljevic, MD,** associate professor of medicine, Division of Hematology-Oncology at Vanderbilt University Medical Center. "Our current standards of care have significantly improved, and we now live in an era of front-line so-called quadruplet regimens for both transplant-eligible and -ineligible patients."

These quadruplet regimens—comprising a monoclonal antibody, a proteasome inhibitor, an immunomodulatory drug, and a corticosteroid—provide a "functional cure for a subset of patients," Dr. Baljevic said, "so that patients diagnosed later in life can achieve a 'near-normal' lifespan."

"Unfortunately, despite this progress, we are still not in a place where we can say that we reliably cure the majority of patients," Dr. Baljevic said.

For patients with relapsed or refractory MM (RRMM), similar progress has been made with the introduction of therapies that engage immune T cells. Chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies have both become important options for patients.

Two CAR T-cell therapies are currently being used for patients with MM previously treated with other agents: idecabtagene vicleucel (ide-cel) and

In Focus

ciltacabtagene autoleucel (cilta-cel), both targeting BCMA.[3] Four bispecific therapies are approved by the FDA: three targeting CD3 and BCMA (teclistamab, elranatamab, linvoseltamab) and talquetamab, which targets CD3 and GPRC5D.[4,5]

These new classes of drugs have again transformed the treatment landscape for patients with MM, Dr. Richter said.

"The traditional teaching for myeloma is that every remission will be shorter than the one before," Dr. Richter said. "In the era of bispecifics and CAR T-cell therapy, that concept has been inverted. Some people in their third relapse will have 6-month relapse-free survival, but in their fourth, they will get 18 months because the bispecific is better than the treatment they received third-line."

Long-term results of the CARTITUDE-1 trial of cilta-cel showed a median overall survival of more than 5 years. One-third of patients were alive and progression free for 5 years or longer after undergoing CAR T-cell therapy.[6]

"Historically, this was impossible to imagine," Dr. Baljevic said. "But we need to do much better for the other two-thirds of patients."

"Despite this progress, we are still not in a place where we can say that we reliably cure the majority of patients."

—Muhamed Baljevic, MD, FACP, associate professor of medicine, Division of Hematology-Oncology at Vanderbilt University Medical Center

Trispecifics

A multitude of trispecific or "multi"-specific antibodies are under investigation for MM, with several targeting MM having phase 1 results read out in the last year.

SAR442257 is a trispecific antibody targeting CD3 and CD28, with a myeloma cell–directed third target of CD38. Results from a phase 1 study of SAR442257 were presented at the 2024 American Society of Hematology (ASH) Annual Meeting & Exposition, detailing treatment of 40 patients with RRMM. The overall response rate (ORR) was 5% with a disease control rate of 60%. However, the study was terminated during dose escalation because of safety concerns, including high rates of cytokine release syndrome (CRS), Epstein-Barr virus, and cytomegalovirus reactivations.[7]

Another trispecific under investigation is ISB-2001, which targets CD3 and two targets on the myeloma cells, CD38 and BCMA.

"This molecule can potentially overcome the resistance mechanism associated with traditional bispecific therapies," said **Hang Quach, MBBS**, clinical professor of haematology at the University of Melbourne.

Dr. Quach presented results of a phase 1 first-in-human study of ISB 2001 at the 2024 American Society of Hematology Annual Meeting & Exposition.[8] The study tested subcutaneous ISB 2001 administered with two step-up doses on cycle 1 days 1 and 4 before administering the full target dose in cycle 1 on day 8.

"Among patients who had ISB 2001 at 50 micrograms per kilogram or more, we saw a response rate of 83% with a very good partial response—that is reduction of myeloma burden by 90%—in around one-quarter of patients and a complete response in around in 23% of patients," Dr. Quach said.

Another remarkable finding, Dr. Quach said, was a response rate of about 90% among patients who had no prior treatment with CAR T-cell therapy or bispecific T-cell engagers. "For some perspective," Dr. Quach said, "we would expect a response rate in the order of about 60% with the traditional bispecific antibodies in this group of patients."

Among patients who had prior CAR T-cell therapy or treatment with T-cell engagers, the response rate was about 75%.

Overall, the drug was well tolerated, Dr. Quach said, with a rate of infection and hematologic toxicity that was "much lower than anticipated with T-cell engagers in general," leaving room for potential combination treatment in the future.

A third trispecific under investigation in MM is JNJ-5322, which binds to BCMA, GPRC5D, and CD3.[9] According to Dr. Baljevic, JNJ-5322 may be the "most exciting of the bunch" based on follow-up data and the number of patients treated.

A phase 1 trial of JNJ-5322 included 126 patients who received the drug every 4 weeks with one step-up dose of 5 mg. Thirty-six patients received the recommended phase 2 dose with an ORR of 86.1%. Among the 27 patients with no prior BCMA- or GPRC5D-directed therapies, the ORR was 100% with the phase 2 dose.[9,10]

"In terms of safety, there was a lower incidence of GPRC5D-related adverse events compared with the bispecific, with minimal to no weight loss," Dr. Baljevic said. In addition, CRS rates (59%) were all grade 1 or grade 2, and only 28% of patients had grade 3 or higher infections.[9,10]

Fewer step-up doses and the relatively manageable safety profile make JNJ-5322 particularly appealing for use in the community, Dr. Baljevic said.

Here to Stay?

In the future, approaching MM by going after multiple targets will play a role in effective treatment.

"I think there are two big things we are going to see in the next few years," Dr. Richter said. "One is that trispecifics are definitely going to come into play. The other is that MM, in my mind, is about dance partners. Meaning, although many drugs get approved as monotherapies, there is usually ongoing work to partner those drugs with others to make effective combination therapy approaches." For example, the MonumenTAL-2 study is testing the combination of talquetamab with other anti-myeloma agents.

In addition, like most new classes of drugs that are first tested in the multiply relapsed or refractory setting, bispecifics are slowly making their way to earlier lines of treatment, including frontline approaches.

"We have no reason to think they won't be successful in that area," Dr. Baljevic said. "We do want to make sure there are no treatment-related issues in terms of high toxicities or even deaths in the newly diagnosed patient space. We have fantastic data already and do want to improve on it, but [we are] being mindful about requirements for optimal safety and acceptable cost."

Dr. Richter said, "If more therapies look to target both BCMA and GPC5D, researchers must ask, what is the next big target?"

"To me, that is cevostamab," he added, mentioning an Fc receptor–homolog 5 (FcRH5) bispecific antibody that "facilitates T-cell–mediated killing of multiple myeloma cells."

Last year, Dr. Richter and colleagues presented data from a phase 1 study of cevostamab in patients with heavily pretreated RRMM and found that the drug demonstrated "clinically meaningful activity."[11]

"The message here is that we used to cure no one," Dr. Richter said. "Now we cure some, and we are not going to stop until we cure all."

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Regulatory Actions

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

FDA Approval of Tafasitamab R2 Makes History in Relapsed or Refractory Follicular Lymphoma

*By **Nichole Tucker***

The FDA granted approval to tafasitamab (tafa) combined with rituximab and lenalidomide (R2) for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL). This regulatory action marks the first approval of a CD19- and CD20-targeted immunotherapy for this patient population.[1]

"In a disease that can be highly variable and where most patients experience normal overall survival, it is great to have more well-tolerated non-chemotherapy options that extend remissions. The added physical toxicity of tafa appears to be modest, noting the added time commitment for infusions may be considered by some to be significant," **Ajay Gopal, MD,** director, Clinical Research Division, Fred Hutchinson Cancer Center, professor, Division of Hematology and Oncology, University of Washington School of Medicine, told *Blood Cancers Today*.

Results from the pivotal, randomized, double-blind, placebo-controlled phase 3 inMIND trial support the FDA's decision to grant priority review and then approve the biologics license application for tafa with R2. A 57% reduction in the risk of disease progression or death was demonstrated with tafa plus R2 over R2 alone, showing a statistically significant and clinically meaningful improvement in progression-free survival (PFS).

The results come from 548 patients with relapsed or refractory FL between the ages of 31 and 88 years (median age, 64 years) who had a median of 1 prior line of treatment (range, 1-10). Per investigator assessment, the median PFS with the addition of tafasitamab was 22.4 months versus 13.9 months without (hazard ratio [HR], 0.43; 95% CI, 0.32-0.58; $P<0.0001$).[2]

"The addition of tafa was associated with about a 10% improvement in CR [complete response] rate, an approximately 8.5-month improvement in PFS. The AE [adverse event] profile was similar between the two arms and was mainly attributed to the lenalidomide, though there were modestly higher rates of COVID in the tafa group," said Dr. Gopal. "There was no difference in OS [overall survival] with this duration of follow-up. There did not appear to be any reported biological subgroup that benefited more or less from the addition of tafa. Most patients were treated outside North America."

At the time of their 2024 report, Dr. Gopal and colleagues announced that tafa plus R2 would be a new standard of care for relapsed or refractory FL and could be safely administered in both community and tertiary centers.

The FDA-approved dose of tafa is 12 mg/kg, to be administered via intravenous infusion for up to 12 cycles in combination with R2.

"Tafa provides yet another option for patients who are best suited for or prefer an approach that does not include cytotoxic chemotherapy and are able to devote the time to the additional infusion visits. It also builds toward a 'chemo-free' strategy, a long-term goal for many in the field," Dr. Gopal noted.

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FDA Grants Orphan Drug Designation to SENTI-202 for Relapsed or Refractory AML and MDS

*By **Melissa Badamo***

SENTI-202 has received FDA Orphan Drug Designation for the treatment of relapsed or refractory hematologic malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes.[1]

SENTI-202 is a first-in-class, off-the-shelf, logic-gated chimeric antigen receptor natural killer (CAR-NK) cell therapy that targets CD33 or *FLT3*-expressing hematologic malignancies while sparing healthy bone marrow cells. It is being developed by Senti Biosciences, Inc under their Gene Circuit platform.[1]

The agent is currently being evaluated in a dose-finding phase 1 study, which is utilizing a 3+3 study design to determine the maximum tolerated dose or recommended phase 2 dose of SENTI-202 following lymphodepleting chemotherapy.[1,2]

In a study presented at the American Society of Clinical Oncology 2025 Annual Meeting, SENTI-202 provided "exceptional efficacy" against AML in a humanized mouse model while protecting hematopoietic stem and progenitor cells from off-tumor toxicity.[3] Specifically, treatment with SENTI-202 increased the frequency of hematopoietic stem and progenitor cells compared with inhibitory CAR control NK cells (34.2% vs 18.15% of hCD45+; $P=0.00000355$).[3]

"SENTI-202 continues to demonstrate encouraging promise as a potential treatment option for relapsed/refractory AML, an indication with significant unmet need and a dismal median survival rate of 5.3 months," said **Timothy Lu, MD, PhD,** Senti Biosciences cofounder and CEO, in a press release.[1] "Receiving Orphan Drug Designation for SENTI-202 provides further validation to our novel approach to overcoming AML heterogeneity and protecting healthy cells, and underscores the need for new and effective treatment options."

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Menin Inhibitor Revumenib Under FDA Priority Review for Relapsed or Refractory *NPM1*-Mutated AML

*By **Melissa Badamo***

Revumenib has received FDA Priority Review for its supplemental New Drug Application (NDA) for the treatment of relapsed or refractory, *NPM1*-mutated acute myeloid leukemia, according to a press release from Syndax Pharmaceuticals, the developer of the drug.[1]

The FDA is reviewing the supplemental NDA under its Real-Time Oncology Review program, with a Prescription Drug User Fee Act target action date of October 25, 2025.

The oral, first-in-class menin inhibitor previously received FDA approval in November 2024 for the treatment of relapsed or refractory acute leukemia with a *KMT2A* translocation.

The NDA submission is based on the phase 2 AUGMENT-101 trial published in *Blood*. Updated results were presented at the European Hematology Association 2025 Congress, in which revumenib continued to demonstrate "clinically meaningful responses" in heavily pretreated patients.[2]

Of 77 efficacy-evaluable patients, the rate of complete remission (CR) or CR with partial hematologic recovery (CR+CRh) was 26.0% (95% CI, 16.6%-37.2%), the overall response rate was 48.1% (95% CI, 36.5%-59.7%), and the median duration of CR+CRh was 4.7 months (95% CI, 2.1-8.2). Of the 19 patients who achieved CR+CRh with available measurable residual disease (MRD) status, 12 (63.2%) were MRD negative according to findings from polymerase chain reaction or flow cytometry.[2]

Sixty-six patients (78.6%) in the safety population experienced a treatment-related adverse event (TRAE). Fifty patients (59.5%) experienced a grade 3 or higher TRAE, most commonly QTc prolongation, anemia, febrile neutropenia, differentiation syndrome, and decreased platelet count.[2]

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FDA Approves Linvoseltamab for Adults with Relapsed or Refractory Multiple Myeloma

*By **Nichole Tucker***

Linvoseltamab received accelerated FDA approval for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

Results from the pivotal phase 1/2 LINKER-MM1 study serve as the basis for the approval. In the study, linvoseltamab demonstrated an objective response rate (ORR) of 70% and a complete response (CR) rate of 45%, as assessed by an independent review committee.[2]

"Myeloma has become an increasingly complex space, especially in the relapsed setting. Bispecific antibodies have been approved in one way and utilized in the clinic in a somewhat different way; [they are] given q2 and q4 weeks in non-standard/non-studied ways. This approval allows for planned q2 and q4 week dosing with preplanned analysis and confirmation of a more optimal strategy. With monthly dosing built in at week 24, we allow patients to only have to come into the clinic once a month for extremely effective therapy," **Joshua Richter, MD,** associate professor of Medicine, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Mount Sinai, told *Blood Cancers Today*.

Notably, the median time to response was less than a month (0.95 months [range, 0.5-6 months]). Responses appeared durable with the median duration of response (DOR) not reached (95% CI, 12 months to not estimable). There was an 89% estimated DOR at 9 months (95% CI, 77-95 months) and an estimated 12-month DOR rate of 72% (95% CI, 54-84 months).[2]

Safety results showed that 95% of patients in the study experienced treatment-emergent adverse events (TEAEs), of which 66% were grade 3 or higher. The most common any-grade TEAEs included cytokine release syndrome (37%), fatigue (32%), and anemia (28%). Two patients in the study developed grade 3 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).[2]

"The rates of CRS and ICANS are somewhat lower for this asset when compared with others. However, given the recent NCCN inclusion of prophylactic tocilizumab to reduce rates of CRS with bispecifics, we can utilize this approach to even further reduce the incidence of adverse events," Dr. Richter explained.

Based on the safety findings in LINKER-MM1 being consistent across the dose levels explored in phase 2, the FDA approved the 200 mg dose to be administered weekly until week 14, when patients transition to a bi-weekly treatment. The approval includes a box warning for the potential for common TEAEs and common laboratory abnormalities, including decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin, and decreased white blood cell count, which occur in 30% of patients.

Linvoseltamab joins two other bispecific T-cell-engaging antibodies approved for RRMM. "Because there are subtle but important differences in the studies, it is difficult to compare one drug to another," Dr. Richter said. "That being said, linvoseltamab seems to have the highest ORR and the lowest CRS rate, making it a phenomenal option. Furthermore, the step-up strategy is different, which will require less hospitalization, which is favorable on all sides."

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FDA Fast Tracks SGR-1505 for Relapsed Waldenström Macroglobulinemia

*By **Melissa Badamo***

SGR-1505, an oral investigational MALT1 inhibitor, has received FDA Fast Track Designation for the treatment of adult patients with relapsed or refractory Waldenström macroglobulinemia (WM) after at least two lines of therapy, including a Bruton's tyrosine kinase inhibitor.[1]

SGR-1505 has shown promising efficacy and safety in an ongoing, phase 1 dose-escalation study. Safety and tolerability data of 33 patients with relapsed or refractory B-cell malignancies, including four patients with WM, were presented at the European Hematology Association 2025 Congress.[2]

All three patients with WM who had at least 1 year of follow-up achieved objective responses across five dose levels, including one with a partial response and two with a minor response as per the 6th International Workshop on WM guidelines. Investigators observed no dose-limiting toxicities, treatment-related serious adverse events, or deaths related to adverse events.[2]

"Despite the continued therapeutic advances in the treatment of hematologic malignancies, treatment failure and disease progression due to *BTK* resistance remains a challenge for a growing number of patients," said **Karen Akinsanya, PhD,** president, head of therapeutics R&D, and chief strategy officer, partnerships at Schrödinger, in a press release.[1] "This unmet need represents an opportunity for novel mechanisms such as MALT1 as monotherapy and as part of new combination regimens."

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FDA Plans to Use AI to Streamline Approval Processes

*By **Sara Karlovitch***

The FDA plans to use generative artificial intelligence (AI) to streamline the approval process, according to an article by Commissioner **Martin A. Makary, MD, MPH,** and Center for Biologics Evaluation and Research (CBER) Director **Vinayak Kashyap Prasad, MD, MPH,** published in *JAMA*.

Generative AI may be able to make an initial review of documentation submitted as part of the application, which can exceed 500,000 pages, and assist in the generation of standardized tables. To support AI development, the agency plans to change its approach to the technology.[1]

Martin A. Makary, MD, MPH

"The FDA will also modernize how it reviews AI-based technologies. A diversity of use cases and rapid changes in technology make the legacy review mechanism appear byzantine," the authors wrote. "Rethinking our approach to AI, balancing safety and accuracy while fueling innovation, is a leading FDA priority."

On May 8, 2025, the agency implemented an AI-assisted scientific review pilot, with plans to scale the use of the technology across all FDA centers by the end of June. The tool is intended to allow experts to spend less time on repetitive tasks which can slow down the review process. While all centers will be operating on a common generative AI system integrated into internal data platforms by June 30, the system will be tailored to fit the needs of each center after that date. Further changes will focus on expanding use cases and improving functionality.[2]

Vinayak Kashyap Prasad, MD, MPH

The tool, known as Elsa, was launched June 2, 2025. Elsa was built using the GovCloud system, allowing users to access internal documents. The tool is able to summarize adverse events, perform label comparisons, and generate code for nonclinical application databases. The agency plans to push its AI use beyond Elsa, eventually integrating the technology into processes including data processing.[3]

The FDA's AI vision was outlined in an opinion piece titled, "Priorities for a New FDA." Other subjects touched upon in the piece include healthier food for children and speeding up the review process for life-threatening diseases, among other topics.

Beyond increasing the efficiency of the approval process, the FDA has created a roadmap to use AI-based computational models to predict toxicity-leveraging chip technology to reduce the need for animal testing. There is a possibility AI could better predict toxicity in humans, while also reducing waste and speeding up drug development.

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VERONA MDS Trial: Venetoclax Plus Azacitidine Did Not Meet Overall Survival Primary End Point

*By **Andrew Moreno***

AbbVie has released an update regarding results of the VERONA phase 3 clinical trial, an international randomized controlled trial designed to compare oral venetoclax plus azacitidine with placebo plus azacitidine for newly diagnosed higher-risk myelodysplastic syndromes (MDS).

The company reports that the VERONA trial did not meet its primary end point for overall survival outcomes, having a hazard ratio of 0.908 (stratified log-rank, $P=0.377$), but no new safety signals were observed. The results from this trial will be released via presentation at a future medical congress or through publication.

Venetoclax is under development by AbbVie and Roche and is marketed as VENCLEXTA and VENCLYXTO. It is a first-in-class agent with a mechanism of action of binding and inhibiting the B-cell lymphoma-2 (BCL-2) protein to re-enable the apoptosis process in blood cancer cells.

Venetoclax currently has regulatory approvals in more than 80 countries, including the US. Its indications for use include treatment for adults who have chronic lymphocytic leukemia or small lymphocytic lymphoma. It is also used in combination with azacitidine, decitabine, or cytarabine to treat acute myeloid leukemia in adults aged 75 years and older who are unable to receive standard chemotherapy.

AbbVie mentions in its update that these newly reported data from VERONA do not affect any of the currently approved indications for venetoclax. In addition, any patients who received the venetoclax plus azacitidine combination while they were enrolled in an MDS clinical trial will be informed by their managing physician.

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International Collaboration Yields a Model to Predict Risk in Early-Stage cHL

*By **Andrew Moreno***

An individualized risk prediction model has been developed for adult patients with early-stage classic Hodgkin's lymphoma (cHL). The model, termed the *Early-stage Hodgkin International Prognostication Index (E-HIPI),* was jointly developed by researchers from RWJBarnabas Health, Rutgers Cancer Institute of New Jersey, Tufts Medical Center, and The University of Manchester. RWJBarnabas Health and Rutgers Cancer Institute issued a press release announcing the new model.

John Radford, MD, FMedSci

Andrew M. Evens, DO, MBA, MSc

With their international research partners, RWJBarnabas Health, Rutgers Cancer Institute, and Tufts Medical Center previously developed the Advanced-stage Hodgkin lymphoma International Prognostication Index (A-HIPI), a model for predicting 5-year progression-free and overall survival in adults with advanced cHL.

The E-HIPI was developed using data from 3,000 adult patients with early-stage cHL in four international phase 3 clinical trials. The model estimates patients' 2-year progression-free survival using objective measurements and laboratory test results that are routinely recorded for patients in the clinic.

In a validation study, the E-HIPI was tested in more than 2,300 patients with early-stage cHL from two real-world registry cohorts and showed favorable performance results. Findings were published in the *New England Journal of Medicine* (*NEJM*) Evidence and presented at the 18th International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland. At ICML, the results were presented by study co–first author **Andrew M. Evens, DO, MBA, MSc,** system director of Medical Oncology and oncology lead at RWJBarnabas Health Medical Group and deputy director for clinical services at Rutgers Cancer Institute.

"Through this global collaboration with researchers at Tufts Medical Center, The University of Manchester in the United Kingdom, and all our international partners, we developed a robust, dynamic, and data-driven model that leverages common clinical variables to generate more precise predictive insights," Dr. Evens remarked.

The development and validation study of the E-HIPI model received substantial support from the Hodgkin Lymphoma International Study for Individual Care (HoLISTIC) Consortium. The Consortium provides access to global data from randomized clinical trials and cancer registries and continues to be a major resource for the researchers' ongoing work to develop the E-HIPI model.

"The success of this effort underscores the power of cross-border partnership, and its potential to deliver meaningful, real-world benefits to patients with Hodgkin's lymphoma worldwide," commented study co–senior author, **John Radford, MD, FMedSci,** of The University of Manchester, The Christie NHS Foundation Trust, and the Manchester Biomedical Research Centre under the National Institute for Health and Care Research in the UK.

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Ruxolitinib Tops Best Therapy in Steroid-Refractory cGVHD

*By **Nichole Tucker***

Ruxolitinib treatment has resulted in durable clinical benefit among patients with steroid-refractory/dependent chronic graft-versus-host disease (GVHD) treated in the phase 3 REACH3 study. In comparison with best available therapy (BAT), a favorable benefit/risk ratio was observed with ruxolitinib in this study.[1]

Stephanie Lee, MD, MPH

"About half of [the] people developing chronic GVHD have steroid-refractory/steroid-dependent disease. We know that this challenging population often receives multiple other lines of therapy and requires years of treatment. REACH3 showed that ruxolitinib treatment results in high response rates that are frequently durable," **Stephanie Lee, MD, MPH,** a hematologist and blood and marrow transplant physician-scientist serving as professor and associate director in the Clinical Research Division at Fred Hutch Cancer Center, told *Blood Cancers Today*.

REACH3 randomly assigned 329 patients with chronic GVHD to receive either ruxolitinib 10 mg (n =165) or BAT (n=164). Patients were followed up for a median of 73.1 months (1.9-169.0 months) in the ruxolitinib arm and 26.1 months (1.0-171.6 months) in the BAT arm.

Patients treated with ruxolitinib had a median failure-free survival (FFS) of 38.4 months compared with only 5.4 months with BAT (hazard ratio [HR], 0.36; 95% CI, 0.27-0.49). No difference in risk for death was observed between the two treatment arms (HR, 0.85; 95% CI, 0.54-1.33).

The median duration of response (DOR) was not reached for ruxolitinib versus 6.4 months (95% CI, 4.9-11.4 months) for the BAT arm, and patients who received ruxolitinib were more likely to sustain a response up to 36 months. Notably, 3 of the 21 patients who tapered off ruxolitinib experienced disease recurrence.

"This study allowed crossover from the BAT to the ruxolitinib arm. It looks like [the] results after crossover were similar between patients originally assigned to ruxolitinib and those who received it after first getting BAT," explained Dr. Lee. "The study wasn't designed to look at what happens after ruxolitinib was tapered off after patients responded, but it is reassuring that chronic GVHD recurrence rates were <15%."

Patients included in the crossover analysis set had an overall response rate of 50.0 (95% CI, 37.8%-62.2%) and a best overall response of 81.4% (95% CI, 70.3%-89.7%).

"With much longer follow-up, no new safety signals were seen," Dr. Lee added. "This is important because people with chronic GVHD require prolonged treatment so, it is critical that any agent used for chronic GVHD is safe and tolerable with extended administration."

To date, there is an unmet need for new options beyond corticosteroids, according to Dr. Lee and colleagues. Considering that ruxolitinib is already an FDA-approved option for chronic GVHD in later-line settings, ruxolitinib may one day be an option in the first-line.

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Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, section editor* ***Uma Borate, MBBS,*** *associate professor in the Division of Hematology at The Ohio State University, highlights recent research in myelodysplastic syndromes.*

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

Uma Borate, MBBS

MDS

Bexmarilimab Data Support Next Phase in MDS Trial

By ***Nichole Tucker***

The Clever-1 inhibitor, bexmarilimab, showed promising clinical efficacy in patients with myelodysplastic syndrome (MDS) and high-risk features in the phase 2 BEXMAB study. Findings were presented by **Mika Kontro, MD,** of Helsinki University Hospital Comprehensive Cancer Center, during the European Hematology Association 2025 Congress in Milan, Italy.

"When we use bexmarilimab to inhibit Clever-1, we see enhanced expression of antigen-presenting molecules, enhanced cytokine production, and also, importantly, elevated T-cell levels and activation," said Dr. Kontro during his EHA presentation.

In the phase 2 study, treatment with bexmarilimab achieved an 85% objective response rate (ORR) in patients with frontline MDS (International Working Group [IWG] 2006) and a 55% ORR among those with frontline MDS (IWG 2023). In patients with relapsed or refractory MDS who failed prior hypomethylating agents, bexmarilimab treatment led to a 63% ORR (IWG 2006) and 47% ORR (IWG 2023).

"Bone marrow responses were actually observed at all dose levels, between milligram per kilogram, so we need a more favorable profile at this point. Now, when looking at the frontline cohort, we saw a reduction in bone marrow blast in most patients according to 2023 criteria," explained Dr. Kontro.

In terms of survival, the study showed a median overall survival (OS) of 13.4-month (95% CI, 4.8 months to not reached [NR]) in the high-risk, relapsed or refractory MDS population. Moreover, patients with *TP53* mutations had a median OS of 9.3 months (95% CI, 2.5-14.5 months), and in the *TP53* wild-type population, the median OS was NR (95% CI, 4.6 months-NR). Researchers had not yet reached median OS in the frontline MDS population at the time of data cutoff.

Constipation occurred most frequently as a treatment-related adverse event (TEAE; 35.9%). Other common TEAEs included neutrophil count decreased (35.9%), white blood cell counts decreased (32.1%), and anemia (30.2%). Treatment discontinuations from treatment-emergent adverse events (TEAEs) occurred in 13.2% of patients.

One patient from the study discontinued treatment due to a bexmarilimab-related AE. There were no grade 5 or higher events reported. However, immune-related AEs occurred in 3.7% (n=2) of patients, both in the high-risk relapsed or refractory MDS population.

"We currently have quite strong data with regard to safety and efficacy, supporting advancing into the phase 3 trial," Dr. Kontro stated.

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1. Presented at the European Hematology Association 2025 Congress. Abstract No. S178.

Why I chose this research:

"Comparing bexmarilimab dose levels, this abstract reported safety and efficacy data on 20 frontline high-risk MDS and 35 relapsed or refractory MDS patients. An overall response rate of 100% in 5 frontline patients and 80% in 20 relapsed or refractory patients was reported, with a median overall survival estimate of 13.4 months for the relapsed or refractory population. During dose escalation, no dose limiting toxicities were reported. This may indicate a promising therapy for high-risk and relapsed or refractory MDS where we do not have any options currently approved other than HMA therapy."

Luspatercept Brings Reduced Need for Healthcare Resources to Manage MDS Versus ESAs

By ***Andrew Moreno***

In the management of lower-risk myelodysplastic syndromes (MDS), patients have a markedly less need to utilize healthcare resources if the disease is treated with luspatercept rather than erythropoiesis-stimulating agents (ESAs). This is the conclusion supported by the results of a first-of-its-kind, real-world database study published in the *Journal of Medical Economics*.

"Treatment with luspatercept was associated with significantly lower rates of both all-cause inpatient visits and all-cause outpatient visits, as well as lower rates of MDS-related inpatient visits, compared with treatment with ESA," wrote first author **Brian Ball, MD,** of City of Hope National Medical Center, Duarte, California, and colleagues.

This retrospective study was conducted in the US using data from the Symphony Health Integrated Dataverse, a large and nationally representative healthcare claims database. The investigators compiled claims filed by patients with lower-risk MDS who initiated either luspatercept or an ESA to treat the disease between May 1, 2020, and June 30, 2022.

The data for analysis were from 243 patients who received luspatercept to manage MDS and 3,515 patients treated with an ESA. The median age at first claim was 77 years in the luspatercept group and 78 years in the ESA group, and the median follow-up duration was 14.6 months in the luspatercept group and 14.4 months in the ESA group.

The investigators compared the two patient cohorts' respective all-cause and MDS-related healthcare resource utilization using generalized estimating equations. They found that patients in the luspatercept group had a 26% lower rate of all-cause inpatient visits and a 31% lower rate of all-cause outpatient visits than patients in the ESA group, with adjusted incidence rate ratios (aIRRs) of 0.74 ($P<0.05$) and 0.69 ($P<0.001$), respectively. Patients in the luspatercept group also had a 25% lower rate of MDS-related inpatient visits versus patients in the ESA group, with an aIRR of 0.75 ($P<0.05$).

"Further research is necessary to evaluate the financial impact of this lower HRU [healthcare resource utilization] burden among patients who initiated luspatercept more recently," Dr. Ball and colleagues concluded.

Why I chose this research:

"This study compared the healthcare utilization in patients treated with ESAs compared with luspatercept and demonstrated a 26% lower rate of all-cause inpatient visits and a 31% lower rate of all-cause outpatient visits. The rate of MDS-related inpatient visits was also 25% lower among patients treated with luspatercept versus ESA. This study suggests that luspatercept may have additional systemic benefits beyond transfusion independence in patients with lower-risk MDS."

Reference

1. Ball BJ, et al. *J Med Econ.* 2025 Dec;28(1):719-725. doi: 10.1080/13696998.2025.2498852.

COMMANDS: Luspatercept Boosts Survival in ESA-Naive MDS

*By **Nichole Tucker***

Treatment with luspatercept in patients with first-line, erythropoiesis-stimulating agent (ESA)-naïve lower-risk myelodysplastic syndrome (MDS) achieved more durable responses compared with epoetin alfa, according to updated results from the phase 3 COMMANDS trial. Results also showed a trend toward overall survival (OS) advantage for luspatercept-treated patients, and no new safety concerns arose.

Valeria Santini, MD, chair of the Myelodysplastic Syndromes Unit at the University of Florence in Italy, presented the results during a session on prognostication and innovative treatment in MDS at the European Hematology Association 2025 Congress.

"This is the first time that we can show a significant advantage in terms of overall survival in patients with lower-risk MDS, transfusion dependency, receiving luspatercept versus epoetin alfa," Dr. Santini said during her presentation.

The median follow-up for the current analysis was 29.0 months in the luspatercept arm and 27.1 months in the epoetin alfa arm. Among the 182 patients treated with luspatercept, the median OS was not reached, when compared with 46.7 months in the epoetin alfa arm (HR, 0.86; 95% CI, 0.60-1.24).

The 3-year OS rates were 63.8% in the luspatercept-treated population versus 62.2% in the epoetin alfa population. At 4.5 years, the OS rates were 58.9% versus 41.8%, respectively. The signal for OS improvement with luspatercept versus epoetin alfa was similar in the subgroups evaluated in the study.

Dr. Santini said, "There was a clear trend of an advantage of survival in patients treated with luspatercep. The median overall survival for the luspatercept group is not reached, [while] the median survival for the group treated with epoetin alfa [was] 46 [months]."

Red blood cell transfusion independence (RBC-TI) greater than or equal to 12 weeks was shown in 76.4% of those treated with luspatercept versus 55.8% of those treated with epoetin alfa.

Why I chose this research:

"This abstract addressed the impact on overall survival (OS) in the intention-to-treat population, where the median OS was not reached for the luspatercept arm and 46.7 months for the epoetin alfa arm. The 3-year OS rates were 63.8% and 62.2%, respectively, and 4.5-year OS rates were 58.9% and 41.8%. While this study was not powered to detect a survival benefit, the impressive trend of increased OS with the luspatercept arm may indicate additional benefits of luspatercept therapy that may extend beyond transfusion independence."

"The median duration of the transfusion independence is 126 weeks versus 86 weeks… very significant prolongation," said Dr. Santini.

There was a 187.3-week median cumulative duration of RBC-TI greater than or equal to 12 weeks in the luspatercept arm compared with the epoetin alfa arm and had a median duration of 94.9 weeks (HR, 0.51; 95% CI, 0.34-0.77).

With 24.7% of the luspatercept remaining on treatment at data cutoff versus 11.2% of the epoetin alfa arm, dose escalations were rare—specifically, 84.6% of the luspatercept arm versus 82.7% of the epoetin alfa group.

According to Dr. Santini and colleagues, longer follow-up is necessary to confirm these updated results from the COMMANDs trial.

"Even with a follow-up of more than two and a half years, luspatercept still continues to improve response rate, longer duration of response, and significantly more patients achieve transfusion independence longer than 12 weeks," she said.

Reference

1. Presented at the European Hematology Association 2025 Congress. Abstract No. S177.

Driven by His Patients, a Veteran Oncologist Pushes for Innovation in Blood Cancer

*By **Katie Kosko***

Few would guess that **Michael Styler, MD,** a distinguished hematologist-oncologist, is also a master chess player. But the two titles have more similarities than one might expect. Dr. Styler thrives in environments that demand strategic thinking, pattern recognition, and the ability to make high-stakes decisions under pressure.

In the halls of Fox Chase Cancer Center in Philadelphia, Pennsylvania, Dr. Styler is known as a beacon of hope for his patients as he weighs the best treatment options and stays several steps ahead of potential outcomes.

Michael Styler, MD

Dr. Styler was drawn to medicine—and hematology in particular—by a fascination with genetics and molecular biology and the ways in which they are interconnected.

Recognized this year by the National Comprehensive Cancer Network (NCCN) with its 2025 *Outstanding Contributor Awards,* Dr. Styler was honored for his commitment to improving cancer care, which he has been passionate about for more than 40 years. He serves as a member of the NCCN Guidelines Panel for Chronic Myeloid Leukemia and has served as a volunteer member of the NCCN Chemotherapy Order Templates Committee. Dr. Styler's contributions and thoughtful insight have helped to significantly expand the library of blood cancer templates, according to an NCCN press release.

Patient-Centered Care

Born in Pottsville, Pennsylvania, he earned his medical degree from the Medical College of Wisconsin in Milwaukee in 1984. He then headed back east, where he interned for a year at Hahnemann University Hospital in Philadelphia, Pennsylvania. Dr. Styler stayed at the institution for his fellowship in hematology/oncology from 1988 to 1991.

"Prior to hematology, I was debating being a cardiologist based on family history," Dr. Styler said in an interview with *Blood Cancers Today*. "But then I fell in love with hematologic malignancies, such as leukemia and lymphoma. At the time I started out, we had our best successes in these areas, and they also tied in with my interest in the molecular science."

Dr. Styler, an associate professor in the Department of Bone Marrow Transplant and Cellular Therapies, spends most of his days caring for patients, whom he described as the driving force that keeps him inspired.

"I consider myself primarily a clinician. I like to take care of patients," Dr. Styler said. "To see success with my individual patients and to allow them to return to living a normal life are some of my most meaningful contributions to hematology."

In addition to day-to-day patient care, Dr. Styler has dedicated himself to advancing cutting-edge research over the span of his career. He participated in some of the earliest studies exploring haploidentical transplants. "Prior to joining Fox Chase, he was leading the Bone Marrow Transplant program at Hahnemann, which had pioneered bone marrow transplants in Philadelphia," said **Asya Nina Varshavsky-Yanovsky, MD, PhD,** who works alongside Dr. Styler in the Department of Bone Marrow Transplant and Cellular Therapies. "Not only has he been an immense source of mentorship and expertise, but also a very kind person who's always willing to help."

His clinical trial work also expands into multiple myeloma, a blood cancer that develops in plasma cells in the bone marrow. One study that he is particularly proud of explores the use of an antibody after autologous transplant to see whether it results in better and longer remissions for patients.

Despite the slow pace of advancement in acute leukemia, Dr. Styler is drawn to the disease's complexity and has contributed to several clinical trials investigating new treatment approaches for this challenging disease. One ongoing trial, still in its early stages, is evaluating the use of a targeted therapy to treat a specific subtype of acute leukemia.

Revolutionizing the Field

Over the years, Dr. Styler has had a front row seat for the evolution of hematologic malignancy treatment. He pointed out the remarkable progress in chronic myeloid leukemia (CML), for which bone marrow transplant was once the standard of care and often came with significant toxicities for patients. Today, because of oral targeted therapies, many patients with CML can lead normal lives—and in some cases be cured—with less disruption to their quality of life.

As treatments have become less toxic, they have become available to a broader group of patients.

"When I first started out, if someone was much over 50 years old, we wouldn't consider an allogeneic transplant," Dr. Styler said. "Nowadays, we will do them for patients in their 70s and, in select patients, even their 80s."

Dr. Styler envisions a future in which gene therapy, bispecific antibodies, and cellular therapies such as chimeric antigen receptor (CAR) T-cell therapy (CAR-T) play significant roles in treating blood cancers.

"CAR-T is an exciting area that will further revolutionize our field in the near future," Dr. Styler said. "We're hopeful for longer, durable remissions and less toxic therapy."

Looking ahead, he believes that gene therapy may eventually replace bone marrow transplantation altogether, offering a more precise treatment option for many patients with blood cancers.

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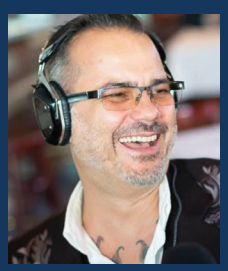

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