TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

bct BLOOD CANCERS TODAY

May 2025

bloodcancerstoday.com

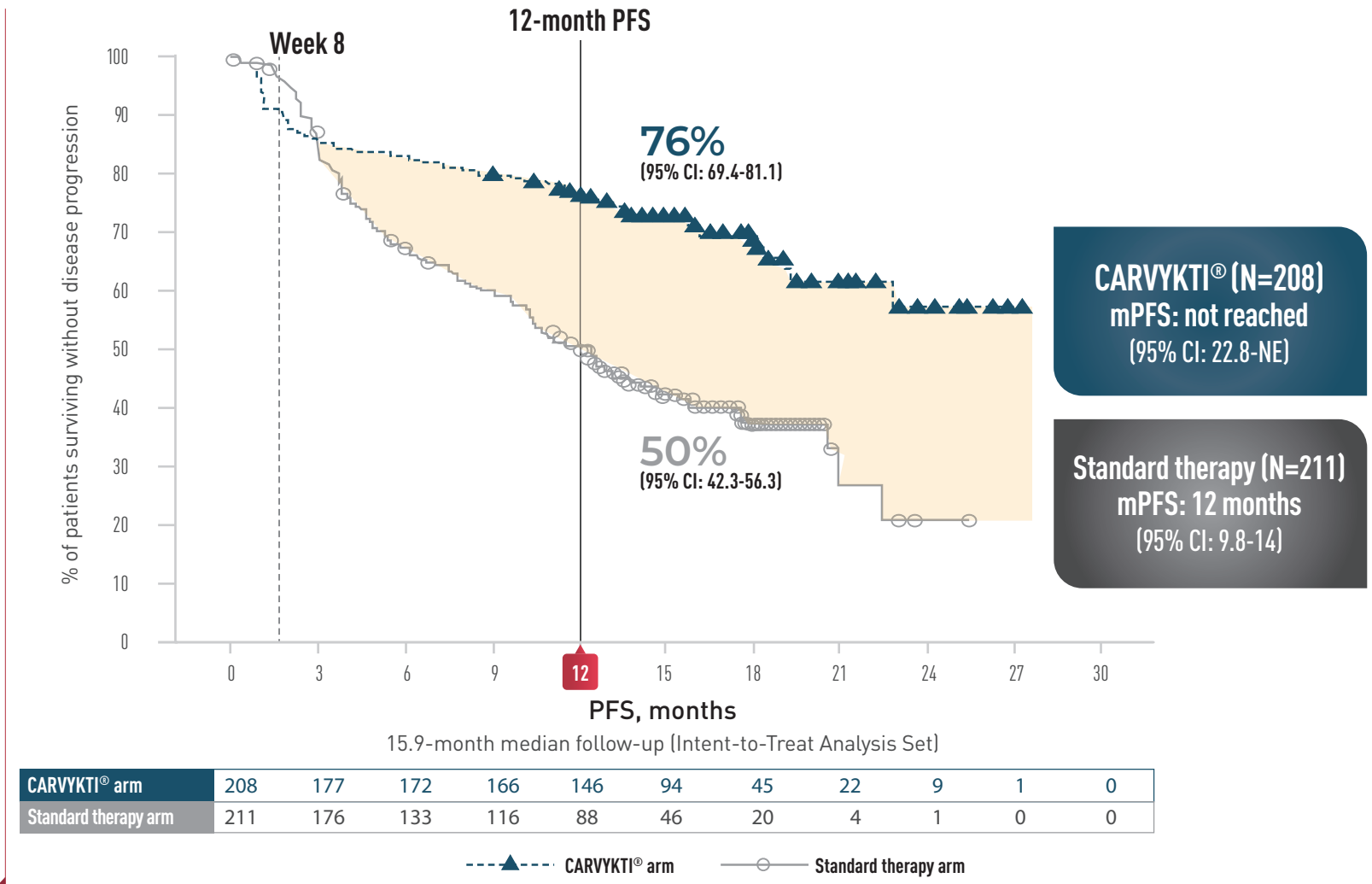
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

POWERFUL RESULTS

In CARTITUDE-4 AT 15.9 MONTHS

CARVYKTI® SIGNIFICANTLY PROLONGED PROGRESSION-FREE SURVIVAL VS STANDARD THERAPY (DPd or PVd)[1]*

PROGRESSION-FREE SURVIVAL



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® 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]*

Percentages rounded to nearest whole number.
CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; mPFS=median progression-free survival; NE=not estimable; PFS=progression-free survival; PVd=pomalidomide, bortezomib, and dexamethasone.
*15.9 months follow-up (Intent-to-Treat Analysis Set).

SELECTED IMPORTANT SAFETY INFORMATION

Fatal or life-threatening reactions occurred in patients following treatment with CARVYKTI® including Cytokine Release Syndrome (CRS), Parkinsonism and Guillain-Barré syndrome and their associated complications, and Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). HLH/MAS can occur with CRS or neurologic toxicities. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which can be fatal or life-threatening, occurred after treatment, before CRS onset, concurrently with CRS, after CRS resolution, or in absence of CRS. A numerically higher percent of early mortality was observed as compared to the control arm in CARTITUDE-4. Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies occurred following treatment. CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

cp-300288v4

Please see Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information, including Boxed Warning, for CARVYKTI®.

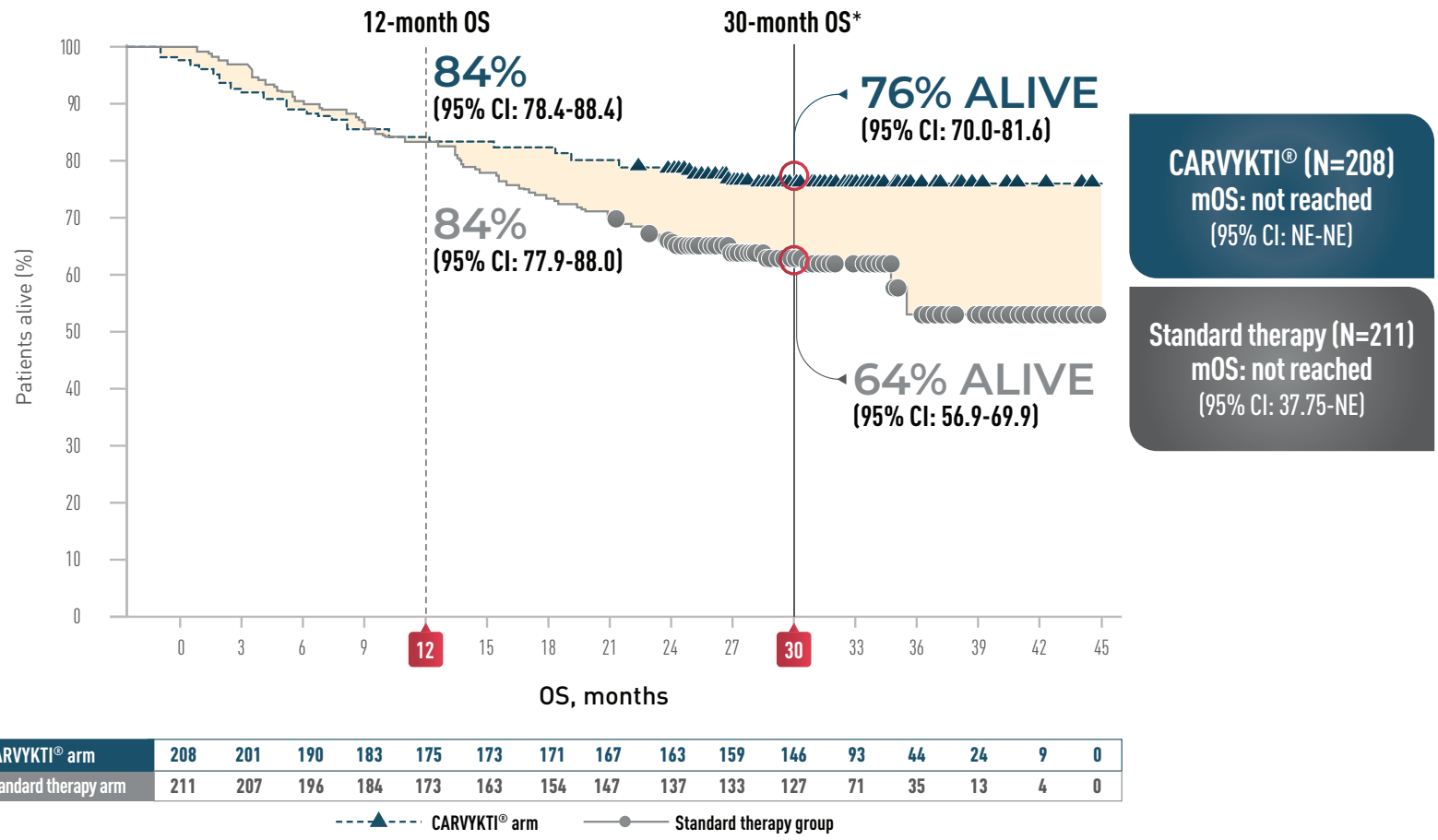
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

CARVYKTI® DEMONSTRATED A STATISTICALLY SIGNIFICANT OVERALL SURVIVAL BENEFIT IN 2L+[2]

IN CARTITUDE-4 AT 33.6 MONTHS*

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=bortezomib, pomalidomide, and dexamethasone; USPI=US Prescribing Information.
*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.
†Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

SELECTED IMPORTANT SAFETY INFORMATION

Fatal or life-threatening reactions occurred in patients following treatment with CARVYKTI® including Cytokine Release Syndrome (CRS), Parkinsonism and Guillain-Barré syndrome and their associated complications, and Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). HLH/MAS can occur with CRS or neurologic toxicities. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which can be fatal or life-threatening, occurred after treatment, before CRS onset, concurrently with CRS, after CRS resolution, or in absence of CRS. A numerically higher percent of early mortality was observed as compared to the control arm in CARTITUDE-4. Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies occurred following treatment. CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

cp-300288v4

Please see Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information, including Boxed Warning, for CARVYKTI®.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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.

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.

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.

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.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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.

cp-258862v9

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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

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.

Johnson&Johnson

LEGEND BIOTECH

TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

bct BLOOD CANCERS TODAY

May 2025

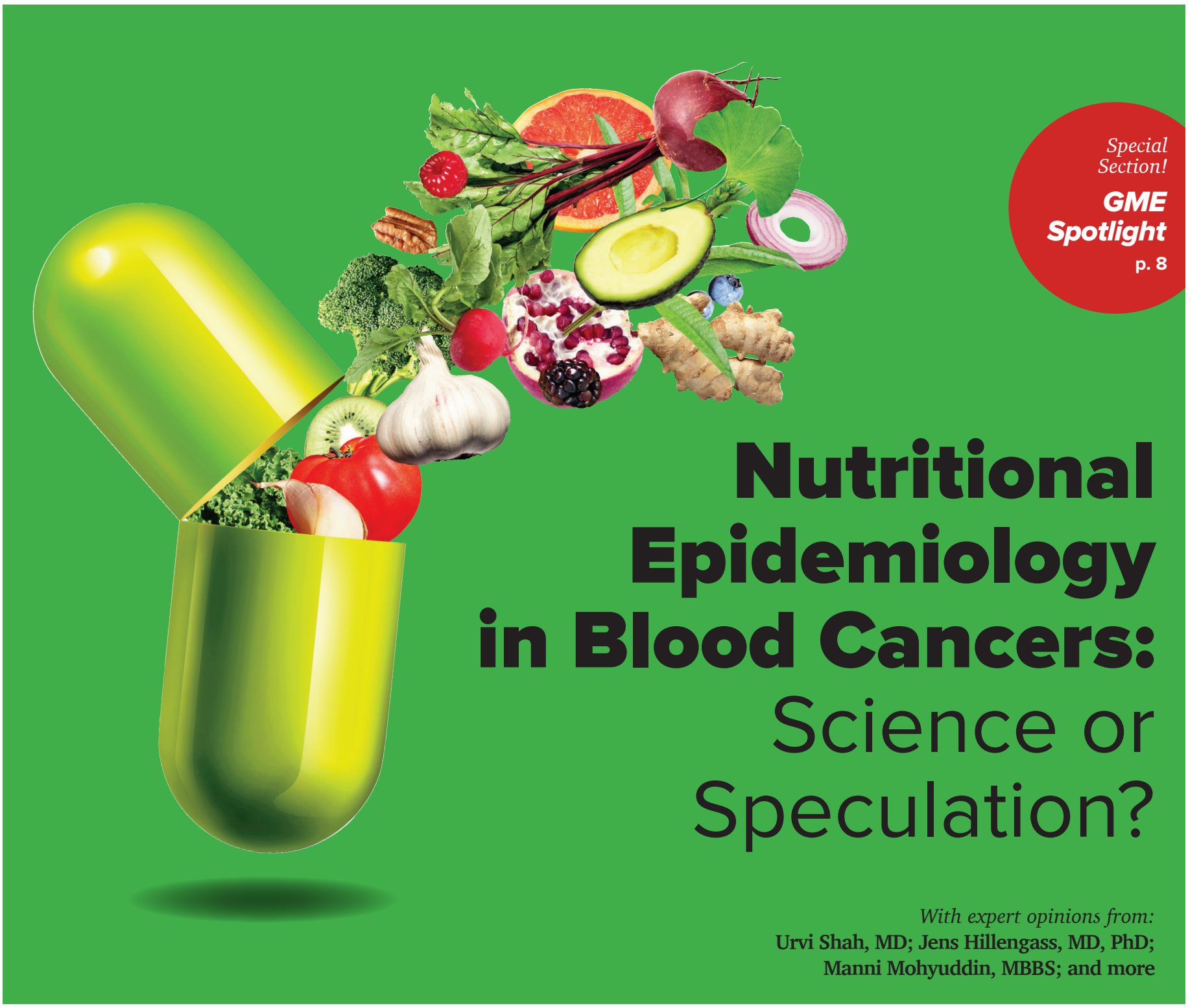
bloodcancerstoday.com

FDA Clears Way for Phase 3 Trial of Linperlisib in Advanced PTCL
p. 10

Unpacking the COA Prescription for Health Care Reform
p. 12

ISB 2001 Yields New Prospects as Multiple Myeloma Treatment
p. 14

ASPHO Recognizes Pediatric Hematologist Oncologists
p. 17



Special Section!
GME Spotlight
p. 8

Nutritional Epidemiology in Blood Cancers: Science or Speculation?

With expert opinions from:
Urvi Shah, MD; Jens Hillengass, MD, PhD; Manni Mohyuddin, MBBS; and more

MAIL TO:

ROBERT STUVER, MD:
Highlighting Recent Research in Hodgkin Lymphoma

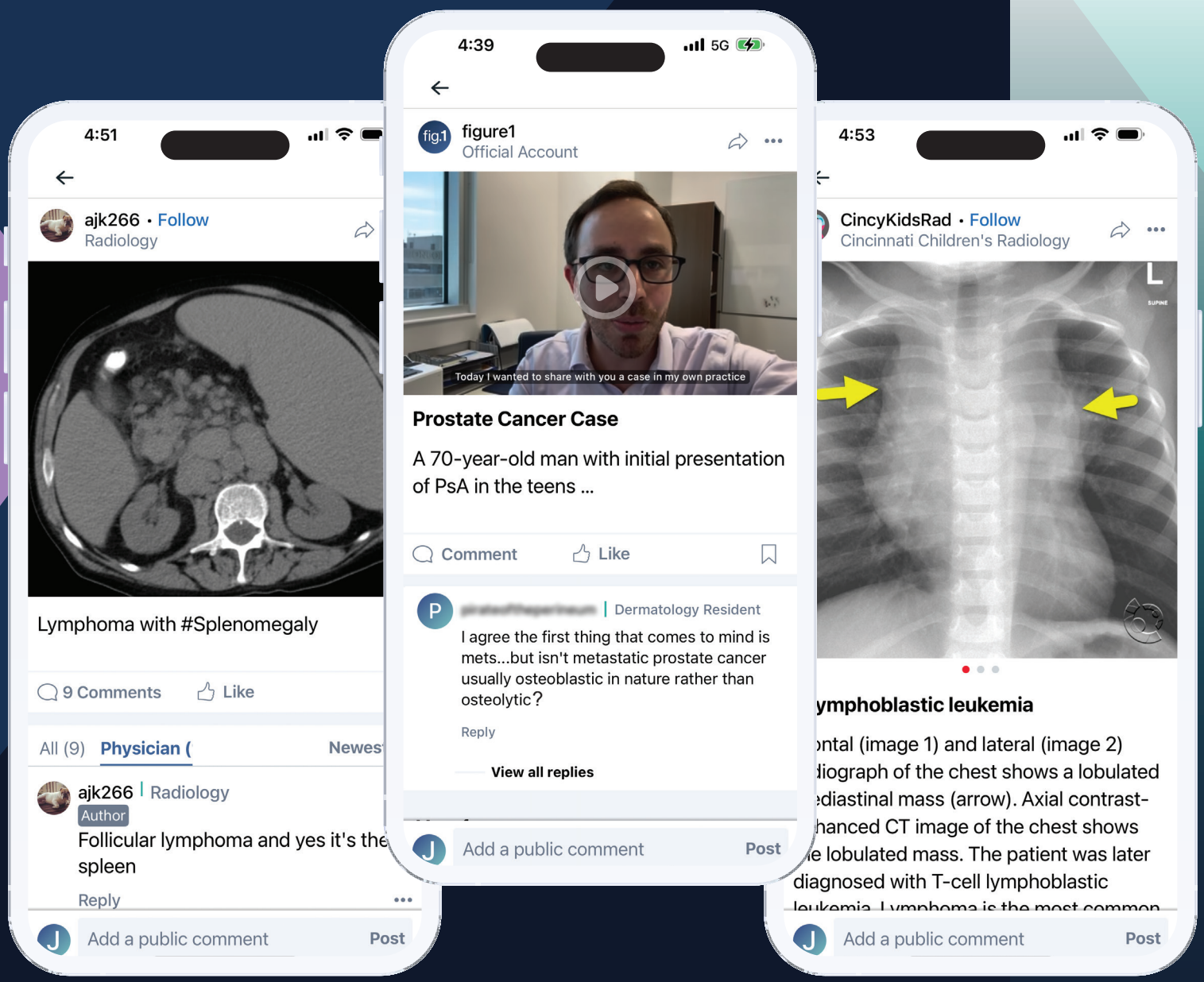
figure1

Where Clinicians Come to Collaborate

New!
Video case posts are here.

Join us as we take clinical social media to the next level!

figure1



CONTENTS

Volume 4 | Number 5 | May 2025

Nutritional Epidemiology in Blood Cancers: Science or Speculation?

News

The HemOnc Pulse

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

GET TO KNOW

Kerry Rogers, MD

Dr. Rogers discussed her career trajectory, her current CLL research, and what being a doctor is about—and even shared a glimpse of her pet guinea pigs, Maple and Brady.
3

ONLINE FIRST

Visit ***bloodcancerstoday*** to read everything we couldn't fit in print.

- New Clinical Trial to Evaluate GPC-100 for the Treatment of AML
- Commercialization Approval Granted to Selinexor for Multiple Myeloma, DLBCL in Indonesia

Sign up to receive our weekly eNewsletters to have the latest headlines delivered to your inbox.

Subscription inquiries should be sent to:
MashupFinance@Formedics.com

Blood Cancers Today is published by Formedics, at 630 Madison Ave., 2nd Floor, Manalapan, NJ 07726.
Printed in the USA.

Calendar

July 24-27
Debates and Didactics in Hematology and Oncology
Sea Island, GA

July 26
Physicians' Education Resource 9th Annual Live Medical Crossfire: Hematologic Malignancies
New York, NY

August 15-16
2025 Seattle Cellular Therapy Summit
Seattle, WA

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

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

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

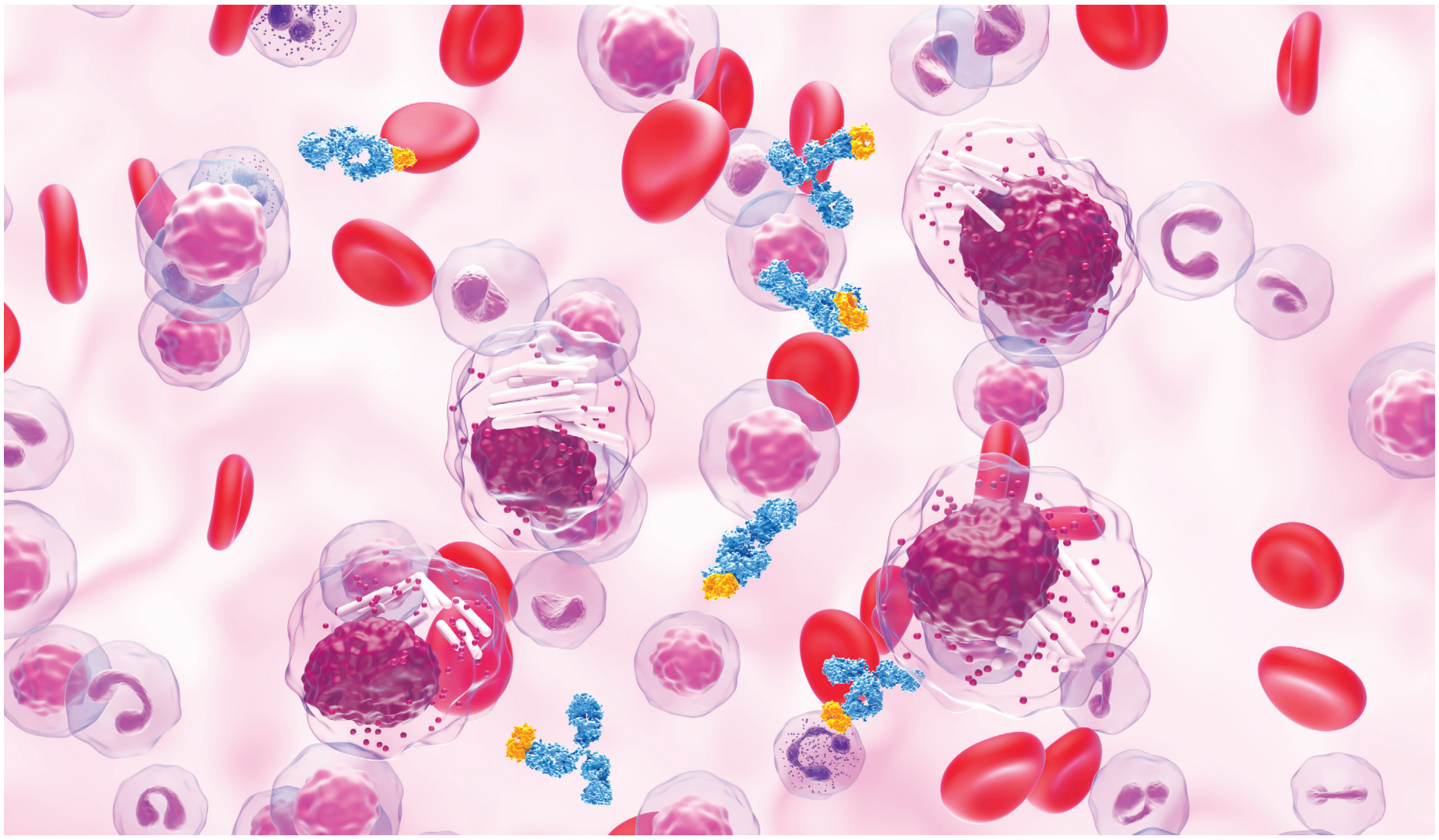
October 10-12
European School of Haematology-International CML Foundation (ESH-iCMLf) 27th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy
Estoril, Portugal

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



Kerry Rogers, MD

Kerry Rogers, MD, an Associate Professor in the College of Medicine at The Ohio State University Comprehensive Cancer Center, sat down with *Blood Cancers Today* to discuss her career trajectory, her current chronic lymphocytic leukemia (CLL) research, and what being a doctor is about—and even shared a glimpse of her pet guinea pigs, Maple and Brady.

*By **Melissa Badamo***

How did you know that you wanted to become a hematologist-oncologist?
When I was a kid, I thought medicine was so interesting. Being a doctor is the combination of science and biology, which I've always liked, and the other half is people and their stories. Medicine is the sometimes-messy interplay of science—or using science to solve problems—and trying to help a person with a problem.

I'm fortunate in my current practice to work at an academic center where we have patients that are very educated about CLL. Sometimes we have people in the community we serve—which is not only Columbus, but the rural surrounding communities—whose health literacy is not as good and don't know much about it. It's fun to try to meet people where they're at.

I've always liked that about medicine. I like helping people and hearing their stories. It's the nature of what being a doctor is. I pursued an undergraduate degree in biological sciences with a concentration in molecular genetics at Northwestern, studying cells and how they work.

At Chicago Medical School, I grew an appreciation for the practice of medicine and hearing people's stories. After medical school, I wanted to have an academic residency experience and went to the University of Michigan. I was drawn to internal medicine, and then specifically hematology and oncology because of the cell molecular biology aspects of the disease. I really liked the patient relationships that I observed there and the way that physicians interact with patients.

I went to Ohio State for fellowship because of their huge hematology program and the opportunities to get involved in some of the academic aspects. I liked what I was doing and the people I worked with. It's a great comprehensive cancer center with a huge cancer hospital. Not many places have a financially

Get to Know

“If you can’t cure something, the next best thing is trying to get people to live with it as well as possible with the least impact on their life.”

freestanding cancer hospital like we do. Having such excellent cancer care in Central Ohio has been really fun to be a part of.

When did you know you wanted to specialize in CLL?
I ended up in CLL during fellowship. I love being a doctor, but research adds a whole other dimension because you can address problems that you’re seeing in your patients through deeper science than just reviewing the literature or using your knowledge of science. You actually get to generate some of that knowledge.

At Ohio State, I got to know the group that was doing CLL and hairy cell leukemia and thought, “This is what I’d like to be a part of.” It was fun and productive, and I liked what I could contribute here. I liked the patient population and that a lot of patients with CLL and hairy cell leukemia are quite well. Even if they’re experiencing a lot of disease symptoms or aren’t doing well right now, the general expectation is that they’ll get to be healthy, functional people for years to come.


Dr. Rogers’ pet guinea pigs, Maple and Brady

I spend more time in my clinic trying to convince people that they’re well than trying to get someone through a severe illness episode. You do still get some patients that are quite sick, so you do have to use that skill set too.

What exciting new research are you working on right now?
The field has been focused on targeted agents for the last 15 years rather than chemotherapies. These targeted agents are safer and more effective. We would love to cure CLL, but we can’t in a feasible way right now. If you can’t cure something, the next best thing is trying to get people to live with it as well as possible with the least impact on their life.

Some patients don’t need treatment and can be observed until they need treatment, but there’s been a lot of focus on making treatments for CLL safer and more effective. I’m really excited about the combination of targeted agents with BTK [Bruton’s tyrosine kinase] inhibitors and BCL-2 inhibitors.

I’m leading a couple of clinical trials in a resistance setting. Patients whose CLL is resistant to targeted agents are taking these combinations, and we’re trying to understand how to best utilize these combinations. They are usually given for a fixed duration, unlike BTK inhibitors, which are given indefinitely until people develop side effects and have to discontinue treatment, or their CLL becomes resistant. It’s been fun to look at these combinations and try to understand how to best utilize these treatments in what combination, and in what order, across someone’s lifespan.

Since 2014, I’ve had a clinical trial of ibrutinib, venetoclax and obinutuzumab as a fixed-duration treatment. We now have data for how people have done over many years to try to better understand how these fixed duration regimens impact people over the whole disease course or lifetime. The major benefit is that people stop treatment and are in remission for years after finishing it, and we’re seeing that you can use those classes of drugs again to treat people. That’s really exciting.

I also have [a] study of pirtobrutinib, a BTK inhibitor that works after covalent BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) have stopped working or the CLL cells are resistant to them. We have a single institution study looking at a combination of pirtobrutinib and venetoclax given for a fixed duration of around a year and a half for people whose CLL has recurred or progressed while they’re taking a covalent BTK inhibitor. We’re looking at getting deep responses and being able to stop treatment.

We’ve had earlier studies adding venetoclax to ibrutinib for resistance, suggesting that this works better. We’re trying to change disease expectations or treatment expectations for patients by using these combinations in both the initial and the resistance setting.

What do you hope to see in CLL over the next 10 years?
There are unmet needs for younger people with high-risk disease who don’t currently have enough treatments to expect to get through their whole lifespan. We also have a lot of people who are very elderly. We should continue to focus on how to treat people who are very unfit or elderly so that they can get effective care.

I hope the field continues to work on supportive care. CLL cells impact immune function, and patients live at a higher risk of second cancer or infections. The original mortality from COVID-19 in CLL patients was around 30%. This is a huge problem, so I hope we continue to work on that.

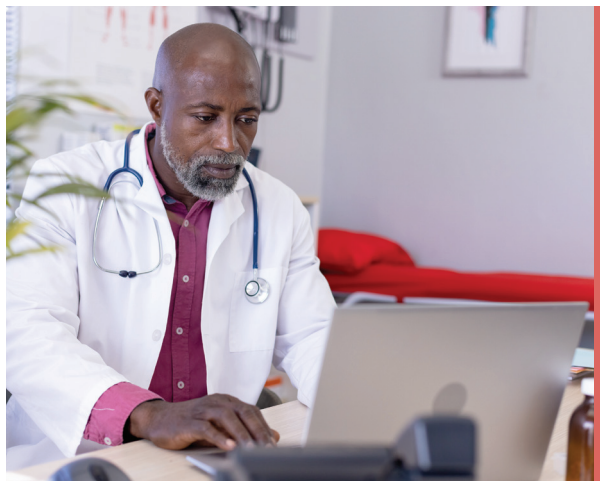
The overall goal is to make sure that the survival expectation for everybody is a normal lifespan and to continue to reduce the impact of CLL on people’s lives through safer, more effective treatment that they don’t need as much.

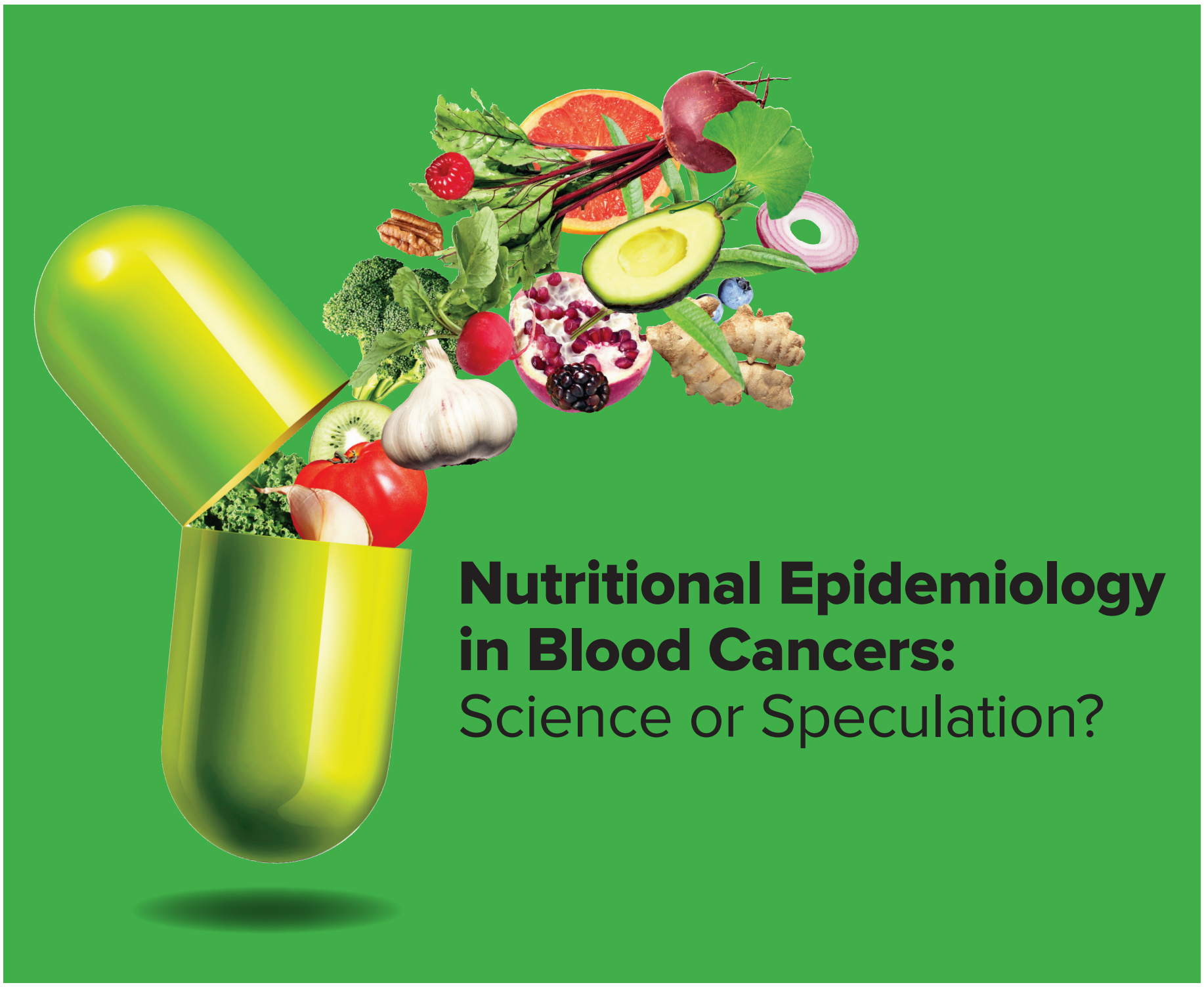
What hobbies or activities do you enjoy outside of work?
I have two rescue guinea pigs named Maple and Brady. They’re very playful and fun to interact with, but they will only wake up if you have vegetables for them. I’ve had guinea pigs since medical school; they are the perfect pet.

I also enjoy college football. I’m a Northwestern fan because that’s where I went for undergrad.

I like cooking for fun. My favorite thing to cook is optimized macaroni and cheese, like using different cheeses. I also have a hydroponic lettuce grow; there’s water in the base, and you can have hydroponic lettuce growing in your house whenever you want. You have extra fresh vegetables for your pets!

“I like helping people and hearing their stories. It’s the nature of what being a doctor is.”





Nutritional Epidemiology in Blood Cancers: Science or Speculation?

It is commonly believed that "an ounce of prevention is worth a pound of cure." But does this platitude ring true when it comes to diet and cancer prevention?

The hematology-oncology community has witnessed a surge of research examining the potential impact of dietary habits on blood cancer prevention, including multiple myeloma (MM). *Blood Cancers Today* spoke with several experts on the association between dietary patterns and blood cancer risk, the shortcomings of nutritional epidemiological studies, and how this contributes to the overall discourse about how dietary research in cancer is conducted.

Diet and Myeloma/MGUS Risk

Janine Joseph, MS, MBA, a Senior Research Specialist at Roswell Park Comprehensive Cancer Center, has been researching this question with **Urvi Shah, MD,** a Myeloma Specialist at the Memorial Sloan Kettering Cancer Center.

Their case-control study, "Dietary Risk Factors for Monoclonal Gammopathy of Undetermined Significance in a Racially Diverse Population," evaluated data from the National Health and Nutrition Examination Survey (NHANES) to assess the health and nutritional status of the U.S. population. The study comprised of 373 patients with monoclonal gammopathy of undetermined significance (MGUS) and 1,406 matched controls.

NHANES administered a structured 24-hour recall, asking participants to report which foods they consumed over the past 24 hours. MGUS was inversely associated with whole-grain bread, oats, rice, fruits, and vegetables, and directly associated with sugar-sweetened beverages and artificially sweetened soft drinks.[1] However, they found no association between MGUS risk and sugar-sweetened foods.

"There's benefit to looking at dietary patterns," Dr. Joseph said. "These findings are important for messaging regarding prevention."

Another study led by **Francesca Castro, MS, RDN,** a Clinical Research Dietitian Nutritionist at Memorial Sloan Kettering Cancer Center, evaluated three dietary patterns: the healthy eating index, which compares an individual's intake with how well they are meeting the U.S. Department of Agriculture dietary guidelines; the alternate Mediterranean diet (aMED) score, which compares intake with the Mediterranean diet score; and the plant-based dietary index, which evaluates vegetarian and vegan diets.

A healthy, plant-based diet had a "significant" association with reduced myeloma risk, which

In Focus

Castro attributed to the increased fiber intake in a plant-based diet.[2]

"Plant-based diets are higher in fiber and phytonutrients," she emphasized. "There's a huge fiber gap in the population, specifically in the American population."

More than 90% of women and 97% of men do not meet recommended intakes for dietary fiber, according to the U.S. Department of Agriculture Dietary Guidelines for Americans.[3]

an Assistant Professor at the University of Utah's Huntsman Cancer Institute. "You can plug in a few different numbers and have a few different variables and assumptions, and you'll get a different answer."

Aaron Goodman, MD, an Associate Professor of Medicine at the University of California, San Diego, agrees. "There are too many things that confound with these data, and it's very hard to tease apart in observational studies. You can really get any results you want," he said.

"The consistency I see across all these studies is showing that higher fiber and plant foods reduce risk, whether it's MGUS or myeloma progression."

—Urvi Shah, MD, Myeloma Specialist at the Memorial Sloan Kettering Cancer Center

As senior author of the myeloma and MGUS studies, Dr. Shah noted that these findings are consistent with previously published dietary evidence. "We have summarized a lot of the nutrition information and dietary evidence that's available before these two papers in a review article in *Leukemia* that looked at dietary and microbiome factors for myeloma," she explained.

The World Cancer Research Fund (WCRF) and the American Association for Cancer Research (AACR) also recommend high consumption of plant-based foods and low consumption of sugary drinks to reduce the risk of several cancers.[4,5]

As Chief of Myeloma at the Roswell Park Comprehensive Cancer Center, **Jens Hillengass, MD, PhD,** is leading another study on how various lifestyle interventions—such as exercise, nutrition, and stress—impact quality of life and immune function in patients with MM.[6]

As Dr. Hillengass explained, the immune system has the job of killing cancer cells once they appear. "To fight the cancer, we have to strengthen the immune system," he said. "Both solid and liquid tumors have developed certain capabilities to suppress the immune system."

"Nutrition can affect so many different mechanisms, like the immune system," Dr. Shah added. "For risk of progression, it's a balance between the immune system and the genes. If we can modify the immune system through these different mechanisms, then we could maybe affect the disease in a different way."

Shortcomings of Nutritional Epidemiology

Despite these findings, some hematologist-oncologists remain skeptical of observational studies linking cancer risk to dietary patterns.

"One of the main issues with nutritional epidemiology is that the studies don't fully adjust for confounding, and there's no way to do that because you can only adjust for the confounders that you can measure," said **Manni Mohyuddin, MBBS,**

Physical exercise and energy intake are variables that can confound the relationship between nutrient intake and disease risk. When studying dietary factors and myeloma risk, Castro and colleagues aimed to remove possible confounders and adjust for age, body mass index (BMI), education, and gender.[2]

"We used a residual method for adjusting for energy intake, which is important when using large cohorts because everyone eats differently, and somebody's body size and activity level affect their energy intake. We also removed outliers of energy intake, [like] those who were eating extremely high or low caloric intakes," Dr. Castro explained. "Everything is judged on the same wavelength."

However, Dr. Mohyuddin believes that this method of excluding outliers in caloric intake from the overall dataset can be arbitrary. "Because you've thrown away so much of the data, what does that tell you about the data that's left behind?" he questioned.

Dr. Mohyuddin also noted that the studies do not fully account for socioeconomic differences and that patients who adhere to a plant-based diet generally have higher socioeconomic status.

"This is the biggest shortcoming of most nutritional epidemiology," he said.

When putting randomized, controlled trials of dietary interventions to the test, Dr. Mohyuddin and colleagues found that most trials measure non-clinical endpoints and that trials that did measure clinical endpoints (ie, progression-free survival, response rates) did not show an improvement in outcomes with dietary interventions for patients with cancer.[7]

"This is a stark contrast to the observational literature," he noted. "There's a right way of doing studies like this, and the right way is not doing retrospective, confounded, observational studies. We need high-quality, randomized trials that look at specific nutritional interventions, combine it with other therapeutic anti-cancer interventions, then measure endpoints that are actually looking at cancer."

"There's a lot of hesitation from oncologists, and doctors in general, when they look at epidemiologic studies," Dr. Shah added. "Some of it is rightly so in the sense that we are looking at large populations, and that could be confounding in terms of whether the population is healthy overall. But we do the best we can with the data we have, and we adjust for all these things."

Feasibility of Patient Self-Reporting and Adherence

The unreliability of patient adherence and self-reporting is another potential flaw of nutritional epidemiology. Is a time-limited dietary recall or fasting intervention enough to make accurate conclusions about a patient's risk for cancer?

In Dr. Hillengass' study, patients fast for 16 hours per day as researchers monitor their dietary diaries, microbiomes in stool, quality of life, and immune markers by flow cytometry to evaluate the effects of intermittent fasting intervention.[6]

However, Dr. Hillengass described the process of self-documenting food as "bothersome" for some patients. "Sometimes, [patients] are not perfect in their diary when it comes to dietary intake," he said. "It's a bit more challenging to assess because it's not just a lab check. They document everything they eat, [but] they do it half an hour later or an hour later. For a research study, we need it to be very precise."

"This issue is highly prevalent across nutritional epidemiology in how people fill out surveys," Dr. Mohyuddin said. "You're asking people what they remember eating in the last 24 hours, and you're using that to draw firm conclusions about their lifestyle. You have not longitudinally followed people to see what they're eating, how their dietary intake has stayed over time."

"If you rely on people reporting what they ate, that's not really controlled," Dr. Goodman added.

Dr. Shah also noted that collecting data for nutritional studies poses a greater challenge than traditional clinical trials evaluating a specific drug or therapy.

"When you do a nutrition trial, you may want a person to eat a certain diet for a month, but people are human and they may follow it 50% or 70%," she said. "That already reduces the effect of what we can see from that intervention. Whereas if it's a drug or a therapy, it's either 100% there or not there. It becomes much easier to study and quantify."

In 2024, **Laura F. Mendez Luque, MD,** of the University of California, Irvine School of Medicine, and colleagues conducted a randomized, parallel-arm study to measure the feasibility of adhering to an education-focused Mediterranean diet among patients with myeloproliferative neoplasms (MPN). Patients were randomly assigned to either a Mediterranean diet or standard U.S. Dietary Guidelines for Americans (USDA) and received registered dietician counseling and written dietary resources.[8]

About 80% of the patients in the Mediterranean diet group achieved a Mediterranean Diet Adherence Score of greater than or equal to 8 throughout the intervention period, while less than 50% of the USDA group achieved a score of greater than or equal to 8 at any time point.[8]

"With dietician counseling and written education, patients with MPN can adhere to a Mediterranean eating pattern," wrote Dr. Mendez Luque and colleagues.[8] "Diet interventions may be further developed as a component of MPN care and potentially incorporated into the management of other hematologic conditions."

Growing Research

At the 66th Annual American Society of Hematology (ASH) Annual Meeting, Dr. Shah and colleagues took their research further. They conducted the first interventional clinical trial and *in vivo* study to show that a high-fiber diet may delay progression from MGUS to MM.

The single-arm trial consisted of 20 patients with MGUS or smoldering MM with a BMI of 25 or greater. Patients were given a controlled high-fiber plant-based dietary (HFPBD) intervention for 12 weeks and health coaching for 24 weeks.[9]

They found that the HFPBD intervention was safe, feasible, improved quality of life, and improved metabolic markers (BMI, insulin resistance, adiponectin leptin ratio), microbiome (increased alpha-diversity and butyrate producers), and immune response (decreased inflammation and increased anti-inflammatory classical monocyte).[9]

In transgenic Vk*MYC mice, the high-fiber diet also delayed the progression of smoldering MM to MM and increased the median progression-free survival from 12 weeks in the control arm to 30 weeks in the high-fiber diet intervention arm.[9]

Another study presented at ASH 2024 by **Jenny Paredes, PhD,** of the Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, explored the effects of a high-fiber diet on graft-versus-host disease (GVHD) risk after hematopoietic stem cell transplantation (HSCT).[10]

"We need high-quality, randomized trials that look at specific nutritional interventions."
—Manni Mohyuddin, MBBS, Assistant Professor, University of Utah Huntsman Cancer Institute

Dr. Paredes and colleagues collected dietary data from 173 patients who underwent allogeneic HSCT at the Memorial Sloan Kettering Cancer Center from 10 days before HSCT to 30 days after HSCT, totaling 3,837 patient days. They also collected 16S rRNA sequencing data of fecal samples and measured fecal short-chain fatty acids using gas chromatography-mass spectrometry (GC-MS) in a subset of patients with acute lower gastrointestinal (GI) GVHD and matched patients without GVHD.[10]

Increased fiber intake was associated with increased overall survival, lower incidence of acute GI-GVHD, higher microbial α-diversity, and increased butyrate. In a preclinical mouse model, mice receiving a fiber-rich diet had a lower rate of death from GVHD, higher microbial α-diversity, and a higher concentration of cecal butyrate.[10]

"These results suggest that dietary fiber could be used in the prevention of GVHD," wrote Dr. Paredes and colleagues.[10]

Fate Versus Free Will

Dr. Hillengass noted that patients take a keen interest in altering their diet to improve their health. "We give patients chemotherapy, we give them modern drugs. They often ask, 'what else can I do right?' Oftentimes, nutrition comes up fairly early in the discussion," he said.

Patient adherence to dietary patterns raises a vital question: to what extent can patients become the pilots of their health?

"When a diagnosis of cancer happens, there's a sense of loss of autonomy," Dr. Mohyuddin said. "That is why [nutrition] is an immense interest to patients, and it's a way of giving autonomy back to patients. It is a very relevant and hot question."

Dr. Goodman pointed out that not only is preventative medicine difficult to execute, but it is unnecessary when considering MGUS.

"I think dietary interventions in a pre-cancer like MGUS where the majority of patients will never develop cancer is a low research priority," he said.

According to the Weill Cornell Medicine Myeloma Center, 20% of patients with MGUS will progress to myeloma, and the risk for a patient's progression from MGUS to myeloma is 1% per year.[11]

"The magnitude of benefit of a plant-restricted diet in MGUS would have to be so dramatic to do anything," Dr. Goodman added.

However, others stress the importance of altering one's diet and taking an active role in their health.

"I think it's very helpful for patients to know that diet does play a role in overall cancer risk and myeloma risk and that even if they potentially move a little bit in the right direction, it can make a difference in outcomes," Castro said.

In a Nutshell

The concept of dietary patterns is crucial to the larger conversation on diet and cancer risk, according to Dr. Shah. "Instead of only focusing on an individual food group, it's important to think about the pattern that is consistent between these studies," she explained. "The consistency I see across all these studies is showing that higher fiber and plant foods reduce risk, whether it's MGUS or myeloma progression."

While oncologists like Drs. Goodman or Mohyuddin take observational nutritional studies with a grain of salt, they do not discount the importance of keeping a healthy diet.

"I think that all of the general dietary advice still applies," Dr. Mohyuddin emphasized. "There are far more compelling reasons to eat healthy and avoid obesity than to avoid MGUS."

"We need no further study to suggest that exercising and eating healthy is a good thing to do,"

"As doctors it is our duty not to ignore this." *—Urvi Shah, MD*

Dr. Goodman agreed. "We need a very meticulous study with appropriately designed endpoints."

Despite the reluctance from some oncologists, Dr. Shah and her team continue to spread awareness of the role of nutrition in myeloma and MGUS risk. This way, doctors can be better prepared to answer patients' questions regarding diet and nutrition, she said.

"As doctors, we don't get enough nutrition training," she expressed. "I think that's also why there's a lot of hesitation from doctors because you assume that it doesn't exist if you don't know it. Often, doctors have not read enough about this topic and understand how these studies are done. Despite [the] adjustment, if we are seeing significance in not just one study, but in many studies and consistently over time, then as doctors it is our duty not to ignore this."

References

1. Joseph J, et al. *Blood Advances.* 2024;8(3):538–548. Doi.org/10.1182/bloodadvances.2023011608
2. Castro F, et al. *Leukemia.* 2024;38(2):438-44. doi:10.1038/s41375-023-02132-3.
3. U.S. Department of Agriculture. Dietary Guidelines for Americans. Accessed May 1, 2025. https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf
4. World Cancer Research Fund International. Accessed May 1, 2025. https://www.wcrf.org/diet-activity-and-cancer/cancer-prevention-recommendations/
5. American Association for Cancer. Accessed May 1, 2025. https://www.aacr.org/patients-caregivers/progress-against-cancer/reducing-cancer-risk-healthy-eating-alcohol/
6. Hillengass J. Non-chemotherapeutic interventions for the improvement of quality of life and immune function in patients with multiple myeloma. Accessed May 1, 2024. https://clinicaltrials.gov/study/NCT05312255
7. Ilerhunmwuwa NP, et al. *J Natl Cancer Inst.* 2024;116(7): 1026-1034. doi:10.1093/jnci/djae051
8. Mendez Luque LF, et al. *Cancer Res Commun.* 2024;4(3):660-670. doi:10.1158/2767-9764.CRC-23-0380
9. 66th American Society of Hematology Annual Meeting & Exposition. Abstract #671.
10. 66th American Society of Hematology Annual Meeting & Exposition. Abstract #259.
11. Weill Cornell Medicine Myeloma Center. Accessed May 1, 2025. https://www.myelomacenter.org/patients/other-plasma-cell-disorders/precursor-conditions-multiple-myeloma

Blood Cancers Today *spotlights the latest research from medical residents and fellows in the field of hematologic malignancies.*

Leukemia Fellow Highlights Modest Gains With Azacitidine-Venetoclax in HR-MDS Patients

Spotlight on

Julie Braish, MBBCh

Julie Braish, MBBCh, is a third-year fellow in the Leukemia Fellowship Program at The University of Texas MD Anderson Cancer Center, where she has been honing her expertise since July 2023. With a focus on the biology and treatment of leukemia, her research interests center on clonal hematopoiesis (CHIP), clonal cytopenia of undetermined significance (CCUS), and the role of inflammaging in leukemic transformation. Passionate about equitable cancer care, Dr. Braish volunteers with ASC-CAN to address healthcare disparities.

Originally from Lebanon, she earned her medical degree with distinction from Beirut Arab University in 2017, followed by postgraduate training at the American University of Beirut. She then completed an accelerated Internal Medicine residency at the University of Connecticut, where she was named "Intern of the Year" and graduated in just two years—an honor granted by the American Board of Internal Medicine.

Outside the clinic, Dr. Braish finds inspiration in the arts and nature, often painting or capturing landscapes during road trips with loved ones.

*By **Nichole Tucker***

Azacitidine improves survival in high-risk myelodysplastic syndrome [HR-MDS] compared to conventional care, but outcomes remain poor after failure with a median overall survival [OS] of 5.6 months," said **Julie Braish, MBBCh**, a clinical fellow, Department of Leukemia, The University of Texas MD Anderson Cancer Center (MD Anderson) told *Blood Cancers Today.*

Dr. Braish was a co-investigator of a phase 1/2 study conducted at MD Anderson under the leadership of Guillermo Garcia-Manero, MD, professor, Department of Leukemia and chief, Section of Myelodysplastic Syndromes, Division of Cancer Medicine. During *The HemOnc Pulse Live!* Fellows Panel Discussion, Braish presented data from the study, which evaluated the safety, tolerability, and efficacy of azacitidine and venetoclax in patients with HR-MDS and CMML.

"In our study, adding venetoclax post-HMA failure was feasible but did not meaningfully extend survival with a median OS of 7 months," Dr. Braish said.

Results were from 33 patients who previously failed on four or more cycles of hypomethylating agent (HMA) therapy and no prior treatment with a BCL-2 inhibitor. Patients received azacitidine 75 mg/m^2 by intravenous or subcutaneous infusion for 5 days plus venetoclax 100-400 mg for 14 days in a 28-day cycle.

Results showed that the overall response rate (ORR) was 49% (95% CI, 31.4%-65.5%). Response data come from a phase 1 ORR of 58% (95% CI, 30.6%-86%) from a cohort of 12 patients and phase 2 ORR of 43% (95% CI, 21.7%-64%) from a cohort of 21 patients. Complete remission (CR) was observed in 3% (95% CI, 0%-9%). Marrow CR with hematologic improvement was shown in 24% (95% CI, 9.7%-38.8%), and 21% of patients (95% CI, 7.3%-35.2%) experienced marrow CR alone. The median number of cycles to the first response was one cycle (range, 1-4).

Median overall survival was estimated to be 7 months (95% CI, 3.5-10.5 months), and median progression-free survival was estimated to be 6 months (3.019-8.98 months).

Investigators also assessed efficacy in patients with key mutations, including *TP53* and *ASXL1*. Of the 33 patients, 10 presented with *TP53* mutations. In the *TP53*-positive cohort, the median OS was 3 months (95% CI, 0.9-5.0).

Fifteen patients presented with *ASXL1* mutations, and among those patients, the median OS was 8 months (95% CI 3.5-13.4).

"Three of the four patients that remained alive at the time of last follow-up received a stem cell transplant, raising the question of this combination being used as a bridge to transplantation," Dr. Braish explained.

Safety results showed that 68% of patients experienced low-grade treatment-emergent adverse events (TEAS). There were also grade 3 TEAEs in 20% of patients, grade 4 events in 10%, and grade 5 in 2%. The most common low-grade TEAEs were nausea and vomiting (16%), disturbed liver function tests (4%), neutropenia (2%), and thrombocytopenia (1%).

"I'm grateful as a fellow to learn from some of the world's leading leukemia experts who are truly dedicated to teaching and supporting my growth," said Dr. Braish, regarding her involvement in this research.

Reference:

2nd Annual The HemOnc Pulse Live!; May 2-3, 2025; Austin, TX.

MD Anderson Fellow Dives Deep into the Unknowns of *FLT3-TKD*–Mutated AML

Sankalp Arora, MBBS, is a rising physician-scientist currently in his second year of a Hematology-Oncology fellowship at the University of Texas MD Anderson Cancer Center. His work has a strong focus on acute leukemias and myeloproliferative neoplasms (MPNs), particularly acute myeloid leukemia (AML).

Originally from Mumbai, Dr. Arora earned his medical degree from GS Medical College & KEM Hospital, where he also completed a year-long clinical internship. He then moved to the United States to pursue residency training in internal medicine at The University of Alabama at Birmingham, sharpening both his clinical acumen and his drive to pursue research.

Dr. Arora is now honing his expertise with an eye toward becoming a clinical investigator and leading early-phase clinical trials.

By ***Nichole Tucker***

Among clinicians who treat patients with *FLT3* tyrosine kinase domain (TKD)-mutated acute myeloid leukemia (AML), the use of FLT3 inhibitors and venetoclax has been increasing; however, the impact of using these therapies represents an unanswered question in AML.

"*FLT3-TKD* mutations occur in 7%-10% of newly-diagnosed AML, but their characteristics and outcomes are not well described in the literature. In addition, how the incorporation of venetoclax and targeted FLT3 inhibitor therapy would impact outcomes in *FLT3-TKD*-mutated AML is unknown. Our research is aimed to address these points and utilized one of the largest retrospective cohorts of frontline *FLT3-TKD*-mutated AML," **Sankalp Arora, MBBS,** clinical fellow, The University of Texas MD Anderson Cancer Center, told *Blood Cancers Today*.

During *The HemOnc Pulse Live!* in Austin, Texas, Dr. Arora gave a live Emerging Experts presentation centered around unanswered questions and shared data from a retrospective study. Dr. Arora and colleagues set out to better understand the use of FLT3 inhibitors or venetoclax as frontline treatment by comparing outcomes with the use of intensive chemotherapy.

The analysis set included 124 patients of which 44% had a *NPM1* co-mutation. These patients were divided into three cohorts: the full cohort (n = 54), *NPM1* mutant (n = 24), and *NPM1* wild-type (wt; n = 30).

With intensive chemotherapy only, findings showed that responses varied based on the existence of *NPM1* mutations and *NPM1*wt mutations. The trend continued when investigators observed patients who also received venetoclax and/or FLT3 inhibitors.

Introducing Venetoclax and FLT3 Inhibition

When venetoclax was added to intensive chemotherapy, the CR rate among 17 patients was 88%, and the CRi rate was 6%. In 10 patients who received intensive chemotherapy in combination with FLT3 inhibition, the CR rate was 70% with no CRis. In the 27 patients who received intensive chemotherapy alone, the CR rate was 63%, and the CRi rate was 15%.

At a median follow-up of 43 months in the full cohort, the median overall survival (OS) was not reached, and the 3-year overall survival rate was 56%. The media event-free survival (EFS) was also not reached, and the 3-year EFS rate was 53%.

"The most surprising finding was the very poor outcomes noted in patients with *FLT3-TKD* AML without co-mutated *NPM1* who received low-intensity therapy. The median OS for this population was only 6 months. This may be due to enrichment of adverse risk karyotype/mutations in this patient population," Dr. Arora explained.

Among patients with *NPM1*-mutated disease, the median OS was not reached, and the 3-year OS rate was 74%. In the *NPM1*wt group, the median OS was 13.8 months, and the 3-year OS rate was 40%. In terms of EFS, the median was not reached in the *NPM1*-mutant group, and the 3-year EFS rate was 65%. In the *NPM1*wt group, the median EFS was 12.5 months, and at 3 years, the EFS rate was 42%.

The Role of Transplant

Outcomes appeared to be slightly better for patients who also underwent allogeneic stem cell transplant (alloSCT) compared with those who did not, based on the landmark analysis. While median OS was not reached for those with *FLT3-TKD*- mutant, *NPM1*-mutant AML, the 3-year OS rate in patients who underwent alloSCT was 77% versus 70% in patients who did not undergo alloSCT.

In the *FLT3-TKD*- mutant, *NPM1*wt group, the median OS was not reached in patients who underwent alloSCT, and the 3-year OS was 88%. For those who did not undergo alloSCT, the median OS was 20.2 months, and the 3-year OS rate was 30%.

"The key message is that *NPM1* mutations commonly co-occur in *FLT3 TKD*-mutated AML and seem to influence outcomes in this population, including the role of alloSCT. Patients with *FLT3-TKD* AML who also have the *NPM1* mutation have improved response rates and survival outcomes with therapy compared to those without *NPM1* mutation," Dr. Arora said.

"AlloSCT in first CR was not associated with an overall survival benefit in *FLT3-TKD* AML patients with NPM1 co-mutation, but it was found to increase overall survival in patients without co-mutated NPM1. Therefore, assessing *NPM1* mutation status is crucial in *FLT3-TKD*-mutated AML," he said.

Reference

Arora, Sankalp. Blood Cancers Today Presents: Emerging Experts. Presented at The HemOnc Pulse Live! May 2-3, 2025; Austin TX.

Regulatory Actions

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

FDA Clears Way for Phase 3 Trial of Linperlisib in Advanced Peripheral T-Cell Lymphoma

*By **Nichole Tucker***

Late-phase research on the use of the next-generation, highly-selective PI3 kinase inhibitor, linperlisib for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) will soon commence. The plan follows a Type B End-of-Phase 2 Meeting during which the FDA gave clearance for the drug developer to proceed with a pivotal phase 3 protocol.[1]

Linperlisib will be investigated in a global registration study versus physician's choice of standard treatment for relapsed or refractory PTCL, a study expected to add more favorable results to a growing body of data, which has involved approximately 6,000 patients with T-cell lymphoma.[1]

Previously, treatment with linperlisib achieved early responses in relapsed or refractory PTCL and was well tolerated. The phase 2 investigation included 35 patients with relapsed or refractory PTCL and 10 with cutaneous T-cell lymphoma who received 80 mg of the agent once daily for 28 cycles or until achievement of a complete response (CR). After a CR was achieved, patients received continuous maintenance therapy with linperlisib 40 mg once daily.[2]

In 33 evaluable patients, an overall response rate of 48.5% was observed. Of the patients who responded to linperlisib, 11 achieved a CR, 5 achieved a partial response, and 4 had stable disease, for a disease control rate of 60.6%. The responders included patients with select PTCL subtypes including PTCL, not otherwise specified (n=7), angioimmunoblastic T-cell lymphoma (n= 8), and anaplastic large cell lymphoma (n=1). Responses to linperlisib lasted for a median duration of 5.8 months (1.9 months to not evaluable).

The median progression-free survival was 3.6 months (95% CI, 1.9-5.3) in the evaluable population. The median overall survival was not reached.

In 25 patients (55.6%), treatment-related adverse events (TRAEs) occurred. Neutropenia was the most frequently occurring TRAE. Grade 3 TRAEs observed in the study included neutropenia (8.9%), rash (4.4%), pneumonia (4.4%), decreased leukocyte count (2.2%), thrombocytopenia (2.2%), hypertriglyceridemia (2.2%), pneumonia (4.4%), transaminitis (2.2%), increased γ-glutamyltransferase (2.2%), and cellulitis (2.2%). Dose interruption was necessary for 23 patients; 1 interruption was due to 2 occurrences of grade 4 neutropenia, and 22 were due to other AEs. One study discontinuation occurred due to *Pneumocystis jiroveci* pneumonia.

Overall, the results were positive, but further investigation is warranted, according to the study investigators.

"This is a major milestone for linperlisib," said **Michael Hui,** chairman and chief executive officer of Yingli Pharma, developer of linperlisib, in a press release.[1] "We are very excited that linperlisib has entered the global pivotal study stage with the agreement from FDA. We will continue our mission to address patient unmet clinical needs globally and to accelerate the linperlisib clinical development program to bring more treatment options for patients with R/R PTCL."

References

1. Yingli Pharma announces successful End-of-Phase 2 Meeting with FDA and clearance of global multi-center phase 3 registration study design of linperlisib for the treatment of relapsed and/or refractory peripheral T-cell lymphoma. News release. PR Newswire. April 1, 2025. Accessed April 11, 2025. https://www.prnewswire.com/news-releases/yingli-pharma-announces-successful-end-of-phase-2-meeting-with-fda-and-clearance-of-global-multi-center-phase-3-registration-study-design-of-linperlisib-for-the-treatment-of-relapsed-andor-refractory-peripheral-t-cell-lymphoma-302416397.html

2. Iyer S, Nair R, Mehta-Shah, N, et al. A phase II clinical study exploring the safety and efficacy of the oral PI3Kδ inhibitor, linperlisib, in relapsed refractory T cell lymphoma. *Blood*. 2024;144(suppl 1): 4449. doi:1182/blood-2024-209340

Novel CLEVER-1-Targeting Immunotherapy Agent Holds FDA Orphan Drug Designation for MDS, AML

*By **Andrew Moreno***

Bexmarilimab, an investigational immunotherapy in development by Faron Pharmaceuticals Ltd., has received Orphan Drug Designation (ODD) from the FDA for myelodysplastic syndromes (MDS).

"Receiving FDA's orphan drug designation for bexmarilimab for the treatment of myelodysplastic syndrome marks a significant milestone for Faron Pharmaceuticals as we continue to develop *bexmarilimab* for MDS and other cancers," Faron chief medical officer **Petri Bono, MD, PhD,** commented.

A novel humanized antibody, bexmarilimab targets and binds to the CLEVER-1 immunosuppressive receptor on macrophages. This brings alteration of myeloid cell functions and recalibrates the immune system to attack hematological and solid tumors. It also increases the susceptibility of cancer cells to standard of care treatments.

The FDA already granted bexmarilimab fast track designation status and, in August 2023, an ODD for the treatment of acute myeloid leukemia (AML). The BEXMAB open-label phase 1/2 clinical trial evaluates this agent in combination with standard-of-care azacitidine for AML and MDS.

Reference

Inside information: FDA grants Orphan Drug Designation for bexmarilimab in MDS. News release. Faron Pharmaceuticals Ltd. March 3, 2025. Accessed April 1, 2025. https://faron.com/releases-and-publications/inside-information-fda-grants-orphan-drug-designation-for-bexmarilimab-in-mds

Bexobrutideg Receives FDA Orphan Drug Designation for Waldenström Macroglobulinemia

*By **Melissa Badamo***

The FDA has granted Orphan Drug Designation to bexobrutideg (NX-5948) for the treatment of Waldenström macroglobulinemia (WM), according to a press release from Nurix Therapeutics, the developer of the drug.

Bexobrutideg, an orally bioavailable, brain-penetrant Bruton tyrosine kinase (BTK) degrader, is being evaluated in an ongoing dose-escalation (phase 1a) and cohort-expansion (phase 1b) study in adult patients with relapsed or refractory B-cell malignancies.

Efficacy and safety data were presented at the 12th International Workshop on Waldenström's Macroglobulinemia. Seven of 9 patients (77.8%) achieved an overall response rate, and 8 had a steady decrease in immunoglobulin M (IgM) levels beginning at 8 weeks of treatment. One patient achieved a more than 90% reduction in IgM level. The most common adverse events were purpura/contusion, neutropenia, and thrombocytopenia, and were mostly low-grade.

"Granting of the designation highlights bexobrutideg's potential to provide patients with WM a promising new therapeutic option," said **Arthur T. Sands, MD, PhD,** president and chief executive officer of Nurix, in the press release.

References

Nurix announces U.S. FDA Orphan Drug Designation granted to bexobrutideg (NX-5948) for the Treatment of Waldenström Macroglobulinemia. News release. Nurix Therapeutics, Inc. https://ir.nurixtx.com/news-releases/news-release-details/nurix-announces-us-fda-orphan-drug-designation-granted

ClinicalTrials.gov. A study of NX-5948 in adults with relapsed/refractory B-cell malignancies. ClinicalTrials.gov identifier: NCT05131022. Updated March 25, 2025. Accessed April 2, 2025

O'Conner P. NX-5948: BTK degrader with activity in lymphoid malignancies. Presented at: 12th

FDA Barred from Regulating Laboratory-Developed Tests After Industry Lawsuit

*By **Nichole Tucker***

In a court judgment, the American Clinical Laboratory Association (ACLA), Association for Molecular Pathology (AMP), and their members won a case against the FDA, which has prohibited the FDA from regulating laboratory-developed tests (LDTs) under section 564 of their regulations.[1]

United States District Judge Sean D. Jordan entered the final judgment to vacate the FDA's rule on March 31, 2025.

FDA draft guidance from mid-2024 mentioned the agency's plan to regulate LDTs using the guidelines it uses to regulate in vitro diagnostics and medical devices.[2] In accordance with the draft guidance process, this became a "Final Rule" within the FDA after a period of review. Professional pathology organizations like ACLA immediately responded that the FDA was operating outside its authority.[3]

"FDA's Final Rule is the wrong approach, both as a matter of law and public policy, and represents regulatory overreach. The medical device framework is inappropriate and ill-suited for regulating laboratory-developed tests, which are services provided by trained professionals rather than manufactured products. These professional services incorporate the latest scientific advances to offer innovative testing solutions to physicians and the patients they serve," stated Susan Van Meter, president of ACLA.[3]

In court, the FDA's attempt was considered a direct violation of the Food, Drug, and Cosmetic Act and the Clinical Laboratory Improvement Amendments set by The United States Congress. Following the decision, the other plaintiff, AMP, responded in a press release.[4]

"AMP is extremely pleased with the court's clear and decisive ruling in our favor, and we hope this will finally end the FDA's attempts to exert an unwarranted overreach of authority of LDTs," said **Jane S. Gibson, PhD,** president of AMP and chair of the Department of Clinical Sciences and director of molecular diagnostics at the University of Central Florida College of Medicine.

President **Donald Karcher, MD, FCAP** of the College of American Pathologists (CAP), told *Blood Cancers Today,* "the FDA's LDT rulemaking was burdensome, and the court rightly struck it down." Like many organizations representing the cancer pathology community, CAP noted that the Final Rule could have greatly interfered with cancer pathology.

Pathology reports provide hematologists/oncologists with data on how treatment is selected. CBC results are still key for detecting leukemia, lymphoma, and multiple myeloma, as are blood protein tests.[5] In modern years, select blood cancers can be detected using circulating tumor cell tests, and even multicancer early-detection blood tests have shown utility in diagnosing blood cancer.[6]

"LDTs are crucial for us to give our patients an accurate diagnosis so we can both be confident we are embarking on the best treatment for their cancer, **Uma Borate, MBBS,** Clinical Section Head, Acute Leukemia and Clinical Research Director, Acute Leukemia at the Ohio State University Comprehensive Cancer Center told *Blood Cancers Today*.

Overall, LDTs have offered additional information for a more targeted approach to cancer treatment.

"The regulation failed to target FDA oversight and threatened patient access to countless numbers of safe LDTs by saddling laboratories with unnecessary requirements. The CAP and its members are relieved that the court agreed with our arguments," Karcher said.

In a press release from ACLA, Van Meter also foresaw the impact, stating the FDA-regulated LDTS could "disrupt the paradigm, creating negative consequences for the entire health care system, including millions of vulnerable patients who depend on the essential clinical testing services that only laboratory professionals can provide."[3]

However, not all cancer pathology happens in the diagnostic stages. Every day, hematologists/oncologists depend on laboratory data to ensure patient-centered and evidence-based treatment.

"All treatment decisions are based on the pathology, and now, in particular, because of the targeted therapies we have, the pathology is more important than ever," **Steven T. Rosen, MD,** executive vice president and director emeritus, Beckman Research Institute, City of Hope, told *Blood Cancers Today*. "Any impediment to getting the necessary tests available for our patients is detrimental," he added.

Future regulations may continue to impact how laboratories operate, ultimately affecting patient care. Borate stated, "We would hope that the tests that tell us which disease that our patients have especially diseases like cancer, are held to the highest standards to make sure we are prescribing the most effective treatments for these patients."

References

1. United States District Court Eastern District of Texas Sherman Division. Case 4:24-cv-00479-SDJ; Document 94: Page ID 2731. Filed March 31, 2025. Accessed April 8, 2025.

2. United States Department of Health and Human Services, United States Food and Drug Administration. Docket No. FDA-2024-D-008. Filed April 29, 2024. Accessed April 8, 2025.

3. ACLA Challenges FDA's Final Rule to Regulate Laboratory Developed Testing Services as Medical Devices. News release. American Clinical Laboratory Association website. Published May 29, 2024. Accessed April 8, 2025. https://www.acla.com/acla-challenges-fdas-final-rule-to-regulate-laboratory-developed-testing-services-as-medical-devices/

4. Association for Molecular Pathology Celebrates U.S. District Court's Decision to Vacate FDA Rule on Laboratory-Developed Test Procedure Regulation. News release. The Association of Molecular Pathology. Published March 31, 2025. Accessed April 8, 2025. https://www.amp.org/AMP/assets/File/pressreleases/2025/AMP-FDA-Positive-Ruling-FINAL_033125.pdf?pass=37

5. Cleveland Clinic Health Library. Blood Tests for Cancer. Cleveland Clinic. https://my.clevelandclinic.org/health/diagnostics/22338-blood-tests-for-cancer Last updated May 6, 2024. Accessed April 8, 2025.

6. Rubinstein W, Patriotis C, Dickherber A, et al. Cancer screening with multicancer detection tests: A translational science review. *CA Cancer J Clin.* 2024;74(4):368-382. doi:10.3322/caac.21833.

Unpacking the COA Prescription for Health Care Reform: What Does it Mean for Patients and Oncologists?

*By **Melissa Badamo***

The Community Oncology Alliance (COA) has released its Prescription for Health Care Reform, a policy blueprint outlining solutions for Congress to address systemic challenges of the United States healthcare system. These challenges include consolidating and monopolizing hospitals and health systems, workforce shortages in rural areas, outdated Medicare policies, escalating costs, and access barriers.[1]

Rooted in the experience of community oncology practices, the COA offers a 5-part legislative roadmap that aims to stabilize the broader healthcare system, prioritize patients, and preserve access to high-quality, affordable care.[1]

"Our healthcare system has reached a critical tipping point as Americans pay more than ever for healthcare that is becoming increasingly out of reach. Consolidation, administrative burdens, and skyrocketing costs are hurting patients and providers alike," COA President **Debra Patt, MD, PhD, MBA, FASCO,** said in the press release.[1]

Hospitals and Health System Consolidation

The first part of the plan addresses the monopolization and consolidation of hospitals into nonprofit health systems. Many independent, physician-owned practices close or merge with hospitals due to the financial benefits hospitals receive through federal programs, such as the 340B Drug Pricing Program.[2] This can lead to higher prices for patients, less choice in providers, and less competition, according to the COA.[1]

To mitigate these issues, the COA calls for site-neutral payment policies to ensure fair reimbursements, an overhaul of the 340B Drug Pricing Program to ensure patients are benefiting, evaluating the definition of a nonprofit institution, and placing restrictions on debt collection practices.[1]

Insurance and Pharmacy Benefit Manager (PBM) Consolidation and Market Dominance

The COA pushes for legislation that disallows PBMs to own pharmacies, steer patients towards affiliated pharmacies, or impose mandatory mail order requirements. These practices lead to disproportionate power, cost inflation, and limited access to drugs, the COA wrote.[1]

According to an analysis by the American Medical Association (AMA), the four largest PBMs (CVS Health, OptumRx, Express Scripts, and Prime Therapeutics) have a collective 70% share of the national PBM market.[3]

"The call for increased regulatory oversight of PBM business practices is overwhelmingly welcomed by physicians as a check against possible anticompetitive harm resulting from low competition and high vertical integration in the PBM industry," AMA President **Bruce A. Scott, MD,** said in a press release.[3]

Fixing Physician Reimbursement and Modernizing Structural Centers for Medicare & Medicaid Services (CMS) Policies

To modernize Medicare's payment system, the COA calls for a payment approach that better balances equitable reimbursements across hospitals and independent practices to cultivate a level, free market playing field.[1]

The COA also recommends halting Medicare Physician Fee Schedule (PFS) cuts, aligning reimbursement prices with inflation, and eliminating payment sequestration.[1] The CMS issued a final rule reducing the Medicare conversion factor from $33.29 to $32.35 in January 2025, resulting in a 2.93% average pay cut for physicians.[4]

According to the CMS website, "The CY [calendar year] 2025 PFS final rule is one of several final rules that reflect a broader Administration-wide strategy to create a more equitable health care system that results in better accessibility, quality, affordability, empowerment, and innovation for all Medicare beneficiaries."[4]

The CMS has not responded to *Blood Cancers Today's* request for comment.

"A decade ago, we repealed the sustainable growth rate (SGR). It appears we're back in that SGR rigmarole where there's cuts going into place from the fee schedule standpoint, and it requires an act of Congress to mitigate those cuts," **Frank McStay, MPA,** an Assistant Research Director for Medicare Accountable Care Transformation at the Duke-Margolis Institute for Health Policy, told *Blood Cancers Today.* "This underscores the need to move to more person-centered, population-based payment systems in an accelerated fashion."

According to McStay, moving to a population-based payment system can improve the health system's value, resiliency, and efficiency while limiting drug shortages and unaffordability. A population-based payment system offers healthcare providers upfront, flexible payments, according to the Center for Health Care Strategies.[5]

"The cuts could have implications for physicians, but most importantly for patients," McStay added. "Moving away from these antiquated payment policies to more accountable type payment systems to support physicians in the type of healthcare they want to be delivering is important."

McStay explained that although the Trump administration wants to accelerate towards this payment system, it is challenging.

"There's budget neutrality implications with Medicare physician fee scheduling, and there's only so much money in the pot," he said. "Where Congress ultimately chooses to invest its time and limited resources is the biggest barrier."

Fixing Workforce Shortages

To fix workforce shortages, the COA encourages Congress to expand residency positions, offer incentives for practicing in rural areas, and ensure that Medicare reimbursement models support practices in underserved areas.[1]

According to a study published in the *Journal of Rural Health,* 67.5% of 1,963 oncologists practiced in exclusively urban locations, 11.3% in exclusively rural locations, and 21.1% in rural and urban locations. In addition, 16.4% of oncology, hematology, and hematology-oncology specialties in rural areas were billed for Medicare-covered services, compared with 9.4% in urban areas.[6]

A study published in *JCO Oncology Practice* also found a negative association between the availability of oncology workforce and cancer rates (corr.$=-0.085$, $P<0.01$), with the largest shortage of oncologists found in the West North Central and West South Central states.[7]

"Greater access to care rurally by the presence of care providers and facilities is essential for cancer diagnosis, treatment, and supportive care," **Ruben Mesa, MD, FACP,** a hematologist oncologist and President & Executive Director of Atrium Health Wake Forest Baptist Comprehensive Cancer Center, told *Blood Cancers Today.*

He also explained that cancer outcomes are strongly driven by being identified at earlier stages or before undergoing metastases. "Patients in rural areas can find profound health disparities by delays of initial presentation, application of definitive therapy, presenting at a more advanced stage, and having delays in receiving care if complications to treatment occur, which can also lead to worse or fatal outcomes," he added.

Ensuring Access to Oncology Therapies (Drugs)

According to the COA, reduced access to affordable cancer therapies stems from rising drug costs, chronic shortages of generic sterile injectable (GSI) drugs, and uncertainty in the biosimilar market. Therefore, the organization urges for reforms to address supply chain issues, stabilize GSI and biosimilar prices, and fix the Inflation Reduction Act (IRA) to financially protect independent medical practices from Medicare price negotiations.[1]

References

1. Community Oncology Alliance Releases a Comprehensive Legislative Framework for Health Care Reform. News Release. Community Oncology Alliance. February 5, 2025. Accessed April 22, 2025. https://mycoa.communityoncology.org/news-updates/press-releases/community-oncology-alliance-releases-a-comprehensive-legislative-framework-for-health-care-reform-

2. COA Prescription for Health Care Reform: A Policy Blueprint for Congress. Community Oncology Alliance. Accessed April 22, 2025. https://mycoa.communityoncology.org/education-publications/report/coa-prescription

Highlights From the **AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) ANNUAL MEETING 2025**

CD47, CD20-Targeting Bispecific Fusion Protein Evaluated for Refractory NHL in First-in-Human Trial

*By **Andrew Moreno***

JMT601, a bispecific left-right asymmetrical fusion protein that targets CD47 and CD20, is being investigated for the management of relapsed or refractory CD20-positive B-cell non-Hodgkin lymphoma (NHL).

Preliminary efficacy and safety data from the first-in-human trial of this agent showed favorable anti-tumor effects and acceptable safety. The results were presented at the American Association for Cancer Research (AACR) Annual Meeting 2025 in Chicago, Illinois.

In remarks forwarded to *Blood Cancers Today,* **Paolo Strati, MD,** an associate professor and researcher in the Department of Lymphoma and Myeloma at the University of Texas MD Anderson Cancer Center, Houston, commented on the presented trial and JMT601.

"While bispecific antibodies engaging T cells are FDA approved for indolent and aggressive B-cell lymphoma, and those engaging NK cells show promising activity in HL, bispecific antibodies engaging macrophages are still at very early phase of development. The clinical development of agents targeting CD47 has been limited by hematological toxicity, underscoring the safety of this drug class," Dr. Strati explained.

The trial enrolled 36 patients aged 18 to 70 years with histologically confirmed disease who had undergone at least two prior lines of therapy. The median age of the cohort was 59 years and 23 patients were male. 75% of the total cohort had received three or more prior lines of therapy and 75% of the total cohort had disease refractory to rituximab-based combination therapy. Twenty-five patients specifically had diffuse large B-cell lymphoma (DLBCL).

Regarding the trial's total enrolled cohort, Dr. Strati noted that "it is unclear how many were chemo-refractory and how many had previously received CAR T-cell therapy or standard bispecifics."

In this two-part trial, 30 patients participated in a 3 plus 3 dose-escalation of JMT601 where they received weekly intravenous administration of the agent at eight dose levels until disease progression, intolerable toxicity, or consent was withdrawn. This was followed by the dose-expansion phase in which the recommended dose was administered to six patients with select tumor types. There was one instance of dose-limiting toxicity as a grade 4 thrombocytopenia which occurred at a dose of 12 mg/kg, and the maximum tolerated dose was not reached.

For the 32 patients in whom efficacy was evaluable, the calculated objective response rate (ORR) was 25%, and the disease control rate (DCR) was 50%. Among patients with DLBCL, the calculated OOR was 28% and DCR was 52%.

"Response rates were low (25%), but it is not clear how many of these were CR, and duration of response data are not reported," Dr. Strati wrote in response to these efficacy results from the trial.

Safety was evaluated in 36 patients and 86.1% experienced a treatment-related adverse event (TRAE) of any grade. 44.4% of patients experienced a TRAE of grade 3 or worse severity; the most common types were neutropenia which occurred in 19.4%, thrombocytopenia in 13.9%, leukopenia in 11.1%, lymphocytopenia in 8.3%, hypertriglyceridemia in 5.6%, anemia in 5.6%, and infectious pneumonia in 5.6%.

Serious adverse events (SAEs) occurred in 25% of the patients. There were three TRSAEs, specifically two instances of thrombocytopenia and one of infectious pneumonia. There was one patient mortality due to disease progression deemed unrelated to the study agent.

Dr. Strati assessed that "[w]hile severe anemia was not reported frequently, 10-20% of patients experienced severe neutropenia or thrombocytopenia, whose mechanisms remains to be clarified."

Following his review of the presented trial and its findings, Dr. Strati concluded regarding JMT 601 that "[w]hile initial activity is encouraging, macrophage biology yet remains to be unveiled for better harnessing for the treatment of lymphoma."

Reference

AACR Annual Meeting 2025. Abstract No. CT060 / 5.

Clinical Study Finds Continuous Lenalidomide Delivery Effective and Well Tolerated in RRMM

*By **Nichole Tucker***

Administration of lenalidomide continuously for six or more cycles shows meaningful efficacy in patients with relapsed or refractory multiple myeloma (RRMM) without serious toxicity, according to a phase 1b study.

Results were presented at the AACR Annual Meeting 2025. No drug-related grade 3 or 4 hematologic toxicities were observed, all nonhematologic toxicities were below grade 2, and no significant increase in immune checkpoints was associated with T-cell exhaustion. Moreover, all patients achieved an objective response to treatment.

In the study, six patients were receiving their second line of therapy for relapsed or refractory multiple myeloma. All patients in the cohort were White, and the male-to-female ratio was 1:1. At baseline, two patients in the cohort had refractory disease, and the remaining four patients had experienced relapse during their prior therapy. Four patients had been exposed to lenalidomide, and all six patients had previously received bortezomib. The cohort received bortezomib 1.3 mg/m2 and dexamethasone 20-40 mg weekly for 28 days. Lenalidomide was administered by subcutaneous infusion at a rate of 400 µg/h for 28 days.

As of data cutoff, five patients are continuing treatment with lenalidomide with a median progression-free survival (PFS) of more than 10 months. The best response was a complete response in a patient who had only one prior line of therapy, and the PFS in this patient was 11 months. In the patients with the most prior therapies (n=4), the response was partial with PFS of 9 months.

The most frequently occurring treatment-emergent adverse events were fatigue, diarrhea, injection site erythema, and injection site reaction.

These data suggest that low-dose lenalidomide, administered on a continuous basis, improves the therapeutic index in comparison with oral lenalidomide. Furthermore, it may result in avoidance the hematologic toxicity of more than 22% observed in a literature-based report on oral lenalidomide as second-line therapy for RRMM.

Reference:

116th Annual Meeting of the American Association for Cancer Research. Abstract No. LB207 / 4.

ISB 2001 Yields New Prospects as Multiple Myeloma Treatment

*By **Robert Zadotti***

The first-in-human (FIH) phase 1 study of ISB 2001, a novel BCMA-targeting trispecific antibody, demonstrated both increased cytokine levels and increased expression of T-cell activation cell surface markers in patients with heavily pretreated relapsed or refractory multiple myeloma (MM).

Patients responding to ISB 2001 demonstrated a rapid reduction in soluble BCMA levels within the first two treatment cycles, which were comparable in patients regardless of prior T-cell directed therapies. Expression of T-cell proteins (Ki-67 and HLA-DR) also increased in patients treated at effective dose levels of ISB 2001.

The phase 1 dose escalation trial included 21 patients treated across seven dose levels between 5 to 1200 µg/kg, with no dose-limiting toxicity observed. ISB 2001 was administered subcutaneously once per week in 28-day cycles. Step-up dosing was implemented on days 1 and 4, followed by full target dose starting on day 8.

The overall response rate was 89.5% (n=19) across the effective dose levels and 78% among the nine patients treated with prior T-cell directed therapy.

To monitor pharmacokinetics (PK) and pharmacodynamics profiles, the researchers assessed ISB 2001 serum concentrations, T-cell activation markers and serum concentrations of soluble biomarkers at several time points after treatment. Overall, ISB 2001 showed favorable dose proportional PK in patients with relapsed or refractory MM.

Optimized dosing of ISB 2001 was conducted to minimize cytokine release syndrome (CRS) and associated serum cytokine level changes. Grades 1 and 2 CRS occurred in 14 and two patients, respectively, following the first or second ISB 2001 doses. No immune effector cell-associated neurotoxicity syndrome, grade 5 adverse events (AEs), or AEs leading to treatment discontinuation were observed.

Overall, the study demonstrated clinical efficacy of ISB 2001 at target dose levels of 50 µg/kg and above. The next phase of study, focusing on dose expansion, will evaluate different putative doses and schedules.

Reference

American Association for Cancer Research Annual Meeting 2025. Abstract No. CT147. https://www.abstractsonline.com/pp8/#!/20273/presentation/10468

MicroRNA-Based Therapy Shows Promising Molecular Activity in AML

*By **Melissa Badamo***

Treatment with CR1-02 (5-FU-miR-15a), a synthetic double-stranded mimic of miR-15a (miRNA), was well-tolerated and led to stable disease in patients with relapsed or refractory acute myeloid leukemia (AML), according to a study presented at the American Association for Cancer Research Annual Meeting 2025.

"Since the discovery of microRNA in 1993 and the recognition by the Nobel Prize in 2024, there is still no FDA approved miRNA-based cancer medicine," senior author and presenter **Jingfang Ju, PhD,** of Stony Brook University, told *Blood Cancers Today*. "5-FU-miR-15a will have the potential to be the first miRNA-based multi-targeted medicine to treat AML. Beyond AML, the 5-FU modified miRNA-based platform will have the potential to change the landscape of future cancer medicine."

The phase 1, dose-escalation study used a 3+3 design to evaluate the safety and efficacy of intravenous CR1-02 at four dose levels: 7.5 mg, 11.25 mg, 15 mg, and 18.75 mg/administration weekly.

In 11 patients (average age, 70), CR1-02 was well-tolerated through 58 doses administered across each dose level. Chills during infusion, the most common adverse event, subsided after the infusion time was increased to 2 hours. Five patients achieved stable diseases as defined by the European LeukemiaNet.

According to single-cell profiling mass cytometry, at the lowest dose level of 7.5 mg, CR1-02 displayed molecular activity on known targets of miR-15a, such as BMI1, WEE1, and MCL-1. BAX, a pro-apoptotic protein, also increased after treatment.

After four doses of CR1-02, one patient achieved elimination of extramedullary pericardial AML disease but progressed in bone marrow after 8+8 doses of CR-001, followed by trametinib in another study.

"This is the first miRNA-based, multi-targeted agent to show efficacy in patients with relapsed or refractory AML," said Dr. Ju. "It will be an important drug for future clinical trials to combine with other therapeutic agents to improve quality of life and survival benefit for patients with relapsed or refractory AML."

Reference

American Association for Cancer Research Annual Meeting 2025. Abstract No. CT059 / 4.

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* ***Robert Stuver, MD,*** *of Memorial Sloan Ketting Cancer Center, highlights recent research in Hodgkin lymphoma.*

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

Robert Stuver, MD

HODGKIN LYMPHOMA

Tumor Size, Radiotherapy Have Relapse Implications After Chemotherapy for Hodgkin Lymphoma

By ***Andrew Moreno***

An international team of researchers conducted the H10 study to externally validate findings from the RAPID trial regarding patients with limited-stage Hodgkin lymphoma (HL) who received doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy and achieved positron emission tomography (PET) negativity.

The team's work confirms findings from the RAPID trial that after therapy in this population, having higher maximum tumor diameter (MTD) carries a strong association with relapse risk, as does receiving chemotherapy alone without radiotherapy. The team published its findings in *Blood Advances*.

"These findings refine assessment of risk in LS [limited-stage] HL and can inform clinical discussions for risk-adapted application of radiotherapy," wrote first author **Elizabeth H Phillips, MD,** of the Christie Hospital, Manchester, United Kingdom, and colleagues.

The study populations for both the RAPID and H10 trials consisted of patients with stage 1/2A HL without mediastinal bulk who achieved PET negativity with the ABVD regimen. In the RAPID trial, 208 patients received 3× ABVD with radiotherapy, and 211 patients received 3× ABVD without radiotherapy. In the H10 trial, 556 patients received 3 to 4× ABVD with radiotherapy, and 303 patients received 4 to 6× ABVD without radiotherapy.

In the RAPID trial, MTD was found to be strongly associated with event-free survival, with a hazard ratio (HR) of 1.19 (P=0.02). The H10 trial had a similar result with an HR of 1.22 (P=0.003). Phillips and colleagues noted, "Findings were consistent when adjusting for baseline risk stratification and chemotherapy cycles."

From these data, the H10 investigators determined MTD to be an independent risk factor for HL relapse, and they estimated a 21% increase in risk for each centimeter of MTD, with a pooled HR of 1.21 (P<0.001). Moreover, treating patients with chemotherapy alone carried a pooled HR of 1.19 (P=0.005), and treatment with both chemotherapy and radiotherapy had a pooled HR of 1.24 (P=0.009), having an effect size similar to that calculated with MTD.

From their findings, the investigators determined that MTD and inclusion versus non-inclusion of radiotherapy with chemotherapy were independent risk factors for disease relapse and that this risk is highest in patients who have high MTD and in whom chemotherapy was not accompanied by radiotherapy.

Reference

Phillips EH, Counsell N, Illidge TM, et al. Maximum tumor diameter is associated with relapse risk in limited-stage Hodgkin lymphoma: an international study. *Blood Adv.* Published online January 7, 2025. doi:10.1182/bloodadvances.2024015140

Why I chose this research:

"Modern use of advanced imaging through state-of-the-art CT and PET imaging can guide prognostication in Hodgkin lymphoma. Maximum tumor diameter (MTD) is readily measured on CT scans and has been shown to be associated with risk of relapse. This study evaluated the associated between MTD and risk of relapse in early-stage Hodgkin lymphoma, in particular evaluating chemotherapy-free and combined-modality approaches."

Which Pediatric cHL Patients Should Receive Transplant-Free Salvage Therapy?

By ***Melissa Badamo***

Fludeoxyglucose-18 positron emission tomography (FDG-PET) response-guided salvage therapy may identify which pediatric patients with relapsed or refractory classic Hodgkin lymphoma (cHL) achieve excellent outcomes with transplant-free salvage therapy, according to the phase 3, non-randomized, EuroNet-PHL-R1 trial published in *JAMA Oncology*.

According to lead author **Stephen Daw, MD,** and colleagues, the current standard-of-care salvage therapy for relapsed or refractory cHL consists of consolidation high-dose chemotherapy (HDCT) and autologous stem cell transplant (aSCT). However, they investigated whether presalvage risk factors and FDG-PET response to reinduction chemotherapy "can guide escalation or de-escalation between HDCT/aSCT or transplant-free consolidation with radiotherapy to minimize toxic effects while maintaining high cure rates."

The study included 118 patients younger than 18 years (median age, 16.3) with relapsed or refractory cHL across 68 sites in 13 European countries. The primary endpoint was 5-year event-free survival (EFS), and secondary endpoints included overall survival (OS) and progression-free survival (PFS). As the PFS and EFS were identical, the researchers only reported PFS data in the study.

Patients received alternating ifosfamide, etoposide, prednisolone (IEP) with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) as reinduction chemotherapy. Patients with low-risk cHL (n=59) received a second cycle of IEP, ABVD, and radiotherapy, while patients with high-risk cHL (n=59) received a second cycle of IEP and ABVD plus HDCT and aHSCT with or without radiotherapy.

For the overall cohort, the 5-year PFS was 71.3% (95% CI, 63.5%-80.1%), and the 5-year OS was 82.7% (95% CI, 75.8%-90.1%). Forty-one low-risk patients who received non-transplant salvage therapy had a 5-year PFS of 89.7% (95% CI, 80.7%-99.8%) and a 5-year OS of 97.4% (95% CI, 92.6%-100%). Eighteen low-risk patients who received HDCT and aHSCT had a 5-year PFS of 88.9% (95% CI, 75.5%-100%) and a 5-year OS of 100%. All 59 high-risk patients received HDCT and aHSCT, with a 5-year PFS of 53.3% (95% CI, 41.8%-67.9%) and a 5-year OS of 66.5% (95% CI, 54.9%-80.5%).

"In patients with relapsed/refractory classic Hodgkin lymphoma, risk stratification by FDG-PET response can identify patients that may be cured by chemoradiotherapy only, avoiding toxic effects of HDCT/aSCT [autologous HSCT] and reserving HDCT/aSCT [autologous HSCT] for patients with high-risk disease," wrote Dr. Daw and colleagues.

Why I chose this research:

"The standard treatment for advanced-stage Hodgkin lymphoma has shifted rapidly in the past 5 years from ABVD to regimens that now incorporate brentuximab vedotin and checkpoint inhibitors. This paper explores the use of a novel regimen that eliminates bleomycin and vinblastine and replaces with brentuximab vedotin and nivolumab (BV-N-AD) in stage 2 bulky and advanced stage Hodgkin lymphoma. This innovative trial is the first to combine an anti-CD30 antibody drug conjugate (BV) with an anti-PD1 antibody (N) in the first-line setting."

Reference

Daw S, Claviez A, Kurch L, et al. Transplant and Nontransplant Salvage Therapy in Pediatric Relapsed or Refractory Hodgkin Lymphoma: The EuroNet-PHL-R1 Phase 3 Nonrandomized Clinical Trial. *JAMA Oncol*. 2025;11(3):258-267. doi:10.1001/jamaoncol.2024.5636

BrECADD Recommended as Standard Treatment for Advanced-Stage, Classical Hodgkin Lymphoma After Promising PFS Results

*By **Melissa Badamo***

BrECADD guided by positron emission tomography (PET) after 2 cycles showed better tolerability and efficacy than eBEACOPP for the first-line treatment of adult patients with newly diagnosed, advanced-stage, classical Hodgkin lymphoma, according to a study published in *The Lancet*.

The randomized, multicenter, parallel, open-label, phase 3 trial was led by **Peter Borchmann, MD,** of the University Hospital of Cologne. Of 1,500 patients (median age, 31 years) included in the study, 749 received BrECADD guided by PET after 2 cycles, and 751 received eBEACOPP [escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone]. Patients received cycles of BEACOPP and BrECADD in 21-day intervals, and treatment was administered at the highest dose level.

The primary end points were tolerability, as defined by treatment-related morbidity, and efficacy as assessed by progression-free survival (PFS). Secondary end points included adverse events, frequency of complete response, overall survival, gonadal toxicity and function, secondary primary malignancies, event-free survival, and patient-reported outcomes.

Although most patients in both treatment groups had at least 1 adverse event, patients in the BrECADD group had a lower incidence of at least 1 treatment-related morbidity event (42% vs 59%, respectively; 95% CI, 0.65-0.80; $P<0.0001$). The incidence of grade 3 or higher infections was similar between the 2 groups (19% vs 20%), and the incidence of grade 3 or higher neutropenic fever was lower with eBEACOPP than with BrECADD (21% vs 28%, respectively).

There were also more dose reductions in the eBEACOPP group than in the BrECADD group. For patients receiving BrECADD, the most common reasons for dose reductions included leukopenia in 34% and thrombocytopenia in 23%.

At a median follow-up of 48 months, BrECADD improved PFS with a hazard ratio (HR) of 0.66 (0.45-0.97; $P=0.035$). Estimates of 4-year PFS were 94.3% (95% CI, 92.6%-96.1%) for BrECADD and 90.9% (95% CI, 8.87%-93.1%) for eBEACOPP. The 4-year overall survival rates were comparable between the BrECADD and eBEACOPP groups (98.6% vs 98.2%, respectively).

Dr. Borchmann and colleagues wrote that "after finding non-inferiority of BrECADD at an interim analysis, the superiority test revealed a significant progression-free survival benefit of BrECADD versus eBEACOPP…The increase in efficacy was driven by a reduction in refractory cases and early relapses, thereby reflecting the importance of early definitive disease control in classical Hodgkin lymphoma to achieve favourable, long-term outcomes."

Why I chose this research:

"This large, randomized phase 3 trial evaluated BrECADD versus eBEACOPP in advanced-stage Hodgkin lymphoma. BrECADD is a novel regimen incorporating brentuximab vedotin on a backbone of BEACOPP-based therapy. BrECADD was better tolerated and more effective than eBEACOPP and is a new standard of care."

As for secondary end points, 2% of patients in the eBEACOPP group and 3% of patients in the BrECADD group had second primary malignancies. The rates of gonadal function recovery were higher in both male (86.0%) and female (95.3%) patients in the BrECADD group compared with male (39.2%) and female (72.5%) patients in the eBEACOPP group.

Study limitations include the exclusion of patients older than 60 from the study as eBEACOPP is only recommended for patients aged 18 to 60 years.

"With the individualised PET-2-guided, shortened treatment, the BrECADD regimen shows a favourable risk–benefit profile for most patients," Dr. Borchmann and colleagues concluded. "Therefore, we recommend BrECADD as a standard treatment option for adult patients with newly diagnosed, advanced-stage, classical Hodgkin lymphoma."

This research was funded by Takeda Oncology.

Reference

Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. *Lancet*. 2024;404(10450):341-352. doi:10.1016/S0140-6736(24)01315-1

HemOnc Happenings

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

ASPHO Recognizes Pediatric Hematologist-Oncologists at Annual Meeting

*By **Melissa Badamo***

The American Society of Pediatric Hematology/Oncology (ASPHO) presented several annual awards at the 2025 ASPHO Conference from May 7 to 10 in Louisville, Kentucky, to recognize early-, mid-, or senior-career experts who display excellence in the field of pediatric hematology/oncology. Among the accolades are the Distinguished Career Award, the George R. Buchanan Lectureship Award, and the Childhood Cancer Survivorship Award for Excellence.

Distinguished Career Award

William L. Carroll, MD, of New York University (NYU) Langone Health, received the 2025 Distinguished Career Award. This accolade recognizes a senior physician who made a major impact in the field of pediatric hematology/oncology through research, education, patient care, and advocacy.

William L. Carroll, MD

As a professor in the Department of Pathology at NYU Grossman School of Medicine, Dr. Carroll focuses his research on pediatric acute lymphoblastic leukemia (ALL) and using modern genomic and epigenomic methods to understand the genesis and evolution of the disease, according to his faculty profile.

"I am honored and profoundly grateful to receive the American Society of Pediatric Hematology Oncology's Distinguished Career Award," Dr. Carroll told *Blood Cancers Today*. "My success has been predicated on collaborating with a remarkable community of colleagues, all dedicated to the cure of childhood cancer. Personally, my greatest accomplishment has been training the next generation of clinician-investigators who continue to move the field forward at an astonishing speed."

George R. Buchanan Lectureship Award

The 2025 George R. Buchanan Lectureship Award was presented to **James H. Feusner, MD,** of the University of California, San Francisco (UCSF) Benioff Children's Hospital Oakland.

James H. Feusner, MD

The award honors **George R. Buchanan, MD,** founding member and former president of ASPHO, and is presented to a nationally or internationally recognized educator, mentor, and effective speaker with significant research, education, and clinical expertise. At the annual meeting, Dr. Feusner will present data on all-trans retinoic acid in acute promyelocytic leukemia and share advice to younger colleagues on obtaining satisfaction and long-lasting careers.

Dr. Feusner's research includes nelarabine in pediatric and young adult T-cell ALL, central nervous system relapse in ALL, and obesity in pediatric acute promyelocytic leukemia, according to his faculty profile.

"I was quite surprised when notified about this reward. It is something I had never thought about receiving, although we, George and I, do have some career similarities," Dr. Feusner told *Blood Cancers Today*.

Childhood Cancer Survivorship Award for Excellence

Lucie M. Turcotte, MD, MPH, MS, of the University of Minnesota, received the Childhood Cancer Survivorship Award for Excellence for her efforts in advancing patient survivorship. Dr. Turcotte's research focuses on the outcomes of cancer and hematopoietic stem cell transplantation therapies.

Lucie M. Turcotte MD, MPH, MS

Funded by Northwestern Mutual, this award honors a mid-career childhood cancer survivorship investigator with a growing portfolio of research and project funding. Dr. Turcotte received a $10,000 honorarium to supplement innovative projects aiming to enhance the quality of life of pediatric cancer survivors.

Dr. Turcotte leads the Childhood Cancer Survivor Study's Second Malignancy Working Group and is the silo leader for the Subsequent Malignant Neoplasm and Cancer Screening Task Force for the Children's Oncology Group Long-Term Follow-Up Guidelines, according to her faculty profile.

"Receiving the Childhood Cancer Survivorship Award for Excellence is an incredible honor," Dr. Turcotte told *Blood Cancers Today*. "The survivorship community is small, and I have always felt so supported and have had incredible mentorship from Dr. Joe Neglia at the University of Minnesota and also from the amazing network of researchers and mentors he has connected me with around the country. I hope I can support the next generation and provide them with the same mentorship and guidance that I was fortunate enough to receive."

Reference: American Society of Pediatric Hematology/Oncology. Honoring excellence. Accessed April 30, 2025. https://aspho.org/career-development/awards/overview

Frederick Locke, MD, Awarded Researcher of the Year by Moffitt Cancer Center

Frederick Locke, MD, received the W. Jackson Pledger Researcher of the Year Award from the Moffitt Cancer Center for his impact and contributions to cancer research.[1] Dr. Locke serves as chair of Moffitt's Blood and Marrow Transplant and Cellular Immunotherapy Department and co-leader of the Immuno-Oncology Program.

Frederick Locke, MD

Dr. Locke's research focuses on chimeric antigen receptor (CAR) T-cell therapy for patients with lymphoma and multiple myeloma. He is a lead investigator of the ZUMA-1 and ZUMA-7 trials, which led to the FDA approval of axicabtagene ciloleucel (axi-cel).[1] In ZUMA-7, patients with large B-cell lymphoma treated with axi-cel lived without their cancer getting worse and without needing new cancer treatment for a median of 8 months, compared with 2 months for patients treated with chemotherapy-based standard of care.[2]

"This is an award that really means a lot coming from my fellow investigators and researchers here at Moffitt who have selected me," Dr. Locke told *Blood Cancers Today* in an interview. "I've spent my entire professional life trying to figure out new ways to treat cancer and to develop and run clinical trials for patients with lymphoma. This recognition is a testament to the hundreds of people who are part of our cell therapy team here at Moffitt that have allowed us to have these incredible and impactful scientific reports."

After his father was diagnosed with lymphoma and successfully treated in a clinical trial, Dr. Locke recognized the value and possibility of clinical trials and scientific investigation into new therapies. Reflecting on this experience, Dr. Locke provided advice to younger clinicians or trainees in the field.

"Follow your interests," he encouraged. "Take a long view of the career and think about what you want to contribute to the world and spend your time doing. Careers can take decades to shape up, and new opportunities come up all the time. It's really about positioning yourself to be ready to take those."

References:

1. Jones A. Moffitt Cancer Center Honors Dr. Frederick Locke as Researcher of the Year. Accessed April 30, 2025. https://www.moffitt.org/endeavor/archive/moffitt-cancer-center-honors-dr.-frederick-locke-as-researcher-of-the-year

2. Locke FL, et al. *Future Oncol.* 2025;21(4):393-407. doi:10.1080/14796694.2024.2435214

mashup MD

A first-of-its-kind digital platform for HCPs, MashupMD provides a customizable feed of headlines curated by trusted physicians and medical experts.

"MashupMD's personal feed makes it so easy to navigate X and saves me time as a busy physician."

—Monica Gandhi, MD, MPH
University of California, San Francisco

Join this new platform, a social media alternative for doctors.

- Grow your following as a trustworthy source of notable medical news.
- Speak to all of MashupMD's interested audiences instantly, including verified health care providers.
- Avoid the confrontational discourse that can distract from complex issues on other platforms.
- Benefit from extremely high engagement levels—our average open rate is 3x higher than industry standard.

Scan to visit mashupmd.com

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

cp-258863v5

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[1-3]

CARTITUDE-4 primary analysis demonstrated[†]:

POWERFUL

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

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)

DEEP

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

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

Safety profile

- **Boxed Warning:** cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), parkinsonism and Guillain-Barré syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged and/or recurrent cytopenias, secondary hematological malignancies, and Risk Evaluation and Mitigation Strategy (REMS)
- **Warnings and precautions** include: increased early mortality, prolonged and recurrent cytopenias, infections, hypogammaglobulinemia, hypersensitivity reactions, secondary malignancies, and effects on ability to drive and use machines
- The most common nonlaboratory **adverse reactions** (≥20%) included: 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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

CAR-T=chimeric antigen receptor-T cell therapy; CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.
*From January 2021 to November 2024.
†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.
§Since March 2022.

SELECTED IMPORTANT SAFETY INFORMATION

Fatal or life-threatening reactions occurred in patients following treatment with CARVYKTI® including Cytokine Release Syndrome (CRS), Parkinsonism and Guillain-Barré syndrome and their associated complications, and Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). HLH/MAS can occur with CRS or neurologic toxicities. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which can be fatal or life-threatening, occurred after treatment, before CRS onset, concurrently with CRS, after CRS resolution, or in absence of CRS. A numerically higher percent of early mortality was observed as compared to the control arm in CARTITUDE-4. Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies occurred following treatment. CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

cp-30028v4

Please see Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information, including Boxed Warning, for CARVYKTI®.