TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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April 2025

bloodcancerstoday.com

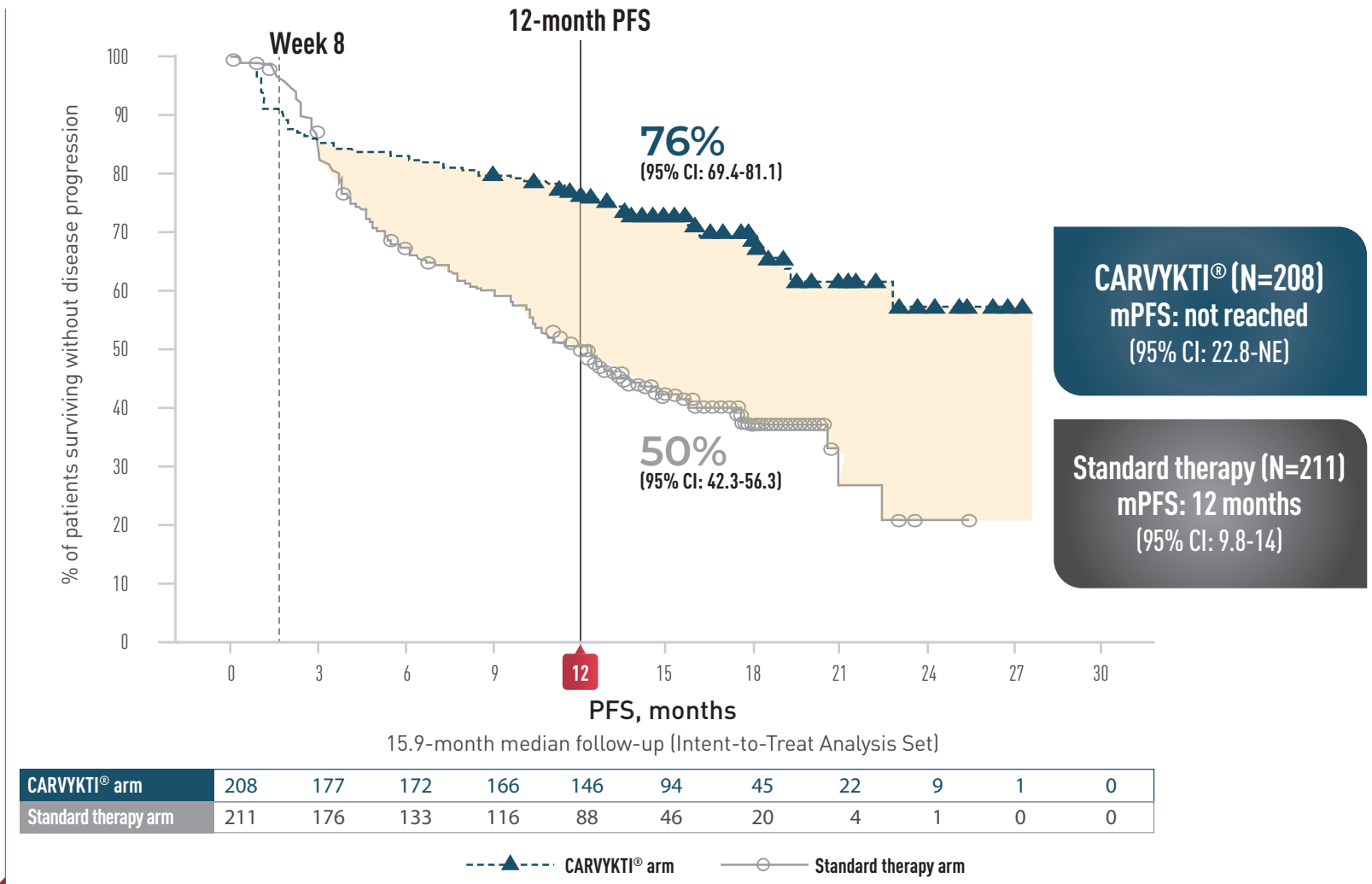
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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®.

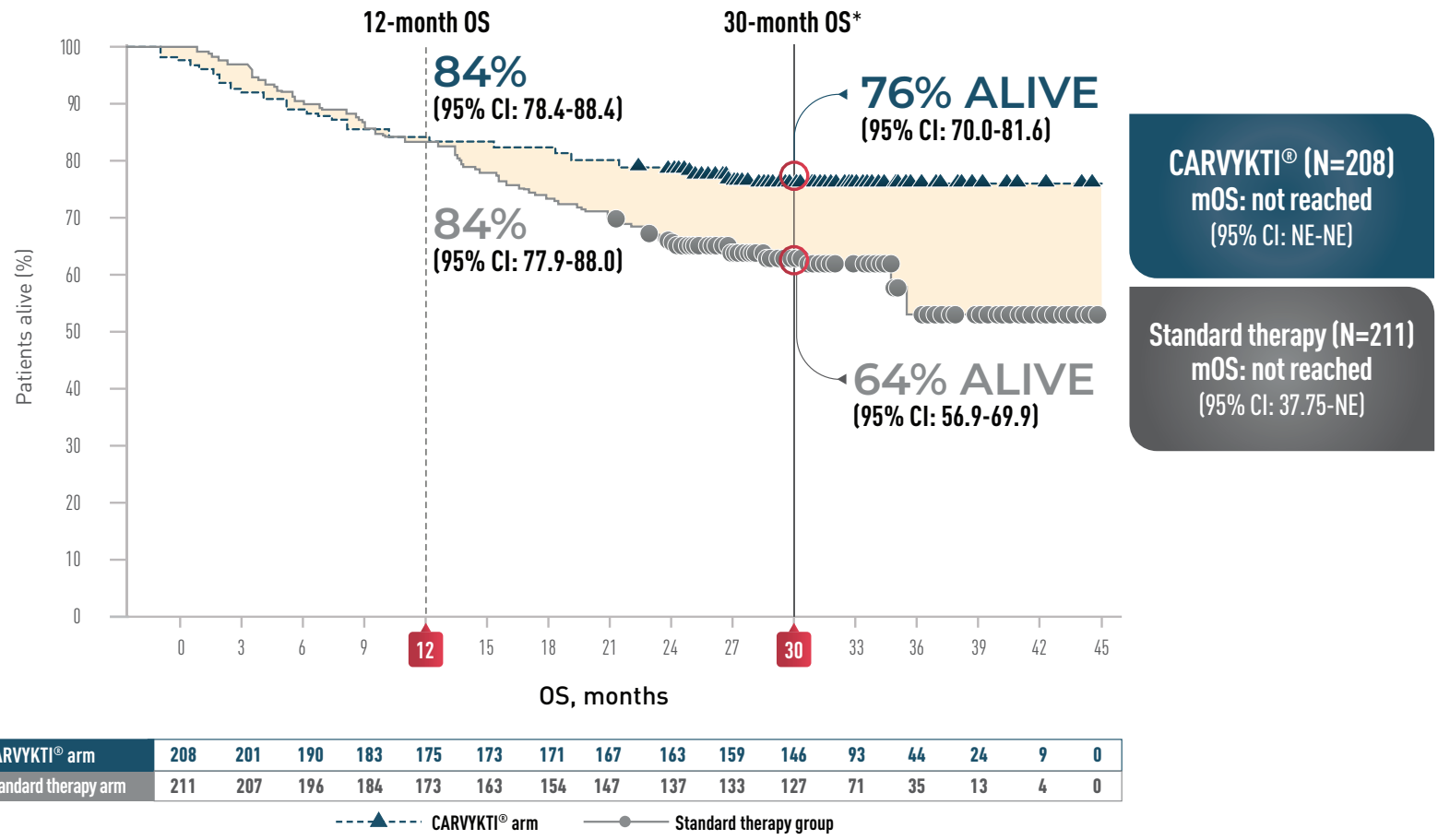
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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.

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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®
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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.

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LEGEND BIOTECH

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First Clinical Trial of Actimab-A Triplet Combination to Begin in AML
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Survivorship in Acute Leukemia: How MRD Monitoring and Treatment Choice Improves Outcomes
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THE BIG CHILL

How a freeze on government scientific meetings and funding interruptions can impact hematologic oncology.

With expert opinions from:
Gwen Nichols, MD, Pavan Reddy, MD, Theodore Wun, MD, and more

MAIL TO:

MEHDI H. HAMADANI, MD:
Global Advances in Blood Cancer Take Center Stage

Join the discussion on Figure 1

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figure1

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How a freeze on government scientific meetings and funding interruptions can impact hematologic oncology

Blood Cancers Today spoke with several hematologic oncology experts about recent policy changes and their potential impact.

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The HemOnc Pulse

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Mayo Clinic

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Calendar

May 30-June 3
American Society of Clinical Oncology Annual Meeting
Chicago, IL

June 12-15
European Hematology Association 2025 Congress
Milan, Italy

June 21-25
International Society on Thrombosis and Haemostasis Congress
Washington, DC

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

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 Annual Meeting
Toronto, Canada

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

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

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

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

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

November 5–9
Society for Immunotherapy of Cancer 40th Annual Meeting
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Editor's Message

Global Advances in Blood Cancer Take Center Stage

Medhi H. Hamadani, MD
Co-Editor-in-Chief

April is a month that never fails to command attention in hematologic oncology—and this year is no exception. From the Americas to Asia, hematologists and oncologists are gathering to exchange ideas, review the latest clinical trial data, and shape the future of patient care. The sheer volume of activity during this month reflects the urgency, collaboration, and innovation that define our field.

We began the month with momentum on both coasts of the world. On **April 5,** the **Leukemia & Lymphoma Society Tri-State Blood Cancer Conference** convened in New York City. This regional meeting continues to provide a vital platform for oncologists, patients, and caregivers to align on the latest standards in leukemia, lymphoma, and myeloma care. Key sessions spotlighted personalized treatment strategies and evolving approaches to survivorship care planning.

That same weekend, on **April 5 and 6,** the **EHA–Hong Kong Society of Hematology Tutorial** brought together leading voices in Hong Kong. This educational meeting—backed by the European Hematology Association (EHA)—delved into updated diagnostics, new indications for Janus kinase inhibitors in myeloproliferative neoplasms, and novel data on the use of bispecific antibodies in relapsed and refractory B-cell malignancies. The tutorial-style format encouraged deep dialogue between trainees and seasoned clinicians.

Mid-month, we turned our focus to Latin America, where hematology and oncology leaders gathered in **Lima, Peru,** for the **European Society for Medical Oncology Summit Latin America 2025,** held **April 11 and 12.** A central theme here was equity—specifically, how to expand access to molecular testing and clinical trials in resource-limited settings. Disease-specific sessions offered updates on acute myeloid leukemia and myelodysplastic syndrome management, with a particular emphasis on integrating new agents into frontline treatment.

As the month draws to a close, the energy only intensifies. On **April 25 and 26, Highlights of ASH in Latin America takes place in Punta del Este, Uruguay,** offering practitioners a chance to revisit the most impactful findings from the 2024 American Society of Hematology (ASH) Annual Meeting. Expect focused sessions on chimeric antigen receptor T-cell therapy advances in lymphoma, emerging risk stratification tools for myeloproliferative neoplasms, and real-world evidence on Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia. This program is always an excellent translation of key ASH insights into regionally relevant clinical practice.

Finally, we converge in **Chicago, Illinois,** from **April 25 to 30** for the **AACR Annual Meeting 2025.** Although the American Association for Cancer Research (AACR) spans the full spectrum of cancer science, its impact on hematologic malignancies is unmistakable. Cutting-edge sessions will highlight the role of the tumor microenvironment in drug resistance, emerging applications of artificial intelligence in risk modeling, and novel translational research across myeloma and acute leukemias. Expect big science, early-phase trials, and no shortage of innovation.

Together, these meetings form a global circuit of learning and exchange. The takeaways extend far beyond new protocols: they shape how we think, collaborate, and push the boundaries of what's possible in hematologic oncology.

This month, we not only follow the science; we advance it.

Warm regards,

Mehdi H. Hamadani, MD
Co-Editor-in-Chief

Behind Clinic Doors

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

Mayo Clinic Laboratories

*By **Melissa Badamo***

In early 2025, Mayo Clinic Laboratories announced a collaboration with Lucence to expand international access to cancer testing services and improve patient outcomes. Lucence will provide access to LiquidHALLMARK, its next-generation sequencing liquid biopsy, through Mayo Clinic Laboratories. This assay detects clinically relevant biomarkers by analyzing circulating tumor DNA (ctDNA) and ctRNA through blood-based tests.[1]

William Morice, MD, PhD

William Morice, MD, PhD, President and Chief Executive Officer of Mayo Clinic Laboratories in Rochester, Minnesota, spoke with *Blood Cancers Today* about the collaboration with Lucence, the role of emerging technology and artificial intelligence at Mayo Clinic, and other initiatives to improve diagnostics and outcomes of patients with hematological malignancies.

Can you please describe the Mayo Clinic and Lucence collaboration and how it will impact patients with hematological malignancies?

Lucence has developed a novel technology, and this will enable us to make that testing more available to patients. They're a Singapore-based company, but they do have a presence in the United States. We are taking our distribution channel of Mayo Clinic Laboratories and bringing the Lucence test to market through that channel. Our oncologists work with

them institutionally as well. From the Mayo Clinic Laboratories and Lucence perspective, it's really about helping them bring their tests to the U.S. market.

How can Lucence's LiquidHALLMARK assay help clinicians make treatment decisions?

This is a field that's really taken off over the last 3-5 years, where we're really starting to see this technology impacting clinical care. Over 10 years ago, we first realized that solid tumors shed nucleic acid into the peripheral blood, and that you can analyze peripheral blood, or genomic abnormalities housed within a tumor, both blood-based and solid tumors.

Liquid biopsy is the general term that's used for analyzing the peripheral blood for genetic abnormalities shed from neoplasms, from malignancies. This is a technology which does that, but it also has some unique attributes compared to some of the other things that are out there. If a patient has a known cancer, you can now look into the peripheral blood to look for the signature of the cancer. This is what's called a theragnostic test, so it can help with therapy selection as well, because you can find genetic abnormalities in a tumor in the peripheral blood that can lead to a targeted therapy. That's where this has a real advantage as well.

What other initiatives or technologies are available at Mayo Clinic Laboratories that could impact patients with blood cancers?

We have over 4,000 tests in our academic department that we offer, and many are focused on hematological malignancies. We have both flow- and molecular-based methods to look for minimal residual disease, which is a standard of care in many of those malignancies. In solid tumors, we have tumor-based tissue assays, including some that are more focused on specific disease types, which can be quite helpful in the care of patients.

That's why Lucence is such a nice complement to that, because we did not have a liquid biopsy type test that could provide the type of interrogation that Lucence can do. One of the shortcomings in blood-based cancer testing is that when we look for genetic abnormalities in tumors, we look at both DNA and RNA. Because some of the genetic abnormalities are much more readily detected with RNA transcripts—particularly like in hematological malignancies, gene fusions, and some of those things that are too big to be seen by next-generation sequencing (NGS) of DNA—Lucence allows you to look for both DNA and RNA in the peripheral blood.

Prior to this, the other liquid biopsies have a blind spot into an important area of genomic testing and cancer. That's one of the reasons why we're excited to be working with Lucence on this technology. They have the ability to look for both RNA and DNA, which is unique.

Artificial Intelligence (AI) is growing in the field of hematological malignancies to advance diagnosis and treatment. What role does AI have at Mayo Clinic Laboratories?

I would say it's a growing one, and it really spans the gamut. One of the reasons I love working at Mayo is that we are very patient-focused. Technologies are great, but the most important thing is to provide answers to complex questions. We're using AI to help us scale our ability to do that.

Some of the tests I mentioned, like flow cytometry, can be very complex. We're using AI to interpret some of the histograms and data coming off the instrument to shorten the turnaround time from 2 hours to 30 seconds. We're also considering using large language models to look across multiple data sets and help provide answers as we look for diagnostics across technology.

What do you hope to see in blood cancer research in the next 5-10 years? How can Mayo Clinic take part in getting there?

As we get more and more sophisticated diagnostic tools, we'll start to recognize different types or subtypes of disease which require different treatments and approaches. We're seeing this even in neurodegenerative diseases, such as Alzheimer's, which allows for more specific treatments.

Certainly, cancer is the same way. We still think of cancer primarily from an organ-based perspective, like breast cancer or lung cancer, where we'll start to have molecular subtypes of cancer. In the next 5 years, I think we'll have a much more sophisticated approach to diagnosing cancer, and therefore a much greater ability to have specific therapies. This will also make it much more convenient for patients.

For example, with the Lucence assay, patients can now get therapy selection without having to have another biopsy. At some point soon, we'll start to see patients monitor for disease recurrence with more blood-based testing without having to undergo so many radiologic procedures. Over the next 5 years, the paradigm about how we think about cancer and how a person lives with cancer is going to change. That's going to start with diagnostics.

Our role at Mayo Clinic Laboratories is to look across the spectrum of technologies, understanding how to put the puzzle together for a patient, and then making that puzzle solved and accessible. We're going to help bring together a holistic offering so that a patient or doctor can go to one spot and understand how to use the most routine and advanced assays to care for their patients—and do that not just domestically, but globally.

One thing we're seeing off the COVID pandemic is the global recognition of the importance and the investment in healthcare where infectious disease, as well as cancer, is still a heavy burden. We'll participate in that not just domestically, but globally. It's the right thing for patients.

Can you further expand on Mayo Clinic's global initiatives?

If you've ever visited our campus, you can go to the oval office and see that Will and Charlie Mayo visited the world, both sharing and learning surgical techniques. This is something that's been part of the Mayo Clinic fabric since its inception.

Right now on the care side, we have Mayo Clinic International, where we're going and building relationships with hospitals and healthcare delivery systems and other parts of the world to help share knowledge and learn. We're doing the same thing with Mayo Clinic Laboratories. We already have activities in over 60 countries, so we've been a global business for some time. As the appetite for global diagnostics grows, we want to help that grow in a way that's responsible for patients.

Mayo Clinic landed #1 on Newsweek's World's Best Hospitals 2025. What does this mean to you as President and CEO of Mayo Clinic Laboratories?

It means a lot. I've been here my whole career, since 1987. Every year, I see that it's an affirmation of our mission and our need to keep the patient at the center. The fact that we're grounded in our Franciscan values—going back to the founding of Mayo Clinic Hospital by the Franciscan nuns. Those are still the values that cue our institution together and draw together talented people from many different parts of the world. It's a validation of our practice model, which was unique at the time, and the power of having a mission and values. Most importantly, it's a validation of the power of teamwork. I feel very humbled to be part of such an incredible team that gets that recognition.

Are there any final thoughts you would like to share?

It's a very exciting time for patients with cancer to start to think about cancer not as a disease that you die from, but that you live with and manage and hopefully it can be cured. Tools like the Lucence assay are going to be an important part of that. We're really excited to work with our own Mayo Clinic practice as well as partners like Lucence to create the solutions patients need going forward.

"Over the next 5 years, the paradigm about how we think about cancer and how a person lives with cancer is going to change."

—William Morice, MD, PhD, President and Chief Executive Officer of Mayo Clinic Laboratories

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In Focus

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

THE BIG CHILL

State of the NIH Yields Myriad Concerns, Uncertainty

By ***Leah Lawrence***

Concern and confusion are common words to summarize how the healthcare research and scientific community is feeling since Donald J. Trump began his second term as President of the United States. In the few months since, President Trump has issued several executive orders or policy changes directed at the NIH that have attempted to reduce indirect cost reimbursements, freeze research funds, and terminate grants.

"There is a lot of confusion and anxiety, and people are just trying to understand what the actual effects will be," said **Gwen Nichols, MD,** chief medical officer of The Leukemia & Lymphoma Society (LLS).

Blood Cancers Today spoke with several experts in the hematology/oncology research community about these policy changes and their potential impact now and in the future.

NIH Impact

Research funding from the NIH has had a foundational role in many of the biggest advances seen in hematology oncology research over the last 30 to 40 years, according to **Pavan Reddy, MD,** director of the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine.

"I would say that everything we do in modern medicine as it relates to hematology/oncology has its roots in research that was funded by or supported, either minimally or extensively, by the NIH," Dr. Reddy said. "It is fundamental to everything we do."

NIH funds have supported early research that led to critical breakthroughs in early targeted therapies such as imatinib, development of monoclonal antibodies such as rituximab, the development of immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, CRISPR gene editing, and more.

More broadly, a study examining how NIH investment in pharmaceutical innovation compared with investment from the pharmaceutical industry showed that funding from the NIH contributed to 99.4% of new drugs approved from 2010 to 2019.[1]

During a recent forum on Capitol Hill hosted by Senators Tammy Baldwin and Peter Welch, former NIH Director **Monica Bertagnolli, MD**, summarized the way in which the NIH affects not only patient care, but the economy.

"Today, we are just beginning to see progress against devastating disease, which has long been hopeless—Alzheimer's disease, ALS [amyotrophic lateral sclerosis], diabetes, even pancreatic cancer—all because of NIH funding," Dr. Bertagnolli said. "This has proven to be a great investment for American taxpayers, producing both extraordinary improvements in health and significant profits for our nation's economy. How can we afford to see this progress stall? Overall, the loss to our nation on so many levels will be way too great."[2]

Indirect Caps

One of the first unanticipated changes occurred in early February, when the NIH announced that there would be "a standard indirect rate of 15% across all NIH grants for indirect costs in lieu of a separately negotiated rate for indirect costs in every grant."[3]

"Indirect costs are instrumental to the overall research enterprise and the infrastructure that supports that research," explained **Jon Retzlaff, MBA, MPA,** chief policy officer and vice president, Science Policy and Government Affairs at the American Association for Cancer Research (AACR). "Every institution and organization has a negotiated rate, whether that be 40% or 50%, when you make such a dramatic cut down to 15% for everyone

that is going to be very difficult for institutions or universities to maintain that necessary support."

The direct costs of a research project are things "that can be identified specifically with a particular sponsored project" and might include salaries for a principal investigator, equipment, and supplies directly supporting the grant-supported project.[4] Indirect costs include costs that are frequently referred to as overhead expenses (for example, rent and utilities) and general and administrative expenses (for example, officers' salaries, accounting department costs, and personnel department costs).[5]

Shortly after these caps to indirect costs were announced, a federal judge in Massachusetts ordered a nationwide pause temporarily blocking the NIH from reducing grants; this injunction was then extended until a ruling is made by a higher federal court.[6]

"There is a sense that indirect costs equal overhead, and while in theory it does, these things are not perks," Dr. Nichols said. She mentioned an example used by a lawyer in the federal case discussing medical waste, the disposal of which would be considered an indirect cost. "The indirects go to paying for people to clean glassware, maintain freezers, and dump medical waste in a safe way. These are all the underpinnings that don't get direct coverage in the grant."

Dr. Reddy mentioned other examples such as costs related to research animal management, accounting, salaries, building maintenance, and electricity.

"Institutions do not have pots of money to support this kind of work for research," he said. "If you cut indirects, the institution can't support that research, and then even the research supported by the directs can't be done."

Dr. Nichols said that few would deny that there is probably some waste in the system of indirects, but that it needs to be looked at carefully. Rapid, across the board cuts—with no understanding of where the waste actually is—is not the right approach, she said.

Grant Freezes, Terminations

The status of caps on indirect costs is not the only thing in limbo. Not long after taking office, President Trump ordered a freeze on all federal grants, including NIH grants. NIH grant applications must go through an extensive and rigorous review process, and this freeze was estimated to have stalled about 16,000 grant applications vying for $1.5 billion in NIH funding, according to NPR [National Public Radio].[7]

Several Democratic attorneys general filed suit against the Administration arguing that the funds were not under the authority of the President. Federal Judge John J. McConnell, Jr., granted a preliminary injunction against the executive order; however, the injunction only applies to the 22 states and the District of Columbia that filed the suit.[8,9] The decision was expected to be appealed. As of this writing, it appeared that some of these meetings would resume in late March; the NIH has submitted notices for 4 meetings to the *Federal Register*.[10]

"The suspension of these meetings has meant that researchers are waiting longer for review of their applications. How is research funded during that time?" Retzlaff said. "We are talking about the potential dismantling of the entire medical research enterprise. People are frightened."

The Trump Administration also issued an executive order on January 20, 2025, aimed at "ending radical and wasteful government DEI [diversity, equity, and inclusion] programs."[11] Subsequently, the FDA appeared to have removed the website for its Project Equity, a program launched to ensure that cancer drugs were studied based on a diverse group of participants.[12] Later, the NIH terminated millions of dollars in research awards based on restrictions for research related to diversity, equity, and inclusion.[13]

"We have had both early and senior career researchers impacted by that decision," said **Theodore Wun, MD,** chief, Division of Hematology and Oncology at UC Davis Comprehensive Cancer Center. "It is hard to understand because there really is no accepted definition for what might fall into 'DEI,' and believe me, I have looked."

Within hematology and oncology, research looking at different populations of patients is very important because it relates to incidence of disease, genetic makeup of the people diagnosed, and response to therapy, among other things.

"The work that has used wide populations of people has given us new insights into different prognostic factors, new targets, and the basic biology of the diseases that we deal with, as well as potential new therapies," Dr. Wun said. "If you are only looking through a small window at things, you are not going to see the whole picture."

For example, the incidence of Philadelphia chromosome–like acute lymphoblastic leukemia (ALL) is higher in some populations.

"By studying this disease in people at higher risk of having it, we learned about Philadelphia chromosome–like ALL—which does occur in other populations as well—and we learned how best to treat it," Dr. Wun said. "This is not about politics. We need to study broad populations. It is good science and leads to greater insights."

Dr. Reddy agreed. There are aspects of DEI that the scientific community views as research into disparities in care.

"Why do disparities happen, whether it be rural versus urban, by socioeconomic class, across demographics?" Dr. Reddy asked. "I feel that as scientists and doctors we need to minimize those things. To do that, we need to understand them."

In late March, the NIH publicized that applications for funding opportunities would no longer require diversity plans and that diversity plans included in applications will not be evaluated or considered in funding decisions. Recruitment plans to enhance diversity are no longer required.[14]

Effects

This onslaught of change and the pending litigation related to it have left many unsure about what to do next. It has put a chill on scientific creativity, Dr. Nichols said.

"People are afraid. What are you allowed to say or not allowed to say?" Dr. Nichols said. "Information that you might be looking up one day may suddenly disappear and you can't speak to anyone at the NIH for weeks to ask about it."

Some of the immediate effects of these executive orders and policy changes are already evident.

"Institutions are struggling to deal with this freeze in funding, and it has only been a few weeks," Dr. Reddy said. "People are trying to patch things up here and there, working a few extra hours if someone has been laid off, but that is not a sustainable solution."

Dr. Wun said it is important to dispel the notion that this research funding is going only to research carried out in labs and done in Petri dishes and mice.

"The effects span research from very basic to clinical trials to population research," Dr. Wun said. "This is research where we get new insights into the pathways of cancer development that is used to eventually develop new therapies. All of it is threatened."

Dr. Reddy provided an example related to a clinical trial at Baylor's Dan L Duncan Comprehensive Cancer Center, which includes a Veterans Affairs hospital. Let's say this trial in veterans was supposed to include 5 patients that need access to a drug and need to be monitored while on the drug, Dr. Reddy said. With these types of proposed cuts, only 2 of the 5 patients can be included because the institution can no longer afford to enroll 5.

"We are not talking about missing a dose of a hypertension pill, which itself has ramifications," Dr. Reddy said. "But missing a dose of critical therapy in the world of cancer and hematologic malignancies is literally life and death."

Dr. Reddy said that the longer this uncertainty goes on, the more likely it is that a lot of the phase 1 units may have been shut down. In addition to the effect on patients, Dr. Wun and others mentioned the potentially devastating impact on the research community.

"People won't have jobs," Dr. Wun said. "Many people may choose to leave careers in research."

Dr. Nichols said she worries about the early-to-mid–career investigators who may struggle to keep their labs open. "They are often the people with some of the most novel ideas, and they are the future of the research enterprise," she said. "It is

> **"This is research where we get new insights into the pathways of cancer development... All of it is threatened."**
>
> *—Theodore Wun, MD, chief, Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center*

going to be even more competitive with less funding available, so there will be people that are going to quit, go to industry, or go work in another country."

The LLS is looking into how it could potentially help support young researchers, and Dr. Nichols hopes that other societies or institutions will try to step up to try to "plug the holes" in funding as best as they can.

For example, in March, the American Society of Hematology (ASH) announced that it would expand eligibility of its Bridge Grants, awards that provide a 1-year installment of $150,000 to ASH members who have applied for an NIH R01 grant but were not funded.[15]

"Recognizing the recent disruptions to NIH study sections, ASH has waived the requirement that an NIH proposal be discussed and critiqued prior to submission to the ASH program. Additionally, the limit on other research funding/resources has increased to $500,000, the institutional match requirement is suspended, and individuals who have previously received a Bridge Grant can now apply for funding for a new proposal," ASH announced in a statement.[15]

Dr. Wun echoed Dr. Nichols' concern about the loss of research talent. "We are especially worried about early career people. They are very vulnerable, and we stand to lose an entire generation of researchers," he said.

Dr. Nichols emphasized that although this loss may not be immediately tangible, "We will feel it 10 years from now when the U.S. is no longer the leader of scientific enterprise."

Take Action

Dr. Nichols said that when discussing the current situation at the NIH, she tries not to focus on the policy of things, or whether or not these cuts should or should not be made.

"I focus on what the impact will be and what we can do to step up to avoid damaging results," Dr. Nichols said. "A lot of people are politicizing it instead of saying, 'This is the reality. Let's talk about what it means and how to mitigate the effects.'"

On its website, the LLS encourages anyone who is concerned to contact their members of Congress to call on them to urge the Administration to rescind these devastating cuts. The LLS will send anyone who is interested simple ways to communicate with their elected officials; just text SPEAK to 73727.

"It is easy to get angry and complain, but it is not hard to advocate and educate," Dr. Nichols said. "Go out there and talk about it and help people understand what these cuts mean and try to find solutions."

The AACR also put out a statement of concern related to actions affecting the NIH and called upon the Administration to "abandon its numerous executive orders and other proposals that would irreparably damage NIH."[16]

"We need our members, and every advocate in the medical research community, to be contacting members of Congress, and telling them to prioritize NIH funding to ensure the health of every citizen in our country," Retzlaff said. "This is how we make sure the U.S. is at the top in terms of remaining a leading nation for medical research and ensuring we have the next generation of individuals to fight current and future disease."

The AACR has resources available for those interested in legislative action, including a form that can be used to contact U.S. Senators and Representatives at https://www.aacr.org/professionals/policy-and-advocacy/aacr-legislative-action-center/.

Dr. Wun said that as an individual, he is a member of professional societies, such as ASH, that engage in advocacy at a national level, but he also encouraged physicians to be involved at a local level. That doesn't just mean engaging local government officials, but also engaging patients.

"I feel I benefit from having a patient population that appreciates the critical importance of research; they are mindful of the fact that the treatments I am giving them now were developed through robust clinical research," Dr. Wun said. "Engaging your patients allows them to be advocates. It is important because patients can understand more than most what the stakes are."

Patients are also very effective at sharing their stories with their elected representatives, Dr. Reddy said.

"When you sit in a room and are only looking at how much something costs—which is a legitimate thing to look at—your vantage point is very different," Dr. Reddy said. "We need people to have an expansive view and to engage scientists and doctors when making decisions about where the reforms need to happen."

Reforms are important and are a normal part of progress, Dr. Reddy said.

"Most people would agree that reform is long overdue, but the way it is being rolled out at the moment has caused a lot of apprehension and confusion among institutions, investigators, and patients and has left a lot of science in a frozen state, for lack of a better word," he said. "Let's not throw the baby away with the bathwater. If the consequence was only money, innovation, or competition, that approach might work, but when the consequences are life or death, clinicians don't have the luxury of that kind of creative destruction."

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Regulatory Actions

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

FDA Issues Fast Track Designation for New CAR T-Cell Therapy for Relapsed Refractory DLBCL

*By **Andrew Moreno***

The FDA has granted Fast Track Designation to the chimeric antigen receptor (CAR) T-cell therapy azercabtagene zapreleucel (azer-cel) for the management of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Imugene Limited, the immuno-oncology company which is developing azer-cel, issued a press release announcing the FDA's decision.

Azer-cel is an allogeneic, CD19-targeting CAR T-cell therapy for DLBCL and other blood cancers. It applies a novel approach of combining lymphodepletion chemotherapy with interleukin-2 to bolster the agent's efficacy, especially against disease resistant to multiple therapy lines. It is also designed to be a faster and more accessible treatment option for patients than autologous CAR T-cell therapy.

An ongoing phase 1b trial has reported encouraging efficacy data from azer-cel against DLBCL, especially for patients with disease for which several previous therapies, including autologous CAR T-cell therapy, have been unsuccessful. Clinical investigations have also found azer-cel to have a manageable safety profile and an absence in key patient cohorts of immune effector cell-associated neurotoxicity syndrome.

"Receiving FDA Fast Track Designation is a testament to the transformative potential of azer-cel for patients battling relapsed or refractory DLBCL. We are committed to working closely with the FDA to bring this important therapy to patients as efficiently as possible," said Leslie Chong, chief executive officer and managing director of Imugene, in the press release.

Reference

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Imetelstat Approved in European Union for Anemia, Lower-Risk MDS

*By **Melissa Badamo***

The European Commission (EC) has approved imetelstat for adult patients with transfusion-dependent anemia due to lower-risk myelodysplastic syndromes (LR-MDS), according to a press release from Geron Corporation, the developer of the drug.[1]

The drug is indicated for patients without an isolated deletion 5q cytogenetic (non-del 5q) abnormality who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agents.[1]

Imetelstat was previously approved in the United States in June 2024. Both approvals were based on results of the phase 3, double-blind, placebo-controlled IMerge study, which showed disease-modifying activity and durable transfusion independence of about 1 year with imetelstat. The rate of transfusion independence was 40% in the imetelstat group versus 15% in the placebo group (P=0.0008).[2]

Ninety-one percent of patients receiving imetelstat and 47% receiving placebo experienced grade 3-4 treatment-emergent adverse events, most commonly neutropenia (68% with imetelstat vs 3% with placebo) and thrombocytopenia (62% vs 8%). No treatment-related deaths were reported.[2]

"I am thrilled that the European Commission has approved RYTELO [imetelstat] in LR-MDS," **Uwe Platzbecker, MD,** co–lead author of the IMerge trial and chief medical officer at the University Hospital Carl Gustav Carus Dresden in Germany, said in the press release. "Physicians and patients in Europe are now one step closer to accessing a novel treatment that, in addition to having a generally manageable safety profile, has the potential to provide extended and continuous red blood cell transfusion independence."

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FDA Approves Phase 1b/2 Trial for CTD402 in T-ALL/LBL

*By **Melissa Badamo***

The FDA has approved an Investigational New Drug (IND) application for CTD402, a CD7-targeted universal chimeric antigen receptor T-cell (UCAR-T) therapy, for the treatment of pediatric and adult patients with relapsed or refractory T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL), according to a press release from Bioheng Therapeutics.[1]

After the IND approval, CTD402 will be studied in a single-arm, open-label, phase 1b/2 trial aimed at optimizing dosing with a simplified dose-finding design and accelerating clinical development of CTD402.[1]

The off-the-shelf UCAR-T therapy is genetically modified to prevent graft-vs-host-disease and host-vs-graft rejection while improving antitumor activity, according to the company.[1]

"We are delighted that CTD402 has received IND clearance from the U.S. FDA for a Phase Ib/II trial with a simplified dose-finding design, accelerating our clinical development timeline in the United States," said **Jiangtao Ren, PhD,** president and chief scientific officer of Bioheng, in the press release.[1] "IIT [investigator-initiated trial] study results showed an impressive ORR [overall response rate], alongside a favorable safety profile. These results validate our ANSWER® platform's ability to deliver both rapid therapeutic impact and reduced patient risk, positioning CTD402 as a potential best-in-class therapy for T-cell malignancies."

Since 2020, the company has treated about 100 patients with CD7 UCAR-T therapy through their ANSWER platform, a novel and proprietary UCAR-T therapy technology platform.[2]

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Experts Review Considerations in Cilta-Cel Versus Ide-Cel, Bispecific Antibodies for Relapsed or Refractory MM

*By **Andrew Moreno***

In a review article, experts from the Cleveland Clinic, the Fred Hutchinson Cancer Center, and the Mayo Clinic examined recent clinical trial data to clarify the role of ciltacabtagene autoleucel (cilta-cel) in the management of relapsed or refractory multiple myeloma (MM). Their article was published in *Cancer Management and Research*.

"Overall, cilta-cel has demonstrated remarkable activity in both early and later lines of therapy for RRMM [relapsed or refractory MM]. Notably, it is a maintenance-free treatment option, which is important for patients' quality of life, who often need to receive continuous therapy without breaks until progression," wrote first author **Utkarsh Goel, MD,** and colleagues.

Cilta-cel, an autologous second-generation chimeric antigen receptor (CAR) T-cell therapy, was originally only approved by the FDA for MM treatment after 4 prior lines of therapy. Following its success in the phase 3 CARTITUDE-4 trial, it was approved in April 2024 for use after 1 or 2 lines of therapy.

The authors reviewed the previous clinical trials that investigated cilta-cel for heavily pretreated MM—the LEGEND-2, CARTITUDE-1, and CARTIFAN-1 trials, along with the ongoing multi-cohort CARTITUDE-2 trial, which also explores use in newly diagnosed disease. The success of the CARTITUDE-4 trial has spurred research into the use of cilta-cel for earlier lines of therapy, with the upcoming CARTITUDE-5 and CARTITUDE-6 trials to be focused on newly diagnosed MM, and the CAR-PRISM study, on high-risk smoldering MM.

The authors also surveyed these trials' data for prevalence of adverse events associated with cilta-cel. These include cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), neurotoxicity-linked movement and cognitive disorders, hematologic toxicities, and second primary malignancy.

Regarding the use of cilta-cel or idecabtagene vicleucel (ide-cel) for relapsed or refractory MM, the 2 FDA-approved CAR T-cell therapies for this disease, the authors recommend they be considered for all patients with at least 4 prior lines of therapy. However, because of toxicities, such as those measured by the authors in the cilta-cel trials, CAR T-cell therapy should only be used in earlier lines of treatment if patients have a high-risk disease phenotype.

When a choice between CAR T-cell therapy and a bispecific antibody—another treatment approved by the FDA for patients with relapsed or refractory MM—is being made, the authors advise attempting CAR T-cell therapy first. They acknowledge, however, that CAR T-cell therapy is a more time-consuming and clinically taxing approach and is not as widely or quickly available as bispecific antibodies.

The authors then made specific comparisons of cilta-cel with ide-cel and bispecific antibodies as treatments for relapsed or refractory MM. Real-world and trial data show cilta-cel is more effective than ide-cel, but cilta-cel carries greater toxicity concerns than either ide-cel or bispecific antibodies, such as in the incidence of CRS and ICANS.

"Most importantly, cilta-cel has been linked with unique non-ICANS delayed MNTs [movement and neurocognitive treatment-emergent adverse events] such as nerve palsies, Guillain–Barré syndrome, and parkinsonism," wrote Dr. Goel and colleagues.

Moreover, despite greater overall effectiveness, in some subpopulations with high-risk disease, cilta-cel has diminished effectiveness. Certain noteworthy clinical trial findings, such as those from the phase 1b/2 RedirecTT-1 study, also suggest that a bispecific antibody management approach might be more effective in these patients, such as those with extramedullary disease.

"Given these impressive outcomes, bispecific combination may become the preferred regimen in heavily pretreated patients with extramedullary disease soon, even among those who qualify for standard-of-care or experimental CAR T-cell therapies," elaborated Dr. Goel and colleagues.

The authors point out the difficultly of determining the role of these treatments relative to one another in relapsed or refractory MM management, given the need for more clinical research. Head-to-head randomized trials to compare these approaches are lacking, and it is difficult to draw reliable conclusions from cross-trial comparisons. Moreover, other CAR T-cell therapies under development, such as anitocabtagene autoleucel or arlocabtagene autoleucel, may offer efficacy comparable to that of cilta-cel with less toxicity.

"Optimal sequencing of these agents remains unclear, and treatment selection is mostly influenced by patient parameters, disease characteristics, patient and physician preference, and logistics," explained Dr. Goel and colleagues.

Reference

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First Clinical Trial of Actimab-A Triplet Combination to Begin in AML

*By **Melissa Badamo***

A clinical trial will evaluate the safety, optimal dosing, and rate and duration of complete remission of Actimab-A in combination with venetoclax and ASTX-727 in the frontline setting for patients with acute myeloid leukemia (AML), according to a press release from Actinium Pharmaceuticals, Inc.

This is the first clinical trial of Actimab-A under Actinium's Cooperative Research and Development Agreement with the National Cancer Institute. Actimab-A, a humanized anti-CD33 antibody conjugated to actinium-225 that targets CD33, has shown tolerability and a manageable safety profile in combination with venetoclax in a phase 1 trial.[1] The combination also yielded an overall response rate (ORR) of 67%, a 1-year overall survival (OS) of 53%, and a 2-year OS of 32%.[2] At the recommended phase 2 dose, the ORR was 83% and the measurable residual disease rate was 75%.[2]

Venetoclax in combination with hypomethylating agents (HMAs) is currently approved for patients with newly diagnosed AML.[1]

"While Ven-HMA has positively impacted outcomes in AML, a significant number of patients have poor responses or relapse quickly resulting in dismal outcomes. We believe Actimab-A's potentially synergistic, and mutation agnostic mechanism of action can improve clinical outcomes for these patients by producing deeper remissions, including measurable residual disease negativity, that are more durable," said **Avinash Desai, MD,** chief medical officer of Actinium, in the press release.[1]

Actimab-A's mutation agonistic mechanism allows the antibody to overcome high-risk features such as *TP53* mutations, Dr. Desai added.[1]

"This triplet regimen can be conveniently administered in the outpatient setting, as venetoclax and ASTX-727 are both oral agents and Actimab-A does not require isolation given that it is an alpha-particle emitter," he explained in the press release.[1]

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Study Highlights Racial and Ethnic Disparities in AML Trials

*By **Melissa Badamo***

Studies have reported racial and ethnic disparities in the survival and incidence of patients with acute myeloid leukemia (AML), which may stem from underrepresentation in clinical trial enrollment.

To investigate these disparities, **Nathalie Loeb,** of McMaster Children's Hospital, and colleagues performed a systemic review of literature on the enrollment of members of racial and ethnic minority groups and older adults into randomized controlled trials for AML. In total, the review included 90 studies across 157 full texts and 7759 titles and abstracts discovered through the MEDLINE database.

The researchers also conducted a meta-analysis of enrollment incidence ratios (EIRs), defined as "the ratio of trial proportions of members of a racial and ethnic subgroup divided by the U.S. population–based incidence in the corresponding racial and ethnic subgroup in the SEER [Surveillance, Epidemiology, and End Results] database."

Twenty-one of 90 trials (23.3%) reported patients' race or ethnicity. Of these, 15 (71.4%) included data on Black patients, 21 (100%) on White patients, 14 (66.7%) on Asian or Pacific Islander patients, 2 (9.52%) on Native American/Alaska Native patients, and 4 (19.0%) on Hispanic patients. The percentage of trials reporting on race increased from 19.5% before 2014 to 46.2% after 2024. In addition, 26 of 90 trials (28.9%) reported age of 65 years and older.

Of the 21 trials that reported race, 4.7% of patients were Black, 9.8% were Asian/Pacific Islander, 0.5% were Native American/Alaska Native, 80.8% were White, and 3.4% were Hispanic. The proportion of members of racial minority groups enrolled in trials also increased in the last 20 years.

The proportion of trials reporting race and ethnicity was also stratified by geographic location. Of the 14 trials conducted in the United States, 4 (28.6%) reported on race or ethnicity, and 4 (28.6%) reported the proportion of older adults enrolled. In the 4 U.S. trials that reported on race and ethnicity, Hispanic patients (EIR, 0.28; 95% CI, 0.15-0.50; I2=46.9%) and Asian patients (EIR, 0.16; 95% CI, 0.09-0.28; I2=0%) were significantly underrepresented, and White patients (EIR, 1.23; 95% CI, 1.13-1.35; I2=0%) were significantly overrepresented.

"Most trials did not report data on race and ethnicity or on enrollment proportion of participants aged ≥65 years," the researchers concluded. "Efforts should continue to include patients from underrepresented minority groups in clinical trials to prevent racial disparities in research."

The researchers acknowledged limitations of the study, including the fact that a low number of randomized trials had data on race or ethnicity. "Another limitation is the publication bias of the studies included in the systematic review, in which more studies conducted in countries with a majority White population would be published," they wrote.

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Expert Panel Updates NCCN Guidelines on Pediatric ALL with Focus on T-ALL

*By **Andrew Moreno***

The National Comprehensive Cancer Network (NCCN) recently convened a multidisciplinary panel of experts from children's hospitals across the U.S. to update the NCCN Clinical Practice Guidelines in Oncology for pediatric acute lymphoblastic leukemia (ALL). Applying current evidence, the panel's update focuses on pediatric T-cell lineage ALL (T-ALL) and was published in the *Journal of the National Comprehensive Cancer Network*.

The panel begins the update by establishing the overall state of ALL management. This clinical area has seen significant progress in prior decades, although increases in survival benefit have been markedly greater for pediatric patients than for adults.

"Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, the use of allogeneic hematopoietic cell transplantation (HCT), and improvements in supportive care," according to **Hiroto Inaba, MD, PhD,** of St. Jude Children's Research Hospital, Memphis, Tennessee, and colleagues.

The section on diagnosis in the updated guidelines addresses how to clinically differentiate ALL from leukemia and lymphoblastic lymphoma and T-ALL from B-cell lineage ALL (B-ALL). It encompasses patients' presenting symptoms, blood count, laboratory biomarkers, immunophenotyping, bone marrow lymphoblast findings, central nervous system (CNS) involvement, and imaging of the head and chest. Two distinguishing features of T-ALL highlighted by the panel are that mediastinal mass is found in more than 50% of patients and that more than 50% of patients have *NOTCH1* mutations.

To ascertain risk and prognoses for patients who have pediatric ALL, clinical researchers have identified patient age, white blood cell count, CNS disease, immunophenotype, and genetic features of the disease to be significant factors. However, the expert panel repeatedly stresses the importance of measurable residual disease (MRD) findings for prognosis and management decision-making in both T-ALL and B-ALL, although next-generation sequencing (NGS) to detect MRD is approved by the FDA for the latter but not the former.

Inaba and colleagues make the following point: "Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies."

As described in the update, management of pediatric T-ALL generally involves use of multiple chemotherapy agents, starting with an induction therapy regimen that usually includes vincristine, asparaginase, and corticosteroids, with or without an anthracycline. This is followed by consolidation, then interim maintenance, delayed intensification therapy, and then maintenance therapy.

"The consolidation phase is the treatment phase most affected by risk stratification, such that patients with lower-risk disease receive less intensive consolidation and patients with higher-risk disease receive consolidation that is more intensive," noted Inaba and colleagues.

Regarding the induction therapy phase, the panel explains that in most protocols for pediatric T-ALL, a 4-drug regimen is used. The nucleoside metabolic inhibitor nelarabine and the proteasome inhibitor bortezomib are recommended in this setting, and in the update, the panel reviews clinical trial findings for these agents, along with findings comparing the corticosteroid types that can be used in frontline regimens. For relapsed and refractory T-ALL, nelarabine- and bortezomib-based regimens are also recommended, as are daratumumab- or venetoclax-based regimens. Revumenib may also be considered for *KMT2Ar* disease.

For both frontline management of T-ALL and treatment of refractory T-ALL, the panel recommends that patients be entered into a clinical trial, if one is available. Moreover, allogeneic HCT remains the only curative treatment for T-ALL at this time, although it still requires induction of successful remission beforehand.

"In general, MRD positivity at the EOI [end of induction] in B-ALL and EOC [end of consolidation] in T-ALL, predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD before allogeneic HCT should be considered," recommended Inaba and colleagues on the panel.

Reference

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Highlights From the **2025 INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM**

From Curative to Palliative: Navigating DLBCL Care in Older, Frail Patients

*By **Nichole Tucker***

Fitness—not just age—is the key consideration in treating older adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL). A significant portion of this population is classified as frail, making optimal treatment a "persistent challenge," according to **Pallawi Torka, MD**, assistant attending physician at Memorial Sloan Kettering Cancer Center.

Pallawi Torka, MD

During a mini-symposium on DLBCL at the 2025 International Ultmann Chicago Lymphoma Symposium (IUCLS), Dr. Torka explored the nuances of assessing fitness, outlined practical tools such as the Simplified Geriatric Assessment and the Timed Up and Go test, and emphasized the need to distinguish between curative and palliative approaches early in care planning.

In an interview with *Blood Cancers Today,* Dr. Torka expanded on her IUCLS presentation and discussed current guidelines and evidence-based strategies for managing DLBCL in older adults.

What did you discuss during IUCLS, and how does it fit into the overall conversation around newly diagnosed DLBCL management?

I was part of the mini-symposium on diffuse large B-cell lymphoma, and my talk was on the challenges that we face in treating unfit, frail, older adults. So, a lot was unpacked in that talk. The highlights were, number 1, not all older adults are the same. We should really be talking about functional age, or functionomics, rather than chronological age. There are many ways of figuring out functional age. Some of the simple measures are the Simplified Geriatric Assessment and the Vulnerable Elders Survey-13, which is also a patient-administered questionnaire. The simplest, though, is the Timed Up and Go test, which takes about 15 seconds to do and can really identify what kind of risk a patient is at for toxicities.

I also touched upon different kinds of treatments, both current treatments and upcoming treatments, and I shared an algorithm about how to think about these patients and talked in brief about relapsed/refractory DLBCL and how CAR T-cell therapy is still the best option for our older patients.

For those who are CAR T ineligible or those whose disease comes back after CAR T-cell therapy, outcomes are poor, regardless of age, but that's where there are many ongoing clinical trials, which are evaluating novel combinations. I think they're going to move the needle forward in a few years.

What do guidelines say about treating this patient population, and how does that guide you in treatment optimization?

So, I think the first question is, what do you call an older adult? In general, if you look at the guidelines, anybody who's above the age of 65 qualifies as older, in terms of lymphoma. I think anybody who's above 70 should have some sort of functional assessment, which could be very simple. It could just be the Timed Up and Go test, as I said, or the Simplified Geriatric Assessment. The most important thing is that we have to decide up front whether a patient is fit for curative treatment or palliative treatment. What do I mean by that? If a patient is eligible for any amount of anthracycline, for example, if they can even get R-mini-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone], they can potentially receive curative treatment. So, that's the first decision that we have to make. And then, based on that, we decide if a patient is completely fit.

Regardless of age, they should get either our R-CHOP or POLA-R-CHP [polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone] —whatever the preference is. Patients above 80 years of age are automatically classified as unfit based on the Simplified Geriatric Assessment, and there's plenty of data, which show that R-mini-CHOP and POLA R-mini-CHP have similar outcomes compared to full doses of these treatments. So, I generally prefer attenuated chemotherapy in these patients because we need a balance of efficacy but also toxicity, and this seems to fit the bill.

All these patients should be considered for enrollment in clinical trials because we want to take the onus away from chemotherapy and try many of these novel treatments that are coming up to achieve cures, so that it's less toxic for our patients.

With ongoing clinical trials in mind, how do you see treatment of older adult patients with DLBCL evolving over time?

The way I think about clinical trials in our older patients is that you have to really decide fitness. As I mentioned, for somebody who's fit, they should go on similar trials that are earmarked for our younger patients. One of the large ongoing trials is the SKYGLO study, which is looking at the combination of glofitamab with polatuzumab and R-CHOP. Then we have the EPCORE study, which is looking at epcoritamab with R-CHOP. Our fit patients are best served by these trials. For unfit patients who are still candidates for chemotherapy—but maybe they are at higher risk of toxicities from full-dose chemotherapy—I think they are the best clinical trials for our patients who are unfit. We want to use trials where they do have a backbone of mini R-CHOP or POLA R-mini-CHP. Why? Because we know that these patients do derive benefit from chemotherapy.

In that setting, we have a couple of large trials that are ongoing. For example, the POLABEAR study, which is R-mini-CHOP versus POLA R-mini-CHP. We have the large intergroup North American S1918 study, which is evaluating R-mini-CHOP with or without oral azacitidine. Lastly, we have the ARCH study, which is looking at R-mini-CHOP with or without acalabrutinib. So, these are the large trials, and we do have some smaller trials, which seem very interesting. For example, at Memorial Sloan Kettering Cancer Center, we have the GLORY study, which is a PET-adapted treatment utilizing glofitamab and polatuzumab with the R-mini-CHOP backbone. Also, there are data from China, looking at zanubrutinib, rituximab, lenalidomide, and mini-CHOP, which had some excellent results presented at the ASH [American Society of Hematology] meeting last year. Lastly, for our patients who are truly chemo ineligible, a slew of frontline trials are looking at nonchemotherapy-based approaches.

One trial worth mentioning is the LOTUS-9 study, which was evaluating loncastuximab tesirine with rituximab, seemed like a good concept, but the population it was designed for was truly very frail patients above the age of 80. So, while the regimen had good response rates, there was increased toxicity due to COVID-19 and pneumonia. So, this regimen fell to the wayside in the wake of this trial.

How do real-world data factor into optimal treatment for older adult patients with DLBCL?

It's very true that we need to do these fitness assessments in the real world because most of the patients who go on clinical trials historically are really fit, so they don't represent the majority of patients who are coming into our clinic. So, as I mentioned, the gold standard is a kind of comprehensive geriatric assessment, but that requires a full geriatric clinic, a social worker, a physical therapist, a pharmacist, a lot of resources. Not all of us are blessed to have an inbuilt geriatric clinic as part of our cancer center. So, what can a busy lymphoma physician do? The most validated fitness assessment is the Simplified Geriatric Assessment, which was developed by the Italian Lymphoma Group.

Highlights From the **TRI-STATE BLOOD CANCER CONFERENCE**

Survivorship in Acute Leukemia: How MRD Monitoring and Treatment Choice Improves Outcomes

*By **Nichole Tucker***

With an expanding treatment paradigm and a better understanding of minimal residual disease (MRD), hematologists/oncologists who treat acute leukemias have better chances of getting patients into prolonged remission.

Joseph G. Jurcic, MD

"We say the patient is in remission because the marrow looks normal and their blood counts are normal, but we know that the leukemia can still be lurking there and eventually grow and reach critical mass and cause relapse," said **Joseph G. Jurcic, MD,** a professor of Medicine, and the director, Hematologic Malignancies Section, Division of Hematology/Oncology, Columbia University Medical Center, in an interview with *Blood Cancers Today.*

At the Tri-State Blood Cancer Conference held in New York, NY, Dr. Jurcic, joined peers, blood cancer survivors, and caregivers to discuss the treatment of acute leukemias, including providing attendees with the understanding that the journey to survivorship for adults with either acute myeloid leukemia or acute lymphocytic leukemia is just as dependent upon the use of modern MRD measurement techniques as it is on utilizing the most optimal therapies.

In the interview with *Blood Cancers Today,* Dr. Jurcic gave expert insights on how physicians can potentially guide their patients from diagnosis to survivorship.

Can you talk about what the most important steps to take as a hematology/oncology specialist to get patients from diagnosis to survivor of an acute leukemia?

Jurcic: One of the one of the key issues is that diagnosis is also used for prognosis, and our findings can help direct therapy. So, this is a key theme that I'm stressed in my talk at the at the Tri-State Blood Cancer Conference.

That initial diagnostic workup should include things like chromosome analysis, cytogenetics, and molecular analysis, and this should not just be for diagnosis, but if a patient were to relapse, because we know that the diseases can change over time, and this is key to offer the best available therapy for patients. We now know that various molecular lesions are targetable with drugs or antibodies. And of course, we also use this to determine whether patients should go on to an allogeneic stem cell transplant or not.

Which agents in AML are showing the most promise?

Jurcic: My presentation is about acute leukemias, and there are two major types, acute myeloid leukemia and acute lymphoblastic leukemia. After 40 years of really having only few agents available to treat acute myeloid leukemia, cytarabine and anthracycline, either daunorubicin or idarubicin, over the past decade or so, there have been 12 new agents approved for this disease. So, it's quite remarkable progress. Utilizing these agents in the best possible way is key.

So, there are various targetable mutations that we have. There are the *FLT3* abnormalities, and there are two different types of *FLT3* abnormalities, internal tandem duplications, and then tyrosine kinase domain mutations. And we have agents, midostaurin, quizartinib and gilteritinib, which target those. When used in combination with chemotherapy, midostaurin and quizartinib have shown to improve outcomes over chemotherapy alone. Gilteritinib is useful as a single agent, and there's promising data from early clinical trials showing that when added to other agents like azacitidine and venetoclax, gilteritinib is also extremely promising in the upfront setting, as well as useful in the in the second-line setting. In the event of relapse, we have three drugs that target 1 mutation.

Similarly, there's another group of mutations, *IDH1* and *IDH2* mutations, and we have three drugs that target those: ivosidenib, enasidenib, and olutasidenib. We know that what is particularly promising is the combination ivosidenib and azacitidine for older individuals with *IDH1* mutations. And that, to my mind, has really become the standard of care for that population.

The other major group of targeted small molecules I spoke about are Menin inhibitors, and the agent has already been licensed is lenalidomide. This drug has been approved for patients with relapsed rearrangements of a gene called *KMT2A,* and it has shown promise. And of course, the next steps in in developing these drugs are really to combine them with our best chemotherapies. There's a whole plethora of studies combining these agents now with other agent with standard chemotherapy drugs. So, it's an exciting time in developing these Menin inhibitors.

Which agents are most optimal for modern treatment of ALL to date?

It's a rare disease and adults. It's the lowest childhood leukemia and things I discussed include the use of antibody-based therapy that targets CD19 called blinatumomab. And what we have seen in recent years with multiple clinical studies, both in pediatrics and adults, is that the early incorporation of blinatumomab with standard chemotherapy improves outcomes. And so, I think that's a key finding in recent years, and something that's going to be studied more and more with various regimens.

There's also another agent inotuzumab ozogamicin, which is a targeted chemotherapeutic agent. It targets an antibody called CD22 and again, there's promising data that that led to approval of this agent for patients with relapsed disease.

Again, incorporating it into chemotherapeutic regimens up front can actually spare patients from chemotherapy, and this is particularly important for the older population, but this disease that may not tolerate intensive chemotherapy as well.

Finally, the other promising therapy in acute lymphoblastic leukemia is CAR T-cell therapy. The way this works is we harvest patients T cells then genetically engineer them to express a receptor that typically targets CD19, but other targets are being investigated. We then infuse these cells back into the patient, where they can attack and destroy leukemia cells. And it's been extremely promising, and we now have three agents that are licensed for adults with one is specifically for young adults up to age 25. CAR T cells have been an important addition to our armamentarium for ALL.

Let's say you gave a patient a targeted treatment for a time, they are in remission. How do you follow the patients to ensure a good survivorship journey?

One of the major issues in acute leukemia is assessing residual disease, meaning MRD, but in fact, it's not so minimal. In order to achieve a remission, you need to kill about 99% of the cells in order to restore normal hematopoiesis and for the bone marrow to look normal. Typically, somebody is presenting with full blown leukemia has about 10 to the twelfth leukemia cells in their body. So, if you do the math that that reduces the disease burden to around 10 to the ninth cells, and that's a lot of leukemia cells. So, without these special measurements to look at residual disease, we really are operating in a black box.

We say the patient is in remission because the marrow looks normal and their blood counts are normal, but we know that the leukemia can still be lurking there and eventually grow and reach critical mass and cause relapse. But we now have techniques where we can measure this MRD, and we do this with flow cytometry, we do it with next-generation sequencing, we do it with PCR techniques. It really depends on the molecular subtype of the disease.

For acute lymphoblastic leukemia, there's a commercially available assay called clonoSEQ, which takes advantage of the unique mutations that occur as a signature for the leukemia cells. We know that achieving MRD negativity predicts a better outcome. These tests are still not perfect, and even as we get below the level of detection with these sensitive tests, there still may be leukemia cells there. People can still relapse, even if they achieve so called MRD negative status. But the fact is, we know that if you get the leukemia down to these very, very low levels, people will have longer remissions, and more patients will be cured. So, looking at MRD is being incorporated into clinical trials and in fact, routine clinical practice now.

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 Raajit K. Rampal, MD, PhD, highlights recent research in myelofibrosis.*

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

Raajit K. Rampal, MD, PhD

MYELOFIBROSIS

Can a BET/JAK Inhibitor Combination Break Pathobiological Barriers in Myelofibrosis Treatment?

*By **Nichole Tucker***

It is widely known that standard JAK inhibitor (JAKi) monotherapy offers limited depth of response and durability of response in patients with myelofibrosis. In a phase 3 MANIFEST trial, the combination of pelabresib and ruxolitinib surpassed the efficacy shown with the standard of care, showing substantial clinical benefit and treatment tolerability[1].

"The study is very important in that it introduces the concept of JAK inhibitor-based combination therapy with a rationale agent that targets NFkB. The combination produces much deeper spleen responses, numerically better symptom benefit, and other markers of disease modification such as greater reduction in driver mutation level, inflammatory cytokines, bone marrow fibrosis, and megakaryocyte distancing," **John O. Mascarenhas, MD,** professor of medicine and director of the center of excellence for blood cancer and myeloid disorders at the Icahn School of Medicine at Mount Sinai, told *Blood Cancers Today*.

The study reached its primary endpoint with a 30.4% improvement in splenomegaly with pelabresib plus ruxolitinib versus ruxolitinib alone. A spleen volume of greater than or equal to 35% from baseline at week 24 in 65.9% of the 214 patients in the pelabresib combination arm versus 35.3% of the 216 patients in the ruxolitinib monotherapy arm (95% CI, 21.6%-39.3%; $P<0.0001$).[1]

Results for the secondary endpoint in the phase 3 MANIFEST study also favored the pelabresib combination arm. The absolute change in total symptom score (TSS) from baseline to week 24 was -15.99 among patients treated with pelabresib and ruxolitinib versus -14.05 in the ruxolitinib monotherapy arm, showing a difference of -1.94 (95% CI, -3.92-0.04; $P=0.0545$). Another endpoint, greater than or equal to 50% reduction in TSS showed a rate of 52.3% in the pelabresib plus ruxolitinib arm versus 46.3% in the ruxolitinib-only arm.

The overall frequency of treatment-related adverse events in the study was lower with the pelabresib combination (49.1%) versus ruxolitinib monotherapy (57.0%).

According to Dr. Mascarenhas and colleagues, myelofibrosis has unique pathobiological characteristics. The exploratory analyses conducted in MANIFEST provided important context on how the addition of BET inhibitors to JAKi improves outcomes in this patient population. The research began nearly 10 years prior.

Early Promise of BET/JAKi Therapy

Preclinically, pelabresib demonstrated the ability to target several driver mechanisms in myelofibrosis. It also had synergy when combined with JAKi therapy. Once investigated in the clinical setting, pelabresib alone and in combination with JAKi induced favorable responses in terms of disease symptoms and spleen volume[2].

"Myelofibrosis is a JAK-STAT driven disease but also has other inflammatory pathways that are active in the MPN stem and progenitor cell pool that prime the microenvironment to support malignant hematopoiesis and promote bone marrow fibrosis. NFkB has been shown to be actively expressed in these cells and contributes further to the inflammatory state through the expression of many key cytokines such as interleukin [IL]-8. IL-8 has been shown to have both adverse prognostic impact and therapeutic potential," Dr. Mascarenhas told *Blood Cancers Today*.

"Targeting both NFkB through BET inhibition and down-regulating STAT activity through JAK1/2 inhibition has been shown in preclinical studies to have synergistic activity in murine modeling and serves as the basis of the combination of ruxolitinib and pelabresib in the phase 2 MaNIFEST trial and the recently published randomized phase 3 MANIFEST-2 comparing this combination to ruxolitinib and placebo in JAK inhibitor naive intermediate and high-risk MF [myelofibrosis] patients with measurable spleen and symptom burden," explained Dr. Mascarenhas.

Ongoing Manifestations of BETi/JAKi Synergy

The exploratory analyses of the phase 3 MANIFEST study assessed how pelabresib combined with ruxolitinib affected hemoglobin and the need for transfusions, changes in proinflammatory cytokines, bone marrow morphology, and the pattern of driver and high-molecular-risk mutations. Overall, investigators considered pelabresib plus ruxolitinib to offer improvement in outcomes on a short-term basis, which may later translate to better outcomes compared with ruxolitinib monotherapy[1].

Results showed that during the first 24 weeks of treatment, 27.6% of patients receiving pelabresib plus ruxolitinib and 37.5% of those on placebo–ruxolitinib required transfusions. Pelabresib plus ruxolitinib also decreased concentrations of IL-8, which correlated with a reduction in spleen size. In terms of bone marrow morphology, fewer changes from baseline in bone marrow fibrosis were shown with the pelabresib combination versus ruxolitinib alone.

The study also showed that responses to treatment with pelabresib plus ruxolitinib were independent of driver and high-molecular-risk mutations like *ASXL1* and *EZH2*. Among patients with myelofibrosis and a *JAK2 V617F* mutation, pelabresib plus ruxolitinib showed an early trend towards improvement in *JAK2 V617F* variant allele fraction compared with ruxolitinib monotherapy (-23.9% vs -16.8). The difference was 09.5% (95% CI, -23.6-2.9).

"Whether these collective changes with this combination will ultimately associate with improved survival is not yet proven and is being followed in longer-term follow up. This pivotal trial heralds a new era of combination therapy and opens the possibility of attaining deeper and more durable clinical responses," Dr. Mascarenhas stated.

References:

1. Rampal, RK, Grosicki S, Chraniuk D, et al. Pelabresib plus ruxolitinib for JAK inhibitor-naive myelofibrosis: a randomized phase 3 trial. *Nat Med.* Published online ahead of print March 10, 2025. doi: 10.1038/s41591-025-03572-3

2. Gomes Guadalupe Ferreira, and Harrison Claire. Pelabresib (CPI-0610): An exciting novel drug for the treatment of myelofibrosis. *Curr Hematol Malig Rep.* 2023;18(14):113-120. doi: 10.1007/s11899-023-00696-6

New Trial Data Emerges on Rusfertide for Erythrocytosis Control in Phlebotomy-Dependent Polycythemia Vera

*By **Andrew Moreno***

The international phase 2 REVIVE trial has explored the efficacy and safety of rusfertide, an injectable hepcidin mimetic, for control of erythrocytosis in patients with phlebotomy-dependent polycythemia vera. An expert team has examined data from the trial and published their analysis in *The New England Journal of Medicine*.

"Rusfertide is a potentially effective treatment option for achieving and sustaining hematocrit control in patients with polycythemia vera, reducing the use of phlebotomy and the occurrence of debilitating disease-related symptoms," wrote first author **Marina Kremyanskaya, MD, PhD,** of the Icahn School of Medicine at Mount Sinai, and colleagues.

Part 1 of the trial was a 28-week dose-finding assessment of rusfertide, which involved 70 patients with polycythemia vera. Fifty-nine of these patients were included in part 2 of the trial, a 12-week, double-blind, randomized withdrawal period during which 30 patients received rusfertide and 29 received placebo.

Regarding hematocrit control as a measure of rusfertide's efficacy, the average maximum hematocrit among the patients was 50.0% during the 28 weeks before the first dose of rusfertide and fell to 44.5% during part 1. Regarding the number of phlebotomies per year, the estimated average number was 8.7 during the 28 weeks before the first rusfertide dose and fell to 0.6 during part 1.

"Between baseline and the end of part 1, rusfertide treatment was associated with a decrease in individual symptom scores on the MPN-SAF [modified Myeloproliferative Neoplasm Symptom Assessment Form] in patients with moderate or severe symptoms at baseline," Kremyanskaya and colleagues mentioned.

During part 2, the investigators observed that 60% of the patients who received rusfertide responded, compared with 17% of the patients who received placebo (P=0.002).

Regarding adverse events in parts 1 and 2, injection-site reactions of grade 1 or 2 severity were prevalent. Grade 3 adverse events affected 13% of the patients, and there were no grade 4 or 5 events.

Study coauthor **Andrew Kuykendall, MD,** of the Moffitt Cancer Center, told *Blood Cancers Today* that the REVIVE study "showed that there may be a preferred alternative to phlebotomy and hematocrit control in general in managing patients with polycythemia vera. The hepcidin mimetic, rusfertide, can effectively eliminate patients' needs for phlebotomy and maintain consistent hematocrit control via a well-tolerated once weekly subcutaneous injection. The unique trial design that called for half of patients to be taken off of rusfertide and treated with placebo after 28 weeks provided a glimpse into the comparative benefit of rusfertide. Though brief, this period of comparison showed rapid loss of hematocrit control in patients who did not remain on rusfertide and showed that patients who remained on rusfertide had better control of disease-related symptoms that have long been difficult to manage. Ultimately, these findings led to the ongoing phase 3 VERIFY study which recently reported positive results."

In remarks forwarded to *Blood Cancers Today,* Dr. Kremyanskaya explained, "[W]hat is especially exciting about the REVIVE study is that it utilized a completely novel approach as a potential treatment for polycythemia vera. It used a peptide hormone that is normally made by the liver to regulate iron homeostasis, to restrict iron availability for erythropoiesis, and thus controlled the hematocrit in patients with polycythemia vera. This phase 2 study showed in randomized fashion that this approach utilizing hepcidin mimetic rusfertide significantly decreased the need for therapeutic phlebotomies compared to placebo. It also indicated potential improvement in polycythemia vera related symptoms. The phase 3 VERIFY study is currently ongoing and is confirming these findings in a larger cohort of patients."

The REVIVE trial is funded by Protagonist Therapeutics.

Reference

Kremyanskaya M, Kuykendall AT, Pemmaraju N, et al. Rusfertide, a hepcidin mimetic, for control of erythrocytosis in polycythemia vera. *N Engl J Med.* 2024;390(8):723-735. doi:10.1056/NEJMoa2308809

Driver Mutation Clearance After HSCT Associated With Improved Survival, Lower Relapse in Myelofibrosis

*By **Melissa Badamo***

Patients with myelofibrosis who achieved driver mutation clearance after allogeneic hematopoietic stem cell transplantation (HSCT) experienced improved survival and lower relapse, according to a study published in *The New England Journal of Medicine*.

"Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for myelofibrosis," wrote co-lead authors, Drs. **Nico Gagelmann** and **Marie Quarder,** and colleagues. "Driver mutations are the pathophysiological hallmark of the disease, but the role of mutation clearance after transplantation is unclear."

Using highly sensitive polymerase-chain-reaction technology, the researchers assessed driver mutations in peripheral blood samples from patients who underwent HSCT after reduced-intensity conditioning. The primary endpoints were relapse-free survival and disease-free survival.

Of the 324 patients in the study, 73% had *JAK2* mutations, 23% had *CALR* mutations, and 4% had *MPL* mutations. To measure mutation clearance, the researchers reported mutations before HSCT and on days 30, 100, and 180 after HSCT.

On day 30 after HSCT, 42% of patients with *JAK2* mutations, 73% with *CALR* mutations, and 54% with *MPL* mutations had mutation clearance. On day 100, these percentages increased to 63% of patients with *JAK2* mutations, 82% of patients with *CALR* mutations, and 100% of patients with *MPL* mutations.

The 1-year cumulative incidence of relapse was 6% (95% CI, 2-10) among patients who achieved mutation clearance on day 30, compared with 21% (95% CI, 15-27) among those who didn't.

Patients who had mutation clearance on day 30 also had a higher incidence of disease-free survival and overall survival at 6 years (61% and 74%, respectively) compared with those who didn't (41% and 60%, respectively).

"In patients with myelofibrosis, clearance of driver mutations at day 30 after transplantation appeared to influence relapse and survival, irrespective of the underlying driver mutation," the researchers concluded.

Reference

Gagelmann N, Quarder M, Badbaran A, et al. Clearance of Driver Mutations after Transplantation for Myelofibrosis. *N Engl J Med.* 2025;392(2):150-160. doi:10.1056/NEJMoa2408941

HemOnc Happenings

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

*By **Melissa Badamo***

NCCN Foundation Announces 2025 Young Investigator Award Recipients

The National Comprehensive Cancer Network (NCCN) announced the recipients of their 2025 Young Investigator Award on April 3, 2025. The award provides early-career researchers at NCCN Member Institutions with $150,000 in funding over 2 years to support research aimed at improving cancer care.

Among the 4 recipients are **Kathryn Tringale, MD, MAS,** a radiation oncologist at the University of California San Diego (UCSD) Moores Cancer Center specializing in leukemia and lymphoma, and **Mathew Angelos, MD, PhD,** an assistant professor of medicine at the University of Colorado Anschutz Medical Campus specializing in leukemia, blood and marrow transplant, and myelodysplastic syndromes.

Kathryn Tringale, MD

Matthew Angelos, MD

"I'm honored to receive this award in support of a project developed in collaboration with an incredible multidisciplinary team," Dr. Tringale told *Blood Cancers Today*. "As a new faculty member at UCSD and someone in the early stages of my career as a clinician-scientist treating both central nervous system and hematologic malignancies, it's especially meaningful to have support for an idea that brings together these dual interests."

Dr. Tringale's study, titled "Comprehensive Neuroimaging and Molecular Biomarkers of Neurotoxicity Following CAR T-Cell Therapy," aims to better understand and predict neurotoxicity in patients receiving chimeric antigen receptor (CAR) T-cell therapy by using advanced brain imaging, cognitive testing, and blood-based biomarkers.

"CAR T-cell therapy has revolutionized treatment for blood cancers like large B-cell lymphoma and multiple myeloma, significantly improving survival. Unfortunately, it comes with serious side effects—one of the most concerning being ICANS [immune effector cell–associated neurotoxicity syndrome], a neurologic complication that affects up to 70% of patients," Dr. Tringale explained. "As CAR-T becomes more widely used, understanding and managing these side effects is more important than ever. Although early studies have linked ICANS to certain inflammatory markers in the blood and brain MRI changes, no large, in-depth prospective studies have been done. This project aims to fill that gap."

Dr. Angelos's study shines a different light on CAR T-cell therapy, focusing on the safety and preliminary clinical activity of autologous anti-CD64 CAR T cells in patients with relapsed or refractory acute myeloid leukemia.

"Early-career researchers bring fresh perspectives to some of the most complex challenges in cancer care," said **Crystal S. Denlinger, MD,** chief executive officer of the NCCN and former Young Investigator Award recipient, said in a news release. "Supporting these investigators and their work is critical for advancing cancer treatment and outcomes. This program is an investment in their potential—and in the discoveries that will improve cancer outcomes in the future."

Reference

NCCN Foundation celebrates 2025 Young Investigator Award recipients shaping the future of cancer research. National Comprehensive Cancer Network. News release. PR Newswire. Published April 3, 2025. Accessed April 11, 2025. https://www.prnewswire.com/news-releases/nccn-foundation-celebrates-2025-young-investigator-award-recipients-shaping-the-future-of-cancer-research-302419756.html

Hematologist-Oncologist Named Among Atlanta Magazine's 2025 Atlanta 500 Most Powerful Leaders: Education & Healthcare List

Douglas Graham, MD, PhD, a hematologist-oncologist specializing in pediatric leukemia, was named in *Atlanta Magazine's* 2025 Atlanta 500 Most Powerful Leaders: Education & Healthcare list.

Douglas Graham, MD

Dr. Graham serves as chief and William G. Woods, MD, Chair of the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, chief of the Division of Pediatric Hematology/Oncology/BMT, and professor in the Department of Pediatrics at Emory University School of Medicine.

Dr. Graham's laboratory at Children's Healthcare of Atlanta and Emory University focuses on studying tyrosine kinase signaling pathways in pediatric leukemia and brain cancer and developing novel therapeutics that inhibits cancer-promoting proteins such as MerTK.

"I am honored that the *Atlanta Magazine* has brought additional awareness and recognition to our team of physicians at the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta," Dr. Graham told *Blood Cancers Today*. "We strive to bring exceptional clinical care to children with cancer and hematological diseases and are thankful to patients and families who trust us with their care. While we are thankful for significant improvements in patient outcomes over the last few decades, we are dedicated to continuing to enhance treatment options and cure rates through cutting edge research such as cellular and gene therapy, precision medicine, and drugs that are more specifically targeted to drivers of disease."

Reference

Atlanta Magazine. 2025 Atlanta 500: Education & Healthcare. Published January 30, 2025. Accessed April 11, 2025. https://www.atlantamagazine.com/news-culture-articles/2025-atlanta-500-education-healthcare

Samir Parekh, MD, Appointed Director of the Center of Excellence for Multiple Myeloma at Mount Sinai

Samir Parekh, MD, has been named Director of the Center of Excellence for Multiple Myeloma at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York, New York.

Samir Parekh, MD

Dr. Parekh's laboratory focuses on developing personalized treatment strategies for patients with multiple myeloma using genomics and immunology.

"It's a very humbling position, and I'm honored to be chosen to lead a very talented group of physicians and scientists at Mount Sinai, as well as a large team of nurse practitioners, nurses, and researchers that do clinical research," Dr. Parekh told *Blood Cancers Today*. "The team was set up by **Sundar Jagannath, MBBS,** and has been growing since. We have about 150 people who help support myeloma patients, including social workers and ancillary staff."

Mount Sinai operates 3 sites in New York City for treating patients and conducting clinical research: the Upper East Side, Chelsea, and Brooklyn. In the future, the hospital will expand its practice to New Jersey and Long Island, Dr. Parekh said.

"I'm happy to be helping lead this program, and I'm happy that the lab I lead has been publishing and finding new things that can help patients directly, whether it's making observations about CAR-T [chimeric antigen receptor T-cell] resistance and bispecific resistance or coming up with new therapeutic options when patients face challenging situations in the clinic," he concluded.

Reference

Mount Sinai names Samir Parekh, MD, as director of the Center of Excellence for Multiple Myeloma. Mount Sinai. News release. Published March 26, 2025. Accessed April 11, 2025. https://www.mountsinai.org/about/newsroom/2025/mount-sinai-names-samir-parekh-md-as-director-of-the-center-of-excellence-for-multiple-myeloma

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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®.