TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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March 2025

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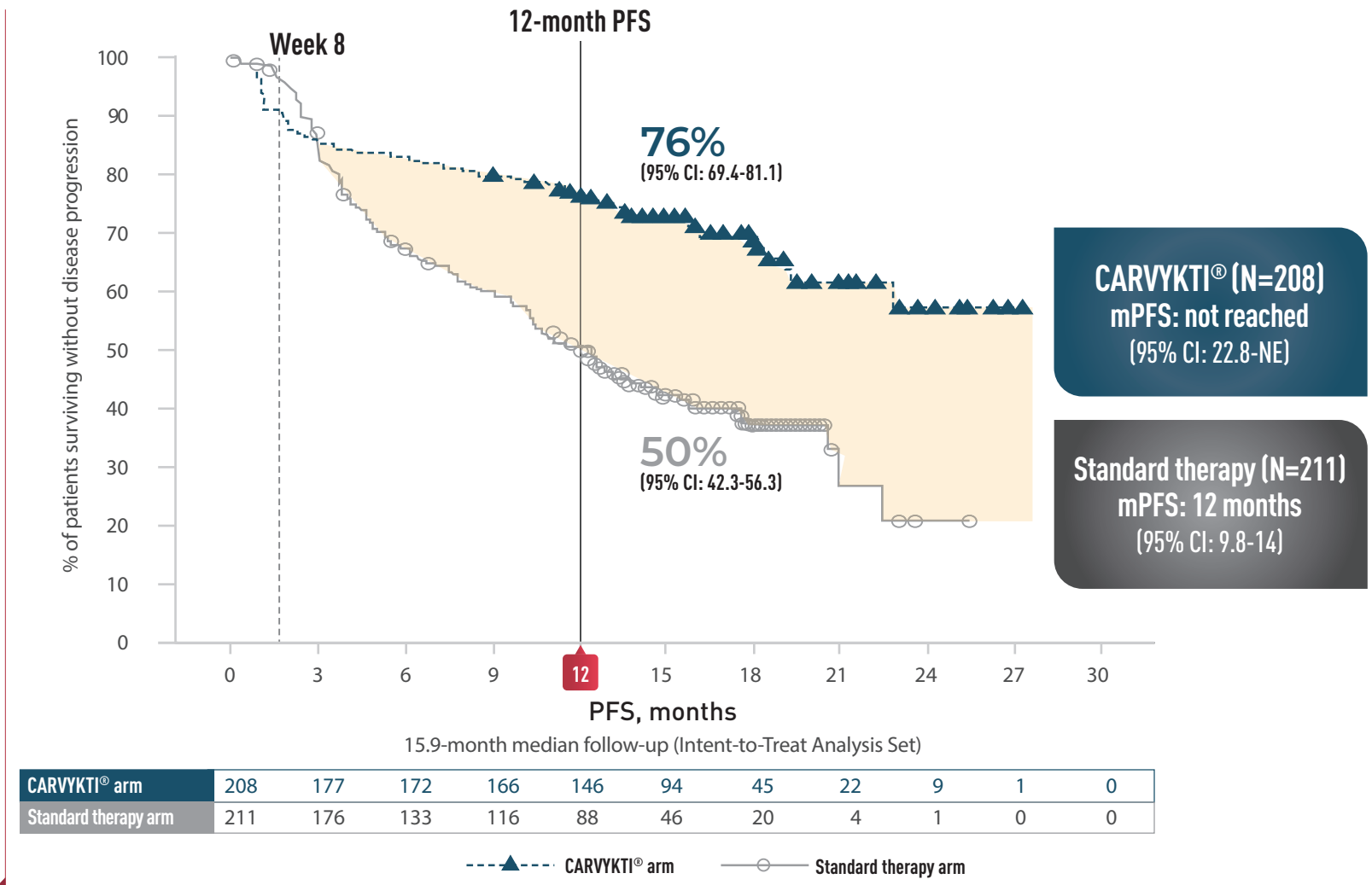
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

POWERFUL RESULTS

In CARTITUDE-4

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

PROGRESSION-FREE SURVIVAL



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

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

CARVYKTI® arm — Standard therapy arm

CARVYKTI® demonstrated a

↓59%

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

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®.

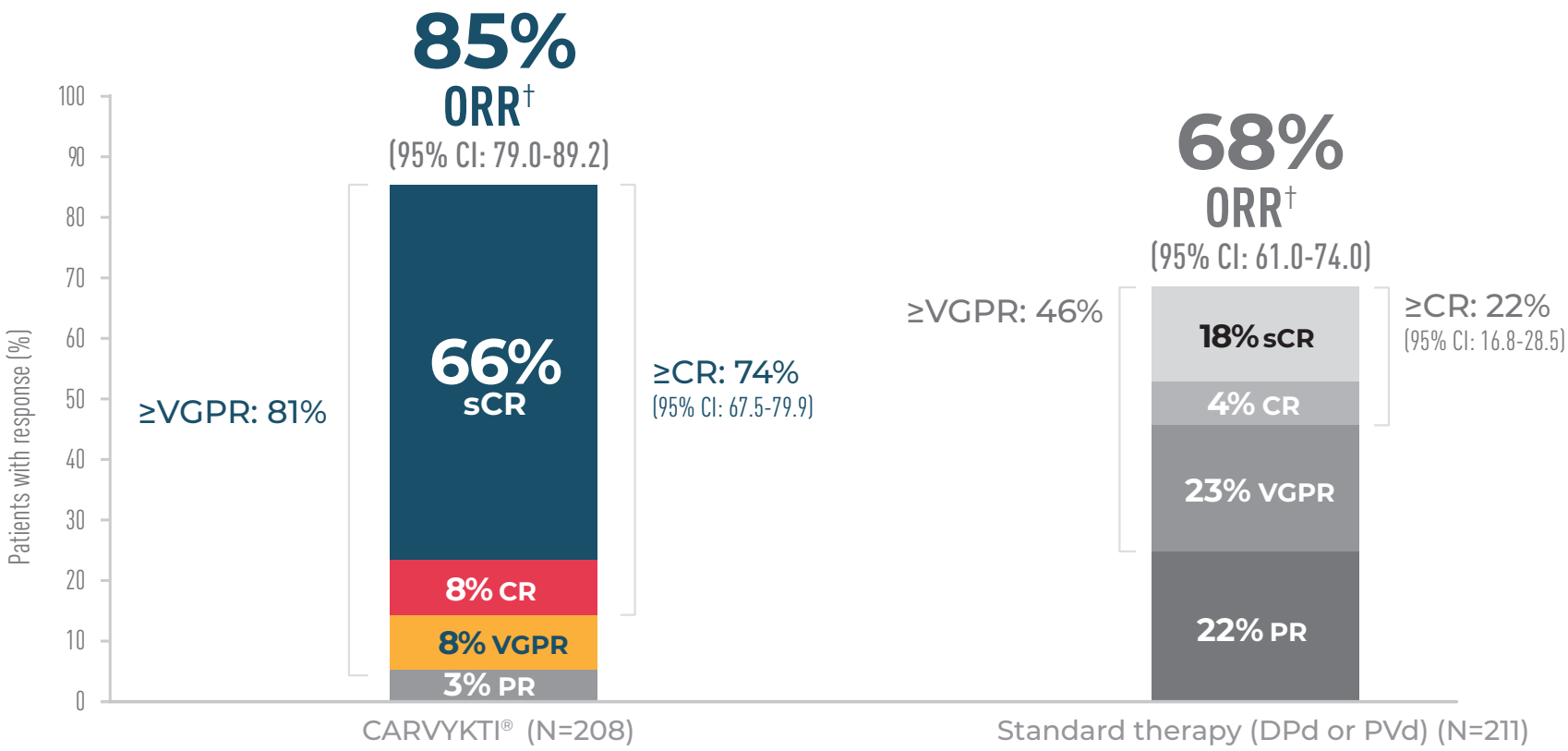
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

DEEP RESPONSES[2*]

In CARTITUDE-4

85% OVERALL RESPONSE RATE WAS ACHIEVED WITH CARVYKTI®, AND 81% OF PATIENTS ACHIEVED A DEEP RESPONSE[1,3*]

Deep response is defined as ≥VGPR



DURABLE RESPONSES

MEDIAN DURATION OF RESPONSE FOR CARVYKTI® WAS NOT REACHED[1*]

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

Percentages rounded to nearest whole number and may not add up due to rounding.
CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, and dexamethasone; mDOR=median duration of response; ORR=overall response rate; PR=partial response; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent complete response; VGPR=very good partial response.
*15.9 months follow-up (Intent-to-Treat Analysis Set).
†Includes patients who achieved PR or better.
‡Estimated mDOR.

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®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (CONT'D)

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

cp-258862v9

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

DISCOVER MORE AT
CARVYKTIHCP.com

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

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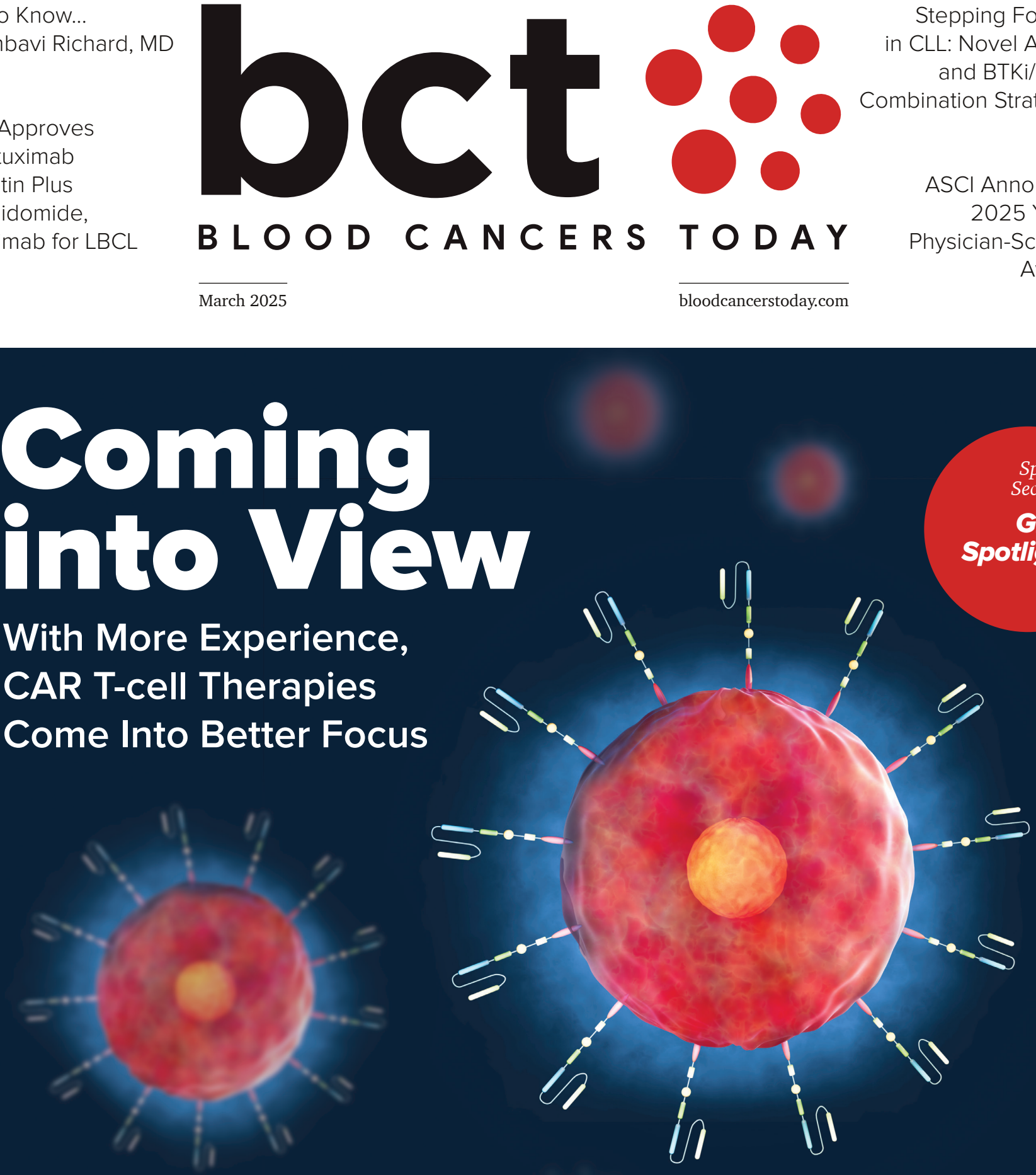
Coming into View

With More Experience, CAR T-cell Therapies Come Into Better Focus



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With expert opinions from: **Joshua Brody, MD, Tania Jain, MBBS**, and more

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NISHA JOSEPH, MD:
Highlighting Recent Research in Multiple Myeloma

Join the discussion on Figure 1

Start collaborating on cases with your colleagues today.

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figure1

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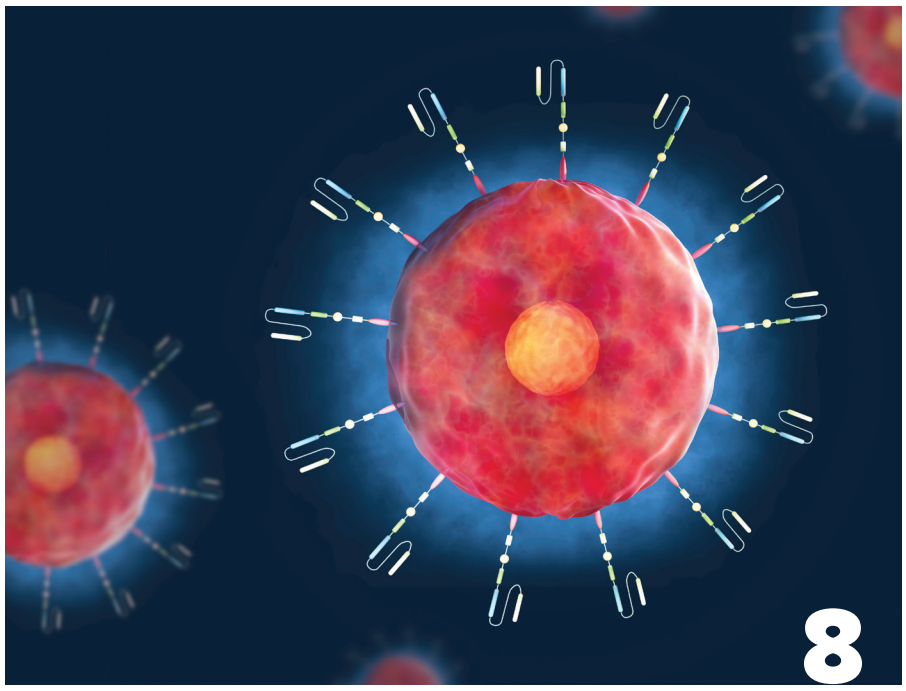

With More Experience, CAR T-cell Therapies Come Into Better Focus

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Shambavi Richard, MD

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Calendar

May 3
The Leukemia & Lymphoma Society Texas Blood Cancer Conference
Dallas, Texas

May 5–6
21st Global Summit on Hematology and Blood Disorders
Rome, Italy

May 7–10
American Society of Pediatric Hematology/Oncology
Louisville, Kentucky

May 13-17
American Society of Gene & Cell Therapy 28th Annual Meeting
New Orleans, Louisiana

May 23–25
23rd International CML Horizons Conference
Bucharest, Romania

May 30–June 3
American Society of Clinical Oncology Annual Meeting
Chicago, Illinois

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

June 21–25
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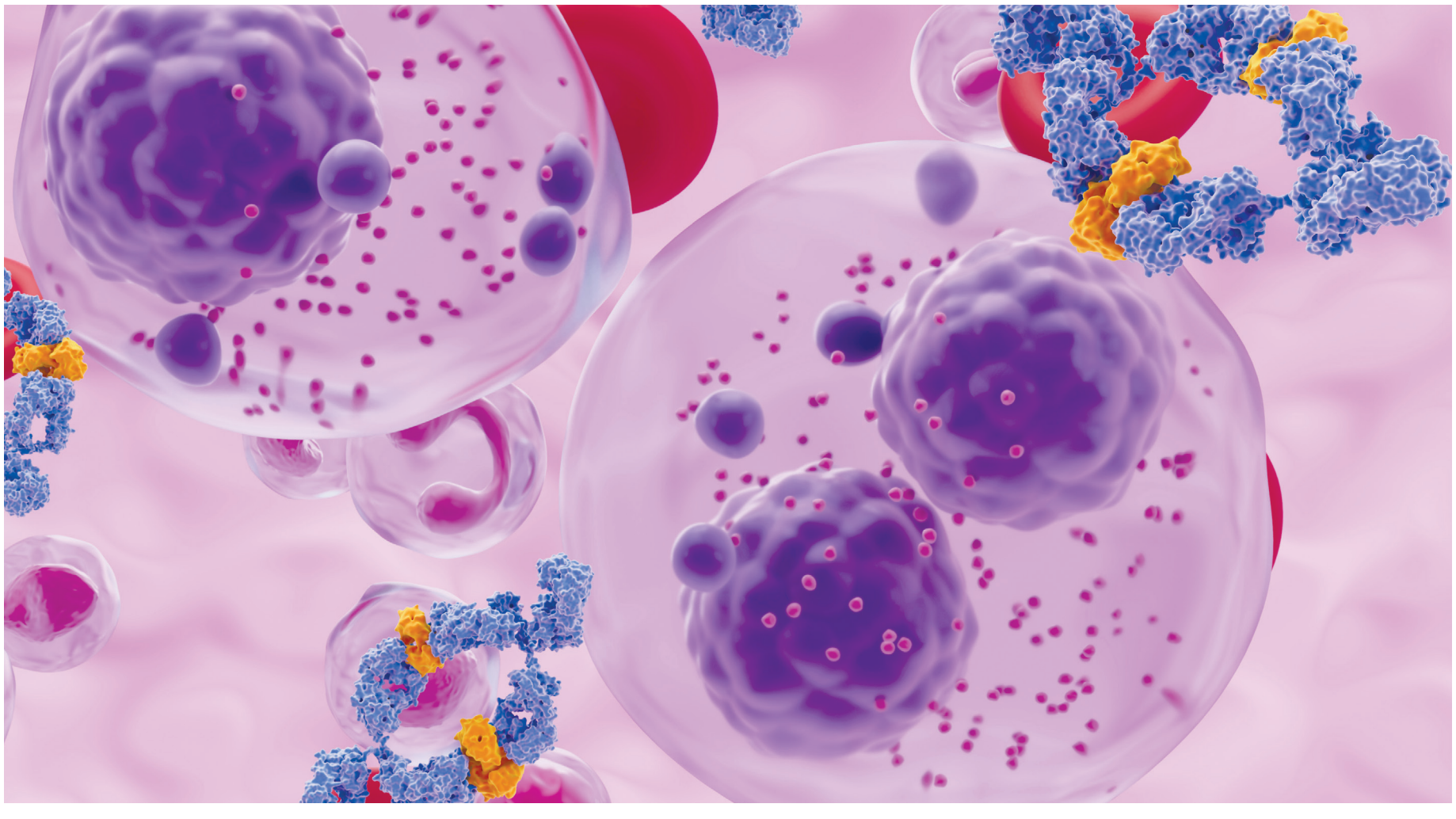

Shambavi Richard, MD

Shambavi Richard, MD, Associate Professor of Medicine (hematology and medical oncology) with the Center of Excellence for Multiple Myeloma at Mount Sinai, shares her passion for cellular therapy, how her mother's leukemia diagnosis shaped her career, and more.

By ***Melissa Badamo***

Where did you grow up, and when did you know you wanted to be a hematologist/oncologist?
I was born in the southernmost state of India called Kerala, in a small town called Calicut. Then, I moved to a bigger city in Kerala called Trivandrum and spent all my childhood there. When I was about 15 or 16 years old, my mom got diagnosed with chronic myeloid leukemia. I was still in high school at the time. It was a big deal. She was a totally healthy woman prior to that. Back in the 1980s when she was diagnosed, there were no treatment options. There was no Gleevec; the only curative was allogeneic transplant. But in India, especially in my small town, that was not an option.

She went on medications that were not expected to change the natural course of the disease at all. The natural history of the disease at that time with palliative therapies was about 3½ years survival. She lived with the disease for about 6 years, but she died when I was in medical school.

It sent my world into a tailspin. That was the genesis of my ongoing career goals. I thought maybe I want [to be] a doctor, a hematologist, a bone marrow transplanter. Years later, that's what I did.

When did you know you wanted to specialize in myeloma?
Myeloma was a much later development in my career. I trained as a transplanter, then stayed in the transplant and heme malignancy field. Then, my career meandered and took various directions over time. I even did a 5-year stint in private practice where I wasn't necessarily practicing either transplant or malignant hematology, just chronic hematologic diseases and other cancers.

At one point, I started missing academic medicine. I saw they were recruiting in Mount Sinai at the time, but interestingly was hired for a completely different role. But then there was a need in myeloma, so I morphed into the myeloma field. About a year into it, there was a need in CAR [chimeric antigen receptor] T-cell therapy in myeloma, and I came full circle because of my background in training in cellular therapies. It seemed like the obvious fit.

Life sometimes takes you in funny and roundabout ways to get back to where there's a good fit. It's like the stars aligned!

Were there any mentors who shaped your career path?
It's been a village to get to this point. You learn so many things from so many people along the way. In a field like medicine, there are so many steps because your training is so many years. **Shirley Levine, MD,** was the fellowship director in hematology at Einstein Montefiore, where I did my fellowship. At Montefiore, much of the transplant and acute leukemias were handled by Oncology. Hematology was more of the benign, classical hematology. I opted for 2 years in oncology and 1 year in hematology.

My first mentor was Dr. Levine in benign hematology. She inspired me with a love for academic medicine, for the pathophysiology and pathways of classical hematology. Although I never thought I was interested in classical hematology as a field, she was such a great scholar and mentor. It was so amazing learning from her to be interested in the field and not so much about trying to get my day done and getting home at the end of the day. I remember that time very fondly.

The other mentor who worked very closely with Shirley Levine was **Henny Billett, MD.** I did my first research paper with Henny, and it was such an interesting experience because that was my first foray into clinical research. She inspired me with an interest in the scholarship. Once I finished my hematology oncology fellowship, there was one spot in all of New York for a fellowship in bone marrow transplant. It was an extra year of fellowship, but I really wanted to do transplant again. It was in line with my original goal that I started when I was 15. I got the spot in Mount Sinai in New York, and the director of the transplant program was **Steven Fruchtman, MD,** who was amazing, and **Luis Isola, MD,** who was one of the attendings in transplant. I had such a great experience learning transplant from them. It was probably the best year of all of my training years. It just made sense to me, and it felt like the culmination of all the things that I had been dreaming of. It felt like coming home.

Mentorship in Medicine goes on even when you are an adult in the field. You never stop learning from other people. **Ajai Chari, MD,** was a wonderful mentor to me after I joined myeloma. I talk to him and get advice on things even now.

Can you describe your current clinical research?

I'm really interested in CAR-T therapies in myeloma. They've been such a game changer. There's so much in line with my field of cellular therapies, so I'm really interested in innovative CAR-T products and approaches. There is much that we have to learn in terms of toxicities. I am now on the Blood & Marrow Transplant Clinical Trials Network (BMT CTN) Toxicology and Supportive Care Committee, which will help further in learning about and mitigating risk from these very new and cutting-edge therapies.

I am the principal investigator [PI] for a very interesting dual CAR-T product, the CD19 x BCMA dual CAR-T. The original reports came out from China on this product with excellent response rates and toxicity profile with a median progression-free survival of 38 months. It's one of the best results for new and innovative CAR-T products as things stand right now for myeloma.

When they brought this trial from China to the United States for the first time, I was able to enroll the first 4 patients on this clinical trial in the United States, so I'm very excited about it. I'm hoping for great things from this product.

I'm also a PI for several other CAR-T trials. I've been part of the CARTITUDE-2 and KARMA-2 trials. I'm also the PI for other non–CAR-T first-in-human clinical trials. One is a BCMA ADC [B-cell maturation antigen-targeted antibody-drug conjugate] called *Hdp-101,* and another is a CELMoD [cereblon E3 ligase modulator] from C4 Therapeutics called *CFT7455*.

"I think we should be able to cure myeloma in 10 years. We're looking at various approaches, whether it's MRD [measurable residual disease]–adapted therapy or finding new targets on cancer cells, to change the way the myeloma journey looks like right now." *—Shambavi Richard, MD, Associate Professor of Medicine at Mount Sinai*

Innovation in myeloma is what I'm very interested in. Much of my clinical research is hoping for that Holy Grail of a cure for myeloma. "C" should no longer be the "cancer" word; it should be the "cure" word.

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

I'm hoping to have much more innovation in the CAR-T products. That's where we have seen such a game-changing response rate and longevity of response. We should continue to strike where the iron is hot.

I think we should be able to cure myeloma in 10 years. We're looking at various approaches, whether it's MRD [measurable residual disease]–adapted therapy or finding new targets on cancer cells, to change the way the myeloma journey looks like right now.

Once they get diagnosed with myeloma, patients are committed to therapy as long as they live with myeloma. We have increased the survival, but it's still distressing to be tied to doctors and infusion centers for the rest of your life. Many of these therapies are either daily, oral, weekly, or monthly. The frequency is still so high for them to constantly have to be in the doctors' offices. It would be great for myeloma to be something you can treat for a while and give patients long chemotherapy holidays and eventually get to a place where they no longer need treatment, that the disease is considered cured.

I also want to see a better way to monitor patients rather than doing repeated bone marrow biopsies, which is an uncomfortable test. I hope to have an alternative, like a blood-based test, as our technology improves.

What advice would you give to younger physicians or trainees in the field?

Being a physician is probably one of the most rewarding things. It's intellectually satisfying. But, if you're not in this for the long haul and don't have passion for the field, then it's a really difficult road. It doesn't make a lot of sense if you're not committed to it. Some people go into it to help people, others for other reasons. But to me, the intellectual stimulation of hematology oncology and cellular therapies is amazing. You never have a boring day.

What hobbies or activities do you enjoy outside of work?

I love traveling. I have traveled to over 40 countries, and my most recent travel was to Antarctica, which is my top favorite. Any time I'm not working, I'm looking for new places to travel. The more remote and unexplored they are, the more I'm attracted to them. I love European cities as well, but going to places that have been untouched by humans is such an amazing thing.

If I ever retire, I have 10 different things that I'm planning. I'm going to take up a musical instrument, learn a bunch of languages, travel more, write a book, and learn to paint. I have so many things I would love to do before I call it a day!

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

Low-Income Patients With AML Face Higher Readmission—Can We Close the Gap?

Spotlight on

Ayobami Olafimihan, MD

Dr. Olafimihan grew up in Nigeria where he obtained his medical degree at the University of Ilorin. He recently completed his internal medicine residency at John H Stroger, Jr. Hospital of Cook County in Chicago, during which time he led a retrospective interrupted trends study on economic disparities and their relationship to hospital readmissions among patients with acute myeloid leukemia. His research interests include eliminating disparities in healthcare delivery, advancing cancer risk prevention, and exploring implementation science to optimize care models. He is also passionate about sickle cell disease advocacy. He has recently taken on a post as an attending physician.

*By **Nichole Tucker***

Among patients with acute myeloid leukemia (AML) who have low incomes, 30-day all-cause readmission rates were higher than among patients with high incomes, signaling a need for new programs that focus on transition of care and postdischarge interventions that address social economic disparities, according to a retrospective study.[1]

The results were presented by **Ayobami Olafimihan, MD,** attending physician, John H. Stroger, Jr. Hospital of Cook County in Chicago, Illinois, at the 66th American Society of Hematology Annual Meeting & Exposition.

The Problem

Hematologists/oncologists know that prevention of hospital readmission for patients with AML can lead to improvements in patients' quality of life and reduction in healthcare costs, according to Dr. Olafimihan. But the literature exploring the correlation between socioeconomic status and hospital readmission among patients with AML is scarce, warranting more research.

"In AML, particularly following chemotherapy treatments, there is bound to be some unplanned readmission, which is necessary. However, there is a subset of the population who have a higher risk of readmission due to their low socioeconomic status," Dr. Olafimihan told *Blood Cancers Today,* during an interview. "This is the subset of patients that need to be identified by the healthcare system."

Healthcare Utilization

In the US AML population, the historic CURRENT study evaluated both older and younger patients who were not candidates for intensive chemotherapy. As one of the most extensive real-world studies of this patient group, it highlighted the significant healthcare resources required for those undergoing low-intensity treatment. Kumar et al[2] projected that integrating newer treatment approaches into the AML landscape could reduce overall healthcare utilization.

In 2024, a study looked at oral azacitidine maintenance 4 years after its approval by the FDA.[3] Azacitidine was specifically approved for the continued treatment of adult patients with AML who achieved complete remission or complete remission with incomplete blood count recovery after intensive induction chemotherapy and who are not able to complete intensive curative therapy.[4] Overall, oral azacitidine maintenance therapy prolonged remission in patients with AML and resulted in lower healthcare utilization costs compared with patients who did not receive maintenance therapy.[4]

"Hospital admissions are a major financial burden in the United States health system. In 2018, the cost of hospital readmissions

was $58 billion, and in just 2 years, this increased by over $5 billion," said Dr. Olafimihan. "Blood diseases and cancers have the highest rate of readmission, estimated at about 23.9 and 19.0 per 100 index admissions. Notably, AML has also been reported to have an average unplanned readmission rate of about 30% to 60%."

Economic Burden

Hospital-level, retrospective data published in 2022 highlighted substantial costs among patients with newly diagnosed AML who receive intensive induction chemotherapy.[5] The high cost largely resulted from inpatient hospitalization, which lasted for long periods. Moreover, undergoing subsequent hematopoietic stem cell transplantation resulted in even higher costs.

The financial burden of hospital care varies significantly depending on the type of visit, with outpatient services averaging a median cost of $1,083 per visit, ranging from $481 to $2,189, and total outpatient expenses per patient reaching $2,904, spanning $1,054 to $7,217. Inpatient hospitalization presents a steeper financial impact, with a median cost of $34,558 per stay, fluctuating between $25,419 and $49,460; and total inpatient costs per patient soar to $83,440, ranging from $63,067 to $113,985. Intensive care unit (ICU) admissions add another financial layer, with a median per-visit cost of $15,771, falling between $7,209 and $27,564; and total ICU-related costs per patient amounting to $16,550, with a broader range of $7,368 to $36,968.[5]

A Better Understanding

With information on adult patients with AML from the Nationwide Readmissions Database who were treated in 2010, 2012, 2014, 2016, and 2018, the study investigators determined that subsequent hospitalization of the same patient within 30 days was considered a readmission. Patients with neutropenic fever and those who had elective and traumatic admissions and readmissions were not included in the study population.[1]

"We classified these admissions and readmissions based on the median household income into the low-income quartile [LIQ] group and the high-income quartile [HIQ] group," explained Dr. Olafimihan. Patients in the LIQ group had an income below $46,000, and those in the HIQ group had an income above $64,000, according to Olafimihan.

Of the 181,432 index hospitalizations included in the retrospective analysis by Olafimihan and colleagues, 24.1% were from the LIQ group, and 24.6% were from the HIQ group. The patient population had a mean age of 61.6 years. A total of 44,417 hospitalizations among these patients were readmissions within 30 days, with a larger number occurring in the LIQ group (25.0%) than in the HIQ group (23.2%). Of those readmitted, the median age was 59.9 years, and patients in the HIQ group were notably older than those in the LIQ group. Readmitted patients were also predominantly male (53.5%).[1]

The study revealed a 30-day all-cause readmission rate of 29.7%, which varied year over year, signaling a trend of increasing chances of readmission ($P<0.001$). The trend was demonstrated between 2010 and 2018, showing that patients in the LIQ group had a higher probability of being readmitted than those in the HIQ group.

Looking specifically at the 30-day neutropenic fever–specific readmission rate, patients with AML in the HIQ group had a 5.1% higher probability of readmission than those in the LIQ group.

"Hospital admissions are a major financial burden in the United States health system. In 2018, the cost of hospital readmissions was $58 billion, and in just 2 years, this increased by over $5 billion." *—Ayobami Olafimihan, MD, attending physician, John H. Stroger, Jr. Hospital of Cook County*

Notably, mortality among those readmitted declined from 10.0% in 2010 to 7.8% in 2018, and a trend toward better odds related to inpatient mortality after readmission was observed ($P<0.001$).

Advancing Strategies to Reduce Readmissions

Overall, the past decade has shown an increasing all-cause 30-day readmission rate among patients with AML. Although the retrospective, real-world data offer more insight for health systems to understand the problem, more data are needed along with solutions.

"This is still a subset that needs to be identified, and when they are identified by the health system, then support should be provided, such as use of evidence-based transition-of-care programs and postdischarge interventions tailored to address their specific social needs to decrease their risk of readmission. So, that would be a good way to curb readmission in this population at risk of readmission due to their socioeconomic status," explained Dr. Olafimihan.

This study stands as the most comprehensive epidemiologic analysis to date, shedding light on the profound impact of socioeconomic disadvantage on AML readmissions. Olafimihan et al[1] emphasize that the LIQ AML population represents a critically vulnerable group, underscoring the urgent need for targeted interventions to bridge gaps in care and improve patient outcomes.

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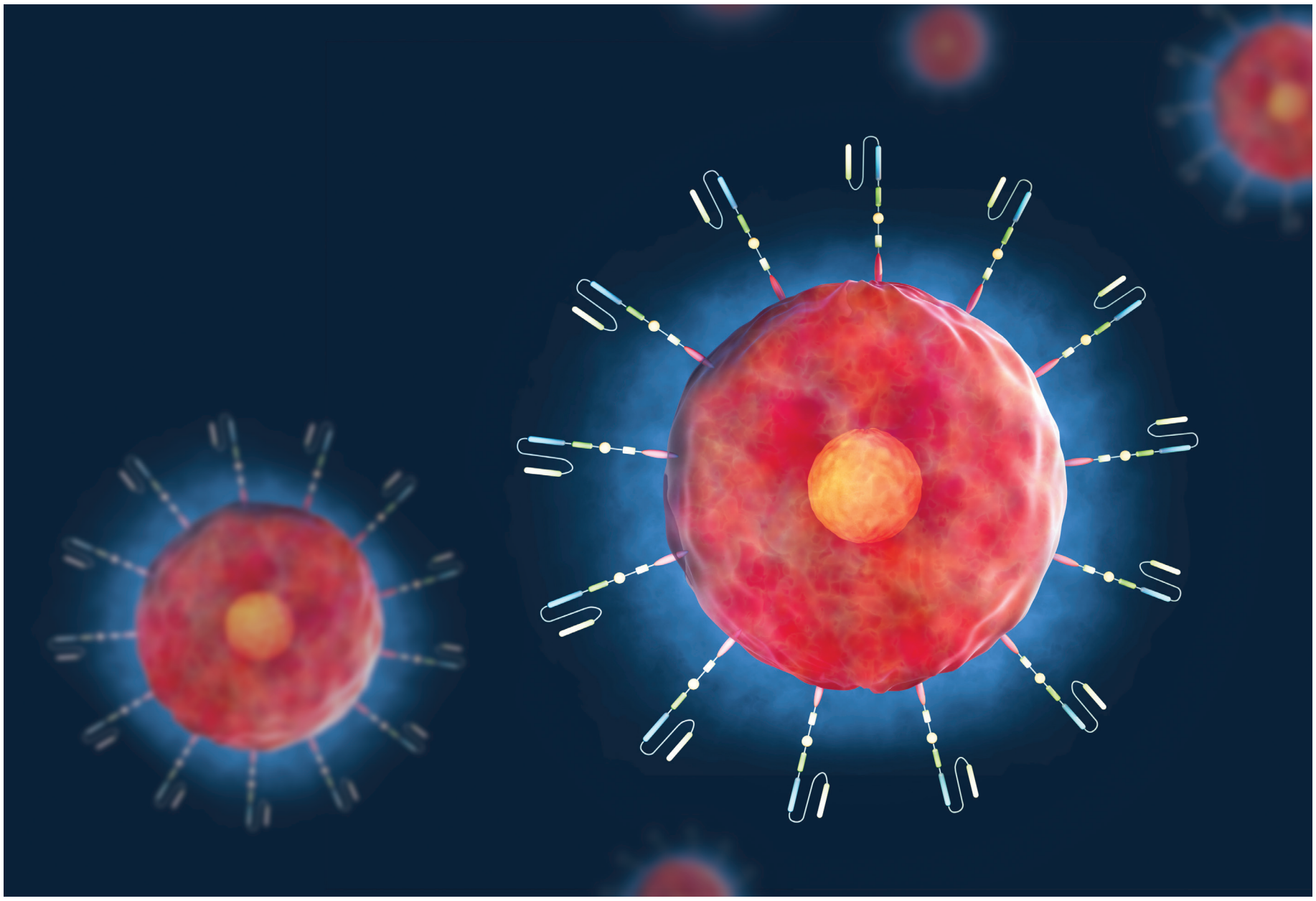

With More Experience, CAR T-cell Therapies Come Into Better Focus

By ***Leah Lawrence***

The FDA approved the first chimeric antigen receptor (CAR) T-cell therapy in August 2017, with 5 additional therapies approved in the years since.[1] The approvals of these CAR T-cell therapies have changed the treatment landscape for several hematologic malignancies, including diffuse large B-cell lymphoma, acute lymphoblastic leukemia, and multiple myeloma.

However, this game-changing treatment is not without adverse effects, according to **Kai Rejeski, MD,** of the Memorial Sloan Kettering Cancer Center.

"This is a therapy that is a living drug," Dr. Rejeski said. "There are interactions between the host and the genetically modified T cells that persist for months and years after the infusion."

Although each of the approved therapies—axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, ciltacabtagene autoleucel, obecabtagene autoleucel—has a slightly unique safety profile, many of the short-term and long-term effects of CAR T-cell therapy overlap.

Blood Cancers Today recently spoke with several physicians familiar with CAR T-cell therapy–related toxicities about identifying and managing these risks.

CRS, ICANS, Cytopenias

When CAR T-cell therapies were first studied and approved, the most significant and concerning toxicities were cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndromes (ICANS).

CRS and ICANS are estimated to occur in at least half of patients with hematologic malignancies who undergo CAR T-cell therapy,[2,3] although not all cases are severe, and rates can vary with specific therapies.

According to **Tania Jain, MBBS,** director of the Immune Effector Cell Therapy Program at Johns Hopkins University, rates of CRS and ICANS have not necessarily changed in the years since these therapies were first approved, but clinicians' comfort level with managing these toxicities has.

"When we were initially studying CAR T, it was unclear whether or when we could use [mitigation strategies like] steroids or tocilizumab, and if they would affect the efficacy of the CAR or not," Dr. T. Jain said. "We have since learned more and know that we don't have to wait for these to progress to grade 3 or beyond before treating."

Dr. Rejeski agreed, "We still observe these side effects, but the rate of high-grade CRS has diminished over time. We proactively, or in some cases prophylactically, treat for these."

Although there has been some connection between CRS and the efficacy of CAR T-cell therapy, one recent study found that development of CRS does not affect survival or response in lymphoma-directed therapies.[4]

"When we started out 7 or 8 years ago, we worried that CRS was necessary for the efficacy of CAR T cells, but the pendulum seems to have swung in the other direction," said **Michael Jain, MD, PhD,** ICE-T medical director in the Moffitt Cancer Center Department of Blood and Marrow Transplant and Cellular Immunotherapy. "In tumor models and in mice, there are studies that indicate we may be able to uncouple CRS from efficacy of CAR T cells and envision a world without CRS in the future."

As clinicians have gained a better understanding of CRS and ICANS, they have also identified consequential toxicities related to cytopenias and other hematologic complications.

"Initially, these were attributed to the lymphodepleting chemotherapy given before CAR-T, but we are observing that cytopenias can persist longer than would be expected with lymphodepleting chemotherapy," Dr. Rejeski said.

These prolonged cytopenias are a concern, he said. With increased insight, clinicians have learned that patients typically have a rapid recovery of neutrophils after lymphodepletion, an intermittent or biphasic pattern of recovery, or an aplastic pattern, Dr. Rejeski said.

"It is patients who have counts drop after lymphodepletion and never recover that are at particularly high risk for infectious complications," he said.

Infection Risk

Many patients who undergo CAR T-cell therapy are at risk for early and late infectious complications. The magnitude of the risk became more clear last year after Dr. Rejeski and colleagues published a meta-analysis of nonrelapse mortality after CAR T-cell therapy.[5]

The analysis looked at 7,604 patients from 18 clinical trials and 28 real-world studies of CAR T-cell therapy for lymphoma and multiple myeloma. Of the nonrelapse deaths reported, more than half (50.9%) were attributed to infections. In comparison, CRS, ICANS, and hemophagocytic lymphohistiocytosis were responsible for 11.5% of nonrelapse mortality.

Clinicians have long been aware of issues related to immune reconstitution after CAR T-cell therapy, according to Dr. M. Jain.

"When you have active CAR T cells, they eat up the B cells, and B cells make antibodies," said Dr. M. Jain. "In about half of patients, B cells recover, but in other patients, the CAR T cells may be active for as much as a decade, and they can have lifelong impairment of antibodies."

Other patients may have lifelong T-cell deficits, Dr. M. Jain said, adding that it is hard to know whether these immune deficits are caused by the CAR T cells, the cumulative effect of other therapies in addition to CAR-T, or a dysregulated immune system that allowed the myeloma or lymphomas to develop in the first place.

"I think we all knew that there was risk for infections, but we did not have these numbers in our head that infections are by far the prominent cause of death," said **Joshua Brody, MD,** director of the Lymphoma Immunotherapy Program at The Tisch Cancer Institute at Mount Sinai, New York.

The best strategy for improving infection-related outcomes is preventing infections, according to Dr. T. Jain. "Over the years, there has been more and more data to support prophylactic strategies, and we have to continue to build them up and get them widely adopted."

"T-cell lymphomas caused by CAR T-cell therapy are far and away the least common of secondary malignancies that occur. It appears to be more common to get a secondary T-cell lymphoma not related to the CAR."

—Michael Jain, MD, PhD, Moffitt Cancer Center

In the immediate term, the first weeks or month, infectious concerns are mainly bacterial or fungal, Dr. T. Jain said. For patients with an absolute neutrophil count (ANC) under 500 cells/mm^3, most institutions start antibacterial prophylaxis and antifungal prophylaxis, she said. If the ANC remains under 500 for a couple of weeks, or after 3 or more days of steroids, then more active antifungal agents should be used.

In the long term, viral infections are also a risk. Revaccination of patients, similar to what is done after autologous transplant, is also important, according to Dr. Brody.

"I don't think there is absolute clarity on which vaccines and when," Dr. Brody said. "That information is somewhat incomplete because we have a new RSV [respiratory syncytial virus] vaccine, a new shingles vaccine, but at a minimum, there should be an annual flu shot and an annual COVID shot."

Other mitigation strategies include the use of intravenous immunoglobulin in patients with hypogammaglobulinemia, which is associated with increased risk for infections.

"There is emerging evidence for the use of immunoglobulin replacement therapy for secondary immune deficiency induced by CAR T-cell therapy," Dr. Rejeski said. "But we are abstracting that from other diseases. We are awaiting prospective evidence [in CAR T-cell patients], but I would say that right now it is almost standard of care to have a lower threshold to apply immunoglobulin in these patients that have high risk for infections."

There is also some evidence for use of granulocyte colony-stimulating factor to mitigate neutropenia in patients who have undergone CAR T-cell therapy, but there is some concern about it increasing CRS risk, and there is no consensus on strategy.[6]

In general, clinicians should have a low threshold for concern and should take infectious symptoms seriously, Dr. Brody said.

"Someone who is 6 weeks post CAR-T and gets a low fever should not be treated like a regular healthy patient," Dr. Brody said. "They should go to the emergency room."

Certain patients are likely to be at higher risk for infectious complications. Risk can be calculated using the CAR-HEMATOTOX score, a risk stratification score that measures markers associated with hematopoietic reserve and baseline inflammation.[7]

Research has shown that patients with higher baseline CAR-HEMATOX scores are at increased risk for prolonged neutropenia and severe infections.[8]

"This allows you to pick the best candidates for CAR T-cell therapy," Dr. Brody said, "and to know which patients are at higher risk and are in need of close monitoring and infection prevention strategies."

MNTs and SPMs

Another toxicity that has come to light as CRS and ICANS have become better managed is what has been called *movement and neurocognitive toxicities (MNTs),* according to Dr. T. Jain. This is considered to be an on-target, off-tumor effect of B-cell maturation agent (BCMA)–targeting CAR T-cell therapy.

"These are nervous system toxicities that occur with cilta-cel [ciltacabtagene autoleucel] and can occur anywhere from a month to several months after infusion," Dr. T. Jain said.

MNTs are characterized by a variety of movement, cognitive, and personality changes including micrographia, tremors, memory loss, disturbance in attention, and reduced facial expression.[9]

Among the first to describe this toxicity were Parekh and colleagues who published a case report detailing a patient who had enrolled in the CARTITUDE-1 trial and was treated with ciltacabtagene autoleucel, a BCMA-targeted CAR T-cell therapy.[10] The patient developed "a progressive movement disorder with features of parkinsonism."

It was estimated that MNTs occurred in about 6% of patients treated in CARTITUDE-1,[11] and risk factors are thought to include high tumor burden, any-grade ICANS, high CAR T-cell expansion, and severe CRS.[12] A retrospective study of patients treated with BCMA-targeting CAR T cells at Massachusetts General found that about 8% of patients had new severe neurologic symptoms, and ICANS was often

In Focus

accompanied "by tremors and myoclonus." Two of the identified patients went on to develop parkinsonism.[13] Treatment approaches are still being determined but may result in reversal of the disorder.[14]

"A severe case of this is quite rare, and it is specific only to BCMA CAR T-cell therapy," Dr. Brody said. "Although it is not very common, it is absolutely important for discussion in the risks and benefits for BCMA-targeting therapy."

In addition, patients undergoing BCMA-targeting CAR T-cell therapy should be closely monitored for these unusual toxicities.[15]

Now that some patients who have undergone CAR T-cell therapy are multiple years out from the time of their infusion, entering a "survivorship" stage, more is being understood about late toxicities associated with the therapy.

In early 2024, the FDA mandated a boxed warning for all of its approved CAR T-cell therapies to highlight "the serious risk of T-cell malignancies."[16]

However, studies looking at risk for T-cell lymphoma and secondary primary malignancy (SPM) suggested low risk after CAR T-cell therapy.[17] Dr. Rejeski and colleagues published a meta-analysis of data on more than 5,000 patients from 18 clinical trials and 7 real-world studies of CAR T-cell therapy. The analysis showed that although there was a clinically relevant long-term risk for SPM in patients undergoing CAR T-cell therapy, T-cell malignancies comprised a minority of events (1.5%).[18]

"T-cell lymphomas caused by CAR T-cell therapy are far and away the least common of secondary malignancies that occur," said Dr. M. Jain. "It appears to be more common to get a secondary T-cell lymphoma not related to the CAR."

According to Dr. M. Jain, patients with a B-cell lymphoma have a 10-fold higher risk for T-cell lymphoma, absent any CAR T-cell therapy. These patients are also at risk for secondary myeloid malignancies, such as myelodysplastic syndrome or acute myeloid leukemia, or secondary solid tumors.

"Here though, it is a bit difficult to know if the risks for these cancers are higher than they otherwise would be because of prior chemotherapy exposure or patient age," Dr. M. Jain said. "We haven't entirely determined if the occurrence of these secondary cancers is increased by the fact that the patient received CAR T-cell. That is still being worked out."

Move Into the Community

In the coming years, the availability of CAR T-cell therapy is only expected to grow as it becomes available as an outpatient treatment or as an inpatient treatment at community sites.

The phase 2 OUTREACH study looked at CAR T-cell treatment with lisocabtagene maraleucel in a community setting and showed that patients with relapsed or refractory large B-cell lymphoma seemed to respond well to the therapy. Most centers involved in the study had not previously treated patients with CAR T-cell therapy. There was no grade 3 or higher CRS, and rates of neurotoxicity were similar to those observed in previous trials.[19]

"This is a necessary development," Dr. Rejeski said. "If we want CAR T-cell therapy to be broadly applied as we spread it to more indications, we can't treat all patients in large academic centers."

A key to broadening availability is educating community physicians about these therapies and their side effects and integrating CAR T-cell therapy availability into an integrated system, he said.

Dr. T. Jain agreed, "It needs to be scaled up and we need to involve community partners."

Pharmaceutical companies will play a big role in this effort, Dr. T. Jain said. The manufacturers can help to make sure that centers onboarding these products have the right services available.

"They need some sort of consultative services and have to have other specialties involved, such as neurology, ICU, pulmonology, and infectious diseases," Dr. T. Jain said. "As our experience as a whole grows, there is more knowledge that can be shared. More of these adverse effects can be predicted and prevented, and then less of these can be done in a tertiary setting."

For example, a retrospective study published last year examined rates of CRS and ICANS onset and duration in 475 patients who underwent CAR T-cell therapy at 9 centers. Data indicated that new-onset CRS and ICANS were rarely seen more than 2 weeks after infusion, despite the FDA Risk Evaluation and Mitigation Strategy calling for monitoring of these toxicities for 4 weeks.[20]

In fact, Dr. Rejeski said that as experience and knowledge of CAR T-cell therapy continue to grow, hematologists will be left facing more of the adverse effects that they have been most familiar with for years.

"There are some specific side effects unique to CAR-T, but now we are talking about side effects that have been known to hematologists for more than 80 years," Dr. Rejeski said. "The potential for cytopenias, emergence of infectious complications, and, as with some of the first chemotherapy given, the potential for secondary malignancy. We have almost come full circle."

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Regulatory Actions

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

FDA Approves Brentuximab Vedotin Plus Lenalidomide, Rituximab for LBCL

*By **Andrew Moreno***

The FDA has approved combination of brentuximab vedotin with lenalidomide and a rituximab product to treat relapsed or refractory large B-cell lymphoma (LBCL) in adult patients ineligible for autologous hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor (CAR) T-cell therapy who have undergone at least two lines of systemic therapy. This new approval, announced by the FDA in a news release, includes diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma.

Brentuximab vedotin is marketed as Adcetris by Seagen Inc., a subsidiary of Pfizer Inc.

This new approval was based on data from the ECHELON-3 randomized, double-blind, placebo-controlled trial. In this trial, 230 patients were randomized 1:1 to receive either brentuximab vedotin plus lenalidomide and rituximab or placebo plus lenalidomide and rituximab.

In terms of efficacy, the brentuximab vedotin combination arm produced a median overall survival (OS) of 13.8 months, and the placebo combination arm, a median OS of 8.5 months, with a hazard ratio (HR) of 0.63 (P=0.0085). The median progression-free survival (PFS) was 4.2 months in the brentuximab vedotin combination arm and 2.6 months in the placebo combination arm, with an HR of 0.53 (P<0.0001). The objective response rate (ORR) was 64.3% in the brentuximab vedotin combination arm and 41.5% in the placebo combination arm.

Adverse reactions in the brentuximab vedotin combination arm that occurred with a frequency of 20% or greater were COVID-19 infection, diarrhea, fatigue, peripheral neuropathy, pneumonia, and rash. In this arm, 27% of patients experienced onset or worsening of peripheral neuropathy. The neuropathy was mostly sensory and led to brentuximab vedotin dose reduction in 6% of patients and discontinuation in 4.5%.

Grade 3 or 4 laboratory abnormalities that affected 10% or more of patients in the brentuximab vedotin combination arm were decreased hemoglobin, decreased lymphocytes, decreased neutrophils, and decreased platelets.

The FDA listed the recommended brentuximab vedotin dose to be 1.2 mg/kg up to a maximum of 120 mg in combination with lenalidomide and rituximab, to be administered every 3 weeks until the occurrence of unacceptable toxicity or disease progression.

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CD5-Targeting CAR T-Cell Therapy Receives FDA Orphan Drug Designation for T-Cell Lymphoma Use

By Andrew Moreno

The FDA has granted orphan drug designation to MB-105, a first-in-class autologous CD5-targeting chimeric antigen receptor (CAR) T-cell therapy, for use in relapsed or refractory T-cell lymphoma. The new designation was announced in a press release from March Biosciences, Inc, a clinical stage biotechnology company the developer of this new CAR T-cell therapy.

"Beyond an important regulatory milestone, securing orphan drug designation for MB-105 from the FDA underscores the critical need for new therapeutic options for patients with T-cell lymphoma," commented March Biosciences co-founder and chief executive officer **Sarah Hein, PhD,** in the release.

MB-105 is the lead program for March Biosciences and was launched by the company from the Center for Cell and Gene Therapy, Houston, Texas. Work at the Center on this treatment is a collaboration of Baylor College of Medicine, Houston Methodist Hospital, and Texas Children's Hospital, each located in Houston, Texas.

This new CAR T-cell therapy is being developed for management of CD5-positive T-cell lymphomas, as well as CD5-positive T-cell acute lymphoblastic leukemias, chronic lymphocytic leukemias, and mantle cell lymphomas. It is distinguished by a proprietary CAR design that enables the treatment to preserve certain normal T-cell functions while it targets malignant cells.

MB-105 is currently being evaluated in a phase 1 clinical trial for relapsed or refractory T-cell lymphoma and T-cell acute lymphoblastic leukemia. Among patients with T-cell lymphoma in the trial, the therapy has produced a 44% overall response rate.

"The MB-105 Phase 1 trial has shown promising safety and efficacy signals in relapsed [or] refractory T-cell lymphoma patients. This designation further validates our development strategy as we prepare to initiate our Phase 2 clinical trial in early 2025," Dr. Hein explained.

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E1A-Binding, CREB-Binding Protein Inhibitor Receives FDA Multiple Myeloma Orphan Drug Designation

By Andrew Moreno

For multiple myeloma treatment, the FDA has newly granted Orphan Drug designation (ODD) to OPN-6602, a small molecule inhibitor of both the E1A-binding protein (EP300) and CREB-binding protein (CBP). This oral agent is under development by biopharmaceutical company Opna Bio, which announced the new designation in a press release.[1]

"We are pleased to have received ODD for OPN-6602 for the treatment of multiple myeloma, a further validation of the drug's therapeutic potential in patients with this disease who have limited treatment options once they have relapsed," commented Opna Bio cofounder and chief scientific officer **Gideon Bollag, PhD.**

This drug is currently under evaluation in a first-in-human phase 1 trial in patients with relapsed or refractory multiple myeloma in progress at several sites across the United States. Opna Bio has sponsored this trial and expects to finish its single agent, dose-escalation phase in 2026.

In December 2024, Opna Bio presented multiple myeloma mouse xenograft model data on OPN-6602 at the 66th American Society of Hematology Annual Meeting & Exposition in San Diego, California. In a press release, the company reported that OPN-6602 monotherapy produced 71% tumor suppression and resulted in 100% tumor regression when used in combination with dexamethasone, pomalidomide, or mezigdomide. The agent also showed potential to defeat resistance mechanisms of disease to standard-of-care regimens along with reduced toxicity.[2]

Beyond the phase 1 trial currently underway, Opna Bio plans to develop OPN-6602 in combination with other standard-of-care agents for treatment of multiple myeloma.[1]

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Highlights From **THE FOURTH ANNUAL NATIONAL GENERAL MEDICAL ONCOLOGY SUMMIT**

Navigating the Road Ahead: Treatment Strategies Reshaping MM Care

*By **Nichole Tucker***

Quadruplet therapies (quads) are transforming the treatment of multiple myeloma, pushing the boundaries of what is possible. Some regimens are already changing standards of care, and others are emerging with promising potential.

During the Fourth Annual National General Medical Oncology Summit, **Natalie C. Callander, MD,** a faculty member in the Division of Hematology, Medical Oncology and Palliative Care within the Department of Medicine at the University of Wisconsin, School of Medicine and Public Health, reviewed current and emerging quads in a presentation. According to Dr. Callander, the future of multiple myeloma treatment is being shaped by key clinical trials, including, PERSEUS, IMROZ, and CEPHEUS, which were practice changing, and others, which could alter the treatment of multiple myeloma soon.[1]

Natalie C. Callander, MD

Crossing the Border Into Innovation

The historic success of the phase 3 GRIFFIN study (NCT02874742) paved the road ahead for treatment of multiple myeloma.[2] The addition of daratumumab (Dara) to bortezomib plus lenalidomide and dexamethasone (VRd) enhanced depth of response and prolonged progression-free survival (PFS) among transplantation-eligible patients with newly diagnosed multiple myeloma (NDMM). It warranted further exploration in phase 3 studies, which began with PERSEUS (NCT03710603).[3]

"I think the success of quadruplet induction plus transplant and maintenance with IMID [immunomodulatory drugs] and anti-CD38 agents has really set a new bar, particularly the amazing PFS and rates of minimal residual disease negativity seen in PERSEUS," Dr. Callander told *Blood Cancers Today,* in an interview.

PERSEUS

Subcutaneous Dara added to VRd induction and consolidation therapy and to lenalidomide maintenance was assessed in transplantation-eligible patients with NDMM in the PERSEUS trial, according to results published in 2023. At a median follow-up of 47.5 months, the quad achieved a major reduction in the risk of disease progression or death of 60% (hazard ratio [HR], 0.42; 95% CI, 0.30- 0.59; $P<0.001$).[3,4]

Results from PERSEUS led to the FDA approval of Dara and hyaluronidase in combination with VRd for induction and consolidation in patients with NDMM who are eligible for autologous stem cell transplant (ASCT) in July 2024. The quad was approved at the recommended dose of Dara 1,800 mg and hyaluronidase 30,000 units with the standard dose of VRd.

A year after PERSEUS, data from another phase 3 study of anti-CD38 agents with VRd showed improved outcomes—this time in the transplant-ineligible population.

IMROZ

In comparison with VRd alone, isatuximab plus VRd improved PFS and responses in patients with NDMM who were ineligible to undergo transplantation.[4] Median follow-up in the IMROZ study was 59.7 months, and the 60-month PFS rate was 63.2% with isatuximab plus VRd versus 45.2% with VRd alone (HR, 0.60; 98.5% CI, 0.41-0.88; $P<0.001$). Notably, complete responses were observed in 74.7% of the isatuximab plus VRd arm versus 64.1%, in the control arm ($P=0.01$).

In September 2024, results from IMROZ were the basis for the accelerated FDA approval of isatuximab 10 mg/kg plus VRd for the treatment of adults with NDMM who are not eligible for ASCT. According to the FDA label, isatuximab is required to be administered IV based on the patients' body weight.[5]

Another study mentioned during Callander's presentation, BENEFIT (NCT04751877), confirmed the clinical benefit of isatuximab-VRd for patients with NDMM.[1]

Inching Closer to Breakthroughs

At the start of 2025, final results from the phase 3 CEPHEUS study (NCT03652064) added to data around anti-CD38/VRd quad therapy among transplant-ineligible patients.[6]

CEPHEUS

Overall, data from CEPHEUS positions Dara-VRd as a new standard of care for patients with NDMM who are ineligible for transplant or who have been transplant deferred. At a median follow-up of 58.7 months, the quad achieved a 60.9% rate of measurable residual disease negativity versus only 39.4% with VRd alone (odds ratio, 2.37; 95% CI, 1.58-3.55; $P<0.0001$). Moreover, Dara/VRd had a higher complete response rate (81.2%) compared with VRd alone (61.6%; $P< 0.0001$).

In terms of survival in CEPHEUS, the risk of disease progression or death was reduced with Dara-VRd by 43% (HR, 0.57; 95% CI, 0.41-0.79; $P=0.0005$). These findings could lead to another indication for Dara-VRd.[1]

"We now have great quadruplet options for transplant-deferred or transplant-ineligible patients—which we saw in IMROZ, BENEFIT, and CEPHEUS—that can produce almost the same depth of response," said Dr. Callander.

Notably, across the studies of quads for the treatment of NDMM, safety profiles were acceptable.[1-6]

AQUILA

"The treatment of smoldering myeloma has been quite controversial," explained Dr. Callander, during her presentation. Despite quads taking over in the newly diagnosed population, a recent study is looking at monotherapy with an anti-CD38 agent in this population (AQUILA; NCT03301220).

In the phase 3 AQUILA study, patients with high-risk smoldering MM were treated with subcutaneous Dara monotherapy, which achieved prolonged PFS compared with active monitoring. At a median follow-up of 65.2 months, the risk of disease progression or death was reduced by 51% with subcutaneous Dara (HR, 0.49; 95% CI, 0.27-0.98).

As of November 2024, an application for approval of Dara for high-risk smoldering MM is pending at the FDA.[1]

On the Horizon

Many ongoing studies have the potential to change the course of MM treatment even more. According to Dr. Callander, protocols that evaluate different end points, such as overall survival (OS) and novel therapies, are also reshaping the field.[1]

"I believe one of the most exciting areas of research—one we did not have time to cover in the presentations—is the investigation of T-cell engagers as part of initial therapy. I think this strategy may be able to help improve the outcome for high-risk myeloma patients and potentially shorten the length of treatment for all patients, but still produce the same depth of response," said Dr. Callander, in the interview.

Aside from these, Dr. Callander said, "The new IMID agents, iberdomide and mezigdomide look strong in multiple combinations, and we expect them to available some time in 2026."

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Stepping Forward in CLL: Novel Agents and BTKi/BCL2i Combination Strategies

*By **Melissa Badamo***

In recent years, trials such as CAPTIVATE, IVO, and AMPLIFY have evaluated Bruton tyrosine kinase inhibitor (BTKi) and B-cell lymphoma-2 inhibitor (BCL-2i) combinations for the treatment of chronic lymphocytic leukemia (CLL). **Kerry Rogers, MD,** associate professor in the Division of Hematology at The Ohio State University, presented on novel agents and combination strategies in CLL at the Fourth Annual National General Medical Oncology Summit February 28 to March 2, 2025.

BTKi/BCL2i Combinations

Kerry Rogers, MD

Dr. Rogers believes that BTKi/BCL-2i combinations should be increasingly utilized in the treatment of CLL due to their high efficacy, durable responses, and ability to reduce the risk of molecular resistance.

"These combinations may change how treatment is offered over a patient's lifespan," she told *Blood Cancers Today*. "As CLL is not currently curable, patients can anticipate receiving multiple treatments. In clinical trials with BTKi/BCL-2i combinations that have longer follow-ups than AMPLIFY, we have seen that both classes of drugs can be reused at time of next treatment. While there is still a lot to learn about sequencing of therapies in CLL, avoiding resistance to targeted agents is expected to be beneficial."

Ibrutinib Plus Venetoclax With and Without Anti-CD20 Antibodies

In the phase 2 CAPTIVATE study, a fixed-duration cohort of patients received 15 total cycles of treatment: 3 cycles of ibrutinib and 12 subsequent cycles of ibrutinib plus venetoclax. Dr. Rogers noted differences in progression-free survival (PFS) by risk group. Patients with unmutated IGHV had a shorter 5-year PFS than those with mutated *IGHV* (56% vs 80%, respectively), and patients with high-risk features such as del(17p), *TP53* mutations, and/or complex karyotype had a shorter PFS than those without high-risk features (54% vs 77%, respectively).[1]

The phase 2 IVO study combined ibrutinib, venetoclax, and obinutuzumab in 3 cohorts of patients with treatment-naive and relapsed or refractory CLL. The PFS was 7.4 years in the treatment-naive cohort, compared with 6.5 years with just venetoclax and obinutuzumab and 9 years with continuous ibrutinib.[1] However, when the phase 3 A041702 trial randomized older adult patients to ibrutinib, venetoclax, and obinutuzumab, ibrutinib and obinutuzumab, or continuous ibrutinib, the hazard ratio was similar in each arm, showing that the 3-drug combination was not superior in terms of PFS. A similarly designed trial with young patients is ongoing.[1]

AMPLIFY Trial

The phase 3 AMPLIFY trial evaluated fixed-duration acalabrutinib and venetoclax with or without obinutuzumab versus investigator's choice of fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR) as first-line therapy for fit patients with CLL. Both acalabrutinib and venetoclax with obinutuzumab (AVO) or without obinutuzumab (AV) had improved PFS compared with FCR/BR (not reached vs 47.6 months, respectively).[2]

The results of the AMPLIFY trial were also broken down by *IGHV* status, and the benefit of obinutuzamab was shown to be greatest in *IGHV*-unmutated CLL.[1] "For AVO, the IGHV-mutated and unmutated CLL patient PFS is overlapping, showing that when you add obinutuzamab in, you make the outcomes equal between IGHV-mutated and unmutated CLL patients," said Dr. Rogers in her presentation. "The obinutuzamab doesn't add much for IGHV-mutated patients. This did not include del(17p). The majority of benefit to the O [obinutuzumab] is in IGHV-unmutated CLL."

However, obinutuzamab does increase toxicity and infection risks, Dr. Rogers noted. "AV had the fewest COVID deaths at 10, with both antibody-containing arms having either 25 or 21," she said. "This is highlighting that this is a very real risk of adding an antibody here. While certainly I wouldn't expect this many COVID deaths at the current timeframe, this means that obinutuzamab adds some risk that we have to consider carefully when we're looking at the benefit."

Undetectable measurable residual disease (MRD) was evaluated as a secondary end point in the AMPLIFY trial. At the end of treatment, the undetectable MRD rates were 95.0% for AVO, 45.0% for AV, and 72.9% for FCR/BR.[1] Despite showing lower rates of undetectable MRD, AV had a longer PFS compared with FCR/BR, Dr. Rogers noted. These results may warrant further investigation into the prognostic value of MRD in CLL.

"I think we are still working on defining the role of MRD in CLL treatment, and it likely means different things with different treatments," Dr. Rogers told *Blood Cancers Today*. "It is true that even with lower rates of MRD undetectable status, AV had a longer PFS compared to the chemoimmunotherapy arm (FCR/BR). However, within each arm, patients who had undetectable MRD appeared to have a longer PFS compared to those who had detectable disease. This means that for patients who were treated with AV, patients who had undetectable MRD appeared to have a longer PFS than those where MRD was still detected. So, MRD status is helpful within treatment arms, but its use in understanding outcomes between very different types of treatments (eg, chemotherapy vs targeted agents) is probably limited."

Other BTKi Venetoclax Combinations

Next in her presentation, Dr. Rogers discussed other BTKi combinations with venetoclax. In arm D of the SEQUOIA trial, zanubrutinib plus venetoclax yielded a 12- and 24-month PFS of 95% and 94%, respectively, in patients with del(17p) CLL or SLL.[1]

A phase 1/1b trial (BGB-11417-101) looked at zanubrutinib (320 mg) combined with sonrotoclax, a novel BCL2i, at 2 dose levels (160 mg and 320 mg). By week 48, sonrotoclax 160 mg achieved a complete response (CR) rate of 60% and a partial response (PR) rate of 40%, and sonrotoclax 320 mg achieved a CR rate of 58% and a PR rate of 42%.[1] The combination is now being compared with venetoclax plus obinutuzumab in the phase 3 CELESTIAL-TNCLL

trial. "I'm really looking forward to this and hope that it gives us another BTK inhibitor/BCL-2 inhibitor combination," Dr. Rogers said during her presentation.

Novel Agents

The phase 1 BRUIN CLL-321 trial compared pirtobrutinib with idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in covalent BTKi-pretreated CLL or SLL. The median PFS was improved with pirtobrutinib compared with the standard arm, but the overall survival was similar between the arms. "This is showing that this is not the benefit we need for a lot of our CLL patients," said Dr. Rogers.[1]

Dr. Rogers also presented updated follow-up data from the TRANSCEND CLL 004 trial of lisocabtagene maraleucel in relapsed or refractory CLL. "Complete remission or complete remission with incomplete marrow recovery is really what the patients need to be able to get a very durable remission," she explained.[1] For the 20% of patients who achieved a CR, the duration of response was not reached. The toxicities were manageable, with a high rate of cytokine release syndrome, albeit low grade.[1]

A cohort of the TRANSCEND CLL 004 trial was treated with ibrutinib before collection, through lymphodepletion, and after cell infusion. About twice as many patients (45%) achieved a CR, expecting to achieve durable remission.[1]

Looking Ahead

Phase 3 trials are under way to evaluate pirtobrutinib as monotherapy and in combination with other agents such as ibrutinib, bendamustine plus rituximab, or venetoclax plus rituximab, as well as in earlier lines of therapy.[1]

"These combinations offer another important option for CLL patients and are in keeping with what the field has done to make CLL treatment not only more effective, but also safer and more feasible for more patients," Dr. Rogers told *Blood Cancers Today*. "The addition of BTKi/BCL-2i regimens allow for more options so that each individual can receive the CLL therapy that is best for them."

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NHL Experts Explore: What Do New Data Say About How to Use CAR T-Cells, Bispecific Antibodies, Novel Therapies?

*By **Andrew Moreno***

At the Fourth Annual National General Medical Oncology Summit held in Miami, Florida, host **Neil Love, MD,** president and CEO of Research to Practice, moderated an expert panel on non-Hodgkin lymphoma (NHL) management. The panel included **Krish Patel, MD,** of Sarah Cannon Research Institute, **Christopher Flowers, MD, MS,** of MD Anderson Cancer Center, and **Vikas Malhotra, MD,** of Florida Cancer Specialists and Research Institute.

Dr. Patel gave a presentation, which was an overview of and update on chimeric antigen receptor (CAR) T-cell therapy for NHL. With the success of the ZUMA 7, TRANSFORM, and PILOT large B-cell lymphoma clinical trials, CD19-targeting T cells are now being considered for second-line diffuse large B-cell lymphoma (DLBCL) therapy. Another instance of progress is the production of benefit by lisocabtagene maraleucel (liso-cel) in patients who would not have been candidates for autologous stem cell transplant.

Neil Love, MD

Christopher Flowers, MD, MS

Krish Patel, MD

Vikas Malhotra, MD

Dr. Patel said that CAR T-cell therapy approaches, specifically for mantle cell lymphoma (MCL), are "a double-edged sword": patients have better response but also more cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). However, he cited liso-cel as resulting in high overall survival (OS) and complete response (CR) rates, with less CRS than that seen with brexucabtagene autoleucel.

Dr. Flowers mentioned that there is an increasing trend toward administering CAR T-cell therapy in an outpatient setting. However, issues remain, including the question of whether to give prophylactic steroids, the need for a caregiver, and how to avoid CRS.

"It is best to have a patient be at a center where they can manage the CRS—especially in cycle 1— to be able to administer tocilizumab," Dr. Flowers elaborated.

About bispecific antibodies, Dr. Patel underscored in his presentation that glofitamab and epcoritamab have comparable efficacy and long-term outcomes, but they differ in how they are administered, and some patients see earlier benefit. He also cited the STARGLO trial as illustrating the move of bispecifics into second-line therapy.

The panel also discussed the relationship between bispecifics and CAR T-cell therapy in NHL care. Dr. Flowers said there is increasingly more data being gathered on CAR T-cell use after treatment with a bispecific, and Dr. Malhotra commented on the importance of an individualized approach when using a bispecific plus CAR T-cell therapy.

"Most patients recognize the curative potential to CAR-T, but there's a lot of access challenges. Bispecifics are next best option," Dr. Patel remarked.

Dr. Flowers also gave a presentation on novel therapies under investigation for NHL. He said the 5-year data from the POLARIX study on Pola-R-CHP (polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone) versus R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) was significant for frontline DLBCL care. The inMIND trial of tafasitamab plus lenalidomide and rituximab for follicular lymphoma was practice changing, although further study is needed.

"How do you sequence your agents is a question. There are some data. With diseases being different and timing different, we will need to see this means for follicular lymphoma," Dr. Flowers clarified.

Studies Dr. Flowers said were significant specifically in MCL were the ENRICH study, in which rituximab plus ibrutinib showed superior survival to rituximab plus chemotherapy, and the TRIANGLE study of ibrutinib plus immunochemotherapy, which had favorable efficacy and toxicity data.

"The patients who got ibrutinib in first-line therapy look to have a significant benefit, where stem cell transplantation may not even be needed." Dr. Flowers said.

"About younger patients with MCL, transplant doesn't play a role for most anymore. They look at more combinations of targeted therapies. Older and younger patients both," Dr. Patel mentioned.

For patients who have relapsed DLBCL, Dr. Flowers said many novel approach options are available now, such as loncastuximab tesirine, which has produced durable response. He noted this combination has certain increased toxicities and dexamethasone is needed on hand, with Dr. Patel adding that the first 2 cycles are very indicative of a patient's toleration.

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Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. For Multiple Myeloma Awareness Month, section editor* ***Nisha Joseph, MD,*** *associate professor in the Department of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University, highlights recent research in multiple myeloma.*

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

Nisha Joseph, MD

MYELOMA

Can Teclistamab Address Renal Impairment in Relapsed or Refractory MM?

By ***Nichole Tucker***

The FDA-approved therapy teclistamab, which targets the B-cell maturation antigen, has been proven to induce deep and durable responses in patients with relapsed or refractory (MM).[1] MM-related renal impairment (RI) is a significant issue, and guidelines for management are provided in the International Myeloma Working Group clinical practice recommendations.[2] But in the MajeTEC-1 clinical trial, which supported the FDA's approval of the agent, patients with RI were excluded, warranting additional research.[1]

A multicenter retrospective study involving 13 US centers was conducted to determine whether teclistamab is safe and effective for use in the subset of patients with RI (defined as creatinine clearance <40 mL/min at study initiation).[3] The study included 384 patients with relapsed or refractory MM; 81 of whom had RI (45 with severe RI and 18 undergoing dialysis). Most of the patients with RI received teclistamab ramp-up treatment as inpatients. The median age of patients with RI was 71 years, and the median age of patients without RI was 67 years. Patients with RI had a median of 7 prior therapies, and those without RI had a median of 6 prior therapies.

Results showed that renal function did not significantly change in most patients after teclistamab treatment was initiated. The overall response rate among patients with RI was 52% versus 56% among those without RI (P=0.61). Complete responses were observed in 20% versus 24%, respectively (P=0.53), and very good partial responses were observed in 47% versus 46%, respectively (P=0.92).

Median follow-up was 9.9 months, and the median progression-free survival (PFS) was 4.6 months among patients with RI versus 6.5 months among those without RI (P=0.62). Multivariable analysis showed that RI was not independently associated with PFS. Furthermore, for patients with RI, the 1-year overall survival rate was 60.5% (95% CI, 49.9%-73.3%) versus 62.1% (95% CI, 56.2%-68.6%) for patients without RI (P=0.77).

Overall, the toxicity profile of teclistamab in patients with relapsed or refractory MM and RI was comparable to that in patients without RI. Investigators observed nonrelapse mortality from toxicity in 26% patients, which included 12% who died of teplizumab-related toxicity. Grade 3 or higher thrombocytopenia was an outlier, having occurred in 17% of patients with RI versus only 6% of those without RI P=0.002).

The retrospective study supported the safety of teclistamab and demonstrated a PFS benefit for patients with relapsed or refractory MM and RI.

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KarMMa-2 Trial: Ide-cel Shows Deep, Durable Responses in Newly Diagnosed MM

By ***Melissa Badamo***

A study published in *The Lancet Haematology* outlined patient-reported outcomes of the CARTITUDE-4 trial of ciltacabtagene autoleucel (cilta-cel) versus standard of care in lenalidomide-refractory multiple myeloma (MM).

Investigators of the randomized, open-label, phase 3 trial previously reported that cilta-cel significantly improved progression-free survival (PFS) compared with standard of care.

A total of 419 patients from 81 sites in the United States, Europe, Asia, and Australia were randomly assigned 1:1 to receive either cilta-cel at a target dose of 0.75 × 10^6 chimeric antigen receptor T cells/kg (n=208) or standard-of-care therapy (daratumumab, pomalidomide, and dexamethasone or pomalidomide, bortezomib, and dexamethasone; n= 211). Patients had 1-3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and an Eastern Cooperative Oncology Group performance status of 0 or 1. The median follow-up was 15.9 months.

The primary endpoint was PFS. Secondary endpoints included time to sustained worsening of symptoms as reported through the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) and change in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire Core C30 and EuroQol 5-Dimension 5-Level (EQ-5D-5L).

Baseline assessments were completed by 191 of 208 patients (92%) in the cilta-cel group and 190 of 209 evaluable patients (91%) in the standard- of-care group. After baseline, the MySIm-Q compliance was 70% to 81% for cilta-cel and 79% to 89% for standard of care. The median time to sustained worsening of symptoms, as reported through MySIm-Q, was 23.7 months with cilta-cel and 18.9 months with standard of care (hazard ratio, 0.42; 95% CI, 0.26-0.68).

The average change in EORTC global health status from baseline to 12 months was +10.1 points (95% CI, 7.0-13.1) for cilta-cel and –1.5 points (95% CI, –5.3 to 2.3) for standard of care. The average change in EQ-5D-5L visual analogue scale (VAS) from baseline to 12 months was +8.0 points (95% CI, 5.2-10.7) for cilta-cel and +1.4 points (95% CI, –1.9 to 4.7) for standard of care.

"Rates of clinically meaningful improvements in GHS and VAS were higher with cilta-cel than with standard of care," the researchers wrote. "Health-related QoL improvements and delayed symptom worsening support cilta-cel's clinical efficacy in lenalidomide-refractory disease."

This research was funded by Janssen Research & Development, Legend Biotech USA.

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What Is the Difference in Ide-Cel Efficacy, Toxicity Between Age Groups of Patients With MM?

*By **Melissa Badamo***

A study presented at the 66th American Society of Hematology Annual Meeting & Exposition compared the efficacy and toxicity of idecabtagene vicleucel (ide-cel) in patients with multiple myeloma (MM) aged 70 years and older versus younger patients.

The multicenter cohort study included 136 patients with relapsed or refractory MM receiving ide-cel treatment at 7 tertiary German centers. Patients were grouped by age at the time of chimeric antigen receptor (CAR) T-cell infusion, either younger than 70 years (n=91; median age, 61) or aged 70 years and older (n=45; median age, 72). Both groups had a median of 5 prior lines of therapy (P=0.49) and shared similar characteristics regarding Eastern Cooperative Oncology Group score 0-2 (74.4% vs 84.4%, P=0.27), Revised Multiple Myeloma International Staging System stage III at diagnosis (28.6% vs 42.2%, P=0.38), high-risk cytogenetics (51.8% vs 35.9%, P=0.12), median time from first diagnosis to CAR T-cell infusion (6.9 vs 8.0 years, P=0.26), penta-refractory status (51.6% vs 62.2%, P=0.36), prior B-cell maturation antigen-directed therapy (14.4% vs 15.6%, P=1.0), and prior autologous hematopoietic stem cell transplantation.

Grade 3 or 4 cytokine release syndrome (CRS) occurred in 7.7% of patients in the younger group and in 4.4% of patients in the older group (P=0.71). All grades of immune effector cell–associated neurotoxicity syndrome (ICANS) occurred in 24.4% of patients in the younger group and in 6.6% of patients in the older group (P=0.005). The rate of grade 3 or 4 ICANS was similar between the two groups (0% vs 2.2%, respectively; P=1.0), as well as the rate of infections within 30 days after infusion (P=0.19).

The overall response rates were comparable between younger patients and older patients (87.8% vs 92.7%, respectively; P=0.274). With a median follow-up of 8.1 months, the median progression-free survival (PFS) was 9.2 months (95% CI, 6.7-14.1) for the younger group and 9.6 months (95% CI, 6.9-not reached) for the older group (P=0.39). The 1-year PFS rates were 42.9% and 48.7%, respectively.

The median overall survival (OS) was not reached, but the 1-year OS was 67.1% in the younger group and 66.8% in the older group (P=0.95). The cumulative incidence of 1-year nonrelapse mortality (P=0.17) and the cumulative relapse incidence (P=0.08) were comparable in the 2 groups.

In a multivariate regression analysis, covariates included age groups, number of treatment lines, and disease status before CAR T-cell therapy. The only factor associated with decreased PFS was extramedullary disease at initiation of CAR T-cell therapy (hazard ratio, 1.96; 95% CI, 1.11-3.48; P=0.021).

"With the paucity of long-term data, our real-world analysis provides additional support that CAR T-cell therapy is feasible and effective in patients with r/r [relapsed or refractory] MM aged 70 years or older, demonstrating outcomes and toxicities comparable to those observed in younger patients," the researchers concluded. "Therefore, CAR T-cell therapy should not be withheld for eligible patients above 70 years with r/r MM."

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American Society for Clinical Investigation Announces 2025 Young Physician-Scientist Awards

*By **Melissa Badamo***

The American Society for Clinical Investigation (ASCI) announced the recipients of the 2025 Young Physician-Scientist Awards, which recognizes physician-scientists who have made notable research achievements early in their first faculty appointment. Of the 50 recipients, the Society recognized the following physician-scientists with a clinical and research focus on hematologic malignancies and/or cellular therapy.


Sheng Cai, MD, PhD

Sheng Cai, MD, PhD, serves as a leukemia specialist and early drug development specialist at the Memorial Sloan Kettering Cancer Center, where he also completed his oncology fellowship studying how leukemia cells become resistant to targeted epigenetic therapies. His clinical and laboratory interests include developing early-phase trials for patients with leukemia and characterizing the therapeutic vulnerabilities of *TP53*-mutated myeloid malignancies.

"I am deeply honored to receive the 2025 ASCI Young Physician-Scientist Award," Dr. Cai told *Blood Cancers Today*. "This recognition reaffirms my commitment to advancing scientific discovery and bridging the gap between research and patient care, a mission that is at the heart of the ASCI."


Susan DeWolf, MD

Susan DeWolf, MD, a leukemia specialist at the Memorial Sloan Kettering Cancer Center, has a background in studying T-cell immunity in patients with leukemia, with a goal of developing new immune-based treatments. She previously received the Memorial Sloan Kettering Louis V. Gerstner, Jr. Physician Scholar Award and the National Cancer Institute Mentored Clinical Scientist Research Career Development Award, which supports the translational science initiatives of early-career physician scientists.

"I am incredibly grateful to have received the ASCI Young Physician Scientist Award," Dr. DeWolf told *Blood Cancers Today*. "It is a privilege to be part of such a dynamic academic community, and I know that the opportunities arising from this award will help propel me on my trajectory as a clinician-scientist dedicated to the study of T-cell immunity in leukemia."


Francesca Ferraro, MD, PhD

As an assistant professor at the Washington University School of Medicine, **Francesca Ferraro, MD, PhD,** has a clinical and laboratory interest in acute myeloid leukemia (AML). Specifically, she focuses on modeling mutations in mice to understand how they affect AML progression and to develop personalized approaches to improving the accuracy of chemotherapies. Having grown up in Italy, she completed a hematology residency at the University of Parma before moving to Philadelphia for an internal medicine residency at Pennsylvania Hospital, then to St. Louis for a hematology-oncology fellowship at Washington University.


Melody Smith, MD, MS

Melody Smith, MD, MS, is an assistant professor of medicine (blood and marrow transplantation and cellular therapy) at Stanford University School of Medicine, where she established an independent laboratory for the study of allogeneic chimeric antigen receptor (CAR) T cells and the impact of the intestinal microbiome on CAR T-cell response in preclinical models. She is also the investigational new drug sponsor of a clinical trial evaluating bone marrow transplant and CAR T-cell therapy in adult patients with high-risk B-cell acute lymphoblastic leukemia.


Adam Sperling, MD, PhD

At his independent laboratory at Harvard Medical School and Brigham and Women's Hospital, Assistant Professor of Medicine **Adam Sperling, MD, PhD,** investigates the biology of hematologic malignancies with a focus on multiple myeloma, clonal hematopoiesis, mechanisms of disease evolution, and the development of therapy resistance.

"I am deeply honored to receive the ASCI YPSA Award, which really reaffirms my dedication to scientific discovery as a way to improve patients' lives," Dr. Sperling told *Blood Cancers Today*. "I especially appreciate that the YPSA represents the recognition of other scientists for my prior and potential future work as well as the opportunity it provides to connect with and learn from an incredible network of fellow young investigators."


Santosha Vardhana, MD, PhD

Santosha Vardhana, MD, PhD, is a lymphoma specialist at the Memorial Sloan Kettering Cancer Center with a focus on Hodgkin lymphoma, non-Hodgkin lymphoma, and immunotherapy. His independent research program studied the impact of COVID-19 infection on patients with hematologic malignancies, and his current research program focuses on the relationship between altered nutrient uptake and metabolism and T-cell response regulation during cancer development and progression. He previously received the 2024 Pershing Square Sohn Prize for Young Investigators, which grants early-career scientists in the greater New York area a stipend of $250,000 a year for 3 years to pursue research.

"The members of the American Society of Clinical Investigation are the truest representation of physician-scientists, leveraging fundamental biological insights to further the understanding and treatment of human disease," he told *Blood Cancers Today*. "I am humbled and honored to have been selected for a Young Physician-Scientist Award by a group of individuals whose acumen, work ethic, leadership, and compassion has inspired me throughout my training and early career."


Waihay Josiah Wong, MD, PhD

Waihay Josiah Wong, MD, PhD, assistant professor of pathology at Northwestern University Feinberg School of Medicine, studies how mutations in leukemia-causing genes alter hematopoietic stem cell behavior by utilizing genetic mouse models, cell biology tools, and multi-omics approaches. He has a background in clonal hematopoiesis and identifying associated risks with clonal hematopoiesis of indeterminate potential, such as chronic liver disease, gout, osteoporosis, and cardiovascular disease.


Caitlin C. Zebley, MD, PhD

Caitlin C. Zebley, MD, PhD, is an assistant member in the Department of Bone Marrow Transplantation and Cellular Therapy at St. Jude Children's Research Hospital. Dedicated to advancing T cell–based immunotherapy for pediatric patients, her research interests include understanding the mechanisms of T-cell biology, studying mutations that drive clonal hematopoiesis, and improving antitumor T cells.

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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.

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

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

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.

[b] Fatigue includes Asthenia, Fatigue, and Malaise.

[c] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.

[d] Pain includes Anorectal discomfort, Catheter site pain, Flank pain, Inflammatory pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Rhinalgia, and Sacral pain.

[e] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion or standard therapy.

[f] Upper respiratory tract infection includes Bronchitis, Nasal congestion, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Rhinitis, Rhinorrhea, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral pharyngitis.

[g] Viral infection includes Adenovirus infection, Asymptomatic COVID-19, COVID-19, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viremia, Hepatitis B reactivation, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Human herpesvirus 6 infection, Influenza, Lymphadenitis viral, Metapneumovirus infection, Parainfluenza virus infection, Parvovirus B19 infection, Parvovirus infection, Respiratory syncytial virus infection, Respiratory tract infection viral, and Rotavirus infection.

[h] Bacterial infection includes Bordetella infection, Bronchitis bacterial, Campylobacter infection, Catheter site infection, Cellulitis, Chalazion, Citrobacter infection, Clostridium difficile colitis, Device related infection, Gingivitis, Perichondritis, Pyelonephritis acute, Salmonellosis, Skin infection, Staphylococcal infection, Superinfection bacterial, Vascular access site infection, and Vascular device infection.

[i] Pneumonia includes COVID-19 pneumonia, Lower respiratory tract infection, Metapneumovirus pneumonia, Pneumonia, Pneumonia moraxella, Pneumonia pseudomonal, and Pneumonia streptococcal.

[j] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Bursitis, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Myositis, Neck pain, Non-cardiac chest pain, Osteoarthritis, Pain in extremity, Plantar fasciitis, Rotator cuff syndrome, Spinal pain, and Tendonitis.

[k] Headache includes Headache and Tension headache.

[l] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Immune effector cell-associated neurotoxicity syndrome, Lethargy, and Psychomotor retardation.

[m] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.

[n] Hypotension includes Hypotension, and Orthostatic hypotension.

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

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

[a] Coagulopathy includes Blood fibrinogen decreased, Coagulation test abnormal, Coagulopathy, Disseminated intravascular coagulation, and Hypofibrinogenemia.

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

[c] Cardiac arrhythmias includes Atrial fibrillation, and Atrioventricular block second degree.

[d] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Dyspepsia.

[e] Gastroenteritis includes Enterocolitis viral, Enterovirus infection, Gastroenteritis, Gastroenteritis rotavirus, Gastroenteritis salmonella, Gastrointestinal infection, and Large intestine infection.

[f] Sepsis includes Bacteremia, Candida sepsis, Device related bacteremia, Enterococcal bacteremia, Hemophilus sepsis, Neutropenic sepsis, Pseudomonal sepsis, Sepsis, Septic shock, Staphylococcal bacteremia, Systemic candida, and Urosepsis.

[g] Urinary tract infection includes Cystitis, Escherichia urinary tract infection, and Urinary tract infection.

[h] Fungal infection includes Candida infection, Oral candidiasis, Tongue fungal infection, and Vulvovaginal candidiasis.

[i] Hematologic malignancy includes Myelodysplastic syndrome, Acute myeloid leukemia, and T-cell lymphoma. Incidence based on cutoff date of 01 November 2022 (median follow-up time of 115.9 months).

[j] Dizziness includes Dizziness, Dizziness postural, Presyncope, Syncope, and Vertigo.

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

Laboratory Abnormalities

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

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

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

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

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

CARTITUDE-1

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

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

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

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

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

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

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

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

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

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

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:
- *Cardiac disorders:* cardiac arrhythmias[a] (8%), chest pain[b] (7%)
- *Eye disorders:* diplopia (1%)
- *Gastrointestinal disorders:* dysphagia (1%)
- *Immune system disorders:* HLH (1%), hypersensitivity reaction (5%)
- *Infections and Infestations:* bacterial infections[c] (9%), urinary tract infection[d] (4.1%)
- *Injury, Poisoning and Procedural complications:* fall (3.1%)
- *Metabolism and Nutrition Disorders:* tumor lysis syndrome (1%)
- *Musculoskeletal and Connective tissue disorders:* posture abnormal (1%)
- *Nervous system disorders:* aphasia[e] (8%), ataxia[f] (8%), peripheral neuropathy[g] (7%), tremor (6%), parkinsonism (4.1%), micrographia (4.1%), dysgraphia (3.1%), reduced facial expression (3.1%), cranial nerve palsies (3.1%), bradykinesia (2.1%), paresis[h] (1%), cogwheel rigidity (1%), cerebrovascular accident (1%), seizure (1%), slow speech (1%), nystagmus (1%)
- *Psychiatric disorders:* delirium[i] (5%) depression[j] (4.1%), psychomotor retardation (1%)
- *Renal and urinary disorders:* renal failure[k] (7%)
- *Skin and subcutaneous tissues:* rash[l] (8%)
- *Vascular Disorders:* thrombosis[m] (5%)

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

REFERENCES

1 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25: 625-638.

2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0; 2017.

PATIENT COUNSELING INFORMATION

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

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

Prolonged and Recurrent Cytopenias

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

Infections

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

Hypersensitivity Reactions

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

Secondary Malignancies

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

Advise patients of the need to:

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

Manufactured/Marketed by:
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 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

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.

*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.

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®.