TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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BLOOD CANCERS TODAY

July 2025

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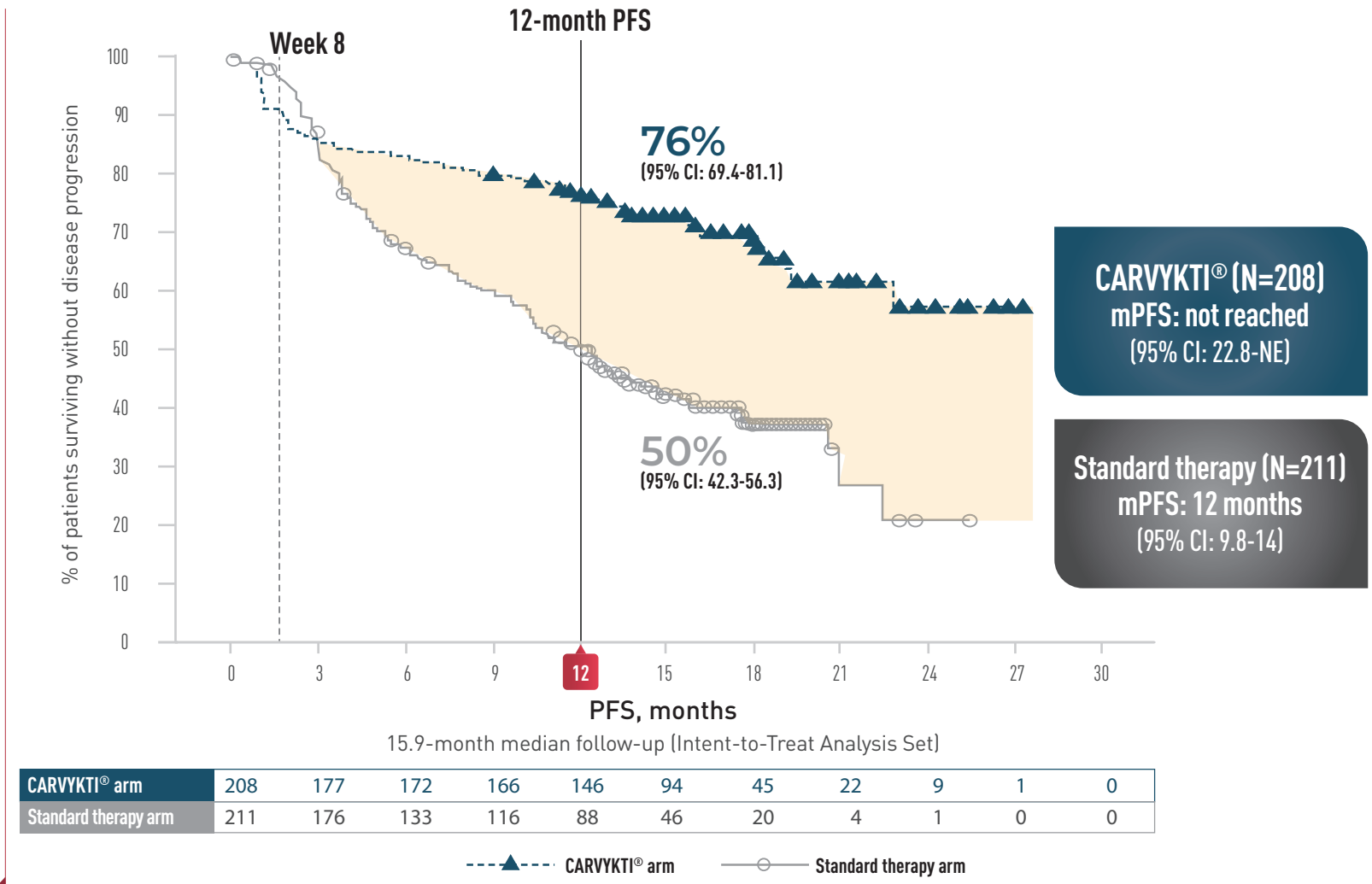
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

POWERFUL RESULTS

In CARTITUDE-4 AT 15.9 MONTHS

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

PROGRESSION-FREE SURVIVAL



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®.

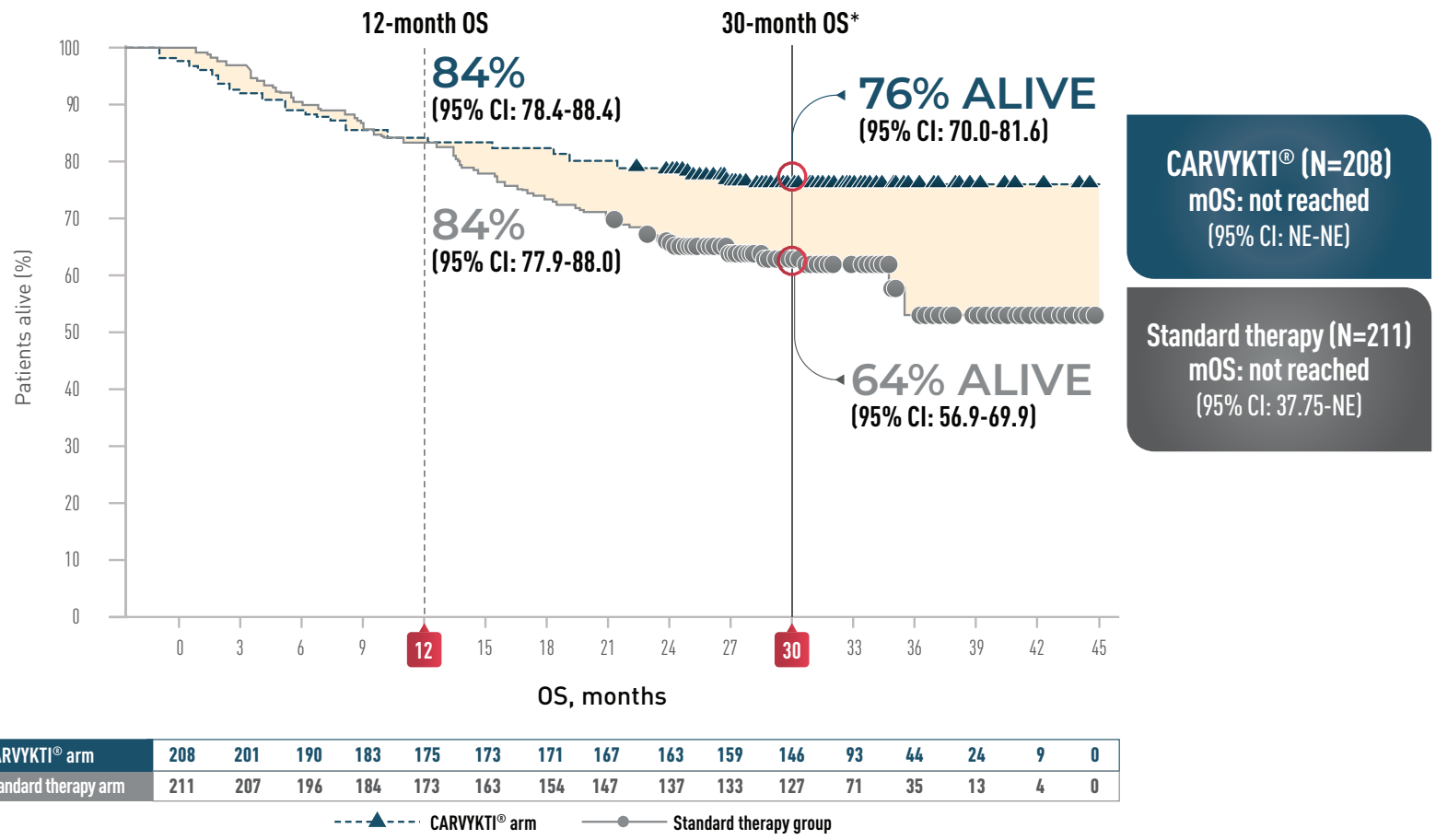
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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

IN CARTITUDE-4 AT 33.6 MONTHS*

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

OVERALL SURVIVAL[1-4*†]



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

CARVYKTI® arm — Standard therapy group

CARVYKTI® demonstrated a

↓45% **Reduction in the risk of death vs standard therapy (DPd or PVd)** (HR=0.55; 95% CI: 0.39-0.79)[4]

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

SELECTED IMPORTANT SAFETY INFORMATION

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

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CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (CONT'D)

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

cp-258862v9

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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

References: 1. CARVYKTI®. Prescribing information. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.* 2023;389(4):335-347. doi:10.1056/NEJMoa2303379 **4.** Mateos MV, San-Miguel J, Dhakal B, et al. Overall survival with ciltacabtagene autoleucel versus standard of care in lenalidomide-refractory multiple myeloma: phase 3 CARTITUDE-4 study update. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Oral Presentation.

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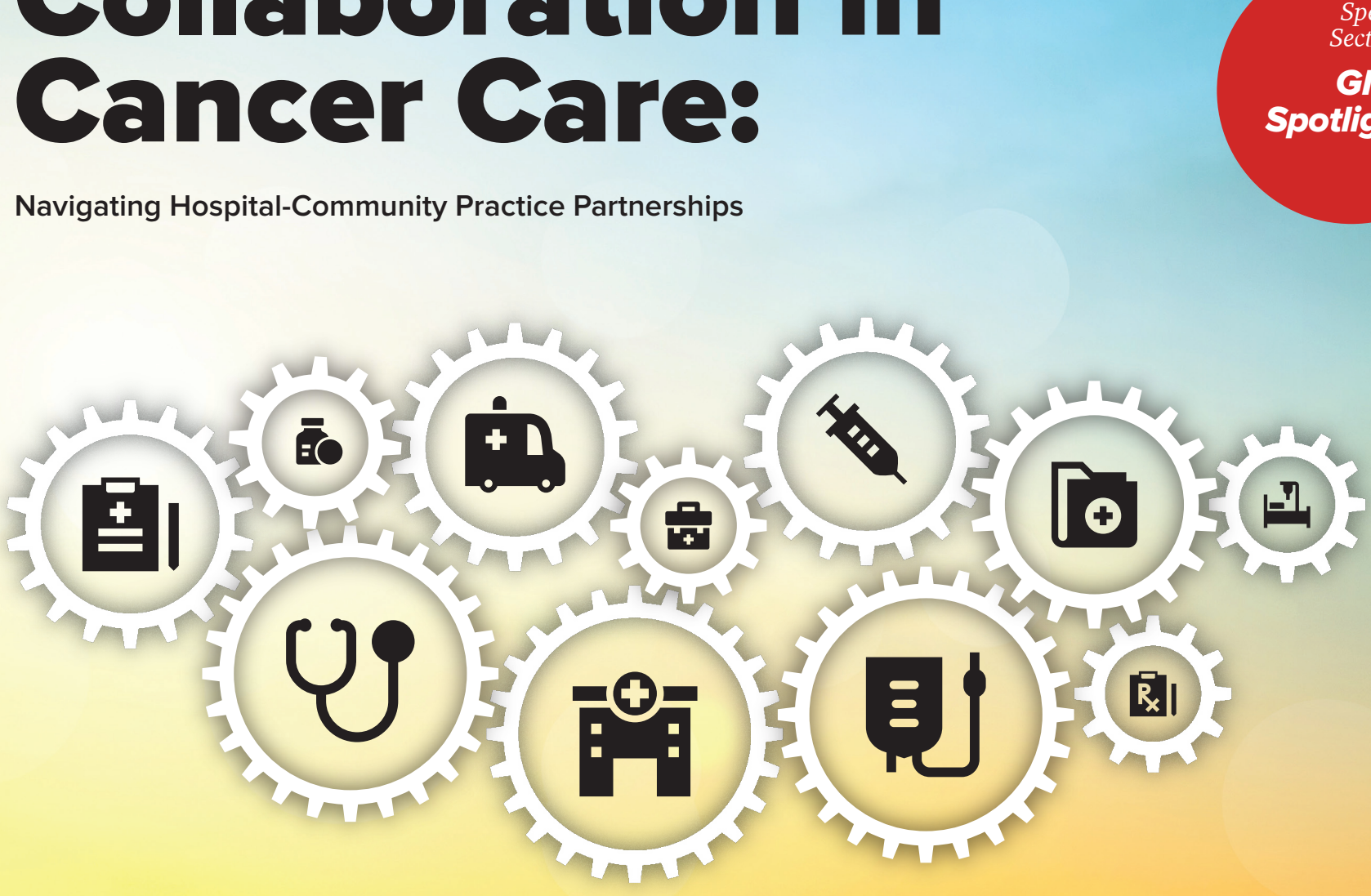


With expert opinions from:
Viola Dsouza, PhD; Nicholas Tatonetti, PhD; and Bart Westerman, PhD

MAIL TO:

CHARLES GAULIN, MBBS:
New Directions in First-Line Therapy for *TP53*-Mutated MCL

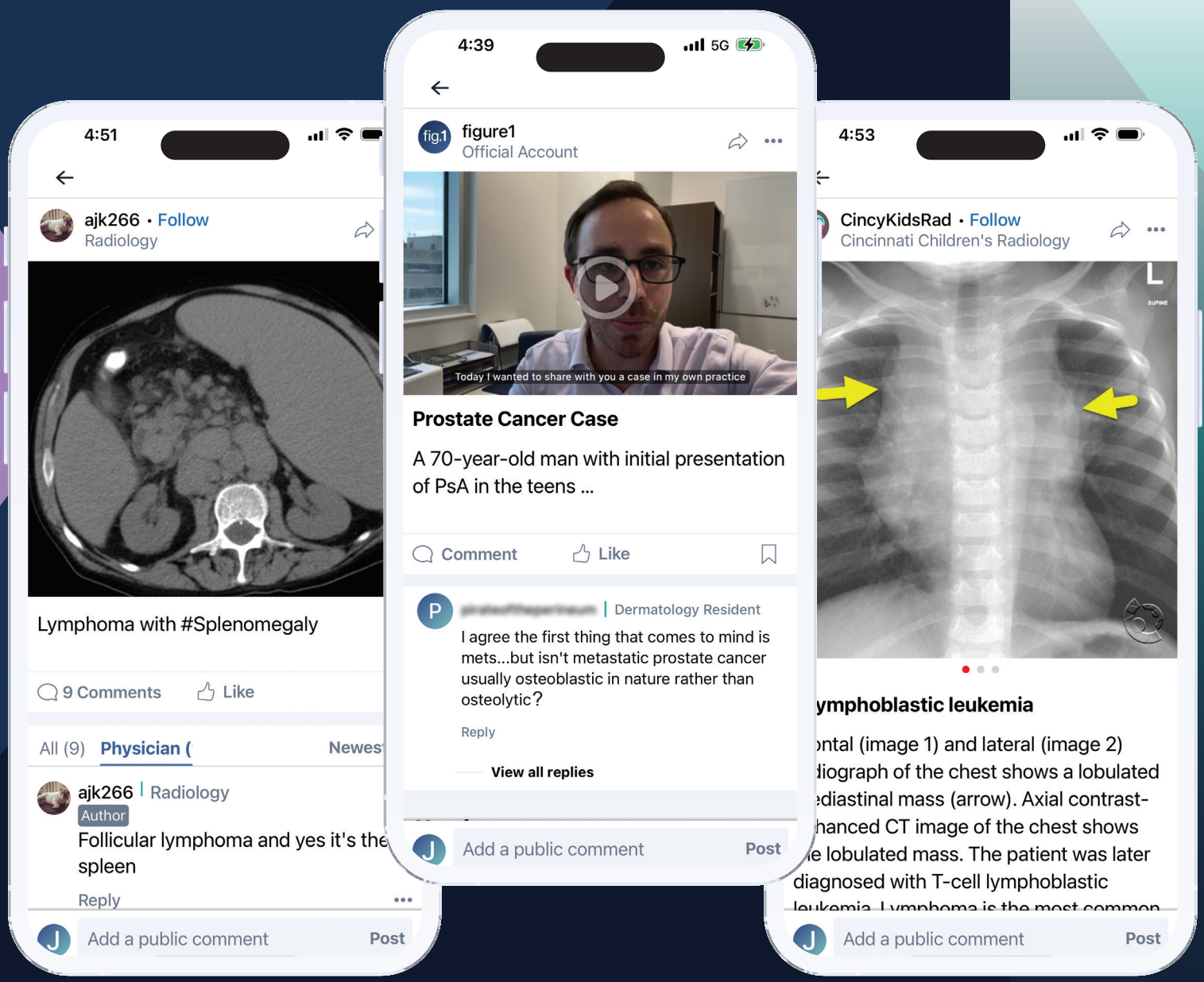
figure1

Where Clinicians Come to Collaborate

New!
Video case posts are here.

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

figure1



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Navigating Hospital-Community Practice Partnerships

Community oncologists and their practices are an integral part of the cancer care continuum, caring for 50% to 80% of patients diagnosed with cancer. *Blood Cancers Today* spoke with several oncologists about the types of partnerships and the benefits and drawbacks to each.

News

The HemOnc Pulse

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

GET TO KNOW

David Swoboda, MD

Dr. Swoboda, a hematologist-oncologist at Tampa General Hospital specializing in AML and MDS, discussed the family influences on his medical career, his role as a clinical investigator of the QuANTUM-Wild study, and the future of AI in oncology.
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Calendar

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

September 13
Leukemia & Lymphoma Society National Blood Cancer Conference
Virtual

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

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

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

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

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

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

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

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

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

October 23-26
JADPRO Live
National Harbor, MD

New Directions in First-Line Treatment for *TP53*-Mutated Mantle Cell Lymphoma

By ***Charles Gaulin, MBBS***


Charles Gaulin, MBBS

Patients with mantle cell lymphoma (MCL) harboring *TP53* mutations have an aggressive disease course, reduced benefit from chemoimmunotherapy, and a poor prognosis.[1] Analyses of the Nordic MCL2 and MCL3 trials revealed a median overall survival (OS) of 1.8 years for patients with *TP53*-mutated disease, in stark contrast to 12.7 years for those without the mutation.[2] This profound difference highlights the unmet need for effective treatments for this high-risk subgroup, comprising up to 20% of previously untreated patients.

Although the optimal risk-adapted strategy remains unclear, this past year has seen a flurry of important updates on the first-line treatment of *TP53*-mutated MCL. Across studies, the use of targeted therapies—Bruton tyrosine kinase inhibitors (BTKi) and/or B-cell lymphoma 2 inhibitors (BCL2i) alone or in combination with other agents—have shown promising efficacy.

Targeted Therapies in the First-Line Setting for *TP53*-Mutated MCL

The phase 3 TRIANGLE trial,[3] initially presented at ASH 2022 with updated results at ASH 2024, demonstrated that the addition of ibrutinib to intensive chemoimmunotherapy and rituximab maintenance eliminates the need for autologous stem cell transplantation (ASCT) in younger patients with MCL. Patients with high-risk features—including high *p53* expression (>50%), a surrogate for *TP53* mutation—derived substantial benefit from the addition of ibrutinib to i ntensive chemoimmunotherapy and rituximab maintenance. In the subgroup of patients with high *p53* expression, the hazard ratio (HR) for failure-free survival was 0.14 (one-sided 98.3% CI 0-0.57) when comparing ibrutinib + chemoimmunotherapy + ASCT (Group A+I) versus chemoimmunotherapy + ASCT alone (Group A). These results suggested that integrating ibrutinib into both induction and maintenance therapy may improve outcomes among younger patients with MCL in this high-risk subgroup.

In the phase 3 ECHO trial[4] first presented at EHA 2024, adding acalabrutinib to bendamustine and rituximab (BR) significantly improved progression-free survival (PFS) in older patients with MCL. Data focusing on high-risk subgroups were presented at ASH 2024. Although numbers were relatively small (22 patients in the acalabrutinib arm and 29 in the placebo arm had *TP53* mutations), adding acalabrutinib to BR did not appear to improve PFS compared to BR alone in patients with *TP53*-mutated MCL (HR, 0.88; 95% CI, 0.42-1.78). The lack of significant PFS benefit likely reflects intrinsic chemoresistance, suggesting that the impact of adding a BTKi might vary depending on the specific backbone used and the population treated.

The phase 3 SYMPATICO trail$_5$, presented at ASCO 2024 and EHA 2024, established the benefit of adding venetoclax to ibrutinib in *TP53*-mutated MCL. The ASCO 2024 abstract reported pooled efficacy and safety data for 74 patients with *TP53* mutations across all cohorts (29 first-line and 45 relapsed or refractory). In the first-line setting, the overall response rate (ORR) was 90%, the complete response (CR) rate was 55%, the median PFS was 22 months, and the median OS was not reached. Measurable residual disease (MRD)–negative remission rates by 8-color flow cytometry were 70% and 67% in the peripheral blood and bone marrow, respectively. These results demonstrated the potential of combined BCL2i and BTKi in previously untreated *TP53*-mutated MCL.

The phase 2 BOVen trial[6] evaluated zanubrutinib plus obinutuzumab and venetoclax in previously untreated patients with *TP53*-mutated MCL. The best ORR was 96% (n=24/25), with an impressive CR rate of 88% (n=22/25). Responses were rapid, with most occurring within the first 3 months of treatment. At cycle 13, undetectable MRD by immunosequencing at a sensitivity level (10^{-5}) was achieved in 95% of evaluable patients (n=18/19), and at 10^{-6} in 84% (n=16/19). With a median follow-up of 28.2 months, the 2-year PFS was 72%, disease-specific survival was 91%, and OS was 76%. Two patients experienced disease progression after stopping treatment. Both were re-treated with zanubrutinib and venetoclax and initially responded, but subsequently progressed again after restarting therapy. The impressive efficacy of the BOVen regimen represents a new standard of care for this high-risk population.

Reconsidering MRD-Guided Therapy Discontinuation

The experience from the BOVen study also highlights a complex clinical decision point: whether MRD-directed discontinuation of therapy is truly an effective long-term strategy in *TP53*-mutated MCL. Concerns were raised regarding the rapid clinical progression in two patients who reinitiated therapy after disease re-emergence. This suggests that while achieving MRD negativity is a highly desirable end point, the aggressive nature of *TP53*-mutated MCL may necessitate longer treatment durations or alternative consolidation strategies even after deep responses. The prognostic value of MRD for treatment cessation might differ in this high-risk subgroup compared to other patients, requiring more cautious interpretation and potentially longer follow-up to ensure sustained remission.

While targeted therapies have significantly improved outcomes and are the new standard, these patients remain at high risk for disease progression. Furthermore, the optimal duration of targeted therapy to maximize therapeutic efficacy and minimize toxicity is unclear. Until more robust long-term data are available, particularly from studies with extended follow-up after MRD-driven cessation, continuous therapy or alternative consolidation strategies may be necessary to maximize the duration of response in this subgroup with aggressive disease.

Immune effector cell therapies in the first-line setting could further change the treatment paradigm. The phase 1 WINDOW-3 trial will evaluate the safety and preliminary clinical efficacy of acalabrutinib and rituximab for a maximum of 12 cycles followed by brexucabtagene autoleucel in previously untreated patients with high-risk features. Similar strategies with glofitamab in combination with targeted therapies are also being investigated. These approaches may result in deeper, more durable responses in a population otherwise at high-risk for disease progression following targeted therapy alone.

Personalizing Treatment in the Future

While identifying *TP53* mutations remains an essential first step, further molecular characterization (eg, specific *TP53* variant, and other co-mutations conferring risk or treatment resistance) is likely needed for precise risk stratification. This implies a future move towards a more granular, risk-adapted approach for this challenging population, where treatment intensity and duration are fine-tuned based on a deeper understanding of the tumor's biological profile beyond just *TP53* status. Thus, in the current landscape, clinical trial options with key correlatives should be explored in all patients when feasible.

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Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: From Discovery to the Edge of Cure

By ***Moaath K. Mustafa Ali, MD, MPH***

It all began in 1960 in Philadelphia, when David Hungerford, MD, and Peter Nowell, MD, observed that cells from patients with chronic myeloid leukemia (CML) harbored an abnormally small chromosome.[1] Later, in 1973, Janet Rowley, MD, at the University of Chicago, improved cytogenetic techniques and demonstrated that the Philadelphia chromosome results from a reciprocal translocation between chromosomes 9 and 22 (ie, *t(9;22)(q34;q11)*).[2] This translocation results in a chimeric BCR-ABL1 fusion protein, with a constitutively active tyrosine kinase that drives unchecked proliferation of hematopoietic cells. These discoveries were pivotal; they not only illuminated the pathogenesis of CML and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) but also laid the foundation for the development of imatinib, the first targeted cancer therapy, which was approved by the FDA in 2001 based on results of a phase 1 trial conducted by Brian J. Druker, MD, and colleagues.[3,4]

Moaath K. Mustafa Ali, MD, MPH

The Philadelphia chromosome is present in nearly all patients with CML. In contrast, acute lymphoblastic leukemia (ALL) follows a bimodal age distribution, peaking between ages 4 and 5 years and again around age 50. Approximately 25% of adult patients with ALL have Ph+ ALL, whereas among children with ALL, it is less prevalent and present in less than 5% of patients. Depending on the breakpoint within the *BCR* gene, different BCR-ABL fusion proteins are formed. The two most common isoforms are p190 and p210, with p190 expressed in about 75% of Ph+ ALL cases.

Historically, Ph+ ALL was associated with a dismal prognosis. The 5-year overall survival (OS) rarely exceeded 20% with standard multi-agent chemotherapy. Allogeneic hematopoietic stem cell transplantation (alloHSCT) was considered the only potential curative option once remission was achieved. However, alloHSCT was often not feasible, given the older age and comorbidities common at the time of diagnosis in many patients with ALL.

Between 2001 and 2002, imatinib was introduced in the refractory setting of Ph+ ALL, with encouraging results.[4] In 2004, Thomas and colleagues[5] reported that imatinib could be safely combined with the hyper-CVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride [Adriamycin], and dexamethasone) chemotherapy backbone, showing further promise. Since then, the management of Ph+ ALL has evolved dramatically.

Currently, treatment is determined based on age and comorbidities. According to the 2025 National Comprehensive Cancer Network (NCCN) guidelines for management of ALL, patients younger than 65 years and without significant comorbidities may be treated with a second- or third-generation tyrosine kinase inhibitor (TKI) in combination with either hyper-CVAD or blinatumomab.[6] For patients older than 65, therapy often includes a TKI with blinatumomab with or without steroids and with or without low-intensity chemotherapy, depending on performance status and comorbidities.

Evidence supporting TKI plus chemotherapy combinations comes from multiple studies, including the single-arm trial by Jabbour et al,[7] in which ponatinib plus hyper-CVAD resulted in a 2-year event-free survival (EFS) of 81% (95% CI, 64%-90%). Despite the proven efficacy of newer TKIs, head-to-head comparisons remain limited. Second- and third-generation TKIs often induce faster molecular responses than imatinib, although survival benefits remain unclear, particularly among adult patients with Ph+ ALL. In a recent phase 3 randomized trial comparing ponatinib (30 mg/d) with imatinib (600 mg/d)—both with reduced-intensity chemotherapy—measurable residual disease (MRD)–negative complete remission was significantly greater with ponatinib (34.4% vs 16.7%).[8] However, no difference in EFS or OS was observed, likely due to higher toxicity-related mortality in the ponatinib arm.[9]

The introduction of blinatumomab, a bispecific T-cell engager that redirects T cells to kill CD19+ leukemia cells, has been transformative in the treatment of Ph+ and Ph– ALL. Its tolerability and potent antileukemic activity have encouraged investigators to explore chemotherapy-free regimens, placing traditional chemo in the background. One key study is the D-ALBA trial (GIMEMA LAL2116), a phase 2 study combining dasatinib and steroids for induction, followed by blinatumomab consolidation. This approach achieved a remarkable 98% complete remission rate, with molecular responses up to 60% after two blinatumomab cycles, and a 3-year OS of 80%.[10] Impressively, nearly half of the patients did not need salvage chemotherapy and alloHSCT, even though the median age was 54 years.

Such findings have led clinicians to question whether alloHSCT is still necessary for patients with Ph+ ALL who achieve deep molecular remission, particularly those who become MRD negative according to next-generation sequencing–based BCR::ABL1 testing. In the most recent NCCN guidelines publication, the use of alloHSCT is considered a suggestion for patients who achieve MRD-negative disease.[11] An even more provocative question is whether we need chemotherapy at all. Currently, no randomized trials directly compare TKI + blinatumomab versus TKI + chemotherapy, but this critical question is being addressed in ongoing trials such as GIMEMA LAL2820 and ECOG-ACRIN EA9181.

Meanwhile, asciminib, a first-in-class allosteric BCR::ABL1 inhibitor, has emerged as a promising agent. Although currently approved for CML, its role in Ph+ ALL is being actively studied. At the American Society of Clinical Oncology 2025 Annual Meeting, **Marlise Rachael Luskin, MD, MSCE,** of the Dana-Farber Cancer Institute, presented phase 1 data (NCT03595917) on combining dasatinib, asciminib, and blinatumomab, which showed encouraging results: 100% complete response, 100% MRD-negative by flow cytometry, 67% MRD-negative by clonoSEQ testing, and 45% MR3 molecular response.[12] Although these results are impressive, the true benefit of adding asciminib to a blinatumomab + TKI backbone still requires confirmation in randomized trials, especially given concerns about added toxicity and the significant financial impact associated with these novel regimens. Such trials usually require a large sample size to have adequate power to detect minor differences between highly efficacious regimens.

In conclusion, the management of Ph+ ALL has evolved rapidly, from a disease once managed solely with chemotherapy and alloHSCT to regimens incorporating TKIs, then TKIs + blinatumomab, and now novel combinations that may obviate the need for chemotherapy or alloHSCT altogether. We are now entering an era when Ph+ ALL can be cured in a substantial proportion of patients, without ever resorting to an alloHSCT.

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

The Delicate Balance of Immunotherapy and Immune Complications

*By **Nichole Tucker***

Joseph Van Galen, MD

What tips the scale between immune activation and unintended harm? This question sits at the heart of immunotherapy, where the power to eliminate cancer can also trigger serious immune-related adverse events (irAEs). **Joseph Van Galen, MD**, a hematology/oncology fellow at Fox Chase Cancer Center in Philadelphia, PA, is investigating the mechanisms behind this delicate balance. His research focuses on how immune checkpoint inhibitors can provoke off-target effects and what happens to T cells once immunosuppressive therapy is introduced to manage irAEs.

Laying the Groundwork

"There's quite a bit of information out there to guide biomarker development before patients begin immunotherapy, helping to predict who may develop irAEs," Dr. Van Galen told *Blood Cancers Today.* "But there has been less study of what happens once patients already have immune-related needs, especially when it comes to predictive or prognostic biomarkers after treatment has started."

"There's enormous opportunity to enlist patients in understanding why immunotherapies work for some and cause toxicities in others."

A major advantage of Dr. Van Galen's current work is his background in translational research, which provides him with a unique opportunity to establish a foundation for future clinical studies that aim to explore irAEs more comprehensively. "The power of translational research lies in the fact that both clinical and laboratory researchers must be involved to cover the full spectrum of methodologies," he explained. This collaboration enables more targeted questions, grounded in both patient experience and molecular science.

"Translational projects require more in-depth, collaborative approaches to answer clinically meaningful questions," he added.

This emphasis on clinically meaningful outcomes naturally leads to the next phase of this research, which involves conducting studies that directly engage patients and aim to translate these insights into real-world care strategies.

The Next Phase

As research in immunotherapy and cellular therapies continues to advance, Dr. Van Galen emphasizes the importance of two parallel approaches: developing entirely new, more tolerable therapies and maximizing the impact of existing ones. He sees a critical opportunity for deeper collaboration among immunologists, oncologists, and geneticists, not just to innovate, but to better understand how current treatments affect different patients. This kind of collaboration, he notes, is especially powerful in research environments that tightly integrate clinical and laboratory teams.

Dr. Van Galen said, "We've seen real progress in developing therapies that are more effective and better tolerated, especially in diseases like multiple myeloma, creating new treatment opportunities even for older and frailer patients...There's enormous opportunity to enlist patients in understanding why immunotherapies work for some and cause toxicities in others and to use that insight to guide how we use the therapies already available."

Dr. Van Galen's work represents a crucial step toward understanding and optimizing immunotherapy, with the ultimate goal of delivering safer, more effective treatments to patients.

***Dr. Van Galen** is a graduating chief fellow in hematology and medical oncology at Fox Chase Cancer Center, where his clinical focus lies in the treatment of hematologic malignancies and the use of immunotherapies, including allogeneic transplantation and cellular therapies. His academic foundation began with an undergraduate degree in biochemistry, followed by research experience at the National Institute of Allergy and Infectious Diseases. During his internal medicine residency at the University of Virginia, he also earned a Master of Science in Clinical Research.*

His research interests span clinical trial design, translational collaborations, and retrospective methodologies, with many projects developed alongside co-fellows and internal medicine residents. In recognition of his work, Dr. Van Galen was named a 2025 recipient of the Young Investigator Award from ASCO's Conquer Cancer Foundation. The award includes a $50,000 1-year grant to support his ongoing research, which is being conducted under the mentorship of Matthew Zibelman, MD, and co-leadership of Johnathan Whetstine, PhD, and Hayan Lee, PhD, at Fox Chase.

Get to Know

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

David Swoboda, MD

With roots in both Florida and Tennessee, David Swoboda, MD, is a hematologist-oncologist at Tampa General Hospital specializing in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Dr. Swoboda spoke with *Blood Cancers Today* about the family influences on his medical career, his role as a clinical investigator of the QuANTUM-Wild study, and his growing passion for artificial intelligence (AI) research and how it can transform oncology.

*By **Melissa Badamo***

Where did you grow up, and when did you know that you wanted to be a hematologist-oncologist?
I grew up in Memphis, Tennessee. I have three brothers, and we moved from Florida to Tennessee for my dad's job. We lived there my whole life, until I decided to move back to Florida for undergrad and medical school because my parents were moving back to Florida at the same time.

My mom, who was a computer programmer, decided to become a doctor of obstetrics and gynecology. While I was in middle and high school, she was going through medical school and then residency. Seeing the hard work and how much she enjoyed it, I started to learn from her and eventually work with her and obtain opportunities to work within the hospital system. That fueled my interest in becoming a physician, and I found working at cancer clinics to be extremely rewarding.

I particularly became a hematologist and a leukemia specialist when I was doing a sub-internship at the University of Chapel Hill. I went to Florida State for medical school, so this was my first true academic leukemia service. I loved meeting the patients, meeting their families, and seeing how challenging but rewarding it is to take care of this high-risk acute patient population. I grew a lot in that month, and that solidified my interest in not only being a doctor, but also being an oncologist and a leukemia specialist.

Were there any mentors who shaped your career path?
I've been lucky enough to have a lot of great mentors. While I knew I had a passion for leukemia, I actually did most of my research in melanoma during my residency at Georgetown. I found that a few of the melanoma providers, Drs. Michael Atkins and Geoffrey Gibney, fit my style of patient-centered care and helped me build a strong foundation of research.

When I moved to Moffitt Cancer Center, I wanted to find mentors who were similar to them in the leukemia space. I met Dr. Rami Komrokji, who was a big influence in my career. After talking to him and seeing his passion for MDS, I felt like he was someone I could shadow my career after and get mentorship from. That was a huge factor in moving to Moffitt and ultimately working under Dr. Komrokji.

Over time, Dr. David Sallman also took me under his wing and was a great mentor for me. He built out a lot of very strong projects, and I continue to think of Drs. Komrokji and Sallman as my main mentors. I still reach out to them all the time, even as a faculty now, to get career advice and continue to grow as a leukemia physician.

Can you further discuss your style of patient-centered care?
In my clinic, I try to put the patient first. I think about myself as if I were the patient. How do you create an environment that is extremely patient focused and referral provider focused, making it as easy as possible to navigate a system?

"In my clinic, I try to put the patient first... I hope patients leave our clinic with more knowledge, understanding, and comfort rather than confusion."

The reality is that getting diagnosed with leukemia or MDS is challenging enough, and if we can take some of the pressures of getting into the system and scheduling things off the patient's plate, they can really focus on taking care of themselves and the disease.

At Tampa General Hospital, we've tried to streamline a lot of processes. We've tried to work with patients to make it as easy as possible for them to navigate their care overall. In our clinic specifically, we want to bring on physicians and staff that are great communicators. We want people to think about Tampa General Hospital as a place where they're going to enjoy the staff, feel like they're part of the family, and feel that we are real people who communicate in a real and understandable way. I hope patients leave our clinic with more knowledge, understanding, and comfort rather than confusion.

Are you working on any exciting clinical trials?
One clinical trial I'm excited about is the QuANTUM-Wild study of "7+3" quizartinib versus placebo in *FLT3* wild-type patients. I was lucky enough to be at the center that enrolled the first patient on that clinical trial. It's an interesting concept of using a targeted therapy for a specific mutation in patients that lack the mutation, because we know that a lot of patients have expression of *FLT3* even though they don't actually have that mutation.

I'm also the principal investigator of a menin inhibitor trial, which is another class of drugs that is rapidly evolving. Getting *KMT2A* patients—which is a very advanced and often times very challenging subset of AML—on these therapies that can hopefully have the potential to be lifesaving is really rewarding.

Aside from being a clinical investigator, my second and growing passion is artificial intelligence research. I've been working with Dr. Aziz Nazha at Jefferson Health on building out AI agent frameworks. The goal of our current research is how do we improve on these generalized large language models (LLM) like ChatGPT to be able to be utilized in real-life clinical scenarios?

If you put in a patient case in a general LLM, the output is not always accurate and can even generate false information. General LLMs are not ready for prime time in clinical practice. However, we've been able to use the technology behind these LLMs in a more specific way to a particular disease state and have found much better results.

In one of the most far along projects, we have built out a multiagent framework with five

different AI agents. One of the AI agents is a moderator that takes a prompt, or in this case a clinical case. It can structure an unstructured clinical case; feed it to another agent that evaluates the diagnosis of a patient; then an agent that evaluates prognosis, treatment, and clinical trial recommendations; send it back to the moderator; and then provide the full recommendation. It is an autonomous MDS virtual tumor board that interacts with and provides information to the physician.

We found that using this multi-AI agent framework is significantly better than traditional generalized LLMs like ChatGPT. We're expanding on the work and are having more investigators involved in validating this in a larger dataset and patient population. That's my growing passion, and there's a lot of different areas where we can use these AI agents. I think that AI is going to have a significant impact on healthcare and oncology, and I'm really excited to be a part of that.

"We found that using this multi-AI agent framework is significantly better than traditional generalized LLMs like ChatGPT... I think that AI is going to have a significant impact on healthcare and oncology."

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

One of the biggest questions in AML is: "Do we need induction therapy for all patients, or can we start using a lower intensity–based therapy and a lower-intensity backbone for patients even if they're not elderly and unfit?" Answering that question will open up a lot of opportunities for novel combinations with menin inhibitors, FLT3 inhibitors, or IDH1 and IDH2 inhibitors.

At Tampa General Hospital, we are not only looking at mutations and translocations, but the actual gene expression profiling through RNA. That allows you to think about some of these patients and clinical cases differently and potentially offer certain therapies to patients that we might not think would respond to therapy based on traditional molecular testing.

A good example is the proof of concept with QuANTUM-Wild. We think that patients with a *FLT3*-like gene expression profile will likely benefit the most in an *FLT3* wild-type setting. We also know that patients most likely to benefit from menin inhibitors are those with *KMT2A* translocated, *NPM1*, or *NUP98*, but I think the common thread is that they have *HOXA9* overexpression. There are other potential mutations and translocations that could have a similar increased expression and ultimately could be targeted by menin inhibitors.

In the short-term future, that's one of the areas we're going to learn a lot from. I think we're going to start designing clinical trial therapies based on gene expression signatures as much as—or even more than—individual mutations. I think we're going to have better outcomes doing it in that way.

What hobbies or activities do you enjoy outside of work?

I love the ocean. I love being on a boat fishing, surfing, or anything that is water involved. I spend almost every day after work in the pool with my two daughters, aged 4 and 7. When we have more time, we're on the boat at the beach and spending as much time [as we can] enjoying the beautiful Florida weather.

Outside of that, another hobby of mine is playing golf. I love getting out in nature and trying to take my brain away from all the stresses and complications of being a physician. Hitting a golf ball is a great stress relief.

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

I love to travel. I've been to a ton of different countries, including hiking the Great Wall of China in sandals. I've had lunch and a picnic on a glacier. My wife and I always try to find unique opportunities to experience other countries in ways that sometimes only the locals are able to do.

Collaboration in Cancer Care: Navigating Hospital-Community Practice Partnerships

*By **Leah Lawrence***

Community oncologists and their practices are an integral part of the cancer care continuum, caring for 50% to 80% of patients diagnosed with cancer.[1,2]

However, the growing complexity of cancer care—combined with a transition from volume-based to value-based cancer care—means that a majority of care involves partnerships between community oncologists, local hospitals and health systems, and academic centers.

Hospital and community practice partnerships can take many shapes. *Blood Cancers Today* spoke with several oncologists about the types of partnerships and the benefits and drawbacks to each.

A Local Partnership

Independent practices are often unable to provide access to all the resources necessary for patients to receive the full continuum of care, thereby fostering the need for care partnerships, according to **Stephen "Fred" Divers, MD,** a practicing oncologist and hematologist at Genesis Cancer and Blood Institute in Hot Springs, Arkansas.

Dr. Divers said that these partnerships or collaborations often take one of two forms. The first is a contractual relationship that is compliant with the Federal Trade Commission (FTC). Other partnerships are those that exist or are born "out of necessity or limited resources."

His practice has a partnership that is borne of the latter, with a footprint covering approximately 20 to 25 counties throughout Arkansas. Although the practice interacts with numerous hospitals, depending on the location of some of its satellite services, its largest partner is CHI St. Vincent in Hot Springs and Little Rock.

"There is no legal or binding contract," Dr. Divers said. "It has been a patient-centric path forward where we try to streamline who has access to which resources and fill the gaps when it comes to patient care."

Dr. Divers provided an example of the cooperative effort required to provide appropriate care for patients. Pathologists, medical oncologists, and urologists are employed by his clinic. The hospital employs surgeons and radiation oncologists, while diagnostic and interventional radiologists are independent practitioners.

Both sides benefit from this symbiotic relationship. The hospital avoids the cost of employing full-time oncology providers and $100 million per year in pharmacy expenses, while having access to a complete oncology service line. As the hospital's non-contractual preferred referral provider for oncology services, Dr. Divers' practice avoids the

“It has been a patient-centric path forward where we try to streamline who has access to which resources and fill the gaps when it comes to patient care.”

—Stephen “Fred” Divers, MD, hematologist and oncologist, Genesis Cancer and Blood Institute

expense of radiation build-out and has access to the hospital’s multispecialty support.

“The independent oncologist is laser-focused on the oncology aspect of care, and any hospital has a myriad of objectives it is trying to accomplish; it has orthopedic service lines, cardiology service lines, in addition to the emergency department, surgery, and more,” Dr. Divers said.

The oncology practice needs the hospital for its services, but the hospital needs the oncology practice to continue cancer care outside of the hospital setting, he said.

“This is where being good partners and being respectful of the ways one center creates revenue and creates risk is important,” Dr. Divers added. For example, he said he tries not to order next-generation sequencing until a patient is 14 days out of the hospital. Otherwise, the hospital, which is paid on a set fee per day, is stuck with the expense of that test.

Tension occurs, he said, when revenue drivers overlap, creating competition. This can be especially true between independent groups and large health systems in metropolitan areas.

Expanding Reach

Mutually beneficial working relationships also exist between community-based oncology practices and academic medical centers. One strong example is the collaboration between New York Cancer & Blood Specialists (NYCBS) and Memorial Sloan Kettering Cancer Center (MSKCC).

“MSKCC patients typically undergo surgeries and procedures in the city, with follow-up oncology care provided both at MSKCC’s main Manhattan campus and its satellite locations,” explained **Gurmohan Syali, MD,** co-chief medical officer at NYCBS. “Chemotherapy, radiation, and imaging services are also delivered by MSKCC physicians at these sites. However, MSKCC doctors generally do not round at the local community hospitals near their satellite locations. To maintain continuity of care, NYCBS physicians step in to manage MSKCC patients admitted to local hospitals, creating a true partnership between the two practices.”

With more than 40 locations across New York, NYCBS delivers comprehensive cancer care, including chemotherapy and radiation therapy, and provides hospital coverage at nearly all major facilities on Long Island. When MSKCC patients are admitted to these local hospitals, NYCBS physicians manage their care while staying in close, real-time communication with the MSKCC teams. This creates a seamless experience, ensuring patients receive high-quality, coordinated care every step of the way.

“MSKCC needed a partner to cover these hospitals,” Dr. Syali said. “NYCBS fulfills that need because our providers are already embedded in these facilities. With access to MSKCC medical records, we’re able to provide care that’s informed, connected, and efficient.”

Beyond inpatient care, NYCBS also supports MSKCC in areas such as dedicated hematology and palliative care services.

“There are also times when a patient reaches out to MSKCC but finds the center isn’t in-network with their insurance,” Dr. Syali noted. “In those cases, MSKCC can confidently refer patients to NYCBS, knowing we already have a strong working relationship. This is especially important when distance or coverage creates a barrier to timely care. We step in to ensure patients still receive prompt, quality treatment.”

This collaboration laid the foundation for the two organizations to open a co-managed, state-of-the-art cancer center in Brooklyn’s Flatbush neighborhood.[3] The center blends MSKCC’s academic depth with NYCBS’s community reach, bringing world-class cancer care directly into the heart of the borough.

Dr. Syali acknowledged the learning curve at the start of the partnership. “Early on, there was concern in our group that referring patients to MSKCC might mean losing them permanently,” he said. “But over time, it became clear that patients move freely between our practices. There’s mutual trust, and we know they’ll come back to us for their ongoing oncology care.”

Partnership Challenges

Despite these two examples of working relationships, both Dr. Divers and **Moshe C. Chasky, MD, FACP,** an independent hematologist-oncologist at Alliance Cancer Specialists, part of the US Oncology Network, acknowledged that not all partnerships between community oncology practices and hospitals or health systems are seamless and successful.

Dr. Chasky trained at a National Cancer Institute–designated cancer center but decided to join an independent community oncology practice that operated as part of a local hospital.

Soon after, the market around his practice started to consolidate, driven in part by the growth of Jefferson Health. After Jefferson took over the local hospitals, Dr. Chasky and colleagues were told that their practice would be allowed to remain independent. However, that turned out not to be the case; they were kicked off staff and eventually filed a lawsuit.

Part of the incentive for health systems acquiring these hospitals and practices, Dr. Divers said, is the 340B Drug Pricing Program. Established in 1992, the 340B program provides eligible safety net providers with substantial discounts on outpatient drugs, while also ensuring full reimbursement from private and public insurers. Eligible hospitals might include certain Medicare disproportionate share hospitals, freestanding cancer hospitals, rural referral centers, or sole community hospitals.[4]

An unintended consequence has been the incentive for 340B-participating hospitals to purchase community practices “that have the greatest opportunity to benefit from dispensing medications acquired through the 340B program, including practices in oncology, ophthalmology, and rheumatology.”[5] This is aided by site neutrality, a parameter of the 340B program that qualifies all hospitals within a certain distance of the 340B site to qualify for the discounted pricing.

On the opposite end of the spectrum, Dr. Divers discussed examples of health systems that are letting go of oncologists and oncology practices because they don’t want to bear the burden of employing them in a non-340B environment.

“This has really been the downfall for many independent oncologists,” Dr. Chasky said.

Now, Dr. Chasky has a thriving independent practice in Bensalem, Pennsylvania, and is once again able to successfully collaborate with a local hospital. Maintaining his independent practice was not an easy choice, he said. It took courage and a lot of hard work.

“There are definitely some hospitals out there that have decided to employ medical oncologists because of these financial incentives,” Dr. Chasky said. “There are others out there like MSKCC that have instead chosen to be collaborators.”

Regardless of the level of independence or collaboration chosen, Dr. Divers emphasized that it should ultimately come back to the patient and what is best for their cancer care.

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STARGLO Glofitamab DLBCL Trial Inapplicable for US Populations

*By **Andrew Moreno***

The FDA's Oncologic Drugs Advisory Committee (ODAC) regards the STARGLO international clinical trial of glofitamab plus gemcitabine and oxaliplatin (GemOx) for diffuse large B-cell lymphoma (DLBCL), in its enrolled cohort and outcome results, to be inapplicable to patient populations in the United States.[1] It heard arguments for and against applicability in a meeting at the Center for Drug Evaluation and Research (CDER) on the FDA White Oak Campus in Silver Spring, Maryland, on May 20, 2025.[2]

Glofitamab is a CD20xCD3 bispecific antibody, developed and marketed by Genentech, Inc under the brand name Columvi.[3] The FDA in June 2023 granted accelerated approval to monotherapy of this agent for relapsed or refractory DLBCL not otherwise specified (DLBCL NOS) or large B-cell lymphoma developed from follicular lymphoma in adults who have undergone at least two lines of systemic therapy.[4]

Currently before the FDA is a supplemental Biologics License Application (sBLA) submitted by Genentech for a combination of glofitamab injection with GemOx to treat relapsed or refractory DLBCL NOS in adults ineligible for autologous stem cell transplant (ASCT).[2] This sBLA involves STARGLO, a global phase 3 open-label randomized clinical trial in which glofitamab plus GemOx was compared against rituximab plus GemOx in patients with relapsed or refractory DLBCL NOS who had received at least one line of systemic therapy and were ASCT-ineligible. The trial met its primary end point of statistically significant improvement in overall survival (OS) and two of its three secondary end points in progression-free survival (PFS) and complete response (CR).[3]

Before the ODAC, the FDA raised several concerns about the generalizability of STARGLO to patient populations and medical practice specifically within the US. It argued that the number of US patients enrolled in STARGLO was insufficient, regionally inconsistent, and lacked representativeness of the US population.[1,4]

Moreover, the FDA's subgroup statistical analysis of STARGLO's results found differences in OS and other statistical measures for outcomes between Asian and non-Asian patients in the trial, with a reduced benefit from the study treatment in North American and European patients compared with Asian patients. Disparities became apparent over the course of the trial, and Genentech requested an additional 9 months to analyze and address them.[1,4]

"With an additional follow-up of approximately 11 months, the inconsistent treatment effect in overall survival persisted. While a positive result was observed in the ITT [intention-to-treat] analysis, with a hazard ratio of 0.62, the inconsistent results between the regions persisted with similar discordant treatment effects observed for patients treated in the Asian region, with a hazard ratio of 0.39, compared to the Non-Asian region, with a hazard ratio of 1.06," stated **Margret Merino, MD,** of the FDA's Division of Hematologic Malignancies II and the cross-disciplinary team lead for the related sBLA.[1,4]

Other concerns that the FDA raised regarding the Asian-versus-Non-Asian-region dimension within STARGLO were that the patient cohorts that statistically drove the study, specifically the Asian regional subgroup, differed in key aspects from the US patient population. This included patients' baseline disease characteristics, disease cell of origin, reasons for transplant ineligibility, treatment exposures, schedule of study regimen administration, and reasons for treatment discontinuation.[1,4]

The responses Genentech presented at the meeting to the FDA's critiques were led by the company's senior vice president and global head of oncology and hematology drug development, **Charles Fuchs, MD, MPH.** The company insisted that the enrolled cohort and findings in STARGLO applied to a US patient population, that the subgroup analysis–based concerns raised by the FDA did not affect the results, and that the low enrollment at US centers in the study was an effect of the COVID-19 pandemic. It repeatedly argued that the STARGLO results were impressive and that the treatment approach under investigation in the trial would meet an unmet need in the US population.[1,3]

Among the points of disagreement between the company and the FDA was whether imbalances in new anti-lymphoma therapy (NALT) use across the study centers affected the study's outcome statistical results. The company maintained that there was an effect, while the FDA maintained that there was not.[1,3,4] Genentech also objected to the subgroup assessment applied by the FDA to STARGLO, holding that the trial had not been designed for that type of analysis.

The FDA noted that it was not seeking the opinion of the ODAC as to whether the STARGLO trial could be used to convert the accelerated approval of glofitamab to a traditional approval, but only on whether the trial's enrolled population and results applied to US patient populations.[1,4] To this question, eight ODAC members voted "No" and one voted "Yes."[1]

Several members of the Committee, before and after the vote, expressed concern about the small number of US patients enrolled in STARGLO.

"If there's a low percentage of patients enrolled in a trial and we see this directionality in multiple endpoints, we have to call into question, and we can't know if this therapy may be effective in this specific population," stated **Neil Vasan, MD, PhD,** of NYU Langone Health in New York City, who voted "No" on the discussion question.[1]

Linked to this concern of the small number of US patients enrolled in STARGLO, **Heidi McKean, MD,** from Avera Cancer Institute in Sioux Falls, South Dakota, who voted "No" on the discussion question, spoke from her own experience in community practice of a need to be conscious of the high cytokine release syndrome (CRS) risk faced by patients who may receive glofitamab.[1]

"We as community oncologists need to make sure this is safe and really effective, and 25 patients is really tough to make that call," Dr. McKean said.[1]

Committee member **Daniel Spratt, MD,** of University Hospitals Seidman Cancer Center and Case Western Reserve University in Cleveland, Ohio, who voted "No" on the discussion question, said that the subgroup analysis applied by the FDA to STARGLO was appropriate, given the study design's established organizations of patient region and race.[1]

"There is a significant difference in the differential benefit of this therapy by the subgroups that were prespecified. It's not simply that all of this is just post hoc subset-of-subset analysis. There's actually a differential in treatment effect," Dr. Spratt said.[1]

The FDA is not legally bound to follow the recommendations it receives from the ODAC but typically has done so.[2]

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AQUILA Trial Supports Favorable Benefit-Risk of SQ Daratumumab in SMM

*By **Andrew Moreno***

Results from the international AQUILA clinical trial support a favorable benefit-risk profile for subcutaneous daratumumab in patients with high-risk smoldering multiple myeloma (SMM), the FDA's Oncologic Drugs Advisory Committee (ODAC) has decided.[1] The ODAC convened on May 20, 2025, at the Center for Drug Evaluation and Research (CDER) on the FDA White Oak Campus in Silver Spring, Maryland, to hear arguments on and discuss this topic.[1,2]

The discussion is relevant to a supplemental Biologics License Application (sBLA) currently before the FDA, submitted by Janssen Biotech, Inc, for use of injection daratumumab and hyaluronidase as monotherapy for high-risk SMM in adult patients.[2,3] Daratumumab and hyaluronidase, manufactured by Janssen as DARZALEX FASPRO, is already FDA-approved for several indications in multiple myeloma (MM).[1,3,4] There are currently no FDA-approved therapies for SMM, and the standard of care for high-risk disease is a clinical trial or active monitoring.[1,4]

The primary clinical trial evidence Janssen has marshalled in their submitted sBLA for the monotherapy's efficacy and safety is the results from the AQUILA trial. Launched in 2017, AQUILA is a randomized, open-label, phase 3 study that enrolled 390 patients with high-risk SMM who received either subcutaneous daratumumab monotherapy or active monitoring without treatment. The trial thus was a comparison of the treatment injection against active monitoring.[1,4]

Representatives from Johnson & Johnson, led by the company's vice president for oncology research and development **Sen Zhuang, MD, PhD,** argued that the trial met its primary end point of a statistically significant improvement in progression-free survival (PFS), defined as time from randomization to progression to MM or death. Furthermore, regarding secondary end points, there was early evidence of overall survival (OS) benefit and positive trends in overall response rate (ORR) and progression-free survival 2 (PFS2). They described the safety results as also favorable and as expected.[1,4]

The FDA has raised concerns about the design of AQUILA, which, it argued, makes the trial results' applicability to patients with high-risk SMM questionable. According to the FDA, the endpoints chosen to measure efficacy in the trial might not have been appropriate in high-risk SMM. Moreover, regarding AQUILA's having met its primary end point in PFS, the FDA said this was primarily due to delaying diagnosis of emergent MM. It also cited inconsistencies in the criteria used to clinically define MM, and when patients began MM therapy after MM diagnosis, of what type, or if at all.[1,3]

"The clinical meaningfulness of the PFS end point as defined in the AQUILA trial, and the impact of treatment prior to the development of multiple myeloma, and the effect on long-term outcomes, is unknown," stated **Payal Aggarwal, DO, MS,** a hematologist-oncologist from the multiple myeloma team at the FDA's Division of Hematologic Malignancies II.[1]

Regarding secondary end points of efficacy, the FDA said AQUILA was underpowered for measuring OS results and that PFS2 results are easily confounded. Of the safety findings, the FDA said the patient-reported outcomes (PROs) data were not sufficiently informative and there remained high rates of clinically relevant toxicities shown with the treatment.[1,3]

The FDA pointed out that clinical definitions and risk assessment models of MM and SMM have been revised in the time since AQUILA commenced, and enrollees who were categorized in the trial as having SMM might not be by current standards. For instance, SMM in less than half of the cohort had a high-risk for progression according to the Mayo 2018 risk criteria. The FDA noted that the high risk criteria in the trial's protocol did not completely match any particular established model.[1,3]

"While the AQUILA trial was conducted prior to the establishment of the Mayo 2018 model, the criteria used in the protocol did not completely align with any of the available models, but instead incorporated criteria from multiple models and additional criteria, such as IGA smoldering multiple myeloma and clonal bone marrow plasma cells greater than 50% to 60%, to define patients with high-risk smoldering multiple myeloma," Dr. Aggarwal continued.[1]

Johnson and Johnson maintained that AQUILA's design and cohort applied to real-world patient populations and that the trial's results showed a meaningful benefit from the study treatment. The company also emphasized daratumumab and hyaluronidase as able to meet an unmet need in patients with high-risk SMM.[1,4] Testimony then followed at the ODAC meeting from patients with SMM and clinicians who manage the disease, expressing a desire for more options than only "watchful waiting."[1]

"There's nothing premalignant in smoldering myeloma. Waiting for further cancer progression and genomic evolution until patients develop fractures in their bones or renal failure only harms our patients because it allows for evolution and drug resistance. It is like waiting for metastatic cancer to happen before we treat our patients," said **Irene Ghobrial, MD,** professor of medicine at Dana-Farber Cancer Institute in Boston, Massachusetts, who stated having received no financial support from the presentation sponsor.[1]

In the final vote, six members of the Committee voted "Yes" and two voted "No" to the discussion question of whether the AQUILA results support a conclusion that subcutaneous daratumumab has a favorable benefit-risk profile in high-risk SMM.[1]

Several of the "yes"-voting committee members found the PFS and OS improvements to be promising but still had critiques about the data, such as the data's potential immaturity.[1]

"I think these risk groups are phenomenal, but I think they are terrible for regulatory approval. These are prognostic risk groups. These are not predictive," noted Committee member **Daniel Spratt, MD,** of University Hospitals Seidman Cancer Center and Case Western Reserve University in Cleveland, Ohio, who voted "Yes" on the discussion question.[1]

The two Committee members who voted "No" on the discussion question both expressed a concern that the data showed that certain patients were over- or undertreated. Moreover, it is unclear which patients benefit from the treatment and by how much.[1]

"We're probably overtreating more than 50% of patients at three years. Out of the patients getting treated, 40% of them are having grade 3-4 toxicity, and that didn't translate to any real clear signal in PFS or overall survival, therefore clouding my view of what the early treatment is really doing," elaborated **Ravi Madan, MD,** Senior Clinician at the National Cancer Institute, who voted "No" on the discussion question.[1]

An issue that was repeatedly raised in the Committee discussion was safety and the risk for overmanagement in a patient population that is asymptomatic. There was a concern about whether a management approach for SMM truly treats the disease or if it merely delays a diagnosis of MM.[1]

"Make no doubt about it, this is going to lead to overtreatment for a population of patients. And those patients may experience toxicity, particularly infection from this," said **Christopher Lieu, MD,** professor at the University of Colorado in Aurora. However, he voted "Yes" on the discussion question, explaining that he would like patients and clinicians to be able to have the benefit-risk discussions of this treatment.[1]

"I think that conversation includes the fact that there are toxicities from this drug. That there's a chance that you can prevent a life-altering fracture. That you might be able to prevent, or delay, at least, the onset of treatment. That you might be able to delay or prevent end-organ damage," Dr. Lieu clarified.[1]

The FDA is not legally bound to follow the recommendations it receives from the ODAC but typically has done so.[2]

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Study Finds 'Significant' Racial and Ethnic Disparities in Pregnancy Outcomes Among Women With Cancer

*By **Melissa Badamo***

Women with cancer among racial and ethnic minority groups in the US have a higher risk of adverse pregnancy outcomes (APOs) compared with non-Hispanic White women, according to a study presented at the American Association for Cancer Research (AACR) Annual Meeting.

After collecting data from 16.5 million childbirth deliveries from the National Inpatient Sample, the researchers used logistic regression models to estimate the odds ratios (ORs) and 95% (CI) for associations between race and ethnicity and APOs among 47,450 women with cancer. They also accounted for comorbidity and sociodemographic, behavioral, and lifestyle factors.

Non-Hispanic Black women had the highest odds for hypertensive disorders of pregnancy (OR,1.67; CI,1.53-1.82), fetal growth restriction (OR,1.61; CI,1.34-1.94), preterm birth (OR,1.36; CI,1.19-1.55) and fetal death (OR,2.75, CI, 1.78-4.27), while Asian or Pacific Islander women had the highest odds for gestational diabetes (OR,2.37; CI, 2.05-2.74). Multiracial women had the highest odds for maternal mortality (OR,1.72; CI, 1.08-2.75).

"I suspect that racial and ethnic disparities in this particular patient population are related to a number of factors related to the nature of the underlying cancer diagnosis and the treatment being pursued, as well as other medical conditions the patient has," **Bhavana Bhatnagar, DO,** director of Hematology and Medical Oncology at WVU Cancer Institute, told *Blood Cancers Today*.

Bhavana Bhatnagar, DO

The study further broke down the risk of APOs by cancer type, including breast cancer (OR,1.32; CI,1.17-1.49), cervical cancer (OR,1.20; CI, 1.003-1.44), and blood cancer (OR,1.30; CI, 1.16-1.45).

"Some of the more aggressive hematologic malignancies like acute leukemia and lymphomas can present major challenges for pregnant patients, since they require urgent therapy and cannot wait until after their pregnancy," Dr. Bhatnagar said. "The considerable care needs of patients with these types of blood cancers, coupled with pregnancy, makes it all the more necessary for them to receive their care at a center with the necessary resources and clinical expertise to properly address their needs."

Reference

2025 American Association for Cancer Research Annual Meeting. Abstract No. 1214.

Continuous Medicaid Coverage Associated With Lower Incidence of Stage IV Lymphoma Among Children and Young Adults

*By **Melissa Badamo***

Continuous Medicaid coverage is associated with lower likelihood of late-stage disease among pediatric and young adult patients with lymphoma, according to a study published in *Blood Advances*.

Xu Ji, Phd, MSPH

"Steady access to Medicaid insurance helps ensure early recognition of symptoms, timely referrals to cancer specialists, quick diagnosis, prompt initiation of treatment, and continuous cancer care—all of which are essential for better survival, especially given that blood cancers often appear suddenly and lack routine screening options," **Xu Ji, PhD, MSPH,** senior author of the study and assistant professor in the Department of Pediatrics at Emory University School of Medicine, told *Blood Cancers Today*.

Using the SEER–Medicaid linked data resource, Dr. Ji and colleagues identified 3,524 patients aged 0 to 39 years with newly diagnosed lymphoma from 12 US states. Patients were categorized by Medicaid enrollment patterns; 37.8% had continuous Medicaid coverage, 35.2% had newly acquired Medicaid coverage, and 27.0% had other Medicaid enrollment patterns.

Medicaid enrollment patterns also varied by patient sociodemographic characteristics. The percentage of patients with newly acquired Medicaid was higher for non-Hispanic White patients (39.1%) compared with non-Hispanic Black (32.5%) or Hispanic patients (30.4%), but the percentage of patients with continuous Medicaid was lower for non-Hispanic White patients (34.3%) compared with non-Hispanic Black (41.2%) or Hispanic patients (41.4%).

Patients with newly acquired Medicaid coverage had the highest incidence of stage IV lymphoma diagnosis (41.0%) compared to patients with other Medicaid enrollment patterns (29.5%) and continuous Medicaid coverage (25.8%).

Dr. Ji noted that patients with blood cancers with continuous Medicaid coverage also had the lowest risk of death compared with patients with newly acquired Medicaid or other types of noncontinuous Medicaid coverage, according to a study published in the *Journal of the National Cancer Institute*.

"Together, our findings highlight the critical role of continuous Medicaid coverage in ensuring timely diagnosis, cancer treatment, and improved survival for young people facing serious illnesses such as blood cancers," Dr. Ji explained.

In both studies, less than half of patients insured with Medicaid had continuous coverage. Dr. Ji outlined several actionable strategies to improve access, such as implementing 12- or 24-month continuous Medicaid eligibility for all children and adolescents and young adults to prevent coverage gaps, adopting Medicaid expansion in all states, streamlining administrative processes, and promoting targeted enrollment assistance for patients transitioning out of pediatric care.

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Highlights From the **2025 AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) ANNUAL MEETING** May 30 to June 3, 2025, in Chicago, Illinois

Belantamab Linked to High Eye Toxicity in Patients With Myeloma, Study Finds

*By **Izzah Nawaz***

In 2020, belantamab mafodotin was approved by the FDA for patients with relapsed or refractory multiple myeloma (RRMM). In the United States, the drug was taken off the market in 2023 because the DREAMM-3 trial did not demonstrate that it helped patients survive without the disease getting worse. The results from the DREAMM-7 and DREAMM-8 trials, published in 2024, indicated that progression-free survival improved with belantamab, which may lead the FDA to consider approving it for use again. Despite the benefits, there are still concerns regarding possible occular side effects.

In this systematic review and meta-analysis presented at the 2025 ASCO Annual Meeting, experts looked at how frequently and seriously eye-related side effects occurred among patients with RRMM who received belantamab in three phase 3 clinical trials (DREAMM-3, DREAMM-7, and DREAMM-8). More than 1,100 patients were included in the study, and their occular side effects were compared with those seen in patients treated with standard myeloma treatments.

Patients who received belantamab were found to have far more eye problems than those who received other treatments. A total of 76.85% of patients who received belantamab experienced eye toxicity, which is much more than the 24.95% in the control group (risk ratio [RR], 3.30; $P<0.00001$). Serious adverse eye issues developed in 34.65% of patients receiving belantamab compared with just 2.03% of patients receiving other treatments (RR, 17.61; $P<0.00001$).

Many patients reported dry eyes, blurred vision, sensitivity to light, eye irritation, and eye pain. Almost 60% of patients who were receiving belantamab had any-grade blurred vision, but only 10% of patients in the control group experienced this side effect. About half of the patients treated with belantamab developed dry eyes, whereas this side effect was very rare among patients in the control group.

Cataracts and the sensation of a foreign body in the eye were reported more frequently among patients treated with belantamab. Although symptoms such as severe eye pain and the sensation of something in the eye were similar between groups, many other eye-related problems were more likely to be reported by patients receiving belantamab.

The findings indicate the importance of regular eye checks and quick interventions when belantamab mafodotin is administered. The drug may help with treatment, but because of its potential to cause serious eye problems, it must be used with care. Educating patients and regularly checking their eyes, along with assistance from eye care experts, may minimize these complications and help patients continue their treatment when needed.

Reference

2025 American Society of Clinical Oncology Annual Meeting. Abstract No. 12040

Epcoritamab Delivers 3-Year Remission in R/R LBCL

*By **Nichole Tucker***

Two years after starting treatment with epcoritamab (EPCOR), a subgroup of patients with relapsed or refractory large B-cell lymphoma (LBCL) are showing long-term disease remission and overall survival, according to post hoc analysis data from EPCORE-NHL-1.

Yasmin H. Karimi, MD

The subgroup analysis results were presented by **Yasmin H. Karimi, MD,** clinical assistant professor of Medicine, Division of Hematology/Oncology, University of Michigan, during a poster session at the 2025 ASCO Annual Meeting. The data from Dr. Karimi and colleagues also demonstrated manageable long-term safety and the potential for cure, which the experts note is due to the fixed-duration approach to treating relapsed or refractory LBCL.

"Many of the new studies now are testing the time-limited (fixed duration) approach either by specific months of therapy or a specific time-limited approach after MRD [measurable residual disease] negativity. With concerns about long-term immunosuppression and infection risks, a safe time-limited approach that is still efficacious with long-term disease-free survival demonstrated would be ideal," **Julie M. Vose, MD, MBA, FASCO,** a co-investigator of EPCORE-NHL-1 and chief, Hematology/Oncology, University of Nebraska Medical Center told *Blood Cancers Today*.

The study team evaluated 157 patients for long-term study outcomes. Of those included, 65 patients (41%) achieved a complete remission (CR) after a median follow-up of 37 months (range, 32-46 months). Notably, 32 patients (42%) remained in CR at the 2-year mark. Investigators also noted that responses occurred early on in treatment, with only one patient not responding to treatment by week 12.

Responses to fixed-duration treatment were durable. The median duration of response was not reached; however, at 3 years, approximately 96% of patients remained in CR. The longest CR as of the data cutoff date of May 3, 2024, was more than 43 months. In terms of survival, the median progression-free survival and overall survival were not reached in this analysis.

Patients in EPCORE-NHL-1 were on treatment for 35 months (range, 8-43), and many continued treatment into the second year (n=26, 81%). Safety findings from the 32 patients showed that five patients (19%) developed at least one serious infection. Two patients died as a result of infections. One patient developed progressive disease and discontinued study treatment. Other discontinuations occurred for 12 patients, mostly as a result of adverse events.

The study investigators reported that EPCOR is beneficial in third-line LBCL, and these results may be helpful as hematologic oncologists decide on personalized care plans. Further research is needed to confirm their findings.

"Patients who are less heavily pretreated and with less volume of disease tend to have a higher response rate and durability," explained Dr. Vose. "However, molecular and immunologic analyses of the tumor specimens and tumor microenvironment are ongoing to determine who might be a good candidate for this therapy."

Reference

2025 American Society of Clinical Oncology Annual Meeting. Abstract No. 7043

Blood Immune Biomarkers Predict Response to Mosunetuzumab for FL and MZL

*By **Andrew Moreno***

Charles J. Milrod, MD

Inside a clinical trial evaluating the CD3xCD20 bispecific antibody mosunetuzumab for first-line treatment of follicular lymphoma (FL) and marginal zone lymphoma (MZL), investigators conducted an exploratory study to determine if patients' circulating immune biomarkers were predictive of response to the drug. Their findings were presented at the 2025 ASCO Annual Meeting.

"Although CD8+ T cells are the main effector cells engaged by mosunetuzumab, our observations in previously untreated FL/MZL suggest that increased naïve CD4+ helper T cells and NK [natural killer] cells PreTx [at baseline], along with lower CTLA-4 levels during Tx [treatment] may better predict CR [complete response]," wrote **Charles J Milrod, MD,** of Brown University Health, and colleagues.

The investigators performed this study within BrUOG-401, a phase 2 trial in which patients with untreated, high-burden FL and MZL received eight cycles of mosunetuzumab. Disease in the patients was evaluated with PET/CT after the fourth cycle of treatment and at the end of the eight -cycle treatment. Those who did not have CR by the fourth cycle of treatment were given additional lenalidomide for cycles 4 through 8, with an option to extend treatment up to 12 cycles.

Peripheral blood samples were collected from the patients at treatment baseline, on day 8 of the first cycle, on day 1 of the second cycle, at the fourth cycle, and at the end of treatment. The investigators used a multiplex Luminex assay to measure 25 plasma cytokines associated with T-cell activation and regulation, along with flow cytometry to assess immune cell subsets. They then compared the markers using rank-sum tests and mixed-effects generalized linear models.

Response to mosunetuzumab by the end of the eight-cycle treatment was evaluable in 34 patients. Among them, 65% achieved CR by the fourth cycle and 85% by the end of treatment. Of 22 patients who had baseline cytokine level information available, 15 had achieved CR by the fourth cycle and 19 by the end of treatment. The investigators found no significant association between patient baseline cytokine levels and CR at the fourth cycle or at end of treatment.

Regarding T-cell activation markers, specifically GZMA/B, interferon-γ, IL-2, and IL-7, the investigators found by cycle 1 day 8 that these had increased overall ($P<0.05$ for all). However, only lower CTLA-4 levels were significantly predictive of achieving CR by cycle 4 ($P=0.0031$), and persistently lower CTLA-4 levels at cycle 4 were found to correlate with CR at cycle 4 ($P=0.008$). None of the cytokines was significantly associated with achieving CR at the end of treatment.

In the 26 patients whose samples were assessed via flow cytometry, the investigators observed an overall increase in circulating NK cells during treatment ($P<0.05$ at all timepoints). They found that having greater NK cell amounts at baseline significantly correlated with achieving CR at cycle 4 ($P=0.043$). Having elevated NK or elevated HLA-DR+ NK cells at cycle 2 was found to correlate with achieving CR at cycle 4 ($P=0.011$ and $P=0.0042$, respectively).

Having elevated CD4+CD45RA+ T cells at baseline or reduced CD4+CD45RO+CD25– T cells at baseline was associated with CR achievement at the end of treatment ($P=0.0035$ and $P=0.0061$, respectively). At cycle 4 the CD8+CD45RO+CCR7-CD27– effector memory T-cell subset was found to be elevated overall in patients ($P=0.025$), but at no timepoint was CD8+ subset predictive of CR.

The investigators noted that the *P* values calculated were not corrected for multiplicity.

"These findings suggest that cytokine-driven immune priming could influence response to BsAbs [bispecific antibodies], providing a basis for future investigations of combinations therapies to enhance their efficacy," Dr. Milrod and colleagues concluded.

Reference

2025 American Society of Clinical Oncology Annual Meeting. Abstract No. 7063. https://www.asco.org/abstracts-presentations/ABSTRACT502672

Blood Clot Risk Remains High for Patients With Newly Diagnosed Myeloma, Even With Aspirin Use

*By **Izzah Nawaz***

In a retrospective review of patient records presented at the 2025 ASCO Annual Meeting, researchers examined the occurrence of blood clots in patients who had only recently been diagnosed with multiple myeloma. The focus was on how well the scores on the risk tools SAVED and IMPEDE can predict who is at higher risk for clots and whether using aspirin or blood thinners helps prevent them.

The researchers reviewed electronic medical records of 178 patients who were treated between January 2017 and May 2022. The average age of patients was 65 years (range, from 39 to 88). Each patient had been observed for at least 2 years or until they died. The majority of patients (63.5%) were given an immunomodulatory drug, which can cause an increased risk for clots. Nearly half of the patients (43%) had stem cell transplants in addition to drug therapy.

The SAVED and IMPEDE scores help doctors estimate whether someone is likely to experience a venous thromboembolism (VTE) in their legs or lungs. Patients were seen as high risk if they had a SAVED score of 2 or higher or an IMPEDE score of 4 or higher.

Twenty-one percent of patients (n=39) had a blood clot after spinal surgery. Of the patients, about 35 had VTEs that included deep vein thrombosis and pulmonary embolism, and four experienced clots in arteries. It took an average of 7.7 months after treatment for a clot to develop.

When the treatment began, 74% of patients received aspirin, 15% were taking anticoagulants, and 11% had no preventive treatment. Of the patients with clots, the majority (71%) were prescribed aspirin. Most of the patients had no form of protection, and just a few were prescribed anticoagulants.

Patients who were at higher risk experienced clots more frequently (23.8%) than those who were at lower risk (16.7%), but the difference was not considered statistically significant. Rapid clot formation occurred more frequently in patients considered high risk. Anticoagulant therapy was associated with less clotting in high-risk patients (11%) compared with those who took only aspirin (27%), which may mean that anticoagulants are more effective for this group.

The results showed that clots were still a significant issue in all groups, with 19.1% taking aspirin, 19.2% taking anticoagulants, and 30% not taking any preventatives.

Overall, the study found that patients predicted to have a low risk for clot formation still had a high number of clots, and this was most noticeable after 6 months of treatment. Taking aspirin by itself may not be enough to prevent blood clots for patients with myeloma, but taking a closer look at risks and increasing the use of preventive measures may be warranted.

Reference

2025 American Society of Clinical Oncology Annual Meeting. Abstract No. 7561

Highlights From the **EUROPEAN HEMATOLOGY ASSOCIATION (EHA) 2025 CONGRESS** June 12 to June 16, 2025, in Milan, Italy

Phase 3 IMROZ Trial Spotlights Isa-VRd Survival Benefit for Patients With Newly Diagnosed Myeloma

*By **Melissa Badamo***

Meletios A. Dimopoulos, MD

Isatuximab added to bortezomib, lenalidomide, and dexamethasone (Isa-VRd) showed a significant progression-free survival (PFS) benefit for patients with newly diagnosed multiple myeloma, according to the phase 3 IMROZ study.

The results were presented at the EHA 2025 Congress by **Meletios A. Dimopoulos, MD,** of the National and Kapodistrian University of Athens.

A total of 446 patients were randomized 3:2 to receive Isa-VRd followed by Isa-Rd maintenance (n=265) or VRd followed by Rd (n=181). In the study, 35.9% of patients in the Isa-VRd group and 38.7% of patients in the VRd group had 1q21+ status, including gain(1q21) and amp(1q21). At least one high-risk cytogenetic abnormality was seen in 7.2% of patients in the Isa-VRd arm and 8.3% in the VRd arm.

Isa-VRd prolonged PFS for patients with 1q21+ or isolated 1q21+ compared with VRd. The median PFS was not reached in the Isa-VRd arm for patients with 1q21+, isolated 1q21+, and standard risk myeloma. Meanwhile, the median PFS in the VRd arm was 39.13 months for patients with 1q21+, 43.01 months for those with isolated 1q21+, and 53.91 months for those with standard risk.

Isa-VRd also showed higher rates of complete response (CR) and measurable residual disease (MRD) negativity at 10^{-5} sensitivity. In the Isa-VRd arm, 76.9% of patients with 1q21+, 78.7% of patients with isolated 1q21+, and 72.5% of patients with standard risk achieved a CR or better. The MRD rates were 63.2% versus 41.4% for 1q21+, 65.3% versus 40.0% for isolated 1q21+, and 58.9% versus 40.7% for standard risk, respectively.

"These findings are in line with similar analyses done with Isa-pomalidomide-dexamethasone and Isa-carfilzomib-dexamethasone in phase 3 studies," Dr. Dimopoulos and colleagues concluded.

Reference

European Hematology Association 2025 Congress. Abstract No. PF729.

Early Data Suggest DNA Damage Boost in Relapsed or Refractory AML with Talazoparib Plus Gemtuzumab Ozogamicin

*By **Sabrina Ahle***

Ross McCauley, MD

Combining the poly (ADP ribose) polymerase inhibitor talazoparib with cytotoxic agents like gemtuzumab ozogamicin (GO), a CD33 antibody-drug conjugate, could enhance DNA damage in relapsed or refractory acute myeloid leukemia (AML), recent data suggest.

However, further evaluation of the safety, tolerability, and preliminary efficacy of this combination is warranted following a poster presentation at the EHA 2025 Congress by **Ross McCauley, MD,** a hematology/oncology fellow at the Roswell Park Comprehensive Cancer Center.

The phase 1/2b, open-label, multicenter trial enrolled 24 patients with relapsed or refractory CD33+ AML (median age, 70.8 years), Patients had undergone a median of three prior therapies, and most (79%) had failed venetoclax and hypomethylating agents and 17% had prior allogeneic transplant.

Common mutations included *TET2* (32%), *IDH1* (27%), *RUNX1* (27%), and *FLT3-ITD* (23%). During the dose-escalation phase, patients received oral talazoparib 0.5, 0.75, or 1 mg daily plus fixed-dose GO 3 mg/m² on days 1, 4, and 7 using a 3+3 design. The dose-limiting toxicity (DLT) window was 28 days. The recommended phase 2 dose of talazoparib 1 mg daily was further evaluated in an expansion cohort. Patients received bone marrow assessments on day 28 of cycles 1 and 2.

No DLTs were observed, and the most frequent adverse events (AEs) included sepsis (54%), lung infection (50%), nausea (50%), diarrhea (42%), febrile neutropenia (38%), thrush (38%), and peripheral edema (38%). AEs specific to GO included neutropenia (25%), thrombocytopenia (50%), and elevated liver enzymes (ALT 21%, AST 21%, hyperbilirubinemia 12.5%, alkaline phosphatase 8%). The median duration of therapy was 28.5 days.

In 20 response-evaluable patients, the regimen achieved a complete remission (CR) rate of 33% (n=6). Four of these patients had *IDH* mutations, with one surviving after subsequent allogeneic transplant, suggesting a potential biomarker-driven response. Three patients (17%) had stable disease for at least two cycles. Among those who achieved CR, the median leukemia-free survival was 75.5 days (range, 21-622). The median overall survival was 2.9 months (range, 1.8-4.8) with a median follow-up of 15.2 months.

Reference

European Hematology Association 2025 Congress. Abstract No. PF493.

Talquetamab Still Works Well in Patients With Myeloma, Even With Immune Response

*By **Izzah Nawaz***

The MonumenTAL-1 trial presented at the EHA 2025 Congress found that talquetamab continues to be effective in patients with relapsed or difficult-to-treat multiple myeloma (MM), despite patients developing an immune response against it.

Talquetamab is a bispecific antibody that aids the immune system to locate and destroy cancer cells by binding to two proteins: CD3 and GPRC5D. It is administered subcutaneously and has demonstrated robust findings in earlier trials, also in patients who have undergone numerous other procedures.

The study aimed to provide further insight into the frequency of patients forming antidrug antibodies (ADAs), proteins that the body might make in response to a treatment, and determine whether the antibodies decrease the efficacy or safety of talquetamab. Investigators also examined a form of ADA known as *neutralizing antibodies (NAbs),* which can inhibit the mechanism of action of the drug in the body.

This study involved 363 patients with relapsed or refractory MM treated with talquetamab at two dosing regimens: 0.4 mg/kg once weekly (QW) or 0.8 mg/kg every other week (Q2W). Patients received at least three previous lines of treatment, with a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Some also had a prior history of other T-cell–redirecting therapies.

While ADAs were observed in 36% of patients and NAbs in 18% by September 2024, the treatment effectiveness did not seem to be reduced by the presence of these antibodies. The response rates were equivalent or even greater in patients who developed ADAs or NAbs than in those who did not.

Ninety-two percent of the ADA-positive patients were sensitive to therapy among those receiving weekly therapy as compared to 69% of the ADA-negative patients. In patients treated every other week, response rates were 90% in ADA-positive patients and 60% in ADA-negative patients. Likewise, the rates of response in NAb-positive patients were 96% and 100% in the QW and Q2W arm, compared to 72% and 64% in NAb-negative patients.

The initial response time was about 5 weeks and the antibodies were produced 4 to 5 months later, suggesting that immune response did not interfere with early or overall treatment success.

In terms of safety, the principal variations in side effects were not identified between patients with and without antibodies development. This suggests that talquetamab was well tolerated regardless of immune response.

In conclusion, this study shows that talquetamab can be further administered in relapsed or refractory MM, even when a patient acquires antidrug or neutralizing antibodies.

Reference

European Hematology Association 2025 Congress. Abstract No. PF747

ZUMA-3 Underscores Durable Survival Gains With Brexu-Cel in Relapsed or Refractory B-Cell ALL

*By **Robert Zadotti***

Patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) experienced a clear benefit in their overall survival rate when treated with brexucabtagene autoleucel (brexu-cel), according to results from the ZUMA-3 study. These findings were presented at the EHA 2025 Congress by **Olalekan Oluwole, MD,** of the Vanderbilt-Ingram Cancer Center.

Olalekan Oluwole, MD

Brexu-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for patients with relapsed or refractory B-ALL who are over 18 in the United States and over 26 in the European Union based on the high complete remission (CR) or CR with incomplete hematologic recovery (CRi) rate observed in the phase 2 ZUMA-3 study. The research presented by Dr. Oluwole reported updated 5-year survival rates, safety, and causes of mortality in the patients of the ZUMA-3 study, including outcomes in key subgroups.

The primary end point was the overall CR/CRi rate, with key secondary end points being objective survival (OS) rates and safety. Eligible patients with relapsed or refractory B-ALL underwent leukapheresis, optional bridging therapy, and lymphodepleting chemotherapy, followed by one infusion of brexu-cel (1×10^6 CAR T cells/kg).

The 4-year OS rate among the 78 phase 1 & 2 patients was 40%, with survival benefits being observed across key subgroups. The median follow-up time of the study was 65.7 months, with responders (CR/CRi; n=57) reaching a median OS of 60.4 months and those with a CR (n=47) not yet reaching a median OS.

The 5-year OS rates for patients with (n=38) and without (n=40) prior blinatumomab were 25% and 54%; for patients with (n=17) and without (n=61) prior inotuzumab, rates were 21% and 45%; and for patients (n=29) and without (n=49) prior allogeneic stem cell transplantation (alloSCT), the rates were 36% and 42%, respectively. The 5-year OS rates were 42% (16.4-65.4) and 52% (35.8-66.5) overall.

One new adverse event and death, both in the same patient, occurred within the 4-year analysis: cervical cancer and death due to pulmonary failure (both unrelated to brexu-cel). At data cutoff, 44 of 78 patients had died, with 20 patients (26%) alive and 14 patients (18%) lost to follow-up or having withdrawn consent.

Overall, patients in ZUMA-3 experienced a survival benefit with a 40% 5-year OS rate. Patients benefited from brexu-cel regardless of age, prior therapy, or subsequent alloSCT status, though small subgroups and unbalanced patient characteristics limited the interpretation of post hoc subgroup analyses.

Despite encouraging results, the researchers concluded, “New studies are needed to fully understand how prior therapies and subsequent alloSCT impact long-term outcomes in patients with R/R [relapsed or refractory] and B-ALL treated with brexu-cel.”

Reference

European Hematology Association 2025 Congress. Abstract No. PF374

Eric Smith, MD, PhD, Receives Outstanding New Investigator Award from the American Society of Gene + Cell Therapy

*By **Jill Elaine Hughes***

The American Society of Gene + Cell Therapy (ASGCT) recognized the groundbreaking research of Eric Smith, MD, PhD, at its 2025 Annual Meeting, which took place May 13-17, in New Orleans, Louisiana.

Dr. Smith received the Outstanding New Investigator Award, granted each year to a select group of researchers across academia, research foundations/organizations, industry, and government to recognize exemplary achievements in the field of gene/cell therapies, cellular engineering, and related disciplines by persons who have served as active investigators for 10 years or fewer.

Eric Smith, MD, PhD

Dr. Smith currently serves as director of Research Translation for Immune Effector Cell Therapies at the Dana-Farber Cancer Institute (DFCI) at Harvard Medical School. Dr. Smith's primary responsibility at Dana-Farber is principal investigator of a gene and cellular-engineering laboratory. He also serves as faculty director of a unique research group at the Massachusetts Life Sciences Center: Immunotherapy Platform for Antibody and CAR-Therapeutics discovery and Translation (IMPACT).[2]

One of four recipients in the 2025 awardee cohort, Dr. Smith presented his lecture, "Pushing the Boundaries of CAR-T Cell Therapy for Immunotherapy of Cancer," at the ASGCT Annual Meeting as part of his award recognition.

"Ongoing work in [our] lab is focused on tackling some of the biggest challenges in the CAR [chimeric antigen receptor] T-cell field, which includes extending CAR T cells to solid tumors, enhancing persistence of cellular therapies, direct in vivo delivery approaches, and the study of the biology of interaction between CAR T cells and disease or microenvironment interactions," Dr. Smith said in a recent interview. He noted that his lab colleagues were also widely successful at this year's meeting. "We had four other presentations at ASGCT of some of these advances we are pursuing," Dr. Smith said.

According to Dr. Smith, he received the New Investigator Award primarily for his work on exploring ways to expand clinical applications for CAR T-cell therapy, particularly in multiple myeloma (MM). "We both identified GPRC5D [G protein–coupled receptor class C group 5 member D] as an attractive target for immunotherapy of MM and were also one of the first groups (in parallel to others) that targeted BCMA [B-cell maturation antigens] with novel CARs," he explained. "We translated CARs we engineered targeting both these targets into the clinic in collaboration with our critical colleagues in clinical research and manufacturing." The resulting lead CARs, orvacabtagene autoleucel (orva-cel) and arlocabtagene autoleucel (arlo-cel), are now in trials.

"I am honored to be selected for such an award by a committee of my peers," Dr. Smith said, adding that close collaboration is key to his success. "We work closely with our clinical scientist colleagues, as we did with Sham Mailankody, MBBS [of Memorial-Sloan-Kettering Cancer Center], who led the seminal CAR T-cell studies in MM on CARs we developed."

Active in CAR T-cell therapy research innovation since its infancy, Dr. Smith was attracted to the oncology research field through a research fellowship after first completing training in internal medicine and a PhD in genetic and genomic sciences.

"Medical oncology…drew my interest because it was a rare field where deep relationships are quickly made [with] patients and where the research environment was fast-paced…making tremendous progress," Dr Smith said. "I was always interested in gene therapies and marrying my research expertise in genetics with opportunities in cancer and immunotherapy."

After starting his research career at Memorial-Sloan-Kettering Cancer Center in New York City, Dr. Smith eventually made the move to Harvard and Dana-Farber to take advantage of the cutting-edge laboratory facilities and the depth of expertise at these institutions. "[Dana-Farber] is a phenomenal institute with incredible collaborators across many disciplines, including the clinical immune effector cell program," said Dr. Smith. "There is a fantastic GMP [Good Manufacturing Practices] CAR T-cell production facility and group here."

Dr. Smith also runs the Eric Smith Lab for Synthetic Biology and Cellular Engineering at DFCI, where he trains and mentors the next generation of gene and cell therapy scientists. Students and research fellows at Smith Lab range from undergraduates through postdoctoral researchers, and he remains deeply involved in their training—even in today's political era of federal grant cuts. "My advice to those considering entering the field, or those new to science, is to keep going," he said.

"I feel incredibly fortunate to work with an outstanding lab team with a culture of collaboration, dedication to our dual missions of developing new therapies for patients and advancing the field of immunotherapy, and intellectual curiosity that makes coming to work every day a thrill," he concluded.

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

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increased Early Mortality

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

Cytokine Release Syndrome

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

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

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

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

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

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

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

Neurologic Toxicities

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

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

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

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

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

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

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

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

Parkinsonism

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

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

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

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

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

Guillain-Barré Syndrome

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

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

Immune Mediated Myelitis

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

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

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

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

Monitor patients for signs and symptoms of peripheral neuropathies.

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

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

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

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

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

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

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

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

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

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

CARVYKTI REMS

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

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

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

Prolonged and Recurrent Cytopenias

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

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

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

Infections

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

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

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

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

Viral Reactivation

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

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

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

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

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

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

Use of Live Vaccines

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

Hypersensitivity Reactions

Hypersensitivity reactions occurred following treatment with CARVYKTI.

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

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

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

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

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

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

Effects on Ability to Drive and Use Machines

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

CARTITUDE-4

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

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

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

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

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.

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

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

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

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

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

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

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

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

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

[k] Headache includes Headache and Tension headache.

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

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

[n] Hypotension includes Hypotension, and Orthostatic hypotension.

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

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

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

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

CARTITUDE-1

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

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

Prolonged and Recurrent Cytopenias

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

Infections

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

Hypersensitivity Reactions

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

Secondary Malignancies

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

Advise patients of the need to:

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

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

Marketed by:
Legend Biotech
Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

cp-258863v5

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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

POWERFUL. DEEP. DURABLE.

After a One-Time Infusion[1-3]

CARTITUDE-4 primary analysis demonstrated[†]:

POWERFUL

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

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

DEEP

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

DURABLE

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

Safety profile

- **Boxed Warning:** cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), parkinsonism and Guillain-Barré syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged and/or recurrent cytopenias, secondary hematological malignancies, and Risk Evaluation and Mitigation Strategy (REMS)
- **Warnings and precautions** include: increased early mortality, prolonged and recurrent cytopenias, infections, hypogammaglobulinemia, hypersensitivity reactions, secondary malignancies, and effects on ability to drive and use machines
- The most common nonlaboratory **adverse reactions** (≥20%) included: pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

CAR-T=chimeric antigen receptor-T cell therapy; CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.
*From January 2021 to November 2024.
†Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
‡Based on a stratified Cox proportional hazards model. An HR <1 indicates an advantage for CARVYKTI® arm. For all stratified analyses, stratification was based on investigator's choice (DPd or PVd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized.
§Since March 2022.

SELECTED IMPORTANT SAFETY INFORMATION

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

cp-30028v4

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