TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

bct BLOOD CANCERS TODAY

February 2025

bloodcancerstoday.com

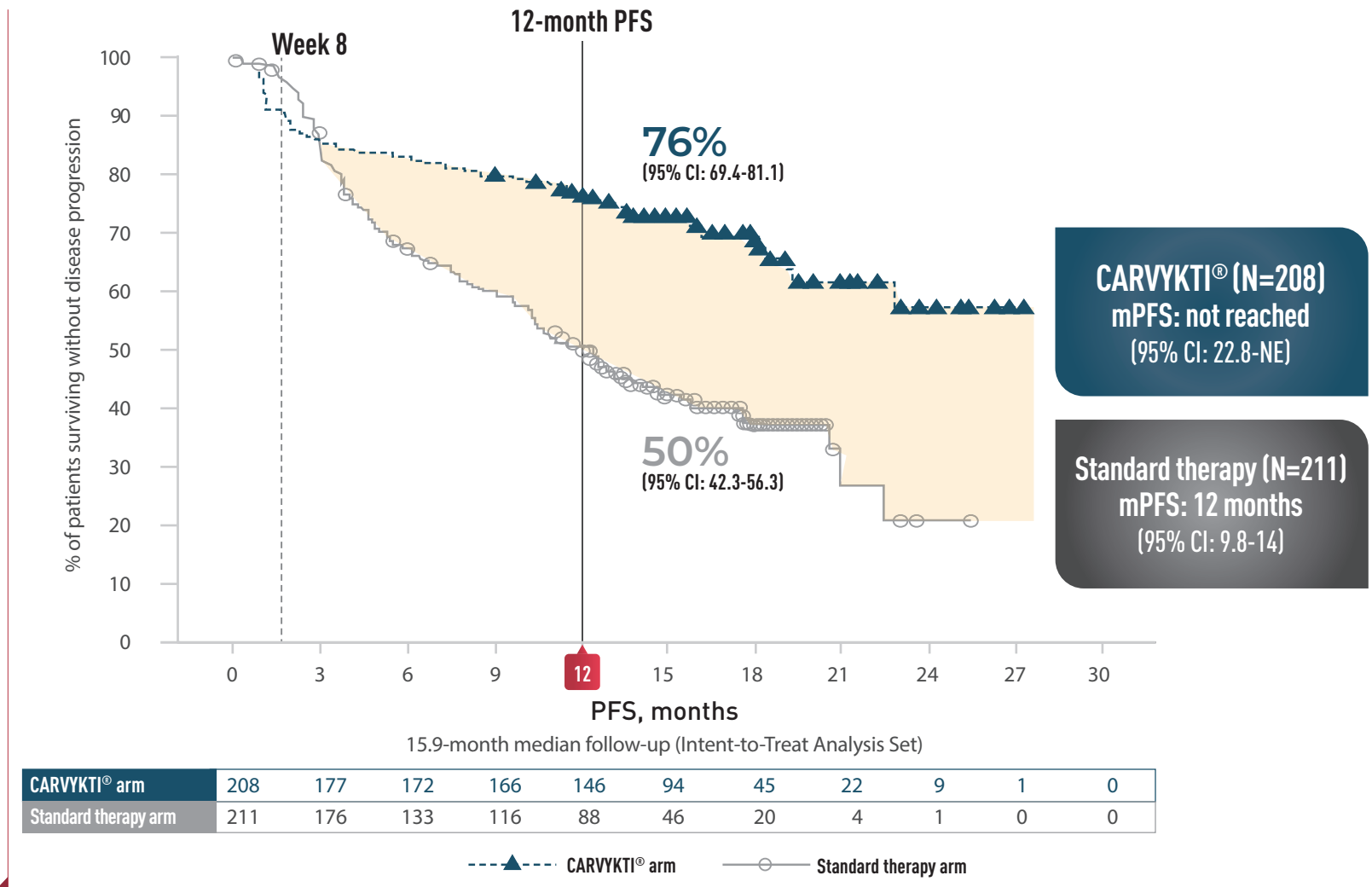
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

POWERFUL RESULTS

In CARTITUDE-4

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

PROGRESSION-FREE SURVIVAL



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-30028v4

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

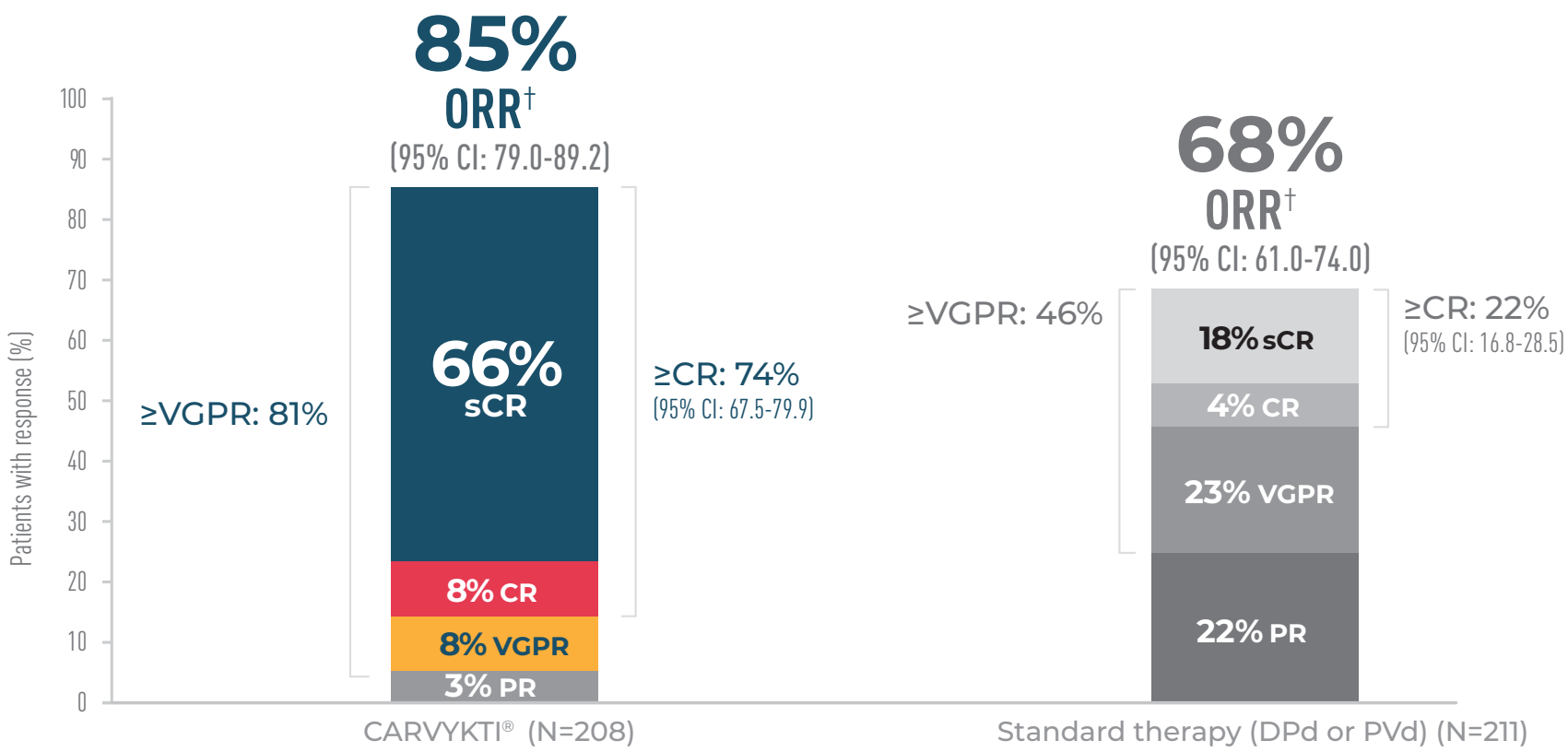
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

DEEP RESPONSES[2*]

In CARTITUDE-4

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

Deep response is defined as ≥VGPR



DURABLE RESPONSES

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

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

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

SELECTED IMPORTANT SAFETY INFORMATION

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

cp-300288v4

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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.

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(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
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References: 1. CARVYKTI®. Prescribing information. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.* 2023;389(4):335-347. doi:10.1056/NEJMoa2303379

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February 2025

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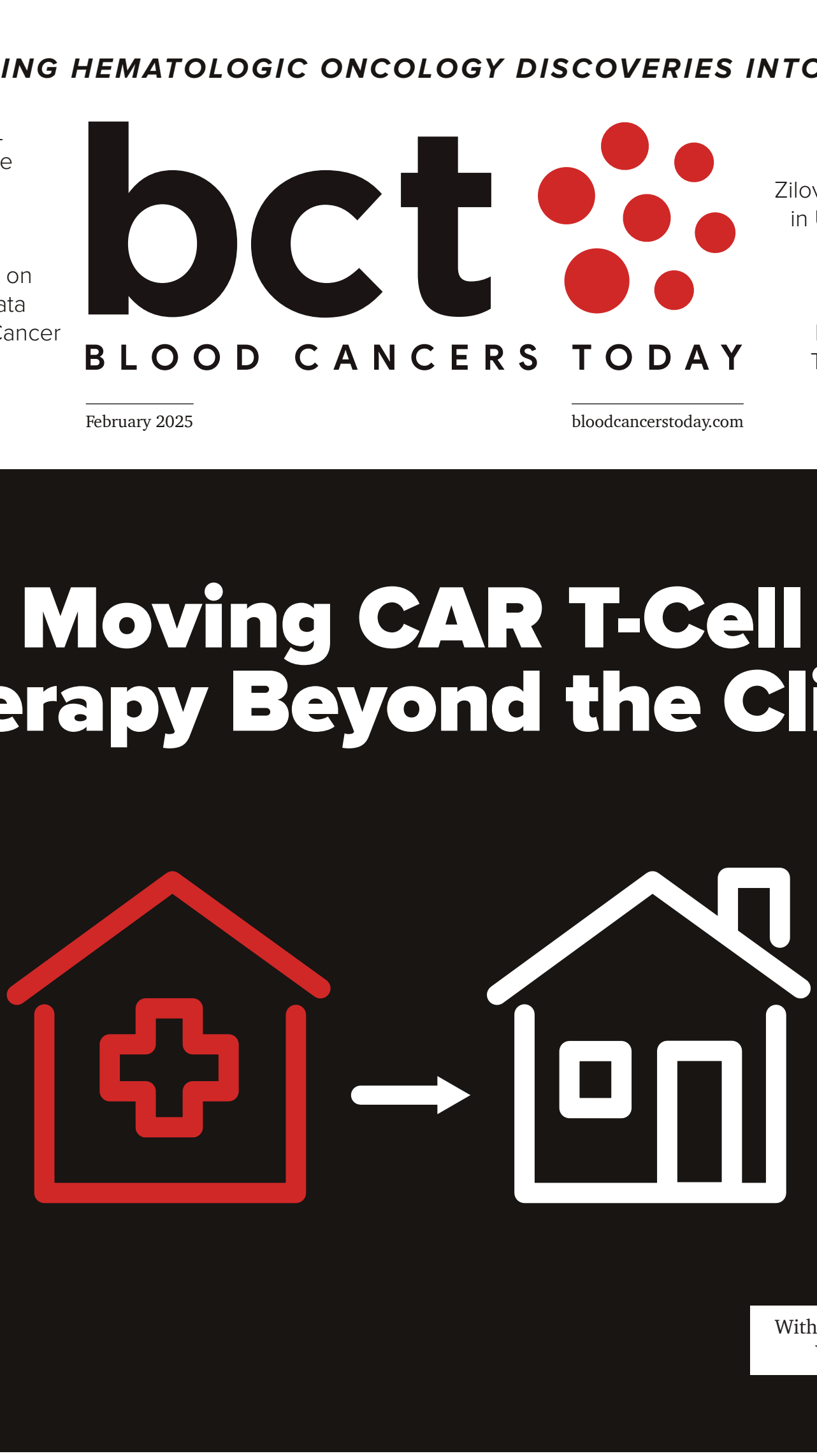
Moving CAR T-Cell Therapy Beyond the Clinic



With expert insight from
Yuliya Linhares, MD

MAIL TO:

Raajit K. Rampal, MD, PhD:
Highlighting Recent Research in Myelofibrosis

Join the discussion on Figure 1

Start collaborating on cases with your colleagues today.

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figure1

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Aaron Gerds, MD, MS

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Calendar

April 4–5
International Ultmann Chicago Lymphoma Symposium
Chicago, Illinois

April 4–5
Highlights of ASH in the Mediterranean, Middle East, and North Africa
Casablanca, Morocco

April 5
The Leukemia & Lymphoma Society Tri-State Blood Cancer Conference
New York, New York

April 5–6
European Hematology Association (EHA)-Hong Kong Society of Hematology Tutorial
Hong Kong, China

April 11–12
European Society for Medical Oncology Summit Latin America 2025
Lima, Peru

April 25–26
Highlights of ASH Latin America
Punta del Este, Uruguay

April 25–30
American Association for Cancer Research Annual Meeting
Chicago, Illinois

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

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

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

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

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

June 5–7
International Summit on Hematology and Blood Disorders (Hematology 2025)
Rome, Italy (hybrid)

June 12–15
EHA 2025 Congress
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Aaron Gerds, MD, MS

Hailing from a small, rural town in Michigan, Dr. Gerds describes his journey to becoming a hematologist oncologist at the Cleveland Clinic and the mentors who inspired him along the way.

*By **Melissa Badamo***

Where did you grow up, and when did you know you wanted to be a hematologist oncologist?
I grew up in a tiny, rural town in Michigan called Melvin. The population for the 2020 census is 148 people. I'd always been interested in science and math, and I knew that I would end up in a field that would apply science in a very tangible and humanistic way.

I got some exposure as a medical assistant, at a local primary care practice. I would room patients, take their vitals, and help with phlebotomy and x-rays. That experience is when I knew that medicine is the right choice for me. Hematology didn't come along until later. Heading to medical school, I thought I would do primary care in a rural area. But between my first and second year of medical school, I took an opportunity to join a lab working on melanoma cell lines, trying to better understand the pathways that drive melanocytes into melanoma cells. While I was all thumbs in the lab, the experiments taught me the power in the interface between raw scientific discovery and the practical application of medicine. This experience set me on a path toward hematology oncology, then I did a sub-internship on the hematology service during my fourth year of medical school, which solidified the idea that hematology is what I want to do.

Were there any mentors who shaped your career path?
Credit goes to a lot of the people who helped me along the way. During residency, one of the biggest influences was Patrick Stiff, MD, at Loyola University Chicago. He taught me patient care and how to think about the application of clinical trial data in everyday patient care. He also gave me my first opportunity to get involved with clinical research. Without him, I certainly wouldn't have been able to go down this path. He got me involved very early on.

I did my fellowship at the Fred Hutch Cancer Center in Seattle. There, I worked under the mentorship of Drs. Joachim Deeg and Bart Scott, who influenced my career tremendously. I also had the opportunity to work with Drs. Eli Estey, Janis Abkowitz, and Fred Appelbaum, among many others, who helped me learn how to be a hematologist and clinical researcher.

Can you talk about your current clinical research?
I joined the Leukemia and Myeloid Disorders Program at the Cleveland Clinic after fellowship, which was led by Mikkael Sekeres, MD. I had the opportunity to start working on myeloproliferative neoplasms [MPNs] shortly after I arrived. I liked the patient population and the disease space, so I thought it could be a really great opportunity. Clinical trials for patients with MPNs—myelofibrosis, polycythemia vera, and essential thrombocythemia—remains the big focus of what I'm doing.

There have been a couple of themes of the research program here over the last decade. A big one has been the treatment of anemia in myelofibrosis. Anemia is very common in myelofibrosis. It's often a presenting symptom and a prognostic marker. There are treatments available, but they're certainly not complete.

What are the different ways we can start to treat anemia in myelofibrosis? We focused on things like luspatercept, ACVR1 [activin A receptor, type 1] inhibitors, and newer agents harnessing the power of the hepcidin pathway to alleviate anemia in myelofibrosis. We've also worked on clinical trials in polycythemia vera trying to do the opposite and lower the red cell count in those diseases. There's a nice contrast there.

There are also trials looking at agents that want to massively change the direction of treatment. The only thing that can cure these diseases as of today is allogeneic hematopoietic stem cell transplant. Can we develop treatments that can either eliminate the need for transplant for some patients or put it off? Can we truly change the course of disease? So, I had a keen interest in developing those treatments as well.

What do you hope to see in the field over the next 10 years?
Janus kinase inhibitors, the drugs that are commonly used to treat myelofibrosis, have been revolutionary. Patients are living longer; they're living better. But, we want therapies that truly change the course of disease and root out disease in a deep and meaningful way where patients are living not only better, but substantially longer.

The hope is that while these therapies aren't going to be curative, they can chronically control it. Right now, we're in the same position as multiple myeloma, where treatments have stretched the average survival by decades. I think that's really where the field is focused on and where the field is going.

"We want therapies that truly change the course of disease and root out disease in a deep and meaningful way where patients are living not only better, but substantially longer."

What advice would you give to younger physicians or trainees in the field?
Just try stuff. Be brave. Be bold. If it works, great. If not, there's always an opportunity to retool and go a different direction. Inactivity limits creativity.

Which hobbies or activities do you enjoy outside of work?
Laura Michaelis, MD, who's a mentor, friend, and colleague at the Medical College of Wisconsin, and I often joke that our hobby is collecting hobbies. My list of hobbies is long and eclectic, including everything from road cycling to repairing and modifying old Nintendo Gameboys. Although it lay dormant for quite some time, I recently resurrected playing guitar. In medical school and residency, I was part of a cover band with my classmates. Being winter right now, the dominant hobby is ice hockey. I've been playing the sport my whole life and now coach my son's team. It is an absolute blast to be on the ice with him and his teammates!

Inside the PETAL Consortium at the Salvia Jain Lab: How Researchers Designed a Novel Scoring System for T-Cell Lymphoma

*By **Melissa Badamo***

From the Salvia Jain Lab at Massachusetts General Hospital comes the PETAL Consortium, a global team of T-cell lymphoma experts spanning 19 sites and 10 countries. Focusing on the rarity of this hematologic malignancy, this coalition integrates machine learning and genomics to predict outcomes for newly diagnosed, relapsed, and refractory mature T-cell and natural killer (NK)–cell neoplasms.

Blood Cancers Today spoke with researchers from the Salvia Jain Lab to learn more about the goals and initiatives of the PETAL Consortium. **Leora Boussi, MD, Angela Koh,** and **Jessy Xinyi Han** discuss their study of a novel scoring system using one of the largest international global cohorts of 925 patients with relapsed or refractory mature T-cell NK-cell lymphomas.

Can you please describe the study's background and design?

Leora Boussi, MD: The idea behind the study is we're dealing with a rare and heterogeneous group of patients who, in the relapsed or refractory setting, don't have a standard of care for how to approach their clinical management. We compiled a large database that came together into the PETAL Consortium.

The questions we wanted to ask are: "How do novel single-agent therapies that have been introduced into the disease space in recent years stack up against conventional chemotherapy regimens that have been around for a long time that come with associated toxicity and challenges with administration? Can we understand which patients are going to derive benefit from these novel single agents or what type of novel single agents? Is there a way to prognosticate who is going to do well with a single agent, and can we make sure to make that drug available to that patient?"

Angela Koh: We recognize that numerous prognostic risk factors and scoring systems, like the Prognostic Index for T-cell lymphoma (PIT) and International Prognostic Index (IPI) we use in the clinic, were available and that there are histological subtype-specific prognostic scores for extranodal NK T-cell lymphoma, angioimmunoblastic T-cell lymphoma (AITL), and adult T-cell leukemia/lymphoma patients. But, there's no scoring system that specifically addresses the variability in survival outcomes for relapsed or refractory patients. So, we aimed to design a new scoring system using one of the largest international global cohorts. Our study is a retrospective global cohort of 925 relapsed or refractory mature T-cell NK-cell lymphomas from 13 institutions representing 10 countries across the six continents. We believe this is one of the largest retrospective global cohorts. They were diagnosed with lymphoma between 2010 and 2021 and had to receive either cytotoxic or chemotherapy or novel single agent as a second-line therapy to be eligible.

For the Methods section, we first split this global cohort into 80% training and 20% testing set. We identified 21 available demographic histological laboratory and radiologic nontreatment

From left to right: Sean McCabe, Kusha Chopra, Ronald Nemec, Jamie Weller, Olivia Economides, Anna Rider, Shambhavi Singh, Khyati Kariya, Caroline MacVicar, Salvia Jain (PI). Photo courtesy of Salvia Jain Lab.

characteristics we had in the data, and we identified 11 variables on univariable analysis to be associated with inferior overall survival from the start of second-line treatment. We did the step-by-step selection in the multivariable Cox regression, and with clinical consideration, our final variable model included six of the 11 variables based on the highest concordance index using the testing set. The six variables in the final model included age greater than 60, primary refractory disease in contrast to relapsed status, histological subtypes other than AITL, extranodal sites greater than one, Ki-67 proliferation index greater than or equal to 40, and absolute lymphocyte count around diagnosis being lower than the lower limit of normal. This led to the six-point scoring system named the PIRT score, which stands for Prognostic Index for Relapsed or Refractory Mature T-cell and Natural Killer Cell Lymphomas.

Can you please explain the new scoring system used in your study?

Jessy Xinyi Han: We have this new scoring system with six different scores, from score zero as the minimum to score six as the maximum. We assign a score of 1 to each unfavorable feature. All the clinician needs to do is take the patient profile and look at the six different features and see if the result matches with the unfavorable feature identified in our scoring system. We observed that as the score goes up for the patient, there is a decline trend of overall survival since second-line treatment. This matches with our hypothesis that the greater the score is, the worse the survival outcome is.

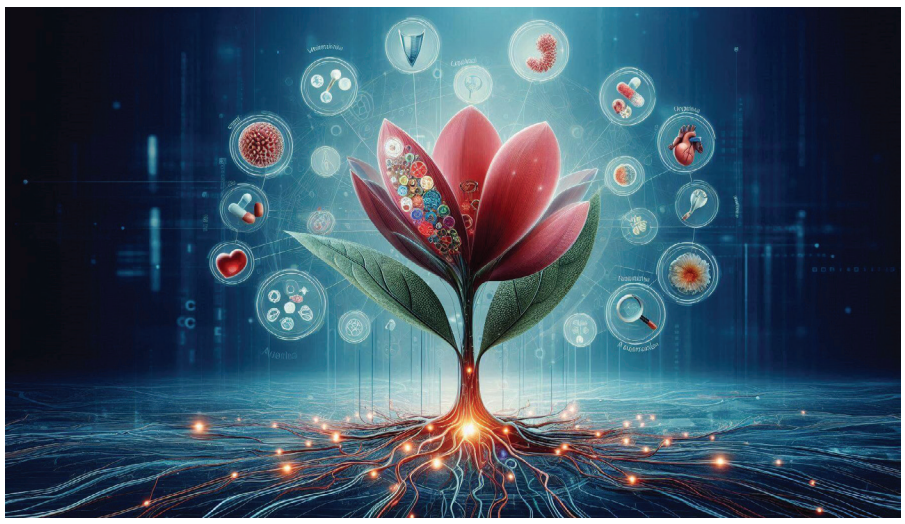
Later, the patients are stratified into three different final risk groups. The low-risk group has zero to one risk factor, the intermediate-risk group has two to three risk factors, and the high-risk group has four or more risk factors. We see similarity of survival between the predicted survival and their actual survival. Later, we also compared our performance of the PIRT score with other commonly used scores like PIT score or IPI score using our test set and an external validation set.

The way we do this validation is by bootstrapping the testing sets 1,000 times and then taking the average to see how the performance goes. We see that our PIRT score has a better prediction probability with an average C-index of 0.7 compared to the IPI score, which has an average C-index of 0.56, and the PIT score that has an average C-index of 0.59. We also conducted paired t tests between IPI and PIRT and PIT versus PIRT, and we saw that there is a statistical significance of performance difference. This shows that our PIRT score does better than existing scoring systems like PIT and IPI on the testing set and on the independent set.

We also want to make this scoring system available for clinical use. So, we developed this web-based calculator specifically for the PIRT score that can be available to investigators, clinicians, and patients who are interested in knowing more about the disease. This online calculator is hosted on our PETAL Consortium website. This is a very easy to use tool that will really help clinicians have a more comprehensive understanding of patient survival, especially for relapsed or refractory patients, when they are making clinical decisions.

How is this study important to the field of T-cell lymphoma?

Leora Boussi, MD: We had several centers throughout the United States, Australia, Brazil, South Korea, South Africa, Saudi Arabia, Japan, Italy, and India. We have representation from all over the world, and I think one question that could come up when extrapolating these conclusions is, "Is this just a United States dataset? Is this localized to a certain area?" An effort was made to include patients from all over the world so that the conclusions could be as generalizable as possible. There's a need for consortiums like this in rare diseases to take a



Photos Courtesy of Salvia Jain Lab.

multinational foot first and include a lot of different centers in compiling data like this so that we have enough power in our studies to come to meaningful and statistically significant conclusions.

This is one big step forward within the field of T-cell lymphoma. This is a rare and heterogenous group of diseases. Using genomic and molecular data and having highly annotated information from a diverse group of patients allows us to ask the important questions that were sometimes a bit limited in clinical trials and other settings where we have fewer patients enrolled on the study. This study frames a new way that questions could be approached and asked within the T-cell lymphoma world outside of clinical trials.

Angela Koh: This is a new calculator specifically designed for relapsed or refractory patients who have inferior survival outcomes than the general T-cell lymphoma population. Since this is the largest global cohort, we were able to do a lot of subgroup analysis that we weren't able to do with a smaller cohort previously. That takes into account the heterogeneous nature of T-cell lymphoma in terms of treatment regimens and the histological subtypes.

What are the limitations of your study?

Angela Koh: One of the limitations of our study was missing data. We had a total of 925 patients and had to exclude 162 patients who were not followed up since second-line therapy. Then, 515 were again excluded because we had missing laboratory variables such as Ki-67 and absolute lymphocyte count. We had enough patients to create this calculator, but we hope to overcome this missing data issue in the prospective cohort study that we plan to launch through the PETAL Consortium.

Leora Boussi, MD: In building this consortium involving numerous different countries, there are varied treatment practices in the second-line setting among different academic centers and restricted access to novel single agents in some countries relative to others. There's also a lack of central pathology and radiology review, and all of those things may impact study conclusions. Our limitations are to be acknowledged, but at the same time, this is a meaningful effort to draw statistically significant and informative conclusions from this patient population. This is something that we have to acknowledge is there, but also still continue with the work of compiling these datasets to get the best information we can.

Jessy Xinyi Han: One very important feature about our datasets is the heterogeneity within the patient cohort. One other challenge is that we don't have the luxury of having millions of patients' data. We only have 925 patients to start with. To avoid problems like overfitting, we emphasize having this training testing split and an external validation set to test our scoring system. This way, we can make sure that it not just works within the training set—which is fitted perfectly for the model—but also on the testing set and external validation so that the conclusion will be valid outside our datasets. We also have the online calculator so that the clinicians can start using them, and maybe they will also provide feedback in the future to see how they feel about the calculator and if they have input within new data and other perspectives.

What's next for the PETAL Consortium?

Angela Koh: Mark Sorial, MD, one of our leading investigators at the PETAL Consortium, compared optimal treatment sequences in relapsed or refractory T-cell lymphoma patients, which compared the overall survival since second-line treatment between subgroups that receive different sequences of treatment of either conventional chemo or single agent, such as epigenetic modifiers or small molecule inhibitors. They have 12 different scenarios in the second- and third-line treatment, and he identified the more ideal treatment sequence scenarios in specific subgroups. There is more to come!

Leora Boussi, MD: There's an additional project looking at time to relapse that is pending manuscript submission as well.

Jessy Xinyi Han: We hope to advance novel machine learning algorithms, like causal survival analysis methods to debias the retrospective data, which often has some data collection bias or other problems. We hope to have more advanced methods that can help uncover the underlying causal mechanism within the datasets and have more accurate estimation prediction from the retrospective data.

Leora Boussi, MD: Ultimately, the goal is to expand this further. In addition to looking at all these questions and data prospectively within the PETAL Consortium, the goal is to expand to additional countries. There is some interest from additional sites to collaborate on this consortium. We're looking forward to more growth there.

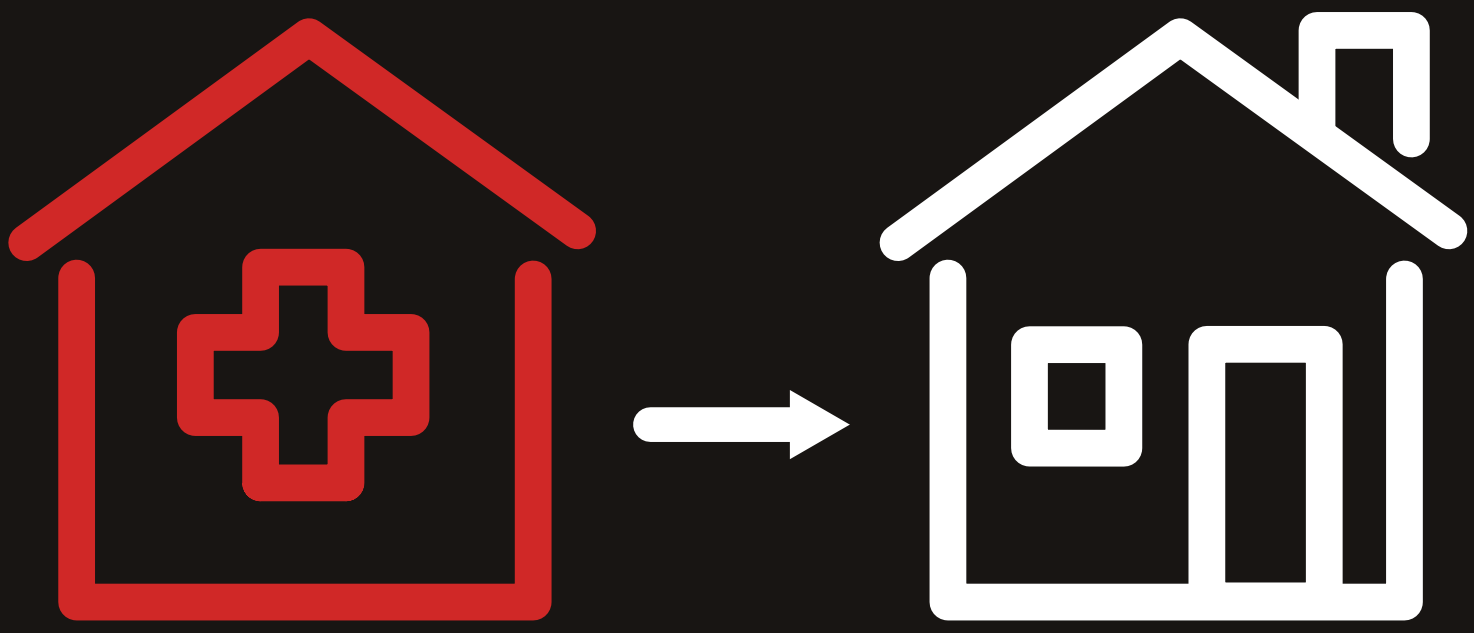
The other component with the prospective lens is that hopefully we can incorporate high-quality molecular annotation for all these patients. That is one thing that will be added in the next phase of this project that was not as well annotated in our retrospective cohort. Ultimately, with this highly annotated clinical and molecular data from a diverse array of countries with a robust number of patients, we're hopeful that this PETAL Consortium can support a clinical trial network across the world for expedited approval and access to drugs. That would benefit these patients and is one of the challenges within the field.

Angela Koh: We will have exhaustive clinical data in addition to what we had for the retrospective study, including quality of life and pathology confirmed by the pathologist panel, and genomics data confirmed by the genomics experts and incorporation of machine learning. We believe that by incorporating all of these very granular data, we can move on to precision medicine with use of artificial intelligence that will allow us to understand the outcomes and treatment personalization for specific groups to support the clinical decisions in the real world—not just in the United States and sites with great resources, but also in developing countries around the world by sharing our results.

Jessy Xinyi Han: We also want to use the PETAL Consortium as a platform where researchers from different backgrounds can collaborate. People with machine learning backgrounds and clinicians can come together to work on, collaborate, and understand each other's questions or challenges. This way, we can come together to combat this very rare but dangerous cancer.

Angela Koh: We believe that this is just the beginning of the many multinational consortiums fighting for rare diseases like T-cell lymphoma.

Moving CAR T-Cell Therapy Beyond the Clinic



*By **Yuliya Linhares, MD***
Chief of Lymphoma, Miami Cancer Institute, Baptist Health Medical Group

Emerging scientific evidence indicates that complex immunotherapeutic interventions such as chimeric antigen receptor (CAR) T-cell therapy can be safely administered on an outpatient basis at specialized medical centers. This is a significant shift from previous clinical practices that necessitated inpatient management, predominantly at tertiary academic medical centers.

Paving the Way

Early on in research, CAR T-cell therapy was only administered in the inpatient setting. Concern about the occurrence of adverse events (AEs), such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), kept registration trials in inpatient settings. Over the years, more understanding of toxicity management and an overall decrease in the incidence of high-grade toxicity opened the door to studies of outpatient CAR T-cell therapy administration.[1]

In 2021, Gatwood et al[1] proposed an outpatient cellular therapy workflow designed to optimize support for patient needs, including managing emergencies and properly monitoring their status. Feasibility of the outpatient approach was demonstrated in 2022 by McGann et al[2] in a real-world study, catalyzing countless protocols of outpatient CAR T-cell therapy across various blood cancers.

Redefining Treatment

Data to support the feasibility of CAR T-cell therapy administration at specialized medical centers, utilizing the outpatient monitoring model, were published in *Blood Advances*. The phase II OUTREACH clinical trial (NCT03744676) is the largest known prospective clinical trial to study the use of CD19-directed CAR T-cell therapy in outpatients with relapsed or refractory large B-cell lymphoma (LBCL). Previously, outpatient outcomes were reported only from single-center programs.

Primary endpoints for the OUTREACH study included the occurrence of grade ≥3 CRS, neurologic events (NEs), prolonged cytopenia. and infections. Efficacy was a secondary endpoint. The nonrandomized study examined patient-reported outcomes and health-related quality of life to determine whether these factors were preserved during treatment.

The study's population included 82 patients who received lisocabtagene maraleucel (liso-cel) at 18 sites across the US: 57 patients (70%) were monitored as outpatients, and 25 (30%) were followed up as inpatients upon receipt of liso-cel. More than half the patients were age 65 or older, and more than 90% had disease that was refractory to previous therapy. The median follow-up was 10.6 months.

Liso-cel treatment, whether provided in an outpatient or inpatient setting, demonstrated high, durable responses and manageable safety. The objective response rate was 80% (95%CI, 70.3%-88.4%). Overall response rates were similar between outpatients (82%; 95% CI, 70.1%-91.3%) and inpatients (76%; 95% CI, 54.9%-90.6%). The complete response rate was 54% (95% CI, 42.3%-64.7%), which is similar to response rates in the TRANSCEND, PILOT, and TRANSFORM studies performed with outpatients at academic medical centers.[3]

Among the safety results, grade ≥3 CRS was not observed in any outpatients, and NEs were not reported in 12% of outpatients and 4% of inpatients; infections occurred in 12% of outpatients and 8% of inpatients. The most common complication of CAR T-cell therapy in the study was prolonged cytopenia, which was reported in 33% of outpatients and 32% of inpatients.

No hospitalizations were reported after liso-cel infusion for 25% of the outpatient population. However, 32% of outpatients were hospitalized at 72 hours after the day of infusion or sooner. The median initial hospitalization duration after liso-cel administration was 6.0 days (range, 1-28) for outpatients and 15.0 days (range, 3-31) for inpatients. During study follow-up, the median duration of all hospitalizations, including multiple stays, was 7.0 days (range, 0-67) for outpatients and 16.0 days (range, 6-64) for inpatients.

In general, inpatients in the OUTREACH study had higher disease-risk characteristics, such as a higher tumor burden and risk of AEs, complicated comorbidities, or other reasons that prevented them from being good candidates for outpatient care, such as lack of caregiver support. The overall safety results in OUTREACH were similar to results shown in the JULIET study, which assessed the efficacy and safety of another CD19-directed CAR T-cell therapy, tisagenlecleucel, for the treatment of patients with relapsed or refractory LBCL after two or more lines of therapy.

The OUTREACH trial did not require participating facilities to be certified by the Foundation for the Accreditation of Cellular Therapy (FACT), and 44% did not have FACT accreditation, but it did mandate that the centers have phase I or hematopoietic stem cell transplant capabilities. In addition, 72% of the centers had not provided CAR T-cell therapy before the study.[2]

The study showed that for appropriate candidates, outpatient CAR T-cell treatment is feasible and safe when delivered at specialized community medical centers with a multidisciplinary team trained in CAR T-cell toxicity management.

Envisioning the Future

The ability to provide such sophisticated care on an outpatient basis at community medical centers increases accessibility to cellular therapy. To date, issues such as the high cost of care are already a barrier to receipt of CAR T-cell therapy,[4] and the cost of outpatient care is typically lower than that of inpatient care, reducing the financial burden on patients and the health care system. In addition, provision of care on an outpatient basis would benefit patients in rural or underserved communities, since these individuals often experience delays in care due to limited access, which can lead to poorer outcomes.

Once the oncology community can combat problems with access to CAR T-cell therapy, and as care for patients with blood cancers continues to evolve with new CAR T-cell agents, oncologists are hopeful that remission can be prolonged and new strategies to help patients overcome resistance mechanisms can be identified.

"To date, issues such as the high cost of care are already a barrier to receipt of CAR T-cell therapy, and the cost of outpatient care is typically lower than that of inpatient care, reducing the financial burden on patients and the health care system." *—Yuliya Linhares, MD*

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Regulatory Actions

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

FDA Approves Axatilimab-csfr 9-mg, 22-mg Vial Use for Chronic GVHD

*By **Andrew Moreno***

The FDA has issued approval of 9-mg and 22-mg vial axatilimab-csfr to treat chronic graft-versus-host disease (GVHD) after failure of at least two lines of systemic therapy. The approval is for use in adult and pediatric patients who weigh at least 40 kg, dosed at 0.3 mg/kg up to a maximum dose of 35 mg and administered via 30-minute intravenous infusion every two weeks.

The FDA approval was announced in a press release from Incyte and Syndax Pharmaceuticals, two global biopharmaceutical companies which co-develop and commercialize axatilimab-csfr as Niktimvo. Niktimvo is a trademark of Incyte and the agent is expected to be available in the US in early February.

"We are thrilled to build on our strong commitment to the GVHD community with the US launch of Niktimvo, a first-in-class therapeutic agent that has demonstrated remarkable responses in patients with chronic GVHD whose response was suboptimal after at least two prior lines of systemic therapy," stated Incyte Chief Executive Officer **Hervé Hoppenot.**

Axatilimab-csfr is an antibody which blocks the colony-stimulating factor-1 receptor (CSF-1R), treating chronic GVHD by decreasing drivers of fibrosis and inflammation.

"As the first and only FDA-approved anti-CSF-1R antibody targeting the drivers of inflammation and fibrosis in chronic GVHD, Niktimvo represents a major breakthrough for patient care," commented Syndax CEO **Michael Metzger.**

FDA granted approval for this indication on August 14, 2024, based on positive results from the AGAVE-201 international clinical trial published in the *New England Journal of Medicine*. The trial data showed that axatilimab-csfr, administered at 0.3 mg/kg every two weeks, produced a response at six months in 75% of patients, and all cohorts that received the agent achieved the trial's primary endpoint.

Regarding safety findings in AGAVE-201, serious adverse reactions affected 44% of patients who received axatilimab-csfr. Adverse reactions led to dose interruption in 44% of patients, dose reduction in 8% of patients, and permanent discontinuation of the agent in 10% of patients. Specific reaction types that affected 15% or more of patients were bacterial infection, cough, diarrhea, dyspnea, fatigue, headache, musculoskeletal pain, nausea, pyrexia, unspecified-pathogen infection, and viral infection, as well as laboratory abnormalities. There were infusion-related reactions in 18% of recipients and in 1.3% these were grade 3 or 4 severity.

Axatilimab-csfr is also now included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. It has a category 2A recommendation to treat chronic GVHD after failure of at least two prior lines of systemic therapy in adult and pediatric patients who weigh at least 40 kg.

Clinical trials are currently testing frontline use of axatilimab-csfr in combination with ruxolitinib to treat chronic GVHD, as well as with steroids. It is also being evaluated for treatment of idiopathic pulmonary fibrosis.

Reference: Incyte and Syndax announce U.S. Food and Drug Administration (FDA) approval of Niktimvo™ (axatilimab-csfr) 9 mg and 22 mg vial sizes. Press Release. PR Newswire. January 15, 2025. Accessed January 16, 2025.

FDA Issues Complete Response Letter for Tabelecleucel for EBV-positive PTLD

*By **Melissa Badamo***

The FDA has issued a Complete Response Letter (CRL) to Atara Biotherapeutics for the Biologics License Application (BLA) of tabelecleucel monotherapy for the treatment of adult and pediatric patients aged two years and older with Epstein-Barr virus–positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy, including an anti-CD20–containing regimen.[1]

The CRL is related to observations of a third-party manufacturing facility as part of a standard prelicense inspection. The manufacturing process, clinical efficacy, and clinical safety of the drug were not identified as factors related to the CLR.[1]

The BLA for tabelecleucel, an allogeneic, EBV-specific T-cell immunotherapy designed to target and eliminate EBV-infected cells, is supported by results of the ALLELE study published in The Lancet Oncology. In this phase III trial, tabelecleucel demonstrated a statistically significant objective response rate of 50%. The most common grade 3 or 4 treatment-related adverse events were disease progression (29%) and decreased neutrophil count (29%).[2]

"We are working closely with our partner Pierre Fabre Laboratories, the FDA, and the third-party manufacturer to address the feedback to support marketing approval for [tabelecleucel]," said **Cokey Nguyen, PhD,** President and Chief Executive Officer of Atara, in a press release. "Once the third-party manufacturer GMP compliance issues have been adequately addressed, we will file for a resubmission, which we would expect to be potentially approved within six months of resubmission."

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FDA Approves Preparation Treosulfan With Fludarabine before Allogeneic HSCT for AML, MDS

*By **Andrew Moreno***

The injection form of the alkylating agent treosulfan has received a newly approved indication from the FDA. The approval is for use in combination with fludarabine as preparation for allogeneic hematopoietic stem cell transplantation (HSCT) to treat acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) in adult or pediatric patients aged one year and older. The approval was announced by Medexus Pharmaceuticals Inc. in a press release.

Medexus has developed injection treosulfan as Grafapex, and the agent has Orphan Drug Designation under the Orphan Drug Act. The company holds exclusive commercial rights to this agent in the US via an agreement with medac GmbH, and the approval granted by the FDA is for the sale and use of this agent only in the US. Medexus plans on commercial launch of the agent in the first half of 2025.

"We are pleased to report this positive development, which marks a strategically important step forward for our business and, importantly, will now benefit eligible patients across the United States," remarked Medexus Chief Executive Officer **Ken d'Entremont.**

Treosulfan was evaluated in MC-FludT.14/L Trial II, a randomized active-controlled study in which the agent was compared to busulfan plus fludarabine as allogeneic HSCT preparation for adults aged up to 70 years with AML or MDS.

Regarding overall survival (OS) results in the study, measured as time from randomization until death from any cause, the hazard ratio of treosulfan compared with busulfan was 0.67 in the randomized population, 0.73 in patients with AML, and 0.64 in patients with MDS. Adverse reactions that affected 20% or more of patients were edema, infection, musculoskeletal pain, nausea, pyrexia, stomatitis, and vomiting. Laboratory anomaly findings included grade 3 or 4 increases in alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and γ-glutamyl transferase.

The dosing recommended for treosulfan is 10 g/m^2 daily on days -4, -3, and -2 in combination with fludarabine 30 mg/m^2 daily on days -6, -5, -4, -3, and -2, and allogeneic HSCT infusion on day 0.

Reference: Medexus announces FDA approval of GRAFAPEX (treosulfan) for injection and provides business update. Press Release. Medexus Pharmaceuticals, Inc. (MDP). January 22, 2025. Accessed January 24, 2025.

FDA Issues Clinical Hold on Tabelecleucel Monotherapy, Anti-CD19 CAR T-Cell Therapy INDs

*By **Andrew Moreno***

The FDA has implemented a clinical hold on two active Investigational New Drug (IND) applications from Atara Biotherapeutics, Inc., Atara has announced in a press release.

The clinical hold concerns foremost Atara's program on tabelecleucel monotherapy for Epstein-Barr virus (EBV)–positive post-transplant lymphoproliferative disease (PTLD) in adult and pediatric patients aged two years and older. This drug is under development by Atara as Ebvallo.

During the prelicense inspection of the third-party manufacturing facility referenced in the Ebvallo Complete Response Letter (CRL), released on January 16, 2025, Good Manufacturing Practice (GMP) compliance issues were identified. The issues have not been adequately addressed and have led to the FDA's clinical hold on Ebvallo.

The second Atara program affected by the clinical hold is ATA3219, an allogeneic CD19-targeted chimeric antigen receptor (CAR) T-cell therapy for non-Hodgkin lymphoma and systemic lupus erythematosus. ATA3219 is manufactured at a GMP-compliance–certified facility different from Ebvallo's, but the compliance issues at the same third-party facility cited in the Ebvallo CRL affect the base materials used for its production.

The issues leading to the clinical hold from the FDA pertain only to the third-party manufacturing facility that was named in the CRL. They do not concern the facility in Thousand Oaks, California, operated by FUJIFILM Diosynth Biotechnologies, another third-party manufacturer utilized by Atara.

Under the FDA clinical hold, screening and enrollment of new participants for the two affected Atara programs has been halted. However, specific participants who are already enrolled in clinical studies who might benefit from these treatments can continue to receive them according to the ongoing study protocols.

Atara is currently cooperating with the FDA to quickly remedy the issues behind the clinical hold.

"We are encouraged with ongoing correspondence with the Agency and a potential path to submitting the necessary data to release the clinical hold. Patient safety remains our priority and maintaining the highest standards for our programs," stated Atara President and Chief Executive Officer **Cokey Nguyen, PhD.**

Reference: Atara Biotherapeutics provides update on clinical programs related to Ebvallo™ (tabelecleucel) and ATA3219. Press Release. Atara Biotherapeutics. January 21, 2025. Accessed January 23, 2025.

Singapore Health Sciences Authority Accepts NDA for Equecabtagene Autoleucel for Relapsed, Refractory Myeloma

*By **Melissa Badamo***

The Singapore Health Sciences Authority (HSA) has accepted a New Drug Application (NDA) for equecabtagene autoleucel for patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, according to a press release from IASO Biotherapeutics, the developer of the drug.[1]

"Singapore is the first country where we have submitted an overseas NDA," said Jinhua Zhang, founder, chairwoman, and CEO of IASO Biotherapeutics in the press release. "Upon NDA approval, we plan to implement an innovative model of 'Manufactured in China, supplied overseas', enabling the export of domestically produced autologous CAR [chimeric antigen receptor]-T therapies to other countries."

Equecabtagene autoleucel demonstrated early, deep, and durable responses with manageable safety in the single-arm, open-label, phase 1b/2 FUMANBA-1 trial.[2] The overall response rate was 96%, and 75 of 103 patients (74.3%) achieved a complete response or better. The median progression-free survival (PFS) was not reached, and the 12-month PFS rate was 78.8%. Ninety-six patients (95.0%) achieved measurable residual disease negativity at a sensitivity threshold of 10^{-5}.

In terms of safety, 96 patients (93.2%) experienced cytokine release syndrome, with 94 (97.9%) cases resolving with treatment. Two patients (1.9%) experienced immune effector cell–associated neurotoxicity syndrome that resolved with treatment.

Equecabtagene autoleucel previously received NDA approval from the FDA in August 2024 and is being developed in the United States for the treatment of autoimmune diseases and multiple myeloma.[3]

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1. IASO Bio announces acceptance of new drug application for equecabtagene autoleucel (FUCASO) by the Singapore Health Sciences Authority (HSA). PR Newswire. January 29, 2025.
2. Li C, Zhou K, Hu Y, et al. Equecabtagene autoleucel in patients with relapsed or refractory multiple myeloma: the FUMANBA-1 nonrandomized clinical trial. *JAMA Oncol*. 2024;10(12):1681-1688. doi:10.1001/jamaoncol.2024.4879
3. IASO Bio receives U.S. FDA approval of Investigational New Drug Application for Equecabtagene autoleucel for two new autoimmune disease indications. PR Newswire. August 12, 2024. Accessed January 29, 2025.

FDA Approves In-Vitro Assay to Identify B-Cell Lymphomas, Plasma Cell Neoplasms

*By **Andrew Moreno***

A new, highly sensitive in situ hybridization (ISH) test to help clearly identify B-cell lymphomas and plasma cell neoplasms in patients has received 510(k) clearance from the FDA. The test is under development by Roche as the Ventana Kappa and Lambda Dual ISH mRNA Probe Cocktail assay. The company announced the FDA clearance in a press release.

This assay is a single-slide, in vitro diagnostic test, which uses ISH to detect expression of kappa and lambda immunoglobulin light chains in formalin-fixed, paraffin-embedded human hematolymphoid specimens. It helps clinicians distinguish more than 60 subtypes of mature B-cell lymphomas and plasma cell neoplasms from normal immune system responses in patients.

"Accurately differentiating lymphoma from an infection is critical in ensuring accurate and timely diagnosis, especially as the symptoms can appear similar," remarked **Jill German,** head of the pathology lab at Roche Diagnostics.

The assay had already received CE Mark approval in June 2024, and it is now the first test of its type to receive FDA approval.

"With this new test, clinicians can have confidence in their diagnosis, while the test reduces the need for multiple samples and time consuming follow up tests, giving patients certainty sooner, and enabling faster access to the right treatment," German elaborated.

The Ventana Kappa and Lambda Dual ISH mRNA Probe Cocktail assay is currently indicated for use when findings from lymph node or bone marrow biopsy are inconclusive. As clinicians use this test in making a diagnosis, its results should be considered alongside patient clinical history and findings from other tests.

Reference: Roche receives FDA clearance for new, highly-sensitive test to aid clinicians in diagnosing B-cell lymphoma. Press release. PR Newswire. January 13, 2025. Accessed January 29, 2025.

Highlights From **THE 2025 TANDEM TRANSPLANTATION & CELLULAR THERAPY MEETINGS OF ASTCT AND CIBMTR**

REACH3 Analysis: Patient-Reported cGVHD Improvement Correlated With Overall Response, TSS Response

*By **Melissa Badamo***


Joseph Pidala, MD, PhD

Patient-reported responses in chronic graft-versus-host disease (cGVHD) improvement are associated with overall response, total symptom score (TSS) response, and failure-free survival (FFS), according to an analysis of the phase III REACH3 trial.

The results were presented by **Joseph Pidala, MD, PhD,** of the H. Lee Moffitt Cancer Center, at the 2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR.

Using prospective data from the REACH3 trial of ruxolitinib versus best available therapy for cGVHD, the researchers assessed correlations of patient-reported response with National Institutes of Health overall response and TSS response at six months. Using the Patient Global Impression of Change (PGIC), 160 patients rated their cGVHD as either improved (a little better to very much better) or not improved (no change to very much worse) at six months. The researchers assessed overall survival (OS), FFS, TSS response (defined as at least a 7-point reduction in cGVHD TSS), and overall response, including complete and partial response.

Of the 120 (75.0%) patients who reported cGVHD improvement, 88.1% received ruxolitinib and 60.5% received best available therapy. Of the 40 (25.0%) patients who reported no improvement, 11.9% received ruxolitinib and 39.5% received best available therapy.

Of the 97 patients who achieved an overall response, 86 (88.7%) reported cGVHD improvement and 11 reported no improvement (11.3%). Of the 63 (39.4%) patients who did not achieve an overall response, 34 (54.0%) reported cGVHD improvement and 29 (46.0%) reported no improvement. According to Kappa (κ) and positive/negative percent agreement (PPA/NPA), there was fair agreement between overall response and PGIC (κ=0.37; PPA=0.89; NPA=0.46).

Fifty-four patients (33.8%) had a TSS response. Of those, 47 (87.0%) reported cGVHD improvement, and 7 (13.0%) reported no improvement. Among the 106 (66.3%) patients who did not have a TSS response, 73 (68.9%) reported cGVHD improvement and 33 (31.1%) reported no improvement. Kappa showed minimal agreement between TSS and PGIC (κ =0.14; PPA=0.87; NPA=0.31).

The researchers also noted a significantly longer median FFS among the overall population for patients who reported cGVHD improvement compared with those who reported no improvement (32.9 vs 0.92 months, P=.002). There was no difference in OS, and the median FFS was not evaluable in either PGIC subgroup for ruxolitinib (*P*=.18). "The findings continue to support that this outcome captures a unique dimension of clinical benefit and that 6-month patient-reported response is associated with subsequent FFS," Dr. Pidala and colleagues concluded.

Reference

Im A, Kintsch E, Xue Z, et al. Patient-reported response captures unique dimension of clinical benefit in chronic graft-versus-host disease (cGVHD): an analysis from the ruxolitinib versus best available therapy REACH3 trial. Abstract #187. Presented at the 2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 12-15, 2025; Honolulu, Hawai'i.

Prolonging Life Without Progression in Large B-Cell Lymphoma: Real-World Insights

*By **Nichole Tucker***


Marina Gomez-Llobell, MD

After treatment with tisagenlecleucel (tisa-cel), there may be a 2-year period for observation of disease progression in patients with large B-cell lymphoma (LBCL). Comparably, complete remissions (CRs) may be sustained at one year in these patients after treatment with either axicabtagene ciloleucel (axi-cel) or lisocabtagene maraleucel (liso-cel) with low probability of relapse, according to a presentation by **Marina Gomez-Llobell, MD,** of the Memorial Sloan Kettering Cancer Center, at the 2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR.

With the number of chimeric antigen receptor (CAR) T-cell therapies available for large B-cell lymphoma, response rates in this patient population have greatly improved, but relapse rates remain an area of concern for hematologic oncologists. A retrospective, multicenter analysis was conducted with 479 patients with LBCL in effort to address these concerns.

The patients were treated with tisa-cel, axi-cel, or liso-cel between April 2018 and June 2023. The patients were evaluated for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS). The PFS curves were also used to evaluate complete responses (CRs).

The median duration of follow-up was 18 months in the axi-cel group, 34 months in the tisa-cel group, and 12 months in the liso-cel group. The median PFS was 12 months in patients treated with axi-cel, 3.2 months in the tisa-cel group, and not reached in patients treated with liso-cel. A CR observed at day 28 appeared to continue through day 100. Notably, among the axi-cel– and liso-cel–treated patients, conversion from a partial response to a CR was observed more frequently than among patients with a CR who developed disease progression. When the correlation between CR at day 28 and PFS was examined, results showed that in the 195 patients who had a CR at day 28, the PFS rate was 64%. The findings suggest that treatment with either axi-cel or liso-cel provides potential to sustain disease-free survival in patients with LBCL.

Reference

Gomez-Llobell M, Shouval R, Brown S, et al. When can we define disease-free status post-CAR-T therapy in LBCL? Findings from dynamic landmark analyses. Abstract #213. Presented at 2025 Transplantation & Cellular Therapy Meetings of the ASTCT and CIBMTR; February 12-15, 2025; Honolulu, Hawai'i.

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News Roundup

The latest news and updates in hematologic oncology research

Leukemia Cases on the Rise: New Data from American Cancer Society Report

By ***Melissa Badamo***

The cancer mortality rate has declined by 34% from 1991 to 2022 in the United States, according to a report by the American Cancer Society.[1] However, the incidence of leukemia and other malignancies is increasing.

The report estimates that there will be 2,041,910 new cancer diagnoses and 618,120 cancer deaths in the United States in 2025.[1] This includes 66,890 new leukemia cases and 23,540 leukemia deaths, as well as 89,070 new lymphoma cases and 20,540 lymphoma deaths.[2]

"Incidence rates of leukemia are rising for both forms of acute leukemia in adults based on SEER data going back as far as 1975. Many believe these are changes due to children and young adults living longer over that period, with death from other causes going down," **Keith Pratz, MD,** director of the Leukemia Program at Penn Medicine's Abramson Cancer Center, told *Blood Cancers Today*. "There may be issues with classification and reporting over the period, which may lead to more complete data in the recent era for leukemia diagnosis."

Dr. Pratz also explained that more people are being exposed to potential leukemogenic causes at younger ages, including diagnostic and therapeutic radiation and environmental toxins.

"There is a small but meaningful increase in younger adults with leukemia, and we need improved reporting of risks found in these young adults to improve our understanding of this issue," he added.

Cancer Incidence and Mortality in Children and Adolescents

The incidence of cancer in children (14 years of age and younger) has declined by 0.8% per year after decades of increase but has continued to rise by 0.7% per year among adolescents (15-19 years of age) due to increasing rates of lymphoid leukemia and non-Hodgkin lymphoma.[2] Leukemia, the most common childhood cancer, accounts for 28% of cases.[2]

"It's important to note that this rise in incidence is relatively small," **E. Anders Kolb, MD,** president and CEO of The Leukemia & Lymphoma Society, told *Blood Cancers Today*. "Because we have gotten better at diagnosing these diseases, incidence rates are ultimately going to rise. These diseases have been harder to diagnose, and our ability to identify these blood cancers 20 years ago is much different than our ability now."

Although the cause of the increasing incidence is unknown, Dr. Kolb explained, lymphomas are more common in children and young adults with an autoimmune disease treated with immunosuppressive agents, such as lupus and rheumatoid arthritis.

"This rise in cases highlights the fact that we don't fully understand the root causes of leukemia and lymphoma," Dr. Kolb added. "These are unique diseases in young adults, and we need to better understand the causes as well as the long-term effects of these blood cancers."

Cancer mortality has declined by 70% in children and by 63% in adolescents since 1970, attributed to the improved treatment for leukemia.[1] However, survival is higher among children with lymphoid leukemia than among adolescents (92% vs 76%), attributed to differences in tumor biology, clinical trial enrollment, treatment protocols, and treatment tolerance and adherence.[2]

"Survival rates for lung cancer and colon cancer over the years have improved in large part because of screening and prevention. We haven't been as successful in finding that yet for leukemia and lymphoma," said Dr. Kolb. "Today, in the era of molecular medicine, we are developing tools that are still in the research phases that can help predict and refine the risk for getting these blood cancers."

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2. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin.* 2025;75(1):10-45. doi:10.3322/caac.21871

New Trial to Test Novel Combination in Relapsed, Refractory MCL

By Blood Cancers Today *Staff Writers*

Researchers are launching a new clinical trial that will evaluate the combination of the bispecific antibody glofitamab with the noncovalent Bruton tyrosine kinase (BTK) inhibitor pirtobrutinib in patients with relapsed or refractory mantle cell lymphoma (MCL) who are BTK inhibitor naive or BTK inhibitor intolerant.

On the basis of single-agent activity of both pirtobrutinib and glofitamab in relapsed and refractory MCL, the immunomodulatory effects of BTK inhibition, and the largely nonoverlapping toxicities these drugs, the researchers anticipate the combination of pirtobrutinib and glofitamab will be safe and highly effective for patients with relapsed and refractory MCL.

The study will have two primary objectives: evaluation of safety of the combination according to incidence and severity of adverse events in the safety lead-in cohort and examination of preliminary efficacy of the combination as determined by complete response rate in the entire population.

The phase II open-label study will enroll patients previously treated with an anti-CD20 antibody and an alkylating agent who are either BTK inhibitor naive or intolerant. The study is expected to enroll 30 patients.

Study treatment will be obinutuzumab 2,000 mg on cycle 1 days 1 and 2, followed by glofitamab step-up dosing of 2.5 mg on cycle 1 day 8, 10 mg on cycle 1 day 15, and 30 mg on day 1 of cycles 2 through 12 (21-day cycles). For the first six patients enrolled, treatment with pirtobrutinib 200 mg PO daily will start on cycle 2 day 8 (Cohort 1: the six patients), and for subsequent patients, treatment with pirtobrutinib 200 mg PO daily will start on cycle 1 day 1 (Cohort 2: 24 patients).

PET and CT imaging will be performed every four to six cycles, and measurable residual disease (MRD) will be assessed by peripheral blood using ClonoSEQ assay on cycle 13 day 1 and every six cycles after that. Any patient who achieves a complete response with undetectable MRD can discontinue pirtobrutinib.

Reference

Seshadri MR, Huang C-Y, Donner H, et al. Combination of glofitamab with pirtobrutinib in BTK inhibitor (BTKi)-naive or BTKi-intolerant patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL): a multicenter phase 2 study of the University of California Hematologic Malignancies Consortium. Abstract #3042.3. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Real-World Use of Tafasitamab Supports Clinical Benefit in Relapsed, Refractory DLBCL

By Blood Cancers Today *Staff Writers*

A recent study of the real-world effectiveness of tafasitamab for relapsed and refractory diffuse large B cell lymphoma (DLBCL) supported the findings of clinical benefit of the drug in this patient population, according to a poster presentation at the 66th American Society of Hematology Annual Meeting & Exposition.

Tafasitamab is a CD19-targeting immunotherapy used in combination with lenalidomide for treatment of relapsed and refractory DLBCL in patients who are not eligible for autologous stem cell transplantation.

At the meeting, **Kimberly Saverno, PhD,** of Incyte Corporation, Wilmington, Delaware, and colleagues presented data examining the use of tafasitamab in the community practice setting. The retrospective study used physician-abstracted medical chart review data, provided by 23 physicians from Cardinal Health's Oncology Provider Extended Network. Patients included US adults who began treatment with tafasitamab with or without lenalidomide on or after October 21, 2020.

Two different data collection periods were used, and the median follow-up time from initiation was 14.7 months. Of the 181 patients included, 71% had discontinued treatment with tafasitamab. The most common reason for discontinuation was disease progression (71%). Of the 106 patients that were still alive, half were receiving tafasitamab.

About one-quarter (23.2%) of patients had a real-world complete response and half (50.3%) had a real-world partial response as their best response. The real-world overall response rate was 73.5%. Among responders, the median duration of response was 9.6 months: 19.2 months among those with a complete response and 8.5 months among those with a partial response. Median progression-free survival (PFS) was 11.3 months with a median overall survival of 24.8 months from treatment initiation.

The multivariable models of real-world overall survival and real-world PFS suggest that tafasitamab provides the greatest benefit when it is used as second-line therapy compared with later lines of therapy, the researchers concluded.

According to the poster, the data should be considered with certain limitations in mind. These include biases introduced by missing data or underreported data and the fact that the data were from only a limited number of community oncologists.

Reference

Saverno K, Nastoupil L, Feinberg B, et al. Real-world effectiveness of tafasitamab (Tafa) for the treatment of relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) in the United States. Abstract #2375. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Olutasidenib and Azacitidine Combination Expands Options for mIDH1 Relapsed or Refractory AML

By ***Nichole Tucker***

Durable remissions were shown in patients with high-risk, relapsed or refractory, *IDH1*-mutant acute myeloid leukemia (AML) treated with the experimental combination of olutasidenib and azacitidine in multiple studies.

"Olutasidenib plus azacitidine showed a notable overall response rate in 51% of patients, with a median overall survival of 12.9 months, a significant milestone in the treatment of relapsed/refractory AML using a targeted combination approach," **Justin M. Watts, MD,** an oncologist in the Division of Hematology, Department of Medicine, at the University of Miami Hospital told *Blood Cancers Today*.

Findings come from pooled data from three cohorts of patients with relapsed or refractory *IDH1*-mutant AML treated in a phase II study and two cohorts of patients from a phase I study. All cohorts received the same dose of the combination, which consisted of olutasidenib, 150 mg, twice daily for 28-day cycles and azacitidine, 75 mg/m^2, daily for seven consecutive days in 28-day cycles. The analysis cohort included 67 patients who were treated at 32 sites across the United States and Canada and in Europe and Asia Pacific. Twenty of the patients were from the phase I study, and 47 were from the phase II study.

Results show that 21 of 67 patients achieved a complete response (CR) or CR with partial hematologic recovery (CRh), resulting in a CR/CRh rate of 31% (95% CI, 21%-44%). The median duration of CR/CRh was 14.7 months (95% CI, 4.6-not reached). CR only occurred in 27% of patients (95% CI, 17%-39%), with a 20.3-month median duration of CR (95% CI, 3.7-not reached).

"A subset of patients had a very durable response, and we are working to understand who these patients are that have the greatest benefit," said Watts.

The subset analysis observed 51 patients with relapsed or refractory AML who had prior exposure to olutasidenib. In the subset, the CR/CRh rate was 37% (95% CI, 24%-52%), and the CR rate was 31% (95% CI, 19%-46%). The result was an overall response rate of 59% (95% CI, 44%-72%).

Treatment with the combination of olutasidenib and azacitidine also led to transfusion independence in some patients. In the overall study population, patients who achieved a CR/CRh had a 64% rate of transfusion independence, and those who were transfusion dependent at baseline had a 57% rate of transfusion independence after treatment.

According to Cortes et al, olutasidenib plus azacitidine has a well characterized and manageable safety profile. Any-grade treatment-emergent adverse events (TEAEs) occurred in 97% of patients, and grade 3/4 TEAEs occurred in 90%.

The most common any-grade hematologic AEs included decreased platelet count (39%), decreased red blood cell count (27%), and decreased neutrophil count (25%). The AEs were high grade in 37%, 25%, and 24% of patients, respectively. The most common nonhematologic AEs were nausea (52%), constipation (42%), and vomiting (40%); and these AEs were grade 3/4 in 4%, 4%, and 4% of patients, respectively.

This was the first study to evaluate the efficacy and safety of an IDH1 inhibitor and hypomethylating agent in the setting of relapsed or refractory AML. The efficacy observed was deemed clinically meaningful, positioning the combination of olutasidenib and azacitidine as a new option that is molecularly targeted to treat *IDH1*-mutant, relapsed or refractory AML.

"Multiple studies are currently examining the olutasidenib plus venetoclax and azacitidine triplet in the frontline setting, which may represent the future for many patients with *IDH1*-mutated AML," Watts said.

Reference

Cortes JE, Roboz GJ, Baer MR, et al. Olutasidenib in combination with azacitidine induces durable complete remissions in patients with relapsed or refractory mIDH1 acute myeloid leukemia: a multicohort open-label phase 1/2 trial. *J Hematol Oncol.* 2025;18(1):7. doi: 10.1186/s13045-024-01657-z

Zanubrutinib Outperforms Ibrutinib in Delivering Lasting Benefit in Relapsed and Refractory CLL

*By **Nichole Tucker***

Zanubrutinib continues to outperform ibrutinib in terms of efficacy among patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), and zanubrutinib has an enhanced safety and tolerability profile.[1]

"The key takeaway is not only is zanubrutinib more effective than ibrutinib in the setting of relapsed CLL, with higher response rates and longer progression-free survival [PFS], but also has significantly less atrial fibrillation, a significant cardiac side effect in patients with CLL," **Susan O'Brien, MD,** professor in the Division of Hematology/Oncology, Department of Medicine, UCI Health, told *Blood Cancers Today*.

The findings come from the phase III ALPINE study (NCT03734016), which revealed the superiority of zanubrutinib over ibrutinib in the primary analysis.[1,2] At a median follow-up of 29.6 months, zanubrutinib showed a 32% reduction in the risk of disease progression or death versus ibrutinib (hazard ratio [HR], 0.65; 95% CI, 0.49-0.86; *P*=.002).[2] Extended follow-up was conducted for 652 patients with relapsed or refractory CLL or SLL. Patients were randomized 1:1 to received zanubrutinib, 160 mg twice daily, or ibrutinib, 420 mg once daily, with no possibility of crossover.[1]

At a median follow-up of 42.5 months, the PFS rate at 36 months was 65.4% with zanubrutinib versus 54.4% with ibrutinib (HR, 0.68; 95% CI, 0.54-0.84). The PFS benefit of zanubrutinib over ibrutinib was maintained across select subgroups including high-risk patients with 17p deletions (del[17p]) or *TP53* mutations (HR, 0.79; 95% CI, 0.61-1.02). According to sensitivity analyses, the PFS benefit observed with zanubrutinib in the study may have been associated with antileukemic effect and tolerability.

The overall survival (OS) rates at 36 months were 82.6% in the zanubrutinib arm compared with 79.7% in the ibrutinib arm. The median OS was not reached for either group, but results showed that 21.1% of the zanubrutinib arm had died at the time of data cutoff compared with 25.5% of the ibrutinib arm (HR, 0.77; 95% CI, 0.55-1.06).[1]

Zanubrutinib also demonstrated a higher objective response rate (ORR) of 85.6% compared with a 75.4% ORR with ibrutinib (response ratio, 1.13; 95% CI, 1.05-1.22). Responses to Bruton tyrosine kinase inhibitor (BTKi) therapy deepened over time in both treatment arms; however, complete responses (CR) and CR with incomplete count recovery were only achieved in patients treated with zanubrutinib.

Observing safety year over year in the ALPINE study, investigators reported that the majority of adverse events were stable. Between the 36- and 48-month time points, the most common adverse events in the zanubrutinib arm versus the ibrutinib arm were infections (49.5% vs 45.1%), hypertension (21.5% vs 20.6%), COVID-19 (22.9% vs 13.7%), and bleeding (19.6% vs 21.7%).

As a result of sustained benefit after three years of treatment in the zanubrutinib arm, investigators decided to close the ALPINE study, allowing eligible patients originally assigned to receive ibrutinib to enroll in the LTE1 study (NCT04170283), which investigates zanubrutinib monotherapy in patients with B-cell malignancies.

"The final impact of the ALPINE study is that physicians will be more likely to choose zanubrutinib as their go-to BTKi in CLL," said O'Brien.

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WaveLINE-010 Trial to Evaluate Zilovertamab Vedotin in Untreated DLBCL

*By **Melissa Badamo***

The randomized, open-label, phase III waveLINE-010 trial will evaluate zilovertamab vedotin in combination with R-CHP versus R-CHOP for the treatment of previously untreated diffuse large B-cell lymphoma (DLBCL), according to a press release from Merck.[1] The trial is enrolling approximately 1,046 adult patients globally.

Zilovertamab vedotin, an investigational antibody-drug conjugate, targets the receptor tyrosine kinase–like orphan receptor 1, a protein overexpressed in several hematologic malignancies.1 The drug will be administered intravenously at the recommended phase II dose of 1.75 mg/kg.[2]

The study's primary endpoint is progression-free survival. Secondary endpoints include complete response (CR) at end of treatment, overall survival, event-free survival, duration of complete response (DOR), number of patients who experience an adverse event, number of patients who discontinue the study due to an adverse event, and change from baseline in health-related quality of life.[2]

Zilovertamab vedotin plus R-CHP demonstrated promising efficacy and safety in the phase II waveLINE-007 trial presented at the 66th American Society of Hematology Annual Meeting & Exposition. At the recommended phase II dose of 1.75 mg/kg, the combination achieved an objective response rate of 100%, a CR rate of 100%, and a 12-month DOR of 90%. Six of 15 (40%) patients experienced grade 3-4 adverse events, most commonly neutropenia. One patient had disease progression after 12 weeks of follow-up.[3]

"Following the encouraging results observed in the Phase II waveLINE-007 trial, we look forward to evaluating the potential clinical benefits of a combination regimen with zilovertamab vedotin in patients with diffuse large B-cell lymphoma compared to the current standard treatment," said **Gregory Lubiniecki, MD,** vice president of oncology clinical research at Merck Research Laboratories, in the press release.[1]

References

1. Merck announces phase 3 waveLINE-010 trial initiation evaluating zilovertamab vedotin, an investigational antibody-drug conjugate, for the treatment of patients with previously untreated diffuse large B-cell lymphoma. BusinessWire. February 6, 2025. Accessed February 10, 2025.

2. A study to evaluate zilovertamab vedotin (MK-2140) combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) versus rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in participants with previously untreated DLBCL (MK-2140-010). Clinical Trials. Last updated January 30, 2025. Accessed February 10, 2025.

3. Ozcan M, Gonzalez Barca E, Kim TM, et al. Waveline-007: dose escalation and confirmation, and efficacy expansion trial of zilovertamab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone plus rituximab in patients with diffuse large B cell lymphoma. Abstract #578. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Editor's Picks

In each issue of Blood Cancers Today*, we will take a closer look at a particular topic in hematologic malignancies. This month, section editor* ***Raajit K. Rampal, MD, PhD,*** *of the Memorial Sloan Kettering Cancer Center, highlights recent research in myelofibrosis.*

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

Raajit K. Rampal, MD, PhD

MYELOFIBROSIS

BOREAS: MDM2 Inhibitor Shows Promising Efficacy Results for Relapsed, Refractory Myelofibrosis

By **Blood Cancers Today** *Staff Writers*

Navtemadlin, a murine double minute 2 (MDM2) inhibitor, showed meaningful spleen volume reduction (SVR) and significant symptom improvements in participants with myelofibrosis (MF) who relapsed with or were refractory to Janus kinase (JAK) inhibitors, the global phase III BOREAS trial showed. Navtemadlin showed potential disease modification, with improved variant allele frequencies and bone marrow fibrosis.

"Navtemadlin is the current best orally bioavailable drug that binds MDM2, blocking p53 binding and thereby allowing activation of p53 and the induction of apoptosis," explained **John Mascarenhas, MD,** of the Icahn School of Medicine at Mount Sinai, and colleagues.

The trial was conducted across 92 global sites in 24 countries and randomized participants with *TP53* wild-type mutations (n=183) 2:1 to navtemadlin or best available therapy (BAT). Navtemadlin was administered at 40 mg/day on days 1 to 7 of a 28-day cycle, and BAT administration was the physician's choice. Crossover to navtemadlin was allowed at week 24 or the time of disease progression.

The primary endpoint was the rate of SVR ≥35% (SVR35) at week 24, and the main secondary endpoint was the rate of total symptom score reduction of 50% or more (TSS50) at week 24. Baseline characteristics were similar yet advanced across groups; both groups had median spleen volume of more than 2,000 cm2 and total symptom scores (TSS) higher than 20; more than 70% of all participants presented with a grade 2 or 3 bone marrow fibrosis score.

The primary endpoint of SVR35 by week 24 was reached by 15% of navtemadlin-treated participants versus 5% in the BAT group (P=.0815). A significantly greater number of participants achieved SVR25%, as additional clinically meaningful readout, in the navtemadlin arm (27% vs 10%; P=.012). The secondary endpoint, TSS50 at week 24, was reached by 24% in the navtemadlin group compared with 12% in the BAT-treated group. The least-squares mean difference in TSS was –5.5 (95% CI, –9.6 to 1.5; P=.0078). Variant allele frequency change of more than 50% was observed in 21% of participants receiving navtemadlin compared with 12% of those receiving BAT. Similarly, 47% of participants receiving navtemadlin showed decreased bone marrow fibrosis compared with 24% receiving BAT.

In the navtemadlin arm, 28% of participants discontinued treatment before week 24, compared with 39% in the BAT arm. Hematologic and gastrointestinal symptoms were predictable and usually resolved within approximately seven days of the treatment.

BOREAS is the first global phase III study to demonstrate clinical efficacy of a single-agent treatment for patients with relapsed or refractory MF. "There is clinically relevant efficacy and safety, with navtemadlin nearly tripling SVR35 and doubling TSS50," Dr. Mascarenhas and colleagues concluded.

The next step is adding navtemadlin to ruxolitinib, which is already ongoing in the phase III POIESIS trial (NCT06479135).

Reference

Mascarenhas JO, et al. Results from the randomized, multicenter, global phase 3 BOREAS study: navtemadlin versus best available therapy in JAK inhibitor relapsed/refractory myelofibrosis. Abstract #1000. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

PROMise: Early Results for Combination Ruxolitinib and BET-Inhibitor Treatment Show Promising Tolerability and Spleen Size Reductions in Myelofibrosis

By **Blood Cancers Today** *Staff Writers*

Combining the bromodomain and extra-terminal motif (BET) inhibitor OPN-2853 with ruxolitinib reduced spleen size in participants with advanced myelofibrosis (MF) who have not adequately responded to ruxolitinib alone in a phase I trial. Early results indicated that the combination therapy is generally well tolerated, with manageable adverse events and spleen length reductions.

MF can cause splenomegaly and a high symptom burden in many cases despite advances with ruxolitinib treatment. In murine models, the combination of BET inhibitors with ruxolitinib provided synergistic clinical effects. Building on that finding, the PROMise trial (EudraCT 2019-000916-27) aims to examine the safety and preliminary efficacy of adding BET inhibitor OPN-2853 to ruxolitinib for treatment of participants with advanced MF and poor responses to ruxolitinib as a single agent. **Adam Mead, MD, PhD,** of the University of Oxford, presented the interim results of the ongoing, phase I, multicenter, clinical PROMise study.[1]

The trial aims to recruit a maximum of 60 participants receiving stable doses of ruxolitinib to establish safe and tolerable doses of OPN-2853 at 20 mg, 40 mg, or 60 mg daily. As of February 2024, 16 participants had been recruited, treated, and evaluated.

Of the 16 participants who were receiving OPN-2853, seven presented with thrombocytopenia. One case of dose-limiting toxicity of unknown origin and one case of dose-limiting toxicity due to an elevated liver transaminase level were observed. A single death with a disease-related cause was reported. Adverse events tended to be tolerable. The most frequent grade 3 events were reduced platelet counts (31%) and anemia (12.5%). In the subset of 12 participants who could be evaluated for change in spleen length, there was a median spleen reduction of 5 cm (range, 0–10 cm).

"The combination of OPN-2853 (formerly PLX2853) and rituximab was well-tolerated, with the majority of so far included participants completing 8 cycles and encouraging levels of spleen reduction," Dr. Mead and colleagues concluded.

Reference

Mead AJ, et al. Interim analysis of promise, a clinical study combining the BET inhibitor OPN-2853 with ruxolitinib in patients with advanced myelofibrosis experiencing an inadequate response to ruxolitinib. Abstract #3186. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

Transfusions Have Major Impact on Quality of Life for Patients With Myelofibrosis

By **Blood Cancers Today** *Staff Writers*

Patients with myelofibrosis (MF) experience significant burdens from anemia and transfusions, which negatively affect daily activities, emotional well-being, and physical health, as shown by analysis of a patient self-report survey. Reductions in the frequency of transfusions and alleviation of anemia symptoms were identified as interventional priorities for improving quality of life.

Anemia is a frequent effect of MF that can worsen quality of life due to its symptoms and accompanying treatments. Patients with MF and anemia experience fatigue, require blood transfusions, and have an overall worse prognosis than patients with MF alone. **Thomas LeBlanc, MD, MA,** of the Duke Cancer Institute, and colleagues used an online self-report survey to investigate the impact of anemia on the quality of life of patients with MF.[1]

The investigators surveyed 155 patients with symptomatic MF with and without anemia of all transfusion-dependence statuses from six countries who had previously received Janus kinase (JAK) inhibitors. Survey questions and answers were derived from a targeted literature review.

Most patients with anemia (n=133) and patients without anemia initially (n=19) reported that anemia-related symptoms negatively affected their daily activities, exercise, ability to think, and emotional well-being. Similarly, 81% of patients with anemia and 63% of those without anemia felt that relieving anemia was "extremely" or "quite a bit" important in their overall treatment.

Transfusions were experienced as "extremely" or "quite a bit" bothersome by most (60%) patients, regardless of whether they had ever received one. Transfusion-dependent patients (receiving transfusions at least once every three months) indicated that their top concerns were reducing stress caused by emotional issues, sleep disturbances, health insurance, and daily activities. Overwhelmingly, 80% of patients thought that reducing transfusions to once every 16 weeks was "extremely" or "quite a bit" important.

Overall, perceived anemia symptom burden, the bothersome nature of transfusions, and their impact on daily life were central to most patients.

"Our findings highlight the importance of treatment options that can help achieve and maintain transfusion independence for MF patients," Dr. LeBlanc and colleagues concluded.

Reference

LeBlanc TW, Collacott H, García Gutiérrez V Sr, et al. Experienced or perceived burdens and associated quality of life impacts of anemia and transfusion dependence in myelofibrosis: a patient self-report survey analysis. Abstract #3815. Presented at the 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, California.

HemOnc Happenings

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

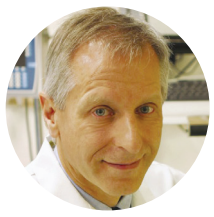
Hematologists Honored at 2025 Tandem Meetings

*By **Melissa Badamo***

Several hematologists were recognized for their contributions to the fields of hematopoietic stem cell transplantation (HSCT) and cellular therapy at the 2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR. The annual meeting took place February 12-15, 2025, in Honolulu, Hawai'i.

ASTCT Lifetime Achievement Award

Joseph Antin, MD, of the Dana-Farber Cancer Institute, received the ASTCT Lifetime Achievement Award for his contributions to the field of blood and marrow transplantation. Dr. Antin's clinical interests include aplastic anemia, bone marrow failure, graft-versus-host disease (GVHD), and stem cell and bone marrow transplantation.



Joseph Antin, MD

"This award by my peers in recognition of 40+ years of work could not be more meaningful to me," Dr. Antin told *Blood Cancers Today*. "Transplantation has provided me with wonderful colleagues and friends and a fantastic journey making transplantation safer and more effective."

CIBMTR Distinguished Service Award

Fernando Barroso Duarte, PhD, head of the Hematology and Bone Marrow Transplant Service at Walter Cantídio University in Brazil, received the CIBMTR Distinguished Service Award for his contributions to CIBMTR's mission to advance hematopoietic cell transplantation and cellular therapy research worldwide.

Fernando Barroso, Duarte, PhD

Dr. Duarte established the Bone Marrow Transplant Service at the Hospital Universitário Walter Cantídio in partnership with Hemoce and currently serves as president of the Brazilian Society of Cell Therapy and Bone Marrow Transplant (SBTMO).

"This award is an honor to me and my team, because it recognizes the work that we are doing in the northeast of Brazil, a very poor region," Dr. Duarte told *Blood Cancers Today*. "Many other colleagues from other countries have merit to receive this award, and we represent all of them, especially in Latin America. We did more than 900 HSCTs and an academic CAR-T [chimeric antigen receptor T-cell therapy] in the Hospital Universitário Walter Cantídio/Universidade Federal do Ceará with Hemoce. It's very important our strength with partnership of SBTMO with ASTCT and CIBMTR."

ASTCT Public Service Award

Marcos de Lima, MD, director of the Blood and Bone Marrow Transplant and Cellular Therapy Program at the Ohio State University Comprehensive Cancer Center, and **Mary Flowers, MD,** professor emeritus at the Fred Hutchinson Cancer Center, Seattle, Washington, received the ASTCT Public Service Award for advancing the interests of the bone marrow transplant and cellular therapy field.

Marcos de Lima, MD

Mary Flowers, MD

Dr. de Lima's clinical and research focus includes HSCT for patients with leukemia. He also serves as a professor in the Division of Hematology at The Ohio State University College of Medicine.

"The award reflects our work with collaborators in Latin America, especially in Brazil. We have been involved in a variety of training and program development initiatives there, most recently with helping advocate and 'jump start' cellular therapy ideas with point-of-care manufacturing, enabling local creation of innovative ecosystems," Dr. de Lima told *Blood Cancers Today*. "I share the award with Dr. Mary Flowers, who also happens to be Brazilian like myself—and who has trained generations of Latin American physicians in addition to her contributions in the field of GVHD."

Dr. Flowers pioneered and established a public HSCT clinical and research program in Rio de Janeiro, Brazil, before immigrating to Seattle in 1987. Her clinical focus includes chronic GVHD and other effects of HSCT.

"I am deeply honored and grateful to receive the ASTCT 2025 Public Service Award, of which I have been a proud member since its establishment in 1993," Dr. Flowers told *Blood Cancers Today*. "Such merit does not belong to an individual alone, as it represents the efforts and contributions of hundreds of people from a variety of disciplines with whom I have had the privilege of collaborating with and mentoring from all parts of the word."

Dr. Flowers also provided advice for young investigators. "Find your own niche of interest in HSCT, work very hard, know your strength and weakness, and surround yourself with bright and good people," she said.

Reference

Awards. Tandem Meetings |Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR. Accessed February 10, 2025. https://www.tandemmeetings.com/About/Awards

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

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increased Early Mortality

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

Cytokine Release Syndrome

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

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

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

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

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

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

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

Neurologic Toxicities

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

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

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

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

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

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

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

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

Parkinsonism

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

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

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

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

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

Guillain-Barré Syndrome

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

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

Immune Mediated Myelitis

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

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

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

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

Monitor patients for signs and symptoms of peripheral neuropathies.

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

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

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

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

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

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

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

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

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

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

CARVYKTI REMS

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

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

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

Prolonged and Recurrent Cytopenias

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

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

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

Infections

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

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

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

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

Viral Reactivation

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

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

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

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

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

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

Use of Live Vaccines

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

Hypersensitivity Reactions

Hypersensitivity reactions occurred following treatment with CARVYKTI.

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

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

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

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

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

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

Effects on Ability to Drive and Use Machines

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

CARTITUDE-4

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

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

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

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

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

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

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

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.

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

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

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

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

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

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

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

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

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

[k] Headache includes Headache and Tension headache.

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

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

[n] Hypotension includes Hypotension, and Orthostatic hypotension.

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

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

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

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

CARTITUDE-1

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

REFERENCES

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

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

Prolonged and Recurrent Cytopenias

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

Infections

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

Hypersensitivity Reactions

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

Secondary Malignancies

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

Advise patients of the need to:

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

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

Marketed by:
Legend Biotech
Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

cp-258863v5

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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

POWERFUL. DEEP. DURABLE.

After a One-Time Infusion[1-3]

CARTITUDE-4 demonstrated*:

POWERFUL

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

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

DEEP

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

DURABLE

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

Safety profile

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

CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.

*Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.

†Based on a stratified Cox proportional hazards model. An HR <1 indicates an advantage for CARVYKTI® arm. For all stratified analyses, stratification was based on investigator's choice (DPd or PVd), ISS staging (I, II, III) and number of prior lines (1 vs 2 or 3) as randomized.

SELECTED IMPORTANT SAFETY INFORMATION

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

cp-300288v4

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