TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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June 2025

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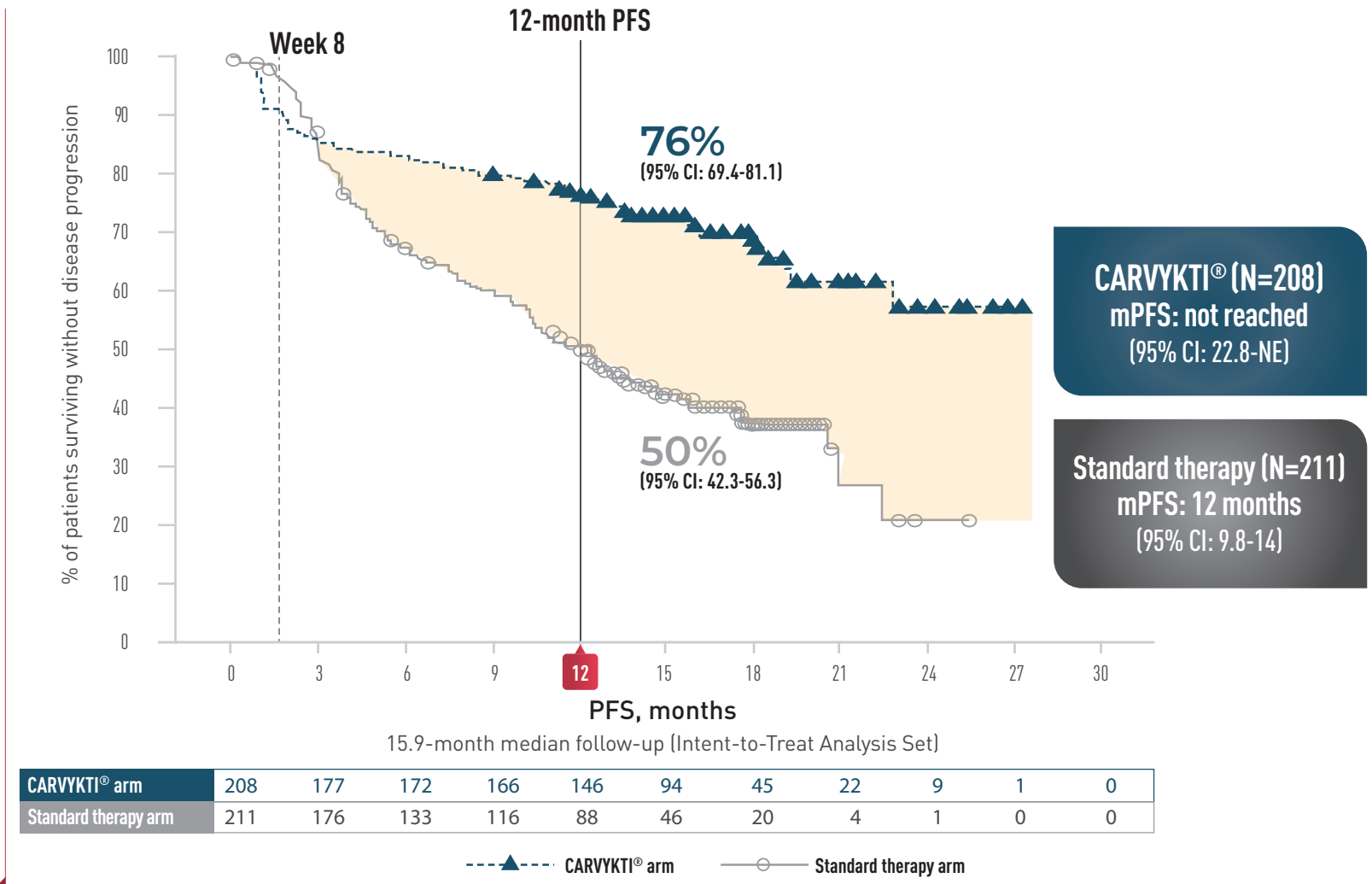
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

POWERFUL RESULTS

In CARTITUDE-4 AT 15.9 MONTHS

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

PROGRESSION-FREE SURVIVAL



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

CARVYKTI® demonstrated a

↓59%

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

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

SELECTED IMPORTANT SAFETY INFORMATION

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

cp-300288v4

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

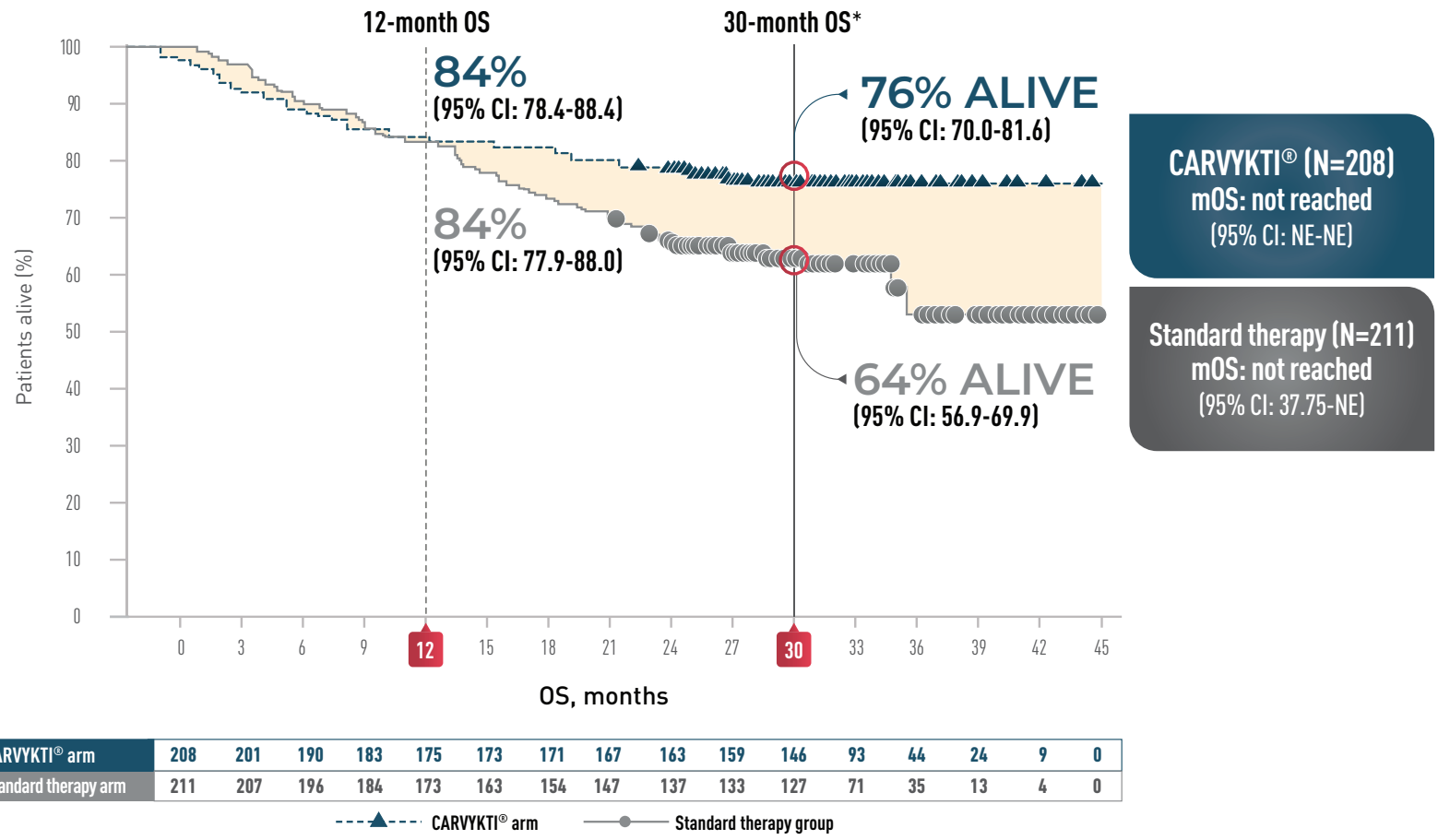
CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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

IN CARTITUDE-4 AT 33.6 MONTHS*

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

OVERALL SURVIVAL[1-4*†]



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

CARVYKTI® arm — Standard therapy group

CARVYKTI® demonstrated a

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

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

SELECTED IMPORTANT SAFETY INFORMATION

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

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CARVYKTI®
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IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CARVYKTI®
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IMPORTANT SAFETY INFORMATION (CONT'D)

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

cp-258862v9

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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

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

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LEGEND BIOTECH

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Novel Radiotherapy Offers Strong AML Combo Therapy Backbone
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Vinay Prasad Named Director of FDA's Center for Biologics Evaluation and Research
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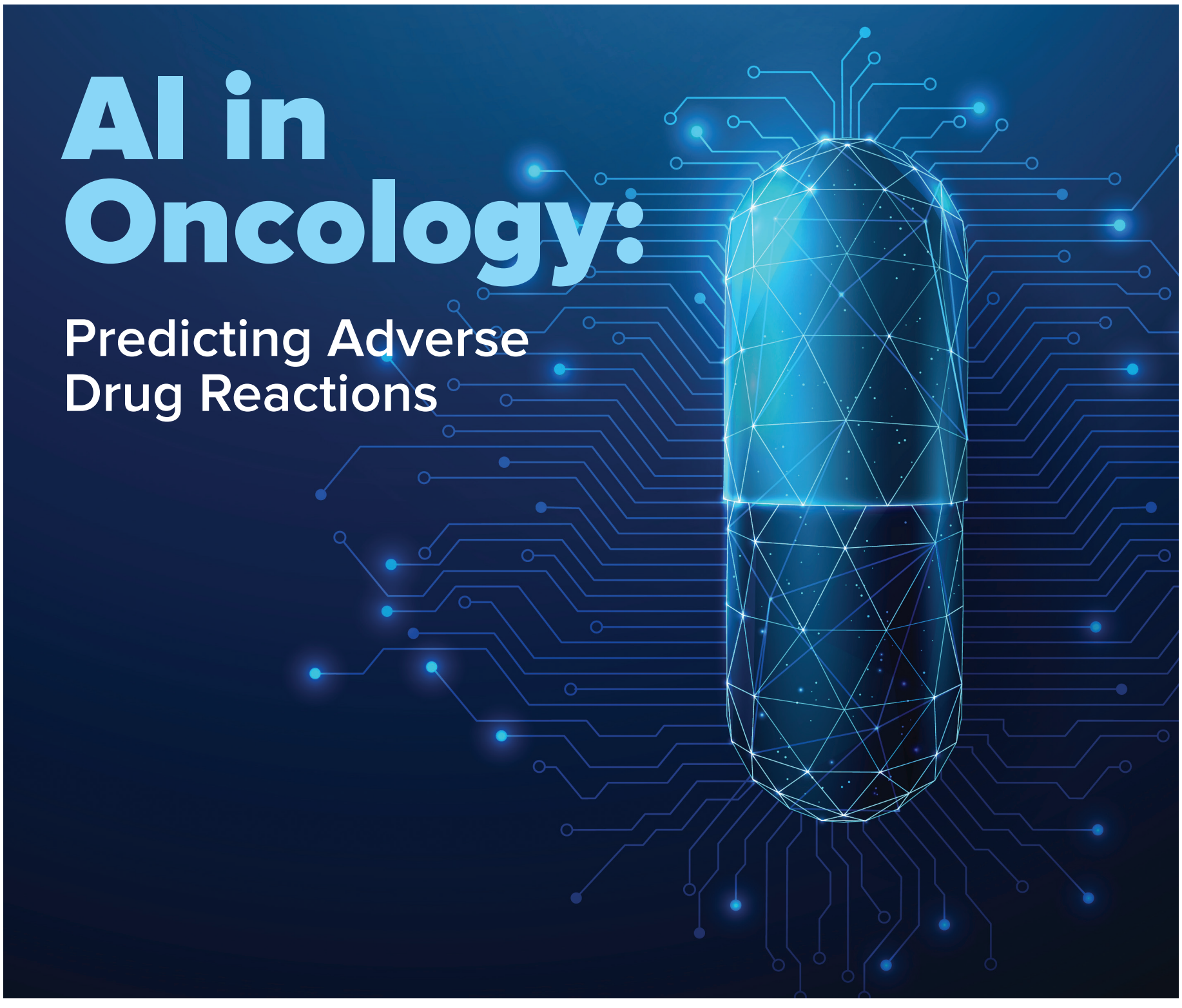
AI in Oncology:

Predicting Adverse Drug Reactions



MAIL TO:

KRINA K. PATEL, MD, MSc & RAHUL BANERJEE, MD, FACP :
Turning Corners in Myeloma Care

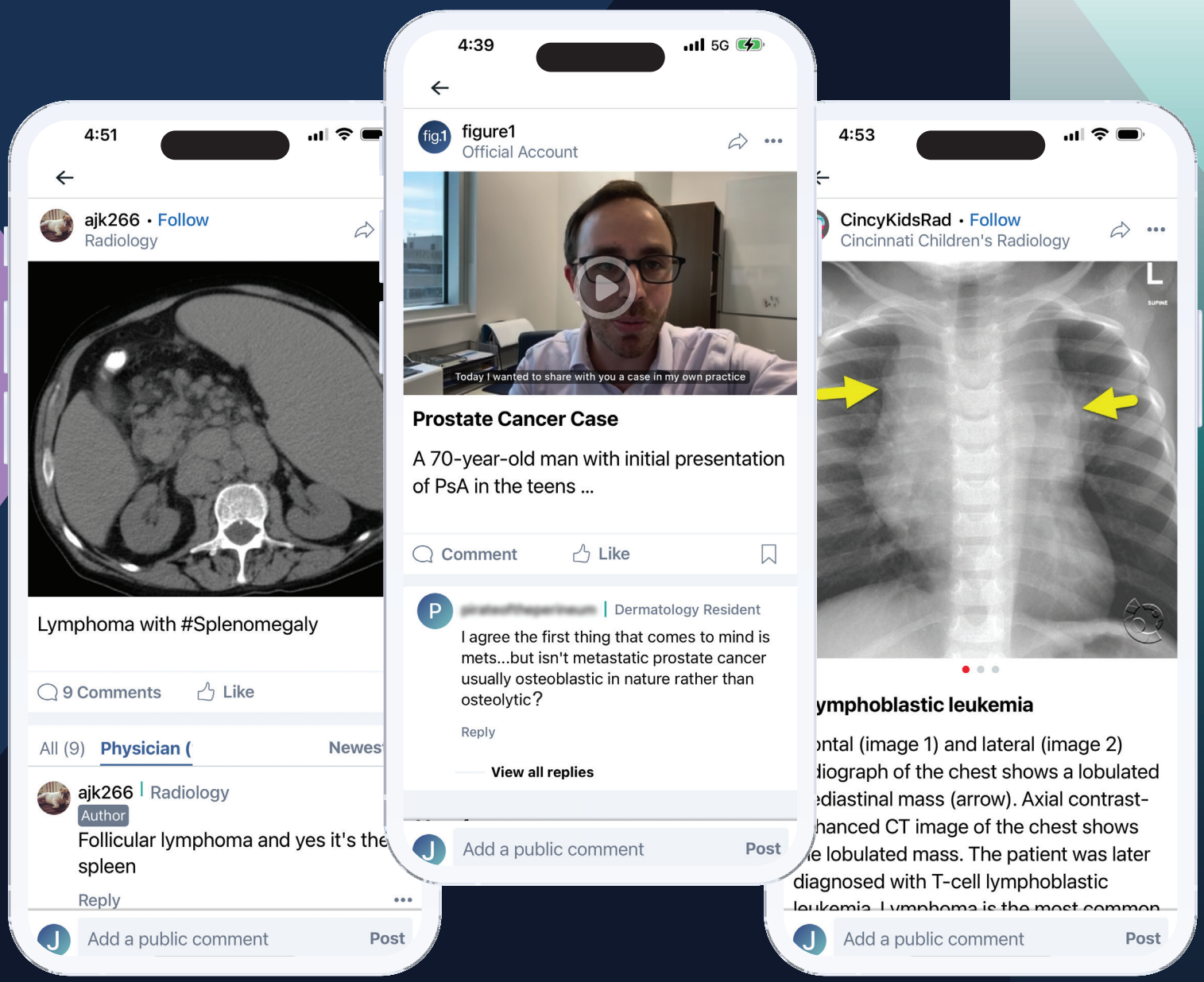
figure1

Where Clinicians Come to Collaborate

New!
Video case posts are here.

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

figure1



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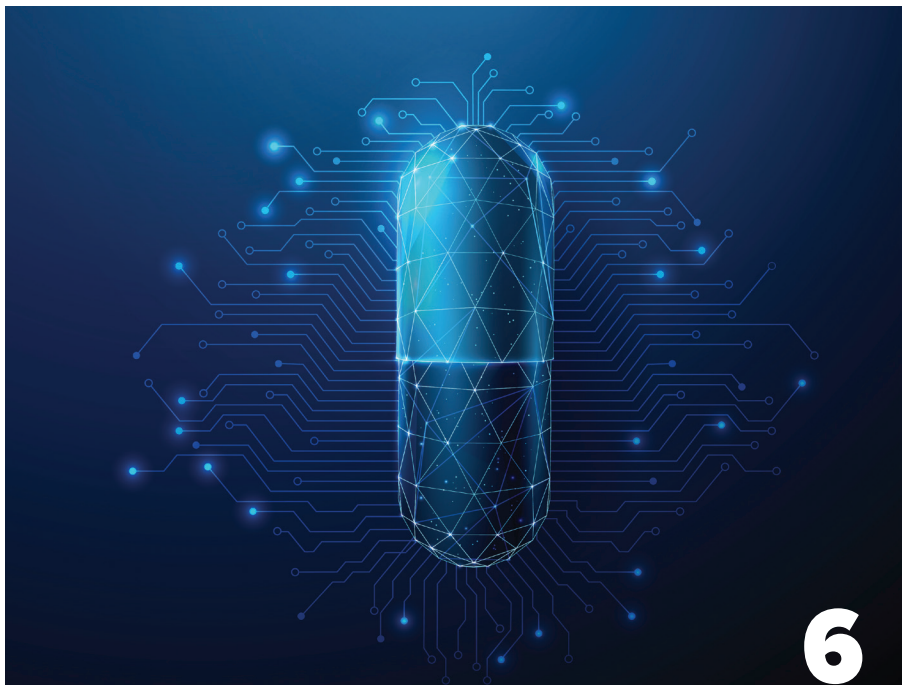

AI in Oncology:

Predicting Adverse Drug Reactions

Adverse drug reactions represent a significant challenge in the treatment of hematologic malignancies. The advent of artificial intelligence technologies such as machine learning, deep learning, and natural language processing has opened new avenues for predicting adverse drug reactions with greater accuracy and efficiency.

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News

GET TO KNOW

Bhavana Bhatnagar, DO

Dr. Bhatnagar, Director of Hematology and Medical Oncology at the West Virginia University Cancer Institute at Wheeling Hospital, discussed why she pursued a career in hematology oncology and the differences between working at an academic medical center versus a community-based setting.
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Calendar

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

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

September 13
Leukemia & Lymphoma Society National Blood Cancer Conference
Virtual

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

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

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

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

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

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

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

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

October 23-26
JADPRO Live
National Harbor, MD

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

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Editor's Message

Turning Corners in Myeloma Care

Krina K. Patel, MD, MSc
Co-Editor-in-Chief of Blood Cancers Today

Rahul Banerjee, MD, FACP
Associate Editor of Blood Cancers Today
and Host of "The HemOnc Pulse"

By: ***Krina K. Patel, MD, MSc*** *and* ***Rahul Banerjee, MD, FACP***

This year's presentations on multiple myeloma at the American Society of Clinical Oncology (ASCO) Annual Meeting, particularly the phase 3 studies, are a testament to the remarkable evolution of the treatment landscape. From deepened measurable residual disease (MRD) responses to the promise of one-time cellular therapies, the research shared offers both clinical depth and hope for a future in which multiple myeloma may not only be managed but potentially cured.

One of the central themes across several studies is MRD—specifically the relevance of achieving and sustaining MRD negativity at increasingly sensitive thresholds (10^{-5} and 10^{-6}). In the MIDAS trial, investigators examining an MRD-adapted strategy using isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) showed that patients who had achieved MRD negativity after six induction cycles did not see deepened MRD benefits from autologous stem cell transplantation (ASCT) compared with IsaKRd consolidation alone. The same principle applied for patients who did not achieve MRD negativity with regard to a tandem ASCT versus single ASCT. Although we await data on sustained MRD negativity and progression-free survival (PFS), this strategy holds promise for personalizing care and potentially sparing some patients from the toxicities of ASCT in the future.

The mode of administration for these novel therapies is also receiving attention, with the IRAKLIA study addressing a longstanding concern: the patient experience during monoclonal antibody infusion. Isatuximab delivered subcutaneously demonstrated noninferiority in efficacy and pharmacokinetics compared to intravenous administration, with fewer infusion-related reactions and greater patient satisfaction. With comparable safety and no new adverse signals, subcutaneous isatuximab via an on-body delivery system (which does not require as much active attention from nurses during administration) offers not only convenience, but also potential improvements in clinical workflow—and possibly an avenue toward home-based self-administration in the future.

Perhaps the most paradigm-shifting data in myeloma came from the CARTITUDE-1 study, which reported 5-year follow-up data for patients with heavily pre-treated multiple myeloma with a median of six prior lines of therapy following a single infusion of ciltacabtagene autoleucel (cilta-cel). Remarkably, 33% of patients remain alive and disease-free at five years. This is the first compelling evidence in a prospective trial from the modern era suggesting a potential cure with chimeric antigen receptor (CAR) T-cell therapy for myeloma, a disease historically defined by inevitable relapses. Future work is needed to identify and mitigate risk factors for delayed toxicities and complications following CAR-T therapy, including parkinsonism and second primary malignancies. Regardless, the durability of responses seen in CARTITUDE-1 is both scientifically and emotionally profound.

Together, these studies underscore the dual pillars shaping the future of myeloma care: personalized, MRD-guided strategies and innovative therapies capable of inducing deeper, more durable remissions. Although questions remain—particularly around long-term outcomes and sequencing—these data hint at a treatment era in which decisions are based not only on staging at diagnosis, but also on biologic response over time. Even for patients with multiple prior relapses, ASCO 2025 has shown us that the future of myeloma is brighter than ever—and for some patients, the elusive goal of a cure may be within reach.

Rahul Banerjee, MD, *is a physician and researcher specializing in multiple myeloma, a blood cancer that affects plasma cells and can lead to bone and kidney complications. He also treats patients with AL amyloidosis, a related but less common condition that requires a multidisciplinary approach involving specialists in oncology, nephrology, and cardiology.*

Krina Patel, MD, MSc *is an Associate Professor in the Department of Lymphoma and Myeloma within the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas. She is a dedicated physician-scientist whose research focuses on advancing treatments and improving outcomes for patients with multiple myeloma and other plasma cell disorders, including POEMS syndrome, Waldenström's macroglobulinemia, plasmablastic lymphoma, and amyloidosis.*

Bhavana Bhatnagar, DO

Bhavana "Tina" Bhatnagar, DO, director of Hematology and Medical Oncology at the West Virginia University Cancer Institute at Wheeling Hospital, sat down with *Blood Cancers Today* for a deep dive into her career trajectory and clinical interests. Dr. Bhatnagar discussed why she pursued a career in hematology-oncology, her current research on rural disparities in acute myeloid leukemia (AML), and the differences between working at an academic medical center versus a community-based setting.

By ***Melissa Badamo***

Where did you grow up, and when did you know that you wanted to become a hematologist-oncologist?

I grew up in a suburb of Pittsburgh. It was a really nice, idyllic childhood. My mom is a neurologist, so medicine has always been a part of my life for as long as I can remember. My mom used to take me along with her when I was much younger, so I had a chance to go to hospitals and see patients when I was under the age of 10.

I knew early on that I wanted to be a physician. I leaned away from neurology because I've always had a special place in my heart for people with cancer, which was sparked by things I would watch on TV when I was younger. I would watch human interest stories on patients and families struggling with cancer. I remember as a kid thinking, "When I grow up, I'm going to help those people."

During my college years and in medical school, I had impactful interactions with patients who had acute leukemia. Those patients are usually in the hospital for such a long period of time when they're initially diagnosed, which is unique in oncology because most patients with cancer are treated in the outpatient setting. But acute leukemia patients spend several weeks in the hospital, and if you're a rotating medical student or a resident, you develop very powerful, intimate relationships with the patients and their families from the time they're diagnosed to the time they leave the hospital and beyond. It was those relationships and the opportunity to care for those people that drove me.

Were there any mentors who shaped your career path?

I've been fortunate to have many mentors in different areas of hematology help shape my career. When I was a resident at the Cleveland Clinic, I had the opportunity to work with Drs. Mikkael Sekeres and Anjali Advani as their intern. That was the first time I rotated as a resident or as an intern on the acute leukemia service, so I got a chance to see stylistically how they practiced and how they spoke to their patients. I got to understand their thought processes, which only deepened my interest for acute leukemia.

Then, I moved to fellowship and had the opportunity to work with Drs. Maria Baer and Ashkan Emadi, who allowed me to participate in several fellow-led retrospective studies looking at hypomethylating agents [HMAs] and their place in the management of patients with acute leukemia and myelodysplastic syndromes. I then went on to my first faculty position at the Ohio State University and had a chance to work with the late Dr. Clara Bloomfield on several prognostic studies in the AML space.

I also worked under the tutelage of Drs. John Byrd, Ramiro Garzon, and Sharyn Baker, who helped provide a senior level of mentorship and guided my career. I have countless people to thank for getting me to where I currently am.

My practice setting has now moved. In my initial faculty position at the Ohio State University, I was a specialist in acute leukemia and acute lymphoblastic leukemia, as well as several other chronic leukemias and myeloproliferative neoplasms. For family/personal reasons and the opportunity to translate my skills from an academic center to a more community setting, I now work at a regional affiliate of West Virginia University Cancer Institute called Wheeling Hospital.

What are your current research interests?

While at Ohio State University, I was the lead author on a plenary presentation for the 2020 American Society of Hematology Annual Meeting & Exposition. The publication pertained to survival disparities and differences in genetics in AML between young Black AML patients and young White AML patients. That developed my interest in disparities research, and I now work primarily in Appalachia, which is diverse in the sense that this is a rural population.

There are significant issues with resources and the financial status of a lot of the patients who work here. It's a different type of setting. I'm trying to study AML biology—which seems to be a little bit worse here in Appalachia compared to other large places I've worked—and trying to determine if there are any occupational exposures or environmental exposures that could be responsible for the worse disease biology of the patients I have taken care of.

I'm also very interested in studying the incidence of clonal hematopoiesis mutations in the Appalachian population. West Virginia only has a population of 1.7 million, but there's a disproportionate amount of cancer in the region. One of my theories is that there's a lot of clonal hematopoiesis mutations, but it has not been deeply explored. I have some research projects that intend to look at clonal hematopoiesis in rural populations.

"You develop very powerful, intimate relationships with patients and their families from the time they're diagnosed to the time they leave the hospital and beyond. It was those relationships that drove me."

What are the differences between working at an academic medical center versus a community-based setting?
There are countless resources and staff at an academic medical center, which helps facilitate the care of those patients more smoothly. It's easier and faster to get a lot of things done. In a community setting, I had to transition a bit. I'm the only person in my practice to take care of patients with AML. While I still focus on acute leukemia, I did have to branch out and start taking care of patients with other types of blood cancers, which was very good for me because I got a broader scope within hematology.

Because you don't have the same staffing, laboratory-based resources, or infrastructure in a community setting, you're also trying to juggle so many other things. It's a little more challenging, and it takes longer to figure out the ropes. But my patients are very happy that I'm here because they don't have to travel very far to see somebody who specializes in blood cancers.

How has AML treatment shifted throughout your career?
It has shifted dramatically. When I was in medical school, every patient got 7+3 chemotherapy, which is a 4- to 6-week–long inpatient hospital stay. There was very little you could do for patients over the age of 65 with AML and people who had lots of comorbidities. Often times, it was hospice or low-intensity chemotherapy that wasn't very effective in treating those patients.

The biggest shift I've seen is the introduction of HMAs and targeted therapies that are designed to treat AML with specific gene mutations like *IDH1*, *IDH2*, or *FLT3*. The advent of venetoclax and HMAs has been a huge game changer. I administer a lot of that in the community and have had very good results with it. It's amazing how many drugs have gotten approved.

"Even if we're not able to cure their disease, we can give [patients] more time, which allows them to do things they might want to accomplish in their lifetime. Right now, that's a win."

It's nice to have options for patients now. Earlier in my career when patients relapsed, we always had to have the hospice talk or say, "There's nothing more I can offer you." Now, it's much more gratifying to tell patients that I have potential options for them, and even if we're not able to cure their disease, we can give them more time, which allows them to do things that they might want to accomplish in their lifetime. Right now, that's a win. Hopefully, we'll move towards even better survival outcomes in the future.

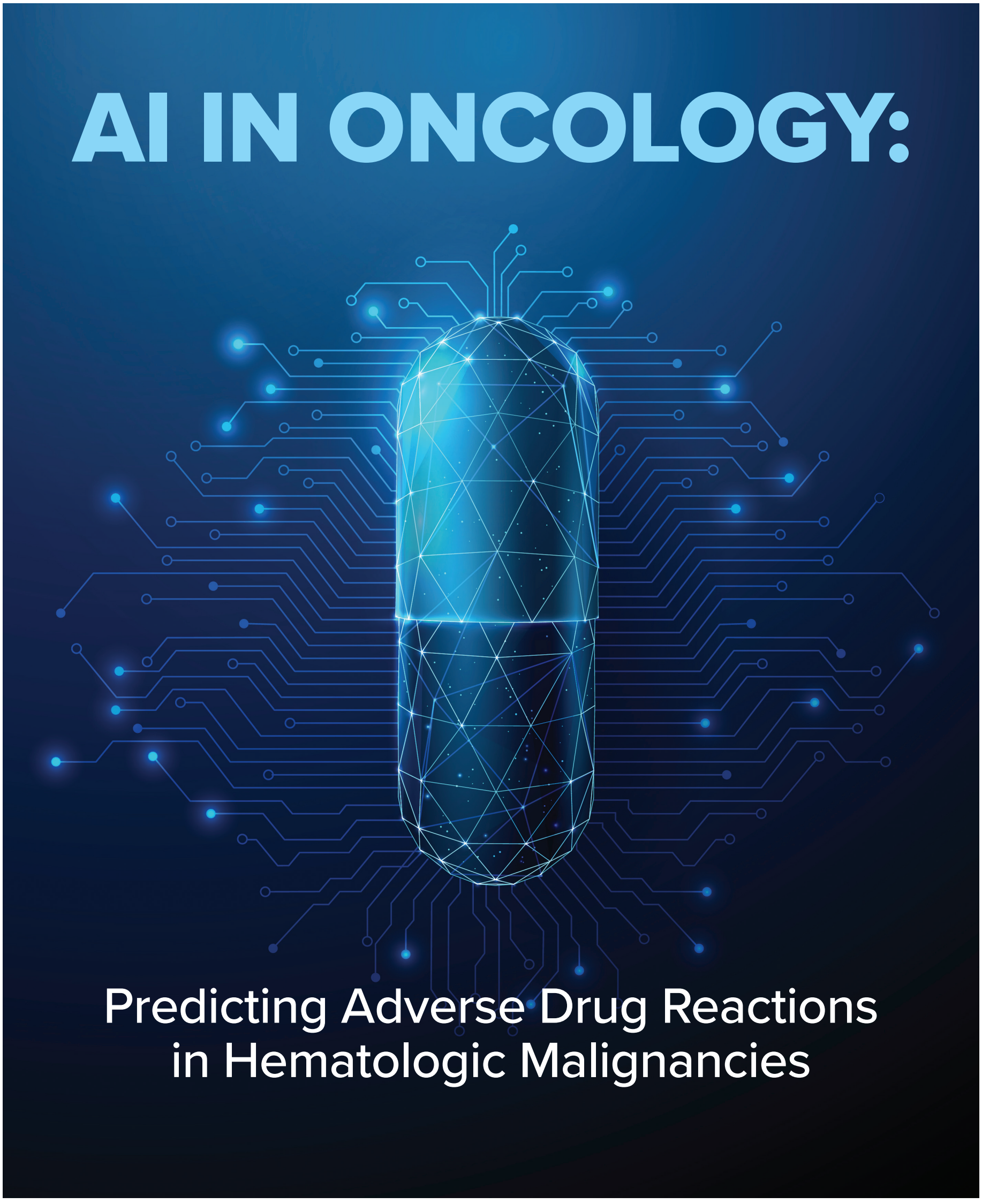
The long-term survival for patients with AML, whether they're younger or older, is still not quite where we would like it to be. I would like to see more well-tolerated treatments and treatments that keep patients out of the hospital when they're initially diagnosed. Patients with AML spend a lot of time in the hospital for either induction chemotherapy, complications related to infections, or if they move on to transplant. Having AML is such an onerous responsibility for the patient, so I'd like to see treatments that are easier and allow patients to have a good quality of life and achieve good disease control.

Do you have any hobbies outside of work that most people would be surprised to learn?
My main hobby is tutoring my kids. I have three young children aged 8, 6, and 3. Typically, my life is centered around taking care of my patients and taking care of them.

I'm hoping that once I get to a stage where they don't need me as much, I'll have a little more time on my hands. I'm hoping to develop my interest in photography and scrapbook making. I want to make each of my kids a scrapbook every few years, so they can have something to share with other people when they get older. It's nice to tap into whatever creative faculties you have and make good memories!

In Focus

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



By ***Christos Evangelou, PhD***

Adverse drug reactions (ADRs) represent a significant challenge in oncology, particularly in the treatment of hematologic malignancies. These reactions can lead to increased morbidity and higher healthcare costs. The advent of artificial intelligence (AI) technologies such as machine learning, deep learning, and natural language processing (NLP) has opened new avenues for predicting ADRs with greater accuracy and efficiency.

Burden of ADRs in Hematologic Malignancies

ADRs are a significant concern in patients with hematologic malignancies because of the cytotoxicity of anticancer drugs, the high rates of infections, and the complications associated with infections.[1,2] The prevalence of ADRs in patients with hematologic malignancies is high, with up to 85% of patients undergoing treatment experiencing grade 3 or 4 ADRs.[3]

"For patients with hematologic malignancies, AI systems provide critical real-time monitoring of dangerous complications," explained **Viola Dsouza, PhD,** a researcher at Maastricht University specializing in the use of AI for pharmacovigilance. "Algorithms have been developed to predict thrombocytopenia, neutropenia, and cytokine release syndromes based on patient profiles and treatment regimens; for instance, CAR [chimeric antigen receptor] T-cell therapies and kinase inhibitors."

ADRs can negatively influence treatment outcomes in patients with hematologic malignancies. Blood cancer treatments such as chemotherapy and stem cell transplantation can disrupt the gut microbiota, potentially leading to negative treatment outcomes and increased infection risks.[4] This microbiota disruption can affect drug metabolism and efficacy, as well as modulate the host immune response, which is crucial for treatment effectiveness.[4] Furthermore, ADRs impose a financial burden on patients and healthcare systems, increasing healthcare costs due to additional treatments and hospitalizations.[5]

Challenges With conventional ADR Prediction Approaches

Traditional approaches for predicting ADRs rely heavily on clinical expertise and data from pharmacovigilance systems and population-based studies.[6–8] However, these methods often fail to capture the complex interplay of factors contributing to ADR risk in individual patients. The heterogeneity of blood cancers and the variability in patient responses to treatment further complicate the prediction of ADRs using conventional methods.[6–8]

"A key barrier to the development of reliable ADR prediction models is data heterogeneity," noted Dr. Dsouza. "The development of generalizable models in hematologic malignancies is hampered by differences in electronic health record systems, inconsistent terminology, such as ICD versus SNOMED, and inconsistent reporting of lab values or genomic data."

AI Technologies in ADR Prediction

Bart Westerman, PhD, an Associate Professor at Amsterdam University Medical Center, and his team used data from the FDA Adverse Event Reporting System (FAERS) to train a convolutional neural networks (CNN) model to predict adverse events for combination therapies. According to Dr. Westerman, AI technologies can identify patterns and risk factors based on vast amounts of data from diverse sources and can therefore address some of the challenges with conventional ADR prediction approaches.

What is the role of machine learning in ADR prediction?

Machine learning algorithms, such as logistic regression, decision trees, and artificial neural networks, have been used to predict chemotherapy-induced ADRs using demographic, clinical, and pharmacological data from electronic health records (EHRs).[9] **Jeongah On**, of Seoul National University, and colleagues analyzed 6,812 chemotherapy cycles from 935 adult patients treated with four chemotherapy regimens to train three machine learning algorithms (logistic regression, decision tree, and artificial neural networks) to develop predictive models. In validation studies, machine learning models achieved an area under the curve (AUC) of 0.62-0.83 for predicting ADRs, with logistic regression models performing best.[9]

Deep learning, a subset of machine learning that uses artificial neural networks to process and analyze information, has also shown promise in predicting ADRs, owing to its ability to process large and complex datasets.[10] A study using deep neural networks (DNNs) achieved a mean validation accuracy of 89.4% in predicting ADRs across various drugs.[10] The DNN models integrated gene expression data from the Open TG-GATEs database and FDA adverse event reports from the FAERS database.[10]

Can AI predict ADRs from pharmacovigilance data?

Pharmacovigilance databases are a valuable resource for training data in ADR prediction models, as they contain vast amounts of data on drug safety and adverse events. Machine learning models have been increasingly used to extract patterns and predict ADRs from pharmacovigilance data.[12]

In a recent study, Dr. Dsouza and colleagues synthesized findings from 13 studies using various machine learning algorithms (regression-based, flexible, and ensemble models) to predict ADR in hospitalized patients.[12] Meta-analysis showed pooled sensitivity and specificity of 78.1% and 70.6% for development-only studies, while externally validated models performed better, with 81.5% sensitivity and 79.5% specificity.[12]

However, variations in data quality and heterogeneity in different pharmacovigilance databases could limit the generalizability of machine learning models for ADR prediction.[12] The authors argued that multifactorial models integrating diverse predictors (demographics, lab values, and comorbidities) are needed for improved ADR prediction.[12]

"Recent advances in AI for pharmacovigilance have shown potential in the early detection and prediction of ADRs," Dr. Dsouza explained. "Machine learning models have been used to retrieve EHRs, unstructured clinical notes, and data from pharmacovigilance databases like VigiBase and FAERS to identify ADR signals that traditional surveillance systems might have missed."

> **"AI enables us to move beyond population averages and find patient-specific drug interactions."** *—Nicholas Tatonetti, PhD, Associate Professor of Biomedical Informatics at Columbia University Data Science Institute*

NLP is a deep learning method for extracting and analyzing unstructured data. NLP algorithms pre-trained on clinical notes and discharge summaries have been used in drug safety monitoring.[11] A recent study employed a DeBERTa-based NLP model to predict ADR probability from annotated discharge summaries, achieving an AUC of 0.955.[11]

However, **Nicholas Tatonetti, PhD,** Associate Professor of Biomedical Informatics at Columbia University Data Science Institute, highlights a key challenge in this area. "The primary challenge in building these models is phenotype extraction from EHRs," he explained. "Structured fields only tell part of the story; most clinically meaningful detail, particularly about ADRs, is buried in unstructured notes. To address this, we've developed LLM-based pipelines and customized algorithms for information extraction."

Can AI predict ADRs for combination therapies?

Predicting ADRs is particularly challenging when patients receive multiple therapies. A team led by Dr. Westerman used CNNs to identify ADR patterns from 15 million patient records.[13]

"Our approach using a CNN model was aimed at capturing subtle higher-order patterns that might occur because of drug combinations," Dr. Westerman explained. "Overall, drug combinations show an additive effect, so it can be estimated what the frequency of severe adverse events would be with the limitation that this was only assessed in combinations of two drugs."

The study findings suggest that adverse drug interactions are mostly additive rather than synergistic. Pattern recognition using CNN autoencoders validated that adverse events occur in

broad, recognizable patterns rather than as isolated occurrences.[13] Benchmark analysis confirmed that even drug combinations known to be problematic primarily result in additive effects rather than unexpected toxicities.[13] The study provides a framework for the use of CNN to evaluate adverse drug interactions in patients receiving combination therapies.

However, Dr. Westerman noted that their approach has limitations. "Our statistical assessment showed that sufficient power is needed to assess the effect of drug combinations because lower frequencies for some combinations led to noisy data," he explained. "Therefore, the real-world data can be used only for frequently used drug combinations associated with sufficient adverse event data."

Commenting on their future work, Dr. Westerman said, "We are interested in bringing our approach to a personalized level by incorporating pharmacodynamics and toxicogenomics. This is challenging but also interesting since local drug effects converge to both desired as well as undesired effects in patients."

Integrating Multi-Omic Data for Personalized ADR Prediction

The integration of genomic and other -omic data with clinical information represents a promising frontier in ADR prediction. Commenting on their work on the Molecular Twin project at Cedars-Sinai, Dr. Tatonetti said, "The Molecular Twin project is a flagship initiative where we consent patients [with cancer] to donate biospecimens and clinical data, enabling us to generate multi-omic profiles, including genomics, transcriptomics, and proteomics, at scale."

The team has enrolled several thousand patients across all cancer types, including hematologic malignancies. Dr. Tatonetti explained that these data feed into predictive models of prognosis and treatment response, and as the dataset matures, it provides a unique opportunity to anticipate ADRs based on a patient's molecular and clinical context. Dr. Tatonetti added that the combination of depth (omics) and breadth (EHR data) makes this resource a foundation for individualized ADR prediction.

"For patients with hematologic malignancies, AI systems provide critical real-time monitoring of dangerous complications." *—Viola Dsouza, PhD, Maastricht University*

Can AI predict ADRs from medication label information?

To address the scarcity of machine-readable resources for ADR information, a team led by Dr. Tatonetti used natural language processing models to extract ADRs from drug labels.[14] The team compiled a machine-readable ADR database termed OnSIDES, which achieved high accuracy (F1 score of 0.90) in extracting ADRs and contains over 3.6 million drug-ADR pairs from 47,211 drug labels.[14] OnSIDES can be used to predict new drug targets, analyze ADRs by drug class, and predict novel adverse events from chemical compound structures.

Dr. Tatonetti described how his team uses AI to advance ADR prediction. "AI enables us to move beyond population averages and find patient-specific drug interactions," he explained. "We're using introspective model architectures like sparse autoencoders to help us understand not just what the model predicts but also why, allowing us to identify specific drug-drug and drug-gene interactions associated with adverse outcomes. These insights are being incorporated into the next generation of our widely-used databases, OffSIDES and TwoSIDES v2, which curate and contextualize large-scale evidence of ADRs and interactions from clinical and post-marketing data."

Practical Considerations and Challenges

Although AI models have shown potential in predicting ADRs,[12–14] the implementation of AI tools in clinical practice faces several challenges, including the requirement for extensive model validation.

"Model validation is multifaceted," explained Dr. Tatonetti. "We emphasize retrospective validation on held-out and external datasets, but we also aim for translational relevance. When possible, we test predictions using prospective laboratory systems, including patient-derived organoids and other model systems. This allows us to assess not only model accuracy but also biological plausibility before considering clinical integration."

Dr. Dsouza emphasized the importance of regulatory oversight. "Regulatory frameworks are beginning to acknowledge the transformative potential of AI in pharmacovigilance, but oncology presents unique challenges requiring tailored guidance," she said. "The FDA's recently proposed framework for AI models used in drug and biological product submissions is a significant first step towards increasing the trustworthiness, transparency, and reliability of AI-driven tools. Likewise, the European Medicines Agency via the Big Data Steering Group has published a multi-year work plan to maximize the use of AI and big data in medicine regulation."

According to Dr. Dsouza, integrating AI into a hospital setting requires not just technological readiness, but also infrastructure and culture change. "To facilitate smooth integration, hospitals must make investments in decision support systems, a strong IT infrastructure, and workforce training," Dr. Dsouza said, adding that clinicians must be equipped through targeted education on AI capabilities, limitations, and interpretation to foster confidence and responsible use. Importantly, to maintain clinician trust, the explainability of AI outputs, why a patient is flagged at risk, must be given the highest priority, she added.

Looking ahead, Dr. Tatonetti noted that the future of AI in hematologic malignancies safety lies in integration and personalization. "I anticipate continued growth in multimodal foundation models, better harmonization of real-world data, and increasing use of synthetic data to improve generalizability and fairness," he said. "But the most exciting shift will be from reactive to proactive safety to identify patients at risk for harm before treatment decisions are made."

Dr. Dsouza added that international collaboration will be crucial for the successful clinical implementation of AI models to predict ADRs. "International cooperation presents an opportunity to access rare event profiles, diverse patient populations, and drug response that strengthen model training. Collaboration can be facilitated without jeopardizing patient privacy using common data standards, federated learning models, and secure data enclaves. Building high-performing, generalizable AI tools for pharmacovigilance requires pooling data from different nations, especially in rare hematologic conditions," she concluded.

Westerman and Dsouza report no relevant financial relationships. Tatonetti reports financial relationships with CARI Health (advisor with equity).

References

1. O'Brien SN, et al. *Hematology Am Soc Hematol Educ Program*. 2003;438-472. doi:10.1182/asheducation-2003.1.438
2. Rusu RA, et al. *J Res Med Sci.* 2018;23:68. Published 2018 Jul 26. doi:10.4103/jrms.JRMS_960_17
3. Finnes HD, et al. Presented at JADPRO Live Virtual 2020. Doi:10.6004/jadpro.2021.12.3.12
4. Guevara-Ramírez P, et al. *Int J Mol Sci.* 2024;25(19):10255. doi:10.3390/ijms251910255
5. Formica D, et al. *Expert Opin Drug Saf*. 2018;17(7):681-695. doi:10.1080/14740338.2018.1491547
6. Wilke RA, et al. *Nat Rev Drug Discov*. 2007;6(11):904-916. doi:10.1038/nrd2423
7. Chamberlain C, et al. *Atkinson's Principles of Clinical Pharmacology*. 2022;Chapter 26:499-517. doi.10.1016/B978-0-12-819869-8.00036-7
8. Dsouza VS, et al. *Explor Res Clin Soc Pharm.* 2025;18:100592. Published 2025 Mar 17. doi:10.1016/j.rcsop.2025.100592
9. On J, et al. *Eur J Oncol Nurs*. 2022;56:102066. doi:10.1016/j.ejon.2021.102066
10. Mohsen A, et al. Front. Drug Discov. 2021;1:768792. doi:10.3389/fddsv.2021.768792
11. McMaster C, et al. *J Biomed Inform*. 2023;137:104265. doi:10.1016/j.jbi.2022.104265
12. Dsouza VS, et al. *Res Social Adm Pharm*. 2025;21(6):453-462. doi:10.1016/j.sapharm.2025.02.008
13. Küçükosmanoglu A, et al. *Clin Cancer Res*. 2024;30(8):1685-1695. doi:10.1158/1078-0432.CCR-23-0914
14. Tanaka Y, et al. *Med*. Published online March 27, 2025. doi:10.1016/j.medj.2025.100642

Regulatory Actions

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

FDA Grants Fast Track Designation to Oral Histone Deacetylase Inhibitor for PV

*By **Andrew Moreno***

Givinostat, developed by Italy-based global pharmaceutical company Italfarmaco S.p.A., has been granted Fast Track Designation by the FDA for the treatment of polycythemia vera (PV). The company announced this new designation in a press release.

Givinostat is an oral histone deacetylase inhibitor designed to target abnormal gene expression in patients with PV, such as the JAK2V617F mutation. Through this mechanism, the agent is meant to control excessive cell proliferation that occurs in PV, thereby improving patients' symptoms, disease burden, and long-term outcomes.

The agent has previously received Orphan Drug Designation for use in PV from the FDA and the European Medicines Agency (EMA). A phase 3 study is currently enrolling patients for clinical sites in Europe, Israel, North America, and the UK, with additional sites planned.

"[T]he FDA decision to grant givinostat Fast Track Designation underscores the urgent need for innovative treatments for PV and highlights the potential of givinostat to make a meaningful difference. We look forward to working closely with the FDA as we plan for completion of our phase 3 clinical trial," said Italfarmaco Group chief medical officer **Paolo Bettica, MD, PhD,** in the press release.

Reference

Italfarmaco. Accessed May 12, 2025. https://www.globenewswire.com/news-release/2025/05/06/3074789/0/en/Italfarmaco-Announces-U-S-FDA-Grants-Fast-Track-Designation-to-Givinostat-in-Treatment-of-Polycythemia-Vera.html

FDA Issues Fast Track Designation to First-In-Class Trispecific Antibody for Refractory Multiple Myeloma

*By **Andrew Moreno***

The FDA has granted Fast Track Designation to ISB 2001 from Ichnos Glenmark Innovation (IGI) to treat relapsed or refractory multiple myeloma (MM). This designation is specifically for adult patients who have undergone at least three prior lines of therapy, including an anti-CD38 monoclonal antibody, an immunomodulatory agent, and a proteasome inhibitor. ISB 2001 has had Orphan Drug Designation from the FDA since July 2023, and this newly received designation was announced by IGI in a press release.

ISB 2001 is a first-in-class, T-cell-engaging trispecific antibody that targets BCMA and CD38 on myeloma cells and CD3 on T cells. IGI developed this agent with its proprietary BEAT protein platform to be a treatment option for patients with MM that has progressed despite several interventions, while also having better safety than first-generation bispecifics.

"At IGI, we have long recognized the urgent need for novel treatment options, particularly for patients who have already received first-generation bispecifics or CAR T-cell therapies. Our trispecific candidate is designed to enhance tumor targeting while reducing on-target, off-tumor toxicity," said IGI president and chief executive officer **Cyril Konto, MD,** in a press release.

An ongoing phase 1, first-in-human clinical trial is evaluating ISB 2001 in patients with heavily-pretreated MM. In initial results with this agent, presented at the American Society of Hematology Annual Meeting in December 2024, showed a high overall response rate, durable responses, and favorable safety. Findings from the trial's dose-escalation portion will be presented at the 2025 American Society of Clinical Oncology Annual Meeting in June, and enrollment of patients for the dose-expansion portion of the trial is currently underway in Australia and the US.

Reference

Ichnos Glenmark Innovation. Accessed May 6, 2025. https://iginnovate.com/2025/05/03/ichnos-glenmark-innovation-igi-receives-usfda-fasttrack-designation-for-isb-2001-for-relapsed-refractory-multiple-myeloma

UK MHRA: First Approvals Granted to Belantamab Mafodotin Combos for Relapsed or Refractory Multiple Myeloma

*By **Andrew Moreno***

In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) has approved the use of belantamab mafodotin, a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate (ADC), in combination with bortezomib plus dexamethasone to treat relapsed or refractory multiple myeloma (MM) in adults who have received at least one prior therapy.

MHRA also approved the use of the conjugate in combination with pomalidomide plus dexamethasone for the same indication in adults who have received at least one prior therapy, including lenalidomide. These approvals are the first in the world for this conjugate for use in this disease.

GlaxoSmithKline (GSK) is developing and marketing belantamab mafodotin as Blenrep and announced the new approvals in a press release. This conjugate includes a humanized monoclonal antibody generated using the POTELLIGENT Technology licensed from BioWa Inc. of the Kyowa Kirin Group and applies drug linker technology licensed from Seagen Inc.

"[A]s the only BCMA-targeted ADC therapy, Blenrep has the potential, supported by robust phase III data, to extend survival and remission versus standard-of-care and redefine treatment at or after first relapse, GSK company senior vice president and global head of oncology research and development, **Hesham Abdullah, MD, MSc,** said in a press release."[1]

The MHRA approvals were based on favorable phase 3 data from DREAMM-7 and DREAMM-8; two multicenter, open-label, randomized clinical trials which compared a belantamab-mafodotin combination against a standard-of-care triplet.

In DREAMM-7, belantamab mafodotin combined with bortezomib and dexamethasone was evaluated against daratumumab plus bortezomib and dexamethasone triplet in 494 patients with MM refractory to at least one line of therapy. Over a median follow-up of 28.2 months, patients on the test combination had more grade 3 or worse severity adverse events than patients on the standard-of-care triplet at 95% versus 78%, respectively. However, the test combination produced superior median progression-free survival (PFS) of 36.6 months versus 13.4 months, respectively, and overall survival (OS) at 18 months of 84% versus 73%, respectively.[2] Median OS had not been reached in either study arm at the time of the first interim analysis, but there was an evident trend in favor of the test combination with a hazard ratio of 0.57.[3]

In DREAMM-8, belantamab mafodotin combined with pomalidomide and dexamethasone was evaluated against pomalidomide plus bortezomib and dexamethasone triplet in 302 patients refractory to at least one line of therapy, including lenalidomide. Over a median follow-up of 21.8 months, patients on the test combination had more grade 3 or worse severity adverse events than patients on the standard-of-care triplet, at 94% versus 76% respectively, and OS data were immature. However, the 12-month estimated PFS was 71% with the test combination versus 51% with the standard-of-care triplet.[4]

The FDA accepted and is currently reviewing a Biologics License Application for use of these two combinations in relapsed or refractory MM, with a Prescription Drug User Fee Act action date set for July 23, 2025.[1,5] Belantamab mafodotin combinations for relapsed or refractory MM are also under regulatory review in Canada, China, the European Union, Japan, and Switzerland.[1]

The DREAMM-7 and DREAMM-8 trials were funded by GlaxoSmithKline.

References

1. GSK. Accessed May 2, 2025. https://www.gsk.com/en-gb/media/press-releases/blenrep-belantamab-mafodotin-combinations-approved-by-uk-mhra-in-relapsedrefractory-multiple-myeloma
2. Hungria V, et al. *N Engl J Med.* 2024;391(5):393-407. doi:10.1056/NEJMoa2405090
3. Hungria V, et al. *Blood* 2024; 144 (Supplement 1): 772. doi:10.1182/blood-2024-200336
4. Dimopoulos MA, et al. N Engl J Med. 2024;391(5):408-421. doi:10.1056/NEJMoa2403407
5. GSK. Accessed May 2, 2025. https://www.gsk.com/en-gb/media/press-releases/blenrep-combinations-accepted-for-review-by-the-us-fda-for-the-treatment-of-relapsedrefractory-multiple-myeloma

Oncologists Are Resigning at Unprecedented Rates: Are Academic Medical Centers Ready to Respond?

*By **Melissa Badamo***

Studies have shown that oncologists are leaving the workforce at increasing rates in association with career dissatisfaction and growing workloads and patient care hours.

According to a 2023 survey by the American Society of Clinical Oncology (ASCO), 21% of active oncologists reported that it was "likely" or "definite" that they would leave their current practice within 2 years or reduce their clinical work hours in the next 12 months, compared with 16% of oncologists surveyed in 2013 (P=0.009). Almost half (42%) of retired oncologists had retired 2 to 4 years earlier than planned, and 56% of oncologists left their clinical practice to pursue nonclinical roles at a median age of 58 for reasons such as a lack of satisfaction with clinical practice and a desire for more work flexibility.[1]

Clifford A. Hudis, MD

Why are these percentages climbing? In ASCO's strategic plan for promoting positive and productive clinical and research environments for oncologists, **Eric P. Winer, MD,** of Yale Cancer Center, and colleagues identified high clinical expectations and administrative, research, and teaching responsibilities as contributors to clinician burnout and decreased satisfaction.[2] In 2023, a total of 68% of oncologists reported an increase in hours spent on administrative work, 57% reported an increase in total work hours, and 49% reported an increase in patient care hours.[1]

Ariela Marshall, MD

Establishing Reasonable Workloads and Increasing Clinical Support

Because administrative responsibilities such as documentation requirements can limit time for clinical care and place a greater burden on the clinician, ASCO proposes establishing reasonable clinical workloads for academic medical oncologists.[2]

Electronic Health Records

Studies have shown that although electronic health records (EHRs) are an indispensable tool used by 88.2% of office-based physicians in the U.S,[3] they are also time-consuming and contribute to oncologists' stress.[2] In fact, 47% of oncologists identified EHRs as a major work stressor.[1]

"The problem is how we use electronic records, what it does to the way we work, and the amount of time and effort it takes," **Clifford A. Hudis, MD,** CEO of ASCO, told *Blood Cancers Today,* reflecting on his own experience as a former breast cancer clinician in an academic medical center.

In Dr. Hudis' experience, the shift from paper-based records to EHRs has increased the time requirements for patient documentation, which may also decrease the number of patients oncologists see in a day.

"Every aspect of the model has been stretched in the wrong direction, placing a greater productivity burden on the physician while reducing their actual productivity," Dr. Hudis continued. "There are certainly still systems and practices where, with adequate support, people have been able to maintain volumes. But even there, that means hiring more people such as scribes."

Advanced Practice Providers

According to a 2024 survey, 42.1% of APPs and 29.3% of physicians reported burnout, and more than 50% of physicians felt that working with APPs had reduced their burnout.[4]

Ariela Marshall, MD, an associate professor of Medicine in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota, and lead author of the study, outlined her experience working with APPs as a hematologist-oncologist.

"Both at my current and immediate prior institution, we have had an APP specifically dedicated to our inpatient consult setting, which allows them to accumulate over time the very specialized knowledge necessary for these complex inpatient consults," Dr. Marshall told *Blood Cancers Today*. "Eventually, the APPs are able to see and evaluate patients independently (as a fellow would) before staffing with the attending. APPs are also able to do bone marrow biopsies, which is a significant improvement in time and workflow for a busy consult service."

APPs seeing patients for follow-up visits or chemotherapy teaching visits in the outpatient setting can allow clinicians to spend more time on "complex and intellectually challenging visits" such as new diagnoses and change of plans for disease progression, Dr. Marshall said. In the inpatient setting, APPs carrying out and billing simple visits can also allow clinicians to see new patients for consults or admissions.

However, it is important to note that association is not evidence of causation, Dr. Marshall said. "In studies we have observed that physicians who work more with APPs have reported lower burnout but that this is not yet directly attributable to APP support," she explained.

The Complexity of Burnout

While Dr. Hudis recognizes the challenges of burnout, he also warns of potential bias in studies measuring burnout.

"There has always been burnout. I think the problem is real, but there is a risk of either observer bias or awareness bias," he said. "Is burnout truly worse today than it was X years ago? Our sense, subjectively and qualitatively, is that it is worse. But in a world that likes data and evidence and numbers, we may or may not have an accurate assessment…The best we can do is ask people for their recall and to project into the future about their career plans. In all those cases, you do get a fairly consistent association between reports of burnout and either dissatisfaction or plans to make career changes."

Despite these limitations, Dr. Hudis hopes that ASCO's strategic plan can help cultivate supportive clinical and research environments for oncologists.

"Career satisfaction for academic oncologists is a critical resource for the whole world, because it is that group of people who not only deliver patient care to varying degrees but also conduct both basic and translational and clinical research," he said. "They serve as the seed of future oncologists. No matter where you are becoming an oncologist, you're being trained by an academic oncologist—somebody who's dedicated their life to education or research."

References

1. Schenkel C, et al. JCO Oncol Pract. 2023;19(11)42-42.doi:10.1200/OP.2023.19.11_suppl.42
2. Winer EP, et al. J Clin Oncol. doi:10.1200/JCO-24-02246
3. Centers for Disease Control and Prevention. Accessed April 24, 2025. https://www.cdc.gov/nchs/nehrs/results/index.html#cdc_generic_section_1-2021
4. Marshall AL, et al. Blood Adv. 2024;8(5):1179-1189. doi:10.1182/bloodadvances.2023011927
5. Association of American Medical Colleges (AAMC). Accessed May 8, 2025. https://www.aamc.org/media/38266/download?attachment

Study Finds Link Between Gut Health and Leukemia Risk

*By **Melissa Badamo***

Researchers from the Cincinnati Children's Hospital Medical Center in Ohio and the Oxford Centre for Haematology in the UK have discovered a link between gut health and leukemia risk due to rising amounts of ADP-heptose, a bacterial sugar, in the intestines of older individuals. The researchers published their findings in *Nature*.

Once circulating in the blood, ADP-heptose accelerates the expansion of *DNMT3A*-mutant, pre-leukemic blood cells by activating the receptor protein ALPK1.[1,2] *DNMT3A*-mutant hematopoietic stem cells are associated with clonal hematopoiesis of indeterminate potential (CHIP).[2]

Patients with myelodysplastic syndromes (MDS) had significantly higher ALPK1 mRNA levels in their hematopoietic stem cells compared with healthy control participants of the same age, which correlated with worse prognosis. Those with high ALPK1 expression also had more *DNMT3A* mutations.[2]

Therefore, the researchers identified the ADP-heptose–ALPK1 axis as a promising therapeutic target to prevent the progression of CHIP to leukemia.[1]

"One of our goals is to develop an ALPK1 inhibitor that can be used in humans," **Daniel Starczynowski, PhD,** director of the Advanced Leukemia Therapies and Research Center at Cincinnati Children's Hospital Medical Center and senior author of the study, said in a press release.[1]

The researchers performed experiments on mouse models to explore the mechanisms in which circulating ADP-heptose promotes pre-leukemic cell expansion. Mice with *DNMT3A*-deficient hematopoietic cells received dextran sulfate sodium that damaged the intestinal epithelial barrier, mimicking ulcerative colitis in humans. This process induced "significant expansion" of *DNMT3A*-mutant hematopoietic cells, and expansion was not observed in young mice.[2]

However, ADP-heptose is also found in individuals of all ages with irritable bowel syndrome (IBD).[2]

Using integrated flow cytometry and fluorescence microscopy, Dr. Starczynowski and colleagues also confirmed that circulating ADP-heptose in the plasma of older individuals and those with CHIP and MDS rapidly induced TIFAsome formation in leukemia cells.

Plasma from young healthy individuals did not induce TIFAsomes, but plasma from young individuals with IBD did induce TIFAsomes.[2]

"This study significantly advances our understanding about how blood cancers develop and progress, especially in older adults," Dr. Starczynowski said in a press release.[1] "The exciting news is that we also may have a way to intervene early—before these pre-leukemic cells evolve into more aggressive disease."

References

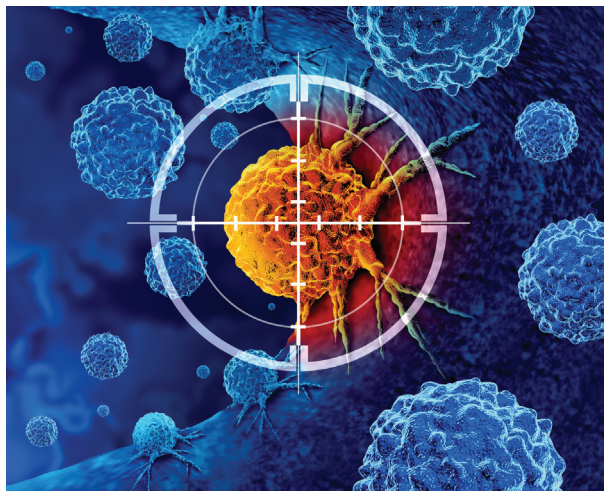
1. PR Newswire. Accessed May 16, 2025. https://www.prnewswire.com/news-releases/bacteria-in-our-aging-guts-can-elevate-risk-of-leukemia-302436300.html
2. Agarwal P, et al. *Nature*. 2025. https://www.nature.com/articles/s41586-025-08938-8

Novel Immunotherapeutic Strategy May Advance Treatment for AML, MDS

*By **Melissa Badamo***

A new study published in *Cell* highlights the potential of neoantigen-based T-cell receptor (TCR) T-cell therapies as a novel immunotherapeutic strategy for patients with myeloid leukemia.

The study was conducted in collaboration with researchers from the Memorial Sloan Kettering (MSK) Cancer Center in New York, New York, and the Fred Hutchinson Cancer Center in Seattle, Washington.



"There are currently no effective immunotherapies for most patients with MDS and AML," **Omar Abdel-Wahab, MD,** Chair of the Molecular Pharmacology Program at MSK and co-senior author of the study, told *Blood Cancers Today*. "One major limitation to developing effective immunotherapies for AML/MDS patients is the challenge in identifying cell surface proteins unique to the MDS/AML cells that are not expressed on vital normal tissues."

Identifying Neoantigens

RNA splicing factor gene mutations such as *SF3B1, SRSF2, U2AF1,* and *ZRSR2* are prevalent in AML and chronic myelomonocytic leukemia and are observed in 50% to 70% of patients with MDS, according to Dr. Abdel-Wahab and colleagues. These mutations affect alternative RNA splicing in healthy cells while creating new RNA isoforms observed across patients with the same mutations.

First, the researchers identified neoantigens derived from RNA mis-splicing in patients with *SRSF2* and *ZRSR2* mutations. Using these neoantigens, they constructed HLA-I dextramers to discover rare, circulating neoantigen-reactive CD8+ T cells in patients, examine their transcriptional characteristics, and isolate their TCRs. T cells engineered from neoantigen-reactive TCRs were ultimately able to recognize and kill *SRSF2*-mutant leukemia cells.

In Vivo Mice Models

Next, the researchers tested the antitumor activity of neoantigen-reactive TCR-T cells in vivo. In a xenograft model, mice infused with *SRSF2*-mutant AML were randomized to receive phosphate-buffered saline (PBS; n=5), cytomegalovirus-reactive TCR-T cells as a specificity control (n=5), or CLK3 TCR9-T cells (n=8). Mice treated with CLK3 TCR9-T cells had a "significantly lower tumor burden" compared with mice that received PBS or CMV TCR-T controls.

"If successful, this therapeutic approach could develop a selective cell therapy that could be administered to [more than] 50% of patients with MDS and [more than] 25% of patients above the age of 60 with AML," Dr. Abdel-Wahab told *Blood Cancers Today*.

References

1. Grisham J. Accessed May 5, 2025. https://www.mskcc.org/news/new-cellular-immunotherapy-approach-may-offer-treatment-for-aml-and-mds
2. Kim WJ, et al. *Cell*. Published online April 21, 2025. doi:10.1016/j.cell.2025.03.047

New Data from ALPINE Trial May Guide Salvage Therapy Decisions in Relapsed CLL

*By **Melissa Badamo***

Two-year follow-up data from the ALPINE trial support the use of non-covalent Bruton tyrosine kinase inhibitors (ncBTKis) as a salvage therapy option for patients with relapsed or refractory chronic lymphocytic leukemia (CLL) following treatment with zanubrutinib or ibrutinib.

Results published in *Blood Advances* showed that a short duration of covalent BTKi therapy and early disease progression were associated with a low incidence of *BTK* and *PLCG2* mutations, warranting closer evaluation of treatment with ncBTKis, such as pirtobrutinib.

Jennifer R. Brown, MD, of the Dana-Farber Cancer Institute, and colleagues collected matched baseline and peripheral blood samples from 52 evaluable patients who progressed on zanubrutinib (n=24) or ibrutinib (n=28) at a median follow-up of 25.7 months.

BTK/PLCG2 *Mutations*

While no *BTK* mutations were observed at baseline, five patients treated with zanubrutinib and three patients treated with ibrutinib acquired *BTK* mutations at disease progression. The median number of acquired mutations was three for patients treated with zanubrutinib and one for patients treated with ibrutinib.

The cancer cell fraction (CCF) of acquired *BTK* mutations, estimated by dividing the variant allele frequency (VAF) by absolute lymphocyte count/white blood cell count, was 5.31% for zanubrutinib-treated patients and 1.84% for ibrutinib-treated patients.

Most of the single-nucleotide variants in BTK (77.8%) occurred at position C481 and were more common in patients treated with zanubrutinib (n=11/14) versus ibrutinib (n=3/4). Three patients who progressed on zanubrutinib had non-C481 mutations, including *L528W* (n=2; CCF=9.58% and 17.6%) and *A428D* (n=1; CCF=37.03%).

Of the two patients on ibrutinib who acquired *PLCG2* mutations at disease progression, one had concurrent *BTK* and *PLCG2* mutations. No *PLCG2* mutations were found in patients treated with zanubrutinib.

Driver Mutations

Most patients (48/52; 92.3%) had at least one driver mutation at baseline, including *NOTCH1* (n=21), *TP53* (n=19), *BRAF* (n=10), *SF3B1* (n=8), and *ATM* (n=8). Patients had a median of three driver mutations.

At disease progression, one patient treated with zanubrutinib acquired *TP53* and *XPO1* mutations, while five patients treated with ibrutinib acquired *TP53* (n=1), *SETD2* (n=1), *SF3B1* (n=1), or *ASXL1* (n=2) mutations.

While baseline driver gene mutations were not associated with the development of *BTK* mutations, patients with two or more baseline driver gene mutations were more likely to acquire *BTK* mutations at disease progression compared to patients with fewer than two mutations.

"Among patients with relatively early relapse on ibrutinib or zanubrutinib, the known resistance mutations in *BTK* and *PLCG2* are relatively uncommon (17%)," Dr. Brown told *Blood Cancers Today*. "At present, the mechanisms of resistance that affect these patients are relatively poorly understood. We are working to try to better understand predictors of early relapse because these patients may particularly benefit from combination therapy."

Reference

Brown JR, et al. Blood Adv. 2025;9(8):1918-1926. doi:10.1182/bloodadvances.2024014206

Highlights From the **2ND ANNUAL HEMONC PULSE LIVE MAY 2-3, 2025 IN AUSTIN, TEXAS**

Blazing a Trail in Ph-ALL: Chemotherapy-Free Options Gain Ground

*By **Nichole Tucker***

The pillars of recent success in the treatment of acute lymphoblastic leukemia (ALL) include a better breakdown of high-risk subgroups and the introduction of novel therapies, according to **Nick J. Short, MD,** associate professor, Department of Leukemia at The University of Texas MD Anderson Cancer Center.

During *The HemOnc Pulse Live* held on May 2 and 3, 2025, in Austin, TX, Dr. Short gave a presentation homing in on paradigm shifts. One of the biggest paradigm shifts, according to Dr. Short, has been in the Philadelphia chromosome-positive (Ph) ALL, a rather aggressive subtype of the disease.[1]

Nick J. Short, MD

"PH-positive ALL was historically one of the most aggressive subtypes of leukemia that needed chemotherapy, allogeneic transplant, and still had relatively poor outcomes. And now we're talking about chemotherapy-free regimens where many of these patients were not transplanted," said Dr. Short.

Evolving the Treatment Landscape

In the phase 3 PhaLLCON study (NCT03589326), ponatinib plus reduced-intensity chemotherapy achieved better MRD-negative complete remission (CR) at the end of induction therapy compared with imatinib in adult patients with newly diagnosed disease.[2]

Of the 245 patients enrolled in the study, the MRD-negative CR with ponatinib was 34.4% versus 16.7% with imatinib, showing a risk difference of 0.18 (95%

CI, 0.06-0.29; *P*=0.002). Among patients treated with ponatinib, the median event-free survival (EFS) was not reached vs 29 months in the imatinib-treated patients.

Safety results showed that the two agents had similar adverse event profiles. Occurrences of arterial occlusion were observed in 2.5% of the ponatinib arm compared with 1.25% of the imatinib arm.

Another clinical trial causing a shift in the way hematologic oncologists treat Ph-ALL is the GIMEMA LAL2116 (D-ALBA) trial, which offered the chemotherapy-free option of dasatinib and blinatumomab as induction and consolidation therapy for adults with newly diagnosed Ph-ALL. According to the long-term findings published in the *Journal of Clinical Oncology,*[2] as of data cutoff, 96.5% of responders remain in complete hematologic response (CHR) at a median follow up of 48 months (range 22-64 months).

Finally, new research presented at the American Society of Hematology Annual Meeting & Exposition showed that ponatinib in combination with blinatumomab achieved high rates of MRD negativity along with durable remissions.[3] As another chemotherapy-free combination, ponatinib/blinatumomab may further shift the paradigm, according to Dr. Short.[1]

"We're now achieving a four-year survival rate of around 80% with chemotherapy-free regimens. That's an incredible shift in the treatment landscape," he said.

Future Treatment Considerations

Each year, more possibilities are being introduced at medical meetings, explained Dr. Short. However, unanswered questions remain around the power and implications of MRD, the utility of transplant in the frontline setting, and how chimeric antigen receptor (CAR) T-cell therapy factors in.[1]

Dr. Short said, "a really big factor that dictates outcomes is MRD response, and we now have better MRD tools and understanding of the dynamics during frontline therapy." At MD Anderson, research is reportedly ongoing to generate more information around the correlation between MRD and efficacy outcomes.

In terms of transplant, there is no definitive evidence to support excluding it from care, but Dr. Short noted that "in the E1910 study, there was no clear benefit of transplant—even among patients with unfavorable risk ALL. In fact, non-transplanted patients did better numerically."

As experts continue to consider the future of treatment, there is no doubt that CAR-T cells have a role. However, Dr. Short explained that their role is for a specific subgroup of patients.

"We're very interested in CAR-T cells as consolidation for high-risk frontline patients. Early data show strong expansion and very low relapse, but more investigation is needed," he stated.

References

1. Short, Nick, Acute Lymphoblastic Leukemia. Presented at: The HemOnc Pulse Live; May 2-3, 2025; Austin, TX.
2. Jabbour E, et al. *JAMA*. 2024;331(21):1814-1823. doi:1001/jama.2024.4783
3. Foa R, et al. *J Clin Oncol.* 2024: 10;42(8):881-885. doi:1200/JCO.23.01075

Can CPI Move Up in Line for Relapsed Hodgkin Lymphoma?

By ***Robert Zadotti***

Patients with relapsed or refractory Hodgkin lymphoma (HL) may have more upfront options than previously thought. According to **Philippe Armand, MD, PhD,** chief, Division of Lymphoma, Dana-Farber Cancer Institute, new research highlights exciting developments in the use of checkpoint inhibition (CPI) in HL salvage therapy.

At the 2nd Annual HemOnc Pulse Live, Dr. Armand led a discussion of new treatment options in the management of relapsed or refractory Hodgkin's lymphoma. According to Dr. Armand, incorporating CPI as a part of second-line salvage therapy rather than just as consolidation provides clear benefits to progression-free survival (PFS) rates for patients.[1]

An Evolution in Salvage Therapy

In the historical paradigm, CPI would only be used in consolidation, following the administration of chemotherapy with the intention of proceeding to autologous stem cell transplants (ASCT). Now, Dr. Armand argues all of that is about to change, with evidence showing that CPI has clear benefits as a major aspect of salvage therapy, potentially helping to avoid harsher transplants or therapies.

According to findings in a 2023 multicenter, retrospective study (36629030) of approximately a thousand patients who underwent ASCT, event-free survival was significantly higher for patients who received checkpoint inhibition as part of their salvage therapy compared to those who received BV, BV + chemotherapy or chemotherapy alone. CPI-based treatment maintained a PFS rate of around 0.8 over a 60-month range, while other treatments managed only around 0.5, or as low as 0.2 in the case of BV alone.[2]

"There have been a number of studies looking at checkpoint not as consolidation but as part of salvage therapy," Dr. Armand explained, noting "phenomenally high" response rates across all these studies.[1] To support this, he showcased a range of studies that observed an objective response rate of approximately 90%-100%. Additionally, a complete response rate of approximately 85%-95% occurred within a 2-year PFS of 70%-95%.[1]

The Value of Transplants

Amid these promising results, questions remain regarding the optimal placement of CPI as well as the role of autologous transplants in salvage treatment for relapsed or refractory HL. In the aftermath of chemotherapy, many patients may be looking for options besides transplants, and Dr. Armand isn't wholly comfortable disregarding it.

"The hard thing is this is a lot of interlocking pieces because everything we change in one place affects what happens in another," Dr. Armand cautioned. "The level of evidence we have for making recommendations or for making clinical choices is quite variable."

Dr. Armand mentioned several studies, both in pediatrics and using German data, where specially selected patients who did not receive ASCT still maintained very high PFS levels, around 90-95%. In select cases, CPI and chemotherapy may be powerful enough to eliminate the need for ASCT altogether.

The question remains: "When you have results as good as the ones that we showed you, do we need to transplant patients anymore?" For Dr. Armand, that answer is still yes. This is due to established risk stratification schemes not being applicable to these new treatments, as risk factors for survival after ASCT were identified prior to CPI integration.[3] As exciting as the potential of CPI in salvage is, Dr. Armand believes that ASCT may be the driver of such excellent outcomes, rather than something to be avoided.[1]

With the evidence presented, Dr. Armand hopes he has convinced his colleagues of the magnitude of the benefit of CPI in second-line therapy; beyond this, it'd send patients to more aggressive treatments that he'd prefer to avoid. Dr. Armand concluded, "This is your last chance to cure patients—that's really important."

References

1. Armand P, et al. Controversies & Unanswered Qs in R/R Hodgkin Lymphoma. Presented at: TheHemOnc Pulse Live; May 2-3, 2025; Austin, TX
2. Desai SH, et al. *Am J Hematol.* 2023;98(3):464-471. doi:1002/ajh.26827
3. Bröckelmann PJ, et al. *Ann Oncol.* 2017;28(6):1352-1358. doi:1093/annonc/mdx072

The Smoldering Debate: Treat or Monitor Early Myeloma Risk?

*By **Robert Zadotti***

Is it time to treat smoldering multiple myeloma (SMM) as a disease in its own right? Once considered merely a precursor to multiple myeloma, this asymptomatic condition is now under fresh scrutiny. With advances in risk stratification and growing evidence supporting early intervention, experts like **Binod Dhakal, MD, MS,** associate professor of Medicine at the Medical College of Wisconsin, believe it's time to reconsider the golden standard.

Binod Dhakal, MD, MS

At the 2nd Annual HemOnc Pulse Live, Dr. Dhakal presented on smoldering myeloma, describing it as a "heterogeneous entity" and noting its relatively recent identification as a clinical category in the 1980s.

"You would argue that most of the progression might happen in the first ten years", he explained, observing a 2007 study by Robert A Kyle, viewing the probability of SMM's progression into MM, which potentially merited its treatment early before progression into true [MM].

The research from 2007 remains a working theory, and the choice of whether to treat or pursue the watch-and-wait approach is an ongoing area of contention in the field.

Rethinking "Smoldering"

Because of its heterogeneity, SMM has enough variance to merit further study. Highlighting phase 2 and 3 clinical trials, he demonstrated that the immune system is less dysfunctional in SMM, warranting comparative research between SMM and relapsed or refractory MM.

In the phase 3 QuiRedex trial of lenalidomide in combination with dexamethasone versus observation, the treatment arm showed a survival advantage. There was a significant decrease in the risk of disease progression or death (Hazard ratio [HR], 0.24, 95% CI, 0.14-0.41; $P<0.0001$). Moreover, the overall survival benefit was shown with an HR of 0.43 (95% CI, 0.21-0.92; $P=0.024$).[2]

Other trials like the phase 3 AQUILA study, which assessed the use of daratumumab vs active monitoring in high-risk SMM, also showed a survival benefit.[3] According to Dr. Dhakal, the existing research signals that there is rationale for treating SMM. In criticism, Dr. Dhaklal explained that studies on the watch-and-wait approach are not considering all the factors.

"They're relying on the disease factors that [are] possibly changing over time and not the true biological risk that we cannot identify with these models," he said.

Proactive treatment may be the next step forward in clinical care. According to Dr. Dhakal, the potential benefit is significant: "If you go big, you could potentially cure this, and the patients won't progress into multiple myeloma."

References

1. Dhakal Binod, et al. Smoldering Multiple Myeloma: To Treat or Not To Treat? Presented at the 2nd Annual HemOnc Pulse in Austin, TX.
2. Mateos M, Hernandez M, Salvador C, et al. Lenalidomide-dexamethasone versus observation in high-risk smoldering myeloma after 12 years of median follow-up time: A randomized, open-label study. *Eur J Cancer.* 2022;174:243-250. doi: 10.1016/j.ejca.2022.07.030
3. Dimopoulos M, Voorhees, Schjesvold F, et al. Daratumumab or active monitoring for high-risk smoldering multiple myeloma. *N Engl J Med.* 2025;392:1777-1788. doi: 10.1056/NEJMoa2409029

Balancing Speed and Stamina in CLL Treatment

*By **Nichole Tucker***

In the near future, treatment of chronic lymphocytic leukemia (CLL) will be a choice between infinite therapy or time-defined therapy, according to **Ryan W. Jacobs, MD,** clinical director of the Lymphoma Division and an associate professor of medicine at Atrium Health Levine Cancer, Wake Forest University School of Medicine.[1]

Ryan W. Jacobs, MD

"Historically, we only had chemoimmunotherapy. There was no discussion of indefinite versus time-defined therapy. The chemotherapy was too toxic to give indefinitely, so we were only talking about fixed-duration therapy then," said Dr. Jacobs in a presentation during the CLL session at The HemOnc Pulse Live.

New Contenders

In recent years, the introduction of Bruton's tyrosine kinase (BTK) monotherapy revolutionized practice for hematologists-oncologists treating CLL in the upfront setting. It is the most used treatment approach, according to Dr. Jacobs. With ongoing clinical trials, options exist beyond BTK inhibitor monotherapy, including fixed-duration BCL2/BTK inhibitor doublets and triplets.

Based on outcomes seen with novel combinations, clinicians can help patients with first-line CLL win the race against their disease. The unanswered question, according to Dr. Jacobs, is whether the race will be a marathon or a sprint.

Shorter Strides, Stronger Results

According to Dr. Jacobs, the phase 3 CLL14 study demonstrates how time-defined therapy offers stability during the race. "We have this time-defined option with really excellent outcomes," he shared. "At six years, roughly 66% are still free of progression—and I think that just talking about time to next treatment might be underselling [the] venetoclax benefit quite a bit."

Because CLL is an indolent disease, it is not necessary to treat the disease at progression, Dr. Jacobs explained. Therefore, time to next therapy (TTNT) is the key endpoint to look at when making the case for time-defined therapy.[1]

The CLL14 study randomized 432 patients 1:1 to either venetoclax plus obinutuzumab or obinutuzumab plus chlorambucil. Patients received 12 cycles of treatment. After six years of follow-up, results showed a median TTNT of not reached in the venetoclax-containing arm compared with 52.9 months with obinutuzumab/chlorambucil. The 6-year TTNT rate observed with venetoclax/obinutuzumab was 65.2% versus 37.1% with obinutuzumab/chlorambucil.[1,2]

Another study, the phase 3 AMPLIFY trial, showed that acalabrutinib in combination with venetoclax with or without obinutuzumab extended progression-free survival (PFS) compared with chemoimmunotherapy in fit patients with first-line CLL.[3]

Patients in the AMPLIFY trial (n=867) were randomized 1:1:1 to acalabrutinb/venetoclax, acalabrutinb/venetoclax/obinutuzumab, or chemoimmunotherapy consisting of either fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab. The 36-month PFS rates were 76.5% with the doublet, 83.1% with the triplet, and 66.5% with chemoimmunotherapy (hazard ratio [HR], 0.65; 95% CI, 0.49-0.87; $P=0.004$).[3]

Aside from the efficacy endpoints, the true benefits of time-defined therapy include the amount of time off therapy, cost-effectiveness, and lower toxicity, Dr. Jacobs explained. Whereas with the alternative, he concluded, "indefinite therapy is more like a marathon… it'll take its toll."[1]

References

1. Jacobs R. The HemOnc Pulse Live.
2. Fischer K, et al. *Blood*. 2024;144(18):1924-1935.doi:10.1182/blood.2024024631
3. Brown J, et al. *N Engl J Med*. 2025;392(8):748-762. doi:10.1056/NEJMoa2409804

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,* ***Uma Borate, MBBS,*** *Associate Editor of* Blood Cancers Today *and Associate Professor in the Division of Hematology at The Ohio State University, highlights recent research in acute myeloid leukemia (AML).*

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

Uma Borate, MBBS

ACUTE MYELOID LEUKEMIA

CAVEAT Trial Hints at New AML Path for Fit Seniors

By ***Andrew Moreno***

To manage AML in older, fit patients, venetoclax plus a modified intensive chemotherapy regimen offers an effective, well-tolerated, time-limited approach. This was the assessment of investigators who evaluated the phase 1b CAVEAT study and published their findings in *Blood Advances*.

The evaluation of CAVEAT concerned a cohort of 85 patients from the trial aged 65 years and older, who had a median age of 71 years and a median follow-up of 41.8 months. For up to 14 days, these patients received induction therapy of cytarabine and idarubicin in five dose escalation cohorts for venetoclax of 50, 100, 200, 400, and 600 mg.

The overall response rate (ORR) calculated in the cohort was 75%, and the median overall survival (OS) was 19.3 months. Specifically in patients with de novo AML, the ORR was 88% and the median OS was 33.1 months. Nearly one-third of the responding patients did not have relapse, and their median treatment-free remission was 17.9 months.

By gene mutation variants of disease, complete response rates were highest for patients who had *IDH1/2* or *NPM1* mutations, at 75% and 81%, respectively, and lowest for patients with *TP53* mutation at 27%. The two-year OS rate was highest in patients with *IDH1/2, SRSF2*, or *NPM1* mutation at 76%, 72%, and 69%, respectively, and lowest in patients with *TP53* mutation at 13%.

Safety results of the induction therapy included a 4% prevalence of high-grade gastrointestinal toxicity and a mortality rate of 4%. Delays to hematologic recovery experienced by patients after consolidation were improved by removing idarubicin from post-remission therapy.

Reference

Chua C, et al. *Blood Adv.* 2025; 9(8):1827–1835. doi: https://doi.org/10.1182/bloodadvances.2024014900

Tuspetinib Triplet Shows Antileukemic Activity in AML

By ***Melissa Badamo***

Tuspetinib in combination with standard-of-care venetoclax and azacitidine showed promising clinical safety and antileukemic activity in patients with newly diagnosed AML who are ineligible for induction chemotherapy, according to an update of the phase 1/2 TUSCANY trial from Aptose Biosciences, Inc.

In the TUSCNAY trial, four patients in the first cohort received 40 mg of tuspetinib and three patients in the second cohort received 80 mg of tuspetinib. In the 40 mg cohort, three patients (two with *FLT3*-wildtype and one with both *FLT3*-wildtype and *TP53*-mutated complex karyotype) achieved measurable residual disease negativity and either complete remission or complete remission with incomplete count recovery (CR/CRi). The fourth patient did not respond while receiving 40 mg and discontinued treatment. No dose-limiting toxicities were observed.

In the 80 mg cohort, all three patients with diverse mutation profiles achieved blast reductions and CR/CRi in the first cycle and are expected to show further improvement as they continue treatment. Eighty milligrams was determined to be the optimal tuspetinib dose.

"The treatment paradigm for AML is shifting to triplet combination therapy," said **Rafael Bejar, MD, PhD,** chief medical officer of Aptose, in a press release. "We have always maintained that tuspetinib, with its notable safety profile and ability to treat the larger, difficult-to-treat AML populations with high-risk mutations, could be an ideal drug for a triplet combination therapy in the frontline setting. With the majority of patients already achieving complete responses—including early responses in patients with adverse mutations—the clinical findings to date are bearing that out."

Reference

GlobeNewswire. Accessed May 12, 2025. https://www.globenewswire.com/news-release/2025/05/05/3073937/35575/en/Aptose-Provides-Clinical-Update-for-the-Tuspetinib-based-Triple-Drug-Frontline-Therapy-in-Newly-Diagnosed-AML-Patients-from-the-Phase-1-2-TUSCANY-Trial.html

Novel Radiotherapy Offers Strong AML Combo Therapy Backbone

By ***Andrew Moreno***

Lintuzumab-Ac-225 (Actimab-A) shows promise as a treatment backbone for relapsed or refractory AML, according to a press release from Actinium Pharmaceuticals, Inc. The company bases this assertion on impressive efficacy data presented at the American Association for Cancer Research (AACR) Annual Meeting in Chicago, Illinois, in April 2025.[1]

Lintuzumab-Ac-225 is a CD33-targeting radiotherapy that hones a powerful alpha-emitter radioisotope, actinium-225, for antileukemic effect. It is Actinium Pharmaceuticals' lead product candidate and in development for management of AML, myelodysplastic syndromes (MDS), and other myeloid malignancies.[1]

"Actimab-A has demonstrated potent single agent activity, synergy with other therapeutic modalities and efficacy in patients with high-risk features such as a *TP53* mutation," Actinium Pharmaceuticals chair and chief executive officer **Sandesh Seth** commented in a press release. [1]

In preclinical models, lintuzumab-Ac-225 was combined with standard-of-care targeted therapies for relapsed and refractory AML: azacitidine, the *FLT3* inhibitors gilteritinib and quizartinib, and the *KMT2A* inhibitors revumenib and ziftomenib. The results showed a significant antileukemic effect against AML cell lines that featured *FLT3, KMT2A, NPM1,* and *TP53* mutations.[2]

"The data presented at AACR further support Actimab-A's mutation agnostic mechanism of action across several of the most commonly expressed mutations and synergy with the targeted therapies approved for patients with these mutations," Seth elaborated in the press release.[1]

Clinical trial work on use of lintuzumab-Ac-225 within polytherapy approaches for AML continues, including in a phase 2/3 trial in which the radiotherapy will be combined with the CLAG-M (cladribine, high-dose cytarabine, granulocyte colony-stimulating factor, and dose-escalated mitoxantrone) chemotherapy regimen for relapsed or refractory disease. Another trial, to take place under a Cooperative Research and Development Agreement between Actinium Pharmaceuticals and the National Cancer Institute, will evaluate triplet therapy consisting of lintuzumab-Ac-225 plus venetoclax and the novel oral hypomethylating agent ASTX-727 for frontline AML management. Prior clinical results of treatment with lintuzumab-Ac-225 for high-risk relapsed and refractory disease have also been positive, including findings in patients with prior venetoclax treatment or bone marrow transplant.[1]

References

1. Actinium Pharmaceuticals, Inc. Accessed May 8, 2025. https://ir.actiniumpharma.com/press-releases/detail/501

2. Chin AS, et al. AACR Annual Meeting 2025. Abstract no. 594. https://doi.org/10.1158/1538-7445.AM2025-594

HemOnc Happenings

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

A New Era for Drug Development: Vinay Prasad Takes the Helm at FDA's Biologics Division

*By **Nichole Tucker***

A long-standing contributor to research and conversations around drug policy, medical evidence, and government regulation in oncology, **Vinayak (Vinay) Prasad, MD, MPH,** has been appointed director of the Food and Drug Administration (FDA) Center for Biologic Evaluation and Research (CBER).

Vinayak Prasad, MD, MPH

In a statement to the public, the 27th Commissioner of Food and Drugs, **Martin Makary, MD, MPH** said, "I'm proud to welcome Dr. Vinay Prasad as the new head of FDA's Center for Biologics Evaluation & Research. With 500+ peer-reviewed publications and two books, Dr. Prasad brings the kind of scientific rigor, independence, and transparency we need at CBER—a significant step forward."

Historically, Dr. Prasad's laboratory at the University of California, San Francisco (UCSF) has examined the practices of biopharmaceutical companies and government agencies, particularly about clinical trials. His work has raised questions about the potential risks and benefits of certain trials, including whether some may offer limited clinical value or involve unknown risks to patients. Additionally, the FDA's review process for such trials has been noted for its complexity and duration, which can sometimes delay outcomes or lead to results that differ from initial expectations.

Today, Dr. Prasad is hoping to make an impact from the inside out. In an *FDA Direct* conversation with the commissioner, he said, "At CBER, we govern a huge portfolio of medical products, including vaccines, gene therapy, cellular therapy, a lot of the most innovative things you read about in the news are things coming from CBER. Not to say the other departments here don't do innovative products. They do, but I think I'm particularly excited about what's been coming out in the last decade through [the] CBER division, and we hope to always strike the balance between data, evidence, innovation, and [the] entrepreneurial spirit of America."

Vaccines, gene therapies, and cellular therapies all have a place in treating hematologic malignancies today. Some exist mainly in the clinical trial setting, but many have reached the clinic. A common public belief about Dr. Prasad has been that he is against vaccinations.

During the *FDA Direct* conservation, Dr. Prasad denied being "anti-vax." He explained that instead, he is careful about what to vaccinate and when, and if there is enough clinical evidence to support it. As an example, he discussed criticisms he raised during the COVID-19 pandemic.

"I think vaccines are like drugs—when given at the right time, in the right moment [for] the right person, they're lifesaving. But just like drugs, they need to be evaluated on a case-by-case basis and always taken to the context that you're giving. Marty and I, throughout the pandemic, were proponents of vaccines for the people in whom it had a huge benefit, but we were always a bit skeptical, from a scientific standpoint, about perhaps overdoing it in some low-risk populations."

CBER has played a role in Vividencel receiving FDA Fast Track Designation for the treatment of acute myeloid leukemia (AML). As demonstrated in the phase 2 ADVANCE trial, this cell-based vaccine has shown potential to boost the production of T-cells that target and kill cancer cells, reducing immune-suppressive T-cells in patients with AML. Additionally, the FDA has granted two investigational new drug (IND) applications for cancer vaccines being studied in blood cancers. One is WGC-043, an mRNA-based vaccine targeting Epstein-Barr virus–associated cancers, which has shown preliminary efficacy and tolerability. The other is DSP-7888, a peptide vaccine under investigation for hematologic malignancies and solid tumors, which has also been granted FDA Orphan Drug Designation for treating myelodysplastic syndromes.

Overall, Dr. Prasad's stance is that vaccines are important for the practice of medicine in general, but that there needs to be a better balance of moving at a reasonable pace and getting the necessary evidence to move forward. He explained his plan for vaccines at the FDA in detail, again using the pandemic as a backdrop.

"I think ultimately, we get excited about innovative medical products, just as the FDA always has. We all continue to believe in a flexible regulatory standard, taking into account the context of a disease—whether it's rare, if it's dire—we will continue to be flexible. There's not going to be a light switch change here. But around the edges, I think there were a number of missteps along the way," Dr. Prasad said.

The same plan Dr. Prasad and his team have to bring to the development and review of vaccines will carry over into the development of therapeutics. Specifically, Dr. Prasad wants to lead on new requirements for surrogate endpoints in clinical research. Also, under the commissioner's new implementations, FDA reviews going forward will be guided by AI, and less paperwork will be needed from industry.

"We have to make our submissions easier. We have to make it so sponsors don't have to fill out information over and over again," Dr. Prasad stated. "[We] just can't be the same. [We] have to always be changing and adapting, and too often in big institution[s], that doesn't happen."

About his appointment, Dr. Prasad expressed excitement about getting started and being in the FDA facility during his first week. "I do feel sort of an energy being here, and I'm coming from a college campus. It's a very different energy—a productive energy."

References

1. Youtube. Accessed Online May 19, 2025. https://www.youtube.com/watch?v=sB4rr_JK2Ak
2. Mendus. Accessed Online May 19, 2025. https://mendus.com/news/mendus-receives-u-s-fda-fast-track-designation-for-vididencel-in-acute-myeloid-leukemia-aml
3. PR Newswire. Accessed Online May 19, 2025. https://www.prnewswire.com/news-releases/westgenes-mrna-therapeutic-cancer-vaccine-receives-fda-approval-302142067.html
4. Biospace. Accessed Online May 19, 2025. https://www.biospace.com/boston-biomedical-announces-orphan-drug-designation-by-fda-for-investigational-wt1-cancer-peptide-vaccine-dsp-7888-in-myelodysplastic-syndrome

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

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increased Early Mortality

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

Cytokine Release Syndrome

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

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

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

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

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

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

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

Neurologic Toxicities

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

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

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

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

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

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

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

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

Parkinsonism

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

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

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

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

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

Guillain-Barré Syndrome

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

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

Immune Mediated Myelitis

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

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

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

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

Monitor patients for signs and symptoms of peripheral neuropathies.

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

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

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

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

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

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

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

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

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

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

CARVYKTI REMS

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

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

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

Prolonged and Recurrent Cytopenias

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

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

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

Infections

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

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

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

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

Viral Reactivation

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

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

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

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

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

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

Use of Live Vaccines

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

Hypersensitivity Reactions

Hypersensitivity reactions occurred following treatment with CARVYKTI.

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

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

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

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

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

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

Effects on Ability to Drive and Use Machines

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

CARTITUDE-4

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

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

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

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

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.

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

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

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

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

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

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

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

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

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

[k] Headache includes Headache and Tension headache.

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

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

[n] Hypotension includes Hypotension, and Orthostatic hypotension.

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

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

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

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

CARTITUDE-1

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

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

Prolonged and Recurrent Cytopenias

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

Infections

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

Hypersensitivity Reactions

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

Secondary Malignancies

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

Advise patients of the need to:

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

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

Marketed by:
Legend Biotech
Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

cp-258863v5

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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

POWERFUL. DEEP. DURABLE.

After a One-Time Infusion[1-3]

CARTITUDE-4 primary analysis demonstrated[†]:

POWERFUL

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

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

DEEP

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

DURABLE

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

Safety profile

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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

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

SELECTED IMPORTANT SAFETY INFORMATION

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

cp-30028v4

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