TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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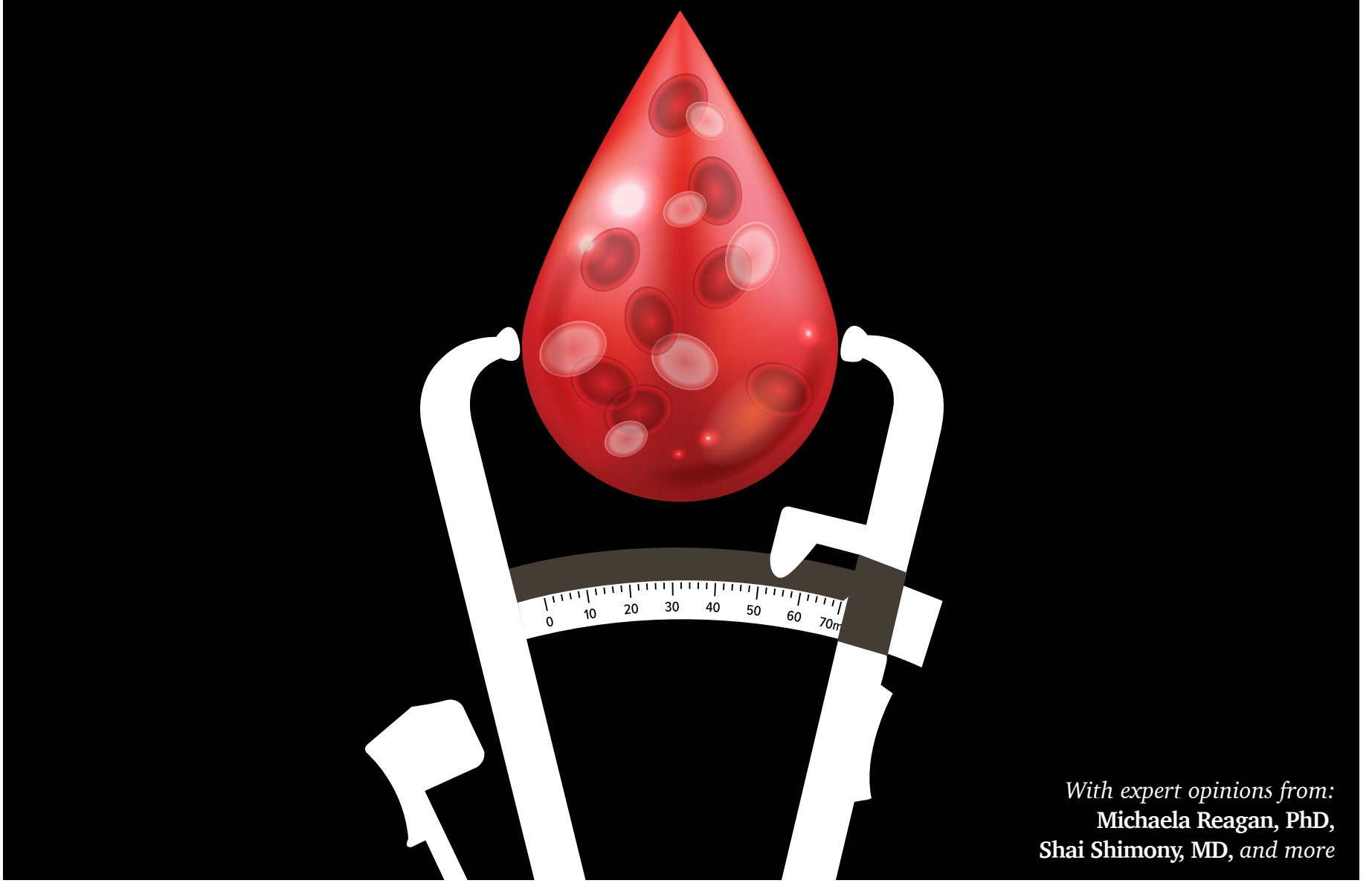
The Ozempic Effect:

How GLP-1 Receptor Agonists May Reduce Blood Cancer Risk and Improve Patient Outcomes



With expert opinions from:
Michaela Reagan, PhD,
Shai Shimony, MD, *and more*

MAIL TO:

MOAATH K. MUSTAFA ALI, MD, MPH:
Which Menin Inhibitor Will Win in AML?

OJJAARA for myelofibrosis (MF) with anemia

Multifaceted disease management starts here

Ojjaara (momelotinib)
200 mg • 150 mg • 100 mg tablets

Not an actual patient.

FDA=US Food and Drug Administration; JAK=Janus kinase.

Take on multiple aspects of myelofibrosis

Start with OJJAARA–The first & only FDA-approved JAK inhibitor indicated specifically for patients who have myelofibrosis with anemia.[1,2]

OJJAARA was assessed for:

- Total Symptom Score Reduction
- Spleen Volume Reduction
- Transfusion Independence

Explore the data in JAKi-naïve and JAKi-experienced patients

INDICATION

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

IMPORTANT SAFETY INFORMATION

Risk of Infections

- Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients. Delay starting therapy until active infections have resolved. Monitor patients for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B Reactivation

- Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Thrombocytopenia and Neutropenia

- New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients had baseline platelet counts less than 50×10^9/L.

Please see additional Important Safety Information on the following page with accompanying Brief Summary of the full Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont'd)

Thrombocytopenia and Neutropenia (cont'd)

- Severe neutropenia, absolute neutrophil count (ANC) less than 0.5 × 10^9/L, was observed in 2% of patients treated with OJJAARA.
- Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia.

Hepatotoxicity

- Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.
- Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment.
- Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 within the Prescribing Information.

Severe Cutaneous Adverse Reactions (SCARs)

- Severe cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis (TEN), have been observed in some patients treated with OJJAARA.
- If signs or symptoms of SCARs occur, interrupt OJJAARA until the etiology of the reaction has been determined. Consider early consultation with a dermatologist for evaluation and management.
- If etiology is considered to be associated with OJJAARA, permanently discontinue OJJAARA and do not reintroduce OJJAARA in patients who have experienced SCARs or other life-threatening cutaneous reactions during treatment with OJJAARA.

Major Adverse Cardiovascular Events (MACE)

- Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

- Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Evaluate patients with symptoms of thrombosis and treat appropriately.

Malignancies

- Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Adverse Reactions

- The most common adverse reactions (≥20% in either study) are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea.

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

- Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC), which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications.

Breast Cancer Resistance Protein (BCRP) Substrates

- Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions. When administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

Pregnancy

- Available data in pregnant women are insufficient. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

Lactation

- It is not known whether OJJAARA is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Females and Males of Reproductive Potential

- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

Hepatic Impairment

- Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Please see Brief Summary of the full Prescribing Information for OJJAARA on the following pages.

References: 1. OJJAARA (momelotinib). Prescribing Information. GSK; 2025.
2. Chifotides HT, Bose P, Verstovsek S. Momelotinib: an emerging treatment for myelofibrosis patients with anemia. *J Hematol Oncol.* 2021;15(1):7. doi:10.1186/s13045-021-01157-4

PMUS-MMLJRNA250002 May 2025
Produced in USA.

Ojjaara (momelotinib) GSK

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

OJJAARA (momelotinib) tablets, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.OJJAARAhcp.com

1 INDICATIONS AND USAGE

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Infections

Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients treated with OJJAARA *[see Adverse Reactions (6.1)]*. Delay starting therapy with OJJAARA until active infections have resolved. Monitor patients receiving OJJAARA for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B Reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

5.2 Thrombocytopenia and Neutropenia

OJJAARA can cause thrombocytopenia and neutropenia *[see Adverse Reactions (6.1)]*.

New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients treated with OJJAARA had baseline platelet counts less than 50×10^9/L. Severe neutropenia, absolute neutrophil count (ANC) less than 0.5×10^9/L, was observed in 2% of patients treated with OJJAARA.

Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia *[see Dosage and Administration (2.4) of full prescribing information]*.

5.3 Hepatotoxicity

Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.

Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment *[see Dosage and Administration (2.3) of full prescribing information]*.

Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 *[see Dosage and Administration (2.4) of full prescribing information]*.

5.4 Severe Cutaneous Adverse Reactions (SCARs)

Severe cutaneous adverse reactions, including toxic epidermal necrolysis (TEN), have been observed in some patients treated with OJJAARA. If signs or symptoms of severe cutaneous reactions occur, interrupt OJJAARA until the etiology of the reaction has been determined. Consider early consultation with a dermatologist for evaluation and management. If etiology is considered to be associated with OJJAARA, permanently discontinue and do not reintroduce OJJAARA in patients who have experienced SCARs or other life-threatening cutaneous reactions during OJJAARA treatment.

5.5 Major Adverse Cardiovascular Events (MACE)

Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

5.6 Thrombosis

Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Evaluate patients with symptoms of thrombosis and treat appropriately.

5.7 Malignancies

Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

6 ADVERSE REACTIONS

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

- Risk of Infections and Hepatitis B Reactivation *[see Warnings and Precautions (5.1)]*
- Thrombocytopenia and Neutropenia *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.5)]*
- Thrombosis *[see Warnings and Precautions (5.6)]*
- Malignancies *[see Warnings and Precautions (5.7)]*

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OJJAARA was evaluated in 215 patients in 2 clinical trials (MOMENTUM and SIMPLIFY-1 anemic subgroup [hemoglobin (Hb) <10 g/dL]) *[see Clinical Studies (14) of full prescribing information]*.

MOMENTUM

Patients in the MOMENTUM trial had been previously treated with a JAK inhibitor and were randomly assigned 2:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 130) or danazol 300 mg orally twice daily (n = 65) for 24 weeks, after which they were eligible to receive open-label OJJAARA in an extended treatment phase. Among patients who received OJJAARA, 72% were exposed for 24 weeks or longer and 52% were exposed for 48 weeks or longer *[see Clinical Studies (14) of full prescribing information]*.

Serious adverse reactions occurred in 35% of patients who received OJJAARA during the randomized treatment period of the MOMENTUM trial; the most common serious adverse reactions (≥2%) included bacterial infection (8%), viral infection (5%), hemorrhage (4%), acute kidney injury (3%), pneumonia (3%), pyrexia (3%), thrombosis (3%), syncope (2%), thrombocytopenia (2%), and renal and urinary tract infection (2%). Fatal adverse reactions occurred in 12% of patients who received OJJAARA; the most common (≥2%) fatal adverse reaction was viral infection (5%).

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 18% of patients during the randomized treatment period of the MOMENTUM trial. Adverse reactions that resulted in permanent discontinuation (≥2%) included viral infection (2%) and thrombocytopenia (2%). Dosage reduction or treatment interruption due to an adverse reaction occurred in 34% of patients.

Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) included thrombocytopenia (13%), bacterial infection (2%), diarrhea (2%), and neutropenia (2%).

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6 ADVERSE REACTIONS (*cont'd*)

6.1 Clinical Trials Experience (*cont'd*)

Among the 130 patients treated with OJJAARA during the randomized treatment period of MOMENTUM, the most common adverse reactions (≥20%) were thrombocytopenia, diarrhea, hemorrhage, and fatigue (Table 1).

Table 1: Adverse Reactions Occurring in ≥5% of Patients Receiving OJJAARA during Randomized Treatment in MOMENTUM

Adverse Reaction	OJJAARA n = 130		Danazol[a] n = 65	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Thrombocytopenia[c]	28	22	17	12
Diarrhea[c]	22	0	9	2
Hemorrhage[c]	22	2	18	8
Fatigue[c]	21	2	20	5
Nausea[c]	16	2	9	3
Bacterial infection[c,d]	15	8	18	8
Abdominal pain[c]	13	1	18	3
Viral infection[c,d]	12	5	3	0
Pruritus[c]	11	2	11	0
Elevated liver enzymes[c]	10	2	9	3
Pyrexia[c]	10	2	8	0
Cough[c]	8	0	5	0
Paresthesia[c]	8	1	2	0
Dizziness[c]	8	2	2	0
Vomiting[c]	8	1	0	0
Rash[c]	6	0	11	0
Renal and urinary tract infection[c,d]	6	2	11	5
Arrhythmia[c]	5	1	6	2
Neutropenia	5	5	3	3

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.5.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

SIMPLIFY-1

Patients in the SIMPLIFY-1 trial were JAK inhibitor naïve and randomly assigned 1:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 215) or ruxolitinib 5 to 20 mg orally twice daily (n = 217). Upon completion of the double-blind treatment phase, all patients were eligible to receive OJJAARA during the open-label phase. The safety of OJJAARA was evaluated in the population of patients with MF who were anemic at study entry. SIMPLIFY-1 enrolled 180 anemic patients who received OJJAARA (n = 85) or ruxolitinib (n = 95). Among these anemic patients who received OJJAARA, 78% were exposed for 24 weeks or longer and 61% were exposed for 48 weeks or longer [*see Clinical Studies (14) of full prescribing information*].

Serious adverse reactions occurred in 28% of the anemic patients who received OJJAARA during the randomized treatment period of the SIMPLIFY-1 trial; the most common serious adverse reactions (≥2%) included bacterial infection (7%), pneumonia (6%), heart failure (4%) arrhythmia (2%), and respiratory failure (2%). A fatal adverse reaction (bacterial infection) occurred in 1 patient who received OJJAARA.

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 19% of the anemic patients during the randomized treatment period of the SIMPLIFY-1 trial. Adverse reactions that resulted in permanent discontinuation of OJJAARA (≥2%) included bacterial infection (2%), dizziness (2%), fatigue (2%), hypotension (2%), and thrombocytopenia (2%). Dosage reductions or treatment interruptions of OJJAARA due to an adverse reaction occurred in 21% of patients. Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) were thrombocytopenia (8%), pneumonia (4%), bacterial infection (2%), abdominal pain (2%), elevated liver enzymes (2%), and hypotension (2%).

Among the 85 anemic patients treated with OJJAARA during the randomized treatment period of SIMPLIFY-1, the most common adverse reactions (≥20%) were dizziness, fatigue, bacterial infection, hemorrhage, thrombocytopenia, diarrhea, and nausea (Table 2).

Table 2: Adverse Reactions Occurring in ≥5% of Anemic Patients Receiving OJJAARA during Randomized Treatment in SIMPLIFY-1

Adverse Reactions	OJJAARA n = 85 Baseline Hb <10 g/dL		Ruxolitinib[a] n = 95 Baseline Hb <10 g/dL	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Dizziness[c]	24	1	15	2
Fatigue[c]	22	0	25	1
Bacterial infection[c,d]	21	8	12	2
Hemorrhage[c]	21	1	18	2
Thrombocytopenia[c]	21	11	34	6
Diarrhea[c]	20	1	20	1
Nausea[c]	20	0	3	1
Abdominal pain[c]	18	1	14	1
Cough[c]	14	0	11	0
Hypotension[c]	14	2	0	0
Pain in extremity	12	0	5	0
Pyrexia[c]	12	1	11	0
Rash[c]	12	0	3	0
Renal and urinary tract infection[c,d]	12	1	4	0
Elevated liver enzymes[c]	11	4	9	0
Headache[c]	11	0	16	0
Peripheral edema	11	0	8	0
Arrhythmia[c]	8	2	2	1
Paresthesia[c]	8	0	3	0
Pneumonia[c]	8	8	5	3
Vomiting[c]	8	0	5	0
Back pain	7	1	2	0
Viral infection[c,d]	6	0	13	2
Vitamin B1 deficiency	6	0	7	0

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.4.03.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

Other Adverse Reactions

Clinically relevant adverse reactions occurring in <5% of anemic patients in the MOMENTUM and SIMPLIFY-1 studies include:
Eye Disorders: Blurred vision.
Infections and Infestations: Fungal infection (excludes opportunistic infections).
Nervous System Disorders: Neuralgia, peripheral neuropathy, peripheral motor neuropathy, polyneuropathy.
Vascular Disorders: Flushing.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OJJAARA. Because these reactions 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 drug exposure.

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis (TEN).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on OJJAARA

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC) *[see Clinical Pharmacology (12.3) of full prescribing information]*, which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications *[see Dosage and Administration (2.4) of full prescribing information]*.

7.2 Effect of OJJAARA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions [*see Clinical Pharmacology (12.3) of full prescribing information*]. When administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose

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7 DRUG INTERACTIONS (*cont'd*)

7.2 Effect of OJJAARA on Other Drugs (*cont'd*)

adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of OJJAARA in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. Based on animal reproduction studies conducted in rats and rabbits, momelotinib may cause embryo-fetal toxicity at exposures lower than the expected exposure in patients receiving 200 mg once daily *(see Data)*. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: In an embryofetal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally, during the period of organogenesis (Gestation Day 6 to 17). Embryo-fetal toxicity (embryonic death, soft tissue anomalies, skeletal variations, and lower mean fetal body weights) was observed at 12 mg/kg (in the presence of maternal toxicity). Skeletal variations were observed (in the absence of maternal toxicity) at 6 mg/kg/day at exposures 3.5 times the exposure at the recommended human dose of 200 mg daily based on combined momelotinib and M21 (a major human metabolite) AUC. No developmental toxicity was observed at 2 mg/kg/day at exposures equivalent to the recommended dose (based on combined momelotinib and M21 AUC).

In an embryofetal developmental study, pregnant rabbits received momelotinib at 7.5, 30 or 60 mg/kg/day orally during the period of organogenesis (Gestation Day 7 to 20). Momelotinib was associated with maternal toxicity at 60 mg/kg/day, which resulted in reduced mean fetal weight, delayed bone ossification, and an abortion at less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC). No developmental toxicity was observed at lower doses tested in rabbits.

In a pre- and post-natal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally from organogenesis through lactation (Gestation Day 6 to lactation Day 20). Decreased pup body weights and embryo-lethality were observed in the dams administered 6 and 12 mg/kg/day. Pup survival was significantly reduced in the 12 mg/kg/day group from birth to Day 4 of lactation. Momelotinib exposure in dams at 12 mg/kg and 6 mg/kg were approximately 2 times the exposure at the recommended dose (based on combined momelotinib and M21 AUC). The exposure in dams at the No Observed Adverse Effect Level (NOAEL) dose of 2 mg/kg was less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of momelotinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. It is not known whether OJJAARA is excreted in human milk. Momelotinib was present in rat pups following nursing from treated dams with adverse effects observed in the offspring. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Data

Animal Data: In a pre- and postnatal development study, momelotinib was administered orally to rats during the lactation period; the drug was detected in plasma of nursing pups, which adversely affected pup survival.

8.3 Females and Males of Reproductive Potential

Contraception

Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

8.5 Geriatric Use

There were 275 patients aged 65 years and older in the clinical studies for MF *[see Clinical Studies (14) of full prescribing information]*. Of the total number of OJJAARA-treated patients in these studies, 163/216 (75%) were aged 65 years and older, and 63/216 (29%) were aged 75 years and older. No overall differences in safety or effectiveness of OJJAARA have been observed between patients aged 65 years and older and younger adult patients.

8.6 Hepatic Impairment

The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily *[see Dosage and Administration (2.3) of full prescribing information]*. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Momelotinib is extensively metabolized *[see Clinical Pharmacology (12.3) of full prescribing information]*. Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). No clinically significant changes in momelotinib exposure were observed in subjects with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B) *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

There is no known antidote for overdose with OJJAARA. If overdose is suspected, the patient should be monitored for signs or symptoms of adverse reactions or effects, and appropriate supportive treatment should be instituted immediately. Further management should be as clinically indicated. Hemodialysis is not expected to enhance the elimination of momelotinib.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Patient Information).

Infections

Inform patients that OJJAARA can increase the risk of infections (including COVID-19) and instruct them to promptly report to their healthcare provider any signs and symptoms of infection *[see Warnings and Precautions (5.1)]*.

Thrombocytopenia and Neutropenia

Inform patients that OJJAARA can cause thrombocytopenia and neutropenia, and of the need to monitor complete blood count, including platelet and neutrophil counts, before and during treatment. Advise patients to observe for and report any bleeding to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that OJJAARA can cause hepatotoxicity, and of the need to monitor liver blood tests before and during treatment *[see Warnings and Precautions (5.3)]*.

Severe Cutaneous Adverse Reactions (SCARs)

Inform patients that SCARs have been reported in some patients treated with OJJAARA and instruct them to promptly report any signs and symptoms of SCARs to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Major Adverse Cardiovascular Events (MACE)

Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients, especially current or past smokers and patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events and to report them to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Thrombosis

Advise patients that events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.6)]*.

Malignancies

Advise patients, especially current or past smokers, that lymphoma and other malignancies (excluding non-melanoma skin cancers (NMSC)) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated *[see Warnings and Precautions (5.7)]*.

Pregnancy

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed during treatment with OJJAARA and for at least 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.2)]*.

GlaxoSmithKline
Durham, NC 27701

OJJ:1BRS 05/25

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GSK

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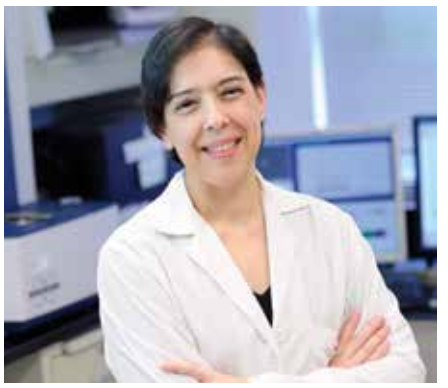

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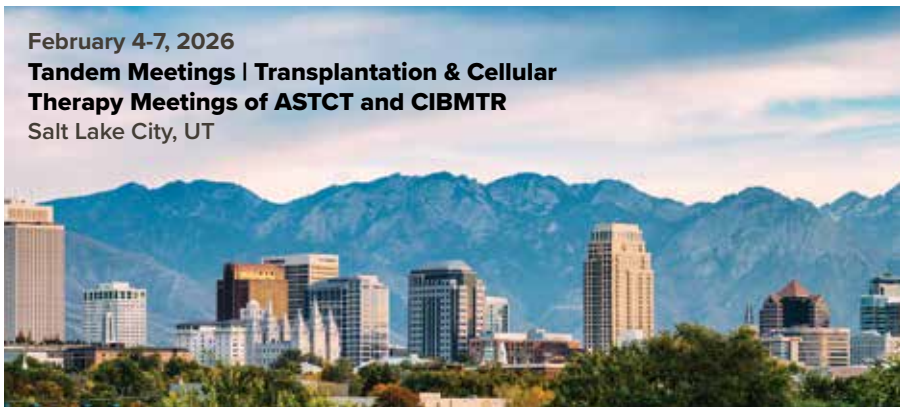
Calendar

2025

December 4-6, 2025
AACR Special Conference in Cancer Research: Cancer Evolution: The Dynamics of Progression and Persistence
Albuquerque, NM

2026

January 16-18, 2026
2nd Annual Cleveland Clinic Cancer Conference
Hollywood, FL



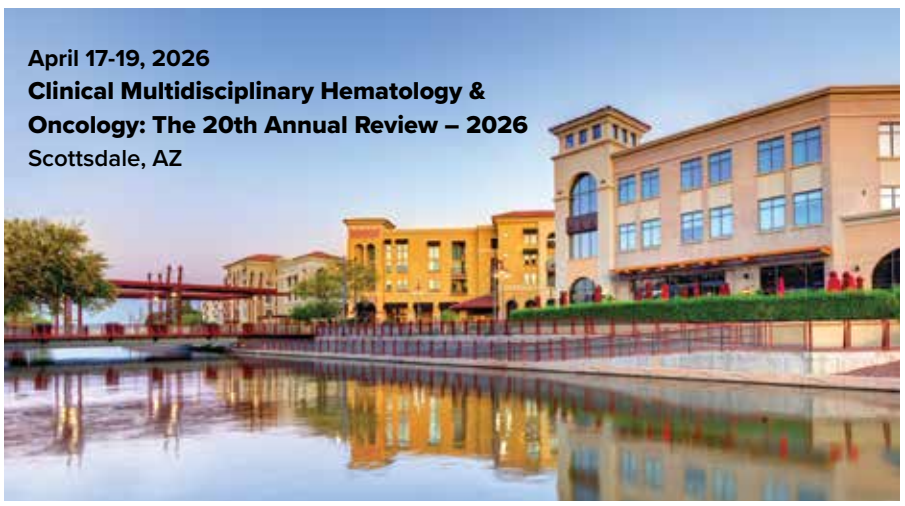
February 12-14, 2026
EHA-EBMT 8th European CAR T-Cell Meeting
Palma de Mallorca, Spain

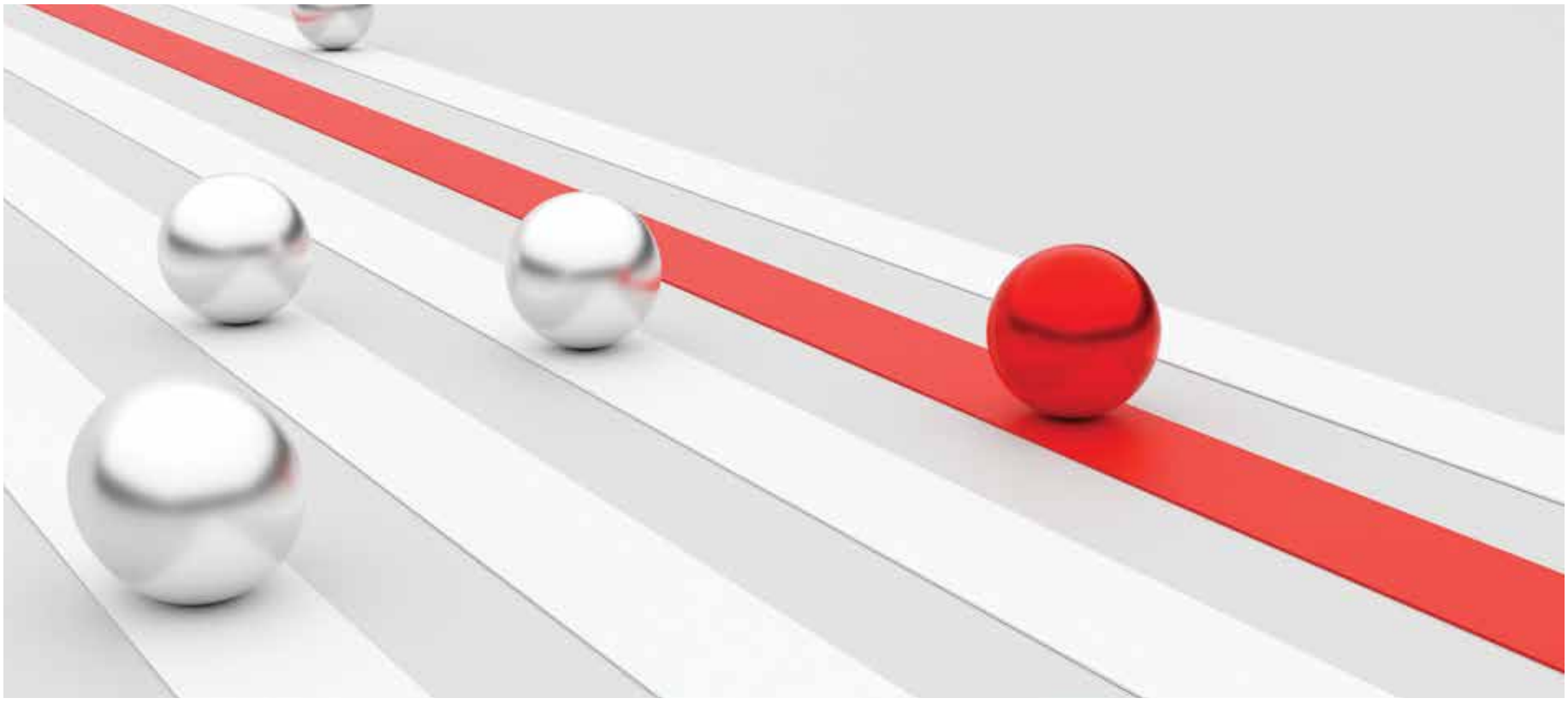
February 26-28, 2026
30th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
Miami Beach, FL

March 14, 2026
Tri-State Blood Cancer Conference
New York, NY

March 25-27, 2026
Society for Immunotherapy of Cancer (SITC) Sparkathon 2026: Next-Generation Cellular Therapies, T-Cell Engagers, and Combinations
Tucson, AZ

April 17-22, 2026
American Association for Cancer Research (AACR) Annual Meeting 2026
San Diego, CA





Racing for Glory: Which Menin Inhibitor Will Win in AML?

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

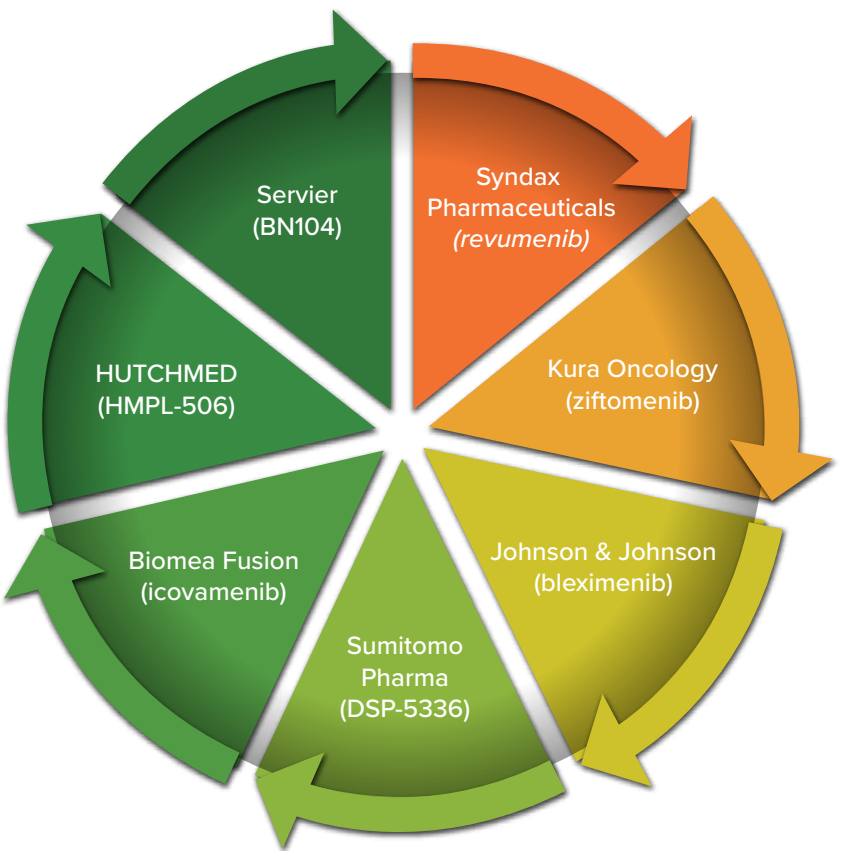
Moaath K. Mustafa Ali, MD, MPH

Menin, the product of the *MEN1* gene, is a 615-amino acid protein that functions as an essential component of the MLL/SET1 histone methyltransferase complex, which methylates lysine 4 of histone H3.[1] Menin plays a key role in normal hematopoiesis through activation of *HOXA9* expression. Inhibition of menin has shown efficacy in preclinical models of leukemia cells harboring either *NPM1* mutations or *KMT2A* rearrangements.[2,3] Menin inhibitors disrupt the menin-*KMT2A* interaction, resulting in downregulation of *HOX/MEIS1* expression and induction of myeloid differentiation. These findings have opened a new avenue for targeted therapies for acute leukemias with *KMT2A* rearrangements or *NPM1* mutations.

Currently, multiple companies are testing menin inhibitors in clinical trials (**FIGURE 1**), creating a highly competitive landscape. *NPM1* mutations occur in nearly 30% of de novo acute myeloid leukemia (AML) cases, and *KMT2A* rearrangements are found in about 5% of AML cases,[4,5] which explains the strong interest in developing drugs targeting these subgroups (**TABLE 1**).
On November 15, 2024, the FDA approved revumenib (Revuforj, Syndax Pharmaceuticals) for the treatment of relapsed or refractory acute leukemia with *KMT2A* rearrangements in adult and pediatric patients aged 1 year and older. On October 24, 2025, the FDA approved revumenib for relapsed or refractory AML with a susceptible *NPM1* mutation in adult and pediatric patients 1 year and older who have no satisfactory alternative treatment options. To date, revumenib remains the only FDA-approved menin inhibitor for relapsed or refractory acute leukemia (**TABLE 2**).

Although approval in the relapsed and refractory settings is important, frontline approval is even more critical, as targeted therapies tend to be less effective when used in later lines of therapy. As of September 17, 2025, a

FIGURE 1. Pharmaceutical companies (US and non-US) currently or previously known to be developing menin inhibitors.



Clinician's Corner

TABLE 1. Currently Used Menin Inhibitors in Acute Leukemias in the US and Their Regulatory Status[a]

Drug Name	Developer	FDA Approval	Name of Study: FDA Approval	FDA Review	Name of Study: FDA Review
Revumenib (SNDX-5613)	Syndax Pharmaceuticals	R/R acute leukemia with rr-*KMT2A* translocation (adults & pediatric pts ≥1 y)	AUGMENT-101: 94 pts		
		R/R *NPM1*-mutated AML (adults & pediatric pts ≥1 y)	AUGMENT-101: 65 pts		
Ziftomenib (KO-539)	Kura Oncology	Pending review for mutated *NPM1* AML	—	R/R *mNPM1* AML: PDUFA (action) date for decision is 11/30/2025	KOMET-001: multicenter phase 1b/2 trial: 83 pts
Bleximenib (JNJ-7526617)	Johnson & Johnson/Janssen	Not under review yet; received orphan drug designation	—	Not under review yet	cAMeLot-1: multicenter phase 1 trial: 108 AML and 6 ALL
Enzomenib (DSP-5336)	Sumitomo Pharma America	Not under review yet; received orphan drug designation	—	Not under review yet	DSP-5336-101 trial: As of June 24, 2024, 81 pts enrolled

ALL, acute lymphocytic leukemia; *AML,* acute myeloid leukemia; *PDUFA,* Prescription Drug User Fee Act; *pts,* patients; *R/R,* relapsed or refractory.

[a] The table is not exhaustive of all menin inhibitors.

TABLE 2. Key Clinical Studies of Menin Inhibitors in Acute Leukemias, Including Study Design and Reported Outcomes

Study/Year	Name of Drug	Study Phase	Inclusion Criteria	Outcome Composite Complete Response	Outcome Survival	Outcome MRD Negative Responses	Grade 3 DS	Grade 3 QTC prolongation
Issa et al[7]/2025	Revumenib	Phase 1/2	Age ≥30 d with R/R *KMT2Ar* acute leukemia	In 57 pts: 22.8%	Median OS: 8 mo	In 22 pts: 68.2%	16%	14%
Arellano et al[8]/2025	Revumenib	Phase 1/2	Age ≥30 d with R/R *NPM1*-mutated AML	In 64 pts: 23.4%.	Median OS: 4 mo; median EFS: 3 mo	Not reported	13.1%	22.6%
Wang et al[9]/2024	Ziftomenib	Phase 1/2	Age ≥18 y with R/R *NPM1*-mutated or *KMT2Ar* AML	In 26 *NPM1* pts: 31%. In 32 *KMT2A* pts: 6%	In *NPM1* pts: 3.5 mo; in 2 *KMT2A* pts: 5.4 mo	In 8 *NPM1* pts: 63%; in 2 *KMT2A* pts: 100%	14%	1%
Searle et al[10]/2024	Bleximenib	Phase 1/2	Age ≥18 y with R/R *NPM1*-mutated or *KMT2Ar* or rNUP98/214 altered acute leukemia	In 12 *NPM1* pts: 33.3%. In 9 *KMT2A* pts: 33.3%.	Not reported	Not reported	6.8%	Not observed
Wei et al[11]/2024	Bleximenib	Phase 1B	Age ≥12 y, R/R or ND *NPM1*-mutated or *KMT2Ar* AML	*NPM1* RR: 8/12=67% *NPM1* ND: 12/16=75% *KMT2A* RR: 5/10=50% *KMT2A* ND: 3/4=75%	Not reported	Not reported	4%	0%
Zeidner et al[12]/2024	Enzomenib	Phase 1/2	Adult pts with R/R acute leukemia characterized by *KMT2Ar, NPM1m*, and other *HOXA9/MEIS1*-driven leukemia subsets	In 13 *NPM1* pts: 23.1%; in 22 *KMT2A* pts: 22.7%.	Not reported	Not reported	~3%	0%

AML, acute myeloid leukemia; *DS,* differentiation syndrome; *KMT2Ar, KMT2A* rearranged; *MRD,* measurable residual disease; *ND,* newly diagnosed; *pts,* patients; *R/R,* relapsed or refractory.

search of ClinicalTrials.gov showed that the only menin inhibitor currently being studied in an actively recruiting phase 3, double-blind trial in the US is bleximenib (Johnson & Johnson). In this study, bleximenib is combined with venetoclax and azacitidine for the treatment of patients with AML and *NPM1* or *KMT2A* mutations.[6] Kura Oncology is planning a phase 3 trial combining ziftomenib with intensive chemotherapy, as well as with venetoclax and azacitidine; however, this study has not yet begun recruiting patients. Syndax is also conducting several trials investigating revumenib in the first-line setting, but no randomized phase 3 trials have been initiated in the US to date.

The future questions and research endeavors that remain open encompass several key areas. A major challenge is therapy prioritization in co-mutated AML, particularly when multiple actionable mutations such as *FLT3* and *NPM1* coexist, raising the question of how best to select treatment. The optimal duration of menin inhibitor therapy also remains undefined, with ongoing debate over fixed versus indefinite administration. Another area of uncertainty is the post-transplant setting, in which the potential role of menin inhibitors as maintenance therapy after allogeneic hematopoietic stem cell transplantation requires further investigation. Measurable residual disease (MRD)–driven decisions are also under study, including whether *NPM1* MRD negativity can safely guide treatment discontinuation or de-escalation. Strategies to prevent the emergence of resistance mutations represent another crucial focus. Comparative efficacy among menin inhibitors is not yet established, leaving open whether superior outcomes will be determined by efficacy itself or by factors such as tolerability and potential for combination therapies. Finally, the question remains: which menin inhibitor will achieve first-line approval through a gold-standard randomized clinical trial? The race is intense, and the coming years promise to be highly exciting for the leukemia community.

"Although approval in the relapsed and refractory settings is important, frontline approval is even more critical..." *—Moaath K. Mustafa Ali, MD, MPH, hematologist and medical oncologist, Cleveland Clinic*

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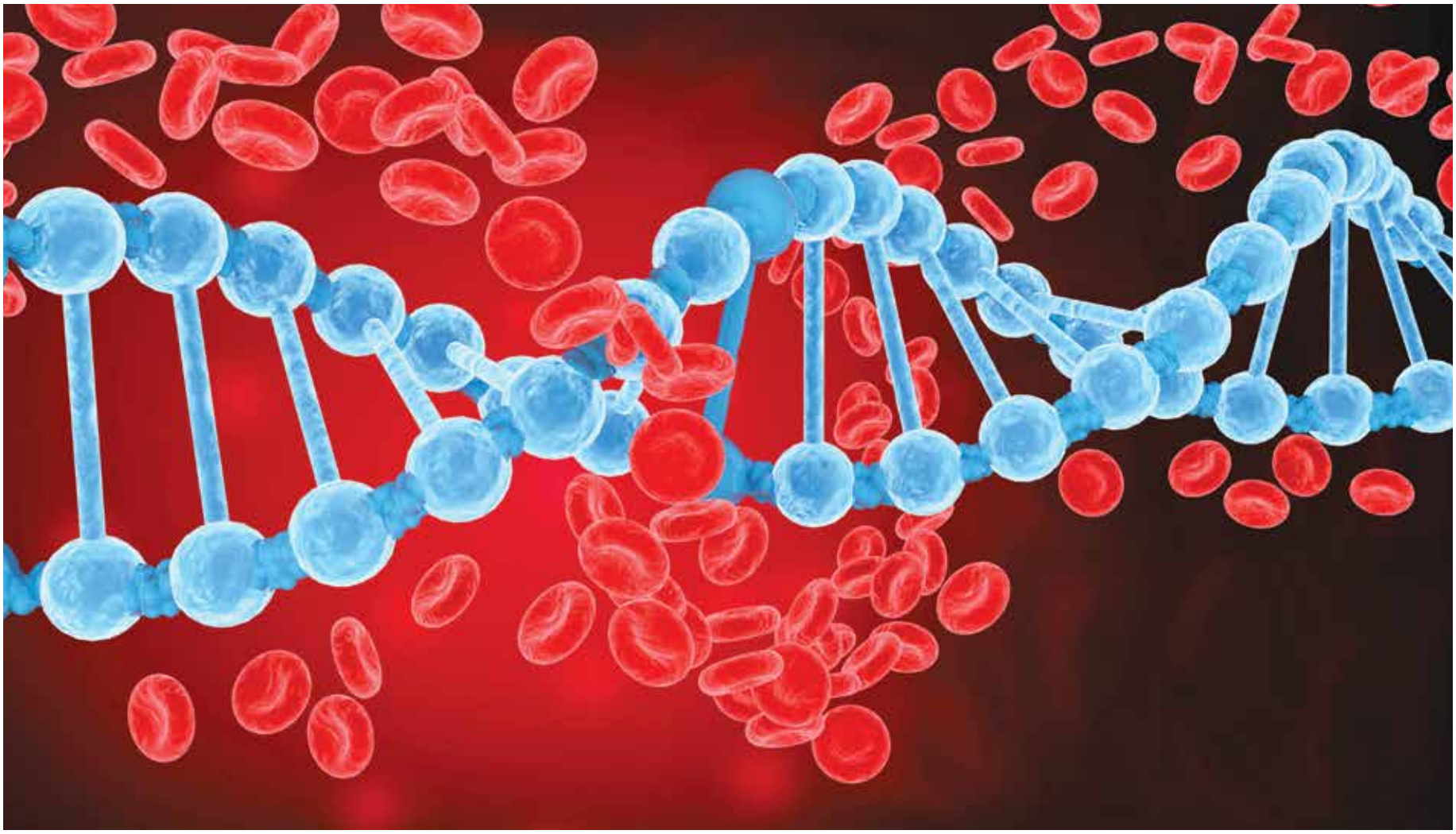

Memorial Sloan Kettering Cancer Center Develops New Liquid Biopsy Test for Hematologic Malignancies

*By **Melissa Badamo***

A new liquid biopsy test, developed at Memorial Sloan Kettering (MSK) Cancer Center in New York, is reinventing how hematologic malignancies are diagnosed, monitored, and treated.

MSK-ACCESS, short for "Analysis of Circulating Cell-Free DNA (cfDNA) to Evaluate Somatic Status," identifies genomic alterations found in the blood at low frequencies using hybridization capture and ultradeep next-generation sequencing.[1] Unique molecular indexing is used to tag individual molecules in a sample before sequencing, enabling identification and filtering of sequencing errors, thereby improving its accuracy.

The original design of MSK-ACCESS "was made specifically to detect small fragments of DNA that are released by different tumors into circulation, and specifically targeted solid tumor biomarkers," explained **Maria E. Arcila, MD,** deputy chief of the Molecular Diagnostic Service and medical director of Molecular Hematopathology at MSK. "These small fragments of DNA can be tested with this assay, sparing the patient from invasive tumor biopsy procedures. A unique feature of all of our assays is that we also incorporate the sequencing of a patient-specific normal control to unequivocally determine if mutations identified in a sample are somatic, and not reflecting germline variants or clonal hematopoiesis."

Maria E. Arcila, MD

While the MSK-ACCESS solid assay utilizes DNA isolated from white blood cells in the whole blood sample as the normal control, MSK-ACCESS Heme required a different approach.

MSK-ACCESS Heme

MSK-ACCESS Heme was developed to diagnose and monitor patients with hematologic malignancies. Dr. Arcila explained that in contrast to solid tumors, hematologic malignancies often arise in blood and bone marrow and, therefore, may have tumor cells circulating in the blood. As a result, testing can be performed directly from genomic DNA isolated from the white blood cells themselves.

However, some hematologic malignancies—such as diffuse large B-cell lymphoma (DLBCL) and other B- and T-cell lymphomas—are tissue based. These behave similarly to solid tumors in that they do not have significant bone marrow involvement or circulating disease, and invasive procedures are needed to sample the tumor.

"Further, their distribution may be widespread, with distinct molecular characteristics from site

Know the Practice

to site, such that single-tumor biopsies may not adequately capture the heterogeneity present across multiple sites," Dr. Arcila said. "In these cases, testing cfDNA from peripheral blood may represent a valuable approach to noninvasively sample and more comprehensively characterize the disease."

Historically, the standard of care for most hematologic malignancies has involved testing neoplastic cells from blood, solid tissues, or bone marrow, according to Dr. Arcila. Now, MSK-ACCESS Heme offers a less invasive method for assessing non-circulating disease, while also enabling easy serial sampling. This high-sensitivity assay can help classify and risk-stratify patients based on their mutational profile, monitor measurable residual disease, and assess treatment responses—providing an additional strategy that could guide treatment decisions and further personalize management of individual patients.

"In DLBCL, for example, cfDNA profiling could help infer cell of origin, enable molecular subtyping for relevant risk stratification, and help guide treatment selection. In classical Hodgkin lymphoma, a disease distinctly difficult to profile on a tumor biopsy due to the low content of Reed-Sternberg cells, cfDNA could represent a superior sample for testing. Similarly, in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma, testing of cfDNA may facilitate a more comprehensive assessment of the nodal compartment of the disease," Dr. Arcila explained.

Aside from testing cfDNA, MSK-ACCESS Heme can also be used to test genomic DNA (gDNA) from the blood or bone marrow. In this context, the assay provides high-sensitivity mutation detection to monitor residual disease at levels that may be undetectable by other testing modalities. Whether testing is performed on cfDNA or gDNA, this assay requires the use of alternate sources of patient-specific normal control DNA, as white blood cells may include neoplastic cells.[2]

"We are the first laboratory to use cfDNA isolated from nail clippings as the normal control for sequencing," Dr. Arcila elaborated.

Development and Validation

The content of both the MSK-ACCESS solid and heme panels was developed and optimized using data from more than 25,000 solid tumors and over 10,000 hematologic malignancies previously sequenced by MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a comprehensive tumor-sequencing test also developed at MSK. The MSK-ACCESS panels reflect the most commonly mutated genes and key biomarkers across the different cancers.[1,3,4]

"It was important to keep the content narrow to maintain high sensitivity," Dr. Arcila explained.

In a validation study, MSK-ACCESS demonstrated 99% specificity and 92% sensitivity in de novo mutation calling down to 0.5% variant allele frequency (VAF) based on 70 cfDNA samples with 100 known single-nucleotide variants and mutations in *AKT1, ALK, BRAF, EGFR, ERBB2, ESR1, KRAS, MET, PIK3CA,* and *TP53*.[5]

Validation data for MSK-ACCESS Heme were based on 130 unique patient samples, demonstrating similar performance to the solid version of the assay. The accuracy for de novo variant calling, down to 0.5% VAF, was 93% and higher (~0.1%) for known variants when a tumor-informed (genotyping) analysis was possible due to prior positive test results. The research team further compared the VAFs of genetic mutations between the MSK-ACCESS Solid and MSK-ACCESS Heme versions of the assay and calculated a coefficient of determination of 99.6.[6]

Both assays were clinically validated in the MSK Clinical Laboratory Improvement Amendments laboratory and received New York State Department of Health (NYSDOH) regulatory approval in 2019 and 2023, respectively.

Limitations and Future Research

Like other liquid biopsy-based assays, testing by MSK ACCESS Solid and MSK ACCESS HEME comes with several challenges and limitations despite their high accuracy, sensitivity, and specificity.

"Liquid biopsy diagnostics rely on the release of fragmented tumor DNA into the bloodstream. The amount of DNA that is shed in circulation can be highly variable depending on many factors, including the tumor type, the location, and the disease burden, among many others," said Dr. Arcila. "Tumor-derived DNA may be very low in circulation, and hence, the proportion of tumor-derived DNA may be comparatively very low compared to DNA derived from normal cells." As a result, mutations from the tumor may become undetectable despite the sensitivity of the assay, Dr. Arcila explained.

Next, the MSK team is launching a whole-transcriptome assay for tumor samples. This comprehensive assay can assess fusion genes and splicing variants that DNA-based tests may not detect.

"This will also provide new capabilities for gene expression analysis, offering a broader view of disease biology and potentially uncovering new therapeutic targets for antibody-directed agents, for instance, or diagnostic markers to further guide personalized treatment decisions," Dr. Arcila concluded.

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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

POWERFUL RESULTS AS EARLY AS 2L[1]

PRESCRIBED CAR-T CELL THERAPY FOR RRMM[2*] #1

CARVYKTI® demonstrated a

↓59% **Reduction in the risk of disease progression or death vs standard therapy (DPd or PVd)[1†]**
(HR=0.41; 95% CI: 0.30-0.56; *P*<0.0001)

CARTITUDE-4 STUDY DESIGN

CARTITUDE-4 is a randomized, open label, multicenter controlled study evaluating the efficacy and safety of CARVYKTI® for the treatment of adult patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a PI and an immunomodulatory agent. A total of 419 patients were randomized 1:1 to receive either CARVYKTI® (n=208) or standard therapy, which included daratumumab, pomalidomide, and dexamethasone (DPd) or pomalidomide, bortezomib, and dexamethasone (PVd) selected by physician prior to randomization based on patient's prior antimyeloma therapy (n=211). The primary efficacy measure was PFS analyzed based on the Intent-to-Treat Analysis Set.[1]

2L=second-line; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival; PI=proteasome inhibitor; RRMM=relapsed or refractory multiple myeloma.

*From January 2021 to November 2024.
†15.9 month median follow-up (Intent-To-Treat Analysis Set).

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.

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®.

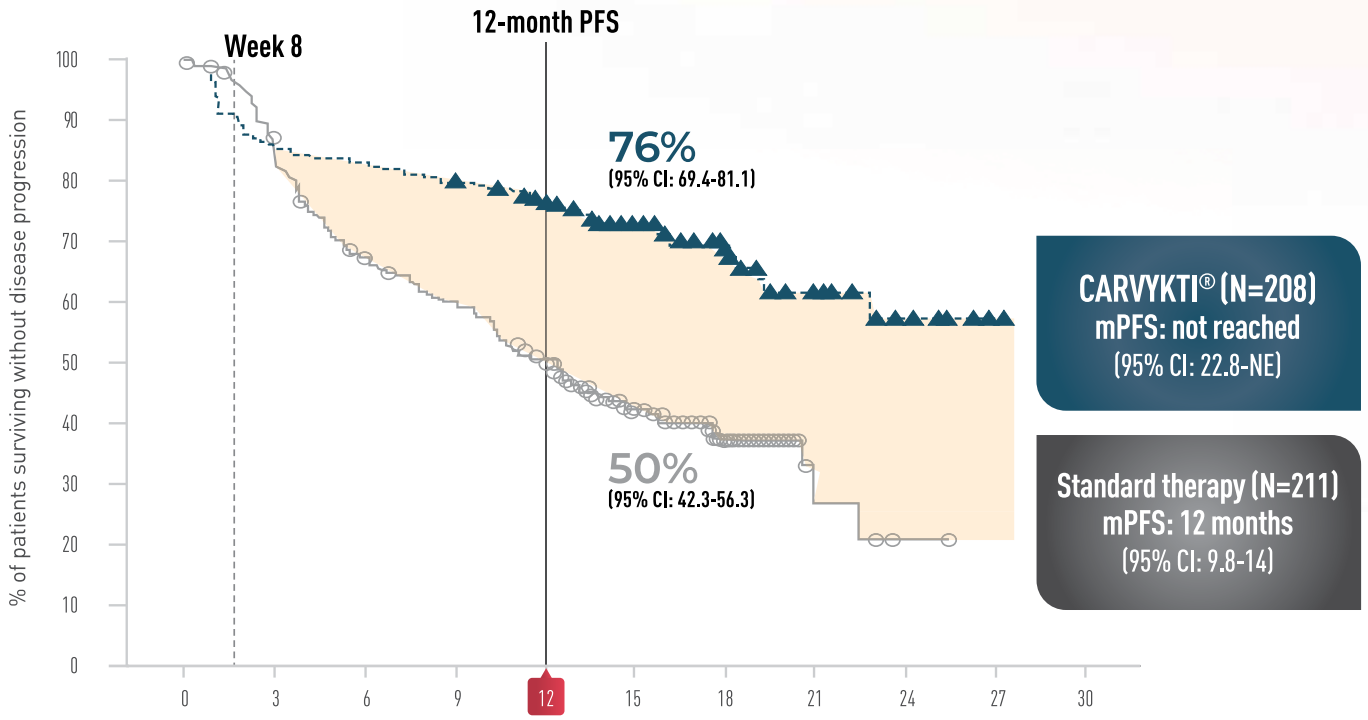
CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

POWERFUL RESULTS

CARTITUDE-4 median follow-up of 15.9 months

CARVYKTI® SIGNIFICANTLY PROLONGED PROGRESSION-FREE SURVIVAL (PRIMARY ENDPOINT) vs STANDARD THERAPY (DPd or PVd)

PROGRESSION-FREE SURVIVAL[1,3*]



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

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

CARVYKTI® arm — Standard therapy arm

CARVYKTI® demonstrated a

59%

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

DEEP RESPONSES[2]

85% overall response rate was achieved with CARVYKTI®

81% of patients achieved a deep response with CARVYKTI®[1,3*]

- Deep response is defined as ≥VGPR
- **With CARVYKTI® (N=208): 85% ORR[†] (95% CI: 79.0-89.2), 74% ≥CR (95% CI: 67.5-79.9), 81% ≥VGPR** (66% sCR, 8% CR, 8% VGPR), and 3% PR
- With standard therapy (DPd or PVd) (N=211): 68% ORR[†] (95% CI: 61.0-74.0), 22% ≥CR (95% CI: 16.8-28.5), 46% ≥VGPR (18% sCR, 4% CR, 23% VGPR), and 22% PR

DURABLE RESPONSES

Median duration of response for CARVYKTI® was not reached[1*]

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

Percentages rounded to nearest whole number.

CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mDOR=median duration of response; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; PFS=progression-free survival; PR=partial response; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent complete response; VGPR=very good partial response.

*Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.
[†]Includes patients who achieved PR or better.
[‡]Estimated mDOR.

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

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

OVERALL SURVIVAL

CARTITUDE-4 median follow-up of 15.9 months

MEDIAN OVERALL SURVIVAL WAS NOT REACHED WITH CARVYKTI® OR STANDARD THERAPY[1]

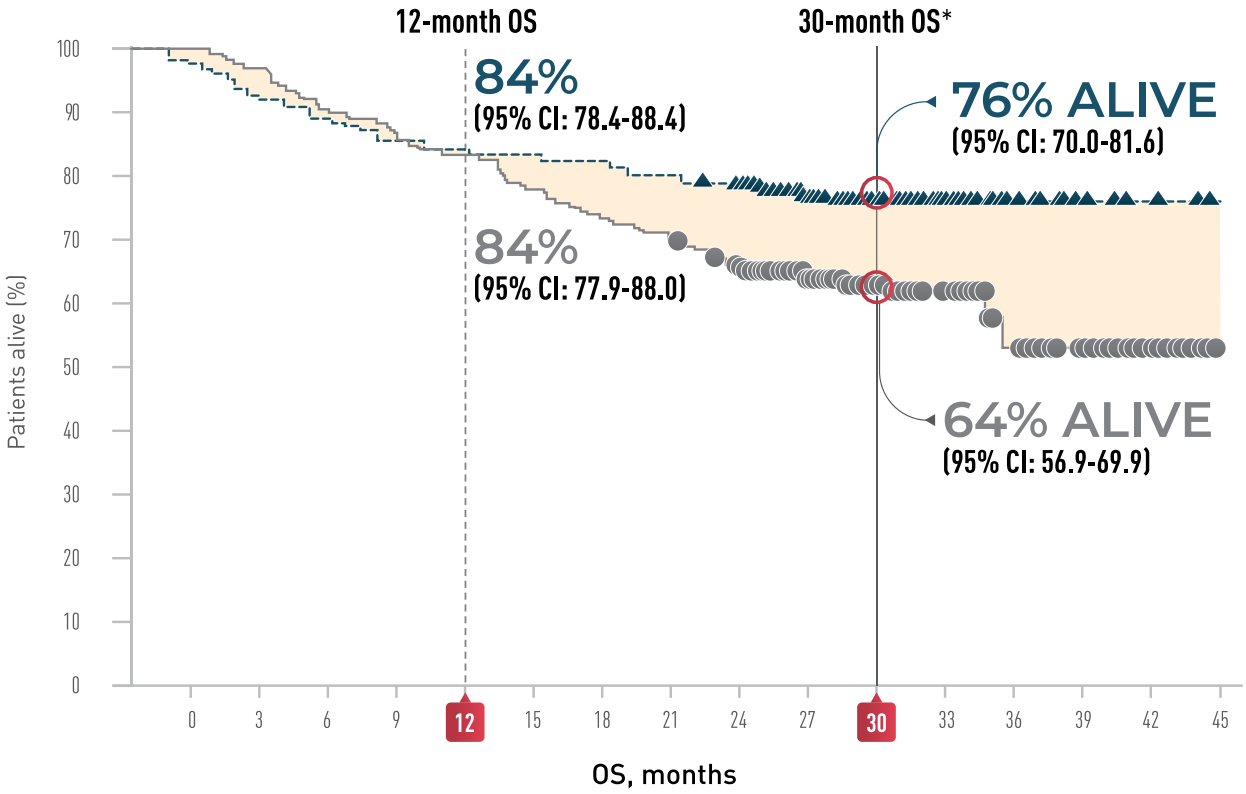
- 34% of the planned OS events have occurred
- Within the first 10 months of randomization, a higher proportion of patients in the CARVYKTI® arm died compared with the standard therapy arm

CARTITUDE-4 median follow-up of 33.6 months

OVERALL SURVIVAL FOR CARVYKTI® vs STANDARD THERAPY IN 2L+

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® (N=208)
mOS: not reached
(95% CI: NE-NE)

Standard therapy (N=211)
mOS: not reached
(95% CI: 37.75-NE)

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=pomalidomide, bortezomib, and dexamethasone; USPI=US Prescribing Information.
*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.
†HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

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

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

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.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (cont'd)

Neurologic toxicities (cont'd)

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.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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.

CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

IMPORTANT SAFETY INFORMATION (cont'd)

Hypogammaglobulinemia (cont'd)

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.

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

cp-258862v9

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. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.1.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed January 31, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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[1,2]*

CARTITUDE-4 primary analysis demonstrated†:

POWERFUL

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

59% reduction in the risk of disease progression or death vs standard therapy‡
(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

81% of patients achieved a deep response of VGPR or better

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

DISCOVER MORE AT
CARVYKTIHCP.com
Data rates may apply.

NCCN CATEGORY 1

***THE FIRST AND ONLY* CAR-T CELL THERAPY TO BE DESIGNATED AS NCCN CATEGORY 1** in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for multiple myeloma after 1 prior therapy[5]

Listed under "Therapy for Previously Treated Multiple Myeloma Relapsed/Refractory Disease After 1-3 Prior Therapies" as an option after 1 prior line of therapy, including an IMID and a PI, and refractory to lenalidomide. Additionally, ciltacabtagene autoleucel is designated as Category 2A after 3 prior therapies.[5]

CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; CR=complete response; DPd=daratumumab, pomalidomide, dexamethasone; HR=hazard ratio; IMID=immunomodulatory drug; ISS=International Staging System; mDOR=median duration of response; mPFS=median progression-free survival; NCCN=National Comprehensive Cancer Network; NE=not estimable; ORR=overall response rate; PI=proteasome inhibitor; PR=partial response; PVd=pomalidomide, bortezomib, dexamethasone; RRMM=relapsed or refractory multiple myeloma.

*As part of a 5-step process.
†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.

Johnson&Johnson

LEGEND BIOTECH

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

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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:

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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:
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For patent information: www.janssenpatents.com

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As NCI Funding Cuts Loom, Early Detection Could be an Early Casualty

By ***Sara Karlovitch***

The National Cancer Institute (NCI) is facing a nearly 40% funding cut under President Trump's 2026 fiscal year budget. Under the proposed plan, the NCI would receive $4.531 billion, which is approximately $2.7 billion less than it received the previous year.[1] If the budget passes, there could be significant consequences for the oncology industry, potentially leading to brain drain, study disruption, staffing shortages, and more.

"A reduction in NIH [National Institutes of Health] and NCI funding could have severe long-term consequences, jeopardizing the remarkable progress that has led to a record 18 million cancer survivors alive in the US today. The cuts would directly slow the pace of innovation, delaying breakthroughs in prevention, detection, and treatment," said **Julie Gralow, MD,** chief medical officer and executive vice president of the American Society of Clinical Oncology (ASCO).

While the NCI cuts will significantly affect ongoing cancer care and treatments, they will also affect ongoing efforts in early detection. Early detection is crucial to improving survival rates and stalling disease progression. However, approximately 50% of cancers are at an advanced stage at the time of diagnosis.[2] Researchers are currently facing many challenges surrounding efforts related to early detection, including a lack of understanding of the biology of early-stage disease, determining who is most at risk, validating early disease biomarkers, a lack of technology, and how to evaluate early detection approaches.[2]

The Early Detection Backbone

NCI funding has played an outsized role when it comes to early detection, as such programs have relied heavily on NCI funding. Not only will funding cuts stall the development of new technologies, they will also hinder our understanding of cancer risk factors, according to Dr. Gralow.

"Funding reductions may also hinder studies aimed at understanding risk factors for early-onset cancers, which have increased by nearly 80% among people aged 18 to 49 since the 1990s. Without continued investment, innovations in early detection may take longer to reach clinical practice, leading to delayed diagnoses and fewer lives saved," Dr. Gralow remarked.

Field Dispatch

NCI funding has led to the development of major tools and resources used by oncologists. One notable example is The Cancer Genome Atlas Program (TCGA), which has molecularly characterized over 20,000 primary cancers, along with normal sample matching across 33 cancer types. Over the course of approximately 12 years, the program has produced more than 2.5 petabytes of data. TCGA data are available for anyone in the research community to use, leading to developments in cancer diagnosis, treatment, and prevention.[3]

Another notable example is the My Pediatric and Adult Rare Tumor (MyPART) network. This network, which focuses on rare solid tumors with no cures, collects samples to study how rare tumors grow and identify potential treatments. With the help of NCI funding, the MyPart network has been able to share data on rare cancers globally, develop new treatment testing procedures, design clinical trials for rare cancers, and more.[4]

"Cuts to early detection research will lead to patients presenting with more advanced, higher-risk disease, reducing their chances for cure and affecting their quality of life, progression-free survival, and overall survival," said **Belinda Avalos, MD,** 2025 American Society of Hematology (ASH) president and professor of medicine at Atrium Health Levine Cancer.

Brain drain could be another long-term impact of the cuts. NCI cuts could disproportionately affect oncologists at the beginning of their careers, largely due to a reduction in grant funding. This could significantly stall innovation, including early detection. The NCI is already starting to reduce funding. In July, the institute announced it was dropping the number of accepted grant applications in the final 2 months of fiscal year 2025 from 9% to 4%. This would mean only 1 in 25 applicants will receive funding.[5]

"The long-term consequences are significant—fewer clinical trials, a diminished pipeline of scientific innovation, and a lost generation of promising investigators. Early-career scientists may leave or avoid ambitious projects altogether," said **Ryan Schoenfeld, PhD,** chief executive officer of The Mark Foundation for Cancer Research.

Oncologists may feel pressured to leave academic oncology altogether. A 2023 study published in the *Journal of Clinical Oncology* found that 22% of oncologists reported being somewhat likely to leave their current institution. Of those likely to leave, 46% plan to leave academic oncology altogether.[6]

The study used data from the Association of American Medical Colleges' StandPoint Faculty Engagement Survey—which was conducted between 2017 and 2020 and included 25 US medical schools—and found that female oncologists were more likely to leave academic oncology compared to their male counterparts. Of the faculty surveyed, 26% of female oncologists reported they were likely to leave their institutions compared to 19% of male oncologists.[6]

Funding cuts have led many scientists to seek careers outside the US, which could further exacerbate healthcare shortages.[7]

"This would also lead to a brain drain as early-career researchers leave academia or the US, weakening the workforce pipeline and causing the US to lose its global leadership in biomedical research. Ultimately, fewer resources would mean delayed clinical trials, fewer innovative therapies, and higher healthcare costs, resulting in more lives lost to cancer," said Dr. Gralow.

The Future of Early Detection

To prepare for potential cuts and help mitigate their impacts on patients, researchers can consider pursuing private funding.

"There are some areas where oncologists can find additional funding, like grants and awards. For example, ASH has committed $12 million to expand its awards and mentorship programs in response to the threats to hematology research. However, this cannot make up for robust, sustained government funding through NIH," said Dr. Avalos.

Professional organizations are stepping into a vital role for oncologists as they navigate funding shortages. These organizations can not only help provide funding, they can also create a support network for professionals during uncertain times. Less government funding ultimately means that oncologists will have to play a larger role in connecting patients with clinical trials, assisting other researchers, and mentoring early-career researchers.

"While oncologists themselves have limited ability to compensate for cuts directly, they can support cancer research indirectly by connecting patients to clinical trials, collaborating on translational research with academic centers, mentoring early-career investigators, and advocating to lawmakers for sustained and predictable NIH and NCI funding," said Dr. Gralow.

Still, there is only so much private funding available to mitigate NCI cuts, which will affect ongoing research and delay other projects. Any cuts to NIH or NCI funding will set back the field of cancer research by at least 10 years, according to Dr. Avalos. NCI funding allows researchers to take risks and drive innovation, which is incredibly crucial for continued breakthroughs.

"Progress in early detection depends on bold investments in innovative technologies that can identify the earliest signals of cancer. For example, researchers are now using AI [artificial intelligence]–enabled models to predict which patients with precancerous conditions, like myelodysplastic syndromes or smoldering myeloma, may progress into aggressive blood cancers such as AML [acute myeloid leukemia] or multiple myeloma. With steep cuts to NCI funding, the kind of high-risk, high-reward research needed to drive these breakthroughs is increasingly vulnerable, unless alternative sources step in to fill the gap," said Dr. Schoenfeld.

The House Appropriations Committee passed the 2026 Labor, Health and Human Services, Education, and Related Agencies appropriations bill on September 10, which would maintain funding for the NCI and NIH at the 2025 level.[8] While the House bill signals some level of bipartisan support, the funding isn't secure until it is made into law. As of the time of writing, the future of NCI funding has yet to be determined.

> **"Cuts to early detection research will lead to patients presenting with more advanced, higher-risk disease, reducing their chances for cure, and affecting their quality of life, progression-free survival, and overall survival."** *— Belinda Avalos, MD, professor of medicine at Atrium Health Levine Cancer and 2025 ASH President*

"Medical research funding is not political," said Dr. Avalos. "It's important that Congress continues to support institutions like NIH with sustained and robust funding."

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The Ozempic Effect:

How GLP-1 Receptor Agonists May Reduce Blood Cancer Risk and Improve Patient Outcomes

*By **Melissa Badamo***

By lowering body mass index (BMI), popular weight loss drugs such as Ozempic and Wegovy may offer a new pathway for reducing the risk or improving survival for multiple myeloma (MM) and other hematologic malignancies among patients with obesity.

Made with the active ingredient semaglutide, these glucagon-like peptide-1 receptor agonists (GLP-1 RAs) work by emulating GLP-1 hormones in the gut that slow digestion while regulating hunger and blood sugar levels.[1] Originally used for the treatment of type 2 diabetes, these drugs are increasingly being used off-label for weight loss. According to data from Epic Research, 1.7% of Americans were prescribed a semaglutide drug in 2023, 40 times more than over the past 5 years.[2]

The soaring popularity of these drugs has opened conversations about their potential effects outside of weight loss. *Blood Cancers Today s*poke with several experts to dive into the links among obesity, cancer risk, and treatment outcomes and the potential for GLP-1 RAs to reduce cancer risk.

Obesity and Increased Cancer Risk

Obesity and elevated BMI are associated with an increased risk for 13 types of cancers, including myeloma and its precursor condition, mass spectrometry–detected monoclonal gammopathy of undetermined significance (MGUS).[3,4] In a study published in *Blood Advances*, obesity was associated with 73% higher odds of MGUS compared with a healthy BMI after adjusting for age, sex, Black race, education, and income.[4]

Around 890 million adults and 160 million children worldwide have obesity, defined by a BMI of 30 or higher.[5] Similarly, type 2 diabetes is associated with increased risk for obesity-related cancer,[6,7] and patients with MGUS or MM are more likely to have a preceding diagnosis of diabetes compared with matched controls.[8]

"It's becoming increasingly clear that obesity is a risk factor for developing myeloma and for worse overall survival in myeloma patients," said **Michaela Reagan, PhD,** faculty scientist II at the MaineHealth Institute for Research and an associate professor at Tufts University School of Medicine. "How and why this is is still under review. Obesity causes many different effects across the body. It's physiologically so diverse that it's hard to pin down one thing."

Adipose tissue, or body fat, is known to increase with weight gain and elevated BMI. Adipocytes, cells that make up adipose tissue, have inflammatory markers that help create resistance mechanisms to chemotherapy. An increase in adipocytes results in the secretion of molecules that promote progression to MM, and increased bone marrow adipose tissue causes drug resistance in MM cells.[9]

"Changes in the adipose tissue itself can lead to systemic inflammation and potentially affect cancer growth," Dr. Reagan explained. "In obesity, there's increased bone marrow adipose as well as visceral adipose and subcutaneous adipose. Increased adipose in the bone marrow appears to also contribute to tumor growth."

By modeling obesity-driven myeloma in mice, Dr. Reagan studies the mechanistic relationship of body weight with myeloma progression to understand how obesity affects myeloma cell phenotype and signaling at a molecular level. Mice fed a high-fat diet to induce obesity are compared with mice fed a low-fat diet without obesity. However, not all obese mice had an increased risk for myeloma. They expect this work to be published in *Cancer Prevention Research*.

"It depends on the mouse model that we use. By comparing outcomes in different types of mice, we can start to figure out why obesity contributes to myeloma," she explained. "We believe it has to do with the immune system along with other factors. Obesity often leads to insulin resistance and metabolic syndromes, which can also affect how tumors grow. Additionally, inflammation, inflammatory cytokines, hormone, and lipid-related changes resulting from obesity can all contribute to cancer growth. Now, we're trying to pinpoint specific ways that obesity leads to or accelerates cancer to develop better prevention or intervention approaches."

Another study of 563 patients showed that BMI at the time of MM diagnosis was not associated with overall survival and that higher BMI at diagnosis was associated with *better* overall survival in female patients, highlighting the complex nature of obesity and myeloma risk.[10]

Still, a growing body of literature suggests that obesity is associated not only with MM but also with other blood cancers such as non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, acute myeloid leukemia, and myelodysplastic syndromes.[11-13]

Obesity and Treatment Outcomes in Leukemia

Obesity is not only linked to an increased risk for blood cancer but also worse treatment outcomes. A study led by **Shai Shimony, MD,** a medical oncologist at the Dana-Farber Cancer Institute and an instructor in medicine at Harvard Medical School, revealed that elevated BMI is associated with adverse outcomes and higher toxicity in adolescent and young adult patients with acute lymphoblastic leukemia (ALL).[14]

Patients with a BMI of 25 or higher had lower event-free survival (63% vs 77%), lower overall survival (64% vs 83%), and a higher rate of nonrelapse mortality (11.7% vs 2.8%) compared with patients with a healthy BMI. Conversely, patients with normal BMI had comparable overall survival rates if they were younger (15-29 years) or older (30-49 years; 83% vs 85%, respectively).[14]

"Patients with normal BMI, even if they're older

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than 40, have excellent outcomes," Dr. Shimony said. "Traditionally, it was thought that age is driving survival in this group. However, when we adjusted and evaluated the interaction between age and BMI, we saw that BMI is driving survival rather than the age group."

In addition, patients with higher BMI experienced higher rates of toxicity, including hyperglycemia and elevated liver enzymes.

What might explain this association between elevated BMI and poor treatment outcomes? Since nonrelapse mortality rates were higher among patients with higher BMI, Dr. Shimony hypothesizes that these patients are more prone to toxicities. However, in older patients (30-49 years) in the highest BMI group (BMI > 30 kg/m^2), there was also a signal for higher relapse rates, implying that chemotherapy resistance might play a role in the lower survival rates among patients with higher BMI.

GLP-1 RAs and Reduced Cancer Risk

Since healthy BMI is associated with reduced cancer risk, better treatment outcomes, and lower toxicities, can weight loss drugs such as Ozempic also reduce cancer risk? A retrospective study published in *JAMA Oncology* put this question to the test.[15]

Researchers compared cancer risk in 43,317 adults who were obese or overweight and using GLP-1 RAs for weight management with a cohort of 43,315 adults who were not using GLP-1 RAs. Patients using the drugs had a 17% lower risk for the 13 obesity-related cancers, including MM, compared with patients who did not use the drugs.[15]

"If people with obesity and MGUS or myeloma can reduce their weight, it is possible they can improve their outcomes," Dr. Reagan said. "I think there's huge potential for these drugs to safely decrease tumor burden and increase survival in obese patients."

Another study evaluated GLP-1 RA use among 1,097 patients with MGUS and type 2 diabetes compared with a matched cohort of 2,194 patients who never used a GLP-1 RA. In the study cohort, 2.6% of patients who used a GLP-1 RA progressed from MGUS to MM, compared with 5.0% of patients who never used a GLP-1 RA. Independent of BMI, GLP-1 RA use was associated with a 55% reduction in risk of progression from MGUS to MM compared with no use.[16]

"For these patients, using a GLP-1 RA is beneficial to prevent progression to a devastating cancer in addition to their diabetes control," said **Su-Hsin Chang, PhD,** associate professor of surgery in the Division of Public Health Sciences at Washington University School of Medicine in St. Louis and senior author of the study. "This is like killing two birds with one stone."

Although the study did not evaluate the biological or metabolic mechanisms of GLP-1 RAs on progression risk, Dr. Chang theorizes that modulating inflammatory responses reduces oxidative stress and suppresses tumor cell growth.

"Also, insulin and insulin-like growth factor 1 are key myeloma growth factors. GLP-1 RAs can help control blood sugar, enhance insulin secretion, and improve metabolic syndrome," she explained. "Moreover, its effects on neural pathways that regulate food intake, ultimately leading to a reduction in appetite, food cravings, and ad libitum intake may contribute to weight loss, which may be another pathway leading to reduced risk of MGUS progression among users."

Although Dr. Chang and her team did not study the weight loss effect of GLP-1 RAs, patients using the medication may experience weight loss after they receive an MGUS diagnosis, she noted.

"This weight loss induced by GLP-1 RA may potentially reduce the risk of MGUS progression. If there is any effect on MGUS progression coming from weight loss, this is included in the estimated association of GLP-1 RA use," she said. "We need more studies to confirm [our findings] and comprehensively evaluate whether GLP-1 RAs may be used in patients with MGUS for primary prevention of multiple myeloma."

Other antidiabetes medications, such as metformin, also have the potential to reduce blood cancer risk. For example, a systematic review and meta-analysis of 166 studies showed that patients who take metformin for their diabetes are less likely to develop leukemia, lymphoma, or MM compared with those who don't take metformin.[17]

Further Research and Unanswered Questions

Despite promising results, experts agree that more prospective research is needed to determine the role of GLP-1 RAs in reducing cancer risk.

"What we've seen so far in the literature is not clear," said Dr. Reagan. "It's hard to compare these different retrospective analyses. What we really need going forward is a prospective analysis of the effects of GLP-1 RAs for people with obesity or diabetes who have MGUS or myeloma. This would allow us to test if these agonists affect their disease or progression to myeloma or to later stages of myeloma."

Dr. Reagan also warns against "weight cycling," as it may have a negative impact on cancer risk. "We have to be careful about weight loss in patients because work from Dr. Catherine Marinac and her team has shown that weight cycling, where patients gain and lose weight, can often lead to worse outcomes than maintaining a steady weight," she said.

Patients who experienced weight cycling had an increased risk for MM compared with those who maintained weight, showing that keeping a lean weight may provide the strongest MM prevention.[18]

"If we're going to think about intercepting people's weight, we need to be sure that they can decrease weight without gaining it back," Dr. Reagan added. "Often, when patients come off GLP-1 agonists, they'll regain their weight. So, we have to be careful."

According to Drs. Reagan and Chang, many unanswered questions remain about the link between GLP-1 RAs and cancer risk: what the direct mechanisms of GLP-1 RAs are, how different patient characteristics may impact its effect, and, lastly, what the side effects are.

In terms of safety, GLP-1 RAs have been linked to ocular adverse events[19] and increased risk for depression.[20] Ozempic is indicated for type 2 diabetes and cardiovascular disease, and Wegovy is indicated for weight management in adults and children aged 12 years and older with obesity or those who are overweight with a weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. Both drugs received initial FDA approval in 2017.[21,22]

"We don't understand all the effects of the GLP-1 receptor agonists," Dr. Reagan added. "We're still learning about their effects on the immune system, but we know that they're cardioprotective. They can induce robust weight loss, they can reverse diabetes, they protect nephrons in the kidney, and they lead to decreased all-cause mortality."

Moving forward, Dr. Shimony suggests that BMI be incorporated and stratified in every clinical trial for ALL to determine its effects on patient outcomes. However, one unanswered question remains: How can *altering* BMI affect treatment outcomes?

"Our study only measured BMI at diagnosis. As such, we do not know how BMI dynamics throughout the treatment period would influence efficacy and toxicity outcomes," he said. "As GLP-1 RAs reduce weight and inflammation, they may alter the effect of BMI on toxicity and outcomes, but that's just a hypothesis. Future studies will evaluate the impact in adolescents and young adults treated for ALL, but it's definitely a point of interest to try and improve outcomes for our patients."

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News Roundup

The latest news and updates in hematologic oncology research

Oncologists Face Increasingly Complicated Payer-Practice Relationships

By ***Sara Karlovitch***

The payer-practice relationship is becoming increasingly entrenched in legal updates amid proposed changes to prior authorization and 2026 Medicare Physician Fee Schedule (MPFS) and Hospital Outpatient Prospective Payment System (OPPS) rules.

In late June, US Health and Human Services (HHS) Secretary Robert F. Kennedy, Jr., and Centers for Medicare & Medicaid Services (CMS) Administrator Dr. Mehmet Oz participated in a roundtable discussion with industry leaders to discuss changes to the prior authorization processes for Medicare Advantage, Medicaid Managed Care, Health Insurance Marketplace, and commercial plans. Representatives from CareFirst BlueCross BlueShield, Centene Corporation, The Cigna Group, Elevance Health, GuideWell, Highmark Health, Humana, Inc., Kaiser Permanente, and UnitedHealthcare were all present at the discussion.

Mary-Elizabeth Percival, MD

During the roundtable, participating insurers pledged to undertake six reforms intended to reduce red tape, enhance transparency for patients and providers, and increase the speed of care decisions. Specifically, insurers have pledged to standardize electronic prior authorization submissions using Fast Healthcare Interoperability Resources, reduce volume of services that require prior authorization, honor existing authorizations during insurance transitions, enhance transparency and communication, expand real-time responses, and ensure medical professionals review all denials.[1]

"We appreciate the pledge from industry leaders to address the challenges of prior authorization and look forward to seeing this commitment translated to meaningful action. Ultimately, we hope that healthcare stakeholders and the Administration work together to achieve lasting reforms to prior authorization practices and deliver real relief to physicians and the patients they care for," **Mary-Elizabeth Percival, MD,** chair of the American Society of Hematology Committee on Practice, told *Blood Cancers Today*.

Changes to the MPFS and OPPS rules also stand to affect oncologists and their ability to treat patients. The Community Oncology Alliance (COA) supports reforms to both rule sets, including the increase to MPFS conversion factor and site-neutral payments. However, other policy changes threaten to overshadow any progress made by changes to the MPFS and OPPS rules. For example, Medicare has declined nearly 30% in real terms over the past 20 years, and the proposed rule changes don't address structural problems, according to the COA.

Policy changes by the CMS could also threaten patient access to chimeric antigen receptor T-cell therapy and other cell-based immunotherapies. Proposed changes would replace the current reimbursement policy with bundled product payments, which would create access barriers for independent practices. The COA is calling for payment options that reflect actual care delivery to increase the accessibility of cell-based immunotherapies.[2]

"The American Society of Hematology strongly advocates for streamlined, transparent, and data-driven prior authorization practices and shorter turnaround times to ensure patients receive timely and essential medical care," said Percival.

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New Donor Strategy Boosts Transplant Success for Hard-to-Match Patients

*By **Melissa Badamo***

Despite the curative role of hematopoietic stem cell transplant (HSCT) for patients with blood cancers, some patients are unable to find a matched related or unrelated donor, therefore delaying transplant and leading to worse outcomes.[1] However, a new donor search prognosis scoring system can help prevent transplant delays for patients unlikely to find a matched unrelated donor.

A study published in the *Journal of Clinical Oncology* found no difference in HSCT outcomes for patients with blood cancers who are unlikely to find a matched unrelated donor when this donor search prognosis strategy is used to help accelerate patients to transplant.[2,3] This highlights that transplant speed is more important for improving outcomes than using a matched donor.[1]

Stephanie Lee, MD, MPH

The donor search prognosis strategy, developed by the National Marrow Donor Program (NMDP), uses patients' human leukocyte antigen type and race or ethnicity to estimate their chance of finding a matched unrelated donor.[2] For example, the likelihood of finding a matched unrelated donor is lower for patients of ethnic and racial minorities (33%) compared with patients of European ancestry (67%), according to a study published in *Blood Advances*.[4] The strategy consists of shifting to alternative donors—such as mismatched unrelated donors, haploidentical related donors, or umbilical cord blood—when the likelihood of finding a matched unrelated donor is low.[2]

In the multicenter, biological assignment trial, 1,751 patients with blood diseases such as lymphoma and leukemia were stratified by the likelihood of finding a matched unrelated donor: very likely (54.7%), less likely (29.5%), or very unlikely (15.8%). Patients in the very likely group used a matched unrelated donor, while patients in the very unlikely group used an alternative donor.[2,3]

After comparing transplant outcomes of these three groups, the researchers found that 2-year survival did not differ in both univariate and multivariate analyses. Multivariate analyses also found no difference in relapse, treatment-related mortality, disease-free survival, and chronic or acute graft-versus-host disease after transplant.[2,3] These results show that transplant should not be delayed for patients while waiting for a fully matched donor.[1]

"As a physician, a primary concern following a blood cancer diagnosis is getting my patient to transplant quickly, as the benefits of transplant diminish as the disease progresses. Patients can face complications, greater resistance to treatment, and worse outcomes if a prolonged search for a fully matched unrelated donor delays transplant," said **Stephanie Lee, MD, MPH,** first author of the study, professor, and section head of hematologic malignancies in the Clinical Research Division at Fred Hutch Cancer Center, in a press release.[2]

The study was conducted by investigators from the Blood and Marrow Transplant Clinical Trials Network, which consists of the NMDP, Consortium of US transplant centers, Center for International Blood and Marrow Transplant Research (CIBMTR), and the Emmes Company.[2]

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BTX A51 Produces Early Signal in Relapsed AML and MDS

*By **Dean Patterson***

A first-in-human trial of the oral kinase inhibitor BTX A51 has shown it can be given safely at active doses, with hints of benefit in a tough-to-treat group of patients with relapsed or refractory acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (MDS). Results were reported in the *Journal of Hematology & Oncology*.

BTX A51 is designed to pull two levers at once. It blocks casein kinase 1α, which normally suppresses *p53,* and it shuts down CDK7 and CDK9, which keep RNA polymerase II driving transcription of pro-survival genes like *MCL1* and *MYC*. Preclinical work suggested this dual hit could restore apoptosis in leukemic cells, even those that had stopped responding to standard therapy.

The phase 1 study enrolled 31 adults, almost all with prior exposure to venetoclax and hypomethylating agents. Twenty-eight had AML, and three had high-risk MDS. The trial used an adaptive dose-escalation plan, moving from 1 mg up to 42 mg, given orally 3 or 5 days a week in repeating cycles. The goal was to find a tolerable schedule, check whether the drug hit its targets, and watch for early activity.

Toxicities were common but not unexpected. Most patients reported nausea, vomiting, or diarrhea. Cytopenias and febrile neutropenia also appeared. Two liver-related events at higher doses led investigators to shut down the 42 mg arm. Going forward, the recommended dose is 21 mg 3 days a week given continuously. No treatment-related deaths were seen.

Pharmacokinetics showed that the drug stuck around: it had a half-life of about 28 hours, with steady state by the middle of the first cycle. In marrow samples, BTX A51 cut down *MCL1* levels, reduced phosphorylation of RNA polymerase II, and boosted p53. The level of γH2AX, a marker of DNA damage, also rose. Some patients showed serum increases in MIC-1, another signal of *p53* activation.

Clinical responses were limited but notable. Three patients achieved complete remission with incomplete blood count recovery. All three carried *RUNX1* mutations. In fact, among patients with *RUNX1*-mutated disease treated at 11 mg or higher, the response rate hit 30%. Ex vivo assays backed this up: RUNX1-mutant blasts showed striking sensitivity to BTX A51, in some cases more than to venetoclax. Laboratory work also suggested the drug combines well with venetoclax or azacitidine.

The trial was small and not designed to prove efficacy, but the investigators argue that these data point toward a path forward. BTX A51 appears to engage its targets and produce manageable side effects at the recommended dose. *RUNX1* mutation status could help identify patients most likely to benefit, and combination regimens may deepen responses and stretch their duration.

The next step will be larger studies that test the drug in biomarker-selected patients and in combination with backbones already in use for AML and MDS.

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Highlights From the **EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY 2025 CONGRESS OCTOBER 17-21, 2025 IN BERLIN, GERMANY**

Orelabrutinib Emerges With Promising Results in Advanced Marginal Zone Lymphoma

By ***Nichole Tucker***

In patients with marginal zone lymphoma (MZL), the addition of a novel, selective, irreversible Bruton's tyrosine kinase inhibitor (BTKi), orelabrutinib to chemoimmunotherapy has been demonstrated promising results in a phase 2 clinical trial with no dose or regimen modifications required.

Results were presented in a poster during the European Society for Medical Oncology 2025 Congress in Berlin, Germany. The results showed an objective response rate of 100% in the eight patients treated. Of the responders, 12.5% achieved complete responses and 87.5% achieved partial responses.

The protocol utilized two orelabrutinib/chemoimmunotherapy combinations: orelabrutinib combined with bendamustine/rituximab and orelabrutinib combined with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). Orelabrutinib plus bendamustine/rituximab was administered to seven of the eight patients, while one patient received R-CVP.

Patients included in the study were predominantly male (75.0%), and five of eight had relapsed disease while three had refractory MZL. Baseline characteristics also showed that patients had a mean age of 69 years (range, 55-82), 62.5% of the study population had stage IVA disease, 50.5% had an International Prognostic Index score of greater than or equal to 2, and Ki67 was less than 20% in half of patients. Most patients (n=5; 62.5%) did not have comorbidities at baseline, but three patients (37.5%) did.

The study was conducted to address the need for more effective treatment options for patients with relapsed or refractory MZL. Although chemoimmunotherapy remains the standard approach, there is a high potential for relapse with no next-line options. Because orelabrutinib is in the BTKi class, it was hypothesized that it would demonstrate targeted activity in various B-cell lymphoma subtypes, especially when combined with standard-of-care and anti-CD20 antibody therapy.

The study investigators report that recruitment for this study is ongoing. More detailed results for other study outcomes will be announced in the future. Aside from response, the outcomes being explored in the study include progression-free survival, overall survival, and safety.

Reference

European Society for Medical Oncology 2025 Congress; October 17–21, 2025. Abstract 1264P.

Tafasitamab Plus Lenalidomide Outshines Glofitamab Monotherapy for DLBCL

*By **Andrew Moreno***

A study has performed a matched-adjusted indirect comparison (MAIC) between two management approaches for diffuse large B-cell lymphoma (DLBCL): tafasitamab plus lenalidomide versus glofitamab. In this comparison, the study's investigators found the combination regimen to have greater efficacy and safety than the monotherapy approach.

The Guangdong Academy of Medical Sciences in China was legally responsible for the study. Findings were presented at the European Society for Medical Oncology 2025 Congress in Berlin, Germany.

The analysis centered on data from the internationally conducted L-MIND study for 81 patients who received combination tafasitamab plus lenalidomide for DLBCL. The investigators calibrated and weighted these data to be compatible for comparison with data from another cohort of 155 patients who had received glofitamab for DLBCL with a median follow-up of 12.6 months. Patients were then matched by age, disease's cell origin type, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, sex, prior treatments, and proportions of non-Hodgkin's lymphoma subtypes.

"Ultimately, ORR [objective response rate], CRR [complete response rate], PRR [partial response rate], DOR [duration of response], PFS [progression-free survival], OS [overall survival], and safety outcomes of Tafa-len [tafasitamab plus lenalidomide] were compared with glofitamab in a population with well-balanced baseline characteristics," wrote the investigators.

The investigators reported in their efficacy results that the combination group's median PFS of 12.1 months and median OS of 34.2 months were both markedly longer than in the glofitamab group, and they determined a statistically significant difference between them ($P<0.01$).

Likewise in response to treatment, the investigators found that the median DOR was markedly longer in the combination group than in the glofitamab group, at 43.9 versus 18.4 months, respectively ($P<0.01$). Both the ORR and PRR were longer in the combination group than in the glofitamab group, at 63.16% versus 51.6% and 22.46% versus 12.3% respectively.

Regarding CRR, the investigators noted these were similar between the two groups at 40.7% in the combination group and 39.35% in the glofitamab group. The two groups also had comparable frequencies of serious adverse events.

The investigators expressed confidence in the reliability of their study's findings and acknowledged that "since the baselines of the two groups cannot be completely consistent and are affected by the inherent statistical performance of the MAIC method, this may cause certain uncertainties in the efficacy of this study to a certain extent."

Reference

European Society for Medical Oncology 2025 Congress; October 17–21, 2025. Abstract 1276P

Isatuximab-Based Regimens Show Clinical Benefit, Increased Adverse Events in Relapsed or Refractory Myeloma

*By **Melissa Badamo***

When added to dexamethasone, the CD38-targeting monoclonal antibody isatuximab delays disease progression in patients with relapsed or refractory multiple myeloma (MM) compared with non-isatuximab therapies. However, isatuximab also brings an increased risk of infusion reactions and respiratory-related adverse events.[1]

Results from the systematic review and meta-analysis were presented at the European Society for Medical Oncology 2025 Congress. Using PRISMA [Preferred Reporting Items for Systematic reviews and Meta-Analyses] guidelines, the researchers searched PubMed, Embase, and Cochrane Central for randomized controlled trials comparing isatuximab-based regimens with non–isatuximab-based regimens. The study included 774 patients across all clinical trials. Researchers estimated hazard ratios (HRs) and risk ratios (RRs) for time to next treatment (TTNT), overall survival (OS), infusion-related reactions, and upper respiratory tract infections.[1]

By significantly delaying disease progression, isatuximab reduced the risk of requiring subsequent therapy by 44% (HR,=0.56; 95% CI, 0.46–0.69; $P<0.001$; $I^2 = 0\%$). Although improvements in OS could not be determined, isatuximab showed a trend towards superior OS (HR,=0.88; 95% CI, 0.69–1.11, $P=0.27$; $I^2 = 26\%$).[1]

By locking onto the myeloma cell-surface protein,[2] isatuximab has been consistently shown to outperform non-isatuximab combinations in relapsed or refractory MM. In the randomized phase 3 IKEMA trial published in *Lancet*, isatuximab combined with carfilzomib and dexamethasone improved progression-free survival compared with just carfilzomib and dexamethasone (not reached vs 19 months, respectively; one-sided $P=0.0007$).[3]

However, isatuximab significantly increased the risk of infusion-related reactions (RR=15.62; 95% CI, 5.30–113.92; $P=0.06$; $I^2=86\%$), and upper respiratory tract infections (RR=1.51; 95% CI, 1.19–1.93; $P<0.001$; $I^2=0\%$) compared with non-isatuximab regimens, according to the meta-analysis. These adverse events should be monitored closely, the researchers noted.[1]

In the IKEMA trial, a higher proportion of patients in the isatuximab, carfilzomib, and dexamethasone group experienced grade 3 or higher treatment-emergent adverse events compared with the non-isatuximab regimen (77% vs 67%, respectively).[3] Other adverse events related to isatuximab include low blood counts, fatigue, and gastrointestinal disturbances.[2]

Although the meta-analysis supports treatment with isatuximab for patients with relapsed or refractory MM, the researchers urge for more long-term studies that consider patient characteristics to gain a clearer view of the survival benefit and long-term safety profile of isatuximab.[1]

Isatuximab is approved in the US and European Union in combination with carfilzomib-dexamethasone and pomalidomide-dexamethasone for relapsed or refractory disease and in combination with bortezomib, lenalidomide, and dexamethasone for newly diagnosed disease.[4-6]

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Editor's Picks

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, section editor* ***Matthew Davids, MD,*** *director of clinical research for the lymphoma division at Dana-Farber Cancer Institute and associate professor of medicine at Harvard Medical School, highlights recent research in chronic lymphocytic leukemia (CLL).*

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Matthew Davids, MD

CHRONIC LYMPHOCYTIC LEUKEMIA

Triplet Therapy Achieves Deep Responses in Relapsed or Refractory CLL

By ***Keightly Amen***

Most patients with relapsed CLL achieved deep responses with zanubrutinib, venetoclax, and obinutuzumab, according to a study published in *Blood*. The triplet therapy was well tolerated, with no unexpected toxicities.

Bruton's tyrosine kinase (BTK) inhibitors and B-cell lymphoma-2 (BCL2) inhibitors have significantly changed outcomes for patients with CLL, including measurable residual disease (MRD) and progression-free survival (PFS), in different risk groups. Combinations of these two drug classes with anti-CD20 antibodies have also shown promise. However, data are limited regarding outcomes for patients with relapsed or refractory disease, especially those who have previously received a BTK inhibitor or BCL2 inhibitor. The study in *Blood* aimed to fill that gap.

"Given the shift toward time-limited combinations in the first-line treatment of patients with CLL, there is a high need for time-limited second- or later-line therapies that promise efficacy even in a post-BTKi/post-BCL2 inhibitor setting," wrote **Moritz Fürstenau, MD,** of the University Hospital Cologne in Germany, and colleagues. "With the implementation of an MRD-guided treatment discontinuation approach in this study, we aimed to keep the treatment exposure as low as possible while ensuring an adequate treatment duration for those patients with a slower response dynamic."

Their ongoing phase 2 CLL2-BZAG trial is testing MRD-guided treatment with the triplet combination of BTK inhibitor zanubrutinib, BCL2 inhibitor venetoclax, and anti-CD20 antibody obinutuzumab after optional debulking with bendamustine in adult patients with relapsed or refractory CLL.

Inclusion criteria were previous treatment and active disease requiring treatment per criteria established by the International Workshop on Chronic Lymphocytic Leukemia. Patients who experienced disease progression during a prior treatment with a BTK inhibitor or venetoclax and patients with potentially resistant mutations were excluded.

The study enrolled 42 patients, with 40 eligible for analysis. Participants had received a median of one prior therapy, with a range of one to five. Prior therapies included a BTK inhibitor (n=18, 45%), venetoclax (n=7, 17.5%), or both (n=5, 12.5%). A total of 15 patients (37.5%) had a *TP53* mutation/deletion, and 31 (77.5%) had an unmutated immunoglobulin heavy chain variable region gene.

Patients received 1,000 mg of intraveneous obinutuzumab on days 1 and 2 (full dose on day 1 or split over the 2 days), 8, and 15 of the first cycle and on day 1 of any following cycles. They received 160 mg oral zanubrutinib twice daily, starting in the second induction cycle and continuing until the end of study treatment. The third cycle added 400 mg oral venetoclax. Induction therapy included a total of eight cycles, six with the triplet combination, before final restaging.

After final restaging, patients received maintenance treatment with obinutuzumab (1,000 mg every 3 months), zanubrutinib (160 mg twice daily), and venetoclax (400 mg daily) until they achieved a complete response (CR) or a clinical CR in addition to undetectable MRD in the peripheral blood for two consecutive measurements or a total of 24 months.

After 6 months of treatment with the triple combination, all patients responded. Just more than half (n=21, 52.5%) had undetectable MRD. For many patients, remission deepened over time. At the time of publication, no patients had required additional treatment. Analyses estimated 18-month PFS would be 96% and overall survival would be 96.8%.

Why I chose this research:

"This study demonstrates a proof of principle that even for high-risk patients with R/R CLL, it is possible to achieve deep remissions that may allow meaningful time off treatment. However, patient selection remains important, as the triplet regimens have demonstrated higher rates of more severe infection, so these approaches should be generally considered only for patients with CLL who are fit and without significant medical comorbidities."

Adverse events were reported mostly in the induction period. The most common were COVID-19 (n=26), infusion reactions (n=15), diarrhea (n=15), thrombocytopenia (n=14), fatigue (n = 12), nausea (n=12), and neutropenia (n=12). Two patients had fatal adverse events (COVID-19 and fungal pneumonia secondary to COVID-19). Grade 3 or higher adverse events were neutropenia (n=10), COVID-19 (n=9), thrombocytopenia (n=7), and pneumonia (n=5).

"Given the potential of this MRD-driven, individualized treatment approach to achieve deep remissions in most patients even when preexposed to targeted treatments, this time-limited triple combination warrants further exploration in relapsed/refractory CLL," the authors concluded.

Reference

Fürstenau M, et al. *Blood*. 2025;145(12):1282–1292. doi:10.1182/blood.2024026685

Acalabrutinib Effective for Older or Frail Patients With CLL

By ***Lauren Evoy Davis***

In a phase 2 clinical trial, researchers evaluated how older and frail patients with CLL would tolerate acalabrutinib, a tyrosine kinase inhibitor. The CLL-Frail trial is an ongoing trial conducted by the German CLL Study Group.

Fifty-three older adult patients were recruited for the trial, and 34 were still receiving treatment. The median age of the patients was 81 years, and 47.2% were considered frail. Although the cohort is small, the significance is notable because few clinical trials include older adults, according to first author **Florian Simon, MD**, of the University Hospital Cologne, and colleagues.

The researchers used the FRAIL score to determine which patients were eligible. The FRAIL score is based on patient-reported assessment, and patients needed to have an Eastern Cooperative Oncology Group (ECOG) score of 3 or lower. Frailty is loosely defined as being at increased risk for comorbidities, polypharmacy, weight and muscle loss, and loss of the ability to recover from illness or withstand biological stressors.

Trial participants receive 100 mg of acalabrutinib twice a day in 28–day cycles (for up to 24 cycles) and continued treatment unless adverse effects (AEs) or disease progression occurred. Adverse effects included high blood pressure, infections with a common toxicity criteria (CTC) grade higher than 2, cardiac events, falls, fractures, cognitive impairment/dementia, and late–onset neutropenia (>4 weeks after treatment completion) of at least grade 3.

The primary end point was overall response rate (ORR) after six full cycles of acalabrutinib. The secondary end point was progression-free survival. As

follow-up data become available, the researchers will report ORR after 24 full cycles of treatment, event-free survival, duration of response, and time to next treatment, as well as measures of quality of life. Because six patients stopped therapy before the first dose in cycle four, 46 patients completed three full cycles of acalabrutinib treatment.

At the time of this report, 34 patients were still receiving acalabrutinib therapy and 18 discontinued treatment. Five patients died as a result of infections, including two who had COVID-19. Twenty-one other patients also had COVID-19 but survived, making this the most common AE. Three patients withdrew consent. Of the remaining patients, 25 had one or more dose adjustments due to AEs.

Overall, acalabrutinib was well tolerated by the patients recruited to participate, and the researchers emphasize that careful patient selection and shared decision-making are key to successful trials. These results were first reported in the journal *Blood*, a publication of the American Society of Hematology.

Why I chose this research:

"This paper reports on the CLL-Frail trial, the first prospective trial in CLL to focus exclusively on an older adult population aged 80 or older, a common population that is often underrepresented in prospective CLL clinical trials. This study provides high-quality evidence supporting acalabrutinib monotherapy as an effective and safe frontline treatment option for older patients with CLL, who represent the majority of patients seen in routine clinical practice."

Reference

Simon F, et al. *Blood*. 2025 Sep 4:blood.2025028550. doi:10.1182/blood.2025028550

Fitness Does Not Hinder Safety, Efficacy of Ven-Obi for CLL

By ***Lauren Evoy Davis***

Researchers evaluated the clinical outcomes of treatment-naive patients with CLL who received venetoclax-obinutuzumab (Ven-Obi). Patients with *TP53* aberrations were excluded, and a key focus was on how age, comorbidities, and treatment dose intensity influenced efficacy and safety. The findings were published in the journal *Blood*.

Fitness status was defined by the cumulative illness rating scale (CIRS) (>6) or creatinine clearance of 70 mL/min or lower, which indicates kidney function. The CIRS helps researchers understand the impact of chronic diseases and comorbidities and influences treatment decisions.

The researchers recruited 410 patients with a median age of 67 years. More than half (55.7%) were classified as unfit, with a median age of 72, based on higher CIRS scores or reduced kidney function. The median age for the fit patients was 58. The protocol recommended 12 cycles of Ven-Obi, lasting 28 days, for each group.

Why I chose this research:

"This is a helpful study for the field, as it shows encouragingly similar efficacy and toxicity data for Ven-Obi in fit and unfit patients with CLL. The data do suggest potentially shorter PFS in the setting of dose reduction, although it is difficult to account for confounding factors, as this finding may be driven more by frailer patients or those with more comorbidities being more likely to experience toxicities leading to dose reduction. Overall, the results are reassuring that Ven-Obi is a safe and effective regimen that can be used for patients with CLL and a wide range of age and fitness levels."

Patients received obinutuzumab IV for six cycles, starting with 100 mg on the first day and 900 mg on the second day (or 1,000 mg on day 1). Administration of obinutuzumab continued with 1,000 mg on day 8 and 1,000 mg on day 15 of cycle 1, followed by 1,000 mg on day 1 of cycles 2 through 6. On day 22 of cycle 1, patients received oral venetoclax daily, starting with a 5-week dose increase and then continuing at 400 mg daily until cycle 12 was complete.

Adverse events occurred in both groups and led to cessation of treatment for 15.8% of unfit patients and 5% of fit patients. Neutropenia occurred in 56.9% of fit patients, lasting about 11 days, and in 62.7% of unfit patients, lasting about 8 days. Of the fit patients, 35.9% experienced fatigue, 56.9% had infusion-related reactions, and 69.9% reported infections. Of the unfit patients, 15.8% experienced fatigue, 44.3% had infusion-related reactions, and 57.5% reported infections.

The overall response rate reached 89.5% among unfit patients and 96.1% among fit patients. Rates of undetectable measurable residual disease ($<10^{-4}$) were also comparable, with 80.3% in the unfit group and 85.1% in the fit group. At 3 years, progression-free survival (PFS) was nearly identical between unfit and fit patients (86.4% vs 87.5%). Overall survival at 3 years was slightly lower in unfit patients (91.8%) compared with fit patients (96.9%).

Overall, the findings indicate that Ven-Obi offers comparable efficacy and safety for both fit and unfit patients with previously untreated CLL. Dose intensity influenced outcomes. Dose intensity reductions below 80% were more common in unfit patients yet did not compromise long-term efficacy. However, dose intensity reductions below 70% correlated with shorter PFS.

Reference

Al-Sawaf O, et al. *Blood*. 2025 Aug 27:blood.2025028899. doi:10.1182/blood.2025028899

SITC to Recognize Cancer Immunotherapy Researchers at Annual Conference

*By **Melissa Badamo***

The Society for Immunotherapy of Cancer (SITC) announced its award recipients ahead of its annual conference, November 5-9, 2025, honoring several oncologists who have made an impact in the field of cancer immunotherapy.[1]

2026 Richard V. Smalley Memorial Award & Lectureship

Catherine J. Wu, MD, professor of medicine and chief of the Division of Stem Cell Transplantation and Cellular Therapies at the Dana-Farber Cancer Institute, received the 2026 Richard V. Smalley Memorial Award & Lectureship. The award honors the late Richard V. Smalley, MD, one of SITC's charter members.

Catherine J. Wu, MD

With clinical interests in acute myeloid leukemia, chronic lymphoblastic leukemia, and chronic myeloid leukemia, Dr. Wu's research focuses on identifying immunogenic antigen targets using genomics-based approaches. Specifically, her research contributed to the discovery of CML28 and CML66 as targets for antigen-specific immunotherapy in leukemia and other hematologic malignancies due to their overexpression in tumor samples.[2,3]

2025 Richard V. Smalley Memorial Award & Lectureship

Ira Mellman, PhD, president of the Parker Institute for Cancer Immunotherapy, received the 2025 Richard V. Smalley Memorial Award & Lectureship for his decades of research on immunotherapies, from cancer vaccines to anti-TIGIT therapies.

Ira Mellman, PhD

Dr. Mellman is known for his discovery of endosomes and the role of dendritic cells in immunity and vaccine responses. He also played a role in identifying TREX1 as a key immune checkpoint and a potential immunotherapeutic target as monotherapy or in combination with T-cell–targeted therapies for patients with cancer.[4]

2025 SITC Lifetime Achievement Award

Francesco Marincola, MD, chief scientific officer and global head of research at Translational and Advanced Medicine Global in Nashville, Tennessee, received the 2025 SITC Lifetime Achievement Award for his work developing strategies for adoptive cell therapies and leading therapeutic programs based on nuclease-deactivated CRISPR circuits.

Francesco Marincola, MD

In his previous role as senior vice president and global head of research at Kite Pharma, he led research efforts to identify novel therapies for hematologic malignancies and solid tumors. Before that, he served as a senior investigator in cancer immunotherapy at the National Institutes of Health and National Cancer Institute for more than 20 years.

2025 Pedro J. Romero Service to *JITC* Award

Sjoerd van der Burg, PhD, received the 2025 Pedro J. Romero Service to *JITC* Award for his contributions and commitment to the *Journal for ImmunoTherapy of Cancer (JITC)*, the official journal of SITC. Dr. van der Burg is the deputy editor-in-chief of *JITC* and serves as professor in experimental cancer immunology and therapy at the department of medical oncology of the Leiden University Medical Center.

Sjoerd van der Burg, PhD

Dr. van der Burg leads the experimental cancer immunology and therapy group at Leiden University Medical Center, which conducts clinical trials focusing on the immune control of cancer, therapeutic vaccines, and T-cell transfer therapy. He also leads Oncode Accelerator's international consortium on therapeutic vaccines, which focuses on developing new vaccines, discovering new antigens, and conducting first-in-human clinical trials.

"My research focuses on identifying and solving the hurdles for effective immunotherapy, and these days in particular, on the interaction between T cells and myeloid cells during immunotherapy," Dr. van der Burg told *Blood Cancers Today*. "The award means a recognition of my peers for the drive I have and the work I do to ensure that the *Journal for ImmunoTherapy of Cancer* is and remains a high-impact journal in the field of immune oncology."

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Pediatric Hematologist Oncologist Receives Excellence Award

*By **Melissa Badamo***

Jessica A. Pollard, MD, received the 2025 Healing Hero of Excellence in Pediatric Oncology Award from Kids Beating Cancer, an organization that provides resources and support for children with leukemia and other cancers.[1] The award honors a pediatric oncologist who delivers compassionate, comprehensive care, advances the science of curing childhood cancer through safe, effective treatments, and advocates for patients and their families.[2]

Jessica A. Pollard, MD

With expertise in myeloid malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), Dr. Pollard serves as associate professor of pediatrics at Harvard Medical School, senior physician at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, and interim co-director of the Hematologic Malignancy Program at Dana-Farber.[3]

Through trials from the Children's Oncology Group, Dr. Pollard helped identify CD74 expression as a therapeutic target for a subset of patients with pediatric AML[4] and studied the prognostic impact of co-occurring mutations in *FLT3-ITD* pediatric AML, finding that patients with *FLT3-ITD*-positive AML and poor-risk *NUP98::NSD1* mutations had worse outcomes than patients with favorable-risk mutations.[5]

After earning her MD from Columbia University in 2000, Dr. Pollard completed a residency in pediatrics at the University of Washington and Seattle Children's Hospital and a pediatric hematology oncology fellowship at the Fred Hutchinson Cancer Research Center. She has been at Dana-Farber since 2014, after serving as an attending physician at Seattle Children's Hospital/Fred Hutchinson Cancer Research Center for 8 years.[3]

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