Advances in Relapsed or Refractory Multiple Myeloma

Research Working Toward a Potential Cure for an Incurable Disease

Multiple Myeloma Considered an Incurable and Painful Disease

It has been estimated that 36,110 new cases of multiple myeloma will be diagnosed in 2025 in the United States, of which 20,030 being men and 16,080 being women.[1] In addition, 12,030 deaths are expected to occur (6,540 in men and 5,490 in women).[1] For patients with heavily pretreated relapsed or refractory multiple myeloma, current studies report a median progression-free survival of <6 months and median overall survival of approximately 1 year[2,3] Multiple myeloma is currently considered to be an incurable disease associated with a staggering death.[4] Individuals in the end state of multiple myeloma may experience various physical symptoms from fatigue to extreme pain that can significantly impact quality of life.[5]

Most Common Physical Symptoms in Patients with Advanced Multiple Myeloma[5]

Physical Symptom	Description
Bone Fractures	Weakened bones due to bone damage; fractures may occur even after a minor injury or fall
Fatigue	Severe fatigue, which can affect ability to perform daily activities and affect mood and mental state over time
Kidney Problems	Kidney damage may cause symptoms such as changes in urination, fluid retention, and high blood pressure; left untreated, kidney problems can lead to renal failure
Severe Pain	Severe pain in the bones, particularly in the spine, ribs, or pelvis; pain may be constant or intermittent and may worsen with movement or activity
Weight Loss	Unintentional weight loss due to reduced appetite, nausea, and other gastrointestinal symptoms; overall wellbeing can decline over time

Relapsed or Refractory Multiple Myeloma Patients Go Through Multiple Treatments

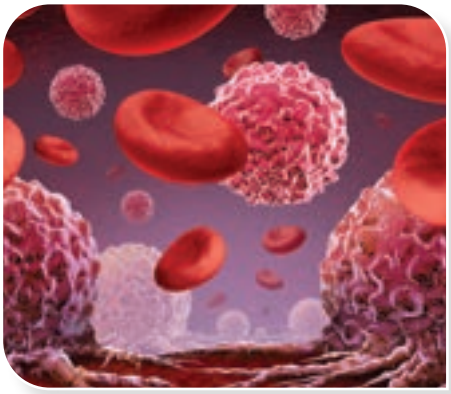
There have been treatment advances that have increased median survival from 2 years to 10 years over the past two decades, but research is still working towards a cure.[4,6] Multiple myeloma is often described as a relapsing-remitting disease, meaning patients typically experience periods of remission followed by relapse.[6] Recent advances led to novel treatments that can effectively control the disease and manage symptoms, improving survival outcomes in patients.[6,7] However, despite treatment, multiple myeloma patient are at high risk of relapse and need prompt treatment to reduce the morbidity and mortaility associated with the disease and complications.[5-7] Over time, the cancer can become resistant to treatments, leading to relapsed or refractory multiple myeloma.[5,6] This can involve multiple lines of treatment as the disease progresses.[7]

Types of Refractory Myeloma[6]

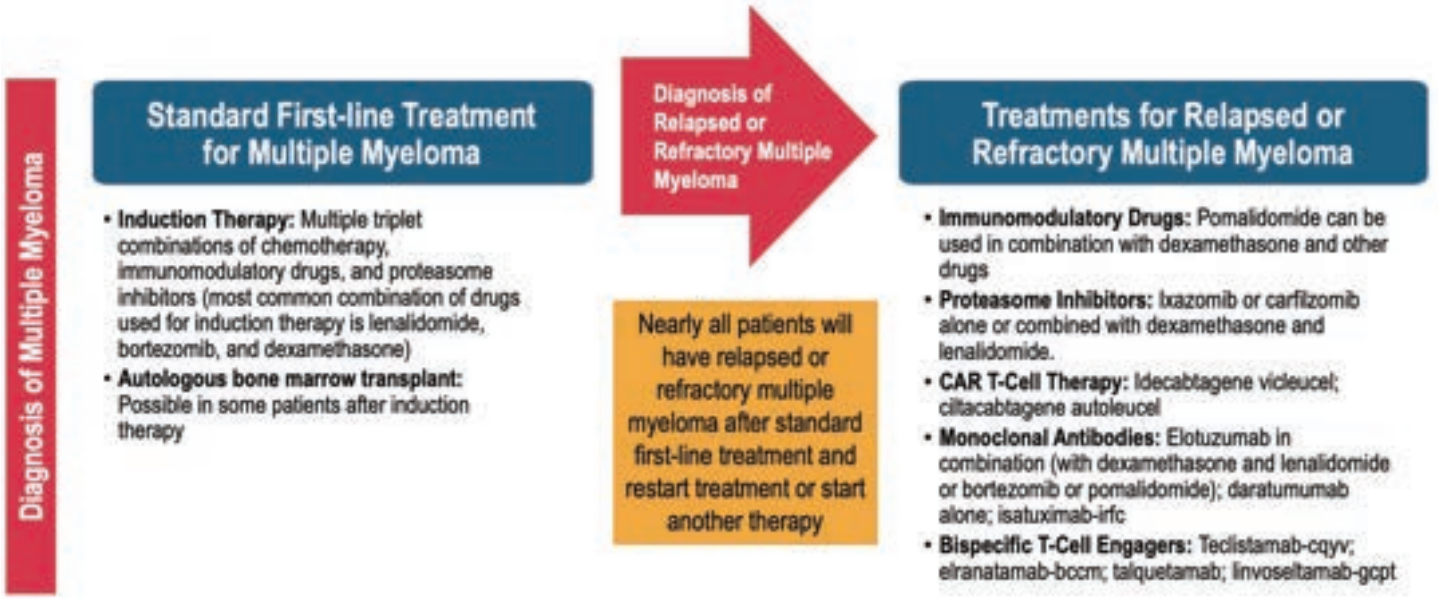
Primary Refractory Multiple Myeloma	• Patients who fail to achieve at least minimal response on initial therapy and progress while on treatment
Double Refractory Multiple Myeloma	• Disease has progressed during or after treatment with a protease inhibitor and an immunomodulatory agent
Triple-class Refractory Multiple Myeloma	• Resistant to adding monoclonal antibodies, confers a poor prognosis

Cycles of Relapse in Multiple Myeloma Necessitate Multiple Lines of Treatment with Standard Therapy

Currently, standard first-line therapy for multiple myeloma consists of a three-drug induction regimen based on an immunomodulatory agent and proteasome inhibitor combined with possible autologous stem cell transplantation.[6,7] During the course of disease, most patients with multiple myeloma will have several cycles of remissions and relapse, necessitating multiple lines of combination therapies.[6] Many patients with multiple myeloma become refractory to lenalidomide as early as first relapse, and as a result lenalidomide-refractory patients have a poor prognosis and need an effective standard of care.[8] Therapies for patients with relapsed or refractory multiple myeloma, with disease becoming nonresponsive or progressive on therapy within 60 days of last treatment, are emerging and evolving rapidly.[9] Chimeric antigen receptor T-cell (CAR-T) and bispecific T-cell engagers are novel immunotherapies that have revolutionized the treatment of relapsed or refractory multiple myeloma.[6,7] Multiple studies have shown the efficacy of CAR-T-cell therapy as a potential treatment for long-term disease control with a higher response rate in patients with high-risk cytogenetics, progressive disease, or extra-medullary disease at baseline.[10] Response rates up to 83% have been observed with CAR-T-cell therapies in patients with multiple myeloma refractory to previous treatments.[11]



Multiple Treatments for Relapsed or Refractory Multiple Myeloma[7]



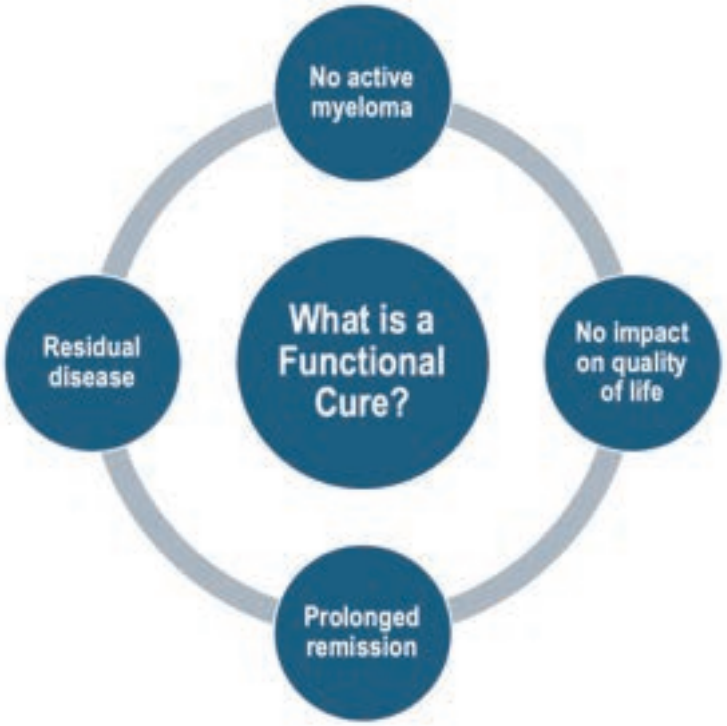
Defining a Cure for Multiple Myeloma

Despite great treatment advances in multiple myeloma, relapses are frequent and the disease remains a considerable source of morbidity and mortality.[12,13] As treatments advance and remission is prolonged, the definition of a cure for multiple myeloma becomes increasingly relevant.[4] As response to treatment has increased, the definitions regarding a cure in multiple myeloma remain ever changing and a greater understanding of what potential cure means is needed.[4] A unified definition of cure is still being developed and debated, with two main schools of thought emerging when defining a cure for multiple myeloma.[14]

Functional Cure

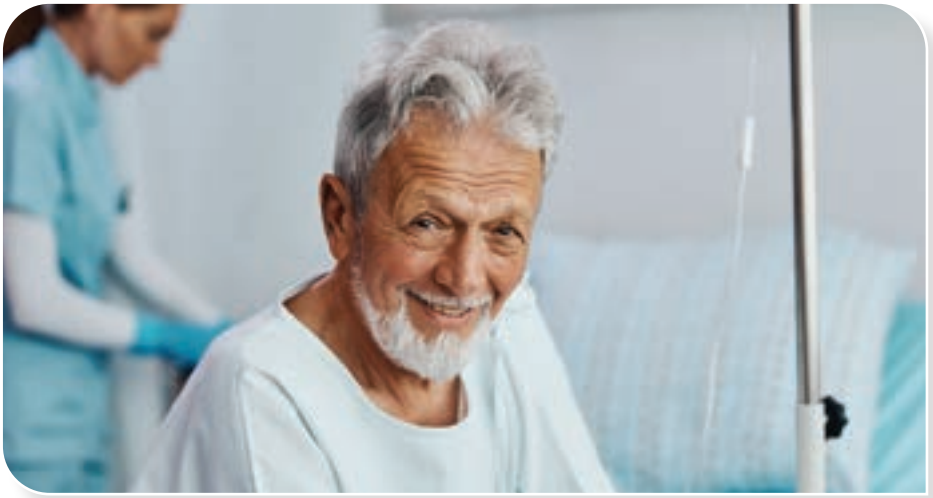
Many have chosen to use the term "functional cure" when defining a cure to include a group of patients who are old enough that another nonmyeloma cause or non–treatment-related event is responsible for their death, or alternatively, those who have near or above the expected survival for an age-matched population.[14] In patients with chronic myeloid leukemia, the concept of a functional cure was described as patients who had no evidence of disease but remained on therapy indefinitely.[15] However, a similar unified definition does not exist for patients with multiple myeloma.[15] Patients with multiple myeloma often respond well to particular treatments, but cure remains poorly defined. Functional cure in multiple myeloma has been variably defined in the literature, including a good response to bone marrow transplant and prolonged progression-free survival, but with some residual disease.[16-18] This approach focuses on achieving a state where the myeloma doesn't negatively impact the patient's quality of life or lead to relapse, rather than achieving complete eradication of all myeloma cells.[16-18]

Defining and Achieving Functional Cure in Multiple Myeloma[14]



Approaches to Achieving Functional Cure

- **Intensive Treatment Regimens:** Induction therapy, stem cell transplantation, consolidation, and maintenance therapy
- **Immunotherapies:** CAR T-cell therapy, bispecific antibodies, monoclonal antibodies
- **Targeted therapies:** Drugs that target specific molecules on myeloma cells or pathways involved in their growth and survival
- **Personalized medicine:** Treatments tailored to the individual's specific disease characteristics and genetic profile
- **Monitoring and surveillance:** Regular monitoring for relapse is crucial



Biological Cure

Another school of thought is to define what it actually means to have a biological cure for a patient with myeloma.[14] A traditional definition of biological cure would state that there is no evidence of cancer using the most sensitive detection measures in the absence of ongoing therapy, with no increased risk of the malignancy recurring compared with the general population. [14] Biological cure has been demonstrated in many other cancers that are currently considered to be curable.[14]

Minimal Residual Disease Negativity and Complete Response Are Not Considered Definitive Cure for Multiple Myeloma

Minimal residual disease (MRD) Negativity	Complete Response
• Minimal residual disease (MRD) negativity in multiple myeloma refers to the absence of detectable myeloma cells in a patient's bone marrow sample after treatment, indicating a very deep response to therapy.[19] • Achieving MRD negativity is associated with improved progression-free and overall survival and can be a valuable prognostic indicator, but is not a definitive cure for multiple myeloma as all myeloma cells may not have been eradicated and patients may still have a risk of relapse.[19-21]	• Complete response, defined by the absence of detectable multiple myeloma cells, no presence of myeloma proteins in the blood or urine, and normal bone marrow plasma cells, has been stated to be the goal of treatment in multiple myeloma.[21,22] • Achieving a complete response in multiple myeloma is not considered a cure, but it is a significant indicator of treatment effectiveness and is associated with improved survival rates.[21,22]

Research Working Toward a Cure in Multiple Myeloma

Developing personalized treatment approaches based on individual patient characteristics and disease biology will be crucial for achieving functional cure. There is an emergence of new therapies to achieve a much higher tumor cell kill rate, and the goal has to be to get to a stage where we have disease eradication that does not require ongoing therapy. Time-limited therapy that leads to eradication of disease is a true cure for patients. Some of the newer approaches include T-cell engagers, antibodies designed to guide immune system T cells to destroy cancerous cells, and CAR T-cell therapy, which similarly engineers T cells to seek out and kill identified cancer cells. With these new therapies evolving at a rapid pace, research is working towards a cure to multiple myeloma and it is not an unrealistic goal as it was once thought to be.[4]

CART-T Therapy Approved for Earlier Lines of Therapy

CAR-T therapy has revolutionized prospects for patients with other types of blood cancer, like leukemia, and has been developed to work in multiple myeloma. CART-T cell therapy for the treatment of multiple myeloma has fundamentally changed the treatment landscape for relapsed and refractory therapeutic landscape.[23] Two CAR-T products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have been FDA- and EMA-approved for the treatment of relapsed or refractory multiple myeloma. Both of these CAR-T treatments target B-cell maturation antigen (BCMA), a surface glycoprotein highly expressed on multiple myeloma cells. These two treatments were initially approved for patients who had received **>4 prior lines of therapy.**[23] An extension of indication has been approved by the US FDA and EMA (2024) for earlier lines of therapy: for ide-cel for patients with relapsed or refractory multiple myeloma after **2 or more prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and for cilta-cel 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 (IMiD) and are refractory to lenalidomide.[23] Based upon the expanded approval, it has been questioned if CAR-T-cell therapy with cilta-cel can be used even earlier in the treatment paradigm.[23]

> Two CAR-T products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have been FDA- and EMA-approved for the treatment of relapsed or refractory multiple myeloma.

Cilta-cel CAR-T Therapy Treats Multiple Myeloma by Targeting BCMA

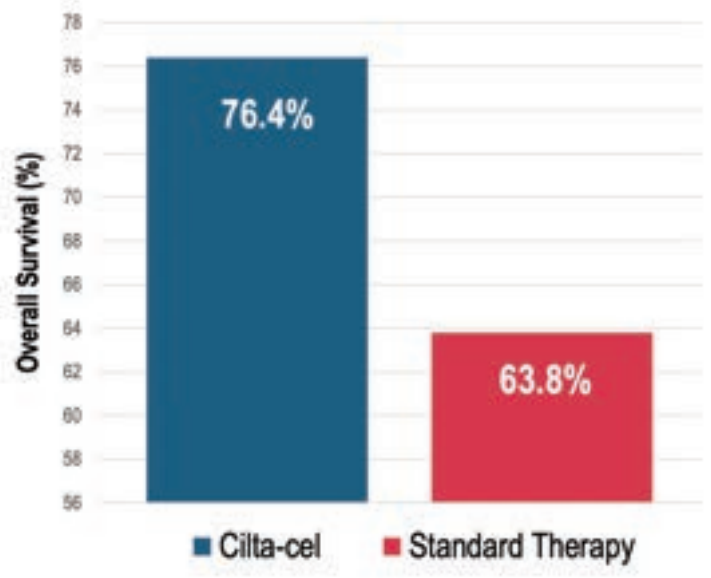
Cilta-cel is an autologous immunotherapy in which T-cells are genetically modified to encode a chimeric antigen receptor (CAR) to find and destroy BCMA–expressing cells. BCMA is overexpressed on the surface of malignant multiple myeloma B-lineage cells; it is also expressed on the surface of late-stage B cells and plasma cells.[24,25] Cilta-cel is a 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. [24,25]

Follow-up at >30-Months Showed Clear Overall Survival Benefit with Cilta-Cel in Patients in Relapsed or Refractory Multiple Myeloma Who Had Overcome at Least One Standard Treatment

The most compelling argument in favor of earlier-line CAR T-cell therapy use is its unprecedented efficacy, high minimal residual disease negativity rates, and significantly improved progression free survival and overall survival rates.[23] Notably, updated data with > 30-month follow-up showed clear overall survival benefit with cilta-cel in CARTITUDE-4.[23] In the CARTITUDE-4 (NCT04181827) phase 3, randomized, open label, multicenter controlled study, cilta-cel was tested in patients whose myeloma had overcome at least one standard treatment.[24,25] In the study, 419 patients who had received one to three previous lines of treatment were randomized 1:1 to receive either cilta-cel or standard therapy which included daratumumab, pomalidomide, and dexamethasone (DPd) or bortezomib, pomalidomide, and dexamethasone (PVd).[24,25] At 12 months, progression-free survival was 75.9% in the cilta-cel group compared with 48.6% in the standard-care group.[25] More patients in the cilta-cel group than in the standard-care group had an overall response (84.6% vs. 67.3%), a complete response or better (73.1% vs. 21.8%), and an absence of minimal residual disease (60.6% vs. 15.6%).[25] Results at a median follow-up of 33.6 months, showed a significant overall survival benefit compared to standard of care, with a 30-month overall survival rate of 76.4% for the cilta-cel arm versus 63.8% in the standard of care arm, and a median overall survival that was not reached in either group.[26] This indicates that cilta-cel significantly improved survival in patients with lenalidomide-refractory multiple myeloma who received at least two prior lines of therapy. CARTITUDE-4 is the first study in multiple myeloma that showed a survival benefit with BCMA CAR-T, using cilta-cel, and significantly reduced the risk of death in those patients who received cilta-cel as early as first relapse.[25,26] The significant difference in overall survival at that follow-up of 33.6 months is quite significant and is a very important clinical trial result that can inform clinical practice and optimize patient care.

Risk of death was significantly reduced in those patients who received cilta-cel as early as first relapse.

Significant Overall Survival Benefit for Cilta-cel Compared with Standard of Care at Median Follow-up of 33.6 Months



Evidence that Cilta-cel Is Potentially Curative in Patients with Relapsed or Refractory Multiple Myeloma

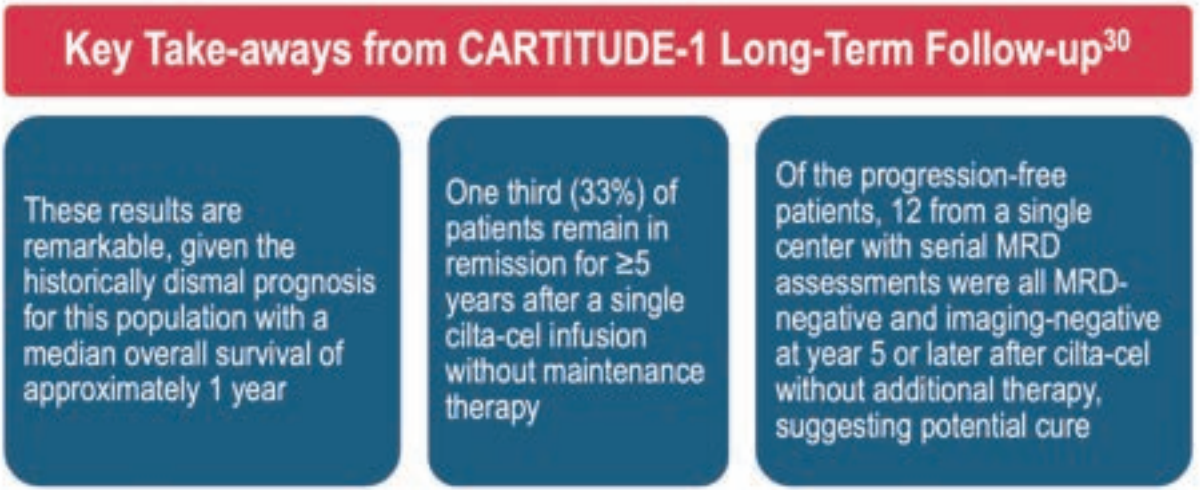
Before cilta-cel was found to significantly prolong progression free survival and overall survival in patients with 1-3 previous lines in the phase 3 CARTITUDE-4 trial,[25,26] the BCMA–directed CAR-T cell therapy led to deep and durable responses in heavily pretreated patients with relapsed or refractory multiple myeloma in the phase 1b/2 CARTITUDE-1 trial.[27-29] CARTITUDE-1 evaluated cilta-cel in patients with heavily pretreated relapsed/refractory multiple myeloma. The study assessed overall survival, ≥5-year progression-free outcomes, associated biomarkers, and safety.

At study closeout (median follow-up, 33.4 months), median PFS was 34.9 months, and median overall survival was not reached.[28] A *post-hoc* analysis was conducted to gain additional insight into those patients who had long-term clinical benefit ≥5 years after a single cilta-cel infusion. The *post-hoc* analysis assessed overall survival, ≥5-year progression-free outcomes, associated biomarkers, and safety from CARTITUDE-1, with 61.3-month median follow-up.[30]

CARTITUDE-1 included patients with longstanding multiple myeloma who had gone through a series of treatments, each of which controlled their disease for a while, but then it relapsed, as it always does.[4,27-30] These patients reached the stage where they had no more options and were facing hospice and a certain, and extremely painful, death within about a year.[30] For these 97 patients treated with cilta-cel, median OS was 60.7 months.[30] One third (33%; n=32/97) of patients remain alive and progression-free for ≥5 years after a single cilta-cel infusion, without maintenance treatment.[30] Twelve of these patients treated at a single center underwent serial MRD and positron emission tomography-computed tomography assessments, and all (100%) were MRD-negative and imaging-negative at year 5 or later after cilta-cel.[30]

One-third of the patients in the CARTITUDE-1 clinical trial lived without detectable cancer after facing certain death.

Baseline characteristics were generally comparable for the 32 patients who were progression-free for ≥5 years versus patients who had progressive disease by year 5.[30] A trend of lower baseline tumor burden, higher fraction of naïve T-cells in the cilta-cel drug product, higher T cell-to-neutrophil ratio, higher hemoglobin and platelets at baseline, and higher effector-to-target ratio were associated with ≥5-year progression-free status.[30] The safety profile of cilta-cel remained consistent with previous clinical studies.[30] These *post-hoc* analysis data provide the first evidence that cilta-cel is potentially curative in patients with relapsed or refractory multiple myeloma.[30]



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)[†]**
(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®.

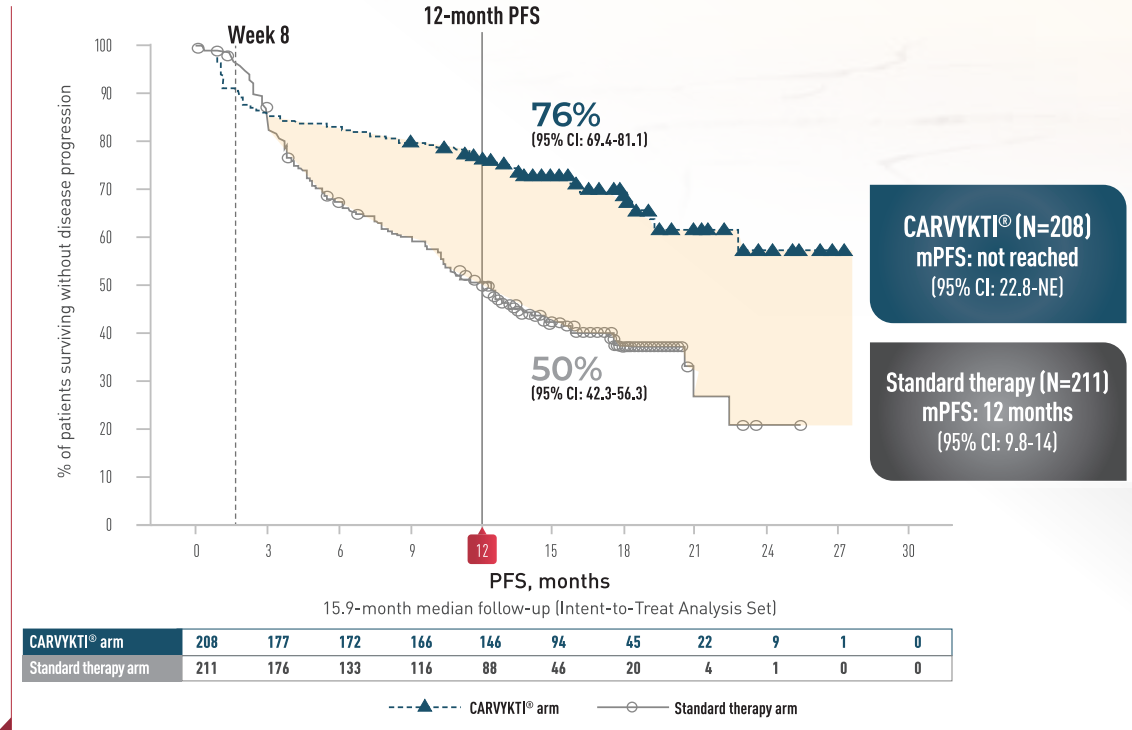
CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

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*]



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]

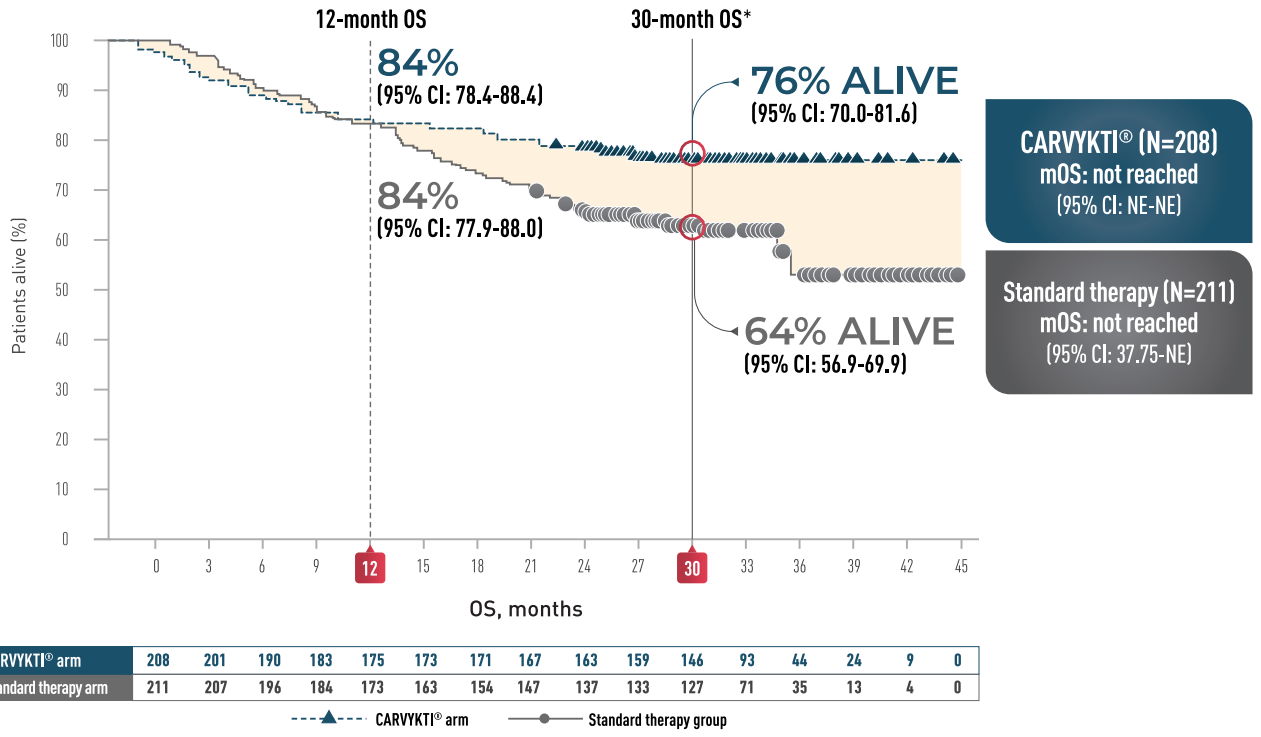
- 34% of the planned OS events have occurred
- Within the first 10 months of randomization, a higher proportion of patients in the CARVYKTI® arm died compared with the standard therapy arm

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® 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.

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CARVYKTI®
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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.

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.

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

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

Adverse reactions are reported using MedDRA version 25.0

[a] Diarrhea includes Colitis, and Diarrhea.

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

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

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

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

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

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

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

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

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

[k] Headache includes Headache and Tension headache.

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

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

[n] Hypotension includes Hypotension, and Orthostatic hypotension.

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

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

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

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

CARTITUDE-1

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

Immunogenicity

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

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

Postmarketing Experience

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

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

Neoplasms: T cell malignancies

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

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

Infertility

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

Pediatric Use

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

Geriatric Use

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

CARVYKTI® (ciltacabtagene autoleucel)

Increased Early Mortality

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

ICANS: e.g., aphasia, encephalopathy, depressed level of consciousness, seizures, delirium, dysgraphia

Parkinsonism: e.g., tremor, micrographia, bradykinesia, rigidity, shuffling gait, stooped posture, masked facies, apathy, flat affect, lethargy, somnolence

Guillain Barré Syndrome: e.g., motor weakness and polyradiculoneuritis

Peripheral neuropathy: e.g., peripheral motor and/or sensory nerve dysfunction

Cranial Nerve Palsies: e.g., facial paralysis, facial numbness

Prolonged and Recurrent Cytopenias

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

Infections

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

Hypersensitivity Reactions

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

Secondary Malignancies

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

Advise patients of the need to:

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

Manufactured/Marketed by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
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Marketed by:
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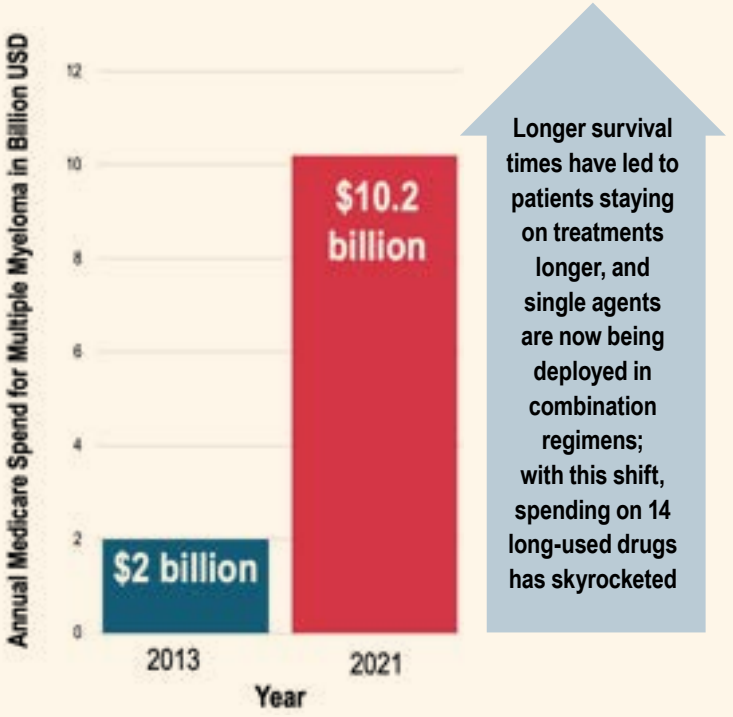
cp-258863v5

High Cost and Complexity of Multiple-Myeloma Treatment

Like treatments for many other cancers, treatments for multiple myeloma are complex and come with a high price.[31] The complexity comes from a wealth of highly effective, multidrug regimens that have gained FDA approval in a relatively short amount of time.[31] Adding additional complexity into the myriad of clinical choices is the relatively limited amount of data available on the optimal treatment sequence for the multiple treatments.[31] Despite representing only 1.8% of new cancers in the United States, it is in the top three for payer spend, which demonstrates the high cost of treatment for multiple myeloma, as well as the treatment success with lines of therapy and patients living longer.[31] Frontline treatment includes combinations containing several novel agents, which has increased the cost of care.[31,32] The total cost of treatment for multiple myeloma over the years can be millions of dollars, usually paid by insurers without cure.[31] CAR-T therapy can be expensive, but it is a one-time treatment.[4,31-32] The thought is that perhaps by giving it earlier in the course of the disease, it could cure patients early on and lower treatment costs.[4,31-32]

Cost for 14 Common Therapies for Multiple Myeloma from 2013 to 2021[32]



Studies in the Use of BMCA CAR-T in Early Lines of Treatment and Newly Diagnosed Multiple Myeloma

Treating early with the most effective therapies is paramount in multiple myeloma, given that patient attrition increases with each successive line of therapy[33] As a protein found on the surface of multiple myeloma cells and normal plasma cells, BCMA is a good target for therapies like antibody-drug conjugates, CAR T-cell therapy, and bispecific antibodies. While effective, BCMA-targeted therapies can lead to T-cell exhaustion and may be less effective in heavily pretreated patients. Research is exploring new ways to enhance the effectiveness of BCMA-targeted therapies, such as combining them with checkpoint inhibitors or using them earlier in the treatment course. In recent years, BCMA-targeted drugs have greatly improved the prognosis of patients with relapsed or refractory multiple myeloma.[34,35]

BCMA CAR-T cell therapy is increasingly being investigated and used in earlier lines of treatment for certain cancers, particularly large B-cell lymphoma and multiple myeloma, rather than being reserved for later-stage, relapsed/refractory cases.[23] This shift is driven by the potential for improved outcomes and the observation that CAR-T cells may be more effective when used earlier in the treatment course.[23] Studies suggest that using CAR-T cells earlier may lead to better overall survival, improved progression-free survival, and higher rates of MRD negativity.[23] This is partly because T cells used in earlier lines are less likely to be exhausted from prior treatments.[23] While the potential benefits of earlier CAR-T use are significant, it's crucial to consider the risks and costs associated with this therapy.[23] The high cost of CAR-T and the potential for toxicities (like cytokine release syndrome) need to be carefully weighed against the potential benefits.[23]

The phase 1 CARTITUDE-1 clinical trial evaluated cilta-cel in patients with heavily pretreated relapsed/refractory multiple myeloma. The study assessed overall survival, ≥5-year progression-free outcomes, associated biomarkers, and safety.[28] A *post-hoc* analysis was conducted to assess overall survival and ≥5-year progression-free outcomes from CARTITUDE-1 with 61.3-month median follow-up.[30] For these 97 patients treated with cilta-cel, Median overall survival was 60.7 months, with one third of patients remaining alive and progression-free for ≥5 years after a single cilta-cel infusion, without maintenance treatment.[30] In addition, the phase 3 CARTITUDE-4 trial, which compared the efficacy differences between cilta-cel and standard of care in relapsed or refractory multiple myeloma demonstrated that at the median follow-up of 34 months, the MRD negative rate of evaluable patients receiving cilta-cel treatment was 89%, compared to 38% in the standard of care group.[36] In addition, 44% of patients in the cilta-cel group can be assessed as having sustained MRD negative and ≥ CR for at least 12 months, compared with 8% of patients in the standard of care group.[36] In addition, the proportion of patients achieving MRD-negativity (at 10^{-5} threshold) with cilta-cel was 73% in CARTITUDE-4 versus 59% here in CARTITUDE-1,[36] suggesting the potential for more patients to experience extended treatment-free remissions in earlier lines. Use of cilta-cel in less heavily pretreated patients could also improve the effectiveness of bridging therapies and result in a fitter CAR-T cell profile and an improved E:T ratio,[37] shown previously to be associated with durable long-term efficacy. Cilta-cel is being investigated in patients with newly diagnosed multiple myeloma in two studies—CARTITUDE-5 (ClinicalTrials.gov identifier: NCT04923893) and CARTITUDE-6 (ClinicalTrials.gov identifier: NCT05257083)—with the potential to displace autologous stem-cell transplant and demonstrate cure in the frontline setting.[38] If cilta-cel is used as a first-line treatment, cure would now be a realistic expectation.[4]

Currently Active Phase 3 Studies of Cilta-cel in Patients with Newly Diagnosed Multiple Myeloma

Study	ClinicalTrials.gov Identifier		Primary and Study Completion Date
CARTITUDE-5: A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by Cilta-cel, a CAR-T Therapy Directed Against BCMA Versus VRd Followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants With Newly Diagnosed Multiple Myeloma for Whom ASCT is Not Planned as Initial Therapy	NCT04923893	n=743 (Active, not recruiting)	06/11/2026 12/13/2034
CARTITUDE-6: A Study of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Ciltacabtagene Autoleucel Versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Autologous Stem Cell Transplant (ASCT) in Participants With Newly Diagnosed Multiple Myeloma	NCT05257083	Estimated 750 (Enrolling)	06/2033 08/2040

Sequencing Guidelines for the Management of Relapsed or Refractory Multiple Myeloma

The management of relapsed or refractory multiple myeloma presents a significant clinical challenge, despite recent advancements in treatment modalities. Novel immunotherapies, particularly CAR-T cell therapies targeting BCMA, have demonstrated promising results in improving overall response rates and extending survival.[39] Large randomized trials, such as CARTITUDE 4, have demonstrated the superiority of CAR T-cell therapy over standard triplet therapy in terms of overall response rate and progression-free survival.[39] Optimized management of unique toxic effects associated with CAR T-cell therapy is crucial for its widespread implementation.[39] Although not approved as frontline therapy, ongoing clinical trials are exploring the use of CAR T-cell therapy in frontline treatment. [39] As treatments expand, clinicians need guidance on how one immunotherapy might impact the safety and effectiveness of the next.[39,40] Based on the evidence to date, the International Myeloma Working Group expert panel developed 9 recommendations for the optimal sequential use of immunotherapy in multiple myeloma.[40]

Large randomized trials, such as CARTITUDE 4, have demonstrated the superiority of CAR T-cell therapy over standard triplet therapy in terms of overall response rate and progression-free survival.

Nine Recommendations from International Myeloma Working Group Immunotherapy Committee on Sequencing Immunotherapy for Treatment of Multiple Myeloma[40]

1.	There are no concerns about proceeding with TCRT in patients receiving a PI, IMiD, (naked) monoclonal antibody, a corticosteroid or any combination of these as most recent therapy. When used as "holding therapy" before T-cell collection, a washout of 2 weeks between last dose of conventional agent and apheresis of mononuclear cells for CAR T-cell manufacturing is recommended. Similarly, a 2-week washout for these agents before the first dose of TCE is recommended.
2.	If feasible, avoid collection of mononuclear cells for CAR T-cell manufacturing in patients receiving a TCE. If necessary, aim for a minimum of 4-week washout between the last dose of the TCE and apheresis collection or consider T-cell collection prior to TCE initiation if possible.
3.	Avoid high-dose alkylators and bendamustine in patients for whom next therapy is likely to be CAR T-cell and/or a TCE.
4.	Strongly consider "bridging therapy" after apheresis for CAR T-cell manufacturing in patients with high disease burden or at risk of developing morbidity from multiple myeloma during the 4-6 weeks of manufacturing; ideal bridging therapy will contain agent(s) without known resistance from the patient's myeloma, be short, with low risk of infection or prolonged cytopenias.
5.	Assuming equal access, in patients who are reasonable candidates to both BCMA-targeted ADC and BCMA-targeted TCRT, we recommend pursuing TCRT first given its higher activity and lower efficacy of TCRT after prior BCMA-targeted ADC.
6.	Assuming equal access, in patients who are reasonable candidates to both BCMA CAR T-cell and TCE pursuing CAR T-cell therapy is recommended.
7.	For patients with rapidly progressing disease and unlikely to transit through apheresis and bridging without disease-related morbidity, proceed with TCE due to faster access.
8.	Both BCMA-targeted and GPRC5D-targeted immunotherapy are safe and active in patients with prior BCMA-targeted CAR T-cell therapy. Post BCMA-targeted CAR T-cell therapy, responses to BCMA-targeting therapies are likely less frequent and durable than in patients not previously treated with BCMA-targeted CAR T-cell therapy.
9.	Therapy with different mechanism of action or immunotherapy targeting a different antigen for patients progressing while receiving or shortly after receiving BCMA-targeting TCE is recommended.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T; IMiD, immunomodulatory agent; PI, proteasome inhibitor; TCE, T-cell engager; TCRT, T-cell redirecting therapies.

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