CARTITUDE-4: A randomized, Phase 3 trial of ciltacabtagene autoleucel (cilta-cel) versus standard of care (PVd or DPd) in lenalidomide-refractory multiple myeloma

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Full prescribing information available here

Introduction*

Relapse is common in patients with MM receiving standard therapies, and outcomes worsen with each subsequent LOT.[1] The widespread use of len in early LOT has given rise to an increased population of lenalidomide-refractory patients, and survival outcomes in these patients are poor when treated with SOC[2,3]

Here, we report the findings of the Phase 3 CARTITUDE-4 trial of cilta-cel vs SOC (PVd or DPd) in patients with lenalidomide-refractory MM after 1–3 prior LOT[1]

CARTITUDE-4 study design[1–5]

The open-label, randomized, Phase 3 CARTITUDE-4 trial compared cilta-cel with physician's choice of SOC regimen in patients with lenalidomide-refractory MM after 1–3 prior LOT[1]

Key inclusion criteria:

- Age ≥18 years with MM
- 1–3 prior to LOT (including PI + immunomodulator)
- Lenalidomide refractory
- ECOG PS ≤1

Key exclusion criteria:

- Prior CAR-T or BCMA-targeting therapy

Stratified by:

- Choice of PVd/DPd
- ISS stage
- Number of prior LOT

1:1 Randomization (N=419)

SOC arm
PVd or DPd†‡
Collect efficacy and safety data every 28 days

Cilta-cel arm
Collect efficacy and safety data every 28 days

Bridging PVd or DPd†
≥1 cycle

Days -7 to -5: Lymphodepletion
Day 1: Cilta-cel infusion
(Target: 0.75 x 10^6 CAR+ T cells/kg)

Day 1–112: Collect PK/PD data every 28 days

Follow-up

Apheresis (start of study treatment)

T-cell transduction and expansion

Endpoints[1,5]

Primary: PFS§,¶
Secondary: ≥CR, ORR, MRD-negativity rate, OS,¶ PROs, cilta-cel PK, and safety**

Results

419 patients were randomized to receive either cilta-cel (n=208) or SOC (n=211) in the ITT population; 208 patients each received apheresis/bridging and SOC therapy (safety population). In total, 176 patients received cilta-cel as study treatment. These 176 patients were the as-treated population[1]

Primary analysis: As of data cutoff (November 1, 2022), median follow-up was 15.9 months[1]
Long term follow-up: As of data cutoff (May 1, 2024), median follow-up was 33.6 months††,[5]

Key patient characteristics[1]

	Median age, years (range)	Black patients, n (%)‡‡	ISS I/II/III, n (%)	High cytogenetic risk, n/N (%)§§	Soft-tissue plasmacytoma, n (%)¶¶	Prior anti-CD38 antibody, n (%)	Triple-class refractory, n (%)***
Cilta-cel (n=208)	61.5 (27–78)	6 (2.9)	136 (65.4)/ 60 (28.8)/ 12 (5.8)	123/207 (59.4)	44 (21.2)	53 (25.5)	30 (14.4)
SOC (n=211)	61.0 (35–80)	7 (3.3)	132 (62.6)/ 65 (30.8)/ 14 (6.6)	132/210 (62.9)	35 (16.6)	55 (26.1)	33 (15.6)

*This infographic summarizes results from the CARTITUDE-4 publication in the *New England Journal of Medicine* (published online June 5, 2023); oral presentations at the ASCO 2023 Annual Meeting (June 2–6, 2023) and IMS 2023 Annual Meeting (September 27–30, 2023); oral and poster presentations at the ASH 2023 Annual Meeting (December 9–12, 2023), and an oral presentation from IMS 2024 Annual Meeting (September 25–28, 2024). †Physicians' choice. ‡Administered until disease progression. §Time from randomization to disease progression/death. ¶Prespecified first and second interim analyses performed after approximately 75% or 100% of planned 250 PFS events were accumulated, respectively. **Assessed per CTCAE version 5.0. CRS and ICANS were graded per ASTCT criteria. ††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. ‡‡Race or ethnic group was reported by patients. Among the patients who were enrolled in the United States, 9 (14.1%) were Black. §§High-risk cytogenetic features defined as del(17p), t(4;14), t(14;16), or gain/amp(1q). ¶¶Includes extramedullary and bone-based plasmacytomas with a measurable soft-tissue component. ***Includes 1 PI, 1 immunomodulatory drug, and 1 anti-CD38 monoclonal antibody.[1]

ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD38, cluster of differentiation 38; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; D, daratumumab; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell-associated neurotoxicity syndrome; ISS, International Staging System; ITT, intent-to-treat; LOT, lines of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; P, pomalidomide; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; SOC, standard of care; V, bortezomib.

1. San-Miguel J, et al. *N Engl J Med.* 2023;389:335–347. **2.** Dhakal B, et al. IMS 2022; Poster presentation P-240. **3.** Dhakal B, et al. IMS 2022; Poster presentation P-241. **4.** Dhakal B, et al. ASCO 2023; Oral presentation LBA-106. **5.** Mateos M-V, et al. IMS 2024; Oral presentation OA-65

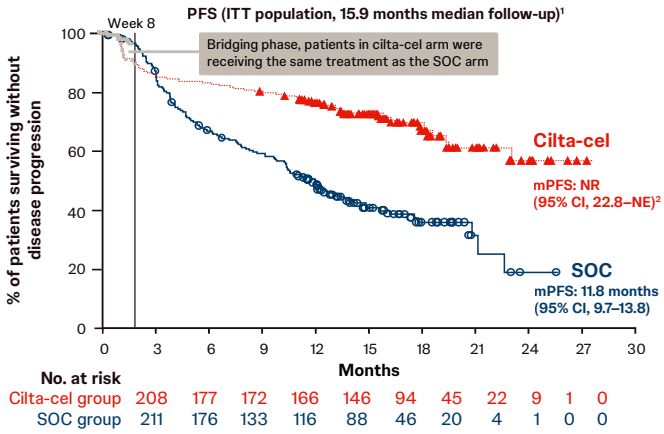
Efficacy

Long term data are based on 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. These data are presented for descriptive purposes only.

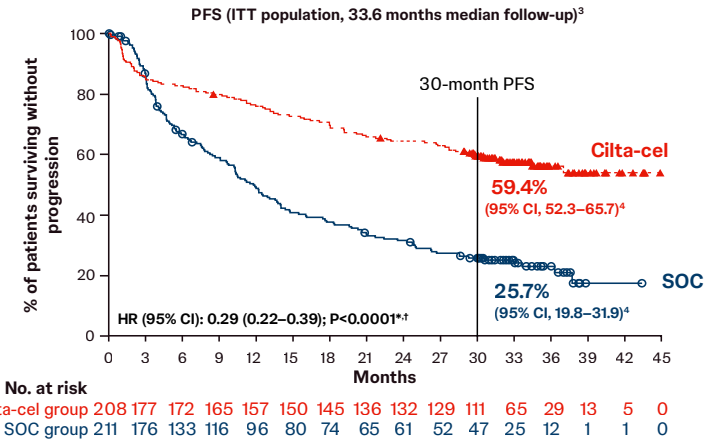
PFS

In the primary analysis (median follow-up 15.9 months), cilta-cel significantly improved PFS vs SOC (P<0.0001).[1,2] At long term follow-up (median follow-up 33.6 months), cilta-cel maintained significant improvement in PFS vs SOC (P<0.0001).[3] Consistent reduction in the risk of progression or death was observed across all prespecified subgroups with cilta-cel vs SOC in both the primary analysis,[1] and in the long term follow-up[3]

Primary analysis



Long term follow-up



In **unweighted** sensitivity analyses at 15.9 months median follow-up:[1]

- **Cilta-cel significantly reduced the risk of progression or death versus SOC** (HR, 0.40; 95% CI, 0.29–0.55; P<0.0001)

In **weighted** sensitivity analyses at 15.9 months median follow-up:[1]

- 12-month PFS rates were 75.9% (95% CI, 69.4–81.1) in the cilta-cel group versus 48.6% (95% CI, 41.5–55.3) in the SOC arm
- HR was 0.26 (95% CI, 0.18–0.38)* to account for patients in the cilta-cel arm receiving the same treatment as the SOC after randomization and before they received cilta-cel infusion per protocol design, by including only PFS events that occurred after 8 weeks post-randomization in the analysis

- **30-month** PFS was 59.4% (95% CI, 52.3–65.7) with cilta-cel and 25.7% (95% CI, 19.8–31.9) in the SOC arm[3,4]
- There was a ~70% reduction in the risk of progression or death in patients who received cilta-cel, and mPFS has not been reached (HR, 0.29; 95% CI, 0.22–0.39; P<0.0001)[3,4]

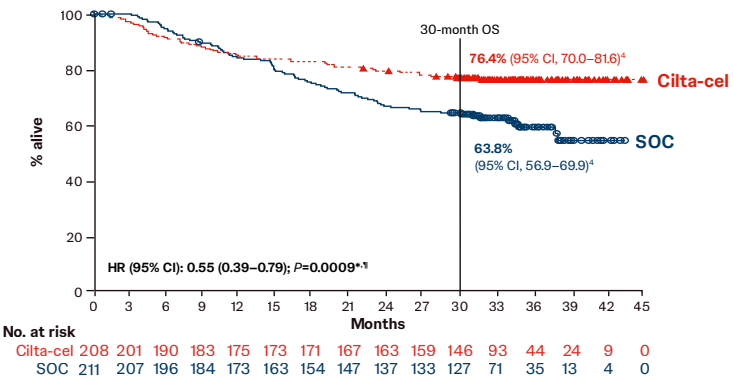
- High cytogenetic risk‡ (HR, 0.29, 95% CI, 0.20–0.41)[3]
- Soft-tissue plasmacytoma (HR, 0.36, 95% CI, 0.20–0.66)[3]
- Triple-class refractory§ (HR, 0.17, 95% CI, 0.08–0.38)[3]

OS With Long Term Follow-up

- At 12 months, an estimated 84.1% of patients in the cilta-cel group were alive, as compared with 83.6% in the SOC group[1]

- With a median follow-up of 33.6 months, median OS was not reached for either arm (HR, 0.55, 95% CI, 0.39–0.79, P=0.0009)[3]
- **Thirty-month** OS was 76.4% (95% CI, 70.0–81.6) with cilta-cel and 63.8% (95% CI, 56.9–69.9) in the SOC group[3,4]
- There was a 45% reduction in risk of death in patients receiving cilta cel, demonstrating OS benefit in MM[3]

OS (ITT population, 33.6 months median follow-up)[3]



*HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization. Stratified constant piecewise weighted log-rank test (weight of 0 for Weeks 0–8 and 1 afterwards) to account for time when patients in the cilta-cel arm were receiving bridging therapy, same treatment as SOC arm.

†Nominal P-value. ‡Positive for del(17p), t(14;16), t(4;14), and/or gain/amp(1q) by fluorescence in situ hybridization testing. Protocol-defined high-risk cytogenetics refers to "Any of 4 markers abnormal." §PI + anti-CD38 + immunomodulatory drug. ¶Log-rank test. P-value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2.

CD, cluster of differentiation; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; ITT, intent-to-treat; MM, multiple myeloma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; SOC, standard of care; USPI, US Prescribing Information.

1. San-Miguel J, et al. *N Engl J Med*. 2023;389:335–347. **2.** Dhakal B, et al. ASCO 2023; Oral presentation LBA-106. **3.** Mateos M-V, et al. IMS 2024; Oral presentation OA-65. **4.** Data on file.

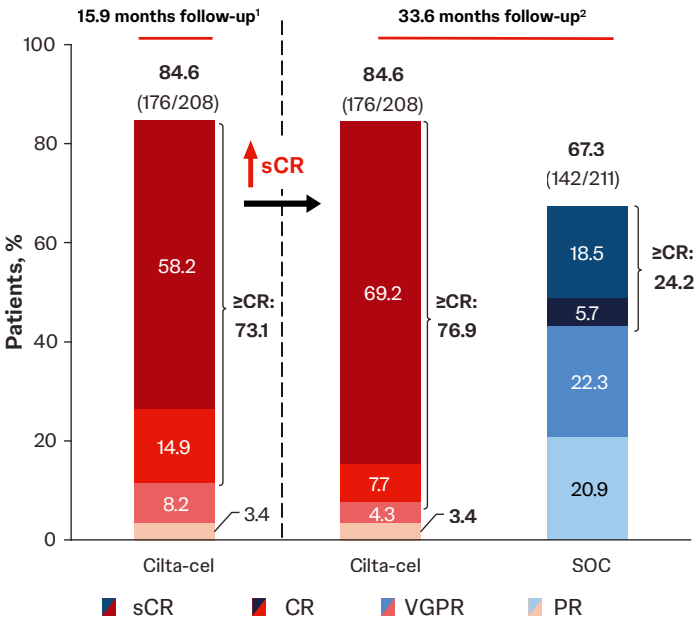
Efficacy

Long term data are based on 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. These data are presented for descriptive purposes only.

Response

In both the primary analysis and the long term follow-up, cilta-cel improved ≥CR, ORR, and DOR vs SOC[1–3]

ORR*



Primary analysis

- At **15.9 months** median follow-up (**ITT population**), ORR in the cilta-cel arm was 84.6% vs 67.3% in the SOC arm (OR, 3.0; 95% CI, 1.8–5.0; P<0.0001)[1,4]
- Among responders, 84.7% (95% CI, 78.1–89.4) and 63.0% (95% CI, 54.2–70.6) maintained response for ≥12 months in the cilta-cel and SOC arm, respectively[1]

Long term follow-up[2]

- At **33.6 months**, ORR and sCR/CR rate were high with cilta-cel, with sustained DOR

DOR (median 33.6 months follow-up)[2]

	Cilta-cel	SOC
DOR,† months, median (95% CI)	NR (NE–NE)†	18.7 (12.9–23.7)†
30-month DOR rate, % (95% CI)	67.4 (59.7–74.0)	35.5 (27.6–43.6)

Safety

In the primary analysis, AEs occurring in ≥20% of patients in either arm (safety population; median follow-up: 15.9 months)[1]

	Cilta-cel (n=208)		SOC (n=208)	
	Any grade, n (%)	Grade 3/4, n (%)	Any grade, n (%)	Grade 3/4, n (%)
Any AE	208 (100)	201 (96.6)	208 (100)	196 (94.2)
Serious AE[4]	92 (44.2)	67 (32.2)	81 (38.9)	70 (33.7)
Hematologic	197 (94.7)	196 (94.2)	185 (88.9)	179 (86.1)
Neutropenia	187 (89.9)	187 (89.9)	177 (85.1)	171 (82.2)
Thrombocytopenia	113 (54.3)	86 (41.3)	65 (31.2)	39 (18.8)
Anemia	113 (54.3)	74 (35.6)	54 (26.0)	30 (14.4)
Lymphopenia	46 (22.1)	43 (20.7)	29 (13.9)	25 (12.0)
CRS‡	134 (76.1)	2 (1.1)	-	-
Infections	129 (62.0)	56 (26.9)	148 (71.2)	51 (24.5)
Upper respiratory tract§	39 (18.8)	4 (1.9)	54 (26.0)	4 (1.9)
COVID-19¶	29 (13.9)	6 (2.9)	55 (26.4)	12 (5.8)
Nausea	101 (48.6)	0	38 (18.3)	2 (1.0)
Hypogammaglobulinemia	88 (42.3)	15 (7.2)	13 (6.2)	1 (0.5)
Diarrhea	70 (33.7)	8 (3.8)	56 (26.9)	5 (2.4)
Fatigue	60 (28.8)	4 (1.9)	68 (32.7)	2 (1.0)
Headache	55 (26.4)	0	27 (13.0)	0
Constipation	49 (23.6)	1 (0.5)	44 (21.2)	2 (1.0)
Insomnia	23 (11.1)	2 (1.0)	52 (25.0)	6 (2.9)

*Assessed using a validated computerized algorithm; ORR is defined as the proportion of subjects who achieve a PR or better per IMWG criteria. †Analyzed among responders.
‡Incidence of CRS in 176 patients in cilta-cel arm who received study treatment. §Includes preferred terms nasopharyngitis, sinusitis, rhinitis, tonsillitis, pharyngitis, laryngitis, and pharyngotonsillitis. ¶Includes preferred terms COVID-19 pneumonia and asymptomatic COVID-19. Grade 5 events occurred in 7 patients and 1 patient in the cilta-cel and SOC arm, respectively.[1]

AE, adverse event; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; IMWG, International Myeloma Working Group; ITT, intent-to-treat; NE, not estimable; NR, not reached; OR, odds ratio; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SOC, standard of care; US Prescribing Information; VGPR, very good partial response.

1. San-Miguel J, et al. *N Engl J Med*. 2023;389:335–347. **2.** Mateos M-V, et al. IMS 2024; Oral presentation OA-65. **3.** Data on file. **4.** Dhakal B, et al. ASCO 2023; Oral presentation LBA-106.

Safety cont'd

Long term data are based on 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. These data are presented for descriptive purposes only.

Primary analysis[1]

- An increased risk of early mortality (within 10 months from randomization) was observed in the cilta-cel arm vs the SOC arm
  - 14% (29/208) in the cilta-cel arm vs 12% (25/211) in the SOC arm
  - 10/29 (34%) deaths that occurred in the cilta-cel arm occurred prior to cilta-cel infusion; 19 deaths occurred after cilta-cel infusion

Long term follow-up[2]

- At median 33.6 months follow-up, there were 50 deaths in the cilta-cel arm vs 82 deaths in the SOC arm
  - 21 due to progressive disease and 12 due to TEAE in the cilta-cel arm vs 51 due to progressive disease and 8 due to TEAE in the SOC arm

CAR-T–related AEs after cilta-cel infusion (median 15.9 months follow-up as-treated population; n=176)[3]

	Any grade, n (%)	Grade 3/4, n (%)
CRS	134 (76.1)	2 (1.1)
Neurotoxicity	36 (20.5)	5 (2.8)
ICANS	8 (4.5)	0
Other*	30 (17.0)	4 (2.3)
Cranial nerve palsy	16 (9.1)	2 (1.1)
Peripheral neuropathy	5 (2.8)	1 (0.6)
MNT	1 (0.6)	0

At long-term follow-up, the safety profile was consistent with previous analysis[2,3]

Long term follow-up (median 33.6 months)[2]

Infections	Cilta-cel (n=208)	SOC (n=208)
All grade TEAE infections, %	63.5	76.4
Grade 3/4 TEAE infections, %	28.4	29.8
Deaths due to TE- and non-TE infections, n	16	19
In first year, n	13	8
In second year, n	2	8

SPM	Cilta-cel (n=208)	SOC (n=208)
SPMs, n (%)	**27 (13.0)**	**24 (11.5)**
Hematologic, n (%)†	7 (3.4)	1 (0.5)
MDS, n	4	0
Progressed to AML, n	2	–
AML, n	1	0
Peripheral T-cell lymphoma, n	2	0
EBV-associated lymphoma, n	0	1
Cutaneous/non-invasive, n (%)†	15 (7.2)	15 (7.2)
Non-cutaneous/invasive, n (%)†	6 (2.9)	8 (3.8)

At median 33.6 months follow-up, there were no new cases of cranial nerve palsy or MNT for the cita-cel arm since the primary analysis (median 15.9 months follow-up)[2]

Both treatment arms had Grade 3/4 TEAE around 97%, most frequently cytopenia[2]

CARTITUDE-4 key takeaways

- Compared with SOC regimens, cilta-cel reduced the risk of progression or death (HR, 0.29; P<0.0001) at median follow-up of 33.6 months, and led to higher response rates with deeper and more durable treatment responses in patients with lenalidomide-refractory MM after 1–3 prior LOT[2,3]
- At median follow-up 15.9 months, CRS occured in 134 (76.1%) patients treated with cilta-cel (Grade 3/4, 1.1%) and most neurotoxicities were low grade.[3] At long term follow-up, SPMs occurred in 27 (13%) patients and there were no new reports of cranial nerve palsy or MNT[2]
- The benefit-risk profile of cilta-cel was favorable, with strong efficacy and at a longer follow-up safety consistent with the previous data cut[2,3]

*Investigator-assessed non-ICANS neurotoxicity graded per NCI-CTCAE, version 5.0. †Multiple SPMs could occur in the same patient.

AE, adverse event; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; EBV, Epstein-Barr virus; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; LOT, line of therapy; MDS, myelodysplastic syndrome; MM, multiple myeloma; MNT, movement and neurocognitive treatment-emergent adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SPM, second primary malignancy; SOC, standard of care; TE, treatment-emergent; USPI, US Prescribing Information.

1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Mateos M-V, et al. IMS 2024; Oral presentation OA-65. **3.** San-Miguel J, et al. *N Engl J Med*. 2023;389:335–347.

Johnson & Johnson

LEGEND BIOTECH

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®.

Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, 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®.

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.

Confirm that a minimum of 2 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 1 dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 7 days following CARVYKTI® infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 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 cutoff. Of patients with ICANS, 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients, respectively.

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

Monitor patients at least daily for 7 days following CARVYKTI® infusion for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed. Advise patients to avoid driving for at least 2 weeks following infusion.

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 cutoff. 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 cutoff.

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

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

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

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

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

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

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.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), including cases with fatal outcomes, have been reported following treatment. Perform appropriate diagnostic evaluations in patients with neurological adverse events.

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 500 mg/dL after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion occurred in 94% (267/285) of patients treated. Fifty-six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI® for either an adverse reaction or prophylaxis.

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

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

Hypersensitivity Reactions occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤2 Grade. 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.

Immune effector cell-associated enterocolitis (IEC-EC) has occurred in patients treated with CARVYKTI®. Manifestations include severe or prolonged diarrhea, abdominal pain, and weight loss requiring parenteral nutrition. IEC-EC has been associated with fatal outcome from perforation or sepsis. Manage according to institutional guidelines, including referral to gastroenterology and infectious disease specialists.

In cases of refractory IEC-EC, consider additional workup to exclude alternative etiologies, including T-cell lymphoma of the GI tract, which has been reported in the post marketing setting.

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 lifelong 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.

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 full Prescribing Information, including Boxed Warning, for CARVYKTI®.

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