▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

CARVYKTI®

CILTACABTAGENE AUTOLEUCEL

AUSTRALIAN PRODUCT INFORMATION

BOXED WARNING

CYTOKINE RELEASE SYNDROME
Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving 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
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, has 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.

1. NAME OF THE MEDICINE

ciltacabtagene autoleucel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CARVYKTI ciltacabtagene autoleucel suspension for intravenous infusion.

A single dose of CARVYKTI is $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T-cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T-cells suspended in a patient-specific infusion bag (see **section 4.2** Dosage and Method of Administration).

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

Suspension for intravenous infusion

CARVYKTI (ciltacabtagene autoleucel) is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The

mononuclear cells are enriched for T-cells and genetically modified *ex vivo* by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain, which consists of two single domain antibodies linked to 4-1BB costimulatory domain and CD3-zeta signalling domains.

The transduced anti-BCMA CAR T-cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed and then infused back into the patient, where the anti-BCMA CAR T-cells can recognize and eliminate BCMA expressing target cells.

In addition to T-cells, CARVYKTI may contain NK cells. The formulation contains 5% dimethyl sulfoxide (DMSO).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma:

- who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, and are refractory to lenalidomide or;
- who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody

4.2 DOSE AND METHOD OF ADMINISTRATION

For autologous use only. For intravenous use only.

Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with ciltacabtagene autoleucel.

CARVYKTI should be administered at a certified healthcare facility. Prior to infusion ensure at least two doses of tocilizumab are available on site and emergency equipment are available for use. Ensure timely access to additional doses of tocilizumab within 8 hours of each previous dose during the recovery period.

Dose - Adults (≥18 years)

CARVYKTI is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T-cells.

The dose is $0.5\text{-}1.0\times10^6$ CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells per single infusion.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of CARVYKTI in children aged below 18 years of age have not been established.

No data are available.

Elderly (65 years of age and older)

No dose adjustment is required in patients ≥65 years of age.

Method of administration

Preparing Patient for CARVYKTI Infusion

Confirm availability of CARVYKTI prior to starting the lymphodepleting regimen.

Lymphodepleting regimen

Administer a lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. Administer CARVYKTI infusion 5 to 7 days after the start of the lymphodepleting regimen. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, resulting in delays to CARVYKTI dosing, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting regimen. For dose modifications, see corresponding manufacturers prescribing information.

Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity).

Clinical assessment prior to CARVYKTI infusion

CARVYKTI infusion should be delayed if a patient has any of the following conditions:

- clinically significant active infection or inflammatory disorders.
- Grade ≥3 non-haematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhoea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤1
- active graft versus host disease

Premedication

Administer the following pre-infusion medications to all patients (30 to 60 minutes) prior to CARVYKTI infusion:

- Antipyretics (oral or intravenous paracetamol/acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity of CARVYKTI.

Precautions to be taken before handling or administering CARVYKTI

CARVYKTI contains genetically modified human blood cells. Local biosafety guidelines applicable for handling and disposal of such products should be followed (see Special Precautions for Disposal).

CARVYKTI is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and CARVYKTI may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or CARVYKTI to avoid potential transmission of infectious diseases as for any human derived materials.

Preparation of CARVYKTI for infusion

Do not thaw the product until it is ready to be used. Coordinate the timing of CARVYKTI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CARVYKTI is available for infusion when the patient is ready.

- Confirm patient identity: Prior to CARVYKTI preparation, match the patient's identity with the patient identifiers on the CARVYKTI cassette. Do not remove the CARVYKTI product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the CARVYKTI product bag from the cassette.

- Inspect the product bag for any breaches of container integrity such as breaks or cracks before and after thawing. Do not administer if the bag is compromised and follow the local guidelines (or contact the company).
- Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.
- Thaw CARVYKTI at 37°C±2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes.
- Remove the infusion bag from the sealable plastic bag and wipe dry. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not pre-filter into a different container, wash, spin down, and/or resuspend CARVYKTI in new media prior to infusion.
- Once thawed, the CARVYKTI infusion must be administered and completed within 2.5 hours at room/ambient temperature (20°C to 25°C).
- Do not re-freeze or refrigerate thawed product.

Administration

- Confirm the patient's identity with the patient identifiers on the infusion bag. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, administer the entire contents of the CARVYKTI bag by intravenous infusion within 2.5 hours using infusion sets fitted with an in-line filter.
- Do NOT use a leukodepleting filter.
- Gently mix the contents of the bag during CARVYKTI infusion to disperse cell clumps.
- After the entire content of the product bag is infused, flush the administration line inclusive of the in-line filter, with sodium chloride 9 mg/mL (0.9%) solution (normal saline) to ensure all product is delivered.

For special precautions for disposal, see **section 6.6** Instructions for Use and Handling and Disposal.

Monitoring after infusion

Monitor patients daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion for signs and symptoms of cytokine release syndrome (CRS), neurologic events and other toxicities (see **section 4.4** Special Warnings and Precautions for Use).

Instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following infusion.

Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation (see **section 4.4** Special Warnings and Precautions for Use).

If CRS is suspected, manage according to the recommendations in Table 1 Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Other monoclonal antibodies-targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T-cells may be considered for

patients who develop high grade CRS and hemophagocytic lymphohistiocytosis (HLH), that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to the CRS grade in Table 1,
- Anti-seizure medication according to the neurologic toxicity in Table 2.

Table 1: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 1 Temperature ≥38°C[c]	Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered	N/A
Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38°C[c] with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via canula[e] or blow-by, or, Grade 2 organ toxicity.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 litre or increasing supplemental oxygen.	Consider methylprednisolone 1 mg/kg intravenously (IV) twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 12 hours). After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 3 Symptoms require and respond to aggressive intervention. Temperature ≥38°C[c] with: Hypotension requiring one vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal cannula[e], facemask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 4 Life-threatening symptoms.	Per Grade 2	Administer dexamethasone 20 mg IV every 6 hours.

Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD). Temperature ≥38°C[c] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis).	After 2 doses of tocilizumab, consider alternative anti-cytokine agents[d]. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (e.g. other anti-T cell therapies).

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details.
[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause
[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
f Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days

Neurologic Toxicities

General management for neurologic toxicity e.g., Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is summarized in Table 2.

At the first sign of neurologic toxicity including ICANS, consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see **section 4.4** Special Warnings and Precautions for Use).

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to CRS grade in Table 1,
- Anti-seizure medication according to neurologic toxicity in Table 2.

Table 2: Guideline for management of ICANS	
ICANS Grade[a]	Corticosteroids
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[c] 10 mg intravenously every 6 to 12 hours for 2 to 3 days Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6[b]	Administer dexamethasone[c] 10 mg intravenously every 6 hours for 2-3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days.

or depressed level of consciousness: awakens to voice	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2[b] (If ICE score is 0, but the patient is arousable (e.g. awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimaging[d.]	Administer dexamethasone[c]10 mg-20 mg intravenously every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[c] dose to at least 20 mg intravenously every 6 hours; taper within 7 days, OR escalate to high-dose methylprednisolone (1 g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 4 ICE score-0[b] (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[e]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral edema, with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	Administer dexamethasone[c] 10 mg-20 mg intravenously every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

[a] ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et.al, 2019),

[b] If patient is arousable and able to perform Immune Effector Cell-associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] All references to dexamethasone administration are dexamethasone or equivalent

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

[e] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1** List of Excipients.

Contraindications of the lymphodepleting chemotherapy and supportive therapy should be considered.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Patients with active or prior history of significant central nervous system (CNS) disease, or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine Release Syndrome

Cytokine release syndrome, including fatal or life-threatening reactions, can occur after CARVYKTI infusion.

In Study MMY2001, nearly all patients experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2. (see **section 4.8** Adverse effects (undesirable effects)). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range of 1 to 12 days). Approximately 90% of patients experienced onset of CRS after Day 3 of receiving the CARVYKTI infusion.

In almost all cases, duration of CRS ranged from 1 to 14 days (median duration 4 days), with 88% of patients having a CRS duration of ≤ 7 days.

In Study MMY3002, 151/196 (77%) experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2 (see **section 4.8** Adverse effects (undesirable effects)). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 8 days (range of 1 to 23 days). In all cases, duration of CRS ranged from 1 to 17 days (median duration 3 days), with 89% of patients having a CRS duration of ≤ 7 days.

Clinical signs and symptoms of CRS may include but are not limited to fever (with or without rigors), chills, hypotension, hypoxia and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. Patients who develop HLH may have an increased risk of severe bleeding. Patients should be closely monitored for signs or symptoms of these events, including fever. Risk factors for severe CRS include high pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment.

Delay the infusion of CARVYKTI if the patient has unresolved serious adverse reactions from preceding lymphodepleting or bridging therapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression and clinically significant active infection (see **section 4.2** Dosing and Method of Administration). Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to CARVYKTI infusion. Infections may also occur concurrently with CRS and may increase the risk of a fatal event.

Ensure that at least two doses of tocilizumab are available on site prior to infusion of CARVYKTI. Also have timely access to additional doses of tocilizumab. Monitor patients for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for hospitalisation and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 (see **section 4.2** Dosing and Method of Administration).

Evaluation for HLH should be considered in patients with severe or unresponsive CRS. For patients with high pre-infusion tumour burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden.

Neurologic toxicities

Neurologic toxicities occur frequently following treatment with CARVYKTI and can be fatal or life-threatening (see **section 4.8** Adverse effects (undesirable effects)). Neurologic toxicities included ICANS, movement and neurocognitive toxicity with signs and symptoms of parkinsonism, Guillain-Barré Syndrome, 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.

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. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.

Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden, which may mitigate the risk of developing neurologic toxicity (see **section 4.8** Adverse effects (undesirable effects)). Monitor patients for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, immediately evaluate patient for hospitalisation and institute treatment with supportive care as indicated in Table 2 (see **section 4.2** Dosing and Method of Administration). Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Neurologic toxicity of movement and neurocognitive toxicity with signs and symptoms of parkinsonism has been reported in trials of CARVYKTI. A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including movement (e.g., micrographia, tremor, bradykinesia, rigidity, stooped posture, shuffling gait), cognitive (e.g., memory loss, disturbance in attention, confusion), and personality change (e.g., reduced facial expression, flat affect, masked facies, apathy), often with subtle onset (e.g., micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. Most of these patients presented a combination of two or more factors such as high tumour burden (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T-cell expansion and persistence. Treatment with levodopa/carbidopa (n=4), was not effective in improving symptomatology in these patients.

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures.

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) has been reported after treatment with CARVYKTI. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis (see Adverse Reactions).

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment with intravenous immunoglobulin (IVIG) and escalate to plasmapheresis, depending on toxicity severity.

Peripheral Neuropathy

Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of CARVYKTI.

Monitor patients for signs and symptoms of peripheral neuropathies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Cranial Nerve Palsies

Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in patients with cranial nerve palsy have been reported in trials of CARVYKTI.

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

Prolonged and Recurrent Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and CARVYKTI infusion and should be managed according to local guidelines. In clinical trials of CARVYKTI, nearly all patients had one or more Grade 3 or 4 cytopenic adverse reactions. Most patients had a median time from infusion to first onset of Grade 3 or 4 cytopenia of less than two weeks, with the majority of patients recovering to ≤Grade 2 by Day 30 (see **section 4.8** Adverse effects (undesirable effects)).

Monitor blood counts after CARVYKTI infusion. For thrombocytopenia, consider supportive care with transfusions. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CARVYKTI or until CRS has resolved.

Serious Infections and febrile neutropenia

Serious infections, including life-threatening or fatal infections, occurred in patients after CARVYKTI infusion (see **section 4.8** Adverse effects (undesirable effects)).

Monitor patients for signs and symptoms of infection, employ surveillance testing prior to and during treatment with CARVYKTI and treat patients appropriately. Administer prophylactic antimicrobials according to local guidelines. Infections are known to complicate the course and management of concurrent CRS. Patients with clinically significant active infection should not start CARVYKTI treatment until the infection is controlled.

In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Patients treated with CARVYKTI may be at an increased risk of severe/fatal COVID-19 infections. Counsel patients on the importance of prevention measures.

Viral reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV and other infectious agents must be performed in accordance with local clinical guidelines before collection of cells for manufacturing.

Hypogammaglobulinemia

Hypogammaglobulinemia may occur in patients receiving CARVYKTI.

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

Live vaccines

The safety of immunisation 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.

Immune Effector Cell-associated Enterocolitis

Patients treated with CARVYKTI may develop Immune Effector Cell-associated Enterocolitis (IEC-EC) (e.g. immune-mediated enterocolitis), presenting as severe or prolonged diarrhoea typically with an onset range from 1 month to 3 months after CARVYKTI infusion. Infectious workups were negative for most of the patients. Clinically significant weight loss has been reported following IEC-EC in some patients after receiving CARVYKTI in clinical studies. IEC-EC have been reported in the post marketing setting (see **section 4.8** Adverse effects (undesirable effects)). Supportive care, including total parenteral nutrition (TPN), may be warranted. Consider prompt referral to CARVYKTI treatment physicians as well as gastroenterology and infectious disease specialists. Treatment with corticosteroids or other immunosuppressants have been reported with variable response. Cases of gastrointestinal perforation, including fatal outcomes, have been reported after CARVYKTI particularly in patients treated with prolonged or high dose corticosteroids. In cases of refractory IEC-EC, consider additional workup to exclude alternative aetiologies, including T-cell lymphoma of the gastrointestinal tract, which has been reported in the post marketing setting (see **section 4.4** Special Warnings and Precautions for Use and **section 4.8** Adverse effects (undesirable effects)).

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

T-cell malignancies have occurred following treatment with BCMA- and CD-19-directed genetically modified autologous T-cell immunotherapies and may present as soon as weeks following infusion. T-cell lymphoma, including CAR-positive tumours, have occurred in patients after CARVYKTI infusion (see **section 4.8** Adverse effects (undesirable effects)).

Myelodysplastic syndrome and acute myeloid leukemia, including cases with fatal outcomes, have occurred in patients after CARVYKTI infusion (see **section 4.8** Adverse effects (undesirable effects)).

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company for reporting and to obtain instructions on patient samples to collect for testing of secondary malignancy of T-cell origin. In patients with HIV infection, contact the company for the testing of all types of secondary malignancy, including those of non-T-cell origin.

Hypersensitivity

Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO), or residual kanamycin 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.

Blood, organ, tissue and cell donation

Patients treated with CARVYKTI should not donate blood, organs, tissues and cells for transplantation.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with CARVYKTI.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of CARVYKTI on fertility. Effects of CARVYKTI on male and female fertility have not been evaluated in animal studies.

Use in pregnancy

Category C

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI. It is not known whether CARVYKTI has the potential to be transferred to the foetus and cause foetal toxicity. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised there may be risks to the foetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

Pregnant women who have received CARVYKTI may have hypogammaglobulinemia. Assessment of immunoglobulin levels in new-borns of mothers treated with CARVYKTI should be considered.

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

There are insufficient exposure 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.

Use in lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the potential for neurologic events, 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 neurological symptoms.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of CARVYKTI was evaluated in 396 adult patients with multiple myeloma infused with CARVYKTI in three open label clinical trials: Study MMY2001 (N=106), which included patients from the main Phase 1b/2 cohort (United States; n=97; with a median duration of follow-up of 27.7 months) and an additional cohort (Japan; n=9), Phase 2 Study MMY2003 (n=94) and Phase 3

Study MMY3002 (N=196). Patients who complete Study MMY2001, MMY2003, or MMY3002 are eligible to enrol in a separate long-term follow-up study (MMY4002).

The most common CARVYKTI adverse reactions (≥20%) were neutropenia, CRS, pyrexia, anaemia, thrombocytopenia, leukopenia, lymphopenia, hypotension, transaminase elevation, musculoskeletal pain, fatigue, upper respiratory tract infection, diarrhoea, nausea, headache, hypogammaglobulinemia and cough,

Serious adverse reactions occurred in 45% of patients; serious adverse reactions reported in ≥5% of patients were CRS (11%), pneumonia (9%), sepsis (5%) and viral infection (5%).

The most common (≥10%) Grade ≥ 3 non-haematological adverse reactions was transaminase elevation (11%).

The most frequent (≥25%) Grade ≥3 haematological abnormalities were neutropenia (88%), anaemia (44%), thrombocytopenia (44%) lymphopenia (36%) and leukopenia (32%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions that occurred in patients receiving CARVYKTI.

Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

Table 3: Adverse reactions in patients with multiple myeloma treated with CARVYKTI (N=396)

System Organ Class	Frequency	Adverse Reaction	Incidence (%)	
			All Grades	Grade ≥ 3
Infections and infestations	Very common	Upper respiratory tract infection[1]	30	2
		Viral infection[2]	17	4
		Bacterial infection[3#]	13	5
		Pneumonia[4#]	12	9
	Common	Sepsis[5#]	9	7
		Gastroenteritis[6]	6	1
		Urinary tract infection[7]	5	1
		Fungal infection[8]	3	<1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Haematologic malignancy[#38]	5	4
Blood and lymphatic system disorders	Very common	Neutropenia	89	88
		Anaemia[9]	60	44
		Thrombocytopenia	60	44
		Leukopenia	33	32
		Lymphopenia	34	33
		Coagulopathy[10]	12	3
	Common	Febrile neutropenia	8	8
		Lymphocytosis[11]	3	1
Immune system disorders	Very common	Cytokine release syndrome[#]	83	4
		Hypogammaglobulinaemia[12]	29	5
	Common	Haemophagocytic lymphohistiocytosis[#]	3	2
	Not known	Infusion related reactions[*]		
Metabolism and nutrition disorders	Very common	Hypocalcaemia	16	3
		Hypophosphataemia	17	4
		Decreased appetite	15	1
		Hypoalbuminaemia	11	<1

		Hyponatraemia	10	2
		Hypokalaemia	17	2
		Hypomagnesaemia	12	<1
		Hyperferritinemia[13]	10	2
Psychiatric disorders	Common	Delirium[14]	3	<1
		Personality changes[15]	3	1
		Headache	24	0
Nervous system disorders	Very common	Motor dysfunction[16]	13	2
		Dizziness[17]	13	1
		Encephalopathy[18]	10	2
		Immune effector cell-associated neurotoxicity syndrome[#]	11	2
		Sleep disorders[19]	10	1
		Cranial nerve palsies[20]	7	1
	Common	Neuropathy peripheral[21]	7	1
		Aphasia[22]	5	<1
		Tremor[23]	5	<1
		Ataxia[24]	4	<1
		Paresis[25]	1	<1
		Neurotoxicity[#]	1	1
		Guillain-Barre syndrome	<1	<1
	Uncommon	Tachycardia[26]	13	1
Cardiac disorders	Very common	Cardiac arrhythmias[27]	4	2
	Common	Hypotension[28]	33	6
Vascular disorders	Very common	Hypertension	11	4
		Haemorrhage[29]	10	2
		Thrombosis[30]	4	1
	Common	Capillary leak syndrome	1	0
		Cough[31]	21	0
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea[32#]	14	3
		Hypoxia[33]	13	4
		Diarrhoea[34]	31	3
Gastrointestinal disorders	Very common	Nausea	23	<1
		Constipation	15	0
		Vomiting	12	0
		Abdominal pain[35]	8	0
	Not known	Gastrointestinal perforation*[#]		
Hepatobiliary disorders	Common	Hyperbilirubinemia	3	1
Skin and subcutaneous tissue disorders	Common	Rash[36]	9	0
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain[37]	38	3
Renal and urinary disorders	Very common	Renal failure[38]	6	4
General disorders and administration site conditions	Common	Pyrexia	84	6
	Very common	Fatigue[39]	35	4
		Chills	14	0
		Oedema[40]	16	1
		Pain[41]	11	1
Investigations	Very common	Transaminase elevation[42]	25	11
		Gamma-glutamyltransferase increased	10	6
	Common	C-reactive protein increased	7	1
		Blood alkaline phosphatase increased	8	3

Adverse events are reported using MedDRA version 25.0

\# Contains fatal event/s.

* Events not reported in clinical studies and cannot be estimated from the available data. The adverse reactions have been included in the table as a result of post marketing from the use of CARVYKTI

1 Upper respiratory tract infection includes bronchitis, nasal congestion, nasopharyngitis, pharyngeal inflammation, pharyngitis, respiratory tract congestion, respiratory tract infection, rhinitis, rhinorrhoea, rhinovirus infection, sinus congestion, sinusitis, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.

2 Viral infection includes adenovirus infection, adenovirus test positive, asymptomatic covid-19, covid-19, coronavirus infection, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus syndrome, cytomegalovirus viraemia, hepatitis b reactivation, herpes simplex reactivation, herpes virus infection, herpes zoster, herpes zoster disseminated, human herpesvirus 6 infection, human rhinovirus test positive, influenza, lymphadenitis viral, metapneumovirus infection, oral herpes, parainfluenzae virus infection, parvovirus b19 infection, parvovirus infection, respiratory syncytial virus infection, respiratory tract infection viral, and rotavirus infection.

3 Bacterial infection includes abscess limb, bordetella infection, breast cellulitis, bronchitis bacterial, campylobacter infection, catheter site infection, cellulitis, chalazion, citrobacter infection, clostridium difficile colitis, clostridium difficile infection, device related infection, enterococcal infection, escherichia infection, folliculitis, hordeolum, klebsiella infection, lung abscess, perichondritis, perirectal abscess, post procedural infection, pyelonephritis acute, salmonellosis, sinusitis bacterial, skin infection, soft tissue infection, staphylococcal infection, superinfection bacterial, tooth infection, vascular access site infection, and vascular device infection.

4 Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, covid-19 pneumonia, lower respiratory tract infection, lung infiltration, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia moraxella, pneumonia pseudomonal, pneumonia streptococcal, and pneumonia viral.

5 Sepsis includes bacteremia, bacterial sepsis, candida sepsis, device related bacteremia, enterococcal bacteremia, haemophilus sepsis, neutropenic sepsis, pseudomonal bacteremia, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteremia, streptococcal sepsis, systemic candida, and urosepsis.

6 Gastroenteritis includes enterocolitis bacterial, enterocolitis infectious, enterocolitis viral, enterovirus infection, gastroenteritis, gastroenteritis cryptosporidial, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastrointestinal infection, and large intestine infection.

7 Urinary tract infection includes cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, and urinary tract infection viral.

8 Fungal infection includes candida infection, cerebral aspergillosis, oral candidiasis, sinusitis aspergillus, tongue fungal infection, and vulvovaginal candidiasis.

9 Hematologic malignancy includes acute myeloid leukaemia, myelodysplastic syndrome, myelodysplastic syndrome with multilineage dysplasia, acute myeloid leukemia, peripheral T-cell lymphoma unspecified and T-cell lymphoma of the gastrointestinal tract.

10 Anaemia includes anaemia and iron deficiency anaemia.

11 Coagulopathy includes activated partial thromboplastin time prolonged, blood fibrinogen decreased, coagulation test abnormal, coagulopathy, disseminated intravascular coagulation, hypofibrinogenemia, international normalised ratio increased, prothrombin level increased, and prothrombin time prolonged.

12 Hypogammaglobulinaemia includes blood immunoglobulin G decreased, and hypogammaglobulinaemia.

13 Hyperferritinaemia includes hyperferritinaemia, and serum ferritin increased.

14 Delirium includes agitation, delirium, disorientation, euphoric mood, hallucination, irritability, and restlessness.

15 Personality changes includes flat affect, indifference, personality change, and reduced facial expression.

16 Motor dysfunction includes agraphia, dysgraphia, eyelid ptosis, micrographia, motor dysfunction, muscle rigidity, muscle spasms, muscle tightness, muscular weakness, myoclonus, and parkinsonism.

17 Dizziness includes dizziness, dizziness exertional, dizziness postural, presyncope, syncope, and vertigo.

18 Encephalopathy includes amnesia, bradyphrenia, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, mental impairment, mental status changes, psychomotor retardation, and slow response to stimuli.

19 Sleep disorders includes hypersomnia, insomnia, sleep disorder, and somnolence.

20 Cranial nerve palsies include Bell`s palsy, cranial nerve paralysis, facial nerve disorder, facial paralysis, facial paresis, iiird nerve paralysis, trigeminal palsy, and VIth nerve paralysis.

21 Neuropathy peripheral includes neropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

22 Aphasia includes aphasia, dysarthria, slow speech, and speech disorder.

23 Tremor includes resting tremor and tremor.

24 Ataxia includes ataxia, balance disorder, dysmetria, and gait disturbance.

25 Paresis includes hemiparesis, paresis, and peroneal nerve palsy.

26 Tachycardia includes sinus tachycardia, and tachycardia.

27 Cardiac arrhythmias include atrial fibrillation, atrial flutter, atrioventricular block second degree, supraventricular tachycardia, ventricular extrasystoles, and ventricular tachycardia.

28 Hypotension includes hypotension and orthostatic hypotension.

29 Hemorrhage includes catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, epistaxis, eye contusion, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, lower gastrointestinal haemorrhage, pulmonary haemorrhage, retinal haemorrhage, retroperitoneal haemorrhage, subarachnoid haemorrhage, and subdural haematoma.

30 Thrombosis includes deep vein thrombosis, device related thrombosis, embolism, jugular vein thrombosis, pulmonary embolism, and venous thrombosis limb.

31 Cough includes cough, productive cough, and upper-airway cough syndrome.

32 Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, tachypnoea, and wheezing.

33 Hypoxia includes hypoxia and oxygen saturation decreased.

34 Diarrhoea includes colitis and diarrhoea and T-cell lymphoma of the gastrointestinal tract.

35 Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and dyspepsia.

36 Rash includes bullous haemorrhagic dermatosis, dermatitis exfoliative generalised, dermatitis psoriasiform, drug eruption, erythema, pityriasis lichenoides et varioliformis acuta, rash, rash erythematous, rash maculo-papular, rash pustular, rash vesicular, and urticaria.

37 Musculoskeletal pain includes arthralgia, back pain, bone pain, joint stiffness, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myositis, neck pain, non-cardiac chest pain, osteoarthritis, pain in extremity, rotator cuff syndrome, spinal pain, and tendonitis.

38 Renal failure includes acute kidney injury, blood creatinine increased, chronic kidney disease, renal failure, and renal impairment.
39 Fatigue includes asthenia, fatigue, and malaise.
40 Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, palatal oedema, periorbital oedema, peripheral swelling, pulmonary congestion, and pulmonary oedema.
41 Pain includes anorectal discomfort, catheter site pain, ear pain, eye pain, flank pain, fracture pain, inflammatory pain, odynophagia, pain, pain in jaw, pain of skin, pelvic pain, proctalgia, rhinalgia, sacral pain, sinus pain, testicular pain, and toothache.
42 Transaminase elevation includes alanine aminotransferase increased, and aspartate aminotransferase increased.

Of the 196 patients in Study MMY3002, 20 patients who had higher risk disease progressed early and rapidly on bridging therapy prior to infusion with CARVYKTI and received CARVYKTI as subsequent therapy (See section 5.1 Pharmacodynamic properties - Clinical trials). In these patients, MNT was reported in one patient (5%) and was mild in severity (Grade 1 or 2). CRS was reported at a higher rate for Grade 3 and Grade 4 (25%), including events of CRS complicated by HLH (10%) or DIC (10%). ICANS was reported at a higher rate (35%) and severity (10%) for Grade 3. Five patients died of fatal events related to CARVYKTI (2 due to haemorrhage in the context of HLH or DIC and 3 due to fatal infections [pulmonary aspergillosis, sepsis and sepsis due to pseudomonas aeruginosa]).

Description of selected adverse reactions

Cytokine release syndrome

In the pooled studies (N=396), CRS was reported in 83% of patients (n=330); 79% (n=314) CRS events were Grade 1 or Grade 2, 4% (n=15) Grade 3 or 4, and <1% (n=1) was Grade 5. Ninety-eight percent of patients (n=323) recovered from CRS.

The duration of CRS was ≤18 days for all but one patient who had a duration of CRS of 97 days, complicated by secondary HLH with a subsequent fatal outcome. The most frequent (≥10%) signs or symptoms associated with CRS included pyrexia (81%), hypotension (28%), Aspartate aminotransferase (AST) increased (12%), and hypoxia (10%). See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Neurologic toxicities

In the pooled studies (N=396), neurologic toxicity occurred in 23% (n=89) of patients with 5% (n=21) being Grade 3 or Grade 4 and 1% Grade 5 (n=3; one due to ICANS, one due to movement and neurocognitive toxicity with signs and symptoms of parkinsonism and one due to encephalopathy). In addition, eleven patients had fatal outcomes with ongoing neurologic toxicity at the time of death; eight deaths were due to infection including two deaths in patients with ongoing signs and symptoms of parkinsonism, as discussed below, and one death each was due to respiratory failure, cardio-respiratory arrest and intraparenchymal haemorrhage (See section 4.4. Special Warnings and Precautions for use for monitoring and management guidance).

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

In the pooled studies (N=396), ICANS occurred in 11% of patients (n=45), with 2% (n=7) experiencing Grade 3 or 4 ICANS and <1% (n=1) Grade 5 ICANS. . Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state. The median time from CARVYKTI infusion to first onset of ICANS was 8.0 days (range: 2 to 15 days, except for 1 patient with onset at 26 days) and the median duration was 3 days (range: 1 to 29 days, except for 1 patient who had a subsequent fatal outcome at 40 days).

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Of the 89 patients in the pooled studies (N=396)experiencing any neurotoxicity, nine male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. The maximum toxicity grades of parkinsonism were: Grade 1 (n=1) Grade 2 (n=2) and Grade 3 (n=6). The median onset of parkinsonism was 38 days (range: 14 to 914 days) from infusion of CARVYKTI. One patient (Grade 3) died of neurologic toxicity with ongoing parkinsonism 247 days after administration of CARVYKTI, and two patients (Grade 2 and Grade 3) with ongoing parkinsonism died of infectious causes 162 and 119 days after administration of CARVYKTI. One patient recovered (Grade 3). In the remaining 5 patients, symptoms of parkinsonism were ongoing up to 996 days after administration of CARVYKTI. All 9 patients had a history of prior CRS (n=1

Grade 1; n=6 Grade 2; n=1 Grade 3); n=1 Grade 4, while 6 of 9 patients had prior ICANS (n=5 Grade 1; n=1 Grade 3).

Guillain-Barré Syndrome

In the pooled studies (N=396), one patient was reported to have GBS after treatment with CARVYKTI. Although GBS symptoms improved after receiving treatment with steroids and IVIG, the patient died 139 days after administration of CARVYKTI due to encephalopathy post gastroenteritis with ongoing GBS symptoms.

Peripheral Neuropathy

In the pooled studies (N=396), 27 patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 57 days (range: 1 to 914 days), median duration of peripheral neuropathies was 140 days (range: 1 to 766 days) including those with ongoing neuropathy. Of these 27 patients, 5 experienced Grade 3 or 4 peripheral neuropathy (which resolved in 1 patient with no treatment reported, and was ongoing in the other 4 patients, including one patient who improved after treatment with dexamethasone). Of the remaining 22 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no treatment reported in 6 patients, and following treatment with duloxetine in 2 patients, and was ongoing in the other 10 patients.

Cranial Nerve Palsies

In the pooled studies (N=396), 27 patients experienced cranial nerve palsies. Median time to onset was 22 days (range: 17 to 101 days) following infusion of CARVYKTI, and median time to resolution was 56 days (range: 1 to 209 days) following onset of symptoms.

Prolonged and recurrent cytopenias

In the pooled studies (N=396), Grade 3 cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following CARVYKTI infusion, included thrombocytopenia (33%), neutropenia (29%), and lymphopenia (25%) and anaemia (3%). After Day 60 following CARVYKTI, 23%, 21%,7% and 4% of patients had an occurrence of Grade 3 lymphopenia, neutropenia, anaemia and thrombocytopenia respectively, after initial recovery of their Grade 3 or Grade 4 cytopenia.

Table 4 lists the incidences of Grade 3 or Grade 4 cytopenias occurring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60 respectively.

Table4: Incidences of Prolonged and Recurrent Cytopenias Following Treatment with CARVYKTI in studies MMY2001, MMY2003 and MMY3002 (N=396)[b]

	Grade 3/4 (%) After Day 1 Dosing	Initial Grade 3/4 (%) Not Recovered[a] to ≤Grade 2 by Day 30	Initial Grade 3/4 (%) Not Recovered[a] to ≤Grade 2 by Day 60	Occurrence of Grade 3/4 (%) > Day 60 (after Initial Recovery[a] of Grade 3/4)
Thrombocytopenia	191 (48%)	132 (33%)	76 (19%)	14 (4%)
Neutropenia	381 (96%)	114 (29%)	44 (11%)	81 (21%)
Lymphopenia	391 (99%)	98 (25%)	46 (12%)	90 (23%)
Anaemia	180 (46%)	11(3%)	12 (3%)	26 (7%)

[a] The laboratory result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade ≤2 results on different days if recovery period ≤10 days.

Notes: Lab results assessed after Day 1 until Day 100 for MMY2001 and MMY2003 or Day 112 for MMY3002, or the start of subsequent therapy, whichever occurs first, are included in the analysis.

Thrombocytopenia: Grade 3/4 – Platelets count <50000 cells/μL.

Neutropenia: Grade 3/4 - Neutrophil count <1000 cells/μL.

Lymphopenia: Grade 3/4 - Lymphocytes count <0.5 x 10^9 cells/L.

Anaemia: Grade 3 – haemoglobin <8g/dL. Grade 4 not defined by laboratory count per NCI-CTCAE v5

Percentages are based on the number of treated subjects

[b] The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N = 196); Randomized Clinical Trials: MMY3002.

Serious infections

Infections occurred in 206 patients (52%) in the pooled studies (N=396); 66 (17%) experienced Grade 3 or Grade 4 infections, and fatal infections (COVID-19 pneumonia, pneumonia, sepsis, Clostridium difficile colitis, septic shock, bronchopulmonary aspergillosis, pseudomonal sepsis, neutropenic sepsis, and lung abscess) occurred in 17 patients (4%). The most frequently reported (≥2%) Grade 3 or higher infections were pneumonia, COVID-19 pneumonia and sepsis. Febrile neutropenia was observed in 6% of patients with 2% experiencing serious febrile neutropenia. See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Hypogammaglobulinemia

In the pooled studies (N=396) hypogammaglobulinemia was reported in 30% of patients with 5% of patients experiencing Grade 3 hypogammaglobulinemia laboratory IgG levels fell below 500 mg/dL after infusion in 91% (359/396) of patients treated with CARVYKTI. Fifty-three percent of patients received IVIG post CARVYKTI for either an adverse reaction or prophylaxis. See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Immune Effector Cell-associated Enterocolitis

Patients treated with CARVYKTI may develop IEC-EC (e.g. immune-mediated enterocolitis), presenting as severe or prolonged diarrhoea typically with an onset range from 1 month to 3 months after CARVYKTI infusion. In the pooled studies (N=396), IEC-EC occurred in 1% (5/396) of patients (all Grade 3) which resulted in clinically significant weight loss in some of these patients. See **section 4.4** Special Warnings and Precautions for Use.

Haematologic malignancy

Myeloid Neoplasms

In study MMY2001 (N=106), myeloid neoplasms occurred in 8% (n=9) of patients (4 events per 100 person-years post CARVYKTI infusion) up to study close out (median follow-up of 33.0 months). There were 6 cases of myelodysplastic syndrome, 2 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 478 days (range: 162 to 870 days) after CARVYKTI infusion. Seven of these 9 patients died following the development of myeloid neoplasms; 4 deaths were deemed related to the myeloid neoplasm. Two of the 9 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. The 9 patients who developed myeloid neoplasms were heavily pre-treated with a range of 4 to 18 prior therapies, all were previously treated with alkylators, and all previously received an autologous stem cell transplant. All patients had genetic mutations associated with the development of MDS or AML present prior to receipt of CARVYKTI.

In study MMY3002 (N=196), myeloid neoplasms occurred in 3% (n=5) of patients (1.2 events per 100 person-years post CARVYKTI infusion) as of 27-Feb-2024 cutoff date (median follow-up of 28.1 months). There were 2 cases of myelodysplastic syndrome, 1 case of acute myeloid leukemia, and 2 cases of myelodysplastic syndrome followed by acute myeloid leukemia. The median time to onset of myeloid neoplasms was 385 days (range: 56 to 758 days) after CARVYKTI infusion. All 5 patients died following the development of myeloid neoplasms; 5 deaths were deemed related to the myeloid neoplasm. No cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. All patients were previously treated with alkylators and lenalidomide and the majority of patients previously received an autologous stem cell transplant. Two patients previously received treatment for other hematologic malignancies. All patients had genetic mutations associated with the development of MDS or AML present prior to receipt of CARVYKTI.

As of the 27-Feb-2024 cutoff date, 3 additional cases of myeloid neoplasms occurred in the long-term follow-up study (median follow-up of 31.8 months), representing a cumulative long-term incidence rate of 2 events per 100 person-years post CARVYKTI infusion. The median time to onset of myeloid neoplasm in the long-term follow-up study was 954 days after CARVYKTI

infusion. Cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in the post marketing setting.

T-cell Lymphoma

In study MMY3002 (N=196), T-cell lymphoma occurred in two patients (1%) (0.5 events per 100 person-years post CARVYKTI infusion). These patients were diagnosed with peripheral T-cell lymphoma unspecified on Day 159 and Day 688 post CARVYKTI infusion. Presence of the CAR transgene was detected in the tumours.

As of the 27-Feb-2024 cutoff date, no additional cases of T-cell lymphoma have occurred in the long-term follow-up study (median follow-up of 31.8 months), representing a cumulative long-term incidence rate of 0.2 events per 100 person-years post CARVYKTI infusion. Cases of T cell lymphoma, including CAR-positive T-cell lymphoma, have been reported in the post marketing setting.

Post marketing data

The following adverse reactions have been identified during post-approval use of CARVYKTI. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to product exposure.

Neoplasms: T cell malignancies including T-cell lymphoma of the gastrointestinal tract.

Gastrointestinal Disorders: immune effector cell-associated enterocolitis (event terms including colitis, diarrhoea, enterocolitis and immune-mediated enterocolitis) and gastrointestinal perforation (event terms including large intestine perforation, diverticular perforation, gastrointestinal perforation and intestinal perforation). Some of the gastrointestinal perforations had fatal outcomes (see **section 4.4** Special Warnings and Precautions for Use).

Immune System Disorders: hypersensitivity including infusion related reactions.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Treatment

There are no data regarding the signs or sequelae of overdose with CARVYKTI. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

CARVYKTI is a BCMA-directed, genetically modified autologous T cell immunotherapy, which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B

cells and plasma cells. The CARVYKTI CAR protein features two BCMA-targeting single domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signalling cytoplasmic domain. Upon binding to BCMA expressing cells, the CAR promotes T-cell, activation, expansion and elimination of target cells.

In vitro co-culture experiments demonstrated that ciltacabtagene autoleucel-mediated cytotoxicity and cytokine release (interferon-gamma, [IFN-γ], tumour necrosis factor alpha [TNF-α], interleukin [IL]-2) were BCMA-dependent.

Pharmacodynamic effects

After a single infusion of CARVYKTI, expansion of CAR positive T-cells coincided with decreases of serum soluble BCMA, serum M-protein, and/or free light chains. Across all patients, levels of IL-6, IL-10, IFN-γ and IL-2 receptor alpha increased post-infusion and peaked at Days 7-14. The serum levels of all cytokines generally returned to baseline levels within 2-3 months post-infusion.

Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against CARVYKTI pre-dose and at multiple timepoints post-infusion. Among 235 subjects treated with CARVYKTI in Studies MMY2003 (N=39) and MMY3002 (N=196), 50 subjects (21%) were positive for anti-CAR antibodies.

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

Clinical trials

Study MMY2001 (CARTITUDE-1)

MMY2001 was an open label trial evaluating CARVYKTI for the treatment of patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or after the last regimen.

In total, 113 patients underwent leukapheresis; CARVYKTI was manufactured for all patients. Sixteen patients were not treated with CARVYKTI (n=12 after leukapheresis and n=4 after lymphodepleting therapy), due to either withdrawal by patient (n=5), progressive disease (n=2) or death (n=9).

Of the 97 patients treated, the median time from the day after receipt of leukapheresis material at manufacturing facility to release of product for infusion was 29 days (range: 23 to 64 days) and the median time from initial leukapheresis to CARVYKTI infusion was 47 days (range: 41 days to 167 days).

Following leukapheresis and prior to administration of CARVYKTI, 73 of the 97 patients (75%) received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days). Ninety-seven patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.51 to 0.95×10^6 cells/kg). All patients were hospitalized for CARVYKTI infusion and for a minimum of 10 days afterward.

Of the 97 patients treated, 59% were male, 71% were Caucasian and 18% were Black or African-American. The median patient age was 61 years (range: 43 to 78 years). Patients had received a median of 6 (range: 3 to 18) prior lines of therapy and 90% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy and 88% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody.

Patients with known active, or prior history of significant central nervous system (CNS) disease, including CNS multiple myeloma, allogenic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance < 40mL/min, absolute lymphocyte concentration < 300/µL, hepatic transaminases > 3 times the upper limit of normal, cardiac ejection fraction < 45%, or with active serious infection were excluded from the trial.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 5).

Table 5: Efficacy results for Study MMY2001

	All Treated (N=97)	**All Leukapheresed (N=113)**
Overall Response Rate (sCR[a] + VGPR + PR) n (%)	95 (97.9)	95 (84.1)
95% CI (%)	(92.7, 99.7)	(76.0, 90.3)
Stringent complete response (sCR[a]) n (%)	80 (82.5)	80 (70.8)
Very good partial response (VGPR) n (%)	12 (12.4)	12 (10.6)
Partial response (PR) n (%)	3 (3.1)	3 (2.7)
Duration of Response (DOR)[b]		
Number of responders DOR (Months): Median (95% CI)	95 NE (23.3, NE)	-
Number of responders with sCR[a] DOR if best response is sCR[a] (Months):Median (95% CI)	80 NE (28.3, NE)	-
Number of responders with VGPR or better DOR if best response is VGPR or better (Months): Median (95% CI)	92 NE (24.4, NE)	-
Time to Response (months)		
Number of responders Median Range	95 0.95 (0.9; 10.7)	-
Time to sCR[a] (months)		
Number of responders with sCR[a] Median Range	80 2.89 (0.9; 17.8)	-

Notes: Based on a median duration of follow up of 28 months

[a] All complete responses were stringent CRs

[b] The estimated DOR rate was 60.3% (95% CI: 49.6%, 69.5%) at 24 months and 51.2% (95% CI: 39.0%, 62.1%) at 30 months

Table 6: Summary of MRD negativity rate

	All Treated (N=97)	**All Leukapheresed (N=113)**
MRD negativity rate n (%)	56 (57.7)	56 (49.6)
95% CI (%)	(47.3, 67.7)	(40.0, 59.1)
MRD negative patients with sCRn (%)[a]	42 (43.3)	42 (37.2)
95% CI (%)	(33.3. 53.7)	(28.3, 46.8)
	Evaluable patients (N=61)	
MRD negativity rate n (%)	56 (91.8)	-
95% CI (%)	(81.9, 97.3)	-

MRD= Minimal Residual Disease

Notes:Based on a median duration of follow up of 28 months

[a] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered. All complete responses were stringent CRs

With a median duration of follow up of 28 months, median Progression Free Survival (PFS) was not reached (95% CI: 24.5, not estimable). The 12-month PFS rate (95% CI) was 76.3% (66.5%, 83.6%). The 24-month PFS rate (95% CI) was 62.7% (52.2%, 71.5%).

For patients who achieved sCR (all complete responses were stringent CRs), median PFS was not reached (95% CI: 30.1 not estimable) with an estimated 12-month PFS rate of 88.8% (95% CI: 79.5%, 94.0%). The 24-month PFS rate was 73.5% (95% CI: 62.3%, 81.9%).

Median overall survival (OS) was not reached (95% CI: not estimable not estimable). The OS rate at 12 months was 87.6% (95% CI: 79.2%, 92.8%). The 24-month OS rate was 76.2% (95% CI: 66.5%, 83.5%).

Health-related quality of life (HRQoL) was evaluated by the EORTC QLQ-C30 and completed at baseline (n=63) and during the post-infusion phase. The adjusted mean (95% CI) change from baseline in the EORTC QLQ-C30 Pain subscale was -1.9 (-8.5, -4.6) at Day 7, -9.9 (-16.5, -3.3) at Day 28, -6.3 (-12.9, -0.4) on Day 56, -9.4 (-16.3, -2.5) at Day 78, and -10.5 (-17.3, -3.8) on Day 100, indicating overall reduction in pain following CARVYKTI infusion. Clinically, meaningful improvements at Day 100 were seen in 72.2% of patients for the pain subscale, 53.8% for the fatigue subscale, 57.7% for the physical functioning subscale, and 53.7% for the global health status subscale.

MAMMOTH analysis

A retrospective, patient-level, pooled analysis of outcomes of patients with multiple myeloma refractory to CD38 monoclonal antibodies was conducted to provide context for interpreting the efficacy results reported in Study MMY2001.

From the MAMMOTH dataset, the analysis identified a patient population (N=122). corresponding to the Study MMY2001 all-treated population.

For the patients from the MAMMOTH dataset, Day 1 of the study was 47 days after the start of standard of care conventional therapy.

For the patients from the MAMMOTH dataset, the overall response rate (ORR) was 38%, 12-month PFS rate (95% CI) was 7% (1%,13%), and 12-month OS rate (95% CI) was 40% (30%, 50%).

The MAMMOTH retrospective outcomes analysis indicated that patients receiving CARVYKTI (Study MMY2001) had better outcomes than patients receiving other available treatments assessed in the MAMMOTH study, as measured by ORR, PFS and OS.

Study MMY3002 (CARTITUDE-4)

MMY3002 is a Phase 3 randomised, open label, multicentre trial evaluating the efficacy of CARVYKTI for the treatment of patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a proteasome inhibitor and an immunomodulatory agent. A total of 419 patients were randomised to receive either a sequence of apheresis, bridging therapy, lymphodepletion and CARVYKTI (n=208) or standard of care which included physician's choice of daratumumab, pomalidomide and dexamethasone or bortezomib, pomalidomide and dexamethasone (n=211).

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.

Of the 419 patients who were randomised (208 to CARVYKTI and 211 to standard of care), 57% were male, 75% were Caucasian, 3% were Black or African American, and 7% were Hispanic or Latino. The median patient age was 61 years (range: 27 to 80 years). Patients had received a median of 2 (range: 1 to 3) prior lines of therapy and 85% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy. Forty-eight percent were refractory to a proteasome inhibitor (PI) and 100% were refractory to an immunomodulatory agent.

All 208 patients randomised to the CARVYKTI arm underwent apheresis. Following apheresis and prior to administration of CARVYKTI, all 208 randomised patients received protocol mandated bridging therapy (standard of care). Of these 208 patients, 12 were not treated with

CARVYKTI due to progressive disease (n=10) or death (n=2), and 20 progressed prior to infusion with CARVYKTI but were able to receive CARVYKTI as subsequent therapy.

In the 176 patients that received CARVYKTI as study treatment, the median time from the day after receipt of apheresis material at manufacturing facility to release of product for infusion was 44 days (range: 25 to 127 days) and the median time from first apheresis to CARVYKTI infusion was 79 days (range: 45 days to 246 days).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days) at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.39 to 1.07×10^6 cells/kg).

The primary efficacy measure was progression-free survival (PFS) analyzed based on the Intent-To-Treat Analysis Set (see Table 7 and Figure 1). After a median follow-up of 15.9 months, median PFS was 11.8 months (95% CI: 9.7, 13.8) for standard of care arm and NE (95% CI: 22.8, NE) for CARVYKTI arm (Hazard ratio: 0.26 [95% CI: 0.18, 0.38]) The estimated PFS rate at 12 months was 75.9% (95% CI: 69.4%, 81.1%) in the CARVYKTI arm and 48.6% (95% CI: 41.5%, 55.3%) in the standard of care arm. In the CARVYKTI arm, the estimated median duration of response (DOR) has not been reached. In the standard of care arm, the estimated median DOR was 16.6 months (95% CI: 12.9, NE).

Table 7: Efficacy results for Study MMY3002 (Intent-To-Treat Analysis Set)

	CARVYKTI (N=208)	**Standard of Care (N=211)**
Progression-Free Survival[a]		
Number of events, n (%)	65 (31.3)	122 (57.8)
Median, months [95% CI][b]	NE [22.8, NE]	11.8 [9.7, 13.8]
Hazard ratio [95% CI][c]	0.26 [0.18, 0.38]	
p-value[d]	<0.0001	
Complete Response or Better Rate[a], % [95% CI]	73.1 [66.5, 79.0]	21.8 [16.4, 28.0]
p-value[e]	<0.0001	
Overall Response Rate (ORR)[a], % [95% CI]	84.6 [79.0, 89.2]	67.3 [60.5, 73.6]
p-value[e]	<0.0001	
Overall MRD Negativity Rate, % [95% CI]	60.6 [53.6, 67.3]	15.6 [11.0, 21.3]
p-value[f]	<0.0001	
Overall Survival (OS)		
Number of events, n (%)	48 (23.1)	77 (36.5)
Median, months [95% CI][b]	NE [NE, NE]	NE [34.0, NE]
Hazard ratio [95% CI][g]	0.57 [0.40, 0.83]	

NE=not estimable; CI=confidence interval; MRD=minimal residual disease

Notes: Based on a median duration of follow up of 15.9 months. Overall survival based on a median duration of follow-up of 28.7 months.

[a] Per the International Myeloma Working Group (IMWG) consensus, as assessed by computerized algorithm

[b] Kaplan-Meier estimate

[c] Based on a stratified Cox proportional hazards model, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for TRADENAME Arm. For all stratified analyses, stratification was based on investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.

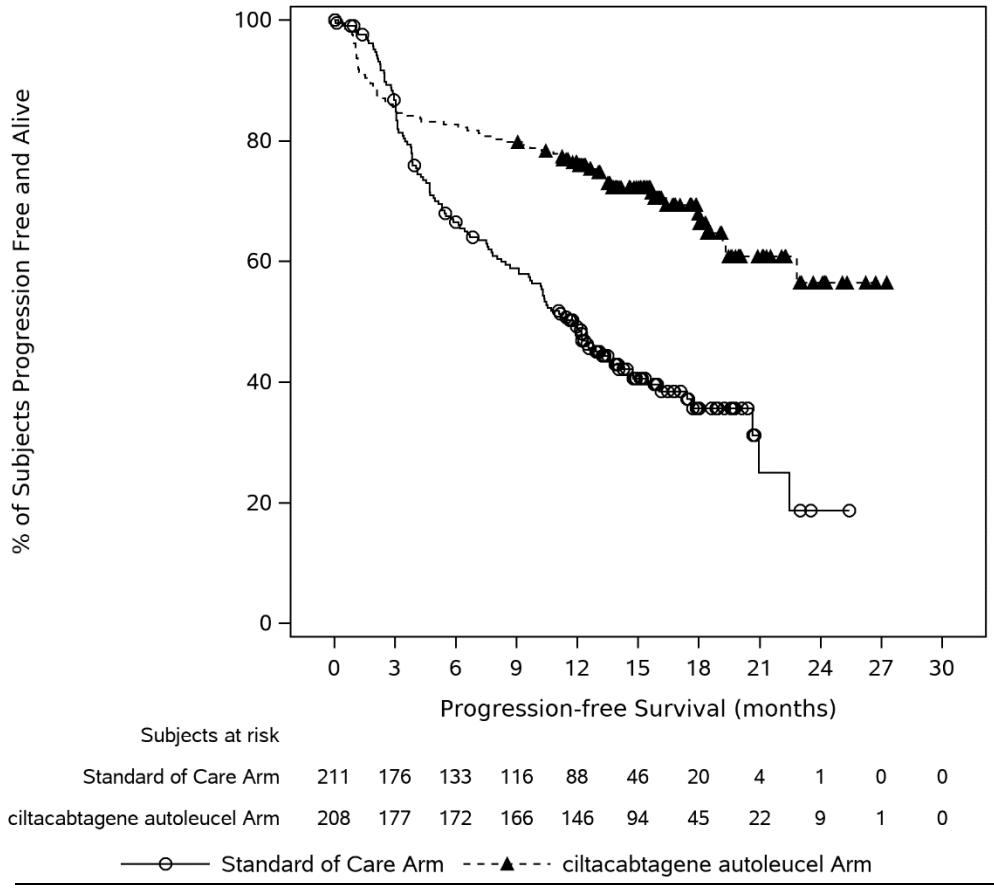
[d] Stratified weighted log-rank test (weight of 0 in the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards)

[e] Stratified Cochran-Mantel-Haenszel Chi-Squared test

[f] Fisher's exact test

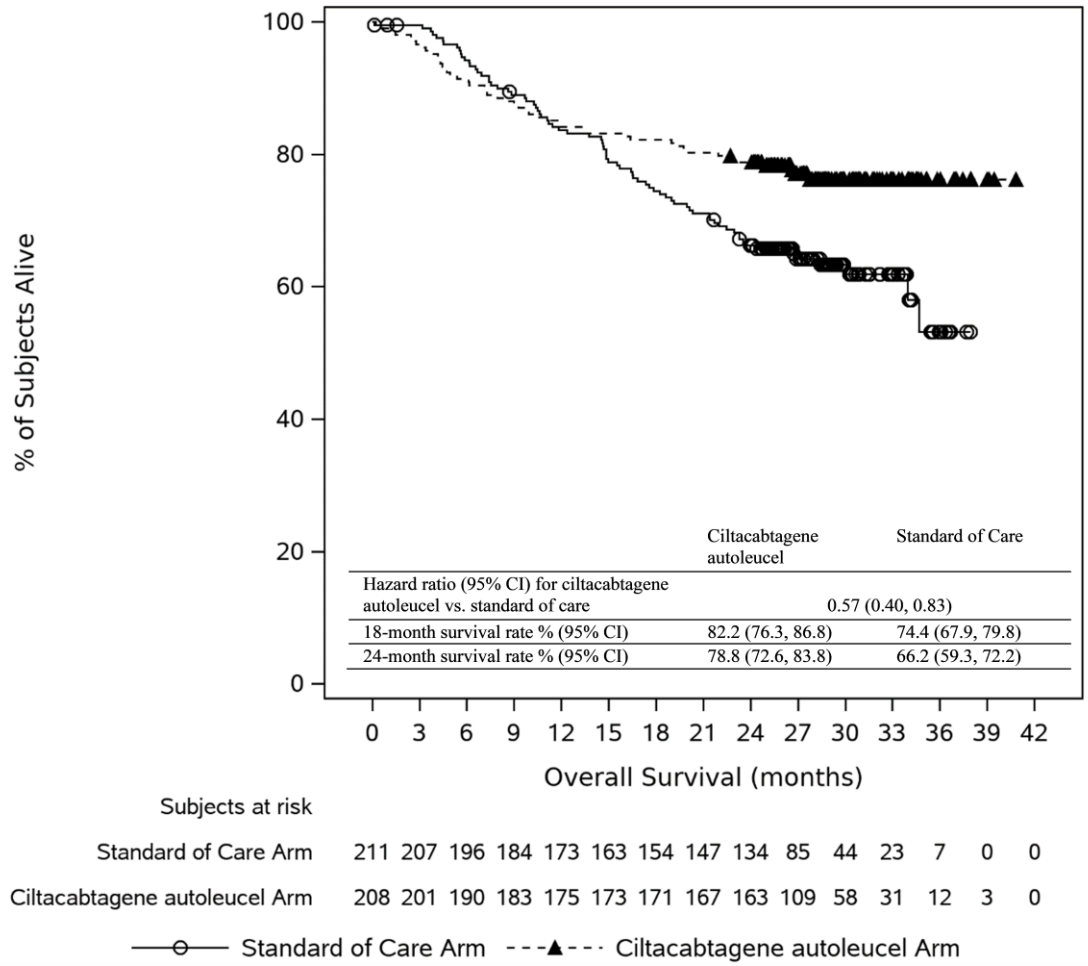
[g] Based on a stratified Cox proportional hazards model. A hazard ratio <1 indicates an advantage for CARVYKTI Arm.

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3002 (Intent-To-Treat Analysis Set)



Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Figure 2: Kaplan-Meier Curve of OS in Study MMY3002 (Intent-To-Treat Analysis Set)



Note: Intent-to-treat analysis set consists of subjects who were randomised in the study. Overall survival based on a median duration of follow-up of 28.7 months.

Of the 176 patients who received CARVYKTI as study treatment, the median progression free survival (PFS) was not estimable (95% CI: not estimable, not estimable) with a 12 months PFS rate of 89.7%. The overall response rate (ORR) in these patients was 99.4% (95% CI: 96.9%, 100.0%). The rate of CR/sCR was 86.4% (95% CI: 80.4%, 91.1%).

Of the 20 patients who experienced early and rapid disease progression and received CARVYKTI as subsequent therapy, after CARVYKTI infusion, the median PFS was 7.39 months (95% CI: 1.61, not estimable) with 12-month PFS rate of 39.4% (95% CI: 18.6, 59.7). ORR of 65% (95% CI: 40.8%, 84.6%), and CR/sCR of 40% (95% CI: 19.1%, 63.9%).

In the 208 patients who were randomised to receive CARVYKTI a delay in median time to worsening of multiple myeloma symptoms was reported compared to the 211 who were randomised to receive standard of care (23.7 months vs 18.9 months, respectively) as measured with the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q).

5.2 PHARMACOKINETIC PROPERTIES

CARVYKTI pharmacokinetics (PK) was assessed in 97 adult patients with relapsed or refractory multiple myeloma in Study MMY2001 receiving a single CARVYKTI infusion at the median dose of 0.71×10^6 CAR positive viable T-cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).

Following a single infusion, CARVYKTI exhibited an initial expansion phase followed by a rapid decline and then a slower decline. However, high interindividual variability was observed.

Table 8: Pharmacokinetic parameters of CARVYKTI in patients with multiple myeloma

Parameter	Summary Statistics	MMY2001 (N=97)	MMY3002 (N=175)
C_{max} (copies/µg genomic DNA)	Mean (SD), n	48692 (27174), 97	38258 (24133), 175
t_{max} (day)	Median (range), n	12.71 (8.73 – 329.77), 97	12.75 (7.80 – 222.83), 175
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	Mean (SD), n	504496 (385380), 97	361038 (270918), 174
$AUC_{0\text{-}last}$ (copies*day/µg genomic DNA)	Mean (SD), n	109803 (1387010), 97	602674 (862607), 175
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	Mean (SD), n	1033373 (135539), 96	723717 (736198), 115
$t_{1/2}$ (day)	Mean SD, n	23.5 (24.2), 42	21.8 (30.4), 49
t_{last} (day)	Median (range), n	125.90 (20.04 – 702.12), 97	83.01 (12.86 – 630.89), 175

After the cell expansion, the persistence phase of the CARVYKTI levels was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28 to 365 days) post-infusion. The PK of CARVYKTI was assessed in 176 adult patients with lenalidomide refractory multiple myeloma in MMY3002 and were generally consistent with those in Study MMY2001.

Detectable CARVYKTI exposures in bone marrow indicate a distribution of CARVYKTI from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high interindividual variability.

Some patients required tocilizumab, corticosteroids and anakinra for management of CRS. CARVYKTI continues to expand and persist following tocilizumab administration. In Study MMY2001, treated with tocilizumab (n=68) had 81% and 72% higher CARVYKTI C_{max} and $AUC_{0\text{-}28d}$, respectively, as compared to patients (n=29) who did not receive tocilizumab. Patients who received corticosteroids (n=28) had 75% and 112% higher C_{max} and $AUC_{0\text{-}28d}$, respectively, compared with patients who did not receive corticosteroids (n=69). In addition, patients who received anakinra (n=20) had 41% and 72% higher C_{max} and $AUC_{0\text{-}28d}$, respectively, compared with patients who did not receive anakinra (n=77). In Study MMY3002, the results related to tocilizumab and corticosteroid were consistent with Study MMY2001.

Special populations

The pharmacokinetics of CARVYKTI (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by age (range: 27 to 78 years), including patients <65 years of age [n=215; 64.8%], 65-75 years (n=105; 31.6%) and >75 years of age (n=12; 3.6%).

Similarly, the pharmacokinetics of CARVYKTI (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by gender, body weight, and race.

Renal impairment

Renal impairment studies of CARVYKTI were not conducted. Based on population PK analysis, estimated CARVYKTI C_{max} and $AUC_{0\text{-}28d}$ in patients with mild renal dysfunction (60 mL/min ≤

creatinine clearance [CRCL] < 90 mL/min), or moderate renal dysfunction (30 mL/min ≤ creatinine clearance < 60 mL/min) were similar to and in patients with normal renal function (CRCL ≥ 90 mL/min).

Hepatic impairment

Hepatic impairment studies of CARVYKTI were not conducted. Based on population PK analysis, estimated CARVYKTI C_{max} and $AUC_{0\text{-}28d}$ were similar in patients with mild hepatic dysfunction [(total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase >ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)] and patients with normal hepatic function.

5.3 PRECLINICAL SAFETY DATA

Nonclinical safety assessment of CARVYKTI confirmed the on-target specificity of CARVYKTI to BCMA.

Genotoxicity

No genotoxicity studies have been performed.

The risk for insertional mutagenesis occurring during the manufacturing of ciltacabtagene autoleucel following transduction of autologous human T-cells with an integrating lentiviral vector (LV) was assessed by evaluating the integration pattern of the vector in pre-infusion CARVYKTI. This genomic insertional site analysis was performed on CARVYKTI products from 7 patients and 3 healthy volunteers. There was no evidence for preferential integration near genes of concern.

The potential for enhanced proliferation of CARVYKTI was assessed in an in vitro cytokine independent growth assay. Integration of LV into primary T cell genome during transduction did not lead to cytokine independent uncontrolled growth in the absence of IL-2 (the cytokine that regulates T-cell growth and promotes T-cell survival) of CARVYKTI.

Carcinogenicity

No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cryostor CS5, which contains dimethyl sulfoxide.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

See expiry date on the outer pack.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store and transport below -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen.

Store in the original packaging containing the cassette protecting the infusion bag.

Once thawed, the product should be administered immediately and the infusion should be completed within 2.5 hours at room/ambient temperature (20°C to 25°C). Thawed product should not be shaken, refrozen or refrigerated.

6.5 NATURE AND CONTENTS OF CONTAINER

Ethylene vinyl acetate (EVA) 30 mL or 70 mL infusion bag with sealed addition tube and two available spike ports.

Each infusion bag is individually packed in an aluminium cryo cassette.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Do not irradiate as this could lead to inactivation of the product.

CARVYKTI should be transported within the facility in closed, break-proof, leak-proof containers.

Unused CARVYKTI must be disposed of in compliance with local guidelines for the disposal of medicinal products containing genetically modified cells. All material that has been in contact with CARVYKTI (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

CARVYKTI (ciltacabtagene autoleucel) is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. Consequently, a defined structure is not available for ciltacabtagene autoleucel.

CAS number

No data available.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Class 4 Biological

8. SPONSOR

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Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

6 June 2023

10. DATE OF REVISION

2 October 2025

Summary table of changes

Section changed	Summary of new information
4.4	Added information on Immune Effector Cell-associated Enterocolitis
4.8	Added information on Immune Effector Cell-associated Enterocolitis. Also added information in Post marketing subsection on T cell malignancies including T-cell

	lymphoma of the gastrointestinal tract and hypersensitivity including infusion related reactions.