PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCARVYKTI®

ciltacabtagene autoleucel

Cell suspension in infusion bag, 0.5-1.0x10^6 CAR-positive viable T-cells per kg body weight with a maximum of 1x10^8 CAR-positive viable T-cells, for intravenous infusion

Professed standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01XL05)

CARVYKTI® indicated for:

- the treatment of adult patients with multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and who are refractory to their last treatment

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Carvykti please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

CARVYKTI® indicated for:

- the treatment of adult patients with multiple myeloma, who have received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide

has been issued market authorization without conditions.

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 multiple myeloma, who have received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide.
- the treatment of adult patients with multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and who are refractory to their last treatment.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Of the 97 patients in Study MMY2001 that received Carvykti, 28% were 65 to 75 years of age, and 8% were older than 75 years of age. In Study MMY3002, of the 208 patients in the Carvykti arm, 38% were 65 to 75 years of age and 2% were older than 75 years of age. Evidence from Study MMY3002 suggests differences in clinical safety between subjects <65 years of age compared to ≥65 years of age (see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Carvykti is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving Carvykti. Do not administer Carvykti to patients with clinically significant active infection. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids (see 7 WARNINGS AND PRECAUTIONS).

Neurologic toxicities (Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Parkinsonism, Guillain-Barré Syndrome and other neurologic toxicities), including fatal or life-threatening reactions, occurred in patients receiving Carvykti, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic toxicities after treatment with Carvykti. Provide supportive care and/or corticosteroids as needed (see 7 WARNINGS AND PRECAUTIONS).

Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS), including

fatal or life-threatening reactions, occurred in patients receiving Carvykti in association with CRS and/or neurological toxicities (see 7 WARNINGS AND PRECAUTIONS).

Carvykti should be administered by experienced health professionals at qualified treatment centres (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- For autologous use only; do not infuse Carvykti if the information on the patient-specific label does not match the intended patient.
- For intravenous use only; do NOT use a leukodepleting filter.
- Carvykti infusion should be delayed if a patient has any of the following conditions: clinically significant active infection, Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhea, or constipation. Carvykti infusion should be delayed until resolution of these events to Grade ≤1.

4.2 Recommended Dose and Dosage Adjustment

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.

Pediatric (<18 years): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose adjustment is required in patients over 65 years of age (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

- Administer Carvykti at a qualified healthcare facility.
- Prior to infusion and during the recovery period, ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available for use.
- 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.
- Do NOT use a leukodepleting filter.

For special precautions for handling and disposal, see 12 SPECIAL HANDLING INSTRUCTIONS.

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 the corresponding Product Monographs.

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.
- clinically significant active inflammatory disorder.
- Grade ≥ 3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhea, 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 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.

<u>Preparation of Carvykti for infusion</u>

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.

1. 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.
2. Once patient identification is confirmed, remove the Carvykti product bag from the cassette.
3. 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 Janssen).
4. Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.
5. 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.
6. 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.
7. Once thawed, the Carvykti infusion must be administered and completed within 2.5 hours at room/ambient temperature (20°C to 25°C).
8. Do not re-freeze or refrigerate thawed product.
9. 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.

Monitoring after infusion

Monitor patients daily for 14 days after the Carvykti infusion at a qualified healthcare facility and then periodically for an additional two weeks for signs and symptoms of cytokine release syndrome (CRS), neurologic events and other toxicities (see 7 WARNINGS AND PRECAUTIONS).

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

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

There are no data regarding the signs or sequelae of overdose with Carvykti.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Cell suspension for intravenous infusion. A single dose of Carvykti is 0.5-1.0$\times 10^6$ CAR-positive viable T-cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T-cells in a patient-specific infusion bag containing 30 mL or 70 mL of frozen suspension.	Cryostor® CS5 which contains 5% dimethyl sulfoxide (DMSO).

Container: Ethylene vinyl acetate (EVA) infusion bag with sealed addition tube and two available spike ports, containing either 30 mL (50 mL bag) or 70 mL (250 mL bag) of cell suspension.

Each infusion bag is individually packed in an aluminium cassette.

7 WARNINGS AND PRECAUTIONS

General

Carvykti should be administered at a qualified healthcare facility by healthcare professionals trained in handling and administering Carvykti, and in the management of patients treated with Carvykti, including the monitoring and managing of cytokine release syndrome (CRS) and neurotoxicity. The centre should have immediate access to appropriate emergency equipment and intensive care unit, and have on-site, immediate access to tocilizumab. Qualified healthcare facilities should ensure that healthcare professionals who prescribe, dispense and administer Carvykti are trained on the management of CRS and neurologic toxicities.

Carvykti is intended solely for autologous use and should under no circumstances be administered to other patients. Prior to infusion, the patient's identity should be confirmed with the patient identifiers on the Carvykti infusion bag. Do not infuse Carvykti if the information on the patient-specific label does not match the intended patient.

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.

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

When considering patients for Carvykti treatment, physicians should assess the impact of rapidly progressing disease on the ability of patients to receive CAR-T infusion. Some patients may not benefit from CARVYKTI treatment due to potential increased risk of early death if disease progresses rapidly during bridging therapy.

Carcinogenesis and Mutagenesis

Secondary Malignancies

Patients treated with Carvykti may develop secondary hematological malignancies.

Myelodysplastic syndrome and acute myeloid leukemia, including cases with fatal outcomes, have occurred in patients after Carvykti infusion. Myeloid neoplasms occurred in 8.2% (8/97) of patients in Study MMY2001 and in 1.0% (2/196) of patients in Study MMY3002.

T-cell malignancies have occurred following treatment with genetically modified autologous T-cell immunotherapies and may present as soon as weeks following infusion. T-cell lymphoma, including CAR-positive tumors, have occurred in patients after Carvykti infusion.

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 to obtain instructions for the testing of all types of secondary malignancy, including those of non-T-cell origin.

Driving and Operating Machinery

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.

Hematologic

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 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 8 ADVERSE REACTIONS).

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.

In the event of febrile neutropenia, infections (see 7 WARNINGS AND PRECAUTIONS, Infections) should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Immune

Cytokine Release Syndrome

Cytokine release syndrome (CRS), 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 8 ADVERSE REACTIONS). 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 8 ADVERSE REACTIONS). 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 4 DOSAGE AND 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 prior to infusion of Carvykti. Monitor patients for signs and symptoms of CRS daily for 14 days after the Carvykti infusion at a qualified 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 hospitalization and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 2 (see 4 DOSAGE AND 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.

Management of Cytokine release syndrome

If CRS is suspected, manage according to the recommendations in Table 2. Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen) 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 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 Table 2 and Table 3,
- Tocilizumab according to the CRS grade in Table 2,
- Anti-seizure medication according to the neurologic toxicity in Table 3.

Table 2: 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	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 liter 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	

cannula[e] or blow-by, or, Grade 2 organ toxicity.	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.	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 liter or increasing supplemental oxygen.	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. 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	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 liter or increasing supplemental oxygen.	Administer dexamethasone 20 mg IV every 6 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. 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).	

(excluding transaminitis).	

[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.

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

In Study MMY2001, fatal HLH/MAS occurred in one patient following treatment with Carvykti. The HLH event was preceded by prolonged CRS lasting 97 days. The manifestations of HLH/MAS include hypotension, hypoxia with diffuse alveolar damage, coagulopathy, cytopenia and multi-organ dysfunction, including renal dysfunction.

In Study MMY3002, one patient with Grade 4 HLH/MAS (who progressed on bridging therapy and received Carvykti as subsequent therapy) developed fatal intracerebral and gastrointestinal hemorrhage in the setting of coagulopathy and thrombocytopenia 12 days after treatment.
HLH is a life-threatening condition with a high mortality rate if not recognized and treated early.

Infections

Serious infections, including life-threatening or fatal infections, occurred in patients after Carvykti infusion (see 8 ADVERSE REACTIONS).

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.

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 or antiviral prophylaxis and monitoring for infection.

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.

Monitoring and Laboratory Tests

Monitor patients for signs and symptoms of CRS daily for 14 days after the Carvykti infusion at a qualified healthcare facility and then periodically for an additional two weeks.

Instruct patients to remain within proximity of a qualified healthcare facility for at least 4 weeks following infusion (see 4 DOSAGE AND ADMINISTRATION).

Neurologic

Neurologic toxicities occur frequently following treatment with Carvykti and can be severe, life-threatening or fatal (see 8 ADVERSE REACTIONS). 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 8 ADVERSE REACTIONS). Monitor patients for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, immediately evaluate patient for hospitalization and institute treatment with supportive care as indicated in Table 3. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.

Management of Immune Effector Cell-associated Neurotoxicity Syndrome

General management for neurologic toxicity e.g., Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is summarized in Table 3.

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.

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 Table 2 and Table 3,
- Tocilizumab according to CRS grade in Table 2,
- Anti-seizure medication according to neurologic toxicity in Table 3.

Table 3: 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] or depressed level of consciousness: awakens to voice.	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. 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	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

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	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.

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 tumor 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.

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

Guillain-Barré Syndrome

A fatal outcome following Guillain-Barré Syndrome (GBS) has been reported after treatment with Carvykti in another ongoing study. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis (see 8 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.

Reproductive Health: Female and Male Potential

- **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.

Sensitivity/Resistance

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.

7.1 Special Populations

7.1.1 Pregnant Women

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 fetus and cause fetal 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 fetus. 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 testing

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

Contraception

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 product monograph for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (<18 years of age)**:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the 97 patients in Study MMY2001 that received Carvykti, 27 (28%) were 65 to 75 years of age, and 8 (8%) were older than 75 years of age. In Study MMY3002, of the 208 patients in the Carvykti arm, 78 (38%) were 65 to 75 years of age and 4 (2%) were older than 75 years of age. Of the 118 patients that received Carvykti in Study MMY3002 and were less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 16.9% (20/118) and 3.4% (4/118), respectively. Of the 78 patients that received Carvykti and were ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 33.3% (26/78) and 6.4% (5/78), respectively. There were too few patients older than 75 years of age to assess any important clinical differences in these elderly patients compared to younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of Carvykti was evaluated in adult patients with relapsed or refractory multiple myeloma infused with Carvykti in two open label clinical trials, including: single-arm Phase 1b/2 Study MMY2001

(N=97, with a median duration of follow-up of 27.7 months) and Phase 3 Study MMY3002 (N=196, with a median duration of follow-up of 15.9 months).

The most common nonlaboratory Carvykti adverse reactions (≥20%) in Study MMY2001 were pyrexia, CRS, 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 infection, coagulopathy, constipation and vomiting. The most common (≥10%) Grade 3 or higher nonlaboratory adverse reactions in Study MMY2001 were infections – pathogen unspecified, pneumonia and hypotension.

Serious adverse reactions in Study MMY2001 were reported for 54% of patients. The most common serious adverse reactions reported in ≥5% of patients were CRS (21%), infections - pathogen unspecified (16%), encephalopathy (10%), pneumonia (8%), sepsis (7%) and viral infection (6%).

The most common nonlaboratory adverse reactions (≥20%) in Study MMY3002 were pyrexia, CRS, hypogammaglobulinemia, musculoskeletal pain, diarrhea, fatigue, upper respiratory tract infection, headache, hypotension, viral infection and nausea. There were no Grade 3 or higher adverse reactions ≥ 10%.

Serious adverse reactions were reported for 36% patients in Study MMY3002. The most common serious adverse reactions reported in ≥5% of patients were pneumonia (10 %), CRS (7%), viral infections (6%) and cranial nerve palsies (5%).

Cytokine release syndrome

In Study MMY2001 (N=97), CRS was reported in 95% of patients (n=92); 90% (n=87) CRS events were Grade 1 or Grade 2, 4% (n=4) Grade 3 or 4, and 1% (n=1) was Grade 5. Ninety-nine percent of patients (n=91) recovered from CRS.

The duration of CRS was ≤14 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 (95%), hypotension (41%), Aspartate aminotransferase (AST) increased (21%), chills (14%), Alanine aminotransferase (ALT) increased (13%) and sinus tachycardia (10%). See 7 WARNINGS AND PRECAUTIONS for monitoring and management guidance.

In Study MMY3002 (N=196), CRS was reported in 77% of patients (n=151), 73% (n=144) events were Grade 1 or 2 and 4% (n=7) were Grade 3 or 4. Ninety-eight percent of patients (n=148) recovered from CRS. The median duration of CRS was 3 days (range:1 to 17 days). The most frequent (≥10%) signs or symptoms associated with CRS included pyrexia (77%), hypotension (21%), hypoxia (11%).

Neurologic toxicities

In Study MMY2001 (N=97), neurologic toxicity occurred in 22% (n=21) of patients with 9% (n=9) being Grade 3 or Grade 4 and 2% Grade 5 (n=2; one due to ICANS, one due to movement and neurocognitive toxicity with signs and symptoms of parkinsonism). In addition, three patients had fatal outcomes with ongoing neurologic toxicity at the time of death; two deaths were due to infection in patients with ongoing signs and symptoms of parkinsonism (see *Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism*), and one death was due to respiratory failure.

In Study MMY3002 (N=196), neurologic toxicity occurred in 24% (n=46) of patients of which 4% (n=7) of patients experienced Grade 3 or 4 events.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

In Study MMY2001, ICANS occurred in 18% of patients (n=17), with 2% (n=2) experiencing Grade 3 or Grade 4 ICANS and 1% (n=1) Grade 5 ICANS. The median time from Carvykti infusion to first onset of ICANS was 8.0 days (range: 3 to 12 days, except for 1 patient with onset at 26 days) and the median duration was 4 days (range: 1 to 12 days, except for 1 patient who had a subsequent fatal outcome at 40 days).

In Study MMY3002 (N=196), ICANS occurred in 8% (n=15) of patients receiving Carvykti with 1% (n=2) experiencing Grade 3 ICANS. The median time from Carvykti infusion to first onset of ICANS was 9 days (range: 2 to 15 days). ICANS resolved in 14 patients (93%), and the median duration was 2 days (range: 1 to 6 days).

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Of the 21 patients in Study MMY2001 (N=97) experiencing any neurotoxicity, 6 (6%) male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. The maximum toxicity grades of parkinsonism were: Grade 2 (n=1) and Grade 3 (n=5). The median onset of parkinsonism was 64 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 2 patients (Grade 3), symptoms of parkinsonism were ongoing up to 996 days after administration of Carvykti. All 6 patients had a history of prior CRS (n=5 Grade 2; n=1 Grade 3), while 4 of 6 patients had prior ICANS (n=4 Grade 1).

Of the 46 patients in the MMY3002 study (N=196) experiencing any neurotoxicity, two patients had neurologic toxicity with signs and symptoms of parkinsonism. The maximum toxicity grade was 2. The onset of parkinsonism was 16 and 85 days from infusion of Carvykti and the symptoms of parkinsonism were ongoing up to 294 days after administration of Carvykti. Both patients had a history of prior CRS (n=1 Grade 1 and n=1 Grade 2).

Peripheral Neuropathy

In Study MMY2001 (N=97), 7% of patients (n=7) developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 66 days (range: 4 to 914 days), median duration of peripheral neuropathies was 138 days (range: 2 to 692 days) including those with ongoing neuropathy. Of these 7 patients, 2 experienced Grade 3 peripheral neuropathy (1 of which resolved with no treatment reported, and the other improved after treatment with dexamethasone); of the remaining 5 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no treatment reported in 2 patients, and was ongoing in the other 3 patients.

In Study MMY3002 (N=196), 7% of patients (n=14) developed peripheral neuropathy. Median time of onset of symptoms was 51 days (range: 1 to 189 days), median duration of peripheral neuropathies was 168 days (range: 1 to 503 days) including those with ongoing neuropathy. Of these 14 patients, 1 patient experienced Grade 3 peripheral neuropathy, which was ongoing, and 9 patients had resolution of neuropathy.

Cranial Nerve Palsies

In Study MMY2001 (N=97), 3% of patients (n=3) experienced cranial nerve palsies. Median time to onset was 26 days (range: 21 to 101 days) following infusion of Carvykti, and median time to resolution was 70 days (range: 1 to 79 days) following onset of symptoms.

In Study MMY3002 (N=196), 9% of patients (n=17) experienced cranial nerve palsies. Median time to onset was 21 days (range: 17 to 60 days) following infusion of Carvykti. Of the 17 patients, 14 recovered and the median time to resolution was 61 days (range: 15 to 209 days) following onset of symptoms.

Prolonged and recurrent cytopenias

In Study MMY2001 (N=97), Grade 3 or higher cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following Carvykti infusion, included thrombocytopenia (41%), neutropenia (30%), and lymphopenia (12%). After day 60 following Carvykti, 31%, 12%, and 6% of patients had an occurrence of Grade 3 or higher lymphopenia, neutropenia 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 occuring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60 respectively.

Table 4: Incidences of Prolonged and Recurrent Cytopenias Following Treatment with Carvykti in Study MMY2001 (N=97)

	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	60 (62%)	40 (41%)	25 (26%)	6 (6%)
Neutropenia	95 (98%)	29 (30%)	10 (10%)	12 (12%)
Lymphopenia	96 (99%)	12 (12%)	8 (8%)	30 (31%)

[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 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.
Percentages are based on the number of treated patients.

In Study MMY3002 (N=196), Grade 3 or 4 cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following Carvykti infusion, included lymphopenia 59 (30%), thrombocytopenia 58 (30%), neutropenia 51 (26%) and anemia 6 (3%). After Day 60 following Carvykti, occurrence of Grade 3 or 4 neutropenia, lymphopenia, anemia and thrombocytopenia was seen in 46 (24%), 32 (16%), 9 (5%) and 8 (4%) patients, respectively, after initial recovery of their Grade 3 or 4 cytopenia.

Infections

Infections occurred in 56 patients (58%) in Study MMY2001 (N=97); 20 (21%) experienced Grade 3 or Grade 4 infections, and fatal infections occurred in 3 patients (3%); lung abscess, sepsis, and septic shock. The most frequently reported (≥5%) Grade 3 or higher infections were pneumonia and sepsis. Febrile neutropenia was observed in 10% of patients with 4% experiencing serious febrile neutropenia. See 7 WARNINGS AND PRECAUTIONS for monitoring and management guidance.

In Study MMY3002 (N=196), infections occurred in 111 (57%) patients who received Carvykti. Grade 3 or 4 infections occurred in 35 (18%) patients and 12 (6%) patients had fatal infections (including pneumonia, COVID-19 pneumonia and sepsis). The most frequently reported (≥2%) Grade 3 or higher infections were pneumonia and COVID-19 pneumonia.

Hypogammaglobulinemia

In Study MMY2001 (N=97) hypogammaglobulinemia was reported in 12% of patients with 2% of patients experiencing Grade 3 or Grade 4 hypogammaglobulinemia; laboratory IgG levels fell below 500 mg/dL after infusion in 92% (89/97) of patients treated with Carvykti. Hypogammaglobulinemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL, after Carvykti infusion occurred in 93% (90/97) of patients. Thirty-eight percent of patients received IVIG post Carvykti for either an adverse reaction or prophylaxis. See 7 WARNINGS AND PRECAUTIONS for monitoring and management guidance.

In Study MMY3002, hypogammaglobulinemia was reported in 95 (49%) patients with 16 (8%) patients experiencing Grade 3 hypogammaglobulinemia and laboratory IgG levels fell below 500 mg/dL after infusion in 182 (93%) of patients treated with Carvykti. Sixty nine percent of patients (n=136) received intravenous immunoglobulin (IVIG) post Carvykti for either an adverse reaction or prophylaxis.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Patients with Multiple Myeloma Who Have Received 1 to 3 Prior Lines of Therapy

Study MMY3002

Adverse reaction table below is presented from Study MMY3002 (see 14 CLINICAL TRIALS).

Table 5: Adverse Reactions (≥10%) in Patients with Multiple Myeloma in Study MMY3002

	Adverse Reaction	Carvykti (N=196)		PVd/DPd (N=208)	
		All Grades n (%)	Grade≥3 n (%)	All Grades n (%)	Grade≥3 n (%)
Gastrointestinal disorders	Diarrhea[1]	56 (29)	6 (3)	56 (27)	5 (2)
	Nausea	39 (20)	0	38 (18)	2 (1)
	Constipation	21 (11)	0	44 (21)	2 (1)
General disorders and administration site conditions	Pyrexia	153 (78)	12 (6)	33 (16)	2 (1)
	Fatigue[2]	57 (29)	5 (3)	104 (50)	7 (3)
	Edema[3]	22 (11)	1 (1)	42 (20)	2 (1)
Immune system disorders	Cytokine release syndrome	151 (77)	7 (4)	1 (<1)	0
	Hypogammaglobulinemia	92 (47)	16 (8)	13 (6)	1 (<1)
Infections and infestations	Upper respiratory tract infection[4]	48 (24)	2 (1)	83 (40)	10 (5)
	Viral infection[5]	46 (23)	8 (4)	64 (31)	12 (6)
	Bacterial infection[6]	31 (16)	13 (7)	36 (17)	9 (4)
	Pneumonia[7]	29 (15)	18 (9)	38 (18)	23 (11)
Metabolism and nutrition disorders	Decreased appetite	20 (10)	1 (1)	11 (5)	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[8]	67 (34)	4 (2)	98 (47)	9 (4)
Nervous system disorders	Headache[9]	47 (24)	0	28 (13)	0
Respiratory and thoracic and mediastinal disorders	Cough[10]	30 (15)	0	38 (18)	0
	Hypoxia	23 (12)	6 (3)	2 (1)	2 (1)
Vascular disorders	Hypotension[11]	48 (24)	8 (4)	6 (3)	0

Adverse events are reported using MedDRA version 25.0

1 Diarrhea includes Colitis, and Diarrhea.

2 Fatigue includes Asthenia, Fatigue, and Malaise.

3 Edema includes Face edema, Fluid retention, Generalised edema, Hypervolemia, Localised edema, Edema, Edema peripheral, Oral leukoedema, Peripheral swelling, Pharyngeal edema, Skin edema, Swelling, and Swelling face.

4 Upper respiratory tract infection includes Bronchitis, Laryngitis, Nasal congestion, Nasopharyngitis, Pharyngitis, Pharyngotonsillitis, Respiratory tract infection, Rhinitis, Rhinorrhea, Rhinovirus infection, Sinusitis, Tonsillitis, Upper respiratory tract infection, and Viral pharyngitis.

5 Viral infection includes Adenovirus infection, Asymptomatic COVID-19, Bronchitis viral, COVID-19, Cytomegalovirus colitis, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viremia, Hepatitis B reactivation, Herpes ophthalmic, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Influenza, JC virus infection, Lymphadenitis viral, Metapneumovirus infection, Norovirus infection, Oral herpes, Parainfluenzae virus infection,

Parvovirus B19 infection, Parvovirus infection, Progressive multifocal leukoencephalopathy, Respiratory syncytial virus infection, Respiratory tract infection viral, and Rotavirus infection.

[6] Bacterial infection includes Anal abscess, Bacterial pericarditis, Bordetella infection, Bronchitis bacterial, Campylobacter infection, Catheter site infection, Cellulitis, Chalazion, Citrobacter infection, Clostridium difficile colitis, Device related infection, Endophthalmitis, Erysipelas, Escherichia infection, Eye infection, Gingivitis, Haemophilus infection, Hordeolum, Impetigo, Infected dermal cyst, Infection, Ludwig angina, Mastitis, Nail infection, Oral infection, Perichondritis, Post procedural infection, Prostatitis, Pustule, Pyelonephritis acute, Respiratory tract infection bacterial, Salmonellosis, Skin infection, Staphylococcal infection, Superinfection bacterial, Tooth abscess, Tooth infection, Vascular access site infection, and Vascular device infection.

[7] Pneumonia includes Bronchopulmonary aspergillosis, COVID-19 pneumonia, Lower respiratory tract infection, Lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia haemophilus, Pneumonia legionella, Pneumonia moraxella, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal, and Pneumonia streptococcal.

[8] Musculoskeletal pain includes Arthralgia, Back pain, Bone contusion, Bone pain, Bursitis, Limb discomfort, Muscle strain, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myositis, Neck pain, Non-cardiac chest pain, Osteoarthritis, Pain in extremity, Plantar fasciitis, Rotator cuff syndrome, Spinal pain, Temporomandibular joint syndrome, and Tendonitis.

[9] Headache includes Headache, and Tension headache.

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

[11] Hypotension includes Hypotension, and Orthostatic hypotension.

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 14 CLINICAL TRIALS). In these patients, movement and neurocognitive toxicity 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 4 (25%), including events of CRS complicated by HLH (10%) or disseminated intravascular coagulation (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 hemorrhage in the context of HLH or DIC and 3 due to fatal infections).

Patients with Multiple Myeloma Who Have Received at least 3 Prior Lines of Therapy

Study MMY2001

Adverse reaction table below is presented for 97 patients from Study MMY2001 with a median duration of follow-up of 18.0 months (see 14 CLINICAL TRIALS). The safety profile of Carvykti observed in Study MMY2001 after a median follow-up of 27.7 months was generally consistent with the safety profile observed after a median follow-up of 18.0 months.

Table 6: Adverse Reactions (≥10%) in Patients with Multiple Myeloma in Study MMY2001 (N=97)

	Adverse Reaction	Incidence n (%)	
		All Grades	Grade≥3
Blood and lymphatic system disorders	Coagulopathy[1]	21 (22)	2 (2)
	Febrile neutropenia	10 (10)	9 (9)
Cardiac disorders	Tachycardia[2]	26 (27)	1 (1)
Gastrointestinal disorders	Diarrhea[3]	32 (33)	1 (1)

	Nausea	30 (31)	1 (1)
	Constipation	21 (22)	0
	Vomiting	19 (20)	0
General disorders and administration site conditions	Pyrexia	93 (96)	5 (5)
	Fatigue[4]	46 (47)	7 (7)
	Chills	32 (33)	0
	Edema[5]	22 (23)	0
Immune system disorders	Cytokine release syndrome[6#]	92 (95)	5 (5)
	Hypogammaglobulinemia[7]	90 (93)	2 (2)
Infections and infestations[8]	Infections - pathogen unspecified[9#]	40 (41)	17 (18)
	Upper respiratory tract infection[10]	27 (28)	3 (3)
	Viral infection[11]	22 (23)	7 (7)
	Pneumonia[12#]	13 (13)	12 (12)
	Bacterial infection[13]	10 (10)	3 (3)
	Sepsis[14#]	10 (10)	7 (7)
Metabolism and nutrition disorders	Decreased appetite	28 (29)	1 (1)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[15]	47 (48)	2 (2)
Nervous system disorders	Encephalopathy[16]	29 (30)	6 (6)
	Headache	26 (27)	0
	Dizziness[17]	22 (23)	1 (1)
	Motor dysfunction[18]	16 (16)	3 (3)
Psychiatric disorders	Insomnia	13 (13)	0
Respiratory, thoracic and mediastinal disorders	Cough[19]	38 (39)	0
	Dyspnea[20#]	22 (23)	3 (3)
	Nasal congestion	15 (15)	0
	Hypoxia	12 (12)	4 (4)
Vascular disorders	Hypotension[21]	49 (51)	10 (10)
	Hypertension	18 (19)	6 (6)

	Hemorrhage[22]	16 (16)	4 (4)

Adverse reactions are reported using MedDRA version 23.0

Contains fatal event/s

1 Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalised ratio increased, and Prothrombin time prolonged. Coagulopathy also includes terms reported under investigation SOC.

2 Tachycardia includes Sinus tachycardia, and Tachycardia.

3 Diarrhea includes Colitis, and Diarrhea.

4 Fatigue includes Asthenia, Fatigue, and Malaise.

5 Edema includes Face edema, Generalised edema, Localised edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.

6 Cytokine release syndrome includes Cytokine release syndrome, and Systemic inflammatory response syndrome.

7 Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia (12%) and/or laboratory IgG levels that fell below 500 mg/dL after infusion (92%).

8 Infections and infestations System Organ Class Adverse Events are grouped by pathogen type and selected clinical syndromes.

9 Infections - pathogen unspecified includes Abscess limb, Atypical pneumonia, Bacteremia, Bronchitis, Conjunctivitis, Enterocolitis infectious, Folliculitis, Gastroenteritis, Lung abscess, Lung opacity, Osteomyelitis, Otitis media, Parotitis, Perirectal abscess, Pneumonia, Rash pustular, Rhinitis, Sepsis, Septic shock, Sinusitis, Skin infection, Soft tissue infection, Tooth infection, Upper respiratory tract infection, and Urinary tract infection.

10 Upper respiratory tract infection includes Human rhinovirus test positive, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection. Also includes terms reported under investigation SOC. Upper respiratory tract infections may also be included under pathogen categories.

11 Viral infection includes Adenovirus test positive, Coronavirus infection, Cytomegalovirus syndrome, Cytomegalovirus viremia, Enterovirus infection, Gastroenteritis viral, Herpes zoster, Herpes zoster disseminated, Influenza, Influenza like illness, Oral herpes, Parainfluenza virus infection, Rhinovirus infection, Urinary tract infection viral, and Viral upper respiratory tract infection.

12 Pneumonia includes Atypical pneumonia, Lung abscess, Lung opacity, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.

13 Bacterial infection includes Abscess limb, Cholecystitis, Cholecystitis acute, Clostridium difficile colitis, Clostridium difficile infection, Enterocolitis bacterial, Osteomyelitis, Perirectal abscess, Soft tissue infection, Staphylococcal infection, and Tooth infection.

14 Sepsis includes Bacteremia, Bacterial sepsis, Pseudomonal bacteremia, Sepsis, Septic shock, and Staphylococcal bacteremia.

15 Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Joint stiffness, Muscle strain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, and Pain in extremity.

16 Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, and Somnolence.

17 Dizziness includes Dizziness, Presyncope, and Syncope.

18 Motor dysfunction includes Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, and Myoclonus.

19 Cough includes Cough, Productive cough, and Upper-airway cough syndrome.

20 Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Tachypnea.

21 Hypotension includes Hypotension, and Orthostatic hypotension.

22 Hemorrhage includes Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eye contusion, Hematochezia, Hemoptysis, Infusion site hematoma, Oral contusion, Petechiae, Post procedural hemorrhage, Pulmonary hemorrhage, Retinal hemorrhage, and Subdural hematoma.

8.3 Less Common Clinical Trial Adverse Reactions

Patients with Multiple Myeloma Who Have Received 1 to 3 Prior Lines of Therapy

Study MMY3002

Adverse reactions occurring in <10% of all Carvykti-treated patients in Study MMY3002 (N=196) are summarized below:

Blood and lymphatic system disorders: coagulopathy[1], lymphocytosis, febrile neutropenia
Cardiac disorders: tachycardia[2], cardiac arrhythmias[3]
Gastrointestinal disorders: abdominal pain[4], vomiting
General disorders and administration site conditions: pain[5], chills
Immune system disorders: hemophagocytic lymphohistiocytosis
Infections and infestations: sepsis[6#], gastroenteritis[7], urinary tract infection[8], fungal infection[9]
Investigations: C-reactive protein increased
Metabolism and nutrition disorders: hypophosphatemia, hyperferritinemia
Nervous system disorders: dizziness[10], cranial nerve palsies[11], motor dysfunction[12], encephalopathy[13], immune effector cell-associated neurotoxicity syndrome, neuropathy peripheral[14], sleep disorder[15], tremor, aphasia[16], ataxia[17]
Psychiatric disorders: delirium[18], personality changes[19]
Renal and urinary disorders: renal failure[20]
Respiratory, thoracic and mediastinal disorders: dyspnea[21]
Skin and subcutaneous tissue disorders: rash[22]
Vascular disorders: hemorrhage[23#], hypertension, thrombosis[24], capillary leak syndrome

Adverse events are reported using MedDRA version 25.0

Contains fatal event/s.

1 Coagulopathy includes Blood fibrinogen decreased, Coagulation test abnormal, Coagulopathy, Disseminated intravascular coagulation, and Hypofibrinogenemia.

2 Tachycardia includes Sinus tachycardia, and Tachycardia.

3 Cardiac arrhythmias includes Atrial fibrillation, Atrioventricular block complete, Atrioventricular block second degree, and Ventricular tachycardia.

4 Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Dyspepsia.

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

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

7 Gastroenteritis includes Enterocolitis viral, Enterovirus infection, Gastroenteritis, Gastroenteritis rotavirus, Gastroenteritis salmonella, Gastrointestinal infection, and Large intestine infection.

8 Urinary tract infection includes Cystitis, Escherichia urinary tract infection, and Urinary tract infection.

9 Fungal infection includes Candida infection, Oral candidiasis, Tongue fungal infection, and Vulvovaginal candidiasis.

10 Dizziness includes Dizziness, Dizziness postural, Presyncope, Syncope, and Vertigo.

11 Cranial nerve palsies includes Facial paralysis, Facial paresis, IIIrd nerve paralysis, and Trigeminal palsy.

12 Motor dysfunction includes Bradykinesia, Coordination abnormal, Dysgraphia, Extrapyramidal disorder, Eyelid ptosis, Micrographia, Muscle spasms, Muscular weakness, and Parkinsonism.

13 Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, and Psychomotor retardation.

14 Neuropathy peripheral includes Peripheral motor neuropathy, Peripheral sensory neuropathy, and Polyneuropathy.

15 Sleep disorder includes Insomnia, Sleep disorder, and Somnolence.

16 Aphasia includes Aphasia, and Dysarthria.

17 Ataxia includes Ataxia, Balance disorder, Dysmetria, and Gait disturbance.

18 Delirium includes Agitation, Disorientation, and Hallucination.

19 Personality changes includes Apathy, Flat affect, Personality change, and Reduced facial expression.

20 Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, Renal failure, and Renal impairment.

21 Dyspnea includes Dyspnoea, Dyspnoea exertional, Respiratory failure, Tachypnoea, and Wheezing.

22 Rash includes Dermatitis psoriasiform, Drug eruption, Erythema, Pityriasis lichenoides et varioliformis acuta, Rash, Rash erythematous, Rash maculo-papular, Rash papular, and Urticaria.

[23] Hemorrhage includes Catheter site hemorrhage, Cerebral hemorrhage, Conjunctival hemorrhage, Contusion, Epistaxis, Gastrointestinal hemorrhage, Hematemesis, Hematoma, Hematuria, Lower gastrointestinal hemorrhage, Retroperitoneal hemorrhage, and Subarachnoid hemorrhage.

[24] Thrombosis includes Deep vein thrombosis, Pulmonary embolism, and Venous thrombosis limb.

Patients with Multiple Myeloma Who Have Received at least 3 Prior Lines of Therapy

Study MMY2001

Clinically important adverse reactions occurring in less than 10% of all Carvykti treated patients in Study MMY2001 (N=97) are summarized below:

Cardiac disorders: cardiac arrhythmias[1], chest pain[2]
Eye disorders: diplopia
Gastrointestinal disorders: dysphagia
Immune system disorders: hemophagocytic lymphohistiocytosis, hypersensitivity reaction
Infections and infestations: urinary tract infection[3]
Injury, poisoning and procedural complications: fall
Metabolism and nutrition disorders: tumour lysis syndrome
Musculoskeletal and connective tissue disorders: posture abnormal
Nervous system disorders: aphasia[4], ataxia[5], tremor, peripheral neuropathy[6], paresis[7], parkinsonism, micrographia, dysgraphia, reduced facial expression, bradykinesia, cogwheel rigidity, cerebrovascular accident, seizure, slow speech, nystagmus
Psychiatric disorders: delirium[8], depression[9], psychomotor retardation
Renal and urinary disorders: renal failure[10]
Skin and subcutaneous tissue disorders: rash[11]
Vascular disorders: thrombosis[12]

[1] Cardiac arrhythmias includes Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular extrasystoles, and Ventricular tachycardia.
[2] Chest pain includes Angina pectoris, Chest discomfort, and Chest pain.
[3] Urinary tract infection includes Urinary tract infection, and Urinary tract infection viral.
[4] Aphasia includes Aphasia, Dysarthria, and Speech disorder.
[5] Ataxia includes Ataxia, Balance disorder, and Gait disturbance.
[6] Peripheral neuropathy includes Peripheral motor neuropathy and Peripheral sensory neuropathy.
[7] Paresis includes Cranial nerve paralysis, Facial paralysis, and Peroneal nerve palsy.
[8] Delirium includes Agitation, Hallucination, Irritability, Personality change, and Restlessness.
[9] Depression includes Depression, and Flat affect.
[10] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, and Renal impairment.
[11] Rash includes Erythema, Rash, Rash maculo-papular, and Rash pustular.
[12] Thrombosis includes Deep vein thrombosis, and Device related thrombosis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Patients with Multiple Myeloma Who Have Received 1 to 3 Prior Lines of Therapy

Study MMY3002

Table 7: Laboratory Abnormalities Following Treatment with Carvykti in Study MMY3002

Laboratory Abnormality	Carvykti (N=196)		PVd/DPd (N=208)	
	Any Grade n (%)	Grade 3 or 4 n (%)	Any Grade n (%)	Grade 3 or 4 n (%)
Lymphopenia	196 (100)	194 (99)	182 (88)	129 (62)
White blood cell decreased	196 (100)	185 (94)	207 (>99)	143 (69)
Anemia	196 (100)	66 (34)	202 (97)	35 (17)
Neutropenia	195 (99)	186 (95)	203 (98)	182 (88)
Thrombocytopenia	187 (95)	92 (47)	181 (87)	42 (20)
Hypoalbuminemia	130 (66)	1 (1)	94 (45)	1 (<1)
Alanine aminotransferase increased	105 (54)	9 (5)	67 (32)	8 (4)
Aspartate aminotransferase increased	100 (51)	12 (6)	45 (22)	4 (2)
Gamma Glutamyl Transferase increased	95 (48)	17 (9)	11 (5)	4 (2)
Hypocalcemia	91 (46)	2 (1)	34 (16)	2 (1)
Hypokalemia	82 (42)	10 (5)	43 (21)	5 (2)
Alkaline phosphatase increased	78 (40)	8 (4)	63 (30)	1 (<1)
Hypomagnesemia	75 (38)	5 (3)	13 (6)	0
Hyponatremia	62 (32)	7 (4)	68 (33)	9 (4)
Hypertriglyceridemia	49 (25)	7 (4)	1 (<1)	0
Blood bilirubin increased	27 (14)	3 (2)	28 (13)	1 (<1)
Fibrinogen decreased	23 (12)	19 (10)	0	0

Laboratory Abnormalities reported using Common Terminology Criteria for Adverse Events version 5.0

Patients with Multiple Myeloma Who Have Received at least 3 Prior Lines of Therapy

Study MMY2001

Table 8: Laboratory Abnormalities Following Treatment with Carvykti in Study MMY2001 (N=97)

Laboratory Abnormality	Any Grade n (%)	Grade 3 or 4 n (%)
Lymphopenia	97 (100)	96 (99)
Neutropenia	97 (100)	95 (98)
White blood cell decreased	97 (100)	95 (98)

Anemia	97 (100)	70 (72)
Thrombocytopenia	96 (99)	61 (63)
Hypoalbuminemia	85 (88)	5 (5)
Aspartate aminotransferase increased	68 (70)	20 (21)
Alanine aminotransferase increased	66 (68)	9 (9)
Hyponatremia	53 (55)	7 (7)
Hypocalcemia	52 (54)	3 (3)
Gamma Glutamyl Transferase increased	51 (53)	8 (8)
Alkaline phosphatase increased	44 (45)	4 (4)
Hypokalemia	42 (43)	5 (5)
Hypomagnesemia	24 (25)	0
Blood bilirubin increased	14 (14)	2 (2)
Fibrinogen decreased	10 (10)	9 (9)

Laboratory Abnormalities reported using Common Terminology Criteria for Adverse Events version 5.0

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed with Carvykti.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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) signaling

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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of ciltacabtagene autoleucel was assessed in 97 adult patients with 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, ciltacabtagene autoleucel exhibited an initial expansion phase followed by a rapid decline and then a slower decline. However, high interindividual variability was observed.

Table 9: Pharmacokinetic Parameters of Ciltacabtagene Autoleucel in Patients with Multiple Myeloma

Parameter	Summary Statistics	N=97
C_{max} (copies/µg genomic DNA)	Median (range), n	47806 (7189 - 115234), 97
t_{max} (day)	Median (range), n	12.7 (8.7 – 329.8), 97
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	Median (range), n	371569 (58691 - 2024126), 97
$t_{1/2}$ (day)	Median (range), n	15.3 (3.0 - 95.4), 42

After the cell expansion, the persistence phase of the ciltacabtagene autoleucel 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 ciltacabtagene autoleucel was assessed in 176 adult patients with lenalidomide-refractory multiple myeloma in Study MMY3002 and were generally consistent with those in Study MMY2001.

Detectable ciltacabtagene autoleucel exposures in bone marrow indicate a distribution of ciltacabtagene autoleucel 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 the management of CRS. Ciltacabtagene autoleucel continues to expand and persist following administration of tocilizumab, corticosteroids, and anakinra. In Study MMY2001, ciltacabtagene autoleucel median C_{max} and $AUC_{0\text{-}28d}$ in patients treated with tocilizumab (n=68) for CRS were 168% and 209% of those in patients (n=29) who did not receive tocilizumab for CRS, respectively. The median C_{max} and $AUC_{0\text{-}28d}$ of ciltacabtagene

autoleucel in patients who received corticosteroids (n=21) for CRS were 186% and 307% of those in patients who did not receive corticosteroids (n=76) for CRS, respectively. In addition, the median C_{max} and AUC_{0-28d} of ciltacabtagene autoleucel in patients who received anakinra (n=18) for CRS were 139% and 232% of those in patients who did not receive anakinra (n=79) for CRS, respectively. In Study MMY3002, the results related to tocilizumab and corticosteroid were consistent with Study MMY2001.

Special Populations and Conditions

- **Geriatrics:** The pharmacokinetics of Carvykti (C_{max} and AUC_{0-28d}) 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%).
- **Sex:** The pharmacokinetics of Carvykti (C_{max} and AUC_{0-28d}) were not impacted by gender.
- **Ethnic Origin:** The pharmacokinetics of Carvykti (C_{max} and AUC_{0-28d}) were not impacted by race.
- **Hepatic Insufficiency:** Hepatic impairment studies of Carvykti were not conducted. Carvykti C_{max} and AUC_{0-28d} 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.
- **Renal Insufficiency:** Renal impairment studies of Carvykti were not conducted. Carvykti C_{max} and AUC_{0-28d} 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 patients with normal renal function (CRCL ≥ 90 mL/min).
- **Obesity:** The pharmacokinetics of Carvykti (C_{max} and AUC_{0-28d}) were not impacted by body weight.

11 STORAGE, STABILITY AND DISPOSAL

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

Store and transport at or 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.

12 SPECIAL HANDLING INSTRUCTIONS

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.

Carvykti contains human blood cells that are genetically modified with replication incompetent lentiviral vector. Follow standard precautions and local guidelines for handling and disposal of unused medicinal product or all material that has been in contact with Carvykti (solid and liquid waste) to avoid potential transmission of infectious diseases.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ciltacabtagene autoleucel

Physicochemical properties: colourless to white, including shades of white, yellow, and pink, cell suspension.

Product Characteristics:

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 signaling 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).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Patients with Multiple Myeloma Who Have Received 1 to 3 Prior Lines of Therapy

Table 10: Summary of Patient Demographics for Clinical Trials in Adult Patients with Multiple Myeloma Who Have Received 1 to 3 Prior Lines of Therapy

Study # Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
68284528MMY3002 (CARTITUDE-4) Phase 3, randomized, open-label, multicentre trial to evaluate the efficacy and safety of ciltacabtagene autoleucel versus pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd) in patients with relapsed and lenalidomide-refractory multiple myeloma who previously received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent.	Patients were randomized in a 1:1 ratio to 1 of 2 treatment arms: Single intravenous infusion of Carvykti within the recommended dose of 0.5-1.0×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells. Investigator's choice of: Pomalidomide 4 mg, bortezomib 1.3 mg/m^2 and dexamethasone 20 mg (PVd) Or Daratumumab 1800 mg, pomalidomide 4 mg and dexamethasone 40 mg (DPd)	Total randomized: 419 Carvykti: 208 randomized and underwent leukapheresis and received bridging therapy; 196 received Carvykti PVd/DPd: 211 randomized (28 received PVd and 183 received DPd)	Overall study population: 61 years (27 to 80 years)	Overall study population: 240 (57%) males

MMY3002: Phase 3 study of ciltacabtagene autoleucel versus pomalidomide + bortezomib + dexamethasone (PVd) or daratumumab + pomalidomide + dexamethasone (DPd) in patients with relapsed and lenalidomide-refractory multiple myeloma who received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent.

Trial Design and Study Demographics

Patients with known active or prior history of central nervous system involvement, patients who exhibit clinical signs of meningeal involvement of multiple myeloma and patients with a history of Parkinson's disease or other neurodegenerative disorder, were excluded from the trial.

Patients randomized to standard of care were to start either PVd or DPd, as determined by the physician prior to screening based on prior exposure to anti-myeloma therapies, within 7 days after randomization.

PVd: Pomalidomide was administered at a full dose of 4 mg PO on Days 1 through 14 of each cycle. Bortezomib was administered at a full dose of 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 during the first 8 cycles and then on Days 1 and 8 of each cycle from Cycle 9 onwards. Dexamethasone was administered PO at 20 mg/day (≤75 years of age) or 10 mg/day (>75 years of age) on Days 1, 2, 4, 5, 8, 9, 11, and 12 during the first 8 cycles and on Days 1, 2, 8 and 9 of each cycle from Cycle 9 onwards.

DPd: Daratumumab was administered at a dose of 1800 mg SC at weekly intervals for Cycles 1 and 2, then every 2 weeks for Cycles 3 to 6, then every 4 weeks from Cycle 7 onwards of each cycle. Pomalidomide was administered at a full dose of 4 mg PO on Days 1 through 21 of each cycle. Dexamethasone was administered PO/IV at a total dose of 40 mg weekly (20 mg weekly for participants >75 years of age) of each cycle.

Patients randomized to Carvykti underwent apheresis 3-6 days post randomization, followed by bridging therapy with PVd or DPd (determined by the physician based on prior anti myeloma therapy). Following a wash out period, 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).

Randomization was stratified by physician's choice of treatment (DPd vs. PVd), ISS (I vs. II vs. III) and number of prior lines of therapy (1 vs. 2 or 3). The primary efficacy endpoint was progression-free survival (PFS) as assessed by a validated computer algorithm per the International Myeloma Working Group (IMWG) consensus. Key secondary efficacy endpoints included complete response/stringent complete response (CR/sCR) rate, overall response rate (ORR), and overall survival (OS). The study design planned the first interim analysis to take place when approximately 188 PFS events had occurred, where the interim analysis for PFS and the first of 4 pre-planned OS analyses were performed. The final OS analysis will take place when approximately 250 OS events have occurred. A total of 419 patients were randomized (1:1) to receive either a sequence of apheresis, bridging therapy, lymphodepletion and Carvykti (n=208) or physician's choice of PVd or DPd (n=211).

Of the 419 patients who were randomized, 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 and 100% were refractory to an immunomodulatory agent. Of the 417 patients for whom baseline cytogenetic data were available, high-risk cytogenetics were present in 61% of patients.

All 208 patients randomized to the Carvykti arm underwent apheresis. Following apheresis and prior to administration of Carvykti, all 208 randomized patients received protocol mandated bridging therapy (PVd or DPd). 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).

Study Results

The median follow-up duration at the time of the PFS analysis was 15.9 months (range: 0.1 to 27.3 months). Efficacy results of the first interim analysis for Study MMY3002 are summarized in Table 11 and Figure 1.

Table 11: Efficacy results for Study MMY3002 (Intent-To-Treat Analysis Set)

	Carvykti (N=208)	**PVd/DPd (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/ Stringent Complete Response (CR/sCR) 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	

NE=not estimable; CI=confidence interval.

Notes: Based on a median duration of follow up of 15.9 months. 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.

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

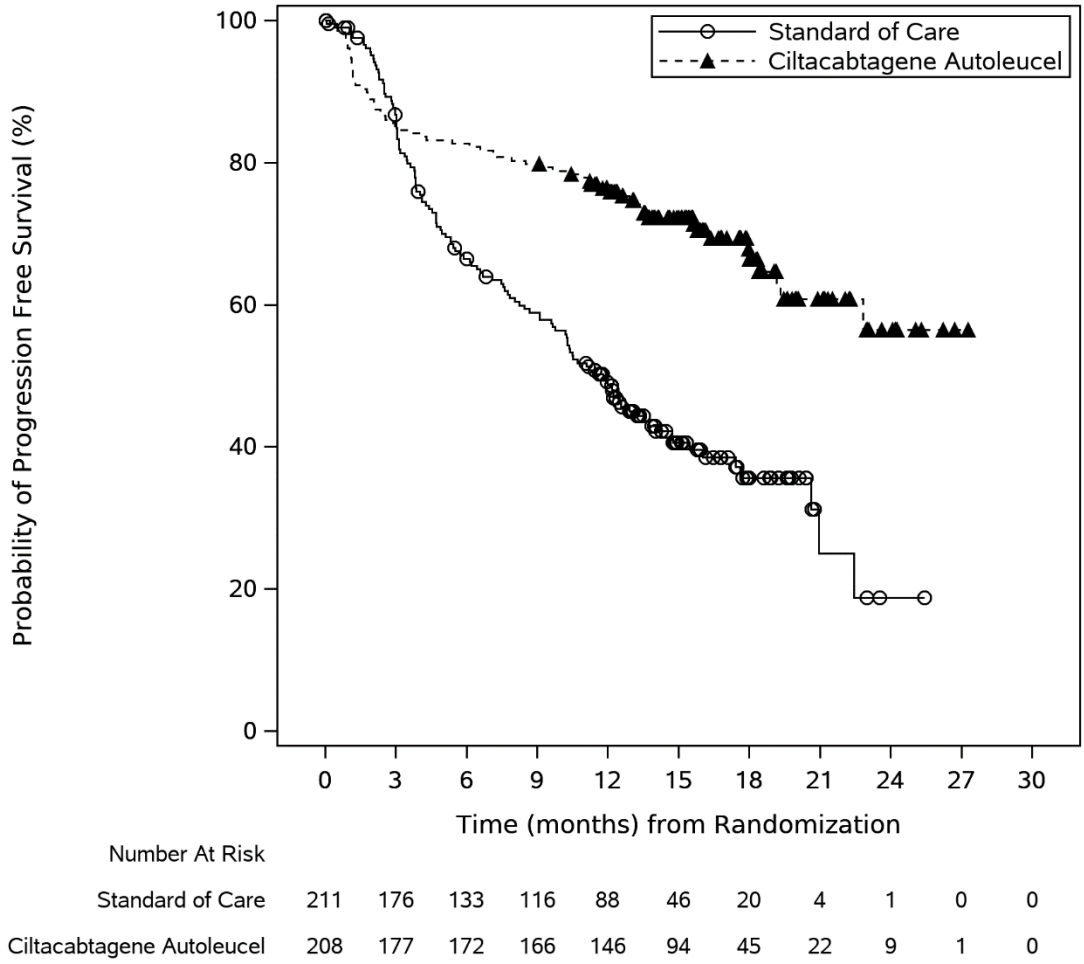
[b] Kaplan-Meier estimate

[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 the Carvykti arm.

[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

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



At the time of the first interim analysis, OS was immature. Thirty-nine patients (18.8%) in the Carvykti arm and 47 (22.3%) in the PVd/DPd arm died. Within the first 6 months following randomization 18 patients (8.7%) in the Carvykti arm and 12 patients (5.7%) in the PVd/DPd arm died. Of the 18 deaths in the Carvykti arm, 9 deaths occurred prior to Carvykti infusion and 9 deaths occurred after Carvykti infusion. The most common adverse events in patients who died after receiving Carvykti infusion were due to infection (n=6).

Patients with Multiple Myeloma Who Have Received at least 3 Prior Lines of Therapy

Table 12: Summary of Patient Demographics for Clinical Trials in Adult Patients with Multiple Myeloma Who Have Received at least 3 Prior Lines of Therapy

Study # Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
68284528MMY2001 (CARTITUDE-1) Phase 1b/2, multicentre, open-label, single-arm study to evaluate the efficacy and safety of ciltacabtagene autoleucel in patients with relapsed or refractory multiple myeloma	Single intravenous infusion of Carvykti within the recommended dose of 0.5-1.0×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells.	Underwent leukapheresis: 113 Treated: 97	Treated: 61 years (range: 43 to 78 years)	Treated: 57 (59%) males

MMY2001: Phase 1b/2 study of ciltacabtagene autoleucel in patients with relapsed or refractory multiple myeloma who received at least 3 prior lines of therapy

Trial Design and Study Demographics

MMY2001 was an open-label, single-arm study evaluating Carvykti for the treatment of patients with multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody and who had disease progression on their last regimen.

In total, 113 patients underwent leukapheresis; Carvykti was manufactured for all patients.

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%). No patients had a complete response (CR) following bridging therapy, prior to receiving Carvykti.

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). 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. 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, 59% were male, 71% were Caucasian and 18% were African-American. The median patient age was 61 years (range: 43 to 78 years), 36% of patients were 65 year or older, and 8% were 75 years or older. Twenty-four percent of patients had high-risk cytogenetic abnormalities, which included del17p (20%), t[4;14] (3%), and t[14;16] (2%). Sixty-three percent of patients had International Staging System (ISS) Stage I, 23% had ISS Stage II and 14% had ISS stage III disease. Twenty percent of patients had a presence of plasmacytomas at baseline. 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, 88% were triple-class refactory (refractory to a PI, IMiD, and anti-CD38 antibody), and 42% were penta-refractory (refractory to at least two PIs, at least 2 IMiDs, and one 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.

Study Results

Efficacy results were based on a median follow up of 18 months (range 1.5 months [subject died] to 30.5 months), and overall response rate as determined by the Independent Review Committee assessment using International Myeloma Working Group (IMWG) criteria (see Table 13).

Table 13: Efficacy Results for Study MMY2001 in Adult Patients with Multiple Myeloma

	All Treated (N=97)	**All Enrolled[a] (N=113)**
Primary Endpoint		
Overall Response Rate (sCR[b] + VGPR + PR) n (%)	95 (97.9)	95 (84.1)
95% CI (%)	(92.7, 99.7)	(76.0, 90.3)
Stringent complete response (sCR[b]) n (%)	78 (80.4)	78 (69.0)
Very good partial response (VGPR) n (%)	14 (14.4)	14 (12.4)
Partial response (PR) n (%)	3 (3.1)	3 (2.7)
Secondary Endpoint		
Median Duration of Response (DOR): Months (95% CI)	21.8 (21.8, NE)	-
VGPR or better: Months (95% CI)	21.8 (21.8, NE)	-
sCR[b]: Months (95% CI)	NE (21.8, NE)	-

CI=confidence interval; NE=not estimable

Notes: Based on a median duration of follow up of 18 months (range 1.5 months [subject died] to 30.5 months)

[a] All enrolled patients underwent leukapheresis

[b] All complete responses were stringent CRs

The median time to response in 95 responders was 0.95 months (range 0.9 to 10.7 months). The median time to sCR in 78 responders with sCR was 2.63 months (range 0.9 to 15.2 months).

After a median follow-up of 27.7 months, the ORR remained at 97.9% (95% CI: 92.7%, 99.7%) with sCR and VGPR changing to 82.5% and 12.4%, respectively. The median DOR was NE (95% CI: 23.3 months, NE) for responders (n=95). The median time to response remained at 0.95 months (range 0.9 to 10.7 months), and the median time to sCR (n=80) was 2.89 months (range 0.9 to 17.8 months).

14.3 Immunogenicity

Carvykti has the potential to induce anti-CAR antibodies. The immunogenicity of Carvykti was evaluated using a validated assay for the detection of binding antibodies against Carvykti pre-dose and at multiple timepoints post-infusion. In Study MMY2001, 19 of 97 patients (19.6%) were positive for anti-CAR antibodies. In Study MMY3002, 37 of 176 patients (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.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Due to the nature of this product, traditional toxicity, fertility, and pharmacokinetic studies with Carvykti were not conducted.

Genotoxicity and carcinogenicity: No genotoxicity or carcinogenicity 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.

Reproductive and Developmental Toxicology: No reproductive and developmental toxicity animal studies have been conducted with Carvykti.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CARVYKTI®

(ciltacabtagene autoleucel)

Read this carefully before you receive Carvykti. This is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Carvykti.

Serious Warnings and Precautions

- Fever and chills which may be symptoms of a serious side effect called cytokine release syndrome, which can be severe or fatal. Other symptoms include difficulty breathing, dizziness or feeling light-headed, feeling the need to throw up, headache, fast heartbeat, low blood pressure, feeling tired, vomiting, diarrhea, muscle pain and joint pain.
- Neurologic toxicities include problems like confusion, difficulty with memory, difficulty speaking or slowed speech, difficulty understanding speech, loss of balance or coordination, confused about time or surroundings, being less alert or excessive sleepiness, passing out, fits (seizures), shaking, or weakness with loss of movement on one side of the body.
- Hemophagocytic lymphohistiocytosis/ Macrophage activation syndrome, a strong and uncontrolled immune response, in which activated immune cells can build up in organs like liver, kidney, and spleen, and cause damage to these and other organs.

What is Carvykti used for?

Carvykti is used to treat patients with a type of cancer of the bone marrow called multiple myeloma. It is given when your cancer has not responded to or has come back after at least one treatment, and your cancer is not responding to your most recent therapy.

For the following indication Carvykti has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- the treatment of adult patients with multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and who are refractory to their last treatment.

For the following indication Carvykti has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- the treatment of adult patients with multiple myeloma, who have received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Carvykti work?

Carvykti is a chimeric antigen receptor (CAR) T-cell therapy, a type of treatment that helps your immune system fight cancer. Carvykti is made from your own T cells (a type of white blood cells). These cells are taken from your blood and are modified to recognize and attack cancer cells. Specifically, the cells are modified to target a protein expressed on multiple myeloma cells. You may be given other therapies to treat your cancer while Carvykti is being made.

What are the ingredients in Carvykti?

Medicinal ingredients: Ciltacabtagene autoleucel

Non-medicinal ingredients: Cryostor® CS5 (a substance used to preserve frozen cells), including dimethyl sulfoxide (DMSO). Carvykti may contain trace amounts of kanamycin.

Carvykti comes in the following dosage forms:

Carvykti is a colourless to white (including shades of white, yellow, and pink) cell suspension for infusion, supplied in an infusion bag.

Do not use Carvykti if:

You are allergic to Carvykti or any of the other ingredients of this medicine (listed in "What are the ingredients in Carvykti"?). If you think you may be allergic, ask your doctor for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Carvykti. Talk about any health conditions or problems you may have, including if you:

- have current or past problems with your nervous system - such as fits, stroke, new or worsening memory loss.
- have any lung, heart or blood pressure (low or raised) problems.
- have kidney problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhea and bloody stools.
- have had hepatitis B virus, hepatitis C virus or human immunodeficiency virus infection
- have an infection. An infection will be treated before you receive Carvykti
- have had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

- notice the symptoms of your cancer getting worse. In myeloma this might include fever, feeling weak, bone pain, unexplained weight loss.
- are pregnant, or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Carvykti in pregnant or breast-feeding women are not known and it may harm your unborn baby or breastfed child.
- are a man and you plan to father a child after Carvykti treatment.

Other warnings you should know about:

- Do not drive or use tools or machines until at least 8 weeks after having Carvykti, or if you feel tired, have balance and coordination problems, feel confused, weak or dizzy.
- Do not donate blood, organs, tissues or cells for transplants after you have had Carvykti.
- Carvykti contains substances that may cause allergic reactions. Your doctor will check you to look for any signs of a possible allergic reaction.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you will receive Carvykti:

Carvykti will always be given to you by a healthcare professional at a qualified treatment centre.

Making Carvykti from your own blood cells

- Carvykti is made from your own white blood cells. Your blood cells will be collected from you to prepare your medicine.
- Your doctor will take some of your blood using a catheter (tube) placed in your vein.
- Some of your white blood cells are separated from your blood - the rest of your blood is returned to your vein. This process is called 'leukapheresis'. This process can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent to the manufacturing centre to make Carvykti.
- While Carvykti is made, your healthcare provider may prescribe other medicines to continue to manage your multiple myeloma.

Medicines given before Carvykti treatment

A few days before - you will be given treatment called "lymphodepleting therapy" to prepare your body to receive Carvykti. This treatment reduces the number of white blood cells in your blood, so the modified white blood cells in Carvykti can grow in numbers when they are returned to your body.

30 to 60 minutes before - you may be given other medicines. These may include:

- medicines called anti-histamines for an allergic reaction - such as diphenhydramine
- medicines for fever - such as acetaminophen

Your doctor or nurse will check carefully that the Carvykti treatment is from your own modified white blood cells.

How you are given Carvykti

- Your doctor or nurse will give you a one-time infusion of Carvykti into your vein. This is called an 'intravenous infusion' and takes about 30-60 minutes.

After you receive Carvykti

- Plan to stay near the centre where you were treated for at least 4 weeks after you receive Carvykti.
    - You will need to be monitored at the treatment centre daily for at least 14 days after you receive Carvykti. This is so your doctor can check if your treatment is working and treat you if you get any side effects. If you develop serious side effects, you may need to stay in the hospital until your side effects have been managed and it is safe for you to leave.
    - If you miss any appointments, call your doctor or treatment centre as soon as possible to make a new appointment.

Usual dose:

Carvykti comes as a cell suspension in an infusion bag. The target 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. Carvykti should be given to you as a one-time infusion.

What are possible side effects from using Carvykti?

These are not all the possible side effects you may have when taking Carvykti. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people):

- low number of platelets' (cells that help blood to clot), and red blood cells
- low number white blood cell (neutrophils) which can occur with a fever
- pain, including muscle and joint pain
- feeling very tired, difficulty sleeping
- infected nose, sinuses or throat (a cold)
- nausea, decreased appetite, constipation, vomiting, diarrhea
- headache
- swelling caused by fluid buildup in the body
- high level of bilirubin in the blood
- laboratory test results showing increased levels of liver enzymes (abnormal liver function test) or a higher level of a protein (C-reactive protein) in blood that may indicate inflammation
- laboratory test results showing low levels of antibodies, called immunoglobulins (hypogammaglobulinemia) that are important in fighting infections

Common (may affect up to 1 in 10 people):

- low level of 'fibrinogen', a type of protein in the blood, making it more difficult to form clots
- stomach pain
- increased levels of a protein called 'ferritin' in the blood
- muscle tremor
- tightness, muscular weakness
- weak muscles that cause partial paralysis
- severe confusion
- fungal infections
- blood clots
- sleep problems

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON (may affect more than 1 in 10 people)			
Fever, chills, reduced blood pressure which may cause symptoms such as dizziness and lightheadedness, fluid in the lungs (all symptoms of a condition called cytokine release syndrome which may be severe and can be fatal)		✓	✓
Any signs of an infection, which may include fever, chills or shivering, rapid pulse, or depending on the location of infection, you may also experience sore throat, cough, shortness of breath or rapid breathing, chest pain, or pain with urination or blood in urine (increased risk of life-threatening infections that may lead to death)		✓	✓
Feeling tired, muscle weakness or cramps or an irregular heartbeat which may be a sign of low levels in the blood of calcium, potassium, sodium, magnesium, phosphate or albumin		✓	
Abnormal heartbeat		✓	
Problems being able to produce or control movement including muscle spasms, muscle tightness, muscular weakness, writing difficulty, changes in handwriting		✓	
Difficulty reading, writing, understanding words, slow speech, depressed level of consciousness, feeling confused (symptoms of a condition called Immune Effector Cell-Associated Neurotoxicity Syndrome or may be signs and symptoms of parkinsonism)		✓	✓
Spontaneous or prolonged and excessive bleeding (coagulopathy)		✓	✓
Shortness of breath, confusion or drowsiness which may be a sign of		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
low oxygen level in the blood (hypoxia)			
Nerve damage that may cause tingling, numbness, pain or loss of pain sensation		✓	
COMMON (may affect up to 1 in 10 people)			
Bleeding, which can be severe, called a 'hemorrhage'		✓	✓
Decreased or lack of urination, feeling sick to the stomach, swelling of the ankles, legs or feet, feeling tired, confusion, seizures or coma (kidney failure)		✓	✓
Facial numbness, difficulty moving muscles of face and eyes (signs and symptoms of cranial nerve palsies)		✓	✓
Tingling, numbness, and pain of hands and feet, difficulty walking, leg and/or arm weakness, difficulty breathing (signs and symptoms of Guillain-Barré syndrome)		✓	✓
UNCOMMON (may affect up to 1 in 100 people)			
Serious immune reaction with activated immune cells building up in organs like liver, kidney, spleen, causing damage to these organs, and could be life-threatening (hemophagocytic lymphohistiocytosis). Symptoms may include fever, decrease in blood cell levels, difficulty breathing, low blood pressure and an increased risk of bleeding.		✓	✓
Quick breakdown and death of large number of cancer cells leading to release of their contents causing a change in certain chemicals in the blood (tumour lysis syndrome). Symptoms may include feeling sick to the stomach, vomiting, diarrhea, muscle tightness or spasms, weakness,		✓	✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
numbness or tingling, feeling tired, decreased urination, irregular heart rate, feeling confused, hallucinating and seizures.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about Carvykti:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.janssen.com/canada, or by calling 1-800-567-3331 or 1-800-387-8781.

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