Ciltacabtagene autoleucel (Carvykti®) for the treatment of relapsed and refractory multiple myeloma (MM)

General information

Drug description [1]

Ciltacabtagene autoleucel (Carvykti®, cilta-cel, JNJ-68284528) is a chimeric antigen receptor T-cell (CAR-T) therapy directed against B-cell maturation antigen (BCMA).

Indication

Ciltacabtagene autoleucel (Carvykti®) is indicated for the treatment of adult patients with relapsed and refractory MM, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

Incidence [2]

In Austria, in 2022, the age-standardised incidence rate[1] of plasmacytoma and myeloma was 7.2/100,000 men and 4.9/100,000 women.

Current treatment [3]

The treatment recommendation for second-line therapy of MM available from the Onkopedia website is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [4]	FDA [5]
Approval status for this indication: On 22 February 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Carvykti®. The CHMP adopted an extension to the existing indication: ❖ Carvykti® is indicated for the treatment of adult patients with relapsed and refractory MM, who have received **at least one prior therapy**, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[2]	**Approval status for this indication**: not approved. **Other indications:** ❖ On 28 February 2022, the FDA approved ciltacabtagene autoleucel (Carvykti®) for the treatment of adult patients with relapsed or refractory MM after **four or more prior lines of therapy**, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Manufacturer

Carvykti® is manufactured by Janssen-Cilag International NV.

Costs

Currently, there is no cost information available.

Posology [6]

[1] European Standard Population 2013.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- ❖ Carvykti® must be administered in a qualified treatment centre. Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Carvykti®.
- ❖ Prior to infusion, the qualified treatment centre must have at least 1 dose of tocilizumab available for use in the event of cytokine release syndrome (CRS), with access to an additional dose within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- ❖ Emergency equipment must be available prior to infusion and during the recovery period.
- ❖ Carvykti® is intended for autologous use.
- ❖ Treatment consists of a single dose for infusion containing a dispersion of CAR-positive viable T cells in one infusion bag.
- ❖ The target dose is 0.75×10^6 CAR-positive viable T cells/kg of body weight (not exceeding 1×10^8 CAR-positive viable T cells). Patients 100 kg and below: $0.5 - 1 \times 10^6$ CAR-positive viable T cells/kg body weight. Patients above 100 kg: $0.5 - 1 \times 10^8$ CAR-positive viable T cells (non-weight based).

Bridging therapy

- ❖ Consider bridging therapy according to prescriber's choice prior to infusion with Carvykti® to reduce tumour burden or stabilise the disease.

Pre-treatment (lymphodepleting regimen)

- ❖ 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).
- ❖ The availability of Carvykti® should be confirmed prior to starting the lymphodepleting regimen. A lymphodepleting regimen of cyclophosphamide 300 mg/m² intravenous and fludarabine 30 mg/m² intravenous should be administered daily for 3 days. Carvykti® infusion should be administered 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, thereby 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.

Premedication

- ❖ The following pre-infusion medications should be administered to all patients 30 to 60 minutes prior to Carvykti® infusion:
  - Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg).
  - Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).
- ❖ The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of Carvykti®.

Warnings and precautions [6]

- ❖ **Traceability**
  - The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the medicinal product, the batch number and the name of the treated patient should be kept for a period of 30 years after the expiry date of the medicinal product.
- ❖ **Autologous use**
  - Carvykti® is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Carvykti® must not be infused if the information on the product labels and Lot Information Sheet does not match the patient's identity.
- ❖ **Clinical assessment prior to Carvykti® infusion**
  - Carvykti® infusion should be delayed if a patient has any of the following conditions:
    - o clinically significant active infection or inflammatory disorders,
    - o grade ≥ 3 non-haematologic toxicities of cyclophosphamide and fludarabine lymphodepletion regimen, except for Grade 3 nausea, vomiting, diarrhoea, or constipation. Carvykti® infusion should be delayed until resolution of these events to Grade ≤ 1,
    - o active graft versus host disease.
  - 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. There is no experience of use of Carvykti® in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.
  - The efficacy/safety of Carvykti® in patients previously exposed to other anti-BCMA treatments is unknown.
  - There is limited evidence available on efficacy/safety of Carvykti® in re-treated patients.
  - Monitoring after infusion

- Patients should be monitored daily for 14 days after the Carvykti® infusion at a qualified clinical facility, and then periodically for an additional 2 weeks after Carvykti® infusion, for signs and symptoms of CRS, neurologic events, and other toxicities. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

❖ **CRS**

- CRS, including fatal or life-threatening reactions, can occur after Carvykti® infusion.
- Nearly all patients experienced CRS after Carvykti® infusion, with majority of these being Grade 1 or Grade 2. The median time from Carvykti® infusion (Day 1) to onset of CRS was 7 days (range: 1 to 12 days). Approximately 90% of patients experienced CRS onset after Day 3 of receiving the Carvykti® infusion.
- In almost all cases, duration of CRS ranged from 1 to 15 days (median duration, 4 days). 90% of patients had 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 haemophagocytic lymphohistiocytosis (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.
- The infusion of Carvykti® should be delayed 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. 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.
- The availability of at least one dose of tocilizumab for use in the event of CRS should be ensured prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS. Patients should be monitored for signs and symptoms of CRS daily for 14 days after the Carvykti® infusion at a qualified clinical facility, and then periodically for an additional two weeks after Carvykti® infusion.
- Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, the patient should be immediately evaluated for hospitalisation and treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids should be instituted as indicated in product information.
- 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 associated with Carvykti®
  - If CRS is suspected, manage according to the recommendations in product information. Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation, haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered. 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 remain 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 product information,
    - Tocilizumab according to the CRS grade in product information,
    - Anti-seizure medication according to the neurologic toxicity in product information.

❖ **Neurologic toxicities**

- Neurologic toxicities occur frequently following treatment with Carvykti® and can be fatal or life-threatening. Neurologic toxicities included ICANS, movement and neurocognitive toxicity with signs and symptoms of parkinsonism, Guillain-Barré syndrome, peripheral neuropathies, and cranial nerve palsies. Patients should be counselled on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Patients should be instructed 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, concurrent with CRS, following resolution of CRS or in the absence of CRS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.
  - Reduction of baseline burden of disease with bridging therapy prior to infusion with Carvykti® in patients with high tumour burden should be considered, which may mitigate the risk of developing neurologic toxicity. Patients should be monitored for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, the patient should be immediately evaluated for hospitalisation and treatment instituted with supportive care as indicated in product information. Early detection and aggressive treatment of CRS or ICANS may be

important to prevent neurologic toxicity from occurring or worsening. Continue to monitor patients for signs and symptoms of neurologic toxicities after recovery from CRS and/or ICANS.

- Management of neurologic toxicity associated with Carvykti®
  - At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. 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 product information,
    - Tocilizumab according to CRS grade in product information,
    - Anti-seizure medication according to neurologic toxicity in product information.

❖ **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. These patients all presented a combination of two or more factors such as high tumour burden at baseline (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5,000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Treatment with levodopa/carbidopa (n=2), was not effective in improving symptomatology in these patients. Patients should be monitored for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures.

❖ **Guillain-Barré syndrome**

- Guillain-Barré syndrome (GBS) has been reported after treatment with Carvykti®. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis. Patients should be monitored for GBS. Patients presenting with peripheral neuropathy should be evaluated for GBS. Treatment with intravenous immunoglobulin and escalation to plasmapheresis should be considered, depending on toxicity severity.

❖ **Peripheral neuropathy**

- Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of Carvykti®. Patients should be monitored for signs and symptoms of peripheral neuropathies. Management with short-course systemic corticosteroids should be considered, 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®. Patients should be monitored for signs and symptoms of cranial nerve palsies. Management with short-course systemic corticosteroids should be considered, depending on the severity and progression of signs and symptoms.

❖ **Prolonged and recurrent cytopenias**

- Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Carvykti® infusion and should be managed according to local guidelines. In Study MMY2001 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 or lower by Day 30.
- Blood counts should be monitored prior to and after Carvykti® infusion. For thrombocytopenia, supportive care with transfusions should be considered. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after Carvykti® or until CRS has resolved.

❖ **Serious infections and febrile neutropenia**

- Serious infections, including life-threatening or fatal infections, occurred in patients after Carvykti® infusion.
- Patients should be monitored for signs and symptoms of infection prior to and during treatment with Carvykti® and treated appropriately. Prophylactic antimicrobials should be administered according to local guidelines. Infections are known to complicate the course and management of concurrent CRS. Patients with clinically significant active infection should not start Carvykti® treatment until the infection is controlled.
- In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. Patients treated with Carvykti® may be at an increased risk of severe/fatal COVID-19 infections. Patients should be counselled 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 treated with medicinal products directed against B cells. 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 before collection of cells for manufacturing.

- **Hypogammaglobulinaemia**
  - Hypogammaglobulinaemia may occur in patients receiving Carvykti®. Immunoglobulin levels should be monitored after treatment with Carvykti®; IVIG should be administered for IgG <400 mg/dL. Manage according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.
- **Secondary malignancies**
  - Patients treated with Carvykti® may develop secondary malignancies. A case of CAR-positive T-cell lymphoma has been reported in an ongoing study. Patient should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.
- **Interference with virological testing**
  - Due to limited and short spans of identical genetic information between the lentiviral vector used to create Carvykti® and HIV, some HIV nucleic acid tests may give a false positive result.
- **Blood, organ, tissue, and cell donation**
  - Patients treated with Carvykti® should not donate blood, organs, tissues, and cells for transplantation. This information is provided in the Patient Alert Card which should be given to the patient.
- **Hypersensitivity**
  - Allergic reactions may occur with infusion of Carvykti®. Serious hypersensitivity reactions, including anaphylaxis, may occur due to the dimethyl sulfoxide 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.
- **Long-term follow-up**
  - Patients are expected to enrol and be followed in a registry in order to better understand the long-term safety and efficacy of Carvykti®.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
CARTITUDE-4 NCT04181827	419 (1:1)	apheresis, followed by at least one bridging therapy cycle and lymphodepletion[3]; 5-7 days after the initiation of lymphodepletion, a single cilta-cel infusion (target dose, 0.75×10^6 CAR+ viable T cells per kg of body weight)	physician's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd)[4]	PFS	15.9 months vs. 11.8 months	**ongoing**[5], open-label, randomized, phase 3 trial	BCMA	Janssen and Legend Biotech	CARTITUDE-4 [1]

Inclusion criteria[6]

- At least 18 years of age with documented diagnosis of MM as defined by the criteria below:
  - MM diagnosis according to the IMWG diagnostic criteria
  - Measurable disease at screening as defined (please see trial protocol)
- Have received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory drug. Patient must have undergone at least 1 complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy.

Exclusion criteria

- Prior treatment with CAR-T therapy directed at any target.
- Any previous therapy that is targeted to BCMA.
- Ongoing toxicity from previous anticancer therapy.
- Subjects with Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy will not be permitted to receive PVd as standard therapy or bridging therapy.
- Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to randomization.
- Was vaccinated with live attenuated vaccines within 4 weeks prior to randomization.

Patient characteristics at baseline (I vs. C, n=208 vs. n=211)

- Median age (range): 61.5 (27–78) vs. 61.0 (35–80) years
- Male sex: 55.8% vs. 58.8%
- Race or ethnic group:
  - Asian: 7.7% vs. 9.5%
  - Black: 2.9% vs. 3.3%
  - White: 75.5% vs. 74.4%
  - Other: 0.5% vs. 0.5%
  - Missing data: 13.5% vs. 12.3%
  - Hispanic or Latino ethnic group:
    - Yes: 8.7% vs. 4.7%
    - No: 73.1% vs. 78.2%

[3] 300 mg of cyclophosphamide per square meter of body-surface area and 30 mg of fludarabine per square meter daily for 3 days.
[4] DPd was administered in 28-day cycles and PVd in 21-day cycles until disease progression.
[5] The CARTITUDE-4 trial is currently ongoing; the estimated study completion date is 06/2027.
[6] For detailed in- and exclusion criteria, please see trial protocol.

- Have documented evidence of progressive disease by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.
- Patients with only 1 prior line of therapy must have progressed within 36 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.
- Refractory to lenalidomide per IMWG consensus guidelines.
- ECOG PS score of 0 or 1.
- Clinical laboratory values meeting the following criteria during the Screening Phase:
  - Haemoglobin ≥8 g/dL
  - ANC ≥1 × 10^9/L
  - Platelet count ≥75 × 10^9/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells; platelet count ≥50 x 10^9/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells;
  - Lymphocyte count ≥0.3 × 10^9/L;
  - AST ≤3 × ULN;
  - ALT ≤3 × ULN;
  - Total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinaemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required);
  - Estimated glomerular filtration rate ≥40 mL/min per 1.73 m^2.
- Women of childbearing potential must have 2 negative pregnancy tests prior to starting PVd or DPd.
- When a woman is of childbearing potential, the subject must commit either to abstaining continuously from heterosexual intercourse or agree to use 2 methods of reliable birth control simultaneously.
- A man must commit either to abstaining continuously from heterosexual sexual intercourse or a man:
  - Who is sexually active with a woman of childbearing potential or a pregnant woman must agree to use a barrier method of contraception.
  - Should agree to practice contraception according to and for the time frame specified in the local pomalidomide pregnancy prevention program.
- Women and men must agree not to donate eggs (ova, oocytes) or sperm.
- Signed informed consent form.

- Subject received any antitumor therapy as follows, prior to randomization:
  - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less;
  - Investigational vaccine within 4 weeks;
  - Monoclonal antibody treatment within 21 days;
  - Cytotoxic therapy within 14 days;
  - Proteasome inhibitor therapy within 14 days;
  - Immunomodulatory agent therapy within 7 days;
  - Radiotherapy within 14 days.
- Active malignancies other than the disease being treated under study. For exceptions, please see trial protocol.
- Plasma cell leukaemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome, or primary AL amyloidosis.
- Contraindications or life-threatening allergies, hypersensitivity, or intolerance to JNJ-68284528 or its excipients, including dimethyl sulfoxide or to fludarabine, cyclophosphamide, tocilizumab, pomalidomide, dexamethasone.
- Pregnant or breast-feeding or planning to become pregnant while enrolled in this study.
- Plans to father a child while enrolled in this study.
- Stroke or seizure within 6 months of signing informed consent.
- Received either of the following:
  - An allogenic stem cell transplant within 6 months before apheresis.
  - An autologous stem cell transplantation ≤12 weeks before apheresis.
- Known active, or prior history of CNS involvement or exhibits clinical signs of meningeal involvement of MM.
- Subject with chronic obstructive pulmonary disease (please see trial protocol for detailed information).
- Any of the following:
  - Seropositive for human immunodeficiency virus (HIV)
  - Hepatitis B infection.
  - Hepatitis C infection
- Serious underlying medical or psychiatric condition or disease, that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.

  - Missing data: 18.3% vs. 17.1%
- Geographic region:
  - Europe: 61.5% vs. 61.1%
  - North America: 15.4% vs. 15.2%
  - Asia: 13.0% vs. 11.8%
  - Australia: 10.1% vs. 11.8%
- ECOG PS score:
  - 0: 54.8% vs. 57.3%
  - 1: 44.7% vs. 42.2%
  - 2: 0.5% vs. 0.5%
- International Staging System stage:
  - I: 65.4% vs. 62.6%
  - II: 28.8% vs. 30.8%
  - III: 5.8% vs. 6.6%
- Median time since diagnosis (range): 3.0 (0.3–18.1) vs. 3.4 (0.4–22.1) years
- Presence of soft-tissue plasmacytomas: 21.2% vs. 16.6%
- Bone marrow plasma cells ≥60%: 20.4% vs. 20.7%
- Cytogenetic risk:
  - Standard: 33.3% vs. 33.3%
  - High: 59.4% vs. 62.9%
  - Missing data: 7.2% vs. 3.8%
- Tumour BCMA expression ≥50%: 67.8% vs. 65.4%
- Previous lines of therapy
  - 1: 32.7% vs. 32.2%
  - 2: 39.9% vs. 41.2%
  - 3: 27.4% vs. 26.5%
- Previous immunomodulatory drug: 100% vs. 100%
  - Lenalidomide: 100% vs. 100%
  - Pomalidomide: 3.8% vs. 4.7%
- Previous anti-CD38 antibody: 25.5% vs. 26.1%
  - Daratumumab: 24.5% vs. 25.6%
  - Isatuximab: 1.0% vs. 0.9%
- Previous proteasome inhibitor: 100% vs. 100.0%
  - Bortezomib: 97.6% vs. 97.2%
  - Carfilzomib: 37.0% vs. 31.3%
  - Ixazomib: 10.1% vs. 10.0%
- Triple-class exposure: 25.5% vs. 26.1%
- Penta-drug exposure: 6.7% vs. 4.7%
- Refractory status:
  - Lenalidomide: 100.0 vs. 100.0%
  - Bortezomib: 26.4% vs. 22.7%
  - Carfilzomib: 24.5% vs. 21.3%
  - Any anti-CD38 antibody: 24.0% vs. 21.8%

❖ Willing and able to adhere to the lifestyle restrictions specified in trial protocol.	❖ Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study.	• Daratumumab: 23.1% vs. 21.3% • Ixazomib: 7.2% vs. 8.1% • Pomalidomide: 3.8% vs. 4.3% • Triple-class: 14.4% vs. 15.6% • Penta-drug[7]: 1.0% vs. 0.5%

Efficacy (I vs. C)

Interim analysis; data-cutoff date 1 November 2022

Median time from the receipt of apheresis material to product release: 44 days (range, 25-127)
Median cilta-cel dose: 0.71×10^6 cells/kg
Risk of disease progression or death: HR 0.26 (95% CI, 0.18-0.38; p<0.001)
Median duration of PFS: not reached vs. 11.8 months (95% CI, 9.7-13.8)
PFS in ITT population at 12 months: 75.9% (95% CI, 69.4-81.1) vs. 48.6% (95% CI, 41.5-55.3)
CR or better: 73.1% vs. 21.8%; risk ratio 2.9 (95% CI, 2.3-3.7; p<0.001); odds ratio 10.3 (95% CI, 6.5-16.4)
Overall response (PR or better): 84.6% and 67.3%; risk ratio 2.2 (95% CI, 1.5-3.1; p<0.001); odds ratio 3.0 (95% CI,1.8-5.0)
MRD negativity at any time during the trial: 60.6% vs. 15.6%; risk ratio 2.2 (95% CI, 1.8-2.6; p<0.001); odds ratio of 8.7 (95% CI, 5.4-13.9).
MRD negativity among the patients who had evaluable samples: 87.5% vs. 32.7%
OS data: immature, HR 0.78; 95% CI, 0.5-1.2; p=0.26
Estimated number of patients who were alive at 12 months: 84.1% vs. 83.6%
Median time until symptom worsening: 23.7 months (95% CI, 22.1-not estimable) vs. 18.9 months (95% CI,16.8-not estimable); HR 0.42; 95% CI, 0.26-0.68).

Cilta-cel Pharmacokinetics

- ❖ Among the 176 patients in the as-treated population who received cilta-cel, CD3+CAR+ cells in blood peaked at a median of 13 days after infusion; the mean (±SD) number of cells was1523±5987 per cubic millimetre.
- ❖ These cells remained detectable for a median of 57 days (range,13-631).
- ❖ During the first 28 days after the administration of cilta-cel, the mean area under the curve was 12,504±55,281 CD3+CAR+ cells.

Safety (I vs. C, n=208 vs. n=208)

AEs grade 3 or 4: 96.6% vs. 94.2%
Serious AEs: 44.2% vs. 38.9%
Discontinuation due to AEs: 1.4% vs. 55.3%
Second primary cancers: 4.3% vs. 6.7%
Infections during treatment: 62.0% vs. 71.2%
Infections during treatment of grade 3 or 4: 26.9% vs. 24.5%
Covid-19 occurred during treatment: 13.9% vs. 26.4%
Hypogammaglobulinemia: 90.9% vs. 71.6%
Death from any cause: n=39 vs. n= 46
Death from disease progression: n=14 vs. n=13
Deaths due to AEs during treatment[8]: n=10 vs. n=15
Deaths due to AEs that were not considered by the investigator to be related to a trial treatment[9]: n=15 vs. n=11
CRS in patients who received cilta-cel: 76.1%[10]
CAR-T–related neurotoxic events: 20.5%[11]
ICANS: 4.5% (grade 1 or 2)
Cranial nerve palsies: 9.1%[12]
CAR-T–related peripheral neuropathies: 2.8%

Patient-reported outcomes [10]

Cut-off 1 November 2022:

- ❖ 99 patients in the cilta-cel arm and 66 in the SOC arm had both baseline and 12-month PRO assessments, representing data prior to progression.
- ❖ PRO compliance was 100% at baseline and decreased with subsequent visits to 74% in the cilta-cel arm and 81% in the SOC arm at month 12.
- ❖ Patients reported improved functioning and symptom reduction from baseline in the cilta-cel arm, while PRO scores in the SOC arm trended towards worsening or lower degrees of improvement from baseline for most domains and symptoms.
- ❖ The average improvement from baseline to month 12 (LS mean change) for patients who received cilta-cel exceeded clinically meaningful thresholds for global health status (10.1 points), pain (-10.2 points), and the visual analogue scale (8.0 points); improvements in fatigue (-9.1 points) and emotional functioning (9.5 points) neared clinically meaningful thresholds (Table). For all other EORTC QLQ-C30 domains, results numerically favoured cilta-cel.

[7] Penta-drug therapy includes at least two proteasome inhibitors, at least two immunomodulatory drugs, and one anti-CD38 monoclonal antibody.
[8] Associated with Covid-19 in 7 patients and 1 patient, respectively.
[9] These deaths occurred after the start of subsequent therapy or more than 112 days after the cilta-cel infusion or more than 30 days after the last dose of a standard care treatment.
[10] Grade 1 or 2 in 132 patients and grade 3 in 2 patients.
[11] Grade 1 or 2 in 31 patients and grade 3 or 4 in 5 patients.
[12] Cranial nerve palsies most commonly affected cranial nerve VII; grade 1 or 2 in 14 patients and grade 3 in 2 patients.

- On the MySIm-Q total symptom scale, the median time until MM symptom worsening in the cilta-cel arm was 23.7 months (95% CI, 22.1-not estimable) and was 18.9 months (95% CI, 16.8-not estimable) in the SOC arm (HR, 0.42).
- Patients with lenalidomide-refractory MM who had 1-3 prior lines of therapy demonstrated clinically meaningful improvements in health-related quality of life and meaningful reductions in disease-specific symptoms on multiple PRO endpoints after a single cilta-cel infusion.
- Improvements in health-related quality of life were numerically greater with cilta-cel than with continuously administered SOC treatments across all scales.

ESMO-MCBS for Haematological Malignancies v. 1.0 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS for Haematological Malignancies could not be applied because the PE was not reached.											

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear[13] unclear risk	yes[14] high risk	unclear

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT04181827/CARTITUDE-4	Please see above.	06/2027

Available assessments

- In May 2023, CADTH published a Reimbursement Recommendation for Ciltacabtagene autoleucel, indicated for the treatment of adult patients with MM, who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and who are refractory to their last treatment [14].
- G-BA assessed the efficacy of ciltacabtagene autoleucel in adults with relapsed and refractory MM who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and who showed disease progression during the last therapy [15].
- In September 2021, NIHR published a Health Technology Briefing "Ciltacabtagene autoleucel for relapsed and refractory multiple myeloma" [16].
- In September 2021, ICER conducted a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of 3 new treatments targeting the BCMA for heavily pretreated patients with relapsed and refractory MM, including ciltacabtagene autoleucel [17].
- No further assessment was identified via NICE.

Other aspects and conclusions

- In February 2024, the **CHMP adopted an extension to the existing indication** for Carvykti®, indicated for the treatment of adult patients with relapsed and refractory MM, who have **received at least one prior therapy**, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide. In the **U.S.**, this indicated is currently **not approved**. However, in February 2022, the **FDA** approved Carvykti® for the treatment of adult patients with relapsed or refractory MM after **four or more prior lines** of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- **CARTITUDE-4** (NCT04181827) is an **ongoing**, randomized, open-label **phase 3** trial, comparing cilta-cel with the physician's choice of either of two highly effective standard of-care therapies in patients with lenalidomide-refractory MM after one to three lines of therapy. **Eligible patients** had lenalidomide resistance and had received one to three lines of therapy, including a proteasome inhibitor and an immunomodulatory drug. All the patients had an ECOG PS score of ≤1. Patients who received prior treatment with CAR-T therapy or any previous therapy that is targeted to BCMA, were **excluded**.
- The **primary endpoint is PFS**; at a median follow-up of 15.9 months, **median PFS was not reached in the cilta-cel group and was 11.8 months in the standard-care group** (HR 0.26; 95% CI, 0.18-0.38; p<0.001).
- Evaluation of **patient-reported outcomes** showed **clinically meaningful improvements in HRQoL of life** and meaningful reductions in disease-specific symptoms on multiple PRO endpoints after a single cilta-cel infusion. Improvements in HRQoL of life were numerically greater with cilta-cel than with continuously administered SOC treatments across all scales.
- The **ESMO-MCBS for Haematological Malignancies** was **not applicable**, as the primary endpoint was not reached.
- Since the CARTITUDE-4 trial is currently ongoing, the **risk of bias was considered unclear**. However, it is increased by the open-label-design and its industry-funded background.
- Beside CARTITUDE-4, **no further phase 3 trials**, assessing ciltacabtagene autoleucel in pretreated patients with relapsed and refractory MM, was identified.

[13] The CARTITUDE-4 trial is ongoing; currently, only interim analysis data is available.

[14] Representatives of the funders were involved in the collection, analysis, and interpretation of the data. Medical writing assistance was funded by the sponsor.

❖ In conclusion, it must be stated that currently, there are only interim analysis results available for the assessed indication. Robust phase 3 data is required to determine the role of ciltacabtagene autoleucel in earlier treatment lines.
First published: 03/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, BCMA= B-cell maturation antigen, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CAR-T=chimeric antigen receptor T-cell, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CRS=cytokine release syndrome, DPd=Daratumumab, Pomalidomide and Dexamethasone, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GBS=Guillain-Barré syndrome, GM-CSF=granulocyte macrophage-colony stimulating factor, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HLH= haemophagocytic lymphohistiocytosis, HR=hazard ratio, I=intervention, ICANS=Immune effector cell-associated neurotoxicity syndrome, ICER=Institute for Clinical and Economic Review, IMWG= International Myeloma Working Group, Int.=intention, IVIG=intravenous immunoglobulin, LS=least squares, MG=median gain, MM=multiple myeloma, MRD=minimal residual disease, MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, POEMS=polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes, PRO=patient-reported outcome, PVd=Pomalidomide, Bortezomib and Dexamethasone, QoL=quality of life, SAE=serious adverse event, SD=standard deviation, SOC=standard of care, ST=standard treatment, ULN= upper limit of normal

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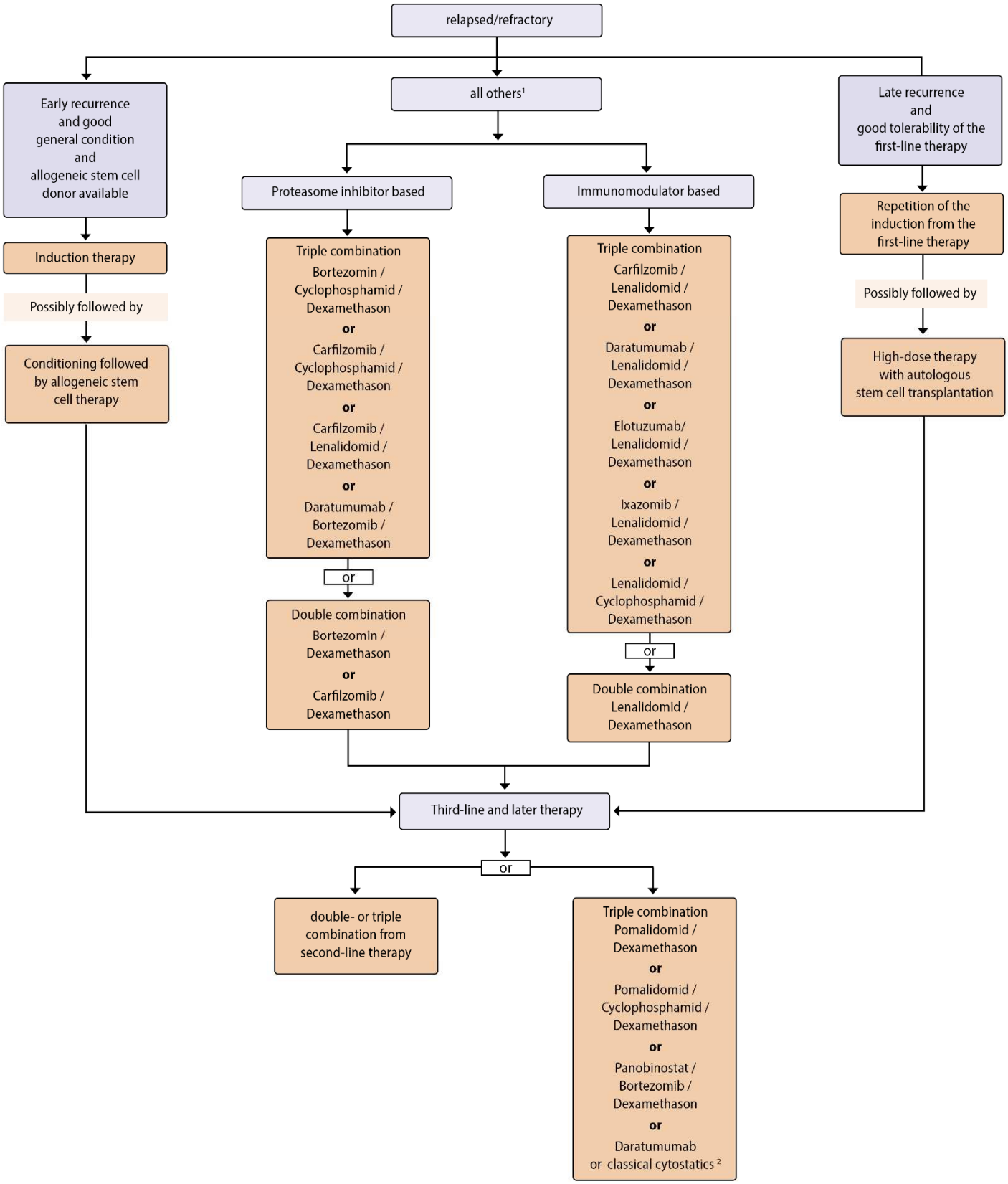
Appendix - Figure 1: Therapy algorithm for relapsed/refractory multiple myeloma.



Legend:

[1] *The treatment choice is determined not only by the approval conditions but also by the effectiveness of first-line therapy and compatibility.*

[2] *Antrazykline, Bendamustin, Cyclophosphamid, Melphalan*