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

General information [1]

Drug description	Indication
Ciltacabtagene autoleucel (Carvykti®, cilta-cel) is a genetically modified autologous T cell immunotherapy consisting of modified T-cells bearing a chimeric antigen receptor (CAR) targeting B-cell maturation antigen (BCMA). BCMA is primarily expressed on the surface of malignant MM B-lineage cells, as well as late-stage B cells and plasma cells. Upon binding to BCMA-expressing cells, the CAR promotes T cell activation, expansion, and elimination of target cells.	Ciltacabtagene autoleucel (Carvykti®) is indicated for the treatment of adult patients with relapsed and refractory MM, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

Current treatment

- Despite the development and approval of a range of new medicines for the treatment of MM over the past few years, there are limited therapeutic options for patients who have already received 3 major classes of drugs (immunomodulatory agents, proteasome inhibitors and monoclonal antibodies) and whose disease has come back or no longer responds to these medicines. Therefore, new medicines are needed for these patients [2].
- NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM [3]:
  - In instances of first relapse, the guidelines recommend the use of:
    - Daratumumab plus bortezomib plus dexamethasone.
    - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
    - Bortezomib monotherapy – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.
  - Subsequent relapse treatment may include:
    - Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
    - Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
    - Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.
    - Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory MM patients after 3 previous therapies.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Carvykti®. As Carvykti® is an advanced therapy medicinal product, the CHMP positive opinion is based on an assessment by the Committee for Advanced Therapies. **UPDATE**: Date of issue of marketing authorisation valid throughout the European Union: 25/05/2022 [5] <u>The full indication is:</u> ❖ Carvykti® is indicated for the treatment of adult patients with relapsed and refractory MM, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an	**Approval status for this indication**: 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. ✓ Priority review ✓ Breakthrough designation ✓ Orphan drug designation **Other indications**: none

anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

Other indications: none

✓ **Orphan status**
✓ **Medicine is under additional monitoring**
✓ **Medicine received a conditional marketing authorisation**[1]

Costs

Currently, no cost information is available for Europe.
In the United States, cilta-cel has a list price of $465,000 for a one-time infusion (although the final cost to a patient will depend on their insurance coverage) [5].
For comparison, the costs for the anti-CD19 chimeric antigen receptor T-cell therapy Kymriah® (Tisagenlecleucel) are approx. € 320, 000 [6].

Dosage and administration [6]

- For autologous use only. For intravenous use only.
- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Carvikty™.
- Do NOT use a leukodepleting filter.
- Verify the patient's identity prior to infusion.
- Premedicate with acetaminophen and an H1-antihistamine.
- Avoid prophylactic use of systemic corticosteroids.
- Confirm availability of tocilizumab prior to infusion.
- Dosing of Carvikty™ is based on the number of CAR-positive viable T cells.
- Recommended dose range is 0.5-1.0×106 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×108 CAR-positive viable T cells per single-dose infusion.
- Administer Carvykti™ at a REMS-certified healthcare facility.

Warnings and precautions [6]

- **Cytokine release syndrome (CRS)**
  - CRS including fatal or life-threatening reactions, occurred in patients following treatment with Carvykti™.
  - Do not administer Carvykti™ to patients with active infection or inflammatory disorders.
  - Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - ICANS, which may be fatal or life-threatening, occurred following treatment with Carvykti™, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.
  - Monitor for neurologic events after treatment with Carvykti™. Provide supportive care and/or corticosteroids as needed.
- **Parkinsonism and Guillain-Barré syndrome** and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with Carvykti™.
- **Hemophagocytic lymphohistiocytosis/Macrophage activation syndrome (HLH/MAS),** including fatal and life-threatening reactions, occurred in patients following treatment with Carvykti™.
  - HLH/MAS can occur with CRS or neurologic toxicities.
- **Prolonged and/or recurrent cytopenias** with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with Carvykti™.
  - Patients may exhibit ≥Grade 3 cytopenias following Carvykti™ infusion. One or more recurrences of Grade 3 or higher cytopenias may occur after partial or complete recovery of cytopenias.
  - Monitor blood counts prior to and after Carvykti™ infusion. Prolonged neutropenia has been associated with increased risk of infection.
- **Infections**
  - Monitor patients for signs and symptoms of infection; treat appropriately.
- **Hypogammaglobulinemia**
  - Monitor and consider immunoglobulin replacement therapy.
- **Hypersensitivity reactions**

[1] 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.

- Hypersensitivity reactions have occurred. Monitor for hypersensitivity reactions during infusion.

❖ **Secondary malignancies**

- In the event that a secondary malignancy occurs after treatment with Carvykti™, contact the manufacturer.

❖ **Effects on ability to drive and use machines**

- Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving Carvykti™ and in the event of any new onset of neurologic toxicities.

❖ Carvykti™ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy **(REMS)** called the CARVYKTI REMS.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CARTITUDE-1, MMY2001, NCT03548207	113/97[2]	single cilta-cel infusion (target dose 0.75 × 10^6 CAR-positive viable T cells per kg) administered 5–7 days after start of lymphodepletion	-	safety and confirmation of the recommended phase 2 dose (phase 1b), + overall response rate (phase 2)	**ongoing**[3], single-arm, open-label, multicentre, phase 1b/2 trial	-	Janssen Research & Development and Legend Biotech	[8]

Efficacy, n=97 patients (n=29 in phase 1b and n=68 in phase 2)

Overall response rate (at a median follow-up of 12.4 months): 97% (95% CI 91.2–99.4)
Patients achieving stringent complete response: 67%
Median time to first response: 1.0 month (IQR 0.9–1.0)
First response within 1.0 month of cilta-cel infusion: 79%
Median time to best response: 2.6 months (1.0–6.1)
Median time to complete response or better: 1.9 months (1.0–6.5)
Ongoing responses at the time of data cut-off: 72%
Median duration of response: not reached (95% CI 15.9–not estimable)
Median PFS: not reached (95% CI 16·8–not estimable)
Overall 12-month PFS rate: 77% (95% CI 66.0–84.3)
12-month PFS rate for patients who achieved complete response or better: 85% (72.0–91.8), median PFS not reached (95% CI, 16.8-NE)
12-month PFS rate for patients who achieved very good partial response or partial response: 62% (42.1–76.9), median PFS not reached (95% CI, 95% CI 16.8–not estimable)
PFS event in: 26 %; the most common reasons for disease progression were new plasmacytomas, new or worsening bone lesions, or both.
12-month OS rate: 89% (80.2–93.5)

Safety, n=97

Any AEs grade 3-4: n=91/97 (94%)
CRS: n=92/97 (95%); n=49/97 (51%) patients had grade 1, n=38/97 (39%) grade 2, n=3/97 (3%) grade 3, and n=1 (1%) each had grade 4 and 5.
CRS resolved in n=91/92 (99%)[4]
ICANS: n=16/97 (17%)[5]
Deaths that occurred during the study after cilta-cel administration: n=14/97
Deaths due to AEs considered related to treatment: n=6/14[6]

[2] 113 patients were enrolled and all underwent apheresis; n=16/113 (14%) did not receive cilta-cel infusion because of disease progression, death, or study withdrawal.
[3] CARTITUDE-1 is currently ongoing; the estimated study completion date is 08/2022.
[4] The patient with grade 5 CNS and haemophagocytic lymphohistiocytosis died on day 99 subsequent to sequelae of prolonged grade 4 CRS.
[5] 10% had ICANS grade 1, 4% grade 2, 1% had grade 3, and 1% had grade 4.
[6] Sepsis or septic shock (n=2), and CRS and haemophagocytic lymphohistiocytosis (n=1), lung abscess (n=1), respiratory failure (n=1), neurotoxicity (n=1).

Number of patients evaluable for MRD at 10^{-5}: 57 **MRD negativity rate at 10^{-5}:** 93% **Median time to MRD negativity at 10^{-5}:** 1.0 month (IQR 0.9–1.0) **UPDATE: Efficacy results based on a median duration of follow up of 18 months [10]:** **Overall response rate** (sCR + VGPR + partial response): 97.9% (95% CI, 92.7-99.7) **Stringent complete response** (sCR): 80.4% **Very good partial response (VGPR):** 14.4% **Partial response**: 3.1% **Median duration of response**: 21.8 months (95% CI, 21.8-NE) **Median time to response**: 0.95 months (range 0.9-10.7) **MRD negativity rate**: 57.7% (95% CI, 47.3-67.7) **MRD negative patients with sCR**: 43.3% (95% CI, 33.3-53.7)	

Risk of bias - study level (case series) [11]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	yes	yes
Overall risk of bias: low/moderate/high								

First published: 04/2022
Last updated: 06/2022

Abbreviations: AE=adverse event, AJ=adjustment, BCMA=B-cell maturation antigen, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, cilta-cel=ciltacabtagene autoleucel, CRS=cytokine release syndrome, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HLH=hemophagocytic lymphohistiocytosis, HR=hazard ratio, I=intervention, ICANS=Immune effector cell-associated neurotoxicity syndrome, Int.=intention, MAS=macrophage activation syndrome, MG=median gain, MM=multiple myeloma, MRD=minimal residual disease. =n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, REMS= Risk Evaluation and Mitigation Strategy, SAE=serious adverse event, sCR=stringent complete response, ST=standard treatment, VGPR=very good partial response

References:

1. European Medicines Agency (EMA). Medicines. Carvykti. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/carvykti].
2. European Medicines Agency (EMA). New gene therapy to treat adult patients with multiple myeloma. [Available from: https://www.ema.europa.eu/en/news/new-gene-therapy-treat-adult-patients-multiple-myeloma].

3. National Institute for Health Research (NIHR). Ciltacabtagene autoleucel for relapsed and refractory multiple myeloma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/30273-Ciltacabtagene-Autoleucel-for-Multiple-Myeloma-V1.0-SEPT2021-NONCONF.pdf].
4. U.S. Food and Drug Administration (FDA). FDA approves ciltacabtagene autoleucel for relapsed or refractory multiple myeloma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma].
5. European Medicines Agency (EMA). Medicines. EPAR. Carvykti. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti].
6. U.S. Food and Drug Administration (FDA). Carvykti. Label Information. [Available from: https://www.fda.gov/media/156560/download].
7. Supplement to: Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021.
8. Berdeja JG, Madduri, Usmani S, Jakubowiak A, et al. Ciltacabtagene autoleucel, a B-cell maturation antigendirected chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021; 398: 314–24. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673621009338].
9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma (CARTITUDE-1). [Available from: https://clinicaltrials.gov/ct2/show/NCT03548207].
10. European Medicines Agency (EMA). Carvykti: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/carvykti-epar-product-information_en.pdf].
11. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].