Report CARVYKTI® - Ciltacabtagene autoleucel

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Ciltacabtagene autoleucel **Brand Name:** Carvykti **Originator/licensee:** Janssen-Cilag International NV **Classification:** NI **ATC code:** L01XL05 **Orphan Status:** **Eu:** Yes **Us:** / **Mechanism of action:** Cilta-cel, which consist of the patient's own T cells (a type of white blood cell) that have been modified genetically in the laboratory, so that they make a protein called CAR. CAR can attach to a protein called BCMA that is present on the surface of multiple myeloma cells. When Carvykti is given to the patient, the modified T cells attach to BCMA and then kill the myeloma cells, thereby helping to clear the multiple myeloma from the body.	**Authorized Indication:** **EMA:** Ciltacabtagene autoleucel is indicated for the treatment of adult pts with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy and are refractory to lenalidomide [1]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:** 22/02/2024 **FDA M.A. date:** / **EU Speed Approval Pathway:** Yes **FDA Speed Approval Pathway:** / --- **ABBREVIATIONS:** **AE:** Adverse Event **BCMA:** B Cell Maturation Antigen **CAR**: Chimeric Antigen Receptor **CHMP:** Committee for Medicinal Products for Human Use **CILTA-CEL:** Ciltacabtagene autoleucel **CR:** Complete Response **DPd:** Daratumumab, Pomalidomide, and Dexamethasone **ECOG:** Eastern Cooperative Oncology Group **HCT:** Autologous Hematopoietic Cell Transplantation **IMiD:** Immunomodulatory Agent **ISS:** International Staging System **LEN**: Lenalidomide **LOT:** Lines Of Therapies **M.A.:** Marketing Authorization **MRD:** Minimal Residual Disease **NR:** Not Reached **PFS:** Progression Free survival **PI:** Proteasome Inhibitor **P.O.:** Positive Opinion **PS:** Performance Status **Pts:** patients **PVd:** Pomalidomide, Bortezomib and Dexamethasone **SOC:** Standard of care	**Summary of clinical EFFICACY:** **CARTITUDE-4 (NCT04181827):** is a global, phase 3, randomized, controlled, open label trial comparing cilta-cel with SOC (PVd or DPd) in pts with LEN-refractory multiple myeloma. Eligible pts had 1–3 prior LOT, including PI and IMiD, and were LEN-refractory. All the pts had an ECOG-PS score of 1 or less (on a scale ranging from 0 to 5, with higher scores indicating greater disability). In addition, none of the pts had received CAR-T therapy or BCMA-targeted treatment [2-3]. Pts (n=419) were assigned in a 1:1 ratio by means of computer-generated randomization to receive SOC physician's choice (n=211; [PVd n=28; DPd n=183]) or a single cilta-cel infusion (n=208), administered after the physician's choice of bridging therapy (PVd or DPd). Randomization was stratified according to the selection of PVd or DPd, disease severity according to the ISS at screening (I, II, or III), and the number of previous lines of therapy (1 or 2 to 3). In the SOC group, DPd was administered in 28-day cycles and PVd in 21-day cycles until disease progression. Pts in the cilta-cel group underwent apheresis, followed by at least one bridging therapy cycle and lymphodepletion (300 mg of cyclophosphamide per square meter of body-surface area and 30 mg of fludarabine per square meter daily for 3 days). Five to seven days after the initiation of lymphodepletion, a single cilta-cel infusion (target dose, 0.75×106 CAR+ viable T cells per kilogram of body weight) was administered [2]. The primary outcome was PFS in the intent-to-treat population, which was defined as the time from randomization to the first documentation of disease progression or death. At a median follow-up of 15.9 months (range, 0.1 to 27.3), the median PFS was not reached in the cilta-cel group and was 11.8 months in the SOC group (hazard ratio, 0.26; 95% CI, 0.18 to 0.38; P<0.001) [2]. **Summary of clinical SAFETY**: AEs were evaluated in the safety population, which included all pts, who received any part of study treatment (n=208 in each of the cilta-cel and SOC arms). The most common hematologic AEs (≥15%) of any grade in the cilta-cel arm were neutropenia (89.9%), thrombocytopenia (54.3%), anaemia (54.3%) and lymphopenia (22.1%). The most common hematologic AEs (≥15%) of any grade in the standard care arm were neutropenia (85.1%), thrombocytopenia (31.2%), and anaemia (26.0%). Infections of any grade occurred in 62.0% of cilta-cel patients (n=129) and in 71.2% of standard care arm pts (n=148). Second primary malignancies were reported in 4.3% (n=9) and 6.7% (n=14) of pts in the cilta-cel arm and standard care arm, respectively. A total of 39 cilta-cel pts and 46 standard care pts died [2]. **Ongoing studies:** ● ***For the same indication:*** *Yes* ● ***For other indications:*** *No* **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/variation/carvykti [2] https://www.nejm.org/doi/10.1056/NEJMoa2303379?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [3] https://ascopubs.org/doi/10.1200/JCO.2023.41.17_suppl.LBA106 [4] https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2820%2943169-2 [5] La terapia del Mieloma Multiplo: linee guida della Società Italiana di Ematologia [6] https://jnccn.org/view/journals/jnccn/21/12/article-p1281.xml	**Cost of therapy:** the price is not available yet. **Epidemiology**: the annual incidence of new cases in Italy is 11.1/100,000 inhabitants, or 5.759 new case/year [4-5]. --- **POSSIBLE PLACE IN THERAPY**: For pts with relapsed and refractory multiple myeloma the choice of appropriate therapy depends on the context of clinical relapse. PI (bortezomib, carfilzomib), IMiD (pomalidomide) and monoclonal antibodies (daratumumab, elotuzumab) are now considered first-line treatments. Taking into account combination therapies and HCT (for eligible pts), ciltacabtagene autoleucel will provide an additional treatment option for adults with relapsed and lenalidomide-refractory multiple myeloma [6]. **OTHER INDICATIONS IN DEVELOPMENT:** relapsed and refractory myeloma with extrameduLlary disease (NCT05666700) **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** bb2121 (NCT03651128) *Service reorganization: No *Possible off label use: Yes

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