Autologous anti-CD19-transduced CD3+ cells (Tecartus®, formerly KTE-X19) for the treatment of relapsed or refractory mantle cell lymphoma (MCL)

General information [1]

Drug description	Indication
Tecartus® is genetically modified autologous anti-CD19-transduced CD3+ cells. By binding to CD19-expressing cancer cells and normal B cells, the medicine starts T-cell activation and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.	Autologous anti-CD19-transduced CD3+ cells are indicated for the treatment of adult patients with relapsed or refractory MCL after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Current treatment [2]

- ❖ Guidelines recommend the use of chemotherapy in combination with rituximab for first line treatment for people with advanced-stage MCL who are symptomatic.
- ❖ If there is at least a partial response to induction chemotherapy then NICE guidelines suggest that autologous stem cell transplantation (ASCT) can be considered in patients who are fit enough.
- ❖ Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated MCL in adults for whom haematopoietic stem cell transplantation (HSCT) is unsuitable.

Regulatory status

EMA [1]

Approval status for this indication: On 15 October 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Tecartus®, intended for the treatment of relapsed or refractory MCL. As Tecartus® 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: 14/12/2020

The full indication is:

- ❖ Tecartus® is indicated for the treatment of adult patients with relapsed or refractory MCL after two or more lines of systemic therapy including a BTK inhibitor.

Other indications: none

- ✓ **Advanced therapy medicinal product**[1]
- ✓ **Orphan status**
- ✓ **Medicine received a conditional marketing authorisation**[2]
- ✓ **Accelerated assessment**[3]

FDA [3]

Approval status for this indication: On 24 July 2020, the FDA approved Tecartus® (brexucabtagene autoleucel) for the treatment of adult patients diagnosed with MCL who have not responded to or who have relapsed following other kinds of treatment.

Other indications: none

- ✓ **Accelerated approval**
- ✓ **Priority review**
- ✓ **Breakthrough therapy**
- ✓ **Orphan Drug designation**

Costs

Currently **no cost information** available.

Posology and method of administration [4]

- ❖ Tecartus® must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus®.
- ❖ At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- ❖ Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus®.

Posology

- ❖ Tecartus® is intended for autologous use only.

[1] A medicine for human use that is based on genes, cells or tissue engineering.
[2] Medicines that address unmet medical needs of patients on the basis of less comprehensive data. 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.
[3] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

- A single dose of Tecartus® contains 2 × 106 CAR-positive viable T cells per kg of body weight (range: 1 x 106–2 x 106 cells/kg), or maximum of 2 × 108 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.
- Tecartus® is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus®.

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended.

Monitoring after infusion

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Method of administration

- Tecartus® is for intravenous use only.
- Tecartus® must not be irradiated. Do NOT use a leukodepleting filter.
- Precautions to be taken before handling or administering the medicinal product: This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus® should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Warnings[4] [5]

- **CRS**, including life-threatening reactions, occurred in patients receiving Tecartus®. Do not administer Tecartus® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- **Neurologic toxicities,** including life-threatening reactions, occurred in patients receiving Tecartus®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with Tecartus®. Provide supportive care and/or corticosteroids, as needed.
- Tecartus® is available only through a restricted program under a **Risk Evaluation and Mitigation Strategy (REMS)** called the YESCARTA and TECARTUS REMS Program.
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfoxide or residual gentamicin in Tecartus®.
- **Severe Infections**:
  - **Severe or life-threatening infections** occurred in patients after Tecartus® infusion. In ZUMA-2, infections (all grades) occurred in 56% of patients. Grade 3 or higher infections, including bacterial, viral, and fungal infections, occurred in 30% of patients. Tecartus® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after Tecartus® infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.
  - **Febrile neutropenia** was observed in 6% of patients after Tecartus® infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.
  - **Viral Reactivation**: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines before collection of cells for manufacturing.
- **Prolonged Cytopenias:** Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus® infusion. In ZUMA-2, Grade 3 or higher cytopenias not resolved by Day 30 following Tecartus® infusion occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). Monitor blood counts after Tecartus® infusion.
- **Hypogammaglobulinemia:**
  - B cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with Tecartus®. In ZUMA-2, hypogammaglobulinemia occurred in 16% of patients. Monitor immunoglobulin levels after treatment with Tecartus® and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

[4] According to FDA-prescribing information

- The safety of immunization with live viral vaccines during or following Tecartus® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least six weeks prior to the start of lymphodepleting chemotherapy, during Tecartus® treatment, and until immune recovery following treatment with Tecartus®.

❖ **Secondary Malignancies:** Patients treated with Tecartus® may develop secondary malignancies. Monitor life-long for secondary malignancies.

❖ **Effects on Ability to Drive and Use Machines:** Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Tecartus® are at risk for altered or decreased consciousness or coordination in the eight weeks following Tecartus® 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.

Study characteristics [4, 6-8]

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ZUMA-2 NCT02601313	74	leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 at a dose of 2×10^6 CAR T cells per kilogram of body weight	-	percentage of patients with an objective response (complete/partial response)[5]	single-group, multicentre, open-label, phase 2 trial	-	Kite (a Gilead company)	Link

Efficacy[6] (I vs. C)

<u>60 patients in the primary efficacy analysis:</u>
Objective response: 93% (95% CI, 84-98)
Complete response: 67% (95% CI, 53-78)
<u>ITT analysis involving all 74 patients:</u>
Objective response: 85% (CI: NA)
Complete response: 59% (CI: NA)
Median time to an initial response: 1.0 month (range, 0.8-3.1)
Median time to a complete response: 3.0 months (range, 0.9-9.3)
Minimal residual disease (analysed in 39% of patients): 83% had no detectable residual disease at week 4, and 79% of patients with available data had negative results at month 6. At a median follow-up of 12.3 months, 57% of the 60 patients in the primary efficacy analysis were in **remission**.
Estimated PFS at 12 months: 61%, median PFS: NR (95% CI, 9.2–NE)
Estimated OS at 12 months: 83%; median OS: NR (95% CI, 24.0–NE)
QoL: EQ-5D scores revealed decreases from baseline in patient-reported HRQoL at week 4; better scores in mobility, self-care, usual activities, and overall health were observed by month 3, with overall health returning to baseline status or better in most patients by month 6.
UPDATE:
Median **duration of response**, months: NR (10.4-NE)
Ongoing responses: Complete remission+partial remission=43%; complete remission=42%
Median PFS, months: 16.2 (95% CI, 9.9-NE)
<u>OS:</u>
Median, months: NR (95% CI, 24.6-NE)
6 month OS: 83.6% (95% CI, 72.9-90.3)
12 month OS: 76.6% (95% CI, 65.1-84.8)
24 month OS: 66.5 (95% CI, 52.8-77.1)

Safety (I vs. C)

Grade 3 AEs: n= 11 (16%)
Grade 4 AEs: n=54 (79%)
SAEs: n=46 (68%)
Death[7]: n=2 (3%)

❖ **<u>CRS</u>** occurred in 91% of patients. 15% of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

❖ **<u>Neurologic adverse reactions</u>** <u>occurred in 68% of patients. 33% of patients experienced Grade 3 or higher (severe or life-threatening) AEs.</u>

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**

[5] As assessed by an independent radiologic review committee according to the Lugano classification
[6] Primary efficacy analysis; ZUMA-2 is ongoing, estimated study completion date: May 2034
[7] Two patients grade 5 adverse events, including organizing pneumonia related to conditioning chemotherapy and staphylococcus bacteremia related to conditioning chemotherapy and KTE-X19 therapy

no	no	no, open-label	no[8]	yes[9]	high risk
					First published: 11/2020 **Last updated**: 02/2021

Abbreviations: AE=adverse event, AJ=adjustment, ASCT=autologous stem cell transplantation, BTK=Bruton's tyrosine kinase, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRS=cytokine release syndrome, HBV=Hepatitis B virus, HCV= hepatitis C virus, HIV=human immunodeficiency virus, HRQol=health-related quality of life, HSCT=haematopoietic stem cell transplantation, EMA=European Medicines Agency, EQ-5D=European Quality of Life–5 Dimensions, FDA=Food and Drug Administration, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, ITT=intention-to-treat analysis, MCL=mantle cell lymphoma, MG=median gain, n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, NR=not reached, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

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8. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382:1331-42.

[8] The ZUMA-2 trial is currently ongoing (until 07/2038). However, not all confidence intervals of the results are reported.

[9] The trial protocol and statistical analysis plan were designed in a collaboration between the sponsor and the authors. Medical writing assistance was funded by the sponsor. All the authors (including both academic authors and those who are employees of the sponsor) contributed to the analysis and interpretation of the data.