Autologous anti-CD19-transduced CD3+ cells (Tecartus®) for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)

General information [1]

Drug description	Indication
The active substance of Tecartus® (KTE-X19) are autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured.	Tecartus® is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL.

Current treatment [2]

- **Treatment of ALL** is usually split into different phases, which briefly include:
  - Induction stage (weeks to months) - the aim of this stage is to kill leukaemia cells in the bone marrow and restore the balance of healthy cells in the blood. It can comprise oral and intravenous chemotherapy, targeted therapies (imatinib and monoclonal antibodies), steroids, blood transfusions, antibiotics and pegaspargase.
  - Consolidation stage (months) – the aim of this stage is to ensure any remaining cancer cells are killed by administering chemotherapy injections.
  - Maintenance stage (two years) – the aim of this stage is to prevent the leukaemia returning by administering oral chemotherapy and monitoring (by regular check-ups).

- **Treatment for relapsed and refractory ALL** will include further chemotherapy (using different drugs from the initial treatment) or a stem cell transplant.
- There are two chemotherapy drugs recommended for the treatment of relapsed or refractory B-precursor ALL in adults by NICE:
  - Blinatumomab (on condition of the discount agreed in the patient access scheme)
  - Ponatinib – for patients who are resistant or cannot tolerate dasatinib, who are resistant to imatinib or where the T315I gene mutation is present (on condition of the discount agreed in the patient access scheme).

Regulatory status

EMA [1]

Approval status for this indication: On 21 July 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Tecartus®.

The CHMP adopted a new indication:

- Tecartus® is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL.

UPDATE: Tecartus® (for treatment of ALL) has been authorised in the EU since 2 September 2022.

Other indications:

- Tecartus® is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor.

✓ **Orphan status**
✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional approval**[1]

FDA [3, 4]

Approval status for this indication: not approved

On 1 October 2021, the FDA approved brexucabtagene autoleucel (Tecartus®) for adult patients with relapsed or refractory B-cell precursor ALL.

Other indications:

- Tecartus® is indicated for the treatment of adult patients with relapsed or refractory MCL (this indication is approved under accelerated approval based on overall response rate and durability of response).

[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.

Costs

Currently, there is no cost information available.

Posology and method of administration [5]

- Pre-treatment (lymphodepleting chemotherapy) for ALL patients
  - A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m² over 60 minutes must be administered prior to infusing Tecartus®. This is recommended on the 2nd day before infusion of Tecartus®.
  - Fludarabine 25 mg/m² over 30 minutes must be administered prior to infusing Tecartus®. The recommended days are on the 4th, 3rd, and 2nd day before infusion of Tecartus®.
- Mantle cell lymphoma and acute lymphoblastic leukaemia
  - 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 IV or oral (or equivalent) approximately 1 hour prior to infusion.
    - Prophylactic use of systemic corticosteroids is not recommended.
  - Monitoring prior to infusion
    - In some patient groups at risk, a delay of the Tecartus® infusion may be indicated (see product information):
  - Monitoring after infusion
    - Patients must 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 is to be monitored at the physician's discretion.
    - Patients must be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Warnings and precautions [3, 5]

- Cytokine release syndrome (CRS)
  - 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
  - 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.
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
  - Administer treatment per institutional standards.
- Hypersensitivity reactions
  - Monitor for hypersensitivity reactions during infusion.
- Severe infections
  - Monitor patients for signs and symptoms of infection; treat appropriately.
- Prolonged cytopenias
  - Patients may exhibit Grade 3 or higher cytopenias for several weeks following Tecartus® infusion.
  - Monitor complete blood counts.
- Hypogammaglobulinemia
  - Monitor and provide replacement therapy.
- Secondary malignancies
  - Patients treated with Tecartus may develop secondary malignancies. Monitor life-long for secondary malignancies.
  - In the event that a secondary malignancy occurs, contact the manufacturer to obtain instructions on patient samples to collect for testing.

- ❖ 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 Tecartus®.
- ❖ Tecartus® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program.
- ❖ Viral reactivation
  - Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.
- ❖ Tumour lysis syndrome (TLS)
  - TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus® infusion.
  - Signs and symptoms of TLS must be monitored, and events managed according to standard guidelines.
- ❖ Prior stem cell transplantation (GvHD)
  - It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus® worsening GvHD.
- ❖ Prior treatment with anti-CD19 therapy
  - Tecartus® is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.
- ❖ Sodium content
  - This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- ❖ Long-term follow up
  - 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®.
- ❖ Traceability
  - The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years.
- ❖ Autologous use
  - Tecartus® is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Tecartus infusion bag and cassette. Do not infuse Tecartus if the information on the patient-specific cassette label does not match the intended patient's identity.
- ❖ General
  - Warnings and precautions of lymphodepleting chemotherapy must be considered.
- ❖ Monitoring after infusion
  - Patients must 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 infusion, the patient is to be monitored at the physician's discretion.
  - Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions must be considered depending on the severity of the reaction.
- ❖ Reasons to delay treatment
  - Due to the risks associated with Tecartus® treatment, infusion must be delayed if a patient has any of the following conditions:
    - Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies
    - Active uncontrolled infection or inflammatory disease.
    - Active GvHD.
  - In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen must be administered again.
- ❖ Serological testing
  - Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Tecartus®.
- ❖ Blood, organ, tissue and cell donation
- ❖ Patients treated with Tecartus® must not donate blood, organs, tissues, or cells for transplantation.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

ZUMA-3 NCT02614066	71 patients enrolled; 55 treated	after leukapheresis and conditioning chemotherapy, a single KTE-X19 infusion was administered at a target dose of 1×10^6 CAR T cells per kg bodyweight on day 0[2]	-	rate of overall complete remission or complete remission with incomplete haematological recovery by central assessment	**ongoing**[3], international, multicentre, single-arm, open-label, phase 2 study	-	Kite, a Gilead Company.	[7]

Efficacy; primary analysis data	**Safety;** primary analysis data
Complete remission or complete remission with incomplete haematological recovery by central assessment: 71% (95% CI, 57–82, p<0.0001), of whom 56% had complete remission. **Complete remission or complete remission with incomplete haematological recovery based on investigator assessment**: 73%, with 60% reaching complete remission. **Complete remission or complete remission with incomplete haematological recovery rates among most subgroups:** - patients aged 65 years or older: 100% - patients with one previous line of therapy: 90% - patients who previously received blinatumomab: 60% - patients who previously received pinotuzumab ozogamicin: 67% - patients who previously received allo-SCT: 70% **Median time to first complete remission or complete remission with incomplete haematological recovery in 39 patients with complete remission or complete remission with incomplete haematological recovery**: 1.1 months (IQR 1.0–1.9) **Complete remission or complete remission with incomplete haematological recovery by central assessment among all enrolled patients:** 55% **MRD negativity among all treated patients**: 76% (p<0.0001) **MRD negativity among responders**: 97% **Patients who received allo-SCT after KTE-X19 infusion** (at the discretion of the treating physician): 18% **Median time to allo-SCT after KTE-X19 infusion**: 98 days (IQR 72–134) **Median duration of remission both with and without censoring patients at subsequent allo-SCT**: 12.8 months (95% CI, 8.7–not estimable with censoring, 9.4–not estimable without censoring). **Patients with complete remission or complete remission with incomplete haematological recovery in ongoing remission at data cutoff:** 31% **Patients who proceeded to subsequent allo-SCT**: 23% **Patients who proceeded to other anticancer therapies**: 13% **Patients who relapsed**: 31%	**Serious AEs:** n=41/55 (75%) **CRS:** n=49/55 (89%) **CRS grade 3 or 4 cytokine release syndrome:** n=13/55 (24%) **Neurological events:** n=33/55 (60%) **Neurological events grade 3 or higher:** n=14/55 (25%) **Patients who had died as of the data cutoff date:** 36% (primarily from progressive disease (24%)) **Deaths due to grade 5 AEs other than acute lymphoblastic leukaemia:** n=6/55 (11%)[4]

[2] Patients with a bodyweight greater than 100 kg received a flat dose of 1×10^8 CAR T cells.

[3] The ZUMA-3 trial is currently ongoing; estimated study completion date is 11/2034.

[4] N=2 related to KTE-X19 (brain herniation, day 8 and septic shock, day 18) and n=4 unrelated to KTE-X19 treatment. One patient died due to another reason.

Patients who died: 3%
Median relapse-free survival both with and without censoring patients at subsequent allo-SCT: 11.6 months (2.7–15.5) in all treated patients and 14.2 months (11.6–not estimable) in responders
Relapse-free survival rate at 6 months: 58% (95% CI, 43–70)
OS rate at 12 months: 71% (57–82)
Median time to peak CAR T-cell levels in blood after KTE-X19 infusion: 15 days (IQR 11–16)
CAR T cells were no longer detectable by PCR in 79% of patients with evaluable samples at 6 months.
Median peak CAR T-cell level in blood: 40.47 cells per µL (IQR 6.04–76.70) among 29 evaluable patients with complete remission
Median OS: 22.4 months among responders
Median OS among responders: not reached

Patient-reported outcomes measured by EQ-5D-5L by month 3:

- The proportion of evaluable patients reporting no problems for each dimension was similar to or higher than at baseline.
- VAS scores were stable or improved after KTE-X19 infusion for the majority of evaluable patients across timepoints (79% at day 28, 92% at month 3, 80% at month 6, 70% of at month 9, and 93% at month 12).

ESMO-MCBS version 1.1 [9, 10][5]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because the primary endpoint "rate of overall complete remission or complete remission with incomplete haematological recovery" could not be assessed.											

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	unclear
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	unclear	yes
Overall risk of bias: low								

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Abbreviations: AE=adverse event, AJ=adjustment, allo-SCT=allogeneic stem-cell transplant, ALL=acute lymphoblastic leukaemia, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRS=cytokine release syndrome EMA=European Medicines Agency, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level 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, GvHD=graft-versus-host disease, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, Int.=intention, MCL=mantle cell

[5] **Disclaimer:** Though not finally validated, but feasibility tested in [10], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

lymphoma, MG=median gain, 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, SAE=serious adverse event, ST=standard treatment, VAS=visual analogue scale, TLS=tumuor lysis syndrome,

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