Lay summary

CTL019 is a new drug for treating acute lymphoblastic leukaemia (ALL), which is a cancer of white blood cells that starts in the bone marrow and develops quickly. It is the most common type of leukaemia to affect children and leads to anaemia, bruising, infections, fever and enlarged lymph nodes (glands). If CTL019 is licensed for use in the UK, it could offer a new treatment option for patients with this cancer that may help improve survival if initial treatments stop working.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- B-cell acute lymphoblastic leukaemia (ALL): relapsed or refractory; paediatric and young adult patients (aged 3 to 21 years) – at one of the following lines of therapy:
  - following second or greater bone marrow relapse,
  - following any bone marrow relapse after allogeneic stem cell transplantation (SCT) and must be ≥6 months from SCT,
  - for primary refractory disease, defined by not achieving a complete response after 2 cycles of standard chemotherapy regimens, or chemorefractory, defined by not achieving complete response after 1 cycle of standard chemotherapy for relapsed leukaemia,
  - for Philadelphia chromosome positive ALL, intolerant to or having failed 2 lines of tyrosine kinase inhibitor (TKI) therapy (or where TKI therapy is contraindicated),
  - for patients ineligible for allogeneic SCT.

TECHNOLOGY

DESCRIPTION

CTL019 (Tisagenlecleucel-T; LG740; CART-19; anti-CD19-CAR retroviral vector-transduced autologous T cells) is an autologous, targeted chimeric antigen receptor (CAR) T cell therapy. The therapy involves modifying the patient's own peripheral blood mononuclear cells with tumour antigen recognition and T-cell activation domains. The patient's cells are transduced with a gamma-retroviral vector encoding the CAR. Upon re-introduction into the patient, the cells are designed to become activated upon binding CD19. The activation induces T cell cytotoxic activity, which has the potential to selectively destroy CD19-expressing cells. CTL019 is intended for the treatment of B-cell ALL that is relapsed or refractory to chemotherapy or SCT. In the phase II clinical trial, a single dose of CTL019 is administered intravenously (IV)\(^1\). The dose has not been reported.

CTL019 does not currently have Marketing Authorisation in the EU for any indication.

CTL019 is also in phase II development for relapsed or refractory diffuse large B-cell lymphoma in adult patients.

INNOVATION and/or ADVANTAGES

If licensed, CTL019 will offer an additional treatment option for paediatric and young adult patients with relapsed or refractory B-cell ALL, a group who currently have a very poor prognosis.

DEVELOPER

Novartis Oncology.

AVAILABILITY, LAUNCH OR MARKETING

CTL019 for relapsed or refractory paediatric ALL was accepted into the EMA’s PRIME scheme in June 2016 and it was granted Breakthrough designation by the FDA in April 2016. It is in Phase II clinical trials.
PATIENT GROUP

BACKGROUND

ALL is a malignancy of lymphocytes and lymphocyte-producing cells. In patients with ALL, there is excess production of immature lymphocyte-precursor cells called blast cells, in the bone marrow. Eventually this overgrowth affects normal haemopoiesis and there is a reduction in the number of red cells, white cells and platelets in the blood\(^2\). The most common symptoms of ALL are:\(^3\):

- Anaemia, which results in fatigue and breathlessness.
- Low platelet counts, which may result in bruising and bleeding from mucous membranes and the gut.
- Low white cell counts, high numbers of abnormal cells and high metabolic rate, resulting in persistent infections and fever or lymphadenopathy.

ALL can be classified into three groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL, and T-cell ALL\(^4\). B-precursor ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22, and CD79a expression\(^5\).

CLINICAL NEED and BURDEN OF DISEASE

ALL is the only form of leukaemia that is more common in childhood (under 15 years of age)\(^3\), accounting for 75% of leukaemia diagnoses in paediatric patients\(^6\). The condition is characterised by a bimodal age pattern, with a peak incidence at one to four years of age and a second increase in incidence at ages over 60 years\(^7\). In England there were 654 new diagnoses of ALL (ICD-10 C91.0) registered in 2014\(^8\). In the same year there were 216 deaths due to ALL registered in England\(^9\). In 2014-15, there were 26,438 hospital admissions for ALL in England, resulting in 41,046 bed-days and 27,325 finished consultant episodes\(^10\). In childhood ALL, there is an overall survival rate of 80% at five years\(^11\). Approximately 20-25% of children will relapse following first line treatment\(^3\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

NHS England Policies and Guidance


Other Guidance

- European Society for Medical Oncology (ESMO). Acute Lymphoblastic Leukaemia. 201612.

CURRENT TREATMENT OPTIONS

Treatment for ALL aims to induce clinical remission (induction phase), target cells that are clinically undetectable (consolidation phase) and maintain the patient in remission (maintenance treatment). Additional CNS prophylaxis, which consists of concurrent chemotherapy, usually methotrexate, is also given throughout the entire period of treatment13,14. Patients typically receive chemotherapy for 2–3 years13,15. Children with CNS involvement at diagnosis may require cranial radiotherapy in addition to the above treatment regimen13.

Treatment of relapsed disease includes re-induction chemotherapy followed by an allogeneic stem cell transplant, where a suitably matched related or unrelated donor is found3. Cord blood transplantation or haploidentical transplantation offer possibilities for allogeneic transplant in the small number of patients in whom a suitable matched related or unrelated donor cannot be found3.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>ELIANA, NCT02435849, CCTL019B2202; CTL019; phase II.</th>
</tr>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry’.</td>
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<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada, Norway, Australia and Japan.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=78 (planned); aged 3-21 years; B-cell ALL; relapsed/refractory; bone marrow with ≥5% lymphoblasts; Karnofsky (age ≥16 years) or Lansky (age &lt;16 years) performance status ≥50.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Follow-up for five years.</td>
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<tr>
<td>Primary outcome</td>
<td>Overall remission rate.</td>
</tr>
</tbody>
</table>
Secondary outcomes | Duration of remission, complete response, relapse-free survival, event-free survival, overall survival, safety, pharmacokinetics, quality of life.
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Expected reporting date | Study completion date reported as Aug 2021.

### ESTIMATED COST and IMPACT

#### COST

The cost of CTL019 is not yet known.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- ☑ Reduced mortality/increased length of survival
- ☐ Other
- ☑ Reduced symptoms or disability
- ☐ No impact identified

**Impact on Health and Social Care Services**
- ☐ Increased use of existing services
- ☐ Re-organisation of existing services
- ☐ Other
- ☑ Decreased use of existing services
- ☑ Need for new services
- ☑ None identified

**Impact on Costs and Other Resource Use**
- ☐ Increased drug treatment costs
- ☐ Other increase in costs
- ☑ Other: uncertain unit cost compared to existing treatments
- ☑ Reduced drug treatment costs
- ☑ Other reduction in costs
- ☑ None identified

**Other Issues**
- ☐ Clinical uncertainty or other research question identified
- ☑ None identified

### REFERENCES


