

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

### Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

#### Final Scope

##### Remit /appraisal objective

To appraise the clinical and cost effectiveness of tisagenlecleucel-T within its marketing authorisation for treating relapsed or refractory B-cell acute lymphoblastic leukaemia..

##### Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL and T-cell ALL.<sup>1</sup> B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 3-7% of paediatric and young adults with ALL.<sup>2</sup>

ALL is most common in children, adolescents and young adults, with 68% of cases diagnosed in people aged under 25 years. A second increase in incidence is observed in people aged over 60 years. In England, 654 people were diagnosed with ALL, and 201 people died from ALL, in 2014.<sup>3</sup>

The aim of treatment in ALL is to achieve a cure. Treatment can take up to 3 years to complete and is generally divided into 3 phases; induction phase, consolidation and maintenance. The choice of chemotherapy regimen can depend on the phase and although selection of drugs, dose schedules and treatment duration may differ slightly between different subtypes of ALL, the basic treatment principles remain similar. During induction, newly diagnosed ALL in children and adults is generally treated with chemotherapy combinations including vincristine, an anthracycline and asparaginase. NICE technology appraisal guidance 408 recommends pegaspargase (a polyethylene glycol conjugate of E. coli-derived L-asparaginase) as part of antineoplastic combination therapy, as an option for treating ALL in children, young people and adults when they have untreated newly diagnosed disease. Targeted therapy with tyrosine kinase inhibitors (such as imatinib and dasatinib; no longer available through the Cancer Drugs Fund for the

treatment of ALL) can be used for treating Philadelphia-chromosome-positive ALL. During the consolidation phase, intensified chemotherapy is used, which may include high dose methotrexate with mercaptopurine, high dose asparaginase or a repeat of the induction therapy. During the maintenance phase, low dose chemotherapy is used, which typically consists of weekly methotrexate and daily mercaptopurine for an extended period of time to prevent relapse. For high risk ALL, stem cell transplantation and chemotherapy are both considered first line treatment options.<sup>4</sup>

Initial treatment is not effective in approximately 45% of people with newly diagnosed B-cell ALL. The overall survival rate at 5 years is approximately 10%.<sup>5</sup> Adults with relapsed or refractory B-cell ALL may have combination chemotherapy and for most people this would be fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) with idarubicin (FLAG-IDA). Clofarabine is sometimes used, but its marketing authorisation is only for children. It is available in England through the Cancer Drugs Fund (at the time the draft scope was written) for people with relapsed or refractory ALL 'with intent to use the treatment to bridge to bone marrow transplant. Adults with Philadelphia-chromosome-positive disease can have FLAG-based therapy with tyrosine kinase inhibitors or tyrosine kinase inhibitors alone. In adults with relapsed or refractory disease, NICE technology appraisals recommend:

- blinatumomab for Philadelphia-chromosome-negative precursor B-cell ALL (technology appraisal guidance 450)
- ponatinib for Philadelphia-chromosome-positive ALL with T315I gene mutation or for whom dasatinib or imatinib cannot be used (technology appraisal guidance 451).

Other treatment options may include stem cell transplantation if a suitable donor can be found, or best supportive care (including palliative care).

There is currently no NICE guidance on treating relapsed or refractory ALL in people who are younger than 18 years old. For people aged 18 to 21, the above NICE technology appraisal guidance applies. Possible treatment options for people who are younger than 18 years old may include FLAG. Clofarabine has a marketing authorisation in the UK as a treatment for ALL 'in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response'. The safety and efficacy of clofarabine have been assessed in studies of patients aged 21 years and younger at initial diagnosis. It is available in England through the Cancer Drugs Fund (at the time the draft scope was written) for people with relapsed or refractory ALL 'with intent to use the treatment to bridge to bone marrow transplant'. Stem cell transplantation (SCT) may be an option for children who relapse early or who have multiple relapses.

## The technology

Tisagenlecleucel-T (Kymriah, Novartis) is a chimeric antigen receptor (CAR) T cell therapy that changes the patient's T-cells to target a protein called CD19. When tisagenlecleucel-T binds to CD-19 expressing cells, the T-cell is activated to destroy the target cancer cell. It is administered as an intravenous infusion once only.

Tisagenlecleucel-T does not currently have a marketing authorisation in the UK for treating B-cell ALL. It is being studied in 2 single-arm clinical trials in people with relapsed or refractory B-cell ALL who were aged 3 to 21 years at initial diagnosis. Trial follow-up is 5 years. To be included in the trials, people must have received previous treatments for ALL and have either:

- second or greater bone marrow relapse, or
- had bone marrow relapse after allogeneic SCT and be 6 months or more from SCT at the time of tisagenlecleucel infusion, or
- primary refractory disease, defined by not achieving a complete response after 2 cycles of a standard chemotherapy regimen, or disease that is chemo-refractory, defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukaemia, or
- Philadelphia chromosome positive ALL that is intolerant to tyrosine kinase inhibitor (TKI) therapy or where 2 lines of TKI therapy has been unsuccessful, or
- disease that is ineligible for allogeneic SCT.

It is also being studied in another single arm trial, which recruited people age 1 to 24 years.

<b>Intervention(s)</b>	Tisagenlecleucel-T
<b>Population(s)</b>	People aged 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia

<b>Comparators</b>	<p>Established clinical management without tisagenlecleucel-T at one of the following lines of therapy:</p> <ul style="list-style-type: none"> <li>• Bone marrow relapse <ul style="list-style-type: none"> <li>○ following second or greater bone marrow relapse,</li> <li>○ following any bone marrow relapse, within 6 months or less, after allogeneic stem cell transplantation (SCT).</li> </ul> </li> <li>• primary refractory disease</li> <li>• Philadelphia chromosome positive ALL <ul style="list-style-type: none"> <li>○ intolerant to or having failed 2 lines of tyrosine kinase inhibitor (TKI) therapy (or where TKI therapy is contraindicated),</li> <li>○ patients ineligible for allogeneic SCT.</li> </ul> </li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival (including relapse-free and event-free survival)</li> <li>• response rate (including minimal residual disease and haematologic responses and complete remission)</li> <li>• rate of allogeneic stem cell transplant</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.</p>

<p><b>Other considerations</b></p>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<p><b>Related NICE recommendations and NICE Pathways</b></p>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">‘Pegaspargase for treating acute lymphoblastic leukaemia’</a> (2016). NICE Technology Appraisal 408. Review date September 2019.</p> <p>In adults only:</p> <p><a href="#">‘Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia’</a> (2017). NICE Technology Appraisal 451. Review date June 2020.</p> <p><a href="#">‘Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia’</a> (2017). NICE Technology Appraisal 450. Review date June 2020.</p> <p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">‘Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia’</a> NICE technology appraisals guidance [ID1008]. Publication expected February 2019.</p> <p><a href="#">‘Blinatumomab for acute lymphoblastic leukaemia’</a> NICE technology appraisals guidance [ID1036]. Publication expected November 2018.</p> <p><a href="#">‘Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia’</a> NICE technology appraisals guidance [ID893]. Publication date to be confirmed.</p> <p><a href="#">‘Leukaemia (acute lymphoblastic) - erythrocyte encapsulated asparaginase’</a> NICE technology appraisals guidance [ID864]. Suspended in 2016 because of delays in regulatory proceedings.</p> <p><a href="#">‘Nelarabine for treating acute lymphoblastic leukaemia after two therapies’</a> NICE technology appraisals guidance [ID1034]. Discontinued in 2016.</p> <p><a href="#">‘Clofarabine for treating acute lymphoblastic leukaemia in children after 2 therapies’</a> NICE technology appraisals guidance [ID1033]. Discontinued in 2016</p> <p><a href="#">‘Leukaemia (acute lymphoblastic) - dasatinib’</a> NICE</p>

	<p>technology appraisals guidance [ID386]. Discontinued 2008.</p> <p><b>Related Guidelines:</b></p> <p><a href="#">‘Haematological cancers: improving outcomes’</a> (2016). NICE Guideline 47. Review date to be confirmed.</p> <p>Related Quality Standards:</p> <p><a href="#">Haematological cancers</a> (2017) NICE quality standard 150.</p> <p>Related NICE Pathways:</p> <p><a href="#">Blood and bone marrow cancers</a> (2016) NICE pathway</p>
<p><b>Related National Policy</b></p>	<p>Department of Health (2016) <a href="#">NHS outcomes framework 2016 to 2017</a>: Domains 1–5.</p> <p>NHS England (2017) <a href="#">Next steps on the five year forward view</a></p> <p>NHS England (2017) <a href="#">Manual for Prescribed Specialised Services 2017/18</a>. Chapters 105 and 106.</p> <p>NHS England (2013) <a href="#">NHS standard contract for cancer: teenagers and young adults Section B Part 1 Service Specifications</a>. Clinical Commissioning Policy. Reference B17/S/a.</p> <p>NHS England (2013) <a href="#">NHS standard contract for cancer: Chemotherapy (Adult) Section B part 1 Service specifications</a>. Clinical Commissioning Policy. Reference B15/S/a.</p> <p>NHS England (2013) <a href="#">NHS standard contract for cancer: Chemotherapy (Children teenagers and young adults) Section B part 1 service specifications</a>. Clinical Commissioning Policy. Reference B15/S/b.</p> <p>NHS England Cancer Drugs Fund List:  <a href="https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-68.pdf">https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-68.pdf</a></p>

## References

1. Eden T (2017) [Acute Lymphoblastic Leukaemia](#). In: Warrell DA, Cox TM, Firth JD, editors. Oxford Textbook of Medicine. UK: Oxford University Press [accessed November 2017].
2. National Comprehensive Cancer Network (2017) NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukaemia. Version 1.

3. Cancer Research UK (2016) [Acute lymphoblastic leukaemia \(ALL\) incidence statistics](#) [accessed November 2017].
4. Macmillan Cancer Support (2016) [Treatment overview for acute lymphoblastic leukaemia](#) [accessed November 2017].
5. Oriol A, Vives S, Hernández-Rivas JM et al. (2010) [Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group](#). *Haematologica* 95(4):589–96.