NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of autologous anti-CD19-transduced CD3+ cells within its marketing authorisation for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults.

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 number 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. In adults, around 75-80% of ALL cases are classified as B-precursor ALL.[1] B-precursor 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 20 to 30% of adults with ALL.[2]

ALL is most common in children, adolescents and young adults, with around 65% of cases diagnosed in people aged under 25.[3] A second increase in incidence is observed in people aged over 60 (around 13% of cases).[3] It is also more common in men (around 6 out of 10 cases) than women.[3] In the UK, around 350 cases of ALL are diagnosed in adults each year.[4]

The aim of treatment in ALL is to achieve a cure. Treatment for newly diagnosed ALL can take up to 3 years to complete and is generally divided into 3 phases: induction, consolidation and maintenance.

During induction, newly diagnosed ALL is generally treated with chemotherapy combinations including prednisolone, vincristine, an anthracycline and asparaginase. Consolidation treatment typically includes intensified chemotherapy, followed by low-dose chemotherapy in the maintenance phase. A tyrosine kinase inhibitor (such as imatinib or dasatinib) would also be offered to people with Philadelphia-chromosome-positive ALL at all phases of treatment (i.e., in addition to induction, consolidation and maintenance therapy).

Around 45% of ALL relapses after or becomes refractory to initial treatment and requires further treatment.[5] There is no universally accepted treatment approach for relapsed or refractory ALL.[6] Treatment may include conventional combination chemotherapy and for most people this would be fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) with idarubicin. Adults with Philadelphia-chromosome-positive relapsed or refractory disease can have a tyrosine kinase inhibitor alone or in combination with conventional chemotherapy.

In adults with relapsed or refractory disease, the following NICE technology appraisal (TA) guidance is relevant:

- TA450 recommends blinatumomab as an option for Philadelphia-chromosome-negative relapsed or refractory precursor B-cell ALL in adults
- TA451 recommends ponatinib as an option for Philadelphia-chromosome-positive ALL in adults with the T315I gene mutation or for whom dasatinib or imatinib cannot be used
- TA541 recommends inotuzumab ozogamicin as an option for treating relapsed or refractory CD22-positive B-cell precursor ALL in adults
- TA554 recommends tisagenlecleucel therapy for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell ALL in people aged up to 25.

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

The technology

Autologous anti-CD19-transduced CD3+ cells (Tecartus, Kite, a Gilead company) is a type of immunotherapy that uses autologous T cells directed against the tumour antigen CD19. The technology is administered intravenously as a single infusion.

The technology does not currently have a marketing authorisation in the UK for treating B-precursor ALL. It is being studied in a single-arm open-label clinical trial (ZUMA-3) in adults with relapsed or refractory B-precursor ALL, after administration of a conditioning chemotherapy regimen of fludarabine and cyclophosphamide.

Intervention(s)	Autologous anti-CD19-transduced CD3+ cells
Population(s)	Adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia
Comparators	• Philadelphia-chromosome-negative ALL: ○ fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy ○ inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ blinatumomab • Philadelphia-chromosome-positive ALL: ○ inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ a tyrosine kinase inhibitor (such as imatinib, dasatinib or ponatinib), alone or in combination with FLAG-based combination chemotherapy • Best supportive care (including palliative care)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • treatment response rate (including minimal residual disease, haematologic responses and complete remission) • rate of allogeneic stem cell transplant • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	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.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma (2021) NICE technology appraisal guidance 677 Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (2018) NICE technology appraisal guidance 554 Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (2018) NICE technology appraisal guidance 541 Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 451

	Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 450 **Terminated appraisals:** Nelarabine for treating acute lymphoblastic leukaemia after two therapies NICE technology appraisal guidance [ID1034] Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia in adults and children after treatment with Escherichia coli derived asparaginase NICE technology appraisal guidance [ID864] Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia NICE technology appraisal guidance [ID1008] **Appraisals in development (including suspended appraisals):** KTE-X19 for previously treated B-precursor acute lymphoblastic leukaemia in people aged 2 to 21 NICE technology appraisal guidance [ID1336]. Publication date to be confirmed. Dasatinib for treating Philadelphia-chromosome-positive acute lymphoblastic leukaemia in children and adults NICE technology appraisal guidance [ID1297]. Suspended June 2021. **Related Guidelines:** Haematological cancers: improving outcomes (2016) NICE guideline NG47 **Related Quality Standards:** Haematological cancers (2017) NICE quality standard 150 **Related NICE Pathways:** Blood and bone marrow cancers (2019) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapters 105 and 106. Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1-5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Department of Health (2016) NHS outcomes framework 2016 to 2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy

	for cancer Department of Health (2009) Cancer commissioning guidance

References

1. Leukaemia Foundation. Acute lymphoblastic leukaemia. Accessed June 2021.

2. Cancer Research UK. Research into acute lymphoblastic leukaemia. Accessed June 2021.

3. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) statistics. Accessed June 2021.

4. Leukaemia Care. Acute Lymphoblastic Leukaemia (ALL). Accessed June 2021.

5. Fielding AK, Richards SM, Chopra R et al. (2007) Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 109(3):944-50.

6. BMJ Best Practice. Acute lymphocytic leukaemia. Accessed June 2021.