NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

KTE-X19 for previously treated B-precursor acute lymphoblastic leukaemia in adults

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of KTE-X19 within its marketing authorisation for previously treated B-precursor 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 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 England, 666 people were diagnosed with ALL in 2017 and 232 people died from ALL in 2018.[3]

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 may also be offered to people with Philadelphia-chromosome-positive ALL.

Around 45% of ALL relapses after or becomes refractory to initial treatment, and requires further treatment.[4] This may include combination chemotherapy and for most people this would be fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) with idarubicin. Adults with Philadelphia-chromosome-positive disease can have tyrosine kinase inhibitors (such as imatinib or dasatinib) alone or in combination with FLAG-based chemotherapy. Other treatment options may include stem cell transplantation if a suitable donor can be found, or best supportive care (including palliative care).

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 years.

The technology

KTE-X19 (brand name unknown, Kite, a Gilead company) is a type of immunotherapy that uses autologous T cells directed against the tumour antigen CD19. It is administered intravenously as a single infusion.

KTE-X19 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)	KTE-X19
Population(s)	Adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia

Comparators	For people who are able to take chemotherapy and have • Philadelphia-chromosome-negative ALL: o fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy o inotuzumab ozogamicin (CD22-positive B-precursor ALL) o blinatumomab • Philadelphia-chromosome-positive ALL: o imatinib or dasatinib alone or in combination with FLAG-based chemotherapy o inotuzumab ozogamicin (CD22-positive B-precursor ALL) o ponatinib For people who are unable to take 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:** 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]. Publication date to be confirmed. **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

Questions for consultation

Have all relevant comparators for KTE-X19 been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory B-precursor acute lymphoblastic leukaemia? In particular:

- Are imatinib or dasatinib (used alone or in combination with chemotherapy) relevant comparators?
- Is clofarabine-based chemotherapy a relevant comparator?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom KTE-X19 is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider KTE-X19 will fit into the existing NICE pathway Blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which KTE-X19 will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider KTE-X19 to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of KTE-X19 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

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

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

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

4. 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.