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KTE-C19 for relapsed/refractory B-precursor acute lymphocytic leukaemia in adults

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LAY SUMMARY

Acute Lymphocytic Leukaemia (ALL) is a type of cancer affecting lymphocytes (a type of white blood cell), which results in overproduction of faulty lymphocytes. The cancer cells take over the bone marrow leading to anaemia, infection, bruising and bleeding. ALL is a rare condition, usually affecting more children than adults. Some people will not respond to treatment (refractory) or some will respond to treatment but develop ALL again (relapsed). For those with relapsed or refractory ALL, there are limited treatments available.

KTE-C19 is new type of therapy where T-cells (a type of immune white blood cell) are collected from a patient and engineered to be able to recognise molecules on the surface of cancer cells, which triggers the T-cells to attack and kill the cancer cells. KTE-C19 is given to patients by a single infusion. If KTE-C19 is licenced for use in adults with refractory/relapsed acute lymphoblastic leukaemia, it will provide an additional, cancer-specific treatment option for this population who currently have limited treatment options.

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TARGET GROUP

Acute Lymphocytic Leukaemia (B-precursor, relapsed/refractory)

TECHNOLOGY

DESCRIPTION

KTE-C19 (Anti-CD19 CAR T-cell therapy) is a therapy comprised of genetically engineered autologous T-cells with anti-CD19 Chimeric Antigen Receptors (CARs). The CAR consists of an antibody fragment (or target binding domain) which allows the CAR to recognise CD19, which is present on the surface of cancer cells, and signalling domains which activate the T-cells to attack and kill the cancer cells.[1] KTE-C19 is intended for use in the treatment of various cancers that express CD19.

In the phase I/II clinical trial, ZUMA-3 (NCT02614066), a conditioning chemotherapy regime of fludarabine and cyclophosphamide was administered, followed by a single infusion of CAR transduced autologous T cells (KTE-C19) administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg.[2]

KTE-C19 does not currently have Marketing Authorisation in the EU for any indication.

Axicabtagene ciloleucel, another anti-CD19 CAR-T with the same CAR construct but manufactured by a slightly different process, is currently in pre-registration in the EU for use in Diffuse Large B-cell Lymphoma, Primary Mediastinal B-cell Lymphoma, and transformed Follicular Lymphoma.[3]

INNOVATION and/or ADVANTAGES

As a targeted immunotherapy, KTE-C19 may have the potential to improve remission rates in adults with relapsed or refractory B-precursor Acute Lymphocytic Leukaemia (ALL) after second or later lines of therapy or after transplant. This is especially important in the adult population where there are poor overall survival rates in comparison to children.[4]

If licensed, KTE-C19 will offer an additional treatment option for adults with relapsed or refractory ALL, for which there are few available treatments.

DEVELOPER

Kite (a Gilead Sciences Ltd owned company)

REGULATORY INFORMATION/ MARKETING PLANS

KTE-C19 is a designated orphan drug in the EU and USA for the treatment of acute lymphoblastic leukaemia.[5] [6]

PATIENT GROUP

BACKGROUND

Acute lymphoblastic leukaemia, also known as acute lymphocytic leukaemia (ALL) is a fast growing type of blood cancer that starts from young white blood cells called lymphocytes in the bone marrow (the soft inner parts of the bones, where new blood cells are made). Normal lymphoblast cells can become either B lymphocytes, T lymphocytes or Natural Killer Cells, but in ALL there is uncontrolled growth of immature white blood cells (blast cells). These immature cells are unable to fight infections as well as mature white blood cells, leaving the individual vulnerable to infection. They fill up the bone marrow, meaning there is not adequate space to make sufficient numbers of healthy white blood cells, red blood cells and platelets. This type of cancer usually develops quickly over days or weeks and is the most common type of leukaemia to affect children, but can also affect adults.[7, 8, 9] There are two types of ALL: B-precursor lymphocytic leukaemia, the most common type, and T-precursor lymphocytic leukaemia.[8] In B-precursor ALL, too many B-cell lymphoblasts (immature B cells) are produced.[10]

It is not known what causes ALL but exposure to certain risk factors can increase the likelihood of developing the disease. Risk factors include: radiation exposure, previous chemotherapy (including etoposide, mitoxantrone, amsacrine and idarubicin); presence of certain genetic disorders (including Down's syndrome, fanconi anaemia and ataxia telangiectasia); various environmental factors (including smoking and being overweight or obese); and having a weakened immune system (as a result of HIV/AIDS or from taking immunosuppressants).[8, 11]

ALL develops quickly over days or weeks.[7] The symptoms of ALL are vague and non-specific, resembling the symptoms of flu. The symptoms of ALL are caused when there are too many abnormal white blood cells (in the case of B-precursor ALL, B lymphocytes) and too few normal red and white blood cells and platelets. Symptoms include general weakness, fatigue, fever, frequent infections, bruising or bleeding easily, weight loss, swollen lymph nodes, pain in the bones or joints, shortness of breath, feeling of fullness or discomfort in the abdomen and pale skin.[12]

CLINICAL NEED and BURDEN OF DISEASE

ALL is a rare condition, with 832 new cases of ALL occurring in the UK in 2015. The incidence of ALL is strongly related to age, dropping sharply after childhood and reaching its lowest point at 30-34 years old in males (at an incidence rate of 0.5 per 100,000) and 35-39 years old in women (at an incidence rate of 0.2 per 100,000) in the UK in 2015. From this lowest point, incidence slightly increases with incidence reaching 1 per 100,000 in men and women at age 70-74 years in the UK in 2015. In the UK in 2013-2014, there were 175 new ALL cases reported in men aged over 20 years and 142 new ALL cases reported in women aged over 20 years.[13]

The five year survival rate for ALL in England between 2008 and 2010 was 70%. However this survival rate varied according to age:[14]

- Five year survival rate of 70% for 15 – 24 year olds
- Five year survival rate of 40% for 25 – 64 year olds
- Five year survival rate of 15% for over 65 year olds

ALL accounts for less than 1% of all cancer deaths in the UK, with 201 deaths (equating to a mortality rate of 0.4 per 100,000) occurring due to ALL in England in 2014. Mortality is strongly related to age, with the highest mortality rates seen in older people. In the UK in 2012-2014, 47% of deaths due to ALL were in people aged 60 years and older. The highest mortality rates in the UK in 2012-2014 were seen in the 85-80 year old age group for men (with a mortality rate of 1.5 per 100,000) and 80 to 84 year old in women (with a mortality rate of 0.8 per 100,000).[15]

According to HES for England in 2016-17, there were 31,098 admissions and 32,449 finished consultant episodes for acute lymphocytic leukaemia (ICD 10: C91.0) and there were 32,449 people aged 18 years and above diagnosed with ALL.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.
- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). NHS England 16068/P. February 2017.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. NHS England B04/P/a. January 2015.

OTHER GUIDANCE

National Comprehensive Cancer Network. *Acute Lymphoblastic Leukaemia.* 2017.[17]

European Society for Medical Oncology (EMSO). *Acute Lymphoblastic Leukaemia: EMSO Clinical Practice Guidelines*. 2016.[18]

CURRENT TREATMENT OPTIONS

Treatment of ALL is usually split into different phases, which briefly include:[19, 20, 21, 22]

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.[19] There are two chemotherapy drugs recommended for the treatment of relapsed or refractory B-precursor ALL in adults by NICE:[23]

- 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)

EFFICACY and SAFETY

Trial	ZUMA-3, NCT02614066, EudraCT-2015-005009-35; KTE-C19; phase I/II
Sponsor	Kite, A Gilead Company
Status	ongoing - recruiting
Source of Information	trial registry[2]
Location	USA
Design	non-randomised, uncontrolled, multicentre
Participants	n=75 (planned); aged 18 years and older; B-precursor acute lymphoblastic leukaemia; relapsed or refractory
Schedule	All participants are allocated to the treatment arm of a conditioning chemotherapy regimen of fludarabine and cyclophosphamide followed by a single infusion of CAR transduced autologous T cells (KTE-C19), administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg
Follow-up	Treatment – single infusion Follow up – 12 months
Primary Outcomes	1. Phase 1: Safety - incidence of adverse events defined as dose-limiting toxicities (DLT) [Time Frame: 30 Days] 2. Phase 2 - Overall complete remission rate [Time Frame: 8 weeks]
Secondary Outcomes	1. Duration of Remission [Time Frame: 12 Months] 2. Minimum Residual Disease Negative Remission Rate [Time Frame: 8 Weeks] 3. Allogeneic Stem Cell Transplant Rate [Time Frame: 12 Months] 4. Overall Survival [Time Frame: 12 Months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as March 2019.

ESTIMATED COST and IMPACT

COST

The cost of KTE-C19 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: *new staff training requirements,*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: *additional staff training required, additional costs for preparation of patients cells*

☒ Other reduction in costs: *as a one off treatment this potentially reduces the need for further treatments for refractory/relapsed disease*

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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