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HEALTH TECHNOLOGY BRIEFING
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Axicabtagene ciloleucel for relapsed/refractory indolent non-Hodgkin lymphoma

NIHRIO ID	14980	**NICE ID**	10013
Developer/Company	Gilead Sciences Ltd	**UKPS ID**	652100

Licensing and market availability plans	Currently in phase II trials.

SUMMARY

Axicabtagene ciloleucel is in clinical development as treatment for adult patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL). In NHL, the affected lymphocytes start to multiply in an abnormal way and begin to collect in certain parts of the body, such as the lymph nodes. Indolent, or low grade NHL tends to grow very slowly. Types of low-grade NHL include follicular and marginal zone lymphoma. Relapse means that the lymphoma has come back after going into complete remission. Lymphoma that does not go into remission with treatment is known as refractory lymphoma. Treatment options for relapsed/refractory indolent NHL after two priori treatments are limited.

Axicabtagene ciloleucel is an advanced therapy that contains the patient's own white blood cell (T-cells) that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). The CAR T-cells attach to another protein on the surface of cancer cells and causing the cells to die. If licensed, axicabtagene ciloleucel will offer an additional treatment for patients with relapsed/refractory indolent NHL including follicular and marginal zone lymphoma.

PROPOSED INDICATION

Treatment of adult patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL).[1,a]

TECHNOLOGY

DESCRIPTION

Axicabtagene ciloleucel (Yescarta, KTE-C19) is an engineered autologous T-cell immunotherapy product, which binds to CD19 expressing cancer cells and normal B-cells. Following anti-CD19 chimeric antigen receptor T-cell (CAR T) engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19 expressing target cells.[2]

Axicabtagene ciloleucel is in clinical development for relapsed/refractory indolent NHL as treatment in the third-line or greater setting. In the phase II clinical trial (ZUMA-5; NCT03105336), treatment consists of lymphodepleting chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine on days 5, 4, and 3 prior to a target of a single infusion of axicabtagene ciloleucel, 2 x 10^6 CAR T-cells/kg infusion on day 0.[1,3]

INNOVATION AND/OR ADVANTAGES

Axicabtagene ciloleucel is the first CAR T therapy for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (NHL), accounting for three out of every five cases.[4]

In contrast to cytoreductive therapy, the decrease in tumour burden is not as rapid, but sustained after a single dose infusion of axicabtagene. Although CAR T-cells have the potential to cause serious toxicities such as cytokine release syndrome and neurotoxicity, the targeted action of axicabtagene ciloleucel against CD19 limits additional adverse effects related to the damage of healthy cells to on-target off-tumour effects.[5]

Axicabtagene ciloleucel is an advanced therapy medicinal product (ATMP) within the definition of a gene therapy. The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Axicabtagene ciloleucel is indicated in the UK for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.[2]

The most serious and frequently occurring adverse reactions are cytokine release syndrome, encephalopathy, and infections. In a single arm study, serious adverse reactions occurred in 55% of patients. The most common serious adverse reactions include encephalopathy, unspecified pathogen infections, bacterial infections, viral infections, pyrexia, and febrile neutropenia.[2]

[a] Information provided by Gilead Sciences Ltd

Axicabtagene ciloleucel is in phase III clinical development for diffuse large B-cell lymphoma.[7]

Axicabtagene ciloleucel is in phase II clinical development for large B-cell lymphoma, acute lymphoblastic leukaemia and chronic lymphocytic lymphoma.[8]

Axicabtagene ciloleucel was granted EU orphan designation in November 2015 for the treatment of follicular lymphoma.[9]

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer of the lymphatic system. The lymphatic system is a system of lymphatic vessels and lymph nodes that run throughout the body. Tissue fluid called lymph circulates around the body in these vessels and flows through the lymph nodes. The lymphatic system is an important part of our immune system. It plays a role in fighting bacteria and other infections and it tries to destroy old or abnormal cells, such as cancer cells.[10]

There are 2 main types of lymphoma. They are called Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[10] In NHL, the affected lymphocytes start to multiply in an abnormal way and begin to collect in certain parts of the lymphatic system, such as the lymph nodes.[11]

NHL is grouped into 2 grades; low grade and high grade. Low grade NHL tends to grow very slowly and is called indolent lymphoma. Types of low-grade NHL include follicular and marginal zone lymphoma. Follicular lymphoma is the most common type of low grade lymphoma. It mainly affects adults over the age of 60 years. Marginal zone lymphoma is called so since it starts in an area of lymphoid tissue called the marginal zone.[12]

Lymphoma can sometimes come back after successful treatment. This is called relapse. Relapse means that the lymphoma has come back after going into complete remission (no evidence of lymphoma). In the case of indolent NHL, it might mean the lymphoma has flared up after being stable for some time. Lymphoma that does not go into remission with treatment is known as refractory lymphoma. Other treatments may be more successful. Refractory lymphoma is often treated in the same way as relapsed lymphoma.[13]

Symptoms of NHL include enlarged lymph nodes, night sweats, fever that comes and goes, weight loss, unexplained itching, enlarged tonsils, lump in the abdomen and breathlessness.[10] The exact cause of non-Hodgkin lymphoma is unknown, however, the risk of developing the condition is increased if a person has a medical condition that weakens the immune system, taking immunosuppressant medication, exposed to a common virus called the Epstein-Barr virus. The risk of developing NHL also increases if a first-degree relative (such as a parent or sibling) has had the condition.[11]

CLINICAL NEED AND BURDEN OF DISEASE

The latest available Cancer Registration Statistics, England, 2017-18 shows 12,065 newly diagnosed cases of NHL (ICD-10 code C82 – C85) for all ages. Out of these 2,168 have follicular lymphoma which is about 18% of the total number of new cases.[12,14]

According to the 2017-18 Hospital Episodes Statistics data, there were 21,961 and 1,981 admissions which led to 19,916 and 1,807 day cases, and 12,809 and 871 bed days due to follicular lymphoma and marginal zone NHL (ICD-10 code: C82 and C88.5).[15]

According to the Haematological Malignancy Research Network, in 2016, the number of people with marginal zone lymphoma per year and follicular lymphoma per year in the UK was estimated to be 2,730 and 2,220 respectively.[16]

Overall, for non-Hodgkin Lymphoma (ICD-10 code C82-C86) European age-standardised incidence rates are projected to decrease from 32.45 per 100,000 in 2014 to 31.56 per 100,000 in 2035 in males, and from 22.67 per 100,000 in 2014 to 21.92 per 100,000 in 2035 in females.[17]

In England in 2017, there were a total of 4,096 registrations of deaths due to NHL (ICD-10 code: C82-C85). Of these, 202 were due to follicular lymphoma.[14]

The age-standardised one-year and five-year survival rates for NHL (all subtypes combined) in England over the period 2012 and 2016 show that 78% of men are expected to survive for at least 1 year, with almost 64% surviving 5 years or more. The survival rates for women are slightly higher with 80% expected to live for 1 year and almost 69% for at least 5 years.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main types of treatment for NHL involve chemotherapy, targeted cancer drugs and radiotherapy. Other treatments may include stem cell transplant and surgery.[19]

For relapsed/refractory follicular lymphoma, European Society of Medical Oncology (ESMO) guidelines recommend to obtain a new biopsy in order to exclude transformation into an aggressive lymphoma. At first presentation, observation is an accepted approach in asymptomatic patients with low tumour burden. Selection of salvage treatment depends on efficacy of prior regimens.[20]

CURRENT TREATMENT OPTIONS

According to ESMO guidelines, in early relapses of asymptomatic cases in follicular lymphoma, a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), or vice versa). In symptomatic cases with low tumour burden, rituximab monotherapy may be applied.[20]

PLACE OF TECHNOLOGY

If licensed, axicabtagene ciloleucel will offer an additional treatment option for patients with relapsed/refractory indolent NHL.

CLINICAL TRIAL INFORMATION

Trial	**ZUMA-5, NCT03105336, EudraCT-2017-001912-13, KTE-C19-105; pts aged 18 yrs and older; axicabtagene ciloleucel; phase II**
Sponsor	Kite, A Gilead Company
Status	Ongoing

Source of Information	Trial registry;[1,21] Presentation[3]
Location	EU countries [not incl UK] and USA
Design	Single group assignment, open label
Participants	n=160 (planned); aged 18 yrs and older; relapsed/refractory after two lines of treatment, indolent NHL, follicular lymphoma, marginal zone lymphoma
Schedule	Treatment consists of a single shot of lymphodepleting chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine on day -5, day -4, day -3 followed by a target of 2 x 10^6 CAR T-cells/kg on day 0.[b]
Follow-up	Follow-up 15 yrs
Primary Outcomes	Objective response rate per central read [Time frame: Up to 15 yrs]
Secondary Outcomes	• CR Rate per central read [Time frame: Up to 15 yrs] • DOR [Time frame: Up to 15 yrs] • PFS [Time frame: Up to 15 yrs] • Percentage of Participants Experiencing Treatment-Emergent Adverse Events [Time frame: Up to 2 yrs] • Overall Survival (OS) [Time frame: Up to 15 yrs] • Levels of anti-CD19 CAR T-cells in blood [Time frame: At enrolment, day 7, wk 2, wk 4, mth 3, mth 6, mth 12, mth 18, mth 24, annually up to yr 5] • Levels of cytokines in serum [Time frame: At enrolment, prior to axicabtagene ciloleucel infusion on day 0, day 3, day 7, wk 2, wk 4] • Percentage of participants experiencing anti-axicabtagene antibodies [Time frame: At enrolment, wk 4, mth 3, every 3 mths up to mth 12] • Percentage of participants experiencing clinically significant changes in lab values [Time frame: Up to 5 yrs]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Mar 2020

ESTIMATED COST

Axicabtagene ciloleucel is already marketed in the UK for relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.[2]

The company has an agreement with the NHS. This makes axicabtagene ciloleucel available to the NHS with a discount. More evidence on axicabtagene ciloleucel is being collected, until around February 2022. After this, NICE will decide whether or not to recommend it for use on the NHS and update the guidance. It will be available through the Cancer Drugs Fund until then.[22]

[b] Information provided by Gilead Sciences Ltd

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Lenalidomide for previously treated follicular lymphoma and marginal zone lymphoma (GID-TA10323). Expected date of publication: TBC.
- NICE technology appraisal guidance in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (GID-TA10223). Expected date of publication: TBC.
- NICE technology appraisal guidance in development. Idelalisib for treating follicular lymphoma refractory to 2 treatments. Expected date of publication: TBC.
- NICE technology appraisal guidance in development. Duvelisib for treating relapsed follicular lymphoma after 2 systemic therapies. Expected date of publication: TBC.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016.
- NICE Quality Standards. Haematological cancers (QS150). 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevance guidance found.

OTHER GUIDANCE

- European Society of Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[20]
- London Cancer. Guidelines for the management of non-Hodgkin's and Hodgkin's lymphoma in adults. 2015.[23]
- Belgian Hematology Society. BHS guidelines for the treatment of marginal zone lymphomas. 2014.[24]
- European Society of Medical Oncology. ESMO Consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. 2013.[25]

ADDITIONAL INFORMATION

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