

## HEALTH TECHNOLOGY BRIEFING AUGUST 2019

### Axicabtagene ciloleucel for relapsed/refractory diffuse large B-cell lymphoma – second-line

<b>NIHRIO ID</b>	23801	<b>NICE ID</b>	10038
<b>Developer/Company</b>	Gilead Sciences Ltd	<b>UKPS ID</b>	652099

#### Licensing and market availability plans

Currently in phase III clinical trials.

### SUMMARY

Axicabtagene ciloleucel is in clinical development as second-line treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). DLBCL is a cancer affecting a type of white blood cells called lymphocytes or B-cells. DLBCL is an aggressive cancer and although it can be cured in more than half of people affected, it remains a serious and life threatening disease. A relapse is when the lymphoma comes back after successful treatment and refractory means the lymphoma did not respond to the first course of treatment.

Axicabtagene ciloleucel contains the patient's own T-cells (a type of white blood cell) that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). CAR can attach to another protein on the surface of cancer cells and kill the cancer cells. If licensed, axicabtagene ciloleucel will offer an additional second-line treatment option for adult patients with relapsed or refractory DLBCL.

*This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.*

## PROPOSED INDICATION

Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) – second-line.<sup>1,a</sup>

## 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.<sup>2</sup>

Axicabtagene ciloleucel is in clinical development for relapsed or refractory DLBCL. In the phase III trial (ZUMA-7, NCT03391466), patients will undergo leukapheresis, then lymphodepleting chemotherapy (fludarabine 30 mg/m<sup>2</sup>/d and cyclophosphamide 500 mg/m<sup>2</sup>/d for 3 d), followed by a single infusion of axicabtagene ciloleucel at 2 × 10<sup>6</sup> CAR T cells/kg. Corticosteroid bridging therapy is allowed for patients with high disease burden at screening.<sup>1,3</sup>

### INNOVATION AND/OR ADVANTAGES

Axicabtagene ciloleucel is the first chimeric antigen receptor T-cell (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.<sup>4</sup>

Currently for patients with DLBCL who fail first-line therapy, the only potentially curative treatment is salvage chemotherapy followed by autologous stem cell transplant.<sup>3</sup> In contrast to cytoreductive therapy, the decrease in tumour burden is not as rapid, but sustained after a single dose infusion. 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.<sup>5</sup> Axicabtagene ciloleucel represents a new and potentially curative treatment option for B-cell lymphoma. It is expected to have long-term survival benefits; however, long-term survival data are limited.<sup>6</sup>

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).<sup>7</sup>

### 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.<sup>2</sup>

<sup>a</sup> Information provided by Gilead Sciences Ltd on UK PharmaScan

The most serious and frequently occurring adverse reactions are cytokine release syndrome, encephalopathy, and infections. The most common serious adverse reactions include encephalopathy, unspecified pathogen infections, bacterial infections, viral infections, pyrexia, and febrile neutropenia.<sup>2</sup>

Axicabtagene ciloleucel is in phase II clinical development for non-Hodgkin's lymphoma (including mantle cell lymphoma), acute lymphoblastic leukaemia and chronic lymphocytic lymphoma.<sup>8</sup>

Axicabtagene ciloleucel was granted EU orphan drug designation for the treatment of DLBCL in December 2014.<sup>9</sup>

Axicabtagene ciloleucel was granted EU PRIME designation for the treatment of DLBCL in May 2016.<sup>4,10</sup>

## 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.<sup>11</sup>

There are 2 main types of lymphoma. They are called Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).<sup>11</sup> 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.<sup>12</sup>

Diffuse large B-cell lymphoma (DLBCL) is the most common high grade variant on NHL.<sup>13</sup> DLBCL develops from abnormal mature B-cells. The abnormal cells are larger than normal, healthy B-cells, and are spread diffusely throughout the tumour, wiping out the normal structure of the lymph node. The causes of lymphoma are not known, but most people diagnosed with DLBCL are aged 65 years and over, and the disease affects slightly more men than women.<sup>14</sup>

The first symptoms of DLBCL are usually painless lumps, often in the neck, armpit or groin, which are enlarged lymph nodes. DLBCL can also develop in lymph nodes deep inside the body which cannot be felt from the outside. DLBCL can be hard to diagnose as people have different symptoms depending what organs and tissues are affected, but diagnosis can be confirmed by a biopsy. Stage I and II are 'early-stage' DLBCL. 'Advanced-stage' DLBCL is stage III and stage IV. Most people have advanced-stage DLBCL when they are diagnosed.<sup>14</sup>

A relapse is when the lymphoma comes back after successful treatment and refractory means the lymphoma did not respond to the first course of treatment. Relapse is more likely to happen within the first 2 years after treatment. As time goes on, relapse generally becomes less likely.<sup>15</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

The latest available Cancer Registration Statistics, England, 2017 shows 4,816 newly diagnosed cases of large cell (diffuse) non-Hodgkin's lymphoma (ICD-10 code C83.3) for all

ages.<sup>16</sup> For hospital activity, in 2017/18 there were 39,004 finished consultant episodes, 35,148 admissions with primary diagnosis of DLBCL (ICD-10 code C83.3), resulting in 85,833 bed days and 27,918 day cases.<sup>17</sup>

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.<sup>18</sup>

In England in 2017, there were a total of 1,105 registrations of death due to diffuse non-Hodgkin's lymphoma (ICD-10 code C83),<sup>16</sup>

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 about 81% expected to live for 1 year and almost 69% for at least 5 years.<sup>19</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

DLBCL is an aggressive cancer that needs immediate treatment. The aim of treatment (first-line) in most patients is complete remission and cure.<sup>20</sup> However, when the cancer has relapsed after the first treatment the ESMO consensus guidance on how to predict, prevent and treat early central nervous system relapse after first-line treatment of DLBCL has made the following recommendations:<sup>21</sup>

- International Prognostic Index (IPI) parameters (age >60 years, high lactate dehydrogenase (LDH) levels, poor performance status (PS), advanced disease stage and more than one extranodal site) are risk factors for early CNS relapse following first-line treatment of DLBCL, with a direct relationship between the number of unfavourable features and the CNS risk. The involvement of the testes, kidneys, adrenals, breast, bone marrow and bone has also been reported to increase the risk of CNS disease.
- Patients with DLBCL considered as high risk for CNS relapse should be assessed by brain MRI and CSF assessment by conventional cytology examination and flow cytometry.
- There is little or no role for intrathecal (i.t.) chemotherapy for patients with DLBCL considered as high risk for CNS relapse. Intravenous (i.v.) prophylaxis is an option for high-risk patients without evidence of CNS involvement, even though the level of supporting evidence is low. Patients with MRI or CSF evidence of CNS involvement at presentation should receive a combination of anti-lymphoma drugs with good CNS bioavailability, aimed at controlling both CNS and systemic disease, preferably within a clinical trial.

A combination of chemotherapy and the monoclonal antibody rituximab (Rituxan), with or without radiation therapy, can lead to disease remission in a large number of patients with this form of lymphoma.<sup>22</sup> Salvage therapy with multi-agent immunochemotherapy may be offered to people with relapsed or refractory DLBCL who are fit enough to tolerate intensive therapy. Autologous stem cell transplantation may be offered to people with chemosensitive DLBCL who are fit enough for transplantation.<sup>23</sup>

### CURRENT TREATMENT OPTIONS

In the UK, the most widely used treatment for DLBCL presently is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The R-

CHOP regimen is usually given in 21-day cycles (once every 21 days) for an average of 6 cycles. However, the length and number of cycles given can vary based on the patient's individual disease and health status. In certain cases 14-day cycles may be used, and for limited stage disease (Stage I or II) 3-4 cycles may be used followed by radiation therapy.<sup>22</sup>

Currently, there are no NICE guidelines regarding relapsed or refractory disease after failure of first-line chemoimmunotherapy.<sup>24</sup>

## PLACE OF TECHNOLOGY

If licensed, axicabtagene ciloleucel will offer an additional second-line treatment option for adult patients with relapsed or refractory DLBCL.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	ZUMA-7, <a href="#">NCT03391466</a> , <a href="#">EudraCT2017-002261-22</a> , KTE-C19-107; patients aged 18 yrs and older; axicabtagene ciloleucel vs standard of care (SOC) therapy; phase III
<b>Sponsor</b>	Kite, A Gilead Company
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry; <sup>1,25</sup> Abstract <sup>3</sup>
<b>Location</b>	EU (incl UK), USA, Canada, Australia, and Israel
<b>Design</b>	Randomised, open-label, parallel assignment
<b>Participants</b>	n=350 (planned); aged 18 yrs and older; DLBCL, relapsed or refractory disease after first-line chemoimmunotherapy, must have received adequate first-line therapy including at a minimum anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20 negative, and an anthracycline containing chemotherapy regimen.
<b>Schedule</b>	Patients will undergo leukapheresis, then lymphodepleting chemotherapy (fludarabine 30 mg/m <sup>2</sup> /d and cyclophosphamide 500 mg/m <sup>2</sup> /d for 3 d), followed by a single infusion of axicabtagene ciloleucel at 2 × 10 <sup>6</sup> CAR T cells/kg. Corticosteroid bridging therapy is allowed for patients with high disease burden at screening. Pts in the SOC arm will receive investigator's choice of second-line salvage therapy; pts who respond after 2–3 cycles will receive high-dose therapy and ASCT.
<b>Follow-up</b>	Follow up events will occur at 12, 24 and 60 mths. Remission is generally considered to be 12 mths and discharge from the oncology service at 24 mths. 5 years is the long term follow up point. <sup>b</sup>
<b>Primary Outcomes</b>	Event Free Survival [Time frame: 150 days post infusion] <sup>c</sup> EFS is defined as the time from randomization to the earliest date of disease progression per the Lugano Classification (Cheson et al, 2014) <sup>d</sup>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>Objective Response Rate (ORR) [Time frame: Up to 5 yrs]</li> <li>Overall Survival [Time frame: Up to 5 yrs]</li> </ul>
<b>Key Results</b>	-

<sup>b</sup> Information provided by Gilead Sciences Ltd

<sup>c</sup> Information provided by Gilead Sciences Ltd

<sup>d</sup> Information provided by Gilead Sciences Ltd

Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Jan 2022

## 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.<sup>2</sup>

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.<sup>26</sup>

## RELEVANT GUIDANCE

### NICE GUIDANCE

- 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

- The European Society for Medical Oncology. ESMO Consensus Conference on malignant lymphoma: management of 'ultra-high-risk' patients. 2018.<sup>21</sup>
- The British Committee for Standards in Haematology. Guidelines for the management of diffuse large B-cell lymphoma. 2016.<sup>27</sup>
- The European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.<sup>28</sup>

## ADDITIONAL INFORMATION

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