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# HEALTH TECHNOLOGY BRIEFING
# APRIL 2021

# Tisagenlecleucel for relapsed or refractory follicular lymphoma

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| NIHRIO ID | 26557 | NICE ID | 10430 |
| Developer/Company | Novartis Pharmaceuticals UK Ltd | UKPS ID | 648449 |

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| Licensing and market availability plans | Currently in phase II clinical trials |

## SUMMARY


Tisagenlecleucel is in clinical development for the treatment of relapsed or refractory follicular lymphoma. Follicular lymphoma is the most common type of slow-growing lymphoma that develops in B-cells (a type of immune cell). Relapsed refers to a disease that grows again after a period of remission while refractory refers to a disease that does not respond to treatment. Most common symptoms of follicular lymphoma include enlargement of lymph nodes in the neck, underarms, abdomen or groin. Follicular lymphoma is usually not considered to be curable although patients can live for many years. Therefore, there is an unmet need for a more effective treatment option.

Tisagenlecleucel contains the patient's modified T-cells (a type of white blood cell) to make a protein called chimeric antigen receptor (CAR). CAR can attach to another protein on the surface of cancer cells called CD19. When tisagenlecleucel is given to the patient intravenously, the modified T-cells attach to and kill the cancer cells, thereby helping to clear the cancer from the body. If licensed, tisagenlecleucel will provide an additional treatment option for patients with relapsed or refractory follicular lymphoma.

# PROPOSED INDICATION

Treatment of adult patients with relapsed or refractory follicular lymphoma.[1]

# TECHNOLOGY

## DESCRIPTION

Tisagenlecleucel (Kymriah, CTL019) is an autologous, immunocellular cancer therapy which involves reprogramming a patient's T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single-chain antibody fragment which recognises CD19 and is fused to intracellular signalling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and anti-tumour activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T-cell expansion and persistence of tisagenlecleucel.[2]

Tisagenlecleucel is in clinical development for the treatment of relapsed or refractory follicular lymphoma. In the phase II clinical trial (ELARA; NCT03568461) patients received lymphodepleting chemotherapy followed by a single tisagenlecleucel infusion of 0.6-6×$10^8$ CAR-T cells.[1,3]

## INNOVATION AND/OR ADVANTAGES

Tisagenlecleucel is an individualised therapy that reprograms a patient's T cells with a CAR containing a 4-1BB costimulatory domain.[4] Tisagenlecleucel is a one-time treatment designed to empower a patient's immune system to fight the cancer.[5] Preliminary results from the pivotal trial, ELARA, suggest that tisagenlecleucel is effective in treating patients with relapsed or refractory follicular lymphoma, resulting in high complete response rates (CRRs) and overall response rates (ORRs), including in high-risk patients. The overall safety profile is favourable, with no severe cytokine release syndrome (CRS) and very low neurologic events reported. As such, limited anti-cytokine therapy is needed and therefore tisagenlecleucel may provide a potentially definitive treatment option for patients with relapsed and refractory follicular lymphoma.[3,5]

In the early stage academic trial UPEnn, investigating 14 patients with relapsed or refractory follicular lymphoma, complete or partial responses were observed in 79% of the patients. At 5 years, 43% of patients (95% CI, 18 to 66) were progression-free, suggesting long-term, durable complete remissions to single tisagenlecleucel infusion.[6]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tisagenlecleucel is currently licensed in the EU/UK for treatment of:[2]

- Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

Tisagenlecleucel is currently in phase II and/or III clinical development for several other indications, including recurrent mantle cell lymphoma, non-Hodgkin lymphoma and high risk paediatric. and adult acute lymphoblastic lymphoma.[7]

Very common adverse events of tisagenlecleucel (affecting more than one in ten people) include infections (viral, bacterial, fungus), anaemia, haemorrhage, febrile neutropenia, neutropenia, thrombocytopenia, cytokine release syndrome, hypogammaglobulinaemia, decreased appetite, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, anxiety, delirium, sleep disorder, headache, encephalopathy, arrhythmia, hypotension, hypertension, cough, dyspnoea, hypoxia, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, arthralgia, acute kidney pain, pyrexia, fatigue, oedema, pain, chills, decreased lymphocytes, white blood cells, haemoglobin, neutrophils, platelets and increased aspartate aminotransferase.[2]

In 2020, the US Food and Drug Administration (FDA) granted Regenerative Medicine Advanced Therapy (RMAT) designation to tisagenlecleucel in relapsed/refractory follicular lymphoma, based on preliminary results from the ELARA trial.[5]

# PATIENT GROUP

## DISEASE BACKGROUND

Lymphomas are cancers of the lymphatic system, which is part of the body's immune system, and involve abnormal production of lymphocytes (a type white blood cell). They are divided into Hodgkin and non-Hodgkin lymphomas (NHL). NHL are a heterogeneous group of conditions ranging from indolent (low-grade) to aggressive (high-grade) depending on the rate at which the abnormal lymphocytes divide. Indolent lymphomas are slow growing. Follicular lymphoma, which affects B cells, is the most common type of indolent NHL.[8,9] Lymphoma can sometimes come back after successful treatment. This is called a relapse. Refractory lymphoma is a disease that does not respond well to the first choice of treatment.[10]

Follicular lymphoma is usually very slow growing type of non-Hodgkin lymphoma, so symptoms develop gradually over time. Many patients have few symptoms, and some show no symptoms. The most common symptom of follicular lymphoma is a lump or several lumps in the neck or just above collar bones, but they can also develop in other places such as armpits or groin. Other common symptoms include unexplained weight loss, fevers, drenching sweats, frequent infections or having difficulty getting over infection and fatigue.[11]

The exact cause of follicular lymphoma is unknown. However, certain factors including lifestyle (diet, alcohol, smoking), environmental (pesticides, hair dyes, solvents with benzene) and previous medical conditions (particularly those that cause a suppressed immune system i.e. HIV/AIDS, autoimmune diseases and medications) have been linked to the occurrence of follicular lymphoma.[12] There is not normally any family history of follicular lymphoma.[11]

## CLINICAL NEED AND BURDEN OF DISEASE

Follicular lymphoma is the most common type of low-grade lymphoma.[13] In the latest available Cancer Registration Statistics, there were 12,065 newly diagnosed cases of NHL (ICD-10 code C82 – C85) in England in 2017-18. Out of these 2,168 have follicular lymphoma, which is about 18% of the total number of new cases.[14]

The 2019-2020 Hospital Episodes Statistics (HES) for England recorded a total of 10,179 finished consultant episodes (FCE) for follicular lymphoma grade I, II and IIIa (ICD-10 code C82.0, C82.1 and C82.3), resulting 9,928 hospital admissions, 4,108 FCE bed days and 8,852 day cases.[15]

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 (nodular) NHL (ICD-10 code 82.0).[14]

Between 2013-2017, the age-standardised net survival rate at 1-year and 5-year for NHL (all subtypes combined) in England were 79% and 66% respectively.[16]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

A specialist multidisciplinary (haematologists, specialist cancer nurses, pathologists, radiotherapy specialists, pharmacists, and radiologists) team is normally employed throughout the treatment.[17] Treatment options for follicular lymphoma depends on the stage, signs and symptoms of the disease.[11] The main types of treatment for follicular lymphoma include radiotherapy, chemotherapy, steroids, stem cell transplant and targeted therapy drugs.[18]

## CURRENT TREATMENT OPTIONS

Currently NICE recommend the following treatment for patients with relapsed or refractory follicular lymphoma:[19]

- Obinutuzumab with bendamustine followed by obinutuzumab maintenance is recommended, within its marketing authorisation, as an option for treating follicular lymphoma that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen.
- Lenalidomide with rituximab is recommended, within its marketing authorisation, as an option for previously treated follicular lymphoma (grade 1 to 3A) in adults.
- Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

## PLACE OF TECHNOLOGY

If licensed, tisagenlecleucel will provide a treatment option for adult patients with relapsed or refractory follicular lymphoma.[1]

# CLINICAL TRIAL INFORMATION

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| **Trial** | **ELARA;** NCT03568461, EudraCT 2017-004385-94; A Phase II, Single Arm, Multicenter Open Label Trial to Determine the Efficacy and Safety of Tisagenlecleucel (CTL019) in Adult Patients With Refractory or Relapsed Follicular Lymphoma<br>**Phase II** - Active, not recruiting<br>**Location (s):** Europe (incl UK), USA and other countries<br>**Primary completion date:** November 2020 |
| **Trial design** | Non-randomised, single group, open label |
| **Population** | N=113; aged 18 years and older; refractory or relapsed follicular lymphoma (grade 1, 2 and 3A) |
| **Intervention(s)** | All patients received lymphodepleting chemotherapy followed by tisagenlecleucel intravenous infusion of 0.6- |

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| | $6\times10^8$ CAR-T cells (bridging therapy prior to infusion was permitted)[3] |
| **Comparator(s)** | No comparator |
| **Outcome(s)** | Primary outcome: CRR based on Lugano classification response criteria (Time frame: 2 years)<br><br>For full list of outcomes, see trial record |
| **Results (efficacy)** | - |
| **Results (safety)** | The overall safety profile is favourable, with no severe CRS.[3] |

# ESTIMATED COST

Tisagenlecleucel is already marketed in the UK. The list price for tisagenlecleucel is £282,000 per infusion (company submission).[20]

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal in development. Duvelsib for treating relapsed follicular lymphoma after 2 systemic therapies. (GID-TA10209). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (GID-TA10223). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ofatumumab (Arzerra) in combination with chemotherapy for follicular lymphoma; second line – refractory to rituximab. (GID-TA10437). Expected date of issue to be confirmed.
- NICE technology appraisal. Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab (TA 629). May 2020.
- NICE technology appraisal. Lenalidomide with rituximab for previously treated follicular lymphoma (TA627). April 2020.
- NICE technology appraisal. Idelalisib for treating refractory follicular lymphoma. (TA604). October 2019.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE guidance. Non-Hodgkin's lymphoma: diagnosis and management. (NG52). July 2016.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

## OTHER GUIDANCE

- Pan-London Haemato-Oncology. Lymphoid Malignancies Part 3: Follicular Lymphoma. 2018.[21]
- Belgian Hematology Society. BHS guidelines for the treatment of marginal zone lymphomas. 2018.[22]

- European Society of Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[23]
- 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.[24]

# ADDITIONAL INFORMATION

# REFERENCES


1 ClincalTrials.gov. *A Phase II, Single Arm, Multicenter Open Label Trial to Determine the Efficacy and Safety of Tisagenlecleucel (CTL019) in Adult Patients With Refractory or Relapsed Follicular Lymphoma. Trial ID: NCT03568461.* 2018. Status: Active, not recuiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03568461 [Accessed 15 March 2021].

2 Electronic Medcines Compendum (emc). *Kymriah cells dispersion for infusion.* Available from: https://www.medicines.org.uk/emc/product/9456 [Accessed 15 March 2021].

3 Fowler N, et al. *1149 Efficacy and Safety of Tisagenlecleucel in Adult Patients with Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 Elara Trial.* 2020. Available from: https://ash.confex.com/ash/2020/webprogram/Paper138983.html [Accessed 15 March 2021].

4 Novartis. *Kymriah (tisagenlecleucel): Mechansim of action.* Available from: https://www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/mechanism-of-action/ [Accessed 15 March 2021].

5 Novartis. *Novartis announces Kymriah® meets primary endpoint at interim analysis of pivotal study in follicular lymphoma.* 2020. Available from: https://www.novartis.com/news/media-releases/novartis-announces-kymriah-meets-primary-endpoint-interim-analysis-pivotal-study-follicular-lymphoma [Accessed 15 March 2021].

6 Chong E, Ruella M, Schuster S. Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy. *New England Journal of Medicine*. 2021;284:673-4. Available from: https://www.nejm.org/doi/10.1056/NEJMc2030164?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

7 ClincalTrials.gov. *Search of: Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Tisagenlecleucel | Phase 2, 3.* Available from: https://www.clinicaltrials.gov/ct2/results?intr=Tisagenlecleucel&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 15 March 2021].

8 Cancer Research UK. *How doctors group non-Hodgkin lymphomas.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types [Accessed 15 March 2021].

9 Cancer Research UK. *Follicular lymphoma.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/follicular-lymphoma [Accessed 15 March 2021].

10 Lymphoma Action. *What happens if lymphoma relapses?* Available from: https://lymphoma-action.org.uk/about-lymphoma-living-and-beyond-lymphoma/what-happens-if-lymphoma-relapses [Accessed 15 March 2021].

11 Lymphoma Action. *Follicular lymphoma.* Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/follicular-lymphoma [Accessed 15 March 2021].

12 Anticancer Fund. *Follicular lymphoma: A guide for patients patient information based on ESMO clinical practice guidelines.* 2014. Available from: https://www.esmo.org/content/download/52236/963497/file/EN-Follicular-Lymphoma-Guide-for-Patients.pdf [Accessed 15 March 2021].

13 Cancer Research UK. *Low grade NHL.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/low-grade [Accessed 15 March 2021].

14 Office for National Statistics (ONS). *Cancer registration statistics, England: 2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 15 March 2021].
15 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 15 March 2021].
16 Office for National Statistics. *Cancer survival in England - adults diagnosed: 2013-2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 15 March 2021].
17 Cancer Research UK. *Non-Hodgkin lymphoma: Treatment decisions.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/treatment/decisions [Accessed 15 March 2021].
18 Macmillan Cancer Support. *Follicular Lymphoma.* Available from: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/follicular-lymphoma [Accessed 15 March 2021].
19 National Insititute for Health and Care Excellence. *Treating follicular lymphoma.* Available from: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma#path=view%3A/pathways/non-hodgkins-lymphoma/treating-follicular-lymphoma.xml&content=view-node%3Anodes-treating-relapsed-or-refractory-disease [Accessed 15 March 2021].
20 National Insititute for Health and Care Excellence. *Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554).* Last Update Date: Available from: https://www.nice.org.uk/guidance/ta554/chapter/2-Information-about-tisagenlecleucel [Accessed 15 March 2021].
21 Pan-London Haemato-Oncology. *Lymphoid Malignancies Part 3: Follicular Lymphoma* Last Update Date: Available from: https://rmpartners.nhs.uk/wp-content/uploads/2018/11/PanLondon_FL_Guidelines_Sept2018_v2.pdf [Accessed 15 March 2021].
22 Bron D, Maerevoet M, Neste Evd, Delrieu V, Offner F, Schroyens W, et al. BHS guidelines for the treatment of marginal zone lymphomas: 2018 update. *Belgian Journal of Hematology.* 2018;5:12-7. Available from: https://www.ariez.nl/wp-content/uploads/2019/06/BJH4_2019_Art._Bron.pdf.
23 Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016 Sep;27(suppl 5):v83-v90. Available from: https://doi.org/10.1093/annonc/mdw400.
24 Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol.* 2013 Apr;24(4):857-77. Available from: https://doi.org/10.1093/annonc/mds643.