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Newcastle University

Health Technology Briefing
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Lisocabtagene maraleucel for treating relapsed or refractory indolent follicular lymphoma

Company/Developer	Bristol-Myers Squibb

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29351	NICE ID: Not available	UKPS ID: 663427

Licensing and Market Availability Plans

Currently in phase II clinical trial

Summary

Lisocabtagene maraleucel is in clinical development for the treatment of relapsed or refractory indolent B-cell follicular lymphoma (FL). FL is a type of non-Hodgkin lymphoma (NHL). NHL is a type of cancer that affects white blood cells which help the body to fight against infections. The affected cells (B cells) start to multiply in an abnormal way and begin to collect in certain parts of the body, such as the lymph nodes or other body organs. A relapsed FL is one that comes back after treatment and refractory FL refers to lymphoma that fails to respond to medical treatment. Indolent lymphomas are also known as low-grade lymphomas and are a group of slow growing NHLs. Symptoms of FL include painless swellings in the neck, armpit or groin, heavy sweating at night, high temperatures and weight loss. The exact cause of FL is unknown, however taking immunosuppressant medicines, exposure to Epstein-Barr virus and having a close relative with FL could contribute to its development. The condition can become more difficult to treat if it is relapsed or refractory, as treatment options are limited and often not very effective.

Lisocabtagene maraleucel is administered as an infusion intravenously. It is prepared using the patient's own white blood cells and modified to make a protein called chimeric antigen receptor (CAR). CAR attaches to CD19, a protein found on the surface of B-cells and kills them, thereby helping to clear the cancer from the body. If licensed lisocabtagene maraleucel will offer an additional treatment option for patients with relapsed or refractory indolent B-cell FL.

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.

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Proposed Indication

Treatment of relapsed or refractory indolent B-cell follicular lymphoma (FL) in adults.[1]

Technology

Description

Lisocabtagene maraleucel (Breyanzi, liso-cel, JCAR017) is an autologous, CD19-directed, chimeric antigen receptor (CAR) T-cell product.[2,3] It is a combination of two types of the patient's white blood cells (CD4+ T cells and CD8+ T cells). These T cells are genetically modified in the laboratory to express a CAR protein and are administered back to the patient. CAR attaches to CD19, a protein that is found on the surface of B cells, including cancerous B cell, resulting in the death of these cancer cells.[3]

Lisocabtagene maraleucel is in clinical development for the treatment of relapsed or refractory indolent B-cell FL. In the phase II clinical trial (TRANSCEND FL, NCT04245839), patients are infused on day 1 at a target dose of 100×10^6 CAR-positive viable T cells (CAR+ T cells), 2 to 7 days after completion of lymphodepleting chemotherapy. Each lisocabtagene maraleucel dose includes CD4+ CAR+ T cells and CD8+ CAR+ T cells.[1]

Key Innovation

FL has a relapsing and remitting course with the potential to progress to an aggressive disease. The duration of remission has prognostic significance, as patients who relapse within 24 months of chemotherapy are reported to have a poor prognosis, approximately 30%; median overall survival, 6-10 months).[4,5] In the treatment of relapsed or refractory FL, there are few options that offer significant and lasting responses, particularly for patients with high-risk disease features and those who experience early disease progression after front-line therapy.[5,6] Lisocabtagene maraleucel represents a differentiated CAR T-cell therapy with demonstrated rapid and durable complete responses and a manageable safety profile.[7] CAR T-cell therapy has the advantage of being a one-off treatment with a single infusion required for its completion. In addition, because it is a "living drug", it persists in the body long-term, and may recognise and attack cancer cells if there is a relapse.[8]

Lisocabtagene maraleucel is an advanced therapy medicinal product (ATMP) within the definition of a gene therapy.[3] The scientific recommendation for an ATMP classification is issued by the European Medicines Agency's Committee for Advanced Therapies (CAT).[9]

If licensed, lisocabtagene maraleucel will offer an additional treatment option for patients with relapsed or refractory indolent B-cell FL.

Regulatory & Development Status

In the UK, lisocabtagene maraleucel has Marketing Authorisation for the following:[3]

- Diffuse large B-cell lymphoma
- High grade B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- FL grade 3B

in patients who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

Lisocabtagene maraleucel is in phase II clinical development for the treatment of Richter syndrome, chronic lymphocytic leukaemia and small lymphocytic lymphoma.[10]

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Patient Group

Disease Area and Clinical Need

FL is a common type of slow growing (low grade, indolent) NHL. It is called follicular because the cells usually develop in clumps called follicles. NHL is a cancer of the lymphatic system. Lymphoma develops when lymphocytes grow out of control. There are two types of lymphocytes: T lymphocytes (T cells) and B lymphocytes (B cells). FL develops when the body makes abnormal B lymphocytes, therefore it is a type of B cell lymphoma. The abnormal lymphocytes build up in the lymph nodes or other body organs and affects the body's ability to fight infections.[11] If a patient initially goes into complete remission and the lymphoma returns, this is referred to relapsed lymphoma. Sometimes, the lymphoma will not respond to the first treatment, and will not go into remission. This is called a refractory lymphoma.[12] FL is characterized by periods of remission and relapse, and the disease becomes more difficult to treat after relapse or disease progression.[13] The main symptom of FL is painless swelling in the neck, armpit or groin. Other symptoms include drenching night sweats, anaemia, bruising or bleeding easily, coughing or breathlessness, fatigue, fever and unexplained weight loss.[14] The causes of FL are mostly unknown. Having a close relative (parent or sibling) with FL may slightly increase the risk of developing it. A medical condition that weakens the immune system, taking immunosuppressant medicines and previous exposure to Epstein-Barr virus could increase the risk of developing NHL.[14,15]

Each year around 2,300 people are diagnosed with FL in the UK. Out of all people with NHL in the UK, around 20% have FL. It mainly affects adults over the age of 60 years.[11] In England (2023-24), there were 21,798 finished consultant episodes (FCEs) and 20,960 admissions for FL (ICD-10 code C82), which resulted in 19,514 day cases and 11,954 FCE bed days.[16]

Recommended Treatment Options

National Institute for Health and Care Excellence (NICE) recommends the following pharmacological treatment options for relapsed or refractory FL:

- Axicabtagene ciloleucel[17]
- Mosunetuzumab[18]
- Obinutuzumab with bendamustine[19]
- Lenalidomide with rituximab[20]
- Idelalisib[21]
- Rituximab.[22]

Clinical Trial Information

Trial	**TRANSCEND FL**, NCT04245839, EudraCT 2019-004081-18; A Phase 2, open-label, single arm, multicohort, multicenter trial to evaluate the efficacy and safety of JCAR017 in adult subjects with relapsed or refractory indolent B-cell Non-Hodgkin Lymphoma (NHL) **Phase II** - Recruiting **Locations:** Six EU countries, UK, USA, Canada, and Japan **Primary completion date:** September 2031
Trial Design	Single group assignment, open label
Population	N=276 (estimated); subjects with relapsed or refractory FL who have received at least one prior line of therapy; aged 18 years and older

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Intervention(s)	Lymphodepleting (LD) chemotherapy: subjects treated with 30mg/m2/day fludarabine intravenously (IV) and cyclophosphamide IV 300mg/m2/day for 3 days prior to lisocabtagene maraleucel infusion. Lisocabtagene maraleucel IV infusion Day 1 at a target dose of 100 x 10^6 CAR+ T cells, 2 to 7 days after completion of LD chemotherapy. Each lisocabtagene maraleucel dose includes CD4+ CAR+ T cells and CD8+ CAR+ T cells.
Comparator(s)	-
Outcome(s)	**Primary outcome measure:** Overall Response Rate (ORR) [Time frame: Up to 60 months] See trial record for full list of other outcomes.
Results (efficacy)	Results showed study met the primary endpoint of ORR, with lisocabtagene maraleucel demonstrating statistically significant and clinically meaningful responses in relapsed or refractory FL.[13]
Results (safety)	No new safety signals were reported.[13]

Estimated Cost

The cost of lisocabtagene maraleucel is not yet known.

Relevant Guidance

NICE Guidance

- 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. Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular or marginal zone lymphoma after 1 or more anti-CD20 treatments [GID-TA11488]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more treatments [GID-TA11385]. Expected date of issue to be confirmed.
- NICE technology appraisal. Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma [TA894]. June 2023.
- NICE technology appraisal. Mosunetuzumab for treating relapsed or refractory follicular lymphoma [TA892]. May 2023.
- NICE technology appraisal. Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab [TA629]. 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 clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE quality standard. Haematological cancers [QS150]. June 2017.

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NHS England (Policy/Commissioning) Guidance
NHS England. 2013/14 NHS standard contract for cancer: Chemotherapy (Adult). B15/S/a.
Other Guidance
• European Society of Medical Oncology (ESMO). Diffuse Large B-Cell Lymphoma (DLBCL), Follicular Lymphoma (FL) and Chronic Lymphocytic Leukaemia (CLL). 2022.[23] • ESMO. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2021.[24] • ESMO. Consensus Conference on malignant lymphoma: management of 'ultra-high risk' patients. 2018.[25]

Additional Information

References

1 Clinicaltrials.gov. *A Study to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects With Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (NHL) (TRANSCEND FL)*. 2020. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04245839?term=NCT04245839&draw=2&rank=1 [Accessed 8 November 2024].

2 Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-52. Available from: https://doi.org/10.1016/s0140-6736(20)31366-0.

3 European medicines Agency. *Breyanzi*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi#ema-inpage-item-overview [Accessed 8 November 2024].

4 Singh D, Singh A, Mukkamalla S. Relapsed and Refractory Follicular Lymphoma. *National Library of Medicine*. 2023. https://www.ncbi.nlm.nih.gov/books/NBK589677/.

5 Wang M, Siddiqi T, Gordon LI, Kamdar M, Lunning M, Hirayama AV, et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. *Journal of Clinical Oncology*. 2024;42(10):1146-57. Available from: https://doi.org/10.1200/jco.23.02214.

6 Medthority. *Breyanzi delivers deep and durable responses in relapsed or refractory follicular lymphoma*. 2023. Available from: https://www.medthority.com/news/2023/6/breyanzi-delivers-deep-and-durable-responses-in-relapsed-or-refractory-follicular-lymphoma-and-mantle-cell-lymphoma-in-transcend-clinical-trials-presented-at-icml-2023.--bms/ [Accessed 8 November 2024].

7 Bristol Myers Squibb. *Bristol Myers Squibb Receives European Commission Approval for CAR T Cell Therapy Breyanzi (lisocabtagene maraleucel) for Certain Forms of Relapsed or Refractory Large B-cell Lymphoma*. 2022. Available from: https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-CAR-T-Cell-Therapy-Breyanzi-lisocabtagene-maraleucel-for-

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Certain-Forms-of-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx [Accessed 8 November 2024].

8 Rutgers Cancer Institute. *Advantages of CAR-T Cell Therapy*. 2024. Available from: https://www.cinj.org/patient-care/advantages-car-t-cell-therapy [Accessed 8 November 2024].

9 European medicines Agency. *Advanced therapy medicinal products: Overview*. 2024. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview [Accessed 8 November 2024].

10 Clinicaltrials.gov. *13 Studies found for: lisocabtagene maraleucel | Phase 2, 3*. 2023. Available from: https://clinicaltrials.gov/search?intr=lisocabtagene%20maraleucel&aggFilters=phase:2%203 [Accessed 8 November 2024].

11 Cancer Reasearch UK. *Follicular lymphoma*. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/follicular-lymphoma [Accessed 8 November 2024].

12 Lymphoma Action. *What do 'relapsed lymphoma' and 'refractory lymphoma' mean?* 2023. Available from: https://lymphoma-action.org.uk/about-lymphoma-living-and-beyond-lymphoma/lymphoma-comes-back-relapses-or-doesnt-respond-treatment [Accessed 8 November 2024].

13 Bristol Myers Squibb. *Bristol Myers Squibb's TRANSCEND FL and TRANSCEND NHL 001 Studies of Breyanzi (lisocabtagene maraleucel)in Relapsed or Refractory Follicular Lymphoma and Mantle Cell Lymphoma Meet Primary Endpoint of Overall Response Rate*. 2023. Available from: https://investors.bms.com/iframes/press-releases/press-release-details/2023/Bristol-Myers-Squibbs-TRANSCEND-FL-and-TRANSCEND-NHL-001-Studies-of-Breyanzi-lisocabtagene-maraleucelin-Relapsed-or-Refractory-Follicular-Lymphoma-and-Mantle-Cell-Lymphoma-Meet-Primary-Endpoint-of-Overall-Response-Rate/default.aspx [Accessed 8 November 2024].

14 Macmillan Cancer Support. *Follicular Lymphoma (FL)*. 2021. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/non-hodgkin/types/follicular [Accessed 8 November 2024].

15 National Health Service (NHS). *Non-Hodgkin lymphoma*. 2022. Available from: https://www.nhs.uk/conditions/non-hodgkin-lymphoma/ [Accessed 8 November 2024].

16 National Health Service (NHS) England. *Primary diagnosis: 3 character*. 2024. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FA5%2F5B8474%2Fhosp-epis-stat-admi-diag-2023-24-tab.xlsx&wdOrigin=BROWSELINK [Accessed 8 November 2024].

17 National Institute for Health and Care Excellence (NICE). *Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma*. 2023. Available from: https://www.nice.org.uk/guidance/ta894 [Accessed 8 November 2024].

18 National Institute for Health and Care Excellence (NICE). *Mosunetuzumab for treating relapsed or refractory follicular lymphoma*. 2023. Available from: https://www.nice.org.uk/guidance/ta892 [Accessed 8 November 2024].

19 National Institute for Health and Care Excellence (NICE). *Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab*. 2020. Available from: https://www.nice.org.uk/guidance/ta629 [Accessed 8 November 2024].

20 National Institute for Health and Care Excellence (NICE). *Lenalidomide with rituximab for previously treated follicular lymphoma*. 2020. Available from: https://www.nice.org.uk/guidance/ta627 [Accessed 8 November 2024].

21 National Institute for Health and Care Excellence (NICE). *Idelalisib for treating refractory follicular lymphoma*. 2019. Available from: https://www.nice.org.uk/guidance/ta604 [Accessed 8 November 2024].

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22 National Institute for Health and Care Excellence (NICE). *Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma*. 2008. Available from: https://www.nice.org.uk/guidance/ta137 [Accessed 8 November 2024].

23 Horwitz S, Ansell S, Ai W, Barnes J, et al. T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2022;20(3). https://jnccn.org/view/journals/jnccn/20/3/article-p285.xml.

24 Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):298-308. Available from: https://doi.org/10.1016/j.annonc.2020.11.008.

25 Hutchings M, Ladetto M, Buske C, Imhoff G, Walewski J. ESMO Consensus Conference on malignant lymphoma: management of 'ultra-high-risk' patients. *Annals of Oncology*. 2018;29(8):1687-700. https://www.annalsofoncology.org/article/S0923-7534(19)34106-7/fulltext.

26 National Comprehensive Cancer Network (NCCN). *Non-Hodgkin's Lymphomas*. 2015. Available from: https://www2.tri-kobe.org/nccn/guideline/hematologic/nhl/english/foll.pdf [Accessed 8 November 2024].

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