Health Technology Briefing
April 2022

Zamtocabtagene autoleucel for relapsed or refractory diffuse large B-cell lymphoma after at least 2 therapies

Company/Developer	Miltenyi Biotec Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 31547	NICE ID: 10765	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III/II clinical trials

Summary

Zamtocabtagene autoleucel is currently in clinical development for adults with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after receiving at least two lines of therapy. DLBCL is a cancer of B cells (a type of immune cell) and the most common type of fast-growing non-Hodgkin's lymphoma (NHL). In DLBCL, the body makes abnormal B cells which build up in lymph nodes or other body organs. The affected cells start to divide constantly before they are fully mature and lose their infection-fighting properties, which makes the body more vulnerable to infection. Relapsed or refractory DLBCL refers to the disease reappearing after a period of remission or when the lymphoma becomes non-responsive to treatment. There is a high incidence of disease relapse or becoming refractory after treatment with currently available therapies.

Zamtocabtagene autoleucel is made by modifying the patient's own T cells (cells of the immune system) which can kill cancer cells by targeting the two proteins (CD19 and CD20) found on the surface of DLBCL cancer cells. Zamtocabtagene autoleucel is type of advanced therapy (gene therapy) and is administered intravenously (IV). Evidence shows that zamtocabtagene autoleucel could provide better results than some other chimeric antigen receptor (CAR)-T cell medicines that have one target, and also provide benefit to patients with relapsed or refractory DLBCL. If licensed, zamtocabtagene autoleucel will offer an additional treatment option for these patients who currently have few effective therapies available.

Proposed Indication

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after receiving at least two lines of therapy.[1]

Technology

Description

Zamtocabtagene autoleucel (MB-CART2019.1) is made from the patient's own T cells. T cells are cells of the immune system (the body's natural defences) that can kill cancer cells. The T cells have been modified in the laboratory by a virus that carries a gene into the cells, enabling them to produce a receptor that targets proteins CD19 and CD20 (which are produced in patients with DLBCL). When given back to the patient, with this receptor on their surface the modified cells, called CAR-T cells, are expected to attach to CD19 and CD20 on the cancer cells and kill them, thus reducing the growth and spread of the tumour. The virus used in this medicine ('lentivirus') is modified so that it does not cause disease in humans.[2]

Zamtocabtagene autoleucel is currently in clinical development for adults with relapsed or refractory DLBCL after receiving at least two lines of therapy. In the phase II trial (NCT04792489), zamtocabtagene autoleucel is administered intravenously (IV) at a dose of 2.5 x 10^6 CAR+ cells/kg body weight.[1]

Key Innovation

Zamtocabtagene autoleucel is shown to have an advantage over other medicines for patients with DLBCL whose cancer did not respond to previous treatments. CAR T-cell therapies which target a single B-cell antigen lead to selective pressure with potential antigen-escape and subsequent relapse. However, zamtocabtagene autoleucel has been developed to overcome this limitation by targeting two proteins (CD19 and CD20). Evidence suggests that zamtocabtagene autoleucel could therefore provide better results than CAR-T cell medicines that have one target. In addition, early results in patients whose cancer did not respond to previous treatments or had come back indicate that they may benefit from treatment with zamtocabtagene autoleucel.[2,3]

Zamtocabtagene autoleucel may meet the criteria for an advanced therapy medicinal product (ATMP) classification (gene therapy medicinal product) by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).

If licensed, zamtocabtagene autoleucel will offer an additional treatment option for patients with relapsed or refractory DLBCL who currently have few effective therapies available.

Regulatory & Development Status

Zamtocabtagene autoleucel does not currently have Marketing Authorisation in the EU/UK for any indication.

Zamtocabtagene autoleucel is currently in phase I/II trial for B-cell Non Hodgkin Lymphoma.[4]

Zamtocabtagene autoleucel has the following regulatory designations/awards:[2,5]

- an orphan drug in the EU in 2020 for the treatment of DLBCL
- a PRIME status for the treatment of DLBCL by the EMA in October 2019

Patient Group

Disease Area and Clinical Need

Diffuse large B-cell lymphoma (DLBCL) is a cancer of B cells and the most common type of fast-growing non-Hodgkin's lymphoma (NHL).[6] In DLBCL, the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs.[7] The affected lymphocytes start to divide before they are fully mature and lose their infection-fighting properties which makes the patient more vulnerable to infection.[8] Relapsed/refractory DLBCL refers to the disease reappearing after a period of remission or when the lymphoma becomes non-responsive to treatment.[9] The cause of DLBCL is unknown, however factors that may increase the risk of developing DLBCL include: a weak immune system; autoimmune diseases such as rheumatoid arthritis and heredity (having a parent, brother or sister with DLBCL may slightly increase your risk of developing it). Symptoms of DLBCL include painless swelling in the neck, armpit or groin, night sweats, fevers and unexplained weight loss.[10]

Each year about 5,500 people are diagnosed with DLBCL in the UK.[11] This makes up about 40 out of 100 cases (40%) of NHL in adults.[7] The age standardised registrations of newly diagnosed cases of diffuse NHL in England, in 2017, were 15.2 per 100,000 in males and 9.8 per 100,000 in females. There were 4,816 newly diagnosed cases of DLBCL (ICD-10 code C83.3).[12] According to the 2020-21 Hospital Episodes Statistics data, there were 35,113 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) which resulted in 31,231 admissions, 23,709 day cases and 76,363 FCE bed days.[13] For deaths registered in England in 2017, there were 1,105 deaths where diffuse NHL (ICD10 code C83) was recorded as the underlying cause. The age standardised rates per 100,000 population of registered deaths from diffuse NHL (ICD10 code C83) was 2.8 for males and 1.6 for females.[12] In England, between 2013 and 2017 for a total of 56,350 NHL patients, the age standardised one-year and five-year survival rate was 79.4% and 65.6% respectively.[14]

Recommended Treatment Options

The following treatments are recommended for relapsed or refractory DLBCL:[11,15]

- R-GDP – rituximab with gemcitabine, dexamethasone and cisplatin
- R-DHAP – rituximab with dexamethasone, high-dose cytarabine and cisplatin
- R-ICE – rituximab with ifosfamide, carboplatin and etoposide

NICE recommends the following treatment options for relapsed or refractory DLBCL:[16,17]

- Tisagenlecleucel, after 2 or more systemic therapies
- Axicabtagene ciloleucel, after 2 or more systemic therapies
- Polatuzumab vedotin with rituximab and bendamustine in adults who cannot have a haematopoietic stem cell transplant

Clinical Trial Information

Trial	NCT04792489; A Multi-center Single Arm Phase II Study to Evaluate the Safety and Efficacy of Genetically Engineered Autologous Cells Expressing Anti-CD20 and Anti-CD19 Specific Chimeric Antigen Receptor in Subjects With Relapsed and/or Refractory Diffuse Large B Cell Lymphoma **Phase II –** Recruiting **Location(s):** USA **Primary completion date:** May 2022

Trial Design	Single group assignment, open-label
Population	N=65; adults (18 years and older) who have histologically confirmed DLBCL or associated subtype
Intervention(s)	Zamtocabtagene autoleucel (IV) 2.5 x 10^6 CAR+ cells/kg body weight
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: overall response rate [time frame: 1 month] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of zamtocabtagene autoleucel is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (ID3943). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (ID3970). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma (ID3795). Expected August 2022.
- NICE technology appraisal. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (TA649). September 2020.
- NICE technology appraisal. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567). March 2019.
- NICE technology appraisal. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA559). January 2019.
- NICE clinical guideline. 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.

Other Guidance

- European Society for Medical Oncology (ESMO). Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[15]
- National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Non-Hodgkin's Lymphomas. 2010.[18]

Additional Information

Miltenyi Biotec Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines

References

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