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Health Technology Briefing
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Zamtocabtagene autoleucel for treating relapsed or refractory diffuse large B-cell lymphoma

Company/Developer	Miltenyi Biotec Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27846	NICE TSID: 10477	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Zamtocabtagene autoleucel is currently in clinical development for adults with relapsed or refractory diffuse large B cell lymphoma (DLBCL), not eligible for high-dose chemotherapy and autologous stem cell transplantation. DLBCL is a cancer of B cells (a type of immune cell) and the most common type of fast-growing non-Hodgkin's lymphoma. In DLBCL, abnormal B cells build up in lymph nodes or other organs. The affected cells divide constantly before they are fully mature and lose their infection-fighting properties, causing vulnerability to infection. Relapsed or refractory DLBCL disease reappears 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 may be advantageous over other treatment options, especially when patients do not respond to treatment.

Zamtocabtagene autoleucel is made by modifying the patient's own T cells (cells of the immune system) which can kill cancer cells by targeting two proteins (CD19 and CD20) found on the surface of DLBCL cancer cells. Zamtocabtagene autoleucel is type of advanced therapy (gene therapy), administered intravenously. If licensed, zamtocabtagene autoleucel will offer an additional treatment option for these patients who currently have few effective therapies available.

Proposed Indication

Treatment for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), who are not eligible for high-dose chemotherapy and autologous stem cell transplantation.[1]

Technology

Description

Zamtocabtagene autoleucel (MB-CART2019.1) is composed of autologous CD4- and CD8-enriched T cells, which are transduced with a lentiviral vector encoding the chimeric antigen receptor (CAR) construct for CD20 (Leu16) and CD19 (FMC63) and incorporating a 4-1BB co-stimulatory domain.[2] When given back to the patient, with this receptor on their surface, the modified cells (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.[3]

Zamtocabtagene autoleucel is currently in clinical development for patients with relapsed/refractory diffuse large B-cell lymphoma, who are not eligible for high-dose chemotherapy and autologous stem cell transplantation.[1] In the phase I/II clinical trial, zamtocabtagene autoleucel was administered via intravenous infusion (IV).[4]

Key Innovation

Not all patients with DLBCL achieve durable benefit with approved CD19 CAR-T cell therapies, indicating a significant unmet clinical need. Up to 50% of patients relapse after CD19-directed CAR-T cell therapy, possibly due to CD19 antigen escape and T cell exhaustion. Targeting one B cell antigen may lead to selective pressure with antigen escape and subsequent relapse, suggesting that targeting more than one antigen may improve efficacy by reducing potential downregulation of cell-surface markers and subsequent relapse.[2]

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 relapsed, suggests they may benefit from treatment with zamtocabtagene autoleucel.[3,5] Finally, in the phase I/II clinical trial (NCT03870945), zamtocabtagene autoleucel showed very good safety and the first evidence of promising efficacy in a truly elderly patient cohort (median age 72). It was successfully manufactured and infused in all 12 patients, and both dose levels were well tolerated, with no dose-limiting toxicity.[2] If licensed, zamtocabtagene autoleucel will offer an additional treatment option for patients with relapsed/refractory DLBCL, who currently have few effective therapies available.

The zamtocabtagene autoleucel may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[6]

Regulatory & Development Status

Zamtocabtagene autoleucel does not currently have marketing authorisation in the EU/UK for any indication.

Zamtocabtagene autoleucel is currently in phase II/III clinical development for DLBCL.[7]

Zamtocabtagene autoleucel has the following regulatory designations/awards:[8]

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

Patient Group

Disease Area and Clinical Need

DLBCL is a cancer of B cells and the most common type of fast-growing non-Hodgkin's lymphoma (NHL).[9] In DLBCL, the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs.[10] 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.[11] Relapsed/refractory DLBCL refers to the disease reappearing after a period of remission or when the lymphoma becomes non-responsive to treatment.[12] 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 having a parent, brother or sister with DLBCL. Symptoms of DLBCL include painless swelling in the neck, armpit or groin, night sweats, fevers and unexplained weight loss.[13]

Each year about 5,500 people are diagnosed with DLBCL in the UK.[14] This accounts for 40% of NHL cases in adults.[10] 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).[15] 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.[16] 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) were 2.8 for males and 1.6 for females.[15] 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.[17]

Recommended Treatment Options

The following treatments are recommended for relapsed or refractory DLBCL:[14,18]

- 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:[19,20]

- 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	**DALY 1;** NCT03870945; A Phase I/II Safety, Dose Finding and Feasibility Trial of MB-CART2019.1 in Patients With Relapsed or Resistant CD20 and CD19 Positive B-NHL **Phase I/II** - Active, not recruiting **Location(s):** Germany **Primary completion date:** December 2020
Trial Design	Non-randomised, sequential assignment, open label
Population	N=12 (actual); adults with refractory/relapsed DLBCL (including malignant transformation like Richter's transformation) with no available approved standard therapy
Intervention(s)	• IV dose level 1 with 1x10^6 zamtocabtagene autoleucel per kg bodyweight • IV dose level 2 with 2.5x10^6 zamtocabtagene autoleucel per kg bodyweight
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Determination of the maximum tolerated dose of MB-CART2019.1 [time frame: day 28 after infusion of MB-CART2019.1] • Safety and toxicity assessment of MB-CART2019.1 [time frame: day 28 after infusion of MB-CART2019.1] See trial record for full list of other outcomes
Results (efficacy)	"Zamtocabtagene autoleucel (MB-CART2019.1) showed [...] the first evidence of promising efficacy in a truly elderly patient cohort. [...] It was notable that MB-CART2019.1 induced CR [complete remission] in five out of 12 patients. Clinical response was accompanied by higher peak CAR-T cell expansion. Importantly, CRs were durable as all patients who achieved CR had 2-year follow-up visits with no evidence of relapse or need for new anti-lymphoma therapy".[2]
Results (safety)	"Zamtocabtagene autoleucel (MB-CART2019.1) showed very good safety [...]. It was successfully manufactured and infused in all 12 patients, and both DLs [two dose levels] were well tolerated, with no DLT [dose-limiting toxicity]. The favourable safety profile comprised no Grade ≥3 CRS events nor neurotoxicity at either DL, leading to the recommended dose of MB-CART2019.1 of 2.5×106 CAR-T cells/kg body weight".[2]
Clinical Trial Information	
Trial	**DALY 2-EU;** NCT04844866; EudraCT 2020-003908-14; A Pivotal Phase II Randomised, Multi-centre, Open-label Study to Evaluate the Efficacy and Safety of MB-CART2019.1 Compared to SoC Therapy in Participants With r/r DLBCL, Who Are Not Eligible for HDC and ASCT **Phase II** – Recruiting **Location(s):** 12 EU countries **Primary completion date:** September 2023

Trial Design	Randomised, parallel assignment, open label
Population	N=168 (estimated); adults with histologically proven DLBCL and associated subtypes who had relapsed or refractory disease after first-line chemoimmunotherapy
Intervention(s)	Single infusion of 2.5 × 10^6 CAR-transduced autologous T cells per kg/body weight
Comparator(s)	Standard of care
Outcome(s)	Primary outcome measure: progression-free survival [time frame: up to 99 weeks after randomisation] 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 October 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.[18]

- National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Non-Hodgkin's Lymphomas. 2010.[21]

Additional Information

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