Health Technology Briefing
November 2021

Epcoritamab for diffuse large B-cell lymphoma after two previous treatments

Company/Developer	AbbVie

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID:30809	NICE ID: 10673	UKPS ID: 654305

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Epcoritamab is currently in development for treatment of diffuse large B-cell lymphoma (DLBCL). 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 lymphocytes start to divide before they are fully mature and lose their infection-fighting properties, which makes the body more vulnerable to infection. High incidence of disease relapsed/refractory occurs after treatment with currently available monoclonal antibody (mAb) treatments. Eporitamab could provide an additional treatment option for these individuals.

Epcoritamab is a type of antibody called a 'T-cell bispecific antibody' (TCB). It is administered via subcutaneous (SC) injection. Most antibody treatments attach to one target protein but TCBs can attach to two targets on different cells (they are 'bispecific'). Epcoritamab attaches to a protein called CD20 on B cells and to a protein called CD3 on T cells. This brings healthy T cells into close contact with the cancerous B cells, boosting the immune response to the cancer. This is the only treatment in patients with DLBCL that helps the body utilise the body's own T-cells against cancerous B cells. Therefore, it could provide an additional treatment option for relapsed or refractory DLBCL where previous treatments have failed.

Proposed Indication

This technology is being developed for patients with relapsed or refractory DLBCL, who have either failed or are ineligible for haematopoietic stem cell transplantation (HSCT).[1]

Technology

Description

Epcoritamab (DuoBody®-CD3xCD20, GEN3013) is a novel full-length IgG1 bispecific antibody (bsAb).[2] Epcoritamab attaches to a protein called CD20 on B cells and to a protein called CD3 on T cells, inducing T-cell activation and T-cell-mediated cytotoxicity towards malignant B cells.[3,4]

Epcoritamab is being developed for patients with relapsed or refractory DLBCL, who have either failed or are ineligible for HSCT. In the phase III trial, NCT04628494, epcoritamab will be administered in cycles of 28 days via SC injection until disease progression.[1]

Key Innovation

Several CD20-targeting mAbs, have been successfully applied for the treatment of B-cell NHL, however a high incidence of disease relapse occurs after treatment with currently available CD20-targeting mAbs.[5] For patients who relapse or don't respond to initial therapy, there are limited treatment options that provide durable responses and median life expectancy is approximately six months.[6] While conventional mAbs can eliminate target cells via several mechanisms, they do not exploit the powerful cytotoxic machinery of T-cells. Epcoritamab is a novel full-length IgG1 bsAb redirecting CD3+ T-cells to CD20 expressing cells which has been shown to induce T-cell activation and T-cell-mediated cytotoxicity towards malignant B cells.[2,3,4]

Regulatory & Development Status

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

Epcoritamab is currently in Phase II clinical trials for various types of lymphoma as well as relapsed/refractory chronic lymphocytic leukaemia.[7]

Patient Group

Disease Area and Clinical Need

DLBCL is a cancer of B cells and the most common type of fast-growing NHL.[8] In DLBCL, the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs.[9] The affected lymphocytes start to divide before they are fully mature and lose their infection-fighting properties which makes the body more vulnerable to infection.[10] Relapsed/refractory DLBCL refers to the disease reappearing after a period of remission or when the lymphoma becomes non-responsive to treatment.[11] 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; heredity; ethnicity (more likely in Caucasians); and gender (slightly higher in men). Symptoms of DLBCL include painless swelling in the neck, armpit or groin, night sweats, fevers and unexplained weight loss.[12]

Each year about 5,500 people are diagnosed with DLBCL in the UK.[13] This makes up about 40 out of 100 cases (40%) of NHL in adults.[9] 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).[14] Roughly one-third of patients with DLBCL relapse after receiving first-line treatment and 10% have refractory disease. 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 76363 FCE bed days.[15] 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 (ICD-code C83.3) was 2.8 for males and 1.6 for females.[14] In England, between 2013 and 2017 for a total of 56,350 NHL patients up to 2018, the age standardised one-year and five-year survival rate was 79.4% and 65.6% respectively.[16]

Recommended Treatment Options

Salvage treatment regimens with multi-agent immunochemotherapy are recommended for treatment for relapsed or refractory DLBCL to those that are fit enough to tolerate intensive treatment.[17] These include:[13,18]

- 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

For adults whose DLBCL is relapsed or refractory after at least two systemic therapies, the National Institute of Health and Care Excellence (NICE) recommends:[17]

- Polatuzumab vedotin with rituximab and bendamustine for adults who cannot have a HSCT.

The following therapies are recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory DLBCL in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed:[17]

- Tisagenlecleucel
- Axicabtagene ciloleucel

Clinical Trial Information

Trial	NCT04628494, A Randomized, Open-Label, Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in Relapsed/Refractory Diffuse Large B-cell Lymphoma **Phase III** - Recruiting **Location(s):** 10 EU, UK, Canada, United States and other countries **Primary completion date:** June 2023
Trial Design	Randomised, parallel assignment, open label
Population	N = 480, patients with relapsed or refractory disease and previously treated with at least 1 line of systemic antineoplastic therapy including anti-CD20 mAb-containing combination chemotherapy since lymphoma diagnosis; failed previous HDT-ASCT or not eligible for HDT-ASCT at screening; adults aged 18 years and older
Intervention(s)	Epcoritamab (SC)
Comparator(s)	Investigator's choice of chemotherapy

Outcome(s)	Primary Outcome: Compare the clinical efficacy of epcoritamab to standard of care (SOC) - Overall Survival (OS) [Time frame: throughout the study and up to 2 years following the last patient first dose] OS is calculated as the time from first dose to death date or last date known to be alive. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT04663347; Safety and Efficacy Trial of Epcoritamab Combinations in Subjects With B-cell Non-Hodgkin Lymphoma **Phase II** - Recruiting **Location(s):** 10 EU countries, UK, United States and Australia **Primary completion date:** April 30, 2023
Trial Design	Non-randomised, parallel-assignment, open label
Population	N = 270, patients with DLBCL; adults aged 18 years and older
Intervention(s)	Epcoritamab (SC) alongside one of the following dependent on study arm: • rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) • rituximab and lenalidomide (R2) • rituximab and bendamustine (RB) • rituximab, cytarabine, dexamethasone, and oxaliplatin/carboplatin (R-DHAX/C) • gemcitabine and oxaliplatin • rituximab and lenalidomide • epcoritamab maintenance
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures: • Number of dose-limiting toxicities (DLTs) [Time frame: DLTs are evaluated during the first cycle (28 days) in each cohort] • Number of Adverse Events [Time frame: From first dose up to safety follow-up (60 days after last trial treatment)] • Preliminary anti-tumour activity [Time frame: Up to approximately 3 years after the last subject's first treatment] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT03625037; GEN3013 Trial in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma **Phase I/II** - Recruiting **Location(s):** 10 EU countries (including the UK), United States, Canada and other countries **Primary completion date:** January 30, 2022
Trial Design	Sequential assignment, open label
Population	N = 486 patients with relapsed, progressive and/or refractory DLBCL following treatment with an anti-CD20 monoclonal antibody; adults aged 18 years and older
Intervention(s)	Epcoritamab (SC)
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures: • Escalation: Adverse Events (safety) to determine the Recommended Phase 2 Dose RP2D [Time frame: Adverse Events are assessed during the first cycle (28 days) in each cohort.] • Tolerability to determine the RP2D. [Time frame: DLTs are assessed during the first cycle (28 days) in each cohort.] • Safety, Adverse Event AE Evaluation. [Time frame: Until 1 year after last patient enters the trial, through study completion.] • Clinical Efficacy Evaluation. [Time Frame: Until 1 year after last patient enters the trial, through study completion.] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of Epcoritamab is not yet known.

Relevant Guidance

NICE Guidance

- 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 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.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
- NHS England. Interim Clinical Commissioning Policy Statement: Use of Plerixafor for Stem Cell Mobilisation. B04/PS/a. September 2013.
- NHS Commissioning Board. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. NHSCB/B04/P/a. April 2013.

Other Guidance

- European Society for Medical Oncology. 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[19]

Additional Information

References

1 Clinicaltrials.gov. *A Phase 3 Trial of Epcoritamab in R/R DLBCL*. *Trial ID*. 2021. Status: Recruiting. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04628494 [Accessed 16 November 2021].

2 van der Horst, H. J., de Jonge A. V., Hiemstra I. H., Gelderloos A. T., Berry D. R. A. I., Hijmering N. J., et al. *Epcoritamab induces potent anti-tumor activity against malignant B-cells from patients with DLBCL, FL and MCL, irrespective of prior CD20 monoclonal antibody treatment*. Blood Cancer Journal. Available from: https://doi.org/10.1038/s41408-021-00430-6

3 Engelberts, P. J., Hiemstra I. H., de Jong B., Schuurhuis D. H., Meesters J., Beltran Hernandez I., et al. *DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing*. EBioMedicine. 2020 2020/02/01/;52:102625. Available from: https://doi.org/10.1016/j.ebiom.2019.102625

4 *The Bispecific Antibody Epcoritamab Produces Responses in Lymphoma*. Cancer Discov. 2021 Sep 17. Available from: 10.1158/2159-8290.Cd-rw2021-133

5 Casan, J. M. L., Wong J., Northcott M. J., Opat S. *Anti-CD20 monoclonal antibodies: reviewing a revolution*. Human vaccines & immunotherapeutics. 2018;14(12):2820-41. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6343614/

6 Novartis. *Novartis JULIET trial of Kymriah demonstrates more than one-year durability of responses in adults with relapsed or refractory DLBCL.* 2018. Available from: https://www.novartis.com/news/media-releases/novartis-juliet-trial-kymriah-demonstrates-more-one-year-durability-responses-adults-relapsed-or-refractory-dlbcl [Accessed 12 October 2021].

7 Clinicaltrials.gov. *Epcoritamab.* 2021. Available from: https://clinicaltrials.gov/ct2/results?cond=Epcoritamab&term=&cntry=&state=&city=&dist= [Accessed 16 November 2021].

8 WebMD. *Diffuse Large B-Cell Lymphoma.* 2021. Available from: https://www.webmd.com/cancer/lymphoma/diffuse-large-b-cell-lymphoma#1 [Accessed 12 Oct 2021].

9 Cancer Research UK. *Diffuse large B cell lymphoma.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma [Accessed 12 October 2021].

10 NHS. *Overview Non-Hodgkin lymphoma.* 2018. Available from: https://www.nhs.uk/conditions/non-hodgkin-lymphoma/ [Accessed 12 October 2021].

11 Lymphoma Research Foundation. 2021. Available from: https://lymphoma.org/aboutlymphoma/nhl/dlbcl/relapseddlbcl/#:%7E:text=The%20term%20%E2%80%9Crelapsed%E2%80%9D%20refers%20to,does%20not%20last%20very%20long [Accessed 12 October 2021].

12 Macmillan Cancer Support. *Diffuse large B-cell lymphoma (DLBCL).* 2021. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/diffuse-large-b-cell [Accessed 12 October 2021].

13 Lymphoma Action. *Types of non-Hodgkin lymphoma.* 2021. Available from: https://lymphoma-action.org.uk/types-lymphoma/non-hodgkin-lymphoma [Accessed 12 October 2021].

14 Office for National Statistics (ONS). *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 14 October 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 14 October 2021].

16 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

17 National Institute for Health and Care Excellence (NICE). *Treating diffuse large B-cell lymphoma.* 2021. Available from: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma/treating-diffuse-large-b-cell-lymphoma#content=view-node%3Anodes-relapsed-or-refractory-disease [Accessed 12 October 2021].

18 Tilly, H., Gomes da Silva M., Vitolo U., Jack A., Meignan M., Lopez-Guillermo A., et al. *Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25. Available from: 10.1093/annonc/mdv304

19 Zelenetz, A. D., Abramson J. S., Advani R. H., Andreadis C. B., Byrd J. C., Czuczman M. S., et al. *NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas*. J Natl Compr Canc Netw. 2010 Mar;8(3):288-334. Available from: 10.6004/jnccn.2010.0021

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.