

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2021

Loncastuximab Tesirine for relapsed or refractory diffuse large B-cell lymphoma – third line

NIHRIO ID	26558	NICE ID	10505
Developer/Company	ADC Therapeutics SA	UKPS ID	N/A

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

Loncastuximab tesirine is currently in clinical development for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). DLBCL is a type of blood cancer that develops when white blood cells, called lymphocytes, grow out of control. The affected lymphocytes lose their infection fighting ability making the body more susceptible to infection. Relapsed cancer refers to cancer that initially responded to treatment but then returned. Refractory cancer refers to cancer that did not respond to treatment. The prognosis for patients with relapsed or refractory DLBCL remains poor, so there is a need to develop additional treatment options.

Loncastuximab tesirine is administered by intravenous infusion. It is an antibody-drug conjugate (ADC) where an antibody is joined to a drug that is designed to kill lymphoma cells. The antibody targets a protein called CD19, which is found on the surface of lymphoma cells. The drug is then released into the lymphoma cells resulting in the death of these cells. If licenced, loncastuximab tesirine will offer an additional treatment option for patients with relapsed or refractory DLBCL.

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.

PROPOSED INDICATION

Third line or greater treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL).¹

TECHNOLOGY

DESCRIPTION

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) composed of a humanized monoclonal antibody directed against human CD19- a protein found on the surface of lymphoma cells. Once bound to a CD19-expressing cell, the investigational drug is designed to be internalized by the cell, after which the cytotoxic payload is released. The payload is designed to bind irreversibly to DNA to create highly potent interstrand cross-links that block DNA strand separation, thus disrupting essential DNA metabolic processes such as replication and ultimately resulting in cell death.²

Loncastuximab tesirine is currently in clinical development for the treatment of patients with relapsed or refractory DLBCL.¹ In the phase II clinical trial (NCT03589469, EudraCT 2017-004288-11) participants will receive loncastuximab tesirine as an IV infusion over 30 minutes on day 1 of each cycle (every 3 weeks) at a dose of 150 µg/kg for 2 cycles, then 75µg/kg every 3 weeks for subsequent cycles for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.^{1,3}

INNOVATION AND/OR ADVANTAGES

There are not currently antibody-drug conjugate (ADC) interventions licensed in the treatment of DLBCL.⁴ ADCs represent a novel class of anticancer agents that enhance targeted killing of tumours while sparing normal tissues, thereby maximizing efficacy and minimizing systemic toxicity.⁵ Loncastuximab tesirine treatment has demonstrated positive outcomes and manageable toxicity.²

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Loncastuximab was granted orphan drug designation by the US FDA in June 2017 for the treatment of DLBCL.⁶

Loncastuximab is also in phase II clinical development for the treatment of mantle cell lymphoma and follicular lymphoma.⁷

DISEASE BACKGROUND

Lymphoma is a cancer of the lymph nodes that occurs when lymphocytes grow and multiply uncontrollably.⁸ Lymphomas are categorised into two broad groups: non-Hodgkin (NHL) and Hodgkin, NHL can be further divided into over 30 different subtypes.^{9,10} Around 40% of NHL cases are DLBCL which is a fast growing lymphoma subtype that develops when the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs. These abnormal cells are spread out (diffuse) rather than group together when they are examined under a microscope.^{11,12} 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.^{13,14} Refractory NHL is when the disease has not responded to initial treatment and is getting worse or staying the same. Relapsed NHL is when the NHL initially responded to treatment but then returned.¹⁵

The lymphatic system runs throughout the entire body and therefore NHL can appear anywhere.¹³ The first symptom of DLBCL is often a painless swelling in the neck, armpit or groin due to enlarged lymph nodes. Sometimes other parts of the body outside the lymph nodes can also be affected such as the stomach, bowel, liver, testis, skin, brain or eye. Symptoms are directly related to the amount of pressure the lymphoma is putting on the particular body part affected.¹² Some people with DLBCL may have other more general symptoms which include night sweats, unintentional weight loss or high temperature.¹¹ NHL, including DLBCL, are caused by a mutation in the DNA of lymphocytes resulting in them multiplying and growing uncontrollably but the exact reason why this happens is not known. A person's risk of developing the disease is increased by factors including: if they have a medical condition that weakens the immune system, have an autoimmune condition such as lupus or Sjogren's syndrome, they take immunosuppressant medication, they have previously received chemotherapy or radiotherapy for an earlier cancer or if they have previously been exposed to a common virus called Epstein-Barr virus which causes glandular fever. There is also a slightly increased risk of developing NHL if a first degree relative has the condition.^{16,17}

CLINICAL NEED AND BURDEN OF DISEASE

NHL is the 6th most common cancer in the UK, accounting for 4% of all new cancer cases.¹⁸ 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).¹⁹

For deaths registered in England in 2017, there were 1,105 deaths where diffuse NHL (ICD-10 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) was 2.8 for males and 1.6 for females.¹⁹ In England, between 2013 and 2017 a total of 56,350 NHL patients followed up to 2018, the age standardised one-year and five-year survival rate was 79.4% and 65.6% respectively.²⁰

According to the 2019-20 Hospital Episodes Statistics data, there were 39,515 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) which resulted in 35,369 admissions, 27,422 day cases and 86,774 FCE bed days.²¹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

At any stage, DLBCL is usually treated with the aim of curing it. It often responds well to treatment and many people go into complete remission. Treatment will depend on the stage of lymphoma the patient has, as well as age, general health and fitness and the patient's feelings towards treatment.¹² Since DLBCL can advance quickly, it usually requires immediate treatment which can lead to disease remission in a large number of patients with this form of lymphoma.²²

Approximately 50-60% of DLBCL patients achieve and maintain complete remission after first-line therapy. The prognosis of relapsed and refractory DLBCL is poor.²³ Most people with relapsed or refractory lymphoma are offered further chemo-immunotherapy, known as salvage treatment. The aim of salvage treatment is to reduce the lymphoma as much as possible rather than provide curative or overall survival benefit. In those patients who are fit enough after salvage treatment a stem cell transplant may increase the chance of have long-lasting remission.^{4,12,24}

CURRENT TREATMENT OPTIONS

The most commonly used salvage treatment regimens for relapsed or refractory DLBCL include:^{12,25}

- 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 2 or more systemic therapies NICE recommends:²⁶

- Tisagenlecleucel
- Axicabtagene ciloleucel

PLACE OF TECHNOLOGY

If licenced, loncastuximab tesirine will offer an additional treatment option for adults who have DLBCL that is relapsed or refractory to two or more multi-agent systemic treatment regimens.¹

CLINICAL TRIAL INFORMATION

Trial	NCT03589469 , EudraCT 2017-004288-11 ; A Phase 2 Open-Label Single-Arm Study to evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Phase II – Active, not recruiting Locations: UK, USA, Italy and Switzerland Estimated primary completion date: 24 May 2020
Trial design	Single group assignment, Open-label

Population	N=145; adults aged 18 years and older; pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma and high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements; relapsed or refractory disease following two or more multi-agent systemic treatment regimens
Intervention(s)	Loncastuximab tesirine (intravenous infusion)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: <ul style="list-style-type: none"> Overall response rate (ORR) [Time Frame: Up to 3 years] See trial record for full list of outcome measures
Results (efficacy)	To date, loncastuximab tesirine has achieved an ORR of 48.3% (70/145 patients), including 24.1% complete responses and 24.1% partial responses, across a broad population of relapsed or refractory DLBCL patients even those who are difficult to treat. The median duration of response is 10.25 months. ²⁷
Results (safety)	Overall, 143 (98.6%) patients had ≥1 treatment-emergent adverse event (TEAE), 105 (72.4%) patients had grade ≥3 TEAE, and 24 patients (16.6%) had TEAEs leading to treatment withdrawal. The most common (≥10%) grade ≥3 TEAEs were neutropenia (25.5%), thrombocytopenia (17.9%), GGT increased (16.6%), and anemia (10.3%). ²⁷

ESTIMATED COST

The estimated cost of loncastuximab tesirine 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 publication date to be confirmed.
- 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. Tisaenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma and 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

- British Society for Haematology. Management of Diffuse Large B-cell Lymphoma. 2016.²⁹
- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.³⁰

ADDITIONAL INFORMATION

ADC therapeutics 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

- 1 Clinicaltrials.gov. *A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)*. Trial ID NCT03589469. 2018. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT03589469> [Accessed 10 November 2020].
- 2 ADC Review. *Loncastuximab Tesirine Demonstrates an Overall High Response Rates in Pivotal Phase II Single-agent Trial*. 2020. Available from: <https://www.adcreview.com/news/loncastuximab-tesirine-demonstrates-an-high-response-rates-in-pivotal-phase-ii-single-agent-trial/> [Accessed 10 November 2020].
- 3 EU Clinical Trials Register. *A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)*. Trial ID 2017-004288-11. 2018. Status: Ongoing. Available from: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004288-11/GB> [Accessed 10 November 2020].
- 4 National Institute for Health and Care Excellence (NICE). *Non-Hodgkin's lymphoma: diagnosis and management (NG52)*. Last Update Date: 20 July 2016. Available from: <https://www.nice.org.uk/guidance/ng52/chapter/Recommendations> [Accessed 11 November 2020].
- 5 Yu, B., Liu D. *Antibody-drug conjugates in clinical trials for lymphoid malignancies and multiple myeloma*. *Journal of Hematology & Oncology*. 2019 2019/09/10;12(1):94. Available from: <https://doi.org/10.1186/s13045-019-0786-6>
- 6 BioSpace. *ADC Therapeutics Receives Orphan Drug Designation For ADCT-402 For The Treatment Of Diffuse Large B-Cell Lymphoma And Mantle Cell Lymphoma*. 2017. Available from: <https://www.biospace.com/article/releases/adc-therapeutics-receives-orphan-drug-designation-for-adct-402-for-the-treatment-of-diffuse-large-b-cell-lymphoma-and-mantle-cell-lymphoma-/> [Accessed 10 November 2020].
- 7 Clinicaltrials.gov. *Search for loncastuximab tesirine clinical trials: Phase II and III*. 2020. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=Loncastuximab+tesirine&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=

- [1&phase=2&rsb=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=](#) [Accessed 10 November 2020].
- 8 Live Science. *Lymphatic System: Facts, Functions & Diseases*. 2018. Available from: <https://www.livescience.com/26983-lymphatic-system.html> [Accessed 17 November 2020].
- 9 Memorial Sloan Kettering Cancer Center. *Types of Lymphoma*. 2020. Available from: <https://www.mskcc.org/cancer-care/types/lymphoma/types> [Accessed 11 November 2020].
- 10 Cancer Treatment Centers of America. *Non-Hodgkin lymphoma types*. 2020. Available from: <https://www.cancercenter.com/cancer-types/non-hodgkin-lymphoma/types> [Accessed 17 November 2020].
- 11 Cancer Research UK. *Diffuse large B cell lymphoma*. 2019. Available from: <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma> [Accessed 11 February 2020].
- 12 Lymphoma Action. *Diffuse large B-cell lymphoma*. 2020. Available from: <https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma> [Accessed 11 November 2020].
- 13 Cancer Research UK. *What is non-Hodgkin lymphoma?* 2018. Available from: <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/about> [Accessed 11 November 2020].
- 14 National Health Service (NHS). *Non-Hodgkin Lymphoma: Overview*. 2018. Available from: <https://www.nhs.uk/conditions/non-hodgkin-lymphoma/> [Accessed 11 November 2020].
- 15 Leukemia & Lymphoma Society. *Relapsed And Refractory NHL*. 2020. Available from: <https://www.lls.org/lymphoma/non-hodgkin-lymphoma/treatment/refractory-and-relapsed> [Accessed 11 November 2020].
- 16 NHS inform. *Non-Hodgkin lymphoma*. 2020. Available from: <https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/non-hodgkin-lymphoma> [Accessed 11 November 2020].
- 17 NHS inform. *Causes of non-Hodgkin lymphoma*. 2020. Available from: <https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/non-hodgkin-lymphoma#causes-of-non-hodgkin-lymphoma> [Accessed 11 November 2020].
- 18 Cancer Research UK. *Non-Hodgkin Lymphoma (NHL) incidence statistics*. 2020. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma#heading-Zero> [Accessed 11 November 2020].
- 19 Office for National Statistics (ONS). *Cancer registration statistics, England*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Downloaded 26 April 2019].
- 20 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> [Downloaded 12 August 2019].
- 21 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20> [Downloaded 17 September 2020].
- 22 Lymphoma Research Foundation. *Diffuse Large B-cell Lymphoma: Treatment Options*. 2020. Available from: <https://lymphoma.org/aboutlymphoma/nhl/dlbcl/dlbcltreatment/> [Accessed 11 November 2020].
- 23 Raut, L. S., Chakrabarti P. P. *Management of relapsed-refractory diffuse large B cell lymphoma*. South Asian journal of cancer. 2014;3(1):66-70. Available from: <https://www.thieme-connect.de/products/ejournals/pdf/10.4103/2278-330X.126531.pdf>
- 24 British Society for Haematology. *Management of Diffuse Large B-cell Lymphoma*. 2016. Available from: <https://b-s-h.org.uk/guidelines/guidelines/management-of-diffuse-large-b-cell-lymphoma/> [Accessed 11 November 2020].
- 25 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*. Annals of Oncology. 2015;26:v116-v25. Available from: <https://doi.org/10.1093/annonc/mdv304>
- 26 National Institute for Health and Care Excellence (NICE). *Non-Hodgkin's lymphoma - everything NICE says in an interactive flowchart*. 2020. Available from:

- <https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma/non-hodgkins-lymphoma-overview> [Accessed 11 November 2020].
- 27 ADC Therapeutics. *ADC Therapeutics Announces Positive Results from Pivotal Phase 2 Clinical Trial of Single Agent Loncastuximab Tesirine (ADCT-402) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma*. 2020. Available from: <https://www.globenewswire.com/news-release/2020/01/09/1968282/0/en/ADC-Therapeutics-Announces-Positive-Results-from-Pivotal-Phase-2-Clinical-Trial-of-Single-Agent-Loncastuximab-Tesirine-ADCT-402-in-Patients-with-Relapsed-or-Refractory-Diffuse-Larg.html> [Accessed 10 November 2011].
- 29 Chaganti, S., Illidge T., Barrington S., McKay P., Linton K., Cwynarski K., et al. *Guidelines for the management of diffuse large B-cell lymphoma*. *British Journal of Haematology*. 2016 2016/07/01;174(1):43-56. Available from: <https://doi.org/10.1111/bjh.14136>
- 30 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: <https://doi.org/10.1093/annonc/mdv304>

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