

**NIHR Innovation Observatory
Evidence Briefing: February 2018**

**Lisocabtagene maraleucel (Liso-Cel) for
relapsed/refractory diffuse large B-cell lymphoma**

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LAY SUMMARY

Non-Hodgkin's lymphoma (NHL) is a type of cancer of the lymphatic system, and diffuse large B-cell lymphoma (DLBCL) is a common type of NHL. DLBCL develops from abnormal B-cells (a type of white blood cell), with the abnormal cells being larger than normal, healthy B-cells. The abnormal cells in DLBCL are spread diffusely throughout the tumour. The causes of DLBCL are not known, but most people diagnosed with the disease are aged 65 years and over, and the disease affects slightly more men than women.

Lisocabtagene maraleucel (Liso-Cel) is a therapy that uses the patient's own cells to fight the cancer. Healthy white blood cells are taken from the patient's blood and re-programmed to fight the cancer cells in DLBCL. When these cells are returned to the body, the programmed cells act by tracking down and destroy the cancer cells. If licensed, this therapy would provide a new kind of treatment for patients whose DLBCL has come back after previous successful treatment (relapsed) or where the disease has not responded to previous treatment (refractory). This therapy also has the potential to improve patient treatment by being available in an outpatient setting when compared to similar treatments that have to be administered in a hospital/specialist setting.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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.

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TARGET GROUP

Diffuse large B-cell lymphoma (DLBCL), relapsed or refractory – third-line or second-line non-transplant eligible

TECHNOLOGY

DESCRIPTION

Lisocabtagene maraleucel (Liso-Cel, JCAR017) is a CD19-directed 4-1BB CAR T-cell product administered in a defined composition at a precise dose of CD8 and CD4 CAR T cells.¹ Chimeric antigen receptors (CAR) are recombinant receptor constructs composed of an extracellular single-chain variable fragment (scFv) derived from an antibody, joined to a hinge/spacer peptide and a transmembrane domain, which is further linked to the intracellular T cell signalling domains of the T-cell receptor. CAR-T cells combine the specificity of an antibody with the cytotoxic and memory functions of T cells.²

Lisocabtagene maraleucel is a therapy that uses the patient's own healthy T-cells to fight the cancer. The CAR-T technology acts to re-programme T-cells to target cells that express a specific protein (CD19) that is commonly found on DLBCL cells. To produce lisocabtagene maraleucel, T-cells are first extracted from the patient's blood and are genetically modified to produce a CAR protein. The CAR consists of an antibody, a protein that interacts with CD19, which can stimulate a signalling domain, sending a message to the T-cell when CD19 binds to it. Prior to the modified T-cells being returned to the body, patients are given a chemotherapy aiming at lymphocyte depletion. This creates a better environment for the modified T-cells to expand and persist in the body. Lisocabtagene maraleucel is administered as an intravenous infusion, and is designed to track down and destroy the cancer cells.³

In the phase I trial TRANSCEND-NHL-001 (NCT02631044⁴), lisocabtagene maraleucel was administered as a flat dose at dose level 1 (DL1) of 5×10^7 CAR+ T cells (2.5×10^7 CD4+CAR+ T cells and 2.5×10^7 CD8+CAR+ T cells) or at dose level 2 (DL2) 1×10^8 CAR+ T cells (5×10^7 CD4+CAR+ T cells and 5×10^7 CD8+CAR+ T cells). At the site, the product was administered at a patient-specific volume.⁵

Lisocabtagene maraleucel does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Preliminary safety data show lower rates of all grade cytokine release syndrome (CRS) and neurotoxicity (NT) than reported for other CD19-directed CAR T cell products with broad heterogeneity of CAR T cell dosing and cell composition characteristics, though all grade events for all of those products have not been reported. Based on its safety and tolerability data, Lisocabtagene maraleucel has been administered in the outpatient setting and there are plans to have a proportion of patients in the pivotal cohort treated as outpatients.⁶

If licensed, lisocabtagene maraleucel will offer an additional treatment option for patients with relapsed/refractory DLBCL after at least two previous lines of therapy, who currently have few (well-

tolerated) effective therapies available. It also has the potential to improve patient treatment by being available in an outpatient setting.

DEVELOPER

Celgene and Juno Therapeutics.

REGULATORY INFORMATION/ MARKETING PLANS

Lisocabtagene maraleucel has been granted the following statuses for DLBCL:

- PRIME status awarded by EMA in December 2016
- orphan drug in the EU in July 2017
- orphan drug in the USA in April 2016
- Breakthrough Therapy Designation awarded by FDA in December 2016
- Regenerative Medicine Advanced Therapy (RMAT) Designation by FDA in October 2017

PATIENT GROUP

BACKGROUND

Non-Hodgkin's lymphoma (NHL) is a type of cancer of the lymphatic system, and diffuse large B-cell lymphoma (DLBCL) is the most common type of high grade (fast-growing) NHL.⁷ DLBCL develops from abnormal B-cells, with the abnormal cells being larger than normal, healthy B-cells, and the abnormal cells are spread diffusely throughout the tumour and wipe out the normal structure of the lymph node. The causes of lymphoma are not known, but most people diagnosed with DLBCL are aged 65 years and over, and the disease affects slightly more men than women.⁸

The first symptoms of DLBCL are usually painless lumps, often in the neck, armpit or groin, which are enlarged lymph nodes. DLBCL can also develop in lymph nodes deep inside the body which cannot be felt from the outside. DLBCL can be hard to diagnose as people have different symptoms depending what organs and tissues are affected, but diagnosis can be confirmed by a biopsy. Most people have advanced-stage DLBCL when they are diagnosed.⁸

CLINICAL NEED and BURDEN OF DISEASE

The latest available statistics in the Cancer Registration Statistics, England, 2016 showed 6,400 new registrations of diffuse NHL (ICD-10 code C83).⁹ It is estimated that about a third of people with NHL have DLBCL⁷, which would equate to 2,133 registrations per year.

Although most patients are cured with 6-8 cycles of first-line R-CHOP chemotherapy, about 10-15% have primary refractory disease and a further 20-30% relapse.¹⁰ This would equate to around 270 patients having primary refractory disease, and 530 having relapsed disease, per year.

The latest five-year survival for NHL was reported as 66.9% (age-standardised persons, patients diagnosed between 2011 and 2015).¹¹

For hospital activity, in 2015/16 there were 35,255 admissions with primary diagnosis ICD-10 code C83.3 Diffuse large B-cell lymphoma, of which 27,933 were day cases.¹² For the wider primary diagnosis C83 there were 58,916 admissions, indicating that DLBCL accounted for 59.8% of NHL admissions.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for treatment relapsed or refractory diffuse large B-cell lymphoma [ID986] (GID-TA10140). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma ID1166 (GID-TA10269). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115] (GID-TA10214). Expected date of issue to be confirmed.
- NICE quality standard. Haematological cancers (QS150). June 2017.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE interactive flowchart. Treating diffuse large B-cell lymphoma.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

British Society for Haematology. Management of Diffuse Large B-cell Lymphoma. May 2016.¹⁰

European Society for Medical Oncology. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016.¹³

European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2015.¹⁴

CURRENT TREATMENT OPTIONS

Patients with relapsed/refractory DLBCL who are eligible for transplant should receive intensive salvage regimens with rituximab and chemotherapy followed by (in responsive patients) autologous or allogeneic stem cell transplantation (ASCT).¹⁴ Salvage regimens such as R-DHAP or R-ICE appear to have similar outcomes.¹⁴ The main goal of salvage is to reduce disease burden and demonstrate

continued chemotherapy sensitivity prior to ASCT¹⁰, but salvage chemotherapy is also beneficial even if not followed by transplantation. ¹⁵ NICE also recommends considering R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimens and less toxic.¹⁵

Pixantrone monotherapy is recommended as an option for treating patients with multiple relapsed or refractory aggressive DLBCL only if the person has previously been treated with rituximab and the person is receiving third- or fourth-line treatment and the manufacturer provides pixantrone with the discount agreed in the patient access scheme.¹⁶

Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GEMOX.¹⁴

EFFICACY and SAFETY

Trial	TRANSCEND-NHL-001, NCT02631044; Lisocabtagene maraleucel; phase I
Sponsor	Celgene, Juno Therapeutics Inc
Status	Ongoing, not reported
Source of Information	Trial registry ⁴
Location	USA
Design	Non-randomised, parallel assignment
Participants	N=274 (planned); aged 18 yrs and older; B-cell NHL; relapsed or refractory after at least 2 prior lines of therapy or after auto hematopoietic stem cell transplantation (auto-HSCT)
Schedule	Lisocabtagene maraleucel will be administered at a single flat dose of 5×10^7 CAR+T cells or 1×10^8 CAR+T cells. A few patients will receive a 2-dose schedule at 5×10^7 CAR+T cells.
Follow-up	24 mths following infusion
Primary Outcomes	<ul style="list-style-type: none"> • Treatment-related adverse events [Time Frame: Up to 730 days after the final infusion] • Dose-limiting toxicity (DLT) of lisocabtagene maraleucel [Time Frame: 28 days after first (single-dose schedule) or second (2-dose schedule) infusion] • Objective response rate [Time Frame: 24 mths] • Maximum concentration of lisocabtagene maraleucel in the peripheral blood and bone marrow [Time Frame: Up to 365 days after the final infusion] • Time to maximum concentration of lisocabtagene maraleucel in the peripheral blood and bone marrow [Time Frame: Up to 365 days after the final infusion] • Area under the concentration vs time curve in the peripheral blood and bone marrow [Time Frame: Up to 365 days after the final infusion]
Secondary Outcomes	<ul style="list-style-type: none"> • Complete response rate [Time Frame: 24 mths] • Duration of response [Time Frame: 24 mths]

	<ul style="list-style-type: none"> • Progression-free survival [Time Frame: 24 mths] • Overall survival [Time Frame: Up to 15 yrs] • Health-related quality of life [Time Frame: 24 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as Oct 2018. Preliminary results reported December 2017. ⁶

Trial	TRANSCEND WORLD, JCAR017-BCM-001; Lisocabtagene maraleucel in combination with Durvalumab; phase II
Sponsor	Celgene
Status	Not started recruiting (not registered on CT.gov at time of writing)
Source of Information	Company ^a
Location	Not known
Design	Non-randomised, multi-cohort
Participants	N=124 (planned); age not stated; aggressive B-cell NHL; DLBCL NOS (de novo and transformed indolent B-NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 re-arrangements with DLBCL histology (DHL/THL), DLBCL with secondary CNS involvement and Richter's transformation; after ≥ 2 lines of therapy, including an anthracycline and rituximab (or other CD20-targeted agent)
Schedule	Not reported
Follow-up	Not reported
Primary Outcomes	Overall response rate
Secondary Outcomes	<ul style="list-style-type: none"> • Complete response rate • Event free survival • Progression free survival • Overall survival • Duration of response • Pharmacokinetics • Patient reported outcomes
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date not reported

^a Company provided information on UK PharmaScan (645601).

ESTIMATED COST and IMPACT

COST

The cost of lisocabtagene maraleucel is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input checked="" type="checkbox"/> Re-organisation of existing services (from day case to outpatient setting if appropriate) | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input checked="" type="checkbox"/> Other: unable to state if cost of single treatment with Liso-Cel would be cheaper than current available treatments | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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