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HEALTH TECHNOLOGY BRIEFING
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Lisocabtagene maraleucel for relapsed or refractory, aggressive B-cell non-Hodgkin Lymphoma – second line

NIHRIO ID	25477	**NICE ID**	10384
Developer/Company	Celgene Ltd	**UKPS ID**	655778

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

SUMMARY

Lisocabtagene maraleucel is in clinical development as a treatment for adult patients with aggressive B-cell non-Hodgkin lymphoma (NHL) who are relapsed or refractory to a single line of immunochemotherapy (and whom are ineligible for stem cell transplantation). In NHL, the affected lymphocytes start to multiply in an abnormal way and begin to collect in certain parts of the body such as the lymph nodes. Aggressive or high-grade lymphomas tend to grow very quickly. Relapsed means the lymphoma has responded to treatment but then returns, and refractory means the lymphoma has not responded to the initial treatment. Treatment options for relapsed/refractory aggressive B-cell lymphoma are limited.

Lisocabtagene maraleucel is an advanced immunotherapy administered intravenously that contains the patient's own white blood cells (T-cells) that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). The CAR T-cells attach to a particular protein called CD19 on the surface of cancer cells resulting in the death of these cells. If licensed, will offer an additional treatment option for patients with relapsed/refractory, aggressive B-cell NHL who are not eligible for stem cell transplant.

PROPOSED INDICATION

Second line treatment of adults who have relapsed from, or are refractory to, a single line of immunochemotherapy for aggressive B-cell non-Hodgkin lymphoma (NHL) and are ineligible for haematopoietic stem cell transplant.[1]

TECHNOLOGY

DESCRIPTION

Lisocabtagene maraleucel (Liso-cel) is a chimeric antigen receptor (CAR) T-cell therapy designed to target CD19 which is a surface glycoprotein expressed during normal B-cell development and maintained following malignant transformation of B cells. Lisocabtagene maraleucel aims to target CD-19 expressing cells through a CAR construct that includes an anti-CD19 single chain variable fragment targeting domain for antigen specificity, a transmembrane domain, a 4-1BB costimulatory domain hypothesized to increase T-cell proliferation and persistence, and a CD3-zeta T-cell activation domain.[2] Studies suggest CD-19 CAR-T cell-based immunotherapies effectively recognize and kill CD-19-postive target cells and result in a high clinical response rate in the treatment of refractory B-cell malignancies.[3]

In the phase II clinical trial TRANSCEND-PILOT-017006 (NCT03483103) participants are given a single dose of lisocabtagene maraleucel ($100x10^6$ CAR+ T cells) by intravenous injection on day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy).[1]

INNOVATION AND/OR ADVANTAGES

An advantage of CAR T-cell therapy is the short treatment time needed because the therapy is administered with a single infusion. The recovery time is also much more rapid compared to stem cell transplants where aggressive chemotherapy is also used.[4]

Liso-cel has a highly controlled manufacturing process that, unlike other CAR T cell therapies, enables administration of a defined composition with a precise dose of CD8+ and CD4+ CAR T cells. The manufacturing process and control strategy reduces the risk of complete manufacturing failure and minimises product variability in quality attributes, which may contribute to an improved safety and efficacy profile.[5] Lisocabtagene maraleucel appears to exhibit a safer toxicity profile compared to axicabtagene ciloleucel and tisagenlecleucel, which are the other CD19-targeted CAR-T cell therapies approved in the treatment of relapsed/refractory, aggressive NHL, and has the potential for outpatient administration.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lisocabtagene maraleucel does not currently have Marketing Authorisation in the EU/UK for any indication, however a marketing authorisation application was submitted in June 2020 for adults with relapsed/refractory DLBCL, PMBCL and FL3B after at least two prior therapies.[7]

Lisocabtagene maraleucel was granted an orphan designation for the treatment of primary mediastinal large B-cell lymphoma by the EMA in November 2018.[8]

Lisocabtagene is currently in phase II clinical development for the treatment of other forms of lymphoma and lymphocytic leukaemia.[9]

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer of the lymphatic system. The lymphatic system is a system of lymphatic vessels and lymph nodes that run throughout the body. Tissue fluid called lymph circulates around the body in these vessels and flows through the lymph nodes. The lymphatic system is an important part of our immune system that plays a role in fighting bacteria and other infections and it tries to destroy old or abnormal cells, such as cancer cells. In people who have lymphoma, white blood cells divide abnormally before they are fully mature. This means they can't fight infection as normal white blood cells do and they begin to collect in the lymph nodes or other places such as the bone marrow or spleen. They can then grow into tumours and begin to cause problems in the lymphatic system or in the organ in which they are growing.[10]

There are two main types of lymphoma: Hodgkin lymphoma and NHL. In NHL, the affected lymphocytes start to multiply in an abnormal way and begin to collect in certain parts of the lymphatic system, such as the lymph nodes.[11] NHL is divided into more than 30 types, classified based on the type of lymphocyte involved: B lymphocytes (B cells) or T lymphocytes (T cells). NHL can be further classified by other factors such as whether it is aggressive (fast-growing) or indolent (slow-growing).[12] Relapsed lymphoma is when the lymphoma comes back after successful treatment and a period of remission (no evidence of lymphoma on tests and scans). Refractory lymphoma is when the lymphoma does not respond well to the first choice of treatment.[13]

The most common symptom of non-Hodgkin lymphoma is a painless swelling in a lymph node, usually in the neck, armpit or groin. Other more general symptoms can night sweats, unintentional weight loss, a high temperature, breathlessness or persistent itching of the skin all over the body.[14] NHL is caused by a mutation in the DNA of lymphocytes although the exact reason for this mutation isn't known. Risk factors for developing NHL include having: a medical condition that weakens the immune system, medical treatment that weakens the immune system, autoimmune conditions, been infected with the Epstein-Barr virus, or Helicobacter pylori, received chemotherapy or radiotherapy for an earlier cancer and coeliac disease.[15]

CLINICAL NEED AND BURDEN OF DISEASE

According to the Haematological Malignancy Research Network, in the UK in 2016, there was expected to be 5,510 people with diffuse large B-cell lymphoma (DLBCL) and 2,220 with follicular lymphoma.[16]

Overall, for NHL, European age-standardised incidence rates are projected to decrease by 2.75% from 32.45 per 100,000 in 2014 to 31.56 per 100,000 in 2035 in males, and by 3.32% from 22.67 per 100,000 in 2014 to 21.92 per 100,000 in 2035 in females.[17]

In England, in 2017, there were a total of 4,348 registrations of deaths due to NHL (ICD-10 code: C82-C85).[18]

The age-standardised one-year and five-year survival rates for NHL (all subtypes combined) in England over the period 2013 and 2017, followed up to 2018, show that 78.4% of men are expected to survive for at least 1 year, and 63.7% are expected to survive for 5 years. The survival rates for women are slightly higher with 80.6% expected to survive for at least 1 year and 68.1% expected to survive for 5 years.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NHL is determined by a multidisciplinary team which usually includes a haematologist, cancer nurse, a pathologist, a radiotherapy specialist, a pharmacist and radiologist. Treatment depends on the type and grade of NHL, the stage of NHL, general health of the patient and the patient's age.[20]

The main types of treatment for NHL are chemotherapy, targeted cancer drugs and radiotherapy. Other treatment types include stem cell transplant and surgery.[20]

CURRENT TREATMENT OPTIONS

For treatment of relapsed or refractory to one prior treatment for follicular lymphoma, NICE currently recommends:[21]

- Obinutuzumab with bandamustine (following treatment with rituximab)
- Lenalidomide with rituximab
- Rituximab

There are currently no treatment options recommended by NICE for the treatment of DLBCL that is relapsed/refractory to one prior line of treatment.[22]

PLACE OF TECHNOLOGY

If licensed, lisocabtagene maraleucel will offer an additional treatment option for patients with aggressive B-cell non-Hodgkin lymphomas who are relapsed or refractory to a single line of immune-chemotherapy for whom haematopoietic stem cell transplant is not suitable.

CLINICAL TRIAL INFORMATION

Trial	**TRANSCEND-PILOT,** NCT03483103; A Phase 2 Study of Lisocabtagene (JCAR017) as Second-Line Therapy in Adult Patients With Aggressive B-cell NHL (017006) **Phase II** – Recruiting **Location**: United States **Primary completion date**: April 2021
Trial design	Single group assignment, open-label
Population	N=56 (planned); adults aged 18 years and older; confirmation of relapsed or refractory aggressive B-cell non-Hodgkin lymphoma; previous treatment with a single line of chemo-

	immunotherapy containing an anthracycline and a CD20 targeted agent
Intervention(s)	Lisocabtagene maraleucel (intravenous infusion)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Overall response rate – anti-tumour activity [Time frame: through month 24] See trial record for full list of other outcomes.
Results (efficacy)	At data cut off, 25 patients had lymphodepleting chemotherapy followed by lisocabtagene maraleucel infusion. At median follow-up of 3.5 months the objective response rate was 80%. 48% of patients achieved complete response.[23]
Results (safety)	72% of patients had grade ≥3 treatment emergent adverse events (TEAEs), 40% of which were cytopenias. No grade 5 adverse events (AEs) occurred within the first 30 days after lisocabtagene infusion. Five patients (20%) had cytokine release syndrome (CRS) and 3 (12%) had neurological events (NE). No grade 3 or 4 CRS was observed; 2 patients (8%) had grade 3 or 4 NEs. Five patients (20%) received toclizumab and/or dexamethasone for CRS/NEs.[23]

ESTIMATED COST

The estimated cost of Lisocabtagene maraleucel is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (TA10223). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tafastiamab with lenalidomide for previously treated diffuse large B-cell lymphoma (TA10645). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy (TA10580). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (TA10463). Expected publication date: September 2020.
- NICE technology appraisal. Lenalidomide with rituximab for previously treated follicular lymphoma (TA627). April 2020.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016.
- NICE quality standard. Haematological cancers (QS150). 2017

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[24]
- European Society of Medical Oncology (ESMO). Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[25]
- London Cancer. Guidelines for the management of non-Hodgkin's and Hodgkin's lymphoma in adults. 2014.[26]

ADDITIONAL INFORMATION

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