National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: July 2017

KTE-C19 for relapsed or refractory mantle cell lymphoma

NIHRIO (HSRIC) ID: 11846 NICE ID: 9122

LAY SUMMARY

Mantle cell lymphoma is an uncommon type of non-Hodgkin lymphoma. It occurs when B lymphocytes in the mantle zone of the lymph node begin to create too much of a protein called cyclin D1. Cyclin D1 helps to control cell growth, however too much cyclin D1 causes uncontrolled growth and leads to the development of mantle cell lymphoma. Mantle cell lymphoma is more likely to occur in older people and in men. Many patients relapse after first line treatment.

KTE-C19 is a therapy where some of the patient's blood cells are removed, engineered to contain a compound which targets and kills the lymphoma cells, and re-injected into the patient. It requires blood to be taken from the patient and then a single intravenous administration of treated cells, which may stay active in the body and reduce relapse.

Currently patients with relapsed or refractory mantle cell lymphoma require chemotherapy and (if possible) autologous stem cell transplant, so the new treatment represents an innovative way of treating these patients.

TARGET GROUP

Relapsed or refractory mantle cell lymphoma, following (i) anthracycline or bendamustine-containing chemotherapy, and (ii) anti-CD20 monoclonal antibody therapy, and (iii) ibrutinib.[1]

TECHNOLOGY

DESCRIPTION

KTE-C19 is an immunotherapy in which a patient's T cells are engineered to express a chimeric antigen receptor (CAR) to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphoma, and redirect the T cells to kill cancer cells. It is designed for patients who have relapsed and/or are refractory to standard therapy.

A single intravenous infusion of engineered T cells, at a target dose of 2 x 10^6 anti-CD19 CAR T cells per kg, is a complete course of therapy.[2]

KTE-C19 is in phase II development for acute lymphoblastic leukaemia.

Axicabtagene ciloleucel, a similar product manufactured using a different process, is in pre-registration for follicular lymphoma, diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma. Finally, it is also in phase 1 development for follicular lymphoma.

Neither KTE-C19 nor axicabtagene ciloleucel currently has Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

KTE-C19 is likely to be the first ever CAR-T therapy to gain regulatory approval in mantle cell lymphoma, and represents a major breakthrough in innovative treatments for patients with relapsed or refractory mantle cell lymphoma.

Whereas patients tend to relapse after current treatment, CAR-T therapy is more likely to guard against recurrence because the CAR-T cells may remain in the body long after the infusion has been completed.

DEVELOPER

Kite Pharma, Inc; National Institutes of Health

AVAILABILITY, LAUNCH or MARKETING

In phase II trials.

PATIENT GROUP

BACKGROUND

Mantle cell lymphoma is an uncommon type of non-Hodgkin lymphoma. It occurs when B lymphocytes in the mantle zone of the lymph node begin to create too much of a protein called cyclin D1 which helps to control cell growth. Too much cyclin D1 causes uncontrolled growth and leads to the development of mantle cell lymphoma. As with other lymphomas, the exact cause of the disease is unknown but it may be associated with a weakened immune system, certain infections, or some lifestyle factors.[3]

The commonest symptom of mantle cell lymphoma is one or more swollen lymph nodes (glands). Mantle cell lymphoma can also affect other areas such as the bone marrow, leading to anaemia and resultant tiredness, or the bowel, causing diarrhoea. Rarely, the disease can spread to the brain and spinal cord, leading to headaches, nausea, dizziness, or confusion.[3]

CLINICAL NEED and BURDEN OF DISEASE

Of those diagnosed with non Hodgkin lymphoma, 5-10% have mantle cell lymphoma. The incidence of mantle cell lymphoma in the UK is 0.86 per 100,000, with a median survival of 3-5 years and five year overall survival of 25%. It is more than twice as likely to occur in men, and most likely to occur in people over the age of 50.[4] It tends to be diagnosed in the later stages of disease, and is considered largely incurable using standard Rituxan-based chemotherapy approaches.[2]

In 2015-16, there were 6,950 admissions for mantle cell lymphoma (ICD-10 code C83.1) in England, resulting in 9,590 bed days and 7,340 finished consultant episodes.[5]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lymphoma (mantle cell, relapsed, refractory) - ibrutinib (GID-TAG497). Expected date of issue December 2016 (delayed to unspecified date).
- NICE technology appraisal (suspended February 2016). Lymphoma (mantle cell, relapsed, refractory) - lenalidomide (GID-TAG508).
- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract For Ophthalmic Pathology Service (All Ages). D12/S(HSS)/b.
- 2013/14 NHS Standard Contract for Brachytherapy and Molecular Radiotherapy (All Ages). B01/S/b
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

- NHS England. Clinical Commissioning Policy: Use of Plerixafor for Stem Cell Mobilisation (Update). B04/P/b. January 2015.

OTHER GUIDANCE

- Dreyling M, Geisler C, Hermine O, Kluin-Nelemans HC, Le Gouill S, Rule S, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2014;25(suppl_3):iii83-iii92.
- Dreyling, M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O et al. ESMO Consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Annals of Oncology* 24, no. 4 (2013): 857-877.
- McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. *British Journal of Haematology*. 2012;159(4):405-26.

CURRENT TREATMENT OPTIONS

Guidelines recommend the use of chemotherapy in combination with rituximab for first line treatment for people with advanced-stage mantle cell lymphoma who are symptomatic. If there is at least a partial response to induction chemotherapy then NICE guidelines suggest that autologous stem cell transplantation can be considered in patients who are fit enough. Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable.

EFFICACY and SAFETY

Trial	ZUMA-2, GDCT0233302, GDC30006437, NCT02601313, KTE-C19-102, ILYM-15080, NCI-2015-02028, 16-134, 2015-005008-27, EudraCT-2015-005008-27; phase II
Sponsor	Kite Pharma Inc
Status	Ongoing
Source of Information	Trial registry[1]
Location	Netherlands, USA
Design	Non-randomised, uncontrolled, single group assignment study
Participants	n=70 (planned); aged 18+ years; relapsed or refractory mantle cell lymphoma; up to 5 prior regimens including anthracycline or bendamustine-containing chemotherapy and anti-CD20 monoclonal antibody therapy and ibrutinib
Schedule	Patients receive conditioning chemotherapy regimen of fludarabine and cyclophosphamide, followed by a single infusion of chimeric antigen receptor (CAR) transduced autologous T cells administered intravenously at a target dose of 2 x 106 anti-CD19 CAR+ T cells per kg
Follow-up	12 mths
Primary Outcomes	Overall response rate, objective response rate
Secondary Outcomes	Pharmacokinetics, pharmacodynamics, and predictive biomarker analyses; duration of response; best objective response; objective response rate per IRRC; progression free survival; overall survival; incidence of adverse events and clinically significant changes in

	laboratory values; incidence of anti-KTE-C19 antibodies, levels of anti CD19 CAR+ T cells in blood and levels of cytokines in serum
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	2018

ESTIMATED COST and IMPACT

COST

The cost of KTE-C19 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☒ Need for new services: CAR-T

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

1 ClinicalTrials.gov. *A Phase 2 multicenter study evaluating subjects with relapsed/refractory mantle cell lymphoma (ZUMA-2)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02601313?term=ZUMA-2&cond=Mantle+Cell+Lymphoma&rank=1 [Accessed 30-06-2017].

2 Global Data. *Axicabtagene ciloleucel*. Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=242420 [Accessed 14-07-2017].

3 Lymphoma Association. *Mantle cell lymphoma*. Available from: https://www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma/mantle-cell-lymphoma [Accessed 30-06-2017].

4 Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, et al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *British journal of cancer*. 2015;112(9):1575-84.

5 NHS Digital. *Hospital episode statistics for England. Admitted patient care statistics, 2015-16* Report 2015.