NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2023

Obecabtagene autoleucel for treating refractory or relapsed B cell acute lymphoblastic leukaemia

Company/Developer	Autolus Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30444	NICE ID: N/A	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase II clinical trial

Summary

Obecabtagene autoleucel is an advanced therapy medicinal product (gene therapy product) known as 'Chimeric Antigen Receptor' (CAR) T cell therapy which is in clinical development for relapsed/refractory B-cell acute lymphoblastic leukaemia (B-ALL) in adults. B-ALL is an aggressive type of leukaemia (cancer of the blood and bone marrow), that can progress rapidly without treatment and has a high mortality rate. The cancer causes immature white blood cells to be released too early into the blood which blocks other types of blood cells (such as red blood cells and platelets) from circulating. Relapsed and refractory disease is where the disease goes through periods of being active or in remission, but as the disease progresses periods of remission often become shorter and less frequent. This results in symptoms such as frequent infections, bleeding, breathlessness, and fatigue. There are currently limited treatment options available for patients with B-ALL.

Obecabtagene autoleucel is created by modifying the genes in the patient's own T cells (immune cells) so that they make the CAR protein. Once infused back into the patient, these modified cells can recognise and bind to a protein found on the cancer cells, killing them, and helping to remove them from the body. Obecabtagene autoleucel has been developed to limit toxicity seen in previous CAR T treatments, and for the effects to last longer in the body to increase long-term remission rates. If licenced obecabtagene will provide a novel and targeted therapy for treatment of adult patients with relapsed/refractory B-ALL.

Proposed Indication

Treatment of adult patients with relapsed or refractory (r/r) B cell acute lymphoblastic leukaemia (B-ALL).[1]

Technology

Description

Obecabtagene autoleucel (AUTO1, Obe-cel, CAT19-41BB-Z) is an autologous CD19 chimeric antigen receptor (CAR) T cell therapy with a unique CD19 CAR.[2] Like all CD19 CAR T cell therapies, this treatment programmes immune T cells to make an artificial protein called a CD19 (CAR) on their surface, directing them to specifically recognise cancerous cells. It has a fast off rate, designed for more physiologic T -cell activation to reduce toxicity and improve engraftment.[3]

Obecabtagene autoleucel is currently in clinical development for treatment of adult patients with r/r B-ALL. In a phase I/II clinical trial (NCT04404660), following pre-conditioning with chemotherapy (cyclophosphamide and fludarabine) patients will be treated with a total target dose of 410E+6 of CD19-positive CAR T cells as a split dose on day 1 and on day 10 (±2 days) administered as infusion.[1,3]

Key Innovation

Obecabtagene autoleucel is an advanced therapy medicinal product (ATMP) (a gene therapy product).[4] The scientific recommendation for an ATMP classification is issued by the European Medicines Agency's (EMA) Committee far Advanced Therapies (CAT).[5]

In standard CAR T cell therapy, the immune system can become over-activated causing a toxic reaction called cytokine release syndrome. Another consequence of over-activation is that the engineered T cells become immunologically exhausted and no longer persist in the patient's body, which can allow the cancer to relapse.[6] Obecabtagene autoleucel is designed to overcome the limitations in clinical activity and safety compared to current CD19 CAR T cell therapies. Designed to have a fast target binding off-rate to minimize excessive activation of the programmed T cells, obecabtagene autoleucel may reduce toxicity and be less prone to T cell exhaustion, which could enhance persistence and improve the ability of the programmed T cells to engage in serial killing of target cancer cells.[7] This new type of therapy design is known as a "fast off-rate CAR".[6] If licenced, obecabtagene autoleucel will provide a novel therapy for the treatment of adults with r/r B-ALL.

Regulatory & Development Status

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

Obecabtagene autoleucel has the following designation/awards for the treatment of ALL.[4,7,8]

- An orphan drug in the EU in April 2022.
- A PRIME designation by the EU in April 2021.
- Innovative Licensing and Access Pathway (ILAP) by the UK in June 2021.

Patient Group

Disease Area and Clinical Need

ALL is a type of cancer that affects white blood cells. It progresses quickly and aggressively and requires immediate treatment. Both adults and children can be affected. Most cases of ALL develop in children, teenagers, and young adults. A genetic mutation in the stem cells causes immature white blood cells to be released into the bloodstream, resulting in the number of platelets and red blood cells circulating to decrease. Risk factors include previous chemotherapy, smoking, obesity, genetic disorders like Down's syndrome and having weakened immune system. Symptoms of ALL might include pale skin, feeling tired and breathless, repeated infections over a short period, unusual and frequent bleeding such as bleeding gums or nose bleeds, high temperature, night sweats, bone, and joint pain. The lack of healthy blood cells can make the person extremely vulnerable to life-threatening infections and prone to uncontrolled and serious bleeding.[9]

ALL is rare, with around 790 people diagnosed with the condition each year in the UK.[9] ALL accounted for less than 1% of all new cancer cases in the UK in 2016-2018.[10] In England (2021-22), there were 36,101 finished consultant episodes (FCEs) and 35,035 admissions for ALL (ICD-10 code C91.0), which resulted in 51,283 FCE bed days and 29,042 day cases.[11] In England (2017), there were 4,226 patients diagnosed with ALL and 1,085 deaths registered where ALL was the underlying cause.[12] Prognosis for patients based on current treatments is very poor. Combination chemotherapy enables 90% of adult patients to enter complete remission, but only 30-40% of these patients will achieve long term remission. The median overall survival is <1 year in r/r adult ALL.[2] The one-year survival rate for patients diagnosed with leukaemia in England between 2013 and 2017 was 72.4%, dropping to 53.5% over five years.[13]

Recommended Treatment Options

The main treatment for ALL is chemotherapy but other treatment options can include a targeted cancer drug, immunotherapy, or a stem cell or bone marrow transplant depending on the stage and subtype of the cancer.[14]

The following treatments are currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment acute lymphoblastic leukaemia.[15]

- Blinatumomab
- Tisagenlecleucel
- Inotuzumab ozogamicin
- Ponatinib
- Pegaspargase

Clinical Trial Information

Trial	**FELIX;** NCT04404660; 2019-001937-16; An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating the Safety and Efficacy of AUTO1, a CAR T Cell Treatment Targeting CD19, in Adult Patients With Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia **Phase I/II -** Recruiting **Location(s):** UK, Spain, and USA **Primary completion date:** June 2023
Trial Design	Single group assignment, open label
Population	N=215 (estimated); adult patients with relapsed or refractory ALL; aged 18 years and older.

Intervention(s)	Obecabtagene autoleucel
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Phase Ib - Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) occurring after obecabtagene autoleucel infusion [Time frame: Up to 24 months] • Phase II - Cohort IIA: ORR defined as proportion of patients achieving CR or CRi as assessed by an IRRC. Cohort IIB: Proportion of patients achieving MRD-negative remission by NGS, with results also including PCR/flow cytometry as supportive analysis. [Time frame: Up to 24 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT02935257; Immunotherapy for High Risk/Relapsed CD19+ Acute Lymphoblastic Leukaemia, B-cell Non-Hodgkin's Lymphoma (B-NHL) and Chronic Lymphocytic Leukaemia (CLL)/ Small Lymphocytic Lymphoma (SLL) Using CAR T-cells to Target CD19. **Phase I** - Recruiting **Location(s):** UK **Primary completion date:** December 2024
Trial Design	Single group assignment, open label, non-randomised
Population	N=60 (estimated); patients with high risk of relapsed/refractory (r/r) CD19+ B-ALL, r/r Diffuse large B-cell lymphoma (DLBCL), r/r Chronic Lymphocytic Leukaemia (CLL)/ Small Lymphocytic Lymphoma (SLL), r/r Follicular lymphoma (FL), and r/r mantle cell lymphoma. adults (age ≥16).
Intervention(s)	Infusion with obecabtagene autoleucel
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Toxicity evaluated by the incidence of grade 3-5 toxicity causally related to the ATIMP [Time frame: 28 days] • Feasibility of manufacturing CD19CAR T-cells evaluated by the number of therapeutic products generated [Time frame: 30 days]
Results (efficacy)	25 patients were leukapheresed, 24 products were manufactured, and 20 patients were infused with obecabtagene autoleucel. The median age was 41.5 years; 25% had prior blinatumomab, 50% prior inotuzumab ozogamicin, and 65% prior allogeneic stem-cell transplantation. At the time of preconditioning, 45% had ≥ 50% bone marrow blasts. No patients experienced ≥ grade 3 cytokine release syndrome; 3 of 20 (15%) experienced grade 3 neurotoxicity

	that resolved to ≤ grade 1 within 72 hours with steroids. Seventeen of 20 (85%) achieved minimal residual disease–negative complete response at month 1, and 3 of 17 underwent allogeneic stem-cell transplantation while in remission. The event-free survival at 6 and 12 months was 68.3% (42.4%-84.4%) and 48.3% (23.1%-69.7%), respectively. High-level expansion (Cmax 127,152 copies/µg genomic DNA) and durable CAR-T persistence were observed with B-cell aplasia ongoing in 15 of 20 patients at last follow-up.[3]
Results (safety)	Obecabtagene autoleucel demonstrates a tolerable safety profile, high remission rates, and excellent persistence in r/r adult B-ALL. Preliminary data support further development of obecabtagene autoleucel as a stand-alone treatment for r/r adult B-ALL.[3]

Estimated Cost

The cost of obecabtagene autoleucel is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [GID-TA10424]. Expected publication date June 2023.
- NICE technology appraisal in development. KTE-X19 for previously treated B-precursor acute lymphoblastic leukaemia in people aged 2 to 21 [GID-TA10316]. Expected date of publication to be confirmed.
- NICE technology appraisal. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [TA554]. December 2018.
- NICE technology appraisal. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [TA541]. September 2018.
- NICE guideline. Haematological cancers: improving outcomes [NG47]. May 2016.
- NICE quality standards. Haematological cancers [QS150]. June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology; Acute Lymphoblastic Leukaemia, Version 2.2021.[16]
- European Society for Medical Oncology (ESMO). Acute Lymphoblastic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2020.[17]

Additional Information

Autolus Ltd 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

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