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# Health Technology Briefing
# October 2022

# Letetresgene autoleucel for treating synovial sarcoma and myxoid round cell liposarcoma

| Company/Developer | GlaxoSmithKline UK Ltd |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 28785 | NICE TSID: 10652 | UKPS ID: 663074 |
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## Licensing and Market Availability Plans

Currently in phase II trials

## Summary

Letetresgene autoleucel is in clinical development for the treatment of advanced synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCLS) in children and adults. Both SS and MRCLS are two different types of soft tissue sarcomas, rare forms of cancer that develop in the tissues that connect, support, and surround other body structures and organs. Advanced SS or MRCLS means that the cancer has spread to other parts of the body. Currently there are limited therapies available for these patients, so there is a need to develop additional treatment options.

Letetresgene autoleucel is a medicinal product made from the patient's own T-cells (a type of immune cell). The T-cells are modified to target a particular protein called NY-ESO-1, which is a marker expressed on most tumour cells of SS and MRCLS. Once administered, letetresgene autoleucel attaches to the cancer cell surface, promoting death of the cancer cell. If licensed, letetresgene autoleucel would offer a novel treatment option for affected adults and children.

## Proposed Indication

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.

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Treatment of children aged 10 years or older and adults with NY-ESO-1 positive synovial sarcoma (SS) or myxoid/round cell liposarcoma (MRCLS).[1]

# Technology

## Description

Letetresgene autoleucel (GSK3377794) is an autologous polyclonal T-cell immunotherapy based on Adaptimmune SPEAR T-cells (Specific Peptide Enhanced Affinity Receptor T-cells) which are designed to target New York Oesophageal Squamous Cell Carcinoma-1 (NY-ESO-1) or Cancer/Testis Antigen 2 (CTAG2/LAGE-1a) antigenic peptides in complex with human leukocyte antigen (HLA-A2). T-cells are collected from the patient by leukapheresis (a process used for white blood cell collection) and then transduced by a self-inactivating lentiviral vector to express an affinity-enhanced T-cell receptor.[2]

Letetresgene autoleucel is currently in clinical trials for children aged 10 years or older and adults with SS and MRCLS. In the phase II clinical trial IGNYTE-ESO (NCT03967223), participants in two separate sub-studies undergo leukapheresis (to collect and modify T-cells), and then receive a single unspecified dose of letetresgene autoleucel.[1]

## Key Innovation

Letetresgene autoleucel for SS and MRCLS may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[2]

Chemotherapy is the only pharmaceutical intervention currently available for SS patients.[3] Both SS and MRCLS are often initially sensitive to chemotherapy, however, both diseases can be aggressive and have dismal outcomes in the refractory metastatic setting.[4] Patients with metastatic SS and MRCLS have limited therapeutic options. NY-ESO-1 is highly expressed in most tumours, including SS and MRCLS, and prior phase I studies investigating T-cell therapies targeting this protein has shown clinical significance.[2,5]

If licensed, leteresgene autoleucel will offer a novel therapeutic treatment option for patients with SS and MRCLS.

## Regulatory & Development Status

Letetresgene autoleucel does not currently have marketing authorisation in the EU/UK for any indication.

Letetresgene autoleucel has the following regulatory awards/designations:[2]

- European Medicines Agency (EMA) Priority Medicine (PRIME) status for the treatment of HLA-A*201, HLA-A*205, or HLA-A*206 allele positive patients with inoperable or metastatic SS who have received prior chemotherapy and whose tumour expresses the NY-ESO-1 tumour antigen, in July 2016
- Granted orphan drug status in EU for synovial sarcoma in July 2016
- FDA breakthrough therapy status for HLA-A*201, HLA-A*205 or HLA-A*206 allele-positive patients with inoperable or metastatic SS who received prior chemotherapy and whose tumour expressed the NY-ESO-1 tumour antigen, in February 2016

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Letetresgene autoleucel is currently in phase II trials for advanced MRCLS, SS and non-small cell lung cancer.[6]

## Patient Group

### Disease Area and Clinical Need

SS is a rare and aggressive soft tissue sarcoma (STS) that develops in cells around the joints and tendons; it is most commonly associated with young adults.[7,8] SS can occur anywhere throughout the body but most often occurs near the knee and the arms. Less frequently the disease can develop in the trunk, head, neck, or the abdomen.[9] SS can be slow growing tumours and in the early stage, the disease often goes unnoticed until the tumour grows larger and results in a lump, swelling or pain.[8,9] In some cases, the tumour can limit range of motion or cause numbness and/or pain if it presses on nearby nerves. The exact cause of SS is poorly understood are there are no well-established risk factors for SS. However, the disease is associated with an oncogenic driver translocation between chromosome X and chromosome 18.[8]

Myoxid liposarcoma and round cell liposarcoma are both subtypes of liposarcoma (a type of cancer that grows in the cells that store fat in the body) which can be grouped together into one category known MRCLS, one of the four subtypes of adult liposarcoma.[10-12] These tumours are commonly found in the limbs, and in one third of MRCLS cases the tumour will metastasize and spread to distant tissues in other unusual bone and soft tissue locations.[13] Many patients with liposarcoma have no symptoms until the tumour is large and interferes with neighbouring structures. Symptoms vary depending on the location of the tumour but can include swelling; decreased range of motion; numbness; fatigue; abdominal pain; weight loss; nausea; and vomiting.[11]

Soft tissue sarcomas are a rare type of cancer, accounting for 1% of cancers diagnosed in the UK.[14] In England (2017-2019) there were 4,295 new cases of soft tissue sarcoma (STS).[15] In England (2021/22) there were 1,112 finished consultant episodes (FCE) for malignant neoplasm of connective and soft tissue, unspecified (ICD-10 code C49.9), which resulted in 1,029 admissions, 755 day cases and 1,363 FCE bed days.[16] Synovial sarcoma is a rare subtype of STS, accounting for 5-10% of all soft tissue sarcoma cases. It is most commonly associated with teenagers and young adults.[7] Prognostic outcomes in patients with metastatic synovial sarcoma are poor with 5-year overall survival estimated to be around 10%, and survival rates further decreasing with additional lines of therapy.[17,18] Liposarcoma is one of the most common subtypes of STS in the UK, accounting for around 13% of diagnoses.[19,20] MRCLS often presents at a younger age than other liposarcoma subtypes, with a typical age of diagnosis ranging between 35-55 years.[13] In England, (2009), the age standardised incidence rate of MRCLS was 1.1 per million.[21]

### Recommended Treatment Options

Currently The National Institute for Health and Care Excellence (NICE) only recommends trabectedin for advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide or if these agents are contraindicated.[22]

Treatment for SS and MRCLS depends on whether it has spread. Given that SS can grow for a while before it is found, there is a greater chance that it will spread to other parts of the body. Surgery is the first choice of treatment for SS. When all of the tumour is removed and there is no sign of cancer anywhere else in the body, there is a better chance of survival. Success of the surgery depends on the size of the tumour and its location in the body. Other treatment options include radiation therapy and chemotherapy.[10,23]

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## Clinical Trial Information

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| Trial | **IGNYTE-ESO,** NCT03967223, Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, Alone or in Combination With Other Agents, in HLA-A2+ Participants With NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)<br>**Phase II:** Recruiting<br>**Location(s):** 4 EU countries, UK, US, Canada and other countries<br>**Primary completion date:** November 2022 |
| Trial Design | Non-randomised, parallel assignment, open label |
| Population | N=97; children and adults 10 years and older; must be positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a designated central laboratory; tumour is positive for NY-ESO-1 expression; diagnosis of SS or MRCLS |
| Intervention(s) | 1. Letetresgene autoleucel in previously untreated advanced (metastatic or unresectable) SS or MRCLS<br>2. Letetresgene autoleucel in advanced (metastatic or unresectable) SS or MRCLS post anthracycline chemo |
| Comparator(s) | - |
| Outcome(s) | Primary outcome(s):<br>1. Substudy 1: Overall response rate (ORR) [time frame: until disease progression (up to 5 years)]<br>2. Substudy 2: ORR as assessed by central independent review [time frame: up to 5 years]<br>See trial record for all other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The estimated cost of letetresgene autoleucel is currently unknown.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. NY-ESO-1 for treating synovial sarcoma (GID-TA10205). Expected date of issue to be confirmed.
- NICE technology appraisal. Trabectedin for the treatment of advanced soft tissue sarcoma (TA185). February 2010.
- NICE quality standard. Sarcoma (QS78). January 2015.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

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- NHS England. 2013/14 NHS Standard Contract for NHS Standard Service Specification Template for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.

Other Guidance

- European Society for Medical Oncology (ESMO). Soft Tissue and Visceral Sarcomas: ESMO-EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. 2018.[24]
- Clinical Sarcoma Research. UK guidelines for the management of soft tissue sarcomas. 2016.[25]

## Additional Information

## References

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