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HEALTH TECHNOLOGY BRIEFING
JULY 2021

Afamitresgene autoleucel for advanced synovial sarcoma or myxoid/round cell liposarcoma

NIHRIO ID	28109	**NICE ID**	10648
Developer/Company	AdaptImmune	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Afamitresgene autoleucel is in clinical development for the treatment of advanced synovial sarcoma or myxoid/round cell liposarcoma (MRCLS) in patients who have previously had chemotherapy. Both synovial sarcoma and MRCLS are two different types of soft tissue sarcomas (STS), a rare form of cancer that develops in the tissues that connect, support and surround other body structures and organs. Advanced synovial sarcoma 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.

Afamitresgene autoleucel is a medicinal product designed using a patient's own T-cells (a type of white blood cell). The T-cell is genetically modified so that it produces a protein that attaches to a protein known as MAGE-A4. MAGE-A4 is found on cancerous cells in synovial sarcoma and MRCLS. When afamitresgene autoleucel is administered as a single intravenous infusion it recognises and attaches to MAGE-A4 cancerous cells via the human leukocyte antigen (HLA)-A*02 protein which is found at the surface of the cancerous cells, and kills them. If licenced, afamitresgene autoleucel would offer an additional treatment option for advanced synovial sarcoma or MRCLS, and would be the first approved T-cell therapy for these patients.

PROPOSED INDICATION

Treatment of HLA-A*02 allele positive patients with metastatic or inoperable (advanced) synovial sarcoma or MRCLS whose tumours express the Melanoma-associated antigen 4 (MAGE-A4) protein and have been previously treated with an anthracycline or ifosfamide containing regimen.[1,2]

TECHNOLOGY

DESCRIPTION

Afamitresgene autoleucel (ADP-A2M4), is a type of autologous cell therapy designed using specific peptide enhanced affinity receptor T-cells (SPEAR) technology.[3,4] It contains the patient's own T cells that have been genetically modified so that the comlementarity-determining regions (CDRs) of the patient's T-cells have enhanced affinity to the human leucocyte antigen (HLA) peptide complex on cancer cells that express the protein MAGE-A4.[2,5] When afamitresgene autoleucel is administered to the patient, the modified T-cells attach to the MAGE-A4 protein expressed on cancer cells and results in death of the cancerous cells.[3]

Afamitresgene autoleucel is currently in clinical development for the treatment of advanced synovial sarcoma and MRCLS. In the phase II trial, SPEARHEAD 1 (NCT04044768, EudraCT 2019-000589-39), patients will receive a single intravenous infusion of afamitresgene autoleucel (1-10x10^9) after receiving lymphodepleting chemotherapy consisting of fludarabine (30 mg/m^2/day x 4 days) and cyclophosphamide (600 mg/m^2/day x 3 days).[1,2]

INNOVATION AND/OR ADVANTAGES

If approved, this medicinal product would be the first engineered T-cell therapy recommended by NICE as treatment for advanced synovial sarcoma and MRCLS.[6] Using a patient's own T-cells reduces the chances of an immunological reaction and of graft-versus host disease compared to allogeneic transplantation.[7] The T-cells persist in the patient's body eliciting a long-term response so only a single infusion is needed.[7,8] Additionally, because aggressive chemotherapy is not used, the recovery time for patients is more rapid than stem cell transplants where aggressive chemotherapy is required.[8]

Prognosis for patients with metastatic (advanced) synovial sarcoma or MRCLS, in the refractory setting is very poor, creating a need to develop additional, more effective treatment options for these patients.[9,10] Emerging evidence from the phase II trial indicates that afamitresgene autoleucel has the potential to offer substantial benefit to patients with MRCLS or advanced synovial sarcoma with an response rate (ORR) of 39.3% in these patients.[11]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Afamitresgene autoleucel is not currently licenced in the EU/UK for any indication.

Afamitresgene autoleucel is not currently in phase II or III clinical development for any other indications.[12]

Afamitresgene autoleucel received an orphan designation by the EMA in August 2020 for the treatment of soft tissue sarcoma.[3] Afamitresgene autoleucel was awarded a PRIME status by the EMA in July 2020 for the treatment of synovial sarcoma.[13]

Afamitresgene autoleucel was awarded a PRIME status by the EMA in July 2020 for the treatment of synovial sarcoma.[14]

PATIENT GROUP

DISEASE BACKGROUND

Synovial sarcoma 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.[15,16] Synovial sarcoma can occur anywhere throughout the body but most often occurs near the knee and then second most commonly, the arms. Less frequently the disease can develop in the trunk, head, neck or the abdomen.[17] Synovial sarcomas 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.[16,17] In some cases, the tumour can limit range of motion or cause numbness and/or pain if it presses on nearby nerves.[16] The exact cause of synovial sarcoma is poorly understood are there are no well-established risk factors for synovial sarcoma. However, the disease is associated with an oncogenic driver translocation between chromosome X and chromosome 18 in more than 90% of cases.[18]

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.[19-21] 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.[22] 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.[20]

90% of MRCLS lesions have a characteristic chromosomal translocation that results in the creation of a FUS-DDIT3 hybrid protein that promotes malignant transformation by dysregulating ribonucleic acid (RNA) transcription which results in dysregulated adipocyte differentiation and cell-cycle control.[22] The specific cause of liposarcoma is still unknown but clinically it can be first noticed particularly in an area of recent trauma, however the cause and effect are quite likely to be coincidental.[21]

CLINICAL NEED AND BURDEN OF DISEASE

STS are a rare type of cancer, accounting for 1% of cancers diagnosed in the UK.[23] In England (2010) there were 2,740 people diagnosed with STS.[24] In England (2019/20) there were 819 finished consultant episodes (FCE) for malignant neoplasm of connective and soft tissue, unspecified (ICD-10 code C49.9), which resulted in 759 admissions, 516 day cases and 1,258 FCE bed days.[25]

Synovial sarcoma is a rare subtype of STS, accounting for 5-10% of all soft tissue sarcoma cases. It is most commonly associated with young adults and reaches a peak incidence in the third decade of life.[15] 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.[26,27]

Liposarcoma is one of the most common subtypes of STS in the UK, accounting for around 13% of diagnoses.[28,29] MRCLS often presents at a younger age than other liposarcoma subtypes, with a typical age of diagnosis ranging between 35-55 years.[22] In England, (2009), the age standardised incidence rate of MRCLS was 1.1 per million.[30]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the UK, oncological management of metastatic STS is typically based at the department of health designated STS centres.[31]

Treatment of soft tissue sarcomas including synovial sarcoma and MRCLS depends on the age of the patient, the size and location of the tumour and the severity of the disease.[16] The most common treatment option is surgical resection to remove the entire tumour. However, in patients with advanced or metastatic disease the prognosis is poor. There are no curative treatment options and chemotherapy treatment is recommended instead to control the tumour.[32,33]

CURRENT TREATMENT OPTIONS

NICE currently recommends trabectedin for the treatment of advanced soft tissue sarcomas where treatment with anthracyclines and ifosfamide has failed or patients are intolerant to these treatments.[6,34]

Pazopanib may also be a cost effective therapy for non-adipogenic metastatic STS, including synovial sarcoma patients in the UK.[35-37]

Eribulin has Marketing Authorisation for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease, however this has not been recommended by NICE.[38,39]

PLACE OF TECHNOLOGY

If licenced, afamitresgene autoleucel will offer an additional treatment option for patients with advanced synovial sarcoma or MRCLS who currently have a poor prognosis and will be the first approved treatment option that uses T-cell therapy.[6,33]

CLINICAL TRIAL INFORMATION

Trial	**SPEARHEAD 1, NCT04044768, EudraCT 2019-000589-39**; A Phase 2 single arm open-label clinical trial of ADP-A2M4 SPEAR™ T-cells in subjects with synovial sarcoma or myxoid/round cell liposarcoma **Phase II** – Recruiting **Locations:** 2 EU countries, UK, Canada and USA. **Estimated Primary Completion Date:** October 2021
Trial design	Open-label, single group assignment
Population	N=90; ages 16 to 75 years old; diagnosis of advanced synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma confirmed by cytogenetics; previously received either an anthracycline or ifosfamide containing regimen; HLA-A*02 positive; tumour MAGE-A4 expression
Intervention(s)	Autologous genetically modified afamitresgene autoleucel ($1.0\text{-}10x10^9$) by single intravenous infusion
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measure: Efficacy - Overall response rate [Time Frame: 2.5 years] See trial record for full list of outcome measures
Results (efficacy)	At the time of data cut-off, 37 patients had received afamitresgene autoleucel (32 with synovial sarcoma, and 5 with MRCLS). Of the 37 patients who had received treatment, 33 had at least one scan as of data cut-off (29 with synovial sarcoma, 4 with MRCLS). The overall response rate was 39.3%; 41.4% (12/29) for synovial sarcoma and 25.0% (1/4) for MRCLS. Of the 29 patients with synovial sarcoma with at least one scan: 2 had complete responses; 10 had partial responses; 13 had stable disease; and 4 had progressive disease. Of the 4 patients with MRCLS with at least one scan: 1 patient had a partial response, 2 had stable disease, and 1 had progressive disease.[11]
Results (safety)	To date, the safety profile of afamitresgene autoleucel has been favourable, with mainly low-grade cytokine release syndrome and tolerable/reversible haematologic toxicities.[11]

ESTIMATED COST

The estimated cost of afamitresgene autoleucel is not yet known.

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 2015 (last updated February 2021).
- 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.

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.[40]
- Clinical Sarcoma Research. UK guidelines for the management of soft tissue sarcomas. 2016.[33]

ADDITIONAL INFORMATION

AdaptImmune 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

1 Clinicaltrials.gov. *A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects With Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma. Trial ID: NCT04044768*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04044768 [Accessed 26 June 2021].

2 Araujo DM, Druta M, Agulnik M, D'Angelo SP, Blay J-Y, Strauss SJ, et al. SPEARHEAD-1: A phase II trial of ADP-A2M4 SPEAR T cells in patients with advanced synovial sarcoma or myxoid/round cell liposarcoma. *Journal of Clinical Oncology*. 2020;38(15_suppl):TPS11569-TPS. Available from: https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS11569.

3 European Medicines Agency (EMA). *Public summary of opinion on orphan designation Autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding an affinity enhanced T cell receptor specific to MAGE-A4 for the treatment of soft tissue sarcoma.* 2020. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/20/2286-

public-summary-opinion-orphan-designation-autologous-cd4-cd8-t-cells-transduced-lentiviral_en.pdf [Accessed 07 July 2021].
4 Cancer Network. *Synovial Sarcoma Sees Impressive Responses With T-Cell Therapy Afamitresgene Autoleucel.* 2021. Available from: https://www.cancernetwork.com/view/synovial-sarcoma-sees-impressive-responses-with-t-cell-therapy-afamitresgene-autoleucel [Accessed 28 June 2021].
5 Adaptimmune. *Technology Overview.* 2021. Available from: https://www.adaptimmune.com/technology [Accessed 28 June 2021].
6 National Institute for Health and Care Excellence (NICE). *NICE Pathways: Sarcoma Overview.* 2021. Available from: https://pathways.nice.org.uk/pathways/sarcoma [Accessed 07 July 2021].
7 Horizon Discovery. *The future of cell-based immunotherapy: autologous vs allogeneic treatment.* 2020. Available from: https://horizondiscovery.com/en/blog/the-future-of-cell-based-immunotherapy [Accessed 07 July 2021].
8 RWJ Barnabas Health. *Advantages of CAR T-cell Therapy.* 2021. Available from: https://www.cinj.org/patient-care/advantages-car-t-cell-therapy [Accessed 07 July 2021].
9 Pollack SM, Somaiah N, Araujo DM, Druta M, Van Tine BA, Burgess MA, et al. Clinical outcomes of patients with advanced synovial sarcoma or myxoid/round cell liposarcoma treated at major cancer centers in the United States. *Cancer Medicine*. 2020;9(13):4593-602. Available from: https://doi.org/10.1002/cam4.3039.
10 Kelly CM, Antonescu CR, Bowler T, Munhoz R, Chi P, Dickson MA, et al. Objective Response Rate Among Patients With Locally Advanced or Metastatic Sarcoma Treated With Talimogene Laherparepvec in Combination With Pembrolizumab. *JAMA Oncology*. 2020;6(3):402. Available from: https://doi.org/10.1001/jamaoncol.2019.6152.
11 Adaptimmune. *Two Complete Responses and Response Rate of 41% for People with Synovial Sarcoma Reported at ASCO in Adaptimmune's Phase 2 SPEARHEAD-1 Trial.* 2021. Available from: https://www.adaptimmune.com/investors-and-media/news-events/press-releases/detail/193/two-complete-responses-and-response-rate-of-41-for-people [Accessed 26 June 2021].
12 Clinicaltrials.gov. *Search for afamitresgene autoleucel clinical trials: Phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=afamitresgene+autoleucel&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 26 June 2021].
13 European Medicines Agency (EMA). *List of medicines currently in PRIME scheme*. Available from: https://www.ema.europa.eu/documents/report/list-products-granted-eligibility-prime_en-0.xlsx [Downloaded 09 June 2021].
14 European Medicines Agency (EMA). *List of products granted eligibility to PRIME*. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines [Downloaded 01 July 2021].
15 Sarcoma UK. *Synovial Sarcoma.* 2021. Available from: https://sarcoma.org.uk/sarcoma-types/synovial-sarcoma [Accessed 26 June 2021].
16 National Cancer Registration and Analysis Service (NCRAS). *Synovial Sarcoma.* 2015. Available from: https://rarediseases.info.nih.gov/diseases/7721/synovial-sarcoma [Accessed 01 July 2021].
17 Oxford University Hospitals (NHS Trust). *Synovial sarcoma: Information for patients.* 2014. Available from: https://www.ouh.nhs.uk/patient-guide/leaflets/files/10677Psynovial.pdf [Accessed 01 July 2021].
18 National Center for Advancing Translational Sciences. *Synovial Sarcoma.* 2015. Available from: https://rarediseases.info.nih.gov/diseases/7721/synovial-sarcoma [Accessed 28/06/2021].
19 National Cancer Institute. *Myxoid/Round Cell Liposarcoma.* 2021. Available from: https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-soft-tissue-tumors/myxoid-round-cell-liposarcoma [Accessed 07 July 2021].
20 National Center for Advancing Translational Sciences. *Myxoid liposarcoma.* 2016. Available from: https://rarediseases.info.nih.gov/diseases/7157/myxoid-liposarcoma [Accessed 07 July 2021].

21 National Organisation for Rare Disorders (NORD). *Liposarcoma*. 2018. Available from: https://rarediseases.org/rare-diseases/liposarcoma/ [Accessed 07 July 2021].
22 Orphanet. *Myxoid/round cell liposarcoma*. 2013. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=99967 [Accessed 14 July 2021].
23 NHS Inform. *Soft tissue sarcomas*. 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/soft-tissue-sarcomas [Accessed 07 July 2021].
24 Cancer Research UK. *Soft tissue sarcoma incidence by sex and UK region*. 2013. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma/incidence#heading-Zero [Accessed 07 July 2021].
25 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Downloaded 17 September 2020].
26 Riedel R, Jones R, Italiano A, Bohac C, Thompson J, Mueller K, et al. Systemic Anti-Cancer Therapy in Synovial Sarcoma: A Systematic Review. *Cancers*. 2018;10(11):417. Available from: https://doi.org/10.3390/cancers10110417.
27 Savina M, Le Cesne A, Blay JY, Ray-Coquard I, Mir O, Toulmonde M, et al. Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. *BMC Med*. 2017 Apr 10;15(1):78. Available from: https://doi.org/10.1186/s12916-017-0831-7.
28 Cancer Research UK. *Soft tissue sarcoma incidence*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma#heading-Zero [Accessed 07 July 2021].
29 Adaptimmune. *Synovial Sarcoma*. 2021. Available from: https://www.adaptimmune.com/patients-families/cancer-information/synovial-sarcoma [Accessed 07 July 2021].
30 National Cancer Intelligence Network. *Soft Tissue Sarcoma Incidence and Survival Tumours Diagnosed in England Between 1985 and 2009*. 2012. Available from: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/sarcomas/ [Accessed 07 July 2021].
31 NHS England. *Sarcoma (all ages) (170122S)*. Last Update Date: July 2019. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/07/Sarcoma-Service-Specification.pdf [Accessed 24 July 2021].
32 National Cancer Institute. *Synovial Sarcoma*. 2019. Available from: https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-soft-tissue-tumors/synovial-sarcoma#:~:text=How%20common%20is%20synovial%20sarcoma,per%20year%20in%20the%20US. [Accessed 07 July 2021].
33 Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016;6:20. Available from: https://doi.org/10.1186/s13569-016-0060-4.
34 National Institute for Health and Care Excellence (NICE). *Trabectedin for the treatment of advanced soft tissue sarcoma (TA185)*. Last Update Date: 08 February 2021. Available from: https://www.nice.org.uk/guidance/ta185/resources/trabectedin-for-the-treatment-of-advanced-soft-tissue-sarcoma-pdf-82598497821637 [Accessed 07 July 2021].
35 Electronic Medicines Compendium (EMC). *Votrient 400 mg film coated tablets*. 2021. Available from: https://www.medicines.org.uk/emc/product/572/smpc#gref [Accessed 26 July 2021].
36 National Institute for Health and Care Excellence (NICE). *PAZOPANIB*. 2021. Available from: https://bnf.nice.org.uk/drug/pazopanib.html [Accessed 26 July 2021].
37 Amdahl J, Manson SC, Isbell R, Chit A, Diaz J, Lewis L, et al. Cost-Effectiveness of Pazopanib in Advanced Soft Tissue Sarcoma in the United Kingdom. *Sarcoma*. 2014;2014:1-14. Available from: https://doi.org/10.1155/2014/481071.
38 Electronic Medicines Compendium (EMC). *Halaven 0.44 mg/ml solution for injection*. 2021. Available from: https://www.medicines.org.uk/emc/product/4517/smpc [Accessed 26 July 2021].

39 National Institute for Health and Care Excellence (NICE). *Eribulin*. 2021. Available from: https://bnf.nice.org.uk/drug/eribulin.html#indicationsAndDoses [Accessed 26 July 2021].
40 Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018 Oct 1;29(Suppl 4):iv51-iv67. Available from: https://doi.org/10.1093/annonc/mdy096.

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