National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: June 2018

Seviprotimut-L for malignant melanoma after surgery

NIHRIO (HSRIC) ID: 7810 NICE ID: 9902

LAY SUMMARY

Melanoma is a type of skin cancer that can appear anywhere on the body and usually begins with a mole. The back, legs and face are commonly affected areas of the body. Melanoma is the fifth most common cancer in the UK with a third of people diagnosed under the age of 55 years. Malignant melanoma indicates that the melanoma cells have spread deeper into the skin, lymph vessels or lymph glands close to the melanoma. Treatment of melanoma by surgery is often successful at first, but may begin to fail as the cancer spreads and enters end-stage disease. Treatments following tumour removal in malignant melanoma are not widely used in UK practice.

Seviprotimut-L is a type of cancer vaccine that is being developed for the treatment of adult patients with malignant melanoma who have had surgical resection. It is designed to stimulate the body's immune system to fight cancer cells, to stop the cancer coming back. Seviprotimut-L is injected under the skin in different parts of the body. The unique way it acts may offer a new treatment option for malignant melanoma patients after surgery.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to provide comment. 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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Malignant melanoma (stage IIb, IIc and III) – after surgery

TECHNOLOGY

DESCRIPTION

Seviprotimut-L (POL-103A) is under development for the treatment of malignant melanoma. It is a polyvalent, shed-antigen vaccine that is prepared from vaccine from pooled partially purified soluble melanoma antigens shed from 3 human melanoma cell lines during tissue culture.[1] Seviprotimut-L elicits both humoral and cell based anti-tumor immunity. The protective immunity is based in part on CD8+ T cell and antibody responses. The vaccine candidate may stimulate an antitumoral cytotoxic T-cell immune response in the host, resulting in inhibition of tumor cell proliferation and tumor cell death.[2,3]

Seviprotimut-L is being developed for the treatment of adult patients with stage IIb, IIc, III malignant melanoma who have had surgical resection within 90 days of first dosing.[3]

In the phase III clinical trial (MAVIS; NCT01546571), seviprotimut-L is administered intradermally, divided into 4 injections (0.2 mL each injection) into the volar surface of forearms and into the anterior upper thighs.[3] In the phase II trial the vaccine was given every 3 weeks for four cycles, monthly for three cycles, every 3 months for two cycles, and then every 6 months for a total of 5 years or until disease progression.[4] The treatment schedule is not stated in the phase III clinical trial.[3]

Seviprotimut-L does not currently have Marketing Authorisation in the EU for any indication.[5]

INNOVATION and/or ADVANTAGES

Seviprotimut-L as a type of cancer vaccine designed to elicit both humoral and cell based anti-tumor immunity. Clinical trials have shown that protective immunity is based in part on CD8+ T cell and antibody responses. Cellular immune responses can be induced in patients with various genetic (HLA) genotypes, which allows the vaccine to be used for all patients regardless of HLA type. There is evidence of an association between vaccine induced antibody and cellular immune responses against specific antigens and improved clinical survival data.[1]

Vaccines have been demonstrated to be effective in preventing melanoma in animals models. Moreover, they have few side effects in humans and may stimulate humoral and/or cellular immune responses against melanoma antigens. As a polyvalent vaccine, seviprotimut-L contains a broad range of different tumor antigens, increasing the likelihood that the vaccine will contain antigens that both stimulate protective immunity and are expressed by the tumour to be treated.[4] The vaccine can therefore be used to treat broad populations. In phase II trials the vaccine has been found to demonstrated strong efficacy in terms of significantly improved recurrence-free survival (RFS) and overall survival (OS), and has a strong safety profile.[6]

If licensed, seviprotimut-L will offer an alternative treatment option for the treatment after surgery of patients with late-stage malignant melanoma.

DEVELOPER

Polynoma LLC

REGULATORY INFORMATION and AVAILABILITY/MARKETING PLANS

Seviprotimut-L was designated an orphan drug by FDA for the treatment of stage IIb to stage IV melanoma in June 2006.[7]

At the time of the writing of this briefing note, no information regarding licensing and marketing in the EU/UK could be obtained.

PATIENT GROUP

BACKGROUND

Malignant melanoma is the most aggressive and life-threatening form of skin cancer. It develops in the cells that give the skin its colour (melanocytes) and has a very high tendency to spread to other parts of the body. Malignant melanoma occurs among all adequately studied racial and ethnic groups. The frequency of its occurrence is closely associated with the constitutive colour of the skin, and depends on the geographical zone. Incidence among dark-skinned ethnic groups is 1 per 100,000 per year or less, but among light-skinned Caucasians up to 50 per 100,000 and higher in some areas of the world.[8]

Melanomas fall into four basic categories. Three of them (superficial spreading, lentigo and acral lentiginous melanoma) begin in situ - meaning they occupy only the top layers of the skin - and sometimes become invasive; the fourth (nodular melanoma) is invasive from the start. Invasive melanomas are more serious, as they have penetrated deeper into the skin and may have spread to other areas of the body.[9]

The stage of melanoma describes how deeply it has grown into the skin and whether it has spread. At stages I and II, there is no evidence that the tumour has spread anywhere else in the body, although there is a possibility of microscopic spread. Stage III melanoma indicates that the melanoma cells have spread into skin, lymph vessels or lymph glands close to the melanoma. Stage III melanomas are considered intermediate to high risk as they are more likely to spread to other distant parts of the body (stage IV melanoma) than earlier melanoma stages.[10]

Factors that are associated with a higher risk of developing melanoma include:

- A fair complexion (including fair skin that burns or freckles easily, blue or green eyes, and blonde or red hair)
- Exposure to sunlight and other sources of ultraviolet (UV) energy (e.g. tanning beds)
- A history of sunburns that caused blistering, especially in childhood
- Having some large moles, many small moles, or moles that look different from normal moles
- A family history of unusual moles or melanoma
- A personal history of skin cancer, including melanoma
- Xeroderma pigmentosum, a rare genetic condition that prevents the skin from repairing itself from UV damage
- Exposure to certain environmental factors, including radiation, and some chemicals (e.g. solvents)
- A weakened immune system from disease or side effects of medicines
- Age – about half the people who develop melanoma are older than 50

- Sex of the patient – in Australia and New Zealand, melanoma is more common in men than in women.[11]

Symptoms of advanced melanoma can develop years after the original melanoma was diagnosed and removed. For some people, a change to an existing mole or freckle, or a change in normal-looking skin is the first sign. The symptoms also depend on which parts of the body the melanoma has spread to.[12] General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue.[12]

CLINICAL NEED and BURDEN OF DISEASE

Melanoma is the third most common skin cancer in the UK. It accounts for more cancer deaths than all other skin cancers combined.[13] Furthermore, melanoma is the fifth most common cancer overall in the UK. Skin cancer rates in Great Britain are more than 4 times higher than they were in the late 1970s.[14]

In England in 2016 there were 13,748 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[15] Across the UK, the incidence rate for malignant melanoma is expected to increase from 30.44 per 100,000 European age-standardised rate (EASR) (15,413 cases) in 2014 to 32.42 per 100,000 EASR (22,175 cases) in 2035.[16]

In England and Wales in 2016 there were 2,080 deaths with malignant melanoma of skin (ICD-10 code C43) recorded as the underlying cause.[17] The latest published survival statistics for melanoma of skin (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 97.8% and 5-year survival rate of 91.7% (age-standardised).[18]

In England in 2016/2017 there were 18,514 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C243), resulting in 11,378 bed days and 15,255 day cases.[19]

In 2012, the proportion of people in the UK diagnosed with melanoma at stage III was 3%. Five-year survival rates are approximately 50-55% for stage III disease.[20]

Survival for melanoma skin cancer is strongly related to stage of the disease at diagnosis. Five-yearsurvival rates for melanoma skin cancer show a gradual decrease in survival between Stages I and IV.[12] In men, five-year relative survival ranges from more than 100% at Stage I to 8% at Stage IV for patients diagnosed during 2002-2006 in the former Anglia Cancer Network.[12] In women, five-year survival ranges from 100% at Stage I to 25% at Stage IV.[12] At stage III, five-year survival rates in men and women are estimated to be around 50 and 55%.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for adjuvant treatment of resected stage III and IV melanoma (GID-TA10286). Expected publication date to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrent (GID-TA10247). Expected publication date to be confirmed.
- NICE technology appraisal. Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma (GID-TA10188). Expected December 2018.

- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.
- NICE public health guidance. Skin cancer prevention (PH32). January 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England Manual for Prescribed Specialised Services 2016/17. Chapter 105. Specialist cancer services (Adults).
- Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1–5.

OTHER GUIDANCE

- Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G and Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2015. Annals of Oncology 26 (Sup 5):v126-132.

CURRENT TREATMENT OPTIONS

NICE guidelines recommend:[21]

Stage II melanoma:

- Offer excision with a clinical margin of at least 2cm

Stage III melanoma:

- Consider completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro‑metastases
- Offer therapeutic lymph node dissection to people with palpable stage IIIB–IIIC melanoma or nodal disease detected by imaging
- Do not offer adjuvant radiotherapy to people with stage IIIA melanoma
- Do not offer adjuvant radiotherapy to people with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects

Adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in UK practice.[20]

EFFICACY and SAFETY

Trial	MAVIS, NCT01546571; POL-103A vs placebo (POL-103A without API); phase III
Sponsor	Polynoma LLC
Status	Ongoing, not reported

Source of Information	Trial registry[3]
Location	USA and Canada
Design	Randomised, placebo-controlled
Participants	n=1,059 (planned); aged 18-80 years; histologically confirmed Stage IIb, IIc, III melanoma; must have had surgical resection within 90 days of first dosing; persons with positive sentinel nodes must have a complete lymphadenectomy; ECOG performance status 0 or 1
Schedule	Randomised to Seviprotimut-L intradermally and divided into 4 injections (0.2 ml each injection); or placebo (POL-103A without API) intradermally and divided into 4 injections (0.2 ml each injection)
Follow-up	Not reported
Primary Outcomes	Recurrence free survival (RFS) [Time frame: 362 events]
Secondary Outcomes	Overall survival (OS) [Time frame: 472 events]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as January 2019

ESTIMATED COST and IMPACT

COST

The cost of seviprotimut-L is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☒ Other: Re-organisation of existing services

☐ Need for new services

☐ 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 – unable to state if cost of single treatment with seviprotimut-L would be less expensive than current available treatments.

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Polynoma. *Technology.* Available from: https://polynoma.com/technology/ [Accessed 8th June 2018]

[2] Global Data. *Study of melanoma vaccine in stage IIb, IIc, and III melanoma patients (MAVIS)*. Available from: https://pharma.globaldata.com/ClinicalTrialsView/ClinicalProductsView?ClinicalID=gs8F@OMbUtuiV7lYPi9OBw== [Accessed 8th June 2018]. Log in required.

[3] ClinicalTrials.gov. *Study of melanoma vaccine in stage IIb, IIc, and III melanoma patients (MAVIS): NCT01546571.* Available from: https://clinicaltrials.gov/ct2/show/NCT01546571 [Accessed 8th June 2018]

[4] Bystryn JC, Zeleniuch-Jacquotte A, Oratz R, et al. Double-Blind Trial of a Polyvalent, Shed-Antigen, Melanoma Vaccine. Clinical cancer research. 2001;7: 1882-1887. Available from: http://clincancerres.aacrjournals.org/content/clincanres/7/7/1882.full.pdf

[5] British National Formulary. *Search results.* Available from: https://bnf.nice.org.uk/#Search?q=Seviprotimut-L [Accessed 8th June 2018]

[6] Business wire. *Polynoma commences phase III melanoma vaccine clinical trial.* Available from: https://www.businesswire.com/news/home/20120604005733/en/Polynoma-Commences-Phase-III-Melanoma-Vaccine-Clinical [Accessed 8th June 2018]

[7] U.S. Food and drug administration. *Polyvalent, shed-antigen melanoma vaccine.* Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=223206 [Accessed 8th June 2018]

[8] Skincancer.dermis.net. *Malignant Melanoma - Patient Information.* Available from: http://skincancer.dermis.net/content/e04typesof/e154/e155/index_eng.html [Accessed 8th June 2018]

[9] Skcancer.dermis.net. *Types of melanomas.* Available from: https://www.skincancer.org/skin-cancer-information/melanoma/types-of-melanoma [Accessed 8th June 2018]

[10] National Institute for Health and Care Excellence. *Health Technology Appraisal: Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence. Draft scope*. Available from https://www.nice.org.uk/guidance/gid-ta10247/documents/draft-scope-post-referral [Accessed 8th June 2018]

[11] Cancer Australia. *Melanoma of the skin.* Available from: https://melanoma.canceraustralia.gov.au/risk-factors [Accessed 8th June 2018]

[12] Macmillan Cancer Support. *Advanced melanoma: signs and symptoms*. Available from: https://www.macmillan.org.uk/information-and-support/melanoma/advanced-melanoma/understanding-cancer/signs-symptoms-advanced-melanoma.html [Accessed 8th June 2018]

[13] National Institute for Health and Care Excellence. *NICE guideline (NG14): Melanoma: assessment and management.* Available from https://www.nice.org.uk/guidance/ng14/chapter/Introduction [Accessed 8th June 2018]

[14] U.S Food and Drug Administration. *Search Orphan Drug Designation and Approvals: Epacadostat.* Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=493015 [Accessed 8th June 2018]

[15] Office for National Statistics. *Cancer Registration Statistics, England, 2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland. [Downloaded 6th February 2018] [Accessed 8th June 2018]

[16] Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four . [Downloaded 9th March 2018] [Accessed 8th June 2018]

[17] Office for National Statistics. *Death Registrations Summary Statistics, England and Wales, 2016*. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables. [Downloaded 6th February 2018] [Accessed 8th June 2018]

[18] Office for National Statistics. *Cancer Survival in England: adults diagnosed between 2011 and 2015 and followed up to 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 6th February 2018] [Accessed 8th June 2018]

[19] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Downloaded 23rd October 2017] [Accessed 8th June 2018]

[20] National Institute for Health and Care Excellence. *Health Technology Appraisal: Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence.* Available from www.nice.org.uk/guidance/gid-ta10247/documents/final-scope [Accessed 8th June 2018]

[21] National Institute for Health and Care Excellence. *NICE guideline (NG14): Melanoma: assessment and management.* Available from https://www.nice.org.uk/guidance/ng14/chapter/1-Recommendations [Accessed 8th June 2018]