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Newcastle University

Health Technology Briefing
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Nivolumab-relatlimab adjuvant therapy for stage III-IV resected melanoma

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33790	NICE ID: Not available	UKPS ID: 673890

Licensing and Market Availability Plans

In phase III clinical development.

Summary

Nivolumab-relatlimab is currently clinical development for the adjuvant treatment of patients with resected stage III-IV melanoma. Melanoma is a type of skin cancer. The stage of a cancer tells how big it is and how far it has spread. Stage III melanomas are regional, meaning the cancer has spread beyond the primary tumour (local) to the closest lymph nodes, but not too distant sites. Stage IV (metastatic) melanomas involve distant sites from the original tumour, which can include the lungs and the brain. Adjuvant therapy (treatment given after the main therapy, e.g. surgery), can reduce the risk of micrometastes following surgery, which can limit/prevent further progression of melanoma in these patients.

Nivolumab-relatlimab is made up of two different antibodies (proteins), which when administered simultaneously act cooperatively to induce the immune system to kill tumour cells. Nivolumab-relatlimab acts systemically, meaning it acts around the whole body. This reduces the likelihood of cancer cells spreading to distant sites away from the original tumour. If licensed, nivolumab-relatlimab would offer an additional adjuvant treatment option for patients with resected stage III-IV melanoma.

Proposed Indication

Adults and adolescents (≥12 years old) with resected stage IIIA-IV melanoma.[1]

Technology

Description

Nivolumab-relatlimab (Opdualag, BMS-986213) is a fixed dose combination (FDC) of nivolumab and relatlimab.[1] This means both medicinal products are administered simultaneously.[2] Relatlimab is a lymphocyte activation gene 3 inhibitor (anti-LAG3).[2] It is a human IgG4 monoclonal antibody that binds to the LAG 3 receptor. LAG3 negatively regulates T-cells by inhibiting proliferation and effector T-cell function. LAG3 is upregulated in melanoma.[3] By binding to LAG3, relatlimab is able to block LAG3 inhibition of T-cell proliferation. Antagonism of this pathway promotes T cell proliferation and cytokine secretion, which enhances the ability of the body's immune system to attach and kill cancer cells.[2,4] Nivolumab is a programmed death 1 inhibitor (anti-PD-1). It is a human IgG4 monoclonal antibody that binds to the PD-1 receptor on T-cells.[2] PD-1 receptors are targeted by ligands released from tumour cells, PD-L1 and PD-L2. PD-L1/2 bind to PD-1 receptors which inhibits T-cell proliferation and production of cytokines which kill tumour cells.[5] By binding to PD-1, nivolumab prevents inhibition of T-cells. This increases immune system activation through T-cell production and release of cytokines which kill tumour cells.[2,6]

Nivolumab-relatlimab is in clinical development for adjuvant treatment of stage IIIA-IV melanoma.[1]

Key Innovation

Following surgical resection of tumours in stage IIIA-IV melanoma patients, adjuvant therapy can reduce the occurrence of micrometastases, therefore increasing recurrence free survival time.[7] Patients with stage IV melanoma have a particularly poor prognosis, as their cancer has spread to other parts of the body.[8,9] The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T cell activation compared to the activity of either antibody alone.[2] Adjuvant therapy with nivolumab-relatlimab may reduce the occurrence of micrometastes, preventing further disease progression.[3] In the phase II/III trial RELATIVITY-047 (NCT03470922), progression-free survival at 12 months was 47.7% for patients who received relatlimab-nivolumab compared to 36.0% in patients who received nivolumab alone.[3] If licensed, nivolumab-relatlimab would offer an additional adjuvant treatment option for patients with stage III-IV melanoma.

Regulatory & Development Status

Nivolumab-relatlimab FDC is licensed for first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.[2]

Nivolumab-relatlimab is in phase II/III clinical development for:[10]

- Stage II cutaneous melanoma
- Melanoma brain metastases
- Microsatellite-high tumours
- Merkel cell carcinoma
- Cutaneous squamous cell carcinoma
- Gastroesophageal cancer
- Colorectal adenocarcinoma
- Chordoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma

- Colon carcinoma
- Recurrent glioblastoma
- Haematologic neoplasms
- Advanced solid tumours

Patient Group

Disease Area and Clinical Need

Melanoma is a type of skin cancer, which can metastasise to other areas of the body.[11] It can start in a mole or in normal-looking skin and develops from skin cells called melanocytes. These cells make melanin which gives the skin its colour. Ultraviolet radiation from sunlight, sunbeds or sunlamps can build up and damage the DNA in melanocytes. They then start to grow and divide more quickly than usual and can develop into melanomas.[12] Initial symptoms of melanoma are a change in the shape, colour or size of mole. A melanoma can start either as a new mole or in a mole you already have.[13] The majority of melanomas start with a new, abnormal-looking mole on the skin; usually represented by a dark area in the mole, although melanomas can have more than one colour. It can be difficult to tell the difference between a normal mole and melanoma.[13] Stage III melanomas are tumours that have spread beyond the primary tumour to regional lymph nodes or have developed in transit deposits of disease, but there is no evidence of distant metastasis.[14] There are four subgroups of stage III melanoma, namely IIIA, IIIB, IIIC, and IIID. Stage IV melanomas, also called metastatic melanoma, is when tumour cells have spread to distant parts of the body such as other areas of skin, the lungs or the brain.[14]

Melanoma is the 5th most common cancer in the UK. In 2025, 3,119 people are expected to die from melanoma and 19,513 people are expected to be diagnosed with melanoma in the UK.[15] Between 2016-2018, there were 16,744 new cases of melanoma on average in the UK. Between 2017-2019, there were 2,341 deaths from melanoma.[16] In England (2022-23), there were 27,453 finished consult episodes (FCE) for melanoma (ICD10 code: C43), with 26,667 hospital admissions resulting in 23,739 day cases and 10,762 FCE bed days.[17] For patients with stage IIIA-D melanoma, survival after 5 years is approximately 70%, and for patients with stage IV melanoma survival after 5 years is approximately 30%.[8]

Recommended Treatment Options

The following pharmacological treatment options are recommended by National Institute for Health and Care Excellence for stage III-IV resected melanoma:[18,19]

- Pembrolizumab adjuvant therapy for resected stage III melanoma with lymph node involvement in adults, if the company provides it according to the commercial arrangement.[15]
- Nivolumab adjuvant therapy for resected melanoma with lymph node involvement or metastatic disease in adults, if the company provides it according to the commercial arrangement.[16]
- Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma.[20]

Clinical Trial Information

Trial	NCT05002569; **EudraCT** 2021-001641-13; A phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab + relatlimab fixed-dose combination versus nivolumab monotherapy after complete resection of stage III-IV melanoma

	Phase III – Active, not recruiting **Location(s):** 13 EU countries, UK, and other countries **Primary completion date:** February 2026
Trial Design	Randomised, parallel assignment, quadruple blinded study.
Population	N (estimated) = 1,050; 12 years or older with diagnosis of stage IIIA-IV melanoma with complete surgical resection of disease.
Intervention(s)	Participants will receive a fixed dose combination of nivolumab plus relatlimab.
Comparator(s)	Nivolumab monotherapy.
Outcome(s)	Primary outcome measure: Recurrence free survival [Time frame: Up to 52 months]. For full list of outcomes see trial record.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of nivolumab-relatlimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Nivolumab for adjuvant treatment of completely resected melanoma at high risk of recurrence in people aged 12 and over. (ID6189). Expected publication date: To be confirmed.
- NICE technology appraisal. Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma. TA766. February 2022.
- NICE technology appraisal. Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma. TA544. October 2018
- NICE clinical guideline. Melanoma: assessment and management. NG14. July 2015
- NICE quality standard. Skin cancer. QS130. September 2016

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- European Society for Medical Oncology (ESMO). ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. 2020.[21]
- British Association of Dermatologists (BAD). Stage 3 melanoma. 2019.[22]
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Additional Information

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