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HEALTH TECHNOLOGY BRIEFING
AUGUST 2019

Nivolumab and relatlimab for untreated advanced or metastatic melanoma – first line

NIHRIO ID	24118	**NICE ID**	10064
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	647940

Licensing and market availability plans	Currently in pre-registration

SUMMARY

A fixed dose combination of nivolumab and relatlimab is in development for the treatment of advanced and metastatic melanoma patients that have not received previous treatment. Melanoma is a cancer of the skin, when is advanced or metastatic, the cancer has spread to other organs and tissues such as lymph nodes and the brain. Metastatic melanoma can present a range of different symptoms including lumps under the skin, swollen lymph nodes, bone pain and headaches. At this stage the cancer can't be cured.

Nivolumab works by improving the activity of white blood cells increasing the ability of the immune system to kill cancer cells. Relatlimab has the potential to increase the immune system response and kill cancer cells. If licenced for this indication, a fixed dose combination of intravenous nivolumab and relatlimab may provide a new therapeutic option for untreated patients that shows similar adverse effects than treatment with nivolumab alone.

PROPOSED INDICATION

Previously untreated advanced or metastatic melanoma – first line.[a]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo; BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[1]

Relatlimab (BMS-986016) is a monoclonal antibody directed against the inhibitor receptor lymphocyte activation gene-3 (LAG-3), with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, relatlimab binds to LAG-3 on tumour infiltrating lymphocytes (TILs). This may activate antigen-specific T lymphocytes and enhance cytotoxic T cell-mediated tumour cell lysis, which leads to a reduction in tumour growth. LAG-3 is a member of the immunoglobulin superfamily (IgSF) and binds to major histocompatibility complex (MHC) class II. LAG-3 expression on TILs is associated with tumour-mediated immune suppression.[2]

A fixed dose combination (FDC) of nivolumab and relatlimab (BMS-986016) is in clinical development as first line treatment of patients with advanced or metastatic melanoma. In the clinical trial (NCT03470922, EudraCT-2017-003583-12) a FDC of relatlimab and nivolumab IV in a ratio of 1:3 is administered every 4 weeks (BMS-986213). For adults, the dose will be relatlimab 160 mg/nivolumab 480mg in a FDC every 4 weeks.[3,4,b] Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is relatlimab 2 mg/kg/nivolumab 6 mg/kg every 4 weeks.[b]

INNOVATION AND/OR ADVANTAGES

Signalling via LAG-3 and other T-cell inhibitory receptors can lead to T-cell dysfunction and tumour immune escape. Simultaneous blockade of LAG-3 and PD-1 may synergistically restore T-cell activation and enhance antitumor immunity.[5] Relatlimab is the first anti-LAG3 mAb to have been developed.[6] The combination of relatlimab and nivolumab has been tested in patients with melanoma whose disease progressed on/after prior anti–PD-1/PD-L1 therapy demonstrating encouraging efficacy and safety profile.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Relatlimab as monotherapy or in combination with nivolumab does not currently have Marketing Authorisation in the EU/UK for any indication.

In the UK, nivolumab as monotherapy or in combination with other cancer therapies has the following therapeutic indications:[1]

[a] Information provided by Bristol Myers-Squibb Ltd on UK PharmaScan
[b] Information provided by Bristol Myers-Squibb Ltd

- Melanoma: as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

- Adjuvant treatment of melanoma: as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

- Non-Small Cell Lung Cancer (NSCLC): as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

- Renal Cell Carcinoma (RCC): as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. In combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

- Classical Hodgkin Lymphoma (cHL): as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

- Squamous Cell Cancer of the Head and Neck (SCCHN): as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

- Urothelial Carcinoma: as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Common or very common side effects of nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[7]

Nivolumab in combination with relatlimab is currently in phase II development for advanced or metastatic colorectal cancers, gastric or gastroesophageal cancers, renal cell carcinoma, non-small cell lung cancer. Additionally, this drug combination is currently being studied at phase II for virus-associated tumours including anal canal cancer, cervical cancer, Epstein Barr Virus (EBV) positive gastric cancer, Merkel cell cancer, penile cancer and vaginal and vulvar cancer.[8]

PATIENT GROUP

DISEASE BACKGROUND

Malignant melanoma is the most aggressive and life-threatening form of skin cancer. It develops in the melanocytes, the cells that produce melanin, 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.[9]

The stage of melanoma refers to the thickness, depth of penetration, and the degree to which the melanoma has spread. More advanced melanomas (stages III and IV) have metastasised to other parts of the body.[10] 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. General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue.[11]

Factors that are associated with a higher risk of developing melanoma include a fair complexion, exposure to sunlight and other sources of ultraviolet (UV) energy, and a history of sunburns or moles.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the fifth most common cancer in the UK. Skin cancer rates in Great Britain are more than 4 times higher than they were in the late 1970s.[13]

In England in 2017 there were 13,740 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[14] Across the UK, the European age-standardised incidence rate for malignant melanoma is expected to increase by 7% between 2014 and 2035 to from 30 cases per 100,000 to 32 cases per 100,000 people. It is projected that 22,175 cases of melanoma skin cancer (11,897 males, 10,278 females) will be diagnosed in the UK in 2035.[15]

In England in 2017/2018 there were 19,911 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), 20,416 finished consultant episodes, resulting in 11,088 bed days and 16,650 day cases.[16]

More melanoma skin cancer patients with a known stage are diagnosed at an early stage (91% are diagnosed at stage I or II), than a late stage (9% are diagnosed at stage III or IV). In England in 2016 about 866 and 307 patients were diagnosed at stage III and IV respectively.[17] Late stage at diagnosis is associated with higher deprivation. Among adults aged 15-99 years in England, 10% of those in the most deprived areas are diagnosed at stage III or IV, versus 8% in the least deprived areas. Late stage melanoma is more common in adults aged 60-79 years (10% diagnosed at stage III or IV) versus those aged 15-59 years (8% diagnosed at stage III or IV). Late stage diagnosis is more common in males in England. Among adults aged 15-99 years, 10% of males are diagnosed at stage III or IV versus 7% of females.[18]

Melanoma accounts for more cancer deaths than all other skin cancers combined.[19] In England and Wales in 2017 there were 2,106 deaths with malignant melanoma of skin (ICD-10 code C43) recorded as the underlying cause.[20] The latest published survival statistics for melanoma of skin (patients diagnosed between 2012 and 2016 and followed up to 2017) report 1-year survival rate of 98% and 5-year survival rate of 91.6% (age-standardised).[21] Survival statistics fall with more advanced stages of melanoma with around 50% of people diagnosed with stage III melanoma will be alive 5 years later. At stage IV, five-year relative survival is around 8% in men and around 25% in women.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Advanced or metastatic melanoma is currently treated using systemic anticancer treatments such as targeted therapies, immunotherapy or cytotoxic chemotherapy. Completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases should be considered in addition

to therapeutic lymph node dissection for people with palpable stage IIIB-IIIC melanoma or nodal disease detected by imaging.[19]

CURRENT TREATMENT OPTIONS

For stage III melanoma, NICE guidelines advise the following:[23]

- Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IIIB or IIIC) melanoma that has not spread to bone, brain, lung or other internal organs, only if the treatment with systemically administered immunotherapies is not suitable and the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.

For stage IV melanoma, the following NICE guidelines state:[23-28]

- Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if the treatment with systemically administered immunotherapies is not suitable and the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.
- Dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable.
- Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
- Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.
- Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.

PLACE OF TECHNOLOGY

If licenced, FDC of nivolumab and relatlimab for the treatment of patients with advanced or metastatic melanoma that have not received previous treatment, will add an additional first line treatment option for this population.

CLINICAL TRIAL INFORMATION

Trial	**NCT03470922, EudraCT-2017-003583-12; children aged 12 years and over and adults; relatlimab in combination with nivolumab vs nivolumab alone; phase II/III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry[3,4]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled, double-blind study

Participants	n=700 (planned); aged 12 and over; previously untreated metastatic or unresectable (Stage III or Stage IV) melanoma
Schedule	Randomised to: • Arm A: Relatlimab/ Nivolumab 1:3 FDC 4mg/ml and 12 mg/ml respectively • Arm B: Nivolumab monotherapy 10mg/ml (used for monotherapy only)
Follow-up	Follow-up 5 years
Primary Outcomes	• Progression Free Survival (PFS) [Time Frame: Up to 5 years] Phase 3 portion of trial. Assessed by a Blinded Independent Central Review (BICR) • PFS [Time Frame: Up to 5 years] Phase 2 portion of trial, assessed by a BICR
Secondary Outcomes	• Overall Survival (OS) [Time Frame: Up to 5 years] Phase 3 portion of trial • ORR [Time Frame: Up to 5 years] Phase 3 portion of trial, assessed by a BICR • ORR [Time Frame: Up to 5 years] Phase 2 portion of trial, assessed by a BICR. In the randomized population and in subgroups • Duration of Response (DOR) [Time Frame: Up to 5 years] Phase 2 portion of trial. In the randomized population and in subgroups • PFS [Time Frame: Up to 5 years] Phase 2 portion of trial. In subgroups. • OS [Time Frame: Up to 5 years] Phase 2 portion of trial. In the randomized population and in subgroups • Number of Adverse Events (AEs) [Time Frame: Up to 5 years] Phase 2 portion of the trial • Number of Serious Adverse Events (SAEs) [Time Frame: Up to 5 years] Phase 2 portion of the trial • Number of AEs Leading to Discontinuation [Time Frame: Up to 5 years] Phase 2 portion of the trial • Number of Deaths [Time Frame: Up to 5 years] Phase 2 portion of the trial • Number of Laboratory Abnormalities [Time Frame: Up to 5 years] Phase 2 portion of the trial
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2020

ESTIMATED COST

The NHS indicative price for nivolumab (Opdivo) 100mg/10ml, 240mg/24ml and 40mg/4ml concentrate for solution for infusion vials is £1,097.00, £2,633.00 and £439.00 respectively.[29]

The price of nivolumab and relatlimab FDC is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

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- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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NB: 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.