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EVIDENCE BRIEFING
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Relatilmab in combination with nivolumab for advanced melanoma – second line

NIHRIO ID	14940	**NICE ID**	10041
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	649025

Licensing and market availability plans	Currently in phase I/II clinical trial

SUMMARY

Relatlimab in combination or as a fixed dose with nivolumab, is in clinical development for patients with malignant (advanced or metastatic) melanoma that has previously been treated with immunotherapy (second line). Malignant melanoma is the most aggressive and life-threatening form of skin cancer. General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue. Factors 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 sunburn or moles.

Relatlimab binds to and inhibits a protein called LAG-3 which is present on immune cells (T-cells) while nivolumab works by blocking a different protein called PD-1 also present on the surface of T-cells. Simultaneous blockade of LAG-3 and PD-1 may synergistically restore T-cell activation and enhance antitumour immunity. The addition of relatlimab to nivolumab has demonstrated encouraging results in early clinical trials and has a safety profile similar to nivolumab when administered alone. Relatlimab in combination with nivolumab may offer an effective treatment option for patients with malignant melanoma that has spread and cannot be removed by surgery and have previously been treated with immunotherapy.

PROPOSED INDICATION

Advanced (metastatic and/or unresectable) melanoma, in patients 12 years and older, previously anti-PD1 treated, second line. [a]

TECHNOLOGY

DESCRIPTION

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 and binds to major histocompatibility complex class II. LAG-3 expression on TILs is associated with tumour-mediated immune suppression.[1]

Nivolumab (Opdivo) is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with 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 the ligands 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 antitumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[2]

Relatlimab in combination with nivolumab is in clinical development for a different types of advanced solid tumours that includes metastatic and/or unresectable melanoma. In the phase I/II clinical trial (2014-002605-38; NCT01968109), relatlimab and nivolumab are administered via intravenous infusion.[3,4] The combination and fixed dose is administered in a ratio of 1:3 (relatlimab 80mg: Nivolumab 240mg vial) every four weeks. The study will also explore the co-administration arm using a two weekly schedule.[b]

INNOVATION AND/OR ADVANTAGES

Signalling via LAG-3 and other T-cell inhibitory receptors (e.g., PD-1) can lead to T-cell dysfunction and tumour immune escape. Simultaneous blockade of LAG-3 (relatlimab) and PD-1 (nivolumab) may synergistically restore T-cell activation and enhance antitumour immunity.

Early data shows that the addition of relatlimab to nivolumab has encouraging efficacy in patients with progressive melanoma that is refractory to anti-PD-1/PD-L1 therapy. Additionally, the safety profile is similar to nivolumab monotherapy.[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.

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

Nivolumab in combination with relatlimab is also currently in phase III development for unresectable locally advanced or metastatic LAG-3 positive gastric or gastroesophageal junction adenocarcinoma.[6]

Nivolumab in combination with relatlimab is currently in phase I/II development for solid tumours that have spread and/or cannot be removed by surgery and as a treatment for both first and second line therapy:[3]

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.[7]

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.[8] 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.[9] 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.[10]

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.[11] 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.[12]

In England in 2016 there were 13,748 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[13] Across the UK, the European age-standardised incidence rate for malignant melanoma is expected to increase by 7% between 2014 and 2035 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.[14]

In England in 2016/2017 there were 18,514 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), resulting in 11,378 bed days and 15,255 day cases.[15]

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.[16] 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).[17]

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). 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 associated with male sex in England. Among adults aged 15-99 years, 10% of males are diagnosed at stage III or IV versus 7% of females.[18]

Survival statistics fall with more advanced stages of melanoma. Between 40-50% of people diagnosed with stage III melanoma will be alive 5 years later. For stage IV this is 20-30% diagnosed will be alive 5 years later.[19]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Advanced or metastatic melanoma is currently treated using surgery or through the use of 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.[20]

CURRENT TREATMENT OPTIONS

For stage III melanoma, NICE guidelines advise the following:[21]

- 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:[20, 21, 22, 23, 24, 25]

- 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.
- Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only

when the company provides pembrolizumab in line with the commercial access agreement with NHS England.

PLACE OF TECHNOLOGY

If licensed, relatlimab in combination with nivolumab would offer an effective second line treatment option for previously anti-PD1 pre-treated advanced (metastatic and/or unresectable) melanoma.

CLINICAL TRIAL INFORMATION

Trial	**NCT01968109, EudraCT 2014-002605-38; relatlimab vs relatlimab in combination with nivolumab; phase I/II**a
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry;[3,4] abstract[5], Company
Location	EU (incl. UK), USA, Canada, Australia and Japan
Design	Randomised, dose escalation, open label, parallel assignment
Participants	n=1000 (planned); aged ≥12 years old; advanced or metastatic melanoma progressed while on or after immunotherapy, with or without anti-CTLA-4
Schedule	Patients are randomised to either: • Relatlimab specified dose on specified days (dose escalation arm) • Relatlimab in combination with nivolumab (co-administration: 160mg relatlimab/480mg nivolumab Q4W) • Relatlimab in fixed dose combination with nivolumab (fixed dose combination [BMS986213]; 160mg relatlimab/480mg nivolumab Q4W) Note: Study will also explore co-administration only using Q2W schedule
Follow-up	The maximum active treatment period is twelve 8 week cycles, confirmed CR, or until meeting criteria for discontinuation as described within the study protocol. Subjects may be on study for a total of up to approximately 2 years, including a 28-day screening period, up to twelve 8-week cycles of treatment, a 135-day clinical follow-up period, and up to 2-5 years of follow-up for survival (from first study dose). Upon progression during clinical follow up subjects may be able to receive further treatment (monotherapy or fixed dose combination) under certain clinical criteria specified within the protocol. Subjects will not be re-challenged a second time. The total study duration is expected to be approximately 7 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled.
Primary Outcomes	Primary outcomes assessed for up to 2 years (based on BICR assessments using RECIST v 1.1): • Overall response rate (ORR) • Disease control rate (DCR) • Safety of BMS-986016 alone or in combination with nivolumab measured by the number of adverse events, deaths and laboratory abnormalities
Secondary Outcomes	Secondary outcomes assessed depending on outcome: • Progression free survival

	• Overall survival (Landmark OS at 1 & 2 Years) • Duration of response • Disease control rate • Assess the effect of relatlimab administered alone or in combination with nivolumab on QTc. Timepoint - Pre-dose and 4 hours post-dose during Cycle 1 and Cycle 3, and at 30 days following the last dose of study drug per central reader assessments. Pre-dose for each cycle (up to 12 eight-week cycles) done locally. • Assess pharmacokinetics of relatlimab administered alone or in combination with nivolumab. Timepoint - Up to 1.8 years + 135 days post-treatment follow-up (total of up to approximately 2.3 years). The most frequent PK collections occur during Cycle 1 and Cycle 3: up to 15. Timepoints over the 24 week period through Cycle 3. • Assess preliminary efficacy of relatlimab administered alone or in combination with nivolumab. Timepoint - Week 8 of each cycle (up to 12 eight-week cycles) and at 30 days following the last dose of study drug for a total of up to approximately 2 years. • Assess immunoginicity of relatlimab administered alone or in combination with nivolumab. Timepoint - Up to 1.8 years + 135 days post-treatment follow-up (total of up to approximately 2.3 years)
Key Results	At data cutoff, 43 pts with MEL had been treated with BMS-986016 + nivo following PD on/after prior anti–PD-1/PD-L1 with known prior best responses of 1 CR, 9 PR, 12 SD, and 16 PD. Of the 43 pts, 30 (70%) also had prior anti–CTLA-4, 20 (47%) had ≥ 3 prior therapies, and 15 (35%) had BRAF mutations. In the 31 efficacy-evaluable pts to date, ORR was 16% (confirmed/unconfirmed) and DCR was 45% with benefit observed even in some pts refractory to prior anti–PD-1. Evaluations are ongoing for most pts, with median treatment duration of 10 wk for all 43 pts. Immunopathologic (e.g., PD-1/PD-L1 and LAG-3 expression) and clinical characteristics of responder's vs nonresponders will be presented. Addition of Relatlimab to nivolumab demonstrates encouraging initial efficacy in patients with melanoma whose disease progressed on or after prior anti-PD-1/PD-L1 therapy, and a safety profile similar to nivolumab monotherapy.
Adverse effects (AEs)	Any grade and grade 3/4 treatment-related AEs occurred in 46% and 9%, respectively, across all dose expansion pts (n = 129).
Expected reporting date	Primary completion date reported as Aug 2020

ESTIMATED COST

The cost of relatlimab in combination with nivolumab is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence (GID-TA10247). Expected publication date December 2018.
- NICE technology appraisal guidance. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). September 2017.
- NICE technology appraisal guidance. Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410). September 2016.
- NICE technology appraisal guidance. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal guidance. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016.
- 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 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).

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines for patients: Melanoma. 2018.[26]
- Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1–5.[27]
- European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016. 2016.[28]
- European Society for Medical Oncology (ESMO). Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2015.[29]

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