Innovation Observatory

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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Nivolumab in combination with ipilimumab for the adjuvant treatment of melanoma

NIHRIO ID	13751	**NICE ID**	9588
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	645156

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Nivolumab in combination with ipilimumab is in development for the treatment of melanoma following surgery. Melanoma is a type of skin cancer which arises from the pigment cells (melanocytes) in the skin. One of the most important causes of melanoma is exposure to too much ultraviolet light in sunlight. Melanoma is considered to be the most serious type of skin cancer because it is more likely to spread from the skin to other parts of the body than other types of skin cancer. The primary treatment of melanoma is usually surgery. Additional ('adjuvant') treatment is usually recommended after surgery to reduce their chances of recurrence.

Nivolumab works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab works in a different way but also to increase the activity of T-cells. It is thought that when used together, both drugs may be more effective than each on its own. Both drugs given by injection are already used in combination in the treatment of advanced melanoma. If licenced as an adjuvant treatment option, nivolumab in combination with ipilimumab has the potential to improve long-term outcomes in melanoma patients.

PROPOSED INDICATION

Melanoma - adjuvant treatment after complete surgical removal of stage IIIb/c/d/ or stage IV melanoma[1]

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.[2]

Ipilimumab (Yervoy; BMS-734016) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intra-tumoural T-effector/T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is in development for the adjuvant treatment of melanoma. In the phase III trial (NCT03068455; CheckMate 915) subjects will be randomised (stratified by tumour PD-L1 expression and AJCC stage) to receive nivolumab at dose of 240mg every 2 weeks in combination with ipilimumab at dose of 1mg/kg every 6 weeks (Q6) or nivolumab monotherapy at 480mg every 4 weeks (Q4W). For adolescents, nivolumab dose will be weight based at 3mg/kg (Q2W) or 6mg/kg Q4W. All participants will be treated until recurrence of disease, unacceptable toxicity, or participant withdrawal of consent with a maximum of 1 year of treatment.[a,4]

INNOVATION AND/OR ADVANTAGES

Although melanoma is amenable to early detection, there has been no decline in the mortality rate of this disease and the prognosis of patients with high-risk primary melanoma or with macroscopic nodal involvement remains poor. The best option for patients with high-risk melanoma is to receive effective adjuvant therapy in order to reduce their chances of recurrence.[5]

Melanoma patients develop resistance to most therapies, including chemo- and targeted-therapy drugs. Single-agent therapies are ineffective due to the heterogeneous nature of tumors comprising several subpopulations. Treatment of melanoma with immune-based therapies such as anti-cytotoxic T-lymphocyte activation-4 and anti-programmed death-1 antibodies has shown modest but long-lasting responses. Unfortunately, only subsets of melanoma patients respond to antibody-based therapies. Heterogeneity in lymphocyte infiltration and low frequency of anti-melanoma-reactive T-cells in tumor lesions are partly responsible for a lack of response to antibody-based therapies. Both antibodies have same biological function but they bind to different ligands at various phases of T-cell

[a] Information provided by Bristol Myers-Squibb

activity. Thus, combination therapy of antibodies has shown superior response rates than single-agent therapy.[6]

Previously reported results from the phase III CheckMate 067 trial (NCT01844505) showed a significant improvement in objective responses, progression-free survival, and overall survival with nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone as a first-line treatment in patients with advanced melanoma.[7]

Nivolumab as adjuvant treatment following complete resection of stage III/IV melanoma has demonstrated a statistically significant improvement in Relapse Free Survival (RFS) versus ipilimumab (CheckMate-238). [8] Further, in study CA184-029 of ipilimumab versus placebo, ipilimumab demonstrated in significantly higher RFS, overall survival, and distant metastasis–free survival than placebo.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with ipilimumab is licensed in the EU/UK for the treatment of advanced (unresectable or metastatic) melanoma in adults and for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. The most common adverse reactions (≥1/10) associated with treatment with nivolumab in combination with ipilimumab are: hypothyroidism, decreased appetite, headache, dyspnoea, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue and pyrexia.[3]

Nivolumab in combination with ipilimumab is currently in development for the treatment of various types of cancers including breast, ovarian, and gastric.[10]

PATIENT GROUP

DISEASE 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.[11]

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.[12]

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.[13]

Factors that are associated with a higher risk of developing melanoma include: a fair complexion, exposure to sunlight and other sources of ultraviolet energy, a history of sunburns that caused blistering, moles, family history, personal history of skin cancer, xeroderma pigmentosum (a rare genetic condition), environmental factors (including chemical), a weakened immune system, age and sex.[14]

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.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In 2015, melanoma was the fifth most common cancer overall in the UK.[16] In England in 2016 there were 13,748 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43). Of these, 1,173 cases (8.5%) were diagnosed at stage III or IV. Across the UK, the incidence rate for malignant melanoma (ICD-10 code C43) 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.[17]

In England in 2017-18 there were 20,416 finished consultant episodes (FCEs) of malignant melanoma of skin (ICD-10 code C43), of which 16,650 were day cases.[18]

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.[19] 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).[20]

Survival for melanoma is strongly related to stage of the disease at diagnosis. Five-year survival rates for melanoma skin cancer show a gradual decrease in survival between Stages I and IV. At stage III, five-year relative survival rates in men and women are estimated to be around 50-55%, and ≤25% at stage IV.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Adjuvant cancer therapy is additional treatment given after the primary treatment for melanoma, usually surgery. The goal of adjuvant therapy is to reduce the risk of melanoma returning. Physicians often recommend adjuvant therapy for patients with melanoma with involvement of lymph nodes or patients with metastatic disease who have undergone complete resection.[22]

For patients with stage III resectable melanoma, treatment pathways may include:[23,25,26,27]

- Completion lymphadenectomy for patients whose sentinel lymph node biopsy shows micro-metastases
- Lymph node dissection for patients with palpable stage IIIb-IIIc melanoma or nodal disease detected by imaging
- Adjuvant therapy

For stage IV patients, treatment pathways may include:[23,25]

- Surgery or other ablative treatments for oligometastatic stage IV
- Adjuvant therapy

- Surgery or stereotactic radiotherapy for brain metastases
- Systemic anticancer treatments (including targeted therapies, immunotherapy, and cytotoxic chemotherapy)

There is no universally agreed standard adjuvant therapy for melanoma.[24]

CURRENT TREATMENT OPTIONS

NICE recommends the following adjuvant treatment option for completely resected stage III and IV melanoma:[25]

- Nivolumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.

NICE recommends the following adjuvant treatment options for completely resected stage III melanoma: [26,27]

- Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection.
- Dabrafenib with trametinib is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults.

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab will offer an additional treatment option for melanoma patients who currently have few well-tolerated effective adjuvant therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 915, NCT03068455, EudraCT 2016-003729-41; nivolumab combined with ipilimumab vs nivolumab monotherapy; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry[1,4], manufacturer
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, active-controlled, parallel assignment, double-blind
Participants	n=2,000 (planned); ≥12 years of age; completely surgically resected stage IIIb/c/d or stage IV melanoma within 12 weeks of participation in study; must have full activity or, if limited, must be able to walk and carry out activities such as light house work or office work; no prior anti-cancer treatment for melanoma (except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy after neurosurgical resection for central nervous system lesions)
Schedule	**Experimental: nivolumab + ipilimumab** • Subjects receive nivolumab flat dose of 240mg every 2 weeks (Q2W) in combination with ipilimumab at dose of 1mg/kg every 6 weeks (Q6W) on specified days. **Experimental: nivolumab**

	• Subjects receive nivolumab monotherapy as flat dose at 480mg every 4 weeks (Q4W) on specified days. Weight based nivolumab dose of 3mg/kg (Q2W) or 6mg/kg (Q4W) for adolescents aged between 12 and 18 years. All participants will be treated until recurrence of disease, unacceptable toxicity, or participant withdrawal of consent with a maximum of 1 year of treatment.
Follow-up	• Maximum study follow up for up to 5 years • Relative to the first dose of study treatment, participants will continue to have surveillance assessment every 12 weeks for the first 12 months • From > 12 months to 36 months after randomization, efficacy assessments should be every 12 week • From > 36 months until Year 5 after first dose of study treatment, efficacy assessments should be performed every 6 months
Primary Outcomes	Recurrence-free survival (RFS) [Time Frame: Approximately 30 months] • measured by time
Secondary Outcomes	Overall Survival (OS) [Time Frame: Up to 5 years] • Measured by time RFS by PD-L1 expression [Time Frame: Approximately 3 years] • Measured by immunoassay
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date Nov 2020. Estimated study completion date Feb 2023.

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg/10mL concentrate for solution for infusion vial costs £1,097, a 240mg/24mL concentrate for solution for infusion vial costs £2,633, and a 40mg/4ml concentrate for solution for infusion vial costs £439.[28]

Ipilimumab (Yervoy) is already marketed in the UK; a 200mg/40mL concentrate for solution for infusion vial costs £15,000 and a 50mg/10mL concentrate for solution for infusion vial costs £3,750.[29]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (TA558). January 2019.

- NICE technology appraisal. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (TA553). December 2018.
- NICE technology appraisal. Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (TA544). October 2018.
- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016.
- NICE technology appraisal. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.
- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.

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: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/s/b.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. SIGN 146: Cutaneous melanoma. January 2017[30]

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