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Nivolumab (Opdivo) for Melanoma after complete resection of Stage IIIb/c or Stage IV Melanoma (adjuvant therapy)

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LAY SUMMARY

Melanoma is a cancer of the skin that may spread to other parts of the body, and the progression of the disease is classified by stage. Patients with Stage III melanoma have cancer cells that have spread into the skin, lymph vessels, or lymph glands close to the original cancer site, while Stage IV patients have cancer cells that have spread into other parts of the body further away. As part of the treatment options for Stage III and IV, patients may undergo surgery (i.e. "resection") to remove the melanoma, surrounding tissue, and lymph nodes. Accompanying adjuvant therapies are additional treatments given to the patient to help reduce the risk of the cancer returning.

Nivolumab is a drug which blocks a protein, called the programmed death-1 (PD-1) receptor, on the surface of certain immune cells (called T-cells). By blocking the PD-1 receptor, nivolumab stops the cancer cells evading immune-mediated tumour destruction. This restores T-cell activity and the patient's own immune system is able to directly fight and kill cancer cells. Nivolumab is given as a drip directly into a vein in the hand or arm. Studies of nivolumab in this population are currently being conducted to determine if its use as an accompanying therapy to cancer removal surgery may extend survival or reduce the likelihood of disease recurrence.

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TARGET GROUP

Melanoma population after complete resection of Stage IIIb/c or Stage IV Melanoma with no evidence of disease (NED) who are at high risk for recurrence

TECHNOLOGY

DESCRIPTION

Nivolumab [BMS-936558; MDX-1106; NSC-732442; ONO-4538; Opdivo] is a fully-human IgG4 monoclonal antibody which targets and blocks the PD-1 (programmed death-1) receptor on the surface of T-cells. This action triggers a T-cell mediated immune response against cancer cells. Nivolumab is administered by intravenous (IV) infusion at 3mg/kg over 60 minutes every 2 weeks for its currently licensed indications.[1,2,3]

Nivolumab has been approved/licensed for use in the EU for the following indications:[3]

- First and second line locally advanced unresectable or metastatic melanoma (*monotherapy or in combination with ipilimumab*) in adults
- Advanced or metastatic (squamous and non-squamous) non-small cell lung cancer (*monotherapy*) after prior chemotherapy in adults
- Advanced renal cell carcinoma after prior therapy in adults (*monotherapy*)
- Relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (*monotherapy*)
- Squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (*monotherapy*)
- Locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy

Recognised common adverse events (>10%) of nivolumab in the currently licenced indications include: neutropenia, diarrhoea, nausea, rash, pruritus (itching), fatigue, increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatine, lymphopaenia, leucopoenia, thrombocytopenia, anaemia, hypercalcaemia, hyperkalaemia, hypomagnesaemia and hyponatraemia.[3]

Nivolumab is currently in phase II trials for the following indications:

- Advanced gastric & gastro-oesophageal junction cancer (monotherapy; *combination*)
- Advanced oesophageal cancer (monotherapy)
- Renal cell carcinoma (*combination; adjuvant monotherapy*)
- Relapsed or refractory non-Hodgkin's lymphoma (*combination*)
- Advanced non-small cell lung cancer (*combination*)
- Solid tumours, virus-associated and non (*combination; monotherapy*)
- Acute myeloid leukaemia (*combination; monotherapy*)
- Follicular lymphoma (*monotherapy*)
- Triple negative, metastatic breast cancer (*monotherapy*)
- Recurrent, castration resistant prostate (*combination*)
- Myelodysplastic syndromes (*combination*)
- Melanoma that has spread to the brain (*combination*)

Nivolumab is currently in phase III trials for the following indications:

- Ovarian cancer (*monotherapy*)
- Oesophageal cancer (*combination; monotherapy; adjuvant monotherapy*)
- Head and neck cancer, first-line (*monotherapy*)
- Urothelial carcinoma (combination therapy; *adjuvant monotherapy*)
- Gioblastoma (*combination*)
- Non-small cell lung cancer, first line (*combination*)
- Multiple myeloma (*combination*)
- Gastric cancer, first line (*combination*)

INNOVATION and/or ADVANTAGES

Nivolumab is already licensed for first and second line advanced unresectable or metastatic melanoma and, if licensed, will offer an additional adjuvant treatment option for post-resection Stage III b/c and Stage IV NED patients who are at high risk of recurrence.

DEVELOPER

Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd

AVAILABILITY, LAUNCH or MARKETING

Nivolumab is currently in phase III clinical trials for the treatment of melanoma after complete resection of Stage 111b/c or Stage IV NED melanoma.

Nivolumab was awarded PIM status for melanoma by the Medicines and Healthcare products Regulatory Agency (MHRA) in January 2015.

Nivolumab is a designated orphan drug in the United States for the following indications:

- Glioblastoma
- Gastric cancer and gastro-oesophageal junction cancer
- Hepatocellular Carcinoma
- Small cell lung cancer
- Stage IIIb to stage IV melanoma
- Oesophageal cancer

Nivolumab was designated Breakthrough Therapy by the Food & Drug Administration (FDA) for treatment for the following indications:

- Unresectable advanced or metastatic urothelial cancer that has progressed on or after a platinum-containing regimen in June 2016
- Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum based therapy in April 2016
- Previously treated patients with non-squamous non-small cell lung cancer in September 2015
- Hodgkin's lymphoma after failure of autologous stem cell transplant and brentuximab in May 2014
- Previously treated advanced melanoma in September 2014
- Advanced or metastatic renal cell carcinoma in September 2015

Nivolumab was designated fast track status by the FDA for the following indications in April 2013:

- Non-small cell lung cancer
- Melanoma
- Renal Cancer

Nivolumab was designated priority review status by the FDA for the following indications:

- Unresectable advanced or metastatic urothelial cancer that has progressed on or after a platinum-containing regimen in October 2016
- Mismatch repair deficient or microsatellite instability high metastatic colorectal cancer after prior fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy in April 2017
- Advanced squamous non-small cell lung cancer after prior therapy in March 2015
- Classical hodgkins lymphoma after prior therapies in April 2016
- Previously treated advanced melanoma in September 2014
- Previously untreated advanced melanoma in August 2015
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy in November 2015

Nivolumab was designated accelerated approval status by the FDA for the treatment of unresectable or metastatic melanoma who no longer respond to other drugs in January 2015.

PATIENT GROUP

BACKGROUND

Melanoma accounts for more cancer deaths than all other skin cancers combined. Although melanoma is more often diagnosed in older people, it is increasingly affecting younger people, and it is the second most common cancer in adults aged between 25 and 49. Melanoma therefore leads to more years of life lost overall than many more common cancers.

Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn.

Staging of primary melanoma can be carried out in 2 steps. The initial staging is based on the histopathological features reported by the pathologist looking at the microscopic sections of the tumour. The melanoma is staged as 0–IIC, based on factors such as the thickness of the tumour and the presence or absence of ulceration. In many hospitals in the UK, this first step is followed by the option of a second, which is a sampling of the lymph nodes most likely to contain secondary melanoma cells (sentinel lymph node biopsy). If a sentinel lymph node biopsy is performed and microscopic disease is detected, the melanoma becomes stage III. If no microscopic disease is detected then the initial stage is used.[4]

There is currently no consensus on the standard of care for patients with completely resected stage IIIB/C or stage IV melanoma with no evidence of disease who are at high risk for recurrence,[5] though another monoclonal antibody product (ipilimumab) has been approved in the United States for use as an '[a]djuvant treatment of patients with cutaneous melanoma with pathologic involvement of

regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy'.[6,7]

CLINICAL NEED and BURDEN OF DISEASE

In the UK in 2014, there were around 15,400 new cases of melanoma skin cancer and it was the fifth most common cancer. Around half of melanoma skin cancer cases in the UK each year are diagnosed in people aged 65 and over, and incidence rates for melanoma skin cancer in the UK are highest in people 85 years and older. Approximately 9% of melanoma skin cancer cases are diagnosed at a late stage (III or IV).[8]

According to the American Cancer Society, the five and ten-year survival rates for Stage IIIC patients are forty and twenty percent, respectively; for Stage IV patients, the five-year survival falls as low as fifteen percent, while the ten-year survival drops to approximately ten percent.[9] While new, targeted systemic therapies have provided tools for potentially extending patient survival, overarching clinician concerns in regards to toxicity, low/short response rates, and rapid disease progression demonstrate a clear unmet clinical need for this disease.[10] This unmet need is only furthered heightened in patients who have undergone complete resection but who remain at high risk for recurrence.

Hospital Episode Statistics for England indicate that malignant melanoma of the skin accounted for 17,649 finished consultant episodes (FCE), 17,230 admissions and 12,090 FCE bed days.[11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal. Nivolumab for treating advanced (unresectable or metastaic) melanoma (TA 384). 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 technology appraisal in development. Melanoma (resected stage IV, high risk stage III) – ipilimumab (adjuvant) [ID721].
- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Cancer Drugs Fund list. V1.31. 15th June 2017.
- 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). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

CURRENT TREATMENT OPTIONS

There is no universally agreed standard adjuvant therapy for melanoma.[5] A range of treatments may be used to treat malignant melanoma depending on tumour stage and site, *inter alia*.

For Stage III patients treatment options include:[4]

- Completion lymphadenectomy
- Lymph node dissection
- Adjuvant radiotherapy

For Stage IV patients treatment options include:[4]

- Surgery or other ablative treatments for oligometastatic stage IV
- Surgery or stereotactic radiotherapy for brain metastases
- Systemic anticancer treatment
    - Targeted treatments (i.e. dabrafenib, vemurafenib)
    - Immunotherapy (i.e. ipilimumab)
    - Cytotoxic chemotherapy

EFFICACY and SAFETY

Trial	Checkmate 238, NCT02388906; children, adults, or seniors fifteen years or older; nivolumab vs ipilimumab; phase III
Sponsor	Bristol-Myers Squibb; Ono Pharmaceutical Co. Ltd
Status	Ongoing
Source of Information	Trial Registry;[12] Publication[5]
Location	EU (including UK), USA, Canada and other countries
Design	Randomized, placebo-controlled, double-blind
Participants	n (planned) = 800; aged 15 years or older; completely removed melanoma by surgery performed within 12 weeks of randomization; Stage IIIb/C or Stage IV NED melanoma before complete resection; no previous anti-cancer treatment
Schedule	Randomized 1:1 to nivolumab 3 mg/kg every 2 weeks (Q2W) or ipilimumab 10 mg/kg Q3W for 4 doses then Q12W starting at week 24, and treated until disease recurrence, unacceptable toxicity, or consent withdrawal, for up to 1 year
Follow-up	Up to 48 months
Primary Outcomes	Recurrence -free-survival
Secondary Outcomes	Overall survival
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary Completion Date: November 2018; Study Complete Date: November 2019

ESTIMATED COST and IMPACT

COST

Nivolumab is already marketed in the UK; the list price of nivolumab is £439 per 4 ml (40 mg) vial and £1,097 per 10 ml (100 mg) vial (excluding VAT).[13]

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

☐ 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 reduction in costs: *reduced risk of recurrence for advanced melanoma may reduce costs of treatment usually associated with those later stages*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Bristol-Myers Squibb

UK PharmaScan ID number 641475

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