

# Health Technology Briefing

## August 2022

### Nivolumab adjuvant for treating for stage IIB/IIC resected melanoma

Company/Developer

Bristol-Myers Squibb

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 28076

NICE ID: 10603

UKPS ID: 653377

### Licensing and Market Availability Plans

Currently in phase III clinical trials.

### Summary

Nivolumab is in clinical development as a therapy to be given to patients who have had stage IIB-IIC melanoma removed via surgery but who are at high risk of recurrence. Melanoma is a type of skin cancer that is commonly caused by sun exposure and is often first noticed as a new mole or a change in the colour, shape, or size of an existing mole. Stage IIB and IIC melanoma is where the cancer has developed through only the top 2-4mm of the skin and may also be ulcerated which means the top layer of skin covering the cancer has started to break down. Currently, there are no recommended treatments to help prevent melanoma from coming back after the cancer has been removed by surgery, in patients who are at high risk of recurrence.

Nivolumab is an antibody that is designed to help the immune system fight tumour cells and slow tumour growth, helping to stop recurrence of cancer once it has been removed. Nivolumab is administered via intravenous (IV) injection and if licensed would offer a new treatment option to patients who have had stage IIB/C melanoma surgically removed, but who remain at high risk of recurrence.

## Proposed Indication

Adjuvant therapy for subjects aged 12 years and older who have had complete resection of stage IIB/C cutaneous melanoma, with no evidence of disease but are at high risk of recurrence.<sup>1</sup>

## Technology

### Description

Nivolumab (Opdivo) is a fully humanised immunoglobulin G4 (IgG4) programmed death-1 (PD-1) immune checkpoint inhibitor monoclonal antibody that blocks PD-1 and promotes antitumor immunity. PD-1 is engaged by ligands PD-L1 and PD-L2, which are expressed by tumour cells and infiltrating immune cells. Inhibition of the interaction between PD-1 and PD-L1 can enhance anti-tumour responses, delay tumour growth, and facilitate tumour rejection.<sup>2</sup>

In the phase III trial (NCT04099251), nivolumab will be administered via IV infusion (10mg/ml) to patients who have undergone complete resection of stage IIB/C cutaneous melanoma who are at high risk of recurrence.<sup>1,3</sup>

### Key Innovation

There are currently no NICE recommended treatment options for fully resected stage IIB/C melanoma other than surgery, leaving an unmet need for these patients as they often have higher baseline risk of recurrence than patients with more advanced stage disease.<sup>4,5</sup> Studies examining the effects of nivolumab as an adjuvant therapy for patients with fully resected stage IIB/IIC melanoma at high risk of recurrence found that administration of nivolumab resulted in 87.8% recurrence free survival (RFS) after two years whereas the RFS in those who hadn't received nivolumab was 70% at two years.<sup>5</sup> If licensed, nivolumab will offer a new treatment option for patients at high risk of recurrence after complete resection of stage IIB/C melanoma.

### Regulatory & Development Status

Nivolumab currently has Marketing Authorisation in the EU/UK for:<sup>6</sup>

- Advanced/ unresectable melanoma in adults, monotherapy or in combination with ipilimumab
- Adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, monotherapy
- Malignant pleural mesothelioma, in combination with ipilimumab
- Non-small cell lung cancer, monotherapy or in combination with ipilimumab and platinum-based chemotherapy
- Renal cell carcinoma, in combination with ipilimumab or cabozantinib
- Classical Hodgkin lymphoma, monotherapy
- Squamous cell cancer of the head and neck, monotherapy
- Urothelial carcinoma, monotherapy
- Colorectal cancer, in combination with ipilimumab
- Oesophageal, gastric, and gastro-oesophageal cancer, monotherapy or in combination with ipilimumab or fluoropyrimidine or platinum-based chemotherapy

Nivolumab is in phase III clinical trials for the treatment of:<sup>7</sup>

- Brain metastasis
- Bladder cancer
- Hepatocellular carcinoma
- Small cell lung cancer

- Ovarian cancer
- Multiple myeloma
- Prostate cancer
- Glioblastoma
- Breast cancer

## Patient Group

### Disease Area and Clinical Need

Melanoma is a type of skin cancer that most commonly presents as a new mole or a change in an existing mole such as change in shape, colour, or size. This can happen anywhere on the body but is most common on the back for men and the legs for women. Melanoma is caused by the skin cells beginning to develop abnormally and is commonly caused by exposure to ultraviolet (UV) light from the sun or artificial sources such as sunbeds. People most at risk of melanoma tend to have lots of moles or freckles, pale skin that burns easily, red or blonde hair, or have a family history of melanoma.<sup>8</sup> Stage IIB melanoma is where the cancer is thicker than 4mm, or is 2-4mm and ulcerated; stage IIC melanoma is thicker than 4mm and ulcerated.<sup>9</sup>

Melanoma is the 5<sup>th</sup> most common cancer in the UK and 86% of cases are deemed preventable. Incidence is highest in those aged 85-89 years old but 1 in 4 skin cancers are diagnosed in people aged under 50 years old.<sup>8,10</sup> In the UK (2016-18) there are an average of 16,744 new cases of melanoma diagnosed each year, with 2,341 deaths between 2017-19 attributable to melanoma.<sup>10</sup> Stage II melanoma, has an 80% survival rate for five years or more after diagnosis.<sup>9,11</sup> In England (2020-21), there were 20,739 finished consultant episodes (FCE) for melanoma (ICD-10 code: C43), with 20,264 hospital admissions that resulted in 17,055 day cases and 8,179 FCE bed days.<sup>12</sup>

### Recommended Treatment Options

In stage II melanoma it is recommended to have surgery to remove the cancer and a small area of skin around it. In most cases, once it has been removed there is little chance of it returning so patients need no further treatment and are monitored for 1-5 years, then discharged with no further problems.<sup>13</sup> In cases where there is a high risk of recurrence, there are currently no NICE recommended treatment options for adjuvant treatment for stage II resected melanoma.<sup>4</sup>

## Clinical Trial Information

Trial	<p><b>CheckMate76k</b>; <a href="#">NCT04099251</a>, <a href="#">2019-001230-34</a>; A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy With Nivolumab Versus Placebo After Complete Resection of Stage IIB/C Melanoma  <b>Phase III</b> – Active, not recruiting  <b>Location(s)</b>: 14 EU countries, UK, USA and other countries  <b>Primary completion date</b>: November 2022</p>
Trial Design	Randomised, parallel assignment, triple-masked, placebo controlled
Population	N= 790; Subjects who have undergone complete resection of stage IIB/C melanoma with no evidence of disease and are at high risk of recurrence; aged 12 years and older
Intervention(s)	Nivolumab (IV, 10mg/ml)

Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: Recurrence-free survival (RFS) [Time frame: approximately 68 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

### Estimated Cost

The hospital indicative price of nivolumab (100mg/10ml) is £1,097.<sup>14</sup>

### Relevant Guidance

#### NICE Guidance

- NICE technology appraisal in development. Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence (ID3908) [GID-TA10786]. Expected date of issue to be confirmed.
- NICE 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.<sup>15</sup>
- American Academy of Dermatology. Guidelines of care for the management of primary cutaneous melanoma. 2019.<sup>16</sup>
- Healthcare Improvement Scotland. QRG 146 – Cutaneous melanoma. 2016.<sup>17</sup>

### Additional Information

## References

- 1 ClinicalTrials.gov. *Effectiveness Study of Nivolumab Compared to Placebo in Prevention of Recurrent Melanoma After Complete Resection of Stage IIB/C Melanoma (CheckMate76K)*. Trial ID: NCT04099251. 2019. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT04099251> [Accessed July 14th, 2022].
- 2 Guo L, Zhang H, Chen B. Nivolumab as Programmed Death-1 (PD-1) Inhibitor for Targeted Immunotherapy in Tumor. *J Cancer*. 2017;8(3):410-6. Available from: <https://doi.org/10.7150/jca.17144>.
- 3 EU Clinical Trials Register. *Efficacy Study of Nivolumab Compared to Placebo in Prevention of Recurrence of Melanoma After Complete Resection of Stage IIB/C Melanoma (CheckMate 76K)*. Trial ID: 2019-001230-34. 2019. Status: Ongoing. Available from: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001230-34/GB> [Accessed July 14th, 2022].
- 4 National Institute for Health and Care Excellence (NICE). *98 results for melanoma*. 2022. Available from: <https://www.nice.org.uk/search?q=Melanoma> [Accessed July 15th, 2022].
- 5 Wilson M, Geskin LJ, Carvajal RD, Mehnert JM, Chiuзан C, Leiby B, et al. Adjuvant nivolumab in high-risk stage IIb/IIc melanoma patients: Results from investigator initiated clinical trial. *Journal of Clinical Oncology*. 2021;39(15\_suppl):9583-. Available from: [https://doi.org/10.1200/JCO.2021.39.15\\_suppl.9583](https://doi.org/10.1200/JCO.2021.39.15_suppl.9583).
- 6 Electronic Medicines Compendium (EMC). *OPDIVO 10 mg/mL concentrate for solution for infusion*. 2022. Available from: <https://www.medicines.org.uk/emc/medicine/30476#gref> [Accessed July 14th, 2022].
- 7 ClinicalTrials.gov. *92 Studies found for: nivolumab | Interventional Studies | Phase 3 | Industry*. 2022. Available from: [https://www.clinicaltrials.gov/ct2/results?term=nivolumab&age\\_v=&gndr=&type=Intr&rslt=&phase=2&fund=2&Search=Apply](https://www.clinicaltrials.gov/ct2/results?term=nivolumab&age_v=&gndr=&type=Intr&rslt=&phase=2&fund=2&Search=Apply) [Accessed July 15th, 2022].
- 8 National Health Service (NHS). *Overview: skin cancer (melanoma)*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/> [Accessed July 15th, 2022].
- 9 National Health Service (NHS). *Melanoma skin cancer: diagnosis*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/diagnosis/> [Accessed July 15th, 2022].
- 10 Cancer Research UK. *Melanoma skin cancer statistics*. 2022. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer#heading-Zero> [Accessed July 15th, 2022].
- 11 Cancer Research UK. *Melanoma skin cancer: survival*. 2020. Available from: <https://www.cancerresearchuk.org/about-cancer/melanoma/survival> [Accessed July 15th, 2022].
- 12 National Health Service (NHS) Digital Office for National Statistics. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis*. 2021. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21#chapter-index> [Accessed February 10th, 2022].
- 13 National Health Service (NHS). *Treatment: skin cancer (melanoma)*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/treatment/> [Accessed July 14th, 2022].
- 14 National Institute for Health and Care Excellence (NICE), British National Formulary (BNF). *Nivolumab: Medicinal forms*. 2022. Available from: <https://bnf.nice.org.uk/drugs/nivolumab/medicinal-forms/> [Accessed July 14th, 2022].
- 15 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. Available from:

<https://www.esmo.org/guidelines/guidelines-by-topic/melanoma/cutaneous-melanoma/consensus-recommendations-locoregional-melanoma> [Accessed July 14th, 2022].

16 American Academy of Dermatology. *Guidelines of care for the management of primary cutaneous melanoma*. 2019. Available from: [https://www.jaad.org/article/S0190-9622\(18\)32588-X/fulltext](https://www.jaad.org/article/S0190-9622(18)32588-X/fulltext) [Accessed July 14th, 2022].

17 Healthcare Improvement Scotland. *QRG 146 – Cutaneous melanoma*. 2016. Available from: <https://www.sign.ac.uk/assets/qrg146.pdf> [Accessed July 14th, 2022].

***NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***