

HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Pembrolizumab as adjuvant therapy for resected high-risk stage II melanoma

| | | | |
|--------------------------|-------------------------|----------------|--------|
| NIHRIO ID | 24352 | NICE ID | 10403 |
| Developer/Company | Merck Sharp & Dohme Ltd | UKPS ID | 655842 |

Licensing and market availability plans

Currently in phase III clinical trials.

SUMMARY

Melanoma is the most common skin cancer in the UK and is characterised by changes to mole size or shape. It is when melanocytes (cells that give skin its tan or brown colour) grow uncontrollably. Stage II melanoma is where the cancer has spread locally, as opposed to other areas of the body, and can result in a larger tumour sometimes with broken skin. Patients with high-risk stage 2 melanoma cancer may have an increased chance of the cancer returning after surgical resection (removal of the tumour) because of the tumour being thicker and deeper in the skin, which makes it difficult to remove all cancerous cells. There is currently no recommended systemic treatment after surgical resection if the cancer comes back in patients with stage II melanoma.

Pembrolizumab is an antibody that promotes the body's immune response against cancerous cells, by preventing cancerous cells from stopping immune cells being produced. Pembrolizumab is given by an intravenous infusion (injection into the vein) once every three weeks and if licensed, will offer an additional treatment option following surgery for patients with stage II melanoma.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

As an adjuvant therapy in patients with resected high-risk stage II melanoma.^a

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to 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.¹

In the phase III KEYNOTE-716 trial, adult patients are given 200mg (or 2mg/kg in paediatric patients) pembrolizumab by intravenous infusion once every three weeks (21-day cycle) for up to 17 cycles. In some circumstances, such as unresectable disease recurrence, the patient may be allowed to continue treatment for up to 35 cycles.²

INNOVATION AND/OR ADVANTAGES

There are currently no adjuvant therapies after surgical resection on the NICE pathway for stage IIB and IIC melanoma.³ Patients with high-risk stage IIB and IIC melanoma experience high rates of recurrence after surgical resection. Pembrolizumab has shown clinical benefit in reducing recurrence in resected stage III melanoma, and it is hypothesized that it will provide the same benefit to stage IIB and IIC patients.^{4,5}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licensed in the UK as both a monotherapy and a combination therapy for the following cancers:¹

- Advanced (unresectable or metastatic) melanoma in adults
- Adults with stage III melanoma and lymph node involvement who have undergone complete resection
- Non-small cell lung carcinoma – metastatic or locally advanced
- Classical Hodgkin lymphoma – relapsed or refractory
- Urothelial carcinoma – metastatic or locally advanced
- Head and neck squamous cell carcinoma – metastatic or unresectable
- Renal cell carcinoma - advanced

^a Information provided by Merck Sharp & Dohme Ltd on UK PharmaScan

Pembrolizumab is associated with immune-related adverse reactions. Very common ($\geq 1/10$) side effects include anaemia, hypothyroidism, decreased appetite, headaches, coughing, dyspnoea (difficulty breathing), diarrhoea, abdominal pain, nausea, vomiting, constipation, rashes, pruritus, musculoskeletal pain, arthralgia (joint pain), fatigue, oedema and pyrexia.¹

Pembrolizumab is currently in phase II/III clinical development for:⁶

- Solid tumours
- Lymphoma
- Adenocarcinoma
- Anal carcinoma
- Bladder cancer
- Ovarian cancer
- Non-small cell lung cancer
- Stomach neoplasms
- Urinary bladder cancer
- Urothelial carcinoma
- Oesophageal neoplasms
- Breast cancer
- Endometrial neoplasms
- Cervical cancer
- Gastric cancer

PATIENT GROUP

DISEASE BACKGROUND

Melanoma is a type of skin cancer. It starts in cells in the skin called melanocytes. There are two main types of skin cancer: non-melanoma skin cancer (which includes basal cell skin cancer, squamous cell skin cancer and other rare types) and melanoma skin cancer.⁷ The first sign of a melanoma is often a new mole or a change in the appearance of an existing mole, for example increase size, change of shape or colour, bleeding, itchiness or soreness.⁸

Most skin cancer is caused by UV light which accounts for 85% of cases.⁹ Other risk factors include use of artificial sources of light (e.g. tanning beds), high number of moles, pale skin that does not tan easily, red or blonde hair, blue eyes, freckles, previously damaged skin through sunburn or radiotherapy, immunosuppressive diseases, a family history of melanoma and/or a previous diagnosis of skin cancer.^{7,10}

When diagnosed, melanomas are staged from 0-4.¹¹ Stage 2 (also displayed in roman numerals as Stage II) melanoma is divided into three subgroups:^{11,12}

- Stage IIA – the melanoma is 2mm to 4mm thick without ulceration (broken skin), or it is 1mm to 2mm thick and ulcerated
- Stage IIB – the melanoma is thicker than 4mm without ulceration, or it is 2mm to 4mm thick and ulcerated
- Stage IIC – the melanoma is thicker than 4mm and ulcerated

High-risk melanoma is where the tumour is deeper or thicker (>4mm), which makes it difficult to completely remove all cancerous cells during surgical resection and increases the risk of recurrence.¹³

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the fifth most common cancer in the UK.⁹ There are around 16,200 new melanoma skin cancer cases in the UK, which approximates to 44 new cases every day (2015-17).¹⁴ In England, in 2017 there were 13,740 registrations of newly diagnosed cases of melanoma of the skin (ICD-10, code C43).¹⁵

In England (2019-20) there were 25,219 finished consultant episodes (FCE) for patients admitted with a primary diagnosis of C43 resulting in 11,492 FCE bed days and 21,367 day cases.¹⁶ In England and Wales in 2017 there were 2,106 deaths with C43 recorded as the underlying cause.¹⁷

Survival statistics fall with more advanced stages of melanoma. Patients with Stage II have a 1-year age-standardised survival of 98.2% and a 5-year age-standardised survival of 80.4%.¹⁸

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Stage II patients are recommended to have curative-intent removal of a cancerous tumour and some of the surrounding tissue. Sentinel lymph node biopsy can be offered to people with stages IB – IIC to determine if there is any cancer that has spread to the lymph nodes.^{19,20}

CURRENT TREATMENT OPTIONS

There are currently no recommended adjuvant treatment options for patients after surgical resection for stages IIB and IIC melanoma.³

PLACE OF TECHNOLOGY

If licenced pembrolizumab would offer the first adjuvant treatment for patients with stage II melanoma.

CLINICAL TRIAL INFORMATION

| | |
|--------------|--|
| Trial | KEYNOTE-716; NCT03553836; 2018-000669-35; Adjuvant Therapy With Pembrolizumab Versus Placebo in |
|--------------|--|

| | |
|---------------------------|---|
| | <p>Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE-716)</p> <p>Phase III – Active, not recruiting</p> <p>Location(s): EU (incl. UK), USA, Canada and other countries</p> <p>Primary completion date: 26th October 2022</p> |
| Trial design | Randomised, double-masked, parallel assignment |
| Population | N=954 (planned); aged 12 years and older; surgically resected and histologically/pathologically confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma; has not been previously treated for melanoma beyond complete surgical resection |
| Intervention(s) | <p>Part 1:</p> <ul style="list-style-type: none"> Paediatric participants receive 2mg/kg (200mg maximum) pembrolizumab by intravenous (IV) infusion every 3 weeks (Q3W; 21-day cycles) for up to 17 cycles Adult participants receive 200mg pembrolizumab by IV infusion Q3W <p>Part 2:^b</p> <ul style="list-style-type: none"> Participants on the pembrolizumab arm during the initial phase of treatment who are greater than 6 months from last dose of pembrolizumab treatment and who experience a recurrence will be offered re-challenge with pembrolizumab Participants who have local recurrence, including local metastatic lymph nodes or distant metastases that are surgically resected may receive up to 17 cycles of therapy with pembrolizumab Participants with an unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or an unresectable distant recurrence may receive up to 35 cycles of therapy with pembrolizumab Participants who receive placebo in part 1 of the trial who experience recurrence and meet all crossover criteria will be offered cross over to receive pembrolizumab |
| Comparator(s) | Matched placebo |
| Outcome(s) | Recurrence-free Survival (RFS) [Time frame: up to 4 years] See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

^b Information provided by Merck Sharp & Dohme Ltd

ESTIMATED COST

The NHS indicative price of pembrolizumab 100mg/4ml concentrate for solution for infusion is £2630.00 per vial (hospital only).²¹

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidance in development. Skin cancers including Melanoma: assessment and management. [GID-NG10155]. Estimated publication date: May 2022
- NICE guideline. Melanoma: assessment and management [NG14]. July 2015

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS Guidelines for Cutaneous Malignant Melanoma Management. 2019
- NHS Standard Contract for Cancer: Skin (Adult). 2013/14. A12/S/b

OTHER GUIDANCE

- European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics – update 2019. 2020.²²
- European Society of Medical Oncology. Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2019²³
- European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – update 2019. 2020.²⁴
- European Society of Medical Oncology. Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2019.²³
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 146 Cutaneous Melanoma. 2017.²⁵
- BAD Guidelines. Revised UK guidelines for the management of cutaneous melanoma. 2010.²⁶
- NICE Cancer Service Guideline. Improving outcomes for people with skin tumours including melanoma. [CSG8]. February 2006. (Last updated: May 2010).²⁷

ADDITIONAL INFORMATION

REFERENCES

- 1 Electronic Medicines Compendium (emc). *Keytruda 25 mg/ml concentrate for solution for infusion*. 2020. Available from: <https://www.medicines.org.uk/emc/product/2498> [Accessed 13 Nov 2020].
- 2 Clinicaltrials.gov. *Adjuvant Therapy With Pembrolizumab Versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE-716)*. Trial ID: NCT03553836. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT03553836> [Accessed 13 Nov 2020].
- 3 National Institute for Health and Care Excellence (NICE). *Managing melanoma*. 2015. Available from: <https://pathways.nice.org.uk/pathways/melanoma/melanoma-overview#content=view-index&path=view%3A/pathways/melanoma/managing-melanoma.xml> [Accessed 13 Nov 2020].
- 4 Luke J, Ascierto P, Carlino M, Gershenwald J, Grob J, Hauschild A, et al. KEYNOTE-716: Phase III study of adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma. *Future Oncology*. 2020 Jan;16(3):4429-38. Available from: <https://doi.org/10.2217/fon-2019-0666>.
- 5 Yushak M, Mehnert J, Luke J, Poklepovic A. Approaches to High-Risk Resected Stage II and III Melanoma. *American Society of Clinical Oncology (ASCO) Educational Book*. 2019 May;39:e207-e11. Available from: https://ascopubs.org/doi/full/10.1200/edbk_239283.
- 6 Clinicaltrials.gov. *Phase II and III clinical trials for pembrolizumab*. Available from: https://clinicaltrials.gov/ct2/results?term=Merck+Sharp+%26+Dohme+Ltd%2C+Pembrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 18 Nov 2020].
- 7 Cancer Research UK. *What is melanoma?* 2020. Available from: <https://about-cancer.cancerresearchuk.org/about-cancer/melanoma/about> [Accessed 13 Nov 2020].
- 8 NHS. *Skin cancer (melanoma) - Symptoms*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/symptoms/> [Accessed 13 Nov 2020].
- 9 Cancer Research UK. *Risks and causes of melanoma*. 2020. Available from: <https://about-cancer.cancerresearchuk.org/about-cancer/melanoma/risks-causes> [Accessed 13 Nov 2020].
- 10 NHS. *Skin cancer (melanoma) - Causes*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/causes/> [Accessed 13 Nov 2020].
- 11 NHS. *Skin cancer (melanoma) - Diagnosis*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/diagnosis/> [Accessed 13 Nov 2020].
- 12 Melanoma Research Alliance. *Stage 2 Melanoma*. Available from: <https://www.curemelanoma.org/about-melanoma/melanoma-staging/stage-2/> [Accessed 13 Nov 2020].
- 13 Melanoma Research Alliance. *Melanoma Treatment - Adjuvant Therapy*. 2020. Available from: <https://www.curemelanoma.org/patient-eng/melanoma-treatment/adjuvant-therapy/> [Accessed 13 Nov 2020].
- 14 Cancer Research UK. *Melanoma skin cancer statistics*. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer#heading-Zero> [Accessed 13 Nov 2020].
- 15 Office for National Statistics (ONS). *Cancer registration statistics, England*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Accessed 13 Nov 2020].
- 16 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20> [Accessed 13 Nov 2020].
- 17 Office for National Statistics (ONS). *Death registrations summary tables - England and Wales*. 2017. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesendlandandwalesreferencetables> [Accessed 13 Nov 2020].
- 18 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed between 2013-17*. Available from:

- <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> [Accessed 13 Nov 2020].
- 19 Cancer Research UK. *Melanoma skin cancer - Stage 2*. 2020. Available from: <https://www.cancerresearchuk.org/about-cancer/melanoma/stages-types/stage-2> [Accessed 13 Nov 2020].
- 20 NHS. *Skin cancer (melanoma) - Treatment*. 2020. Available from: <https://www.nhs.uk/conditions/melanoma-skin-cancer/treatment/> [Accessed 13 Nov 2020].
- 21 British National Formulary. *Pembrolizumab*. Available from: <https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html> [Accessed 13 Nov 2020].
- 22 Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2019. *European Journal of Cancer*. 2020 Feb;126:141-58. Available from: <https://doi.org/10.1016/j.ejca.2019.11.014>.
- 23 Michielin O, van Akkooi A, Ascierto P, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2019 Dec;30(12):1884-901. Available from: <https://doi.org/10.1093/annonc/mdz411>.
- 24 Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019. *European Journal of Cancer*. 2020 Feb;126:159-77. Available from: <https://doi.org/10.1016/j.ejca.2019.11.015>.
- 25 Scottish Intercollegiate Guidelines Network (SIGN). *Cutaneous melanoma (SIGN 146)*. Last Update Date: September 2016. Available from: <https://www.sign.ac.uk/assets/qrq146.pdf> [Accessed 08 Dec 2020].
- 26 Marsden J, Newton-Bishop J, Burrows L, Cook M, Corrie P, Cox N, et al. Revised UK guidelines for the management of cutaneous melanoma 2010. *Journal of Plastic, Reconstructive & Cosmetic Surgery*. 2010 Sep;63(9):1401-19. Available from: <https://doi.org/10.1016/j.bjps.2010.07.006>.
- 27 National Institute for Health and Care Excellence (NICE). *Improving outcomes for people with skin tumours including melanoma [CSG8]*. 2010. Available from: <https://www.nice.org.uk/guidance/csg8> [Accessed 08 Dec 2020].

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.