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HEALTH TECHNOLOGY BRIEFING OCTOBER 2021

Pembrolizumab for treatment of solid tumours – second line

NIHRIO ID	23916	**NICE ID**	10682
Developer/Company	Merck Sharp & Dohme (UK) Ltd	**UKPS ID**	661473

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

SUMMARY

Pembrolizumab is currently in clinical development for unresectable or metastatic microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR) endometrial, gastric, biliary, small intestine, or pancreatic cancer in adult patients. MSH-H or dMMR cancers occur when the process for replicating and repairing DNA (genetic material) is not working properly. When a cells misatch repair system stops working, errors in the DNA start accumulating and may cause cancer. There are currently no treatments recommended for the treatment of MSI-H or dMMR tumours specifically in endometrial, gastric, biliary, small intestine, or pancreatic cancer.

Pembrolizumab intravenous (IV) injection is in a class of medications called monoclonal antibodies. It works by helping the immune system to slow or stop the growth of cancer cells. Pembrolizumab has been shown to be more effective than chemotherapy for MSI-H or dMMR colorectal cancers,and therefore it may also be effective in other cancers with this type of mutation. If licenced, pembrolizumab would offer a treatment option for adults with endometrial, gastric, biliary, small intestine, or pancreatic tumours whose disease has progressed with other treatment approaches and therefore have no satisfactory other treatment options.

PROPOSED INDICATION

Pembrolizumab is being developed for unresectable or metastatic MSI-H or dMMR tumours in adult patients who have progressed following prior treatment and who have no satisfactory alternative treatment options.

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-347) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands programmed cell death ligand 1 and 2 (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 phase II clinical trial (NCT02628067, EudraCT 2015-002067-41) participants will receive pembrolizumab 200mg intravenously on day 1 of each 3-week cycle for up to 35 administrations. Participants with any advanced solid tumour that has failed at least one line of therapy and is tumor- mutational burden-high (excluding participants with mismatch repair deficient tumors) will recive 400 mg every 6 weeks for up to 18 administrations.[2]

INNOVATION AND/OR ADVANTAGES

This is a new line of treatment for the CRC indication and entirely new for endometrial, gastric, biliary, small intestine, or pancreatic cancers, as pembrolizumab is not currently licensed for the treatment of these solid tumours. [1]
Results from a phase III trial, NCT02563002, found that pembrolizumab led to significantly longer progression free survival compared to chemotherapy as a first line treatment for metastatic CRC patients with MSI-H or dMMR tumours. Therefore,immunotherapy may also be advantageous in other MSI-H or dMMR tumours.[3] Pembrolizumab is administered faster and less frequently than chemotherapy with less adverse side effects, meaning it may also be a better tolerated treatment option for patients. [4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy for the following indications:[1]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ⩾ 1% TPS and who have received at least one prior chemotherapy regimen
- treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option
- treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy

- treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ⩾ 10treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1
- treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum-containing chemotherapy
- first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults

The very common adverse effects (occurring in ≥10% patients) associated with pembrolizumab monotherapy are pneumonia, anaemia, infusion-related reaction, hypothyroidism, decreased appetite, dry eye headache, dyspnoea, cough, pruritus', arthralgia, muscoskeletal pain, fatigue, asthenia, oedema, pyrexia and gastrointestinal complaints.[1]

Pembrolizumab is currently in over 1300 phase II and III clinical trials including 120 phase III trials for indications such as non small lung cell cancer, adenocarcinoma of esophagogastric junction, advanced gastric cancer, breast cancer, bladder cancer and melanoma.[5]

PATIENT GROUP

DISEASE BACKGROUND

Solid tumours are abnormal masses of tissue that usually do not contain cysts or liquid areas. Solid tumours may be benign (not cancer), or malignant (cancer). Different types of solid tumours are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas.[6]

MSI-H/dMMR tumours occur when a system called DNA mismatch repair (MMR) that corrects errors that occur during cell DNA replication no longer works correctly. Defects in MMR can lead to MSI-H, which can be found in many types of cancer including solid tumours. MSI-H or dMMR tumours have an accumulation of errors in genetic sequences that are normally repeated (called microsatellites).[7]

We do not know the exact cause of these tumours, however risk factors include age, family history of cancer, being overweight, smoking, drinking alcohol and exposure to certain chemicals and UV rays. Regular physical activity, a healthy diet and protecting the skin against UV rays all lower risk of cancer. Symptoms and disease severity will vary depending on the type of tumour and cancer stage.[8]

CLINICAL NEED AND BURDEN OF DISEASE

Overall MSI-H prevalence based on 25 tumours was estimated at 14%. Overall, dMMR prevalence across 13 tumour types was estimated at 16%. Endometrial cancer had the highest pooled MSI-H and dMMR prevalence (26% and 25% all stages, respectively).[9]

The population of patients with MSI-H/dMMR solid tumours who would be eligible to receive pembrolizumab could not be estimated from available published sources. Information on 5 year survival and morbidity was also unavailable for these specific tumour mutations.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The decision about the best approach to treat and care for cancer should be discussed among a multidisciplinary team and the choice of treatment depends on several factors such as where the cancer is, how far it has grown or spread (the stage), type of cancer, how abnormal the cells look under a microscope (the grade), and general health and level of fitness of the patient.[10]

CURRENT TREATMENT OPTIONS

There are multiple treatment options currently available for the generic treatment of solid tumours which include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapies (e.g. monoclonal antibodies) and targeted cancer drugs (e.g. cancer growth blockers). The treatment provided will vary according to type of cancer, how big the cancer is, if the cancer has spread to other areas of the body and according to the patients' general health.[10]

Regarding the specific treatment of MSI-H/dMMR tumours, NICE guidance recommends use of nivolumab plus ipilumumab as a first line therapy for patients with metastatic colorectal cancer with MSI-H or dMMR.[11] There are currently no other treatments licenced specifically for tumours with MSI-H or dMMR.

PLACE OF TECHNOLOGY

If licenced, pembrolizumab will offer an additional treatment option for adults with MSI-H or dMMR tumours who have progressed following prior treatment and who have no satisfactory alternative treatment options.

CLINICAL TRIAL INFORMATION

Trial	NCT02628067; 2015-002067-41; A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158) **Phase II** – recruiting **Locations:** 7 EU countries, USA, Canada and other countries **Estimated primary completion date:** June 2026
Trial design	Non-randomised, parallel assignment, open label
Population	N=1595, participants over 18 years old with multiple types of advanced (unresectable and/or metastatic) solid tumors who have not progressed on standard of care therapy
Intervention(s)	200mg or 400mg pembrolizumab
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures - Objective Response Rate (ORR) defined as the percentage of participants who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the

	sum of diameters of target lesions) [Time Frame: Up to approximately 2 years] - For full list of other outcomes, see trial record
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The list price of pembrolizumab is £2,630 per 100-mg vial (excluding VAT; BNF online, accessed March 2021). The cost of a single administration is £5,260. This represents 3 weeks of treatment.[12]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. (TA716). July 2021.

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

OTHER GUIDANCE

No relevant guidance identified

ADDITIONAL INFORMATION

REFERENCES

1 Electronic medicines compendium (EMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2021. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 21 September 2021].

2 Clinicaltrials.gov. *Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158). Trial ID*. December 11, 2015. Status: Available from: https://www.clinicaltrials.gov/ct2/show/NCT02628067 [Accessed 31/08/2021].

3 André, T., Shiu K.-K., Kim T. W., Jensen B. V., Jensen L. H., Punt C., et al. *Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer*. New England Journal of Medicine. 2020 2020/12/03;383(23):2207-18. Available from: 10.1056/NEJMoa2017699 https://doi.org/10.1056/NEJMoa2017699 2021/09/13

4 Lucy Parsons. *NICE recommends Keytruda for colorectal cancer patients with rare mutations.* 2021. Available from: http://www.pmlive.com/pharma_news/nice_recommends_keytruda_for_colorectal_cancer_patients_with_rare_mutations_1370047 [Accessed 13 September 2021].

5 Clinicaltrials.gov. *Pembrolizumab.* 2021. Available from: https://www.clinicaltrials.gov/ct2/results?cond=Pembrolizumab+&term=&cntry=&state=&city=&dist= [Accessed

6 Cancer.gov. *Solid Tumours.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/solid-tumor [Accessed 01 September 2021].

7 Keytruda. *Is Keytruda right for you?* 2021. Available from: https://www.keytruda.com/msi-h/treatment-options/ [Accessed 01 September 2021].

8 Macmillan Cancer Support. *Causes and risk factors.* 2021. Available from: https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/causes-and-risk-factors [Accessed 06 September 2021].

9 Lorenzi, M., Amonkar M., Zhang J., Mehta S., Liaw K.-L. *Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review*. Journal of Oncology. 2020 2020/03/09;2020:1807929. Available from: 10.1155/2020/1807929 https://doi.org/10.1155/2020/1807929

10 Cancer Research UK. *Treatment for Cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment [Accessed 10/09/2021].

11 National Institute for Health and Care Excellence. *Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716).* Last Update Date: 28 July 2021. Available from: https://www.nice.org.uk/guidance/ta716 [Accessed 28 September 2021].

12 National Institute for Health and Care Exellence. *Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency* Last Update Date: Available from: https://www.nice.org.uk/guidance/ta709/resources/pembrolizumab-for-untreated-metastatic-colorectal-cancer-with-high-microsatellite-instability-or-mismatch-repair-deficiency-pdf-82611081504709 [Accessed 31 August 2021].

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