NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency

Draft Scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating solid tumours with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

Background

Solid tumours are abnormal localised masses of tissue. They can be cancerous (malignant) or not cancerous (benign) and are classified according to the type of cells that form them. The two major types of cancerous solid tumours are sarcomas and carcinomas. Sarcomas are developed from cells of muscles, bone or fat tissue and carcinomas start from the epithelial cells in the skin or tissues that line or cover internal organs. Advanced solid tumours can be locally advanced (tumour that has spread to surrounding tissues or lymph nodes but has not yet spread to other parts of the body) or metastatic (tumour that has spread to other parts of the body).

Mismatch repair (MMR) is a process where cells of the body recognise and repair nucleotide mismatches or insertion of excess DNA during replication of the DNA as cells divide. Deficiencies in MMR (dMMR) are associated with genomic instability and the accumulation of simple repetitive DNA sequences, which are known as microsatellites (MSI).[1] The accumulation of numerous MSI is classified as an MSI high (MSI-H) phenotype and, if these MSI affect regions of the genome associated with apoptosis (programmed cell death) and cell growth, it can result in the development of tumours.

The presence of dMMR and MSI-H phenotypes vary between cancer types but one estimate from a global systematic review and meta-analysis found 15% MSI-H prevalence across 25 tumour types and 16% dMMR prevalence across 13 tumour types.[1] MSI-H is reported to be most commonly associated with colorectal, endometrial, oesophageal, renal and certain gastric cancers, such as cancers of the, biliary tract and pancreas.[1,2]

In 2019, there were 327,174 new cases of cancer recorded in England and 137,096 deaths from cancer.[3] Of these cases, 78,868 were colorectal, endometrial, oesophageal, renal, gastric, intestinal, biliary or pancreatic cancers, making up 24.1% of diagnoses in 2019. These cancers also made up 18% (37,836) of cancer deaths in 2019.[3]

Treatment options

Nivolumab with ipilimumab (TA716) and pembrolizumab (TA709) are treatment options that target colorectal cancers with MSI-H and dMMR. The following second-line treatment options (see NICE TA405) are recommended for all colorectal cancers:

- single-agent irinotecan (after folinic acid plus fluorouracil plus oxaliplatin (FOLFOX))

- folinic acid plus fluorouracil plus irinotecan (FOLFIRI) (after either FOLFOX or capecitabine plus oxaliplatin) [CAPOX]

- raltitrexed (for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable

- trifluridine–tipiracil (if fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-EGFR agents have failed or when these therapies are not suitable).

Dostarlimab (TA779) is a treatment option that is available through the Cancer Drugs Fund for treating advanced or recurrent endometrial cancer with MSI-H and dMMR in adults who have had platinum-based chemotherapy.

There are currently no treatment options available which broadly target a range of MSI-H and dMMR classified solid tumours. Current treatments for different solid tumour cancers generally include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapy, small molecule inhibitor treatments, or a combination of these treatments.

The technology

Pembrolizumab has a marketing authorisation for the treatment of the following MSI-H or dMMR cancers in adults:

- for unresectable or metastatic colorectal cancer after fluoropyrimidine-based combination therapy;

- for advanced or recurrent endometrial cancer whose disease has progressed on or following treatment with a platinum-containing therapy and are not suitable for curative surgery or radiation; and

- for unresectable or metastatic gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.

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Intervention(s)	Pembrolizumab
Population(s)	Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy. Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer previously treated with fluoropyrimidine-based combination therapy.
Subgroups	If the evidence allows the following subgroups will be considered: • tumour site • previous therapy

Comparators	For people with previously treated MSI-H or dMMR classified solid tumours: • Established management without pembrolizumab For people with previously treated MSI-H or dMMR colorectal cancer: • Established management without pembrolizumab • Nivolumab with ipilimumab • Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer: • Established management without pembrolizumab • Dostarlimab (subject to NICE evaluation)
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • duration of response • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The use of pembrolizumab for this indication is conditional on the presence of either MSI-H or dMMR classified tumours. The economic modelling should include the costs associated with diagnostic testing for MSI-H or dMMR in people with solid tumours who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** 'Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair' (2021) NICE Technology Appraisal 716. Review date 2024 'Trifluridine–tipiracil for previously treated metastatic colorectal cancer' (2016) NICE Technology Appraisal 405. Review date to be confirmed. 'Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy' (2014, Reviewed 2016) NICE Technology Appraisal 307. Review date to be confirmed 'Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the

	treatment of metastatic colorectal cancer after first-line chemotherapy' (2012, Reviewed 2015) NICE Technology Appraisal 242. Review date to be confirmed. 'Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer' (2021)NICE Technology Appraisal 688.Review date 2023 Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency' (2022) NICE Technology Appraisal 779. Review date to be confirmed. **Related Guidelines:** 'Suspected cancer: recognition and referral' (2015; updated 2021) NICE guideline 12. Review date to be confirmed. 'Molecular testing strategies for Lynch syndrome in people with colorectal cancer' (2017) Diagnostics Guidance 27. Review date to be confirmed 'Testing strategies for Lynch syndrome in people with endometrial cancer' (2020) Diagnostics guidance 42. Review date to be confirmed **Related Quality Standards:** **'**Suspected cancer' (2017) NICE quality standard 124. 'Sarcoma' (2015) NICE quality standard 78
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) – Chapter 105 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1-5.

Questions for consultation

What is the population size for unresectable or metastatic solid tumours with MSI-H or dMMR in England?

Which solid tumour sites are most commonly associated with MSI-H or dMMR?

Are screening strategies for MSI-H and dMMR in solid tumours routinely available and established in NHS practice?

Which treatments are considered to be established clinical practice in NHS for MSI-H or dMMR unresectable or metastatic tumours in people who have progressed following prior therapies?

Would pembrolizumab be used differently based on tumour site?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Lorenzi M, Amonkar M, Zhang J et al. Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumours: A Structured Literature Review. Journal of Oncology (2020)

2. Bateman A. DNA mismatch repair proteins: scientific update and practical guide. Journal of Clinical Pathology. (2021)

3. NHS Digital. Cancer Registration Statistics, England 2019. (2021) Accessed, December 2021