NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

Final scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.

Background

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer often first spreads to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

Microsatellite instability

The prevalence of high microsatellite (a repetitive DNA sequence) instability (MSI) depends on the stage of colorectal cancer. Approximately 15% of people with early stage colorectal cancer show high MSI, whereas around 4% of metastatic disease show high MSI.[1,2] MSI status is determined by PCR (polymerase chain reaction)-based analysis of tissue samples from colorectal cancer tumours to detect a standardised panel of DNA markers. NICE diagnostics guidance (DG27) recommends testing all people with colorectal cancer, when first diagnosed using immunohistochemistry for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair.

DNA mismatch repair deficiency

DNA mismatch repair (MMR) deficiency results in mutations, tumour development and progression. DNA MMR-deficient tumours are associated with a higher rate of MSI mutations.[3]

Treatment options

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. There are currently no treatments available specifically for tumours with high MSI or MMR deficiency. Metastatic colorectal cancer treatment can involve a combination of surgery (to resect the primary tumour or the metastases), chemotherapy (to make the tumour or metastases resectable, or to manage the cancer), biological therapy, and radiotherapy.

For advanced or metastatic colorectal cancers, NICE recommend that initial chemotherapy can be given alone, or combined with biological epidermal growth factor receptor (EGFR) inhibitors for patients with RAS wild-type disease (see NICE NG151, NICE TA61 and NICE TA439). Treatment options include:

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- capecitabine plus oxaliplatin (CAPOX)

- capecitabine or tegafur with uracil (in combination with folinic acid)
- cetuximab or panitumumab in combination with FOLFOX or folinic acid plus fluorouracil plus irinotecan (FOLFIRI)
- raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable).

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal antibody that targets and blocks a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. It is administered intravenously.

Pembrolizumab does not currently have a marketing authorisation in the UK for treating metastatic colorectal cancer with high MSI or MMR deficiency. It has been studied in clinical trials in adults with metastatic colorectal cancer with high MSI or MMR deficiency.

Intervention(s)	Pembrolizumab
Population(s)	Adults with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.
Comparators	**For all patients** • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine • Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) **For patients with RAS wild-type metastatic colorectal cancer** • Panitumumab in combination with FOLFOX or folinic acid plus fluorouracil plus irinotecan (FOLFIRI) **For patients with EGFR expressing, RAS wild-type metastatic colorectal cancer** • Cetuximab in combination with FOLFOX or FOLFIRI

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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 economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
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. If the evidence allows the subgroup of people with RAS wild-type colorectal cancer will be considered.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (2017) NICE Technology Appraisal guidance TA439. Next review: 2020. Laparoscopic surgery for colorectal cancer (2006) NICE Technology Appraisal guidance TA105. Reviewed: Decision to move to static list. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE Technology Appraisal guidance TA61. Reviewed: Decision to move to

	static list. **Appraisals in development (including suspended appraisals):** Nivolumab with ipilimumab for treating metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency NICE Technology Appraisals [ID1332]. Expected publication date: 14 July 2021. **Related Guidelines:** Colorectal cancer (2020) NICE guideline NG151. **Related Diagnostic Programme:** Molecular testing for Lynch syndrome in people with colorectal cancer. NICE diagnostic guidance [DG27]. Publication: February 2017. Review: February 2020. **Related Quality Standards**: Colorectal cancer (2020) NICE Quality Standard QS20 Suspected Cancer (2017) NICE Quality Standard QS124 **Related NICE Pathways**: Colorectal cancer (2020) NICE pathway http://pathways.nice.org.uk/pathways/colorectal-cancer
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS manual for prescribed specialist services (2018/2019). (See: Specialised Colorectal Services) NHS England (2015) Colorectal Cancer PROMs Report Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1 and 4. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1. Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015;5(1):16-8.

2. Fujiyoshi K, Yamamoto G, Takenoya T, et al. Metastatic Pattern of Stage IV Colorectal Cancer with High-Frequency Microsatellite Instability as a Prognostic Factor. Anticancer Res. 2017;37(1):239-47

3. Gologan A, Sepulveda AR. Microsatellite instability and DNA mismatch repair deficiency testing in hereditary and sporadic gastrointestinal cancers. Clin Lab Med. 2005 Mar; 25(1):179-96.