NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab for previously treated 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 nivolumab with ipilimumab within its marketing authorisation for previously treated 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] Although high MSI levels may been associated with a better prognosis in early stage colorectal cancer, poorer outcomes have been reported in metastatic disease.[2-5] 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. MMR-deficient tumours are associated with a higher rate of MSI mutations.[6]

Treatment options

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. There are currently no treatments available specifically for 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.

The following second-line treatment options (see NICE TA405) are recommended:

- 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).

If standard therapies are unsuccessful, not tolerated or contraindicated, people are treated with supportive care to manage the symptoms and complications of the condition.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) 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.

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human antibody that binds to and blocks the activity of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), thereby sustaining the immune attack on cancer cells. It is administered intravenously.

Nivolumab in combination with ipilimumab does not currently have a marketing authorisation in the UK for treating metastatic colorectal cancer with high MSI or MMR. It has been studied in clinical trials in adults with high microsatellite instability (MSI-H) recurrent or metastatic colorectal cancer.

Intervention	Nivolumab with ipilimumab
Population	Adults with previously treated recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.
Comparators	• Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • FOLFOX (after either FOLFIRI or CAPOX) • Raltitrexed (if 5‑fluorouracil and folinic acid are not suitable) • Trifluridine–tipiracil • Best supportive care

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.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Trifluridine–tipiracil for previously treated metastatic colorectal cancer (2016) NICE Technology appraisal guidance 405. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (2014) NICE Technology appraisal guidance 307. Reviewed: Decision to move to static list. 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) NICE Technology Appraisal guidance TA242. Reviewed: Decision to move to static list. 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. **Terminated appraisals:** Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal) (2011) NICE Technology Appraisal TA240. Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) (2015) NICE Technology Appraisal TA334. **Appraisals in development (including suspended appraisals):** Nivolumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency NICE technology appraisals guidance [ID1136]. Suspended. MABp1 for treating metastatic or unresectable colorectal cancer after oxaliplatin and irinotecan. NICE technology appraisal guidance [ID917]. Suspended. Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency. NICE Technology Appraisals [ID1071]. Suspended. **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

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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. Sinicrope, F, Rego, R, Halling, K, et al. Prognostic Impact of Microsatellite Instability and DNA Ploidy in Human Colon Carcinoma Patients. Gastroenterology 2006;131(3):729-737.

4. Goldstein J, Tran B, Ensor J, et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). Ann Oncol. 2014;25(5):1032-8.

5. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014;20(20):5322-30.

6. 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.