NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab 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]. High MSI has been shown to be a marker for better prognosis than low MSI or microsatellite stable tumours during the early stages of colorectal cancer MSI status is determined by a MSI testing, which involves 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[3].

Treatment options

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. There are currently no specific treatments available specifically for high MSI or MMR deficiency. Metastatic colorectal cancer treatment can involve a combination of surgery (to re-sect 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 have been recommended as part of NICE guidance:

- 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 [XELOX])
- raltitrexed (for patients with advance 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.

Cetuximab, bevacizumab and panitumumab are not recommended for treating metastatic colorectal cancer after first-line chemotherapy (TA242). Aflibercept in combination with irinotecan and fluorouracil-based therapy is also not recommended for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen (TA307).

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.

Nivolumab does not currently have a marketing authorisation in the UK for previously treated metastatic colorectal cancer with high MSI or MMR deficiency. It has been studied in trials alone and in combination with ipilimumab and other anti-cancer agents (cobimetinib, aratumumab, and an anti-LAG-3 antibody) in adults with recurrent or metastatic colorectal cancer.

Intervention	Nivolumab
Population(s)	Adults with previously treated metastatic colorectal cancer with high microsatellite instability or mismatched repair deficiency.

Comparators	• Single agent irinotecan (after folinic acid plus fluorouracil plus oxaliplatin only [FOLFOX]) • Folinic acid in combination with fluorouracil and irinotecan [FOLFIRI] (after either FOLFOX or capecitabine plus oxaliplatin only [XELOX]) • Raltitrexed (if 5‑fluorouracil and folinic acid are not suitable) • Trifluridine–tipiracil (after fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor [VEGF] agents and anti- epidermal growth factor receptor [EGFR] agents) • 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 patient access schemes for the intervention or comparator 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. Review: August 2019 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. **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)** 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]. Expected publication date: September 2017 **Related Guidelines**: Colorectal cancer: diagnosis and management of colorectal cancer (2014) NICE Guideline CG131. Update expected: October 2019 **Related Diagnostic Programme:** Molecular testing for Lynch syndrome in people with colorectal cancer. NICE diagnostic guidance [DG27]. Publication: February 2017. Review: August 2020 **Related Quality Standards**: Colorectal cancer (2012) NICE Quality Standard QS20 Suspected Cancer (2016) NICE Quality Standard QS124 **Related NICE Pathways**: Colorectal cancer (2016) NICE pathway http://pathways.nice.org.uk/pathways/colorectal-cancer
Related National Policy	NHS England (2015) Colorectal Cancer PROMs Report NHS England (2016) Manual for prescribed specialised services 2016/17 (See: Specialised Colorectal Services)

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.