NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab for treating metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with ipilimumab within its marketing authorisation for treating 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 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 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 EGFR inhibitors (see NICE CG131 and NICE TA61). Treatment options include:

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- capecitabine plus oxaliplatin (XELOX)
- 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).

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

- single-agent irinotecan (after FOLFOX)
- FOLFIRI (after either FOLFOX or 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.

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 recurrent or metastatic colorectal cancer.

Intervention	Nivolumab with ipilimumab

Population	Adults with recurrent or metastatic colorectal cancer with high microsatellite instability or mismatched repair deficiency.
Comparators	For people having first-line treatment: • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Capecitabine plus oxaliplatin (XELOX) • Cetuximab in combination with FOLFOX or folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Panitumumab in combination with FOLFOX or FOLFIRI • Capecitabine • Tegafur with uracil (in combination with folinic acid) For people having second- or subsequent-line treatment: • Single-agent irinotecan • FOLFIRI • Raltitrexed (if 5‑fluorouracil and folinic acid are not suitable) • Trifluridine–tipiracil • Nivolumab monotherapy (subject to ongoing NICE appraisal ID1136) • 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. 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]. Publication expected April 2018. 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: 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)

Questions for consultation

Have all relevant comparators for nivolumab with ipilimumab been included in the scope?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom nivolumab with ipilimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider nivolumab with ipilimumab will fit into the existing NICE pathway, colorectal cancer http://pathways.nice.org.uk/pathways/colorectal-cancer?

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 nivolumab with ipilimumab 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 nivolumab with ipilimumab 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 nivolumab with ipilimumab 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.

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 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).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

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.