Draft scope

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for metastatic colorectal cancer with or without high microsatellite instability.

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
Up to one in five metastatic colorectal cancers show high microsatellite (a repetitive DNA sequence) instability (MSI). High MSI has been shown to be a marker for better prognosis than low MSI or microsatellite stable tumours. High MSI is associated with a poorer response to fluorouracil chemotherapy. 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.

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. 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 epidermal growth factor receptor (EGFR) inhibitors, and radiotherapy.

The following first-line treatment options have been recommended as part of NICE Guideline CG131 ‘Colorectal cancer: diagnosis and management’ (2011):

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- capecitabine plus oxaliplatin (XELOX)
- capecitabine (NICE technology appraisal [TA] guidance 61)
- tegafur with uracil (in combination with folinic acid, NICE TA 61).
FOLFOX, FOLFIRI and XELOX can be combined with cetuximab (currently funded through the Cancer Drugs Fund) or panitumumab (currently funded through the Cancer Drug Fund).

For second-line, the following treatment options recommended as part of NICE Guideline CG131 are:

- single agent irinotecan
- folinic acid plus fluorouracil plus irinotecan (FOLFIRI)
- raltitrexed (for patients with advance colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable, CG131)
- 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, TA405).

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). Afiblercept 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 metastatic colorectal cancer. It has been studied in a trial 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.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population(s)</td>
<td>Adults with metastatic colorectal cancer with or without high microsatellite instability</td>
</tr>
</tbody>
</table>
### Comparators

<table>
<thead>
<tr>
<th>For people receiving first-line treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Folinic acid plus fluorouracil plus oxaliplatin or capcitabine plus oxaliplatin (FOLFIRI)</td>
</tr>
<tr>
<td>• FOLFIRI in combination with cetuximab or panitumumab</td>
</tr>
<tr>
<td>• Capcitabine plus oxaliplatin (XELOX)</td>
</tr>
<tr>
<td>• XELOX in combination with cetuximab or panitumumab</td>
</tr>
<tr>
<td>• Capcitabine</td>
</tr>
<tr>
<td>• Tegafur with uracil (in combination with folinic acid).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For people receiving second-line treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single agent irinotecan (after folinic acid plus fluorouracil plus oxaliplatin only)</td>
</tr>
<tr>
<td>• Folinic acid in combination with fluorouracil and irinotecan (after FOLFIRI)</td>
</tr>
<tr>
<td>• Trifluridine–tipiracil</td>
</tr>
<tr>
<td>• Pembrolizumab (subject to ongoing NICE appraisal)</td>
</tr>
<tr>
<td>• MABp1 (after oxaliplatin and irinotecan) (subject to ongoing NICE appraisal)</td>
</tr>
<tr>
<td>• Best supportive care</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>The outcome measures to be considered include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• overall survival</td>
</tr>
<tr>
<td>• progression-free survival</td>
</tr>
<tr>
<td>• response rates</td>
</tr>
<tr>
<td>• adverse effects of treatment</td>
</tr>
<tr>
<td>• health-related quality of life.</td>
</tr>
</tbody>
</table>
### 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 use of nivolumab for metastatic colorectal cancer with high microsatellite instability is conditional on the microsatellite instability status. 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:**


- **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. Decision to move to static list.


**Terminated appraisals**


**Appraisals in development (including suspended appraisals)**

MABp1 for treating metastatic or unresectable colorectal cancer after oxaliplatin and irinotecan. NICE technology appraisal guidance [ID917]. Publication date to be confirmed.

Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency. NICE Technology Appraisals [ID1071]. Publication date to be confirmed.

**Related Guidelines:**

Update expected: October 2019

**Related Diagnostic Programme:**


**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

Questions for consultation
Will nivolumab be used as monotherapy or combination therapy for metastatic colorectal cancer?

Will nivolumab be used for previously untreated or treated metastatic colorectal cancer?

Will nivolumab be used for relapsed or refractory metastatic colorectal cancer?

Will nivolumab be used to treat metastatic colorectal cancer:
- with or without high microsatellite instability?
- with DNA mismatch repair deficiency?

Which treatments are considered to be first-line and second-line therapy?
What is current clinical practice for relapsed or refractory metastatic colorectal cancer?

Which treatments are considered to be current clinical practice for previously treatment metastatic colorectal cancer with high microsatellite instability?

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

How should best supportive care be defined?

Are there any subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Are high microsatellite instability and DNA mismatched repair deficiency distinct subgroups groups?

Are the outcomes listed appropriate?

Is high microsatellite instability tested in clinical practice or how are these conditions diagnosed? If yes, what is the test used? Are all patients with relapsed metastatic colorectal cancer to be tested prior receiving nivolumab? Would routine testing in clinical practice have an effect on costs and on health and social care services?

Where do you consider nivolumab will fit into the existing NICE pathway, 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 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 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 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