

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Regorafenib for treating metastatic colorectal cancer

Draft scope

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of regorafenib within its marketing authorisation for treating metastatic colorectal cancer.

**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. Most colorectal cancers are adenocarcinomas, these start in glands that line the insides of the colon and rectum.

There were 33,815 cases of colon cancer and 16,628 cases of rectum cancer in the UK in 2020, accounting for 11% of all cancers in the UK.<sup>1</sup> Five-year prevalence of colon cancer is 149.34 per 100,000, and 5-year prevalence of rectum cancer is 80.16 per 100,000.<sup>1</sup> 58% of new cases of colorectal cancer in the UK were in people aged over 65 years, but it can also affect young people too.<sup>2</sup>

The cause of colorectal cancer is uncertain, however studies have shown the frequency of colorectal cancer is higher in countries where people eat a diet high in fat and low in fibre.<sup>3,4</sup> Two inherited disease can also increase the risk of developing colorectal cancer: familial adenomatous polyposis and hereditary non-polyposis colon cancer.<sup>4</sup> A history of severe ulcerative colitis or Chron's disease affecting the large bowel may increase the risk of developing colorectal cancer.<sup>4</sup>

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. 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 people with untreated metastatic colorectal cancer, [NICE technology appraisal 61](#) recommends intravenous fluorouracil/folinic acid (5-FU/FA) or capecitabine. [NICE guideline 151](#) also recommends either folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) for untreated disease.

For people with previously treated metastatic colorectal cancer [NICE guideline 151](#) recommends folinic acid plus fluorouracil plus irinotecan (FOLFIRI), after either FOLFOX or CAPOX. Established clinical management for previously treated metastatic colorectal cancer is considered to be single-agent irinotecan (after FOLFOX) or raltitrexed (for patients with advanced colorectal cancer who are intolerant to 5-FU/FA, or for whom these drugs are not suitable). [NICE technology appraisal 405](#) recommends 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 best supportive care to manage the symptoms and complications of the condition.

Nivolumab with ipilimumab can be offered as a treatment for those with high microsatellite instability or mismatch repair deficiency after fluoropyrimidine-based combination chemotherapy ([NICE TA716](#)). For those with BRAF V600E mutation-positive metastatic colorectal cancer who have had previous systemic treatment encorafenib plus cetuximab is a treatment option ([NICE TA668](#)).

**The technology**

Regorafenib (Stivarga, Bayer) is a multi-kinase inhibitor. It blocks several enzymes that are important for the development of a blood supply to the tumours and development of cancer cells, stopping the growth and spread of the cancer. It is administered orally.

Regorafenib has a marketing authorisation in the UK for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies.

<b>Intervention</b>	Regorafenib
<b>Population</b>	Adults with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Single-agent irinotecan (after FOLFOX)</li> <li>• FOLFIRI (after either FOLFOX or CAPOX)</li> <li>• FOLFOX (after either FOLFIRI or CAPOX)</li> <li>• Raltitrexed (if 5-FU/FA are not suitable)</li> <li>• Trifluridine–tipiracil</li> <li>• Nivolumab with ipilimumab (if colorectal cancer with high microsatellite instability or mismatch repair)</li> <li>• Encorafenib plus cetuximab (if BRAF V600E mutation-positive)</li> <li>• Best supportive care</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rates</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<p><b>Economic analysis</b></p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account.</p>
<p><b>Other considerations</b></p>	<p>If the evidence allows subgroups will be considered based on previous treatment received for metastatic colorectal cancer.</p> <p>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.</p>
<p><b>Related NICE recommendations and NICE Pathways</b></p>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">‘Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency’</a> (2021). NICE Technology Appraisal 716. Review 2024.</p> <p><a href="#">‘Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency’</a> (2021). NICE Technology Appraisal 709. Review 2024.</p> <p><a href="#">‘Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer’</a> (2021). NICE Technology Appraisal 668. Review 2023.</p> <p><a href="#">‘Cetuximab and panitumumab for previously untreated metastatic colorectal cancer’</a> (2017). NICE Technology Appraisal 439. No current plans to review this guidance.</p> <p><a href="#">‘Trifluridine–tipiracil for previously treated metastatic colorectal cancer’</a> (2016). NICE Technology Appraisal 405. No current plans to review this guidance.</p> <p><a href="#">‘Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy’</a> (2014). NICE Technology Appraisal 307. Reviewed: Decision to move to static list.</p> <p><a href="#">‘Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy),</a></p>

[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 242. Reviewed: Decision to move to static list.

[Laparoscopic surgery for colorectal cancer](#)' (2006). NICE Technology Appraisal 105. 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 61. 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 240.

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

[Atezolizumab for treating metastatic colorectal cancer after 2 therapies](#)' NICE technology appraisals guidance [ID1298]. Publication date to be confirmed.

[Colorectal cancer \(metastatic\) - MABp1 \(after previous treatment\)](#)' NICE technology appraisals guidance [ID917]. Publication date to be confirmed.

[Nintedanib for previously treated metastatic colorectal cancer](#)' NICE technology appraisals guidance [ID1030]. Publication date to be confirmed.

[Nivolumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency](#)' NICE technology appraisals guidance [ID1136]. Publication date to be confirmed.

[Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency](#)' NICE technology appraisals guidance [ID1071]. Publication date to be confirmed.

#### **Related Guidelines:**

[Colorectal cancer](#)' (2021). NICE guideline 151. No current plans to review this guideline.

[ColonFlag for identifying people at risk of colorectal cancer](#)' (2018). Medtech innovation briefing 142.

[Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care](#)' (2017). Diagnostics guidance 30.

[Virtual chromoendoscopy to assess colorectal polyps during colonoscopy](#)' (2017). Diagnostics guidance 28.

[Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas](#)'

	<p>(2011). Clinical guideline 118.</p> <p><b>Related Interventional Procedures:</b></p> <p><a href="#">‘Selective internal radiation therapy for unresectable colorectal metastases in the liver’</a> (2020). NICE interventional procedures guidance 672.</p> <p><a href="#">‘Radiofrequency ablation for colorectal liver metastases’</a> (2009). NICE interventional procedures guidance 327.</p> <p><b>Related Quality Standards:</b></p> <p><a href="#">‘Colorectal cancer’</a> (2022). NICE quality standard 20.</p> <p><a href="#">‘Suspected Cancer’</a> (2017) NICE Quality Standard 124</p>
<p><b>Related National Policy</b></p>	<p>The NHS Long Term Plan, 2019. <a href="#">NHS Long Term Plan</a></p> <p>NHS England (2018/2019) <a href="#">NHS manual for prescribed specialist services (2018/2019)</a></p> <p>NHS England (2015) <a href="#">Colorectal Cancer PROMs Report</a></p> <p>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 to 5. <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p>

### Questions for consultation

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

- Which treatments are considered to be established clinical practice in the NHS for metastatic colorectal cancer?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in other considerations appropriate?

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

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 regorafenib is 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 regorafenib 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 regorafenib 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 Evaluation (STE) 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.

<https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

### References

1. United Kingdom Fact sheet, [International Agency for Research on Cancer](#). Accessed February 2022.
2. Office for National Statistics, [Cancer registration statistics, England](#). Accessed February 2022.
3. Cancer Research UK, [Bowel cancer statistics](#). Accessed February 2022.
4. The Royal Marsden NHS Foundation Trust, [Colorectal cancer](#). Accessed February 2022.