

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Encorafenib with binimetinib and cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer**Draft scope****Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of encorafenib with binimetinib and cetuximab within their marketing authorisation for previously treated BRAF V600E mutation-positive 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.

Approximately 10% of people with colorectal cancer have tumours with the BRAF V600E mutation, which more than doubles the risk of mortality.¹ NICE diagnostics guidance ([DG27](#)) recommends routinely testing all people with colorectal cancer for the BRAF V600E mutation if they have either an abnormal MLH1 immunohistochemistry result or a positive microsatellite instability test.

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. There are currently no treatments available specifically for tumours with BRAF V600E mutations.

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. NICE recommends the following options for untreated metastatic colorectal cancer (see [NICE CG131](#) and [NICE TA61](#)):

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- capecitabine plus oxaliplatin (XELOX)
- capecitabine or tegafur with uracil (in combination with folinic acid)
- raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable).

NICE recommends the following treatment options for previously treated metastatic colorectal cancer (see NICE [CG131](#) and NICE [TA405](#)):

- irinotecan – after initial treatment with FOLFOX

- folinic acid plus fluorouracil plus irinotecan (FOLFIRI) – after initial treatment with FOLFOX or XELOX
- trifluridine-tipiracil (after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, or when these therapies are not suitable).

The biological therapies aflibercept, bevacizumab, cetuximab and panitumumab are not recommended (alone or in combination) by NICE for the treatment of metastatic colorectal cancer (see NICE [TA118](#), NICE [TA212](#), NICE [TA242](#) and NICE [TA307](#)).

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

Encorafenib with binimetinib and cetuximab is a triple therapy which inhibits multiple parts of the cell signaling pathway in BRAF V600E positive tumours.

Encorafenib (Braftovi, Pierre Fabre) is an oral rapidly accelerated fibrosarcoma (RAF) kinase inhibitor with anti-tumour activity which blocks the cell signaling pathway in BRAF V600E mutation-positive tumours, which may decrease the spread and growth of tumour cells.

Binimetinib (Mektovi, Pierre Fabre) is an oral MEK 1 and 2 kinase inhibitor with anti-tumour activity. It blocks the MEK signaling pathway by both inhibiting MEK and preventing BRAF activation of MEK. The addition of binimetinib improves the anti tumour activity of encorafenib.

Cetuximab (Erbix, Merck) is a recombinant monoclonal antibody that blocks the epidermal growth factor receptor and thereby inhibits the spread and growth of tumour cells. It is administered intravenously.

Encorafenib with binimetinib and cetuximab does not currently have a marketing authorisation in the UK for treating BRAF V600E mutation-positive metastatic colorectal cancer. It has been studied compared with irinotecan with cetuximab or FOLFIRI with cetuximab in a clinical trial in adults with previously treated BRAF V600E mutation-positive metastatic colorectal cancer.

Intervention(s)	Encorafenib with binimetinib and cetuximab
Population(s)	People with previously treated BRAF V600E mutation-positive metastatic colorectal cancer

Comparators	<ul style="list-style-type: none"> • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Irinotecan • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable) • Best supportive care
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	<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, comparator and subsequent treatment technologies will be taken into account.</p>
Other considerations	<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>
Related NICE recommendations and NICE Pathways	<p>Related Technology Appraisals:</p> <p>Trifluridine–tipiracil for previously treated metastatic colorectal cancer (2016) NICE Technology Appraisal TA405. Review date: August 2019</p> <p>Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic</p>

	<p>colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (2014) NICE technology appraisal guidance TA307. Reviewed: Decision to move to static list.</p> <p>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.</p> <p>Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (2010) NICE Technology Appraisal TA212. Reviewed: Decision to move to static list.</p> <p>Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (2007) NICE Technology Appraisal TA118. Reviewed: Decision to move to static list.</p> <p>Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE Technology Appraisal TA61. Reviewed: Decision to move to static list.</p> <p>Terminated appraisals</p> <p>Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal) (TA240)</p> <p>Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) (TA334)</p> <p>Related Guidelines:</p> <p>Colorectal cancer: diagnosis and management of colorectal cancer (2014) NICE Guideline CG131. Update expected January 2020.</p> <p>Related Diagnostic Programme:</p> <p>Molecular testing for Lynch syndrome in people with colorectal cancer. NICE diagnostic guidance [DG27]. Publication: February 2017. Review: August 2020.</p> <p>Related Quality Standards:</p>
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	<p>Colorectal cancer (2012) NICE Quality Standard QS20</p> <p>Suspected Cancer (2016) NICE Quality Standard QS124</p> <p>Related NICE Pathways:</p> <p>Colorectal cancer (2016) NICE pathway</p> <p>http://pathways.nice.org.uk/pathways/colorectal-cancer</p>
Related National Policy	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan NHS manual for prescribed specialist services (2018/2019). (See: Specialised Colorectal Services)</p> <p>NHS England (2015) Colorectal Cancer PROMs Report</p> <p>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</p>

Questions for consultation

Have all relevant comparators for encorafenib with binimetinib and cetuximab for previously treated colorectal cancer been included in the scope? BMJ best practice guidance also recommends FOLFOX and XELOX for patients initially treated with FOLFIRI.²

- Are FOLOX, XELOX and capecitabine monotherapy used for previously treated colorectal cancer in clinical practice?

How should best supportive care be defined?

Is testing for the BRAF V600E mutation in people with colorectal cancer routine in clinical practice?

Are the outcomes listed appropriate?

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

Where do you consider encorafenib with binimetinib and cetuximab 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 encorafenib with binimetinib and cetuximab 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 encorafenib with binimetinib and cetuximab 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 encorafenib with binimetinib and cetuximab 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>).

References

1 Safaee Ardekani G, Jafarnejad SM, Tan L, et al. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. *PLoS One*. 2012;7(10):e47054.

2 BMJ Best Practice, Colorectal cancer treatment algorithm. Available at <https://bestpractice.bmj.com/topics/en-gb/258/treatment-algorithm> (accessed: June 2019)