NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of encorafenib in dual or triple therapy for treating 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 for testing for Lynch syndrome in people with colorectal cancer (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, NICE TA61 and NICE TA439):

- 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)
- cetuximab or panitumumab with FOLFOX or FOLFIRI (for people with RAS wild-type metastatic colorectal cancer).

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 in dual therapy with cetuximab or triple therapy with binimetinib and cetuximab, 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. It is administered orally.

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. It is administered orally.

Cetuximab (Erbitux, 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 as a dual or triple therapy 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 cetuximab, or Encorafenib with cetuximab and binimetinib
Population(s)	People with previously treated BRAF V600E mutation-positive metastatic colorectal cancer
Comparators	• 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	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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of encorafenib in dual or triple therapy is conditional on the presence of BRAF V600E mutation. The economic modelling should include the costs associated with diagnostic testing for BRAF V600E mutation 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 TA405. Review date: 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 TA307. Reviewed: Decision to move to static list. 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 TA242. Reviewed: Decision to move to static list. 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. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (2007) NICE Technology Appraisal TA118. 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 TA61. Reviewed: Decision to move to static list. **Terminated appraisals** Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal) (TA240) Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) (TA334) **Related Guidelines:** Colorectal cancer: diagnosis and management of colorectal cancer (2014) NICE Guideline CG131. Update expected January 2020. **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	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS manual for prescribed specialist services (2018/2019). (See: Specialised Colorectal Services) NHS England (2015) Colorectal Cancer PROMs Report 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

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)