National Institute for Health and Care Excellence

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Pierre Fabre	The anticipated licensed indication for encorafenib (BRAFTOVI®) and binimetinib (MEKTOVI®) in combination with cetuximab is for the treatment of patients with metastatic colorectal cancer (mCRC) who have received prior systemic treatment and whose tumours harbour a BRAFV600E mutation. [confidential in confidence information removed]	Comment noted. No action required.
Timing Issues	Pierre Fabre	The appraisal date has been scheduled for early December 2019. This date was revised following a request from Pierre Fabre Ltd to ensure that all available evidence from the BEACON trial dataset will be available to support a suitably comprehensive and robust evidence submission. There is a significantly high unmet need for effective treatments that specifically target the BRAFV600E mutation. BRAFV600E mutations occur in approximately 10% of the mCRC population and are associated with poor prognosis for patients using existing available regimens.[1]	Comment noted. No action required.
Additional comments	Pierre Fabre	[confidential in confidence information removed]	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pierre Fabre	BRAFV600E mutations occur in approximately 10% of the mCRC population and are associated with poor prognosis for patients using existing available regimens. Thus, there is a significantly high unmet need for effective treatments that specifically target the BRAFV600E mutation	Comment noted. No action required.
The technology/ intervention	Pierre Fabre	Yes. In addition to the current text it would be helpful to add that encorafenib and binimetinib in combination with cetuximab is one of the first regimens to specifically target BRAF mutations in mCRC.	Comment noted. No action required.
Population	Pierre Fabre	Yes, and as stated above, the anticipated licensed indication for encorafenib (BRAFTOVI®) and binimetinib (MEKTOVI®) in combination with cetuximab is for the treatment of patients with mCRC who have received prior systemic treatment and whose tumours harbour a BRAFV600E mutation. There are no sub-groups within this population which need to be considered separately.	Comment noted. No action required.
Comparators	Pierre Fabre	It is important to note that the BEACON trial is the first and only Phase 3 study specifically investigating patients with BRAFV600E mCRC. As such there is a paucity of comparative data available to compare outcomes within the BRAFV600E mutated patient population above the comparators considered in the BEACON trial. The control arm in this trial includes the active comparators of cetuximab in combination with FOLFIRI or irinotecan. Cetuximab is widely available in later lines of therapy in Europe, but is only available in the UK as a first-line treatment (for RAS wild type mCRC) in line with NICE recommendations.[2] Of the comparators listed in the draft scope: • **Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)** Feedback from consultant oncologists has confirmed that the current practice in the UK is for the majority of patients with RAS mutant mCRC to receive FOLFOX first line and FOLFIRI second-line. Patients with with RAS wild type	Comments noted. Justification of comparators can be made in submission. No action required.

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		mCRC may receive FOLFOX + EGFRi (cetuximab or panitumumab) first-line and FOLFIRI second-line; this is line with NICE CG131 recommendations.[3] Based on this from a real world NHS perspective in the second-line setting, FOLFIRI represents the most relevant and appropriate comparator for the BEACON trial for cost-effectiveness analysis. • **Irinotecan** The use of single agent Irinotecan is not considered a relevant comparator after first-line treatment. This is further supported by data from IPSOS Monitor 2019 which suggest market share of the single agent is less than 5% in a post first-line setting. • **Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable)** Trifluridine-tipiracil is commonly reserved as a third-line agent. Since encorafenib, binimetinib and cetuximab will likely be used earlier in the treatment pathway this may not be an appropriate comparator. • **Best supportive care (BSC)** BSC refers to palliative care, when patients have exhausted all treatment options including cytotoxic chemotherapy. The anticipated use of encorafenib, binimetinib and cetuximab would be earlier in the treatment pathway. Therefore, BSC is not an appropriate comparator. *1.* In response to the consultation question '*Are FOLOX, XELOX and capecitabine monotherapy used for previously treated colorectal cancer in clinical practice?'* Oral therapy with single agent capecitabine is an option only for the first-line treatment of mCRC and is not a relevant comparator.[4] While FOLFOX and	

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		XELOX are used in clinical practice, FOLFIRI is the most widely used chemotherapy regimen **after first-line** treatment and remains the most appropriate comparator. It is important to note that given the paucity of published clinical trial data for any comparative analysis, it is anticipated that a network meta-analysis or indirect treatment comparison may not be feasible due to the small population numbers in the BRAF V600E mutant population. Therefore, an indirect naïve analysis is likely to be considered as the only plausible option available.	
Outcomes	Pierre Fabre	Yes, the outcomes listed are appropriate.	Comment noted.
Economic analysis	Pierre Fabre	Previous health technology appraisals, as listed in the draft scope, have used 8-15 year time horizons with 10 years the most commonly used. Given that, as per the draft scope, patients with mCRC who have a BRAFV600E mutation are considered to have a mortality rate more than double that of those without a 10 year time horizon could be considered a conservative but appropriate approach.	Comment noted. No action required.
Equality and Diversity	Pierre Fabre	No issues identified	Comment noted.
Other considerations	Pierre Fabre	It may be helpful to note that a positive NICE recommendation for encorafenib and binimetinib in combination with cetuximab needs to be accompanied with an NHS England mandate for BRAFV600E testing and funding to ensure patients can access treatment in practice to avoid the issues associated following NICE diagnostics guidance DG27.[5] Currently this guidance 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. However, this will not identify all BRAFV600E mCRC patients,	Comments noted. A draft update to clinical guideline CG131 has been published in August 2019. The draft update includes a recommendation to "test all people with metastatic colorectal

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		since the purpose of the aforementioned guidance is for Lynch syndrome screening. In addition, testing is not associated with a funding mandate, resulting in variable access to testing across the UK. Several factors currently limit access to BRAF testing in the UK. These include: • Tests are not requested due to unclear clinical utility – the NICE CG 131 on the management of mCRC does not recommend BRAF testing[2] and needs to be updated to ensure clinicians are aware of the testing requirements • BRAF testing is not offered by all labs Test results are not always available on time, with turnaround time as long as 28 days in some UK labs.	cancer suitable for systemic anti-cancer treatment for RAS and BRAF V600E mutations." The text of the background section has been amended to reflect these draft recommendations.

Innovation	Pierre Fabre	Yes, the technology can be considered innovative:
		• BEACON is the first and only positive phase 3 trial in the BRAF-mutant mCRC patient population to demonstrate both statistically significant and clinical meaningful differences vs. the active comparator of cetuximab in combination with FOLFIRI or irinotecan:[6,7]
		  • ORR (as assessed by Blinded Independent Central Review [BICR]) BICR)
		  ○ 26.1% vs. 1.9%, p<0.0001, triplet combination vs control
		  • Median OS
		  ○ 9.0 months vs. 5.4 months, [HR 0.52, (95% CI 0.39, 0.70), p<0.0001], triplet combination vs control]
		  • Median progression-free survival (mPFS)
		  ○ 4.3 months vs. 1.5 months [HR: 0.38, (95% CI: 0.29–0.49), p<0.0001) triplet combination vs control]
		• Encorafenib in combination with binimetinib and cetuximab is one of the
			Comments noted.
			The committee will consider the innovative nature of the technology during the appraisal.

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		first regimens to target BRAFV600E mCRC patients. There are currently no licensed treatments available specifically for patients with colorectal tumours with BRAFV600E mutations. These patients have a mortality risk more than double that of mCRC patients without the mutation. After first-line therapy, current standard second-line therapies provide limited benefit, with ORRs < 10%, and OS of 4 to 6 months.[8] In addition, there are currently no recommended BRAF targeted treatments with (as per the draft scope). Current NICE recommendations in second- and third-line treatment consist of chemotherapy based regimens. • Encorafenib in combination with binimetinib and cetuximab is one of the first combinations to target the BRAF and MEK pathway together and has the advantage that the regimen is cytotoxic chemotherapy free. Encorafenib and binimetinib have the advantage that both can be taken orally.[9,10]	
Questions for consultation	Pierre Fabre	*Where do you consider encorafenib with binimetinib and cetuximab will fit into the existing NICE pathway, colorectal cancer?* Encorafenib in combination with binimetinib and cetuximab is one of the first regimens to target BRAFV600E mCRC patients. In line with the anticipated licensed indication the triple regimen will be provided to patients with metastatic colorectal cancer who have received prior systemic treatment and whose tumours harbour a BRAFV600E mutation. It should also be noted that feedback from UK consultant oncologists has suggested that if encorafenib in combination with binimetinib and cetuximab was approved by NICE as a treatment option in the second line setting then subsequently the current first-line treatment pathway for patients with RAS wild type mCRC may also change. It could be anticipated that given encorafenib and binimetinib in combination with cetuximab is the first specific	Comments noted. No action required.

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		targeted regimen for patients with the BRAFV600E mutation that clinicians may choose to prescribe a chemotherapy only regimen first-line, as opposed to current practice of cetuximab or panitumumab in combination with FOLFOX or FOLFIRI. Cetuximab containing regimens (i.e. in combination with encorafenib and binimetinib) would then be reserved for the second line setting if the BRAFV600E mutation was present. If such a change in the treatment pathway was to occur, it may be reasonable to consider a scenario to assess the health economic impact of this change. *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*? No	
Additional comments on the draft scope	Pierre Fabre	No additional comments	Response noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Merck, Sanofi.