Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2312

encorafenib 50mg and 75mg hard capsules (Braftovi®)

Pierre Fabre Ltd

9 April 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life and orphan equivalent process:

encorafenib (Braftovi®) is accepted for use within NHSScotland.

Indication under review: In combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

Treatment with encorafenib plus cetuximab was associated with an improvement in overall survival when compared with investigator's choice of cetuximab plus differing chemotherapy in BRAF V600E mutated patients who had received first and second-line therapies for metastatic CRC.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS / list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

In combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.[1]

Dosing Information

The recommended dose of encorafenib for metastatic CRC is 300mg (four 75mg capsules) once daily, with or without food, when used in combination with cetuximab. The capsules should be swallowed whole with water.

Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.

Encorafenib treatment should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.

For more information, see Summary of product characteristics (SPC).[1]

Product availability date

September 2018
Encorafenib meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Encorafenib is a serine/threonine-protein (RAF) kinase inhibitor, suppressing RAF / mitogen-activated extracellular signal-regulated kinase (MEK) / extracellular signal regulated kinase (ERK) pathways in tumour cells that express BRAF V600E, D and K mutations. Cetuximab is a monoclonal IgG1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR). One of the main mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors has been identified as the re-activation of EGFR with bypassing signal transduction via BRAF. Combinations of a BRAF inhibitor such as encorafenib and agents targeting EGFR such as cetuximab improve the anti-tumour activity.[1]

The key evidence supporting encorafenib plus cetuximab in metastatic CRC with BRAF V600E mutation comes from an international, randomised, open-label, parallel group, phase III study, BEACON CRC, which evaluated the efficacy and safety of encorafenib plus cetuximab with or without binimetinib compared with investigator's choice of either irinotecan plus cetuximab or folinic acid/fluorouracil/irinotecan (FOLFIRI) plus cetuximab in the control group.[2, 3]

The study recruited adults with histologically or cytologically confirmed metastatic CRC with BRAF V600E mutation in tumour tissue as determined or confirmed (if determined by local assay) by central laboratory and an Eastern Cooperative Oncology Group performance-status (ECOG PS) score of 0 or 1. Patients could participate if they were eligible to receive cetuximab per locally

approved label with regard to tumour RAS status. Patients must have been treated and have disease progression after one or two prior line of therapies in the metastatic setting but no prior treatment with a RAF inhibitor, a MEK inhibitor, or cetuximab, panitumumab or other EGFR inhibitors was allowed.[3]

Patients were randomised equally to receive a triplet therapy consisting of encorafenib (300mg orally daily), binimetinib (45mg orally twice daily), and cetuximab (400mg/m^2 as an initial dose, then 250mg/m^2 weekly by intravenous [IV] infusion) (n=224); or a dual therapy with encorafenib and cetuximab at the same doses (n=220); or investigator's choice of either cetuximab (at the same dose) plus irinotecan (180mg/m^2 by IV infusion every 2 weeks) or cetuximab plus FOLFIRI by IV infusion every 2 weeks (folinic acid [180mg/m^2, administered on days 1 and 15], fluorouracil [400mg/m^2 as an initial dose, then 1200mg/m^2/day for 2 days every 2 weeks], and irinotecan [at the same dose]) (n=221). Treatment was to continue until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death, or study treatment discontinuation for any other reason. Randomisation was stratified according to ECOG PS (0 or 1), prior use of irinotecan (yes or no), and cetuximab source (US-licensed versus EU-approved). The number of patients who had received two prior lines of therapy (that is third-line patients) was limited to 35%.[3]

The study had two co-primary outcomes: overall survival (defined as the time between date of randomisation and death due to any cause) and confirmed objective response rate (ORR, defined as the percentage of patients achieving a best overall response [BOR] of complete response [CR] or partial response [PR] by blinded independent central review [BICR] per RECIST, v1.1). The study primarily assessed both co-primary outcomes in the triplet therapy group versus the control group. A hierarchical statistical testing strategy was applied in the study for primary and four secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The hierarchical order used for primary and secondary outcomes was as follows: 1) ORR by BICR for triplet therapy versus control, 2) overall survival for triplet therapy versus control, 3) overall survival for dual therapy versus control, 4) ORR for dual therapy versus control, 5) progression-free survival (PFS) by BICR for triplet therapy versus control and 6) PFS by BICR for dual therapy versus control.[3]

At the time of the primary ORR analysis and interim overall survival analysis (cut-off date February 2019), median overall survival was 9.0 months in the triplet therapy group and 5.4 months in the control group: hazard ratio (HR) 0.52 (95% confidence interval [CI]: 0.39 to 0.70), p<0.001. The ORR was 26% (29/111) versus 1.9% (2/107) respectively, p<0.001. At the updated analysis (cut-off date August 2019), median overall survival was 9.3 months in the triplet therapy group and 5.9 months in the control group: HR 0.60 (95% CI: 0.47 to 0.75), p<0.001. The ORR was 27% (60/224) versus 1.8% (4/221) respectively, p<0.001. However, since the marketing authorisation for triplet therapy was not sought, it is not relevant to this submission. This document will therefore consider results for the licensed dual therapy group versus control.

The key secondary outcome of overall survival and other secondary outcomes for the dual therapy group versus control are relevant to the licensed indication and were tested following the hierarchical procedure. Encorafenib plus cetuximab was associated with a statistically significant improvements in overall survival, ORR and PFS compared with control in study patients at the primary ORR and interim overall survival analyses (cut-off date February 2019) and at the planned updated interim analysis (cut-off date August 2019); see Table 1 for details. Survival results were confirmed by an unplanned May 2020 cut-off analysis. [4]

Table 1: Secondary outcome results of BEACON CRC for the dual therapy group versus control.[1, 3]

	Encorafenib + cetuximab	**Control**	**Encorafenib + cetuximab**	**Control**
Data cut-off date	11 February 2019		15 August 2019	
Median duration of follow-up, months	7.6	7.2	12.3	12.9
Overall survival				
Number of patients	220	221	220	221
Number of events	93	114	128	157
Median overall survival, months	8.4	5.4	9.3	5.9
HR (95% CI)	0.60 (0.41 to 0.88)		0.61 (0.48 to 0.77)	
p-value	<0.001		<0.001	
ORR by BICR				
Number of patients	113[a]	107[a]	220	221
ORR, n (%)	20% (23/113)	1.9% (2/107)	20% (43/220)	1.8% (4/221)
CR,%	5.3%	0	3.2%	0
PR,%	15%	1.9%	16%	1.8%
p-value	<0.001		<0.001	
PFS by BICR				
Number of patients	220	221	220	221
Number of events	133	128	167	147
Median PFS, months	4.2	1.5	4.3	1.5
HR (95% CI)	0.40 (0.30 to 0.55)		0.44 (0.35 to 0.55)	
p-value	<0.001		<0.001	

BICR= blinded independent central review; CI= confidence interval; CR= complete response; HR= Hazard ratio; ITT= intention-to-treat population; NA= not available; ORR= overall response rate; PFS= progression-free survival; PR= partial response.

[a] Among the first 331 randomised patients.

Health Related Quality of Life (HRQoL) was assessed using four questionnaires: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C), EuroQoL-5D-5 Level (EQ-5D-5L) and patient global impression of change (PGIC). HRQoL results were generally similar between the dual therapy group and the control group. The estimated median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status, EQ-5D-5L VAS and FACT-C functional well-being scores were longer in the dual therapy group compared with the control arm.[3]

The submitting company presented a Bucher indirect treatment comparison (ITC) of encorafenib plus cetuximab with FOLFIRI in the second-line treatment of patients with metastatic CRC with BRAF V600E mutation. The indirect comparison included two studies: BEACON CRC and a post hoc subgroup of patients with BRAF mutated disease (n=45) from the Peeters study which compared FOLFIRI plus panitumumab with FOLFIRI.[2, 5] Since the Peeters study compared FOLFIRI plus panitumumab, and not FOLFIRI plus cetuximab with FOLFIRI, the submitting company assumed that cetuximab was equivalent to panitumumab in order to connect the two studies. The submitting company also assumed that both FOLFIRI and irinotecan, when used in combination with cetuximab in the control arm of BEACON CRC, would have equivalent efficacy and used their pooled results in the indirect comparison. The treatments were indirectly compared using the outcomes of overall survival and PFS. The results indicated that encorafenib plus cetuximab significantly improved both outcomes compared with FOLFIRI: overall survival HR of 0.39 (95% CI: 0.19 to 0.81) and PFS HR of 0.30 (95% CI: 0.14 to 0.68).

The submitting company also presented a naive indirect comparison of encorafenib plus cetuximab with trifluridine-tipiracil in the third-line treatment of patients with metastatic CRC. The indirect comparison included two studies: BEACON CRC and RECOURSE which compared trifluridine-tipiracil with placebo in patients with metastatic CRC who have received at least two previous standard chemotherapies.[2, 6] The BRAF status of patients in RECOURSE was unknown and it was estimated that 10% of KRAS wild type patients (5% of the total study population) had a BRAF mutation. Additional results from a subgroup of patients who had received two previous lines of therapy and were receiving trifluridine-tipiracil in the third-line were used. Since the outcomes were expected to be worse in a BRAF-mutated population, the submitting company used HRs for BRAF-mutated versus wild type patients from the Peeters study of 4.0 for overall survival and of 3.57 for PFS to adjust the Kaplan-Meier survival curves for trifluridine-tipiracil patients from RECOURSE. The company did not present the relative treatment effect of encorafenib plus cetuximab versus trifluridine-tipiracil.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

In the BEACON CRC study at the data cut-off 15 August 2019, the median duration of exposure in the dual therapy group was 19.3 weeks compared to 7.0 weeks in the control group. Any treatment-emergent adverse event (AE) was reported by 98% (212/216) of patients in the dual therapy group and 98% (190/193) in the control group.[3]

In the dual therapy and control groups respectively, patients reporting a grade 3 or higher AE were 57% versus 64%, patients with a reported serious AE were 40% versus 40% (and these were considered treatment-related in 9.7% and 13%), patients with a dose reduction due to AEs were 12% versus 32%, the proportion of AEs that led to dose interruptions were 51% versus 55% and patients discontinuing any study therapy due to an AE was 12% versus 17%.[3]

The most frequently observed treatment emergent AEs within the dual therapy (cut-off 15 August 2019) were nausea (38%), diarrhoea (38%), fatigue (33%), decreased appetite (31%), acneiform dermatitis (30%), abdominal pain (28%), vomiting (27%), asthenia (24%) and arthralgia (23%).. The treatment-emergent AEs of any grade with a difference >10% between the dual therapy group and the control group were: arthralgia (23% versus 1.6%), myalgia (15% versus 2.1%), musculoskeletal pain (13% versus 2.6%), melanocytic naevus (16% versus none) and headache (20% versus 2.6%), pain in extremity (12% versus 1.0%), diarrhoea (38% versus 49%), stomatitis (6.0% versus 23%), neutropenia (1.4% versus 19%) and neutrophil count decreased (0.5% versus 11%).[3]

On-treatment deaths were reported in 18% in the dual group and 15% in the control group. The EMA noted that "most of the on-treatment deaths were due to progression of metastatic CRC. The applicant stated that the on-treatment deaths that were considered due to events other than disease progression were not treatment related." [3]

Overall, the EMA considered that the safety profile of encorafenib plus cetuximab "seems to be acceptable and manageable".[3]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Despite recent advances, metastatic CRC remains a serious, life-threatening condition. The mutation BRAF V600E, present in less than 10% of metastatic CRC patients, is associated with a worse prognosis, and with extremely poor survival outcomes (median overall survival for patients in the second-line setting is 4 to 6 months).[5, 8, 9] Current first line options for the systemic treatment of metastatic CRC include: folinic acid-fluorouracil-oxaliplatin (FOLFOX), folinic acid-fluorouracil-irinotecan (FOLFIRI), folinic acid-fluorouracil-irinotecan-oxaliplatin (FOLFOXIRI), capecitabine-oxaliplatin (CAPOX). Some of these may be used with an EGFR inhibitor such as cetuximab.[10, 11] The choice of treatment is guided by patient fitness, comorbidities and preferences. The choice of second-line treatment is guided by the same factors plus consideration of the treatment received in the first-line. [10-12] Clinical experts consulted by SMC considered that irinotecan based chemotherapies (mainly FOLFIRI) are most commonly used in second line. Treatment with trifluridine plus tipiracil is accepted for use by SMC for patients with metastatic CRC who have previously been treated with or are not suitable for these first/second-line treatments and so is an option for later lines of therapy. There are no therapies specifically licensed and recommended for patients with BRAF V600E mutant metastatic CRC. Clinical experts consulted by SMC considered that there is an unmet need in adult patients with previously treated metastatic CRC who have BRAF mutation and encorafenib plus cetuximab is the first medicine to be licensed specifically for the management of this condition.

The BEACON CRC study primarily compared triplet therapy with control but this is not relevant to the licensed indication under review, and dual therapy with encorafenib plus cetuximab was tested as a key secondary outcome. Treatment with encorafenib plus cetuximab was associated

with an improvement of 3.4 months in overall survival when compared with investigator's choice of either cetuximab plus irinotecan or cetuximab plus FOLFIRI in previously treated patients with metastatic CRC with a BRAF mutation. The EMA noted that this observed overall survival gain was "meaningful, compelling, robust, mature, and clinically relevant". While final overall survival results are awaited, the EMA considered that the August 2019 published results were already mature. Other secondary outcomes such as PFS and ORR as well as subgroup and sensitivity analyses were supportive of the key secondary outcome.[3] However, the study was not designed to assess the specific benefit of adding cetuximab to encorafenib, nor to compare against the two individual regimens used in the control group.

A risk of bias was potentially introduced by the open-label design of BEACON CRC, the between-group differences in the number of patients which were randomised but not treated (more patients were randomised but not treated in the control group [13% versus 1.8% in the dual therapy group]) and in the number of study discontinuations due to withdrawal of consent (more patients discontinued the study for withdrawal of consent in the control group [9.0% versus 2.3% in the dual therapy group]). Tumour assessments for ORR and PFS were performed by investigators and BICR to reduce potential bias.

The exclusion of patients with prior cetuximab, panitumumab or other EGFR inhibitors may limit the generalisability of the study results to the Scottish population. Advice from SMC restricts the use of cetuximab and panitumumab to first-line use in combination with FOLFOX or FOLFIRI. [10, 11] No data are available specifically in EGFR inhibitor-experienced patients, however, clinical experts consulted by SMC confirmed that they would use encorafenib plus cetuximab in BRAF V600E metastatic CRC patients despite previous treatment with an EGFR inhibitor (cetuximab or panitumumab) in first or second line. Study patients had an ECOG PS of 0 or 1 (four had a ECOG PS of 2) and not more than two prior lines of metastatic CRC therapies, which may limit applicability of the study results to patients with poorer performance status and more than two prior lines of therapy in clinical practice.

There are no direct comparative data versus the relevant comparators in patients BRAF V600E mutant metastatic CRC. The submitting company concluded that the results of the Bucher ITC suggest that encorafenib plus cetuximab is associated with statistically significantly improved overall survival and PFS compared with FOLFIRI. However, a number of limitations affect the validity of these results including the simple Bucher method, the lack of a common comparator group, heterogeneity between the studies and the need to assume equivalence of cetuximab and panitumumab to connect the studies, however clinical experts considered that this assumption was reasonable. It was also necessary to assume that FOLFIRI plus cetuximab and irinotecan plus cetuximab were equivalent to use the pooled results from the control arm of BEACON CRC in the indirect comparison. In the Peeters study, only a small subgroup of patients had a BRAF mutation; although efficacy data were available from this subgroup, they were analysed post hoc and it was not possible to compare their baseline characteristics with patients from BEACON CRC. Due to these limitations, the company's conclusions are uncertain.

For the naive indirect comparison with trifluridine-tipiracil, the submitting company concluded that the resulting adjusted Kaplan-Meier curves for overall survival and PFS used in the economic case are highly uncertain but in the absence of other data, this was considered the only plausible approach.

The introduction of encorafenib plus cetuximab offers patients with metastatic CRC who have a BRAF mutation a new treatment option with improvement in overall survival, PFS and ORR. This therapy is also the first to specifically target the BRAF V600E mutation. Clinical experts consulted by SMC considered that encorafenib plus cetuximab is a therapeutic advancement for patients with BRAF V600E mutation. They considered that the impact of the introduction of encorafenib plus cetuximab on the service would be low.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of encorafenib, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic colorectal cancer (CRC) is an incurable and life-limiting disease, which is associated with significant symptoms and morbidity. The disease and burden of standard chemotherapy have a substantial impact on the well-being and quality of life of patients and their families and carers. Metastatic BRAF mutated CRC is a particularly aggressive form of the disease which affects a small proportion of patients (10%).

- There is a high unmet need for effective treatments for patients with metastatic CRC who have a BRAF mutation. They have a worse prognosis and typically gain less benefit from conventional chemotherapy than those without the mutation.

- Encorafenib plus cetuximab offers an alternative to chemotherapy and is the first targeted treatment for these patients. It may significantly improve overall survival, delay disease progression and maintain quality of life. Encorafenib plus cetuximab may offer patients and their families, the hope of extended quality life together. PACE clinicians considered this a major advance and a life-changing development for the small number of patients with this mutation.

- Encorafenib plus cetuximab is less intensive and invasive to administer than standard chemotherapy. It has a different, potentially more favourable side effect profile. This would reduce the burden of treatment on the patient and their family and carers.

Additional Patient and Carer Involvement

We received a patient group submission from Bowel Cancer UK, which is a registered charity. Bowel Cancer UK has received 1.2% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Bowel Cancer UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing encorafenib plus cetuximab for the second or third line treatment of adult patients with metastatic CRC with a BRAF V600E mutation. The economic analysis was presented for FOLFIRI as the comparator for second-line treatment and trifluridine-tipiracil as the comparator for third-line treatment.

A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states; pre-progression (starting health state), post-progression and death. The cycle length was one month with patients either remaining in state, transitioning to post-progression or death at the end of each cycle. The model projected two primary outcomes – overall survival and PFS. An NHS perspective and a 10-year time horizon were selected in the base case of the economic model.

The cost-utility analysis was based on clinical effectiveness data from three main sources:

- BEACON-CRC study (May 2020 data cut) for encorafenib plus cetuximab.[4]
- A grouped treatment nodes ITC for encorafenib plus cetuximab versus FOLFIRI using a single RCT.[5] This generated HRs of relative effectiveness which were then applied to the BEACON CRC encorafenib plus cetuximab survival curves. Since there were no common comparators between the studies, two assumptions of clinical equivalence were needed – between cetuximab and panitumumab; and between FOLFIRI and irinotecan.
- A naive comparison was conducted using results from a trifluridine-tipiracil versus placebo study (RECOURSE).[6] Digitised Kaplan-Meier (KM) curves from RECOURSE were used to generate an estimate of the study individual patient data (IPD) for trifluridine-tipiracil.

Extrapolation of overall survival and PFS was required. Parametric models were fitted to the BEACON-CRC KM data using fully fitted parametric curves for overall survival and PFS. The log-logistic distribution was selected for overall survival and PFS based on internal validity and clinical plausibility. The log-logistic model predicted approximately 4% of patients in the encorafenib plus cetuximab arm and 2.4% of patients in the control arm of BEACON were still alive at 60 months.

The base-case analysis versus FOLFIRI used the outputs of the ITC to adjust the overall survival and PFS curves for encorafenib plus cetuximab to generate curves for FOLFIRI. The method implemented in the model applied the HRs directly to the curves generated from the parameters. Study KM survival curves and the number of patients at risk for overall survival and PFS from RECOURSE were used to construct an estimate of the IPD for trifluridine-tipiracil. As the RECOURSE

study was conducted in a population which was assumed to be primarily BRAF wild-type, a HR was applied to the fitted parametric models for overall survival and PFS to adjust for the fact that BRAF mutation positive patients have significantly worse overall survival and PFS outcomes than BRAF wild-type patients. The HRs used in the model are displayed in the table below.

Table 2: Base case hazard ratios applied to comparators in the model

Outcome	HR (95% CI) vs FOLFIRI	HR (95% CI) vs trifluridine-tipiracil
Overall survival	2.56 (1.23, 5.26)	4.00 (2.78, 5.56)
PFS	3.33 (1.47, 7.14)	3.57 (2.50, 5.00)

Abbreviations: CI, confidence interval; FOLFIRI, folinic acid/fluorouracil/irinotecan; HR, Hazard ratio; PFS, progression-free survival

Utility values were based on EQ-5D-5L data from the BEACON CRC study. These values were cross-walked to generate EQ-5D-3L values. Utilities were defined by progression status and were determined as a mean across the encorafenib plus cetuximab and control arm of BEACON CRC. The decision to pool utilities was informed by clinical expert feedback suggesting that progression status would be the main driver of quality of life. Treatment- specific utilities were therefore not explored in the analysis. Mean pre-progression utility was 0.743 and mean post-progression utility was 0.627. Age-related utility decrements were applied appropriately, but no adverse event disutilities were included in the base case.

Acquisition and administration costs for encorafenib, cetuximab and all comparators were included in the analysis, as were the costs associated with any subsequent treatments. Unit costs for managing adverse events, disease management, and a one-off cost for terminal care were also accounted for.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price for encorafenib. PAS are also in place for cetuximab and trifluridine-tipiracil.

The base case analysis presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of 96,448 £/QALY at list price against FOLFIRI for second line treatment. This results from an incremental quality-adjusted life year (QALY) gain of 0.57 and an estimated difference in costs of £55,094. For third line treatment against trifluridine-tipiracil, the ICER was 72,914 £/QALY at list price. This results from an incremental QALY gain of 0.72 and an estimated difference in costs of £52,701.

The results presented do not take account of the PAS for cetuximab and trifluridine-tipiracil but estimates of the PAS prices were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for comparator medicines and medicines used in combination with encorafenib due to commercial confidentiality and competition law issues.

Table 3: Base case cost-effectiveness results at list price

Technologies	Total costs	Total LYG	Total QALY	Incremental costs	Incremental LYG	Incremental QALY	ICER (£/QALY)
Encorafenib plus cetuximab	£67,482	1.46	0.98	-	-	-	-
FOLFIRI	£12,388	0.60	0.41	£55,094	0.86	0.57	96,448
Trifluridine-tipiracil	£14,782	0.38	0.26	£52,701	1.08	0.72	72,914

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 4: Selected scenario analysis versus all comparators at list price

	Scenario	ICER vs FOLFIRI (£/QALY)	ICER vs trifluridine-tipiracil (£/QALY)
	Base Case	***96,448***	***72,913***
1	Fully parametric model - Weibull	116,123	82,133
2	Company scenario 1 – No ITC; FOLFIRI : BEACON control arm	156,247	-
3	Company scenario 2 – Alternate HR (2.24)	-	81,194
4	Company scenario 3 – Naïve comparison uses only patients with 2 prior treatment lines from RECOURSE	-	64,259
5	Combined scenario 1 + 2	168,708	-
6	Combined scenario 1 + 3	-	93,938
7	Combined scenario 1 + 3 + 4	-	74,820
8	KM and parametric hybrid model – Log-logistic	97,827	75,047
9	KM and parametric hybrid model - Weibull	117,682	85,365

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; HR, Hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier data

There were a number of limitations with the analysis which include the following:

- There is substantial uncertainty surrounding the clinical evidence base informing the model. The BEACON-CRC study used cetuximab in combination with FOLFIRI or irinotecan in the control arms which is not the relevant comparator in NHSScotland. Efficacy of the two control arm regimens was assumed to be equivalent. Although consistent with the trial design, the study could not assess relative effectiveness of these two treatment regimens.

Further, BEACON CRC could not be used as the source of adverse event data for FOLFIRI due to the confounding effect of cetuximab in the BEACON control arm; adverse event data from a FOLFIRI trial of patients with mCRC was used in the company model to reflect the adverse event profile of this comparator. There remains some residual uncertainty about the assumed equivalent effectiveness for FOLFIRI and irinotecan in the ITC.

- The results of the naive comparison with trifluridine-tipiracil are highly uncertain. There was considerable heterogeneity in potential prognostic factors between the study populations (BEACON CRC and RECOURSE) included in the company's naive comparison. The RECOURSE overall survival curves should be adjusted to account for differences in BRAF mutation status, and it is unclear whether the HRs applied are sufficient to account for the various confounders.
- The results showed some sensitivity to the choice of parametric distribution used for the extrapolation of data, as shown in table 4. The company chose the log-logistic distribution to model overall survival/PFS in the base case. While this distribution may have had the best statistical fit to the trial data at the August 2019 data cut, it was also the most optimistic extrapolation. The Weibull distribution was also considered to be plausible by oncology experts consulted by the company and its application had an upward impact on the ICER. Further support for the use of the log-logistic distribution was provided by the company given a later cut of data (May 2020), showing a reasonable fit to the observed data but extrapolation over the later stages of the time horizon are still associated with uncertainty.
- The economic model utilises a fully fitted parametric curve to replace the available data in the base case. The company was asked to use a piecewise approach to model overall survival to investigate the impact of using variation from different extrapolation approaches. The company provided a revised model which allowed for parametric models to be applied from the end of the KM data and not, in the true sense of a piecewise approach, from specific breakpoints within the KM data set. The revised application of the parametric curves lead to an increase in ICERs and provides a more conservative estimate than the base case (table 4, scenarios 8 and 9).
- Some subsequent treatments employed in BEACON-CRC may not reflect those that are available for routine use in NHSScotland, which has the potential to impact on survival data feeding into the model. The company did not attempt to adjust for these treatments, which could bias results.
- There is some uncertainty regarding the utility estimates that has not been adequately explored by the company. While employing state-specific utilities in the model is acceptable, strong arguments can be made for the use of treatment-specific utilities in the present context. There is an assumption that pre- and post-progression utilities are the same for both second and third line treatment. The health of patients on third line treatment may be lower than patients on second line treatment, which is not captured by the current model. Similarly, adverse event disutility may potentially differ by treatment line. It is unclear what impact the exclusion of scores from patients on irinotecan in the BEACON-CRC control arm may have had on the pooled utility values. There also does not seem to have been any attempts to compare trial-based utility values with those from the wider literature, both as a means of sense-checking as well as informing scenario analyses.

The Committee also considered the benefits of encorafenib plus cetuximab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission modifier was satisfied. In addition, as encorafenib plus cetuximab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted encorafenib plus cetuximab for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 126 'Diagnosis and management of colorectal cancer' in December 2011 and revised in August 2016.[10] For metastatic CRC the following recommendations are made for first-line and second-line treatment. No specific recommendation was made for third or further lines of treatment.

First-line

- All patients with metastatic CRC should be considered for chemotherapy.
- Combination treatment with either 5-FU/leucovorin/oxaliplatin, or capecitabine/oxaliplatin, or 5-FU/leucovorin/irinotecan is the preferred options in patients with good performance status and organ function.
- Cetuximab should be considered in combination with 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan chemotherapy as first-line treatment with RAS wild type metastatic CRC. The use of cetuximab in combination with oxaliplatin and capecitabine cannot currently be recommended.
- Consider raltitrexed for patients with metastatic CRC who are intolerant to 5-flurouracil and leucovorin or for whom these drugs are not suitable.
- The choice of first-line chemotherapy for patients with metastatic CRC will depend on patient fitness, co-morbidity, and overall aim of treatment.

Second-line

- Second-line chemotherapy should be considered for patients with metastatic CRC with good performance status and adequate organ function.
- Irinotecan should be used as second-line therapy following first line oxaliplatin (or vice versa).
- The choice of second-line chemotherapy for patients with metastatic CRC will depend on patient fitness, co-morbidity and previous chemotherapy exposure.

The National Institute for Health and Care Excellence (NICE) published clinical guideline NG151, 'Colorectal cancer' in January 2020, which replaces its previous 131 guideline.[11] For advice on systemic anti-cancer therapy for people with metastatic CRC, the guideline refers to the NICE

pathway, which include the following recommendations in patients suitable for systemic anti-cancer therapy:

First line chemotherapy:

- Oral therapy with capecitabine is recommended as an option for the first-line treatment of metastatic CRC.
- The choice of regimen (intravenous 5-FU/folinic acid or capecitabine) should be made jointly by the individual and the clinician(s) responsible for treatment.
- The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.

First-line biological therapy:

- Cetuximab is recommended as an option for previously untreated EGFR-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI.
- Panitumumab is recommended as an option for previously untreated RAS wild-type metastatic CRC in adults in combination with FOLFOX or FOLFIRI.

Subsequent or alternative therapy:

- Trifluridine–tipiracil is recommended, as an option for treating metastatic CRC, in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable.
- Aflibercept in combination with irinotecan + fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic CRC that is resistant to or has progressed after an oxaliplatin containing regimen.

No specific recommendations were made for patient with BRAF-mutant metastatic CRC; however, it does recommend that all people with metastatic CRC suitable for systemic anti-cancer treatment are tested for BRAF V600E and RAS mutations.

European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic CRC published in 2016 recommend that the tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials).[12]

First line therapy:

- Biologicals are indicated in the first-line treatment of most patients unless contraindicated
- The VEGF antibody bevacizumab should be used in combination with: the cytotoxic doublets FOLFOX/CAPOX/FOLFIRI, the cytotoxic triplet FOLFOXIRI in selected fit and motivated patients and potentially also in fit patients with tumour BRAF mutations, fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment.
- EGFR antibodies should be used in combination with: FOLFOX/FOLFIRI; capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies.

Second line therapy:

- Patients who are bevacizumab naive should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second line. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen.

- Patients who received bevacizumab first line should be considered for treatment with: Bevacizumab post-continuation strategy; aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin; EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type (BRAF wild-type) disease. Relative benefit of EGFR antibodies is similar in later lines compared with second line.

Third-line therapy:

- In RAS wild-type and BRAF wild-type patients not previously treated with EGFR antibodies, cetuximab or panitumumab therapy should be considered.
    - Cetuximab and panitumumab are equally active as single agents.
    - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan-refractory patients.
    - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies.
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies.
    - Regorafenib is superior to placebo in terms of overall survival, although there are toxicity concerns in frail patients.
- Trifluridine/tipiracil is a new option for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies.

There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies.

Additional information: comparators

Irinotecan single agent, FOLFIRI. Trifluridine plus tipiracil.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 28 day cycle (£)
Encorafenib plus cetuximab	**Encorafenib: 300mg (four 75mg capsules) once daily** **Cetuximab: 400mg/m^2 initially dose, then 250mg/m^2 weekly by intravenous infusion**	**First cycle: 7,829** **Subsequent cycles: 7,295**

Costs from BNF online on 30 October 2020. Costs are based on a body surface area of 1.8m^2. Costs calculated using the full cost of vials assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 28 patients eligible for treatment with encorafenib in each year and that 14 patients would be treated in year 1 rising to 25 by year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 December 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.