Indication	For previously treated BRAF V600E mutation positive colorectal cancer. The patient must have received one or two previous therapies for advanced/metastatic disease and must have a RAS wild type adenocarcinoma. NB Patients must not have received previous treatment with any BRAF inhibitor, MEK inhibitor, cetuximab, panitumumab and any other EGFR inhibitors.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until progressive disease, unacceptable toxicity or patients' choice. A formal medical review should be scheduled by the end of the first 8 weeks of treatment to assess tolerability and whether treatment should continue.
Monitoring Parameters pre-treatment	• ECG at baseline, prior to cycle 2, then repeated every 3 months or more frequently if clinically indicated. Risk factors for QT prolongation should be controlled before initiation of treatment. • U&Es, including calcium and magnesium, at D1 for every cycle and at D15 for cycles 1 and 2 only. • FBC baseline and every cycle. • If PLT <100 and / or neuts <1.5 d/w consultant. • LFTS baseline and every cycle for 6 months and then as clinically indicated. • BP baseline and at each cycle. • Patients should be assessed at each visit for symptoms of visual disturbance (see below). • Dermatologic evaluations for cutaneous malignancies should be performed prior to initiation of therapy, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. • The patient must have no symptomatically active brain metastases or leptomeningeal metastases. • **Hepatic Impairment:** Use encorafenib with caution in patients with hepatic impairment. Patients with mild hepatic impairment (Child-Pugh class A) should be closely monitored at a dose of 300mg. Not recommended in moderate to severe hepatic impairment (Child-Pugh Class B & C) due to lack of data. • **Renal Impairment:** Encorafenib should only be used at the clinicians' discretion in severe renal impairment (<30ml/min), no data available. No adjustment in mild to moderate renal impairment. • **Dose modification:** • For patients receiving 300mg encorafenib once daily, the first dose reduction should be 225mg once daily. If a 2nd dose reduction is required reduce to 150mg once a day. If encorafenib is permanently discontinued, cetuximab should be discontinued. If cetuximab is permanently discontinued, encorafenib should be discontinued. See information below and tables 1, 2, 3 and 4 for management of adverse reactions. For new primary non-cutaneous RAS mutation positive malignancies, consider discontinuing treatment. • **Adverse reactions:** • **Cetuximab infusion rate and infusion related reactions (IRRs):** Cetuximab can cause severe infusion related reactions, pre meds must be given 1 hour prior to the infusion and patients must be monitored every 30 minutes during the infusion and for a 1 hour period after. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to

	maintain this lower infusion rate in all subsequent infusions. For severe reactions discontinue treatment. • **Interstitial lung disease (ILD):** Patients should report any new or worsening respiratory symptoms. Cetuximab should be permanently discontinued in patients with confirmed ILD. • **Haemorrhage:** Haemorrhages, including major haemorrhagic events, can occur when encorafenib is administered; the risk may be increased with concomitant use of anticoagulants and antiplatelets. The occurrence of Grade ≥ 3 haemorrhagic events should be managed with dose interruption, reduction or treatment discontinuation and as clinically indicated (see table 2). • **Ocular toxicities:** Eye disorders have been reported with the use of cetuximab and encorafenib. Cetuximab should be used with caution in patients with a history of keratitis ulcerative keratitis or severe dry eye. If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Ocular toxicities including uveitis, iritis, and iridocyclitis can occur with encorafenib, see table 1 for guidance. • **Skin reactions:** Skin reactions are very common and treatment interruption or discontinuation may be required, see tables 1-4 for guidance. • **<u>Common drug/food interactions (for comprehensive list refer to BNF/SPC)</u>:** • Concurrent use of strong CYP inhibitors (ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice) during treatment should be avoided. • Moderate CYP inhibitors (amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib) should be co-administered with caution. If the use of a CYP inhibitor is unavoidable these patients should be carefully monitored for toxicity. • Avoid use of strong or moderate CYP enzyme inducers (carbamazepine, rifampicin, phenytoin and St. John's Wort), consider alternative agents with no or minimal CYP enzyme induction. • Encorafenib is potentially both a CYP3A4 inducer and inhibitor. Agents that are CYP substrates (eg hormonal contraceptives) should be used with caution. • Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution. • Encorafenib can potentially inhibit a number of renal and hepatic transporters, agents that are transporter substrates (e.g. statins) should be co-administered with caution. • **Missed dose:** If a dose of encorafenib is missed it should not be taken if it is less than 12 hours until next dose is due. In case of vomiting after administration of encorafenib, the patient should not take an additional dose and should take the next scheduled dose. • **Further Guidance:** • Patients should ensure adequate fluid intake during treatment. • Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines. • Encorafenib for oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	KMCC protocol COL-041 v1 SPC accessed online 10.12.20

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Recommended dose modifications for encorafenib when used in combination with cetuximab

Severity of adverse reaction[a]	**Encorafenib**
Cutaneous reactions	
• Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
• Grade 3	Encorafenib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence, or resumed at a reduced dose if recurrent Grade 3.
• Grade 4	Encorafenib should be permanently discontinued.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• Grade 2	Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
• Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.
Uveitis including iritis and iridocyclitis	
• Grade 1-3	If Grade 1 or 2 uveitis does not respond to specific (e.g. topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.
• Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.
QTc Prolongation	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld (see monitoring in section 4.4). Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF>500 ms and increased by >60 ms from pre-treatment values	Encorafenib should be permanently discontinued (see monitoring in section 4.4).
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x- ≤5x upper limit of normal (ULN))	Encorafenib should be maintained. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resumed at the same dose.
• First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of Grade 4 (AST or ALT >20 ULN)	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Table 2: Recommended dose modifications for encorafenib when used in combination with cetuximab for other adverse reactions

Severity of adverse reaction	Encorafenib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, It should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of any Grade 4 adverse reaction	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib should be permanently discontinued.

Do not use CTCAE grading to assess **cetuximab induced rash**.

The rash is classified as follows:
Moderate: requires 1st line treatment on development of rash
Severe: failed 1st line treatment

Table 3: Acne-like cetuximab induced rash: Treatment Principles

Severity of rash.	**Moderate: on development of rash requires 1st line treatment**	**Severe: requires 2nd line treatment**
Systemic antibiotics	YES Doxycycline 100mg od or alternatively Minocycline 100mg od	YES Doxycycline 100mg od or alternatively Minocycline 100mg od
Delay Cetuximab	NO	YES Consultant referral required
General remarks	• All patients should use an emollient whilst on cetuximab • Oral tetracyclines: treat for a prolonged period to benefit from their anti-inflammatory properties. Advise patients to take appropriate precautions against prolonged sun exposure • Consider oral anti histamine for symptomatic relief	

Table 4: Cetuximab treatment interruption and re-introduction in response to skin toxicity

Occurrence of grade ≥3 skin toxicity	**Adjustment to cetuximab treatment**	
	SEVERE (failed 1st line treatment)	On resolution to MODERATE
First time	Interrupt treatment	Treatment may be resumed at previous dose
Second time	Interrupt treatment	Treatment may be resumed but at reduced dose (20% DOSE REDUCTION)
Third time	Interrupt treatment	Treatment may be resumed but at reduced dose (40% DOSE REDUCTION)
Fourth time	Discontinue treatment	

Repeat every 28 days:

Day	Drug	Dose	Route	Infusion Duration	Administration
1 and 15	Dexamethasone	8mg	PO		To be administered 1 hour prior to cetuximab
	Chlorphenamine	10mg	IV	stat	
	CETUXIMAB	**500mg/m²**	IV	1st dose 2hrs 2nd dose onwards – over 90mins (or 60 if tolerated)	To be given undiluted or diluted in 0.9% sodium chloride to a total volume of 250ml Flush line with sodium chloride 0.9% IV post cetuximab infusion.
TTO	Drug	Dose	Route	Directions	
Day 1	**ENCORAFENIB**	**300mg**	PO	Daily swallowed whole with water continuously. (Available as 50mg and 75mg capsules) Do not take with grapefruit juice.	
	Metoclopramide	10mg	PO	Up to TDS PRN Do not take for more than 5 days continuously	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1, then only if required.	
	If required prescribe doxycycline at onset of rash.				