CETUXIMAB (Erbitux) ENCORAFENIB (Braftovi)

INDICATION (ICD10) C18, C20

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

Encorafenib in combination with cetuximab for previously treated BRAF V600E mutation positive metastatic colorectal cancer (TA668):

2. Has a histologically proven diagnosis of colorectal adenocarcinoma.
3. Colorectal cancer has been shown to be of RAS wild type.
4. Colorectal cancer has been shown to contain a BRAF V600E mutation.
5. Failed one or two prior regimens for advanced/metastatic disease. NB if the patient progressed through adjuvant chemotherapy or within 6 months of completing adjuvant chemotherapy, the patient can be classed as having received one line of treatment for metastatic disease.
6. Has not received prior treatment with any BRAF inhibitor or MEK inhibitor unless this was received for this specific indication via interim COVID19 funding.
7. Has not received prior treatment with cetuximab or panitumumab or any other EGFR inhibitors unless this was received for this specific indication via interim COVID19 funding for this combination.
8. Will be treated with encorafenib at an initial continuous dose of 300mg daily as a 28-day cycle.
9. Will be treated with cetuximab at a dose of 500mg/m^2 every two weeks as a 28-day cycle.
10. ECOG performance status (PS) of 0 or 1.
11. No active brain metastases or leptomeningeal metastases.
12. Encorafenib with cetuximab is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment, whichever is the sooner.
13. A formal medical review as to how the combination of encorafenib plus cetuximab is being tolerated and whether treatment with the combination of encorafenib plus cetuximab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
14. Where a treatment break of more than 6 weeks beyond the expected cycle length is needed, I will complete a treatment break approval form to restart treatment, including indicating as appropriate if the patient had an extended break because of COVID 19.
15. Encorafenib and cetuximab will be otherwise used as set out in their respective Summary of Product Characteristics (SPCs).

REGIMEN

Days 1 and 14	Premedication 30-60 minutes prior to infusion:	
	Chlorphenamine 10mg IV bolus	
	Dexamethasone 8mg IV bolus	
	CETUXIMAB	500mg/m^2 in 500ml sodium chloride 0.9% IV infusion
Days 1 to 28	ENCORAFENIB	300mg capsule orally once daily

NB Cetuximab administer first dose over 120 minutes. If tolerated the second dose and subsequent doses may be given at a rate that does not exceed the maximum rate of 10mg/min. Close monitoring is required during the cetuximab infusion and for at least 1 hour after the end of the infusion

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression

ADMINISTRATION

Encorafenib is available as 50mg and 75mg capsules
Swallow both whole with water, with or without food.

ANTI-EMETICS

Low emetogenic risk

CONCURRENT MEDICATION REQUIRED

Cetuximab	Ensure premedication chlorphenamine and dexamethasone (or steroid component of antiemetic regimen) given 30-60 minutes prior to treatment

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cetuximab - neutral

Filter not required
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
Serum creatinine
ECG and ECHO at baseline, 1 month then every 3 months
Blood pressure baseline, then monthly
CK every monthly for 6 cycles then as indicated
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Cetuximab	Dyspnoea - as part of a hypersensitivity reaction, or after several weeks of therapy. Older, poor PS or underlying pulmonary disorders may be at increased risk. May be severe and/or long-standing. Hypersensitivity - mild or moderate reaction infusion rate may be decreased. Maintain lower infusion rate for subsequent infusions. Severe - usually during the initial infusion and up to 1 hour after the end of infusion, but may occur after several hours. Requires immediate and permanent discontinuation of cetuximab and may necessitate emergency treatment. Infusion related reactions – If during the 1st infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped, risk assessment undertaken. If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity: Grade 1: continue slow infusion under close supervision. Grade 2: continue slow infusion and immediately administer treatment for symptoms. Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab. Skin reactions - severe skin reaction cetuximab must be interrupted. Treatment may only be resumed, if the reaction has resolved. With the 2nd occurrence of a severe reaction, treatment may be resumed at 75% after interruption. With the 3rd occurrence of a severe reaction, treatment may be resumed at 50% after interruption. If severe skin reactions occur a 4th time or do not resolve during treatment interruption, stop treatment permanently.
Encorafenib	Cutaneous reactions Palmar-plantar erythrodysaethesia syndrome Uveitis QT prolongation

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Encorafenib	Potent enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) should be avoided, as may decrease encorafenib. Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin) should be avoided, as may increase the risk of encorafenib toxicity. Moderate CYP3A4 inhibitors (e.g. amiodarone, erythromycin, fluconazole, diltiazem) may be used with caution and extra monitoring. Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g. hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents.

DOSE MODIFICATIONS
Encorafenib

Dose level	Dose
Full dose	300mg once daily
First reduction	225mg once daily
Second reduction	150mg once daily

If encorafenib is permanently discontinued, cetuximab should be discontinued.
If cetuximab is permanently discontinued, encorafenib should be discontinued.

Haematological
Cetuximab
If neutrophils <1.5x10^9/L (or <1.0x10^9/L at Clinician's discretion) and/or the platelet count <100x10^9/L (or <80x10^9/L at Clinician's discretion) delay the second dose by one week, recheck blood count.

Non-haematological
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 improved to 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 a reduced dose if recurrent grade 3.
Grade 4	Encorafenib should be permanently discontinued.

Liver laboratory abnormalities

Grade 2 (AST or ALT >3x–≤5xULN)	Encorafenib dose 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 >5xULN and blood bilirubin >2xULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to grade 0 or 1 or baseline level, it should be resumed at reduced dose. • If not improved, encorafenib should be permanently discontinued.
First occurrence of grade 4 (AST or ALT >20xULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to grade 0 or 1 or 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 >5xULN and blood bilirubin >2xULN)	It should be considered to permanently discontinue encorafenib.
Recurrent grade 4 (AST or ALT >20ULN)	Encorafenib should be permanently discontinued.

Other toxicities

Recurrent or intolerable grade 2 adverse reactions or 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.

Palmar-plantar erythrodysaethesia syndrome

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.

QTc prolongation

QTcF >500ms and change ≤60ms from pre-treatment value	Encorafenib should be withheld. Encorafenib should be resumed at a reduced dose when QTcF ≤500ms. Encorafenib should be discontinued if more than one recurrence
QTcF>500ms and increased by >60ms from pre-treatment values	Encorafenib should be permanently discontinued

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.

Hepatic impairment
Encorafenib
Mild hepatic impairment (Child-Pugh Class A) use with caution at a reduced dose of 300mg once daily.
Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment not recommended.

Renal impairment
Encorafenib
No dosage adjustment is required in patients with mild or moderate renal impairment.
For patients with severe renal impairment, use with caution.

REFERENCES
1. SPC