

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/) (ENC2)

1. Encorafenib in combination with cetuximab for previously treated BRAF V600E mutation positive, RAS wildtype metastatic colorectal adenocarcinoma and failed one or two prior regimens for advanced/metastatic disease (but not received prior treatment with any BRAF inhibitor or MEK inhibitor nor received prior treatment with cetuximab or panitumumab or any other EGFR inhibitors. No active brain metastases or leptomeningeal metastases. PS 0 or 1. (TA668)

REGIMEN

Days 1 and 15	Premedication 30-60 minutes prior to cetuximab: Chlorphenamine 10mg IV bolus Dexamethasone 8mg IV bolus			
	CETUXIMAB	500mg/m ²	IV infusion	in #ml sodium chloride 0.9%
Days 1 to 28	ENCORAFENIB	300mg	oral	once daily continuously

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression.

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.

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
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ADMINISTRATION

Cetuximab	Administer first dose over 120 minutes (maximum rate 5mg/min). 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.
Encorafenib	available as 50mg and 75mg capsules Swallow both whole with water, with or without food. Grapefruit and grapefruit juice should be avoided.

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 including Mg ⁺⁺ and LFTs Neutrophils $\geq 1.5 \times 10^9/L$ Platelets $\geq 100 \times 10^9/L$	baseline and every cycle
EDTA GFR or calculated CrCl at consultant's discretion.	baseline and every cycle
Serum creatinine	baseline and every cycle
ECG	baseline, before cycle 2 then every 3 months (QT prolongation see dose modifications)
Blood pressure	baseline, then monthly
Weight	baseline and every cycle

MAIN TOXICITIES 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 Infusion related reactions Skin reactions
Encorafenib	Cutaneous reactions Palmar-plantar erythrodysesthesia syndrome QT prolongation Uveitis

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.
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DOSE MODIFICATIONS

If encorafenib is permanently discontinued, cetuximab should be discontinued.

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Cetuximab

Dose level	Dose
Full dose	500mg/m ²
First reduction	400mg/m ²
Second reduction	300mg/m ²

Encorafenib

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

Haematological

Cetuximab

Neutrophils $<1.5 \times 10^9/L$ (or $<1.0 \times 10^9/L$ at clinician's discretion) and/or the platelet count $<100 \times 10^9/L$ (or $<80 \times 10^9/L$ at clinician's discretion)	delay the second dose by one week, recheck blood count.
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Non-haematological

Cetuximab

Infusion reactions

<p>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.</p> <p>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:</p>	
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.

<p>Skin reactions</p>	<p>Severe skin reaction (\geqgrade 3) 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.</p>
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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 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 erythrodysesthesia 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

Cetuximab

No dose adjustment required.

Encorafenib

Mild (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)	not recommended.

Renal impairment

Cetuximab

No dose adjustment required.

Encorafenib

Mild or moderate	No dosage adjustment is required
Severe	Use with caution

REFERENCES

1. SPC

Assessments

	Pre	Cycle 1	Cycle 1D15	Cycle 2	Cycle 2D15	Ongoing
Clinical Assessment	X			X	X	Alternate cycles
SACT Assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X		X		Every cycle
U&E, magnesium & LFT	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	Day 1 of every cycle
Ophthalmic exam*	X					As clinically indicated
Dermatological evaluation if worsening symptoms	X					Every 2 months while on therapy and for up to 6 months following treatment discontinuation.
CT scan	X					12 weekly or as clinically indicated
Informed consent	X					
Blood pressure measurement	X					Repeat if clinically indicated
Respiratory rate						If clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
ECG	X			X		Every 12 weeks or more frequently as clinically indicated
Height	X					