

Encorafenib and Cetuximab

Indication

Previously treated BRAF V600E mutation positive metastatic colorectal adenocarcinoma.

Based on Interim COVID19 Form – EN02CV.

No prior treatment with any BRAF, MEK or EGFR inhibitors.

ICD-10 codes

Codes with a prefix C18 – C20

Regimen details

Day	Drug	Dose	Route
1 & 15	Cetuximab	500mg/m ²	IV
1-28	Encorafenib	300mg OD	PO

	Drug	Dose	Route	Fluid	Time
30 min pre treatment	Dexamethasone	8mg	IV		
30 min pre treatment	Chlorphenamine	10mg	IV		
	Cetuximab	500mg/m ²	IV	500ml 0.9% NaCl	1 hour (1 st dose over 2 hours)

Use IV hydrocortisone in the event of allergic reaction noted at the time of cetuximab administration.

Cycle frequency

As above. The cetuximab dose and schedule approved by NHS England differs from that used in the BEACON trial.

Number of cycles

Continuous until disease progression or unacceptable toxicity.

Administration

Encorafenib

Encorafenib is available as 50mg and 75mg capsules. Capsules should be swallowed whole with water and may be taken with or without food. If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.

Grapefruit and grapefruit juice should be **avoided** whilst taking encorafenib.

Cetuximab

Warn patients of possible delayed onset infusion reaction

Dyspnoea can be early or delayed

Observe patient for 1 hour after infusion

Keep resus trolley nearby

Allergic reaction

Grade 1 allergic reaction with cetuximab – reduce infusion rate by 50% and monitor closely.

Grade 2 allergic reaction with cetuximab – administer bronchodilators, oxygen etc as medically indicated, resume infusion at 50% of previous rate once allergic hypersensitivity has resolved.

Grade 3 or 4 allergic reaction with cetuximab – stop infusion immediately; administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen etc as medically indicated.

Pre-medication

Dexamethasone and Chlorphenamine as above.

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Antiemetics if required.

Prophylaxis for skin toxicity as per “Colorectal Skin management Pathway”:

Doxycycline, emollient, topical steroid, Suncream (SPF50)

Extravasation

Non-vesicant

Investigations – pre first cycle

Before commencing treatment BRAF V600E mutation must be confirmed

Investigation	Validity period (or as per consultant instruction)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Pregnancy test (if applicable)	14 days
Blood pressure	Baseline
ECG (QTc < 500ms)	Baseline

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
Blood pressure	Monthly
ECG	should be monitored before treatment, after the first month, then approximately 3 monthly or more frequently if clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
Creatinine clearance (CrCl)	$\geq 30ml/min$
AST/ALT	$\leq 2.5 \times ULN$ (or $<5 \times ULN$ if liver metastases)
Bilirubin	$\leq 1.5 \times ULN$
QTc	$< 500ms$ and $<60ms$ increase from baseline

Dose modifications

Dose modifications should be made as per the table below:

Dose level	Encorafenib dose
Full dose	300mg OD
First reduction	225mg OD
Second reduction	150mg OD

Dose reductions beyond these levels are not recommended.

Dose level	Cetuximab dose
Full dose	500 mg/m ²
First occurrence of grade 3 skin reaction	Defer until ≤ grade 2 – Resume at full dose
Second occurrence of grade 3 skin reaction	Defer until ≤ grade 2 – Resume at 400 mg/m ²
Third occurrence of grade 3 skin reaction	Defer until ≤ grade 2 – Resume at 300 mg/m ²
Fourth occurrence of grade 3 skin reaction	Discontinue

If either agent is permanently discontinued, then both should be discontinued.

- **Haematological toxicity**

If neutrophils < 1.0 x 10⁹/L and/or platelets < 75 x 10⁹/L consider withholding treatment.

See below for management of pyrexia.

- **Renal impairment**

No encorafenib dose reduction necessary for mild to moderate renal impairment. Use with caution and closely monitor if severe renal impairment.

There is little experience of administering cetuximab in patients with renal impairment. Consider dose reduction in CrCl <10 ml/min.

- **Hepatic impairment**

No encorafenib dose modification is required for mild hepatic impairment. Encorafenib is not recommended in moderate or severe hepatic impairment.

There is little experience of administering cetuximab in patients with hepatic impairment. Hepatic insufficiency is unlikely to require dose reduction.

- **Other toxicities**

Pyrexia

Treatment should be interrupted if the patient's temperature is ≥ 38.5°C. Patients should be evaluated for signs and symptoms of infection. Treatment can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. If fever is associated with other severe signs or symptoms, treatment should be restarted at a reduced dose once fever resolves and as clinically appropriate.

Toxicity	Grade	Action
Cutaneous	Grade 1-2	Continue If worsens or does not improve within 2 weeks withhold encorafenib and cetuximab until ≤ Grade 1 then resume at same dose. If recurs resume with one dose level reduction.
	Grade 3	Withhold encorafenib and cetuximab until ≤ Grade 1 then resume at same dose. If recurs resume with one dose level reduction.
	Grade 4	Discontinue

Palmar Plantar Erythrodysesthesia (PPE)	Grade 2	Continue with supportive measures If worsens or does not improve within 2 weeks withhold encorafenib until \leq Grade 1 then resume at full dose or with one dose level reduction.
	Grade 3	Withhold encorafenib and use supportive measures. Assess weekly. When improved to \leq Grade 1 then resume at same dose or with one dose level reduction.
Ocular	Uveitis	If Grade 1-2 does not respond to topical therapy or if Grade 3 withhold encorafenib and repeat ophthalmic monitoring. If Grade 1 and improves to Grade 0 resume with same dose. If Grade 2-3 and improves to Grade 0 or 1 then resume with one dose level reduction. If not improved in 6 weeks discontinue. Grade 4 – discontinue
Cardiac	QTc prolongation >500 ms and ≤ 60 ms from baseline	Withhold encorafenib. Resume with one dose level reduction when ≤ 500 ms If recurs – discontinue
	QTc prolongation >500 ms and > 60 ms from baseline	Discontinue
LFT abnormalities	Grade 2 AST/ALT 3-5 x ULN	Continue. If no improvement within 2 weeks withhold encorafenib until <3 x ULN or baseline and continue with same dose.
	1 st occurrence Grade 3 AST/ALT > 5 x ULN and bilirubin > 2 x ULN	Withhold for up to 4 weeks If improved to grade 0-1 continue encorafenib with one dose level reduction If not improved – discontinue
	1 st occurrence Grade 4 AST/ALT > 20 x ULN	Withhold encorafenib for up to 4 weeks If improved to grade 0-1 continue encorafenib with one dose level reduction If not improved – discontinue
	Recurrent Grade 3 AST/ALT > 5 x ULN and bilirubin > 2 x ULN	Discontinue
	Recurrent Grade 4 AST/ALT > 20 x ULN	Discontinue

Any other adverse reaction	Recurrent or intolerable Grade 2 or 1 st occurrence Grade 3	Withhold encorafenib for up to 4 weeks If improved to grade 0-1 continue encorafenib with one dose level reduction If not improved – discontinue
	1 st occurrence Grade 4	Withhold encorafenib for up to 4 weeks If improved to grade 0-1 continue encorafenib with one dose level reduction If not improved – discontinue
	Recurrent Grade 3	Discontinue
	Recurrent Grade 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cutaneous squamous cell carcinoma
 QT prolongation
 Haemorrhage
 VTE
 Hypersensitivity reactions
 Ophthalmic reactions, including uveitis, iritis, and iridocyclitis
 Myelosuppression
 Interstitial lung disease

- **Frequently occurring side effects**

Peripheral neuropathy
 Headache, dizziness
 Pyrexia
 Arthralgia, myalgia
 Photosensitivity
 Rash, pruritus
 Nausea and vomiting
 Diarrhoea
 Alopecia
 Raised LFTs
 Hypertension

- **Other side effects**

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants (e.g. warfarin): avoid.

Encorafenib

Strong CYP3A4 inhibitors: Concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided due to increased encorafenib exposure and potential increase in toxicity.

Moderate CYP3A4 inhibitors: Should be co-administered with caution.

CYP3A4 inducers: A reduction in encorafenib exposure is likely and may result in reduced efficacy.

Transporters: Potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OATP1B1 and OATP1B3 at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut and BCRP at the expected clinical concentrations.

CYP3A4 substrates: 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. Agents that are CYP3A4 substrates should be co-administered with caution.

Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 may have increased exposure and should be administered with caution.

Please see the SPC for a full list of potential medicinal interactions.

Additional comments

Women of child bearing potential must be advised to use adequate barrier contraception throughout treatment

References

- Summary of Product Characteristics – Encorafenib via www.medicines.org.uk
- Summary of Product Characteristics – Cetuximab via www.medicines.org.uk
- Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E– mutated colorectal cancer. N Engl J Med 2019;381:1632-43.

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAU

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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