# Encorafenib and Cetuximab

## Indication

Previously treated BRAF V600E mutation positive metastatic colorectal adenocarcinoma.
No prior treatment with any BRAF, MEK or EGFR inhibitors.

## 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 | See below |

**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.

For patients unable to swallow, capsules may be opened and the content dispersed in a small quantity (approximately 20 mL) of apple sauce and taken immediately.

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

**Cetuximab**

Initial dose: Cetuximab is administered as an intravenous infusion over at least 120 minutes (maximum infusion rate must not exceed 5mg/min – refer to infusion rate chart).
Maintenance dose: Cetuximab is administered as an intravenous infusion over at least 60 minutes (maximum infusion rate must not exceed 10mg/min – refer to infusion rate chart).
Cetuximab is supplied in 500ml 0.9% sodium chloride.
Patients should be observed for fever and chills and other symptoms of infusion-related reaction during and for at least 1 hour after the completion of the infusion (heart rate, blood pressure, temperature, respiration rate should be taken prior to commencing infusion, at 30 minutes and post infusion). Interruption and slowing down the infusion rate may help control such symptoms.
If a mild or moderate infusion-related reaction occurs, the infusion may be resumed once the symptoms abate. It is recommended to maintain the lower infusion rate for subsequent infusions.
Severe infusion-related reactions have been documented and require immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Resuscitation equipment must be available during administration. If given in combination with chemotherapy, cetuximab is given first, followed by a 1-hour gap before commencing the chemotherapy (or at the consultants' discretion)

**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 | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 75 x $10^9$/L |
| Creatinine clearance (CrCl) | ≥ 30ml/min |
| AST/ALT | ≤ 2.5 x ULN (or <5 x ULN if liver metastases) |
| Bilirubin | ≤ 1.5 x 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 $10^9$/L and/or platelets < 75 x $10^9$/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 ≥ 38.5ºC. 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<br>If worsens or does not improve within 2 weeks withhold encorafenib and cetuximab until ≤ Grade 1 then resume at same dose.<br>If recurs resume with one dose level reduction. |
| | Grade 3 | Withhold encorafenib and cetuximab until ≤ Grade 1 then resume at same dose.<br>If recurs resume with one dose level reduction. |
| | Grade 4 | Discontinue |
| Palmar Plantar Erythrodysaesthesia (PPE) | Grade 2 | Continue with supportive measures<br>If worsens or does not improve within 2 weeks withhold encorafenib until ≤ 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 ≤ 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.<br>If Grade 1 and improves to Grade 0 resume with same dose.<br>If Grade 2-3 and improves to Grade 0 or 1 then resume with one dose level reduction.<br>If not improved in 6 weeks discontinue.<br>Grade 4 – discontinue |
| Cardiac | QTc prolongation >500ms and ≤ 60ms from baseline | Withhold encorafenib.<br>Resume with one dose level reduction when ≤ 500ms<br>If recurs – discontinue |
| | QTc prolongation >500ms and > 60ms from baseline | Discontinue |
| LFT abnormalities | Grade 2<br>AST/ALT 3-5 x ULN | Continue.<br>If no improvement within 2 weeks withhold encorafenib until <3 x ULN or baseline and continue with same dose. |
| | 1st occurrence Grade 3<br>AST/ALT > 5 x ULN and bilirubin > 2 x ULN | Withhold for up to 4 weeks<br>If improved to grade 0-1 continue encorafenib with one dose level reduction<br>If not improved – discontinue |
| | 1st occurrence Grade 4<br>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<br>If not improved – discontinue |
| | Recurrent Grade 3<br>AST/ALT > 5 x ULN and bilirubin > 2 x ULN | Discontinue |
| | Recurrent Grade 4<br>AST/ALT > 20 x ULN | Discontinue |

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

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

Date: Jan 2026