Cetuximab and Encorafenib

Indication
For previously treated advanced or metastatic BRAF V600E mutation positive colorectal cancer (NICE TA668)

ICD-10 codes
Codes prefixed with C18, C19 and C20

Regimen details

Day	Drug	Dose	Route
1-28	Encorafenib	300mg OD	Oral
1 and 15	Cetuximab	500mg/m^2*	IV infusion

***Note**: this dosing regimen is unlicensed

Cycle frequency
28 days

Number of cycles
Continuous until disease progression or unacceptable toxicity

Administration
Encorafenib is available as 50mg and 75mg capsules. Capsules should be swallowed whole with approximately 200mL of water and may be taken with or without food.

Cetuximab
First dose: Cetuximab is administered as an intravenous infusion and maximum infusion rate must not exceed 5mg/min.
Subsequent doses: Cetuximab is administered as an intravenous infusion and maximum infusion rate must not exceed 10mg/min.

Cetuximab is supplied undiluted at a concentration of 5mg/mL. 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.

Pre-medication
The following should be administered 30 minutes prior to each dose of cetuximab:
- Chlorphenamine 10mg IV
- Dexamethasone 8mg IV
- Paracetamol 1g PO

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Antiemetics and Loperamide if required.
For management of skin toxicity follow the guidelines below or refer to local EGFR skin toxicity guidance
- Ensure regular use of moisturiser
- Start doxycycline 100mg OD at treatment initiation and continue throughout treatment
- Oral antihistamine for pruritus

Extravasation

Cetuximab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period (or as per local protocol)
FBC	14 days
U+E (including creatinine)*	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
CEA	14 days
Blood pressure	Baseline
ECG (QTc <500ms)	Baseline

*Electrolyte imbalances must be corrected before treatment is commenced.

Before commencing treatment BRAF V600E mutation must be confirmed.
Consider baseline dermatological review if pre-existing significant skin conditions.

Investigations – pre subsequent cycles

Patients should be reviewed as a minimum, every 4 weeks for first 3 months

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
CEA	2 monthly
Blood pressure	Monthly
ECG (for QTc)	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	$\geq 100 \times 10^9$/L
Creatinine clearance (CrCl)	≥ 30ml/min
AST/ALT	≤ 3 x ULN (or <5 x ULN if liver metastases)
Bilirubin	≤ 2 x ULN
QTc	< 500ms and < 60ms increase from baseline

Dose modifications

Dose modifications should be made as per the table below.

Dose Level	Encorafenib	Cetuximab
Starting Dose	300mg OD	500mg/m^2
Dose level -1	225mg OD	400mg/m^2
Dose level -2	150mg OD	300mg/m^2
Dose level -3	Discontinue	Discontinue

Single agent activity of either drug in BRAF V600E mutant advanced colorectal has not been demonstrated.
If either treatment is discontinued both drugs must be stopped.

- **Haematological toxicity**

Cetuximab has not been studied in patients with pre-existing haematological disorders. Generally cetuximab is not myelosuppressive and treatment may continue during periods of mild myelosuppression.
If neutrophils < 1.0 x 10_9/L and/or platelets < 100 x 10_9/L consider withholding encorafenib treatment.

- **Renal impairment**

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

Cetuximab: Little experience in patients with renal impairment. Discuss with consultant if CrCl <30ml/min

- **Hepatic impairment**

Toxicity Grade	AST/ALT		Bilirubin	Dose adjustment	
				Encorafenib	Cetuximab
Grade 1	> ULN to 3 x ULN	AND	< 2 x ULN	Maintain dose	Maintain dose
Grade 2	3 to 5 x ULN	AND	< 2 x ULN	Maintain dose	At consultant's discretion
	3 to 5 x ULN	AND	≥ 2 x ULN	**Interrupt** until Grade ≤1, then reduce by one dose level	At consultant's discretion
Grade 3	5 to 8 x ULN	AND	< 2 x ULN	**Interrupt** • If improved to Grade ≤1 (or Grade ≤2 if liver metastases) ≤14 days, resume at same dose. • If > 14 days to improve to above levels, reduce by one dose level	At consultants discretion
	> 8 x ULN	AND	< 2 x ULN	Permanently discontinue	Discontinue
	> 5 x ULN	AND	> 2 X ULN	Permanently discontinue	Discontinue
Grade 4	> 20 x ULN	-	-	Permanently discontinue	Discontinue

Elevated bilirubin > 2 x ULN (with AST/ALT < 3 x ULN), discuss with prescriber/consultant

- **Skin reactions**

Cetuximab: rash typically acneiform, more common on face/ head/upper trunk

Encorafenib: skin reaction includes Hand-Foot Syndrome/Palmar-Plantar Erythrodysaesthesia, and maculopapular involving upper trunk, expanding centripetally and associated with pruritus. Increased incidence of skin lesions (including cutaneous squamous cell carcinomas, keratoacanthomas and other suspicious skin lesions) –
consider dermatology review if suspicious or symptomatic lesions (no dose modifications required for new skin lesions).

Interrupt cetuximab and/or encorafenib in severe skin reactions (grade 3 acneiform rash). Cetuximab may only be resumed if the suspected cetuximab-related rash has resolved to grade ≤2, or encorafenib may only be resumed if the suspected encorafenib-related rash has resolved to ≤1, according to the dosing table below:

Grade 3 rash	Encorafenib dose after resolution to ≤Grade 1	Cetuximab dose after resolution to ≤Grade 2
1st occurrence	100% previous dose	100% previous dose
2nd occurrence	Reduce by 1 dose level	Reduce by 1 dose level
3rd occurrence	Reduce by 1 further dose level	Reduce by 1 further dose level
4th occurrence	Discontinue permanently	Discontinue permanently

If the skin reaction does not resolve to ≤ grade 2, treatment should be discontinued.

Patients may be predisposed to super-infection with *S. aureus* and therefore appropriate additional antibiotic treatment may be required.

The long-term use of corticosteroids should be **carefully considered** due to the potential to induce or exacerbate acne and other skin conditions and to interfere with the antibody-dependent cell-mediated cytotoxicity reactions thought to contribute to the anti-tumour effects of cetuximab.

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.

Electrolyte Disturbance

Replace electrolytes as appropriate. Hypomagnesaemia is reversible following Cetuximab discontinuation.

Dyspnoea

May occur as a result of infusion related reaction but may occur several weeks into treatment. Discontinue treatment if interstitial lung disease is diagnosed.

Other toxicities

Toxicity	Grade	Encorafenib	Cetuximab
Palmar Plantar Erythrodysaesthesia (PPE)	Grade 2	Continue with supportive measures 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.	If no other cetuximab related rash, continue whilst encorafenib continues.
	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.	Restart same dose when encorafenib restarted if no other cetuximab related toxicity. If concurrent cetuximab related toxicity, consider one dose level reduction.

Toxicity	Grade	Encorafenib	Cetuximab
Uveitis	Grade 1-2	Ophthalmology review and topical therapy. **(If does not respond to topical therapy, consider management as per Grade 3 toxicity).** If Grade 1 and resolves, continue at same dose If Grade 2 and improves to Grade ≤1, resume with one dose level reduction.	Maintain dose once encorafenib resumed
	Grade 3	Withhold encorafenib and repeat ophthalmic monitoring. If improved to Grade ≤1 then resume with one dose level reduction If not improved to Grade ≤1 in 6 weeks, permanently discontinue	Maintain dose once encorafenib resumed If encorafenib discontinued, discontinue cetuximab
	Grade 4	Permanently discontinue	Discontinue cetuximab
Cardiac	QTc prolongation >500ms and ≤60ms from baseline	Withhold encorafenib. Ensure electrolyte correction. Resume with one dose level reduction when ≤500ms If recurs – permanently discontinue	Maintain dose when encorafenib resumed. If encorafenib discontinued, discontinue cetuximab.
	QTc prolongation >500ms and >60ms from baseline	Permanently discontinue	Permanently discontinue if encorafenib discontinued.
Any other adverse reaction	Recurrent or intolerable Grade 2 or 1st occurrence Grade 3	If related to encorafenib then withhold encorafenib for up to 4 weeks. If improved to Grade ≤1 resume encorafenib with one dose level reduction. If not improved – permanently discontinue (also discontinue cetuximab)	If related to cetuximab then consider withhold cetuximab for up to 4 weeks. If improved to Grade ≤1 resume cetuximab with one dose level reduction. If not improved – permanently discontinue (also discontinue encorafenib)
	1st occurrence Grade 4	If related to encorafenib then withhold encorafenib for up to 4 weeks. If improved to Grade ≤1 resume encorafenib with one dose level reduction. If not improved – permanently discontinue (also discontinue cetuximab)	If related to cetuximab then withhold cetuximab for up to 4 weeks. If improved to Grade ≤1 resume cetuximab with one dose level reduction. If not improved – permanently discontinue (also discontinue encorafenib)
	Recurrent Grade 3 or 4	Permanently discontinue (also discontinue cetuximab)	Permanently discontinue (also discontinue encorafenib)

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

- **Serious side effects**

Cutaneous squamous cell carcinoma
QT prolongation/SVT
Haemorrhage
Hypersensitivity reactions
Ocular toxicity including uveitis
Myelosuppression
Stevens-Johnson syndrome/toxic epidermal necrolysis

- **Frequently occurring side effects**

Fatigue
Decreased appetite
Abdominal/back pain
Pyrexia
Arthralgia and/or myalgia
Rash/pruritus
Nausea and vomiting
Stomatitis/mucositis
Palmar-Plantar Erythrodysaesthesia (PPE)/Hand-Foot Syndrome(HFS)
Diarrhoea or constipation
Electrolyte disturbance (especially magnesium)
Raised LFTs
Melanocytic naevus
Insomnia
Dysgeusia
Conjunctivitis
Peripheral Neuropathy

- **Other side effects**

Blurred vision
Headache or dizziness
Peripheral oedema
Dyspneoa
Keratoacanthoma
Renal impairment
Anaemia
VTE
Hypertension
Drug induced pancreatitis
Alopecia
Skin hyperpigmentation
Paronychia

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

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Cetuximab
No documented significant reactions.
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. Grapefruit and grapefruit juice, Seville oranges or pomelos should be **avoided** within 7 days of starting and whilst taking encorafenib.

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.

Additional comments

Cetuximab use is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reaction.

Cetuximab should be used with caution in patients with active peripheral, cerebral or coronary vascular disease or severe myelosuppression.

It is recommended to warn patients of the possibility of late onset infusion reactions and instruct them to contact their doctor/nurse team if symptoms of an infusion-related reaction occur. If severe, a reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.

Cetuximab causes sun-sensitivity that may exacerbate skin reactions. Protect from sun.

Ensure appropriate contraception is discussed.

References

1. Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E-Mutated Colorectal Cancer *Kopetz S et al.* N Engl J Med. 2019 Oct 24;381(17):1632-1643 (accessed 7 November 2020) https://www.nejm.org/doi/suppl/10.1056/NEJMoa1908075/suppl_file/nejmoa1908075_protocol.pdf

2. Summary of Product Characteristics – Braftovi 75mg hard capsules accessed 7 November 2020 via www.medicines.org.uk
3. Summary of Product Characteristics – Erbitux 5mg/mL solution for infusion accessed 7 November 2020 via www.medicines.org.uk

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Date: 15th February 2021
