

Chemotherapy Protocol
COLORECTAL CANCER
CETUXIMAB-ENCORAFENIB

Regimen

- Colorectal Cancer – Cetuximab-Encorafenib

Indication

- Cetuximab and encorafenib can be used where;
 - the patient has a histologically proven colorectal adenocarcinoma that has been shown to contain a BRAF V600E mutation as well as having been shown to be of RAS wild type
 - the patient has failed one or two prior regimens for advanced/metastatic disease. Note: 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.
 - the patient has not received prior treatment with any BRAF inhibitor or MEK inhibitor unless this was received for this specific indication via interim COVID19 funding
 - the patient 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.
 - that the patient has no active brain metastases or leptomeningeal metastases
 - that encorafenib with cetuximab is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment, whichever is the sooner.
 - that 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.
 - WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Cetuximab	Infusion related reactions, interstitial lung disease, skin reactions, electrolyte abnormalities, fatigue, abdominal pain, constipation
Encorafenib	Gastro-intestinal disturbances, fatigue, pyrexia, arthralgia, myalgia, haemorrhage, hypertension QTc prolongation, uveitis, haemorrhage, cutaneous reactions, palmar-plantar syndrome, cardiac dysfunction

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- Prior to starting therapy confirm a positive BRAF V600E and RAS wild type
- FBC, LFT's and U&E's prior to day one of each cycle
- LFT and U&Es on day 15 of the cycle

Dose Modifications

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for SACT that if a third dose reduction is necessary treatment should be stopped.

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib. If encorafenib is permanently discontinued, cetuximab should be discontinued and vice versa.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing on day one of cycle one the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

Neither cetuximab nor encorafenib are myelosuppressive and no dose reduction is needed for haematological toxicity. Treatment should be delayed for 7 days if the neutrophil count is equal to or less than $0.9 \times 10^9/L$ or the platelets are equal to or less than $75 \times 10^9/L$.

Hepatic / Renal Impairment

Drug	Hepatic	Renal
Cetuximab	Administer only when the transaminases are 5xULN or below and the bilirubin is 1.5xULN or below	Administer only where the serum creatinine is 1.5xULN or below
Encorafenib	Reduce dose of encorafenib to 300mg in	There is no data for encorafenib in severe renal

	patients with mild hepatic impairment (Child-Pugh Class A). Encorafenib is not recommended in patients with severe hepatic impairment (Child-Pugh Class C)	impairment, encorafenib should be used with caution in these patients
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Encorafenib can cause liver abnormalities. Doses should be adjusted as follows;

NCI-CTC Grade	Action
2	Encorafenib 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.
3 (first occurrence)	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
3 (recurrence)	Consider discontinuing encorafenib
4 (first occurrence)	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.
4 (recurrence)	Discontinue

Other

If the cetuximab is permanently discontinued the encorafenib should also be discontinued and vice versa.

Dose Level	Encorafenib	Cetuximab
1 st dose reduction	225mg once a day	400mg/m ²
2 nd dose reduction	150mg once a day	300mg/m ²

Cetuximab

Allergy

Allergic or hypersensitivity reactions have occurred during the administration of cetuximab. For a NCI-CTC grade 1 reaction reduce the infusion rate by 50% (the total should not exceed 240 minutes). For a NCI-CTC grade 2 reaction, stop the infusion and administer supportive therapies as indicated. Once the reaction has resolved to NCI-CTC grade 1 or below resume the infusion at 50% of the previous rate. For a NCI-CTC grade 3 or 4 toxicity stop the infusion immediately and disconnect the tubing from the patient. Administer appropriate supportive therapies. Once recovered, patients should not receive cetuximab again.

Once the rate has been reduced it should not be increased on subsequent infusions.

If a second reaction occurs on the slower infusion rate the infusion should be stopped and no further treatment given.

Eye

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Electrolyte Disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased. Serum electrolyte abnormalities, including low magnesium and potassium need to be corrected to reduce risk of QT prolongation

Skin

An acniform skin rash occurs in over 70% of those receiving cetuximab. The onset is normally within three weeks of starting therapy and often resolves after week twelve. For a NCI-CTC grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the cetuximab. For a NCI-CTC grade 3 toxicity delay treatment until the toxicity resolves to NCI-CTC grade 2 or below. If this occurs within fourteen days resume cetuximab at the same dose. If more than fourteen days is required stop treatment. If the NCI-CTC grade 3 toxicity occurs for a second and third time the cetuximab may again be delayed for up to and including fourteen days with concomitant dose reductions. Cetuximab dose reductions are permanent. The cetuximab must be discontinued if more than two consecutive infusions are withheld or a fourth episode of a NCI-CTC grade 3 skin toxicity develops or a NCI-CTC grade 4 toxicity at any time.

UV radiation may worsen skin reactions. Sun safety practices should be followed during and for up to two months after the end of treatment.

Lung

Stop treatment if there is a confirmed pneumonitis.

Encorafenib

Eye

Uveitis including iritis and iridocyclitis can occur. Patients should be assessed at each visit for symptoms of new or worsening visual disturbance, including;

diminished central vision, blurred vision or loss of vision. If any of these symptoms are identified, a prompt ophthalmologic examination is recommended.

If NCI-CTC 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. Encorafenib should also be permanently discontinued for a NCI-CTC grade 4 uveitis and a follow up with ophthalmologic monitoring should be performed

Heart

QT Prolongation has been observed in patients treated with BRAF-inhibitors. Recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment.

For QTcF greater than 500ms and change less than or equal to 60ms from pre-treatment value encorafenib should be withheld. Encorafenib should be resumed at a reduced dose when QTcF less than or equal to 500ms. Encorafenib should be discontinued if more than one recurrence.

Haemorrhage

Haemorrhagic events were observed in 21% of patients treated with encorafenib. Monitor haemoglobin and for epistaxis and blood in stool or urine.

Skin

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) (including keratoacanthoma) and new primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib. Patients should be instructed to immediately inform their physicians if new skin lesions develop. For new primary cutaneous malignancies then no dose modifications are required for encorafenib.

For new primary non-cutaneous RAS mutation-positive malignancies consider discontinuing encorafenib permanently.

For NCI-CTC grade 2 cutaneous reactions encorafenib treatment should be maintained.

If rash worsens or does not improve within 2 weeks with treatment, encorafenib (and binimetinib) should be withheld until NCI-CTC Grade 0 or 1 and then resumed at the same dose.

For NCI-CTC grade 3 cutaneous reactions encorafenib should be withheld until improved to NCI-CTC grade 0 or 1 and resumed at the same dose if first occurrence, or resumed at a reduced dose if recurrent NCI-CTC grade 3.

For NCI-CTC grade 4 cutaneous reactions encorafenib should be permanently discontinued.

For NCI-CTC grade 2 palmar-plantar erythrodysesthesia syndrome (PPES) 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 NCI-CTC grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.

For NCI-CTC grade 3 PPES encorafenib should be withheld, supportive measures such as topical therapy should be instituted. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to NCI-CTC grade 0 or 1.

[Regimen](#)

28 day cycle until intolerance or disease progression develops (6 cycles will be set in Aria)

Drug	Dose	Days	Route
Cetuximab	500mg/m ²	1, 15	Intravenous infusion over 120 minutes (see administration below)
Encorafenib	300mg	1-28 incl	Oral

[Dose Information](#)

- Cetuximab will be dose banded in accordance with the national dose bands (5mg/ml)
- Encorafenib is available as 50mg and 75mg capsules

[Administration Information](#)

Extravasation

- Cetuximab - neutral

Other

- Individuals should be monitored for hypersensitivity for sixty minutes after finishing the cetuximab infusion. Do not administer other chemotherapy during this period.
- The rate of administration of cetuximab must not exceed 10mg/min. The first infusion is given over 120 minutes. If this infusion rate is well tolerated subsequent infusions may be given over 60 minutes

Additional Therapy

- 30 minutes prior to cetuximab infusion;
 - chlorphenamine 10mg intravenous
 - dexamethasone 8mg oral or intravenous
 - H₂ antagonist according to local formulary choice and availability
 - paracetamol 1000mg oral
- Antiemetics
 - As take home medication
 - metoclopramide 10mg three times a day when required oral (supply day one cycle one only and then as required)
- Prophylaxis with doxycycline 100mg once a day for 28 days
- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References

1.

REGIMEN SUMMARY

Cetuximab-Encorafenib

Day 1, 15

1. Chlorphenamine 10mg intravenous
2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral

Administration Instructions

Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H₂ antagonist according to local formulary choice and availability

Administration Instructions:

Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;

- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

If there is no stock of these products due to national shortages treatment may proceed without the H₂ antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H₂ antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H₂ antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

5. Cetuximab 500mg/m² over 120 minutes intravenous infusion

Administration Instructions

The rate of administration of cetuximab must not exceed 10mg/min. The first infusion is given over 120 minutes. If this infusion rate is well tolerated subsequent infusions may be given over 60 minutes

Take Home Medicines (day 1 only)

6. Encorafenib 300mg once a day for 28 days oral

Administration Instructions

Oral SACT

7. Metoclopramide 10mg three times a day when required for the relief of nausea oral*

Administration Instructions

Please supply 28 tablets or the nearest equivalent pack size

*The metoclopramide will only appear on day one cycle one. If further supplies are required they should be added from the support directory of Aria as necessary.

8. Doxycycline 100mg once a day oral

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2021	None	Dr Deborah Wright Pharmacist	Prof Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury Hospital NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.