Encorafenib and Binimetinib

Indication
Unresectable or metastatic BRAF V600 mutation-positive melanoma.

(NICE TA562)

ICD-10 codes
Codes with a prefix C43

Regimen details

Day	Drug	Dose	Route
1-28	Encorafenib	450mg OD	PO
1-28	Binimetinib	45mg BD	PO

Cycle frequency
As above

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 water and may be taken with or without food.

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

Binimetinib is available as 15mg tablets. The doses should be taken 12 hours apart. Tablets should be swallowed whole with water and may be taken with or without food. If a dose is missed it should not be taken if it is less than 6 hours until the next dose is due. If a patient vomits after taking a dose, the dose should not be retaken and the next dose should be taken at the next scheduled time.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Emollients if required.
Antiemetics if required.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)*	7 days
LFTs	7 days
Magnesium*	7 days
Calcium	7 days
LDH	7 days
Creatinine phosphokinase (CK)	7 days
Pregnancy test (if applicable)	7 days
Blood pressure	Baseline
ECG (QTc < 500ms) and echocardiogram	Baseline
Echocardiogram	Baseline

*Electrolyte imbalances must be corrected before treatment is commenced.
Consider dermatological evaluation.

Before commencing treatment BRAF V600 mutation must be confirmed.

Investigations – pre subsequent cycles

Patients should be reviewed every 4 weeks for the first 3 months.

Investigation	**Validity period** (or as per local policy)
FBC	96 hours or monthly
U+E (including creatinine)	96 hours or monthly
LFTs	96 hours or monthly
Magnesium	96 hours or monthly
LDH	96 hours or monthly
Creatinine phosphokinase (CK)	96 hours or monthly
Blood pressure	Monthly
ECG	should be monitored before treatment, after the first month, then approximately 3 monthly or more frequently if clinically indicated*
Echocardiogram	should be monitored before treatment, after the first month, then approximately 3 monthly or more frequently if clinically indicated *

*Further monitoring is recommended in patients with moderate to severe hepatic impairment (see hepatic impairment section).

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	≥ 100 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
CK	≤ 5 x ULN
QTc	< 500ms and <60ms increase from baseline
LVEF	> LLN for institution

Dose modifications

Dose modifications should be made as per the table below:

Dose level	Encorafenib dose	Binimetinib dose
Full dose	450mg OD	45mg BD
First reduction	300mg OD	30mg BD
Second reduction	200mg OD	Further dose reductions are not recommended. Discontinue if 30mg BD not tolerated.
Third reduction	100mg OD	

Dose reductions beyond these levels are not recommended.

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption because encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If encorafenib is temporarily interrupted (see Table 2), binimetinib should be interrupted. If either agent is permanently discontinued, then both should be discontinued.

If treatment-related toxicities occur, then encorafenib and binimetinib should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) are: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, CK elevation and rhabdomyolysis, and venous thromboembolism (VTE).

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L consider withholding treatment.
See below for management of pyrexia.

- **Renal impairment**

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

No dose adjustment of binimetinib is recommended for patients with renal impairment.

- **Hepatic impairment**

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

- **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 If worsens or does not improve within 2 weeks withhold binimetinib and encorafenib until ≤ Grade 1 then resume at same dose. If recurs resume with one dose level reduction.
	Grade 3	Withhold binimetinib and encorafenib until ≤ Grade 1 then resume at same dose. If recurs resume with one dose level reduction.
	Grade 4	Discontinue
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.
	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	Grade 2-3 Symptomatic retinal pigment epithelial detachments (RPED)	Withhold binimetinib for up to 2 weeks with ophthalmic monitoring. - If improves to ≤ Grade 1 resume at same dose - If improves to ≤ Grade 1 resume with one dose level reduction - If does not improve to ≤ Grade 2 discontinue.
	Grade 4 (RPED with reduced visual acuity) Or Retinal vein occlusion (RVO)	Discontinue
	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	Grade 2 LVEF decrease	Evaluate every 2 weeks. If asymptomatic withhold binimetinib for up to 4 weeks. It may be recommenced at one dose level reduction if all the following occur within 4 weeks: - LVEF ≥ LLN - Absolute decrease from baseline is 10% or less. If LVEF does not recover within 4 weeks – discontinue
	Grade 3-4 LVEF	Discontinue Evaluate LVEF every 2 weeks until recovery
	QTc prolongation >500ms and ≤ 60ms from baseline	Withhold encorafenib. Resume with one dose level reduction when ≤ 500ms If recurs – discontinue
	QTc prolongation >500ms and > 60ms from baseline	Discontinue
CK elevation	Grade 3 (CK 5-10 x ULN) asymptomatic	Continue binimetinib and ensure adequate hydration

	Grade 4 (CK > 10 x ULN) asymptomatic	Withhold binimetinib until Grade 0 or 1. Ensure adequate hydration.
	Grade 3 or 4 (CK > 5 x ULN) with muscle symptoms or renal impairment	Withhold binimetinib until Grade 0 or 1 If resolved within 4 weeks continue with one dose level reduction If does not recover within 4 weeks – discontinue
VTE	Uncomplicated DVT or < Grade 3 PE	Withhold binimetinib until Grade 0 or 1 If improved continue with one dose level reduction If not improved – discontinue
	Grade 4 PE	Discontinue
LFT abnormalities	Grade 2 AST/ALT 3-5 x ULN	Continue. If no improvement within 2 weeks withhold binimetinib and encorafenib until <3 x ULN or baseline and continue with same dose.
	1st 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 binimetinib and encorafenib with one dose level reduction If not improved – discontinue
	1st occurrence Grade 4 AST/ALT > 20 x ULN	Withhold binimetinib and encorafenib for up to 4 weeks If improved to grade 0-1 continue binimetinib and 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
Interstitial lung disease	Grade 2	Withhold binimetinib for up to 4 weeks If improved to grade 0-1 continue binimetinib with one dose level reduction If not improved – discontinue
	Grade 3-4	Discontinue
Any other adverse reaction	Recurrent or intolerable Grade 2 or 1st occurrence Grade 3	Withhold binimetinib and encorafenib for up to 4 weeks If improved to grade 0-1 continue binimetinib and encorafenib with one dose level reduction If not improved – discontinue
	1st occurrence Grade 4	Withhold binimetinib and encorafenib for up to 4 weeks If improved to grade 0-1 continue binimetinib and 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 RVO, RPED, uveitis
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.

Binimetinib

Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation. The extent of drug interactions mediated by UGT1A1 is unlikely to be clinically relevant. **UGT1A1 inducers** (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution.

Inducers of CYP1A2 enzymes (such as carbamazepine and rifampicin) and **inducers of Pgp transport** (such as Saint John's wort or phenytoin) may decrease binimetinib exposure, which could result in a decrease of efficacy.

Binimetinib is a potential inducer of CYP1A2, and caution should be taken when it is used with sensitive substrates (such as duloxetine or theophylline).

Binimetinib is a weak inhibitor of OAT3, and caution should be taken when it is used with sensitive substrates (such as pravastatin or ciprofloxacin).

Additional comments

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

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 562 via www.nice.org.uk
- Summary of Product Characteristics – Encorafenib accessed 2 October 2019 via www.medicines.org.uk
- Summary of Product Characteristics – Binimetinib accessed 2 October 2019 via www.medicines.org.uk
- Drummer R., et al. Encorafenib plus Binimetinib versus vemurafenib or Encorafenib in patients with BRAF- mutant melanoma (COLUMBUS): a multicentre, open label, randomised phase 3 trial. Lancet Oncology. 2018. 19:5, 603-615.

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