ENCORAFENIB BINIMETINIB (Braftovi and Mektovi)

INDICATION (ICD10) C43

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (ENC1)

1. The treatment of treatment naïve to BRAF V600 and MEK inhibitors unresectable stage III or stage IV BRAF V600 mutation positive malignant melanoma. Sufficient PS to tolerate treatment. (TA562)

REGIMEN

Day 1 ENCORAFENIB 450mg orally once daily continuously
BINIMETINIB 45mg orally twice daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression.
A formal medical review as to whether treatment with encorafenib in combination with binimetinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

ADMINISTRATION

Binimetinib is available as 15mg tablets
Encorafenib is available as 50mg and 75mg capsules
Swallow both whole with water, with or without food.

ANTI-EMETICS

Low emetic risk

CONCURRENT MEDICATION REQUIRED

Binimetinib	None required
Encorafenib	None required

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine - GFR each cycle
ECG and ECHO at baseline, 1 month then every 3 months
Blood pressure baseline, then monthly
CK every monthly for 6 cycles then as indicated

MAIN TOXICITES AND ADVERSE REACTIONS

Binimetinib	Cutaneous reactions Ocular events LVEF decrease Rhabdomyolysis / creatine phosphokinase elevation Venous thromboembolism LFT abnormalities Interstitial lung disease
Encorafenib	Cutaneous reactions Palmar-plantar erythrodysaethesia syndrome Uveitis QT prolongation

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Binimetinib	-
Encorafenib	Potent enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) should be avoided, as may decrease encorafenib. Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin) should be avoided, as may increase the risk of encorafenib toxicity. Moderate CYP3A4 inhibitors (e.g. amiodarone, erythromycin, fluconazole, diltiazem) may be used with caution and extra monitoring. 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.

DOSE MODIFICATIONS

If binimetinib is temporarily interrupted, reduce encorafenib to 300mg od during the interruption.
If binimetinib is permanently discontinued, encorafenib should also be discontinued.
If encorafenib is temporarily or permanently interrupted, binimetinib should also be stopped during that period.

Binimetinib

Dose level	Dose
Full dose	45mg twice daily
First reduction	30mg twice daily
Second reduction	Doses below 30mg twice daily are not recommended

Encorafenib

Dose level	Dose
Full dose	450mg once daily
First reduction	300mg once daily
Second reduction	225mg once daily
Subsequent modification	There are limited data for dose reduction to 100mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100mg once daily.

Non-haematological

Cardiac events

Grade 2 left ventricular ejection fraction (LVEF) decrease or asymptomatic, absolute decrease in LVEF of greater than 10 % from baseline that is below lower limit of normal (LLN)	LVEF should be evaluated every 2 weeks. • If asymptomatic: Binimetinib should be withheld for up to 4 weeks. Binimetinib should be resumed at a reduced dose if all of the following are present within 4 weeks: - LVEF is at or above the LLN - Absolute decrease from baseline is 10 % or less. • If the LVEF does not recover within 4 weeks, binimetinib should be permanently discontinued.
Grade 3 or 4 LVEF decrease or symptomatic left ventricular dysfunction (LVD)	Binimetinib should be permanently discontinued. LVEF should be evaluated every 2 weeks until recovery.

Cutaneous reactions

Grade 2	Encorafenib and binimetinib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, binimetinib should be withheld until improved to grade 0 or 1 and then resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent grade 2.
Grade 3	Encorafenib and binimetinib should be withheld until improved to grade 0 or 1 and resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent grade 3.
Grade 4	Encorafenib and binimetinib should be permanently discontinued.

Interstitial lung disease / pneumonitis

Grade 2	Binimetinib should be withheld for up to 4 weeks. • If improved to grade 0 or 1, binimetinib should be resumed at reduced dose, or • If not resolved within 4 weeks, binimetinib should be permanently discontinued.
Grade 3 or grade 4	Binimetinib should be permanently discontinued.

Liver laboratory abnormalities

Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x–≤5x upper limit of normal (ULN)	Encorafenib and binimetinib dose should be maintained. If no improvement within 2 weeks, encorafenib and binimetinib should be withheld until improved to grade 0 or 1 or to baseline levels, and then resumed at the same dose.
First occurrence of grade 3 (AST or ALT >5xULN and blood bilirubin >2xULN)	Encorafenib and binimetinib should be withheld for up to 4 weeks. • If improved to grade 0 or 1 or baseline level, encorafenib and binimetinib should be resumed at reduced dose, or • If not improved, encorafenib and binimetinib should be permanently discontinued.
First occurrence of grade 4 (AST or ALT >20xULN)	Encorafenib and binimetinib should be withheld for up to 4 weeks. • If improved to grade 0 or 1 or baseline levels, encorafenib and binimetinib should be resumed at a reduced dose level, or • If not improved, encorafenib and binimetinib should be permanently discontinued. Or, encorafenib and binimetinib should be permanently discontinued.
Recurrent grade 3 (AST or ALT >5xULN and blood bilirubin >2xULN)	It should be considered to permanently discontinue encorafenib and binimetinib.
Recurrent grade 4 (AST or ALT >20ULN)	Encorafenib and binimetinib should be permanently discontinued.

Ocular events

Symptomatic retinal pigment epithelial detachments (RPED) (grade 2 or 3)	Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment. • If improved to grade 0 or 1, binimetinib should be resumed at same dose. • If improved to grade 2, binimetinib should be resumed at a lower dose. • If not improved to grade 2, binimetinib should be permanently discontinued.
Symptomatic RPED (grade 4) associated with reduced visual acuity (grade 4)	Binimetinib should be permanently discontinued.
Retinal vein occlusion (RVO)	Binimetinib should be permanently discontinued.

Other toxicities

Recurrent or intolerable grade 2 adverse reactions or first occurrence of grade 3 adverse reactions	Encorafenib and binimetinib 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 and binimetinib should be permanently discontinued
First occurrence of any grade 4 adverse reaction	Encorafenib and binimetinib 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 and binimetinib should be permanently discontinued. Or, encorafenib and binimetinib should be permanently discontinued.
Recurrent grade 3 adverse reactions	Permanent discontinuation of encorafenib and binimetinib should be considered.
Recurrent grade 4 adverse reactions	Encorafenib and binimetinib should be permanently discontinued.

Palmar-plantar erythrodysaethesia syndrome

Grade 2	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 grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to grade 0 or 1.

QTc prolongation

QTcF >500ms and change ≤60ms from pre-treatment value	Encorafenib should be withheld. Encorafenib should be resumed at a reduced dose when QTcF ≤500ms. Encorafenib should be discontinued if more than one recurrence
QTcF>500ms and increased by >60ms from pre-treatment values	Encorafenib should be permanently discontinued

Rhamdomyolysis / Creatine phosphokinase elevation

Grade 3 (CK >5–10x upper limit of normal (ULN)) asymptomatic	Binimetinib dose should be maintained and it should be ensured that patient is adequately hydrated.
Grade 4 (CK >10xULN) asymptomatic	Binimetinib should be withheld until improved to Grade 0 or 1. It should be ensured that patient has adequate hydration.
Grade 3 or grade 4 (CK > 5xULN) with muscle symptoms or renal impairment	Binimetinib should be withheld until improved to grade 0 or 1. • If resolved within 4 weeks, binimetinib should be resumed at a reduced dose, or • Binimetinib should be permanently discontinued.

Uveitis (including iritis and iridocyclitis)

Grade 1-3	If 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.
Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.

Venous thromboembolism

Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3	Binimetinib should be withheld. • If improved to grade 0 or 1, binimetinib should be resumed at a reduced dose, or • If not improved, binimetinib should be permanently discontinued.
Grade 4 PE	Binimetinib should be permanently discontinued.

Hepatic impairment

Binimetinib

No dose adjustment is required in patients with mild hepatic impairment.

As encorafenib is not recommended in patients with moderate or severe hepatic impairment, administration of binimetinib is not recommended as they should usually be given in combination.

Encorafenib

Mild hepatic impairment (Child-Pugh Class A) use with caution at a reduced dose of 300mg once daily.

Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment not recommended.

Renal impairment
Binimetinib
No dosage adjustment is required in patients with renal impairment.

Encorafenib
No dosage adjustment is required in patients with mild or moderate renal impairment.
For patients with severe renal impairment, use with caution.

REFERENCES
1. Dummer, R et al; Lancet Oncology 2018; 19 (5): 603–615
1. SPC