Indication	The treatment of unresectable stage III or stage IV BRAF V600 mutation positive malignant melanoma. NB The patient is treatment naïve to BRAF V600 and MEK inhibitors for malignant melanoma unless either the patient has previously received adjuvant dabrafenib and trametinib and did not progress during such therapy or has received dabrafenib plus trametinib for advanced disease which had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days To be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent. A formal medical review must be scheduled to occur by the end of the first 8 weeks of treatment to assess whether to continue therapy.
Monitoring Parameters pre-treatment	• ECG and either ECHO or MUGA prior to cycle 1 and to be repeated prior to cycle 2. Then to be repeated every 3 months or more frequently if clinically indicated. • U&E, to include CK, Ca^{2+} and Mg^{2+}, at baseline and at every cycle. • FBC baseline and every cycle. • LFTS baseline and every cycle for 6 months and then as clinically indicated. • BP baseline and at each cycle. • Risk factors for QT prolongation should be controlled before initiation of treatment. • Patients should be assessed at each visit for symptoms of visual disturbance (see below). • Dermatologic evaluations should be performed prior to initiation of therapy, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. **<u>Hepatic impairment:</u>** • Use encorafenib with caution in patients with mild hepatic impairment (Child-Pugh Class A), a dose reduction to 300mg OD is recommended. Not recommended in moderate to severe hepatic impairment (Child-Pugh Class B & C) due to lack of data. • No dose adjustment required of binimetinib in mild hepatic impairment. As it is only recommended to be given as a dual therapy, binimetinib should not be given in moderate to severe hepatic impairment due to the unsuitability of encorafenib in these patients. **<u>Renal impairment:</u>** • Encorafenib should only be used at the clinicians' discretion in severe renal impairment (<30ml/min), no data available. No adjustment in mild to moderate renal impairment. • No dose reduction of binimetinib required in renal impairment. **<u>Dose modifications & interruptions to manage adverse reactions:</u>** • If treatment-related toxicities occur, then encorafenib and binimetinib should be simultaneously dose reduced, interrupted or discontinued. Exceptions are: o Dose modifications (including where necessary discontinuation) to binimetinib only for: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous

thromboembolism (VTE), see table 3 below for details.
  - Dose modifications to encorafenib (including where necessary discontinuation) only for: palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis including iritis and iridocyclitis and QTc prolongation, see table 1.
- If binimetinib is temporarily interrupted then encorafenib should be dose reduced to 300mg OD during the interruption. If dose interruption is required for encorafenib, binimetinib should also be interrupted.
- For patients receiving 450mg encorafenib once daily, the first dose reduction should be 300mg once daily. If a 2nd dose reduction is required reduce to 200mg once a day, subsequent dose reduction to 100mg once a day can be done but there is limited data for this dose. If 100mg once daily is not tolerated treatment should be permanently discontinued.
- For patients receiving 45 mg binimetinib twice daily, dose reduce where necessary to 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily. Dose re-escalation to 45 mg twice daily may be considered once the adverse reaction has resolved. Dose re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity.
- If either encorafenib or binimetinib are permanently discontinued then the other agent should also be discontinued.
- Consider discontinuing treatment if new primary non-cutaneous RAS mutation-positive malignancies.
- **Left ventricular dysfunction (LVD):** In patients with a baseline LVEF <50% or <LLN and who develop any symptomatic left ventricular dysfunction, Grade 3-4 LVEF, or absolute decrease of LVEF from baseline of ≥ 10 %, binimetinib and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.
- **Haemorrhage:** Haemorrhages, including major haemorrhagic events, can occur when binimetinib is administered; the risk may be increased with concomitant use of anticoagulants and antiplatelets. The occurrence of Grade ≥ 3 haemorrhagic events should be managed with dose interruption, reduction or treatment discontinuation and as clinically indicated (refer to SPC for further details).
- **Pneumonitis/Interstitial lung disease (ILD):** Patients should report any new or worsening respiratory symptoms and treatment should be withheld in patients with suspected pneumonitis or ILD. Binimetinib should be permanently discontinued in patients with confirmed treatment related pneumonitis or ILD.
- **Ocular toxicities:** Ocular toxicities including RPED and RVO can occur, monitor patients for visual disturbance. Binimetinib is not recommended in patients with a history of RVO. The occurrence of symptomatic RPED can be managed with treatment interruption, dose reduction or with treatment discontinuation. Binimetinib should be permanently discontinued with the occurrence of RVO. For guidance on the treatment of uveitis see table 1.
- Special attention should be paid to patients with neuromuscular conditions associated with CK elevation and rhabdomyolysis. Patients should be advised to maintain an adequate fluid intake during treatment.
- Caution with patients with a risk of or history of **VTE.**

Drug Interactions (see SPC for full list):

- Concurrent use of strong CYP inhibitors (ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole) during treatment should be avoided.
  Moderate CYP inhibitors (amiodarone, erythromycin, fluconazole, diltiazem,

	amprenavir and imatinib) should be co-administered with caution. If the use of a CYP inhibitor is unavoidable these patients should be carefully monitored for toxicity. • Avoid use of strong or moderate CYP enzyme inducers (carbamazepine, rifampicin, phenytoin and St. John's Wort), consider alternative agents with no or minimal CYP enzyme induction. • Encorafenib and binimetinib are both potentially CYP inducers; in addition encorafenib is an inhibitor of CYP3A4. Agents that are CYP substrates (eg hormonal contraceptives) should be used with caution. • Encorafenib and binimetinib potentially inhibit a number of renal and hepatic transporters, agents that are transporter substrates (e.g. statins) should be co-administered with caution. **Missed doses:** If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until next dose is due. If a dose of encorafenib is missed it should not be taken if it is less than 12 hours until next dose is due. **Further Guidance:** • Do not drink grapefruit juice or consume grapefruits whilst on this treatment. • Patients should ensure adequate fluid intake during treatment. • Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines.
References	SPC accessed on line 29/01/2019 CDF list v1.124

NB For funding information, refer to the SACT funding spread sheet

Table 1: Recommended dose modifications for encorafenib when used in combination with binimetinib

Severity of adverse reaction	**Encorafenib**
Cutaneous reactions	
• Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
• Grade 3	Encorafenib 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 should be permanently discontinued.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• 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.
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.
QTc Prolongation	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF>500 ms and increased by >60 ms from pre-treatment values	Encorafenib should be permanently discontinued
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x ≤5x upper limit of normal (ULN))	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.
• First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	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
• First occurrence of Grade 4 (AST or ALT >20 ULN)	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
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued.

Table 2: Recommended dose modifications for encorafenib (used in combination with binimetinib) for other adverse reactions

Severity of adverse reaction	**Encorafenib**
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	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
• First occurrence of any Grade 4 adverse reaction	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.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib should be permanently discontinued.

Table 3: Recommended dose modifications for binimetinib when used in combination with encorafenib

Severity of adverse reaction	**Binimetinib**
Cutaneous reactions	
• Grade2	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 Grade2.
• Grade 3	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	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.
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: o LVEF is at or above the LLN o 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.
Rhabdomyolysis/Creatine phosphokinase (CK) 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 > 10x ULN) 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 > 5x ULN) 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.

Venous thromboembolism (VTE)	
• 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.
Liver laboratory abnormalities	
• Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x - ≤ 5x upper limit of normal (ULN)	Binimetinib dose should be maintained. If no improvement within 2 weeks, 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 > 5x ULN and blood bilirubin > 2x ULN)	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or • If not improved, binimetinib should be permanently discontinued.
• First occurrence of Grade 4 (AST or ALT > 20 ULN)	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or • If not improved, binimetinib should be permanently discontinued. Or, binimetinib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue binimetinib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Binimetinib should be permanently discontinued.
Interstitial lung disease (ILD)/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.

Table 4: Recommended dose modifications for <u>binimetinib</u> (used in combination with encorafenib) for other adverse reactions

Severity of adverse reaction	**Binimetinib**
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or • If not improved, binimetinib should be permanently discontinued.
• First occurrence of Grade 4 adverse reactions	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or • If not improved, binimetinib should be permanently discontinued. Or, binimetinib should be permanently discontinued binimetinib
• Recurrent Grade 3 adverse reactions	It should be considered to permanently discontinue binimetinib.
• Recurrent Grade 4 adverse reactions	Binimetinib should be permanently discontinued.

Repeat every 28 days

Day	Drug	Dose	Route	Administration
1	**Encorafenib**	450mg	PO	OD swallowed whole with water. (Available as 50mg and 75mg capsules)
	Binimetinib	45mg	PO	BD 12 hours apart swallowed whole with water. (available as 15mg tablets)
	Metoclopramide	10mg	PO	Up to TDS PRN Do not take for more than 5 days continuously
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1, then only if specified.