

## Chemotherapy Protocol

### SKIN CANCER

#### Binimetinib-Encorafenib

##### Regimen

- Skin – Binimetinib-Encorafenib

##### Indication

- Unresectable or metastatic BRAF V600 mutation-positive melanoma where the following conditions apply;
  - the patient has a confirmed histological diagnosis of malignant melanoma which is BRAF V600 mutation positive.
  - the patient has unresectable stage III or stage IV disease that has been staged according to the AJCC 8th edition.
  - 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.
  - the patient has sufficient WHO performance status to tolerate treatment with the combination of encorafenib plus binimetinib
  - treatment will be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent
  - that 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.
  - that no treatment breaks of more than 6 weeks beyond the expected 4-weekly cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve). Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.

## Monitoring

- FBC, LFTs and U&Es every 4 weeks for 24 weeks, then every 12 weeks
- Serum electrolytes abnormalities, including magnesium and potassium should be corrected before treatment initiation and during treatment.
- LDH every 4 weeks for 24 weeks, then as clinically indicated
- Creatine phosphokinase every 4 weeks for 24 weeks, then as indicated
- Blood pressure baseline, then every 4 weeks initially, then as indicated
- Echo/MUGA at baseline then at 24 weeks unless clinically indicated (note this is not in line with the current SPC but reflects expert clinical practice)
- QTc interval baseline, after 4 weeks, then every 12 weeks as indicated
- Dermatologic evaluations at baseline then every 8 weeks while on therapy and for up to 24 weeks following discontinuation of treatment.
- Visual assessment at baseline and at each clinic visit
- BRAF V600 basis prior to starting treatment

## Toxicity

<b>Drug</b>	<b>Adverse Effect</b>
Binimetinib	Gastro-intestinal disturbances fatigue, abdominal pain, arthralgia or myalgia, hypertension, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease/pneumonitis, cardiac dysfunction, creatinine phosphokinase elevation and rhabdomyolysis, and venous thromboembolism.
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.

## Dose Modifications

The dose modifications listed are for haematological, liver and renal function only and some drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

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

## Dose modification levels

Dose level	Starting dose Level 0	Level -1	Level -2	Level -3
Encorafenib	450mg once a day	300mg once a day	200mg once a day	100mg once a day *
Binimetinib	45mg twice a day	30mg twice a day	Not recommended	

\* 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.

If treatment related toxicities occur, both binimetinib AND encorafenib should be simultaneously interrupted, dose reduced, or discontinued, with the exception of the following situations;

- Dose modifications necessary for just the binimetinib:
  - LVEF reduction
  - retinal pigment epithelial detachment (RPED) or retinal vein occlusion
  - ILD / pneumonitis, CK elevation / rhabdomyolysis
  - VTE
  
- Dose modifications necessary for just the encorafenib:
  - PPE
  - Uveitis
  - QT<sub>c</sub> prolongation

If binimetinib is temporarily interrupted, reduce encorafenib to 300mg once a day during the interruption (encorafenib 450mg once a day as a single agent is not well tolerated)

If binimetinib is permanently discontinued then consider if encorafenib should be discontinued.

### *Haematological*

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

### *Hepatic Impairment*

Reduce dose of encorafenib to 300mg in patients with mild hepatic impairment (Child-Pugh Class A). Encorafenib is not recommended in patients with severe hepatic impairment (Child-Pugh Class C)

AST/ALT (units/L)		Bilirubin (µmol/L)	Dose modifications (binimetinib and encorafenib)
Grade 2	and	any	Both agents doses should be maintained.  If no improvement occurs 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.  If no improvement within a further 2 weeks (4 weeks in total), 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	and	greater than 2x ULN	Both agents should be withheld for up to 4 weeks.  If improvement occurs within this time to grade 0 or 1 or the baseline level, binimetinib and encorafenib should be resumed at a reduced dose.  If there is no improvement, binimetinib and encorafenib should be permanently discontinued.
First occurrence of grade 4	and	any	Both agents should be withheld for up to 4 weeks.  If improvement occurs within this time to grade 0 or 1 or baseline level, binimetinib and encorafenib should be resumed at reduced dose.  If there is no improvement, binimetinib and encorafenib should be permanently discontinued.
Recurrent grade 3	and	greater than 2x ULN	Considered permanent discontinuation of both agents
Recurrent grade 4	and	any	Both agents should be permanently discontinued.

### Renal Impairment

For binimetinib no dose adjustment is recommended for patients with renal impairment.

There is no data for encorafenib in severe renal impairment, encorafenib should be used with caution in these patients.

### Cardiac

#### Binimetinib

For asymptomatic NCI-CTC grade 2 LVEF (absolute decrease in LVEF of greater than 10 % from baseline that is below lower limit of normal) binimetinib should be withheld for up to 4 weeks (and temporarily dose reduce encorafenib). 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 (and encorafenib) should be permanently discontinued.

In the event of NCI-CTC grade 3 or 4 LVEF decrease or symptomatic left ventricular dysfunction (LVD) binimetinib (and encorafenib) should be permanently discontinued.

### *Encorafenib*

For QTc greater 500ms but increased less than or equal to 60ms from baseline, withhold encorafenib (binimetinib may be continued). Once QTc less than or equal to 500ms, re-start treatment, with encorafenib at a reduced dose.

For QTc greater than 500ms and increased by more than 60ms from baseline, permanently stop encorafenib (and binimetinib).

### *Lung*

In the event of NCI-CTC grade 2 pneumonitis/ILD binimetinib should be withheld for up to 4 weeks (and temporarily dose reduce encorafenib).

If improved to NCI-CTC grade 0 or 1, binimetinib should be resumed at reduced dose, or if not resolved within 4 weeks, binimetinib (and encorafenib) should be permanently discontinued.

In the event of NCI-CTC grade 3 or 4 pneumonitis/ILD binimetinib (and encorafenib) should be permanently discontinued.

## Eye

Assess patients at each visit for symptoms of new or worsening visual disturbance. There should be a low threshold for a referral to ophthalmology.

<b>Uveitis (including iritis and iridocyclitis)</b>	
Grade 1 – 2 uveitis which does not respond to specific ocular therapy or grade 3 uveitis	<p>Interrupt encorafenib and binimetinib and repeat ophthalmic monitoring within 2 weeks.</p> <p>If uveitis is grade 1 and it improves to grade 0, resume treatment at the same dose.</p> <p>If uveitis is grade 2 or 3 and it improves to grade 0 or 1, resume treatment, but with a reduced dose of encorafenib.</p> <p>If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib and binimetinib should be permanently discontinued</p>
<b>Retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO)</b>	
Grade 2 - 3 RPED	<p>Interrupt binimetinib (<i>and dose reduce encorafenib for period of interruption only</i>) for up to 2 weeks, then repeat ophthalmic monitoring including visual acuity assessment.</p> <p>If improved to grade 0 or 1, resume binimetinib at same dose.</p> <p>If improved to grade 2, resume binimetinib at a lower dose.</p> <p>If not improved to grade 2, permanently discontinue treatment.</p>
Grade 4 RPED	Permanently discontinue binimetinib (and also encorafenib)
RVO	Permanently discontinue binimetinib (and also encorafenib)

### *Rhabdomyolysis/Creatine phosphokinase (CK) elevation*

For NCI-CTC grade 3 (CK greater than 5–10xupper limit of normal (ULN)) and asymptomatic, binimetinib dose should be maintained and it should be ensured that patient is adequately hydrated.

For NCI-CTC grade 4 (CK greater than 10xULN) asymptomatic binimetinib should be withheld (and temporarily dose reduce encorafenib) until improved to grade 0 or 1. It should be ensured that patient has adequate hydration.

For NCI-CTC grade 3 or 4 (CK greater 5xULN) with muscle symptoms or renal impairment binimetinib should be withheld (and temporarily dose reduce encorafenib) until improved to NCI-CTC grade 0 or 1.

- if resolved within 4 weeks, binimetinib should be resumed at a reduced dose.
- if not resolved binimetinib (and encorafenib) should be permanently discontinued.

## Skin

### Binimetinib

For NCI-CTC grade 2 rash binimetinib treatment should be maintained. If rash worsens or does not improve within 2 weeks with continuing treatment, binimetinib should be withheld until improved to NCI-CTC grade 0 or 1 and then resumed at the same dose, if it is a first occurrence or resumed at a reduced dose if a recurrent grade 2.

For NCI-CTC grade 3 rash binimetinib (and 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 a recurrent NCI-CTC grade 3.

For NCI-CTC grade 4 both binimetinib and encorafenib should be permanently discontinued.

### Encorafenib

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 (and binimetinib) 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 (and binimetinib) 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 (and binimetinib) 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 (binimetinib may be continued) 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 (binimetinib may be continued), 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.

### *Venous thromboembolism (VTE)*

For uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) less than or equal to NCI-CTC grade 3 binimetinib should be withheld (encorafenib may be continued).

- If improved to NCI-CTC grade 0 or 1, binimetinib should be resumed at a reduced dose
- If not improved, binimetinib (and encorafenib) should be permanently discontinued.

### *Other Toxicities*

Recurrent or intolerable grade 2 adverse reactions OR First occurrence of grade 3 adverse reactions	Binimetinib and encorafenib should be withheld for up to 4 weeks. <ul style="list-style-type: none"> <li>• if improved to grade 0 or 1 or baseline level, binimetinib and encorafenib should be resumed at reduced dose.</li> <li>• if not improved, binimetinib and encorafenib should be permanently discontinued.</li> </ul>
First occurrence of grade 4 adverse reactions	Binimetinib and encorafenib should be withheld for up to 4 weeks. <ul style="list-style-type: none"> <li>• if improved to grade 0 or 1 or baseline level, binimetinib and encorafenib should be resumed at reduced dose.</li> <li>• if not improved, binimetinib and encorafenib should be permanently discontinued.</li> </ul>
Recurrent grade 3 adverse reactions	Consider permanently discontinuing binimetinib and encorafenib
Recurrent grade 4 adverse reactions	Binimetinib and encorafenib should be permanently discontinued.



## [Regimen](#)

**28 day cycle continued for as long as there is clinical benefit, or development of unacceptable toxicity (12 cycles will be set in ARIA)**

Drug	Dose	Days	Route
Binimetinib	45mg twice a day	1-28	Oral
Encorafenib	450mg once a day	1-28	Oral

## [Administration Information](#)

- Encorafenib is available as 75mg and 50mg capsules.
- Binimetinib is available as 15mg tablets.
- Both binimetinib and encorafenib should be swallowed whole with water, with or without food.
- If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due.
- If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.
- In case of vomiting after administration of binimetinib or encorafenib, the patient should not re-take the dose and should take the next scheduled dose

## [Additional Information](#)

- Concomitant use of potent CYP3A enzyme inducers or inhibitors with encorafenib (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) should be avoided, as this may increase the risk of therapeutic failure and toxicity respectively.
- 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. Substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) should be administered with caution.
- Binimetinib is a potential inducer of CYP1A2. Sensitive substrates of CYP1A2 (e.g. duloxetine or theophylline) should be used with caution.
- Binimetinib is a weak inhibitor of OAT3, Sensitive substrates of OAT3 (e.g. pravastatin or ciprofloxacin) should be used with caution.

- Binimetinib is primarily metabolised through UGT1A1, UGT1A1 inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution.

### Coding

- Procurement – X70.8
- Delivery – X72.9

### References

1. Dummer R, Ascierto A, Gogas H 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
2. National Institute of Health and Clinical Excellence (2019). Technology Appraisal TA562. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma.

## REGIMEN SUMMARY

### Binimetinib-Encorafenib

#### Day One

#### Take Home Medicines

1. Binimetinib 45mg twice a day oral for 28 days  
Administration Instructions  
Oral SACT
2. Encorafenib 450mg once a day oral for 28 days  
Administration Instructions  
Oral SACT

## DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2019	None	Rebecca Wills Pharmacist  Dr Deborah Wright Pharmacist	Dr I Karydis 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 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 that occur as a result of following these guidelines.