Systemic Anti-Cancer Therapy Protocol

Encorafenib and Binimetinib Malignant Melanoma

PROTOCOL REF: MPHAENBISK (Version No: 1.1)

This protocol has been temporarily amended-please see the ORAL SACT OPERATIONAL CHANGES DURING COVID -19.

Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

- Unresectable stage III or stage IV BRAF V600 mutation positive malignant melanoma until disease progression or unacceptable toxicity.
- Patients not previously treated with a BRAF V6000 and MEK inhibitor for malignant melanoma.
- No treatment breaks for more than 6 weeks beyond the expected 4 weekly cycle length
- ECOG PS 0-1

Blueteq registration required: refer to blueteq for detailed eligibility criteria

Dosage:

Drug	Daily dosage	Route	Schedule
Binimetinib	45mg TWICE daily	Oral	Supplied every 28 days until disease progression or unacceptable toxicity.
Encorafenib	450mg ONCE daily	Oral	

Administration and Counselling Points:

- Binimetinib tablets are available as 15mg tablets.
- Encorafenib capsules are available as 50mg and 75mg capsules.
- Patients should be encouraged to take treatments with water and they may be taken with or without food. These oral medications should be swallowed whole, not crushed or chewed.
- In the case of vomiting after administration of either drug, the patient should not take an additional dose and should take the next scheduled dose.
- 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.
- Patient should avoid any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to start of treatment and until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.
- Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect their ability to drive or operate machinery.
- Binimetinib contains a small amount of lactose, which should be considered where patients have severe lactose intolerance.

Anti-emetic risk:

Mild emetogenicity

Dosing in renal and hepatic impairment:

Renal	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.

Hepatic	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 in these patients as they should usually be given in combination.

	Encorafenib	For patients with mild impairment, administration with encorafenib should be undertaken with caution at a reduced dose of 300mg OD. In the absence of clinical data, encorafenib treatment is not recommended in patients with moderate or severe hepatic impairment.

Drug interactions:

The number of affected medicinal products expected to interact with these drugs are extensive; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to CYP3A4, UGT1A1 inhibitors and inducers, CYP1A2 inducers, P-gp transport inducers, (refer to summary of product characteristics for a current list of potential medicine interactions)

Investigations:

	Baseline	Each cycle	Every 12 weeks	Follow-up
Informed Consent	X			
Medical Assessment	X		X	X
SACT Assessment (with toxicity assessment)		X	X	X
Weight	X	X	X	X
Imaging	X		X	X
FBC	X	X	X	X
U&Es	X	X	X	X
LFTs	X	X*	X	X
Creatinine phosphokinase (CK)	X	X**	X	X
Blood pressure and temperature measurements	X	X	X	X
ECG and Echo/MUGA scan	X	After 1st cycle then 12 weekly	X	As indicated
PS recorded	X	X	X	X
Dermatological examination	X	Every 2 months on therapy***	As indicated	As indicated up to six months after stopping treatment
Ophthalmic examination	X	X***	As indicated	As indicated

* If **ALT/AST** is greater than 3 times the upper limit of normal, seek medical review before continuing treatment

** If **CK level** is greater than 5 times the upper limit of normal, seek medical review before continuing treatment

*** If any **rash** or **ophthalmic symptoms** overserved/reported – escalate to ANP/medical review

Main Toxicities:

Pyrexia	**Pyrexia:** Therapy 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.
Cardiovascular	Deep vein thrombosis (DVT)/Pulmonary embolism (PE). QT prolongation. Haemorrhage. LVD (ejection fraction decreased, cardiac failure and ejection fraction abnormalities). Increases in blood pressure. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management Accessible here: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE
Ocular	Treatments are associated with ocular toxicities, these include papilledema, central serous retinopathy (CSR) and retinal vein occlusion (RVO), uveitis (including chorioretinitis, choroiditis, retinitis, vitritis, cyclitis, iridocyclitis, iritis, and uveitis).
Heamatological toxicity	Neutropenia, Anaemia, Thrombocytopenia
Dermatological reactions	Cutaneous toxicities including rash, acneiform dermatitis (trametinib), palmar-plantar erytrodysesthesia (hand-foot skin reaction or HFSR), hyperproliferative skin diseases (hyperkeratosis, keratoacanthoma), and cutaneous Cutaneous squamous-cell carcinomas/keratoacanthomas and new primary melanomas have been reported as a possible class effect of BRAF inhibitors. Dose interruptions or modifications are not required for squamous-cell carcinomas/keratoacanthoma.

Gastrointestinal disorders	Diarrhoea, nausea, vomiting constipation abdominal pain. Colitis and gastrointestinal perforation, pancreatitis including fatal outcome, have been reported.
Additional adverse reactions	Musculoskeletal and connective tissue disorders: Myalgia, pain in extremities, back pain. Rhabdomyolysis. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated. Fatigue, peripheral oedema, peripheral neuropathy, headaches, dizziness. Hepatic disorders, renal dysfunction, peripheral oedema.

Dose Modifications and Toxicity Management:

CTCAE version 4 Grade of toxicity	Action and Dose Modification
Grade 1	• Continue treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2 (tolerable)	• Monitor closely • Provide supportive care • Interrupt treatment if clinically indicated – when toxicity resolves to grade 1 or baseline, restart treatment at current dose level
Grade 3 (intolerable or recurrent Grade 2)	• Interrupt treatment for up to 4 weeks • Monitor closely • Provide supportive care • When toxicity resolves to grade 1 or baseline, restart treatment **reduced by one dose level,** if it does not improve, both drugs should be permanently discontinued. • If the grade 3 toxicity recurs, interrupt treatment • When toxicity resolves to grade 1 or baseline, restart treatment **reduced by another dose level,** if it does not improve, both drugs should be permanently discontinued.
Grade 4	• Interrupt treatment • Monitor closely • Provide supportive care • Restart with treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline, if it does not improve, both drugs should be permanently discontinued. • If the grade 4 toxicity recurs, either **permanently discontinue treatment or**, if the patient is clinically benefiting, continuation of treatment may be considered by consultant oncologist

For specific guidance on dose modifications for cardiac events, creatine phosphokinase (CK), venous thromboembolism (VTE), liver abnormalities and interstitial lung disease/pneumonitis please refer to the summary of product characteristics.

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)
Urgent ophthalmological assessment is recommended if patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on therapy. In patients who are diagnosed with RVO, treatment **should be permanently discontinued**.

Recommended dose modifications:

If treatment-related toxicities occur, for the majority of cases, both treatments should be simultaneously reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for encorafenib only (AEs related primarily to encorafenib) are palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis/iritis/iridocyclitis and QTc prolongation.

Exceptions where dose modifications are necessary for Binimetinib only (AEs primarily related to binimetinib) are: RPED, retinal vein occlusion, interstitial lung disease/pneumonitis, cardiac dysfunction, CK elevation, rhabdomyolysis and VTE.

Dose Level	Binimetinib	Encorafenib
Starting Dose	45mg twice daily	450mg once daily*
1st Dose reduction	30mg twice daily	300mg once daily
2nd Dose reduction	Discontinue	200mg once daily
3rd Dose reduction		There is limited data for dose reduction to 100mg once daily. If unable to tolerate 100mg once daily, discontinue.

*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 at 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450mg as a single agent.

Haematological Toxicity:

Proceed on day 1 if-

ANC ≥ 1 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week and refer to advice below-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

References:

1. National Institute for Health and Care Excellence (February 2019). Encorafenib with binimetinib for unresectable or metasatic BRAF V600 mutation-positive melanoma [TA 562].
2. Summary of Product Characteristics, Braftovi®, Encorafenib, Pierre Fabre Ltd., last updated February 2019, [accessed on 3rd May 2019]
3. Summary of Product Characteristics, Mektovi®, Binimetinib, Pierre Fabre Ltd., last updated February 2019, [accessed on 3rd May 2019]