Systemic Anti Cancer Treatment Protocol

VEMURAFENIB

PROTOCOL REF: MPHAMMEVEM
(Version No: 1.0)

Approved for use in:

BRAF V600 mutation-positive unresectable or metastatic melanoma

Dosage:

Drug	Daily dosage	Route	Schedule
Vemurafenib	960mg BD	Oral	1920mg in two divided doses until disease progression/unacceptable toxicity

Administration/directions:

Vemurafenib will be supplied every 4 weeks.

Patients should be encouraged to take one dose of Vemurafenib with food, to reduce the risk of gastric irritation.

Tablets are to be swallowed whole with water they should not be chewed or crushed.

If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.

Main Toxicities:

Vemurafenib	
Cutaneous Squamous Cell Carcinoma (cuSCC):	Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with vemurafenib. It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for evaluation and treated as per local standard of care. The prescriber should examine the patient monthly during and up to six months after treatment for cuSCC. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of vemurafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.
New primary melanoma:	Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.
Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC):	Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment. Anal examinations and pelvic examinations (for women) when considered clinically indicated. Following discontinuation of vemurafenib, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to local clinical practices.

Photosensitivity:	All patients should be advised to avoid sun exposure and to wear protective clothing and use a broad spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (Sun Protection Factor ≥ 30) when outdoors to help protect against sunburn. Sunscreen should be applied liberally to all exposed areas half an hour before going outdoors and reapplied at least every two hours.
Arthralgia:	Approximately 50% patients experience pain /discomfort in one or more joints that can be mild to debilitating. Arthralgia cannot be prevented, instead symptoms should be managed with regular analgesia such as paracetamol with/without a non-steroidal anti-inflammatory.
Ophthalmologic reactions:	Monitor patients routinely for serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion.
Prolongation of the QT interval:	QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated.
Dermatologic reactions:	Skin rashes tend to occur within days of commencing treatment. Patients reporting a rash may require a medical review as accurate telephone assessment can be difficult. Any development of intolerable grade 2/3 rashes, then the patient may be advised to interrupt dosing until assessment. Dry skin/scalp occurs widely amongst patients, onset can be delayed or immediate. Maintaining skin integrity is vital to reduce infection risk; patients should be taught how to apply skin care products and advised to bathe in lukewarm water, avoid tight fitting clothing and to choose cotton rich garments.

	In severe cases, a dermatologist review is advised

Investigations:

Investigation	Baseline	Each cycle	Month 1	Every 3 months	Every 6 months	Up to 6 months after discontinuation
Nursing review*		√				
Medical review	√		√	√		
FBC	√	√				
U&Es, LFTs, LDH & Mg^{2+}	√	√				
ECG	√		√	√		
CT scan	√			√		
Head and neck examination including oral exam. & palpation of lymph nodes	√			√		√
Skin review (cuSCC)	√		√	√		√

Toxicity management/ Dose Modifications:

The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).

Skin care management plan:

Grade	Management and advised treatment
GRADE 1 No symptoms. Rash covering <10% body surface area with or without symptoms(e.g. pruritus, burning, tightness)	Observe advise patients to have soap free washes Emollients - Cetraben cream

GRADE 2 Symptoms: itching or soreness affecting <50% of skin surface. With or without symptoms; limiting ADLs	Antihistamines - Hydroxine 10 – 20 mg (sedative antihistamine) Emollients - Cetraben Cream If persistent refer to dermatologist and consider topical steroids If intolerable consider Vemurafenib dose reduction (refer to Dr Marshall)
GRADE 3 Symptoms itching or soreness affecting >50% of skin surface. With or without symptoms, limiting self care ADLs	Refer to dermatologist Antihistamines - Hydroxyzine 10 – 20 mg (sedative antihistamine) Emollient Betnovate Ointment BD Topical steroids 1% Hydrocortisone Ointment for face Consider oral steroids: Prednisolone 0.5mg/kg OD (maximum 60mg/day) for 5-7days Interrupt vemurafenib until grade <1 (refer to Dr Marshall)
GRADE 3 Steven Johns Syndrome or toxic epidermal necrolysis, wide spread skin rash, with peeling or blister formation and mucosal involvement	**Immediate Dermatology referral** Admission to Burns Unit under plastics team (STHK) IV fluids and electrolytes Stop vemurafenib

QTc prolongation management plan:

QTc Interval	Recommended dose modification
QTc>500 ms at baseline	**Treatment not recommended.**
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	**Discontinue permanently**
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	**Discontinue permanently**

Dose Modifications:

Grade (CTCAE v4.0)	Recommended dose modification
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurrence of any grade 2 or 3 AE	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	**Discontinue permanently**
Grade 4	
1st occurrence of any grade 4 AE	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	**Discontinue permanently**

Hepatic impairment

Vemurafenib undergoes hepatic metabolism .There are only very limited data available in patients with moderate to severe hepatic impairment. Close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur, ECG monitoring every month during the first three months is recommended.

Data from clinical trials suggests increases in AST and ALT up to three times the upper limit of normal did not influence the apparent clearance of vemurafenib.

Renal impairment

Mild and moderate renal impairment does not influence the apparent clearance of vemurafenib (creatinine clearance >40 ml/min).

Vemurafenib should be used with caution in patients with severe renal impairment and patients should be closely monitored.

References:

Zelboraf 240 mg Film-coated Tablets.17/02/14 Summary of Product Characteristics. Roche Products limited, Hertfordshire. Available from www.medicines.org.uk/emc/medicine, last updated 21/03/2014.