Vemurafenib (skin)

Indication
BRAF V600 mutation-positive unresectable or metastatic melanoma in patients with a WHO performance status of 0-2.

(NICE TA269)

ICD-10 codes
Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-28*	Vemurafenib	960mg BD	PO

*Continuously until unacceptable toxicity or disease progression

Cycle frequency
As above

Number of cycles
Continuous until disease progression or unacceptable toxicity.

Administration
Vemurafenib is available as 240mg tablets.
Vemurafenib doses should be taken 12 hours apart, swallowed whole with water, not chewed or crushed.
Doses may be taken with or without food but consistent intake of both daily doses on an empty stomach should be avoided (as this may result in reduced levels of vemurafenib).
If a dose is missed it may be taken up to 4 hours before the next dose.
If the patient vomits an additional dose should not be taken but the next dose taken as usual.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Loperamide if required.
Antiemetics if required.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Magnesium	14 days

ECG (QTc < 500ms).

Investigations – pre subsequent cycles

Patients should be reviewed every 4 weeks.

Investigation	**Validity period** (or as per local policy)
FBC	Every 4 weeks
U+E (including creatinine)	Every 4 weeks
LFTs	Every 4 weeks
Magnesium	Every 4 weeks

ECG (QTc <500ms and <60ms increase from baseline). ECG should be monitored before treatment, after the first month and after any dose modifications. Further monitoring is recommended in patients with moderate to severe hepatic impairment (see hepatic impairment section).

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
QTc	<500ms and <60ms increase from baseline
Creatinine clearance (CrCl)	≥ 30ml/min
AST/ALT	≤ 2.5 x ULN (or <5 x ULN if liver metastases)

Dose modifications

- **Haematological toxicity**

Any haematological toxicity should be managed according to the grade of toxicity as per the table below.

- **Renal impairment**

Limited data available. Closely monitor if severe renal impairment.

- **Hepatic impairment**

Vemurafenib is mainly metabolised by the liver, however, no adjustment to the starting dose is recommended. Patients with moderate to severe hepatic impairment may have increased exposure to vemurafenib and require close monitoring, including monthly ECG monitoring for the first 3 months and then 3 monthly thereafter. Any liver abnormalities which develop after treatment has commenced should be managed according to the grade of toxicity as per the table below.

Deteriorating organ function should be discussed with the consultant as this may be a sign of disease progression.

- **Other toxicities**

Dose modification for any adverse drug reaction based on toxicity grading:

Toxicity Grade	Recommended Dose
Grade 1 or 2 (tolerable)	Maintain dose of vemurafenib
Grade 2 (intolerable) or 3	
1st occurrence	Interrupt treatment until grade 0 – 1. Resume at 720 mg BD (or 480 mg BD if the dose has already been lowered).
2nd occurrence or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume at 480 mg BD (or discontinue permanently if the dose has already been lowered to 480 mg BD)
3rd occurrence or persistence after 2nd dose reduction.	Discontinue permanently
Grade 4	
1st occurrence	Interrupt treatment until grade 0 – 1. Resume at 480 mg BD (or discontinue permanently if the dose has already been lowered to 480 mg BD) OR discontinue permanently
2nd occurrence	Discontinue permanently

Dose modifications for prolonged QT interval:

QTc Value	Recommended dose
QTc >500 ms at baseline	Treatment not recommended
QTc increased > 500 ms **and** >60 ms change from pre-treatment value	Discontinue permanently
1st occurrence of QTc >500 ms **and** change from pre-treatment value <60 ms	Interrupt treatment* until QTc decreases below 500 ms. Resume dosing at 720 mg BD(or 480 mg BD if the dose has already been lowered).
2nd occurrence of QTc > 500 ms **and** change from pre-treatment value < 60 ms	Interrupt treatment* until QTc decreases below 500 ms. Resume dosing at 480 mg BD(or discontinue permanently if the dose has already been lowered to 480mg BD).
3rd occurrence of QTc > 500 ms **and** change from pre-treatment value < 60 ms	Discontinue permanently

* Also ensure any electrolyte abnormalities (including magnesium) are corrected and any risk factors for prolonged QTc are controlled.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Photosensitivity
Severe skin reactions, including Stevens-Johnson syndrome
Cutaneous squamous cell carcinoma
Non-cutaneous squamous cell carcinoma
QT prolongation
Hypersensitivity reactions
Ophthalmic reactions, including uveitis

- **Frequently occurring side effects**

Anorexia
Fatigue
Headache
Cough
Arthralgia, myalgia

Rash
Pruritis
Nausea and vomiting
Diarrhoea
Alopecia
Raised LFTs

- **Other side effects**

Palmar-plantar erythema

Significant drug interactions – for full details consult product literature/ reference texts

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to vemurafenib.

Inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir): use with caution

Coumarin anticoagulants, e.g. Warfarin: monitor INR closely

Combined oral contraceptive pill: the efficacy of the contraceptive pill may be reduced.

Medications which prolong QT interval (e.g. amiodarone, quinidine, sotalol, clarithromycin): avoid co-administration.

Ipilimumab: concurrent administration of ipilimumab and vemurafenib is not recommended.

Additional comments

Avoid sun exposure due to risk of sensitivity reactions. Patients should be advised to wear protective clothing and sunscreen and lip balm (SPF 30+).

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 269 accessed 14 May 2014 via www.nice.org.uk
- Summary of Product Characteristics – Vemurafenib (Roche) accessed 14 May 2014 via www.medicines.org.uk
- Chapman, P et al; NEJM 2011; 364: 2507-2516

Written/reviewed by: Dr T Tillett (Consultant Oncologist, Royal United Hosptial, Bath)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

Date: 11 December 2014