Chemotherapy Protocol

SKIN CANCER

VEMURAFENIB

Regimen

- Skin – Vemurafenib

Indication

- Vemurafenib is recommended as an option for the treatment of BRAF mutation positive unresectable or metastaic melanoma
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Vemurafenib	Arthalgia, fatigue, nausea, alopecia, pruritus, hypersensitivity reaction, skin rashes and photosensitivity, headache, QT prolongation and increased risk of arrhythmias, eye symptoms, increased liver transaminases and risk of secondary carcinoma

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, LFT's and U&E's including magnesium prior to day one of each cycle
- Baseline chest CT and then six monthly
- Baseline ECG, repeated after one month and then when required such as after dose changes. Additional ECG monitoring is required in patients with moderate to severe hepatic impairment, monthly for 3 months, then 3 monthly or as clinically indicated
- BRAF V6000 status prior to starting therapy

Dose Modifications

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

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

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

Haematological

Prior to prescribing the following criteria must be met.

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

Hepatic Impairment

There is limited data available in patients with hepatic impairment. Vemurafenib is cleared by the liver, patients with moderate to severe hepatic impairment may have increased exposure and should be closely monitored. No adjustment to the starting dose is needed for patients with mild hepatic impairment. Extended ECG monitoring is required in patients with moderate/ severe hepatic impairment.

Renal Impairment

There is limited data available for the use of vemurafenib in patients with renal impairment. There may be a risk of increased exposure in patients with severe renal impairment. These patients should be closely monitored.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Grading (CTCAE v4)	Vemurafenib Dose Modification Algorithms
Grade 1 or Grade 2 (tolerable)	Continue treatment at same dose; monitor as clinically indicated.
Grade 2 (intolerable) or Grade 3	Step 1. Interrupt treatment until toxicity reduced to grade 1 or below Step 2. - First occurrence: Resume dosing at 720 mg twice a day (or 480 mg twice a day if previously reduced) - Second occurrence or persistent toxicity: Resume dosing at 480 mg twice a day (or discontinue permanently if previously reduced) Third occurrence: Discontinue permanently

Grade 4	Step 1. Discontinue permanently or Interrupt treatment until toxicity reduced to grade 1 or below. (discuss with the consultant) Step 2. (if interrupted) - First occurrence: Resume dosing at 480 mg twice a day (or discontinue permanently if previously reduced) Second occurrence: Discontinue permanently

Heart

QTc Value	Vemurafenib Dose Modification Algorithms
QTc greater than 500 ms at baseline	Treatment not recommended.
QTc increase meets values of both Greater than 500 ms and Greaer than 60 ms change from pre-treatment baseline values	Discontinue permanently
QTc measures as greater than 500 ms and less than 60 ms change from pre-treatment baseline values	Step 1. Interrupt treatment until QTc reduced to < 500 ms Correct electrolyte imbalances (incl. Mg) Assess for cardiac risk factors Step 2. First occurrence: Resume dosing at 720 mg twice a day (or 480 mg twice a day if previously reduced) Second occurrence Resume dosing at 480 mg twice a day (or discontinue permanently if previously reduced) Third occurrence Discontinue permanently

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria

Drug	Dose	Days	Route
Vemurafenib	960mg twice a day	Continuous	Oral

Dose Information

- Dose may be modified in 240mg dose steps based on individual safety and tolerability (see dose modifications section).
- Daily dose below 480mg twice daily is not recommended.

Administration Information

- Take tablets with or without food (consistent intake of both daily doses on an empty stomach should be avoided)

Additional Information

- Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), or a long QT syndrome (QTc > 500ms) or who are taking medicinal products known to prolong the QT interval.

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed in relation to vemurafenib.

Coding

- Procurement – X71.5

- Delivery – X73.1

References
1. Chapman PB, Houschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364; 2407-2416.

REGIMEN SUMMARY

Vemurafenib

Day One

1. Vemurafenib 960mg twice a day oral
   Administration Instructions
   Take tablets with or without food (consistent intake of both daily doses on an empty stomach should be avoided)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 2015	None	Dr Deborah Wright Pharmacist	Prof C Ottensmeier Consultant Medical Oncologist Dr M Wheater 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 Hospital 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 which occur as a result of following these guidelines.