Chemotherapy Protocol

SKIN CANCER

DABRAFENIB

Regimen

- Skin – Dabrafenib

Indication

- Dabrafenib is recommended as an option for the first line treatment of unresectable BRAF V600 mutation positive melanoma.
- Dabrafenib is recommended as an option for the treatment of unresectable BRAF V600 mutation positive melanoma in those who have had a severe intolerance to vemurafenib that has necessitated the discontinuation of vemurafenib within two months of starting treatment.
- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Dabrafenib	Headache, pyrexia, chills, cough, arthralgia, myalgia, fatigue, nausea, vomiting, rash, pruritis, hyperkeratosis, PPE, uveitis, diarrhoea, asthenia, renal failure, pancreatitis, QT prolongation, LVEF decrease, hypophosphataemia, hyperglycaemia, anorexia, alopecia, constipation, risk of secondary carcinoma (cutaneous or non-cutaneous squamous cell 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. 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 dabrafenib 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.

NCI CTC Grade	Dabrafenib dose
Grade 1 or Grade 2 (tolerable)	Continue and monitor
Grade 2 (intolerable) or Grade 3	Interrupt treatment until resolved to grade 0-1 then - First occurrence: Reduce to 100mg twice a day - Second occurrence: Reduce to 75mg twice a day - Third occurrence: Reduce to 50mg twice a day
Grade 4	Discontinue permanently or discuss with consultant - interrupt therapy until resolved to grade 0-1 then reduce to 100mg twice a day. If grade 4 toxicity recurs, discontinue permanently

Heart

QTc Value	Dabrafenib Dose
QTc more than 500 ms at baseline	Treatment not recommended
QTc values More than 500 ms and less than 60 ms change from pre-treatment baseline values	Interrupt treatment until QTc reduced to Less than 500 ms Correct electrolyte imbalances (incl. Mg) Assess for cardiac risk factors - First occurrence: Reduce to 100mg twice a day - Second occurrence: Reduce to 75mg twice a day - Third occurrence: Reduce to 50mg twice a day
QTc values More than 500 ms and more than 60 ms change from pre-treatment baseline values	Discontinue permanently

Regimen

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

Drug	Dose	Days	Route
Dabrafenib	150mg twice a day	Continuous	Oral

Dose Information

- Dose may be modified in 50mg or 75mg dose steps based on individual safety and tolerability (see dose modifications section).

Administration Information

- Swallow whole with water on an empty stomach, either 1 hour before, or 2 hours after a meal, and approximately 12 hours apart.
- Do not chew or crush.

Additional Information

- Treatment with dabrafenib 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 dabrafenib.

Coding

- Procurement – X70.8
- Delivery – X73.1

References
1. Hauschild A et al. Dabrafenib in BRAF mutated metastatic melanoma; a multicentre open label phase three randomised controlled trial. Lancer 2012; 380: 358-365

Dabrafenib

Day One

1. Dabrafenib 150mg twice a day oral
   Administration Instructions
   Swallow whole with water on an empty stomach, either 1 hour before or 2 hours after a meal, and approximately 12 hours apart.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 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.