Chemotherapy Protocol

SKIN CANCER

DABRAFENIB-TRAMETINIB

Regimen

- Skin – Dabrafenib-Trametinib

Indication

- The combination of dabrafenib and trametinib is recommended as an option for the first line treatment of stage III (unresectable) or stage IV BRAF V600 mutation positive malignant melanoma.
- 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)
Trametinib	LVEF reduction, pneumonitis, visual disturbances

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 the patient is 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 of either agent is necessary 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 or trametinib 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.

Dose Level	Trametinib Dose (monotherapy or in combination)	Dabrafenib Dose (combination with trametinib)
Starting dose	2mg once a day	150mg twice a day
1st reduction	1.5mg once a day	100mg twice a day
2nd reduction	1mg once a day	75mg twice a day
3rd reduction	1mg once a day	50mg twice a day

Dose adjustments for trametinib below 1mg per day is not recommended

NCI CTC Grade	Dabrafenib dose	Trametinib
Grade 1 or grade 2 (tolerable)	Continue and monitor	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	Interrupt therapy until toxicity is grade 0 to 1 and reduce by one dose level when resuming therapy.
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	Discontinue permanently, or interrupt therapy until grade 0 to 1 and reduce by one dose level when resuming therapy.

Cardiac

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

Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value then do not modify the dose of dabrafenib but withhold the trametinib for up to four weeks.

If improved to normal LVEF value, resume at a lower dose level. If not improved to normal LVEF value, permanently discontinue the trametinib.

Ocular

If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If RPED is diagnosed follow the following dose modification schedule.

For a NCI CTC grade 1 reaction continue treatment with retinal evaluation until resolution of symptoms. If symptoms worsen withhold trametinib for up to three weeks.

NCI CTC grade 2-3 retinal pigment epithelial detachments (RPED), do not modify the dose of dabrafenib, but withhold trametinib for up to three weeks. If improved to NCI CTC grade 0-1, resume at a lower dose level. If not improved, permanently discontinue.

For retinal vein occlusion, do not modify the dose of dabrafenib. However, permanently discontinue the trametinib.

Uveitis and iritis, then withhold dabrafenib for up to six weeks. If improved to NCI-CTC grade 0-1, then resume at the same dose. If not improved, permanently discontinue the dabrafenib. Do not modify the dose of trametinib.

Interstitial lung disease (ILD) / Pneumonitis

Withhold trametinib in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis.

Pyrexia

If pyrexia occurs first evaluate the patient clinical to rule out infection or hypersensitivity.

There is little need to reduce the dose of or stop treatment with trametinib for pyrexia.

In the first instance administer anti-pyretic treatment, for example, paracetamol or ibroprofen if clinically indicated, and consider interrupting dabrafenib but continue trametinib. Once pyrexia resolves to baseline, restart dabrafenib at the same dose level. If the fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib by one dose level and begin oral corticosteroids (prednisone 10 mg or equivalent) for at least 5 days or as clinically indicated.

For a second event, treat initially as for a first event and consider oral corticosteroids (such as prednisone 10mg) for at least 5 days or as clinically indicated.

For subsequent events then interrupt dabrafenib but continue trametinib. Once the

pyrexia resolves to baseline, restart the dabrafenib (consider dose reduction by one level)

Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia. If corticosteroids have been tapered and pyrexia recurs, restart corticosteroids. If corticosteroids cannot be tapered or escalating doses are required, consider alternative therapies.

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
Trametinib	2mg once a day	Continuous	Oral

Dose Information

- Dose of dabrafenib may be modified in 50mg or 75mg dose steps based on individual safety and tolerability.
- If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next dose.
- Dabrafenib is available as 50mg and 75mg capsules
- If a dose of trametinib is missed, only take the dose if it is more than 12 hours until the next scheduled dose.
- Trametinib is available as 0.5mg and 2mg tablets.
- The dose of trametinib should not be lower than 1mg once a day.

Administration Information

- Swallow the dabrafenib whole with water on an empty stomach, either 1 hour before, or 2 hours after a meal, and approximately 12 hours apart. Do not crush or chew
- Trametinib should be taken, at least 1 hour before or 2 hours after a meal.

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 and trametinib.

Coding

- Procurement – X71.5
- Delivery – X73.1

References
1. Robert C, Karaszewska, B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372:30-39

REGIMEN SUMMARY

Dabrafenib-Trametinib

Day One

1. Dabrafenib 150mg twice a day continuous 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.

2. Trametinib 2mg once a day continuous oral
   Administration Instructions
   Swallow whole with water on an empty stomach, either 1 hour before or 2 hours after a meal.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Oct 2016	None	Dr Deborah Wright Pharmacist	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 that occur as a result of following these guidelines.