Systemic Anti-Cancer Treatment Protocol

Dabrafenib and Trametinib Malignant Melanoma

PROTOCOL REF: MPHADTMSK
(Version No: 1.0)

Approved for use in:

- Unresectable or metastatic melanoma with a BRAF V600 mutation.
- Adjuvant treatment of completely resected stage III BRAF V600 positive malignant melanoma for up to 12 months.

******** Blueteq registration required ********

Dosage:

Day	Drug	Daily dosage	Route	Schedule
Daily	Dabrafenib	150mg TWICE DAILY	Oral	Until disease progression or unacceptable toxicity. In the adjuvant setting – for a maximum 12 months.
Daily	Trametinib	2mg ONCE DAILY	Oral	

Administration:

Patients should be encouraged to take treatments with approximately 200 ml of water under fasting conditions, either 1 hour before or 2 hours after a meal.

These oral medications should be swallowed whole, not crushed or chewed.

The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose.

Patient should avoid any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to start of treatment and until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.

Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect their ability to drive or operate machinery.

Investigations

Investigation	Baseline (Medical r/v)	Each cycle (Nursing r/v)	Every 12 weeks (Medical r/v)	Follow-up (Medical r/v After Completion)
Informed Consent	√			
Medical review	√		√	√
Nursing review		√		
Weight	√	√	√	√
Imaging^	√		√	√
FBC	√	√	√	√
U & E, LFTs	√	√	√	√
Toxicities documented		√	√	√
Blood pressure and temperature measurement	√	√	√	√
ECG	√	*	As indicated	As indicated
PS recorded	√	√	√	√
Dermatological exam	√	**	As indicated	As indicated

* If any complaints of chest pain/shortness of breath/palpitation or hypertension present – escalate to ANP/medical review for ECG.

** If any rash observed/reported – escalate to ANP/medical review.

^ 6 monthly CT scan for adjuvant indication

Main Toxicities:

Pyrexia	**Pyrexia:** Therapy with dabrafenib should be interrupted if the patient's temperature is ≥ 38.5ºC. Patients should be evaluated for signs and symptoms of infection. Dabrafenib can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. If fever is associated with other severe signs or symptoms, dabrafenib should be restarted at a reduced dose once fever resolves and as clinically appropriate.
Cardiovascular	Deep vein thrombosis (DVT)/Pulmonary embolism (PE). QT prolongation. Decreases in LVEF. Increases in blood pressure. Reduced ejection fraction. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management Accessible here: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE
Ocular	Both dabrafenib and trametinib are associated with ocular toxicities, these include papilledema, central serous retinopathy (CSR) and retinal vein occlusion (RVO) associated with trametinib, and uveitis (including chorioretinitis, choroiditis, retinitis, vitritis, cyclitis, iridocyclitis, iritis, and uveitis) associated with dabrafenib.
Heamatological toxicity	Neutropenia, Anaemia, Thrombocytopenia
Dermatological reactions	Cutaneous toxicities including rash, acneiform dermatitis (trametinib), palmar-plantar erytrodysesthesia (hand-foot skin reaction or HFSR), hyperproliferative skin diseases (hyperkeratosis, keratoacanthoma), and cutaneous Cutaneous squamous-cell carcinomas/keratoacanthomas and new primary melanomas have been reported as a possible class effect of BRAF inhibitors. Dose interruptions or modifications are not required for squamous-cell carcinomas/keratoacanthoma.
Gastrointestinal disorders	Diarrhoea, nausea, vomiting constipation abdominal pain.

	Colitis and gastrointestinal perforation, pancreatitis including fatal outcome, have been reported.
Respiratory	Cough, dyspnea, pneumonitis, interstitial lung disease
Additional adverse reactions	Rhabdomyolysis. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated. Hepatic disorders, renal dysfunction, peripheral oedema.

Dose Modifications and Toxicity Management:

CTCAE version 4 Grade of toxicity	Action and Dose Modification
Grade 1	• Continue treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2 (tolerable)	• Monitor closely • Provide supportive care • Interrupt treatment if clinically indicated. When toxicity resolves to grade 1 or baseline, restart treatment at current dose level
Grade 3 (intolerable Grade 2)	• Interrupt treatment • Monitor closely • Provide supportive care • When toxicity resolves to grade 1 or baseline, restart treatment **reduced by one dose level** • If the grade 3 toxicity recurs, interrupt treatment • When toxicity resolves to grade 1 or baseline, restart treatment **reduced by another dose level**
Grade 4	• Interrupt treatment • Monitor closely • Provide supportive care • Restart with treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline • If the grade 4 toxicity recurs, either **permanently discontinue treatment or**, if the patient is clinically benefiting, continuation of treatment may be considered my consultant oncologist

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)
Urgent ophthalmological assessment is recommended if patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on trametinib therapy. In patients who are diagnosed with RVO, treatment with **trametinib, 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 dose modification schedule in the table

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily.
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

Recommended dose modifications

Dose Level	Dabrafenib	Trametinib
Starting Dose	150 mg twice daily	2mg once daily
1ST Dose reduction	100 mg twice daily	1.5mg once daily
2nd Dose reduction	75 mg twice daily	1mg once daily
3rd Dose reduction	50mg twice daily	1mg once daily

Haematological Toxictiy:

Proceed on day 1 if-

ANC ≥ 1 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week and refer to advise below-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Dosing in hepatic impairment:

Dabrafenib and Trametinib No dosage adjustment is required for combination treatment in patients with mild hepatic impairment. Combination treatment should be used with caution in patients with moderate or severe hepatic impairment. There are no clinical data available in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined.

Dosing in renal impairment:

Trametinib No dosage adjustment is required in patients with mild or moderate renal impairment. There are no data of trametinib use in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Dabrafenib No data are available in patients with severe renal impairment. Mild to moderate renal impairment does not appear to affect clearance of dabrafenib.

Drug interactions

Trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (e.g. carboxyl-esterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. However drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.

The number of affected medicinal products expected to interact with the dabafenib is extensive; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to those outlined in the tablet below, (refer to summary of product characteristics for a current list of potential medicine interactions)

Strong inducers of CYP3A4 or CYP2C8, concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsants	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	St-John's wort
Strong inhibitors of CYP3A4, or CYP2C8 increasing concentrations of dabrafenib	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Antiretroviral	ritonavir, saquinavir, atazanavir

References:

Mekinist film-coated tablets, summary of Product Characteristics, Novartis Pharmaceuticals UK Ltd. 30/06/2014. Available from www.medicines.org.uk/emc/medicine. Last updated 25/02/16.

Tafinlar 50 mg & 75 mg hard capsules, summary of Product Characteristics, Novartis Pharmaceuticals UK Ltd. 30/06/2014. Available from www.medicines.org.uk/emc/medicine. Last updated 26/08/13.