DABRAFENIB & TRAMETINIB

Combination therapy for BRAF V600 mutation positive unresectable or metastatic melanoma
NICE approved June 2016

Blueteq registration is required before treatment may start

Drug/Dosage:	Dabrafenib	150mg po	twice daily continuous therapy
	Trametinib	2mg po	once daily continuous therapy

Administration: Dabrafenib available as 50mg and 75mg capsules (patients to be started on 3 x 50mg capsules per dose, to minimise wastage in the event of a dose reduction)
Trametinib is available as 2mg and 0.5mg tablets, which must be stored in the fridge.
Both dabrafenib and trametinib should be taken at least 1 hour before, or at least 2 hours after, a meal.
Both dabrafenib and trametinib should be swallowed whole with water; do not chew or crush, and do not mix with food or liquids. Grapefruit and grapefruit juice should be avoided.

Frequency: continue for as long as there is clinical benefit, or unacceptable toxicity.

Main Toxicities: adverse reactions reported in ≥ 20% patients: pyrexia, fatigue, nausea or vomiting, headache, chills, diarrhoea, rash, arthralgia, hypertension, cough

Anti- emetics: mildly emetogenic

Regular:	FBC	every 4 weeks for 3 months, then every 3 months
Investigations:	LFTs & U&Es	every 4 weeks for 6 months, then every 3 months
	LDH	every 4 weeks for 3 months, then whenever a blood test is done
	Blood pressure	baseline, then every 4 weeks
	Echo/MUGA	baseline, after 1 month, then, if clinician indicates, every 3 months

Clinical examination and orthogonal measurement +/- photography of accessible lesions at baseline, then monthly throughout treatment (see Comments)
Whole body PET or CT neck, chest, abdomen and pelvis (NCAP) baseline, then CT NCAP every 3 months

Comments: Any suspicious skin lesions should be excised, sent for evaluation, and managed according to local practice. In patients who develop cutaneous squamous cell carcinoma or new primary melanoma, treatment may continue without dose adjustment.

Interactions: Concomitant use of potent enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) should be avoided, as this may increase the risk of therapeutic failure.
Concomitant use of strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin) may increase the risk of dabrafenib-associated toxicity.
Dabrafenib is a CYP3A4 enzyme inducer. Interactions with medicines which are eliminated via CYP3A4 metabolism are expected. Onset of induction is likely to be within 3 days of starting dabrafenib. This is one of the most important enzymes involved in the metabolism of drugs, so it is not possible to provide a complete list of medicines eliminated via this pathway. Examples include fentanyl, clarithromycin, cabazitaxel, warfarin, anti-epileptics, calcium channel blockers, dexamethasone, levothyroxine, simvastatin. If in doubt, check with pharmacy.
If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed by monitoring of efficacy or plasma concentrations, these medicines should be avoided or used with caution.

Reason for Update: need for QT monitoring removed	Approved by Consultant: Dr M Ajaz
Version: 4	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 3	Date: 28.3.17
Prepared by: S Taylor	Checked by: C Tucker

The efficacy of contraceptive pills metabolised by CYP3A4 may be decreased.
Theoretical risk that drugs which raise gastric pH may decrease dabrafenib bioavailability.

Dose Modifications The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation. N.B. Dose modifications of dabrafenib below 50mg bd, or trametinib below 1mg od, are not recommended.

If treatment related toxicities occur, both treatments should be simultaneously dose reduced, interrupted or discontinued, *with the exception of the following:*

- Dose modifications only necessary for dabrafenib in the event of pyrexia, uveitis or RAS +ve non cutaneous malignancies
- Dose modifications only necessary for trametinib in the event of LVEF reduction, retinal vein occlusion, retinal pigment epithelial detachment, or interstitial lung disease/pneumonitis.

Pyrexia: Dabrafenib should be interrupted if the patient's temperature is ≥ 38.5°C. Patients should be evaluated for signs and symptoms of infection. Treatment may be restarted once the fever resolves with paracetamol or non-steroidal anti-inflammatory agents.
If the fever is associated with other severe signs and symptoms (e.g. severe rigors, hypotension, acute renal insufficiency), dabrafenib should be restarted with a dose reduction once the fever resolves, as clinically appropriate. No dose reduction is required for trametinib.

Hypertension: Hypertension should be controlled using standard therapy as appropriate

LVEF: Interrupt trametinib in patients who have an asymptomatic, absolute decrease of > 10 % in LVEF compared to baseline and is below 50%. If LVEF recovers, trametinib may be restarted but the dose reduced by one dose level (2mg→1.5mg; 1.5mg→ 1mg) with careful monitoring. No dose reduction required for dabrafenib.

Visual problems: There should be a low threshold for a referral to ophthalmology.

If uveitis is diagnosed, and does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation, and then restarted reduced by one dose level as in the "Any other side effect" table below. No dose modification is required for trametinib.

If retinal pigment epithelial detachment (RPED) is diagnosed, follow the trametinib dose modification schedule below (no dose modification of dabrafenib is required):

Grade 1 RPED	Continue treatment, with retinal evaluation every month.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks of stopping trametinib	Resume trametinib at a lower dose (2mg→1.5mg; 1.5mg→ 1mg), or discontinue trametinib in patients taking trametinib 1mg daily
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib

In patients who are diagnosed with retinal vein occlusion, treatment with trametinib should be permanently discontinued. No dose modification of dabrafenib is required.

Interstitial lung disease / pneumonitis: Withhold trametinib in patients with suspected ILD or pneumonitis, and permanently discontinue if diagnosis of ILD or pneumonitis confirmed.
No dose modification of dabrafenib is required.

Any other side effect:

Grade	Recommended Dose Modification
Grade 1 or 2 (tolerable)	Maintain dose level of both drugs and monitor
Grade 2 (intolerable) or Grade 3	Interrupt both drugs until Grade 0 – 1, then • 1st occurrence: reduce dabrafenib to 100mg bd and trametinib to 1.5mg od • 2nd occurrence: reduce dabrafenib to 75mg bd and trametinib to 1mg od • 3rd occurrence: reduce dabrafenib to 50mg bd and maintain trametinib at 1mg od
Grade 4	Discontinue both drugs permanently *or* Interrupt until Grade 0 – 1, then reduce both drugs by one dose level, as above, when resuming therapy.

Hepatic Impairment: No dose adjustment is required for either drug, in patients with mild hepatic impairment. Use both drugs with caution in patients with moderate or severe hepatic impairment; there are no clinical data, and no dose adjustment can be recommended.

Renal Impairment: No dose adjustment of either drug is required for patients with mild or moderate renal impairment. Use both drugs with caution, in patients with severe renal impairment.

Reference:
Robert, C et al; NEJM 2015; 372 : 30 – 39
Long, G ; NEJM 2014 ; 371 : 1877 - 1888