SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Dabrafenib
Malignant Melanoma

PROTOCOL REF: MPHADAMSK
(Version No. 1.2)

Approved for use in:

Melanoma: Advanced (unresectable or metastatic) melanoma in adults. Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Dosage:

Drug	Daily Dose	Route	Frequency
Dabrafenib	**150mg BD**	**Oral**	**300mg in two divided doses until disease progression/unacceptable toxicity**

Administration /directions

- Dabrafenib oral medication will be supplied every 4 weeks
- 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.
- Dabrafenib tablets are to be swallowed whole with water they should not be chewed or crushed.
- If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.
- 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.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

Nil

Main Toxicities

System Organ Class	Adverse Reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Cutaneous squamous cell carcinoma, Seborrhoeic keratosis, Basal cell carcinoma, Acrochordon (skin tags)
Metabolism and nutrition disorders	Decreased appetite, Hypophosphataemia, Hyperglycaemia
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, constipation
Skin and subcutaneous tissue disorders	Hyperkeratosis, Alopecia, Rash, Palmar-plantar erythrodysaesthesia syndrome, Dry skin, Pruritus, Actinic keratosis, Skin lesion, Erythema, Photosensitivity
Musculoskeletal and connective tissue disorders	Arthalgia, Myalgia, Pain in extremity
General disorders and administration site conditions	Pyrexia, Fatigue, Chills, Asthenia, influenza-like illness

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

Toxicity Management:

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.

Event	Adverse Event Management	Action and Dose modification
1st	If patient well, with no signs infection: • Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment • Encourage patient to increase oral fluids to prevent dehydration If patient unwell: • Clinical evaluation for infection and hypersensitivity • Check FBC and chem. profile • Hydration if required	**Interrupt dabrafenib** • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level • If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd	If patient well, with no signs infection: • Regular anti-pyretic treatment- paracetamol 1g QDS/Ibuprofen 200mg TDS x 3 days • Encourage patient to increase oral fluids to prevent dehydration • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated If patient unwell: • Clinical evaluation for infection and hypersensitivity • Check FBC and chem. profile • Hydration if required	**Interrupt dabrafenib** • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level • If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
Subsequent	If patient well, with no signs infection: • Regular anti-pyretic treatment- paracetamol 1g QDS/Ibuprofen 200mg TDS x 3 days • Encourage patient to increase oral fluids to prevent dehydration • Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia • If corticosteroids have been tapered and pyrexia recurs, restart steroids If patient unwell: • Clinical evaluation for infection and hypersensitivity • Check FBC and chem. profile • Hydration if required	**Interrupt dabrafenib** • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level** • If dabrafenib must be reduced to <75mg BD, permanently **discontinue dabrafenib.**

Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and

increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

Dermatologic reactions: Skin rashes tend to occur within days of commencing treatment. Patients reporting a rash may require review by a HCP as accurate telephone assessment can be difficult. Any development of intolerable grade 2/3 rashes, then the patient may be advised to interrupt dosing until assessment. Dry skin/scalp occurs widely amongst patients, onset can be delayed or immediate. Maintaining skin integrity is vital to reduce infection risks; patients should be taught how to apply skin care products and advised to bathe in lukewarm water, avoid tight fitting clothing and to choose cotton rich garments.

In severe cases, a dermatologist review is advised.

Skin care management plan:

	Grade	Management	Advised
1	No symptoms. Rash covering <10% BSA with or without symptoms (e.g. puritus, burning, tightness)	Observe	Soap free washes
		Emollients	Cetraben cream
2	Symptoms: itching or soreness affecting <50% of skin surface. With or without symptoms; limiting ADLs	Antihistamines	Fexofenadine 120mg OD
		Emollients	Cetraben cream
		If persistent refer to dermatologist and consider topical steroids	
		If intolerable consider Dabrafenib dose reduction.	
3	Symptoms: itching or soreness affecting >50% of skin surface. With or without symptoms; limiting self-care ADLs	Refer to dermatologist	
		Antihistamines	Fexofenadine 180mg OD
		Emollient	Cetraben crea,
		Topical steroids	Betnovate Ointment BD (1% Hydrocortisone ointment/cream for face)
		Consider oral steroids	Prednisolone 0.5mg/kg OD (maximum
		Interrupt dabrafenib until grade <1	

			60mg/day) for 5-7 days
4	Steven Johnson Syndrome or toxic epidermal necrolysis, wide spread skin rash, with peeling or blistering formation and mucosal involvement.	**Immediate dermatology referral**	Admission to Burns unit under plastics team at Whiston hospital (STHK).
		Possibly admit to hospital	
		IV Fluids and electrolytes	
		Stop dabrafenib	

Prolongation of the QT interval: QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with dabrafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval.

Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated.

Avoid / stop any other medication that may cause a prolonged QT interval.

QTc Interval	Recommended dose modification
QTc>500 ms at baseline	**Treatment not recommended.**
QTc increase meets values of both > 500 ms and >60 ms change from pretreatment values	**Discontinue permanently**
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 100mg twice daily (or 75g twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 75mg twice daily (or discontinue permanently if the dose has already been lowered to 75mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	**Discontinue permanently**

Hypertension: 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

If cardiac toxicity is suspected consider an ECG and ECHO.

Ophthalmologic reactions: Monitor patients routinely for serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion.

Arthralgia: Approximately 50% patients experience pain /discomfort in one or more joints that can be mild to debilitating. Arthralgia cannot be prevented; instead symptoms should be managed with regular analgesia such as paracetamol with/without NSAIDs.

Cutaneous Squamous Cell Carcinoma (cuSCC): Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with dabrafenib.

It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for evaluation and treated as per local standard of care. The prescriber should examine the patient monthly during and up to six months after treatment for cuSCC.

In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC): Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment.

Anal examinations and pelvic examinations (for women) when considered clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to local clinical practices.

New primary melanoma: Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

Photosensitivity: All patients should be advised to avoid sun exposure and to wear protective clothing and use a broad spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB)

sunscreen and lip balm (Sun Protection Factor ≥ 30) when outdoors to help protect against sunburn. Sunscreen should be applied liberally to all exposed areas half an hour before going outdoors and reapplied at least every two hours

Dose Modifications

Recommended dabrafenib dose level reductions

Dose level	Resulting dose/schedule
Full dose	150mg Twice Daily
First reduction	100mg Twice Daily
Second reduction	75mg Twice Daily
Third reduction	50mg Twice Daily

Dabrafenib dose modification schedule based on the grade of any Adverse Events (AE)

Grade (CTCAE v4.0)	Recommended dose medication
Grade 1 or Grade 2 (tolerable)	Maintain dabrafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurrence of any grade 2 or 3 AE	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	**Consider discontinuation**
Grade 4	
1st occurrence of any grade 4 AE	Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy
2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	**Discontinue permanently**

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x	x		x	At baseline, month 1 and then every 3 months thereafter
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs & LDH & Mg2+	x	x	x	x	Every cycle
ECG	x				*As clinically indicated
CT scan	x			x	Every 12 weeks/if clinically indicated
Head and neck examination including oral exam and palpation of lymph nodes	x			x	Every 3 months
Skin review (cuSCC)	x				**As clinically indicated
Height	x				
Weight	x	x	x	x	

* 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.
Pregnancy test if applicable.

Non- Haematological toxicity:

Renal	No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined.

Hepatic	No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with trametinib.

Interactions:

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**
Antiobiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressants	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Antiretrovirals	Ritonavir, saquinavir, atazanavir

References:

1. Tafinlar 50 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Tafinlar 100mg, 200mg, 500mg, 1000mg. Summary of Product Characteristics. medac GmbH 28/11/1997. Available from https://www.medicines.org.uk/emc/product/7748/smpc. Last updated 20/11/20.
2. BNF available via: https://bnf.nice.org.uk/
3. NICE: NG14 Melanoma: assessment and management. Published date: July 2015. Last updated: July 2022.
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
10th of June 2016	1.0	Jo Upton / Gareth Hunt Pharmacist	New protocol
18th of April 2023	1.2	Hugh O'Neill Skin SRG Pharmacist	Updated to new template Updated indication Updated dose modification and toxicity management to align with standard IO protocol Hepatic and Renal Impairment section added Interactions segment added