Trametinib and Dabrafenib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	C43	00415a	CDS (01/04/2018)

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Dabrafenib and trametinib are administered daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Dabrafenib	150mg Twice daily	PO 1hour before or two hours after the ingestion of food	Continuous
Trametinib	2mg once daily	PO 1hour before or two hours after the ingestion of food	Continuous
Dabrafenib capsules and trametinib tablets should be swallowed whole with water. They should NOT be chewed or crushed and should NOT be mixed with food or liquids.			
If a dose of dabrafenib is missed, it should not be taken if it is < 6 hours until next dose. Dabrafenib should be taken at similar times each day. If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, only take the dose of trametinib if it is more than 12 hours until the next scheduled dose.			
The once daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib. If a patient vomits after taking trametinib, the patient should not retake the dose and should take the next scheduled dose.			
Dabrafenib is available as 50mg and 75mg capsules. Trametinib is available as 0.5mg and 2mg tablets.			

ELIGIBILTY:

- Indications as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-1
- Life expectancy of at least 3 months
- Sequential treatment may be considered where patients are intolerant to a prescribed BRAF inhibitor and are subsequently changed to an alternative

EXCLUSIONS:

- Hypersensitivity to dabrafenib, trametinib or any of the excipients
- Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Pregnancy (*Reference **Drug Interactions below**: Dabrafenib reduces efficacy of hormonal contraceptives)
- Breast feeding
- Wild type BRAF malignant melanoma
- Treatment failure with a BRAF and /or MEK inhibitor

USE with CAUTION:

Carefully consider benefits and risks before administering dabrafenib to patients with a prior or concurrent cancer associated with RAS mutations.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, Renal and liver profile
- ECG
- Echocardiogram
- Dermatologic evaluation for other skin cancer

Regular tests:

- FBC, Renal and liver profile monthly
- ECG and Echocardiogram: at the end of the first 4 weeks and then every 12 weeks and after dose modification(prior to each cycle)
- Dermatologic evaluation every 60 days (assess for other skin cancers and new primary melanoma) and for up to 6 months following discontinuation of treatment
- Head and neck examination every 3 months
- Chest CT every 6 months

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation.
- Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.

Renal and Hepatic Impairment:

Table 1: Recommended dose modification of dabrafenib and trametinib in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Dabrafenib	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	No dose adjustment required for patients with mild hepatic impairment. No data available for patients with moderate to severe hepatic impairment. Use with caution. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites
Trametinib	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	No dose adjustment required for patients with mild hepatic impairment. No data available for patients with moderate to severe hepatic impairment. Use with caution.

Recommended dose level reductions and recommendations for dose modifications are provided in table 2 and table 3 respectively.

Table 2: Dose reduction steps for dabrafenib and trametinib.

Dose Level	Dabrafenib Dose	Trametinib Dose
Full Dose	150mg BD	2mg once daily
1st Reduction	100mg BD	1.5mg once daily
2nd Reduction	75mg BD	1mg once daily
3rd Reduction	50mg BD	1mg once daily
Dose adjustment for dabrafenib below 50mg BD is not recommended Dose adjustment for trametinib below 1mg once daily is not recommended when used in combination with dabrafenib		

Table 3: Dose modification schedule for dabrafenib and trametinib based on the grade of any adverse events.

Adverse reactions*	Recommended dose modification / discontinuation
Grade 1 or 2 (Tolerable)	Continue treatment and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0 to 1 and reduce by one dose level when resuming therapy
Grade 4	Discontinue permanently or interrupt therapy until grade 0 to 1 and reduce by one dose level when resuming therapy.

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).

- When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered for both dabrafenib and trametinib.
    - The dose of dabrafenib should not exceed 150 mg twice daily.
    - The dose of trametinib should not exceed 2mg once daily.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued Exceptions to dose modifications where only one of the two therapies is dose reduced for selected adverse reactions are included in table 4 below.

Table 4: Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Adverse reactions	Recommended dose modification / discontinuation	
	Dabrafenib	**Trametinib**
Pyrexia (temp ≥38.5^{0}C)	Interrupt therapy with dabrafenib. Initiate therapy with anti-pyretics. Consider oral corticosteroids where anti-pyretics not sufficient. After resolution of pyrexia restart dabrafenib with appropriate anti-pyretic prophylaxis at the same dose level or reduced by one dose level if the pyrexia was recurrent and/or associated with other severe symptoms including dehydration, hypotension or renal failure.	No dose modification required
Uveitis	• No dose reductions are recommended for uveitis as long as effective local therapies can control ocular inflammation. • If uveitis does not respond to local ocular therapy, withhold dabrafenib therapy until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see table 2).	No dose modification required
RAS-mutation-positive non-cutaneous malignancies	Consider the benefits and risks before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation	No dose modification required
LVEF reduction /Left ventricular dysfunction	No dose modification required	Interrupt trametinib therapy in patients with an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued
Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)	No dose modification required	In patients diagnosed with RVO trametinib should be permanently discontinued. If RPED is diagnosed follow the dose modification table for trametinib (Table 5 Below)
Interstitial lung disease (ILD)/Pneumonitis	No dose modification required	Withhold trametinib in patients with suspected ILD or pneumonitis, Permanently discontinue trametinib for patients diagnosed with treatment-related ILD or pneumonitis.

Table 5: Recommended dose modifications for trametinib for Retinal pigment epithelial detachment (RPED)

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.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal -Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:
No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Pyrexia:** Patients with serious non-infectious febrile events have responded well to dose interruption and/or dose reduction and supportive care. Therapy with dabrafenib should be interrupted if the patient's temperature is ≥ 38.5°C. 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.
- **Cutaneous Squamous Cell Carcinoma (cuSCC):** Cases of cuSCC have been reported in patients treated with dabrafenib. They should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop. It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC or until initiation of another anti-neoplastic therapy.
- **New primary melanoma:** Cases have been identified within the first 5 months of therapy. They were managed with excision and did not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.
- **Non-cutaneous secondary/recurrent malignancy:** Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen CT scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. Following

discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

- **Renal failure:** Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.
- **Uveitis:** Ophthalmologic reactions, including uveitis and iritis have been reported. Patients should be routinely monitored for visual signs and symptoms (such as, change in vision, photophobia and eye pain) while on therapy.
- **Pancreatitis:** Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.
- **Severe cutaneous adverse reactions:** Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib/trametinib combination therapy. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be withdrawn.
- **Gastrointestinal disorders:** Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking trametinib in combination with dabrafenib Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognised risk of gastrointestinal perforation.

DRUG INTERACTIONS:

- Potent inducers of CYP3A4 and CYP2C8 should be avoided when possible as these agents may reduce the efficacy of dabrafenib.
- *Dabrafenib may decrease the efficacy of hormonal contraceptives. **Women of childbearing potential should use an alternate effective method of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and 16 weeks following the last dose of trametinib when given in combination with dabrafenib.**
- Concomitant treatment with substances that increase gastric pH (i.e. proton pump inhibitors, H_2 antagonists and antacids) might decrease the bioavailability of dabrafenib and should be avoided.
- Concomitant administration of dabrafenib with warfarin may result in decreased warfarin exposure. Additional INR monitoring is required during treatment and at discontinuation of dabrafenib.
- Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure. Additional monitoring of digoxin is required during treatment and at discontinuation of dabrafenib.
- As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions Drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.
- Trametinib is an in vitro substrate of the efflux transporter P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when coadministering trametininb with medicinal products that are strong inhibitors of P-gp
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Dabrafenib L01XE23
Trametinib L01XE25

REFERENCES:

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3. Robert, C. 2015a. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med, 372, 30-9.
4. ROBERT, C., 2015b. Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. European Journal of Cancer, 51, S663.
5. Tafinlar ®Summary of Product Characteristics Accessed April 2020 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002604/WC500149671.pdf
6. Mekinist ®Summary of Product Characteristics Accessed April 2020 Available http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002643/WC500169657.pdf

Version	Date	Amendment	Approved By
1	20/03/2018		Dr Fergal Kelleher
2	01/05/2019	Updated dose modification of dabrafenib and trametinib in renal and hepatic impairment table Removed black triangle status as per SmPC update	Prof Maccon Keane
3	22/04/2020	Updated adverse effects / regimen specific complications, drug interactions as per SmPC updates	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.