Dabrafenib and Trametinib

Indication
BRAF V600 mutation-positive unresectable or metastatic melanoma.

(NICE TA396)

Adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma.

(NICE TA544)

Advanced non-small cell lung cancer with a BRAF V600 mutation

(NICE NG161 – **Interim COVID19 guidance**)

ICD-10 codes
Codes with a prefix C43 or C34

Regimen details

Day	Drug	Dose	Route
1-28	Dabrafenib	150mg BD	PO
1-28	Trametinib	2mg OD	PO

Cycle frequency
As above

Number of cycles
Metastatic disease: Continuous until disease progression or unacceptable toxicity.

Adjuvant treatment: Total of 12 months unless disease progression or unacceptable toxicity.

Administration
Dabrafenib is available as 75mg and 50mg capsules.
Dabrafenib should be taken at least one hour before or two hours after food. Doses should be taken 12 hours apart, swallowed whole with water, not chewed or crushed.
Grapefruit and grapefruit juice should be **avoided** whilst taking dabrafenib.
If a dose is missed it should be taken if it is more than six hours until the next dose is due. If within six hours the dose should be missed and the next dose taken as planned. Doses should be taken at similar times every day. If the patient vomits an additional dose should not be taken but the next dose taken as usual.

Trametinib is available as 0.5mg and 2mg tablets.
Trametinib should be taken once a day, at the same time each day (with either the morning or evening dabrafenib dose), at least one hour before or two hours after a meal. The tablets should be swallowed whole with a full glass of water.
If a dose is missed it should be taken if it is more than 12 hours until the next dose is due.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Emollients if required.
Antiemetics if required.

Extravasation
N/A

Investigations – pre first cycle
Before commencing treatment BRAF V600 mutation must be confirmed

Investigation	**Validity period** (or as per consultant instruction)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
LDH	14 days
Pregnancy test (if applicable)	14 days
Blood pressure	Baseline
ECG (QTc < 500ms) and echocardiogram*	Baseline

* if urgent treatment is required then this should not be deferred whilst waiting for an echocardiogram if there is no history of or clinical suspicion of heart failure.
Consider dermatological evaluation.

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
LDH*	48 hours
Blood pressure	Monthly
ECG	should be monitored before treatment, after the first month, then approximately 3 monthly and after any dose modifications
Echocardiogram	should be monitored before treatment, after the first month, then approximately 3 monthly and after any dose modifications

*Haemolysed LDH should not stop treatment

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
AST/ALT	≤ 2.5 x ULN (or <5 x ULN if liver metastases)
Bilirubin	≤ 1.5 x ULN
QTc	< 500ms and <60ms increase from baseline
LVEF	> LLN for institution

Dose modifications

Dose modifications should be made as per the table below:

Dose level	Dabrafenib dose	Trametinib dose
Full dose	150mg BD	2mg OD
First reduction	100mg BD	1.5mg OD
Second reduction	75mg BD	1mg OD
Third reduction	50mg BD	Discontinue if unable to tolerate 1mg OD

Dose reductions beyond these levels are not recommended.

- **Renal impairment**

Limited data available. No dose reduction necessary for mild to moderate renal impairment. Use with caution and closely monitor if severe renal impairment.

- **Hepatic impairment**

No dose modification is required for mild hepatic impairment. There is no data in moderate to severe hepatic impairment. Dabrafenib and trametinib should be used with caution.

Additional ECG monitoring is required in patients with moderate or severe hepatic impairment; monthly for the first 3 months, then 3 monthly or as clinically indicated.

- **Toxicities**

Pyrexia:

Any event: Clinical evaluation for infection and hypersensitivity, Laboratory work, Hydration as required

1st event:
Administer anti-pyretic treatment eg paractamol or ibroprofen if clinically indicated,
Interrupt dabrafenib but continue trametinib.
Once pyrexia resolves to baseline, restart dabrafenib at the same dose level
If 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.

2nd event:
As 1st event and consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated.
Subsequent events:
Interrupt dabrafenib
Continue trametinib
Once pyrexia resolves to baseline, restart 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 steroids
If corticosteroids cannot be tapered or escalating doses are required, consider alternative therapies**.**

QT prolongation:
If the QTc exceeds 500 msec, treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 msec with a one level dose reduction of dabrafenib. No dose reduction is required for trametinib.

Permanent discontinuation of dabrafenib and trametinib treatment is recommended if the QTc increase meets values of both > 500 msec and > 60 msec change from pre-treatment values.

Hypertension:
Hypertension should be controlled with standard antihypertensives.

Reduction in LVEF:
If LVEF decreases by > 10% from baseline or is below LLN for the institution, trametinib should be withheld. If LVEF recovers trametinib may be restarted with one dose level reduction and close monitoring. No dose reduction is required for dabrafenib.

If grade 3-4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued.

Uveitis:
If inflammation is controlled with local therapies no dose modifications are required. If uveitis does not respond to local therapy withhold dabrafenib until resolution and restart at reduced dose on resolution. No dose modification of trametinib is required.

Ocular toxicity:
Patients should be encouraged to report visual disturbances and ophthalmological assessment is recommended if symptoms reported.

Retinal pigment epithelial detachment:
Grade 1: continue and monitor monthly until resolved.
Grade 2-3: withhold trametinib for up to 3 weeks. If resolves to ≤ grade 1 restart at reduced dose, if not permanently discontinue.
Dabrafenib may be continued.

Retinal vein occlusion: Permanently discontinue trametinib.
Dabrafenib may be continued.

Pneumonitis:
Trametinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.
Dabrafenib may be continued.

Skin toxicity:
Cutaneous: Intolerable Grade 2 skin toxicity or Grade 3 or 4 skin toxicity:
Withhold dabrafenib for up to 3 weeks. If improved, resume at a lower dose level. If not improved, permanently discontinue.
Withhold trametinib for up to 3 weeks. If improved, resume at a lower dose level. If not improved, permanently discontinue.

Cases of skin squamous cell carcinomas should be treated with surgical excision. No dose adjustment is required.
Dermatological evaluation should continue for 6 months after the cessation of treatment.

Any other toxicities:

Toxicity grade	**Dose modification**
Grade 1 or 2 (tolerable)	Continue treatment and monitor
Grade 2 (intolerable) or Grade 3	Interrupt treatment until ≤ Grade 1. Resume with dose reduction of one level.
Grade 4	Discontinue or interrupt treatment until ≤ Grade 1. Resume with dose reduction of one level. or Permanently discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cutaneous squamous cell carcinoma
Non-cutaneous squamous cell carcinoma
New primary melanoma
QT prolongation
Pancreatitis
Hypersensitivity reactions
Ophthalmic reactions, including uveitis
Myelosuppression

- **Frequently occurring side effects**

Pyrexia
Fatigue
Fever, chills
Headache
Cough
Arthralgia, myalgia
Rash, pruritus
Hyperkeratosis
Nausea and vomiting
Diarrhoea
Alopecia
Raised LFTs
Hypertension

- **Other side effects**

Hypophosphataemia
Hyperglycaemia

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants (e.g. warfarin): avoid.

Dabrafenib
Medication which prolong the QT interval: Concomitant use not recommended as dabrafenib may prolong QT interval.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to dabrafenib.

Inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir): use with caution, increased risk of toxicity.

Contraceptive pill: efficacy may be reduced.

Digoxin: concomitant use may reduce digoxin levels.

There is a theoretical risk that drugs which raise gastric pH may decrease dabrafenib bioavailability.

Dabrafenib can interact with many medicinal products eliminated through metabolism or active transport. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. Please see the SPC for a full list of potential medicinal interactions.

Trametinib
As 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. Drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.

Strong P-gp inhibitors (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole): caution is advised when co-administering trametininb; strong inhibition of hepatic P-gp may result in increased levels of trametinib.

BCRP substrates (e.g. pitavastatin): staggered dosing (2 hours apart) of these agents and trametinib due to risk of transient inhibition of BCRP substrates.

Additional comments

Women of child bearing potential must be advised to use adequate contraception throughout treatment.

References

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- Summary of Product Characteristics – Trametinib via www.medicines.org.uk
- Robert C, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015 Jan 1;372(1):30-9.
- NICE interim treatment guidelines accessed 27/10/2020 - https://www.nice.org.uk/guidance/ng161/chapter/7-Modifications-to-usual-service#interim-nhs-england-treatment-regimens

THIS PROTOCOL HAS BEEN DIRECTED BY DR BOARD, DESIGNATED LEAD CLINICIAN FOR MELANOMA

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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