DABRAFENIB TRAMETINIB (Tafinlar and Mekinist)

INDICATION (ICD10) C34, C43, C73

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

Dabrafenib in combination with trametinib for the adjuvant treatment of completely resected stage III BRAF V600 positive malignant melanoma where the following criteria are met:

2. Confirmed histological diagnosis of malignant melanoma which is BRAF V600 mutation positive
3. Disease that has been staged as stage III disease according to the AJCC 8th edition
4. This stage III disease has been completely resected either via sentinel lymph node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection and/or there has been complete resection of intransit metastases.
5. Naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors
6. Has discussed with the patient the benefits and toxicities of adjuvant trametinib and dabrafenib in stage III disease and has used the expected median figures below in relation to the risk of disease relapse if a routine surveillance policy is followed: - for stage IIIA disease, the 5 and 10 year melanoma-specific survival probabilities with routine surveillance are 93% and 88%, respectively for stage IIIB disease, the 5 and 10 year figures are 83% and 77%, respectively, for stage IIIC disease, the 5 and 10 year figures are 69% and 60%, respectively, for stage IIID disease, the 5 and 10 year figures are 32% and 24%, respectively.
7. ECOG performance status of either 0 or 1
8. Treatment with dabrafenib in combination with trametinib will be continued for a maximum of 12 months from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent
9. A formal medical review as to whether treatment with dabrafenib in combination with trametinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
10. No treatment breaks of more than 6 weeks beyond the expected 4-weekly cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.
11. Dabrafenib in combination with trametinib is to be otherwise used as set out in their respective Summaries of Product Characteristics (TA544)

Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma where the following criteria have been met:

2. Confirmed histological diagnosis of malignant melanoma which is BRAF V600 mutation positive
3. Unresectable stage III or stage IV disease that has been staged according to the AJCC 8th edition
4. Naïve to BRAF V600 and MEK inhibitors for malignant melanoma unless either the patient has previously received adjuvant dabrafenib and trametinib and did not progress during such therapy or has received a sufficient trial of encorafenib plus binimetinib for advanced disease and this has had to be stopped solely as a consequence of persistent dose-limiting toxicity and in the documented absence of disease progression.Note: sequential treatment is not commissioned with encorafenib plus binimetinib and then on disease progression with dabrafenib plus trametinib
5. ECOG performance status to tolerate treatment with the combination of trametinib plus dabrafenib
6. Treatment with trametinib in combination with dabrafenib will be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent. The only exception to this is for

patients enrolled in the NIHR-approved INTERIM trial in which intermittent treatment is allowed and can be given in the experimental arm
7. A formal medical review as to whether treatment with trametinib in combination with dabrafenib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
8. No treatment breaks of more than 6 weeks beyond the expected 4-weekly cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.
9. Trametinib in combination with dabrafenib is to be otherwise used as set out in their respective Summaries of Product Characteristics

Dabrafenib and trametinib for BRAF V600-mutated anaplastic thyroid cancer (ATC) for adult patients where the following criteria have been met:
2. Has been diagnosed with locally advanced inoperable anaplastic thyroid cancer.
3. Has been tested for and has a confirmed BRAFV600 mutation.
4. Has a performance status of 0 or 1 or 2.
5. Dabrafenib and trametinib for BRAFV600-mutated anaplastic thyroid cancer is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment.
6. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
7. Dabrafenib and trametinib will be otherwise used as set out in their respective Summary of Product Characteristics.
8. I confirm Trust policy regarding the use of unlicensed (off-label) treatments has been followed as this treatment is not licensed in this indication.

For the first line treatment of metastatic BRAF V600 mutation positive non-small cell lung cancer where the following criteria have been met:
2. Histologically confirmed diagnosis of non-small cell lung cancer (NSCLC).
3. Has histological or cytological evidence of NSCLC that contains a BRAF V600E mutation based on a validated test OR there is documented agreement by the lung MDT that the radiological appearances are in keeping with metastatic NSCLC AND there is an informative circulating free DNA test result confirming the presence of a BRAF V600E mutation.
4. Metastatic non-small cell lung cancer.
5. Is either treatment naïve to BRAF and MEK inhibitors for the first line treatment of metastatic NSCLC or the patient has commenced dabrafenib in combination with trametinib as a first line treatment for metastatic NSCLC as part of the Interim COVID cancer measures (Blueteq form DABTRA3CV).
Note: patients who started on dabrafenib in combination with trametinib as a second or subsequent line of treatment for metastatic NSCLC as part of the Interim COVID cancer measures (Blueteq form DABTRA3CV) must not be transferred to CDF funding. Such patients who started dabrafenib plus trametinib via the Interim COVID measure can remain on treatment until they and the clinician decide it is appropriate to stop at symptomatic disease progression or intolerance or withdrawal of patient consent.
Note: Novartis did not submit any evidence of the cost effectiveness of dabrafenib plus trametinib in the 2nd or subsequent line of therapy for metastatic NSCLC and hence NICE has had to restrict its positive recommendation solely to the 1st line position in the treatment pathway.
6. The patient has not received previous systemic therapy for metastatic NSCLC with the exception of dabrafenib plus trametinib as a first line treatment as part of the Interim COVID cancer measures (as answered in criterion 5 above).
Note: prior adjuvant or neo-adjuvant chemotherapy or immunotherapy for NSCLC for earlier stage disease does not count as previous systemic therapy in this regard.

7. ECOG performance status of either 0 or 1 or 2.
8. Either has no known brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting dabrafenib in combination with trametinib.
9. Treatment with dabrafenib in combination with trametinib will be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent.
10. A formal medical review as to how the combination of dabrafenib and trametinib is being tolerated and whether treatment with the combination of dabrafenib and trametinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
11. Where a treatment break of more than 6 weeks beyond the expected cycle length is needed, a treatment break approval form will be completed to restart treatment.
12. Dabrafenib in combination with trametinib is to be otherwise used as set out in their respective Summaries of Product Characteristics.

REGIMEN

Day 1	DABRAFENIB	150mg orally twice daily (12 hourly) continuously
	TRAMETINIB	2mg orally daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Adjuvant - every 28 days up to 12 months
Metastatic – every 28 days until disease progression

ADMINISTRATION

Dabrafenib is available as 50mg and 75mg capsules
Trametinib is available as 0.5mg and 2mg tablets. Store in the fridge.
Swallow both whole with water, at least 1 hour before or at least 2 hours after a meal.
Grapefruit and grapefruit juice should be avoided

ANTI-EMETICS

Low emetic risk

CONCURRENT MEDICATION REQUIRED

Dabrafenib	None required
Trametinib	None required

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E, Mg^{++} and LFTs and LDH every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine - GFR each cycle
ECG and ECHO at baseline, 1 month then every 3 months
Blood pressure every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Dabrafenib	Cutaneous squamous cell carcinoma Hepatic toxicity New primary melanoma Non-cutaneous secondary / recurrent malignancy Renal failure Uveitis Pancreatitis QT prolongation Pyrexia
Trametinib	Cutaneous squamous cell carcinoma New primary melanoma Non-cutaneous secondary / recurrent malignancy Haemorrhage Renal failure Pancreatitis LVEF reduction, Hypertension Pyrexia

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Dabrafenib	Effect of anticoagulants many be decreased. Antiviral exposure may be decreased. CYP3A4, CYP2C and CYP2B6 inducers should be avoided. Many interactions check carefully. Grapefruit and grapefruit juice should be avoided

DOSE MODIFICATIONS

Dose level	Dabrafenib dose	Trametinib dose
Full dose	150mg twice daily	2mg od
First reduction	100mg twice daily	1.5mg od
Second reduction	75mg twice daily	1mg od
Third reduction	50mg twice daily	1mg od

Grade (CTCAE)	Recommended dabrafenib and trametinib dose modifications except pyrexia or uveitis
Grade 1 or grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce both by one dose level when resuming therapy.
Grade 4	Discontinue both permanently, or interrupt therapy until grade 0-1 and reduce both by one dose level when resuming therapy.

Pneumonitis / interstitial lung disease
Withhold trametinib in suspected pneumonitis or interstitial lung disease, and permanently discontinue if diagnosis confirmed. No dose reduction of dabrafenib is required.

Pyrexia
Patient's temperature is ≥38.5ºC dabrafenib should be interrupted. Evaluate 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, or alternate day dosing, once the fever resolves, as clinically appropriate. No dose reduction of trametinib is required.

Uveitis
No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required.

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 0.5mg) 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	Discontinue trametinib permanently.

Hepatic impairment
Dabrafenib and trametinib
No dose adjustment for patients with mild or moderate renal impairment.
Use in caution with severe impairment.

Renal impairment
Dabrafenib and trametinib
No dose adjustment for patients with mild hepatic impairment.
Use with caution in moderate or severe impairment.

REFERENCES
1. Robert, C et al; NEJM 2015; 372: 30–39
2. Long, G; NEJM 2014; 371: 1877–1888
3. Long, G et al; NEJM 2017; 377: 1813–1823 (adjuvant)