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/) (TRADAB1) (TRADAB2) (TRADAB3) (DABTRA3)

1. Dabrafenib in combination with trametinib for the adjuvant treatment of completely resected stage III BRAF V600 mutation positive malignant **melanoma**, naïve to systemic therapy PS 0 or 1. (TA544)
2. Trametinib in combination with dabrafenib for treating unresectable or metastatic stage III or stage IV disease BRAF V600 mutation positive **melanoma**. Naïve to BRAF V600 and MEK inhibitors. PS to tolerate treatment with the combination. (TA396)
3. Dabrafenib and trametinib for BRAF V600-mutated locally advanced inoperable anaplastic BRAFV600 mutation **thyroid** cancer (ATC) for adult patients. PS 0, 1 or 2**.**
4. For the first line treatment of metastatic BRAF V600 mutation positive metastatic non-small cell **lung** cancer. Naïve to systemic treatment (except neo-adjuvant or adjuvant treatment for earlier stage disease) and BRAF and MEK inhibitors for the first line treatment of metastatic NSCLC. No known brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting dabrafenib in combination with trametinib. PS 0, 1 or 2. (TA898)

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 maximum 12 months from treatment start. 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.

Metastatic – every 28 days until disease progression. 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.

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)