Indication	For the treatment of metastatic BRAF V600 mutation positive non-small cell lung cancer that is treatment naïve to BRAF and MEK inhibitors. NB This indication has been made available as part of the response to the COVID-19 pandemic. Unresectable or metastatic melanoma with a BRAF V600 mutation Adjuvant treatment of completely resected stage III BRAF V600 positive malignant melanoma.
Treatment Intent	Adjuvant (Stage III melanoma) Palliative (Lung/Unresected or metastatic melanoma)
Frequency and number of cycles	28 day cycle **Adjuvant:** for a maximum of 12 months (13 cycles) from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent. **Palliative:** Continue until progressive disease, unacceptable toxicity or patient choice. A formal medical review should be scheduled by the end of the first 8 weeks of treatment to assess tolerability and whether treatment should continue.

Monitoring Parameters pre-treatment	• Monitor FBC, U&E's and LDH prior to each cycle for 3 months, then every 3 months thereafter. If Neuts < 1.5 and/ or PLT < 100 d/w consultant.
	• Monitor LFT's prior to each cycle for 6 months, then every 3 months thereafter.
	• ECHO at baseline then at one month and then approximately every 3 months.
	• ECG at baseline, monthly for the first 3 months and then as clinically indicated.
	• Blood pressure every cycle.
	• **Hepatic Impairment:** No dose adjustment is required in mild hepatic impairment. Use with caution in patients with moderate to severe hepatic impairment.
	• **Renal Impairment:** No dose adjustment is required in mild or moderate renal impairment. Patients with severe renal impairment d/w consultant – use with caution.
	• **Dose modification**, , **see also Table 1:**
	• When dose reductions are necessary, reduce as follows:
	  ○ 1st dose reduction: dabrafenib 100mg bd, trametinib 1.5mg od
	  ○ 2nd dose reduction: dabrafenib 75mg bd, trametinib 1mg od
	  ○ 3rd dose reduction dabrafenib 50mg bd, trametinib 1mg od
	• Dose adjustment below 1mg OD for trametinib or below 50mg BD for dabrafenib is not recommended. Both treatments should be simultaneously dose reduced, interrupted or discontinued except where reductions/ interruptions are for uveitis, RAS mutation positive non-cutaneous malignancies and left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib). See below. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered (see dose modification schedule table 1). The dose of trametinib should not exceed 2mg od and the dose of dabrafenib should not exceed 150mg bd.
	• Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma or new primary melanoma.
	• **LVEF reduction:** Trametinib should be interrupted in patients who have 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). No dose modification of dabrafenib is required. If the LVEF recovers, treatment with trametinib, may be restarted, reduced by one dose level, with careful monitoring. If Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover, trametinib should be permanently discontinued. Physicians should be alert to the possibility of myocarditis in patients who develop new or worsening cardiac signs or symptoms.

- **Pyrexia:** Therapy with dabrafenib and trametinib should be interrupted if the patient's temperature is >/= 38°C. If reoccurrence, treatment can be interrupted at the first symptom of pyrexia.
  Evaluate for signs of infection and if necessary treat as appropriate. Treatment should re-start when the patient has been symptom free for 24 hours. If fever associated with other severe signs (e.g. dehydration, hypotension, renal failure), or is recurrent, restart dabrafenib and trametinib at reduced dose when the patient is symptom free for at least 24 hours.
- **RAS-mutation-positive non-cutaneous malignancies:** The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.
- **Ophthalmologic reactions:**
  Ophthalmologic reactions, including uveitis, retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) 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.
  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.
  In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. No dose modification of dabrafenib is required.
  If RPED is diagnosed, See dose modification schedule Table 2 for trametinib dosing. No dose modification of dabrafenib is required.
- **ILD or Pneumonitis:** If ILD or pneumonitis is suspected, withhold trametinib and permanently discontinue if diagnosis confirmed. No dose modification of dabrafenib is required.
- **Gastrointestinal disorders:** Use with caution in patients at risk of GI perforation; colitis and GI perforation have been reported.
- 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.
- Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking the combination of dabrafenib with trametinib.
- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
- <u>Dabrafenib</u>
  Dabrafenib is an enzyme inducer (CYP3A4, CYP2Cs, CYP2B6). Interactions with medicines which are eliminated via CYP3A4 metabolism (including anti-epileptics, dexamethasone, calcium channel blockers) are expected. See SpC section 4.5 for full details.

	Avoid concomitant treatment with potent CYP3A4 or CYP2C8 inhibitors (e.g ketoconazole, itraconazole, clarithromycin, erythromycin) or inducers (e.g rifampicin, dexamethasone, phenytoin, St.Johns Wort, carbamazepine) Patients on warfarin should be closely monitored (INR) The efficacy of contraceptive pills metabolised by CYP3A4 may be decreased. Grapefruit and grapefruit juice should be avoided. • Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect their ability to drive or operate machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	SPC accessed online 06.01.22 KMCC protocol SKI-010 v2 BNF accessed online 06.01.2022 Blueteq forms TRADAB2_ver1.0 TRADAB1_ver1.3 DABTRA3CV accessed online 5/8/20

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification schedule for adverse reactions based on grade (excluding pyrexia):

Grade	**Recommended dose modification**
Grade 1 or Grade 2 (Tolerable)	Continue treatment of both drugs and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level of both drugs when resuming therapy.
Grade 4	Discontinue both drugs permanently, or interrupt therapy until grade 0-1 and reduce by one dose level of both drugs when resuming therapy.

Table 2 Dose modification of trametinib for RPED based on grade

Grade 1 RPED	Continue treatment, with retinal evaluation every month.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks of stopping trametinib	Resume trametinib at a lower dose (2mg to 1.5mg or 1.5mg to 1mg) 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	Permanently discontinue trametinib

Repeat every 28 days:

Drug	Dose	Route	Directions
DABRAFENIB	**150mg**	PO	Swallow whole with water twice a day. Take each dose at least one hour before or two hours after a meal. Grapefruit and grapefruit juice should be avoided. The first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. If a dose is missed, it should only be taken if it is more than 6 hours until the next dose. Available as 50mg and 75mg capsules
TRAMETINIB	**2mg**	PO	Once daily with a full glass of water. (May be taken either with the morning dose or with the evening dose of dabrafenib) Take each dose at least one hour before or two hours after a meal. If a dose of trametinib is missed, only take the dose of trametinib if it is more than 12 hours until the next scheduled dose. Available as 2mg and 0.5mg tablets, which must be stored in the fridge.
TTO Drug	Dose	Route	Directions
Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 consecutive days.