Indication	Trametinib for low grade serous ovarian or peritoneal cancer for disease that has recurred or progressed following at least one platinum-based chemotherapy regimen NB the patient must have not received any previous MEK inhibitor. **NB This is an unlicensed indication; clinicians must be mindful of their individual responsibilities, and follow Trust procedures when prescribing unlicensed medicines.**
Treatment Intent	Palliative
Frequency and number of cycles	28 day cycle Continue until disease progression, 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	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&E's 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. • Blood pressure before 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:** The management of adverse reactions may require dose reduction, interruption or discontinuation of treatment. The recommended dose reduction is; first dose reduction 1.5mg OD and second dose reduction 1mg OD. If not tolerated at 1mg OD, no further dose reduction is recommended. See table 1 for dose modification for adverse events. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The trametinib dose should not exceed 2 mg once daily. • **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). 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 within 4 weeks, 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 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 trametinib at reduced dose when patient is symptom free for at least 24 hours.

	• 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. • **Haemorrhage:** Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking trametinib, patients should report any new bleeding events (including but not limited to epistaxis, haematochezia, gingival bleeding, haematuria, and rectal). The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. • **Deep vein thrombosis (DVT)/Pulmonary embolism (PE):** Pulmonary embolism or deep vein thrombosis can occur with trametinib. If patients develop symptoms of PE or DVT they should immediately seek medical care. Permanently discontinue trametinib for life-threatening PE. • **ILD or Pneumonitis:** If ILD or pneumonitis is suspected, withhold trametinib and permanently discontinue if diagnosis confirmed. • **Ophthalmologic reactions:** • Ophthalmologic reactions, including, 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. Trametinib is not recommended in patients with a history of RVO. If RPED is diagnosed, the dose modification schedule in Table 2 should be followed, in patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. • **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 <u>combination therapy</u>. 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, trametinib should be withdrawn. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • Caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole), increased toxicity possible. • **Missed dose:** 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. If a patient vomits after the dose, they should not retake the dose and take the next dose at the usual scheduled time. • **Driving / operating machinery:** 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 19.01.2024 Blueteq form accessed online 19.01.24 KMCC protocol GYN-042 CV

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

Table 1 Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTC-AE)	**Recommended trametinib dose modifications**
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 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.

Table 2 Recommended dose modifications for trametinib for 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.

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**TRAMETINIB**	**2mg**	PO	Once daily with a full glass of water. 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.
	Metoclopramide	10mg	PO	10mg up to 3 times a day when required. Do not take for more than 5 consecutive days.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.