# Trametinib

## Indication
This is a MEK inhibitor.
Second line (or subsequent) treatment for advanced low grade serous ovarian/peritoneal cancer following at least one previous platinum-based chemotherapy regimen and one line of hormonal therapy **(Interim COVID-19 guidance)**

## Regimen details
Trametinib 2mg orally once daily

## Cycle frequency
Treatment given continuously, dispense monthly

## Number of cycles
Until disease progression or unacceptable toxicity

## Administration
Taken orally at the same time each day with a full glass of water (~200ml); at least 1 hour before food or 2 hours after

Tablets should be swallowed whole, not to be crushed or chewed

## Pre-medication
N/A

## Emetogenicity
N/A

## Additional supportive medication
None

## Extravasation
N/A

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFT (including AST) | 14 days |
| CA125 | Baseline |
| Blood pressure | Baseline |
| ECG | Baseline |
| Echocardiogram | Baseline |

Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect their ability to drive or operate machinery

## Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST), CA125, blood pressure
ECG (if clinically indicated)

Echo every 4-6 cycles
See clinic 2 weeks from initiation of therapy and then 4 weekly

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

| Investigation | Limit |
|---|---|
| Neutrophil count | ≥ 1.5 x $10^9$/L |
| Platelet count | ≥ 100 x $10^9$/L |
| Creatinine clearance | ≥ 30 mL/min |
| Bilirubin | ≤ 1.5 x ULN |
| AST | < ULN |

## Dose modifications

**Dosing in renal and hepatic impairment:**

| | |
|---|---|
| **Renal** | GFR ≥ 30 ml/min: no dose adjustment<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>Haemodialysis (HD): no need for dose adjustment is expected |

| | |
|---|---|
| **Hepatic** | Mild (bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN)- no dose adjustment required<br>Moderate (bilirubin 1.5-3 x ULN, with any AST) - 50% dose reduction recommended.<br>Severe (bilirubin >3.0-10 x ULN, with any AST) - Trametinib not recommended. |

**Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)**

If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended (for LTHTr use: eye.emergencies@lthtr.nhs.uk). In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. If RPED is diagnosed, follow the dose modification schedule as outlined below.

| | |
|---|---|
| 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. |

**Other toxicities**

| 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. |
| * The intensity of clinical adverse reactions graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE) | |

**Dosing levels**

| Dose level | Trametinib dose |
|---|---|
| Starting dose | 2 mg once daily |
| 1st dose reduction | 1.5 mg once daily |
| 2nd dose reduction | 1 mg once daily |

## Adverse effects –

for full details consult product literature/ reference texts

| | |
|---|---|
| **Cardiovascular** | Decreases in Left Ventricular Ejection Fraction (LVEF). The medium time to onset of LVEF decrease/cardiac failure is 2-5 months.<br><br>Elevations in blood pressure have been reported in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and during therapy. The choice of antihypertensive therapy should be as per national guidance.<br><br>Deep vein thrombosis (DVT) / Pulmonary embolism (PE). If patient develop symptoms such as shortness of breath, chest pain or leg/arm swelling they should immediately seek medical care. |
| **Ocular** | Disorders associated with visual disturbances, including Retinal Pigment Epithelial Dystrophy (RPED), Retinal Vein Occlusion (RVO) may occur with Trametinib. Symptoms such as blurred vision, decreased acuity and other visual effects have been reported. If diagnosed Trametinib should be permanently discontinued. |
| **Respiratory** | Cough, pneumonitis, dyspnoea, interstitial lung disease. |
| **Gastrointestinal** | Diarrhoea, nausea, vomiting, constipation, abdominal pain, stomatitis, hepatitis, loss of appetite.<br><br>Colitis and gastrointestinal perforation have been reported. Caution required in patients with history of diverticulitis and metastases to the gastrointestinal tract. |
| **Dermatological** | Rash, dry skin, pruritus, alopecia, allergic reactions including Stevens – Johnson syndrome. Skin cancers.<br><br>Cellulitis and folliculitis have been reported. |
| **Haematological** | Anaemia<br><br>Haemorrhagic events have been reported and the risk may be increased with concomitant use of anti-platelets or anticoagulation therapy |
| **General** | Fatigue, pyrexia, peripheral oedema, rhabdomyolysis |

## Significant drug interactions

– for full details consult product literature/ reference texts

Effect of other medicinal products on 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.

Trametinib is an *in vitro* substrate of the efflux transporter P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

Effect of trametinib on other medicinal products

Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interaction with CYP enzymes or transporters. Trametinib may result in transient inhibition of BCRP substrates (e.g. pitavastatin) in the gut, which may be minimised with staggered dosing (2 hours apart) of these agents and trametinib

## Additional comments

Trametinib must be stored in the fridge prior to dispensing but once opened, the bottle may be kept out of the fridge for up to 30 days

## References

Trametinib SPC: https://www.medicines.org.uk/emc/product/5072/smpc#

NRG-GOG 0281 trial protocol: https://clinicaltrials.gov/ProvidedDocs/88/NCT02101788/Prot_SAP_000.pdf

Clatterbridge Cancer Centre Protocol

---

**THIS PROTOCOL HAS BEEN DIRECTED BY DR YIANNAKIS, DESIGNATED LEAD CLINICIAN FOR GYNAECOLOGICAL CANCERS**

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

Date: October 2020
Review: October 2022
VERSION: 1

---