

Trametinib

Indication

- Trametinib is a MEK inhibitor.
- Trametinib monotherapy is indicated for adults with recurrent or progressive low-grade serous ovarian carcinoma or primary peritoneal carcinoma following at least one previous platinum-based chemotherapy regimen.
- This treatment is commissioned in England under NHS England Clinical Commissioning Policy: Trametinib in recurrent or progressive low-grade serous ovarian cancer (Adults), URN 2253, published 6 November 2023.

Commissioning Criteria

Treatment should be prescribed in accordance with NHS England Blueteq TRAM1 (URN 2253).

Patients must meet all of the following criteria:

- Histologically confirmed recurrent low-grade serous ovarian or peritoneal carcinoma (invasive micropapillary serous carcinoma or invasive grade 1 serous carcinoma), including patients whose disease originated as a serous borderline ovarian or peritoneal tumour and subsequently recurred as low-grade serous carcinoma.
- Disease progression following at least one previous platinum-based chemotherapy regimen.
- ECOG performance status 0-1.
- No prior treatment with a MEK inhibitor.
- Trametinib to be administered as monotherapy at a dose of 2 mg once daily.
- Treatment to continue until disease progression, unacceptable toxicity, or patient choice to discontinue treatment.

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

Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

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)

Echocardiogram every 3 months, or earlier if clinically indicated.

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	$\geq 1.5 \times 10^9/L$
Platelet count	$\geq 100 \times 10^9/L$
Creatinine clearance	$\geq 30 \text{ mL/min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
AST	$< \text{ULN}$

Dose modifications

Dosing in renal and hepatic impairment:

Renal	GFR $\geq 30 \text{ ml/min}$: no dose adjustment GFR $< 30 \text{ ml/min}$: no need for dose adjustment is expected Haemodialysis (HD): no need for dose adjustment is expected
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Hepatic	Mild (bilirubin $>1.0-1.5 \times \text{ULN}$ and any AST or bilirubin $\leq \text{ULN}$ and AST $> \text{ULN}$)- no dose adjustment required Moderate (bilirubin $1.5-3 \times \text{ULN}$, with any AST) - 50% dose reduction recommended. Severe (bilirubin $>3.0-10 \times \text{ULN}$, with any AST) - Trametinib not recommended.
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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 LHTTr 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.
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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 v5.0 (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	<p>Decreases in Left Ventricular Ejection Fraction (LVEF). The median time to onset of LVEF decrease/cardiac failure is 2-5 months.</p> <p>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.</p> <p>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.</p>
Ocular	<p>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.</p>
Respiratory	Cough, pneumonitis, dyspnoea, interstitial lung disease.
Gastrointestinal	<p>Diarrhoea, nausea, vomiting, constipation, abdominal pain, stomatitis, hepatitis, loss of appetite.</p> <p>Colitis and gastrointestinal perforation have been reported. Caution required in patients with history of diverticulitis and metastases to the gastrointestinal tract.</p>

Dermatological	Rash, dry skin, pruritus, alopecia, allergic reactions including Stevens – Johnson syndrome. Skin cancers. Cellulitis and folliculitis have been reported.
Haematological	Anaemia 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

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
- NHS England Clinical Commissioning Policy: Trametinib in recurrent or progressive low-grade serous ovarian cancer (Adults), 2023.
- Gershenson DM et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian carcinoma (GOG-281/LOGS). Lancet 2022.

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

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Reviewed by Dr Osama El Masri

Date: June 2026

Review: June 2028

VERSION: 2
