Trametinib (Gynae)

Indication
Low grade serous ovarian or peritoneal cancer that has recurred or progressed following at least one platinum-based chemotherapy regimen.

(NHSE CCP: URN2262)

ICD-10 codes
Codes with a prefix C56 and C48

Regimen details

Day	Drug	Dose	Route
1-28	Trametinib	2mg OD	PO

Cycle frequency
As above

Number of cycles
Continuous until disease progression or unacceptable toxicity.

Administration
Trametinib is available as 0.5mg and 2mg tablets.
Trametinib should be taken once a day, at the same time each day, at least one hour before or two hours after a meal. The tablets should be swallowed whole with a full glass of water.
If a dose is missed it should be taken if it is more than 12 hours until the next dose is due.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Emollients if required.
Antiemetics if required.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Blood pressure	Baseline

Investigations – pre subsequent cycles

Patients should be reviewed every 4 weeks for the first 6 months.

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Monthly
Echocardiogram	At baseline, after the first month, then approximately 3-4 monthly.

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
Bilirubin	≤ 1.5 x ULN
LVEF	> LLN for institution

Dose modifications

Dose modifications should be made as per the table below:

Dose level	**Trametinib dose**
Full dose	2mg OD
First reduction	1.5mg OD
Second reduction	1mg OD
Third reduction	Discontinue if unable to tolerate 1mg OD

Dose reductions beyond these levels are not recommended.

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L or platelets <100 x 10^9/L discuss with consultant.

- **Renal impairment**

Creatinine clearance	**Trametinib dose**
≥30mL/min	No dose adjustment needed
<30mL/min	No need for dose adjustment expected, use with caution

- **Hepatic impairment**

Bilirubin	**Trametinib dose**
<1.5 x ULN	No dose adjustment required
1.5 - 3 x ULN	Consider reduction to 50% dose
> 3 x ULN	Not recommended

- **Other toxicities**

Hypertension:
Hypertension should be controlled with standard antihypertensives.

Reduction in LVEF:
If LVEF decreases by > 10% from baseline or is below LLN for the institution, trametinib should be withheld. Consider review/optimisation of cardiac medication. If LVEF recovers trametinib may be restarted with one dose level reduction and close monitoring.

If grade 3-4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued.

Ocular toxicity:
Patients should be encouraged to report visual disturbances and ophthalmological assessment is recommended if symptoms reported.

Retinal pigment epithelial detachment:
Grade 1: continue and monitor monthly until resolved.
Grade 2-3: withhold trametinib for up to 3 weeks. If resolves to ≤ grade 1 restart at reduce by one dose level, if not permanently discontinue.

Retinal vein occlusion: Permanently discontinue trametinib.

Pneumonitis:
Trametinib should be withheld if pneumonitis is suspected and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

Any other toxicities:

Toxicity grade	Dose modification
Grade 1 or 2 (tolerable)	Continue treatment and monitor
Grade 2 (intolerable) or Grade 3	Interrupt treatment until ≤ Grade 1. Resume at next dose reduction level.
Grade 4	Discontinue permanently or interrupt treatment until ≤ Grade 1. Resume with dose reduction of one level.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Bradycardia
Pancreatitis
Hypersensitivity reactions
Ophthalmic reactions
Myelosuppression
Rhabdomyolysis
Colitis

- **Frequently occurring side effects**

Pyrexia
Fatigue
Cough
Arthralgia, myalgia
Rash, pruritus
Nausea and vomiting
Stomatitis
Diarrhoea, constipation
Alopecia
Raised LFTs
Hypertension
Peripheral oedema

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants (e.g. warfarin): avoid.

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.

Strong P-gp inhibitors (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole): caution is advised when co-administering trametininb; strong inhibition of hepatic P-gp may result in increased levels of trametinib.

BCRP substrates (e.g. pitavastatin): staggered dosing (2 hours apart) of these agents and trametinib due to risk of transient inhibition of BCRP substrates.

Additional comments

Women of childbearing potential must be advised to use adequate contraception throughout treatment and for 16 weeks after stopping treatment.

References

- Gershenson D. M. et al. A randomized phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal cancer. Ann Oncol. 2019; 30 (Suppl 5):897-898
- Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.
- NHS England. Interim treatment options during the COVID-19 pandemic (NICE Guideline 161). Accessed 17 June 2023 via www.nice.org.uk
- Summary of Product Characteristics – Trametinib (GSK) accessed 17 June 2023 via www.medicines.org.uk

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