Systemic Anti-Cancer Therapy Protocol

Trametinib Gynaecological Cancer (Unlicensed Use)

PROTOCOL REF: MPHATRAMGY
(Version No: 1.0)

Interim treatment during COVID-19 as an oral alternative to intravenous chemotherapy.

Approved for use in:

Second line (or subsequent) treatment for advanced low grade serous ovarian/peritoneal cancer following at least one previous platinum-based chemotherapy regimen.

Please NOTE: this is unlicensed use.

Please refer to the 'CCC Unlicensed Medicines Policy' for full details on consenting, prescribing, documentation and supply of unlicensed medicines. As per trust policy please provide the 'Unlicensed Medicines Information' to patients and carers as appropriate

****Blueteq Registration is required: See for full eligibility criteria****

Dosage:

Drug	Dose	Route	Frequency
Trametinib	**2mg once daily**	Oral	**every 28 days**

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.

Caution should be applied when administered in conjunction with inhibitors of P-gp (e.g. verapamil, ciclosporin, ritonavir, itraconazole, quinidine) – risk of increased exposure to trametinib.

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

Dosing in renal and hepatic impairment:

Renal	GFR ≥ 30 ml/min: no dose adjustment GFR < 30 ml/min: no need for dose adjustment is expected 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 Moderate (bilirubin 1.5-3 x ULN, with any AST) - 50% dose reduction recommended. Severe (bilirubin >3.0-10 x ULN, with any AST) - Trametinib not recommended.

Interactions:

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.

Main toxicities:

Cardiovascular	Decreases in Left Ventricular Ejection Fraction (LVEF). The medium time to onset of LVEF decrease/cardiac failure is 2-5 months. 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. 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.
Occular	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, dyspnea, interstitial lung disease.
Gastrointestinal	Diarrhoea, nausea, vomiting, constipation, abdominal pain, stomatitis. 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. 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.

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)	

Dose Modifications and Toxicity Management:

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. In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. If RPED is diagnosed, follow the dose modification schedule in Table 3 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.

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
3rd dose reduction (combination only)	1 mg once daily

Table 3 Recommended dose modifications for trametinib for RPED

Haematological Toxicity:

Proceed on day 1 if:

ANC ≥ 1 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week and refer to advice below:

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Investigations and treatment plan:

Investigation	Pre	Cycle 1	Cycle 2	Cycle 3	On-going
Informed Consent	x				
Medical Assessment	x			x	Every 3 cycles
Nursing assessment	x	x	x	x	Every cycle
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs	x	x	x	x	Every cycle
CT scan**	x				Pre-treatment and then as clinically indicated
Blood pressure measurement	x	x	x	x	Every cycle
ECG	x				Pre-treatment and then as clinically indicated*
Weight recorded	x	x	x	x	Every cycle
Height recorded	x	x	x	x	Every cycle
Toxicities recorded	x	x	x	x	Every cycle

*If any complaints of chest pain/shortness of breath/palpitations or hypertension. Escalate to ANP/medical review for ECG

References:

NHS England interim treatment changes during the COVID-19 pandemic (Last updated on 20th August 2020) available via: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381

Supplement to: 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.

Trametinib 2mg film-coated tablets, summary of Product Characteristics, Novartis Pharmaceuticals UK Ltd. Available via https://www.medicines.org.uk/emc https://www.medicines.org.uk/emc (last updated 31st January 2020).