Systemic Anti Cancer Treatment Protocol

Olaparib Tablets & Bevacizumab Maintenance Gynaecological Cancer

PROTOCOL REF: MPHAOLATAB
(Version No: 1.0)

Approved for use in:

- High grade epithelial stage III or IV ovarian, fallopian tube, or primary peritoneal cancer
- Patients with BRCA1 or BRCA2 mutations or confirmed genomic instability (HRD positive)
- Following FIRST line platinum based chemotherapy where there has been either complete or partial response and the patient has received a minimum of 4 cycles
- Maintenance treatment is started no later than 9 weeks since the last infusion within the last cycle of chemotherapy
- ECOG performance status 0 or 1.

MUST be registered on BLUETEQ as funded by the Cancer Drugs Fund (CDF).

Dosage:

Drug	Dosage	Route	Frequency
Olaparib TABLETS	300mg	Oral	Twice daily, continuously
Bevacizumab	15mg/Kg	Intravenous Infusion	Every 21 days (3 weekly)

Treatment will be supplied every 21 days (olaparib monotherapy can be supplied every 28 days).

- Olaparib should be continued until disease progression or unacceptable toxicity or for a maximum duration of 2 years, whichever is the sooner.
- Bevacizumab should be continued until disease progression, unacceptable toxicity or for a maximum duration of 15 months as measured from start of bevacizumab-containing treatment (whether as chemotherapy or maintenance). See also the paclitaxel/carboplatin/bevacizumab protocol

- Olaparib tablets should not be substituted for capsules due to differences in bioavailability.

Supportive treatments:

Domperidone 10mg oral tablets, up to 3 times a day or as required

Extravasation risk:

Bevacizumab – neutral

Refer to the network guidance for the prevention and management of extravasation

Administration:

Olaparib:

- Olaparib TABLETS should be swallowed whole with water and taken approximately 12 hours apart. Olaparib tablets can be taken with or without food.
- If a patient misses a dose of olaparib – they should take their next normal dose when it is scheduled.
- Olaparib has a moderate influence on the ability to drive and use machines. Patients may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.
- For patients of child-bearing potential, ensure appropriate contraception is discussed. If a patient becomes pregnant whilst on treatment, olaparib should be discontinued immediately.

Bevacizumab:

Day	Drug	Dose	Route	Diluent and rate
1	Sodium Chloride 0.9%	50mL	IV Infusion	Flush
1	Bevacizumab	15mg/kg	IV Infusion	100ml Sodium Chloride 0.9% over 30 to 90minutes*
1	Sodium Chloride 0.9%	100mL	IV Infusion	Flush

*The initial dose should be given as an intravenous infusion over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

If a patient experiences a **mild infusion-related reaction**, give future doses with premedication with paracetamol 1000mg orally and IV chlorphenamine 10mg. If the patient still experiences an infusion-related reaction, consider increasing the infusion time back up to 60 minutes or 90 minutes, as appropriate.

Comments: Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28 to 60 days before elective surgery.

For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery.

Interactions:

Olaparib under goes extensive metabolism by CYP3A4/5 and P-gp therefore inducers or inhibitors of this isoenzymes should be avoided. Olaparib may also induce several hepatic CYP metabolic pathways potentially reducing efficacy of hormonal contraceptives. Please check with pharmacist for further information

CYP3A Inhibitors (not exhaustive list)
Strong inhibitors (Itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no alternative to the above inhibitors, then the dose of olaparib should be reduced as follows:

- **Strong inhibitors** – reduce the dose of olaparib to 100mg twice daily for the duration of the concomitant therapy with the strong inhibitor and for 5 half-lives afterwards
- **Moderate inhibitors** – reduce dose to 150mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives after.

After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

CYP3A Inducers (not exhaustive list)

Strong inducers (Phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) and moderate inducers (bosentan, efavirenz, modafinil) should not be taken with olaparib.

If the use of strong or moderate inducers is considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires the use of a concomitant inducer, they must be monitored carefully for any change in efficacy of olaparib.

Increased exposure to the following medicines may also occur: digoxin, dabigatran, colchicine, methotrexate, rosuvastatin and sulfasalazine, glibenclamide, repaglinide, statins, and valsartan, metformin, cyclosporin, ergot alkaloids, fentanyl, pimozide, tacrolimus and quetiapine.

Main Toxicities:

Olaparib	
Haematological toxicity	Very common - Anaemia, Common - neutropenia, thrombocytopenia and leukopenia. Uncommon – lymphopenia
Gastrointestinal disorders	Very common- Nausea, Vomiting, Diarrhoea, Dyspepsia Common - Upper abdominal pain, Stomatitis
General disorders	Very common Fatigue (including asthenia), Decreased appetite, Headache, Dizziness, taste disturbance
Pneumonitis	Reported in a small number of patients, monitor patients for new or worsening respiratory symptoms such as dyspnoea, cough and fever. If pneumonitis is confirmed, olaparib should be discontinued.
Embryofoetal toxicity	Olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of olaparib.
MDS/AML	If patients' blood parameters remain clinically abnormal after 4 weeks of dose interruption of olaparib, bone marrow analysis is recommended. The incidence of MDS/AML in clinical trials of olaparib was <1.5% and the majority of events had a fatal outcome.

Bevacizumab	
Cardiac	Congestive heart failure, supraventricular tachycardia
Gastrointestinal	Rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, abdominal pain, gastrointestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae Prior radiation is a risk factor for GI perforation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
General Disorders	Asthenia, fatigue, pyrexia, pain, mucosal inflammation
Haematological	Febrile neutropenia, thrombocytopenia. Increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy
Musculoskeletal	Arthralgia, myalgia, muscular weakness, back pain
Nervous system	Peripheral sensory neuropathy, cerebrovascular accident, syncope, somnolence, headache
Renal	Dose dependent proteinuria is very common. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)
Reproductive	Bevacizumab may impair female fertility.
Skin	Very common: Wound healing complications, exfoliative dermatitis, dry skin, skin discoloration
Vascular	Increased risk of dose dependent hypertension. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Monitoring of blood pressure is generally recommended during therapy.
Thromboembolism	Increased risk of thromboembolic reactions including venous thromboembolism, pulmonary embolism, cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) Patients, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with bevacizumab. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Medical Assessment	X			X				Prior to cycle 3, then every 3 cycles or as per patients' management plan
SACT Assessment	X	X	X	X	X	X	X	Every Cycle
FBC	X	X	X	X	X	X	X	Every Cycle
U&E & LFT	X	X	X	X	X	X	X	Every Cycle
CrCl	X	X	X	X	X	X	X	Every Cycle
Blood Pressure	X	X	X	X	X	X	X	Every Cycle
Urine Dipstick	X	X	X	X	X	X	X	Every Cycle
CA125	X	X	X	X	X	X	X	Every Cycle
CT scan	X			X			X	After 3 and 6 cycles
Informed Consent	X							
PS recorded	X	X	X	X	X	X	X	Every Cycle
Toxicities documented	X	X	X	X	X	X	X	Every Cycle
Weight recorded	X	X	X	X	X	X	X	Every Cycle

Dose Modifications and Toxicity Management:

Dose reduction of bevacizumab is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Haematological toxicity

Proceed on day 1 if:-

Hb ≥ 100g/L	ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Interrupt treatment for 1 week on day 1 if:-

Hb 80 to100g/L	ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

If haemoglobin, platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need to be assessed and chemotherapy dose reduced by Oncologist.

Interrupt treatment for a maximum of 4 weeks if: -

Hb ≤ 80g/dL

Upon recovery dose of olaparib should be reduced to 250mg twice daily as a first step and then to 200mg twice daily as a second step in the case of repeat Hb decrease.

Non-haematological toxicities

Treatment must be interrupted for any patient who experiences an intolerable grade 2 or any grade 3 or 4 adverse event using the CTCAE V3/4, treatment can be restarted at a reduced dose when the toxicity returns to grade 1 or less.

Dose adjustments	
Initial dose	300mg twice daily
First dose reduction	250mg twice daily
Second dose reduction	200mg twice daily

Renal and hepatic impairment

Renal impairment	**Olaparib**	
	Creatinine Clearance (mL/min)	**Dose**
	>51	300mg twice daily
	31 to -51	200mg twice daily
	<31	Clinical decision
	Bevacizumab	
	There is no data regarding use of bevacizumab in patients with renal impairment. **See information regarding proteinuria below**	

Hepatic Impairment	**Olaparib**
	No dose adjustments required in mild or moderate hepatic impairment (Child-Pugh A or B). Olaparib is not recommended in patients with severe hepatic impairment (Child-Pugh C).
	Bevacizumab
	There is no data regarding use of bevacizumab in patients with hepatic impairment

Proteinuria

1+ or 2+ on dipstick (0.3 to 2.9g/L)	**3+ on dipstick (3 to 19g/L):**	**4+ on dipstick (≥20g/L)**
Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24 hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with bevacizumab. With continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to < 1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows < 2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.	**Withhold bevacizumab**. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Hypertension

- Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled (usually by GP) before starting bevacizumab treatment.
- If diastolic increase > 20mmHg above baseline or blood pressure rises to >150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilized, is usually best managed via the patient's GP.

- If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure controlled.
- For “white coat syndrome” induced hypertension, please contact patient’s GP for monitoring of blood pressure in between cycles.

References:

Summary of Product Charasteristics: Lymparza 150mg Film-Coated Tablets; AstraZeneca UK Limited. Last updated 01 January 2021

NICE FAD – Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. March 2021

Ray-Coquard, I et al. Olaparib Plus Bevacizumab as First Line Maintenance in Ovarian Cancer. N Engl J Med. Dec 2019; 381:2416-2428 (PAOLA-1 Trial)