SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Olaparib Tablets
Ovarian Cancer

PROTOCOL REF: MPHAOLTGY
(Version No. 2.1)

Approved for use in:

- High grade epithelial ovarian cancer
- International Federation of Gynaecology and Obstetrics (FIGO) Stage III or IV carcinoma
- Patients with germline or somatic BRCA1 or BRCA2 mutations
- Following first and subsequent line platinum based chemotherapy (minimum 4 cycles of platinum-containing treatment) and had complete or partial response – must be initiated within 8 weeks of their last dose of platinum-containing regime.
- ECOG performance status (PS) of 0 or 1.

Blueteq registration required

Dosage:

Drug	Dose	Route	Frequency
Olaparib tablets	**300mg**	PO	Twice daily

Treatment will be supplied **every 28 days**.

First line therapy

Treatment is to be **continued for up to a maximum of 2 years or until disease progression/unacceptable toxicity.**

Note: For those patients with stable residual disease after completing 2 years of treatment, treatment with maintenance olaparib can continue if the treating clinician considers that the patient will derive further benefit. **Further blueteq forms will need to be completed.**

Second or subsequent line therapy

Treatment can be **continued until disease progression/unacceptable toxicity.**

Administration

- Swallowed whole with water and taken approximately 12 hours apart.
- They can be taken with or without food.

Counselling Points

- **Missed doses**: Take the next normal dose at its scheduled time.
- 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.

Supportive treatments:

Metoclopramide 10mg tablets, three times daily as required for a maximum of five consecutive days.

Dosing in renal and hepatic impairment:

	Creatinine clearance (mL/min)	Dose
Renal	≥51	No dose reduction needed
	31-50	200mg twice daily
	≤30	Discontinue treatment

	Child Pugh Score	Dose
Hepatic	Child Pugh A and B (mild or moderate hepatic impairment)	No dose adjustment is needed.
	Child Pugh C (severe hepatic impairment)	Consider starting dose of 150mg BD

Interactions:

No other anticancer therapy (chemotherapy, immunotherapy, hormone therapy, radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving

Olaparib. **Unless the patient is treated in combination with bevacizumab (please refer to separate protocol).**

Olaparib under goes extensive metabolism by CYP3A4/5 and P-gp therefore inducers or inhibitors of this isoenzymes should be avoided where possible.

Olaparib may also induce several hepatic CYP metabolic pathways potentially reducing efficacy of hormonal contraceptives.

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.

For more detailed interactions please refer to the SmPC.

Main toxicities:

Olaparib	
Haematological toxicity	Very common – Anaemia, neutropenia, leukopenia. Common – Lymphopenia, thrombocytopenia
Respiratory disorders	Very common – Cough, dyspnea
Gastrointestinal disorders	Very common - Nausea, vomiting, diarrhoea, dyspepsia Common - Upper abdominal pain, stomatitis
Metabolism and nutrition disorders	Very common - decreased appetite
Nervous System disorders	Very common - headache, dizziness, taste disturbance
General disorders	Very common - Fatigue (including asthenia),
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 6 months after receiving the last dose of olaparib. Women of childbearing potential must use two forms of reliable contraception before starting olaparib treatment, during therapy

	and for 6 months after receiving the last dose of olaparib. Two highly effective and complementary forms of contraception are recommended.
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.

For more detailed toxicities/adverse reactions please refer to the SmPC.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	X					
Clinical Assessment	X			X		Every three cycles as per patients management plan
SACT Assessment (to include PS and toxicities)	X	X	X		X	Every cycle
FBC	X	X	X		X	Every cycle
U&E & LFTs & Magnesium	X	X	X		X	Every Cycle
CA125	X	X	X		X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X		X	Every cycle
CT scan**	X					At the end of treatment and if clinically indicated
Vital signs (BP, RR, HR)	X	X	X		X	Every cycle
Weight recorded	X	X	X		X	Every cycle

Dose Modifications and Toxicity Management:

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

For dose modifications for patients taking CYP3A inhibitors see drug interactions section above.

Haematological toxicity:

Proceed on day 1 if-

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

Delay for 2 weeks on day 1 if-

Hb 8-10g/dL	ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

- Please defer treatment for 2 weeks. If there is no urgent clinical need to administer blood products, ensure patient is given safety net advice.
- Please alert clinical team regarding deferral.
- If no improvement following 2 week deferral contact clinical team for advice.
- Interrupt treatment for a maximum of 4 weeks if **Hb ≤ 8g/dL**

- Upon recovery, the 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.
- Please make a note on the patient's medical record if they have required a blood support product and alert the team.

These haematological guidelines assume that patients are well with good performance status that other acute toxicities have resolved.

Non- Haematological toxicity (if required):

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

References:

1. Electronic Medicines Compendium (2023, 20 April), *Lymparza 100mg Film-Coated Tablets.* https://www.medicines.org.uk/emc/product/9204/smpc#gref

2. 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.

3. NICE TA598 – Olaparib for maintenance treatment of BRCA mutation positive advanced ovarian, fallopian tube or peritoneal cancer after response to first line platinum-based chemotherapy. Published August 2019

4. NICE TA620 – Olaparib for maintenance treatment of relapsed platinum sensitive ovarian, fallopian tube or peritoneal cancer. Published January 2020

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
May 2023	1.0	**Anna Burke** **Advanced Pharmacist**	V2.1 Routine Protocol Update