SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Olaparib
BRCA mutated HER2 negative early breast cancer

PROTOCOL REF: MPHAOBRCA
(Version No. 1.0)

Approved for use in:

See blueteq forms for full inclusion criteria – must be completed at time of discussing treatment with patient to ensure eligibility

- HER2 negative, ER positive or triple negative (ER/PR negative, HER2 negative) stage II-III breast cancer
- Following completion of definitive local therapy and 6 cycles of (neo)adjuvant systemic therapy with an anthracycline (unless contraindicated) and a taxane
- Patients must have a germline pathogenic or likely pathogenic BRCA1 or BRCA2 mutation
- PS 0-1
- For use in “high risk” patients defined as:
    - Patients with TNBC (defined as ER <1%, PR< 1% and HER2 0, 1+, or 2+ FISH negative) who have:
        - not had a pCR to neo-adjuvant chemotherapy
        - have a tumour greater that 2cm on pathological analysis or axillary node positive disease and have been treated with adjuvant chemotherapy
    - Patients with ER+ HER2- breast cancer who have:
        - not had a pCR following at least 6 cycles of neo-adjuvant chemotherapy and have a CPS+EG score of 3 or higher
        - at least four pathologically confirmed positive lymph nodes and have received adjuvant chemotherapy
- Treatment must be started 2 to 12 weeks after local therapy (including radiotherapy)

- NOT eligible to have concurrently with adjuvant abemaciclib

Dosage:

Drug	Dose	Route	Frequency	
Olaparib	**300 mg**	PO	Twice daily	For 52 weeks

Treatment will be supplied every 28 days; it is to be continued for 52 weeks unless discontinued for unacceptable toxicity or if evidence of recurrence of breast cancer

Administration:

- Olaparib tablets should be swallowed whole with water and taken approximately 12 hours apart with or without food.
- If a patient misses a dose of olaparib – they should take their next normal dose at 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.

Supportive treatments:

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

Dosing in renal and hepatic impairment:

	Creatinine Clearance (mL/min)	Dose
Renal	>50	No dose reduction needed
	31 to 50	200mg twice daily
	<31 or haemodialysis	Not studied. Use with caution. Consider starting dose 150mg BD.

<table>
<tr>
<td>Hepatic</td>
<td>
Child-Pugh A and B: no dose adjustment is needed
Child-Pugh C: consider starting dose 150mg BD.

<table>
<tr><th>Parameters</th><th>1 point</th><th>2 points</th><th>3 points</th></tr>
<tr><td>Total bilirubin (µmol/L)</td><td>< 34</td><td>34–50</td><td>> 50</td></tr>
<tr><td>Serum albumin (g/L)</td><td>> 35</td><td>28–35</td><td>< 28</td></tr>
<tr><td>Prothrombin time, prolongation (s)
Or
INR</td><td>< 4

< 1.7</td><td>4–6

1.7-2.3</td><td>> 6

>2.3</td></tr>
<tr><td>Ascites</td><td>None</td><td>Mild to Moderate (diuretic responsive)</td><td>Severe (diuretic refractory)</td></tr>
<tr><td>Hepatic encephalopathy</td><td>None</td><td>Grade I–II (or suppressed with medication)</td><td>Grade III–IV (or refractory to medication)</td></tr>
</table>
INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.
</td>
</tr>
</table>

Interactions:

Refer to SmPC for full list of interactions.

Olaparib under goes extensive metabolism by CYP3A4/5 and P-gp therefore inducers or inhibitors of these isoenzymes should be avoided where possible. Olaparib may also induce several hepatic CYP metabolic pathways potentially reducing efficacy of hormonal contraceptives.

CYP3A Inhibitors

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

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

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Ongoing
Informed Consent	X								
Clinical Assessment	X				X				Every 3 cycles or as per patients management plan
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	X	Every cycle
FBC & LFTs	X	X	X	X	X	X	X	X	Every cycle
U&E	X	X	X	X	X	X	X	X	Every Cycle
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Full observations	X	X	X	X	X	X	X	X	Every Cycle
Height	X								

* Monitor patients for new or worsening pulmonary symptoms indicative pneumonitis (e.g. shortness of breath, cough, and fever

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 1 week on day 1 if-

Hb < 10g/dL if < 8g/dL see below	ANC ≤ 0.9 x 10^9/L	Plt ≤ 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 ≤ 8g/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.

- There is no role for primary prophylaxis with G-CSF, however, in the case of neutropenic sepsis G-CSF may be used as per local protocols however should be avoided within 24 hours of olaparib administration.

Non- Haematological toxicity:

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

References:

1. https://www.medicines.org.uk/emc/product/9204/smpc#gref
2. https://www.nejm.org/doi/full/10.1056/NEJMoa2105215
3. NICE TA 10903, final appraisal document April 2023
4. BNF available via: https://bnf.nice.org.uk/

Circulation/Dissemination

Date added into Q-Pulse	13th September 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
September 2022	1.0	**Gabriella Langton** **Breast SRG Pharmacist**	First version
April 2023	1.1	**Helen Flint** **Consultant Pharmacist**	Funding now via NHS England