DRUP – Drug specific study manual for OLAPARIB (Lynparza)

1. Drug specific in- and exclusion criteria

Olaparib specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, with symptomatic or radiological disease progression after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
a. <u>For patients with a primary brain tumor</u>: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.			
3. Presence of an oncogenic mutation that can potentially be targeted by olaparib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation, has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have acceptable organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin ≥ 6.25 mmol/l, with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days			
c. Platelet count ≥ 100 x 10^9/L			
d. Total bilirubin < 1.5 x ULN			
e. AST (SGOT) and ALT (SGPT) ≤ 2.5 x institutional ULN (or ≤ 5 x ULN in patients with known hepatic metastases)			
f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma and T-cell prolymphocytic leukemia, primary brain tumors or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	Yes	No	n.a.
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor or other tumor types with only intracerebral lesions, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
10. Minimum life expectancy of ≥ 16 weeks			

Inclusion criteria	Yes	No	n.a.
11. Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). Women of childbearing potential must agree to use one highly effective method of birth control. They should continue using their chosen method of birth control for a minimum of 6 months after the last dose. Additionally, non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide throughout this period. - Female participants must not donate, or retrieve for their own use, ova at any time during this study and for at least 6 months after the last dose of olaparib. - Non-sterilized male participants, who intend to be sexually active with a female partner of childbearing potential or a pregnant woman, must be surgically sterile or using an acceptable method of contraception from Cycle 1 Day 1, throughout the total duration of the study and for 3 months after the last dose of study intervention to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period.			

Exclusion criteria	Yes	No	n.a.
1. Patients who are eligible for on-label treatment or ongoing trials with olaparib are excluded from treatment with olaparib within the DRUP trial.			
2. Patients who have previously been treated with PARP inhibitors.			
3. Patients with other malignancy within the last 5 years, except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localized breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.			
4. Known hypersensitivity to olaparib or any of the excipients of the product.			
5. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.			
6. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents			
7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.			

Exclusion criteria	Yes	No	n.a.
8. Major surgery within 2 weeks or significant traumatic injury within 4 weeks of starting study treatment: patients must have recovered from any effects of any major surgery.			
9. Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.			
10. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV). An exception is made for HIV patients with a known prior positive test, currently on effective anti-retroviral therapy with an undetectable viral load within 6 months.			
11. Patients with known active hepatitis (i.e. Hepatitis B (HBV) or Hepatitis C (HCV)) due to risk of transmitting the infection through blood or other body fluids. For patients with evidence of chronic HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of HCV infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.			
12. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).			
13. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, up to 28 days before start of study treatment).			
14. Ongoing toxicity ≥ grade 2, other than alopecia or grade 2 peripheral neuropathy.			
15. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
16. Patient is pregnant or nursing.			
17. Patients with known active progressive brain metastases or spinal cord compression. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			
<u>*For glioblastoma patients*</u>: *a. (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization.* *b. (II) No radiotherapy within the three months prior to the diagnosis of progression.* *c. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
18. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			

Exclusion criteria	Yes	No	n.a.
19. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
20. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			
21. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before treatment start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	At the end of every 2nd treatment cycle[4]	After end of treatment (≤ 30 days after stop)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1]		
Vital signs	x		x[1]		
Performance Status	x		x[1]		
CBC w/diff, platelets	x		x[1,2]		
Serum chemistry	x		x[1]		
Serum pregnancy test	x[6]				
Olaparib (Lynparza)			x[3] (continuous dosing)		
Tumor biopsy	x	x[5]			x[5]
Response evaluation	x[4]			x[4]	

1. According to local standard clinical practice, or as clinically indicated.
2. Anaemia and other haematological toxicities are generally low grade (CTCAE grade 1 or 2) however, there are reports of CTCAE grade 3 and higher events. Baseline testing, followed by monthly monitoring of complete blood counts is recommended to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.
3. Olaparib should be taken continuously in 28 day cycles. Olaparib tablet formulation can be given without regard to food.
4. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 3rd treatment cycle (i.e., every 12 weeks).
5. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be taken. The post-treatment biopsy is optional.
6. During screening, a serum test should be performed within 7 days before the first dose of olaparib for all female participants of childbearing potential.

3. Administration and starting dosage

The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken twice daily, for a total daily dose of 600 mg. Continue treatment until disease progression or unacceptable toxicity. Swallow tablet whole and not chewed, crushed, dissolved or divided. Olaparib tablet can be taken with or without food.
If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

4. How supplied

Olaparib is supplied as tablets (150 mg, or 100 mg in case of dose reductions), in packages of 32 tablets for each dose. Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

5. Dose modifications for toxicity

Please refer to section 4.8 of the SPC, or to section 6 Warnings and precautions below.

6. Warnings and precautions

Toxicity can be managed by dose interruption or dose reductions. Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step, with the exception of cases of CTC grade 3 /4 anaemia when dose should be reduced to 200 mg twice daily as first step. If the reduced dose of 200 mg twice daily is not tolerable, further dose reduction is not recommended and study treatment should be discontinued. Once dose is reduced, escalation is not recommended.
Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

<u>Hematological toxicity</u>

Leukopenia:

Decrease in the total number of white blood cells (leukopenia) and in certain white blood cells (neutropenia) that protect from infection can occur, which can be associated with symptoms of fever.

Management of anemia:

Haemoglobin	Action to be taken
Hb < 10 but ≥ 8 g/dl (CTCAE Grade 2)	<u>First occurrence:</u> Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose for a maximum of 4 weeks. If Hb has recovers to > 9 g/dL, olaparib can be restarted. NOTE: Transfusions should not be given during the protocol-defined dose-limiting toxicity (DLT) evaluation period. If a transfusion is felt to be necessary to treat a participant, the participant will no longer be considered evaluable for an anaemia DLT. <u>Subsequent occurrences:</u> If Hb < 10 but ≥ 9 g/dL, investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or dose interruption (for max of 4 weeks) and upon recovery, a dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step). If Hb < 9 but ≥ 8 g/dL, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dL and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to 250 mg twice daily as a first step and to 200 mg twice daily as a second step in the case haemoglobin decrease recurs.

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions.

Management of neutropenia, leukopenia and thrombocytopenia:

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg twice daily as a first step and 200 mg twice daily as a second step

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary. Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Management of prolonged hematological toxicities while on study treatment:
If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.
Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome and/or AML is confirmed.

Myelodysplastic syndrome/Acute myeloid leukemia (MDS/AML)
The overall incidence of MDS/AML in patients treated in clinical trials with olaparib was <1.5%. If MDS/AML is suspected, the patient should be referred to a hematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged hematological toxicity, MDS/AML is confirmed, olaparib should be discontinued and the patient treated appropriately.

Venous Thromboembolic Events (VTE)
VTEs, predominantly events of pulmonary embolism, have occurred in patients treated with olaparib and had no consistent clinical pattern. Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored appropriately.

Drug-induced liver injury (DILI)
Rare cases of DILI have been reported in patients treated with olaparib in the post-marketing setting. If DILI is suspected, treatment should be interrupted. If DILI is confirmed, treatment should be discontinued.

Hepatotoxicity
If clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected DILI, see section above.

Hepatitis B virus (HBV) reactivation
If evidence of HBV reactivation during the interventional period, study treatment should be interrupted, and the participant should be referred to a hepatologist. Study treatment can be restarted when the exclusion criteria are met and after discussion with study team. For participants with chronic hepatitis B, it is recommended that participants are followed by routine medical practice for reactivation for 12 months after cessation of study therapy.

<u>Renal impairment</u>: a dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD. If creatinine clearance drops below 30 ml/min, it recommended that olaparib be discontinued.

<u>Pneumonitis</u>
Pneumonitis has been reported in patients treated with olaparib monotherapy in clinical studies. When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated (including a high resolution CT scan). If no evidence of abnormality is observed on CT imaging and symptoms resolve, olaparib treatment can be restarted, if deemed appropriate by the investigator. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

<u>Management of nausea and vomiting</u>: nausea and vomiting associated with olaparib treatment is generally mild to moderate (CTCAE grade 1 or 2) in severity, intermittent and manageable on continued treatment. No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines

<u>Surgery, biopsies and radiation therapy</u>: olaparib should be stopped at least 3 days prior to planned surgery and re-started after wound has healed following recovery. No stoppage of olaparib is required for any biopsy procedures. Olaparib should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment.

<u>Embryo-Fetal toxicity:</u> olaparib can cause fetal harm. Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception throughout period of taking study treatment and for 6 month (female patients)/3 months (male patients) after last dose of study drug. NB The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

<u>Dermatologic reaction:</u> a rash is a common side effect that may occur. Uncommon side effects that may occur are:

- Allergic reactions
- Itchy rash on swollen, reddened skin (dermatitis)

Interactions:

- It is not recommended to consume grapefruit juice while on olaparib therapy.
- Co-administration with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced to 100mg BID for strong and 150mg BID for moderate CYP3A inhibitors.
- Co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced.
- Substrates of CYP3A4 should be given with caution in combination with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine).
- Substrates of UGT1A1 should be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).
- Olaparib may cause clinically relevant drug interactions with substrates of Pgp
- Live virus and live bacterial vaccines should not be administered whilst the patient is receiving olaparib and during the 30 day follow up period.

Driving and using machinery

Olaparib has moderate influence on the ability to drive and use machines. Patients who take olaparib may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.