KURZPROTOKOLL
AGO-OVAR 20 PAOLA-1

Öffentlicher Titel	Phase III Studie zu OLAparib bei Patienten mit Ovarial-, Eileiter oder Peritonealkarzinom in Erstlinie
Wissenschaftl. Titel	Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB - IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First-Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance
Kurztitel	AGO-OVAR 20 PAOLA-1
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, doppelblind, zweiarmig
Studienphase	Phase III
Erkrankung	Geschlechtsorgane: Krebserkrankungen der weiblichen Geschlechtsorgane: Eierstockkrebs (Ovarialkarzinom) - Erstlinie
Einschlusskriterien	- Female Patient must be 18 years of age. I-2. Signed informed consent and ability to comply with treatment and follow-up. - Patient with newly diagnosed I-3-1 Ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer, I-3-2 Histologically confirmed (based on local histopathological findings): - high grade serous (see appendix 2) or - high grade endometrioid (see appendix 2) or - other epithelial non mucinous ovarian cancer in a patient with germline BRCA 1 or 2 deleterious mutation I-3-3 at an advanced stage: FIGO stage IIIB, IIIC, or IV of the 1988 FIGO classification (see appendix 1). - Patient who has completed prior to randomization first line platinum-taxane chemotherapy: - 1. Platinum-taxane based regimen must have consisted of a minimum of 6 treatment cycles and a maximum of 9. However if platinum based therapy must be discontinued early as a result of non hematological toxicity specifically related to the platinum regimen, (i.e. neurotoxicity, hypersensitivity etc.), patient must have received a minimum of 4 cycles of the platinum regimen. - 2. Intravenous, intraperitoneal, or neoadjuvant platinum based chemotherapy is allowed; for weekly therapy, three weeks are considered one cycle. Interval debulking is allowed. - Patient must have received prior to randomization a minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based chemotherapy. Bevacizumab treatment should be administered at a dose 15mg/kg q3 weeks up to a total of 15 months. - Patient must be prior to randomization without evidence of disease (NED) or in complete response (CR) or partial response (PR) from her first line treatment. There should be no clinical evidence of disease progression (physical exam, imagery, CA 125) throughout her first line treatment and prior to study randomization. - Patient must be randomized at least 3 weeks and no more than 9 weeks after her last dose of chemotherapy (last dose is the day of the last infusion) and all major toxicities from the previous chemotherapy must have resolved to CTC AE grade 1 or better (except alopecia and peripheral neuropathy). - Patient must have normal organ and bone marrow function: - 1. Hemoglobin 10.0 g/dL. - 2. Absolute neutrophil count (ANC) 1.5 x 109/L. - 3. Platelet count 100 x 109/L. - 4. Total bilirubin 1.5 x institutional upper limit of normal (ULN).

- 5. Aspartate aminotransferase /Serum Glutamic Oxaloacetic Transaminase (ASAT/SGOT)) and Alanine aminotransferase /Serum Glutamic Pyruvate Transaminase (ALAT/SGPT)) 2.5 x ULN, unless liver metastases are present in which case they must be 5 x ULN.
- 6. Serum creatinine 1.25 x institutional ULN and creatinine clearance > 50 mL/min.
- 7. Patient not receiving anticoagulant medication who has an International Normalized Ratio (INR) 1.5 and an Activated ProThrombin Time (aPTT) 1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or APTT is within therapeutic limits (according to site medical standard) and if the patient is on a stable dose of anticoagulants for at least two weeks at the time of randomization.
- 8. Urine dipstick for proteinuria < 2+. If urine dipstick is 2+, 24-hour urine must demonstrate <1 g of protein in 24 hours.
- 9. Normal blood pressure or adequately treated and controlled hypertension (systolic BP 140 mmHg and/or diastolic BP 90 mmHg).
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see appendix 3) I-10. Formalin fixed, paraffin embedded (FFPE) tumor sample from the primary cancer must be available for central BRCA testing and test result must be available for stratification.
- Postmenopausal or evidence of non-childbearing status for women of childbearing potential prior to the first dose of study treatment. (see appendix 4) I-12. For France only: In France, a subject will be eligible for randomization in this study only if either affiliated to, or a beneficiary of, a social security category.

Ausschlusskriterien

- Non-epithelial origin of the ovary, the fallopian tube or the peritoneum (i.e. germ cell tumors).
- Ovarian tumors of low malignant potential (e.g. borderline tumors), or mucinous carcinoma.
- Patient with synchronous primary endometrial cancer unless both of the following criteria are met:
- 1. stage < II,
- 2. Less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade III endometrioid adenocarcinoma OR 60 years old at the time of diagnosis of endometrial cancer with stage IA grade 1 or 2 endometrioid adenocarcinoma.
- 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). Patient with a history of localized malignancy diagnosed over 5 years ago may be eligible provided she completed her adjuvant systemic therapy prior to randomization and that the patient remains free of recurrent or metastatic disease.
- Patient with history of primary triple negative breast cancer may be eligible provided she completed her definitive anticancer treatment more than 3 years ago and she remains breast cancer disease free prior to start of study treatment.
- Patient with myelodysplastic syndrome/acute myeloid leukemia history
- Patient having experienced for at least one cycle, a delay > 2 weeks due to prolonged hematological recovery during the first line chemotherapy
- Major surgery within 4 weeks of starting study treatment and patient must have recovered from any effects of any major surgery
- Previous allergenic bone marrow transplant
- Any previous treatment with PARP inhibitor, including olaparib.

- Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted as are steroidal antiemetics).
- Current or recent (within 10 days prior to randomization) chronic use of aspirin > 325 mg/day.
- Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.
- Prior history of hypertensive crisis (CTC-AE grade 4) or hypertensive encephalopathy.
- Clinically significant (e.g. active) cardiovascular disease, including:
- 1. Myocardial infarction or unstable angina within 6 months of randomization,
- 2. New York Heart Association (NYHA) grade 2congestive heart failure (CHF), (see appendix 5).
- 3. Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting ECG,
- 4. Peripheral vascular disease grade 3 (e.g. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision)
- Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA) or Sub-Arachnoids Hemorrhage (SAH) within 6 months prior to randomization.
- History or evidence of hemorrhagic disorders within 6 months prior to randomization.
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation).
- History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression.
- History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures).
- Significant traumatic injury during 4 weeks prior to randomization. E-22. Non-healing wound, active ulcer or bone fracture. Patient with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection is eligible but require 3 weekly wound examinations.
- History of VEGF therapy related abdominal fistula or gastrointestinal perforation or active gastrointestinal bleeding within 6 months prior to the first study treatment.
- Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease.
- Patient with evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
- Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment related complications.
- Pregnant or lactating women.
- Participation in another clinical study with an investigational product during her chemotherapy course immediately prior to randomization.

	- Patient unable to swallow orally administered medication and patient with gastrointestinal disorders likely to interfere with absorption of the study medication. - Patient with a known hypersensitivity to olaparib or any of the recipients of the product. - Immunocompromised patient, e.g., with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids or patient who is known to be serologically positive for human immunodeficiency virus (HIV).
Alter	18 Jahre und älter
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