# MITO 35a: a multicenter, prospective, single arm trial of Olaparib maintenance therapy in newly diagnosed BRCA wild-type advanced ovarian, primitive peritoneal, and fallopian tube cancer.

EUDRACT number: ……..

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| **Sponsor non-profit:** | National Cancer Institute, Naples, Italy |
| **Principal Investigator:** | Sandro Pignata, National Cancer Institute, Naples, Italy |
| **Study Coordinators:** | Clorinda Schettino, Francesco Perrone, National Cancer Institute, Naples, Italy |
| **Statisticans** | Paolo Chiodini, University of Campania Luigi Vanvitelli, Naples<br>Laura Arenare, National Cancer Institute, Naples |
| **Steering Committee:** (translational project) | Gustavo Baldassarre, Daniela Califano, Ettore Capoluongo, Maurizio D'Incalci, Sergio Marchini, Delia Mezzanzanica, Nicola Normanno, Sandro Pignata. |

Ethics Committee approval Version:

Administrative approval Version:

## AMENDMENTS

| Number | Type | Approval date | Description |
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## Protocol Authorization

I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice and the appropriate national laws.

**Principal Investigator**

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Dr. Sandro Pignata Date

**Local Investigator**

_____ _____

Date

# PROTOCOL SYNOPSIS

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| **Study Title** | MITO 35a: a multicenter, prospective, single arm trial of Olaparib maintenance therapy in newly diagnosed BRCA wild-type advanced ovarian, primitive peritoneal, and fallopian tube cancer. |
| **Principal Investigator** | Dr. Sandro Pignata, M.D., PhD |
| **Coordinating Investigator** | Dr. Francesco Perrone, M.D, PhD Clinical Trials Unit, National Cancer Institute, Naples.<br>Dr. Clorinda Schettino, M.D, Clinical Trials Unit, National Cancer Institute, Naples. |
| **Study sites and number of subjects planned** | 50 centers belonging to the MITO network.<br>200 BRCA wild type patients will be enrolled into the trial. |
| **Sponsor** | Istituto Nazionale Tumori "Fondazione G. Pascale", Napoli |
| **Study period** | Assuming an accrual rate of 8/9 subjects/month, 24 months would be needed to complete the enrollment.<br>An estimation of the total study duration is 48 months.<br>The date of end of study will be the date of the last visit of the last patient (LPLV). |
| **Study Design** | This trial is a multicenter, prospective, single arm, open-label trial in which patients with newly diagnosed advanced epithelial ovarian, primitive peritoneal, and fallopian tube cancer BRCA wild type, in partial or complete response to first line platinum-based chemotherapy, receive Olaparib maintenance therapy (300 mg tablets formulation twice daily). Patients will stop Olaparib maintenance after 24 months of treatment in absence of disease progression. Patients who continue to have evidence of stable disease at two years may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest.<br>Olaparib will be provided by the Company (Astrazeneca/MSD) |
| **Study Drug** | Olaparib single agent 300 mg, twice daily. |

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| **Primary Objectives** | To evaluate the efficacy of Olaparib as maintenance therapy in this setting on PFS.<br>To define if there are prognostic factors among the clinical and biological characteristics of patients and tumor biomarkers in this setting, that can identify a subset of patients with better prognosis in terms of PFS. |
| **Secondary Objectives** | To determine the efficacy of the subsequent treatment after Olaparib progression on PFS.<br>To evaluate the efficacy of Olaparib as maintenance therapy in this setting on OS;<br>To define if there are prognostic factors among the clinical and biological characteristics of patients and tumor biomarkers in this setting that can identify a subset of patients with better prognosis in terms of OS;<br>To evaluate the safety of Olaparib as maintenance therapy in this setting. |
| **Translational Objective** | To validate an HRD academic test |
| **Study Endpoints** | Primary Endpoints:<br>PFS as defined by the Investigator using RECIST 1.1, and clinical criteria as the time frame from enrollment to progression or death for any cause.<br>Secondary Endpoints:<br>PFS2 as defined by the Investigator using RECIST 1.1 and clinical criteria as the time frame from enrollment to the second progression or death for any cause after subsequent treatment.<br>OS as defined by the Investigator as the time from enrollment to death for any cause.<br>The toxicity profile of Olaparib (CTCAE version 5.0)<br>Translational Endpoint:<br>Evaluation of concordance of HRD academic test with the commercial Myriad myChoice test. |
| **Target subject population** | **Inclusion Criteria** |

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| | 1. Signed informed consent obtained prior to initiation of any study-specific procedures.<br><br>2. Female aged ≥18 years on day of signing informed consent.<br><br>3. Patients with histologically diagnosed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III-IV) high grade serous or endometrioid epithelial ovarian cancer (including primary peritoneal, or fallopian tube cancer).<br><br>4. Patients with a complete or partial response to first line platinum-based treatment not including Bevacizumab.<br><br>5. Documented absence of somatic and germline mutations of BRCA 1 /2.<br><br>6. Patients must have a life expectancy ≥ 16 weeks.<br><br>7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.<br><br>8. Availability of sufficient formalin-fixed paraffin-embedded (FFPE) tumor tissue from the primary surgery (chemotherapy – naïve patients) for translational analysis. A quality control analysis of samples will be performed before patient's enrollment.<br><br>9. Patients must be enrolled within 8 weeks of the first day of the last dose of chemotherapy.<br><br>10. Patients must be able to take oral medications.<br><br>11. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1.<br><br>Postmenopausal is defined as:<br><br>– Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments<br><br>– Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for |

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| | women under 50<br>– radiation-induced oophorectomy with last menses >1 year ago<br>– chemotherapy-induced menopause with >1 year interval since last menses<br>– surgical sterilisation (bilateral oophorectomy or hysterectomy)<br><br>12. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:<br>– Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days<br>– Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L<br>– Platelet count ≥ 100 x $10^9$/L<br>– Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)<br>– Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN<br>– Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test :<br>o Estimated creatinine clearance = (140-age [years]) x weight (kg) (x F)[a]<br>o serum creatinine (mg/dL) x 72<br>[a] where F=0.85 for females<br><br>13. Willingness and ability to comply with scheduled visits, |

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| | treatment plan, laboratory tests, and other trial procedures.<br><br>**Exclusion Criteria**<br><br>1. Patients have received Bevacizumab in concomitance with first line platinum-based therapy or as maintenance therapy following chemotherapy.<br><br>2. Clear cell, mucinous and mixed Mullerian tumors/carcinosarcoma, non-epithelian tumors or ovarian tumors with low malignant potential (ie. borderline tumors) are not allowed.<br><br>3. Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.<br><br>4. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).<br><br>5. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable).<br><br>6. Breast feeding women.<br><br>7. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.<br><br>8. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.<br><br>9. Patients with active second malignancy.<br><br>10. Other malignancy unless curatively treated with no evidence of disease for ≥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 |

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| | carcinoma.<br><br>11. Any prior treatment for ovarian cancer, other than first line platinum-based therapy, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study<br><br>12. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment.<br><br>13. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.<br><br>14. Concurrent treatment with other investigational agents.<br><br>15. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.<br><br>16. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).<br><br>17. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).<br><br>18. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.<br><br>19. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome. |

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| | 20. Evidence of any other medical conditions, physical examination or laboratory findings that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment related complications.<br><br>21. Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.<br><br>22. Concomitant use of known strong (e.g. 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.<br><br>23. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.<br><br>24. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.<br><br>25. Received chemotherapy within 14 days prior to first dose of study drug and/or persisting toxicity related to prior therapy of grade 1 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anemia with hemoglobin ≥ 9 g/dL, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug. |
| **Duration of treatment** | Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not |

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| | meet any other discontinuation criteria.<br><br>Patients who continue to have evidence of stable disease at two years may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. |
| **Investigational product, dosage and mode of administration** | Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients on day 1 and every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study.<br><br>Study treatment is available as a film-coated tablet containing 150 mg of Olaparib. The planned dose of 300 mg BID will be made up of two x 150 mg tablets BID with 100 mg tablets used to manage dose reductions. |
| **Sample size** | This is an exploratory study and no a priori hypothesis is defined to calculate the sample size of the trial. With a sample size of 200 patients and after the registration of 143 PFS events, the study will have 80% power to identify a prognostic factor able to select a favorable subgroup with a 0.60 HR, for a presumed expression of the favorable prognostic factors in 30% of the population, with alpha level of 0.05.<br><br>For the translational aim, the Intraclass Correlation Coefficient (ICC) will be used to estimate overall concordance HRD academic test with the commercial Myriad test. Considering an estimated ICC of 0.70, a sample size of 103 subjects with 2 measures produces a 95% confidence interval with a width of 0.20. |
| **Statistical methods** | Descriptive statistics will be used to describe the patient population, and safety. Kaplan-Meier method will be applied to draw PFS and OS curves. Curves will be compared using log-rank test.<br>Correlation between biomarkers will be assessed. This study is exploratory and tries to assess the prognostic role of many clinical, biological characteristics and biomarkers with different prevalence and effect on prognosis. Multivariable Cox regression model will be used for PFS and OS. |

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| | Adjustments for test multiplicity will be used. Specifically, different significance levels are used according to a pre-defined step-down Holm-Bonferroni sequential testing procedure.<br><br>For translational analysis intraclass correlation coefficients will be calculate with 95% confidence interval. |
| **Approximate Duration of Study** | The total estimated duration of the trial is 48 months. |
| **Safety Assessment** | All patients receiving at least one dose of study drug will be considered evaluable for safety. The adverse event incidence rates as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described. Safety assessments will include routine physical examinations and laboratory evaluations. Adverse experiences will be recorded throughout the study and during the follow-up period. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading (according to NCI CTCAE criteria [version 5.0]) and action taken with regard to trial treatment. |