Olaparib beyond progression compared to platinum chemotherapy after secondary cytoreductive surgery in recurrent ovarian cancer patients. The phase III randomized, open label MITO 35b study: a project of the MITO-MANGO groups.

EUDRACT NUMBER ……..

Sponsor non-profit: National Cancer Institute, Naples

Principal Investigators: Sandro Pignata and Stefano Greggi, National Cancer Institute, Naples

Study Coordinators: Francesco Perrone, Clorinda Schettino, Clinical Trials Unit, National Cancer Institute, Naples

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Steering Committee: (translational project) Gustavo Baldassarre, Daniela Califano, Ettore Capoluongo, Maria Paola Costi, Maurizio D'Incalci, Sergio Marchini, Delia Mezzanzanica, Nicola Normanno, Sandro Pignata, Stefania Scala.

Coordinating Independent Ethical Committee: National Cancer Institute, Naples

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 Investigators

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Dr. Sandro Pignata Date

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Dr. Stefano Greggi Date

Local Investigator

_____ _____

Date

PROTOCOL SYNOPSIS

Study Title	Olaparib beyond progression compared to platinum chemotherapy after secondary cytoreductive surgery in recurrent ovarian cancer patients. The phase III randomized, open label **MITO 35b** study.
Principal Investigators	Dr. Sandro Pignata, MD, PhD and Dr. Stefano Greggi, MD, PhD.
Coordinating Investigators	Francesco Perrone, M.D, PhD Clinical Trials Unit, National Cancer Institute, Naples. Dr. Clorinda Schettino, M.D, Clinical Trials Unit, National Cancer Institute, Naples.
Study sites and number of subjects planned	50 centers among the MITO and MANGO networks will be involved in the accrual of 200 patients
Sponsor	Istituto Nazionale Tumore "Fondazione G. Pascale", Napoli
Study period	Assuming an accrual rate of 8/9 subjects/month 24 months would be needed to complete the enrollment. The date of end of study will be the date of the last visit of the last patient (LPLV)
Study design	MITO 35b trial is an open label, randomized, phase III study aimed to evaluate if olaparib maintenance beyond progression after secondary cytoreductive surgery is superior, in terms of progression-free survival, to standard chemotherapy in patients who experience disease recurrence during or after first-line maintenance with a PARPi. Eligible patients will be randomized 1:1 to receive: • **ARM A**: Olaparib 300 mg twice daily, d1-28 continuously • **ARM B**: Platinum-based chemotherapy at the Investigator's choice Patients will be stratified according to a) BRCA 1/2 genes status (mutated *vs* wild type); b) residual disease after secondary surgery (absent *vs* present); type of recurrence (during PARPi *vs* after the end of maintenance therapy). In case of futility at planned interim analysis, the randomization will be stopped, and the experimental arm will be closed. After the protocol emendation, the study will continue, and the patients will be enrolled only in the standard arm. A quality control revision of tumor sample will be performed by the Sponsor within

	8 working days from the date of centralization at NCI of Naples. Only patients with representative tumor sample will proceed to randomization in the current study.
Study Drugs	ARM A: Olaparib single agent 300 mg, twice daily ARM B: Platinum-based chemotherapy at the Investigator's choice
Primary Objective:	• To determine the efficacy (as assessed by Investigators using progression-free survival) of olaparib maintenance beyond progression when compared to standard chemotherapy in patients with recurrent ovarian cancer undergone secondary cytoreductive surgery for recurrent or progressive disease. • To determine the efficacy of the experimental therapies on subsequent treatment (as assessed by Investigators using progression-free survival 2) after progression.
Secondary objectives	• To determine the efficacy (as assessed by overall survival) of olaparib when compared to a platinum-based chemotherapy in patients with recurrent ovarian cancer who have undergone secondary surgery at progression to first line PARPi maintenance • To compare the two arms in terms of the safety and tolerability (CTCAE 5.0 version and PRO-CTCAE) • To assess changes in Quality of Life parameters in patients treated with olaparib maintenance compared to chemotherapy (EORTC QLQ-C30) • To compare the two arms in terms of financial toxicity assessed with PROFFIT
Translational objective	To explore the mechanisms of resistance to olaparib through the molecular analysis of tumor samples collected at surgeries.
Target Subject Population	**Inclusion criteria:** • Signed informed consent prior to any study specific procedures; • Female, age ≥ 18 years at time of signing informed consent • Patients with high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer recurrent or progressive after first line PARPi maintenance are allowed; • Patients must have received only one previous line of a platinum containing regimen not containing bevacizumab; • Patient must have received a first-line maintenance therapy with a PARPi for at least 6 months; patients who experience disease relapse after the end of the 24 months maintenance therapy are eligible;

	• Patients must have undergone secondary cytoreductive surgery. The cytoreduction must result in complete resection (absence of macroscopic residual tumor) or at least resection of the progressive lesion(s) occurring during maintenance • Documented BRCA1/2 status. Both mutated and wild type patients are eligible. Patient with unknown status of BRCA genes agrees to undergo analysis of their germline and somatic BRCA status (testing must be completed prior to randomization in the study); • Patients must have a life expectancy ≥ 16 weeks; • Patients must start the experimental treatments in the current study within 3 to 8 weeks from second surgery; • ECOG performance status of 0 to 1; • Patient must provide archival tumor samples formalin fixed, paraffin embedded (FFPE) from both the primary and secondary surgeries for paired analysis. A quality control analysis of samples will be performed before patient's randomization; • Patient must be able to take oral medications; • Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below: o Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days o Absolute neutrophil count (ANC) ≥ 1.5 x 109/L o Platelet count ≥ 100 x 109/L o Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) o 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 o Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test: Estimated creatinine clearance = (140-age [years]) x weight (kg)(x F)[a] serum creatinine (mg/dL) x 72 ([a] where F=0.85 for

	females and F=1 for males.) • 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. Postmenopausal is defined as amenorrheic for 1 year or more following cessation of exogenous hormonal treatments • Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures; **Exclusion Criteria:** • 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; • Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication; • Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment; • Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of major surgery; • Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT); • Breast feeding women; • 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. • 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 carcinoma; • Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable) except for transfusion done during surgery • Persistent toxicities (>CTCAE grade 2) caused by previous cancer therapy, excluding alopecia. • 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 • 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. • 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. • Patients with myelodysplastic syndrome (MSD)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML. • Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV). • Patients with a known hypersensitivity to olaparib or any of the excipients of the product. • Patients that, at the Investigator's opinion, are not eligible according to ESMO guidelines for a re-treatment with a platinum containing therapy (i.e. patient has experienced a major adverse reaction to platinum salts during first line therapy). • Patients with known active hepatitis (i.e. Hepatitis B or C)

	○ Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. ○ Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. • Participation in another clinical study with an investigational product during the last 3 months
Duration of treatment	Experimental treatment with olaparib maintenance beyond progression will be continued until disease progression, unacceptable toxicity or patient withdraw. Patients in the chemotherapy arm can receive up to 8 treatment's cycles.
Approximate Duration of Study	The total estimated duration of the trial 48 months years.
Investigational products, dosage and mode of administration	Olaparib 300 mg twice daily PO, d1-28 continuously (ARM A) Platinum-based chemotherapy at the Investigator's choice (ARM B) For patients randomized in the ARM B of the study, the following platinum regimens are allowed – Carboplatin (AUC5) plus Pegylated Liposomal Doxorubicin (PLD) 30mg/m^2 on day 1 every 28 days for a maximum of 8 cycles; – Carboplatin (AUC4) plus Gemcitabine 1000mg/m^2 on day 1, 8 every 21 days for a maximum of 8 cycles; – Carboplatin (AUC5) plus Paclitaxel (175mg/m^2) every 21days for a maximum of 8 cycles; Single agent Carboplatin (AUC5) or Cisplatin 75mg/m^2 (or 60 mg/m^2) every 21 days a maximum of 8 cycles

Statistical methods	All the efficacy analyses will be performed on an intention-to-treat basis. Descriptive statistics will be used to describe the patient population, compliance and safety. For PFS, patients alive and for whom an objective disease progression has not been observed will be censored at the last time known to be alive and without objective disease progression. For OS patients lost to follow up or alive at the time of final analysis will be censored the last date they were known to be alive. PFS and OS curves will be described according to the Kaplan-Meier method and treatment groups will be compared using log-rank test. For each PFS endpoint, treatment groups will be compared using two-sided log-rank test with alpha level of 0.025. Multivariable Cox regression model will be used using BRCA genes status (mutated vs wild type), Residual disease after second surgery (present vs absent), Type of progression to first line PARPi (during maintenance vs after its completion), treatment, age and performance status (PS) as covariate. Heterogeneity of treatment effects across the subgroup will be tested by means of treatment-by-subgroup interaction with adjustment for test multiplicity according to Holm-Bonferroni method. Exploratory subgroup analyses will be plotted in a forest plot reporting HRs and 95% CIs. Safety analysis will be performed on safety population, defined as women receiving at least a dose of treatment. For each patient and for each type of toxicity, the worst event suffered will be calculated. Worst-grade (from 0 to 5) and severe toxicity (grade 3-5 vs grade 0-2) will be compared between the two treatment groups with linear rank test and Fisher's exact test, respectively. Unless otherwise noted, all tests will be two-sided with a significance level of 0.05. Interim assessments and study monitoring for efficacy and safety will be done by an independent DSMB, which will review event rates. To warrant safety of patients in the experimental arm, an early formal interim analysis is planned when about one-third of the planned events (50 events) for PFS 1 will be observed, using a futility approach. A user-defined gamma spending function (γ=5) will be used as a beta-spending function to determine the non-binding futility boundary. Based on the choice of β-spending function described above, the futility boundary in terms of Z value scale at the interim is calculated as Z = -0.057 (hazard ratio=0.984) Specifically, if at interim analysis the hazard ratio will be greater than 0.984 the DSMB may consider recommending early termination of the study. Interim analysis, stopping early for futility preserves the overall significance level, and nominal confidence interval and p-value at the end of the trial will be used.