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: 2021-000245-41	Version n.1 1 July, 2021

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 **2021-000245-41**

Sponsor non-profit:	National Cancer Institute, Naples
Principal Investigators:	Sandro Pignata and Stefano Greggi, National Cancer Institute, Naples
Study coordination:	Francesco Perrone, Clorinda Schettino (Responsible for study coordination, Clinical Trials Unit, National Cancer Institute, Naples
Statisticians	Paolo Chiodini, University of Campania Luigi Vanvitelli Laura Arenare, National Cancer Institute, Naples
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

Supplemental material BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s) *Int J Gynecol Cancer*

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

Dr. Sandro Pignata — Date 1/7/2021

Dr. Stefano Greggi — Date 5-7-21

Trial Promoter Coordinating Centre

Dr. ssa Clorinda Schettino — Date 1/7/2021

Schettino C, *et al. Int J Gynecol Cancer* 2023; 32:799–803. doi: 10.1136/ijgc-2022-003435

Local Investigator

_____ — Date _____

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: 2021-000245-41	Version n.1 1 July, 2021

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS……08
SYNOPSIS…… 10
1. INTRODUCTION 19
1.1 Background and rationale for conducting this study 19
2. STUDY DESIGN....21
2.1 Centres 22
3. STUDY OBJECTIVES....25
3.1 Primary objectives 25
3.2 Secondary objectives 25
3.3 Translational objectives 26
4. PATIENTS SELECTION....26
4.1 Inclusion criteria 26
4.2 Exclusion criteria 28
4.3 Subject enrolment and randomization 30
4.4 Procedures for handling incorrectly enrolled or randomized subjects....31
4.5 Screening Failure 31
4.6 Treatment, Patients and Study Discontinuation....32
4.6.1 Study Treatments Discontinuation....32
4.6.2 Patients Discontinuation from Study 32
4.6.2.1 Withdrawal of the informed consent....32
4.6.3 Discontinuation of the study 33
5. TREATMENT PLAN....33
6. ASSESMENTS AND PROCEDURES DURING THE STUDY....34
6.1 Enrolment/screening period....38
6.2 Treatment period....38
6.3 Follow-up period....39
7. STUDY ASSESSMENTS 39
7.1 Informed Consent....39
7.2 Physical examination 39
7.3 Vital signs 40

7.4 Electrocardiograms 40
7.5 Laboratory assessment 40
7.6 Serum or urine pregnancy test 40
7.7 Coagulation 41
7.8 Other safety assessments 42
7.9 Patient Reported Outcome 42
7.9.1 EORTC QLQ-C30 43
7.9.2 PRO-CTCAE 43
7.9.3 PROFFIT 43
7.10 Tumor Response Assessments 43
7.11 Archival Tumor Tissue Samples 44
7.12 Prospective collection of blood samples 45
8. ADVERSE EVENTS REPORTING 45
8.1 Definitions 45
8.2 Pregnancy 47
8.3 Adverse events after the end of treatments visit 47
8.4 Collection and reporting of adverse events 48
8.4.1 Variables 48
8.4.2 Adverse events based on signs and symptoms 49
8.4.3 Adverse events based on examinations and tests 50
8.4.4 Hy's Law 50
8.4.5 Disease progression 50
8.5 Collection and reporting of SAE, AESI, pregnancy. 50
8.6 Assessment of causality between treatment and event 51
8.7 Adverse Event of Special Interest (AESI) 52
8.8 Procedures for safety reporting 52
8.9 Other event requiring reporting 53
8.9.1 Overdose 53
9. MANAGEMENT OF TREATMENTS RELATED TOXICITIES AND DOSE REDUCTIONS 55
9.1 Management of olaparib related toxicities in patients in ARM A and dose modification 55
9.1.1 Management of haematological toxicity during olaparib 55
9.1.1.1 Management of anaemia 55
9.1.1.2 Management of neutropenia, leukopenia and thrombocytopenia 56

9.1.1.3 Management of prolonged hematological toxicities while on study treatment 57
9.1.2 Management of non-haematological toxicity 57
9.1.3 Management of new or worsening pulmonary symptoms 58
9.1.3.1 Management of nausea and vomiting 58
9.1.4 Renal Impairment 58
9.1.5 Interruptions for intercurrent non-toxicity related events 59

9.2 Management of platinum-based regimen related toxicities in patients in ARM B and chemotherapy dose modifications and delay. 60
9.2.1 Hypersensitive Reactions to Chemotherapy 61
9.2.2 Supportive Care for Chemotherapy Treatment 61

10. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS 61

10.1 Olaparib 61
10.1.1 Identity of Investigation product 61
10.1.2 Dose and treatment regimen 62

10.2 Chemotherapeutics 62
10.2.1 Carboplatin 62
10.2.1.1 Carboplatin dose 62
10.2.2 Paclitaxel 63
10.2.2.1 Paclitaxel dose 63
10.2.3 Pegylated Liposomal Doxorubicin (PLD) 63
10.2.3.1 PLD dose 63
10.2.4 Gemcitabine 63
10.2.4.1 Gemcitabine dose 63

10.3 Premedication and Antiemetic Therapy (chemotherapy arm) 64

10.4 Concomitant and other treatments (chemotherapy arm) 64
10.4.1 Anticoagulant Therapy 64
10.4.2 Vaccines 64

10.5 Restriction during the study (chemotherapy arm) 64

11. RESTICTIONS DURING THE STUDY AND CONCOMITANT MEDICATIONS (OLAPARIB) 65

11.1 Anti-emetics/Anti-diarrhoeal 65

11.2 Restriction during the study 65

11.3 Restricted concomitant medications 65
11.3.1 Strong or Moderate CYP3A inhibitors 65
11.3.2 Strong or Moderate CYP3A inducers 66
11.3.3 Anticoagulant therapy 66
11.3.4 Natural/herbal products 66
11.3.5 Effect of olaparib on other drugs 66

11.4 Concomitant anti-cancer treatments 67

11.4.1 Palliative radiotherapy 67
12. STATISTICAL ANALYSES 68
12.1 Statistical considerations 68
12.2 Sample size estimate 68
12.3 Definitions of analysis sets 68
12.3.1 Full Analysis Set 68
12.3.2 Safety analysis set 68
12.3.3 PRO analysis set 68
12.4 Outcome measures for analyses 68
12.4.1 Primary outcomes: 68
12.4.2 Secondary outcomes: 69
12.5 Methods for statistical analyses 69
12.5.1 Analysis of the primary variables 69
12.5.2 Analysis of the secondary variable(s) 70
12.5.3 Exploratory subgroup analysis 71
12.6 Interim analysis 71
12.7 Translational analysis 72
13. STUDY AND DATA MANAGEMENT 72
13.1 Training of study site personnel 72
13.2 Monitoring of the study ..... **Errore. Il segnalibro non è definito.**
13.3 Data Collection Procedures and Data Management 73
13.4 Study timetable and end of study 73
13.5 Independent Data Monitoring Committee 73
14. TRANSLATIONAL PROJECT AND BIOMARKER SAMPLES 74
14.1 Rationale for the translational study 74
14.2 Specimen Types 74
14.2.1 Solid samples 74
14.2.2 Blood samples 75
14.2.3 Samples handling and shipping 75
14.3 Translational Objectives 76
14.3.1 Task 1. Genomic evaluation of PARPi resistance. 76
14.3.2 Task 2 Integration of epigenomics and transcriptomics profiles 76
14.3.3 Task 3 HRD mechanisms and the relationship with angiogenesis and immune related biomarkers 77
14.3.4 Evaluation of immune infiltrate. 77
14.3.5 Tertiary Lymphoid structure (TLS) 78
14.3.6 Evaluation of STING pathway. 78

14.3.7 Evaluation of the angiogenic status. 78
14.3.8 Task 4: Translational studies through Mass Spectrometry Imaging (MSI). 79
14.3.9 Task 5: Pharmacogenetic analysis of olaparib ADME 79
14.4 Samples shipping 80
15. ETHICAL AND REGULATORY REQUIREMENTS 81
15.1 The risk/benefit evaluation 81
15.2 Informed consent 81
16. ADMINISTRATIVE ASPECT 83
16.1 Publication Policy 83
17. COORDINATING CENTER CONTACTS 84
18. LIST OF REFERENCES 86

LIST OF APPENDICES

Appendix A Evaluation of Hy's Law 88
Appendix B RECIST Criteria v 1.1 93
Appendix C Acceptable birth control methods 98

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: 2021-000245-41	Version n.1 1 July, 2021

List of abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BRCA	Breast Related Cancer Antigens
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FFPE	Formalin fixed paraffin embedded
GCP	Good Clinical Practice
HGSOC	High grade serous ovarian cancer
HR	Hazard Ratio
ICF	Informed consent form
ICH	International Conference on Harmonisation
IB	Investigator Brochure
IDMC	Independent Data Monitoring Committee
IP	Investigational Product
ISF	Investigator Site File
IV	Intravenous
ITT	Intent-to- Treat
LSLV	Last Subject Last Visit
MRI	Magnetic Resonance Imaging
OAE	Other Significant Adverse Event
OS	Overall Survival

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: 2021-000245-41	Version n.1 1 July, 2021

Abbreviation or special term	**Explanation**
PARPi	Poly ADP ribose polymerase (PARP) inhibitors
PFS	Progression-free survival
PFS2	Time to second progression
PI	Principal Investigator
PR	Partial Response
PD	Progression Disease
PROCTCAE	Patient Reported Outcome Common Terminology Criteria for Adverse Event
PROFFITT	Patient Reported Outcome for Fighting Financial Toxicity
QTcF	QT interval corrected for heart rate using Frederica's formula
RA	Research Agreement
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
RNA	Ribonucleic acid
RSI	Reference Safety Information – reference information for the expectedness of a serious adverse reaction to the IP
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal
WBDC	Web Based Data Capture

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: 2021-000245-41	Version n.1 1 July, 2021

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	Approximately 45 centers among the MITO and MANGO networks will be involved in the accrual of 200 patients
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 enrolment. The date of end of study will be the date of the last visit of the last patient (LPLV) The total estimated duration of the trial 48 months years.
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). The study is dimensioned to test the hypothesis that olaparib (experimental arm) vs a further line of chemotherapy prolong PFS and/or PFS 2 with an HR of 0.60. Considering a two-sided log-rank test with alpha of 0.025, to attain an 80% power,

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: 2021-000245-41	Version n.1 1 July, 2021

	follow-up will be continued to reach 146 events necessary for the final analysis. Approximately 200 patients will be enrolled in the study. The date of end of study will be the date of the last visit of the last patient. In case of futility at planned interim analysis, the randomization will be stopped, and the experimental arm will be closed. The study will continue, and the patients will be enrolled only in the standard arm to continue translation project, only after the protocol amendment.
Study Drugs	ARM A: Olaparib single agent 300 mg, film-coated tables, twice daily ARM B: Platinum-based chemotherapy at the Investigator's choice
Primary Objectives:	• To determine the efficacy (in terms of 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 (in terms of progression-free survival 2) after progression.
Secondary objectives	To compare the two arms in terms of: • Overall Survival • Safety and tolerability (CTCAE 5.0 version and PRO-CTCAE questionnaire) • Quality of Life (EORTC QLQ-C30 questionnaire) • Financial toxicity (PROFFIT questionnaire)
Translational Project	**Translational Objectives:** To explore the mechanisms of resistance to olaparib through the molecular analysis of tumor samples collected at surgeries. To describe the variations in the soluble biomarker's expression levels collected before, during and at the end of treatment. The translational project includes the collection of biological samples: 1) Formalin- Fixed- Paraffin- Embedded (FFPE) tumor samples will be collected from.primary surgery (chemotherapy-naive patients) and secondary surgery (after PARPi maintenance). 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.

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: 2021-000245-41	Version n.1 1 July, 2021

	2) Blood samples for each patient at 3 time points will be collected: at baseline, at the time of the first radiological evaluation and at the end of treatment (EOT) visit. Translational plan: • Task 1: Genomic evaluation of PARP resistance (HRR functionality by RAD51 foci) • Task 2: Integration of epigenomics and trascriptomics profiles • Task 3: HRD mechanisms and the relationship with angiogenesis and immune related biomarkers: 1. Evaluation of immune infiltrate (TIL) 2. Tertiary Lymphoid structure (TLS) 3. Evaluation of the STING pathway regulation looking at the level of IFNα, IFNβ, CXCL5-10 4. Evaluation of angiogenic status (VEGFA, VEGFB, PlGF, VEGFR1 and 2, CD31, CD34 e αSMA) • Task 4: Traslational studies through Mass Spectrometry Imaging (MSI): 1) spatial distribution of PARPi modulated proteins in cancer tissues, in particular the PARP enzymes family (among which PARP1, PARP2, PARP3); 2) changing of PARPi associated proteins with the cancer progression on PARPi; 3) Specific proteins alterations, which might be associated with the onset of PARPi resistance; i) Cell Cycle markers status. Considering that the response to DNA damage will be different depending on the cell-cycle status18, cell cycle markers will be analyzed among the following ones: Cdh1, Cdc20, cyclin B1, Aurora A, cyclin A, p27kip1 (G0-G1 phase marker); Cyclin E (early S phase); Skp2 (G1-S marker); and phospho Histone-H3 (pHH3), mitotis. ii) DDR (ATM, ATR). iii) BET proteins. iv) ATP-binding cassette (ABC) transporters (ABCB1). • Task 5: Pharmacogenetic analysis of specific genetic polymorphisms (CYP3A4, CYP3A5, ABCB1 e AOTs)
Study Population	**Inclusion criteria:** • Signed informed consent prior to any study specific procedures;

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: 2021-000245-41	Version n.1 1 July, 2021

	• 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; if the prior PARPi used was olaparib then patients must have received treatment without significant toxicity or the need for a permanent dose reduction. 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 enrolment 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 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: ○ Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

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: 2021-000245-41	Version n.1 1 July, 2021

	○ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L ○ Platelet count ≥ 100 x 10^9/L ○ Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) ○ Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) and Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x ULN for institution (or ≤ 5x ULN if liver metastases are present). ○ 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: - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50; - radiation-induced oophorectomy with last menses >1 year ago; - chemotherapy-induced menopause with >1-year interval since last menses; - surgical sterilisation (bilateral oophorectomy or hysterectomy). • Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom, during the treatment (for both treatment arms) and for at least 1 months after last dose of olaparib. For chemotherapy drugs, please refer to fertility section of corresponding Summary of Product Characteristics(SCP); • 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 and /or active,

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: 2021-000245-41	Version n.1 1 July, 2021

	uncontrolled infection that may interfere with planned treatment, affect patient compliance or place the patient at high risk from treatment related complications [Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, New York Heart Association (NYHA) grade II or greater congestive heart failure, uncontrolled hypertension, severe peripheral vascular disease, 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 illness] • Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication; • Patients eligible for a platinum based chemotherapy doublet and bevacizumab • Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment; prior palliative radiation must have been completed at least 7 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of 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 TC/ RMN scan of brain is required at baseline. 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 >grade 2 according Common Terminology Criteria for Adverse (CTCAE) version 5.0 caused by previous cancer therapy, excluding alopecia • Resting ECG indicating uncontrolled, potentially irreversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 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) o 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

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: 2021-000245-41	Version n.1 1 July, 2021

	core antibody and absence of HBsAg) are eligible. o 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
Treatment Plan	**ARM A** (*Experimental*) Olaparib 300 mg, film-coated tablets, twice daily PO, d1-28 continuously **ARM B** *(Standard Arm*) Platinum-based chemotherapy at the Investigator's choice 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; For ARM B: In case of clinical benefit and in the absence of limiting toxicities, chemotherapy can be continued at Investigator's evaluation beyond the 8 cycles planned, according to the Sponsor. For ARM A: Patients will continue to receive olaparib until disease progression, unacceptable toxicity, withdrawal of the consent, whichever comes first. First dose of therapy must be administered within 3 days form randomization.
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 assessed using an interaction test for each subgroup 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 analysis** Interim assessments and study monitoring for efficacy and safety will be done by an Independent Data Monitoring Commitee (IDMC) 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 IDMC 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.
Study setting	The study is promoted by the National Cancer Institute of Naples as an investigator initiated trial according to the Italian law on non-profit research. The study will involve about 45 centres in Italy and will be coordinated and managed by the Clinical Trials Unit of the National Cancer Institute of Napoli, Italy, through a web based platform allowing for randomization, electronic data capture and tools for central monitoring through e-queries. In this trial, the experimental drug Olaparib (in the experimental arm) will be provided at no cost by the manufacturer (Astra-Zeneca), for treatment until progression.

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: 2021-000245-41.	Version n.1 1 July, 2021

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Epithelial ovarian cancer is the main cause of death among gynaecological malignancy in western countries[1]. Patients with newly diagnosed advanced ovarian cancer (OC) are usually managed with cytoreductive surgery followed by a platinum-based chemotherapy. Despite these efforts, disease recurrence is still frequent and the development of resistance to further lines of medical treatment is the main cause of death for OC patients. In recent years, the introduction of targeted therapies has improved the outcome of patients diagnosed with advanced OC. In particular, a new class of drugs that specifically inhibit the poly ADP-ribose polymerase enzymes, called PARP inhibitors (PARPi), have showed unprecedent results when used as maintenance therapy after complete (CR) or partial response (PR) to a platinum-based chemotherapy. In first line setting, PARPi have demonstrated a remarkable gain in progression-free survival (PFS) in recently published pivotal trials. In the SOLO1 study, patients with BRCA 1-2 mutated advanced OC that received a maintenance therapy with olaparib showed a reduction in the risk of progression or death of 70% compared to those that received placebo[2]. The benefit of PARP inhibitors moves beyond BRCA 1-2 carriers and has been detected in a broadened population of patients with a not-BRCA related deficit in the homologous recombination (HR) repair system, like in those defined HR deficient by MyChoice HRD test (Myriad Genetics). Actually, maintenance treatments with niraparib and with olaparib plus bevacizumab have shown to improve PFS not only in BRCA 1-2 mutated patients but even in those defined HR-deficient, respectively in PRIMA and PAOLA-1 trials[3,4]. Even veliparib, a PARPi that had showed minor activity in PARP1 trapping and, as consequence, more suitable to be administered in concomitance with platinum therapy, has reported similar results in the first-line setting[5].

Despite these unprecedent steps forward could hopefully led to survival improvement for patients newly diagnosed with advanced OC, disease relapse is still a clinical concern. Data on the mechanisms of resistance to PARPi are preliminary and are still anecdotical. In small series of patients, acquired somatic mutations in BRCA1/2 positive cancers that restore the BRCA reading frame thereby conferring resistance to PARPi have been described. Other mechanisms of resistance seem related to epigenetic loss of BRCA1 promoter methylation or RAD 51c and RAD51d secondary mutations[6].

Moreover, from a clinical point of view there are no data regarding the best strategy to offer at progression to a PARPi therapy. Since most recurrences appear after 6 months from the last platinum dose, a platinum containing regimen could be an option for these patients, but concerns exist regarding a possible cross-resistance between PARPi and platinum salts. Exploratory data from the MITO real-live experience have shown that BRCA 1/2 patients in progression during olaparib maintenance had a low response rate when re-exposed to a platinum therapy[7]. These data are in line with a secondary analysis from the SOLO2 trial in

which the median PFS of patients treated with a platinum containing regimen after disease progression to olaparib was about 6 months[8].

Knowing the importance of new medical therapies, especially those that trigger tumor-specific molecular alteration, cytoreductive surgery still play a central role. The role of secondary surgery for patients who experience a disease relapse after at least 6 months from the last platinum dose was more debated since it was supported by several but retrospective studies. At the ASCO 2020 Annual Meeting final results of the first randomized, phase III trial specifically designed to test the impact on survival of a secondary cytoreduction have been presented[9]. The Desktop III trial selected patient for secondary surgery basing on the AGO score, a prospectively validated score that was found to be predictive of complete macroscopic resection in patients undergoing secondary surgery[10]. These patients were randomly assigned to receive platinum-based combination alone or preceded by a cytoreductive surgery performed in highly selected centres. The 75% of patients enrolled had a median platinum-free interval of 12 months and also the rate of complete macroscopic resection (R0) was about 75% using the AGO score. There was a clear benefit for patients undergone secondary surgery with Hazard Ration (HR) of 0.75 (0.58-0.96 CI, p=0.02) for OS corresponding to 7.7 months gain in overall survival even if the benefits seen to be concentrated in patients achieving complete resection. The evidence from the Desktop III trial place the second cytoreductive surgery in the treatment's algorithm of recurrent OC.

In the presence of a strong oncogenic driver as BRCA mutation, disease progression to target therapy could be attributed to a small number of resistant cells. In others setting, like oncogene-addicted lung cancer, where oligo-progressive disease is a well-described phenomenon, locoregional therapies (e.g. surgery, radiotherapy, thermo-ablation) are already playing a central role in the patients' management[11]. Assuming that oligo-progression could be driven by a limited number of cancer cells that develop a biological resistance to targeted therapy resulting in a clinical progression in few sites only, loco-regional approaches offer the unique possibility of removing these resistant clones with surgical technique or with ablative dose of radiotherapy. For example, patients who experience oligo-progression during anti-EGFR TKIs for EGFR mutated lung cancer, are recommended for radiotherapy on the progressive lesions, continuing treatment with TKI. The positive impact of secondary surgery in relapse OC and the presence of a targeted therapy for a disease that in many cases is oncogene-addicted, lead to the hypothesis that move the MITO 35b study. The aim of this study is to evaluate if, in ovarian cancer patients in progression during or after olaparib maintenance, undergone to secondary cytoreduction with resection of at least the progressive lesions, the continuation of olaparib after surgery prolong progression-free survival compared to a platinum-based second-line chemotherapy.

2. STUDY DESIGN

MITO 35b is designed as randomized, open label, phase III trial that aims to assess the efficacy of olaparib maintenance beyond progression compared to standard platinum-based chemotherapy after secondary cytoreductive surgery.

Patients will be randomized 1:1 to receive:

- **ARM A (experimental arm)**: Olaparib, film coated tablets, 300 mg twice daily

- **ARM B (control arm)**: Platinum-based chemotherapy at the Investigator's choice among the following:
    - Carboplatin (AUC5) plus Pegylated Liposomal Doxorubicin (PLD) 30mg/m2 on day 1 every 28 days for a maximum of 8 cycles;
    - Carboplatin (AUC4) plus Gemcitabine 1000mg/m2 on day 1, 8 every 21 days for a maximum of 8 cycles;
    - Carboplatin (AUC5) plus Paclitaxel (175mg/m2) every 21days for a maximum of 8 cycles

The target population of this study are ovarian cancer patients who experience a disease recurrence or progression to a first line maintenance therapy with a PARPi; at progression patients must have received a secondary cytoreduction according to clinical practice.

The study is dimensioned to test the hypothesis that olaparib (experimental arm) *vs* a further line of chemotherapy prolong PFS and/or PFS 2 with an HR of 0.60. Considering a two-sided log-rank test with alpha of 0.025, to attain an 80% power, follow-up will be continued to reach 146 events necessary for the final analysis. Approximately 200 patients will be enrolled in the study. The date of end of study will be the date of the last visit of the last patient.

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: 2021-000245-41.	Version n.1 1 July, 2021

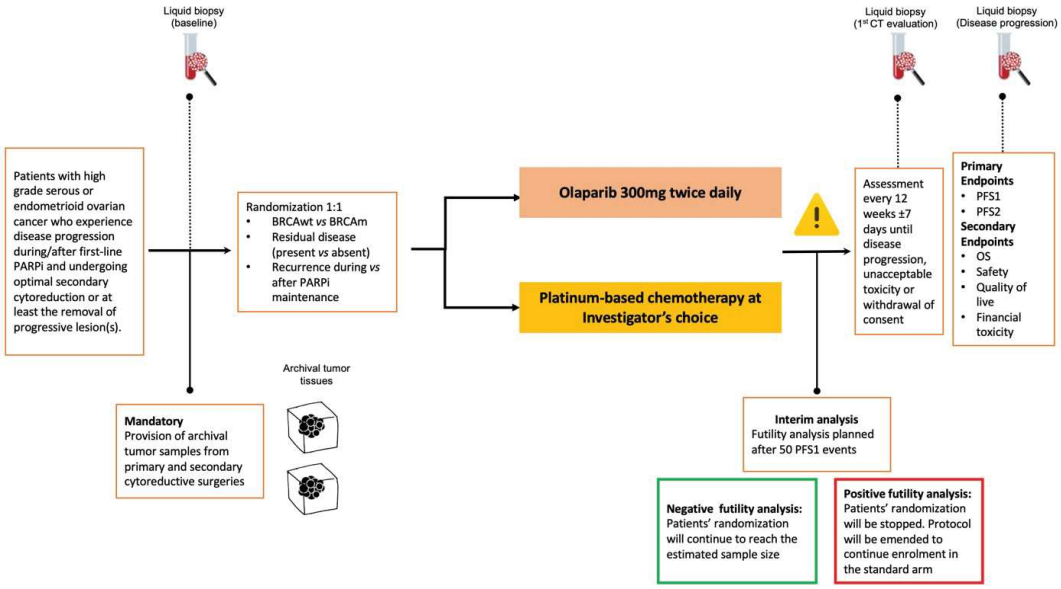
2.1 Centres

This is a multicenter study to be conducted in approximately 45 centers in Italy (MITO and MANGO networks), coordinated by the Clinical Trials Unit of the National Cancer Institute of Naples.

.

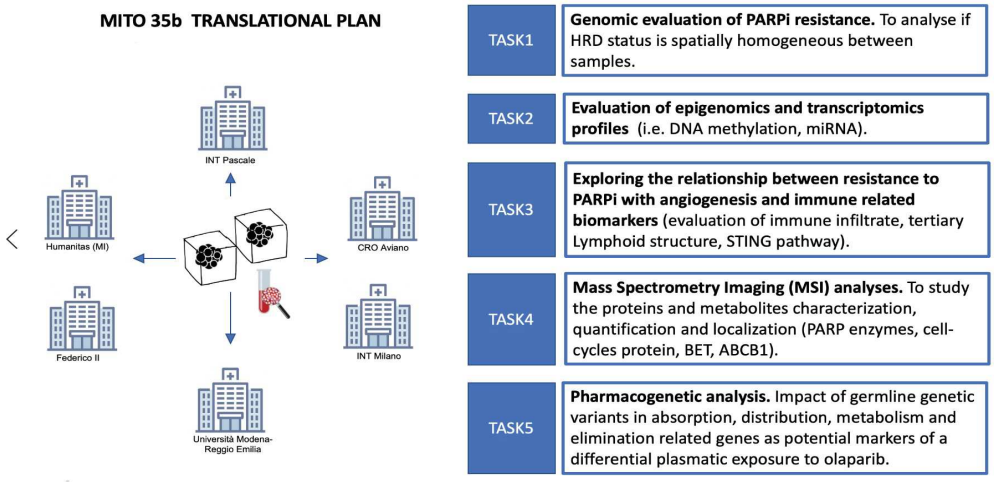
Olaparib beyond progression compared to platinum chemotherapy after secondary cytoreductive surgery in recurrent ovarian cancer patients. The phase III randomized, open label **MITO 35b** study: a project of the MITO-MANGO groups. EudraCT number: 2021-000245-41.	Version n.1 1 July, 2021

Figure 1



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: 2021-000245-41.	Version n.1 1 July, 2021

Figure 2



3. STUDY OBJECTIVES

3.1 Primary objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy (as assessed by progression-free 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.	*PFS as defined by the Investigator using RECIST 1.1, as the time frame from randomization to progression or death for any cause.*
To determine the efficacy of the experimental therapies on subsequent treatment (as assessed by progression-free survival 2) after progression.	*PFS2 as defined by the Investigator using RECIST 1.1 as the time frame from randomization to the second progression or death for any cause after subsequent treatment.*

3.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
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	*OS as defined by the Investigator as the time from randomization to death for any cause.*
To assess changes in Quality of Life parameters in patients treated with olaparib maintenance compared to chemotherapy	*Quality of life assessment using EORTC QLQ C30 – questionnaire*
To compare the two arms in terms of financial toxicity	*Financial Toxicity assessment using PROFFIT questionnaire*
To compare the two arms in terms of the safety and tolerability	*CTCAE version 5.0 and PRO-CTCAE questionnaire*

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: 2021-000245-41	Version n.1 1 July, 2021

3.3 Translational objectives

Exploratory Objective:	**Outcome Measure:**
To explore the mechanisms of resistance to olaparib through the molecular analysis of tumor samples collected at surgeries.	*Comparison of genomics, transcriptomics and proteomics characteristics between tumor samples collected before and after therapy with olaparib for paired patients.*
To describe the variations in the soluble biomarker's expression levels collected before, during and the end of treatment.	*Comparison of genomics, transcriptomics and proteomics characteristics between blood samples collected before, during and the end of treatment in each treatment group.*

4. PATIENTS SELECTION

Each subject should meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances can there be exceptions to this rule.

4.1 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, if the prior PARPi used was olaparib then patients must have received treatment without significant toxicity or the need for a permanent dose reduction.Patients who experience disease relapse after the end of the 24 months maintenance therapy are eligible;

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: 2021-000245-41	Version n.1 1 July, 2021

- 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 enrolment 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 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:

    - Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

    - Platelet count ≥ 100 x 10^9/L

    - Total serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

    - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) and Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x ULN for the institution (or ≤ 5x ULN if liver metastases are present)

    - 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.

- 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 Cycle 1. Postmenopausal is defined as:

- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50;
- radiation-induced oophorectomy with last menses >1 year ago;
- chemotherapy-induced menopause with >1-year interval since last menses;
- surgical sterilisation (bilateral oophorectomy or hysterectomy).

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom, during the treatment and for at least 1 months after last dose of olaparib.For chemotherapy drugs, please refer to fertility section of corresponding Summary of Product Characteristics (SCP);
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures;

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

- Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, and/or active, uncontrolled infection. that may interfere with planned treatment, affect patient compliance or place the patient at high risk from treatment related complications [Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, New York Heart Association (NYHA) grade II or greater congestive heart failure, uncontrolled hypertension, severe peripheral vascular disease, 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 illness];
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication;
- Patients eligible for a platinum based chemotherapy doublet and bevacizumab;
- Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatments; prior palliative radiation must have been completed at least 7 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of 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 TC/RMN scan of brain is required at baseline. 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) and 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 >grade 2 according Common Terminology Criteria for Adverse (CTCAE) version 5.0 caused by previous cancer therapy, excluding alopecia;

- Resting ECG indicating uncontrolled, potentially irreversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation > 470 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 (HIV 1-2 antibody positivity) 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 (European society for Medical Oncology) 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

Procedures for withdrawal of incorrectly enrolled subjects see Section 4.4.

4.3 Subject enrolment and randomization

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed
2. Record the patients in Registration Section of the Electronic Case Report Form (eCRF) and complete this section with required informations. The patient will be assigned a unique patient identification number; it must not be changed. This number will be used to identify the patients throughout the study and must be used on all study documentation related to that patient. The patient numbers will be allocated sequentially in the order in which the patients are enrolled. A Patient Enrolment and Identification Code List must be maintained by the Investigator.
3. Sent to the Sponsor FFPE tumours specimens for biomarkers analysis
4. Assess the subject eligibility (attending a quality control of tumor samples, see below)
5. If the patient is eligible, complete the Randomization section in eCRF.

If a subject withdraws from participation in the study, then patient code cannot be reused.

A quality control revision of tumor sample will be performed by the Sponsor within 8 working days from the date of centralization at National Cancer Institute of Naples. Only patients with representative/ adequate tumor sample will proceed to randomization in the current study.

Randomization will be centralized at the National Cancer Institute of Naples. A computerized minimization procedure will be applied using the following stratification factors:

- 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).

Patient registration and data collection are centralized at the Clinical Trials Unit of the National Cancer Institute of Naples.

Contacts for registration and randomization: see Section 16

4.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented.

4.5 Screening Failure

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Screening Failure (i.e., patient does not meet the required inclusion/exclusion criteria).

4.6 Treatment, Patients and Study Discontinuation

4.6.1 Study Treatments Discontinuation

Subjects may be discontinued from study treatments in the following situations:

- Subject decision (see below);
- Any Adverse Event that requires treatment discontinuation per the guidelines;
- Severe non-compliance with the study protocol;
- Patients that for any reason interrupt olaparib administration for more than 4 consecutive weeks;
- Occurrence of other malignancies that required systemic treatments;
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML);
- Any medical condition that may jeopardize the patient's safety if she continues study treatment;
- Disease Progression per RECIST v 1.1 as assessed by the Investigator;
- If, after the planned futility analysis, treatment with olaparib beyond progression will be consider detrimental by the IDMC;
- Pregnancy;

Patients will return to the clinic site for a treatment discontinuation visit within 30 (± 7) days after the last dose of study treatment. Patients who discontinue study treatment for any reason other than PD will continue to undergo response assessment as outlined in the Table1.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

4.6.2 Patients Discontinuation from Study

4.6.2.1 Withdrawal of the informed consent

Patients have the right to voluntary withdraw from the study at any time for any reason. without prejudice to further treatment. Every effort should be made to obtain information on patients who withdraw from the study. If possible, they will be seen and assessed by an Investigator(s). If the withdraw is related to an AE, any Adverse events will be followed up.

The primary reason for withdrawal from the study should be documented on eCRF and in the source documents by the Investigators.

The investigational drug (olaparib) should be returned by the subject at the Investigators.

If a subject withdraws from participation in the study, then her enrolment/randomisation code cannot be reused, and patients will not be replaced.

Data collected before the withdrawn will be included in the study analyses.

4.6.3 Discontinuation of the study

The study may be stopped if, in the judgment of both the IDMC and the Sponsor, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,

In case of futility at planned interim analysis, the randomization will be stopped, and the experimental arm will be closed. After the protocol amendment, the study will continue, and the patients will be enrolled only in the standard arm in order to continue the translational project.

The Sponsor notify the Investigators if the Sponsor decides to discontinue the study.

5. TREATMENT PLAN

Patients that met all the inclusion/exclusion criteria will be randomly assigned in a 1:1 ratio to receive a standard platinum-based chemotherapy (Standard Arm) or to receive olaparib (Experimental Arm).

- **ARM A (*Experimental):*** Olaparib 300 mg tablet twice daily, d1-28 continuously
- **ARM B *(Standard)***: The following chemotherapy schemes, at Investigator's choice 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;

A centralized computer-based minimization procedure will be applied. 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 treatment vs after the end of maintenance therapy).

For ARM B: In case of clinical benefit and in the absence of limiting toxicities, chemotherapy can be continued at Investigator's evaluation beyond the 8 cycles planned, according to the Sponsor.

For ARM A: Patients will continue to receive olaparib until disease progression, unacceptable toxicity, withdrawal of the consent, whichever comes first.

Notes:

- Patients must have received only one previous first line platinum-based regimen followed by a PARPi maintenance. Patients must have experienced disease progression after 6-months from PARPi starts. Patients who experience disease recurrence after the 24-months of first line PARPi maintenance are evaluable for the study.

- Patients will be enrolled after secondary cytoreductive surgery, if they have reached a complete resection or at least the removal of lesion judged in progression during maintenance (see Inclusion Criteria).

6. ASSESMENTS AND PROCEDURES DURING THE STUDY

Table 1. Study procedures

Assessment	Screening -28 to -1	Cycle 1		Cycle2+		End of treatment (within 30 days after the last dose of study treatment)	*Post treatment assessment (every 3 months)
Days (window)		**1[1] (±3)**	**8[2] (±3)**	**1[1] (±3)**	**8[2] (±3)**		
Written informed consent	X						
Archival tumor samples from primary and secondary surgery	X						

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: 2021-000245-41	Version n.1 1 July, 2021

Assessment	Screening -28 to -1	Cycle 1		Cycle2+		End of treatment (within 30 days after the last dose of study treatment)	*Post treatment assessment (every 3 months)
Days (window)		**1[1] (±3)**	**8[2] (±3)**	**1[1] (±3)**	**8[2] (±3)**		
Demographics	X						
Physical examination[3], height, and weight	X	X				X	
Medical/surgical history	X					X	X
BRCA status	X						
Inclusion/exclusion criteria	X						
12-lead ECG[4]	X						
Echocardiography[4]	X						
Vital signs[5]	X	X	X	X	X	X	
Randomisation to study treatment		X					
Treatment dispensed/returned		X	X	X	X		
Concomitant medication	X	X	X	X	X	X	
Adverse event review (AEs and SAEs)	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry[6]	X	X	X	X	X		
Coagulation Tests (PT, aPTT, INR)	X						
Serum CA125[7]	X	X		X[5]		X	
Urinalysis[8]	X						

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: 2021-000245-41	Version n.1 1 July, 2021

Assessment	Screening -28 to -1	Cycle 1		Cycle2+		End of treatment (within 30 days after the last dose of study treatment)	*Post treatment assessment (every 3 months)
Days (window)		**1[1] (±3)**	**8[2] (±3)**	**1[1] (±3)**	**8[2] (±3)**		
HBV, HCV serology[9]	X						
Pregnancy Test [10]	X	X		X		X	
Tumor assessment [11]	X	**Every 12 weeks from C1D1± 7 days**					X[11]
Blood sample (20 ml) for soluble biomarkers) [12] Blood sample 5 ml for germline DNA[12] (only at screening)	X X	**In concomitance (± 3 days) with the 1st radiological evaluation**				X	
EORTC QLQ – C30-questionnaire[13]	X	X		X		X	
PROFFIT questionnaire[14]	X	X		X		X	
PRO-CTCAE questionnaire[15]	X	X		X		X	
Survival status							X

1. Treatment cycles are 28 days long in ARM A and 28 or 21 days long in ARM B depending on chemotherapy regimen. Clinic visits and laboratory tests will occur at Day 1 of each cycle (every 4 weeks ±3 days in ARM A and every 3 or 4 weeks ±3 in ARM B) through Cycle 8 for both treatment arms and then at Day 1 of each cycle for olaparib arm, until disease progression, withdraw from the study. Gynaecologic visit is recommended every 3-4 months according to the Institution policy.
2. Day 8 is required in patients randomized in ARMB in case that carboplatin-gemcitabine is the regimen of choice. First dose of therapy must be administered within 3 days form randomization.
3. Physical examination: Height will be recorded at screening only. Gynaecologic visit is recommended every 3-4 months according to the Institution policy.

4. A standard 12-lead ECG and Echocardiography will be performed at screening, then, during the study, as clinically indicated.
5. Vital signs include: respiratory rate, pulse rate, body temperature, diastolic and diastolic pressure while the patient is in a seated position and temperature.
6. Haematology includes: haemoglobin, WBC, absolute neutrophil and lymphocytic count, platelet count, MCV. Blood chemistry: includes AST/ALT, alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, blood urea nitrogen (BUN) (or urea), serum creatinine, magnesium and albumin and total proteins. Additional haematology/chemistries panels may be performed as clinically indicated. Laboratory test will be performed at screening and up to 72 hours before treatment administration (within the 3-day study window).
7. Serum CA 125 dosage will be assessed, locally, in blood samples obtained at screening, on Day 1 of each Cycle through Cycle 8, then every 3 cycles (12 weeks) for each treatments' arm.
8. Urinalysis (specific gravity, leukocytes, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.) at screening and then, during the study, as clinically indicated.
9. HBV serology includes: HBsAg and HBcAB, HBV DNA should be obtained if patient has a negative serology for HBsAg and a positive serology for anti- HBcAb. HCV serology includes HCV antibody; HCV RNA should be obtained if a patient test positive for anti-HCV.
10. Pregnancy test: perform serum pregnancy test (BHCG) within 28 days prior to the start of study treatment, on Day 1Cycle 1 (prior to start treatment) and at Day 1 of every cycle during study treatment for women of childbearing potential (unless patients had undergone bilateral ovariectomy), and at EOT visit.
11. Tumor assessment with computed tomography (CT) scans ± mdc of the brain, chest, abdomen and pelvis or, alternative magnetic resonance imaging (MRI) of brain, abdomen and pelvis + CT scan of the chest, will be performed at baseline, then every 12 weeks with a window of ±7 days from date of the first treatment administration (Day1 Cycle1) in each arm independently from the number of cycles received, until disease progression, subsequently every 12 weeks until second disease progression from randomization. The same modality (CT or MRI) should be used throughout the study for a given patient. If brain CT/MRI is clear at screening, repeat imaging of these area is not required in the absence of clinical indication requiring follow-up. Assessment of response will be made using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
12. Blood samples for biomarkers analysis will be collected at 3 timepoints: at baseline (screening); in concomitance (± 3 days) with the 1st radiological evaluation and at EOT visit.
13. The EORTC QLQ C30 questionnaire will be fulfilled at screening (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months, from randomization for both arms. If the patient suffered of disease progression, the last QoL assessment will be fulfilled at day of EOT visit.
14. The PROFFIT questionnaire will be fulfilled at screening (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months, from randomization for both arms. If the patient suffered of disease progression, the last financial toxicity assessment will be fulfilled at day of EOT visit.
15. The PROCTCAE questionnaire will be fulfilled at screening (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) before receiving treatment until 6 months, then at 9 and 12 months, from randomization for both arms. If the patient suffered of disease progression, the last assessment will be fulfilled at day of EOT visit.

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: 2021-000245-41	Version n.1 1 July, 2021

*Survival follow-up and information on subsequent treatment (including type and duration of subsequent chemotherapy, radiotherapy and/or surgery) will be collected every 3 months.

6.1 Enrolment/screening period

All patients must provide written, informed consent before any study-specific assessments or procedures are performed including sampling for biomarker assessments. The consent for the translational research on tumor samples is included in the main subject informed consent form.

Screening examinations should be performed within 28 days before the first day of treatment (see Table 1).

Screening procedures include basal tumor assessment (using CT scan or MRI), laboratory assessment, urinalysis, serum Ca125 levels, QoL assessment (EORTC QLQ-C30 questionnaire), safety assessment (CTCAEv5.0 and PRO-CTCAE questionnaire), evaluation of Financial Toxicity (PROFFIT questionnaire), ECG, echocardiography and the centralization of tumor samples (FFPE archivial tumor samples and blood samples)

Echocardiography and ECG will be performed only at screening and then repeated if clinically required. All the consenting patients should be registered even those result not eligible because of missing/having one or more inclusion/exclusion criteria, in order to allow the description of the generalizability of the study data. Re-screening is not allowed.

A quality control revision of tumor samples will be performed by the Sponsor within 8 working days from the date of centralization at NCI, Fondazione “G. Pascale”of Naples. Only patients with representative/adequate tumor sample will proceed to randomization in this study.

6.2 Treatment period

Descriptions of the procedures for this period are included in the Table 1.

For patients randomized in the ARM B of the study, cycles lengths depend on type of platinum regimen (varying from 21 days to 28 days). For patients enrolled in ARM A cycles lengths is 28 days.

Day 8 is required only for patients assigned to ARM B undergoing carboplatin plus gemcitabine regimen.

Clinic visits and laboratory tests will occur at Day 1 of each cycle (every 4 weeks ±3 days in ARM A and every 3 or 4 weeks ±3 in ARM B) through Cycle 8 for both treatment arms and

then at Day 1 of each cycle for olaparib arm, until disease progression, unexpectable toxicity, withdraw from the study. Gynaecologic visit is recommended every 3-4 months according to the Institution policy. First dose of therapy must be administered within 3 days form randomization.

For patients enrolled in each arm of the study, radiological evaluation will be performed every 12 weeks±7 days from the day of the first treatment administration (Cycle 1 Day1) and if clinically required in case of clinical deterioration or raising CA 125.

For patients in each arm, a blood sample of 20 ml will be collected in concomitance (± 3 days) with the 1st radiological evaluation.

6.3 Follow-up period

Patients will be followed for the collection of post-progression treatments, and outcome (PFS2 OS)

Subsequent therapies for cancer including details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of experimental therapies, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other investigational drugs will be collected. Survival follow-up and information on subsequent treatment (including type and duration of subsequent chemotherapy, radiotherapy and/or surgery) will be collected every 3 months. This information could be collected even by telephone calls if clinical visits cannot be performed and patients agree to this procedure.

7. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided. All activities must be performed and documented for each patient.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries.

7.1 Informed Consent

Written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed Consent Form for enrolled patients and for patients defines as Screening Failure, will be maintained at the clinical site on investigator site file and stored on Investigator Site File (ISF)

7.2 Physical examination

A complete physical examination will be performed on a Day 1 of each cycle (every 4 weeks ±3 days in ARM A and every 3 or 4 weeks ±3 in ARM B) through Cycle 8 for both treatment arms and then at Day 1 of each cycle for olaparib arm, until disease progression, unacceptable

toxicity, withdraw from the study and when required for patients in both arms. A complete physical examination will also be performed at EOT visit.

It includes an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems. Gynaecologic visit is recommended every 3-4 months according to the Institution policy.

7.3 Vital signs

Vital signs measurements, including respiratory rate, pulse rate, body temperature, systolic and diastolic pressure must be performed at screening., Day 1 of each cycle (every 4 weeks ±3 days in ARM A and every 3 or 4 weeks ±3 in ARM B) through Cycle 8 for both treatment arms and then at Day 1 of each cycle for olaparib arm, until disease progression, unexpectable toxicity, withdraw from the study and when required for patients in both arms. Vital Signs measurements will also be performed at EOT visit

7.4 Electrocardiograms

A standard 12-lead ECG will be performed at screening, within 3 days prior Day 1 Cycle 1 and then repeated during the study when clinically indicated. At screening single ECG will be obtained and QTcF must be < 470 msec.

ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

Echocardiography will be performed only at screening and then repeated if clinically required.

7.5 Laboratory assessment

Blood samples for determination of clinical chemistry, haematology, coagulation and urinalysis, will be taken at the times indicated in the Study Plan (Table 1).

7.6 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 Cycle 1 (prior to start treatment) and at Day 1 of every cycle during study treatment unless patients had undergone bilateral ovariectomy, and at End of Treatment (EOT) visit. Tests will be performed by the local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

7.7 Coagulation

Activated partial thromboblastin time (APTT) will be performed at screening and if clinically indicated. International normalised ratio (INR) will be performed at screening and if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Each coagulation test result will be recorded in eCRF.

See Table 2 for the list of clinical laboratory test to be performed.

Table 2 Laboratory Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (including absolute neutrophil and lymphocytic count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
B-Mean Cell Volume (MCV)	S/P-Alanine transaminase (ALT)
Urinalysis	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
U-Leukocites	S/P-Creatine kinase (CK)
U-Biliruibn	S/P Blood Urea Nitrogen (BUN) or Urea
U-Nitrite	S/P Magnesium
U-Urobilinogen	S/P Total Protein
U-Ketones	
Pregnacy Test	**Tumor markers**
BHCG	CA-125

Coagulation	**HBV; HCV serology**
aPTT PT INR	HBsAg; HBcAB; HBV DNA(only if required) HCV Ab; HCV RNA(only if required)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.

NB. In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

7.8 Other safety assessments

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 9.1.1.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued, and a full description of findings should be submitted with an SAE report by the investigator to the Sponsor. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

7.9 Patient Reported Outcome

To more fully characterize the benefit-risk profiles of the two treatment arms, patient reported outcome data will be obtained from patients through use of the following instruments: EORTC QLQ-C30 questionnaire, Patient Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), Patient Reported Outcome for Fighting Financial Toxicity (PROFFIT).

The PRO questionnaires must be compiled by the patients before clinical visit and before receiving treatment. A cover sheet must be compiled by clinical assistants or physicians for all QoL questionnaires, annotating eventual reasons for lack of questionnaires or lack of specific responses, or whether assistance was required.

7.9.1 EORTC QLQ-C30

The EORTC QLQ-C30[13], version 3.0, includes 30 questions, 28 with 4-category response, and 2 with a 7-point scale for response. This questionnaire explores 5 multi-item functional subscales: physical, role, emotional, social and cognitive functioning; three multi-item symptom scales: fatigue, pain, and emesis; a global health status subscale; and six single items: financial impact and symptoms such as dyspnea, sleep disturbance, appetite, diarrhea, and constipation.

The EORTC QLQ C30 questionnaire will be fulfilled at screening (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months from randomization for both arms. If the patient suffered of disease progression, the last QoL assessment will be fulfilled at day of EOT visit.

EORTC questionnaire will be managed according to standard rules for their analysis reported in the EORTC manuals.

7.9.2 PRO-CTCAE

Symptomatic toxicities will be assessed using the PRO-CTCAE.

PRO-CTCAE is an item library comprised of 78 symptom terms drawn from the CTCAE. Each symptomatic AE is evaluated using a combination of one to three attributes (frequency, amount, severity, interference, presence/absence). Patients will be requested to complete questionnaires consisting of selected items of the Italian PRO-CTCAE, at baseline (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months from randomization for both arms. If the patient suffered of disease progression, the last assessment will be fulfilled at day of EOT visit.

7.9.3 PROFFIT

The PROFFIT instrument consists of 16 items for assessing financial toxicity. Patients will be requested to complete questionnaire at screening (within 7 days prior to randomization), on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months from randomization for both arms. If the patient suffered of disease progression, the last Financial Toxicity assessment will be fulfilled at day of EOT visit.

7.10 Tumor Response Assessments

Tumor response will be assessed by the Investigator using RECIST v.1.1 criteria. Patients without measurable disease at baseline will be assessed for progression according to RECIST criteria for non-target and/or new lesions.

Methods for tumor assessment include:

Computed tomography (CT) scans ± mdc of the brain, chest, abdomen and pelvis

or (alternative)

Magnetic resonance imaging (MRI) of brain, abdomen and pelvis + CT scan of the chest

If brain CT/MRI is clear at screening (no evidence of metastases), repeat imaging of these area is not required in the absence of clinical indication requiring follow-up.

Additional tests e.g., histology/cytology, ultrasound techniques, endoscopy, positron emission tomography (PET) can be used as second level tests to confirm a suspected disease progression.

If a serological progression of disease is suspected based on a CA-125 significant increase a radiological re-evaluation has to be performed. No change in the therapy program will be based on Ca125 changes alone.

All baseline radiological tumor assessments must be performed in the screening window (no more than 28 days before the start of study treatment). Scans that were performed as part of standard of care prior to informed consent can be used and analysed like baseline assessment of the study if they were performed within the correct time frame, using the same scanner as planned for the study.

The same method of the assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up

For patients enrolled in each arm of the study, radiological evaluation will be performed every 12 weeks±7 days from the day of the first treatment administration (Cycle 1 Day1), regardless of delays in cycle starts, until disease progression and subsequently until second disease progression from randomization.

7.11 Archival Tumor Tissue Samples

The subject's consent to the use of biological samples is mandatory.

Biological samples (archived tumour samples) will be collected and will analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drugs, clinical outcomes and toxicity.

The Local Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Instructions.

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

Sponsor keeps oversight of the entire life cycle.

7.12 Prospective collection of blood samples

Blood samples will be collected for patients in each arm at three-time point during the study course. (See table1):

1. At baseline (screening);
2. In concomitance (± 3 days) with the 1st radiological evaluation;
3. At End of Treatment visit (EOT);

Blood will be obtained by any standard phlebotomy technique from a peripheral access point or from a central line by trained personnel. The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Instructions.

8. ADVERSE EVENTS REPORTING

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

8.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical trial subject administered the medicinal products and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG results.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent will be recorded as medical history (eg, seasonal llergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, will be recorded as medical history (eg, allergic pollinosis).
- Conditions that started or deteriorated after signing of the ICF will be documented as AEs.

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.
Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE.
A laboratory test abnormality that is considered to have a clinically relevant effect on the subject (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator) should be reported as an AE.

An **adverse reaction (AR)** is an untoward and unintended response to the investigational medicinal products related to any dose administered, judged by either the investigator or the promoter.

An **unexpected adverse reaction (UAR)** is an adverse reaction, the nature or severity of which is not consistent with the applicable products information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

A **Serious Adverse Event (SAE)** is untoward medical occurrence or effect that at any dose results in death, risk of death, permanent disability/incapacity, hospitalisation or prolongation of existing hospitalization or need for urgent medical treatment, a congenital anomaly/birth defect, or another medically important serious event as judged by the investigator. Further, any unexpected changes in relation to the toxicity profile of the drugs used of grade ≥ 3, as well as adverse event(s) which, although not falling within this definition, are considered unexpected and serious by the Investigator should be reported. A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (ie, elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (eg, social hospitalization for purposes of respite care)

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE, dependent on clinical judgment.
If disease recurrence leads to signs and symptoms that meet the criteria for seriousness (eg, hospitalization), the associated signs and symptoms may be reported as an SAE, but the underlying cause (that is, "recurrent disease" or "metastatic disease") should not be reported

as an SAE. In this case, recurrent or metastatic disease should be mentioned on the SAE form as an "alternative explanation."
Additional primary cancers (including skin cancers) regardless of relationship to study treatment should be reported as SAEs.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the coordinating centre.
Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an unexpected adverse reaction judged serious by the Investigator and/or Sponsor, that is not consistent, either in nature or in severity, with the applicable product information.

An **Adverse Event of Special Interest (AESI)** is an adverse event, thought to be potentially associated with investigational medicinal products that, regardless of the seriousness, must be close monitored and reported in an expedited manner (not exceeding 24 hours following knowledge). The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational products.

8.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to Sponsor as SAE on the SAE CRF. If a patient becomes pregnant during the course of the study experimental therapy should be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 1 month after the last dose should be followed up and documented.

8.3 Adverse events after the end of treatments visit

For Pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the 30 days end of treatments visit should be reported to the Sponsor regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient

has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the Sponsor.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off, then all SAEs must continue to be collected and reported to Sponsor within the usual timeframe.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

8.4 Collection and reporting of adverse events

All adverse events recorded from time of signature of informed consent, throughout the treatment period and in the 30 days following the last study treatment, have to be reported in the toxicity case report form, graded according to the corresponding CTCAE term (Version 5.0). All adverse events that are believed to be related to the study drugs, must continue to be recorded and reported using the same form until 90 days after the last dose of study drug. Follow-up of unresolved adverse events.

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

8.4.1 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade of the AE according to CTCAE version 5.0
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product

- If AE caused subject's withdrawal from study
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of SAE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 8.1. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 8.1

8.4.2 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.3 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECG, should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

8.4.4 Hy's Law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix B Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.5 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.5 Collection and reporting of SAE, AESI, pregnancy.

All serious adverse events and all adverse events of special interest regardless of the seriousness, occurring from time of signature of informed consent, throughout the treatment period and in the 30 days after the interruption of treatment, must be recorded and reported using the SAE - AESI- Pregnancy report form.
All serious adverse events and all adverse events of special interest that are belived to be related to the study drugs, must continue to be recorded and reported using the same form until 90 days after the last dose of study drug. Moreover, even after this period, the

Investigator should report any SAE or AESI of which they become aware that are believed to be related to prior study drug treatment.
All pregnancies occurring during treatment and in the 6 months after the last dose of study drug, must be recorded and reported using the SAE - AESI- Pregnancy report form.
The Investigator must immediately report to the sponsor all serious adverse events, all adverse events of special interest regardless of the seriousness and all pregnancies. The report should be made using the SAE - AESI- Pregnancy report form online or by sending the paper copy by fax (+390817702938) to the coordinating office immediately and not exceeding 24 hours following knowledge of the event.

All SAE and AESI and pregnancies must be also reported in the toxicity case report form within the corresponding CTCAE term.
During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.
If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments, or until 90 days after the last dose of the study drugs, whichever comes later.

The Reference Safety Information (RSI) necessary to classify an adverse reaction as SUSAR, based on the nature and seriousness, including the frequency, is located in the specific section of the latest version of Investigator's Brochure of Olaparib and in the specific section of the latest version Summary of Product Characteristics (SCP).

The reference document to classify an adverse reaction as SUSAR, based on the nature and seriousness, including the frequency, is located in the specific section of the latest version of (SPC) for carboplatin, cisplatin, pegylated liposomal doxorubicin and gemcitabine

8.6 Assessment of causality between treatment and event

Term	Description
CERTAIN	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory

Term	Description
	rechallenge procedure if necessary.
PROBABLE/ LIKELY	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
POSSIBLE	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
UNLIKELY	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
NOT RELATED	There is no causal relationship between the treatment and the event
CONDITIONAL/ UNCLASSIFIED	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
UNASSESSIBLE/ UNCLASSIFIABLE	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

8.7 Adverse Event of Special Interest (AESI)

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to the Sponsor within 24 hours. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis. ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to the Sponsor whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality.

8.8 Procedures for safety reporting

NCI Naples will review all adverse and serious adverse events, all the adverse events of special interest and all pregnancies, reported in the Study and issue queries directly to the Investigator reporting the event.

NCI Naples will determine if event qualifies as a SUSAR. NCI Naples will report all SUSARs to) to Eudravigilance through the EVCTM, to all Participating Investigators and to all Ethical

Committees of Participating Centres and to the manufacturer (AstraZeneca), within the timelines of the article 17 of the European Directive 2001/20/EC.

NCI Naples will provide an annual safety report, including all Serious Adverse Events occurring in the Study, to all Participating Investigators and to Ethical Committees of Participating Centres.

The Investigators are responsible for informing their Ethics Committee of the SAE reported in their centre, as per local requirements.

8.9 Other event requiring reporting

8.9.1 Overdose

Use of olaparib in doses in excess of that specified in the protocol is considered to be an overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mgs bid continually (tablet).

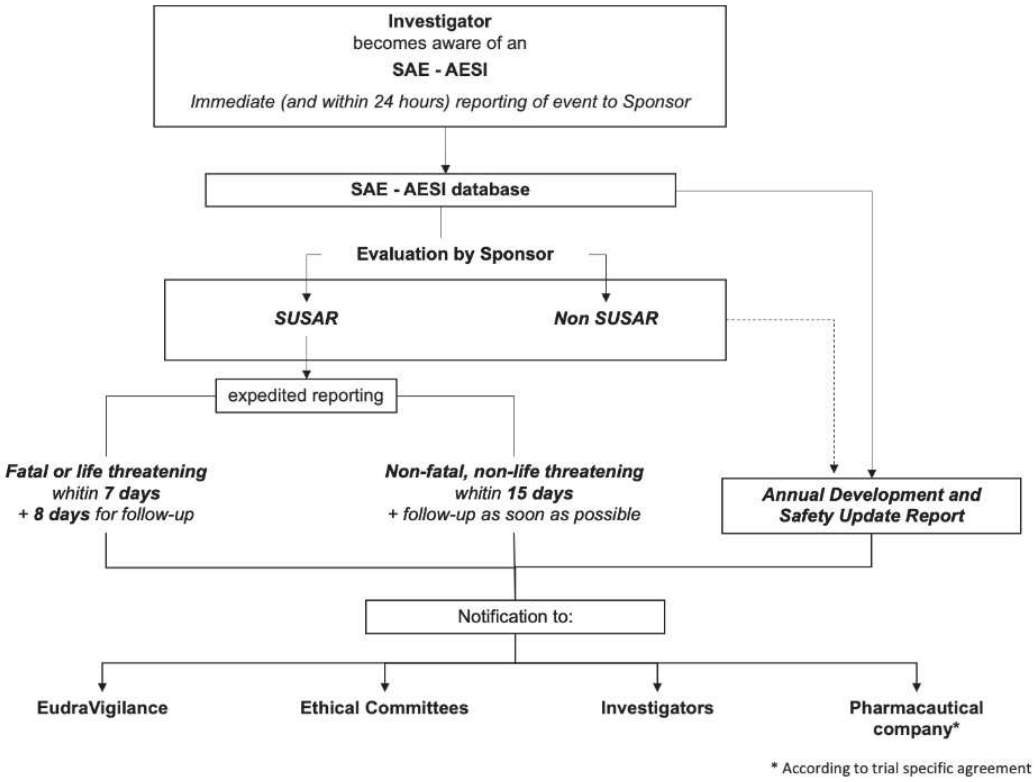
Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of study drug occurs in the course of the study, then the Investigator or other site personnel inform the appropriate Sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The coordinating centre will work with the Investigator to ensure that all relevant information is provided to the Sponsor data entry. For overdoses associated with a SAE, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

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: 2021-000245-41	Version n.1 1 July, 2021

Figure 2. Reporting flow for SAEs and SUSARs



9. MANAGEMENT OF TREATMENTS RELATED TOXICITIES AND DOSE REDUCTIONS

9.1 Management of olaparib related toxicities in patients in ARM A and dose modification

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed.

Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed, and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 11).

9.1.1 Management of haematological toxicity during olaparib

9.1.1.1 Management of anaemia

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 anemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 weeks interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 9.1.1.3.

Table 3: Management of anemia

Haemoglobin	Action to be taken
Hb<10 but ≥8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgment to continue olaparib with supportive treatment (e.g. transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb was recovered to >9g/dL. **Subsequent occurrences**:

	If Hb< **10** but ≥ **9 g**/dl investigator judgement to continue with supportive treatment (eg transfusion) or dose interrupt (for max of 4 weeks) 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). 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 of repeat Hb decrease.

9.1.1.2 Management of neutropenia, leukopenia and thrombocytopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs. 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 be stopped at least 24 h (7 days for PEGylated G-CSF) before the next dose of study treatment. Platelet transfusions, if indicated, should be done according to local hospital guidelines. For cases where patients develop prolonged hematological toxicity (≥2 weeks interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to Section 9.1.1.3.

Table 4: 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

9.1.1.3 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. 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. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption. Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to the Sponsor. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

9.1.2 Management of non-haematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the Sponsor must be informed. Where toxicity re-occurs following re-challenge with study treatment, and where further dose

interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. 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.

9.1.3 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Sponsor

9.1.3.1 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) in severity, intermittent and manageable continuing treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months. 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. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits). As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone.

9.1.4 Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold of ≥50 ml/min, retesting should be performed promptly. A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test 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. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

9.1.5 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Sponsor.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF. Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered. Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 5: Dose reductions for study treatment

Initial dose	Following re-challenge post interruption:	
	Dose reduction 1	**Dose reduction 2**
300 mg twice daily	250 mg twice daily.	200 mg twice daily

When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily, or one 150 mg tablet twice daily or one 100 mg tablet twice daily (see Section 9.1).

9.2 Management of platinum-based regimen related toxicities in patients in ARM B and chemotherapy dose modifications and delay.

The minimum conditions for retreatment at next scheduled cycle of chemotherapy are:

- Absolute Neutrophil Count (ANC) ≥ 1500/mmc
- Platelets ≥ 100.000/mmc
- no organ toxicity Grade ≥ 2 according to CTCAE vers.5.0

If these minimum conditions are not met, the cycle will be postponed for 7 days. Dose modification and/or delay of the platinum doublet or platinum single agent have to be managed according to standard clinical practice in participating centres. The following scheme reports guidelines that can be followed:

- In case of ANC < 500/mm^3 or platelets < 50000/mm^3 for a period of more than 7 days, the doses of all the drugs will be reduced by 25%
- In case of creatinine clearance < 60 ml, the dose of carboplatin will be reduced of 1 AUC level (i.e. if starting dose is AUC5 reduce to AUC4, if the starting dose is AUC4 reduce to AUC3)
- For any Grade 3 (G3) non-hematologic toxicity (except nausea or vomiting) the treatment should be withheld until symptoms resolve to ≤ G1. If the G3 event persists for ≥3 weeks, or recurs, then the case should be discussed with the Sponsor
- In case of peripheral neuropathy G3-G4 discontinue paclitaxel; for G2 delay therapy up to 2 weeks or until toxicity is grade 0-1 and reduce dose by 25%. If after 2 weeks toxicity persists at grade 2, discontinue paclitaxel

Dose levels are adjusted individually for each drug. Up to 2 dose reductions are acceptable for platinum agents (cisplatin and carboplatin) and for paclitaxel, pegylated liposomal doxorubicin and gemcitabine in cases of severe hematologic toxicity. No dose re-escalations are permitted following dose reduction for toxicity.

For patients who experience at least G3 non-hematological or G4 hematological toxicity with the cisplatin, the dose can be reduced by 25%.

In case where the toxicity does not resolve to G0 or G1 within 3 weeks after the last infusion, trial treatment should be discontinued after consultation with the Sponsor. With the Investigator and Sponsor agreement, subjects with a laboratory adverse event still at G2 after 3 weeks may continue in the trial only if asymptomatic and controlled.

For patients selected for a carboplatin plus gemcitabine regimen, if patient does not meet the minimum hematologic conditions for retreatment at Day 8, gemcitabine on Day 8 could be omitted in accordance with Sponsor if dose reduction has been yet performed.

9.2.1 Hypersensitive Reactions to Chemotherapy

Prior to chemotherapy administration, hypersensitivity prophylaxis should be implemented according to local institutional guidelines. Close monitoring of hypersensitivity reactions to both paclitaxel and carboplatin should be performed. Hypersensitivity reactions should be managed as per local institution practice. The decision to retreat (rechallenge) a patient who experienced a hypersensitivity is up to the local investigator based on the reaction features and severity, the personal experience and the local policies. In case of hypersensitivity to carboplatin, cisplatin can be used as alternative, since it demonstrated a reduced probability of reaction although still present. Cisplatin (75 mg/m^2 or 60 mg/m^2) would be administered i.v. over 30 minutes every 3 weeks.

9.2.2 Supportive Care for Chemotherapy Treatment

Subjects should receive full supportive care during and after the administration of chemotherapy. This includes transfusion of blood and blood products and/or the use of erythropoietin, antibiotics for infective complications, prophylatic antiemetic therapy, antidiarrheal and/or laxative therapy as clinically indicated. GCSF can be used accordingly to ESMO and NCCN guidelines.

10. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

10.1 Olaparib

10.1.1 Identity of Investigation product

The AstraZeneca MC Italy will supply olaparib as oval filmcoated tablets from commercial stock to a local manufacturer which will provide distribution to all centres with the appropriate labelling. The study personnel will account for all study drugs dispensed to and returned from the subject.

Table 6. Olaparib dosage.

Investigational product	Dosage form and strength
Olaparib	150 mg tablet
Olaparib	100 mg tablet

10.1.2 Dose and treatment regimen

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 (28 days = 1 cycle) until disease progression, withdraws from the study or unexpectable toxicity. Study treatment is available as a film-coated tablet containing 150 mg of olaparib, and as a film-coated tablet containing 100 mg of olaparib.

Patients will be administered olaparib orally twice daily at 300 mgs bid continually. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets 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. If 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.

10.2 Chemotherapeutics

10.2.1 Carboplatin

Use normally available commercial stock in keeping with the normal practice of the institution. There are no special accountability arrangements for carboplatin. For reconstitution and administration refer to the current version Summary of Product Characteristics.

Reconstitute carboplatin AUC in 250ml of 5% dextrose, or according to the standard practice of the institution. Give over 30-60 minutes (depending on local institutional practice).

10.2.1.1 Carboplatin dose

In this trial Carboplatin dose is AUC 5 when combined with PLD (C-PLD) Paclitaxel (C-TAX) or AUC 4 when combined with Gemcitabine (C-GEM).

The carboplatin dose should be calculated according to the Calvert formula as follows:

Carboplatin dose = Target AUC (GFR + 25).

For the purpose of this protocol the GFR is considered equivalent to the creatinine clearance. The exact dose of carboplatin therefore depends on the GFR calculated by using the Cockroft-Gault formula, or the GFR measured by 24-hour urine collection.

Dose capping of carboplatin may be carried out according to local institutional protocols.

If it becomes necessary to discontinue carboplatin treatment due to hypersensitivity, patients can remain on paclitaxel or gemcitabine or PLD and switch carboplatin to cisplatin or continue paclitaxel/gemcitabine/PLD as single agents.

10.2.2 Paclitaxel

Use normally available commercial stock in keeping with the usual practice of the institution. There are no special accountability arrangements for paclitaxel. Reconstitute and administer via a non-PVC giving set and connectors.

10.2.2.1 Paclitaxel dose

Reconstitute paclitaxel 175 mg/m^2 in 250 or 500 ml of normal saline or 5% dextrose according to the standard practice of the institution. Administer over 3 hours via a rate controlling device. Monitor closely for allergic reactions and cardiac arrhythmias as per local institution guidelines. For reconstitution and administration refer to the current version Summary of Product Characteristics.

If it becomes necessary to discontinue paclitaxel treatment due to other toxicities, patients can remain on carboplatin.

10.2.3 Pegylated Liposomal Doxorubicin (PLD)

Use normally available commercial stock according to the current local practice. No special accountability arrangements will be made for PLD.

10.2.3.1 PLD dose

Dose of PLD is 30 mg/m2 administered on day 1 every 4 weeks. For reconstitution and administration refer to the current version Summary of Product Characteristics.

10.2.4 Gemcitabine

Use normally available commercial stock according to with the current local practice. No special accountability arrangements will be made for Gemcitabine. For reconstitution and administration refer to the current version Summary of Product Characteristics.

10.2.4.1 Gemcitabine dose

For the purpose of this trial, Gemcitabine dose and schedule is 1000 mg/m2 given intravenously on days 1 and 8 of a 3-weekly course. Infusion velocity and reconstitution are those from the Summary of Product Characteristics and according to local practice.

If patients experience Grade >2 haematological toxicities that preclude the Day 8 gemcitabine administration and two dose reduction has been yet performed, investigators can omit Day 8 informing the sponsor.

10.3 Premedication and Antiemetic Therapy (chemotherapy arm)

All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions as per local practice. The investigator may determine the appropriate premedication regimen. Routine anti-emetic therapy is given according to departmental praxis.

10.4 Concomitant and other treatments (chemotherapy arm)

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF) including: Reason for use, Dates of administration including start and end dates, Dosage information including dose and frequency.

10.4.1 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

10.4.2 Vaccines

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 days follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Inactivated vaccines, such as the injectable influenza vaccine are permitted. A SARS-CoV-2 vaccine can be proposed to patients according to local guidelines for cancer patients.

10.5 Restriction during the study (chemotherapy arm)

Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom (as described in Appendix C). These contraception criteria should apply throughout the participation in the study and for a time, after last dose of study drug(s), according to reported in corresponding SCP. For details of acceptable methods of contraception refer to Appendix C Acceptable Birth Control Methods.

11. RESTICTIONS DURING THE STUDY AND CONCOMITANT MEDICATIONS (OLAPARIB)

11.1 Anti-emetics/Anti-diarrhoeal

From screening onwards, should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see section 8.3) and appropriate treatment of the event given.

11.2 Restriction during the study

- It is prohibited to consume grapefruit or Seville orange juice while on olaparib therapy.

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom (as described in Appendix C). These contraception criteria should apply throughout the participation in the study and for at least 1 month after last dose of olaparib. For details of acceptable methods of contraception refer to Appendix C Acceptable Birth Control Methods.

- Live virus vaccines and live bacterial vaccines are not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown. A SARS-CoV-2 vaccine can be proposed to patients according to local guidelines for cancer patients.

11.3 Restricted concomitant medications

11.3.1 Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg bid for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.

- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg bid for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.

- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

11.3.2 Strong or Moderate CYP3A inducers

Strong (e.g. phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer or inhibitor, then they must be monitored carefully for any change in efficacy of olaparib.

11.3.3 Anticoagulant therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g apixaban and rivaroxaban) if possible.

11.3.4 Natural/herbal products

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use

- Dates of administration including start and end dates

- Dosage information including dose and frequency

11.3.5 Effect of olaparib on other drugs

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19 and P-gp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib.

Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered.

Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Examples of substrates include:

- CYP3A4 substrates with narrow therapeutic margin: e.g. cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin.
- Sensitive CYP3A4 substrates: e.g. buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin.
- CYP2B6 substrates: e.g. bupropion and efavirenz.
- OATP1B1 substrates: e.g. bosentan, glibenclamide, repaglinide, statins and valsartan.
- OCT1, MATE1 and MATE2K substrates: e.g. metformin.
- OCT2 substrates: e.g. cimetidine and metformin.
- OAT3 substrates: e.g. furosemide and methotrexate.
- BCRP substrates: e.g. methotrexate and rosuvastatin.
- P-gp substrates: e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine

11.4 Concomitant anti-cancer treatments

Patients must not receive any other concurrent anti-cancer therapy as chemotherapy, immunotherapy, hormonal therapy, radiotherapy (except palliative), biological therapy or other novel agents, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

11.4.1 Palliative radiotherapy

Palliative radiotherapy can be administered for the treatment of pain at the site of bone metastases that were present at baseline. Investigators must provide that worsening in pain is not due to disease progression during the study. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

12. STATISTICAL ANALYSES

12.1 Statistical considerations

Analyses will be performed by the Statistical team or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

12.2 Sample size estimate

The study is dimensioned to test the hypothesis that olaparib (experimental arm) *vs* a further line of chemotherapy prolong PFS and/or PFS 2 with an HR of 0.60. Considering a two-sided log-rank test with alpha of 0.025, to attain an 80% power, follow-up will be continued to reach 146 events necessary for the final analysis. Approximately 200 patients will be enrolled in the study.

12.3 Definitions of analysis sets

12.3.1 Full Analysis Set

The Full Analysis Set (FAS) / Intention-to-Treat (ITT) analysis set will include all subjects who were randomized to study treatment. Analyses performed on the FAS will take into account subjects' allocation to treatment arms as randomized. The FAS will be the primary analysis set for all primary and secondary efficacy endpoints.

12.3.2 Safety analysis set

Safety analysis set will include all subjects who were administered at least one dose of study treatment. Subjects will be classified according to the treatment assigned at randomization unless the incorrect treatment was received in which case subjects will be classified according to the first study treatment received.

12.3.3 PRO analysis set

The patient-reported outcomes set (PROAS) included all patients in the FAS who also filled in at least one item on the patient questionnaire at the baseline visit and at least one follow-up visit.

12.4 Outcome measures for analyses

12.4.1 Primary outcomes:

Progression Free Survival defined as the time elapsing between the registration of the patient and the progression of the disease or the death for any cause, whichever occurs first. 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.

Progression Free Survival 2 (PFS2) is defined as the time elapsing between the registration of the patient and the second progression or the death for any cause, whichever occurs first. Patients alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression.

12.4.2 Secondary outcomes:

Overall Survival (OS) is defined as the time elapsing between the registration and the death for any cause. For OS patients lost to follow up or alive at the time of final analysis will be censored at the last date they were known to be alive. Safety: 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. Toxicities will be characterized in terms of seriousness, causality, toxicity grading (according to CTCAE 5 criteria) and action taken with regard to trial treatment.

QoL Assessment: The EORTC QLQ-C30 questionnaire will be used to evaluate QoL. QoL measurement will be planned at screening, on Day 1 of each Cycle (during treatment) until 6 months, then at 9 and 12 months, from randomization for both arms. If the patient suffered of disease progression, the last QoL assessment will be fulfilled at day of EOT visit.

The EORTC QLQ-C30 is a 30-item questionnaire composed of 5 multi-item functional subscales (physical, role, emotional, social and cognitive functioning), 3 multi-item symptom scales (fatigue, pain, and emesis), a global health status subscale, and 6 single items to assess financial impact and symptoms (dyspnoea, sleep disturbance, appetite, diarrhoea, and constipation). Scores for multi-item scales are calculated by deriving the mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100. For single items, only linear transformation is performed. For the functional and global health status subscales of the QLQ-C30 higher values represent better function (i.e. better). For all the other scales, higher values represent greater severity of symptoms (i.e. worse). The QoL of patients will be assessed using the EORTC QLQ-C30 core questionnaire

For PRO-CTCAE and PROFFIT, description of responses at the different time points will be done for all the items and scores; changes over time will be compared between the two arms using standard statistical tests.

12.5 Methods for statistical analyses

12.5.1 Analysis of the primary variables

PFS curves will be described according to the Kaplan-Meier method with their respective two-sided 95% confidence interval (CI) limits. The study will be considered formally positive if at least one of the two primary endpoints will be met. For each PFS endpoint, treatment groups will be compared using two-sided log-rank test with alpha level of 0.025 according to Bonferroni method for multiple comparisons. 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 and PFS or PFS 2 as dependent variables to estimate Hazard Ratios (HR) and confidence intervals. As reported in the following Interim Analysis section, the interim analysis, stopping early only for futility preserves the overall significance level, and nominal confidence interval and p-value at the end of the trial will be used.

12.5.2 Analysis of the secondary variable(s)

Descriptive statistics will be used to describe the patient population by treatments groups and will be composed of means and standard deviations, medians and interquartiles range, absolute and relative frequencies, according to the type of considered variables.

OS curves will be described according to the Kaplan-Meier method with their respective two-sided 95% CI limits. For OS treatment groups will be compared using two-sided log-rank test with alpha level of 0.05. A 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 PS as covariate and OS as dependent variable to estimate HR.

Safety analysis will be performed on safety population, 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 describe and then compared between the two treatment groups with linear rank test and Fisher's exact test. All tests will be two-sided with a significance level of 0.05. No adjustment was applied for multiple comparisons.

QoL missing data patterns will be described according to the National Cancer Institute of Canada Clinical Trials Group QoL framework under three different scenarios: (a) rate of patients completing baseline and subsequent assessments over the total number of patients enrolled into the trial (QoL intention-to-treat [ITT] population); (b) rate of patients completing QoL assessments out of those completing the baseline one (QoL efficacy population); and (c) rate of patients completing QOL assessments out of those expected (QoL expected population), thus excluding patients progressed or dead at a date before the date of planned QoL assessment. No strategy for missing data substitution will be applied. Possible selection biases due to missing values will be checked by comparing the baseline characteristics of subjects without and with baseline QoL questionnaire and the baseline QoL scores between the two arms.

Mean score changes from baseline at each cycle will be reported to describe behaviour of QOL items. Only patients with available values at baseline and at least one subsequent time point will be included in the analysis. A linear regression adjusted model will be applied to test the statistical significance of the differences at each time point.

Best QOL response from baseline for each domain or symptom will be calculated defining a change score of at least 10 points from baseline as clinically relevant. Patients will be considered improved if they reported a score 10-points better than baseline at any time, and

will be considered worsened if they reported a score 10-points worse than baseline without having improved at any time; those with scores changing less than 10 points from baseline will be considered stable. Only patients that will complete the baseline and at least one questionnaire after the baseline will be included. Chi-square test will be applied to test statistical significance with alpha level of 0.05. No adjustment will be applied for multiple comparisons.

Time-to-deterioration will be defined as the time from randomization to QOL deterioration using progression or death as competing events, that prevented the occurrence of QOL assessment. Deterioration of QOL will be defined as a worsening of 10-points from baseline at any time during QOL assessment, irrespective of any improvement. In the competing risk approach, the different types of events are not considered independent, and subjects who experience progression or death before documented QOL deterioration will not be censored at the time of progression/death. Accordingly, cumulative incidence functions, defined as the probability of deteriorating by the time t, will be estimated for each domain and for each arm. Treatments will be compared with the Fine & Gray regression model with 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 and Age and PS as covariate. For each symptom, all patients who have a baseline and at least one follow-up QOL assessment for this symptom will be included in the time-to-deterioration analysis. Patients will be censored at the time of the last QOL questionnaire completion if they had not deteriorated before that.

12.5.3 Exploratory subgroup analysis

Exploratory subgroup analyses will be performed for PFS and OS endpoints. Heterogeneity of treatment effects across the subgroup will be assessed using an interaction test for each subgroup 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.

12.6 Interim analysis

Interim assessments and study monitoring for efficacy and safety will be done by an independent IDMC, 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 IDMC 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.

12.7 Translational analysis

Statistical analysis of biomarkers data will be conducted with the aim of hypothesis generation. To explore the mechanisms of resistance to olaparib through the molecular analysis of tumor samples collected at surgeries a comparison of genomics, transcriptomics and proteomics characteristics between tumor samples collected before and after therapy with olaparib. Molecular analysis will be blinded from clinical data, and correlative analyses will be performed when all molecular analyses have been completed. Due to the exploratory nature of these analyses, no fixed analyses schedule can be specified. Exploratory analyses of individual biomarker and combinations of markers will be conducted using appropriate statistical methods will be detailed in the statistical analysis plan (SAP) when prepared.

A complete description of data from biomarkers will be done before and after treatment with olaparib for detecting variations in the biomarker's expression levels. Correlation between biomarkers at baseline will be assessed. Longitudinal analysis of biomarker values during follow-up evaluation will be done by treatment group. 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.

13. STUDY AND DATA MANAGEMENT

13.1 Training of study site personnel

Before the first subject is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study specific procedures (remote visit).

The Local Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain at site and send at Sponsor a record (Delegation List) of all individuals involved in the study (medical, nursing and other staff).

The study will be carried out adhering to local legal requirements and the applicable national law, whichever represents the greater protection for the individual. In principle, this protocol plans only centralized monitoring activities, on site visits (peripheral auditing visits) will be planned only in case of need.

During the study, a Sponsor representative will have regular contacts with the study site, to:

- Provide information and support to the Investigator(s) and the staff for the study conduction
- Verify that facilities remain acceptable

- Verify that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Instructions

13.2 Data Collection Procedures and Data Management

The study will be managed by the Clinical Trials Unit of the National Cancer Institute of Napoli, Italy, through a web-based platform allowing randomization and electronic data capture, including tools for central monitoring through e-queries. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.
Patient registration and randomization is web-based (http://www.usc-intnapoli.net). Data collection is electronic through the above website (http://www.usc-intnapoli.net), or by paper CRF transmitted by fax to +39 081-7702938, immediately after completion. **For contacts for registration and randomization, see contacts page.**

It remains the responsibility of the Local Principal Investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly. The Sponsor's data manager will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data.

13.3 Study timetable and end of study

The date end of the study is defined as 'the last visit of the last patient (LPLV). Assuming an accrual rate of 8/9 subjects/month we plan to accrue 200 patients in around 24 months.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, Sponsor may also terminate the patient's accrual prematurely if concerns for safety arise within this study.

13.4 Independent Data Monitoring Committee

An IDMC will be incorporated into the trial design to periodically review safety data defined and graded according to NCI CTCAE criteria (version 5.0). Moreover, after the pre-planned interim analysis for futility the IDMC may consider recommending early termination of the study.

The IDMC will be composed by one medical oncologist, one expert trialist and one statistician.

The IDMC will be nominated after the list of participating Institutions will be definitive, to select among experts not directly involved in the study.

The IDMC will be responsible for:

- reviewing safety data produced by the promoter and recommending modifications in case of unexpected or unexpectedly severe toxicities for any of the study treatments. These corrections may be modifications of the treatments, the inclusion criteria or conditions for retreatment, or early closure of a study arm or early study termination.
- evaluating the effect on the study of possible changes in scientific evidence, such as results of other studies, and recommending modifications on the basis of such external data.

14. TRANSLATIONAL PROJECT AND BIOMARKER SAMPLES

Due to the objectives of this trial, major attention will be paid to the sample collection and analysis. FFPE tumor specimen's collection is mandatory for patient's enrolment.

14.1 Rationale for the translational study

Little is known about the mechanisms driving PARPi resistance in HGSOC patients. This is mostly due to the lack of tumor sample from patients that progress to PARPi maintenance therapy. To address this issue, we will evaluate possible mechanisms of PARPi resistance studying paired tumor samples from patients in progression to PARPi and undergoing second surgery at recurrence, before enrolment in the current trial.

Due to complexity of the planned analysis and the different skills among laboratories, 6 different institutions [Oncologia Molecolare, Centro Riferimento Oncologico (CRO) Aviano;,Laboratorio di Farmacologia Molecolare, IRCCS, Humanitas Research Hospital di Rozzano; Dipartimento di Medicina Molecolare, Università Federico II di Napoli; Unità di Terapie Molecolari, Dipartimento di Oncologia Molecolare e Sperimentale Fondazione IRCCS Istituto Nazionale Tumori (INT) Milano, Unità di Genomica Funzionale Istituto Nazionale Tumori (INT) Fondazione "G.Pascale", and Dipartimento Scienze della Vita, Università di Modena] will collaborate to perform the translational project.

14.2 Specimen Types

14.2.1 Solid samples

Formalin-fixed embedded in paraffin (FFPE) tumor tissue blocks from primary surgery (chemotherapy-naive patients) and secondary surgery (after PARPi maintenance) with minimal necrosis will be collected along with one haematoxylin/eosin slide. These tissues may be from the primary tumor, or a metastatic site if the primary tumor is unavailable, or if possible, from both primary tumor and a metastatic site. Tumour tissue blocks will be used to set up a tissue microarray (TMA) for IHC (Immunohistochemistry) analysis and for the extraction of DNA and RNA, stain entire tissue sections to evaluate immune cells infiltrates. All the blocks will be centralized and processed at laboratory of Unità di Genomica Funzionale (Responsible Dott.ssa Daniela Califano), NCI of Naples. Samples for biomarkers

analysis will be possibly stored for up to 10 years after the trial completion, according to informed consent. During this time, the samples might be reanalysed for newly identified markers or with new or improved technology, once specific protocols were approved and consent procedures were discussed and set. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period.

14.2.2 Blood samples

Blood samples will be centralized at the Division of Molecular Oncology of CRO (Responsible Dott G. Baldassarre) of Aviano, accordingly to previous successful experiences in the centralized management of samples for translational clinical trials. Blood samples for biomarkers analysis will be possibly stored for up to 10 years after trial completion, according to informed consent. During this time, the samples might be reanalysed for newly identified markers or with new or improved technology, once specific protocols were approved and consent procedures were discussed and set. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period.

Blood samples will have collected for each patient at 3 time points: baseline (during the screening) and at the time of the first radiological evaluation and at the end of treatment (EOT) visit for: soluble biomarkers, proteins and genomic DNA analysis.

14.2.3 Samples handling and shipping

Samples for germinal DNA analysis (at baseline)

1. Check the patient signature on the consent.
2. Draw 5 mls of blood into EDTA tubes with a Vacutainer system and avoiding tourniquet (in order to avoid hemolysis)
3. Gently invert the tube 8-10 times to mix the anticoagulant with the blood and store a -70°C to -80°C freezer until the shipment to the collecting centre (If only -20°C is available, it is acceptable)

Samples for soluble biomarkers, proteins, cfDNA and miRNA

1. Check the patient signature on the consent.
2. Draw 20 mls of blood into 2 EDTA tubes with a Vacutainer system and avoiding tourniquet (in order to avoid hemolysis)

3. Gently invert the tubes 8-10 times to mix the anticoagulant with the blood
4. Within 30 minutes of blood collection, spin the blood in a refrigerated centrifuge at 4° C at 1500g for 10 minutes.
5. Immediately after centrifugation, carefully transfer the plasma into the labelled transfer tube using a plastic pipette RNAse free. Please be sure to not aspirate the interface containing the platelets.
6. Store the plasma obtained in a -70°C to -80°C freezer until the shipment to the collecting centre (If only -20°C is available, it is acceptable)

14.3 Translational Objectives

14.3.1 Task 1. Genomic evaluation of PARPi resistance.

Based on the deep investigation of HRD mechanisms we will verify if any of the approaches tested to identify HRD, could be useful also to clarify some mechanisms of acquired resistance to PARPi both in first line and recurrence. Paired samples at basal diagnosis from the first surgery are available in the MITO tissue bank and will be used to explore spatial heterogeneity. Samples from patients undergoing surgery at progression to PARPi will be used to investigate longitudinal resistance. These samples will be analysed with the approaches described in as described in MITO 35 A trial to verify if: 1) HRD status is spatially homogeneous; 2) HRD status changes with the progression after PARPi; 3) Specific genes alterations are associated with the onset of PARPi resistance in BRCA wild-type patients. In order to capture the dynamic changes in DNA repair that occur throughout tumor evolution, HRR functionality by RAD51 foci will be test in paired samples using immunofluorescent microscopy.

14.3.2 Task 2 Integration of epigenomics and transcriptomics profiles

Integrating epigenomics (i.e. DNA methylation, miRNA) and transcriptional data can be a useful approach for establishing functional correlations associated to PARPi response. Our preliminary data on 124 samples derived from MITO 2 trial show that by applying a method combining Similarity Network Fusion and Consensus Clustering on three “omic” levels (miRNAs, genes and proteins) we have been able to construct a decisional three summarizing complex information with the expression of 8 proteins:

- Generation of a sample-similarity network for each “omic” and integration in one similarity network.
- Correlation analysis for subtypes’ identification.
- Outcome prediction, patients’ classification.

- Decisional tree.

For this purpose, transcriptome and miRNA analyses will be performed by RNA-seq and miRNA-seq. For RNASeq we will use the TruSeq RNA Exome that allows the detection of whole transcriptome, splicing variants, and transcript fusions. miRNA-seq analysis will be performed using QIAseq miRNA Library Kit (Qiagen). Samples will be then sequenced with NextSeq500 (Illumina). Obtained data will be analysed to obtain a multi "omic" signature of PARPi response.

Regarding epigenomic characteristics that could lead to PARPi resistance, analysis of the promoter's methylation of BRCA1 and RAD51C will be performed in paired tumor samples from primary and secondary cytoreduction. Quantification of BRCA1 and RAD51C methylation levels in tumor samples will be performed by quantitative methylation-sensitive digital droplet polymerase chain reaction (MS-ddPCR) methodology. For assessing RAD51C methylation, primers will be designed for a 142 bp amplicon in the RAD51C untranslated region. Minor groove binder probes hybridizing to the fully methylated (2′-chloro-7′phenyl-1,4-dichloro-6-carboxyfluorescein [VIC] labeled) and the fully unmethylated sequences (6-carboxyfluorescein [FAM] labeled) will be used.

14.3.3 Task 3 HRD mechanisms and the relationship with angiogenesis and immune related biomarkers

The clinical trials in HGSOC are attempting to incorporate all targeted treatments that include antiangiogenic, PARPi and checkpoint inhibitors-based immunotherapy in the first line therapies. A better understanding of the interactions among these pathways is needed. Accumulating evidences suggest that HRD positive OC had more tumor infiltrating (CD3+ or CD8+) lymphocytes (TILs) and the association of HRD and TILs status predicts longer survival). Based on these considerations and our preliminary data, we propose here to identify and integrate possible biomarkers of response to PARPi, bevacizumab and immune-checkpoint inhibitors for a better patients' stratification.

14.3.4 Evaluation of immune infiltrate.

Available studies were performed with samples collected outside controlled clinical trials diminishing the relevance of the results. Similarly, a precise quantification of TILs was generally done using IHC making difficult and less reproducible the generation of an optimal prognostic/predictive cut off. Our preliminary data collected in previous MITO studies have demonstrated that it is possible to evaluate the expression of immune related biomarkers (i.e. CD4, CD8, CD68 and PD-L1) using a multiplex approach that allows the precise quantification and localization of immune infiltrating cells using the multispectral technology.

Based on these data we will characterize the expression and localization of TILs (CD4+ or CD8+) and macrophages (CD68+) in tissue sections form trial samples. The expression and localization of PD-L1 positive tumor and immune cells will be scored. All data will be then related to patients' clinical outcome and to HRD status of the tumor to select, basing on a combined score, patients that might benefit from the combination of PARPi and checkpoint

inhibitors. Finally, using longitudinally collected samples we will verify if immune infiltrate and/or PD-L1 expression change with the acquisition of PARPi resistance.

14.3.5 Tertiary Lymphoid structure (TLS)

TLS are ectopic lymphoid formations found in inflamed, infected, or tumoral tissues and characterized by the presence of mature Dendritic Cells (DCs) (i.e. DC-LAMP^{+}) and B/T lymphocytes within lymphoid aggregates. Recent evidences in melanoma, renal cancer and soft tissue sarcomas tumors have demonstrated that the presence of B cells and TLS is associated with favorable outcomes when individuals undergo immunotherapy. Our preliminary data confirm this hypothesis.

Since tumor infiltration of B and mature DCs cells predicts the prognosis HGSOC patients and reflects the activation of clinically relevant anticancer immunity, we will evaluate the TLS number in the trial specimens through Multiparametric Immunofluorescence as evaluating the presence of DCs/B-cells/T-cells/TLS. The number of TLS will be then correlated with the response to PARPi and patients' survival.

14.3.6 Evaluation of STING pathway.

Recent evidence showed that PARPis' antitumor activity also involves the coordinated activation of robust local and systemic antitumor immune responses. In triple-negative breast cancer (TNBC) olaparib induces proinflammatory cytokine production and subsequent T-cell infiltration that is dependent on cGAS/STING pathway activation exclusively in tumor cells and is more prominent in HR-deficient compared with HR-proficient models. In a BRCA1-deficient syngeneic genetically engineered mouse model of HGSOC, olaparib increased the number of intratumoral CD4+ and CD8+ T cells, increased the production IFNγ and TNFα from these cells, increased the recruitment of dendritic cells displaying potent antigen-presentation capacity in the tumor microenvironment, and significantly reduced myeloid-derived suppressor cells in the tumor tissue, spleen, and blood[14]. Strikingly, PARPi-triggered STING-dependent antitumor immunity was subsequently shown also in BRCA-WT, HR-proficient tumor models (i.e., independent from BRCA status and HRD). Based on these evidences we will evaluate the STING pathway regulation looking at the level of IFNα, IFNβ, CXCL5-10 in serum from patients at baseline, during treatment and at disease progression. Using a validated qRT-PCR approach we will verify if the tumor expression of IFNα IFNβ, CXCL5-10 correlates with their circulating levels. The expression of circulating/tumoral STING pathway members will then be correlated with response to PARPi and patient's survival.

14.3.7 Evaluation of the angiogenic status.

PAOLA-1 trial demonstrated that the association of bevacizumab and PARPi as first line maintenance therapy is feasible and provided a significant PSF benefit in patients with HRD-positive tumors with BRCA wild type status. Despite this, no clinical nor biological biomarkers are actually available to predict which patients could benefit the most from the association of the two targeted therapies. Thus, better patients' stratification is needed.

We have recently demonstrated that a selected group of miRNA potentially affecting angiogenesis could be used to select platinum resistant and refractory ovarian cancer patients. Our preliminary data collected using RNA extracted from MITO16A patients and a dedicated TMA provided new information and suggest that selected miRNA expression could be used to stratify patients who may benefit from the bevacizumab maintenance therapy. Therefore we will use this approach to better characterize the population included in the current trials in order to verify if the combined expression of selected miRNAs and selected angiogenic markers (including VEGFA, VEGFB, PlGF, VEGFR1 and 2, CD31, CD34 and αSMA) could stratify patients that benefit from PARPi. The availability of longitudinally collected samples will allow understand if "anigomiRs" and/or the tumor vasculature and angiogenic markers expression changes with the acquisition of PARPi resistance.

14.3.8 Task 4: Translational studies through Mass Spectrometry Imaging (MSI).

Task 4 is aimed to achieve more detailed information on mechanistic molecular aspects of PARPi (PARP inhibitors) drug resistance using a recent and largely informative analytical approach Imaging Mass Spectrometry (MSI). This technology provides information on the protein and metabolites characterization, quantification and localization.

This Task will be performed on tissue specimen with at least 6-micron slide and 1x1mm minimum surface area. Paired samples (one from archival and one from second surgery post progression to PARPi) will be analyzed with the approaches described in the reported references[15,16,17]. Specifically, we propose to study the following biological proteins and pathways 1) spatial distribution of PARPi modulated proteins in cancer tissues, in particular the PARP enzymes family (among which PARP1, PARP2, PARP3); 2) changing of PARPi associated proteins with the cancer progression on PARPi; 3) Specific proteins alterations, which might be associated with the onset of PARPi resistance; i) Cell Cycle markers status. Considering that the response to DNA damage will be different depending on the cell-cycle status[18], cell cycle markers will be analyzed among the following ones: Cdh1, Cdc20, cyclin B1, Aurora A, cyclin A, p27kip1 (G0-G1 phase marker); Cyclin E (early S phase); Skp2 (G1-S marker); and phospho Histone-H3 (pHH3), mitotis. ii) DDR (ATM, ATR). iii) BET proteins. iv) ATP-binding cassette (ABC) transporters (ABCB1). Paraffin-Embedded (FFPE) tissues will be used. These analyses will be performed at the Department of Life Science, University of Modena and Reggio Emilia, headed by Prof. Maria Paola Costi.

14.3.9 Task 5: Pharmacogenetic analysis of olaparib ADME

Task 5 has the aim to address the effect of germline genetic variants in Absorption, distribution, Metabolism and Elimination (ADME) related genes as potential markers of a differential plasmatic exposure to the drug.

Olaparib bioavailability is strongly affected by cytochromes (CYPs) mediated liver metabolism. In particular, the use of enzymatic inhibitors or inducers of CYP3A4 and CYP3A5 isoforms were demonstrated to strongly alter the pharmacokinetic profile of the drug. MITO35A and B protocols consider not eligible patients assuming strong CYP3A inhibitors/ inducers co-medication, to avoid inter-patient's variability in drug metabolism[19.] However,

CYPs encoding genes, and CYP3A4 and CYP3A5 in particular are reported to be polymorphic and specific genetic polymorphisms were demonstrated to affect enzyme expression and substrate drugs pharmacokinetics. This could result in inter-patient pharmacokinetic variability even in absence of inhibitors or inducers of CYP3A4 and CYP3A5. No information is presently available about the effect of CYPs polymorphisms on the outcome (toxicity and efficacy) of an olaparib based treatment. This protocol represents an ideal clinical platform to study the relationship between CYPs pharmacogenetics and olaparib treatment outcome due to the homogeneity in the co-medication therapy (absence of CYP3A interfering drugs). Information on other extrinsic factors (such as herbal treatments, smoking habits, hormonal status, etc) reported to potentially affect CYPs enzymatic activity will be taken into account. In addition, olaparib is a PgP substrate that beside the drug pharmacokinetics could also affect the drug efficacy at the tumor cells level (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000ClinPharmR.pdf). Germline genetic polymorphisms in ABCB1 gene and OATs transporters known to be intra-cellular carriers of olaparib will be also considered as predictive markers of treatment outcome. This task will be carried out at the Unit of Experimental and Clinical Pharmacology of CRO Aviano by Dr. Giuseppe Toffoli and Dr. Erika Cecchin).

14.4 Samples shipping

FFPE tumor samples will be shipped by local laboratory, according to laboratory instructions, at:

Unità Sperimentazioni Cliniche

Istituto Nazionale Tumori, IRCCS “Fondazione G.Pascale”

Mariano Semmola - 80131 Napoli.

Blood samples will be shipped by local laboratory at the CRO di Aviano:

Division of Molecular Oncology

Centro di Riferimento Oncologico (CRO) di Aviano

Via Franco Gallini, 2, Aviano

15. ETHICAL AND REGULATORY REQUIREMENTS

The procedures set out in this study protocol are designed to ensure that the promoter and the Investigators abide by the principles of the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH) and the Declaration of Helsinki in the conduct, evaluation and documentation of this study. The study will be carried out adhering to local legal requirements and the applicable national law, whichever represents the greater protection for the individual.

15.1 The risk/benefit evaluation

The value of continuing Olaparib beyond progression, main objective of the trial, is not fully clear. However, it is known that patients with recurrent disease may develop resistance to platinum-based chemotherapy. Response to chemotherapy in patients treated after progression to olaparib is lower than expected response rate to subsequent chemotherapy compared with what is expected according to the platinum-free interval[7].

There are two main aspects to be considered: the risk of undertreatment (lack of efficacy) and the safety profile In principle, the risk of lack of efficacy concerns the patients in the experimental arm as they do not receive chemotherapy, which is the standard treatment for this population.

This risk will be tackled with a planned interim analysis throughout the study. 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. If a significant difference in terms of rate of progression disease is found at interim analysis, the randomization will be stopped, and the experimental arm will be closed. The study will continue, and the patients will be enrolled only in the standard arm to continue translation project, only after the protocol amendment. However, in case of changes in scientific evidence, such as results of other studies, that would affect the ethicality of study treatments, the promoter and IDMC will be responsible for evaluating the effect of such external data on the study. Then, the IDMC can recommend, and the promoter con make, the appropriate corrections, such as study amendment with modifications of the treatments or study evaluation procedures, or study premature closure.

Safety of single agent olaparib has been fully investigated and data indicate a safe toxicity profile. Moreover, the promoter and the IDMC will be responsible for periodically reviewing safety data.

15.2 Informed consent

The Local Principal Investigator or his/her representative will explain the nature of the study to participant and answer all questions regarding the study and will:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Inform each patients that their participation is voluntary and that may withdraw their consent at any time and for any reason.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each subject provides signed and dated informed consents before conducting any procedure specifically for the study
- Ensure that the original, signed Informed Consent Forms are stored in the Investigator's Study File
- Ensure that a copy of the signed Informed Consent Forms is given to the subject

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: 2021-000245-41	Version n.1 1 July, 2021

16. ADMINISTRATIVE ASPECT

This stuy is a non-profit investigator initiated trial. In this trial, the experimental drug Olaparib (in the experimental arm) will be provided at no cost by the manufacturer (Astra-Zeneca), for treatment until progression. The promoter (National Cancer Institute of Naples) will provide an insurance policy to cover possible damages caused to patients participating in the trial. The policy will cover all participating centres in Italy.
An agreement between the Coordinating Centre and each participating centre will be stipulated. Study protocol, patient information and informed consent will be submitted to the appropriate Ethical Committees for approval. At each centre, the study will only be started after being approved by the institutional Ethical Committee. The promoter will inform the Ethical Committees about any changes in the study protocol which could interfere with the patient's safety. Furthermore, the institutional review board will be informed of the planned or premature end of the study.

16.1 Publication Policy

Publications arising from study data will be determined by the Study Steering Committee.
Co-authorship to be reported in the front page will be selected on the basis of the specific contribution or the number of enrolled patients. All the Authors reported in the front page will be actively involved in manuscript preparation. All study publications will report the statement "… on behalf of the MITO35b Investigators".
All those who will take part in the study will be acknowledged in the appendix.

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: 2021-000245-41	Version n.1 1 July, 2021

17. COORDINATING CENTER CONTACTS

Principal Investigators

Dr. Sandro Pignata, MD, PhD
Division of Medical Oncology – Uro-Gynecology Department
Tel: +39 081-5903637
Fax: +39 081-5903861
Email: s.pignata@istitutotumori.na.it
National Cancer Institute Naples

Dr. Stefano Greggi, MD, PhD.
Gynaecology Oncology Unit– Uro-Gynecology Department
Tel: +39 081-5903417
Fax: +39 081-5903851
Email: s.greggi@istitutotumori.na.it
National Cancer Institute Naples

Coordinating center

Clinical Trials Unit
National Cancer Institute Naples
Dr. Francesco Perrone, MD, PhD
Dr. Clorinda Schettino, MD,
Tel: +39 081 - 5903571
Fax: +39 081 - 7702938
Email:f.perrone@istitutotumori.na.it c.schettino@istitutotumori.na.it

Study Statisticians

Prof. Paolo Chiodini
Medical Statistics
University of Campania Luigi Vanvitelli
E-mail: paolo.chiodini@unicampania.it

Dr. Laura Arenare
Medical Statistics
Clinical Trials Unit
National Cancer Institute Naples
E-mail: l.arenare@istitutotumori.na.it

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: 2021-000245-41	Version n.1 1 July, 2021

Contacts for registration and randomization:

Simona Bevilacqua, Manuela Florio, Valentina Barbato, Giovanni De Matteis
Clinical Trials Unit
National Cancer Institute Naples
http://www.usc-intnapoli.net
e-mail:
tel: + 39 081-5903571
fax: + 39 081-7702938
Monday through Friday: 9.30 – 15.30

Contacts for regulatory issues:

Marilena Martino, Giuliana Canzanella, Teresa Ribecco
Clinical Trials Unit
National Cancer Institute Naples
http://www.usc-intnapoli.net
e-mail: usc-segreteria@istitutotumori.na.it
tel: + 39 081-5903571
fax: + 39 081-7702938
Monday through Friday: 9.00 – 15.30

18. LIST OF REFERENCES

[1] Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424, doi:10.3322/caac.21492.

[2] Moore, K.; Colombo, N.; Scambia, G.; Kim, B.-G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; Sonke, G.S.; et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N. Engl. J. Med. 2018, 379, 2495–2505, doi:10.1056/NEJMoa1810858.

[3] González-Martín, A.; Pothuri, B.; Vergote, I.; DePont Christensen, R.; Graybill, W.; Mirza, M.R.; McCormick, C.; Lorusso, D.; Hoskins, P.; Freyer, G.; et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N. Engl. J. Med. 2019, 381, 2391–2402, doi:10.1056/NEJMoa1910962.

[4] Ray-Coquard, I.; Pautier, P.; Pignata, S.; Pérol, D.; González-Martín, A.; Berger, R.; Fujiwara, K.; Vergote, I.; Colombo, N.; Mäenpää, J.; et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N. Engl. J. Med. 2019, 381, 2416–2428, doi:10.1056/NEJMoa1911361.

[5] Coleman, R.L.; Fleming, G.F.; Brady, M.F.; Swisher, E.M.; Steffensen, K.D.; Friedlander, M.; Okamoto, A.; Moore, K.N.; Efrat Ben-Baruch, N.; Werner, T.L.; et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N. Engl. J. Med. 2019, 381, 2403–2415, doi:10.1056/NEJMoa1909707.

[6] McMullen, M.; Karakasis, K.; Madariaga, A.; Oza, A.M. Overcoming Platinum and PARP-Inhibitor Resistance in Ovarian Cancer. Cancers 2020, 12, 1607.

[7] Cecere SC, Giannone G, Salutari V, et al. Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome. Gynecol Oncol. 2020;156(1):38-44. doi:10.1016/j.ygyno.2019.10.023

[8] Patterns of progression and subsequent management of patients with BRCA1/2 mutated platinum-sensitive recurrent epithelial ovarian cancer (EOC) progressing on olaparib versus placebo: the SOLO2/ENGOT Ov-21 trial (NCT01874353). Available online: https://meetinglibrary.asco.org/record/187230/abstract (accessed on Jun 20, 2020).

[9] Andreas Du Bois, J.S.; et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: Final analysis of AGO DESKTOP III/ENGOT-ov20. DOI:10.1200/JCO.2020.38.15_suppl.6000

[10] Harter P, Sehouli J, Reuss A, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer. 2011;21(2):289-295. doi:10.1097/IGC.0b013e31820aaafd

[11] Tumati V, Iyengar P. The current state of oligometastatic and oligoprogressive non-small cell lung cancer. J Thorac Dis. 2018;10(Suppl 21):S2537-S2544. doi:10.21037/jtd.2018.07.19

[13] Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.

[14] Ding, Liya et al. "PARP Inhibition Elicits STING-Dependent Antitumor Immunity in Brca1-Deficient Ovarian Cancer." Cell reports vol. 25,11 (2018): 2972-2980.e5. doi:10.1016/j.celrep.2018.11.054

[15] Dirix L, Swaisland H, Verheul HM, et al. ·N-glycan MALDI Imaging Mass Spectrometry on Formalin-Fixed Paraffin-Embedded Tissue Enables the Delineation of Ovarian Cancer Tissues. Mol Cell Proteomics. 2016 Sep; 15(9): 3003–3016. Published online 2016 Jul 13. doi: 10.1074/mcp.M116.059816

[16] Delcourt V., Franck J., Leblanc E., Combined Mass Spectrometry Imaging and Top-down Microproteomics Reveals Evidence of a Hidden Proteome in Ovarian Cancer. EBioMedicine. 2017 Jul; 21: 55–64. Published online 2017 Jun 3. doi: 10.1016/j.ebiom.2017.06.001

[17] Dória ML, S. McKenzie J.S., Mroz A, et al. Epithelial ovarian carcinoma diagnosis by desorption electrospray ionization mass spectrometry imaging.Sci Rep. 2016; 6: 39219. Published online 2016 Dec 15. doi: 10.1038/srep39219.

[18] O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547-560.

[19] Dirix L, Swaisland H, Verheul HM,et al. Effect of Itraconazole and Rifampin on the Pharmacokinetics of Olaparib in Patients With Advanced Solid Tumors: Results of Two Phase I Open-label Studies. Clin Ther. 2016 Oct;38(10):2286-2299. doi: 10.1016/j.clinthera.2016.08.010. Epub 2016 Oct 10.

[20] Saiz-Rodríguez M, Almenara S, Navares-Gómez M, Effect of the Most Relevant CYP3A4 and CYP3A5 Polymorphisms on the Pharmacokinetic Parameters of 10 CYP3A Substrates. Biomedicines. 2020 Apr 22;8(4):94. doi: 10.3390/biomedicines8040094.

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: 2021-000245-41	Version n.1 1 July, 2021

Appendix A

ACTION REQUIRED IN CASE OF INCREASE IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together **with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the Sponsor that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

5. Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the Sponsor

The Sponsor contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Sponsor
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

6. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

7. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients << with liver metastases>> who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  - If there is no significant change no action is required

  - If there is a significant change notify the Sponsor representative, who will inform the Company, then follow the subsequent process described in **Errore. L'origine riferimento non è stata trovata.** o of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Company if there is any uncertainty.

8. Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required

When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment >>?

If No: follow the process described in in Potential Hy's Law Criteria met of this Appendix of this

If Yes:

Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change, follow the process described in Section 4.2 of this Appendix

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Company if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation': http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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: 2021-000245-41	Version n.1 1 July, 2021

Appendix B RECIST Criteria v 1.1

1. Measurability of tumor lesions at baseline

Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Provide detail on the conditions under which such lesions would be considered measurable.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions.** When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.
- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 3 weeks before the beginning of the treatment.

2. Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI.** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- **Tumor Markers**. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

3. Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later (adjust as appropriate). Refer to the table below.

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

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: 2021-000245-41	Version n.1 1 July, 2021

Table 1: Integration of target, non-target and new lesions into response assessment:

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this category also requires**
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ **4 wks. from baseline [note, protocol may define; 6-8 weeks is recommended]**
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, all tumour nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

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: 2021-000245-41	Version n.1 1 July, 2021

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point **at least 4 weeks later (adjust as appropriate)**. The best overall response can be interpreted as below:

Table on confirmation

Response: First time point	**Subsequent time point**	**BEST overall response**	**Also requires**
CR	CR	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

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: 2021-000245-41	Version n.1 1 July, 2021

Appendix C Acceptable Birth Control Methods

Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective form of contraception and their partner must use a male condom [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse (see below).

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom