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

Clorinda Schettino,[1] Lucia Musacchio,[2] Michele Bartoletti ,[3] Paolo Chiodini,[4] Laura Arenare,[1] Gustavo Baldassarre,[5] Daniela Califano,[6] Ettore Capoluongo,[7,8] Maria Paola Costi,[9] Maurizio D'Incalci,[10,11] Sergio Marchini,[11] Delia Mezzanzanica ,[12] Nicola Normanno,[13] Stefania Scala,[6] Stefano Greggi,[14] Francesco Perrone ,[1] Sandro Pignata[15]

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For numbered affiliations see end of article.

Correspondence to
Professor Sandro Pignata, Gynaecological Oncology, National Cancer Institute Napels, Naples, Italy; s.pignata@istitutotumori.na.it

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ABSTRACT

Background Poly (ADP-ribose) polymerase inhibitors have transformed the management landscape for patients with ovarian cancer, demonstrating remarkable improvements in progression-free survival and overall survival. Unfortunately, most relapses are due to an acquired mechanism of resistance to these agents. We hypothesize that secondary cytoreductive surgery, removing resistant clones, might help to overcome the development of resistance to poly (ADP-ribose) polymerase inhibitors, prolonging their therapeutic effect.

Primary Objective To determine the efficacy of olaparib beyond progression compared with standard platinum-based chemotherapy in patients with recurrent ovarian cancer progressed during or after poly (ADP-ribose) polymerase inhibitor maintenance therapy after secondary cytoreductive surgery.

Study Hypothesis Olaparib administered beyond progression is more effective in increasing progression-free survival and progression-free survival 2 compared with second-line platinum-based chemotherapy in patients after secondary cytoreductive surgery.

Trial Design Phase III, randomized, open-label, multicenter trial. Eligible patients will be randomized in a 1:1 ratio to receive olaparib or platinum-based chemotherapy of the investigator's choice.

Major Eligibility Criteria Eligible patients must have high-grade serous or endometrioid ovarian cancer progressed during or after first-line poly (ADP-ribose) polymerase inhibitor maintenance therapy and must have undergone secondary cytoreductive surgery.

Primary Endpoint The dual primary endpoints will include progression-free survival and progression-free survival 2. Progression-free survival is defined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the time between randomization and progression or death from any cause. Progression-free survival 2 is defined by the investigator using RECIST version 1.1 as the time frame from randomization to the second progression or death from any cause after subsequent treatment.

Sample Size Approximately 200 patients will be enrolled in this study.

Estimated Dates for Completing Accrual and Presenting Results Enrollment will be completed in 2024. Results will be presented in 2026.

Trial Registration EudraCT 2021-000245-41 NCT05255471

INTRODUCTION

Epithelial ovarian cancer is the main cause of death from gynecological malignancies with 313 959 new cases and 207 252 deaths in 2020.[1] In the last few years the introduction of poly (ADP-ribose) polymerase inhibitors into the therapeutic algorithm has remarkably reshaped the outcomes of women with ovarian cancer, with notable improvements in terms of progression-free survival and overall survival regardless of BRCA gene mutational status.[2–9] Despite these unprecedented results, disease recurrence is still frequent and the development of resistance to further lines of medical treatment is the main cause of death for patients with ovarian cancer. The mechanisms of resistance to poly (ADP-ribose) polymerase inhibitors are still largely unknown.[10] In a small series of patients, acquired somatic reversion mutations in *BRCA1/2* positive cancers that restore the BRCA reading frame thereby conferring resistance to poly (ADP-ribose) polymerase inhibitors have been described. Other mechanisms of resistance seem to be related to epigenetic loss of *BRCA1* promoter methylation or *RAD51c* and *RAD51d* secondary mutations.[11] Since most recurrences appear after 6 months from the last platinum dose, a platinum-containing regimen could be an option for these patients but there are concerns regarding a possible cross-resistance between poly

(ADP-ribose) polymerase inhibitors and platinum salts.[10] Despite the introduction of new medical therapies for the ovarian cancer therapeutic algorithm, cytoreductive surgery still plays a central role both in the upfront and recurrent settings. Final analysis of the DESKTOP III trial demonstrated a clear benefit for patients who met the study inclusion criteria and underwent secondary cytoreductive surgery, with a significantly longer median overall survival (HR 0.76, 95% CI 0.59 to 0.97, p=0.03), median progression-free survival (HR 0.66, 95% CI 0.54 to 0.82, p<0.001), and median time to start of first subsequent therapy (HR 0.65, 95% CI 0.52 to 0.81, p<0.001) in favor of the surgery arm compared with similar patients who did not undergo secondary surgery.[12]

In the presence of a strong oncogenic driver such as BRCA mutation, disease progression during poly (ADP-ribose) polymerase inhibitor maintenance therapy could be attributed to a small number of resistant cells that develop a biological resistance to targeted therapy resulting in clinical progression. The positive impact of secondary cytoreductive surgery in relapsed ovarian cancer and the presence of a targeted therapy for this disease led to the hypothesis of the MITO 35b study. The aim of this study is to evaluate whether, in patients with ovarian cancer who progress during or after poly (ADP-ribose) polymerase inhibitor maintenance therapy and who have undergone secondary cytoreduction with resection of at least the progressive lesions, olaparib treatment administered beyond progression and after surgery prolongs progression-free survival compared with a platinum-based second-line chemotherapy.

METHODS AND ANALYSIS

Study Hypothesis

The MITO 35b trial will assess the hypothesis that the use of olaparib (experimental arm) beyond progression in patients after secondary cytoreductive surgery and poly (ADP-ribose) polymerase inhibitor therapy prolongs progression-free survival and progression-free survival 2 compared with platinum-based chemotherapy (standard arm). In addition, this trial will compare the two treatment arms in terms of safety, overall survival, and quality of life.

Trial Design

MITO35b is a phase III, randomized, multicenter, open-label trial (Figure 1). Patients will be assigned in a 1:1 ratio to receive either olaparib 300 mg twice daily in Arm A (experimental arm) or physician's choice platinum-based chemotherapy in Arm B (control arm). Patients randomized in the control arm will receive platinum-based chemotherapy of the investigator's choice among the following: (1) carboplatin area under the curve 5 mg/mL/min (AUC5) intravenously plus pegylated liposomal doxorubicin (PLD) 30 mg/m^2 on day 1 every 28 days for a maximum of eight cycles; (2) carboplatin (AUC4) plus gemcitabine 1000 mg/m^2 on day 1 and day 8 every 21 days for a maximum of eight cycles; (3) carboplatin (AUC5) plus paclitaxel (175 mg/m^2) every 21 days for a maximum of eight cycles. Patients randomized in the experimental arm will continue to receive olaparib until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. Patients assigned to Arm B may, at the investigator's discretion, continue beyond the eight cycles planned if it is thought to add clinical benefit and in the absence of limiting toxicities.

This trial will be conducted in approximately 40 centers in MITO and MANGO networks and will be coordinated by the Clinical Trials Unit of the National Cancer Institute of Naples. Protocol study is available for consultation, see Online Supplemental File 1.

Participants

Key inclusion and exclusion criteria are listed in Table 1. Briefly, eligible patients must have a histologically documented diagnosis of recurrent high-grade serous or endometrioid ovarian, fallopian,

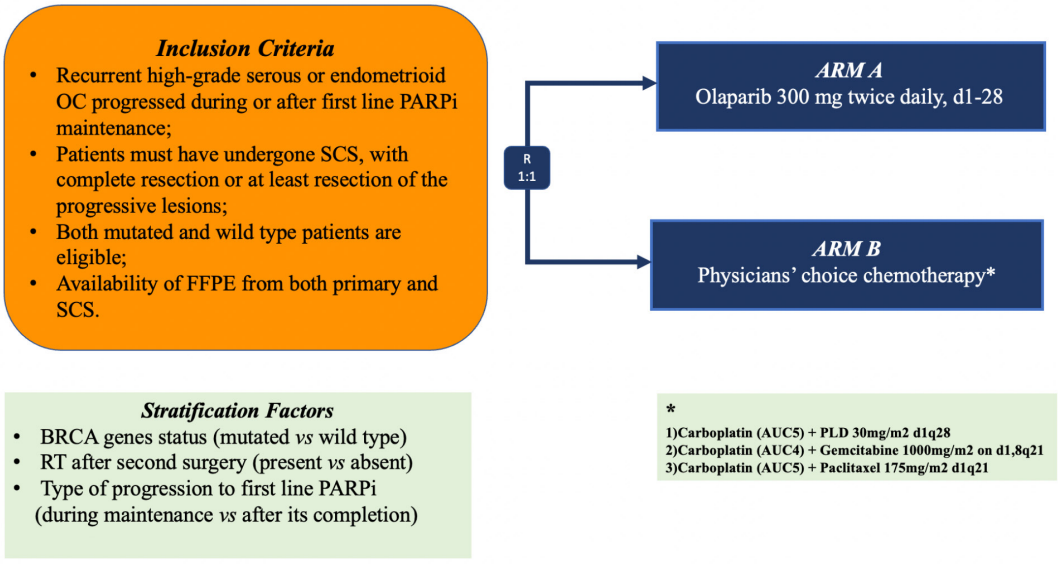

Figure 1 MITO35b study design. In Arm A, olaparib will be administered until disease progression or unacceptable toxicity. In Arm B, patients will receive up to eight cycles of carboplatin (plus paclitaxel or gemcitabine or PLD); however, chemotherapy treatment beyond eight cycles may be permitted (with the sponsors' approval) for patients who continue to derive clinical benefit. AUC, area under the curve (unit, mg/mL/min); FFPE, formalin-fixed, paraffin-embedded; PARPi, poly (ADP-ribose) polymerase inhibitors; PLD, pegylated liposomal doxorubicin; RT, residual tumor; SCS, secondary cytoreductive surgery.

Table 1 Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
► Patients with high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer recurrent or progressive after first-line PARPi maintenance ► Only one previous line of a platinum-based chemotherapy not containing bevacizumab ► 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 ► Patients must have received first-line maintenance therapy with a PARPi for at least 6 months; patients who experience disease relapse after the end of 24 months maintenance therapy are eligible ► Documented BRCA1/2 status. Both mutated and wild type patients are eligible. Patients with unknown status of BRCA genes must agree to undergo analysis of their germline and somatic BRCA status (testing must be completed prior to randomization in the study) ► Patients must start the experimental treatments in the current study within 3–8 weeks from second surgery ► Patients 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 randomization	► Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment ► Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of major surgery ► Other malignancy unless curatively treated with no evidence of disease for ≥5 years* ► Patients who, in the investigator's opinion, are not eligible according to ESMO guidelines for retreatment with a platinum-containing therapy (ie, patient has experienced a major adverse reaction to platinum salts during first-line therapy) ► Persistent toxicities (>CTCAE grade 2) caused by previous cancer therapy, excluding alopecia

*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.
CTCAE, Common Terminology Criteria for Adverse Events; ESMO, European Society of Medical Oncology; PARPi, poly (ADP-ribose) polymerase inhibitors.

or primitive peritoneal cancer progressed during or after first-line poly (ADP-ribose) polymerase inhibitor maintenance therapy (received for at least 6 months). All patients must have received only one previous line of a platinum-based regimen not containing bevacizumab and at the time of recurrence 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) that occurred during or after maintenance. Patients must start the experimental treatments in the current study within 3–8 weeks from secondary surgery and provide archival tumor samples formalin-fixed, paraffin-embedded (FFPE) from both the primary and secondary surgeries for paired analysis.

Endpoints

The objective of this study is to compare the efficacy and safety of olaparib beyond progression versus platinum-based chemotherapy in patients with recurrent ovarian cancer who progressed during or after poly (ADP-ribose) polymerase inhibitor maintenance therapy and who have undergone secondary cytoreductive surgery. The co-primary endpoints will include progression-free survival and progression-free survival 2. Progression-free survival is defined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the time between randomization and progression or death from any cause. Progression-free survival 2 is defined by the investigator using RECIST version 1.1 as the time frame from randomization to the second progression or death from any cause after subsequent treatment.

Secondary endpoints will include overall survival, the assessment of quality of life, financial toxicity, and safety and tolerability. Overall survival is defined as the time between randomization and death from any cause. Quality of life will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, financial toxicity will be assessed using the Patient Reported Outcome for Fighting Financial Toxicity (PROFFIT) questionnaire, and safety and tolerability will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the PRO-CTCAE questionnaire.

The trial will also explore the possible mechanisms of drug resistance through the molecular analysis of tumor samples from patients in progression to poly (ADP-ribose) polymerase inhibitors and who have undergone second surgery at the first recurrence, before enrollment in the current trial as exploratory endpoints. Comparisons will be made of genomics, transcriptomics, and proteomics characteristics between tumor samples collected before and after treatment with olaparib for paired patients.

Randomization and Blinding

Patients will be randomized in a 1:1 ratio to receive an olaparib 300 mg tablet twice daily, days 1–28 continuously, in the

experimental arm or platinum based-therapy of the investigator's choice in the control arm. Randomization will be centralized at the National Cancer Institute of Naples. A computerized minimization procedure will be applied using the following stratification factors: BRCA gene status (mutated vs wild type), residual disease after second surgery (present vs absent), and type of progression to first-line (during poly (ADP-ribose) polymerase inhibitor maintenance therapy vs after its completion).

Sample Size

The study is powered to test the hypothesis that olaparib (experimental arm) versus a further line of chemotherapy prolongs progression-free survival and/or progression-free 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.

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. Progression-free survival and overall survival curves will be described according to the Kaplan–Meier method and treatment groups will be compared using a log-rank test. For each progression-free survival endpoint, treatment groups will be compared using a two-sided log-rank test with alpha level of 0.025. 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 poly (ADP-ribose) polymerase inhibitors (during maintenance vs after its completion), treatment, age, and performance status as covariates. To evaluate the 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 progression-free survival will be observed using a futility approach.

DISCUSSION

Despite the considerable progress in the management of epithelial ovarian cancer, many patients relapse and die from their disease. The mechanism of resistance to poly (ADP-ribose) polymerase inhibitors remains unclear and represents a topic of great interest on which many researchers and studies are focusing. Some preclinical studies suggest that this phenomenon is probably attributable to restoration of the homologous recombination repair pathway and preliminary analyses indicate that patients who have progressed during treatment with poly (ADP-ribose) polymerase inhibitors have a lower than expected response to subsequent treatments, especially to platinum-based therapies.[11]

Exploratory data from the MITO real-life experience have shown that patients with BRCA 1/2 in progression while on olaparib maintenance had a low response rate when re-exposed to a platinum-based therapy with an objective response rate of only 29.2% in patients with a platinum-free interval of more than 12 months.[13] Other data from a retrospective Australian multicohort study found an objective response rate of 24.7% in 77 patients receiving chemotherapy after poly (ADP-ribose) polymerase inhibitors.[14] These data are in line with a secondary analysis from the SOLO2 trial in which the median progression-free survival of patients treated with a platinum-containing regimen after disease progression to olaparib was only about 6 months.[15]

On the other hand, the beneficial role of secondary cytoreductive surgery has been amply demonstrated. The results of the DESKTOP III perspective randomized trial showed a great advantage in terms of progression-free survival, time to first subsequent therapy, and overall survival in favor of the surgery arm, highlighting the crucial role that surgery continues to play in the treatment of epithelial ovarian cancer, even at the time of disease recurrence.[12] Assuming that progression could be driven by a limited number of cancer cells that develop a biological resistance to targeted therapy resulting in clinical progression, secondary cytoreduction with resection of at least the progressive lesions might make the remaining disease sensitive to poly (ADP-ribose) polymerase inhibitors.

Author affiliations
[1]Clinical Trial Unit, Istituto Nazionale Tumori, IRCCS, "Fondazione Giovanni Pascale", Naples, Italy
[2]Department of Women and Child Health, Division of Gynecologic Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Rome, Italy
[3]Unit of Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
[4]Department of Mental Health and Public Medicine, Section of Statistics, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy
[5]Division of Molecular Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
[6]Microenvironment Molecular Targets Unit, Istituto Nazionale Tumori IRCCS - Fondazione G. Pascale, Naples, Italy
[7]Department of Molecular Medicine and Medical Biotechnology, Università degli Studi di Napoli Federico II, Naples, Italy
[8]Azienda Ospedaliera per L'Emergenza, Cannizzaro, Catania, Italy
[9]Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy
[10]Laboratory of Molecular Pharmacology, Group of Cancer Pharmacology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[11]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[12]Molecular Therapies Unit, Department of Research, Istituto Nazionale dei Tumori IRCCS, Milan, Italy
[13]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori "Fondazione Giovanni Pascale", Naples, Florida, USA
[14]Gynecologic Oncology Surgery, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy
[15]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS "Fondazione Giovanni Pascale", Naples, Italy, 80131

Twitter Michele Bartoletti @Barto_Med and Francesco Perrone @fperrone62

Contributors SP is responsible for study design. LM, MB, and CS are responsible for drafting the manuscript. PC and LA are responsible for statistical analysis and data interpretation. All authors are responsible for the acquisition and quality control of the data. SP, FP, and SG are responsible for the critical revision of the manuscript for important intellectual content. SP is guarantor.

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Patient consent for publication Not applicable.

Ethics approval This study involves human partecipants and was approved by the Institutional Review Board. Patients gave informed consent to participate in the study. EudraCT:2021-000245-41 NCT05255471.

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ORCID iDs
Michele Bartoletti http://orcid.org/0000-0002-9631-5693
Delia Mezzanzanica http://orcid.org/0000-0002-9664-6871
Francesco Perrone http://orcid.org/0000-0002-9738-0526

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