Supplementary Appendix

Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OReO/ENGOT-ov38): a phase IIIb trial

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This appendix has been provided by the authors to give readers additional information about their work.

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INVESTIGATORS

The table below lists the principal investigator for each site that randomized patients in the study.

Site no.	Principal Investigator	No. of patients randomized	Country
2308	Isabelle Ray-Coquard	16	France
4106	Giovanni Scambia	13	Italy
4125	Claudio Zamagni	7	Italy
7020	Beatriz Pardo Búrdalo	6	Spain
7001	Ana Oaknin/Victor Rodriguez Freixinos*	6	Spain
7005	Maria Jesús Rubio-Pérez	6	Spain
7006	Andres Redondo Sanchez	6	Spain
7026	Ana Santaballa Bertrán	5	Spain
4102	Nicoletta Colombo	5	Italy
2608	Ahmed El-Balat	5	Germany
2603	Florian Heitz	5	Germany
5201	Kristina Lindemann	5	Norway
4123	Francesco Raspagliesi/ Domenica Lorusso*	5	Italy
4130	Graziana Ronzino	5	Italy
4129	Paolo Scollo	5	Italy
7025	Antonia Márquez Aragonés	4	Spain
2602	Ulrich Canzler	4	Germany
2324	Philippe Follana	4	France
2304	Laurence Gladieff	4	France
0510	Stéphanie Henry/Peter Vuylsteke*	4	Belgium
7023	Luis Manso Sánchez	4	Spain
2604	Fabienne Schochter/ Nikolaus de Gregorio*	4	Germany
2309	Frédéric Selle	4	France
2320	Dominique Berton-Rigaud	3	France
2311	Anne Donnadieu/Coraline Dubot*	3	France
2327	Anne Claire Hardy-Bessard	3	France
5710	Radoslaw Madry	3	Poland
4126	Giorgia Mangili	3	Italy
2001	Mansoor Mirza	3	Denmark
2329	Marie-Ange Mouret-Reynier	3	France
7004	Ignacio Romero Noguera	3	Spain
5706	Magdalena Sikorska	3	Poland
2323	Benoit You	3	France
4122	Alessandra Bologna	2	Italy

2607	Michael Eichbaum/Tanja Neunhöffer*	2	Germany
2325	Michel Fabbro	2	France
7007	Lydia Gaba Garcia	2	Spain
4001	Limor Helpman/Jacob Korach*/ Tamar Perri*	2	Israel
2822	David Jackson	2	UK
2321	Elsa Kalbacher	2	France
2824	Jonathan Krell	2	UK
1003	Stephanie Lheureux	2	Canada
2306	Alain Lortholary	2	France
2620	Frederik Marmé	2	Germany
5711	Justyna Podlodowska/ Elzbieta Kutarska*	2	Poland
2328	Sandrine Richard	2	France
2312	Manuel Rodrigues	2	France
2601	Andreas Schneeweiss/Frederik Marmé*	2	Germany
0501	Els Van Nieuwenhuysen	2	Belgium
7002	Raúl Márquez Vázquez/ Raquel Bratos Lorenzo*	2	Spain
4120	Paolo Zola	2	Italy
2330	Cyril Abdeddaim	1	France
2805	Susana Banerjee	1	UK
4010	Mario Beiner	1	Israel
5705	Mariusz Bidzinski	1	Poland
2610	Alexander Burges	1	Germany
2825	Emma Louise Cattell	1	UK
7024	José Pérez Fidalgo	1	Spain
2302	Anne Floquet	1	France
7021	Margarita Amenedo Gancedo	1	Spain
2310	Céline Gavoille	1	France
2820	Rosalind Glasspool	1	UK
5702	Tomasz Huzarski	1	Poland
2305	Florence Joly	1	France
2003	Anja Knudsen	1	Denmark
2823	Rosemary Lord	1	UK
2002	Bente Lund	1	Denmark
2301	Jacques Medioni/Emilie Boissier*	1	France
4101	Sandro Pignata	1	Italy
4011	Ora Solange Rosengarten	1	Israel
2605	Barbara Schmalfeldt	1	Germany
4121	Germana Tognon	1	Italy
4127	Giorgio Valabrega	1	Italy

*Former site Principal Investigator.

METHODS

Full eligibility criteria

Inclusion criteria

For inclusion in the study, patients should fulfill all of the following criteria:

1. Provision of informed consent prior to any study-specific procedures
2. Patients must be aged ≥18 years
3. Female patients with histologically diagnosed relapsed non-mucinous epithelial ovarian cancer (EOC), including primary peritoneal and/or fallopian tube cancer. Non-mucinous EOC includes patients with serous, endometrioid, and transitional cell tumors, and those with mixed histology where one of these subtypes is predominant (>50%). Inclusion of other subtypes should first be discussed with the Medical Monitor
4. Documented *BRCA1*/*BRCA2* status:
    - To be regarded as *BRCA1*/*BRCA2*-positive, the patient must have a mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)
5. Patients must have received one prior poly(ADP-ribose) polymerase (PARP) inhibitor therapy:
    - PARP inhibitor therapy includes any agent (including olaparib) used in a maintenance setting
    - For the *BRCA1*/*BRCA2*-positive cohort, the duration of first PARP inhibitor exposure must have been ≥18 months following a first line of chemotherapy or ≥12 months following a second or subsequent line of chemotherapy
    - For the *BRCA1*/*BRCA2*-negative cohort, the duration of first PARP inhibitor exposure must have been ≥12 months following a first line of chemotherapy or ≥6 months following a second or subsequent line of chemotherapy

    For the last chemotherapy course immediately prior to randomization on the study:
    - Patients must have received a platinum-based chemotherapy regimen (carboplatin, cisplatin, or oxaliplatin) and have received at least four cycles of treatment
    - Patients must be, in the opinion of the investigator, in response (partial or complete radiological response), or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125, as defined below, following completion of the chemotherapy course
    - Pre-treatment CA-125 measurements must meet criterion specified below:

    - If the first value is less than or equal to the upper limit of normal (ULN), the patient is eligible to be randomized and a second sample is not required
    - If the first value is greater than ULN, a second assessment must be performed at least 7 days after the first. If the second assessment is ≥15% more than the first, the patient is not eligible
  - Patients must not have received bevacizumab during this course of treatment. Bevacizumab use as part of an earlier line of chemotherapy is permitted
  - Patients must not have received any investigational agent during this course of treatment
  - Patients must be randomized within 8 weeks of their last dose of chemotherapy (last dose is the day of the last infusion)
6. Patients must have normal organ and bone marrow function measured within 28 days of randomization, as defined below. In the event of minor deviations from these values that would lead to screen failure, repeat testing within the 28-day screening period (limited to the tests listed below) is allowed before the patient is declared a screen failure:
  - Hemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days
  - Absolute neutrophil count ≥1.5 × 10^9/L
  - Platelet count ≥100 × 10^9/L with no platelet transfusion in the last 14 days
  - Total bilirubin ≤1.5 × institutional ULN
  - Aspartate aminotransferase, serum glutamic oxaloacetic transaminase/alanine aminotransferase, and serum glutamic pyruvate transaminase ≤2.5 × institutional ULN unless liver metastases are present, in which case they must be ≤5 × ULN
  - Patients must have creatinine clearance estimated using the Cockcroft–Gault equation of ≥51 mL/min or based on a 24-hour urine test
7. Eastern Cooperative Oncology Group performance status 0–1
8. Patients must have a life expectancy ≥16 weeks
9. 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
10. Patient is willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations
11. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline with computed tomography (CT) or magnetic resonance imaging and is suitable for repeated assessment or no measurable disease following a complete response to most recent chemotherapy (± surgery)

12. A formalin-fixed, paraffin-embedded (FFPE) tumor sample from the cancer of sufficient quantity and quality (as specified in the Covance Central Laboratory Services Manual) must be available for future central testing of tumor genetic status. If a recent biopsied sample is provided, the biopsied tumor should not be assessed as target lesions as part of the Response Evaluation Criteria in Solid Tumors (RECIST) assessments if there are other lesions available, and the biopsy should be taken after the baseline scan has been performed. Archival tissue samples may be from the primary tumor or metastatic tumor deposits. Archival bone metastases are not acceptable. Provision of blocks is preferred. Alternatively, pre-cut 5 µm thick, unstained sections from the FFPE block may be provided. Any exceptions to these conditions should be discussed with the sponsor before randomization of the patient
13. For inclusion in the optional biomarker research, patients must fulfill the following criterion:
    - Provision of informed consent for biomarker research

    If a patient declines to participate in the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study

Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. Previous randomization in the present study
3. Participation in another clinical study with an investigational product during their chemotherapy course immediately prior to randomization
4. Other malignancy within the last 5 years, except adequately treated non-melanoma skin cancer; curatively treated *in situ* cancer of the cervix; ductal carcinoma *in situ*; Stage 1 grade 1 endometrial carcinoma; or other solid tumors, including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with history of breast cancer may be eligible, provided they completed their definitive anticancer treatment more than 3 years ago and they remain breast cancer disease free prior to start of study treatment
5. Resting electrocardiogram with a corrected QT interval >470 msec on two or more time points within a 24-hour period or family history of long QT syndrome
6. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment

7. Concomitant use of known potent cytochrome P450 (CYP) subfamily 3A (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 study treatment is 2 weeks
8. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St John's wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents
9. Persistent toxicities (Common Terminology Criteria for Adverse Events grade ≥2) caused by previous cancer therapy, excluding alopecia and stable grade 2 peripheral neuropathy
10. Patients with current or previous myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML
11. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study, as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days
12. Major surgery within 2 weeks of starting study treatment, and patients must have recovered from any effects of any major surgery
13. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high-resolution CT scan, or any psychiatric disorder that prohibits obtaining informed consent
14. Patients unable to swallow orally administered medication, and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
15. Breastfeeding women
16. Immunocompromised patients (e.g. patients who are known to be serologically positive for HIV)
17. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
18. Patients with known active hepatitis (i.e. hepatitis B or C)
19. Patients who have received a whole-blood transfusions within 30 days prior to screening tests (packed red blood cells and platelet transfusions are acceptable)

Platinum sensitivity

For the purposes of this study, platinum sensitivity meant that the patient had a complete or partial response (per RECIST v1.1 as determined by the investigator) to their most recent line of platinum-based chemotherapy or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125 level.

Patients who had no evidence of disease following optimal cytoreductive surgery were recorded as having a complete response on the electronic case report form.

Rationale for the duration of prior PARP inhibitor therapy

In OReO, eligibility criteria specified that the minimum duration of prior PARP inhibitor exposure was ≥18 months following first-line chemotherapy or ≥12 months following a second or subsequent line of chemotherapy for the BRCA-mutated cohort and ≥12 months following first-line chemotherapy or ≥6 months following a second or subsequent line of chemotherapy for the non-BRCA-mutated cohort.

At the time OReO was designed, studies in patients with advanced ovarian cancer who received no maintenance therapy following first-line platinum-based chemotherapy showed a median progression-free survival (PFS) of between 12 and 18 months, with a longer PFS duration observed more commonly in patients with BRCA mutations (e.g. a median PFS of 13.8 months was reported in the placebo arm of the SOLO1 study in patients with newly diagnosed advanced BRCA-mutated ovarian cancer[1]). This provided the rationale for requiring patients who had received prior PARP inhibitor therapy after first-line chemotherapy to have ≥18 months of exposure in the BRCA-mutated cohort and ≥12 months of exposure in the non-BRCA-mutated cohort, in order to select those patients benefiting from a PARP inhibitor. A similar approach was adopted for patients receiving prior PARP inhibitor therapy after later lines of chemotherapy, with ≥12 months of exposure required in the BRCA-mutated cohort and ≥6 months exposure required in the non-BRCA-mutated cohort, consistent with the median PFS seen in Study 19.[2]

Treatment initiation and criteria for discontinuation

It was recommended that patients commence study treatment on the day of randomization if possible and, if not, then ideally within 3 days of randomization.

Treatment continued until objective radiological disease progression (RECIST version 1.1) or as long as the patient experienced benefit. Patients may also discontinue study treatment because of:

- Patient decision
- Adverse event
- Severe non-compliance with study protocol
- Bone marrow findings consistent with MDS/AML

Outcomes

Radiological tumor assessment (computed tomography or magnetic resonance imaging) was performed at baseline and then every 12 weeks until objective radiological disease progression (RECIST version 1.1).

In a prespecified exploratory subgroup analysis, PFS according to homologous recombination deficiency (HRD) status was evaluated in the non-BRCA-mutated cohort based on retrospective testing of archival tissue from the primary tumor using the MyChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA). HRD-positive was defined as a genomic instability score (GIS) of ≥42 and/or presence of a qualifying tumor BRCA mutation, HRD-negative as a GIS <42 and the absence of a qualifying tumor BRCA mutation, and HRD-unknown as a missing, canceled, or failed test.

Prespecified subgroup analyses evaluated PFS according to the following clinical factors: use of prior bevacizumab; the number of prior lines of platinum-based chemotherapy; complete or partial response following the most recent course of chemotherapy; the duration of the platinum-free interval (defined as the interval between the last dose of platinum and the detection of relapse, following the penultimate course of platinum-based chemotherapy); the duration of previous PARP inhibitor exposure; and prior surgery for ovarian cancer (if surgery occurred immediately before the most recent line of chemotherapy).

The Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire was completed at baseline, at day 29, then every 4 weeks for the first 12 weeks, and then every 12 weeks until 2 years from the date of randomization. In addition, the FACT-O questionnaire was completed at the discontinuation of study treatment and at 30 days following the last dose of study treatment.

Adverse events were monitored throughout the treatment period (including at routine clinic visits occurring on days 1 and 29, then every 4 weeks for the first 12 weeks, and then every

12 weeks) and for 30 days after discontinuation of study treatment until resolution using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Patients were actively followed for MDS/AML and other new primary malignancies beyond the 30-day post-treatment safety follow-up period. Investigators were required to report any case of MDS/AML or new primary malignancy occurring after the 30-day follow-up period, regardless of their assessment of causality or knowledge of the treatment arm. Active surveillance for MDS/AML and new primary malignancies occurred during follow-up for overall survival (OS).

Amendment to the PFS analysis

In the BRCA-mutated cohort, the original study protocol assumed a median PFS from randomization for patients in the placebo group of approximately 12 months; 74 PFS events from 124 patients would have 80% power to demonstrate a significant PFS benefit at the two-sided 5% level if the assumed true treatment effect resulted in a hazard ratio (HR) of 0.5. To allow for a 10% drop-out rate, approximately 136 patients were planned to be randomized to olaparib or placebo. In the non-BRCA-mutated cohort, the original study protocol assumed a median PFS from randomization for patients in the placebo group of approximately 8 months; 191 PFS events from 254 patients would have 80% power to demonstrate a significant PFS benefit at the two-sided 5% level if the assumed true treatment effect resulted in a HR of 0.65. To allow for a 10% drop-out rate, approximately 280 patients were planned to be randomized to olaparib or placebo. Considering both cohorts, it was expected that approximately 416 patients in total would be enrolled into the study.

Following publication of SOLO2 data reporting a median PFS of 5.5 months in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation who received maintenance placebo,[3] the expected median PFS in the placebo arm was amended to 4.5 months, with sample sizes recalculated to support detection of a HR of 0.5 in both cohorts; the target number of randomly assigned patients was reduced from 416 to 228. This amendment was supported by data from the placebo arms of Study 19[2] and NOVA,[4] which indicated that median PFS was unlikely to exceed 5.5 months with maintenance placebo in the patients with platinum-sensitive relapsed ovarian cancer in the non-BRCA-mutated subgroup.

Duration of follow-up and censoring

The duration of follow-up for PFS was calculated as the time from the date of randomized treatment to the date of progression or death or to the date of censoring for censored patients.

For PFS, patients who had not progressed or had not died at the date of data cut-off (DCO) were censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment. However, if the patient progressed or died after two or more missed visits, the patient was censored at the time of the latest evaluable RECIST version 1.1 assessment prior to the two missed visits.

For time to first subsequent therapy or death, any patient not known to have died and not known to have had a further subsequent therapy was censored at the last date that the patient was known not to have received subsequent therapy (i.e. the last follow-up visit where this was confirmed). Patients who terminated the study for reasons other than death before first subsequent therapy were censored at DCO, their last known to be alive date, or termination date, whichever occurred earliest.

For time to second subsequent therapy or death, any patient not known to have died and not known to have had a further second subsequent therapy was censored at the last known time to have not received second subsequent therapy (i.e. the last follow-up visit where this was confirmed). Patients who terminated the study for reasons other than death before a second subsequent therapy were censored at DCO, their last known to be alive date, or termination date, whichever occurred earliest.

For OS, any patient not known to have died at the date of DCO was censored based on the last recorded date on which the patient was known to be alive.

Results

Table S1. Patient characteristics at baseline[a]

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (*N* = 74)	**Placebo (*N* = 38)**	**Olaparib (*N* = 72)**	**Placebo (*N* = 36)**
Median (range) age, years	58.5 (37-80)	61.5 (44-87)	66.5 (29-81)	62.5 (43-77)
ECOG performance status, *n* (%)				
0	56 (76)	26 (68)	52 (72)	21 (58)
1	18 (24)	12 (32)	20 (28)	15 (42)
FIGO stage, *n* (%)				
I	1 (1)	3 (8)	2 (3)	2 (6)
II	6 (8)	3 (8)	3 (4)	4 (11)
III	45 (61)	22 (58)	46 (64)	16 (44)
IV	16 (22)	5 (13)	17 (24)	10 (28)
Unknown	6 (8)	5 (13)	4 (6)	4 (11)
Primary tumor location, *n* (%)				
Ovary	65 (88)	34 (89)	61 (85)	29 (81)
Fallopian tube	4 (5)	2 (5)	6 (8)	2 (6)
Primary peritoneal	4 (5)	2 (5)	5 (7)	4 (11)
Other	1 (1)	0	0	1 (3)
Histology type, *n* (%)				
Serous	60 (81)	32 (84)	67 (93)	30 (83)
Endometrioid	3 (4)	0	1 (1)	2 (6)
Clear cell	0	0	0	0

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (*N* = 74)	**Placebo (*N* = 38)**	**Olaparib (*N* = 72)**	**Placebo (*N* = 36)**
Undifferentiated	0	1 (3)	1 (1)	1 (3)
Sarcomatoid carcinoma	1 (1)	0	0	0
Mixed adenocarcinoma	3 (4)	5 (13)	2 (3)	2 (6)
Mixed endometrioid	1 (1)	0	0	1 (3)
Mucinous	0	0	0	0
Other	6 (8)	0	1 (1)	0
Histology grade, *n* (%)				
High grade	59 (78)	26 (68)	61 (85)	26 (72)
Intermediate grade	6 (8)	3 (8)	2 (3)	3 (8)
Low grade	0	2 (5)	1 (1)	1 (3)
Unknown	9 (12)	7 (18)	8 (11)	5 (14)
Missing	0	0	0	1 (3)
Number of prior lines of any chemotherapy, *n* (%)				
2[b]	5 (7)	3 (8)	10 (14)	5 (14)
3	31 (42)	16 (42)	31 (43)	17 (47)
4	21 (28)	11 (29)	11 (15)	6 (17)
>4	17 (23)	8 (21)	20 (28)	8 (22)
Number of prior lines of platinum-based chemotherapy, *n* (%)				
2[b]	12 (16)	3 (8)	17 (24)	5 (14)
3	36 (49)	19 (50)	32 (44)	20 (56)
≥4	26 (35)	16 (42)	23 (32)	11 (31)

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (*N* = 74)	**Placebo (*N* = 38)**	**Olaparib (*N* = 72)**	**Placebo (*N* = 36)**
Duration of PFI between the penultimate and latest platinum-based chemotherapies, *n* (%)				
≥6 to <12 months	2 (3)	2 (5)	17 (24)	8 (22)
≥12 to <18 months	20 (27)	8 (21)	28 (39)	18 (50)
≥18 months	48 (65)	27 (71)	27 (38)	10 (28)
Missing	4 (5)	1 (3)	0	0
Median (range) duration of previous PARP inhibitor maintenance therapy, months	21.2 (12-58)	18.3 (12-55)	12.6 (6-102)	12.4 (3-36)
Duration of prior PARP inhibitor exposure, *n* (%)				
<12 months	1 (1)[c]	1 (3)[c]	31 (43)	17 (47)
≥12 to <18 months	26 (35)	15 (39)	20 (28)	12 (33)
≥18 months	47 (64)	22 (58)	21 (29)	7 (19)
Type of previous maintenance PARP inhibitor, *n* (%)				
Olaparib	69 (93)	34 (89)	15 (21)	8 (22)
Niraparib	3 (4)	2 (5)	46 (64)	21 (58)
Rucaparib	1 (1)	2 (5)	7 (10)	6 (17)
Veliparib	0	0	3 (4)	0
Other	1 (1)[d]	0	1 (1)[e]	1 (3)[e]
Response after most recent chemotherapy prior to randomization, *n* (%)				
Complete response[f]	15 (20)	13 (34)	19 (26)	11 (31)
Partial response	58 (78)	25 (66)	53 (74)	25 (69)
Missing	1 (1)	0	0	0

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (*N* = 74)	**Placebo (*N* = 38)**	**Olaparib (*N* = 72)**	**Placebo (*N* = 36)**
BRCAm category at screening, *n* (%)				
Deleterious or suspected deleterious mutation	72 (97)	37 (97)	0	1 (3)[g]
No deleterious or suspected deleterious mutation detected	0	0	71 (99)	34 (94)
Missing[h]	2 (3)	1 (3)	1 (1)	1 (3)
BRCAm type at screening, *n* (%)				
*BRCA1*m	51 (69)	29 (76)	0	1 (3)[g]
*BRCA2*m	20 (27)	7 (18)	0	0
*BRCA1*m and *BRCA2*m	2 (3)	1 (3)	0	0
Missing[h]	1 (1)	1 (3)	0	0
HRD status, *n* (%)				
HRD-positive[i]	–	–	29 (40)	16 (44)
HRD-negative[j]	–	–	30 (42)	11 (31)
HRD-unknown[k]	–	–	13 (18)[l]	9 (25)[l]

[a]Percentages may not total 100 because of rounding.

[b]Patients had received prior PARP inhibitor therapy in the first-line setting. Following relapse, their second line of chemotherapy was administered prior to enrollment in OReO/ENGOT-ov38.

[c]These patients are protocol deviations.

[d]Patient had previously received placebo and was PARP inhibitor naïve.

[e]Patient had previously received blinded therapy and was potentially PARP inhibitor naïve, as permitted in OReO/ENGOT-ov38.

[f]Patients with no evidence of disease were recorded as complete response.

[g]This patient is a protocol deviation.

[h]Patients classified as 'missing' did not have information on their BRCAm category or type recorded on their electronic case report form at screening.

[i]HRD-positive defined as a GIS ≥42 and/or presence of a qualifying tumor BRCAm based on retrospective tumor testing performed at Myriad Genetic Laboratories, Inc. (myChoice® HRD Plus assay).

[j]HRD-negative defined as GIS <42 and the absence of a qualifying tumor BRCAm based on retrospective tumor testing performed at Myriad Genetic Laboratories, Inc.

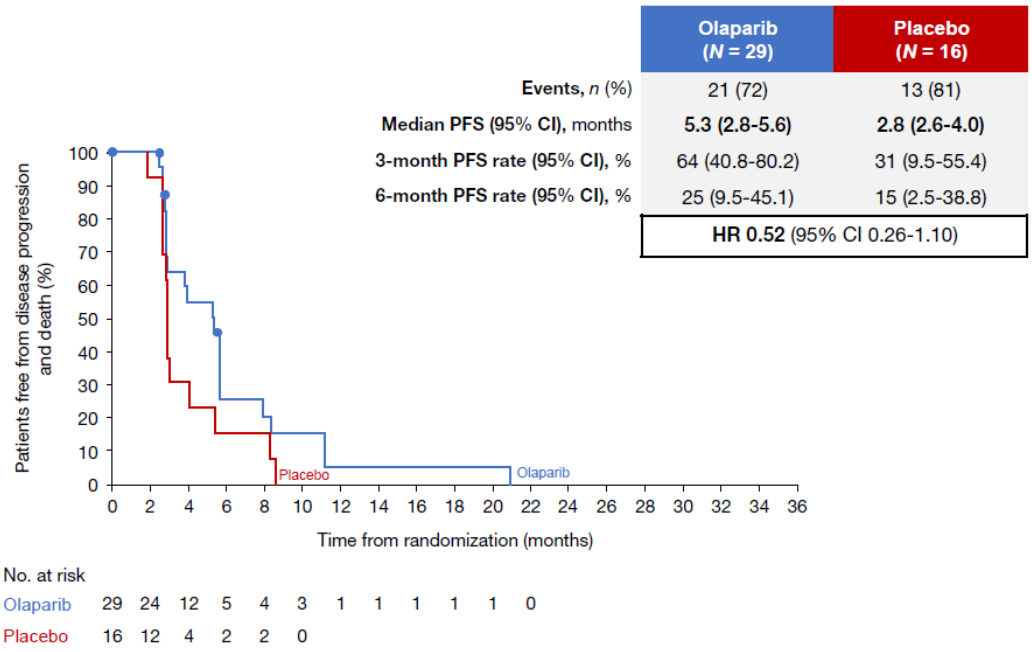
[k]HRD-unknown defined as a missing/canceled/failed test based on retrospective tumor testing performed at Myriad Genetic Laboratories, Inc.

[l]In the olaparib group, tests were missing in 5 (7%) patients and canceled/failed in 8 (11%) patients. In the placebo arm, tests were missing in 3 (8%) patients and canceled/failed in 6 (17%) patients.

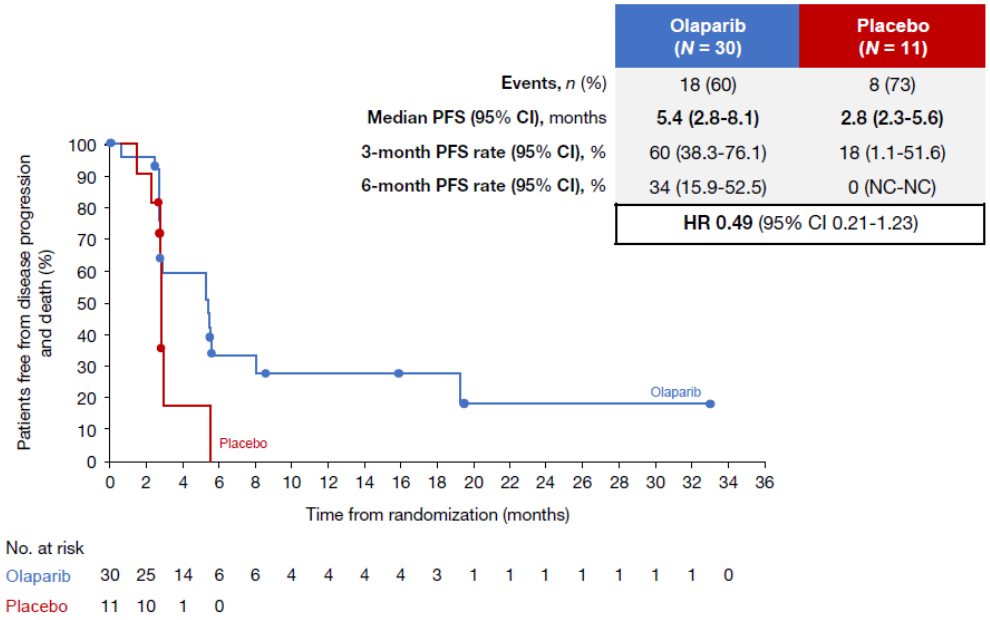
BRCAm, *BRCA1* and/or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; GIS, genomic instability score; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; PFI, platinum-free interval.

Figure S1. Kaplan–Meier estimates of progression-free survival in (A) HRD-positive non-BRCA-mutated patients and (B) HRD-negative non-BRCA-mutated patients

A. HRD-positive non-BRCA-mutated patients



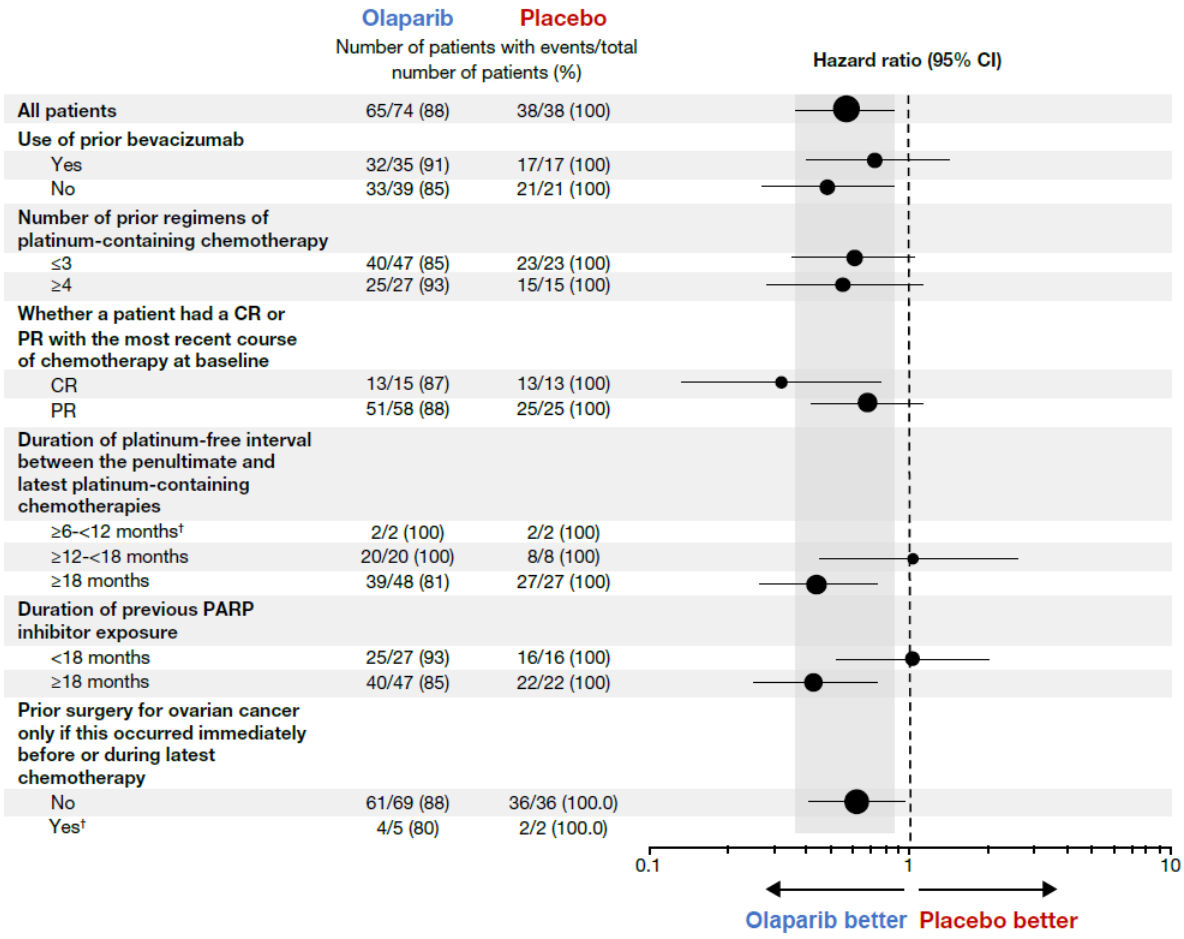
B. HRD-negative non-BRCA-mutated patients



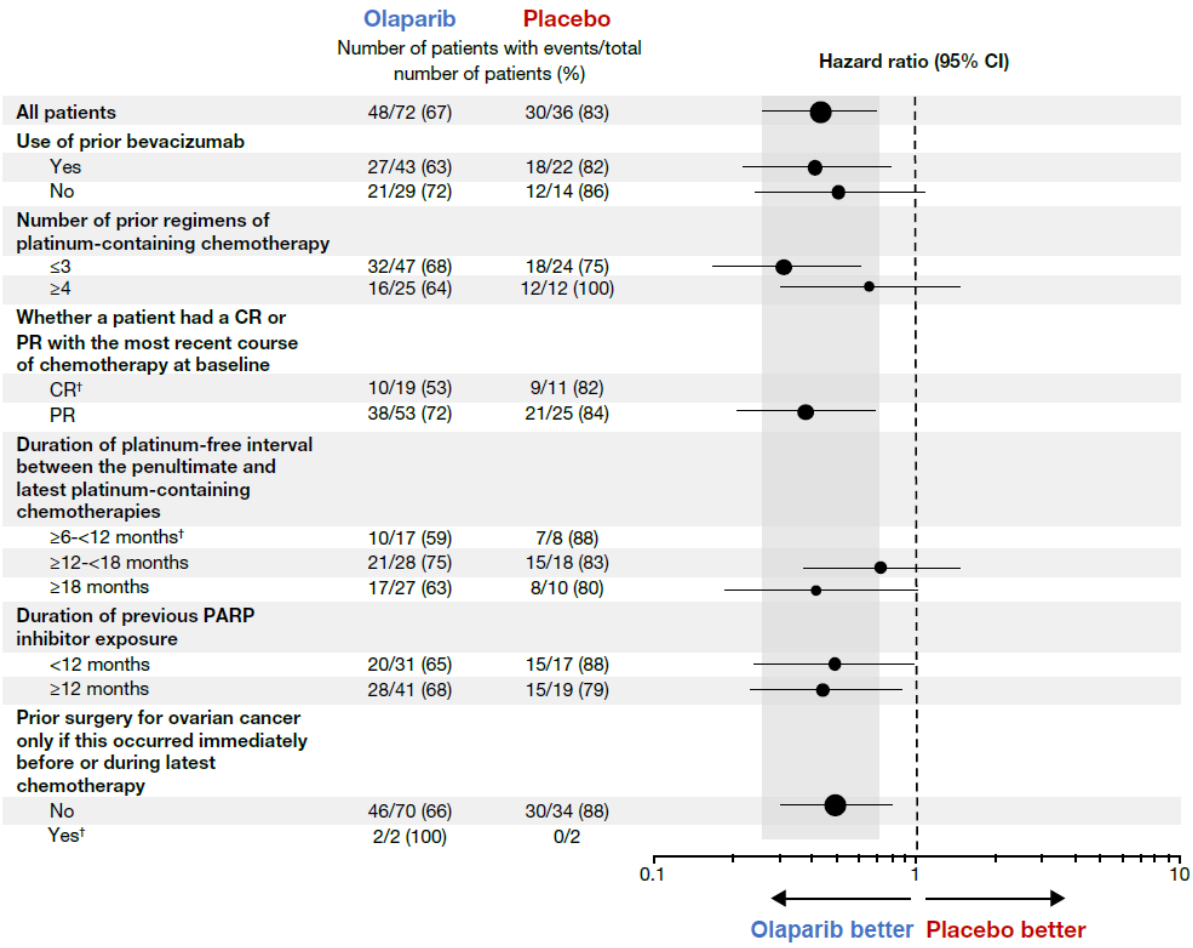
CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NC, not calculable; PFS, progression-free survival.

Figure S2. Subgroup analysis of progression-free survival in the (A) BRCAm and (B) non-BRCAm cohorts*

A. BRCAm cohort



B. Non-BRCAm cohort



*For the hazard ratios, the size of the circle is proportional to the number of events. The gray band represents the 95% CI for all patients, and the dashed line indicates the point of no effect. There was no statistical evidence of interaction. †Subgroup not analyzed due to <20 progression-free survival events, as prespecified in the statistical analysis plan.

BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; CR, complete response; PARP, poly(ADP-ribose) polymerase inhibitor; PR, partial response.

Table S2. Sensitivity analyses of progression-free survival

PFS sensitivity analysis	BRCAm cohort			Non-BRCAm cohort		
	Median PFS (months)		HR (95% CI) *P* value	Median PFS (months)		HR (95% CI) *P* value
	Olaparib (*N* = 74)	Placebo (*N* = 38)		Olaparib (*N* = 72)	Placebo (*N* = 36)	
To assess possible time assessment bias[a]	3.4	1.4	0.55 (0.36-0.85) *P* = 0.0179	3.9	1.4	0.43 (0.27-0.71) *P* = 0.0021
To assess possible attrition bias[b]	4.4	2.8	0.54 (0.35-0.83) *P* = 0.0116	5.3	2.8	0.42 (0.26-0.69) *P* = 0.0021
Following adjustment for additional prognostic factors[c]	4.3	2.8	0.48 (0.31-0.77) *P* = 0.0018	5.3	2.8	0.41 (0.24-0.70) *P* = 0.0011

[a]To assess whether the PFS effect is partly an artefact of one treatment arm being assessed more frequently than the other treatment arm.

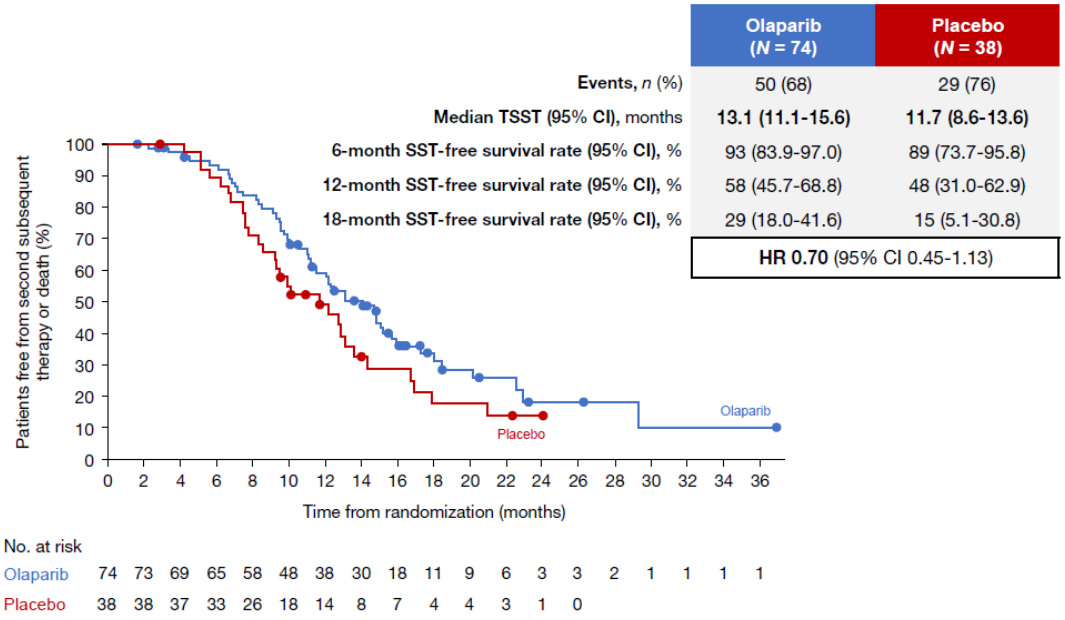
[b]To assess whether the rate and nature of censoring resulted in bias.

[c]To assess if adjustment for covariates other than the stratification variables will modify the results of the primary PFS analysis. Variables considered were the stratification factors (use of prior bevacizumab [yes versus no]; number of prior regimens of platinum-containing chemotherapy [≤3 versus ≥4 regimens]), as well as the number of prior lines of non-platinum chemotherapy, whether a patient had a complete or partial response with the most recent course of chemotherapy, the duration of the platinum-free interval, the duration of previous PARP inhibitor exposure, and prior surgery for ovarian cancer (only if this occurred immediately before most recent line of chemotherapy).

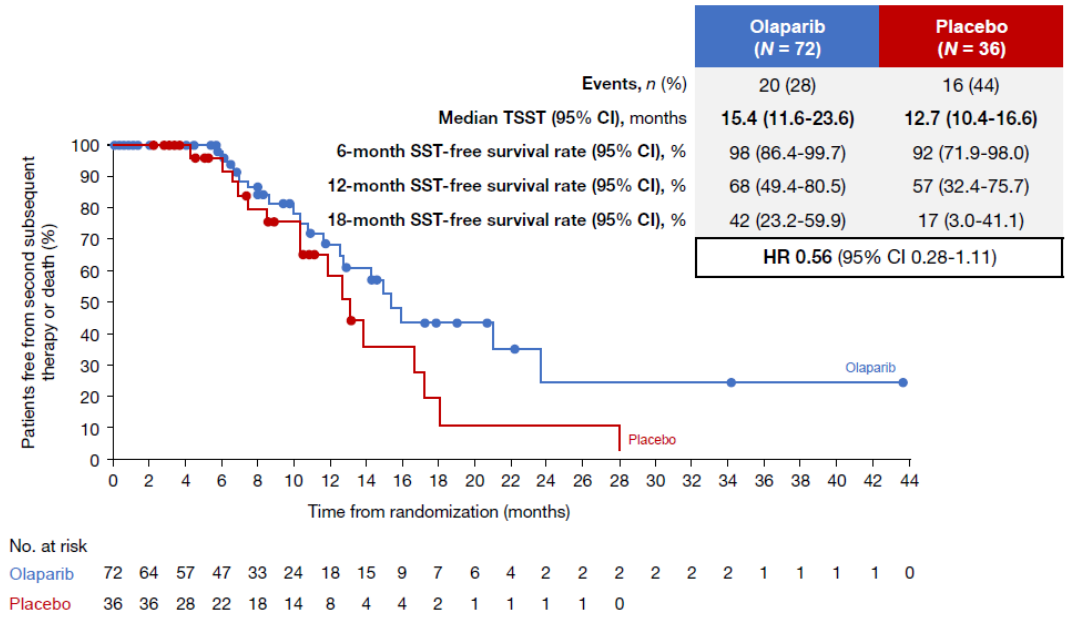
BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; HR, hazard ratio; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

Figure S3. Kaplan–Meier estimates of time to second subsequent therapy or death in (A) BRCA-mutated patients and (B) non-BRCA-mutated patients

A. TSST in BRCA-mutated patients



B. TSST in non-BRCA-mutated patients



CI, confidence interval; HR, hazard ratio; SST, second subsequent therapy; TSST, time from randomization to second subsequent therapy or death.

Table S3. Compliance rates with the FACT-O questionnaire during the treatment period.

Compliance rate, %	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (*N* = 71)	Placebo (*N* = 37)	Olaparib (*N* = 68)	Placebo (*N* = 35)
Baseline	100	100	100	100
Day 29	93	81	97	94
Day 57	94	83	91	88
Day 85	82	75	91	94
Day 169	89	100	96	75
Day 253	96	100	89	100
Day 337	86	100	100	–
Day 421	88	100	100	–
Day 505	83	–	100	–
Day 589	80	–	100	–
Day 673	100	–	100	–

BRCAm, *BRCA1* and/or *BRCA2* mutation; FACT-O, Functional Assessment of Cancer Therapy – Ovarian.

Discussion

The results of OReO raise several future research points:

1. It is currently unknown which patients will experience long-term benefit from PARP inhibitor rechallenge. Further work is needed to identify the patient characteristics responsible for this long-term response.
2. PARP inhibitor maintenance therapy is now a standard of care in ovarian cancer and is increasingly used in the newly diagnosed setting. However, few patients in OReO had received prior first-line maintenance therapy with a PARP inhibitor, as data showing the benefit of PARP inhibitors in the newly diagnosed setting first became available in October 2018[1] and September 2019,[5-7] and PARP inhibitor maintenance therapy was not approved in this setting at the time that OReO was initiated in 2017. It is important to ascertain the outcome of patients who receive PARP inhibitor maintenance therapy in the newly diagnosed setting and are then rechallenged with a maintenance PARP inhibitor as part of their first subsequent therapy.
3. Compared with patients who receive PARP inhibitor maintenance therapy until disease progression, are patients who receive PARP inhibitor maintenance therapy for a fixed duration (i.e. newly diagnosed patients received olaparib[1] or rucaparib[8] for 2 years and niraparib for 3 years[6] in phase III trials) less likely to show resistance on rechallenge?
4. Does the benefit of PARP inhibitor rechallenge differ depending on whether patients had discontinued prior PARP inhibitor therapy because of disease progression or if they were still in response when they discontinued prior PARP inhibitor therapy for another reason (e.g. because of adverse events or completing the prescribed regimen in the first-line setting)?
5. Determining the impact of prior PARP inhibitor therapy on the efficacy of subsequent therapy and longer-term outcomes, including the impact of disease progression on or after receipt of a PARP inhibitor
6. Assessing PARP inhibitor resistance mechanisms, including how and when resistance occurs and how these resistance mechanisms impact subsequent treatment outcomes, is urgently required.
7. Is it possible to minimize PARP inhibitor resistance in the first line in order to increase the proportion of patients achieving a good response when rechallenged with a PARP inhibitor?
8. Finally, the optimal sequencing of therapies and use of combination therapy needs further investigation. Given the efficacy of combination therapy with olaparib and bevacizumab in newly diagnosed HRD-positive patients,[9] it is important to establish if there is a role for

combining olaparib with bevacizumab in the rechallenge setting. The potential of combining olaparib with novel targeted agents (e.g. ATR inhibitors[10, 11] or WEE1 inhibitors[12]) in the rechallenge setting is an area of interest, particularly in terms of achieving PARP inhibitor resensitization in patients who have previously progressed on prior PARP inhibitor therapy.

REFERENCES

1 Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018;379(26):2495-2505.

2 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014;15(8):852-861.

3 Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1*/*2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(9):1274-1284.

4 Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016;375(22):2154-2164.

5 Ray-Coquard IL, Pautier P, Pignata S, et al. Phase III PAOLA-1/ENGOT-ov25 trial: olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Ann Oncol.* 2019;30(Suppl_5):V894-895 abstract LBA892_PR.

6 González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2019;381(25):2391-2402.

7 Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. *N Engl J Med.* 2019;381(25):2403-2415.

8 Monk BJ, Parkinson C, Lim MC, et al. A randomized, Phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol.* 2022;40(34):3952-3964.

9 Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019;381(25):2416-2428.

10 Mahdi H, Hafez N, Doroshow D, et al. Ceralasertib-mediated ATR inhibition combined with olaparib in advanced cancers harboring DNA damage response and repair alterations (olaparib combinations). *JCO Precis Oncol.* 2021;5:PO.20.00439.

11 Kim H, Xu H, George E, et al. Combining PARP with ATR inhibition overcomes PARP inhibitor and platinum resistance in ovarian cancer models. *Nat Commun.* 2020;11(1):3726.

12 Gomez MK, Illuzzi G, Colomer C, et al. Identifying and overcoming mechanisms of PARP inhibitor resistance in homologous recombination repair-deficient and repair-proficient high grade serous ovarian cancer cells. *Cancers (Basel).* 2020;12(6):1503.