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Maintenance olaparib after platinum-based chemotherapy for advanced/metastatic endometrial cancer: GINECO randomized phase IIb UTOLA trial

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Single-agent maintenance poly(ADP-ribose) polymerase (PARP) inhibition may represent an effective strategy in patients with advanced/metastatic endometrial cancer responding to platinum-based chemotherapy, including for molecular subtypes with suboptimal options. To explore this approach, we initiated the randomized phase IIb UTOLA trial (NCT03745950). Female patients without progression following front-line platinum-based chemotherapy for advanced/metastatic endometrial cancer were randomized 2:1 to twice-daily maintenance oral olaparib 300 mg or placebo until progression or intolerance, stratified by p53 status, mismatch repair status, and response to initial chemotherapy. The primary endpoint was progression-free survival (PFS) in the intention-to-treat population. Secondary endpoints were PFS in subgroups, time to second progression or death, time to first and second subsequent therapy, objective response rate, overall survival, patient-reported outcomes, and safety. In the intention-to-treat population ($n = 145$), there was no PFS difference between olaparib and placebo (median 5.6 vs. 4.0 months, respectively; hazard ratio 0.94, 95% confidence interval 0.65–1.35; $p = 0.74$). However, intriguing numerical PFS effects were observed in exploratory analyses of pre-specified subgroups (p53-abnormal, complete response to initial chemotherapy, chromosomal instability). There was no overall survival difference between treatments. Grade 3/4 adverse events occurred in 36% versus 10% of olaparib- versus placebo-treated patients and were consistent with the olaparib safety profile in other cancers. Maintenance olaparib did not improve PFS, but promising numerical effects in subsets of patients warrant prospective evaluation.

Until recently, the prognosis for women with metastatic endometrial cancer (EC) was poor. Median overall survival (OS) was typically <2 years[1], and there had been few advances in treatment options and the management of this disease. Platinum-based chemotherapy was administered universally as there were no known biomarkers to guide treatment or predict likely prognosis.

More recently, diagnosis and treatment have become more personalized, reflecting disease heterogeneity[2,3]. EC is classified according

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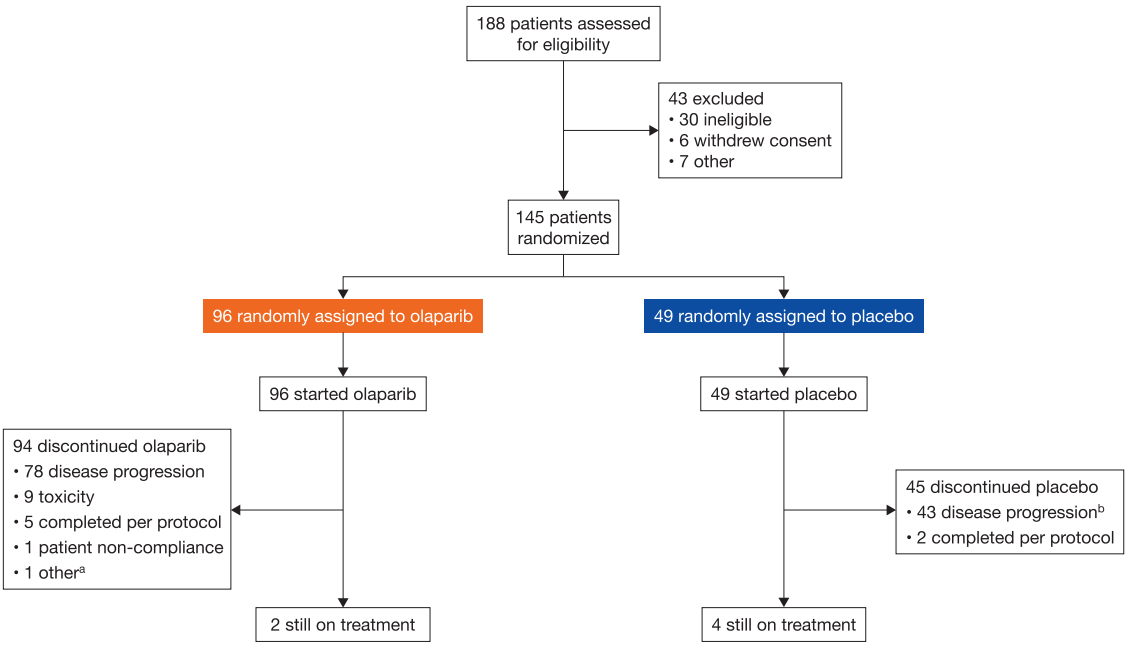

Fig. 1 | Patient flow. [a]Patient required radiotherapy. [b]Including non-RECIST progression in 2 patients. *RECIST*, Response Evaluation Criteria in Solid Tumors.

to molecular subtype, which provides prognostic information and is critical for treatment decision-making and patient selection. The molecular subtype associated with the worst prognosis is p53-abnormal, which is characterized by low tumor mutation burden but high somatic copy number alterations, suggestive of deficiencies in DNA repair pathways[2–4]. In contrast, mismatch repair (MMR)-deficient (dMMR) and DNA polymerase epsilon (POLE) tumors are characterized by a high tumor mutational burden and low somatic copy number alterations. Tumors with no specific molecular profile represent a heterogeneous group with frequent mutations in the PI3K/AKT/PTEN pathway and *ARID1A* tumor suppressor gene[3].

The enzyme poly(ADP-ribose) polymerase (PARP) is involved in base excision repair. Targeted therapies, such as olaparib, that inhibit PARP induce synthetic lethality in tumor cells that harbor homologous recombination deficiency (HRD)[5]. In ovarian cancer, PARP inhibitors are an established maintenance therapy in patients with HRD tumors responding to chemotherapy, particularly tumors harboring a *BRCA* mutation. PARP inhibitors have also demonstrated benefit in several non-gynecologic tumor types with known HRD or *BRCA* mutation, including breast[6,7], pancreatic[8], and prostate[9] cancers.

HRD is an emerging concept in EC and appears to play a role in EC pathogenesis[10]. However, there is currently no validated HRD test in EC. HRD (assessed variously, for example, using HRD signature-3 by whole-exome sequencing, next-generation sequencing [NGS], and array comparative genomic hybridization/SNP array to assess the prevalence of *BRCA*-associated genomic scars as a surrogate marker for HRD) is largely restricted to *TP53*-mutated ECs and approximately 20–40% of p53-abnormal tumors harbor HRD[11,12]. The commercial HRD test MyChoice CDx (Myriad Genetics) has shown preliminary results suggesting clinical utility of these tests in EC[13]. Additional gene alterations beyond HRD could be associated with sensitivity to PARP inhibition.

Here, we report the final analysis of the UTerin OLAparib (UTOLA) trial assessing the efficacy of maintenance therapy with the PARP inhibitor olaparib following disease control with first-line platinum-based chemotherapy for patients with locally advanced incurable or metastatic EC. Although maintenance olaparib did not appear to improve progression-free survival (PFS) in the overall population, sub-analyses of specific subgroups according to molecular profile showed promising results that warrant prospective evaluation.

Results

Patient population

Between April 10, 2019 and September 1, 2021, 147 patients were randomly assigned, of whom two subsequently withdrew consent. Consequently, the intention-to-treat (ITT) population included 96 patients randomly assigned to olaparib and 49 to placebo (Fig. 1). Baseline characteristics are shown in Tables 1 and 2 for the ITT population and Table 3 for the population with p53-abnormal MMR-proficient (pMMR) tumors. All patients had received platinum in the locally advanced/metastatic setting, 93% had received paclitaxel, most (78% of the olaparib group, 76% of the placebo group) had received six cycles of chemotherapy, and 77% had a complete or partial response or no evidence of disease at study entry. Approximately half (52%) had p53-abnormal EC and half (49%) had ≥6 large genomic events (LGEs), classified as LGE_{high} and considered to represent HRD tumors. There was considerable overlap between p53-abnormal status and LGE_{high}: 79% of patients with p53-abnormal disease had LGE_{high} tumors; 80% of those with LGE_{high} tumors had p53-abnormal status; and 41% had both p53-abnormal and LGE_{high} tumors. Among patients with low-grade carcinomas, only 31% had LGE_{high} tumors.

Efficacy

At the data cutoff for the pre-specified primary analysis (May 21, 2024), the median duration of follow-up was 31.9 (interquartile range, 17.4–40.0) months. PFS events had been recorded in 85 patients (89%) in the olaparib group and 43 (88%) in the placebo group. Median PFS in the ITT population was 5.6 months with olaparib and 4.0 months with placebo (hazard ratio [HR] = 0.94, 95% confidence interval [CI] 0.65–1.35; 2-sided stratified log-rank $p = 0.74$) (Fig. 2A). In the p53-abnormal population ($n = 76$), median PFS was 5.5 versus 3.6 months, respectively (HR = 0.78, 95% CI 0.47–1.28; Fig. 2B), and in the p53-normal population ($n = 68$), median PFS was 6.1 versus 7.1 months, respectively (HR = 1.05, 95% CI 0.61–1.81) (Fig. 3A). In the pMMR population, the HR for PFS was 0.93 (95% CI 0.62–1.40), with median PFS of 5.6 versus 3.8 months, respectively, and in the subgroup of 21

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Table 1 | Clinical and demographic characteristics at baseline (ITT population)

Characteristic		No. of patients (%)	
		Olaparib (*n* = 96)	Placebo (*n* = 49)
Median (range) age, years		70 (38–88)	69 (49–87)
ECOG performance status	0	48 (50)	23 (47)
	1	48 (50)	26 (53)
Median (range) BMI, kg/m^2		26.6 (18.1–47.5)	26.6 (18.4–49.5)
Histology	Endometrioid	70 (73)	38 (78)
	Low-grade	44 (46)	24 (49)
	High-grade	24 (25)	13 (27)
	Unknown grade	2 (2)	1 (2)
	Serous	23 (24)	8 (16)
	Clear cell	0	2 (4)
	Mixed cell adenocarcinoma	2 (2)	1 (2)
	Other	1 (1)[a]	0
Estrogen receptor status	Positive	47 (49)	19 (39)
	Negative	12 (13)	7 (14)
	Missing	37 (39)	23 (47)
Progesterone receptor status	Positive	28 (29)	13 (27)
	Negative	27 (28)	10 (20)
	Missing	41 (43)	26 (53)
FIGO stage at initial diagnosis	I/II	35 (36)	18 (37)
	III/IV	50 (52)	21 (43)
	Unknown	11 (11)	10 (20)
Status at initial diagnosis	Not metastatic	56 (58)	26 (53)
	Metastatic	40 (42)	23 (47)
Status at randomization	Relapsed	27 (28)	10 (20)
	Metastatic/advanced	69 (72)	39 (80)
Previous treatment[b]	Surgery	70 (73)	34 (69)
	Radiation therapy[c]	40 (42)	17 (35)
	Radiotherapy alone	6	1
	Vaginal brachytherapy alone	12	4
	Both	22	12
	Adjuvant chemotherapy	25 (26)	8 (16)
	Hormonal therapy	7 (7)	0
Response to prior chemotherapy for advanced/metastatic disease	Complete response	31 (32)	13 (27)
	No evidence of disease	2 (2)	1 (2)
	Partial response	41 (43)	23 (47)
	Stable disease	22 (23)	12 (24)

[a]Poorly differentiated high-grade adenocarcinoma.
[b]More than one answer possible.
[c]Comprising pelvic irradiation (not whole abdominal irradiation) according to standard practice in France; for relapsed/metastatic disease in 6 patients.
BMI body mass index, *ECOG* Eastern Cooperative Oncology Group, *FIGO* International Federation of Gynecology and Obstetrics, *ITT* intention-to-treat.

Table 2 | Molecular characteristics at baseline (ITT population)

	No. of patients (%)	
Characteristic	Olaparib (*n* = 96)	Placebo (*n* = 49)
p53 status		
Abnormal[a]	51 (53)	25 (51)
Normal	44 (46)	24 (49)
Non-informative	1 (1)	0
MMR status		
pMMR	81 (84)	40 (82)
dMMR[b]	13 (14)	8 (16)
Non-informative	2 (2)	1 (2)
MSI status		
MSI	13 (14)	8 (16)
MSS	83 (86)	41 (84)
POLE mutated	1 (1)[c]	0
BRCA1/2 mutation status[d]		
Mutated	2 (2)	2 (4)
Not mutated	88 (92)	42 (86)
Unknown/missing	6 (6)	5 (10)
HRD status		
LGE_{low} (score <6)	43 (45)	24 (49)
LGE_{high} (score ≥6)	49 (51)	22 (45)
Missing	4 (4)	3 (6)

[a]Determined by both immunohistochemistry and NGS in 56 patients, only by immunohistochemistry in 15 patients, and only by NGS in 5 patients.
[b]Determined by both immunohistochemistry and NGS in 2 patients, only by immunohistochemistry in 17 patients, and only by NGS in 2 patients.
[c]pMMR, LGE_{low} (score <6).
[d]One patient had both *BRCA1* and *BRCA2* mutations.
dMMR mismatch repair deficient, *HRD* homologous recombination deficiency, *ITT* intention-to-treat, *LGE* large genomic events, *MMR* mismatch repair, *MSI* microsatellite instability, *MSS* microsatellite stability, *NGS* next-generation sequencing, *pMMR* mismatch repair proficient, *POLE* DNA polymerase epsilon.

(14%) patients with dMMR disease, the HR was 1.09 (95% CI 0.42–2.85) with median PFS of 6.2 versus 5.2 months, respectively (Fig. 4).

In exploratory analyses, PFS in patients with LGE_{high} ($n = 71$) favored olaparib (HR = 0.59, 95% CI 0.35–1.00), with median PFS values of 5.4 months with olaparib versus 3.6 months in the placebo arm (Fig. 2C), whereas in patients whose tumors had an LGE score <6 (LGE_{low}, considered to be homologous recombination proficient), the HR was 1.26 (95% CI 0.73–2.19) and median PFS was 6.0 versus 7.4 months, respectively (Supplementary Fig. 1). In a Cox model for PFS, the interaction p-value of 0.05 suggested that LGE_{high} may predict benefit from olaparib (Supplementary Table 1).

Pre-specified analyses showed no relevant difference between treatments among the subgroups of patients defined by objective radiologic response to initial chemotherapy before randomization (Fig. 3B) or the subgroup with stable disease (Fig. 3C). However, patients experiencing a complete response to initial chemotherapy before maintenance had an enhanced olaparib treatment effect (median PFS 8.8 months with olaparib vs. 3.8 months with placebo; HR = 0.62, 95% CI 0.32–1.22) (Fig. 2D). Additional subgroup analyses of PFS are presented in Fig. 4 and Supplementary Fig. 2.

By the data cutoff date, 60 (63%) olaparib-treated and 29 (59%) placebo-treated patients had died. Median OS was 22.2 (95% CI 16.0–25.3) months with olaparib versus 23.8 (95% CI 19.6–28.6) months with placebo. The HR for OS was 1.25 (95% CI 0.80–1.94) (Fig. 5). There was no difference in OS in any of the subgroups analyzed (data not shown). Similarly, no difference between treatment arms was observed for the secondary endpoints of time to first subsequent therapy (HR = 0.94, 95% CI 0.64–1.37; median 9.2 months with olaparib vs. 8.0 months with placebo), time from randomization until second disease progression or death (PFS2) (HR = 1.06, 95% CI 0.71–1.58; median 13.9 vs. 13.0 months, respectively), and time to second subsequent therapy (HR = 1.11, 95% CI 0.75–1.65; median 13.3 vs. 12.6 months, respectively) (Fig. 5). Among the 33 patients with stable disease at study entry who were evaluable for response, 3 of 22 (14%) in the olaparib arm and 2 of 11 (18%) achieved a response on study therapy. Among those who had already responded to initial chemotherapy, the

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Table 3 | Baseline characteristics in the p53-abnormal pMMR and LGE_{high} subgroups

Characteristic	No. of patients (%)	
	p53-abnormal and pMMR (*n* = 76)	LGE_{high} (*n* = 71)
Median (range) age, years	71 (48–88)	70 (49–88)
ECOG performance status		
0	34 (45)	31 (44)
1	42 (55)	40 (56)
Median (range) BMI, kg/m^2	25.6 (18.1–49.5)	25.5 (18.1–49.5)
Histology		
Endometrioid	43 (57)	46 (65)
Low grade	18 (42)	20 (28)
High grade	22 (51)	24 (34)
Unknown grade	3 (7)	2 (3)
Serous	26 (34)	20 (28)
Clear cell	1 (1)	0
Mixed cell adenocarcinoma	3 (4)	2 (3)
Other	3 (4)	3 (4)
FIGO stage at initial diagnosis		
I	21 (28)	16 (23)
II	6 (8)	8 (11)
III	17 (22)	17 (24)
IV	24 (32)	23 (32)
Unknown	8 (11)	7 (10)
Response to prior chemotherapy for advanced disease		
Complete response	29 (38)	24 (34)
No evidence of disease	2 (3)	2 (3)
Partial response	25 (33)	28 (39)
Stable disease	20 (26)	17 (24)
HRD status		
LGE_{low} (score <6)	15 (20)	0
LGE_{high} (score ≥6)	57 (75)	71 (100)
Missing	4 (5)	0

BMI body mass index, *ECOG* Eastern Cooperative Oncology Group, *FIGO* International Federation of Gynecology and Obstetrics, *HRD* homologous recombination deficiency, *LGE* large genomic events, *pMMR* mismatch repair proficient.

response rates were 13% (5 of 39 patients) in the olaparib arm and 22% (5 of 23 patients) in the placebo arm, giving overall response rates of 13% (95% CI 7–24%) and 21% (95% CI 10–37%), respectively.

Safety

The median duration of treatment was 5.5 (range 0.8–39.1) months in the olaparib group and 3.8 (range 0.7–24.0) months in the placebo group. Grade 3/4 adverse events and adverse events leading to treatment interruption or dose reduction were more common with olaparib than placebo, but treatment discontinuations because of toxicity were infrequent and there were no fatal adverse events (Table 4).

The most common adverse events with olaparib were fatigue, anemia, nausea, and musculoskeletal pain (Supplementary Table 2). The most common grade 3/4 adverse event with olaparib was anemia (17%). There were no cases of myelodysplastic syndrome with olaparib (one grade 4 case in the placebo arm) and two grade 5 cases of acute myeloid leukemia in the olaparib arm (both outside the safety reporting period).

Patient-reported outcomes

European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 and EuroQol EQ-5D-5L questionnaires were completed at baseline by 95 patients (66%); 94 patients (65%) completed the FA-12 and EN24 questionnaires. The most common reasons for missing baseline questionnaires were oversight by site staff and patient non-compliance (for reasons other than illness). All but two patients (1%) filled at least one questionnaire during the study. The only EORTC QLQ-C30 items to show a relevant mean change from baseline in the olaparib arm were fatigue, which showed a transient deterioration in early cycles, and insomnia, which showed a transient improvement in early cycles. Analysis of mean change from baseline in FA-12 results indicated that olaparib was associated with a small transient deterioration in physical fatigue at cycle 3 (Fig. 6), whereas cognitive fatigue improved across several timepoints. There were no meaningful differences between treatment arms for any of the questionnaires. The median time to first 10-point deterioration in QLQ-C30 global health status was 2.4 (95% CI 1.8–3.7) months in the olaparib arm and 2.8 (95% CI 1.8–3.7) months in the placebo arm (Fig. 6).

Discussion

UTOLA provides randomized results evaluating single-agent maintenance PARP inhibition after platinum-based chemotherapy in patients with EC. In the overall population, no PFS benefit from olaparib was detected and the primary objective was not met; however, in molecularly selected populations of patients (p53-abnormal and/or LGE_{high}) and in patients with a complete response to prior chemotherapy, there were numerical effects favoring olaparib, albeit the borderline 95% CIs, small subgroup sizes, and the exploratory nature of subgroup analyses warrant cautious interpretation. Maintenance therapy with olaparib was well tolerated in patients with EC that was under control with first-line platinum-based chemotherapy and there were no new safety findings. The safety profile was consistent with experience of olaparib in other tumor types[6,8,9,14]. Patient-reported outcomes supported this finding, showing a transient deterioration in fatigue symptoms with maintenance PARP inhibition but no other meaningful changes.

When the UTOLA trial was designed, there was limited evidence to support the use of immune checkpoint inhibitors in EC. However, for patients with dMMR/microsatellite instability (MSI)-high EC, immunotherapy has transformed treatment options[15,16]. The combination of chemotherapy and an immune checkpoint inhibitor is now considered standard front-line therapy for advanced/recurrent disease, supported by significantly improved efficacy in four randomized phase III trials (ENGOT-EN6-NSGO/GOG-3031/RUBY evaluating dostarlimab[17], NRG-GY018 evaluating pembrolizumab[18], AtTEnd evaluating atezolizumab[19], and DUO-E evaluating durvalumab[20]). Although smaller benefit from immune checkpoint inhibitors was observed in the pMMR subgroups, regimens combining chemotherapy and immunotherapy (durvalumab, pembrolizumab, and dostarlimab) are approved for pMMR advanced/recurrent EC in some countries, supported by the magnitude of benefit in the DUO-E[20], NRG-GY018[18], and RUBY[21] trials, respectively. Nevertheless, there is still a need for better treatment options in patients with non-dMMR molecular subgroups.

Two of the phase III trials, DUO-E[20] and RUBY Part 2[22], included evaluation of maintenance PARP inhibition; however, the PARP inhibitor was given in combination with immunotherapy and there was no PARP inhibitor-alone arm. In DUO-E, exploratory analyses in the pMMR subgroup (representing 80% of the population) suggested numerically more favorable outcomes in patients receiving maintenance olaparib in addition to durvalumab[23]. In 2024, European regulatory approval was granted for olaparib in combination with durvalumab as maintenance therapy for patients with pMMR EC that has not progressed on first-line treatment with chemotherapy plus durvalumab[24]. Populations with pMMR EC are typically very heterogeneous and in exploratory subgroup analyses of RUBY Part 2 and DUO-E, the benefit from combining immunotherapy and PARP inhibition appeared to be greatest in

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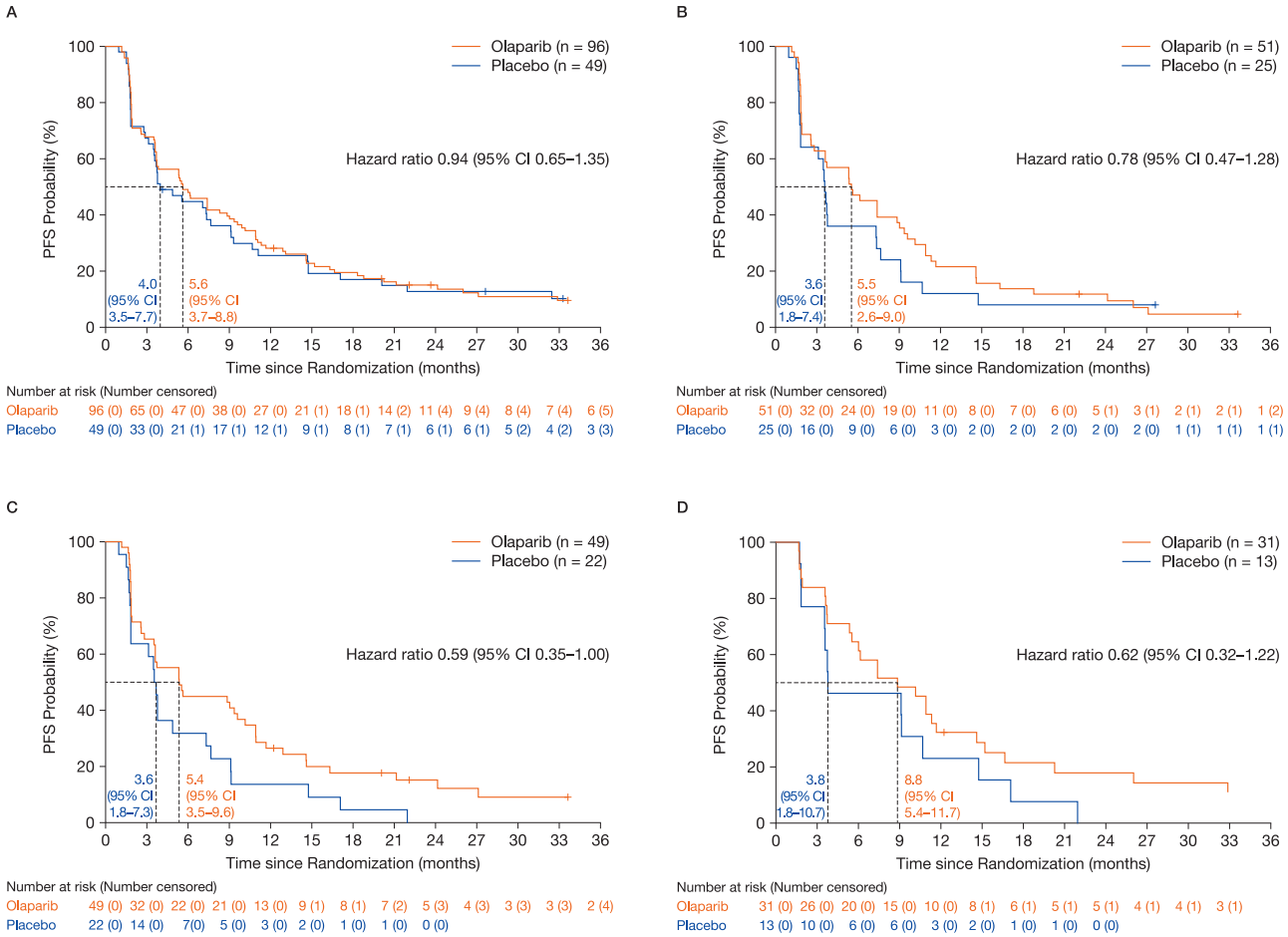

Fig. 2 | Investigator-assessed PFS estimated using Kaplan–Meier methodology. **A** Intention-to-treat population (two-sided log-rank test stratified on predefined stratification factors). **B** p53-abnormal subgroup. **C** LGE_{high} subgroup. **D** Subgroup with complete response to prior chemotherapy. CI confidence interval, LGE large genomic events, PFS progression-free survival. Vertical bars, censoring.

the small subset of patients with p53-abnormal pMMR[23,25]. This observation is supported by a recent meta-analysis of individual patient data from randomized trials, which also showed no benefit from PARP inhibition in the p53-wildtype pMMR population[26]. However, the lack of adjustment for multiple comparisons and the small sample sizes in subgroups of subgroups may lead to false discovery, and conflicting findings between trials make it difficult to make informed decisions. Therefore, careful molecular and clinical characterization to identify patients who may derive the greatest benefit is critical before moving systematically to quadruplet therapy for all patients with pMMR disease. Furthermore, the specific contribution of immunotherapy still needs to be elucidated in the pMMR subpopulation.

The UTOLA trial is unique in giving olaparib as a single agent in the maintenance setting. It provides important insight into the potential role of PARP inhibition and sheds light on the inherent effects of olaparib. The suggestion of greatest effect in patients whose tumors show chromosomal instability (LGE_{high}) is consistent with effects seen in ovarian cancer. Given the enrichment of LGE_{high} in p53-abnormal tumors, these observations are also consistent with findings from exploratory analyses of the RUBY Part 2 and DUO-E trials suggesting that olaparib may add greatest PFS benefit in the population with *TP53* mutations[23,25]. However, benefit from olaparib and durvalumab in DUO-E was not restricted to patients with *TP53*-mutated tumors, with more favorable PFS also observed in those with *TP53*-wildtype tumors; therefore, the population with LGE_{high} *TP53*-wildtype tumors should not be overlooked or excluded from further evaluation of PARP inhibition. However, in UTOLA, this subgroup was too small ($n = 14$) for meaningful interpretation.

Another intriguing insight from UTOLA is the suggestion of an enhanced effect of olaparib in patients experiencing a complete response to initial chemotherapy before maintenance. Although not yet explored in recent phase III trials in EC, this numerical effect is consistent with reports in other tumor types (particularly in ovarian cancer), suggesting that sensitivity to prior platinum may allow identification of patients most likely to benefit from PARP inhibition[27–29]. As information on clinical response to prior chemotherapy is readily available to clinicians when making treatment decisions, it is a practical and relevant factor to guide patient selection for treatment. Similar analyses of other datasets to explore this observation further would be of particular interest.

An obvious limitation of the trial is the relatively small sample size, which prevents robust conclusions on the efficacy of olaparib in patients with p53-abnormal disease despite the apparent trend favoring olaparib. The definition of HRD used in this study can be questioned. Several HRD assays are used in ovarian cancer with good concordance between them[30,31]. However, none of these commercially available or validated academic assays has been evaluated in EC. The present study is the first randomized trial to explore PARP inhibitors in EC according to HRD status. The Genomic Instability Scar (GIScar) assay was selected to explore HRD status based on the median cutoff (corresponding to LGE_{high}) to define HRD status. This study provides a proof of concept that GIScar may help predict response to PARP inhibitors in EC. However, this cutoff may not be optimal, potentially

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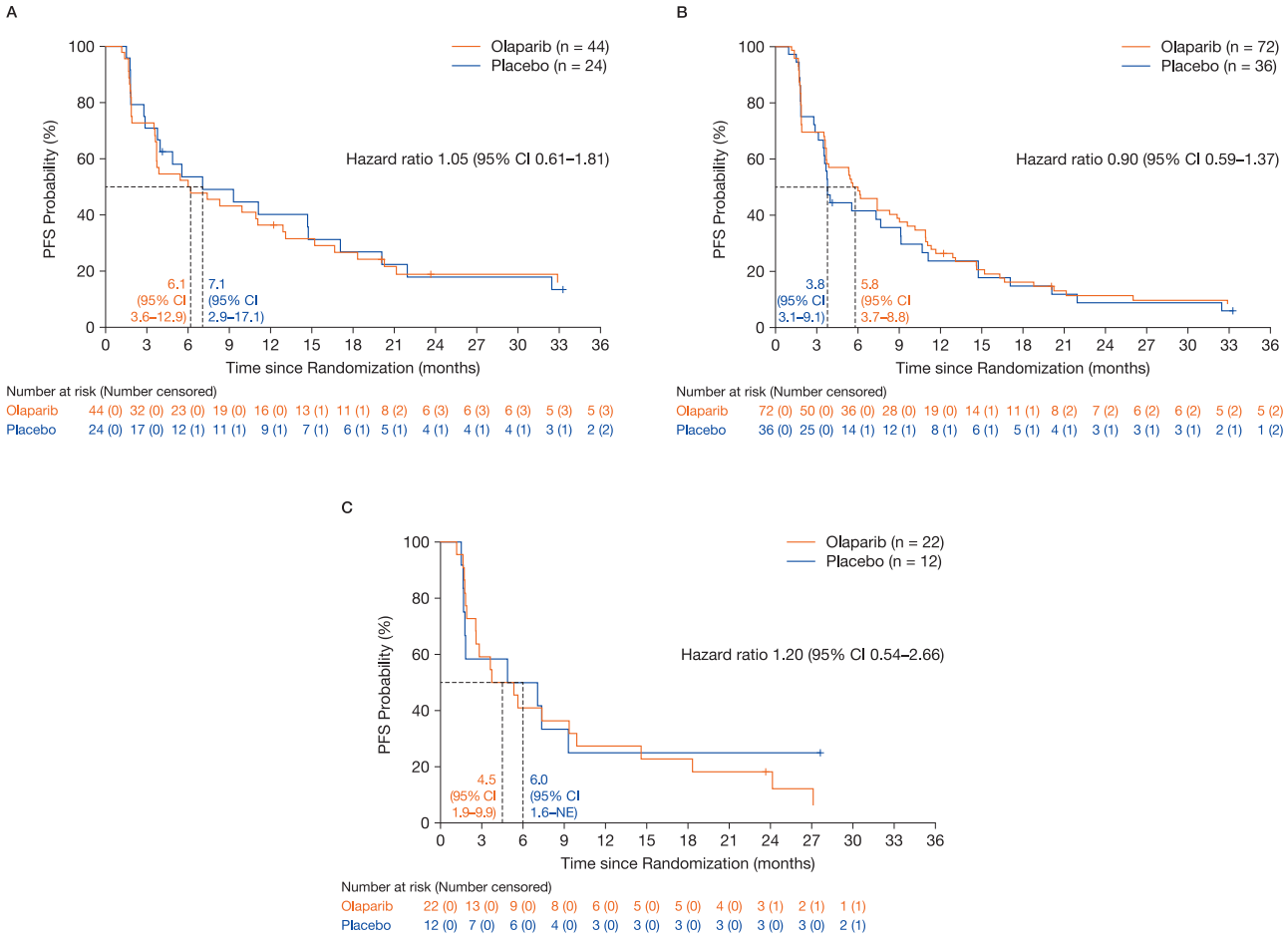

Fig. 3 | Investigator-assessed PFS in subgroups. A p53-normal subgroup. **B** Subgroup with complete or partial response to prior chemotherapy. **C** Subgroup with stable disease with prior chemotherapy. CI confidence interval, PFS progression-free survival.

overestimating the proportion of patients with HRD tumors, and validation of the appropriate GIScar cutoff to identify patients with EC potentially benefitting from PARP inhibition is required. Interestingly, similar outcomes regarding longer PFS were observed in patients with *TP53*-mutated LGE_{high} recurrent EC in the single-arm phase I/II ENDOLA study[32], corroborating our hypothesis.

Although the UTOLA trial was negative for the primary objective and subgroup analyses are limited by small sample sizes, the findings in subgroups with p53-abnormal disease and LGE_{high} are hypothesis generating and may guide future research. Results from UTOLA raise the question whether maintenance PARP inhibition may potentially play a role in HRD/p53-abnormal advanced/metastatic EC, specifically in patients with a complete response after first-line platinum chemotherapy. These intriguing numerical effects should be evaluated prospectively in future trials. For example, an important step for future trial design may be to compare chemotherapy combined with a PARP inhibitor, immunotherapy, or both in a three-arm clinical trial enrolling patients with p53-abnormal advanced/metastatic EC, perhaps focusing on patients with an objective response to prior chemotherapy and potentially excluding patients with low-grade (predominantly LGE_{low}) carcinomas. Ongoing trials evaluating the effect of PARP inhibition in p53-abnormal localized ECs include CAN-STAMP (NCT04159155) and RAINBO/p53abn-RED (NCT05255653).

Methods

Study design and patients

UTOLA (prospectively registered at NCT03745950, https://clinicaltrials.gov/) was a multicenter, randomized, double-blind, placebo-controlled, phase IIb trial conducted at 29 sites with expertise in gynecological cancer in France. Before enrollment of any patient into the study, the protocol (Supplementary Note 2) was approved by the Comité de Protection des Personnes (CPP) Ouest V based in Rennes and the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in France. The trial complied with all relevant ethical regulations. The trial design and conduct complied with all relevant regulations regarding the use of human study participants and the trial was conducted in accordance with the criteria set by the Declaration of Helsinki. Treatment and follow-up in this trial are complete.

Eligible patients were females with advanced or metastatic EC with endometrioid, clear cell, serous, or mixed histology, Eastern Cooperative Oncology Group performance status <2, life expectancy >16 weeks, and normal hematologic, bone marrow, hepatic, and renal function. Patients with a history or features suggestive of myelodysplastic syndrome or acute myeloid leukemia were ineligible.

All patients had received four to six cycles of platinum-based chemotherapy (typically carboplatin plus paclitaxel) and were in complete or partial response, had no evidence of disease, or had stable disease. Adjuvant chemotherapy completed ≥12 months before inclusion in the trial was allowed, as was previous hormone therapy. Patients who had received more than one line of chemotherapy for advanced/metastatic EC or had completely resectable localized advanced disease were ineligible. All patients provided written informed consent before undertaking any study-specific procedures.

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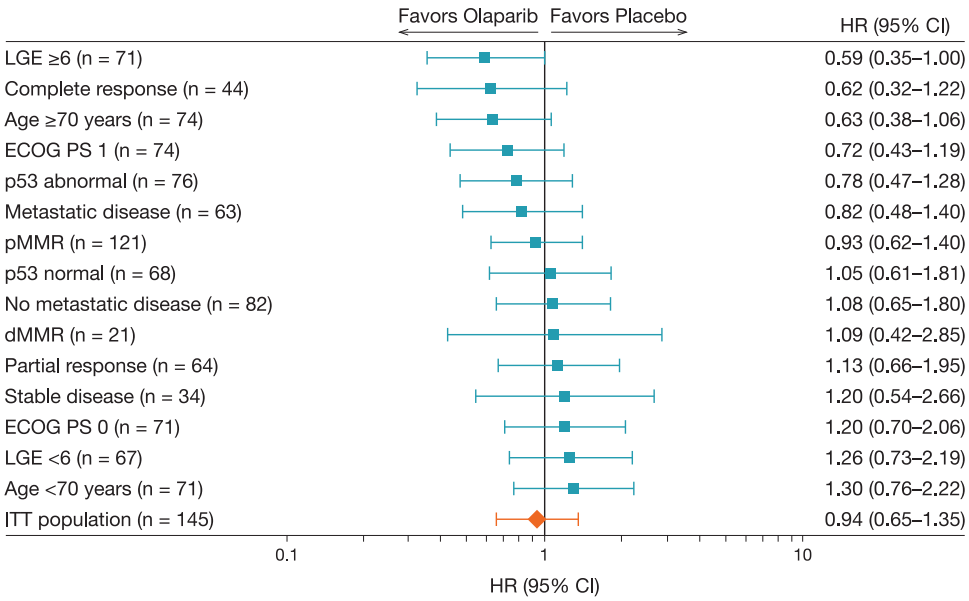

Fig. 4 | Overview of PFS by subgroup. CI confidence interval, dMMR mismatch repair deficient, ECOG PS Eastern Cooperative Oncology Group performance status, HR hazard ratio, ITT intention-to-treat, LGE large genomic events, PFS progression-free survival, pMMR mismatch repair proficient.

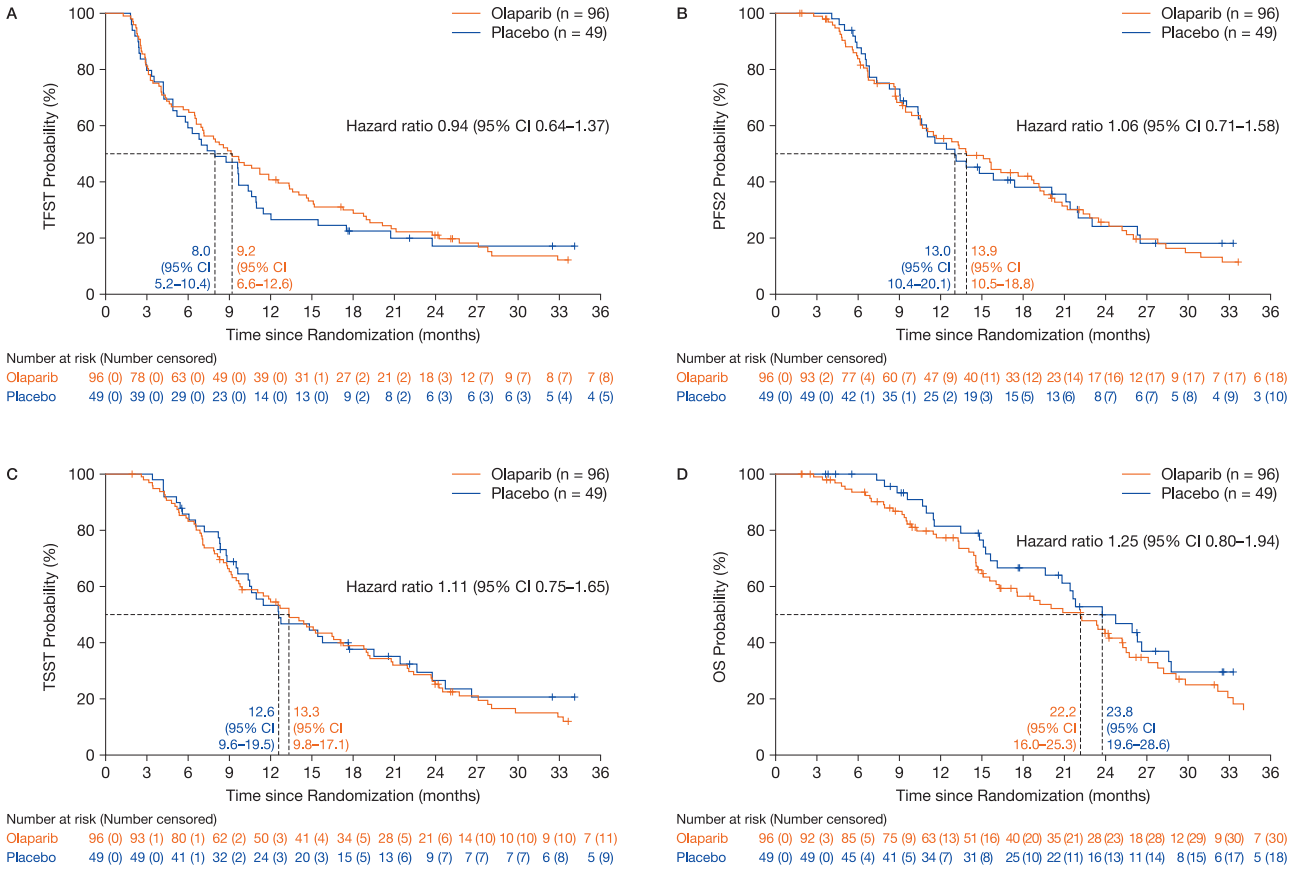

Fig. 5 | Secondary efficacy endpoints in the intention-to-treat population. A Time to first subsequent therapy (TFST). **B** Time to second disease progression or death (PFS2). **C** Time to second subsequent therapy (TSST). **D** Overall survival (OS). CI confidence interval.

Procedures

Patients were enrolled by investigators and randomized via the electronic case report form in a 2:1 ratio using a computer-generated randomization scheme, a minimization method, and an interactive voice response/web system to receive maintenance treatment with oral olaparib 300 mg twice daily or placebo until disease progression (according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) or intolerance. Placebo was provided as film-coated tablets matching the olaparib tablets to ensure that patients and study staff remained blinded to treatment assignment. Stratification factors were p53 status, MMR status (according to Proactive Molecular Risk Classifier for Endometrial Cancer [ProMisE]), and response after platinum

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chemotherapy (objective response vs. stable disease). MMR and p53 status were determined using central immunohistochemistry (IHC) testing within 2 weeks before randomization, retested by NGS within 3 months after randomization. For subgroup analyses, a conservative approach was adopted, with p53-abnormal identified either by IHC or by NGS.

Table 4 | Summary of safety (treatment-emergent AEs)

Patients with treatment-emergent AEs	No. of patients (%)	
	Olaparib (*n* = 96)	Placebo (*n* = 49)
Any grade	91 (95)	44 (90)
Treatment related	83 (86)	34 (69)
Grade 3/4	35 (36)	5 (10)
Treatment related	27 (28)	1 (2)
Leading to dose interruption	31 (32)	6 (12)
Treatment related	26 (27)[a]	4 (8)
Leading to dose reduction	17 (18)	5 (10)
Treatment related	16 (17)	4 (8)
Leading to treatment discontinuation	8 (8)	0
Treatment related	5 (5)[b]	0

[a]Most commonly anemia (12 patients [13%]).
[b]1 patient with grade 2 diarrhea, 1 patient with grade 3 anorexia, 1 patient with grade 2 anemia, 1 patient with grade 2 dyspnea, 1 patient with grade 2 vomiting, grade 2 diarrhea, and grade 3 depression.
AE adverse event.

Outcome measures

The primary endpoint was PFS in the ITT population, defined as the interval from randomization after completion of chemotherapy until progression according to modified RECIST version 1.1. Tumors were assessed by CT scan at baseline and then every 8 weeks until first disease progression.

Secondary endpoints were PFS in subgroups according to p53 and MMR status and response to initial chemotherapy before maintenance; time to first and second subsequent therapy; PFS2; OS; objective response rate; patient-reported outcomes; and safety. MSI was assessed by NGS using MSIsensor version 0.2[33]. No HRD test is validated for EC; consequently, pre-specified subgroup analyses according to chromosomic instability were exploratory. Accumulation of LGEs (deletion or duplication) in the tumor genome is one of the major outcomes of genomic instability and, thus, represents a surrogate marker for HRD status[34]. Therefore, to explore tumor HRD status, we detected LGEs using NGS on a panel of 127 genes already identified in the GIScar. The GIScar academic test for HRD has been validated in ovarian cancer, showing predictive value for sensitivity to maintenance olaparib[35]. As no decision-making threshold for LGE score has been validated in EC, the median LGE score was used as the cutoff to define tumor HRD status and categorize as LGE_{high} or LGE_{low}. Among the 138 samples with available LGE scores, the mean score was 8.1 (SD 7.6) and the median was 6 (range 0–38; interquartile range 2–13). Patient-reported outcomes were assessed using the EORTC QLQs C30, FA-12, and EN24, and the EuroQol EQ-5D-5L. Questionnaires were administered before treatment on day 1 of cycle 1, then at every other cycle, at the end-of-treatment visit, at follow-up visits every 12 weeks until progression, and at

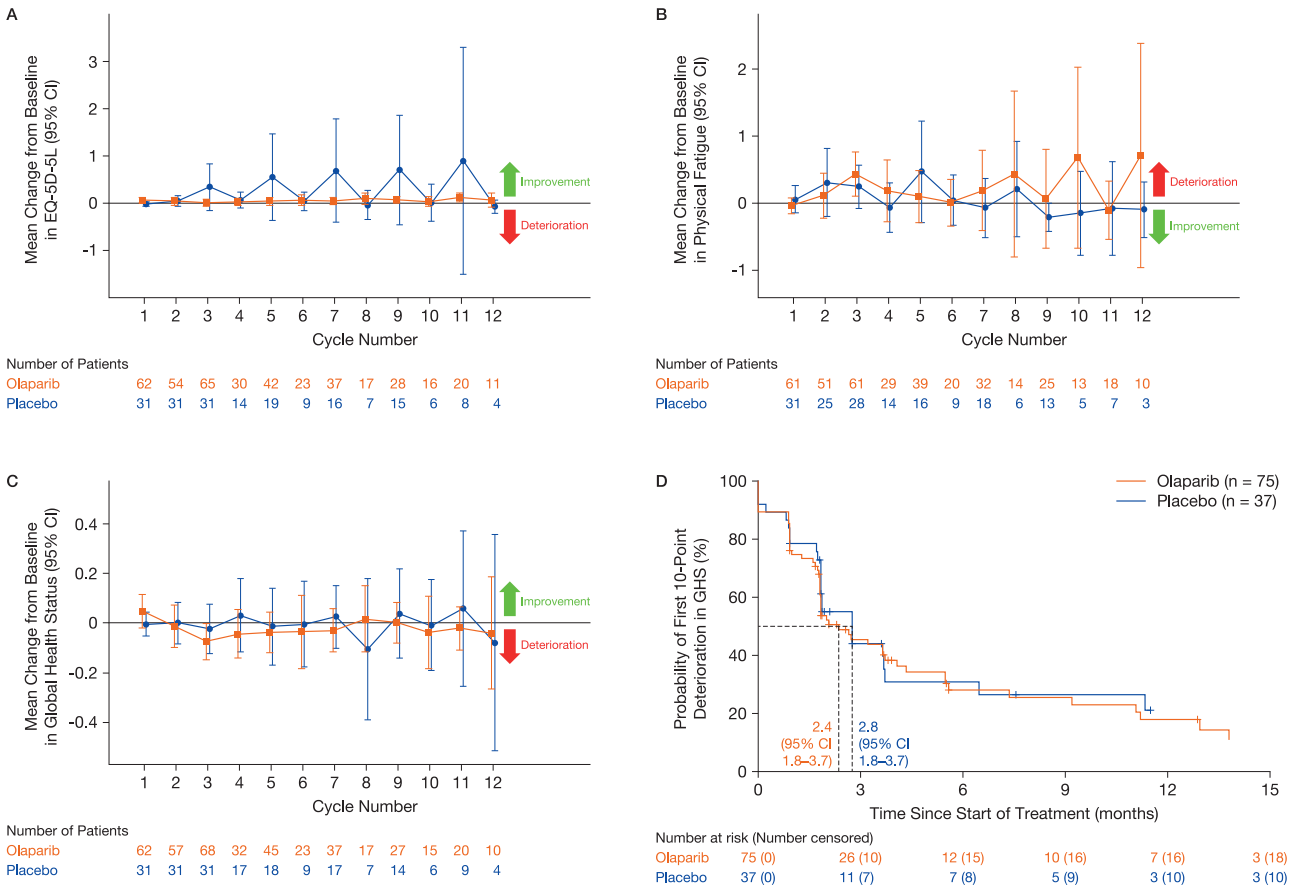

Fig. 6 | Patient-reported outcomes. A Evolution of EQ-5D-5L score over time. **B** Physical fatigue (per FA-12) over time. **C** QLQ-C30 GHS/HRQoL over time. **D** Time to first 10-point deterioration in GHS/HRQoL. CI confidence interval, GHS global health status, HRQoL health-related quality of life.

the OS follow-ups every 3 months after disease progression. For analysis of time to deterioration of quality of life, deterioration was defined as a decrease of ≥10 points (considered a clinically important change)[36,37].

Statistics and reproducibility

The trial was designed to detect an improvement in median PFS from 4.5 months in the placebo arm to 7.5 months with olaparib, corresponding to a HR of 0.60, which we considered to be a clinically relevant treatment effect. Assuming a 5% one-sided type 1 error, 147 patients were to be randomized to provide 80% power (20% type 2 error) according to the Freedman method[38]. The primary analysis was pre-specified to occur after PFS events had been recorded in 122 patients. The primary endpoint was analyzed using a two-sided log-rank test stratified on predefined stratification factors. To handle multiple testing, it was planned to test PFS sequentially, first in the ITT population and if significant at a two-tailed 5% level, then in the p53-abnormal subgroup and if significant at a two-tailed 5% level, then in subgroups according to response to prior chemotherapy. PFS was estimated using Kaplan–Meier methodology.

Data were collected using the Clinsight v8.2.50 clinical data management system, CSonline v8.2.50 web interface, Oracle v19.3 back-end database, and MedDRA v24.0 and WhoDrug Format C - 2021 for medical coding. Two patients withdrew consent for use of their data. These two patients were excluded from all analyses. Apart from exclusion of data from these two patients, analyses were performed on an ITT basis. All data analyses used SAS version 9.4.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Source data for all published figures and tables are provided with this paper. For the remaining raw data, data sharing in a public repository was not planned at the start of the study. Per European and French regulations for personal data privacy, this is not permitted without having informed the study participants, which was not done. This is also linked to a confidentiality agreement with AstraZeneca, which provided the drug and funding. This agreement aims to guarantee protection for the company related to potential sublicensable or patentable information/discovery. Requests to access the de-identified data for further scientific use can be sent to ARCAGY-GINECO (Sébastien Armanet sarmanet@arcagy.org) and will be considered on a case-by-case basis in a timely manner beginning 3 months and ending 5 years after publication of this article. The request must contain a proposal with scientific and methodologically justified objectives. A Data Transfer Agreement will be established to provide a formal framework regarding the use of the data.

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Author contributions

F.J. had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. F.J., I.R-C., B.A., and J.A. conceived and designed the study. F.J., I.R-C., B.A., and J.A. drafted the manuscript. B.A. performed the statistical analysis. F.J. supervised the study. F.J., A.L., I.R.-C., B.A., M.R., L.G., G.M., S.A.-L., C.L., L.B.L., P.Fou., R.La., F.S., J.-S.F., Y.F.D., C.F., P.Fol., J.M., M.F., A.-C.H.B., I.C.-Z., E.K., E.B., A.A., S.R., K.L., P.-A.J., R.Le., C.J., C.C., B.Y., and J.A. contributed to the acquisition and interpretation of data and reviewed and approved the manuscript for important intellectual content.

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Additional information

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