**Olaparib maintenance therapy in patients with platinum-sensitive
relapsed serous ovarian cancer and a *BRCA* mutation: overall
survival adjusted for post-progression PARP inhibitor therapy**

U Matulonis MD,¹ P Harter MD,² C Gourley PhD,³ M Friedlander PhD,⁴ I Vergote MD,⁵
G Rustin MD,⁶ C Scott PhD,⁷ W Meier MD,⁸ R Shapira-Frommer MD,⁹ T Safra MD,¹⁰
D Matei MD,¹¹ A Fielding MBChB,¹² S Spencer MSc,¹² D Parry PhD,¹² L Grinsted MSc¹² and
JA Ledermann MD¹³

¹Dana-Farber Cancer Institute, Boston, USA; ²Kliniken Essen-Mitte, Essen, Germany;
³University of Edinburgh Cancer Research UK Centre, Edinburgh, UK; ⁴Prince of Wales
Hospital, Randwick, New South Wales, Australia; ⁵University of Leuven, Leuven, Belgium;
⁶Mount Vernon Hospital, Northwood, UK; ⁷Royal Melbourne Hospital, Melbourne, Victoria,
Australia; ⁸Evangelical Hospital, Düsseldorf, Germany; ⁹Chaim Sheba Medical Center, Tel
Hashomer, Israel; ¹⁰Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; ¹¹Indiana University
School of Medicine, Indianapolis, USA; ¹²AstraZeneca, Macclesfield, UK; ¹³University
College London, London, UK

Corresponding author:

Ursula A Matulonis MD
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston MA 02215
USA
Tel: 617-632-2334

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Fax: 617-632-3479

Email: Ursula_Matulonis@dfci.harvard.edu

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Condensed Abstract: Maintenance therapy with olaparib, a PARP inhibitor, in patients with platinum-sensitive relapsed serous ovarian cancer and a *BRCA* mutation significantly improved progression-free survival compared with placebo (interim analysis, Study 19: NCT00753545). However, in Study 19, *BRCA* mutation carriers receiving placebo who switched to a PARP inhibitor following disease progression are suggested by post-hoc analysis to have a confounding influence on the interim overall survival analysis

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Conflicts of interest

UM has acted as a consultant or in an advisory role for AstraZeneca and Tesaro; PH has acted as a consultant or in an advisory role for AstraZeneca, and received honoraria from AstraZeneca; CG has received research funding from Aprea, AstraZeneca and Novartis, and has acted as a consultant or in an advisory role for AstraZeneca, Nucana and Roche, and has received honoraria from AstraZeneca and Roche; IV has acted as a consultant or in an advisory role for AstraZeneca; GR has acted as a consultant or in an advisory role for AstraZeneca and Clovis Oncology; CS has acted as a consultant or in an advisory role for AstraZeneca, Clovis Oncology and Ersai Australia, and provided expert testimony for AstraZeneca, and received honoraria from AstraZeneca and Roche; R S-P has acted as a consultant or in an advisory role for AstraZeneca; TS has acted as a consultant or in an advisory role for AstraZeneca and Clovis Oncology; DM has acted as a consultant or in an advisory role for AstraZeneca, and received honoraria from AstraZeneca; AF, SS, DP and LG are employees of AstraZeneca; JL has acted as a consultant or in an advisory role for AstraZeneca; MF and WM have no conflicts of interest to declare.

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project administration. **T Safra:** Investigation, resources, data curation, writing – review and editing, supervision, and project administration. **D Matei:** Investigation, resources, writing – review and editing, supervision. **A Fielding:** Conceptualization, writing – original draft, and writing – review and editing. **S Spencer:** Software, formal analysis, and writing – review and editing. **D Parry:** Conceptualization, methodology, writing – original draft, and writing – review and editing. **L Grinsted:** Conceptualization, formal analysis, and supervision. **JA Ledermann:** Conceptualization, methodology, investigation, resources, writing – original draft, writing – review and editing, visualization, and supervision.

Abstract

Purpose: Maintenance treatment with the oral PARP inhibitor olaparib, in Study 19 (D0810C00019; NCT00753545), significantly improved progression-free survival compared with placebo in patients with platinum-sensitive relapsed serous ovarian cancer with a *BRCA* mutation (*BRCAM*), but interim analysis revealed no statistically significant overall survival (OS) benefit. However, 23% of patients receiving placebo switched to a PARP inhibitor following progression. To investigate whether this had a confounding effect on OS, we report exploratory post-hoc analysis that excluded all patients from sites where ≥ 1 placebo patient received post-progression PARP inhibitor treatment.

Methods: In Study 19, 136/265 patients receiving olaparib or placebo had a *BRCAM*. Sixteen patients treated at 11/82 investigational sites received a PARP inhibitor post-progression; these sites were excluded in this analysis, and 97 *BRCAM* patients at 50 sites were included. OS was assessed using a Cox proportional hazards model analogous to the primary study analysis. A supporting Rank Preserving Structural Failure Time (RPSFT) model analysis was undertaken in all 136 *BRCAM* patients.

Results: The OS Hazard Ratio (HR) was 0.52 (95% CI 0.28–0.97) for the 97 *BRCAM* patients. This is in comparison with the interim OS analysis in all 136 *BRCAM* patients of 0.73 (95% CI 0.45–1.17). The supportive RPSFT analysis HR was approximately 0.66.

Conclusions: The numerical improvement in OS HR suggests that in Study 19, post-progression PARP inhibitor treatment had a confounding influence on the interim OS analysis for *BRCAM* patients. There is a degree of uncertainty owing to small sample size and lack of data maturity.

Introduction

Ovarian cancer is the fifth most common cause of cancer mortality in women in the United States, and patients typically present with advanced stage III or IV disease.¹ Although the majority of patients will experience an initial response to platinum- and taxane-based chemotherapy, most will develop a recurrence of their cancer within 12–18 months.²

The Cancer Genome Atlas Project (TCGA) reported that up to 50% of patients with high-grade serous ovarian cancer (SOC), may have homologous recombination repair (HRR) deficiencies, such as a *BRCA1/2* mutation (*BRCAm*).³ Therapies directed towards DNA damage repair pathways in tumor cells with a *BRCAm* have shown effectiveness in ovarian cancer. The PARP inhibitor class blocks base-excision repair of single-strand DNA breaks and impairs high fidelity repair of double-strand DNA breaks via other mechanisms.⁴ In DNA replication in tumor cells with HRR deficiencies, impaired DNA repair leads to irreparable double-strand breaks being formed, inducing tumor cell death by synthetic lethality.⁴

In 2014, the United States Food and Drug Administration (FDA) granted accelerated approval of olaparib for the treatment of patients with relapsed germline *BRCAm* (*gBRCAm*) ovarian cancer who have received ≥ 3 lines of chemotherapy; the lack of a significant OS benefit in the maintenance setting following platinum-based chemotherapy in platinum-sensitive patients was a concern of the Oncologic Drug Advisory Committee (ODAC).⁵ The European Medicines Agency (EMA) granted approval of olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed *BRCAm* (germline and/or somatic) SOC who are in response to platinum-based chemotherapy based on Study 19 data.⁶

Study 19 (D0810C00019; NCT00753545) was a randomized Phase II clinical trial that assessed the efficacy of olaparib versus placebo for the treatment of patients with platinum-sensitive SOC, following treatment with ≥ 2 platinum-containing regimens. The study demonstrated that maintenance monotherapy with olaparib 400 mg twice daily (BID; capsule formulation) led to a significant improvement in progression-free survival (PFS) compared with placebo (hazard ratio [HR]=0.35, 95% CI 0.25–0.49, $P<0.001$),⁷ most notably in patients with a *BRCAm* (HR=0.18, 95% CI 0.10–0.31, $P<0.0001$).⁸ However, no statistically significant benefit on interim (58% maturity) OS was observed in either the overall (HR=0.88, 95% CI 0.64–1.21, $P=0.44$) or *BRCAm* populations (HR=0.73, 95% CI 0.45–1.17, $P=0.19$).⁸

The degradation of OS benefit from olaparib maintenance therapy, especially in *BRCAm* patients, was hypothesized to have occurred because of subsequent therapies patients may have received, in particular, patients randomized to placebo who have received a PARP inhibitor in a subsequent trial; thus confounding the treatment effect on OS. Switching from placebo to olaparib was not permitted within the design of Study 19, but once patients receiving olaparib or placebo had discontinued study medication, other treatment options, including PARP inhibitors, were at the discretion of the investigator; patients continued to be followed for survival.

To investigate if OS results in Study 19 may have been confounded by patients initially receiving placebo switching to active PARP inhibitor treatment post-progression or post-discontinuation, we report the post-hoc exploratory analysis of interim OS data that excluded all patients from the sites where at least one patient received post-progression

treatment with a PARP inhibitor. We also report an alternative supporting analysis, the rank-preserving structural failure time (RPSFT) model approach,⁹ which utilizes the full dataset and applies statistical methodology to adjust for treatment switching, and allows for the estimation of crossover-corrected treatment effect.

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Methods

Study design

Study 19 was a Phase II, randomized, double-blind, multicenter trial, undertaken at 82 sites in 16 countries. The study design, patient population and statistical analyses have previously been published in detail.^{7,8} In brief, the primary endpoint of Study 19 was PFS determined by Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.0, and OS was a secondary endpoint. Eligible patients were aged 18 years or older and had serous (Grade 2 or 3) relapsed ovarian cancer, which was platinum sensitive. Sensitivity was defined as no disease progression in the first 6 months after the last dose of the penultimate line of platinum-based chemotherapy. Patients entering the study were required to have received ≥ 2 previous courses of platinum-based chemotherapy and an objective response (complete or partial) according to RECIST or Gynecologic Cancer InterGroup criteria.

Patients were randomly assigned to olaparib 400 mg capsules BID or matching placebo in a 1:1 ratio, and randomization was stratified by time from completion of penultimate platinum-based regimen to disease progression (6–12 months vs >12 months), objective response to platinum therapy prior to randomization (complete response vs partial response), and ethnic descent (Jewish vs non-Jewish). The classification of *BRCA* variants for the exploratory analysis reported here was performed blinded and retrospectively, and was based on the American College of Medical Genetics recommendations.¹⁰ Patients were included in the *BRCAm* group if they harbored a deleterious, or suspected deleterious, *gBRCAm* or tumor (somatic) DNA mutation (*sBRCAm*).

Tumor assessments were performed every 12 weeks until week 60, and every 24 weeks thereafter, until objective disease progression or withdrawal of patient consent. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. The study was blinded, and all participants, clinicians and those assessing outcomes were masked to treatment assignment. All patients provided written informed consent, and the trial protocol was approved by all relevant institutional ethical committees or review bodies. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice (ICH-GCP) and the AstraZeneca policy on Bioethics.¹¹

Study objectives for the post-hoc exploratory analysis

To investigate if OS results from Study 19 may have been confounded by the post-progression use of PARP inhibitors, we conducted exploratory post-hoc analysis of OS that, to control for treatment switch, excluded all patients from the sites where at least one patient received post-progression treatment with a PARP inhibitor using the RPSFT approach.⁹ RPSFT models were developed originally to correct statistical analyses for observed non-compliance in clinical trials. The method reduces the weighting of the information contributed by crossover patients, therefore reducing their impact to observed effect. The key assumption underpinning the method is that the effect of the treatment is constant and does not depend on when it is received, ie before or after. Excluding only the patients who had received post-progression PARP inhibitor treatment, as opposed to excluding all patients from the sites where at least one patient received post-progression PARP inhibitor treatment, was not considered statistically feasible, because patients who went on to receive a PARP inhibitor in a subsequent study were patients we hypothesized

would have had a comparably good prognosis, which would likely have been an entry criterion to the study where the additional PARP inhibitor treatment was received. Excluding patients with a potentially good prognosis from just the placebo treatment arm would therefore result in a biased statistical analysis. Thus, to retain a balanced cohort following the removal of patients who switched treatment, all patients from the sites where at least one patient received post-progression treatment with a PARP inhibitor were removed from the analysis. This also includes patients who may have died. The reasons for patients switching treatments were not known, but likely attributable to access to other clinical trials of PARP inhibitors, since these agents were only available on a clinical study. An alternative supporting RPSFT analysis, which included all sites and all patients, was also conducted.

Statistical analyses

In Study 19, PFS and OS (defined as the time from randomization to the date of death from any cause) were assessed using a Cox proportional hazards model adjusted for treatment, ethnic descent (Jewish vs non-Jewish), time to progression on penultimate platinum therapy (6–12 months vs >12 months), and response to platinum therapy prior to randomization (complete response vs partial response).

The post-hoc exploratory OS analysis reported here analyzed interim data (52% maturity in the *BRCAm* population of Study 19). The same definition of OS was used as for the primary analysis. The exploratory analysis was also consistent with the methodology for the primary OS analysis in that a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy was applied.⁷ The RPSFT model employed in this analysis reduces the treatment switching bias and allows

treatment effects to be assessed more accurately by reconstructing data for the placebo arm to mimic a setting, as though switching had not occurred.^{9,12} RPSFT approach assumes that the effect of the investigational treatment starts at the first dose, ends when the investigational treatment stops, and that the treatment effect is equal, regardless of whether the treatment is initiated at the start of the study prior to disease progression, or after disease progression has occurred.

To help understand whether placebo patients benefited from subsequent PARP inhibitor, in the absence of RECIST scans, the duration of treatment (i.e. time a patient was receiving placebo compared with time receiving a subsequent PARP inhibitor) was used as a proxy for PFS, which was not collected past the primary analysis. This is considered appropriate because the protocol specified that patients were to continue on study treatment until RECIST progression, and thus in Study 19, median PFS and duration of treatment was very similar at 11 months. Additionally, to further characterize the placebo patients who received a subsequent PARP inhibitor, individual patient profiles of subsequent PARP inhibitor therapy, progression, time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST) were created.

Results

Patient characteristics and demographics

In Study 19, 265 patients met eligibility criteria and of those, 136 were randomly assigned to receive olaparib and 129 placebo. In total, 74/136 (54%) patients who received olaparib and 62/129 (48%) receiving placebo were identified as having *BRCAm* ovarian cancer (based on germline and/or tumor testing). The majority of investigational sites (71/82) reported no patients who had received a PARP inhibitor following disease progression. Once all patients from the sites where at least one patient received post-progression treatment with a PARP inhibitor were removed, the resulting patient population consisted of 97/136 (71%) *BRCAm* patients. Fourteen out of 62 (23%) *BRCAm* placebo patients were known to have received a PARP inhibitor post-study treatment period (13 g*BRCAm*, one s*BRCAm*). Additionally, two further patients known to have received a PARP inhibitor post study treatment period had a *BRCAm* variant of unknown significance (VUS) (Figure 1).

Prior to progression, no placebo patients were reported to have received a PARP inhibitor, and no olaparib patients received any other PARP inhibitor therapy. The demographic characteristics of the *BRCAm* patients (n=97) included in the post-hoc analysis were similar when compared with the *BRCAm* patients (n=136) (Table 1).⁸ Additionally, the demographic characteristics of patients receiving placebo, who also received a subsequent PARP inhibitor, were further compared with those receiving placebo who did not receive a PARP inhibitor (Table 2).

Although there was only a small number of patients (n=16; 13 g*BRCAM*, one s*BRCAM*, two *BRCAM* VUS) who received a subsequent PARP inhibitor, the 14 *BRCAM* patients represented nearly a quarter (23%) of the 62 placebo patients identified as having *BRCAM* ovarian cancer. Table 2 highlights that there was a greater proportion of younger patients (<50 years old), patients of Jewish descent and patients with a *BRCAM* in the group who received a subsequent PARP inhibitor, compared with patients who did not.

These 16 patients had a longer treatment duration with their subsequent PARP inhibitor than with the original Study 19 randomized placebo therapy (Figure 2). This observation, in conjunction with the study observation that duration of treatment was a reasonable proxy for PFS, suggests that despite its later use, patients still derived benefit from the PARP inhibitor. This analysis was conducted in all placebo patients who received a subsequent PARP inhibitor (n=16), however, an analysis of the 14 *BRCAM* placebo patients showed similar results.

To further characterize the 14 *BRCAM* placebo patients who received a subsequent PARP inhibitor, individual patient profiles were plotted showing TFST and TSST (Figure 3). Figure 3 shows that patients did not generally receive a PARP inhibitor as part of immediate further therapy because the mean gap between progression and treatment switching was 12 (range 0.5–36) months.

Overall survival results

Effect on OS

OS outcomes for olaparib-treated populations were similar whether sites at which post-trial PARP inhibitor treatment was received were excluded or not (median 34.9 months in both cases, Figure 4). OS outcomes for placebo-treated patients were different; median 26.6

months at sites without post-trial PARP inhibitor access compared with median 31.9 months when sites with post-trial PARP inhibitor were included. The OS analysis in the *BRCAm* subgroup (n=97) resulted in a HR of 0.52 (95% CI 0.28, 0.97) (Figure 4). The supportive RPSFT approach resulted in a HR of 0.654 and 0.664 (CI not estimated), with corresponding acceleration factors of 0.20 and 0.31, respectively. Both these analyses suggest that the OS result in the overall *BRCAm* population (n=136) unadjusted for treatment switching and reported by Ledermann *et al* (OS HR of 0.73 [95% CI 0.45, 1.17]),⁸ were confounded by placebo randomized *BRCAm* patients switching treatment to a PARP inhibitor (Figure 4).

Discussion

In this post-hoc exploratory OS analysis from Study 19 reported here, all patients from the sites that had any placebo randomized *BRCAM* patients who received a PARP inhibitor treatment post-progression (n=39) were removed from the analysis. This resulted in an OS HR result from the Cox proportional hazards model of 0.52 (95% CI 0.28, 0.97) compared with an OS HR of 0.73 (95% CI 0.45, 1.17) before these patients were removed.⁷

The observed change in HR, having excluded all patients from sites at which any placebo-randomized patients received post-trial PARP inhibitor, suggests that there was an underestimation of the OS differences between patients receiving placebo and patients receiving olaparib in the *BRCAM* population of Study 19. Thus, switching to PARP inhibitor therapy following disease progression may have diminished the apparent beneficial impact of olaparib on OS within the context of the study, by virtue of the switching of patients in the control arm gaining an OS benefit from receiving a PARP inhibitor post-progression. Although switching to olaparib or another PARP inhibitor from initial placebo was not allowed in Study 19, and there were no approved PARP inhibitors available, patients who switched treatments received a PARP inhibitor as part of a different clinical study. Demographics (Table 1) for the reduced population (n=97) were not dissimilar to the total Study 19 *BRCAM* population (n=136), suggesting no obvious demographic bias.

Furthermore, the RPSFT analysis approach also corroborated the suggestion of an underestimation of OS differences introduced by the 14 placebo randomized patients who switched treatment to a PARP inhibitor.

Patients receiving active treatment post-study

In Study 19, patients went into long-term follow-up after disease progression or data cut-off for the primary PFS analysis (30 June 2010), with no further scans, therefore limited information is available on patients at the time of initiation of PARP inhibitor therapy. Additional understanding of the circumstances of the subsequent PARP inhibitor treatment was gained from the individual patient profiles (Figure 3), which indicates that patients did not generally receive a PARP inhibitor as part of their immediate further therapy.

It is a common occurrence, and largely unpreventable in oncology trials, for patients assigned to receive placebo to later switch to active therapy after the primary endpoint has been reached.¹³ This is particularly the case where the investigational therapy has demonstrated beneficial activity. In placebo-controlled trials, switching to active therapy could be in the best interest of patients, and may be mandated by investigators and ethics committees.¹⁴ However, switching treatments has the potential to confound key efficacy endpoints such as OS if standard statistical methods, for example, the ITT analysis, are employed. To minimize the impact of patients switching treatment, the most common approach is to adjust for switching effects in the statistical analysis, as opposed to changes in the initial study design, which are suggested to be seldom feasible or rarely implemented in practice.¹³ In the ongoing olaparib Phase III ovarian trials SOLO 1 (NCT01844986) and SOLO 2 (NCT01874353), there is an expectation that placebo patients will similarly gain access to PARP inhibitor post progression, either in clinical trials or through licensed prescription. This is expected to similarly impact the ability to demonstrate an OS benefit. To mitigate the impact of switching, statistical analyses that compensate for switching (such as the RPSFT,⁹ IPCW¹⁵ and other methods in development) should be pre-specified in the

study protocol and comprehensive data collection conducted on post-progression treatments, including the reasons for switching.

Statistical methodology

In Study 19, RECIST scans were not performed following the primary analysis of PFS, consequently an assessment of PFS on subsequent PARP inhibitor treatment was not possible. It is therefore difficult to quantify the magnitude of the benefit afforded to the switched patients. However, patients were treated until progression and accordingly data from the ITT population in Study 19 demonstrated that the duration of randomized therapy could serve as a substitute for PFS. This has enabled us to conclude that the switched patients did receive benefit from olaparib (or another PARP inhibitor) treatment, biasing the analysis of OS against olaparib.

Since it is not possible to know what the treatment effect would have been if no patients switched treatment, we attempted to adjust the analysis to explore this bias. Here we have investigated two approaches. The first method adjusted the population by removing all patients from a site where any patient received a PARP inhibitor maintaining the benefits of randomization and reducing the impact of selective exclusion, evaluated using Cox proportional hazards analysis, consistent with the PFS and OS analysis.⁷ The second method adjusts the switched patients and uses the RPSFT model which enabled additional evidence supporting the hypothesis that the true treatment effect had been confounded. Health technology assessment bodies, such as the UK's National Institute for Health and Care Excellence (NICE), have accepted the RPSFT methodology as valuable supporting

evidence.¹⁶ Further detail of the reasoning for use of the statistical methodology, its advantages and disadvantages, are described in the Supplementary material.

Conclusions

The post-hoc exploratory analysis reported here, which excluded all patients from the sites where at least one patient received post-progression treatment with a PARP inhibitor, resulted in a change in OS HR that may suggest a confounding influence has had the effect of masking the beneficial impact of olaparib on OS in patients with platinum-sensitive recurrent HGSOc and a *BRCA*m. More mature data would allow further profiling and a more precise estimate of the non-confounded effect.

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Figure legends

Figure 1. Patient disposition

Figure 2. Comparison of the duration of treatment for placebo patients compared with the duration of treatment for placebo patients who subsequently received a PARP inhibitor post-progression

Figure 3. Individual patient profiles of the 14 BRCAm placebo patients who received a subsequent PARP inhibitor post-progression

Figure 4. OS of BRCAm population treated with placebo or olaparib (all sites) and BRCAm population (post-progression PARP inhibitor sites excluded)

Table 1. Baseline characteristics of patients in the intention-to-treat BRCAm population and the patients in the exploratory post-hoc analysis

Demographics characteristic		Total BRCAm population (original ITT analysis, n=136)		Population following exclusion of post- progression PARP inhibitor sites (additional analysis set, n=97)	
		Olaparib 400 mg bid (n=74)	Placebo (n=62)	Olaparib 400 mg bid (n=57)	Placebo (n=40)
Age group, years (%)	<50	19 (25.7)	16 (25.8)	15 (26.3)	12 (30.0)
	≥50 to <65	38 (51.4)	35 (56.5)	27 (47.4)	20 (50.0)
	≥65	17 (23.0)	11 (17.7)	15 (26.3)	8 (20.0)
Race, n (%)	White	70 (94.6)	61 (98.4)	54 (94.7)	40 (100)
	Jewish descent				
	Yes	14 (18.9)	14 (22.6)	7 (12.3)	3 (7.5)
	No	60 (81.1)	48 (77.4)	50 (87.7)	37 (92.5)
Response to prior platinum therapy, n (%)	Complete response	36 (48.6)	34 (54.8)	27 (47.4)	26 (65.0)
	Partial response	38 (51.4)	28 (45.2)	30 (52.6)	14 (35.0)
Time from penultimate prior platinum therapy to progression	>6 to ≤12 months	28 (37.8)	26 (41.9)	21 (36.8)	18 (45.0)
	>12 months	46 (62.2)	36 (58.1)	36 (63.2)	22 (55.0)

Table 2. Demographic characteristics of patients receiving placebo (n=129) who subsequently did or did not receive a PARP inhibitor

Demographics characteristic		Patients who received a subsequent PARP inhibitor (N=16*)	Patients who did not receive a subsequent PARP inhibitor (N=113)
Age group, years (%)	<50	4 (25.0)	16 (4.2)
	≥50 to <65	10 (62.5)	64 (56.6)
	≥65	2 (12.5)	33 (29.2)
Race, n (%)	White	16 (100)	110 (97.4)
	Jewish descent		
	Yes	9 (56.3)	8 (7.1)
Response to prior platinum therapy, n (%)	Complete response	5 (31.3)	58 (51.3)
	Partial response	11 (68.8)	55 (48.7)
Time from penultimate prior platinum therapy to progression (%)	>6 to ≤12 months	8 (50.0)	46 (40.7)
	>12 months	8 (50.0)	67 (59.3)
BRCA status	Mutant	14 (87.5)	48 (42.5)
	Wild type	0	57 (50.4)
	Variant of unknown significance	2 (12.5)	2 (1.8)
	Missing	0	6 (5.3)

*Based on all placebo patients who received a subsequent PARP inhibitor (n=16), which includes 13 patients with gBRCAm, one patient with sBRCAm and two patients with BRCAm variants of unknown significance

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Figure 1

pts, patients; VUS, variant of unknown significance; wt, wild type

Figure 1
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Figure 2

Figure 2
17x13mm (600 x 600 DPI)

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Figure 3

Figure 3
17x13mm (600 x 600 DPI)

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Figure 4

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Accept

Supplementary material:

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and a *BRCA* mutation: overall survival adjusted for post-progression PARP inhibitor therapy

U Matulonis,¹ P Harter,² C Gourley,³ M Friedlander,⁴ I Vergote,⁵ G Rustin,⁶ C Scott,⁷ W Meier,⁸ R Shapira-Frommer,⁹ T Safra,¹⁰ D Matei,¹¹ A Fielding,¹² S Spencer,¹² D Parry,¹² L Grinsted¹² and JA Ledermann¹³

Statistical methodology

When treatment switching, an ITT analysis may provide biased estimates of OS on treatment compared to control,¹ and when the investigational treatment is efficacious this bias will be against the estimate of treatment effect. Olaparib has demonstrated that it is an active treatment that offers significant benefit to patients, therefore the placebo patients are expected to have received benefit from switching treatments.

In Study 19, RECIST scans were not performed following the primary analysis of PFS, therefore an assessment of PFS on subsequent PARP inhibitor treatment was not possible. It is therefore difficult to quantify the magnitude of the benefit afforded to the switched patients, however, patients were to be treated until progression and accordingly data from the ITT population in Study 19 demonstrated that the duration of randomized therapy could serve as a substitute for PFS. This has enabled us to conclude that the switched patients did receive benefit from olaparib (or another PARP inhibitor) treatment, biasing the analysis of OS against olaparib.

Since it is not possible to know what the treatment effect would have been if no patients switched treatment, we attempt to adjust the analysis to explore this bias. Here we have investigated two approaches; one which adjusts the population and a second that adjusts the switched patients.

An analysis that simply removes the patients who cross over would be biased against placebo, this is because we would be selectively excluding patients who have, at the

time of their switching, a reasonably good prognosis (needed for entry to a clinical trial). To alleviate this potential bias we propose that removing all patients from a site where any patient got a PARP maintains the benefits of randomization and reduces the impact of selective exclusion. The same analysis methodology can then be used on the patient population once all patients from the sites where at least one patient received post-progression treatment with a PARP inhibitor were removed, namely a Cox proportional hazards analysis, which is consistent with the methodology for the PFS and OS analysis previously reported.² The additional RPSFT model approach we employed enabled additional evidence supporting that the true treatment effect had been confounded. Health technology assessment bodies, such as the UK's National Institute for Health and Care Excellence (NICE), have accepted the RPSFT methodology as valuable supporting evidence.³

RPSFT models were developed originally to correct statistical analyses for observed non-compliance in clinical trials. The method reduces the weighting of the information contributed by crossover patients, therefore reducing their impact to observed effect. The key assumption underpinning the method is that the effect of the treatment is constant and does not depend on when it is received, ie before or after progression. Our assessment of duration of placebo and duration of PARP inhibitor treatment in these patients suggests that this assumption is not unreasonable. Advantages of the RPSFT model include use of the complete data set and preservation after adjustment of the ranking of the observed time-to-event data. Limitations include the assumption that mortality decreases constantly during treatment.⁴ Additionally in the study, we report that there remains a large degree of uncertainty in the treatment effect due to the small sample sizes (n=97 *BRCAm* patients analyzed) and the data maturity (52%). More mature data would allow further profiling and a more precise estimate of the non-confounded effect.

In addition to the methods reported here, two additional statistical analyses were considered for determining the impact on OS results of switching; the inverse probability of censoring weights (IPCW) and the two-stage Weibull model. These two methods, and the RPSFT approach, were considered on the basis of recent work by Latimer *et al.* on behalf of NICE.⁵ The IPCW treatment-switching adjustment results were ultimately not considered applicable for this study because there were insufficient data available for time-dependent factors considered to affect the decision to switch treatment, which is a

key requisite to the conduct of IPCW.⁶ Similarly, results from the two-stage Weibull model were not considered applicable due to the duration of time between progression and treatment switching, where the mean (range) gap between progression and treatment switching was 12.18 (1.0–36.1) months.

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Author/s:

Matulonis, UA;Harter, P;Gourley, C;Friedlander, M;Vergote, I;Rustin, G;Scott, C;Meier, W;Shapira-Frommer, R;Safr, T;Matei, D;Fielding, A;Spencer, S;Parry, D;Grinsted, L;Ledermann, JA

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