



## Original Research

# Population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 trials evaluating maintenance olaparib or bevacizumab or the combination of both in newly diagnosed, advanced BRCA-mutated ovarian cancer



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## KEYWORDS

Olaparib;  
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BRCA mutation

**Abstract Background:** In the absence of randomised head-to-head trials, we conducted a population-adjusted indirect treatment comparison (PA-ITC) of phase III trial data to evaluate the relative efficacy and safety of maintenance olaparib and bevacizumab alone and in combination in patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation (BRCAm).

**Methods:** An unanchored PA-ITC was performed on investigator-assessed progression-free survival (PFS) data. Individual patient data from SOLO1 (olaparib versus placebo) and from BRCA-mutated patients in PAOLA-1/ENGOT-ov25 (olaparib plus bevacizumab versus placebo plus bevacizumab) were pooled. Each arm of PAOLA-1 was weighted so that key baseline patient characteristics were similar to the SOLO1 cohort. Analyses were performed in patients with complete baseline data. Weighted Cox regression analysis was used to estimate the comparative efficacy of different maintenance therapy strategies, supplemented by weighted Kaplan–Meier analyses.

**Results:** Data from SOLO1 patients (olaparib,  $n = 254$ ; placebo,  $n = 126$ ) were compared with data from BRCA-mutated PAOLA-1 patients (olaparib plus bevacizumab,  $n = 151$ ; placebo plus bevacizumab,  $n = 71$ ). Adding bevacizumab to olaparib was associated with a numerical improvement in PFS compared with olaparib alone (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.45–1.09). Statistically significant improvements in PFS were seen with olaparib alone versus placebo plus bevacizumab (HR 0.48; 95% CI 0.30–0.75), olaparib plus bevacizumab versus placebo (0.23; 0.14–0.34), and placebo plus bevacizumab versus placebo (0.65; 0.43–0.95).

**Conclusions:** Results of this hypothesis-generating PA-ITC analysis support the use of maintenance olaparib alone or with bevacizumab in patients with newly diagnosed, advanced ovarian cancer and a BRCAm.

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## 1. Introduction

The majority of women with newly diagnosed, advanced ovarian cancer relapse within 3 years despite undergoing cytoreductive surgery and first-line platinum-based chemotherapy [1]. The presence of a *BRCA1* and/or *BRCA2* mutation (BRCAm) has been associated with primary platinum sensitivity and improved survival in ovarian cancer [2].

Maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors represents a new standard of care in newly diagnosed, advanced ovarian cancer. In the primary analysis of the SOLO1 trial

(NCT01844986; GOG 3004), maintenance olaparib provided a significant progression-free survival (PFS) benefit versus placebo in newly diagnosed, BRCA-mutated advanced ovarian cancer (hazard ratio [HR] 0.30; 95% confidence interval [CI] 0.23–0.41) [3]. With longer-term follow-up, median PFS was 56.0 months with olaparib versus 13.8 months with placebo [4]. Maintenance olaparib is approved in various countries for women with advanced ovarian cancer and a BRCAm who are in response after first-line platinum-based chemotherapy [5–8].

The PAOLA-1/ENGOT-ov25 trial (NCT02477644) evaluated the addition of maintenance olaparib to the

antiangiogenic agent bevacizumab in patients with newly diagnosed, advanced ovarian cancer [9]. A substantial PFS benefit was seen with olaparib plus bevacizumab versus bevacizumab alone in patients with a tumour BRCAm (HR 0.31; 95% CI 0.20–0.47) and in patients who tested positive for homologous recombination deficiency (HRD) (HR 0.33; 95% CI 0.25–0.45) [9]. Based on this result, maintenance olaparib plus bevacizumab was approved in various countries for HRD-positive (BRCAm and/or genomic instability [i.e. a positive genomic instability score on HRD testing]) women with advanced ovarian cancer in response after first-line platinum-based chemotherapy plus bevacizumab [5,6,10].

To date, no randomised, phase III, head-to-head trials have compared maintenance therapy with a PARP inhibitor alone with maintenance therapy with a PARP inhibitor combined with an antiangiogenic agent in patients with BRCA-mutated newly diagnosed, advanced ovarian cancer. We conducted a hypothesis-generating population-adjusted indirect treatment comparison (PA-ITC) to evaluate the relative efficacy and safety of olaparib plus bevacizumab versus olaparib alone versus bevacizumab alone versus placebo in patients with BRCA-mutated newly diagnosed, advanced ovarian cancer.

## 2. Methods

As previously reported, SOLO1 [3] and PAOLA-1/ENGOT-ov25 [9] were randomised, double-blind, multicentre phase III trials. Both trials included patients with newly diagnosed, International Federation of Gynecology and Obstetrics (FIGO) stage III or IV, high-grade serous or high-grade endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer (Fig. 1). Patients were eligible irrespective of surgical status and were in response after first-line treatment with platinum-based chemotherapy (SOLO1) [3] or platinum-based chemotherapy plus bevacizumab (PAOLA-1) [9]. Patients in SOLO1 had a BRCAm [3], and patients in PAOLA-1 were eligible irrespective of biomarker status [9]. The primary endpoint in both SOLO1 [3] and PAOLA-1 [9] was investigator-assessed PFS (modified Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1). Radiological scans were performed every 3 months for 3 years and then every 6 months until objective disease progression in SOLO1 [3] and every 24 weeks (or at planned visits every 12 weeks if there was evidence of clinical progression or CA-125 progression) up to month 42 or until data cut-off (DCO) in PAOLA-1 [9]. Additional study design details are reported in the Appendix.

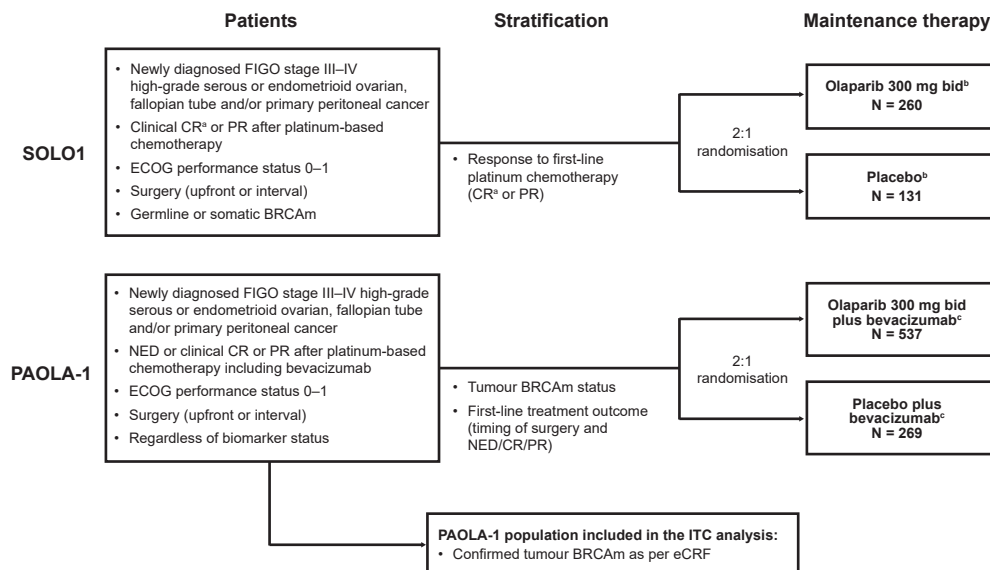


Fig. 1. SOLO1 and PAOLA-1 study designs. <sup>a</sup>CR in SOLO1 included both patients with NED and CR (see the Appendix for response definitions). <sup>b</sup>In SOLO1, study treatment continued until disease progression, was stopped at 2 years in patients with CR or NED, or could continue beyond 2 years in patients with ongoing PR. <sup>c</sup>In PAOLA-1, study treatment continued for up to 2 years from randomization or until disease progression in accordance with investigators' assessment of imaging (modified Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1 criteria). Intravenous bevacizumab 15 mg/kg was administered every 3 weeks for a total duration of up to 15 months. bid, twice daily; BRCAm, *BRCA1* and/or *BRCA2* mutation; CR complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FIGO, International Federation of Gynecology and Obstetrics; ITC, indirect treatment comparison; NED, no evidence of disease; PR, partial response.

ITCs are usually performed by comparing relative treatment effects across two or more studies with a common comparator arm, such as a placebo. Where the studies of interest do not share a common comparator arm, as is the case for PAOLA-1 (bevacizumab plus placebo) and SOLO1 (placebo), an unanchored PA-ITC must be performed. This method involves the comparison of absolute effects across studies using propensity scores or outcome regression-based approaches to minimise the effects of confounding from differences in patient characteristics across studies.

An unanchored PA-ITC was performed on the endpoint of investigator-assessed PFS (RECIST version 1.1), in line with published methodology guidance [11]. The analysis pooled individual patient data from SOLO1 (olaparib versus placebo) and from the subgroup of patients in PAOLA-1 with a confirmed tumour BRCaM (in order to match the SOLO1 eligibility criteria), as per the electronic case report form (eCRF) (olaparib plus bevacizumab versus placebo plus bevacizumab).

Adjustments were made for imbalances between treatment arms in prespecified baseline characteristics (i.e. matching variables). Prior to analysis, the matching prognostic variables identified for adjustment were primary tumour location, Eastern Cooperative Oncology Group (ECOG) status, International Federation of Gynecology and Obstetrics (FIGO) stage, the timing of surgery, postoperative residual disease status, response to first-line treatment, age and histological type. The final analysis did not adjust for histological type because most tumours were high-grade serous (96% in both trials [3,9]).

A propensity score weighting technique [12] was used to adjust for imbalances in matching variables; BRCaM patients in each arm of PAOLA-1 were weighted so that the cohort had similar overall baseline matching variables to the olaparib arm of SOLO1 (Fig. S1). For each patient, the propensity score was estimated using a logistic regression model in which arm membership (SOLO1 olaparib arm versus PAOLA-1 treatment arm) was regressed on the matching variables and interactions. The estimated propensity scores were then used to weight the individuals in PAOLA-1 by their odds of being in the olaparib arm of SOLO1 [13]. The appropriateness of the derived weights to control for population imbalances was assessed (Appendix).

The effective sample size (ESS) was calculated, whereby ESS is defined as the number of unweighted patients that would be required in order to achieve the same precision in an estimate as in the weighted sample.

Weighted Cox regression analyses were performed to estimate the comparative efficacy of different maintenance therapy strategies in the SOLO1 population, and weighted Kaplan–Meier analyses were also carried out. The 95% CIs for the estimated HRs were based on non-parametric bootstrapping-based standard errors that allow for uncertainty in the estimation of the weights.

The primary analysis used a weighting-based approach because this methodology utilises all patient data from SOLO1 and PAOLA-1. Unweighted analyses were also conducted to assess the implications of the population adjustment. A sensitivity analysis was conducted using 1:1 propensity score matching to understand the impact of the choice of matching method on results (Appendix).

A safety analysis reported adverse events (AEs) in each of the four treatment arms in unadjusted and weighted analyses. The weighted safety analysis used the same weights as in the primary efficacy analysis.

All analyses were performed in patients with complete data on matching variables. The PA-ITC was not adjusted for multiple comparisons and used 5% as the nominal significance level.

### 3. Results

SOLO1 randomised 260 patients to olaparib and 131 patients to placebo [3], and PAOLA-1 randomised 537 patients (157 with a BRCaM) to olaparib plus bevacizumab and 269 patients (80 with a BRCaM) to placebo plus bevacizumab [9] (Fig. S2). At the time of the primary PFS analysis, median follow-up was 40.7 months (interquartile range [IQR] 34.9–42.9) for olaparib and 41.2 months (32.2–41.6) for placebo in SOLO1 (DCO 17 May 2018) [3] and 22.7 months (range 18.0–27.7) for olaparib plus bevacizumab and 24.0 months (18.7–27.7) for placebo plus bevacizumab in PAOLA-1 (DCO 22 March 2019) [9].

The PA-ITC analysis included complete case data from 380 patients in SOLO1 (254 olaparib patients and 126 placebo patients) and from 222 patients with a BRCaM in PAOLA-1 (151 olaparib plus bevacizumab patients and 71 placebo plus bevacizumab patients) (Fig. S2).

The baseline characteristics of patients in each treatment arm of PAOLA-1 and SOLO1 prior to weighting are shown in Table 1. Excluding patients with missing values for matching variables had negligible impact, as shown by the similar baseline characteristics seen in the olaparib target population and the original olaparib sample from SOLO1. Prior to weighting, patients in PAOLA-1 were more likely to be FIGO stage IV, have residual disease, and be older than patients in SOLO1.

The baseline characteristics of patients in each treatment arm of the weighted PAOLA-1 BRCaM cohort and SOLO1 are shown in Table 1 and Fig. S3. The weighted PAOLA-1 BRCaM cohort had similar baseline data to the SOLO1 cohort, apart from a numerically lower value for a first-line treatment outcome of partial response in the PAOLA-1 treatment arms than in the SOLO1 treatment arms.



Table 1  
Patient baseline characteristics preweighting and postweighting.

Baseline characteristic	SOLO1			PAOLA-1 preweighting		PAOLA-1 postweighting to target olaparib arm	
	Olaparib (original sample) n = 260	Olaparib (target for matching) n = 254	Placebo n = 126	Olaparib + bev n = 151	Placebo + bev n = 71	Olaparib + bev n = 151 <sup>a</sup>	Placebo + bev n = 71 <sup>a</sup>
Primary tumour location (% ovary)	85	85	86	85	92	84	88
ECOG (% status 1 [restricted activity])	23	23	19	25	24	23	29
FIGO stage (% IV)	15	14	18	28	31	14	16
Surgery (% interval)	36	37	34	43	38	40	37
Residual disease (%)	21	22	23	32	30	26	22
First-line outcome (% PR)	27	26	21	15	17	19	17
Mean age (years)	53.6	53.6	53.4	57.0	55.0	54.3	53.9
Age (% ≥65 years)	13	13	15	22	15	16	13

bev, bevacizumab; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PR, partial response.

<sup>a</sup> The effective sample size (i.e. the number of unweighted patients that would be required in order to achieve the same precision in an estimate as in the weighted sample) was 110.8 for the olaparib plus bevacizumab group and 54.7 for the placebo plus bevacizumab group.

Weighting PAOLA-1 patients to be similar in baseline characteristics to the olaparib arm of SOLO1 had the effect of increasing the proportion of patients who were free from disease progression and death in both treatment groups in PAOLA-1 (Fig. S4).

Although not statistically significant, the addition of bevacizumab to olaparib was associated with a numerical improvement in PFS compared with olaparib alone (HR 0.71; 95% CI 0.45–1.09) (Fig. 2A and Table 2); 82% versus 73% of patients, respectively, were progression free at 24 months.

Statistically significant improvements in PFS were seen with olaparib alone compared with placebo plus bevacizumab (HR 0.48; 95% CI 0.30–0.75) (73% versus 50% of patients were progression free at 24 months), olaparib plus bevacizumab compared with placebo (HR 0.23; 95% CI 0.14–0.34) (82% versus 36% of patients were progression free at 24 months), and placebo plus bevacizumab compared with placebo (HR 0.65; 95% CI 0.43–0.95) (50% versus 36% of patients were progression free at 24 months) (Fig. 2B–D and Table 2).

Results of the main analysis were supported by the findings of a sensitivity analysis using 1:1 propensity score matching (Table S1) and adjusting for the difference in baseline response rates between the PAOLA-1 and SOLO1 treatment arms (Table S2).

Results of unadjusted analyses reporting landmark data and HRs using the unweighted BRCam subset of PAOLA-1 are shown in the Appendix (Table S3).

Overall, weighting PAOLA-1 BRCam patients to be similar in baseline characteristics to SOLO1 had little impact on the PAOLA-1 safety results (Table S4).

As expected, patients receiving maintenance olaparib plus bevacizumab were more likely than those receiving maintenance olaparib alone to experience AEs that are

frequently associated with bevacizumab, such as hypertension (43% versus 4%), although the highest incidence of hypertension was seen with bevacizumab alone (55%) (Table S4).

The higher incidence of grade ≥3 AEs seen with olaparib plus bevacizumab than with olaparib alone (58% versus 39%) mainly reflects the between-group difference in grade ≥3 hypertension (15% versus <1%) (Table S4). The difference between olaparib plus bevacizumab and olaparib alone in discontinuation of treatment because of AEs (21% versus 12%) (Table S4) may be partly explained by the different methods used to handle discontinuations.

The unadjusted incidence of myelodysplastic syndrome and acute myeloid leukaemia in patients in SOLO1 and in BRCam patients in PAOLA-1 is reported in the Appendix.

#### 4. Discussion

This PA-ITC analysis provides the best available comparative evidence of efficacy and safety in the absence of head-to-head trials. PA-ITC analyses provide hypothesis-generating evidence of the comparative efficacy of treatment in cases where standard indirect comparison or network meta-analysis methods cannot be used due to the lack of a common comparator arm between studies [11]. Results of this PA-ITC analysis support the use of maintenance olaparib alone or in combination with bevacizumab in patients with BRCA-mutated newly diagnosed, advanced ovarian cancer and, together with results from SOLO1 [3] and PAOLA-1 [9], demonstrate that olaparib, when given alone or in combination with bevacizumab, provides a PFS benefit versus bevacizumab alone or placebo.

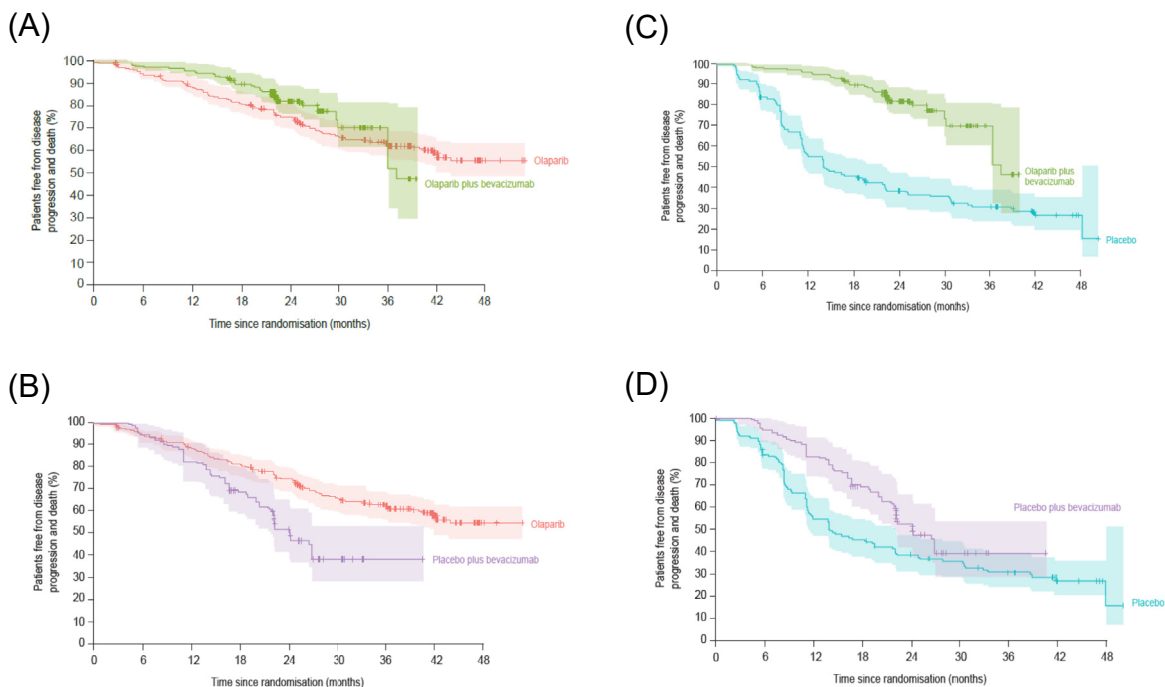


Fig. 2. Population-adjusted indirect treatment comparison of progression-free survival for (A) Olaparib plus bevacizumab versus olaparib alone. (B) Olaparib alone versus placebo plus bevacizumab. (C) Olaparib plus bevacizumab versus placebo. (D) Placebo plus bevacizumab versus placebo. The shaded regions represent 95% CIs. Censoring and the reduction in the number of patients at risk contribute to the wide 95% CIs seen towards the end of the follow-up period. The median duration of follow up for PFS was 40.7 months (IQR 34.9–42.9) for the olaparib group and 41.2 months (32.2–41.6) for the placebo group in SOLO1 [3] and 22.7 months (range 18.0–27.7) in the olaparib plus bevacizumab group and 24.0 months (18.7–27.7) in the placebo plus bevacizumab group in PAOLA-1 [9]. CI, confidence interval, IQR, interquartile range.

Table 2

Population-adjusted indirect treatment comparison: PFS probability estimates and HR.<sup>a</sup>

	Patients free from disease progression and death, % (95% CI) <sup>b</sup>		PFS HR (95% CI)
	12 months	24 months	
Olaparib plus bevacizumab versus olaparib			
Olaparib plus bevacizumab (n = 151)	96 (93–99)	82 (76–89)	0.71 (0.45–1.09)
Olaparib (n = 254)	88 (84–92)	73 (68–79)	
Olaparib versus placebo plus bevacizumab			
Olaparib (n = 254)	88 (84–92)	73 (68–79)	0.48 (0.30–0.75)
Placebo plus bevacizumab (n = 71)	81 (73–91)	50 (39–64)	
Olaparib plus bevacizumab versus placebo			
Olaparib plus bevacizumab (n = 151)	96 (93–99)	82 (76–89)	0.23 (0.14–0.34)
Placebo (n = 126)	53 (45–63)	36 (28–45)	
Placebo plus bevacizumab versus placebo			
Placebo plus bevacizumab (n = 71)	81 (73–91)	50 (39–64)	0.65 (0.43–0.95)
Placebo (n = 126)	53 (45–63)	36 (28–45)	

BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR hazard ratio; PFS, progression-free survival.

<sup>a</sup> Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, the timing of surgery (interval versus upfront), residual disease status after surgery (yes or no), response to first-line treatment, and age in the PAOLA-1 BRCAm subgroup to SOLO1.

<sup>b</sup> Kaplan–Meier estimates.

Data suggest a potential improvement in PFS with olaparib plus bevacizumab versus olaparib alone (PFS HR 0.71; 95% CI 0.45–1.09). Even though the 95% CI

crossed 1.0 (as the analysis was not powered for this comparison), it should be noted that the 29% reduction in the risk of progression or death was achieved against

a comparator arm (olaparib alone) that has shown substantial efficacy in this setting [3]. As this was an exploratory analysis, the number of included patients is limited in contrast to a prospective trial that is powered for a direct comparison.

The treatment benefit of bevacizumab appeared additive in this PA-ITC analysis, with a consistent benefit seen when added to placebo or olaparib, which may have implications for the optimal sequencing of treatment in this setting. The PFS benefit seen with bevacizumab versus placebo (HR 0.65; 95% CI 0.43–0.95) and the shape of the Kaplan–Meier curve were consistent with those reported in GOG 0218 [14] and ICON-7 [15], which evaluated the addition of bevacizumab to first-line carboplatin plus paclitaxel followed by maintenance bevacizumab (Appendix). Findings from AVANOVA2 evaluating the addition of bevacizumab to a PARP inhibitor [16] are discussed in the Appendix.

At baseline, patients in PAOLA-1 [9] generally had more advanced disease and less favourable prognostic characteristics than those in SOLO1 [3] (Appendix). This PA-ITC analysis adjusted for imbalances between the studies in these and other baseline characteristics.

Weighting PAOLA-1 BRCaM patients to be similar in baseline characteristics to SOLO1 had little impact on the PAOLA-1 safety results, although results of this analysis should be interpreted with caution as it was not adjusted for factors that may be prognostic of safety outcomes. The higher rate of grade  $\geq 3$  AEs with olaparib plus bevacizumab than with olaparib alone mainly reflects bevacizumab-related hypertension rather than exacerbation of other AEs related to olaparib or bevacizumab. The different methods of handling discontinuations may have contributed to the higher rate of discontinuation for AEs observed in PAOLA-1 than in SOLO1 (Table S4). According to unadjusted data in PAOLA-1 patients with a tumour BRCaM and the SOLO1 population [3], the overall discontinuation rate (excluding discontinuations for disease progression or completion of protocol-defined therapy at 2 years) was similar for olaparib plus bevacizumab (24%) and olaparib (28%) [3] (Appendix).

Results of this PA-ITC analysis provide important information and flexibility for clinicians who would like to give the combination of olaparib plus bevacizumab to newly diagnosed patients with a BRCaM. When considering combination therapy with olaparib plus bevacizumab, factors such as tolerability, the need for regular bevacizumab infusions, and warnings and precautions for bevacizumab should be considered [17,18].

It should be noted that this PA-ITC analysis is hypothesis generating, is subject to certain limitations and does not provide the same level of evidence as a randomised, controlled phase III trial, which could confirm the findings of this analysis. This PA-ITC analysis is a non-randomised comparison and could not address

imbalances in baseline characteristics for which there was insufficient overlap between trials (e.g. regional differences). This analysis was also not adjusted for the differing frequency of planned radiological scans or the differing lengths of follow-up (Appendix). Once both studies are mature, it would be of interest to repeat the PA-ITC analysis to compare the effect of different PARP inhibitor maintenance strategies on second progression-free survival and overall survival. In terms of other potential limitations, PAOLA-1 patients were randomised to olaparib or placebo after the decision to administer bevacizumab in addition to platinum-based chemotherapy had been made, and the effect of administering bevacizumab in combination with platinum-based chemotherapy was not adjusted for in this analysis [9]. Although some patients were excluded (15 PAOLA-1 BRCaM patients and 11 SOLO1 patients) because of incomplete case data, this loss of information is expected to have had little impact on the results of the analysis. It is not known if the results of the PA-ITC analysis would have differed if the SOLO1 population had been adjusted to match the less favourable prognostic characteristics of the PAOLA-1 population.

## 5. Conclusions

Results of this hypothesis-generating PA-ITC analysis support the use of maintenance olaparib alone or in combination with bevacizumab in patients with BRCaM-mutated newly diagnosed, advanced ovarian cancer. The analysis indicates that the relative clinical benefit of bevacizumab appears to be additive and consistent across regimens.

## Contributors

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## Conflict of interest statement

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**Robert Hettle:** reports full-time employment with AstraZeneca and AstraZeneca stock ownership.

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## Appendix A. Supplementary data

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