

# Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab *versus* bevacizumab alone in women with newly diagnosed advanced ovarian cancer

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## Abstract

**Background:** In patients with newly diagnosed ovarian cancer, bevacizumab and poly(ADP-ribose) polymerase (PARP) inhibitors, alone or in combination, have shown benefit as maintenance treatment following platinum-based chemotherapy. However, no trials have compared a PARP inhibitor plus bevacizumab *versus* a PARP inhibitor, or a PARP inhibitor *versus* bevacizumab. We performed an unanchored population-adjusted indirect treatment comparison to estimate the relative efficacy and safety of maintenance treatments for newly diagnosed advanced ovarian cancer.

**Methods:** Analyses were performed using aggregate data from the PRIMA trial and patient-level data from a subset of patients from the PAOLA-1 trial that met surgery and staging eligibility criteria of PRIMA. Propensity weights were used to match baseline characteristics of the PAOLA-1 subset to those of the PRIMA population. Analysis was performed in overall (biomarker-unselected) and homologous recombination repair deficiency (HRD)-positive populations.

**Results:** A total of 595/806 (266/387 HRD-positive) PAOLA-1 patients were included. After matching, the effective sample size for PAOLA-1 was 532 (242 HRD-positive). Maintenance olaparib plus bevacizumab reduced the risk of disease progression or death by 43% [hazard ratio (HR) 0.57; 95% confidence interval (CI): 0.47–0.69] *versus* niraparib and by 40% (HR 0.60; 95% CI: 0.49–0.74) *versus* bevacizumab in the biomarker-unselected population and by 43% (HR 0.57; 95% CI: 0.41–0.79) and 60% (HR 0.40; 95% CI: 0.29–0.55), respectively, in the HRD-positive population. Progression-free survival (PFS) benefits of maintenance niraparib and bevacizumab arms were comparable in the biomarker-unselected population (HR 1.07; 95% CI: 0.87–1.32); however, niraparib showed a 30% reduced risk compared with bevacizumab (HR 0.70; 95% CI: 0.51–0.97) in the HRD-positive population.

**Conclusions:** In biomarker-unselected and HRD-positive patients, combination treatment with olaparib plus bevacizumab as maintenance treatment improves PFS for women with newly diagnosed advanced ovarian cancer compared with either bevacizumab or niraparib alone. Results are hypothesis generating and could guide randomised trial design.

**Keywords:** bevacizumab, homologous recombination deficiency, indirect treatment comparison, niraparib, olaparib, ovarian cancer

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## Introduction

The majority (approximately 70%) of patients with newly diagnosed advanced ovarian cancer relapse within 3 years following cytoreductive surgery and platinum-based chemotherapy.<sup>1</sup> Over the past decade, the addition of intravenous bevacizumab to platinum-based chemotherapy followed by maintenance bevacizumab has become a standard of care. This includes treatment of patients at high risk of progression due to poor prognosis or suboptimal debulking surgery.<sup>2–7</sup>

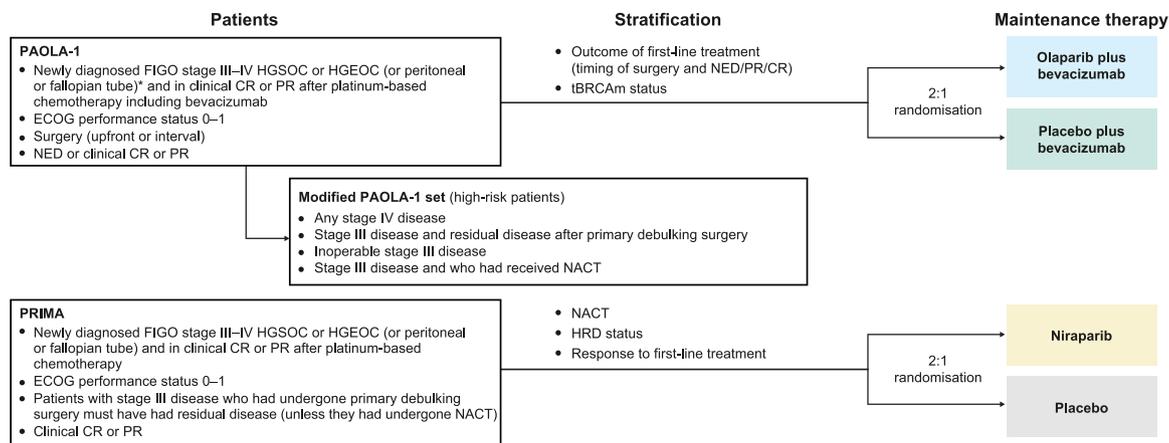
The introduction of poly(ADP-ribose) polymerase (PARP) inhibitors has changed the landscape of ovarian cancer treatment. Sensitivity to PARP inhibition occurs due to synthetic lethality in tumour cells with defects in the homologous recombination repair pathway.<sup>8,9</sup>

The landmark SOLO1 study was the first to assess the efficacy and safety of a PARP inhibitor as maintenance therapy for patients with advanced ovarian cancer and a germline *BRCA1* and/or *BRCA2* (BRCA) mutation in the newly diagnosed setting.<sup>10</sup> More recently, results from a number of other phase III studies with PARP inhibitors in the newly diagnosed setting have demonstrated significant progression-free survival (PFS) benefits for patients with newly diagnosed advanced ovarian cancer who were in clinical response following completion of first-line platinum-based chemotherapy, including PAOLA-1, which assessed maintenance olaparib plus bevacizumab *versus* bevacizumab alone [median follow up 22.9 months; median PFS 22.1 *versus* 16.6 months, respectively; hazard ratio (HR) 0.59; 95% confidence interval (CI): 0.49–0.72;  $p < 0.001$ ],<sup>11</sup> and PRIMA, which assessed maintenance niraparib *versus* placebo (median follow up 13.8 months; median PFS 13.8 *versus* 8.2 months, respectively; HR 0.62; 95% CI: 0.50–0.76;  $p < 0.001$ ).<sup>12</sup>

In both PAOLA-1 and PRIMA, the benefit of PARP inhibition was observed in the overall population; however, a greater benefit was observed in the subgroup of patients with a positive homologous recombination deficiency (HRD) test result (based on the presence of a BRCA mutation or genomic instability). In the subgroup of patients with HRD-positive tumours, median PFS in PAOLA-1 was 37.2 months for olaparib plus bevacizumab *versus* 17.7 months for bevacizumab (HR 0.33; 95% CI: 0.25–0.45),<sup>11</sup> and in PRIMA

was 21.9 months for maintenance niraparib *versus* 10.4 months for placebo (HR 0.43; 95% CI: 0.31–0.59;  $p < 0.001$ ).<sup>12</sup> The safety profile of these regimens was consistent with previous reports, with anaemia and hypertension the most common grade  $\geq 3$  adverse events with olaparib plus bevacizumab and anaemia and thrombocytopenia most common with niraparib.<sup>11,12</sup>

Based on these trial results, PARP inhibitors are now approved as maintenance therapy in the US and Europe for eligible patients with newly diagnosed ovarian cancer and represent a new standard of care in this setting.<sup>13,14</sup> For reimbursement decision-makers there is a need to determine optimal treatment pathways, taking into account the net health benefits and harms of different therapeutic options and testing strategies, as well as their costs. While the PRIMA and PAOLA-1 randomised controlled trials provide valuable insights on the efficacy and safety of PARP inhibitors *versus* placebo (with or without background bevacizumab), they do not address important questions related to the use of maintenance PARP inhibitor monotherapy as an alternative to bevacizumab, and the addition of bevacizumab to maintenance PARP inhibitor therapy *versus* PARP inhibitor monotherapy. Further, comparison of trial results are confounded by differences in the design of the studies, including the recruitment of a high-risk patient population in the PRIMA study and use of an active background treatment in PAOLA-1.<sup>11,12</sup> The open-label phase II AVANOVA trial [ClinicalTrials.gov identifier: NCT02354131] has provided evidence that the addition of bevacizumab to PARP inhibitor (niraparib) improves PFS *versus* PARP inhibitor alone;<sup>15</sup> however, it is investigating upfront treatment rather than maintenance therapy in platinum-sensitive recurrent ovarian cancer and therefore results may not be generalisable to maintenance olaparib plus bevacizumab in the newly diagnosed setting following response to platinum-based chemotherapy. Three studies are planned to assess PARP inhibitor plus bevacizumab *versus* PARP inhibitor alone in the newly diagnosed setting: ENGOT-ov57 (niraparib), NIRVANA/ENGOT-ov63 (niraparib), and MITO-25 [ClinicalTrials.gov identifier: NCT03462212; rucaparib]. In the absence of head-to-head studies, indirect treatment comparison (ITC) methods can be used to bridge the current evidence gap. These include population-adjusted ITCs, which can enable the comparison of study results despite differences in populations



**Figure 1.** PAOLA-1 and PRIMA study designs.

\*Patients with other epithelial non-mucinous ovarian cancers were eligible if they had a germline BRCA mutation.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; NACT, neoadjuvant chemotherapy; NED, no evidence of disease; PR, partial response; tBRCAm, tumour BRCA mutation.

and the absence of randomised evidence to bridge between the different control arms of PRIMA and PAOLA-1.

We conducted a series of population-adjusted ITCs to estimate the relative efficacy and safety of combination PARP inhibitor plus bevacizumab, PARP inhibitor monotherapy, bevacizumab monotherapy and placebo. Consistent with the approvals of PARP inhibitors, the ITC is reported for patients with biomarker-unselected newly diagnosed ovarian cancer per the full intention-to-treat (ITT) populations of PAOLA-1 and PRIMA, and for a subgroup of patients with a positive HRD test result. The results of this analysis are intended to provide insight into the efficacy and safety of PARP inhibitors and bevacizumab in newly diagnosed ovarian cancer, inform the economic assessment of maintenance treatment options for newly diagnosed ovarian cancer and identify research priorities, including guiding future head-to-head studies.

## Methods

Figure 1 summarises the study designs of PAOLA-1 [ClinicalTrials.gov identifier: NCT 02477644] and PRIMA [ClinicalTrials.gov identifier: NCT02655016], including the randomised double-blind design, key patient inclusion criteria and treatment regimens.<sup>11,12</sup> PAOLA-1 and PRIMA were performed in accordance with the principles of the Declaration of Helsinki and Good

Clinical Practice guidelines under the auspices of independent data monitoring committees, and all patients provided written informed consent.<sup>11,12</sup> Compared with PRIMA, patients from PAOLA-1 represent a broader population with less restrictive criteria for eligibility based on surgical outcomes and the requirement to demonstrate a platinum response. PAOLA-1 included patients with newly diagnosed stage III/IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer irrespective of previous surgical outcome. In contrast, PRIMA included patients with newly diagnosed stage III/IV high-grade serous or endometrioid ovarian cancer, peritoneal cancer or fallopian-tube cancer in which patients with stage III disease required incompletely resected cancer after primary debulking surgery or inoperable disease or receipt of neoadjuvant chemotherapy. Furthermore, whereas PRIMA initially excluded patients with disease >2cm and excluded those with CA-125 levels that were not decreased by >90%, PAOLA-1 permitted patients with disease >2cm, as well as patients with any CA-125 levels, provided they were not rising.

In both trials, the primary endpoint of PFS was defined as the time from randomisation to disease progression (by Response Evaluation Criteria in Solid Tumours v1.1) or death; PAOLA-1 data were based on investigator assessment, whereas PRIMA data were based on real-time blinded independent central review.

HRD-positive subgroups were analysed in both trials. Patients were classified as HRD-positive if they had a tumour BRCA mutation or an HRD score of  $\geq 42$  on the Myriad myChoice<sup>®</sup> CDx test (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA).

In order to estimate the relative efficacy of these regimens, an unanchored population-adjusted ITC was carried out in line with published guidance.<sup>16</sup> The lack of a common comparator arm across studies (the comparator was placebo in PRIMA and placebo plus bevacizumab in PAOLA-1) and the absence of randomised studies of bevacizumab *versus* placebo in the maintenance-only setting prevented the use of conventional ITCs or network-based methods. Further, as outlined above, a population-adjusted method was required to adjust for differences in study inclusion criteria. Accordingly, the analysis was performed on the subset of PAOLA-1 that would have met the staging and surgical eligibility criteria for PRIMA (see Supplemental Figure 1 for an infographic of the methodology used). This resulted in a modified set of PAOLA-1 patients with any stage IV disease; stage III disease and residual disease after primary debulking surgery; inoperable stage III disease; and patients with stage III disease who had received neoadjuvant chemotherapy (Figure 1).

The modified PAOLA-1 set was matched to the PRIMA cohort using a reweighting method similar to inverse propensity-score weighting.<sup>16,17</sup> Weights were estimated using the methods of moments approach outlined by Signorovitch *et al.*<sup>17</sup> For each cohort in the analysis (biomarker-unselected and HRD-positive), we derived a set of weights that minimised the difference in baseline characteristics between the modified PAOLA-1 set and the data reported for the niraparib arm of PRIMA. Weights were generated separately for each arm of the modified PAOLA-1 set (e.g. the olaparib plus bevacizumab in the HRD-positive cohort was matched to the baseline data for niraparib in the HRD-positive cohort).

Weights were estimated to match on all relevant prognostic and effect modifiers for PFS. These factors were identified *via* a series of multivariate Cox regression analyses of individual patient data in PAOLA-1. Matching variables included factors that were either prognostic or were an effect modifier for PFS at the 20% significance level. The

PRIMA stratification factors of response to therapy and prior use of neoadjuvant chemotherapy were included regardless of their association with PFS in PAOLA-1.

The estimated weights were summarised using histogram plots and presented alongside estimates of the effective sample size (ESS; see Supplemental Figures 2 and 3). The ESS represents the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate.<sup>16</sup> A large reduction in ESS would indicate a lack of population overlap between studies, which may lead to unstable weight estimates. The weight distributions were inspected for extreme or highly variable weights.

Following matching, weighted Kaplan–Meier curves for PFS were generated for the modified PAOLA-1 set using individual patient data; regenerated Kaplan–Meier curves for the niraparib and placebo arms of PRIMA were created using pseudo-patient-level data from the published PRIMA Kaplan–Meier curves using the methods of Guyot *et al.*<sup>18</sup> HRs were calculated using unstratified semi-parametric Cox regression analysis; 95% CIs were calculated using a robust sandwich estimator. Median PFS times and the probability of being progression free at landmark time points were calculated using weighted Kaplan–Meier methodology.

Efficacy analyses were carried out on the primary endpoints of radiological PFS in both the biomarker-unselected and HRD-positive populations. Results were considered nominally significant at a 5% level without controlling for multiplicity.

Safety analyses were conducted on the risk of any grade, and any grade 3 or above adverse events, as well as individual adverse events commonly associated with PARP inhibitors (haematological, fatigue, nausea, vomiting) and bevacizumab maintenance treatment (hypertension). The analysis was limited to the biomarker-unselected population due to the absence of safety data reported for the HRD-positive population in PRIMA. Data were generated using the propensity weights for the PFS analysis and compared with safety data reported in PRIMA. A sensitivity analysis was performed using safety data from the individualised dosing subgroup of PRIMA.

## Results

### Populations

Of the 806 total patients randomised in PAOLA-1, 595 met the surgical and staging inclusion criteria for PRIMA and were included in this analysis. For the PRIMA trial, pseudo-patient-level data for all 733 patients randomised in the study were used. For the HRD-positive population, 266 of the 387 patients in PAOLA-1 met the surgical and staging inclusion criteria for PRIMA and were used in this analysis alongside pseudo-patient-level data for all 373 HRD-positive patients from PRIMA.

A series of multivariate Cox regression analyses of prognostic factors and effect modifiers in PAOLA-1 identified variables for the matching analysis in both the ITT and HRD-positive populations (Supplemental Table 1). Eight variables were matched in the ITT population and seven for the HRD-positive population; these included the stratification variables for PRIMA, as well as International Federation of Gynecology and Obstetrics stage, BRCA and HRD status, and age in years.

Following weighting of PRIMA-eligible PAOLA-1 patients to match the PRIMA cohort, the ESSs for the PAOLA-1 cohorts were  $n = 357.5$  for olaparib plus bevacizumab biomarker-unselected,  $n = 163.5$  for olaparib plus bevacizumab HRD-positive,  $n = 173.7$  for placebo plus bevacizumab biomarker-unselected and  $n = 78.8$  for placebo plus bevacizumab HRD-positive. Post-matching, baseline characteristics were fully balanced across the PAOLA-1 and PRIMA cohorts in the biomarker-unselected and HRD-positive populations (Table 1). Matching PAOLA-1 patients to PRIMA baseline data had a small positive impact on PFS curves for PAOLA-1 in both the biomarker-unselected and HRD-positive populations (Supplemental Figure 4).

### Efficacy in the biomarker-unselected population

After matching, median PFS in the biomarker-unselected population was 21.4 months (95% CI: 19.2–22.1) for patients in the olaparib plus bevacizumab arm, 16.0 months (95% CI: 14.3–17.7) for patients in the placebo plus bevacizumab arm, 13.8 months (95% CI: 11.5–15.3) for patients in the niraparib arm and 8.1 months (95% CI: 7.31–8.51) for patients in the placebo arm (Figure 2).

Figure 3(a) shows that maintenance olaparib plus bevacizumab was associated with statistically significant improvements in PFS compared with either placebo plus bevacizumab, niraparib or placebo, reducing the risk of disease progression by 40% (HR 0.60; 95% CI: 0.49–0.74), 43% (HR 0.57; 95% CI: 0.47–0.69) and 67% (HR 0.33; 95% CI: 0.26–0.42), respectively. Maintenance niraparib and maintenance placebo plus bevacizumab were both associated with statistically significant improvements in PFS compared with placebo, reducing the risk of disease progression by 41% (HR 0.59; 95% CI: 0.47–0.74) and 45% (HR 0.55; 95% CI: 0.43–0.70), respectively [Figure 3(a)]. The risk of disease progression was similar between maintenance niraparib and placebo plus bevacizumab [Figure 3(a)].

### Efficacy in the HRD-positive population

Results for the HRD-positive population showed a median PFS of 36.0 months [95% CI: 23.2–not available (NA)] for patients in the olaparib plus bevacizumab arm, 17.6 months (95% CI: 14.7–19.6) for patients in the placebo plus bevacizumab arm, 22.0 months (95% CI: 19.3–NA) for patients in the niraparib arm and 10.5 months (95% CI: 8.05–12.1) for patients in the placebo arm (Figure 4).

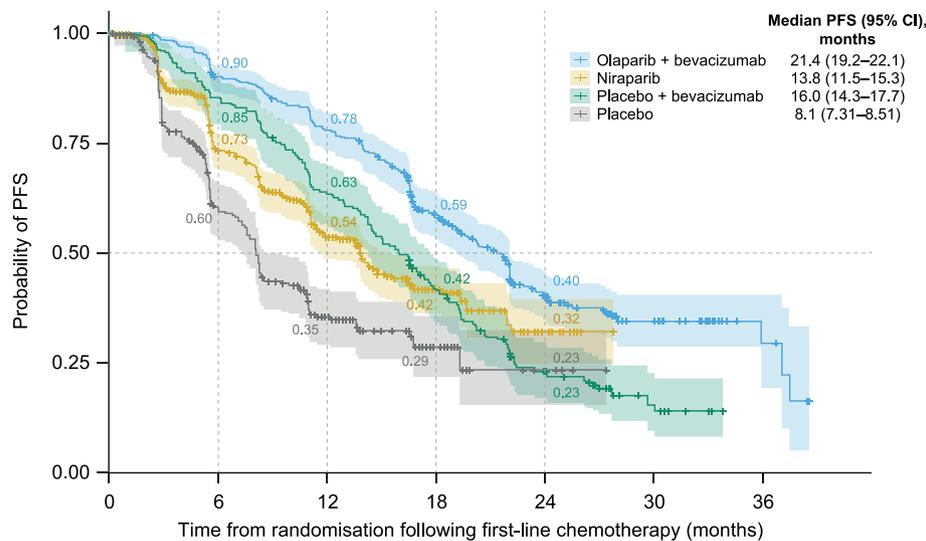
Figure 3(b) shows that for HRD-positive patients, maintenance olaparib plus bevacizumab was associated with statistically significant improvements in PFS compared with either placebo plus bevacizumab, niraparib or placebo alone, reducing the risk of disease progression by 60%, 43% and 77%, respectively. Maintenance niraparib was associated with statistically significant improvements in PFS compared with either placebo plus bevacizumab or placebo, reducing the risk of disease progression by 30% and 59%, respectively. Placebo plus bevacizumab was associated with a statistically significant improvement in PFS compared with placebo, reducing the risk of disease progression by 42% [Figure 3(b)].

### Efficacy in the HRD-negative population

Due to the limited reporting of baseline summary data for the HRD-negative subgroup of PRIMA, it was not feasible to repeat the population-adjusted indirect comparison methodology used for the HRD-positive and biomarker-unselected populations in the HRD-negative population.

**Table 1.** Baseline characteristics, pre- and post-matching.

Characteristic	Pre-matching		Post-matching		Target	
	Olaparib + bevacizumab	Placebo + bevacizumab	Olaparib + bevacizumab	Placebo + bevacizumab	Niraparib <sup>12</sup>	Placebo <sup>12</sup>
<b>Biomarker-unselected patients</b>						
	n=399	n=196	ESS=358	ESS=174	n=487	n=246
FIGO stage IV, %	39.8	42.3	34.7	34.7	34.7	35.8
Neoadjuvant chemotherapy, %	66.7	66.8	66.1	66.1	66.1	67.9
Partial response to prior chemotherapy, %	29.3	30.1	30.8	30.8	30.8	30.0
BRCAm, %	28.3	26.5	31.2	31.2	31.2	28.9
Positive HRD test, %	44.4	45.4	50.7	50.7	50.7	51.2
Age, years*	61.2	60.3	62	62	62	62
CA-125 ≤ ULN, %	83.5	84.2	92.4	92.4	92.4	91.9
ECOG performance status 0, %	68.9	68.4	69.2	69.2	69.2	70.7
No residual disease post-surgery**	46.4	44.4	45.4	44.1	47 <sup>19</sup>	NA
<b>HRD-positive patients</b>						
	n=177	n=89	ESS=164	ESS=79	n=247	n=126
FIGO stage IV, %	41.2	47.2	34.8	34.8	34.8	38.1
Neoadjuvant chemotherapy, %	62.1	59.6	63.2	63.2	63.2	63.5
Partial response to prior chemotherapy, %	27.1	29.2	25.1	25.1	25.1	26.2
BRCAm, %	63.8	58.4	61.5	61.5	61.5	56.3
Positive HRD test, % <sup>†</sup>	100	100	100	100	100	100
Age, years*	58.5	58.5	58.0	58.0	58	58
CA-125 ≤ ULN, %	87.6	88.8	95.5	95.5	95.5	95.2
ECOG performance status 0, %	74.6	76.4	73.7	73.7	73.7	77.0
*Mean for PAOLA-1, median for PRIMA.						
**Variable not matched.						
BRCAm, deleterious BRCA1 and/or BRCA2 mutation; CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; NA, not available; ULN, upper limit of normal.						



**Figure 2.** Population-adjusted indirect treatment comparison\* of progression-free survival: Kaplan-Meier curves in biomarker-unselected patients.

\*Analyses were performed using aggregate data from the PRIMA trial and patient-level data from a subset of patients from the PAOLA-1 trial that met surgery and staging eligibility criteria of PRIMA. Propensity weights were used to match baseline characteristics of the PAOLA-1 subset to those of the PRIMA population. Following matching, weighted Kaplan-Meier curves for progression-free survival were generated.

CI, confidence interval; PFS, progression-free survival.

Hence, an alternative approach was used (see Supplemental Appendix), and results are reported in Supplemental Table 2.

#### Safety in biomarker-unselected population

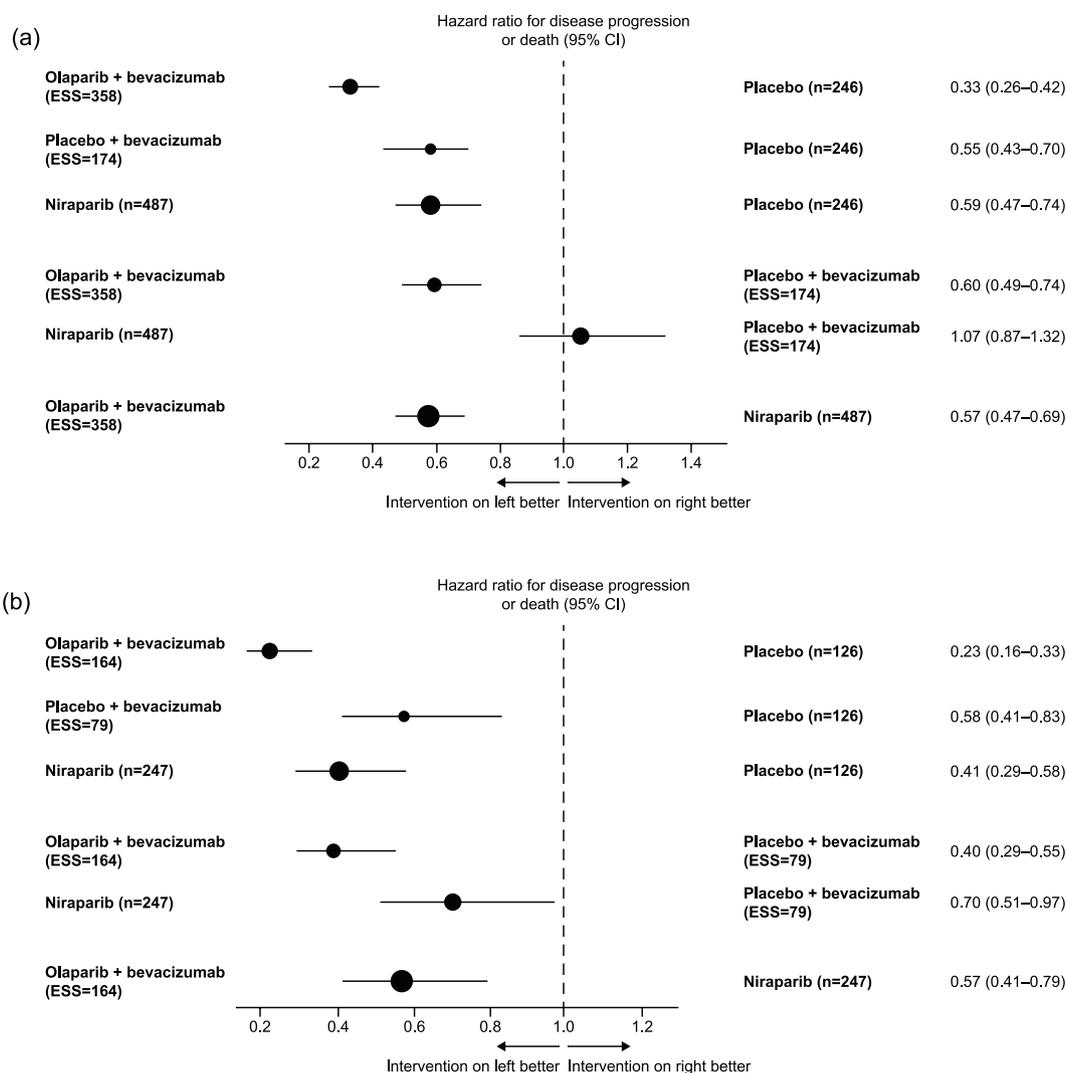
Table 2 shows a summary of safety data after matching of the modified PAOLA-1 set to PRIMA. Most patients experienced adverse events (any grade: 100% olaparib plus bevacizumab; 96% placebo plus bevacizumab; 99% niraparib and 92% placebo).<sup>12</sup> The frequency of adverse events of grade  $\geq 3$  was higher for maintenance niraparib (70%) *versus* olaparib plus bevacizumab (60%) (Table 2). Haematological adverse events (any grade) of anaemia (42% olaparib plus bevacizumab; 64% niraparib), neutropenia (18% olaparib plus bevacizumab; 42% niraparib) and thrombocytopenia (9% olaparib plus bevacizumab; 66% niraparib) were all more common with niraparib compared with olaparib plus bevacizumab. Adverse-event data in patients who received an individualised starting dose of niraparib in PRIMA are reported in Supplemental Table 3.

Fatigue, nausea and vomiting (any grade) occurred with similar frequency in the maintenance olaparib plus bevacizumab (52% fatigue;

51% nausea; 20% vomiting) and maintenance niraparib (51% fatigue; 57% nausea; 22% vomiting) arms (Table 2). Hypertension, a known adverse event of bevacizumab, occurred with higher incidence in both the olaparib plus bevacizumab (46%) and placebo plus bevacizumab (64%) arms compared with niraparib (18%) and placebo (7%).

#### Discussion

In the absence of randomised head-to-head phase III trials, ITCs provide an approach for assessing the relative efficacy and safety of treatment regimens. The conventional approach to indirect comparisons relies on a network of studies, which are connected by a common set of comparators. However, in the absence of a common comparator arm or additional trials that can bridge between studies, methods such as unanchored population-adjusted ITCs can be used. With overlapping populations, under no unobserved confounding, this approach has been shown appropriate for cross-trial comparisons<sup>20</sup> with similar matching-adjusted analyses reported across a range of cancer types.<sup>21–27</sup> The method, nevertheless, makes strong assumptions (detailed later) and thus the results are primarily hypothesis generating rather than confirmatory.



**Figure 3.** Population-adjusted indirect treatment comparison\* of progression-free survival.

Forest plot showing results in (a) biomarker-unselected patients and (b) HRD-positive patients.

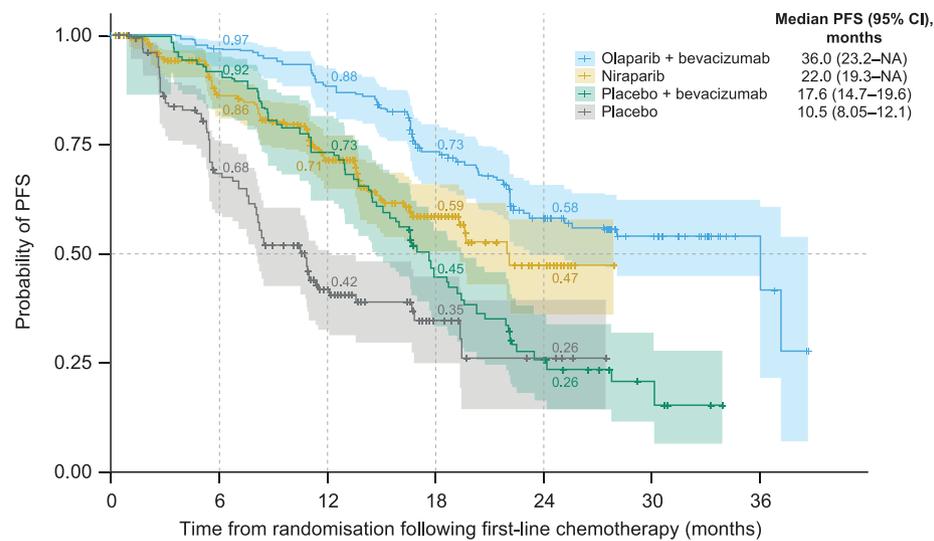
\*Analyses were performed using aggregate data from the PRIMA trial and patient-level data from a subset of patients from the PAOLA-1 trial that met surgery and staging eligibility criteria of PRIMA. Propensity weights were used to match baseline characteristics of the PAOLA-1 subset to those of the PRIMA population. Following matching, hazard ratios and 95% CIs were calculated.

CI, confidence interval; ESS, effective sample size; HRD, homologous recombination deficiency.

In our analysis, a population-adjusted ITC method was used to generate hypotheses to address the absence of a PARP inhibitor monotherapy arm in PAOLA-1 and the absence of a bevacizumab monotherapy arm in PRIMA. As individual patient data were only available for PAOLA-1, these data were weighted so that the baseline characteristics matched those of PRIMA. Matching was possible due to the broad surgical and staging inclusion criteria of PAOLA-1, which encompassed a subset of patients with high-risk disease in line with the eligibility criteria for

PRIMA. There was strong overlap in the characteristics of the higher-risk PAOLA-1 and PRIMA cohorts, resulting in a relatively small loss in ESS after reweighting PAOLA-1 to match PRIMA.

The results of the population-adjusted ITC suggest that treatment with olaparib in combination with bevacizumab as maintenance therapy provided greater PFS benefit *versus* either niraparib or bevacizumab alone in both the biomarker-unselected and HRD-positive populations. Comparison of niraparib and bevacizumab



**Figure 4.** Population-adjusted indirect treatment comparison\* of progression-free survival: Kaplan–Meier curves in HRD-positive patients.

\*Analyses were performed using aggregate data from the PRIMA trial and patient-level data from a subset of patients from the PAOLA-1 trial that met surgery and staging eligibility criteria of PRIMA. Propensity weights were used to match baseline characteristics of the PAOLA-1 subset to those of the PRIMA population. Following matching, weighted Kaplan–Meier curves for progression-free survival were generated.

CI, confidence interval; NA, not available; PFS, progression-free survival.

maintenance monotherapy arms suggested that there was no difference in PFS between these regimens in the biomarker-unselected population; however, in the HRD-positive population, maintenance niraparib suggested greater PFS benefit compared with bevacizumab. These results highlight the importance of HRD testing in determining patient groups most likely to benefit from PARP inhibitor treatment compared with existing standards of care.

Our findings are consistent with data from other ITCs that have assessed a PARP inhibitor plus bevacizumab *versus* PARP inhibitor alone and results of other trials. A recently reported population-adjusted ITC used individual data from the SOLO1 trial (maintenance olaparib *versus* placebo in newly diagnosed advanced ovarian cancer patients with a BRCA mutation) and the subset of patients with a tumour BRCA mutation from PAOLA-1.<sup>28</sup> A PFS benefit was observed with the combination of olaparib plus bevacizumab *versus* olaparib alone as maintenance therapy (HR 0.71; 95% CI: 0.45–1.09), consistent with our findings in the HRD-positive population. Additionally, the HR of 0.55 (95% CI: 0.43–0.70) for bevacizumab *versus* placebo in the ITT population of our ITC is consistent with the results of the phase III GOG-0218 randomised trial, which reported an investigator-assessed PFS HR of 0.62 (95%

CI: 0.52–0.75) for bevacizumab plus chemotherapy followed by maintenance bevacizumab *versus* platinum-based chemotherapy plus placebo.<sup>29</sup> The corresponding Kaplan–Meier curves for PFS show a consistent trend with those in the GOG-0218 trial and predict an improvement in PFS for bevacizumab that ultimately diminishes over time. As with previous randomised studies of bevacizumab, there was evidence of non-proportional hazards across populations in the ITC (see Supplemental Appendix and Supplemental Figures 5 and 6). To assess its impact on results, we performed a restricted mean survival time analysis of PFS up to 24 months. The results of this analysis support the overall conclusions of the study (Supplemental Table 4).

Our results are subject to the limitations and assumptions underpinning the unanchored population-adjusted ITC methodology. This includes the assumption of conditional consistency of absolute effects, which refers to the matching of all prognostic and effect modifiers across studies. While reported baseline data were successfully matched in the ITC, including known prognostic factors such as response to prior chemotherapy and use of neoadjuvant therapy, any differences in unobserved or unreported prognostic or effect modifiers may have confounded the results.

**Table 2.** Safety in biomarker-unselected population (%).

	Post-matching			
	Olaparib + bevacizumab (n = 398; ESS = 357)	Placebo + bevacizumab (n = 194; ESS = 172)	Niraparib <sup>13</sup> (n = 484)	Placebo <sup>13</sup> (n = 244)
<b>Adverse event, % (n)</b>				
Any grade: all causes <sup>12</sup>	100	96	99	92
Grade $\geq 3$ <sup>12</sup>	60	53	70	19
<b>Haematological</b>				
Anaemia*				
Any grade	42	10	64	18
Grade $\geq 3$	18	0	31	2
Neutropenia*				
Any grade	18	16	42	8
Grade $\geq 3$	6	3	21	1
Thrombocytopenia*				
Any grade	9	5	66	5
Grade $\geq 3$	2	1	39	<1
<b>Non-haematological</b>				
Nausea				
Any grade	51	23	57	28
Grade $\geq 3$	2	1	1	1
Vomiting				
Any grade	20	11	22	12
Grade $\geq 3$	2	2	1	1
Fatigue*				
Any grade	52	30	51	41
Grade $\geq 3$	5	2	3	1
Hypertension*				
Any grade	46	64	18	7
Grade $\geq 3$	19	33	6	1
*Grouped terms; neutropenia grouped term includes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia. ESS, effective sample size.				

At the time of the analysis, we were unable to match on post-surgical residual disease status due to the lack of published PRIMA data. Since conducting the analysis, data on the total proportion of PRIMA patients (47%) with no residual disease has been reported.<sup>19</sup> These data are comparable with the proportion of patients with no residual disease in the higher-risk biomarker-unselected PAOLA-1 cohort used in the matching analysis; 46% of olaparib plus bevacizumab and 44% of placebo plus bevacizumab. The matching of other clinical characteristics had little impact on the proportion of patients with no residual disease (45% for olaparib plus bevacizumab and 44% for bevacizumab plus placebo). Despite not matching on surgical status, the prevalence of no residual disease after debulking surgery was well balanced across groups in the ITC (47% in PRIMA *versus* 44–45% in the matched biomarker-unselected PAOLA-1 cohort). This finding provides some reassurance that the results of the ITC may be at a low risk of bias from unmatched prognostic factors or effect modifiers.

Additionally, the ITC results may be confounded by differences in the design of the studies, which could not be adjusted for in the ITC. These include differences in the assessment of PFS (investigator assessment every 24 weeks in PAOLA-1 compared with real-time blinded independent central review every 12 weeks in PRIMA), geographical location (Europe and Japan for PAOLA-1; Europe and North America for PRIMA), follow-up time (median follow up was 22.9 months in PAOLA-1 compared with only 13.8 months in PRIMA)<sup>11,12</sup> and the treatment regimen given prior to randomisation in the studies.

The comparison of different assessments of PFS (investigator assessment for PAOLA-1 compared with blinded independent central review for PRIMA) was necessary due to limited reporting of the Kaplan–Meier plot for investigator-assessed PFS in PRIMA, which prevented comparison with PAOLA-1 investigator-assessed PFS. PFS results from investigator-assessed and real-time blinded independent central review in PRIMA were, however, aligned [median PFS in both assessments was 13.8 months for niraparib *versus* 8.2 months for placebo; HR for investigator assessment was 0.63 (0.51–0.76) and HR for blinded independent central review was 0.60 (0.49–0.73)], making comparison of these endpoints appropriate.<sup>12</sup> In terms of the impact of differences in the scheduled frequency of scan

assessments on the results of unanchored population-adjusted ITCs (24 weeks for PAOLA-1; 12 weeks for PRIMA), results of an analysis conducted by Kapetanakis *et al.*<sup>30</sup> suggest that potential bias may be minimal in settings where the survival curve for PFS declines steadily, as is the case in the PRIMA and PAOLA-1 trials. The extent to which differences in follow up, geography and prior therapy use leads to bias after matching on other clinical parameters such as response to therapy is unknown.

Safety results were determined for the safety analysis set of the biomarker-unselected population, with the probability of experiencing an adverse event in the post-matched PAOLA-1 population being generally consistent with the safety results in the main study population for PAOLA-1.<sup>11</sup> Despite shorter median duration of treatment with niraparib compared with olaparib [11.1 months for niraparib (range 0.03–29 months)<sup>13</sup> *versus* 17.3 months for olaparib (range 0.0–33.0 months)],<sup>11</sup> the overall risk of grade  $\geq 3$  adverse events was higher in the niraparib monotherapy arm compared with the olaparib and bevacizumab arm (70 *versus* 60%). This difference may be driven by the higher incidence of haematological adverse events in the niraparib arm; haematological events were higher than in the other treatment arms in our analysis and also higher than reported with other PARP inhibitors.<sup>31</sup> A comparison of treatment discontinuations due to adverse events is not reported due to differences in study design between PAOLA-1 and PRIMA, which would impact on the validity of such an analysis. Additionally, in PAOLA-1, patients who discontinued study treatment were proactively asked about the presence of adverse events at that time, whereas this approach was not taken in PRIMA.<sup>11,12</sup>

Our ITC was performed using data from the full-study population of PRIMA, which comprised niraparib treatment regimens at a fixed starting dose of 300 mg (65% of patients) and an individualised starting dose of 200–300 mg based on body weight and platelet count (35% of patients).<sup>12</sup> The individualised starting dose was introduced during the PRIMA follow up to improve the safety profile of niraparib given high frequencies of dose interruptions and reductions with the fixed starting dose. The individualised starting dose is the recommended posology for niraparib in clinical practice.<sup>32</sup> Where available, we sought to compare safety results using both the full-study and individualised starting-dose data. With the individualised starting dose, the overall risk of grade  $\geq 3$

adverse events for niraparib was equivalent to the risk for the combination of olaparib and bevacizumab, whereas the risk of grade  $\geq 3$  haematological events remained numerically higher for niraparib (Supplemental Table 2).<sup>13,33</sup>

At the time of analysis, insufficient data were available to compare the efficacy of the individualised starting dose for niraparib with the regimens of PAOLA-1. However, recently reported efficacy data suggest similar, albeit numerically lower, efficacy based on PFS for the individualised *versus* fixed starting dose in the biomarker-unselected and HRD-positive cohorts of PRIMA.<sup>34</sup> If the effect of individualised dosing is consistent with fixed dosing, then the results of the ITC are generalisable to clinical practice regardless of the dosing regimen used. Otherwise, the ITC results may overestimate the efficacy of the individualised dose of niraparib.

Our study used established methodology to address differences between the studies that would otherwise prevent an informative ITC between PAOLA-1 and PRIMA. It has been argued that population-adjusted ITCs between PRIMA and PAOLA-1 are not feasible due to lack of overlap in the populations enrolled in the studies.<sup>35</sup> Specifically, it has been noted that the PAOLA-1 study has wider inclusion criteria than PRIMA, including stage III patients with no residual disease after primary debulking surgery. The exclusion of these patients from PRIMA prevents comparison of PRIMA with the broader full-study population of PAOLA-1. However, as the higher-risk PRIMA population is a subgroup of PAOLA-1, we were able to match this cohort of PAOLA-1 to PRIMA and estimate the comparative efficacy and safety of treatments in the higher-risk population.

The results of the ITC are hypothesis generating and may inform areas of future clinical research. Our results showed a benefit for niraparib and combination olaparib plus bevacizumab *versus* bevacizumab alone in HRD-positive patients. Outside of HRD-positive patients, and in a biomarker-unselected population, niraparib monotherapy does not appear to confer significant PFS benefit *versus* bevacizumab alone. Further study of the role of PARP inhibitors and bevacizumab in HRD-negative or unknown patients is warranted. The inclusion criteria of PRIMA also limited the scope of the ITC to higher-risk patients. These results may not be generalisable to the population with stage III disease and complete resection after

primary surgery. Hence, further study of the role of niraparib *versus* bevacizumab, with or without olaparib, in patients with lower-risk disease may also be warranted. Other areas of potential future clinical study include the role of individualised dosing in the comparative efficacy and safety of niraparib *versus* other treatment options, as well as further study of the comparative safety of treatments in clinical practice.

The use of different PARP inhibitors in PAOLA-1 (olaparib) and PRIMA (niraparib) may have affected the results of the ITC when comparing between monotherapy PARP inhibitor and combination PARP inhibitor and bevacizumab. For example, the improvement in PFS suggested for olaparib plus bevacizumab *versus* niraparib alone may relate to differences in the efficacies of olaparib and niraparib, as well as the effect of adding bevacizumab to olaparib. Potential for efficacy differences across PARP inhibitors in the first-line setting is currently unknown, owing to a lack of head-to-head studies. The ITC results should therefore be interpreted as a comparison of the regimens in PAOLA-1 (olaparib plus bevacizumab, bevacizumab) and PRIMA (niraparib), and care should be taken when extrapolating these results to other PARP inhibitor monotherapy or combination regimens.

Effective trial design to ensure clinically relevant questions are addressed is of great importance. Our results may guide more specific aspects of trial design, for example, indirect comparison of adverse events may allow trial designers to make a more informed decision regarding the risk–benefit ratio of PARP inhibitor plus bevacizumab *versus* PARP inhibitor alone, and therefore to balance whether a head-to-head study should be conducted. In addition, the point estimates and 95% CI for effect size determined by our analysis provide critical information to trial designers who must prospectively state the size of the anticipated effect and use this to calculate sample size. Utilisation of point estimates based on robust ITC methodology is superior to other determinants of effect size, such as retrospective analyses of institutional databases, highlighting the utility of our work.

In conclusion, we used a population-adjusted ITC method to compare the efficacy and safety of olaparib plus bevacizumab *versus* niraparib as maintenance treatment in the newly diagnosed advanced ovarian cancer setting due to the absence of a common comparator arm in the PAOLA-1 and PRIMA trials. Results suggest that in patients with either biomarker-unselected or

HRD-positive tumours, the combination of olaparib plus bevacizumab as maintenance treatment improves PFS for women with newly diagnosed advanced ovarian cancer, compared with either bevacizumab or niraparib alone. These data provide important insight into the roles of PARP inhibitors and bevacizumab, which may guide the design of future ovarian cancer trials. Additionally, these findings support the use of HRD testing at diagnosis to determine the most appropriate treatment for women with newly diagnosed advanced ovarian cancer.

### Author note

Richard Davidson during the study of this article was an employee of AstraZeneca, and owned stock.

### Conflict of interest statement

Robert Hettle and Charles McCrea are employees of AstraZeneca, and own stock. Chee Khoon Lee reports honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, GSK, Pfizer, Roche and Takeda; consulting or advisory roles for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Pfizer, Roche and Takeda; institutional research funding from AstraZeneca; and travel support from AstraZeneca and Boehringer Ingelheim.

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### Supplemental material

Supplemental material for this article is available online.

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