



Society of Gynecologic Oncology

# SGO 20/20

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# Population-adjusted indirect comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 studies of olaparib with or without bevacizumab, bevacizumab alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation

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# Disclosures

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# Introduction

- There is a need to understand the role of **bevacizumab** in the maintenance treatment of patients with newly diagnosed **BRCA-mutated** ovarian cancer (GOG218)<sup>1</sup>
- With data from the Phase III SOLO1<sup>2</sup> and PAOLA-1<sup>3</sup> trials of olaparib maintenance in patients with newly diagnosed advanced ovarian cancer, a **population-adjusted indirect treatment comparison** was conducted to assess the comparative efficacy of:
  - Bevacizumab monotherapy versus placebo
  - Olaparib monotherapy versus bevacizumab monotherapy
  - Olaparib plus bevacizumab versus olaparib monotherapy
  - Olaparib plus bevacizumab versus placebo

1. Norquist BM *et al.* *Clin Cancer Res* 2018;24:777–83; 2. Moore K *et al.* *N Engl J Med* 2018;379:2495–505; 3. Ray-Coquard I *et al.* *N Engl J Med* 2019;381:2416–28

# PAOLA-1 and SOLO1 trial designs

## PAOLA-1

- Newly diagnosed FIGO stage III–IV HGSOC or HGEOC (or peritoneal)\* and in clinical complete response or partial response after **platinum-based chemotherapy including bevacizumab<sup>†</sup>**
- ECOG performance status 0–1
- Surgery (upfront or interval)
- **tBRCAm or non-tBRCAm status**

### Stratification

- tBRCAm status<sup>‡</sup>
- First-line treatment outcome<sup>§</sup>

2:1  
randomization

**Olaparib (300 mg bid)  
plus bevacizumab<sup>†</sup>**  
N= 537

**Placebo plus  
bevacizumab<sup>†</sup>**  
N=269

### Maintenance therapy

## SOLO1

- Newly diagnosed, FIGO stage III–IV HGSOC or HGEOC (or peritoneal)\* and in clinical complete response or partial response after **platinum-based chemotherapy**
- ECOG performance status 0–1
- Surgery (upfront or interval)
- **Germline or somatic BRCAm**

### Stratification

- Response to first-line platinum chemotherapy

2:1  
randomization

**Olaparib (300 mg bid)**  
N=260

**Placebo**  
N=131

\*Patients with other epithelial non-mucinous ovarian cancers were eligible if they had a germline BRCAm; <sup>†</sup>Bevacizumab: 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy;

<sup>‡</sup>By central laboratories; <sup>§</sup> According to timing of surgery and NED/CR/PR

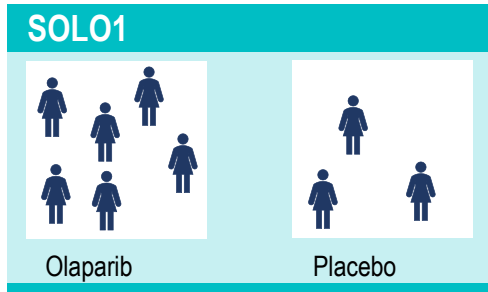
bid, twice daily; BRCAm, BRCA1 and/or BRCA2 mutation; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; NED, no evidence of disease; PR, partial response; tBRCAm, tumor BRCA1 and/or BRCA2 mutation

# Methods

- An **unanchored, population-adjusted indirect comparison** was performed for the endpoint of investigator-assessed PFS (RECIST v1.1).<sup>1</sup> This comparison **used individual patient data** from the SOLO1 trial and from the subset of patients with a **tBRCAm in PAOLA-1**
- A **propensity score weighting technique** was used to minimize differences in observable characteristics between the trial populations
  - The weights assigned to individuals in PAOLA-1 were related to the probability of being in the olaparib arm of SOLO1\*
  - Matching variables identified for adjustment were tumor location, ECOG status, histologic type, FIGO stage, type of surgery, residual disease, response to first-line treatment, and age
- **Weighted Cox regression and Kaplan–Meier** analyses were performed to estimate the comparative efficacy of different treatment strategies

All analyses were performed in patients with complete baseline data. Although this indirect treatment analysis is based on accepted methodology, it was not possible to address all differences in baseline characteristics as the analysis was non-randomized. \*The olaparib arm of SOLO1 was selected as the target population as it represents the current standard of care for patients with newly diagnosed advanced ovarian cancer and a BRCAm  
1. Phillippo DM *et al.* NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2018  
PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

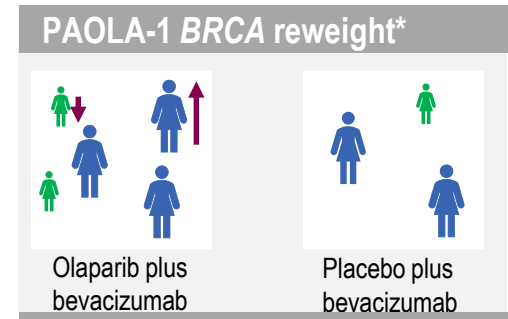
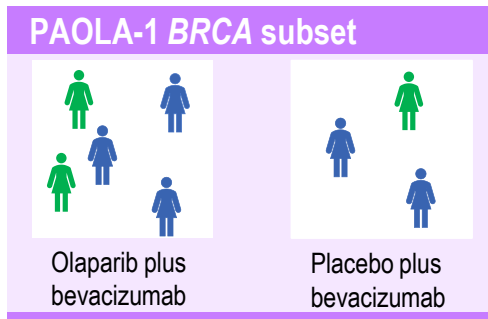
# Methods



## Propensity weighting

Patients were reweighted to achieve balance in key baseline characteristics

PAOLA-1 patients who were SOLO1-like received greater weight than those who were not SOLO1-like



The olaparib arm of SOLO1 was selected as the target population as it represents the current standard of care for patients with newly diagnosed advanced ovarian cancer and a BRCAm. All analyses were performed in patients with complete baseline data. \*Icons sized to denote weights

# Key baseline characteristics (pre-adjustment)

	PAOLA-1 (tBRCAm subset)			SOLO1		
	Olaparib plus bevacizumab N=151	Placebo plus bevacizumab N=71	Overall N=222	Olaparib N=254	Placebo N=126	Overall N=380
Tumor location (% ovary)	85	92	87	85	86	85
ECOG (% status 1)	25	24	25	23	19	22
<b>FIGO (% stage IV)</b>	<b>28</b>	<b>31</b>	<b>29</b> ←	<b>14</b>	<b>18</b>	<b>16</b> ←
Surgery (% interval)*	43	38	41	37	34	36
<b>Residual disease (%)</b>	<b>32</b>	<b>30</b>	<b>32</b> ←	<b>22</b>	<b>23</b>	<b>22</b> ←
First-line outcome (% PR)	15	17	16	26	21	24
Mean age (years)	57.0	55.0	56.4	53.6	53.4	53.5
Age (% ≥65 years)	22	15	20	13	15	14

Population imbalances could potentially lead to differences in PFS outcomes between arms, irrespective of treatment assignment

The analyses were performed on the SOLO1 data and the subset of patients in PAOLA-1 who had confirmed tBRCAm. All analyses were performed in patients with complete data on matching variables. Ten patients from the original PAOLA-1 olaparib + bevacizumab cohort, nine patients from the original PAOLA-1 placebo + bevacizumab cohort, six patients from the original SOLO1 olaparib cohort, and five patients from the original SOLO1 placebo cohort had missing values for matching variables; therefore, they were excluded. The implications of removing those with missing data was assessed. Although this indirect treatment analysis is based on accepted methodology, it was not possible to address all differences in baseline characteristics as the analysis is non-randomized. In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. \*Patients who did not have surgery were excluded from this population-adjusted indirect treatment comparison



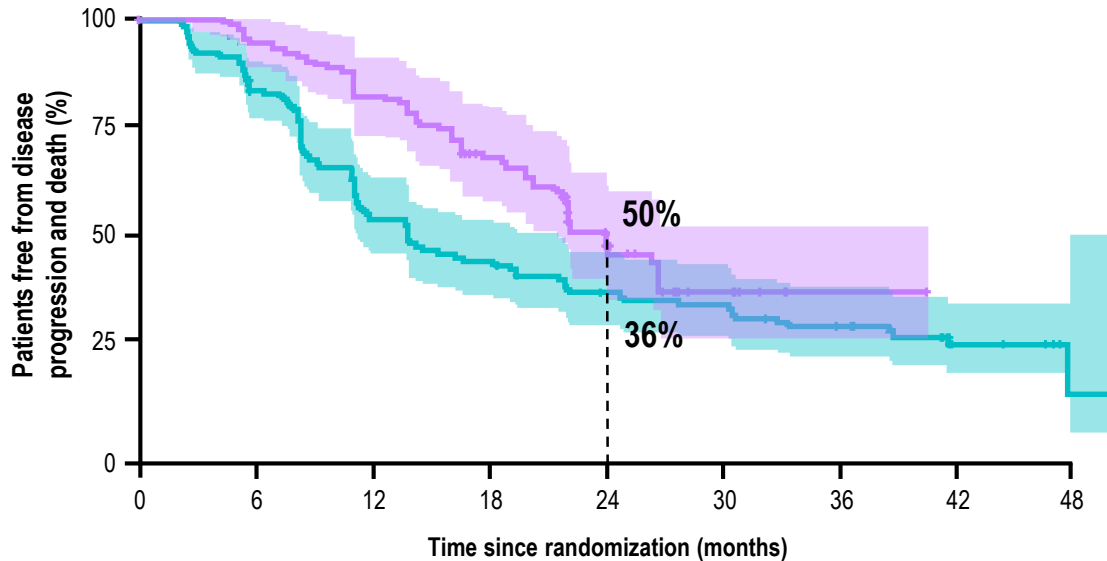
# Adjusted baseline characteristics

	PAOLA-1 (tBRCAm subset)		SOLO1	
	Olaparib plus bevacizumab* N=151 ESS=110.8	Placebo plus bevacizumab* N=71 ESS=54.7	Olaparib N=254	Placebo N=126
Tumor location (% ovary)	84	88	85	86
ECOG (% status 1)	23	29	23	19
<b>FIGO (% stage IV)</b>	<b>14</b>	<b>16</b> ←	<b>14</b>	<b>18</b> ←
Surgery (% interval)†	40	37	37	34
<b>Residual disease (%)</b>	<b>26</b>	<b>22</b> ←	<b>22</b>	<b>23</b> ←
First-line outcome (% PR)	19	17	26	21
Mean age (years)	54.3	53.9	53.6	53.4
Age (% ≥65 years)	16	13	13	15

The weighted PAOLA-1 BRCAm subset of patients had comparable baseline data to the SOLO1 patients, with 14% with FIGO stage IV and 26% with residual disease after surgery, with the exception of first-line outcome

All analyses were performed in patients with complete data on matching variables. The analyses were performed on the SOLO1 data and the subset of patients in PAOLA-1 who had confirmed tBRCAm. A sensitivity analysis was conducted to assess the impact of the difference in first-line outcome. This sensitivity analysis found that the different CR rates across arms had little impact on the hazard ratios estimated from the weighted Cox proportional hazards models. \*Values are weight adjusted to match baseline characteristics to the olaparib arm of the SOLO1 trial; †The values for patients who did not have surgery were not weight adjusted. ESS, effective sample size, represents the approximate number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample

# PFS outcomes in the population-adjusted indirect comparison: Bevacizumab monotherapy versus placebo

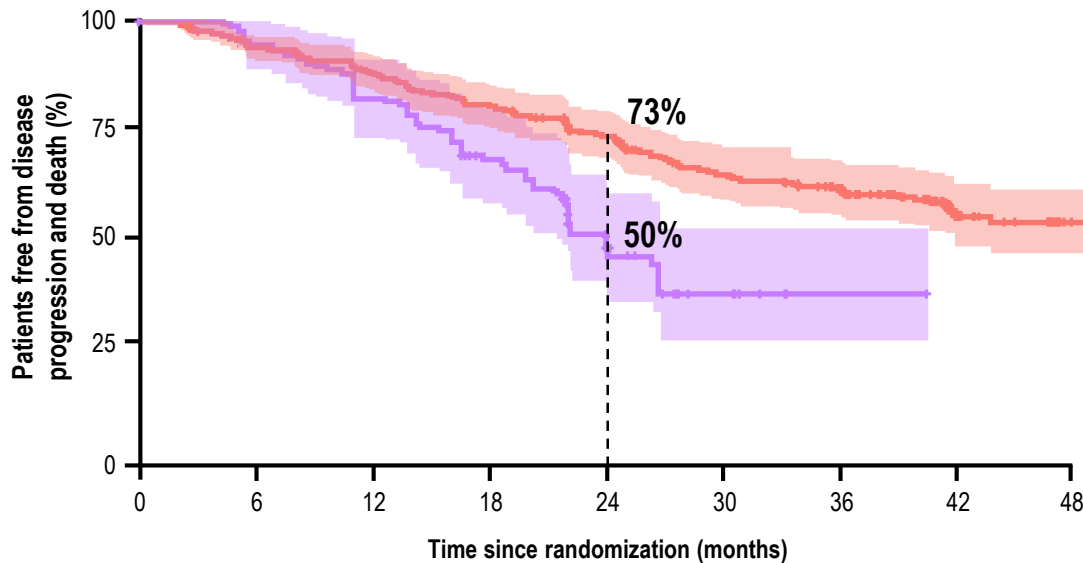


Kaplan–Meier estimate of patients progression-free

	PAOLA-1 tBRCAm subset	SOLO1
	Placebo plus bevacizumab* N=71	Placebo N=126
12 months	81	53
24 months	50	36
<b>HR 0.65 (95% CI 0.43–0.95)†</b>		

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. \*These results are based on weighted outcomes after matching tumor location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment, and age to SOLO1; †CIs generated by bootstrapping  
CI, confidence interval; HR, hazard ratio

# PFS outcomes in the population-adjusted indirect comparison: Olaparib monotherapy versus bevacizumab monotherapy

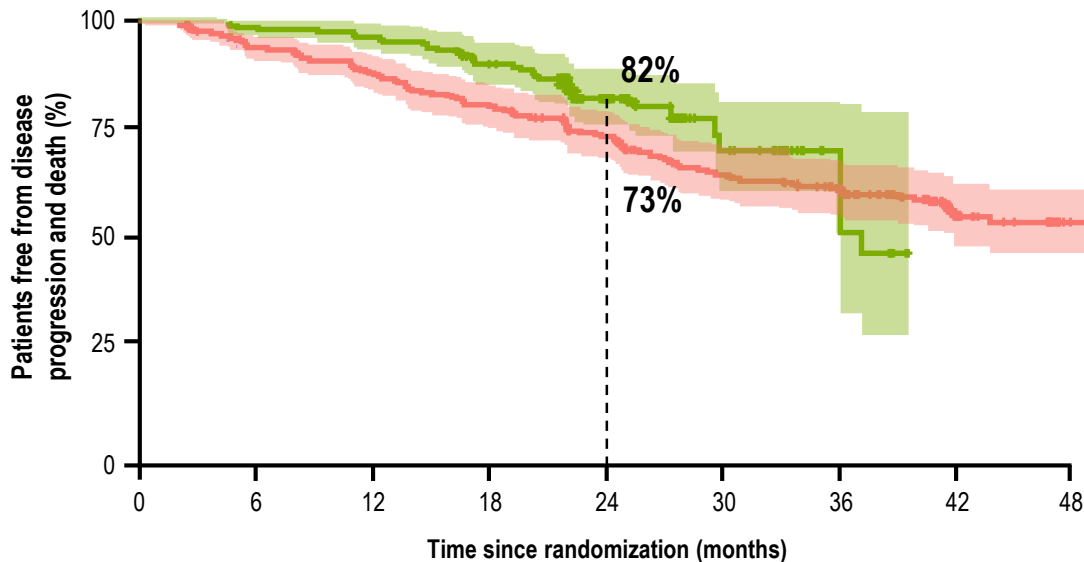


Kaplan–Meier estimate of patients progression-free

	SOLO1	PAOLA-1 tBRCAm subset
	Olaparib	Placebo plus bevacizumab*
	N=254	N=71
12 months	88	81
24 months	73	50
	HR 0.48 (95% CI 0.30–0.75) <sup>†</sup>	

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. \*These results are based on weighted outcomes after matching tumor location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment, and age to SOLO1; <sup>†</sup>CI's generated by bootstrapping

# PFS outcomes in the population-adjusted indirect comparison: Olaparib plus bevacizumab versus olaparib monotherapy

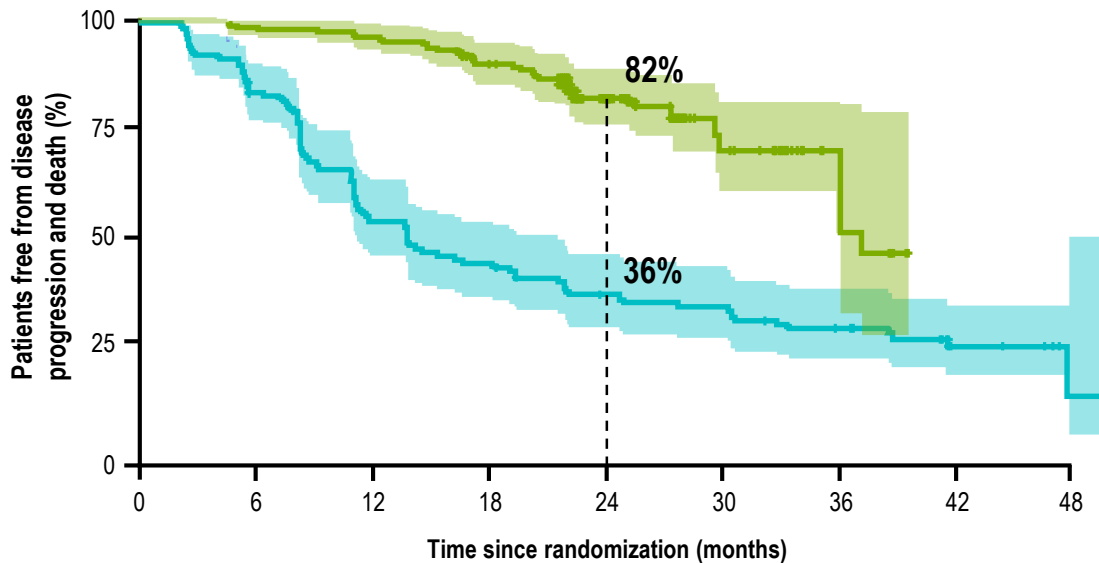


Kaplan–Meier estimate of patients progression free

	PAOLA-1 tBRCAm subset	SOLO1
	Olaparib plus bevacizumab* N=151	Olaparib N=254
12 months	96	88
24 months	82	73
<b>HR 0.71 (95% CI 0.45–1.09)<sup>†</sup></b>		

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. \*These results are based on weighted outcomes after matching tumor location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment, and age to SOLO1; <sup>†</sup>CI's generated by bootstrapping

# PFS outcomes in the population-adjusted indirect comparison: Olaparib plus bevacizumab versus placebo



Kaplan–Meier estimate of patients progression-free

	PAOLA-1 tBRCAm subset	SOLO1
	Olaparib plus bevacizumab* N=151	Placebo N=126
12 months	96	53
24 months	82	36
<b>HR 0.23 (95% CI 0.14–0.34)†</b>		

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. \*These results are based on weighted outcomes after matching tumor location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment, and age to SOLO1; †CIs generated by bootstrapping

# Conclusions

- The PAOLA-1 trial showed that patients with newly diagnosed BRCA-mutated ovarian cancer had a PFS benefit with combination olaparib plus bevacizumab maintenance therapy versus bevacizumab alone<sup>1</sup>
- An unprecedented PFS benefit to patients with a BRCAm receiving maintenance monotherapy was observed with olaparib in the SOLO1 trial<sup>2</sup>
- This population-adjusted indirect treatment comparison suggests that olaparib plus bevacizumab leads to an improvement in PFS versus olaparib alone as maintenance for patients with BRCA-mutated newly diagnosed advanced ovarian cancer

Median follow-up was different for the SOLO1 and PAOLA-1 trials

1. Ray-Coquard I et al. *N Engl J Med* 2019;381:2416–28; 2. Moore K et al. *N Engl J Med* 2018;379:2495–505

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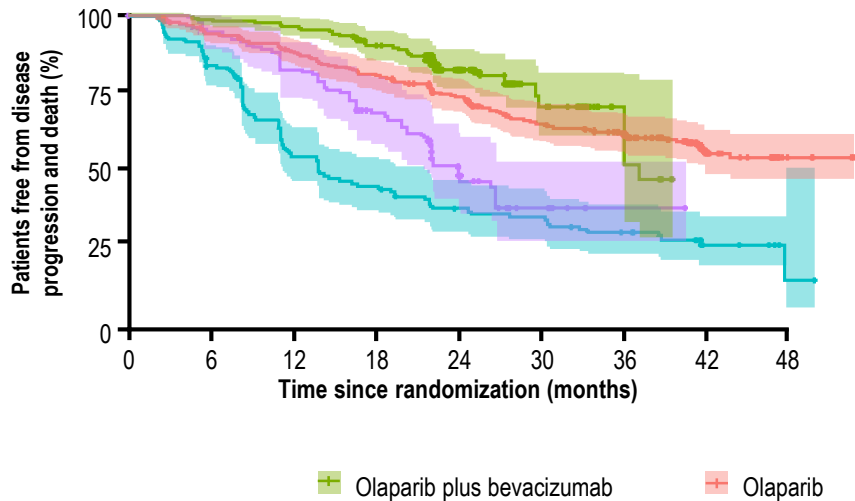
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# Comparison of PFS outcomes in the adjusted and the unadjusted populations

Population-adjusted indirect comparison



Unadjusted population

