Efficacy of maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer according to BRCA mutation genotype in the Phase III PAOLA-1/ENGOT-ov25 trial

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Abstract 5571
Poster 447

INTRODUCTION

- In the Phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644), the addition of maintenance olaparib (ola) to bevacizumab (bev) in patients with newly diagnosed advanced high-grade ovarian cancer (HGOC) resulted in prolonged progression-free survival (PFS), particularly for patients with homologous recombination deficiency (HRD)-positive tumors as determined by a tumor *BRCA1* and/or *BRCA2* mutation (tBRCAm) and/or a genomic instability score ≥42.[1]
- Preclinical data suggest that patients with mutations in the Really Interesting New Gene (RING) domain of BRCA1 are less sensitive to olaparib.[2,3]
- The magnitude of benefit from olaparib plus bevacizumab, according to mutation location in the functional domains of BRCA, remains to be explored.

METHODOLOGY

- This was a *post hoc* analysis of patients with BRCAm from PAOLA-1/ENGOT-ov25, a randomized, double-blind, placebo-controlled, international trial.
- Central genetic analyses performed by Myriad were used.
- **Functional domains of *BRCA1* were defined as:** i) RING domain: amino acids [AA] 8–96; ii) DNA-binding domain [DBD]: AA 452–1092; iii) C-terminal domain of *BRCA1* (BRCT): AA 1646–1736 and 1760–1855.
- **Functional domains of *BRCA2* were defined as:** i) RAD51-binding domain (RAD51-BD): AA 900–2000; ii) DBD: AA 2459–3190.

STATISTICS

- PFS was estimated using the Kaplan–Meier method, and log-rank tests were used to assess the differences between the two treatment arms. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and their associated 95% confidence intervals (CIs).
- A two-tailed $P<0.05$ was considered statistically significant, and data were analyzed using R v4.1.0.

RESULTS

Table 1. Characteristics for patients with a BRCAm

Characteristic	Ola plus bev (n=157)	Pbo plus bev (n=76)	Overall (n=233)
Median age (min.–max.), years	57.0 (37.0–77.0)	56.0 (35.0–82.0)	57.0 (35.0–82.0)
Mutated gene			
BRCA1	112 (71.3)	47 (61.8)	159 (68.2)
BRCA2	45 (28.7)	29 (38.2)	74 (31.8)
FIGO stage			
III	113 (72.0)	50 (65.8)	163 (70.0)
IV	44 (28.0)	26 (34.2)	70 (30.0)
Surgery			
No surgery	5 (3.2)	6 (7.9)	11 (4.7)
Initial	83 (52.9)	45 (59.2)	128 (54.9)
Interval (after neoadjuvant chemotherapy)	69 (43.9)	25 (32.9)	94 (40.3)
Had residual macroscopic disease	103 (67.8)	48 (68.6)	151 (68.0)
Response after surgery/chemotherapy			
CR/NED	126 (80.3)	56 (73.7)	182 (78.1)
PR	31 (19.7)	20 (26.3)	51 (21.9)
Location of mutation			
BRCA1			
RING	13 (11.6)	5 (10.6)	18 (11.3)
DBD	24 (21.4)	16 (34.0)	40 (25.2)
BRCT	24 (21.4)	9 (19.1)	33 (20.8)
Other locations	51 (45.5)	17 (36.2)	68 (42.8)
BRCA2			
RAD51-BD	21 (46.7)	15 (51.7)	36 (48.6)
DBD	10 (22.2)	3 (10.3)	13 (17.6)
Other locations	14 (31.1)	11 (37.9)	25 (33.8)
Exon 11			
No	81 (51.6)	29 (38.2)	110 (47.2)
Yes	76 (48.4)	47 (61.8)	123 (52.8)

Data are n (%) unless otherwise stated. CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease; pbo, placebo; PR, partial response.

KEY CONCLUSIONS

- Patients with advanced stage BRCAm HGOC had a PFS benefit from maintenance olaparib and bevacizumab regardless of mutation location.
- The benefit was particularly high for patients with mutations located in the DBD of *BRCA1*.
- *BRCA1* mutations located in the RING or BRCT domains were enriched in missense and splicing mutations.
- Mutations located in the DBD of *BRCA2* were also associated with excellent outcome, consistent with previous reports.[4]

Figure 1. PFS according to the location of mutations in *BRCA1*

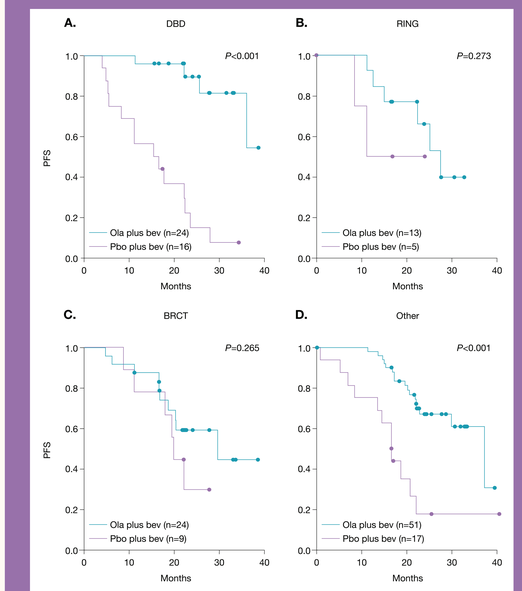


Figure 2. PFS according to the location of mutations in *BRCA2*

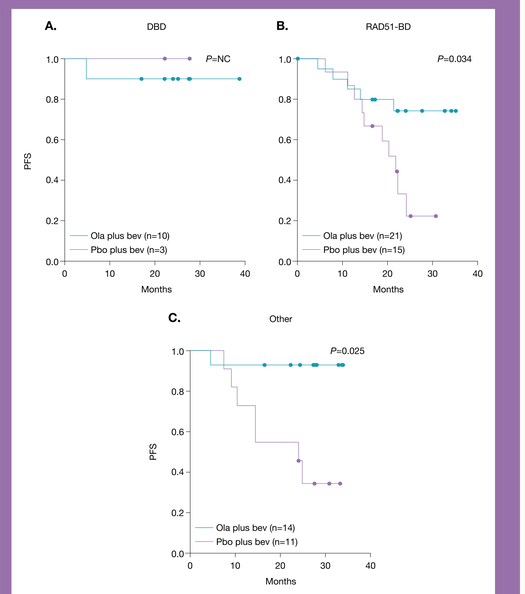
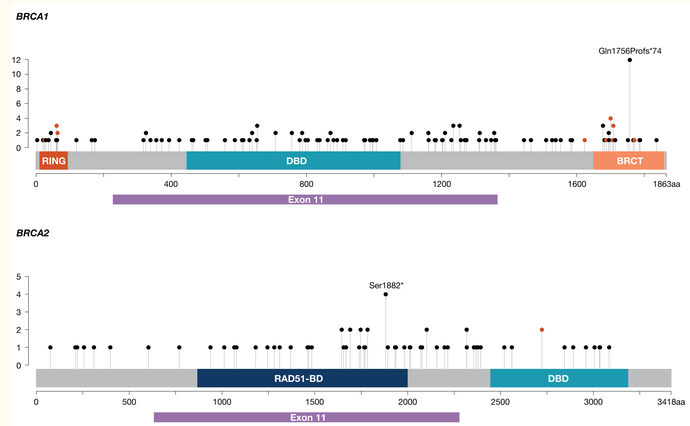


Figure 3. Graphical summary of distribution of mutations in *BRCA1* and *BRCA2*



Orange circles represent missense or splicing mutations.
Mutation plot generated using cBioPortal MutationMapper.

Table 2. PFS according to the location of mutations in *BRCA1* and *BRCA2*

	Pbo plus bev, n/N	Ola plus bev events, n/N	Pbo plus bev 24-mo PFS, %	Ola plus bev 24-mo PFS, %	Multivariate HR (95% CI)	*P*
***BRCA1* functional domains**						
RING (n=19)	3/6	6/13	40	66	0.38 (0.07–2.13)	0.273
DNA-BD (n=41)	15/17	4/24	14	89	0.08 (0.02–0.26)	<0.001
BRCT (n=34)	7/10	10/24	27	59	0.55 (0.20–1.56)	0.265
Other (n=68)	12/17	17/51	18	67	0.24 (0.11–0.51)	<0.001
***BRCA2* functional domains**						
RAD51-BD (n=37)	10/15	5/22	33	76	0.31 (0.11–0.92)	0.034
DNA-BD (n=14)	0/3	1/11	100	91	NC	NC
Other (n=25)	7/11	1/14	55	93	0.09 (0.01–0.75)	0.025

mo, months; NC, not calculated.

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