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Maintenance olaparib plus bevacizumab in patients with newly diagnosed, advanced high-grade ovarian carcinoma: final analysis of second progression-free survival (PFS2) in the Phase III PAOLA-1/ENGOT-ov25 trial

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PAOLA-1/ENGOT-ov25 trial design

Patients:
- Newly diagnosed, FIGO stage III–IV high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer*

First-line treatment:
- Upfront or interval surgery
- Platinum-taxane based chemotherapy plus ≥2 cycles of bevacizumab†

≤9 weeks

NED/CR/PR

Maintenance therapy

Olaparib tablets 300 mg bid x 2 years

+ bevacizumab‡

2:1 randomization stratified by:
- Tumour BRCAm status
- First-line treatment outcome§

Placebo x 2 years

+ bevacizumab‡

- Primary endpoint: investigator-assessed PFS (RECIST v1.1)
- In the primary analysis, a statistically significant PFS benefit was observed[1]

Primary PFS analysis (DCO 22 March 2019)

	Olaparib + bev (N=537)	Placebo + bev (N=269)
Median PFS, months	22.1	16.6
HR (95% CI); *P* value	0.59 (0.49–0.72) *P*<0.001	

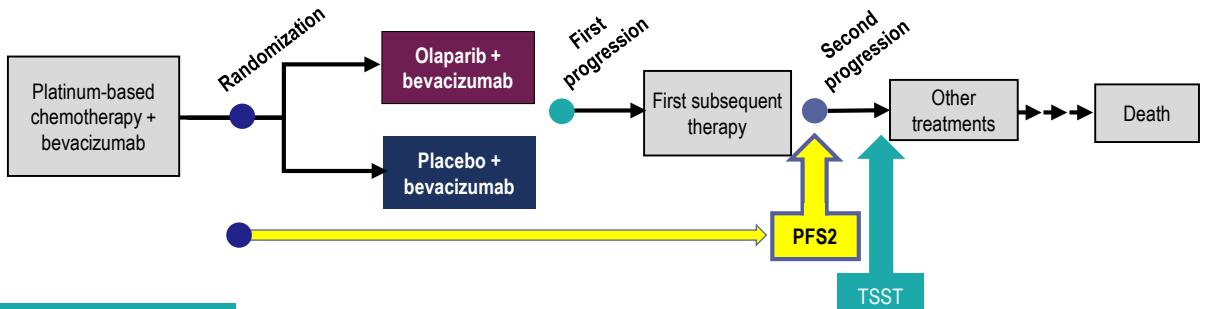
*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; †Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; ‡Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; §According to timing of surgery and NED/CR/PR

bid, twice daily; BRCAm, BRCA mutation; CI, confidence interval; CR, complete response; DCO, data cut-off; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; PFS; time from randomization to progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours;

1. Ray-Coquard I *et al*. *N Engl J Med* 2019;381:2416–28

PAOLA-1/ENGOT-ov25 PFS2 analysis

PFS2 is measured from the time of randomization to second progression or death and evaluates the effect of maintenance therapy with olaparib plus bevacizumab beyond first progression



Primary endpoint
- Investigator-assessed PFS

Secondary endpoints
- TFST
- **PFS2**
- TSST
- OS
- HRQoL
- Safety and tolerability

- PFS2 was immature at the time of primary PFS analysis (DCO 22 March 2019)
- We present the **prespecified final PFS2 analysis** planned for ≈53% data maturity or 1 year after primary analysis (DCO 22 March 2020)
- We also present post hoc analyses of PFS2 by biomarker status

DCO, data cut-off; HRQoL, health-related quality of life; OS, overall survival; PFS2, time from randomization to second progression or death; TFST, time from randomization to first subsequent therapy or death; TSST, time from randomization to second subsequent therapy or death

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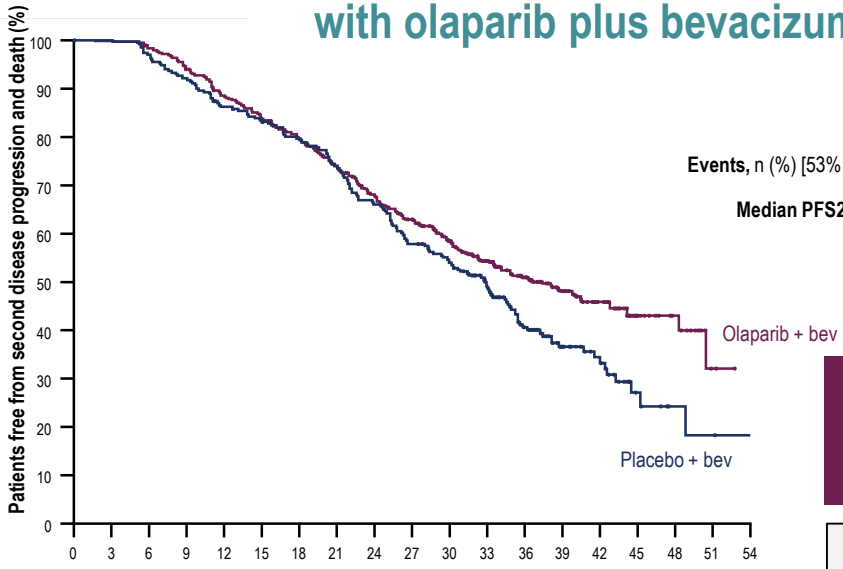
A statistically significant PFS2 benefit was observed with olaparib plus bevacizumab in the ITT population



	Olaparib + bev (N=537)	Placebo + bev (N=269)
Events, n (%) [53% maturity]	260 (48)	164 (61)
Median PFS2, months	**36.5**	**32.6**

HR 0.78 (95% CI 0.64–0.95)
***P*=0.0125**

Patients receiving a PARP inhibitor during first subsequent treatment:
Olaparib plus bevacizumab: **9.1%** (49/537)
Placebo plus bevacizumab: **26.8%** (72/269)

Median PFS2 follow-up of 35.5 months for olaparib plus bevacizumab and 36.5 months for placebo plus bevacizumab

bev, bevacizumab; ITT, intent to treat

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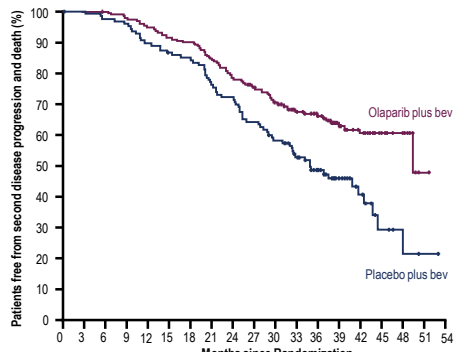
PFS2 subgroup analysis by HRD status

HRD positive,* including tumour BRCAm



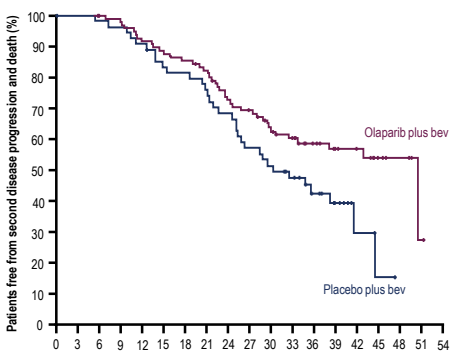
Number of patients at risk:

Ola + bev	255	253	252	247	239	230	223	211	196	184	161	137	102	70	54	17	11	3	0
Pla + bev	132	130	127	125	117	111	109	99	93	83	71	61	44	26	17	8	4	1	0

	Olaparib + bev (n=255)	Placebo + bev (n=132)
Events, n (%)	85 (33)	70 (53)
Median PFS2, months	**50.3†**	**35.3**

HR 0.56 (95% CI 0.41–0.77)

HRD positive,* excluding tumour BRCAm



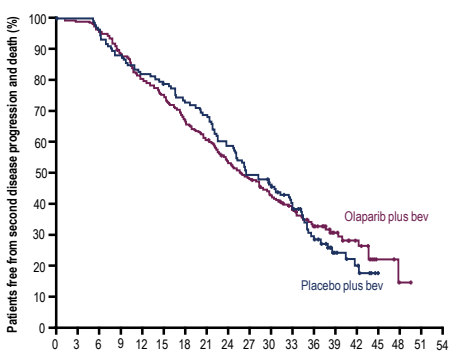
Number of patients at risk:

Ola + bev	97	96	95	92	87	83	81	77	67	63	53	46	31	24	20	7	5	1	0
Pla + bev	55	54	53	52	49	44	43	40	36	30	27	23	15	8	3	1	0		

	Olaparib + bev (n=97)	Placebo + bev (n=55)
Events, n (%)	41 (42)	33 (60)
Median PFS2, months	**50.3†**	**30.1**

HR 0.60 (95% CI 0.38–0.96)

HRD negative/unknown



Number of patients at risk:

Ola + bev	282	274	263	244	220	204	185	165	143	125	102	80	48	27	18	5		
Pla + bev	137	136	131	120	109	104	97	91	78	66	60	45	28	14	10	1		

	Olaparib + bev (n=282)	Placebo + bev (n=137)
Events, n (%)	175 (62)	94 (69)
Median PFS2, months	**26.3**	**28.1**

HR 0.98 (95% CI 0.77–1.27)

*HRD positive defined as a tumour BRCAm and/or genomic instability score of ≥42 on the Myriad myChoice CDx® assay; †Unstable median due to lack of events

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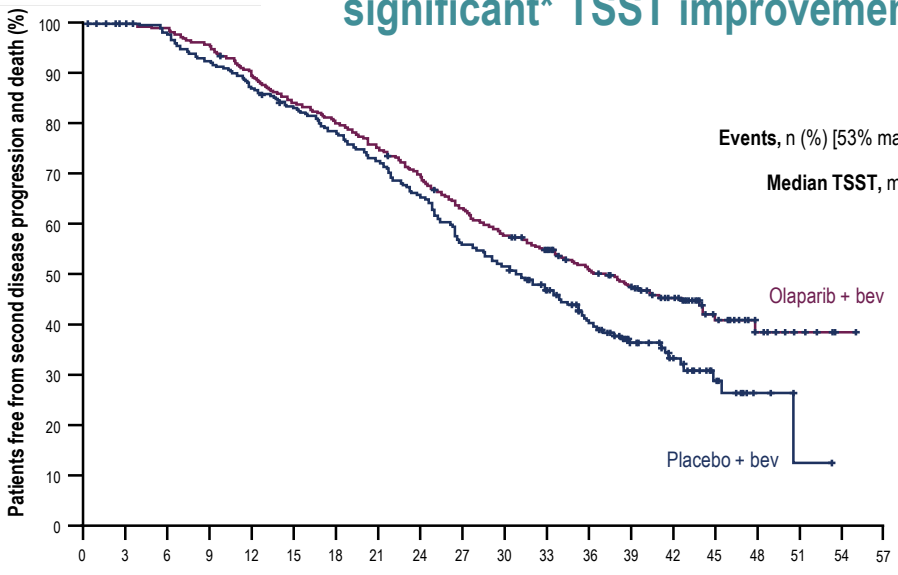
The PFS2 benefit was supported by a statistically significant* TSST improvement in the ITT population



Number of patients at risk:

Olaparib + bev	537	528	520	505	469	442	421	394	364	329	297	245	184	127	86	39	19	6	1
Placebo + bev	269	267	260	247	232	218	207	191	172	149	135	113	75	49	31	17	5	1	0

	Olaparib + bev (N=537)	Placebo + bev (N=269)
Events, n (%) [53% maturity]	266 (50)	164 (61)
Median TSST, months	**38.2**	**31.5**

HR 0.78 (95% CI 0.64–0.95)
P*=0.0115

Biomarker subgroup	TSST HR (95% CI)
Tumour BRCAm	0.48 (0.31–0.75)
HRD positive	0.48 (0.35–0.66)
HRD negative/unknown	1.05 (0.82–1.36)

*TSST analysis not adjusted for multiplicity

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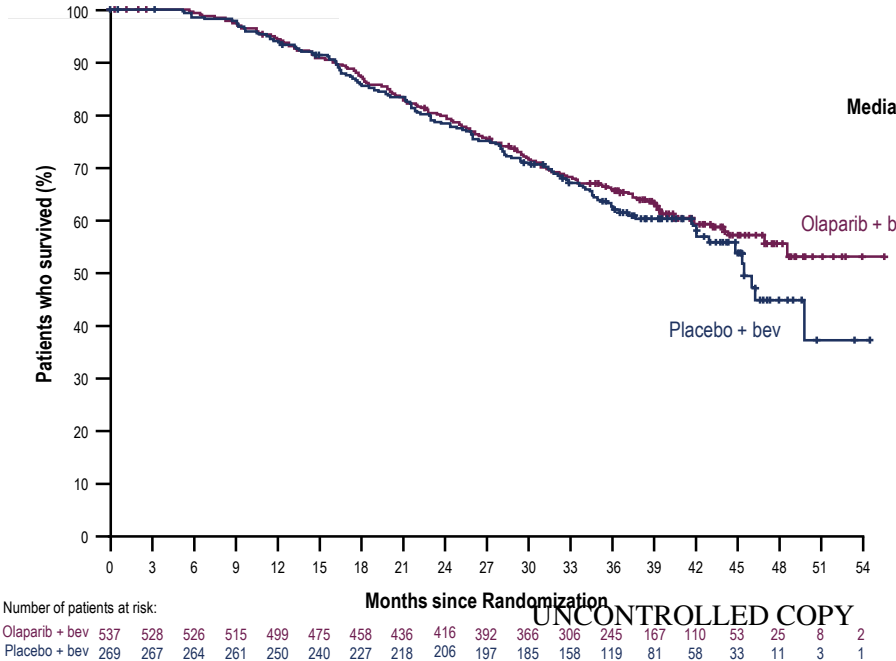
Interim OS analysis



	Olaparib + bev (N=537)	Placebo + bev (N=269)
Events, n (%)	195 (36)	108 (40)
Median OS, months	**NR**	**45.8**

HR 0.93 (95% CI 0.74–1.18)
***P*=0.5631**

- Immature OS analysis:
  - The low event rate (38%) means that definitive conclusions cannot be drawn
- Updated OS data will be presented at greater data maturity:
  - Prespecified final OS analysis planned at ≈60% data maturity or 3 years after primary PFS analysis (March 2022)

NR, not reached

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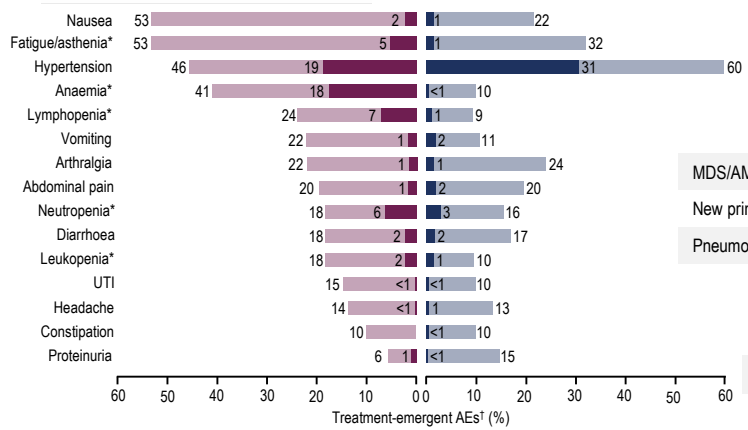
Safety analyses



- Olaparib + bev: All grades (frequency ≥10%)
- Olaparib + bev: Grade ≥3
- Placebo + bev: All grades (frequency ≥10%)
- Placebo + bev: Grade ≥3

AEs of special interest

	Primary PFS analysis (DCO 22 March 2019)		Final PFS2 analysis (DCO 22 March 2020)	
	Olaparib + bev (n=535)	Placebo + bev (n=267)	Olaparib + bev (n=535)	Placebo + bev (n=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	6 (1.1)	4 (1.5)‡
New primary malignancies,§ n (%)	7 (1.3)	3 (1.1)	14 (2.6)	5 (1.9)
Pneumonitis/ILD/bronchiolitis, n (%)	6 (1.1)	0	6 (1.1)	0

	Olaparib + bev (n=535)	Placebo + bev (n=267)
Median duration of olaparib/placebo treatment, months	17.3	15.6
Median duration of bev treatment, months	11.0	10.6
Discontinuation due to AEs, n (%)	112 (21)	15 (6)

*Grouped-term AEs; †All-grade grouped-term thrombocytopenia occurred in 8% of olaparib plus bevacizumab patients and 3% of placebo plus bevacizumab patients; grade ≥3 grouped-term thrombocytopenia occurred in 2% of olaparib plus bevacizumab patients and <1% of placebo plus bevacizumab patients; ‡3 of the 4 patients in the placebo plus bevacizumab group who developed MDS/AML/AA received a PARP inhibitor as first subsequent treatment before onset of AML. §At primary PFS analysis, new primary malignancies in the olaparib plus bevacizumab group were acute lymphocytic leukaemia (n=1), breast cancer (n=2), lung cancer (n=1), myeloma (n=1), squamous skin cancer (n=1), and pancreatic cancer (n=1), and in the placebo group were breast cancer (n=2) and thyroid cancer (n=1). Additional new primary malignancies reported at final PFS2 analysis in the olaparib plus bevacizumab group were breast cancer (n=5), squamous skin cancer (n=1), and colon cancer (n=1), and in the placebo group were breast cancer (n=1) and malignant neoplasm (n=1)

AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; UTI, urinary tract infection

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Conclusions

- In PAOLA-1/ENGOT-ov25, the addition of maintenance olaparib to bevacizumab provided continued benefit beyond first progression, with a statistically significant improvement in PFS2:
  - A substantial PFS2 benefit was seen in patients who were HRD positive, regardless of tumour BRCAm status
- The significant PFS2 improvement was supported by a significant delay in TSST
- No new safety signals were observed with longer-term follow-up
- OS data are still immature

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