

Supplementary Appendix

Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial

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This appendix has been provided by the authors to give readers additional information about their work.

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ENGOT, European Network for Gynecological Oncological Trial groups.

METHODS

Stratification Factors

Randomization was stratified according to:

- Outcome of first-line treatment at screening:
 - No evidence of disease (defined as complete macroscopic resection after cytoreductive surgery and no radiological evidence of disease and a normal cancer antigen 125 [CA-125] level after chemotherapy) with complete macroscopic resection at upfront cytoreductive surgery versus
 - No evidence of disease or complete response (defined as the disappearance of all measurable/assessable disease present at the start of chemotherapy and normalization of CA-125 levels) with complete macroscopic resection at interval cytoreductive surgery versus
 - No evidence of disease or complete response in patients with either incomplete resection at upfront or interval cytoreductive surgery or no cytoreductive surgery versus
 - Partial response (defined as radiologic evidence of disease and/or an abnormal CA-125 level)
- Tumor *BRCA1* and/or *BRCA2* (BRCA) status:
 - Deleterious mutation versus
 - No deleterious mutation, including tumor BRCA wild-type, a variant of uncertain significance or an unknown result

Discontinuation of Study Treatment

Maintenance therapy with olaparib or placebo continued for up to 24 months from randomization or until investigator-assessed objective radiological disease progression (modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1¹) as assessed by the investigator or unacceptable toxicity, whichever occurred first, as long as the patient experienced benefit and did not meet other discontinuation criteria. Patients were to continue with maintenance olaparib or placebo to RECIST progression despite rises in CA-125 levels. Patients could be discontinued from maintenance olaparib or placebo for the following reasons:

- The patient had no evidence of disease after 2 years' maintenance therapy with olaparib or placebo. If after 2 years of study treatment the investigator considered that the patient may get a clinical benefit from prolonging maintenance olaparib or placebo, the investigator and the sponsor would discuss the best option for the patient
- Patient decision
- Adverse event
- Bone marrow findings consistent with myelodysplastic syndrome or acute myeloid leukemia
- Severe noncompliance with the study protocol
- Objective disease progression according to modified RECIST version 1.1 (unless in the investigator's opinion the patient was benefiting from treatment and did not meet any other discontinuation criteria)

Biomarker Subgroup Analyses

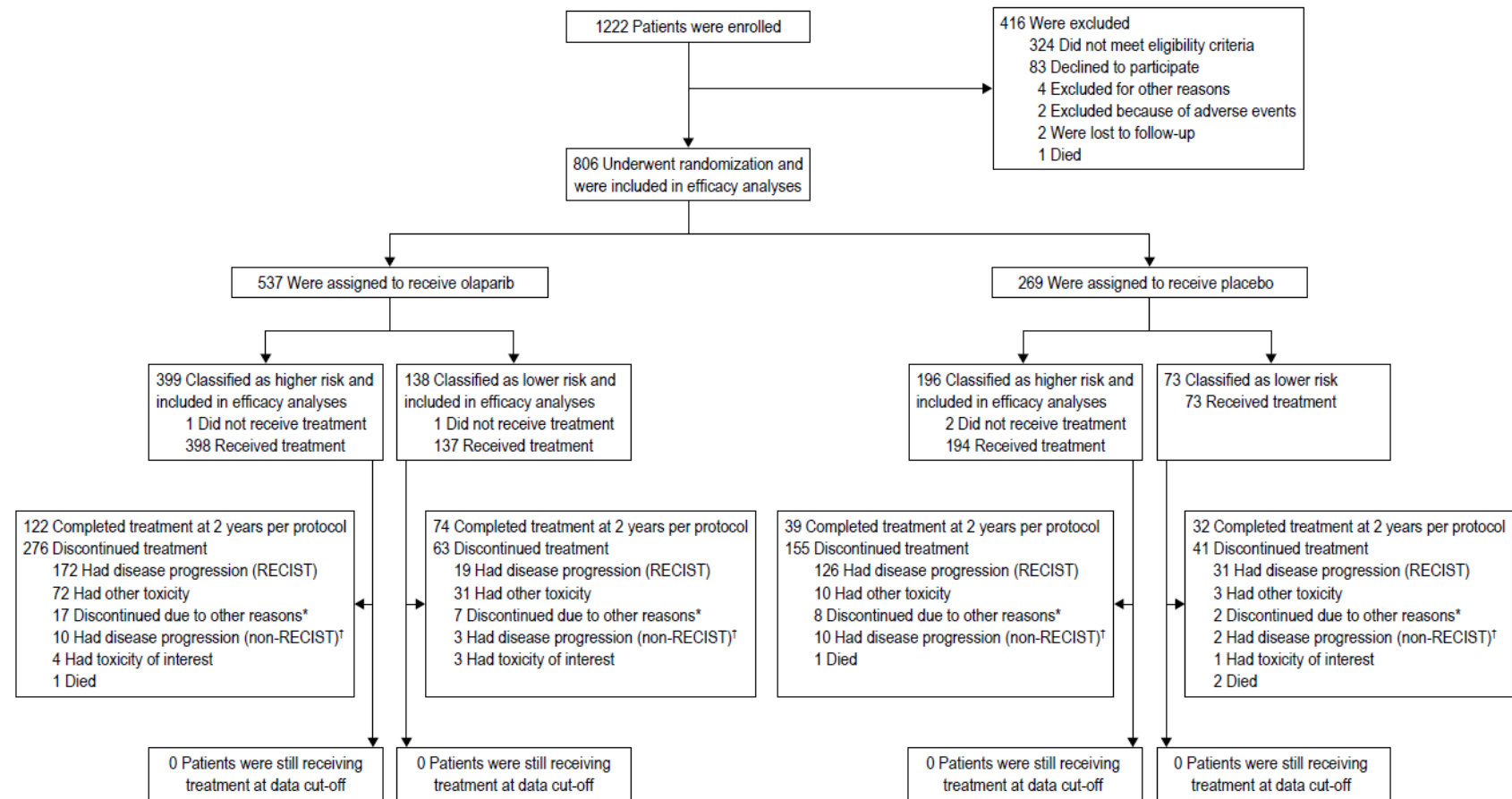
For the biomarker subgroup analyses, the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from a single Cox proportional hazards model that includes

a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term. The treatment effect HR was obtained for each level of the subgroup from this model. The Cox model was fitted with the Efron method² to handle ties.

- For tumor BRCA status, the covariate used was BRCA mutation versus BRCA wild-type
- For homologous recombination deficiency (HRD) status, we performed analyses using one model excluding the missing data, one model considering the missing data as a modality, and one model including the missing data grouped with the HRD-negative subgroup, so we were able to present the most appropriate model. For example, for survival curves showing HRD-positive versus HRD-negative versus HRD-unknown, we used the second model
- For HRD-positive without a BRCA mutation, the covariate used in the model was HRD-positive excluding BRCA versus HRD-negative

RESULTS

Figure S1. Patient disposition



*Other reasons included consent withdrawn (higher-risk group: n=3, olaparib plus bevacizumab and n=1, placebo plus bevacizumab; lower-risk group: n=1, olaparib plus bevacizumab and n=2, placebo plus bevacizumab), lost to follow-up (lower-risk group: n=1, olaparib plus bevacizumab), and other (higher-risk group: n=14, olaparib plus bevacizumab and n=7, placebo plus bevacizumab; lower-risk group: n=5, olaparib plus bevacizumab).

†Disease progression defined by criteria other than RECIST (higher-risk group: n=5, olaparib plus bevacizumab and n=7, placebo plus bevacizumab; lower-risk group: n=3, olaparib plus bevacizumab and n=2, placebo plus bevacizumab) or symptomatic deterioration (higher-risk group: n=5, olaparib plus bevacizumab and n=3, placebo plus bevacizumab).

RECIST, Response Evaluation Criteria in Solid Tumors.

Table S1. Characteristics of the patients at baseline*³

	Overall population		Higher-risk subgroup [†]		Lower-risk subgroup [†]	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=399)	Placebo + bevacizumab (N=196)	Olaparib + bevacizumab (N=138)	Placebo + bevacizumab (N=73)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)	62.0 (32.0–87.0)	61.0 (26.0–85.0)	59.0 (38.0–78.0)	56.0 (35.0–77.0)
ECOG performance status, n (%)						
0	378 (70)	189 (70)	275 (69)	134 (68)	103 (75)	55 (75)
1	153 (28)	76 (28)	119 (30)	59 (30)	34 (25)	17 (23)
Missing	6 (1)	4 (1)	5 (1)	3 (2)	1 (1)	1 (1)
Primary tumor location, n (%)						
Ovary	456 (85)	238 (88)	337 (84)	171 (87)	119 (86)	67 (92)
Fallopian tubes	39 (7)	11 (4)	25 (6)	7 (4)	14 (10)	4 (5)
Primary peritoneal	42 (8)	20 (7)	37 (9)	18 (9)	5 (4)	2 (3)
FIGO stage, n (%)						
III	378 (70)	186 (69)	240 (60)	113 (58)	138 (100)	73 (100)
IV	159 (30)	83 (31)	159 (40)	83 (42)	0 (0)	0 (0)
Histology, n (%)						
Serous	519 (97)	253 (94)	387 (97)	189 (96)	132 (96)	64 (88)
Endometrioid	12 (2)	8 (3)	8 (2)	4 (2)	4 (3)	4 (5)
Other [§]	6 (1)	8 (3)	4 (1)	3 (2)	2 (1)	5 (7)
History of cytoreductive surgery, n (%)						
Upfront surgery	271 (50)	138 (51)	133 (33)	65 (33)	138 (100)	73 (100)
Macroscopic residual disease	111 (41)	53 (38)	111 (83)	53 (82)	–	–
Complete resection	160 (59)	85 (62)	22 (17)	12 (18)	138 (100)	73 (100)
Interval surgery	228 (42)	110 (41)	228 (57)	110 (56)	0	0
Macroscopic residual disease	65 (29)	35 (32)	65 (29)	35 (32)	–	–
Complete resection	163 (71)	75 (68)	163 (71)	75 (68)	–	–
No surgery	38 (7)	21 (8)	38 (10)	21 (11)	0	0
Response after first-line therapy, n (%)						
NED [¶]	290 (54)	141 (52)	153 (38)	70 (36)	137 (99)	71 (97)
Clinical CR ^{**}	106 (20)	53 (20)	106 (27)	53 (27)	–	–
Clinical PR ^{††}	141 (26)	75 (28)	140 (35)	73 (37)	1 (1) ^{‡‡}	2 (3) ^{‡‡}
Normal serum CA-125 level						
Yes	463 (86)	234 (87)	333 (83)	165 (84)	130 (94)	69 (95)
No	74 (14)	34 (13)	66 (17)	30 (15)	8 (6)	4 (5)
Missing	0	1 (<1)	0	1 (1)	0	0

Deleterious tumor BRCAm, ^{§§,} n (%)						
Yes	157 (29)	80 (30)	109 (27)	55 (28)	48 (35)	25 (34)
No	380 (71)	189 (70)	290 (73)	141 (72)	90 (65)	48 (66)
Myriad tumor HRD status, ^{,¶¶} n (%)						
HRD-positive	255 (47)	132 (49)	177 (44)	89 (45)	78 (57)	43 (59)
HRD-negative/unknown	282 (53)	137 (51)	222 (56)	107 (55)	60 (43)	30 (41)
HRD-negative	192 (36)	85 (32)	144 (36)	62 (32)	48 (35)	23 (32)
Unknown	90 (17)	52 (19)	78 (20)	45 (23)	12 (9)	7 (10)

*Percentages may not total 100 because of rounding.

†Patients with FIGO stage III disease who had undergone upfront surgery and had residual disease or who had received neoadjuvant chemotherapy, or FIGO stage IV patients.

‡Patients with FIGO stage III disease who had undergone upfront surgery and had complete resection.

§In the overall ITT population, other defined as clear-cell (n=2, olaparib plus bevacizumab), undifferentiated (n=1, olaparib plus bevacizumab; n=6, placebo plus bevacizumab), or other (n=3, olaparib plus bevacizumab; n=2, placebo plus bevacizumab). In the higher-risk subgroup, other defined as clear-cell (n=2, olaparib plus bevacizumab), undifferentiated (n=1, olaparib plus bevacizumab; n=2, placebo plus bevacizumab), or other n=1, olaparib plus bevacizumab; n=1, placebo plus bevacizumab). In the lower-risk subgroup, other defined as undifferentiated (n=4, placebo plus bevacizumab) or other (n=2, olaparib plus bevacizumab; n=1, placebo plus bevacizumab).

||Patients with FIGO stage IV disease.

¶NED defined as no measurable or assessable disease after cytoreductive surgery plus no radiologic evidence of disease and a normal CA-125 level after chemotherapy.

**Clinical CR defined as the disappearance of all measurable or assessable disease and normalization of CA-125 levels after chemotherapy.

††Clinical PR defined as radiologic evidence of disease, an abnormal CA-125 level, or both.

‡‡No residual disease was reported at the time of surgery; however, computed tomography images compatible with residual disease were reported at postsurgical radiographic evaluation.

§§As per the electronic case report form.

||Tumor BRCAm status was determined by one of five central French academic laboratories before trial entry and HRD status was determined retrospectively by the MyChoice® HRD Plus assay (Myriad Genetic Laboratories, Salt Lake City, UT, USA). HRD-positive defined as a tumor BRCA mutation and/or a GIS of ≥ 42 ; HRD-positive without a BRCA mutation defined as a GIS of ≥ 42 and no tumor BRCA mutation. The number of patients in the tumor BRCAm and HRD-positive without tumor BRCAm subgroups does not equal the total number of patients in the HRD-positive subgroup because of these different testing methods.

¶¶HRD-positive defined as a tumor BRCAm and/or a genomic instability score of 42 or higher on the MyChoice® HRD Plus assay; HRD-negative defined as a genomic instability score of less than 42 and no tumor BRCAm; unknown HRD status defined as an inconclusive, missing or failed test.

BRCA, *BRCA1* and/or *BRCA2*; CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; NED, no evidence of disease; PR, partial response.

Table reproduced from Harter *et al.* Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Gynecol Oncol* 2022;164:254–64.³ (<https://doi.org/10.1016/j.ygyno.2021.12.016>) under a CC-BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Table S2. Outcomes in higher-risk and lower-risk patients in the intent-to-treat population

	Higher risk		Lower risk	
	Olaparib + bevacizumab (n=399)	Placebo + bevacizumab (n=196)	Olaparib + bevacizumab (n=138)	Placebo + bevacizumab (n=73)
PFS				
Events, n (%)	298 (75)	170 (87)	68 (49)	52 (71)
Median PFS, months	20.4	14.6	60.7	22.9
HR (95% CI)	0.63 (0.52 to 0.76)		0.53 (0.37 to 0.77)	
5-year PFS rate,* %	22	11	52	28
TFST				
Events, n (%)	316 (79)	171 (87)	68 (49)	55 (75)
Median TFST, months	22.0	16.5	64.0	23.9
HR (95% CI)	0.65 (0.54 to 0.79)		0.48 (0.34 to 0.69)	
5-year TFST rate,* %	20	11	52	25
OS				
Events, n (%)	249 (62)	128 (65)	39 (28)	30 (41)
Median OS, months	44.2	42.2	NR	NR
HR (95% CI)	0.93 (0.75 to 1.15)		0.66 (0.41 to 1.07) [†]	
5-year OS rate,* %	39	35	73	58
Patients receiving a PARP inhibitor during any subsequent treatment, n (%)	78 (20)	90 (46)	27 (20)	33 (45)

Five-year PFS and TFST data from the final overall survival data cut-off (March 22, 2022).

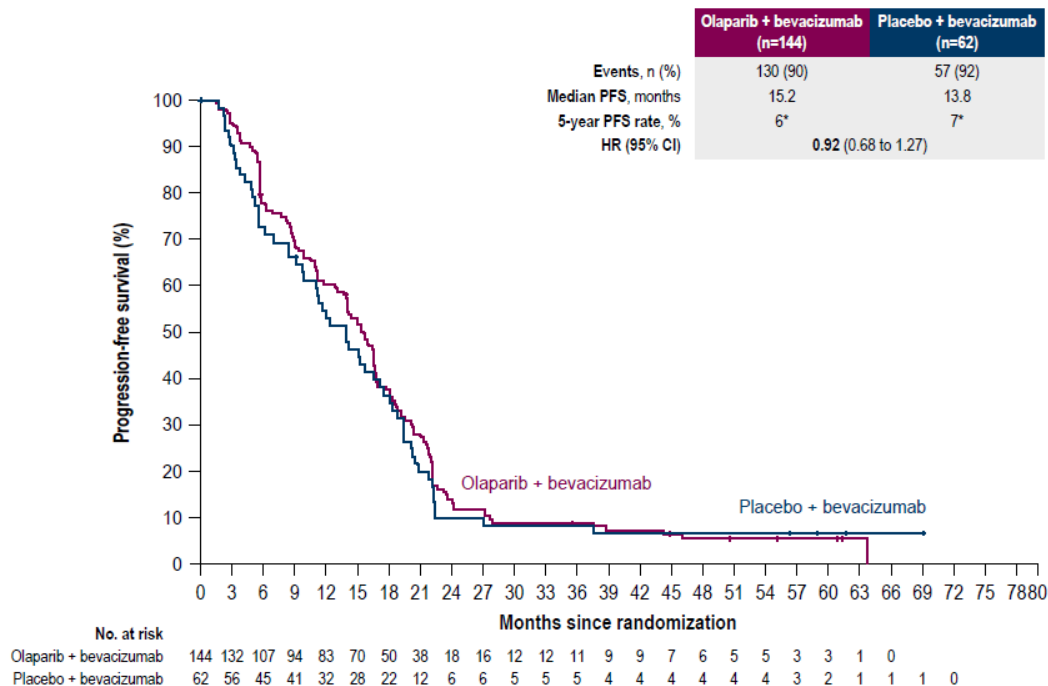
*Kaplan-Meier estimates.

[†]Too few events; interpret HR with caution.

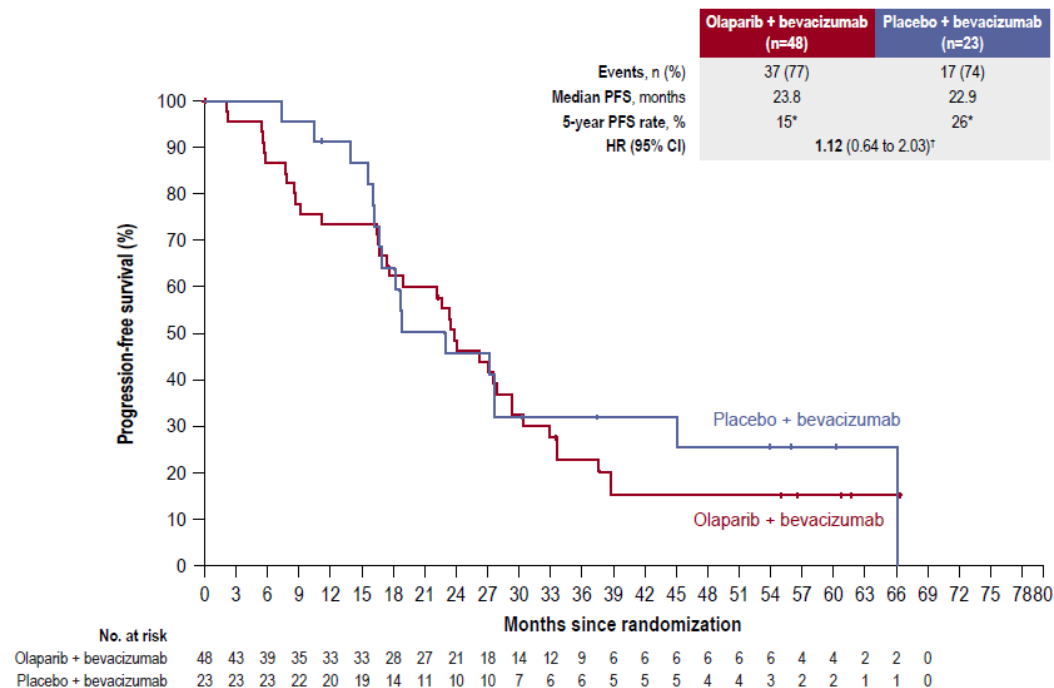
CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival, PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; TFST, time to first subsequent therapy or death.

Figure S2. Kaplan-Meier estimate of progression-free survival in **(A)** higher-risk patients with HRD-negative tumors and **(B)** lower-risk patients with HRD-negative tumors

A Higher-risk patients with HRD-negative tumors



B Lower-risk patients with HRD-negative tumors



Five-year PFS data from the final overall survival data cut-off (22 March 2022).

The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points.

HRD-negative defined as GIS of <42 and no tumor BRCA mutation (MyChoice® HRD Plus).

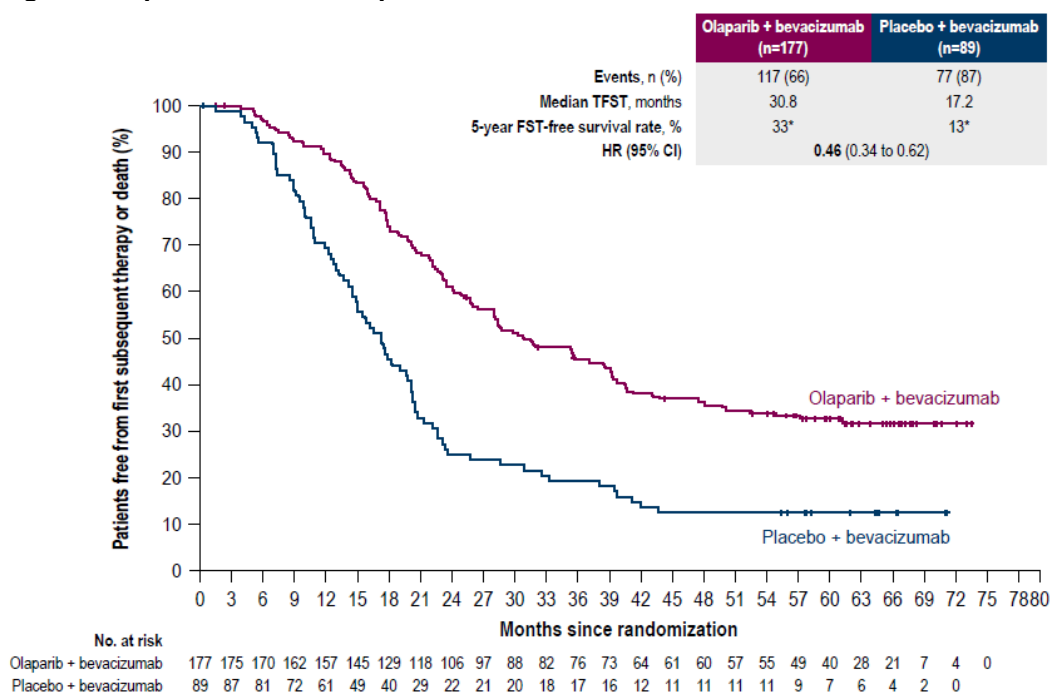
*Kaplan-Meier estimates.

†Survival curves cross; interpret HRs with caution.

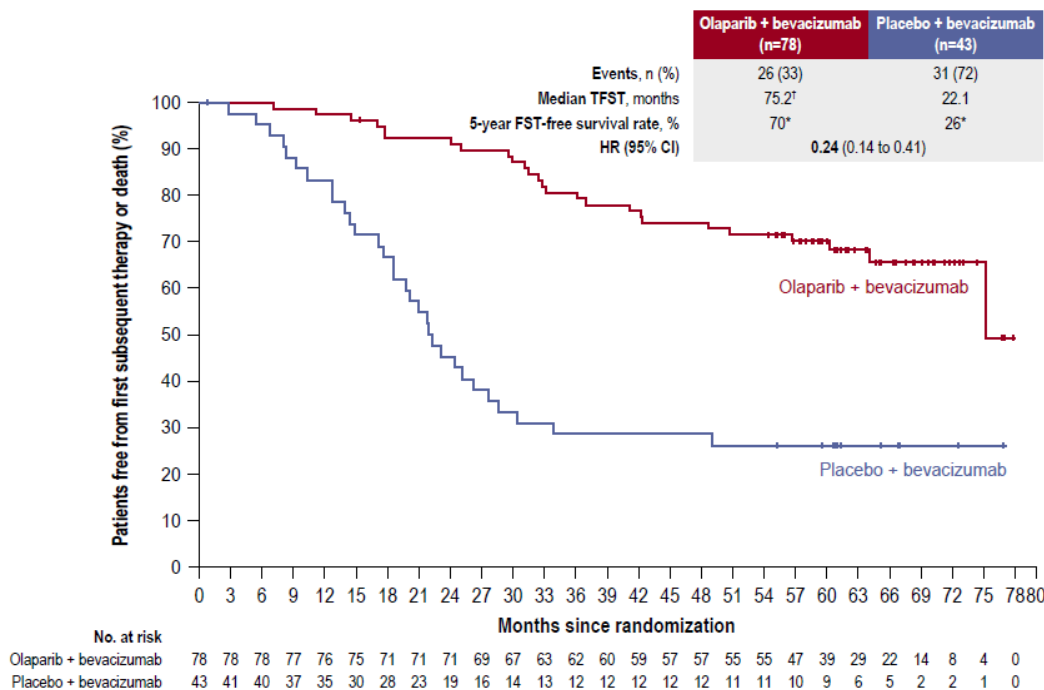
BRCA, *BRCA1* and/or *BRCA2*; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.

Figure S3. Kaplan-Meier estimate of time to first subsequent therapy or death in (A) higher-risk patients with HRD-positive tumors, (B) lower-risk patients with HRD-positive tumors, (C) higher-risk patients with a BRCA mutation, (D) lower-risk patients with a BRCA mutation, (E) higher-risk patients with HRD-positive tumors without a BRCA mutation, (F) lower-risk patients with HRD-positive tumors without a BRCA mutation, (G) higher-risk patients with HRD-negative tumors, and (H) lower-risk patients with HRD-negative tumors

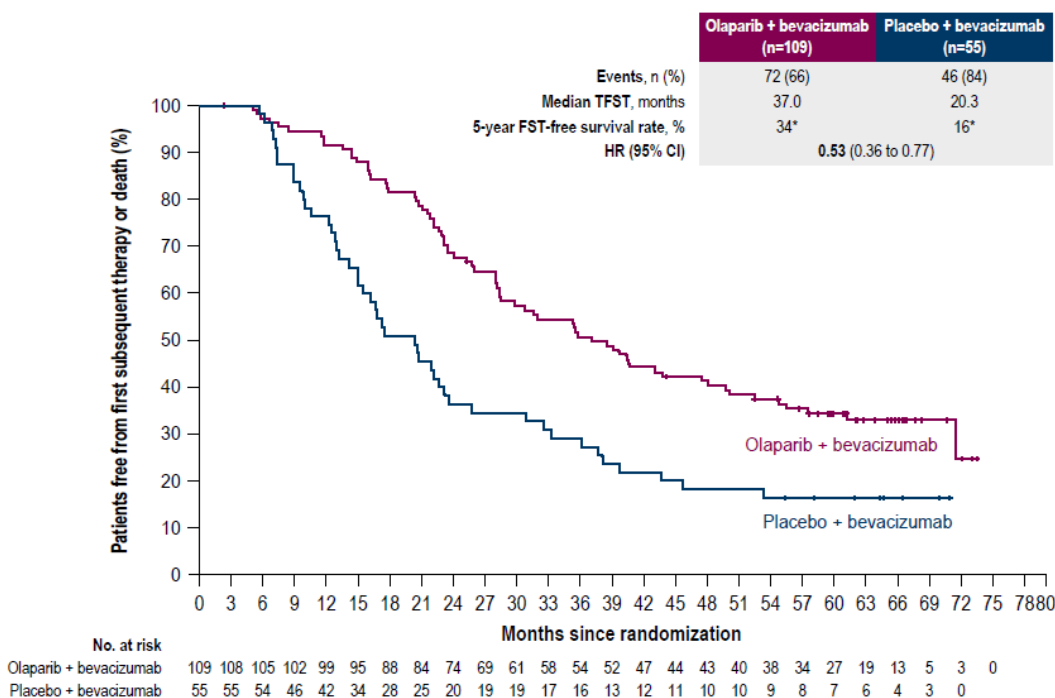
A Higher-risk patients with HRD-positive tumors



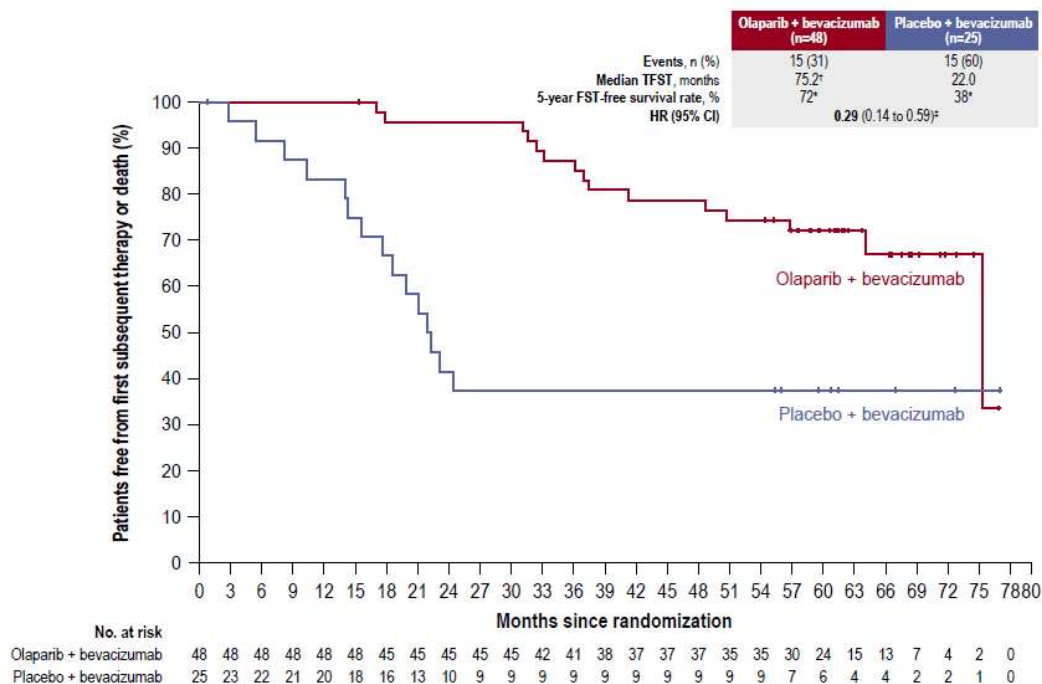
B Lower-risk patients with HRD-positive tumors



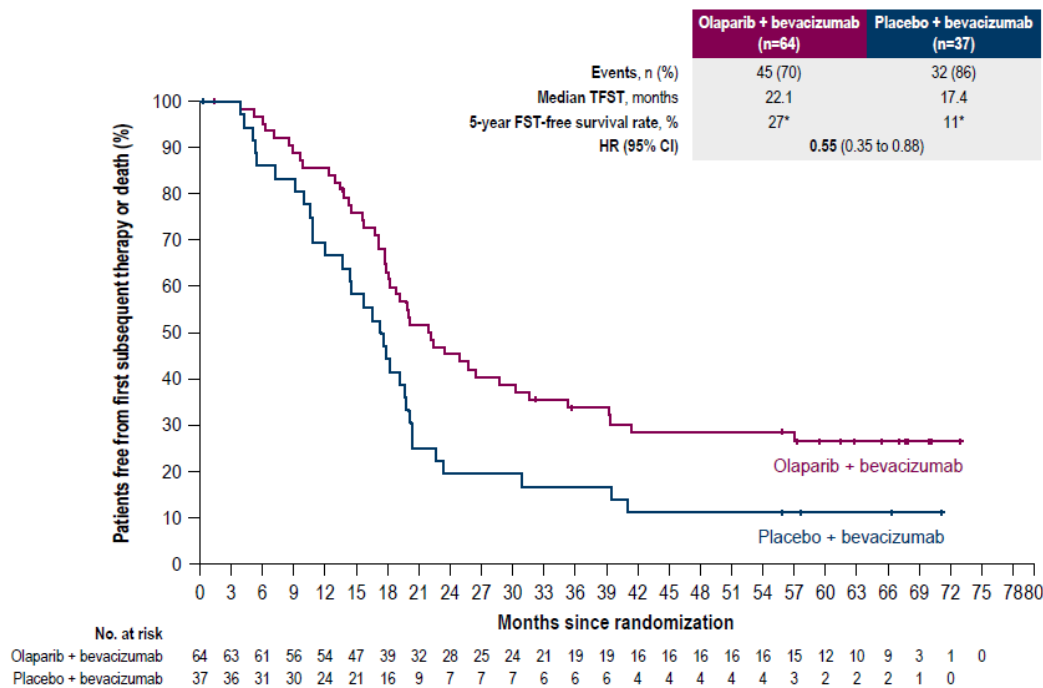
C Higher-risk patients with a BRCA mutation



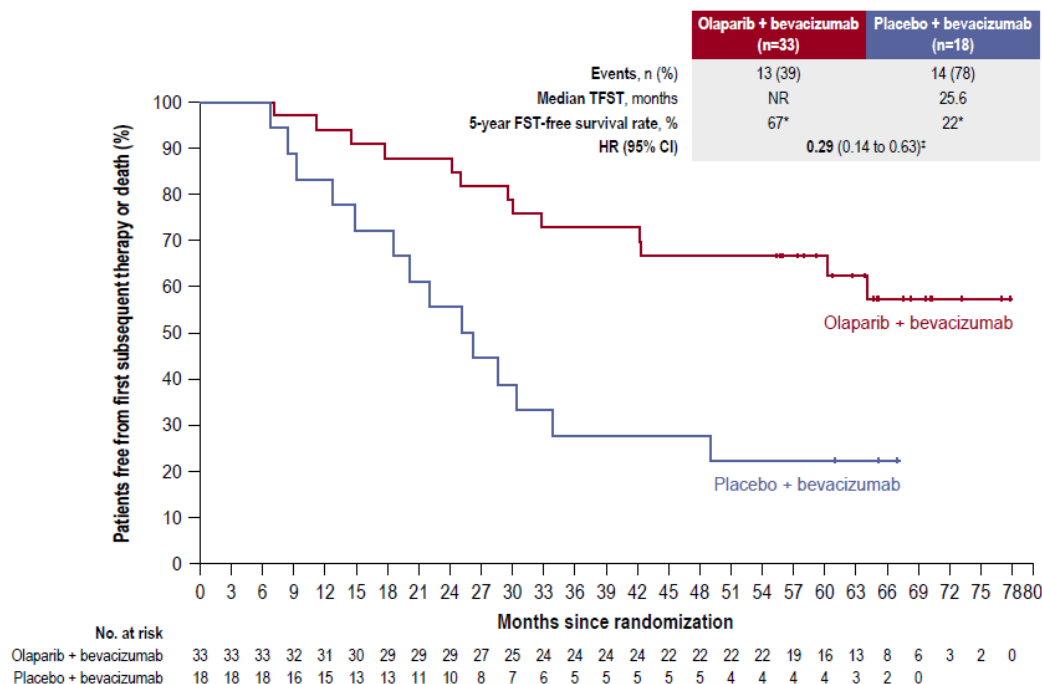
D Lower-risk patients with a BRCA mutation



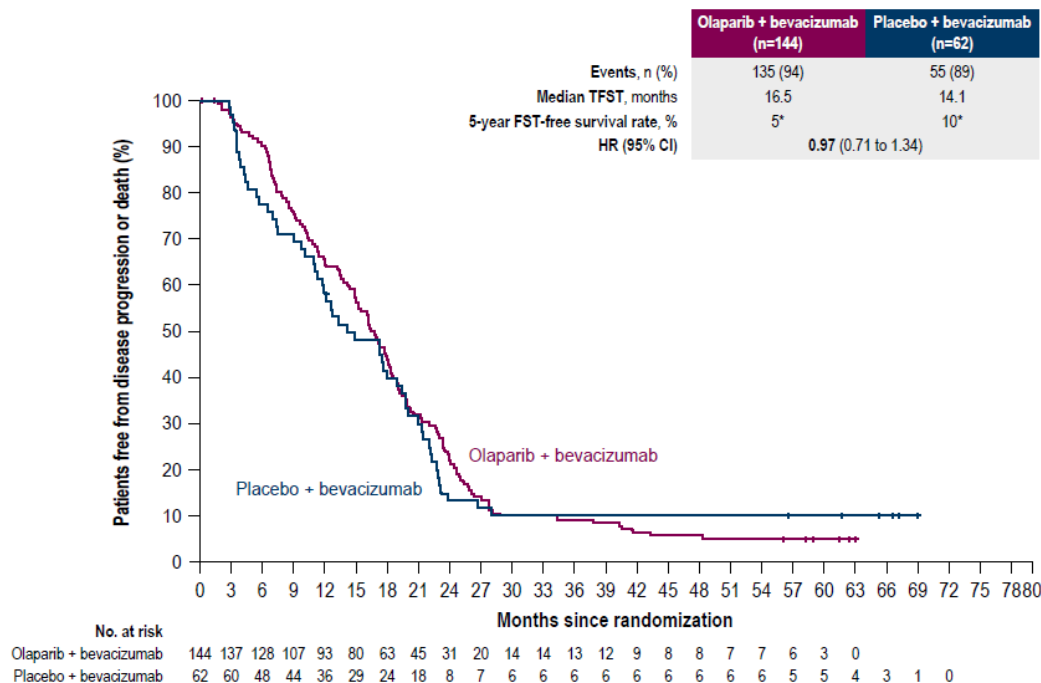
E Higher-risk patients with HRD-positive tumors without a BRCA mutation



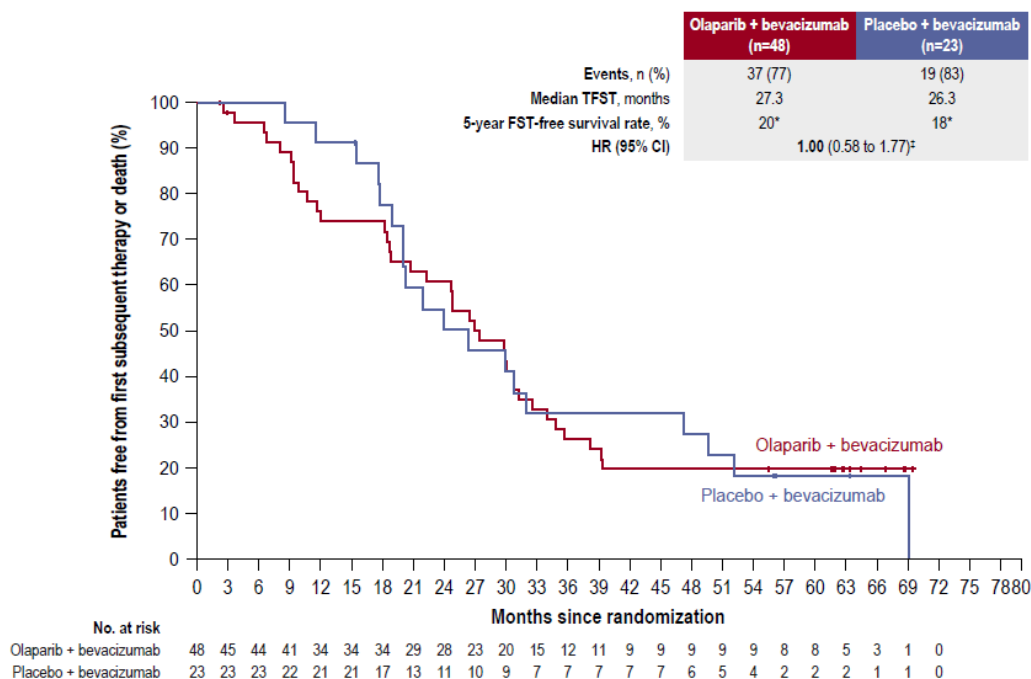
F Lower-risk patients with HRD-positive tumors without a BRCA mutation



G Higher-risk patients with HRD-negative tumors



H Lower-risk patients with HRD-negative tumors



Five-year TFST data from the final overall survival data cut-off (March 22, 2022).

The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points.

HRD status assessed using the MyChoice® HRD Plus assay. HRD-positive defined as a tumor BRCA mutation and/or a GIS of ≥ 42 ; HRD-positive without a BRCA mutation defined as a GIS of ≥ 42 and no tumor BRCA mutation; and HRD-negative defined as GIS of < 42 and no tumor BRCA mutation.

*Kaplan-Meier estimates.

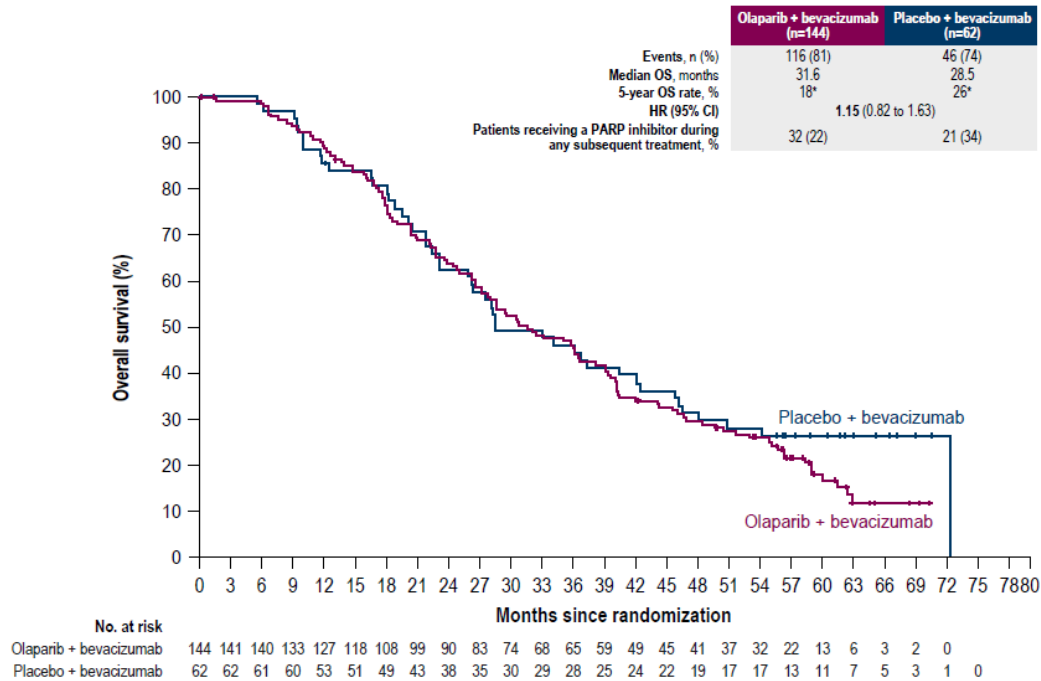
†Unstable median due to lack of events.

‡Too few events and/or survival curves cross; interpret HRs with caution.

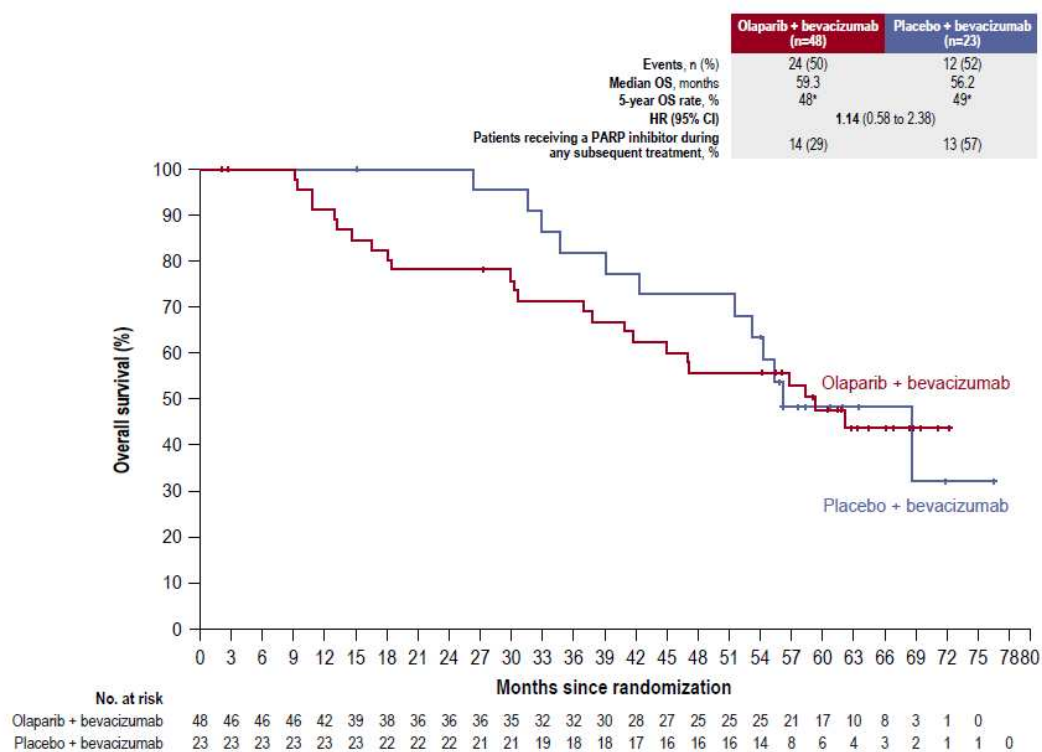
BRCA, BRCA1 and/or BRCA2; CI, confidence interval; FST, first subsequent therapy; GIS, genomic instability score; HR, hazard ratio; HRD, homologous recombination deficiency; TFST, time to first subsequent therapy or death.

Figure S4. Kaplan-Meier estimate of overall survival in **(A)** higher-risk patients with HRD-negative tumors and **(B)** lower-risk patients with HRD-negative tumors

A Higher-risk patients with HRD-negative tumors



B Lower-risk patients with HRD-negative tumors



The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points.

HRD-negative defined as GIS of <42 and no tumor BRCA mutation (MyChoice® HRD Plus).

*Kaplan-Meier estimates.

BRCA, *BRCA1* and/or *BRCA2*; CI, confidence interval; GIS, genomic instability score; HR, hazard ratio; HRD, homologous recombination deficiency; OS, overall survival; PARP, poly(ADP-ribose) polymerase.

Table S3. Outcome by clinical risk in phase III trials of bevacizumab or PARP inhibitor maintenance monotherapy in patients with newly diagnosed ovarian cancer

Study	Patient population	Treatment (number of patients)	Outcome by clinical risk
Bevacizumab trials			
GOG-0218 ⁴	Newly diagnosed ovarian cancer, FIGO stage III with gross residual disease post-surgery or FIGO stage IV	Platinum-based chemotherapy + bevacizumab followed by maintenance bevacizumab (n=623) vs platinum-based chemotherapy (n=625)*	FIGO stage III: HR for OS 1.05 (95% CI 0.91 to 1.22) FIGO stage IV: HR for OS 0.75 (95% CI 0.59 to 0.95)
ICON7 ⁵	Newly diagnosed ovarian cancer, early stage high-risk (FIGO stage I–IIa with grade 3 or clear-cell histology) or more advanced disease (FIGO stage IIb–IV)	Platinum-based chemotherapy + bevacizumab followed by maintenance bevacizumab (n=764) vs platinum-based chemotherapy (n=764)	Non-high-risk patients: HR for OS 1.14 (95% CI 0.93 to 1.40) Higher-risk† patients: HR for OS 0.78 (95% CI 0.63 to 0.97)
PARP inhibitor maintenance monotherapy trials			
SOLO1 ⁶	Newly diagnosed ovarian cancer, FIGO stage III–IV, CR/PR after platinum-based chemotherapy, BRCA mutation	Olaparib (n=260) vs placebo (n=131)	Lower-risk‡ patients: HR for PFS 0.38 (95% CI 0.25 to 0.59) Higher-risk‡ patients: HR for PFS 0.34 (95% CI 0.24 to 0.49)
ATHENA-MONO ⁷	Newly diagnosed ovarian cancer, FIGO stage III–IV, CR/PR after platinum-based	Rucaparib (n=427) vs placebo (n=111)	FIGO stage III: HR for PFS 0.64 (95% CI 0.46 to 0.87) FIGO stage IV: HR for PFS 0.40 (95% CI 0.25 to 0.64) Upfront surgery: HR for PFS 0.64 (95% CI 0.43 to 0.95) Interval surgery: HR for PFS 0.44 (95% CI 0.31 to 0.62)

chemotherapy, regardless of
biomarker status

No residual disease: HR for PFS 0.59 (95% CI 0.43 to 0.80)

Residual disease: HR for PFS 0.44 (95% CI 0.27 to 0.73)

*A third treatment arm which evaluated platinum-based chemotherapy + bevacizumab (n=625) is not shown.

†Stage III with residual disease following cytoreductive surgery (>1 cm), inoperable stage III disease, stage IV disease.

‡Lower risk defined as stage III disease without residual disease following upfront surgery. Higher risk defined as stage IV disease or stage III disease with either residual disease following upfront surgery or had undergone interval surgery.

BRCA, *BRCA1* and/or *BRCA2*; CI, confidence interval; CR, complete response; PR, partial response; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

References

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