Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial

The authors have provided this appendix to give readers additional information about their work.

Supplement to: González-Martín A, Desauw C, Heitz C, Cropet C, Gargiulo P, Berger R et al. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial

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ENGOT, European Network for Gynecological Oncological Trial Groups

Materials and methods

Full eligibility criteria

Inclusion criteria

For inclusion in the study, patients should fulfil the following criteria:

1. Female and aged ≥18 years old
2. Signed informed consent and ability to comply with treatment and follow-up
3. Patients with newly diagnosed:
    - Ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer
    - Histologically confirmed (based on local histopathological findings):
        - High-grade serous or
        - High-grade endometrioid or
        - Other epithelial non-mucinous ovarian cancer in patients with a deleterious germline *BRCA1* and/or *BRCA2* mutation
    - Advanced stage: International Federation of Gynecology and Obstetrics (FIGO) stage IIIB, IIIC or IV (1988 FIGO classification):
        - Using the current 2014 FIGO classification for stage III disease, women would be classified as having stage IIIA–IV ovarian cancer for this to be considered advanced stage
4. Completed first-line platinum-taxane chemotherapy prior to randomisation:
    - Platinum-taxane-based regimen must have consisted of a minimum of six and a maximum of nine treatment cycles. However, if platinum-based therapy was discontinued early as a result of nonhematological toxicity specifically related to the platinum regimen (including neurotoxicity and hypersensitivity), the patient must have received a minimum of four cycles of the platinum regimen
    - Intravenous, intraperitoneal or neoadjuvant platinum-based chemotherapy is allowed. For weekly therapy, 3 weeks is considered one cycle. Interval debulking surgery is allowed
5. Prior to randomisation, patients must have received a minimum of three cycles of bevacizumab in combination with the three last cycles of platinum-based chemotherapy. Only in the case of interval cytoreductive surgery are patients permitted to receive only two cycles of bevacizumab in combination with the last three

cycles of platinum-based chemotherapy. Bevacizumab treatment should be administered at a dose 15 mg/kg every 3 weeks up to a total of 15 months

6. Prior to randomisation, patients must be without evidence of disease (NED) or in complete response or partial response from the first-line treatment. There should be no clinical evidence of disease progression (through physical examination, imaging or cancer antigen [CA]-125 test) throughout first-line treatment and prior to study randomisation:
    - Patients without assessable disease after initial cytoreductive surgery were considered to have NED at the end of the first-line chemotherapy and surgery strategy if disease has not progressed
    - Patients with measurable or assessable disease after initial cytoreductive surgery or at the start of neoadjuvant chemotherapy and whose disease was no longer detectable at the end of the chemotherapy and surgery strategy were considered to have a complete response
7. Patients must be randomised at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and all major toxicities from prior chemotherapy must have resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or better (except alopecia and peripheral neuropathy)
8. Patients must have normal organ and bone marrow function:
    - Haemoglobin ≥10.0 g/dL
    - Absolute neutrophil count ≥1.5 × 10^9/L
    - Platelet count ≥100 × 10^9/L
    - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN)
    - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase and alanine aminotransferase/serum glutamic pyruvate transaminase ≤2.5 × ULN unless liver metastases are present, in which case, they must be ≤5 × ULN
    - Serum creatinine ≤1.5 × institutional ULN
    - Patients not receiving anticoagulant medication who have an international normalised ratio (INR) ≤1.5 and an activated prothrombin time (aPTT) ≤1.5 × ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the site's medical standard). If the patient is on oral anticoagulants, the dose must be stable for at least 2 weeks at the time of randomisation

- Urine dipstick for proteinuria <2+. If urine dipstick is ≥2+, 24-hour urine must demonstrate <1 g of protein in 24 hours
- Normal blood pressure (BP) or adequately treated and controlled hypertension (systolic BP ≤140 mmHg and/or diastolic BP ≤90 mmHg)

9. Eastern Cooperative Oncology Group performance status 0–1
10. Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central BRCA testing and test result must be available for stratification
11. Postmenopausal or evidence of non-childbearing status for women of childbearing potential prior to the first dose of study treatment
12. For France only: in France, a patient will be eligible for randomisation in this study only if either affiliated to, or a beneficiary of, a social security category

Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Non-epithelial origin of the ovary, the fallopian tube or the peritoneum (ie germ cell tumours)
2. Ovarian tumours of low malignant potential (eg borderline tumours) or mucinous carcinoma
3. Synchronous primary endometrial cancer unless both of the following criteria are met:
   - Stage <II
   - Aged <60 years at the time of diagnosis of endometrial cancer with stage IA or IB grade I or II, or stage IA grade III endometrial carcinoma OR aged ≥60 years at the time of diagnosis of endometrial cancer with stage IA grade I or II endometrioid adenocarcinoma. Patients with serous or clear-cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible
4. Other malignancy within the last 5 years except: (1) adequately treated nonmelanoma skin cancer, (2) curatively treated *in situ* cancer of the cervix, (3) ductal carcinoma *in situ.* Patients with a history of localised malignancy diagnosed over 5 years ago may be eligible provided they completed adjuvant systemic therapy prior to randomisation and remain free of recurrent or metastatic disease. Patients with a history of primary triple-negative breast cancer may be eligible provided they completed definitive anticancer treatment >3 years ago and remain breast cancer free prior to the start of study treatment

5. Patients with myelodysplastic syndromes (MDS)/acute myeloid leukaemia (AML) history
6. Patients who, for at least one cycle, experienced a delay of >2 weeks due to prolonged hematologic recovery during first-line chemotherapy
7. Patients receiving radiotherapy within 6 weeks prior to study treatment
8. Major surgery within 4 weeks of starting study treatment. Patients must have recovered from any effects of any major surgery
9. Previous allogeneic bone marrow transplantation
10. Any previous treatment with poly(ADP-ribose) polymerase inhibitor, including olaparib
11. Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or antineoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted as are steroidal antiemetics)
12. Current or recent (within 10 days prior to randomisation) chronic use of aspirin >325 mg/day
13. Concomitant use of known potent cytochrome P450 3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir
14. Prior history of hypertensive crisis (CTCAE grade 4) or hypertensive encephalopathy
15. Clinically significant (eg active) cardiovascular disease, including:
    - Myocardial infarction or unstable angina pectoris within ≤6 months of randomisation
    - New York Heart Association grade ≥2 congestive heart failure
    - Poorly controlled cardiac arrhythmia despite medication (patients with rate-controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on a resting electrocardiogram
    - Peripheral vascular disease grade ≥3 (eg symptomatic and interfering with activities of daily living requiring repair or revision)
16. Previous cerebrovascular accident, transient ischaemic attack or subarachnoid haemorrhage within 6 months prior to randomisation
17. History or evidence of haemorrhagic disorders within 6 months prior to randomisation
18. Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation)
19. History or clinical suspicion of brain metastases or spinal cord compression. Computed tomography (CT)/magnetic resonance imaging (MRI) of the brain is

mandatory (within 4 weeks prior to randomisation) in the case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomisation) in the case of suspected spinal cord compression

20. History or evidence upon neurological examination of central nervous system disease (eg uncontrolled seizures), unless adequately treated with standard medical therapy
21. Significant traumatic injury during 4 weeks prior to randomisation
22. Non-healing wound, active ulcer, or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible, but require 3-weekly wound examinations
23. History of vascular endothelial growth factor therapy-related abdominal fistula, gastrointestinal perforation, or active gastrointestinal bleeding within 6 months prior to the first study treatment
24. Current clinically relevant bowel obstruction, including sub-occlusive disease, related to the underlying disease
25. Patients with evidence of abdominal free air not explained by paracentesis or a recent surgical procedure
26. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment related complications
27. Pregnant or lactating women
28. Participation in another clinical study with an investigational product during the chemotherapy cycle immediately prior to randomisation
29. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
30. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
31. Immunocompromised patients, for example, with known active hepatitis (ie hepatitis B or C) due to the risk of transmitting the infection through blood or other body fluids or patients known to be serologically positive for human immunodeficiency virus

Assessment of disease progression

Tumour assessment scans (CT or MRI) were performed at baseline and then every 24 weeks (or at planned visits every 12 weeks if there was evidence of clinical progression

or progression according to the serum level of CA-125) up to month 42 or until the primary progression-free survival data cut-off. Following objective disease progression, tumour assessments were conducted at the investigator's discretion until second disease progression or death. Second disease progression was assessed according to local clinical practice and could involve any criteria of objective radiological progression, serum CA-125 level, symptomatic progression or death.

Trial oversight

This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, under the auspices of an independent data monitoring committee. The trial was designed by the European Network for Gynecological Oncological Trial Groups (ENGOT) lead group Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) and sponsored by Association de Recherche Cancers Gynecologiques (ARCAGY) Research, according to the ENGOT model A [1, 2].

Results

Table S1.
Patient characteristics by randomised treatment

At baseline	Olaparib plus bevacizumab (*n* = 537)	Placebo plus bevacizumab (*n* = 269)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)
ECOG performance status, n (%)		
0	378 (70)	189 (70)
1	153 (28)	76 (28)
Missing	6 (1)	4 (1)
Primary tumour location, n (%)		
Ovary	456 (85)	238 (88)
Fallopian tubes	39 (7)	11 (4)
Primary peritoneal	42 (8)	20 (7)
FIGO stage, n (%)		
III	378 (70)	186 (69)
IV	159 (30)	83 (31)
Histology, n (%)		
Serous	519 (97)	253 (94)
Endometrioid	12 (2)	8 (3)
Other[a]	6 (1)	8 (3)
History of cytoreductive surgery, n (%)		
Upfront surgery	271 (50)	138 (51)
Macroscopic residual disease	111 (41)	53 (38)
Complete resection	160 (59)	85 (62)
Interval surgery	228 (42)	110 (41)
Macroscopic residual disease	65 (29)	35 (32)
Complete resection	163 (71)	75 (68)
No surgery	38 (7)	21 (8)
Response after first-line therapy, n (%)		
No evidence of disease[b]	290 (54)	141 (52)
Clinical complete response[c]	106 (20)	53 (20)
Clinical partial response[d]	141 (26)	75 (28)

Normal serum CA-125 level		
Yes	463 (86)	234 (87)
No	74 (14)	34 (13)
Missing	0 (0)	1 (<1)
Deleterious tBRCAm[e], n (%)		
Yes	157 (29)	80 (30)
No	380 (71)	189 (70)
Myriad tumour HRD status[f], n (%)		
HRD-positive	255 (47)	132 (49)
HRD-negative or unknown	282 (53)	137 (51)
HRD-negative	192 (36)	85 (32)
Unknown	90 (17)	52 (19)
gBRCAm status[e], n (%)		
g*BRCA1*m	45 (8)	14 (5)
g*BRCA2*m	15 (3)	14 (5)
g*BRCA1*m and g*BRCA2*m	2 (<1)	0 (0)
No gBRCAm	104 (19)	64 (24)
gBRCAm status unknown	370 (69)	77 (66)
gBRCAm status missing	1 (<1)	0 (0)
First subsequent therapy[g], n (%)		
PARP inhibitor	49 (9)	72 (27)
Bevacizumab	41 (8)	27 (10)
Platinum-based regimen	273 (51)	159 (59)
Non-platinum-based regimen	295 (55)	183 (68)

Intent-to-treat population. Percentages may not total 100 due to rounding.

[a] 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)

[b] Defined as no measurable or assessable disease after cytoreductive surgery, in addition to no radiologic evidence of disease and a normal CA-125 level after chemotherapy

[c] Defined as the disappearance of all measurable or assessable disease and normalisation of CA-125 levels following chemotherapy

[d] Defined as radiologic evidence of disease, an abnormal CA-125 level, or both

[e] Per the electronic case report form

[f] HRD-positive was defined as a tBRCAm and/or genomic instability score of ≥42 on the myChoice® CDx assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA). HRD-negative was defined as a genomic instability score <42. Unknown was defined as an inconclusive, missing or failed myChoice® CDx assay

[g] Patients could receive >1 first subsequent therapy in combination; categories are not mutually exclusive.

CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline mutation in *BRCA1* and/or *BRCA2;* HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase (PARP); tBRCAm, tumour mutation in *BRCA1* and/or *BRCA2.*

Table S2.

Overview of AEs

	Olaparib plus bevacizumab (N=535)	Placebo plus bevacizumab (N=267)
Any AE	531 (99.3)	256 (95.9)
Any AE of grade ≥3	306 (57.2)	137 (51.3)
Any SAE	168 (31.4)	84 (31.5)
Any AE leading to dose reduction	223 (41.7)	21 (7.9)
Any AE leading to dose interruption	290 (54.2)	65 (24.3)
Any AE leading to discontinuation of trial intervention	112 (20.9)	15 (5.6)
Any AE with an outcome of death	1 (0.2)	4 (1.5)

Safety analysis set. Data are n (%). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Data shown are treatment-emergent AEs that occurred during study treatment or up to 30 days after discontinuation of the intervention.

AE, adverse event; SAE, serious AE.

Table S3.

Summary of AEs

	Olaparib plus bevacizumab (N=535)		Placebo plus bevacizumab (N=267)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	285 (53.3)	13 (2.4)	58 (21.7)	2 (0.7)
Fatigue or asthenia	284 (53.1)	28 (5.2)	86 (32.2)	4 (1.5)
Hypertension	244 (45.6)	100 (18.7)	161 (60.3)	82 (30.7)
Anaemia[a]	219 (40.9)	94 (17.6)	27 (10.1)	1 (0.4)
Lymphopenia[b]	128 (23.9)	38 (7.1)	25 (9.4)	3 (1.1)
Vomiting	119 (22.2)	8 (1.5)	29 (10.9)	5 (1.9)
Abdominal pain	118 (22.1)	8 (1.5)	59 (22.1)	5 (1.9)
Arthralgia	117 (21.9)	3 (0.6)	65 (24.3)	4 (1.5)
Diarrhoea	98 (18.3)	12 (2.2)	46 (17.2)	5 (1.9)
Neutropenia[c]	98 (18.3)	33 (6.2)	42 (15.7)	8 (3.0)
Leukopenia[d]	95 (17.8)	11 (2.1)	26 (9.7)	4 (1.5)
Urinary tract infection	79 (14.8)	1 (0.2)	27 (10.1)	1 (0.4)
Headache	73 (13.6)	2 (0.4)	36 (13.5)	2 (0.7)
Musculoskeletal pain	62 (11.6)	5 (0.9)	28 (10.5)	1 (0.4)
Neuropathy peripheral	59 (11.0)	3 (0.6)	18 (6.7)	3 (1.1)
Constipation	54 (10.1)	0 (0)	27 (10.1)	1 (0.4)
Thrombocytopenia[e]	42 (7.9)	9 (1.7)	9 (3.4)	1 (0.4)
Proteinuria	31 (5.8)	5 (0.9)	40 (15.0)	1 (0.4)
Intestinal obstruction	21 (3.9)	12 (2.2)	9 (3.4)	6 (2.2)

Safety analysis set. Data are n (%). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Data shown are all treatment-emergent AEs that occurred in at least 10% of patients in either treatment group and all grade ≥3 events occurring in at least 2% of patients in either treatment group (except where noted) during study treatment or up to 30 days after discontinuation of the intervention. In total, two patients in the olaparib plus bevacizumab group (aplastic anaemia: n=1; pneumonia: n=1) and three patients in the placebo plus bevacizumab group (dyspnoea: n=1; intestinal perforation: n=1; myocardial infarction: n=1) experienced a grade 5 AE.

[a] Includes patients with anaemia, decreased haemoglobin concentration, decreased haematocrit, decreased red-cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia or normocytic anaemia

[b] Includes patients with a decreased lymphocyte count, lymphopenia, a decreased B-lymphocyte count or a decreased T-lymphocyte count

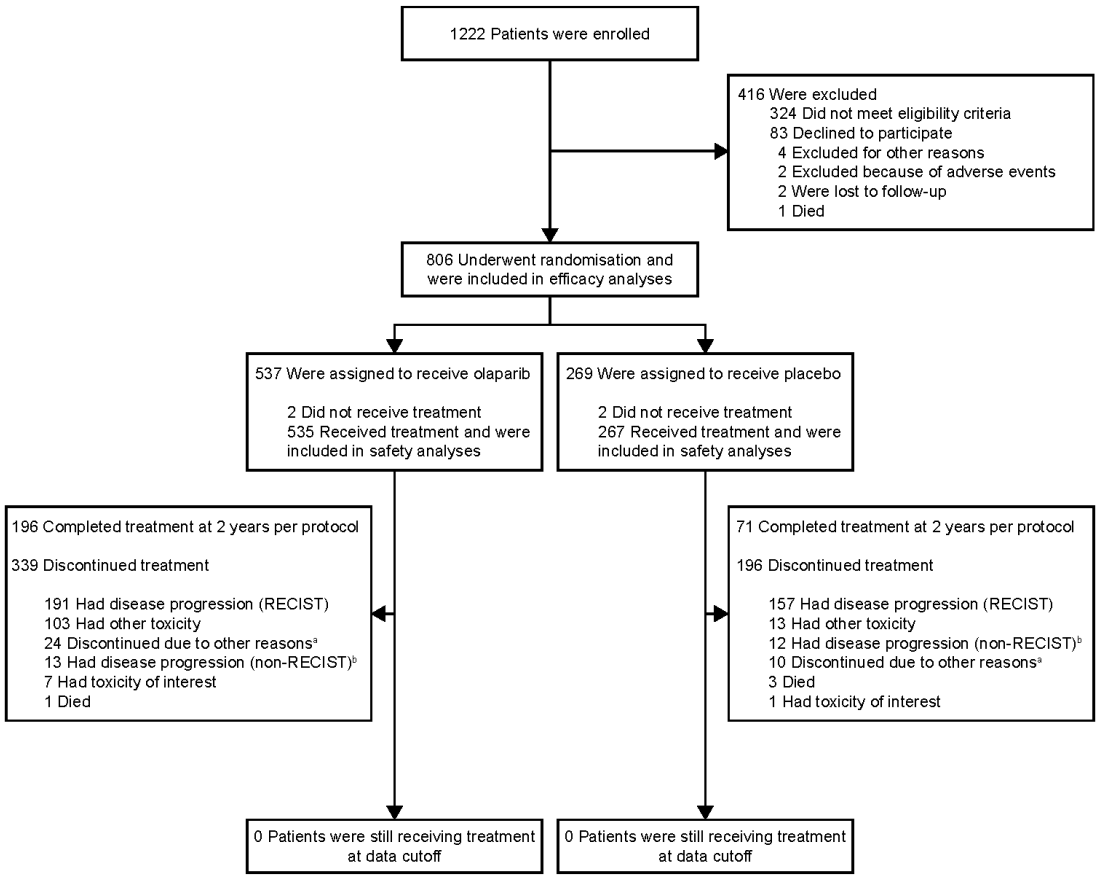
[c] Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count or agranulocytosis

[d] Includes patients with leukopenia or a decreased white-cell count

[e] Thrombocytopenia occurred in less than 10% of the patients in each trial group, but the data are provided to complete the profile of haematologic toxic effects. The data include patients with thrombocytopenia, decreased platelet production, a decreased platelet count, or a decreased plateletcrit.

AE, adverse event.

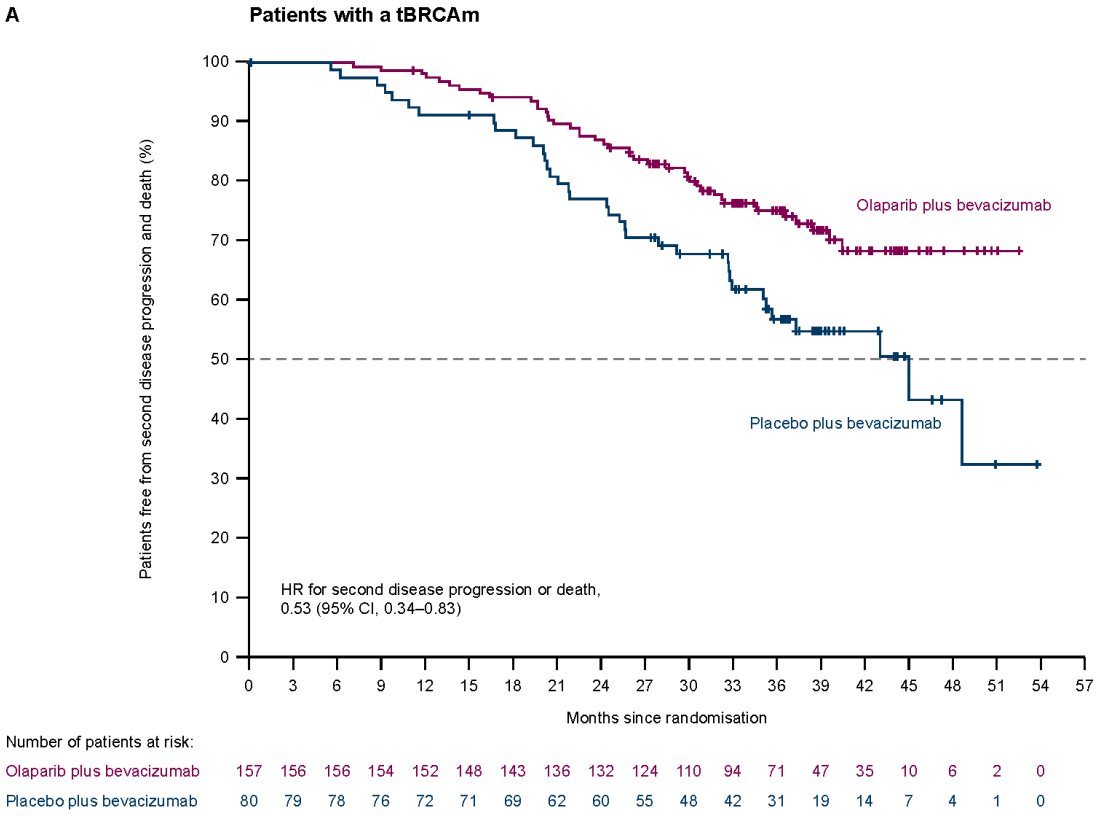
Fig. S1. Trial enrolment, randomisation and interventions

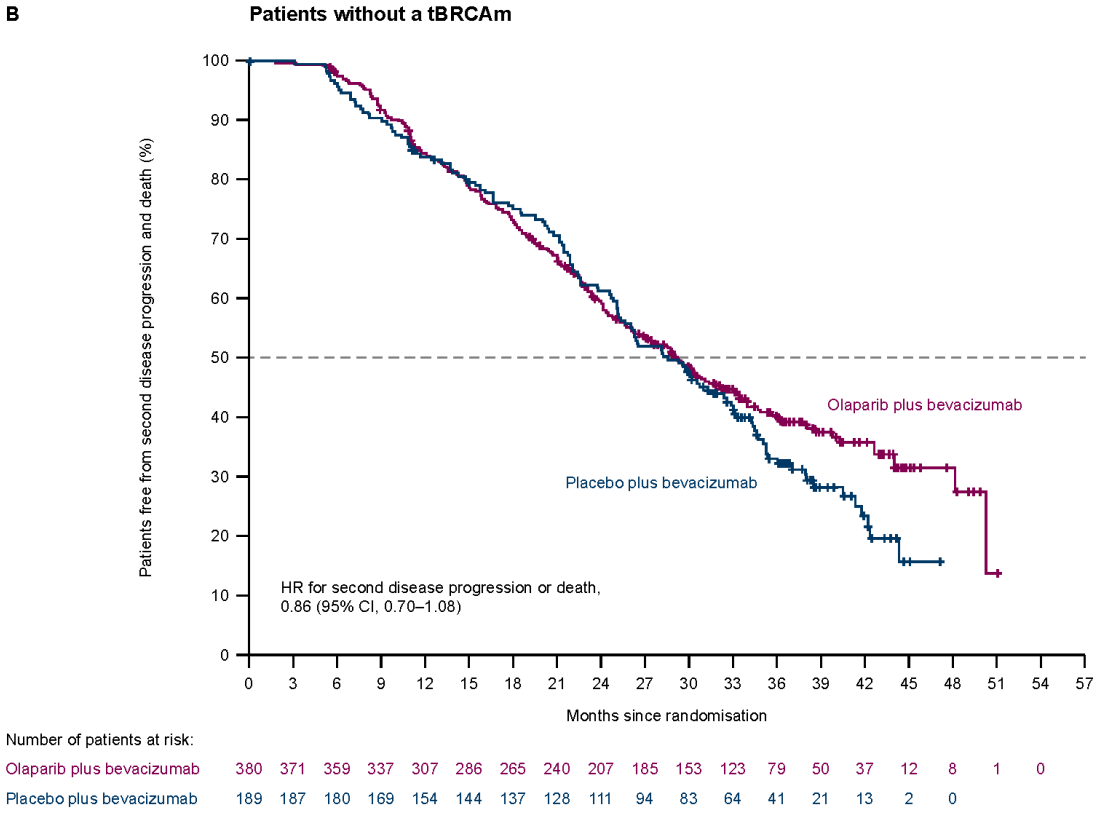


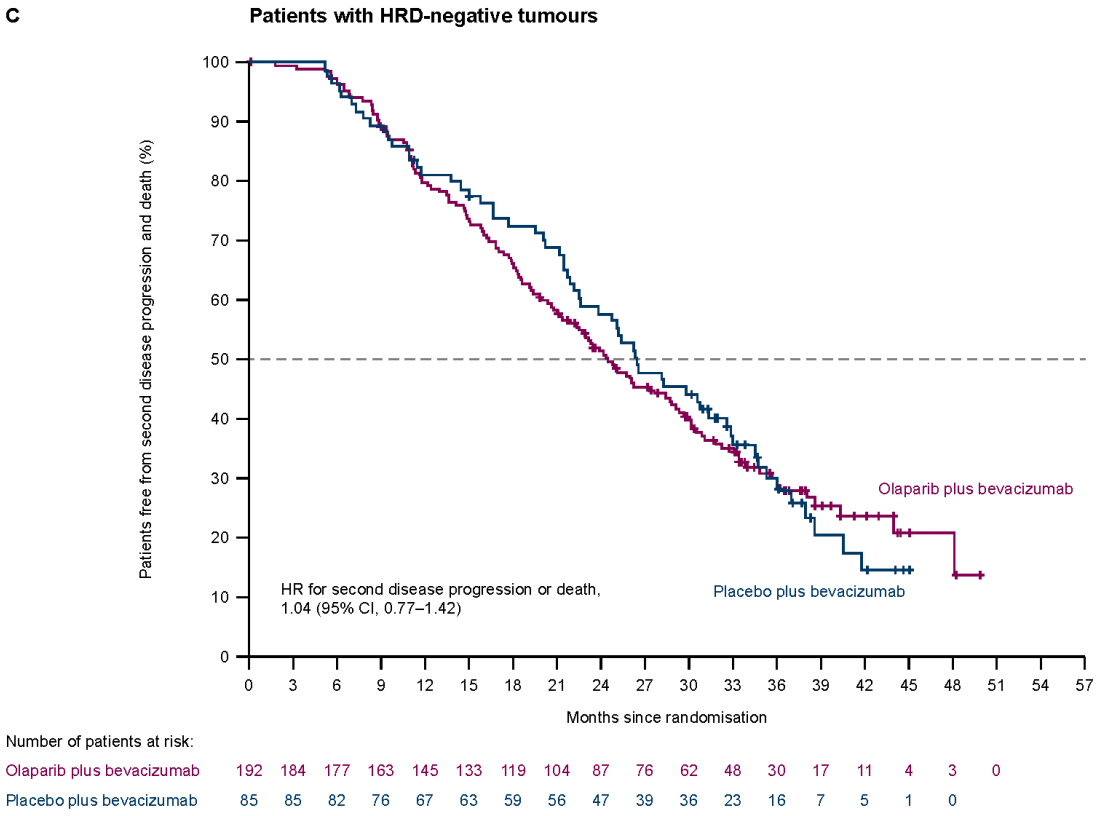
[a] Other reasons included consent withdrawn (n=4, olaparib plus bevacizumab; n=3, placebo plus bevacizumab), lost to follow-up (n=1, olaparib plus bevacizumab) and other (n=19, olaparib plus bevacizumab, n=7, placebo plus bevacizumab); [b] Disease progression defined by criteria other than RECIST (n=8, olaparib plus bevacizumab; n=9, placebo plus bevacizumab) or symptomatic deterioration (n=5, olaparib plus bevacizumab; n=3, placebo plus bevacizumab).

RECIST, Response Evaluation Criteria in Solid Tumors.

Fig. S2. Kaplan–Meier estimates of investigator-assessed PFS2 in (A) patients with a tBRCAm, (B) patients without a tBRCAm and (C) HRD-negative patients







Subgroups were defined post hoc for analysis of PFS2. Tumour HRD status was determined for 82% of the tumour samples.

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS2, time from randomisation to second progression or death; tBRCAm, tumour mutation in *BRCA1* and/or *BRCA2*.

References

[1] du Bois A, Reuss A, Pujade-Lauraine E, Pignata S, Ledermann J, Casado A, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and industry partners--first update 2015. Int J Gynecol Cancer. 2015;25:1328–30.

[2] Vergote I, Pujade-Lauraine E, Pignata S, Kristensen GB, Ledermann J, Casado A, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. Int J Gynecol Cancer. 2010;20:476–8.