Health-related quality of life in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib plus bevacizumab (PAOLA-1/ENGOT-ov25)

Florence Joly, MD, PhD,[1] Amélie Anota, PhD,[2] Sylvie Chabaud, MSc,[2] Claire Cropet, MSc,[2] Frank Priou, MD,[3] Philipp Harter, MD, PhD,[4] Sandro Pignata, MD, PhD,[5] Isabel Palacio, MD,[6] Edgar Petru, MD,[7] Hiroaki Kobayashi, MD,[8] Ignace Vergote, MD, PhD,[9] Gabriella Parma, MD,[10] Johanna Mäenpää, MD, PhD,[11] Eric Raymond, MD,[12] Beyhan Ataseven, MD,[13] Carmela Pisano, MD,[5] Nuria Lainez, MD,[14] Irina Tsibulak, MD,[15] Kan Yonemori, MD,[16] Peter Vuylsteke, MD,[17] Maria Teresa Lapresa, MD,[18] Mansoor Raza Mirza, MD,[19] Patrick Bouchaert, MD,[20] Paul Buderath, MD,[21] Domenica Lorusso, MD, PhD,[22] Ana Herrero, MD,[23] Lauriane Eberst, MD,[24] Alexander Burges, MD,[25] Giovanni Scambia, MD, PhD,[26]* Eugenia Ortega, MD,[27] Cécile Guillemet, MD,[28] Eric Pujade-Lauraine, MD, PhD,[29] Jean-Emmanuel Kurtz, MD, PhD,[24] Isabelle Ray-Coquard MD, PhD[30]

[1]Centre François Baclesse, and University Unicaen, Inserm U1086 Anticipe, Caen, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), France; [2]Centre Léon BERARD, Lyon, France; [3]CHD Les Oudairies, La Roche Sur Yon, and GINECO, France; [4]Ev. Kliniken Essen-Mitte, Essen, Philipps University, Marburg, and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Studiengruppe, Germany; [5]Istituto Nazionale Tumori IRCCS, 'Fondazione G Pascale', Naples, and Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO), Italy; [6]Hospital Universitario Central de Asturias, Oviedo, and Grupo Español de Investigación en Cáncer de Ovario (GEICO), Spain; [7]Medical University Graz, Graz, and Arbeitsgemeinschaft Gynaekologische Onkologie (AGO-Austria), Austria; [8]Kagoshima

University Hospital, Kagoshima, and Gynecologic Oncology Trial and Investigation Consortium (GOTIC), Japan; [9]University Hospital Leuven, Leuven Cancer Institute, Leuven, and Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Belgium, European Union; [10]European Institute of Oncology, Milan, and Mario Negri Gynecologic Oncology Group (MaNGO), Italy; [11]Tampere University and University Hospital, Tampere, and Nordic Society of Gynecologic Oncology (NSGO), Finland; [12]Groupe Hospitalier Saint-Joseph, Paris, and GINECO, France; [13]Ev. Kliniken Essen-Mitte, Essen, and AGO Studiengruppe, Germany; [14]Hospital Universitario de Navarra, Pamplona, and GEICO, Spain; [15]Medical University Innsbruck, Innsbruck, and AGO-Austria, Austria; [16]National Cancer Center Hospital, Tokyo, and GOTIC, Japan; [17]CHU UCL Namur, Namur, UC Louvain, CHU Brugmann, Brussels and BGOG, Belgium; [18]European Institute of Oncology, Milan, and MaNGO, Italy; [19]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [20]Hôpital de la Milétrie, Centre Hospitalier Universitaire de Poitiers, Pôle Régional de Cancérologie - Poitiers, and GINECO, France; [21]West German Cancer Center, University Hospital Essen, Universitätsklinikum Essen, Essen, and AGO, Germany; [22]Humanitas San Pio X and Humanitas University, Milan, and MITO, Italy; [23]Hospital Universitario Miguel Servet, Zaragoza, and GEICO, Spain; [24]ICANS (Institut de Cancérologie Strasbourg Europe), Strasbourg, and GINECO, France; [25]University Hospital, LMU Munich, Munich, and AGO, Germany; [26]Fondazione Policlinico Universitario A. Gemelli IRCCS and Università Cattolica del Sacro Cuore di Roma, Rome, and MITO, Italy; [27]Hospital Universitario Miguel Servet, Zaragoza, and GEICO, Spain; [28]Center Henri Becquerel, Rouen, and GINECO, France; [29]ARCAGY Research, Paris, France; [30]Centre Léon BERARD, University Claude Bernard Lyon I, Lyon, and GINECO, France

*Professor Giovanni Scambia died on February 20, 2025.

Funding: This work was supported by ARCAGY Research; AstraZeneca; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and F. Hoffmann-La Roche Ltd.

Corresponding author:

Prof Florence Joly, MD, PhD, Centre François Baclesse, 3 avenue Général Harris, 14000 Caen, France

Telephone: +33231455002

Email: f.joly@baclesse.unicancer.fr

Prior presentation: These data were presented in part in poster presentations at the American Society of Clinical Oncology (ASCO) 2022 Annual Meeting (June 3-7, 2022).

Title word limit (max 14): 18

Word count (max 3000): 2980

Figure/tables (max 8): 5/2

Abstract

Background: We analyzed health-related quality of life (HRQoL) and time until definitive HRQoL deterioration (TUDD) for patients with newly diagnosed advanced ovarian cancer receiving olaparib plus bevacizumab or placebo plus bevacizumab in PAOLA-1.

Methods: HRQoL and TUDD, prespecified secondary endpoints, were assessed by EORTC Core Quality of Life Questionnaire (QLQ-C30) and Ovarian Cancer module (QLQ-OV28) at baseline and then every 12 weeks for 2 years. HRQoL and TUDD by homologous recombination deficiency (HRD) status and effect of progression on HRQoL were *post hoc* analyses.

Results: 806 patients were randomized (olaparib plus bevacizumab n=537; placebo plus bevacizumab n=269). There were no clinically meaningful between-group differences in adjusted mean global change from baseline in QLQ-C30 or QLQ-OV28 domains overall (between-group difference in QLQ-C30 Global Heath Status (GHS) score [95% CI] 1.65 [−0.27, 3.56]) or in the HRD-positive subgroup (1.23 [−1.25, 3.71]). TUDD estimates of QLQ-C30 GHS scores did not differ between treatment arms in the modified intention-to-treat population (hazard ratio [HR]=0.88; 95% CI=0.72, 1.07) and favored olaparib plus bevacizumab versus placebo plus bevacizumab in the HRD-positive subgroup (HR=0.70; 95% CI=0.52, 0.93). Analyses of patients (103/465 [22.2%]) following disease progression showed clinically meaningful deterioration in QLQ-C30 emotional and social scores.

Conclusion: Adding maintenance olaparib to bevacizumab showed no clinically meaningful detrimental effect on global HRQoL either overall or in the HRD-positive subgroup. ClinicalTrials.gov ID: NCT02477644.

Word count (max 250): 222

Keywords: PAOLA-1; newly diagnosed advanced ovarian cancer; olaparib; bevacizumab; health-related quality of life; time without significant symptoms or toxicity.

Introduction

A key goal of ovarian cancer (OC) maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors is to improve progression-free survival (PFS) and overall survival (OS) while maintaining health-related quality of life (HRQoL). Patients with advanced OC (AOC) in clinical response after first-line treatment frequently experience few or no disease-related symptoms, and the benefits of delaying progression must be balanced against treatment-related adverse events (AEs), which may negatively impact HRQoL.[1] Few PARP inhibitor trials have assessed HRQoL beyond progression.[1,2]

The phase III PAOLA-1/ENGOT-ov25 trial showed significant PFS benefit with the addition of maintenance olaparib to bevacizumab in patients with newly diagnosed AOC.[3] Substantial PFS benefit was seen in patients whose tumors tested positive for homologous recombination deficiency (HRD; defined as the presence of a *BRCA1* and/or *BRCA2* mutation [BRCAm] mutation and/or genomic instability), with a median PFS of 37.2 months with olaparib plus bevacizumab versus 17.7 months with placebo plus bevacizumab (hazard ratio [HR]=0.33; 95% CI=0.25, 0.45).[3] These results led to the approval of maintenance olaparib plus bevacizumab in patients with HRD-positive AOC in response to first-line platinum-based chemotherapy (PBC) plus bevacizumab.[4,5] Olaparib plus bevacizumab was also associated with a clinically meaningful improvement in OS in patients with HRD-positive tumors, with 5-year OS rates of 65.5% versus 48.4% in the olaparib plus bevacizumab and placebo plus bevacizumab arms, respectively.[6]

As previously reported, global HRQoL, assessed via the adjusted mean change from baseline of the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) score, was not affected to a

clinically significant extent after the addition of placebo or olaparib to bevacizumab maintenance therapy in PAOLA-1.[3]

Here, we report detailed HRQoL analyses in the intention-to-treat (ITT) population and by HRD status, time until definitive HRQoL deterioration (TUDD), and *post hoc* exploratory analyses of HRQoL following disease progression and time without significant symptoms or toxicity (TWiST).

Methods

Study design and patients

The design of the PAOLA-1 phase III randomized, double-blind, placebo-controlled, multicenter trial (NCT02477644[7]) has been previously reported.[3] The protocol was approved by ethics committees at each participating site, and the trial performed in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Eligible patients had newly diagnosed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) high-grade serous or high-grade endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer; other epithelial non-mucinous OCs were permitted if patients had a deleterious germline BRCAm. Patients were eligible irrespective of biomarker or surgical status. Patients had no evidence of disease or were in clinical complete or partial response following surgery and PBC plus bevacizumab (**Supplementary Methods**).

The MyChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc, Salt Lake City, UT, USA) was used retrospectively to determine the prespecified tumor HRD status of patients (a positive test was defined as a tumor BRCAm [tBRCAm] and/or genomic

instability score ≥42) before the primary analysis. Before trial entry, tBRCAm status was determined by central French academic laboratories.

Study treatment

Patients were randomized 2:1 to olaparib tablets (300 mg twice daily) or placebo 3-9 weeks after their last chemotherapy dose. Randomization was stratified by first-line treatment outcome at screening and tBRCAm status. Maintenance therapy continued for up to 24 months or until investigator-assessed radiological disease progression (according to modified RECIST v1.1), unacceptable toxicity, or other discontinuation criteria were met. All patients received bevacizumab 15 mg/kg every 3 weeks for up to 15 months (including alongside PBC).

Study endpoints

The primary endpoint of PFS (data cutoff [DCO] March 22, 2019)[3] and the key secondary endpoint of OS (DCO March 22, 2022)[6] have been reported previously. Prespecified secondary endpoints included HRQoL, reported as mean change in Global Health Status (GHS) score and functional and symptomatic scale scores over time using the EORTC QLQ-C30[8] and EORTC Quality of Life Questionnaire Ovarian Cancer module (QLQ-OV28),[9] and TUDD (defined as the time interval between randomization and the occurrence of the first clinically relevant deterioration in QLQ-C30 and QLQ-OV28 scores from baseline with no further clinically relevant improvement from baseline, or all-cause death). HRQoL and TUDD by HRD status, HRQoL pre- versus post-progression, and TWiST were *post hoc* exploratory analyses.

Study assessments

QLQ-C30,[8] a validated 30-question instrument specific to patients with cancer, includes a GHS scale, five functional scales (physical, role, emotional, cognitive, and social

functioning), and nine symptomatic scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). QLQ-OV28[9] is a validated OC-specific 28-question instrument designed for use in patients with local or advanced disease who undergo surgery with or without chemotherapy. It includes three functional scales (body image, sexual function, and attitude to disease/treatment) and five symptomatic scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, hormonal/menopausal symptoms, other chemotherapy side effects, and hair loss). For both QLQ-C30 and QLQ-OV28, scores range from 0 to 100, with higher scores for GHS and functional scales representing higher global quality-of-life (QoL) and higher functional level, respectively, and higher scores for symptomatic scales representing higher symptomatic burden.

Patients self-completed questionnaires (on paper) in their native language at baseline and every 12 weeks (±6-week window) for 2 years following randomization during clinic visits, irrespective of whether they experienced disease progression. Only the questionnaire closest to the planned measurement timepoint was used if >1 questionnaire was available. Questionnaires were no longer completed once patients discontinued the study, completed 2 years of follow-up, or died.

Statistical analyses

The ITT population included all randomized patients regardless of intervention received. HRQoL analyses were performed on patients who completed both a baseline and at least one post-baseline questionnaire (modified ITT [mITT] population).

HRQoL data were analyzed in the mITT population and in HRD-positive and HRD-negative subgroups. All questionnaires completed during 2 years of follow-up were included in the HRQoL analysis, even if the patient had progressed. Each scale of QLQ-

C30 and QLQ-OV28 was analyzed independently. Adjusted mean change from each HRQoL score was analyzed by mixed model for repeated measures until 2 years of follow-up. The Kaplan-Meier method was used to generate time-to-event curves for TUDD with a univariate Cox model used to estimate HRs and 95% Cls. The prespecified minimal important difference (MID) for clinically relevant change in any HRQoL scale and TUDD was fixed at 10 points.[10] All P values <.05 were considered statistically significant.

The HRQoL post-progression analysis was conducted on all available HRQoL data for both treatment arms combined. QLQ-C30 scores following diagnosis of RECIST progression (up to a maximum of 60 days after progression) were compared with the last measurement collected prior to progression (up to a maximum of 60 days before progression). Results were expressed as mean change in HRQoL score between pre- and post-progression with 95% CI.

TWiST was analyzed in the ITT population and by HRD status (DCO March 22, 2019) and calculated as the total number of days without symptoms or toxicity (TOX) between randomization and first disease progression or censoring for progression (PFS minus TOX) for three TOX states (see **Supplementary Methods** and **Figure S1**).

Detailed methodology is provided in the **Supplementary Methods**.

Results

Patient disposition

806 eligible patients were randomly assigned to olaparib plus bevacizumab (n=537) or placebo plus bevacizumab (n=269) (ITT population) and 535 and 267 patients, respectively, received investigational treatment (**Figure 1**). A total of 770 patients (517 in

the olaparib plus bevacizumab arm and 253 in the placebo plus bevacizumab arm) had a baseline and at least one follow-up score and constitute the mITT population.

Baseline characteristics were well balanced between treatment arms in the ITT population, and HRD-positive subgroup (**Table 1**).[3] Baseline QLQ-C30 GHS scores were also similar between treatment arms (**Table 1**).

Treatment exposure

Among the patients who received investigational treatment, the median (range) duration of treatment for olaparib was 17.3 months (0.0-33.0) and for placebo was 15.6 months (0.1-26.2) in the olaparib plus bevacizumab and placebo plus bevacizumab arms, respectively, and the median (range) duration of treatment for bevacizumab since randomization was 11.0 (0.7-21.4) and 10.6 months (0.7-17.1), respectively (DCO March 22, 2019).

QLQ-C30 and QLQ-OV28 compliance and completion rates

In the ITT population, baseline QLQ-C30 compliance rates were high and well balanced between treatment arms (96.1% [516/537] and 94.1% [253/269] with olaparib plus bevacizumab and placebo plus bevacizumab, respectively) (**Table S1**). Compliance rates remained high through Week 96 (72.1% [302/419] and 71.0% [147/207], respectively), with little difference between treatment arms at any timepoint (**Table S1**). Similar compliance rates were reported for the QLQ-OV28 (**Table S2**). Completion rates are reported in **Tables S1 and S2**; 'site missed administration' was generally the most common reason for questionnaires not being completed (**Table S3**).

Adjusted mean change from baseline in HRQoL

In the mITT population, the adjusted mean (95% CI) global change from baseline in QLQ-C30 GHS score was −1.12 (−2.21, −0.02) and −2.76 (−4.34, −1.19) with olaparib

plus bevacizumab and placebo plus bevacizumab, respectively (difference between arms: 1.65 [−0.27, 3.56]) (**Table 2**). Since the time-by-treatment interaction for this dimension was significant (*P*=.0015), results by timepoint should also be considered (**Table S4**). The mean change from baseline in GHS remained close to zero through Week 96 in both treatment arms (**Fig 2A**).

QLQ-C30 scores for nausea and vomiting favored placebo plus bevacizumab versus olaparib plus bevacizumab from Weeks 12 to 72 (**Figure 2B**). QLQ-C30 appetite loss scores favored placebo plus bevacizumab versus olaparib plus bevacizumab from Weeks 12 to 48 (**Figure 2C**). QLQ-C30 fatigue scores initially favored placebo plus bevacizumab (Week 12) but favored olaparib plus bevacizumab from Week 60 onwards (**Figure 2D**). QLQ-C30 insomnia scores favored olaparib plus bevacizumab versus placebo plus bevacizumab from Weeks 12 to 96 (**Figure 2E**). Over time there was minimal difference between treatment arms in QLQ-C3 scores for constipation (**Figure 2F**). None of the differences between treatment groups exceeded the MID (**Table S4**).

In other dimensions of the QLQ-C30 and QLQ-OV28, none of the between-group differences with mixed model were clinically relevant at the 10-point MID (**Tables 2**, **S4,** and **S5** and **Figures S2**, **S3**,and **S4**).

Adjusted mean change from baseline in HRQoL by HRD status

In the HRD-positive and HRD-negative subgroups, clinically relevant worsening or improvement in some QLQ-C30 and QLQ-OV28 domain scores was seen with olaparib plus bevacizumab or placebo plus bevacizumab at certain timepoints (**Tables S6**, **S7**, **S8** and **S9**). For example, with olaparib plus bevacizumab, clinically relevant worsening of nausea or vomiting and appetite loss were observed at Week 12 in the HRD-positive subgroup (**Table S6**). However, no between-group differences in any adjusted mean

QLQ-C30 or QLQ-OV28 change from baseline scores were clinically relevant at the 10-point MID, either at specific timepoints or globally in the HRD-positive or HRD-negative subgroups (**Figures S5** and **S6**). In the HRD-positive subgroup, the difference between the olaparib plus bevacizumab and placebo plus bevacizumab arms in the adjusted mean (95% CI) global change from baseline in QLQ-C30 GHS score was 1.23 (−1.25, 3.71) (**Table S6**).

Mean change in QLQ-C30 scores post-progression

HRQoL questionnaires completed following progression were available for 103 of 465 (22.2%) patients who had RECIST progression during the 2 years of follow-up. For treatment arms combined, clinically meaningful deterioration in QLQ-C30 scores following progression was seen in emotional functioning (mean [95% CI] change pre- to post-progression −12.30 [−16.46, −8.13]) and social functioning (−11.17 [−16.21, −6.12]) (**Figure 3**). Mean changes in QLQ-C30 scores by treatment arm following progression are reported in **Table S10**.

TUDD

In the mITT population, TUDD estimates of QLQ-C30 GHS did not differ between treatment arms (HR=0.88; 95% CI=0.72, 1.07) (**Figure 4A**). In the HRD-positive subgroup, TUDD estimates of QLQ-C30 GHS favored olaparib plus bevacizumab versus placebo plus bevacizumab (HR=0.70; 95% CI=0.52, 0.93) (**Figure 4B**). In the mITT population, TUDD estimates for each QLQ-C30 and QLQ-OV28 scale score are reported in **Figure 5**. In summary, apart from QLQ-C30 appetite loss (HR=1.36; 95% CI=1.10, 1.67) and nausea and vomiting (HR=1.63; 95% CI=1.35, 1.98) scores, which were numerically in favor of placebo plus bevacizumab versus olaparib plus bevacizumab,

TUDD estimates for each QLQ-C30 and QLQ-OV28 scale score did not significantly differ between treatment arms.

TWiST in the overall population and by HRD status

Median TWiST significantly (*P*<.0001) favored olaparib plus bevacizumab over placebo plus bevacizumab overall and in the HRD-positive subgroup for all three TOX states (see **Supplementary Results** and **Figure S7**).

Discussion

The addition of olaparib to bevacizumab had no detrimental effect on global HRQoL, indicating that HRQoL was maintained in women with newly diagnosed AOC, either overall or in the HRD-positive subgroup.

The most common non-hematologic AEs reported by patients receiving olaparib include fatigue, nausea, and vomiting.[3,11,12] Although worsening in QLQ-C30 scores for fatigue, nausea or vomiting, and appetite loss appeared to peak at Week 12 with olaparib plus bevacizumab, it should be noted that symptom scores at earlier timepoints were not available as patients did not complete their first post-baseline questionnaire until Week 12. Particular attention should be paid to AEs during the first few months of maintenance therapy during routine clinical practice to optimize adherence. QLQ-C30 scores for fatigue, nausea or vomiting, and appetite loss all resolved to the level of placebo plus bevacizumab over time, which could be explained by habituation or dose modification of olaparib. TUDD HRs for QLQ-C30 appetite loss and nausea and vomiting also favored placebo plus bevacizumab over olaparib plus bevacizumab, suggesting that these symptoms may be bothersome in some patients receiving olaparib plus bevacizumab. Importantly, in the HRD-positive subgroup, no clinically relevant differences between treatment arms were seen in mean change from baseline in HRQoL

306 scores, suggesting that maintenance olaparib was not detrimental to HRQoL in this
307 subgroup. Furthermore, olaparib plus bevacizumab therapy resulted in TUDD benefit in
308 the HRD-positive subgroup. Interestingly, constipation was not found to be a major
309 HRQoL symptom for patients receiving olaparib plus bevacizumab in PAOLA-1, whereas
310 it was worse over time in patients who received maintenance niraparib in the PRIMA
311 trial.[13]

312 Despite the inclusion of bevacizumab in PAOLA-1, our findings are consistent
313 with those seen with maintenance olaparib monotherapy in the phase III SOLO1 trial in
314 patients with newly diagnosed AOC and a BRCAm.[1] In SOLO1, maintenance olaparib
315 monotherapy had no detrimental effect on HRQoL.[1]

316 Guidelines for analyzing HRQoL in cancer trials recommend evaluating time-to-
317 event outcomes and the magnitude of events (improvement or worsening using the
318 linear mixed model),[14] rather than evaluating endpoints such as TWiST. However,
319 TWiST provides important insight into the effect of maintenance treatment on otherwise
320 symptom-free patients, and olaparib monotherapy demonstrated a substantial TWiST
321 benefit in SOLO1.[1] In our *post hoc* exploratory analysis of the ITT population, we
322 observed a substantial, significant TWiST benefit across three TOX states,
323 demonstrating robustness of the TWiST results. Furthermore, a recent analysis of the
324 association between toxicity and QoL supported selection of all grade ≥2 AEs with
325 symptoms to accurately reflect QoL.[15] An even greater TWiST benefit was observed with
326 olaparib plus bevacizumab over placebo plus bevacizumab in the HRD-positive
327 subgroup, which may reflect the substantial PFS benefit observed in the HRD-positive
328 subgroup.[3] These findings support the association between TWiST and HRQoL and
329 suggest that the delayed disease progression[3] and clinically meaningful OS benefit[6]

seen with olaparib plus bevacizumab versus placebo plus bevacizumab in patients with HRD-positive tumors was not offset by adverse effects of maintenance olaparib.

In our *post hoc* exploratory combined treatment arm analysis of HRQoL before and after RECIST progression, most QLQ-C30 domains (including GHS) revealed post-progression deterioration in HRQoL, with clinically meaningful deterioration in emotional functioning and social functioning. Deterioration of HRQoL following first recurrence in patients with AOC has been demonstrated in several studies.[1,2,16] Anxiety and depression items in the EuroQol 5-Dimension 5-Level, which partially correspond to emotional functioning in the QLQ-C30, were the most frequently affected domains post-progression in SOLO1.[1] Of QLQ-C30 domains assessed in the phase III PRIMA trial of maintenance niraparib, only emotional functioning exhibited clinically meaningful deterioration post-progression, which was sustained throughout the 24-week follow-up period.[2] These studies indicate an emotional burden associated with disease progression. PARP inhibitor maintenance therapy has the potential to help a proportion of patients avoid the substantial burden associated with disease progression; in the HRD-positive subgroup in PAOLA-1, 46.1% of patients in the olaparib plus bevacizumab arm had not relapsed at 5 years versus 19.2% in the placebo plus bevacizumab arm.[6]

The limitations of PAOLA-1 have been described previously[3] and include the absence of an olaparib monotherapy comparator arm and lack of prespecified analyses by HRD status from the multiple testing procedure. Low compliance can be a challenge for patient-reported outcomes studies;[17,18] however, compliance rates in this analysis were high throughout the study with no notable difference between treatment arms. Disease progression adversely affected HRQoL data collection, with post-progression questionnaires completed by only 22.2% of patients. HRQoL instruments administered via electronic devices are now available, which may facilitate higher completion rates

and mitigate the risk of collection bias in future studies. Other digital tools (eg, smartphone apps) may also prove useful for monitoring HRQoL.[19] Underestimation or overestimation of patient-reported HRQoL may result from underreporting of symptoms during remission and overreporting of symptoms following relapse. Fatigue/asthenia was one of the most common AEs reported in PAOLA-1;[3] the three QLQ-C30 items contributing to the fatigue score can be easily implemented in clinical practice. A specific questionnaire to analyze fatigue (EORTC QLQ-FA12) is also available. Wearable technologies also have potential for monitoring symptoms such as fatigue.[20] Furthermore, while there were instances of missing data, this was likely mitigated by the large sample size and high compliance rates.

Conclusions

The addition of maintenance olaparib to bevacizumab had no clinically meaningful impact on global HRQoL either overall or in the HRD-positive subgroup. TUDD estimates of QLQ-C30 GHS favored olaparib plus bevacizumab over placebo plus bevacizumab. Maintenance therapy with olaparib plus bevacizumab may allow an important fraction of patients with HRD-positive OC to evade the substantial burden imposed by disease progression. In conclusion, in patients with newly diagnosed AOC in response after first-line PBC plus bevacizumab, the addition of olaparib provided a substantial PFS benefit while maintaining HRQoL.

Data Availability

ARCAGY-GINECO has a long history of academic data sharing for research purposes. The process is similar for every trial sponsored by ARCAGY-GINECO (or ARCAGY Research). Researchers have to submit a request to the sponsor directly or through the

principal investigator. The request should be written in a predefined format of a short synopsis indicating the objective of the research, the methodology intended to be used, including the statistical analysis plan, and the variables within the database required for the research. A scientific board will review and approve the requests on a case-by-case basis.

Only encoded datasets will be used, which enables us to fulfill legal and ethical obligations to protect our patients while at the same time utilizing patient data in progressing medical research to its full potential in the best interests of public health.

A specific agreement between the sponsor and the researcher is requested for data transfer. This data transfer agreement details both parties responsibilities to ensure the required level of data integrity and legal and ethical obligations.

In the case of sharing encoded patient-level data, please note that the full dataset may not be shared in view of the following: clinical consent for some countries prohibits secondary use of the data; patients may withdraw their consent for participation in the trial at any point; other aspects might also be taken into consideration to protect patient privacy (eg, review of rare clinical events where information is aggregated to a higher level before sharing).

Funding

This work was supported by ARCAGY Research; AstraZeneca; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and F. Hoffmann-La Roche Ltd. Medical writing assistance was provided by Gillian Keating, MBChB, Tobias Hedison, PhD, and Callan Atwell, PhD, of Amiculum, funded by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conflicts of Interest

Florence Joly reports consulting fees from GlaxoSmithKline (GSK) (consulting for the European Medicines Agency); payment/honoraria (advisory board) from AstraZeneca, Merck Sharp & Dohme LLC (MSD), and Seagen; payment/honoraria (advisory board, lectures) from GSK and Clovis; and support for attending meetings and/or travel (symposium) from GSK, AstraZeneca, and MSD.

Amélie Anota reports consulting fees and travel expenses from AstraZeneca, BMS, and Roche; travel expenses from Novartis and Pfizer; and consulting fees from Amgen.

Sylvie Chabaud reports no conflicts of interest.

Claire Cropet reports no conflicts of interest.

Frank Priou reports payment/honoraria (advisory board) from AstraZeneca, Daiichi, and Novartis; and support for attending meetings from Novartis.

Philipp Harter reports honoraria from Amgen, AstraZeneca, GSK, Immunogen, Roche, Sotio, Stryker, Zai Lab, MSD, Clovis, Miltenyi, Eisai, Mersana, Exscientia, Daiichi Sankyo, and Karyopharm; membership on an advisory board for AstraZeneca, Roche, GSK, Clovis, Immunogen, MSD, Miltenyi, Novartis, Eisai, Corcept, and Biontech; and research funding (institutional) from AstraZeneca, Roche, GSK, Genmab, Immunogen, Seagen, Clovis, Novartis, MSD, and Exscientia.

Sandro Pignata reports honoraria from AstraZeneca, MSD, Roche, Pfizer, GSK, and Clovis Pharma; and research funding from Roche, MSD, AstraZeneca, and Pfizer.

Isabel Palacio reports personal fees and travel accommodation from AstraZeneca, GSK, Bristol Myers Squibb, MSD, Merck, and Clovis Oncology.

Edgar Petru reports honoraria for lectures from AstraZeneca and Roche; and honoraria for AstraZeneca and Roche.

Hiroaki Kobayashi reports no conflicts of interest.

Ignace Vergote reports consulting fees (personal) from Agenus, Akesobio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, Jazzpharma, Karyopharm, Mersana, MSD, Novocure, Novartis, Oncoinvent, OncXerna, Sanofi, Regeneron, Seagen, Sotio, Verastem Oncology, and Zentalis.

Gabriella Parma reports no conflicts of interest.

Johanna Mäenpää reports honoraria from Eisai, GSK, and AstraZeneca.

Eric Raymond reports holding stock in Genoscience Pharma, Axoltis Pharma, StromaCare, and SCOR; consulting for SCOR; scientific board member for Onward Therapeutics; scientific advisor for Genfit; board member for INCa; and president and scientific director for Institut des Vaisseaux et du Sang (IVS).

Beyhan Ataseven reports honoraria for lectures from Roche, GSK, Celgene, Clovis, AstraZeneca, Novartis, MSD, Eisai, Lilly, Medconcept, Medupdate, Eickeler, BSH, NCO, StreamedUp, ClinSol, Onkowissen, Esteve, and Pfizerl participation in advisory boards for Roche, GSK, Amgen, MSD, Sanofi Aventis, and Eisai; and travel/congress support from Roche, AstraZeneca, GSK, PharmaMar, Lilly, AbbVie, and Gilead.

Carmela Pisano reports honoraria from Eisai, GSK, MSD, and AstraZeneca.

Nuria Lainez reports payment for a consulting or advisory role from Ipsen, AstraZeneca, Bayer, Eisai, BMS, and MSD; and payment for participation in a speakers' bureau from Ipsen, Merck, and MSD.

Irina Tsibulak reports participation in advisory boards for AstraZeneca; honoraria from Roche, PharmaMar, and AstraZeneca; and travel expenses from Roche, PharmaMar, Astra Zeneca, Eisai, and DSK.

Kan Yonemori reports honoraria for lectures from Pfizer, Eisai, AstraZeneca, Eli Lilly, Takeda, Chugai, Fuji Film Pharma, PDR pharma, MSD, Boehringer Ingelheim, Ono, Daiichi-Sankyo, Bayer, Janssen, Astellas, Bristol Myers Squibb, Novartis, Sanofi, and Merck Biopharma; advisory board fees from Eisai, Astra Zeneca, Sanofi, Genmab, Gliead, OncXerna, Takeda, Novartis, MSD, Henlius, EP Biopharma, LTT Biopharma, Haihe, and Chugai; research support (institutional) from MSD, Daiichi-Sankyo, Merck Biopharma, AstraZeneca, Taiho, Pfizer, Novartis, Takeda, Chugai, Ono, Sanofi, Seattle Genetics, Eisai, Eli Lilly, Genmab, Boehringer Ingelheim, Kyowa Hakko Kirin, Nihon Kayaku, and Haihe; and principal investigator support (institutional) from MSD, Daiichi-Sankyo, Genmab, Seagen, AstraZeneca, Taiho, Merck Biopharma, Pfizer, Novartis, Takeda, Chugai, Ono, Sanofi, Seattle Genetics, Eisai, Eli Lilly, Genmab, Boehringer Ingelheim, Kyowa Hakko Kirin, Nihon Kayaku, and Haihe.

Peter Vuylsteke reports honoraria from Roche/Genentech, Novartis, and MSD Oncology; and support for travel, accommodation, and expenses from Roche and MSD Oncology.

Maria Teresa Lapresa reports being an invited speaker for GSK and AstraZeneca/MSD.

Mansoor Raza Mirza reports advisory board participation for Acrivon Therapeutics Inc., Allarity Therapeutics, AstraZeneca, Biocad, BioNTech, Boehringer Ingelheim, Clovis, Daiichi-Sankyo, DualityBio, Eisai, Genmab, GSK, Immunogen, Incyte, Karyopharm, Merck/MSD, Mersana, Novartis, NyKode, Regeneron, Roche, SeaGen, Takeda, Tesaro, and Zailab; member of board of directors and stocks/shares for Karyopharm

Therapeutics Inc. US and Sera Prognostics Inc. US; research grant (institutional) from Allarity Therapeutics, Apexigen, AstraZeneca, Boehringer Ingelheim, Clovis, GSK, Novartis, Tesaro, and Ultimovacs; trial chair for AstraZeneca, BioNTech, Boehringer Ingelheim, Deciphera, Daiichi-Sankyo, GSK, Merck, Mersana, NuvationBio, and Tesaro; and employment (Chief Medical Officer) for Acrivon Therapeutics Inc.

Patrick Bouchaert reports honoraria from Astellas, BMS, Eisai, GSK, Ipsen, and Janssen, and support for attending meetings and/or travel from Astellas, Bayer, BMS, Daiichi Sankyo, Ipsen, Janssen, and Merck.

Paul Buderath reports honoraria for advisory boards and lectures from Genmab, AstraZeneca, MSD, and GSK.

Domenica Lorusso reports consultancy fees (personal) from Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, Immunogen, MSD, PharmaMar, and Seagen; membership on an advisory board (personal) for AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, Immunogen, Merck Serono, MSD, Oncoinvent, PharmaMar, Seagen, and Sutro; research funding (institutional) from AstraZeneca, Clovis Oncology, Genmab, GSK, Immunogen, Incyte, MSD, Novartis, PharmaMar, Roche, and Seagen; and travel support from Roche, PharmaMar, AstraZeneca, Clovis Oncology, and GSK.

Ana Herrero reports participation in speakers' bureaus sponsored by GSK, AstraZeneca, MSD, and Clovis; and support for attending meetings and/or travel from GSK and AstraZeneca.

Lauriane Eberst reports no conflicts of interest.

Alexander Burges reports lecture/advisory board honoraria from AstraZeneca, Roche, and Tesaro.

Giovanni Scambia reports grant/research support from MSD Italia S.r.l.; consulting fees from Johnson & Johnson and Tesaro Bio Italy S.r.l.; and speakers' bureau fees/honoraria from Clovis Oncology Italy S.r.l. and and MSD Italia Srl.

Eugenia Ortega reports support for attending meetings and/or travel from AstraZeneca, Clovis, Merck, GSK, MSD, and Eisai; and payment or honoraria for presentations, speakers' bureaus, or educational events from Merck, AstraZeneca, PharmaMar, Clovis, MSD, Eisai, and GSK.

Cécile Guillemet reports no conflicts of interest.

Eric Pujade-Lauraine reports membership on an advisory board (personal) for Roche, GSK, and AstraZeneca; Independent Data Monitoring Committee board membership (personal) for Agenus and Incyte; and employment (personal) at ARCAGY Research.

Jean-Emmanuel Kurtz reports honoraria or consultation fees from GSK, MSD, and AstraZeneca; and employment of a close relative by MSD unrelated to the current work.

Isabelle Ray-Coquard reports honoraria (personal) from AbbVie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, AstraZeneca, Roche, GSK, MSD, Deciphera, Mersana, Merck Sereno, Novartis, Amgen, Tesaro, and Clovis Oncology; honoraria (institution) from GSK, MSD, Roche, and BMS; advisory/consulting fees from AbbVie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, AstraZeneca, Roche/Genentech, GSK, MSD, Deciphera, Mersana, Merck Sereno, Novartis, Amgen, Tesaro, and Clovis Oncology; research grant/funding (personal) from MSD, Roche, and BMS; research grant/funding (institution) from MSD, Roche, BMS, Novartis, AstraZeneca, and Merck Sereno; and travel support from Roche, AstraZeneca, and GSK.

Author Contributions

Florence Joly, MD, PhD: Conceptualization; Investigation; Resources; Writing – original draft; Writing – review & editing

Amélie Anota, PhD: Methodology; Formal analysis; Writing – original draft; Writing – review & editing

Sylvie Chabaud, MSc: Methodology; Formal analysis; Writing – original draft; Writing – review & editing

Claire Cropet, MSc: Methodology; Formal analysis; Writing – original draft Writing – review & editing

Frank Priou, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Philipp Harter, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Sandro Pignata, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Isabel Palacio, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Edgar Petru, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Hiroaki Kobayashi, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Ignace Vergote, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Gabriella Parma, MD: Investigation, Resources; Writing – original draft; Writing – review & editing

Johanna Mäenpää, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Eric Raymond, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Beyhan Ataseven, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Carmela Pisano, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Nuria Lainez, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Irina Tsibulak, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Kan Yonemori, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Peter Vuylsteke, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Maria Teresa Lapresa, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Mansoor Raza Mirza, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Patrick Bouchaert, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Paul Buderath, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Domenica Lorusso, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Ana Herrero, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Lauriane Eberst, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Alexander Burges, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Giovanni Scambia, MD, PhD: Investigation; Resources; Writing – original draft; Writing – review & editing

Eugenia Ortega, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Cécile Guillemet, MD: Investigation; Resources; Writing – original draft; Writing – review & editing

Eric Pujade-Lauraine, MD, PhD: Conceptualization; Writing – original draft; Writing – review & editing

Jean-Emmanuel Kurtz, MD, PhD: Conceptualization; Investigation; Resources; Writing – original draft; Writing – review & editing

Isabelle Ray-Coquard, MD, PhD: Conceptualization; Investigation; Resources; Writing – original draft; Writing – review & editing

Acknowledgements

The trial was designed by the European Network for Gynaecological Oncological Trial groups (ENGOT) lead group Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovariens (GINECO) and sponsored by Association de Recherche Cancers Gynécologiques (ARCAGY) Research, according to the ENGOT model A (academic sponsor).[21,22] ARCAGY Research was responsible for overseeing the collection, analysis, and interpretation of the data. AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and F. Hoffmann-La Roche Ltd, were given the opportunity to review the draft manuscript(s) but were not asked to approve the final content because this was an academic-sponsored study. The funders had no role in the design of the study, the writing of the manuscript or the decision to submit it for publication.

We would like to give special acknowledgement to the late Professor Giovanni Scambia for his contribution to the PAOLA-1 study and the findings reported here and more broadly to the field of gynecological oncology. Professor Scambia was a Professor of Obstetrics and Gynaecology at Università Cattolica del Sacro Cuore and Scientific Director of Fondazione Policlinico Universitario Agostino Gemelli IRCCS where his innovative and groundbreaking research transformed patient care. Professor Scambia was a committed teacher and founded the Catholic Laparoscopy Advanced Surgery

608 School. Professor Scambia was an active member in numerous international and
609 national scientific societies including MITO (Multicenter Italian Trials in Ovarian Cancer)
610 and the European Society for Gynaecological Endoscopy, where he was the Chair of the
611 Board of Directors.

612

References

1. Friedlander M, Moore KN, Colombo N, et al. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. *Lancet Oncol.* 2021;22(5):632-642.
2. Chase DM, Marín MR, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - pooled analysis from the PRIMA trial. *Gynecol Oncol.* 2022;166(3):494-502.
3. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019;381(25):2416-2428.
4. AstraZeneca. *LYNPARZA® (olaparib) tablets, for oral use: prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf. Accessed November 25, 2025
5. AstraZeneca. *Lynparza film-coated tablets: summary of product characteristics*. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. Accessed November 25, 2025
6. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol.* 2023;34:681-692.
7. ClinicalTrials.gov. *Platine, Avastin and OLAparib in 1st Line (PAOLA-1)*. https://clinicaltrials.gov/study/NCT02477644. Accessed November 25, 2025
8. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.
9. Greimel E, Bottomley A, Cull A, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer.* 2003;39(10):1402-1408.
10. Osoba D, Bezjak A, Brundage M, Pater J. Evaluating health-related quality of life in cancer clinical trials: the National Cancer Institute of Canada Clinical Trials Group Experience. *Value Health.* 2007;10:S138-S145.
11. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018;379(26):2495-2505.

12. Colombo N, Moore K, Scambia G, et al. Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial. *Gynecol Oncol.* 2021;163(1):41-49.
13. Pothuri B, Han S, Chase D, et al. Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. *Gynecol Oncol.* 2024;184:168-177.
14. Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol.* 2020;21(2):e83-e96.
15. Lequesne J, Joly F, Peron J, et al. Evaluation of scores to reflect toxicity impact on quality of life of patients with platinum-resistant ovarian cancer: AURELIA substudy. *J Natl Compr Canc Netw.* 2023;21(5):473-479.
16. Harter P, Ataseven B, Burges A, et al. Diagnosis of first relapse and its impact on quality of life in patients with advanced ovarian cancer (AGO-OVAR 19/II). *J Clin Oncol.* 2022;40(16_suppl):e17609 (abstr).
17. Banerjee S, Rustin G, Paul J, et al. A multicenter, randomized trial of flat dosing versus intrapatient dose escalation of single-agent carboplatin as first-line chemotherapy for advanced ovarian cancer: an SGCTG (SCOTROC 4) and ANZGOG study on behalf of GCIG. *Ann Oncol.* 2013;24(3):679-687.
18. Vergote I, Jimeno A, Joly F, et al. Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platin-based chemotherapy for ovarian carcinoma: a European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup Study. *J Clin Oncol.* 2014;32(4):320-326.
19. Ancona C, Caroppo E, De Lellis P. Digital solutions supporting the quality-of-life of European cancer patients and their caregivers: a systematic literature review. *Health Technol.* 2025;15:243–272.
20. Barillaro A, Feoli C, Tramontano A, et al. Fatigue trajectories by wearable remote monitoring of breast cancer patients during radiotherapy. *Sci Rep.* 2024;14(1):27276.
21. du Bois A, Reuss A, Pujade-Lauraine E, 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(7):1328-1330.
22. Vergote I, Pujade-Lauraine E, Pignata S, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. *Int J Gynecol Cancer.* 2010;20(3):476-478.

680 **Table 1.** Baseline characteristics in the ITT population and the HRD-positive subgroup

Baseline characteristic	**ITT population**		**HRD-positive subgroup**	
	Olaparib plus bevacizumab (N = 537)	**Placebo plus bevacizumab (N = 269)**	**Olaparib plus bevacizumab (N = 255)**	**Placebo plus bevacizumab (N = 132)**
Age, years, median (range)	61.0 (32.0-87.0)	60.0 (26.0-85.0)	58.0 (32.0-77.0)	58.0 (35.0-82.0)
ECOG performance status, No. (%)				
0	378 (70)	189 (70)	190 (75)	100 (76)
1	153 (28)	76 (28)	61 (24)	31 (23)
Missing	6 (1)	4 (1)	4 (2)	1 (1)
Primary tumor location, No. (%)				
Ovary	456 (85)	238 (88)	217 (85)	118 (89)
Fallopian tubes	39 (7)	11 (4)	24 (9)	5 (4)
Primary peritoneal	42 (8)	20 (7)	14 (5)	9 (7)
FIGO stage, No. (%)				
III	378 (70)	186 (69)	182 (71)	90 (68)
IV	159 (30)	83 (31)	73 (29)	42 (32)
Histology, No. (%)				
Serous	519 (97)	253 (94)	242 (95)	124 (94)
Endometrioid	12 (2)	8 (3)	9 (4)	4 (3)
Other	6 (1)	8 (3)	4 (2)	4 (3)

History of cytoreductive surgery, No. (%)				
Upfront surgery	271 (50)	138 (51)	145 (57)	79 (60)
Macroscopic residual disease	111 (41)	53 (38)	55 (38)	30 (38)
Complete resection	160 (59)	85 (62)	90 (62)	49 (62)
Interval surgery	228 (42)	110 (41)	100 (39)	45 (34)
Macroscopic residual disease	65 (29)	35 (32)	24 (24)	13 (29)
Complete resection	163 (71)	75 (68)	76 (76)	32 (71)
No surgery	38 (7)	21 (8)	10 (4)	8 (6)
Response after first-line therapy, No. (%)				
No evidence of disease[a]	290 (54)	141 (52)	150 (59)	71 (54)
Clinical complete response[b]	106 (20)	53 (20)	52 (20)	26 (20)
Clinical partial response[c]	141 (26)	75 (28)	53 (21)	35 (27)
Deleterious tumor BRCA mutation,[d] No. (%)				
Yes	157 (29)	80 (30)	150 (59)	65 (49)
No	380 (71)	189 (70)	105 (41)	67 (51)
Tumor HRD status,[e] No. (%)				
HRD-positive	255 (47)	132 (49)	255 (100)	132 (100)
HRD-negative/unknown	282 (53)	137 (51)	0	0
HRD-negative	192 (36)	85 (32)	0	0
Unknown	90 (17)	52 (19)	0	0

681 Percentages may not total 100 because of rounding.

[a]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.

[b]Defined as the disappearance of all measurable or assessable disease and normalization of CA-125 levels following chemotherapy.

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

[d]Per the electronic case report form.

[e]HRD-positive was defined as a tumor BRCA mutation 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.

Abbreviations: CA-125 = cancer antigen 125; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; FIGO = International Federation of Gynecology and Obstetrics; GHS = Global Health Status; HRD = homologous recombination deficiency; ITT = intention-to-treat; SD = standard deviation.

697 **Table 2.** Baseline EORTC QLQ-C30 scores and adjusted mean global change from baseline in the modified ITT population

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Functional scales				
Global Health Status				
Baseline	N = 512	N = 250		
Mean (SD)	68.6 (18.0)	67.2 (16.2)		
Median (range)	66.7 (0-100)	66.7 (25-100)		
Adjusted mean global change from baseline (95% CI)	−1.12 (−2.21 to −0.02)	−2.76 (−4.34 to −1.19)	1.65 (−0.27 to 3.56)	*P*=.0015
Physical functioning				
Baseline	N = 513	N = 252		
Mean (SD)	78.8 (17.6)	75.7 (19.1)		
Median (range)	80.0 (20-100)	80.0 (20-100)		

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Adjusted mean global change from baseline (95% CI)	0.48 (−0.56 to 1.53)	0.38 (−1.11 to 1.87)	0.11 (−1.72 to 1.93)	*P*=.1318
Role functioning				
Baseline	N = 514	N = 252		
Mean (SD)	73.4 (27.2)	72.2 (27.0)		
Median (range)	83.3 (0-100)	66.7 (0-100)		
Adjusted mean global change from baseline (95% CI)	0.46 (−1.00 to 1.93)	−1.33 (−3.42 to 0.76)	1.79 (−0.76 to 4.35)	*P*=.0740
Emotional functioning				
Baseline	N = 515	N = 251		
Mean (SD)	76.9 (21.5)	77.2 (19.7)		
Median (range)	83.3 (0-100)	83.3 (0-100)		
Adjusted mean global change from baseline (95% CI)	−2.98 (−4.25 to −1.71)	−4.68 (−6.50 to −2.85)	1.69 (−0.53 to 3.92)	*P*=.4289

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Cognitive functioning				
Baseline	N = 515	N = 251		
Mean (SD)	82.6 (20.9)	81.4 (19.5)		
Median (range)	83.3 (0-100)	83.3 (0-100)		
Adjusted mean global change from baseline (95% CI)	−1.61 (−2.80 to −0.42)	−2.76 (−4.47 to −1.05)	1.15 (−0.93 to 3.24)	*P*=.9978
Social functioning				
Baseline	N = 515	N = 251		
Mean (SD)	75.0 (26.9)	74.6 (25.3)		
Median (range)	83.3 (0-100)	83.3 (0-100)		
Adjusted mean global change from baseline (95% CI)	2.44 (0.99 to 3.89)	1.80 (−0.28 to 3.88)	0.64 (−1.89 to 3.18)	*P*=.5827
Symptomatic scales				

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Fatigue[a]				
Baseline	N = 513	N = 251		
Mean (SD)	33.7 (22.8)	34.5 (22.5)		
Median (range)	33.3 (0-100)	33.3 (0-100)		
Adjusted mean global change from baseline (95% CI)	1.61 (0.29 to 2.93)	1.93 (0.05 to 3.81)	−0.32 (−2.62 to 1.98)	*P*=.0006
Nausea and vomiting[a]				
Baseline	N = 514	N = 252		
Mean (SD)	4.6 (12.5)	3.6 (9.2)		
Median (range)	0.0 (0-100)	0.0 (0-50)		
Adjusted mean global change from baseline (95% CI)	6.24 (5.26 to 7.22)	3.02 (1.62 to 4.41)	3.22 (1.51 to 4.93)	*P*<.0001
Pain[a]				

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Baseline	N = 516	N = 253		
Mean (SD)	22.4 (24.2)	23.8 (22.9)		
Median (range)	16.7 (0-100)	16.7 (0-100)		
Adjusted mean global change from baseline (95% CI)	3.48 (1.98 to 4.98)	7.33 (5.19 to 9.47)	−3.85 (−6.47 to −1.24)	*P*=.3168
Dyspnea[a]				
Baseline	N = 509	N = 252		
Mean (SD)	23.1 (25.7)	23.0 (27.3)		
Median (range)	33.3 (0-100)	16.7 (0-100)		
Adjusted mean global change from baseline (95% CI)	0.25 (−1.28 to 1.78)	−0.13 (−2.30 to 2.04)	0.38 (−2.28 to 3.04)	*P*=.0796
Insomnia[a]				
Baseline	N = 512	N = 252		

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Mean (SD)	27.0 (30.1)	24.6 (27.2)		
Median (range)	33.3 (0-100)	33.3 (0-100)		
Adjusted mean global change from baseline (95% CI)	2.81 (1.18 to 4.44)	6.10 (3.78 to 8.43)	−3.29 (−6.13 to −0.45)	*P*=.7097
Appetite loss[a]				
Baseline	N = 513	N = 252		
Mean (SD)	8.3 (18.2)	9.7 (20.2)		
Median (range)	0.0 (0-100)	0.0 (0-100)		
Adjusted mean global change from baseline (95% CI)	5.24 (3.88 to 6.60)	3.84 (1.89 to 5.78)	1.40 (−0.97 to 3.77)	*P*<.0001
Constipation[a]				
Baseline	N = 512	N = 250		
Mean (SD)	17.8 (26.8)	17.6 (27.6)		

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Median (range)	0.0 (0-100)	0.0 (0-100)		
Adjusted mean global change from baseline (95% CI)	0.61 (−0.85 to 2.06)	1.72 (−0.36 to 3.79)	−1.11 (−3.65 to 1.42)	*P*=.2833
Diarrhea[a]				
Baseline	N = 510	N = 252		
Mean (SD)	10.1 (20.3)	13.1 (23.6)		
Median (range)	0.0 (0-100)	0.0 (0-100)		
Adjusted mean global change from baseline (95% CI)	−0.59 (−1.77 to 0.58)	1.50 (−0.18 to 3.17)	−2.09 (−4.14 to −0.04)	*P*=.1862
Financial difficulties[a]				
Baseline	N = 508	N = 246		
Mean (SD)	14.6 (27.6)	16.3 (28.0)		
Median (range)	0.0 (0-100)	0.0 (0-100)		

Scale Scores	Olaparib plus bevacizumab (N = 517)	Placebo plus bevacizumab (N = 253)	Between-group difference	Treatment-by-time interaction
Adjusted mean global change from baseline (95% CI)	−1.40 (−2.74 to −0.06)	−0.69 (−2.61 to 1.24)	−0.72 (−3.06 to 1.63)	*P*=.9181

Longitudinal analysis of HRQoL data was conducted using a mixed model for repeated measures until 2 years of follow-up for each HRQoL scale separately. When time-by-treatment interactions are significant, time-specific estimates (**Table S4**) may be more relevant than estimates of mean global change.

[a]Symptomatic scale where higher scores represent higher symptomatic burden. For all other HRQoL scales, higher scores represent higher QoL level.

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRQoL = health-related quality of life; ITT = intention-to-treat; QoL = quality of life; SD = standard deviation.

Figure Legends

Figure 1. CONSORT diagram (DCO March 22, 2019).

[a]Other reasons included consent withdrawn (n = 4, olaparib plus bevacizumab; n = 4, placebo plus bevacizumab), lost to follow-up (n = 1, olaparib plus bevacizumab), missing (n = 1, olaparib plus bevacizumab), and other (n = 19, olaparib plus bevacizumab, n = 6, placebo plus bevacizumab).

[b]Disease progression defined by criteria other than RECIST (n = 9, olaparib plus bevacizumab; n = 10, placebo plus bevacizumab) or symptomatic deterioration (n = 5, olaparib plus bevacizumab; n = 3, placebo plus bevacizumab).

DCO = data cutoff.

Figure 2. Adjusted mean change over time in EORTC QLQ-C30 scores for (**A**) Global Health Status, (**B**) nausea and vomiting, (**C**) appetite loss, (**D**) fatigue, (**E**) insomnia, and (**F**) constipation in the modified ITT population.

Adjusted mean change using mixed model for repeated measures at each follow-up timepoint;.error bars represent 95% CI. Horizontal dotted lines represent 10-point MID. For Global Health Status, higher scores represent higher global quality of life. For symptomatic scales, higher scores for represent higher symptomatic burden.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; ITT = intention-to-treat; MID = minimal important difference.

Figure 3. Mean change in (**A**) functional and (**B**) symptomatic EORTC QLQ-C30 scores following RECIST progression.

Data are shown for olaparib plus bevacizumab and placebo plus bevacizumab treatment arms combined. EORTC QLQ-C30 scores following diagnosis of RECIST progression were compared with the last measurement collected prior to progression. Assessments were conducted up to a maximum of 60 days before and 60 days after progression. EORTC QLQ-C30 scores with clinically meaningful deterioration following RECIST progression are highlighted.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; pts = patients.

Figure 4. TUDD of EORTC QLQ-C30 Global Health Status scores (**A**) in the modified ITT population and (**B**) in the HRD-positive subgroup.

[a]In the modified ITT population, there were 375 events of HRQoL deterioration and 56 deaths.

[b]In the HRD-positive subgroup, there were 181 events of HRQoL deterioration and 10 deaths.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HR = hazard ratio; HRD = homologous recombination deficiency; HRQoL, health-related quality of life; ITT = intention-to-treat; TUDD = time until definitive health-related quality of life deterioration.

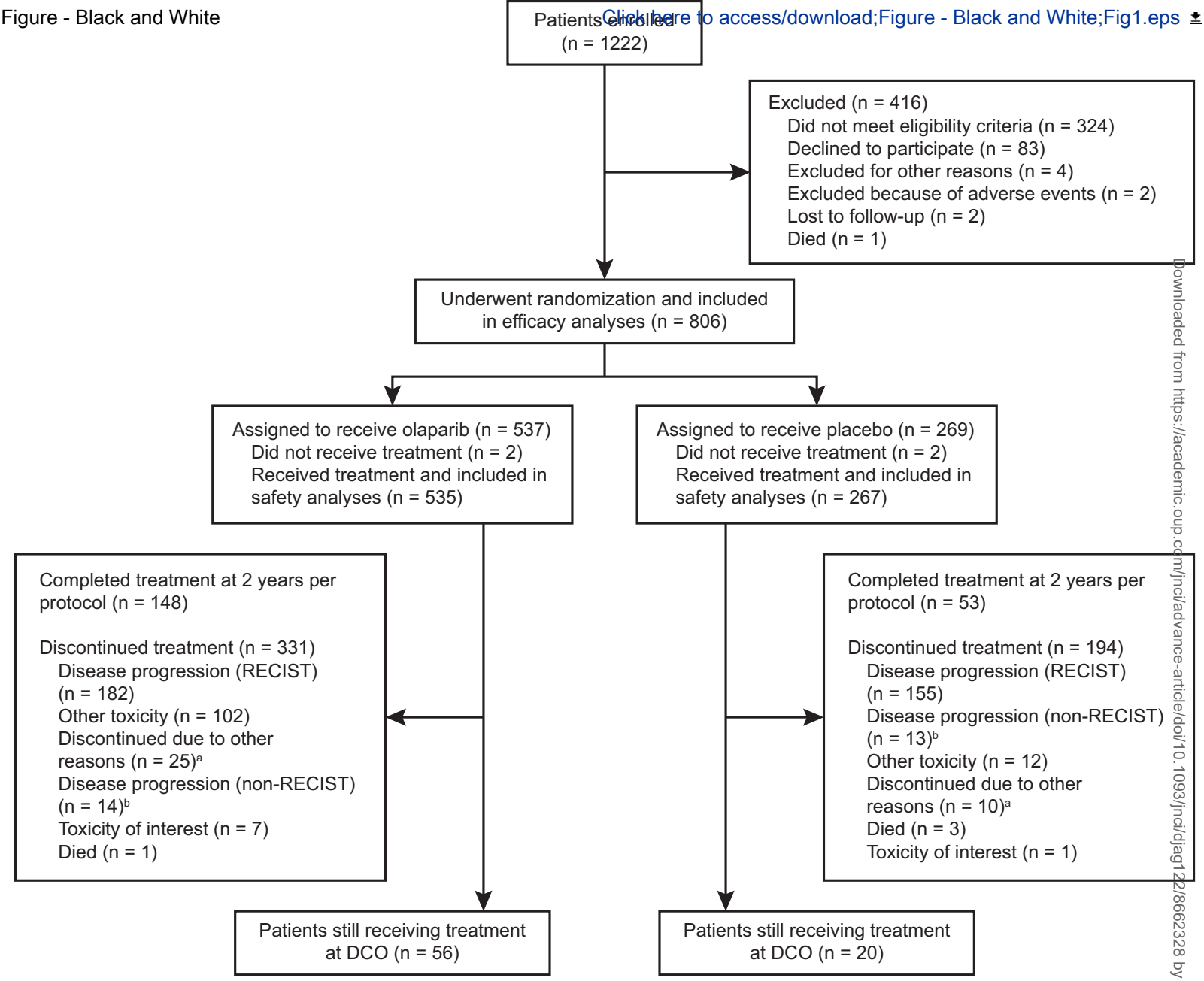
Figure 5. Time until definitive deterioration of the (A) EORTC QLQ-C30 scales and (B) EORTC QLQ-OV28 scales in the modified ITT population

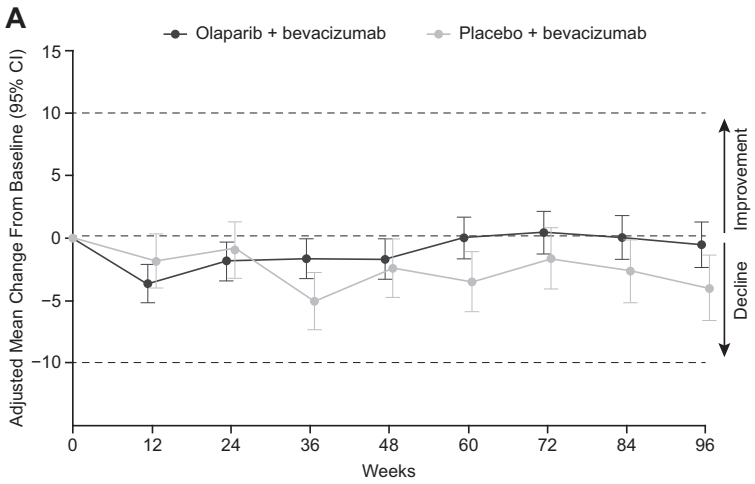
Error bars represent 95% CI.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-OV28 = European Organisation for

749 Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer module; ITT =

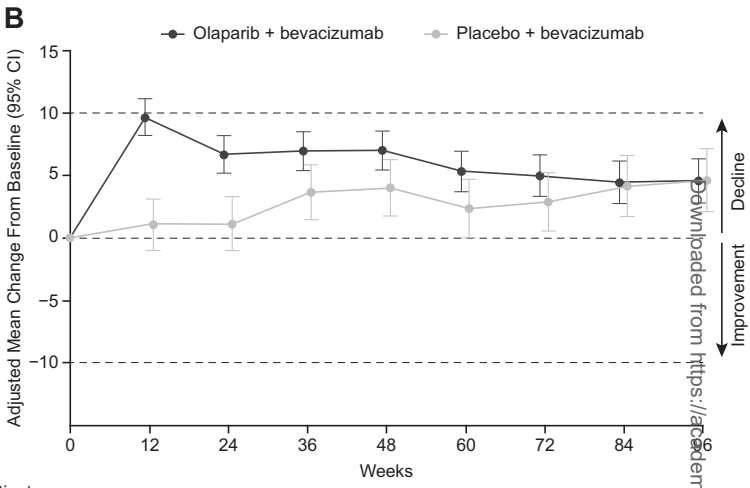
750 intention-to-treat; pts = patients.





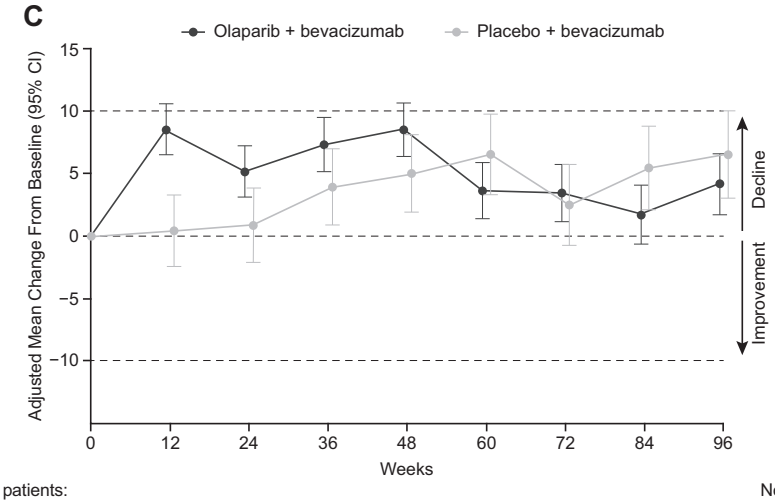
No. of patients:

Olaparib + bevacizumab	512	461	436	399	395	355	342	313	289
Placebo + bevacizumab	250	229	208	200	186	172	166	154	139



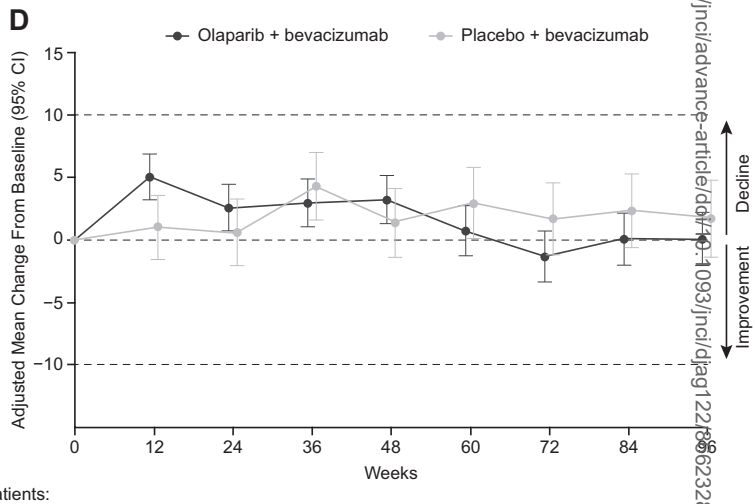
No. of patients:

Olaparib + bevacizumab	514	461	441	401	399	359	343	316	292
Placebo + bevacizumab	252	231	211	202	189	174	172	158	142



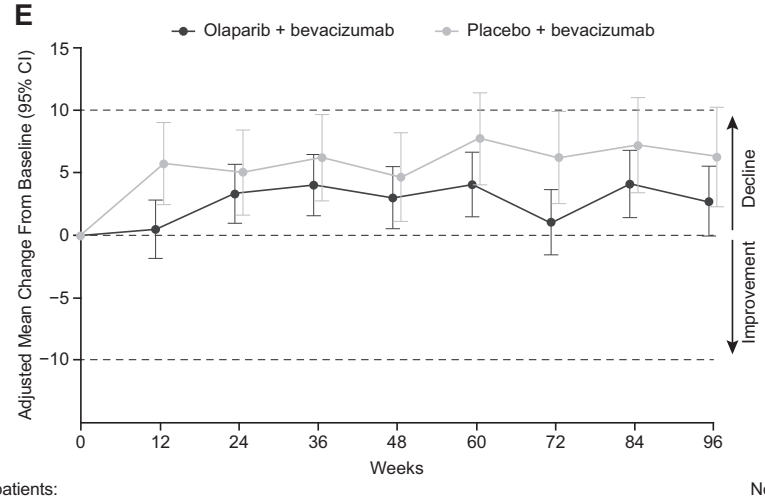
No. of patients:

Olaparib + bevacizumab	513	459	436	397	397	357	342	314	289
Placebo + bevacizumab	252	231	210	199	189	174	172	157	142



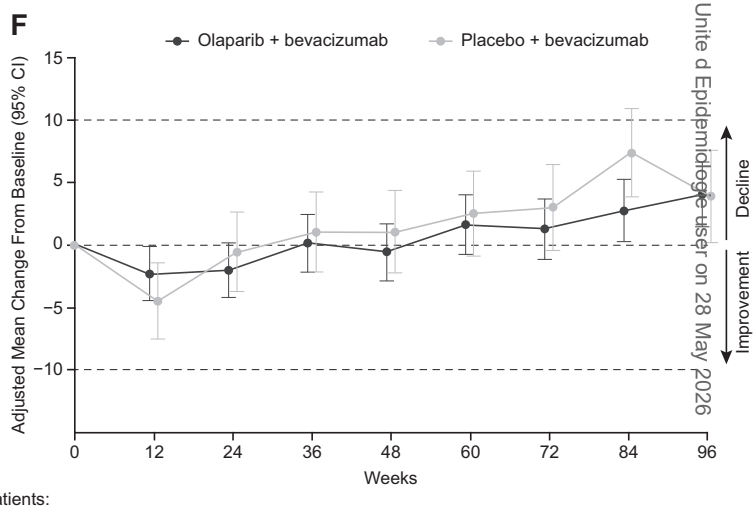
No. of patients:

Olaparib + bevacizumab	513	459	439	400	399	359	342	316	292
Placebo + bevacizumab	251	230	210	202	189	174	172	158	141



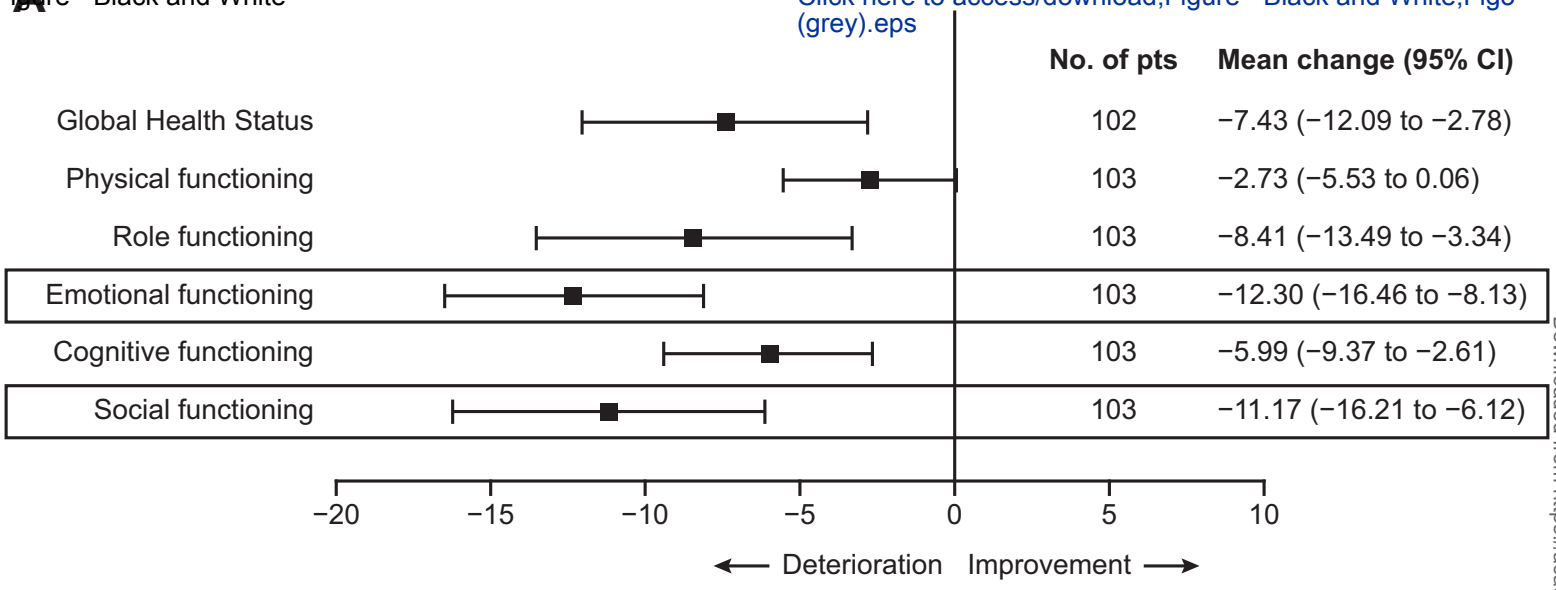
No. of patients:

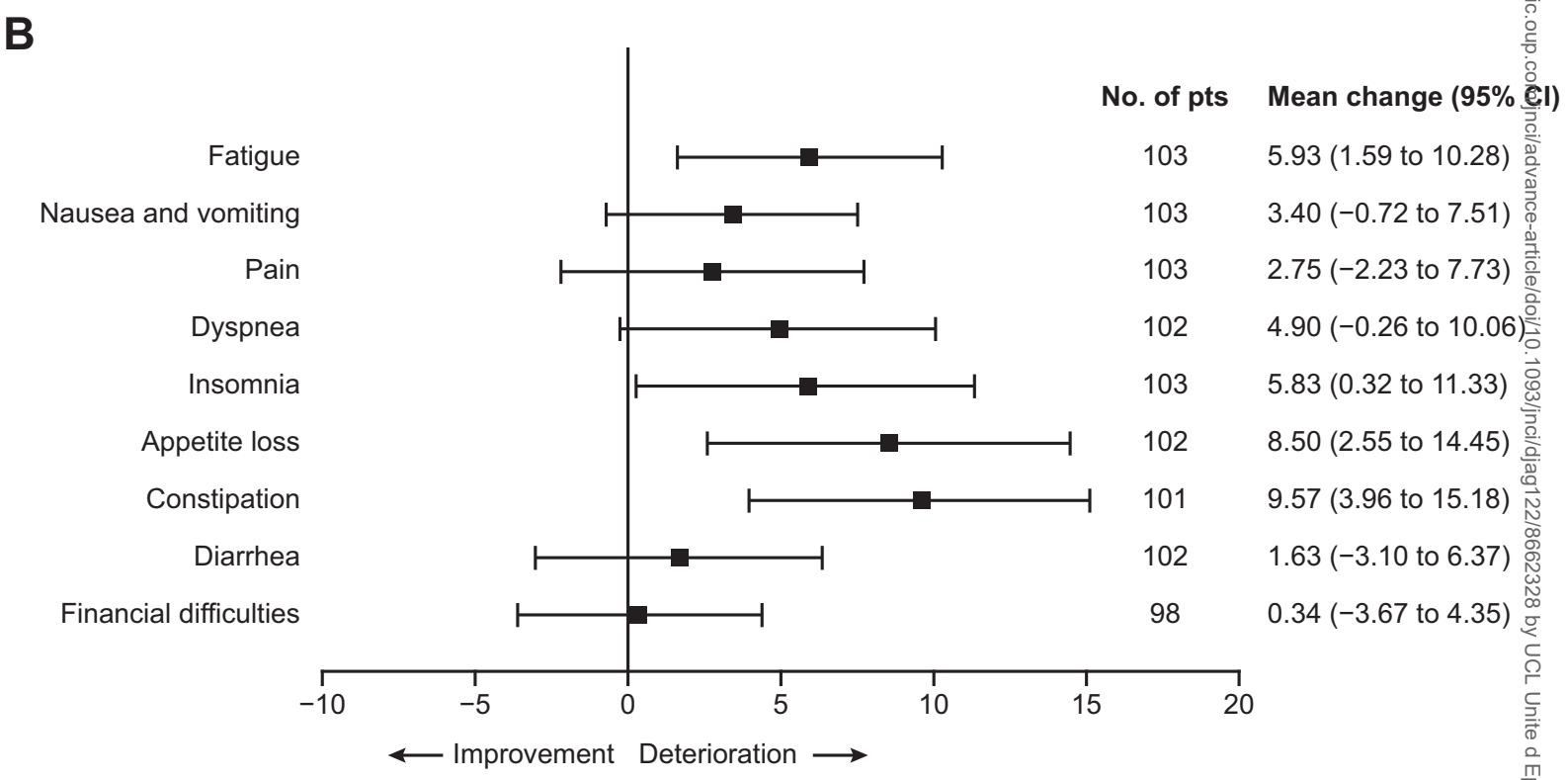
Olaparib + bevacizumab	512	461	439	399	398	356	341	314	289
Placebo + bevacizumab	252	231	210	201	189	173	172	158	141



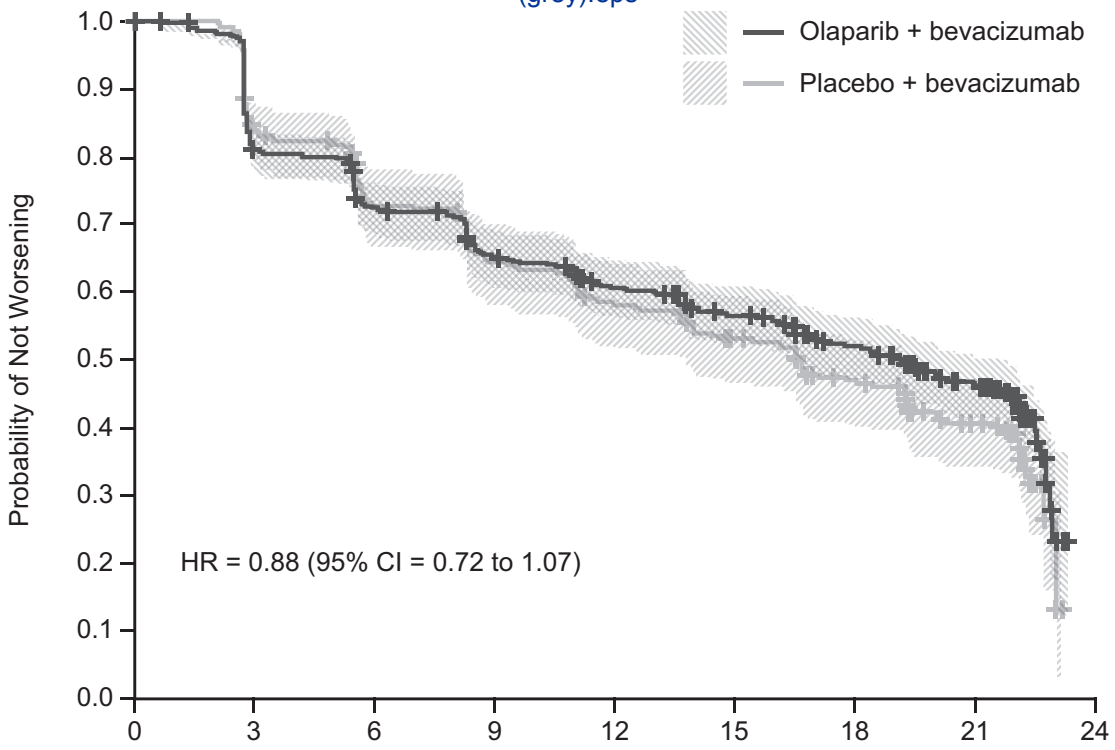
No. of patients:

Olaparib + bevacizumab	512	457	435	397	394	353	338	311	289
Placebo + bevacizumab	250	229	205	201	188	173	170	157	141



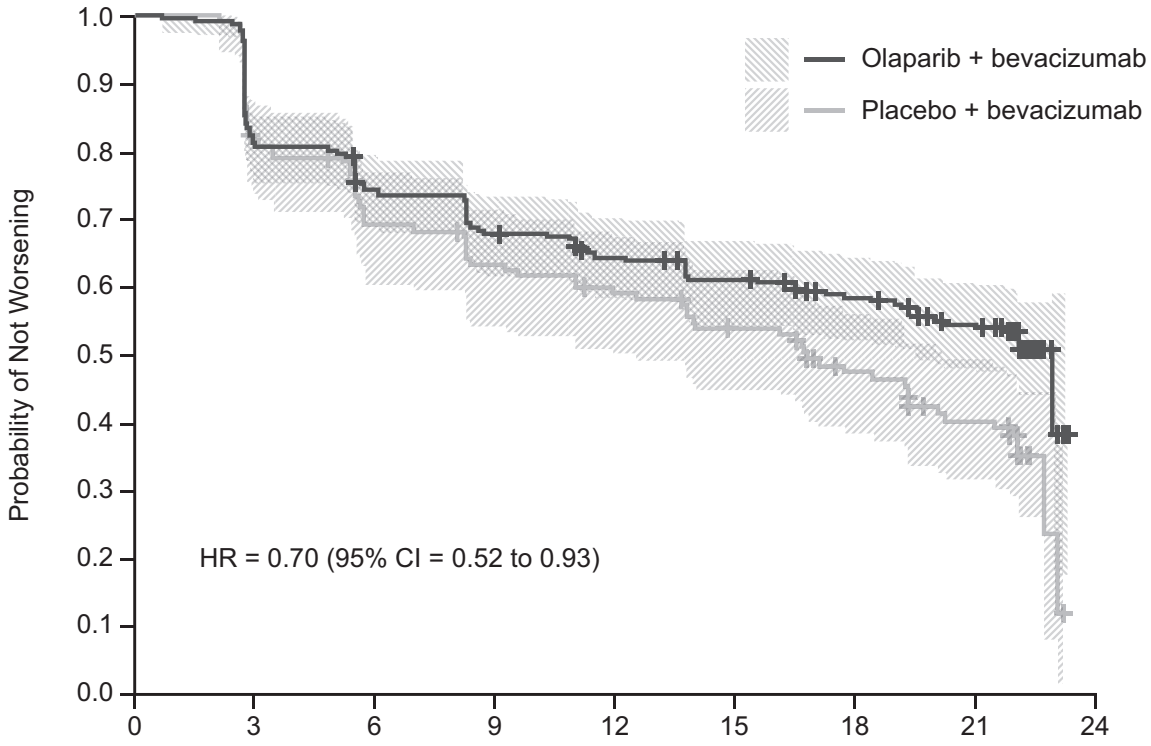


A



No. at risk (no. censored):									
Olaparib + bevacizumab	512 (0)	405 (11)	360 (14)	319 (18)	291 (25)	264 (33)	230 (46)	179 (73)	0 (234)
Placebo + bevacizumab	250 (0)	208 (3)	176 (7)	155 (8)	139 (9)	123 (13)	103 (19)	76 (33)	0 (97)

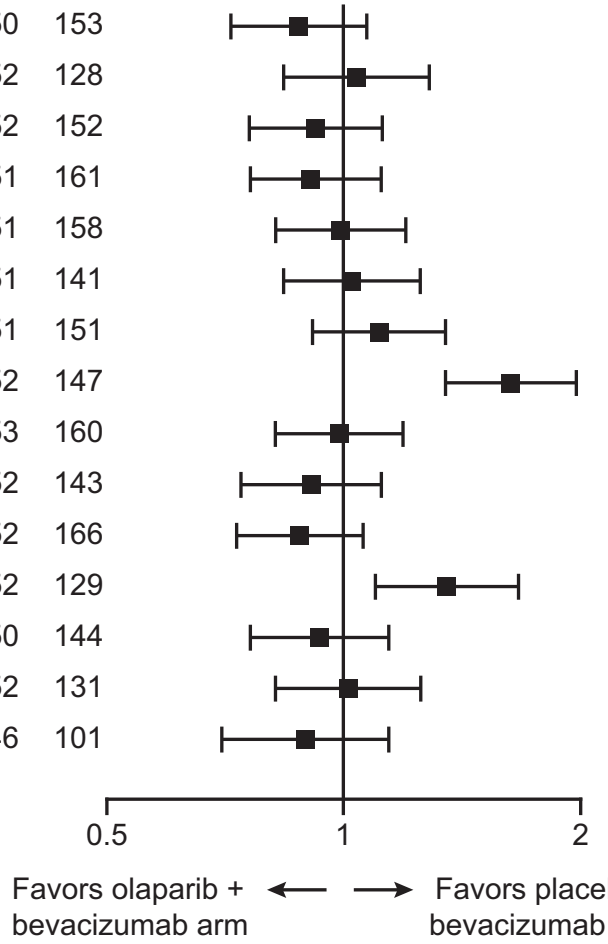
B



No. at risk (no. censored):									
Olaparib + bevacizumab	247 (0)	198 (2)	180 (4)	163 (5)	151 (9)	141 (11)	128 (18)	107 (31)	0 (132)
Placebo + bevacizumab	125 (0)	100 (2)	83 (4)	75 (5)	69 (6)	60 (9)	48 (14)	37 (18)	0 (49)

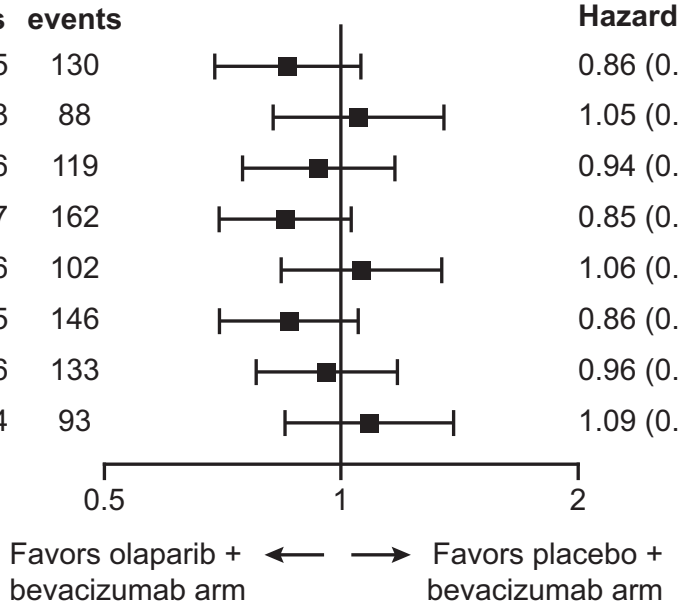
A

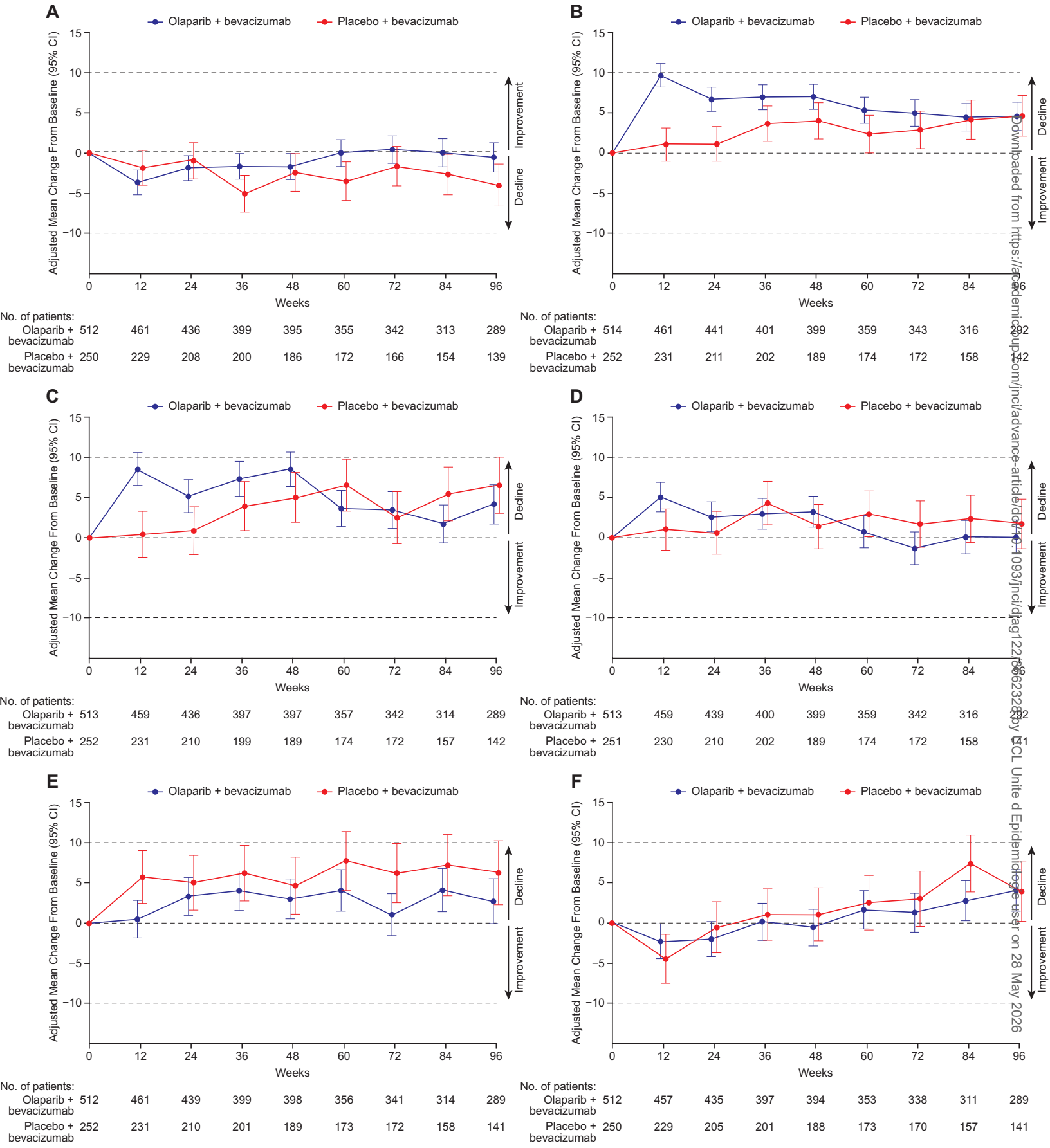
	Olaparib + bevacizumab No. pts	Olaparib + bevacizumab No. events	Placebo + bevacizumab No. pts	Placebo + bevacizumab No. events	Hazard ratio (95% CI)
Global Health Status	512	278	250	153	0.88 (0.72 to 1.07)
Physical functioning	513	265	252	128	1.04 (0.84 to 1.29)
Role functioning	514	290	252	152	0.92 (0.76 to 1.12)
Emotional functioning	515	302	251	161	0.91 (0.76 to 1.12)
Cognitive functioning	515	321	251	158	0.99 (0.82 to 1.20)
Social functioning	515	282	251	141	1.02 (0.84 to 1.25)
Fatigue	513	315	251	151	1.10 (0.91 to 1.34)
Nausea and vomiting	514	360	252	147	1.63 (1.35 to 1.98)
Pain	516	322	253	160	0.99 (0.82 to 1.19)
Dyspnea	509	260	252	143	0.91 (0.74 to 1.12)
Insomnia	512	311	252	166	0.88 (0.73 to 1.06)
Appetite loss	513	306	252	129	1.36 (1.10 to 1.67)
Constipation	512	268	250	144	0.93 (0.76 to 1.14)
Diarrhea	510	257	252	131	1.02 (0.82 to 1.25)
Financial difficulties	508	191	246	101	0.90 (0.70 to 1.14)

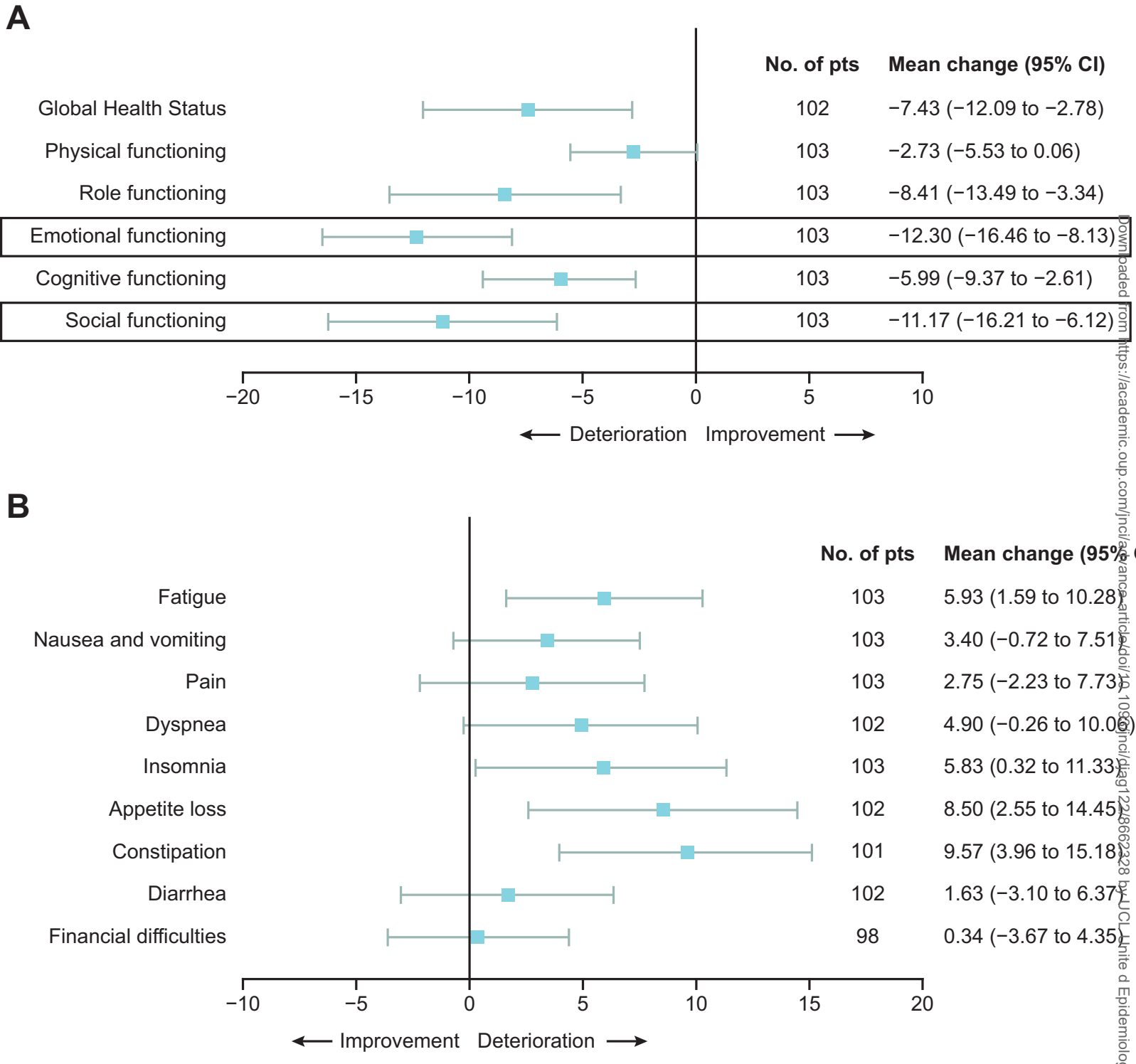


B

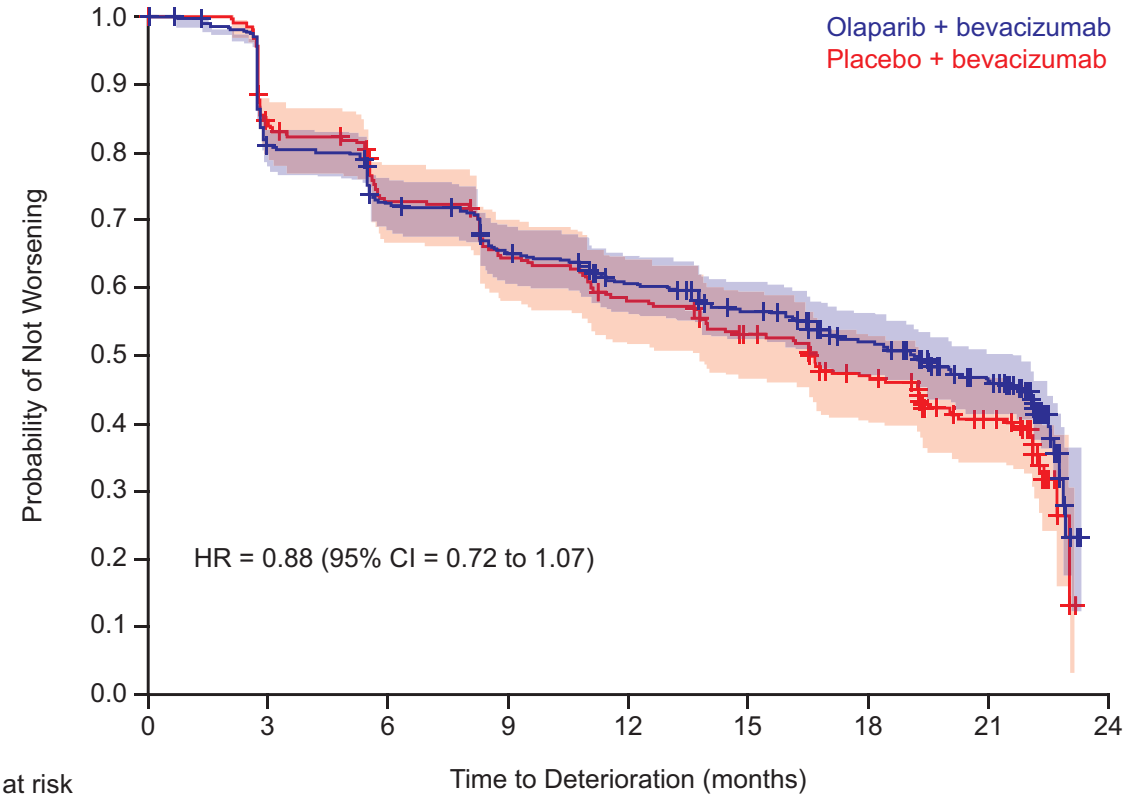
	Olaparib + bevacizumab No. pts	Olaparib + bevacizumab No. events	Placebo + bevacizumab No. pts	Placebo + bevacizumab No. events	Hazard ratio (95% CI)
Body image	514	237	245	130	0.86 (0.69 to 1.06)
Sexual function	489	182	238	88	1.05 (0.82 to 1.36)
Attitude to disease/treatment	511	224	246	119	0.94 (0.75 to 1.17)
Abdominal/GI symptoms	517	301	247	162	0.85 (0.70 to 1.03)
Peripheral neuropathy	517	211	246	102	1.06 (0.84 to 1.34)
Hormonal menopausal symptoms	516	280	245	146	0.86 (0.70 to 1.05)
Other chemotheraphy side effects	517	259	246	133	0.96 (0.78 to 1.18)
Hair loss	502	199	244	93	1.09 (0.85 to 1.39)





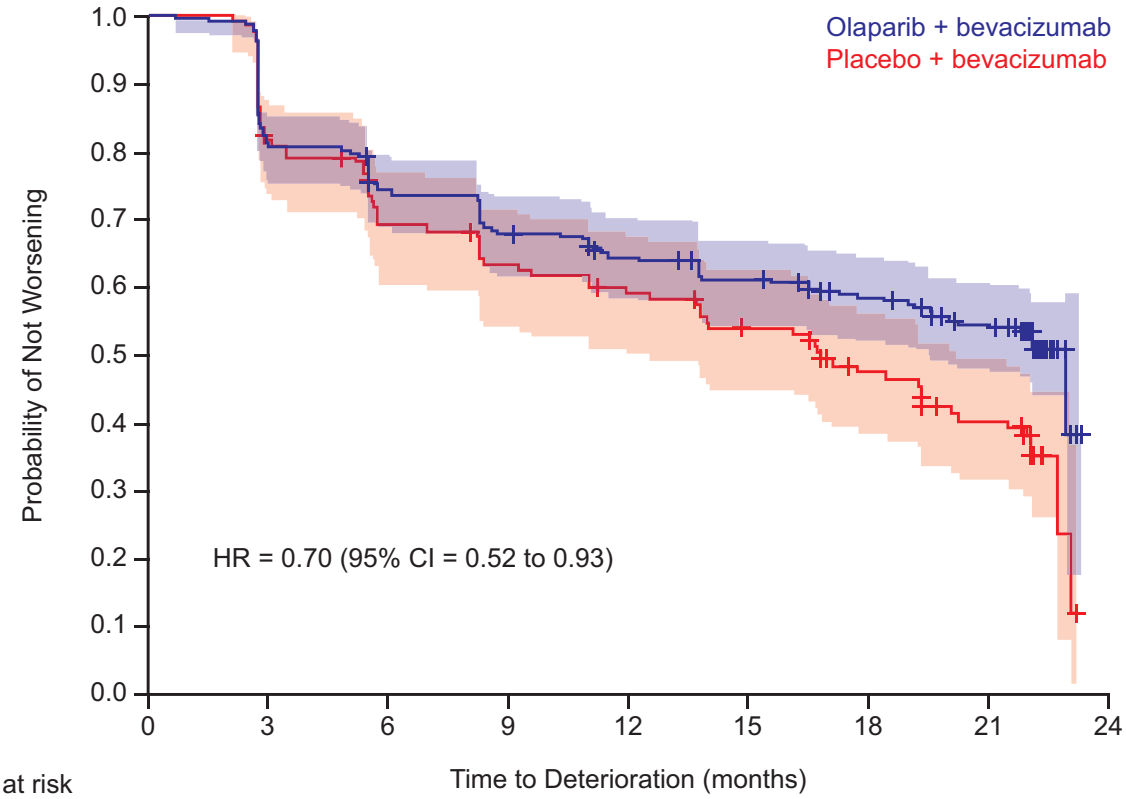


A



No. at risk (no. censored):									
Olaparib + bevacizumab	512 (0)	405 (11)	360 (14)	319 (18)	291 (25)	264 (33)	230 (46)	179 (73)	0 (234)
Placebo + bevacizumab	250 (0)	208 (3)	176 (7)	155 (8)	139 (9)	123 (13)	103 (19)	76 (33)	0 (97)

B



No. at risk (no. censored):									
Olaparib + bevacizumab	247 (0)	198 (2)	180 (4)	163 (5)	151 (9)	141 (11)	128 (18)	107 (31)	0 (132)
Placebo + bevacizumab	125 (0)	100 (2)	83 (4)	75 (5)	69 (6)	60 (9)	48 (14)	37 (18)	0 (49)