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Patient-Centered Outcomes in ARIEL3, a Phase III Randomized, Placebo-Controlled Trial of Rucaparib Maintenance Treatment in Patients With Recurrent Ovarian Carcinoma

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abstract

PURPOSE To investigate quality-adjusted progression-free survival (QA-PFS) and quality-adjusted time without symptoms or toxicity (Q-TWiST) in a post hoc exploratory analysis of the phase III ARIEL3 study of rucaparib maintenance treatment versus placebo.

PATIENTS AND METHODS Patients with platinum-sensitive, recurrent ovarian carcinoma were randomly assigned to rucaparib (600 mg twice per day) or placebo. QA-PFS was calculated as progression-free survival function × the 3-level version of the EQ-5D questionnaire (EQ-5D-3L) index score function. Q-TWiST analyses were performed defining TOX as the mean duration in which a patient experienced grade ≥ 3 treatment-emergent adverse events (TEAEs) or the mean duration in which a patient experienced grade ≥ 2 TEAEs of nausea, vomiting, fatigue, and asthenia. Q-TWiST was calculated as μTOX × TOX + TWiST, with μTOX calculated using EQ-5D-3L data.

RESULTS The visit cutoff was Apr 15, 2017. Mean QA-PFS was significantly longer with rucaparib versus placebo in the intent-to-treat (ITT) population (375 randomly assigned to rucaparib *v* 189 randomly assigned to placebo; difference, 6.28 months [95% CI, 4.85 to 7.47 months]); *BRCA*-mutant cohort (130 rucaparib *v* 66 placebo; 9.37 months [95% CI, 6.65 to 11.85 months]); homologous recombination deficient (HRD) cohort (236 rucaparib *v* 118 placebo; 7.93 months [95% CI, 5.93 to 9.53 months]); and *BRCA* wild-type/loss of heterozygosity (LOH) low patient subgroup (107 rucaparib *v* 54 placebo; 2.71 months [95% CI, 0.31 to 4.44 months]). With TOX defined using grade ≥ 3 TEAEs, the difference in mean Q-TWiST (rucaparib *v* placebo) was 6.88 months (95% CI, 5.71 to 8.23 months), 9.73 months (95% CI, 7.10 to 11.94 months), 8.11 months (95% CI, 6.36 to 9.49 months), and 3.35 months (95% CI, 1.66 to 5.40 months) in the ITT population, *BRCA*-mutant cohort, HRD cohort, and *BRCA* wild-type/LOH low patient subgroup, respectively. Q-TWiST with TOX defined using select grade ≥ 2 TEAEs also consistently favored rucaparib.

CONCLUSION The significant differences in QA-PFS and Q-TWiST confirm the benefit of rucaparib versus placebo in all predefined cohorts.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Although most women with ovarian cancer respond to first-line treatment (typically surgery plus platinum-based chemotherapy), many experience relapse and may receive multiple lines of chemotherapy.[1,2] Among those initially diagnosed with advanced ovarian cancer, only 29% survive for ≥ 5 years.[3]

Recently, maintenance treatment with a targeted agent such as bevacizumab or a poly(ADP-ribose) polymerase (PARP) inhibitor has become the standard of care for patients with ovarian cancer after a response to chemotherapy.[4] Maintenance treatment aims to extend clinically meaningful survival by delaying disease progression and to prolong the period between chemotherapy treatments, thereby allowing patients to avoid the associated toxicities that can affect quality of life (QoL).[5,6] Consequently, it is important to evaluate whether adding maintenance treatment to a patient's therapeutic regimen prolongs survival at the expense of toxicities that compromise the patient's overall health status.[6]

The PARP inhibitor rucaparib is approved in the United States and European Union for the maintenance treatment of adult patients with recurrent

CONTEXT

Key Objective

We evaluated the effect of rucaparib maintenance treatment on patient-centered outcomes, which incorporate measures of quality and quantity of life, in patients with recurrent ovarian cancer.

Knowledge Generated

Quality-adjusted progression-free survival and quality-adjusted time without symptoms or toxicity (Q-TWiST) were longer with rucaparib than with placebo in the intent-to-treat population and in all other analysis groups, irrespective of *BRCA* mutation status.

Relevance

To our knowledge, this is the first report of quality-adjusted patient-centered outcomes for rucaparib maintenance treatment and the first report of these outcomes for a poly(ADP-ribose) polymerase (PARP) inhibitor in an all-comer population that includes patients with ovarian cancer without a *BRCA* mutation. To our knowledge, our report is also the first to include Q-TWiST analyses for a PARP inhibitor in ovarian cancer. Across analysis groups, including patients with *BRCA* wild-type carcinomas, rucaparib maintenance treatment provided a significant benefit despite the impact of toxicities on patients' health status, and rucaparib-treated patients had longer periods without clinically relevant symptoms compared with those receiving placebo.

epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a complete or partial response to platinum-based chemotherapy.[7,8] Approval was based on the results from the ARIEL3 trial (CO-338-014; ClinicalTrials.gov identifier: NCT01968213), in which the primary efficacy end point of investigator-assessed progression-free survival (PFS) was significantly improved with rucaparib maintenance treatment versus placebo in all 3 prespecified, nested cohorts: patients with a *BRCA1* or *BRCA2 (BRCA)*-mutated carcinoma (germline, somatic, or unknown origin); patients with a homologous recombination deficient (HRD) carcinoma (*BRCA* mutation plus *BRCA* wild type/high loss of heterozygosity [LOH]); and the intent-to-treat (ITT) population.[9]

Quality-adjusted PFS (QA-PFS) and quality-adjusted time without symptoms or toxicity (Q-TWiST) are methods that incorporate both the quality and quantity of life to provide additional insight into the impacts of a therapy. QA-PFS represents the duration of survival without disease progression adjusted for the value the patient placed on their health status (ie, it is a measure that adjusts for treatment toxicity and any associated detrimental effects as reported by the patient). TWiST is an outcome in which periods of treatment toxicity or disease symptoms are subtracted from the survival end point, and the Q-TWiST variation of this outcome incorporates patients' assessments of their QoL in a health state (eg, time with toxicity of treatment) by weighting it with a patient-derived utility value.[10] Assessments that draw on patient-centered quality adjustments are particularly relevant for targeted oncology therapies that are given continuously and for therapies, such as PARP inhibitors, administered to asymptomatic patients.[11]

Here we present analyses of QA-PFS and Q-TWiST from ARIEL3 to further evaluate the clinical benefits of rucaparib maintenance treatment from a patient-centered perspective. To our knowledge, our analyses are the first report of a Q-TWiST analysis for a PARP inhibitor in ovarian cancer and are the first report of quality-adjusted outcomes for a PARP inhibitor that includes patients with ovarian cancer without a known deleterious *BRCA* mutation.

PATIENTS AND METHODS

Study Design, Patients, and Procedures

The design of this randomized, double-blind, multicenter, international, phase III trial (ARIEL3; ClinicalTrials.gov identifier: NCT01968213) has been reported previously.[9] Patients were enrolled between April 7, 2014, and July 19, 2016.

Eligible patients were ≥ 18 years of age, had platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, had received ≥ 2 previous platinum-based chemotherapy regimens, and had achieved any of the following: a complete response according to RECIST version 1.1, a partial response according to RECIST, or a serologic response based on Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 response criteria to their last platinum-based regimen. Full eligibility criteria have been reported previously.[9]

National or local institutional review boards approved the trial, which was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. Patients provided written informed consent before participation.

Central testing of DNA derived from patient archival tumor tissue samples was performed to detect mutations in homologous recombination pathway genes and to assess genomic LOH. A cutoff of ≥ 16% for ARIEL3 was prespecified

as a discriminator for high genomic LOH.[9] Full details of the testing protocol have been reported previously.[9]

Patients were randomly assigned 2:1 to receive oral rucaparib (600 mg twice per day) or matched placebo with stratification factors of homologous recombination repair gene mutation status (based on gene mutation only: mutation in *BRCA1* or *BRCA2*, mutation in a non-*BRCA* gene associated with homologous recombination, or no mutation in *BRCA* or a homologous recombination gene); progression-free interval after penultimate platinum-based regimen (6 to $\leq$ 12 months or $>$ 12 months); and best response to most recent platinum-based regimen (complete or partial response). Rucaparib or placebo was administered in continuous 28-day cycles until disease progression (as assessed by RECIST), death, or other reason for discontinuation. Patients completed the 3-level version of the EQ-5D questionnaire (EQ-5D-3L) at screening, on day 1 of each treatment cycle, at the treatment discontinuation visit, and at the 28-day follow-up visit.

Outcomes

The primary efficacy end point in ARIEL3, investigator-assessed PFS, and secondary end points of PFS by blinded, independent central review, time to worsening in the FOSI-18, and safety have been reported previously.[9] Here we report post hoc analyses of QA-PFS and Q-TWiST, both using utility values derived from the EQ-5D-3L questionnaire. For all analyses, the EQ-5D-3L index score was calculated using the UK value set obtained using time–trade-off methodology. Only questionnaires with all 5 EQ-5D-3L items completed were eligible for inclusion.

Statistical Analysis

The rationale for the sample size has been reported previously.[9] Analyses were performed for the 3 prespecified, nested cohorts: the ITT population, patients with an HRD carcinoma (*BRCA* mutation or *BRCA* wild type/LOH high), and patients with a *BRCA*-mutated carcinoma. Analyses were also conducted in subgroups of patients with *BRCA* wild-type carcinomas based on LOH status: *BRCA* wild type/LOH high, *BRCA* wild type/LOH low, and *BRCA* wild type/LOH indeterminate.

QA-PFS was calculated as the product of the investigator-assessed PFS function and the EQ-5D-3L index score function. Mean QA-PFS was obtained by computing the area under the quality-survival product function up to the last follow-up date available in each group. Because differences in censoring and/or follow-up time in the rucaparib and placebo groups could introduce bias, a sensitivity analysis was also performed in which the area under the quality-survival product function was computed using a follow-up time of 24 months for both groups. Additional details are provided in the Appendix and in Appendix Fig A1 (online only).

Mean time without toxicity or symptoms of disease progression (TWiST state) was calculated as the mean PFS time minus the mean time with toxicities (TOX state). Mean time with symptoms of disease (REL state), usually calculated as the mean overall survival (OS) time minus the mean PFS time, was not included because ARIEL3 OS data were not mature at the time of this analysis.

Q-TWiST was calculated as μTOX $\times$ TOX + TWiST. μTOX denotes the utility weight for the TOX state, and the utility weight for the TWiST state was set to 1 (highest possible), because this state is the best state for patients in the clinical trial (additional details are provided in the Appendix and in Appendix Fig A2 (online only).

For each patient, time with toxicity of treatment was defined as the number of days with grade $\geq$ 3 treatment-emergent adverse events (TEAEs) after random assignment and before disease progression or censoring for progression. An additional analysis was conducted in which time with toxicity of treatment was defined using grade $\geq$ 2 TEAEs of nausea, vomiting, fatigue, and asthenia only, because these TEAEs are frequently observed with rucaparib and other PARP inhibitors. Additional details on calculations are included in the Appendix.

The level of significance was set to 5%, and CIs were calculated using 2-sided bootstrap methods. No method to control for multiple testing was applied because this was an exploratory, post hoc analysis. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

As reported previously,[9] we randomly allocated 564 patients in ARIEL3: 375 (66%) to rucaparib and 189 (34%) to placebo. The safety population included 372 patients (99.2%) who received rucaparib (3 patients [0.8%] withdrew before receiving rucaparib), and 189 patients (100%) who received placebo. The analyses presented here used the primary efficacy data after unblinding (April 15, 2017, visit cutoff). Baseline characteristics were balanced between treatment groups (Table 1); full details have been reported previously.[9]

Adverse Events

As of the April 15, 2017, visit cutoff, the most frequent TEAEs (reported in $\geq$ 35% of patients in either group) of any grade were nausea, asthenia/fatigue, dysgeusia, anemia/decreased hemoglobin concentration, constipation, and vomiting (Fig 1).[9] The most frequent TEAEs of grade $\geq$ 3 (reported in $\geq$ 3% of patients) included anemia/hemoglobin decreased, alanine aminotransferase/aspartate aminotransferase increased, asthenia/fatigue, neutropenia/neutrophil count decreased, thrombocytopenia/platelet count decreased, vomiting, and nausea (Fig 1). The following TEAEs of interest were reported at grade $\geq$ 2: asthenia/fatigue (130 patients [34.9%] in the rucaparib group *v* 25 [13.2%] in the placebo group), nausea

(108 [29.0%] *v* 12 [6.3%]), and vomiting (48 [12.9%] *v* 9 [4.8%]).

Patient-Centered Outcomes

Details of EQ-5D-3L records included in this analysis are provided in the Appendix. In the ITT population, mean EQ-5D-3L index scores were relatively stable over the course of the study in both groups (Appendix Fig A3, online only); similar trends in mean EQ-5D-3L index scores were observed in all other analytical cohorts.

Mean QA-PFS was significantly longer in the rucaparib group than in the placebo group in the 3 prespecified, nested cohorts, with a mean difference of 6.28 months (95% CI, 4.85 to 7.47 months) in the ITT population (Fig 2A), 9.37 months (95% CI, 6.65 to 11.85 months) in the *BRCA*-mutant cohort (Fig 2B), and 7.93 months (95% CI, 5.93 to 9.53 months) in the HRD cohort (Fig 2C). Mean QA-PFS was also longer with rucaparib than with placebo in the *BRCA* wild-type/LOH high (difference, 6.65 months [95% CI, 3.65 to 8.40 months]),

TABLE 1. Patient Demographics and Baseline Characteristics in the Intent-to-Treat Population

Characteristic	Rucaparib Group (n = 375)	Placebo Group (n = 189)
Age, years, median (IQR)	61.0 (53.0 to 67.0)	62.0 (53.0 to 68.0)
ECOG performance status		
0	280 (74.7)	136 (72.0)
1	95 (25.3)	53 (28.0)
Diagnosis		
Epithelial ovarian cancer	312 (83.2)	159 (84.1)
Fallopian tube cancer	32 (8.5)	10 (5.3)
Primary peritoneal cancer	31 (8.3)	19 (10.1)
High-grade serous adenocarcinoma	0	1 (0.5)
BRCA mutation in carcinoma		
BRCA mutant	130 (34.7)	66 (34.9)
BRCA1	80 (21.3)	37 (19.6)
BRCA2	50 (13.3)	29 (15.3)
Germline	82 (21.9)	48 (25.4)
Somatic	40 (10.7)	16 (8.5)
Unknown[a]	8 (2.1)	2 (1.1)
BRCA wild type	245 (65.3)	123 (65.1)
LOH high	106 (28.3)	52 (27.5)
LOH low	107 (28.5)	54 (28.6)
LOH indeterminate[b]	32 (8.5)	17 (9.0)
No. of previous platinum-based regimens		
2	236 (62.9)	126 (66.7)
≥ 3	139 (37.1)	63 (33.3)
Time to progression with penultimate platinum-based regimen, months		
6 to ≤ 12	151 (40.3)	76 (40.2)
> 12	224 (59.7)	113 (59.8)
Response to last platinum-based regimen		
CR according to RECIST[c]	126 (33.6)	64 (33.9)
PR according to RECIST[c] or serologic response according to GCIG CA-125 criteria	249 (66.4)	125 (66.1)

NOTE. Data are presented as No. (%) unless indicated otherwise. (Reprinted from *The Lancet*, vol. 390, pp. 1949–1961. Coleman RL et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. [9] Copyright 2017, with permission from Elsevier.)

Abbreviations: CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer InterGroup; IQR, interquartile range; LOH, loss of heterozygosity; PR, partial response.

[a]Tumor sample was *BRCA* mutant according to Foundation Medicine's T5 next-generation sequencing assay, but a blood sample was not available for central germline testing.

[b]Tumor sample was not evaluable for percentage of genomic LOH because of low tumor content or aneuploidy.

[c]Version 1.1.

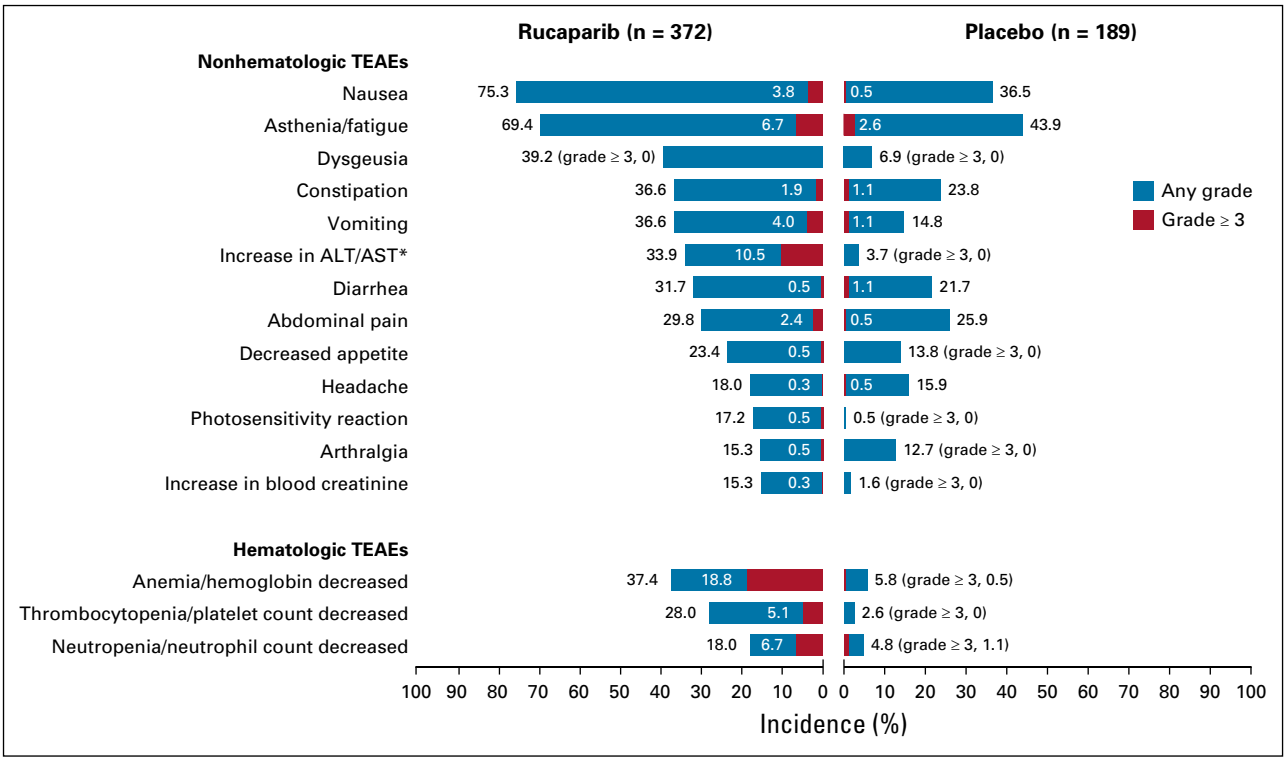

FIG 1. Most frequent treatment-emergent adverse events (TEAEs; reported in ≥ 35% of patients) in ARIEL3. (*) Elevations were transient, self-limiting, and not associated with other signs of liver toxicity. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

BRCA wild-type/LOH low (2.71 months [95% CI, 0.31 to 4.44 months]), and *BRCA* wild-type/LOH indeterminate (7.53 months [95% CI, 3.26 to 10.67 months]) patient subgroups (Figs 2D-2F). Consistent results were obtained in a sensitivity analysis of QA-PFS calculated based on 24 months of follow-up, with longer mean QA-PFS with rucaparib than with placebo in all prespecified cohorts and *BRCA* wild-type subgroups (Appendix Table A1, online only).

In the ITT population, mean PFS was significantly longer with rucaparib than with placebo (mean difference, 6.94 months [95% CI, 5.67 to 8.20 months]; Table 2). Although mean duration with grade ≥ 3 TEAEs (TOX state) was also significantly longer in the rucaparib group than in the placebo group (mean difference, 0.54 months [95% CI, 0.38 to 0.69 months]), mean TWiST remained significantly longer with rucaparib (mean difference, 6.40 months [95% CI, 5.50 to 7.30 months]; Table 2 and Fig 3). In the quality-adjusted analysis, the mean difference in mean Q-TWiST was 6.88 months (95% CI, 5.71 to 8.23 months; Table 2). In the *BRCA*-mutant and HRD cohorts, the difference in mean Q-TWiST was 9.73 months (95% CI, 7.10 to 11.94 months) and 8.11 months (95% CI, 6.36 to 9.49 months), respectively (Table 2). In the subgroups of patients with a *BRCA* wild-type ovarian carcinoma, Q-TWiST consistently favored rucaparib, with a mean difference of 6.07 months (95% CI, 2.76 to 8.52 months), 3.35 months (95% CI, 1.66 to 5.40 months), and 8.60 months (95% CI, 1.89 to 12.12 months) in patients with LOH high, LOH low, and LOH indeterminate, respectively (Table 2).

Q-TWiST analyses in which the TOX state was defined using grade ≥ 2 TEAEs of nausea, vomiting, fatigue, and asthenia were consistent with the Q-TWiST analyses in which the TOX state was defined as any grade ≥ 3 TEAEs. Outcomes favored rucaparib in all subgroups, as listed in Table 3 and Appendix Fig A4 (online only).

DISCUSSION

By evaluating quality-adjusted survival, which incorporates assessments of quality and quantity of life, we demonstrated that rucaparib maintenance treatment provided significant benefit despite the impact of toxicities on patients' health status during rucaparib treatment and that patients receiving rucaparib had longer periods without clinically relevant symptoms.

QA-PFS was 2.1-fold longer in the rucaparib group than in the placebo group among patients in the ITT population, and ranged from approximately 1.5-fold (*BRCA* wild type/LOH low) to 3.0-fold (*BRCA* wild type/LOH indeterminate) longer in the other analytical groups. This showed that, when weighted by patients' perceptions of their health status, the PFS benefit of rucaparib persisted.

Results for Q-TWiST also consistently favored rucaparib over placebo in the ITT population and other analytical groups, ranging from approximately 1.5-fold (*BRCA* wild type/LOH low)

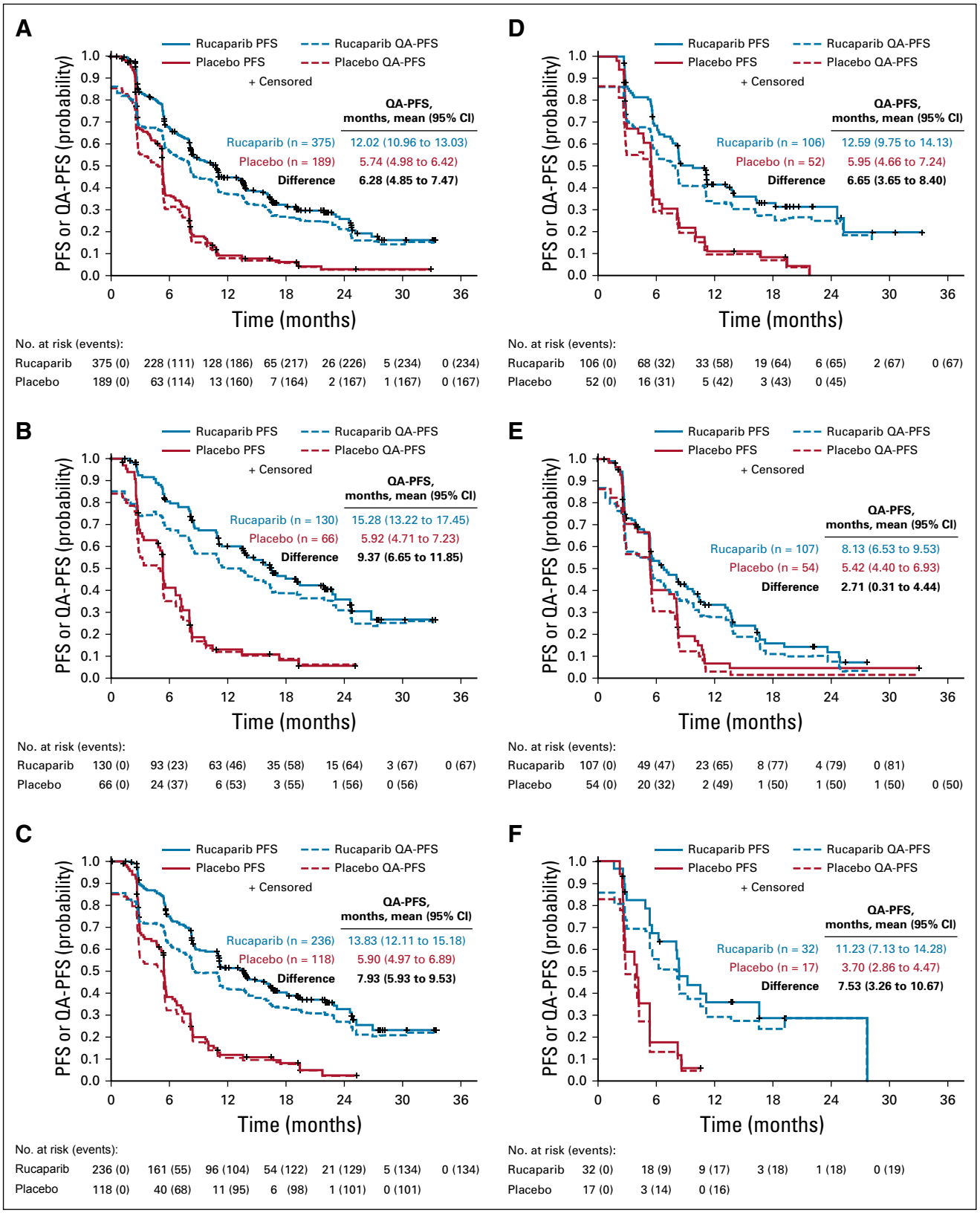

FIG 2. Quality-adjusted progression-free survival (QA-PFS) in the intent-to-treat population (A), *BRCA*-mutant cohort (B), homologous recombination deficient cohort (C), *BRCA* wild-type/loss of heterozygosity (LOH) high (D), *BRCA* wild-type/LOH low (E), and *BRCA* wild-type/LOH indeterminate (F) patient subgroups. Patients at-risk data are shown for the progression-free survival (PFS) analysis.

TABLE 2. Mean Duration of Health States per Study Subgroup With Toxicity Defined as All Grade ≥ 3 Adverse Events

	Mean Duration (months)		
Health State	**Rucaparib**	**Placebo**	**Difference**
ITT[a]			
PFS	13.39 (12.35 to 14.43)	6.45 (5.74 to 7.17)	6.94 (5.67 to 8.20)
TOX	0.64 (0.49 to 0.78)	0.10 (0.04 to 0.16)	0.54 (0.38 to 0.69)
TWiST	12.75 (12.01 to 13.50)	6.36 (5.85 to 6.86)	6.40 (5.50 to 7.30)
Q-TWiST[b]	13.32 (12.11 to 14.46)	6.44 (5.78 to 7.18)	6.88 (5.71 to 8.23)
BRCA mutant[c]			
PFS	16.49 (14.75 to 18.22)	6.71 (5.41 to 8.00)	9.78 (7.63 to 11.93)
TOX	0.64 (0.39 to 0.88)	0.10 (0.02 to 0.18)	0.54 (0.28 to 0.79)
TWiST	15.85 (14.61 to 17.09)	6.61 (5.69 to 7.53)	9.25 (7.71 to 10.78)
Q-TWiST[b]	16.42 (14.29 to 18.18)	6.70 (5.49 to 8.02)	9.73 (7.10 to 11.94)
HRD[d]			
PFS	14.97 (13.67 to 16.27)	6.81 (5.79 to 7.82)	8.17 (6.53 to 9.81)
TOX	0.65 (0.46 to 0.84)	0.08 (0.03 to 0.13)	0.57 (0.38 to 0.77)
TWiST	14.32 (13.40 to 15.25)	6.73 (6.01 to 7.45)	7.59 (6.43 to 8.76)
Q-TWiST[b]	14.91 (13.28 to 16.06)	6.80 (5.87 to 7.73)	8.11 (6.36 to 9.49)
BRCA wild type/LOH high[e]			
PFS	12.92 (11.10 to 14.74)	6.80 (5.27 to 8.33)	6.12 (3.76 to 8.48)
TOX	0.64 (0.37 to 0.92)	0.05 (-0.01 to 0.10)	0.59 (0.31 to 0.88)
TWiST	12.28 (10.98 to 13.58)	6.75 (5.67 to 7.83)	5.53 (3.85 to 7.20)
Q-TWiST[b]	12.86 (9.81 to 14.85)	6.79 (5.42 to 8.23)	6.07 (2.76 to 8.52)
BRCA wild type/LOH low[f]			
PFS	9.45 (7.91 to 10.98)	6.05 (5.15 to 6.95)	3.39 (1.63 to 5.16)
TOX	0.41 (0.29 to 0.54)	0.13 (0 to 0.26)	0.29 (0.11 to 0.47)
TWiST	9.03 (7.94 to 10.12)	5.93 (5.28 to 6.57)	3.11 (1.85 to 4.36)
Q-TWiST[b]	9.38 (7.82 to 10.96)	6.03 (5.11 to 6.86)	3.35 (1.66 to 5.40)
BRCA wild type/LOH indeterminate[g]			
PFS	13.07 (8.93 to 17.21)	4.45 (3.34 to 5.57)	8.62 (4.36 to 12.87)
TOX	0.53 (0.27 to 0.78)	0 (0 to 0.01)	0.53 (0.27 to 0.78)
TWiST	12.54 (9.61 to 15.47)	4.45 (3.66 to 5.24)	8.09 (5.08 to 11.11)
Q-TWiST[b]	13.06 (6.93 to 16.06)	4.45 (3.28 to 5.64)	8.60 (1.89 to 12.12)

NOTE. Data are presented as mean duration (95% CI).

Abbreviations: HRD, homologous recombination deficient; ITT, intent-to-treat; LOH, loss of heterozygosity; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

[a]Rucaparib (n = 375); placebo (n = 189).

[b]Calculated as μTOX × TOX + TWiST; for each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the 3-level version of the EQ-5D questionnaire assessments during a health state and normalized relative to a utility weight of 1 for the TWiST state; μTOX values: 0.89 (ITT), 0.90 (*BRCA* mutant), 0.90 (HRD), 0.91 (*BRCA* wild type/LOH high), 0.85 (*BRCA* wild type/LOH low), and 0.97 (*BRCA* wild type/LOH indeterminate).

[c]Rucaparib (n = 130); placebo (n = 66).

[d]Rucaparib (n = 236); placebo (n = 118).

[e]Rucaparib (n = 106); placebo (n = 52).

[f]Rucaparib (n = 107); placebo (n = 54).

[g]Rucaparib (n = 32); placebo (n = 17).

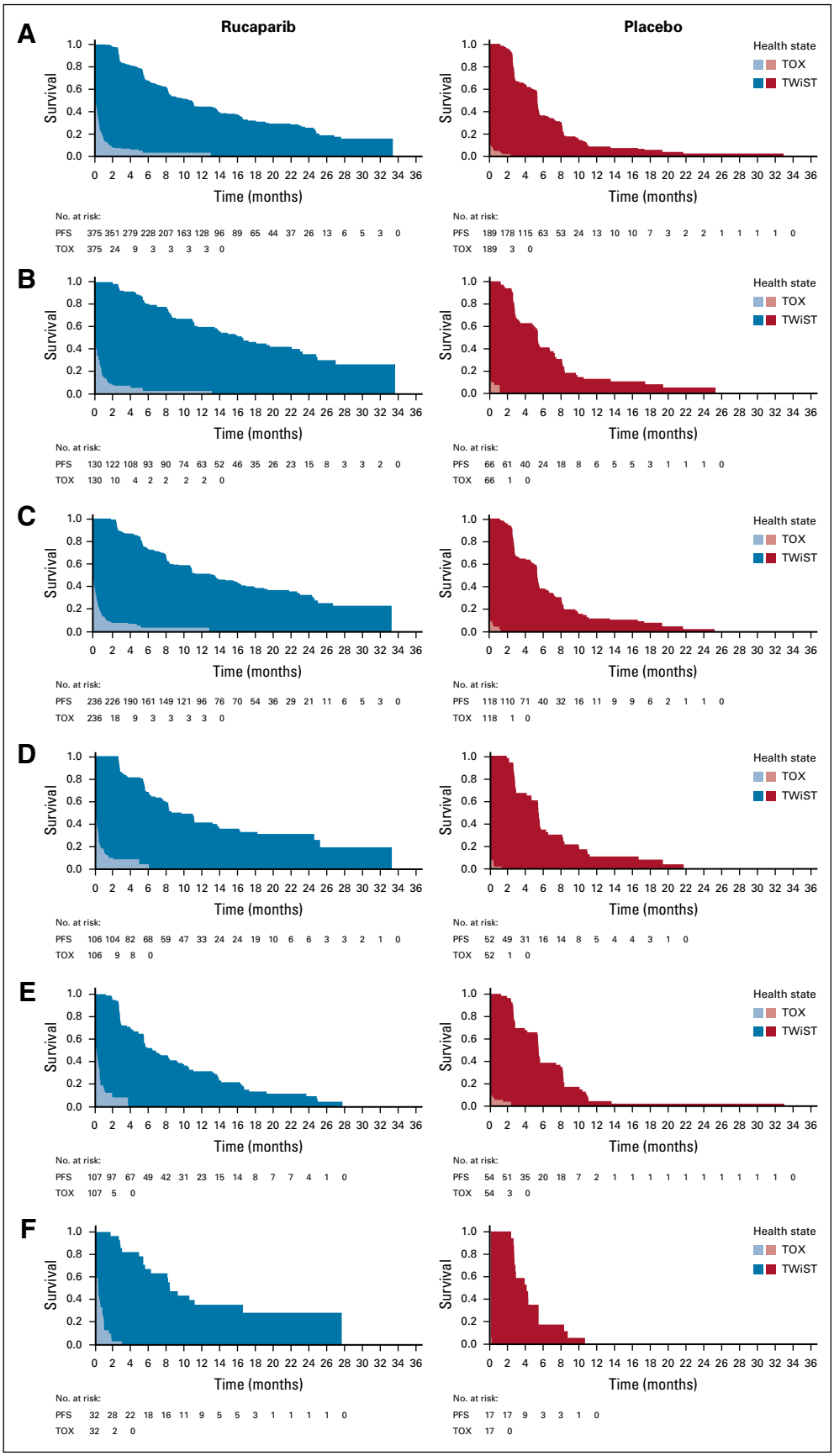

FIG 3. Time without symptoms or toxicity (TWiST) analysis, with toxicity defined as all grade ≥ 3 treatment-emergent adverse events in the intent-to-treat population (A), *BRCA*-mutant cohort (B), homologous recombination deficient cohort (C), *BRCA* wild-type/loss of heterozygosity (LOH) high (D), *BRCA* wild-type/LOH low (E), and *BRCA* wild-type/LOH indeterminate (F) patient subgroups. PFS, progression-free survival. TOX, time with toxicity of treatment.

TABLE 3. Mean Duration of Health States per Study Subgroup With Toxicity Defined as Grade ≥ 2 Adverse Events of Nausea, Vomiting, Fatigue, and Asthenia Only

	Mean Duration (months)		
Health State	**Rucaparib**	**Placebo**	**Difference**
ITT[a]			
PFS	13.39 (12.35 to 14.43)	6.45 (5.74 to 7.17)	6.94 (5.67 to 8.20)
TOX	1.54 (1.15 to 1.93)	0.40 (0.21 to 0.58)	1.15 (0.72 to 1.58)
TWiST	11.84 (11.06 to 12.63)	6.06 (5.54 to 6.58)	5.79 (4.84 to 6.73)
Q-TWiST[b]	13.16 (12.01 to 14.33)	6.40 (5.75 to 7.15)	6.77 (5.64 to 8.14)
BRCA mutant[c]			
PFS	16.49 (14.75 to 18.22)	6.71 (5.41 to 8.00)	9.78 (7.63 to 11.93)
TOX	1.39 (0.93 to 1.84)	0.14 (0.05 to 0.23)	1.25 (0.78 to 1.71)
TWiST	15.10 (13.83 to 16.37)	6.57 (5.65 to 7.49)	8.53 (6.98 to 10.09)
Q-TWiST[b]	16.24 (14.11 to 17.95)	6.68 (5.45 to 8.00)	9.56 (6.99 to 11.81)
HRD[d]			
PFS	14.97 (13.67 to 16.27)	6.81 (5.79 to 7.82)	8.17 (6.53 to 9.81)
TOX	1.53 (1.12 to 1.94)	0.44 (0.20 to 0.68)	1.09 (0.61 to 1.56)
TWiST	13.45 (12.48 to 14.41)	6.37 (5.63 to 7.10)	7.08 (5.87 to 8.29)
Q-TWiST[b]	14.74 (13.16 to 15.91)	6.74 (5.83 to 7.70)	8.00 (6.27 to 9.36)
BRCA wild type/LOH high[e]			
PFS	12.92 (11.10 to 14.74)	6.80 (5.27 to 8.33)	6.12 (3.76 to 8.48)
TOX	1.46 (0.86 to 2.06)	0.48 (0.10 to 0.86)	0.98 (0.28 to 1.69)
TWiST	11.46 (10.10 to 12.82)	6.32 (5.21 to 7.44)	5.14 (3.40 to 6.88)
Q-TWiST[b]	12.74 (9.66 to 14.73)	6.74 (5.37 to 8.21)	6.00 (2.67 to 8.45)
BRCA wild type/LOH low[f]			
PFS	9.45 (7.91 to 10.98)	6.05 (5.15 to 6.95)	3.39 (1.63 to 5.16)
TOX	1.18 (0.53 to 1.84)	0.03 (0.01 to 0.05)	1.16 (0.50 to 1.81)
TWiST	8.26 (7.09 to 9.44)	6.03 (5.39 to 6.66)	2.24 (0.91 to 3.57)
Q-TWiST[b]	9.28 (7.76 to 10.88)	6.05 (5.09 to 6.85)	3.23 (1.58 to 5.35)
BRCA wild type/LOH indeterminate[g]			
PFS	13.07 (8.93 to 17.21)	4.45 (3.34 to 5.57)	8.62 (4.36 to 12.87)
TOX	0.57 (0.29 to 0.85)	0	0.57 (0.29 to 0.85)
TWiST	12.50 (9.57 to 15.43)	4.45 (3.67 to 5.24)	8.05 (5.03 to 11.06)
Q-TWiST[b]	13.00 (6.88 to 16.53)	4.45 (3.28 to 5.64)	8.54 (1.80 to 12.03)

NOTE. Data are presented as mean duration (95% CI).

Abbreviations: HRD, homologous recombination deficient; ITT, intent-to-treat; LOH, loss of heterozygosity; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

[a]Rucaparib (n = 375); placebo (n = 189).

[b]Calculated as μTOX × TOX + TWiST; for each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the 3-level version of the EQ-5D questionnaire assessments during a health state and normalized relative to a utility weight of 1 for the TWiST state; μTOX values: 0.85 (ITT), 0.82 (*BRCA* mutant), 0.85 (HRD), 0.88 (*BRCA* wild type/LOH high), 0.86 (*BRCA* wild type/LOH low), and 0.87 (*BRCA* wild type/LOH indeterminate).

[c]Rucaparib (n = 130); placebo (n = 66).

[d]Rucaparib (n = 236); placebo (n = 118).

[e]Rucaparib (n = 106); placebo (n = 52).

[f]Rucaparib (n = 107); placebo (n = 54).

[g]Rucaparib (n = 32); placebo (n = 17).

to 2.9-fold (*BRCA* wild type/LOH indeterminate) longer durations of Q-TWiST in both the grade ≥ 3 and selected grade ≥ 2 TEAE-based analyses. The Q-TWiST results also indicate that rucaparib maintenance treatment extended the time in which patients had good health status or QoL without cancer-related symptoms, which is a key objective for patients.[12,13]

The QA-PFS and Q-TWiST findings together suggest that rucaparib maintenance treatment provides a broad clinical benefit to women with recurrent ovarian cancer. Notably, clinical benefit was observed in all cohorts analyzed, with the greatest benefit (ie, largest mean differences) observed in patients with a documented *BRCA* mutation. Analyses in the subgroups of patients with a *BRCA* wild-type carcinoma demonstrate that the benefits observed in the HRD cohort and the ITT population were not driven solely by the improvements in the *BRCA*-mutant and HRD cohorts. QA-PFS and Q-TWiST are able to align the impact of toxicity on patient outcomes with the time that toxicity is experienced by patients and, therefore, reflect more faithfully the overall experience of patients.

Other clinical trials of PARP inhibitors as second-line maintenance treatment of ovarian cancer have also assessed patient-centered outcomes using EQ-5D and toxicity data. In the SOLO2/ENGOT-Ov21 study comparing maintenance olaparib with placebo in women with platinum-sensitive, recurrent ovarian cancer and a *BRCA1/2* mutation, QA-PFS was almost twice as long in the olaparib group (13.96 *v* 7.28 months; $P < .0001$). Based on TWiST analysis, patients who received olaparib also had approximately 2-fold longer survival with good health status than those who received placebo (15.03 *v* 7.70 months; $P < .0001$; toxicity defined as grade ≥ 2 TEAEs of nausea, vomiting, or fatigue).[14] In the ENGOT-OV16/NOVA study, mean TWiST was at least 2-fold longer with niraparib than with placebo; the mean difference in TWiST was 2.95 years (35.4 months) in patients with a germline *BRCA* mutation and 1.34 years (16.1 months) in patients without a germline *BRCA* mutation (including patients with somatic *BRCA* mutations).[15] The TWiST analysis in NOVA was limited to grade ≥ 2 TEAEs of nausea, vomiting, and fatigue. Furthermore, the NOVA analysis calculated mean PFS with extrapolated survival curves under the assumption that patients could remain progression free for up to 20 years. The differences in how each of these analyses were conducted demonstrate the need for consistency in reporting TWiST analyses in studies of maintenance therapies for recurrent ovarian cancer, to enable the results to be compared across clinical trials.

Patient-centered outcome assessments are particularly important as health-related QoL is of great importance to women with ovarian cancer because of the significant morbidity they experience as a result of the disease and its treatment.[16] Indeed, organizations such as the GCIG, the Society of Gynecologic Oncology, the European Society for Gynaecological Oncology, and the European Society for Medical Oncology recognize that the benefits of PFS can be supported by QoL measures.[4,17,18] New treatments that increase PFS may not be of sufficient value to patients with advanced-stage cancer unless they also convey tangible QoL benefits.[19] Moreover, women with recurrent or advanced ovarian cancer may be willing to tolerate treatment toxicities if the goal is curative but may be less tolerant when the goal is a PFS benefit[18]; therefore, physicians and patients must carefully consider a wide variety of factors including expectations about efficacy, treatment toxicities, QoL, frequency of clinic visits and blood tests, and direct and indirect treatment costs when choosing whether to initiate maintenance therapy.[20,21] Of particular note, physicians and patients must be aware of the potential trade-offs between quality and quantity of life,[19,22] and data such as that presented here may be helpful in discussing this particular aspect. Equally important, disease relapse has a negative psychological and physical impact, with a subsequent deterioration in QoL, underlining the importance of prolonging time without recurrence or progression.[23]

The strengths of these analyses include the incorporation of a direct measurement of EQ-5D-3L (from which utility values were derived) and the consistency of outcomes favoring rucaparib over placebo in the context of a randomized clinical trial. The QA-PFS and Q-TWiST analyses did not rely on extrapolation or assumptions with respect to survival time, and the current analysis was conservative in that it penalized time with toxicities yet still showed results in PFS time similar to those in the original ITT analysis. The QA-PFS and Q-TWiST analyses consistently favored rucaparib even in subgroups of patients with *BRCA* wild-type carcinomas, a population in which clinical benefits are less pronounced than in those with *BRCA*-mutant carcinomas. Importantly, to our knowledge, Q-TWiST data have not been reported previously for PARP inhibitors in the maintenance setting for ovarian cancer, and the incorporation of quality-adjusted methodology in our analysis demonstrates the impact of patients' perceptions of QoL on the TWiST analyses.

Limitations of this post hoc, retrospective analysis include the lack of adjustment for multiple analyses, the small sample sizes for some of the subgroup analyses, and the fact that the TWiST analysis with TOX defined as grade ≥ 2 TEAEs was restricted to nausea, vomiting, fatigue, and asthenia. Another limitation is that the analyses presented here are based on EQ-5D-3L and toxicity data, rather than on other QoL assessments, such as FOSI-18. Because EQ-5D-3L data were collected on the first day of each treatment cycle and were not designed to be collected during adverse events (AEs), EQ-5D-3L data were not available at the time of each AE. Therefore, our methods required the assumption of interpolation between 2 assessments to define values; for our analysis, a linear function was used. Thus, if only 1 assessment was available during the period of a patient's TEAE,

we assumed that the EQ-5D-3L value was constant for the duration of the TEAE. Some patients may also have had TEAEs that occurred between EQ-5D-3L assessments, resulting in missing data. Furthermore, the mean time difference estimates should be interpreted in the light of the maximum length of follow-up (eg, a mean difference of 6 months is not interpreted in the same way when the global timeframe of the analysis is approximately 30 months [as was the case here] as it would be for a follow-up duration of 10 years). In addition, the OS data for ARIEL3 were not mature at the time of these analyses and, therefore, could not be incorporated into the Q-TWiST analysis; however, the analysis could be repeated after OS maturation. Last, these results require confirmation in larger, prospective studies, which could include observational cohort studies that evaluate the effects of rucaparib maintenance therapy on QA-PFS in daily clinical practice.

In our analyses, rucaparib provided significant benefits to patient health status even when accounting for toxicities, as demonstrated by QA-PFS and Q-TWiST analyses. These benefits were observed in the ITT population and in subgroups of patients with a *BRCA*-mutant carcinoma and those with a *BRCA* wild-type carcinoma. Taken together, these findings demonstrated that rucaparib extended PFS in the maintenance setting without detrimental effects on patient health status.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient-Centered Outcomes in ARIEL3, a Phase III, Randomized, Placebo-Controlled Trial of Rucaparib Maintenance Treatment in Patients With Recurrent Ovarian Carcinoma

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No other potential conflicts of interest were reported.

APPENDIX

Methods

Calculation of quality-adjusted progression-free survival.

Quality-adjusted progression-free survival (QA-PFS) was calculated as the product of the investigator-assessed progression-free survival function, obtained by Kaplan-Meier estimation up to the April 15, 2017, visit cutoff and the 3-level version of the EQ-5D questionnaire (EQ-5D-3L) index score function (flowchart in Appendix Fig A1). The EQ-5D-3L index score function was obtained by computation of the mean EQ-5D-3L index score of patients who were alive and uncensored at each visit scheduled in the double-blind treatment period. No adjustment was made for patient dropout, and there was no imputation in the EQ-5D-3L data. To create a quality-of-life function over continuous time, estimates of the mean EQ-5D-3L index score at each visit were connected assuming a linear change. Mean QA-PFS was obtained by computing the area under the quality-survival product function. The 95% CI for the mean QA-PFS in the rucaparib and placebo groups and for the difference between groups was computed using the bootstrap method,[24] with 200 replications of the sample.

Calculation of quality-adjusted time without symptoms or toxicity. Quality-adjusted time without symptoms or toxicity (Q-TWiST) was calculated as μTOX $\times$ TOX + TWiST. μTOX denotes the utility weight for the TOX state and was determined as described later in the Appendix (flowchart in Appendix Fig A2). The mean durations for the TOX and TWiST states were estimated by the area under each survival curve and calculated using Kaplan-Meier estimates. In Q-TWiST analyses based on all grade $\geq$ 3 TEAEs, time with toxicity for treatment of each patient was defined as the number of days with grade $\geq$ 3 treatment-emergent adverse events (TEAEs) after random assignment and before disease progression or censoring for progression. All grade $\geq$ 3 TEAEs before progression were included in the calculation of time with toxicity of treatment. If several adverse events (AEs) overlapped, the number of days was calculated between the start date of the first AE and the end date of the last AE. For analyses that were based on grade $\geq$ 2 TEAEs of nausea, vomiting, fatigue, and asthenia, the same methods were used for inclusion and treatment of overlap.

Determination of μTOX. Observed utility data from the EQ-5D-3L, EuroQol's 5-dimension questionnaire 3-level version, were incorporated in the Q-TWiST analysis. For each patient, the average utility weight derived from EQ-5D-3L assessments during a health state was assigned as a per-person utility weight for the TOX and TWiST states. The overall average utility was then calculated for each state to determine the μTOX utility weight for the TOX state, and the μTWiST utility weight for the TWiST state. The utility weight for the TOX state was then normalized relative to a utility weight of 1 (best possible utility weight) for the TWiST state.

Results

In the April 15, 2017, cut of the ARIEL3 trial data, a total of 5,503 EQ-5D-3L nonmissing records (4,042 from the rucaparib group; 1,461 from the placebo group) were analyzed. These comprised 5,084 records (3,796 rucaparib; 1,288 placebo) from a maximum of 39 treatment cycles, 245 records (144 rucaparib; 101 placebo) from the end of treatment, and 174 records (102 rucaparib; 72 placebo) from the day 28 follow-up visit after treatment discontinuation.

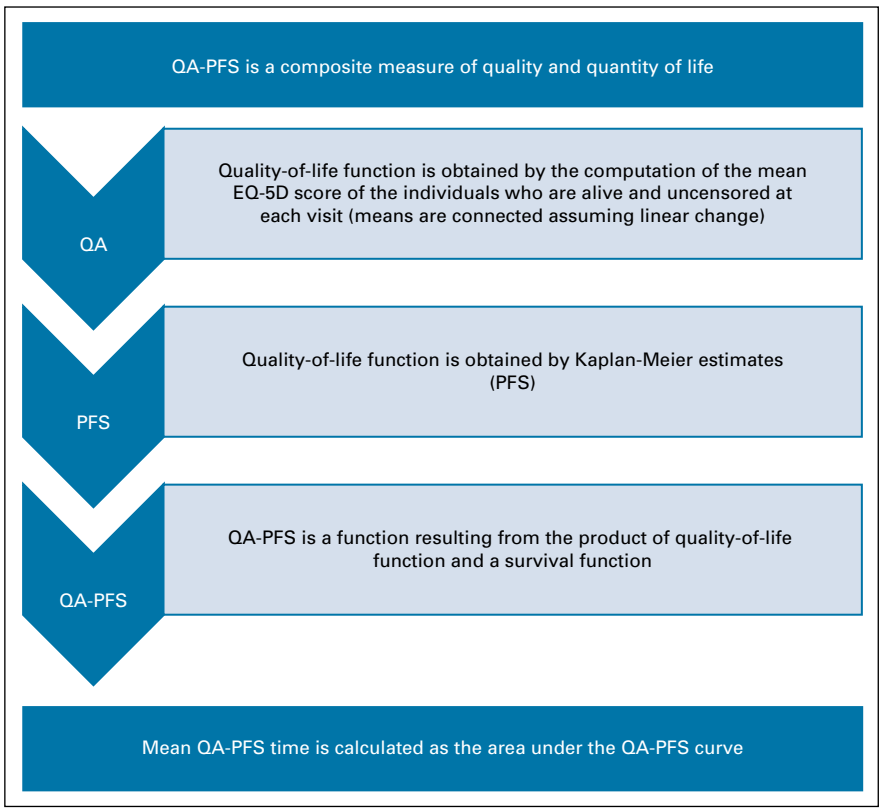

FIG A1. Flowchart for calculation of quality-adjusted (QA) progression-free survival (PFS; QA-PFS).

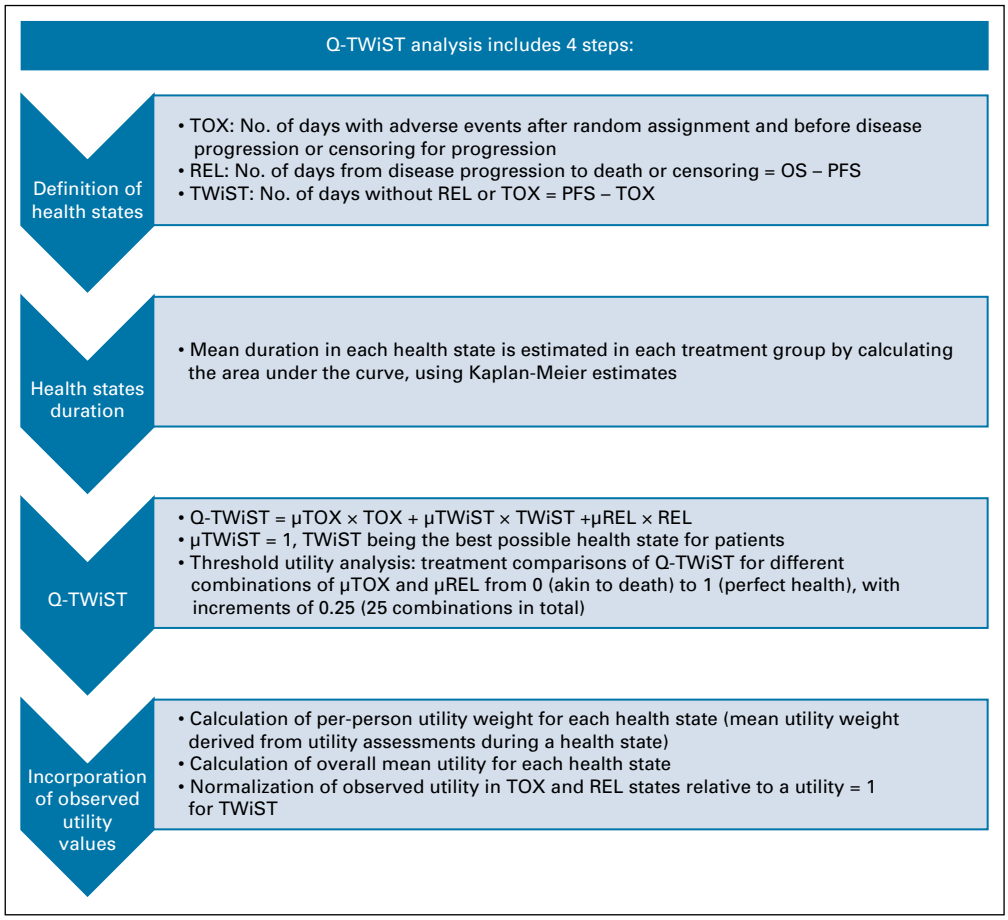

FIG A2. Flowchart for calculation of quality-adjusted time without symptoms or toxicity (TWiST; Q-TWiST). The mean time with symptoms of disease (REL state) was not included in these analyses because ARIEL3 OS data were not mature at the time of this analysis. AEs, adverse events; OS, overall survival; PFS, progression-free survival; TOX, time with toxicity of treatment.

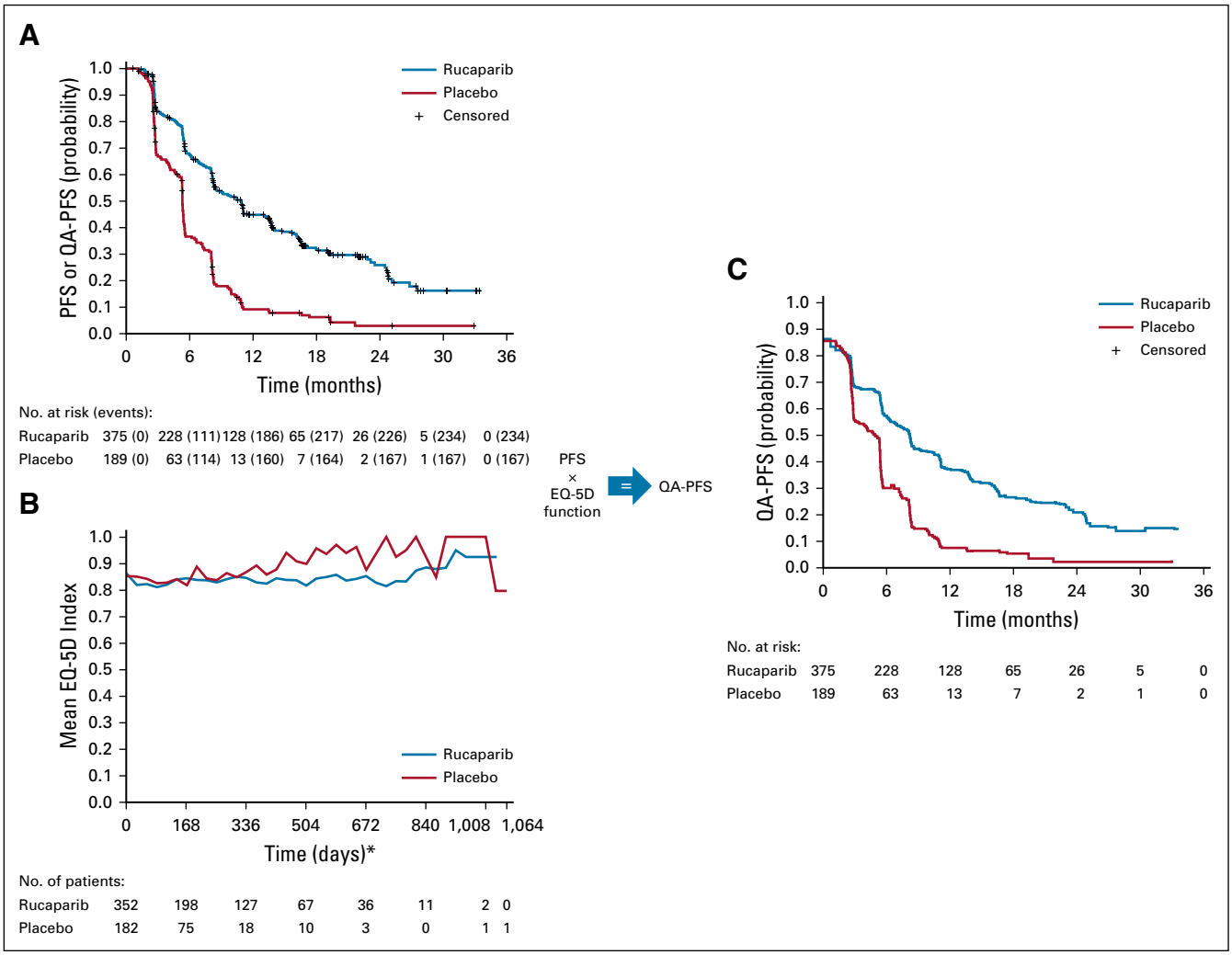

FIG A3. Quality-adjusted progression-free survival (QA-PFS) for the intent-to-treat population determined by multiplying the investigator-assessed progression-free survival (PFS) function (A) by the EQ-5D-3L index score function (B) to obtain a QA-PFS function (C). (*) EQ-5D-3L data were collected on day 1 of each 28-day treatment cycle. PFS, progression-free survival; QA-PFS, quality-adjusted progression-free survival.

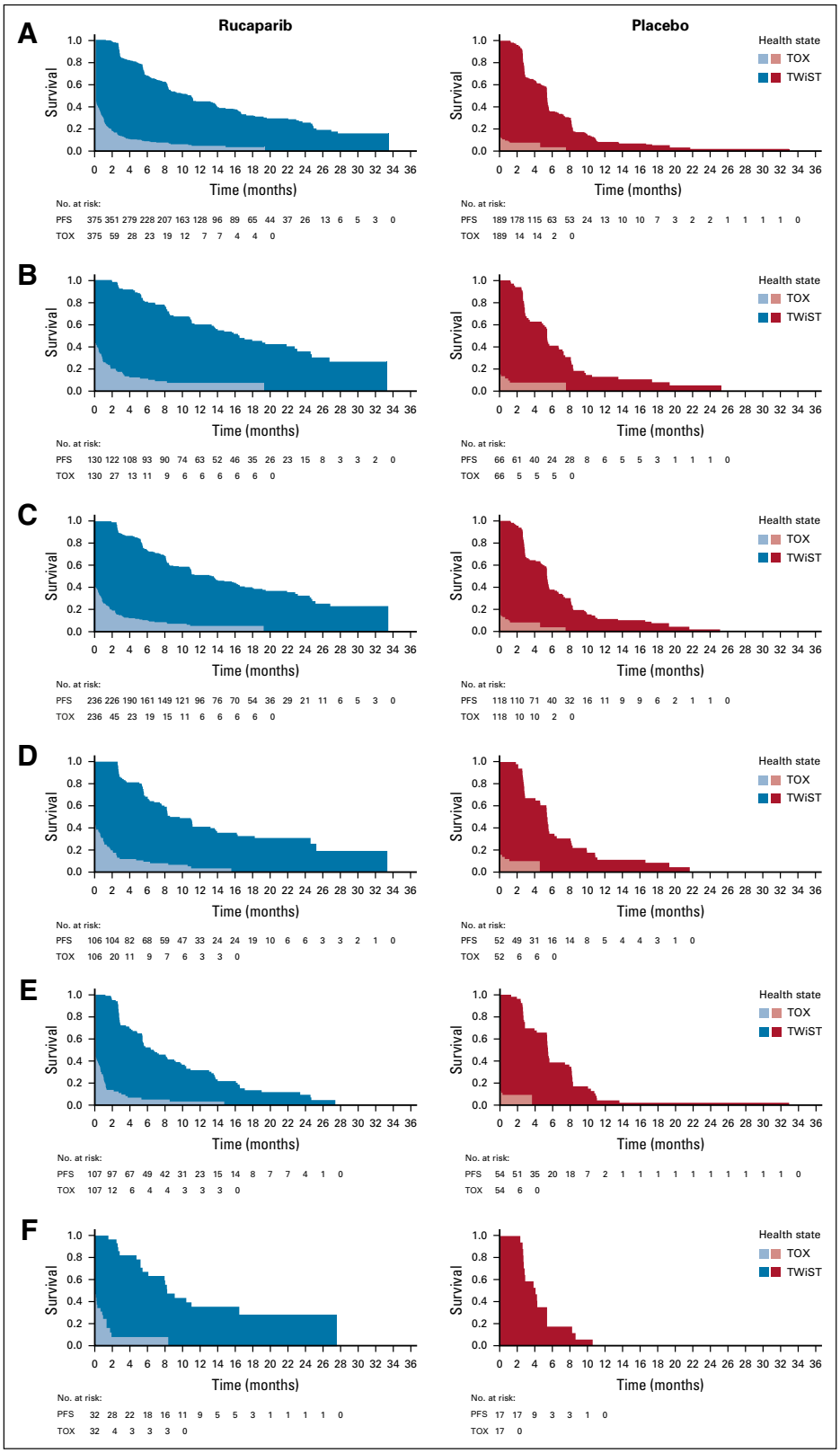

FIG A4. Time without symptoms or toxicity (TWiST) analysis with toxicity defined as grade ≥ 2 treatment-emergent adverse events of nausea, vomiting, fatigue, and asthenia only in the intent-to-treat population (A), *BRCA*-mutant cohort (B), homologous recombination deficient cohort (C), *BRCA* wild-type/loss of heterozygosity (LOH) high (D), *BRCA* wild-type/LOH low (E), and *BRCA* wild-type/LOH indeterminate (F) patient subgroups. TOX, time with toxicity of treatment.

TABLE A1. QA-PFS Sensitivity Analysis per Study Subgroup

Subgroup	Mean Duration (months)	
	QA-PFS (through last follow-up date)	QA-PFS – Sensitivity Analysis (through 24 months of follow-up)
ITT[a]		
Rucaparib	12.02 (10.96 to 13.03)	10.57 (9.87 to 11.27)
Placebo	5.74 (4.98 to 6.42)	5.53 (4.88 to 6.10)
Difference	6.28 (4.85 to 7.47)	5.04 (4.09 to 5.90)
BRCA mutant[b]		
Rucaparib	15.28 (13.22 to 17.45)	12.95 (11.76 to 14.07)
Placebo	5.92 (4.71 to 7.23)	5.86 (4.69 to 7.12)
Difference	9.37 (6.65 to 11.85)	7.09 (5.30 to 8.76)
HRD[c]		
Rucaparib	13.83 (12.11 to 15.18)	11.80 (10.73 to 12.73)
Placebo	5.90 (4.97 to 6.89)	5.88 (4.97 to 6.85)
Difference	7.93 (5.93 to 9.53)	5.92 (4.36 to 7.27)
BRCA wild type/LOH high[d]		
Rucaparib	12.59 (9.75 to 14.13)	10.54 (9.11 to 11.84)
Placebo	5.95 (4.66 to 7.24)	5.95 (4.66 to 7.24)
Difference	6.65 (3.65 to 8.40)	4.59 (2.63 to 6.27)
BRCA wild type/LOH low[e]		
Rucaparib	8.13 (6.53 to 9.53)	7.96 (6.45 to 9.23)
Placebo	5.42 (4.40 to 6.93)	5.23 (4.37 to 6.32)
Difference	2.71 (0.31 to 4.44)	2.72 (0.57 to 4.16)
BRCA wild type/LOH indeterminate[f]		
Rucaparib	11.23 (7.13 to 14.28)	10.20 (6.90 to 12.78)
Placebo	3.70 (2.86 to 4.47)	3.70 (2.86 to 4.47)
Difference	7.53 (3.26 to 10.67)	6.51 (3.09 to 9.32)

NOTE. Data are presented as mean duration (95% CI).

Abbreviations: HRD, homologous recombination deficient; ITT, intent-to-treat; LOH, loss of heterozygosity; QA-PFS, quality-adjusted progression-free survival.

[a]Rucaparib (n = 375); placebo (n = 189).

[b]Rucaparib (n = 130); placebo (n = 66).

[c]Rucaparib (n = 236); placebo (n = 118).

[d]Rucaparib (n = 106); placebo (n = 52).

[e]Rucaparib (n = 107); placebo (n = 54).

[f]Rucaparib (n = 32); placebo (n = 17).