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

Amit M. Oza, MD; Domenica Lorusso, MD; Carol Aghajanian, MD; Ana Oaknin, MD, PhD; Andrew Dean, MD; Nicoletta Colombo, MD; Johanne I. Weberpals, MD; Andrew R. Clamp, MD, PhD; Giovanni Scambia, MD; Alexandra Leary, MD; Robert W. Holloway, MD; Margarita Amenedo Gancedo, MD; Peter C. Fong, MBBS; Jeffrey C. Goh, MBBA; David M. O'Malley, MD; Deborah K. Armstrong, MD; Susana Banerjee, PhD; Jesus Garcia-Donas, MD; Elizabeth M. Swisher, MD; David Cella, PhD; Juliette Meunier, MSc; Sandra Goble, MS; Terri Cameron, MSc; Lara Maloney, BA; Ann-Christin Mork, PhD; Josh Bedel, MSc; Jonathan A. Ledermann, MD; and Robert L. Coleman, MD

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 7.74 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.
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.

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.\textsuperscript{9} Full details of the testing protocol have been reported previously.\textsuperscript{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 \textit{BRCA1} or \textit{BRCA2}, mutation in a non-\textit{BRCA} gene associated with homologous recombination, or no mutation in \textit{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-3L 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.\textsuperscript{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.\textsuperscript{9} Analyses were performed for the 3 prespecified, nested cohorts: the ITT population, patients with an HRD carcinoma (\textit{BRCA} mutation or \textit{BRCA} wild type/LOH high), and patients with a \textit{BRCA}-mutated carcinoma. Analyses were also conducted in subgroups of patients with \textit{BRCA} wild-type carcinomas based on LOH status: \textit{BRCA} wild type/LOH high, \textit{BRCA} wild type/LOH low, and \textit{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 $\mu_{\text{TOX}} \times \text{TOX} + \text{TWiST}$. $\mu_{\text{TOX}}$ 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).

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,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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)               |
| Germine                               | 82 (21.9)                 | 48 (25.4)               |
| Somatic                               | 40 (10.7)                 | 16 (8.5)                |
| Unknown<sup>a</sup>                  | 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<sup>b</sup>        | 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<sup>c</sup>   | 126 (33.6)                | 64 (33.9)               |
| PR according to RECIST<sup>c</sup> 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. © 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.

<sup>a</sup>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.

<sup>b</sup>Tumor sample was not evaluable for percentage of genomic LOH because of low tumor content or aneuploidy.

<sup>c</sup>Version 1.1.
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).

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.

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

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| ITTa                | 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-TWiSTb            | 13.32 (12.11 to 14.46)  | 6.44 (5.78 to 7.18)   | 6.88 (5.71 to 8.23)   |

### BRCA mutantc

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| 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 (0.04 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-TWiSTb            | 16.42 (14.29 to 18.18)  | 6.70 (5.49 to 8.02)   | 9.73 (7.10 to 11.94)  |

### HRDd

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| 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 (5.61 to 7.45)   | 7.59 (6.43 to 8.76)   |
| Q-TWiSTb            | 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 highe

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| 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-TWiSTb            | 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 lowf

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| 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 (0.01 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-TWiSTb            | 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 indeterminateg

| Health State       | Rucaparib               | Placebo               | Difference            |
|--------------------|-------------------------|-----------------------|-----------------------|
| 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-TWiSTb            | 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.

* Rucaparib (n = 375); placebo (n = 189).

1 Calculated as $\mu_{TOX} \times TOX + TWiST$; for each subgroup, $\mu_{TOX}$ 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; $\mu_{TOX}$ 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).

* Rucaparib (n = 130); placebo (n = 66).

* Rucaparib (n = 236); placebo (n = 118).

* Rucaparib (n = 106); placebo (n = 52).

* Rucaparib (n = 107); placebo (n = 54).

* Rucaparib (n = 32); placebo (n = 17).
FIG 3. Time without symptoms or toxicity (TWiST) analysis, with toxicity defined as all grade $\geq 3$ 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

| Health State | Rucaparib | Placebo | Difference |
|--------------|-----------|---------|------------|
| **ITT**      |           |         |            |
| 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      | 13.16 (12.01 to 14.33) | 6.40 (5.75 to 7.15) | 6.77 (5.64 to 8.14) |
| **BRCA mutant** |           |         |            |
| PFS          | 16.44 (14.75 to 18.22) | 6.71 (5.41 to 8.00) | 9.74 (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      | 16.24 (14.11 to 17.95) | 6.68 (5.45 to 8.00) | 9.56 (6.99 to 11.81) |
| **HRD**      |           |         |            |
| 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      | 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** |           |         |            |
| 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      | 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** |           |         |            |
| 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) | 1.15 (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      | 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** |           |         |            |
| 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      | 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.

Rucaparib (n = 375); placebo (n = 189).

1Calculated as \( \mu_{\text{TOX}} \times \text{TOX} + \text{TWiST} \); for each subgroup, \( \mu_{\text{TOX}} \) 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; \( \mu_{\text{TOX}} \) 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).

Rucaparib (n = 130); placebo (n = 66).

Rucaparib (n = 236); placebo (n = 118).

Rucaparib (n = 106); placebo (n = 52).

Rucaparib (n = 107); placebo (n = 54).

Rucaparib (n = 32); placebo (n = 17).
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 (i.e., 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, and 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 benefit16; 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.

AFFILIATIONS
1Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
2Fondazione Policlinico Universistario A. Gemelli IRCCS, Rome, Italy
3Memorial Sloan Kettering Cancer Center, New York, NY
4Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology, Barcelona, Spain
5St John of God Subiaco Hospital, Subiaco, WA, Australia
6University of Milan-Bicocca and European Institute of Oncology, Milan, Italy
7Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
8The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom
9Gustave Roussy Cancer Center, INSEMM U981, and Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, Villejuif, France
10AdventHealth Cancer Institute, Orlando, FL
11Oncology Center of Galicia, Doctor Camilo Veiras, La Coruña, Spain
12Auckland City Hospital, Auckland, New Zealand
13Royal Brisbane and Women’s Hospital and University of Queensland, St Lucia, Australia
14The Ohio State University, James Cancer Center, Columbus, OH
15Johns Hopkins University School of Medicine, Baltimore, MD
16The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom
17HM Hospitales—Centro Integral Oncológico Hospital de Madrid Clara Campal, Madrid, Spain
18University of Washington, Seattle, WA
19Feinberg School of Medicine, Northwestern University, Chicago, IL
20Modus Outcomes, Lyon, France
21Clovis Oncology, Inc., Boulder, CO
22Clovis Oncology UK Ltd., Cambridge, United Kingdom
23Clovis Oncology Denmark, ApS, Copenhagen, Denmark
24Clovis Oncology Switzerland, GmbH, Zurich, Switzerland
25UCL Cancer Institute, University College London, and UCL Hospitals, London, United Kingdom
26The University of Texas MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR
Amit M. Oza, MD, Princess Margaret Cancer Centre, University Health Network and Sinai Health System, University of Toronto, 610 University Ave, Toronto Ontario M5G 2M9, Canada; e-mail: amit.oza@uhn.ca.

NOTE
A.-C.M. and J.B. have declared their affiliations based on the time during which the analyses were conducted.

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AUTHOR CONTRIBUTIONS
Conception and design: Elizabeth M. Swisher, David Cell, Sandra Goble, Terri Cameron, Josh Bedel, Jonathan A. Ledermann, Robert L. Coleman
Provision of study material or patients: Amit M. Oza, Domenica Lorusso, Carol Agahajanian, Ana Okijn, Andrew Dean, Nicoletta Colombo, Johanne I. Weberpals, Andrew R. Clamp, Giovann Scambio, Alexandra Leary, Robert W. Holloway, Margarita Amenedo Gancedo, Peter C. Fong, Jeffrey C. Goh, David M. O’Malley, Deborah K. Armstrong, Susana Banerjee, Jesus Garcia-Donas, Elizabeth M. Swisher, Jonathan A. Ledermann, and Robert L. Coleman.
Collection and assembly of data: Amit M. Oza, Domenica Lorusso, Carol Agahajanian, Ana Okijn, Andrew Dean, Nicoletta Colombo, Johanne I. Weberpals, Andrew R. Clamp, Giovann Scambio, Alexandra Leary, Robert W. Holloway, Margarita Amenedo Gancedo, Peter C. Fong, Jeffrey C. Goh, David M. O’Malley, Deborah K. Armstrong, Susana Banerjee,
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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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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Amit M. Oza
Uncompensated Relationships: Ozmosis Research

Domenica Lorusso
Honoraria: Roche, AstraZeneca, Tesaro, Clovis Oncology, Merck, Genmab, Immunogen
Consulting or Advisory Role: PharmaMar
Speakers’ Bureau: AstraZeneca, Clovis Oncology, Tesaro, PharmaMar
Research Funding: PharmaMar (Inst), Clovis Oncology (Inst), Tesaro (Inst), Merck (Inst)
Expert Testimony: Clovis Oncology
Travel, Accommodations, Expenses: Tesaro, Roche, PharmaMar, AstraZeneca, Clovis Oncology

Carol Aghajanian
Consulting or Advisory Role: Tesaro, Mersana, Eisai, Roche, AbbVie
Research Funding: Genentech/Roche (Inst), AbbVie (Inst), Clovis Oncology (Inst), AstraZeneca (Inst)

Ana Ouknine
Consulting or Advisory Role: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro, Immunogen, Genmab
Research Funding: AbbVie Deutschland (Inst), Ability Pharmaceuticals (Inst), Advaxis (Inst), Aeterna Zentaris (Inst), Amgen (Inst), Aprea Therapeutics (Inst), Clovis Oncology (Inst), Eisai (Inst), Hoffmann La Roche (Inst), Regeneron Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Tesaro, Roche, PharmaMar, AstraZeneca, Roche

Andrew Dean
Travel, Accommodations, Expenses: Novartis

Nicoletta Colombo
Honoraria: Roche/Genentech, AstraZeneca, Tesaro, PharmaMar
Consulting or Advisory Role: Roche/Genentech, PharmaMar, AstraZeneca, Clovis Oncology, Pfizer, MSD Oncology, Takeda, Tesaro, BioCad, GlaxoSmithKline

Johanne I. Weberpals
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca

Andrew R. Clamp
Consulting or Advisory Role: AstraZeneca, GlaxoSmithKline
Speakers’ Bureau: Clovis Oncology
Research Funding: AstraZeneca (Inst), Clovis Oncology (Inst), Millennium (Inst), Pfizer (Inst), Immunogen (Inst), Lilly (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Tesaro

Giovanni Scambia
Consulting or Advisory Role: Clovis Oncology, AstraZeneca, PharmaMar, Roche, Tesaro
Speakers’ Bureau: Clovis Oncology Italy, MSD Italia

Alexandra Leary
Honoraria: AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Clovis Oncology (Inst), AstraZeneca (Inst), Tesaro (Inst), BioCad, Grifols Oncology, Seattle Genetics,Ability Pharma (Inst), MSD (Inst), GlaxoSmithKline (Inst), Merck Serono (Inst)
Research Funding: Merus (Inst), GamaMabs Pharma (Inst), Invitae (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Tesaro

Robert W. Holloway
Consulting or Advisory Role: Clovis Oncology, AbbVie
Speakers’ Bureau: AstraZeneca, Clovis Oncology, Tesaro, Bard/Davol

Margarita Amenedo Gancedo
Consulting or Advisory Role: Clovis Oncology
Speakers’ Bureau: AstraZeneca, PharmaMar, Roche, Tesaro
Travel, Accommodations, Expenses: Roche, Lilly

Peter C. Fong
Consulting or Advisory Role: MSD, Pfizer
Travel, Accommodations, Expenses: Pfizer

Jeffrey C. Goh
Stock and Other Ownership Interests: Immune
Honorary: Ipsen Australia
Consulting or Advisory Role: Tesaro, AstraZeneca
Speakers’ Bureau: Novartis, Ipsen, Janssen, Mundipharma, AstraZeneca India
Travel, Accommodations, Expenses: Astellas Pharma, AstraZeneca

David M. O’Malley
Consulting or Advisory Role: Janssen Oncology, AstraZeneca, Clovis Oncology, Tesaro, Novocure, AbbVie, Genentech/Roche, OncoQuest, Immunogen, GOG Foundation, Translational Genomics/Cordevgenics, Agenus, Marker Therapeutics, Eisai, Geneius, Iovance Biotherapeutics, Amybi Genetics, Tarveda Therapeutics, Leap Therapeutics, Myriad Genetics, GlaxoSmithKline, Regeneron
Research Funding: Amgen (Inst), AstraZeneca (Inst), Genentech/Roche (Inst), Regeneron (Inst), Immunogen (Inst), Janssen Research & Development (Inst), Clovis Oncology (Inst), EMD Serono (Inst), Ergomed (Inst), Ajinomoto (Inst), Immunogen (Inst), Cerulean Pharma (Inst), PharmaMar (Inst), Array BioPharma (Inst), Bristol Myers Squibb (Inst), Agenus (Inst), Tesaro (Inst), Tracor Pharma (Inst), Genmab (Inst), Seattle Genetics (Inst), Iovance Biotherapeutics (Inst), Leap Therapeutics (Inst), Merck (Inst), AbbVie, Stemcentrx (Inst), AbbVie (Inst)

Deborah K. Armstrong
Consulting or Advisory Role: Cure Biopharma, AbbVie, Eisai
Research Funding: Clovis Oncology (Inst), AstraZeneca (Inst), Advaxis (Inst), Syndax (Inst), Pfizer (Inst), Tesaro (Inst), Eisai (Inst)

Other Relationship: AstraZeneca

Susana Banerjee
Honoraria: Roche
Consulting or Advisory Role: AstraZeneca/MedImmune, Tesaro, Clovis Oncology, Merck, Seattle Genetics, Genmab, Carick Therapeutics (Inst), Amgen, Roche, GlaxoSmithKline, MSD Oncology
Research Funding: AstraZeneca (Inst), Janssen-Cilag (Inst), GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: NuCana BioMed, AstraZeneca

Jesús García-Donas
Consulting or Advisory Role: Bristol Myers Squibb, Clovis Oncology
Speakers’ Bureau: Roche, Bristol Myers Squibb, AstraZeneca, PharmaMar, GlaxoSmithKline, Agenus, Clovis Oncology, Janssen-Cilag
Research Funding: Pfizer, Bristol Myers Squibb, Roche, AstraZeneca, Merck, GamaMabs, InvitroCue
Travel, Accommodations, Expenses: Roche

Elizabeth M. Swisher
Leadership: Ideaya Biosciences

David Cella
Stock and Other Ownership Interests: FACIT.org
Consulting or Advisory Role: AbbVie, GlaxoSmithKline, Pfizer, Astellas Pharma, Novartis, PediaPharma, IDIDi, Bristol Myers Squibb, Asahi Kasei Pharma, Ipsen, Mei Pharma
Research Funding: Novartis (Inst), Genentech (Inst), Ipsen (Inst), Pfizer (Inst), Bayer (Inst), GlaxoSmithKline (Inst), PledPharma (Inst), Bristol Myers Squibb (Inst), AbbVie (Inst), Regeneron (Inst), Clovis Oncology (Inst)
Travel, Accommodations, Expenses: Ipsen, PediaPharma

Juliette Meunier
Employment: Modus Outcomes

Sandra Goble
Employment: Clovis Oncology

Teresa Cameron
Employment: Clovis Oncology

Other Relationship: Clovis Oncology

Patents, Royalties, Other Intellectual Property: Patent application submitted January 2020 for dosing methodology (Inst)
Lara Maloney
Employment: Clovis Oncology
Stock and Other Ownership Interests: Clovis Oncology

Ann-Christin Mork
Employment: Clovis Oncology, UCB Pharma
Stock and Other Ownership Interests: UCB Pharma, Clovis Oncology

Josh Bedel
Employment: Clovis Oncology
Stock and Other Ownership Interests: Clovis Oncology
Travel, Accommodations, Expenses: Clovis Oncology

Jonathan A. Ledermann
Honoraria: AstraZeneca/MedImmune
Consulting or Advisory Role: AstraZeneca/MedImmune, Clovis Oncology, Pfizer, Cristal Therapeutics, Artios, Seattle Genetics, Tesaro, Merck, Eisai
Speakers’ Bureau: Clovis Oncology, Pfizer, Tesaro/GlaxoSmithKline
Research Funding: AstraZeneca (Inst), MSD Oncology (Inst)
Travel, Accommodations, Expenses: Clovis Oncology
Other Relationship: Regeneron

Robert L. Coleman
Consulting or Advisory Role: Clovis Oncology, Genentech/Roche, Esperance Pharmaceuticals, AstraZeneca/MedImmune, Genmab, Tesaro, OncoMed, Soto, Oncolytics, AbbVie/Stemcentrx, Immunogen, AbbVie, Agensys, OncoSec, Novocure
Research Funding: AstraZeneca/MedImmune, Esperance Pharmaceuticals, OncoMed, Array BioPharma, Clovis Oncology, Johnson & Johnson, Merck, Roche/Genentech, Abbott/AbbVie
Travel, Accommodations, Expenses: Merck, AstraZeneca/MedImmune, Array BioPharma, Clovis Oncology, Roche/Genentech, Research to Practice, GOG, Clovis Oncology, Soto, Vaniam Group

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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, 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 \( m_{\text{TOX}} \times \text{TOX} + \text{TWiST} \). \( m_{\text{TOX}} \) 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 \( m_{\text{TOX}} \). 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 \( m_{\text{TOX}} \) utility weight for the TOX state, and the \( m_{\text{TWiST}} \) 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.
Q-TWiST analysis includes 4 steps:

**Definition of health states**
- TOX: No. of days with adverse events after random assignment and before disease progression or censoring for progression
- REL: No. of days from disease progression to death or censoring = OS – PFS
- TWiST: No. of days without REL or TOX = PFS – TOX

**Health states duration**
- Mean duration in each health state is estimated in each treatment group by calculating the area under the curve, using Kaplan-Meier estimates

**Q-TWiST**
- Q-TWiST = µTOX \times TOX + µTWiST \times TWiST + µREL \times REL
- µTWiST = 1, TWiST being the best possible health state for patients
- Threshold utility analysis: treatment comparisons of Q-TWiST for different combinations of µTOX and µREL from 0 (akin to death) to 1 (perfect health), with increments of 0.25 (25 combinations in total)

**Incorporation of observed utility values**
- Calculation of per-person utility weight for each health state (mean utility weight derived from utility assessments during a health state)
- Calculation of overall mean utility for each health state
- Normalization of observed utility in TOX and REL states relative to a utility = 1 for TWiST

**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 $\geq 2$ 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/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                          | QA-PFS (through last follow-up date) | QA-PFS – Sensitivity Analysis (through 24 months of follow-up) |
|-----------------------------------|--------------------------------------|---------------------------------------------------------------|
| **ITT**                           |                                       |                                                               |
| 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**                   |                                       |                                                               |
| 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**                           |                                       |                                                               |
| 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 9.93)                  | 5.92 (4.36 to 7.27)                                          |
| **BRCA wild type/LOH high**       |                                       |                                                               |
| 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**        |                                       |                                                               |
| 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** |                                       |                                                               |
| 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.

* Rucaparib (n = 375); placebo (n = 189).
* Rucaparib (n = 130); placebo (n = 66).
* Rucaparib (n = 236); placebo (n = 118).
* Rucaparib (n = 106); placebo (n = 52).
* Rucaparib (n = 107); placebo (n = 54).
* Rucaparib (n = 32); placebo (n = 17).