Abstract PCN295

Patient-Centered Outcomes in ARIEL3, a Phase 3, Randomized, Placebo-Controlled Study of Rucaparib Maintenance Treatment in Patients with Recurrent Ovarian Carcinoma

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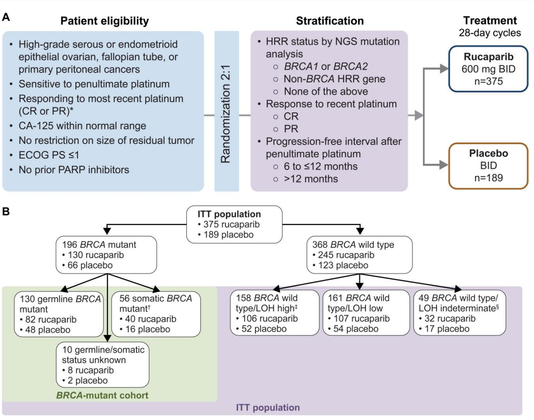
INTRODUCTION

- Rucaparib is a potent, oral, small molecule inhibitor of poly(ADP-ribose) polymerase (PARP) 1, PARP2, and PARP3[1]
- In the phase 3 study ARIEL3 (NCT01968213; **Figure 1A**), rucaparib maintenance treatment significantly improved investigator-assessed progression-free survival (PFS; primary endpoint) compared with placebo in patients with recurrent ovarian cancer following response to platinum-based chemotherapy, regardless of *BRCA* mutation or loss of heterozygosity (LOH) status[2]
  - Based on results from ARIEL3, rucaparib is approved in the United States and European Union for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a complete or partial response to platinum-based chemotherapy[1,3]
- The goal of maintenance therapy for recurrent ovarian cancer is to extend clinically meaningful survival by delaying disease progression without compromising a patient's quality of life[4,5]
- Here we present analyses of quality-adjusted PFS (QA-PFS) and quality-adjusted time without symptoms or toxicity (Q-TWiST) from ARIEL3 to further evaluate the clinical benefits of rucaparib maintenance treatment, incorporating a patient-centered perspective
  - QA-PFS represents the duration of PFS adjusted for patients' report of their own health status
  - In Q-TWiST, periods in which patients experience treatment toxicity or disease symptoms are weighted using a patient-derived utility value and subtracted from the survival endpoint

METHODS

Figure 1. ARIEL3 Study Design: (A) Schema and (B) Analysis Subgroups



*CR (defined by RECIST) or PR (defined by RECIST and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks of last dose of chemotherapy). †Deleterious *BRCA* mutation detected by NGS of tumor tissue but not by central germline blood test. ‡For LOH high, a cutoff of ≥16% genomic LOH was prespecified for ARIEL3. §Tumor sample was not evaluable for percentage of genomic LOH due to low tumor content or low aneuploidy.
BID, twice daily; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCIG, Gynecologic Cancer InterGroup; HRR, homologous recombination repair; ITT, intent to treat; LOH, loss of heterozygosity; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

- Patients were asked to complete the EQ-5D-3L, EuroQol's 5-dimension, 3-level questionnaire, at screening, on day 1 of each treatment cycle, at the treatment discontinuation visit, and at the 28-day follow-up visit

Patient-Centered Outcomes Analyses

- QA-PFS was calculated as PFS function × EQ-5D index score function
- Q-TWiST was calculated as (μTOX × TOX) + TWiST
  - μTOX represents the utility weight for the TOX state; observed utility data from EQ-5D was incorporated as a per-person utility weight
  - TOX represents the duration with treatment-emergent adverse events (TEAEs); 2 analyses were performed with TOX defined using:
    - All grade ≥3 TEAEs, or
    - Grade ≥2 TEAEs of nausea, vomiting, fatigue, and asthenia
  - TWiST represents the duration without toxicity or symptoms of progression; the utility weight for the TWiST state was set to 1, the highest possible health state patients can have
- Patient-centered outcomes were examined in the intent-to-treat (ITT) population (all randomized patients), in patients with a *BRCA* mutation, and 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; **Figure 1B**)

RESULTS

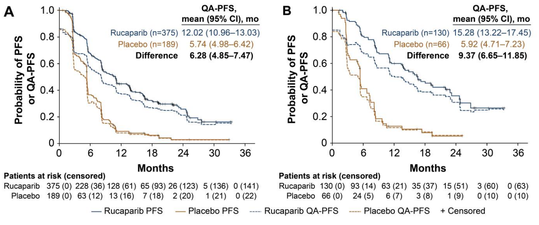
Patient Demographics

- The visit cutoff date for these analyses was April 15, 2017
- Baseline characteristics were balanced between the rucaparib and placebo groups
  - The majority of patients in the rucaparib and placebo groups had epithelial ovarian cancer (312 [83.2%] and 159 [84.1%], respectively), had an Eastern Cooperative Oncology Group Performance Status of 0 (280 [74.7%] and 136 [72.0%]), had a *BRCA* wild-type carcinoma (245 [65.3%] and 123 [65.1%]), and received 2 previous platinum-based chemotherapy regimens (236 [62.9%] and 126 [66.7%])
- Full details of the baseline characteristics have been reported previously[2]

QA-PFS Analyses

- QA-PFS was significantly longer in the rucaparib group than in the placebo group for the ITT population (**Figure 2A**) and for patients with a *BRCA* mutation (**Figure 2B**)
- In patients with a *BRCA* wild-type carcinoma, QA-PFS was longer in the rucaparib group than in the placebo group, regardless of LOH status (**Table 1**)

Figure 2. QA-PFS in the (A) ITT Population and (B) *BRCA*-Mutant Cohort



Patients at risk data are shown for the PFS analysis.
CI, confidence interval; ITT, intent to treat; PFS, progression-free survival; QA-PFS, quality-adjusted progression-free survival.

Table 1. QA-PFS by LOH Status in Patients with a *BRCA* Wild-Type Carcinoma

	QA-PFS, mean (95% CI), mo		
Cohort	**Rucaparib**	**Placebo**	**Difference**
BRCA wild type/LOH high[a]	12.59 (9.75–14.13)	5.95 (4.66–7.24)	6.65 (3.65–8.40)
BRCA wild type/LOH low[b]	8.13 (6.53–9.53)	5.42 (4.40–6.93)	2.71 (0.31–4.44)
BRCA wild type/LOH indeterminate[c]	11.23 (7.13–14.28)	3.70 (2.86–4.47)	7.53 (3.26–10.67)

[a]Rucaparib (n=106); placebo (n=52). [b]Rucaparib (n=107); placebo (n=54). [c]Rucaparib (n=32); placebo (n=17).
CI, confidence interval; LOH, loss of heterozygosity; QA-PFS, quality-adjusted progression-free survival.

Q-TWiST Analyses: All Grade ≥3 TEAEs

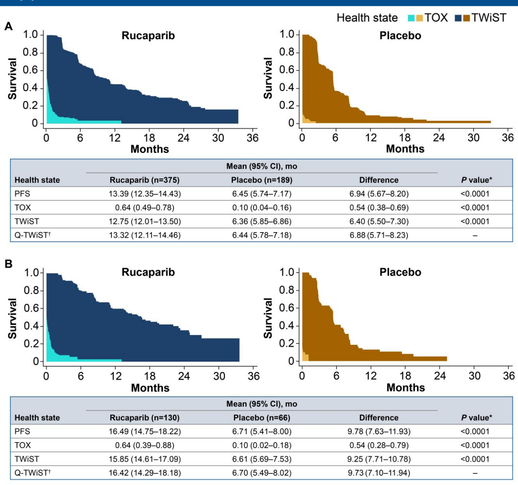
Table 2. Grade ≥3 TEAEs Occurring in ≥3% of Patients

	n (%)	
	Rucaparib (n=372)	**Placebo (n=189)**
Any grade ≥3 TEAE	209 (56.2)	28 (14.8)
Anemia/hemoglobin decreased[a]	70 (18.8)	1 (0.5)
ALT/AST increased[a]	39 (10.5)	0
Asthenia/fatigue[a]	25 (6.7)	5 (2.6)
Neutropenia/neutrophil count decreased[a]	25 (6.7)	2 (1.1)
Thrombocytopenia/platelet count decreased[a]	19 (5.1)	0
Vomiting	15 (4.0)	2 (1.1)
Nausea	14 (3.8)	1 (0.5)

TEAEs that occurred in <3% of patients are also included in the TWiST and Q-TWiST analyses, with TOX defined as all grade ≥3 TEAEs, as presented in Figure 3 and Table 4.
[a]To ensure full representation of similar TEAEs, certain terms were combined.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

- In the ITT population and the subgroup of patients with a *BRCA* mutation, mean PFS, mean TOX (all grade ≥3 TEAEs), and mean TWiST were all significantly longer with rucaparib than placebo; in the quality-adjusted analysis, mean Q-TWiST was also longer with rucaparib than placebo (**Figure 3**)
  - Results were similar in the subgroups of patients with a *BRCA* wild-type carcinoma (**Table 3**)

Figure 3. TWiST and Q-TWiST Analyses (All Grade ≥3 TEAEs) in the (A) ITT Population and (B) *BRCA*-Mutant Cohort



	Mean (95% CI), mo			
Health state	**Rucaparib (n=375)**	**Placebo (n=189)**	**Difference**	***P* value***
PFS	13.39 (12.35–14.43)	6.45 (5.74–7.17)	6.94 (5.67–8.20)	<0.0001
TOX	0.64 (0.49–0.78)	0.10 (0.04–0.16)	0.54 (0.38–0.69)	<0.0001
TWiST	12.75 (12.01–13.50)	6.36 (5.85–6.86)	6.40 (5.50–7.30)	<0.0001
Q-TWiST†	13.32 (12.11–14.46)	6.44 (5.78–7.18)	6.88 (5.71–8.23)	–

	Mean (95% CI), mo			
Health state	**Rucaparib (n=130)**	**Placebo (n=66)**	**Difference**	***P* value***
PFS	16.49 (14.75–18.22)	6.71 (5.41–8.00)	9.78 (7.63–11.93)	<0.0001
TOX	0.64 (0.39–0.88)	0.10 (0.02–0.18)	0.54 (0.28–0.79)	<0.0001
TWiST	15.85 (14.61–17.09)	6.61 (5.69–7.53)	9.25 (7.71–10.78)	<0.0001
Q-TWiST†	16.42 (14.29–18.18)	6.70 (5.49–8.02)	9.73 (7.10–11.94)	–

*P values were calculated based on comparing means using a 2-sample *t*-test.
†For each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the EQ-5D-3L assessments during a health state and normalized relative to a utility value of 1 for the TWiST state; μTOX values: 0.89 (ITT), 0.90 (*BRCA* mutant).
CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; TEAE, treatment-emergent adverse event; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

Table 3. Q-TWiST Analyses (All Grade ≥3 TEAEs) by LOH Status in Patients with a *BRCA* Wild-Type Carcinoma

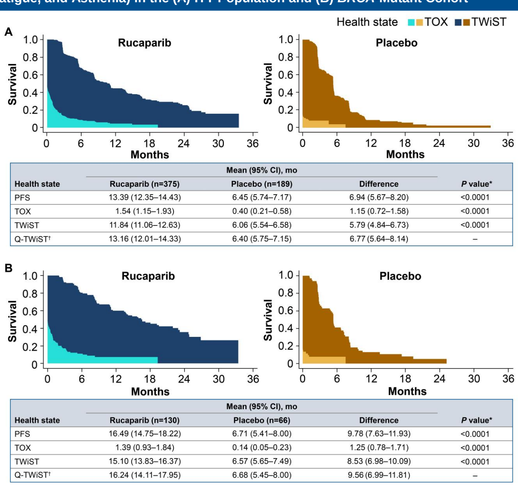
		Q-TWiST, mean (95% CI), mo		
Cohort	**μTOX[a]**	**Rucaparib 600 mg BID**	**Placebo**	**Difference**
BRCA wild type/LOH high[b]	0.91	12.86 (9.81–14.85)	6.79 (5.42–8.23)	6.07 (2.76–8.52)
BRCA wild type/LOH low[c]	0.85	9.38 (7.82–10.96)	6.03 (5.11–6.86)	3.35 (1.66–5.40)
BRCA wild type/ LOH indeterminate[d]	0.97	13.06 (6.93–16.60)	4.45 (3.28–5.64)	8.60 (1.89–12.12)

[a]For each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the EQ-5D-3L assessments during a health state and normalized relative to a utility value of 1 for the TWiST state. [b]Rucaparib (n=106); placebo (n=52). [c]Rucaparib (n=107); placebo (n=54). [d]Rucaparib (n=32); placebo (n=17).
BID, twice daily; CI, confidence interval; LOH, loss of heterozygosity; Q-TWiST, quality-adjusted time without symptoms or toxicity; TEAE, treatment-emergent adverse event; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

Q-TWiST Analyses: Grade ≥2 TEAEs of Nausea, Vomiting, Fatigue, and Asthenia

- For TEAEs of interest, the incidence of grade ≥2 events in the rucaparib group vs the placebo group was asthenia/fatigue (130/372 [34.9%] vs 25/189 [13.2%]), nausea (108/372 [29.0%] vs 12/189 [6.3%]), and vomiting (48/372 [12.9%] vs 9/189 [4.8%])
- In the analyses in which the TOX state was defined using the grade ≥2 TEAEs of nausea, vomiting, fatigue, and asthenia, Q-TWiST was longer with rucaparib in all subgroups (**Figure 4** and **Table 4**)

Figure 4. TWiST and Q-TWiST Analyses (Grade ≥2 TEAEs of Nausea, Vomiting, Fatigue, and Asthenia) in the (A) ITT Population and (B) *BRCA*-Mutant Cohort



	Mean (95% CI), mo			
Health state	**Rucaparib (n=375)**	**Placebo (n=189)**	**Difference**	***P* value***
PFS	13.39 (12.35–14.43)	6.45 (5.74–7.17)	6.94 (5.67–8.20)	<0.0001
TOX	1.54 (1.15–1.93)	0.40 (0.21–0.58)	1.15 (0.72–1.58)	<0.0001
TWiST	11.84 (11.06–12.63)	6.06 (5.54–6.58)	5.79 (4.84–6.73)	<0.0001
Q-TWiST†	13.16 (12.01–14.33)	6.40 (5.75–7.15)	6.77 (5.64–8.14)	–

	Mean (95% CI), mo			
Health state	**Rucaparib (n=130)**	**Placebo (n=66)**	**Difference**	***P* value***
PFS	16.49 (14.75–18.22)	6.71 (5.41–8.00)	9.78 (7.63–11.93)	<0.0001
TOX	1.39 (0.93–1.84)	0.14 (0.05–0.23)	1.25 (0.78–1.71)	<0.0001
TWiST	15.10 (13.83–16.37)	6.57 (5.65–7.49)	8.53 (6.98–10.09)	<0.0001
Q-TWiST†	16.24 (14.11–17.95)	6.68 (5.45–8.00)	9.56 (6.99–11.81)	–

*P values were calculated based on comparing means using a 2-sample *t*-test.
†For each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the EQ-5D-3L assessments during a health state and normalized relative to a utility value of 1 for the TWiST state; μTOX values: 0.85 (ITT) and 0.82 (*BRCA* mutant) obtained using observed EQ-5D data and normalized relative to a utility value of 1 for the TWiST state.
CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; TEAE, treatment-emergent adverse event; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

Table 4. Q-TWiST Analyses (Grade ≥2 TEAEs of Nausea, Vomiting, Fatigue, and Asthenia) by LOH Status in Patients with a *BRCA* Wild-Type Carcinoma

		Q-TWiST, mean (95% CI), mo		
Cohort	**μTOX[a]**	**Rucaparib 600 mg BID**	**Placebo**	**Difference**
BRCA wild type/LOH high[b]	0.88	12.74 (9.66–14.73)	6.74 (5.37–8.21)	6.00 (2.67–8.45)
BRCA wild type/LOH low[c]	0.86	9.28 (7.76–10.88)	6.05 (5.09–6.85)	3.23 (1.58–5.35)
BRCA wild type/ LOH indeterminate[d]	0.87	13.00 (6.88–16.53)	4.45 (3.28–5.64)	8.54 (1.80–12.03)

[a]For each subgroup, μTOX was calculated for each state based on the average per-person utility weight derived from the EQ-5D-3L assessments during a health state and normalized relative to a utility value of 1 for the TWiST state. [b]Rucaparib (n=106); placebo (n=52). [c]Rucaparib (n=107); placebo (n=54). [d]Rucaparib (n=32); placebo (n=17).
BID, twice daily; CI, confidence interval; LOH, loss of heterozygosity; Q-TWiST, quality-adjusted time without symptoms or toxicity; TEAE, treatment-emergent adverse event; TOX, time with toxicity of treatment; TWiST, time without symptoms or toxicity.

CONCLUSIONS

- The benefit of rucaparib over placebo was confirmed by the quality-adjusted analyses (QA-PFS and Q-TWiST) in the ITT population and the *BRCA*-mutant, *BRCA* wild-type/LOH high, *BRCA* wild-type/LOH low, and *BRCA* wild-type/LOH indeterminate groups
  - QA-PFS was approximately 2- to 3-fold longer in the rucaparib group than in the placebo group across analysis groups
  - Q-TWiST analysis also consistently favored rucaparib over placebo in the ITT population and other analyses groups; it was 2- to 3-fold longer in duration in both the grade ≥3 and selected grade ≥2 TEAE-based analyses
- Taken together, these findings suggest that the impact of TEAEs associated with rucaparib on patients does not outweigh its clinical efficacy benefits in the maintenance setting

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