Postprogression Efficacy Outcomes From the Phase 3 ARIEL3 Study of Rucaparib in Patients With Platinum-Sensitive Recurrent Ovarian Carcinoma Associated With Either BRCA1 or BRCA2 Mutations

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## Presenting Author Disclosures

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<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
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Introduction

• Previous studies showed that patients with advanced OC associated with a \textit{BRCA2} mutation had longer OS following platinum-based chemotherapy than those with a \textit{BRCA1} mutation and those without a \textit{BRCA1} or \textit{BRCA2} mutation\textsuperscript{1,2}
  
  o This may be due to the differences in the functional roles of these genes:
    
    ‒ \textit{BRCA2} is more directly involved in the process of homologous recombination repair\textsuperscript{3}
    
    ‒ \textit{BRCA1} acts upstream and plays a more diverse role in DNA damage response and repair\textsuperscript{3}

• In ARIEL3 (NCT01968213), rucaparib maintenance treatment for recurrent OC significantly improved PFS and postprogression efficacy outcomes versus placebo regardless of biomarker status\textsuperscript{4,5}
  
  o PFS was also improved in the subgroups of patients with a \textit{BRCA1} (HR, 0.32 [95% CI, 0.19–0.53]) or \textit{BRCA2} mutation (0.12 [0.06–0.26])\textsuperscript{4}
  
  o TFST, CFI, PFS2, and TSST were all significantly longer with rucaparib than placebo in the overall BRCA cohort\textsuperscript{5}

• This exploratory analysis of ARIEL3 further examined the \textit{BRCA1}- and \textit{BRCA2}-mutant subgroups to assess the durability of the clinical benefit of rucaparib maintenance treatment following disease progression

ARIEL3 Study Design

**Patient eligibility**
- High-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancers
- Sensitive to penultimate platinum
- Responding to most recent platinum (CR or PR)*
- CA-125 within normal range
- No restriction on size of residual tumor
- ECOG PS ≤1
- No prior PARP inhibitors

**Stratification**
- HRR status by NGS mutation analysis
  - BRCA1 or BRCA2
  - Non-BRCA HRR gene
  - None of the above
- Response to recent platinum
  - CR
  - PR
- Progression-free interval after penultimate platinum
  - 6 to ≤12 months
  - >12 months

**Treatment phase**
Disease progression assessment every 12 weeks
- **Rucaparib**
  - 600 mg BID
  - n=375
- **Placebo**
  - BID
  - n=189

**Long-term follow-up phase**
Assessments every 12 weeks
- Overall survival
- Subsequent anticancer treatment, including best response and PD on each regimen
- Secondary malignancies

*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).

BID, twice daily; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCIG, Gynecological Cancer InterGroup; HRR, homologous recombination repair; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.
Baseline Characteristics and Prior Therapies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRCA1 Rucaparib (n=80)</th>
<th>Placebo (n=37)</th>
<th>BRCA2 Rucaparib (n=50)</th>
<th>Placebo (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>54 (43–74)</td>
<td>54 (36–84)</td>
<td>61 (42–81)</td>
<td>62 (48–77)</td>
</tr>
<tr>
<td>ECOG PS 0, n (%)</td>
<td>66 (82.5)</td>
<td>23 (62.2)</td>
<td>35 (70.0)</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
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<tr>
<td>Epithelial ovarian cancer</td>
<td>65 (81.3)</td>
<td>31 (83.8)</td>
<td>40 (80.0)</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>Fallopian tube cancer</td>
<td>6 (7.5)</td>
<td>4 (10.8)</td>
<td>5 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
<td>9 (11.3)</td>
<td>2 (5.4)</td>
<td>5 (10.0)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Serous</td>
<td>77 (96.3)</td>
<td>34 (91.9)</td>
<td>49 (98.0)</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2 (2.5)</td>
<td>2 (5.4)</td>
<td>1 (2.0)</td>
<td>2 (6.9)</td>
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<tr>
<td>Mixed or other</td>
<td>1 (1.3)</td>
<td>1 (2.7)</td>
<td>0</td>
<td>1 (3.4)</td>
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<tr>
<td>Bulky disease, n (%)</td>
<td>11 (13.8)</td>
<td>6 (16.2)</td>
<td>10 (20.0)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>No. of prior chemotherapy regimens, median (range)</td>
<td>2 (2–6)</td>
<td>2 (2–5)</td>
<td>2 (2–5)</td>
<td>2 (2–5)</td>
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<tr>
<td>Time to progression with penultimate platinum, median (range), mo</td>
<td>13.1 (6.0–105.9)</td>
<td>16.2 (6.4–107.6)</td>
<td>13.8 (6.1–71.5)</td>
<td>12.6 (6.9–58.0)</td>
</tr>
<tr>
<td>Response to last platinum, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>CR per RECIST</td>
<td>32 (40.0)</td>
<td>14 (37.8)</td>
<td>11 (22.0)</td>
<td>8 (27.6)</td>
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<tr>
<td>PR per RECIST or serological response per GCIG CA-125 criteria</td>
<td>48 (60.0)</td>
<td>23 (62.2)</td>
<td>39 (78.0)</td>
<td>21 (72.4)</td>
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</tbody>
</table>

*Bulky residual disease was defined as any tumour >2 cm per blinded independent central review.

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCIG, Gynecologic Cancer InterGroup; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.
Postprogression Efficacy Endpoints

Chemotherapy → Rucaparib maintenance treatment or placebo → First subsequent therapy → Second subsequent therapy

- **PFS**, time from randomisation to disease progression or death
- **TFST**, time from randomisation to start of first subsequent therapy
- **CFI**, time from the last dose of prior chemotherapy to initiation of first subsequent anticancer therapy
- **PFS2**, time from randomisation to disease progression on subsequent line of therapy or death
- **TSST**, time from randomisation to start of second subsequent therapy

All endpoints are inclusive of the time on rucaparib maintenance treatment or placebo.

*PFS2 and TSST can serve as surrogates for overall survival.

PD, progressive disease; R, randomisation.
Time to First Subsequent Therapy

**TFST**, time from randomisation to start of first subsequent therapy

**Chemotherapy** → R → **Rucaparib maintenance treatment or placebo** → PD → **First subsequent therapy** → PD → **Second subsequent therapy**

**BRCA1 mutant**
- Median, mo: 16.8 (Rucaparib) vs 8.1 (Placebo)
- 95% CI: 11.5–20.3 (Rucaparib) vs 5.1–9.9 (Placebo)
- HR, 0.41
- 95% CI, 0.27–0.64

**BRCA2 mutant**
- Median, mo: 30.4 (Rucaparib) vs 7.1 (Placebo)
- 95% CI: 17.5–41.4 (Rucaparib) vs 5.4–9.1 (Placebo)
- HR, 0.17
- 95% CI, 0.09–0.33

*Visit cutoff 31 December 2019.*

*P value was significant for treatment by BRCA mutation (BRCA1 vs BRCA2) interaction test (P=0.0167).*

HR, hazard ratio; PD, progressive disease; R, randomisation.
Chemotherapy-Free Interval

CFI, time from the last dose of prior chemotherapy to initiation of first subsequent anticancer therapy

**BRCA1 mutant**

<table>
<thead>
<tr>
<th></th>
<th>Median, mo</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Rucaparib (n=80)</td>
<td>18.4</td>
<td>13.4–22.6</td>
</tr>
<tr>
<td>Placebo (n=37)</td>
<td>9.4</td>
<td>6.6–11.5</td>
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<tr>
<td>HR, 0.40</td>
<td></td>
<td>95% CI, 0.26–0.62</td>
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**BRCA2 mutant**

<table>
<thead>
<tr>
<th></th>
<th>Median, mo</th>
<th>95% CI</th>
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<tr>
<td>Rucaparib (n=50)</td>
<td>36.1</td>
<td>19.1–NR</td>
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<tr>
<td>Placebo (n=29)</td>
<td>8.7</td>
<td>6.8–11.0</td>
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<tr>
<td>HR, 0.16</td>
<td></td>
<td>95% CI, 0.08–0.32</td>
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</table>

**At risk (events)**

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<thead>
<tr>
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<tr>
<td><strong>BRCA1 mutant</strong></td>
<td>80 (0)</td>
<td>37 (0)</td>
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<tr>
<td><strong>BRCA2 mutant</strong></td>
<td>50 (0)</td>
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**Visit cutoff 31 December 2019.**

*P* value was significant for treatment by BRCA mutation (**BRCA1** vs **BRCA2**) interaction test (*P*=0.0230).

HR, hazard ratio; NR, not reached; PD, progressive disease; R, randomisation.
Progression-Free Survival 2

**Chemotherapy** → **Rucaparib maintenance treatment or placebo** → **First subsequent therapy** → **Second subsequent therapy**

**PFS2**, time from randomisation to disease progression on subsequent line of therapy or death.

**BRCA1 mutant**
- Median, mo: Rucaparib (n=80) 25.1, 95% CI 19.4–29.5; Placebo (n=37) 21.8, 95% CI 14.6–24.4
- HR, 0.84; 95% CI, 0.53–1.32

**BRCA2 mutant**
- Median, mo: Rucaparib (n=50) 34.1, 95% CI 22.9–NR; Placebo (n=29) 18.4, 95% CI 13.4–35.3
- HR, 0.51; 95% CI, 0.29–0.91

*Visit cutoff 31 December 2019.*

*P value was nonsignificant for treatment by BRCA mutation (BRCA1 vs BRCA2) interaction test (P=0.1497).*

**HR**, hazard ratio; **NR**, not reached; **PD**, progressive disease; **R**, randomisation.
Time to Second Subsequent Therapy

**BRCA1 mutant**
- Median, mo: Rucaparib (n=80) 25.9, Placebo (n=37) 18.5
- 95% CI: 18.9–31.8, 15.8–24.8
- HR: 0.65, 95% CI, 0.41–1.04

**BRCA2 mutant**
- Median, mo: Rucaparib (n=50) 34.2, Placebo (n=29) 19.4
- 95% CI: 24.4–54.3, 13.6–38.9
- HR: 0.55, 95% CI, 0.31–0.96

Visit cutoff 31 December 2019.

*P* value was nonsignificant for treatment by BRCA mutation (BRCA1 vs BRCA2) interaction test (*P*=0.4639).

HR, hazard ratio; PD, progressive disease; R, randomisation.
Updated Safety in ARIEL3: TEAEs Occurring in ≥25% of Patients with a BRCA mutation

Of the patients treated with rucaparib, MDS was reported by 1 patient in the BRCA1 subgroup and 2 patients in the BRCA2 subgroup; no patients in the placebo arm reported MDS or AML.

AML, acute myeloid leukaemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.
Conclusions

• Rucaparib maintenance treatment led to a clinically meaningful delay in starting subsequent therapy and provided lasting clinical benefits versus placebo in patients with BRCA1- or BRCA2-mutant ovarian cancer
  o All postprogression efficacy endpoints were longer with rucaparib maintenance treatment than with placebo in both subgroups
  o While both subgroups benefited, results suggest greater efficacy in patients with a BRCA2 mutation versus those with a BRCA1 mutation

• Safety data for the two subgroups were similar and consistent with previous reports for the overall safety population¹

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