The Effect of Age on Efficacy and Safety Outcomes with Rucaparib: A Post Hoc Exploratory Analysis of ARIEL3, a Phase 3, Randomized, Placebo-Controlled Maintenance Study in Patients with Recurrent Ovarian Carcinoma

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Introduction

• In ARIEL3 (NCT01968213), rucaparib maintenance treatment significantly improved PFS vs placebo in patients with recurrent ovarian cancer following response to platinum-based chemotherapy\(^1\)

• Based on these data, 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 are in a complete or partial response to platinum-based chemotherapy\(^2,3\)

• This exploratory subgroup analysis of ARIEL3 compares the outcomes for 3 subgroups based on patient age at baseline (<65, 65–74, or ≥75 years)

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 (complete or partial response)*
- CA-125 within normal range
- No restriction on size of residual tumor
- ECOG performance status ≤1
- No prior PARP inhibitors

Stratification

- HRR status by next-generation sequencing mutation analysis
  - BRCA1 or BRCA2
  - Non-BRCA HRR gene
  - None of the above
- Response to recent platinum
  - Complete response
  - Partial response
- Progression-free interval after penultimate platinum
  - 6 to ≤12 months
  - >12 months

Randomization 2:1

Rucaparib 600 mg twice daily
n=375

Placebo twice daily
n=189

*Complete response (defined by RECIST) or partial response (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).
CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer InterGroup; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.
## Patient Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age &lt;65 years</th>
<th>Age 65–74 years</th>
<th>Age ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rucaparib (n=237)</strong></td>
<td>Rucaparib (n=113)</td>
<td>Rucaparib (n=25)</td>
<td>Placebo (n=117)</td>
</tr>
<tr>
<td><strong>Placebo (n=117)</strong></td>
<td>Placebo (n=64)</td>
<td>Placebo (n=8)</td>
<td></td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>56.0 (39.0–64.0)</td>
<td>68.0 (65.0–74.0)</td>
<td>76.0 (75.0–84.0)</td>
</tr>
<tr>
<td>Diagnosis, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>86.5 (205)</td>
<td>77.0 (87)</td>
<td>80.0 (20)</td>
</tr>
<tr>
<td>Fallopian tube cancer</td>
<td>5.5 (13)</td>
<td>13.3 (15)</td>
<td>16.0 (4)</td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
<td>8.0 (19)</td>
<td>9.7 (11)</td>
<td>4.0 (1)</td>
</tr>
<tr>
<td>BRCA status, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA mutant</td>
<td>40.5 (96)</td>
<td>25.7 (29)</td>
<td>20.0 (5)</td>
</tr>
<tr>
<td>BRCA wild type</td>
<td>59.5 (141)</td>
<td>74.3 (84)</td>
<td>80.0 (20)</td>
</tr>
<tr>
<td>ECOG performance status 0, % (n)</td>
<td>79.7 (189)</td>
<td>68.1 (77)</td>
<td>56.0 (14)</td>
</tr>
<tr>
<td>Number of prior chemotherapy regimens, median (range)</td>
<td>2.0 (2.0–6.0)</td>
<td>2.0 (2.0–6.0)</td>
<td>2.0 (2.0–5.0)</td>
</tr>
<tr>
<td>Response to last platinum (investigator assessed), % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response per RECIST</td>
<td>39.2 (93)</td>
<td>23.0 (26)</td>
<td>28.0 (7)</td>
</tr>
<tr>
<td>Partial response per RECIST or serologic response per GCIG CA-125 criteria</td>
<td>60.8 (144)</td>
<td>77.0 (87)</td>
<td>72.0 (18)</td>
</tr>
</tbody>
</table>

Visit cutoff date: April 15, 2017.

*One (1.6%) additional patient had a diagnosis of high-grade serous adenocarcinoma that was fallopian and/or ovarian in origin.

CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer InterGroup; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.
Investigator-Assessed PFS – ITT Analysis

### Age <65 years

- **Rucaparib**: Median (months) 11.1, 95% CI 8.5–13.7
- **Placebo**: Median (months) 5.4, 95% CI 5.3–5.6

- **HR**: 0.33; 95% CI, 0.25–0.43

**At risk (events)**
- **Rucaparib**: 237 (0) 147 (65) 87 (111) 48 (130) 19 (138) 4 (143) 0 (143)
- **Placebo**: 117 (0) 41 (69) 10 (99) 4 (103) 2 (104) 1 (104) 0 (104)

### Age 65–74 years

- **Rucaparib**: Median (months) 8.3, 95% CI 8.0–11.1
- **Placebo**: Median (months) 5.3, 95% CI 2.8–5.6

- **HR**: 0.43; 95% CI, 0.29–0.64

**At risk (events)**
- **Rucaparib**: 113 (0) 65 (38) 33 (62) 13 (73) 7 (73) 1 (76) 0 (76)
- **Placebo**: 64 (0) 20 (39) 3 (53) 3 (53) 0 (55)

### Age ≥75 years

- **Rucaparib**: Median (months) 9.2, 95% CI 5.5–NR
- **Placebo**: Median (months) 5.5, 95% CI 3.0–8.3

- **HR**: 0.47; 95% CI, 0.16–1.35

**At risk (events)**
- **Rucaparib**: 25 (0) 16 (8) 8 (13) 4 (14) 0 (15)
- **Placebo**: 8 (0) 2 (6) 0 (8)

Visit cutoff date: April 15, 2017. HRs were estimated using the Cox proportional hazards model.

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.
BICR-Assessed PFS – ITT Analysis

**Age <65 years**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>13.7</td>
<td>10.9–22.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.4</td>
<td>4.7–5.7</td>
</tr>
</tbody>
</table>

HR, 0.36; 95% CI, 0.26–0.50

**Age 65–74 years**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>13.7</td>
<td>8.3–NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.3</td>
<td>2.9–5.5</td>
</tr>
</tbody>
</table>

HR, 0.38; 95% CI, 0.24–0.60

**Age ≥75 years**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>10.4</td>
<td>5.5–NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.4</td>
<td>2.6–5.7</td>
</tr>
</tbody>
</table>

HR, 0.19; 95% CI, 0.05–0.74

Visit cutoff date: April 15, 2017. HRs were estimated using the Cox proportional hazards model.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.
## Summary of Safety

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;65 years</th>
<th>Age 65–74 years</th>
<th>Age ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rucaparib (n=235)*</td>
<td>Placebo (n=117)</td>
<td>Rucaparib (n=113)</td>
</tr>
<tr>
<td>Treatment duration, median (range), mo</td>
<td>8.7 (0.1–43.4)</td>
<td>5.5 (1.2–43.9)</td>
<td>6.4 (0.2–38.1)</td>
</tr>
<tr>
<td>Any grade TEAE, % (n)</td>
<td>100.0 (235)</td>
<td>95.7 (112)</td>
<td>100.0 (113)</td>
</tr>
<tr>
<td>Grade ≥3 TEAE</td>
<td>54.0 (127)</td>
<td>16.2 (19)</td>
<td>69.9 (79)</td>
</tr>
<tr>
<td>Treatment interruption and/or dose reduction due to TEAE, % (n)</td>
<td>65.5 (154)</td>
<td>9.4 (11)</td>
<td>82.3 (93)</td>
</tr>
<tr>
<td>Treatment interruption due to TEAE</td>
<td>60.0 (141)</td>
<td>8.5 (10)</td>
<td>73.5 (83)</td>
</tr>
<tr>
<td>Dose reduction due to TEAE</td>
<td>46.8 (110)</td>
<td>2.6 (3)</td>
<td>70.8 (80)</td>
</tr>
<tr>
<td>Discontinued due to TEAE,† % (n)</td>
<td>11.9 (28)</td>
<td>1.7 (2)</td>
<td>21.2 (24)</td>
</tr>
<tr>
<td>Deaths due to TEAE, % (n)</td>
<td>2.1 (5)</td>
<td>0 (0)</td>
<td>0.9 (1)</td>
</tr>
<tr>
<td>Deaths due to disease progression</td>
<td>0.9 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Visit cutoff date: December 31, 2017. *Three patients randomized to the rucaparib arm did not receive a dose of rucaparib and are excluded from the safety population. †Excluding disease progression. TEAE, treatment-emergent adverse event.
Most Common (≥35%) Any Grade TEAEs by Age Group

Visit cutoff date: December 31, 2017. Age <65 years (rucaparib, n=235; placebo, n=117); age 65–74 years (rucaparib, n=113; placebo, n=64); age ≥75 years (rucaparib, n=24; placebo, n=8). Three patients randomized to the rucaparib arm did not receive a dose of rucaparib and are excluded from the safety population.

*Indicates combined terms.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; TEAE, treatment-emergent adverse event.
Grade ≥3 Events in the Most Common TEAEs by Age Group

Visit cutoff date: December 31, 2017. Age <65 years (rucaparib, n=235; placebo, n=117); age 65–74 years (rucaparib, n=113; placebo, n=64); age ≥75 years (rucaparib, n=24; placebo, n=8). Three patients randomized to the rucaparib arm did not receive a dose of rucaparib and are excluded from the safety population.

*Indicates combined terms. 0 indicates that there were no grade ≥3 events reported for a given TEAE.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; TEAE, treatment-emergent adverse event.
Conclusions

• Maintenance treatment with rucaparib improved median PFS and reduced the risk of progression vs placebo regardless of age subgroup

• In general, the safety profile of rucaparib was consistent across the 3 age subgroups
  – In the rucaparib arm, rates of dose modifications and treatment discontinuations tended to be higher in patients aged ≥65 years than in patients aged <65 years
Acknowledgments

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