Postprogression Outcomes in Patients With Ovarian Carcinoma Associated With a Mutation in a Non-BRCA Homologous Recombination Repair Gene Receiving Rucaparib Maintenance Treatment: Results From the Phase 3 Study ARIEL3

David M. O’Malley,1 Amit M. Oza,2 Domenica Lorusso,3 Carol Aghajanian,4 Ana Oaknin,5 Andrew Dean,6 Nicoletta Colombo,7 Johanne I. Weberpals,8 Andrew R. Clamp,9 Giovanni Scambia,3 Alexandra Leary,10 Robert W. Holloway,11 Margarita Amenedo Gancedo,12 Peter C. Fong,13 Jeffrey C. Goh,14 Deborah K. Armstrong,15 Susana Banerjee,16 Jesus García-Donas,17 Elizabeth M. Swisher,18 Terri Cameron,19 Lara Maloney,20 Sandra Goble,20 Kevin K. Lin,20 Jonathan A. Ledermann,21 Robert L. Coleman22

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Presenting Author Disclosures

• Advisory boards: Clovis Oncology, AstraZeneca, Gynecologic Oncology Group, Janssen, Myriad, and Tesaro
• Steering committees: Clovis Oncology, Amgen, and ImmunoGen
• Consultancy: AbbVie, Ambry, AstraZeneca, Health Analytics, and Tesaro
Introduction

• Maintenance therapy for patients with recurrent ovarian cancer is intended to extend PFS without compromising postprogression survival

• In the phase 3 ARIEL3 study (CO-338-014; NCT01968213), rucaparib maintenance treatment significantly improved PFS vs placebo in all predefined patient cohorts
  
  ○ Greatest effects were seen in carcinomas deficient in HRR (eg, a mutation in BRCA or other HRR pathway gene, or high genomic LOH)

• Here, we analyzed postprogression outcomes to evaluate the durability of the clinical benefit of rucaparib maintenance treatment following disease progression in the subgroup of patients with tumors associated with a mutation in a prespecified, non-BRCA HRR gene

HRR, homologous recombination repair; LOH, loss of heterozygosity; PFS, progression-free survival.
### 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

<table>
<thead>
<tr>
<th>Rucaparib 600 mg BID</th>
<th>n=375</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo BID</td>
<td>n=189</td>
</tr>
</tbody>
</table>

#### Randomization 2:1
- Treatment phase
- Disease progression assessment every 12 weeks

#### Long-term follow-up phase
- Overall survival
- Subsequent anticancer treatment, including best response and PD on each regimen
- Secondary malignancies

#### 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.

ARIEL3 Study Design

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- HRR status by NGS mutation analysis
  - BRCA1 or BRCA2
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Rucaparib
600 mg BID
n=375

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

**Prespecified Non-BRCA HRR Genes**

<table>
<thead>
<tr>
<th>ATM</th>
<th>ATR</th>
<th>ATRX</th>
<th>BARD1</th>
<th>BLM</th>
<th>BRIP1</th>
<th>CHEK1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>FANCA</td>
<td>FANCC</td>
<td>FANCD2</td>
<td>FANCE</td>
<td>FANCF</td>
<td>FANCG</td>
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<tr>
<td>FANCI</td>
<td>FANCL</td>
<td>FANCM</td>
<td>MRE11A</td>
<td>NBN</td>
<td>PALB2</td>
<td>RAD50</td>
</tr>
<tr>
<td>RAD51</td>
<td>RAD51B</td>
<td>RAD51C</td>
<td>RAD51D</td>
<td>RAD52</td>
<td>RAD54L</td>
<td>RPA1</td>
</tr>
</tbody>
</table>

- Mutations in BARD1, BRIP1, PALB2, RAD51C, and RAD51D are significantly associated with hereditary ovarian cancer

*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.
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**Patient eligibility**
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- Responding to penultimate platinum (CR or PR)
- CA-125 within normal range
- No restriction on size of residual tumor
- ECOG PS ≤1
- No prior PARP inhibitor

**Stratification**
- HRR status by NGS mutation analysis
  - BRCA1 or BRCA2
  - Non-BRCA HRR gene
  - None of the above

**Treatment phase**
- Disease progression assessment every 12 weeks

**Long-term follow-up phase**
- Assessments every 12 weeks

**Prespecified Non-BRCA HRR Genes**

<table>
<thead>
<tr>
<th>ATM</th>
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<td>NBN</td>
<td>PALB2</td>
<td>RAD50</td>
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<tr>
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<td>RAD51C</td>
<td>RAD51D</td>
<td>RAD52</td>
<td>RAD54L</td>
<td>RPA1</td>
</tr>
</tbody>
</table>

- Mutations in **BARD1**, **BRIP1**, **PALB2**, **RAD51C**, and **RAD51D** are significantly associated with hereditary ovarian cancer
- Mutations in **PALB2**, **RAD51C**, and **RAD51D** are causally associated with clinical sensitivity to PARP inhibitors

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*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.

Genomic Characteristics of Carcinomas Associated With a Non-\textit{BRCA} HRR Gene Mutation in ARIEL3

### Rucaparib-treated patients (n=28)

<table>
<thead>
<tr>
<th>Pt</th>
<th>HRR gene</th>
<th>Mutation type</th>
<th>Mutation zyosity in tumor\textsuperscript{a}</th>
<th>Genomic LOH status</th>
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<tbody>
<tr>
<td>1</td>
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<td>Deletion</td>
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<td>FANCD2</td>
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<td>LOH low</td>
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<td>10</td>
<td>FANC1</td>
<td>Frameshift</td>
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<tr>
<td>22</td>
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<td>Homozygous</td>
<td>LOH high</td>
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<tr>
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<tr>
<td>27</td>
<td>RAD54L</td>
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<tr>
<td>28</td>
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<td>Frameshift</td>
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</tbody>
</table>

\textsuperscript{a}Based on Foundation Medicine sequencing results, in which a tumor is classified as homozygous if both copies in the tumor carry the mutant allele and heterozygous if both the wild-type and mutant alleles are present. HRR, homologous recombination repair; LOH, loss of heterozygosity; NA, not available; Pt, patient.

### Placebo-treated patients (n=15)

<table>
<thead>
<tr>
<th>Pt</th>
<th>HRR gene</th>
<th>Mutation type</th>
<th>Mutation zyosity in tumor\textsuperscript{a}</th>
<th>Genomic LOH status</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>BRIP1</td>
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<td>Homozygous</td>
<td>LOH low</td>
</tr>
<tr>
<td>30</td>
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<td>Homozygous</td>
<td>LOH high</td>
</tr>
<tr>
<td>31</td>
<td>BRIP1</td>
<td>Nonsense</td>
<td>Homozygous</td>
<td>LOH high</td>
</tr>
<tr>
<td>32</td>
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<td>Homozygous</td>
<td>LOH low</td>
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<td>LOH low</td>
</tr>
<tr>
<td>34</td>
<td>FANCA</td>
<td>Splice site</td>
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<td>Unknown</td>
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<tr>
<td>35</td>
<td>FANCC</td>
<td>Frameshift</td>
<td>Heterozygous</td>
<td>LOH low</td>
</tr>
<tr>
<td>36</td>
<td>FANCD2</td>
<td>Frameshift</td>
<td>Heterozygous</td>
<td>LOH low</td>
</tr>
<tr>
<td>37</td>
<td>FANCE</td>
<td>Frameshift</td>
<td>Homozygous</td>
<td>LOH low</td>
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<tr>
<td>38</td>
<td>FANCF</td>
<td>Frameshift</td>
<td>NA</td>
<td>Unknown</td>
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<tr>
<td>39</td>
<td>RAD50</td>
<td>Splice site</td>
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<tr>
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<td>42</td>
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<td>43</td>
<td>RAD54L</td>
<td>Splice site</td>
<td>Heterozygous</td>
<td>LOH low</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Based on Foundation Medicine sequencing results, in which a tumor is classified as homozygous if both copies in the tumor carry the mutant allele and heterozygous if both the wild-type and mutant alleles are present. HRR, homologous recombination repair; LOH, loss of heterozygosity; NA, not available; Pt, patient.
Initial Results: PFS and Safety from ARIEL3 in Patients With Carcinomas Associated With a Non-\textit{BRCA} HRR Gene Mutation

- The safety profile of rucaparib in patients with a carcinoma associated with a non-\textit{BRCA} HRR gene mutation was consistent with the overall safety population.
  - In the non-\textit{BRCA} HRR gene mutation subgroup vs the overall population, incidence of grade $\geq 3$ AEs and AEs leading to dose reduction and/or treatment interruption of rucaparib were 55.6\% vs 59.7\% and 66.7\% vs 71.8\%, respectively.

Visit cutoff date for PFS April 15, 2017; visit cutoff date for safety December 31, 2017.
AE, adverse event; HR, hazard ratio; HRR, homologous recombination repair; PFS, progression-free survival.
Schema Comparing Different Efficacy Endpoints

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

- **PFS**, time from randomization to disease progression or death
- **TFST**, time from randomization 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 randomization to disease progression on subsequent line of therapy or death
- **TSST**, time from randomization to start of second subsequent therapy

PD, progressive disease; R, randomization.
Patients With Carcinomas Associated With a Non-BRCA HRR Gene Mutation: Time to First Subsequent Therapy

<table>
<thead>
<tr>
<th></th>
<th>Rucaparib (n=28)</th>
<th>Placebo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>16.9</td>
<td>6.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.1–19.3</td>
<td>4.5–9.0</td>
</tr>
<tr>
<td>HR</td>
<td>0.16</td>
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</tr>
<tr>
<td>95% CI</td>
<td>0.06–0.40</td>
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</tr>
</tbody>
</table>

Visit cutoff date December 31, 2017.
HR, hazard ratio; PD, progressive disease; R, randomization; TFST, time to first subsequent therapy.
Patients With Carcinomas Associated With a Non-\textit{BRCA} HRR Gene Mutation: Chemotherapy-Free Interval

<table>
<thead>
<tr>
<th></th>
<th>Median, mo</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=28)</td>
<td>18.2</td>
<td>9.9–21.1</td>
</tr>
<tr>
<td>Placebo (n=15)</td>
<td>7.7</td>
<td>6.7–10.9</td>
</tr>
</tbody>
</table>

HR, 0.21
95% CI, 0.09–0.52

Visit cutoff date December 31, 2017.
CFI, chemotherapy-free interval; HR, hazard ratio; PD, progressive disease; R, randomization.
Patients With Carcinomas Associated With a Non-BRCA HRR Gene Mutation: Time to Disease Progression on Subsequent Therapy or Death

At risk (events)

<table>
<thead>
<tr>
<th></th>
<th>Rucaparib</th>
<th>Placebo</th>
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<tbody>
<tr>
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<td>15 (0)</td>
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<tr>
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<td>1 (15)</td>
<td>0 (15)</td>
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</table>

Median, mo 95% CI

- Rucaparib (n=28) 21.1 (13.9–NR)
- Placebo (n=15) 17.3 (8.5–23.9)

HR, 0.30
95% CI, 0.12–0.72

Visit cutoff date December 31, 2017.
HR, hazard ratio; HRR, homologous recombination repair; NR, not reached; PD, progressive disease; PFS2, time to disease progression on subsequent line of therapy or death; R, randomization.
Patients With Carcinomas Associated With a Non-\textit{BRCA} HRR Gene Mutation: Time to Second Subsequent Therapy

At risk (events)

<table>
<thead>
<tr>
<th></th>
<th>Rucaparib (n=28)</th>
<th>Placebo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0)</td>
<td>28 (0)</td>
<td>15 (0)</td>
</tr>
<tr>
<td>6 (1)</td>
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<td>0 (14)</td>
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<tr>
<td>42 (14)</td>
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</tr>
</tbody>
</table>

Median, mo

- Rucaparib: 24.4, 16.6–NR
- Placebo: 17.9, 10.2–27.3

HR, 0.43
95% CI, 0.18–1.04

Visit cutoff date December 31, 2017.

HR, hazard ratio; HRR, homologous recombination repair; NR, not reached; PD, progressive disease; R, randomization; TSST, time to second subsequent therapy.
## Summary of Postprogression Outcomes in Patients With Carcinomas Associated With a BRCA or Non-BRCA HRR Gene Mutation

<table>
<thead>
<tr>
<th></th>
<th>Non-BRCA HRR mutation</th>
<th>BRCA mutation</th>
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<tbody>
<tr>
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<td></td>
<td>Placebo (n=15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rucaparib (n=130)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (n=66)</td>
<td></td>
</tr>
<tr>
<td><strong>TFST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>16.9</td>
<td>6.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.16 (0.06–0.40)</td>
<td>0.28 (0.20–0.41)</td>
</tr>
<tr>
<td><strong>CFI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>18.2</td>
<td>7.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.21 (0.09–0.52)</td>
<td>0.28 (0.19–0.41)</td>
</tr>
<tr>
<td><strong>PFS2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>21.1</td>
<td>17.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.30 (0.12–0.72)</td>
<td>0.56 (0.38–0.83)</td>
</tr>
<tr>
<td><strong>TSST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>24.4</td>
<td>17.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.43 (0.18–1.04)</td>
<td>0.53 (0.36–0.80)</td>
</tr>
</tbody>
</table>

Visit cutoff date December 31, 2017.
HRs estimated with a Cox proportional hazards model.
CFI, chemotherapy-free interval; HR, hazard ratio; HRR, homologous recombination repair; PFS2, time to disease progression on subsequent therapy or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.
Time on Study Treatment: Patients With Carcinomas Associated With a Non-\textit{BRCA} HRR Mutation

Visit cutoff date December 31, 2017.
HRR, homologous recombination repair.
Time on Study Treatment: Patients With Carcinomas Associated With a Non-**BRCA** HRR Mutation

**RAD51C/D** gene mutation
- **Rucaparib**: Median time 25.0 months (10 patients)
- **Placebo**: Median time 5.5 months (3 patients)

**Other non-**BRCA/**RAD51C/D** HRR gene mutation
- **Rucaparib**: Median time 8.6 months (18 patients)
- **Placebo**: Median time 5.5 months (12 patients)

Visit cutoff date December 31, 2017.
HRR, homologous recombination repair; LOH, loss of heterozygosity.
Time on Study Treatment: Patients With Carcinomas Associated With a RAD51C/D Mutation

Visit cutoff date December 31, 2017.
HRR, homologous recombination repair; PFS, progression-free survival.
Time on Study Treatment: Patients With Carcinomas Associated With a *RAD51C/D* Mutation

- Three patients with a *RAD51C/D* mutation had measurable disease at baseline, and all 3 achieved a confirmed response with rucaparib treatment (1 complete response and 2 partial responses)

Visit cutoff date December 31, 2017. PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumors version 1.1.
Time on Study Treatment: Patients With Carcinomas Associated With a RAD51C/D Mutation

• Three patients with a RAD51C/D mutation had measurable disease at baseline, and all 3 achieved a confirmed response with rucaparib treatment (1 complete response and 2 partial responses)

Visit cutoff date December 31, 2017.
PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumors version 1.1.
Conclusions

- Although the number of patients in this subgroup was small, rucaparib improved the clinically meaningful postprogression endpoints TFST, CFI, PFS2, and TSST vs placebo in patients with platinum-sensitive, recurrent ovarian cancer harboring a non-BRCA HRR gene mutation
  - Prior rucaparib treatment did not adversely impact the possibility for patients in this subgroup to benefit from subsequent therapy
- Mutations in a subset of HRR genes, such as RAD51C/D, may confer greater sensitivity to PARP inhibitor treatment
Acknowledgments

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… and all ARIEL3 study patients and their families and caregivers

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