BRCA1 and RAD51C Promoter Hypermethylation Confer Sensitivity to the PARP Inhibitor Rucaparib in Patients with Relapsed, Platinum Sensitive Ovarian Carcinoma in ARIEL2 Part 1

Elizabeth Swisher, MD, University of Washington
VERBAL DISCLOSURE

• No financial relationships to disclose
Disclosure

- Rucaparib approved by the Food and Drug Administration (FDA) for recurrent *BRCA*-mutated OC following 2 previous lines of chemotherapy
- Off-label uses from the ARIEL2 trial are discussed
ARIEL2 (Part 1) designed to assess rucaparib sensitivity in 3 prospectively defined subgroups

**Key eligibility**
(N=206 pts; 204 treated)
- HGOC (serous or endometrioid)
  - Known germline $BRCA$ enrollment capped at N=15
- $\geq 1$ prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

**Tumor tissue**
- $BRCA^{mut}$
- $BRCA^{wt}$/LOH$_{high}$ (BRCA like)
- $BRCA^{wt}$/LOH$_{low}$ (Biomarker negative)

**Analysis of HRD subgroups**
- Primary endpoint
  - PFS
- Secondary endpoints
  - ORR
    - RECIST
  - RECIST and/or CA-125
- Safety
- PK

**Monotherapy, measurable disease, and pre-treatment and archival biopsies**
BRCA1 methylation results in attenuated gene expression but no difference of overall survival in TCGA HGSOC

BRCA1 methylation is associated with down-regulation of BRCA1 gene expression. BRCA1 methylated cases exhibit similar overall survival to BRCA wild-type cases in TCGA HGSOC.

ARIEL2 Part 1: Improved PFS in BRCA-mutated and BRCA\textsuperscript{wt}/LOH\textsuperscript{high} vs BRCA\textsuperscript{wt}/LOH\textsuperscript{low} patients

Data cutoff date: January 18, 2016.
Adapted from Coleman RL et al. ASCO 2016. Abstract 5540.
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### OC with Damaging Mutations in Some HR Genes Responded to Rucaparib

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### Damaging Mutations in Other HR Genes Was not Associated with Response to Rucaparib

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<td>PD</td>
<td>0.7</td>
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**BRCA1** and **RAD51C** methylation and mutation are mutually exclusive

- **BRCA1** methylated tumors found in 12.7% (21/165) of patients
- **RAD51C** methylated tumors found in 2.4% (4/165) of patients

<table>
<thead>
<tr>
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<th>Mutated</th>
<th>WT</th>
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<tbody>
<tr>
<td>Meth</td>
<td>0</td>
<td>25</td>
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<tr>
<td>Unmeth</td>
<td>27</td>
<td>113</td>
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\( P = 0.015 \)

Data cutoff date: January 18, 2016.
Swisher et al. Unpublished data.
Correlation of \textit{BRCA1/RAD51C} methylation with LOH

80\% of \textit{BRCA1} and all \textit{RAD51C} methylated cases have high LOH

\begin{tabular}{|c|c|}
\hline
\textit{BRCA1} methylated & \textit{BRCA1} unmethylated \\
\hline
\textbf{LOH}^{\text{high}} & 16 & 58 \\
\textbf{LOH}^{\text{low}} & 4 & 59 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|}
\hline
\textit{RAD51C} methylated & \textit{RAD51C} unmethylated \\
\hline
\textbf{LOH}^{\text{high}} & 4 & 70 \\
\textbf{LOH}^{\text{low}} & 0 & 63 \\
\hline
\end{tabular}

\(P=0.015\) \(P=0.12\)

Data cutoff date: January 18, 2016.
Swisher et al. Unpublished data.
**BRCA1 and RAD51C methylation in archival and pretreatment biopsies from ARIEL2**

- **BRCA1 and RAD51C methylation** were assessed in 90 and 99 pairs of archival and pretreatment biopsies.
- Of 77 cases without **BRCA1** methylation in archival, only 1 (1.3%) methylated in pre-treatment biopsy.
- Of 13 cases with **BRCA1** methylation in archival, 4 (31%) were unmethylated in pre-treatment biopsy.
- **RAD51C** methylated cases were always concordant between archival and pre-treatment biopsy, but we only had paired samples on 2 **RAD51C** methylated cancers.
Rucaparib is active in BRCA1 and RAD51C methylated OC

- Confirmed investigator-assessed RECIST responses:
  - 52.4% (11/21) of BRCA1 methylated cases
  - 75.0% (3/4) of RAD51C methylated cases
  - 29% of BRCA-wild type/LOH high

- Duration of response:
  - Median of 6.1 months (95% CI, 4.8–8.9) for BRCA1 methylated cases
  - Median of 9.5 months (95% CI, 5.2–9.8) for RAD51C methylated cases

- Progression-free survival:
  - Median of 7.4 months (95% CI, 5.3–9.7) for BRCA1 methylated cases
  - Median of 11.1 months (95% CI, 3.2–14.1) for RAD51C methylated cases

Data cutoff date: January 18, 2016.
Swisher et al. Unpublished data.
Two *CDK12* mutant cases had long durable responses

- CDK12 involved in regulation of RNA splicing
- Loss leads to down-regulation of many DNA repair genes and could result in HRD
- One of “frequently” mutated genes in HGSOC (3%, TCGA)

<table>
<thead>
<tr>
<th>CDK12 Mutation</th>
<th>LOH Status</th>
<th>Best Overall Response</th>
<th>Target Lesion % Change</th>
<th>PFS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic <em>CDK12</em> (Y279fs*1)</td>
<td>High</td>
<td>Stable Disease</td>
<td>-25.4</td>
<td>3.5</td>
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<tr>
<td>Somatic <em>CDK12</em> (F89fs*3)</td>
<td>High</td>
<td>Partial Response</td>
<td>-41.9</td>
<td>16.7</td>
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<tr>
<td>Somatic <em>CDK12</em> (homozygous deletion)</td>
<td>High</td>
<td>Partial Response</td>
<td>-73.7</td>
<td>29.3</td>
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</table>
TCGA estimate of HRD in HGSOC

No HRD*, 50%

Germline BRCA1, 8%

Somatic BRCA1, 3%

Germline BRCA2, 6%

Somatic BRCA2, 2%

BRCA1 methylation, 11%

EMSY amplification, 6%

PTEN loss, 5%

Fanconi Anemia genes, 7%

*Includes mismatch repair gene defects and Cyclin E1 amplifications.
What molecular alterations confer HRD in HGSOC?

- Germline BRCA1, 11%
- Somatic BRCA1, 4%
- Germline BRCA2, 5%
- Somatic BRCA2, 2%
- BRCA1 methylation, 10%
- CDK12 mutation, 2%
- RAD51C methylation, 2%
- Mutation in non-BRCA core HR genes, 10%
- No HRD, 56%
**BRCA**<sub>wt</sub> patients with LOH-high tumors have significantly longer PFS than those with LOH-low tumors

- The genomic LOH cutoff prespecified for testing in ARIEL2 Part 1 was 14%
- Optimal separation of PFS curves was found at the refined cutoff of 16%
Conclusions

• *BRCA1* and *RAD51C* methylation in ovarian carcinomas is associated with high LOH and sensitivity to rucaparib

• Loss of *BRCA1* methylation is common after exposure to platinum chemotherapy, even in “platinum sensitive” patients

• If methylation was to be used as a predictor of PARP inhibitor sensitivity, it would need to be assessed in a pre-treatment (not archival) specimen

• *CDK12* mutations may confer PARP inhibitor sensitivity as well as mutations in other core HR genes

• Routine sequencing of high-grade OC would identify at least 10-15% of cases with somatic mutations and 20% with germline mutations likely to respond to PARP inhibition

• Refined LOH cutoff for HRD from ARIEL2 is being tested in ARIEL3
Acknowledgments

ARIEL2 patients, their families, and caregivers

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