ARIEL2: A phase 2 study to prospectively identify ovarian cancer patients likely to respond to rucaparib

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Today’s Presentation

• A genetic signature identifying a BRCA-like phenotype has been developed by Clovis Oncology
• Ovarian cancer is commonly associated with homologous recombination (HR) deficiency, both BRCA-mutated and BRCA-like
• The ARIEL2 study assesses the utility of tumor BRCA mutations and the BRCA-like signature in predicting response to rucaparib, a potent PARP inhibitor, in women with platinum-sensitive, relapsed ovarian cancer
• Interim data from the ARIEL2 trial will be presented

PARP=poly (ADP-ribose) polymerase.
PARPi, used in the genetic context of HRD, drive synthetic lethality

HR is a complex process requiring coordinated function of many gene products, such as BRCA1, BRCA2, PALB2, RAD51, etc.

HRD=HR deficiency; PARPi=PARP inhibitor.
PARPi, used in the genetic context of HRD, drive synthetic lethality.

Loss of any one of these genes may lead to deficiency of HR, and consequent sensitivity to PARPi therapy.
How do we identify patients who will benefit from PARPi therapy?

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>PALB2</th>
<th>RAD51</th>
<th>etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous gene deletion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nonsense and frameshift mutation (germline and somatic)</td>
<td></td>
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</tr>
<tr>
<td>Epigenetic gene silencing</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA-mediated gene silencing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other mechanisms</td>
<td></td>
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</tbody>
</table>

Tumor BRCA1/2 gene sequencing identifies these BRCA alterations

How to identify these mechanisms of HRD: “BRCA-like signature”?
Defining a BRCA-like signature through single gene analysis is complex – not all genes are functionally relevant.

**Rucaparib IC\textsubscript{50} Fold Change After siRNA Knockdown in OVCAR-3 Cell Line**

IC\textsubscript{50} = half maximal inhibitory concentration.
HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS.

Hypothesis 1:
Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

Hypothesis 2:
Ovarian cancer patients who are “biomarker negative” (ie, with low genomic LOH) will not respond to PARPi.

*mut=* mutation; *NGS=* next-generation sequencing; *wt=* wild type.
Diagnostic development: Cutoff defined for BRCA-like signature, being tested and refined

TCGA and AOCS Overall Survival Data Used to Develop LOH Cutoff to Identify High-Grade Ovarian Cancer Patient Tumors with BRCA-Like Signature

Prospective testing of prespecified cutoff in ARIEL2 and ARIEL3

ARIEL2 goal: Assess rucaparib sensitivity in prospectively defined molecular subgroups

Key Eligibility
- High-grade serous or endometrioid ovarian cancer
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Adequate tumor tissue (screening biopsy and archival)
- No prior PARPi

Primary Endpoint
- PFS (RECIST) in:
  - BRCA\textsuperscript{mut}
  - BRCA-like (excludes BRCA\textsuperscript{mut})
  - Biomarker negative

Secondary Endpoints
- ORR (RECIST & CA-125)
- Safety
- Pharmacokinetics

N = 180
Cap on known germline BRCA\textsuperscript{mut}

600 mg BID rucaparib continuously until progression by RECIST

CA-125=cancer antigen 125 test; ORR=overall response rate; PFS=progression-free survival; RECIST=Response Evaluation Criteria In Solid Tumors.
Demographics and baseline characteristics (N=121*)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (range or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years</strong></td>
<td>66 (39–86)</td>
</tr>
<tr>
<td><strong>ECOG PS grade</strong></td>
<td></td>
</tr>
<tr>
<td>0 / 1 / Pending</td>
<td>81 / 39 / 1</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>92</td>
</tr>
<tr>
<td>Primary peritoneal / fallopian tube cancer / pending</td>
<td>15 / 9 / 5</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Serous / endometrioid / pending</td>
<td>116 / 3 / 2</td>
</tr>
<tr>
<td><strong>No. of prior treatment regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Median no. of regimens (n=115)</td>
<td>1 (1–6)</td>
</tr>
<tr>
<td>1–2</td>
<td>93 (81)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Median no. of platinum-based regimens (n=112)</td>
<td>1 (1–5)</td>
</tr>
<tr>
<td>1–2</td>
<td>95 (85)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>17 (15)</td>
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*Data as of 27 October 2014. ECOG PS=Eastern Cooperative Oncology Group Performance Status.
Rucaparib is well tolerated – no discontinuations due to AEs

### Treatment-Related AEs in ≥15% of Patients (N=121)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Worst Grade (NCI-CTCAE v4) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Grade 1: 32%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 1: 37%</td>
</tr>
<tr>
<td>ALT / AST Increased</td>
<td>Grade 1: 26%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Grade 1: 24%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>Grade 1: 23%</td>
</tr>
<tr>
<td>Anemia / Low Hgb</td>
<td>Grade 1: 22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 1: 21%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 1: 20%</td>
</tr>
</tbody>
</table>

AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; Hgb=hemoglobin; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
The majority of BRCA\textsuperscript{wt} patient tumors exhibit BRCA-like signature

Tumor BRCA/BRCA-like Status as Determined by HRD Test (N=121)

- 17 germline BRCA\textsuperscript{mut}
- 12 somatic BRCA\textsuperscript{mut}
- 1 indeterminate
- High genomic LOH
Target lesion reduction seen in majority of patients classified by screening biopsy

**Best Target Lesion Response**

38% ORR (RECIST)

77% disease control rate (CR, PR, or SD >24 weeks)

61% of patients continuing on treatment (+)

Data reported for n=61 patients with screening biopsy results who are evaluable by RECIST v1.1.

+=ongoing; CR=complete response; PR=partial response; SD=stable disease.
Greatest rucaparib activity observed in BRCA\textsuperscript{mut} patients...

- Robust clinical activity observed in BRCA\textsuperscript{mut} patients (n=23)
  - 61% ORR (RECIST)
  - 70% ORR (RECIST & CA-125)
  - 83% of patients continuing on treatment (+)

- Responses observed in germline and somatic BRCA\textsuperscript{mut} tumors

Best Target Lesion Response

Germline
Somatic
Indeterminate

Change from Baseline (%)

+=ongoing.
...and differential rucaparib activity seen in patients with/without BRCA-like signature

- Clinical activity observed in BRCA<sup>wt</sup> patients <strong>with</strong> BRCA-like signature (n=25)
  - 32% ORR (RECIST)
  - 40% ORR (RECIST & CA-125)
  - 52% of patients continuing on treatment (+)
- Few responses observed in BRCA<sup>wt</sup> patients <strong>without</strong> BRCA-like signature (n=13)
  - 8% ORR (RECIST)
  - 8% ORR (RECIST & CA-125)
  - 38% of patients continuing on treatment (+)

**Best Target Lesion Response**

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+ = ongoing.

26<sup>th</sup> EORTC-NCI-AACR SYMPOSIUM ON
‘MOLECULAR TARGETS & CANCER THERAPEUTICS’
ARIEL program will prospectively validate the clinical utility of the HRD test

**Phase 2 Study (ARIEL2)**
- High-grade ovarian cancer
- Platinum sensitive
- Treatment setting
- Efficacy (PFS) in prespecified HRD subgroups
- Optimize definition of rucaparib-sensitive patients

**Pivotal Study (ARIEL3)**
- High-grade ovarian cancer
- Platinum sensitive
- Maintenance setting
- Efficacy (PFS) in prospectively defined HRD subgroups

Test all ARIEL3 tumor samples, classify HRD status

(Refine) HRD test

Final Analysis
Conclusions

- Rucaparib is active and well-tolerated in high-grade ovarian cancer
- Comprehensive genomic analysis of tumor based on NGS can prospectively identify ovarian cancer patients who respond to rucaparib
  - Identifies all relevant BRCA1/2 mutations and BRCA-like signature
- Updated results from ARIEL2 (N=180) will be presented in 1st half of 2015
- The BRCA-like signature could have utility in other cancer types beyond ovarian cancer

Tumor genetic data: N=121; efficacy data: N=61. Germline portion of BRCA mutations (medium blue) identified by current blood-based assays: 15%.
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