Maintenance Therapy for Recurrent Platinum-Sensitive Ovarian Cancer

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• Scientific Steering Committee:
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Ovarian Cancer Natural History

- Symptoms
- Diagnosis
- Staging/debulking
- Evaluation
- ? SLL
- Chemo #1
  - Concomitant
- Chemo #2
  - Concomitant
- Maintenance
- Chemo #3
  - M
- Chemo #4+
  - M
- Progression
- Supportive care
Ovarian Cancer Natural History

Diagnosis

Symptoms

Chemo #1
Concomitant

Evaluation

? SLL

Progression

Maintenance

Chemo #2
Concomitant

M

Chemo #3
Concomitant

M

Chemo #4+

Staging/debulking
Ovarian Cancer Natural History

Symptoms

Diagnosis

Evaluation

? SLL

Staging/debulking

Progression

Chemo #1

Concomitant

Maintenance

Chemo #2

M

Concomitant

Chemo #3

M

Chemo #4+

Concomitant

?
Current US FDA Approvals for Maintenance

• **Primary**
  
  – Bevacizumab (2018)
    
    • Concomitant with chemotherapy
    
    • No restrictions on patient population
    
    • Exposure limited: 21 cycles
  
  – Olaparib (2018)
    
    • Following chemotherapy response
    
    • Restricted to g/sBRCA
    
    • Exposure limited: 24 months

• **Recurrent (Platinum-Sensitive)**
  
  – Bevacizumab (2016)
    
    • Concomitant with chemotherapy
    
    • No restrictions on patient population
    
    • Exposure not limited
  
  – PARP inhibitors (niraparib [2017], olaparib [2017], rucaparib[2018])
    
    • Following chemotherapy response
    
    • No restrictions on patient population
    
    • Exposure not limited
Clinical Debate

Anti-angiogenesis VS. PARPi
Platinum-Sensitive Maintenance:

Bevacizumab

**OCEANS**

<table>
<thead>
<tr>
<th></th>
<th>GC + PL (n = 242)</th>
<th>GC + BV (n = 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>187 (77)</td>
<td>151 (62)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.4</td>
<td>12.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8.3 to 9.7)</td>
<td>(11.4 to 12.7)</td>
</tr>
<tr>
<td>Stratified analysis HR</td>
<td>0.494</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.388 to 0.605)</td>
<td></td>
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<tr>
<td>Log-rank P</td>
<td>&lt; .0001</td>
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</table>

**GOG-213**

Aghajanian, J Clin Oncol 2012

Coleman, Lancet Onc 2017
Platinum-Sensitive Maintenance: PARPi

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS (inv Review – Primary)</th>
<th>Rucaparib</th>
<th>Placebo</th>
<th>HR</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>ARIEL 3</td>
<td>tBRCA</td>
<td>16.8</td>
<td>5.4</td>
<td>0.23</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>tBRCA + HRD</td>
<td>13.6</td>
<td>5.4</td>
<td>0.32</td>
<td>P&lt;0.0001</td>
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<tr>
<td></td>
<td>ITT</td>
<td>10.8</td>
<td>5.4</td>
<td>0.37</td>
<td>P&lt;0.0001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS (BICR – Primary)</th>
<th>Niraparib</th>
<th>Placebo</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVA</td>
<td>tBRCA</td>
<td>21.0</td>
<td>5.5</td>
<td>0.26</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>SOLO2</td>
<td>All non-gBRCA (sBRCA+ HRD + HRC)</td>
<td>9.3</td>
<td>3.9</td>
<td>0.45</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>ITT (FDA analysis)</td>
<td>11.3</td>
<td>4.7</td>
<td>0.42</td>
<td>Not Given</td>
</tr>
</tbody>
</table>

Key Issues to Understand the Data

• The strategies for bevacizumab and PARPi are different.

• While both bevacizumab and PARPi’s are approved in biomarker unrestricted populations, PARPi’s primarily function under a predictive biomarker (g/sBRCA).

• Cross trial comparisons are particularly hazardous, not only because they differ in design and primary endpoints but also how those endpoints are measured and patient enrichment.

• Impact of front-line maintenance approval will be different in the recurrent setting.
Clinical Trial Design Considerations

- **Symptoms**
- **Diagnosis**
  - Evaluation
  - ? SLL
- **Staging/debulking**
- **Chemo #1**
  - Concomitant
- **Maintenance**
- **Progression**
  - Bevacizumab
  - Progression
- **Chemo #2**
  - Concomitant
- **Chemo #3**
  - M

**PFS**
Clinical Trial Design Considerations

- Symptoms
- Diagnosis
- Evaluation
  - ? SLL
- Progression
  - PARPi
- Chemo #1
  - Concomitant
- Maintenance
- Chemo #2
  - M
  - Concomitant
- Chemo #3
  - M
- Staging/debulking
- PFS
Clinical Trial Design Considerations

- **PFS - Assessment**
  - Trials of concomitant/maintenance assigned treatment start the PFS clock at pre-treatment randomization.
  - Trials of “switch maintenance” used in the PARPi phase III trials start the PFS clock at pre-treatment randomization but **after** induction therapy.
Clinical Trial Design Considerations

- **Pre-randomization trial eligibility:**
  - In trials supporting bevacizumab, only patients with PD before completing chemotherapy were excluded.
  - Phase III PARPi trials required a response to platinum-doublet therapy.
Clinical Trial Design Considerations

• When is maintenance considered
  • Since bevacizumab accompanies chemotherapy, the decision to use or not use bevacizumab occurs at recurrence
  • Since PARPi are considered when a response has been achieved, discussion can be delayed until after chemotherapy

• However, bevacizumab improved objective response (an enrollment requirement for PARPi) from 60% to 80%

• Potentially missing 10% of PARPi eligible patients by not using bevacizumab with chemotherapy
Clinical Trial Design Considerations

- **Pre-randomization trial eligibility:**
  - Platinum-sensitive recurrent trials enrich for patients with BRCA-mutated and HRD cancers
  - PARPi trials enrich for patients with BRCA-mutated and HRD cancers

<table>
<thead>
<tr>
<th>Trial</th>
<th>BRCA-mt</th>
<th>BRCA-wt</th>
<th>Total HRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVA</td>
<td>203 (37%)</td>
<td>162 (29%)</td>
<td>66%</td>
</tr>
<tr>
<td>ARIEL3</td>
<td>196 (35%)</td>
<td>158 (28%)</td>
<td>63%</td>
</tr>
<tr>
<td>SOLO 2</td>
<td>25 (100%)</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Double ovarian cancer population prevalence
Clinical Trial Design Considerations

- **Stratification Variables**
  - In trials supporting bevacizumab, prognostic considerations were PFI, prior bevacizumab (GOG-213), secondary cytoreduction (OCEANS) were considered.
  - In trials supporting PARPi, prognostic considerations were PFI, BRCA-mutation status (not SOLO2), best response to platinum, prior second-line bev (NOVA).
Clinical Trial Design Considerations

- **Interpretation of the data**
  - GOG-213 primary endpoint was OS; 8% of patients randomized to surgery, prior bevacizumab 10%
  - OCEANS primary endpoint was PFS; 10% had surgery but were still measurable/assessable
  - NOVA primary endpoint was BICR-PFS; two isolated cohorts (gBRCA and non-gBRCA (included sBRCA); final analysis included a merged ITT population
  - SOLO2 primary endpoint was investigator-PFS but 100% gBRCA; Study 19 data used for ITT
  - ARIEL3 primary endpoint was investigator-PFS but the ITT analysis specified a “step-down” which included g/sBRCA, then HRD (included g/sBRCA), then ITT (included HRD)
Current US FDA Approvals for Maintenance

- **Recurrent (Platinum-Sensitive)**
  - Bevacizumab (2016)
    - Concomitant with chemotherapy
    - No restrictions on patient population
    - Exposure not limited

- PARP inhibitors (niraparib [2017], olaparib [2017], rucaparib [2018])
  - Following chemotherapy response
  - No restrictions on patient population
  - Exposure not limited
Maintenance Therapy: Concepts

• Maintenance therapy is
Maintenance Therapy: Concepts

- Prior exposure is likely **IMPORTANT for PARPi**

**Diagram:**
- **Symptoms**
  - **Chemo #1**: Bevacizumab
  - **PARPi (BRCA+)**
  - Evaluation: ? SLL
- **Diagnosis**
- **Evaluation**
- **Progression**
  - **Chemo #2**: M (Concomitant)
  - **Chemo #3**: M
  - **Chemo #4+**
Maintenance Therapy: Concepts

- Prior exposure is likely IMPORTANT for PARPi

**Kaplan-Meier survival estimates**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
<td>137</td>
<td>83</td>
</tr>
<tr>
<td>179</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>0</td>
<td>0</td>
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</table>

- **MITO-16B - Bev after Bev: no detriment**

**Mechanisms of resistance**

<table>
<thead>
<tr>
<th></th>
<th>PARPi</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic reversion</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Epigenetic reversion</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Hypomorphic allele</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Loss of PARP1 expression</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Loss of end resection regulation</td>
<td>Resistant</td>
<td>Sensitive (53BP1); ? (REV7)</td>
</tr>
<tr>
<td>TLS activation</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Pgp drug efflux</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Extensive stromal reaction</td>
<td>Resistant*</td>
<td>Resistant</td>
</tr>
<tr>
<td>Deficient NHEJ</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>

Aghajanian, J Clin Oncol 2012

McCormick, Clin Cancer Res 2017
Maintenance Therapy: Concepts

- Prior exposure is likely **IMPORTANT** for PARPi

MITO-16B - Bev after Bev: no detriment

Kaplan-Meier survival estimates

OREO Trial

- gBRCA+ or sBRCA+
  - 1 prior PARPi treatment
  - 18mo+ after 1st line CT
  - 12mo+ after 2nd line CT

- wtBRCA- all-comers
  - 1 prior PARPi treatment
  - 12mo+ after 1st line CT
  - 06mo+ after 2nd line CT

Stratification factors
- Prior bevacizumab
- <3 vs ≥3 chemo lines

Platinum-based chemotherapy (no Bev)

Olaparib tablets*

Placebo

Powered 80% for PFS primary endpoint.
BRCA+ HR=0.5, 74 events.
BRCA- HR=0.65, 191 events.

*300 mg bid or last tolerable dose
ENGOT-ov 26 (PRIMA) Study Design

Niraparib maintenance in First-line therapy
High Risk patients: Stage IV; residual Stage III

Stratification factors:
- Use of NACT: yes or no
- Best tumor response: CR or PR
- HRD status: pos or neg/nd

- Patients with sBRCA or tBRCAmut will be stratified as HRDpos
- Patients with unknown or wild type BRCA will be stratified based on HRD test results

Primary Endpoint

PFS in HRDpos patients; hierarchical analysis for all patients regardless of HRD status

Key Secondary Endpoints

Overall survival (OS), patient reported outcomes (PRO’s), time to first subsequent treatment, progression-survival-2, time to CA-125 progression, safety and tolerability of study therapy

ClinicalTrials.gov Identifier: NCT02655016
PARPi Combination With Anti-Angiogenesis

PAOLA-1

Primary endpoint: PFS

Secondary endpoints: OS, post-progression survival, health-related quality of life by TOI of the FACT-O, and safety and tolerability

Veliparib: VELIA/GOG3005

- High-grade serous tumors, Stage III, IV
- Election for NACT-ICS and scheduling of paclitaxel (no IP therapy)
- Primary endpoint PFS (ARM I vs Arm III): (1) g/sBRCA1/2 Population; (2) HRD; (3) Entire Population
- Stratifications: Stage, Residual Disease, NACT-ICS, Region, gBRCA status

ClinicalTrials.gov Identifier:NCT02470585

Open: Jul 2015
Closed: May 2017
Target Accrual: ~1100 pts (264 BRCA1/2 +)
Ovarian Cancer: Emerging Paradigm

- Maintenance therapy appears to be of value in patients with platinum-sensitive recurrent disease.

- Clinical pathway will likely change:
  - Exposure in earlier lines of therapy
  - With combinations that make sense in biomarker unrestricted patients
  - With new dynamic biomarkers of HRD
Thanks!