Ovarian Cancer Update: PARP inhibitors in Ovarian Cancer
The who, why, and how in 2018

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Ovarian Cancer Update

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Clovis Oncology

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Outline and Aims

• Goal: To understand how, when, and to whom to give PARP inhibitor therapy

• Overview of PARP inhibitors and FDA approved indications
• PARP for treatment in BRCA
• PARP for maintenance after platinum-sensitive recurrence
• Teaser about PARP combination therapy and next steps
• Summary and conclusions
Ovarian Cancer Treatment – FDA Approvals

- Cisplatin
  - 1978
- Carboplatin²
  - 1989
  - 1990
  - 1991
  - 1992
- Paclitaxel
- Liposomal Doxorubicin (Accelerated)
- Gemcitabine
- Olaparib (platinum-sensitive, BRCAmut carriers)
- Rucaparib (somatic + germline BRCA)
- Niraparib (platinum-sensitive)
- Olaparib (platinum-sensitive)
- Bevacizumab (platinum-sensitive)

Modified from Dr. Matt Powell
The FDA Approved PARP Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Niraparib</th>
<th>Rucaparib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharma</strong></td>
<td>AstraZeneca</td>
<td>Tesaro</td>
<td>Clovis</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>2014</td>
<td>2017</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Maintenance indication:</strong> <em>Platinum-sensitive recurrence</em></td>
<td>All patients (2017)</td>
<td>All patients</td>
<td>All patients (2018)</td>
</tr>
<tr>
<td><strong>Treatment indication</strong></td>
<td>gBRCA only, 3 prior lines, platinum-resistant</td>
<td>None</td>
<td>gBRCA and sBRCA only, platinum-sensitive</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>300mg tablet BID</td>
<td>300mg QD</td>
<td>600mg BID</td>
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</tbody>
</table>
Figure 6: PARP inhibitors function by blocking DNA repair mechanisms. When a SSB occurs, the repair is accomplished by BER, NER and MMR. If BER is impaired, through the inhibition of PARP, single strand breaks become double strand breaks. In patients with HR defects, such as a BRCA mutation carrier, this damage causes the cancer cell death since PARP inhibitors induce aberrant activation of NHEJ.
PARP Toxicity

**SOLO-2**
*Grades 1-4*

- Nausea: 76% vs 33%
- Vomiting: 38% vs 19%
- Anemia: 43% vs 8%
- Neutropenia: 19% vs 6%
- Elevated Cr: 11% vs 1%
- Fatigue: 66% vs 39%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib (n=195)</th>
<th>Placebo (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Non-haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>143 (73%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>120 (62%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>68 (35%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>62 (32%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>52 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>48 (25%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>42 (22%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>43 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>40 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>32 (16%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>29 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25 (13%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>21 (11%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>22 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>21 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>47 (24%)</td>
<td>36 (18%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28 (14%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (13%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>28 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>21 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>17 (9%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

Pujade-Lauraine Lancet Oncol 2017
PARPi for treatment: Olaparib

Fig 1. Progression-free survival.
PARPi for treatment: *Niraparib* - *QUADRA*

**Figure 6. Tumor Response in All Patients Treated in 4th Line or Later**

*Benefit Observed Across All Patient Populations*

In all evaluable patients treated in 4th line or later:
- **ORR** - 10%
- **CBR16** - 35%
- **mDOR** - 9.4 months (95% CI: 6.6–18.3)
- 44% of responses lasted ≥12 months*

Patients with at least one follow-up scan with an evaluable target lesion treated in 4th or later line (n=379) included on the waterfall plot.

Patients previously treated with PARP inhibitors are included.

*Based on KM estimate.

CBR16 = clinical benefit rate (CR+PR+SD for at least 16 weeks).
PARPi for treatment: *Rucaparib – ARIEL-2*
PARPi for maintenance: Olaparib – SOLO-2 and Study 19

Study 19 – All women

SOLO-2 – gBRCA only

Ledermann NEJM 2012
Pujade-Lauraine Lancet Oncol 2017
PARPi for maintenance: Niraparib - NOVA

**A. Germline BRCA Mutation**

- Hazard ratio, 0.27 (95% CI, 0.17–0.41)
- P<0.001

**B. No Germline BRCA Mutation with HRD Positivity**

- Hazard ratio, 0.38 (95% CI, 0.24–0.59)
- P<0.001

**C. No Germline BRCA Mutation**

- Hazard ratio, 0.45 (95% CI, 0.34–0.61)
- P<0.001

Mirza NEJM 2016
PARPi for maintenance: *Rucaparib* – *ARIEL-3*

**A**
- Progression-free survival (%)
- Number at risk (censored)
  - **Rucaparib**:
    - 130 (0)
    - 93 (14)
    - 63 (21)
    - 35 (37)
    - 15 (51)
    - 3 (60)
    - 0 (63)
    - 0 (16)
  - **Placebo**:
    - 66 (0)
    - 24 (5)
    - 6 (7)
    - 3 (8)
    - 1 (9)
    - 0 (10)
    - 0 (16)

**B**
- Progression-free survival (%)
- Number at risk (censored)
  - **Rucaparib**:
    - 236 (0)
    - 161 (20)
    - 96 (36)
    - 54 (60)
    - 21 (85)
    - 5 (97)
    - 0 (102)
  - **Placebo**:
    - 118 (0)
    - 40 (10)
    - 11 (12)
    - 6 (14)
    - 1 (16)
    - 0 (17)
    - 0 (17)

**C**
- Progression-free survival (%)
- Number at risk (censored)
  - **Rucaparib**:
    - 375 (0)
    - 228 (36)
    - 128 (61)
    - 65 (93)
    - 26 (122)
    - 5 (136)
    - 0 (141)
  - **Placebo**:
    - 189 (0)
    - 63 (12)
    - 13 (16)
    - 7 (18)
    - 2 (20)
    - 1 (21)
    - 0 (22)

Coleman Lancet 2017
PARPi combination: Cediranib / Olaparib

Liu Lancet 2014
PARPi combination: *Niraparib / Pembrolizumab*

**TOPACIO**

<table>
<thead>
<tr>
<th>Response</th>
<th>All (%)</th>
<th>tBRCAmut (%)</th>
<th>HRDpos* (%)</th>
<th>tBRCAw t (%)</th>
<th>HRDneg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>11/47 (23%)</td>
<td>2/8 (25%)</td>
<td>4/16 (25%)</td>
<td>9/37 (24%)</td>
<td>7/26 (27%)</td>
</tr>
<tr>
<td>DCR</td>
<td>30/47 (64%)</td>
<td>5/8 (63%)</td>
<td>11/16 (69%)</td>
<td>24/37 (65%)</td>
<td>15/26 (58%)</td>
</tr>
</tbody>
</table>

Konstantinopoulos
ASCO 2018
Coming soon: PARPi as first line maintenance for gBRCA – Olaparib – SOLO-1

SOLO-1: A Phase III Trial of Olaparib
Monotherapy for BRCA-Mutated Ovarian Cancer

Accrual (n = 397)
- Newly diagnosed, high-risk ovarian cancer
- Prior platinum-based chemotherapy
- Presence of deleterious or suspected deleterious BRCA1/2 mutation

Primary endpoint: PFS
Summary

• PARP inhibitors have FDA approved indications in both treatment and maintenance settings in ovarian cancer

• Women with a complete or partial response to platinum-based chemotherapy for platinum-sensitive recurrence are eligible for PARP inhibitor maintenance, regardless of BRCA status

• Targeting DNA repair with PARP inhibitors in ovarian cancer leads to significant progression free survival benefit

• Patients with germline and somatic BRCA mutations derive relatively greater benefit

• Combination therapy holds promise for improving response to PARP inhibitors in non-BRCA