OVARIAN CANCER – FIRST LINE AND PLATINUM SENSITIVE - THE CURRENT LANDSCAPE

David O’Malley, M.D.
Professor
Division Director, Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

GOG-P Ovarian Cancer Clinical Trialist

Creating a cancer-free world. One person, one discovery at a time.
Agenda

- Background
- First Line
  - Maintenance
  - PROs
  - Dose Intensity
- Platinum Sensitive
  - PARPi Resistance?
  - Molecular Signature
Ovarian Cancer: Clinical Impact

Age-adjusted SEER ovarian cancer incidence and prevalence from 2001–2017

SEER=Surveillance, Epidemiology and End Results.
12 (Plus Two Pembrolizumab approvals MSI and TMB) Approvals in the Last 6+ Years
What Is the Standard Systemic Treatment for Newly Diagnosed Advanced EOC 2021?

1. NACT = Neoadjuvant chemotherapy
2. EOC = Epithelial ovarian cancer
3. HRD = Homologous recombination deficient
4. HRP = Homologous recombination proficient
5. PARPi = Poly ADP Ribose inhibitor
6. NEJM = New England Journal of Medicine

Decision #1
NACT vs Primary debulking

Testing
- Germ line panel testing (all EOC)
- Tumor HRD testing (if germ line BRCAwt)

IV q 3 week carboplatin + paclitaxel

Decision #2
Bevacizumab Y/N

No bevacizumab

Decision #3
Add PARPi?

BRCA mut + HRD: Add PARPi (preferred)

HRP: Add PARPi or Observation

BRCA mut HRD: Add PARPi (preferred)

HRP: Continue bevacizumab

Supporting NEJM
Phase 3 trial

SOLO-1
PRIMA
PAOLA-1
GOG 218
GOG 262

Quality-Adjusted Time Without Symptoms or Toxicity (QA-TWiST) and Quality-Adjusted Progression-Free Survival (QA-PFS) of First-line Maintenance Niraparib in Patients With Advanced Ovarian Cancer – Results from the PRIMA Trial

Table 2. Mean duration of PFS and QA-PFS per study population at last PFS of the treatment group

<table>
<thead>
<tr>
<th>Population</th>
<th>Duration, restricted mean (95% CI), months</th>
<th>Niraparib</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ITT at 27.8 months</td>
<td></td>
<td>n=487</td>
<td>n=246</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td>15.5 (14.3, 16.5)</td>
<td>11.9 (10.2, 13.3)</td>
<td>3.6 (1.8, 5.7)</td>
</tr>
<tr>
<td>QA-PFS</td>
<td></td>
<td>14.0 (12.6, 15.0)</td>
<td>9.9 (8.6, 11.0)</td>
<td>4.1 (2.2, 5.8)</td>
</tr>
<tr>
<td>HRd at 27.8 months</td>
<td></td>
<td>n=247</td>
<td>n=126</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td>19.3 (17.6, 20.7)</td>
<td>13.4 (11.0, 15.1)</td>
<td>5.9 (3.5, 8.7)</td>
</tr>
<tr>
<td>QA-PFS</td>
<td></td>
<td>17.7 (15.6, 19.1)</td>
<td>11.2 (9.1, 12.6)</td>
<td>6.5 (3.9, 8.9)</td>
</tr>
</tbody>
</table>

Figure 3. QA-TWiST gain for the overall ITT population and HRd population at last PFS of the treatment group

Mean (95% CI) QA-TWiST gain with niraparib vs. placebo

Overall ITT (n=733) 3.5 (1.7, 5.6)

HRd (n=373) 5.9 (3.5, 8.6)
Quality-Adjusted Time Without Symptoms or Toxicity (QA-TWiST) and Quality-Adjusted Progression-Free Survival (QA-PFS) of First-line Maintenance Niraparib in Patients With Advanced Ovarian Cancer – Results from the PRIMA Trial

- Maintenance treatment was associated with a significant gain in QA-PFS compared with placebo, indicating a patient-relevant improvement in PFS.
- TWiST demonstrates treated patients remained symptom-free for longer.

Table 3. Restricted mean duration of health states for the overall ITT population and HRd population at last PFS of the treatment group

<table>
<thead>
<tr>
<th>Population</th>
<th>Restricted mean duration (95% CI), months</th>
<th>difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ITT at 27.8 months</td>
<td>Niraparib (n=487)</td>
<td>Placebo (n=246)</td>
</tr>
<tr>
<td>TOX</td>
<td>1.4 (0.9, 1.9)</td>
<td>0.4 (0.3, 0.5)</td>
</tr>
<tr>
<td>TWiST</td>
<td>16.0 (14.5, 17.5)</td>
<td>11.5 (10.0, 13.0)</td>
</tr>
<tr>
<td>HRd at 27.8 months</td>
<td>Niraparib (n=247)</td>
<td>Placebo (n=126)</td>
</tr>
<tr>
<td>TOX</td>
<td>0.7 (0.4, 1.0)</td>
<td>0.4 (0.2, 0.6)</td>
</tr>
<tr>
<td>TWiST</td>
<td>18.6 (16.9, 20.3)</td>
<td>12.8 (10.6, 14.6)</td>
</tr>
</tbody>
</table>

*TOX included grade ≥2 AEs of interest (fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating).
There was a **statistically significant decline** in HRQoL from pre-progression to **EOT** (post-progression) across FOSI, EORTC-C30, EQ-5D VAS and EORTC-OV28 measures.

Preservation of HRQoL is an important therapy goal in the maintenance setting, particularly for asymptomatic patients, and can be **achieved with PFS prolongation**.

HRQoL is **negatively impacted** by disease progression.

---

**Impact of Disease Progression on Health-related Quality of Life of Advanced Ovarian Cancer Patients – Pooled Analysis From the PRIMA Trial**

Dana Chase ESGO 2021
AGO OVAR BOOST TRIAL

**Stratification factors**
- FIGO IIIB–IIIC and no residual tumor
- FIGO IIIB–IIIC with residual tumor or FIGO IV

**BEV15** (standard arm)
- BEV 15 mg/kg q3 weeks for 32 cycles (15 months)
- Paclitaxel 175 mg/m²
- Carboplatin AUC5 q3 weeks

**BEV30** (experimental arm)
- BEV 15 mg/kg q3 weeks for 48 cycles (30 months)
- Paclitaxel 175 mg/m²
- Carboplatin AUC5 q3 weeks

**Primary endpoint: PFS**

<table>
<thead>
<tr>
<th></th>
<th>BEV15</th>
<th>BEV30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>24.2 (22.2–26.5)</td>
<td>26.0 (23.7–29.7)</td>
</tr>
<tr>
<td>PFS hazard ratio (95% CI)</td>
<td>0.99 (0.85–1.15)</td>
<td>Log-rank p=0.90</td>
</tr>
</tbody>
</table>

**Subgroup analysis of PFS:**
- Stratum FIGO IIIB–IIIC and no residual tumor

**BEV15**
- PFS events, n (%) 147 (60)
- Median PFS, months (95% CI) 38.4 (28.5–46.6)
- PFS hazard ratio (95% CI) 0.93 (0.74–1.18)

**BEV30**
- PFS events, n (%) 139 (60)
- Median PFS, months (95% CI) 38.8 (35.2–44.6)
- PFS hazard ratio (95% CI) 0.93 (0.74–1.18)

**Subgroup analysis of PFS:**
- Stratum FIGO IIIB–IIIC with residual tumor or FIGO IV

**BEV15**
- PFS events, n (%) 191 (83)
- Median PFS, months (95% CI) 19.3 (16.4–20.0)
- PFS hazard ratio (95% CI) 1.06 (0.87–1.29)

**BEV30**
- PFS events, n (%) 201 (86)
- Median PFS, months (95% CI) 18.2 (16.7–19.7)
- PFS hazard ratio (95% CI) 1.06 (0.87–1.29)

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>BEV15</th>
<th>BEV30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>54.3 (51.0–64.6)</td>
<td>60.0 (54.0–68.6)</td>
</tr>
<tr>
<td>OS hazard ratio (95% CI)</td>
<td>1.04 (0.87–1.23)</td>
<td>Log-rank p=0.68</td>
</tr>
</tbody>
</table>

The James
The First-Line Ovarian Cancer Development

<table>
<thead>
<tr>
<th>First Line Treatment w/ Maintenance</th>
<th>First Line Switch Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAVELIN100 (avelumab) - NEG</td>
<td></td>
</tr>
<tr>
<td>ImaGyn50/GOG-3015 (bevacizumab/atezolizumab) – NEG</td>
<td></td>
</tr>
<tr>
<td><strong>FIRST</strong></td>
<td><strong>ATHENA/GOG-3020 (rucaparib, nivolumab)</strong></td>
</tr>
<tr>
<td>(niraparib/dostarlimab ± bevacizumab)</td>
<td></td>
</tr>
<tr>
<td>GOG-3036/ENGOT-ov43</td>
<td></td>
</tr>
<tr>
<td>(olaparib/pembrolizumab ± bevacizumab)</td>
<td></td>
</tr>
<tr>
<td>GOG-3025/ENGOT-ov46</td>
<td></td>
</tr>
<tr>
<td>(olaparib/durvalumab ± bevacizumab)</td>
<td></td>
</tr>
<tr>
<td>FLORA-5/GOG-3035</td>
<td></td>
</tr>
<tr>
<td>(Oregovomab)</td>
<td></td>
</tr>
</tbody>
</table>

AAi: Angiogenesis inhibitor

IOi: PD-1/PD-L1 inhibitor

PARPi: PARP inhibitor
Platinum Sensitive

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Rechallenge with maintenance olaparib following response to platinum-based chemotherapy provided a statistically significant improvement in PFS compared with placebo, regardless of BRCAm status.

- Being Driven by the tails? Small number of responders?
- Platinum sensitivity a clinical predictor?

A statistically significant PFS benefit was observed with olaparib in the BRCAm cohort.

- A proportion of patients derived clinically relevant long-term benefit

A statistically significant PFS benefit was observed with olaparib in the non-BRCAm cohort.

- A proportion of patients derived clinically relevant long-term benefit

Eric Pujade-Lauraine ESMO 2021
Combination of PARP & ATR inhibition (olaparib & ceralasertib) shows clinical activity in acquired PARP inhibitor resistant recurrent ovarian cancer

**Core inclusion criteria**
- Platinum sensitive recurrent HGSOC
- Homologous recombination deficiency
  - Germline/somatic BRCA\textsuperscript{MUT}
  - Other HRD mutation
  - HRD positive (≥42 on Myriad My Choice)
- Derived clinical benefit from prior PARPi therapy and then progressed with measurable disease on imaging
- No intervening chemotherapy since PARPi
- Clinical benefit from prior PARPi
  - Maintenance ≥12 months in the front line setting
  - Maintenance ≥6 months in platinum sensitive recurrence
  - Treatment with a decline in CA125 or response on imaging

**Aim**
- Determine the efficacy and tolerability of the combination of olaparib (PARPi) and ceralasertib (ATRi) in patients who have progressed with prior PARPi (Cohort C)

**13 subjects**

**BRCA/HRD**
- Germline BRCA\textsuperscript{MUT} 69% (n=9)
- Somatic BRCA\textsuperscript{MUT} 23% (n=3)
- Positive HRD score 8% (n=1)

**Prior PARPi**
- 1\textsuperscript{st} line maintenance 8% (n=1)
- 2\textsuperscript{nd} line maintenance 38% (n=5)
- Treatment 54% (n=7)

**ORR 46% (n=6)**
**PFS 7.5 months (95% CI 4.7-9.4)**

Wethington & Simpkins ASCO 2021
In ARIEL3, 21% of patients in the rucaparib-treated arm derived exceptional benefit (progression-free survival ≥2 years) versus only 2% of those in the placebo arm

Exceptional benefit in ARIEL3 was more common in, but not exclusive to, patients with favorable clinical characteristics and known mechanisms of poly(ADP-ribose) polymerase inhibitor sensitivity, including BRCA1, BRCA2, RAD51C, and RAD51D mutations
Association of homologous recombination deficiency (HRD) with clinical outcomes in a phase 3 study of olaparib or cediranib and olaparib compared to platinum based chemotherapy in recurrent platinum sensitive ovarian cancer (PSOC): biomarker analyses from NRG GY004

**Gene1** | **Gene2** | # Patients | % Patients
---|---|---|---
ATM | ATM | 1 | 0.68
BRCA1 | 1 | 0.68
BRCA2 | 1 | 0.68
alone | 4 | 2.72
BARD1 | BRCA1 | 1 | 0.68
alone | 2 | 1.36
BRCA1 | PALB2 | 1 | 0.68
alone | 77 | 52.38
BRCA2 | BRCA2 | 1 | 0.68
NBN | 1 | 0.68
PALB2 | 1 | 0.68
alone | 40 | 33.33
PALB2 | alone | 2 | 1.36
RAD51C | alone | 2 | 1.36
RAD51D | alone | 3 | 2.04
All | 147 | 100

**E Swisher ESMO 2021**

- 90% HRD mutations were BRCA
- Both olaparib and cediranib/ olaparib demonstrated activity in patients with HRRmt tumors
- Unclear development plan

**J Liu ASCO 2020 The James**
Summary

• Five ongoing phase III first line trials
  • 4 completed – at least 1 will likely change the landscape of ovarian cancer
• Maintenance Therapy
  • Keeping cancer away improves Quality of Life
  • BUT Sometimes more isn’t better
• What is PARPi resistance? How to overcome?
• Personalized Medicine…..beyond BRCA
Thank you