ESMO SUMMIT AFRICA 2020

Current Standard of Care and Practice changing studies in Ovarian Cancers

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Milan, Italy
Consulting and advisory services, speaking or writing engagements, public presentations:
Roche, Astra Zeneca, MSD, Pharmamar, Tesaro- GSK, Clovis, Pfizer, Takeda, Immunogen, Biocad, Amgen

Institutional financial interests:
Roche, Pharmamar, Astra Zeneca, Pfizer

Non-financial interests:
Subject editor for gynecological cancer, ESMO clinical Guidelines
Estimated number of new cases in 2018, Africa, all cancers, females, all ages

- Breast: 168,690 (27.7%)
- Cervix uteri: 119,284 (19.6%)
- Colorectum: 31,196 (5.1%)
- Ovary: 21,925 (3.6%)
- NHL: 21,555 (3.5%)
- Liver: 21,249 (3.5%)
- Leukaemia: 14,304 (2.4%)
- Other cancers: 210,413 (34.6%)

Total: 608,616

Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
© International Agency for Research on Cancer 2020
1st ESGO-ESMO Consensus Conference on Ovarian Cancer

12-14 April 2018 in Milano, Italy

Annals of Oncology, Volume 30, Issue 5, May 2019, Pages 672–705

# EARLY STAGE AND BORDERLINE

1) Are there exceptions to the standard surgical management for early stage ovarian carcinoma?

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparotomy is the standard surgical approach to treat and stage patients with apparent early stage ovarian carcinoma</td>
<td>V</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
<tr>
<td>Minimally invasive surgery can be performed for restaging</td>
<td>IV</td>
<td>B</td>
<td>Yes: 75% (30 voters)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 12.5% (5 voters)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abstain: 12.5% (5 voters)</td>
</tr>
<tr>
<td>Whatever the approach used, rupture of an intact tumour with spillage of cancer cells at the time of surgery must be avoided</td>
<td>IV</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
</tbody>
</table>
### EARLY STAGE AND BORDERLINE

#### 3) Should all stage I carcinoma receive adjuvant chemotherapy and if not which ones?

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
</table>
| Adjuvant chemotherapy should be offered to patients with early stage ovarian cancer (stage I-IIA) with the **exception** of fully staged patients with the following:  
  - Low grade serous IA  
  - Grade 1 and 2 endometrioid IA  
  - Grade 1 and 2 mucinous IA (expansile invasion) | II  | A | Yes: 100% (40 voters) |
| Adjuvant chemotherapy is not recommended in the management of incidentally detected isolated STIC lesions | V  | A | Yes: 100% (40 voters) |
| The benefit of adjuvant chemotherapy is **uncertain** for patients with the following and should be discussed on an individual patient basis:  
  - Clear cell carcinoma stage IA, and IB/C1  
  - Grade 1 and 2 Endometrioid IB/C  
  - Low grade serous IB/C  
  - Grade 1 and 2 mucinous IC (expansile invasion)  
  - Mucinous IA (infiltrative invasion) | III | C | Yes: 92.5% (37 voters)  
  No: 7.5% (3 voters) |
### Summary of recommendations

**For patients with early stage disease requiring adjuvant chemotherapy, acceptable treatment regimens are:**
- carboplatin alone or
- carboplatin /paclitaxel

<table>
<thead>
<tr>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
<tr>
<td>II</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
</tbody>
</table>

**For patients receiving single agent adjuvant carboplatin, 6 cycles are recommended**

<table>
<thead>
<tr>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
</tbody>
</table>

**For patients receiving carboplatin and paclitaxel, a minimum of 3 cycles is recommended except for the serous subgroup or stage IC (any histological type) in whom 6 cycles are recommended**

<table>
<thead>
<tr>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>B</td>
<td>Yes: 77.5% (31 voters) Abstain: 22.5% (9 voters)</td>
</tr>
</tbody>
</table>
How to select patients for primary debulking surgery or neoadjuvant chemotherapy?

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>The selection of patients for primary debulking surgery or neo-adjuvant treatment must be performed in a specialist ovarian cancer centre (according to the ESGO Quality recommendations 2017) in a multidisciplinary setting</td>
<td>IV</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
<tr>
<td>Complete tumour resection at upfront debulking is the most important prognostic factor for patients with advanced ovarian cancer and is the main goal of surgery</td>
<td>IV</td>
<td>A</td>
<td>Yes: 100% (40 voters)</td>
</tr>
<tr>
<td>When complete surgery with no macroscopic visible disease appears feasible (both spread of disease and general condition of the patient), primary upfront debulking should be offered</td>
<td>IV</td>
<td>B</td>
<td>Yes: 100% (40 voters)</td>
</tr>
<tr>
<td>Diagnostic work-up with computed tomography, positron emission tomography-computed tomography, or diffusion-weighted whole body magnetic resonance imaging, and expert ultrasound or diagnostic laparoscopy should be used to assess the extent of disease</td>
<td>III</td>
<td>C</td>
<td>Yes: 100% (40 voters)</td>
</tr>
</tbody>
</table>

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First-Line Treatment of Advanced Ovarian Cancer: Stuck with Carboplatin-Paclitaxel Since 2003

According to the Consensus Conference 3-weekly carboplatin-paclitaxel remains the standard-of-care chemotherapy of first-line ovarian cancer treatment

### ADVANCED STAGE

**What is the current role of bevacizumab in first-line treatment?**

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab</strong> (15mg/kg or 7.5 mg/kg every 3 weeks for maximum of 15 months) improves progression-free survival in patients with stage III-IV ovarian cancer and <strong>should be considered</strong> in addition to carboplatin and paclitaxel</td>
<td>I</td>
<td>A</td>
<td>Yes: 97.5% (39 voters) Abstain: 2.5% (1 voter)</td>
</tr>
<tr>
<td><strong>Bevacizumab in the neoadjuvant setting can be considered</strong> although the additional improvement in efficacy is not proven with level I evidence</td>
<td>II</td>
<td>B</td>
<td>Yes: 97.5% (39 voters) No: 2.5% (1 voter)</td>
</tr>
<tr>
<td>Bevacizumab can be safely administered in the neo-adjuvant setting before and after IDS providing the interval between surgery and administration is at least 4-6 weeks</td>
<td>II</td>
<td>B</td>
<td>Yes: 100% (40 voters)</td>
</tr>
</tbody>
</table>
Paradigm Shift 1:
First-Line Chemotherapy Standard of Care (BRCAwt)
Carboplatin, Paclitaxel & Bevacizumab + Maintenance

GOG 218\(^1\)
Advanced epithelial ovarian cancer
- Paclitaxel + carboplatin + placebo
- Paclitaxel + carboplatin + bevacizumab
  Cycles 1–6; + bevacizumab at cycle 2
- Placebo
  Placebo (Bev Initiation)
  Bevacizumab (Bev throughout)
  Until disease progression or up to 22 cycles

Bevacizumab vs. Chemotherapy
Progression-Free Survival (%)
Time from Randomisation (months)
- Bevacizumab: 19.0 months
- Chemotherapy: 17.3 months
- Bev initiation: 14.1 months
- Bev throughout: 10.3 months

No. at risk
Chemotherapy 625 199 33 8
Bev initiation 625 219 29 6
Bev throughout 623 254 38 8

ICON7\(^2\)
Advanced epithelial ovarian cancer
- Paclitaxel + carboplatin
- Paclitaxel + carboplatin + bevacizumab
  Cycles 1–6
- Bevacizumab
  Bevacizumab
  Until disease progression or 12 cycles

Bevacizumab vs. Chemotherapy
Progression-Free Survival (%)
Time from Randomisation (months)
- Bevacizumab: 19.0 months
- Chemotherapy: 17.3 months

No. at risk
Chemotherapy 764 693 464 216 91 25
Bevacizumab 764 715 585 263 73 19

In the Last 12 Months.....
Great news!!!!!
Paradigm Shift 2: SOLO-1
Olaparib as Maintenance (*BRCAmut*)

No obvious change in Kaplan-Meier curves after 2 years

60.4% progression free at 3 years

26.9% progression free at 3 years

Events (%) [50.6% maturity]
- Olaparib (N=260): 102 (39.2)
- Placebo (N=131): 96 (73.3)

Median PFS, months
- Olaparib: NR
- Placebo: 13.8

HR (95% CI)
- Olaparib: 0.30 (0.23, 0.41)
- Placebo: P<0.0001

No. patients at risk
- Olaparib: 260
- Placebo: 131

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>260</td>
<td>131</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>118</td>
</tr>
<tr>
<td>6</td>
<td>229</td>
<td>103</td>
</tr>
<tr>
<td>9</td>
<td>221</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>212</td>
<td>65</td>
</tr>
<tr>
<td>15</td>
<td>201</td>
<td>56</td>
</tr>
<tr>
<td>18</td>
<td>194</td>
<td>53</td>
</tr>
<tr>
<td>21</td>
<td>184</td>
<td>47</td>
</tr>
<tr>
<td>24</td>
<td>172</td>
<td>41</td>
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<td>27</td>
<td>149</td>
<td>39</td>
</tr>
<tr>
<td>30</td>
<td>138</td>
<td>38</td>
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<tr>
<td>33</td>
<td>133</td>
<td>31</td>
</tr>
<tr>
<td>36</td>
<td>111</td>
<td>28</td>
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<tr>
<td>39</td>
<td>88</td>
<td>22</td>
</tr>
<tr>
<td>42</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>45</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>57</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NR = not reached.

Figure adapted from: Moore K et al. N Engl J Med 2018;379:2495–505.
First-Line Treatment: Standard of Care (Until ESMO 2019)

First line until September 2019:
- *BRCAt:* Carboplatin/paclitaxel +/- bevacizumab
- *BRCAm:* Carboplatin/paclitaxel followed by olaparib

Test all patients for *BRCa* mutation at diagnosis !!!

What about *BRCa* wild-type patients?
These 3 Trials Will Change the Paradigm Yet Again for BRCAwt

<table>
<thead>
<tr>
<th>Study Design</th>
<th>GOG-0218 (N=1873)</th>
<th>SOLO-1 (N=451)</th>
<th>Velia (N=1140)</th>
<th>PRIMA (N=620)</th>
<th>PAOLA-1 (N=806)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms vs placebo</td>
<td>Bevacizumab (n=625)</td>
<td>Olaparib (n=260)</td>
<td>Veliparib</td>
<td>Niraparib</td>
<td>Bevacizumab ± Olaparib</td>
</tr>
<tr>
<td>Key Patient Population</td>
<td>All comers</td>
<td>BRCA mutation</td>
<td>All comers</td>
<td>All comers</td>
<td>All comers</td>
</tr>
<tr>
<td>Undergo tumor testing</td>
<td>HRR (post-hoc)</td>
<td>BRCA</td>
<td>BRCA</td>
<td>HRD</td>
<td>BRCA</td>
</tr>
<tr>
<td>Stage</td>
<td>III</td>
<td>73.8%</td>
<td>84.6%</td>
<td>Eligible</td>
<td>Eligible: Attempt upfront debulking</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>26.2%</td>
<td>15.4%</td>
<td>Eligible</td>
<td>Eligible: Any debulking attempts</td>
</tr>
<tr>
<td>Surgery</td>
<td>Residual disease after surgery</td>
<td>Stage III incomplete</td>
<td>Macroscopic: 32.8%</td>
<td>Primary or Interval</td>
<td>Required for Stage III</td>
</tr>
<tr>
<td></td>
<td>Inoperable disease</td>
<td>0</td>
<td>1.5%</td>
<td></td>
<td>Primary or intervalb</td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>15 months</td>
<td>24 months</td>
<td>24 months</td>
<td>Until PD</td>
<td>15 months for Bev 24 months for Olaparib</td>
</tr>
</tbody>
</table>

VELIA: Primary Endpoint

Paradigm Shift 3: PRIMA
Niraparib as Maintenance

PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population

57% reduction in hazard of relapse or death with niraparib

<table>
<thead>
<tr>
<th></th>
<th>Niraparib (n=247)</th>
<th>Placebo (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>21.9 (95% CI 19.3-NE)</td>
<td>10.4 (8.1-12.1)</td>
</tr>
<tr>
<td>Patients without PD or death (%)</td>
<td>86%</td>
<td>68%</td>
</tr>
<tr>
<td>6 months</td>
<td>72%</td>
<td>42%</td>
</tr>
<tr>
<td>12 months</td>
<td>59%</td>
<td>35%</td>
</tr>
</tbody>
</table>

PRIMA Primary Endpoint, PFS Benefit in the Overall Population

38% reduction in hazard of relapse or death with niraparib

<table>
<thead>
<tr>
<th></th>
<th>Niraparib (n=487)</th>
<th>Placebo (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>13.8 (95% CI 11.5-14.9)</td>
<td>8.2 (7.3-8.5)</td>
</tr>
<tr>
<td>Patients without PD or death (%)</td>
<td>73%</td>
<td>60%</td>
</tr>
<tr>
<td>6 months</td>
<td>73%</td>
<td>60%</td>
</tr>
<tr>
<td>12 months</td>
<td>53%</td>
<td>35%</td>
</tr>
<tr>
<td>18 months</td>
<td>42%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Paradigm Shift 4: PAOLA 1

Olaparib and Bevacizumab as Maintenance

**PFS* (ITT population, primary endpoint)**

- **Events, n (%):**
  - Olaparib + bevacizumab (N=537): 280 (52)
  - Placebo + bevacizumab (N=269): 194 (72)
- **Median PFS, months:**
  - Olaparib + bevacizumab: 22.1
  - Placebo + bevacizumab: 16.6
- **HR 0.59 (95% CI 0.49-0.72; P<0.0001)**

*Investigator assessment.

Ray-Coquard IL, et al. ESMO 2019, NEJM 2020
PAOLA-1: PFS by HRD Status

Standard of care in first line ovarian cancer
What next?

- Moving PARP inhibitors to first-line for all or subset BRCA/HRD +ve?
- How will first-line PARP inhibitors impact on use in recurrent disease?
- Can patients benefit from a rechallenge with same or different PARP inhibitor?
- Will combination therapy be needed in recurrent disease?

In 2018 front-line use of a PARP inhibitor in BRCA mutated ovarian cancer heralded a change. In 2019 new front-line data introduce a paradigm shift in PARP inhibitor use with a major improvement in progression-free survival of ovarian cancer.
Looking at the treatment of relapses...
Ovarian Cancer Consensus Conference

Treatment of relapse

Patients with recurrent ovarian cancer

- tumour biology/histology
- number of prior lines of treatment
- prior response
- TFI for platinum
- persistent toxicity
- symptoms
- patient’s preference

unfit or not willing to receive anticancer therapy

Surgery an option?
(AGO Score etc.)

Best supportive care
Best supportive care

Patients with recurrent ovarian cancer

Unfit or not willing to receive anticancer therapy

Surgery an option? (AGO Score etc.)

Platinum might not be the best option
- Early symptomatic relapse
- Progression on prior platinum
- Platinum intolerance/suboptimal response

Potentially platinum non-responsive

Non-platinum therapy
- Trabectedina/PLD

If indicated: plus bevacizumab

Platinum contraindicated
Javelin Ovarian 200
A prospective randomized Phase III

Progression-free survival by BICR

<table>
<thead>
<tr>
<th></th>
<th>Avelumab (N=188)</th>
<th>Avel. + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events, n (%)</td>
<td>154 (81.9)</td>
<td>134 (71.3)</td>
<td>125 (65.8)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>1.9 (1.8-1.9)</td>
<td>3.7 (3.3-5.1)</td>
<td>3.5 (2.1-4.0)</td>
</tr>
<tr>
<td>Stratified HR vs PLD (repeated CI)</td>
<td>1.68 (1.320; 2.101)</td>
<td>0.78 (0.567; 1.244)</td>
<td>-</td>
</tr>
<tr>
<td>p value vs PLD*</td>
<td>&gt;0.999</td>
<td>0.0301†</td>
<td>-</td>
</tr>
</tbody>
</table>

* 1-sided log-rank test; nominal p values (futility boundary was crossed at interim analysis)
† Did not reach significance threshold (>0.0025)

HR, hazard ratio
Patients with recurrent ovarian cancer

- unfit or not willing to receive anticancer therapy
- Surgery an option? (AGO Score etc.)
- Platinum might be the best option / re-challenge appears justified
  - response to prior platinum and no contraindication
- Eligible for platinum / potentially platinum responsive
  - No priority for symptomatic response or contraindications to bevacizumab or prior BEV
  - Platinum followed by PARPi after response to platinum (observed platinum response)
  - Priority for symptomatic response and no contraindications to bevacizumab, no prior BEV
  - offer platinum-based re-challenge plus bevacizumab

- tumour biology/histology
- number of prior lines of treatment
- prior response
- TFI for platinum
- persistent toxicity
- symptoms
- patient’s preference

Best supportive care
How to choose between bevacizumab and PARP-i
Phase 3 studies of bevacizumab in combination with chemotherapy for EOC: platinum-sensitive, recurrent setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>N</th>
<th>Median PFS (mo)</th>
<th>HR, p-value</th>
<th>Median OS (mo)</th>
<th>HR, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCEANS¹</td>
<td>C/gem + placebo</td>
<td>242</td>
<td>8.4</td>
<td>HR = 0.484</td>
<td>32.9</td>
<td>HR = 0.952</td>
</tr>
<tr>
<td></td>
<td>C/gem + bev until progression</td>
<td>242</td>
<td>12.4</td>
<td>p&lt;0.0001</td>
<td>33.6</td>
<td>p = 0.6479</td>
</tr>
<tr>
<td>GOG-0213²</td>
<td>C/P</td>
<td>337</td>
<td>10.4</td>
<td>HR = 0.628</td>
<td>37.3</td>
<td>HR = 0.829</td>
</tr>
<tr>
<td></td>
<td>C/P + bev</td>
<td>377</td>
<td>13.8</td>
<td>p&lt;0.0001</td>
<td>42.2</td>
<td>p = 0.056</td>
</tr>
</tbody>
</table>

C = carboplatin; P = paclitaxel
* eCRF analysis
Study 19: maintenance olaparib following response to platinum-based chemotherapy

Entry based on response to platinum-based therapy

Whole population with HGSOC


Design Concepts- Phase III Maintenance trials

- Treats residual disease after chemotherapy
  - Tumour shrinkage
  - Fall in CA125 levels
- Aim is to delay progression, extend time before further line of chemotherapy and increase survival

 Patients:
- Platinum-sensitive high-grade ovarian cancer
- $\geq 2$ previous platinum regimens
- Last chemotherapy was platinum-based, to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

SOLO-2
NOVA
ARIEL3
- OLAPARIB
- NIRAPARIB
- RUCAPARIB

PARP inhibitor
Randomised
Placebo
Treatment until disease progression

Primary end point: PFS

Efficacy of PARP inhibitors in \textit{BRCAm} patients

Primary endpoint: PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>g\textit{BRCAm}</th>
<th>PFS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO-2</td>
<td>g\textit{BRCAm}</td>
<td>19.1 vs 5.5</td>
<td>0.30 (0.22–0.41)</td>
</tr>
<tr>
<td>NOVA</td>
<td>g\textit{BRCAm}</td>
<td>14.8 vs 5.5</td>
<td>0.27 (0.18–0.40)</td>
</tr>
<tr>
<td>ARIEL-3</td>
<td>g\textit{BRCAm}</td>
<td>16.6 vs 5.4</td>
<td>0.23 (0.16–0.34)</td>
</tr>
</tbody>
</table>

\textit{BRCAm} patients should receive a PARP-i at time of PSR

**BRCA1/2 Mutations - a biomarker for activity of PARP inhibitors**

Hazard ratio for PFS benefit in maintenance studies in platinum sensitive relapse

<table>
<thead>
<tr>
<th>Study</th>
<th>BRCA mutant</th>
<th>BRCA wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 19 (olaparib)</td>
<td>0.18</td>
<td>0.54</td>
</tr>
<tr>
<td>SOLO 2 (olaparib)</td>
<td>0.30</td>
<td>NA</td>
</tr>
<tr>
<td>NOVA (niraparib)</td>
<td>0.27</td>
<td>0.45*</td>
</tr>
<tr>
<td>ARIEL 3 (rucaparib)</td>
<td>0.23</td>
<td>0.44/0.58</td>
</tr>
</tbody>
</table>

*included some somatic BRCA mutant patients

Platinum response defines this group

RECURRENT DISEASE

How should molecularly targeted therapy be integrated into the management of recurrent ovarian cancer?

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab in combination with platinum-based 2\textsuperscript{nd}-line chemotherapy (gemcitabine or paclitaxel) followed by bevacizumab maintenance has proven benefit with respect to tumour response rate and progression-free survival, and could be recommended</td>
<td>I</td>
<td>A</td>
<td>Yes : 95% (38 voters) Missing : 5% (2 voters)</td>
</tr>
<tr>
<td>Bevacizumab in combination with 2\textsuperscript{nd} or 3\textsuperscript{rd} line non-platinum chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin, topotecan) has proven benefit with respect to tumour response rate and progression-free survival, and has been associated with improvement in Quality of Life, and could be recommended</td>
<td>I</td>
<td>A</td>
<td>Yes : 95% (38 voters) Missing : 5% (2 voters)</td>
</tr>
<tr>
<td>PARP inhibitors (olaparib, niraparib and rucaparib) when given as maintenance therapy following a response to platinum-based 2\textsuperscript{nd}- or higher line of treatment have proven benefit with respect to progression-free survival, and could be recommended. The benefit is greatest in but not limited to patients with a BRCA\textsuperscript{mut}</td>
<td>I</td>
<td>A</td>
<td>Yee: 87.5% (35 voters) Missing:12.5% (5 voters)</td>
</tr>
<tr>
<td>PARP inhibitors (rucaparib*, olaparib) are active as monotherapy in patients with a BRCA mutation and could be considered (* 5/2018 only rucaparib currently licensed by EMA).</td>
<td>III</td>
<td>B</td>
<td>Yes : 95% (38 voters) Missing : 5% (2 voters)</td>
</tr>
</tbody>
</table>
Front-Line Treatment for Advanced Ovarian Cancer
May Include PARPi for all?

What is Our Plan for Treatment in a Post-PARPi World?

- Surgery (primary or IDS) + primary or adjuvant chemotherapy +/- bevacizumab + PARPi

First-Line Treatment Stage III, IV → First Response* → Relapse/Progression (70%-80%) → Second Response/Disease Stabilisation → Relapse/Progression (100%)

Follow-up

*Around 5% of patients are primary treatment-refractory, meaning disease progressed during therapy or within 4 weeks after the last dose.
IDS = Interval debulking surgery.
OReO: Olaparib Retreatment in Platinum-Sensitive Recurrent Ovarian Cancer

**Primary endpoint:** Investigator-assessed PFS

**Secondary endpoints:**
- OS
- TTP per GCIG
- TFST and TSST
- TDT
- HRQoL (FACT-O)
- Safety

- Relapsed non-mucinous EOC
- ≥4 cycles of platinum-based chemotherapy
- Documented BRCA1/2 status
- Treatment with one course of PARP inhibitor

### gBRCAmut or sBRCAmut

- 1 prior PARPi
  - ≥18 months after 1L chemotherapy
  - ≥12 months after ≥2L chemotherapy

### non-BRCAmt

- 1 prior PARPi
  - ≥12 months after 1L chemotherapy
  - ≥6 months after ≥2L chemotherapy

CR or PR to most recent platinum-based chemotherapy (no BEV)

Olaparib tablets 300 mg BID or last tolerable dose

Placebo
Besides maintainance…….
Chemotherapy–free PARP-i therapy
CAN PARP-I REPLACE CHEMOTHERAPY IN PLATINUM SENSITIVE SETTING?
**Olaparib Monotherapy versus Chemotherapy for Germline BRCA-Mutated Platinum-Sensitive Relapsed Ovarian Cancer Patients: Phase III SOLO3 Trial**

- **Study treatment administered until disease progression**

**Non-platinum chemotherapy**
- **PLD** (n=47)
- **Paclitaxel** (n=20)
- **Gemcitabine** (n=13)
- **Topotecan** (n=8)

**Primary endpoint**
- ORR by BICR (RECIST v1.1)

**Secondary endpoints**
- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

**Open-label**

* Prior treatment with a PARP inhibitor was not permitted;
† Fully platinum sensitive: progression >12 months after platinum-based chemotherapy; partially platinum sensitive: progression 6–12 months after platinum-based chemotherapy;
‡ For each patient, the investigator declared their choice of non-platinum chemotherapy before randomization;
§ PLD, 50 mg/m² on day 1 q4w; paclitaxel, 80 mg/m² on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m² on days 1, 8, and 15 q4w; topotecan, 4 mg/m² on days 1, 8, and 15 q4w

BICR, blinded independent central review; BRCAm, BRCA1 or BRCA2 mutation; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PLD, pegylated liposomal doxorubicin; q4w, every 4 weeks; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Penson et al ASCO 2019, JCO accepted
SOLO 3 Primary Endpoint: ORR by BICR

ORR 72%  

ORR 51%  

All patients*  
OR 2.53 (1.40, 4.58) $P=0.002$

*Patients with measurable disease at baseline

Penson et al ASCO 2019, JCO accepted
SOLO3: PFS (Intention-To-Treat Population)

Penson et al ASCO 2019, JCO accepted
What about chemotherapy-free PARP-i combinations?
Combining PARP Inhibitors With Anti-angiogenic Drugs

Increasing tumour hypoxia increases HRD

Randomized phase II trial of olaparib with or without cediranib in ‘platinum-sensitive’ ovarian cancer


AVANOVA2: Niraparib + bevacizumab versus niraparib in ‘platinum-sensitive’ relapsed ovarian cancer

Primary endpoint: PFS in the ITT population

Adjusted HR=0.35 (95% CI 0.21–0.57) p<0.0001

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At 5 Months</th>
<th>At 10 Months</th>
<th>At 15 Months</th>
<th>At 20 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib + bevacizumab</td>
<td>37</td>
<td>27</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Niraparib</td>
<td>25</td>
<td>12</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio

Mizra et al ASCO 2019
Anticipated Landscape of Future DDR Inhibitor Clinical Trials

Paradigm Changes

- **Front line**
  - 3-weekly Carboplatin–paclitaxel standard of care
  - Bevacizumab with and to follow chemotherapy (*BRCA*wt)
  - Olaparib to follow chemotherapy (*BRCA*+)
  - Olaparib, niraparib, veliparib to follow chemotherapy in all comers, with bevacizumab?

- **Second line: Platinum is an option**
  - Platinum based combination (paclitaxel, PLD or gemcitabine)
  - PARPi to follow chemotherapy (*BRCA*+ preferred but all comers)
  - Bevacizumab with and to follow chemotherapy (*BRCA*wt)

- **Second line: Platinum is not an option**
  - Single agent (PLD, Gemcitabine, Weekly paclitaxel)
  - Bevacizumab with and to follow chemotherapy (*BRCA*wt)

- **What’s next?**
  - New combinations in front line (PARP-i +/- IO +/- Bev)
  - PARPi +/- antiangiogenics +/-IO instead of chemo?
  - New combinations as maintenance? (PARP-i+cediranib; IO+Bev, PARP-i+IO)