Systemic Management of Ovarian Cancer

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Conflict of Interest Disclosure

- Participates in Advisory Boards of:
  
  Carrick Therapeutics Limited, Cue Biopharma, Debiopharm, Immunomedics, Innate Pharma, Merck-Serono, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, WntResearch

- Lecturer fee from:
  
  Merck-Serono, BMS, MSD
ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†

Epithelial Ovarian Cancer

Epidemiology

• Life-time risk is 1 in 54
• The crude incidence of ovarian cancer in the European Union is 18/100,000 women per year, the mortality is 12/100,000 women per year

• The median age at diagnosis is 63 years. The incidence increases with age and peaks in the 8th decade. Between the age of 70-74 years the age-specific incidence is 57/100,000 women per year

* ESMO minimum Clinical Recommendations 2008 and 2013 (Ann Oncol)
## Epithelial Ovarian Cancer

### Risk factors

- **Age, older** \(\uparrow\)
- **Nulliparity** \(\uparrow\)
- **Early menarche** \(\uparrow\)
- **Late menopause** \(\uparrow\)
- **Obesity and use of talcum**
- **Positive family history**
  - first degree relative with OC \(\rightarrow\) 2 fold increased risk
- **BRCA-1 mutation** \(\rightarrow\) 15%-45% OC risk (\(\leq 85\%\) BC risk)
- **BRCA-2 mutation** \(\rightarrow\) 10%-20% OC risk (\(\leq 85\%\) BC risk)

Ledermann et al. Ann Oncol 2013; 24 (suppl.6): vi24-vi32

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## Epithelial Ovarian Cancer: Subtypes

<table>
<thead>
<tr>
<th></th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percentages:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO I-II</td>
<td>39%</td>
<td>33%</td>
<td>22%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>FIGO III-IV</td>
<td>86%</td>
<td>2%</td>
<td>7%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Genetic Risk</strong></td>
<td>BRCA1/2</td>
<td>HNPCC</td>
<td>HNPCC</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td><strong>Other Risk Factors</strong></td>
<td>↓ Risk with OC, pregnancy</td>
<td>None known</td>
<td>↓ Risk with OC, ↑ Risk with HRT</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td><strong>Precursors</strong></td>
<td>STIC</td>
<td>Endometriosis</td>
<td>Endometriosis</td>
<td>Unknown</td>
<td>SBT</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Ascites, GI sx</td>
<td>Adnexal mass</td>
<td>Adnexal mass</td>
<td>Adnexal mass</td>
<td>GI sx</td>
</tr>
<tr>
<td><strong>Pattern of Spread</strong></td>
<td>Peritoneal, nodal</td>
<td>Peritoneal, nodal, distal</td>
<td>Peritoneal, nodal, distal</td>
<td>Peritoneal +/- Pseudomyxoma</td>
<td>Peritoneal, nodal</td>
</tr>
<tr>
<td><strong>Chemotherapy Response</strong></td>
<td>Sensitive, then resistant</td>
<td>Resistant</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td><strong>Molecular Genetics</strong></td>
<td>p53, BRCA1/2, PI3K, HRD</td>
<td>PI3K, ARID1A, MSI</td>
<td>PTEN, β catenin, ARID1A, MSI</td>
<td>KRAS, HER2</td>
<td>BRAF, KRAS, NRAS</td>
</tr>
<tr>
<td><strong>Targets</strong></td>
<td>PARP, Angiogenesis</td>
<td>Angiogenesis</td>
<td>ER, PR, mTOR</td>
<td>HER2/neu</td>
<td>BRAF, MEK/ERK</td>
</tr>
</tbody>
</table>

*Valencia Meeting 2015 (Bookman)*
Management of Early-Stage Ovarian Cancer FIGO I-IIa

- Grade and completeness of staging are the most strongest prognostic factors
- Low risk patients do not need chemotherapy as an adjuvant treatment (5-yr survival ≥ 95%)
- High-risk patients do need adjuvant platinum-based chemotherapy: combined analysis of ICON-1 and ACTION trial* showed 5-yr OS 82% vs 74%, p=.008
- Three vs six cycles: no significant difference in outcome, but recurrence rate with 6 cycles was 24% lower than with 3 cycles, and significantly more toxic**

*Trimbos et al, JNCI 2003; **Bell et al, Gynecol Oncol 2006
“Early-Stage” HGSC should be treated similar to advanced-stage HGSC.

The role of adjuvant chemotherapy in early-stage non-HGSC remains to be established.
Management of Advanced Epithelial Ovarian Cancer

Initial diagnosis
Advanced EOC
Assessment by qualified Gyn Oncol Surgeon

Primary debulking surgery
Complete resection of macroscopic disease
Incomplete resection
Extent of residual disease must be clearly documented

Neo-adjuvant chemotherapy
Not suitable for surgery
Interval debulking surgery
Macroscopic residual
No macroscopic residual

5th Ovarian Cancer Consensus Conference, Tokyo, Japan, November 2015
(Courtesy of Antonio González Martín)
Optimal Cytoreduction after PDS the Most Important Prognostic Factor in ADOVCA


Du Bois et al. Cancer 2009
Stage III Disease: Role of Histology

Data from GOG 111, 114, 132, 142, 158, 172 (IV only)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>412</td>
<td>980</td>
<td>1,392</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>60</td>
<td>106</td>
<td>166</td>
</tr>
<tr>
<td>Clear cell</td>
<td>21</td>
<td>41</td>
<td>62</td>
</tr>
<tr>
<td>Mucinous</td>
<td>6</td>
<td>28</td>
<td>34</td>
</tr>
</tbody>
</table>

Milestones in PFS for Epithelial Ovarian Cancer in Front-line Therapy

- **1986**: GOG-47, Cisplatin, HR 0.75
- **1996**:
- **2006**: GOG-111, Paclitaxel, HR 0.7
- **2011**:
- **2018**: SOLO-1, Olaparib, HR 0.3
- **2011**: GOG-172, Intraperitoneal, HR 0.8
- **2011**: GOG-218, Bevacizumab, HR 0.71

Courtesy of Antonio González Martin
Advanced Ovarian Cancer
1998-2019 Treatment

• Paclitaxel + Carboplatin (TC)
  – Generally agreed standard
  – “Control Arm” of most recent randomized trials
  – No other regimen shown to outperform it

• However, results far from perfect:
  – Median TTP: 12-18 mo
  – 5-Year OS: <35%
Systemic Therapy for Ovarian Cancer 2020
NCCN Guidelines: OC, version 1.2019


- Acceptable alternative schedules a/o route of administration
  - Weekly IV paclitaxel plus 3-weekly IV carboplatin (JGOG#3016)
  - Bevacizumab-containing regimens per ICON-7 or GOG-218
  - Intraperitoneal platinum-based chemotherapy (IPCT) in stage III patients after primary surgery with <1 cm residual disease*
  - HIPEC can be considered during IDS in stage III after NACT*

Fujiwara. Valencia meeting, 22.02.2019
*Not endorsed in the ESMO-ESGO conference (Milan 2018)
## Targeted Therapies in Ovarian Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ErbB kinases</strong></td>
<td>Gefitinib, erlotinib, lapatinib, canertinib, cetuximab, pertuzumab, matuzumab, trastuzumab</td>
</tr>
<tr>
<td><strong>MUC1 / PEM</strong></td>
<td>Pemtumomab</td>
</tr>
<tr>
<td><strong>MUC16 (CA 125)</strong></td>
<td>Oregovomab</td>
</tr>
<tr>
<td><strong>mTOR / AKT</strong></td>
<td>Temsirolimus, everolimus, deforolimus</td>
</tr>
<tr>
<td><strong>PARP</strong></td>
<td>Oleparib, veliparib, niraparib, rucaparib</td>
</tr>
<tr>
<td><strong>EpCAM</strong></td>
<td>Catumaxomab</td>
</tr>
<tr>
<td><strong>Apoptosis pathway</strong></td>
<td>AEG35156, OGX-011</td>
</tr>
<tr>
<td><strong>Angiogenesis</strong></td>
<td>Bevacizumab, sunitinib, sorafenib, pazopanib, cediranib, vatalanib</td>
</tr>
<tr>
<td><strong>Endothelial cells</strong></td>
<td>Combretastatin, Oxi4503</td>
</tr>
<tr>
<td><strong>Matrix metalloproteinases</strong></td>
<td>BAY 12-9566, marimastat</td>
</tr>
</tbody>
</table>
# Primary Anti-vascular Therapy with Maintenance or Only Maintenance in OC

<table>
<thead>
<tr>
<th></th>
<th>GOG 218 First Line with Maintenance(^1)</th>
<th>ICON 7 First Line with Maintenance(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>PFS (RECIST/CA 125/clinical)</td>
<td>PFS (RECIST)</td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td>OS</td>
<td>OS, RR</td>
</tr>
<tr>
<td><strong>Maintenance duration</strong></td>
<td>15 months maximum</td>
<td>12 months maximum</td>
</tr>
<tr>
<td><strong>Stopping rules</strong></td>
<td>GCIG (CA125)</td>
<td>RECIST PD</td>
</tr>
<tr>
<td><strong>Results (PFS in (\Delta) months)</strong></td>
<td>6 months (censored for CA125 only events)</td>
<td>5.4 months (high risk subgroup)</td>
</tr>
<tr>
<td><strong>Results (OS)</strong></td>
<td>NS</td>
<td>NS (all stages)</td>
</tr>
</tbody>
</table>

\(^1\) = Burger et al. NEJM 356: 2011, \(^2\) = Perren et al. NEJM 365: 2011, \(^3\)=Dubois et al.

*Modified from: Paul Sabbatini, MD; ASCO 2013*
Final Outcome Results

Survival of ICON 7 by Risk Group
(High Risk: Residual disease >1 cm/Stage IV)

Interaction: p=0.01

Non-high risk
HR 1.14
(0.93–1.40)
37% events

High risk
HR 0.78
(0.63–0.97)
66% events

Control
Research

BEV exposure

Time (months)
Recurrent Ovarian Cancer

Vermorken JB. Second line randomized trials in epithelial ovarian cancer; Int J Gynecol Cancer 2008; vol. 18 (suppl. 1): 59-66
Trials of Anti-Angiogenic Therapy in ROC

Platinum-refractory/resistant

- **AURELIA trial***
  - Single agent non-Pt vs non-Pt+bev→PFS↑ with combo
- **MITO-11 trial**
  - Wkly paclitaxel vs same plus pazopanib→ PFS↑ with combo

Platinum-sensitive disease

- **OCEANS trial** *
  - GCx6 vs GC/bevx6 → bevacizumab maintenance→PFS↑
- **ICON 6 trial** ++
  - Pt-based CTx6 vs Pt-based CTx6 plus cediranib vs Pt-based CTx6+cediranib→cediranib maintenance→PFS↑.

* JCO 2014; **Lancet Oncol 2015; + JCO 2012; ++ECCO 2013; ASCO 2017
Impact of Germline BRCA1/2 Mutations and PARP Inhibitors

- Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) is a key enzyme in the repair of DNA. Inhibition of PARP leads to accumulation of breaks in DS-DNA and cell death.

- Germline BRCA1/2 mutations are prognostic, and identify a population with improved outcomes, regardless of treatment.

- Mutations are also predictive for response to DNA-targeted chemotherapy (in general) and PARP inhibitors (in particular).

- PARP inhibitors might also be effective in high-grade serous tumors with BRCA-ness (loss of BRCA function).
Randomized Trial of Maintenance Olaparib in Platinum-sensitive High-Grade Serous Relapsed Ovarian Cancer

Study aim and design

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

265 patients

Olaparib 400 mg po bid
Randomized 1:1
Treatment until disease Progression
Placebo po bid

Primary end point: PFS

PFS in BRCA mutated patients

HR 0.18 (95% CI: 0.10-0.31)

# Confirmatory Studies in Platinum-Sensitive ROC with Germline BRCA Mutation

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>formul.</th>
<th>Pts</th>
<th>Median PFS (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledermann¹</td>
<td>Olaparib</td>
<td>caps</td>
<td>136</td>
<td>11.2 vs 4.3 (0.18)</td>
</tr>
<tr>
<td>Pujade²</td>
<td>Olaparib</td>
<td>tabl</td>
<td>295</td>
<td>19.1 vs 5.5 (0.30)</td>
</tr>
<tr>
<td>Coleman³</td>
<td>Rucaparib</td>
<td>tabl</td>
<td>196</td>
<td>16.6 vs 5.4 (0.23)</td>
</tr>
<tr>
<td>Mirza⁴</td>
<td>Niraparib</td>
<td>caps</td>
<td>203</td>
<td>21.0 vs 5.5 (0.27)</td>
</tr>
</tbody>
</table>

## Randomized Trial of Olaparib ± Cediranib in ‘Pt-sensitive’ relapsed ovarian cancer

**Dx platinum-sensitive recurrent ovarian cancer**

**Randomize 1:1**

**Olaparib capsules 400mg BID**

**Cediranib 30mg daily + Olaparib capsules 200mg BID**

**Disease progression by RECIST v1.1 criteria**

<table>
<thead>
<tr>
<th>BRCA mutation status</th>
<th>Olaparib (N = 46)</th>
<th>Cediranib/olaparib (N = 44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier</td>
<td>24 (52.2%)</td>
<td>23 (52.3%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Non-carrier</td>
<td>11 (23.9%)</td>
<td>12 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (23.9%)</td>
<td>9 (20.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior platinum-free interval</th>
<th>Olaparib (N = 46)</th>
<th>Cediranib/olaparib (N = 44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 months</td>
<td>26 (56.5%)</td>
<td>23 (52.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>20 (43.5%)</td>
<td>21 (47.7%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of prior lines</th>
<th>Olaparib (N = 46)</th>
<th>Cediranib/olaparib (N = 44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (37.0%)</td>
<td>26 (59.1%)</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>18 (39.1%)</td>
<td>10 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>11 (23.9%)</td>
<td>8 (18.2%)</td>
<td></td>
</tr>
</tbody>
</table>

*Presented by J. Liu (ASCO 2014; LBA #5500) and discussed by JA Ledermann*

*Published on-line in Lancet Oncology; September 10, 2014*
Combining Olaparib and Cediranib

• Increased overall response (n=90)
  – 47.8 % versus 79.6 % (p=0.002)
• Improved progression-free survival
  – Median PFS 9.0 versus 17.7 months (HR 0.42; 95% CI -.23-0.76)

No Chemotherapy!

Presented by J. Liu (LBA abstract #5500) and discussed by JA Ledermann
Published on-line in Lancet Oncology: September 10, 2014
Algorithm for selecting biological therapy in PS-ROC 2018

PFI > 6 months
BRCA?
Previous BEV 1L?

BEV 1L: YES
BRCA wt
Carbo Combo

BEV 1L: YES
BRCA mut
Carbo Combo

BEV 1L: NO
BRCA wt
Carbo-Gem-BEV Carbo-Pacli-BEV

BEV 1L: NO
BRCA mut
Carbo-Gem-BEV Carbo-Pacli-BEV

Olaparib maintenance

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# PARP-inhibitors Moving to First-Line*

<table>
<thead>
<tr>
<th>Study</th>
<th>PARPi</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG3005 (Abbvie)</td>
<td>veliparib</td>
<td>TC+placebo → placebo vs TC+veliparib → placebo vs TC+veliparib → veliparib</td>
</tr>
<tr>
<td>PAOLA-1 (GINECO)</td>
<td>olaparib</td>
<td>TC+Bev → Bev + olaparib vs TC+Bev → Bev + placebo</td>
</tr>
<tr>
<td>SOLO-1 (AZ)</td>
<td>olaparib</td>
<td>Olaparib vs placebo maintenance in BRCAm OC after Pt-based CT</td>
</tr>
<tr>
<td>PRIMA (tesaro)</td>
<td>niraparib</td>
<td>Niraparib vs placebo maintenance in BRCAm OC after Pt-based CT</td>
</tr>
</tbody>
</table>

Ray-Coquard, ESMO 2019
SOLO-1: Study Design

**Primary Endpoint:**
PFS (RECIST, BICR)

**Key Secondary Endpoints**
- OS, PFS2
- TFST, TSST, TDT
- HRQoL
- Safety

SOLO-1: Progression-free Survival

PAOLA-1: Study Design

Randomise 2:1 at end of chemotherapy N=806

Olaparib 300mg bid until progression

Placebo bid until progression

Primary Endpoint:
PFS (RECIST, BICR)

Key Secondary Endpoints
• OS, PFS2
• TFST, TSST, TDT
• HRQoL
• Safety

Newly diagnosed Stage III-IV

CR/PR/no evidence of disease upon completion of 1st line platinum plus bevacizumab. followed by bevacizumab. Maintenance

PAOLA-1 Progression-free Survival

Immunotherapy in Epithelial Ovarian cancer*

- Single agent CPI
  Response rates to CPIs are low, ranging from 6% to 22%
  Some impressive prolonged responses

- Multimodality immunotherapy (IT) strategies:
  - IT with chemotherapy
  - IT with other IT agents
  - IT with antiangiogenic therapy
  - IT with PARP inhibitors
  - IT + PARPi + antiangiogenic therapy

*Levinson et al. 2019 ASCO Eductional Book
Take-Home Messages (1)

- Upfront surgery ➔ 6 x TC-based CT standard for ADOVCA
- NACT with IDS reasonable alternative for some patients
- Three-weekly TC is still standard
- IPCT is a standard in patients with optimally resected EOC; HIPEC needs to be further investigated
- Anti-angiogenic agents added to cytotoxic therapy in first line may lead to survival benefit in far advanced disease
Take-Home Messages (2)

• Anti-angiogenic (AA) drugs are of benefit in patients with ROC: true for bevacizumab, also for oral TKIs with AA properties.

• PARP inhibitors are of benefit in patients with HGSC, in particular in patients with BRCAm.

• Combining olaparib and cediranib may herald the beginning of treatments that avoid cytotoxic chemotherapy in some OC patients.

• Reactivation of immune surveillance by blocking PD1 interaction with its ligands a promising approach for OC?
Thank you