4TH ESO-ESMO LATIN-AMERICAN MASTERCLASS IN CLINICAL ONCOLOGY

18-22 April 2018
Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
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Scientific Co-ordinators:
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Under the auspices of
CMO - European Society for Medical Oncology
SMeO - Sociedade Brasileira de Oncologia Médica
Epithelial Ovarian Cancer
Surgical and Systemic treatment

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4th ESO-ESMO Masterclass in Clinical Oncology in Latin-America, Mexico city, Mexico, April 18-22, 2018,
Conflict of Interest Disclosure

• Participates in Advisory Boards of:
  AstraZeneca, Incyte, Innate Pharma,
  Merck KGaA, Merck Sharp & Dome Corp,
  PCI Biotech, Synthon Biopharmaceuticals,

• Lecturer fee from:
  Merck-Serono, Sanofi, Bristol Myers Squibb
Epithelial Ovarian Cancer
Milestones

• Surgery according to FIGO guidelines
  – At least LND and peritoneal staging in early ovarian cancer
  – Upfront maximal surgical debulking in advanced ovarian cancer

• Chemotherapy evolution
  – Introduction of platinum compounds
  – Introduction of taxanes

• The set-up of international collaboration (1997)
Ovarian Cancer: FIGO Staging
Surgical exploration

Diagnostic
- Vertical incision
- Peritoneal fluid → cytology (or saline irrigation)
- Scrupulous inspection - right diaphragm
  - liver, serosa, parenchyma
- Biopsies of contralateral ovary, retroperitoneal LN and suspicious changes on the peritoneum, omentum

Therapeutic
- Early disease – TAH + BSO, omentectomy, LND
- Advanced disease – debulking surgery
FIGO Staging (2017) of Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Confined to one ovary, intact capsule, no tumor on surface (Ov;FT), no malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>IB</td>
<td>Confirmed to both ovaries (same criteria as IA)</td>
</tr>
<tr>
<td>IC</td>
<td>IA or IB + surgical spill/capsule rupture/tumor on surface/pos. cells</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension a/o implants on uterus a/o FT(s) a/o ovary(ies)</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic tissues, including bowel within the pelvis</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involves one or both ovaries or FTs or PPC with confirmed spread to peritoneum outside pelvis a/o metastases to retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>IIIA1i</td>
<td>LN metastasis ≤ 10 mm in greatest diameter</td>
</tr>
<tr>
<td>IIIA1ii</td>
<td>LN metastasis &gt; 10 mm in greatest diameter</td>
</tr>
<tr>
<td>IIIA2</td>
<td>Microscopic extrapelvic involvement w/wo RPLN, including bowel involvement</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastases beyond pelvis, ≤ 2 cm in diameter, including bowel involvement w/wo RPLN</td>
</tr>
<tr>
<td>IIIC</td>
<td>Peritoneal metastases beyond pelvic brim &gt; 2 cm a/o RPLN metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>Pleural metastases with positive cytology</td>
</tr>
<tr>
<td>IVB</td>
<td>Parenchymal metastases and metastases to extra-abdominal organs</td>
</tr>
</tbody>
</table>
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-Stage Ovarian Cancer
Stages IIb-III (IV)

- Upfront radical cytoreductive surgery*

- In case this is not possible, a second attempt should be made

- Platinum-taxane based chemotherapy

- Six cycles

- No second-look

*5th Consensus Meeting 2015 Tokyo (Japan): PCS or NACT→±ICS
# Prognostic Factors in Advanced-Stage Ovarian Cancer Stages IIb-IV

<table>
<thead>
<tr>
<th>Postsurgery Pre-chemotherapy</th>
<th>During Chemo</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Residual disease</td>
<td>Type of chemo</td>
<td>Time since last CT</td>
</tr>
<tr>
<td>• Performance status</td>
<td>CA 125 fall**</td>
<td>Disease bulk</td>
</tr>
<tr>
<td>• Stage</td>
<td>Interval debulking</td>
<td>Histology</td>
</tr>
<tr>
<td>• Grade</td>
<td></td>
<td>No. disease sites</td>
</tr>
<tr>
<td>• Age</td>
<td></td>
<td>Perf. Status</td>
</tr>
<tr>
<td>• Ascites</td>
<td></td>
<td>Time since DX</td>
</tr>
<tr>
<td>• Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Proliferation markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quantitative pathol. features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Molecular markers*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Eisenhauer EE et al. Ann Oncol 1999 (modified)*

*Bookman MA et al. Ann Oncol 2017 (including gBRCA1/2 and sBRCA1/2)*

Advanced Ovarian Cancer
1998-2018 Treatment

• 3-weekly 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%

How to Improve Outcome in Advanced OC Beyond PAC-CARBO

- Increase rate of optimal cytoreduction
  - NACT followed by IDS of benefit for some patients
- Increase efficacy of cytotoxic chemotherapy
  - Adding a third cytotoxic drug → no OS benefit
  - Maintenance/consolidation with cytotoxics → no OS benefit
  - Maintenance with targeted therapy improves PFS
  - Dose-dense therapy with taxanes improves PFS/OS??
- Modulate resistance
  - modulating agents no benefit in the clinic
  - Intraperitoneal chemotherapy improves OS (12 mo in OD pts)
- The use of targeted therapies
  - anti-angiogenic compounds and PARP inhibitors beneficial
Selection of Patients for NACT

- Two trials of NACT-ICS vs PDS in advanced stage III and IV EOC → similar poor outcome*

- NACT → reduction in perioperative morbidity related to
  - venous thromboembolism
  - infection
  - wound healing

- Candidates for NACT → bulky tumor deposits, large volume ascites, advanced physiologic age, comorbidities

* Vergote et al. NEJM 2010; 363: 943-953 and Kehoe et al. JCO 2013; 31: (suppl; abstr 5500)
# Targeted Therapies in Ovarian Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ErbB kinases</td>
<td>Gefitinib, erlotinib, lapatinib, canertinib, cetuximab, pertuzumab, matuzumab, trastuzumab</td>
</tr>
<tr>
<td>MUC1 / PEM</td>
<td>Pemtumomab</td>
</tr>
<tr>
<td>MUC16 (CA 125)</td>
<td>Oregovomab</td>
</tr>
<tr>
<td>mTOR / AKT</td>
<td>Temsirolimus, everolimus, deforolimus</td>
</tr>
<tr>
<td>PARP</td>
<td>Oleparib, veliparib, nirapanib</td>
</tr>
<tr>
<td>EpCAM</td>
<td>Catumaxomab</td>
</tr>
<tr>
<td>Apoptosis pathway</td>
<td>AEG35156, OGX-011</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Bevacizumab, sunitinib, sorafenib, pazopanib, cediranib, vatalanib</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Combretastatin, Oxi4503</td>
</tr>
<tr>
<td>Matrix metalloproteinases</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>
<th>Pazopanib Maintenance(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>PFS (RECIST/CA 125/ clinical)</td>
<td>PFS (RECIST)</td>
<td>PFS (RECIST)</td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td>OS</td>
<td>OS, RR</td>
<td>OS, Safety, PFS by GCIG, 3 yr PFS, QOL</td>
</tr>
<tr>
<td><strong>Maintenance duration</strong></td>
<td>15 months maximum</td>
<td>12 months maximum</td>
<td>24 months maximum</td>
</tr>
<tr>
<td><strong>Stopping rules</strong></td>
<td>GCIG (CA125)</td>
<td>RECIST PD</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>
<td>5.6 months</td>
</tr>
<tr>
<td><strong>Results (OS)</strong></td>
<td>NS</td>
<td>NS (all stages)</td>
<td>NS</td>
</tr>
</tbody>
</table>


Presented by: Paul Sabbatini, MD; ASCO 2013
Survival of ICON 7 by Risk Group
(High Risk: Residual disease >1 cm/ Stage IV)
## 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>
<th>Pazopanib Maintenance(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected Adverse Events (≥ G 3 unless specified)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Perforation (≥ G 2)</td>
<td>0.2%</td>
<td>1.3%</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>HTN (≥ G 2)</td>
<td>17%</td>
<td>18%</td>
<td>31% (grade ¾)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>n/r</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>n/r</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

\(^1\) Burger et al. NEJM 356: 2011, \(^2\) Perren et al. NEJM 365: 2011, \(^3\) Dubois et al. LBA 5503 / JCO 2014
Recurrent Ovarian Cancer

Vermorken JB. Second line randomized trials in epithelial ovarian cancer; Int J Gynecol Cancer 2008; vol. 18 (suppl. 1): 59-66
Recommended Guidelines for Chemotherapy in Relapsed Ovarian Cancer

- **Platinum resistant**
- **Platinum-free interval <6 months**
  - Non-platinum single agent: PLD, wkI paclitaxel, gemcitabine, topotecan

- **Partially Platinum sensitive**
- **6-12 months**
  - Combination chemotherapy: Platinum-based or trabectedin-PLD

- **Fully Platinum sensitive**
- **>12 months**
  - Carboplatin combination: PLD, paclitaxel, gemcitabine

PLD: pegylated liposomal doxorubicin

Valencia Meeting 2015 (E.Pujade-Laurain)
Trials of Anti-Angiogenic Therapy in ROC

Platinum-refractory/resistant

- **AURELIA trial***
  - Single agent non-Pt vs non-Pt+bev $\rightarrow$ PFS $\uparrow$ with combo

- **MITO-11 trial**
  - Wkly paclitaxel vs same plus pazopanib $\rightarrow$ PFS $\uparrow$ with combo

Platinum-sensitive disease

- **OCEANS trial**
  - GCx6 vs GC/bevx6 $\rightarrow$ bevacizumab maintenance $\rightarrow$ PFS $\uparrow$

- **ICON 6 trial**
  - Pt-based CTx6 vs Pt-based CTx6 plus cediranib vs Pt-based CTx6+cediranib $\rightarrow$ cediranib maintenance $\rightarrow$ PFS $\uparrow$.

* JCO 2014; **Lancet Oncol 2015; †JCO 2012; ‡ECCO 2013; ASCO 2017
Two Novel Approaches in ROC with Potential Impact for First-line Treatment

• The use of 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.
  - 30%-50% of HGSC may be susceptible to PARPi due to mutations in other HR repair genes in inhibition of BRCA function

• Immunotherapy, using immune checkpoint inhibitors (ICIs)
  - There are currently no approved immune therapies in ovarian cancer
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

Placebo
po bid

Randomized 1:1

Treatment until disease Progression

Primary end point: PFS

PFS in BRCA mutated patients

**Olaparib**
- Events/total patients (%): 26/74 (35%)
- Median PFS, months (95% CI): 11.2 (8.3-NC)
- HR 0.18 (95% CI: 0.10-0.31); p<0.0001

**Placebo**
- Events/total patients (%): 46/62 (74%)
- Median PFS, months (95% CI): 4.3 (3.0-5.4)

## 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>Ledermann</td>
<td>Olaparib</td>
<td>caps</td>
<td>136</td>
<td>11.2 vs 4.3 (0.18)</td>
</tr>
<tr>
<td>Pujade</td>
<td>Olaparib</td>
<td>tabl</td>
<td>295</td>
<td>19.1 vs 5.5 (0.30)</td>
</tr>
<tr>
<td>Coleman</td>
<td>Rucaparib</td>
<td>tabl</td>
<td>196</td>
<td>16.6 vs 5.4 (0.23)</td>
</tr>
<tr>
<td>Mirza</td>
<td>Niraparib</td>
<td>caps</td>
<td>203</td>
<td>21.0 vs 5.5 (0.27)</td>
</tr>
</tbody>
</table>

*Ledermann Lancet Oncol 2014; Pujade Lancet Oncol 2017; Coleman Lancet Oncol 2017; Mirza NEJM 2016*
Mirza MR et al. 

Kaplan-Meier estimates of PFS

A. Germline BRCA Mutation

B. No Germline BRCA Mutation with HRD Positivity

C. No Germline BRCA Mutation

Kaplan-Meier estimates of PFS
## Toxicity of PARP Inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Drug</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelmon 2011</td>
<td>phase II</td>
<td>Olaparib</td>
<td>fatigue, nausea, vomiting, decreased appetite</td>
</tr>
<tr>
<td>Kaufman 2015</td>
<td>phase II</td>
<td>Olaparib</td>
<td>fatigue, emesis, grade 3 or 4 anemia in 17%</td>
</tr>
<tr>
<td>Swisher 2017</td>
<td>phase II</td>
<td>Rucaparib</td>
<td>nausea in 75% (G3 in 4%) anemia, liverfunction test↑</td>
</tr>
<tr>
<td>Mirza 2016</td>
<td>maintenance</td>
<td>Niraparib</td>
<td>nausea in 74% (≥G3, 3%) ≥G3 PLT (33%), ANC(20%), anemia (25%)</td>
</tr>
</tbody>
</table>
Algorithm for selecting biological therapy in PS-ROC 2017

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

Carbo Combo

Olaparib maintenance

Trabectedin-PLD
If platinum is not an option

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# Drugs Interacting with PD-L1/PD1 Pathway in Ovarian Cancer*

<table>
<thead>
<tr>
<th>Drug</th>
<th>#Pts</th>
<th>Previous lines</th>
<th>Response %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>20</td>
<td>≥ 4 in 55%</td>
<td>15</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>26</td>
<td>≥ 5 in 38.5%</td>
<td>11.5</td>
</tr>
<tr>
<td>Avelumab</td>
<td>124</td>
<td>≥ 3 in 65.3%</td>
<td>9.7</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>12</td>
<td>≥ 6 in 58%</td>
<td>25</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>20</td>
<td>median 4</td>
<td>NR</td>
</tr>
</tbody>
</table>

*From Pujade-Lauraine, ESGO 2016
Take-Home Messages (1)

• Upfront surgery ➔ 6 x TC-based CT standard for ADOVCA
• NACT with IDS reasonable alternative for some patients
• Three-weekly paclitaxel/carboplatin (TC) still standard
• IPCT is standard in patients with optimally resected EOC
• 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 of benefit in patients with ROC: true for bevacizumab, also for oral TKIs with AA properties

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

• There is interest in 1) combined use of PARPi and AA drugs, 2) PARPi combined with cytotoxic agents, 3) the potential utility of a PARPi after a PARPi and 4) other novel approaches (e.g. combination with CPIs)

• Reactivation of immune surveillance by blocking PD1 interaction with its ligands a promising approach for OC?
Thank you
Interaction Between PARP Inhibitors and Anti-Angiogenic Therapies

- PARP inhibition reduces angiogenesis (Tentori 2007; Pyriochoou et al 2008)
- BRCA1 knockdown leads to increased VEGF production (Navaraj 2009)
- Lower levels of VEGF in breast cancer patients with BRCA1 mutation (Tarnowski et al 2004)
- Hypoxic cells more susceptible to PARP inhibitors (Olcina et al 2010)

Presented by: JA Ledermann (discussing abstract #LBA 5500)
Studies with Neoadjuvant Chemotherapy followed by IPCT or HIPEC

Provencher et al. OV21/PETROC
Ann Oncol 2018; 29: 431-438

Van Driel et al. HIPEC study
N Engl J Med 2018; 378;230-240

Arm 1: IV TC 3-weekly
Arm 2: IP cisplatin + paclitaxel IV (d1) and IP (d8)
Arm 3: IP carboplatin + paclitaxel IV (d1) and IP (d8)
Primary endpoint PD9 arm 3 vs arm 1 (24.5% vs 38.6%; p=0.065)

Three cycles NACT. When at least stable and debulkable to ≤ 10 mm → ICS either with or without HIPEC with cisplatin 100 mg/m².
Primary endpoint: PFS (HR 0.66 95%CI 0.50-0.87;p=0.003)