Optimal Treatment of Ovarian Cancer

Jan B. Vermorken, MD, PhD
Department of Medical Oncology
Antwerp University Hospital
Edegem, Belgium

XXVI Curso Avanzado de Oncologia Medica – El Escorial,
June 19, 2014
Outline

• Milestones in the treatment of ovarian cancer
• Standard management of advanced ovarian cancer
• Various ways to improve results beyond PAC-CARBO
• Potential roles of targeted therapies
• Types of relapsed ovarian cancer
• Strategies towards treatment of relapsed disease
• Take-home messages
Epithelial Ovarian Cancer
Epidemiology

- The 5th most common cancer type in women
- The 4th most common cause of cancer death in women
- 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

- Gender (women > men)  Multiple pregnancies↓
- Age, older↑  breast feeding↓
- Nulliparity↑  Oral contraceptives↓
- Early menarche↑  Tubal ligation↓
- Late menopause↑
- Obesity and use of talcum
- Positive family history
  - first degree relative with OC→ 2 fold increase
- BRCA-1 mutation →15%-45% OC risk (≤85% BC risk)
- BRCA-2 mutation→10%-20% OC risk (≤85% BC risk)

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

Common “Epithelial” Tumors

- Serous
- Endometrioid
- Clear cell
- Mucinous
- Brenner (transitional cell)
- Mixed epithelial tumors
- Undifferentiated
- Unclassified

Scully RE, Sobin LH, Serov SF, 1999 (WHO classification of Ovarian Epithelial Tumors)
# Two Types of Ovarian Cancer

<table>
<thead>
<tr>
<th>Type 1*</th>
<th>Type 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>High grade</td>
</tr>
<tr>
<td>Early stage</td>
<td>Advanced stage</td>
</tr>
<tr>
<td>Slow growing</td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

- Resistant to platinum-based therapy
- Ras/Raf and PTEN mutations
- IGFR expression
- Wild-type p53

- Responsive to platinum-based therapy
- Frequent p53 mutations
- BRCA1/2 mutations (20%)
- Activation of the PI3K pathway

*Low grade serous, endometrioid, mucinous, clear cell and malignant Brenner: ** HGSC, HGEC, malignant MMT and undifferentiated tumors

# Ovarian Cancer: FIGO Staging

## Surgical exploration

### Diagnostic
- Vertical incision
- Peritoneal fluid $\rightarrow$ 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
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Confirmed to one ovary, no ascites, intact capsule</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 + tumor surface/capsule rupture/pos. cells</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension to the uterus or tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIC</td>
<td>IIA or IIB + tumor surface/capsule rupture/pos. cells</td>
</tr>
<tr>
<td>III</td>
<td>One or both ovaries + extension outside pelvis or limited to true pelvis + extension to small bowel or omentum</td>
</tr>
<tr>
<td>IIIA</td>
<td>LN Θ, extension only microscopically</td>
</tr>
<tr>
<td>IIIIB</td>
<td>LN Θ, extension not exceeding 2 cm in diameter</td>
</tr>
<tr>
<td>IIIIC</td>
<td>LN + (RP/inguinal) and/or extension &gt;2 cm in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>One or both ovaries + DM (or parenchymal liver mets)</td>
</tr>
</tbody>
</table>
Epithelial Ovarian Cancer Milestones

• Surgery according to FIGO guidelines
  – At least LNS 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 the GCIG in 1997
Early-Stage Ovarian Cancer: Management 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 toxicity

*Trimbos et al, JNCI 2003
Bell et al, Gynecol Oncol 2006
Advanced-Stage Ovarian Cancer: Management Stages IIb-III (IV)

- Upfront radical cytoreductive surgery
- In case this is not possible, a second attempt should be made
- Platinum-based chemotherapy
- Six cycles
- No second-look

Consensus meeting, 1998 Bergen (the Netherlands)
### Prognostic Factors in Advanced-Stage Ovarian Cancer

**Stages IIb-IV**

<table>
<thead>
<tr>
<th>Postsurgery</th>
<th>During Chemo</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Postsurgery**
  - Residual disease
  - Performance status
  - Stage
  - Grade
  - Age
  - Ascites
  - **Histology**
  - Proliferation markers
  - Quantitative pathol. features
  - Ploidy
  - Molecular markers

- **During Chemo**
  - Type of chemo
  - CA 125 fall
  - Interval debulking

- **Relapse**
  - Time since last CT
  - Disease bulk
  - Histology
  - No. disease sites
  - Perf. Status
  - Time since DX

*Eisenhauer et al, 1999 (modified)*
# The Importance of Complete Cytoreduction

- Griffith 1975: cut-off >1.5 cm
- Hacker 1983: cut-off ≤ 5mm, and biology important
- Farias-Eisner 1992: no residual → median OS 56.5 months
  - moderate residual → OS 30.6 months
  - ext. carcinomatosis → OS 16.6 months
- Hoskins 1992: even when optimal debulked (≤ 1 cm)
  - extent of disease and no. of metastases prior to surgery prognostic
- Eisenkop 1998: complete rather than optimal
  - median OS 62.1 vs 20 months (p=0.001)

Advanced Ovarian Cancer
1998-2014 Treatment

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

- However, results far from perfect:
  - Median TTP: 15-18 mo
  - Median OS: <3 yrs
How to Improve Outcome in Advanced OC
Beyond PAC-CARBO

- Increase rate of optimal cytoreduction
  - NACT followed by IDS of benefit for some patients (2 trials)
- Increase efficacy of cytotoxic chemotherapy
  - adding a third cytotoxic drug → no OS benefit
  - maintenance/consolidation with cytotoxics → no OS benefit
  - Maintenance with targeted therapy??
  - 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)
Intraperitoneal Chemotherapy (IPCT)

**Optimally resected EOC**

- Combined use of IV and IP chemotherapy leads to a significant survival benefit in women with optimally debulked EOC (median + 12 mo).

- Based on the most recent trials, strong consideration should be given to a regimen with IP cisplatin (100 mg/m²) and a taxane (whether IV or IP).

- Toxicities, inconvenience and costs of IP therapy are justified by the improved survival.

January 5, 2006: Clinical Announcement of US NCI (3 large randomized trials [Alberts 1996; Markman 2001; Armstrong 2006])
IP Chemotherapy in ADOVCA

“It requires expertise and should be standard of care for optimally resected EOC patients”

Vermorken JB. Ann Oncol 2006; 17 (suppl. 10): x241-x246
Walker JL. Ann Oncol 2013; 24 (suppl. 10): x41-x45
# 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</td>
</tr>
<tr>
<td>EpCAM</td>
<td>Catumaxomob</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>Primary Endpoint</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>PFS (RECIST/CA 125/ clinical)</td>
<td>PFS (RECIST)</td>
<td>PFS (RECIST)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>OS</th>
<th>OS, RR</th>
<th>OS, Safety, PFS by GCIG, 3 yr PFS, QOL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Maintenance duration</th>
<th>15 months maximum</th>
<th>12 months maximum</th>
<th>24 months maximum</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Stopping rules</th>
<th>GCIG (CA125)</th>
<th>RECIST PD</th>
<th>RECIST PD</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Results (PFS in ∆ months)</th>
<th>6 months (censored for CA125 only events) subgroup</th>
<th>5.4 months (high risk) subgroup</th>
<th>5.6 months subgroup</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Results (OS)</th>
<th>NS</th>
<th>NS (all stages)</th>
<th>NS (immature)</th>
</tr>
</thead>
</table>

\(^1\) Burger et al. NEJM 356: 2011, \(^2\) Perren et al. NEJM 365: 2011, \(^3\) Dubois et al. LBA 5503

*Presented by: Paul Sabbatini, MD; ASCO 2013*
# Primary Anti-vascular Therapy with Maintenance or 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%</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, Dubois et al. LBA 5503
Molecular Subgroup of HGSOC as Predictor of outcome following Bevacizumab (Gourley et al, ASCO abstract #5502)

Edinburgh dataset; unsupervised hierarchical clustering

Discussed by: J. Ledermann
Outcome of ‘Immune’ and ‘Pro-angiogenic’ Groups of Ovarian Cancer in ICON 7*

**Control arm ICON 7**

Immune and pro-angiogenic groups

Gourley et al (ASCO abstract #5502)
Discussed by J. Ledermann
Outcome of ‘Immune’ and ‘Pro-angiogenic’ Groups of Ovarian Cancer in ICON 7*

Control arm
ICON 7
Immune and pro-angiogenic groups

Bevacizumab
Arm
Adverse effect on PFS in the immune subgroup
Benefit in pro-angiogenic group

Gourley et al (ASCO abstract #5502)
Discussed by J. Ledermann
Recurrent Ovarian Cancer: Important Issues

- Presentation (asymptomatic 55-70%; TFI*)
- Realistic goals
- When to treat
- How to treat
- New combinations and compounds

*<6 months; 6-12 months; <12 months
Chemotherapy Options in Platinum-Sensitive Recurrent Ovarian Cancer (ROC)

- ROC patients with TFI > 6 mo are retreated with Pt-based chemotherapy (*ICON-4 trial: TC>Pt-alone (PFS and OS↑*)

- Alternatives for TC in case of persistent neurotoxicity after first-line chemotherapy
  - Gemcitabine/carboplatin (GC)
  - Pegylated liposomal doxorubicin/carboplatin (PLDC)

- Targeted therapies can be added to these regimens, such as:
  - PARP inhibitors (e.g. olaparib)
  - Anti-angiogenic compounds (e.g. bevacizumab, pazopanib)
Chemotherapy Options in Platinum-Resistant or Partially Pt-sensitive (TFI 6-12 mo) ROC

- Numerous agents are available that can be used as a single agent:
  - gemcitabine, PLD, topotecan, paclitaxel, docetaxel, oral etoposide, altretamine, trabectedin, lurbinectedin, and hormonal agents and other targeted agents

- Take into consideration the patient’s anticipated tolerability and cumulative toxicity from front-line therapy
**Trials of Anti-Angiogenic Therapy in ROC**

### Platinum-sensitive disease
- **OCEANS trial** (JCO 2012)
  - GCx6 vs GC/bevx6 → bev maintenance (**improved PFS**)
- **ICON 6 trial** (ECCO 2013)
  - Placebo controlled trial of Pt-based CTx6 vs Pt-based CTx6 + cediranib vs Pt-based CTx6+cediranib → maintenance cediranib
  - The maintenance arm showed significantly **improved PFS and OS**

### Platinum-refractory/resistant
- **AURELIA trial** (JCO 2014)
  - Single agent non-Pt vs single agent non-Pt+bevacizumab (**PFS↑**)
- **MITO-11 trial** (ASCO 2014, abstract#5503)*
  - Adding pazopanib to weekly paclitaxel until PD or unacceptable toxicity in a phase II study, showing significantly **improved PFS** (OS, p=0.07)

*Presented by S. Pignata and discussed by J. Ledermann at ASCO 2014*
Trials of Anti-Angiogenic Therapy in ROC

Platinum-sensitive disease

- **OCEANS trial** (JCO 2012)
  - GCx6 vs GC/bevx6 → bev maintenance (*improved PFS*)
- **ICON 6 trial** (ECCO 2013)
  - Placebo controlled trial of Pt-based CTx6 vs Pt-based CTx6 plus cediranib vs Pt-based CTx6+cediranib → maintenance cediranib
    The maintenance arm showed significantly *improved PFS and OS*

Platinum-refractory/resistant

- **AURELIA trial** (JCO 2014)
  - Single agent non-Pt vs single agent non-Pt+bevacizumab (**PFS↑**)
- **MITO-11 trial** (ASCO 2014, abstract#5503)*
  - Adding pazopanib to weekly paclitaxel until PD or unacceptable toxicity in a phase II study, showing significantly *improved PFS (OS, p=0.07)*

*Presented by S. Pignata and discussed by J. Ledermann at ASCO 2014*
Anti-Angiogenic Therapy Augments Tumor Response to Chemotherapy

Presented by: Jonathan Ledermann
Progression-free survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>36</td>
<td>36</td>
<td>3.5</td>
<td>2.0-5.7</td>
</tr>
<tr>
<td>Paclitaxel + Pazopanib</td>
<td>37</td>
<td>37</td>
<td>6.3</td>
<td>5.4-11</td>
</tr>
</tbody>
</table>

1-tailed P=0.0002 HR 0.42 (95% CI 0.25-0.69)

Patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>wP</th>
<th>WPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Presented by: S.Pignata and discussed by J. Ledermann
Progression-free survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>36</td>
<td>36</td>
<td>3.5</td>
<td>2.0-5.7</td>
</tr>
<tr>
<td>Paclitaxel + Pazopanib</td>
<td>37</td>
<td>37</td>
<td>6.3</td>
<td>5.4-11</td>
</tr>
</tbody>
</table>

1-tailed P=0.0002, HR 0.42 (95% CI 0.25-0.69)

Presented by: S. Pignata and discussed by J. Ledermann
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.

- PARP inhibitors are in particular exciting in cancers with germline mutations in the BRCA gene, but benefit might be wider (> 50% of patients with high-grade sporadic EOC possibly have loss of BRCA function)
  - Continuous oral olaparib (AZD 2281) → 57.6% clinical benefit
  - Randomized phase II (TC vs TC+olaparib→olaparib) showed HR for PFS 0.51 (p=0.0012) ASCO 2012
Progression-free survival*

Events: Total patients (%) 47:81 (58.0) 55:81 (67.9)
Median (months) 12.2 9.6
Hazard ratio = 0.51
95% CI (0.34, 0.77)

P = 0.0012

Presented by J. Ledermann, ASCO 2012
Olaparib in Platinum Sensitive Relapsed Ovarian Ca

**Trial Design**
- Randomized double blind placebo controlled phase II study, n = 265\(^1\)
- Platinum sensitive relapse with CR or PR
- Primary endpoint = PFS
- Secondary endpoints = PFS (CA-125), ORR, QOL
- Subsequent analysis BRCA\text{m} vs. BRCA\text{wt}

**Results**

- **PFS by BRCA\text{m} status**

  - BRCA\text{m} vs. BRCA\text{wt}
  - No change OS, Increase QOL

- **Time to second subsequent therapy (PFS2)**

  - BRCA\text{m} vs. BRCA\text{wt}
  - No change OS, Increase QOL

---

\(^1\)Ledermann et al. NEJM 366, 2012; Ledermann et al. ASCO 2013; abstract #5505
Interaction Between PARP Inhibitors and Anti-Angiogenic Therapies

- PARP inhibition reduces angiogenesis (Tentori 2007; Pyriochou 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 #IBA 5500)
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 (LBA #5500) and discussed by JA Ledermann
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)

Presented by J. Liu (LBA abstract #5500) and discussed by JA Ledermann
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-.76)

No Chemotherapy!

Presented by J. Liu (LBA abstract #5500) and discussed by JA Ledermann
PFS in Pt-Sensitive ROC: Pt-based chemotherapy a/o Targeted Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>PFS (med months)</th>
<th>% 1st relapse</th>
<th>% 6-12 m PFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCEANS C/Gem</td>
<td>8.4</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td><strong>OCEANS + bev</strong></td>
<td><strong>12.4</strong></td>
<td><strong>100</strong></td>
<td><strong>41</strong></td>
</tr>
<tr>
<td>CALYPSO C/Pax</td>
<td>9.4</td>
<td>83</td>
<td>36</td>
</tr>
<tr>
<td>CALYPSO C/PLD</td>
<td>11.3</td>
<td>83</td>
<td>36</td>
</tr>
<tr>
<td>ICON 4 C/Pax</td>
<td>12.0</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>OVAR 2.5 C/Gem</td>
<td>8.6</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>ICON 6 Plat-based</td>
<td>8.7</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td><strong>ICON 6 +cediranib</strong></td>
<td><strong>11.1</strong></td>
<td><strong>100</strong></td>
<td><strong>30</strong></td>
</tr>
<tr>
<td>OLAPARIB</td>
<td>9.0</td>
<td>37</td>
<td>57</td>
</tr>
<tr>
<td><strong>OLAPARIB + CEDIRANIB</strong></td>
<td><strong>17.7</strong></td>
<td><strong>59</strong></td>
<td><strong>52</strong></td>
</tr>
</tbody>
</table>

Abstract #5500 discussed by JA Ledermann
Toxicity

- Most side effects driven by cediranib
  - Hypertension
  - Diarrhoea
  - Fatigue
- Very little myelotoxicity
- 77% dose reduction cediranib/olaparib - one or both?
- 24% dose reduction in olaparib alone (400mg bd)
- 6 patients withdrawn from combination arm for toxicity and other non progression reasons (4 from olaparib alone)

Presented by: JA Ledermann
Take-Home Messages (1)

- Upfront surgery followed by 6 cycles of Pt-Tax-based CT is still standard for the treatment of advanced EOC
- For patients with bulky tumor deposits, large volume ascites, advanced physiologic age, or comorbidities NACT with IDS might be a reasonable alternative
- Dose-dense TC seems preferable over standard TC
- 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
- We are beginning to identify patients who might/might not benefit from first-line bevacizumab
Take-Home Messages (2)

- Anti-angiogenic drugs are of benefit also in patients with recurrent ovarian cancer; this is true for bevacizumab, but also for the oral tyrosine kinase inhibitors with anti-angiogenic properties.

- PARP inhibitors are of benefit in patients with BRCAm, but also in those with BRCAwt.

- Combining olaparib and cediranib may herald the beginning of treatments that avoid cytotoxic chemotherapy in some patients with ovarian cancer.