OVARIAN CANCER

Domenico Priolo

Oncologia Medica Taormina
ADVANCED OVARIAN CANCER

**treatment strategy**

- 80% of patients have carcinosis at initial diagnosis (stage III – IV)
- Multidisciplinary treatment (dedicated team: gynecologic surgeon, oncologist, pathologist, radiologist)
- Initial maximal cytoreductive effort (expertise in a high-volume activity Center)
- Platinum-taxane based chemotherapy (bevacizumab)
- No maintenance chemotherapy (antiangiogenic therapy)
Data from an individual patient meta-analysis of three randomised phase III trials with 3,126 patients from AGO GINECO

5-year survival rate

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–10mm vs 0mm:</td>
</tr>
<tr>
<td>2.70 (2.37, 3.07)</td>
</tr>
<tr>
<td>&gt;10mm vs 1–10mm:</td>
</tr>
<tr>
<td>1.34 (1.21, 1.49)</td>
</tr>
</tbody>
</table>

log-rank: p<0.0001

Overall survival (%) vs Time (months)

0mm

1–10mm

>10mm

Primary Therapy → \( P_1 S \) → 1st complete remission → \( P_2 S \) → potentially platinum sensitive disease → \( P_3 S \) → \( P_4 S \) → Clinical complete remission

Refractory/Persistent Disease

DEATH

from Dizon et al, JCO 2002
OVARIAN CANCER

- Standard front-line chemotherapy
- Weekly regimens
- Maintenance therapy
- Role of neoadjuvant chemotherapy
- Second-line chemotherapy
- BRCAness and PARP inhibitors
OVARIAN CANCER

- Standard front-line chemotherapy
- Weekly regimens
- Maintenance therapy
- Role of neoadjuvant chemotherapy
- Second-line chemotherapy
- BRCAness and PARP inhibitors
# PACLITAXEL-CARBOPLATIN still the gold standard ?!

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Treatment</th>
<th>PFS</th>
<th>OS</th>
<th>Toxicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>GOG 111, OV10</td>
<td>CDDP-TAX</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&lt;&lt;</td>
<td>PFS &gt;&gt; OS &gt;&gt; Toxicity &lt;&lt;</td>
</tr>
<tr>
<td></td>
<td>Dutch-Danish, AGO, GOG158</td>
<td>CBDCA-TAX</td>
<td></td>
<td></td>
<td></td>
<td>No advantage &gt;&gt; Toxicity</td>
</tr>
<tr>
<td></td>
<td>AGO-GINECO Euro Canadian</td>
<td>CBDCA-TAX-EPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AGO-GINECO MITO1</td>
<td>CBDCA-TAX ➔ TPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GOG182 - ICON 5</td>
<td>5 regimens: triplets sequential doublets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>SCOTROC1 MITO2</td>
<td>CBDCA-TXT CBDCA-PLD</td>
<td></td>
<td></td>
<td></td>
<td>NS, different tox</td>
</tr>
<tr>
<td></td>
<td>GOG 218, ICON 7</td>
<td>CBDCA-TAX-BEVA ➔ BEVA</td>
<td></td>
<td></td>
<td></td>
<td>PFS &gt; costs &gt;&gt; New standard !?</td>
</tr>
</tbody>
</table>
**GOG-0218: study schema**

**Front-line:** epithelial OV, PP or FT cancer
- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1.873

- Stratification variables
- GOG performance status
- Stage/debulking status

OV: ovarian; PP: primary peritoneal; FT: fallopian tube; BEV: bevacizumab

---

**Study Schema**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-P</td>
</tr>
<tr>
<td>II</td>
<td>CP + BEV</td>
</tr>
<tr>
<td>III</td>
<td>CP + BEV</td>
</tr>
</tbody>
</table>

Paclitaxel (P) 175 mg/m$^2$
Carboplatin (C) AUC 6

15 months

Burger et al. ASCO 2010
GOG-0218: significantly increased PFS with continued bevacizumab compared with standard CT

<table>
<thead>
<tr>
<th>Arm</th>
<th>Event (%)</th>
<th>Median PFS (months)</th>
<th>Stratified analysis HR (95% CI)</th>
<th>p value one-sided (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CP + Pla → Pla (n=625)</td>
<td>423 (67.7)</td>
<td>CP + Bev → Pla (n=625)</td>
<td>10.3</td>
</tr>
<tr>
<td>II</td>
<td>CP + Bev → Pla (n=625)</td>
<td>418 (66.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>CP + Bev → Bev (n=623)</td>
<td>360 (57.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p value boundary = 0.0116
GOG-0218: significant, 6-month improvement in PFS in regulatory analysis (CA-125 censored) with continued beva vs chemotherapy

<table>
<thead>
<tr>
<th>I CP + PI</th>
<th>III CP + B15 → B15</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=625)</td>
<td>(n=623)</td>
</tr>
</tbody>
</table>

- No. of patients with event (%): 339 (54.2) vs 255 (40.9)
- Median PFS (months): 12.0 vs 18.0
- Stratified analysis HR (95% CI): 0.645 (0.551–0.756)
- p value one-sided (log rank): <0.0001*

Censored for CA-125 (%): 20% vs 29%

*p value boundary = 0.0116
Stratification variables:

- Stage & extent of debulking: I–III debulked ≤1 cm vs stage I–III debulked >1 cm vs stage IV and inoperable stage III
- Timing of intended treatment start: ≤4 vs >4 weeks after surgery
- GCIG group

18 cycles

Bevacizumab 7.5 mg/kg q3w

Paclitaxel 175 mg/m²
Carboplatino AUC6

*Dec 2006 to Feb 2009
OS: High-risk subgroup

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>234</td>
<td>231</td>
</tr>
<tr>
<td>234</td>
<td>219</td>
<td>222</td>
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<tr>
<td>219</td>
<td>194</td>
<td>208</td>
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<tr>
<td>194</td>
<td>166</td>
<td>186</td>
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<tr>
<td>166</td>
<td>107</td>
<td>134</td>
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<tr>
<td>107</td>
<td>46</td>
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<tr>
<td>46</td>
<td>15</td>
<td>18</td>
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</table>

Deaths, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>109 (47)</td>
<td>79 (34)</td>
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</tbody>
</table>

Median, months

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>28.8</td>
<td>36.6</td>
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Log-rank test

<table>
<thead>
<tr>
<th></th>
<th>p=0.002</th>
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HR (95% CI)

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<thead>
<tr>
<th></th>
<th>0.64 (0.48 – 0.85)</th>
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</table>

1-year OS rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86</td>
<td>92</td>
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Number at risk

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>107</td>
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<td>46</td>
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<td>18</td>
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<td>15</td>
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</tbody>
</table>
Front-line chemotherapy + BEVA
Conclusions

- Two randomized studies show chemotherapy plus BEVA prolongs PFS (stage III B – IV)
- Overall survival benefit to date observed only in high-risk subgroup (ICON-7)
- Maintenance duration still to establish
- Molecular subtypes influencing outcome?
OVARIAN CANCER

- Standard front-line chemotherapy
- **Weekly regimens**
- Maintenance therapy
- Role of neoadjuvant chemotherapy
- Second-line chemotherapy
- BRCAness and PARP inhibitors
Role of weekly paclitaxel in ovarian cancer

**JGOG Study**

**Stratification**
- Residual disease
- FIGO stage
- Histology

**OVARIAN CANCER**
**FIGO III-IV**

- TC (c-TC) paclitaxel 180 mg/m² g1 carboplatino AUC 6,0 g1 ogni 21 giorni per 6-9 cicli
- Dose-dense weekly TC (dd-TC) paclitaxel 80 mg/m² g1, 8, 15 carboplatino AUC 6,0 g1 ogni 21 giorni per 6-9 cicli

- **Primary end-point:** PFS
- **637 patients**

*Katsumata N et al. Lancet 2009*
JGOG Study: PFS

Katsumata N et al. Lancet 2009

<table>
<thead>
<tr>
<th>Trattamento</th>
<th>n</th>
<th>Eventi</th>
<th>PFS mediana, mesi</th>
<th>p</th>
<th>HR</th>
<th>IC 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-TC</td>
<td>319</td>
<td>200</td>
<td>17,2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>160</td>
<td>28,0</td>
<td>0,0015</td>
<td>0,714</td>
<td>0,581-0,879</td>
</tr>
</tbody>
</table>
JGOG Study: Overall Survival

Katsumata N et al. Lancet 2009

<table>
<thead>
<tr>
<th>Trattamento</th>
<th>n</th>
<th>Eventi</th>
<th>Overall Survival a 3 anni, (%)</th>
<th>p</th>
<th>HR</th>
<th>IC 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-TC</td>
<td>319</td>
<td>124</td>
<td>65,1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>96</td>
<td>72,1%</td>
<td>0,03</td>
<td>0,75</td>
<td>0,57-0,98</td>
</tr>
</tbody>
</table>

HR 0.75 (95% CI 0.57–0.98); p=0.03
Aim of the trial is to compare the two schedules in terms of quality of life and PFS.

**Conclusions:** Compared to standard CP every 3 weeks, weekly CP did not demonstrate a significant benefit in PFS, but was associated with better QoL and toxicity.

Primary end-point: QoL, PFS (amendment)
Secondary end-points: OS, ORR, toxicity
Estimated accrual: 650 pts
OVARIAN CANCER

- Standard front-line chemotherapy
- Weekly regimens
  - **Maintenance therapy**
  - Role of neoadjuvant chemotherapy
  - Second-line chemotherapy
  - BRCAness and PARP inhibitors
Maintenance Taxol therapy

**Markman M, JCO 2003**

Advanced Ovarian, Fallopian Tube, or Primary peritoneal cancer after Cytoreductive surgery + Platin-paclitaxel chemotherapy

Clinically defined CR

TAX q 4 wks x 3 months

TAX q 4 weeks x 12 months

Is 7 month improvement in PFS sufficient to justify the additional 9 months of therapy and related toxicity?
AGO-OVAR16

A phase III study to evaluate the efficacy and safety of pazopanib monotherapy versus placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer

**Conclusions:** Pazopanib maintenance therapy provided a statistically significant and clinically meaningful PFS benefit in patients with AEOC; OS data are not mature.

Patients=900

Leading=AGO-OVAR

Participating=AGO Austria, ANZGOG, BGOG, GEICO, GINECO, ICORG, JGOG, KGOG, MANGO, MITO, NSGO, US-Sites: California Consortium, NY GOG, SWOG
OVARIAN CANCER

- Standard front-line chemotherapy
- Weekly regimens
- Maintenance therapy

- Role of neoadjuvant chemotherapy
- Second-line chemotherapy
- BRCAness and PARP inhibitors
Primary optimal debulking surgery (i.e. no residual tumor) by a gynecologic oncologist remains the standard of care.

The role of neoadjuvant chemotherapy followed by interval debulking surgery can only be defined in a randomized study.
Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

Ovarian, tuba or peritoneal cancer
FIGO stage IIIc-IV (n = 718)

NACT + IDS versus PDS: ITT

**Progression-free survival**

- Median PFS
  - PDS: 12 months
  - IDS: 12 months
  - HR for IDS: 0.99 (0.87, 1.13)

NACT + IDS versus PDS: ITT

**Overall survival**

- Median survival
  - PDS: 29 months
  - IDS: 30 months
  - HR for IDS: 0.98 (0.85, 1.14)
**MRC CHORUS trial**

*Sean Kehoe et al, ASCO 2013*

550 women (276 PS, 274 NACT) were randomized from 74 centres (72 UK, 2 NZ) between Mar 2004 and Aug 2010.

Conclusions: NACT was associated with increased optimal debulking, less early mortality and similar survival in this poor prognosis group. CHORUS results are consistent with EORTC55971 and strengthen evidence that NACT is a viable alternative to PS.

**JCOG0602 trial**

*Takashi ONDA et al, ASCO 2014*

JCOG0602 is now ongoing and the primary analysis of OS is planned in 2016. 301 women (149 PS, 152 NACT) were randomized.

Conclusions: invasiveness of treatment (Tx) with NACT was inferior than with standard treatment. When non-inferior survival will be confirmed in this trial and new staging system is established, Tx with NACT can become a new standard Tx for advanced ovarian cancer.
OVARIAN CANCER

- Standard front-line chemotherapy
- Weekly regimens
- Maintenance therapy
- Role of neoadjuvant chemotherapy
- Second-line chemotherapy
- BRCAness and PARP inhibitors
Advanced ovarian cancer: a chronic disease

After first-line chemotherapy ...

The largest group (>60% of pts) can achieve real benefit from salvage chemotherapy
Prognostic factors in recurrent ovarian cancer

- long interval from diagnosis
- long chemotherapy-free interval
- good performance status
- small number of tumor sites
- small diameter of lesions
- non mucinous / clear cell carcinoma
- normal hemoglobin levels
Recurrent Ovarian Cancer: Definition of Disease Sensitivity

- **Sensitivity Categories**
  - Very sensitive
  - Sensitive
  - Resistant
  - Refractory

- **Time to Recurrence (Mos)**
  - 0
  - 3
  - 6
  - 12
  - 18
  - 24
RELAPSED DISEASE

three subsets of patients

- **PLATINUM-SENSITIVE**
  - PFI = > 12 months

- **PARTIALLY-SENSITIVE**
  - PFI = 6-12 months

- **PLATINUM-RESISTANT**
  - PFI = < 6 months

Three different scenarios with several open questions
ICON 4: Platinum vs Platinum-Paclitaxel

N = 802 (776 evaluable)

<table>
<thead>
<tr>
<th></th>
<th>Platinum</th>
<th>Platinum + Paclitaxel</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum sensitive, %</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Response rate, %</td>
<td>54</td>
<td>66</td>
<td>.06</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>9</td>
<td>12</td>
<td>.0004</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>24</td>
<td>29</td>
<td>.02</td>
</tr>
</tbody>
</table>

Phase III Trial of Carboplatin/Gemcitabine: AGO Study Design

Gemcitabine 1000 mg/m² Days 1, 8
Carboplatin AUC 4 Day 1
q3w for 6 cycles*

Carboplatin AUC 5 Day 1
q3w for 6 cycles*

*Patients were treated for 6 cycles in the absence of progressive disease or unacceptable toxicity.
At investigator discretion, benefiting patients could receive a maximum of 10 cycles.

**PLATINUM-SENSITIVE**

**CALYPSO Study Schema**

International, Intergroup, Open-label, Randomized Phase III Study

Ovarian cancer in relapse > 6 mos after first- or second-line platinum + taxane chemotherapy

Stratification
- Center
- Measureable disease (yes vs no)
- Therapy-free interval (6-12 mos vs > 12 mos)

Experimental arm: CD
- PLD 30 mg/m² IV Day 1
- Carboplatin AUC 5 Day 1
- q28 days x 6 courses

Control arm: CP
- Paclitaxel 175 mg/m² IV Day 1
- Carboplatin AUC 5 Day 1
- q21 days x 6 courses
Calypso  Progression-Free Survival (ITT): Primary Endpoint


<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>11.3</td>
<td>9.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.72-0.94)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value (superiority)</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>P value (noninferiority)</td>
<td>&lt; .001</td>
<td></td>
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</tbody>
</table>

Patients at Risk, n

<table>
<thead>
<tr>
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<th>CP</th>
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<tbody>
<tr>
<td>Mos From Randomization</td>
<td>467</td>
<td>397</td>
</tr>
<tr>
<td></td>
<td>509</td>
<td>405</td>
</tr>
</tbody>
</table>

Calypso  PFS 6-12 Month Segment

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>CP</th>
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</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>9.4</td>
<td>8.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.58, 0.90)</td>
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</tr>
<tr>
<td>Log-rank P-value (superiority)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>P-value (non-inferiority)</td>
<td>&lt;0.001</td>
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</table>

Months from Randomisation
Carboplatin + PLD is the only platinum-based combination compared with the standard regimen (paclitaxel+carboplatin)

A non-inferiority study achieving a PFS advantage in experimental arm

More trombocytopenia in PLD-carboplatin arm

Less neuropathy and alopecia in PLD-carboplatin arm

Less allergic reactions to carboplatin rechallenge in PLD arm
OCEANS: Study Design

Platinum-sensitive recurrent ovarian cancer (N = 484)
- Measurable disease
- 1 prior chemotherapy regimen
- No prior bevacizumab
- ECOG PS 0-1

Randomize

1:1

Carboplatin AUC 4
Gemcitabine 1000 mg/m²
Placebo

Carboplatin AUC 4
Gemcitabine 1000 mg/m²
Bevacizumab 15 mg/kg

Stratification variables
- Platinum-free interval (6-12 months vs > 12 months)
- Cytoreductive surgery for recurrent disease
OCEANS: PFS

<table>
<thead>
<tr>
<th></th>
<th>CG + PL (n=242)</th>
<th>CG + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>187 (77)</td>
<td>151 (62)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.4 (8.3–9.7)</td>
<td>12.4 (11.4–12.7)</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.484 (0.388–0.605)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
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No. at risk

<table>
<thead>
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<th>CG + PL</th>
<th>CG + BV</th>
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<tbody>
<tr>
<td>0</td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>6</td>
<td>177</td>
<td>203</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>92</td>
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<td>18</td>
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<td>11</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
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</tbody>
</table>
OCEANS: objective response

Difference: 21.1%

$p < 0.0001$

Duration of response

<table>
<thead>
<tr>
<th></th>
<th>CG + PL (n=139)</th>
<th>CG + BV (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>7.4</td>
<td>10.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.534</td>
<td>0.408–0.698</td>
</tr>
</tbody>
</table>

*p < 0.0001*

*aCompared for descriptive purposes only*
MITO-16/MaNGO OV-2: bevacizumab plus chemotherapy at progression after front-line bevacizumab plus chemotherapy in platinum sensitive

Stage IIIIB–IV EOC, FT or PPC progressing or recurring at least 6 months after front-line chemotherapy plus bevacizumab (n≈400)

- Primary endpoint: PFS
- Secondary endpoint: OS
- 60 Italian centres involved and involvement of others European groups (ENGOT – Italy, Germany, France, Greece, Switzerland) (sponsor: INT Napoli)

Principal investigators: Sandro Pignata, Nicoletta Colombo

Bevacizumab 15mg/kg q3w until PD
PARTIALLY PLATINUM-SENSITIVE

A new interesting category representing 30-40% of all relapsed patients

Primary Treatment

0 Mos  6 Mos  12 Mos

Refractory  Resistant  Partially-sensitive  Sensitive

End of Frontline Therapy

Rechallenge platinum RR <30%
OVA-301: Study Design

- **PLD 50 mg/m² 90-min infusion q4w**
- **PLD 30 mg/m² 90-min infusion followed by Trabectedin 1.1 mg/m² 3-hr infusion q3w**

**OVA-301: PFS Primary Endpoint by Independent Radiologist—Measurable**

PFS events: 389  
HR: 0.79 (0.65-0.96; P = .0190)  
# censored: 256

*27 subjects nonmeasurable (9 trab + PLD [2 not treated], 18 PLD [1 not treated])

Overall Survival in the partially platinum-sensitive population (PFI 6-12 months)

Events/censored: 177/37
HR: 0.64 (0.47-0.86)
p=0.0027 (log-rank)
Cox regression:
HR*: 0.65 (0.48-0.88)
p=0.0056

Patients at risk
<table>
<thead>
<tr>
<th>PLD</th>
<th>91</th>
<th>85</th>
<th>78</th>
<th>66</th>
<th>58</th>
<th>50</th>
<th>37</th>
<th>30</th>
<th>24</th>
<th>18</th>
<th>17</th>
<th>16</th>
<th>13</th>
<th>12</th>
<th>11</th>
<th>7</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+PLD</td>
<td>123</td>
<td>116</td>
<td>110</td>
<td>103</td>
<td>96</td>
<td>91</td>
<td>79</td>
<td>62</td>
<td>55</td>
<td>50</td>
<td>43</td>
<td>37</td>
<td>33</td>
<td>29</td>
<td>23</td>
<td>16</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR and p-value for treatment comparison based on Cox regression analysis after adjustment for key prognostic factors (ECOG PS, PFI (continuous), race, baseline CA-125, Age, baseline liver/lungs involvement and prior taxane)
Trabectedin + PLD significantly prolongs survival in pts with partially platinum sensitive ovarian cancer receiving platinum as sequential treatment

**OVA-301:** pts 672
PFI 6-12 mos: 214
third-line platinum after OVA-301: 94
PLD arm (45 pts) OS = 18.7 mos
T- PLD arm (49 pts) OS = 27.7 mos
HR = 0.57

Colombo et al. ESGO, 2011
The primary objective is to demonstrate that trabectedin plus PLD prolongs OS over carboplatin plus PLD, but the study design allows rechallenge with the platinum-based therapy in the non-platinum arm after PD. This would allow the prospective evaluation of the effect of PFI extension with a non-platinum combination on response to subsequent platinum and survival in patients with relapsed PPS ovarian cancer.
PLATINUM-RESISTANT

Cytotoxic regimens

Platinum-resistant disease

Single-agent (non-platinum based)

- PLD
- Docetaxel
- Gemcitabine
- Etoposide (oral)
- Topotecan
- Paclitaxel (wkly)

Targeted therapy: Bevacizumab

NCCN. Clinical Practice Guidelines in Oncology. Ovarian Cancer 2013
AURELIA trial design

Platinum-resistant OC
- ≤2 prior anticancer regimens
- No history of bowel obstruction/abdominal fistula, or clinical/radiological evidence of rectosigmoid involvement

Stratification factors:
- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)

Chemotherapy options (investigator’s choice):
- Paclitaxel 80 mg/m² days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m² days 1, 8, & 15 q4w (or 1.25 mg/m², days 1–5 q3w)
- PLD 40 mg/m² day 1 q4w

- PD = progressive disease
- \( ^a \)Epithelial ovarian, primary peritoneal, or fallopian tube cancer; \( ^b \)Or 10 mg/kg q2w;
- \( ^c \)15 mg/kg q3w, permitted on clear evidence of progression
The graph depicts the progression-free survival (PFS) for two treatment groups: CT (n = 182) and BEV + CT (n = 179). The median PFS months are 3.4 for CT and 6.7 for BEV + CT. The hazard ratio (HR) unstratified is 0.48, with a 95% CI of 0.38 to 0.60. The log-rank P value is < .001 (2-sided, unstratified).

The table below shows the number of events and the corresponding percentages:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median PFS, months</th>
<th>95% CI</th>
<th>HR (unstratified)</th>
<th>95% CI</th>
<th>Log-rank P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>166 (91%)</td>
<td>3.4</td>
<td>2.2 to 3.7</td>
<td>0.48</td>
<td>0.38 to 0.60</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BEV + CT</td>
<td>135 (75%)</td>
<td>6.7</td>
<td>5.7 to 7.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table also includes the number of patients at risk over time:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>CT: No. at risk</th>
<th>BEV + CT: No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>182</td>
<td>179</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
OS (probability)

Events, n (%) 136 (75%) 128 (72%)
Median OS, months 13.3 16.6
95% CI 11.9 to 16.4 13.7 to 19.0
HR (unstratified) 0.85
95% CI 0.66 to 1.08
Log-rank P value (< .174

No. at risk
CT 182 130 98 63 29 12 1 0
BEV + CT 179 148 106 75 39 13 1 0

Time (months)
MITO-11

Phase-II study

resistant/refractory ROC. Primary endpoint: PFS

Conclusions: the addiction of pazopanib to weekly paclitaxel might produce a significant prolongation of PFS (HR 0.45) and OS (HR 0.60). A phase-III trial is strongly supported.

Randomized

Pazopanib 800 mg/day
Paclitaxel 80 mg/mq
day 1,8,15 - every 28 days

Proc ASCO, 2014
OVARian CANCER

- Standard front-line chemotherapy
- Weekly regimens
- Maintenance therapy
- Role of neoadjuvant chemotherapy
- Second-line chemotherapy

- BRCAness and PARP inhibitors
Ovarian cancer: sporadic vs hereditary

- BRCA1: 70%
- BRCA2: 20%
- MMR (MSH1, MLH2): 8-10%
- Other genes: 2%

- Sporadic: 90%
- Hereditary: 10%
Survival in women with ovarian cancer
BRCA1/2 carriers vs non-carriers

Survival in women with ovarian cancer

BRCA1/2 carriers vs non-carriers

Carriers
Non-carriers

Cum Survival

TIME (months)

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

0
20
40
60
80
Ovarian cancer

Hereditary = 24%
Sporadic = 76%

BRCA mutations
14% overall
17% of serous cancer
23% of HGSC

44% of mutation carriers had no significant family history

AUSTRALIAN POPULATION

Nonmucinous ovarian cancer patients (N= 1001)
Prevalence of germline BRCA mutations in serous ovarian cancer

- At least 17-20% of unselected ovarian cancer patients harbor a mutation in BRCA
- 25-30% of those with high-grade serous histology have a BRCA mutation
- Up to 44% have no family history

Ahop et al, JCO 2012
Schrader et al: Obst Gynecol 2012
Pennington et al, Clin Cancer Res, 2014
Who should be tested?

- NCCN guidelines recommend all women with epithelial ovarian cancer undergo genetic testing regardless of age or family history.
- Identifying BRCA mutation status needs to be concurrent with the diagnosis of ovarian cancer.

Which patient groups?

- All ovarian cancer patients
- All non-mucinous
- All high-grade serous and endometrioid
- All serous
Impairment of homologous recombination repair in ovarian cancer

- 10-15% of ovarian cancers has an impairment of homologous recombination repair due to a mutation of BRCA1 or BRCA2.

- Almost 50% of high-grade serous tumors may have the same impairment for:
  - acquired germ-line or somatic mutation of BRCA1 or BRCA2
  - epigenetic inactivation of BRCA1
  - BRCA1/2-independent deficit for homologous recombination

Gene Expression Profile of BRCAness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer

PARP inhibition and synthetic lethality


HR: homologous recombination; SSB: single-strand break; DSB: double-strand break
Olaparib: an oral PARP inhibitor

<table>
<thead>
<tr>
<th>Olaparib dose</th>
<th>200 mg bid</th>
<th>400 mg bid</th>
<th>400 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST</td>
<td>28%</td>
<td>33%</td>
<td>BRCA+ 41%</td>
</tr>
<tr>
<td>CR/PR</td>
<td></td>
<td></td>
<td>BRCA- 24%</td>
</tr>
<tr>
<td>Disease control rate*</td>
<td>34%</td>
<td>69%</td>
<td>BRCA+ 76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA- 62%</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>7.0 months</td>
<td>9.5 months</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Disease control rate* includes complete response (CR) + partial response (PR) + stable disease (SD); NR, not reported.

Provides clinical evidence of activity in patients with and without BRCA1/2 mutations

Olaparib: phase-II study

- Maintenance after chemotherapy in platinum-sensitive high-grade serous ROC
- Randomized, double-blind, placebo-controlled

- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
  - time to disease progression on penultimate platinum therapy
  - objective response to last platinum therapy
  - ethnic descent

Olaparib 400 mg po bid
Placebo po bid

Treatment until disease progression
Randomized 1:1
Progression-free survival

No. of events: Total patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 60:136 (44.1)</th>
<th>Placebo 93:129 (72.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>8.4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Hazard ratio 0.35 (95% CI, 0.25–0.49)  
$p<0.00001$

HR 0.18 in BRCA carriers

Ledermann et al NEJM 2012
A randomized phase 2 trial comparing efficacy of the combination of the PARP inhibitor olaparib and the antiangiogenic cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer.

Joyce Liu et al, ASCO 2014

90 pts with platinum sensitive HGSC (50% BRCA carriers)
- Olaparib 400 mg/d
- Olaparib 200 mg/d + Cediranib 30 mg/d

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Olaparib + Cediranib</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (mos)</td>
<td>9.0</td>
<td>17.7</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>56</td>
<td>84</td>
</tr>
<tr>
<td>Toxicity G3-4 (%)</td>
<td>7</td>
<td>70</td>
</tr>
</tbody>
</table>