Targeting Angiogenesis in Ovarian Cancer

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Italy
Therapeutic targeting of angiogenesis

- One of the most prolific areas of drug research
- Many drugs are in development
  - **Compounds:** Modelled for direct and/or indirect anti-angiogenic (AA) properties
  - **Approaches:** Ligand, receptor, signal, and regulators
  - **Targets:** Endothelial cells, tumour cells, pericytes, immune effectors
- Approved indications: more than 15 (at least 2 others with indirect effects) in oncology treatment
The angiogenic switch and anti-angiogenic therapy

Somatic mutation → Small avascular tumor → Tumor secretion of proangiogenic factors stimulates angiogenesis → Rapid tumor growth and metastasis → Angiogenic inhibitors may reverse this process

Targeting VEGF in ovarian cancer

- VEGF over expressed in ovarian cancer, associated with:
  - Ascites production
  - Progression of disease
  - Worse prognosis
  - Key survival factor for endothelial cells (Activating PI3-kinase and Akt)

- In pre-clinical models the anti-VEGF therapy
  - Slows tumour progression
  - Improves the peritoneal effusion
  - Synergistic effect with cytotoxic drugs

Han ES and Monk BJ. Expert Rev Anticancer Ther 2007;7(10):1339-1345;
Serum VEGF level and survival in ovarian cancer

Front-line therapy treatment options in 2014

- Paclitaxel + carboplatin Q3 weeks IV
  - Standard since 1995, still the standard comparator arm
- Paclitaxel weekly + carboplatin Q3 weeks IV
  - According to JGOG data. Not confirmed by MITO7 (different schedule) Ongoing confirmatory studies (ICON-8)
- Paclitaxel + carboplatin + bevacizumab
  - First trials showing benefit of adding a 3rd agent/targeted therapy
  - PFS benefit. OS benefit for high-risk patients. Translational results pending
- Paclitaxel + carboplatin iv + i.p. chemotherapy
  - Optimal debulked population. Not standard in the clinical practice
- Clinical trials STILL NECESSARY!!!
  - Investigational agents (i.e., nintedanib, trebananib, pazopanib,...)
  - Non-serous (clear cell, mucinous,...)
Targeting angiogenesis in first-line treatment
# Bevacizumab in recurrent ovarian cancer: Single agent activity higher than in other cancers

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Therapy</th>
<th>Response Rate</th>
<th>Progression free survival at 6 months (%)</th>
<th>Prior Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 170-D</td>
<td>63</td>
<td>BV 15 mg/kg IV Q3 wk</td>
<td>18</td>
<td>39</td>
<td>42% platinum sensitive, 2 prior lines</td>
</tr>
<tr>
<td>NCI 5789</td>
<td>29</td>
<td>BV 10 mg/kg IV Q2 wk + CTX 50 mg daily</td>
<td>28</td>
<td>57</td>
<td>42% platinum sensitive, 2 prior lines</td>
</tr>
<tr>
<td>Cannista et al.</td>
<td>44</td>
<td>BV 15 mg/kg IV Q3 wk</td>
<td>16</td>
<td>27,4</td>
<td>Platinum resistant, 3 prior lines</td>
</tr>
</tbody>
</table>

**GOG-0218 phase III trial**

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

n=1.873

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

**Randomisation**

1:1:1

- **Placebo**
  - Carboplatin (C) AUC 6
  - Paclitaxel (P) 175 mg/m²

- **Bevacizumab 15 mg/kg**
  - Carboplatin (C) AUC 6
  - Paclitaxel (P) 175 mg/m²

15 months

**Paclitaxel (P) 175 mg/m²**

**Carboplatin (C) AUC 6**

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

GOG-0218 phase III trial

GOG-0218 phase III trial

ICON7 phase III study

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

Carboplatin AUC6
Paclitaxel 175 mg/m²

Carboplatin AUC6
Paclitaxel 175 mg/m²

Bevacizumab 7.5 mg/kg Q3 wk

18 cycles

ICON7 phase III study: Progression-free survival

### Academic analysis

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Control</th>
<th>Research</th>
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</thead>
<tbody>
<tr>
<td>392 (51)</td>
<td>367 (48)</td>
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<table>
<thead>
<tr>
<th>Median, months</th>
<th>Control</th>
<th>Research</th>
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<tr>
<td>17.3</td>
<td>19.0</td>
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</table>

<table>
<thead>
<tr>
<th>Log-rank test</th>
<th>p=0.0041</th>
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</table>

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>0.81 (0.70–0.94)</th>
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</table>

#### Number at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Control</th>
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<tbody>
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<td>764</td>
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<tr>
<td>3</td>
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Final Overall Survival (n=1528)

Number at risk

<table>
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<tr>
<th></th>
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<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Deaths, n</td>
<td>352</td>
<td>362</td>
<td>714 (47)</td>
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</tbody>
</table>

Proportion alive

Time (months)

Deaths, n

Control: 352
Research: 362
Total: 714 (47)

BEV exposure

Number at risk

<table>
<thead>
<tr>
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<th>Control</th>
<th>Research</th>
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<tr>
<td>60</td>
<td>676</td>
<td>707</td>
<td>1383</td>
</tr>
</tbody>
</table>

Restricted mean, months

Control: 44.6
Research: 45.5
Difference: +0.9

Median, months

Control: 58.6
Research: 58.0
Difference: –0.6

Log-rank test p=0.85

HR (95% CI) 0.99 (0.85–1.14)

Presented at ESMO 2013

Courtesy of Oza AM et al.
ICON7 phase III study: Unplanned analysis in high-risk patients

Stage III (n=1,045)
- Surgery (n=1,034)
  - Optimal (n=744)*
    - 0 cm (n=418)
    - >0, ≤1 cm (n=301)
  - Sub-opt >1cm (n=290)
- No surgery (n=11)

Stage IV (n=201)
- Surgery (n=182)
  - Optimal (n=84)†
    - 0 cm (n=43)
    - >0, ≤1 cm (n=39)
  - Sub-opt >1cm (n=98)
- No surgery (n=19)

Perren et al. ESMO 2010:LBA4; Oza AM et al. ECCO 2013:LBA6
ICON7 phase III study: Overall Survival per risk groups

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

Courtesy of Oza AM et al. ECCO 2013:LBA6
Data seems to suggest that after bevacizumab withdrawn the effect on PFS is lost

GOG-0218 and ICON7: Treatment duration and dose

- **GOG-0218**
  - Dose: 15 mg/kg
  - Treatment duration: 22 cycles
  - 24-43% of patients with potential to continue beyond 22 cycles

- **ICON7**
  - Dose: 7.5 mg/kg
  - Treatment duration: 18 cycles
  - 62% of patients with potential to continue beyond 18 cycles

References:
- Perren T et al. Ann Oncol 2010;21(suppl 8):LBA4
BOOST trial

- ENGOT-ov15/AGO OVAR 17 evaluation of optimal initial treatment duration of bevacizumab in combination with standard chemotherapy in patients with ovarian cancer

Enrollement closed  
N:800

Stratification:
- FIGO stage
- Residual macroscopic disease (no/yes)
- Center
Conclusion of GOG-0218 and ICON7 results

PFS
- Primary endpoint (PFS) met in both trials; basis for EMA (European Medicines Agency) bevacizumab label
- Subgroup analyses show that the bevacizumab treatment effect is consistent across various pre-defined subgroups
- Dose and duration of therapy still open questions

Overall Survival (OS)
- OS not significant in both trials, however there is no detriment
- Subgroup analyses in ICON7 were not pre-planned or powered, and should be interpreted with caution

Exploratory analysis suggests a different effect according to risk but this needs to be proved prospectively
Other anti-angiogenic drugs in first-line
Tumours require new blood vessels (angiogenesis) to stimulate their growth.

VEGF is a growth factor that promotes angiogenesis via its receptor, VEGFR. The VEGFR is a protein kinase.

Pazopanib blocks the kinase of the VEGFR, and PDGFR thus inhibiting angiogenesis and tumour growth.
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.
1st Endpoint: Progression-free Survival (RECIST)

<table>
<thead>
<tr>
<th></th>
<th>Pazopanib (n=472)</th>
<th>Placebo (n=468)</th>
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</thead>
<tbody>
<tr>
<td>Events, n</td>
<td>237</td>
<td>273</td>
</tr>
<tr>
<td>Median, months</td>
<td>17.9</td>
<td>12.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.68, 0.96)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0190</td>
<td></td>
</tr>
</tbody>
</table>

Blockade of FGF axis in addition to other proangiogenic pathways may increase antiangiogenic efficacy\textsuperscript{6,11,12}

FGF has been shown to increase proliferation, survival, and motility of ovarian cancer cell lines in vitro

Potent inhibitor of VEGFR, FGFR and PDGFR
Multicenter, randomised, double-blind, phase III trial to investigate the efficacy and safety of BIBF 1120 (nintedanib) in combination with standard treatment of carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in advanced ovarian cancer.

C = Carboplatin AUC 5-6 D1
T = Paclitaxel 175 mg/m2 (3h) d1
Q21D / 6 courses

BIBF 1120* / Placebo:
- no intake on days of chemotherapy
- dose: 200 mg po bid (combi + mono)
- dose adaptation in case of undue toxicity
- max. duration of 120 weeks in non-progressing pts

Placebo

Total duration 120 days

*BIBF 1120 2 x 200 mg po qd

Available at http://clinicaltrials.gov/ct2/show/NCT01015118.
Du Bois A et al. IJGC 2013;23(Suppl 1):7-8
### Primary Endpoint: Progression-Free Survival

RECIST 1.1 and CA-125 in conjunction with Clinical MBO Criteria

All patients (N=1366) – Cut-off date: 29 April 2013

<table>
<thead>
<tr>
<th></th>
<th>TC + Nintedanib (n=911)</th>
<th>TC + Placebo (n=455)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>486 (53.3)</td>
<td>266 (58.5)</td>
</tr>
<tr>
<td>Median, months</td>
<td>17.3</td>
<td>16.6</td>
</tr>
<tr>
<td>HR* (95% CI)</td>
<td>0.84 (0.72, 0.98)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.0239</td>
</tr>
</tbody>
</table>

Du Bois A et al. IJGC 2103;23(Suppl 1):7-8
AMG386, angiopoietins and angiogenesis

TRINOV-A-3-ENGOT-ov2: TC ± AMG 386 as first-line therapy of stage III–IV ovarian cancer

Concurrent treatment

ARM A:
AMG 386*
Paclitaxel**
Carboplatin**

ARM B:
AMG 386/Placebo*
Paclitaxel**
Carboplatin**

Maintenance phase

AMG 386 monotherapy until progression or 18 months

AMG 386 placebo monotherapy until progression or 18 months

End before treatment (Progressive disease or unacceptable toxicity or withdrawal of consent or death)

Treatment phase

Neoadjuvant chemo + Interval Debulking allowed in both arms After 3 courses

Paclitaxel 175 mg/m² IV Q3W
Carboplatin AUC 5 or 6 IV Q3W for maximum of 6 cycles
Plus
AMG 386 15 mg/kg IV QW or AMG 386 placebo IV QW

Up to 7 days from randomisation to 1st dose

Ongoing
Summary for first-line treatment of ovarian cancer

- Bevacizumab able to prolong PFS in 2 trials (GOG218 and ICON7): only drug approved
- TKI inhibitors able to prolong PFS when given concurrently (nindetanib) or as maintenance (pazopanib)
- Other drugs under investigation
- No predictive biomarker available but translational research ongoing
Treatment of platinum-sensitive relapse
Bevacizumab: OCEANS study

- Platinum-sensitive recurrent OC
- Measurable disease
- ECOG 0/1
- No prior chemo for recurrent OC
- No prior BV

(n=484)

Stratification variables:
- Platinum-free interval (6-12 vs. >12 months)
- Cytoreductive surgery for recurrent disease (yes vs. no)

CG + PL

- CBDCA AUC 4
- GEM 1,000 mg/m² d1, 8
- PL q3w until progression

CG + BV

- CBDCA AUC 4
- GEM 1,000 mg/m² d1, 8
- BV 15 mg/kg q3w until progression

Epithelial ovarian, primary peritoneal, or fallopian tube cancer
OCEANS: PFS results

![Graph showing progression free survival (PFS) results for CG + PL and CG + BV treatments. The graph includes a Kaplan-Meier survival curve with event times and the log-rank P value.]

<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</td>
<td>0.484</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(0.388–0.605)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Aghajanian C et al. J Clin Oncol 2011;29(suppl):LBA5007
OCEANS: Response rates results

Difference: 21.1%  
P < .0001

- **CG + PL**: ORR = 57%, PR = 48%, CR = 9%  
  - n = 139
- **CG + BV**: ORR = 78.5%, PR = 61%, CR = 17%  
  - n = 190

**Median duration of response (months)**  
- CG + PL: 7.4 months  
- CG + BV: 10.4 months

**HR for duration of response**  
- 0.0534  
- P < .0001

- Compared for descriptive purposes only.
OCEANS: Third interim OS analysis

<table>
<thead>
<tr>
<th></th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>142 (58.7)</td>
<td>144 (59.5)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>33.7</td>
<td>33.4</td>
</tr>
<tr>
<td>(29.3–38.7)</td>
<td>(30.3–35.8)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.960 (0.760–1.214)</td>
<td>p=0.7360</td>
</tr>
</tbody>
</table>

GC + PL: gemcitabine+carboplatin+placebo; GC+BV: gemcitabine+carboplatin+bevacizumab
Courtesy of Aghajanian C et al. J Clin Oncol 2011;29(suppl):LBA5007
Cediranib (AZD2171)

- Potent oral inhibitor of vascular endothelial growth factors
- >800-5000 fold selectivity for VEGFR-2
- *In vitro* activity for VEGFR-1 and -3
- Inhibits growth of established xenografts- lung, colorectal, prostate, breast and ovary
- → Phase II trials showed activity as single agent in ovarian cancer

ICON 6 trial

- Cediranib with platinum-based chemotherapy in “platinum-sensitive” relapsed ovarian cancer

ICON 6 trial, Progression-free survival

- **PFS events, n (%):**
  - Chemo.: 112 (94.9)
  - Conc.: 152 (87.4)
  - Maint.: 139 (84.8)

- **Median, months:**
  - Chemo.: 8.7
  - Conc.: 10.1
  - Maint.: 11.1

- **Log-rank test (trend):**
  - p=0.0003

- **HR vs. Chemo only (95% CI):**
  - Chemo.: 0.67 (0.53–0.87)
  - Conc.: 0.57 (0.44–0.74)

- **Restricted means, months:**
  - Chemo.: 9.4
  - Conc.: 11.4
  - Maint.: 12.5

**Courtesy of Ledermann JA et al. Eur J Cancer 2013;49(Suppl 3):LBA10**
ICON 6 trial, Overall survival

Restricted mean survival time increases by 2.7 months with maintenance treatment (over two years)

<table>
<thead>
<tr>
<th></th>
<th>Chemo.</th>
<th>Maint.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n (%)</td>
<td>63 (53.3)</td>
<td>75 (45.7)</td>
</tr>
<tr>
<td>Median, months</td>
<td>20.3</td>
<td>26.3</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.042</td>
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</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.70 (0.51 – 0.99)</td>
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</tr>
<tr>
<td>Test for non-proportionality p</td>
<td>0.0042</td>
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<tr>
<td>Restricted means, months</td>
<td>17.6</td>
<td>20.3</td>
</tr>
</tbody>
</table>

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

MITO-16/MaNGO OV-2: bevacizumab plus chemotherapy at progression after front-line bevacizumab plus chemotherapy in platinum-sensitive

Primary endpoint: PFS
Secondary endpoint: OS
60 Italian centres involved and involvement of other European groups (ENGOT – Italy, Germany, France, Greece, Switzerland): ONGOING

*EOC: epithelial ovarian cancer; FT: Fallopian tube cancer; PPC: primary peritoneal cancer
Summary for platinum-sensitive recurrent ovarian cancer

- Bevacizumab able to prolong PFS when associated to chemotherapy (Carboplatin + gemcitabine)
- Cediranib able to prolong PFS and OS when associated to carboplatin and paclitaxel (study prematurely closed)
- No data in patients pre-treated with bevacizumab
- Treatment with bevacizumab beyond progression under evaluation (MITO 16)
Treatment of platinum-resistant relapse
Bevacizumab: AURELIA study

Platinum-resistant OC\textsuperscript{a}
- ≤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/m\textsuperscript{2} days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m\textsuperscript{2} days 1, 8, & 15 q4w (or 1.25 mg/m\textsuperscript{2}, days 1–5 q3w)
- PLD 40 mg/m\textsuperscript{2} day 1 q4w

PD: progressive disease
\textsuperscript{a} Epithelial ovarian, primary peritoneal, or fallopian tube cancer; \textsuperscript{b} Or 10 mg/kg q2w; \textsuperscript{c} 15 mg/kg q3w, permitted on clear evidence of progression
AURELIA trial results

PFS

OS

Aurelia Study. Paclitaxel cohort: OS

<table>
<thead>
<tr>
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<th>CT (N=55)</th>
<th>BEV + CT (N=60)</th>
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<tbody>
<tr>
<td>Events, n (%)</td>
<td>41 (75)</td>
<td>36 (60)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>13.2 (8.2–19.7)</td>
<td>22.4 (16.7–26.7)</td>
</tr>
<tr>
<td>HR (unadjusted) (95% CI)</td>
<td>0.65 (0.42–1.02)</td>
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No. at risk:

<table>
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TRINOVA-1 trial design

**Recurrent EOC**
- ≤ 3 prior anticancer regimens
- Evaluable or measurable disease
- GOG performance status of 0 or 1
- PFI <12 months

**Stratification factors**
- Platinum-free interval (PFI) (≤6 vs. >6 months)
- Measurable disease (Yes/No)
- Region (North America, Western Europe/Australia, rest of world)

**Weekly paclitaxel**
- Paclitaxel 80 mg/m² IV on days 1, 8, 15 Q4W
- Trebananib 15 mg/kg IV QW

**Treat to PD/toxicity**

EOC: epithelial ovarian cancer including primary peritoneal, or fallopian tube cancer; PD: progressive disease

ClinicalTrials.gov Identifier: NCT01204749

Courtesy of Monk BJ. Eur J Cancer 2013;49(suppl 3):LBA41
Trinova-1 trial. Progression-free Survival (Primary Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel + Placebo (n = 458)</th>
<th>Paclitaxel + Trebananib (n = 461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>361 (79)</td>
<td>310 (67)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.4</td>
<td>7.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.66 (95% CI, 0.57–0.77)</td>
<td></td>
</tr>
<tr>
<td>P (stratified log rank)</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

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OV6 TRINOVA-2

Recurrent partially platinum sensitive or resistant OC, PP, FTC, (PFI <12 months, >6 months after the beginning of the first-line platinum-based chemotherapy)
Radiographically evaluable disease, documented PD
Prev Chemo <3 Toxicity <G3 N = 380

Primary endpoint: PFS
Ongoing

OC: Ovarian Cancer, PP: primary peritoneal, FTC: fallopian tubes cancer, PFI: progression free interval, PD: progression of disease
MITO 11

RANDOM

Paclitaxel 80 mg/mq
Day 1, 8, 15 - every 28 days

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

Primary endpoint: PFS
Arm N Events Median (months) 95% CI
Paclitaxel 36 36 3.5 2.0-5.7
Paclitaxel + Pazopanib 37 37 6.3 5.4-11

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

Progression-free survival

Summary for Platinum-resistant Recurrent Ovarian Cancer

- Bevacizumab and trebanabib able to prolong PFS when associated to chemotherapy
- Combination of anti-angiogenetic drugs with weekly paclitaxel seems the most effective
- Multiple agents under investigation
- No data in patients pre-treated with bevacizumab
Conclusions

- Bevacizumab first biological drug approved in ovarian cancer
- 3-4 different drugs targeting angiogenesis possibly approved in the future
- Anti-angiogenetic drugs active in first line, maintenance, resistant, sensitive: no doubt that targeting angiogenesis is crucial in ovarian cancer
- No predictive factor identified
- No data on sequences
- No data on treatment beyond progression
- No data on cross resistance
Thank you!