Anti-Angiogenics in Ovarian Cancer: Where are we now?

Elizabeth A. Eisenhauer MD FRCPC
Department of Oncology
Queen’s University, Kingston ON Canada
Outline

• The biological basis of clinical research of VEGF/R inhibition in OVCA

• Randomized clinical studies since GOG-0218

• Interpretation of Findings:
  – Biological effects and clinical benefits

• Questions and Controversies
  – Endpoints
    – Selection biomarkers for angiogenesis inhibitors
Vascular Endothelial Growth Factor (VEGF) and Receptor (VEGFR): Rational Targets in Ovarian Cancer

• VEGF expression in OVCA:
  – Promotes ascites and effusions
  – Is an independent predictor of patient prognosis

• Preclinical Studies of VEGF(R) inhibition:
  – Decreases ascites formation in murine OVCA
  – Is active in human ovarian xenografts

• Phase II clinical trials in recurrent OVCA:
  – Response rates seen with several angiogenesis inhibitors including bevacizumab (21% in GOG 172)

GOG 0218: First Reported Randomized Trial of Bevacizumab in Ovarian Cancer
GOG-0218: Schema

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

n=1800 (planned)

Stratification variables:
- GOG performance status (PS)
- Stage/debulking status

Arm

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

II (CP + BEV)
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- BEV 15 mg/kg
- Placebo

III (CP + BEV → BEV)
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- BEV 15 mg/kg

15 months

Cytotoxic (6 cycles)
Maintenance (16 cycles)
### GOG-0218: Investigator-Assessed PFS

<table>
<thead>
<tr>
<th></th>
<th>Arm I CP (n=625)</th>
<th>Arm II CP + BEV (n=625)</th>
<th>Arm III CP + BEV → BEV maintenance (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>423 (67.7)</td>
<td>418 (66.9)</td>
<td>360 (57.8)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
<td>11.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.908 (0.759–1.040)</td>
<td>0.717 (0.625–0.824)</td>
<td></td>
</tr>
<tr>
<td>One-sided p-value (log rank)</td>
<td>0.080&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>p-value boundary = 0.0116
GOG-0218: Overall Survival Analysis

23.7% of Patients had died

- Arm I: CP (n=625)
- Arm II: CP + BEV (n=625)
- Arm III: CP + BEV → BEV (n=623)

<table>
<thead>
<tr>
<th>Patients with events, n (%)</th>
<th>Arm I CP (n=625)</th>
<th>Arm II CP + BEV (n=625)</th>
<th>Arm III CP + BEV → BEV (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>39.3</td>
<td>38.7</td>
<td>39.7</td>
</tr>
<tr>
<td>HR^a (95% CI)</td>
<td>1.036 (0.827–1.297)</td>
<td>0.915 (0.727–1.152)</td>
<td></td>
</tr>
<tr>
<td>One-sided p-value</td>
<td>0.361</td>
<td>0.252</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk: 625/625/623
442/432/437
173/162/171
46/39/40

^aStratified analysis
GOG-0218 - Progression Free Survival
(analysis as of August 26, 2011)
(N = 1873 patients)

Control vs. Bev throughout:
HR 0.770 PFS gain ~ 4 months

GOG-0218 - Overall Survival
(analysis as of August 26, 2011)
47% of patients have died

HR 1.078 in Bev initiation - NS
HR 0.885 in Bev throughout - NS
### Six additional Phase III Trials Evaluating Addition of an Angiogenesis Inhibitor in Epithelial OVCA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial ID</th>
<th>N</th>
<th>Line of therapy</th>
<th>Chemo</th>
<th>Primary Efficacy Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>GOG0218</td>
<td>1873</td>
<td>First</td>
<td>TC</td>
<td>PFS</td>
<td>Published</td>
</tr>
<tr>
<td></td>
<td>ICON7</td>
<td>1528</td>
<td>First</td>
<td>TC</td>
<td>PFS and OS</td>
<td>Published</td>
</tr>
<tr>
<td></td>
<td>OCEANS</td>
<td>484</td>
<td>Recurrent – <em>P sens</em></td>
<td>GC</td>
<td>PFS</td>
<td>Published</td>
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<tr>
<td></td>
<td>AURELIA</td>
<td>361</td>
<td>Recurrent – <em>P res</em></td>
<td>T or Topo or Lipodox</td>
<td>PFS</td>
<td>Presented (ESMO 2012)</td>
</tr>
<tr>
<td>BIBF</td>
<td>AGO-OVAR 12</td>
<td>1300</td>
<td>First</td>
<td>TC</td>
<td>PFS</td>
<td>Closed</td>
</tr>
<tr>
<td>Cediranib</td>
<td>ICON6 (GCIG study)</td>
<td>2000</td>
<td>Recurrent – <em>P sens</em></td>
<td>TC</td>
<td>PFS and OS</td>
<td>Closed</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>AGO-OVAR 16</td>
<td>900</td>
<td>First <em>(maintenance only)</em></td>
<td>TC (Bev allowed)</td>
<td>PFS</td>
<td>Active</td>
</tr>
</tbody>
</table>
Results of Reported Randomized Trials

All are Bevacizumab Studies
ICON7: Study Design

Frontline EOC, PP or FT cancer
- Stage I-IIA (Gr 3 or CC)
- Stage IIIB/C
- Stage III
- Stage IV
n=1528

Arm A
- Carboplatin AUC 6*
- Paclitaxel 175 mg/m²

Arm B
- Carboplatin AUC 6*
- Paclitaxel 175 mg/m²

Stratification variables:
- Stage / surgery
- Time since surgery
- GCIG group

Bevacizumab 7.5 mg/kg
12 months

Primary endpoint: PFS
Secondary endpoints: OS, RR, safety, QOL, cost-effectiveness, translational
No IRC present

* Might vary based on GCIG group.
† Omit cycle 1 bevacizumab if < 4 weeks from surgery.
ICON7 PFS Benefit: Academic Analysis

ESMO 2010

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>CPB7.5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>392 (51%)</td>
<td>367 (48%)</td>
</tr>
<tr>
<td>Median, months</td>
<td>17.3</td>
<td>19.0</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>$P = 0.0041$</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.70-0.94)</td>
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</table>

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>CPB7.5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>764</td>
<td>764</td>
</tr>
<tr>
<td>3 months</td>
<td>723</td>
<td>748</td>
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<tr>
<td>6 months</td>
<td>693</td>
<td>715</td>
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<tr>
<td>9 months</td>
<td>656</td>
<td>647</td>
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<tr>
<td>12 months</td>
<td>464</td>
<td>585</td>
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<tr>
<td>15 months</td>
<td>307</td>
<td>399</td>
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<tr>
<td>18 months</td>
<td>216</td>
<td>263</td>
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<tr>
<td>21 months</td>
<td>143</td>
<td>144</td>
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<tr>
<td>24 months</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>27 months</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>30 months</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

ICON7: Preliminary Analysis of Overall Survival*

ESMO 2010

Proportion Surviving

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>CP</th>
<th>CPB7.5+</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>9</td>
<td>0.70</td>
<td>0.70</td>
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<tr>
<td>12</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>15</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>18</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>21</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>24</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>27</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>30</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with event, n (%)</th>
<th>CP</th>
<th>CPB7.5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 (17)</td>
<td></td>
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</tr>
</tbody>
</table>

| Log-rank test               | P = 0.098 |

| Hazard ratio (95% CI)       | 0.81 (0.63-1.04) |

| 1-year survival rate, %     | 93 | 95 |

<table>
<thead>
<tr>
<th>Anti-VEGF after progression, n (%)</th>
<th>CP</th>
<th>CPB7.5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (4)</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>CP</th>
<th>CPB7.5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>764</td>
<td>764</td>
<td>764</td>
</tr>
<tr>
<td>741</td>
<td>753</td>
<td>737</td>
</tr>
<tr>
<td>724</td>
<td>716</td>
<td>716</td>
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<tr>
<td>701</td>
<td>678</td>
<td>687</td>
</tr>
<tr>
<td>652</td>
<td>486</td>
<td>525</td>
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<td>486</td>
<td>368</td>
<td>404</td>
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<tr>
<td>368</td>
<td>252</td>
<td>259</td>
</tr>
<tr>
<td>252</td>
<td>159</td>
<td>162</td>
</tr>
<tr>
<td>159</td>
<td>83</td>
<td>89</td>
</tr>
<tr>
<td>83</td>
<td>33</td>
<td>40</td>
</tr>
</tbody>
</table>

*Based on immature OS data (241 of 715 required events, 16% of all patients) as required by regulatory authorities (approved by IDMC and TSC).

Updated ICON 7 PFS and OS Perren T et al, NEJM 2011
**OCEANS: Study schema**

**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**
- C AUC 4
- G 1000 mg/m\(^2\), d1 & 8
- PL q3w until progression

**CG + BV**
- C AUC 4
- G 1000 mg/m\(^2\), d1 & 8
- BV 15 mg/kg q3w until progression
- CG for 6 (up to 10) cycles

**BV = bevacizumab; PL = placebo**

*a*Epithelial ovarian, primary peritoneal, or fallopian tube cancer
OCEANS: Primary analysis of 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>
</table>

Aghajanian et al. J Clin Oncol 2011;29 (suppl; abstr LBA5007)
OCEANS – Overall Survival Data

- Still not mature – and results not stable
- 31% of GC pts have received Bev post PD
- 15% of GC-Bev pts have received Bev post PD

<table>
<thead>
<tr>
<th></th>
<th>First Interim OS Analysis (29% died)</th>
<th>Second Interim OS Analysis (48.6% died)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GC</td>
<td>GC Bev</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>29.9</td>
<td>35.5</td>
</tr>
<tr>
<td></td>
<td>35.2</td>
<td>33.3</td>
</tr>
<tr>
<td>HR</td>
<td>0.751</td>
<td>1.027</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.537-1.052</td>
<td>0.792 – 1.331</td>
</tr>
</tbody>
</table>
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; PLD = pegylated liposomal doxorubicin

*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

Primary objective: To compare PFS with CT alone vs BEV + CT according to RECIST v1.0

Secondary objectives: To compare
• Objective response rate (ORR) according to RECIST v1.0 and/or GCIG CA-125 criteria
• Overall survival
• Quality of life
• Safety and tolerability

Exploratory objectives: Including evaluation of safety and efficacy according to CT cohort (investigator’s choice)

CT choice was a stratification factor but patients were not randomised between the CT cohorts

RECIST = Response Evaluation Criteria in Solid Tumours
Progression-free survival: Overall population

- **Events, n (%):**
  - CT (N=182): 166 (91)
  - BEV + CT (N=179): 135 (75)

- **Median PFS, months (95% CI):**
  - CT: 3.4 (2.2–3.7)
  - BEV + CT: 6.7 (5.7–7.9)

- **HR (not stratified), (95% CI):**
  - 0.48 (0.38–0.60)

- **Log-rank p-value**
  - <0.001

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**No. at risk:**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th></th>
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<th></th>
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</thead>
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<tr>
<td></td>
<td>182</td>
<td>93</td>
<td>37</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BEV + CT</td>
<td>179</td>
<td>140</td>
<td>88</td>
<td>49</td>
<td>18</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Median duration of follow-up:**
- CT arm: 13.9 months
- BEV + CT arm: 13.0 months
### Summary of Randomized Trials – *All are Bevacizumab Studies*

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Line of therapy</th>
<th>Therapy</th>
<th>PFS</th>
<th>PFS HR</th>
<th>OS HR</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>ICON7</td>
<td>First</td>
<td>TC</td>
<td>TC</td>
<td>17.3</td>
<td>0.81</td>
<td>NS (TE)</td>
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<tr>
<td></td>
<td></td>
<td>Bev</td>
<td>Bev</td>
<td>&gt; Bev</td>
<td></td>
<td></td>
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<tr>
<td>GOG0218</td>
<td>First</td>
<td>TC</td>
<td>TC</td>
<td>10.3</td>
<td>0.908</td>
<td>NS (TE)</td>
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<td></td>
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<td>Bev</td>
<td>&gt; Bev</td>
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<tr>
<td>OCEANS</td>
<td>Recurrent &lt; 6 mo</td>
<td>GC</td>
<td>GC</td>
<td>8.4</td>
<td>0.48</td>
<td>NS (TE)</td>
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<td></td>
<td></td>
<td>Bev</td>
<td>Bev</td>
<td>&gt; Bev</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURELIA</td>
<td>Recurrent &gt; 6 mo</td>
<td>Tax/Topo/LDox</td>
<td>Tax/Topo/LDox</td>
<td>3.4</td>
<td>0.48</td>
<td>NR</td>
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<tr>
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<td></td>
<td>Bev</td>
<td>Bev</td>
<td>&gt; Bev</td>
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</tbody>
</table>

NS = not significant; TE = too early, NR = not reported

- Clear **biological** effect of bevacizumab in OVCA
- Survival data not mature in any trial – preliminary data suggest lesser effect than on PFS.
- Toxicity greater in bevacizumab arms and cost of treatment is considerable (data not shown)

**QUESTIONS:**

- *Should bevacizumab be used in OVCA treatment?*
- *If so, in what line of therapy?*
- *And in which patients?*
Issues in Interpreting Benefit of PFS

• Progression definitions are arbitrary (RECIST, GCIG criteria) –
  – created to categorize observed changes in tumour size
  – not based on a degree of change known to be associated with specific clinical implication – i.e. definition created first - clinical meaning assigned post hoc

• Nevertheless, use of Progression Free Survival in advanced disease trials has migrated from secondary to primary endpoint.

• What are implications?
Arguments for Use of PFS to Change Practice

1. Longer PFS may signal better disease symptom control
2. Longer PFS may be a indicate improved overall survival
3. In circumstance of no evidence of disease, longer PFS (RFS) may provide patient with time free of disease and symptoms
4. Longer PFS may be all that can be measured if second/third line obscures survival benefit
1. **Symptom Control** – What do first line data show?

- Data reported to date have not shown QoL differences.
  - GOG- 0218: FACT-O TOI in post-chemo period no differences.
  - ICON7: SYMPTOM data, particularly at time when PFS curves diverging will be important

*Perren T et al, NEJM 2011, Suppl Appendix Fig 3S*
1. Symptom Control – what do recurrent disease data show?

• Arguably much more important in recurrent disease where symptom improvement or delay in symptom progression highly relevant.
  – OCEANS study – QoL / symptom benefit not endpoints according to clinicaltrials.gov listing
  – AURELIA study – QoL secondary endpoint. Not reported yet.

• This trial most likely of all to show disease-related symptom benefit based on PFS findings.
2. Longer PFS may $\rightarrow$ Improved OS

- PFS has been reliable in predicting OS gains in 1\textsuperscript{st} line OVCA trials – in chemo era.
- Data not mature in OVCA bevacizumab trials - survival most likely to be positive in AURELIA where gain in PFS is near end of disease trajectory – these data needed.

HR PFS vs. OS in First-Line OVCA trials of chemotherapy
4. **PFS has to be used – because OS impact obscured by second/third line treatment**

- Somewhat tautological argument that could potentially lead to adoption of ineffective therapies.
- This argument implies **absolute gains** from post progression treatment has to be **greater in the standard arm than the treated arm** (provided trial is powered to detect same **absolute** gain in OS as was seen in PFS)
**PFS large effect, OS NS**

*Cross over design or experimental treatment widely available.*

- PFS Arm 1 >> Arm 2
- PFS Arm 2 >> Arm 1 after crossover

*New treatment possibly has impact on OS*

**PFS modest effect, OS NS**

*Cross over design or experimental treatment widely available.*

- PFS Arm 1 > Arm 2
- PFS similar after crossover
- PFS effect too small, or false +, or disease more aggressive post Arm1 treatment.

*New treatment of dubious value*

**PFS modest effect, OS NS**

*“active” 2nd line Rx, no or < 50% crossover*

- PFS Arm 1 > Arm 2
- PFS effect too small, or false +, or disease more aggressive post Arm1 treatment.

*New treatment of dubious value*

**PFS modest effect, OS Superior**

*“active” 2nd line Rx, no or < 50% crossover*

- PFS Arm 1 > Arm 2
- PFS effect translates into OS benefit

*New treatment has impact on OS*

---

**Legend:**
- Red: Experimental treatment
- Black: Standard treatment
- Blue: “other” treatment for relapse
- Progression
- Death

*Booth, Eisenhauer J Clin Oncol 2012*
Biomarkers for Selection of Patients for Anti-Angiogenesis Treatments

• Knowing which patients do not / do benefit could aid greatly in debate - sparing toxicity and cost from those who will not being helped

• IDEAL biomarker:
  – Easily measurable, validated
  – Measurable PRIOR to treatment to select “who to treat”
  – Clearly delineates subgroup with NO benefit versus those with SOME benefit (KRAS in CRC good example)
  – This is ONLY possible to determine from randomized trial data where differential impact of treatment can be evaluated within biomarker defined subsets.
Biomarkers for Selection of Patients for Anti-Angiogenesis Treatments

• What are the options?
  – Clinical features of disease
  – Biological measures of tumour
  – Biological measures of patients
Clinical Features – Tumor burden?

- Decreasing PFS, worse prognosis patients
- Greater **relative** effect of bevacizumab (lower HR)
- *Increasing anti-angiogenesis effect??*

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>N</th>
<th>Line of therapy</th>
<th>Chemo</th>
<th>Med PFS</th>
<th>PFS HR</th>
<th>OS HR</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON7</td>
<td>1528</td>
<td>First</td>
<td>TC Bev</td>
<td>&gt; Bev</td>
<td>17.3 19.0</td>
<td>.81</td>
<td>NS (TE) (sub-group?)</td>
</tr>
<tr>
<td>GOG0218</td>
<td>1873</td>
<td>First</td>
<td>TC Bev</td>
<td>TC Bev</td>
<td>10.3 11.2 14.1</td>
<td>.908 .717</td>
<td>NS (TE)</td>
</tr>
<tr>
<td>OCEANS</td>
<td>484</td>
<td>Recurrent</td>
<td>GC Bev</td>
<td>&gt; Bev</td>
<td>8.4 12.4</td>
<td>.48</td>
<td>NS (TE)</td>
</tr>
<tr>
<td>AURELIA</td>
<td>361</td>
<td>Recurrent</td>
<td>Tax/ Topo / LDox</td>
<td>Tax/ Topo / LDox + Bev</td>
<td>3.4 6.7</td>
<td>.48</td>
<td>NR</td>
</tr>
</tbody>
</table>

NS = not significant; TE = too early, NR = not reported
High Tumor Burden as Predictive Factor?

- ICON 7 subgroup analysis suggests greater relative impact of bevacizumab in high risk patients (subopt. Stage IIIC, IV)
- HR for PFS 0.68 in high risk (in contrast to overall HR 0.81 – low risk HR not given)
- Preliminary/subgroup analysis of OS in same direction (caution in interpretation – only about 33% patients have died)
GOG-0218: Optimal/Suboptimal data show different trend – **optimal** cases had lower HR

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio</th>
<th>Experimental arm (CP + BEV → BEV; Arm III) better</th>
<th>Control arm (CP; Arm I) better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3 optimal (n=434)</td>
<td>0.618</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 suboptimal (n=496)</td>
<td>0.763</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4 (n=318)</td>
<td>0.698</td>
<td></td>
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<tr>
<td>PS 0 (n=616)</td>
<td>0.710</td>
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<tr>
<td>PS 1/2 (n=632)</td>
<td>0.690</td>
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</tr>
<tr>
<td>Age &lt;60 years (n=629)</td>
<td>0.680</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 60–69 years (n=409)</td>
<td>0.763</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥70 years (n=210)</td>
<td>0.678</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment hazard ratio range: 0.33 to 3.0
Nevertheless...

- If AURELIA study shows a survival gain, there would be an argument in favour of defining recurrent/resistant OVCA patients as the group who should receive bevacizumab.

- Rationale would be: why give the drug early to everyone when it can be given later only to the subset who recur – and who truly benefit?
Biological Selection Markers: Applies not only to Ovarian Cancer!

- Search for biomarkers for anti-angiogenic treatment has been long and challenging – generally studies have been exploratory in non-randomized cohorts

- Examples of potential candidate markers:
  - Malignant tissue:
    - Microvessel density, VEGF-A, VEGFR
  - Patient:
    - Plasma VEGF, circulating endothelial cells, genetic polymorphisms in VEGF, or VEGFR

Findings variable, inconclusive
Host VEGFR Variants?

VEGF pathway genetic variants as biomarkers of treatment outcome with bevacizumab: an analysis of data from the AViTA and AVOREN randomised trials

Diether Lambrechts*, Bart Claes*, Paul Delmar, Joke Reumers, Massimiliano Mazzone, Betül T Yesilyurt, Roland Devlieger, Chris Verslype, Sabine Tejpar, Hans Wildiers, Sanne de Haas, Peter Carmeliet, Stefan J Scherer, Eric Van Cutsem

• VEGF Receptor 1 allelic variant identified that showed **significant genotype by treatment interaction** in pancreatic cancer trial of gemcitabin/erlotinib +/- bevacizumab (p=0.01)
Survival by Genotype in Bevacizumab and Placebo Treated Patients.

**B Placebo-treated group**
- AA median=7.7 (95% CI 5.3-11.2)
- AC median=5.8 (95% CI 4.5-8.9)
- CC median=5.9 (95% CI 4.1-NA)

AC vs AA: HR=1.62 (95% CI=0.97)
CC vs AA: HR=1.53 (95% CI=0.75)

**A Bevacizumab-treated group**
- AA median=10.2 (95% CI 7.8-14.9)
- AC median=5.9 (95% CI 4.0-11.5)
- CC median=4.7 (95% CI 4.3-NA)

AC vs AA: HR=2.00 (95% CI=1.19-3.36) p=0.0091
CC vs AA: HR=4.72 (95% CI=2.08-10.68) p=0.0002

Number at risk:
- rs9582036 AA: 40 32 20 11 3 2
- rs9582036 AC: 28 16 9 2 2 0
- rs9582036 CC: 9 3 0 0 0 0
In a trial of chemotherapy +/- bevacizumab, in gastric cancer, trend to greater impact of bevacizumab in patients with higher baseline plasma VEGFA (test for interaction 0.07)
Survival impact of Bevacizumab Stratified by > or ≤ median pVEGF-A

A

Overall Survival (%)

Study Month

No. at risk
Placebo + chemo (≤ median) 173 161 139 112 83 57 33 9 0
Placebo + chemo (> median) 184 158 115 80 56 37 21 6 0
Bevacizumab + chemo (≤ median) 184 174 144 119 94 57 31 9 0
Bevacizumab + chemo (> median) 171 156 130 101 79 44 18 10 0
Biomarkers for Ovarian Cancer?

• VEGF-A levels, genetic pathway variants of VEGF/R are exciting potential markers to evaluate in the 4 RCTs of bevacizumab in OVCA – work is ongoing

• Unclear, even if validated predictive biomarker for bevacizumab can be found in one trial, if it will apply to:
  – All cancers
  – All stages of the cancer in which it appears to be useful
  – All angiogenesis inhibitors

• But these studies raise possibility that there is hope that selection biomarkers can be found.
Summary – Angiogenesis Inhibitors in Ovarian Cancer

• Great progress in completion of phase III trials of angiogenesis inhibitors in OVCA over past 2-3 years.

• Clear phase III evidence of biological effect (PFS) of bevacizumab. Trials of other agents not yet reported.

• Overall survival data not mature.

• Will PFS gains will translate into symptom benefit or OS gains? In which patients? – highest priority questions.

• Also critical: use data and biological samples from these trials to test selection biomarker hypotheses – esp. those found promising in other cancers.
Thank You

To my colleagues Dr. Amit Oza, Dr. Eric Pujade-Lauraine for sharing slides and data

To you for your attention