ANTIANGIOGENIC AGENTS IN OVARIAN CANCER: 2015

Bradley J. Monk, MD, FACS, FACOG
Professor and Director
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Creighton University School of Medicine at St. Joseph’s Hospital and Medical Center, a Dignity Health Member
University of Arizona Cancer Center-Phoenix Arizona USA

bradley.monk@chw.edu
Disclosure

• I have received grants and honoraria from Roche, Amgen, and Glaxo SmithKline as an advisor, speaker, chairman and investigator

• The medical claims that I am going to present are depending on evidence based medicine and my clinical expertise
Objectives

• Outline the development of anti-vascular agents in ovarian cancer (new trials and new agents)
  – Anti-VEGF
  – Anti-Angiopoietin
  – Vascular disrupting agents
  – Other
• Consider recent and future FDA approvals
• Discuss biomarker development
• Discuss the research of novel combinations
• Summarize best practice guidelines
B-2 What Are the Promising Targets for Future Therapeutic Approaches?

- The most promising targets in clinical trials are angiogenesis and homologous recombination deficiency.
Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homlesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Frédéric Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators
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
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- Placebo

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

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

Cytotoxic (6 cycles)
Maintenance (16 cycles)
15 months

GOG-0218: significantly increased PFS with continued bevacizumab compared with standard chemotherapy

<table>
<thead>
<tr>
<th>Group</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 CP + PI → PI (n=625)</td>
<td>10.6</td>
<td>0.89 (0.78–1.02)</td>
<td>0.0437&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>II CP + B15 → PI (n=625)</td>
<td>11.6</td>
<td>0.70 (0.61–0.81)</td>
<td>&lt;0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>III CP + B15 → B15 (n=623)</td>
<td>14.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*<sup>a</sup>p value boundary = 0.0116

Data cut-off date: 25 February 2010

Avastin Summary of Product Characteristics
Roche, data on file
# GOG-0218

## CA-125 To Determine Progression

<table>
<thead>
<tr>
<th></th>
<th>Protocol-defined PFS analysis</th>
<th>CA-125-censored PFS analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP (Arm I)</td>
<td>10.3 months</td>
<td>12.0 months</td>
</tr>
<tr>
<td>CP + BEV → BEV (Arm III)</td>
<td>14.1 months</td>
<td>18.0 months</td>
</tr>
<tr>
<td><strong>Absolute diff. median PFS</strong></td>
<td>3.8 months</td>
<td>6.0 months</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.717</td>
<td>0.645</td>
</tr>
<tr>
<td><strong>Censored for CA125, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP (Arm I)</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>CP + BEV → BEV (Arm III)</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

GOG-0218
Ad Hoc Survival Analysis in Stage IV

Proportion Surviving

Overall Survival (months)

CPP (n=153)  CPB (n=165)  CPB+B (n=165)

Median OS (months) 32.8  32.9  40.6

HR 0.72, 95% confidence interval 0.53-0.97

NEJM Data cut-off date August 26, 2011
(ASCO 2010 cut-off date February 5, 2010)
Randall LM et al SGO 2013
ICON7: Study Design

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

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

Primary endpoints:
PFS

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

Perren, et al. ESMO 2010

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

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

**Bevacizumab 7.5 mg/kg
12 months

*Might vary based on GCIG group
**Omit cycle 1 bevacizumab if <4 weeks from surgery
Perren, et al. ESMO 2010
Final OS: High-risk (n=502)

Stage III suboptimally debulked, any stage IV or no debulking surgery

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Research</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (%)</td>
<td>174</td>
<td>158</td>
<td>332</td>
</tr>
<tr>
<td>Restricted mean, months</td>
<td>34.5</td>
<td>39.3</td>
<td>+4.8</td>
</tr>
<tr>
<td>Median, months</td>
<td>30.3</td>
<td>39.7</td>
<td>+9.4</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.63–0.97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-proportionality test: $p=0.0072$

BEV exposure

Number at risk

Control | 254 | 208 | 156 | 101 | 82 | 21
Research | 248 | 224 | 180 | 135 | 95 | 27

Oza AM et al ESMO 2013
• Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer

• Bevacizumab is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier

• The recommended dose of Bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion
The addition of bevacizumab is recommended for patients with advanced ovarian cancer with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON-7 trial [I, B].

Bevacizumab should be given ....with a treatment duration of one year.

Trials with other anti-angiogenic drugs and extended therapy with bevacizumab are ongoing.

ENGOT-ov15/ AGO OVAR 17
Evaluation of Optimal Initial Treatment Duration of Bevacizumab in Combination With Standard Chemotherapy in Patients With Ovarian Cancer: **BOOST**

**Randomisation**

Bevacizumab 15 mg/kg q 21 days
Paclitaxel 175 mg/m²
Carboplatin AUC5

**Until cycle 22 (15 months)**

Bevacizumab 15 mg/kg q 21 days
Paclitaxel 175 mg/m²
Carboplatin AUC5

**Until cycle 44 (30 months)**

**Stratification:**
- FIGO stage
- residual macroscopic disease (no/yes)
- Center

Open: November 2011
Enrolled: 67
N: 800
OCEANS

Platinum-sensitive, recurrent OC, PP, FTC
No prior bevacizumab n=480

Stratification variables:
• Time to recurrence
• Cytoreductive surgery

Arm A

Carboplatin AUC 4
Gemcitabine 1000 mg/m² d1/8

Placebo to progression

Arm B

Carboplatin AUC 4
Gemcitabine 1000 mg/m² d1/8

Bevacizumab 15 mg/kg to progression

Primary endpoint: PFS
Secondary endpoints: ORR, OS, DR, safety
Exploratory endpoints: IRC, CA 125 response, ascites
IRC present

ClinicalTrials.gov Identifier: NCT00434642

Aghajanian C et al J Clin Oncol 29: 2011 (suppl; abstr LBA5007)
**OCEANS: Primary analysis of PFS**

- **Events, n (%):**
  - CG + PL (n=242): 187 (77)
  - CG + BV (n=242): 151 (62)

- **Median PFS, months (95% CI):**
  - CG + PL: 8.4 (8.3 – 9.7)
  - CG + BV: 12.4 (11.4 – 12.7)

- **Stratified analysis**
  - HR (95% CI): 0.484 (0.388 – 0.605)
  - Log-rank p-value: <0.0001

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**Proportion progression free**

**Pts at risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>CG + PL (242)</th>
<th>CG + BV (242)</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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The “OS” Creep...

The “OS” Creep...


Aghajanian C et al Society of Gynecologic Oncology 2014 Tampa FL
NCCN Guideline Recommendations for Bevacizumab in Platinum-Resistant Ovarian Cancer

<table>
<thead>
<tr>
<th>Category 2A</th>
<th>Bevacizumab + paclitaxel (weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2A</td>
<td>Bevacizumab + liposomal doxorubicin</td>
</tr>
<tr>
<td>Category 2A</td>
<td>Bevacizumab + topotecan</td>
</tr>
</tbody>
</table>

- Bevacizumab in combination with weekly paclitaxel, liposomal doxorubicin, or topotecan are NCCN category 2A recommendations for platinum-resistant ovarian cancer
  - In patients who have not previously received bevacizumab
  - Contraindicated for patients at increased risk of gastrointestinal perforation

Bevacizumab solution in combination with Paclitaxel

On November 14, 2014, the U. S. Food and Drug Administration approved bevacizumab solution for intravenous infusion (Avastin, Genentech, Inc.) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The approval is based on the results of an international, randomized, two-arm trial (AURELIA) with the primary comparison of investigator-assessed progression-free survival (PFS). This trial compared bevacizumab plus chemotherapy versus chemotherapy alone. The trial enrolled 361 patients: 179 patients were assigned to receive bevacizumab plus chemotherapy, and 182 patients were assigned to receive chemotherapy alone. The chemotherapy included paclitaxel, pegylated liposomal doxorubicin, or topotecan.

Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. All enrolled patients had received no more than two prior chemotherapy regimens, had ECOG performance status of 0 to 2 and had recurred within less than six months from the most recent platinum-based therapy.

The PFS assessment demonstrated a statistically significant improvement in patients who received bevacizumab plus chemotherapy compared to those who received chemotherapy alone (HR=0.38; 95% CI: 0.30, 0.49; p<0.0001, stratified log-rank test). The median PFS of patients who received bevacizumab plus chemotherapy was 8.8 months (95% CI: 5.6, 7.8) compared to 3.4 months (95% CI: 2.1, 3.8) for those receiving chemotherapy alone. There was no significant difference in overall survival (OS) (median OS: 16.6 vs. 13.3 months; HR 0.89; 95% CI: 0.69, 1.14).
Ongoing clinical trials will extend our knowledge of how best to use bevacizumab in ovarian cancer.

5,060 patients treated in completed trials

Completed trials
- Front-line trials:
  - GOG-0218
    - NCT00262847
    - n=1,873
  - ICON7
    - NCT00483782
    - n=1,528
  - GOG-0262
    - NCT01167712
    - n=625
  - OCTAVIA
    - NCT00937560
    - n=189

- Recurrent trials:
  - OCEANS
    - NCT00434642
    - n=484
  - AURELIA
    - NCT00976911
    - n=361

Ongoing trials
- AGO-Ovar 17
  - NCT01462890
  - n=927
- GOG-0252
  - NCT00951496
  - n=1,500
- ROSiA
  - NCT01239732
  - n=1,032

Planned trials
- GOG-0213
  - NCT00565851
  - n=660
- MITO16/MaNGO/OV2
  - NCT01802749
  - n=400
- AGO-OVAR 2.21
  - NCT01837251
  - n=654

5,173 patients to be enrolled in ongoing trials
Abstract 5502: Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab

Charlie Gourley,1 Andrea McCavigan,2 Timothy Perren,3 James Paul,4 Caroline Ogilvie Michie,5 Michael Churchman,1 Alistair Williams,6 W. Glenn McCluggage,7 Mahesh Parmar,8 Richard S. Kaplan,8 Laura A. Hill,2 Iris A Halfpenny,2 Eamonn J. O'Brien,2 Olaide Raji,2 Steve Deharo,2 Timothy Davison,2 Patrick Johnston,9 Katherine E. Keating,2 D. Paul Harkin,2,9 Richard D. Kennedy2,9

1University of Edinburgh Cancer Research UK Centre, MRC IGMM, Edinburgh, UK
2Almac Diagnostics, 19 Seagoe Industrial Estate, Craigavon, UK
3St. James’s Institute of Oncology, St. James’s University Hospital, Leeds, UK
4Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK
5Ninewells Hospital, Dundee, UK
6Division of Pathology, University of Edinburgh, Edinburgh, UK
7Department of Pathology, Royal Group of Hospitals Trust, Belfast, UK
8MRC Clinical Trials Unit, London, UK
9Center for Cancer Research and Cell Biology, Queen’s University of Belfast, UK

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Methods

Discovery

Edinburgh: 387 ovarian cancers

Validation 1 (in silico)

Australia (Tothill): 285 ovarian cancers

Validation 2

ICON7: 375 ovarian cancers

FFPE tumour macrodissection

mRNA isolation

Expression microarray analysis (Almac Ovarian DSA®)

Independent pathology review

Analysis of high grade serous tumours

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Edinburgh dataset; unsupervised hierarchical clustering

- 25% cell cycle
- 31% metabolic processes
- 44% vascular development angiogenesis

Clusters:
- Immune
- Angioimmune
- Angio

Class Labels:
- Immune only
- Pro-angiogenic
Edinburgh dataset; survival analysis

### Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune vs Angioimmune</td>
<td>0.60</td>
<td>0.44-0.82</td>
<td>0.002</td>
</tr>
<tr>
<td>Immune vs Angio</td>
<td>0.64</td>
<td>0.45-0.92</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune vs Angioimmune</td>
<td>0.58</td>
<td>0.41-0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Immune vs Angio</td>
<td>0.55</td>
<td>0.37-0.80</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Edinburgh dataset; Immune subgroup signature generation

63-gene signature developed to distinguish Immune subgroup patients from those in the Angio and Angioimmune subgroups.

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Application of 63 gene signature to Tothill dataset

Progression free survival

Univariate: $HR = 0.611 [0.439-0.996]$, $p = 0.048$
Multivariable: $HR = 0.645 [0.423-0.982]$, $p = 0.041$

Overall survival

Univariate: $HR = 0.357 [0.219-0.582]$, $p<0.001$
Multivariable: $HR = 0.343 [0.206-0.571]$, $p<0.001$

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Immune signature prognostic within the control arm of ICON7

Progression free survival

Univariate: HR = 0.47 [0.32-0.71], p < 0.001
Multivariable: HR = 0.52 [0.33-0.81], p = 0.004

Overall survival

HR = 0.45, [0.26-0.79], p = 0.005
HR = 0.53 [0.29-0.96], p = 0.04

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Immune subgroup patients have inferior progression free survival when treated with bevacizumab

Immune subgroup; 41% of ICON7 TR patients

Test for interaction, p=0.015

<table>
<thead>
<tr>
<th></th>
<th>Immune subgroup</th>
<th>Proangiogenic subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proportionality test</td>
<td>p=0.048</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Restricted mean PFS in months (se)</td>
<td>C/P 29.7 (2.2)</td>
<td>C/P 18.3 (1.5)</td>
</tr>
<tr>
<td></td>
<td>C/P/Bev 23.8 (1.8)</td>
<td>C/P/Bev 19.3 (1.3)</td>
</tr>
<tr>
<td>Diff in restricted mean PFS (95% ci)</td>
<td>-5.9 (-11.5 to -0.3)</td>
<td>1.0 (-2.9 to 4.9)</td>
</tr>
<tr>
<td>Median PFS in months</td>
<td>C/P 35.8</td>
<td>C/P 12.3</td>
</tr>
<tr>
<td></td>
<td>C/P/Bev 18.5</td>
<td>C/P/Bev 17.4</td>
</tr>
</tbody>
</table>

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Immune subgroup patients have inferior overall survival when treated with bevacizumab

**Immune subgroup**

**Non-immune (pro-angiogenic) subgroup**

**Test for non-proportionality negative in both molecular subgroups**

<table>
<thead>
<tr>
<th></th>
<th>Immune subgroup</th>
<th>Proangiogenic subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td>HR 2.00 (1.11-3.61), p=0.022</td>
<td>HR 1.19 (0.80-1.78), p=0.386</td>
</tr>
<tr>
<td><strong>Test for interaction</strong>, p=0.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td>HR 2.37 (1.27-4.41), p=0.007</td>
<td>HR 1.10 (0.73-1.66), p=0.637</td>
</tr>
<tr>
<td><strong>Test for interaction</strong>, p=0.020</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)
Pros & Cons
Multi-targeting vs Isolated VEGF Inhibition

• **Pros**
  – May more effectively block angiogenesis
  – Potentially reduced likelihood of resistance due to activity of compensatory pathways
  – Oral (PO) route → convenience

• **Cons**
  – Oral (PO) route → bio-distribution
  – Broader range of adverse effects (dermatologic, GI mucosal)

Pazopanib* Mechanism of Action

*Pazopanib is an investigational agent in ovarian cancer.
Phase III randomized, placebo-controlled, double-blind, multicenter
- N=940 patients randomized (1:1) from June 2009 to August 2010
- Pazopanib administered at 800 mg daily for up to 24 months*

First-line surgery and chemotherapy (allowed: dose-dense, IP, neoadjuvant)

If not PD + tumor < 2 cm

Median 7 months from diagnosis to randomization

Randomize

Pazopanib 24 months

Placebo 24 months

Observation (to PD)

Survival follow-up (post-PD)

*Original design was for 12 months and later amended to 24 months

Du Bois A et al J Clin Oncol 31, 2013 (suppl; abstr LBA5503)
Primary Endpoint: Progression-free Survival (RECIST)

Median time from Diagnosis: 7 months

Δ = 5.6 months

Pazopanib: 472 pts. / 237 events
median 17.9 (15.9 - 21.8) mos

Placebo: 468 pts. / 273 events
median 12.3 (11.8 - 17.7) mos

Δ = 5.6 months

Patients at risk

Du Bois A et al J Clin Oncol 31, 2013 (suppl; abstr LBA5503)
### AGO-OVAR 16

**Adverse Events Grade 3-4 per Patient occurring in at least 1% in the Pazopanib Arm**

<table>
<thead>
<tr>
<th>Grade 3/4 adverse events</th>
<th>Placebo (N=461)</th>
<th>Pazopanib (N=477)</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>26 (6%)</td>
<td>147 (31%)</td>
<td>121 (25%)</td>
</tr>
<tr>
<td>Hypertension (including Grade 2)</td>
<td>80 (17%)</td>
<td>248 (52%)</td>
<td>168 (35%)</td>
</tr>
<tr>
<td>Liver-related toxicity</td>
<td>3 (&lt;1%)</td>
<td>45 (9%)</td>
<td>42 (9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (2%)</td>
<td>47 (10%)</td>
<td>40 (8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (1%)</td>
<td>39 (8%)</td>
<td>34 (7%)</td>
</tr>
<tr>
<td>Asthenia / Fatigue</td>
<td>1 (&lt;1%)</td>
<td>13 (3%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (&lt;1%)</td>
<td>12 (3%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysesthesia</td>
<td>1 (&lt;1%)</td>
<td>9 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (&lt;1%)</td>
<td>8 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (1%)</td>
<td>8 (2%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (&lt;1%)</td>
<td>6 (1%)</td>
<td>4 (&lt;1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (&lt;1%)</td>
<td>5 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

Du Bois A et al J Clin Oncol 31, 2013 (suppl; abstr LBA5503)
Cediranib (AZD 2171)

- Potent oral inhibitor of vascular endothelial growth factors
- >800–5000 fold selectivity for VEGFR-2
- In vitro activity against VEGFR-1 and -3
- Inhibits growth of established xenografts – lung, colorectal, prostate, breast and ovary

- Phase II trials showed activity as a single agent in ovarian cancer\(^1\)

\(^1\) Matulonis et al 2009; Hirte et al 2010
ICON6: Cediranib with platinum-based chemotherapy in ‘platinum-sensitive’ relapsed ovarian cancer

6 Cycles platinum-based Chemotherapy
- Carboplatin/paclitaxel
- Carboplatin/gemcitabine
- Single agent platinum

Maintenance phase

Study schema

Relapse > 6 months after completion of first line platinum-based chemotherapy

Randomise 2 : 3 : 3

Arm A (Chemo only)
- Chemotherapy + placebo
- Continue placebo

Arm B (Concurrent)
- Chemotherapy + cediranib
- Switch to placebo

Arm C (Maintenance)
- Chemotherapy + cediranib
- Maintenance cediranib

Treatment continued to 18 months or until progression (>18 for patients continuing to benefit)

Ledermann JA et ESMO 2010
Progression-free survival – all three arms

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>112 (94.9)</td>
<td>152 (87.4)</td>
<td>139 (84.8)</td>
</tr>
<tr>
<td>Median, months</td>
<td>8.7</td>
<td>10.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Log-rank test (trend)</td>
<td>p=0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR vs. Chemo only (95% CI)</td>
<td>0.67 (0.53–0.87)</td>
<td>0.57 (0.44–0.74)</td>
<td></td>
</tr>
<tr>
<td>Restricted means, months</td>
<td>9.4</td>
<td>11.4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Ledermann JA et ESMO 2010
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>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.70 (0.51 – 0.99)</td>
<td></td>
</tr>
<tr>
<td>Test for non-proportionality</td>
<td>p=0.0042</td>
<td></td>
</tr>
<tr>
<td>Restricted means, months</td>
<td>17.6</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Ledermann JA et ESMO 2010
Angiopoietin Axis –
Ang1 and Ang2 Interact With Tie2 Receptor to Mediate Vascular Remodeling

Ang1 stabilizes endothelial junctions and increases pericyte coverage\(^1,2\)
“Vessel quality”

Ang2 promotes endothelial sprouting and increases blood vessel density\(^1,2,3\)
“Vessel quantity”

Angiopoietins also regulate lymphangiogenesis\(^1\)

Ang1 and Ang2 levels are elevated in patients with ovarian carcinoma\(^4\)


Presented by Monk BJ at European Cancer Congress
European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41; Lancet Oncol. 2014 Jun 17. [Epub ahead of print]
Trebananib (AMG 386) – Peptibody That Binds and Neutralizes Ang1 and Ang2

- Trebananib is an investigational recombinant peptide-Fc fusion protein (peptibody)
- In clinical studies trebananib has shown:
  - Single-agent activity in relapsed ovarian cancer in a phase 1 study
  - Prolongation of PFS in a randomized phase 2 study in combination with paclitaxel in recurrent ovarian cancer


Presented by Monk BJ at European Cancer Congress European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41
TRINOVA-1 Trial Design

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

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

Weekly Paclitaxel + Placebo
- Treat to PD/toxicity
Weekly Paclitaxel + Trebananib
- Treat to PD/toxicity

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

Presented by Monk BJ at European Cancer Congress
European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41

ClinicalTrials.gov Identifier: NCT01204749
TRINOVA-1: Progression-free Survival (Primary Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Pac + Placebo (n = 458)</th>
<th>Pac + 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>
<td></td>
</tr>
</tbody>
</table>

Presented by Monk BJ at European Cancer Congress
European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41; Lancet Oncol. 2014 Jun 17. [Epub ahead of print]
## TINOVA-1: Treatment-emergent AEs of Specific Interest

<table>
<thead>
<tr>
<th>Patient Incidence, n (%)</th>
<th>Paclitaxel + Placebo N = 458</th>
<th>Paclitaxel + Trebananib N = 461</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, all grades</td>
<td>16 (4)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Hypertension, grade ≥2</td>
<td>9 (2)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Proteinuria, all grades</td>
<td>13 (3)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Venous thrombotic events, grade ≥3</td>
<td>13 (3)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Arterial thrombotic events, all grades</td>
<td>3 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Impaired wound healing, all grades</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>GI perforation or fistula, all grades</td>
<td>1 (&lt;1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>CNS hemorrhage, all grades</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Non-CNS hemorrhage, grade ≥3</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Presented by Monk BJ at European Cancer Congress
European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41; Lancet Oncol. 2014 Jun 17. [Epub ahead of print]
TRINOVA-1: Overall Survival (Interim Analysis)

- Pac + Placebo (n = 458):
  - Events, n (%): 163 (36)
  - Median OS, months: 17.3
- Pac + Trebananib (n = 461):
  - Events, n (%): 150 (33)
  - Median OS, months: 19.0

HR = 0.86 (95% CI, 0.69 – 1.08)

P (stratified log rank) = 0.19

Presented by Monk BJ at European Cancer Congress
European Journal of Cancer 49; suppl 3, Sept 2013 LBA 41; Lancet Oncol. 2014 Jun 17. [Epub ahead of print]
RANDOMIZED PHASE 2 EVALUATION OF BEVACIZUMAB VERSUS BEVACIZUMAB/FOSBRETABULIN IN RECURRENT OVARIAN, TUBAL OR PERITONEAL CARCINOMA: A NRG ONCOLOGY AND GOG STUDY

Bradley J. Monk, MD¹, Michael Sill, PhD², Joan L. Walker, MD³, Paul A. DiSilvestro, MD⁴, Greg Sutton MD⁵, Krishnansu S. Tewari, MD⁶, Eduardo R. Pajon, MD⁷, Lainie P. Martin, MD⁸, Jeanne M. Schilder, MD⁹, Robert L. Coleman, MD¹⁰, Jai Balkissoon, MD¹¹, Carol Aghajanian, MD¹²


ClinicalTrials.gov identifier: NCT01305213

Monk BJ et al Presented at The 15th Biennial Meeting of the International Gynecologic Cancer Society November 2014 in Melbourne, Australia
Vascular Disrupting Agents (VDAs): Target Established Tumor Vasculature

- Anti-angiogenesis agents target the migration, growth, and differentiation of new tumor associated endothelial cells
- VDAs collapse and occlude established tumor blood vessels
- Blood flow reduction leads to tumor necrosis
- Unlikely to cause resistant mutations
- Broad combination potential: chemo and anti-angiogenic drugs

Tumor blood flow before VDA*

Tumor blood flow after VDA*

* Dynamic Contrast Enhanced - Magnetic Resonance Imaging (DCE-MRI) using the paramagnetic contrast agent gadopentetate dimeglumine (Gd-DTPA)

Monk BJ et al Presented at the The 15th Biennial Meeting of the International Gynecologic Cancer Society November 2014 in Melbourne, Australia
Fosbretabulin

- Fosbretabulin is a water-soluble prodrug of cis-combretastatin A4 (cis-CA4)
- Combretastatin A4 (CA4) is a natural product isolated from the African bush willow (Combretum caffrum)

Chemical Formula: C_{22}H_{32}NO_{11}P
Exact Mass: 517.171
Molecular Weight: 517.463
Fosbretabulin: Mechanism-of-Action

- Potent and reversible tubulin depolymerizing agent
- Selectively targets immature endothelial cells typically seen in solid tumors
  - Lack smooth muscle and pericytes, rely more on tubulin to maintain the flat shape of vessel wall
  - Tubulin inhibition rounds up affected endothelial cells, obstructing blood vessel lumen
- Blockage at any point in a vessel segment will shut off blood flow – upstream and downstream
  - Leads to rapid cell death and necrosis
Phase II Study Design-GOG 186i

1–3 prior chemo regimens with no more than 1 non-platinum, non-taxane regimen

Target n=103  
Enrolled n=107

1:1 randomization

Bevacizumab 15 mg/kg  
IV q3 weeks* (n=54)

Bevacizumab 15 mg/kg + fosbretabulin 60 mg/m²  
IV q3 weeks* (n=53)

*Treatment continued until disease progression or adverse events prohibited further therapy

Monk BJ et al Presented at the The 15th Biennial Meeting of the International Gynecologic Cancer Society November 2014 in Melbourne, Australia
Progression-free Survival Analysis by Intention to Treat

Measurable disease ORR:
Bevacizumab = 28.2% (90% CI 16.7 ~ 42.3%)
Bevacizumab + fosbretabulin = 35.7% (90% CI 23.5 ~ 49.5%)

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>HR*</th>
<th>90% CI</th>
<th>1-sided P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp to ref</td>
<td>0.685</td>
<td>[0.47, 1.00]</td>
<td>0.049</td>
</tr>
</tbody>
</table>

*Hazard Ratios of the experimental level to the reference level of the treatment comparison were stratified by measurable disease status (Yes/No), prior bevacizumab use (Yes/No), and platinum sensitivity (>12 months/≤ 12 months) using a Cox proportional hazards model; Bev = bevacizumab; Bev+fos = bevacizumab+fosbretabulin

Monk BJ et al Presented at the The 15th Biennial Meeting of the International Gynecologic Cancer Society November 2014 in Melbourne, Australia
Progression-free Survival by Treatment

Among platinum resistant subjects

**Treatment comparison**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Total</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Bev</td>
<td>13</td>
<td>14</td>
<td>3.4</td>
</tr>
<tr>
<td>2: Bev+Fos</td>
<td>10</td>
<td>13</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Exp to ref | HR* | Log-rank P value |
-----------|-----|------------------|
          | 0.57| 0.01             |

*Hazard Ratio of the experimental level to the reference level of the treatment comparison were stratified by measurable disease status (Yes/No) and prior bevacizumab use (Yes/No), using a Cox proportional hazards model. The C.I. is questionable and therefore not available, which may be due to the small number of patients within some strata; Bev = bevacizumab; Bev+Fos = bevacizumab+fosbretabulin
A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

Joyce F. Liu1, William T. Barry1, Michael Birrer2, Jung-Min Lee3, Ronald Buckanovich4, Gini Fleming5, BJ Rimel6, Mary Buss7, Sreenivasa Nattam8, Jean Hurteau9, Weixiu Luo1, Philippa Quy1, Lisa Obermayer1, Christin Whalen1, Hang Lee2, Eric Winer1, Elise Kohn3, S. Percy Ivy3, Ursula A. Matulonis1

1Dana-Farber Cancer Institute, 2Massachusetts General Hospital, 3National Cancer Institute, 4University of Michigan, 5University of Chicago, 6Cedars-Sinai Medical Center, 7Beth Israel Deaconess Medical Center, 8Fort Wayne Medical Oncology and Hematology, 9NorthShore Medical Group

Presented by: Joyce Liu, MD, MPH ASCO 2014 J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
Study Design

• Phase 2 open-label randomized study
• Stratification factors
  – germline BRCA status (known deleterious mutation carrier vs. non-carrier vs. unknown)
  – prior receipt of anti-angiogenic
• Target accrual 90 pts
  – Powered to detect a hazard ratio (HR) of 0.57, with an alpha of 0.10 and 86% power

Dx platinum-sensitive recurrent ovarian cancer

Randomize 1:1

Cediranib 30mg daily + Olaparib capsules 200mg BID

Olaparib capsules 400mg BID

Disease progression by RECIST v1.1 criteria

Presented by: Joyce Liu: J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
Primary Outcome: Cediranib/olaparib significantly increased PFS compared to olaparib alone

- Cediranib/olaparib:
  - PFS events: 19
  - Median PFS: 17.7 mo
  - p = 0.005
  - HR 0.42 (95% CI: 0.23-0.76)

- Olaparib:
  - PFS events: 28
  - Median PFS: 9.0 mo

Presented by: Joyce Liu: J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
Secondary Outcome: Cediranib/olaparib significantly increased overall response rate (ORR) compared to olaparib alone

Best overall response

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treated</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Olap</td>
<td>46</td>
<td>2</td>
<td>4.4</td>
<td>20</td>
<td>43.5</td>
</tr>
<tr>
<td>Ced/Olap</td>
<td>44</td>
<td>5</td>
<td>11.4</td>
<td>30</td>
<td>68.2</td>
</tr>
</tbody>
</table>

Comparison of overall response rate (ORR)

<table>
<thead>
<tr>
<th>Arm</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Olaparib alone</td>
<td>22</td>
</tr>
<tr>
<td>Cediranib/Olaparib</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

Presented by: Joyce Liu: J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

**BRCA mutation carrier**

<table>
<thead>
<tr>
<th>Treatment Assignment</th>
<th>Olaparib</th>
<th>Ced/Olap</th>
<th>Median PFS</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Olaparib</td>
<td>13</td>
<td>10</td>
<td>16.5 mo</td>
<td>0.16</td>
<td>0.55 (0.24-1.27)</td>
</tr>
<tr>
<td>2: Olaparib/Cediranib</td>
<td></td>
<td></td>
<td>19.4 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BRCA non-carrier/unknown**

<table>
<thead>
<tr>
<th>Treatment Assignment</th>
<th>Olaparib</th>
<th>Ced/Olap</th>
<th>Median PFS</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Olaparib</td>
<td>15</td>
<td>9</td>
<td>5.7 mo</td>
<td>0.008</td>
<td>0.32 (0.14-0.74)</td>
</tr>
<tr>
<td>2: Olaparib/Cediranib</td>
<td></td>
<td></td>
<td>16.5 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Joyce Liu: J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
### Treatment-related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib alone (N = 46)</th>
<th>Cediranib/Olaparib (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum Grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Non-Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (15)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (26)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>4 (9)</td>
<td>-</td>
</tr>
<tr>
<td>WBC decreased</td>
<td>3 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Platelet decreased</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Presented by: Joyce Liu: J Clin Oncol 32:5s, 2014 (suppl; abstr LBA5500)
NRG OVM1403: Platinum-Sensitive Concept

- Recurrent HGSC with PFI >6 months (following most recent platinum)
- No more than 3 prior treatment regimens (including primary therapy)
- RECIST measurable or evaluable disease with accessible tumor
- No prior PARPi therapy, prior bevacizumab permitted
- Stratify for BRCA status, number of prior treatment regimens
- Primary endpoint: PFS 85% Power with HR 0.625

Olaparib 300 mg BID

Cediranib 30 mg QD
Olaparib 200 mg BID

Platinum-based combo* (IV)

*Carboplatin + gemcitabine or paclitaxel or PLD

Open: GCSC Review approved pending activation
Target Accrual: 450 pts (135 BRCA1/2 +)

Liu J, for GOG
NRG OVM1405: Platinum-Resistant Concept

- Recurrent HGSC with PFI <6 months (following most recent platinum)
- No more than 2 prior treatment regimens (including primary therapy)
- RECIST measurable or evaluable disease, biopsy accessible
- No prior PARPi therapy, prior bevacizumab permitted
- Stratify for BRCA status, number of prior treatment regimens
- Primary endpoint: OS 90% Power with HR 0.625

Randomized Phase II (n = 180)
- Cediranib + Placebo (PO)
- Olaparib + Placebo (PO)
- Cediranib + Olaparib (PO)
- Non-Platinum Chemo* (IV)

Randomized Phase III (n = 280)
- Selected Regimen (PO)
- Non-Platinum Chemo* (IV)
  1:1

Open: GCSC approved pending activation
Target Accrual: 460 pts (135 BRCA1/2 +)

* Weekly paclitaxel or PLD

Liu J, for GOG
**ENGOT Proposed Study: PAOLA 1**

- Phase III randomized, placebo-controlled, double-blind, multicenter
- Olaparib tablets administered at 600 mg daily for up to 2 years.

**Stratification factors:**
First-line treatment outcome (complete resection after initial surgery and NED at screening, complete resection at interval debulking surgery and NED at screening, incomplete resection at initial or interval debulking surgery and in CR at screening, PR at screening) & gBRCA status (yes, no, unknown)
Ovarian Carcinoma
Inhibiting Angiogenesis

Moving forward

- New targets and new agents
  - Trebananib: ANG1 and ANG 2
- Combinations
  - PARPi
  - Vascular disrupting agents
- Prognostic and predictive biomarkers
Thank You

Bradley.monk@chw.edu