Ovarian Cancer
Clinical Trials

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FDA Approved Drugs in Ovarian Cancer
1978 to 2015

• 1978  Cisplatin
• 1990  Altretamine
• 1991  Carboplatin
• 1992  Paclitaxel
• 1996  Topotecan
• 1999  Pegylated liposomal doxorubicin (Accelerated)
• 2005  Pegylated liposomal doxorubicin (Full)
• 2006  Gemcitabine + Carboplatin
• 2014  Bevacizumab (+Paclitaxel, Pegylated liposomal doxorubicin or Topotecan)
• 2014  Olaparib (Accelerated)
NCCN 1 or 2A

Primary Therapy and Recurrence

• Docetaxel

Other Potentially Active Agents Recurrence

• Capecitabine
• Cyclophosphamide
• Doxorubicin
• Etoposide (oral)
• Ifosfamide
• Irinotecan
• Melphalan
• Oxaliplatin
• Paclitaxel, albumin bound (nab-paclitaxel)
• Pemetrexed
• Vinorelbine
EMA/FDA Differences

- **2003**  
  Trabectedin (+Pegylated liposomal doxorubicin)

- **2011**  
  Bevacizumab (+Paclitaxel/carboplatin)  
  » Initial therapy (ICON7)

- **2012**  
  Bevacizumab (+Gemcitabine/carboplatin)  
  » Platinum sensitive recurrence (OCEANS)

- **2014**  
  Olaparib  
  » $\geq 2^{nd}$ remission (study 19)
Ovarian Cancer

• Rare Disease
  – Estimated new cases 2015 - 21,290

• Heterogeneous Group of Diseases
  – 2011 Ovarian Cancer Clinical Trials Planning Meeting
    “Recent years have witnessed important changes in our understanding of epithelial ovarian cancer (EOC), from that of one disease, toward an appreciation of a set of unique diseases, of diverse origin and biology, linked primarily by ovarian localization, with profound therapeutic implications.”

# Ovarian Cancer Type as a Biomarker

<table>
<thead>
<tr>
<th></th>
<th>High Grade Serous</th>
<th>Clear Cell</th>
<th>Endometrioid</th>
<th>Mucinous</th>
<th>Low Grade Serous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Risk Factors</td>
<td>BRCA 1/2</td>
<td>HNPCC</td>
<td>HNPCC</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td>Precursor Lesion</td>
<td>Serous Tubal Intraepithelial Carcinoma (STIC)</td>
<td>Endometriosis</td>
<td>Endometriosis</td>
<td>Unknown</td>
<td>Serous Borderline Tumor</td>
</tr>
<tr>
<td>Molecular Genetics</td>
<td>p53, BRCA, HR Defects, Tumor Microenvironment</td>
<td>PI3K, ARID1A, MSI</td>
<td>PTEN, beta-catenin, ARID1A, MSI</td>
<td>KRAS, HER2</td>
<td>BRAF, KRAS, NRAS</td>
</tr>
<tr>
<td>Potential Drugs</td>
<td>•PARP inhibitors</td>
<td>•mTor</td>
<td>-</td>
<td>•Trastuzumab</td>
<td>•MEKi</td>
</tr>
<tr>
<td></td>
<td>•Angiogenesis</td>
<td>•Angiogenesis</td>
<td></td>
<td>•TDM-1</td>
<td>•Angiogenesis</td>
</tr>
</tbody>
</table>

High Grade Serous

Spread of STIC from the fimbria to the ovarian surface
EARLY STAGE OVARIAN CANCER
Early Stage Ovarian Cancer

- **ICON1 – EORTC ACTION**
  - Early Stage Ovarian Cancer
    - Observation
    - Platinum-based adjuvant therapy
  - Stage IA/B (gr 3 or clear cell), IC or II
    - Paclitaxel + Carboplatin x 3
    - Paclitaxel + Carboplatin x 6

- **GOG157**
  - Stage IA/B (gr 3 or clear cell), IC or II
    - Paclitaxel + Carboplatin x 3

- **GOG175**
  - Stage IA/B (gr 3 or clear cell), IC or II
    - Paclitaxel + Carboplatin x 3
    - Paclitaxel + Carboplatin x 3
    - Weekly Paclitaxel x 24 wks

Early Stage Ovarian Cancer

ICON 1 – EORTC ACTION

Histology (%)

- Clear Cell: 24
- Endometrioid: 19
- Mucinous: 14
- Serous: 5
- Mixed: 4
- Undifferentiated: 2
- Missing: 5

GOG 157

Histology %

- Clear Cell: 30
- Endometrioid: 25
- Mucinous: 10
- Serous: 7
- Mixed: 5
- Undifferentiated: 10
- Other: 23
- Missing: 2

Legend:
- Clear Cell
- Endometrioid
- Mucinous
- Serous
- Mixed
- Undifferentiated
- Missing
Early Stage Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Recurrence Free Survival at 5 yrs</th>
<th>Overall Survival at 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON 1 – ACTION</td>
<td>925</td>
<td>65% vs 76%</td>
<td>74% vs 82%</td>
</tr>
<tr>
<td>Adjuvant Rx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG157</td>
<td>427</td>
<td>74.6% vs 79.9%</td>
<td>81% vs 83%</td>
</tr>
<tr>
<td>PC x 3</td>
<td></td>
<td>(Serous – 60% vs 83%, p=0.007)</td>
<td></td>
</tr>
<tr>
<td>PC x 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG175</td>
<td>542</td>
<td>76.8% vs 80%</td>
<td>86.2% vs 85.4%</td>
</tr>
<tr>
<td>PC x 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC x 3 -&gt; P</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = Paclitaxel; C = Carboplatin

GOG 157
Relative Risk of Recurrence based on Histology

Gynecol Oncol 2010;116:301-6
Early Stage Ovarian Cancer

• Clinical trials based on solely on early stage are not warranted
• Future treatment trials that target histology are needed
ADVANCED STAGE OVARIAN CANCER
Timing of Surgery

• Primary Surgical Debulking
  – Surgery -> Chemotherapy

• Interval Debulking
  – Surgery -> Chemotherapy -> Surgery -> Chemotherapy

• Neoadjuvant Chemotherapy
  – Chemotherapy -> Surgery -> Chemotherapy
# Timing of Surgery

## Interval Debulking

### GOG 152
- **Eligibility:** Stage III/IV; Residual > 1 cm after primary surgery with maximal attempt (n=424)
- Surgery -> Chemotherapy (6 cycles) vs Surgery -> Chemotherapy (3 cycles) -> Surgery -> Chemotherapy (3 cycles)
- **No improvement in PFS or OS**

## Neoadjuvant Chemotherapy

### EORTC – GCG/NCIC 55971
- **Eligibility:** Stage III/IV; Diagnostic biopsy only (no procedures other than biopsy allowed) (n=632)
- Surgery (optimal 41.6%) -> Chemotherapy (6 cycles)
- Chemotherapy (3 cycles) -> Surgery (optimal 80.6%) -> Chemotherapy (3 cycles)
- **Neoadjuvant chemotherapy not inferior**
- Complete resection of all macroscopic disease (at primary or interval) – the strongest independent variable in predicting OS

### MRC CHORUS
- **Eligibility:** Stage III/IV; Diagnostic biopsy only (no procedures other than biopsy allowed) (n=550)
- Surgery (optimal 37.6%) -> Chemotherapy (6 cycles)
- Chemotherapy (3 cycles) -> Surgery (optimal 66.7%) -> Chemotherapy (3 cycles)
- **Neoadjuvant chemotherapy not inferior**

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PRIMARY THERAPY
## Advanced Stage Ovarian Cancer Phase III Trials Intravenous Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suboptimal Stage III and Stage IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 111</td>
<td>-paclitaxel + cisplatin vs -cyclophosphamide + cisplatin</td>
<td>386</td>
<td>18 vs 13 mos (HR 0.7, CI 0.5-0.8; p&lt;0.001)</td>
<td>38 vs 24 mos (HR 0.6, CI 0.5-0.8; p&lt;0.001)</td>
</tr>
<tr>
<td>GOG 132</td>
<td>-cisplatin vs -paclitaxel vs -paclitaxel + cisplatin</td>
<td>614</td>
<td>16.4 vs 10.8 vs 14.1 mos (failure rate 41% &gt; on paclitaxel arm)</td>
<td>30.2 vs 25.9 vs 26.3 mos (no difference; crossover)</td>
</tr>
<tr>
<td><strong>Optimal Stage III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 158</td>
<td>-paclitaxel + carboplatin vs -paclitaxel + cisplatin</td>
<td>792</td>
<td>20.7 mos</td>
<td>57.4 mos</td>
</tr>
<tr>
<td><strong>Stage III/IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG182-ICON5</td>
<td>-paclitaxel + carboplatin vs -triplets/sequential doublets PLD, topotecan, gemcitabine</td>
<td>4312</td>
<td>16 mos</td>
<td>44.1 mos</td>
</tr>
<tr>
<td><strong>Stage II, III, IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OV-10</td>
<td>-paclitaxel + cisplatin vs -cyclophosphamide + cisplatin</td>
<td>680</td>
<td>15.5 vs 11.5 mos (p=0.0005)</td>
<td>35.6 vs 25.8 mos (p=0.0016)</td>
</tr>
</tbody>
</table>

Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimal Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

By Robert F. Ozols, Brian N. Bundy, Benjamin E. Greer, Jeffrey M. Fowler, Daniel Clarke-Pearson, Robert A. Burger, Robert S. Mannel, Koen DeGeest, Ellen M. Hartenbach, and Rebecca Baergen

Purpose: In randomized trials the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide in advanced-stage epithelial ovarian cancer. Although in nonrandomized trials, carboplatin and paclitaxel was a less toxic and highly active combination regimen, there remained concern regarding its efficacy in patients with small-volume, resected, stage III disease. Thus, we conducted a noninferiority trial of cisplatin and paclitaxel versus carboplatin and paclitaxel in this population.

Patients and Methods: Patients with advanced ovarian cancer and no residual mass greater than 1.0 cm after surgery were randomly assigned to receive cisplatin 75 mg/m² plus a 24-hour infusion of paclitaxel 135 mg/m² (arm I), or carboplatin area under the curve 7.5 intravenously plus paclitaxel 175 mg/m² over 3 hours (arm II).

Results: Seven hundred ninety-two eligible patients were enrolled onto the study. Prognostic factors were similar in the two treatment groups. Gastrointestinal, renal, and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in arm I. Grade 2 or greater thrombocytopenia was more common in arm II. Neurologic toxicity was similar in both regimens. Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for arm I compared with 20.7 and 57.4 months, respectively, for arm II. The relative risk (RR) of progression for the carboplatin plus paclitaxel group was 0.88 (95% confidence interval [CI], 0.75 to 1.03) and the RR of death was 0.84 (95% CI, 0.70 to 1.02).

Conclusion: In patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior, when compared with cisplatin plus paclitaxel.

J Clin Oncol 2003;21:3194-3200
GOG0182-ICON 5: Ovarian (Stage III-IV)

**Randomize**

I. Carboplatin AUC 6 (d1)  
Paclitaxel 175 mg/m²  
x8

II. Carboplatin AUC 5 (d1)  
Paclitaxel 175 mg/m² (d1)  
Gemcitabine 800 mg/m² (d1,8)  
x8

III. Carboplatin AUC 5 (d1)  
Paclitaxel 175 mg/m² (d1)  
Doxil 30 mg/m² (d1, every other cycle)  
x8

IV. Carboplatin AUC 5 (d3)  
Topotecan 1.25 mg/m² (d1-3)  
x4

V. Carboplatin AUC 6 (d8)  
Gemcitabine 1 g/m² (d1,8)  
x4

Carboplatin AUC 6  
Paclitaxel 175 mg/m²  
x4

J Clin Oncol 2009;27(9):1419-25

N=4312
GOG0182-ICON5: Ovarian (Stage III-IV)
Advanced vs Early Stage Ovarian Cancer

GOG 182-ICON5 Stage III/IV

- Clear Cell: 9%
- Endometrioid: 3%
- Mucinous: 6%
- Serous: 2%
- Other: 2%

Histology (%)

GOG 157 Stage I/II

- Clear Cell: 30%
- Endometrioid: 25%
- Mucinous: 7%
- Serous: 23%
- Mixed: 10%
- Other: 5%

Histology %
New Ovarian Elaborate trial: NOVEL trial
JGOG 3016

Ovarian Epithelial, Primary Peritoneal or Fallopian Tube cancer
FIGO Stage II-IV

Randomization

Stratification:
- Residual disease: ≤1cm, > 1cm
- FIGO Stage: II vs. III vs. IV
- Histology: clear cell/mucinous vs. serous/others

Conventional PC (c-PC)
Paclitaxel 180mg/m², day 1
Carboplatin AUC 6, day 1
every 21 days for 6-9 cycles

Dose-dense weekly PC (dd-PC)
Paclitaxel 80mg/m², days 1,8,15
Carboplatin AUC 6, day 1
every 21 days for 6-9 cycles

**New Ovarian Elaborate trial: NOVEL trial**

**JGOG 3016**

<table>
<thead>
<tr>
<th></th>
<th>dd-PC</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (mos)</td>
<td>28.2</td>
<td>17.5</td>
</tr>
<tr>
<td>HR</td>
<td>0.76, 95% CI 0.62-0.91; p=0.0037</td>
<td></td>
</tr>
<tr>
<td>OS (mos)</td>
<td>100.5</td>
<td>62.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.79, 95% CI 0.63-0.99; p=0.039</td>
<td></td>
</tr>
</tbody>
</table>
# Advanced Stage Ovarian Cancer

## Phase III Trials Targeting Angiogenesis

<table>
<thead>
<tr>
<th></th>
<th>GOG 218 Bevacizumab Concurrent &amp; Maintenance</th>
<th>ICON 7 Bevacizumab Concurrent &amp; Maintenance</th>
<th>AGO-OVAR16 Pazopanib Maintenance</th>
<th>AGO-OVAR12 Nintedanib Concurrent &amp; Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>PFS (RECIST/CA 125)</td>
<td>PFS (RECIST)</td>
<td>PFS (RECIST)</td>
<td>PFS (RECIST)</td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td><strong>Maintenance duration</strong></td>
<td>15 months</td>
<td>12 months</td>
<td>24 months</td>
<td>120 weeks</td>
</tr>
<tr>
<td><strong>Stopping rules</strong></td>
<td>GCIG (CA125)</td>
<td>RECIST PD</td>
<td>RECIST PD</td>
<td>RECIST PD</td>
</tr>
<tr>
<td><strong>Results (PFS in Δ months)</strong></td>
<td>6 months (censored for CA125 only events)</td>
<td>1.7 months 5.4 months (high risk subgroup)</td>
<td>5.6 months</td>
<td>0.7 months 6.3 months (low risk subgroup)</td>
</tr>
<tr>
<td><strong>Results (OS)</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS (immature)</td>
<td>Immature</td>
</tr>
</tbody>
</table>

GOG 262

Initial Therapy

- Stage II-IV
- Maximal cytoreductive effort
- Optimal or suboptimal
- Neoadjuvant (optional)
- Bevacizumab (optional) prior to randomization

Activated: 4/6/09
Closed to accrual: 1/3/12

EVERY 3 WEEK
Paclitaxel (P) 175 mg/m²

Carboplatin AUC 6

BEVACIZUMAB 15 mg/kg (optional)

DOSE DENSE (WEEKLY)
Paclitaxel (ddP) 80 mg/m²

Carboplatin AUC 6

BEVACIZUMAB 15 mg/kg (optional)

Chemotherapy (6 cycles)

Treat until progression

ESGO 2013
GOG 262: PFS by Randomized Treatment ddP vs. q3wk P stratified by those choosing Bevacizumab (n=580)

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Treatment gp</th>
<th>n</th>
<th>Median PFS (Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev</td>
<td>ddP + C</td>
<td>291</td>
<td>14.92</td>
</tr>
<tr>
<td>q3wkP + C</td>
<td>289</td>
<td>14.92</td>
<td></td>
</tr>
</tbody>
</table>

Stratum

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Tx gp</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev</td>
<td>Weekly : Q3 wk</td>
<td>1.058</td>
<td>0.86 – 1.31</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Months on study
GOG 262: PFS by Randomized Treatment ddP vs. q3wkP stratified by those not choosing Bevacizumab (n=112)

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Treatment gp</th>
<th>n</th>
<th>Median PFS (Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no Bev</td>
<td>ddP + Carbo</td>
<td>55</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>q3wkP + Carbo</td>
<td>57</td>
<td>10.3</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Tx gp</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bev</td>
<td>Weekly :Q3wk</td>
<td>0.596</td>
<td>0.369 – 0.958</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**Graph:**

- Proportion Surviving Progression-Free

- Months on study

- ddP + Carbo

- q3wkP + Carbo
## Advanced Stage Ovarian Cancer

### Phase III Trials Intraperitoneal Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>IV ARM</th>
<th>IP ARM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Stage III</td>
<td>IV cyclophosphamide + IV vs IP cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG104</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>41 mos</td>
<td>49 mos</td>
<td>0.02</td>
</tr>
<tr>
<td>GOG114</td>
<td>IV paclitaxel + IV cisplatin vs IV carbo -&gt; IV paclitaxel + IP cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>22 mos</td>
<td>28 mos</td>
<td>0.01</td>
</tr>
<tr>
<td>OS</td>
<td>52 mos</td>
<td>63 mos</td>
<td>0.05</td>
</tr>
<tr>
<td>GOG172</td>
<td>IV paclitaxel + IV cisplatin vs IV/IP paclitaxel + IP cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>18.3 mos</td>
<td>23.8 mos</td>
<td>0.05</td>
</tr>
<tr>
<td>OS</td>
<td>49.7 mos</td>
<td>65.6 mos</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### NCI Issues Clinical Announcement for

Preferred Method of Treatment for Advanced Ovarian Cancer in 2006


GOG 252

Eligibility:
• Stage II-IV
• No prior chemotherapy

Primary Endpoint: PFS
Activated: July 27, 2009
Closed: November 30, 2011
Accrual: 1560

Stratification:
Stage (II vs III vs IV)
Residual Disease (NGR vs \( \leq 1 \text{ cm} \) vs >1 cm)

**Randomize**

Paclitaxel 80 mg/m\(^2\) IV Days 1, 8, 15
Carboplatin AUC 6 IV Day 1
Bevacizumab 15 mg/kg IV Day 1*
  x 6 cycles

Bevacizumab Cycles 7-22

Paclitaxel 80 mg/m\(^2\) IV Days 1, 8, 15
Carboplatin AUC 6 IP Day 1
Bevacizumab 15 mg/kg IV Day 1*
  x 6 cycles

Paclitaxel 135 mg/m\(^2\) IV Day 1
Cisplatin 75 mg/m\(^2\) IP Day 2
Paclitaxel 60 mg/m\(^2\) IP Day 8
Bevacizumab 15 mg/kg Day 1*
  x 6 cycles

*Beginning with cycle 2
FIRST PLATINUM SENSITIVE RECURRENCE
First Platinum-Sensitive Recurrence Randomized Phase III Trials
Platinum Doublet Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>RR (%)</th>
<th>PFS (mos)</th>
<th>HR</th>
<th>OS (mos)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON4 (n=802)</td>
<td>C</td>
<td>54</td>
<td>9</td>
<td>0.76</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>C + P</td>
<td>66</td>
<td>12</td>
<td>0.76</td>
<td>29</td>
<td>0.82</td>
</tr>
<tr>
<td>AGO (n=366)</td>
<td>C</td>
<td>31</td>
<td>5.8</td>
<td>0.72</td>
<td>17.3</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>47</td>
<td>8.6</td>
<td>0.72</td>
<td>18</td>
<td>0.96</td>
</tr>
<tr>
<td>Calypso (n=976)</td>
<td>C + P</td>
<td>–</td>
<td>9.4</td>
<td>0.82</td>
<td>31.5</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>C + PLD</td>
<td>–</td>
<td>11.3</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = paclitaxel; C = carboplatin; G = gemcitabine; PLD = pegylated liposomal doxorubicin

OCEANS: Study Schema

Platinum-sensitive recurrent ovarian cancer\textsuperscript{a}
- Measurable disease
- Eastern Cooperative Oncology Group PS of 0 or 1
- No prior chemotherapy for recurrent ovarian cancer
- No prior bevacizumab

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

\textbf{GC + PL}
- C AUC 4
- G 1000 mg/m\textsuperscript{2}, days 1 and 8
- PL q3w until progression

\textbf{N=484 1:1}

\textbf{GC + BV}
- C AUC 4
- G 1000 mg/m\textsuperscript{2}, days 1 and 8
- BV 15 mg/kg q3w until progression

\textbf{GC for 6 (up to 10) cycles}

\textsuperscript{a}Epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
AUC, area under the curve; BV, bevacizumab; C, carboplatin; GC, gemcitabine + carboplatin; PL, placebo; PS, performance status; q3w, every 3 weeks

J Clin Oncol 2012;30(17):2039-45
OCEANS: PFS, ORR, and DOR

**INV-assessed**

<table>
<thead>
<tr>
<th></th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS by INV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>8.4</td>
<td>12.4</td>
</tr>
<tr>
<td>Stratified analysis, HR (95% CI)</td>
<td>0.484 (0.388 – 0.605)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>PFS by IRC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>8.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Stratified analysis, HR (95% CI)</td>
<td>0.451 (0.351 – 0.580)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>ORR and DOR by INV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>Median DOR, mo</td>
<td>7.4</td>
<td>10.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.53 (0.41–0.70)</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff date: September 17, 2010

BV, bevacizumab; CI, confidence interval; DOR, duration of response; GC, gemcitabine + carboplatin; HR, hazard ratio; INV, investigator-assessed; IRC, independent review committee–assessed; mo, month; ORR, objective response rate; PFS, progression-free survival; PL, placebo
OCEANS: Final OS Analysis

**Events, n (%)**
- GC + PL: 176 (72.7)
- GC + BV: 177 (73.1)

**Median OS, mo**
- GC + PL: 32.9
- GC + BV: 33.6

**HR (95% CI)**
- GC + PL: 0.952 (0.771–1.176)
- GC + BV: 0.6479

**Number at risk:**
- GC + PL: 242 235 222 191 160 128 104 87 64 41 20 7 1 0
- GC + BV: 242 239 226 201 172 138 105 87 68 47 25 7 1 0

aData cutoff date: July 19, 2013. Median follow-up 56.4 months in PL arm and 58.2 months in BV arm, with 353 deaths (72.9% of patients)

BV, bevacizumab; CI, confidence interval; GC, gemcitabine + carboplatin; HR, hazard ratio; mo, month; OS, overall survival; PL, placebo
OCEANS: Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Adverse events, no. (%)</th>
<th>GC + PL (n=233)</th>
<th>GC + BV (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thromboembolic event (all grade)</td>
<td>1 (0.4)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Venous thromboembolic event (grade ≥3)</td>
<td>6 (2.6)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Bleeding (central nervous system) (all grade)</td>
<td>2 (0.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Congestive heart failure (grade ≥3)</td>
<td>2 (0.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Febrile neutropenia (any grade)</td>
<td>4 (1.7)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Neutropenia (grade ≥4)</td>
<td>51 (21.9)</td>
<td>52 (21.1)</td>
</tr>
<tr>
<td>Fistula/abscess (all grade)a</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Gastrointestinal perforation (all grade)a</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Reversible posterior leukoencephalopathy syndrome (all grade)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Wound-healing complication (grade ≥3)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Proteinuria (grade ≥3)</td>
<td>2 (0.9)</td>
<td>27 (10.9)</td>
</tr>
<tr>
<td>Bleeding (non–central nervous system) (grade ≥3)</td>
<td>2 (0.9)</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>Hypertension (grade ≥3)</td>
<td>2 (0.9)</td>
<td>45 (18.2)</td>
</tr>
</tbody>
</table>

Yellow highlighted data refer to >2% difference in incidence between treatment arms
AEs summarized here occurred within the window of the first dosing date and 30 days after the last dosing date for the study treatment
BV, bevacizumab; GC, gemcitabine + carboplatin; PL, placebo

*aDue to coding changes to using the gastrointestinal perforation (GIP) standardized medical query, this is different than what was previously reported in the primary analysis, where no GIPs were reported and fistula/abscess were reported in 1 patient in the GC + PL arm and 4 patients in the GC + BV arm. GIPs were reported in 2 additional patients outside the safety reporting window.
### OCEANS: Subsequent Anticancer Therapy

<table>
<thead>
<tr>
<th>Type of therapy, no. (%)(^a)</th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subsequent anticancer therapy</td>
<td>221 (91.3)</td>
<td>215 (88.8)</td>
</tr>
<tr>
<td>Subsequent BV</td>
<td>92 (38.0)</td>
<td>56 (23.1)</td>
</tr>
<tr>
<td>Subsequent chemotherapy</td>
<td>217 (89.7)</td>
<td>210 (86.8)</td>
</tr>
<tr>
<td>Pegylated liposomal doxorubicin</td>
<td>163 (67.4)</td>
<td>155 (64.0)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>121 (50.0)</td>
<td>118 (48.8)</td>
</tr>
<tr>
<td>Platinum agent</td>
<td>96 (39.7)</td>
<td>104 (43.0)</td>
</tr>
</tbody>
</table>

\(^a\)Percentage does not total 100% as patients may have received multiple therapies.

BV, bevacizumab; GC, gemcitabine + carboplatin; PL, placebo
## OCEANS: Exposure to Anticancer Therapy

<table>
<thead>
<tr>
<th>Total lines of anticancer therapy,^a^ no. (%)</th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more</td>
<td>221 (91.3)</td>
<td>213 (88.0)</td>
</tr>
<tr>
<td>5 or more</td>
<td>148 (61.2)</td>
<td>135 (55.8)</td>
</tr>
<tr>
<td>7 or more</td>
<td>77 (31.8)</td>
<td>57 (23.6)</td>
</tr>
<tr>
<td>9 or more</td>
<td>24 (9.9)</td>
<td>21 (8.7)</td>
</tr>
<tr>
<td>11 or more</td>
<td>6 (2.5)</td>
<td>4 (1.7)</td>
</tr>
</tbody>
</table>

^a^Includes frontline and OCEANS regimens  
BV, bevacizumab; GC, gemcitabine + carboplatin; PL, placebo
ICON6: Cediranib with platinum-based chemotherapy in ‘platinum-sensitive’ relapsed ovarian cancer

Study schema

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

Maintenance phase

Randomise 2 : 3 : 3

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

Arm A (Chemo only)
- Chemotherapy + placebo
- Continue placebo
- Treatment continued to 18 months or until progression (>18 for patients continuing to benefit)

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

Arm C (Maintenance)
- Chemotherapy + cediranib
- Maintenance cediranib
Progression-free survival – arms A vs. C

Restricted mean survival time increases by 3.1 months with maintenance treatment

<table>
<thead>
<tr>
<th></th>
<th>Chemo.</th>
<th>Maint.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>112 (94.9)</td>
<td>139 (84.8)</td>
</tr>
<tr>
<td>Median, months</td>
<td>8.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.00001</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.57 (0.45 – 0.74)</td>
<td></td>
</tr>
<tr>
<td>Test for non-proportionality</td>
<td>p=0.024</td>
<td></td>
</tr>
<tr>
<td>Restricted means, months</td>
<td>9.4</td>
<td>12.5</td>
</tr>
</tbody>
</table>
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>

Chemo. 118  90  24  8  3
Conc. 174  152  53  20  12
Maint. 164  148  65  21  7
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>

<table>
<thead>
<tr>
<th>Chemo.</th>
<th>118</th>
<th>106</th>
<th>89</th>
<th>46</th>
<th>27</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maint.</td>
<td>164</td>
<td>159</td>
<td>139</td>
<td>89</td>
<td>48</td>
<td>22</td>
</tr>
</tbody>
</table>
RECURRENT DISEASE
## Bevacizumab in Ovarian Cancer Phase II Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>RR (%)</th>
<th>PFS at 6 months (%)</th>
<th>Prior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 170D¹</td>
<td>62</td>
<td>BV 15 mg/kg IV q 3 wk</td>
<td>21</td>
<td>40</td>
<td>1-2 priors; 58% platinum resistant</td>
</tr>
<tr>
<td>NCI 5789²</td>
<td>70</td>
<td>BV 10 mg/kg IV q 2 wk + CTX 50 mg daily</td>
<td>24</td>
<td>56</td>
<td>1-3 priors; 40% platinum resistant</td>
</tr>
<tr>
<td>Cannistra et al.³</td>
<td>44</td>
<td>BV 15 mg/kg IV q 3 wk</td>
<td>16</td>
<td>28</td>
<td>1-3 priors; platinum-refractory or resistant AND progression on/within 3 months of topotecan or PLD</td>
</tr>
</tbody>
</table>

BV, bevacizumab; CTX, cyclophosphamide; RR, response rate; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin (Doxil)

AURELIA

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

**Stratification factors:**
- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (PFI <3 vs 3–6 months)

**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

*Or 10 mg/kg q2w
^15 mg/kg q3w, permitted on clear evidence of progression

J Clin Oncol 2014;32(13):1302-8
Progression-free survival (PFS).

Pujade-Lauraine E et al. JCO 2014;32:1302-1308
Overall survival (OS).

- **Events, n (%)**
  - CT: 136 (75%)
  - BEV + CT: 128 (72%)

- **Median OS, months**
  - CT: 13.3
  - BEV + CT: 16.6

- **95% CI**
  - CT: 11.9 to 16.4
  - BEV + CT: 13.7 to 19.0

- **HR (unstratified)**
  - BEV + CT: 0.85

- **95% CI**
  - BEV + CT: 0.66 to 1.08

- **Log-rank P value**
  - BEV + CT: < .174

---

Pujade-Lauraine E et al. JCO 2014;32:1302-1308

©2014 by American Society of Clinical Oncology
Overall Response Rates

- **Responders (n=350)**
  - CT: 12.6%
  - BEV + CT: 30.9%
  - *p*<0.001

- **RECIST responders (n=287)**
  - CT: 11.8%
  - BEV + CT: 27.3%
  - *p*<0.001

- **CA-125 responders (n=297)**
  - CT: 11.6%
  - BEV + CT: 31.8%
  - *p*<0.001

*aTwo-sided chi-square test with Schouten correction*

---

J Clin Oncol 2014;32(13):1302-8
Additional grade $\geq 3$ adverse events$^a$ in $\geq 2\%$ of patients in either arm

$HFS = \text{hand-foot syndrome}$

$^a$Preferred terms. $^b$Includes abdominal pain upper
Mutually exclusive potential driver events in HGS-Ovarian Cancer

Data provided by Douglas Levine, MD, MSKCC on behalf of tcga.cancer.gov
Olaparib Study 42
Deleterious Germline BRCA 1/2 Mutation

<table>
<thead>
<tr>
<th>Response</th>
<th>Ovarian n=193*</th>
<th>Breast n=62</th>
<th>Pancreas n=23</th>
<th>Prostate n=8</th>
<th>Other n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>ORR</td>
<td>60</td>
<td>31.1</td>
<td>8</td>
<td>12.9</td>
<td>5</td>
</tr>
<tr>
<td>CR</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>54</td>
<td>28</td>
<td>8</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

*137/193 had received 3 or more prior lines of chemotherapy
ORR 34%, median response duration 7.9 months

Treatment:
Olaparib 400 mg oral BID (capsule formulation)
50 mg capsules
8 capsules oral BID

Approved FDA 12/19/14
gBRCAm & 3 or more priors

J Clin Oncol 2015;33(3):244-250
TARGETING HISTOLOGY
MUCINOUS
Mucinous Epithelial Ovarian Cancer (MEOC)
GCIG Intergroup Study

Eligibility:
• Stage II-IV (newly diagnosed or recurrent)
• Stage I (recurrent)
• No prior chemotherapy

Primary Endpoint: OS
Activated: October 12, 2010
Target Accrual: 332
CLEAR CELL
# Ovarian Clear Cell Carcinoma

## Stage III/IV

### Progression-Free Survival at 12 months

<table>
<thead>
<tr>
<th>Progression-Free Survival at 12 months</th>
<th>Histologic Type</th>
<th>Non-Clear Cell</th>
<th>Clear Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td><strong>Optimal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3937</td>
<td>2821</td>
<td>71.7%</td>
</tr>
<tr>
<td>158</td>
<td>770</td>
<td>563</td>
<td>73.1%</td>
</tr>
<tr>
<td>172</td>
<td>393</td>
<td>286</td>
<td>72.8%</td>
</tr>
<tr>
<td>182</td>
<td>2774</td>
<td>1972</td>
<td>71.1%</td>
</tr>
<tr>
<td><strong>Suboptimal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1725</td>
<td>994</td>
<td>57.6%</td>
</tr>
<tr>
<td>111</td>
<td>377</td>
<td>244</td>
<td>64.7%</td>
</tr>
<tr>
<td>132</td>
<td>600</td>
<td>335</td>
<td>55.8%</td>
</tr>
<tr>
<td>182</td>
<td>748</td>
<td>415</td>
<td>55.5%</td>
</tr>
</tbody>
</table>

N = number of patients  
M = number of patients surviving progression free for 12 months  
% = M/N
Ovarian Clear Cell Carcinoma
First Line Therapy
Phase III JGOG3017

Stage IC – IV
No prior chemotherapy

Accrual: 619 (eligible)
Confirmed by central pathology review
Stage I: 66.4%
No difference in 2 year PFS/OS

Paclitaxel 175 mg/m² IV Day 1
Carboplatin AUC 6 Day 1
One cycle = 21 days
6 cycles

Irinotecan 60 mg/m² IV Days 1, 8, 15
Cisplatin 60 mg/m² IV Day 1
One cycle = 28 days
6 cycles

J Clin Oncol 32:5s, 2014 (suppl; abstr 5507)
Ovarian Clear Cell Carcinoma
IMPACT OF RADIATION THERAPY

(A) Stage IA/B and IC defined by rupture alone
(gold, with irradiation, n = 57; blue, no irradiation, n = 63)

(B) All other stage IC and stage II
(gold, with irradiation, n = 59; blue, no irradiation, n = 62)

<table>
<thead>
<tr>
<th>Stage</th>
<th>N (241)</th>
<th>5 year DFS</th>
<th>10 year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA/B</td>
<td>64</td>
<td>84%</td>
<td>70%</td>
</tr>
<tr>
<td>IC</td>
<td>147</td>
<td>67%</td>
<td>57%</td>
</tr>
<tr>
<td>Rupture</td>
<td>92%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>48%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>30</td>
<td>49%</td>
<td>44%</td>
</tr>
</tbody>
</table>

RR, relative risk
LOW GRADE SEROUS
Low Grade Serous
GOG 239 – Selumetinib (AZD6244)

Eligibility:
• Prospective Central Pathology
• Recurrent
• Measurable Disease
• No Restrictions on Prior Therapy

Selumetinib 50 mg oral daily

Objective Response Rate = 15% (8/52 patients)

1 Complete Response and 7 Partial Responses

Lancet Oncol 2013;14(2):134-40
Low Grade Serous Ovarian Cancer
Phase III GOG 281

Recurrent or Persistent
> 1 prior therapy
(no limit)

Trametinib 2 mg oral daily

Physician’s Choice:
- Letrozole
- Tamoxifen
- PLD
- Weekly Paclitaxel
- Topotecan

Off Study

Crossover to Trametinib

Activated: February 27, 2014
Primary Endpoint: PFS
Sample Size: 250
Low Grade Serous Ovarian Cancer Phase III MILO Study

Recurrent or Persistent 1-3 prior therapies

2:1

MEK162 45 mg oral BID

Off Study

Physician’s Choice:
PLD
Weekly Paclitaxel
Topotecan

Crossover to MEK162

Primary Endpoint: PFS
Sample Size: 300
Upcoming Results

- IP Carboplatin vs IP Cisplatin vs Weekly IV Paclitaxel treatment in primary therapy
  - GOG252, NCIC-CTG OV21, iPocc
- Weekly vs every 3 week treatment in primary therapy
  - ICON8
- Role of PARP inhibitors in primary therapy
  - GOG 3005
- Length of bevacizumab treatment in primary therapy
  - AGO-OVAR 17 (22 vs 44 cycles)
- Role of secondary cytoreduction
  - GOG213, Desktop III
- Choice of platinum doublet in first platinum sensitive recurrence
  - AGO-OVAR 2.21 (gemcitabine/carboplatin/bevacizumab vs pegylated liposomal/doxorubicin/bevacizumab)
- Role of PARP inhibitors in maintenance
  - 1st Remission SOLO1
  - >2nd Remission SOLO2, ARIEL3, ENGOT-OV16/NOVA
- Role of PARP inhibitor and anti-angiogenesis combinations
  - Cediranib/olaparib
  - Bevacizumab/olaparib (PAOLA1)
- Role of MEK inhibitors in low grade serous
  - GOG281, MILO