Gynecology Abstracts

Susana M. Campos, MD, MPH
Dana Farber Cancer Institute
Boston Mass
<table>
<thead>
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<th>Abstract #</th>
<th>Author</th>
<th>Title</th>
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<tr>
<td>1</td>
<td>Rustin G.J.</td>
<td>A Randomized trial in ovarian cancer of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators</td>
</tr>
<tr>
<td>5504</td>
<td>Karam A</td>
<td>Influence of residual disease and extreme drug resistance assays on outcome in patients with epithelial ovarian cancer</td>
</tr>
<tr>
<td>5505</td>
<td>Levenback CF</td>
<td>Sentinel node biopsy in patients with vulvar cancer: a GOG study</td>
</tr>
<tr>
<td>5507</td>
<td>Duenas-Gonzalez A</td>
<td>A phase II study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant Gem plus Cis vs. concurrent Cis and radiation in patients with stage IIB to IVA carcinoma of the cervix</td>
</tr>
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<td>Carboplatin plus paclitaxel (CP) versus carboplatin plus CLD) in patients with advanced ovarian cancer: MITO 2</td>
</tr>
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</tr>
<tr>
<td>5510</td>
<td>Herrstedt J</td>
<td>A randomized phase II study of gem-paclitaxel-carboplatin versus paclitaxel-carboplatin as first line treatment of ovarian cancer: Survival of FIGO stage I-IIA patients</td>
</tr>
</tbody>
</table>
Ovarian Cancer
### GOG111: Survival By Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Alive (N)</th>
<th>Died (N)</th>
<th>Median PFS Survival (mo)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/cyclophosphamide</td>
<td>28</td>
<td>174</td>
<td>13.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cisplatin/paclitaxel</td>
<td>45</td>
<td>138</td>
<td>18</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Role of IP Chemotherapy for Optimally Debulked Advanced-Stage Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104¹</td>
<td>Improved outcome in CP-treated patients when cisplatin administered IP</td>
<td>0.76</td>
</tr>
<tr>
<td>GOG 114²</td>
<td>Improved outcome in TP-treated patients when cisplatin administered IP</td>
<td>0.78</td>
</tr>
<tr>
<td>GOG 172³</td>
<td>Improved outcome in TP-treated patients when paclitaxel and cisplatin</td>
<td>0.73</td>
</tr>
</tbody>
</table>

CP = Cyclophosphamide and cisplatin; IP = Intraperitoneal; TP = Paclitaxel and cisplatin.


Carboplatin plus Paclitaxel versus Carboplatin plus Stealth Liposomal Doxorubicin in patients with Advanced Ovarian Cancer

S. Pignata et al
Abstract 5508
Study design

Control arm

Carboplatin AUC 5, day 1
Paclitaxel 175 mg/m², day 1

Treatment repeated every 21 days, for 6 cycles

Experimental arm

Carboplatin AUC 5, day 1
PLD 30 mg/m², day 1

Treatment repeated every 21 days, for 6 cycles

Strata:
- Center
- PS (0-1, 2)
- Stage (I, II, III, IV)
- Residual disease after surgery
  (absent, ≤1 cm, >1 cm, no surgery)
Study population/Endpoint

Inclusion criteria
- Cyto/histological diagnosis of ovarian cancer
- FIGO Stage IC - II - III - IV
- Age ≤ 75
- ECOG Performance Status 0-2
- No previous chemotherapy

Main exclusion criteria
- ANC < 2000/µL, platelets < 100000/µL
- Creatinine ≥ 1.25 x UNL, SGOT and SGPT ≥ 1.25 x UNL
- Life expectancy of less than 3 months

Primary Endpoint:
Progression-free survival (PFS)
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Carbo + Paclitaxel (n = 410)</th>
<th>Carbo + PLD (n=410)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57 (21-77)</td>
<td>57 (25-77)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>398 (97%)</td>
<td>397 (97%)</td>
</tr>
<tr>
<td>2</td>
<td>12 (3%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td><strong>FIGO Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>38 (9%)</td>
<td>38 (9%)</td>
</tr>
<tr>
<td>II</td>
<td>40 (10%)</td>
<td>37 (9%)</td>
</tr>
<tr>
<td>III</td>
<td>243 (59%)</td>
<td>247 (60%)</td>
</tr>
<tr>
<td>IV</td>
<td>89 (22%)</td>
<td>88 (22%)</td>
</tr>
<tr>
<td><strong>Residual disease after surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>152 (37%)</td>
<td>150 (37%)</td>
</tr>
<tr>
<td>1 cm</td>
<td>68 (17%)</td>
<td>69 (19%)</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>117 (28%)</td>
<td>114 (28%)</td>
</tr>
<tr>
<td>No surgery</td>
<td>73 (18%)</td>
<td>67 (16%)</td>
</tr>
</tbody>
</table>
### Objective response - RECIST

Women with target lesions

<table>
<thead>
<tr>
<th></th>
<th>Carbo + Paclitaxel (n=156)</th>
<th>Carbo + PLD (n=134)</th>
<th>p (χ²)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response</strong></td>
<td>92 (59%)</td>
<td>76 (57%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Complete response</td>
<td>24 (15%)</td>
<td>22 (16%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>68 (44%)</td>
<td>54 (40%)</td>
<td></td>
</tr>
<tr>
<td><strong>No response</strong></td>
<td>64 (41%)</td>
<td>58 (43%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>45 (29%)</td>
<td>41 (31%)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (6%)</td>
<td>7 (5%)</td>
<td></td>
</tr>
<tr>
<td>Not evaluated</td>
<td>10 (6%)</td>
<td>10 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Objective response vs no response*
## Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Any grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C+P</td>
<td>C+PLD</td>
<td>p*</td>
<td>C+P</td>
<td>C+PLD</td>
<td>p*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>0.8%</td>
<td>0.5%</td>
<td>1</td>
<td>0.8%</td>
<td>0.5%</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>59%</td>
<td>68%</td>
<td>0.007</td>
<td>4%</td>
<td>10%</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC transfusions</td>
<td>2%</td>
<td>6%</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>73%</td>
<td>80%</td>
<td>0.04</td>
<td>49%</td>
<td>43%</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2%</td>
<td>1%</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19%</td>
<td>48%</td>
<td>&lt;0.001</td>
<td>2%</td>
<td>16%</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>0.3%</td>
<td>2%</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.3%</td>
<td>1%</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C+P: carboplatin + paclitaxel, 399 patients; C+PLD: carboplatin + PLD, 386 patients

*Chi square or Fisher exact test as appropriate
Progression free survival

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Median PFS (months)</th>
<th>1-yr PFS</th>
<th>2-yr PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>820</td>
<td>531</td>
<td>17.7</td>
<td>65.0%</td>
<td>41.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95%CI 16.3-19.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing progression free survival with data points and patients at risk](image-url)
Overall survival

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Median OS (months)</th>
<th>1-yr OS</th>
<th>2-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>820</td>
<td>269</td>
<td>56.3</td>
<td>88.8%</td>
<td>73.8%</td>
</tr>
</tbody>
</table>

(95%CI 48.3-n.a.)
Abstract: 5510

A randomized, phase III study
gemcitabine-paclitaxel-carboplatin (TCG) versus
paclitaxel-carboplatin (TC) as first-line treatment of
ovarian cancer: survival of FIGO stage I-IIA patients

Jørn Herrstedt¹, Jens Huober², Franck Priou³, Hans-Helge Müller²,
Mark Baekelandt¹, Christian Kurzeder², Jacobus Pfisterer²,
Anne Stähle², Isabelle Ray-Coquard³, Andreas du Bois² (PI).

1. Nordic Society of Gynecologic Oncology (NSGO)
   Denmark, Finland, Norway, Sweden

2. Arbeitsgemeinschaft Gynäkologische Onkologie
   (AGO) Studiengruppe Ovarialkarzinom

3. Groupe d’Investigateurs Nationaux pour l’Etude
des Cancers Ovariens (GINECO), France

a GCIG Intergroup Study
STUDY DESIGN

RANDOMISATION

- Gemcitabine 800 mg/m² d1+8
- Paclitaxel 175 mg/m² d1
- Carboplatin AUC 5 d1
  q 21 x 6

- Paclitaxel 175 mg/m² d1
- Carboplatin AUC 5 d1
  q 21 x 6

- FIGO Stage and Tumor Residuals
  - Stratum 1: FIGO IA/B G3 or IC – IIA
  - Stratum 2: FIGO IIB – IIIA + Tumor residual ≤ 1 cm
  - Stratum 3: FIGO IV or Tumor residual > 1 cm
OVERALL SURVIVAL BY THERAPY STRATUM 1 (FIGO I-IIA)

HR = 2.19 [95% CI: 0.75-6.41]
p = 0.1419
GOG 182—Primary Therapy

**FIGO III-IV**
All residuum
EOC or PPC
International

- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 6 mg/mL·min
- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 5 mg/mL·min
  Gemcitabine 800 mg/m² days 1, 8
- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 5 mg/mL·min
- Topotecan 1.5 mg/m² days 1 - 3
  Carboplatin AUC 5 mg/mL·min,
  x4 cycles
- Gemcitabine 1,000 mg/m² days 1, 8
  Carboplatin AUC 6 mg/mL·min,
  x4 cycles

**ALTERNATING COURSES**

- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 5 mg/mL·min
  Doxorubicin 30 mg/m²
- Doxorubicin 30 mg/m² 2 courses
- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 6 mg/mL·min,
- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 6 mg/mL·min,
  x4 cycles

**THEN**

- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 6 mg/mL·min,
  x4 cycles

**THEN**

- Paclitaxel 175 mg/m² 3 hours
  Carboplatin AUC 6 mg/mL·min,
  x4 cycles

**PFI = Progression-free interval; FIGO = International Federation of Gynecologic Oncologists; EOC = Epithelial ovarian cancer; PPC = Primary peritoneal cancer; AUC = Area under the concentration-time curve.**
GOG—Frontline Trials

**GOG-218**

Suboptimal (> 1 cm) EOC, PPC, FT cancer

- Paclitaxel
- Carboplatin
- Placebo

- Paclitaxel
- Carboplatin
- Bevacizumab

- Paclitaxel
- Carboplatin
- Bevacizumab

- Placebo
- Placebo
- Bevacizumab

×15 months ×15 months ×15 months

N = 1,200 - 1,400 patients
Survival, PFS primary endpoints
Biologic & QOL endpoints

EOC = Epithelial ovarian cancer; PPC = Primary peritoneal cancer; FT = Fallopian tube; PFS = Progression-free survival; QOL = Quality of life.
Recurrent Ovarian Cancer—
Definition of Disease Sensitivity

- Refractory
- Resistant
- Sensitive
- Very sensitive
A Randomized trial in ovarian cancer of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators.

Does early intervention in patients with a rising CA125 have merit?

Abstract 1: Trial OV05/55955
Rustin et al
Results: No evidence of difference between the two arms
HR 1.01
Commentary

Strengths
- Randomized trial
- Large study
- Balanced for stage
- Endpoints
  - Overall survival
  - Quality of Life

Weakness
- Lack of second/third line therapy
- Lack of surgical considerations
- Heterogeneous patient population
  - Platinum Sensitive
  - Platinum Resistant
Recurrent Disease

Platinum Sensitive

Platinum Resistant
ICON IV—Survival

**Progression-free survival (PFS)**

- Hazard ratio = 0.76
  - (95% CI 0.66 - 0.89; p < 0.001)
  - Absolute difference at 1 year = 10%
    - (40% to 50%; 95% CI 4% to 15%)

**Overall survival (OS)**

- Hazard ratio = 0.82
  - (95% CI 0.69 - 0.97; p = 0.023)
  - Absolute difference at 2 years = 7%
    - (50% to 57%; 95% CI 1% to 12%)

**Median follow-up: 42 months**

**OR: 54 vs. 66% (P = .06)**

PFI = Progression-free interval; OR = Objective response; CI = Confidence interval; Pac = Paclitaxel; Plat = Platinum-based chemotherapy.

Carboplatin/Gemcitabine Design

Stratified at central AGO office by
- Platinum-free interval (PFI) (6-12 or >12 mos)
- Type of 1st-line platinum therapy (platinum/paclitaxel or other platinum therapy)
- Bidimensionally measurable disease (yes or no)

Randomized

Gemcitabine 1000 mg/m² d1, 8
Carboplatin AUC 4 d1 q 3w for 6 cycles

Carboplatin AUC 5 d1 q 3w for 6 cycles
# PFS Gemcitabine /Carboplatin vs Carboplatin: Summary of Subgroup Analysis

<table>
<thead>
<tr>
<th>Median PFS</th>
<th>Gemcitabine/carboplatin</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free interval (6-12 mos)</td>
<td>7.9 mos</td>
<td>5.2 mos</td>
</tr>
<tr>
<td>Progression-free interval (&gt;12 mos)</td>
<td>9.7 mos</td>
<td>6.7 mos</td>
</tr>
<tr>
<td>Prior platinum and paclitaxel</td>
<td>9.7 mos</td>
<td>5.9 mos</td>
</tr>
<tr>
<td>Prior platinum (no paclitaxel)</td>
<td>7.6 mos</td>
<td>5.7 mos</td>
</tr>
</tbody>
</table>
CALYPSO trial

Carboplatin & Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin & Paclitaxel in Relapsed, Platinum-sensitive Ovarian Cancer

Eric Pujade-Lauraine

Abstract 5509
CALYPSO Study Schema

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

Ovarian cancer in late relapse (> 6 months) after 1\textsuperscript{st}– or 2\textsuperscript{nd}-line platinum-based therapy (previous taxane required)

Experimental arm: CD
- PLD 30 mg/m\textsuperscript{2} IV d 1
- Carboplatin AUC 5 d 1
  - Q 28 days x 6 courses

Control arm: CP
- Paclitaxel 175 mg/m\textsuperscript{2} IV d 1
- Carboplatin AUC 5 d 1
  - Q 21 days x 6 courses

*or progression in patients with SD or PR

Stratification:
- Therapy-free interval (6–12 mo vs > 12 mo)
- Measurable disease (yes vs no)
- Center
Key Eligibility/Objectives

- Age ≥ 18 years
- ECOG performance status ≤ 2
- Histologically proven diagnosis of cancer of the ovary, fallopian tube, or extra-ovarian papillary serous tumors
- Disease progression > 6 months after 1st- or 2nd-line platinum-based therapy
- Previous taxane exposure
- Measureable disease (RECIST criteria) or CA 125 assessable disease (GCIG criteria) or histologically proven diagnosis of relapse

Primary: Progression free survival
## Hematologic Toxicity

<table>
<thead>
<tr>
<th>Toxicity, grade (gr)</th>
<th>CD (n=464)</th>
<th>CP (n=500)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia, gr 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gr 4</td>
<td>144 (31)</td>
<td>121 (24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Febrile neutropenia, gr 3-4</strong></td>
<td>10 (2)</td>
<td>21 (4)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Infection, gr 3-4</strong></td>
<td>11 (3)</td>
<td>14 (3)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Thrombocytopenia, gr 3-4</strong></td>
<td>73 (16)</td>
<td>31 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Bleeding, gr 3-4</strong></td>
<td>3 (0.6)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Anemia, gr 3-4</strong></td>
<td>37 (8)</td>
<td>27 (5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.
Progression-Free Survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at Risk</td>
<td>467</td>
<td>509</td>
</tr>
<tr>
<td>Months from Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>397</td>
<td>405</td>
</tr>
<tr>
<td>6</td>
<td>188</td>
<td>152</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median PFS, mo: 11.3 vs 9.4
- HR (95% CI): 0.82 (0.72, 0.94)
- Log-rank p-value (superiority): 0.005
- P-value (non-inferiority): <0.001
Conclusions

- Carboplatin-PLD demonstrated a superior therapeutic index (benefit/risk ratio) versus current standard, carboplatin-paclitaxel.

- PLD- carboplatin offers an evidence-based option for patients with platinum-sensitive recurrent ovarian cancer.
PARP inhibitors

- PARP: poly (ADP-ribose) polymerases
  - Critical regulatory components in DNA damage repair and other cellular processes
- Deficit in PARP-1: delayed DNA repair function
- Therapeutic Exploitation
Phase II trial of oral PARP inhibitor AZD2281 in BRCA-deficient ovarian cancer

- AZD 2281 (Olaparib): PARP inhibitor
- Phase I: 400 mg was the MTD
- Phase II study: 100 mg BID vs 400 mg BID
- Endpoint: Best objective response rate
- N: 57 patients
- ORR: 400 mg BID: 33%
- ORR: 100 BID: 12.5%
- Toxicity: mild, nausea, diarrhea and fatigue

Audeh MW et al. ASCO 2009 Abstract 5500
Agents For Second-Line Therapy
Cumulative Toxicities

- Carboplatin - plts
- Cisplatin - neuro
- Paclitaxel q1wk or q3wk - neuro
- Doxorubicin - hand/foot (PPE)
- Gemcitabine - none
- Etoposide, oral - AML
- Topotecan - none
- Docetaxel - neuro
- Vinorelbine - WBC
- Tamoxifen - none
- 5-FU/leucovorin - GI
- Irinotecan - GI
- Ifosfamide - neuro, bone marrow, renal
- Hexamethylmelamine - neuro, GI
- Epirubicin (wbc)
Selecting therapy...

Chemotherapy Assays

Karam et al

Abstract 5504
EDR Assay Methodology

1. Tumor biopsy
2. Tissue in transport media
3. Dissociated tumor cells
4. Chemotherapy drug is added
5. 72 hour incubation
6. Tritiated thymidine is added
7. Tumor cells in culture (2 days)
8. Tumor cell DNA is harvested
9. Proliferation is measured by scintillation counting
Aims and Methods

Aims:
- Effects of EDR assay-guided therapy in EOC
- Outcomes in the primary and recurrent setting

Retrospective review
- 377 EOC patients
- EDR assays between 1995 and 2005

End points
- Time to first recurrence (TTP)
- Overall survival (OS)
- Survival after recurrence (RS)
## Univariate Analysis OS and TTP

<table>
<thead>
<tr>
<th>Univariate Characteristic</th>
<th>Median OS</th>
<th>p</th>
<th>Median TTP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, yrs</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;40</td>
<td>153.9</td>
<td>&lt;0.001</td>
<td>49.2</td>
<td>0.008</td>
</tr>
<tr>
<td>40-50</td>
<td>59.5</td>
<td>&lt;0.001</td>
<td>33.8</td>
<td>&lt;0.001</td>
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<td>50-60</td>
<td>59.5</td>
<td>0.008</td>
<td>26.0</td>
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<tr>
<td>60-70</td>
<td>46.3</td>
<td>&lt;0.001</td>
<td>19.5</td>
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</tr>
<tr>
<td>&gt;70</td>
<td>42.5</td>
<td>&lt;0.001</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;III</td>
<td>88.8</td>
<td>0.002</td>
<td>55.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥III</td>
<td>48.6</td>
<td>0.002</td>
<td>21.3</td>
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<tr>
<td><strong>Residual at 1° CRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>66.8</td>
<td>0.03</td>
<td>37.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.1-1.0 cm</td>
<td>45.0</td>
<td>&lt;0.001</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0 cm</td>
<td>39.5</td>
<td>&lt;0.001</td>
<td>10.2</td>
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</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>133.7</td>
<td>0.005</td>
<td>100.0</td>
<td>0.008</td>
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<tr>
<td>2 or 3</td>
<td>45.0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDR Assay at 1° CRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61.9</td>
<td>0.002</td>
<td>27.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Yes</td>
<td>44.1</td>
<td>23.7</td>
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## Multivariate Analysis

<table>
<thead>
<tr>
<th>Multivariate</th>
<th>Disease progression</th>
<th>Death</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age decades</td>
<td>1.12</td>
<td>0.98</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage &lt;III</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Stage ≥III</td>
<td>3.61</td>
<td>0.86</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3</td>
<td>1.87</td>
<td>0.68</td>
</tr>
<tr>
<td>1° CRS residual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0.1 to 1.0 cm</td>
<td>1.94</td>
<td>1.33</td>
</tr>
<tr>
<td>&gt;1.0 cm</td>
<td>3.61</td>
<td>2.07</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Platinum and taxane</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.94</td>
<td>0.23</td>
</tr>
<tr>
<td>EDR assay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>At primary surgery</td>
<td>1.13</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Conclusion

- EDR did not predict outcomes in EOC patients
- Age and disease residual important for outcome
- Rationale for assays remains strong
  - Continued research
  - Gene-expression/microarray profiles
Limitations and Strengths

Limitations:
- Retrospective nature
- Selection and ascertainment bias
- Incomplete information on salvage chemotherapy
American Society of Clinical Oncology Technology Assessment: Chemotherapy Sensitivity and Resistance Assays

Recommendations
The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient’s health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.
Vulvar Cancer
Surgical Management of Vulvar Cancer

Current surgical management of vulvar cancer is based in large part on the results of several previous GOG studies. GOG #36 revealed that groin metastases essentially never occur in patients with tumors less than 1 mm thick; therefore groin dissection is not performed in these patients. GOG #74§ found excessive groin failures in patients treated with unilateral superficial inguinal lymphadenectomy compared with historical controls treated with bilateral inguinal femoral lymphadenectomy. For this reason inguinal femoral lymphadenectomy remains the standard surgical management of the groin.
Modern Sentinel Lymph Node Concept

SN Team: DI, Surg, Path

Sentinel node: first site of metastasis

Regional nodes

Injection of blue dye or radiocolloid around tumor
Eligibility criteria

- Squamous cancer only
- Greater than 1 mm invasion
- Clinical stage II
  - T2 (Tumor size 2-6 cm)
  - N0/1 (Clinically negative lymph nodes)
- No imaging or surgeon skill verification required
Protocol

- Blue dye, lymphscintigraphy (LSG) optional
- Unilateral or bilateral SLNB
- Inguinal femoral lymphadenectomy
- Ultra staging of SLN
  - Serial sectioning with H&E staining of SLN
  - Cytokeratin IHC staining if H&E negative
# Results: Sensitivity and FNPV

<table>
<thead>
<tr>
<th>SLN Status</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>116</td>
<td>0</td>
<td>116</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>282</td>
<td>295</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>282</td>
<td>411</td>
</tr>
</tbody>
</table>

- Sensitivity: 89.9%
- False Negative Predictive Value: 4.4%

\[
\text{Sensitivity} = \frac{TP}{TP+FN} = \frac{116}{116+13} = 89.9\% \\
\text{90% CI} = 84.2\% - 93.9\%
\]

\[
\text{Neg Predictive Value} = \frac{TN}{TN+FN} = \frac{282}{282+13} = 95.6\% \\
\text{90% CI} = 93.6\% - 97.6\%
\]

\[
\text{False neg predictive value} = 1 - \text{NPV} = 1 - 95.6\% = 4.4\% \\
\text{90% CI} = 2.4\% - 6.4\%
\]
Conclusions

- GOG met its predetermined goal of >88% sensitivity and a FNPV of ≤ 5%
- Future GOG studies should include SLNB in the management of patients with early vulvar cancer
- SLNB should be limited to patients with tumors < 4 cm
- The combined technique is recommended
- Surgeon skill verification recommended
Cervical Cancer?

Have we not cured this disease?
# Cervical Cancer

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>
| I          | Cervical carcinoma confined to the cervix  
IA: Invasive carcinoma diagnosed by microscopy  
IA1: Stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread  
IA2: Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less  
IB: Clinically visible lesion confined to the cervix or microscopic  
IB1: Clinically visible lesion 4.0 cm or less in greatest dimension  
IB2: Clinically visible lesion more than 4.0 cm in greatest dimension |
| II         | Tumor invades beyond the uterus but not to pelvic wall or lower third of the vagina  
IIA: No parametrial invasion  
IIB: Parametrial invasion |
| III        | Tumor extends to pelvic wall and /or involves the lower third of the vagina and / or causes hydronephrosis  
IIIA: Tumor involves the lower third of the vagina with out extension to the pelvic wall  
IIIB: Tumor extends to the pelvic wall and causes hydronephrosis or renal compromise |
| IVA        | Tumor invades the mucosa of the bladder or rectum, and or extends beyond the true pelvis |
## Chemo-Radiation

### Table 1. Pelvis as Site of First Failure

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin-Based Therapy</th>
<th>Noncisplatin Control</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No. of Patients</td>
<td>No. With Pelvic Failure</td>
<td>Total No. of Patients</td>
<td>No. With Pelvic Failure</td>
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</tr>
<tr>
<td>GOG 85</td>
<td>177</td>
<td>44</td>
<td>191</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>GOG 120</td>
<td>176</td>
<td>33</td>
<td>177</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>GOG 120</td>
<td>173</td>
<td>35</td>
<td>177</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>RTOG 9001</td>
<td>193</td>
<td>37</td>
<td>193</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>GOG 123</td>
<td>183</td>
<td>29</td>
<td>186</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>SWOG 8797</td>
<td>127</td>
<td>11</td>
<td>116</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>NCIC</td>
<td>126</td>
<td>34</td>
<td>123</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,155</td>
<td>223 (19.3%)</td>
<td>986</td>
<td>313 (31.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SWOG, Southwest Oncology Group.
# Metastatic Cervical Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>GOG trial</th>
<th>Agents</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuire et al(^{31})</td>
<td>GOG 76S</td>
<td>paclitaxel</td>
<td>ORR : 17 %</td>
</tr>
<tr>
<td>Rose et al(^{32})</td>
<td>GOG 76X</td>
<td>cisplatin + paclitaxel</td>
<td>ORR: 46%</td>
</tr>
<tr>
<td>Moore et al(^{28})</td>
<td>GOG169</td>
<td>cisplatin + paclitaxel vs cisplatin</td>
<td>RR: 36 % vs 19 %</td>
</tr>
<tr>
<td>Long et al(^{27})</td>
<td>GOG 179</td>
<td>MVAC vs cisplatin vs cisplatin + topotecan</td>
<td>MVAC:D/C Combination of cisplatin and topotecan has improve RR, median PFS and median OS Patients w/o prior cisplatin RR: 36 % vs 19 % Patients with prior cisplatin 15 vs 8 %</td>
</tr>
<tr>
<td>Sill et al(^{33})</td>
<td>GOG 204</td>
<td>cisplatin+ paclitaxel</td>
<td>Closed early: study arms had no difference over cisplatin + paclitaxel</td>
</tr>
<tr>
<td>Tiersten et al(^{34})</td>
<td></td>
<td>paclitaxel + topotecan</td>
<td>RR: 59 % OS 8.6 mo</td>
</tr>
<tr>
<td>Symonds R et al(^{35})</td>
<td>SCOT-CERV</td>
<td>Docetaxel + gemcitabine</td>
<td>1 CR : 4 PR, 6SD and 11 PD</td>
</tr>
<tr>
<td>Monk et al(^{30})</td>
<td>GOG 227C</td>
<td>Bevacizumab</td>
<td>5 PR 11 patients PFS &gt; 6 mo</td>
</tr>
</tbody>
</table>
A Randomized Phase III Study Comparing Concurrent Gemcitabine (Gem) plus Cisplatin (Cis) and Radiation Followed by Adjuvant Gem plus Cis versus Concurrent Cis and Radiation in Patients with Stage IIB to IVA Carcinoma of the Cervix:

Abstract 5009

Alfonso Dueñas-González, et al
## Study Design

### Randomization

- **Eligibility:**
  - CC histology;
  - stage IIB to IVA;
  - clear PA LNs;
  - CTy/RTy naive;
  - KPS ≥70;
  - Randomized and stratified: stage; tumor size; investigator site; radiation equipment (Co60 or LinAc); age.

- **N = 515 patients**

### Chemoradiation

- **Arm A**
  - N = 259
  - 2 cycles of:
    - cisplatin 40 mg/m² +
    - gemcitabine 125 mg/m² weekly for 6 weeks
  - pelvic XRT 50.4 Gy 1.8 Gy/day in 5.4 weeks (Co60 or LinAc)

- **Arm B**
  - N = 256
  - cisplatin 40 mg/m² weekly for 6 weeks
  - pelvic XRT 50.4 Gy 1.8 Gy/day in 5.4 weeks (Co60 or LinAc)

### BCT

- **All patients**
  - 30–35 Gy (low or IM dose rate)
  - REST

### Chemotherapy

- **Arm A**
  - 2 cycles of:
    - cisplatin 50 mg/m² (day 1) +
    - gemcitabine 1 g/m² (days 1 and 8)
    - given q3 weeks

- **Arm B**
  - NO ADJUVANT CHEMOTHERAPY

### Primary Objective

- Progression-free survival (PFS) at 3 years
Progression-Free Survival at 3 Years

PFS overall was statistically superior

PFS at 3 years: 74.4% versus 65.0% (p=0.029)
Overall Survival

- OS probability over time for Gem/cis/rad and Cis/rad.
- Log-rank p = 0.022
- Hazard ratio = 0.68
- 95% CI = 0.49-0.95

- OS was statistically superior for Gem/cis/rad over Cis/rad
- OS at 3 years: 78.2% in Gem/cis/rad versus 69.1% in Cis/rad
## Overall Study Drug-Related Toxicity

<table>
<thead>
<tr>
<th>Drug-related CTCAE Grade 3/4 toxicity (on-study or within 30 days of last study drug dose)</th>
<th>Arm A N=260</th>
<th>Arm B N=255</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Grade 3 (%) 4 (%)</td>
<td>Grade 3 (%) 4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45.0 6.2</td>
<td>5.1 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.7 1.5</td>
<td>1.6 0.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>1.2 0.0</td>
<td>0.004</td>
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<td>Febrile neutropenia</td>
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<td>0.4 0.0</td>
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<tr>
<td>Diarrhea</td>
<td>17.7 0.0</td>
<td>4.7 0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.8 0.4</td>
<td>2.7 0.0</td>
<td>0.473</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>2.4 0.4</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>3.1 0.8</td>
<td>1.6 0.0</td>
<td>0.174</td>
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<tr>
<td>Radiation dermatitis</td>
<td>11.2 0.0</td>
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<td>0.888</td>
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<tr>
<td>Abdominal pain/cramping</td>
<td>2.7 0.0</td>
<td>0.4 0.0</td>
<td>0.068</td>
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<tr>
<td>Anorexia</td>
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<td>0.0 0.0</td>
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<td>Proctitis</td>
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<td>0.4 0.0</td>
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<td>0.0 0.0</td>
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<tr>
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<td>0.0 0.0</td>
<td>0.499</td>
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<td>Creatinine</td>
<td>1.5 0.0</td>
<td>0.4 0.4</td>
<td>0.686</td>
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<tr>
<td><strong>Other</strong>*</td>
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Future For Gynecological Cancers

- Ovarian
  - VEGF
  - EGFR
  - MTOR
  - AURORA KINASE
  - HEDGEHOG

- CERVICAL
  - VEGF

- ENDOMETRIAL
  - VEGF
  - MTOR