GYNECOLOGIC CANCER

Recent Advances in Management

Tate Thigpen, M.D.
Disclosure Information

James Tate Thigpen, M.D.

- I have the following financial relationships to disclose:
  - Consultation: Clovis, Genentech, Merck, Oasmia, Tesaro
  - Speakers’ Bureau Participation: Astra Zeneca, Clovis, Genentech, Novartis, Tesaro
Gynecologic Cancer

Discussion Topics

- Ovarian Cancer
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505
Gynecologic Cancer

Discussion Topics

- **Ovarian Cancer**
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506

- **Cervical Cancer**
  - Neoadjuvant Chemotherapy: ASCO 5523

- **Uterine Cancer**
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505
THE ROLE OF SURGERY IN FRONT-LINE MANAGEMENT

- ASCO Abstract 5500: JCOG 0602
- SGO Abstract 43: Retrospective Study of PDS and NACT
# PDS v NACT: Phase III Studies

<table>
<thead>
<tr>
<th></th>
<th>EORTC PDS</th>
<th>EORTC NACT</th>
<th>CHORUS PDS</th>
<th>CHORUS NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>336</td>
<td>334</td>
<td>276</td>
<td>274</td>
</tr>
<tr>
<td>Residual ≤1 cm</td>
<td>42%</td>
<td>81%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No Gross Residual</td>
<td>18%</td>
<td>45%</td>
<td>15%</td>
<td>35%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Median OS</td>
<td>29</td>
<td>30</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>HR for NACT in OS</td>
<td>0.98</td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>0.84-1.13</td>
<td></td>
<td>0.72-1.05</td>
<td></td>
</tr>
<tr>
<td>Non-inferiority Margin</td>
<td>1.25</td>
<td></td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

1. Vergote et al: NEJM 2010
Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602.


UMIN Clinical Trials Registry: UMIN000000523
Trial Design

Multicenter (34 specialized institutions), Randomized Phase III Trial

**Standard Arm (PDST)**

- PDS → 4x TC → 4x TC
  - PDS: primary debulking surgery

**Experimental Arm (NACT)**

- NAC (4x TC) → IDS → 4x TC
  - IDS: interval debulking surgery

*Optional for pts with suboptimal PDS. Mandatory for pts with any of Ut/Adn/OM Unremoved.*

**Clinically diagnosed Stage III/IV ovarian, tubal, and peritoneal cancers**

**Balancing factors**
- Institution, Stage III/IV
- PS 0-1/2-3, Age <60/≥60

**TC regimen:** PTX 175 mg/m^2^ iv, CBDCA AUC 6.0 iv
### Patient Characteristics by Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EORTC</th>
<th>CHORUS</th>
<th>JCOG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PDS N=336</td>
<td>NACT N=334</td>
<td>PDS N=276</td>
</tr>
<tr>
<td>Median Age (yrs)</td>
<td>62</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>PS 2-3</td>
<td>12%</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>23%</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>CA-125 (median)</td>
<td>1130</td>
<td>1180</td>
<td>NA</td>
</tr>
<tr>
<td>Clear/Mucinous</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Initial Statistical Considerations

Planned sample size was 300
(Expected number of events was 276)

- One-sided alpha of 0.05
- Power of 0.8
- Expected 3-year OS
  PDST = 25%, NACT = 30.3%
- Non-inferiority margin = 5% in 3-year OS
  Corresponding HR of 1.161
- Accrual period: 3 years, Follow-up period: 5 years
# Comparison of Treatment Invasiveness

<table>
<thead>
<tr>
<th>Parameters for treatment invasiveness</th>
<th>PDST (n=149)</th>
<th>NACT (n=152)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of surgery</td>
<td>1.32</td>
<td>0.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median operation time (min)</td>
<td>341</td>
<td>273</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median Blood/Ascites loss (ml)</td>
<td>3447</td>
<td>619.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resection of Abdominal organs</td>
<td>56 (37.6%)</td>
<td>36 (23.7%)</td>
<td>0.0121</td>
</tr>
<tr>
<td>Resection of Distant metastases</td>
<td>16 (10.7%)</td>
<td>6 (3.9%)</td>
<td>0.0272</td>
</tr>
<tr>
<td>Transfusion* RCC</td>
<td>97 (66.0%)</td>
<td>79 (52.7%)</td>
<td>0.0247</td>
</tr>
<tr>
<td>Transfusion* FFP</td>
<td>42 (28.6%)</td>
<td>25 (16.7%)</td>
<td>0.0180</td>
</tr>
<tr>
<td>Post-operative G3/4 adverse events**</td>
<td>23 (15.6%)</td>
<td>6 (4.6%)</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

*among all treated patients, **among all operated patients
Overall Survival (N=301)

HR = 1.05 [90.8% CI 0.83-1.33] (p=0.24)†

† Cox proportional hazard model stratified by clinical stage, PS and age [for non-inferiority]

PHT at risk

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>149</td>
<td>152</td>
</tr>
<tr>
<td>12</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>24</td>
<td>112</td>
<td>115</td>
</tr>
<tr>
<td>36</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>48</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>60</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>72</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>84</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>96</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>108</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>132</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Presented By Takashi ONDA at 2018 ASCO Annual Meeting
Progression-free Survival (N=301)

- **PDST (N=149)**
  - MPFS: 15.1M
  - 95% CI: 13.4-18.1M

- **NACT (N=152)**
  - MPFS: 16.4M
  - 95% CI: 15.0-18.8M

**HR=0.96 [95% CI 0.75-1.23]**

+ Cox proportional hazard model adjusted by clinical stage, PS and age
OS according to Debulking Results

**PDST (N=147)**

<table>
<thead>
<tr>
<th>RT</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 cm</td>
<td>Not estimable</td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>54.9 M</td>
</tr>
<tr>
<td>≥ 1 cm</td>
<td>43.0 M</td>
</tr>
</tbody>
</table>

**NACT (N=130)**

<table>
<thead>
<tr>
<th>RT</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 cm</td>
<td>67.0 M</td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>34.0 M</td>
</tr>
<tr>
<td>≥ 1 cm</td>
<td>32.0 M</td>
</tr>
</tbody>
</table>

**Pts at risk**

PDST:
- RT = 0 cm: 17, 17, 16, 15, 13, 11, 10, 6, 5, 4, 1, 0
- RT < 1 cm: 38, 37, 30, 25, 21, 18, 15, 10, 4, 3, 1, 0
- RT ≥ 1 cm: 92, 86, 66, 51, 42, 28, 25, 18, 13, 8, 2, 0

NACT:
- RT = 0 cm: 83, 81, 71, 59, 46, 43, 37, 28, 17, 8, 3, 0
- RT < 1 cm: 24, 22, 17, 11, 9, 4, 3, 2, 0, 0
- RT ≥ 1 cm: 23, 20, 14, 9, 8, 6, 3, 1, 0, 0, 0
PDS v NACT: Bottom Line

- Overall results suggest that PDS and NACT yield equivalent results; either is acceptable.
- Achieving optimal cytoreduction after NACT is not the same as achieving this with PDS (Manning-Geist et al, SGO 2018 abstract 43).

Caveats
- Patients with poor performance status or other indicators of poor general health may be better served with NACT.
- Variability in optimal debulking rate raises concerns about the quality of surgery across the studies.
- Results in the JCOG study support the need for an experienced, aggressive surgeon for best results.
Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

Patients with \(<1\ cm\) Disease by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Total</th>
<th>PDS (n = 329)</th>
<th>NACT -&gt; IDS (n = 339)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium (n=133)</td>
<td>83%</td>
<td>72%</td>
<td>94%</td>
</tr>
<tr>
<td>Argentina (n=48)</td>
<td>71%</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>The Netherlands (n=104)</td>
<td>59%</td>
<td>40%</td>
<td>77%</td>
</tr>
<tr>
<td>Sweden (n=23)</td>
<td>59%</td>
<td>40%</td>
<td>75%</td>
</tr>
<tr>
<td>Norway (n=82)</td>
<td>55%</td>
<td>35%</td>
<td>73%</td>
</tr>
<tr>
<td>Italy (n=38)</td>
<td>52%</td>
<td>40%</td>
<td>64%</td>
</tr>
<tr>
<td>Spain (n=62)</td>
<td>49%</td>
<td>44%</td>
<td>58%</td>
</tr>
<tr>
<td>UK (n=101)</td>
<td>47%</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Canada (n=84)</td>
<td>44%</td>
<td>29%</td>
<td>59%</td>
</tr>
</tbody>
</table>
Overall results suggest that PDS and NACT yield equivalent results; either is acceptable.

Achieving optimal cytoreduction after NACT is not the same as achieving this with PDS (Manning-Geist et al, SGO 2018 abstract 43).

Caveats:
- Patients with poor performance status or other indicators of poor general health may be better served with NACT.
- Variability in optimal debulking rate raises concerns about the quality of surgery across the studies.
- Results in the JCOG study support the need for an experienced, aggressive surgeon for best results.
HIPEC

- NEJM 378:230-240, 2018
Ovarian Carcinoma

Hyperthermic Intraperitoneal Chemotherapy

- Stages III-IV
- At least stable disease after 3 cycles of TC
- Primary Endpoint: RFS
- N = 245

Randomize

Interval Debulking

Interval Debulking
Plus HIPEC*

Three more cycles of TC

*HIPEC by open technique
- 40°C (104°F)
- Cisplatin 100 mg/m²
- 120 minutes

Van Driel et al: NEJM 378:230-240, 2018
### Ovarian Carcinoma

**Hyperthermic IP Chemotherapy**

#### Results

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>RFS</th>
<th>OS</th>
<th>AEs (% G 3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDS</td>
<td>123</td>
<td>10.7 mos</td>
<td>33.9 mos</td>
<td>25%</td>
</tr>
<tr>
<td>IDS+HIPEC</td>
<td>122</td>
<td>14.2 mos</td>
<td>45.7 mos</td>
<td>27%</td>
</tr>
<tr>
<td>HR (CI)</td>
<td></td>
<td>0.66 (0.50-0.87)</td>
<td>0.67 (0.48-0.94)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.003</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

* Primary endpoint RFS (Relapse-Free Survival)

Van Driel et al: NEJM 378:230-240, 2018
IDS +/- HIPEC: Bottom Line

- Randomized patients were stratified according to whether the surgical was R0 or one or more gross nodules ≤10mm diameter
- Significant improvement in RFS and OS
- Patients with grade 3-4 adverse effects: no difference between treatment arms
- Caveats
  - Overall surgical quality not clear
  - Relatively small trial
  - No bevacizumab
  - No excess toxicity
  - No confirmatory trial as of yet – need to await confirmation
SECONDARY SURGICAL CYTOREDUCTION

- ASCO Abstract 5501: GOG 213
A Phase III Randomized Controlled Trial of Secondary Surgical Cytoreduction followed by Platinum-Based Combination Chemotherapy, With or Without Bevacizumab in Platinum-Sensitive, Recurrent Ovarian Cancer: A NRG Oncology/Gynecologic Oncology Group Study

Robert L. Coleman, Nick Spirtos, Danielle Enserro, Thomas J. Herzog, Paul Sabbatini, Deborah Kay Armstrong, Byoung Kim, Keiichi Fujiwara, Joan L. Walker, Patrick J. Flynn, Angeles Alvarez Secord, David E. Cohn, Mark F. Brady, Robert S. Mannel
Background: DESKTOP III

- Surgery was safe and feasible
- R0 rate: 72.5%
- Patients with residual disease after surgery had the same HR_{PFS} as those receiving chemotherapy alone
- Time to 3rd line significantly longer
- OS: immature at interim analysis

DuBois, Proc ASCO, Abst 5501, 2017
GOG 213: Schema Objective #1

Women with recurrent ovarian, peritoneal primary or fallopian tube cancer and a treatment free interval greater than or equal to 6 months.

N = 107

YES

Surgical Candidate

N = 567

NO

Randomize

Randomize

Surgery

Regimen I

Carboplatin
AUC 5
Paclitaxel
175 mg/m²
q 21 days

Regimen II

Carboplatin
AUC 5
Paclitaxel
175 mg/m²
Bevacizumab
15 mg/kg
q 21 days

Maintenance

Bevacizumab
15 mg/kg
q 21 days until progression or toxicity precludes further treatment.
GOG 213 Objective 1: OS

HR: 0.829 (0.68 - 1.005), P=0.056

HR_{adj}: 0.823 (0.68 - 0.996), P=0.0447

Proportion Surviving

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crb+Tax</td>
<td>214</td>
<td>337</td>
<td>37.3</td>
</tr>
<tr>
<td>Crb+Tax+Bev</td>
<td>201</td>
<td>337</td>
<td>42.2</td>
</tr>
</tbody>
</table>

N=674

Coleman RL, Lancet Oncol 2017

Presented By Robert Coleman at 2018 ASCO Annual Meeting

Women with recurrent ovarian, peritoneal primary or fallopian tube cancer and a treatment free interval greater than or equal to 6 months.

Chemotherapy (2 options):
- Paclitaxel 175 mg/m² +
- Carboplatin AUC5

- Gemcitabine 1000 mg/m² d1,8 +
- Carboplatin AUC5

Bevacizumab (optional):
- 15 mg/kg
- Starting cycle 2 for post-op to a max of 8 cycles
- Maintenance allowed until progression, intolerance or death

Cycle Length: 21 days
Statistical Design

- Primary endpoint: OS
- Assumption of no interaction between the two randomizations (Objective 1 patients, N=107)
- Alpha set two-sided at 0.05 in each randomized comparison
- Stratification variables:
  - Platinum-Free Interval (6-12, ≥12 months)
  - Chemotherapy regimen chosen (4 options)
- Targeted adjusted HR: 0.70 (increase from 50% to 61.5% at 22 months)
- Analysis considered mature: 250 events
CONSORT and Accrual

**Opened:** Dec 6, 2007  
**Closed:** Jun 9, 2017

- **485 participants enrolled**
  - from Korea* 212
  - Japan 17
  - United States 256

- **240 Randomized to Cytoreductive Surgery**
  - 239 Eligible
  - 1 Ineligible

- **225 Received surgery**
  - 14 did not receive surgery.

- **240 Evaluated for PFS and OS**
  - 10 participants lost to follow-up or withdrew consent.
  - 161 alive at last contact.

- **245 Randomized to Surveillance (No Surgery)**
  - 243 Eligible
  - 2 Ineligible

- **238 Received surveillance**
  - 5 received surgery.

- **245 Evaluated for PFS and OS**
  - 12 participants lost to follow-up or withdrew consent.
  - 177 alive at last contact.
Surgical Findings

- Surgical outcomes: (ITT population)
  - R0 = 64% (146/230)
  - 14 patients did not undergo surgery

- Surgical outcomes (Per protocol population)
  - R0 = 68% (146/216)

- Median duration of follow-up: 34.6 months
Primary Endpoint OS: Surgery vs. No Surgery

Overall Survival by Randomized Surgical Treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Cytoreductive Surgery</td>
<td>78</td>
<td>53.6</td>
</tr>
<tr>
<td>2: No Surgery</td>
<td>69</td>
<td>65.7</td>
</tr>
</tbody>
</table>

HR\text{\textsubscript{ITT}}: 1.28 (0.92-1.78)
HR\text{\textsubscript{Non-USA}}: 1.28 (0.6-2.75)

<table>
<thead>
<tr>
<th>Number at-risk (Number censored)</th>
<th>0 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
<th>72 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>240 (0)</td>
<td>180 (52)</td>
<td>122 (84)</td>
<td>78 (110)</td>
<td>47 (130)</td>
<td>23 (146)</td>
<td>16 (150)</td>
</tr>
<tr>
<td>No surgery</td>
<td>245 (0)</td>
<td>188 (50)</td>
<td>143 (83)</td>
<td>91 (111)</td>
<td>52 (138)</td>
<td>32 (153)</td>
<td>19 (162)</td>
</tr>
</tbody>
</table>
Secondary Endpoint PFS: Surgery vs. Chemo

Progression-Free Survival by Randomized Surgical Treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Cytoreductive Surgery</td>
<td>142</td>
<td>240</td>
<td>18.2</td>
</tr>
<tr>
<td>2: No Surgery</td>
<td>161</td>
<td>245</td>
<td>16.5</td>
</tr>
</tbody>
</table>

HR: 0.88 (0.70-1.11)

Number at-risk (Number censored)

<table>
<thead>
<tr>
<th></th>
<th>0 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
<th>72 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>240 (0)</td>
<td>128 (48)</td>
<td>52 (68)</td>
<td>31 (78)</td>
<td>17 (86)</td>
<td>8 (90)</td>
<td>6 (92)</td>
</tr>
<tr>
<td>No surgery</td>
<td>245 (0)</td>
<td>132 (45)</td>
<td>57 (61)</td>
<td>27 (69)</td>
<td>11 (78)</td>
<td>6 (78)</td>
<td>3 (81)</td>
</tr>
</tbody>
</table>
Exploratory Endpoint: Surgery Outcome
RO vs. Non-RO

Progression-Free Survival by Surgery Outcome
- RO
- Other

<table>
<thead>
<tr>
<th>Surgery Outcome</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO</td>
<td>64</td>
<td>84</td>
<td>13.1</td>
</tr>
<tr>
<td>Other</td>
<td>78</td>
<td>146</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Overall Survival by Surgery Outcome
- RO
- Other

<table>
<thead>
<tr>
<th>Surgery Outcome</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO</td>
<td>37</td>
<td>84</td>
<td>38.6</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>146</td>
<td>55.2</td>
</tr>
</tbody>
</table>

HR: 0.51 (0.36-0.72) for RO vs. Non-RO

HR: 0.67 (0.41-1.08) for RO vs. Non-RO
Exploratory Endpoint: Surgical R0 vs. No Surgery

**Progression-Free Survival**
R0 vs No Surgery

- No Surgery: 245, 132, 57, 27, 11, 6, 3
- R0: 146, 90, 42, 26, 15, 7, 5

HR: 0.68 (0.51-0.90)

**Overall Survival**
R0 vs No Surgery

- No Surgery: 245, 188, 143, 91, 52, 32, 19
- R0: 146, 115, 79, 54, 35, 15, 12

HR: 1.11 (0.74-1.66)
## GOG 213: Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>No Surgery (n=233)</th>
<th>Surgery (n=224)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy, grades ≥ 3</td>
<td>12 (5%)</td>
<td>12 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Constitutional Symptoms, grades ≥ 3</td>
<td>8 (3%)</td>
<td>8 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac, grades ≥ 3</td>
<td>20 (9%)</td>
<td>24 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td><strong>– 1 death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatological, grades ≥ 3</td>
<td>2 (1%)</td>
<td>5 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal, grade ≥ 3</td>
<td>15 (7%)</td>
<td>25 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Perforation, necrosis, fistula, grade ≥ 3</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhage/Bleeding, grade ≥ 3</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hematological, grade ≥ 3</td>
<td>191 (82%)</td>
<td>180 (80%)</td>
<td>NS</td>
</tr>
<tr>
<td>Infection, grade ≥ 3</td>
<td>30 (13%)</td>
<td>28 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic, grade ≥ 3</td>
<td>32 (14%)</td>
<td>41 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy, grades ≥ 2</td>
<td>50 (21%)</td>
<td>44 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular grades ≥ 3</td>
<td>4 (2%)</td>
<td>7 (3%)</td>
<td><strong>– 2 deaths</strong></td>
</tr>
</tbody>
</table>

Presented By Robert Coleman at 2018 ASCO Annual Meeting
Secondary Surgical Cytoreduction: Bottom Line

- Secondary surgical cytoreduction that achieves R0 disease status yields an improved PFS compared to those who undergo no surgery.

- Caveats
  - In surgical candidates, R0 status can be achieved 68-72% of the time with minimal added toxicity.
  - Comparison of R0 patient to those with no surgery (chemotherapy only) shows improved PFS, no difference in OS.
    - This is consistent with trials assessing other approaches: improved PFS but no OS difference.
    - The lack of OS difference probably results from the extensive post-progression therapy these patients receive which renders OS an uninterpretable endpoint.
Gynecologic Cancer

Discussion Topics

- **Ovarian Cancer**
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506

- **Cervical Cancer**
  - Neoadjuvant Chemotherapy: ASCO 5523

- **Uterine Cancer**
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505
PARP INHIBITORS AND MAINTENANCE THERAPY FOR OVARIAN CANCER

- ASCO Abstract 5508: Cost Effectiveness of Maintenance
- ASCO Discussions: Aghajanian and Tian
- SGO Abstracts
  - 16: PARPi Cost Effectiveness
  - 19: Clinical Benefit of Maintenance Rx
  - 21: Niraparib Cost Effectiveness
- PARPi maintenance registration trials
PARP Inhibitors

DNA REPAIR

DNA DAMAGE

DNA Single-Strand Break
- Base Excision Repair
- Mismatch Repair
- Nucleotide Excision Repair
- Trans-Lesional Synthesis

Replication

DNA Double-Strand Break
- Homologous Recombination
- Non-Homologous End Joining

BRCA mutation

PARPi

40
# Ovarian Carcinoma

## GERMLINE AND SOMATIC BRCA MUTATIONS\(^{1-4}\)

<table>
<thead>
<tr>
<th></th>
<th>Germline</th>
<th>Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>Inherited</td>
<td>Acquired</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>All cells in the body</td>
<td>Only in tumor cells</td>
</tr>
</tbody>
</table>

Ovarian Carcinoma: HRD+

- In addition to BRCA1 and BRCA2, other genetic aberrations can induce homologous recombination repair deficiency including:
  - Genes in the Fanconi anemia pathway such as RAD51C, RAD51D, BRIP1, PALB2, BARD1
  - Mismatch repair genes such as MLH1, MSH2
- These other genes accounting for HRD+ involve up to 25% of ovarian cancer patients
- In total, as much as 50% of ovarian cancer patients exhibit deficiency of homologous recombination repair
- While PARPi have their greatest impact in patients with BRCA mutations and other genes producing HRD, even wild-type patients benefit from PARPi.
## Companion Diagnostics - BRCA

<table>
<thead>
<tr>
<th>Companion Diagnostic</th>
<th>Company</th>
<th>Sample</th>
<th>Genes Assessed</th>
<th>Type(s) of Analysis</th>
<th>Results</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRACAnalysis CDx</td>
<td>Myriad Genetics</td>
<td>Whole blood</td>
<td>gBRCA1, gBRCA2</td>
<td>Sanger sequencing and multiplex PCR</td>
<td>BRCA1/2 status</td>
<td>Olaparib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline</td>
<td>Complementary Diagnostic:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maintenance</td>
</tr>
<tr>
<td>Foundation Focus CDx BRCA</td>
<td>Foundation Medicine</td>
<td>FFPE</td>
<td>Tumor BRCA</td>
<td>Next generation sequencing</td>
<td>BRCA 1/2 status</td>
<td>Rucaparib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline + Somatic</td>
<td></td>
</tr>
</tbody>
</table>

**FFPE:** Formalin fixed paraffin embedded

https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm
## Companion Diagnostics - HRD

<table>
<thead>
<tr>
<th>Companion Diagnostic</th>
<th>Company</th>
<th>Sample</th>
<th>Genes Assessed</th>
<th>Type(s) of Analysis</th>
<th>Results</th>
<th>Studies</th>
</tr>
</thead>
</table>
| myChoice HRD (Includes Tumor BRACAnalysis CDx) | Myriad Genetics | FFPE   | Tumor BRCA1/2; Tumor Genomic Instability            | LOH, LST, TAI                                                                      | HRD Score:  
HRD high (≥42 or BRCAmut)  
HRD low (<42 & BRCAwt) | Niraparib  
Olaparib  
Veliparib |
| FoundationFocus CDxBRCA LOH           | Foundation Medicine          | FFPE   | 324 genes                                          | Base substitutions, insertion/deletions (indels), CNAs, select gene rearrangements, microsatellite instability (MSI) and tumor mutational burden (TMB) | HRD LOH Cutoff:  
High LOH (≥16% genomic LOH)  
Low LOH (<16% genomic LOH) | Complementary Diagnostic: Rucaparib |

FFPE: Formalin fixed paraffin embedded; LOH: Loss of heterozygosity; LST: Large scale state transitions; TAI: Telomeric allelic imbalance; CNA: Copy number alteration

Presented By Carol Aghajanian at 2018 ASCO Annual Meeting
# PARP Inhibitors

## Maintenance

<table>
<thead>
<tr>
<th>PARPi</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>NOVA</td>
<td>55</td>
<td>≥3%</td>
<td>9.4</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Study 19</td>
<td>193</td>
<td>≥3%</td>
<td>7.9</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>ARIEL3</td>
<td>106</td>
<td>≥2%</td>
<td>9.2</td>
</tr>
<tr>
<td>Veliparib</td>
<td>GOG3005</td>
<td>50</td>
<td>1-3%</td>
<td>8.2</td>
</tr>
</tbody>
</table>

## Treatment

<table>
<thead>
<tr>
<th>PARPi</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>QUADRA g/sBRCA</td>
<td>55</td>
<td>31%</td>
<td>9.4</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Study 42 gBRCA</td>
<td>193</td>
<td>34%</td>
<td>7.9</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>Study 10 ARIEL2 g/sBRCA</td>
<td>106</td>
<td>54%</td>
<td>9.2</td>
</tr>
<tr>
<td>Veliparib</td>
<td>GOG280 gBRCA</td>
<td>50</td>
<td>26%</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Study 19: PFS in PSOC (Olaparib)


<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>60/136</td>
<td>94/129</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.4 mos</td>
<td>4.8 mos</td>
</tr>
<tr>
<td>HR</td>
<td>0.35 (0.25-0.49)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio, 0.35 (95% CI, 0.25–0.49)  
P<0.001
SOLO-2: PFS in BRCA+ Pts (Olaparib)


<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>107 (54.6%)</td>
<td>80 (80.8%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>19.1 mos</td>
<td>5.5 mos</td>
</tr>
</tbody>
</table>

HR=0.30 (0.22-0.41)
NOVA gBRCAmut Progression Free Survival

Presented By Carol Aghajanian at 2018 ASCO Annual Meeting

![Graph showing progression-free survival over time for Niraparib and Placebo groups.](image)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median, months (95% CI)</th>
<th>Hazard Ratio (95% CI) p-value</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (n=138)</td>
<td>21.0 (12.9, NR)</td>
<td>0.27 (0.173, 0.410)</td>
<td>62% 50%</td>
</tr>
<tr>
<td>Placebo (n=65)</td>
<td>5.5 (3.8, 7.2)</td>
<td>p&lt;0.0001</td>
<td>16% 16%</td>
</tr>
</tbody>
</table>

N Engl J Med. 2016 Dec 1;375(22):2154-2164
NOVA Non-gBRCAmut Progression Free Survival

Presented By Carol Aghajanian at 2018 ASCO Annual Meeting

**Graph:**
- X-axis: Time Since Randomization (months)
- Y-axis: Progression-free Survival (%)
- Two lines represent Niraparib and Placebo groups.

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median, months (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>9.3 (7.2, 11.2)</td>
<td>0.45 (0.338, 0.607)</td>
<td>41%</td>
</tr>
<tr>
<td>(n=234)</td>
<td></td>
<td>p&lt;0.0001</td>
<td>30%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.9 (3.7, 5.5)</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>(n=116)</td>
<td></td>
<td></td>
<td>12%</td>
</tr>
</tbody>
</table>

N Engl J Med. 2016 Dec 1;375(22):2154-2164
## NOVA Subgroups of Non-gBRCAmut Cohort

<table>
<thead>
<tr>
<th></th>
<th>HRD-positive</th>
<th>HRD-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sBRCAmut</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>PFS Median, months (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Niraparib (n=35)</td>
<td>20.9 (9.7, NR)</td>
<td>0.27 (0.081, 0.903)</td>
</tr>
<tr>
<td>Placebo (n=12)</td>
<td>11.0 (2.0, NR)</td>
<td>0 (NR)</td>
</tr>
</tbody>
</table>

| **BRCAwt**       |              |              |
| Treatment        | PFS Median, months (95% CI) | Hazard Ratio (95% CI) | p-value | % of Patients without Progression or Death | 12 mo | 18 mo |
| Niraparib (n=71) | 9.3 (5.8, 15.4) | 0.38 (0.231, 0.628) | p=0.0001 | 45% | 27% |
| Placebo (n=44)   | 3.7 (3.0, 5.0) | 0.0001 | p=0.0226 | 11% | 6% |
| Niraparib (n=92) | 6.0 (5.6, 6.6) | 0.58 (0.361, 0.922) | p=0.0361 | 27% | 19% |
| Placebo (n=42)   | 3.8 (3.0, 5.0) | 0.361 | p=0.0226 | 7% | 7% |

NR, Not reached.

N Engl J Med. 2016 Dec 1;375(22):2154-2164

Presented By Carol Aghajanian at 2018 ASCO Annual Meeting
Ariel 3 PFS Regardless of **BRCA** Status

HR=0.36 (0.30-0.45); \( P<0.0001 \)

- **Rucaparib (n=375)**
- **Placebo (n=189)**

- **Rucaparib**: 10.8 mos
- **Placebo**: 5.4 mos

Ariel 3 PFS BRCA+ Patients

HR=0.23 (0.16-0.34); P<0.0001

Rucaparib (n=130)

Placebo (n=66)

16.6 mos
Rucaparib

5.4 mos
Placebo

# ARIEL 3 PFS by Mutation Subgroup

<table>
<thead>
<tr>
<th>BRCA+</th>
<th>Events/Pts</th>
<th>Events/Pts</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>48/80</td>
<td>29/37</td>
<td>0.32 (0.19-0.53)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>19/50</td>
<td>27/29</td>
<td>0.12 (0.06-0.26)</td>
</tr>
<tr>
<td>Germline</td>
<td>47/82</td>
<td>42/48</td>
<td>0.25 (0.16-0.39)</td>
</tr>
<tr>
<td>Somatic</td>
<td>18/40</td>
<td>12/16</td>
<td>0.23 (0.10-0.54)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCA wild</th>
<th>Events/Pts</th>
<th>Events/Pts</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOH high</td>
<td>67/106</td>
<td>45/52</td>
<td>0.44 (0.29-0.66)</td>
</tr>
<tr>
<td>LOH low</td>
<td>81/107</td>
<td>50/54</td>
<td>0.58 (0.40-0.85)</td>
</tr>
<tr>
<td>LOH indet</td>
<td>19/32</td>
<td>16/17</td>
<td>0.25 (0.11-0.56)</td>
</tr>
</tbody>
</table>
Patients with event, n (%) 423 (67.7) 418 (66.9) 360 (57.8)
Median PFS, months 10.3 11.2 14.1
Stratified analysis HR (95% CI) 0.908 (0.759–1.040) 0.717 (0.625–0.824)
One-sided p-value (log rank) 0.080<sup>a</sup> <0.0001<sup>a</sup>

<sup>a</sup>p-value boundary = 0.0116
GOG212: Taxane Maintenance

CT-2103 vs OBS
Paclitaxel vs OBS

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>(97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-2103</td>
<td>0.847</td>
<td>(0.721 - 0.995)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.783</td>
<td>(0.783 - 0.921)</td>
</tr>
</tbody>
</table>

No established role for maintenance therapy using conventional cytotoxic agents, based on multiple phase III trials

Copeland L, et al. SGO 2017
Cost-Effectiveness of Maintenance Therapy in Advanced Ovarian Cancer
Paclitaxel, Bevacizumab, Niraparib, Olaparib, Rucaparib, and Pembrolizumab.

Juliet Wolford, MD¹, Jiaru Bai, PhD³, Lindsey Minion, MD¹, Robin Keller, PhD¹, Ramez Eskander, MD⁴, John Chan, MD⁵, Bradley Monk, MD⁶, Krishnansu Tewari, MD¹

¹School of Medicine and ²Paul Merage School of Business, University of California
³School of Management, Binghamton University, State University of New York, Binghamton, NY
⁴University of California, San Diego, Moores Cancer Center, La Jolla, CA
⁵California Pacific Palo Alto Medical Foundation, Sutter Cancer Institute, San Francisco, CA
⁶Creighton University in Arizona at St. Joseph’s Hospital & Medical Center, Phoenix, AZ
Cost-Effective: What Does This Mean?

- Cost-effective published thresholds
  - $50,000 per quality-adjusted life-year (QALY)
  - Range between $20,000 and $100,000/QALY more recently
  - WHO: 3X per capita GDP per country (US = $150,000/QALY)

- Problems with invoking thresholds
  - Purports to establish the value of human life
  - Assumes consensus
  - Implies central control with a fixed budget
METHODS: Registration Trials

Maintenance Ovarian Cancer Treatments

Niraparib (NOVA)

Olaparib (SOLO-2)

Rucaparib (ARIEL-3)

Bevacizumab (GOG218, ICON7, OCEANS, GOG213)

Pembrolizumab (KEYNOTE-028)

Paclitaxel (GOG 212)
## METHODS: Determining the Costs

### Estimated Cost Breakdown

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Dose</th>
<th>Drug Cost</th>
<th>Pre-Tx Cost</th>
<th>Infusion Cost</th>
<th>Heme Tox Cost</th>
<th>Non-Heme Tox</th>
<th>Combined Cost per Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>NOVA</td>
<td>300mg QD</td>
<td>17,700.00</td>
<td>3351.85</td>
<td>0.00</td>
<td>1187.52</td>
<td>5572.83</td>
<td>$27,812.21</td>
</tr>
<tr>
<td>Olaparib</td>
<td>SOLO 2</td>
<td>300mg BID</td>
<td>16,178.40</td>
<td>3351.85</td>
<td>0.00</td>
<td>925.04</td>
<td>2033.28</td>
<td>$22,488.57</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>ARIEL 3</td>
<td>600mg BID</td>
<td>16,488.00</td>
<td>3048.85</td>
<td>0.00</td>
<td>965.58</td>
<td>5896.68</td>
<td>$26,399.10</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>GOG 218</td>
<td>15mg/kg q 3 weeks</td>
<td>9,557.63</td>
<td>197.11</td>
<td>568.13</td>
<td>1478.66</td>
<td>3173.13</td>
<td>$14,974.66</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>ICON 7</td>
<td>7.5mg/kg q 3 weeks</td>
<td>4,778.82</td>
<td>197.11</td>
<td>568.13</td>
<td>1511.69</td>
<td>5998.73</td>
<td>$13,054.48</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>OCEANS</td>
<td>15mg/kg q 3 weeks</td>
<td>9,557.63</td>
<td>197.11</td>
<td>568.13</td>
<td>2981.77</td>
<td>2845.84</td>
<td>$16,150.48</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>GOG 213</td>
<td>15mg/kg q 3 weeks</td>
<td>9,557.63</td>
<td>197.11</td>
<td>568.13</td>
<td>1518.85</td>
<td>4952.85</td>
<td>$16,794.57</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE 028</td>
<td>200mg q 3 weeks</td>
<td>10,994.20</td>
<td>1266.65</td>
<td>568.13</td>
<td>0.00</td>
<td>2820.83</td>
<td>$15,649.81</td>
</tr>
<tr>
<td>Taxol</td>
<td>GOG 212</td>
<td>175mg/m2 q monthly</td>
<td>152.76</td>
<td>94.81</td>
<td>568.13</td>
<td>577.50</td>
<td>3524.81</td>
<td>$4,918.01</td>
</tr>
</tbody>
</table>
RESULTS: Cost Effectiveness → Cost vs PFS

Presented By Juliet Wolford at 2018 ASCO Annual Meeting
METHODS: ICER Calculation

\[
\text{ICER} = \frac{\text{Cost of Drug A} - \text{Cost of Drug B}}{\text{PFS of Drug A} - \text{PFS of Drug B}}
\]
# RESULTS: QALmonth

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost before next line</th>
<th>PFS</th>
<th>ICER of Neuparth with mutation</th>
<th>ICER of Olaparib</th>
<th>ICER of Rabaparib with no mutation</th>
<th>ICER of Bevacizumab (OCEANS)</th>
<th>ICER of Taxol</th>
<th>ICER of Pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuparth with mutation</td>
<td>$152,11</td>
<td>16.8</td>
<td>$30,759</td>
<td></td>
<td></td>
<td></td>
<td>$30,759</td>
<td>dominated by Taxol</td>
</tr>
<tr>
<td>Olaparib</td>
<td>$64,451</td>
<td>19.0</td>
<td>$29,708</td>
<td></td>
<td></td>
<td></td>
<td>$29,708</td>
<td>dominated by Taxol</td>
</tr>
<tr>
<td>Rabaparib with mutation</td>
<td>$451,499</td>
<td>16.0</td>
<td>$28,219</td>
<td></td>
<td></td>
<td></td>
<td>$28,219</td>
<td>dominated by Taxol</td>
</tr>
<tr>
<td>Bev (OCEANS)</td>
<td>$177,750</td>
<td>12.3</td>
<td>$14,510</td>
<td>$74,991</td>
<td>$57,289</td>
<td>$73,000</td>
<td>dominated by Taxol</td>
<td></td>
</tr>
<tr>
<td>Bev (ICON7)</td>
<td>$175,660</td>
<td>21.8</td>
<td>$8,076</td>
<td>dominated by Bev (ICON7)</td>
<td>dominated by Bev (ICON7)</td>
<td>dominated by Bev (ICON7)</td>
<td>$54,741</td>
<td>$5,679</td>
</tr>
<tr>
<td>Bev (OCEANS)</td>
<td>$172,752</td>
<td>11.8</td>
<td>$14,702</td>
<td>$68,492</td>
<td>$54,027</td>
<td>$65,587</td>
<td>dominated by Taxol</td>
<td></td>
</tr>
<tr>
<td>Bev (GOG213)</td>
<td>$217,882</td>
<td>14.0</td>
<td>$15,563</td>
<td>$108,120</td>
<td>$69,314</td>
<td>$116,809</td>
<td>dominated by Taxol</td>
<td></td>
</tr>
<tr>
<td>Taxol</td>
<td>$25,123</td>
<td>19.0</td>
<td>$1,322</td>
<td>dominated by Taxol</td>
<td>dominated by Taxol</td>
<td>dominated by Taxol</td>
<td>dominated by Taxol</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>$74,853</td>
<td>4.0</td>
<td>$18,713</td>
<td>$34,538</td>
<td>$32,640</td>
<td>$31,387</td>
<td>$18,713</td>
<td>dominated by Taxol</td>
</tr>
</tbody>
</table>
## Maintenance Therapy

### ASCO 5508: Cost Effectiveness

<table>
<thead>
<tr>
<th>Drug</th>
<th>PFS</th>
<th>Cost/PFSyr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>19.1 mos</td>
<td>$356,496</td>
</tr>
<tr>
<td>Niraparib</td>
<td>21.0 mos</td>
<td>$369,108</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>16.6 mos</td>
<td>$338,628</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>14.1 mos</td>
<td>$186,756</td>
</tr>
</tbody>
</table>
# Maintenance Therapy

## SGO 16: Cost Effectiveness in PSOC

<table>
<thead>
<tr>
<th>Drug</th>
<th>gBRCA</th>
<th>Non-gBRCA</th>
<th>HRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFS Diff</td>
<td>ICER</td>
<td>PFS Diff</td>
</tr>
<tr>
<td>Olaparib</td>
<td>13.6 mo</td>
<td>$231,567</td>
<td></td>
</tr>
<tr>
<td>Niraparib</td>
<td>15.5 mo</td>
<td>$244,322</td>
<td>3.1 mo</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>11.2 mo</td>
<td>$248,992</td>
<td>8.2 mo</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td>4.0 mo</td>
<td>$531,151</td>
</tr>
</tbody>
</table>

ICER = incremental cost effectiveness ratio expressed as cost/PF-LYS where PF-LYS = progression-free life year saved

PFS diff = difference between control and experimental arms in mos
Maintenance Therapy

SGO 19: Foot et al

- ASCO Net Health Benefit (NHB) and ESMO Magnitude of Clinical Benefit Scale (MCBS)
- Scores were highest in women with germline or somatic BRCA mutations and tumor HRD positivity
- Scores for non-biomarker positive patients similar to results with bevacizumab
- Cost not a part of this trial
Maintenance Therapy

Bottom Line

- **The clinical benefit of maintenance therapy in epithelial ovarian cancer is clear.**
- **Valid maintenance options include:** PARPi, anti-angiogenic therapy, paclitaxel
- **While the cost of PARPi maintenance is greater than certain other options, the cost effectiveness can be enhanced by:**
  - Selective treatment of those with BRCA/HRD
  - More accurate determination of optimal dose
  - Competition in the market place
- **Absolute magnitude of benefit independent of cost appears to be greatest with PARPi, particularly in patients with HRR deficiency.**
Maintenance Therapy

So What Should We Do? (one opinion)

- Maintenance therapy should be offered in PSOC with clinical benefit from induction.
  - BRCA+, HRD+ patients: PARPi
  - Patients without BRCA or HRD: either PARPi or bevacizumab

- Maintenance therapy should be offered in front-line patients with clinical benefit from induction.
  - Bevacizumab for now
  - Role of PARPi awaits front-line studies

- Taxanes can be considered
Gynecologic Cancer

Discussion Topics

- **Ovarian Cancer**
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - **Bevacizumab: Overview; ASCO 5506**

- **Cervical Cancer**
  - Neoadjuvant Chemotherapy: ASCO 5523

- **Uterine Cancer**
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505
Ovarian Carcinoma

Role of Bevacizumab

- Bevacizumab active against ovarian carcinoma.
  - Based on 3 phase II trials
  - Induces responses, prolonged PFS
- Bevacizumab added to chemotherapy improves PFS in ovarian cancer.
  - 5 phase III trials (2 front-line, 3 recurrent disease)
  - Maintenance bevacizumab critical to success
- Hypertension only significantly increased toxicity across all five trials.
- FDA-approved in platinum-resistant and platinum-sensitive disease as well as newly diagnosed advanced disease
Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups
Ovarian Carcinoma

**MITO16B – MaNGO OV2B – ENGOT OV17**

- Stages III-IV in first relapse
- PFI ≥ 6 mos
- PS 0-2
- RECIST progression +/- measurable disease
- Normal organ function
- Tumor samples for molecular analysis

**RANDOMIZE**

- Platinum-Based Chemotherapy
- Chemotherapy plus Bevacizumab

**Primary Endpoint: PFS**
- Expected PFS: 8 vs 11.9 mos
- Hazard Ratio: 0.67
- Patients: 400 (265 events)
PFS Investigator assessed (primary end-point)

Kaplan-Meier survival estimates

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Experimental</th>
<th>Log Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td># events</td>
<td>161</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.8 mos</td>
<td>11.8 mos</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR* (95%CI)</td>
<td>0.51</td>
<td>(0.41-0.65)</td>
<td></td>
</tr>
</tbody>
</table>

*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery
Overall survival

Presented By Sandro Pignata at 2018 ASCO Annual Meeting

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Experimental</th>
<th>Log Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td>68</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Med OS</td>
<td>27.1 mo</td>
<td>26.6 mo</td>
<td>0.98</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td>0.97 (.70-1.35)</td>
</tr>
</tbody>
</table>

Adjusted by:
Age, PS, center size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery
# Bev after Bev: Response

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo/Bev</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>143</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>94 (65.7%)</td>
<td>97 (74.6%)</td>
<td>0.14</td>
</tr>
<tr>
<td>CR</td>
<td>9 (6.3%)</td>
<td>20 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>85 (59.4%)</td>
<td>77 (59.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Severe Toxicity occurring >4% of patients

<table>
<thead>
<tr>
<th></th>
<th>STD (N=200)</th>
<th>EXP (N=201)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G3</td>
<td>G4</td>
<td>G3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (10%)</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>56 (28%)</td>
<td>25 (12.5%)</td>
<td>48</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (10%)</td>
<td>23 (11.5%)</td>
<td>31</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>6 (3%)</td>
<td>4 (2%)</td>
<td>3</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>11 (5.5%)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (11%)</td>
<td>1 (0.5%)</td>
<td>22</td>
</tr>
</tbody>
</table>

*Chi-square or Fisher’s exact test as appropriate (severe vs non-severe)
Ovarian Carcinoma: Bev after Bev

Conclusions

- Rechallenging PSOC with a platinum-based doublet plus bev significantly prolongs PFS with no unexpected toxicities
- Rechallenging with bev is an option in recurrent patients previously exposed to bev
Gynecologic Cancer

Discussion Topics

• Ovarian Cancer
  • Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  • PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  • Bevacizumab: Overview; ASCO 5506

• Cervical Cancer
  • Neoadjuvant Chemotherapy: ASCO 5523

• Uterine Cancer
  • Papillary Serous: SGO 22
  • Leiomyosarcoma: ASCO 5505
Neoadjuvant Chemotherapy with Cisplatin and Gemcitabine followed by Chemoradiation with Cisplatin in Locally Advanced Cervical Cancer: a Phase II, Prospective, Randomized, Trial

• Samantha Silva, Renata R. C. Colombo Bonadio, Flavia Gabrielli, Andrea Souza Aranha, Maria Luiza Genta, Vanessa Costa Miranda, Daniela Freitas, Elias Abdo Filho, Patricia Alves De Oliveira Ferreira, Karime Kalil, Mariana Scaranti, Maria Del Pilar Estevez-Diz

• Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil
Is there a role for NACT?

2003 Meta-Analysis (n=21 RCT)

Compared to RT alone, NACT followed by RT:
- Benefit in OS if chemotherapy given ≤14 days (HR 0.83, 95%CI 0.69-1.0)
- Benefit in OS if cisplatin dose ≥25 mg/m2 (HR 0.91, 95%CI 0.78-2.05)
- Detrimental to OS if one or other not met

Compared to RT alone, NACT followed by surgery:
- Benefit in OS (HR 0.65, 95%CI 0.53-0.80)
Is there a role for NACT?

N 107 FIGO IIB-IVA cervical cancer

A

Cisplatin 50mg/m² D1 + Gemcitabine 1000mg/m² D1, D8 q21d x 3 cycles

B

Cisplatin 40mg/m²/w/6w + pelvic radiotherapy 45-50.4Gy + brachytherapy

Cisplatin 40mg/m²/w/6w + pelvic radiotherapy 45-50.4Gy + brachytherapy
Results: PFS and OS

**Figure 1. Kaplan-Meier curves for PFS**

<table>
<thead>
<tr>
<th></th>
<th>NAC</th>
<th>CRT</th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3y-PFS</td>
<td>41.1%</td>
<td>59.6%</td>
<td>1.48</td>
<td>0.86-2.82</td>
<td>0.134</td>
</tr>
</tbody>
</table>

**Figure 2. Kaplan-Meier curves for OS**

<table>
<thead>
<tr>
<th></th>
<th>NAC</th>
<th>CRT</th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3y-OS</td>
<td>74.2%</td>
<td>81.9%</td>
<td>1.64</td>
<td>0.71-3.77</td>
<td>0.230</td>
</tr>
</tbody>
</table>
Cervix Carcinoma: NACT v CCRT

NACT: Summary and Conclusions

- No difference in 3-year PFS and OS with the addition of NACT to CCRT for stages IIB-IVA
- CR rate with NACT inferior to CCRT
- Toxicities
  - Acute toxicities more frequent with NACT
  - No differences in late toxicities
- Bottom line: CCRT without NACT remains the standard of care
Gynecologic Cancer

Discussion Topics

• Ovarian Cancer
  • Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  • PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  • Bevacizumab: Overview; ASCO 5506

• Cervical Cancer
  • Neoadjuvant Chemotherapy: ASCO 5523

• Uterine Cancer
  • Papillary Serous: SGO 22
  • Leiomyosarcoma: ASCO 5505
Uterine Papillary Serous Carcinoma

UPSC: Basic Facts

- 10-20% of endometrial carcinomas
- More aggressive, spreads early often with intraperitoneal dissemination
- Reported to account for as much as 50% of EC relapses and 40% of EC-related deaths

GOG 177:
- 61% HER2 overexpression (2+ or 3+) by IHC
- 21% FISH positive (n=38)
Trastuzumab in UPSC

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients</th>
<th>PFS PC</th>
<th>PFS PCT</th>
<th>HR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>58</td>
<td>8.0 mos</td>
<td>17.6 mos</td>
<td>0.44 (0.26-0.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>41</td>
<td>9.3 mos</td>
<td>17.9 mos</td>
<td>0.40 (0.20-0.80)</td>
<td>0.013</td>
</tr>
<tr>
<td>Recurrent</td>
<td>17</td>
<td>6.0 mos</td>
<td>9.2 mos</td>
<td>0.14 (0.04-0.53)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

- Santin et al SGO 22
- All patients overexpress HER2/neu.
- Randomization to Paclitaxel/Carboplatin +/- Trastuzumab (6 cycles PC, trastuzumab to progression or unacceptable toxicity).
Gynecologic Cancer

Discussion Topics

• Ovarian Cancer
  • Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  • PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  • Bevacizumab: Overview; ASCO 5506

• Cervical Cancer
  • Neoadjuvant Chemotherapy: ASCO 5523

• Uterine Cancer
  • Papillary Serous: SGO 22
  • Leiomyosarcoma: ASCO 5505
Adjuvant Gemcitabine plus Docetaxel followed by Doxorubicin versus Observation for Uterus-Limited, High Grade Leiomyosarcoma: a Phase III NRG Oncology/Gynecologic Oncology Group Study

Martee L. Hensley MD, Danielle Enserro PhD, Helen Hatcher PhD, Petronella B. Ottevanger MD PhD, Anders Krarup-Hansen MD PhD, Jean-Yves Blay MD PhD, Cyril Fisher MD, DSc, Katherine M. Moxley MD, Shashikant B. Lele MD, Jayanthi S. Lea MD, Krishnansu S. Tewari MD, Premal Thaker MD, Oliver Zivanovic MD, David M. O’Malley MD, Katina Robison MD, David S. Miller MD, FACS
Uterine Leiomyosarcoma

Leiomyosarcoma: Basic Facts

- High-grade uterine LMS completely resected: 50-70% risk of recurrence
- Neither radiotherapy nor chemotherapy shown to decrease recurrence rate or improve survival
- Gemcitabine-docetaxel and doxorubicin active in metastatic LMS
- SARC005: phase II study of adjuvant gem-doc:
  - 46% recurrence rate
  - 57% disease-free at 3 years
Study Schema

GOG 277

Regimen I
- Gemcitabine 900 mg/m² IV day, 1 and 8
- Docetaxel 75 mg/m² IV day 8
- GCSF 5 mc/kg days 9-15 or pegfilgrastim 6mg day 9 or 10
- Every 21 days Cycles 1-4
- CT/MRI imaging to confirm disease-free

Regimen II
- Observation
- CT/MRI Imaging after 3 to 4 months from study entry to confirm disease free.

- High-grade uterine LMS
- FIGO Stage I (uterus +/- cervix)
- Hysterectomy +/- BSO

Randomize

Presented By Martee Hensley at 2018 ASCO Annual Meeting

- CT CAP or CT chest + MR a/p prior to randomization to confirm NED
- CT CAP or CT chest + MR a/p every 4 months for 3 years, then every 6 months for 2 years
# GOG 277: Results

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Chemotherapy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Recurrences</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>RFS</td>
<td>14.6 mos</td>
<td>18.1 mos</td>
<td>-2.4 to 9.3 mos</td>
</tr>
<tr>
<td>OS</td>
<td>46.4 mos</td>
<td>34.3 mos</td>
<td>-21.5 to -2.7 mos</td>
</tr>
</tbody>
</table>
Leiomyosarcoma

GOG 277: Summary and Conclusions

- Closed early due to slow accrual
- Study endpoints
  - 47% of patients on chemo had at least one G 3-4 event
  - RFS with chemo numerically but not statistically better by 3.4 mos (could be worse by 2.4 mos or better by 9.3 mos)
  - OS worse with chemo by 12.1 mos (-21.5 mos to -2.7 mos)
- OS does not include possibility that survival might be better with chemo
- Bottom line: observation following complete, intact resection of uterus-limited high-grade LMS remains the standard of care
Gynecologic Cancer

Discussion Topics

- **Ovarian Cancer**
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506

- **Cervical Cancer**
  - Neoadjuvant Chemotherapy: ASCO 5523

- **Uterine Cancer**
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505
Gynecologic Cancer

What Have We Learned in 2017-2018?

• **Ovarian Cancer**
  • **Surgery: front-line debulking**
    • PDS and NACT yield similar results overall.
    • The goal of debulking is R0 with hints that R0 debulking by PDS is more meaningful than R0 by IDS after NACT.
    • NACT may have an advantage in patients in poor condition.
  • **Surgery: IDS +/- HIPEC**
    • HIPEC at time of IDS improves PFS, OS
    • Trial needs confirmation and to address caveats
  • **Surgery: secondary surgical debulking**
    • Debulking in this setting achieved R0 status in 68% of patients, similar to 72% in the DESKTOP-III trial.
    • Unlike the DESKTOP-III trial, there was no significant PFS or OS advantage to debulking; the difference may be bevacizumab.
Gynecologic Cancer

What Have We Learned in 2017-2018?

• **Ovarian Cancer**
  • **PARP inhibitors**
    • Three PARP inhibitors are available for ovarian carcinoma.
    • Third line or greater as single agent treatment
    • Maintenance therapy for patients who achieve a CR or PR to second or subsequent platinum-based therapy in PSOC
  • Markers of homologous recombination repair deficiency (BRCA or HRD) identify those most likely to respond.
• **Maintenance therapy in ovarian carcinoma responders**
  • Maintenance options with evidence demonstrating benefit include: PARPi, anti-VEGF therapy, and paclitaxel.
  • Greatest clinical benefit is associated with PARPi.
  • By current proposed standards ($100,000/PFQALY), only paclitaxel is considered cost effective.
  • In my opinion, PARPi, bevacizumab, and paclitaxel should be considered for all patients with CR, PR, or SD.
Gynecologic Cancer

What Have We Learned in 2017-2018?

- **Ovarian Cancer**
  - *Bevacizumab after bevacizumab* improves PFS and possibly eliminates the need for secondary surgical debulking.

- **Cervical Cancer**
  - *Neoadjuvant Chemotherapy* (gemcitabine/cisplatin) followed by CCR yields inferior PFS/OS/CR rate with greater toxicity.

- **Uterine Cancer**
  - **Papillary Serous**: Patients with HER2+ UPSC show significantly improved PFS/OS with PC plus trastuzumab.
  - **Uterine leiomyosarcoma**
    - Observation following complete, intact resection of uterus-limited high-grade LMS remains the standard of care.