Targeted Therapy in Gynecological Cancer

The impact of Targeted Therapy in Endometrial and Cervical Cancer

Ana Oaknin, MD
Gynecological Cancer and Developmental Therapeutics Program
Vall d’Hebron Institute of Oncology
Barcelona, Spain
aoaknin@vhio.net
I have nothing to disclose
OUTLINE

• Endometrial Cancer
  – PI3K Pathway
  – Metformin
  – Angiogenesis

• Cervical Cancer
  – Angiogenesis
Endometrial Cancer (EC): Introduction

- EC is the most common gynecological cancer in developed countries.
- 52,630 estimated new cases and 8590 deaths in 2014 in the USA.
- The majority of EC (72%) are diagnosed in the early stages with a good prognosis, however 15-20% of these carcinoma will recur.
- For women with advanced or recurrent disease, survival has remained unchanged over the last 20 years (median survival: 7-15 months), highlighting the need for better therapies.
- The improved understanding of deregulated pathways in EC have led to clinical trials testing approaches with the key drivers of these pathways.
Pathways alterations in EC

**Table 1.** Molecular alterations in endometrial cancer

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Prevalence in type I (%)</th>
<th>Prevalence in type II (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA mutation(^{29-37})</td>
<td>~30</td>
<td>~20</td>
</tr>
<tr>
<td>Exon 9</td>
<td>7–15.5</td>
<td>0</td>
</tr>
<tr>
<td>Exon 20</td>
<td>10–34</td>
<td>21</td>
</tr>
<tr>
<td>PIK3CA amplification(^{14,26})</td>
<td>2–14</td>
<td>46</td>
</tr>
<tr>
<td>KRAS mutation(^{27,42,48})</td>
<td>11–26</td>
<td>2</td>
</tr>
<tr>
<td>AKT mutation(^{40})</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PTEN loss of function(^{28,29})</td>
<td>83</td>
<td>5</td>
</tr>
<tr>
<td>Microsatellite instability(^{62,64})</td>
<td>20–45</td>
<td>0–5</td>
</tr>
<tr>
<td>Nuclear accumulation of β-catenin(^{55-59})</td>
<td>18–47</td>
<td>0</td>
</tr>
<tr>
<td>E-cadherin loss(^{29,30})</td>
<td>5–50</td>
<td>62–87</td>
</tr>
<tr>
<td>TP53 mutation(^{4,49,51})</td>
<td>~20</td>
<td>~90</td>
</tr>
<tr>
<td>Loss of function of p16(^{54})</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>HER2 overexpression(^{51,52})</td>
<td>3–10</td>
<td>32</td>
</tr>
<tr>
<td>HER2 amplification(^{53})</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>FGFR2 mutations(^{12,42,47})</td>
<td>12–16</td>
<td>1</td>
</tr>
</tbody>
</table>


Endometrioid: 93% PI3KCA Mutations
Serous- Papillary: 42% PI3KCA Mutations

Targeting the PI3K/mTOR Pathway

Myers AP; Clin Cancer Res 2013;19:5264-5274
**PI3K/mTOR Pathway Inhibitors:**

**Rapalogs as Single Agents**

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Target</th>
<th>Treatment population</th>
<th>NCT # (date registered)</th>
<th>Clinical results</th>
<th>Toxicities</th>
</tr>
</thead>
</table>
| Temsirolimus          | mTORC1 | Chemo naive          | NCT00072176 (11/2003)  | CR (9/33)<sup>a</sup>  
PR (4/33)<sup>a</sup>  
SD ≥ 8 weeks<sup>c</sup> (20/33) | Most common ≥ grade 3  
AEs: fatigue, diarrhea, pneumonitis |
| Temsirolimus          | mTORC1 | 1 prior line         | NCT00072176 (11/2003)  | CR (0/27)  
PR (1/27)  
SD ≥ 8 weeks<sup>c</sup> (12/27) | Most common ≥ grade 3  
AEs: fatigue, diarrhea, pneumonitis, dyspnea, hypokalemia |
| Everolimus            | mTORC1 | 1-2 prior lines<sup>d</sup>  
PR (0/35)  
SD ≥ 8 weeks<sup>c</sup> (12/35) | Most common ≥ grade 3  
AEs: fatigue, nausea, lymphopenia, anemia, hyperglycemia |
| Ridaforolimus         | mTORC1 | 1-2 prior lines      | NCT00122343 (7/2005)  | CR (0/45)  
PR (5/45)  
SD ≥ 16 weeks (8/45) | Most common ≥ grade 3  
AEs: anemia, hyperglycemia, mouth sores |
| Ridaforolimus         | mTORC1 | Adjuvant only        | NCT00770185 (10/2008) | CR (0/35)  
PR (2/35)  
SD ≥ 8 weeks<sup>c</sup> (15/35) | Most common ≥ grade 3  
AEs: lymphopenia, anemia |
| Ridaforolimus (vs. progestins) | mTORC1 | 1-2 lines            | NCT00739830 (8/2010) | CR (9/64)<sup>a</sup>  
PR (0/64)<sup>a</sup>  
SD ≥ 8 weeks<sup>c</sup> (22/64)  
median PFS 3.6 vs. 1.9 months (ridaforolimus vs. progestins) | Most common ≥ grade 3  
AEs: anemia, hyperglycemia, back pain, asthenia |
| Everolimus            | mTORC1 | 1-2 prior lines      | NCT00870337 (8/2009)  | CR (0/44)  
PR (4/44)  
SD ≥ 12 weeks (14/44) | Most Common ≥ grade 3  
AEs: fatigue, anorexia, infection, diarrhea, lymphopenia, anemia, thromboembolic event, hyperglycemia |

**Key Points:**

- ORR: 0%-25%
- Higher in chemonaive patients.
- Across histological types
Molecular Determinants of Outcome With Mammalian Target of Rapamycin Inhibition in Endometrial Cancer

TABLE 2. Mutational Analysis and Association With Outcomes Among 73 Evaluable Patients

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Group</th>
<th>No.</th>
<th>Response (%)</th>
<th>Progression (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mutation</td>
<td>Yes</td>
<td>32</td>
<td>43.8</td>
<td>10 (31.3)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>41</td>
<td>56.2</td>
<td>13 (31.7)</td>
<td></td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>Yes</td>
<td>21</td>
<td>28.8</td>
<td>6 (28.6)</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>52</td>
<td>71.2</td>
<td>17 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Type of PIK3CA mutation</td>
<td>R88Q</td>
<td>7</td>
<td>(9.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H104R</td>
<td>6</td>
<td>(8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E545K</td>
<td>4</td>
<td>(5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C420R</td>
<td>2</td>
<td>(2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H1047L</td>
<td>1</td>
<td>(1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P530R</td>
<td>1</td>
<td>(1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E542K</td>
<td>1</td>
<td>(1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>Yes</td>
<td>10</td>
<td>(13.7)</td>
<td>2 (20.0)</td>
<td>.58</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>63</td>
<td>(86.3)</td>
<td>21 (33.3)</td>
<td></td>
</tr>
<tr>
<td>PTEN expression</td>
<td>Negative</td>
<td>46</td>
<td>3 (6.5)</td>
<td>12 (26.1)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>39</td>
<td>5 (12.8)</td>
<td>14 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Statin expression</td>
<td>Negative</td>
<td>2</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Weak</td>
<td>21</td>
<td>2 (9.5)</td>
<td>5 (23.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>27</td>
<td>2 (7.4)</td>
<td>7 (25.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strong</td>
<td>15</td>
<td>2 (13.3)</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Endometrioid</td>
<td>66</td>
<td>6 (9.1)</td>
<td>19 (28.8)</td>
<td>.74</td>
</tr>
<tr>
<td></td>
<td>Clear cell</td>
<td>4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serous</td>
<td>12</td>
<td>2 (16.7)</td>
<td>3 (25.0)</td>
<td></td>
</tr>
</tbody>
</table>

H. Mackay et al; Cancer. February 15; 2014
Other Classes of PI3K/mTOR Pathway Inhibitors

- Pan-PI3K inhibitor: NVP-BKM120
- PI3K/dual mTORC inhibitor: GDC-0980
- mTORC catalytic inhibitor: AZD805, OSI-027, INK-128
- AKT inhibitor: MK-2206, GDC-068

Rapalogs in combination

Temsirilimus with or without megestrol acetate and tamoxifen for endometrial cancer: A gynecologic oncology group study

- The combination therapy resulted in an unacceptable rate of **Thrombotic Events (33%)** which led to an early closure of the study.
- The combination arm did not improve response rates compared to Temsirolimus (14% vs 22%).

Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: A Gynecologic Oncology Group study

**Promising Activity:**
- ORR: 24.5%
- PFS > 6 months: 46%
- mPFS: 5.6 months
- mOS: 16.9 months

**Significant Toxicity:**
- 38.8% stopped due to toxicity.
- 2 G.I-Vaginal fistulas,
- 2 intestinal perforations
- 1 Gr4 thrombosis
Metformin:
Our old friend returns
Metformin is currently used as the first line treatment for type II diabetes mellitus.

Population based studies have suggested a protective role for metformin in the prevention of solid tumor malignancies in diabetic patients.

Metformin is a potent inhibitor of cell proliferation in EC cell lines. This effect is partially mediated through inhibition of the mTOR Pathway.

Metformin in combination with paclitaxel resulted in a synergistic anti-proliferative effect in these cell lines.

Metformin is associated with improved survival in endometrial cancer.

**Mechanism of Action:**

- **Direct:**
  - Activates AMPK- Inhibition of mTOR
- **Indirect:**
  - Increases Insulin Sensitivity
  - Decrease gluconeogenesis
  - Decreases circulating Insulin levels

---

1. Adapted from J Pancreas 2013;14(4); 2.Cantrell LA et al; Gyn Oncol 2010;116(1).
2. Hanna RK et al. Gynecol Oncol 2012;125(2);3.Emily M. Ko et al; Gynecol Oncol 2014; 132: 438-442

26-30 September 2014, Madrid, Spain
Arm 1:
Paclitaxel 175 mg/m² IV over 3 hours day 1
Carboplatin AUC = 5 IV day 1
**Metformin 850 mg** oral QD, beginning on day 1. If tolerated for 4 weeks, the dose will be increased to Metformin 850 mg BID.
Maintenance regimen: Metformin 850 mg oral BID until disease progression or prohibition of further therapy.

Arm 2:
Paclitaxel 175 mg/m² IV over 3 hours day 1
Carboplatin AUC = 5 IV day 1
**Placebo for Metformin 850 mg** oral QD, beginning on day 1. If tolerated for 4 weeks, the dose will be increased to placebo for Metformin 850 mg BID.
Maintenance regimen: Matched Placebo oral until disease progression or prohibition of further therapy.

Eligibility:
- Stage III or IVA EC measurable disease
- Stage IVB or Recurrent EC (whether there is measurable disease or not)
- No prior chemotherapy

GOG#0286B

Phase II/III
N= 240/300 pts (500pts)
1º End-Point: PFS/OS

PI: Victoria Bae-Jump, M.D. PhD
Open: 17/March/2014
ClinicalTrials.gov Identifier: NCT02065687
Angiogenesis

- VEGF is a key driver of angiogenesis and has been recognized as a potentially important mechanism of tumor growth, survival and metastasis in EC.

- In many reports, increased levels of VEGF and angiogenic markers are associated with poor outcome.

- Angiogenesis is an attractive target but VEGF inhibition has not been extensively studied in EC.

Lheureux et al 2014 Exp Opin Investig Drugs

Kamat A. et al; Clin Cancer Res 2007;13(24); McMeekin DS; Gynecol Oncol 2007;105(2)
Phase II Trial of Bevacizumab in Recurrent or Persistent Endometrial Cancer: A Gynecologic Oncology Group Study

Carol Aghajanian, Michael W. Sill, Kathleen M. Darcy, Benjamin Greer, D. Scott McMeekin, Peter G. Rose, Jacob Rotmensch, Mack N. Barnes, Parviz Hanjani, and Kimberly K. Leslie

- Persistent or recurrent EMC.
- N=52 assessable pts
- 1-2 prior cytotoxic regimens
  - 36.5% 2 prior lines
- Prior RDT: 55.8%
- Measurable disease
- PS ≤ 2

Toxicity Profile:
- No fistulas or perforations seen
- 1Gr4 gastric hemorrhage
- 1Gr3 rectal hemorrhage
- 2Gr3 thrombotic events

BEV 15mg/kg/21 days IV

- 7 pts (13.5%): ORR
- 21 pts (40.4%) ≥6 mths PFS
- Median PFS: 4.17 mths
- Median OS: 10.55 mths

Responses across histologic types

A PHASE 2 TRIAL OF LENVATINIB IN PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER: ANGIPOIETIN-2 AS A PREDICTIVE MARKER FOR CLINICAL OUTCOMES


1. University Hospitals Leuven, Leuven, Belgium; European Union; 2. US Oncology, The Woodlands, Texas; 3. Washington University School of Medicine, St. Louis, Missouri; 4. University of Texas Southwestern Medical Center, Dallas, Texas; 5. University of Southern California, Los Angeles, California; 6. State Healthcare-Institution Leningrad Regional Oncology Center, St. Petersburg, Russia; 7. Hadassah-Hebrew University Hospital, Jerusalem, Israel; 8. Maria Sklodowska-Curie Memorial Institute, Warsaw, Poland; 9. Institute of Oncology, “Prof. Dr. Ion Chiriac,” Chișinău, Moldova; 10. Eisai Inc., Woodcliff Lake, New Jersey; 11. Eisai Inc., Andover, Massachusetts; 12. Massachusetts General Hospital Cancer Center and DFMC, Boston, Massachusetts

- **Lenvatinib**: TKI of VEGFR1-3; FGFR1-4, PDGFR, RET, KIT
- **N=133 pts advanced or recurrent EC**
- **All 1 prior Platinum QT**
- **Prior RDT: 82%**
- **Lenvatinib**: 24mg qd in a 28-day cycle

**Phase II Single-Arm Objectives:**
- Safety and efficacy of lenvatinib
- Identify predictive markers for lenvatinib response

**Maximum % Change in Sum of Diameter From Baseline**

- 19 pts (14.3%): ORR
- Median PFS: 5.4mths
- Median OS: 10.6 mths

**Observed Progression Free Survival and Overall Survival in low and High Ang-2 Subgroups**

Vergote I et al; J Clin Oncol 31, 2013 (suppl; abstr 5520)
### Other AntiAngiogenic Agents: Toxicity was an issue

<table>
<thead>
<tr>
<th>AGENT</th>
<th>SETTING</th>
<th>RR%</th>
<th>PFS@ 6 Mths</th>
<th>PFS/OS (Mths)</th>
<th>Toxicity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SORAFENIB¹</td>
<td>EC: 1&lt;sup&gt;st&lt;/sup&gt; or 2&lt;sup&gt;nd&lt;/sup&gt; line (including Carcinosarcomas)</td>
<td>5%</td>
<td>29%</td>
<td>NR/11.4</td>
<td>Gr3/4: HTA:13% HFS:13% Diarrhea:5% Fatigue:5%</td>
</tr>
<tr>
<td>SUNITINIB²</td>
<td>EC 1&lt;sup&gt;st&lt;/sup&gt; or 2&lt;sup&gt;nd&lt;/sup&gt; line (including Carcinosarcomas)</td>
<td>18.2%</td>
<td>30%</td>
<td>3.0/19.4</td>
<td>50% dose reduction. Gr3/4: Fatigue:50% HTA:23% HFS:17%</td>
</tr>
<tr>
<td>AFLIBERCEPT</td>
<td>EC :1 or 2 prior lines</td>
<td>7%</td>
<td>23%</td>
<td>2.9/14.5</td>
<td>32% removed from study for Toxicity. 2 Gr 5: g.i perforation/ruptured artery Leukoencephalopatay (2 events)</td>
</tr>
</tbody>
</table>

1. Nimeiri HS, Gynecol Oncol. 2010;111(1):37-40
2. Castonguay V, Gynecol Oncol 134 (2014) 274–280
Arm 1:
Paclitaxel 175 mg/m² IV over 3 hours day 1
Carboplatin AUC = 6 IV day 1
**Bevacizumab** 15mg/kg IV day 1
Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

Arm 2:
Paclitaxel 175 mg/m² IV over 3 hours day 1
Carboplatin AUC = 5 IV day 1
**Temsirolimus** 25 mg IV days 1 and 8
Maintenance regimen – Temsirolimus 25 mg IV weekly. Days 1, 8 and 15 until disease progression or prohibition of further therapy.

Arm 3:
Ixabepilone 30 mg/m² IV over 1 hour day 1
Carboplatin AUC = 6 IV day 1
**Bevacizumab** 15mg/kg IV day
Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or until prohibition further therapy.

Eligibility:
- Stage III or IVA EC measurable disease
- Stage IVB or Recurrent EC (whether there is measurable disease or not)
- No prior Chemotherapy

PI: Carol Aghajanian, M.D.
From: 9/14/2009 to 9/9/2014
ClinicalTrials.gov Identifier:NCT00977574
Cervical Cancer: Introduction

- CC is still the second leading cause of cancer death in women worldwide.

- Risk of recurrent disease is 10–20% FIGO stages Ib–IIa and 50–70% in locally advanced cases (stages IIb–IVa).

- Patients with recurrent disease not amenable to local control or distant metastases, having a very poor prognosis: 1 Year Survival < 20%

- Cervical carcinogenesis is driven in the majority of cases, by HPV infection.

- Oncoproteins, HPV-E6 and HPV-E7 led a biological events that affect different molecular pathways: DNA Repair, cell cycle and angiogenesis.

<table>
<thead>
<tr>
<th>Main molecular targets (and agents in development) in cervical cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological pathway</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Angiogenesis</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>EGF</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>mTOR/P13K/Akt</td>
</tr>
<tr>
<td>DNA repair</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cell cycle</td>
</tr>
<tr>
<td>Apoptosis</td>
</tr>
</tbody>
</table>

Angiogenesis in Cervical Cancer:

- **Bevacizumab** activity in cervical cancer was demonstrated in a phase 2 single-agent study *(GOG 227C)*

HPV E6 → p53 degradation → TSP-1 → ↑VEGF → angiogenesis

Displacement of HDAC1, HDAC4, HDAC7

HPV E7 → pRb inactivation → p21-RB pathway dysregulation

↑HIF1α

Anti-VEGF therapy

http://www.microbiologybytes.com/virology/Papillomaviruses.html
**GOG#240: Incorporation of Bevacizumab in the treatment of Recurrent and Metastatic Cervical Cancer**

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

**Carcinoma of the cervix**
- Primary stage IVB
- Recurrent/persistent
- Measurable disease
- GOG PS 0–1
- No prior chemotherapy for recurrence (N=452)

**Stratification factors:**
- Stage IVB vs. recurrent/persistent disease
- Performance status
- Prior cisplatin Rx as radiation-sensitizer

**1º END-POINTS:**
- If adding BEV to Chemo improves OS
- If a non-platinum doublet improves OS

**Treatments**

**I**
- Paclitaxel 135 or 175 mg/m² IV
- Cisplatin 50 mg/m² IV

**II**
- Paclitaxel 135 or 175 mg/m² IV
- Cisplatin 50 mg/m² IV
- Bevacizumab 15 mg/kg IV

**III**
- Paclitaxel 175 mg/m² IV
- Topotecan 0.75 mg/m² d1-3
- Bevacizumab 15 mg/kg IV

**IV**
- Paclitaxel 175 mg/m² IV
- Topotecan 0.75 mg/m² d1-3

**Rx to PD, toxicity, CR**

**Presented by:** Krishnansu S. Tewari, MD, FACOG, FACS

### GOG #240:

**OS for Chemo vs Chemo + Bev**

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n=225)</th>
<th>Chemotherapy + Bev (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>140 (62)</td>
<td>131 (58)</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>13.3</td>
<td>17.0</td>
</tr>
<tr>
<td>HR</td>
<td>0.71 (97% CI, 0.54-0.94)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0035</td>
<td></td>
</tr>
</tbody>
</table>

**Median follow-up:** 20.8 mos

---

26-30 September 2014, Madrid, Spain
## GOG #240:
### PFS for Chemo vs Chemo + Bev

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n=225)</th>
<th>Chemotherapy + Bev (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>184 (82)</td>
<td>183 (81)</td>
</tr>
<tr>
<td><strong>Median PFS, mos</strong></td>
<td>5.9</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.67 (95% CI, 0.54-0.82)</td>
<td>2-sided P=0.0002</td>
</tr>
<tr>
<td><strong>2-sided P</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RR, %</strong></td>
<td>36 (CR, n=14)</td>
<td>48 (CR, n=28)</td>
</tr>
<tr>
<td></td>
<td>2-sided P=0.00807</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing progression-free survival (PFS) for chemotherapy vs chemotherapy + Bev](image)
### GOG #240: Treatment Exposure and Specific Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Chemo Alone (n=219)</th>
<th>Chemo + Bev (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cycles, median (range)</td>
<td>6 (0-30)</td>
<td>7 (0-36)</td>
</tr>
<tr>
<td>Grade 5 AE(s)</td>
<td>4 (1.8)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>GI events, non-fistula (grade ≥2)</td>
<td>96 (44)</td>
<td>114 (52)</td>
</tr>
<tr>
<td><strong>GI fistula (grade ≥3)</strong></td>
<td>0 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>GI perforation (grade ≥3)</strong></td>
<td>0 (0)</td>
<td>5 (2)</td>
</tr>
<tr>
<td><strong>GU fistula (grade ≥3)</strong></td>
<td>1 (0)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Hypertension (grade ≥2)*</td>
<td>4 (2)</td>
<td>54 (25)</td>
</tr>
<tr>
<td>Proteinuria (grade ≥3)</td>
<td>0 (0)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Pain (grade ≥2)</td>
<td>62 (28)</td>
<td>71 (32)</td>
</tr>
<tr>
<td>Neutropenia (grade ≥4)*</td>
<td>57 (26)</td>
<td>78 (35)</td>
</tr>
<tr>
<td>Febrile neutropenia (grade ≥3)</td>
<td>12 (5)</td>
<td>12 (5)</td>
</tr>
<tr>
<td><strong>Thromboembolism (grade ≥3)</strong>*</td>
<td>3 (1)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Bleeding CNS (any grade)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bleeding GI (grade ≥3)</td>
<td>1 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Bleeding GU (grade ≥3)</td>
<td>1 (0)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

*p<0.05
GOG #240:
HRQoL Mean FACT-Cx TOI

Mean FACT-Cx TOI Scores

- Bev pts 1.2 points lower on average
  (98.75% CI: -4.1 ~ 1.7)

$p = 0.3$
Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D.,
Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D.,
Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D.,
Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

First targeted agent licensed for gynecologic malignancy in the USA
Targeted Therapies underway

- **Targeting the PI3K/PTEN/AKT Pathway**
  - Link between mTOR and HPV (E6 interacts TSC2, 4E-BP1 and E7)
  - 36% (5/14) PIK3CA mutations squamous cell cervix. Response rate PIK3CA mutant 40% (2/5) (Janku JCO 2012)
  - **Phase II temsirolimus (mTOR) (Tinker Gyn Onc 2013)**
    - 3% PR; 58% stable (duration 6.5 m); 6m PFS 28% median PFS 3.5 months
    - No molecular markers for benefit identified

- **PARP inhibitors**
  - **GOG#0076¹**: Paclitaxel, Cisplatin, and Veliparib; **GOG#0127²** Topotecan+Veliparib

- **Immunotherapy**
  - **GOG phase II live-attenuated L. monocytogenes cancer vaccine** (against viral oncoprotein E7) (ADXS-001) in persistent/recurrent cervical cancer
  - **NCI phase II ipilimumab³** (HPV-related)

---

1. ClinicalTrials.gov Identifier: NCT01281852
2. ClinicalTrials.gov Identifier: NCT01266447
3. ClinicalTrials.gov Identifier: NCT01711515
CONCLUSIONS

Endometrial Cancer

• Targeting the PI3KCA Pathways needs further investigation and clarification of relevant biomarkers.
• Metformin is an interesting drug, which is likely to be the subject to a number of upcoming trials.
• Antiangiogenesis agents seem to be an useful strategy.

Cervical Cancer

• Bevacizumab improved overall survival in recurrent/metastatic disease.
• New agents including immunotherapy are under investigation.
THANK YOU FOR YOUR ATTENTION

GRACIAS POR SU ATENCION