Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platin-based chemotherapy for ovarian carcinoma: A GCIG and EORTC-GCG study.

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Olaparib plus paclitaxel plus carboplatin (P/C) followed by olaparib maintenance treatment in patients (pts) with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): A randomized, open-label phase II study.

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Background: The oral PARP inhibitor olaparib has shown antitumor activity in pts with SOC. Our multicenter study compared the efficacy of (Arm A) olaparib capsules plus P/C for 6 cycles then maintenance olaparib monotherapy vs (Arm B) P/C alone for 6 cycles and no further therapy in pts with PSR SOC (NCT01081951).

Methods: Pts received 6 x 21-day(d) cycles of olaparib (200 mg bid, d1–10/21) + P (175 mg/m² iv, d1) + C (AUC4 iv, d1), then olaparib monotherapy as maintenance (400 mg bid, continuous) (Arm A), or 6 x 21d cycles of P (175 mg/m² iv, d1) + C (AUC6 iv, d1) then no further therapy (Arm B), until progression. Randomization (1:1) was stratified by number of platinum treatments and platinum-free interval. Primary endpoint: progression-free survival (PFS) by central review (RECIST 1.1). Secondary endpoints: overall survival (OS), objective response rate (ORR), safety. Archival tissue was collected where available for analysis of biomarker correlation.

Results: Of 162 pts randomized (n=81 per arm), 156 received treatment (Arm A, n=81; Arm B, n=75) and 121 began the maintenance/no further therapy phase (Arm A, n=66; Arm B, n=55). Olaparib + P/C (AUC4) followed by maintenance olaparib showed a significant improvement in PFS vs P/C (AUC6) alone (HR = 0.51, 95% CI 0.34, 0.77; P=0.0012; median = 12.2 vs 9.6 months). OS data are immature (total events: 14%). ORR was similar for Arm A and Arm B (64 vs 58%). Most common AEs during the combination phase were alopecia (74 vs 59%), nausea (69 vs 57%) and fatigue (64 vs 57%) for Arm A vs Arm B, respectively. Pts with grade ≥3 AEs (65 vs 57%), serious AEs (SAEs: 15 vs 21%) and AEs leading to treatment discontinuation (19 vs 16%) were similar for Arm A vs Arm B. Most common AEs during maintenance/no further therapy were nausea (50 vs 6%) and vomiting (29 vs 7%). 29 vs 16% of pts had grade ≥3 AEs, 9 vs 7% had SAEs and 8% vs N/A discontinued due to AEs in the olaparib vs no treatment arms, respectively. There were no fatal AEs.

Conclusions: In pts with PSR SOC, olaparib plus P/C (AUC4) followed by olaparib 400 mg bid monotherapy maintenance treatment resulted in a significant improvement in PFS vs P/C (AUC6) alone.
AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC).

Eric Pujade-Lauraine, Felix Hilpert, Béatrice Weber, Alexander Reuss, Andres Poveda, Gunnar Kristensen, Roberto Sorio, Ignace B. Vergote, Petronella Witteveen, Aristotelis Bamias, Deolinda Pereira, Pauline Wimberger, Ana Oaknin, Mansoor Raza Mirza, Philippe Follana, David T. Bollag, Isabelle Ray-Coquard, AURELIA Investigators; GINECO and Université Paris Descartes, Paris, France; AGO and Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany; GINECO and Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France; AGO and Coordinating Center for Clinical Trials, Marburg, Germany; GEICO and Instituto Valenciano de Oncologia, Valencia, Spain; NSGO and Norwegian Radium Hospital, Oslo, Norway; MITO and Centro di Riferimento Oncologico-IRCCS, Aviano, Italy; BGOG and University Hospital Leuven, Leuven, Belgium; DGOG and University Medical Center Utrecht, Utrecht, Netherlands; HECOG and University of Athens, Athens, Greece; GINECO and IPO-Porto, Porto, Portugal; AGO and Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; GEICO and Vall d’Hebron University Hospital, Barcelona, Spain; NSGO-Nordic Society of Gynaecological Oncology, Copenhagen, Denmark; GINECO and Department of Medical Oncology, Centre Antoine-Lacassagne, Nice, France; F. Hoffmann-La Roche Ltd., Basel, Switzerland; GINECO and Centre Léon Bérard, Lyon, France

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Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: JGOG 3016 trial.

Noriyuki Katsumata, Makoto Yasuda, Seiji Isonishi, Hirofumi Michimae, Eizo Kimura, Daisuke Aoki, Toshiko Jobo, Shoji Kodama, Fumitoshi Terauchi, Hiroshi Tsuda, Toru Sugiyama, Kazunori Ochiai, Japanese Gynecologic Oncology Group; Nippon Medical School Musashikosugi Hospital, Kanagawa, Japan; Jikei University School of Medicine, Tokyo, Japan; Kitasato University, Tokyo, Japan; Kousei General Hospital, Tokyo, Japan; Keio University, Tokyo, Japan; Social Insurance Sagamino Hospital, Sagamihara, Japan; Niigata Cancer Center Hospital, Niigata, Japan; Tokyo Medical University, Tokyo, Japan; Iwate Medical University, Morioka, Japan

Background: The primary analysis of the JGOG3016 trial (Lancet 2009, 374:1331) showed that dose-dense weekly administration with paclitaxel and carboplatin (dd-TC) demonstrated statistically significant efficiency over tri-weekly administration with TC (c-TC) as first-line chemotherapy in patients with stage II-IV epithelial ovarian, fallopian tube or primary peritoneal cancer. We report the long-term follow-up results on progression-free survival (PFS) and overall survival (OS).

Methods: Patients with stage II to IV ovarian cancer were randomly assigned to receive c-TC (carboplatin AUC 6 and paclitaxel 180 mg/m² on day 1) or dd-TC (carboplatin AUC 6 on day 1 and paclitaxel 80 mg/m² on day 1, 8, 15). The treatments were repeated every 3 weeks for six cycles; in responding patients, additional three cycles were administered. Results: The analysis included eligible 631 patients. At 6.4 years of median follow-up, there continues to be a highly statistically significant improvement in median PFS in favor of the dd-TC group compared with the c-TC group (28.1 vs. 17.5 months, hazard ratio [HR] 0.75, 95% CI, 0.62-0.91; \( P = 0.0037 \)). Median survival has not yet been reached in the dd-TC group, and OS at 5 years was higher in the dd-TC group than the c-TC group (58.6% vs. 51.0%, HR 0.79, 95% CI, 0.63-0.99; \( P = 0.0448 \)). Conclusions: The dd-TC improves long-term PFS and OS in patients with advanced epithelial ovarian cancer.
Prospective assessment of cost, morbidity, and survival associated with lymphadenectomy in low-risk endometrial cancer.

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Background: Since 1999, patients with low-risk endometrial cancer (EC) as defined by the Mayo criteria have preferably not undergone lymphadenectomy (LND) at our institution. We assess survival, sites of recurrence, morbidity, and cost per up-staged case in this low-risk cohort. Methods: Consecutive patients with Mayo-defined low-risk EC managed without (non-LND) and with LND were compared. Cause-specific survival (CSS) was estimated using the Kaplan-Meier method and compared using the log-rank test. 30-day cost analyses were equated to 2010 Medicare dollars. Results: Among 1,393 consecutive surgically managed EC cases, 385 (27.6%) met the Mayo low-risk criteria, accounting for 34.1% of type I EC. The 5-year CSS of the low-risk cases was 98.6%. There were 80 LND cases (median # nodes, 29) and 305 non-LND cases. Complications within 30 days occurred in 37.5% and 19.3% of LND and non-LND cases, respectively (P<0.001). Nodal metastasis was identified in a single LND case (1.3%). There were 11 recurrences, 6 of which were vaginal. Not a single recurrence was detected in the pelvic or paraaortic nodal areas in these 385 patients, with a median follow-up of 5.4 years. The estimated prevalence (combining surgery and surveillance) of lymph node metastasis was 0.3%. The 5-year CSS in LND and non-LND cases was 97.3% and 99.0%, respectively (P=0.32). Patients were more than seven times as likely to die of co-morbidities than from EC. The 30-day median cost of care was $15,678 for LND cases compared to $11,028 for non-LND cases (P<0.001). The estimated cost per up-staged low-risk case was $439,990 if performed via endoscopy and $327,866 via laparotomy. If the 305 non-LND cases had been subjected to LND, an estimated additional $1,418,189 would have been expended. Conclusions: For patients with low-risk EC as defined by the Mayo criteria, lymphadenectomy dramatically increases morbidity and 30-day cost of care without discernible short- or long-term benefits: CSS was 99% with a 0.3% rate of nodal metastasis. In these low-risk patients, hysterectomy with salpingo-oophorectomy alone is appropriate surgical management and should be standard of care.
Outcome of patients with borderline ovarian tumors: Results of the multicenter AGO ROBOT study.

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Background: Borderline ovarian tumors (BOT) are a rare entity; current standard of care is based on the available data of predominantly small retrospective trials. Therefore we performed a pattern of care study including central pathology review. Methods: All consecutive patients diagnosed with BOT between 1998 and 2008 in 24 German institutions were included. Tumor samples were prospectively sent for central histopathological review to specialized gynecopathologists, clinical data were collected and patient follow-up was prospectively updated. Results: Pathological review was obtained in 1,042 of 1,236 pts resulting in 950 confirmed BOT cases analyzed here. Under- and overdiagnosis occurred in 3.8% and 5.0% of cases, respectively. Median age was 49 years; 84% of patients had FIGO stage I disease; serous type (S-BOT) was diagnosed in 64% and mucinous type (M-BOT) in 31%. Primary/re-staging surgery led to complete debulking in 92.3% of pts (residual disease 1.3%, unknown 6.4%). Adjuvant chemotherapy was given to 33 (3.5%) pts only. 165 (17%) underwent fertility preserving surgery and 31 (19%) of these patients had documented pregnancies thereafter. Overall, 74 (7.8%) pts experienced relapse and 43 (4.5%) died. Disease progression in the form of invasive carcinoma occurred in 30% of the relapses. Inadequate surgical staging, residual tumor, fertility sparing surgery and higher FIGO stage were associated with shorter progression-free survival (PFS). M-BOT showed a non-significant trend to longer PFS compared to S-BOT (p = 0.07). No differences were observed for laparotomy vs. laparoscopy as initial surgical approach or application of adjuvant chemotherapy. Conclusions: To this day, this is the largest data set available for BOT. Prognosis is favorable even without adjuvant therapy if correct surgical staging is performed. Both tumor characteristics and treatment variables had a significant impact on relapse rate and outcome. In contrast to previous studies, disease progression in the form of invasive carcinoma occurred in a significant amount of patients with relapsed disease.
A randomized, phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVb, persistent or recurrent cervical cancer: Japan Clinical Oncology Group study (JCOG0505).

**Background:** TC is a less toxic regimen in terms of milder nephropathy, neuropathy and no need of hospitalization. This multicenter phase III trial was designed to evaluate the clinical benefits of TC compared with TP which is current standard chemotherapy for stage IVB or recurrent cervical cancer. **Methods:** Patients (pts) with stage IVB or recurrent cervical cancer; not amenable to curative therapy; 0-1 prior platinum; no prior taxanes; were randomized with minimization method to either TP (T 135 mg/m$^2$ 24h d1 + P 50 mg/m$^2$ 2h d2) or TC (T 175 mg/m$^2$ 3h d1 + C AUC5 1h d1), both for maximum 6 cycles every 21 days. Primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), toxicities, and the proportion of non-hospitalization periods (NHP) as a surrogate for QoL. The trial was powered at least 70% to confirm the non-inferiority of TC to TP (threshold hazard ratio [HR] 1.29) in terms of OS, and the planned sample size was 250 pts with one-sided alpha 5%. HR is estimated by a stratified Cox regression. **Results:** From 2/06 to 11/09, 253 pts were enrolled. 71% pts of TP arm and TC arm each received 6 cycles. Median follow-up is 17.4 mo. Results are as below. As an alpha level for an interim analysis was less than 0.0001, significance level for the final analysis is approximately 5% even after the multiplicity adjustment. **Conclusions:** This first randomized controlled trial comparing carboplatin doublet with cisplatin doublet showed significant non-inferiority of TC in terms of OS. More feasible and less toxic TC can be recommended as the new standard treatment for stage IVB or recurrent cervical cancer.

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>TC</th>
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<tbody>
<tr>
<td>OS (median) HR 0.99 (multiplicity adjusted 90%CI: 0.79-1.25), noninferiority p=0.032</td>
<td>18.3 mo</td>
<td>17.5 mo</td>
</tr>
<tr>
<td>PFS (median) HR 1.04 (95%CI: 0.80-1.35)</td>
<td>6.90 mo</td>
<td>6.21 mo</td>
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<tr>
<td>Neutropenia G3-4</td>
<td>85.1%</td>
<td>76.4%</td>
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<tr>
<td>Thrombocytopenia G3-4</td>
<td>3.3%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Febrile neutropenia G3-4</td>
<td>16.0%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Creatinine G2-4</td>
<td>9.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Neuropathy (motor) G3-4</td>
<td>0.8%</td>
<td>2.4%</td>
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<tr>
<td>Neuropathy (sensory) G3-4</td>
<td>0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Early treatment discontinuation (toxicity-related)</td>
<td>11.4%</td>
<td>10.0%</td>
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<tr>
<td>NHP (p&lt;0.0001, Wilcoxon rank sum test)</td>
<td>46.4%</td>
<td>61.9%</td>
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Impact of adjuvant therapy in lymph-node positive vulvar cancer: The AGO CARE I study.

Sven Mahner, Julia Kathrin Jueckstock, Felix Hilpert, Dirk Lubbe, Philipp Harter, Nikolaus De Gregorio, Severine Iborra, Frank Chen, Adela Stoenescu, Peter Hillemanns, Sophie Fuerst, Hans-Georg Strauss, Klaus H. Baumann, Falk Thiel, Alexander Mustea, Philipp Hofer, Pauline Wimberger, Lis-Femke Griebel, Linn Lena Woelber, AGO-CaRE-I Investigators; University Medical Center Hamburg-Eppendorf, Department of Gynecology, Hamburg, Germany; Frauenklinik Innenstadt Munich University, Munich, Germany; Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany; Koordinierungszentrum für Klinische Studien Philipps-Universität Marburg, Marburg, Germany; Kliniken Essen Mitte, Essen, Germany; University of Ulm Medical Center, Ulm, Germany; Universitätssenkenkulum Freiburg, Freiburg, Germany; Charite University Medicine of Berlin, Berlin, Germany; Universitatsklinik Magdeburg, Magdeburg, Germany; Hannover Medical School, Hannover, Germany; Universitätsfrauenklinik Muenchen - Grosshadern, München, Germany; Universitätsklinikum Halle, Halle, Germany; Philipps University Marburg, Marburg, Germany; Erlangen University Hospital, Erlangen, Germany; Universitätsfrauenklinik Greifswald, Greifswald, Germany; Evangelical Hospital, Düsseldorf, Germany; AGO and Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: While the majority of patients with vulvar cancer can be cured by surgery alone, women with lymph-node metastases often show unfavorable outcome. Improved treatment strategies are therefore strongly needed. Methods: Patients with primary squamous-cell vulvar cancer treated at 29 gynecologic cancer centers in Germany between 1998 and 2008 were included in a centralized database and analyzed retrospectively. Results: A total of 1,637 patients were documented with a median follow-up of 121 months. UICC-Stage distribution was 597 (36.5 %) T1, 816 (49.8 %) T2, 160 (9.8 %) T3 and 31 (1.9 %) T4, 33 (2.0 %) were missing. 491 patients had lymph-node metastasis to the groins (N+). 214 N+ patients (43.6 %) developed recurrent disease within a median of 21.4 months. 190 N+ patients (38.7%) died, median overall survival (OS) was 43.4 months, compared to 212 months for node-negative patients. An increasing number of metastatic lymph-nodes was associated with shorter OS: 169 (34.4%) patients had 1, 101 (20.6%) patients 2, 62 (12.6%) patients 3 and 86 (17.5%) patients >3 positive lymph-nodes, with a corresponding OS of 22.4, 17.2, 18.4 and 10.2 months, respectively (for 73 patients the number of nodes was not available). 240 N+ patients were treated with adjuvant radiotherapy (85.8%) or radiochemotherapy (14.2%). Median OS in these patients was significantly longer (66.9 months) compared to N+ patients without adjuvant treatment (35.7 months), the corresponding hazard ratio (HR) was 0.72 (95 % CI: 0.53 - 0.97 p = 0.029). This impact on OS remained consistent in multivariate analysis adjusted for age, ECOG, stage, grading, invasion depth and number of positive nodes (HR 0.68; 95% CI: 0.49 - 0.94 p = 0.020) and was observed irrespective of the number of affected nodes. Conclusions: To this day, this is the largest multicenter study on vulvar cancer. Our findings strongly suggest that the unfavorable prognosis of patients with node positive vulvar cancer can be improved by adjuvant therapy irrespective of the number of affected nodes. As adjuvant radiochemotherapy was shown to be superior to radiotherapy alone in many other squamous cell carcinomas, we are preparing a prospective phase III trial in node-positive vulvar cancer (AGO-CaRE 2 trial).
Survival after radiation therapy for early-stage endometrial carcinoma: The Oslo study revisited after up to 43 years of follow-up.

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Background: There is an ongoing debate regarding the benefit of radiation in patients with early stage endometrial carcinoma. Data on long time risk conferred by radiation is scarce. This study is a long-term follow-up on survival and secondary cancers of a previously published randomized study (Aalders J. et al., Obstet Gynecol 1980; 56: 419-27). Methods: Between 1968 and 1974, 568 patients with endometrial cancer FIGO stage I primarily treated with abdominal hysterectomy and bilateral salpingo-oophorectomy were included in the study. Patients were postoperatively randomized to receive either vaginal radium brachytherapy followed by external pelvic radiation 40 Gy (N=288) or brachytherapy alone (N=280). Survival data and data on incident secondary cancers were obtained by individual linkage to the Registry of Statistics Norway and Cancer Registry of Norway. By the end of follow-up at 1 November 2011, 45 (7.9%) patients were still alive. We used Cox proportional hazards model to estimate hazard ratios (HR) with 95% confidence intervals (95% CI). We also conducted analyses stratified by age groups. Results: After median 21 (range 0-43.4) years of follow-up there was no significant difference in overall survival or relapse free survival between treatment arms with HR of 1.12 (95% CI: 0.95-1.33) and HR 0.88 (95% CI: 0.55-1.40), respectively. Patients treated with external radiation had significantly lower risk of developing locoregional relapse (p<0.001). However, women younger than 60 years had a significant poorer survival after external radiation (HR 1.36; 95% CI: 1.06-1.76). In this patient group the risk of secondary cancer was significantly increased (HR 1.9; 95% CI: 1.23-3.03). Conclusions: We observed no survival benefit of external pelvic radiation in early stage endometrial carcinoma. In women younger than 60 years, pelvic radiation decreased survival, probably due to increased risk of subsequent second neoplasms. Adjuvant external radiotherapy cannot be recommended to this patient group. Those who have received such treatment might eventually benefit from prolonged post treatment surveillance with respect to secondary cancer.

Impact of metformin use on risk of recurrence in high-grade endometrial cancers.

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Background: Obesity and diabetes (DM) have been linked to increased recurrence rates and worse survival in endometrial cancer. Metformin is widely used as the first line treatment for type II DM. Recent epidemiological evidence suggests that metformin may lower cancer risk and reduce cancer-related deaths among DM patients. However, no studies have assessed the effect of metformin use on endometrial cancer outcomes. Methods: A retrospective cohort analysis was conducted of all grade 3 endometrial cancer patients with DM at a single institution from 2005-2010. Clinical-pathologic data was abstracted, including metformin, insulin, sulfonamide and thiazolidinedione use at the time of cancer diagnosis. Statistical analysis were performed using summary statistics and multivariate cox analysis, with two tailed p-values <0.05 considered significant. Results: 55/329 patients with grade 3 cancer had DM. Mean age was 68.3 (sd 8.4), and BMI 35.7 (sd 9.4). Stage distribution consisted of 58.2% stage I, 7.3% stage II, 27.3% stage III, and 7.3% stage IV. Histology included 41.8% endometrioid, and 58.2% serous or clear cell. 56.4% of diabetics used metformin and 43.6% did not. Mean follow-up was 21.6 months (sd 15.0). After adjusting for BMI, myometrial invasion, stage, histology, adjuvant treatment, and non-metformin DM medications, metformin use was significantly associated with decreased cancer recurrence (HR 0.06, 95CI 0.01, 0.40; p<0.004). Conclusions: Metformin use was associated with a decreased risk of recurrence in high-grade endometrial cancer, suggesting that it may have a role as adjuvant and maintenance therapy for this obesity-driven disease.

<table>
<thead>
<tr>
<th></th>
<th>Metformin user (%)</th>
<th>Metformin non-user (%)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>67.5 (9.1)</td>
<td>69.4 (7.4)</td>
</tr>
<tr>
<td>BMI</td>
<td>35.4 (8.5)</td>
<td>36.2 (10.5)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (48.4)</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>II</td>
<td>3 (9.7)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>III</td>
<td>9 (29.0)</td>
<td>6 (23.0)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (12.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>11 (35.5)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Serous + Clear cell</td>
<td>20 (64.5)</td>
<td>12 (50)</td>
</tr>
<tr>
<td><strong>Other medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamide (Sulfo)</td>
<td>5 (16.1)</td>
<td>8 (0)</td>
</tr>
<tr>
<td>Thiazolidinedione (Thz)</td>
<td>2 (6.5)</td>
<td>2 (8.4)</td>
</tr>
<tr>
<td>Sulfo + Thz</td>
<td>0 (0)</td>
<td>4 (14.7)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insulin + Sulfo</td>
<td>0 (0)</td>
<td>2 (8.3)</td>
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<tr>
<td><strong>Adjuvant treatment</strong></td>
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Molecular determinants of outcome with mTOR inhibition in endometrial cancer (EC).

Helen Mackay, Elizabeth A. Eisenhauer, Suzanne Kamel-Reid, Blaise Clarke, Wendy Walsh, Katherine Karakasis, Helga B Salvesen, Amit M. Oza; Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; NCIC Clinical Trials Group, Kingston, ON, Canada; University Health Network, Princess Margaret Hospital, and University of Toronto, Toronto, ON, Canada; Toronto General Hospital, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; The University of Bergen, Haukeland University Hospital, Bergen, Norway

Background: Deregulation of PI3K/AKT/mTOR signaling plays a significant role in EC biology. NCIC CTG has completed three phase II trials of 2 mTOR inhibitors (temsirolimus and ridaforolimus) in EC (IND 160A, IND 160B, IND192) demonstrating anti-tumor activity. PTEN expression, however, was not associated with response. In this study we are conducting additional molecular analyses on samples obtained from patients (pts) participating in these trials to identify mutations or other findings associated with mTOR response.

Methods: Formalin fixed paraffin embedded (FFPE) tumor samples were collected from pts treated on the three trials. Tumor DNA was isolated and mutational profiling (MP) was performed using the OncoCarta Panel v1.0 which can detect 238 mutations in 19 oncogenes including AKT1, 2, BRAF, CDK-4, EGFR, ERBB2, MET, H-, K-, N- RAS, PDGFRA, PIK3CA, RET. All mutations were verified by Sanger sequencing. For each gene found to be mutated in at least 1 patient, the relationship between presence/absence of mutations in that gene and objective anti-tumor response (RR) was assessed (RR vs. no response; early progression (PD) vs. no PD) using Fisher’s exact test. In addition, the presence of any mutation vs. no mutations was assessed in relationship to the same clinical outcomes.

Results: MP was feasible in 73 of the 94 eligible pts treated on the three trials. 44% (32 pts) had a mutation in at least one gene: 21 pts (29%) in PIK3CA, 10 (14%) KRAS, 4 (5%) MET, 3 (4%) NRAS, 3 (4%) AKT and 1(1%) EGFR. 9 pts (12%) had > 1 mutation. No significant correlations were seen, in individual trials or within the pooled data set of 3 studies, between the presence/absence of any mutation and RR (p=1.0) or early PD (p=1.0). No significant association was seen between the presence of mutations within individual genes and RR or PD (including PIK3CA). Of interest, no response was observed in any of the 13 pts with a Ras mutation (non-significant). Additional analyses involving gene expression (including stathmin) and correlation of MP with tumor morphology are underway.

Conclusions: Mutations are common in EC but we have not identified a statistical association between presence of mutations in PIK3CA or any other gene and response to mTOR inhibition. Further analyses are ongoing.
KRAS and EGFR mutations to distinguish adenocarcinomas and squamous cell carcinomas of the cervix.

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Background: Cervical adenocarcinomas (AC) have higher rates of recurrence and distant metastasis, compared with squamous cell carcinomas (SCC), and decreased survival in advanced disease. Yet, tailored treatments for cervical cancers have not emerged. The aim of this study was to compare the frequency and type of somatic mutations in cervical AC and SCC to identify novel therapeutic targets for both subtypes.

Methods: Tumors from 61 patients with cervical cancer (36 AC, 25 SCC) underwent genomic profiling by OncoMap, a multiplexed mass spectrometric genotyping technology that interrogates more than 400 known mutations in 33 cancer genes.

Results: Overall, 31/61 (50.8%) tumors harbored candidate mutations, and 6/61 (9.8%) had ≥2 mutations. PIK3CA mutations were present in 21/64 (34.4%) of cervical cancers, with a trend towards higher rates in SCC compared with ACC (21/25 or 48.0% vs. 9/27 or 33.3%, p=0.10). KRAS mutations were present in 6/31 (16.7%) of AC, but none of the SCC (0%; 0/25). EGFR mutations were present in 9/25 (36.0%) of SCC, including G719S, but none of AC (0%; 0/31).

Conclusions: The identification of distinct genomic alterations in SCC and AC of the cervix suggest different therapeutic rationales for each subtype. EGFR amplification in cervical SCC has been previously reported, but this is the first identification, to our knowledge, of activating EGFR mutations in cervical SCC. Together, this suggests that EGFR-inhibitors might be useful in selected patients with cervical SCC. Similarly, activating mutations in KRAS and PIK3CA in AC suggest that inhibition of the MAPK pathway (MEK inhibitors) and/or PI3K pathway may be beneficial in this subtype. Future studies should include more comprehensive genomic profiling strategies, such as targeted massively parallel sequencing, to detect multiple types of genomic alterations.
A phase II, open-label, multicenter study of IMC-1121B (ramucirumab; RAM) monotherapy in the treatment of persistent or recurrent epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) carcinoma (CP12-0711/NCT00721162).

Richard T. Penson, Kathleen N. Moore, Gini F. Fleming, Patricia S. Braly, Veronica L. Schimp, Hoa Nguyen, Ursula Matulonis, Susana N. Banerjee, Paul Haluska, Martin Eric Gore, Diane C. Bodurka, Alexei Morozov, Yihuan Xu, Mark D. Rutstein, Jonathan D. Schwartz, William P. McGuire; Massachusetts General Hospital, Boston, MA; University of Oklahoma Health Sciences Center, Oklahoma City, OK; The University of Chicago Medical Center, Chicago, IL; Hem Onc Specists, Marrero, LA; M. D. Anderson Cancer Center Orlando, Orlando, FL; Gynecologic Oncology Associates, Hollywood, FL; Dana-Farber Cancer Institute, Boston, MA; Royal Marsden Hospital, Surrey, United Kingdom; Mayo Clinic, Rochester, MN; Royal Marsden Hospital, London, United Kingdom; University of Texas M. D. Anderson Cancer Center, Houston, TX; ImClone Systems, a wholly-owned subsidiary of Eli Lilly & Co, Bridgewater, NJ; Franklin Square Hospital, Baltimore, MD

Background: VEGF receptor-mediated-signaling contributes to ovarian cancer pathogenesis. Elevated VEGF expression and serum levels are associated with poor clinical outcomes. We investigated RAM, a fully human VEGFR-2 antagonist antibody, in patients (pts) with persistent or recurrent EOC/FTC/PPC.

Methods: Adult women with EOC/FTC/PPC who had completed ≥1 platinum (P)-based chemotherapeutic (ct) regimen and had a P-free interval (PFI) of <12 months (m), progression on, or persistent disease after P-based therapy were eligible. Any number of prior ct regimens was allowed. ECOG PS 0-1 and adequate organ function were required. Pts received 8 mg/kg RAM IV every 2 weeks. Primary endpoints were progression-free survival at 6m (PFS-6) and confirmed objective response rate (ORR) by RECIST 1.0.

Results: 60 pts were treated; 1 remains on study as of Dec 2011. Median age was 62 years (range 27-80). Median number of prior regimens was 3 (range 1–14). 51 pts (85%) received ≥ 2 prior regimens; 25 pts (42%) received ≥3 prior regimens. 45 pts (75%) were P resistant or refractory, with 65% (39 pts) serous tumors. PFS-6: 34.2% (95% CI: 21.7% – 47%). Best overall response: 3 PR (5%), 34 SD (57%), 20 PD (33%) and 3 not evaluable (5%). Median duration of PR: 5.6m (3.7, 5.6, 17.5); median PFS: 3.5m (95% CI: 2.3 – 5.3). Median OS: 11.1m (95% CI: 8.3 – 17.0). No unexpected toxicities were observed. Grade (G) 3 adverse events (AEs) observed in >5% of pts were: headache (10%) and fatigue (8%). No G4 AEs were observed in >5% of pts. 5 deaths occurred on RAM or within 30 days of discontinuation; 4 due to PD, and 1 due to intestinal perforation. 1 G4 bowel perforation and one G4 colo-vaginal fistula were noted. All 3 cases of perforation/fistula occurred in the setting of progressive, large-volume disease. Correlative biomarker studies are ongoing to identify patients most likely to benefit. Conclusions: Ramucirumab was reasonably tolerated and demonstrated single-agent activity in persistent or recurrent ovarian carcinoma, with approximately one-third of patients progression free at 6 months.
Phase II trial of bevacizumab and pemetrexed for recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

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Background: This phase II clinical trial evaluated the efficacy and safety of the combination of bevacizumab, a VEGF inhibitor, and pemetrexed, a multi-targeted antifolate agent inhibiting thymidylate synthase, for recurrent or persistent epithelial ovarian, fallopian tube (FT) or primary peritoneal (PP) cancer.

Methods: Patients with measurable recurrent/persistent epithelial ovarian, FT or PP cancer after at least one prior platinum- and taxane-containing regimen were eligible. Patients might have received < 2 prior cytotoxic chemotherapy regimens but no prior bevacizumab. Pemetrexed 500 mg/m² IV and bevacizumab 15 mg/kg IV were given every 3 weeks until progression, unacceptable adverse effects, or patient/physician choice. 32 patients were needed to have 90% power to detect the primary endpoint of 6-month PFS ≥ 40% with a two-sided 0.05 significance. Secondary endpoints included toxicity and response by RECIST and CA-125 criteria.

Results: Thirty-four patients received a median of 7 treatment cycles (range, 2-26). Twenty-eight patients (82%, 95% CI: 66-92) were platinum-sensitive. Median follow-up was 17.1 months (range, 2.7-31.2). The 6-month PFS was 58.2% (95%CI: 40-73) for all patients and 50% (19-81) for platinum-resistant patients. Objective response rates by RECIST criteria included (%; 95%CI): 0 CR, 14 PR (41%; 25-59), 18 SD (53%; 35-70) and 2 PD (6%; 1-20). Of 27 patients evaluable by CA-125, levels declined ≥50% in 17 (62%; 44-79), and ≥75% in 8 (30%; 16-49). 12-month OS was 88% (95%CI: 71-95) and median PFS was 7.8 months (95%CI: 4.7-10.7). Of the 34 patients, grade 3-4 hematologic toxicities occurred in 53% (neutropenia 50%, leukopenia 26%, thrombocytopenia 12%, anemia 9%). Other grade 3-4 toxicities included metabolic (29%), constitutional (18%), pain (18%) and gastrointestinal (15%). No bowel perforations occurred. Conclusions: Combined bevacizumab/pemetrexed is well tolerated and highly active for the treatment of recurrent ovarian cancer. The dose and schedule tested here warrant further investigation in phase III trials.
Phase I trial of metronomic oral topotecan in combination with pazopanib utilizing a daily dosing schedule to treat recurrent or persistent gynecologic tumors.

Todd D. Tillmanns, Mark E. Reed, Melissa C. Privett, Amanda L. Johns, Mark S. Walker, Arthur C. Houts; The West Clinic, Memphis, TN; ACORN Research, Memphis, TN

Background: Metronomic oral topotecan has antiangiogenic properties. Oral pazopanib is also a potent inhibitor of VEGF angiogenesis with clinical benefit. This study investigated the safety and efficacy of daily topotecan and pazopanib. Methods: This phase I, single-center, open-label, dose ranging study comprised 28-day cycles of daily oral topotecan/pazopanib at dose levels of 0.50/400, 0.25/800, 0.25/600, and 0.25/400 mg. A standard 3 + 3 dose escalation design was used. Dose limiting toxicity (DLT) was defined as ≥ grade 3 adverse event (AE) occurring in cycle 1, noncompletion of cycle 1 at prescribed dose, or inability to start cycle 2 as scheduled due to toxicities. Imaging was conducted after every 2 cycles for response assessment. Confirmed responses were evaluated per RECIST 1.0. Results: 25 extensively pretreated patients (pts) with gynecologic tumors (6 cervical, 7 endometrial, 8 ovarian, 4 other) were enrolled. Mean age was 61 years; 19 Caucasian, 6 African American. Median number of cycles received was 4 (range 1-19). DLTs occurred ≥ 2 pts for A (2/6), B (2/7), C (3/7). For level D, 1/5 had a DLT, but one dose level C pt with a DLT received level D dosing due to unavailability of pazopanib. 9/25 pts had any serious adverse event (SAE), and respiratory SAEs were most common (4/16 SAEs). Nausea, fatigue, dysgeusia, diarrhea, and vomiting were the most common conditions reported as non-serious AEs. The Table shows best overall response (28%) by dose level. Conclusions: DLTs in dose levels C and D were effectively managed with minor dose and schedule adjustments. 4 pts with DLTs at these doses remained on treatment for 4, 5, and 6 months, with one pt still on treatment at 9 months. Given the initial biologically favorable signal in this heavily pretreated group and low toxicity, we recommend a randomized phase II trial to define efficacy using the 0.25/600 regimen allowing for dose reduction if needed.

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Randomized phase II study of docetaxel plus vandetanib (D+V) versus docetaxel followed by vandetanib (D-V) in patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (OC): SWOG S0904.

Robert L. Coleman, James Moon, Anil Sood, Donna Branham, James Edwin Delmore, Albert J. Bonebrake, Garnet L. Anderson, David Samuel Alberts, Maurie Markman; University of Texas M. D. Anderson Cancer Center, Houston, TX; Southwest Oncology Group Statistical Center, Seattle, WA; Wichita CCOP/Associates In Women’s Health, Wichita, KS; Cancer Research for the Ozarks-Cox Health, Springfield, MO; Fred Hutchinson Cancer Research Center, Seattle, WA; Arizona Cancer Center, Tucson, AZ; Cancer Treatment Centers of America, Zion, IL

Background: Antiangiogenesis therapy has led to antitumor effects both preclinically and clinically. Vandetanib (V) is an oral tyrosine kinase inhibitor of VEGFR-2/3, EGFR and RET. These targets are of interest in OC care, as targeting has shown anti-tumor efficacy, particularly in combination with taxanes. We explored the efficacy, safety, and toxicity of docetaxel (D) and V in women with recurrent OC. Methods: Women with resistant, refractory, or progressive/persistent OC were eligible for this randomized phase II study provided they had not received D or V for recurrent disease. Patients were allowed to receive other anti-VEGF targeted agents for primary therapy (stratification variable). Up to 3 additional cytotoxic regimens for recurrence were allowed. Patients were allocated 1:1 to D(75 mg/m², I.V.)+V (100 mg daily, p.o.) or D(75 mg/m²). Patients receiving single agent D were allowed to crossover to V upon progression (D-V). The primary endpoint was PFS. Other objectives were: OS, objective response (ORR), and frequency/severity of adverse events. The study was designed with 84% power to detect a 1.55 PFS hazard ratio using a one-sided P of 0.1. Results: 131 patients were enrolled; 5 were excluded (1 ineligible, 4 eligible but untreated). 9% had received prior anti-angiogenic therapy. 61 patients on D+V were assessable for toxicity; 19 (31%) had treatment-related G4 events, primarily hematologic. Similarly, 17 (26%) of 65 patients receiving D alone had G4 events, primarily hematologic. 34 (52%) patients crossed over to V; no G4 events were recorded among 32 evaluable patients. G3 diarrhea was observed in 14% of D+V patients; 5% D-V patients. G3 acneiform rash occurred in 2% and 0%, respectively. The median PFS estimates were 3.0 mos (D+V) vs 3.5 (D-V); HR (PFS): 0.98 (80% CI:0.75-1.27). For OS, the median estimates were 14 mos (D+V) vs 12 mos (D-V); HR (OS):0.84 (80% CI:0.56-1.28). ORR was 14% and 17%, respectively. Crossover V response was 4% (1/27 measurable patients). Conclusions: D+V was well tolerated in this population however, did not prolong PFS with respect to D.
Phase II trial of irinotecan plus bevacizumab for heavily pretreated recurrent ovarian cancer.

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Background: Irinotecan and bevacizumab have single agent activity in platinum sensitive (PSen) and resistant (PRes) ovarian cancer patients (pts). We sought to evaluate the efficacy and toxicity of irinotecan plus bevacizumab in these pts. The trial was designed to evaluate whether the progression free survival (PFS) at 6 months is at least 40% and with secondary objectives of estimating response rate (RR), duration of response (DoR), time to progression and toxicity. Methods: No limitation on number of prior regimens was placed, and prior use of study drugs was allowed. Irinotecan 250mg/m2 and bevacizumab 15mg/kg every 3 weeks were given. Due to treatment-related grade 3 toxicity (diarrhea and neutropenia) experienced by the first 5 pts on the study, the dose of irinotecan was amended to 175mg/m2. Results: 20 pts with recurrent ovarian cancer [PSen 5, PRes 15] of a planned 35 have been recruited thus far. Median age is 59 (45-78). Median number of prior regimens is 5 (3-12) with 9 pts demonstrating progressive disease (PD) on prior topotecan-containing regimens and 7 pts exhibiting PD on prior bevacizumab-containing regimens. 4 pts discontinued treatment before 2 cycles (2 for protocol defined toxicity, 2 by patient/physician choice). Partial response (PR) was observed in 2 PSen pts and 1 PRes pt, while stable disease (SD) was seen in 9 (2 PSen, 7 PRes) out of the 15 pts assessable for response at this time. 3 pts demonstrated PD after 2 cycles of treatment. 12 of 13 pts with PR or SD by RECIST also had response by CA125 criteria. Median DoR thus far (SD plus PR) is 18 weeks (4-37). 6 pts have ongoing response (4-18 weeks). Of 19 pts that received > 2 cycles, 3 had grade 3 diarrhea (2 before protocol amendment and 1 after). 2 pts had grade 3/4 neutropenia (1 before and 1 after protocol amendment). Median PFS is 9.6 months (mts). Median overall survival is 15.5 mts. PFS rate at 6 mts is 61% with 95% confidence interval: (40%, 92%). Conclusions: Results of the trial to date suggest the hypothesis that the PFS at 6 mts is less than 40% can be rejected. Activity of this regimen is encouraging given the heavily pretreated nature of the pts. Dose-limiting diarrhea and neutropenia required protocol amendment. We continue to accrue study subjects at the amended dosing.
Safety of front-line bevacizumab (BEV) combined with weekly paclitaxel (wPAC) and q3w carboplatin (C) for ovarian cancer (OC): Results from OCTAVIA.

Antonio Gonzalez-Martín, Laurence Gladieff, Bengt Tholander, Daniel Stroyakovsky, Martin Eric Gore, J.G.M. Segalla, An K.L. Reyners, Nadezhda Kovalenko, Ana Oaknin, Frédéric Selle, David T. Bollag, Sandro Pignata, OCTAVIA Investigators; GEICO and Medical Oncology Service, Centro Oncológico M. D. Anderson International Spain, Madrid, Spain; GINECO and Institut Claudius Regaud, Toulouse, France; NSGO and Uppsala University Hospital, Uppsala, Sweden; Moscow Oncology Hospital no 62, Moscow, Russia; Royal Marsden Hospital, London, United Kingdom; Hospital Ameral Carvalho, Jau, Brazil; DGOG and University Medical Center Groningen, Groningen, Netherlands; Stavropol Regional Clinical Oncology Dispensary, Stavropol, Russia; GEICO and Vall d’Hebron University Hospital, Barcelona, Spain; GINECO and Hôpital Tenon, Paris, France; F. Hoffmann-La Roche Ltd., Basel, Switzerland; MITO and Istituto Nazionale Tumori di Napoli, Napoli, Italy

Background: In two randomized phase III trials in OC (GOG218 and ICON7), front-line BEV + q3w PAC + q3w C followed by BEV alone significantly improved progression-free survival (PFS) vs chemotherapy (CT) alone. In the Japanese NOVEL trial, wPAC + q3w C was more effective than q3w PAC alone, but toxicity limited CT delivery. The single-arm OCTAVIA study evaluated front-line BEV + wPAC + q3w C. Methods: Patients (pts) received 6–8 cycles of BEV (7.5 mg/kg, d1) + wPAC (80 mg/m^2 d1, 8, 15) + C (AUC6, d1) iv q3w, with BEV q3w continued alone for a total of up to 17 cycles (1 y) as front-line therapy for newly diagnosed OC (FIGO stage I–IIa [grade 3/clear cell] or stage IIb–IV [any grade]). The trial was designed to recruit a pt population similar to that enrolled in ICON7. The primary endpoint was PFS. Secondary endpoints included response rate, duration of response, overall survival, biological progression-free interval, and safety. Previously we reported safety findings from the concurrent CT phase. Here we present final safety results from the entire treatment period. Results: Between Jun 2009 and Jun 2010, 189 eligible pts were enrolled. Baseline characteristics: median age 55 y (range 24–79 y); ECOG 0 74%; FIGO stage I/II/III/IV 10%/10%/63%/17%; serous/clear cell/mixed 65%/6%/6%; 71% optimally debulked. Pts received a median of 6 CT cycles (range 1–8) and 17 BEV cycles (range 0–18). Of the 168 pts who received single-agent BEV, 135 completed 1 y of therapy. In the entire treatment period, BEV was discontinued for adverse events (AEs) in 12% and disease progression (PD) in 10%. The most common grade ≥3 hematologic AEs were neutropenia (60%), anemia (8%), and thrombocytopenia (7%). The incidences of grade ≥3 AEs of special interest for BEV were: hypertension 4.2% (grade 2/3/4: 9.0%/3.2%/1.1%); thromboembolic events 6.3% (grade 3/4: 3.7%/2.6%); bleeding 0.5% (grade 3), wound-healing complications 0.5% (grade 3), and GI perforation 0.5% (grade 4). There was no grade ≥3 proteinuria or fistula/abscess. At the time of data cut-off, 9 pts had died, all from PD. Conclusions: BEV combined with wPAC is feasible and well tolerated. BEV AEs were no more frequent with wPAC in OCTAVIA than with q3w PAC in ICON7.
Lenalidomide (REV) in asymptomatic late recurrent ovarian cancer (ROC) patients with increasing CA 125: A GINECO phase II trial.

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Background: REV is a thalidomide analogue, with both immunomodulatory and anti-angiogenic properties that could confer antitumor effect in ROC. Methods: The aim of this study was to evaluate REV efficacy as single agent in patients (pts) with asymptomatic late ROC (>6mos) with increasing CA 125, in 2nd or 3rd line. Primary endpoint was to estimate the rate of non-progressive disease at 4 mos. Pts were treated with REV 20 mg daily in oral continuous regimen with systematically recommended anti-thrombotic prophylaxis (ATP). Imagery and CA 125 were performed every 8 weeks. Results: From 05/2009 to 09/2010, 45 pts were included with a median age of 63 years. Pt characteristics were: serous (78%), previous lines (one 73%, two 27%), median platinum-free interval (PFI) (11.3 mos), PFI > 12 mos (42%), measurable disease (73%), and ECOG performance status 0 (84%). Efficacy: Rate of non progressive disease at 4 mos was 38% (95%CI, 23-53), 59 % (95%CI, 36-82) and 24 % (95%CI, 7-41) for the global population, pts relapsing over 12 mos and those relapsing between 6-12 mos, respectively. Results were independent of the number of previous lines. Median progression-free survival was 3.8 mos (95%CI, 2.1-5.6) and 6.4 mos in the subset of pts with PFI > 12 mos. Response evaluation according to CA 125 (Rustin criteria) was: complete response (CR) 2.4%, partial response (PR) 17%, stable disease (SD) 71%. When using RECIST criteria alone, response evaluation was: 9.5% PR and 45% SD. Median duration of biological response was 6.6 mos. REV efficacy will be correlated to immunological parameters (lymphocyte phenotypes and cytokines). Safety: Grade 3-4 toxicity in more than 5% of pts was neutropenia (29%) and thrombo-embolic events (TEE) (11%). TEE occurred only in pts without ATP. Reasons for stopping treatment due to toxicity were TEE (3), allergy (2), arrhythmia (1), dyspnea (1) and neutropenia (1). Conclusions: REV demonstrated encouraging activity in ROC with good tolerability and manageable adverse events. A phase I of REV combined with platinum-based chemotherapy is currently being conducted.
A phase II study of RO4929097 (RO), a gamma-secretase inhibitor, in advanced platinum (Pt)-resistant (R) ovarian cancer (OC): A study of the PMH, Chicago, and California phase II consortia.

Ivan Diaz-Padilla, Blaise A Clarke, Hal W. Hirte, Stephen Welch, Helen Mackay, James Joseph Biagi, Michael Reedijk, Johanne Ingrid Weberpals, Gini F. Fleming, Lisa Wang, Jennifer Li, Elizabeth Laureen Strevel, Anne Eisenhauer, S. Percy Ivy, Amit M. Oza; Princess Margaret Hospital, Toronto, ON, Canada; University of Toronto, Toronto, ON, Canada; Juravinski Cancer Centre, Hamilton, ON, Canada; London Regional Cancer Program, London, ON, Canada; Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; Cancer Centre of Southeastern Ontario, Kingston, ON, Canada; The Ottawa Hospital, Ottawa, ON, Canada; The University of Chicago Medical Center, Chicago, IL; Department of Biostatistics, Princess Margaret Hospital, Toronto, ON, Canada; Credit Valley Hospital, Mississauga, ON, Canada; National Cancer Institute, Bethesda, MD

Background: Notch signalling pathway plays a critical role in regulating cellular differentiation, proliferation, and apoptosis in preclinical cancer models. The Notch receptor, its ligands, and down-stream effectors are over-expressed in OC. Inhibition of γ-secretase-mediated Notch cleavage is a primary focus for the development of targeted therapeutics. Methods: Women (pts) with progressive, measurable (RECIST), Pt-R OC treated with ≤ 2 chemotherapy regimens for recurrent disease were treated with oral RO at 20mg od, 3 days on/4 days off every week, q3w. The primary objective was to determine the antitumor efficacy of RO in Pt-R OC by the progression-free survival (PFS) rate at the end of 4 cycles. Secondary objectives were to assess the safety of RO and to explore molecular correlates of outcome in archival tumor tissue. A Simon two-stage design was used. The study would open to second stage accrual if > 4 pts of the first 17 accrued remain progression-free at the end of 4 cycles. Results: 39 pts have been enrolled after first-stage criteria were met. Median age was 59 (range 26-81). Median number of cycles was 2 (range 1-18). 30 (83%) pts had high-grade serous OC. 34 pts were evaluable for response. 8 pts (20%) were progression-free after 4 cycles. 12 pts (35%) had stable disease, with a median duration of 3.9 months (range 2.5-12.2). Median PFS was 1.3 months (1.2-2.3). The most common drug-related adverse events (AEs) of any grade (% pts) were: nausea (36), fatigue (28), anorexia (15), hypophosphatemia (15), anemia (13), and increased alanine aminotransferase [ALT] (13). There were 5 G3-4 AEs at least possibly related with RO: increased liver transaminases (2), diarrhea (1), headache (1), and hypophosphatemia (1). Intracellular Notch (NIC) and JAG1 protein expression on high-grade serous OC were correlated with response in 17 pts. Median PFS for pts with high NIC (n=6) was 3.3 months (1.0-not reached), compared to 1.3 months (1.1-2.6) for pts with low NIC (n=11), p=0.09. Conclusions: RO has limited clinical activity in unselected Pt-R OC as a single agent. Future studies need to assess potential for cohort enrichment using NIC expression.

Randomized trial of oral cyclophosphamide (C) with or without veliparib (V), an oral poly (ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent BRCA-positive ovarian, or primary peritoneal or high-grade serous ovarian carcinoma.

Shivaani Kummar, Amit M. Oza, Gini F. Fleming, Daniel Sullivan, David R. Gandara, Charles Erlichman, Miguel Angel Villalona-Cañero, Robert Morgan, Alice P. Chen, Jiuping Jay Ji, Deborah Allen, Chih-Jian Lih, Seth M. Steinberg, P. Mickey Williams, Barbara A. Conley, James H. Doroshow; Developmental Therapeutics Clinic, National Cancer Institute, Bethesda, MD; Princess Margaret Hospital, Toronto, ON, Canada; The University of Chicago Medical Center, Chicago, IL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of California Davis Cancer Center, Sacramento, CA; Mayo Clinic, Rochester, MN; The Ohio State University Medical Center, Columbus, OH; City of Hope, Duarte, CA; National Cancer Institute, Bethesda, MD; SAIC-Frederick, Frederick, MD

Background: V+C was well tolerated in a phase I trial and responses and prolonged disease stabilization were observed in BRCA + patients (pts). To assess the relative contribution of the PARP inhibitor to the efficacy observed for the combination, we conducted a randomized multicenter trial comparing the response rate (RR) of V and C to the RR of C alone in patients with deleterious BRCA mutations and recurrent ovarian, or primary peritoneal, fallopian tube or high-grade serous ovarian cancer. Methods: Pts were ≥ 18 yrs, KPS ≥ 70%, had adequate organ function, prior therapy with PARP inhibitors was allowed. Both drugs were administered orally qd; C 50 mg, V 60 mg; 21 day cycles. Pts were randomized to receive either C alone or V+C. At disease progression, pts on C alone were allowed to cross over to the combination. Radiologic imaging was performed at baseline and q 3 cycles for assessment of response. Dose reduction of V was allowed to 40 mg for gr 3 non-hematologic or gr 4 hematologic toxicities. The study design had an 88% power to detect the difference between a 15% RR for C alone versus 35% for V+C, early closure if fewer responses were observed on the combination arm in the first 65 pts enrolled (half of the total projected accrual). Results: Total of 74 pts were enrolled (36 pts C, 38 pts V+C), median age 58 (37-79 yrs), # of prior therapies: median 4 (1-9), 2 pts had prior PARP therapy. Treatment was well tolerated, Gr ≥ 2 toxicities per arm for initial regimen (# of pts): C alone: lymphopenia (2), mucositis (1); V+C: lymphopenia (4), anemia (2), leucopenia (2), neutropenia (2). Of the 74 pts evaluable for response at the interim analysis, 3 PRs observed in 36 pts on V+C and 5 PRs of 38 pts on C alone arm; thus accrual was stopped. PAR levels assessed by validated ELISA were inhibited (>80%) in PBMCs in 9/10 pts 4 hours post V, no inhibition with C alone. Conclusions: Addition of V, a PARP inhibitor, to C did not improve RR versus C alone. Exomic sequencing, gene expression studies, and Fanconi Anemia triple stain immunofluorescence (FATSI) assay for FancD2 nuclear foci formation using archival tissue are ongoing.
Phase I/II study of weekly paclitaxel with or without MLN8237 (alisertib), an investigative aurora A kinase inhibitor, in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (OC), or breast cancer (BrC): Phase I results.

Gerald Steven Falchook, Barbara Ann Goff, Razelle Kurzrock, Heidi J. Gray, Lainie P. Martin, Robert L. Coleman, Hua Liu, Xiaofei Zhou, Ely Benaim, Russell Schilder; Department of Investigational Cancer Therapeutics, University of Texas M. D. Anderson Cancer Center, Houston, TX; Department of Obstetrics and Gynecology, University of Washington, Seattle, WA; Fox Chase Cancer Center, Philadelphia, PA; Department of Gynecologic Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX; Millennium Pharmaceuticals, Cambridge, MA; Thomas Jefferson University Hospital, Philadelphia, PA

Background: Preclinical data indicate that inhibiting aurora A kinase (AAK), a key mitotic regulator, in OC can enhance the activity of taxane-based chemotherapy. This is the first clinical study to evaluate the AAK inhibitor MLN8237 (A) in combination with paclitaxel (P). Methods: Eligible women (aged ≥18 y) had previously treated, metastatic or locally recurrent OC or BrC. OC pts had previously received a platinum and taxane, and had disease recurrence within 12 mo of discontinuing platinum. Pts received IV P (D1, 8, 15) with oral A (enteric coated tablet, 3 d on, 4 d off, wkly for 3 wks) in 28-d cycles. Doses were escalated in a 3+3 schema. Phase I endpoints were safety, response by RECIST and CA125, and pharmacokinetics (PK).

Results: 28 pts were treated at doses of P80 mg/m² + A10 mg BID (n=5), P80+A20 (n=6), P60+A20 (n=4), P60+A30 (n=6), P60+A40 (n=4) and P60+A50 (n=3). 25 pts had OC (20 ovarian, 4 primary peritoneal, 1 mullerian) and 3 BrC. Median age was 59 y (range 37–72). Pts received a median of 2.5 (1–16) and 2.5 cycles (1–15) of A and P, respectively. 11 pts are ongoing. 3 pts had DLTs: Gr 4 diarrhea (P80+A20), Gr 3 stomatitis (P80+A20) and Gr 4 neutropenia for ≥7 d with fever (P60+A30). MTD has not yet been reached. 27 pts had ≥1 drug-related adverse event (AE); most common were neutropenia (n=18), anemia (n=13) and nausea (n=12). 21 pts had Gr ≥3 drug-related AEs; the most common was neutropenia (n=15). 5 pts had drug-related SAEs. No pts have died on study. Preliminary PK data (n=24) indicated fast absorption of A with a median T max of 3 hr. Geometric means of A AUC 0−12hr on D3 were 3740 nM·hr (CV: 22%), 7180 nM·hr (31%), 11,900 nM·hr (49%) and 15,100 nM·hr (72%) at 10, 20, 30 and 40 mg BID, respectively. A exposures increased approximately dose proportionally. Partial responses by RECIST (n=5) and/or CA125 (n=7) in 8 pts (29%; 7 OC, 1 BrC); 3 pts had stable disease ≥6 mo. Conclusions: Emerging data from this first combination study suggest that P+A is generally well tolerated and has antitumor activity in pts with OC/BrC. Dose-escalation is ongoing to determine the recommended phase II dose.
Use of chemotherapy (CT) in BRCA1/2-deficient ovarian cancer (BDOC) patients (pts) with poly-ADP-ribose polymerase inhibitor (PARPi) resistance: A multi-institutional study.

Joo Ern Ang, Charlie Gourley, Hilda Anne High, Ronnie Shapira-Frommer, C. Bethan Powell, Vincent Castonguay, Jacques De Greve, Timothy Anthony Yap, Peter C.C. Fong, David Olmos, Susana N. Banerjee, Lee-may Chen, Michael Friedlander, Bella Kaufman, Amit M. Oza, Johann Sebastian De Bono, Martin Eric Gore, Stanley B. Kaye; The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, United Kingdom; Edinburgh Cancer Research Centre, MRC IGMM, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom; Prince of Wales Cancer Centre, Sydney, Australia; Chaim Sheba Medical Center, Tel Hashomer, Israel; University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA; Princess Margaret Hospital, Toronto, ON, Canada; Oncologisch Centrum UZ Brussel, Brussels, Belgium

Background: Emerging clinical data point to the clinical utility of PARPi in BDOC. However, the impact of PARPi exposure on the prospects of response to further CT remains unclear. In our previous single centre study, we provided the first clinical data relating to the use of post-PARPi CT (JCO 2010: 28(15S), A5041). Our aim here was to re-examine this issue in a larger multi-institutional population. Methods: We included pts with advanced BDOC who received CT, having progressed on ≥200 mg bd olaparib. Pt, tumor and treatment characteristics and clinical outcomes were documented. Relationships between post-PARPi CT overall survival (OS) and other variables were explored using Cox regression. Results: We collected data on 75 pts (median age 51 y [range 31-77], BRCA1:BRCA2 54:21, mean 3 previous lines of CT [95% CI 2.5-3.4], pre-PARPi platinum (Plt) resistance rate 49% and olaparib RECIST-response rate [RR] 39% [95% CI 28-50]). Following olaparib, most pts received Plt alone or in combination with taxane (Tx) or liposomal doxorubicin (PLD). Weekly Plt was used in 36% of all Plt-treated pts, mainly in combination with weekly Tx. Overall RECIST and CA125 (GCIG) RRs were 38% and 48%, respectively; these responses occurred independently of PARPi response or pre-PARPi Plt sensitivity (all p>.1). The median progression free survival and OS of RECIST responders were 7.9 m (95% CI 5.8-10.9) and 10.5 m (95% CI 1.4-19.6), respectively. In all pts, the median OS from the start of post-PARPi CT was 7.9 m (95% CI 5.7-10.1) while that from diagnosis was 64.9 m (95% CI 52.9-76.9). Factors associated with improved OS on post-PARPi CT in the MVA included best olaparib response of non-disease progression (p=.003, HR 0.28), optimal initial debulking (p=.01, HR 0.36) and pre-PARPi Plt sensitivity (p=.05, HR 0.46). Conclusions: These data indicate potential for meaningful responses to CT in BDOC pts with PARPi resistance. Analysis to identify molecular predictors of response is ongoing.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR (n responses/[n evaluable])</th>
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<tr>
<td></td>
<td>RECIST</td>
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<tr>
<td>Plt single agent/combination</td>
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<tr>
<td>Tx single agent</td>
<td>4/9</td>
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<td>PLD single agent</td>
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<tr>
<td>Others</td>
<td>1/4</td>
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<tr>
<td>Total</td>
<td>22/58 (38%)</td>
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</table>
A novel autologous oxidized whole-tumor antigen vaccine therapy for recurrent ovarian cancer.

Lana Kandalaft; University of Pennsylvania, Philadelphia, PA

**Background:** Despite surgical and chemotherapeutic advances, the death rate from ovarian cancer has not changed. We report here an enhanced dendritic cell vaccine platform developed for clinical testing. Furthermore we report the application of this novel platform comprising of dendritic cell (DC)-based autologous whole tumor antigen vaccination in a pilot study of patients with recurrent ovarian cancer.

**Methods:** To determine the optimal tumor lysate preparation for loading DCs, ovarian tumor lines were prepared by HOCl-oxidation, UVB-irradiation or freeze and thaw. Normal donor DCs were evaluated for tumor lysate uptake, cytokine and chemokine productions and phenotype. The optimal lysate preparation, was used in a phase I study where five patients with recurrent ovarian cancer with available tumor lysate from secondary debulking surgery underwent intranodal vaccination with OC-DC, an autologous DC preparation pulsed with HOCL oxidized autologous tumor cells. Feasibility, safety, and biological and clinical efficacy were evaluated.

**Results:** Normal donor DCs pulsed with HOCl-oxidized tumor lines demonstrated the highest tumor lysate uptake, matured efficiently after LPS and IFN-gamma stimulation, and produced higher levels of proinflammatory cytokines and chemokines. In vitro, these lysates loaded DCs primed T cell responses against ovarian tumor associated antigens and effectively expanded against tumor specific T cells from donors and patients. Therapy was feasible and well tolerated in all subjects. Vaccination with OC-DC produced limited grade 1 toxicities and elicited tumor-specific T cell responses. Moreover specific HLA-A2-restricted responses were documented following vaccination and HER-2/neu specific T cells were expanded following 10 days of in vitro culture. Patients exhibiting immune response demonstrated clinical benefit including two patients who demonstrated remission inversion on vaccine maintenance.

**Conclusions:** We developed a DC-HOCl oxidized whole tumor lysate vaccine which was safe and well-tolerated by patients. The vaccine was highly proinflammatory and elicited cellular and humoral anti-tumor responses establishing a platform for immune-combinatorial therapy.
Phase II trial of temsirolimus and bevacizumab for initial recurrence of endometrial cancer.

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Background: We report the interim results of the endometrial arm of a multi-tumor protocol using temsirolimus and bevacizumab in endometrial cancer (EMCA) patients at the time of their initial recurrence. The primary aim of this trial is to assess treatment efficacy in terms of both confirmed tumor response and 6-month progression free survival (PFS). Methods: Women with a performance status of 0 or 1 who have had their first recurrence for EMCA were eligible. Subjects who had chemotherapy as part of their adjuvant treatment after front line surgical staging were also eligible. The regimen included Temsirolimus 25 mg IV weekly followed by bevacizumab 10mg/kg IV on days 1 and 15 of a 28 day cycle. A modified two-stage Simon design with fixed sample size was adopted with the null hypothesis being that the true tumor response rate is at most 25% and the true 6 month PFS rate is at most 50%. Results: We enrolled 26 evaluable subjects to the first stage of which one did not proceed with treatment. The median age at enrollment was 60 (range 40-80). 22 (85%) were white and 19 (73%) were not Hispanic/Latino. 19 (73%) of subjects had prior radiation therapy, with 4 having a prior para-aortic boost. 5 (20%) subjects had a confirmed PR and 12 (48%) were progression-free at 6 months, which fell short of the futility stopping rule. An additional 5 (20%) subjects had a best response of confirmed SD, so 10 (40%) had overall clinical benefit from this regimen. AEs attributable to treatment were modest and included 16 grade 3 adverse events, of which the most common ones included hypertension, hyperglycemia, and neutropenia. There were 2 grade 4 events that were possibly treatment related including a duodenal perforation and an anorectal infection. Conclusions: While there was clinical benefit of this regimen in women at the time of their first recurrence of EMCA, the combination of temsirolimus and bevacizumab did not achieve our prespecified efficacy assumptions. This differs from what has been reported with this combination as a second line therapy for recurrent EMCA, where prespecified response assumptions differ. Also, the regimen had comparable safety and toxicity to other cytotoxic chemotherapy regimens used in this setting.
Brief family history questionnaire for identification of Lynch syndrome in women with newly diagnosed endometrial cancer.

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Background: Endometrial cancer (EC) is often the sentinel cancer for women with Lynch syndrome (LS); however, it is underappreciated in this population. The Brief Family History Questionnaire (bFHQ) was developed to identify women with EC who have family histories suggestive of LS. The objective of our study was to evaluate the bFHQ compared to an extended family history (eFHQ) and medical record in identifying women with EC who may benefit from genetic cancer risk assessment. Methods: All women with newly diagnosed EC from July 2010 to June 2011 were asked to participate in a prospective screening protocol for LS which included completing two family history questionnaires; the bFHQ which is a 4-item self-report measure and the 37-item eFHQ administered by a research assistant. Family history was also extracted from the medical record. Using the bFHQ women were flagged as requiring additional investigation for LS based on predetermined criteria and the predictive ability of the flag was evaluated treating eFHQ as the gold standard. Comparisons were made between the bFHQ, eFHQ and medical record for families meeting Amsterdam II, Society Gynecologic Oncologist (SGO) 20-25% or the Ontario Ministry of Health (MOH) testing criteria for LS, using generalized estimating equation logistic regression models. Results: 119 (N = 182, 65%) consented to the study and 106 (89%) completed the bFHQ. The median age was 61 (26-91). The number of women who met testing criteria by the eFHQ was 17 (16%) and 33 (31%) were flagged by the bFHQ. The sensitivity, specificity, PPV and NPV of the bFHQ was 88.2%, 79.8%, 45.5% and 97.3%. There was no significant difference in the number of women who met Amsterdam II or SGO 20-25% testing criteria between the bFHQ, eFHQ and medical record (P > 0.05). The numbers of women meeting MOH criteria using the bFHQ (N=16, 15%) and the eFHQ were similar (N=17, 16%) (P = 0.7); however, more women met MOH criteria using the bFHQ and the eFHQ compared to the medical record (N=8, 7.6%) (P = 0.011; P = 0.006). Conclusions: The patient-administered bFHQ is a highly effective tool in identifying women who meet MOH testing criteria for LS and is a good screening tool to identify women with EC for further genetic assessment.
Efficacy and safety of the APE (actinomycin D, cisplatin, etoposide) regimen for the management of high-risk gestational trophoblastic neoplasia.

Catherine Lhomme, Caroline Even, Pierre Davillard, Patricia Pautier, Anne Floquet, Pierre Kerbrat, Frederic Troalen, Annie Rey, Corinne Balleyguier, Philippe Morice, Karim Fizazi, Jean Pierre Droz; Institut Gustave Roussy, Villejuif, France; Department of Pathology, Institut Gustave Roussy, Villejuif, France; Institut Bergonié, Bordeaux, France; Centre Eugène Marquis, Rennes, France; Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; Centre Léon Berard, Lyon, France

Background: Patients (pts) with high risk gestational trophoblastic neoplasia (GTN) or who fail low risk single agent chemotherapy (CT) require multi agent CT to be cured. The most common regimen is etoposide (E), methotrexate and actinomycin D (A) alternating weekly with cyclophosphamide and vincristine (EMA/CO). Cisplatin (P) is a very active drug but its role is controversial and usually restricted to second line. We report results of a platinum based therapy: APE.

Methods: We evaluated the efficacy and safety on 103 pts treated at Institut Gustave Roussy (IGR) (n=80) or other French centers (n=23) between 1983 and 2010 with APE for high risk GTN (defined by IGR criteria [Azab, Cancer, 1988] and/or FIGO score >6). Pts with brain metastasis were excluded. Results: Efficacy was evaluated on 59 pts treated for high risk GTN in first line, and on 39 pts in >2nd line including 13 pts after multi agent CT. We excluded pts with placental site trophoblastic tumors (n=2), or with FIGO score <7 and without IGR criteria (n=3). Complete remission (CR) rate was 95%. Seven pts (7 %) relapsed and a second CR was obtained for all with surgery and/or CT. Only one patient died due to GTN, after successive CRs obtained with 3 regimens. Five year overall survival (median follow-up 6.6 years) was 98%. Toxicity was evaluated on 95 pts. No toxic death occurred. Given good efficacy and to avoid acute hematotoxicity and long-term G1 neuro and ototoxicity APE regimen was modified as detailed in the Table (below). Long-term neuro (5 pts, G1), oto (2 pts, G1 and 2 pts, G2) and renal toxicities (1 pt, G1 ) were recorded. No long-term G2 toxicities were observed with APE3. One pt developed an AML 4 after 4cy APE and 6 cy EMA/CO. 37 pts of 40 who wished to be pregnant succeeded and all of them had at least one live birth. Conclusions: With a 98% long-term overall survival rate, an excellent reproductive outcome, and no detectable long-term toxicity, APE-3 should be regarded as an alternative standard option to EMA/CO for high-risk GTN.

<table>
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<tr>
<th></th>
<th>A 0.3 mg/m²/d</th>
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<td>APE 1</td>
<td>J 1-3, J 14-15</td>
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<td>J1</td>
<td>J1 – J28 38</td>
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<td>APE 3</td>
<td>J 1-3</td>
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<td>J1</td>
<td>J1 – J21 23</td>
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A snapshot of potentially personalized care: Molecular diagnostics in gynecologic cancer.

Elizabeth Sales, Richard T. Penson, Laura A Sullivan, Darrell R. Borger, Carolyn N. Krasner, Annekathryn Goodman, Marcela G del Carmen, Whitfield Board Growdon, John O. Schorge, David M. Boruta, Michael J. Birrer; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital/Dana-Farber Harvard Cancer Center, Boston, MA

Background: Genetic abnormalities underlie the development of cancer. It has been proposed that tumors be recategorized by gene mutation such as \textit{BRAF} in LG serous, \textit{TP53} in HG serous, and \textit{PIK3CA} in clear cell and endometrioid tumors. These targets potentially represent an opportunity for personalizing cancer therapy. Methods: Gynecologic Oncology patients at the MGH Cancer Center can have their tumor genotyped for a panel of mutations by SNaPshot, a validated, CLIA approved assay developed by MGH that uses DNA from FFPE tissue to interrogate 160 site-specific mutations across 15 genes (\textit{AKT1, APC, BRAF, CTNNB1, EGFR, ERBB2, IDH1, KIT, KRAS, MAP2K1, NOTCH1, NRAS, PIK3CA, PTEN, TP53}). At present SNaPshot has no validated endpoints in GYN Cancers but may help identify a useful clinical trial. Results: Between 5/17/10 and 10/17/11, 125 patients consented to SNaPshot genotyping. Patients had a median age of 59 (24-78) yrs. Tumors were ovarian 70(56%), uterine clear, UPSC, or MMMT 16(13%), uterine endometrioid 10(8%), fallopian tube 8(6%), PPC 7(6%), cervical 6(5%), uterine sarcomas (3), ACUP (2), vulvovaginal (2), metastatic (1). A mutation was identified in 41(33%), with 9 of these (23%) having 2 or 3 (n=2) mutations. In the 85 ovarian, FT, and PPC cancers 33% were +ve, but 50% were in \textit{TP53}. The low mutation rate for \textit{TP53} is likely explained by copy number abnormalities (Amplification). 50% of the 10 uterine tumors were +ve, with 3 of those 5 having multiple mutations in the \textit{PIK3CA} pathway, while 69% of the non-endometrioid uterine tumors had mutations. Only 20% of the vulvo-vaginal and Cx tumors had mutations, both \textit{PIK3CA}. 19% of the purely serous tumors (n=58) had \textit{TP53} mutations, and 37% of the purely clear/endometrioid tumors (n=19) had mutations in \textit{PIK3CA, PTEN} or \textit{AKT}. Certain rare tumors did not have identifiable mutations: granulosa cell tumors (2), ovarian small cell (2). 5 pts with a \textit{PIK3CA} mutation were enrolled on a clinical trial (2 phase II, 3 phase I, 3 uterine, 1 ovary, 1 cervix). Conclusions: SNaPshot can identify potentially important therapeutic targets. However, the incidence of "drugable" targets in ovarian cancer is low, and <5% subjects eventually were treated on a relevant clinical trial.
A comprehensive analysis of BRAF and KRAS mutation status in low-grade serous (LGS) and serous borderline (SB) ovarian cancer (OC).

Rachel Nicole Grisham, Karuna Garg, Qin Zhou, Alexia Iasonos, Michael F. Berger, Fanny Dao, David Michael Hyman, Douglas A. Levine, David B. Solit, Carol Aghajanian, Gopa Iyer; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: LGS OC develops in a step-wise pattern from serous cystadenoma to SB tumor to invasive LGSOC. LGSOC accounts for 6-22% of serous OC and is a chemoresistant disease. Prior studies have reported that LGS/SB ovarian tumors harbor BRAF mutations in 28-35% of cases, suggesting that LGS/SB OC may respond to mutant BRAF inhibitors. Methods: We genotyped 75 LGS and SB ovarian tumors for BRAF and KRAS hotspot mutations using a mass spectrometry based Sequenom assay. All samples were collected at MSKCC between 2000-2010. All specimens underwent two independent pathologic reviews for diagnostic confirmation and macrodissection to ensure 80% cellularity. The incidence and identity of BRAF and KRAS mutations were defined and results were correlated with stage, response to treatment, and outcome. Exon capture sequencing is underway to sequence all coding exons of 230 cancer associated genes to identify additional targetable alterations in LGS/SB OC. Results: Of 75 samples examined, 56(75%) were SB and 19(25%) LGS histology. 57% of samples showed KRAS mutation (KRAS +) (n=17, 23%) or BRAF mutation (BRAF +) (n=26, 35%). Mutation status was mutually exclusive. All BRAF+ were V600E, KRAS+ were G12D (n=9) or G12V (n=8). BRAF+ was associated with early stage (I-II) at presentation and SB histology. 22 (29%) patients were treated with chemotherapy, 2 (9%) with KRAS+ and 0 with BRAF+. 4(15%) BRAF+ patients underwent resection of recurrent disease. All BRAF+ patients are alive without evidence of disease at a median follow-up of 43.3 months (range 1.9-129.3 months). Conclusions: V600E BRAF mutations are present in 35% of cases of SB/LGS ovarian cancer. Presence of BRAF+ in SB/LGS OC is associated with good prognosis and surgical cure of disease. Patients with SB/LGS OC who require systemic therapy are unlikely to have BRAF+. Our group is performing a detailed search for additional targetable alterations in multiple signal transduction pathways through next generation sequencing technology.

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<tr>
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<th>KRAS+</th>
<th>BRAF+</th>
<th>WT for KRAS/BRAF</th>
<th>p value</th>
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<td>Stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I/II</td>
<td>10 (58.8%)</td>
<td>24 (92.3%)</td>
<td>11 (34.4%)</td>
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<tr>
<td>III/IV</td>
<td>7 (41.2%)</td>
<td>2 (7.7%)</td>
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<td>Histology</td>
<td></td>
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</tr>
<tr>
<td>SB</td>
<td>14 (82.4%)</td>
<td>25 (96.2%)</td>
<td>17 (53.1%)</td>
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<tr>
<td>LGS</td>
<td>3 (17.6%)</td>
<td>1 (3.8%)</td>
<td>15 (46.9%)</td>
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Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or carboplatin plus pegylated doxorubicin (PLDC): A randomized phase III trial of the NOGGO-AGO-Germany-AGO Austria and GEICO-GCIG intergroup study (HECTOR).

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Background: We present the efficacy data from a phase III study of topotecan (T) plus carboplatin (C) versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or carboplatin plus pegylated doxorubicin (PLDC). Methods: From 02/07 to 12/09, 590 pts were screened and 550 pts were randomized to either T (0.75mg/m²/d1-3/q21d) + C (AUC 5/d1/q21d) or to standard therapy with CP or GC or PLDC based on patient preference. Progression free survival at 1 year was defined as primary endpoint. Results: Median number of cycles was 6 (range 0-9) in both arms. Most patients preferred GC (78%) in the standard therapy arm. Best Response (CR + PR) was 73.1% (95%CI) and 75.1% (95%CI) for the CA. Median follow-up was 18 (0-52) months for TC and 20 (0-48) months for standard therapy. TC failed to show any advantage regarding 1-yr.-PFS or OAS. Conclusions: The combination of topotecan plus carboplatin failed to improve PFS or OAS in platinum sensitive relapsed ovarian cancer. In addition, carboplatin plus gemcitabine was well tolerated with lower rates of severe and long-lasting (neuropathy) toxicities compared to paclitaxel-carboplatin.

<table>
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<tr>
<th></th>
<th>TC arm</th>
<th>CP arm</th>
<th>GC arm</th>
</tr>
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<tbody>
<tr>
<td>1 year PFS rate (%)</td>
<td>p=0.215</td>
<td>37.0%</td>
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<td>PFS, median months (95%)</td>
<td>p=0.472</td>
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<td>12 mo</td>
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<td>OAS, median moths (95%), p=0.346</td>
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<td>(9.1-14.9)</td>
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<td>Neutropenia G3-4; p=0.015</td>
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<td>(23.4-34.6)</td>
<td>(26.8-39.7)</td>
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<td>Thrombocytopenia G3-4; p=0.001</td>
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<td>Anemia G 3-4; p=0.145</td>
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<td>Any non-hematologic toxicity G3-4; p=0.436</td>
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<td>31.6%</td>
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<td>Alopecia G2+; p=0.001</td>
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<td>Neutropathy G2+; p=0.073</td>
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<td>Hand-foot syndrome G2</td>
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<td>Mucositis G2+; p=0.380</td>
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<td>6.3%</td>
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<td>Hypersensitivity, allergic reaction G2+, p=0.100</td>
<td>15.2%</td>
<td>12.7%</td>
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<tr>
<td>Early treatment discontinuation (toxicity related, &lt; 6 cycles); p=0.162</td>
<td>15.9%</td>
<td>7.6%</td>
<td>13.2%</td>
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</table>
Application of micro-RNA (miRNA) expression profiles for prognostication in low-risk endometrial carcinoma (LEC).

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**Background:** Reliably predicting which LEC patients are most likely to recur is a challenge for the clinician with implications on adjuvant therapy. MiRNAs have been exploited for diagnosis and prognostication in a number of malignancies. We hypothesize that miRNA expression profiles differ in tumors from patients with recurrence compared to those without recurrence. **Methods:** The inclusion criteria for this study are informed consent, stage 1 disease, grade 1 or 2 tumors and endometrioid histology. RNA was extracted from formalin-fixed paraffin-embedded tissues and miRNA profiling was done using Agilent Human miRNA. Differentially expressed miRNAs were identified using GeneSpring GX software and the two groups were compared using the student t-test. **Results:** The expression levels of 866 miRNAs were determined from LEC patients with recurrence (n=15) and without recurrence (n=16). The mean follow-up interval was 61.5 months. The average age of cancer diagnosis for patients with and without recurrence was 60.2 (range 42-75) and 59.7 (range 44-86), respectively (p=0.91). Three of 15 patients with recurrence and 6 of 16 patients without recurrence received adjuvant brachytherapy following their primary surgery (p=0.43). 17 miRNAs were identified which can distinguish between the tumors with recurrence and those without recurrence (p<0.05). MiR-146a, miR-18a, miR-222, and miR-30a showed the highest fold change difference (>5 fold) in the tumors with recurrence compared to that did not recur. A decision tree prediction model for recurrent LEC was developed where a miRNA cutoff was used as a branch in the decision tree. This model identified those patients who were most likely to recur based on the expression of 4 dysregulated miRNAs (miR-222, miR-361-3p, miR-181c and miR-125b). **Conclusions:** These preliminary results show the miRNA expression profile differs among LEC and can be used to distinguish an aggressive sub-group. Should future validation studies confirm this result, this information would be valuable in the design of a biomarker study to help decide which patients would benefit most from extended adjuvant treatment.
Randomized, phase III study of carboplatin plus paclitaxel for 8 cycles (CP8) versus carboplatin x 8 cycles plus paclitaxel x 4 cycles (C8P4) in advanced ovarian, fallopian, or primary peritoneal carcinoma.

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Background: The combination of carboplatin/paclitaxel represents the standard 1st-line chemotherapy in advanced OC, FC, and PPC. The optimal duration of paclitaxel treatment has not been defined, while its use is associated with cumulative neurotoxicity in about 50% of patients, which becomes long-term in 15-20% of cases. We, therefore, designed a randomized study to investigate the effect of administering 4 instead of 8 cycles of paclitaxel in the combination carboplatin/paclitaxel on efficacy and tolerability of this treatment.

Methods: Patients with FIGO stages IIC-IV OC, FC, PPC were included. Carboplatin AUC 6 and paclitaxel at 175 mg/m² were used. Both agents were administered for 8 cycles in the CP8 arm, while paclitaxel was administered only for 4 cycles in the C8P4. The study was powered to detect a ± 15% difference in survival rate to a baseline rate of 50% at the 3-year time point. Results: 389 pts were randomized (2/2004-1/2008) and 380 were eligible for analysis (CP8: 192, C8P4: 188). The distribution (CP8 vs C8P4) of baseline characteristics were: stage III: 78% vs. 76%; IV: 12% vs. 15%, residual disease 0 cm: 25% vs. 22%, ECOG PS 0: 68% vs. 64%, serous carcinomas: 79% vs. 68%, tumor grade III: 56% vs. 63%. During a median follow up of 72.3 months 231 patients (111 [58%] in CP8 arm and 120 [64%] in the C8P4 arm) have died. Median PFS was significantly shorter in the C8P4 arm (21.41 vs. 16.46 months, HR [95% CI]: 1.36 [1.07-1.71], Wald’s p = 0.011), while OS was similar between the two arms (53.41 vs. 46.59 months, HR [95% CI]: 1.18 [0.91-1.53], Wald’s p = 0.211). Lower grade 3 or 4 neurotoxicity (1.9% vs. 10.8%, p = 0.001) but higher myelotoxicity (neutropenia 38.8% vs. 28.8%, p = 0.031; thrombocytopenia 20% vs. 8.3%, p = 0.004) was observed in the C8P4 arm. Conclusions: Lowering the total number of cycles of paclitaxel in 1st-line chemotherapy of advanced OC, FC, PPC resulted in similar OS but shorter median PFS and is not recommended in this setting. The reduction of neurotoxicity by limiting the total paclitaxel cycles to 4 is achieved at the expense of higher myelotoxicity.
Use of HE4 and CA125 to predict surgical outcome and for prognostic value for progression-free survival (PFS) and overall survival (OS) in primary epithelial ovarian cancer (EOC) patients (pts).

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Background: Optimal surgical cytoreduction and response to platinum (P) based chemotherapy (ChTh) remain the cornerstones of therapeutic management of primary EOC. Aim of this study was to analyze the predictive role of HE4 and CA125 as biomarkers (BM) for clinical outcome in primary EOC pts at diagnosis and during subsequent follow-up. Methods: In the European OVCAD project 275 pts with primary EOC were enrolled. Pts were eligible if radical cytoreductive surgery and P-based ChTh were applied. Plasma collected at first diagnosis and 6 months after 1st line ChTh in P-sensitive pts was analyzed for HE4 and CA125 levels using ELISA and Luminex technique, respectively. Results: Complete cytoreduction with no residual tumor disease (RTD) was obtained in 69.9% pts. HE4 and CA125 expression in plasma at first diagnosis correlated with RTD, p<0.002 and p=0.002, respectively. The sensitivity (SE) and specificity (SP) of the combinative use of both BM in predicting RTD was 64.8% and 73.5%, respectively. Pts having over-expression of both BM in plasma had a 6.1 greater risk for RTD (p<0.001, OR: 6.107, 95% CI 2.41-15.46). P-resistance occurred more frequently when both BM were over-expressed (p=0.028, OR=3.1, 95%CI 1.13-8.46). Elevated BM levels during follow-up predicted recurrence (SE 90% and SP 71% for CA125 ≥55U/ml; SE 72.7% and SP 81.4% for HE4 ≥150pM) and when HE4 or CA125 were positive, a SE of 86.4% and SP of 72.9% were achieved. Elevated CA125 and HE4 at 6 months following adjuvant therapy was associated with significantly poorer PFS (p<0.001, HR 9.6, 95%CI 3.93-23.44 with elevated HE4 or CA125, and HR=50.52, 95%CI 14.44-176.78, with elevated HE4 and CA125) and OS (p<0.001, HR=7.42 95%CI 1.43-38.42 with elevated HE4 or CA125 and HR=28.38 95%CI 6.50-123.97 with elevated HE4 and CA125). Conclusions: The combinative use of HE4 and CA125 appears to have a significant value in predicting optimal surgical outcome and development of P resistance disease in EOC pts. Elevated plasma levels 6 months after 1st line ChTh significantly correlate with OS and PFS in P-sensitive pts.

Functional profiling of clear cell ovarian cancer.

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Background: Clear cell ovarian cancer represents up to 15% of epithelial ovarian cancers. In comparison to other subtypes, clear cell ovarian carcinomas have a poorer prognosis and are relatively resistant to standard platinum based chemotherapy. Recently, loss of function mutations in the tumour suppressor gene ARID1A were identified in up to 50% of ovarian clear cell carcinomas. We have adopted an integral functional and molecular profiling approach as a route to identify new genetic dependencies and therapeutic targets for this disease. Methods: Clear cell ovarian cancer cell lines were functionally profiled using high throughput screening with chemical and siRNA libraries. This has been integrated with molecular profiling data generated from exome and transcriptome sequencing to aid the discovery of novel targets. Results: Using functional screens we have now identified critical gene dependencies and potential therapeutics in a series of clear cell ovarian cancer models. The comparison of functional viability profiles for models characterized by ARID1A loss of function mutations is now enabling an analysis of synthetic lethal effects that could be used to target clear cell ovarian cancers carrying these mutations. Conclusions: The work undertaken so far provides the framework for the discovery of therapeutic targets for clear cell ovarian cancer using an integrated approach. Revalidation of these preliminary results is now underway to characterize new genetic dependencies for this disease.
Use of an optimized primary ovarian cancer xenograft model to mimic patient tumor biology and heterogeneity.

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**Background:** Current xenograft and transgenic models of ovarian cancer are mainly homogeneous and poorly predict response to therapy. Use of patient tumors may represent a better model for tumor biology and offer potential to test personalized medicine approaches, but poor take rates and questions of recapitulation of patient tumors have limited this approach. We have developed a protocol for improved feasibility of such a model and examined its similarity to the patient tumor. **Methods:** Under IRB and IACUC approval, 23 metastatic ovarian cancer samples were collected at the time of tumor reductive surgery. Samples were implanted either subcutaneously (SQ), intraperitoneally (IP), in the mammary fat pad (MFP), or in the subrenal capsule (SRC) and monitored for tumor growth. Cohorts from 8 xenolines were treated with combined carboplatin and paclitaxel or vehicle, and response to therapy compared between xenografts and patients. Expression of tumor-initiating cell (TIC) markers ALDH1, CD133, and CD44 was assessed by immunohistochemistry in tumors from patients and treated and untreated xenografts. **Results:** At least one SQ implanted tumor developed in 91.3% of xenografts, significantly higher than in the MFP (63.6%), IP (23.5%), or SRC (8%). Xenografts were similar in expression of putative TIC’s compared to patient tumors. The patients and the xenografts also have similar responses to chemotherapy in that xenografts from patients with a partial response responded more slowly than those from patients achieving a complete response (45 vs 21 days, \( p < 0.004 \)). Treated xenografts were more densely composed of TICs. ALDH1 increased to 36.1% from 16.2% (\( p = 0.002 \)) and CD133 increased to 33.8% from 16.2% (\( p = 0.026 \)). **Conclusions:** Xenoline development can be achieved at a high rate when tumors collected from metastatic sites are implanted SQ. These xenografts are similar to patient tumors with regard to chemotherapy response and TIC expression. This model may be a more accurate model for in vivo pre-clinical studies as compared to current models. Also, as treated xenografts become chemoresistant, this model is well positioned to evaluate targeted therapies aimed at the most aggressive populations in a heterogeneous tumor.
Effect of weekly administration of bevacizumab, gemcitabine, and oxaliplatin in patients with heavily pretreated ovarian cancer.

Yuji Ikeda, Yoshihiro Kikuchi, Masashi Takano, Tomoko Goto, Hiroko Kouta, Naoki Sasaki, Kazuya Kudoh, Katsutoshi Oda, Tsuneki Nagasaka, Tsunekazu Kita; Ohki Memorial Cancer Center for Women, Tokorozawa, Japan; National Defense Medical College, Tokorozawa, Japan; Nishisaitama-Chuo National Hospital, Tokorozawa, Japan; Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan; Department of Obstetrics and Gynecology, Kawakita general hospital, Tokyo, Japan; Nara Prefectural Nara Hospital, Nara, Japan

Background: The combination therapy of gemcitabine with oxaliplatin (GEMOX) has high activity in patients with ovarian cancer. Bevacizumab (B), a vascular endothelial growth factor specific antibody, enhances chemotherapeutic efficacy through its anti-angiogenic function in various types of tumors. We evaluated the effect of weekly administration of B and GEMOX in heavily-pretreated patients with recurrent or refractory ovarian cancers (ROC). Methods: Nineteen patients with ROC received at least three or more cycles of weekly-B and GEMOX consisting of B (2mg/kg), gemcitabine (300mg/m^2) and oxaliplatin (30mg/m^2). The treatment was continued until the development of progressive disease. The response and adverse effects (AE) were evaluated using the response evaluation criteria in solid tumors (RECIST), CA125 Gynecologic Cancer Intergroup (GCIG) criteria, and common terminology criteria for adverse events (CTCAE) version 3.0. Results: Seventeen (89%) of the 19 patients were primarily stage 3 or 4. Fifteen patients (79%) had received more than three regimens of chemotherapy. All patients were pretreated with a platinum-containing regimen within 6 months and 16 of these patients (84%) were pretreated within 3 months. According to the RECIST evaluation, 2 patients (11%) had a complete response (CR), 6 patients (32%) had a partial remission (PR) and 5 patients (26%) had a stable disease (SD). The response rate (RR; CR+PR) and clinical benefit rate (CBR; CR+PR+SD) were 42% and 68%, respectively. In 10 patients with serous adenocarcinoma, RR was 60%. In 6 patients pretreated with weekly B and pegylated liposomal doxorubicin (PLD), RR was 50%. Median progression-free survival was 5 months (range: 2-11 months). Hematological adverse effects (AE) with grade 3/4 were leukopenia (16%), neutropenia (10%), thrombocytopenia (5%), however, all AE were manageable. Conclusions: Weekly B and GEMOX administration had significant activity with mild AE in patients with ROC especially in serous adenocarcinoma. Notably, the activity was also observed in patients pretreated with weekly B and PLD. These results warrant further prospective study.
Phase Ib study of AMG 386 in combination with paclitaxel (P) and carboplatin (C) in high-risk stage I and stages II-IV epithelial ovarian, primary peritoneal, or fallopian tube cancers.

Antonio Casado, Ana Oaknin, Jean-Francois Baurain, Shirley S. Wong, Xinquin Yang, Benjamin Wu, Zhanyong Don Zhong, Markus Puhlmann, Ignace B. Vergote; Hospital Clínico San Carlos, Madrid, Spain; Hospital Universitari Vall d’Hebron, Barcelona, Spain; Université Catholique de Louvain, Cliniques Universitaires Saint Luc, Brussels, Belgium; Western Hospital, Parkville, Australia; Amgen, South San Francisco, CA; Amgen, Thousand Oaks, CA; University Hospital, Leuven, Belgium

Background: AMG 386 is a first-in-class investigational peptibody that inhibits angiopoietin-1/-2 binding to Tie2. We report on an ongoing, 2-part, open-label phase 1b study of AMG 386 + PC as first-line treatment of high-risk ovarian cancer. Methods: Part 1 enrolled women, GOG performance status 0/1, with newly diagnosed, FIGO high-risk stage I or stages II, IIIA-B (primary debulking surgery; PDS) or IIIC & IV (PDS or interval debulking surgery; IDS) ovarian cancer. Patients (pts) received AMG 386 at 15 mg/kg QW IV + P at 175 mg/m^2 Q3W + C at AUC 6 Q3W for 6 cycles (or until disease progression or unacceptable toxicity); AMG 386 was withheld 4 weeks pre-/post-debulking. Pts completing 6 cycles continued AMG 386 QW as maintenance for up to 18 months. Part 1: incidence of dose-limiting toxicities (DLTs) dictated expansion to 25 pts (part 2). Primary endpoint: DLT incidence; secondary: adverse events (AEs), PK and efficacy measures. Results: At the time of analysis, 16 pts had received 1 dose of AMG 386 + PC and completed 2 cycles of therapy (PDS, n=8; IDS, n=8). No DLTs occurred in part 1. 15 pts continue on-study; 6 pts have received a median of 6 doses of maintenance AMG 386. One pt discontinued due to progression. AEs are tabulated below. One serious AE (decreased appetite; maintenance phase) required hospitalization. AE incidence and type were similar for PDS or IDS. Combination therapy did not affect the PK of AMG 386 or PC. Non-neutralizing antibodies against AMG 386 were detected in 2 pts. Conclusions: AMG 386 at 15 mg/kg QW + PC is tolerable in pts with high-risk ovarian cancer. AMG 386 maintenance was tolerated and associated with few AEs. Updated toxicity and efficacy data will be presented.

<table>
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<th>AEs</th>
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<th>AMG 386 maintenance</th>
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<td>Of specific interest (grade =2)</td>
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<td>Edema</td>
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The combination of intravenous bevacizumab and metronomic oral cyclophosphamide for recurrent platinum-resistant ovarian cancer.

Emma L. Barber, Nikki Lynn Neubauer, Emese Zsiros, Julian C. Schink; Northwestern University, Department of Gynecologic Oncology, Chicago, IL

Background: This study was undertaken to determine the progression free survival and overall survival in heavily pre-treated patients with recurrent ovarian carcinoma treated with bevacizumab and metronomic oral cyclophosphamide. Methods: An IRB-approved retrospective review was performed for all patients with recurrent ovarian, fallopian tube or primary peritoneal carcinomas treated with intravenous bevacizumab 10mg/kg every 14 days and oral cyclophosphamide 50mg daily between January 2006 and December 2010. Response to treatment was determined by change in disease status according to RECIST criteria and/or CA-125 levels. Results: Sixty-six eligible patients were identified with a median age of 58 years. Fifty-five patients (83%) originally had optimal cytoreduction and all were platinum resistant. Median time from diagnosis to beginning bevacizumab and cyclophosphamide was 36 months. Median number of prior chemotherapy treatments was 7.5 (range 3-16). Eight patients (12.1%) had side effects which required discontinuing bevacizumab and cyclophosphamide, most common were hypertension, proteinuria, and fatigue. There was one bowel perforation (1.5%). A complete response was noted in 7 patients (10.6%), partial response was seen in 21 patients (31.8%) with an overall response rate of 42.4%. Fifteen patients (22.7%) had stable disease and 23 (34.8%) had disease progression. Median progression free survival (PFS) for responders was 5 months (range 2-14) and 11 months (range 4-14) for those with a complete response. Median overall survival (OS) from start of bevacizumab and cyclophosphamide for responders was 20 months (range 2-56) and 9 months (range 1-51) for nonresponders. Conclusions: Bevacizumab and cyclophosphamide is an effective, well-tolerated chemotherapy regimen in heavily pre-treated patients with recurrent ovarian carcinoma which significantly improves PFS and OS in responders. Response rates were significantly better than the rates we have reported in this same group of patients receiving topotecan (22%) or liposomal doxorubicin (25%) and were superior to reported rates for single agent bevacizumab (18%) in patients with only 2-3 prior regimens.
ESA use in women with cancer: Consequences of the 2008 FDA clinical alert.

**Kimberly M. Dickinson, Bachir Joseph Sakr; Warren Alpert Medical School of Brown University, Providence, RI; Program in Women’s Oncology, Women and Infants Hospital of Rhode Island, Providence, RI**

**Background:** Erythropoietin stimulating agents (ESA) are used clinically as an alternative to blood transfusions in cancer patients suffering from symptoms of anemia. However, more recent randomized controlled trials of ESA usage concluded that its use is associated with an increased risk of tumor progression and death. As a result, in July 2008 the FDA issued a clinical alert restricting the use of ESA. A reduction in the prescribing of ESA was immediately seen but changes in blood transfusion rates have not been examined. **Methods:** A retrospective chart review was conducted drawing from patients under treatment in the Program in Women’s Oncology at Women and Infant’s Hospital from one year before the clinical alert (August 2007-July 2008) to one year afterward (August 2008-July 2009). The primary outcomes were blood transfusion and ESA administration rates compared across the two time periods. **Results:** The study population (n=776) included patients with a cancer diagnosis who received chemotherapy during one or both time periods. 165 (21.3%) patients received ESA treatment. The total number of ESA treatments administered in the study period of interest was 1,277, with the majority (60%) given prior to the FDA alert. The mean number of ESA treatments in the first time period was 6.39 per person as compared to 0.61 per person in the second time period. Of the study population, 186 (23.8%) patients received at least one blood transfusion. A total of 463 blood transfusions were administered during the entire study period but a significant difference was not observed in the proportion of those delivered prior to the FDA alert (52%) versus after the FDA alert (48%). The average number of transfusions given in the first time period was 2.34 per person, as compared to 2.17 per person in the second period. **Conclusions:** Our results indicate that despite a steep decline in the use of ESA for chemotherapy-induced anemia, blood transfusion rates were not significantly different between the two periods. Interestingly, a slight downward trend was observed from before the FDA alert to after the alert. While more work is needed to understand the implications of these findings, it suggests that resource utilization did not increase despite the reduction in ESA use.

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Background: Optimal carboplatin dosing (CPRx) for patients (pts) with renal dysfunction or low creatinine (Cr) values in the setting of malnutrition and ascites is unknown. Multiple methods have been utilized to estimate Cr clearance (CrCl) but these perform differently in pts with abnormal Cr values. We sought to determine 1) the relationship between adverse events (AE) and baseline CrCl used for CPRx; 2) the effect on CPRx of using Cockcroft-Gault (CG) +/- the NCI/CTEP recommended limits (CGL), Modification of diet in renal disease (MDRD) or Jelliffe Formula (J) renal function estimates. Methods: Retrospective data were drawn from pts treated on GOG 182, a phase III trial of carboplatin doublet vs triplet or sequential doublet combinations in stage III/IV EOC. For patient safety, the protocol was amended to assign the lower limit of Cr at 0.6mg/dl for CPRx. Area under the receiver operating characteristic curve (AUC) was used to describe associations between CrCl and various AE. Sensitivity and positive predictive values (PPV) described the AE rate in pts with CrCl <60ml/min. CPRx for each pt was calculated using J, CG, CGL and MDRD. Results: 3830 evaluable pts had a mean age 58.7yrs, mean BMI 26.8kg/m^2 and mean baseline CrCl 81.9ml/min (range 23.4-239). The AUC statistics (range 0.52-0.64) show that the log(CrCl) was not a good predictor of grade >=3 AE (anemia, thrombocytopenia, febrile neutropenia, auditory, renal, metabolic, neurologic). A cutoff value of CrCl <60 ml/min would have deemed 15% of pts treated on GOG182 ineligible. The range of PPV for the above AEs in pts with CrCl <60 ml/min was 1.8-15%. Using CG, CGL, MDRD instead of J for CPRx would have resulted in >10% decrease in CPRx in 21%, 32% and 12% of pts, respectively. Using CG, CGL, MDRD instead of J for CPRx would have resulted in >10% increase in CPRx in 45%, 9.6% and 5.2% of pts, respectively. Conclusions: Our data do not support excluding patients with CrCl <60ml/min from clinical trials. The new GOG guidelines replacing J with CGL affect CPRx. The clinical significance of this change with regards to toxicity, particularly in pts with abnormally low Cr values, is yet to be determined.
Detection of disseminated tumor cells in bone marrow as an independent prognostic factor in primary ovarian cancer patients.

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Background: Detection of disseminated tumor cells (DTC) in the bone marrow (BM) of breast cancer patients is associated with poor outcome. Recent studies demonstrated that DTC may serve as a prognostic factor in ovarian cancer. The aim of our study was to evaluate the impact of BM status on survival in a large cohort of ovarian cancer patients. Methods: 365 patients with primary ovarian cancer were included into this three-center prospective study. BM aspirates were collected preoperatively from iliac crest. Disseminated tumor cells were identified by immunocytochemistry using the pancytokeratin antibody A45B/B3 and by cytomorphology. Patient outcomes were evaluated using a multivariable Cox regression model. Results: Disseminated tumor cells were detected in 28% of all BM aspirates. The number of CK-positive cells ranged from 1 to 42 per 2x10^6 mononuclear cells. DTC status did not correlate with any of the established clinicopathological factors. The overall survival was significantly shorter among DTC-positive patients compared to DTC-negative patients (51 mo, 95% CI: 35 – 67 mo versus 32 mo, 95% CI: 22 – 42 mo; p = 0.003). However, disease-free survival was not related to DTC-positivity. In the multivariable analysis, BM status, FIGO stage, nodal status, resection status and age were independent predictors of reduced overall survival. Interestingly, a subset of DTCs may have stem cell properties since a subset of these cells (128 out of 228 cases) were SOX2 positive, which is an embryonic stem cell marker. Conclusions: Tumor cell dissemination into bone marrow is a common phenomenon in ovarian cancer. DTC detection has the potential to become an important biomarker for prognostication and may be included as a therapeutic target in future concepts.
Background: The optimal use of BRCA1 germline testing in patients with HGS-OC is unclear. Moreover, BRCA1 germline testing does not provide information on non-germline mechanisms of BRCA1 loss. We investigated the performance of BRCA1 immunohistochemistry (IHC) testing in HGS-OC with known BRCA1 mutation status.

Methods: Eligible patients had HGS-OC, underwent surgery at a single institution between 1997 and 2010, and were tested for germline BRCA1 mutations under IRB-approved protocols. FFPE tumor tissue was used in triplicate to construct a tissue microarray (TMA). Two pathologists, blinded to BRCA1 status, independently scored each sample as BRCA1 IHC present (normal) or absent (abnormal). Whole sections were stained for all samples with absent BRCA1 staining on TMA. A commercially available monoclonal antibody against BRCA1, clone MS110 from Calbiochem (OP92) was used with previously optimized conditions.

Results: 123 samples (30 BRCA1 mutated; 93 BRCA1 wild-type) were analyzed and 47 (38%) had abnormal BRCA1 IHC. Inter-observer agreement on BRCA IHC was high (kappa=0.87). BRCA IHC had a sensitivity of 83.3% (CI: 70.0-96.7%), specificity of 76.3% (CI: 67.7-85.0%), PPV of 53.2% (CI: 38.9-67.5%), and NPV of 93.4% (CI: 87.9-99.0%) for BRCA1 germline mutation. There was a trend towards improved overall survival in the BRCA IHC abnormal vs. normal patients (median survival 82 vs 61 wks, HR 0.70, p=0.12).

Conclusions: BRCA1 IHC is a reproducible and inexpensive test with a high NPV for absence of a BRCA1 germline mutation. The 22 (17.7%) cases with abnormal BRCA1 IHC and wild-type BRCA1 germline status may have other mechanisms of protein loss such as promoter hypermethylation or somatic mutation and are currently being tested for these changes. This rate of non-germline BRCA1 loss in HGS-OC is consistent with data generated by the Tumor Cancer Genome Atlas Network. BRCA1 IHC may be useful as a reliable biomarker for risk stratification in HGS-OC.

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<thead>
<tr>
<th>Germline BRCA1 status</th>
<th>Wild-type</th>
<th>Mutated</th>
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<tr>
<td>BRCA1 IHC</td>
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<tr>
<td>Normal</td>
<td>71 (57.2%)</td>
<td>5 (4.0%)</td>
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<tr>
<td>Abnormal</td>
<td>22 (17.7%)</td>
<td>25 (20.2%)</td>
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What do 676 primary and recurrent ovarian cancer (OC) patients expect from their doctors and therapy management? Results of a German survey of the northeastern German Society of Gynecological Oncology (NOGGO).

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Background: The primary aim of this study was to investigate information needs and preferences among patients with ovarian cancer, focusing especially on doctor-patient relationships and therapy management. Methods: A 42-item questionnaire was developed and validated in a mono-centre phase I study and was then provided to primary and recurrent ovarian cancer patients via internet (online) or as a print-version. In the first part basic data (age, tumour status, therapy) were requested. In the second part, most of the questions try to evaluate the expectations and needs concerning their therapy management and doctor-patients communication. Results: From January to November 2009, a total of 676 (201 online; 475 print version) patients with ovarian cancer from 44 German centres took part in the survey. The median age of the online group was 49 years (range 19-84), for the print group 62 years (26-92). Nearly all patients (98.7%) had a primary surgery and a primary chemotherapy (89%). Asked for side effects during therapy, the most frequent answers were alopecia, paraesthesia/dysaesthesia and fatigue. Most of the patients were content with the completeness and understandability of the explanations about the therapies from their doctors. The three most important aspects, which were proposed by patients to improve therapy against ovarian cancer were: “Doctors should have more time for explanations”, “The therapy should not lead to any loss of hair”, and “The therapy should be more effective”. Conclusions: This study underlines the high need of ovarian cancer patients to discuss all details concerning treatment options and clinical management. As matter of fact, the physician involved in the treatment is the most important source of information.
Correlative study of low serum creatinine and hematological toxicities in Japanese patients with ovarian cancer treated by dose dense TC therapy.

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Background: Dose dense TC (ddTC) is a novel standard therapy for patients (pts) with advanced ovarian cancer, although hematological toxicities (hemTX), especially anemia, may increase as observed in NOVEL trial (JGOG3016). Low serum creatinine (LCr), especially below 0.7 mg/dl, may lead to overestimation of GFR. GOG announced that pts with LCr should use a minimum value of 0.7mg/dl to estimate GFR. The correlation between LCr and hemTX treated by ddTC is unknown. Methods: GFR was determined using the Cockcroft-Gault formula. Serum creatinine concentrations were measured using enzymatic assays. Minimum value of 0.7 mg/dl was not used during this period of time. The carboplatin clearance was then calculated by Calvert equation. HemTX were defined as, Grade 3 or 4 (by CTC-AE ver.4) neutropenia, anemia, and thrombocytopenia. Using electrical chart, frequency of hemTX and correlation between serum creatinine (less than 0.7 or not) were examined. Results: From Feb. 2010 to Dec. 2011, 61 consecutive pts were treated with ddTC. LCr was observed in 73% of pts. No treatment related death occurred. Among 61 pts, 50 (82%), 31 (51%), and 12 (19.6 %) pts experienced Grade3/4 neutropenia, anemia and thrombocytopenia, respectively. HemTX in pts with LCr and the others were as in the Table. Conclusions: LCr is frequent in Japanese female pts. ddTC in practice setting seems safe, and hemTX of ddTC are similar with those observed in NOVEL trial. The rationale using a minimum value of 0.7 mg/dl should be further studied by larger population, such as pts in NOVEL trial.

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<tr>
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<th>G3/4 neutropenia</th>
<th>G3/4 anemia</th>
<th>G3/4 thrombocytopenia</th>
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<tr>
<td>Pts with LCr</td>
<td>36 (80%)</td>
<td>24 (53.3%)</td>
<td>9 (20%)</td>
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<tr>
<td>Pts without LCr</td>
<td>14 (87.5%)</td>
<td>7 (44%)</td>
<td>3 (18.8%)</td>
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Neo-escape: Neoadjuvant extended sequential chemotherapy with adjuvant postoperative treatment for epithelial nonmucinous advanced inoperable peritoneal malignancy.

Christopher John Poole, Andrea Marshall, Helen B Higgins, Julie Fletcher, Sarah Jane Williams, Nangi Lo, Indrajit Nalinika Fernando, Richard Osborne, S. Michael Crawford, Saeed Rafii, Sandeep Gill, Janet A Dunn; University Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom; Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom; University Hospital Birmingham NHS Trust, Birmingham, United Kingdom; Torbay Hospital, Torquay, United Kingdom; Poole Hospital NHS Foundation Trust, Poole, United Kingdom; Airedale General Hospital, Keighley, United Kingdom

Background: Neo-Escape was designed to exploit fully the modest non-cross resistance of carboplatin (CBDCA) and paclitaxel (ptx) in an extended sequential regimen, with dose-dense ptx, and address feasibility of combining gemcitabine (gem) with either CBDCA or ptx. Methods: A randomised phase II trial in patients (pts) with untreated (FIGO stage 3C/4) inoperable ovarian, fallopian, or primary peritoneal carcinoma to assess feasibility of two regimens of sequential neoadjuvant-then-adjuvant chemotherapy (CT): (a) CBDCA AUC 2.5 and gem 1000mg/m² repeated days 1 and 8 q 3 wks x 6 cycles, then ptx 175mg/m² q 2 wks x 6 cycles (CG-P) or (b) CBDCA AUC 6 q 3 wks x 6 cycles, then ptx 175mg/m² and gem 2000mg/m² q 2 wks x 6 cycles (C-PG). All pts were considered for delayed 1st debulking surgery after neoadjuvant CT. The 1st feasibility outcome was % pts completing 12 cycles of CT. Using Fleming's single stage procedure 44 patients on each arm were needed to test null hypothesis of feasibility /H11349 60% with 5% 1-sided significance level and 90% power. 2nd outcomes included safety, PFS and ORR. Pts were stratified by serum albumin, stage and tumor differentiation. Results: 75 pts were recruited Sept 2007 - May 2011 (28 CG-P; 47 C-PG), median age 62 yr (range 21-75). Recruitment to CG-P closed early due to futility. 52% had albumin >35g/L, 68% FIGO stage 3C and 80% poorly differentiated tumors. 64% on CG-P and 55% on C-PG had debulking surgery as planned and a further 4% on CG-P and 13% on C-PG after completion of all CT. For CG-P 35% achieved 0cm, 35% <1cm and 30% ≥ 1cm residuum; for C-PG 34% 0cm, 13% <1cm and 34% ≥1cm, 19% TBC. 14/28 pts on CG-P completed all 12 cycles (feasibility 50%; 95% CI 31-67%); 37/47 pts on C-PG (feasibility 79% (95% CI 64-88). Main reason for early discontinuation was toxicity on CG-P and disease progression on C-PG. Similar proportions of pts on each arm had dose reductions (68%) or delays (86% on CG-P; 89% on C-PG), mainly for toxicity. 82% of pts experienced grade 3/4 toxicity on CG-P; 72% on C-PG. Median PFS for CG-P is 14.3 mths (95% CI 11.6-15.7mths) and 13.0 mths (95% CI 11.5-15.4mths) for C-PG. Conclusions: CG-P was not feasible at these doses using pre-specified criteria, but C-PG is feasible.
Changes of serum glycome in patients suffering from ovarian cancer.

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**Background:** Protein glycosylation plays an important role in many biological processes. Most human serum proteins, with the exception of albumin, are glycosylated. Glycosylation is known to be altered with development of diseases such as cancer. In the case of ovarian cancer, tumor markers among them CA-125 that are clinically used are known to have poor specificity. In addition, they fail to detect the disease at an early stage. Therefore, better biomarkers are needed. The aim of the present research work is to identify new potential glycan biomarkers by analyzing the serum N-glycome of patients suffering from ovarian cancer.

**Methods:** Serum was collected from 67 patients as well as from 33 healthy age-matching women. N-glycans were released from 10 ul serum by PNGase F digestion, permethylated and subsequently analyzed by means of MALDI-TOF mass spectrometry. The SPSS software was used for the statistical analysis.

**Results:** The N-glycome of patients was found to have more fucosylated structures, especially in tri- and tetraantennary sialylated glycans. The PCA analysis indicates that there are significant differences between the glycome of ovarian cancer patients in all stages of the disease and the glycome of healthy controls. We identified 14 potential structures that were divided in two categories, one of monofucosylated structures with high antennarity (sensitivity 94%, specificity 97%) and one containing high-mannose structures and an asialylated structures (sensitivity 97%, specificity 97%).

**Conclusions:** Our study is the first trial to identify major differences between ovarian cancer sera and control sera, which could potentially be used in the future as biomarkers.

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Background: NKTR-102 is a unique topoisomerase 1 inhibitor that provides continuous exposure to SN38. In heavily pretreated pts with PROC (median of 3 prior therapies; 27 pts were platinum refractory), 145 mg/m² NKTR-102 given q14d or q21d demonstrated significant anti-tumor activity (JCO 28:7s, 5013). We present a PK/PD model for CA125 kinetics that can be used to project GCIG response as an aide to selecting dose and schedule. Methods: Data from 55 pts with PROC and elevated CA125 (median baseline = 515 U/mL) were fit with a PK/PD model developed to correlate CA125 dynamics with SN38 conc-time profiles predicted from individual pt dosing history: d[CA125]/dt = Kin*exp(beta*t)*([1-[SN38]]/[IC50+[SN38]])-Kout*[CA125]. Results: CA125 profiles were well described by the model, with a population mean SN38 IC50 of 1.1 ng/mL. Typical min and max SN38 conc during treatment were 1.5 and 3 ng/mL for q14d and 0.9 and 2.4 ng/mL for q21d, indicating that both schedules resulted in SN38 exposure near the IC50. The half-life of CA125 decline was 6.4 days, similar to literature values. 46 of 55 pts had pre- and post-treatment tumor measurements for correlation of CA125 response and tumor size. Overall best response by GCIG and RECIST correlated in 57% of pts. 33% of pts with GCIG response showed declines in tumor size, albeit insufficient to classify as RECIST response. 72% of pts with GCIG SD showed at least SD by RECIST. CA125 vs time was simulated for 1000 pts receiving 145 mg/m² NKTR-102 q14d or q21d, to allow comparison of CA125 and GCIG response between schedules (see table). The % pts per GCIG response was comparable between schedules, supporting use of the better-tolerated q21d regimen. Conclusions: The PK/PD model described CA125 profiles well, providing a tool to predict drug response from SN38 PK data. Close correlation of CA125 with tumor size is consistent with historical use of CA125 as a surrogate marker. Predicted CA125 profiles for NKTR-102 q14d or q21d were similar, suggesting that the better-tolerated q21d schedule will produce results consistent with those from Ph 2.

Model-predicted % pts by response.

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<tr>
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<td>19</td>
<td>23</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>q21d</td>
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Longitudinal health-related quality of life assessment: Implications for prognosis in ovarian cancer.

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Background: Several studies in the oncology literature have demonstrated the prognostic value of baseline quality of life (QoL). However, there is little to no information on the prognostic effects of changes in QoL during treatment. We investigated whether changes in QoL could predict survival in ovarian cancer patients treated with an integrative model of care. Methods: We evaluated 137 ovarian cancer patients treated at our institution between Jan 2001 and Dec 2009 who were available for a minimum follow-up of 3 months. QoL was evaluated at baseline and after 3 months of treatment using EORTC-QLQ-C30. The QLQ-C30 incorporates a global scale, 5 function scales and 8 symptom scales. Patient survival was defined as the time between date of first patient visit and date of death from any cause/date of last contact. Cox regression was performed to evaluate the prognostic significance of baseline and changes in QoL scores after adjusting for age, treatment history and stage at diagnosis. Results: Mean age at diagnosis was 51.1 years. 28 patients were newly diagnosed while 109 were previously treated. Stage at diagnosis was I, 16; II, 15; III, 72; IV, 28; and 6 indeterminate. Median overall survival was 33.5 months (95% CI: 11.5-55.6 months). Baseline QoL scale predictive of survival upon multivariate analysis was nausea/vomiting (p=0.04). Associations between changes in QoL and survival were observed for global function, appetite loss and constipation. Every 10-point increase (improvement) in global function from baseline to 3 months was associated with a 10% decreased risk of death (HR=0.90; 95% CI=0.81 to 0.99, p=0.03). The corresponding HRs for 10-point increase (deterioration) in appetite loss and constipation scales were 1.20 (1.06 to 1.35; p=0.005) and 1.13 (1.02, 1.24; p=0.02) respectively. Conclusions: This exploratory study provides some preliminary evidence to indicate that ovarian cancer patients whose QoL improves within 3 months of treatment have a significantly increased survival time compared to those who fail to demonstrate improvement. These findings might be used in clinical practice to systematically address QoL-related problems of ovarian cancer patients throughout their treatment course.
Technetium-99m sulfur colloid (TSC) as a phenotypic probe for predicting pharmacokinetics (PK) and palmar-plantar erythrodysesthesia (PPE) toxicity of pegylated liposomal doxorubicin (PLD) in patients (pts) with recurrent epithelial ovarian cancer (EOC).

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Background: There is significant variability in the PK and PD (efficacy and toxicity) of PLD. Clearance (CL) of PLD has been proposed to occur primarily via uptake by cells of the mononuclear phagocyte system (MPS) mainly located in the liver, spleen, and blood. TSC is a radioactive colloid used clinically for diagnostic and functional imaging of the MPS. Our aim is to evaluate TSC as a phenotypic probe of MPS activity, which may predict PLD PK and PPE toxicity in pts (n=9) with EOC. Methods: Prior to administration of PLD on cycle 1 day 1 (C1D1), TSC was administered at 10 mCi IVP. Dynamic planar and SPECT/CT images of the liver, spleen and hands were acquired using a gamma camera. Blood samples were collected up to 60 min after TSC and analyzed for radioactivity using a gamma counter. On C1D1, PLD was administered at 40 mg/m² alone or at 30 mg/m² in combination with carboplatin IV over 1 to 3 h. Serial PK samples were obtained from 0h to 672h post PLD dose. Plasma was processed to measure encapsulated and released doxorubicin (dox) using solid phase separation and HPLC. CL of PLD and TSC were calculated by non-compartmental analysis. The grade of PPE toxicity was determined by NCI CTCAE (v4.03) criteria. Results: Nine patients have undergone TSC imaging and eight patients completed TSC blood PK and PLD plasma PK studies. There was a positive linear relationship between TSC CL and encapsulated dox CL (R² = 0.61, p=0.02). When patients were subdivided, there was a stronger relationship between TSC CL and encapsulated dox CL (R² = 0.81, p=0.03) in pts receiving PLD monotherapy. A positive relationship using Spearman’s correlation (ρ=0.84, p=0.006) was also found between maximum grade PPE toxicity developed and estimated AUC of encapsulated dox in hands [(TSC AUC_Blood)/(TSC AUC_Hand)] × Encapsulated Dox AUC_Plasma. Conclusions: These results suggest that TSC is a probe for MPS function and PLD PK and PD and may be used to individualize PLD therapy in pts with EOC. In addition, our findings suggest TSC may be able to predict the development of PPE in patients.

Sexual function, sexual activity, and quality of life in women with ovarian and endometrial cancer.

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Background: Gynecological cancer (GC) is generally assumed to have an impact on sexual function and activity. Although there are several studies addressing the issue, case control studies are currently limited.

Methods: We performed a cross-sectional investigation of sexual function and activity utilizing the sexual activity questionnaire, the female sexual function index, and parts of the EORTC QLQ C30. Patients with gynecological cancer (GC) like ovarian and endometrial cancer were compared with a control group (C) of non-cancer patients. Inclusion of GC was only allowed if treatment was completed ≥12 months previously and patients were disease-free.

Results: The questionnaires were sent out to 727 women (335 x GC and 392 x C), 22.8% of which responded. Response rates in both groups were equivalent (79 pts with GC [23.6%] and 87 control subjects [22.2%]). Median age was 57 years (C) and 62 years (GC), respectively (p=0.237). 51.5% (C) and 59.5% (GC) were not sexually active, mainly owing to lack of a partner (37%) or lack of interest (21%) in controls and lack of interest (40%, p<0.05), self-reported physical problems (31.9%, p<0.05), and physical problems of the partner (21%, p<0.05). There were significant differences between both groups in the SAQ discomfort score (p<0.05). We did not observe significant differences in quality of life or other scores regarding sexuality.

Conclusions: About half of the women in both groups were not sexually active. However, reasons for non-activity differ. Quality of sexuality tends to be impaired in GC patients, but this seems not to influence quality of life. A shift of priority caused by substantial anxiety regarding cancer specific survival might explain our findings.

Panitumumab and pegylated liposomal doxorubicin in platinum-resistant epithelial ovarian cancer with KRAS wild-type: The PaLiDo study, a phase II nonrandomized multicenter study.

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**Background:** Ovarian cancer (OC) patients with platinum-resistant recurrent disease have few therapeutic options and the response rates are only 10-20% using non-cross-resistant chemotherapeutic agents. The increasing number of negative trials for OC treatment has prompted an evaluation of new biologic agents, which in combination with chemotherapy may result in improvement in survival. Panitumumab is a fully human monoclonal antibody specific to the epidermal growth factor receptor (EGFR). No previous studies have evaluated the effect of panitumumab in OC based on KRAS mutation status. The main purpose was to investigate the response rate in platinum-resistant, KRAS wild-type OC patients treated with pegylated liposomal doxorubicin (PLD) supplemented with panitumumab. **Methods:** Major eligibility criteria were confirmed stage I-IV primary epithelial ovarian/fallopian/peritoneal cancer patients with progression either during or within 6 months after end of first or second line platinum-based chemotherapy. Only patients with measurable disease by CA125 criteria and with KRAS wild type were eligible. Patients were treated with panitumumab 6 mg/kg day 1 and day 15 and with PLD 40 mg/m² day 1, every 4 weeks. Tumor assessment was performed at baseline and at every third cycle according to CA-125 criteria. **Results:** A total of 46 patients were enrolled by 6 study sites in this multi-institutional phase II trial. Within the population evaluable for response (N=33), there was 8 CA125 responders for an overall response rate of 24.3%. Progression-free and overall survival in the intention-to-treat population (N=43) was 2.7 months (2.5-3.2 months, 95%CI) and 8.1 months (5.6-11.7 months, 95%CI), respectively. The most common treatment related grade 3 toxicities included skin toxicity (42%), fatigue (19%) and vomiting (12%). **Conclusions:** The combination of PLD and panitumumab demonstrates efficacy in platinum refractory/resistant patients although the dermatologic toxicity was considerable.
Effect of tumor-infiltrating T-lymphocytes on the aggressiveness of epithelial ovarian tumors.

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Background: Borderline ovarian tumors (BOT) are a low-grade form of ovarian malignancy with significantly less aggressive behavior than epithelial ovarian cancer (EOC). Since there is neither convincing scientific evidence nor a marker capable of predicting BOT’s behavior, we analyzed the role of immune tolerance in differential disease outcome. EOC and BOT were chosen due to similar disease etiology, despite different disease courses. Increased numbers of T-cell subpopulations infiltrate malignant tumors, so we used epigenetic tests to determine the prevalence of regulatory T-cells (Treg) and overall-T-Lymphocytes (oTL) in EOC and BOT. Methods: The ovarian cancer samples were provided by the European multicentric OVCAD study. The BOT samples were obtained from Tumor Bank Ovarian Cancer at Charité Campus Virchow (Germany). Samples and clinical data were prospectively collected and documented using validated SOPs. DNA was bisulphite-converted and forwarded to methylation-specific RT-PCR for CD3 and FOXP3 loci. Results: We evaluated 90 high-grade EOC, 12 BOT with invasive implants and 25 non-invasive BOT samples. Higher oTL-values correlate with mortality (p=0.008) and recurrence (p<0.001), while higher Treg levels correlate with recurrence (p=0.028). Patients with non-invasive BOT have lower oTL (p=0.019) and Treg (p=0.0005) levels than patients with invasive BOT and EOC, while BOT (both invasive and non-invasive) patients have lower Treg-to-oTL ratios than EOC patients (p=0.0005). Finally, oTL levels associate with overall survival in EOC (p=0.042). Conclusions: We observed a strict correlation between tumor-type, Treg and oTL levels, as well as Treg-to-oTL ratio. This is in agreement with our hypothesis that disease aggressiveness is associated with the amount tumor-infiltrating lymphocytes and may provide the explanation for differing disease courses in EOC and BOT.
An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer.

Background: OCEANS met its primary end point with a statistically significant and clinically meaningful hazard ratio for progression-free survival (PFS) of 0.484. Secondary end points included objective response rate, overall survival, and safety. Eleven additional months of safety data were collected after the data cut-off date for the final PFS analysis event and updated safety analyses were performed. Methods: Eligible patients (pts) were randomized to arm A: GC (G [1000 mg/m^2 days 1 and 8] and C [AUC 4, day 1], q21d for 6–10 cycles) + concurrent PL (q21d), followed by PL until PD or unacceptable toxicity; or arm B: GC + concurrent BV (15 mg/kg q21d), followed by BV until PD or unacceptable toxicity. All adverse events (AE) were recorded and graded per NCI-CTCAE v3.0. Results: The incidence of any grade AE was 100% in both arms and of SAEs was 25.3% (PL arm) and 35.6% (BV arm). The rates of proteinuria, hypertension (HTN), reversible posterior leukoencephalopathy syndrome (RPLS), thrombocytopenia and epistaxis were higher in the BV arm. More pts in the BV arm (20.6%) than in the PL arm (4.7%) experienced an AE that led to discontinuation of study drug, in the BV arm most commonly due to HTN (4%), proteinuria (2.8%), epistaxis (1.2%), thrombocytopenia (1.6%) and RPLS (0.8%). Median number of BV cycles in pts with G ≥3 proteinuria was 22.5 and the AE resolved in 91.7% of pts. Among the pts with G ≥3 HTN, the median number of BV cycles was 16.5 and the AE resolved in 72.7% of pts. Conclusions: The overall safety profile was similar to that seen at the time of the final PFS analysis. Higher incidences of proteinuria and HTN were possibly related to longer BV treatment duration and resolved in the majority of pts.

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>GC + PL (n=233)</th>
<th>GC + BV (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding (non-CNS), all G</td>
<td>64 (27.5)</td>
<td>158 (64)</td>
</tr>
<tr>
<td>Bleeding (non-CNS), G ≥3</td>
<td>2 (0.9)</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>Epistaxis, G ≥3</td>
<td>1 (0.4)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>HTN, all G</td>
<td>20 (8.6)</td>
<td>107 (43.3)</td>
</tr>
<tr>
<td>HTN, G ≥3</td>
<td>1 (0.4)</td>
<td>44 (17.8)</td>
</tr>
<tr>
<td>Fistula/abscess, all G</td>
<td>1 (0.4)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>GIP, all G</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proteinuria, G ≥3</td>
<td>2 (0.9)</td>
<td>24 (9.7)</td>
</tr>
<tr>
<td>Thrombocytopenia, G ≥3</td>
<td>79 (34)</td>
<td>99 (40)</td>
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The impact of obesity on time to recurrence in ovarian cancer: A retrospective study.

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**Background:** There has been conflicting data regarding the relationship between obesity and progression free survival in patients with ovarian cancer. There has been some evidence to suggest that obesity results in altered tumor biology and a poorer prognosis in these patients. The aim of this study was to examine whether obesity is a risk factor for time to recurrence in primary epithelial ovarian cancer. **Methods:** A multicenter retrospective chart review was performed at Mercy Medical Center and University of Michigan Medical Center. 591 patients were diagnosed with primary epithelial ovarian cancer between 2004-2009. However, 221 patients were excluded from the analysis because of persistent or progressive disease, treatment with neoadjuvant chemotherapy, presence of synchronous tumors or incomplete follow-up data. 370 patients were eligible for analysis. Data collected included: height and weight at the time of surgery, age, race, medical co-morbid illnesses, tumor stage, grade and histology. Treatment related data such as number of cycles of adjuvant chemotherapy; and optimal versus suboptimal tumor debulking was also collected. Body mass index (BMI) was defined according to WHO 2004 criteria. Women with a BMI greater than 30 were categorized as obese. The diagnosis of recurrence was made by positive radiological or pathological diagnosis of cancer recurrence after patient had surgery, received adjuvant chemotherapy and had no clinical, radiological or serological evidence of recurrence during this time. The time to recurrence was then quantified in terms of months from the initial surgery. Survival analyses were performed with the Kaplan-Meier method and compared using log-rank testing. Time to recurrence was analyzed using Mann-Whitney U and Wilcoxon W tests. **Results:** 130 (35%) obese patients were compared with 240 (65%) non obese patients. A recurrence was documented in 125 (47.9%) non obese patients and 49 (37.7%) obese patients. Time to recurrence between both BMI groups was found to be identical, at 15 months (p=1.0). The progression free survival was similar in both obese and non obese subjects (p=0.118). **Conclusions:** Obesity does not impact the time to recurrence in patients with primary ovarian cancer.
The impact of interval cytoreduction and age in advanced-stage ovarian cancer: A GOG ancillary study.

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Background: To determine if an age group exists for which interval cytoreductive surgery (ICS) in patients with suboptimal residual disease at primary surgery influences progression free survival (PFS) and overall survival (OS) among women with advanced ovarian cancer treated on GOG 182. Methods: GOG 182 was a prospective, randomized trial of first-line chemotherapy in patients with advanced ovarian cancer. Patients with both optimal and suboptimal residual disease were included, and those with suboptimal residual were considered for ICS, with intent registered and stratified prior to randomization. Patients were randomized to one of five chemotherapy arms, employing combinations of either two or three agents delivered intravenously, with a control arm of paclitaxel and carboplatin. A retrospective analysis was approved by the GOG Ancillary Study Committee to investigate the influence of age on treatment and outcomes. In that analysis, Cox regression was used to identify independent prognostic factors and estimate their covariate effects on the adjusted PFS and OS of patients with suboptimal residual disease. Statistical significance was set at \( p < 0.05 \). Results: Among the entire eligible study population, 28% (n=1,042) were registered with suboptimal residual disease (> 1 cm) and 109 of these patients elected to undergo ICS. Hazard ratios (HR) were determined for patients undergoing ICS with reference to patients with suboptimal disease not undergoing ICS. Based on the most current follow-up data, the HR for progression or death was not statistically different between the groups, but the HR of death alone was significant at 0.72 (95% CI: 0.57–0.92, \( p = 0.008 \)). There was no significant association of age with ICS in either the PFS or the OS model. Conclusions: In this trial, a patient’s age did not influence the effect of ICS on PFS or OS. There is no demonstrable benefit in PFS associated with ICS, but there was a statistically significant improvement in OS. To elucidate this finding, further study is warranted, likely in the form of a meta-analysis incorporating data from other prospective trials.
The impact of interval from surgery to chemotherapy and age in advanced-stage ovarian cancer: A GOG ancillary study.

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Background: To determine if an age group exists for which the interval from surgery to the initiation of chemotherapy influences progression free survival (PFS) and overall survival (OS) among women with advanced ovarian cancer treated on GOG 182. Methods: GOG 182 was a prospective, randomized trial of first-line chemotherapy in patients with advanced ovarian cancer, including those with optimal and suboptimal residual disease. Patients were randomized to one of five chemotherapy arms, employing combinations of either two or three agents delivered intravenously, with a control arm of paclitaxel and carboplatin. Chemotherapy was to be initiated within 12 weeks of primary surgery. A retrospective analysis was approved by the GOG Ancillary Study Committee to investigate the influence of age on treatment and outcomes. In that analysis, Cox regression was used to identify independent prognostic factors and estimate their covariate effects on the adjusted PFS and OS of the study population. Statistical significance was set at p<0.05. Results: The primary analysis of GOG 182 showed no differences in PFS or OS for any of the experimental arms when compared to the control regimen, and it was felt that the data from all arms could be aggregated for this analysis. Data for all regimens was pooled, and the time interval from surgery to chemotherapy was examined as a prognostic factor of survival. The interval had no statistically significant association with PFS (p=0.105). In the OS model, though, the functional form of the log interval was both significantly linear and nonlinear (p<0.001). After being flat until about 20 days (21.2 days; 95% CI, 15.0–28.2 days), the plot of log interval against log hazard increases, suggesting a changepoint time after which the associated risk of death increases. Conclusions: In this study, time interval from surgery to chemotherapy had no impact on PFS, but there was evidence of a potential time-dependent relationship with OS, which might be elucidated with a meta-analysis incorporating data from other prospective trials. Our observations did not appear to be influenced by patient age. Overall, these findings can reassure patients who are recuperating from extensive cancer surgery.
Treatment reality in elderly patients with advanced ovarian cancer: A prospective analysis of the OVCAD consortium.

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Background: Approximately one third of women diagnosed with ovarian cancer are 70 years or older. Standard therapy of ovarian cancer including radical cytoreduction and combination chemotherapy has considerable morbidity and information regarding treatment reality in elderly patients with ovarian cancer is very limited. Methods: Patients with primary epithelial ovarian cancer FIGO-stages IIB-IV were prospectively included in 5 European cancer centers. All patients underwent surgery with the intent of maximal cytoreduction and platinum-based chemotherapy. To analyze treatment strategies and outcome in the elderly, patients were subdivided in <70 years and ≥70 years of age and compared regarding clinicopathological variables and prognosis. Results: A total of 275 patients were included and followed for a median of 25 months. Median age of the total cohort was 58 (18-85) years with only 47 patients (17.1%) ≥70 years old. Age itself was not a prognostic factor for progression free survival (PFS) in multivariate analysis. 30-days mortality rate after primary surgery was 3.6% in elderly patients compared to 0.6% in patients <70 years (p=0.153). Surgery was less radical in patients ≥70 (e.g. fewer lymph node dissections p<0.001) and the percentage of patients with residual disease after surgery was higher in elderly (44.7%) compared to younger patients (28.5%) despite similar FIGO stage distribution (p=0.029). Furthermore, elderly received more often mono-chemotherapy (p<0.001). Consequently, outcome was less favorable in patients ≥70 compared to patients <70 years (75% overall survival 16 vs. 28 months; p=0.002 and median PFS 14 vs. 20 months; p=0.182). Conclusions: In this prospective European multicenter study, ovarian cancer patients age 70 and older were treated significantly less radical and had unfavorable outcome compared to younger patients. Specific trials for elderly patients focusing on surgical as well as chemotherapeutic aspects are therefore highly desirable to gain more information in an aging society.

NGR-hTNF and doxorubicin in relapsed ovarian cancer (OC).

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Background: NGR-hTNF (asparagine-glycine-arginine human tumor necrosis factor) is able to promote antitumor immune responses and to improve the intratumoral doxorubicin (D) uptake by selectively damaging tumor vessels. Methods: OC patients (pts) with progressive disease (PD) after n ≥ 1 platinum/taxane regimen and with a platinum free interval lower than 6 months (PFI <6) or ranging from 6 to 12 months (PFI 6-12) received NGR-hTNF (N) 0.8 µg/m² and D 60 mg/m² on day 1 every 3 weeks. Primary endpoint of this phase 2 trial was response rate by RECIST criteria with a target of ≥ 6/37 responding pts. Secondary aims were progression free survival (PFS) and overall survival (OS). Results: 37 pts (median age 57 years; PS 0/1 32/5; PFI <6 25/12; prior regimens 1-5) were enrolled. Median baseline peripheral blood lymphocyte count (PBLC) was 1.6/mL (interquartile range 1.2-2.1). In all, 177 cycles were given, with 18 pts (49%) receiving ≥ 6 cycles and 12 pts (32%) 8 cycles. Neither grade 3/4 adverse events (AEs) related to N nor increase of D-related AEs were noted. Common grade 1/2 AEs included chills (65%). Eight pts (23%; 95% CI 12-39) had partial response (PR; 2 with PFI <6 and 6 with PFI 6-12; median duration: 8.2 months). Fifteen pts had stable disease (SD, 43%; 10 with PFI <6 and 5 with PFI 6-12; median duration: 4.9 months) for an overall disease control (DC, PR+SD) rate of 66%. Mean changes from baseline in target tumor size after 2, 4, 6, and 8 cycles were 2%, -54%, -69%, and -77%, respectively. Median PFS was 5.0 months (95% CI 3.1-6.9) and median OS was 17.0 months (10.4-23.6). In pts with PFI <6 or 6-12, median PFS were 3.8 and 7.8 months (p=.03) and median OS were 14.3 and 20.1 months (p=.14), respectively. Pts with DC had longer median OS than those with early PD (24.0 and 4.9 months, respectively, p=.02). Longer PFI (p=.03) and higher PBLC (p=.01) were associated with better PFS, while OS correlated only with PBLC (p=.001). In the subset with PFI <6, pts with PBLC ≥ or <1.2/mL (1st quartile) had median PFS of 4.9 and 2.6 months (p=.02) and median OS of 15.8 and 4.3 months (p=.0001), respectively. Conclusions: A randomized phase II trial is currently testing D ± NGR-hTNF in pts with PFI <6 (refractory/resistant). The role of PBLC as blood-based biomarker deserves further investigation.

The effect of the APPRISE mandate on use of erythropoiesis-stimulating agents and transfusion rates in ovarian cancer patients.

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Background: Erythropoiesis-stimulating agents (ESAs) have long been used to support chemotherapy-induced anemia in patients with epithelial ovarian cancer (EOC). Recent studies have demonstrated that ESAs may lead to increased tumor growth and shorter survival. The FDA mandated new guidelines (APPRISE, for Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) for consenting patients before ESA administration. We sought to quantify the change in ESA use and RBC transfusion rates after the APPRISE mandate was instituted. Methods: A retrospective chart review identified patients with EOC undergoing chemotherapy after initiating the APPRISE mandate. A similar subset of patients treated prior to the APPRISE guidelines served as a control cohort. Abstracted data included patient demographics, primary or second line treatment status, chemotherapy regimen, number of patients requiring ESA or RBCs, or both, and a cost savings analysis. Results: 84 patients with EOC were identified as having undergone 367 cycles of first or second line chemotherapy after the APPRISE guidelines were instituted. A matched set of 88 patients receiving 613 cycles of chemotherapy within a year prior to institution of the APPRISE guidelines was analyzed for comparison. The two groups were statistically similar. Most patients in each group were initially diagnosed with advanced stage disease, were receiving primary chemotherapy, and were receiving taxane/platinum-based chemotherapy. 45 of 88 patients (51%) in the pre-APPRISE group received a total of 196 ESA injections compared to 0 of 84 patients (0%) in the post-APPRISE group. In spite of discontinuing the use of ESAs and no change in transfusion thresholds, RBC transfusion in the post-APPRISE group was similar to that in the pre-APPRISE group (8.3% vs. 14.8%, p=.28). Omission of ESAs in the post-APPRISE group resulted in a cost-savings of an estimated $700,000 in billable charges. Conclusions: In our institution, the APPRISE guidelines resulted in complete cessation of ESA use in patients with EOC, resulting in considerable cost savings. Importantly, RBC transfusion rates did not increase after the guidelines were imposed.

A phase Ib study of the combination of temsirolimus (T) and pegylated liposomal doxorubicin (PLD) in advanced or recurrent breast, endometrial, and ovarian cancer.

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Background: PLD is active in metastatic breast, endometrial and ovarian cancer. Preclinical studies suggest that mTOR inhibitors (mTORi), such as T, have an additive therapeutic effect to chemotherapy and resistance to doxorubicin can be reversed by adding an mTORi. Therefore, the combination of T and PLD is highly promising. Methods: This phase I study assessed the maximum tolerated dose (MTD), safety and activity of the combination of T and PLD in advanced or recurrent breast, endometrial or ovarian cancer. Patients (pts) who were not previously treated with PLD or T, with adequate organ function were eligible. After a two week run in period with T iv once weekly, PLD iv once every four weeks was added. In case of clinical benefit, pts were treated for a maximum of 9 cycles combination therapy. T could be continued as monotherapy afterwards. The MTD was defined as the highest dose at which ≤ 1 dose limiting toxicity (DLT) had been observed among 6 pts. FDG PET scans were performed at baseline and after 2 and 6 wks to assess the effect on tumor metabolism. Pharmacokinetic (PK) sampling was performed during cycle 1. Results: 20 pts were enrolled. On the 4th dose level with 20 mg T and 40 mg/m² PLD 2 DLTs occurred in 6 pts: a grade 3 thrombocytopenic bleeding and a grade 3 skin toxicity. Therefore, the MTD was assessed at 15 mg T and 40 mg/m² PLD. Adverse events (all grades/grade 3-4 in %) occurring most frequently were fatigue (84/5), nausea (84/16), mucositis (79/21), vomiting (74/16) and anorexia (74/0). Furthermore, rash and hand foot syndrome occurred both in 53% of pts, with 11% and 21% grade 3 respectively. 3 pts had a confirmed PR and 9 had SD (> 3 months). The mean progression free survival (PFS) was 4.9 months with 2 pts still on treatment. Results of FDG PET and PK data are currently being analyzed and will be presented. Conclusions: The combination of T and PLD is safe and tolerable. The MTD was assessed at PLD 40 mg/m² once every 4 weeks and T 15 mg weekly. The activity of this combination in breast, endometrial and ovarian cancer pts is promising and warrants further studies.
Phase I safety study of farletuzumab, carboplatin, and pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive epithelial ovarian cancer (EOC).

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Background: Farletuzumab (FAR) is a humanized monoclonal antibody that binds to folate receptor-α, a target which is largely absent in normal epithelium and over-expressed in EOC. A phase I and a phase II study indicate potential utility of FAR in combination with carboplatin/paclitaxel in recurrent platinum sensitive EOC. This study assessed safety and efficacy of FAR in combination with PLD/carboplatin, which has been demonstrated to have greater efficacy than carboplatin/paclitaxel in women with platinum-sensitive EOC. Methods: A multicenter, single-arm study enrolled 15 patients with platinum-sensitive EOC in first or second relapse defined by either CA-125 or RECIST. The primary endpoint is to assess safety of FAR plus PLD/carboplatin in this population. Patients were treated with weekly FAR 2.5 mg/kg plus carboplatin AUC 4-5 and PLD 30 mg/m² every 4 weeks for 6 cycles, followed by maintenance treatment with single agent FAR until disease progression. Initial dosing of weekly 2.5 mg/kg was later amended to 7.5 mg/kg every 3 weeks. Results: 13 of 15 patients completed 6 cycles of combination therapy; one received a total of 12 cycles of chemotherapy. Two patients progressed during combination therapy: one received 3 cycles, the other 5 cycles. The median number of subsequent single agent maintenance cycles was 8 (range 0-13). No grade 4 toxicities were observed. Of 20 grade 3 toxicities in 14 patients, 3 (1 fatigue; 2 small bowel obstructions in the same patient) were deemed by the investigator to be possibly related to FAR. These events were seen during the combination phase and were deemed by the investigator to be also possibly related to chemotherapy. All patients demonstrated clinical benefit: 1 complete response, 10 partial response and 4 stable disease. 7 patients have come off study, all for disease progression; a median PFS of 11 months was noted. 8 patients remain on study. Conclusions: These preliminary data indicate that the safety profile of FAR in combination with carboplatin and PLD is consistent with that historically recorded for carboplatin and PLD alone. Complete safety profile will be assessed; PK data and final results will be presented.
Factors associated with an increased risk of recurrence in women with ovarian granulosa cell tumors.

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Background: There is emerging data in different malignancies, including gynecologic cancers, demonstrating factors independent of a patient’s tumor characteristics, which are associated with an increased risk of cancer recurrence. The goal of this study is to determine demographic and prognostic factors affecting recurrence of disease (RD) in women with ovarian granulosa cell tumors (GCT).

Methods: A dual-institution retrospective analysis of patients diagnosed with GCT between 1995 and 2010. Demographics including age, race, BMI, stage, diabetes (DM), adjuvant treatment, and progression free survival (PFS) were extracted. Hazard ratios for recurrence were estimated by univariate and multivariate Cox regression models.

Results: One hundred nine women identified with a median age of 50 (range 12-87). Fifty-six (57.1%) were Caucasian, 32 (32.7%) African American, and 10 (10.2%) were other. Median BMI was 29 (range 12-57). Twenty-one patients had DM. The majority of women had stage I disease (89.0%), 7 (6.4%) had stage II/III disease, and 5 were unstaged. In univariate analysis, DM showed the strongest association with recurrence (HR 3.56, 95% CI: 1.57-8.11). Non-white race was also associated with higher risk of RD, though the association was not statistically significant (HR 1.74, 95% CI: 0.78-3.87). The association between DM and RD was also found in multivariate analysis controlling for all factors including non-white race and BMI (HR 2.99, 95% CI: 1.11-8.08). Only 19 (17%) patients received adjuvant chemotherapy consisting of one of two different adjuvant chemotherapy regimens bleomycin, etoposide, and cisplatin or paclitaxel and carboplatin, however there was no difference in outcome based on chemotherapy regimen (p=0.24).

Conclusions: This is the largest study analyzing factors associated with risk of recurrence in women with ovarian GCT. Studies have demonstrated higher morbidity among diabetic patients with breast and colon cancer and this may be modifiable with metformin. Our results emphasize that diabetes is one of the strongest predictors of recurrent disease in patients with ovarian GCT. Further studies are necessary to evaluate the effect of other factors such as adjuvant chemotherapy.
Application of an ointment with high radical protection factor as a prevention strategy against PPE.

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Background: Pegylated liposomal doxorubicin has proved to be highly efficient in the treatment of various tumors. Depending on the application protocol, up to 80% of patients develop palmar-plantar erythrodysesthesia (PPE). So far, a prevention strategy is still unknown. Recently, it was shown that parts of the chemotherapeutics were excreted with the sweat onto the skin surface, spreading there homogeneously and penetrating into the stratum corneum. The formation of free radicals in the tissue results in PPE. The aim of the study was to investigate if a topically applied ointment containing antioxidants with high radical protection factor (RPF) can be a PPE prevention strategy. Methods: 20 patients with ovarian carcinoma, who had been treated with pegylated liposomal doxorubicin (40 mg/m²), were investigated. They applied the ointment at least twice daily, 2 days before and during 3 cycles of chemotherapy. Their skin condition was examined by a trained dermatologist. Results: From 20 patients enrolled in the study, only 12 (60%) met the conditions by applying the cream at least twice daily in the palmar and plantar regions. These patients did not develop PPE. One patient died in the 2nd cycle of therapy. 7 patients (35%) did not follow the ointment application protocol for various reasons; 6 of them developed PPE and resumed ointment application thereafter. As a result, PPE disappeared or was strongly reduced in these patients so that chemotherapy could be continued. Due to the small group of patients, the fact that PPE was not induced in patients who had applied the ointment regularly can be generalized only restrictedly. Far more interesting are the findings in those patients, who had stopped ointment application during chemotherapy and developed PPE, which disappeared after they resumed applying the ointment. The regression or distinct reduction of PPE after re-application of the ointment clearly proves the efficacy of this strategy. Conclusions: The topical application of an ointment containing antioxidants with high radical protection factor (RPF) could be an efficient strategy against the development of PPE during chemotherapy.
A phase I, dose escalation trial to assess the safety and biological activity of recombinant human interleukin-18 (SB-485232) in combination with pegylated liposomal doxorubicin in platinum-resistant recurrent ovarian cancer.

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Background: SB-485232, a recombinant human form of interleukin-18 (IL-18), is being studied as a novel cytokine for tumor immunotherapy. IL-18 has been shown to increase the anti-tumor activity of doxorubicin in other cancer mouse models. Methods: This multi-center study enrolled 16 patients (pts), and evaluated four cycles (28 days each) of standard pegylated liposomal doxorubicin (PLD) (40 mg/m² day 1) in combination with increasing doses of IL-18 (1, 3, 10, 30, and 100 mg/kg) on days 2 and 9 of each cycle with a 1 yr follow-up to further evaluate safety and efficacy. Results: Of the 16 pts, 10 (63%) completed study treatment and 6 (37%) did not because of disease progression (5 pts) and PLD hypersensitivity (1 pt). Thirteen (82%) were platinum resistant/refractory having received a median of > 3 prior lines of therapy. SB-485232 up to 100 mg/kg in combination with PLD had an acceptable safety profile. All 16 pts experienced at least 1 AE including chills (81%), nausea (75%), anemia (63%), fatigue (56%), hyperglycemia, and pyrexia (50% each). Eight of 16 pts had Grade 3 AEs including anemia (19%), and 6% each for abdominal pain, asthenia, dehydration, PLD hypersensitivity, edema, fatigue, hyperglycemia, hyperkalemia, jaundice, pain, nausea, vomiting, and pyelonephritis. There were no grade 4/5 AEs. Four subjects experienced 10 non-fatal SAEs with 3 related to study drug: anemia, PLD hypersensitivity, and cytokine release syndrome. Maximal SB-485232 biological activity, assessed by peripheral blood NK and T cell markers, was observed at 10mg/kg-100mg/kg. This drug combination resulted in a 6% partial response rate (RR) and a 38% stable disease rate using RECIST 1.0. Median (95% CI) time of progression-free survival (PFS) was 4.50 (3.52, --) months. Conclusions: The SB-485232/PLD combination was tolerable with minimal toxicity. These preliminary efficacy data are comparable to the historical RR and PFS observed with PLD monotherapy in platinum-resistant ovarian cancer. However, given the small sample size, this combination warrants further investigation.
Effect of BRCA mutation on prognosis in patients with ovarian cancer: A systematic review and meta-analysis.

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Background: To investigate whether the germ-line mutations of BRCA 1 and 2 in patients with ovarian cancer are associated with disease outcome. Methods: A systematic search of the literature was performed using search terms related to BRCA, ovarian cancer and prognosis. Studies were considered eligible if they reported the outcome of ovarian cancer in patients with BRCA 1 and/or 2 mutations compared with patients with sporadic ovarian cancer or / and no BRCA mutation. Cohort and case-control designs were included. Pooled Hazard Ratios (HR) were estimated with fixed or random effects models, depending on between-studies heterogeneity. Results: Of 2,340 titles identified, 26 articles met the inclusion criteria. Of these, 6 studies were excluded from the analysis due to duplication of results (n=1) and lack of data to calculate HR (n=5). Patients with BRCA 1 or 2 mutations had better survival compared with control group both in cohort (HR: 0.58, 95% Confidence Interval (CI) 0.42-0.79, p-value 0.0005) and in case-control (HR: 0.65, 95% CI 0.45-0.93, p-value = 0.02) studies. When only patients with BRCA 1 mutation were analyzed, the survival benefit remained significant (HR: 0.67, 95% CI 0.53-0.85, p-value = 0.001). Furthermore, the differential survival benefit of the mutation groups was even more evident among patients with BRCA 2 mutation (HR: 0.43, 95% CI: 0.30-0.63, p-value < 0.0001). A direct comparison of patients with BRCA 1 vs. BRCA 2 mutations (4 studies) revealed a significantly better survival for BRCA 2 mutation carriers (HR: 0.53, 95% CI: 0.33-0.85, p-value = 0.009). Conclusions: Our results confirm the hypothesis that BRCA status is a prognostic factor in patients with ovarian cancer. Based on these results, the use of BRCA status as a stratifying factor in therapeutic ovarian cancer trials seems to be fully justifiable. The stronger association between survival and BRCA 2 mutation, compared with BRCA 1, suggests a different nature of the dysfunction of these 2 genes.
Management of antiangiogenics’ renovascular safety in ovarian cancer subgroup and intermediate results of the MARS study.

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Background: Anti-VEGF drugs (AVD) are widely used in cancer patients (pts). Hypertension (HTN) and proteinuria (Pu) are class-side-effects of AVD, related to the inhibition of the VEGF pathway. The MARS study has been conducted to assess the renovascular tolerance of these drugs in the clinical setting. Methods: Hypertension (HTN) and proteinuria (Pu) are class-side-effects of anti-VEGF drugs (AVD), related to the inhibition of the VEGF pathway. The MARS study has been conducted to assess the renovascular tolerance of these drugs in the clinical setting. Results: Among 77 OC pts been included, 38 completed the study to date (1-year follow-up (f/u)). Median age at inclusion (introduction of the AVD) was 62 years. Diabetes and HTN prevalences were 5.2% and 7.9%, respectively. Baseline renal assessment retrieved: Pu 13.2%, Hu 7.9%, mean aMDRD 80.9 ml/min/1.73m² and 3 pts with aMDRD<60. The incidence of de novo Pu during f/u was 36.4% (Table). All pts with Pu at inclusion improved, except one. Among pts with de novo Pu, 58.3% afterwards improved/normalized. No Grade 3/4 Pu has been reported (at inclusion or during f/u) and no Hu. 17.1% developed HTN. In addition, a mean renal function decrease of -2.7 ml/min/1.73m²/year was observed and 4 pts had aMDRD<60 at the end of f/u. 36.4% had grade 1 SCr increase (median increase of 15.9%) No thrombotic micro-angiopathy (TMA) has been reported. Conclusions: The results of the MARS subgroup of OC pts shows that 1) TMA remains rare, 2) Pu develops in 36.4% of the pts, however with no Grade 3/4, 3) less than 20% developed HTN, and 4) renal function was not especially impaired. Furthermore, in case of a renovascular effect, investigators followed the recommendations from the French Society of Nephrology (Halimi JM et Al. Nephrol Ther 2008) and no treatment withdrawal for unmanageable renovascular toxicity occurred.

<table>
<thead>
<tr>
<th>Renovascular effects</th>
<th>Prevalence at inclusion (%)</th>
<th>Incidence during f/u (%)</th>
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<tbody>
<tr>
<td>Pu*</td>
<td>13.2</td>
<td>36.4</td>
</tr>
<tr>
<td>Grade 1</td>
<td>10.5</td>
<td>21.2</td>
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<tr>
<td>Grade 2</td>
<td>2.7</td>
<td>15.2</td>
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<td>Grade 3-4</td>
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<tr>
<td>Hu</td>
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<tr>
<td>Traces/+</td>
<td>5.3</td>
<td>0.0</td>
</tr>
<tr>
<td>+++</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>SCr increase*</td>
<td>-</td>
<td>36.4</td>
</tr>
<tr>
<td>Grade 1</td>
<td>36.4</td>
<td>0.0</td>
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*NCI-CTC v4.03.
A phase II study of pazopanib in recurrent or persistent ovarian (EOC), peritoneal (PPC), or Fallopian tube cancer (FTC): A Spanish Ovarian Cancer Group (GEICO) study.

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Background: Pazopanib (P) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β, and c-kit that inhibits angiogenesis. Signaling blockade of these pathways is associated with anti-tumor and anti-angiogenesis activity. Methods: Eligible patients (pts) had persistent or recurrent EOC/PPC/FTC up to 2 prior cytotoxic regimens. They had to have received at least a platinum-based line and fulfill platinum resistant criteria. Treatment consisted of P 800 mg orally QD until disease progression or prohibitive toxicity. The primary endpoint was Clinical Benefit Rate (CBR) defined as Complete Response (CR) plus Partial Response (PR) plus Stable Disease (SD) / 8 weeks by RECIST v1.1. An optimal two-stage Simon design was utilized with H1 and H0 set at 60% and 40% respectively; Power = 90% significance level of 5% (Stage 1: = 25 pts; total=66). Correlative studies to identify angiogenic biomarkers to predict response to P were performed. Results: From 12/10 to 7/11, 25 pts were enrolled, 21 pts had EOC, 2 PPT, and 2 FTC. Median age: 64 years (range 43-81), ECOG 0/1/2: 12/11/2 pts. Prior chemotherapy regimens 1/2: 10/15 pts. Median weeks on treatment: 8 (range 4-25). Most frequent adverse events (AEs) were asthenia (56%), hypertension (36%) and diarrhea, nausea and anorexia (20% each). Grade 3 toxicities: Hypertension (6pts), ALT/AST elevations (3 pts), asthenia (2 pts), DVT (1pt), Fistula (1 pt), Anemia (1 pt). Six pts required dose reduction to 600 mg due to toxicity. Reasons for stopping study treatment: PD (18 pts), AEs (3 pts) and investigator decision (2 pts). First stage analysis showed: PR:1/25, SD: 9/25, CBR:10/25; 40% (95% CI 21.1%-61.3%). No correlation between GCIG CA-125 response and RECIST criteria was established, 8 versus 1 response respectively. Median PFS was 1.83 months (95% CI 1.67-2). Conclusions: The CBR observed at the first stage did not reach the planned statistical hypothesis (CBR:12 pts). Therefore, the lack of activity of P in platinum resistant EOC/PPT/FT led to discontinuation of the study. Translational study results will be presented in an additional abstract.
A novel treatment for ovarian cancer (OC): Anti-Müllerian inhibiting substance type II receptor (MISRII) humanized monoclonal antibody (mAb) 3C23K—Preclinical validation.

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Background: Expressed on most OC subtypes while displaying a restricted expression profile in adult normal tissues, MISRII represents a potential target for OC immunotherapy. We present here the preclinical assessment of a humanized anti-MISRII EMABling mAb, 3C23K. Methods: Either quantitative RT-PCR or immunohistochemistry (IHC) studies were performed to confirm MISRII expression profile in Granulosa Cell Tumor (GCT) or Epithelial OC (EOC) patient samples and to evaluate tissue cross-reactivity. For in vitro and in vivo experiments, we have generated 4 patient-derived MISRII expressing EOC cell lines. Xenograft studies were conducted in swiss nude mice on established tumors (100 mm³). Mice received 2 to 3 weekly i.p. injections (10 mg/kg/inj) for 4 to 6 wks and tumor volumes were compared with control groups. Comparison of i.p. vs i.v. injections were assessed as well as combination with carboplatin (once a week for 4 weeks, 60 mg/kg/inj). In addition, 3C23K plasma level was monitored to determine half-life.

Results: 1) Target validation: we confirmed by IHC the expression of MISRII in most OC tissue sections (4/4 GCT and 13/14 EOC), meanwhile, MISRII mRNA was only detected in 7/48 normal tissues. 2) In vitro assessment: tested in vitro 3C23K displayed both cytotoxic (ADCC) and anti-proliferative activities. 3) In vivo assessment: in the mouse xenograft models 3C23K exhibited a strong anti-tumoral activity as measured by tumor volume, with T/C ratios reaching values below 0.42 shortly after the initiation of treatment. No differences in efficacy were noticed between i.p. and i.v. injections or between thrice vs twice a week administrations. In addition, similar half lives were observed for 3C23K injected either i.v. (96.9 h) or i.p (113.5 h). Finally, the combination of 3C23K with carboplatin (CP), a standard of care in OC, exhibited an even stronger anti-tumor activity with T/C values at D22 of 0.06 (3C23K+CP), 0.18 (3C23K) and 0.69 (CP) vs vehicle. Conclusions: 3C23K represents a promising candidate for OC targeted therapy and a dose-escalation phase I study is planned in patients with OC.
BRCA1 methylation status in high-grade serous ovarian cancer (HGSOC) patients (pts).

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Background: Mutations in BRCA1/2 genes contribute to increase risk for breast and ovarian cancer (OC). Hypermethylation of CpG islands in gene promoter regions is considered a frequent mechanism associated with inactivation of tumor suppressor genes which contributes to oncogenic transformation. Studies identified methylation changes in OC pts. Most of the studies analyzed a small cohort and combined different histological subtypes. HGSOC is a special entity of OC associated with poorer OS. Aim of this study was to analyze the clinical impact of BRCA1 promoter gene methylation status in HGSOC.

Methods: The cohort comprised 127 HGSOC treated by cytoreduction followed by platinum-based chemotherapy at Department of Gynecology, Charité Medical University Berlin, Germany. Fresh frozen OC tissues provided by TOC were examined to access the tumoral tissue quality. Samples presenting at least 50% of tumour area were included within this study. DNA was extracted followed by sodium bisulfite conversion, and assessment of BRCA1 gene promoter methylation rate was determined by PCR. Statistical analysis has been carried out using SPSS software.

Results: In our study, 14.2% of the pts presented a hypermethylation of the BRCA1 promoter gene. The hypermethylation of BRCA1 promoter gene was significantly more frequently encountered in the younger pts (<59 yrs: 77.8% in the Hypermethylation Group vs 47.7% in the Hypomethylation Group, p=0.022). No differences in methylation status between primary and metastatic tissue from OC pts could be observed. Also no correlation with FIGO stage was observed. Optimal tumor debulking could be reached in most of the pts (57.5%), without significant differences between both groups. Platinum response rates were similar between both groups. No differences in PFS and OS could be observed.

Conclusions: The study shows that HGSOC pts presenting the BRCA1 gene promoter in the methylated status, developed the disease significantly earlier with respect to OC patients with unmethylated BRCA1 gene promoter. The clinical outcome was similar in HGSOC independently from BRCA1 methylation status.

Interval versus primary tumor debulking surgery in advanced ovarian cancer: Analysis of the European OVCAD data.

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Background: The international scenery around optimal primary treatment of advanced ovarian cancer (AOC) patients (pts) is currently being discussed, with large discrepancies and heterogeneity still existing between the national guidelines worldwide. Aim of the present study was to evaluate the differences in outcome of AOC-pts after primary (PDS) versus interval-debulking-surgery (IDS) based on a prospectively assessed multicenter data set. Methods: Overall outcome was analyzed from the OVCAD database; a prospective, observational, multicenter project. AOC-pts who underwent surgery in five specialized gynecological cancer centers across three European countries between 02/2005 and 12/2008 were evaluated. Overall (OS) and progression free survival (PFS) were calculated by Kaplan-Meier-curves. Univariate and Cox-regression-analysis were applied. Results: Overall, 256 AOC pts (FIGO-stage III/IV) were evaluated. Fifty pts (19.5%) underwent IDS and 206 pts (80.5%) PDS. Despite the non-randomized setting both groups were well balanced in terms of FIGO-stage, grading, histological subtype and presence of ascites. Different selection criteria were however present for each center. PDS pts presented significantly higher rates of intestinal resection (44.2% vs.24%; p=0.01) and lymphonodectomy compared to IDS ones (72.3%vs.48%; p=0.001), by equivalent complete tumor resection rates (67.5% vs.68%; p=0.82). Platinum response was significantly higher in PDS vs. IDS pts (80.6% vs. 54%; p=0.001). 3-years OS was with 66.7% (95%CI: 60.2-73.2%) significantly better in PDS- versus 48.3% (95%CI: 34.2-62.5%) in IDS pts (p<0.001). Also 2-years PFS was with 31.9% (95%CI:24.8-39.1%) significantly higher in PDS- vs. 11.4% (95%CI: 0.9-22%) in IDS-pts (p<0.001). In multivariate analysis PDS, but not age, ascites, FIGO-stage, grading, histology or residual tumor were of prognostic significance for platinum response. In addition, multivariate analysis identified PDS and no residual tumor to positively and ascites to negatively affect OS and PFS. Conclusions: PDS appears to be associated with a more favorable outcome compared to IDS in highly specialized centers according to this non-randomized data set.
Exposure-response relationship of open-label (OL) AMG 386 monotherapy in patients (pts) with recurrent ovarian cancer.

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Background: AMG 386, an investigational peptibody, inhibits tumor angiogenesis by preventing angiopoietins 1/2 and Tie2 receptor interaction. A phase II, double-blind, controlled study (NCT00479817) evaluated toxicity and efficacy of AMG 386 + paclitaxel (P) in recurrent ovarian cancer pts. Increased AMG 386 exposure in that study was associated with longer progression-free survival (PFS; Lu et al., JCO 2010; 28 [Suppl]: 5042). Here, these analyses were applied to pts electing OL AMG 386 monotherapy after progression in the placebo group. Methods: Pts with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer (≤3 prior anticancer therapies, GOG ≤1) were randomized 1:1:1 to P IV QW (3 on/1 off) + AMG 386 (3 or 10 mg/kg) or placebo IV QW. In the placebo group, pts who progressed and stayed eligible could receive OL AMG 386 10 mg/kg IV QW monotherapy. In pts receiving AMG 386 monotherapy, post-hoc analyses evaluated PFS per RECIST, objective response rate (ORR), adverse events (AEs), and the relationships between high and low AMG 386 exposure (based on a median AUC_{SS} of 10.6 mg*hr/mL) and efficacy (PFS per RECIST, ORR). Results: 161 pts were randomized. 18 pts received OL AMG 386 monotherapy (range: 1-56 infusions). At the time of analysis, PFS was 3.2 mo. ORR was 0%. 6 pts had stable disease (SD), 7 had progressive disease (PD). Common AEs were abdominal pain (n = 6), fatigue (n = 5), peripheral edema (n = 5), nausea (n = 5), urinary tract infection (n = 5), and vomiting (n = 5); grade ≥ 3 AEs in more than 1 pt were pleural effusion (n = 2; all grade 3), small intestinal obstruction (n = 2; all grade 3), and ovarian cancer (n = 2; all grade 5). PFS was longer in the high- (n = 9) vs low-exposure (n = 9) group (7.2 vs 1.8 mo; HR = .266, p = .041). Precrossover PFS was similar between high- and low-exposure groups (5.5 vs 4.5 mo; HR = 1.146, p = .812). For both groups, ORR was 0%. In the high-exposure group, 4 pts had SD, 3 had PD. In the low-exposure group, 2 pts had SD, 4 had PD. Conclusions: In line with results from a phase II study of AMG 386 + P, pts with recurrent ovarian cancer who received AMG 386 monotherapy and had high AMG 386 exposure had longer PFS than pts with low exposure. Toxicity was similar in both groups.
Targeting therapy based on preclinical analysis of clinical, molecular, and functional characteristics of individual high-grade serous ovarian cancers.

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Background: Recent molecular exploration of high-grade epithelial ovarian cancer (OC) has revealed potential targets for novel therapy based on altered DNA repair function, deregulated pathways and recurrent amplifications (Cancer Genome Atlas Research Network. 2011. Nature 474). Improved pre-clinical models allowing analysis of specific molecular subsets of ovarian cancer are urgently required to test novel treatment strategies. Methods: We have generated a novel xenograft model of human high-grade serous OC (HG-SOC). Histologic, functional and molecular analysis of the novel xenograft cohort (at baseline and following xenotransplantation) allows stratification of individual HG-SOC for testing with appropriate targeted therapy. We perform functional analysis of in vitro Homologous Recombination (HR) DNA repair and drug response capabilities on fresh human HG-SOC immediately following surgical resection. Molecular classification (similar to Tothill [Clin Canc Res. 2008;14]); analysis of NHEJ pathway (Proc Natl Acad Sci. 2011;108) and other DNA repair genes (Proc Natl Acad Sci USA 2011;108) is performed. In vivo drug response is studied in murine xenografts. Results: Sixteen chemotherapy-naive potentially HG-SOC samples and associated clinical data have been collected. Functional evidence of DNA repair (HR) capability and response to DNA damaging agents will be presented, including IHC for markers of DNA damage (gH2AX), DNA repair (RAD51AP1) and apoptosis (capsase 3 cleavage). Molecular classification, DNA repair gene and DNA repair pathway analyses are underway. Twelve HG-SOC have been transplanted and 6 of the first 8 have successfully xenografted, with serial transplantation and phenotyping of xenograft derivatives underway. In vivo drug response will be presented. Conclusions: This xenograft model will enable us to address hypotheses generated by recent molecular analyses of human HG-SOC (Cancer Genome Atlas Research Network. 2011. Nature 474; Clin Canc Res. 2008;14). Clinical, functional and molecular annotation will allow pre-clinical drug testing based on the plausible hypothesis approach.
Proliferation pathway aberration frequencies in BRCA1- and BRCA2-mutated ovarian cancers.

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Background: Large-scale genomic analyses of high-grade, advanced-stage serous ovarian cancers by The Cancer Genome Atlas (TCGA) project revealed aberrations in genes comprising key proliferation and survival pathways (RB-E2F, RAS, PI3K) in the majority of tumors. Patients with germline BRCA1/2-mutations have more favorable prognoses than non-BRCA carriers, and recent work suggests that BRCA2 carriers do better than BRCA1. We hypothesized that concurrent proliferation pathway aberrations and BRCA1/2 mutations in tumors might play a role in patient outcome. 

Methods: Mutation, copy number, and clinical data for 309 TCGA-profiled serous ovarian tumors were downloaded from the MSKCC cBIO web portal. Each tumor was scored as aberrant for a pathway if any gene (RB: RB1, CDKN2A, CCND1, CCND2, E2F3, CCNE1; PI3K: PIK3CA, PTEN, AKT1, AKT2; RAS: KRAS, BRAF, NF1) in that pathway was mutated, amplified, or deleted. 

Results: 205 of 309 tumors had an aberration in at least one of these pathways. The frequency of pathway alteration differed significantly in BRCA1 (82%, 28/34), BRCA2 (52%, 17/33) and BRCA1/2 WT (66%, 160/242) tumors (BRCA1 vs. BRCA2: Fisher’s p = 0.0096). BRCA1 tumors more frequently contained alterations in multiple pathways than BRCA2 or WT tumors (41% vs. 24% or 25%, respectively). RB-E2F pathway alteration frequency was significantly different (BRCA1: 56%, BRCA2: 18%, WT: 43%, p=0.0043), but no significant differences in PI3K and RAS pathway aberration frequencies (BRCA1%: 41, 38; BRCA2%: 36, 27; WT% 28, 27), respectively, were observed. In agreement with the previous report, BRCA2 patients had significantly better overall survival (OS) than either BRCA1 or WT patients (median OS months for BRCA1: 35.9, BRCA2 45.4, BRCA1/2 WT 27.8; p=0.001). Presence of pathway alterations was not significantly associated with OS in BRCA1, BRCA2, or WT patients in this cohort. 

Conclusions: These results show a negative association between BRCA2 mutations and aberrations in key proliferation and survival pathways. Beyond BRCA1 and BRCA2 genetic mutations, the elevated frequency of pathway alteration in BRCA1 vs. BRCA2 tumors highlights differences that may be important for patient prognosis as well as therapy responses.
Secondary surgery with intraoperative chemohyperthermia in recurrent ovarian adenocarcinoma.

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**Background:** Optimal treatment of peritoneal recurrences in ovarian cancer is debating with second line chemotherapies. We proposed association of secondary surgery with heated intraperitoneal per operative chemotherapy (HIPEC). The aim of study is to determine prognostic factors in a single center cohort.

**Methods:** Retrospective study of consecutive 169 patients with peritoneal recurrence from ovarian cancer were performed to evaluate HIPEC and to identify prognostic factors. Peritoneal Cancer Index (PCI) assess tumor load and completeness cytoreductive score (CCS) were used to give quality of resection CCS0 (no visible tumor), CCS1 (persistent diffuse lesions < 2.5mm), CCS2 (2.5mm <CC2< 25mm) and over CCS3 status. HIPEC is performed with platinum based regimen. Endpoint was survival. Cox’s regression model was used for multivariate survival analysis and extending Cox model for modelling survival data. **Results:** We have operated on 197 procedures (HIPEC) in 169 patients from 2000 to 2011. Mean age was 58 years old range [28-75]. Median PCI was 10. After completion of resection, allocation of CCS was CCS0=120, CCS1=70, CCS2 & CCS3 =7. Procedure related mortality was 1% and morbidity 21%, mean length of hospital stay was 17 days range [7-51]. 3 and 5 years overall survival were respectively 64.7% and 37.4 %. Median survival was 47.6 months and the median disease free survival was 20 months. PCI >10 (even if complete resection performed) and CCS2&3 were worse prognostic factors (HR respectively = 2.64 IC 95% [1.29-5.36] and = 3.31 IC 95 % [1.55-7.08]). Modelling of these factors, is very strong to predict risk of death over the 2 first years after HIPEC. **Conclusions:** The chemo-hyperthermia is a standardized and reproducible feasible method. Less extensive disease and the quality of cytoreduction remain an independent factor of better outcome. To date HIPEC allows to reach the longest median time survival in peritoneal recurrent ovarian cancer. Modelling survival data is useful to know the risk of dying.
Inflammatory and nutritional markers as predictors of longer hospital stay and suboptimal residual disease (RD) in ovarian cancer (OVCA).

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Background: Advanced OVCA should be managed aggressively, and extensive surgery has been the most accepted initial treatment. Medically unfit patients or those with extensive disease, in which complete cytoreduction is unlikely, may not benefit from upfront radical surgery, and neoadjuvant chemotherapy might be an appropriate alternative. Thus, reliable preoperative indicators of surgical outcome are necessary for considering primary surgery vs. neoadjuvant chemotherapy. Our aim is to determine if C-reactive protein (CRP), IL-6, albumin and Glasgow Prognostic Score (GPS – score based on CRP and albumin) correlate with overall survival (OS), length of hospital stay (LOS), surgical morbidity, and suboptimal cytoreduction.

Methods: We randomly selected 50 stages III/IV OVCA who underwent surgery as a primary treatment between July 2002 and June 2009 at Mayo Clinic with serum albumin levels and frozen serum available. CRP and IL-6 were measured in stored serum. Univariate and multivariate regression models were fit to evaluate associations with each of the outcomes.

Results: Among the 50 patients, the mean age was 67.7 years. 34% had pretreatment albumin <3.5 g/ml, 22.4% had CRP level ≥10 mg/l, 26.5% had IL-6 ≥24 pg/ml and 45% had abnormal GPS score. At 1, 3 and 5 years following surgery, the OS was 75.6%, 49.8% and 36.9%, respectively. RD (0, <1, ≥1cm; p<0.001) was the only independent predictor of OS. Also, IL-6 (p=0.028) and stage (p=0.046) were independently associated with LOS, but no inflammatory or nutritional markers were significant associated with post surgical complications. Stage IV (p=0.019) and elevated CRP (p=0.044) were independent predictors of suboptimal surgery (RD ≥ 1cm).

Conclusions: One-third of the patients in our series had low serum albumin at the time of the OVCA diagnosis, and at least one-fourth had elevated inflammatory markers. Advanced stage and elevated inflammatory markers (CRP and IL-6) were independent predictors of longer hospital stay and suboptimal debulking. These pilot data, if confirmed in a larger population, may help in the selection of candidates for neoadjuvant chemotherapy.
**Background:** A standard of care (SOC) for the adjuvant treatment of ovarian and primary peritoneal cancer is a platinum-based intravenous (IV) chemotherapy doublet. Intraperitoneal (IP) chemotherapy is also a SOC, but the high incidence of grade 3/4 adverse events has limited its acceptance among clinicians. To identify genetic markers for completion of IP chemotherapy, we analyzed SNPs in four genes known to play a role in metabolism of platinum or taxane drugs. **Methods:** Patients diagnosed with primary or recurrent stage III or IV epithelial ovarian or primary peritoneal cancer who had primary or secondary debulking surgery at Mayo Clinic (Rochester, MN) between January 2007 and February 2009 followed by IP chemotherapy were included in this study. A cycle was defined as IV paclitaxel (135mg/m²) on day one, IP cisplatin (100mg/m²) on day two, and IP paclitaxel (60mg/m²) on day eight. With prior consent from the patient, peripheral blood was obtained before treatment for extraction of germline DNA. Using a custom Illumina BeadXpress 96-plex panel, SNPs in \textit{GSTM1} (N=7), \textit{ABCB1} (N=57), \textit{CYP3A4} (N=7), and \textit{CYP2C8} (N=25) were genotyped. The association between SNPs in these subsets of genes and completion of IP chemotherapy was analyzed using linear regression. **Results:** Thirty-seven patients were included in this study and 16 (43.2%) completed IP chemotherapy. Twenty-two out of the fifty-seven \textit{ABCB1} SNP’s were associated with the number of cycles (p<0.15). There were no significant associations for \textit{GSTM1}, \textit{CYP3A4} and \textit{CYP2C8} SNP’s. The minor A allele at missense SNP rs2229109 in the \textit{ABCB1} gene was present in five (31.2%) who completed treatment and only one (4.8%) who did not (p<0.007). However, the later was due to catheter complication. There was no association between rs2229109 and overall or progression-free survival. **Conclusions:** Our findings suggest that SNP rs2229109 in \textit{ABCB1} gene is associated with completion of IP chemotherapy, and potentially, less toxicity from chemotherapy. Thus, these patients may be optimal candidates for IP chemotherapy. Further studies in a larger population are needed.
BRCA mutations and outcome in epithelial ovarian cancer (EOC): Experience in ethnically diverse groups.

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Background: EOC patients with BRCA mutations have been reported to have better prognosis than non-hereditary (NH) matched cases, an advantage shown especially in the Ashkenazi-Jewish (AJ) population. We have analyzed our experience in our ethnically diverse patient cohort from NYC, Israel and Italy. Methods: A retrospective chart review of patients diagnosed with Stage IC-IV EOC between 1995-2008 at the NYU Cancer Institute, Tel Aviv Sourasky MC and Padova Clinical Cancer Centers. Out of >700 patients, 183 were tested for BRCA mutations and evaluated. Results: Median age was 55.5 (range 31–83 years). Out of 183, 86 are carriers of BRCA1/2 mutations and 97 tested negative, 67 and 19 are carriers of BRCA1 and BRCA2 mutation respectively. Carrier frequency in EOC population is 46% (45/97) in AJ’s and 48% (41/86) in non-AJ’s. AJ patients had the following BRCA1 mutations: 185delAG (29), 5382insC (5), unknown (UK) (2) and BRCA2 mutations: 6174delT (8), UK (1). Non-AJ’s were divided by ethnicities into non-AJ, Caucasian, African-American, Hispanic, Middle Eastern or unknown. Non-AJ Jewish patients had BRCA1 mutations in 185delAG (7) and BRCA2 in 6174delT (1), UK (1). Non-Jewish Caucasians exhibited the widest variation of mutation types, with the following BRCA1 sites: 185delAG, K1702X (5223A>T), E1373X, 3829delIT, 185delAT, IVS11+1G>A, 5385insC, 5083del19>stop1670, 1720delAF>stop536, 1806C>T>Igu536Ter, del ex1a-2, cod1486ex14:4575delAstop1504, 5563G7A; Trp1815stop, 5181delGT1(val1688del) and UK and the following BRCA2 sites: 6174delT (2), 5301insA (1), 802delAT (1), cod2960ex22:9106C/t (1), cod68ex3:432delAstop79 (1), 7408A/T;Arg2394stop (1). One African-American patient with BRCA1 at 1294del40, 1 Hispanic BRCA1 at 185delAG. OS was significantly prolonged for BRCA carriers at 93.6 months versus 63.2 months [95% CI: 44.5-91.7] (p=0.0016) for NH. Conclusions: Our data reports a wide variety of BRCA mutations in an ethnically diverse EOC population and confirms that BRCA mutations carriers have a better prognosis with a longer median survival compared to NH population. A larger cohort might manifest prognostic differences between the different types of mutations.
Serum IGFBP4 levels in combination with miliary disease: A candidate predictor of ovarian cancer progression-free survival.

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Background: Insulin-like growth factor binding protein, IGFBP4, was shown to be highly expressed across all stages of epithelial ovarian cancer (EOC) and serum levels are elevated in EOC. Moreover, IGFBP4 levels are ~3x greater in women with malignant pelvic masses. We investigated whether ascites volume and the presence of miliary disease in combination with serum levels of IGFBP4 are independent predictors of survival. Methods: A prospective and retrospective analysis was performed. Patients were enrolled at the time of cytoreductive surgery. Ascites volume was either absent, <500 cc (low), or ≥ 500 cc (high), and the presence of miliary disease was recorded. The IGFBP4 cutoff was 1064.5 ug/ml based upon previous results. The Kaplan-Meier product limit method was used to estimate PFS probabilities. The Cox proportional hazards model was used to estimate hazard ratios (HR) and corresponding 95% CI. Results: 57 cases were included in the analysis of ascites volume and miliary disease. Cytoreductive outcomes were complete gross resection (44.8%), optimal (<1 cm residual disease; 44.8%), and suboptimal (>1 cm residual disease; 10.3%). Histologic subtypes: papillary serous (n=35; 61.4%), mucinous (n=15; 26.3%), endometrioid (n=4; 7.0%), and clear cell (n=3; 5.3%). Stage distribution was 21.1% I/II, and 78.9% III/IV. PFS was unaffected by ascites volume (p=0.341) or miliary disease. Among this cohort, 29 had IGFBP4 levels available for a separate analysis. Patients with high IGFBP4 and miliary disease were 5.5 times as likely to recur compared with patients with miliary disease and low IGFBP4 (HR=5.55 [0.77, 39.82]), and the statistical significance was borderline (p=0.088). No statistically significant differences were detected between rates of recurrence among patients with high and low IGFBP4 values in combination with ascites volume. Conclusions: These exploratory studies suggest that patients with high IGFBP4 serum levels and miliary disease were > 5 times as likely to recur compared to women with miliary disease and low IGFBP4 levels. Future studies examining these variables using a larger population and examining the biologic basis of this relationship are planned. © 2012 American Society of Clinical Oncology. Reprinted with permission.
A matched pair analysis of intra- and postoperative catumaxomab in patients with ovarian cancer from a multicenter, single-arm phase II trial versus a consecutive single-center collective of ovarian cancer patients without immunotherapy.

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Background: Advanced ovarian cancer is still connected to high mortality rates due to intraperitoneal tumor cells that survive radical cytoreductive surgery as well as adjuvant chemotherapy. These persistent tumor cells need to be targeted in order to improve survival. Catumaxomab has demonstrated the ability to kill EpCAM-positive intraperitoneal tumor cells of ovarian cancer patients in studies aiming to control malignant ascites in the recurrent setting. This analysis was conducted to investigate the efficacy of intraperitoneal catumaxomab at the timepoint of primary cytoreductive surgery and postoperative period, prior to standard adjuvant chemotherapy.

Methods: Ovarian cancer patients undergoing radical surgery received one intraoperative (10 µg) followed by four subsequent intraperitoneal (i.p.) dosages (10, 20, 50 and 150 µg) of catumaxomab on days 7, 10, 13, and 16, respectively. Because of the single arm design of the study, the patients treated with catumaxomab were compared in a matched pair analysis to consecutive patients with primary ovarian cancer who received standard treatment without catumaxomab in a large center, in order to compare survival. The two main prognostic factors of stage and level of tumorreduction were chosen as matching criteria. Results: Of 58 patients screened, 41 were treated with catumaxomab and available for survival evaluation. Median age was 57 years in the catumaxomab group and 59 years in the matched-pair control group. The most common histology was the serous subtype with 70.7% in the catumaxomab and 80.5% of the patients in the control group. The median for overall survival was reached for the historical consecutive matched-pair control collective, but is not yet reached for the catumaxomab group. However, 3-year survival data were available for both groups and showed survival of 85.4% (35) in the catumaxomab group and 63.4% (26) in the matched-pair control group (p-value: 0.041; HR 2.073)

Conclusions: There seems to be a trend to beneficial 3-year survival in the catumaxomab group, suggesting that a phase III trial is warranted.
Progression-free survival (PFS) as a surrogate end point for overall survival (OS) in first-line treatment of advanced epithelial ovarian cancer (EOC).

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Background: The duration and cost of clinical trials of first-line chemotherapy in advanced EOC could be reduced if a surrogate endpoint were used in place of OS. The consensus of the Gynecological Cancer Intergroup was that PFS is the preferred primary end point for these trials due to potential confounding of post-progression therapy on OS. We performed a systematic review to assess the extent to which treatment effect on PFS is predictive of OS in this patient population. Methods: Randomised trials of first-line chemotherapy comparing platinum containing regimens in advanced EOC were identified; trials with non-platinum backbone, maintenance strategies or biological containing therapies were excluded. Summary data (hazard ratios (HR), median PFS and OS and the ratios of medians between treatment arms) were extracted. Weighted least-square (WLS) $R^2$ by trial sample size derived using linear regression was used to report correlation. Results: 15 eligible trials with 19 treatment comparisons were identified comprising a total of 16,598 patients. There was a good correlation between treatment effect on PFS and OS (correlation of HR: $r$, 0.88, WLS $R^2$, 0.71; correlation of ratios of medians: $r$, 0.84, WLS $R^2$, 0.72). Good correlation between treatment effect on PFS and OS was also observed in various prognostic subgroups (Table). Conclusions: In clinical trials of first-line platinum based chemotherapy without biological agents in advanced EOC, treatment effect on PFS and OS is highly correlated. PFS could be considered as a primary end point when evaluating future first line strategies in advanced EOC.

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<tr>
<th>Prognostic factors across trials</th>
<th>Correlation for HR ($r$)</th>
<th>WLS $R^2$</th>
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<tr>
<td>Stage IV (16%)</td>
<td>0.94 vs. 0.75, 0.79 vs. 0.57</td>
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<td>Optimal debulking (62.6%)</td>
<td>0.86 vs. 0.95, 0.69 vs. 0.83</td>
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<td>Age (59 years)</td>
<td>0.93 vs. 0.86, 0.77 vs. 0.66</td>
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<td>ECOG performance status ECOG 2 and 3 (10.1%)</td>
<td>0.95 vs. 0.89, 0.81 vs. 0.76</td>
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Final results of a phase II trial of weekly nab-paclitaxel with GM-CSF as chemoinmuno therapy for platinum-resistant epithelial ovarian cancer.

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Background: Ovarian cancer patients with an anti-tumor immune response have a prolonged survival, suggesting that augmenting anti-tumor immunity may be therapeutic. We hypothesized that weekly nab-paclitaxel (nabP) followed by GM-CSF may enhance anti-tumor immunity and prolong time to progression (TTP). Methods: Eligible subjects had platinum resistant ovarian, primary peritoneal or fallopian tube cancer, and an elevated CA125. Conditional power estimate after 11 subjects showed 22 subjects had 80% power to show a response rate (RR) >21% if the true study RR is 35%. Study end points were RR and TTP. Progression (DP) was doubling of CA125 above the nadir. Complete response (CR) was a decline of CA125 below institutional normal. Partial response (PR) was a decline of >50% from baseline. Stable disease (SD) was all other scenarios. Subjects received nabP, 100mg/m² days 1,8,15 followed by GM-CSF 250mcg days 16-26 of a 28 day cycle until progression or 6 cycles were complete. Responding subjects received up to 6 more cycles of GM-CSF on days 14-28. Results: 21 subjects received at least one dose of study medications. Median age was 61 (30-91) and had a median of 3 (1-13) prior regimens. Among those completing the study, the median TTP was 132 days vs. 272 days on the prior platinum regimen. 9/21 (43%) had a PR and 4/21 (19%) had a CR. Subjects with a response had a median TTP of 140 days. Assay of serial T-lymphocyte counts against CEA, MUC1, CA125 and influenza controls are planned. Conclusions: Weekly nabP with GM-CSF had manageable toxicity and induced a high response rate (62% by CA125) in patients with platinum resistant ovarian cancer, however this regimen did not prolong the TTP beyond the TTP observed in the prior platinum regimen.
Prospective multicenter study evaluating the survival of patients with locally advanced cervical cancer (LACC) and negative positron emission tomography with computerized tomography (PET-CT) in the para-aortic area undergoing laparoscopic para-aortic (PA) lymphadenectomy before chemoradiation therapy.

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Background: In three comprehensive cancer centers, patients with LACC were systematically staged using conventional and PET-CT imaging before chemoradiotherapy. If patients had no uptake in the PA area, laparoscopic extraperitoneal PA surgery was then performed to define radiation field limits more accurately. The aim of this study was to evaluate the therapeutic impact of this management. Methods: A prospective multicenter series of 237 patients treated from 2004 to 2011 for LACC with a negative PET-CT of the PA area and undergoing laparoscopic PA lymphadenectomy. Radiation fields were extended to PA area when PA nodes were involved. Chemoradiotherapy modalities were homogeneous between Institutions. Patients with a poor prognosis histologic subtype, peritoneal carcinomatosis or ovarian metastasis were excluded. Results: Clinical stages were IB2 (n=79), IIA (n=10), IIB (n=120), III (n=23), IVA (n=5). The histologic types were squamous carcinoma (n=197), adenocarcinoma (n=34) and others (n=6). Twenty-nine (11%) patients had nodal involvement (false negative PET-CT results): 16 with PA nodal metastasis measuring < 5 mm and 13 ≥ 5 mm. With a median follow-up of 18 (range, 0-67) months, disease-free survival (DFS) at 2 years in patients without and with PA involvement was respectively 76% (68%-83%) and 61% (37%-80%)(p=.007). DFS at 2 years in patients without PA involvement or with PA metastasis measuring < or ≥ 5 mm was respectively 76% (68%-83%), 89% (57%-98%) and 38% (14%-68%)(p=.0006). Conclusions: This is the largest series of patients reported undergoing such strategy. We obtained a similar survival rate for patients with PA nodal metastasis < 5 mm and patients without PA lymph node involvement suggesting that this strategy is highly efficient in such patients. Conversely, the survival of patients with PA nodal involvement ≥ 5 mm remained poor, despite no extrapelvic disease at PET-CT imaging in this subgroup. Other treatment modalities should be evaluated for these patients.

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Background: To estimate the prevalence and genotypes of high-risk human papillomavirus (HPV) among older Japanese women, using liquid-based cytology (LBC). Methods: ThinPrep LBC specimens were collected from 11,039 Japanese women (age range, 14-98 years). After classifying cytodiagnosis, specimens were analyzed for HPV DNA using the multiplex polymerase chain reaction method. Cervical smear specimens from 1,302 women showed positive results. To examine the prevalence of HPV in women defined as negative for intraepithelial lesion or malignancy (NILM), 2,563 samples were randomly selected from the remaining 9,737 women. Comparisons were made between women ≥50 years of age (older age group) and women <50 years of age (younger age group). Written informed consent was obtained from all patients. In this study, the high-risk HPV genotypes encountered were 16, 18, 31, 33, 35, 45, 52, and 58.

Results: In the older age group with abnormal smear findings, HPV genotypes were detected in 49.7% (148/298), including high-risk HPV genotypes in 40.9% (122/298). In the younger age group with abnormal smear findings, HPV genotypes were detected in 71.7% (720/1004), including high-risk HPV genotypes in 58.1% (583/1,004). In NILM, HPV-positive rates were 4.5% (39/873) in the older age group and 11.8% (199/1,690) in the younger age group. In high-grade squamous intraepithelial lesion (HSIL) or more severe cytological findings, HPV genotypes of each group (older age group/younger age group) were detected in 61.7%/83.1%, and high-risk HPV genotypes were detected in 56.4%/74.7% of women. In positive cervical smears, HPV 16 was the most frequently detected (28.5%) in the younger age group, while HPV 52 (31.3%) and 58 (27.2%) were detected more frequently than HPV 16 (18.4%) in the older age group. Conclusions: In Japan, although HPV infection as a cause of abnormal cervical cytology is more frequent among younger age groups than in older age groups, high-risk HPV infection was more highly associated with older individuals (older age group/younger age group: abnormal smear findings, 82.4%/81.0%; HSIL or more severe cytological findings, 91.3%/89.9%). In older age groups, HPV 52 and 58 were more frequent than HPV 16.
Nuclear Y-box binding protein-1 expression as a prognostic marker and correlation with epidermal growth factor receptor expression in cervical cancer.

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Background: Y-box binding protein-1 (YB-1) is a member of the cold shock protein family and functions in transcription and translation. Many reports indicate that YB-1 is highly expressed in tumor cells and is a marker of tumor aggressiveness and clinical prognosis. Overexpression of epidermal growth factor receptor (EGFR) has been associated with poor outcomes in cervical cancer (CC). Clinical trials have shown that EGFR inhibitors are effective against CC (JCO 2011). Nuclear YB-1 expression correlates with EGFR expression in various types of cancer. Methods: Nuclear YB-1 expression was immunohistochemically analyzed in tissue specimens obtained from 204 CC patients who underwent surgery. Associations of nuclear YB-1 expression with clinicopathological factors such as survival and EGFR (HER1 and HER2) expression were investigated. Results: Nuclear YB-1 expression was observed in 41 (20%) of 204 cases and correlated with stage, tumor diameter, stromal invasion, and lymph-node metastasis. Nuclear YB-1 expression also correlated with both HER1 expression (p=0.0114) and HER2 expression (p=0.0053). Kaplan-Meier survival analysis showed that nuclear YB-1 expression was significantly associated with poor outcomes in terms of progression-free survival (p=0.0033) and overall survival (p=0.0003). On multivariate analysis, stromal invasion, parametrial invasion, and nuclear YB-1 expression were independent predictors of survival. Conclusions: Nuclear YB-1 expression is a prognostic marker and correlates with EGFR expression in CC.
Concurrent chemoradiotherapy with paclitaxel and cisplatin for adenocarcinoma of the cervix.

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Background: Adenocarcinoma of the cervix has a worse prognosis than its squamous counterpart, particularly when cancer cells spread beyond the uterine cervix. This is derived from the observation that adenocarcinoma is less sensitive to radiotherapy (RT) and chemotherapy. It is unclear whether cisplatin-based concurrent chemoradiotherapy (CCRT) has the same effect on adenocarcinoma as on squamous cell carcinoma. Methods: We retrospectively analyzed 32 patients with stage IIB–IVA cervical adenocarcinoma who were treated with RT or CCRT. Fourteen patients were treated with RT from 1983–1996, 8 with CCRT using cisplatin alone (CCRT-P) from 1997–2002, and 10 with CCRT using cisplatin + paclitaxel (CCRT-TP) after 2003. The patients were treated with external beam radiotherapy, and low-dose or high-dose rate intracavitary brachytherapy. For CCRT-P, the patients received 20 mg/m² cisplatin for 5 days every 3 weeks, and for CCRT-TP, the patients received 50 mg/m² cisplatin every 3 weeks and 50 mg/m² paclitaxel weekly. Results: A complete response was achieved in 7/14 patients in the RT, 4/8 patients in the CCRT-P, and 9/10 patients in the CCRT-TP group. Ten of the 14 patients in the RT, 7/8 patients in the CCRT-P, and 2/10 patients in the CCRT-TP group experienced locoregional recurrence. The 5-year overall survival rate in the RT, CCRT-P, and CCRT-TP groups was 7.1%, 25.0%, and 74.1%, respectively (p = 0.0094), and their central disease-free survival rate was 21.4%, 12.5%, and 78.8%, respectively (p=0.0119). The acute toxicities associated with CCRT-TP are manageable. Regarding late toxicity of CCRT-TP, no grade 3/4 adverse effect was observed. Conclusions: The present study demonstrated that CCRT-TP achieved much better local control for adenocarcinoma of the cervix, leading to a decrease in locoregional recurrence. Prospective trials in larger series of patients are urgently needed.
How is the current clinical management of endometrial cancer worldwide? An international survey by the North-Eastern German Society of Gynaecological Oncology (NOGGO).

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Background: Indication, technique and extent of lymph-node-dissection (LND) in endometrial cancer (EC) remains controversial and is strongly debated in cancer community. We conducted a national- and at a second step an international-survey evaluating the current status-quo of the surgical and medical management of EC.

Methods: A validated 15-item-questionnaire regarding surgical and adjuvant procedures of EC was sent to all major gynecological cancer societies and study groups worldwide. The questionnaire could also be answered online.

Results: In a phase-I-national trial, the questionnaire was validated on basis of 316 German institutions. On the phase-II-international survey a total of 302 questionnaires were answered from 24 countries, mainly from Japan (38.7%), Spain (8.3%), Austria (7%), United-Kingdom (6.3%), Italy (6%), USA (4.3%) and Canada (4%). The vast majority of the participating clinics were academic (62.8%), while 75.2% of them belonged to gynaecology. Only 0.7% of the clinics internationally reported never performing LND in EC. 62.3% of the clinics perform both a pelvic and paraaortic lymph node dissection. 59.1% of the participants performed a systematic lymph node dissection with the intention of both adequate staging and for therapeutic value. 15.05% of the clinics perform LND up to the common-iliac-arteries, 9.03% up to the inferior-mesenteric-artery and 70.6% up to the renal-veins. The most common risk-factors to indicate LND were: high-grading (93%), non-endometrioid-histology (90.1%), lymphovascular-invasion (55.3%), blood-veinvasion (45.4%) and tumor-diameter >2cm (38.4%). For advanced stage III&IV disease the vast majority (60% and 80%, respectively) of the physicians indicated systemic chemotherapy alone.

Conclusions: This study presents the large variety in clinical management of EC worldwide, underlining so the high need of future prospective randomised trials which will establish standard and evidence based treatment guidelines for EC- disease.
The impact of racial disparity on outcomes of patients with early-stage uterine endometrioid carcinoma in an equal-access environment.

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Background: To determine if racial disparity exists between African American (AA) and non-African American (NAA) patients with early stage uterine endometrioid carcinoma who had similar multidisciplinary management. Methods: Our prospectively-maintained database of 1,450 uterine cancer patients was reviewed for this IRB-approved study. We identified 766 consecutive patients with endometrioid carcinoma 1988 FIGO stages I-II who underwent hysterectomy between 1987-2009. Patients with non-endometrioid carcinoma, mixed histologies and those who received preoperative treatments were excluded. For the purpose of data analysis, patients were divided into two groups; AA and NAA. Recurrence-free survival (RFS), disease specific (DSS) and overall survival (OS) was calculated from the date of hysterectomy using the Kaplan-Meier method. Cox regression modeling was used to explore the risks of various factors on recurrence. Results: Median follow-up was 5.1 years. 27% were AA and 73% were NAA. All patients underwent hysterectomy and oophorectomy. 80% had peritoneal cytology and 69% underwent lymphadenectomy. AA patients were more likely to have higher grade tumors, and more lymphovascular space involvement (LVSI). Although the two groups were balanced in regards to surgical staging and adjuvant treatment received, the five-year RFS and DSS were significantly lower in AA compared to NAA patients (91% vs 84%, p=0.030; 95% vs 88%, p=0.011, respectively). Between the two groups, OS was not significantly different. On multivariate analysis and after adjusting for other prognostic factors, race (AA vs NAA) was not a significant predictor of outcome. Grade 3 tumors and the presence of LVSI were the only two independent predictors of RFS and DSS with p=<0.001 and p=<0.001, respectively. Conclusions: In this large hospital-based study, AA race was associated with a higher incidence of adverse pathological features and worse recurrence-free and disease-specific survival. However, on multivariate analysis race was not an independent prognostic factor. Further studies are needed to elucidate possible underlying molecular mechanisms for these poorer outcomes.

Association of smoking with pulmonary recurrences among women with intermediate- to high-risk early-stage endometrial adenocarcinoma.

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Background: While a number of histologic risk factors have been identified in endometrial carcinoma, host factors are less well studied. Our aim was to examine the influence of smoking on the risk of pulmonary recurrences in women with early stage intermediate to high-risk endometrioid uterine cancer (EC).

Methods: Women with surgically treated stage I or II EC from 1994 to 2010 were included in this study if they had lymphovascular space invasion (LVSI), FIGO grade 2 or 3 histology (G2/3), or outer half myometrial invasion (OI). All demographic, medical and oncologic data were obtained from chart review. Patients were excluded if their follow-up period was less than six months or if they had a diagnosis of a second primary invasive cancer. We performed univariate and multivariate logistic regression analyses and Fisher’s Exact test for two-way analyses of categorical variables to identify prognostic factors of pulmonary recurrences. Significance was determined by two-sided tests with $\alpha=0.05$. Results: 349 patients were identified to meet histologic criteria, 3% were excluded. The remaining 337 patients had a median follow-up of 60 months (range 6 to 194). The median age of this cohort was 68 years and median BMI was 30.7 kg/m2. 81 patients (24%) had a past or present history of smoking. There were 14 pulmonary recurrences (4.1%), 36 (10.7%) distant recurrences and 58 (17.2%) total recurrences in the cohort. Smoking (present or past) was significantly associated with pulmonary recurrences, with an odds ratio of 1.09 (95% CI 1.04-1.15; $P=0.0002$). In a multivariate analysis adjusting for age, BMI, grade, LVSI, OI, cervical invasion, and adjuvant therapy, smoking was still a predictor of pulmonary recurrences. Conclusions: Smoking is a significant and independent predictor of pulmonary recurrences among women with early stage EC. Refining our understanding of host factors that influence risk may further allow us to identify those who may benefit most from adjuvant therapies as well as intensive surveillance.
External validation of a nomogram predicting overall survival (OS) of women with uterine leiomyosarcoma (ULMS).

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Background: A nomogram for predicting OS of women with ULMS was developed, given the poor prognostic performance of FIGO and AJCC staging systems. We aimed to determine the validity of the ULMS nomogram using independent, external cohorts. Methods: The ULMS nomogram incorporates 7 clinical characteristics: age at diagnosis, tumor size, grade, involvement of cervix, locoregional metastases (direct extrauterine spread, locoregional lymph node), distant metastases, and mitotic index (per 10 HPF) to predict OS following primary surgery. Two independent cohorts from sarcoma centers (1 US, 1 Europe) were included. Eligible women were treated at the institutions (1994-2010) and had undergone hysterectomy. Women with locally advanced or metastatic disease who underwent more extensive surgery were included if the primary tumor (uterus) was resected. Women who previously underwent resection of the primary tumor or recurrences at other institutions were included if they received followup care at 1 of the centers. Women who presented with unresectable disease who never underwent surgery and those with insufficient information on any of the nomogram variables were excluded. Results: 187 women with ULMS were identified who met the above criteria (median age 51 yrs, median tumor size 9 cm, median mitotic index 20). Tumors were generally high grade (88%), FIGO stage I-II (61%) without cervical involvement (93%) and without locoregional (77%) or distant metastases (83%). Median and 5-yr OS rates were 4.5 (95% CI 3.2-5.3) yrs and 46%, respectively; 65 women (35%) were alive at last follow up. The nomogram concordance index was 0.67(SE=0.02) which was as high as the concordance index from the initial cohort used for nomogram development. The concordance between actual OS and nomogram predictions suggests excellent calibration of the nomogram in the validation cohort. Predictions were within 1% of actual 5-yr OS rates, except for the patients with a 5-yr OS rate of greater than 0.68. Conclusions: The ULMS nomogram was externally validated and can be generalized to independent cohorts. The nomogram provides a more individualized and accurate estimation of OS of women diagnosed with ULMS following primary surgery.

Pair box (PAX8) protein to predict disease recurrence and its association with outcome in women with endometrial cancer: A retrospective study of 229 patients.

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Background: Pax-8 is a member of the pair-box (PAX) family of transcription factor genes and it has been found to be overexpressed in numerous cancer cell lines including ovarian and endometrial. Possibly, inhibition of Pax8 activity may even have an impact on cancer treatment. However the role of Pax8 in human endometrial cancer has not yet been explored. Thus, the aim of this study is to determine its predictive value in disease outcome of endometrial cancer. Methods: 229 patients with available clinical data and paraffin-embedded tissue were available for review and analysis. The clinical parameters used for modeling were age, histologic subtypes, myometrial depth of invasion, lympho-vascular invasion (LVI), FIGO grade, lymph nodes positive, recurrence, disease status, recurrence time and survival time. To test the association between Pax8 and the clinical parameters, Fisher’s exact test was performed. For survival analysis, Kaplan-Meier method was performed. Results: We found a strong association between PAX8+ and high tumor grade (p=0.002), LVI + (p<0.018), and type II tumor subtype. Patients with tumor expressing Pax8 were more likely to present with shorter OS and DFS p= 0.00096 and p=0.018 respectively. There was an association of PAX8 with OS (p=0.01486) with 5-years OS probability of 80.04% for patients with Pax8- and 55.9% for patients with Pax8+. There was also an association of PAX8 and DFS probability (p=0.02028) with 5-years DFS probability was of 72.12% for patients with Pax8- versus 49.88% for patients with Pax8+ expression. Conclusions: Pax8 is a reliable marker in endometrial cancer and its overexpression can predict poor outcome.
Prognostic value of lower uterine segment involvement in high-grade endometrial cancers.

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Background: To determine the relationship of lower uterine segment (LUS) involvement and clinical-pathologic outcomes in high grade endometrial cancers (EC). Although LUS and prognosis has been previously reported in the literature, the results have been conflicting and limited to early stage cases without focus upon the highest risk histologies. Methods: A single-institution retrospective cohort analysis of all grade 3 EC from Jan 2005- Sept 2010 was performed. Clinical-pathologic data were abstracted. LUS status was determined based on permanent-section pathology. Statistical analyses were performed using univariate and bivariate analyses with t-tests, X2, and log-rank tests. Multivariate regressions were performed by cox modeling. Two sided p-values<0.05 were considered significant. Results: Of 329 cases, 52% were LUS+. Mean age was 66.1(SD 10.8) and BMI 31.7(SD 8.3). The majority were Caucasian (63.2%) and 30.1% were African-American (AA). Most women (80.2%) were overweight or obese, 58.7% had hypertension, and 22.5% were diabetic. Most women had stage I disease (54.8%), but 8.6% had stage II disease, and 36.6% had stage III-IV disease. Histologic subtypes included 32.2% endometrioid, 47.4% serous/clear cell, and 17% carcinosarcoma. Thirty-nine percent had > 50% myometrial invasion (MI) and 43.2% had LVSI. Most of the women (80.8%) underwent retroperitoneal node dissection (77.9% pelvic, 70.0% periaortic). Mean follow-up time was 24.5 months (range 0.13, 73.3). Age, HTN, and DM did not differ by LUS status. Statistically significant factors associated with LUS positivity included race AA (38.3 v 26.5%), obesity (57.5 v 46.7%), serous/clear cell (65.7 v 53.8%), LVSI (56.2 v 30.5%), deep MI (52.1 v 25.3%), and positive nodes (42.4 v 12.7%). LUS+ was significantly associated with an increased rate of recurrence (HR 2.3, CI 1.16-4.47, p =0.02) after adjusting for obesity, deep MI, LVSI, nodal status, stage, serous/clear cell histology, and adjuvant therapy. Conclusions: Lower uterine segment was independently associated with an increased rate of recurrence in high grade EC. This should be confirmed in prospective endometrial trials to see if this remains an independent predictor of recurrence.
Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer.

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Background: The aim of this study is to evaluate the efficacy, in terms of overall survival and progression free survival, and safety of adjuvant chemotherapy after neoadjuvant chemotherapy followed by radical surgery both in patients with and without node metastases. Methods: Between June 2000 to May 2007, all patients with diagnosis of locally advanced cervical cancer referred to the Division of Gynecologic Oncology of the University Campus Bio-Medico of Rome were eligible for this protocol. All enrolled patients received 3 cycles of platinum-based chemotherapy every 3 weeks according to the scheme cisplatin 100 mg/mq and paclitaxel 175 mg/mq. After neoadjuvant chemotherapy all patients with stable or progression to treatment were excluded from the protocol, all other were submitted classical radical hysterectomy and bilateral systematic pelvic lymph node dissection, and after to adjuvant treatment with 6 cycles of platinum based chemotherapy with cisplatin 100 mg/mq and paclitaxel 175 mg/mq. Results: 110 patients with local advanced cervical cancer received the treatment with neoadjuvant chemotherapy followed by radical surgery and adjuvant chemotherapy. Our study focused on clinical and operative data, in terms of overall survival and disease free survival at 5 and 3 years. 5-year OS of our series was 78% at five years and 86% at 3-years, with encouraging results also in subgroup with and without node metastases. Conclusions: The adjuvant chemotherapy regimen after neoadjuvant chemotherapy and radical surgery represents a valid treatment option for patients with locally advanced cervical cancer without lymph node involvement, both in terms of overall survival than in terms of disease-free interval, the results have also confirmed the validity of this approach in lymph node metastases, with a complication rate lower than the standard radio-chemotherapy regime.
The novel biomarker HE4 versus CA125 in detecting endometrial cancer: A case control prospective study.

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Background: In endometrial cancer, there are no markers routinely used in clinical practice. This study prospectively investigates the sensitivity and specificity of new marker HE4 in detection of endometrial cancer. Methods: Serum samples were prospectively obtained 24 hours before surgery from 25 patients with endometrial cancer and from 25 patients with uterine benign pathology, operated from January 2011 to October 2011 at University Campus Bio-Medico of Rome. Preoperative CA125 levels were evaluated by a one-step “sandwich” radioimmunoassay. HE4 levels were determined using the HE4 enzymatic immune assay. The CA125 normal value is considered less than 35 U/mL. Two HE4 cut-off are considered: less than 70 pmol/L and less than 150 pmol/L. The specificity analysis was performed using the parametric T-Test for comparing the HE4 series and the Mann-Whitney test for the CA125 series. The level of statistical significance is set at p < 0.05. Results: The sensitivity of CA125 in detecting endometrial cancer is 16% whereas the sensitivity of HE4 is 48% and 28 % for 70 pmol/L and 150 pmol/L cut-off respectively. The specificity of HE4 is 100% (positive predictive value = 100%, negative predictive value = 65.79% and 58.14% considering the two HE4 cut-off, respectively), whereas the CA125 specificity is 72 % (positive predictive value = 36.36%, negative predictive value = 46.15%) in detection of endometrial cancer. Conclusions: HE4 has a good sensitivity and a specificity of 100% in detection of endometrial cancer and may be useful for detecting early stage endometrial cancer. In particular the HE4 at cut-off of 70 pmol/L yields the best sensitivity and specificity.
Association of adjuvant therapy in early-stage low-risk endometrial cancer with increased mortality: A statewide cancer registry analysis.

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Background: National Comprehensive Cancer Network (NCCN) guidelines state that patients with early stage low risk endometrial cancer (defined with 2009 criteria as stage IA endometrioid endometrial cancer) may be managed with observation with consideration of adjuvant therapy. The premise of this study is to review the patterns of care of those patients who received adjuvant therapy and its impact on survival.

Methods: This is a retrospective cohort analysis of 1044 women from 2004-2008 in the Kentucky Cancer Registry (KCR) one of the affiliates utilized in the Surveillance, Epidemiology and End Results (SEER) Program database. Inclusion criteria for the patients in this analysis were those women with 2009 Stage IA uterine cancer of endometrioid histology, moderate and well differentiated tumor grade, who received definitive primary surgery. Adjuvant therapy was defined as any postoperative radiotherapy and/or chemotherapy after definitive surgical treatment. Patients with adjuvant therapy after surgery (AT) were compared to those patients who underwent surgery only (SO). Chi-square tests were used to identify associations between type of treatment and clinical/demographic factors. K-M plots and Cox regression models were used to examine survival between the two treatment groups.

Results: 5.3% (55/1044) of patients with early stage low risk endometrial cancer were treated with AT compared to 94.7% (989/1044) of SO patients. No statistical differences in mean age, race, tumor size, smoking status, insurance status, lymph node dissection and gynecologic oncology care were found among the AT or SO groups. Five year survival was significantly better in the SO cohort compared to the AT cohort (92% alive at 5 years for SO vs. 66% alive at 5 years; p<0.0001). Controlling for other confounders in the multivariate Cox regression analysis, SO patients had substantially less risk for death compared to the AT groups (HR: 0.21; 95%CI 0.12-0.38; p<0.0001).

Conclusions: In this statewide cancer registry analysis, adjuvant therapy after surgery in early stage low risk endometrial cancer patients is uncommon and is associated with an increased risk of mortality.
Phase II trial on cisplatin-doxorubicin hydrochloride-paclitaxel (TAP) combination as neoadjuvant chemotherapy (NACT) for locally advanced cervical adenocarcinoma (LACA).

**Background:** NACT followed by surgery is a different therapeutic approach to locally advanced cervical cancer that seems to offer specific advantages over chemoradiation such as potential activity against distant micrometastases, a debulking effect improving subsequent surgical outcome, less toxicity, and an easier management of salvage therapy. This phase II trial was designed to evaluate the toxicity and activity of NACT with TAP in patients with LACA. **Methods:** Patients (pts) with FIGO stage IB2 (9 pts)- II (21 pts) uterine adenocarcinoma were treated with cisplatin 70 mg/mq, doxorubicin hydrochloride 45 mg/mq and paclitaxel 150 mg/mq day 1 every 21 days for 3 cycles. Eight pts (26.6%) presented with positive lymphnodes (+LY) at diagnosis (5 pelvic and 3 pelvic/paraortic). After the last cycle of chemotherapy patients underwent radical surgery with lymphnode dissection. Clinical responses to chemotherapy was evaluated according to Recist criteria. Pathological response was classified as no residual tumor (pCR), residual disease with <3 mm stromal invasion (pR1) or residual disease with >3 mm stromal invasion (pR2). Due to the slow accrual the trial was closed before the target population of 45 pts was reached. **Results:** Between 2003 to 2010, 30 women were enrolled. Two complete clinical responses (6.7%), 21 partial responses (70%) and 7 stabilizations of disease (23.3%) were registered. All the patients underwent radical surgery and were assessable for pathologic responses. Five patients (16.6%) achieved a pCR, 8 (26.6 %) a pR1 response; 17 patients (56.7%) a pR2 response. At pathological assessment 10 pts (33.3%) presented with +LY (7 pelvic, 1 paraortic, 2 pelvic+paraortic). At a median follow up of 45 months progression free survival and overall survival were 37 months (95% CI 1-98) and 45 months (95% CI 9-101+) respectively. Hematologic toxicity was the most relevant side effect with 13 pts (43 %) reporting grade 3-4 neutropenia. **Conclusions:** The TAP combination seems to be feasible with an acceptable toxicity profile and a promising response rate for the treatment of LACA. The effect of NACT on lymphnodes status warrant further investigation.
Analysis of somatic mutation in miRNAs and miRNA regulation-related genes in gynecological cancers: New frameshift mutation of TNRC6A found in endometrial cancer.

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Background: Micro RNAs (miRNAs) are small non-coding RNAs which plays an important role in tumorigenesis and mutation of a miRNA gene or miRNA regulation-related gene may cause butterfly effect on alteration of global gene expression. In order to investigate this hypothesis, high resolution melting analysis (HRM) and denaturing high-performance liquid chromatography (DHPLC) were used to screen 20 miRNA genes and 6 miRNA regulation-related genes for mutations in gynecologic cancers. Methods: In this study, 182 DNA samples from breast cancer tumors, 42 from ovarian cancers and 28 from endometrial cancers were obtained. 18 human cancer cell lines were also included. We used HRM and/or DHPLC to screen mutations of these genes in human cancer cell lines and tumor tissues. All samples with curves that differed in shape compared to wild-type were directly sequenced for confirmation. Secondary structures for the wild-type and variant primary precursor of miRNA sequences obtained from sequencing were predicted using RNAfold software. Western blot and immunohistochemistry were used to evaluate the related protein change in cancer cell line and tumor tissues. Results: Polymorphisms of these genes were very frequently observed in gynecologic cancers. Two rare variants were found in the primary precursor sequences of mir-200c and mir-142 gene. Moreover, a novel frameshift mutation (c.3547_3548insA) in TNRC6A gene was found in two endometrial cancer cell lines (RL95-2 and Hec-1A) and endometrial cancers (1/28). Western blot and immunohistochemistry showed loss of expression of TNRC6A protein in the endometrial cancer cell lines and endometrial cancers with this mutation. Conclusions: Two rare novel variants in 20 miRNA genes and a novel frameshift mutation in TNRC6A gene were identified in gynecologic cancers. Our data indicate that mutations in TNRC6A gene may contribute to the cancer development and might be a potential new therapeutic target in endometrial cancer.
Background: Poor data exist on clinico-pathological description of endometrial cancer (EC) in Lynch syndrome (LS) compared with sporadic ones. To evaluate the clinico-pathological findings of Lynch-related EC to establish histological criteria to discriminate familial and sporadic EC and to decide the optimal management of patients. Methods: Retrospective study of prospective cohort of patients with LS in our institution from 1999 to 2011. We identified and described all cases of endometrial cancers. Management and follow-up were detailed. Results: Of a cohort of 126 patients with LS, 10 women developed endometrial carcinoma. The median age at diagnosis was 51 years (41-58). Five patients had an identified mutation (2 hMLH1, 2 hMSH2 and 1 hMSH6). In 9 cases, EC was the first Lynch-related tumor to occur. No patient developed ovarian cancer. All, except 2 patients (1 serous carcinoma and 1 clear cell carcinoma), had endometrioid adenocarcinoma (80%). Tumor grade was grade 1 in 3 patients, grade 2 in 5 and grade 3 in 2 patients. Forty per cent of patients had lymphovascular space involvement (LVSI). The FIGO stages were as follows: stage IA (n=7), stage IB (n=2) and stage IIIC (n=1). Four in ten patients had tumor located in the lower uterine segment. With a median follow-up of 14 months (range 9 – 40 months), recurrence occurred in one patient with a stage IB grade 2 endometrioid adenocarcinoma with LVSI. Conclusions: EC in LS is characterized by early age at onset, localization in lower uterine segment, and high rate of LVSI. Other data on histology and survival do not differ from sporadic cancers. These results suggest that we can consider conservative treatment in patients with good prognosis tumors. Further studies are required.
Prognostic factors and treatment-related outcomes in patients with uterine serous cancer (USC).

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Background: USC an uncommon (10%) but aggressive form of uterine cancer, causes 50% of uterine cancer deaths. The purpose of this study is to report a large single-institution experience with USC investigating the effects of clinicopathological parameters and treatment on overall (OS) and disease-free survival (DFS). Methods: Records from our institution were reviewed from 1987-2009. All 334 USC patients (pts) identified were surgically staged. Postoperative treatments used were: (1) observation (OBS, n=33); (2) platinum-based chemotherapy (PCH, n=78); (3) whole pelvis radiation therapy (WPRT, n=16); (4) PCH and vaginal apex brachytherapy (PCHR, n=165); (5) vaginal apex brachytherapy (VAB, n=35). The cancer stages were 121 pts IA (36.2%), 36 IB (10.8%), 27 II (8.1%), 39 IIIA (11.7%), 2 IIIB (0.6%), 32 IIIC1 (9.6%), 9 IIIC2 (2.7%), 28 IVA (8.4%) and 40 IVB (12%). Results: The 5-year OS for stage IA/IB, II, IIIA/IIIB, IIIC1/IIIC2, IVA/IVB were 82%, 70%, 64%, 36%, and 9%, respectively. The 5-year DFS for stage IA/IB, II, IIIA/IIIB, IIIC1/IIIC2, IVA/IVB were 82%, 70%, 64%, 36%, and 9%, respectively. The 5-year OS for stage IA/IB disease was 94% for pts who received PCHR, 90% for OBS, 75% for PCH, 65% for VAB and 0% for WPRT. The 5-year DFS for PCHR, OBS, PCH, VAB and WPRT for Stage IA/IB were 89%, 82%, 86%, 72% and 0% respectively. For stage II-IVB pts, the 5-year OS was 51% for PCHR, 0% for OBS, 23% for PCH and 20% for WPRT. The 5-year DFS for stage II-IVB with PCHR, OBS, PCH and WPRT were 42%, 0%, 17% and 13% respectively. Older age pts had worse survival, (p<0.01). Race and BMI did not impact survival. Incomplete surgical debulking (p<0.01), depth of myometrial invasion >50% (p<0.01) and lymph node metastasis (p<0.01) were all associated with worse prognosis. Conclusions: PCHR overall exhibited better OS and DFS regardless of disease stage. Age, incomplete surgical debulking, depth of myometrial invasion and lymph node involvement were independent prognostic factors in USC patients in this study.
The effects of age on treatment and outcomes in women with stage IB-IIB cervical cancer.

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Background: Advanced age may affect the treatment choice and subsequent outcome in elderly patients with cervical cancer. Given the potential for cure with either surgery or chemoradiation in early stage disease, we aimed to determine whether a patient’s age influenced the treatment received and the outcome.

Methods: Our retrospective cohort identified a total of 303 patients diagnosed with Stage IB1 through IIB cervical carcinoma who were treated at our institution between 2000 and 2010. The eligible patients were divided into two groups based on age at the time of diagnosis: <65 and ≥ 65 years. Adjusted odd ratios were calculated to determine variables associated with treatment received (chemoradiation or surgery). Single and multivariate Cox proportional hazards modeling were used to estimate hazard ratios for variables associated with disease specific survival.

Results: Of the patients meeting inclusion criteria, 253 were <65 years and 50 were ≥ 65 years. The distribution of tumor histology, stage and grade was not different between the two groups. After adjusting for histology, stage and a validated comorbidity score, the odds ratio of receiving chemoradiation vs. surgery for the cohort ≥ 65 years was 1.69 (OR 95% CI: 0.68-4.17). There was no significant difference in the type of primary treatment received between the two groups (P = 0.16). Persistent disease was seen in 46 (18%) of the younger patients and in 19 (38%) of the older patients (P = 0.02). In the elderly cohort the treatment received did not influence disease-specific or all-cause mortality. However, compared to women under 65, older women treated surgically had increased disease specific (HR 3.18, 95% CI: 0.98-10.3) and all-cause mortality (HR 6.53, 95% CI: 2.57-16.6).

Conclusions: Age does not appear to be a factor influencing the treatment received by patients with Stage IB1-IIB cervical cancer. The type of treatment received does not seem to affect disease-specific mortality among older versus younger women. However, surgery was associated with a 6.5-fold increased risk of all cause mortality among older women when compared to women under 65 years.
Phase II trial of topotecan, cisplatin, and bevacizumab for recurrent or persistent cervical cancer.

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Background: The prognosis associated with recurrent or persistent cervical cancer is exceedingly poor. GOG-179 demonstrated a survival benefit with the combination of cisplatin and topotecan compared to single-agent cisplatin, with the former showing median PFS of 4.6 months, median OS of 9.4 months, and a 27% objective response rate. The role of angiogenesis in cervical carcinogenesis and progression has been well documented. We evaluated the activity and safety of the combination of topotecan, cisplatin and bevacizumab in patients with incurable carcinoma of the cervix.

Methods: Patients with histologically proven measurable recurrent or persistent cervical carcinoma not amenable to curative intent treatment were eligible. No prior chemotherapy for recurrence was allowed. Cisplatin 50 mg/m² day 1, topotecan 0.75 mg/m² days 1, 2 and 3 and bevacizumab 15 mg/kg day 1 were prescribed in a 21-day cycle. Cytokine support was allowed at physician discretion. The primary endpoint was 6-month PFS. Additionally, objective clinical response and toxicity were evaluated. Accrual goal (N=27) was based on a 50% improvement goal in 6-month PFS in relation to GOG-179 (40% to 60%), with a one-sided 0.10 significance and 80% power. Results: 27 eligible patients received a median of 3 treatment cycles (range, 1-19). All patients received radiotherapy as part of their first line treatment. Median follow-up was 8.5 months (1.2-32.9). The 6-month PFS was 59% (95%CI: 38.0-74.7). Among 26 RECIST-evaluable patients, objective response rates were (%; 95%CI): 1 CR (4%; 1-19.6), 7 PR (27%; 11.6-47.8), 11 SD (42%; 23.4-63.1) and 7 PD (27%; 11.6-47.8). Median OS was 9.8 months (95%CI: 7.7-20.6) and median PFS was 7.1 months (95%CI: 2.0-12.1). Grade 3-4 hematologic toxicity occurred in 96% of patients (thrombocytopenia 93% leukopenia 70%, anemia 70%, neutropenia 59%). Other grade 3-4 toxicities were also common (metabolic 48%, pain 37%, genitourinary 30%, constitutional 22% and gastrointestinal 19%). Conclusions: The addition of bevacizumab to topotecan and cisplatin results in a highly active but toxic regimen. Future efforts should focus on identification of predictive biomarkers and treatment modifications to minimize toxicity.
Phase II trial of robotic stereotactic radiosurgery (SBRT) in patients with recurrent gynecologic malignancies.

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Background: Ablative radiation dose delivered by a robotic SBRT platform has shown progression-free survival benefit in two limited case series among patients with recurrent gynecological malignancies. The therapeutic impact of SBRT on disease progression (PD) was evaluated in the recurrent setting in this phase II trial. Methods: Fifty patients with recurrent and measurable gynecologic malignancy were treated with SBRT. The cohort included patients with recurrent ovarian (n = 25), endometrial (n = 14), cervical (n = 9), or vulvar (n = 2) cancer, 1 prior chemotherapy or radiation regimen, and GOG performance status 0, 1, 2. Patients underwent image-guided SBRT in 3 daily doses of 800 cGy = 2400 cGy. SBRT planning target volumes were determined by both the radiation and gynecologic oncologist using non-contrasted CT and 18F-FDG PET/CT overlays. The primary endpoints were 6-month clinical benefit rate (# complete response + # partial response + # stable disease without PD [by RECIST v1.0] / 50), and less than 30-day posttherapy toxicity. Results: Between July 2009 and September 2011, 50 patients were enrolled and have a median posttherapy follow-up of 9 months. At 3 months, 50% (n = 25) had complete response, 46% (n = 23) had partial response, and 4% (n = 2) had stable disease in SBRT-targeted lesions. Twenty-six patients (52%) have had non-SBRT target PD and 18 (36%) have died of PD. Of the 50 patients, 33 had a PD-free interval of at least 6 months, for an overall clinical benefit rate of 66%. Less than 30-day posttherapy SBRT-related toxicities were grade 2 fatigue (n = 9 [18%]), grade 2 nausea (n = 3 [6%]), grade 3 nephropathy (n = 2 [4%]), and grade 4 hyperbilirubinemia (n = 1 [2%]). Conclusions: This is the first phase II clinical trial of SBRT showing a clinically relevant benefit of ablative radiation in the setting of recurrent gynecological disease. Despite excellent control of targeted lesions with minimal toxicity, non-SBRT target PD rates are high, spurring interest for future SBRT-chemotherapy clinical trials.

Neoadjuvant chemotherapy of docetaxel and carboplatin in patients with stage Ib2 to IIb non-squamous cervix cancer of the uterus.

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**Background:** Non-squamous carcinoma of the uterine cervix has a resistance to radiation therapy and chemotherapy, and this is associated with worse prognosis compared with squamous carcinoma. This is a phase II study to assess an efficacy and safety of neoadjuvant chemotherapy of docetaxel and carboplatin (DC therapy) in patients with stage Ib2 to II non-squamous cervix cancer of the uterus. **Methods:** Patients with histologically confirmed, stage Ib2-II non-squamous uterine cervix cancer were received DC therapy prior to type III radical hysterectomy. IV docetaxel was administered at 60 mg/m$^2$ followed by IV carboplatin administration based on AUC=6. The treatment was repeated every 21 days for a total of 1 to 3 cycles. Surgery was performed as soon as sufficient response was obtained. **Results:** Fifty-three women with non-squamous cervical carcinoma (FIGO stage Ib2, 15; IIa, 7; IIb, 31) received DC therapy. Median age and tumor size were 49 years old (range: 27-71) and 52mm (range: 10-92), respectively. Fourty of 47 patients (74%) received 2 cycles of chemotherapy. Clinical response occurred in 69.8% of patients (complete response, 5; partial response, 32; stable disease, 15; disease progression, 1), and 96% (52/54) of patients completed the surgery. Incidences of grade 3/4 hematological toxicities were 98% (53/54) for neutrocytopenia, 4% (2/54) for thrombocytopenia, and 9% (5/54) for anemia. Febrile neutropenia was observed in three patients. Observed grade 3/4 non-hematological toxicities included were 5 for nausea, 2 for vomiting, 3 for constipation, 4 for allergic reaction. Median follow-up duration was 860 days with a range of 147-1635 days. The 2-years progression-free survival rate and 2-years overall survival rate were 63% and 79% in stage IB2, 71% and 86% in stage IIA2, and 67% and 86% in stage IIB, respectively. Twenty patients recurred and twelve patients died. **Conclusions:** Neoadjuvant chemotherapy using DC therapy was well tolerated and had good response. It seems to be beneficial in patients with stage Ib2 to II non-squamous cervical cancer.
A phase II study of dose-dense neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma.

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Background: We prospectively studied dose dense neoadjuvant chemotherapy (NACT) designed for an enhanced cell kill, better local control and eradication of micrometastases prior to standard concurrent chemoradiation (CRT) in locally advanced cervical cancer. Methods: Between June 2010 and December 2011, 21 patients (median age - 51 years, range 35 - 67) of cervical cancer with locally advanced disease received NACT using paclitaxel (60mg/m²) and carboplatin (AUC-2) weekly for 6 doses. Patients (pts) then received concurrent CRT (external and brachytherapy) with weekly cisplatin (40mg/m² for 6 doses) at a mean interval of 15 days (range 7–20 days). The primary end-point was response rate i.e. complete response (CR) and partial response (PR) 12 weeks post CRT. Results: Baseline stages were: stage 2A - 19%, 3B - 71.4%, 4A - 9.5%. Squamous cell carcinoma and adenocarcinoma constituted 95.2% and 4.7% pts respectively. Following NACT, 66.6% pts responded (CR -9.5% ; PR – 57.1 %), 23.8% had stable disease (SD) and 4.7% had progressive disease (PD). A total of 18 pts completed NACT and CRT of which 17 were in CR and 1 in PR. One patient with stage 4A disease developed vesicovaginal fistula at end of NACT for which she underwent pelvic exenteration and was in pathological CR. After NACT, one patient developed choroid metastases and was taken off study protocol while another patient was lost to follow up. At a mean follow up 5.8 months (range 1 - 14), 90% pts were in CR, 5% in PR and 5% had PD. During NACT, Grade 3/4 neutropenia, thrombocytopenia and anemia were seen in 33.3%, 4.7% & 9.5% of pts, respectively and grade 3/4 non-hematological toxicities in 9.5% pts. Following CRT, Grade 3/4 neutropenia, thrombocytopenia and anemia were seen in 25%, 5% and 10% of pts, respectively while 20% pts had grade 3/4 non-hematological toxicities. G-CSF was used in 30% pts during NACT and 25% pts during CRT, respectively. Conclusions: NACT with weekly paclitaxel and carboplatin followed by radical CRT is feasible and is associated with a high response rate in locally advanced cervical cancer. This approach needs to be studied in a phase III trial.
Prognostic significance of high-risk human papilloma virus (HPV), p16, and p53 status in women with vulvar squamous cell carcinoma (VSCC).

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**Background:** The incidence of VSCC is increasing. Studies suggest the presence of two histologically and molecularly distinct subsets of VSCC; one contingent on and another independent of HPV infection. However, it is uncertain if HPV status has prognostic significance. HPV oncoproteins can result in degradation of the tumor suppressor p53, cell cycle deregulation and abnormal expression of cyclin dependant kinase inhibitor p16. The aim of this study was to investigate HPV infection, p16 and p53 in relation to clinical parameters in women with VSCC. **Methods:** Sequential cases of VSCC from patients (pts) treated at Princess Margaret Hospital (PMH) from 2000 to 2008 were reviewed. HPV infection was evaluated by Roche Linear array. A tissue microarray was constructed. p16 and p53 immunohistochemistry was performed. Clinical data was abstracted from medical records and PMH Cancer Database. Survival analysis was performed using Kaplan-Meier curves and log rank test. **Results:** We identified 124 pts with VSCC. HPV was detected in 43/123 (35%) pts (median age 71 ± 16 yrs). HPV16 was the most common serotype (38/43; 88.4%). p16 was expressed in 30/115 (26%) pts and p53 in 59/117 (50.4%) pts. Median age of pts was not different in relation to HPV, p16 and p53 status. Expression of p16 (p<0.0001) and loss of p53 (p=0.007) were associated with HPV infection. Pts with HPV positive tumors were less likely to recur (recurrence rate at 5 years (RR) 12.5% vs 50.3%, p=0.009). HPV positive VSCC were not associated with better 5 yr disease free survival (DFS), 58% vs 31%; p=0.15, or overall survival (OS), 61% vs 61%; p=0.94. p16 positive tumors had a lower RR at 5 yrs, 23.8% vs 59%, p=0.006 and better 5yr DFS (61% vs 27%; p=0.009) but not significant for OS (65% vs 59%; p=0.94). Among pts with HPV positive VSCC, OS and DFS were not different between p16 positive and negative VSCC. In the 46 pts treated with radiotherapy, HPV and p16 positive tumors were associated with a lower RR (p=0.004 and 0.005). p53 expression was not prognostic in any pt group. **Conclusions:** Women with HPV-positive VSCC have a lower risk of disease recurrence. p16-expressing VSCC are associated with reduced disease recurrence and improved DFS.
ADXS11-001 immunotherapy targeting HPV-E7: Preliminary survival data from a phase II study in Indian women with recurrent/refractory cervical cancer.

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Background: ADXS11-001 immunotherapy is a live attenuated Listeria monocytogenes (Lm) bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells. The Lm vector serves as its own adjuvant and infects APC where it naturally cross presents, stimulating both MHC class 1 and 2 pathways resulting in specific T-cell immunity to tumors. Here we describe the preliminary survival data associated with ADXS11-001 administration in Lm-LLO-E7-015, a randomized phase II study being conducted in India in 110 patients with recurrent/refractory cervical cancer who have been treated previously with chemotherapy, radiotherapy or both. Methods: Patients are randomized to either 3 doses of ADXS11-001 at 1 x 10^9 CFU or 4 doses of ADXS11-001 at 1 x 10^9 CFU with cisplatin chemotherapy. Naprosyn and oral promethazine are given as premedications and a course of ampicillin is given 72h after infusion thereby clearing any residual vector. Patients receive CT scans at baseline and Days 84, 184, 273, 365 and 545. The primary endpoint is 12 month survival. Results: As of January 26, 2012, 88 patients have received 200 doses of ADXS11-001; with the percentage of patients alive at 6 months at 62% (34/55); at 9 months at 41% (15/37) and at 12 months at 40% (6/15). Tumor responses have been observed in both treatment arms with 3 complete responses (elimination of tumor burden) and 4 partial responses (≥30% reduction in tumor burden) by RECIST. One serious (Gr3) adverse event and 77 mild-moderate (Gr 1-2) adverse events possibly related to study treatment have been reported in 35% (31/88) of patients. The non-serious adverse events consisted predominately of transient, non-cumulative flu-like symptoms associated with infusion that responded to symptomatic treatment, or resolved on their own within hours of treatment. Conclusions: This immunotherapy can be safely administered to patients with advanced cancer alone and in combination with chemotherapy. ADXS11-001 is well tolerated and presents a predictable and manageable safety profile. Early signs of clinical benefit merit further investigation. Updated findings will be presented at the meeting.
Cervical cancer treatment for operable lesions in a low-resource contemporary setting.

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**Background:** To compare HIV+ and HIV- women with operable cervical cancer in a low resource contemporary setting. **Methods:** A retrospective study using well-matched controls from a Kenyan teaching and referral hospital. **Results:** 183 women were treated for cervical cancer between October 2007 and June 2011. The histologic subtype was squamous cell in all but one case. At presentation, 28 had operable lesions (Stage IA1–IIB1); 7 more received neoadjuvant chemotherapy prior to surgery. HIV seroprevalence was 54% (18/33) among initial operative cases and 57% among the neoadjuvant group (p=ns). Mean age was 42 (HIV+), and 43 (HIV-), (range 25-64). HIV- vs. HIV+ cervical cancer patients (mean CD4 count 373, 50%-<200) were detected by visual inspection with acetic acid (VIA) (18% (2/11) vs 68% (15/22) p=.099), symptoms (27%(3/11) vs 14%(3/22) p=.43), or Pap smear (45% (5/11) vs .09% (2/22) p=.06), respectively. HIV+ patients (two Stage IB1, two Stage IB2) did not require more downstaging than HIV- patients (two stage IIB, one stage IIIA) before surgery (18% (4/22) vs 27% (3/11) p=.63). Surgical treatments were not statistically different in either group and included radical hysterectomy(25), total abdominal hysterectomy(2), cesarean hysterectomy(1), and total vaginal hysterectomy(5). Postoperative complications included fever, dehiscence, DVT, ileus, fistula, and infectious complications (chest, urinary tract, wound). One HIV- patient suffered postoperative fever, vesicovaginal fistula, and wound dehiscence (overall complications .06%). Lymph node involvement was noted in 7 HIV+ and 3 HIV- patients who underwent full staging procedures (p=.004). **Conclusions:** In patients with operable cervical cancer, HIV serostatus does not affect complication rate or influence need for downstaging prior to surgery compared to a well-matched control group. HIV+ patients were not more likely to receive neoadjuvant chemotherapy but were more likely to have positive lymph nodes. VIA detected the majority of cervical cancers HIV+ patients.
Preoperative geriatric assessment (GA) and surgical outcomes in older women with gynecological (gyn) cancer.

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Background: GA can predict surgical outcomes in older patients (pts); however, pre-surgical evaluation for older pts with gyn malignancies has not been well-described. This study will determine the association between GA variables with post-operative morbidity and mortality. Methods: Women 75yrs or older who had geriatric evaluation before any gyn surgery at Memorial Sloan Kettering Cancer Center (MSKCC) between 1/2010-6/2011 were identified. Pre-operative GA included: Mini-Cog Test (cognition), full history, medication list, nutritional status (weight loss >10lbs, albumin), functional status (activities of daily living (ADL), instrumental I-ADL), and Charlson comorbidity index. Outcomes included: delirium, length of hospital stay (LOS), 30-day surgical adverse events (AE, grade 1-5, via prospective-MSKCC surgical database), 30-day hospital readmission and 6-month mortality. Utilizing bivariate analyses, associations between GA measures and post-operative outcomes were evaluated. Results: 72 pts (median age 79yrs, range 75-92) with gyn cancer (54% uterine, 36% ovarian/peritoneal/tubal, 10% cervical/vaginal/vulvar) had gyn surgery. 34 pts (47%) had stage III/IV disease. 21pts (30%) had secondary cancer history. Pt’s baseline GA measures: ADL-dependent (13%), IADL-dependent (19%), weight loss (18%), fall history (18%), mini cog score (median 4, range 0-5), Charlson score (median 2, range 0-9). 24pts (33%) had surgical AE; no significant association with age or GA. Median LOS was 2 days (range 0-20); 11pts (15%) required 30-day readmission. Delirium (p=0.01), nutrition (weight loss p=0.04, albumin p=0.04), anemia (p=0.003) and high comorbidity index (p=0.013) were associated with longer LOS. Six-month mortality was 8%; older age (p=0.02), poor functional status (lower ADL and IADL, p<0.001 and p=0.007), number of medications (p=0.05) and poor cognition (p<0.001) were associated with shorter survival. Conclusions: Surgical morbidity is common in older pts. Although AE’s were not associated with GA variables, GA can detect high-risk features for longer LOS and shorter survival. Further prospective studies with pre-operative GA and interventions are warranted.

Genome-wide association analysis in host characteristics of progression to high-grade cervical intraepithelial neoplasia for women with human papilloma virus infection and normal cytology.

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Background: Although it is well accepted that persistent human papillomavirus (HPV) is necessary for carcinogenesis of cervical neoplasms, the molecular mechanism for progression is unclear. HPV testing is widely used for cervical cancer screening. The hazard ratio of developing cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) in baseline HPV-positive/normal cytology women is 30-50 fold as compared with HPV-negative/normal cytology women. HPV positivity would cause substantial anxiety. It is important to identify a prognostic profile for predicting progression. Methods: We collected blood samples from women aged ≥ 30 years in a population-based nested cohort study enrolling women with HPV infection (n = 871) or HPV-negative (n = 902) with normal cytology in 2004-2009 for prospective follow-up. To identify the host genetic characteristics associated with cervical carcinogenesis, a genome-wide association study (analyzing 530,194 SNPs) was conducted in 23 cases who developed CIN2+ and 62 viral type- and age-matched controls who were HPV-positive at baseline without developing CIN throughout the follow-up period. Results: One SNP with significant P values (rs16969682; P = 4.58 x 10^{-5}, OR=5.9, 95% CI = 2.52-13.96) located in SEC14-like 1 (SEC14L1) gene localized to chromosome 17 was identified with association between progression to CIN2+ and controls without CIN throughout follow-up. SEC14L1 belongs to the widely-expressed SEC14-superfamily. This superfamily consists of > 500 members that are involved in biological functions including membrane trafficking and phospholipid metabolism. Furthermore, using T-cell based cDNA screening, SEC14L-1a is identified as a regulator of HIV-1 replication. Conclusions: The potential role of SEC14L1 in host-viral interaction will be further elucidated. Additional statistically significant SNPs including rs16969682 will be validated on cases with CIN2+ (n = 250) and normal controls (normal cytology/HPV-negative at baseline without acquisition of HPV or abnormal cytology/histology during follow-up, n = 500).
Validation of the predictive value of modeled HCG residual production “P” in low-risk gestational trophoblastic neoplasia (GTN) patients treated in GOG-174 phase III trial.

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Background: In low-risk GTN, chemotherapy is changed according to serum hCG levels. We previously showed mathematical modeling of hCG kinetics provides a parameter production “P”, a useful early predictor of methotrexate (MTX) resistance (You et al; Ann Oncol 2010; ASCO and ISSTD 2011). We applied this approach to patient cohort of GOG-174 trial, in which weekly MTX (Arm 1) was compared to dactinomycin (Arm 2).

Methods: Database (210 patients, including 78 with resistance) was split into 2 sets. A 126 patient Model Set was initially used to adjust model parameters. Patient hCG kinetics from day7 to day50 were fit with NONMEM™ program to: \[
\frac{\text{hCG(time)}}{\text{hCG}_0} = \frac{\text{exp}(-k \times \text{time})}{\text{P}}
\]
where P is residual hCG tumor production, hCG0 is the initial hCG level, and k is the rate constant. Three putative P-based classifiers of resistance were assessed using ROC analyses. Then an 84 patient Test Set with blinded-resistance status was used to assess the validity of predictions. The primary endpoint was treatment resistance defined as relapse and/or lack of hCG normalization.

Results: Due to initial surge in 14% patients, hCG kinetic modeling was started on day7. Individual hCG decline profiles of Model Set patients were modeled. There was no impact of treatment arm on variability of kinetic parameter estimates. The best P cut-offs to discriminate resistant vs. sensitive patients were 7.7 in Arm 1 and 74.0 in Arm 2. They were combined to define 2 predictive groups with low vs. high risks of resistance (ROC AUC = 0.82; Se = 93.8%; Sp = 70.5%). The model was then applied to Test Set patient cohort. The predictive value of P-based predictive groups regarding resistance was reproducible (ROC AUC = 0.81; Se = 88.9% (95% CI: 70.8%-97.7%); Sp = 73.1% (95% CI: 60.0%-84.4%)). Both P and treatment arm were associated with resistance using multivariate logistic regression tests. Predictive value of P was less accurate in dactinomycin arm.

Conclusions: The early predictive value of the modeled kinetic parameter P regarding resistance appears promising in GOG-174 study, especially in MTX arm. This is the second positive evaluation of this procedure study. Prospective validation is warranted.
Nomogram prediction for overall survival of patients diagnosed with cervical cancer.

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Background: Cervical cancer is clinically staged based upon the International Federation of Gynecologists and Obstetricians (FIGO) system. FIGO stage is well established as prognostic parameter. It is well known that other additional parameters are useful to estimate overall survival (OS) in patients with cervical cancer. The aim of this multi-center was to create a nomogram to predict OS in patients diagnosed with cervical cancer.

Methods: Cervical cancer databases of two large Austrian institutions were analysed. Characteristics known to predict OS were collected. For each patient association between each prognostic parameter and OS was assessed by multivariable modeling. The corresponding 3-year and 5-year OS probabilities were then determined using the nomogram. The constructed nomogram was then validated using the bootstrap correction technique.

Results: Mean 5-year OS rates for patients with FIGO stage IA, IB, II, III, and IV were 99.0% (1.0), 88.6% (3.0), 65.8% (5.2), 58.7% (11.0), and 41.5% (14.7), respectively (p<0.001). Mean five-year OS time was 44.2 (30.9) months. Based on the multivariable model FIGO stage, tumor size, age, histologic subtype, lymph node ratio, and parametrial involvement were identified as nomogram parameters. The bootstrap sample corrections provided an estimated concordance probability (interquartile range) of 0.794 (0.779-0.805).

Conclusions: Based on 6 easily available parameters a novel nomogram to predict 3-year and 5-year OS of patients diagnosed with cervical cancer was constructed and internally validated. Application of this nomogram allows more accurate and individual prediction of patients’ prognosis.
OPSALIN: A phase II placebo-controlled randomized study of ombrabulin in patients with platinum-sensitive recurrent ovarian cancer treated with carboplatin (Cb) and paclitaxel (P).

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Background: Most women with ovarian cancer have disease recurrence after responding to their first treatment with platinum-based chemotherapy and are considered to have platinum-sensitive disease if the relapse-free period is more than 6 months. Although CbP is standard first-line chemotherapy for ovarian cancer, patients with platinum-sensitive recurrent disease are often retreated with CbP. Ombrabulin (AVE8062) is a vascular disrupting agent and analogue of combretastatin A4 that damages established tumor vasculature causing tumor necrosis and has synergistic antitumor activity with platinum agents in tumor models in vivo (Cancer Sci. 2003;94:200). A phase I study showed that treatment with vivo ombrabulin plus CbP is feasible in patients with advanced solid tumors (NCI-AACR-EORTC 2010;Abs 386). We initiated OPSALIN, a phase II randomized trial, to evaluate whether the addition of ombrabulin to CbP improves outcomes in patients with platinum-sensitive recurrent ovarian cancer (NCT01332656; EFC10260). Methods: Eligibility criteria include age of at least 18 years, ECOG PS 0–2, measurable carcinoma of the ovarian epithelium, fallopian tube, or primary peritoneum that is platinum sensitive, and completion of only one previous line of platinum-based chemotherapy. Exclusion criteria include uncontrolled brain metastases, peripheral neuropathy ≥ grade 1, and a prior history of cardiovascular disease. Patients are being randomized (1:1) to receive either ombrabulin 35mg/m² or placebo plus CbP every 3 weeks. Assigned treatment will continue until disease progression or death, unacceptable toxicity, or consent withdrawal. The primary endpoint is progression-free survival stratified by the time of first disease recurrence (6–12 months or >12 months). Secondary endpoints include safety, response rate, overall survival, pharmacokinetics, and analysis of predictive/prognostic biomarkers. Planned randomization is a total of 150 patients at approximately 45 sites globally. Sixty-five patients have been randomized as of January 2012.
A study of autologous dendritic cell therapy targeting mucin-1 for treatment of patients with epithelial ovarian cancer in first remission.

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**Background:** Cvac (Cvac) is an autologous dendritic cell immune stimulant targeting mucin-1 positive tumors. A phase IIa study demonstrated potential for treating mucin-1 positive epithelial ovarian carcinoma (EOC). A phase IIb study was designed to determine on a pilot basis if Cvac could demonstrate an effect on progression free and overall survival in patients with EOC in first or second remission. The current study, CANVAS (CANCer VAccine Study) is evaluating Cvac treatment of EOC patients in first remission after surgery and standard chemotherapy, with at least three cycles of platinum and taxane therapy. Endpoints include progression free survival, overall survival, safety evaluation and quality of life scores. **Methods:** Patients are eligible if they have stage III or IV mucin-1 positive EOC and have had optimal cytoreductive (≤1cm residual disease) surgery. Apheresis to obtain immature dendritic cells occurs prior to chemotherapy. Cvac is manufactured during chemotherapy. Patients remain eligible for the study if they have a complete response to standard chemotherapy after surgery. Cvac or placebo is dosed every four weeks for three doses, and every twelve weeks for three additional doses. 1000 patients will be randomized to Cvac or placebo in 22 countries, with 800 expected to receive vaccine or placebo. CT or MRI imaging determines progression, and is centrally read prior to inclusion and at each timepoint. Recruitment commenced January 2012. Over 100 centers are participating in the study globally, with majority in Europe. Enrollment is expected to take 18-24 months. An interim analysis is planned after 400 PFS events, and final analysis after 620 PFS events. Observation of 620 events would have approximately 90% power to detect a hazard ratio of 0.77 in PFS at a significance level of p=0.049 (approximately a 30% increase in median PFS in the Cvac group compared with the placebo group).
ACRIN 6695 perfusion CT as prognostic imaging biomarker in ovarian cancer.

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Background: Tumor size and the cell surface glycoprotein CA125 levels have been traditional biomarkers for ovarian carcinoma, but remain suboptimal for assessing patients receiving chemotherapy. Current morphological criteria do not adequately evaluate lesion necrosis from anti-angiogenic therapy when no tumor volume change is measured. The evaluation of functional biomarkers rather than tumor volume may better distinguish responders from non-responders early in treatment with anti-angiogenic therapy. Perfusion CT can evaluate changes in tumor vascularity including blood flow (BF), blood volume (BV), mean transit time (MTT) and capillary permeability surface product (PS) before and after anti-angiogenic therapy with/out decrease in tumor volume. Objectives: The aims of the study are to evaluate the relationship between changes in tumor perfusion parameters and clinical outcomes of progression free survival, overall survival, and standard RECIST anatomic response criteria. A test-retest perfusion CT scan will also be performed to evaluate reproducibility of perfusion parameters in a subset of participants. Methods: In this collaborative trial, participants will be co-enrolled in the GOG-262 treatment trial. Participants will receive doublet chemotherapy of paclitaxel and carboplatin, followed by anti-angiogenic monoclonal therapy at cycle two. Perfusion CT will be performed at three time points: at baseline prior to therapy (T0), between days 18 and 21 of cycle one chemotherapy (T1), and at 8-10 days (T2) in anti-angiogenic monoclonal therapy. Participants with primary epithelial ovarian, peritoneal or fallopian tube cancer with optimally or suboptimally debulked FIGO Stage II, III or IV disease are eligible for the trial. Lesion eligibility will be evaluated by size and attenuation criteria. Accrual: ACRIN 6695 is activated at 12 GOG sites; 4/78 participants have accrued Discussion: Perfusion CT has been readily incorporated into the pre-existing clinical CT protocols and during scheduled RECIST scans. These perfusion CT functional maps of BF, BV, MTT and PS have been generated using vendor provided software without issue. Contact: Please contact Chaan Ng, MD cng@mdanderson.org for additional information.

A phase II study of live-attenuated *listeria monocytogenes* immunotherapy (ADXS11-001) in the treatment of persistent or recurrent cancer of the cervix (GOG-0265).

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**Background:** This is a GOG/NCI sponsored phase II study (NCT01266460, GOG 0265) of ADXS11-001 in patients with persistent or recurrent cancer of the cervix. ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*) immunotherapy bioengineered to secret a HPV E7 fusion protein targeting HPV-E7 transformed cells. A previous phase I dose escalation study determined the safety of ADXS11-001 in patients with late stage cervical cancer (Maciag PA. Vaccine. 2009 Jun 18;27(30):3975-83). The primary objectives of this study are: to evaluate the tolerability and safety of ADXS11-001; and to assess the activity of ADXS11-001 in patients with persistent or recurrent cancer of the cervix. Secondary objectives are progression-free survival, overall survival and objective tumor response. **Methods:** Patient eligibility criteria: Females age ≥ 18 years with persistent or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (disease not amenable to curative therapy). Patients must have measurable disease as defined by RECIST 1.1; at least one “target lesion” as defined by RECIST 1.1; have had one prior systemic chemotherapeutic regimen for management of their disease; have adequate organ function and must be free of active infection and not on antibiotics. This protocol is a Simon 2-stage design with a planned sample size of up to 67 patients. Patients will receive ADXS11-001 at a dose of 1x10⁹ CFU on Day 1 and repeat every 28 days for 3 total doses in the absence of disease progression or unacceptable toxicity, with each dose followed at 72 hours by a 7 day course of ampicillin, 500 mg QID. Tumor tissue and serum samples may be collected periodically for translational research. After completion of study treatment, patients are followed every 3 months for 2 years and then every 6 months for 3 years. This phase II study just began enrolling and as of January 27, 2012, 2 patients have been enrolled.
A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The OUTBACK TRIAL.

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Background: Cervical cancer is a global health problem and the most common cause of cancer-related death among women in developing nations. Despite the recently developed cervical cancer vaccine, many women will continue to die from cervical cancer for many decades unless existing treatments can be improved. Unscreened women often present with locally-advanced disease that has a 5 year overall survival (OS) rate of 60% or less following standard chemo-radiation. Although some evidence suggests that adjuvant chemotherapy following chemo-radiation may be of value, its role remains controversial.

Methods: OUTBACK is a randomized phase III Gynecologic Cancer InterGroup (GCIG) trial designed and led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) in collaboration with the NHMRC Clinical Trials Centre. Participating countries (groups) include Australia and New Zealand (ANZGOG), India, the USA and Canada (GOG, RTOG). OUTBACK is suitable for women with locally advanced cervical cancer (FIGO stage IB₁ and node positive, IB₂, II, IIIB or IVA). The primary objective is to determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves OS. Women are randomized to either A) standard cisplatin-based chemo-radiation or B) standard cisplatin-based chemo-radiation followed by 4 cycles of carboplatin and paclitaxel chemotherapy. Secondary objectives are to compare progression-free survival, treatment-related toxicity, patterns of disease recurrence, quality of life and psycho-sexual health, and the association between radiation protocol compliance and outcomes. Blood and tumour samples are collected from consenting patients for future translational studies. 780 women will be enrolled to determine if the addition of adjuvant chemotherapy can improve the 5-year OS rate by ≥ 10%. OUTBACK opened in Australia and New Zealand in 2011. In early 2012 the trial opened in the USA and activation of GOG sites is ongoing. 15 patients have been randomized. It is expected that RTOG and India will open the trial later this year with recruitment increasing substantially once all sites are activated.