

Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer: Results from the MRC CHORUS trial.

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Background: First line treatment of advanced ovarian cancer (OC) is accepted to be primary surgery (PS) followed by adjuvant platinum-based chemotherapy (P-CT). However, the EORTC55971 trial suggested neoadjuvant chemotherapy (NACT) is an alternative, showing increased optimal debulking rates and reduced surgical complications without detriment to survival. CHORUS (CRUK 07/009) is the 2nd phase III randomized controlled trial to investigate timing of initial surgery in OC. **Methods:** Patients (pts) with clinical FIGO stage III-IV OC (pelvic mass, extrapelvic metastases and CA125/CEA ratio >25) were randomized to standard treatment (PS followed by 6 cycles P-CT) or NACT (3 cycles P-CT either side of surgery). CHORUS was designed to demonstrate non-inferiority of NACT, excluding a 6% absolute detriment in 3yr survival from 50% expected with PS (1-sided alpha 10%). Primary outcome was overall survival (OS) and secondary outcomes were progression free survival (PFS), toxicity and quality of life. **Results:** 550 women (276 PS, 274 NACT) were randomized from 74 centres (72 UK, 2 NZ) between Mar 2004 and Aug 2010. Baseline characteristics were well balanced: median age 65yrs, median tumor size 80mm, 25% FIGO stage IV, 19% WHO PS 2. Median follow-up was 3yrs, 410 pts have died. Treatment data are summarized in the Table. 3yr survival in the control arm was 32%. Intention to treat analysis showed a median OS of 22.8 months for PS vs 24.5 months for NACT (hazard ratio (HR) 0.87 in favor of NACT, 80% CI 0.76 – 0.98) and median PFS of 10.2 vs 11.7 months (HR 0.91, 0.81 – 1.02). OS results represent a 5% absolute benefit in 3yr survival for NACT to 37% and the upper 80% CI allows us to exclude a survival benefit for PS. **Conclusions:** NACT was associated with increased optimal debulking, less early mortality and similar survival in this poor prognosis group. CHORUS results are consistent with EORTC55971 and strengthen evidence that NACT is a viable alternative to PS. Clinical trial information: ISRCTN74802813.

	PS (n=276)	NACT (n=274)
Treatment received	Surgery 90% P-CT 76%	P-CT 92% Surgery 78%
Surgery + 6 cycles P-CT	64%	68%
Postop AEs (grade 3+)		
Infection	6%	3%
Hemorrhage	3%	7%
VTE	2%	0%
Discharge within 14 days	74%	92%
Debulked to 0cm residual disease	15%	35%
12-month survival rate	70%	76%

LBA5501

Oral Abstract Session, Sat, 3:00 PM-6:00 PM

A randomized multicenter phase III study comparing weekly versus every 3 week carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicentre Italian Trials in Ovarian Cancer (MITO-7)– European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10)–Gynecologic Cancer Intergroup (GCIG) trial.

Sandro Pignata, Giovanni Scambia, Rossella Lauria, Francesco Raspagliesi, Pierluigi Benedetti Panici, Gennaro Cormio, Dionyssios Katsaros, Roberto Sorio, Giovanna Cavazzini, Gabriella Ferrandina, Enrico Breda, Viviana Murgia, Cosimo Sacco, Nuria Maria Asensio Sierra, Carmela Pisano, Vanda Salutari, Beatrice E. Weber, Eric Pujade-Lauraine, Ciro Gallo, Francesco Perrone; National Cancer Institute, Napoli, Italy; Catholic University of the Sacred Heart, Roma, Italy; AOU Federico II, Naples, Italy; IRCCS Istituto Nazionale Tumori, Milan, Italy; "Sapienza" University, Roma, Italy; University of Bari, Bari, Italy; Sant'Anna Hospital - University of Torino, Turin, Italy; National Cancer Institute CRO, Aviano, Italy; "C.Poma" Hospital, Mantova, Italy; Catholic University of the Sacred Heart, Campobasso, Italy; Fatebenefratelli Hospital, Roma, Italy; Santa Chiara Hospital, Trento, Italy; University Hospital, Udine, Italy; Arcispedale "S. Maria Nuova" IRCCS, Reggio Emilia, Italy; Catholic University of the Sacred Heart, Rome, Italy; Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France; Université Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre, Site Hôtel-Dieu, Paris, France; Medical Statistics, Department of Medicine and Public Health, Second University, Napoli, Italy; National Cancer Institute, G.Pascale Foundation, Napoli, Italy

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Saturday, June 1, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

Final results of OV16, a phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel (CP) versus CP in first-line chemotherapy for advanced epithelial ovarian cancer (EOC): A GCIG study of NCIC CTG, EORTC-GCG, and GEICO.

Andres Cervantes-Ruiperez, Paul Hoskins, Ignace Vergote, Elizabeth A. Eisenhauer, Prafull Ghatage, Mark Carey, Dionyssios Katsaros, Andres Poveda, Diane M. Provencher, Dongsheng Tu, Gavin Stuart; Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; British Columbia Cancer Agency, Vancouver, BC, Canada; Leuven Cancer Institute and Gynaecological Oncology, University Hospital Leuven, KU Leuven, Leuven, Belgium; Queen's University, Department of Oncology, Kingston, ON, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Vancouver Coastal Health, Vancouver, BC, Canada; S. Anna Hospital, Turin, Italy; GEICO and Instituto Valenciano de Oncologia, Valencia, Spain; Chum-Pavillon Notre-Dame, Montreal, QC, Canada; NCIC Clinical Trials Group, Kingston, ON, Canada; University of British Columbia, Vancouver, BC, Canada

Background: Topotecan was evaluated in a novel combination regimen in comparison to standard therapy in front-line EOC. **Methods:** Women with newly diagnosed advanced EOC stages IIB-IV, ECOG performance status (PS) 0-1, age < 75, were randomized to either Arm 1: cycles 1 - 4: cisplatin 50 mg/m² d1 plus topotecan 0.75 mg/m² d1-5 IV; cycles 5 - 8: paclitaxel 175 mg/m² over 3 hrs d1 followed by carboplatin AUC5 day 1 or Arm 2: paclitaxel plus carboplatin as in Arm 1 for 8 cycles. The primary endpoint was progression free survival (PFS) and secondary endpoints included objective response, overall survival (OS), adverse event (AE) and Quality of Life (QoL). The sample size required 800 pts and 631 events to detect an improvement in PFS from 16 to 20 months (power 80%, 2-sided alpha 0.05). Results with 3.6 years median follow-up (MFU) were reported previously: there was no significant difference in PFS (Hoskins P, JNCI 2010). Final results including OS after MFU of 8.2 years are reported. **Results:** From 2001 to 2005, 819 pts (409 Arm 1, 410 Arm 2) were randomized. 704 PFS events and 605 deaths have occurred. PFS results are similar to first report: Median (months [mo]): 14.6 (Arm 1) and 16.2 (Arm 2), hazard ratio (HR) 1.03 (95% CI:0.81-1.30; p = 0.83). Median OS is 44.2 mo (Arm 1) and 44.8 mo (Arm 2), HR: 0.92 (95% CI:0.71-1.19; p=0.54). Baseline factors found to be independent predictors of OS in multivariate analysis are: a) pre-randomization surgery (debulking with no macro residual disease (MRD) to no debulking HR: 0.47; 95%CI:0.37-0.58; p < 0.0001; debulking with MRD (<1 cm) to no debulking HR: 0.76; 95%CI:0.61-0.94; p = 0.01), b) Stage (stage II to III or IV HR:0.52; 95%CI:0.36-0.76; p = 0.0007) and c) PS (0 vs 1 HR:0.76; 95%CI:0.63-0.91; p = 0.004). Post-treatment AEs were not significantly different in the two arms. **Conclusions:** OV16 final results confirm that sequential doublets of topotecan and cisplatin followed by carboplatin and paclitaxel offer no improvement in outcomes compared to carboplatin and paclitaxel. Pretreatment debulking, stage II and PS 0 are predictive of longer OS. Clinical trial information: NCT00028743.

LBA5503

Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, Fallopian tube, or primary peritoneal cancer (AOC): Results of an international intergroup trial (AGO-OVAR16).

Andreas Du Bois, Anne Floquet, Jae Weon Kim, Jörn Rau, Jose Maria Del Campo, Michael Friedlander, Sandro Pignata, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Mansoor Raza Mirza, Bradley J. Monk, Pauline Wimberger, Isabelle Ray-Coquard, Rongyu Zang, Ivan Diaz-Padilla, Klaus H. Baumann, Jae Hoon Kim, Philipp Harter, on behalf of an Intergroup consortium; Kliniken Essen Mitte, Essen, Germany; Institut Bergonié, Bordeaux, France; Seoul National University College of Medicine, Seoul, South Korea; Philipps University Marburg, Marburg, Germany; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Prince of Wales Hospital, Sydney, Australia; National Cancer Institute of Naples, Naples, Italy; Saitama Medical University International Medical Center, Saitama, Japan; UZ Leuven, Leuven, Belgium; University of Milan-Bicocca, Milan, Italy; Department of Oncology; Rigshospitalet; Copenhagen University Hospital, Copenhagen, Denmark; Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; Centre Léon Bérard, Lyon, France; Shanghai Fudan University, Shanghai, China; Department of Medical Oncology, Centro Integral Oncologico "Clara Campal", Madrid, Spain; Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

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Phase II trial of volasertib (BI 6727) versus chemotherapy (CT) in platinum-resistant/refractory ovarian cancer (OC).

Eric Pujade-Lauraine, Beatrice E. Weber, Isabelle Ray-Coquard, Ignace Vergote, Frédéric Selle, Jose Maria Del Campo, Jozef Sufliarsky, Inga Tschöpe, Pilar Garin Chesa, Serge Nazabadioko, Korinna Pilz, Florence Joly; Unité D'Oncologie Médicale, Hôpital Hôtel Dieu, AP-HP, Paris, France; Medical Oncology, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France; Medical Oncology, Centre Léon Bérard, Lyon, France; Leuven Cancer Institute and Gynaecological Oncology, University Hospital Leuven, KU Leuven, Leuven, Belgium; Medical Oncology, Hôpital Tenon, Paris, France; Vall d'Hebron Institute of Oncology, Barcelona, Spain; National Cancer Institute, Bratislava, Slovakia; Boehringer Ingelheim GmbH, Reims, France; Boehringer Ingelheim GmbH, Vienna, Austria; Boehringer Ingelheim GmbH, Biberach, Germany; Centre François Baclesse, Caen, France

Background: Volasertib (V) is a potent and selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinases. This study investigated V vs CT as 3rd- or 4th-line therapy in patients (pts) with platinum-refractory or resistant OC. **Methods:** Pts were randomized to V 300 mg IV Q3W or investigator's choice single-agent CT (pegylated liposomal doxorubicin, topotecan, paclitaxel, gemcitabine) until progression or intolerance. Primary endpoint was 24-wk disease control rate (DCR; % of pts with complete/partial response [PR] or stable disease [SD]). Secondary endpoints included safety, progression-free survival (PFS), best overall response (RECIST 1.1) and explorative biomarkers. **Results:** 109 pts received V (n=54) or CT (n = 55) for a median (range) of 95 (22–716) and 114 (7–351) days, respectively. Demographic data were balanced between the treatment arms. Overall, median age was 62.0 yr; ECOG PS 0–1: 103 pts; 2 prior CTs: 51 pts; ≥3 prior CTs: 57 pts; platinum-resistant: 78 pts; platinum-refractory: 31 pts; measurable disease: 89 pts. 24-wk DCR (95% CI) for V vs CT was 31% (18–43) vs 43% (30–57), and median PFS was 13.1 vs 20.6 wks (HR = 1.01; 95% CI: 0.66–1.53). Six V pts vs 0 CT pts are ongoing for PFS 1 yr after randomization. Best overall response in pts with measurable disease (V/CT) was: PR, 7/8 pts; SD, 24/24 pts. Adverse events (AEs) led to discontinuation in 20 pts (V, n = 5; CT, n = 15); no V pts and 8 CT pts discontinued due to treatment-related AEs (including neuropathy in 3 CT pts). Most frequent all grade AEs (% of pts) regardless of relatedness were neutropenia (61%), anemia (54%), thrombocytopenia (46%), nausea (37%) and asthenia (33%) with V, and asthenia/nausea (47% each), abdominal pain (38%), anemia (36%) and neutropenia/vomiting (31% each) with CT. There were 3 fatal AEs per arm. **Conclusions:** Single-agent V showed antitumor activity in OC in a range similar to CT. AEs with V were mainly hematologic and manageable, with fewer non-hematologic AEs than CT. Exploration of potential predictive biomarkers for V activity is ongoing. Clinical trial information: NCT01121406.

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm).

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Background: Previously, we reported that maintenance treatment with the oral PARP inhibitor olaparib (400 mg bid) led to a significant PFS improvement vs placebo in patients (pts) with platinum-sensitive relapsed SOC (Ledermann et al *NEJM*2012). A preplanned subgroup analysis from this randomized, double-blind Phase II trial (NCT00753545) suggested that olaparib may lead to a greater PFS, and an OS, benefit in pts with a known germline BRCAm (gBRCAm). Since gBRCA wild-type (gBRCAwt) pts may develop somatic tumor (t)BRCAm, efficacy analyses were performed for all pts with BRCAm. **Methods:** gBRCAm status was determined retrospectively for all consenting pts (n = 166) using blood samples taken before randomization. tBRCAm status was determined from archival tumor samples of 196 pts. We analyzed PFS/OS by gBRCAm and total BRCAm status. Preliminary data are reported. **Results:** gBRCA status was known for 218/265 pts (gBRCAm, 96; gBRCAwt, 122). Including tBRCAm, 136 pts had a BRCAm (BRCAwt, 116). gBRCAm pts had the greatest PFS benefit with olaparib maintenance vs placebo (median: 11.2 vs 4.1 months [m]; HR, 0.17; 95% CI 0.09-0.32; $P < 0.001$) and a significant QoL improvement, as measured with Trial Outcome Index (OR, 4.08; 95% CI 1.11-19.85; $p = 0.03$). The PFS benefit was consistent when tBRCAm pts were included (median: 11.2 vs 4.3 m; HR, 0.19; 95% CI 0.11-0.32; $p < 0.0001$). In an interim analysis of OS (58% maturity), a comparison of olaparib vs placebo in the overall population led to a HR of 0.88 (95% CI 0.64-1.21) with medians of 29.8 vs 27.8 m, respectively. Although HRs from the gBRCAm and gBRCAwt subgroups were similar (0.85 and 0.84, respectively), 13/37 gBRCAm placebo pts received a subsequent PARP inhibitor, confounding the OS data in this subgroup. The analysis of all BRCAm pts was less confounded and resulted in an OS HR of 0.74 (95% CI 0.46-1.19; median: 34.9 vs 31.9 m). 19 pts have received olaparib for > 3 years. Olaparib tolerability was similar in BRCAm pts and the overall population. **Conclusions:** Olaparib maintenance treatment led to the greatest clinical benefit in pts with a BRCAm. These compelling data warrant confirmation in phase III trials. Clinical trial information: NCT00753545.

Phase III placebo controlled double blind randomized trial of radiation therapy for stage 2B-4A cervical cancer with immunomodulator Z-100: JGOG-DT101 study.

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Background: We previously reported that the lower dose (0.2 μ g) of immunomodulator Z-100 showed better overall survival (OS) compared to higher dose (40 μ g) in patients with locally advanced cervical cancer who received radiation therapy (RT). Therefore, we conducted a placebo controlled double-blind randomized trial to elucidate the role of additive immunotherapy in standard RT. **Methods:** Patients of stages 2B to 4A squamous cell carcinoma of the uterine cervix, who were scheduled to receive standard RT with or without platinum-based chemotherapy, were eligible. Z-100 at 0.2 μ g (Z) or placebo (P) was given subcutaneously twice a week during the RT, followed by maintenance therapy by administering either Z or P once every two weeks. Therapy was continued until disease progression or termination of the trial in 2011. Primary endpoint was OS, secondary endpoints were recurrent-free survival (RFS), response rate (RR), and safety. Sample size was calculated by assuming 5-year survival rates (5YSR) as 60% in Arm Z and 38-44% for Arm P, (hazard ratio HR: 0.526-0.625), and was determined to be 120 patients in each arm. **Results:** Between 2004 and 2006, 249 patients were randomized. Total of 244 patients were eligible for safety analysis, and 243 patients were eligible for survival analysis. In Arm Z, 29 deaths were reported, and in Arm P, 42. 5YSR was 75.7% (95%CI: 66.4-82.8%) for Arm Z and 65.8 % (95%CI: 56.2-73.8%) for Arm P; HR was 0.646 (95%CI: 0.400-1.043). Survival benefit in Arm Z was observed regardless of chemoradiation or radiation alone. There were no differences between arms in terms of RR and RFS, and side effects. Neoplasms, including benign cases, observed were 4 in Arm Z, and 13 in Arm P. **Conclusions:** Immunomodulator Z-100, used as an adjuvant therapy after radiation, showed clinically significant improvement of OS in locally advanced cervical cancer, although the statistical power was less than anticipated because survival rates were unexpectedly higher than expected for both arms. Further exploration of Z-100 is warranted. Clinical trial information: C000000221.

5507[^]

Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Final results of 4-monthly screening in the UK Familial Ovarian Cancer Screening Study (UKFOCSS Phase 2).

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Background: Annual transvaginal ultrasound (TVS) and serum CA125 screening for women at high-risk of Ovarian/Fallopian tube cancer (OC/FTC) in Phase 1 of UKFOCSS lacked sensitivity for early stage disease but downstaged disease volume and may have improved optimal debulking rates. More frequent screening might provide greater benefits. Here we report the final results of 4-monthly screening in one of the largest such trials worldwide. **Methods:** Between 14/06/2007 and 29/03/2012, 4,531 women at an estimated $\geq 10\%$ lifetime risk of OC/FTC were recruited and screened by 42 UK centres for 14,263 women screen years. Screening comprised 4-monthly CA125 tests analysed by a risk of ovarian cancer algorithm, adjusted for menopausal status. TVS was annual in those with normal algorithm results, but was triggered sooner if results were non-normal. Women with suspicious scan and/or algorithm results were referred for consideration of surgical intervention. Participants were followed prospectively by centres, questionnaire and national cancer registries. Data was censored 365 days after final screen, withdrawal or death. Clinical trial information: 32794457.

Screening for Lynch syndrome in unselected women with endometrial cancer.

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Background: Endometrial cancer (EC) is often the sentinel cancer in women with Lynch Syndrome (LS) however it is often not recognized in this population. A prospective cohort study comparing family history, immunohistochemistry (IHC) for mismatch repair (MMR) proteins, and tumour morphology to germline mutation status in MMR genes was performed in unselected women with EC to determine which screening strategy was superior in identifying women with LS. **Methods:** All women with newly diagnosed EC between July 2010 and June 2011 were asked to participate in the prospective screening protocol for LS which included completing an extended family history questionnaire (eFHQ), tumor assessment for LS-associated morphologic features and IHC as well as germline mutation testing. **Results:** 119 (n = 182, 65%) consented to the study. The median age was 61 (26-91), 96 (81%) stage I, and 42 (35%) had high risk histology. There were 6 (7.4%, n = 81) women that were germline mutation positive (*MLH1* N=3; *MSH6* n = 2; *MSH2* n = 1), representing a mutation positive rate of at least 5% in this cohort (6/119). All 3 *MLH1* mutation positive women had low grade histology while mutations in *MSH2/6* were exclusively found in women with high risk histology. Two of the six mutation positive women were not identified by family history. Mutation positivity was higher in women under age 50 (23%; 5/22) compared to women > age 50 (1%; 1/97) (p = 0.0008). LS-morphologic features were found in 58 (59%, n = 98) women. The sensitivity, specificity, PPV and NPV of the LS-associated features in predicting LS mutation status was 100%, 42.6%, 7.9% and 100% compared to IHC which was 100%, 76%, 18% and 100% and eFHQ which was 67%, 84%, 27%, 97%. **Conclusions:** In this unselected population of women with newly diagnosed EC the germline mutation rate for LS was 2-3 times that has previously been reported. Previously described LS-associated morphologic features were not specific to germline mutation status and family history missed one third of women with LS. IHC was the best strategy to identify women with EC who should undergo germline mutation testing.

Prognostic significance of differential expression of angiogenic genes in women with invasive high-grade serous ovarian carcinoma.

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Background: High-grade serous ovarian carcinoma (HGSC) is an aggressive type of epithelial ovarian cancer associated with numerous genetic alterations and poor survival. Our objective was to identify novel angiogenic biomarkers that are associated with tumor angiogenesis and clinical outcome in women with HGSC. **Methods:** Between 1988 and 2001, 51 snap frozen samples from women with advanced HGSC were obtained. RNA was extracted and analyzed by the Affymetrix GeneChip U133A array. A panel of 285 probe sets (features) linked to 145 genes involved in angiogenesis were screened. Microvessel density (MVD) counts, surrogates of angiogenesis, were determined using CD31 and CD105, markers of proliferating endothelial cells. The association between mRNA expression levels and overall survival (OS) were assessed using a rank score statistic. The effect size was estimated parametrically as a hazard ratio (HR) under a proportional hazards model. We accounted for multiple testing within the false-discovery rate (FDR) framework using the Storey q-value method. The associations between expression level and OS for the implicated genes were further assessed in a published HGSC cohort from the “The Cancer Genome Atlas” (TCGA) database. **Results:** A panel of 43 features linked to 31 angiogenic genes were significantly associated with long term OS (FDR q-value (q) < 0.05). In the TCGA cohort, four genes exhibited some level of significance and concordant direction of effect as assessed by HRs: *AKT1* (q = 0.018, HR = 0.44; TCGA unadjusted p-value (p) < 0.011, HR = 0.81), and *CD44* (q < 0.003, HR = 0.48; TCGA p < 0.054, HR = 0.89) were associated with better survival; while *EPHB2* (q < 0.009, HR = 8.12; TCGA p < 0.051, HR = 1.23) and *ERBB2* (q < 0.019, HR = 2.86, TCGA p < 0.055, HR = 1.19) were associated with worse survival. After adjusting for multiple comparisons, CD105-MVD and CD31-MVD were not significantly associated with angiogenic gene expression. **Conclusions:** Our data demonstrated that mRNA levels of 31 angiogenic genes were associated with OS in advanced HGSC. Among these 4 were externally confirmed using TCGA data. Further evaluation is warranted to verify our preliminary findings.

Prognostic relevance of gene signatures in high-grade serous ovarian carcinoma.

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Background: Transcriptional profiling of ovarian cancers has proven to be complex. As such it has been difficult to validate existing signatures across studies. Cancer Genome Atlas (TCGA) researchers have identified four molecular subtypes of high-grade serous ovarian cancer (HGSOC). However, survival duration did not differ significantly for the TCGA subtypes. Potential limitations of the TCGA data include short clinical follow-up (45% were alive at the time of last follow-up) and the need to unify gene expression measures from multiple platforms. **Methods:** Clinically annotated stage-II–IV HGSOC samples (n = 175) with >70% tumor cell content were profiled using the Agilent Whole Human Genome 4 x 44K chip. To identify subtypes non-negative matrix factorization (NMF) of mRNA expression was performed using ~2000 genes with the highest variability across patients. In parallel differentially expressed genes were identified using the Rosetta Similarity Search Tool as well as analysis of variance based on genes known to be involved in epithelial to mesenchymal transition. **Results:** Median follow-up time was 35 months (range, 0–202 months, 12% were alive at the time of last follow-up). NMF clustering confirmed four HGSOC subtypes (immunoreactive, differentiated, proliferative, and mesenchymal) on the basis of gene content in the clusters. Pathway signatures with therapeutic potential were identified for individual or multiple subtypes. Survival differed significantly between the four molecular subgroups in univariate (Hazard Ratio [HR] 2.4, 95% CI 1.5–4.1, p = 0.007) and multivariate (HR 2.3, 95% CI 1.3–4.0, p = 0.003) analyses when accounting for age, stage, grade, and postoperative residual tumor. Using the supervised clustering approach two distinct molecular subtypes of HGSOC based on epithelial and mesenchymal gene expression signatures were identified with significantly different survival outcomes. **Conclusions:** Here we independently validate and expand upon the molecular TCGA classification of HGSOC. The potential of these two prognostic classifiers may lie in their ability to recognize categories of patients that are more likely to respond to particular therapies.

Distinct copy number alteration patterns as prognostic of endometrial cancer outcomes.

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Background: Endometrial cancer is classified by tumor stage, histologic subtype and grade. However, a substantial proportion of presumed non-high risk cases recur, supporting the need for improved tools of prognostication. **Methods:** Using clinical and Affymetrix SNP 6.0 data from The Cancer Genome Atlas (TCGA) endometrial carcinoma project, we identified 4 somatic copy number alteration (SCNA) subtypes, established their prognostic value and validated them in an independent, population-based cohort from Norway. Patients had endometrioid, uterine papillary serous carcinoma (UPSC) or mixed histology tumors. Progression-free survival (PFS) was defined as time from diagnosis to recurrence or progression, and estimated by the Kaplan-Meier method. **Results:** Four groups of SCNA patterns were identified using hierarchical clustering: low SCNA, moderate SCNA, SCNA dominated by 1q amplification (1q amplified) and high SCNA level (serous-like). Their prognostic value was assessed in all TCGA patients (N = 292) and in a low risk subset with endometrioid histology, stage 1 disease (N = 210). In the full TCGA cohort, patients with low SCNA (reference group) had excellent 2-year PFS of 94%, while for moderate SCNA it was 84% (hazard ratio[HR] 2.7, p = .08). The 1q amplified and serous-like groups had significantly worse outcomes with 2-year PFS of 74% (HR 5.9, p = .002) and 74% (HR 6.0, p < .001), respectively. On multivariable analysis, adjusting for variables including stage and grade, 1q amplified and serous-like SCNA patterns remained independently prognostic (respectively, adjusted HR 6.2, p = .002 and 4.7, p = .02). Similar results were found in the low risk subset. The prognostic value of the SCNA patterns was validated in an independent group of patients with low risk disease (N = 57). 5-year PFS was 91% for low SCNA, 83% for moderate SCNA (HR 2.0, p = .58), 72% for 1q amplified (HR 3.7, p = .11) and 50% for the serous-like SCNA group (HR 6.7, p = .04). **Conclusions:** Four subtypes of DNA SCNA patterns in endometrial cancer were identified and validated to be prognostic of outcome. These novel biomarkers may be useful in guiding therapeutic decisions, and shed insight on the biology of more, or less, aggressive endometrial cancer.

Pazopanib (Paz) monotherapy in Asian women who have not progressed after first-line chemotherapy for advanced ovarian, Fallopian tube, or primary peritoneal carcinoma.

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Background: Paz, an oral multikinase inhibitor of VEGF, PDGF and c-Kit has showed activity in advanced ovarian cancer. This study evaluated paz as maintenance therapy in Asian women with advanced ovarian cancer. **Methods:** Subjects with FIGO stage II, III, or IV ovarian, fallopian tube, or primary peritoneal cancer whose disease had not progressed after debulking surgery and followed by chemotherapy were randomized 1:1 to paz 800 mg once daily or placebo for up to 24 months. Primary endpoint was PFS by RECIST v1.0 based on visit date. If a progression occurred between the 2 scheduled visits (6 mos apart), progression was considered to have occurred at the next scheduled scan date. This minimized potential bias due to any imbalance of visit frequency between the arms. **Results:** 145 Asian subjects were randomized; 144 were treated. Mean age was 52.9 years. At diagnosis 17% were FIGO stage II, 73% stage III and 10% stage IV. After debulking surgery, 30% (n = 44) had no residual disease and 41% (n = 59) had. 47% (28/59) had residual disease ≤ 1 cm. Prior to randomization, all subjects received median 8 cycles of chemotherapy; all subjects received platinum and taxane. At randomization 81% had ECOG status 0, 97% were disease free and all had normal CA-125. At clinical data cut-off median PFS was 18.1 months in both arms. Because of the small sample size a HR was not calculated but the KM curves indicated a trend in favor of paz from 6 to 18 mos; the curves crossed after 18 mos. The adverse event (AE) profile for paz was similar to previous reports except rates of hypertension and neutropenia were higher. The most frequent AEs ($\geq 20\%$) on the paz arm were hypertension (76%), neutropenia (64%), leucopenia (53%), diarrhea (47%), hair color changes (40%), palm-plantar erythrodysesthesia syndrome (29%), ALT increase (28%), thrombocytopenia (24%), AST increase (22%) and TSH increase (21%). Most of these AEs were Grade 1-2. **Conclusions:** The results of this study alone cannot confirm the efficacy of paz maintenance treatment in Asian women with ovarian cancer, but should be interpreted in conjunction of AGO-OVAR16 study. Clinical trial information: NCT01227928.

5513

Poster Discussion Session (Board #2), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: A randomized phase II study of the Sarah Cannon Research Institute.**

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Background: The combination of paclitaxel and carboplatin is the most widely used chemotherapy regimen for patients (pts) with advanced ovarian cancer, producing a median survival of approximately 36 months. Recently, the addition of bevacizumab, an angiogenesis inhibitor, has improved progression-free survival (PFS) when compared to paclitaxel/carboplatin alone. Sorafenib is an oral multi-kinase inhibitor with effects on tumor angiogenesis through inhibition of the VEGF receptor. The purpose of this randomized phase II study was to compare efficacy of paclitaxel/carboplatin with and without sorafenib. **Methods:** Women with histologically confirmed, maximally debulked, previously untreated stage III/IV epithelial ovarian carcinoma were randomized to receive paclitaxel 175 mg/m² and carboplatin AUC 6 (PC) or PC + sorafenib 400 mg PO BID (S). All patients received 6 cycles, given every 3 weeks; pts receiving PC+S continued single agent sorafenib for 52 weeks total. The primary endpoint was 2-year PFS rate. **Results:** 85 pts were randomized between 1/07 and 10/11 (PC+S 43; PC 42). Pt characteristics were similar between groups, except that more patients with only CA125 elevation received PC+S (65% vs 43%). Overall, 67 pts (79%) completed 6 cycles of chemotherapy (PC+S 74%; PC 83%). More patients stopped PC+S due to toxicity (14% vs 7%). 22 pts (51%) receiving PC+S began single agent S after 6 cycles PC, and 12 pts (28%) completed 52 weeks of S. There was no difference in the 2-year PFS rates: PC+S 40%, PC 39%. Overall survival comparisons were also similar (p = 0.36). Pts receiving PC+S had more grade 3 rash (33% vs 0%) and hand-foot syndrome (9% vs 0%). **Conclusions:** The addition of sorafenib did not improve the efficacy of standard first-line PC in pts with stage III/IV ovarian carcinoma, and resulted in additional toxicity. Clinical trial information: NCT00390611.

A randomized placebo-controlled trial of saracatinib (AZD0530) plus weekly paclitaxel in platinum-resistant ovarian, fallopian-tube, or primary peritoneal cancer (SaPPrOC).

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Background: Weekly paclitaxel (wPxL) has activity in platinum-resistant ovarian cancer (PROC). Upregulated Src kinase activity is seen in Pxl-resistant ovarian cancer models. This trial investigated the combination of wPxL and the oral Src inhibitor saracatinib (AZD0530) in PROC. **Methods:** Patients with PROC (defined as relapse within 6 months of prior platinum chemotherapy, confirmed either by CT scan or symptomatic CA125 rise) were randomised 2:1 to receive four 8 week cycles of wPxL (80mg/m²/week x6 with 2 week break) plus saracatinib (S; 175mg od) or placebo (P) continuously, starting 1 week prior to wPxL, until disease progression. Patients were stratified as <6 months or ≥6 months taxane interval/no prior taxane. The primary endpoint was 6-month progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate (RR), duration of response (DoR), time to progression (TTP) and toxicity. **Results:** 107 patients were randomised during 2011-12, 71 (66.4%) to wPxL+S and 36 (33.6%) to wPxL+P. Taxane interval was <6 months in 23 (22.1%), ≥6 months in 76 (72.4%). 43 (41.0%) had received >2 lines of prior chemotherapy; 78% (wPxL+S) vs 72% (wPxL+P) of patients received ≥1 cycle of wPxL; relative dose intensity was 96% vs 98% for wPxL+S and wPxL+P respectively. The 6-month PFS rate was 29% (wPxL+S) vs 35% (wPxL+P). Median PFS was 3.9 vs 5.3 months (HR 1.04; 95% CI 0.68, 1.59; p=0.86); median OS was 12.7 vs 12.8 months (HR 1.50, 95% CI 0.63, 3.56; p=0.36); RR were 0.0% vs 2.9% (CR) and 29% vs 38.9% (PR) for wPxL+S vs wPxL+P respectively. Median DoR was 5.6 vs 3.6 months; TTP was 3.9 vs 5.5 months (HR 1.10; 95% CI 0.71, 1.72; p=0.67). Grade 3+ Serious Adverse Events were 36.2% vs 30.6%; the most frequent toxicities (any grade) were abdominal pain (4.3%) and febrile neutropenia (4.3%) for wPxL+S, and vomiting (5.6%) for wPxL+P. **Conclusions:** In this randomised phase II trial, the addition of saracatinib to wPxL did not improve 6-month PFS in patients with PROC. Clinical trial information: NCT01196741.

A multicenter open-label phase II study of the efficacy and safety of ganitumab (AMG 479), a fully human monoclonal antibody against insulin-like growth factor type 1 receptor (IGF-1R) as second-line therapy in patients with recurrent platinum-sensitive ovarian cancer.

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Background: IGF signaling has been implicated in the pathogenesis and progression of ovarian cancer (OC). Single agent activity and safety of ganitumab (AMG 479), a fully human monoclonal antibody against IGF-1R that blocks binding of IGF1 and IGF2, were evaluated in asymptomatic patients with platinum-sensitive recurrent OC. Differential expression of IGF-1R pathway genes in OC underscores the potential of developing predictive biomarkers for patient selection. **Methods:** Pts with CA125 progression (GCIG criteria) and/or measurable disease per RECIST failing primary platinum-based therapy received 18 mg/kg of ganitumab q3w. Objective response rate per RECIST or CA125 criteria was the primary end point (complete response, CR; partial response, PR). Secondary end points included, progression-free survival (PFS) and safety. Tumor tissue was collected for gene expression profiling (Nanostring) and sequencing. **Results:** From 02/2009 to 05/2010, 61 pts were accrued from 20 centers. Pt characteristics were: Serous (77%), median platinum-free interval (11 months), measurable disease (74%), and ECOG performance status 0 (67%). According to CA125 criteria median PFS was 6.8 months (95%CI, 2.8-10.8); 2 CR (3.4%) 2 PR (3.4%), and 38 stable disease (SD, 64%) were observed. When using RECIST criteria, median PFS was 2.1 months (95%CI, 2.0-2.8), 2 PR (3.4%) and 22 SD (38%) were observed. Toxicity has been mild; grade 2 hyperglycemia was seen in 5 pts (8.2%). Grade 3 related events included hearing loss (1), nausea (1), asthenia (2), fatigue (1), and hypersensitivity (5). There were no grade 4 or 5 treatment-related events. Efficacy is being correlated with gene expression profiles and mutational data. **Conclusions:** IGF-1R inhibition with ganitumab was well tolerated and demonstrated modest single-agent activity in unselected patients with platinum-sensitive recurrent OC. However, encouraging activity was seen in a subset of patients. Ongoing predictive biomarker analyses may facilitate patient selection. Clinical trial information: NCT00719212.

Opsalin: A phase II placebo (Pbo)-controlled randomized study of ombrabulin in patients with platinum-sensitive recurrent ovarian cancer (OC) treated with carboplatin (Cb) and paclitaxel (P).

Michael J. Birrer, Igor Bondarenko, Sergei Tjulandin, Ignace Vergote, David Cibula, Isabelle Ray-Coquard, Nicoletta Colombo, Aurore Allard, Corina Oprea, Augustin A. Rey, Cristiana Sessa, Eric Pujade-Lauraine; Massachusetts General Hospital/Dana-Farber Harvard Cancer Center, Boston, MA; Dnipropetrovsk Medical Academy, Dnipropetrovsk, Ukraine; N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; University Hospitals Leuven, Leuven, Belgium; First Medical Faculty, Charles University, Prague, Czech Republic; Centre Léon Bérard, Lyon, France; Istituto Europeo di Oncologia, Milano, Italy; Sanofi, Chilly-Mazarin, France; Sanofi, Vitry-sur-Seine, France; Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland; Hôpital Hôtel-Dieu, Paris, France

Background: Patients with platinum-sensitive recurrent OC are often retreated with CbP due to limited treatment options. Ombrabulin (AVE8062), a combretastatin A4 analog, is a vascular disrupting agent that damages established tumor vasculature causing tumor necrosis and has synergistic antitumor activity with platinum agents in vivo (Cancer Sci. 2003;94:200). OPSALIN evaluated whether adding ombrabulin to CbP improves outcomes in patients with platinum-sensitive recurrent OC (NCT01332656; EFC10260). **Methods:** Patients (aged ≥ 18 yrs, ECOG PS ≤ 2) with platinum-sensitive measurable ovarian, fallopian tube, or primary peritoneum carcinoma after completion of one line of platinum-based chemotherapy received ombrabulin 35 mg/m² or Pbo plus CbP (AUC 5–6, 175 mg/m²) every 3 weeks. Randomization (1:1) was stratified by time of first disease recurrence (6–12 or >12 months). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, response rate (RR), and safety. An interim analysis after ~54 PFS events (60% of the target 90 PFS events) was planned. **Results:** From May 2011 to August 2012, 154 patients were randomized (n=77 in each group). Groups were balanced in terms of baseline characteristics. Overall, the median age was 56 yrs (range 34–79), 93% had ovarian primary tumors, and 54% had first disease recurrence >12 months. Planned interim analysis was performed after 53 PFS events (27 ombrabulin; 26 Pbo); median follow-up was 6.8 months. Ombrabulin did not improve PFS vs Pbo in any subgroup (global median 8.4 vs 10.4 months, respectively; HR 1.33; 60%CI 1.06–1.69). Overall, RR was 65% for ombrabulin and 71% for Pbo. Safety profiles were comparable; rates of grade 3–4 adverse events were 51% for ombrabulin and 41% for Pbo, with no particular safety signals. **Conclusions:** This interim analysis has suggested no safety concerns or efficacy advantage of adding ombrabulin to CbP in patients with platinum-sensitive recurrent OC. The study was discontinued due to limited probability of the ombrabulin arm showing PFS superiority at the final analysis. Study sponsored by Sanofi. Clinical trial information: NCT01332656.

A multicenter phase II study of bevacizumab (B) and temsirolimus (T) in women with recurrent epithelial ovarian cancer (OC): A study of the Mayo, Chicago, California, New York, Southeast, and Princess Margaret Phase II Consortia.

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Background: Anti-angiogenic therapy is active in OC; the combination of VEGF and mTOR inhibitors is hypothesized to further improve activity. This report is the OC cohort of a multi-histology phase II study assessing the activity and toxicity of B/T. **Methods:** Patients (Pts) with recurrent epithelial OC who had received ≤ 2 chemotherapy regimens and no prior treatment with a VEGF or mTOR inhibitor were eligible. A two-stage design was used with second stage accrual if >6 pts had objective responses (OR) or >10 pts of the first 25 remained progression-free (PF) at six months (mo). Pre-defined end-points for a recommendation for further clinical trial evaluation included at least 15/50 with OR or 26/50 PF at six mo. Treatment included T 25 mg IV wkly and B 10 mg/kg IV q14 days on 28 day cycles. **Results:** 58 pts were enrolled (the first 50 pts are used to determine a final recommendation). Median age=62 (range 35-82). A median of 4 (range 1-23) cycles were administered. 24 were platinum-sensitive, 34 resistant. Off-study reasons included 13 adverse events and disease progression in 38. 3 refused further therapy due to toxicity. 14 of the first 50 pts had partial response (PR) (9 platinum-resistant); 25/50 remained PF (8 PR, 15 SD, 2 non-progressing) at 6 mo. Grade (gr) 3/4 toxicities occurring >2 events include: fatigue (4), stomatitis (7), hypertension (5), neutropenia (4), thrombocytopenia (4), hypokalemia (3). One rectal and one vaginal fistula, and two colonic perforations (one gr 2 and one gr 3 during cycles 3 and 1 respectively) were observed. Episodes of gr 1/2 oral, nasal, pulmonary, vaginal and gastrointestinal hemorrhage were also observed. **Conclusions:** Although the OR and PFS did not reach pre-defined standards, the numbers of OR and 6 mo PFS suggest potential enhanced activity with a combination of mTOR inhibitor with anti-angiogenic therapy. Other combinations of these targeted agents may result in more satisfactory activity with less toxicity. N01-CM-62203 (PMH) N01-CM-62208 (Southeast Phase 2) N01 CM-62209 (CCCP) N01-CM-62204 (NYCC) N01-CM-2011-0071C (Chicago) N01-CM62205 (Mayo) Clinical trial information: NCT01010126.

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Poster Discussion Session (Board #7), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Targeting p53 mutant ovarian cancer: Phase I results of the WEE1 inhibitor MK-1775 with carboplatin plus paclitaxel in patients (pts) with platinum-sensitive, p53-mutant ovarian cancer (OC).**

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Background: MK-1775 is a highly selective, investigational oral tyrosine kinase inhibitor of WEE1, which regulates G2 cell cycle checkpoint. Functional p53 mutation impairs G1 checkpoint; hence, targeting G2 checkpoint with MK-1775 in p53 mutants should induce synthetic lethality. **Methods:** Pts with platinum-sensitive disease-recurrent OC who had measurable disease (RECIST 1.1) with loss of function (LOF) p53 mutations by Roche AmpliChip were eligible. All pts received MK-1775 225mg twice daily (BID) D1-D3 (5 doses) plus carboplatin AUC5 + paclitaxel 175mg/m² every 21 days (CP) for 6 cycles. The objective for the phase I run-in portion of the study was to determine the recommended phase II dose based on safety data. A Toxicity Probability Interval method [Ji et al, Clin Trials 2010; 7(6):653-63] would determine if additional lower doses should be explored. A randomized phase II portion, assessing the efficacy of the combination vs placebo, would start if ≥ 5 radiological responses and < 5 dose-limiting toxicities (DLTs) were observed among the first 13 pts. **Results:** Of 76 pts screened (26 wt, 43 mutant [24 nonfunctional], 7 undetermined), 19 women had LOF p53 mutations and were eligible. Fifteen consented and were enrolled in the Phase I: median age was 57 (range 38-77); ECOG 0:1 ratio 9:6 pts. Three DLTs were observed: G3 febrile neutropenia, G4 neutropenia, and G4 thrombocytopenia. Diarrhea (84.6%), nausea (76.9%), and fatigue (76.9%) were the most common adverse events (AEs). Seven of 13 pts completed treatment (2 ongoing). Three pts discontinued due to AEs and 3 patients withdrew consent prior to completing treatment. Of 14 evaluable pts by RECIST 1.1 there were 11 partial responses (PRs; 6 confirmed, 5 unconfirmed) and 3 had stable disease; 7 pts were evaluable by CA125 with 3 complete responses and 4 PRs. MK-1775 PK results were similar to those reported for monotherapy studies. **Conclusions:** The combination of MK-1775 225mg BID x 5 doses with CP is well tolerated, with a preliminary radiological response rate of 78.6%, and has met the safety and efficacy bar for randomized phase II assessment in part 2 of the study. Clinical trial information: NCT01357161.

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Poster Discussion Session (Board #8), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**A preoperative window study of metformin for the treatment of endometrial cancer.**

Kevin M. Schuler, Brooke S. Rambally, Megan J. DiFurio, Paola A. Gehrig, Victoria Lin Bae-Jump; UNC Hospitals, Chapel Hill, NC; University of North Carolina Hospitals, Chapel Hill, NC; Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Obesity and diabetes have been linked to poorer survival and increased recurrence rates in endometrial cancer. The anti-diabetic medication, metformin, has been shown to have anti-tumorigenic effects in vitro and in vivo, via AMPK activation and inhibition of the mTOR pathway. We conducted a pre-operative window clinical trial of metformin in obese endometrial cancer patients to evaluate short-term in vivo molecular changes. **Methods:** Women with endometrioid endometrial cancer who were obese (BMI>30) were recruited from a gynecologic oncology clinic. Once enrolled, patients had a repeat pre-treatment endometrial biopsy and then began metformin at a dose of 850 mg PO once daily for 1-4 weeks prior to hysterectomy/surgical staging. A tissue microarray, using triplicate cores from each specimen, was constructed from paired formalin-fixed, paraffin-embedded endometrial biopsy (pre-treatment) and hysterectomy (post-treatment) specimens. The expression of Ki-67, a marker of cell proliferation, was measured by immunohistochemistry. Individual slides were digitized using the Aperio ScanScope (Aperio Technologies, Vista, CA), and digital images were analyzed using Aperio ImageScope software. The Signed Rank Test was used for statistical analysis. **Results:** Sixteen patients have completed the protocol. The mean duration of treatment was 14.5 days. Percent Ki-67 staining decreased significantly with metformin treatment (mean of 19.5% decrease, $p = 0.026$). Two patients experienced grade 1 toxicities, including mild abdominal pain and loose stools. Ten of the 16 patients responded to metformin based on decreased proliferation from their pre- to post-treatment specimens. There were no differences in median age, BMI, HgbA1c, or number of doses taken between responders and non-responders to treatment. Pre-treatment Ki-67 levels were statistically higher in the women that responded to metformin treatment (52% versus 27.5%, $p = 0.0067$). **Conclusions:** Metformin significantly reduced proliferation in a pre-operative window study in obese endometrial cancer patients, providing further support for therapeutic clinical trials of metformin in this obesity-driven disease.

A phase II trial of lenvatinib in patients with advanced or recurrent endometrial cancer: Angiopoietin-2 as a predictive marker for clinical outcomes.

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Background: Lenvatinib is an oral receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFR β . The importance of angiogenesis in endometrial cancer (EC) highlights the need to understand clinical mechanisms of escape (eg, angiopoietin-2 [Ang-2]) from antiangiogenic therapy. **Methods:** Patients (pts) had metastatic/unresectable EC after 1 or 2 prior platinum-based treatments (Tx), ≤ 2 prior chemotherapies, and ECOG PS ≤ 2 . Pts received lenvatinib 24 mg once daily until disease progression or development of unmanageable toxicities. Primary endpoint was objective response rate (ORR: complete + partial response [CR+PR]) by RECIST 1.1. Archival tumor tissue and baseline (BL) and post-Tx plasma samples were collected for molecular analyses (reported elsewhere). **Results:** 133 pts were treated (median age: 62 y) and evaluated for safety, efficacy, and molecular correlative analysis. Dose reduction (31%) or Tx discontinuation (31%) occurred for toxicity. Median Tx duration was 112 days. The most common adverse events were hypertension 55% (Gr 3/4: 33%), fatigue 42% (Gr 3: 12.8%), diarrhea 35% (Gr 3: 5.3%), decreased appetite 35% (Gr 3: 2.3%), and nausea 32% (Gr 3: 3%); 1 pt had Gr 5 asthenia. Bowel obstruction, fistula formation, and perforation occurred in 3.8%, 2.3%, and 1.5%, respectively. Confirmed CR+PRs were observed in 19 pts (14.3%) by independent review (IRR) and 29 pts (21.8%) by investigator assessment (Inv). mPFS was 5.4 mos and mOS was 10.6 mos. Among 50 serum factors tested, only BL plasma Ang-2 correlated with maximal tumor shrinkage, $R = 0.36$ (Spearman), $p < 0.001$; ORR; PFS; and OS. The 24 pts with low BL Ang-2 plasma levels (cut-off value < 2082 pg/mL) were compared with the 98 pts with high BL Ang-2 (> 2082 pg/mL) and improved ORR (61% vs 18%), mPFS (9.5 vs 3.7 mos), and mOS (23 vs 8.9 mos) were observed. **Conclusions:** Lenvatinib in this population was tolerable and resulted in a 14.3% (IRR) and 21.8% (Inv) ORR and mOS of 10.6 mos. Low BL Ang-2 level appears to predict clinical benefit in a subset of pts with advanced EC who may achieve high response rates and prolonged overall survival. Further assessment is warranted. Clinical trial information: NCT01111461.

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Poster Discussion Session (Board #10), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**PTEN loss as a context-dependent determinant of patient outcomes in obese and non-obese endometrioid endometrial cancer patients.**

Zhenlin Ju, Shannon Neville Westin, Russell Broaddus, Jie Li, Navdeep Pal, Karen H. Lu, Robert L. Coleman, Samuel Klemperer, Lewis Cantley, Gordon B. Mills, Andrea P. Myers; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, University of Texas M. D. Anderson Cancer Center, Houston, TX; Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gynecologic Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX; BIDMC, Boston, MA; Harvard University, Cambridge, MA; Dana-Farber Cancer Institute, Boston, MA

Background: Aberrations in the PI3K pathway, the central relay pathway of insulin signals, occur in the majority of endometrioid endometrial cancers. We explored the prognostic utility of PIK3CA, PIK3R1, and PTEN mutations, as well as PTEN protein loss, in the context of patient weight. **Methods:** Patients (pts) treated for endometrial cancer at a single institution between 2000 and 2009 were identified. Tumor DNA was extracted and exome sequencing performed using a 454 platform with confirmation of hot spot mutations by Sequenom. PTEN protein expression was determined by immunohistochemistry and reverse phase protein array (RPPA). RPPA for 135 relevant proteins was performed using a GeneTAC arrayer to create spot arrays. Slides were scanned, analyzed, and quantitated using Microvigene software. **Results:** One hundred eighty seven endometrioid endometrial cancer specimens were included. Median age was 61 yrs and median body mass index (BMI) was 33.5 kg/m². The majority of pts had early stage (I/II) disease (74%) and grade 2 tumors (66%). There were no statistically significant associations between progression free survival (PFS) and PIK3CA, PIK3R1, PTEN mutation or loss. However, when stratified by BMI, PTEN loss was associated with a significantly improved PFS ($p < 0.006$) in obese (BMI > 30 kg/m²) pts. In contrast, PTEN loss was associated with a worse PFS ($p < 0.06$) in non-obese (BMI < 30 kg/m²) pts. Further, PTEN loss in obese and non-obese pts resulted in distinct protein changes by RPPA, with canonical PI3K pathway activation observed only in the non-obese PTEN loss cohort. PTEN loss in obese pts was associated with decreased expression of CATENIN and phosphorylated FOXO3A. **Conclusions:** These data suggest the impact of PTEN loss on tumor biology and clinical outcomes must be interpreted in the context of BMI and provide potential explanation for prior discrepant findings on effect of PTEN status on prognosis in endometrial cancer. These data describe a clinically important interaction between metabolic state and tumor genetics that could potentially unveil the biologic underpinning of obesity-related cancers and may be relevant to ongoing clinical trials with PI3K pathway inhibitors.

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Poster Discussion Session (Board #11), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM

Effect of metformin on recurrence-free survival and overall survival in diabetic patients affected by advanced ovarian cancer.

Cecilia Simonelli, Monica Bertolotti, Paul Sabbatini, Jonathan S. Berek, Jacobus Pfisterer, Monica Binaschi, Isabella Otranto, Carlo Alberto Maggi, Simona Scartoni, Angela Capriati; Menarini Ricerche, Firenze, Italy; Memorial Sloan-Kettering Cancer Center, New York, NY; Stanford Cancer Institute, Stanford, CA; Klinikum Solingen, Solingen, Germany; Menarini Ricerche, Pomezia, Italy

Background: Metformin, has recently shown some anti-cancer activities in ovarian cancer, both in vitro and in vivo. **Methods:** Analysis of Recurrence Free Survival (RFS) and Overall Survival (OS) was performed in patients (pts) with diabetes (D) treated with metformin (DMet⁺) or not (DMet⁻) enrolled in the MIMOSA trial, a randomized double-blind placebo-controlled international trial of Abagovomab maintenance therapy in 888 pts with advanced ovarian cancer. In the MIMOSA trial, no differences in the RFS and OS were observed between Abagovomab (n = 593) and Placebo arm (n = 295); hence, the present RFS and OS analysis (DMet⁺ vs DMet⁻) was run regardless of treatment allocation. A Cox proportional hazards model was used for adjusting the analysis for the predefined prognostic factors: Figo stage (III, IV), tumor size after debulking (residual tumor <1 cm, >1cm); CA125 serum level after 3th cycle (<35U/ml, >35U/ml). In addition, comparison of RFS and OS was done between DMet⁺ and the overall MIMOSA population not exposed to metformin (ALLMet⁻), and between the overall diabetic pts (ALLD⁺) and non-diabetic pts (ALLD⁻). **Results:** In the ALL population (n = 888), 42 pts were affected by diabetes (ALLD⁺) divided to DMet⁺ (n = 27) and DMet⁻ (n = 15), without difference in the prognostic factors distribution. When analysis was done in ALLD⁺, RFS median time was not reached in the DMet⁺ group whereas it was 328 days [CI: 30-660] in DMet⁻ group with HR favoring DMet⁺=0.419 [CI:0.175-1.002]; p = 0.05. Median OS time was also not reached in the DMet⁺ group whereas it was 786 days [CI:262-NE] in DMet⁻ group with HR=0.295 [CI:0.109-0.803]; p = 0.02. Interestingly HR for RFS time was still in favour of DMet⁺ group when compared to the ALLMet⁻ (n=861) with HR=0.575 (CI=0.324-1.022); p = 0.06. When ALLD⁺ were compared with ALLD⁻ (n = 846), no significant differences was detected in RFS and OS time. **Conclusions:** The present results are the first prospectively analyzed data demonstrating a favourable impact of metformin treatment on RFS and OS in pts affected by advanced ovarian cancer. Clinical trial information: NCT00418574.

The impact of diabetes and obesity on endometrial cancer outcomes.

Emily Meichun Ko, Paige Walter, Leslie Horn Clark, Amanda Lynn Jackson, Jason Franasiak, Laura Jean Havrilesky, Angeles Alvarez Secord, Dominic T. Moore, Paola A. Gehrig, Victoria Lin Bae-Jump; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Duke University Medical Center, Durham, NC; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Diabetes (DM) is a known risk factor for endometrial cancer (EC), yet its effect on cancer outcomes remains unclear. We sought to investigate of the relationship between DM, obesity, and anti-diabetic medication on EC recurrence and survival. **Methods:** An IRB approved multi-institution retrospective study included all EC patients diagnosed with carcinosarcoma as well as endometrioid, serous, and clear cell cancers between January 2005 to December 2010. Demographics, comorbidities, and medications were captured at the time of cancer diagnosis. Cohorts for comparison included women with and without DM; and diabetics treated with metformin-only (METFO) were compared to those not treated with METFO. Cox regression models were used to evaluate the effect of selected covariates on PFS and OS. **Results:** Of 1495 EC patients, 364 (24%) had DM. Diabetics were more likely to be African American (30 v 16%, $p < 0.0001$) and have higher BMIs (median 37.0 v 31.2, $p < 0.001$). After adjusting for age, race, stage, and BMI, women with DM had a worse OS (HR 1.40, 95CI 1.03-1.79), but similar recurrence risk (HR 1.16, 95CI 0.91-1.48) to non-diabetics. In a subset analysis of women with endometrioid EC ($n = 1144$), those with DM were 1.6 times more likely to recur (95CI 1.01-1.89, $p = 0.04$) and 2.4 times more likely to die (95CI 1.6-3.46, $p < 0.0001$). METFO use was associated with a decreased risk of recurrence (PFS HR 0.54, 95CI 0.3-0.96, $p = 0.04$), and death (OS HR 0.43, 95CI 0.22-0.83, $p = 0.01$) compared to no METFO use. METFO users had a similar clinical outcome compared to non-diabetics (PFS HR 1.05, $p = 0.82$; OS HR 1.3, $p = 0.46$). Obese women with DM who were treated with non-METFO regimens had a 1.8-fold increased risk of recurrence (95CI 0.94-3.7, $p = 0.07$) and 2.7-fold increased risk of death (95CI 1.2-5.9, $p = 0.01$). No survival differences were seen in women with serous, clear cell, or carcinosarcoma. **Conclusions:** Our data demonstrates worse clinical outcomes for EC patients with DM and improved outcomes for METFO users, suggesting a link between tumor pathogenesis and insulin growth factor and mTOR pathways. Future investigation is required to elucidate the complex relationship between diabetes, anti-hyperglycemic agents, and cancer outcomes.

Phase II, two-stage, two-arm, PIK3CA mutation stratified trial of MK-2206 in recurrent endometrial cancer (EC).

Andrea P. Myers, Russell Broaddus, Vicky Makker, Panagiotis A. Konstantinopoulos, Ronny Drapkin, Neil S. Horowitz, Joyce Liu, Paul Van Hummelen, Funda Meric-Bernstam, Michael J. Birrer, L. Austin Doyle, Robert L. Coleman, Carol Aghajanian, Gordon B. Mills, Lewis Cantley, Ursula A Matulonis, Shannon Neville Westin, SU2C Dream Team: PI3K in Women's Cancers; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; Beth Israel Deaconess Medical Center, Boston, MA; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital/Dana-Farber Harvard Cancer Center, Boston, MA; National Cancer Institute CTEP, Rockville, MD; Harvard University, Cambridge, MA

Background: EC has high rates of PI3K pathway alteration including PTEN mutation (50%) or IHC loss (>50%), PIK3CA mutation (25-40%) and PIK3R1 (20%) mutation. MK-2206 is an allosteric inhibitor of AKT, an effector kinase of PI3K signals. We hypothesized that pts whose tumors harbored PIK3CA mutations would be more likely to benefit from MK-2206 than those without PIK3CA mutation. **Methods:** Pts had recurrent or advanced EC; all histologies except MMMT were eligible. Up to 2 prior chemo lines were permitted; excluding prior treatment with PI3K/MTOR inhibitors. The first 19 pts were treated with MK-2206 200mg QW; due to initial skin toxicity rates, the starting dose was amended to 135mg QW. Co-primary endpoints were objective response and 6 mo PFS. The first 37 pts were stratified retrospectively. PIK3CA MT included R88Q, K111N, E110K, E418K, C420R, E453K, E542K/V, E545K, Q546R, H701P, M1043V, H1047R/L/Y changes. Independent Simon 2-stage tests were planned within PIK3CA MT and WT stratum: for MT, n1=15 and n2=10 pts would allow discrimination of RR<5% and 6moPFS<10% versus RR>25% or 6moPFS>35%; for WT, n1=31 and n2=24 pts would discriminate RR<5% and 6moPFS<10% versus RR>20% or 6moPFS>25%. **Results:** 37 pts were enrolled (1 ineligible) before accrual was stopped as timely CLIA-compliant prospective mutation analysis was not feasible. By PIK3CA mutation analysis, 9 pts were MT: 1 pt had both PR and 6moPFS. 27 pts were WT: 1 pt had PR and 3 pts had 6moPFS. 2 pts with 6moPFS were treated at 200mg; 2 pts with 6moPFS were treated at 135mg. Each group had 1 PR. The most common toxicity was grade 3 rash (19%). Grade 3 and 4 toxicities occurred in 50% and 8% of pts. Exploratory analysis of histology found all pts with 6moPFS were classified as serous (4 of 8) as compared to all other histologies (0 of 28, p=.001). Targeted exome sequencing and copy number analysis of the PI3K pathway and PTEN IHC are underway. Associative studies will be reported. **Conclusions:** There is limited single agent activity of MK-2206 in both PIK3CA MT and PIK3CA WT EC populations. Activity was detected in pts with serous histology tumors and warrants further study. Clinical trial information: NCT01307631.

	Init dose: 200mg (n=18)	Init dose: 135mg (n=18)	Total (n=36)
Grade 3 rash	6	1	7
Any grade 3+	13	9	22
Any grade 4+	5	3	8

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Poster Discussion Session (Board #14), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Recombinant adenovirus-p53 combined with chemotherapy in treatment of locally advanced cervical cancer (a phase II study).***Jian Zhou, Fumin LIU, Jie Xiao; Affiliated Woman and Children's Healthcare Hospital of Xuzhou Medical Collage, Xuzhou, China*

Background: To evaluate the efficacy and safety of recombinant adenovirus-p53 (rAd-p53) combined with chemotherapy in treatment of locally advanced cervical cancer. **Methods:** Forty patients with stage IIB-IV locally advanced cervical cancer were randomly divided into 2 groups: 20 patients receiving gene plus chemotherapy (PCG) and 20 receiving sole chemotherapy (CG). The patients in PCG were given one course of PVB (cisplatin + vincristine + pingyangmycin) and 5 times intratumoral injections of rAd-p53 at a dose of 2×10^{12} viral particles once per 3 days. The CG patients received a sole course of PVB. The study patients were followed up for at least one year. The VEGF, p53, Bax, and p21 protein expression in pre- and post-treatment tumor tissues were examined by immunohistochemistry. **Results:** The response was evaluated at 3 months after treatments. The response rates (CR + PR) were 95% and 75% for the PCG and CG patients, respectively. P53 proteins were strongly expressed in the tumor tissues from both groups. There were no significant changes in expression level of the p53 protein in the tumor tissue from pre- and post-treatment. However, the VEGF, Bax, and p21 protein expressions significantly increased in PCG after treatment. The overall one-year survive rates were 90% and 65%, respectively. A mild to medium grade of fever was found in 90% of the PCG patients. No serious adverse events relative to rAd-p53 were observed. **Conclusions:** Combined the rAd-p53 gene with chemotherapy is an effective treatment for the patients with advanced cervical cancer. The rAd-p53 gene therapy is a safe treatment.

Chemoresistance in gastric-type mucinous adenocarcinoma of the uterine cervix: Multi-institutional study by Sankai Gynecology Study Group (SGSG).

Atsumi Kojima, Muneaki Shimada, Shoji Nagao, Nobuhiro Takeshima, Tadahiro Shoji, Tamotsu Sudo, Eiji Hirata, Kazuhiro Takehara, Yasunobu Kanamori, Ryouji Hayase, Norihiro Teramoto, Takako Kiyokawa, Yoshiki Mikami, Junzo Kigawa, Ryuichiro Nishimura, Sankai Gynecology Study Group (SGSG); Shikoku Cancer Center, Matsuyama, Japan; Tottori University, Yonago, Japan; Saitama Medical University International Medical Center, Saitama, Japan; Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Iwate Medical University School of Medicine, Morioka, Japan; Section of Translational Research, Hyogo Cancer Center, Akashi, Japan; Graduate School of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan; National Hospital Organization Kure Medical Center/Chugoku Cancer Center, Kure, Japan; Yamaguchi Red Cross Hospital, Yamaguchi, Japan; National Hospital Organization Hukuyama Medical Center, Hukuyama, Japan; Chiba University, Chiba, Japan; Kyoto University Hospital, Kyoto, Japan; Tottori University Hospital, Yonago, Japan; Hyogo Cancer Center, Akashi, Japan

Background: Gastric-type adenocarcinoma (GAS) is a novel variant of mucinous adenocarcinoma of the uterine cervix, characterized by aggressive clinical behavior and absence of high risk HPV detection. However, the cause of its aggressive nature remains unknown. **Methods:** We have evaluated the chemosensitivity of GASs, which were diagnosed by central pathological review of cases enrolled in the phase II study of neoadjuvant chemotherapy with docetaxel and carboplatin for stage Ib2 to IIb non-squamous cervical cancer (SGSG-005) as an advance study. **Results:** In a total of 47 cases enrolled in the study, 20 (42.6%), 13 (27.7%), and 12 (25.5%) tumors were diagnosed as usual-type endocervical adenocarcinoma (UEA), GAS, and adenosquamous carcinoma, and each one (2%) as small cell carcinoma and serous adenocarcinoma, respectively. Response rate of UEA and GAS to the protocol was 85.0% and 46.2%, respectively ($p = 0.018$). Among 47 patients, 33 (70.2%) were assigned FIGO stage II, and 31 of these patients underwent surgery, while remaining 2 were inoperable because of progressive disease or intraabdominal dissemination. By microscopic examination of radical hysterectomy specimens, 12 of 14 (80%) UEAs were down-staged, whereas none of 6 (0%) GASs showed any response with residual vaginal and/or parametrial invasion even after chemotherapy ($P < 0.001$). Two inoperative tumors were GAS. Median follow-up duration was 41 months with a range of 10-65 months. The 3-years progression-free survival rate in cases of UEA and GAS were 73.7% and 35.9%, respectively ($p = 0.023$), and 3-years overall survival rate were 88.9% and 51.9%, respectively ($p < 0.001$). **Conclusions:** Our data suggests that GAS is distinguished from UEA by chemoresistance, which appears to be an intrinsic nature of this particular tumor. Alternative treatment strategy should be established for GAS. Clinical trial information: 000000560.

5527

Poster Discussion Session (Board #16), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**GOG0076-GG: A limited access phase II trial of pemetrexed (LY231514) (NSC #698037) in combination with cisplatin (NSC #119875) in the treatment of advanced, persistent, or recurrent carcinoma of the cervix—A Gynecologic Oncology Group study.**

David S. Miller, John A. Blessing, Lois M. Ramondetta, Huyen Pham, Krishnansu Sujata Tewari, Lisa Michelle Landrum, Jubilee Brown, Robert S. Mannel, Gynecologic Oncology Group; The University of Texas Southwestern Medical Center, Dallas, TX; Roswell Park Cancer Institute, Buffalo, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Southern California, Los Angeles, CA; University of California, Irvine, Medical Center, Orange, CA; University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: To estimate the antitumor activity of Pemetrexed and cisplatin with objective tumor response (partial and complete) in patients with advanced, persistent, or recurrent carcinoma of the cervix and to determine the nature and degree of toxicity of this regimen. Secondly, to determine the effects of this regimen on progression-free survival and overall survival. **Methods:** Eligible, consenting patients received pemetrexed 500mg/m² and cisplatin 50 mg/m² IV repeated every 21 days until disease progression or adverse effects prohibited further therapy. Patients had received no prior therapeutic chemotherapy, except when administered concurrent with primary radiation therapy. Subsequent doses were adjusted according to observed toxicity and protocol guidelines. Adverse events were assessed with CTCAE v 3.0. Primary measure of efficacy was tumor response by RECIST. The study was stratified by prior radiation therapy. **Results:** From September 2008 to November 2011, 55 patients were enrolled by 5 GOG member institutions. Of those, 49 patients were eligible and assessable. The regimen was well tolerated with 14 (29%) receiving >9 cycles. Common grade >2 toxicities were neutropenia 35%, leukopenia 28%, and metabolic 28%. The overall response rate was 31% (one complete and 16 partial responses). The median response duration was 7 months and survival 12 months. **Conclusions:** Pemetrexed in combination with cisplatin has demonstrated activity in the treatment of advanced, persistent, or recurrent carcinoma of the cervix. Additional study of this regimen in a phase III setting is justified in this patient population. Clinical trial information: NCT00691301.

Pathologic complete response to cisplatin with dose-dense paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer: Preliminary results of a multi-center phase II study with additional mutation analysis of adeno/adenosquamous carcinoma.

Maki Tanioka, Satoshi Yamaguchi, Shinya Sato, Shoji Nagao, Kazuhiro Takehara, Masato Nishimura, Tamotsu Sudo, Satoshi Morita, Hironobu Minami, Shunichi Negoro, Muneaki Shimada, Junzo Kigawa, Kiyoshi Fujiwara, Sankai Gynecologic Study Group; Medical Oncology Division, Hyogo Cancer Center, Akashi, Japan; Gynecologic Oncology Division, Hyogo Cancer Center, Akashi, Hyogo, Japan; Tottori University Hospital, Yonago, Japan; Saitama Medical University International Medical Center, Saitama, Japan; National Hospital Organization Kure Medical Center/Chugoku Cancer Center, Kure, Japan; Department of Obstetrics and Gynecology, School of Medicine University of Tokushima, Tokushima, Japan; Section of Translational Research, Hyogo Cancer Center, Akashi, Japan; Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan; Division of Medical Oncology/Hematology, Kobe University Hospital, Kobe, Japan; Tottori University, Yonago, Japan

Background: We report efficacy and safety of neoadjuvant cisplatin plus dose-dense paclitaxel (ddTP) within a phase II trial (UMIN-CTR ID: UMIN000006440), designed to investigate recurrence-free survival of neoadjuvant ddTP plus radical hysterectomy followed by adjuvant ddTP without radiotherapy for patients (pts) with stage IB2, IIA2, and IIB cervical cancer, whose driver mutations have been poorly understood. **Methods:** All enrolled pts received 3 cycles of cisplatin 75 mg/mq on day1 with paclitaxel 80 mg/mq on days 1, 8, and 15 every 21 days. Pathologic complete response (pCR) was defined as no evidence of malignancy in all surgical specimens observed. Using a selected panel of 535 oncogenes (Oncogenetics, Norcross, GA), mutations of pretreatment biopsy tissues were analyzed in 6 non-pCR pts with adeno/adenosquamous carcinoma (AC/ASC). **Results:** Among 51 enrolled pts, 50 were evaluable (40 with squamous cell carcinoma [SCC], 9 with AC/ASC, and 1 with small cell carcinoma). Median age was 52 years (range 30-70), the FIGO stage was IB2 in 14 pts, IIA2 in 3, and IIB in 34. Eighteen pts achieved complete response and 29 pts achieved partial response, with response rate of 94% (47/50). A total of 14 pts (28%; 13 with SCC, 1 with AC) achieved pCR. Grade 3/4 adverse events were neutropenia (34%), nausea (12%), appetite loss (10%), fatigue (6%), and anemia (6%). Febrile neutropenia was uncommon (2%). The analysis of oncogenes revealed that all 6 pts had mutations in the mixed-lineage leukemia (MLL3) gene, a histone methyltransferase, whose mutations have recently been reported in breast, pancreas, and colorectal cancers. Specifically, in *MLL3* gene, identical frameshift mutation was found in 2 pts and 2 common non-synonymous point mutations were found in 4 pts, despite no relevance to the ddTP response. No mutations were detected in TP53 and PIK3CA genes. **Conclusions:** The pCR rate with neoadjuvant ddTP for locally advanced cervical cancer was one of the highest reported in a prospective trial setting. Novel mutations of the *MLL3* gene were identified in non-pCR pts with AC/ASC. Clinical trial information: UMIN000006440.

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Poster Discussion Session (Board #18), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**ADXS11-001 immunotherapy targeting HPV-E7: Preliminary survival data from a P2 study in Indian women with recurrent/refractory cervical cancer.**

Robert G. Petit, Partha Basu; Advaxis, Inc., Princeton, NJ; Chittaranjan National Cancer Institute, Kolkata, India

Background: ADXS11-001 immunotherapy is a live attenuated *Listeria monocytogenes* (*Lm*) bioengineered to secrete a HPV16-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 P2 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 were randomized to either 3 doses of ADXS11-001 at 1×10^9 cfu or 4 doses of ADXS11-001 at 1×10^9 cfu with cisplatin chemotherapy. Naprosyn and oral promethazine were given as premedications and a course of ampicillin was given 72h after infusion. Patients received CT scans at baseline and 3, 6, 9, 12 and 18 months. The primary endpoint is overall survival. **Results:** As of February 2013, the trial has completed enrollment and 110 patients have received 264 doses of ADXS11-001. The percentage of patients alive at 6 months is 63% (67/107); at 9 months is 46% (49/106); at 12 months is 34% (30/87) and at 18 months is 15% (8/54). Tumor responses have been observed in both treatment arms with 6 CRs and 6 PRs; 36 additional patients had stable disease > 3 months, for a disease control rate of 44% (48/110). Activity against different high risk HPV strains has been observed. Three serious adverse events and 69 mild-moderate adverse events possibly related/related to ADXS11-001 treatment have been reported in 41% (45/110) of patients. The non-serious adverse events consisted predominately of transient, non-cumulative flu-like symptoms associated with infusion that either resolved on their own or responded to symptomatic treatment. **Conclusions:** ADXS11-001 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. Final 12-month OS, updated safety and translational analyses will be presented at the meeting.

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Poster Discussion Session (Board #19), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Locally advanced adenocarcinoma and adenosquamous carcinoma of the cervix compared to squamous cell carcinoma of the cervix in Gynecologic Oncology Group trials of chemoradiation.**

Peter Graham Rose, James Java, Charles W. Whitney, Henry Keys, Rachael Lanciano, Gillian Thomas; Cleveland Clinic Foundation, Cleveland, OH; Gynecologic Oncology Group, Buffalo, NY; Christiana Gynecologic Oncology, Newark, DE; AO Fox Hospital, Voorheesville, NY; Delaware County Memorial Hospital, Drexel Hill, PA; Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: Conflicting results have been reported for adeno- and adenosquamous carcinomas of the cervix with respect to their response to therapy and prognosis. Adeno- and adenosquamous carcinoma comprise the majority of non-squamous carcinomas of the cervix enrolled in GOG trials of chemoradiation. **Methods:** Adeno- and adenosquamous cervical carcinomas were retrospectively studied and compared to squamous cell carcinomas in GOG trials of chemoradiation. **Results:** Among 1672 patients enrolled in clinical trials of chemoradiation, 182 adeno- and adenosquamous carcinomas were identified (10.8%). A higher percentage of adeno- and adenosquamous carcinomas were stage IB (27% versus 20%) and fewer were stage IIIB (21.4% versus 28.6%). The mean tumor size was larger for squamous than adeno- and adenosquamous carcinomas, but adeno- and adenosquamous carcinomas were more often poorly differentiated (46.2% versus 26.8%). Among patients that received cis-platinum during radiation therapy, 843 with squamous cell carcinoma were compared to 112 with adeno- or adenosquamous carcinoma for overall survival, with no significant difference in risk of death ($p=0.472$). However, among patients that did not receive cis-platinum, 647 with squamous cell carcinoma and 70 with adeno- or adenosquamous carcinoma, there was a slightly higher risk of death for the adeno- or adenosquamous group ($p=0.049$). Adverse effects to treatment were similar across histologies. **Conclusions:** Patients with adeno- and adenosquamous carcinomas of the cervix have worse overall survival when treated with radiation alone, but have progression-free and overall survival similar to patients with squamous cell carcinomas of the cervix when treated with cis-platinum based chemoradiation.

Outcome parameters in node-negative vulvar cancer: A subset analysis of the AGO Care 1 study.

Linn Lena Woelber, Julia Kathrin Jueckstock, Felix Hilpert, Petra Neuser, Nikolaus De Gregorio, Severine Iborra, Frank Chen, Anika Habermann, Peter Hillemanns, Sophie Fuerst, Hans-Georg Strauss, Klaus H. Baumann, Falk Thiel, Alexander Mustea, Werner Meier, Philipp Harter, Pauline Wimberger, Lars Christian Hanker, Barbara Schmalfeldt, Sven Mahner; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Frauenklinik Innenstadt Munich University, Munich, Germany; University Medical Center Kiel, Department for Obstetrics and Gynecology, Kiel, Germany; Koordinierungszentrum für Klinische Studien der Philipps-Universität Marburg, Marburg, Germany; AGO and University of Ulm Medical Center, Ulm, Germany; Universitätsklinikum Freiburg, Freiburg, Germany; Charité-Universitätsmedizin Berlin, Berlin, Germany; Universitätsklinikum 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; Kliniken Essen Mitte, Essen, Germany; Department of Gynecology and Obstetrics, Technical University of Dresden, Dresden, Germany; Universitätsklinikum Schleswig-Holstein, Campus Luebeck, Klinik für Frauenheilkunde und Geburtshilfe, Luebeck, Germany; Department of Gynecology, Technical University Munich, Munich, Germany

Background: Prognosis of node-negative vulvar cancer is generally favorable compared to node positive disease. However, a small proportion of node-negative pts experience early recurrence with subsequent need for radical interventions. Aim of this analysis was to identify possible prognostic factors in this subset of pts. **Methods:** The AGO CaRE 1 study was designed as retrospective survey of treatment patterns and prognostic factors in vulvar cancer. Pts with primary squamous-cell vulvar cancer stage $\geq 1b$ treated at 29 gynecologic cancer centers in Germany 1998-2008 were included in a centralized database. **Results:** A total of 1618 pts were documented, 802 were node negative (pN0) after surgical staging and further analyzed. Median age was 66 yrs (21-94); 399 (49.8%) had pT1b, 365 (45.5%) pT2, 36 (4.5%) pT3 and 1 pT4 tumors; in 1 pt tumor stage was unknown. Median tumor size was 20 mm (1-345) and depth of invasion 4 mm (0.75-60). 703 (87.7%) pts had an R0 resection with a minimal margin of 5 mm (0.2-33); there were 46 R1 (5.7%) resections and 53 (6.6%) pts with unknown margin status. 692 pts (86.3%) received a full groin dissection (178 after sentinel node dissection) and in 85 pts (10.6%) only a sentinel node procedure was performed; surgery type was unknown in 25 pts (3.1%). 73 pts (9.1%) underwent adjuvant radiotherapy to the vulva. Median follow-up was 40 months. 169 pts (21.1 %) developed disease recurrence (thereof 111 (65.7%) at the vulva only and 53 (31.4%) at other locations, in 5 cases the localization was unknown) after a median of 17.7 months. 101 pts (12.6 %) died. To assess potential prognostic factors, multivariate analyses were performed including age, stage, tumor size, invasion depth, tumor grade, resection margin, adjuvant radiation, and mode of groin dissection [sentinel vs. full]) showing age as the only consistent prognostic factors for recurrence-free and overall survival. **Conclusions:** Even in the very large patient cohort of the AGO-CaRE database with more than 800 node-negative pts it was not possible to identify reliable clinicopathologic prognostic factors for node-negative disease. Identification of new biological markers will therefore be necessary to select high risk node negative pts for adjuvant treatment.

Tumor-associated CD66b⁺ neutrophil and CD8⁺ lymphocyte densities as independent prognostic factors for recurrence in localized cervical cancer: Automated digital image analysis and observer-assisted stereological assessments.

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Background: The prognostic impact of tumor-associated immune cells in cervical cancer is unclear. **Methods:** Automated digital image analysis (DIA) software and observer-assisted stereological (OAS) assessments were used to obtain densities of immunostains for CD66b⁺ neutrophils, CD163⁺ macrophages, and CD8⁺ lymphocytes in scanned whole slide images of tumor sections from 101 patients with FIGO stage IB and IIA cervical cancer. Primary end-point was recurrence-free survival (RFS). **Results:** The highest densities of CD66b⁺ neutrophils and CD163⁺ macrophages were observed by OAS in the peritumoral compartment (median 53.1 cells/mm² and 1.3% area fraction, respectively). DIA required far less human resources than OAS assessments. We observed high correlations between DIA and OAS variables of corresponding parameters; spearman ρ was 0.79 for CD8⁺ lymphocytes, 0.85 for CD66b⁺ neutrophils, and 0.92 for CD163⁺ macrophages (all $p < 0.0001$). Hazard rates for DIA assessments in the global tumor area were comparable with the prognostically strongest OAS assessments in the peritumoral compartment. In multivariate analysis, high density of CD66b⁺ neutrophils (HR 2.6; 95% CI 1.2–5.7; $p = 0.02$), low density of CD8⁺ lymphocytes (HR 2.3; 95% CI 1.1–4.9; $p = 0.03$), and presence of lymph node metastases (HR 2.6; 95% CI 1.2–5.5; $p = 0.02$) were independent predictors of poor RFS, whereas FIGO stage and CD163⁺ macrophage density were not. The CD66b/CD8 immunostain index obtained by DIA had excellent discriminatory power for each quartile with 5-year RFS of 92%, 80%, 65%, and 48% for quartile I (< 0.019), II (0.02–0.05), III (0.06–0.24), and IV (> 0.25), respectively ($p = 0.001$). **Conclusions:** High tumor-associated CD66b⁺ neutrophil and low CD8⁺ lymphocyte densities are independent prognostic factors for short recurrence-free survival in cervical cancer assessed by DIA and OAS. Combined CD66b⁺ neutrophil/CD8⁺ lymphocyte immunostain index obtained by DIA is a strong and cost-efficient prognostic variable with potential for routine application.

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Poster Discussion Session (Board #22), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Malignant germ cell ovarian cancer (MGCOC) in the Cancer Registry of Norway (CRN): A long-term follow-up study of presentation, survival, and second cancers.**

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Background: Significant improvements in the management of MGCOC have been achieved during the past two decades. However, data on long term risk conferred by radiation and chemotherapy is scarce. This is a long-term follow-up study of presentation, survival and second cancers. **Methods:** 360 female patients with histologically confirmed MGCOC, recorded in the CRN between 1953 and 2009 were identified. Patients, diagnosed before 1980 were separated from those with a diagnosis 1980+, reflecting the introduction of cis-platin based chemotherapy. Data on survival and second cancer incidence were obtained by linkage to the CRN. Cox Hazards Models and Kaplan Meier estimates were used. **Results:** The annual incidence doubled during the observation time. Malignant teratoma was the most common histological subtype (n = 190 [53%]), followed by dysgerminoma (n = 113 [31%]) and other non - dysgerminoma tumors (n = 57 [16%]). Over two thirds of the patients (median age 34 years [range 2-92]) had localized disease with distant disease in 23%. Before 1980 70% of 159 patients received subdiaphragmatic radiotherapy, this percentage was reduced to 24% after 1980, while chemotherapy increased from 11% to 38%. The 10 years ovarian cancer specific survival (OvCSS) (median follow-up time of 9.8 years [range: 0 - 54]) increased significantly to 93% in women treated in 1980+ compared to 62% to those with an earlier diagnosis (p <0.001) . Significant period-related improvement in OvCSS was observed independently from the extent of the disease and for all histological subtypes. Women aged >50 years had a significantly poorer OvCSS than younger ones, (HR=5.98, 95%CI [3.39 to 10.57]) adjusted for histological type and stage. A second cancer was diagnosed in 27 women, 63% of these cancers were located below the diaphragm within or close to the radiation field. **Conclusions:** The incidence of MGCOC is rising in Norway. We observed significant improvement of ovarian cancer specific survival after the introduction of cisplatin-based chemotherapy. The development of second cancer after treatment for MGCOC seems to be related to abdominal radiotherapy.

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Poster Discussion Session (Board #23), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**An evaluation of survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: A Gynecologic Oncology Group experience.**

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Background: We examined disparities in prognosis between patients with ovarian clear cell carcinoma (OCCC) and serous epithelial ovarian cancer (SOC). **Methods:** Data from stage I-IV epithelial ovarian cancer (EOC) patients who participated in 12 randomized GOG protocols using platinum-based chemotherapy were reviewed. Proportional hazards models adjusted for age and stratified by protocol, treatment arm, stage, performance status (PS), and race were used to compare progression-free survival (PFS) and overall survival (OS) by cell type (clear cell versus serous). **Results:** There were 10,803 patients enrolled, 1272 were not eligible: leaving 9,531, of whom 544 (6%) had OCCC, 7,054 (74%) had SOC, and 1,933 (20%) had other; only the OCCC and SOC are considered here. OCCC were significantly younger, more often of Asian race, stage I, good PS, and optimally surgically debulked than SOC patients. Prior to adjustment, OCCC had better PFS and OS due to better prognostic factors. There was no significant difference in PFS or OS for early stage OCCC patients compared to high-grade (HG) SOC patients. For late stage patients, OCCC had poorer PFS and OS compared to SOC, OS HR= 1.66 (1.43, 1.91; $p < 0.001$). For both optimal, HR = 1.34 (1.10, 1.63; $p = 0.003$) and suboptimal, HR = 3.18 (2.13, 4.75; $p < 0.001$) OCCC had a significantly poorer OS than SOC. After adjusting for age and stratified by protocol and treatment arm, stage, performance status, and race, OCCC had a significantly decreased OS, HR= 1.53 (1.33, 1.76; $p < 0.001$). In early stage cases, there was a significantly decreased treatment effect on PFS for consolidative therapy with weekly taxol versus observation in SOC compared to OCCC ($p = 0.048$). **Conclusions:** This is one of the largest analyses to date of OCCC treated in a uniform manner. OCCC patients have better PFS and OS compared to SOC; this, is due to their better prognostic factors. There was no observed difference in PFS or OS for early stage OCCC versus HGSOC. In late-stage patients, OCCC was significantly associated with decreased OS which was true for both optimal and suboptimally debulked patients. Finally, treatment effect was influenced by histology.

A multiplex methylation-specific PCR assay for detection of early-stage ovarian cancer using cell-free serum DNA.

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Background: Epithelial ovarian cancer (EOC) remains the most lethal disease among gynecological malignancies. Prompt diagnosis is challenging because of the non-specific symptoms exhibited during the early stage of the disease. So there is an urgent need for better detection methods. Here we performed this work to build up a platform of multiplex methylation-specific PCR (MSP) assay to improve the early detection of ovarian cancer, via identifying the methylation status of cell-free serum DNA. **Methods:** After screening, we chose seven genes (*APC*, *RASSF1A*, *CDH1*, *RUNX3*, *TFPI2*, *SFRP5* and *OPCML*) with a high frequency of methylation as candidate genes to construct the multiplex-MSP assay. When methylation of at least one of the seven genes was observed, the multiplex-MSP assay was considered positive. We performed the retrospective and screening study to verify its specificity and sensitivity in the detection of EOC. **Results:** The methylation status of cell-free serum DNA was examined in the preoperative serum of 202 patients, including 87 EOC cases (stage I, n=41, stage II-IV, n=46), 53 benign ovarian tumors and 62 healthy controls. As expected, multiplex MSP assay achieved a sensitivity of 85.3% and a specificity of 90.5% in stage I EOC, strikingly higher than that of single CA125, producing a sensitivity of 56.1% at 64.15% specificity [p=0.0036](Table). **Conclusions:** Multiplex MSP assay analyzing the methylation status of cell-free serum DNA is a suitable and reliable approach to improve the early detection of ovarian cancer, potentially benefiting a broad range of applications in clinical oncology.

		Retrospective study		Screening study	
		CA125	Multiplex-MSP	CA125	Multiplex-MSP
Specificity	All	64.15%	90.57%	72.41%	82.76%
Sensitivity	All	73.56%	89.66%	82.05%	92.31%
	Early stage	56.10%	85.37%	50.00%	83.33%
	Advanced stage	89.13%	93.48%	84.85%	93.94%
ROC-AUC (95% CI)	All	0.8090 (0.7376-0.8805)	0.9126 (0.8643-0.9609)	0.8837 (0.8017-0.9658)	0.8988 (0.8192-0.9783)
	Early stage	0.6986 (0.5904-0.8068)	0.8916 (0.8258-0.9574)	0.8103 (0.5984-1.022)	0.8218 (0.6375-1.006)
	Advanced stage	0.9075 (0.8461-0.9689)	0.9313 (0.8788-0.9838)	0.8970 (0.8146-0.9796)	0.9127 (0.8364-0.9891)

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Poster Discussion Session (Board #25), Sun, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Adult granulosa cell tumors (GCT): 56 years of clinicopathologic outcomes including FOXL2 mutational status.**

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Background: GCT account for 2-3% of ovarian cancers with a tendency for late relapse. Treatment is primarily surgical. The role of chemotherapy and hormonal therapy is more controversial. The FOXL2 mutation (402C→G) has been identified as a potential driver mutation and may be useful in diagnosis and treatment. **Methods:** We performed a retrospective review of GCT patients (pts) referred to the Auckland Gynae-Oncology Multidisciplinary Team from 1955 to 2011. Baseline characteristics, clinical course, histopathology and survival data was recorded. FOXL2 mutation status was determined by DNA sequencing, and correlated with clinical data. **Results:** 56 GCT pts were identified. Median (med) age 48.6 years (y) (22-86). Stage I were 82.1%. 48% of tumours were ≥ 10 cm. Med follow up was 10.0y (0.2-40.4). 25 pts progressed, med time to progression (TTP) was 4.5y (0.1-17.7). Med progression free survival was 14.5y. Med overall survival (OS) was 21.8y but med disease specific survival was not reached. 9/18 pts died of disease. Stage III GCT and size ≥ 10 cm had a higher risk of relapse (RR 3.1 and 2.9) and death (RR 8.2 and 8.6) respectively. 17/46 (37%) Stage I pts progressed. Med TTP was 8.3y (1.3 to 17.7), med OS was 29.0y. Stage I relapse rate was higher in tumours ≥ 10 cm (RR 3.9 $p < 0.01$). 12/17 1st relapses were treated with surgery. 10/17 pts received ≥ 1 line of chemotherapy and 7 ≥ 1 hormonal therapy. Clinical benefit rates (CR, PR and SD >6 m) for first-line chemotherapy was 25% and 71% for hormones. All 7 Stage III pts progressed with med OS of 6.3yr (0.2-12.3y). Currently the FOXL2 mutation statuses are known for 18 patients. 89% carried the mutation. Homozygous, heterozygous and wild-type mutations had no difference in risk of relapse or death. Further FOXL2 mutation analysis is ongoing. **Conclusions:** This long term series confirms the protracted natural history of this disease. Early stage GCT, despite progression has a good prognosis with med OS >25 y. Stage and tumour size remain the most consistent prognostic factors. Whilst surgery remains the mainstay of therapy, the high response rate to hormonal therapy deserves investigation. Currently the FOXL2 mutation status does not appear prognostic but this needs further research.

Phase II trial of oral etoposide plus IV irinotecan for patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503).

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Background: Developing effective chemotherapy for patients (pts) with platinum (Pt) resistant ovarian cancer is unmet medical needs. Topoisomerase inhibitors, such as oral etoposide and iv irinotecan, have been reported to show some efficacy for Pt - resistant ovarian cancer as monotherapy. Combining these two agents should be an intriguing idea. Following phase 1 and feasibility study reported in ASCO2002 and 2005, this study aimed to assess safety and efficacy of oral etoposide plus iv irinotecan for pts with Pt -resistant and taxane pre-treated ovarian cancer (UMIN-CTR ID: UMIN000001837). **Methods:** Eligible pts are given etoposide at 50 mg/m² p.o. from day 1 to 21, and irinotecan 70 mg/m²iv, at day1 and day15, repeated every 28 days, up to 6 cycles. Primary endpoint is response rate (RR), secondary endpoints are adverse events, progression-free survival (PFS), and overall survival (OS). As a SWOG two-stage design, at least 55 pts are required with one-sided alpha of 0.05, beta of 0.2 and expected and threshold value for primary endpoint as 35% and 20%. Sixty pts are to be registered. **Results:** From April 2009 to January 2012, 61 pts were entered to this study. One patient was ineligible, thus 60 pts were analyzed for the study. RR was 21.7% (1 CR + 12 PR, 89% C.I. 13.5 – 31.9 %, one-sided p=0.42). At the data cut-off at November 2012, median PFS and OS were 4.1 (95% C.I. 3.5 – 5.6) and 12.4 (95% C.I. 10.1 – 14.8) months, respectively. Six months-PFS was 35.0 %. For pts with Pt --free interval (PFI) \geq three months (n = 33), RR was 30.3 % (95% C.I. 15.6 -48.7 %), median PFS and OS was 5.8and 16.9 months, respectively. For safety, G3/4 neutropenia, anemia, and thrombocytopenia were 60.0 %, 36.7 % and 11.7%, respectively. G3/4 non-hematological toxicities over 10 % were febrile neutropenia (FN) (18.3%), fatigue (13.3%), nausea (11.7 %) and anorexia (11.7 %). FN was more frequent in elderly pts of 65 years or older (28.6 %). Two treatment-related deaths occurred, both in elderly. **Conclusions:** As a whole, this regimen did not meet primary endpoint for further phase 3 study. Elderly pts should be treated very cautiously with this regimen. However, promising efficacy could be expected for those with PFI \geq 3 months. Clinical trial information: UMIN000001837.

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General Poster Session (Board #44B), Mon, 8:00 AM-11:45 AM

Phase I study of combination chemotherapy with irinotecan and gemcitabine for taxane/platinum resistant ovarian, fallopian tube, or primary peritoneal cancer.

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Background: Development of new regimen is required to overcome platinum resistant ovarian cancer. Irinotecan and gemcitabine have a synergistic effect to inhibit the growth of ovarian cancer cell line in vitro. The objective is to evaluate the feasibility of combination chemotherapy with irinotecan and gemcitabine for taxane/platinum resistant recurrent ovarian, fallopian tube or peritoneal cancer and to determine the recommended dose. **Methods:** Nine patients with measurable disease (age range 51-70 years) were enrolled. Patients were treated with irinotecan and gemcitabine on days 1 and 8 every 3 weeks with starting dose of level 1. Dose levels included irinotecan/gemcitabine: 65/650 (level 0), 80/800 (level 1), 100/1000 (level 2), mg/m² respectively. Level 2 is defined as the maximum dose as used in other malignancies. Dose-limiting toxicity (DLT) was assessed during the first cycle; toxicities were monitored throughout the treatment according to the CTCAE v4.0. Treatment continued until disease progression or unacceptable toxicity. **Results:** In level 1 (n = 6), grade 3/4 neutropenia was observed in 5 patients. Grade 3 nausea and vomiting was observed in 1, grade 3 diarrhea in 1. One patient of level 1 experienced DLTs. In level 2 (n = 3), grade 3/4 neutropenia are observed in 3, anemia in 1, and thrombocytopenia in one patient. Other toxicities were mild. Three patients who received level 2 did not show DLT. The objective response was CR/PR/SD/PD, 0/2/5/2. **Conclusions:** The dose level of irinotecan 100 mg/m² and gemcitabine 1000 mg/m² on day 1 and 8 every 3 weeks is recommended for a phase II study. Clinical trial information: UMIN000005926.

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General Poster Session (Board #44C), Mon, 8:00 AM-11:45 AM

The retention index calculated with dual-phase ^{18}F -FDG PET/CT in ovarian carcinoma: Determination of the optimal cutoff level using ROC analysis.

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Background: Although ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography /computed tomography (PET/CT) is useful as a clinical tool in various malignancies, the maximum standardized uptake value (SUVmax) overlap between malignant and benign lesions is significant. The dual-phase PET/CT has shown its usefulness to differentiate benign from malignant conditions in some solid tumors, but its usefulness has not yet been evaluated in patients with ovarian cancers. **Methods:** Twenty consecutive patients (thirteen with ovarian cancers and seven with benign lesions) were evaluated preoperatively by dual-phase ^{18}F -FDG PET/CT (Time of Flight, Philips), performed 1 and 2 hour after injection of 370-555 MBq of ^{18}F -FDG. The SUVmax at 1 hour (SUVmax1) and at 2 hour (SUVmax2) were determined, and the retention index (RI) was calculated by subtracting the SUVmax1 from the SUVmax2 and dividing by SUVmax1. **Results:** Area under the receiver operating characteristic (ROC) curve of SUVmax1 and SUVmax2 were 0.753 and 0.835, respectively (95% CI; 0.512, 0.915 versus 0.604, 0.961; $p = 0.062$ versus 0.001). Area under the ROC curve of RI was 0.901 (95% CI; 0.684, 0.988; $p < 0.001$). When the SUVmax1 cutoff was set to 3.2, the sensitivity and the specificity of the SUVmax1 were 100% and 57.1%, respectively. When the SUVmax2 cutoff was set to 3.9, the sensitivity and the specificity of the SUVmax2 were 100% and 57.1%, respectively. The sensitivity and the specificity of RI were 92.3% and 71.4% when the cutoff was set to 16.67. By pairwise comparisons, the area under the ROC curve of SUVmax2 was significantly higher than that of SUVmax1 ($p = 0.032$). The area under the ROC curve of the RI was higher than those of SUVmax1 and SUVmax2, but not statistically significant ($p = 0.166$ and 0.459, respectively). **Conclusions:** The RI and SUVmax2 are proved to be useful in differentiating ovarian cancers from benign lesions. The use of dual-phase ^{18}F -FDG PET/CT should be taken into account when the preoperative imaging is ambiguous. **Acknowledgements:** This study was supported by a grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, (A070001) Republic of Korea.

Neoadjuvant chemotherapy with six cycles of carboplatin and paclitaxel in advanced ovarian cancer patients not candidates for optimal primary surgery: Safety and effectiveness.

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Background: Primary debulking surgery (PDS) has been considered the standard of treatment in advanced ovarian cancer, while neoadjuvant chemotherapy, three cycles followed by interval debulking (ID) surgery, is a valid treatment alternative for patients with non-resectable disease. This study aimed to show the efficacy and safety of six cycles of neoadjuvant chemotherapy (N-CT) followed by cytoreduction, a single institution experience. **Methods:** Aretrospective analysis was performed of all patients (pts) with advanced ovarian cancer treated with platinum based N-CT, between January/2004 and February/2012. **Results:** 97 pts underwent N-CT in our institution; 78.1% and 18.8% the patients had extensive stage IIIC or IV disease at diagnosis, respectively. Median age 60 years (36 – 82). Histologic types: serous 84.5%, adenocarcinoma not specified 11.3%, endometrioid 1.0%. A median of six cycles of chemotherapy were performed. Patients did not received chemotherapy after debulking surgery. During the treatment 31.4% had grade 3/4 toxicity, the most commonly observed toxicities were hematologic toxicities and nausea, four (4.1%) patients died during chemotherapy due to disease progression. After N-CT 24.7% achieved clinical complete response, 57.7% partial response and 12.4% disease progression. From this cohort 63.1% underwent a complete resection of all macroscopic and microscopic disease (R0). Median length of hospital stay and postoperative ICU stay was 5 and 0.8 days respectively, surgical complications were not common however five (7.1%) patients needed second surgery due to operatory complications and 19 pts (27.1%) needed blood transfusion after debulking. With a median follow up of 21.8 months (0.5-139.7), median overall survival and chemotherapy-free interval were 57,7 and 9,5 months, respectively. **Conclusions:** Six cycles of neoadjuvant carboplatin and paclitaxel is safe, effective and does not increase perioperative and postoperative complications for patients with stage IIIC-IV not candidates for optimal/R0 PDS. The overall survival of this cohort is higher than those treated with interval debulking surgery.

Feasibility and safety of front-line bevacizumab (BEV)-containing therapy after neoadjuvant (NA) chemotherapy (CT) for ovarian cancer (OC): The ROSiA experience.

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Background: BEV significantly improved the efficacy of front-line CT for OC in the GOG-0218 and ICON7 phase III trials. The ongoing single-arm ROSiA study, which has completed recruitment of 1039 patients (pts), is assessing BEV + CT in routine oncology practice. Unlike GOG-0218 and ICON7, prior NACT is permitted. We assessed the surgical safety of BEV + CT in the subgroup of pts with prior NACT. **Methods:** Inclusion criteria include: FIGO stage IIb–IV or grade 3 stage I–IIa epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; no prior post-surgical therapy for OC; and ECOG PS 0–2. Pts with uncontrolled hypertension or clinical signs/symptoms of GI obstruction or history of abdominal fistula, GI perforation, or intra-abdominal abscess in the preceding 6 mo are excluded. Pts in the NA subgroup were enrolled into the study after up to 4 cycles of NACT without BEV. After interval debulking, pts received BEV 15 mg/kg q3w (or 7.5 mg/kg at the investigator's discretion) in combination with CT (paclitaxel [175 mg/m² d1 q3w or 80 mg/m² qw] + q3w carboplatin [AUC 5 or 6]), to a maximum total of 8 cycles including the pre-study NA cycles. Single-agent BEV was continued until progression, unacceptable toxicity, or for up to 36 cycles in total. The primary objective is evaluation of safety (CTCAE v4.03). Additional endpoints include efficacy (including PFS, response rate, OS) and exploratory translational research. **Results:** Of the 1039 pts enrolled in ROSiA, 150 (14%) had received NACT. Of these, most had stage IIIc (60%) or IV (29%) disease; 65% had residual disease ≤1 cm; and 19% underwent bowel resection. At the data cut-off 22 mo after enrollment began, median follow-up from post-surgery study entry was 12.6 mo; 69 patients (46%) remained on BEV therapy. At cut-off, pts had received a median of 13 cycles of BEV (range 1–31), including 4 cycles (range 1–6) of BEV in combination with CT after surgery. To date, no pts have had grade ≥3 wound-healing complications during study therapy; 1 pt experienced grade 4 GI perforation 10 weeks after surgery (3 weeks after the first BEV dose), which resolved within 4 weeks. **Conclusions:** NACT followed by BEV + CT was feasible and tolerable. Clinical trial information: NCT01239732.

Health-related quality of life (HRQoL) results from the AURELIA trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (OC).

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Background: Adding BEV to CT significantly improved PFS in platinum-resistant OC in the open-label phase III AURELIA trial. As symptom improvement is a major goal of treatment, determining effects on HRQoL was a key secondary aim of AURELIA. **Methods:** After investigator selection of single-agent CT (pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel), patients (pts) with measurable/assessable platinum-resistant OC were randomized to CT \pm BEV. HRQoL and symptoms were assessed at baseline and every 2 or 3 cycles (8/9 wks) until PD using the EORTC OC Module (OV28) and FOSI. The primary HRQoL endpoint was an absolute improvement of $\geq 15\%$ (≥ 15 points) on the 100-point OV28 subscale for abdominal (abdo)/GI symptoms (items 1–6) at wk 8/9. Pts with missing questionnaires (Qs) were included and considered not to have improved. A sensitivity analysis excluded pts with Qs missing for reasons other than PD/death or switch from CT to BEV. Subgroup analyses of symptomatic pts included only those with a baseline score ≥ 15 (sufficient to show ≥ 15 -point improvement). Mixed-model repeated measures (MMRM) analysis was used to compare Qs from all time points until PD/death, not just wk 8/9. The FOSI was analyzed similarly. **Results:** Baseline Qs were available from 89% of 361 randomized pts. At wk 8/9, 81% of BEV–CT vs 68% of CT pts who were alive and PD-free returned OV28 Qs. For the primary HRQoL endpoint, more BEV–CT than CT pts had a $\geq 15\%$ improvement in the OV28 abdo/GI symptom subscale at wk 8/9 (21.9% vs 9.3%, 12.7% difference [95% CI 4.4–20.9]; $p = 0.002$). The sensitivity analysis described above showed a 13.3% difference [95% CI 4.5–22.1]. In the subgroup of 233 pts with a baseline score ≥ 15 , there was a 16.9% difference (95% CI 6.1–27.6) favoring BEV–CT (29.6% vs 12.7%). MMRM analysis of OV28 abdo/GI symptom subscale scores also favored BEV–CT (6.4-point difference [95% CI 1.28–11.6]). More BEV–CT than CT pts had a $\geq 15\%$ improvement in FOSI score at wk 8/9 (12.2% vs 3.1%, 9.0% difference [95% CI 2.9–15.2]). **Conclusions:** Adding BEV to CT resulted in more frequent $\geq 15\%$ improvements in patient-reported abdo/GI symptoms in platinum-resistant OC. Clinical trial information: NCT00976911.

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General Poster Session (Board #44G), Mon, 8:00 AM-11:45 AM

Ovarian cancer distribution of histology, stage, and screening performance.

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Background: Survival in women with ovarian cancer is strongly influenced by stage of disease at diagnosis. As such, strategies have been investigated to identify biomarkers for early detection. This premise assumes a progression of disease from early to late stage. Varying histologic subtypes in ovarian cancer have distinct etiologies. It is likely that early detection strategies will need to be subtype specific. This study sought to evaluate histologic subtypes, stage of disease, and screening performance in a cohort of women diagnosed with ovarian cancer. **Methods:** This analysis was performed as an REB approved sub-study of a single institution ovarian cancer tumor banking protocol for which all patients presenting with suspected ovarian cancer, since February 2011, were eligible. This analysis included all patients with confirmed ovarian cancer. Patients were identified and tracked prospectively. **Results:** There were 135 patients with ovarian cancer (mean age 57 ± 12 years). 67% were post-menopausal. The distribution of histologic subtypes was 42% high-grade serous (HGS), 18% endometrioid, 12% clear cell, 6% low-grade serous (LGS), 6% sex-cord stromal, 5% germ cell, 3% mucinous, 3% mixed, 3% carcinosarcoma, and 2% other. 64 (47%) women presented with advanced disease with a median CA 125 of 260 (range 14 – 21 782), of whom 43 (68%) were found to have HGS histology. 46 (34%) patients presented with stage I disease with a median CA 125 of 41 (range 3 – 9305). Of these, the distribution of histologic subtypes included 13 (28%) endometrioid, 9 (20%) clear cell, 5 (11%) sex-cord stromal, 5 (11%) HGS, 3 (7%) mucinous and 23% other. Risk of Malignancy Index (RMI) scoring for women with stage I disease ($N = 35$) revealed a false negative rate of 31%, including 4 clear cell, 2 LGS, 2 endometrioid and 1 each of HGS, mucinous, and mixed (clear cell and endometrioid) histologies. **Conclusions:** Stage I ovarian cancer consists primarily of non-serous histologies, which are not reliably detected using CA 125 and ultrasound markers. Current approaches to screening for early stage disease may require the identification of biomarkers unique to clear cell and endometrioid histologies and novel strategies for the identification of patients at risk for HGS carcinomas.

Efficacy and safety of front-line bevacizumab (BEV), weekly paclitaxel (wPAC), and q3w carboplatin (C) in elderly patients (pts) with ovarian cancer (OC): Subgroup analysis of OCTAVIA.

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Background: Front-line BEV significantly improved PFS when combined with q3w paclitaxel and C in two randomized phase III OC trials. The single-arm OCTAVIA study combined two successful strategies, anti-angiogenic therapy and wPAC administration, demonstrating median PFS of 24 months at the primary analysis [IGCS 2012]. We report exploratory analyses of safety and efficacy in the subgroup of pts aged ≥ 65 y treated in OCTAVIA. **Methods:** Pts received 6–8 cycles of BEV (7.5 mg/kg, d1) + wPAC (80 mg/m² d1, 8, 15) + C (AUC 6, 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 primary endpoint was PFS. **Results:** Of the 189 treated pts, 37 (20%) were aged ≥ 65 y (11% 65–<70 y; 6% 70–<75 y; 3% ≥ 75 y). Compared with pts aged <65 y, the subgroup of pts aged ≥ 65 y included fewer pts with no residual disease after surgery (24% vs 34%) and more pts with grade 3 OC (62% vs 55%) or comorbidities at baseline (hypertension: 38% vs 17%; dyslipidemia: 14% vs 5%). Pts aged ≥ 65 y received a median of 6 chemotherapy cycles (range 1–8) and 17 BEV cycles (range 0–18). C or wPAC was given for ≥ 6 cycles to 86% and 68% of pts, respectively. AEs led to early discontinuation of C, wPAC, or BEV in 14%, 38%, and 14% of pts, respectively. After median follow-up of 26.5 months and events in 62%, median PFS was 20.5 mo (95% CI 17.8–29.1 mo) in the elderly subgroup. Seven pts (19%) had died, all from disease progression; the 1-y OS rate was 97.3%. The most common grade ≥ 3 AEs were hematologic (neutropenia 62%, thrombocytopenia 14%), with no major differences according to age. Overall, there was a numerically higher incidence of grade 3/4 AEs in pts aged ≥ 65 vs <65 y (86% vs 76%, respectively), driven by non-hematologic AEs. The incidences of grade ≥ 3 AEs of special interest were similar in older and younger pts, except for hypertension (11% in pts ≥ 65 y vs 3% in pts <65 y) and bleeding (3% vs 0%, respectively). **Conclusions:** BEV combined with wPAC and C is a feasible, well-tolerated, active front-line regimen, even in the small subgroup of pts aged ≥ 65 y, many of whom had comorbidities. Clinical trial information: NCT00937560.

Bevacizumab (Bev) for treatment of recurrent serous borderline (SB) or low-grade serous (LGS) ovarian cancer: A retrospective review of the Memorial Sloan-Kettering Cancer Center (MSKCC) experience.

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Background: LGS ovarian cancer is a rare subtype of ovarian cancer, accounting for 10% of ovarian cancer cases. Patients typically present at an early age, exhibit a protracted clinical course, and have response rates to chemotherapy of < 4%. Limited clinical data suggests that bev may have activity in this disease. The objective of this study was to determine the response rate to treatment with bev in patients with SB or LGS ovarian cancer treated at MSKCC. **Methods:** Following IRB approval, all patients with a diagnosis of SB or LGS ovarian or primary peritoneal cancer treated with ≥ 1 dose of bev for persistent or recurrent disease were identified. 17 patients were treated at MSKCC between July 2005 and June 2012. Diagnosis was confirmed by a gynecologic pathologist. All imaging was independently reviewed by the study radiologist and response was determined by RECIST 1.1 criteria. **Results:** 17 patients, 10 with LGS ovarian cancer, 3 with LGS primary peritoneal cancer, and 4 with SB disease were included in the analysis. The mean number of prior therapies was 3.4 (range: 1-9, median: 2). Two patients were treated with bev alone, the remainder (15) received bev in combination with paclitaxel (Pac, 6), topotecan (1), pemetrexed (1), oral cyclophosphamide (3), gemcitabine (Gem, 2), Gem and carboplatin (Carbo) (1), or Pac and Carbo (1). Two patients were not evaluable for response due to termination of treatment prior to first radiographic assessment. The median duration of bev treatment was 23 weeks (mean: 32.2; range 6-79.4). **Conclusions:** This data suggests that the addition of bev to cytotoxic chemotherapy may produce dramatically higher response rates than chemotherapy alone in patients with SB and LGS ovarian cancer. A prospective study of bev for treatment of this chemotherapy resistant disease is warranted.

Response (RECIST 1.1)	Number of patients	Percentage
Partial response (PR)	6	40% (95%CI: 16.3-67.7%)
Stable disease (SD)	5	33.3%
Clinical benefit rate (PR+SD)	11	73.3% (95%CI: 44.9-92.2%)
Progressive disease (PD)	4	26.7%

The role of CHFR expression in ovarian cancer and response to taxane therapy.

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Background: CHFR, an E3 ubiquitin ligase that regulates Aurora A and Pololike Kinase 1, plays a critical role in the cellular response to mitotic stress. In particular, cells containing CHFR arrest in G2 when microtubule dynamics are disrupted. Conversely, low CHFR expression is associated with hypersensitivity to mitotic spindle poisons in breast cancer cell lines. Despite the extensive use of taxanes in front line treatment of epithelial ovarian cancer (EOC), little is known about CHFR expression in this disease. We examined CHFR expression and its relationship with clinical characteristics and outcome in women with EOC. **Methods:** Pretreatment EOC samples from women enrolled in the Mayo Clinic Biospecimen Resource for Ovarian Cancer Research who underwent initial surgical debulking between 1999-2009 were stained in triplicate with anti-CHFR antibodies. Samples were scored in a blinded fashion for CHFR expression. Associations between CHFR staining and histology, grade, and stage were assessed using chi-squared tests; associations between CHFR and overall survival (OS) or time to disease recurrence (TTR) were assessed using Cox proportional hazards models. **Results:** Samples from 354 women were stained; median age at diagnosis was 60.5 (range 21-93). At a median follow-up of 67 months, 221 women (62%) had died. Across all patients, moderate/strong CHFR staining was associated with poor OS (HR = 1.39, 95% CI: 1.07-1.81, $p = 0.015$). Moreover, moderate/strong CHFR expression was strongly associated with serous histology ($p < 0.0001$), high grade ($p < 0.0001$) and advanced stage ($p = 0.0002$). To assess whether the association between CHFR expression and OS was related to taxane sensitivity, a subgroup analysis was performed in the subset of patients ($N=131$) with high-grade serous EOC who received initial platinum/taxane chemotherapy. Moderate/strong CHFR expression failed to correlate with OS (HR=0.91, 95% CI: 0.57-1.45, $p = 0.68$) or TTR from the start of chemotherapy (HR = 0.85, 95% CI: 0.55-1.31, $p = 0.55$) in this subset. **Conclusions:** CHFR expression is associated with poor OS and adverse clinical characteristics in patients with EOC but does not appear to be related to taxane sensitivity in high-grade serous tumors.

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General Poster Session (Board #45C), Mon, 8:00 AM-11:45 AM

Benefit in progression-free survival (PFS) to expect based on CA125 reduction at week 6 in recurrent ovarian cancer (ROC) patients: CALYPSO phase III trial data (a GINECO-GCIG study).

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Background: Prediction of the expected survival benefit based on CA125 change in treated recurrent ovarian cancer (ROC) patients would be very useful. It may help for early selection of the best drug candidates during drug development, and for clinical trials. We used mathematical modeling to: 1) quantify the links between CA125 kinetics and progression-free survival (PFS) benefit, and 2) to estimate the CA125 decline required to observe a 50% PFS improvement. **Methods:** CALYPSO randomized phase III trial database, comparing 2 platinum-based regimens in ROC patients was used. The cohort was randomly split into a “learning dataset” (N=356) to estimate model parameters and a “validation dataset” (N=178) to validate model performances. A full parametric survival model was developed to quantify the links between tumor size changes; CA125 kinetics; prognostic factors and PFS. The predictive performance of the model was evaluated with simulations on the validation dataset. **Results:** PFS from 534 ROC patients was properly described by a parametric model with log-logistic distribution. The factors significantly linked to PFS were fractional changes in CA125 (Δ CA125) and in tumor size (Δ TS) from baseline at week 6; baseline CA125 (CA125_{BL}); and patient therapy free interval. By reducing this model, Δ CA125 was a better predictor of PFS than Δ TS. Simulations verified the predictive performance of this model. Patients should achieve at least 49% Δ CA125 decline induced by treatment to observe 50% PFS improvement. This effect was independent on treatment arm. **Conclusions:** This is the first drug-independent parametric survival model quantifying links between PFS and CA125 kinetics in ROC. The CA125 modeled decline required to observe a 50% improvement in PFS in treated ROC patients was defined. It may be a surrogate marker of PFS gain, and may embody an early predictive tool for go/no go drug development decisions and for clinical trials. Validation in other datasets is warranted.

Analysis of clinical features of ovarian cancer (OC) and breast cancer (BC) among BRCA-mutated (BRCA+) and sporadic (NH) double tumours.

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Background: The clinical outcome of double OC and BC is specifically unknown either BRCA+ and in double tumours NH patients. **Methods:** The present databases made of 106 patients, 67 cases of NH (negative, no-tested or ongoing test for BRCA1/2 mutations) and 39 of BRCA+, were constituted to identify the clinical and pathological features of BC and OC. The primary endpoint was to evaluate biological characteristics of both cancers and clinical outcome of OC in coexistence with BC. Patients were censored at last follow-up or death (any cause) for determination of overall survival (OS). OS were determined using the Kaplan-Meier method and log-rank test to compared the different levels of a variable. Pearson Chi-Square or Fisher's exact test were used to compare relationship between variables in to groups and Mann-Whitney U test to compare the medians. **Results:** 32/39 (82 %) BRCA+ and 44/67 (66 %) NH had BC as their first malignancy. As regards the genetic test on NH patients, 28 were BRCA negative, 22 have not been tested and in 10 patients the test is still in progress. All BRCA2 patients had BC as first malignancy, while 20/22 of BRCA1. Bilateral BC was more frequent in BRCA+ than in NH (33 % vs 9 %), resulted in a fivefold higher risk ($p = 0.002$). III-IV stage OC at diagnosis was 79% in BRCA+ vs 55 % in NH ($p = 0.013$); indeed BRCA+ patients have a threefold higher risk (however moderate) to develop an advanced stage OC. Death for progression of ovarian cancer involved both groups, and third neoplasm was involved in death cause in 1/1 of BRCA and 5/6 of NH. Two BRCA1 with OC as first neoplasm are alive. **Conclusions:** III-IV stage OC is more frequent in BRCA+ than in NH, and the main cause of disease progression and death is due to OC. Eventually the most relevant conclusive assessment is the suggestion of a more conserving management for BC and an intensive follow-up for OC in patients with double tumours, irrespective of their pathological or genetic features. Prospective trials are also indicated.

Surgical outcome score (SOS), a new algorithm based on HE4 and CA125, to predict surgical outcome in primary epithelial ovarian cancer (EOC) patients (pts).

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Background: There are no clinical or biomolecular algorithms to predict surgical outcome in EOC pts. Recently, we showed that the combination of HE4 and CA125 predict surgical outcome in advanced primary EOC (ASCO 2012). We validated the cut-off values in an independent cohort and developed a new algorithm to predict surgical outcome-SOS. **Methods:** Pts with primary EOC (n = 193) were selected for a retrospective study between 2003 and 2011. Preoperative serum HE4 and CA125 levels were measured. The predictive values of HE4 and CA125 were analyzed using the receiver operator characteristic (ROC) with the corresponding area under the curve (AUC). Separate logistic regression algorithms for pre- and postmenopausal women were utilized to categorize pts into low and high-risk for residual disease, using CA125 and HE4 within SOS algorithm. Furthermore we performed a multivariate analysis for prediction of progression free- (PFS) and overall survival (OS). **Results:** Maximal cytoreduction was achieved in 67.4% pts. Serum HE4 expression correlated with residual disease ($p < 0.001$, RR: 2.74, 95%CI 1.65-4.54), reaching a 76.2% sensitivity (Se), 56.9% specificity (Sp) and 83.1% negative predictive value (NPV), with 235 pM cut-off value. CA125 correlated with residual disease in premenopausal pts ($p = 0.031$, RR: 3.13, 95%CI 1.28-7.65). For a CA125 cut-off of 500 IU/l, the Se, Sp and NPV were 39.7%, 69.8%, and 70.3%, respectively. ROMA predicted surgical outcome (AUC = 0.70, $p < 0.001$, 95% CI = 0.624-0.776, RR = 2.54), reaching a 76.2% Se, 53.5% Sp for 81% cut-off value. SOS algorithm performed better than HE4 or CA125 alone, and ROMA (AUC = 0.741, $p < 0.001$, 95% CI 0.670-0.812, RR = 4.98). The Se, Sp and NPV was 90.5%, 46.5% and 90.9%, respectively, for a SOS cut off value of 21.5%. FIGO stage and residual disease were the only prognostic factors for both PFS and OS. SOS was an independent prognostic for PFS ($p = 0.009$, HR = 1.014, 95% CI = 1.004-1.025), but not for OS. **Conclusions:** This independent validation study confirm the predictive value of CA124 and HE4 on surgical outcome. The combination of HE4 and CA125 within the SOS score improve the prediction of surgical outcome, and therefore of PFS.

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General Poster Session (Board #45F), Mon, 8:00 AM-11:45 AM

Polyvalent vaccine-KLH conjugate and OPT-821 with bevacizumab (BEV) in patients with ovarian cancer in second or greater remission.

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Background: We previously completed a phase I study of a polyvalent vaccine containing GM2, Globo-H, Le^Y, Tn-MUC1, Tn(c), STn(c) and TF(c) antigens (AGs) individually conjugated to KLH and mixed with adjuvant OPT-821. We showed safe induction of antibody (ab) responses to 5 of the 7 vaccine AGs. Data has shown that tumor vaccine efficacy may be enhanced through disruption of angiogenesis thus providing a rationale for combining BEV with the polyvalent vaccine. We conducted an IRB-approved pilot study to evaluate the safety and immunogenicity of the poly-KLH-vaccine when given with BEV in OC in remission. **Methods:** Pts with recurrent OC in ≥ 2 nd complete or partial remission were enrolled from 12/2010-03/2012. Pts received 6 vaccines and BEV over 17 weeks. BEV was continued beyond the vaccination phase. Treatment was continued until disease progression or toxicity. Serologic IgM and IgG responses were measured by ELISA against each AG. Wilcoxon signed rank test was used to test changes in cytokines (CKs): FGF β , IL-8, PDGF, VEGF measured by angio multiplex assay. **Results:** $n=21$ Median age 56yrs (51-70). 2, 8, 8, 3 pts were in 2nd, 3rd, 4th, 5th remission, respectively. 1 DLT (gr 4 fever post vaccine #2). Immune Results: $n=19$ IgG +/- IgM: ≥ 3 AGs in 17pts. IgM: ≥ 1 AG in 19pts, ≥ 3 AGs in 15pts. IgG: ≥ 1 AG in 17pts, ≥ 3 AGs in 3pts. CK Results: In 10 pts who completed 6 vaccines there was a mean (median) decrease in VEGF of 144 (111) pg/ml at the 17-week timepoint compared to baseline ($p=0.05$). For 8 pts who did not complete all 6 vaccines there was a mean (median) increase of 76 (69) pg/ml compared to baseline at the off-study visit ($p=0.16$). There was no statistically significant change in the other CKs compared to baseline values. At last follow-up, 18 pts had recurred and 3 pts had died. The median PFS was 5.6mths. **Conclusions:** 89% of pts responded to ≥ 3 AGs comparable to the 89% response in our prior phase I trial without BEV. BEV and polyvalent-KLH vaccine can be safely administered together with retention of the vaccine's immunogenicity. Serum VEGF levels decreased in patients on continued BEV therapy. Clinical trial information: NCT01223235.

Immune response.

AG	GM2	GM2	GloboH	GloboH	Tn	Tn	TF	TF	MUC1	MUC1
Ab	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG
No. pts +	13	0	17	2	8	4	18	5	15	16

Tasisulam-sodium in combination with liposomal doxorubicin in patients with ovarian cancer.

D. Scott McMeekin, Lee S. Rosen, Alberto Bessudo, Datchen Fritz Tai, Robert L. Ilaria, Jian Chen, P. Kellie Turner, Sandia Krueger, Michael S. Gordon; University of Oklahoma Health Sciences Center, Oklahoma City, OK; David Geffen School of Medicine at University of California, Los Angeles, Santa Monica, CA; California Cancer Associates for Research and Excellence, Encinitas, CA; Lilly USA, LLC, Indianapolis, IN; Eli Lilly and Company, Indianapolis, IN; Eli Lilly and Company Limited, Surrey, United Kingdom; Lilly Deutschland GmbH, Bad Homburg, Germany; Pinnacle Oncology Hematology, Scottsdale, AZ

Background: Tasisulam-sodium (TASI) is a novel, highly albumin-bound small molecule that induces tumor cell apoptosis and has antiangiogenic activity. This phase 1b study was designed as a dose-finding study for TASI in combination with liposomal doxorubicin (DX) in patients (pts) with advanced solid tumors, followed by a dose-confirmation phase in platinum-resistant DX-naïve ovarian cancer (OvCa) pts. However, the study was stopped early for business reasons. Nonetheless, the dataset allowed partial characterization of the safety and antitumor activity of TASI + DX among OvCa pts who achieved an albumin-corrected exposure (AUC_{alb}) within a hypothesized therapeutic range identified in phase II monotherapy trials. **Methods:** In the dose-escalation phase (3+3 schema), pts received TASI (escalating C_{max} targets of 300-380 $\mu\text{g/mL}$, 2-h IV) plus DX (40 mg/m^2 , 1-h IV) every 28 days. Pharmacokinetic and safety analyses identified an AUC_{alb} target of 3500 $\text{h} \cdot \mu\text{g/mL}$ for the dose-confirmation phase. We analyzed data for OvCa pts from both phases who achieved TASI AUC_{alb} of 1200-6400 $\text{h} \cdot \mu\text{g/mL}$ in cycle 1. **Results:** Of the 13 OvCa pts who completed the dose-escalation phase and 6 OvCa pts who completed the dose-confirmation phase, 10 had AUC_{alb} of 1200-6400 $\text{h} \cdot \mu\text{g/mL}$ in cycle 1. For these pts, the most common possibly drug-related Grade 3-4 adverse event was neutropenia (see table). Although no pt achieved complete response, 2 pts achieved partial response. Data from the other OvCa pts will also be presented. **Conclusions:** The early closure of the study did not allow complete assessment of TASI in combination with DX; however, acceptable tolerability and some antitumor activity were observed for OvCa pts with TASI AUC_{alb} within the hypothesized therapeutic range. Clinical trial information: NCT01214668.

Variable	TASI + DX(n=10) ^a
Most common possibly-related grade 3-4 AEs; n	
Neutropenia	5
Thrombocytopenia	2
Anemia	2
Mucositis	2
Best overall response; n	
Complete response (CR)	0
Partial response (PR)	2
Stable disease (SD)	6
Response rate (CR+PR)	2
Disease control rate (CR+PR+SD)	8
Kaplan-Meier estimate; median months	
Overall survival	9.2
Progression-free survival	5.8
No. of cycles; median, range	4.5, 1-16

^a Pts with TASI AUC_{alb} 1200-6400 $\text{h} \cdot \mu\text{g/mL}$ in cycle 1.

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General Poster Session (Board #45H), Mon, 8:00 AM-11:45 AM

Benefit of adjuvant chemotherapy for stage I epithelial ovarian cancer according to the histologic type.

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Background: The benefit of adjuvant chemotherapy in stage I epithelial ovarian cancer (EOC) remains controversial. We retrospectively examined stage I EOC patients to clarify the benefits of adjuvant chemotherapy according to the histological type. **Methods:** The outcomes of 131 patients with stage I EOC that was diagnosed by exact staging laparotomy at the Jichi Medical University Hospital over a 22-year period from 1988 to 2009 were evaluated. Eighty-seven of the patients had received adjuvant chemotherapy (stage: IA 17, IC(intraoperative rupture;R) 27, IC(other) 43; histological type: clear cell adenocarcinoma(CCC) 38, mucinous adenocarcinoma(MC) 18, endometrioid adenocarcinoma(EC) 18, serous adenocarcinoma(SAC) 13), while 44 had undergone observation alone (stage: IA 31, IC(R) 12, IC(other) 1; histological type: CCC 11, MC 17, EC 11 and SAC 5). Outcomes for patients were compared between the two groups. **Results:** The overall recurrence rate in the adjuvant chemotherapy group was 18.4% (16/87). The rates of recurrence according to stage were IA 5.9% (1/17), IC(R) 14.8% (4/27), and IC (other) 25.6% (11/43). Recurrence by histological type were CCC 12, SAC 2(G1 and G2), and one each for EC and MC. Recurrence was seen in all stages in CCC patients; however, there was no recurrence in stage IA in patients with non-CCC. The overall recurrence rate in the observation group was 11.4% (5/44). All five recurrences occurred in CCC patients, and no recurrence was observed in the 33 non-CCC patients (IA 26, IC(R) 7). In patients with IC(R) CCC, the recurrence rate was significantly higher in the observation group (80%;4/5) than in the adjuvant chemotherapy group (18.8%; 3/16) ($p = 0.025$). **Conclusions:** This retrospective study showed that the CCC is associated with recurrence in stage I EOC and adjuvant chemotherapy for these patients may improve outcomes. The recommended states for adjuvant chemotherapy in stage I EOC are as follow: 1) all subtype of stage I for CCC, and 2) IC(other) for non-CCC. Although further prospective studies are required, these results afford useful information with which to determine the adjuvant chemotherapy in stage I EOC.

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General Poster Session (Board #46A), Mon, 8:00 AM-11:45 AM

Does alopecia predict response to chemotherapy and prognosis in patients with advanced ovarian cancer? A meta-analysis of prospective randomized phase III trials with 5,114 patients of the AGO meta data base.

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Background: Alopecia is a relevant side effect of chemotherapy. Our aim was to validate and unconfirmed broad patient's opinion that a low rate of alopecia may predict poor response to chemotherapy and poor overall survival (OS). **Methods:** Individual patient data analysis of 5114 patients from four prospective randomised phase III trials conducted between 1995 and 2004 to investigate platinum-taxane based chemotherapy regimens in advanced ovarian cancer. Uni- and multivariate analyses were performed adjusted for age, number of cycles, individual trial, residual mass, tumor stage and histology. **Results:** 5,114 patients with ovarian cancer (OC) were analyzed. Most patients presented with advanced stage FIGO III/IV (87.8%). A median of 6 cycles were applied (range 0-11). Worst alopecia grade was 0 in 2.2%, 1 in 2.7% and 2 in 87.1%. In 8% patients no data about alopecia were documented. Patients with complete alopecia were more likely to achieve remission (OR 2.83, 95% CI 1.68-4.78 for grade 2 compared to grade 0/1) and had favourable progression-free survival of 19.0 months, (95%CI 18.2-19.7) compared to patients with grade 0/1 (13.8, 95%CI 12.2-15.3 and 14.3, 95%CI 10.8-17.8). Median OS was also significantly longer after grade 2 alopecia 48.8 months (95%CI 47.0-50.5), compared to 28.1 months (95%CI 22.3-33.9) and 33.9 months (95%CI 24.3-43.6) for grade 0 and 1, respectively. This prognostic impact was not retained in multivariate analysis. However, onset of alopecia was an independent prognostic factor for OS: patients with complete alopecia after cycle 3 had a favourable outcome compared to patient who experienced alopecia later during therapy (HR 1.22, 95%CI 1.02-1.46) or no alopecia (HR 1.29, 95%CI 0.98-1.70). **Conclusions:** We could show for the very first time that there is no evidence that the rate of alopecia is associated with the effect of chemotherapy is of any prognostic relevance. The observation that early onset of alopecia is associated with OS should be confirmed.

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General Poster Session (Board #46B), Mon, 8:00 AM-11:45 AM

A phase II study of oral metronomic combination therapy in relapsed epithelial ovarian cancer.

Sudeep Gupta, Gautam Goyal, Jaya Ghosh, Bharatsinha Baburao Bhosale, Jyoti Bajpai, Amita Maheshwari, Rajendra Kerkar, Kedar Deodhar, Bharat Rekhi, Santosh Menon, Shripad Banavali; Tata Memorial Centre, Mumbai, India

Background: Etoposide (E), cyclophosphamide (C) and tamoxifen (T) have been used as single agents in relapsed epithelial ovarian cancer (EOC) patients. We tested a low dose, continuous, daily, oral metronomic regimen that combined these 3 agents. **Methods:** This single centre prospective study included patients of relapsed EOC with exposure to at least 2 prior lines of chemotherapy (CT) and at least partial as the best response to most recent regimen. Study regimen comprised daily oral administration of E (50 mg/m²) and C (50 mg/m²) for 21 of a 28 day cycle plus T (20 mg/m², twice per day) continuously. The primary endpoint was serological (CA-125) progression-free survival (PFS) as per Rustin Criteria and secondary endpoints were radiological (RECIST) PFS, overall survival (OS), duration of response (DOR), response rates and toxicity. The data cut-off date was 15 Jan 2013. **Results:** 26 patients with a median age of 48 years were accrued, of whom 21 had received 2 prior lines of CT and 5 had received 3 lines. 25 patients who were evaluable for analysis received a median of 6 (1-19) cycles of metronomic regimen. The median delivered relative dose intensities of E, C and T were 0.71, 0.71 and 0.97 respectively. 13 (52%) patients needed dose reduction after a median of 3 (1-9) cycles. Most common grade 3 or 4 toxicities included anemia, neutropenia, febrile neutropenia, nausea, vomiting and diarrhea in 44%, 36%, 12%, 16%, 16% and 12% patients respectively. 19 (76%) patients had serological CR or PR with a median time to response (TTR) and DOR of 1.8 (0.83-2.96) and 7.0 (95% CI, 5.8-8.2) months respectively. 11 (45.8%) of the 24 evaluable patients achieved radiological CR or PR with median TTR and DOR of 3.7 (1.8-7.2) and 5.5 (95% CI, 3.9-7.2) months respectively. 17, 18 and 7 patients have respectively experienced serological progression, radiological progression and death at the time of analysis. The median serological PFS, radiological PFS and OS are 7.9 (95% CI 7.2-8.6), 7.97 (95% CI, 5.95-9.98) and 22.3 (95% CI, 17.4-27.3) months, respectively. **Conclusions:** The oral metronomic combination of E, C and T has substantial and durable activity in relapsed EOC and is worthy of further evaluation in a larger randomized study.

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General Poster Session (Board #46C), Mon, 8:00 AM-11:45 AM

Comparison of two multimarker serum tests for the prediction of ovarian cancer in women with a pelvic mass.

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Background: Distinguishing between benign and malignant disease in women with a pelvic mass is difficult. OVA1 and ROMA are two multi-marker serum tests that are FDA-cleared to assess risk of malignancy in individuals with a pelvic mass. This study compared the accuracy of these tests for the prediction of ovarian cancer (OCa) in women with a pelvic mass. **Methods:** OVA1 and ROMA risk scores were determined in a subset of 146 serum samples obtained prospectively from pelvic mass patients. Patients were categorized by an initial cancer risk assessment (ICRA) performed by a physician and true cancer status determined surgically. 31 patients with malignancy (6 with a benign ICRA) and 115 patients with benign disease (25 with a malignant ICRA) were evaluated. Quest Diagnostics performed the OVA1 tests (CA-125, prealbumin, apolipoprotein A-1, β_2 -microglobulin, transferrin) and calculated and interpreted the risk score. ROMA tests (CA-125 and HE-4) were determined by automated immunoassay using an Abbott Architect analyzer. ROMA risk scores were calculated using published formulas and interpreted against cutpoints previously established for automated CA-125 and HE-4 performed by manual ELISA. **Results:** There were 70 pre- and 76 post-menopausal subjects. Of the 31 with malignancy, 26 had OCa (54% >stage II), 5 with an ICRA of benign. ROC curve analysis of the entire cohort produced an AUC of 0.88 (95% CI 0.80-0.95) and 0.93 (95% CI 0.87-0.99) for OVA1 and ROMA, respectively. OVA1 had a sensitivity of 0.97 and a specificity of 0.55. ROMA had a sensitivity of 0.84 and a specificity of 0.83. The sensitivity of OVA1 for OCa in the ICRA benign cohort (N = 5) was 0.80 and for ROMA was 0.40. The respective specificity for benign disease in this cohort (N=90) was 0.64 and 0.90. The sensitivity of ROMA for OCa increased to 0.60 with a slight decrease in specificity (0.87) when a cutpoint determined by ROC curve analysis was used. **Conclusions:** Overall, OVA1 and ROMA have similar performance characteristics. In women with an ICRA of benign, OVA1 was more sensitive among those who had OCa but ROMA was more specific among those who did not. The use of a ROMA cutpoint specific for the combination of automated CA-125 and HE-4 tests improved sensitivity.

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General Poster Session (Board #46D), Mon, 8:00 AM-11:45 AM

Clinical relevance of VEGF-receptor status in primary ovarian cancer: A pilot study for future biomarker analyses.

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Background: Antiangiogenic treatment in addition to platinum/taxane based chemotherapy was shown to improve progression-free survival in first- and second-line chemotherapy in ovarian cancer patients. Predictive markers for antiangiogenic treatment are of high interest. Therefore we investigated VEGF-receptor (VEGFR) expression as possible biomarker candidate in primary ovarian cancer tissue and its clinical impact. **Methods:** A total of 82 patients with primary ovarian cancer were enrolled into this study. Primary tumor tissue was analyzed for the expression of VEGFR1, VEGFR2 and VEGFR3 by immunohistochemistry. Moreover, the presence of circulating tumor cells (CTC) in the blood was detected by immunomagnetic enrichment and multiplex reverse transcriptase-polymerase chain reaction (*Adnatest Ovarian Cancer*, Adnagen). Disseminated tumor cells (DTC) in the BM were identified by immunocytochemistry using the pancytokeratin antibody A45B/B3 and subsequent automatic detection based on staining and cytomorphology. **Results:** Positivity for at least one VEGFR was observed in 43% of cases. The positivity rates for VEGFR1, -2 and -3 were 34%, 17% and 27%, respectively. VEGFR-status of the primary tumor neither correlated with established clinicopathological parameters (age, FIGO-stage, nodal status, grading, histological subtype) nor with the presence of CTC or DTC. In addition, VEGFR-status does not provide prognostic significance in regard to progression-free and overall survival (OS). Nevertheless, a trend was observed that patients, being positive for VEGFR3 at primary diagnosis, were more likely to experience suboptimal debulking ($p = 0.074$). CTC-positivity after adjuvant therapy significantly correlated with OS, but multivariable analysis showed only residual tumor as prognostic factor for OS. **Conclusions:** The VEGFR-family, albeit frequently expressed in our patient cohort, provided neither prognostic nor predictive relevance, but could probably be a predictor for debulking efficiency. The implementation of VEGFR-status into future biomarker studies should carefully be considered.

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General Poster Session (Board #46E), Mon, 8:00 AM-11:45 AM

Relationship of microRNA expression profiles and recurrence in advanced serous ovarian carcinoma.

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Background: Most patients with epithelial ovarian cancer eventually succumb to chemo-resistant disease. Although microRNAs have been recognized as important regulators of gene expression, little is known about microRNA expression profiles in recurrent serous ovarian carcinoma. We assessed the microRNA expression profiles which contribute to recurrence in advanced serous ovarian carcinoma. **Methods:** Eight pairs of primary and recurrent tumor samples from 8 patients with advanced serous ovarian carcinoma and 4 normal ovarian samples from patients treated for benign uterine disease between May 2006 and Dec 2012 were examined using miRNA microarray. microRNA profiling were validated using real-time reverse transcription-polymerase chain reaction (RT-PCR). **Results:** Alterations of microRNA expression profiles in primary and recurrent tumor samples have similar patterns when compared with normal ovarian tissues. Among 31 up-regulated microRNAs more than 4-fold in primary tumors, 27 microRNAs were also significantly up-regulated in recurrent tumor samples. Likewise, Among 35 down-regulated microRNAs more than 4-fold in primary tumors, 34 microRNAs were also significantly down-regulated in recurrent tumor samples. Comparing to primary tumor, we found 60 microRNAs which were significantly up-regulated, including *miR-630*, *370*, and *575*, and 52 microRNAs which were significantly down-regulated, including *miR-509-3p*, *514a-3p*, and *506-3p* in recurrent serous ovarian carcinoma. **Conclusions:** Our results indicate that dysregulation of microRNAs may play a role in recurrence of serous ovarian carcinoma.

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General Poster Session (Board #46F), Mon, 8:00 AM-11:45 AM

Clinical study of intraperitoneal injection bevacizumab (BV) combined with intraperitoneal hyperthermic perfusion chemotherapy (CT) in treatment of malignant ascites of ovarian cancer (OC).

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Background: To study the efficacy and safety of intraperitoneal injection BV combined with intraperitoneal perfusion CT in treatment of malignant ascites of OC and to investigate the clinical significance of the concentration change of vascular endothelial growth factor (VEGF). **Methods:** Patients with malignant ascites of OC were randomly divided into treatment group (n = 31) and control group (n = 27). All enrolled patients received TC (paclitaxel 135mg/m², iv d1 + carboplatin AUC=5, iv d1), 1 time/3 weeks for 6 weeks. Patients in the control group were treated with intraperitoneal perfusion CT combined with intraperitoneal cisplatin (40mg/m²) 1 time/2 weeks for 6 weeks. Besides the treatment of the control group, patients in the treatment group received intraperitoneal injection with BV 300mg after each intraperitoneal perfusion CT for 6 weeks. The improvement of life quality, efficacy and adverse effects were evaluated. The concentrations of VEGF and CA-125 in ascites of the two groups were assayed by ELISA method. **Results:** No severe side effect was observed in all the patients. The response rate of the treatment group was higher than that of the control group (90.32% vs. 59.26%, p < 0.05). The improvement rate of quality of life (QOL) of the patients in the treatment group was also higher than that of the patients in the control group (93.55% vs. 48.15%, p < 0.05). The concentration of VEGF in ascites of the treatment group after treatment was lower than that before treatment (p < 0.05). And after treatment, the concentration of VEGF in ascites of treatment group was lower than that of the control group (p < 0.05). **Conclusions:** Intraperitoneal injection BV combined with intraperitoneal perfusion CT in the treatment of malignant ascites of OC is effective and safe. The concentration of VEGF and CA-125 levels, in ascites may be used as monitoring index for treatment effect of malignant ascites of OC with intraperitoneal injection BV.

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General Poster Session (Board #46G), Mon, 8:00 AM-11:45 AM

Phase II study of trabectedin in pretreated patients with recurrent epithelial ovarian cancer (REOC).

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Background: The prognosis of patients with REOC is extremely poor after several lines of chemotherapy. The choice and timing of therapies must be individualized to optimize survival and quality of life. This open-label, nonrandomized, phase II study was aimed at evaluating efficacy and toxicity of Trabectedin as a single-agent therapy in patients with pretreated Recurrent Epithelial Ovarian Cancer (REOC). **Methods:** Sixteen patients (median age 51 yrs, range 44 – 71) with REOC who progressed after 2 (18.7%), 3 (56.3%) or 4 (25.0%) previous lines of chemotherapy were treated with Trabectedin at the dose of 1.1 mg/m² via a 3-hour i.v. infusion with dexamethasone pretreatment every 3 weeks until disease progression, unacceptable toxicity or when a stability of disease was reached. Clinical objective response was the primary efficacy endpoint; the secondary one was safety. Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), and toxicities were graded according to NCI Common Toxicity Criteria, version 2.0. **Results:** The median number of treatment cycles per patients was 5 (range, 2-9 cycles). A total of 81 cycles were administered. A dose reduction was never required. Main toxicities included anemia (20.9%), leucopenia (15.0%), thrombocytopenia (4.5%) and asthenia (22.2%). No deaths were attributable to therapy. No one showed complete response, while 9/16 partial response (56.2%) and 4/16 stable disease (25.0%) were observed. 3/19 pts (18.8%) progressed on therapy. The median progression-free interval was 18 weeks in patients with partial response; stable disease was maintained for a median time of 12 weeks. **Conclusions:** Trabectedin 1.1mg/m² given as a 3-hour i.v. infusion every 3 weeks was well tolerated and has confirmed a very interesting antitumor activity in this heavily pretreated population and it seems also to be a very tolerable regimen. The co-treatment with dexamethasone improves the safety of Trabectedin by reducing drug-induced myelosuppression and hepatotoxicity. Trabectedin has a manageable toxicity profile, and can be safely administered thanks to its secure action profile also in patients with no other viable therapeutic options.

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General Poster Session (Board #46H), Mon, 8:00 AM-11:45 AM

Protein network mapping of platinum-resistant and poor-survival ovarian cancer.

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Background: Epithelial ovarian carcinoma (EOC) is the fifth leading cause of tumor related death in the female population, with only 30% of patients alive at 5 years after diagnosis. Platinum resistance is a major cause of treatment failure. The aim of the study was to perform broad-scale drug target activation mapping of EOC to identify new druggable targets for personalized therapy. **Methods:** 72 ovarian primary lesions collected from chemo-naïve EOC patients were analyzed. Highly enriched tumor epithelial cells were isolated by laser capture microdissection, lysed and subjected to reverse phase protein microarray analysis for multiplexed protein pathway activation mapping. The activation/phosphorylation level of 156 key signaling proteins was analysed. Based on the disease-free interval to platinum therapy, 61 stage II-IV patients were segregated into platinum-resistant (<6 months), platinum-sensitive (6-12 months), and platinum-supersensitive disease (>12 months). One-way analysis of variance was used to detect significant differences among the three groups in the drug target activation profile. **Results:** Expression of the drug target PDGF Receptor β and activation of ErbB2/HER2 (Y1248) were significantly higher in patients with resistant disease compared to sensitive groups (respectively, p 0.0033 and p 0.0134), while the expression of Estrogen receptor α was greater in the supersensitive group (p 0.0295). Moreover, overall survival analysis including all stages revealed that the expression level of Cox2 is significantly higher in patients with shorter survival (HR: 2.48, p 0.0179). **Conclusions:** Functional drug target activation mapping revealed the unique signaling architecture of platinum-resistant EOC. If confirmed in independent study sets, these results suggest that the utilization of drugs targeting PDGF Receptor β and ErbB2/HER2 could be evaluated in platinum resistant EOC and/or in combination with platinum therapy in order to overcome acquired resistance. Finally, this study indicates that Cox2 may play an important role in aggressive EOC, and that the addition of Cox-inhibitors to standard of care could be rationally evaluated as a novel therapeutic regimen for ovarian cancer.

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General Poster Session (Board #47A), Mon, 8:00 AM-11:45 AM

Does aggressive primary debulking surgery influence survival in ovarian cancer?

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Background: Evidence comparing outcomes in patients receiving primary debulking surgery (PDS) to those receiving neoadjuvant chemotherapy (NACT) for advanced stage ovarian carcinoma is conflicting. We conducted a retrospective survival analysis of all patients with stage IIIC and IV serous ovarian cancer treated at our institute by either PDS or NACT. **Methods:** Data was extracted from patient synoptic OR reports and medical records between January 2003 and December 2011. Survival comparisons between patients receiving NACT and PDS were made according to aggressiveness of surgery and residual disease following surgery. Aggressive surgery was defined by one of the following procedures; pelvic peritonectomy, any bowel resection, diaphragm resection, diaphragm peritonectomy and splenectomy. **Results:** Out of 342 patients, 143 (41%) had NACT and 199 (59%) had PDS. Patients undergoing PDS had a median survival (MS) of 58 months compared to 34 months for NACT. Patients undergoing PDS with > 10mm and <10mm residual disease, had a MS of 33 and 55 months, respectively; whereas those with microscopic disease have not yet reached their MS. In the NACT group, MS for < and > 10 mm residual disease was 30 months for both, compared with 39 months for those with microscopic disease. Within the PDS group, those undergoing limited surgery had a MS of 48 months whereas MS has not been reached for those undergoing aggressive surgery. Over 60% of patients undergoing PDS with microscopic residual were alive at 7 years. In the NACT group, there was no difference in survival according to extent of surgery. **Conclusions:** Patients with PDS, whether debulked to < 10mm or to microscopic disease have a significant and lengthy survival advantage over patients receiving NACT.

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General Poster Session (Board #47B), Mon, 8:00 AM-11:45 AM

Continuous low-flow ascites drainage and sequential non-invasive tumor-cell sampling through the urinary bladder via the alfa-pump closed system in platinum-resistant ovarian cancer (PROC): First clinical experience in a cancer patient.

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Background: Malignant ascites in PROC causes significant impairment in quality of life. The Sequana Medical alfapump System (AP), a remotely controlled device connecting the patients' peritoneal cavity to their urinary bladder, has been evaluated for the continuous drainage of ascites in liver cirrhosis, but not as yet for malignant ascites. **Methods:** We implanted the AP in the peritoneal cavity of a 67y old heavily pretreated PROC patient with recurrent malignant ascites requiring 3-5 liters drained 3 times/month. The AP was evaluated for its ability to drain ascites into the urinary bladder using an electronic download of recorded volume pumped, cross correlated with weekly ultrasound, symptomatic scores and QoL evaluation. Early morning urine for evaluation of urinary cytology and tumor-cell molecular analysis was collected weekly. **Results:** The implantation was performed under general anaesthesia in a 60 minute procedure. Before insertion the patient had 3 liters of malignant ascites; 2 liters were drained during surgery. The pump, draining 350ml ascites per day successfully drained the ascites to dryness after 3 days. The patient underwent weekly sonography and monthly cystoscopies. She did not report pollaki- or dysuria, only an increased micturition volume. Histopathological analysis of the urine revealed rich malignant cell content, used to create FFPE cell blocks weekly for molecular- pathological profiling with sequential Caris Target Now analysis and full exome sequencing. **Conclusions:** On initial evaluation, the AP represents a tolerable and effective means of diverting peritoneal ascites into the urinary bladder and thus preventing its recumulation in PROC. This innovative approach not only addresses an area of unmet need for the control of malignant ascites but also provides a method of collecting tumor tissue and evaluating longitudinal change in molecular tumor characterization. A EUTROC multicenter European randomized trial (AMAZE) is planned for evaluation of clinical and translational implications of the AP in PROC.

Validation of urinary HE4 as a biomarker for ovarian cancer.

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Background: Urinary HE4 has been reported as a promising biomarker for ovarian cancer (OC). In the current study, a large validation was performed to evaluate urinary HE4 as a biomarker for the stratification of OC from benign pelvic masses. **Methods:** Normalized HE4 was obtained from the ratio of HE4 (pmol/L measured with HE4 EIA) and creatinine (mg/dL measured with a Jaffe Reaction) in single-point urine samples from female subjects with a pelvic mass (N = 809). The samples were from one case-control prospective study (Moore RG, 2008) and two prospective clinical trials (NCT00315692 and NCT00987649). R Package was used to randomly distribute the subjects into the Training and Testing Sets. Analyze-it was used to analyze the clinical performance. **Results:** Medians of Normalized HE4, sensitivities (SN) and likelihood ratios (LR) (+) of Normalized HE4 at two levels of specificity (SP) are presented in the Table. **Conclusions:** Urinary HE4 normalized with urinary creatinine appears to be a valid biomarker for the stratification of OC from a benign pelvic mass.

	Training set (N = 405)		Testing set (N = 404)	
	N	Median (95% CI)	N	Median (95% CI)
Benign	282	70 (65 - 76)	282	72 (67 - 77)
OC + LMP	123	357 (272 - 484)	122	276 (172 - 439)
LMP	16	97 (72 - 111)	21	113 (70 - 138)
OC	107	458 (314 - 614)	101	438 (277 - 668)
Stage I-II OC	27	178 (74 - 341)	31	145 (96 - 246)
Stage III-IV OC	78	671 (480 - 869)	66	763 (439 - 1009)
Cut point ≥ 134 to reach 90% SP with benign				
LR (+)		SN (95% CI)	LR (+)	SN (95% CI)
OC + LMP	7.0	69.9% (61% - 78%)	8.8	68.9% (60% - 77%)
LMP	1.9	18.8% (4% - 46%)	3.7	28.6% (11% - 52%)
OC	7.8	77.6% (68% - 85%)	9.9	77.2% (68% - 85%)
Stage I-II OC	5.2	51.9% (32% - 71%)	7.0	54.8% (36% - 73%)
Stage III-IV OC	8.9	88.5% (79% - 95%)	11.7	90.9% (81% - 97%)
Cut point ≥ 95 to reach 75% SP with benign				
LR (+)		SN (95% CI)	LR (+)	SN (95% CI)
OC + LMP	3.3	81.3% (73% - 88%)	3.2	83.6% (76% - 90%)
LMP	2.3	56.3% (30% - 80%)	2.6	66.7% (43% - 85%)
OC	3.4	85.0% (77% - 91%)	3.4	87.1% (79% - 93%)
Stage I-II OC	2.7	66.7% (46% - 83%)	2.9	74.2% (55% - 88%)
Stage III-IV OC	3.8	93.6% (86% - 98%)	3.7	95.5% (87% - 99%)

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General Poster Session (Board #47D), Mon, 8:00 AM-11:45 AM

Evaluating the accuracy of frozen section in borderline ovarian tumors.

Natasha Gupta, Tanuja Rajpal, Sameer Sharma; Mount Sinai Hospital, Chicago, IL; Cook Count Hospital, Chicago, IL

Background: The objective of this study was to evaluate accuracy of frozen section in borderline ovarian tumors and to determine the tumor characteristics that lead to higher likelihood of inaccurate intraoperative diagnosis (IAIOD). IAIOD is a clinical problem that restricts the diagnostic accuracy of frozen section in borderline ovarian tumors. **Methods:** This was a retrospective chart review of 622 consecutive cases that were diagnosed with pelvic mass and underwent surgery at busy gynecology services of two institutions, between 2006-2011. Of these cases, 52 were diagnosed as borderline ovarian tumors by frozen section. Experienced pathologists performed frozen section with second opinion from specialized gynecologic pathologists as needed. Terms such as “at least borderline” were also evaluated to help stratify patients. Frozen section and final permanent histology reports were compared. Patient and tumor characteristics that may cause IAIOD such as age of patient, histological subtype, size of tumor, bilaterality, CA-125 levels were studied. Staging was performed when borderline or malignant ovarian tumors were identified by frozen section. **Results:** Agreement of the frozen section results with final pathology was observed in 37 out of 52 patients with a diagnostic accuracy of 71.15 %. Under diagnosis occurred in 12 out of 52 patients and over diagnosis occurred in 3 out of 52 patients. Age >40 years, size of tumor >5 cm, bilaterality of tumors and CA-125 were not found significant in causing IAIOD when chi-square analysis was performed. Characterization by “at-least” borderline terminology at the time of frozen section did not help identify patients with higher likelihood of IAIOD. **Conclusions:** In our study, the rate of IAIOD was high, at 23% despite experienced pathologists and using “at-least borderline” terminology. Traditionally described features leading to inaccuracy with frozen sections, such as large tumors with mucinous histology did not increase the risk of IAIOD in this study. Patients with unilateral, small tumors and non-mucinous histology had greatest risk for IAIOD. Given this information, full staging of all borderline ovarian tumors identified at time of frozen section should remain the standard of practice.

5565

General Poster Session (Board #47E), Mon, 8:00 AM-11:45 AM

Prognostic effect of EIF4EBP1 on ovarian cancer: A single gene biomarker for overall survival and platinum response.

Victor Manuel Villalobos, Yan Wang, Scooter Willis, Brian Leyland-Jones, Branimir I. Sikic; Stanford University, School of Medicine, Stanford, CA; The Edith Sanford Breast Cancer Research Institute, Sioux Falls, SD; Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA

Background: Using a novel computational approach, Gene Set Outcome Analysis (GSOA), we were able to identify an area of amplification on chromosome 8p12 that leads to worse prognosis in high grade/high stage ovarian cancer. Located within this amplicon is EIF4EBP1, an effector of DNA translation that is activated by mTOR. **Methods:** We utilized the MSKCC CBIO cancer genetics portal and the ovarian TCGA clinical dataset, to detect variation in mRNA expression (EXP), (z-scores thresholds ± 2) and copy number variation (CNV), determined using GISTIC 2.0, that are associated with significant differences in PFS and overall survival in grade 3 and stage III/IV ovarian cancer. **Results:** 6.7% of tumors exhibited upregulation of EIF4EBP1 (CNV amplified and mRNA $z > 2$) and poorer prognosis with OS of 30.2 vs. 43.8 months ($p = 0.0007$, $n = 445$) in tumors not upregulated. Patients with upregulated vs. normal expression showed inferior PFS with first line, platinum based therapy, 10.0 vs. 15.2 months ($p = 0.0406$, $n = 400$), respectively. An additional 4.9% of cases had downregulation of EIF4EBP1, with homozygous deletion or mRNA expression z-scores < -2 . Downregulation vs. normal expression also showed worse OS of 27.0 vs. 42.1 months ($p = 0.0178$) and PFS of 11.0 vs. 15.0 months ($p = 0.028$), respectively. As these groups are mutually exclusive and show a similar trend towards poor prognosis, when combined to compare aberrant vs. normal mRNA expression and copy number, we found an OS of 28.2 vs. 44.6 months ($p = <0.0001$) and PFS for first line platinum therapy of 10.2 vs. 15.3 months ($p = 0.0024$), respectively. **Conclusions:** In this dataset of 445 high-risk ovarian cancer patients, 11.8% exhibited aberrant expression of EIF4EBP1. While amplification of this region showed highly significant changes in OS and PFS, inclusion of both increased and decreased EIF4EBP1 mRNA expression achieved high statistical significance, demonstrating a “Goldilocks effect”, wherein normal expression leads to better outcomes. The potential relationship of gene expression levels of EIF4EBP1 to responsiveness to mTOR inhibitors should be explored in ovarian carcinomas.

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General Poster Session (Board #47F), Mon, 8:00 AM-11:45 AM

Exploratory analysis of nibrin in advanced ovarian cancer (AOC) patients treated in the phase III OVA-301 trial.

Miguel Aracil Avila, Antonio Nieto, Adnan Tanovic, Bradley J. Monk, Stanley B. Kaye, Andres Poveda, Thomas J. Herzog, Trilok V. Parekh, Nadia Badri, Carlos Galmarini; Pharmamar, Madrid, Spain; PharmaMar, Madrid, Spain; Pharmamar, Barcelona, Spain; Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ; The Royal Marsden Hospital NHS Foundation Trust, Sutton, United Kingdom; GEICO and Instituto Valenciano de Oncologia, Valencia, Spain; Columbia University Cancer Center, New York, NY; Janssen Research & Development, LLC, Raritan, NJ

Background: Nibrin (p95/NBS1) is a protein with an essential function in DNA double-strand break repair by homologous recombination. Therefore, we have investigated its value as a possible biomarker in patients with AOC by immunohistochemistry (IHC). **Methods:** IHC staining was performed in 138 samples from a subset of patients that have participated in the phase III OVA-301 trial, in which the combination of trabectedin plus pegylated liposomal doxorubicin (PLD) or PLD alone were randomly administered for advanced disease after failure of platinum-based chemotherapy (Monk 2010; Monk 2012). A computerized image analysis system was used to calculate the total percentage of nibrin-positive cells. Nibrin expression was considered as a continuous variable. The analysis of overall response rate (ORR) and progression-free survival (PFS) was based on independent oncologist assessment. Overall survival (OS) was defined from randomization to death/last contact. All the comparisons had an exploratory nature; an alpha cut-off value of 0.05 (two-sided) was established as statistically significant. **Results:** For PFS, there was a statistically significant correlation between high levels of nibrin and short PFS (HR = 1.014, 95% CI: 1.004-1.024, p=0.0047). Similarly, for OS, there was a statistically significant correlation between high levels of nibrin and worse OS (HR = 1.009, 95% CI: 1.001-1.017, p = 0.0295). A multivariate analysis showed that high levels of nibrin were independently correlated to a worse PFS (HR = 1.012, 95% CI: 1.002-1.022, p = 0.0147) and to a worse OS (HR = 1.010, 95% CI: 1.002-1.018, p=0.0192). After stratification according to platinum-sensitivity, high nibrin showed a significant correlation with lower ORR (ORR = 1.02, 95% CI: 1.01-1.03, p=0.0009), short PFS and OS values only in the platinum-sensitive patients. **Conclusions:** The results point out the potential importance of nibrin expression in the clinical outcome of patients with AOC. In particular, high protein expression of nibrin seems to be associated with a worse clinical outcome. Prospective clinical trials evaluating the clinical usefulness of this marker with other standard of care treatments are warranted. Clinical trial information: NCT00113607.

Results of the MARS study on the management of antiangiogenics' renovascular safety in ovarian cancer.

Vincent Launay-Vacher, Nicolas Janus, Frédéric Selle, Francois Goldwasser, Olivier Mir, Jean-Philippe Spano, Jean Christophe Thery, Philippe Beuzeboc, Jean-Baptiste Rey, Christelle Jouannaud, Jean F. Morere, Stephane Oudard, Joseph Gligorov, Michel Azizi, Richard Dorent, Gilbert Deray, Isabelle Laure Ray-Coquard, Florian Scotte; Service ICAR - Pitie-Salpetriere Hospital, Paris, France; Universite Pierre et Marie Curie, Oncology, GHU-Est Tenon, Paris, France; Cochin Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; Cochin Teaching Hospital, AP-HP, Paris Descartes University, Paris, France; Department of Medical Oncology, Pitié-Salpêtrière University Hospital, Paris, France; Pitié-Salpêtrière Hospital, Paris, France; Institut Curie, Paris, France; Institut Jean Godinot, Reims, France; Institut Jean Godinot, Clermont-Ferrand, France; Oncology Department, Bobigny, France; Department of Medical Oncology, Georges Pompidou European Hospital, Paris, France; Assistance Publique-Hôpitaux de Paris, Tenon APREC, CancerEst, University Paris VI, Paris, France; Arterial Hypertensive Department, Hôpital Européen Georges Pompidou, Paris, France; Cardiology Department, Hôpital Tenon, Paris, France; Nephrology Department, Pitie-Salpetriere Hospital, Paris, France; Centre Léon Bérard, Lyon, France; Medical Oncology Department, Georges Pompidou European Hospital, Paris, France

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:** This multicentric, prospective, observational study evaluated the renovascular safety of AVD in pts naive from any AVD, conducted in 7 centres in France, from 2009 to 2012, with a follow-up (f/u) of 1 year. Data collected included: gender, age, serum creatinine (SCr), HTN, hematuria (Hu) and dipstick Pu, at baseline and at each visit. **Results:** 1,124 pts were included. 79 pts had ovarian cancer (OC) and all received bevacizumab. Median age at inclusion was 61 years. Visceral, bone and cerebral metastasis frequencies were 74.1, 52.7 and 6.0%, respectively. HTN prevalence was 16.5%. Baseline renal assessment retrieved: Pu 36.0%, Hu 21.3%, mean aMDRD 83.0 ml/min/1.73m² and 5 pts with aMDRD<60. The incidence of de novo Pu and HTA during f/u was 56.8 and 21.2% (Table). 88.9 % of pts with Pu at inclusion improved or remained stable. Among pts with de novo Pu, 64.0% afterwards improved/normalized. No Grade 4 Pu has been reported (at inclusion or during f/u). Renal function remained stable with a mean aMDRD of 83.2 at the end of f/u. 6.0% had grade 2 SCr increase (no grade 3-4). No thrombotic micro-angiopathy (TMA) was reported. **Conclusions:** These results on the renovascular safety of bevacizumab in OC patients showed that 1) TMA is rare, 2) Pu develops in 56.8% of the pts, however with only 1 Grade 3/4, 3) 21.2% developed HTN, and 4) aMDRD was stable. Furthermore, in case of a renovascular effect, investigators followed the recommendations from the French Society of Nephrology (Halimi JM. Nephrol Ther 2008) and no treatment withdrawal for unmanageable renovascular toxicity occurred.

Renovascular effects	Prevalence at inclusion	Incidence during f/u
Pu*	n=75	n=44
All G	36.0%	56.8%
G1	30.7%	38.6%
G2	5.3%	15.9%
G3	0.0%	2.3%
HTN	n=79	n=66
	16.5%	21.2%
Hu	n=75	n=49
All Hu	21.3%	28.6%
Traces/+	12.0%	20.4%
++	5.3%	6.1%
+++	4.0%	2.1%
SCr increase*		n=67
All G		74.6%
G1		68.6%
G2		6.0%
G3-4		0.0%

* NCI-CTC v4; G: Grade; Number of pts may vary due to missing data.

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General Poster Session (Board #47H), Mon, 8:00 AM-11:45 AM

An open label, randomized, parallel, phase II trial to evaluate the efficacy and safety of cremophor-free, polymeric micelle formulation of paclitaxel compared to paclitaxel in subjects with ovarian cancer.

Yong-Man Kim, Shin-Wha Lee, Chi Heum Cho, Soo-Young Hur, Byoung-Gie Kim, Jae Hoon Kim, Seung Cheol Kim, Seok-Mo Kim, Young-Tae Kim, Hee Sug Ryu, Soon-Beom Kang; Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; Department of Obstetrics and Gynecology, School of Medicine, Keimyung University, Taegu, South Korea; Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, Seoul, South Korea; Department of Obstetrics and Gynecology, Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Department of Obstetrics and Gynecology, Ewha Woman's University Mokdong Hospital, Ewha Woman's University School of Medicine, Seoul, South Korea; Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, South Korea; Department of Obstetrics and Gynecology, Yonsei University, Severance Hospital, Seoul, South Korea; Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, South Korea; Department of Obstetrics and Gynecology, Konkuk University Medical Center, Seoul, Korea, Seoul, South Korea

Background: Cremophor EL, used to enhance drug solubility, may add to paclitaxel's toxicities such as hypersensitivity reactions or peripheral neuropathy. This multi-institutional phase II trial is to evaluate the efficacy and safety of Cremophor-Free, Polymeric Micelle Formulation of Paclitaxel (Genexol-PM) compared to Paclitaxel (Genexol) as a combined chemotherapy with carboplatin in patients with advanced epithelial ovarian cancer. **Methods:** In this phase II, randomized, parallel study, patients with FIGO stage IC-IV epithelial ovarian cancer after debulking surgery received intravenously Genexol-PM 260 mg/m² or Genexol 175 mg/m² combined with carboplatin iv (AUC 5) on day 1 of every 3-week cycle for a maximum of six cycles. The primary endpoint was composite response by GCIG CA-125 Response and Response Evaluation Criteria In Solid Tumors (RECIST). Secondary and exploratory endpoints included overall survival, progression-free survival, time to tumor progression, and safety and tolerability. **Results:** A total of 102 patients were randomized to Genexol-PM plus carboplatin (n = 51) or Genexol plus carboplatin (n = 51). Composite response rate in patients with or without measurable disease was 88.0% in the Genexol-PM plus carboplatin group and 77.1% in the Genexol plus carboplatin group. Noninferiority of Genexol-PM plus carboplatin compared with Genexol plus carboplatin was confirmed for composite response rate by CA-125/RECIST criteria. There were no differences in progression-free survival and overall tumor progression between the groups. Although there was a higher rate of grade 3 neutropenia in the Genexol-PM plus carboplatin group, the overall rate of hemodynamic adverse events was comparable between the 2 groups. There was no difference in peripheral neuropathy and hypersensitivity. No unexpected safety concerns were identified in this study. **Conclusions:** High-dose of Genexol-PM in combination with carboplatin was well tolerated, and its response rate was noninferior to that of Genexol plus carboplatin in patients with advanced epithelial ovarian cancer. Clinical trial information: NCT01276548.

Expression III: What do primary and recurrent ovarian cancer (OC) patients expect from their doctors and therapy management? Results of a survey in eight European countries with 1,743 patients (NOGGO/ENGOT-OV9 study).

Gülten Oskay-Özcelik, Maren Keller, Sandro Pignata, Domenica Lorusso, Florence Joly, Dominique Berton-Rigaud, Ignace Vergote, Joke De Roover, Michal Maciejewski, Marcin Jedryka, Antonio Casado Herraiz, C. Mendiola, Antonio Gonzalez-Martin, Patrick Achimas, Daniel Uwe Reimer, Alain G Zeimet, Hans-Joachim Hindenburg, Rolf Richter, Jalid Sehouli; NOOGO, Berlin, Germany; NOGGO, Berlin, Germany; MITO and Istituto Nazionale Tumori di Napoli, Napoli, Italy; MITO, Rome, Italy; GINECO/Centre François Baclesse, Caen, France; Centre René Gauducheau, Saint-Herblain, France; UZ Leuven, Leuven, Belgium; University Leuven, Leuven, Belgium; Dolnośląskie Centrum Onkologii / Oddział Ginekologii Onkologicznej, Wrocław, Poland; Department of Oncology and Gynaecological Oncology Clinic, Wrocław, Poland; Hospital Universitario San Carlos, Madrid, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; GEICO and Medical Oncology Service, Centro Oncológico M. D. Anderson International Spain, Madrid, Spain; Institutul Oncologic, Cluj-Napoca, Romania; Innsbruck Medical University, Innsbruck, Austria; Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria; Department of Gynecological Oncology, Campus Virchow, Charité Medical University, Berlin, Germany; Department of Gynecology, Campus Virchow Clinic, Charité Medical University, Berlin, Germany

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 in different European countries. **Methods:** A questionnaire was developed based on the experiences of expression II, a German survey, and then provided to primary and recurrent ovarian cancer patients via internet (online) or as a print-version in 8 countries in Europe (Austria, Belgium, France, Germany, Italy, Poland, Rumania, Spain). In the first part basic data (age, tumour status, therapy) were requested from the patient. In the second part, most of the questions tried to evaluate the expectations and needs concerning their therapy management and doctor-patient communication. **Results:** From December 2009 to October 2012, a total of 1743 patients with ovarian cancer from 8 European countries participated in the survey. The median age was 58 years (range 16-89). Nearly all patients (96,3%) had a primary surgery and a first-line chemotherapy (91,5%). About 423 (25,7%) patients were included in another clinical trial. Most of the patients in each country were pleased with the completeness and understandability of the explanations about the therapies from their doctors. About 68% of patients would be interested in having the opportunity to have a second opinion. The three most important aspects, which were proposed by patients to improve therapy against ovarian cancer were: "the therapy should not induce alopecia" (42%), "there must be more done to counter fatigue" (34%), and "the therapy should be more effective" (29%). **Conclusions:** This study underlines the high need of ovarian cancer patients to discuss all details concerning treatment options and clinical management with only minor difference between the countries. Patients also need more information about side effects of cancer therapies and second opinion opportunities. Besides effectiveness of therapy, alopecia and fatigue are the most important side effects bothering the patients.

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General Poster Session (Board #48B), Mon, 8:00 AM-11:45 AM

Venous thromboembolism in advanced ovarian cancer patients undergoing front-line adjuvant chemotherapy.

Alok Pant, Julian C. Schink; Northwestern University, Chicago, IL; Northwestern University, Feinberg School of Medicine, Chicago, IL

Background: To define the incidence and prognostic significance of venous thromboembolism (VTE) in patients with advanced, epithelial ovarian cancer undergoing front-line adjuvant chemotherapy after extended period (28 day) post-operative prophylaxis. **Methods:** A retrospective analysis of patients with advanced, epithelial ovarian cancer who underwent surgery and chemotherapy at a single institution from January 2008 through December 2011 was performed. Exclusion criteria were prior history of VTE, VTE during the post-operative period, clear cell histology, use of anti-coagulation for a different indication, and lack of compliance with 28 days of post-operative prophylaxis with a low molecular weight heparin. **Results:** 128 patients met criteria for inclusion. Sixteen patients had a reported VTE during the time they were on front line chemotherapy (12.5%). Nine patients (7%) had a pulmonary embolus (PE) and 8 (6.3%) had a deep vein thrombus (DVT). The average BMI in the group that developed VTE was 28 and in the group without VTE was 26.5 ($p = 0.23$). Three out of 16 (23%) patients who developed VTE had undergone a suboptimal cytoreduction compared to 12/112 (11%) in the group with no VTE ($p = 0.4$). Six of the 16 (37%) patients who developed VTE during chemotherapy underwent a bowel resection and/or splenectomy during their cytoreductive surgery compared to 18 of 112 (16%) patients who did not develop VTE ($p=0.079$). Eight of the patients in the VTE group had indwelling venous catheters during chemotherapy (50%) compared to 39 (35%) in the group with no VTE ($p = 0.27$). In the group that developed VTE, there was a trend towards increased pre-operative CA-125, higher rates of bowel resection and/or splenectomy during surgery, decreased use of aspirin, and inferior survival. On multivariate analysis, patients who developed VTE had significantly longer post-operative hospital stays (7 vs 5 days [$p = 0.009$]) and lower rates of complete response ($p = 0.01$). **Conclusions:** A 12.5% risk of VTE merits consideration of prophylaxis during chemotherapy in this cohort. A randomized, controlled trial is needed to clarify whether the benefits of long term prophylaxis outweigh the risks and costs of such therapy.

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General Poster Session (Board #48C), Mon, 8:00 AM-11:45 AM

Chemotherapy-induced myelosuppression in ovarian cancer patients with germline *BRCA1/2* mutations: A case control study.

Alan Christie, Amalina Che Bakri, Patricia Roxburgh, Muhammad Imtiaz Khan, Yousuf Iqbal, Tzyvia Rye, Paul Mitchell, Ronald Rye, Fiona Nussey, Melanie J. Mackean, Nicholas Reed, Rosalind Margaret Glasspool, Michelle Ferguson, Charlie Gourley; Western General Hospital, Edinburgh, United Kingdom; University of Edinburgh, Edinburgh, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Ninewells Hospital, Dundee, United Kingdom; University of Edinburgh Clinical Trials Unit, Edinburgh, United Kingdom; Edinburgh Cancer Research UK Centre, MRC IGMM, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom

Background: Ovarian cancer patients with germline *BRCA1* or *BRCA2* (*gBRCA1/2*) mutations frequently respond to multiple lines of chemotherapy. Having noticed significant myelosuppression during chemotherapy in *gBRCA1/2* patients we wished to determine whether this was a chance finding or related to a heterozygous gene dosage effect in the bone marrow. **Methods:** *gBRCA1/2* ovarian cancer patients from Edinburgh, Glasgow and Dundee were identified and matched for chemotherapy regimen, dose and age to controls from the Edinburgh Ovarian Cancer Database. Case notes and transfusion service records were analysed for chemotherapy details, haematology results, G-CSF use, red cell and platelet transfusions during first line chemotherapy. **Results:** Of 91 *gBRCA1/2* patients, 35 patients were excluded who had previously received cytotoxic chemotherapy (mostly for breast cancer) or unusual chemotherapy regimens unable to be matched to controls. 56 were matched to controls. Baseline haematological indices were similar. There was a significant difference in the fall in haemoglobin levels from baseline to cycle 4 in *gBRCA1/2* patients compared to controls (12.23% v 5.14%, $p = 0.0005$) and *gBRCA1/2* patients had longer delays during their chemotherapy (mean 7.73 v 4.51 days, $p = 0.0375$) and more dose reductions for haemotoxicity (14 v 4 $p = 0.0011$). *gBRCA1/2* were more likely to have a red cell transfusion (19 v 11, $p = 0.099$), and received more red cells (69 v 31 units, $p = 0.0318$). G-CSF was required in 3 BRCA patients versus 0 controls. Differences in platelet and white cell counts at cycle 4 were not significant. **Conclusions:** Patients with ovarian cancer and germline *BRCA1/2* mutations were more likely to have significant falls in haemoglobin levels and require red cell transfusions and to experience delays during chemotherapy. This susceptibility to anaemia may be a hemizygous *BRCA1/2* gene dosage effect manifest in the bone marrow and may have implications for the optimisation of cytotoxic and PARP inhibitor therapy in this patient group.

Adverse event profile by therapy cycle for vintafolide plus pegylated liposomal doxorubicin (PLD) versus PLD alone in platinum-resistant ovarian cancer.

James Thomas Symanowski, Elzbieta Kutarska, Mariusz Bidzinski, Binh Nguyen, Reshma A. Rangwala, R. Wendel Naumann; Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC; Centrum Onkologii Ziemi Lubelskiej, Doctor Directing Division, Department of Gynecology Oncology III, Lublin, Poland; Holycross Cancer Center, Department of Gynecological Oncology, Kielce, Poland; Endocyte, Inc., West Lafayette, IN; Merck, Whitehouse Station, NJ; Levine Cancer Institute, Carolinas Medical Center, Charlotte, NC

Background: Vintafolide (EC145), a folic acid/desacetylvinblastine conjugate, binds with high affinity to folate receptors expressed in epithelial ovarian cancers. This analysis evaluated the incidence of adverse events (AEs) by treatment cycle and as a percent of total treatment cycles administered in the PRECEDENT trial, a randomized open-label study of subjects with platinum-resistant ovarian cancer receiving either vintafolide+PLD or PLD alone. **Methods:** Women ≥ 18 years old with ECOG status 0-2 and exposure to ≤ 2 prior systemic cytotoxic regimens were randomized 2:1 to vintafolide (2.5 mg IV tiw, weeks 1 and 3, q28 days)+PLD (50 mg/m² IV day 1, q28 days) or PLD alone (same dose + schedule). AEs in the safety population (received at least 1 dose of study drug) were evaluated by cycle. **Results:** 157 patients received a total of 720 treatment cycles (518 vintafolide+PLD, 202 PLD alone). AEs (all grades, vintafolide+PLD vs PLD alone): 85.9% and 80.2% of cycles. Anemia, neutropenia, and thrombocytopenia were observed in 16.6% (vs 10.4% administered PLD alone), 19.1% (vs 10.4%), and 2.7% (vs 3.0%) of all cycles, respectively. Febrile neutropenia was observed in 0.2% (vs 0.5%) of cycles, respectively. Stomatitis and hand-foot syndrome (HFS) occurred in 16.6% (vs 22.8%) and 19.1% (vs 15.8%) of cycles, respectively. Peripheral sensory, motor, or sensorimotor neuropathy or polyneuropathy occurred in 10.1% (vs 2.5%) of cycles, and constipation and small intestinal obstruction/ileus were observed in 12.7% (vs 10.4%) and 2.9% (vs 4.0%) of cycles, respectively. Fatigue was similar between arms—15.8% of vintafolide+PLD vs 14.9% of PLD cycles. All AEs were noncumulative except for HFS, which for both arms increased in frequency through Cycle 6 compared with Cycles 1 and 2. Grade 3/4 AEs (vintafolide+PLD vs PLD alone): 29.3% vs 18.3% of cycles. **Conclusions:** After the number of treatment cycles was accounted for, anemia, neutropenia, and neuropathy were numerically greater in patients on vintafolide+PLD. Thrombocytopenia, constipation, small intestinal obstruction/ileus, fatigue, and HFS were similar. Stomatitis was numerically greater in patients administered PLD alone. Clinical trial information: NCT00722592.

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General Poster Session (Board #48E), Mon, 8:00 AM-11:45 AM

A panel of biomarkers to improve specificity in presurgical assessment of adnexal masses for risk of ovarian malignancy.

Zhen Zhang, Danni Li, Lori J. Sokoll, Xiaer Sun, Robert Bristow, Daniel W Chan; *The Johns Hopkins University, School of Medicine, Baltimore, MD; University of Minnesota Medical Center Fairview, Minneapolis, MN; Johns Hopkins University School of Medicine, Baltimore, MD; University of California, Irvine, School of Medicine, Orange, CA*

Background: OVA1 is a panel of biomarkers cleared by FDA currently in clinical use for pre-surgical assessment of adnexal masses for risk of ovarian malignancy. To further improve the specificity of OVA1, we evaluated biomarkers using a *designed* set of clinical samples enriched with OVA1 false positive benign patients and selected insulin-like growth factor binding protein 2 (IGFBP2), interleukin 6 (IL6), and follicle-stimulating hormone (FSH) to be further evaluated along with the original five biomarkers of OVA1 on a prospectively collected clinical sample set. The inclusion of FSH was to eliminate the need for menopause-specific cutoffs. **Methods:** Consecutive patients with a documented pelvic mass planned for surgical intervention were prospectively enrolled at 27 sites. Exclusion criteria included a diagnosis of malignancy in the previous 5 years or initial enrollment by a gynecologic oncologist. At the time of analysis, 384 subjects had all biomarker values. Among them 69 were ovarian cancer cases (13 LMPs, 27 stages 1/2, 19 serous, 11 endometrioid, 5 mucinous, and 4 clear cell). Biomarkers were tested by ELISA and reported as continuous values. Using a subset of the samples, the biomarkers were first selected for inclusion in a final panel based on contributions in multivariate models estimated by bootstrap. The selected biomarkers were further assessed for ability to improve specificity of risk stratification at a fixed sensitivity over that of OVA1 using the full data set. This was done by cross-validation of multivariate models with 50/50 split between training and testing. **Results:** The final panel of biomarkers consisted of CA125II, prealbumin, IGFBP2, IL6, and FSH. At a fixed sensitivity of 90%, the mean and median specificity of models using the new panel in testing were 78.2% (95% CI: 76.7 – 79.8%), and 80.6%, respectively. The mean and median absolute improvements over that of OVA1 were 18.6% (95% CI: 16.4% – 20.9%) and 20.3%, respectively. **Conclusions:** The new panel demonstrated the potential to significantly improve specificity over that of the first-generation OVA1 algorithm, while maintaining a high sensitivity in pre-surgical assessment of adnexal masses for risk of malignancy.

γ -synuclein expression in ovarian cancer.

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Background: γ -synuclein (SNCG) expression is associated with advanced disease and chemo-resistance in multiple solid tumors. Our goal was to determine if SNCG expression in ovarian cancer was correlated with clinicopathologic variables and patient outcomes. **Methods:** Tissue microarrays from primary tumors of 358 ovarian, fallopian tube, and primary peritoneal cancer patients, who underwent primary surgery at Roswell Park Cancer Institute between 1995 and 2007 were constructed and stained for SNCG. A blinded pathologist scored tumors as positive if $\geq 10\%$ of the sample stained. Medical records were reviewed for clinicopathologic and demographic variables. Between the positive and negative groups, Wilcoxon rank-sum test was used to compare the median ages and Fisher's exact test was used to compare groups in categorical variables. Cox proportional hazard models were used to determine associations between SNCG and overall (OS) and progression-free survival (PFS). **Results:** The median follow-up was 36 months, median OS was 39 months, and median PFS was 18 months. SNCG presence was significant in patients with serous histology, grade 3 disease, suboptimal debulking, ascites at surgery, FIGO stage III-IV cancer, or initial CA-125 level >485 . There was no significant difference in OS (HR 1.06 95% CI 0.81-1.39 P 0.69) or PFS (HR 1.16 95% CI 0.89-1.50 P 0.28) for patients with SNCG expression. **Conclusions:** SNCG expression in ovarian cancer is more frequent in patients with high-risk features, but it does not correlate with chemotherapy response, OS, or PFS.

SNCG expression			
	Ovarian (N= 300)	PP (N = 53)	P value
FT (N=2)	219 (73.0%)	34 (64.2%)	0.28
Non-serous(N=88)	Serous (N=212)		
38 (43.2%)	181 (85.4%)		< 0.0001
Optimal (N=245)	Suboptimal (N= 52)		
169 (69.0%)	46 (88.5%)		0.004
Grade 1/2 (N= 23)	Grade 3 (N=240)		
11 (47.8%)	177 (73.8%)		0.01
FIGO stage I/II (N=64)	FIGO stage III/IV (N=274)		
30 (46.9%)	215 (78.5%)		<0.0001
No Ascites (N=73)	Ascites (N=178)		
44 (60.3%)	136 (76.4%)		0.01
CA 125 < 485 (N=141)	CA 125 > 485 (N=124)		
93 (66.0%)	98 (79.0%)		0.02
No recurrence (N=64)	Recurrence (N=131)		
40 (62.5%)	217 (74.1%)		0.07
Alive (N=89)	Dead (N=268)		
60 (67.4%)	197 (73.5%)		0.28
Optimal			
Disease/progression (N=63)	NED (N=130)		
50 (79.4%)	89 (68.5%)		0.13
Suboptimal			
Disease/progression (N=21)	NED (N=21)		
19 (90.5%)	18 (85.7%)		0.99

Serum mass spectrometry analysis in primary ovarian cancer (OC) treated with surgery and adjuvant chemotherapy (CT).

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Background: To address the unmet need for non-invasive tests to predict outcomes in OC we investigated the effect of the serum test, VeriStrat (VS), in independent cohorts of OC patients (pts) who were treated with platinum based chemotherapy following surgery. VS assigns “Good” (VSG) and “Poor” (VSP) classifications and has been shown to be prognostic in various tumor types and predictive for certain treatments. **Methods:** Samples from primary OC pts from the University Hospital, Essen (ESSEN), N=108, and from OVCAD consortium (Berlin, Leuven, Hamburg, Vienna), N = 138, were obtained within 1 week before surgery that was followed by platinum-based CT. VS testing was done blinded to clinical data. Overall survival (OS) was analyzed by Kaplan-Meier method and compared using log-rank p-values. Cox models were used in multivariate analysis. Associations with categorical variables were analyzed by Fisher’s exact test. **Results:** The cohorts had similar distribution of VSG/VSP classification: 73% VSG (ESSEN), 71% VSG (OVCAD). The distribution by histology (non-serous/serous), and nodal status were different (p = 0.003 and p = 0.049). The results for OS in all pts (ALL), in pts with tumor (and/or metastases) present post-surgery (TPPS-pos), and in pts with complete resection and no metastases (TPPS-neg) are presented in the Table. VS was not associated with circulating tumor cells (ESSEN, p=0.736). In a Cox model analysis for TPPS-pos groups VS was independently significant (p= 0.016, ESSEN) or trended to significance (p=0.063, OVCAD). **Conclusions:** VS demonstrated similar results in two independent cohorts; in ALL and TPPS-pos populations it significantly correlated with OS in ESSEN, showed same trends in OVCAD, and was not correlated with OS in TPPS-neg pts. While requiring further investigation, VS may provide useful prognostic information.

Cohort		ESSEN				OVCAD			
Pts	Test	N	OS median, months	Hazard ratio (95% CI)	p	N	OS median, month	Hazard ratio (95% CI)	p
ALL	VSG	80	50	0.36 (0.20-0.66)	<0.001	138	NR	0.66 (0.42-1.04)	0.074
	VSP	28	21			50	43		
TPPS-pos	VSG	23	23	0.37 (0.18-0.76)	0.004	52	36	0.60 (0.34-1.08)	0.085
	VSP	10	10			21	27		
TPPS-neg	VSG	42	NR*	0.90 (0.19-4.20)	0.894	60	NR	0.83 (0.30-2.29)	0.719
	VSP	8	NR			15	NR		

* NR= not reached.

Statin and aspirin use and risk of VTEs in ovarian cancer patients.

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Background: Deep vein thrombosis and pulmonary embolism - venous thromboembolic events (VTEs) - are associated with significant morbidity and increased risk of mortality in cancer patients. Ovarian cancer patients are at a particularly increased risk for VTEs. Statins and aspirin have been shown to reduce the risk of VTEs in the general population in randomized trials. However, the effect of these medications on the incidence of VTEs in ovarian cancer patients has not been studied. **Methods:** Patients diagnosed with ovarian cancer between years 2000 and 2011 were identified through the Israeli Cancer Registry (ICR). Patients insured by Clalit Health Services, the largest HMO in Israel, were included. Data regarding medication use, chronic diseases and VTE diagnosis were extracted from the computerized database. Patients taking Warfarin or Low Molecular Weight Heparin for 3 months or longer were excluded. Statistical analysis was performed using SPSS (v 18). Use of medications was analyzed as a time dependent covariate in a Cox regression model. **Results:** Of 1,886 patients 179 (9.5%) had a VTE during a median follow up of 3.13 years. 95 patients (5%) had a VTE 2 years after diagnosis of ovarian cancer. In a multivariate analysis use of chemotherapy and stage 3 or 4 at presentation were associated with an increased risk for VTE's 2 years after diagnosis. Age was associated with a trend for increased risk. Statins were used by 43.2% of the patients, and 31.9% used aspirin. Aspirin use was associated with a reduced incidence of a VTE, which was borderline statistically significant ($p=0.054$). Statin use did not affect the incidence of VTE's in the group of ovarian carcinoma patients. **Conclusions:** Our results suggest that in patients with ovarian cancer aspirin use is a possible protector from deep vein thrombosis and pulmonary embolism. Prospective trials are warranted to assess the benefit of aspirin and statins for prevention of VTE's in the high risk population of ovarian cancer patients.

Variable	HR	P value	95% CI
Aspirin	0.49	0.054	0.182- 1.0130
Statins	1.42	0.159	0.871 – 2.3310
Chemotherapy	3.33	<0.001	2.052 – 5.402
Stage 3 or 4	2.8	0.047	1.012 – 7.744
Age	1.017	0.154	0.994 – 1.0410
Comorbidity index	1.096	0.641	0.744 – 1.615

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General Poster Session (Board #49A), Mon, 8:00 AM-11:45 AM

Utilizing propensity scores to determine the risk of recurrence and death in epithelial ovarian cancer.

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Background: Perioperative red blood cell transfusion (PRBCT) may be a negative prognostic marker in surgical oncology. We assessed PRBCT as an independent risk factor for recurrence and death from epithelial ovarian cancer (EOC) in the largest cohort to date. **Methods:** Patient characteristics and process-of-care variables (NSQIP-defined, >130 variables) were retrospectively abstracted from 587 women who underwent primary staging and cytoreduction for EOC (1/1/03-12/29/08). Evaluated using propensity scoring with univariate logistic regression and odds ratios (OR) and Cox proportional hazards regression and hazard ratios (HR). Factors with $p < 0.1$ used in multivariate models. **Results:** Rate of PRBCT was 77.0% (452/587). In univariable analysis, PRBCT was associated with older age (OR 1.25[95% CI 1.06, 1.48]/10yr increase), stage \geq IIIa (4.66[3.04, 7.13]), splenectomy (26.63[3.67, 193.17]), higher surgical complexity (1.86[1.17, 2.95] score 2; 21.48 [7.37, 62.59] 3; referent 1), serous histology (2.36[1.57, 3.55] vs non-serous), longer operating time (1.58[1.36, 1.83]/hr increase), and residual disease (3.26[1.97, 5.41] \leq 1cm; 1.97[1.09, 3.56] $>$ 1cm), and lower preop hemoglobin (Hb) (1.89[1.59, 2.27] per 1g/dL decrease). In univariable analysis, PRBCT was associated with a higher risk of recurrence (HR 1.96[95% CI 1.43, 2.68]) and death (1.71[1.28, 2.28]). However, in multivariable analysis, stage \geq IIIa (4.03[2.05, 6.49]), splenectomy (1.41[1.02, 1.95]), residual disease (1.86[1.41, 2.46] \leq 1cm; 2.91[2.02, 4.18] $>$ 1cm), and lower preop Hb (1.09[1.01, 1.19]) were associated with higher risk of recurrence. Older age (1.24[1.12, 1.37]), stage \geq IIIa (3.07[1.93, 4.90]), albumin \leq 3 g/dL (2.06[1.28, 3.31]), residual disease (1.63[1.22, 2.19] \leq 1cm; 3.03[2.19, 4.18] $>$ 1cm), and low Hb (1.08[1.00, 1.19]) were associated with higher risk of death. Serous histology (0.70[0.52, 0.95]) associated with lower risk of death. **Conclusions:** PRBCT does not appear to be directly associated with disease-free and overall survival in EOC. Lower preoperative Hb was associated with a higher risk of both recurrence and death. The need for PRBCT appears to be a stronger prognostic indicator than the receipt of PRBCT.

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General Poster Session (Board #49B), Mon, 8:00 AM-11:45 AM

Inhibition of gamma-secretase activity in combination with paclitaxel to reduce platinum-resistant ovarian tumor growth.

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Background: Ovarian cancer (OvCa) is the most lethal gynecologic malignancy in the United States. Chemotherapy is effective but seldom curative, mainly due to the development of chemoresistant recurrent disease. Our current research investigates the efficacy of inhibiting the Notch pathway with a gamma-secretase inhibitor (GSI), MRK-003, in an OvCa xenograft model as a single agent therapy and in combination with standard chemotherapy. **Methods:** Mice bearing xenografts derived from clinically platinum sensitive human ovarian serous carcinomas were treated with GSI or vehicle, or with either vehicle, GSI alone, paclitaxel and carboplatinum (T/C) alone, or the combination of GSI and T/C. In addition, mice bearing xenografts derived from patients with clinically platinum resistant disease were given GSI with or without paclitaxel. Gene transcript levels of several factors in the Notch pathway were analyzed using RT-PCR. Notch1 and Notch3 protein levels were evaluated by western blotting. The Wilcoxon rank-sum test was used to assess significance between the different treatment groups. **Results:** Expression of Notch1 and Notch3 was highly variable across all analyzed OvCa samples. Treatment with GSI alone significantly decreased tumor growth in 3 of 4 platinum sensitive ovarian tumors (all $p < 0.05$), as well as in 1 of 3 platinum resistant tumors ($p = 0.04$). Furthermore, the combination of GSI and paclitaxel was significantly more effective than GSI alone and paclitaxel alone in all platinum resistant ovarian tumors (all $p < 0.05$). The addition of GSI did not alter the effect of T/C in platinum sensitive tumors. Although the response of each tumor to GSI did not correlate with its endogenous level of Notch expression, 2 of the 3 tumors resistant to paclitaxel but sensitive to the combination of GSI and paclitaxel showed elevated Notch activity by RT-PCR. **Conclusions:** Inhibition of the Notch signaling cascade with a gamma-secretase inhibitor reduces tumor growth in vivo, most notably in combination with paclitaxel in a platinum resistant setting. These promising findings underscore the need for further investigation of the preclinical and clinical effectiveness of Notch inhibitors in OvCa.

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General Poster Session (Board #49C), Mon, 8:00 AM-11:45 AM

Expression of glucose-regulated protein 78 (GRP78) and its regulator microRNA-181 during the development and progression of ovarian cancer.

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Background: Ovarian cancer (OVCA) is a lethal malignancy of women with a distinct pattern of metastasis through peritoneal dissemination. Sustained exposure of the ovaries to oxidative stress due to inflammatory processes including ovulatory genotoxicity, makes the ovarian microenvironment conducive to malignant cell proliferation. GRP78 is a stress-inducible protein which resides in the endoplasmic reticulum of the cell. Thus GRP78 may be a marker of ovarian tumor associated stress and could represent a therapeutic target for OVCA. The goal of this study was to examine if GRP78 expression increases in association with OVCA development and determine the molecular mechanism of its increase in ovarian tumors. **Methods:** All tissues were collected from patients who underwent surgery and processed for immunohistochemistry (IHC), proteomic study (2D-WB) and miRNA expression. Expression of GRP78 was examined in paraffin sections of normal ovaries (n = 20), benign (serous cystadenoma, n = 15 and cystadenofibroma, n = 5) and ovaries with papillary serous carcinoma at early stage (n = 20 at stages I and II) and late stage (n = 20, stages III and IV) by IHC and confirmed by 2D-WB (representative samples). Changes in miRNA-181 (post-translation regulator of GRP78) expression were examined by qRT-PCR. **Results:** GRP78 expression by normal ovarian surface epithelium and epithelium of benign tumors was very weak. In contrast, the intensity of GRP78 expression was significantly ($p < 0.05$) high in early stage OVCA and increased further in late stage OVCA. An immunoreactive band of 78kDa detected by 2D-WB confirmed IHC observations. In contrast, expression of miRNA-181 by malignant tumors significantly ($p < 0.05$) decreased as the tumor progressed to late stages. **Conclusions:** The results of the present study suggest that GRP78 expression is associated with the development and progression of malignant ovarian tumors. Increase in GRP78 expression was associated with the down-regulation of miRNA-181. Expression of GRP78 by malignant ovarian epithelium represents a potential marker with usefulness for targeted drug delivery. Support: Elmer and Sylvia Sramek Foundation.

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General Poster Session (Board #49D), Mon, 8:00 AM-11:45 AM

Benefits of neoadjuvant chemotherapy in ovarian, primary peritoneal, or fallopian tube carcinoma.

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Background: NCCN guidelines recommend consideration of neoadjuvant chemotherapy (NACT) for poor surgical candidates with bulky stage III or IV ovarian, fallopian tube, or primary peritoneal cancer. However, new convincing evidence favoring NACT instead of primary tumor reductive surgery (PTRS) has resulted in shifting practices among gynecologic oncologists. This study compares operative and post-operative outcomes between patients receiving NACT and those undergoing PTRS. **Methods:** After IRB approval, patients who received NACT or PTRS were identified through the tumor registry and surgical database at a single institution from 2008-2012. Statistical analyses included Wilcoxon Mann-Whitney, Chi square and Fisher's exact test. **Results:** Of 163 patients, 109 (67%) received NACT and 54 (33%) underwent PTRS. The majority in both groups was Caucasian (82%) and had ovarian cancer (85%). The median age of all patients was 62 years. There was no difference in median age between groups. High-grade serous histology was most common. In the PTRS group, 72% were stage IIIC. During cytoreductive surgery, NACT cases had significantly shorter total operative and anesthesia time compared to PTRS cases ($p = 0.005$). NACT patients had significantly less blood loss ($p=0.002$) than PTRS patients. Based on available data, there was no difference in intraoperative transfusion rate ($p = 0.098$). However, PTRS cases had a higher rate of postoperative transfusion compared to NACT cases ($p = 0.043$). There was no difference in the proportion of optimal surgical cytoreduction between groups ($p = 0.422$). Available data demonstrated that PTRS patients had significantly more complications and intensive care unit (ICU) admissions compared to those receiving NACT ($p = 0.024$, $p = 0.002$ respectively). **Conclusions:** NACT offers advantages regarding operative and anesthesia time, blood loss, postoperative complications, and ICU admissions. NACT may offer a valuable alternative to PTRS. Further studies are warranted to better define the role of NACT in the upfront treatment of advanced ovarian cancer.

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General Poster Session (Board #50A), Mon, 8:00 AM-11:45 AM

Changes in renal function following treatment for ovarian cancer.

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Background: Among women treated for Epithelial Ovarian Cancer (EOC), new or worsening renal dysfunction has been observed but not systematically studied. We conducted a retrospective cohort study to estimate the rate of decline in renal function following a diagnosis of EOC, compared with the rate of decline among the same patients prior to diagnosis. **Methods:** We study a historical cohort of women diagnosed with EOC between 1/1/2000 and 12/31/2011, who received health care services within a large community medical center. Data were retrieved from institutional electronic records. We develop a Generalized Estimating Equations (GEE) model to quantify changes in estimated glomerular filtration rate (eGFR) over time, with the date of EOC diagnosis as the reference point (time zero). All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Carey, NC). **Results:** The cohort is comprised of 323 women. At diagnosis, the mean age was 63.4 (\pm 13.5) years and the mean eGFR was 81.0 (\pm 22.7). There were 74 (22.9%) patients carrying a diagnosis of hypertension, 25 (7.7%) with diabetes, and 73 (22.6%) who were clinical obese. Prior to EOC diagnosis the decline in mean monthly eGFR was not significant (-0.052, 95% CI -0.11-0.009, p = 0.092), after controlling for age, obesity, hypertension, and diabetes. This monthly decline increased by almost 4-fold (p = 0.0007) subsequent to EOC diagnosis. To discern the potential effect of chemotherapy on renal function, we conducted a secondary analysis on the 120 women for whom detailed chemotherapeutic data is available. For women who received standard first-line chemotherapy (paclitaxel and carboplatin) the rate of eGFR decline increased 10-fold (-0.025 vs. -0.25, p = .0066) relative to their baseline rate of decline. For those who received other regimens, the increase was 11.4 times (-0.025 vs. -0.286, p = .0011); this was not significantly higher than those receiving the standard regimen (p = 0.72). **Conclusions:** This ongoing study suggests that women treated for EOC suffer an accelerated rate of renal function decline, independent of major comorbid conditions, that is therefore attributable to the disease and/or its treatment.

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General Poster Session (Board #50B), Mon, 8:00 AM-11:45 AM

Results of a phase II clinical trial to evaluate a re-challenge of intraperitoneal catumaxomab for treatment of malignant ascites (MA) due to epithelial cancer (SECIMAS).

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Background: Catumaxomab is approved in Europe for the i.p. treatment of MA. With a growing number of patients (pts) treated, the question arises, if a re-challenge is feasible and effective despite the immunogenicity of this non-humanised antibody. **Methods:** Pts were eligible if they received 4 i.p. applications of catumaxomab in the CASIMAS study and benefitted with a puncture free interval of > 60 days. Primary endpoint was to determine the proportion of pts who were able to receive at least 3 catumaxomab applications. Secondary endpoints were the development of human anti-drug antibodies (ADA) as well as the safety profile of a second catumaxomab cycle including a composite safety score (CSS) summarizing the worst CTCAE grades for the main adverse reactions (pyrexia, nausea, vomiting, abdominal pain). Efficacy endpoints were time to puncture (TTPu), overall survival (OS) and puncture-free survival (PuFS). **Results:** Median age was 59.0 years. 8 out of 9 screened pts were treated with a second cycle of catumaxomab. The primary tumor was ovarian cancer in 5 (62.5%), breast cancer in 2 (25%) and urachal cancer in 1 (12.5%) pts. All 8 (100%) pts received all 4 infusions within 20 days. Median CSS was 3.0 after the second cycle while it was 3.4 after the first cycle in the CASIMAS study for these 8 pts. Only less pts had AEs with CTC >3 (SECIMAS 25%; CASIMAS 70.1%). All 8 (100%) pts were ADA-positive at study entry. ADA levels were consistently higher in the plasma than in the ascites fluid. During treatment, highest ADA values were found on day 10 for ascites and day 11 for plasma up to values of > 1 mg/ml. PuFS was 47.5 days and TTPu 60 days after the second cycle, and 37 days and 102 days, respectively after the first cycle. Median OS was 406.5. **Conclusions:** This first experience with a re-challenge of catumaxomab in MA, demonstrates a tolerable safety profile without acute allergic reactions, in spite of the high immunogenicity of catumaxomab and the repeated application. Efficacy was not impaired despite ADA response and the advanced disease of the pts. A re-challenge seems feasible for selected pts suffering from recurrent MA after a first cycle of catumaxomab. Clinical trial information: NCT01065246.

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General Poster Session (Board #50C), Mon, 8:00 AM-11:45 AM

Frequently deleted genes in ovarian cancer as indicators of platinum response.

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Background: Integrating chromosomal deletions/amplifications with sequencing alterations is increasingly important in the determination of key drivers of outcome in cancer (Leary 2008, Curtis 2012). We introduce a novel computational approach, Gene Set Outcome Analysis, to determine gene signatures constrained to regions with frequent deletion or amplification events in ovarian cancer identified by TCGA. Differential expressions of mRNA from these genes are used as a proxy for loss of function from deletions or amplifications. **Methods:** Gene signatures from each region were evaluated using log-rank test comparing high and low gene expression groups split by cohort mean. In total, 30,119,708 signatures constrained to 47 deleted and 36 amplified regions were tested for PFS for first line platinum treatment in a random 2/3 split of TCGA ovarian cohort (n=262) resulting in 26,271 gene signatures with $p < .001$. The remaining 1/3 cohort (n=135) and full cohort (n=397) were used as a replication study where 111 signatures have a $p < .01$ located in 2 deletion and 1 amplification region. The signature with the lowest p-value from each region that validated in the replication study, were evaluated in GSE9891 (n=179) (Tothill 2008) for PFS when treated with platinum and taxol resulting in gene signatures from 2 deletion regions with $p < .05$. **Results:** Greater than mean expression in this gene signature [OXTR, SATB1, WNT7A, SH3BP5, CRBN, ATG7, CRELD1, TMEM43] located at 3p23-p26.2 predicts poor response to platinum chemotherapy in TCGA full ovarian cohort (17.9 vs 14 months $p = 1.4E-7$) and validates in GSE9891 (19.6 vs 13.3 months $p = .014$). Using a separate, compact gene signature [CAAP1, LRRC19, IFNA8] located at 9p21.2, samples with lower than mean expression demonstrate increased platinum sensitivity in TCGA full ovarian cohort (12.2 vs 18.2 months $p = 1.0E-6$) and in GSE9891 (15.5 vs 18.6 $p = .055$). **Conclusions:** Response to platinum therapy is an important predictor of survival in high-risk ovarian cancer patients. These signatures arising from common deletion and amplification events in ovarian cancer can anticipate platinum sensitivity and merits further study for use in choosing optimal therapies studying platinum resistance mechanisms.

Pathologic distribution of disease at the time of interval debulking versus primary tumor reduction in women with primary peritoneal, ovarian, or Fallopian tube carcinoma.

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Background: The surgical approach for interval debulking after neoadjuvant chemotherapy (NACT) for primary peritoneal, ovarian, or fallopian tube carcinoma has largely been extrapolated from experience with primary tumor reductive surgery (PTRS). It is unknown whether procedures considered mandatory in PTRS, such as hysterectomy, contribute to comparable removal of macroscopic disease in the NACT setting. Our study compared the difference in pathologic distribution of disease at interval debulking surgery versus primary tumor reduction. **Methods:** After IRB approval, patients who received NACT or PTRS were identified through the tumor registry and surgical database at a single institution from 2008-2012. Involvement of organs at the time of surgery was categorized as either macroscopic, microscopic and no tumor. Statistical analyses included Wilcoxon Mann-Whitney and Fisher's exact tests. **Results:** Of the 163 patients identified, 111 (67%) received NACT and 54 (33%) underwent PTRS. Median age was 62 and the majority of patients had stage IIIC high-grade serous carcinoma (91%). Macroscopic ovarian involvement was more common at time of PTRS (92 % vs 63 %, $p < 0.001$). Gross uterine involvement was significantly less in the NACT group compared to PTRS, with the majority of specimens in the NACT group free of disease (Macroscopic 11 % vs 42%, no tumor 62% vs 44 %, $p < 0.002$). However, 27% of the NACT had microscopic uterine serosal disease. Macroscopic large bowel involvement was 50 % in the PTRS vs 26 % in NACT ($p < 0.005$). There was no difference in disease involvement of the small bowel or omentum. **Conclusions:** The pathologic disease distribution at the time of interval tumor debulking is significantly different from that encountered during primary cytoreductive surgery.. NACT appears to reduce macroscopic large bowel and uterine tumor involvement and may negate the need for hysterectomy and/or large bowel resection at the time of interval debulking to achieve no gross residual.

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General Poster Session (Board #51A), Mon, 8:00 AM-11:45 AM

Multimodal therapy in patients with node-positive (stage IIIC) uterine papillary serous carcinoma: A National Cancer Database study.

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Background: Uterine papillary serous carcinoma (UPSC) is an aggressive endometrial cancer that carries a 30-40% risk of nodal metastasis. Adjuvant systemic chemotherapy has become standard of care in advanced UPSC, but the role of additional adjuvant radiotherapy is unclear. This study aims to evaluate survival outcomes of multimodal therapy through the use of the National Cancer Data Base (NCDB).

Methods: All patients diagnosed with surgically-staged FIGO stage IIIC uterine papillary serous carcinoma were identified in the NCDB from 1/1998 through 12/2010. Patients were divided into those who received chemotherapy only (CT) and both chemotherapy and radiation therapy (CT+RT). Overall survival was estimated using the Kaplan-Meier method. Univariate comparison by log rank test and multivariable analysis by Cox regression modeling were performed to identify and control for prognostic factors. **Results:** A total of 13,356 cases of uterine cancer were identified, of which 794 were UPSC. Of these patients, 387 underwent lymphadenectomy (median 14 nodes removed) with 75 patients (median age 65) found to have stage IIIC disease. Median follow up is 20.4 (range: 0-114) months. There were no significant differences were found between the RT and CT+RT group with regards to patient demographic, medical comorbidity, treatment facility or disease characteristics. The median overall survival was 23.2 (95% CI 14.5-31.9) and 40.3 (95% CI 31.5-49.1) months, ($p < 0.05$) for the CT and CT+RT groups, respectively. Multivariate analysis controlling for age, race, income, Charlson-Deyo comorbidity index, treatment facility type, year of diagnosis, number of lymph nodes removed, number of positive lymph nodes and tumor size found radiotherapy independently predicted improved survival [$HR_{\text{death}} 0.024$ (95% CI 0.001-0.668)].

Conclusions: Patients with stage IIIC UPSC benefit from adjuvant radiotherapy in addition to adjuvant chemotherapy.

Impact of wait times on survival of women with uterine cancer.

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Background: Reducing cancer wait times have been a priority investment for Cancer Care Ontario since 2005. Our objective was to determine whether wait time from histologic diagnosis of uterine cancer to time of definitive surgery by hysterectomy impacted on all cause survival. **Methods:** Cases were identified in the Ontario Cancer Registry using ICD-09 codes 179 and 182. Excluded were women without histologic/cytologic confirmation of cancer prior to surgery, with no definitive surgery, or with wait times of ≤ 14 days or > 2 years. Survival was calculated using the Kaplan-Meier method from the day of hysterectomy. Factors were evaluated for their prognostic ability on survival using Cox proportional hazards regression. Wait time was evaluated as a continuous variable and dichotomized at selected cutpoints in the univariable analyses and in a multivariable model adjusting for significant patient factors identified using forward stepwise selection. **Results:** The final study population included 8,744 women. 51.9% had surgery by a gynaecologist and 69.9% had endometrioid adenocarcinoma. The optimal model is shown below. Multivariable analysis of factors prognostic for survival. Longer wait times remained a statistically significant negative prognostic factor for survival regardless of definition, univariably ($p < 0.002$) and multivariably after adjusting for other significant factors ($p < 0.001$). The final multivariable model is shown. 5-year (95%CI) survival for women with more than 12 week wait times was 61.4 (57.8-64.8)% versus 71.9 (69.9-73.8)% for women with less than 6 week wait time. **Conclusions:** The longer a woman waits from diagnosis of uterine cancer to definitive surgery negatively impacts her overall survival.

Factor	Category	HR (95% CI)	P value
Charlson comorbidity score	≥ 3 versus ≤ 2	2.09 (1.91-2.29)	< 0.001
Previous cancer diagnosis	Yes versus no	1.13 (1.01-1.27)	< 0.001
Multiple cancer diagnoses	Yes versus no	2.28 (1.54-3.37)	< 0.001
Histology (reference is unknown)	Sarcoma	2.45 (2.03-2.95)	< 0.001
	Serous	1.54 (1.27-1.86)	
Wait time	Log (days)	1.18 (1.10-1.28)	< 0.001

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General Poster Session (Board #51C), Mon, 8:00 AM-11:45 AM

Is uterine serous carcinoma a part of hereditary breast cancer syndrome?

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Background: Whilst the association between breast cancer and uterine serous carcinoma (USC) is attributed to tamoxifen treatment, few studies have reported that this increased risk is independent of tamoxifen. **Methods:** To further investigate the relationship between breast cancer and USC, we retrospectively studied 216 patients from 5 hospital trusts in Birmingham, UK who were diagnosed with USC between 1993 and 2012. We collected personal history of cancer in these cases before or after USC diagnosis. In addition FIGO staging, clinical and survival data were collected from our local cancer registry and patients' clinical records. **Results:** In this case series, 56 patients (25.9%) had personal history of at least one cancer before and 18 patients (8.3%) had history of at least one cancer after the diagnosis of USC. Within the group of patients with the history of cancer before the USC, 38 patients (68%, 17.5% of all cases) had personal history of breast cancer prior to the development of USC, higher than the UK expected age standardised relative incidence of breast cancer (350 in 100,000, CRUK 2006-2008). Although 27/38 cases (71%) had endocrine treatment for their primary breast cancer, 11/38 patients (29%) did not have any tamoxifen treatment due to hormone receptor negative breast cancer. Additionally the median age of breast cancer diagnosis for the hormone receptor negative group was significantly lower than those patients who had hormonal treatment for their breast cancer (56 vs. 64 years, $p:0.036$) compatible with the younger age at diagnosis expected of the familial (BRCA mutated) or triple negative breast cancer. Of 18 patients with a second cancer after diagnosis of USC, 6 patients (33%) were diagnosed with breast/ovarian cancer. This group also had no treatment with tamoxifen. **Conclusions:** Lack of exposure to tamoxifen and younger age at diagnosis in this subgroup suggest that other factors such as a common underlying genetic predisposition may be responsible for the development of both malignancies. We propose that at least a subgroup of USC may be a part of hereditary breast cancer syndrome. This may have implications in prevention (prophylactic hysterectomy) or trials of targeted treatments (PARP inhibitors) for a subgroup of USC patients.

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General Poster Session (Board #51E), Mon, 8:00 AM-11:45 AM

High-grade endometrial cancer: Revisiting tumor size and the lower uterine segment.

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Background: Tumor size is an independent poor prognostic factor in endometrial cancer, while tumor location has shown mixed results, with few studies addressing high-grade disease. We aim to determine if tumor size (TS) or lower uterine segment involvement (LUS) is associated with nodal disease and recurrence in high-grade endometrial cancer. **Methods:** In an IRB-approved, multi-institutional cohort study of patients with clinically early-stage, high-grade endometrial cancer (grade 3 and all non-endometrioid histologies), records were reviewed for demographic, pathologic, and treatment data. Recurrence as a function of tumor size and location were analyzed using logistic regression and exact tests for significance. Hazard ratios were calculated. **Results:** 208 patients with high-grade histology were identified from Jan 2005 to Jan 2012 with 188 patients having tumor location identified and 183 having tumor size reported. Both pelvic and para-aortic lymphadenectomy were completed in 100% of patients. There were 75 endometrioid (36.1%), 35 papillary serous (16.8%), 12 clear cell (5.8%), 26 carcinosarcoma (12.5%), and 60 (28.8%) with undifferentiated or mixed histology. Median follow up time was 17.2 months (0.2 – 67.6 mo) with 55 recurrences. LUS tumors were more likely to have pelvic and para-aortic nodal disease (OR 3.83, 95%CI 1.70 – 8.60, OR 5.13, 95% CI 1.96 – 13.45) and increased recurrence rates (HR 2.21, 95% CI 1.16-4.20) on univariate analysis. Tumors size ≥ 2 cm was associated with pelvic nodal disease (27.4% vs. 0%, $p = 0.01$; OR 10.00, $p = 0.01$). TS was not independently associated with recurrence and patterns of failure did not significantly differ with LUS involvement. **Conclusions:** In patients with clinically early stage, high-grade endometrial cancers, TS and LUS tumor location are significantly associated with lymph node metastasis and advanced stage disease at the time of comprehensive surgical staging. Tumor location in particular is strongly associated with distant nodal disease and is a poor prognostic indicator for recurrence. Studies evaluating the role of adjuvant therapy based on tumor size and tumor location would be helpful in improving patient related outcomes.

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General Poster Session (Board #52A), Mon, 8:00 AM-11:45 AM

Gene scoring model to predict recurrence in low- and intermediate-risk uterine endometrial cancer: Establishment of uterine print.

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Background: Endometrial cancers (ECs) classified as low-, intermediate-, and high-risk, based on clinical and pathological features (CPF; Lurain, 2007) associated with 5%, 15%, and 25% risk of recurrence, respectively. The need for adjuvant chemotherapy in intermediate-risk patients is controversial. We examined whether gene expression profiling can more accurately predict the prognosis of ECs, excluding the CPF-based high-risk group. **Methods:** Tumor specimens were obtained from 136 ECs including 14 recurrences, excluding high-risk cases. Gene expression profiles were achieved using a custom array consisting of 85 genes associated with EC recurrence and 20 internal controls that were previously screened. We established the gene scoring model (GSM) for recurrence by the logistic regression model in randomly selected 68 ECs including 7 recurrences, and evaluated the accuracy of GSM in other 68 ECs including 7 recurrences. This process was repeated 100 times. We calculated the mean accuracy of GSM and compared it with the accuracy of CPF. We also compared GSM and CPF with respect to progression-free survival (PFS) by use of the log-rank test. **Results:** Median age of all cases was 58 (29-86) years, and stage, histologic grade, and risk classification based on CPF were as follows: (I, 107; II, 15; III, 14), (G1, 69; G2, 57; G3, 10), and (low, 67; intermediate, 69). The median follow-up period was 1830 (1626-3444) days. The GSM was established based on the expression of 4 genes (*PRCC*, *SPC25*, *PXD*, and *LBXCOR1*) and 10 internal controls. The area under the receiver operating characteristic curve of GSM to predict recurrence was 0.87 in 68 test cases. Based on the CPF, 68 cases were classified as 30 low-risk and 38 intermediate-risk, and the sensitivity and specificity of CPF was 86% and 48% each in the 68 test cases. When sensitivity of GSM was fixed at 86%, specificity of 67% was achieved, and 68 cases were classified as 42 risk (-) and 26 risk (+). PFS was significantly related with GSM ($p = 0.006$); however, it was not related with CPF ($p = 0.09$). **Conclusions:** GSM can predict the prognosis of ECs (low- and intermediate-risk) more precisely than CPF.

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General Poster Session (Board #52B), Mon, 8:00 AM-11:45 AM

Analysis of plasma biomarker and tumor genetic alterations from a phase II trial of lenvatinib in patients with advanced endometrial cancer.

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Background: Lenvatinib is an oral receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFR β . A phase 2 study in patients with advanced endometrial cancer following 1 or 2 prior platinum-based treatments was performed and is presented in a separate abstract. Here we report potential predictive markers of clinical benefit. **Methods:** Pre- and post-treatment plasma samples collected from 122 of 133 treated subjects were analyzed for 50 circulating cytokine and angiogenic factors (CAFs) using ELISA and multiplex assay platforms; 107 archival tumor tissues obtained from 133 enrolled subjects were analyzed for gene mutation (mut) (81 samples) and gene expression profiling (GEP) (64 samples). For GEP analysis, the NanoString nCounter platform was used to measure the expression level of approximately 300 genes identified preclinically as relevant. Correlation with clinical outcome measures including maximal tumor shrinkage (MTS), objective response rate (ORR), PFS, and OS was performed. **Results:** Clinical correlation identified baseline levels of 7 CAFs related to angiogenesis (Ang-2, IL-8, HGF, VEGFA, PlGF, Tie-2, and TNF α) that associated with survival. Only baseline levels of Ang-2 associated with greater MTS (R=0.36 [Spearman], $P<0.001$), ORR (61% vs 18%), mPFS (9.5 vs 3.7 mos), and mOS (23 vs 8.9 mos) as determined using a defined cut-off value for baseline Ang-2. In gene mut analysis, no significant correlations were observed among the genes tested. Mut in PIK3CA showed a trend toward shorter OS ($p = 0.085$). In GEP analysis, expression levels of approximately 90 genes correlated with clinical outcome. Combination of GEP and CAF signatures identified signaling pathways, including Ang-2, that associated with OS. Clinical and preclinical GEP analysis identified overlapping gene signatures involving MAPK and PI3K signaling pathways that contributed to lenvatinib resistance. **Conclusions:** Baseline circulating Ang-2 levels may potentially predict outcomes in patients with advanced endometrial cancer and require further examination. This may provide a basis for stratification of patients in future clinical trials. Clinical trial information: NCT01111461.

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General Poster Session (Board #52C), Mon, 8:00 AM-11:45 AM

Statin use in uterine malignancies.

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Background: Statins, or 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, are commonly used to manage hyperlipidemia. Epidemiologic studies have recently linked statins to improved cancer survival. Molecular pathways that explain this effect are not well defined, but may involve cell death and angiogenesis. Our aim was to determine the association between statin use and overall survival in a cohort of women with uterine malignancies. **Methods:** After IRB approval, a retrospective review of consecutive patients with uterine malignancies diagnosed between 01/2005 and 12/2009 at a single institution was performed. Age, race, diagnosis of hyperlipidemia, diabetes, hypertension, medication use including statins, beta-blockers, aspirin, pathology, and exposure to chemotherapy or radiation were abstracted from the time of initial diagnosis and treatment. Kaplan-Meier analysis, univariate, and multivariate Cox Proportional Hazard Regression were performed to assess the association between statin use, aspirin use, and survival. **Results:** Of 554 patients identified, 333 (60%) were not hyperlipidemic (NH), 165 (30%) were hyperlipidemic on statins (HS), and 56 (10%) were hyperlipidemic and not on statin therapy (HNS). The HS cohort was older, diabetic, hypertensive, used beta-blockers and aspirin. Stage, grade, and chemotherapy use were similar, but HS and HNS received more radiation ($p < 0.05$). Both patients in the HS and HNS groups had improved overall survival compared to NH patients ($p = 0.04$). Further stratifying our subgroups by aspirin use revealed that HS+aspirin users had significantly improved survival compared to other non-HS+aspirin users ($p = 0.01$). In multivariate analysis, women who used statins had a 45% decreased hazard of death compared to NH women (HR = 0.55, 95% CI; 0.35, 0.87). Additionally, aspirin users had improved survival compared to non-users (HR = 0.47, 95% CI; 0.29, 0.76). Women using statins and aspirin had an 84% decreased hazard of death in comparison to other groups (HR = 0.16, 95% CI; 0.07, 0.38, $p < 0.01$). **Conclusions:** Statin and aspirin use are associated with improved overall survival in patients with uterine malignancy. Prospective evaluation of statin and aspirin use in uterine cancer is warranted.

Regional differences in therapy and clinical management of endometrial cancer: Findings of an international survey by the North-eastern German Society of Gynaecological Oncology (NOGGO).

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Background: We conducted an international survey to evaluate the differences in the systemic, radiotherapeutic and operative management of endometrial cancer (EC) in different regions of the world. **Methods:** In 2009 a validated 15-item-questionnaire regarding surgical and adjuvant procedures of EC was sent to all German gynaecological clinics and in 2010 the English adapted questionnaire was set online as well as sent per post in most major gynaecological cancer societies. **Results:** 316 German institutions and 302 Institutions from 24 countries participated. We combined the different countries into regional groups: Central Europe (CE), southern Europe (SE), Asia and USA/UK. In Asian countries and in CE a lymph node dissection (LND) was performed routinely in 72.8% and in 55.6% of the cases, whereas in the USA/UK and in SE a LND was done mainly in selected cases when specific risk factors such as high-grade or non-endometrioid-histology applied (62.8% and 72.5%) than routinely ($p < 0.001$). A systematic pelvic and paraaortic LND was performed most frequently in CE 91.0%, in SE 76.9%, in Asia 70.9% and in USA/UK 68.6% ($p < 0.001$). A systematic LND with the intention of both adequate staging and for therapeutic value was performed in countries of central Europe to 74.6% and in Asia to 67.2%. In USA/UK the LND was seen merely as a staging instrument by 53.5% ($p < 0.001$). The LND was performed up to renal veins in CE in 86.8%, in Asia in 80.8%, in USA/UK in 51.2% and in SE in 45.1 %. A significant difference was found in the treatment for FIGO stage I (high risk factors (high grade, L1,V1)) and stage II disease between the countries: chemotherapy was applied in 84.8% of the participated centers in Asia, 42.3% in SE, 21.2% in CE and only 13.6% in USA/UK ($p < 0.001$). Vaginal brachytherapy was indicated as follows: USA/UK 84.1%, CE 78.8%, SE 78.8%, Asia 5.6% ($p < 0.001$). **Conclusions:** There is a large variety in the operative therapy and the clinical management of EC in different regions of the world. Future international prospective trials, will be necessary to improve and harmonize the evidence based treatment guidelines for EC- disease.

Early diagnosis program for cervical cancer in Tanzania: The “Vanda Project”.

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Background: In Sub-Saharan Africa cervical cancer represents 24% of all cancers and accounts for 23% of all cancer deaths in women. An early diagnosis program for breast and cervical cancer (Vanda Project) is ongoing in Mwanza and the surrounding lake area (12 districts with a population of 14,000,000). The aim of this project was to screen women aged 15-64 years living in the 12 districts. **Methods:** Women were invited to participate through local media and a mobile unit operating within the districts. A multidisciplinary team including medical oncologists was involved. Interventions consisted in Pap smear, clinical breast examination, breast self-examination training and training of district physicians to perform Pap smear and breast examination. **Results:** From May to December 2012, 2155 women from the districts of Shinyanga, Bukumbi, Kibara, Serengema and Musoma took part in the program: of these 91 (4%) had clinically evident cervical cancer. Age distribution classes were: < 18 years, 12% ; 18-35, 38%; 36-50, 41%; > 50, 9%. As expected a high stage distribution at diagnosis was observed: 30% stage III and 20% stage IV. Among the women with no clinical evidence of cancer, 408 samples were analyzed by cytology and 4% consisted of inadequate material. Of the remaining 392 samples, 85 (22%) were normal, 216 (55%) were infections (chiefly mycotic), 72 (18%) were precancerous lesions (50% H-SIL according to Bethesda classification) and 19 (5%) were positive for cancer (mainly stages III-IV). Precancerous lesions turned out to be cancer at histology in 44% of cases. 22% of precancerous lesions and 8% of clinically evident cancer were HIV-positive. **Conclusions:** This experience shows the high feasibility, good compliance and usefulness of a screening program for the early detection of cervical cancer in this high-risk population.

Clinically detected cervical cancer by age and staging.

Age range (years)	Clinical cancer diagnosis	Stage I	Stage II	Stage III	Stage IV
< 18	0	0	0	0	0
=>18-35	37	7	16	11	3
>35-50	40	2	19	12	7
>50-60	11	0	2	4	5
>60	3	0	0	0	3
Total	91	9 (10%)	37 (40%)	27 (30%)	18 (20%)

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General Poster Session (Board #53A), Mon, 8:00 AM-11:45 AM

A retrospective assessment of outcomes of chemotherapy-based versus radiation-only adjuvant treatment for completely resected stage I–IV uterine carcinosarcoma (UCS) with rhabdomyosarcoma (RMS) differentiation.

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Background: UCS with RMS differentiation are aggressive cancers with poor survival, and without an established standard treatment (txt). We aimed to determine the progression-free survival (PFS) and overall survival (OS) in patients (pts) who received either platinum-based chemo with or w/o radiation therapy (pelvic or IVRT), or RT alone (pelvic or IVRT). **Methods:** MSKCC EMR from 1990 to 2012 was reviewed for pt age, diag. date, primary surgery, residual disease at completion of primary surgery, FIGO stage, txt details, dates of progression, death, site(s) of first recurrence. Univariate analysis for PFS/OS utilized Kaplan Meier method. Differences between PFS/OS and categorical variables of stage + txt type were assessed using log-rank test. All analyses utilized SAS version 9.2. Pts who received chemo with or w/o RT or RT alone were included in the analysis. **Results:** 53 pts met study criteria. 41/53 (77.4%) pts received chemo: 30/41 (73.2%) paclitaxel-carboplatin (TC); 3/41 (7.3%) ifosfamide (I)-platinum; 3/41 (7.3%) weekly cisplatin followed by TC; 2/41 (4.9%) other platinum-doublets; 3/41 (7.3%) IT. 34% of the chemo pts also received pelvic or IVRT. 12/53 (22.6%) pts received only pelvic RT+/-IVRT. FIGO stage: I =16 (30%); II =5 (9%); III =14 (26%); IV =18 (34%). Median PFS for the entire cohort: 11.7 mos (95% CI 6.4, 14.1). Median OS for the entire cohort: 21.8 mos (95% CI 14.9, 31.8). Median PFS by stage: 14.3 mos for early stage (stages I and II) vs 9.9 mos for late stage (stages III and IV), $p=0.0217$. Median OS by stage: not reached in the early stage cohort. Median OS for the late stage: 19.9 mos, $p=0.0106$. Median PFS by txt: 10.7 mos for the Pelvic RT+/- IVRT group vs 13.5 mos for chemo+/-Pelvic RT+/- IVRT group, $p=0.5126$. Median OS treatment: 23.9 mos for the chemo+/-Pelvic RT+/- IVRT group vs 17.4 mos for the Pelvic RT+/- IVRT group, $p=0.5191$. **Conclusions:** PFS and OS outcomes in our cohort of pts with UCS with RMS differentiation were similar to survival outcomes among pts treated with platinum-based chemo on GOG 150 and GOG232B. The role of adjuvant RT in addition to chemo warrants further investigation.

Long-term survival in advanced-stage uterine papillary serous carcinoma.

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Background: Advanced-stage (III/IV) uterine papillary serous carcinoma (UPSC) has a median overall survival (OS) of ~ 3 yrs. The study objective was to determine factors associated with long-term survival in advanced stage UPSC. **Methods:** We performed a retrospective review of pts diagnosed with stage III or IV UPSC between 1993 and 2012. Summary statistics were used to describe demographic and clinical characteristics. OS was estimated with the Kaplan-Meier estimator. Fisher's exact test and the Wilcoxon rank sum test were used to compare pts surviving >3 yrs with those surviving <1 yr. **Results:** With a median follow-up of 2.2 years (range 0.06-13.2), 262 pts with advanced stage UPSC were identified. The probability of surviving >3 yrs was 0.462, >4 yrs was 0.310, and >5 yrs was 0.228. Thirty-six (14%) pts survived >3 yrs and 37 (14%) survived <1 yr. There was no difference in median age of pts surviving >3 yrs compared to pts surviving <1 yr (60 vs 66, p=0.21). There was also no difference between groups in demographics or medical history. There were several significant differences in pathologic and treatment variables between groups (Table). **Conclusions:** Though rare, long-term survival in advanced stage UPSC is associated with mixed histology, combination treatment including chemotherapy, and complete response to primary therapy. Further study of the molecular basis for these differences has the potential to improve survival for all pts with this disease.

	Survived > 3 yrs % (N=36)	Survived < 1 yr % (N=37)	P
Stage			0.0474
IIIA	19.4 (7)	5.4 (2)	
IIIB	5.6 (2)	0 (0)	
IIIC1	27.8 (10)	16.2 (6)	
IIIC2	22.2 (8)	18.9 (7)	
IVA	0 (0)	2.7 (1)	
IVB	25 (9)	51.4 (19)	
Histology			0.0407
Pure UPSC	27.8 (10)	43.2 (16)	
Clear Cell + UPSC	11.1 (4)	13.5 (5)	
Endometrioid + UPSC	33.3 (12)	32.4 (12)	
Undiff + UPSC	0 (0)	5.4 (2)	
Endometrioid + Clear Cell + UPSC	19.4 (7)	0 (0)	
Endometrioid + Undiff + UPSC	5.6 (2)	5.4 (2)	
Treatment			0.0017
Surgery + Chemo	69.4 (25)	40.5 (15)	
Neoadjuvant Chemo +/- Surgery	2.8 (1)	24.3 (9)	
Surgery + Radiation +/- Chemo	25 (9)	21.6 (7)	
Surgery			0.29
Suboptimal	5.6 (2)	5.4 (2)	
Optimal	80.5 (29)	54 (20)	
Treatment response			<0.001
Complete response	88.9 (32)	18.9 (7)	
Partial response	5.6 (2)	8.1 (3)	
Progressive disease	2.8 (1)	51.4 (19)	
Recurrence			0.0351
Yes	33.3 (12)	59.5 (22)	
No	66.7 (24)	40.5 (15)	

5597

General Poster Session (Board #53C), Mon, 8:00 AM-11:45 AM

Cridanimod and progestin therapy in hormone-resistant endometrial cancer.

Matthew J. Carlson, Koen De Geest, Xiaofang Wang, Kimberly K. Leslie, Donghai Dai; University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Cridanimod is a novel small molecule that has been shown to increase progesterone receptor (PR) expression in rat endometrium. We hypothesize that cridanimod, in combination with progestin therapy, will increase PR expression and, thus improve survival in a mouse model of advanced, high grade endometrial cancer. **Methods:** Hec50co cells, established in our laboratory to represent genetically and phenotypically type II endometrial cancer, were injected into the peritoneal cavity of 96 athymic mice. These mice were randomly divided into 6 groups, receiving the following therapies: control (no therapy), medroxyprogesterone acetate (MPA) alone, cridanimod 1mg IM twice a week plus MPA, cridanimod 3mg plus MPA, cridanimod 6mg plus MPA, and adenovirus-mediated PR expression plus MPA. PR expression in tumor tissue and serum interferon (IFN) levels were assayed via Western blot and ELISA, respectively. **Results:** Kaplan-Meier survival analysis showed that the group receiving MPA plus 6 mg cridanimod twice a week had a significantly longer survival time than the control or MPA alone (62 ± 7.0 days vs 38 ± 5 or 33 ± 3 , respectively, $p < 0.05$). The group with MPA plus 3 mg cridanimod had a significantly longer survival than the group with MPA alone (56 ± 8.0 days vs 33 ± 3 , $p < 0.05$). Western blot analysis showed that PR proteins were substantially higher in xenograft tumors from animals treated with cridanimod at doses of 3mg and 6mg when comparing to the control and MPA alone groups, ELISA data showed significant increases in IFN α and $-\beta$ in cridanimod-treated mice in a dose-dependent manner. **Conclusions:** Combined progestin and cridanimod therapy significantly improved survival of mice with high-grade, advanced endometrial cancer. Cridanimod significantly increased PR expression, suggesting that the therapeutic benefit of combined therapy is mediated by up-regulation of PR, which is likely to be mediated through cridanimod induction of IFN α and IFN β expression. Further investigation is warranted to determine the utility of this promising agent.

5598

General Poster Session (Board #53D), Mon, 8:00 AM-11:45 AM

Disseminated tumor cells in bone marrow of patients with endometrial and cervical cancer.

Florin-Andrei Taran, Markus Wallwiener, Andreas D. Hartkopf, Christina Walter, Sara Brucker, Ralf Rothmund, Bernhard Kraemer, Diethelm Wallwiener, Tanja N. Fehm; University of Tuebingen, Department of Gynecology and Obstetrics, Tuebingen, Germany; Department of Obstetrics and Gynaecology, University of Heidelberg, Heidelberg, Germany; Department of Gynecology and Obstetrics, University of Tuebingen, Tuebingen, Germany

Background: The presence of disseminated tumor cells (DTC) in the bone marrow (BM) of breast cancer patients is associated with poor prognosis. Several studies demonstrated that tumor cell dissemination may occur in gynecologic cancer and affect clinical outcome. The aim of our study was to evaluate the incidence of DTC and to assess their prognostic significance in patients with gynecologic malignancies. **Methods:** Bone marrow aspirates from 623 patients with primary endometrial (331), cervical (228), and vulvar cancer (64) undergoing surgery at the Department of Gynecology and Obstetrics, University Hospital, Tuebingen, Germany between November 2001 and May 2012, were included into the study. Disseminated tumor cells were identified by immunocytochemistry using the pancytokeratin antibody A45B/B3 and by cytomorphology. **Results:** Disseminated tumor cells were detected in 18% of BM aspirates from patients with gynecological malignancies. Incidences of DTC in endometrial, cervical, and vulvar cancer were 21%, 16% and 16%, respectively. The presence of DTC was associated with a lower tumor grade in endometrial cancer. For patients with vulvar cancer, no correlation with established clinicopathological factors was observed. In case of cervical cancer, BM positivity was correlated with International Federation of Gynecology and Obstetrics stage, nodal involvement and the presence of lymphangiosis carcinomatosa. For all analyzed tumor entities, no association between BM status and clinical outcome could be observed. **Conclusions:** Disseminated tumor cells are a common phenomenon in solid tumors. However, only in cervical cancer DTC positivity was associated with advanced disease. The consequences for DTC positive patients have to be determined.

5599

General Poster Session (Board #53E), Mon, 8:00 AM-11:45 AM

L1-CAM as a predictor of survival in endometrial cancer: An analysis of The Cancer Genome Atlas (TCGA).

Thanh Hue Dellinger, Charles Warden, Ernest Soyoung Han, Mark Tsuneo Wakabayashi; City of Hope National Comprehensive Cancer Center, Duarte, CA; City of Hope, Duarte, CA

Background: Despite a good survival rate for early-stage endometrial cancers (ECs), the prognosis for advanced-stage ECs remains poor, with no biomarkers and few therapeutic options currently in existence. L1-cell adhesion molecule (L1-CAM), a glycoprotein which functions in adhesion and migration of tumor cells, has been associated with a poor prognosis in Type I endometrial cancer (ASCO 2011 Abstract #5091). We evaluated the role of L1-CAM among both Type I and II ECs in TCGA. **Methods:** Partek Genomics Suit was used to define differentially expressed genes with p-values for clinical associations (ANOVA with linear contrast for discrete variables and linear regression for continuous variables). Differences in survival between “high” and “low” expression groups (defined by median expression) were compared using Cox regression analysis, with p-values calculated via log-rank test, using the ‘survival’ package in R. **Results:** Of 451 downloadable tumor samples, 335 tumors with both clinical and gene expression data were analyzed. Median age was 63 yrs. (range 31-90 yrs.). Stage I, II, III, and IV comprised 65%, 7%, 23%, and 5%, respectively. 82% were endometrioid; 16% (n = 52) serous. Grade 1, 2, and 3 comprised 24%, 27%, and 49%, respectively. Median follow-up was 19.5 months. High L1-CAM expression was found in older (p = 0.0005), suboptimally debulked (p=0.002), and African-American patients (p = 0.0003), and those with high grade (p = 0.008), serous histology (p <0.00001), higher stage (p = 0.0004), positive peritoneal cytology (p = 0.007), deep myometrial invasion (p = 0.02), and positive pelvic (p = 0.003) and para-aortic lymph nodes (p = 0.002). High L1-CAM expression was associated with poor survival with a median overall survival of 17.2 months compared to 21.3 months for low L1-expressing endometrial tumors (HR= 3.1, CI=1.3 -7.3, p = 0.007). **Conclusions:** L1-CAM expression is associated with poorer survival and high-risk clinicopathologic factors in endometrial cancer. Its prevalence in Type II ECs, such as high-grade, serous ECs, makes it a particularly attractive target for both novel biomarker discovery and therapeutic targeting.

5600

General Poster Session (Board #53F), Mon, 8:00 AM-11:45 AM

Preoperative risk assessment model for identification of lymph node metastasis in early cervical cancer.

Seung-Hyuk Shim, Dae-Yeon Kim, Shin-Wha Lee, Jeong-Yeol Park, Jong-Hyeok Kim, Yong-Man Kim, Young-Tak Kim, Joo-Hyun Nam; Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Background: The aim of this study was to develop a preoperative risk prediction model for lymph node metastasis in patients with early cervical cancer. **Methods:** The medical records of 504 patients with early cervical cancer who underwent hysterectomy and pelvic/para-aortic lymphadenectomy between 2007 and 2012 in our center were retrospectively reviewed. According to the order of surgery performed, data between 2007 and 2010 were allocated to a model development cohort (n=314), and data between 2011 and 2012 were allocated to an external validation cohort (n=190). By using preoperative clinicopathologic data, magnetic resonance imaging (MRI) data, and positron emission/computed tomography (PET/CT) data, a multivariate logistic model was created. Based on this model, predictive nomogram was developed and externally validated. **Results:** Age, tumor size measured by MRI, and lymph node metastasis on PET/CT were found to be independent risk factors for nodal metastasis. Developed nomogram incorporating these three predictors showed good discrimination and calibration, with a bootstrap-adjusted concordance index of 0.772. Also, the validation set showed good discrimination with a bootstrap-adjusted concordance index of 0.783. **Conclusions:** We have developed a robust model to predict lymph node metastasis in patients with early cervical cancer. This new tool may be useful to clinicians and patients when deciding lymphadenectomy and maybe useful in designing clinical trials.

Preoperative risk factors for lymph node metastasis by multivariate analysis.

	ORs	95% CI	P
Age (yrs)	0.972	0.946 - 0.999	0.042
Tumor size on MRI (cm)	1.40	1.179 - 1.662	<0.001
LNM on PET-CT	4.027	2.158 - 7.514	<0.001

ORs, odds ratios; CI, confidence interval; LNM, lymph node metastasis.

5601

General Poster Session (Board #53G), Mon, 8:00 AM-11:45 AM

Conservative management of young women with endometrial adenocarcinoma with grade 2-3 and/or superficial myometrial invasion.

Jeong-Yeol Park, Dae-Yeon Kim, Tae-Jin Kim, Jae Weon Kim, Jong-Hyeok Kim, Yong-Man Kim, Young-Tak Kim, Duk-Soo Bae, Joo-Hyun Nam; Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; Department of Obstetrics and Gynecology, College of Medicine, University of Ulsan, Seoul, South Korea; Department of Obstetrics and Gynaecology, Cheil General Hospital and Women's Healthcare Center, Kwandong University College of Medicine, Seoul, South Korea; Seoul National University College of Medicine, Seoul, South Korea; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: To estimate the oncologic and pregnancy outcomes after progestin treatment of young women with endometrial adenocarcinoma with grade 2–3 and/or superficial myometrial invasion. **Methods:** Medical records of 48 young women with endometrioid adenocarcinoma of the uterus with grade 2–3 and/or superficial myometrial invasion who were conservatively managed with oral progestin were reviewed. **Results:** Fourteen patients (29.2%) received daily oral megestrol acetate (median dose, 160 mg/day; range, 40–240 mg/day) and 34 (70.8%) received daily oral medroxyprogesterone acetate (median dose, 500 mg/day; range, 80–1000 mg/day). The median treatment duration was 10 months (range, 3–20 months). Complete responses were observed in 37 patients (77.1%) and the median time to complete response was 17 weeks (range, 9–51 weeks). Complete response rates were 76.5%, 73.9%, and 87.5% for patients with grade 2–3 without myometrial invasion (n=17), patients with grade 1 and superficial myometrial invasion (n=23), and patients with grade 2-3 and superficial myometrial invasion (n=8), respectively ($P = 0.731$). Their recurrence rates after a median follow-up time of 48 months (range, 7–136 months) were 23.1%, 47.1%, and 71.4%, respectively ($P = 0.104$). None experienced disease progression or died of the disease. Nine patients gave birth to 10 healthy babies. **Conclusions:** Progestin treatment is safe for patients with grade 2–3 without myometrial invasion and patients with grade 1 and superficial myometrial invasion. However, it should be provided on an individual basis and must be applied cautiously in patients with grade 2–3 and superficial myometrial invasion.

5602

General Poster Session (Board #53H), Mon, 8:00 AM-11:45 AM

Determination of the activated form of the progesterone receptor (PR) in endometrial cancer (EC).

Dinny Graham, Jacques Bosq, Jean-Michel Caillaud, Matthew A. Powell, Eric Leblanc, Keiichi Fujiwara, Thomas J. Herzog, Bradley J. Monk, Christine Clarke, Alexander A. Zukiwski, Erard M. Gilles, Robert L. Coleman; Westmead Institute for Cancer Research, Sydney Medical School – Westmead, Sydney, Australia; Institut Gustave Roussy, Villejuif, France; Biodosis, Paris, France; Washington University School of Medicine in St. Louis, St. Louis, MO; Centre Oscar Lambret, Lille, France; Saitama Medical University International Medical Center, Saitama, Japan; Columbia University Cancer Center, New York, NY; Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ; Westmead Institute for Cancer Research, Sydney Medical School, University of Sydney, Sydney, Australia; ARNO Therapeutics, Flemington, NJ; Invivis Pharmaceuticals, Bridgewater, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Endocrine treatments, in general have limited clinical efficacy in endometrial cancer. Upon ligand binding, PRs in normal tissue form discrete focal subnuclear distribution patterns (FDP), which are associated with DNA transcription. FDP are indicative of functionally activated PRs (APRs), and are observed in EC, independently of menopausal status. The feasibility of using an IHC technique to characterize the PR functional status has previously been reported in breast cancer and the APR phenotype in cell lines correlates with anti-progestin activity. The goal of this study is to determine if APR can be identified in EC and to determine if this IHC technique & APR phenotype could be developed as a companion diagnostic to predict anti-progestin efficacy in patients with EC. **Methods:** 72 archived primary EC specimens were processed with standard IHC for estrogen receptor (ER), PR & proliferation (Ki67). APR status was determined using commercially available antibodies specific to the A and B isoforms of the PR (PRA and PRB) with standard microscopy at 1000x magnification. **Results:** 56 (78%) tumors were of endometrioid histology. Endometrioid tumors were ER⁺ (68%) and PR⁺ (84%). Two PR nuclear distribution patterns were observed: an aggregated pattern (A) which is indicative of APR and a diffuse or finely granular pattern (D) indicative of an inactivated PR. This resulted in three tumor phenotypes: A cells only, D cells only, and a mix of A + D cells. APR was defined as any tumor with more than 5% A cells. An average of 49% of tumor cells were positive with PRA, 35% were positive for PRB. APR was present with PR A in 41% and with PR B in 47% of the PR⁺ endometrioid tumors. The APR status, for both PR A and PR B, was independent of PR positivity rate, PR staining intensity score and % Ki67 positive. APR^{pos} phenotype was associated with a lower % ER^{pos} staining. When observable, endometrial stromal and normal cells were PR positive (D pattern). **Conclusions:** APR can be identified using either PRA or PRB, in ~50 % of the EC samples; there was a pattern consistent with the presence of APR positive cells. The IHC technique to identify APR has the potential to be developed as companion diagnostic as a potential predictor of anti-progestin efficacy.

5603

General Poster Session (Board #54A), Mon, 8:00 AM-11:45 AM

Neoadjuvant chemotherapy followed by chemoradiation in selected locally advanced squamous cervical cancer.

Juan Fernando Cueva, Nieves Martinez Lago, Maria Vieito, Ezequiel Gonzalez Patino, Maria Teresa Curiel Garcia, Nuria salvador Garrido, Patricia Palacios Ozores, Sonia Candamio, Rafael López López; Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain; Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain; Translational Oncology Laboratory, Medical Oncology Department, Santiago de Compostela, Spain; Hospital Clínico de Santiago de Compostela, Santiago de Compostela, Spain; Hospital Clínico Universitario Santiago, Santiago de Compostela, Spain

Background: Although there has not been a direct comparison between neoadjuvant chemotherapy followed by chemoradiation with chemoradiation alone, neoadjuvant chemotherapy is active in squamous cervical cancer. **Methods:** In this one arm phase II trial we accrued 25 patients from 2007 to 2012 diagnosed with squamous cervical cancer deemed poor candidates to initial chemoradiation (decided by a multidisciplinary committee). Patients had > 18 years of age, PS 0-1, adequate organ function and gave informed consent. They received neoadjuvant paclitaxel and cisplatin (80 and 33 mg/m² respectively) on days 1,7, 15 of every 28 for two cycles and then external radiation in 1.8 Gy/ fraction with concurrent weekly cisplatin 40 mg/m² followed by brachytherapy in 5-6 applications. Dose intensity and toxicity was accrued, and both after neoadjuvant and chemoradiation patients were evaluated by RECIST 1.1 criteria for response with CT scan and pelvic MNR. **Results:** Baseline characteristics of the patients are listed in Table. 24 patients were evaluable for efficacy and safety. Response rate after neoadjuvant chemotherapy was 84 % (complete and partial responses in 24 and 60% of patients, respectively), without progression disease. Response rate after radiochemotherapy was 93 % (complete and partial responses in 52 and 41% of patients, respectively). After a mean of 29 months of follow up, 11 patients (45%) thus far have developed recurrent disease. Median progression-free survival and overall survival were 33 (23- 42) and 34+ m (29 – not reached). Treatment was well tolerated, without toxicities grade 3-4. **Conclusions:** Our weekly cisplatin-paclitaxel neoadjuvant regimen has been feasible and very effective in terms of dose delivery, tolerance and radiological responses without compromising definitive treatment with chemoradiation. If this approach is superior than the standard chemoradiation alone in this population should be explored in a randomized trial.

Baseline characteristics of the patients	N
Age	
Median (range)	51 (27 – 72)
ECOG PS	
PS0 / PS1	1 / 24
Stage	
Ib2 bulky / IIb / IIIb / IIIc / IVa	1 / 10 / 7 / 4 / 3

5604

General Poster Session (Board #54B), Mon, 8:00 AM-11:45 AM

Racial disparities in cervical cancer mortality over time.

Jose Alejandro Rauh-Hain, Marcela G del Carmen, John O. Schorge, David M. Boruta, Whitfield Board Growdon, Annekathryn Goodman, Rachel Marie Clark, Leslie Siriya Bradford, Joel Clemmer; Massachusetts General Hospital, Boston, MA

Background: The aim of this study is to examine changes over time in survival for African-American (AA) and white women diagnosed with cervical cancer (CeCa). **Methods:** Surveillance, Epidemiology, and End Results (SEER) Program data 9 for 1983-2007 were used for this analysis. Kaplan-Meier and Cox proportional hazards survival methods were used to assess differences in survival by race at 5-year intervals. **Results:** The study included 23,722 women; including 19,777 whites and 3,945 AA. AAs were older (51.4 vs. 49 years; $p < 0.001$), had a higher rate of regional (38.3% vs. 31.7; $p < 0.001$) and distant metastasis (10.5% vs. 8.5; $p < 0.001$). AAs received less frequently cancer-directed surgery (53.1% vs. 65.7%; $p < 0.001$), and more frequently radiotherapy (56.9% vs. 47.3%; $p < 0.001$). AAs had a hazard ratio (HR) of 1.40 (95% CI, 1.31-1.49) of CeCa mortality compared to whites. Adjusting for SEER registry, marital status, stage, age, surgery, radiotherapy, grade and histology, AA women had a HR of 1.15 (95% CI, 1.07-1.24) of CeCa related mortality. AAs had a higher HR of all cause mortality and CeCa related mortality for all the five-year diagnosis cohorts (Table). After adjusting for the same variables, there was a significant difference in survival in the 1988-1992 group (HR 1.26; 95% CI 1.09-1.47). **Conclusions:** The present data indicates significant survival differences by race for women with invasive CeCa. After adjusting for SEER registry, marital status, stage, age, surgery, radiotherapy, grade and histology, only between 1988-1992 there was a difference in survival between the groups.

Year diagnosis	N	All-cause mortality, HR		Cervical cancer mortality, HR	
		Unadjusted	Adjusted	Unadjusted	Adjusted
1983-1987	4,887	1.48 (1.35-1.61)	1.11 (1.00-1.23)	1.51 (1.32-1.73)	1.12 (0.96-1.30)
1988-1992	5,280	1.57 (1.43-1.72)	1.28 (1.16-1.42)	1.47 (1.29-1.69)	1.26 (1.09-1.47)
1993-1997	4,958	1.55 (1.29-1.72)	1.22 (1.08-1.37)	1.39 (1.20-1.61)	1.15 (0.97-1.35)
1998-2002	4,557	1.44 (1.29-1.62)	1.17 (1.03-1.34)	1.29 (1.10-1.51)	1.08 (0.90-1.28)
2003-2007	4,040	1.29 (1.21-1.59)	1.05 (0.90-1.23)	1.28 (1.09-1.51)	1.03 (0.85-1.25)
All years	23,722	1.49 (1.43-1.57)	1.18 (1.12-1.24)	1.40 (1.31-1.49)	1.15 (1.07-1.24)

5605

General Poster Session (Board #54C), Mon, 8:00 AM-11:45 AM

Impact of socioeconomic status and degree of ethnic isolation on cervical cancer incidence among Hispanics and Asians in California.

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Background: The incidence of cervical cancer in the United States has declined since the introduction of the pap smear. However, differences exist based on ethnicity and socioeconomic status (SES). This study aimed to evaluate the impact of nativity, neighborhood SES and enclave (degree of ethnic isolation) on the incidence of cervical cancer in California. **Methods:** Using data from the California Cancer Registry, comprising three of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program registries, information on all primary invasive cervical cancer diagnosed in California from January 1, 1990, through December 31, 2004 was obtained. We analyzed the influence of enclave, SES, and nativity on cervical cancer incidence. **Results:** Among the 22,189 invasive cervical cancer cases diagnosed between 1990 and 2004, 50% were non-Hispanic white (NHW), 39% Hispanic and 11% Asian women. Seventy percent (70%) of the invasive cervical cancer cases were squamous cell carcinoma (SCC), 19% were adenocarcinoma and 11% other histologies. Approximately half (51%) of patients presented with localized disease, 33% regional disease, 10% distant disease and 6% unknown. By ethnic group, US born women showed lower rates of SCC compared to foreign-born women. Seventy-six percent (76%) of invasive cervical cases were observed in high enclave neighborhoods, and seventy percent (70%) were noted in low SES neighborhoods. Hispanics living in low SES and high enclave had 12.7 times (95% CI; 11.2-14.3) higher rate of cervical cancer than those living in high SES, low enclave neighborhoods. For Asian women incidence rates were 6 times (95% CI; 4.9-7.5) higher in the low SES, high enclave neighborhoods compared to those living in high SES, low enclave neighborhoods. **Conclusions:** More efforts should be done to reach out to and increase pap smear screening for women living in high enclave neighborhoods to help decrease the incidence of invasive cervical cancer cases in these groups of women.

5606

General Poster Session (Board #54D), Mon, 8:00 AM-11:45 AM

Male workers' influence on partners uptake of pap smear screening in a teaching hospital in Nigeria.

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Background: Cervical cancer remains a major global health issue still claiming the lives of African women despite the availability of screening facilities. Male involvement has paid off in enhancing uptake of contraception in Africa as reported by several empirical studies. It may be worthwhile in encouraging women uptake of the screening services. This formed the basis for this study. **Methods:** The study adopted a cross sectional descriptive survey that involved 350 respondents. Their involvement was assessed using a structured questionnaire with cronbach reliability coefficient of 0.78. The study was analyzed using SPSS version 16 by computing the frequency, means and standard deviations. Chi-square was employed to test the significance of associations at $p < 0.05$. **Results:** The results showed that all ($n = 350$) male medical staff of the hospital were aware about cervical cancer and pap smear screening test for premalignant lesions of the cervix compared to 90% and 77% observed in paramedics and non-medical groups respectively. At least, an episode of Pap smear screening test had been done by the partners of 52.4% of the medical staff; while only 30.2% and 13% of the partners of paramedics and non-medical workers respectively had undergone the test. Among those whose partners had participated in screening; 78.9% ($n = 95$) of the men initiated the screening. Eighty two percent (82%, $n = 95$) paid for their wives' transportation while 78.9% ($n = 95$) have at least once followed their partners to the screening centre. Chi square result showed that men with higher level of education are likely to support their partners to participate in screening for cervical cancer ($p < 0.005$). There was no significant association between religion and male support for Pap smear uptake ($p < 0.407$). **Conclusions:** The study showed that the medical male workers were more involved in facilitating partners screening for cervical cancer. This may not be unconnected with their knowledge of the consequences of late identification of the disease. The study therefore concluded that knowledge of cervical cancer and its consequences by men will enhance their involvement in encouraging partners to utilize screening facilities.

5607

General Poster Session (Board #54E), Mon, 8:00 AM-11:45 AM

Long-term survival following robot-assisted surgical treatment of early cervical cancer.

Amanda Lynn Jackson, Joshua Kilgore, Emily Meichun Ko, Renatta Craven, Paola A. Gehrig, John T. Soper, John Boggess; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: To determine progression-free survival (PFS) and overall survival (OS) for patients with early stage cervical cancer surgically treated using robotic-assisted laparoscopy compared to open radical hysterectomy. **Methods:** A retrospective analysis of women that underwent a robotic-assisted surgery (RAS) for early stage cervical cancer was performed. Surgical procedures included radical hysterectomy, parametrectomy, and trachelectomy from 2005 to May 2012. Patient demographics, clinicopathologic data, and disease status were analyzed. Comparison was made to open radical hysterectomies (ORH) from 2000 to May 2012. Survival statistics were analyzed using the Kaplan-Meier method. **Results:** 147 patients underwent RAS; 97 patients underwent ORH in our comparison group. Surgery was aborted in 8 RAS and 5 ORH due to extent of disease. The robotic surgical treatments included 121 (82.3%) radical hysterectomies, 14 (9.5%) trachelectomies, and 12 (8.2%) parametrectomies. In the RAS, the mean age was 44.3 (range 17-75); the mean body mass index (BMI) was 27.7 (range 16-50). Most patients presented with clinical stage IBI disease (79.9%). Squamous cell histology was most common (55.4%) followed by adenosquamous (36.7%). No significant differences were found between the RAS and ORH with regards age, BMI, surgical stage, grade, short and long-term complications, and comorbidities. The mean follow up time was 24.7 (range 0-82.1) months. Recurrence was documented in 3 patients after RAS and 11 patients after ORH; 3 deaths were recorded in the RAS group and 10 in the ORH. One patient had persistent adenocarcinoma in situ after robotic trachelectomy. Compared to ORH, there was a significantly better PFS in RAS (HR .312, CI 0.099-0.98, $p = 0.046$) while no difference was seen in OS ($p = 0.172$). **Conclusions:** The results demonstrate that RAS is associated with lower rates of recurrence and no difference in overall survival. These findings provide further evidence that robotic-assisted surgical treatment is not associated with inferior results when compared to laparotomy or traditional laparoscopy. As robotic-assisted surgery is associated with a less steep learning curve, it may become the surgical approach of choice.

5608

General Poster Session (Board #54F), Mon, 8:00 AM-11:45 AM

Longitudinal quality of life (QOL) and sexual functioning in women undergoing pelvic exenteration for gynecologic malignancies.

Pamela T. Soliman, Charlotte C. Sun, Shannon Neville Westin, Lois M. Ramondetta, Diane C. Bodurka, Andrea Bradford; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pelvic exenteration (PE) is en bloc resection of the pelvic organs including bladder, vagina, and rectum to treat central recurrence of a gynecologic malignancy. While this procedure has high morbidity, it is the only option for cure in some patients. The goal of this study was to assess QOL and sexual functioning in women who underwent PE with vaginal and/or bladder reconstruction. **Methods:** All patients were enrolled prior to PE. Surveys included the SF-12 (functional status), BIS (body image), SAQ (sexual functioning), SWD (satisfaction with decision), CES-D (depression), Stoma QOL, and DUFSS completed preoperatively (preop) and post-operatively at 4-6 wks, 6 mo, 1 yr, and 2 yrs. Descriptive statistics, chi-square, Mann-Whitney, and Kruskal Wallis tests were used to evaluate the data. **Results:** Between 2008 and 2012, 39 women participated. Median age was 56.7 yrs. Mean physical functional status scores (SF-12) declined through 6 mo postop, with improvements at 1 and 2 yrs ($p=.002$) but did not reach preop levels. SF-12 mental functioning scores declined immediately postop but returned to baseline by 6 mo. BIS was significantly worse at 1ys ($p=0.02$) and 2 yrs ($p=0.025$). Mean depression (CES-D) scores decrease but remained above the clinical cutoff of 17 at 6 mo. Poor sexual function was noted preop and did not improve. High scores for social support (DUFSS) remained constant. Stoma QOL improved in the first 2 yrs but not significantly. Pts reported high satisfaction with the decision to undergo PE, which did not change over time. **Conclusions:** While a majority of women remained satisfied with their decision to undergo PE, the procedure was associated with depression, worsening physical functioning and poor body image despite stable social support. Interventions are currently under development to improve QOL in this patient population.

	Preop	4-6 wks	6 mo	1 yr	2 yrs
BIS (0-30)	3	n/a	10.5	15	16.5
CES-D (0-60)	21	n/a	18	15.5	
DUFSS (0-40)	39	n/a	40	37	39.5
Stoma QOL (20-80)	n/a	50	52	54	56.5
SWD (0 - 36)		30	29	29	30
SAQ Pleasure (0-18)	3	n/a	n/a	1.5	8
Discomfort (0 to 6)	3			3	5
SF-12 Physical function (0-100)	45.3	32.6	31.5	38.7	34.4
Mental function (0-100)	41.1	37.2	41.7	38.3	41.4

5609

General Poster Session (Board #54G), Mon, 8:00 AM-11:45 AM

Adjuvant radiation therapy in node-positive vulvar cancer.

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Background: Adjuvant radiation (RT) has been demonstrated to improve overall survival (OS) in vulvar cancer patients with 2+ positive lymph nodes, but its role in patients with one positive lymph node is uncertain. We report on the largest and longest study of survival in patients with and without radiation following surgery in patients with vulvar cancer. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified node-positive women with squamous cell carcinoma of the vulva treated with and without external beam radiation following surgery. The Kaplan-Meier approach, log-rank tests and Cox modeling assessed OS. **Results:** All results are listed as women without vs with adjuvant radiation. From 1988 – 2008, 420 patients received surgery alone vs 753 women who received adjuvant radiation. Patient characteristics were well balanced across cohorts, including tumors \leq or $>$ than 2 cm ($p = 0.31$), grade ($p = 0.41$), marital status ($p = 0.20$), provider type ($p = 0.49$), and AJCC stage ($p = 0.35$). Both groups also had similar incidence of biopsy of any kind ($p = 0.40$), lymph node dissection ($p = 0.77$), median number of nodes excised ($p = 0.12$), and type of surgery ($p = 0.49$). Median age (75 vs 70 y, $p < 0.01$) and race (94% vs 89% white, $p = 0.01$) were adjusted using Cox regression. Median survivor follow-up was 45 m (range 0 - 236 m). Adjuvant radiation was associated with survival across all node-positive patients (22 vs 29 m, $p < 0.01$), as well as in the subset of women with just one positive lymph node (37 vs 70 m, $p < 0.01$) or 2+ positive lymph nodes (14 vs 18 m, $p < 0.01$). On multivariable Cox regression, adjuvant radiation (95% CI 0.85 - 0.96), diameter (CI 1.28 - 2.01), marital status (CI 0.65 - 0.93), the number of positive nodes (CI 1.06 - 1.11), and the ratio of positive-to-excised nodes (CI 1.61 - 2.98) were all associated with survival ($p < 0.01$ for each). **Conclusions:** The largest cohort study of node-positive squamous cell carcinoma of the vulva suggests adjuvant radiation is associated with OS. Studies have reported that adjuvant radiation may provide a survival benefit in women with 2+ positive lymph nodes. Our findings suggest patients with one positive lymph node also may benefit from adjuvant radiation.

5610

General Poster Session (Board #54H), Mon, 8:00 AM-11:45 AM

Comparing intensity modulated radiotherapy and conventional external beam radiotherapy in cervical cancer.

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Background: To compare Intensity-modulated radiation therapy (IMRT) with conventional external beam radiation therapy (CXRT) regarding morbidity, tumor response, and quality of life (QOL) in cervical cancer patients. **Methods:** Between 8/2009-2/2010, 50 patients (pts) with age range 20-85, with FIGO Stage IIA-IIIB were prospectively randomized 2:1 to CXRT and IMRT at Indo-American Cancer Institute. Both groups received concurrent chemotherapy (weekly cisplatin 30-40mg/m²) with external beam radiation (EBRT), 50Gy/25fractions followed by intracavitary brachytherapy at 21Gy/3fractions. Complications and QOL were evaluated during treatment and in follow-up with CTC 4.0 and EORTC QLQ-C30, and disease recurrence was based on pelvic exam. Analysis used Chi square(χ^2) at a significance level of 0.05. **Results:** Average time to completion was 49 and 48 days in CXRT and IMRT arms ($p > .05$). Four pts did not complete the treatment in the CXRT. Two months after completion 31/35 (89%) of CXRT and 15/15 (100%) of IMRT had complete response ($p > .05$). At 5 months, 30/35 (86%) of CXRT, and 14/15 (100%) of IMRT had no loco-regional disease (LRD); 1 IMRT pt died from distant metastasis (DM). At 18 months, 25/35 (72%) in CXRT and 14/15 (93.5%) in IMRT had no LRD or DM. Most common acute side effects in the CXRT were Grade 1 vomiting/cystitis/diarrhea and Grade 2 nausea/skin reactions/proctitis. One pt developed vesicovaginal fistula (VVF) after 50Gy by EBRT. Most common acute side effects in the IMRT were Grade 1 nausea/vomiting/cystitis/proctitis/diarrhea. Two pts had grade 3 neutropenia in the 5th week of RT. QOL was better in IMRT ($p < .01$) based on functional, symptom, single items, and global scales except for pain, insomnia, loss of appetite. Diarrhea, financial problems were worse in the CXRT ($p < .05$). Chronic complications such as radiation induced proctitis in 5 patients, and sub-acute intestinal obstruction in 2 patients during follow-up period in CXRT vs. IMRT ($p < 0.001$). **Conclusions:** IMRT is superior to CXRT with fewer chronic side effects and similar acute side effects and treatment responses. This is the first randomized clinical trial of these treatments in cervical cancer.

5611

General Poster Session (Board #55A), Mon, 8:00 AM-11:45 AM

Vulvar cancer: Presentation and treatment variation among races.

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Background: Vulvar cancer is the fourth most common gynecologic malignancy. We analyzed variation among races in treatment, histology and stage at presentation using the National Cancer Database (NCDB). **Methods:** Between 2000 and 2010, 51,157 women from 1338 hospitals across the US were reported to the NCDB with vulvar cancer. Differences were assessed using Chi square analysis. **Results:** Caucasian patients with vulvar carcinoma in situ received no first course treatment significantly less than African American or Hispanic patients (3% vs 6% and 7%, $p<0.05$). No treatment for stage I and II vulvar cancer was also significantly less than African American patients (1.4% vs 2.5%, $p<0.05$). African Americans overall chose radical surgery less often than Caucasians (13% vs 16%, $p<0.05$), but local tumor excision more (29% vs 24%, $p<0.05$). African Americans and Hispanics chose no surgery of primary sites significantly more than Caucasians (14% and 15% vs 9%, $p<0.05$). As expected, squamous cell carcinoma accounts for over 90% of vulvar cancer cases reported. However, Asian-Pacific Islanders had a significantly higher proportion of Extramammary Paget's disease when compared to Caucasians, African Americans, or Hispanics (20% vs 4.3%, 0.6%, 3.2%. $p<0.05$). African Americans had the lowest proportion of Extramammary Paget's compared to any other race for all stages (0.6%, $p<0.05$). African Americans presented as vulvar carcinoma in situ more often than any other race (33% vs 25-29%, $p<0.05$). **Conclusions:** This is the largest study analyzing racial differences in treatment, histology and stage at presentation in women with vulvar cancer. Caucasians were least likely to opt for no first course treatment overall. African Americans were most likely to choose no treatment and, when having surgery, preferred local excision over radical vulvectomy.

TPS5612

General Poster Session (Board #55B), Mon, 8:00 AM-11:45 AM

A phase I/II study of the vascular disrupting agent BNC105P in combination with gemcitabine-carboplatin in partially platinum-sensitive ovarian cancer patients in first or second relapse: An international collaborative group trial of ANZGOG and HOG.

Danny Rischin, Daniela Matei, Jeffrey C. Goh, Michelle Margaret Vaughan, Philip James Beale, Meaghan Elizabeth Tenney, Julie Martyn, Dirkje Willemien Sommeijer, Jose Luis Iglesias, David C. Bibby, Jeremy Simpson, Elizabeth E. Doolin, Corinne E. Williams, Martin R. Stockler, Australia New Zealand Gynaecological Oncology Group (ANZGOG); Peter MacCallum Cancer Centre, Melbourne, Australia; Indiana University School of Medicine, Indianapolis, IN; Royal Brisbane and Women's Hospital, Brisbane, Australia; Christchurch Hospital, Christchurch, New Zealand; Sydney Cancer Centre, Sydney, Australia; University of Chicago Medical Center, Chicago, IL; NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia; Bionomics Ltd., Thebarton, Australia; Hoosier Oncology Group, Indianapolis, IN

Background: BNC105P is a tubulin polymerization inhibitor and a vascular disrupting agent (VDA). In vivo exposure to BNC105P leads to selective damage of tumor vasculature in both primary and metastatic lesions, causing disruption of blood flow to tumors, hypoxia, and associated tumor necrosis. BNC105P also has a direct anti-proliferative action on cancer cells, including ovarian cancer cell lines. Pre-clinical data has demonstrated synergistic activity of BNC105P when combined with platinum or with gemcitabine, supporting the proposed study design. This study will determine the safety and efficacy of BNC105P in ovarian cancer when used in combination with gemcitabine-carboplatin. The target population is women with ovarian or primary peritoneal cancers who progressed 4 to 9 months after first-line platinum based chemotherapy, or 4 to 12 months after second line platinum based chemotherapy. **Methods:** A single arm phase I will be used to determine the phase II dose for the triplet combination (3-6 subjects per dose level, maximum of 24 subjects). Four dose levels of BNC105P (12-16 mg/m²) and gemcitabine (800-1000 mg/m²) will be assessed. The dose of carboplatin will be set at AUC 4. Enrolment to cohort 2 started in January 2013. The phase II component will consist of a 2-arm, randomized (1:1) study of BNC105P, gemcitabine and carboplatin versus gemcitabine and carboplatin alone. The primary endpoint for the phase II trial is objective response rate (ORR, according to RECIST 1.1 and/or GCIG CA125 criteria. An ORR of 40% or more with the experimental regimen would be considered worthy of further investigation, assuming an ORR of 20% with the control regimen. 110 phase II participants are planned (N = 55/arm). Treatment allocation will be balanced using minimization for the study site, target lesions according to RECIST (present vs. absent), progression free interval from last platinum based chemotherapy regimen (<6 months vs 6 months or more), and first relapse vs. second relapse. Biomarker (tissue and blood-borne) sampling and PK analysis will also be undertaken. Clinical trial information: NCT01624493.

TPS5613

General Poster Session (Board #55C), Mon, 8:00 AM-11:45 AM

A randomized double-blind phase III trial comparing vintafolide plus pegylated liposomal doxorubicin (PLD) versus PLD plus placebo in patients with platinum-resistant ovarian cancer (PROCEED).

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Background: Folate receptor (FR) is expressed on the majority of epithelial ovarian cancers and FR expression appears to be a negative prognostic factor in this setting. Vintafolide (EC145) is a folate-conjugate designed to selectively deliver desacetylvinblastine monohydrazide (DAVLBH) to FR-expressing cells. ^{99m}Tc -Etarfolatide (EC20) is a technetium-labeled folate that identifies FR-expressing tumors. In a phase 2 study comparing vintafolide + PLD with PLD alone, the combination demonstrated a statistically and clinically significant delay in PFS (5.0 months) compared with PLD alone (2.7 months) in women with platinum-resistant ovarian cancer (Naumann et al, ASCO 2011). Data also indicated that ^{99m}Tc -etarfolatide may have utility for selecting patients most likely to benefit from vintafolide therapy. **Methods:** This is an international, randomized, double-blind, placebo-controlled phase 3 study of PLD \pm vintafolide therapy compared in patients with primary or secondary platinum-resistant ovarian cancer (NCT01170650). Key eligibility criteria include: ≥ 18 years, pathology-confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma, prior platinum-based chemotherapy, a RECIST v1.1 measurable lesion, and ECOG performance status 0 or 1. At baseline, patients undergo ^{99m}Tc -Etarfolatide imaging to identify FR-positive lesions and are subsequently randomized to the vintafolide \pm PLD. PLD (50 mg/m^2) adjusted for Ideal Body weight is administered on day 1 of a 4-week cycle and treatment continues until the maximum allowable cumulative dose (550 mg/m^2) is reached or until disease progression or intolerable toxicity. Vintafolide (2.5 mg) or placebo is administered on days 1, 3, 5, 15, 17, and 19 of a 4-week cycle and treatment can continue for up to 20 cycles or until unacceptable toxicity or disease progression. The primary objective is to assess PFS based on investigator assessment (RECIST v1.1) in FR positive patients. Secondary objectives include OS, safety/tolerability, overall response rate, and disease control rate. Enrollment to the study is currently ongoing. Clinical trial information: NCT01170650.

TPS5614

General Poster Session (Board #55D), Mon, 8:00 AM-11:45 AM

PARAGON: Phase II study of aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic gynecologic neoplasms: ANZGOG 0903.

Michael Friedlander, Katrin Marie Sjoquist, Dirkje Willemien Sommeijer, Lisa Bailey, Julie Martyn, Kim Gillies, Linda R. Mileskin, Rachel O'Connel, Val Gebbski, Michelle Margaret Vaughan, Penny Blomfield, Philip James Beale, Michael Quinn, Martin R. Stockler, Janine Margaret Lombard, Alison Maree Hadley, Frederic Amant, Richard J Edmondson, Australia New Zealand Gynaecological Oncology Group; Prince of Wales Hospital, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia; Peter MacCallum Cancer Center, Melbourne, Australia; Christchurch Hospital, Christchurch, New Zealand; Royal Hobart Hospital, Hobart, Australia; Sydney Cancer Centre, Sydney, Australia; Royal Women's Hospital, Melbourne, Australia; Calvary Mater Hospital, New Castle, Australia; Royal Brisbane and Women's Hospital, Brisbane, Australia; University Hospitals Leuven, Leuven, Belgium; Northern Institute for Cancer Research, Newcastle Upon Tyne, United Kingdom

Background: Many gynaecological cancers of different pathological type express estrogen and/or progesterone hormone receptors (ER/PR). Reports of tumour response and clinical benefit with hormonal therapies show variable rates of activity. There is a need to prospectively study the role of aromatase inhibitors in women with potentially hormone responsive recurrent gynaecological cancers to establish response rates, clinical benefit, quality of life (QoL) and identify predictors of response. **Methods:** PARAGON is phase II Gynecologic Cancer InterGroup trial lead by the Australia New Zealand Gynaecological Oncology Group, Cancer Research UK and the Belgian Gynaecological Oncology Group. The study is designed to facilitate research in rare tumours. The protocol allows postmenopausal women with recurrent gynaecological cancers to enrol into one of 7 subgroups; epithelial ovarian cancer (EOC) with only rising CA125 after first line chemotherapy, platinum resistant/refractory EOC, low grade EOC, endometrial carcinomas, endometrial stromal sarcomas, miscellaneous sarcomas and granulosa cell tumours and other sex cord stromal tumours. ER/PR positivity must be confirmed by immunohistochemistry. Each subgroup will enrol 25-50 patients with defined stopping rules based on response and reviewed by independent data monitoring committee (IDMC). Eligible patients receive 1 mg anastrozole daily until disease progression or unacceptable toxicity. Primary objective: clinical benefit (partial or complete response or stable disease). Secondary objectives: progression free survival, response duration, QoL, toxicity. Blood and tumour samples are being collected for translational studies and confirmation of ER/PR positivity. Recruitment commenced in 2011 in Australia, New Zealand and the United Kingdom. One hundred and fourteen of 350 planned patients have been enrolled to January 2013. In November 2012 IDMC recommended continuing recruitment to the EOC with rising Ca125 only and resistant/refractory subgroups based on review of activity outcomes for the first 25 patients. The trial will open in Belgium in April 2013. ACTRN12610000796088 Clinical trial information: 12610000796088.

TPS5615

General Poster Session (Board #55E), Mon, 8:00 AM-11:45 AM

Phase II clinical trial of six mercaptopurine (6MP) and methotrexate in patients with BRCA-defective tumors.

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Background: *BRCA1* and *BRCA2* genes are critical in homologous recombination DNA repair and have been implicated in familial breast and ovarian cancer tumorigenesis. Tumor cells with these mutations demonstrate increased sensitivity to cisplatin and poly(ADP-ribose) polymerase (PARP) inhibitors. 6MP was identified in a screen for novel drugs and found to selectively kill BRCA-defective cells in a xenograft model as effectively as the PARP inhibitor, AGO14699, even after these cells had acquired resistance to a PARP inhibitor or cisplatin (Issaeva 2010). Exploiting the genetic basis of these tumours enables us to develop a more tailored approach to therapy for patients with BRCA mutated cancers. This multi-center phase II single arm trial was set up to investigate the activity and safety of 6MP with methotrexate in patients with breast or ovarian cancer who are known to have a BRCA mutation. **Methods:** Two-stage Simon compromise design (Jung 2001, Jung 2004) with $\alpha=0.20$, power=90% to detect an increase in activity from 10 to 20%. 1st stage: if $\leq 3/30$ evaluable patients respond at 8 weeks the trial will be stopped for futility; 2nd stage: if $\geq 9/65$ evaluable patients respond at 8 weeks the treatment will be regarded as potentially effective and a phase III trial will be considered if the treatment appears safe and well-tolerated. 65 patients with BRCA defective cancer progressing after at least one prior chemotherapy or relapsed platinum resistant ovarian cancer, ECOG performance status 0-2 will be recruited and treated with daily 6MP (75mg/m²) and weekly methotrexate (20mg/m²) until progression. The starting dose was later reduced by 25% due to excess of expected toxicity. Patients with low TPMT activity or a low/low genotype are excluded due to the risk of increased toxicity. Prior treatment with a PARP inhibitor is permissible. Primary outcome: objective response at 8 weeks: complete, partial response or stable disease defined by RECIST 1.1. Secondary outcomes include safety, PFS, OS and quality of life. Of the 46 patients screened for TPMT activity between 15 Jun2009 and 05Dec 2012 from 12 UK sites, 31 patients were recruited. The pre-specified activity goal for the 1st stage was met and accrual into the 2nd stage continues. Clinical trial information: 2009-016846-16.

TPS5616

General Poster Session (Board #55F), Mon, 8:00 AM-11:45 AM

Dovitinib as second-line therapy in patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or non-mutated advanced and/or metastatic endometrial cancer (EC): A single-arm, multicenter, phase II study.

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Background: Despite the use of combination chemotherapy and introduction of novel targeted agents, the prognosis for advanced and/or metastatic EC is challenging. The occurrence of somatic activating FGFR2 mutations in EC suggests an opportunity for testing FGFR inhibitors. Dovitinib (DOV) is a potent receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor and FGFR. The objective of the study is to investigate the efficacy and safety of DOV as second-line therapy in patients (pts) with advanced and/or metastatic EC. **Methods:** This multicenter, non-randomized, open label, single-arm, phase II study (NCT01379534) will enroll adult female pts (N~80) with either FGFR2 mutated (group 1) or non-mutated (group 2) histologically confirmed advanced and/or metastatic EC, who have documented radiological evidence of progressive disease (RECISTv1.1) after 1 prior line of chemotherapy, excluding adjuvant therapy. Eligible pts also need to have ≥ 1 measurable lesion (RECISTv1.1) and ECOG performance status ≤ 2 . Pts will receive oral DOV of 500 mg/day, on a 5-days-on / 2-days-off dosing schedule until disease progression, unacceptable toxicity, death, or discontinuation due to any other reason. Primary endpoint is 18-week progression-free survival (PFS) rate (local review; RECIST v1.1) and secondary endpoints include overall response rate, disease control rate, duration of response, PFS, overall survival, safety, tolerability, pharmacokinetics, and pharmacodynamic effect of DOV on soluble plasma biomarker expression level. A 2-stage design with Bayesian interim monitoring (interim for futility analyses) will be used in each group. For stage 1, 20 pts will be enrolled into each group. If ≥ 8 of the first 20 pts with measurable disease at baseline in either group are progression-free after 18 weeks of treatment, 20 additional pts will be enrolled into that group in stage 2. Preliminary results for each group will be evaluated in the interim analysis. As of 20 January 2013, 43 pts have been enrolled (12 with and 31 without *FGFR2* mutations). Clinical trial information: NCT01379534.