

**Abstract ID:** 10775

**Title:** The use of pembrolizumab and lenvatinib combination therapy in endometrial cancer: An examination of toxicity and treatment efficacy in clinical practice

**Presenting Author:** Jeffrey How, MD MPH

**Objectives:** Pembrolizumab/lenvatinib demonstrated impressive response rates in advanced/recurrent endometrial cancer (EC) in a recent phase II clinical trial, leading to its accelerated FDA approval. However, tolerability of the recommended 20 mg starting dose of lenvatinib may pose clinical challenges. To comprehend how this regimen translates into daily clinical practice, we evaluated our preliminary data regarding toxicity and efficacy of pembrolizumab/lenvatinib in the treatment of advanced/recurrent EC at the University of Texas MD Anderson Cancer Center.

**Methods:** In this single-institution, retrospective cohort study, we evaluated recurrent/advanced EC patients who received  $\geq 1$  cycle of pembrolizumab/lenvatinib treatment. Toxicity was evaluated through rates of hospitalization and treatment interruptions or discontinuations, as well as number of dose reductions. Clinical efficacy was evaluated by best radiologic response to treatment. Clinical benefit was defined as having stable disease or partial/complete response.

**Results:** From October 2019 to July 2020, 83 EC patients were identified but 16 were excluded for unconfirmed administration of pembrolizumab/lenvatinib or lack of toxicity or response data. Thus, 67 EC patients were included in the analysis with a median follow-up of 5 months (range 1 – 11). The median age and number of prior lines of therapy were 67 (range 31–77) and 2 (range 1–9), respectively. The majority had an ECOG performance status of 0 to 1 (91%). The predominant histologic subtype was endometrioid and serous ( $n = 19$  each) followed by carcinosarcoma ( $n = 13$ ), mixed ( $n = 8$ ), clear cell ( $n = 4$ ), and other ( $n = 4$ ). The most common starting dose of lenvatinib was 14 mg ( $n = 43$ ; 64.2%), followed by 20 mg ( $n = 15$ ; 22.4%). Treatment-related hospitalizations occurred in 26.9% of patients but did not differ between lenvatinib dosage groups ( $p = 0.37$ ). Compared to those with a lower starting dosage level, patients started on 20 mg doses had significantly higher treatment discontinuations (100% vs 69.2%,  $p = 0.01$ ) and numbers of lenvatinib dose reductions (1.0 vs 0.38,  $p = 0.004$ ), with a trend of higher treatment interruptions (93.3% vs 73.1%,  $p = 0.09$ ). Among the 56 patients with evaluable radiologic response, there were 21 (37.5%) patients with either a partial ( $n = 18$ ) or complete response ( $n = 3$ ), while 18 patients (32.1%) had stable disease. Of the patients with complete response, all patients had a starting lenvatinib dose of 14 mg. Based on a starting lenvatinib dose of 20 mg vs < 20 mg, there were no differences in response to therapy (23.1% vs 41.9%;  $p = 0.56$ ; respectively) or clinical benefit rates (53.8% vs 74.4%,  $p = 0.18$ ; respectively). There were no differences in response rates among histologic subtypes ( $p = 0.76$ ). Patients with carcinosarcoma histology had a response and clinical benefit rate of 25% (3 of 12) and 58.3% (7 of 12), respectively.

**Conclusions:** In treatment of recurrent/advanced EC, lower starting dosage of lenvatinib was associated with fewer treatment interruptions/discontinuations and dose de-escalations compared to the FDA recommended 20 mg dosage level while maintaining equivalent response and clinical benefit rates. Furthermore, patients with carcinosarcoma histology also appeared to benefit from pembrolizumab/lenvatinib. While larger studies are needed to validate these safety and efficacy findings, our preliminary data supports starting a lower dosage of lenvatinib in clinical practice.

**Abstract ID:** 10321

**Title:** Lenvatinib plus pembrolizumab in advanced recurrent endometrial cancer: A cost-effectiveness analysis

**Presenting Author:** David Barrington, MD

**Objectives:** To determine the cost-effectiveness of lenvatinib plus pembrolizumab (LP) in patients with endometrial cancer without microsatellite instability who failed first-line chemotherapy.

**Methods:** A decision analysis model was created to evaluate the cost-effectiveness of LP relative to doxorubicin, pegylated liposomal doxorubicin (PLD), and bevacizumab in patients with recurrent microsatellite stable endometrial cancer who failed first-line chemotherapy. Clinical estimates were obtained from published data and drug cost estimates were obtained using average wholesale prices. Additional cost estimates were utilized to estimate cost of grade 3-4 toxicity treatment. The measure of effectiveness was quality-adjusted life years (QALYs). Due to the high rate of toxicity in the LP group, a health state utility (HSU) penalty of -0.05 was applied to this group. Incremental cost-effectiveness ratios (ICERs) were calculated to determine the cost per QALY. The willingness to pay threshold (WTP) was set at \$100,000 per QALY saved. Sensitivity analyses were performed on cost, effectiveness, and HSU penalty for LP.

**Results:** Costs of treatment with doxorubicin, PLD, and bevacizumab are \$26.7 million (M), \$51.1 M, and \$225.1 M respectively. Cost of treatment with LP is \$856.5M. Relative to doxorubicin, the ICER for PLD, bevacizumab, and LP are \$46,279, \$345,824, and \$726,483 respectively. Two-way sensitivity analysis varying the cost of LP show that if the combined cost of these two drugs decreases from over \$34,000 per cycle to less than \$9,000 per cycle, this strategy would be cost-effective. At the current cost, even if the median overall survival was double the 16.7 months used in the base model, the ICER for LP remains above the WTP threshold. Eliminating the HSU penalty for LP decreased the ICER \$567,000 while increasing the penalty to 0.10 increased the ICER to over \$1M.

**Conclusions:** LP is not cost-effective in patients with recurrent, MSS endometrial cancer who have failed first line therapy. A dramatic reduction in cost of LP is required for this novel strategy to be cost-effective.

**Abstract ID:** 10753

**Title:** Quality of oncologic care and outcomes of patients with endometrial cancer managed at minority-serving hospitals

**Presenting Author:** Dimitrios Nasioudis, MD

**Objectives:** Evaluate the outcomes of patients with endometrial cancer managed at minority-serving hospitals.

**Methods:** The National Cancer Database was accessed, and patients diagnosed between 2004 and 2016 with a uterine, ovarian or cervical tumor with known race were identified. Minority-serving hospitals (MSH) were defined as those with the highest percentage (> 75th percentile) of Hispanic, Black and Asian patients while non-MSH were defined at those with the lowest (< 25% percentile) percentage. Patients without a history of another tumor, diagnosed with endometrial cancer, and who were managed at a single facility were identified. Patients managed at an MSH or a non-MSH were selected for analysis. Clinico-pathological and treatment characteristics were compared while overall survival was evaluated after controlling for confounders with the construction of a Cox multivariate model.

**Results:** A total of 1,312 facilities reporting patients with gynecologic malignancies were identified. In MSH and non-MSH hospitals, an average of 46.89% and 2.63% of patients were minorities, respectively. A total of 111,222 patients with endometrial cancer who met the inclusion criteria were identified; 62.7% and 38.3% were managed at an MSH and a non-MSH hospital, respectively. Compared to patients managed at non-MSH those managed at an MSH were more likely to have comorbidities (74.2% vs 72.6%,  $p < 0.001$ ) and stage III-IV disease (21.4% vs 15.3%,  $p < 0.001$ ), while they were less likely to have endometrioid tumors (79.9% vs 88.3%,  $p < 0.001$ ) and private insurance (46.6% vs 49.1%,  $p < 0.001$ ). After controlling for insurance status, comorbidities, patient age and disease stage, patients who underwent surgery at an MSH had higher odds of unplanned 30-day readmission (OR: 1.17, 95% CI: 1.09, 1.28), 90-day mortality (OR: 1.24, 95% CI: 1.10, 1.40) and prolonged hospitalization (defined as hospital stay > 10 days) (OR: 1.41, 95% CI: 1.30, 1.55). For patients with apparent-early stage disease, after controlling for age, insurance, histology and comorbidities, those who had a hysterectomy at an MSH had similar odds of undergoing minimally-invasive surgery (OR: 0.97, 95% CI: 0.93, 1.01). Patients with non-endometrioid tumors (OR: 0.90, 95% CI: 0.78, 1.05) or apparent stage IB, grade 2/3 endometrioid tumors (OR: 1.06, 95% CI: 0.92, 1.22) had similar odds of undergoing lymphadenectomy. Patients with stage III-IV disease, who were managed at an MSH had lower odds of receiving chemotherapy (OR: 0.90, 95% CI: 0.84, 0.96) after controlling for insurance, age, comorbidities and histology. After controlling for patient age, insurance status, comorbidities, histology, receipt of chemotherapy and radiation therapy and disease stage, treatment at an MSH was associated with worse survival (HR: 1.12, 95% CI: 1.09, 1.15) compared to treatment at a non-MSH.

**Conclusions:** Significant disparities exist in the management, peri-operative outcomes and survival of patients with endometrial cancer managed at MSH.

**Abstract ID:** 10533

**Title:** Adjuvant chemotherapy and radiation for patients with high-risk stage I endometrial cancer (EC) treated with curative intent surgery: The impact on recurrence and survival

**Presenting Author:** Rachelle Findley, Bsc Pharm, MD, FRCSC

**Objectives:** Survival benefits of post-operative systemic and radiation therapy in high-risk stage I endometrial cancer (EC) are uncertain. The aim of this study was to compare the patterns and survival outcomes of post-surgical treatment in patients with high-risk stage I EC.

**Methods:** High-risk stage I EC was defined as either stage IB grade 3 endometrioid histology or myo-invasive non-endometrioid histology. Consecutive cases of stage I endometrial carcinoma diagnosed between 2000 and 2010 in 8 cancer centres were included. Patient, disease, and treatment characteristics were summarized by descriptive statistics. Overall survival (OS), disease-specific survival (DSS), and relapse-free survival (RFS) were calculated by log-rank statistics and Kaplan Meier curves were constructed.

**Results:** Of 2,327 patients with stage I EC, high-risk disease accounted for 414 of all cases. There was heterogeneity among the centres in regards to the extent of surgical staging. Use of chemotherapy (CT) did not improve OS (median 8.52 vs 7.48 years, HR 0.70, 95% CI 0.46-1.14,  $p = 0.13$ ) or DSS (median not reached in both, HR 1.06, 95% CI 0.61-1.85,  $p = 0.84$ ). However, RFS was improved in patients who received CT (median 8.52 vs 6.92 years, HR 0.61, 95% CI 0.39-0.95,  $p = 0.03$ ). Use of radiation therapy (RT) did not improve OS, RFS or DSS. Higher recurrence and lower survivals were noted in patients age 55 and over, or who had stage IB, a higher grade, or lymphovascular space invasion; histology did not impact survival outcomes. Patients who received 4 or fewer cycles of chemotherapy versus 5-6 cycles had similar OS, DSS, and RFS.

**Conclusions:** Post-operative CT and RT in stage I high-risk endometrial cancer does not improve cancer-specific or overall survival. More than 4 cycles of CT did not improve survival outcomes compared with 4 cycles or less.

**Abstract ID:** 11374

**Title:** Minimally-invasive hysterectomy versus open radical hysterectomy in early-stage cervical cancer: A cost-effective analysis of the LACC trial

**Presenting Author:** Teresa Boitano, M.D.

**Objectives:** To determine the cost-effectiveness of minimally-invasive hysterectomy versus open radical hysterectomy in patients with early-stage cervical cancer.

**Methods:** We created a model to evaluate the cost-effectiveness of minimally-invasive radical hysterectomy compared to open radical hysterectomy in women with newly diagnosed stage 1A1 (with lymphovascular invasion) thru IB2 (FIGO 2018) cervical cancer. We included 6,000 patients in the model which approached cost from a societal perspective. Surgical costs were calculated using the average Medicare reimbursement for the procedures with and without associated complications. Lost wages were calculated using return to normal daily activity per surgical approach and information from the Bureau of Labor Statistics. Estimated complication rates were calculated using the LACC trial data. Effectiveness was calculated as disease-free survival (DFS) at 4.5 years. We calculated incremental cost-effectiveness ratios (ICERs) to determine the cost per 4.5 year survivor. Univariate sensitivity analyses were performed. The willingness to pay threshold was \$100,000 per year of DFS.

**Results:** In the minimally-invasive radical hysterectomy cohort, the cost was \$87.4 million (M) and yielded 5,160 4.5 year survivors. Comparatively, open radical hysterectomy cost \$108.1 M and resulted in 5,760 4.5 year survivors. The ICER for open radical hysterectomy compared to minimally-invasive radical hysterectomy was \$32,824 which fell well below our predetermined willingness to pay threshold of \$450,000 per 4.5 year survivor. Sensitivity analyses were performed to determine the effect of complication rates on the model. The baseline rate of major complications with open radical hysterectomy was similar to minimally invasive radical hysterectomy (18.0 vs 16.0%). In order to evaluate the impact of medically compromised patients (comorbidities, obesity, and age >65), we varied the complication rates from 10-80% in the sensitivity analysis. With increasing complication rates in the open radical hysterectomy cohort, both the total costs and ICER increases (\$64,044) but remains below the willingness to pay threshold.

**Conclusions:** For patients with early-stage cervical cancer, open radical hysterectomy is cost-effective relative to minimally-invasive hysterectomy. Medical comorbidities and complication rates do not impact the results of the model. Open radical hysterectomy appears to be the preferred surgical approach for all patients with early-stage cervical cancer.

**Abstract ID:** 10718

**Title:** A proof of concept randomized phase 2 non-inferiority trial on simple versus modified radical hysterectomy in IA2-IB1 cervical cancer  $\leq$  2cm (LESSER)

**Presenting Author:** Glauco Baiocchi, MD, PhD

**Objectives:** To evaluate the safety and efficacy of simple hysterectomy in early stage cervical cancer.

**Methods:** The LESSER (LESS Surgical radicality for EaRly stage cervical cancer) study was a proof of concept randomized phase 2 non-inferiority trial evaluating the safety and efficacy of simple hysterectomy compared to modified radical hysterectomy in patients with stages IA2-IB1 cervical cancer and tumors of  $\leq$  2cm in size. Primary endpoint was 3y-DFS rates and secondary endpoints were 3y-OS (3-year overall survival), surgical morbidity, indication of adjuvant therapy, and QoL (EORTC QLQ-C30). The study was registered at ClinicalTrials.gov (NCT02613286).

**Results:** A total of 40 patients were randomized 1:1 from May 2015 to April 2018 in 3 oncological centers from Northeast Brazil. All cases had pelvic systematic lymph node dissection. Overall, 10% of patients underwent MIS procedures, 80% of tumors were SCC and 7.5% had lymph node metastasis, whereas inaccuracies for clinical tumor size estimation, LVSI and stromal invasion  $>$  1cm were found in 20%, 22.5% and 30% of cases, respectively. Clinical and pathological characteristics were well balanced between treatment arms, but the length of surgery and the time for bladder catheterization removal were higher after radical hysterectomy ( $p = 0.003$  and  $p = 0.043$ , respectively). There was no postoperative mortality and rates of any grade postoperative complication were not statistically different between arms (15% and 20%;  $p = 1.00$ ). No major differences in the QoL over time were also observed. A quarter of patients received adjuvant therapy, with no significant difference between groups (30% vs. 20%,  $p = 0.48$ ). There was one death at 25 months of follow-up due to pelvic recurrence in the simple hysterectomy arm. A pathological review of this case found *tumor embolus* in the lymphovascular space of left parametrium that was missed at the time of former anatomopathological analysis. Another patient died of lung metastasis from a second primary thyroid cancer at 54.4 months of follow-up in the radical hysterectomy arm. A major late complication was also recorded after 3 months from radical surgery in a patient with distal urethral stenosis that was treated with segmental resection and psoas-hitch ureteroneocystostomy. Survival outcomes with a minimum of 3y follow-up will be mature for presentation during the *SGO 2021 Annual Meeting on Women's Cancer*.

**Conclusions:** Simple hysterectomy is a promising substitute for modified radical hysterectomy in stage IA2-IB1 cervical cancer  $\leq$  2cm.

**Abstract ID:** 10358

**Title:** Minimally invasive versus open surgery for stage 1A1 and 1A2 cervical cancer

**Presenting Author:** Judy Hayek, MD

**Objectives:** Recent studies comparing minimally invasive versus open radical hysterectomy in patients with early stage cervical cancer have reported a worse overall survival with minimally invasive surgery (MIS). However, in the patients with microscopic disease, there was no survival difference and the optimal surgical approach for microscopic cervical cancer remains unclear. Our aim was to compare the overall survival and surgical outcomes between open and MIS in a large cohort of women with stage IA1/IA2 cervical cancer.

**Methods:** Using the National Cancer Database, we identified a cohort of women who underwent hysterectomy as the primary treatment for stage IA1/IA2 cervical cancer between January 2010 and December 2016. Outcomes were compared between the cohorts using the Mann-Whitney U test, the chi-squared test or Fisher's exact test. Multivariable logistic regression was used to determine clinical characteristics that were statistically significant predictors of outcome. P values <0.05 were significant. The data was stratified for radical and simple hysterectomy. We also compared the readmission rates and length of stay (LOS) among the groups.

**Results:** We identified 6230 patients with stage IA1 and IA2 cervical cancer that underwent hysterectomy as primary treatment. 4054 of these women (65%) underwent MIS and 1931 women had a radical hysterectomy. In this group, 1152 had a minimally invasive radical hysterectomy. In the overall cohort, there was no difference in survival between the open and the MIS group (Hazard ratio for the open group 1.23; CI 0.92-1.63). When stratified, the data showed no difference in overall survival for stage IA1 cases (HR 1.15; CI 0.77-1.73). For women with stage IA2, there was a trend towards decreased overall survival in the open group that did not reach statistical significance (HR 1.64; CI 0.84-3.23). Of note, post-operative radiation therapy was more common in the open group (5.24% vs 4.09%, p value <0.02). The mean LOS (1.35 days vs 3.08 days) was shorter in MIS group (pvalue <0.0001). No statistical significance was found in the readmission rates (60% for the MIS group vs 55% for the open group; p value 0.14). For the women who underwent a radical hysterectomy, there was no difference in survival between the open and the MIS cohort (p value 0.31) and as expected, the MIS group was associated with a decreased length of stay.

**Conclusions:** Our data suggest that MIS is associated with similar overall survival and shorter length of hospital stay compared to the open hysterectomy in women with stage IA cervical cancer. When the data was stratified to simple and radical hysterectomy, the results were the same. Those women having open surgery were more likely to get post-operative radiation therapy. Based on this large data set, MIS appears to be a safe and effective surgical approach for women with stage IA1/IA2 cervical cancer.

**Abstract ID:** 10938

**Title:** Association of BRCA1/2, homologous recombination deficiency, and PD-L1 with clinical outcomes in patients receiving atezolizumab versus placebo combined with carboplatin, paclitaxel, and bevacizumab for newly diagnosed ovarian cancer: Exploratory analyses

**Presenting Author:** Charles Landen, MD

**Objectives:** Genomically unstable tumors, characterized by *BRCA1/2* alterations and homologous recombination deficiency (HRD), are hypothesized to be more mutated and potentially more sensitive to immune checkpoint inhibitors. To explore this hypothesis we analyzed outcomes in the IMagyn050 trial according to *BRCA1/2*, HRD, and PD-L1 status [Moore, ESMO 2020].

**Methods:** IMagyn050 (NCT03038100) is a double-blind randomized phase III trial evaluating the efficacy and safety of adding atezolizumab/placebo to carboplatin, paclitaxel, and bevacizumab (CPB) followed by maintenance bevacizumab plus atezolizumab/placebo. PD-L1 status was determined centrally using VENTANA SP142 (PD-L1+ defined as  $\geq 1\%$  tumor-infiltrating immune cells expressing PD-L1). Deleterious tumor germline/somatic *BRCA1/2* alterations (*BRCA1/2*m), genomic loss of heterozygosity (gLOH), tumor mutation burden (TMB), and microsatellite instability (MSI) were evaluated using the FoundationOne assay (Foundation Medicine, Inc., Cambridge, MA). HRD and homologous recombination proficiency (HRP) were defined as gLOH  $\geq 16\%$  and  $< 16\%$ , respectively, regardless of *BRCA1/2*m status. Potential associations between clinical outcome (RECIST-defined progression-free survival [PFS]) and *BRCA1/2*, HRD, and PD-L1 status were evaluated using standard correlation analyses and Kaplan-Meier estimates.

**Results:** Among 1301 randomized patients, samples from 1050 were evaluable for *BRCA1/2* (22% were *BRCA1/2*m, 78% *BRCA1/2* nonmutant) and 980 were evaluable for gLOH (46% were HRD, 54% HRP). Median TMB was similarly low in *BRCA1/2*m and *BRCA1/2* nonmutant (3.78 vs 2.52 Mut/Mb, respectively), and HRD and HRP (3.78 vs 2.52 Mut/Mb, respectively) tumors. Only 3% (29/1024) of evaluable tumors had TMB  $\geq 10$  Mut/Mb and 0.3% (3/1022) were MSI-high (1 mixed, 1 undifferentiated, 1 other). All high-grade serous cases were MS-stable. PFS prognosis (assessed in the placebo + CPB arm) was improved in patients with *BRCA1/2*m (hazard ratio [HR] 0.62, 95% CI 0.46–0.84) and HRD (HR 0.63, 95% CI 0.49–0.80) tumors. There was a suggested association between PD-L1+ and HRD (HRD prevalence: 40% vs 25% in PD-L1+ vs PD-L1– subgroups, respectively; exploratory Fisher's exact test  $p = 0.0001$ ) but not with *BRCA1/2* (*BRCA1/2*m prevalence: 21% vs 14%, respectively; exploratory Fisher exact test  $p = 0.064$ ). Adding atezolizumab to CPB did not improve PFS, irrespective of *BRCA1/2* or HRD status (table). In the PD-L1+ population, HRs were similar in *BRCA1/2*m and *BRCA1/2* nonmutant subgroups, and in HRD and HRP subgroups. In the PD-L1– population, atezolizumab did not improve PFS.

**Conclusions:** We showed that the majority of ovarian tumors have low TMB scores regardless of *BRCA1/2* or HRD. Neither *BRCA1/2*m nor HRD was associated with greater clinical benefit from adding atezolizumab to CPB. PD-L1 status was more reliably associated with numerically longer PFS with atezolizumab + CPB. This is the first randomized double-blind trial in ovarian cancer to demonstrate that genomic instability triggered by *BRCA1/2*m or HRD does not improve sensitivity to immune checkpoint inhibitors.



**Abstract ID:** 10446

**Title:** A randomized, double-blind, placebo-controlled, phase II study to assess the efficacy/safety of farletuzumab in combination with carboplatin plus paclitaxel or carboplatin plus pegylated liposomal doxorubicin (PLD) in women with low CA-125 platinum-sensit

**Presenting Author:** Thomas Herzog, MD

**Objectives:** The primary objective of this study (MORAb-003-011/ENGOT-ov27) was to determine if farletuzumab (FAR) had superior efficacy compared with placebo (PLB) in improving progression-free survival (PFS) when added to carboplatin (carbo)/paclitaxel (pacli) or carbo/PLD, in subjects with platinum-sensitive ovarian cancer in first relapse (platinum-free interval: 6-36 months) with low cancer antigen 125 (CA-125). CA-125 inhibits target cell killing via antibody-dependent cellular cytotoxicity, thereby reducing the efficacy of immunotherapeutic antibodies. Subgroup analysis in a prior randomized Phase III study +/- FAR suggested that subjects with CA-125 levels  $\leq 3$  x upper limit of normal (ULN), showed superior PFS (hazard risk [HR] = 0.49) and overall survival (OS, HR = 0.44) compared with PLB.

**Methods:** Eligibility included age  $\geq 18$  years old, CA-125  $\leq 3$  x ULN (105 U/mL), high-grade serous epithelial ovarian cancer, and previous treatment with debulking surgery and first-line platinum-based chemotherapy. Subjects received 6 cycles with either carbo/pacli every 3 weeks or carbo/PLD in combination with either FAR [5 mg/kg weekly] or PLB in a 2:1 ratio. Maintenance treatment with FAR (5 mg/kg weekly) or PLB was given until disease progression. Tumor assessments were every 6 weeks during the Combination Treatment Phase and every 9 weeks during the Maintenance Treatment Phase. The study was designed to detect a PFS HR of 0.667 (33.3% risk reduction) with FAR compared with PLB with approximately 85% power and a 1-sided type I error rate of 0.10. The comparison of PFS between treatment groups was based on the log-rank test. The HR was estimated based on Cox's proportional-hazards model.

**Results:** A total of 214 subjects were randomized and enrolled, 142 with FAR+chemotherapy (FAR-CT) and 72 with placebo+chemotherapy (PLB-CT). The median PFS in the Intent-to-Treat [ITT] Population was not significantly different between treatment groups; 11.7 months (95% confidence interval [CI]: 10.2, 13.6) versus 10.8 months (95% CI: 9.5, 13.2) for FAR-CT and PLB-CT, respectively (HR = 0.89; 80% CI: 0.71, 1.11). An interim analysis of OS showed no significant difference between treatment groups. The overall response rate (ORR) was 69.6% in 96 subjects treated with FAR-CT versus 73.5% in 50 subjects treated with PLB-CT ( $p = 0.53$ ). No significant differences between treatment groups were observed for any other efficacy parameters. The safety profile of the 2 treatment groups was similar except for an increase in interstitial lung disease among the FAR cohort. Interstitial lung disease occurred in 7 of 141 (5.0%) subjects treated with FAR-CT (1 with Grade 1, 4 with Grade 2, and 2 with Grade 3) and none in subjects treated with PLB-CT.

**Conclusions:** The combination of FAR-CT did not show signals of superior efficacy compared with PLB-CT in improving PFS or other efficacy parameters in subjects with platinum-sensitive recurrent ovarian cancer in first relapse who had low CA-125 levels. No new safety concerns were identified with the combination of FAR-CT. Since FAR binds to the folate receptor alpha, a novel antibody-drug conjugate has been developed and clinical studies are ongoing to assess the safety/efficacy of this modification. (Clinical Trial Registry NCT02289950)

**Abstract ID:** 10601

**Title:** Randomized phase II trial of durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4) administered in combination versus sequentially for the treatment of recurrent platinum-resistant non-clear cell ovarian cancer (NCT03026062)

**Presenting Author:** Emily Hinchcliff, MD, MPH

**Objectives:** Single agent immune checkpoint blockade (ICB) has demonstrated response rates of 5-15% in patients with recurrent high-grade ovarian cancer (HGOC), with another 15-40% of patients achieving stable disease. Combination ICB using ipilimumab and nivolumab resulted in improved response rates in a mixed population with platinum resistant and sensitive disease. The objective of the current trial was to evaluate sequential versus combination CTLA4 and PDL1 blockade strategies for extending progression free survival (PFS) in patients with platinum resistant/refractory HGOC.

**Methods:** Patients were required to have pathologically confirmed platinum resistant or refractory epithelial ovarian cancer, no prior immunotherapy, and PS= 0-1 for enrollment. The current abstract includes data only on subjects with high grade serous ovarian cancer (HGSOC), as enrollment of patients with clear cell histology is still ongoing. The primary endpoint was PFS and response was assessed using modified RECIST v1.1. Unlimited numbers of prior regimens were allowed. Patients were adaptively randomized to sequential arm: tremelimumab (3mg/kg q4 weeks x 4 doses) followed by durvalumab (1.5g IV q4 weeks for up to 9 doses) upon progression, or the combination arm: tremelimumab (1mg/kg IV plus durvalumab 1.5g IV q4wk for up to 4 doses followed by durvalumab monotherapy for up to 9 doses). For the Bayesian adaptive randomization, the probability of being assigned to an arm was proportional to the likelihood the arm had better PFS, such that patients were more likely to be randomized to the more effective arm.

**Results:** A total of 61 subjects were adaptively randomized to sequential treatment (n= 38) or combination therapy (n = 23). 46 (79%) patients had wild-type breast cancer gene (BRCA). Median prior lines of therapy was 4 (range: 1-10). There was no difference in median PFS in the sequential arm (1.84 months ; 95% CI: 1.77 – 2.17)) compared with the combination arm (1.87 months; 95% CI: 1.77 – 2.43), p = 0.402. Similarly, median OS in the sequential and combination arms were 10.61 months (5.95 – 15.34) and 7.26 (4.24 – 15.57), respectively (p = 0.810). In the sequential arm no objective responses were observed, although 12 patients (31.6%) exhibited stable disease. In the combination arm, 2 patients had partial response (8.7%) while one additional patient (4.4%) had stable disease. The adverse event profile was consistent with that previously reported for immune checkpoint therapy.

**Conclusions:** There was no difference in the median PFS between the combination and sequential durvalumab plus tremelimumab treatment strategy arms in a heavily pretreated population of patients with platinum resistant/refractory HGOC. Response rates were comparable to prior reports, though the combination regimen did not add significant benefit as has been previously described with combination of ipilimumab/nivolumab. Further exploration into subpopulations that may have increased benefit from ICB is warranted.

**Abstract ID:** 10565

**Title:** KGOG 3046/TRU-D: A phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage epithelial ovarian cancer

**Presenting Author:** Jung-Yun Lee, MD

**Objectives:** We hypothesized that adding durvalumab and tremelimumab to chemotherapy in advanced-stage epithelial ovarian cancer (aEOC) would increase progression-free survival (PFS) with minimal effects on safety. KGOG 3046 (NCT03899610) is a single-arm phase 2 study evaluating the combination of dual immune checkpoint inhibition and neoadjuvant chemotherapy (NAC) for the upfront treatment of aEOC.

**Methods:** Patients with FIGO stage IIIC-IV EOC were offered three cycles of durvalumab (1500 mg), tremelimumab (75 mg) with chemotherapy for NAC followed by interval debulking surgery (IDS). After surgery, three cycles of durvalumab (1120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1120 mg [total 12 cycles]) were administered. During treatment, serial biopsies were performed at pre-treatment, IDS, and progression to identify immune biomarkers and changes in the tumor microenvironment. The primary endpoint was a 12 months PFS rate. Interim analysis was performed to evaluate outcomes after NAC (RECIST after NAC, R0 rate at IDS, the rate of CRS 3 at IDS, safety, a range of translational parameters) after all patients underwent IDS.

**Results:** A total of 23 patients were enrolled with a median age of 60 years (range:44-77 years). The majority were presented with high-grade serous carcinoma (87.0%) and stage IV disease (60.9%). After NAC, 3 patients experienced a complete response (13.0%) and 20 patients had a partial response (87.0%). At IDS, R0 resection was achieved in 17 patients (73.9%); 9 patients (39.1%) had a CRS of 3; pathologic complete remission was achieved in 4 patients (17.4%). A total of 2 patients (8.7%) delayed IDS due to grade 4 skin rash and pneumonitis, respectively. Skin rashes were the most common adverse events (56.5%) and grade  $\geq 3$  events occurred in 3 patients (13.0%), which completely resolved after steroid use. Treatment was associated with tumor microenvironment conversion to an "inflamed" phenotype, with a significant increase in cytolytic index ( $P=0.015$ ), stromal score ( $P < 0.001$ ) and immune score ( $P = 0.004$ ) on whole-transcriptome sequencing.

**Conclusions:** These interim data highlight the clinical activity and a manageable toxicity profile for the addition of durvalumab and tremelimumab to NAC in aEOC. Additional correlative data will be presented at the meeting. This study is actively enrolling patients in an expansion cohort.

**Abstract ID:** 10972

**Title:** GAS6 inhibition induces platinum sensitivity through increased replication stress in ovarian cancer

**Presenting Author:** Mary Mullen, MD

**Objectives:** More than 80% of women with high grade serous ovarian carcinoma (HGSOC) ultimately develop platinum resistance. There are no FDA approved agents to improve sensitivity to carboplatin. One candidate target is growth arrest-specific 6 (GAS6) which has been associated with prognosis in HGSOC. We hypothesized that GAS6 inhibition with AVB-500 (AVB) sensitizes platinum-resistant cells to platinum chemotherapy by stalling replication forks and increasing replication stress. We also hypothesized that GAS6 expression would predict response to neoadjuvant chemotherapy.

**Methods:** AVB was supplied by Aravive Biologics. Both homologous recombination (HR)-proficient (OVCAR3-TPMES, CAOV3, COV362) and HR-deficient (OVCAR8) cells were used for all experiments. In vitro clonogenic assays were done on chemoresistant ovarian tumor cells treated with carbo +/- AVB. The effect of carbo + AVB on intraperitoneal tumor burden was evaluated in mouse models. For DNA fiber assays, cells were labeled with the thymidine analog IdU for 20 minutes followed by CldU for 60 minutes and treatment with carbo, cisplatin (cis), or AVB. Immunofluorescent (IF) assays targeting  $\gamma$ H2AX for DNA damage, RAD51, BRCA1, and BRCA2 for HR and 53BP1 for non-homologous end joining (NHEJ) were performed. Human HGSOC samples were obtained pre- and post-neoadjuvant chemotherapy. GAS6 expression was measured by tissue immunohistochemistry (IHC) and serum ELISA.

**Results:** Carbo + AVB decreased survival of platinum-resistant cells as measured by clonogenic colonies than carbo alone ( $p < 0.05$ ). Platinum-resistant mouse models treated with chemotherapy + AVB had significantly less tumor burden than those treated with chemotherapy alone (50mg vs 357mg,  $P < 0.01$ ). Combenefit analyses confirmed AVB and carboplatin were synergistic. Treatment with carbo or cis plus AVB led to replication fork perturbation and increased replication fork stress than carbo/cis or AVB alone. Specifically, there was significant shortening of the CldU label and decrease of CldU/IdU ratios in cells treated with carbo/cis plus AVB. Additionally, tumor cells treated with carbo + AVB compared to carbo alone demonstrated an increase in  $\gamma$ H2AX and 53BP1 foci ( $P < 0.01$ ) and a decrease in RAD51, BRCA1, and BRCA2 foci ( $P < 0.05$ ). Patients with high pretreatment tumor GAS6 IHC expression ( $>80\%$ ) ( $n = 7$ ) or serum GAS6 concentrations ( $>25\text{ng/mL}$ ) ( $n = 13$ ) were more likely to have a poor response to neoadjuvant chemotherapy than those with low GAS6 ( $P = 0.002$ ). Additionally, high GAS6 concentration was associated with decreased overall survival (24.4 months versus median not reached,  $P = 0.009$ ).

**Conclusions:** Inhibition of the GAS6 pathway with AVB improves sensitivity of platinum-resistant cells to platinum chemotherapy by increasing replication stress and DNA damage and decreasing HR. GAS6 is a potential biomarker predictive of poor response to platinum-based neoadjuvant chemotherapy and might identify patients who would benefit from treatment with AVB.

**Abstract ID:** 11042

**Title:** Separating the BRCA1 and BRCA2 phenotype: A genomic pathway analysis

**Presenting Author:** Lisa Rubinsak, MD

**Objectives:** Emerging data suggests that key differences exist between BRCA1 and BRCA2 associated ovarian cancer, including response to therapy and survival outcomes. The purpose of this study was to identify gene expression profiles and interacting pathways unique to BRCA1- and BRCA2- associated high grade serous ovarian cancer (HGSOC) samples compared to one another as well as to BRCA wild type, homologous recombination proficient (HRP) tumors.

**Methods:** Of 657 total HGSOC samples, 15 BRCA2 mutated (2.2%), 16 (2.4%) BRCA1 mutated, and 375 (57%) HRP samples were analyzed. BRCA mutated was defined as somatic variants that result in loss of function. The HRP control group was defined as samples negative for aberrations in BRCA1/2 and 28 HR genes. Gene expression data was collected from Tempus and unpaired t-tests were used to identify differentially expressed genes (DEG) with p-value <0.05 and fold change (FC) of 1.5. Meta and pathway analyses were performed among BRCA1, BRCA2 and HRP groups using Venn diagram and Advaita Bio's iPathwayGuide.

**Results:** From 18,284 genes with measured expression, 843 (4.6%) DEG were found between BRCA2 vs BRCA1, 748 (4.1%) between BRCA2 vs HRP and 1,858 (10.2%) between BRCA1 and HRP. 8,296 mutated genes were similarly expressed in both BRCA2 and BRCA1 groups with FC < 1.5, including DNA damage response genes ATM (log<sub>2</sub>FC = -0.43, p = 0.51), CHEK2 (log<sub>2</sub>FC = -0.21, p = 0.79), TP53 (log<sub>2</sub>FC = -0.73, p = 0.52) and PARP1 (log<sub>2</sub>FC = 0.62, p = 0.26). For BRCA1 compared to HRP group, 214 miRNAs and 137 gene upstream regulators were identified unique to BRCA1; top identified pathways were metabolism related. For BRCA2 compared to HRP group, no miRNAs and 108 gene upstream regulators were identified; identified pathways were Wnt signaling related. On meta-analysis of the 3 comparisons, 550 DEGs were found for BRCA2 and 82 DEG for BRCA1 that were not shared by HRP group (Figure 1). Pathway analysis revealed significant involvement of Wnt signaling pathway unique to BRCA2 group compared to fibroblast growth factor signaling and PI3K-Akt signaling for BRCA1.

**Conclusions:** Our study identified genomic signatures for BRCA2 versus BRCA1 associated ovarian cancer, not shared by control HRP tumors in a sample representative of HGSOC tumor heterogeneity. Results suggest BRCA1/2 should not be considered a single entity, but rather separate phenotypes each with unique opportunities for targeted therapy.

**Abstract ID:** 10465

**Title:** Targeting Wnt/beta-catenin signaling in *CTNNB1*-mutant endometrial cancer

**Presenting Author:** Marisa Moroney, MD

**Objectives:** *CTNNB1* (gene encoding for beta-catenin) mutations convey increased rates of recurrence in early stage, low grade endometrial cancer (EC). The role of beta-catenin/TCF transcriptional activity in EC recurrence is not well understood. We aim to assess the impact of Wnt/beta-catenin inhibition in *in vitro* and *in vivo* EC models.

**Methods:** Using The Cancer Genome Atlas (TCGA) of Uterine Corpus Endometrial Carcinoma (PanCancer Atlas), we evaluated *CTNNB1*-mutant vs -wildtype tumors in a low-risk population. We studied *CTNNB1*-wildtype (HEC1B, Ishikawa) and *CTNNB1*-mutant (HEC108, HEC265, HEC1B-S33Y, Ishikawa-S33Y) EC cell lines. *CTNNB1*-S33Y cell lines were created via retroviral transduction. Dose response curves were determined for 5 Wnt/beta-catenin pathway inhibitors (Wnt-C59, XAV-939, PyrPam, PRI-724, SM04690). Cell viability was assessed with Licor Cell Staining. TCF transcriptional activity was determined via TOP/FOP reporter assay. Apoptosis following treatment with SM04690 was evaluated via Annexin V/propidium iodide (PI). HEC1B, HEC1B-S33Y and HEC265 tumor-bearing athymic nude mice were treated with vehicle or SM04690 25mg/kg. Tumor size was measured using calipers. Tumors were evaluated with immunohistochemistry for proliferation (Ki67) and apoptosis (cl-caspase 3).

**Results:** TCGA analysis confirmed that *CTNNB1* mutations are enriched in recurrent low-risk EC and showed that aberrant Wnt/beta-catenin pathway activation is associated with disease recurrence. *In vitro*, XAV939, Wnt-C59 and PyrPam inhibited function upstream of beta-catenin transcriptional activity and were ineffective at inhibiting EC cell viability. In contrast, PRI724 and SM04690 indirectly inhibited beta-catenin transcriptional activity and significantly reduced cell viability in *CTNNB1*-mutant EC cell lines. Treatment with SM04690 reduced cell viability in all EC cell lines, but was significantly lower in HEC108, HEC265 and HEC1B-S33Y compared to HEC1B (24.2%, 32.3%, 44.4%, vs. 71.4%,  $p < 0.01$ ). Compared to control, SM04690 significantly induced apoptosis in HEC265 cells (3.98% vs. 6.91% AnnexinV/PI+,  $p = 0.044$ ) and reduced TCF transcriptional activity in HEC1B-S33Y (-84%,  $p = 0.017$ ) and HEC108 (-74%,  $p = 0.002$ ) cells. *In vivo*, HEC1B, HEC1B-S33Y and HEC265 tumors treated with SM04690 had smaller mean tumor volumes than those treated with vehicle (HEC1B 146.4 vs 335.4mm<sup>3</sup>,  $p < 0.001$ ; HEC1B-S33Y 136.4 vs. 243.1mm<sup>3</sup>,  $p = 0.014$ ; HEC265 105.7 vs. 321.8mm<sup>3</sup>,  $p = 0.06$ ). In HEC1B-S33Y and HEC265 tumors, SM04690 treatment significantly reduced Ki67 H-scores compared to vehicle (129.8 vs. 146.7,  $p = 0.035$  and 87.08 vs.106.4,  $p = 0.024$ , respectively).

**Conclusions:** Targeting the Wnt/beta-catenin pathway in *CTNNB1*-mutant EC effectively inhibited proliferation and beta-catenin/TCF transcriptional activity. Further, the inhibitor SM04690 blunted tumor progression in *in vivo* models. These studies suggest beta-catenin transcriptional inhibitors are effective in EC and have a more significant effect in *CTNNB1*-mutant than -wildtype EC. These findings highlight a potential therapeutic vulnerability for treatment of *CTNNB1*-mutant EC.

**Abstract ID:** 10838

**Title:** Ipatasertib, an oral AKT inhibitor, exhibits anti-proliferative and anti-tumorigenic effects in pre-clinical studies for endometrioid endometrial cancer: Endometrial Cancer Molecularly Targeted Therapy Consortium

**Presenting Author:** Jillian O'Donnell, MD

**Objectives:** Ipatasertib (IPAT) is an orally administered selective protein kinase B (AKT) inhibitor that has demonstrated clinical activity in triple-negative breast and metastatic prostate cancer. Given that the AKT/mTOR pathway is altered in the vast majority of endometrioid endometrial cancers (ECs), it is logical that IPAT may also have efficacy in EC. Thus, we aimed to evaluate the anti-proliferative effects of IPAT in human endometrioid cell lines as well as in the *LKB1fl/flp53fl/fl* genetically engineered mouse model of endometrioid EC.

**Methods:** The human endometrioid EC cell lines ECC-1 (PTEN mutant) and HEC-1A (PTEN wild type, PIK3CA mutant, KRAS mutant) were exposed to varying concentrations of IPAT (Genentech). Cell proliferation was assessed by MTT and colony assays. Cell cycle progression was measured by Cellometer. Apoptosis was assessed by cleaved caspase-3 assay. Cellular stress was assessed using tetramethylrhodamine ester (TMRE) and DCFDA assays. Western immunoblotting determined effects of IPAT on BCL-2, MCL-1, Bip, CDK4, CDK6, cyclin D1, pAKT, pS6, PERK, calnexin, and PDI in both cell lines. *LKB1fl/flp53fl/fl* mice were used to evaluate the effect of IPAT on endometrial tumor growth. The mice were treated with placebo or IPAT (15mg/kg daily intraperitoneally for 4 weeks) starting 8 weeks after tumor induction via AdCre injection.

**Results:** IPAT inhibited cellular proliferation in a dose dependent fashion in both cell lines after 72 hours of treatment. Median IC50 was 0.18 $\mu$ M in ECC-1 and 3.5 $\mu$ M in HEC-1A. IPAT induced the activity of cleaved caspase 3 by 15.6-fold in ECC-1 and 1.41-fold in HEC-1A ( $p < 0.01$ ), while simultaneously reducing expression of the apoptotic proteins MCL-1 and BCL-2. IPAT inhibited cell cycle progression by arrest in G1 phase in both cell lines after 36 hours of treatment and decreased expression of the cell cycle related proteins, CDK4, CDK6, and cyclin D1. DCFDA assay analysis demonstrated that IPAT induced ROS products by 18% and 19% ( $p < 0.01$ ) in the ECC-1 and HEC-1A cell lines, respectively, and increased Bip and PERK protein expression. In addition, IPAT reduced mitochondrial potential by 12% in the HEC-1A cells and 14% in the ECC-1 cells ( $p < 0.01$ ). Treatment of cells with IPAT at 10 $\mu$ M increased phosphorylated-AKT (pAKT) expression and decreased phosphorylated-S6 (p-S6) expression in a time-dependent manner in both cell lines; however, measurable changes in pAKT and pS6 were observed at concentrations as low as 0.1 $\mu$ M. Notably, an increase in phosphorylated-AKT was expected and is indicative of engagement and binding of IPAT with the phospho-AKT complex. Treatment of *LKB1fl/flp53fl/fl* mice with IPAT was well-tolerated and reduced tumor weight by 52.1% as compared with control mice ( $p < 0.05$ ).

**Conclusions:** IPAT significantly inhibited cell proliferation and induced apoptosis and cellular stress via inhibition of the AKT/mTOR pathway in human endometrioid EC cell lines. Furthermore, IPAT reduced tumor growth in a transgenic mouse model of endometrioid EC. These results suggest that IPAT is worthy of further exploration in clinical trials for EC.

**Abstract ID:** 11561

**Title:** Apatinib combined with pegylated liposomal doxorubicin (PLD) versus PLD for platinum-resistant recurrent ovarian cancer (APPROVE): A multicenter, randomized, controlled, open-label, phase II trial

**Presenting Author:** Tiantian Wang, M.D

**Objectives:** Anti-angiogenic therapy combined with chemotherapy could improve survival in patients with platinum-resistant ovarian cancer (OC). APPROVE was conducted to evaluate the efficacy and safety of apatinib, an oral tyrosine kinase inhibitor that selectively inhibits VEGFR-2, in combination with pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant or refractory recurrent OC.

**Methods:** Eligible patients were histologically confirmed non-mucinous ovarian, primary peritoneal cancer, or fallopian-tube cancer who had experienced disease progression during, or within 6 months of discontinuing, any prior line of platinum-based chemotherapy. Patients with at least 1 lesion (measurable and/or nonmeasurable) that could be accurately assessed at baseline by computed tomography/magnetic resonance imaging. Patients were randomly assigned (1:1) to receive PLD alone (Arm PLD, 40mg/m<sup>2</sup> IV every 4 weeks for up to 6 cycles) or with apatinib 250mg orally once daily (Arm A-PLD) until disease progression, unacceptable toxicity, or consent withdrawal. Patients were stratified according to prior platinum-sensitive relapsed (yes vs no) and platinum-free interval (less than 3 vs 3 to 6 months from last platinum therapy to subsequent progression). The primary endpoint was progression-free survival (PFS) by RECIST 1.1 in the intent-to-treat population (ITT population). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety.

**Results:** Between Mar 22, 2018, and Nov 16, 2020, 152 patients were enrolled and randomly assigned to receive A-PLD (n = 78) or PLD (n = 74). Median follow-up was 8.1months (IQR 3.7-12.8). Median PFS was 5.8 months with A-PLD therapy versus 3.3 months with PLD alone (HR 0.41, 95% CI 0.26-0.64, P = 0.0001). In patients with evaluable disease (Arm A-PLD, n = 61; Arm PLD, n = 63), the ORR was 37.7% (23/61) versus 9.5% (6/63) for A-PLD and PLD, respectively (P = 0.0002). The DCR of A-PLD and PLD arms were 82.0% (50/61) and 58.7% (37/63), respectively (P = 0.0050). Overall survival data are immature. Hypertension and hand-foot syndrome were more common with apatinib. No adverse events beyond expectation were reported.

**Conclusions:** Apatinib in combination with PLD statistically significant prolonged PFS in patients with platinum-resistant or refractory recurrent ovarian cancer. ORR and DCR were also significantly improved. Adverse events were consistent with the established safety profiles of apatinib and PLD.



**Abstract ID:** 11584

**Title:** ENPAC: Phase II trial with safety lead of enzalutamide in combination with paclitaxel and carboplatin for advanced or recurrent endometrioid endometrial adenocarcinoma

**Presenting Author:** Shannon Westin, MD

**Objectives:** The androgen receptor (AR) is more widely expressed than the estrogen or progesterone receptor in endometrial cancer (EC), including up to 90% of endometrioid type. Enzalutamide binds to the AR thereby nuclear translocation of receptors and blocking the association of the AR with DNA. We sought to evaluate the efficacy of paclitaxel, carboplatin and enzalutamide in a phase II study of advanced or recurrent endometrioid EC.

**Methods:** Women with chemo-naïve, advanced-stage or recurrent endometrioid EC with measurable disease and adequate end organ function were eligible. Documented AR expression was not required. A safety lead in of the triplet was performed to confirm dose. In phase II, patients received 28 days of enzalutamide (160mg daily) as a single agent before starting triplet therapy. Pre- and post-treatment biopsies were obtained during the single agent lead in for evaluation of molecular markers including AR receptor expression and activation, expression of AR-related genes/proteins, and DNA copy number alterations and mutations. Patients then received carboplatin (AUC 6 IV Q3wk), paclitaxel (175 mg/m<sup>2</sup>), and enzalutamide (160mg daily). Response per RECIST 1.1 was assessed every 3 cycles for a maximum of 9 cycles. Evaluable patients received at least 6 cycles of triplet therapy. Progression free survival (PFS) was calculated from date of treatment initiation to earliest date of progression, death, or last contact. This study was approved and funded in part by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Astellas Pharma Global Development, Inc.

**Results:** A total 81 patients were screened with 49 patients treated to date (safety lead in n = 7; phase II n = 42). Median age was 64 years (range 41-81) and the majority of patients had grade 2 histology (53.1%) and recurrent disease (81.6%). There were no dose-limiting toxicities observed during the safety lead in. Patients received a median of 9 cycles of triplet therapy (range 0-9). 8 patients (16.3%) did not receive chemotherapy due to rapid progression during single agent enzalutamide (n = 3), unrelated death (n = 2), withdrawal (n = 2), and unrelated stroke (n = 1). PFS for the entire cohort was 11.47 months (95% CI 9.86 – 17.94; Figure 1a) and 6-month PFS probability was 0.77 (95% CI 0.61-0.87). Among 35 evaluable patients, confirmed objective response rate was 71% (95% CI 54–85%), 6 months PFS probability was 0.83 (95%CI 0.66-0.92) and median PFS was 14.42 months (95%CI 11.2-25.5; Figure 1B). The most common adverse events were as expected for chemotherapy alone, including neutropenia (20%), anemia (18%), fatigue (18%), neuropathy (10%), hyperglycemia (14%), nausea (8%), and thrombocytopenia (8%).

**Conclusions:** The combination of enzalutamide, carboplatin, and paclitaxel was tolerable and had promising clinical outcomes in chemo-naïve advanced or recurrent endometrioid EC. Further analyses are ongoing regarding predictors of response and resistance to androgen-inhibitor therapy.  
NCT02684227

**Abstract ID:** 11486

**Title:** Complete pathological response following levonorgestrel intrauterine device in clinically stage I endometrial adenocarcinoma: Results of a randomized clinical trial

**Presenting Author:** Andreas Obermair, MD

**Objectives:** Intrauterine levonorgestrel (LNG-IUD) is used to treat patients with endometrial adenocarcinoma (EAC) and endometrial hyperplasia with atypia (EHA) but limited evidence is available on its effectiveness. The study determined the extent to which LNG-IUD with or without metformin (M) or weight loss (WL) achieves a pathological complete response (pCR) in patients with EAC or EHA.

**Methods:** This phase II randomized controlled clinical trial enrolled patients with histologically confirmed, clinically stage 1 FIGO grade 1 EAC or EHA; a body mass index (BMI) >30 kg/m<sup>2</sup>; a depth of myometrial invasion of less than 50% on MRI; a serum CA125 ≤ 30 U/mL. All patients received LNG-IUD and were randomized to observation (OBS), M (500 mg orally twice daily), or WL (pooled analysis). The primary outcome measure was the proportion of patients developing a pCR (defined as absence of any evidence of EAC or EHA) after 6 months.

**Results:** From December 2012 to October 2019, 165 patients were enrolled and 154 completed the 6-months follow up. Women were on average 53 years of age, with BMI 48kg/m<sup>2</sup>. A total of 96 patients were diagnosed with EAC (58%) and 69 patients with EHA (42%). A total of 35 participants were randomized to OBS, 36 to WL and 47 to M (10 patients were withdrawn). After 6 months, the rate of pCR was 61% (95% CI 42% to 77%) for OBS, 67% (95% CI 48% to 82%) for WL and 57% (95% CI 41% to 72%) for M. Across the 3 treatment groups, the pCR was 82% and 43% for EHA and EAC, respectively.

**Conclusions:** Complete response rates at 6 months were encouraging for patients with EAC and EHA across the three groups.

**Abstract ID:** 11636

**Title:** A Randomized, Phase II Study Comparing Single-Agent Olaparib, Single Agent Cediranib, and the Combination of Cediranib/Olaparib in Women with Recurrent, Persistent or Metastatic Endometrial Cancer

**Presenting Author:** B.J. Rimel, MD

**Objectives:** The Cancer Genome Atlas and others identified genomic events suggesting that endometrial cancer (EC) should be susceptible to DNA repair inhibition. Data from pre-clinical models suggest poly ADP-ribose polymerase (PARP) inhibitors alone or in combination with other targeted agents may be an effective therapeutic strategy in EC. Combinations of angiogenic inhibitors and PARP inhibitors have demonstrated synergistic effects and have been well tolerated in other tumor types. This study compared two experimental arms exploring DNA repair inhibition versus cediranib alone which has previously shown promising activity in GOG 229J.

**Methods:** A 1:1:1 randomized phase II study comparing cediranib (C) versus olaparib (O) or the combination of olaparib and cediranib (OC) for women with recurrent EC. Eligible patients had received at least 1 prior platinum containing chemotherapy but  $\leq 2$  prior lines of chemotherapy for recurrent EC. Cediranib was administered 30 mg PO daily, olaparib 300 mg PO BID and in the combination cediranib 20 mg PO daily / olaparib 300 mg PO BID. One cycle in all arms was 28 days. Primary endpoint was progression free survival (PFS) by RECIST1.1. Patients were stratified by histology (serous vs. endometrioid)

**Results:** 120 patients were enrolled. 109 patients were treated: 34 patients C; 39 O and 36 OC. 10 patients withdrew consent prior to treatment. Median age was 66 years (range 41-86); 47 (39.2%) serous, 62 endometrioid (51.7%) and 8 (6.7%) mixed histology. The Kaplan Meir estimated median PFS was 3.8 months for C; 2.0 months O and 5.5 months for OC. The one-sided p value stratified log rank test comparing O vs. C was 0.935; HR 1.45 (95% CI 0.91-2.3) and C vs. OC 0.064; HR 0.7 (95% CI: 0.43-1.14). No new safety signals were reported.

**Conclusions:** The combination of cediranib and olaparib demonstrated modest efficacy in patients with recurrent, metastatic or persistent EC, but was not significantly different compared to cediranib alone. The combination was safe with no unexpected toxicity. Single agent olaparib demonstrated insufficient efficacy to warrant further investigation as monotherapy in this patient population.

**Abstract ID:** 11603

**Title:** Pembrolizumab for vulvar squamous cell carcinoma: Results from the phase 2 KEYNOTE-158 study

**Presenting Author:** Ronnie Shapira Frommer, MD

**Objectives:** Advanced vulvar carcinoma typically affects the elderly and treatment options are limited. Moderate antitumor activity of pembrolizumab (ORR, 6%) was noted in a small population of patients (pts) with PD-L1-positive vulvar cancer in the phase 1b KEYNOTE-028 study. KEYNOTE-158 (ClinicalTrials.gov, NCT02628067) is a larger, nonrandomized, multicohort, open-label, phase 2 study that evaluates pembrolizumab in pts with previously treated advanced cancers irrespective of tumor PD-L1 expression. We report results for pts in the vulvar carcinoma cohort receiving pembrolizumab monotherapy.

**Methods:** Enrolled pts were aged  $\geq 18$  y with histologically/cytologically documented advanced vulvar squamous cell carcinoma with prior treatment failure; measurable disease per RECIST v1.1; ECOG performance status  $\leq 1$ ; and tumor samples available for biomarker analysis, including PD-L1. PD-L1 positivity was defined as combined positive score  $\geq 1$  with expression evaluated using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). Pts received pembrolizumab 200 mg Q3W until disease progression, unacceptable toxicity, or completion of 35 treatment cycles. Tumor imaging was performed every 9 weeks for 1 y and every 12 weeks thereafter. Response was assessed per RECIST v1.1 by independent central radiologic review. The primary endpoint was ORR. Secondary endpoints included duration of response (DOR), PFS, OS, and safety.

**Results:** A total of 101 pts were enrolled. As of October 5, 2020, median time from start of treatment to data cutoff was 36.0 (range, 15.4–55.2) months. Median age was 64.0 (range, 31–87) y; 9 (8.9%) pts had no prior therapy, 57 (56.4%) had 1, 23 (22.8%) had 2, and 11 (10.9%) had 3 or more lines of prior therapy. Tumors were PD-L1-positive in 84 pts (83.2%), PD-L1-negative in 7 pts (6.9%), and non-evaluable/not assessed in 10 pts (9.9%). Overall, ORR was 10.9% (95% CI, 5.6–18.7); 1 pt had a CR and 10 pts had PR. Among pts with PD-L1-positive tumors, 8 of 84 (9.5%; 95% CI, 4.2–17.9) had CR or PR; among pts with PD-L1-negative tumors, 2 of 7 (28.6%; 95% CI, 3.7–71.0) had CR or PR. Among pts with a response, median DOR was 20.4 months (range, 2.1+ to 28.0). Among all enrolled pts (n=101), median PFS was 2.1 months (95% CI, 2.0–2.1) and median OS was 6.2 months (95% CI, 4.9–9.4 months). Treatment-related AEs occurred in 51 pts (50.5%), including 12 pts (11.9%) who had grade 3–5 events (no event occurred in  $>1$  pt). There were 2 deaths (2.0%) considered related to treatment (hepatitis, n=1; fulminant hepatitis, n = 1). Neither pt had comorbidities or pre-existing liver disease to contribute to these events; no other contributing factors were identified. A total of 5 pts (5.0%) discontinued because of treatment-related AEs. Immune-mediated AEs occurred in 18 pts (17.8%).

**Conclusions:** Pembrolizumab monotherapy was associated with durable responses in a subset of pts with vulvar carcinoma (ORR, 10.9%; median DOR, 20.4 months). Responses occurred in both PD-L1-positive and PD-L1-negative pts.

**Abstract ID:** 10398

**Title:** Increasing sensitivity to olaparib through inhibition of discoidin domain receptor 2 (DDR2) in homologous-recombination proficient ovarian cancer models

**Presenting Author:** Elizabeth Stock, MD

**Objectives:** Discoidin Domain Receptor 2 (DDR2) is a tyrosine kinase receptor which binds the most common extracellular matrix protein, fibrillar collagen type 1. DDR2 expression is critical for invasion and migration of ovarian cancer tumor cells, making DDR2 a potential target for new treatments. This study aimed to determine whether genetic inactivation of DDR2 in ovarian cancer cells would increase sensitivity to treatment with PARP inhibitor.

**Methods:** Two ovarian cancer cells lines, ES2 and COV362, were used for *in vitro* assays. Stable hairpin control and DDR2 knockdowns (shSCRM and shDDR2) were used for ES2 and transient small interfering RNA knockdown of DDR2 (siControl and siDDR2) were used for COV362. Homologous recombination (HR) status was determined by quantification of RAD-51 foci relative to controls using immunofluorescence after irradiation. Cell viability and survival after treatment with olaparib was quantified using MTS assays and clonogenics. The DNA damage response after treatment with olaparib was analyzed using immunofluorescence. *In vivo* studies to evaluate the sensitivity to olaparib in the presence or absence of DDR2 expression were performed in nude mice after intraperitoneal injection with ES2shSCRM or shDDR2 cells.

**Results:** ES2 and COV362 cells were found to have a 2-fold increase in RAD51 foci after irradiation indicating HR proficiency. DDR2 genetically inactivated cells (ES2shDDR2) were found to be more HR deficient than DDR2 expressing cells (ES2shSCRM) which remained HR proficient (0.80 vs 4.78 relative RAD51 foci per cell). We found that genetic inactivation of DDR2 in the ES2s and COV362s led to increased sensitivity to olaparib with an 80% (15uM vs 73uM) and 68% (62uM vs 195uM) reduction in IC50s, respectively, compared to DDR2 expressing cells. Additionally, ES2shDDR2 cells had decreased cell survival by clonogenic assay after treatment with olaparib compared to ES2shSCRM cells as measured by absorbance (0.64 vs 0.80,  $p = 0.005$ ). We found that DNA damage and the repair response was altered in DDR2 genetically inactivated cells treated with olaparib with an increase in gamma-H2AX (8 vs 6 foci per cell,  $p < 0.0001$ ) and 53BP1 foci (3 vs 1 foci per cell,  $p < 0.0001$ ) when compared to DDR2 expressing cells. In an intraperitoneal metastatic mouse model with the HR-proficient cell line ES2, we found that genetic inactivation of DDR2 led to decreased tumor burden when treated with olaparib compared to DDR2-expressing cells treated with olaparib (1499mm<sup>3</sup> vs 3236mm<sup>3</sup>,  $p = 0.04$ ).

**Conclusions:** DDR2 knockdown sensitizes HR proficient ovarian cancer cells to treatment with PARP inhibitor in both *in vitro* and *in vivo* models through a mechanism of induced HR deficiency and increased DNA damage. Future experiments will explore whether a DDR2 inhibitor can improve sensitivity to PARP inhibitor in HR proficient ovarian cancer models.

**Abstract ID:** 10505

**Title:** Survival advantage for chemoradiation compared with monotherapy in stage IVB cervical cancer: A propensity score balanced observational investigation

**Presenting Author:** Collin Sitler, DO

**Objectives:** Stage IVB cervical cancer is rare representing less than 5% of all cervical cancers. Treatment options include radiation (RT), chemotherapy (CT), surgery in rare cases and/or multimodality combinations. Current evidence suggests that chemoradiation (CRT) may be more effective than CT or RT alone. This study evaluated the impact of the different types of adjuvant treatment on overall survival (OS) in stage IVB cervical cancer after excluding patients who underwent surgery.

**Methods:** Women diagnosed with stage IVB cervical cancer between 2004 and 2014 and treated with RT alone, CT alone or CRT were evaluated. The source of data was the National Cancer Database. Surgical patients and those with multiple malignancies were excluded. Differences in clinical characteristics between the treatment groups were identified and then balanced using a propensity score approach. Survival was evaluated using weighted Kaplan-Meier method. Adjusted hazard ratio (aHR) and 95% confidence interval (CI) for risk of death were estimated in cohorts before and after balancing using weighted multivariate Cox modeling.

**Results:** There were 3,670 eligible participants including 62.1% treated with CRT, 23.6% with CT alone and 14.3% with RT alone. Median follow-up time was 51 months with 2,962 deaths at the time of the analysis. Patients treated by RT were older and had a higher comorbidity score than those treated with CRT or CT ( $P < 0.0001$ ). Women with adenocarcinoma were more likely to be treated with CT than CRT or RT ( $P < 0.0001$ ). Treatment with CRT was more common in those with a distant lymph node metastasis ( $P < 0.0001$ ). There was an incremental and persistent survival advantage for CT alone and CRT relative to RT alone in the cohort before balancing (Fig. 1A). The best survival was seen for CRT vs RT (aHR = 0.48, 95% CI = 0.42-0.54;  $P < 0.0001$ ). The median survival time pre-balancing was 3.9 months for RT alone, 9.0 months for CT alone and 13.5 months for CRT. After balancing, CRT was associated with superior survival (Fig 1B) over CT alone (aHR = 0.75, 95% CI = 0.68-0.84;  $P < 0.0001$ ) or RT alone (aHR = 0.52, 95% CI = 0.44-0.62;  $P < 0.0001$ ). Median survival time after balancing was 12.7 months for CRT, 9.1 months for CT alone, and 5.2 months for RT alone. The difference in survival between CT and RT was restricted to the first 12 months after diagnosis and then became similar with longer follow up (Fig 1B). The survival advantage of CRT over CT alone persisted across age, race/ethnic, comorbidity score, facility type, histology, grade, tumor size and site of distant metastasis groups with the exception of non-Hispanic Blacks and those with grade 3 disease, tumor size  $\geq 8.0$  cm, and patients who received palliative care (Fig. 1C).

**Conclusions:** CRT was associated with superior survival compared with CT or RT in this observational, hospital-based cohort after adjustment for prognostic covariates and merits further investigation in a prospective clinical trial. The contents of this abstract are those of the authors and do not reflect the views, opinions or policies of the USUHS, the Henry Jackson Foundation, the Department of Defense, the Departments of the Army, Navy, or Air Force or the U.S. Government.

**Abstract ID:** 10827

**Title:** Racial Disparities in Prevalence of Homologous Recombination Deficiency in Ovarian, Uterine, and Cervical Cancer Tumors

**Presenting Author:** David Mysona, MD

**Objectives:** Prior literature suggests that Black individuals exhibit a higher prevalence of aggressive molecular features in different cancers including endometrial cancers. Blacks may also have more defects in homologous recombination deficiency (HRD). It is currently unclear if the difference in somatic mutations in HRD genes between Blacks and Whites extends to other races and varies by cancer site. This study evaluated racial disparities in somatic mutations in HRD genes in ovarian, endometrial, and cervical cancer.

**Methods:** Data were obtained from The Cancer Genome Atlas (TCGA). Somatic mutations in genes associated with HRD including BRCA-1, BRCA-2, PTEN, CDK12, and RAD51C were acquired for the women with invasive ovarian, uterine, or cervical cancer. Race was categorized as White, Black, Asian, American-Indian, Pacific Islander, or Unknown. Chi-square was used to compare differences in the proportion of mutations between racial groups.

**Results:** A total of 280 ovarian, 472 uterine, and 139 cervical cancer patients were included in our analysis and the distribution of somatic mutations in five HRD are displayed in Table 1 by topographic site. Within ovarian cancers, BRCA-1 was the most common mutation (8.57%), followed by CDK12 (7.50%) and BRCA-2 (7.14%). The rate of BRCA-1 mutations in Asian, White, and Black individuals was 10.0%, 7.59%, and 6.25%, respectively ( $P=0.21$ ). In the endometrial cancer cases, 74.6% expressed a PTEN mutation, and 19.3% expressed a BRCA-2 mutation. PTEN mutations were less common in Black women (57.3%) compared to Whites (78.3%) or Asians (90.0%) ( $P=2.19 \times 10^{-18}$ ). Finally, 25.2% of all cervical cancer tumors expressed the PTEN mutation, with a similar distribution of PTEN mutations in Asians (28.6%), Blacks (26.7%), and Whites (23.4%) ( $p=0.78$ ). When considering gynecologic malignancies as an integrated group, 21.6% of Asians had somatic mutations in BRCA-1 (21.6%) compared to 9.9% in Whites (9.94%) or 7.5% in Blacks ( $P=0.001$ ). Asians also had the highest proportion of somatic mutations in BRCA-2 (24.3%) compared with 13.3% in Whites and 14.2% in Blacks ( $P=6.62 \times 10^{-6}$ ).

**Conclusions:** The observed racial differences in the distribution of somatic mutations in HRD across gynecologic malignancies merits further investigation to tailor treatment selection to target these defects.

**Abstract ID:** 11356

**Title:** Outcomes of gynecologic oncology patients at an epicenter of the COVID-19 pandemic

**Presenting Author:** Caitlin Carr, MD

**Objectives:** To describe the clinical course and associated mortality and morbidity of gynecologic cancer patients with COVID-19 infection with respect to cancer status, demographics, and comorbidities.

**Methods:** An IRB approved prospective registry was initiated of all gynecologic oncology patients with COVID-19 infections at a health care system in New York City from March 1 - June 1 2020. Clinical and demographic data was abstracted from the electronic medical record. Univariate and multivariate regression analyses were performed to identify factors associated with development of an adverse event defined as the composite of death, intubation, or ICU admission.

**Results:** In total, 57 gynecologic cancer patients with documented COVID-19 positivity were identified. The median age of identified patients was 68 years (range 32 - 91years). 29 patients (50.9%) required hospital admission and 28 (49.1%) patients required supplemental oxygen. 17 patients (30%) experienced an adverse event, defined as the composite of death, intubation, or ICU admission. Specifically 7 (12%) were intubated, 13 (23%) were admitted to the ICU, and 16 (27%) patients died from acute complications of COVID-19. All patients who were intubated and/or admitted to the ICU died from COVID-19 complications. Patients with elevated white blood cell count (WBC), absolute neutrophil count (ANC) and/or elevated prothrombin time (PT) were significantly more likely to experience an adverse event (WBC: 47 vs 12%,  $p=0.01$ ; ANC: 37 vs 8%,  $p=0.04$ ; PT: 61 vs 17%,  $p=0.04$ ). On multivariable analysis, ECOG status of 1 or greater was associated with a 26-fold increase in the odds of an adverse event (OR=26, 95% CI: 2 – 415,  $p=0.02$ ), and seven or more abnormal lab values was associated with a 305-fold increase in the odds of an adverse event ( $p=0.007$ ). The presence of active cancer ( $n=33$ , 57.9%) or receipt of systemic therapy ( $n=18$ , 31.6%) was not associated with the development of an adverse event ( $p=0.205$ ,  $p=0.81$  respectively). Type of systemic therapy (chemotherapy, immunotherapy, radiation) was not associated with adverse event development.

**Conclusions:** In this study, we analyzed the outcomes of gynecologic oncology patients with COVID-19 infections at an urban New York City hospital. Over 50% of patients required hospital admission for COVID-19 related symptoms, with a case fatality rate of 27%. Age, active cancer status, or recent systemic therapy was not associated with subsequent intubation, ICU admission, or mortality, while performance status and multiple abnormal lab values were significant risk factors. Further characterization of associated poor prognostic factors is needed in order to formulate best oncologic practices during the COVID-19 pandemic.



**Abstract ID:** 10416

**Title:** Cancer lethality: An important burden metric to consider for the allocation of clinical trial research funding from all sources

**Presenting Author:** Connor Wang, MD

**Objectives:** To identify trends and discrepancies between the number of clinical trials funded by public, industry, and other (individuals, universities, and community-based) organizations and measures of individual- and population-level cancer burden.

**Methods:** Clinicaltrials.gov was queried for US trials initiated from 2007-2017 in 18 cancer types. For each cancer, incidence and mortality rates were obtained from the CDC, and person years of life lost (YLL) was obtained from the SEER database. Trials were categorized by funding sources and analyzed by measures of cancer burden: incidence (I), mortality (M), YLL, and lethality (L, years of life lost per new diagnosis). Standardized ratios of the number of new studies each year to cancer burden metrics were generated. These ratios were labeled as studies funded by public sources (#P/I, #P/M, #P/YLL, #P/L), industry sources (#I/I, #I/M, #I/YLL, #I/L), and other sources (#O/I, #O/M, #O/YLL, #O/L). Mean annual ratios for GYN cancers were compared to other cancers using Wilcoxon rank-sum tests. Rates of change (ROC) for these ratios over the 11-year period for each funding source were analyzed by linear regression.

**Results:** Breast cancer was the most studied cancer among public, industry, and other funded sources, averaging 71.3, 101.6, and 101.0 new studies per year. For new studies in GYN cancers, ovary ranks 7th, 7th, and 10th; cervix 13th, 16th, and 13th; uterus 12th, 14th, and 12th. While breast and prostate cancers rank 11th and 17th in Lethality, the mean ratios for breast (#P/L 22.12, #I/L 31.84, #O/L 31.68, Figure 1) and prostate (#P/L 22.61, #I/L 33.37, #O/L 27.21) are the two highest across all 3 funding sources. Ovarian cancer ranks 4th in Lethality with 11.14 years of life lost per new diagnosis, yet it ranks 12th in mean #P/L (2.086 - lower than 10 others at  $p < 0.05$ ), 10th in #I/L (2.886 - lower than 9 others at  $p < 0.05$ ), and 14th in #O/L (1.557 - lower than 13 others at  $p < 0.05$ ). Cervical cancer is the 7th most lethal, but its ratios rank 16th in all funding categories (#P/L 1.373, #I/L 0.886, #O/L 1.108). Uterine cancer is the 12th most lethal with ratios ranking 8th (#P/L 5.755) 11th (#I/L 3.387), and 12th (#O/L 4.246). Over the 11-year period, the mean #P/L ratios for 4 of 18 cancers (uterus, testicular, brain, esophagus) had a significant negative slope or rate of change ( $p < 0.05$ ). Bladder cancer had the only positive ROC. For #I/L over 11 years, 9 of 18 cancers, including ovarian, had a significant positive ROC. None had a negative ROC. In other funded studies, 7 cancers had a significant positive ROC, and 11 were stagnant. For GYN cancers across all four cancer burden parameters, uterine showed a significant negative slope in the number of public funded studies and ovarian cancer had a significant positive slope for industry funded studies.

**Conclusions:** GYN cancers have significantly fewer initiated studies when compared by Lethality across funding categories. Lethality incorporates incidence, mortality, and YLL. It is an important measure of individual cancer burden and should be considered for funding allocation. Within all cancer sites, there is a significant trend towards rising industry and other funded trials and a trend towards decreasing or stagnating number of public funded studies. This data can be used to investigate reasons for the differential allocation of resources regarding clinical trial initiation.

**Abstract ID:** 10809

**Title:** CDKN2A loss-of-function genetic alterations in uterine sarcoma: Prognostic implications and potential therapeutic target

**Presenting Author:** Kathryn Miller, MD

**Objectives:** Uterine sarcomas frequently harbor non-actionable oncogenic mutations, limiting the use of targeted therapies. Alterations in the potentially targetable CDK4/6 pathway have recently been described. We explored clinicopathologic differences between uterine sarcomas with CDKN2A loss-of-function genetic alterations and TP53 loss-of-function mutations and sought to determine whether these molecularly defined uterine sarcomas differ in prognosis among early stage patients.

**Methods:** Patients with uterine sarcoma were consented to a prospective study of tumor-normal targeted massively parallel sequencing of up to 468 cancer-related genes. Clinicopathologic data were abstracted from the medical record. Fisher's exact tests and Mann-Whitney-U tests were employed to compare categorical and continuous variables, respectively. Kaplan-Meier curves were used to estimate survival, compared using log-rank test.

**Results:** A total of 229 patients with uterine leiomyosarcoma (LMS; n = 191) or undifferentiated uterine sarcoma (UUS; n = 38) were identified. The most common genomic alterations were TP53 (62%, n = 142) and RB1 (41%, n = 94) mutations/homozygous deletions. Furthermore, 10% (n = 23) harbored CDKN2A loss-of-function mutations or homozygous deletions, which were mutually exclusive with both TP53 and RB1 alterations ( $p < 0.001$ ). We defined 2 cohorts with uterine-confined sarcoma at diagnosis: 15 with CDKN2A functional loss, and 30 with TP53 alteration but wild-type CDKN2A. The cohorts were clinically and statistically comparable for age at diagnosis, BMI, use of morcellation at initial surgery, tumor size, mitotic rate, presence of LVSI, receipt of adjuvant therapy, and lines of therapy after recurrence. Both cohorts had high rates of hormone receptor positivity (73% vs 83%;  $p = 0.46$ ). The sarcomas harboring CDKN2A loss-of-function genetic alterations demonstrated frequent epithelioid/myxoid features and heterologous osteosarcoma elements (53% vs 7%,  $p = 0.001$ ). With median follow-up time of 49.8 months, the median PFS and 4-year OS in the CDKN2A altered sarcomas was 10.3 months (95% CI 2.7-17.8) and 61% vs 17.8 months (95% CI 13.5-22.0) and 87% in the TP53 altered/CDKN2A wild-type sarcomas,  $p = 0.18$  for PFS,  $p = 0.12$  for OS.

**Conclusions:** CDKN2A loss-of-function alterations, found in 10% of uterine sarcomas, are mutually exclusive with TP53 and RB1 alterations commonly present in this malignancy. CDKN2A altered uterine sarcoma may be a genomically and morphologically distinct tumor. We demonstrate poor survival outcomes for patients with early stage disease harboring these CDKN2A alterations. Identifying uterine sarcomas with CDKN2A loss-of-function alterations provides rationale for testing cyclin-dependent kinase inhibitors in this molecular subset.

**Abstract ID:** 10482

**Title:** The increasing incidence of uterine cancers in younger women

**Presenting Author:** Michael Richardson, MD

**Objectives:** To evaluate the incidence and genetic profiling trends in uterine cancer for women younger than 50 years of age in the United States.

**Methods:** Incidence rates were estimated from the United States Cancer Statistics (USCS) program for uterine cancers diagnosed at < 50 years old between 2001 and 2016 after correcting for hysterectomy and pregnancy prevalence from the Behavioral Risk Factor Surveillance System. SEER\*Stat and Joinpoint regression were used to calculate the incidence rate (per 100,000) and average annual percent change (AAPC). Data from National Cancer Institute Genomic Data Commons Data Portal including The Cancer Genome Atlas Program (TCGA) were obtained to compare genomic profiles by age.

**Results:** There were 93,693 eligible women diagnosed < 50 years old with uterine cancer between 2001 to 2016. The highest incidence was reported for women between the ages of 45 and 49 years old (33.84/100,000) compared with the younger cohorts (< 45 years old). In addition, uterine cancer incidence per 100,000 increased between 2001 and 2016 for each age group < 45 years of age including those 30-34 years old (3.8 to 5.8), 35-39 years old (7.7 to 11.4) and 40-44 years old (15.8 to 19.9, all  $p < 0.001$ ). The highest annual increase in uterine cancer diagnosed in the 30-34 year old age group was 4.4% for Hispanic women compared with 3.5% for Black women and 1.5% for White women. We then evaluated a panel of targetable molecular markers in young women diagnosed with uterine cancer at <50 years old ( $n = 96$ ) relative to older women diagnosed  $\geq 50$  years old ( $n = 1,005$ ). Tumors from younger women were more likely to express BRCA1 (11% vs. 4%;  $P = 0.004$ ), BRCA2 (14% vs. 8%;  $P = 0.06$ ), CDK12 (9% vs 4%;  $P = 0.02$ ), POLE (15% vs 8%;  $P = 0.02$ ), and less likely to express TP53 (14% vs 27%;  $P = 0.005$ ).

**Conclusions:** The incidence of uterine cancer in young women is increasing in the United States, especially for Black and Hispanic women. Tumors from younger patients may have molecular markers associated with targetable agents and may portend better prognosis.

**Abstract ID:** 10870

**Title:** Uterine lavage for the detection of ovarian cancer using an expanded gene panel

**Presenting Author:** Talayeh Ghezelayagh, MD, MPH

**Objectives:** Current screening methods for ovarian cancer have failed to demonstrate a significant reduction in mortality, and molecular methods of early detection are needed. Uterine lavage catheters have been used to detect tumor-specific *TP53* mutations from cells presumably shed from high-grade serous ovarian cancer, but this technique may not identify non-serous subtypes of ovarian cancer or early-stage disease. We aimed to pilot the combination of deep sequencing methods with an expanded gene panel to improve detection of both early stage and non-serous ovarian cancers.

**Methods:** Lavage of the uterine cavity was used to obtain samples from 35 consecutive patients undergoing surgery with preoperative concern for an ovarian malignancy. Lavages were filtered to remove endometrial cell clusters and DNA was extracted from cell pellets. Duplex sequencing, an ultra-accurate error-correction sequencing approach, was used to deeply sequence DNA from lavage samples (average duplex depth ~2500x) with a panel of candidate ovarian cancer driver genes including *TP53*, *ARID1A*, *PTEN*, *PPP2R1A*, *CDKN2A*, *KRAS* (whole genes), *CTNNB1*, *PIK3CA*, and *BRAF* (hotspots only). Tumor DNA was sequenced to identify driver mutations and compare with mutations found in the lavages. The overall mutation frequency in lavage DNA was calculated by dividing identified non-polymorphism mutant alleles by the total number of nucleotides sequenced in coding regions.

**Results:** In total, lavage samples were collected from 14 women with benign disease, 13 with high grade serous carcinoma, 3 with clear cell carcinoma, 3 with endometrioid carcinoma, 1 with granulosa cell carcinoma and 1 with carcinosarcoma. A total of 13 women had stage I or II disease (including five with stage I or II high grade serous). The filtered lavage samples yielded a median of 596.5 ng of DNA. Tumor sequencing is ongoing, but of seven fully sequenced lavage/tumor pairs, the tumor-specific mutation was identified in four lavage samples: *TP53* mutations found in 2 high grade serous carcinomas (stage IIb and stage III), an *ARID1A* mutation from a stage Ic3 clear cell carcinoma, and a *PIK3CA* mutation from a stage Ia endometrioid carcinoma. The tumor-specific mutation was not identified in lavage samples from two patients with endometrioid and one with clear cell carcinoma. Of 21 lavage samples that have presently undergone duplex sequencing, a total of 596 additional somatic mutations were identified in the nine genes. Lavages from patients with high grade serous carcinomas tended to have increased average mutation frequency of *TP53* and *KRAS* compared to patients with benign disease (*TP53*  $2.2 \times 10^{-6}$  vs  $9.2 \times 10^{-7}$ ,  $p = 0.09$ ; *KRAS*  $2.5 \times 10^{-6}$  vs  $1.1 \times 10^{-6}$ ,  $p = 0.10$ ).

**Conclusions:** Increasing sequence depth and using an expanded gene panel allows for the identification of tumor mutations from uterine lavage samples from early stage and non-serous ovarian cancer, as well as identifying significant somatic mutational background. Larger studies are needed to confirm the clinical utility of this method, but this is a promising technique that has the potential to improve the early detection of ovarian cancer.

**Abstract ID:** 10941

**Title:** Occurrence and timing of advanced care discussions in recurrent ovarian cancer patients participating in clinical trials remain to be optimized

**Presenting Author:** Anjalika Gandhi, MD, MS

**Objectives:** In women with recurrent ovarian cancer (OC), advanced care planning (ACP) such as advanced directives (AD), code status, and timely hospice referral should be addressed. In a high-volume, clinical trial focused cancer center, treatment with novel potentially life-prolonging therapies may alter timing of discussions. Our study compares patterns of ACP between trial and non-trial recurrent OC patients.

**Methods:** All patients  $\geq 18$  years who were treated at a single institution for the diagnosis of OC during the year of 2015 and had ever recurred were reviewed. Patients who ever ( $n = 84$ ) versus never ( $n = 41$ ) participated in a therapeutic clinical trial (CT) were compared. Chi-square or Fisher's exact tests and 2 sided t-tests or Wilcoxon Rank-Sum tests compared demographic data and ACP variables of interest using an  $\alpha = 0.05$ . Multivariable logistic regression estimated adjusted odds ratios (aOR) adjusted by CT participation, age, and Charlson comorbidity index.

**Results:** A total of 125 patients were identified, and 84 (67%) participated in CTs. Cohorts were similar in age, BMI, insurance status, and histopathologic characteristics. Median time to follow up after first recurrence was 856 days in trial patients vs 308 days in non-trial patients ( $p < 0.0001$ ). Caucasian patients comprised 95% of the CT cohort compared to 80% of non-trial patients ( $p = 0.0205$ ). Unadjusted analyses showed CT participants more frequently discussed AD (36% vs 17% non-trial patients,  $p = 0.0321$ ). Rates medical power of attorney (MPOA) discussion (54% in both), code status discussion (43% vs 27% in non-trial patients), and palliative care referral (49% vs 37% in non-trial patients) did not significantly differ. Median time between first recurrence and code status discussion was significantly longer in CT versus non-trial participants (731 days (IQR 102-1376) versus 57 days ((IQR 38-565),  $p = .0379$ ). Of the 81 deceased patients, though rates of hospice enrollment were similar (74% CT versus 71% non-trial), CT patients more frequently died in the hospital (22.8% vs 8.7%) or a care facility (14% vs 0%) ( $p = 0.0311$ ). ACP discussions and palliative care referrals tended to occur either during or after the trial (Figure 1). In adjusted analyses, palliative care referral remained the only significant predictor of code status discussions (aOR 3.69, 95% CI 1.67-8.152), AD discussion (aOR 14.46, 95% CI 5.04-41.49), and MPOA discussion (aOR 8.71, 95% CI 3.66-20.73). Participation in neither late phase nor phase 1 trials significantly predicted the odds of ACP.

**Conclusions:** The time between the recurrence and code status discussions was significantly longer in CT participants, and ACP discussions occurred typically during or after a trial. ACP occurred more frequently when patients were referred to palliative or supportive care referral, independent of participation in either late phase or phase 1 CT. Prioritizing ACP and supportive care referral, especially in CT participants, may improve these rates and optimize end of life care.

**Abstract ID:** 10725

**Title:** More than treatment refusal: An NCDB analysis of the impact of endometrial cancer treatment refusal on racial survival disparities

**Presenting Author:** David Barrington, MD

**Objectives:** Disparities in adjuvant treatment between Black and White women with endometrial cancer (EC) are well documented and contribute to worse outcomes among Black women. However, factors leading to disparate treatment patterns are understudied. We examined whether patient refusal of adjuvant treatment (chemotherapy or radiation) differed between Black and White women and whether refusal differences mediate racial disparities in EC survival.

**Methods:** We used the National Cancer Database (NCDB), a hospital-based registry covering ~70% of U.S. cancer diagnoses, to identify non-Hispanic Black (NHB) and non-Hispanic White (NHW) women diagnosed with EC from 2004 to 2015 who either received or refused chemotherapy or radiation. NCDB data are abstracted from medical records by tumor registrars. We used logistic regression to estimate adjusted odds ratios (aOR) of patient refusal of treatment associated with race, and accelerated failure time models to estimate differences in overall survival (OS) by race. We used causal mediation analysis to estimate how much of the difference in OS by race could be attributed to racial differences in treatment refusal. We considered the overall study populations as well as strata defined by histology, and adjusted for factors assessed at diagnosis, including age, comorbidity burden, insurance, hospital characteristics, stage, histology, and zip code-level income and education.

**Results:** We identified 49,518 women (83% NHW, 17% NHB) who received adjuvant chemotherapy and 12,710 women with documented refusal (90% NHW, 10% NHB). After adjusting for covariates, NHB women were more likely to refuse chemotherapy than NHW women (aOR=1.12, p=0.005), particularly among those with low-grade endometrioid (aOR = 1.22, p = 0.02) or serous (aOR = 1.38, p < 0.001) EC. Mean OS for NHB women was 43.5 months shorter than for NHW women. Of this disparity, 0.9 months of may be attributable to differences in chemotherapy refusal (p = 0.01). Among women with serous EC, NHB race was associated with 17.6 months shorter OS, with 1 month potentially attributable to refusal differences (p = 0.002). We identified 66,839 women (88% NHW, 12% NHB) receiving adjuvant radiation and 4,471 (88% NHW, 12% NHB) who refused. Among women with serous EC, NHB women were more likely to refuse radiation (OR = 1.39, p = 0.01), and NHB women had mean OS 13.2 months shorter than NHW women, 0.4 months of which may be attributable to differences in treatment refusal (p = 0.03).

**Conclusions:** We observed differences in treatment refusal by race, and those differences may be responsible for up to 1 month of the OS disparity between NHW and NHB women. This represents a small fraction of the dramatic racial disparity in EC survival. While a better understanding of the reasons for patient treatment refusal and subsequent intervention may help improve outcomes for some women, other causes of disparate outcomes warrant further investigation.

**Abstract ID:** 11111

**Title:** Robotic-assisted radical trachelectomy for early stage cervical cancer: Reproductive outcomes

**Presenting Author:** Sarah Paraghamian, MD

**Objectives:** We sought to evaluate pregnancy-related outcomes in women who elected to undergo uterine-artery preserving robotic-assisted radical trachelectomy (RRT) for fertility-sparing treatment of early stage cervical cancer.

**Methods:** This is a retrospective, multi-institutional, international study of patients who underwent attempted uterine artery-preserving RRT for primary treatment of FIGO 2009 clinical stage IA1, IA2 and stage IB1 cervical cancer. All consecutive patients undergoing surgery at 5 academic centers in Sweden, the US, England, and South Korea between December 2007 and September 2019 were included. RRT was performed as a fertility-sparing treatment for stage IA2 and IB1 disease as well as for stage IA1 disease with lymphovascular space invasion, multifocal disease, adenosquamous histology, or a cone biopsy with positive margins. Demographic and clinical data were collected via chart review. We used Student's T-test or Mann Whitney to compare continuous variables and Pearson's Chi<sup>2</sup>-test for categorical variables. Variables were entered into a Microsoft Excel database and analyzed using SPSS version 12.0 statistical software (SPSS, Chicago, IL, USA).

**Results:** Of 194 patients taken to the OR for attempted RRT, 185 underwent RRT, and 176 had bilateral preservation of the uterine arteries. Mean age was 31 years (range 18 to 51). Histologic classifications included squamous cell (n = 111), adenocarcinoma (n = 65), and adenosquamous (n = 6). A total of 9 patients had aborted RRT for intraoperative finding of a positive node or margin. A total of 8 patients underwent completion hysterectomy based on final pathology. A total of 15 patients received adjuvant treatment. Of the 155 patients who had neither hysterectomy nor adjuvant therapy, 91 (58.7%) attempted pregnancy and 69 (75.8%) achieved pregnancy. Of a total of 100 pregnancies, there were 70 live births (70%), 21 first trimester losses (21%), 5 second trimester losses (5%), and 4 (4%) patients are currently pregnant. Of the live births, 6 (8.6%) were delivered very preterm before 32 weeks gestation and 52 (74.3%) were delivered via planned cesarean section after 36 weeks. Compromise of at least one uterine artery significantly increased the rate of delivery before 36 weeks (17% vs 2%, p = 0.02). The median follow-up was 51 months.

**Conclusions:** Preservation of the uterine arteries bilaterally may lead to improved obstetric outcomes. This is the largest series reporting outcomes of uterine-artery preserving RRT to date and provides important data for counseling patients considering fertility-sparing treatment of early cervical cancer.

**Abstract ID:** 10311

**Title:** The subjective interpretation of negative trial results during oral plenary presentations

**Presenting Author:** Mary Katherine Montes de Oca, MD

**Objectives:** Oral presentations of phase 3 randomized controlled trials (RCTs) at oncology meetings often do not undergo peer review; this may lead to conclusions that do not reflect the primary results of the study. For example, the presentation may include a positive conclusion despite a negative trial result. Presentations at medical society meetings may have significant impact on the oncology community. The purpose of this study is to quantify and categorize not-negative conclusions made in oral plenary presentations of phase 3 RCTs for gynecologic malignancies.

**Methods:** Abstracts related to oral presentations of phase 3 RCTs at the Society of Gynecologic Oncology's Annual Meetings on Women's Cancer between 2005-2020 were reviewed. Studies with a primary endpoint of overall survival (OS) or progression free survival (PFS) and with a formally negative primary endpoint were included. Abstract conclusion sentences were classified as negative or not-negative. Trials with formally negative results were categorized based on the type of not-negative conclusions: 1) positive subgroup emphasis, 2) positive secondary endpoint emphasis, 3) emphasis on better numerical outcome despite nonsignificant p-value, 4) noninferiority interpretation of negative superiority trial. Studies with negative results and not-negative conclusions were compared to respective published manuscripts if available. The results and conclusion from the manuscript were compared to quantify and categorize not-negative conclusions.

**Results:** Oral presentations of 61 phase 3 RCTs met inclusion criteria. Of these, 22 had a formally negative primary PFS or OS endpoint, of which 6/22 (27%) presented a not-negative conclusion. There was a higher proportion of not-negative conclusions among negative trials in more recent years, with 50% (5/10) of abstracts from 2015-2020 including not-negative conclusions, vs just 8.3% (1/12) in studies from the preceding decade 2005-2014 ( $p = 0.03$ ; Figure 1). Authors emphasized a positive subgroup in 4/6 studies and a positive secondary endpoint in 1/6 studies. A numerically better outcome in the experimental arm was highlighted in 2/6 studies despite a nonsignificant p-value, and 1/6 studies made a non-inferiority interpretation of a negative superiority trial. Of 21 studies with formally negative results, 56% (5/9) for-profit studies had not-negative conclusions, whereas 8.3% (1/12) non-profit studies had not negative conclusions ( $p = 0.02$ ). Published manuscripts were available for 3/6 not-negative studies, all similarly incorporating not-negative conclusions despite negative results.

**Conclusions:** Since 2005, 27% of RCTs presented at SGO made not-negative conclusions despite formally negative results, with a majority emphasizing a positive subgroup and funded by for-profit organizations. These results further emphasize the importance of presenters' accurate portrayal of results and attendees' attention to bias during presentations.



**Abstract ID:** 11182

**Title:** Provider perception of racial healthcare disparities among women with gynecologic malignancies

**Presenting Author:** Kimberly Dessources, MD

**Objectives:** To identify patterns in provider perception of healthcare disparities among black patients with gynecologic malignancies.

**Methods:** An anonymous survey was distributed among the US physician members of the Society of Gynecologic Oncology. Participants were queried about demographics and their perceptions of healthcare disparities among patients with gynecologic malignancies. Responses to the outcome questions were collected on a continuous scale from 0-100, where 0 represented 'strongly disagree' and 100 represented 'strongly agree'. For the analysis, we dichotomized the continuous response to a binary outcome where the collected response > 50 is 1, and 0 otherwise. All survey responses, demographic and outcome questions, were analyzed descriptively using frequency (percent). The outcome questions were also summarized by whether the participant self-identified as white/non-White. Chi-square and Fisher's exact tests were performed to test independence.

**Results:** A total of 229 responses to the survey were analyzed. Of the respondents, 74% identified as white/Caucasian, 10% identified as black/African American, 2.2% identified as Hispanic or Latino, 8.7% identified as Asian, 0.4% identified as American Indian or Alaskan native, and 3.9% identified as mixed race. A total of 31% of respondents were male and 69% female. Irrespective of their own identified race, respondents felt strongly that black women with gynecologic malignancies have worse outcomes than white women, with 94% of respondents with a score > 50. However, respondents remained more neutral when queried about their own black patients' outcomes, with only 48% of respondents answering with a score > 50. This did not vary when comparing white to non-white respondents ( $p = 0.9$ ). When queried about the 2 most significant contributors to poor outcomes among black patients, 70% of respondents cited socioeconomic status. Other cited contributors included systemic racism (58%), distrust of the medical field (49%), unconscious bias/prejudice (47%), education/health literacy (45%), and intrinsic biological differences (31%). A total of 86% agreed that they could contribute to addressing healthcare disparities (87% responding > 50 for white respondents vs 84% responding > 50 for non-white respondents;  $p = 0.8$ ). Non-white respondents were more likely than white respondents to disagree that their institutions have measures to address healthcare disparities in black women (73% responding < 50 vs 47%, respectively;  $p = 0.002$ ). The most commonly cited metric addressing disparities at respondents' respective institutions was cancer care navigation, cited by 67% of respondents, followed closely by financial navigation at 64%. These measures were more often identified by white/Caucasian respondents vs non-white (cancer care navigation 72% vs 48%, financial navigation 68% vs 45%). A total of 35% of respondents cited disease prevention and enhanced screening programs as a measure to address disparities in black patients at their institutions. Community outreach was cited as a measure by 59% of the respondents; however, this was cited more by white/Caucasian respondents than non-white respondents (63% vs 41%).

**Conclusions:** Though most respondents agreed that black patients have worse oncologic outcomes, most did not perceive these issues within their own patients. There remains room for improvement in the identification of healthcare disparities within our own patients and implementation of well-studied measures used to address these gaps in outcomes.



**Abstract ID:** 11300

**Title:** Defining immune infiltrate heterogeneity by immunophenotyping of tumor micro-environment at single cell level: A step towards more effective personalized immunotherapy in ovarian cancer

**Presenting Author:** Shobhana Talukdar, MBBS

**Objectives:** Robust biomarkers reflecting tumor immune microenvironment and tumor cell-intrinsic features are needed in ovarian cancer (OC) in order to treat the right patients with the right immunomodulatory therapy. To address this need and to better understand the immune landscape of tumor microenvironment, we initiated this prospective study of women with ovarian cancer, which we refer to as the Ovarian Cancer Precision Medicine Initiative (OCPMI). Part of this initiative includes comprehensive molecular and histopathological analyses of tumor specimens taken during primary debulking, interval debulking and at recurrence. Our goal is to use the molecular and histopathological data from these specimens to develop predictive biomarkers to select candidates for immune therapy.

**Methods:** We have enrolled over 100 women and have examined five different strategies of measuring immune infiltration in 30 ovarian cancer patients: single cell RNA sequencing (scRNA seq), multiplex immunohistochemical assays, immunohistochemistry for PDL1 (Combined Positive Score - CPS), H&E analysis of immune infiltration (Salgado TIL score) and NanoString molecular subtyping. Platinum status in the cohort was: sensitive (20), resistant (4), refractory (3), and not determined (3). ScRNAseq was performed using the 10X genomics platform and multiple bioinformatic algorithms were applied to annotate cell types present in the sample. Comparisons between cell types identified by scRNAseq and multiplex IHC were performed and statistical correlations were made between clinical characteristics such as platinum resistance and molecular phenotypes. TIL scoring was performed using the Salgado scoring criteria and PDL-1 IHC staining was assessed based on Tumor proportion score (TPS) and Combined Proportion score (CPS). Additional slides were stained with antibodies for CD3, CD8, CD56, CD19, FOXP3, cytokeratin, and DAPI. Whole slides were analyzed using CD3 and CD8 density to quantify infiltration.

**Results:** ScRNAseq combined with multiplex IHC revealed extensive heterogeneity both within and between patients. PD-1 and PD-L1 genes were expressed in 23/30 (76%) patients across some cell types (% expression range: 1-22%) while 20/30 (66%) showed expression both in immune and epithelial cells. Highest expression of both genes was noted in 4/30 (12%) patients. PD-L1 gene levels by ScRNAseq demonstrated robust linearity across high and low expression ranges noted on IHC assays. ScRNAseq demonstrated an added advantage of being able to detect genes on tumor samples with absent PD-L1 IHC staining. Differential expression of PD-1/PD-L1 genes among 4 molecular subtypes showed highest expression level in immunoreactive group. Interestingly, 2 patients in this group showed absence of these genes indicating that molecular subtyping alone might not be predictive of immunotherapy response. Stromal TIL scores were binned into high (n = 4, 13%), moderate (n = 10, 33%), and low (n = 16, 53%) categories; no correlation was noted between TIL category and the level of PD-1/PD-L1 gene expression.

**Conclusions:** ScRNAseq identifies more patients with PD-1/ PD-L1 compared to IHC assays, suggesting histologic analysis of a single section might not accurately assess the heterogeneity of the PD-1/PD-L1 axis in the tumor microenvironment. Our study is ongoing and we will present our analysis of molecular phenotypes and correlations with clinical features such as platinum resistance. The goal of this project is

to use comprehensive molecular analyses to identify patients most likely to benefit from immunotherapy and further understand the mechanism of immune evasion in OC.

**Abstract ID:** 10656

**Title:** Employment disruption following diagnosis of gynecologic malignancies

**Presenting Author:** Roni Nitecki, MD, MPH

**Objectives:** Financial toxicity is a significant challenge for cancer survivors, which may be compounded a decrease in work hours or cessation of work altogether after diagnosis. We evaluated the frequency of employment change in the year following diagnosis of a gynecologic cancer, and assessed factors associated with a disruption in employment.

**Methods:** A cohort of patients 18-63 years-old who were diagnosed with cervical, ovarian, endometrial or vulvar cancer (January 2009- December 2017) were identified in the Truven MarketScan database, an insurance claims database of commercially insured patients in the United States. All patients who were working full or part-time at diagnosis were included, and all employment changes during the year following diagnosis were followed monthly. Clinical information, including receipt of surgery, chemotherapy and radiation, were identified using Common Procedural Terminology codes, and International Statistical Classification of Diseases codes. Cox proportional-hazards models incorporating measured covariates were used to evaluate the impact of covariates on change in employment status. Patients were censored when a change in employment was identified.

**Results:** A total of 7,446 women diagnosed with a gynecologic cancer (12.6% cervical, 24.7% ovarian, 2.6% vulvar, and 60.1% endometrial cancer) were identified. All patients held a full-time or part-time job 12 months prior to diagnosis. While most patients continued working following diagnosis, 20.6% cervical, 20.8% ovarian, 15.7% vulvar, and 21.7% of endometrial cancer patients experienced a change in employment from full-or part-time to long-term disability, retirement, or cessation of work. Older age (58-63), presence of comorbidities, and metastatic disease were associated with an increased risk of change in employment ( $P < 0.0001$ ,  $P = 0.0091$ ,  $P = 0.002$  respectively). In a multivariable model controlling for age, region of residence, comorbidities, insurance plan type, presence of adverse events, presence of metastatic disease, and cancer type, recipients of surgery plus adjuvant therapy (chemotherapy, radiation or chemoradiation) were 20% more likely to experience an employment change than those who underwent surgery alone (HR 1.23 95% CI 1.082-1.409).

**Conclusions:** A total of 16-22% women with a gynecologic malignancy and employer-subsidized health insurance experienced a change in employment status in the year following diagnosis. Adjuvant therapy, older age, presence of comorbidities and presence of metastatic disease

**Abstract ID:** 10457

**Title:** Volume-outcome relationship in vulvar cancer treatment: A Japanese Gynecologic Oncology Group study

**Presenting Author:** Shin Nishio, MD, PhD

**Objectives:** To examine the volume-outcome relationship for vulvar cancer treatment among the Japanese Gynecologic Oncology Group (JGOG)-affiliated centers.

**Methods:** This is a secondary exploratory analysis of a previously organized nationwide retrospective observational study in Japan (JGOG-1075S). This nationwide study examined consecutive 1,061 women with stage I-IV vulvar cancer, who received primary treatment care at 109 JGOG-affiliated centers from 2001-2010. The primary objective of analysis was to examine the association between hospital treatment volume of vulvar cancer and survival outcome. For the exposure allocation, hospital treatment volume over the 10-year study period was collected for any treatment modality that involved primary therapy after the vulvar cancer diagnosis. For the outcome measures of survival endpoint, progression-free survival and overall survival were assessed. Cox proportional-hazard regression models with restricted cubic spline transformation were fitted for analysis.

**Results:** The median age of the study cohort was 72 years, and the majority of vulvar cancers were squamous tumors (72.4%). Stage I disease cases were the most frequently diagnosed in this cohort (37.4%), and the majority of patients received surgical treatment (75.4%). The median follow-up was 58.2 months among the censored cases, and disease recurrence/progression and deaths from any causes were recorded in 423 and 349 cases, respectively. The survival effect of hospital treatment volume was examined in the whole cohort with all histology cases ( $n = 1,061$ ). The median hospital treatment volume was 9.5 cases per the 10-year study period. Hospital treatment volume of 23 cases or more over the 10-year study period represented a top-decile volume center. After adjusting for age, histology types, and cancer stage, there was no association between hospital treatment volume and progression-free survival ( $P = 0.820$ ; Figure 1A) or overall survival ( $P = 0.511$ , Figure 1B). The study cohort was then restricted to cases without Paget's disease ( $n = 909$ ). The median hospital treatment volume of this subcohort was 9 cases per the 10-year study period. After controlling for age, histology types, and cancer stage, there was no association between hospital treatment volume and progression-free survival ( $P = 0.591$ ; Figure 1C) or overall survival ( $P = 0.626$ , Figure 1D).

**Conclusions:** Likely due to the extreme narrow range of hospital treatment volume, the volume-outcome relationship was not observed for vulvar cancer survival in this study. Nationwide, depopulation in rural areas continues to occur in recent Japan. This national phenomenon may be another motivation to consider centralizing the care of vulvar cancer treatment. In certain disease conditions, stringent criteria for surgeons and facility capability will surely improve the quality of care. This study result serves as a wakeup call for further attention and investigation. A society based approach for treatment of vulvar cancer is highly warranted.

**Abstract ID:** 10401

**Title:** The accuracy of intraoperative frozen section examination of sentinel lymph nodes in squamous cell cancer of the vulva

**Presenting Author:** Brenna Swift, MD, MASc

**Objectives:** To measure the diagnostic accuracy of intraoperative frozen section examination of sentinel lymph nodes (SLN) in vulvar cancer and to describe associated patient outcomes.

**Methods:** This retrospective cohort study included patients with invasive squamous cell carcinoma of the vulva who underwent SLN biopsy with intraoperative frozen section at one cancer centre from Jan 2008 - Feb 2020. Exclusion criteria were tumor size > 4cm, multifocal tumor, palpable groin lymph nodes and neoadjuvant therapy. The SLN procedure was performed by injection of the primary vulvar tumor or scar with technetium-99m, ICG and/or blue dye. We compared the intraoperative SLN frozen section diagnosis and the paraffin section report for concordance. Recurrence location was described and recurrence free survival (RFS) was compared using the Kaplan-Meier method.

**Results:** A total of 173 patients (258 groins) met inclusion and exclusion criteria. On frozen section, there were 36/258 positive groins on frozen section and 222 negative groins. On final pathology, there were 39/258 positive groin nodes: 30 macro-metastases, 7 micro-metastases, 2 isolated tumor cells (ITCs). There were 219 negative groins. The sensitivity and specificity for frozen section detecting any metastatic disease compared to final pathology, was 89.7% and 99.5%, respectively. The positive-predictive value (PPV) was 97.2% and the negative-predictive-value (NPV) was 98.2%. There were 4 cases of false negative frozen section where final pathology revealed two cases of ITCs, 1 micro-metastasis and 1 macro-metastasis. A total of 30 patients (17.3%) underwent a full inguinal femoral lymphadenectomy during the same operation due to the frozen section results and avoided a second operation. A total of 2 patients (1.2%) required a second operation for lymphadenectomy due to false negative results on frozen section. Median (range) follow up was 38.0 (1-137.8) months. Median RFS was 14.9 (3.6 to 98.2) months. There were 46 recurrences in the study population, of which 29 were confined to the vulva, 9 groin recurrences and 8 distant recurrences. Among patients with a negative SLN biopsy on both frozen section and final pathology, there were 10 (3.9 %) groin and/or distant recurrences. A total of 6 nodal recurrences were ipsilateral, 1 was contralateral, 2 were bilateral and 1 recurrence was distant. After exclusion of patients with local recurrence only, the RFS at 3 years was 91.6% (95% CI 86.2-97.4%) for patients with negative SLN on frozen section and 64.6% (95% CI 46.5-89.7%) for positive SLN on frozen section. On final pathology, patients with negative SLN had a 3-year RFS of 91.7% (95% CI 86.3-97.4%), macro-metastases 58.4% (95% CI 38.5-87.7%), and micro-metastases/ITCs was 100%.

**Conclusions:** Intraoperative frozen section of SLNs in vulvar cancer is an accurate intraoperative guide to determine if complete inguinal femoral lymphadenectomy should be performed. SLN biopsy reduced the need for a second surgical procedure and does not appear to compromise patient outcomes.

**Abstract ID:** 10664

**Title:** Partial response or stable disease after neoadjuvant chemotherapy for advanced ovarian cancer: Time for surgery or more chemotherapy?

**Presenting Author:** Roni Nitecki, MD, MPH

**Objectives:** The association between number of neoadjuvant chemotherapy (NACT) cycles prior to interval tumor reductive surgery (iTRS) and survival is poorly defined. The question of whether to proceed with surgery or more chemotherapy in a patient who does not have a complete response after 3-4 cycles of NACT remains unanswered. We sought to assess survival outcomes stratified by number of chemotherapy cycles and residual disease following iTRS in a population of patients with partial response (PR) or stable disease (SD) following 3-4 cycles of NACT.

**Methods:** We identified a retrospective cohort of patients diagnosed between 2/2013 and 2/2018 who received at least 3 cycles of NACT (based on laparoscopic triage and/or medical and disease criteria) underwent iTRS for advanced ovarian cancer. All patients had a PR or SD following 3-4 NACT cycles based on imaging and CA-125. The population was divided into 4 groups based on number of NACT cycles prior to iTRS and residual disease status after iTRS (R0, no gross residual or R1, any amount of residual disease): (1) 3-4 NACT cycles/R0; (2) 3-4 NACT cycles/R1; (3) >4 cycles/R0; (4) > 4 cycles/R1. Overall-survival (OS) and progression-free survival (PFS) were estimated using Kaplan and Meier product-limit estimator and modeled via the Cox proportional-hazards model.

**Results:** The cohort consisted of 279 patients with a median age of 64. Most of the cohort was White (86.9%) with high-grade serous histology (90.3%) and stage IV disease (56.0%). The majority of patients received 3-4 cycles (73.8%), had a PR to NACT (92.8% vs 7.2% SD), with an overall R0 rate of 79.3%. For the entire cohort, R0 status was associated with improved OS (median of 43 months vs. 26 months;  $p < 0.001$ ). Receipt of > 4 cycles with an R0 resection was not associated with worse OS (HR 1.22, 95% CI 0.76-1.95) when compared to those who received 3-4 cycles with an R0 resection after iTRS. In the presence of R1 resection, receipt of 3-4 cycles or >4 cycles was associated with decreased OS (HR 1.89, 95% CI 1.17-3.05; HR 3.00 95% CI 1.65-5.46 respectively) compared to 3-4 cycles with a R0 resection. Only receipt of >4 NACT cycles with a R1 resection was statistically associated with worse PFS (HR 2.21 95% CI 1.38-3.55) compared to receipt of 3-4 cycles with a R0 resection.

**Conclusions:** Residual disease is significantly associated with OS regardless of number of NACT cycles in patients with PR or SD to NACT. These data suggest that the ability to achieve R0 should take precedence in decision making regarding timing of surgery in patients who do not have a complete response to NACT for advanced ovarian cancer and that surgery can still benefit patients who require additional chemotherapy in order to be considered resectable.



**Abstract ID:** 10243

**Title:** Surgical debulking improves survival in high-grade serous carcinoma regardless of platinum sensitivity

**Presenting Author:** Nicholas Cardillo, MD

**Objectives:** We aimed to assess whether patients who underwent primary optimal cytoreduction experienced improved survival regardless of platinum sensitivity.

**Methods:** We performed a retrospective, case-control study using our institution's ovarian cancer database to evaluate the effect of optimal cytoreduction on advanced stage, high grade serous ovarian cancer. Patients' characteristics were compared using logistic regression and both univariate and multivariate Cox-proportional hazard regression. Validation of the model was then performed within The Cancer Genome Atlas (TCGA) database.

**Results:** A total of 470 patients were assessed for inclusion. A total of 234 patients were included as responders to chemotherapy and 98 were included as non-responders. Significant survival characteristics were identified and included in the multivariate analysis. Figure 2 demonstrates independent predictors of survival. Kaplan-Meier survival curves showed improved survival both for patients who were responders to chemotherapy as well as optimal cytoreduction (Figure 3;  $p < 0.001$ ). Log-rank analysis demonstrated improved survival for patients receiving optimal cytoreduction among both non-responders and responders ( $p < 0.001$ ).

**Conclusions:** Our analysis shows that patients who undergo primary optimal cytoreduction have a survival benefit regardless of their response to chemotherapy. Our model is well-validated within the TCGA database. Therefore, optimal primary cytoreduction should be considered, even in patients with advanced disease. If we are able to someday predict whether or not patients will respond to chemotherapy, cytoreductive surgery should still be considered a part of the treatment of non-responders.

**Abstract ID:** 10336

**Title:** Development and validation of the Gynecologic Oncology Predictor Of Postoperative opioid use (GO-POP) model

**Presenting Author:** Brittany Davidson, MD

**Objectives:** With increasing use of minimally invasive surgical techniques and same-day discharges, the need to predict pain medication use on the day of surgery is critical to post-operative pain control, patient satisfaction and public health concerns. Our goal was to develop and externally validate a statistical model for predicting postoperative opioid use following gynecologic surgery in an increasingly minimally invasive surgical population, incorporating patient-reported surgical concerns.

**Methods:** We prospectively enrolled 382 women scheduled for abdominal surgeries (including laparotomies and minimally invasive approaches [MIS]) in an academic gynecologic-oncology practice to a study to develop and validate a predictor of outpatient opioid pill use. Negative binomial, zero-inflated negative binomial, and ordinal regression models were developed using an initial cohort of 216 women enrolled from February 2018-March 2019 and followed for 6 weeks postoperatively. A total of 39 candidate predictors were considered, including preoperative assessments of anxiety and anticipated pain as well as intra-operative factors. The primary model outcome was the number of opioid pills used postoperatively. After fitting models using best predictors, all models were internally validated with 1000 bootstrap samples to obtain bias-corrected accuracy using ordinal concordance index and calibration curves. All models' predictions were then externally validated using a second cohort (n = 166) enrolled from May 2019-February 2020. The best model (GO-POP) was updated by combining cohorts and an online calculator and nomogram were created. GO-POP included 7 predictors: age, total operating time, patient's self-reported pre-operative anticipated need for pain medication, whether pregabalin was administered pre-operatively, patient educational attainment, smoking history and patients' self-reported preoperative anxiety.

**Results:** Most surgeries were performed using MIS approaches (276; 72.3%) while 52 (13.6%) patients underwent planned laparotomies and 14.1% had planned MIS approaches converted to laparotomies. Median total number of opioid pills was 7 in the combined cohort. Nearly 40% of subjects used 0 pills after hospital discharge. After external validation, an updated combined model had the best fit, with ordinal concordance of 0.646 (95% CI:0.615, 0.679). Over 1/3rd of patients were either not planning to dispose of unused opioids or had not yet decided how to handle unused pills. A nomogram was created to facilitate clinical use of the model.

**Conclusions:** A prospectively constructed and validated model accurately estimates the number of opioid pills used by women after gynecologic surgery. Use of the GO-POP nomogram enables providers to tailor prescriptions using information available immediately following surgery. More work is needed to educate patients on the importance of disposal of unused opioids post-operatively to protect our communities.

**Abstract ID:** 10337

**Title:** Routine early screening for chemotherapy-induced hearing loss and other neuropathies in patients undergoing cancer treatment: A pilot study

**Presenting Author:** Jennessa Rooker, BSN, RN, OCN

**Objectives:** Neuropathies are well-recognized and potentially long-lasting complications of chemotherapy. The purpose of this study was to evaluate the feasibility and potential utility of routinely screening in patients undergoing cancer treatment for chemotherapy-induced neuropathies including: hearing loss (CIHL), peripheral neuropathy (CIPN), and cognitive impairment (CICI).

**Methods:** After obtaining Institutional Review Board (IRB) approval five registered nurses were trained to conduct this prospective observational cohort study. Patients were recruited and consented after being scheduled to receive taxane or platinum based chemotherapy regimens. Prior to each chemotherapy infusion, subjects were invited to undergo on-site, portable automatic iPad-based air-conduction hearing testing and complete questionnaires assessing symptoms associated with peripheral neuropathy (CIPNAT: Chemotherapy-induced peripheral neuropathy assessment tool) and cognitive impairment (AFI: Attentional function index). Descriptive statistics were used to summarize study data.

**Results:** A total of 20 subjects were enrolled. Each subject was able and willing to complete screenings and assessments prior to their chemotherapy infusion. Over 6 months, 2 subjects subjectively reported tinnitus and/or hearing impairment, which subsequently discontinued their chemotherapy. Both were unable to complete auditory testing due to tinnitus-associated pain induced by testing. In addition, objective evidence of auditory impairment was detected in another 7/16 subjects who denied subjective auditory symptoms. No improvements in CIHL were observed after subjects (n = 6) had a treatment delay. A total of 65 percent (n = 13) of subjects reported subjectively experiencing at least one symptom of peripheral neuropathy (CIPN). This was observed as early as the first cycle of chemotherapy (n = 6), after which the proportion of subjects experiencing CIPN increased. After the third treatment, the total number of subjects (n = 10) experiencing CIPN reported a decrease as dose reductions and/or treatment delays were initiated. All subjects (20/20) reported evidence of cognitive impairment (CICI) that progressively worsened over their treatment course. No improvements in CIHL or CICI were observed following dose reductions/delays or pyridoxine use.

**Conclusions:** Routine on-site screening for chemotherapy-induced neuropathies in patients receiving chemotherapy for cancer treatment is feasible. Importantly, these screenings can uncover otherwise unappreciated complications, such as hearing loss and impaired cognition. Given that neither CIHL or CICI improved following treatment delays or pyridoxine use, routine screening may allow for the early implementation of therapies to blunt the impact of long-lasting side effects which lead to decreased quality of life.

**Abstract ID:** 10606

**Title:** Genetic variants predictive of chemotherapy-induced peripheral neuropathy symptoms in gynecologic cancer survivors

**Presenting Author:** Lauren Thomaier, MD

**Objectives:** Identifying gynecologic cancer patients at higher risk of chemotherapy-induced peripheral neuropathy (CIPN), a common and debilitating side effect of cancer treatment, could inform treatment decision-making and quality of life discussions. We sought to identify genetic variants associated with the prevalence of CIPN among gynecologic cancer survivors, and to determine if these variants added predictive power to a model including demographic and clinical factors.

**Methods:** Patients were recruited from an academic gynecologic-oncology practice into a prospective cohort study. Participants included in this analysis provided a voluntary DNA saliva sample and self-reported CIPN symptoms (FACT/GOG-Ntx) along with other emotional, social and physical health items. Clinical and treatment data were abstracted from medical records. Genotyping of 23 single nucleotide polymorphisms (SNPs) in 15 genes identified in the literature as being related to platinum or taxane-induced neuropathy in other cancer populations was performed using iPLEX Gold method. The analyses were restricted to White females (97% of the cohort) and those who received chemotherapy. Risk allele carrier frequencies of individuals with and without high CIPN symptoms (FACT/GOG-Ntx score >9.5, median) were compared using logistic regression adjusting for age; odds ratios (OR) and 95% confidence intervals (CIs) are reported. We generated receiver operating characteristic (ROC) curves to examine the predictive ability of the identified significant SNPs along with known clinical risk factors (age, diabetes, body mass index (BMI), Charlson Comorbidity Index (CCI), previous cancer diagnosis) with regards to CIPN symptomatology.

**Results:** A total of 108 individuals who provided a saliva sample with sufficient DNA for analysis received chemotherapy and were included in the analysis. Mean age was 62.8±10.5 years; 40.4% had obesity and 9% had diabetes. Most were diagnosed with ovarian cancer (58%) or uterine cancer (30%), and were not actively receiving treatment (76%). Having at least one risk allele in two SNPs was significantly associated with high CIPN symptomatology: rs3753753 in *GPX7*, 2.65 (1.18, 5.92) and rs139887 in *SOX10*, 2.55 (1.14, 5.72). Further, including these SNPs in the predictive model improved the ROC curve area under the curve (AUC) over the demographic and clinical characteristics alone (AUC: 0.75 vs. 0.66, p = 0.04; Figure 1).

**Conclusions:** Genetic and clinical characteristics are predictive of higher CIPN symptomatology in gynecologic cancer survivors and combining these factors resulted in superior predictive power. Prospective validation of these results and assessment of their clinical utility are warranted.

**Abstract ID:** 10873

**Title:** Creation of an individualized algorithm for venous thromboembolism prophylaxis on a gynecologic oncology service

**Presenting Author:** Rafael Gonzalez, MD

**Objectives:** To evaluate implementation of a venous thromboembolism (VTE) prophylaxis algorithm on adherence to evidence-based guidelines including the rate of administration of preoperative heparin and the overall VTE rate on the gynecologic-oncology service at a single institution.

**Methods:** Prior to 2018, no consensus VTE prophylaxis protocol existed on the gynecologic oncology service at the authors' academic institution. ACOG and Chest guidelines were used to modify a published gynecology VTE risk algorithm. Interventions to improve preoperative heparin administration included: ID badge algorithm attachments, placards in operating rooms, integration of algorithm into the H&P template and order set in the electronic medical record. Surgical, anesthesia, and nursing teams were contacted to investigate cases in which pre-operative heparin was indicated but not administered. In 2020, three retrospective cohorts of 100 patients each (2016-2017, 2018, and 2019) spanning the pre-, intra- and post-QI implementation periods were consecutively identified using cancer and radical surgery-specific CPT codes to evaluate performance in these highest risk cases; cohorts were filled to 100 using randomly selected additional gynecologic oncology cases. Perioperative heparin administration and VTE rates were evaluated. Proportions were compared using chi-square tests; continuous factors were compared using ANOVA or Kruskal-Wallis tests.

**Results:** A total of 3 retrospective surgical cohorts totaled 312 patients (2016-2017: 100, 2018: 110, 2019: 102); mean age was 60. Indications for surgery were ovarian (36.9%), endometrial (35.6%), and cervical cancer (11.9%), and benign (15.6%). Minimally invasive cases comprised 52% of the cohort in 2016-7, 42.7% in 2018, and 42.2% in 2019 ( $p = 0.070$ ). The mean (SD) number of risk factors for VTE was similar across cohorts (2016-2017: 3.7 (1.6), 2018: 3.6 (1.4), 2019: 3.5 (1.7);  $p = 0.87$ ). When retrospectively applied to all surgical cases reviewed, adherence to VTE algorithm improved from 31.0% in 2016-2017 to 69.1% in 2018 and 82.4% in 2019 ( $p < 0.001$ ). Appropriate administration of pre-operative heparin in high-risk patients improved over time with each cohort: 34.8% in 2016-2017, 83.3% in 2018, and 92.5% in 2019 ( $p < 0.001$ ). The VTE rate within 30 days of surgery was 5.0% in 2016-2017, 3.6% in 2018, and 1.0% in 2019; this was not statistically significant ( $p = 0.25$ ). Adverse event rates were not significantly different between cohorts; peri-operative blood transfusion was 17.0% in 2016-7, 16.4% in 2017, and 10.8% in 2019 ( $p = 0.385$ ). Superficial and subfascial surgical site infections, hematomas, and vaginal cuff dehiscence were rare across cohorts.

**Conclusions:** Implementation of an individualized perioperative VTE prophylaxis algorithm has resulted in improved adherence to evidence-based prophylaxis guidelines and improvement in rates of preoperative heparin administration; observed trends in VTE rates have not achieved significance.