Abstracts Presented for the 48th Annual Meeting of the Society of Gynecologic Oncology
March 12-15, 2017
National Harbor, MD

Opening Scientific Plenary Session I
Sunday, March 12, 2017
Moderators: Jeffrey M. Fowler, MD, *The Ohio State University, James Cancer Hospital, Columbus, OH, USA*
Susan C. Modesitt, MD, *University of Virginia Health System, Charlottesville, VA, USA*

1 - Scientific Plenary
Rucaparib in patients with relapsed, primary platinum-sensitive high-grade ovarian carcinoma with germline or somatic *BRCA* mutations: Integrated summary of efficacy and safety from the phase II study ARIEL2
G.E. Konecny[a], A.M. Oza[b], A.V. Tinker[c], R.L. Coleman[d], D.M. O'Malley[e], L. Maloney[f], K. Wride[f], L. Rolfe[f], I. McNeish[g] and E.M. Swisher[h]. *[a]University of California, Los Angeles, Los Angeles, CA, USA, [b]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [c]British Columbia Cancer Agency, Vancouver, BC, Canada, [d]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [e]The Ohio State University, James Cancer Hospital, Columbus, OH, USA, [f]Clovis Oncology, Inc., Boulder, CO, USA, [g]Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom, [h]University of Washington, Seattle, WA, USA*

Objective: In ARIEL2 part 1, the poly(ADP-ribose polymerase) inhibitor rucaparib demonstrated activity in patients with relapsed, platinum-sensitive high-grade ovarian carcinoma (HGOC) with a germline or somatic *BRCA* mutation (g*BRCA*^{mut} or s*BRCA*^{mut}) (Coleman R et al. *J Clin Oncol* 2016;34:5540). ARIEL2 part 2 includes patients who received 3–4 prior lines of chemotherapy. Updated data from ARIEL2 parts 1 and 2 were pooled to evaluate the objective response rate (ORR) and safety of rucaparib in pts with relapsed, platinum-sensitive HGOC with a g*BRCA*^{mut} or s*BRCA*^{mut}.

Method: Patients who received platinum as their last treatment were sensitive to that treatment and who had a g*BRCA*^{mut} or s*BRCA*^{mut} were included in this analysis. The enrollment and data cutoff dates were May 1, 2016, and September 6, 2016, respectively. All patients received a starting dose of oral rucaparib 600 mg BID in continuous 28-day cycles until disease progression or other reason for discontinuation. Confirmed responses were assessed by the investigators according to Response Evaluation Criteria in Solid Tumors v1.1.

Results: Fifty-eight patients who enrolled in ARIEL2 part 1 (n = 41) or part 2 (n = 17) were eligible for this analysis. Patients received a median of 2 (range 1–6) prior lines of chemotherapy and a median of 2 (range 1–5) prior platinum-based therapies. The investigator-assessed confirmed ORR was 69.0% (95% CI 55.5–80.5). The ORR in patients with a progression-free interval of 6–9 months (n = 26), >9–12 months (n = 10), >12–18 months (n = 12), and >18 months (n = 10) was 61.5% (95% CI 40.6-79.8), 90.0% (95% CI 55.5–99.7), 75.0% (95% CI 42.8–94.5), and 60.0% (95% CI 26.2–87.8), respectively. Median duration of response was 9.2 months (95% CI 6.4–12.9). Common treatment-emergent adverse events included nausea (84.5%; grade ≥3, 3.4%), asthenia/fatigue (75.9%; grade ≥3, 6.9%), vomiting (50.0%; grade ≥3, 3.4%), and anemia/decreased hemoglobin (46.6%; grade ≥3, 27.6%). No treatment-related deaths were reported.

Conclusions: Rucaparib demonstrated activity and had an acceptable safety profile in patients with relapsed, platinum-sensitive HGOC with a g*BRCA*^{mut} or s*BRCA*^{mut}. Updated ORR, DOR, and progression-free survival data will be presented at the meeting.

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2 - Scientific Plenary
Sentinel lymph node biopsy for early cervical cancer: Results of a randomized prospective, multicenter study (Senticol 2) comparing adding pelvic lymph node dissection vs sentinel node biopsy only
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Objective: Given that the sentinel lymph node (SLN) technique is increasingly being used in the context of cervical cancer and that pelvic lymphadenectomy can lead to several complications, we decided to compare the morbidity, quality of life, and 3-year follow-up between women undergoing radical lymphadenectomy and women who didn't, both groups having negative SLN.

Method: Senticol 2 is a prospective randomized multicenter study carried out between March 2009 and July 2012 in 30 centers in France. The inclusion criteria were epithelial cervical cancer (except neuroendocrine type), stage IA-IIA1, and absence of pregnancy. The protocol has been funded by the French National Institute of Cancer and has been reviewed by the

Lyon IV Ethical Committee. The protocol includes a frozen-section evaluation of the SLN and, in the case of negative frozen-section assessment, a randomization between full pelvic lymph node dissection or SLN biopsy only. The main objectives of the study were pre- and postoperative morbidity, quality of life, and 3-year follow-up.

Results: A total of 206 patients were randomized: 101 patients were allocated to the complete pelvic lymphadenectomy group (arm B) and 105 were assigned to the group "SLN alone" (arm A). No false negative case of the SLN biopsy was identified in arm B. The surgical morbidity related to the lymph node dissection was significantly reduced in arm A: 33 cases (31.4%) versus 52 cases (51.5%) in arm B ($P = 0.0046$). Major morbidity related to the lymph node dissection was also reduced: 1 case in arm A versus 6 cases in arm B ($P = 0.06$). The analysis of the quality of life (SF36) questionnaires demonstrates that there are significantly lower scores for the arm B group. The analysis of legs lymphedema shows that there is always a difference between the two groups in the values of root and mid-tight perimeters, the arm A group having lower circumferences. Also leg heaviness and leg fatigue are significantly worse in the arm B group. We will present the 3-year follow-up of the patients.

Conclusion: In this prospective study, SLN biopsy alone induced less surgical morbidity, less lymphedema, and better quality of life than full pelvic lymph node dissection. This study leads to the morbidity-sparing approach in cervical cancer treatment while omitting the full pelvic lymph node dissection if the SLN are negative.

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3 - Scientific Plenary

Isolated tumor cells (ITC) identified by sentinel lymph node (SLN) mapping in endometrial cancer: Does adjuvant treatment matter?

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Objective: To evaluate the role of adjuvant treatment in the management of patients with endometrial cancer and isolated tumor cells (ITCs) identified by sentinel lymph node (SLN) mapping and its impact on outcome.

Method: This single-center study identified all patients undergoing hysterectomy, salpingo-oophorectomy, lymphadenectomy, and (SLN) mapping for endometrial cancer between November 2010 and December 2015. Data were prospectively collected. SLNs were ultrastaged on final pathology. Progression-free survival was analyzed according to the Kaplan-Meier nethod.

Results: A total of 519 patients were included. Overall, 85 patients (16.4%) were found to have SLN metastases, of which 43 (51%) were macrometastasis, 11 (13%) micrometastasis, and 31 (36%) ITC. Of those, 10 were stage IA, 15 stage IB, 4 stage II, 1 stage 3A (serosa +), and 1 stage IV (peritoneal disease). Twenty-eight (90%) were endometrioid tumors, 24 (77%) were grade 1 or 2, and 21 (68%) had lymphovascular space invastion (LVSI). Overall, 11 (35%) of patients with ITCs received adjuvant chemotherapy and 14 (45%) pelvic radiation therapy. Ten (32%) received either vault brachytherapy only or no adjuvant treatment at all. Only 1 patient with ITC recurred (IB, 7-cm carcinosarcoma) despite adjuvant chemotherapy and radiation therapy. The overall progression-free survival at 24 months for the ITC patients was 93.8%; 100% for patients treated with brachytherapy or observation alone, and 91.7% for those receiving external radiotherapy and/or chemotherapy. None of the patients with ITC and endometrioid histology recurred.

Conclusion: Patients with endometrial cancer found to have SLN ITCs have an excellent outcome. The use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of ITCs. Patients with ITCs should not be considered N+ and should not routinely receive adjuvant chemotherapy.

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4 - Scientific Plenary

Comparison of long term impact and clinical outcomes of reduced dose vs standard dose quadrivalent human papillomavirus vaccine in the United States: A database study

B. Zeybek and A. Rodriguez. *The University of Texas Medical Branch, Galveston, TX, USA*

Objective: The objective of this study is to investigate the long-term effects and clinical outcomes of varying humnan papillomavirus (HPV) vaccine doses in the U.S. population.

Method: Health insurance claims from the Clinformatics™Data Mart (CDM) Database over a 9-year period (2006–2015) were used in the study. ICD-9 codes were used for data extraction. All patients who had at least 1 dose of HPV vaccination were included. Exclusion criteria included female patients who were outside the age range, were not continuously enrolled for insurance, or had a prior record of cervical cytologic or histologic abnormality, and all male patients. Final study cohort included females between ages 9 and 26 years with at least 1 dose of the HPV vaccine within a 3-year period and without a

previous diagnosis of cervical dysplasia or cervical cancer. The follow-up period was at least 4 years and started either once patients reached 21 or once the last dose of vaccine was administered (age ≥21). A χ^2 test was used to analyze categorical outcomes. Continuous outcomes were analyzed by ANOVA, and time to event analyses were conducted by the Kaplan-Meier survival method.

Results: Final cohort included 11,335 women, out of whom 1,975 received 1 dose of the vaccine (group 1), 2,089 received 2 doses (group 2), and 7,271 received 3 doses (group 3). Mean age was 21.51 ± 2.67 years in group 1, 20.94 ± 2.85 in group 2, and 20.33 ± 2.85 in group 3. The mean time interval to receive subsequent vaccine shots was 5.25 ± 4.85 months in group 2 and 8.04 ± 4.07 months in group 3. Follow-up periods for all 3 groups were 62.71 ± 12.85, 61.84 ± 12.34, 61.75 ± 11.63 months. The incidence of high-grade cytology, CIN II or III histology, adenocarcinoma in situ, or invasive cancer are summarized in Table 1. Single-dose HPV-vaccinated women had a higher cumulative incidence of high-grade cytology or histology, adenocarcinoma in situ, and cervical cancer when compared to the 2-dose group ($P = 0.04$); however, there was no significant difference in clinical outcomes between the 2- and 3-dose vaccine groups ($P = 0.17$).

Conclusion: Our results show that women who received 2 doses of the HPV vaccine exhibit higher prophylactic efficacy against abnormal high-grade cytology, high-grade histology, adenocarcinoma in situ, and invasive cervical cancer when compared to women who received a single dose. However, no additional protective effect was found with getting a third dose of the HPV vaccine.

Table 1: Incidence Rate of High Grade Cytology, CIN-II or III and High Risk Group

No. doses	High grade cytology Failed N, %, CI			CIN-II or CIN-II histology Failed N, %, CI			High Risk Group Failed N, %, CI		
	Year 1	**Year 3**	**Year 5**	**Year 1**	**Year 3**	**Year 5**	**Year 1**	**Year 3**	**Year 5**
1	16 0.8 (0.5,1.3)	41 2.1 (1.5,2.8)	57 3.0 (2.3,3.8)	9 0.5 (0.2, 0.9)	25 1.3 (0.9,1.9)	43 2.3 (1.7,3.1)	21 1.1 (0.7, 1.6)	52 2.6 (2.1, 3.4)	82 4.3 (3.5, 5.4)
2	7 0.3 (0.2,0.7)	35 1.7 (1.2,2.3)	46 2.2 (1.7, 3.0)	7 0.3 (0.2,0.7)	20 1.1 (0.6,1.5)	32 1.5 (1.1, .2)	12 0.6 (0.3, 1.0)	45 2.2 (1.6, 2.9)	62 3.0 (2.4, 3.9)
>=3	40 0.5 (0.4,0.8)	134 1.8 (1.6,2.2)	199 2.8 (2.5, 3.3)	26 0.3 (0.2, 0.5)	88 1.2 (1.0, 1.5)	129 1.8 (1.5, .2)	58 0.8 (0.6, 1.0)	190 2.6 (2.3, 3.0)	280 3.9 (3.5, 4.4)

Definitions:

- High grade of Cytology: ASC-H or HGSIL
- High risk group: any of ASC-H, HGSIL, CIN-II, CIN-III, adenocarcinoma in situ, and invasive cancer

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5 - Scientific Plenary

Reasons for persistent suboptimal rates of HPV vaccination in the US: Shifting the focus from sexuality to education and awareness

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Objective: One of the major reasons physicians fail to recommend human papillomavrius (HPV) vaccination is their perceived need to discuss sex and sexuality beforehand. Given the importance of the physician recommendation, we sought to determine whether concerns regarding discussion of sexuality are consistent with parental reasons for lack of vaccine initiation.

Method: Provider-verified data from the National Immunization Survey–Teen 2010–2014 was used to calculate survey-weighted prevalence estimates of HPV vaccine initiation and provider recommendation among girls age 13–17 years. Annual prevalence estimates for parent-reported reasons for lack of initiation were calculated, and log binomial regression was used to evaluate trends in reasons over time.

Results: From 2010 to 2014, HPV vaccine initiation in girls increased nationwide from 47% to 60% ($P < 0.001$); among those who had received a provider recommendation, the rate increased from 62% to 69% ($P < 0.001$). The proportion of girls who

received a provider recommendation increased from 51% in 2010 to 74% in 2014 ($P < 0.001$). While concern that a child was not sexually active was a highly prevalent reason for not initiating HPV vaccination in 2010 (18%), this dropped to 9% in 2014 ($P < 0.001$). The 3 most common reasons for not initiating HPV vaccination in 2014 were the belief the vaccine is unnecessary, safety/side effect concerns, and lack of knowledge. Reasons related to necessity and safety decreased slightly over time (21% to 19%, $P = 0.018$; 23% vs 17%, $P < 0.001$, respectively), while lack of knowledge has not changed (14% in 2010 and 2014, $P = 0.8$). Religious beliefs, antivaccination sentiment, and concerns about increased sexual activity postvaccine were reported by less than <1% of parents and remained unchanged over time. (See Fig. 1.)

Conclusion: Despite providers' reported concerns, parents' main reasons for lack of HPV vaccine initiation do not relate to discussing sexuality beforehand. In fact, this has decreased as a reason for lack of initiation by 50% over the last 5 years, and concerns of increased sexual activity have remained <1%. Given that the top reasons for not initiating vaccination are necessity, safety, and knowledge, providers need to tailor vaccination discussions toward education and awareness. Discussing sexuality should not be a barrier to HPV vaccine recommendation.

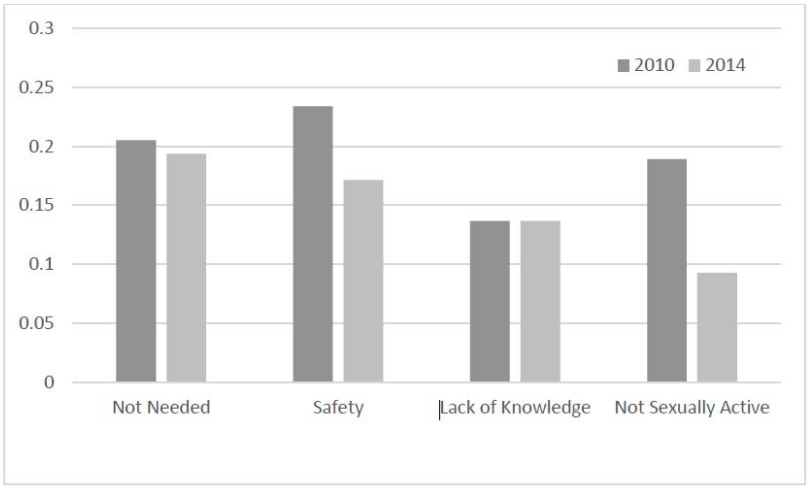

Fig. 1. The most common reasons for not initiating HPV vaccination amongst adolescent girls in the U.S., 2010 compared to 2014.

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6 - Scientific Plenary

Hospital readmission as a quality measure in ovarian cancer surgery

S. Uppal[a], R. Spencer[b], M.G. del Carmen[c], L.W. Rice[b] and J. Griggs[a]. [a]*University of Michigan Health Systems, Ann Arbor, MI, USA,* [b]*University of Wisconsin School of Medicine and Public Health, Madison, WI, USA,* [c]*Massachusetts General Hospital/Harvard University, Boston, MA, USA*

Objective: High readmission rate after surgery has been shown to reflect the poor quality of surgical care. The Affordable Care Act created the Hospital Readmission Reduction Program (HRRP), and as a result, the rates of readmission have declined. Although current clinical conditions under the HRRP do not include oncologic surgery, given the early success of the program, its expansion to include such procedures is likely to occur. In cancer care, surgical quality is defined not only by 30-day outcomes but also by overall patient survival. However, focusing on outcomes, such as 30-day readmissions, may penalize surgeons undertaking complex oncologic procedures, where higher initial morbidity may result in higher readmission rates. We therefore examined the hospital readmission rate as a quality measure in ovarian cancer surgery.

Method: Using the National Cancer Data Base, we identified 36,674 patients with stage III or stage IV serous ovarian carcinoma undergoing primary debulking surgery between January 2004 and December 2012. We then calculated annualized hospital volume and divided the hospitals into four categories (≤10, 11–20, 21–30, and ≥31 cases/year). Case-mix adjustment was done for patient factors (age, race, income, Charlson comorbidity index, and insurance status), tumor factors (stage and grade of disease), and treatment factors (facility type and year of diagnosis). Risk-adjusted rates of 30-day readmission, 90-day mortality, rate of adherence to National Comprehensive Cancer Network (NCCN) guidelines, and 5-year overall survival for each hospital were calculated.

Results: A total of 36,674 patients met inclusion criteria. Hospitals with ≥31 cases/year had the highest risk-adjusted readmission rate. However, these hospitals had significantly lower risk-adjusted 90-day mortality, higher adherence to NCCN guidelines, as well as higher 5-year overall survival rates. (See Fig. 1.)

Conclusion: In our analysis, hospitals with ≥31 ovarian cancer cases/year achieved higher overall survival and had lower 90-day mortality, but may still be unfairly penalized under the HRRP if 30-day readmission rates are the singular metric by which surgical quality is measured in this patient population.

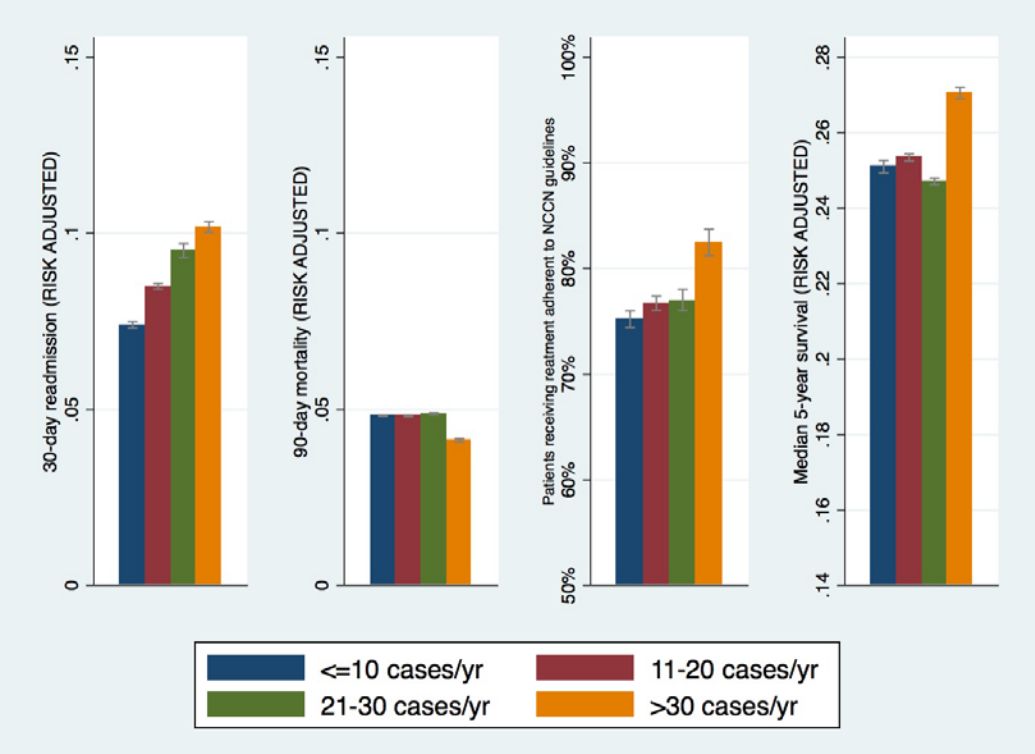

Fig. 1.

Scientific Plenary II: From Cell to Well
Sunday, March 12, 2017
Moderators: Sarah Foster Adams, MD, *University of New Mexico, Albuquerque, NM, USA*
Stephanie V. Blank, MD, *Icahn School of Medicine at Mount Sinai, New York, NY, USA*

7 - Scientific Plenary
***BRCA1* and *RAD51C* promoter hypermethylation confer sensitivity to the PARP inhibitor rucaparib in patients with relapsed, platinum-sensitive ovarian carcinoma in ARIEL2 Part 1**
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[a]University of Washington Medical Center, Seattle, WA, USA, [b]Clovis Oncology Inc., San Francisco, CA, USA, [c]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [d]University of California, Los Angeles, Los Angeles, CA, USA, [e]British Columbia Cancer Agency, Vancouver, BC, Canada, [f]The Ohio State University, Columbus Cancer Council, Hilliard, OH, USA, [g]Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom, [h]Mayo Clinic Minnesota, Rochester, MN, USA

Objective: Germline and somatic mutations in *BRCA1 and BRCA2* (*BRCA*) confer poly(ADP-ribose) polymerase (PARP) inhibitor sensitivity. Promoter hypermethylation is a mechanism of gene downregulation, and *BRCA1* and *RAD51C* promoter methylation have been associated with decreased gene expression in ovarian cancers. The objective of this work was to correlate *BRCA1* and *RAD51C* promoter hypermethylation with markers of homologous recombination deficiency (HRD) and with response to the PARP inhibitor rucaparib.

Method: *BRCA1* and *RAD51C* promoter methylation was assessed using methylation-sensitive polymerase chain reaction in paired archival and pretreatment biopsies in ARIEL2 part 1 (NCT01891344), an international, multicenter phase 2 study

investigating the PARP inhibitor rucaparib in patients with platinum-sensitive high-grade ovarian, peritoneal, or fallopian tube carcinoma.

Results: Of 165 patients with evaluable tumor samples, 21 (12.7%) were methylated at the *BRCA1* promoter, and 4 (2.4%) were methylated at the *RAD51C* promoter. Methylation of *BRCA1* and *RAD51C* was mutually exclusive with mutation in *BRCA* or other homologous recombination genes ($P = 0.015$). All 4 cases with *RAD51C* methylation and 15/19 (78.9%) with *BRCA1* methylation were associated with high LOH (≥14%). In 90 paired samples of archival and pretreatment tissues, *RAD51C* methylation was 100% concordant and *BRCA1* methylation was highly concordant ($P < 0.001$). For 13 cases with *BRCA1* methylation in the archival specimen, 4 (30.8%) were unmethylated in the paired pretreatment tumor. In 77 unmethylated archival specimens, gain of methylation in the pretreatment biopsy was observed just once. Confirmed Response Evaluation Criteria in Solid Tumors (RECIST) responses were seen in 52.4% (11/21) *BRCA1* methylated and 75.0% (3/4) *RAD51C* methylated cases. An updated comparison of the predictive performance of methylation and other HRD biomarkers will be presented.

Conclusion: *BRCA1* and *RAD51C* methylation in ovarian carcinomas correlates with a high response rate to PARP inhibitors and to high LOH, consistent with an HRD phenotype. The loss of *BRCA1* methylation from primary to recurrent carcinomas was common, even in these platinum-sensitive cases. Therefore, if methylation was to be used as a predictor of PARP inhibitor sensitivity, it would optimally be assessed in a pretreatment (not archival) specimen.

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8 - Scientific Plenary

Cluster analysis of chemotherapy non-responders for patients with serous epithelial ovarian cancer

M.E. McDonald, E.A. Salinas, A.M. Newtson, M.J. Goodheart, K.K. Leslie and J. Gonzalez Bosquet. *University of Iowa Hospitals and Clinics, Iowa City, IA, USA*

Objective: Nearly a third of patients with serous ovarian cancer will not respond to initial treatment with platinum therapy. Genomic and clinical characterization of these nonresponders may lead to potential alternative therapies for these patients. The aim of this study was to classify nonresponders to initial therapy through clinical and molecular features.

Method: Patients from The Cancer Genome Atlas with platinum-refractory or -resistant serous ovarian cancer were evaluated. Included were 88 patients with complete biological and clinical information. First, a genome-wide unsupervised "cluster of clusters" integrating gene copy number variation, mRNA expression, gene somatic mutations, and DNA promoter methylation to determine different patterns in these patients with incomplete response was performed. Clinical variables including surgical treatment, microRNA expression, and TP53 mutation to the resulting clusters or groups of patients were then added. A pathway analysis for each of the resulting clusters to identify targetable processes was performed.

Results: Three distinct clusters of nonresponders were identified. The first had overrepresentation of stage IV disease and suboptimal debulking, underexpression of miRNAs and mRNAs, hypomethylated DNA, "loss of function" TP53 mutations, and overexpression of PDGFR-driven pathways. The second had low miRNAs expression, generalized hypermethylation, MUC17 mutations, and significant activation of the WNT/β-catenin pathway. The third had more optimally cytoreduced stage III patients, overexpression of miRNAs, mixed methylation patterns, and "gain of function" TP53 mutations. Survival for all clusters was similar ($P = 0.48$). Pathway analysis of the components of these clusters identified potential alternative therapeutic targets for these groups of nonresponders: (1) anti-VEGF and tyrosine kinase inhibitors for cluster 1, (2) anti-PD1 therapy for cluster 2, and (3) combination of proteasome inhibitor with a histone deacetylase inhibitor for cluster 3.

Conclusion: Integration of genomic and clinical data detects 3 distinct clusters of patients with incomplete response to standard therapy. These clinical-molecular characteristics may lead to alternative therapies for patients who may fail initial standard treatment.

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9 - Scientific Plenary

The impact of physician burnout on clinical and academic productivity of gynecologic oncologists: A decision analysis

T.B. Turner[a], S.E. Dilley[a], H.J. Smith[a], W.K. Huh[a], S.C. Modesitt[b], S.L. Rose[c], L.W. Rice[c], J.M. Fowler[d] and J.M. Straughn Jr.[a]. *[a]University of Alabama at Birmingham, Birmingham, AL, USA, [b]University of Virginia Health System, Charlottesville, VA, USA, [c]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, [d]The Ohio State University, James Cancer Hospital, Columbus, OH, USA*

Objective: Physician burnout is associated with mental illness, alcohol abuse, and job dissatisfaction and disproportionately affects female physicians. Our objective was to estimate the impact of burnout on productivity of gynecologic oncologists (GOs) during the first half of their career.

Method: A decision model evaluated the impact of burnout on total relative work value (RVU) production during the first 15 years of practice for GOs entering the workforce from 2011 to 2015. The Society of Gynecologic Oncology practice survey was used to estimate physician demographics and mean annual RVUs for academic and private practice. Published data were used to estimate probability of burnout for male and female GOs, and the impact of depression, alcohol abuse, and early retirement on RVU production. Data from our institution estimated academic productivity for private and academic GOs. Academic productivity was defined as annual PubMed publications since finishing fellowship (8.6 for academic GOs vs 1.1 for private GOs). Sensitivity analyses (SA) were performed.

Results: An estimated 250 GOs entered the work force from 2011 to 2015 (85 males, 165 females). Without burnout, maximum RVU production for the cohort was 26.2 million RVUs over 15 years. Using burnout estimates (41% for females vs 27% for males), RVU production decreased by 1.6 million (5.9% decrease). Disproportionate rates of burnout among females resulted in 1.1 million lost RVUs for females versus 488,000 for males. Academic production without burnout was estimated at 9,277 publications for the cohort. Burnout resulted in 1,383 estimated fewer publications over 15 years (14.9% decrease). Using SA, we evaluated the impact of a wellness program that decreased burnout by 20%; RVU production would be increased by 212,000 and publications increased by 277.

Conclusions: The impact of burnout on clinical and academic productivity is substantial across all specialties. As health care systems struggle with human resource shortages, this study highlights the need for effective burnout prevention and wellness programs for all physicians. The specialty of gynecologic oncology is at greater risk for loss of productivity because of an increasing percentage of female GOs. Unless significant resources are designated to wellness programs, burnout will increasingly affect the care of our patients and the advancement of our field.

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10 - Education Forum

Enhanced recovery after surgery (ERAS) for ovarian cancer: Analyzing the cost effectiveness of a recovery program in primary cytoreductve surgery

R. Neff[a], J.D. Wright[b], D.E. Cohn[a] and L.J. Havrilesky[c]. [a]*The Ohio State University, Columbus, OH, USA,* [b]*Columbia University College of Physicians and Surgeons, New York, NY, USA,* [c]*Duke University Medical Center, Durham, NC, USA*

Objectives: We sought to determine the cost-effectiveness of a strategy in which all patients undergoing laparotomy for primary cytoreduction for ovarian cancer (OVCA) were managed in an enhanced recovery program (ERP) compared with usual care.

Methods: A modified Markov state transition model was designed to compare an ERP with usual care for all patients undergoing laparotomy with primary cytoreduction for OVCA. A published ERP, with evidence-based alterations to perioperative care, was used to build the model. The Premier database was queried for billing codes corresponding to OVCA primary surgical procedures, as well as any extended procedures (e.g., bowel resection). Total hospitalization costs as well as length-of-stay (LOS) data were extracted. Additional costs in the ERP cohort associated with variations from routine care were modeled. Published data suggest patients in an ERP have a 63% reduction in LOS compared with usual care. This reduction in LOS was simulated in the model for patients in an ERP with regard to costs. We assumed a 20% rate of bowel surgery and that all ERP patients would receive epidural analgesia in the base case model. Costs associated with perioperative medication use were modeled using CMS J-codes when available. Sensitivity analyses were completed to estimate the impact of epidural use and rate of bowel surgery on the model.

Results: On 21,923 modeled surgical procedures, of which 11,833 (54%) underwent an extended procedure, the mean estimated costs for ERP and usual care were $13,177 and $15,481, respectively, a difference of $2,304 favoring ERP. In the base case model and in all sensitivity analyses, ERP was less costly and resulted in a decreased LOS of 2.2 days compared with usual care. Thus, ERP dominated the usual care strategy (and no incremental cost-effectiveness ratio is calculated). When the expected rate of bowel resection at primary debulking was increased from 20% to 50%, the cost savings was $3,925 (an additional $1,621) per patient. Cost savings per patient is increased if fewer people get an epidural (Fig. 1).

Conclusions: ERP, in addition to its published clinical benefits, is more cost-effective than usual care and becomes more cost-effective as surgical complexity increases. Widespread implementation of enhanced recovery after surgery should be considered, but attention to the impact of specific components (such as epidural use) should continue.

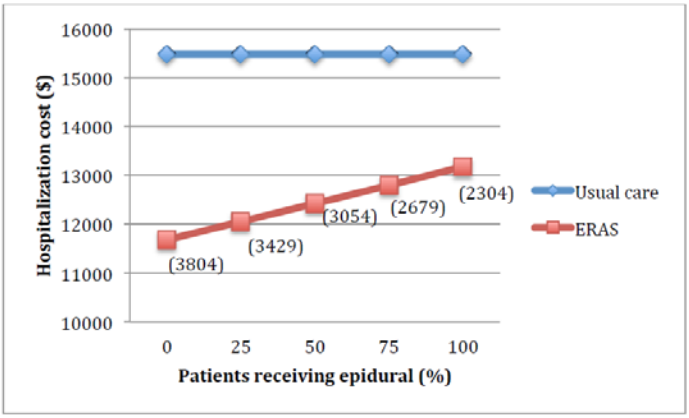

Fig. 1. Sensitivity analysis: As implementation of epidural use increases, cost savings per patient in an ERP decreases (indicated savings between usual care and ERP at each point on analysis)

Education Forum III: Immunotherapy Updates
Sunday, March 12, 2017
Moderator: Samir Khleif, MD, *National Cancer Institute, Bethesda, MD, USA*

11 - Education Forum
Activation of the wnt/β-catenin pathway is associated with an immunosuppressive tumor microenvironment in endometrial cancer
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Objectives: We have previously shown that activation of the Wnt/β-catenin pathway and *CTNNB1*mutation are associated with decreased survival in low-grade, early-stage endometrioid endometrial cancer. Suppression of local tumor immunity is one potential mechanism to explain these findings and may provide important considerations for targeted therapeutic approaches. We hypothesized that activation of the Wnt/β-catenin pathway is associated with increased tumor levels of the immunosuppressive cytokines IL-10 and TGF-β2.

Methods: qRT-PCR for TGF-β2 and IL-10 was performed on 169 well-characterized, frozen endometrial carcinomas (82% endometrioid, 18% mixed endometrioid and non-endometrioid). Values were expressed as molecules of transcript/molecules 18S rRNA. Activation of the Wnt/ β-catenin pathway was assessed by *CTNNB1*gene sequencing and quantification of transcript levels for cyclin D1. Clinical information was extracted from the medical record. Descriptive statistics, Fisher's exact test, Wilcoxon rank sum test, and Spearman's rank correlation were used.

Results: Activation of the Wnt/β-catenin pathway, as judged by high tumor levels of cyclin D1, was associated with younger age at diagnosis but no other clinical or pathological characteristics (Table 1). Higher cyclin D1 levels correlated with higher levels of both TGF-β2 and IL-10. This was also shown by higher median values of each cytokine when cyclin D1 was stratified into low and high levels (Table 1). The presence of *CTNNB1* mutation was associated with significantly higher levels of TGF-β2 compared to wildtype tumors (105.0 vs 2.1 x 10^{-6}, $p = 0.02$). TGF-β2 was also significantly higher in low-grade tumors, as well as in endometrioid compared with mixed histology tumors. IL-10 levels were not associated with *CTNNB1*mutation or any clinical or pathological parameter.

Conclusions: Endometrial carcinomas with activation of the Wnt/β-catenin pathway show evidence of microenvironment immunosuppression. Immunomodulation may be important for improving outcomes in these patients, though using *CTNNB1* mutation alone may miss identifying relevant tumors. A targeted therapeutic for the Wnt/β-catenin pathway in conjunction with immunotherapy may be an effective combination for treating recurrence in this group of endometrial cancer patients.

Table 1: Baseline clinical and pathology characteristics for the entire cohort and stratified across high and low *Cyclin D1* levels.

Characteristic	Overall (n= 169)	Low *Cyclin D1* < 452 x 10^{-6} (n = 78)	High *Cyclin D1* ≥ 452 x 10^{-6} (n= 87)	*p*-value
Age at diagnosis (median), years	59.0	62.5	57.0	0.01
BMI (median), kg/m^2	35.4	37.6	33.5	0.21
Histology, n (%)				0.54
Endometrioid	138 (81.7%)	65 (84.4%)	70 (80.5%)	
Mixed	30 (17.8%)	12 (15.6%)	17 (19.5%)	
Grade, n (%)				0.51
1	18 (10.7%)	9 (11.5%)	9 (10.7%)	
2	96 (56.8%)	48 (61.5%)	45 (53.6%)	
3	52 (30.8%)	21 (26.9%)	30 (35.7%)	
Stage, n (%)				0.91
1	114 (67.5%)	54 (70.1%)	58 (67.4%)	
2	6 (3.6%)	2 (2.6%)	4 (4.7%)	
3	32 (18.9%)	15 (19.5%)	16 (18.6%)	
4	15 (8.9%)	6 (7.8%)	8 (9.3%)	
Tumor size (median), cm	4.5	5	4.55	0.98
Myometrial invasion, n (%)				0.25
< 50%	112 (66.3%)	48 (61.5%)	61 (70.1%)	
≥ 50%	57 (33.7%)	30 (38.5%)	26 (29.9%)	
LVSI, n (%)				0.75
Absent	92 (54.4%)	43 (59.7%)	47 (56.6%)	
Present	67 (39.6%)	29 (40.3%)	36 (43.4%)	
TGF-β2 (median, x10^{-6})				
All	19.2	0	105.0	< 0.001
Endometrioid	56.1	8.8	126.1	< 0.0001
IL-10 (median, x10^{-6})				
All	29.1	21.6	36.2	0.009
Endometrioid	28.3	20.7	37.7	0.003

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Immunoediting, neoantigen frequency, and clinical outcome in patients with ovarian clear cell carcinoma

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Objectives: Recent early-phase clinical trials for immune checkpoint inhibitors have demonstrated durable response in some patients with ovarian clear cell carcinoma (CCC). To understand the immunological background of CCC and to explore potential biomarkers, neoantigen load and local immune profile were assessed by integrated molecular analysis of CCC.

Methods: A total of 74 cases of CCC were analyzed in this study. Exome sequencing and expression array were performed for those tumors. Mutations, neoantigen load, antigen presentation machinery, and immune profile were investigated; the relationship between clinical outcomes was also analyzed.

Results: Neither number of mutations nor neoantigens correlated with clinical outcomes in CCC. Gene expression levels of infiltrated immune cells did not correlate with outcomes as well. However, a high number of mutations in CCC as compared to high-grade serous carcinoma in The Cancer Genome Atlas cohort was observed. To determine whether the high mutation rate observed in CCC could result in immunoediting, the number of neoepitopes per mutation (neoantigen frequency) was further analyzed. A correlation between high neoantigen frequency with decreased progression-free survival (PFS) (P = 0.011) was found. A Cox multivariate regression analysis demonstrated that the high neoantigen frequency was an independent prognostic factor for PFS (P = 0.032). Immune-related genes were frequently highly expressed in tumors with low neoantigen frequency, suggesting evidence of immunoediting in the low-neoantigen-frequency group. In contrast, we observed decreased human leukocyte anigen class I expression (P = 0.036) as well as increased PD1/CD8 ratio (P = 0.017) in tumors with high neoantigen frequency. These results suggest that tumors with high neoantigen frequency in CCC might have received insufficient immunoediting due to an immunosuppressive tumor microenvironment.

Conclusions: Neoantigen frequency in CCC is an independent prognostic factor for clinical outcome and a potential candidate biomarker for an immune checkpoint inhibitor-based treatment