Late-Breaking Abstracts
Monday, March 24, 2014
Ballroom B-C
8:15 a.m. – 9:50 a.m.
Moderator: Diane Yamada, MD, *University of Chicago, Chicago, IL*

1 - Late-Breaking Abstract

A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gynecologic Oncology Group trial

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Objectives: To determine if VCB/C could increase recurrence-free survival (RFS) compared to PXRT. Secondary objectives included comparisons in survival (OS), frequency/severity of adverse events, and recurrence sites between the treatment arms.

Methods: A phase III trial was performed in EC patients meeting risk criteria. All patients (pts) were required to undergo hysterectomy. Staging was encouraged, but not required. Eligible pts had stage I endometrioid disease with GOG 99 based HR criteria (based on age, tumor grade, depth of invasion, and presence of lymphovascular space invasion), stage II, or stage I-II serous (S) or clear cell (CC) tumors. Central pathology review was performed. Patients assigned to PXRT were treated with standard 4-field or IMRT techniques. Additional VCB was optional for patients with S/CC tumors or stage II disease. Patients assigned to VCB/C received HDR or LDR brachytherapy followed by paclitaxel 175 mg/m2 (3 hour) + carboplatin AUC 6 q 21 days for a total of 3 cycles. All pts were to be assessed weekly for toxicity during therapy and at regular intervals for disease assessment.

Results: A total of 601 pts were accrued; PXRT was assigned to 301 (18 did not receive study treatment) and VCB/C to 300 (9 did not receive study treatment). The median age was 63 years, 74% had stage I disease, and 89% underwent lymphadenectomy. Histology included 71% with endometrioid type, 15% S, and 5% CC. Nearly all pts completed the prescribed therapy (91% PXRT, 87% VCB/C). Acute toxicity was more common with VCB/C. Recurrence sites totaled to 5 vs 3 vaginal, 2 vs 19 pelvic, and 32 vs 24 distant failures with PXRT vs VCB/C. With a median follow-up of 24 months, the 24-month RFS was 82% vs 84% for PXRT and VCB/C and treatment hazard ratio (HazR) was 0.97 (95% CI 0.635- 1.43) (VCB/C relative to PXRT). The 24-month survival was 93% vs 92% for PXRT and VCB/C and treatment HazR was1.28 (95% CI 0.689- 2.36) (VCB/C relative to PXRT). There was no statistically significant treatment effect heterogeneity with respect to RFS among clinical-pathologic variables evaluated.

Conclusions: This study did not demonstrate a superiority of VCB/C to PXRT in women with HR endometrial cancer. Both arms appeared to be well tolerated with high completion rates. Health outcomes and translational research are ongoing from participants in this study.

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2 - Late-Breaking Abstract

A phase II study to determine the response to second curettage as initial management for persistent "low-risk" non-metastatic gestational trophoblastic neoplasia: a Gynecologic Oncology Group study

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Objectives: To determine the hCG response of second curettage as initial treatment for patients with low-risk, non-metastatic GTN. Secondary outcomes: to determine if lesion size, myometrial invasion, W.H.O. risk score or hCG level predict surgical failure, and to describe surgical complications.

Methods: Multi-centered phase II study commenced in 2007 and closed April 2013. Eligible patients were staged by hCG assay, pelvic ultrasound, and chest x-ray. Pathology was centrally reviewed. Patients were categorized according to W.H.O. risk score (low risk 0-6), hCG level, lesion size and volume, and myometrial invasion. Surgical cure was defined as absence of rise/plateau in the hCG level (F.I.G.O. 2000 definition) for 6 months post-evacuation.

Results: Sixty-four women with untreated low-risk, non-metastatic GTN were enrolled. To date, 4 patients were excluded, 53 patients (88%) had complete mole, 12% were >39 years old, 7% <19 years old, and 8% had a risk score of 5/6. The hCG level was $>10^4$ miu/ml in 40% and $>10^5$ miu/ml in 7%. Uterine perforation (1) was treated conservatively. Other adverse events included four grade 1, one grade 2 and one grade 3 hemorrhage. Twenty-three patients (38%) successfully completed the study (surgical cure). An additional 2 patients (3%) achieved a complete response but did not complete follow-up. Progression occurred in 33 women (55%) and new metastatic disease (lung) was identified in 2 patients. In 4 patients the second curettage pathology was PSTT.

Conclusions: In this study, second curettage resulted in hCG normalization for 6 months in 38% of patients (95% lower confidence limit: 28%). Analysis of the association of baseline hCG level, W.H.O. risk score and lesion size, volume and depth of invasion with response is underway. PSTT in the second curettage suggests some tumors may undergo unexpected malignant de-differentiation. Initial second curettage may identify PSTT in such patients earlier.

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3 - Late-Breaking Abstract

Geriatric assessment and tolerance to chemotherapy in elderly women with ovarian, primary peritoneal or fallopian tube cancer: a Gynecologic Oncology Group study

V. E. Von Gruenigen[1], H. Huang[2], W. Tew[3], A. H. Hurria[4], H. Lankes[2], P. A. DiSilvestro[5], R. S. Mannel[6], J. H. Beumer[7], A. Heugel[8] and T. J. Herzog[9]

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Objectives: Elderly women with primary ovarian cancer are less likely to be offered standard cancer treatments, develop higher toxicity and have lower survival rates. To better understand this outcome disparity, the Gynecologic Oncology Group conducted a prospective cohort trial to determine whether geriatric assessment (GA) is associated with the ability of elderly patients to complete platinum-based chemotherapy.

Methods: Eligible women were 70 yrs and older with newly diagnosed, pathologic-confirmed adenocarcinoma of the ovary, peritoneum, or fallopian tube. Pts and their physicians decided between Regimen I (carboplatin AUC 5, paclitaxel 135 mg/m^2 plus G-CSF, every 3 wks) and Regimen II (carboplatin AUC 5 every 3 wks) for 4 cycles either after primary surgery or as neoadjuvant. GA (at baseline, pre-cycle 3, and post-cycle 4) included instrumental activities of daily living (IADL), activities of daily living, quality of life, and social support. Primary endpoints were to determine if IADLs predicted ability to complete 4 cycles of chemotherapy without dose reduction or more than 7 days delay and to estimate the number of pts who completed four chemotherapy cycles regardless of reductions or delay. Secondary endpoints included whether age or patient-related outcomes (PROs) were associated with chemotherapy completion without dose reduction or more than 7 days delay.

Results: Two hundred eight evaluable pts enrolled onto Regimen I (n=149) or Regime II (n=59). Pts on Regimen I were younger, mean 73 (70-88) yrs vs. Regimen II, mean 83 (range 71-97) yrs, fitter (PS 2-3: 11% vs. 37%), had higher completion rates (92% vs. 75%) and required less reductions/delays (18% vs. 46%). In the multivariate analysis, the inability to complete 4 cycles of chemotherapy was associated with Regimen II ($P<0.001$), neoadjuvant chemotherapy ($P=0.024$), and limited social activities ($P=0.034$), but not IADLs ($P=0.2$). In both regimens, PROs improved over time with cumulative chemotherapy cycles and at a similar pace.

Conclusions: IADL were not associated with the ability to complete chemotherapy without dose reduction or delay. The limitation of social activities was significantly associated with decreased tolerance to chemotherapy. A third arm of weekly paclitaxel was added to the study and continues to accrue.

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4 - Late-Breaking Abstract

SMARCA4 mutations in small cell carcinoma of the ovary

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Objectives: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare, highly aggressive form of ovarian cancer primarily diagnosed in young women. The molecular basis of this disease is unknown, and there are limited therapeutic options.

Methods: We performed target capture and massively parallel DNA sequencing to a mean depth 442x across 279 key cancer-associated genes in 12 SCCOHT samples. All mutations were validated using orthogonal techniques and their somatic nature was determined by sequencing matched germline DNA. Mutation expression and the consequence of splice site variants were determined through RNA sequencing. Functional significance was determined through *in vitro* manipulation.

Results: All 12 patients (median age 26.5 yrs; range 18-42 yrs) had inactivating bi-allelic variants in the chromatin regulator *SMARCA4,* including splice site, nonsense, and frameshift mutations or exon deletions. One patient had a germline mutation with somatic loss of the wild-type allele. All mutations were detected in RNA transcripts, and splice site variants resulted in transcribed introns. Immunoblotting and immunohistochemistry confirmed loss of *SMARCA4* protein expression in 7 of 9 cases with mutations and available tissue. Ectopic re-introduction of *SMARCA4* resulted in a dose-dependent suppression of cell growth. Stable depletion of *SMARCA4* using short hairpin RNA led to an increase in cell growth.

Conclusions: *SMARCA4* SWI/SNF chromatin-remodeling complex mutations were uniformly identified in all SCCOHT examined. The inactivating mutations are infrequently mutated in other solid tumors and are consistent with the characteristics of a tumor suppressor. Most of the identified mutations reside within the known helicase catalytic domains of *SMARCA4,* suggesting a role in tumorigenesis. These data suggest that canonical mutations in *SMARCA4* are an important therapeutic target for further investigation.

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5 - Late-Breaking Abstract

Risk of developing uterine corpus cancer (Ut Ca) following risk-reducing salpingo-oophorectomy (RRSO) in women with *BRCA* mutations

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Objectives: While RRSO is standard management in women with *BRCA* mutations (*BRCA*+), the role of concomitant hysterectomy has been controversial. Whether either low- or high-risk Ut Ca may be part of the *BRCA*-associated tumor spectrum remains unclear. The goal of this study was to prospectively determine whether or not the risk of Ut Ca in *BRCA*+ women following RRSO is greater than that seen in the general population.

Methods: From 6/1/1995 – 12/31/11, women undergoing *BRCA* testing were offered enrollment in an IRB-approved prospective cohort study. For this analysis, women were included if they were *BRCA*+ and underwent RRSO with their uterus left *in situ*. Time at risk began after both receipt of genetic testing results and RRSO. Follow-up was via annual questionnaires and medical record review. Censoring events were hysterectomy, Ut Ca diagnosis, last follow-up, or death. Expected cancer incidence was determined using age- and race-specific SEER data, adjusted for prevalence of hysterectomy. Ut Ca were categorized into low-risk (endometrioid, mucinous, adenocarcinoma NOS) and high-risk (serous, clear cell, sarcoma) histologies. The ratios of observed-to-expected (O/E) cancers and lower limit of 97.5% CI were analyzed using a 1-sided Poisson distribution events test.

Results: Five hundred twenty-five women met study criteria and were followed for a median of 5.8 yrs (range 0.1-16.9 yrs). During 3,292 woman-years of follow-up, 4 Ut Ca were diagnosed [2.23 expected; O/E=1.80, P=0.19]. No woman developed a low-risk Ut Ca [1.95 expected; O/E=0.0, P=0.14]. However, high-risk Ut Ca was observed in 4 *BRCA1*+ cases (2 serous, 1 carcinosarcoma, 1 leiomyosarcoma) 1.4 to 12.9 yrs following RRSO [0.28 expected; O/E=14.48, P<0.001], including 1 of 168 women with no prior breast cancer [0.06 expected; 0/E=16.7, P=0.06], and 3 of 357 women with prior breast cancer [0.22 expected; O/E=14.01, P=0.001]. When stratified by tamoxifen (tam) exposure, high-risk Ut Ca was observed in 2 of 131 tam (+) women [0.092 expected; O/E=21.68, P=0.004], and 2 of 394 tam (-) women [0.184 expected; O/E=10.87, P=0.015].

Conclusions: *BRCA*+ women may have an increased rate of developing high-risk Ut Ca following RRSO of ~1% at 10 years. While limited by small numbers, if these results are confirmed, these data could have implications for *BRCA*+ individuals considering RRSO.

Table 1. Observed and expected rates for high-risk uterine corpus cancers (serous, clear cell, carcinosarcoma and other sarcoma)								
	Expected	Observed	Follow-up (Women-Yrs)	1-sided p*	O/E Ratio	Lower 97.5% CI of O/E ratio	Estimated 10 year risk	Lower 97.5% CI of 10 year risk
All Participants (n=525)	0.276	4	3291.6	<0.001	14.48	3.94	1.22%	0.33%
Breast Cancer								
Yes (n=357)	0.214	3	2356.8	0.001	14.01	2.89	1.27%	0.26%
No (n=168)	0.062	1	934.8	0.060	16.07	0.41	1.07%	0.03%
Tamoxifen								
Yes (n=131)	0.092	2	995.1	0.004	21.68	2.63	2.01%	0.24%
No (n=394)	0.184	2	2296.4	0.015	10.87	1.32	0.88%	0.11%
*1-sided p values and confidence intervals are reported because with small expected values, the poisson distribution is markedly skewed.								