

the prevalence and prognosis of different molecular subtypes of HGSOc.

**Methods** We retrieved matching data of 455 cases of stage II-IV HGSOc from TCGA and categorized into 4 clusters based first on molecular subtypes (differentiated, immunoreactive, mesenchymal and proliferative) and then subdivided based on obesity and lipid metabolism gene pattern expression (CD36/TGF $\beta$  high vs low). Proportion and survival analyses were carried out. Chi square, Kaplan Meier were used to assess statistical significance.

**Results** Mesenchymal subtype was significantly more prevalent among women expressing CD36/TGF $\beta$  high (51,2% vs 6,9%,  $p < 0.0001$ ). Proliferative and differentiated were more prevalent in women expressing CD36/TGF $\beta$  low (71,3% vs 27,7%,  $p < 0.0001$ ). The 5-year overall survival was significantly different between subgroups with the immunoreactive subtype expressing CD36/TGF $\beta$  low experiencing the best outcome compared to the rest (median 67,7 vs 44,1 months, log-rank  $p < 0.01$ ). Cox analysis (including clustering, age, cytoreduction and therapeutic response) confirmed the immunoreactive CD36/TGF $\beta$ /low as independent prognostic factor.

**Conclusions** Our results confirm the importance of immune response and the negative impact that obesity and lipid metabolism alterations have in defining prognosis in HGSOc (supported by Fondecyt 1160800).

## Plenary 2

### IGCS19-0362

#### 6 INTERPRETING IMMUNE INFILTRATES AND HORMONE BIOMARKERS IN YOUNG WOMEN WITH ENDOMETRIAL CARCINOMA (EC) THROUGH A MODER LENS (POST-TCGA) OF MOLECULAR CLASSIFICATION

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**Objectives** Approximately 15% of ECs are diagnosed in women before the natural age of menopause. Fertility-sparing conservative management options are increasingly utilized, however biomarkers to inform prognosis or direct therapy are lacking. We sought to determine the value of additional immunohistochemical biomarkers in young women with EC in the context of modern TCGA-based molecular classification.

**Methods** Allred scores for estrogen/progesterone/androgen receptor and Ki67 in addition to immune characterization measuring stromal and epithelial expression of CD3/CD8/CD79a/CD138/PD1 and TIL<sup>high</sup> vs. TIL<sup>low</sup> clusters was performed in a cohort of previously characterized (n=257) young women (<50yo) with EC. Testing for association of

biomarkers with clinicopathological parameters, ProMisE molecular subtype (mismatch repair deficient (MMRd), POLE mutated (POLE), p53wildtype (p53wt) and p53abnormal (p53abn)) and outcomes was performed.

**Results** Young women had a high proportion of immune-rich ECs: 80% TIL<sup>high</sup> compared with 60% TIL<sup>high</sup> in non-age stratified cohorts. Expression of all immune biomarkers was enriched within POLE and MMRd subtypes. Within MMRd and p53wt ECs TIL<sup>high</sup> immune cluster was associated with improved overall-(OS)and disease-specific survival (DSS)( $p < 0.05$  for all). High ER and PR expression was associated with low-grade ECs, and increased PD1 expression. A trend (LRT  $p$ -value 0.1) towards improved OS(HR 0.4) and DSS(HR 0.273) in high PR-expression ECs was observed. Inconsistencies in progesterone treatment (dose, duration) precluded our ability to make firm conclusions on PR thresholds and efficacy. In multivariable analysis only ProMisE subtype showed independent prognostic significance.

**Conclusions** Molecular classification with additional selective biomarker testing can provide additional prognostic information and may help stratify young women with ECs for targeted therapies.

### IGCS19-0185

#### 7 EFFECT OF MEGESTROL ACETATE PLUS METFORMIN AS FERTILITY-SPARING TREATMENT FOR PATIENTS WITH ATYPICAL ENDOMETRIAL HYPERPLASIA AND WELL-DIFFERENTIATED ENDOMETRIAL CANCER. A RANDOMIZED CONTROLLED TRIAL

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**Objectives** The clinical remission (CR) rate of Megestrol acetate (MA) as fertility-sparing treatment was still not optimal. This study was to access whether MA plus metformin could lead to better CR rate for patients with atypical endometrial hyperplasia (AEH) and well-differentiated endometrial cancer (EC).

**Methods** This was a randomized, single-center, open-label and controlled trial (July 2013-December 2017). Patients were randomized to receive MA (160mg, orally, daily) or MA (160mg, orally, daily) plus metformin (500mg, orally, three times a day), then underwent hysteroscopy every 3–4 months. The primary efficacy parameter was the CR rates at 16th and 30th weeks of treatment (16w-CR rate and 30w-CR rate); the secondary efficacy parameter was rates of recurrence, pregnancy and live-birth.

**Results** Totally 150 patients received MA (n=74, 62 AEH and 12 EC) or MA/metformin (n=76, 61 AEH and 15 EC). The 16w-CR rates were 34.3% (23/67) and 20.7% (12/58) in MA/metformin- and MA-treated women ( $p = 0.091$ ). However, among 102 AEH patients, MA/

metformin yielded significantly higher CR rate (39.6%, 21/53) than MA alone (20.4%, 10/49,  $p=0.032$ , OR 0.347, 95%CI 0.132–0.914). Regarding 30w-CR rate, it was slightly higher in MA/metformin group than control (69.2% vs 57.4%,  $p=0.167$ ). Nevertheless, the mean treatment time in MA/metformin group was 4 weeks shorter (27 vs 31 weeks). Particularly, the mean weight gain by MA/metformin (2.5kg) was twice lower than MA alone (5.0kg,  $p=0.014$ ). No intra-group difference was found in rates of recurrence, pregnancy or live birth.

**Conclusions** MA/metformin may lead to a higher CR rate, shorter treatment time and less weight gain compared with MA alone.

## IGCS19-0640

### 8 MUTATIONAL ANALYSIS OF CERVICAL CYTOLOGY IN ENDOMETRIAL CANCER: A PROSPECTIVE MULTICENTER TRIAL

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**Objectives** Endometrial carcinoma (EC) is traditionally diagnosed by histopathological assessment of endometrial biopsies, leaving up to 22% of patients undiagnosed. This study explores the feasibility of the clinical implementation of detecting EC using mutational analysis of cervical cytology.

**Methods** This prospective multicentre study included patients that underwent a hysterectomy for histopathologically proven EC or a benign gynecological condition (control group). A Pap brush sample, cervicovaginal self sample, pipelle and hysterectomy specimen were obtained from each patient. A targeted next-generation sequencing panel was used to screen these samples for mutations in eight genes. Diagnostic accuracy was calculated, including sensitivity, specificity and predictive values.

**Results** Fifty-nine EC patients and 31 control patients were included. In these patients traditional histopathological diagnosis had a sensitivity of 78.9% and a specificity of 100%. For EC patients, 96.6% of surgical specimens contained at least 1 mutation. Blinded mutational analysis of Pap brush samples, self-samples, and pipelle endometrial biopsies yielded a sensitivity of 78.0%, 67.3% and 96.5% with a specificity of 96.8%, 96.8% and 93.5%, respectively. Combining these three methods with histopathological pipelle endometrial biopsies evaluations yielded a sensitivity of 95.8%, 93.0% and 96.5 respectively.

**Conclusions** This study has shown the potential of mutational analysis of cervical cytology and pipelle endometrial biopsies to improve diagnosis of EC, whether or not in addition to traditional histopathological assessment. Prospective evaluation is required for validation and clinical implementation.

## IGCS19-0267

### 9 GENOMIC PROFILING OF RECURRENT “ULTRA-LOW RISK” ENDOMETRIAL CANCER

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**Objectives** To characterize the genomic alterations in recurrent low-grade, non-invasive endometrioid endometrial carcinomas (EECs).

**Methods** We retrospectively identified patients with stage IA EEC who underwent primary surgery at our institution, 2/2009–2/2017, and had follow-up of at least 11 months. “Ultra-low risk” was defined as FIGO grade 1/2, non-invasive, and lymphovascular space invasion-negative. DNA extracted from 36 tumors and matched normal tissue/blood was subjected to massively parallel sequencing targeting over 400 cancer-related genes. Microsatellite instability was assessed via MSIsensor.

**Results** 499 patients with “ultra-low risk” EEC were identified. 14/499 (2.8%) had a recurrence. Median follow-up for non-recurrent cases was 33.0 months (range, 11–116) and for recurrent 50.5 months (range, 11–116). Recurrent patients were older than non-recurrent patients ( $p=0.016$ ), and had endometriosis identified during pathologic review of specimen more frequently ( $p=0.015$ ). Other clinical characteristics did not differ.

Mutational profiling of primary tumors from 8 recurrent and 28 non-recurrent patients revealed that most ultra-low risk EECs were microsatellite-stable (7/8, 88% recurrent; 26/28, 93% non-recurrent). Mutational signatures varied widely with no dominant signature identified among either group. *PTEN* and *PIK3CA* were the most frequently mutated genes in both groups. *CTNNB1* hotspot mutations were found in 4/8 (50%) recurrent and 9/28 (33%) non-recurrent EECs ( $p=0.146$ ).

**Conclusions** Patients diagnosed with “ultra-low risk” EEC have an excellent prognosis; however, we noted that 2.8% of patients developed a recurrence without identifiable clinical or pathologic risk factors. Genomic profiling did not reveal unique alterations in either group. Further work is needed to elucidate the mechanism/biomarker for recurrence in this “ultra-low risk” population.