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116 ESR1 HOTSPOT MUTATIONS IN ENDOMETRIAL STROMAL SACROMAS MAY CONFER HORMONAL RESISTANCE

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Objectives Rare low-grade endometrial stromal sarcomas (LGESS) may show high-grade morphology in primary or recurrent tumors. These lesions are classified as high-grade endometrial stromal sarcomas (HGESS), which in general are more aggressive and have higher rates of resistance to endocrine therapy than LGESS. The pathogenesis of hormonal resistance in these tumors has yet to be defined. Here we describe two endocrine-resistant HGESS with *ESR1*hotspot mutations.
Methods For case 1, DNA from the primary estrogen receptor (ER)-positive LGESS and two ER-positive HGESS recurrences, and for case 2, DNA from an ER-positive recurrent LGESS and ER-positive HGESS recurrence were subjected to sequencing targeting 468 cancer-related genes. RNA from each case was also evaluated for the presence of gene fusions using ARCHER FusionPlex. Sequencing data were analyzed using state-of-the-art bioinformatics algorithms.
Results Both patients received at least two lines of hormonal suppressive therapy including letrozole and megestrol. Cases 1 and 2 harbored *JAZF1-PHF1*and *EPC1-PHF1*fusions, respectively. The primary LGESS and the two HGESS recurrences of case 1 shared *MST1*,*KDM5C*and *ARID1B*mutations; however in the second HGESS recurrence post endocrine treatment, clonal *STK40*(R128W) and *ESR1*hotspot (Y537S) mutations were detected. In contrast, both LGESS and HGESS recurrences of case 2 harbored a *LATS2*mutation and a clonal *ESR1*Y537S hotspot mutation. In addition, an *HRAS*Q61R hotspot mutation restricted to the recurrent LGESS was identified.
Conclusions Our findings suggest that the *ESR1*Y537S hotspot mutation in LGESS, either pre-existing or acquired, may be associated with endocrine resistance and/or high-grade transformation in these lesions.

IGCS19-0091

117 COOPERATIVE EFFECT OF HUMAN PAPILLOMAVIRUS TYPE 18 E5, E6 E7 ONCOPROTEINS IN PROMOTING CELL PROLIFERATION, MIGRATION, INVASION AND IN MODULATING CELLULAR REDOX STATE

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Objectives The main aim of this work is to study how E5, E6 and E7 oncogenes of human papillomaviruses type 18 could cooperate among each other to boost key cancer cell features such as uncontrolled cell proliferation, enhanced migration capacity, invasion, and how this relates with oxidative stress.
Methods We generated three HaCaT cell lines, that are spontaneously immortalized, expressing the following combination of oncogenes: HaCaT E5–18, HaCaT E6/E7–18 and HaCaT E5/E6/E7–18 and non-transduced HaCaT cells as a control. Cell proliferation was assessed using a MTT assay. Cellular migration was studied using a wound healing assay by scratching the monolayer in order to generate a "wound". Invasiveness potential of cells was studied using a transwell collagen invasion assay. Intracellular oxidants production in the four cell lines was measured using the fluorescent probe CM-H2DCFDA. Catalase activity was assayed spectrophotometrically, following the decomposition of 10 mM H_2O_2 by catalase contained in the samples at 240 nm. Total glutathione in cell lysates was quantified by HPLC, and PRX1 expression levels was assessed by Western Blot.
Results MTT assay showed a statistically significant increment in cell proliferation in HaCaT E5/E6/E7 cell with respect to the other three cell lines. Similar results were obtained in cell migration assay, and in invasion assays. We measured levels of the three oncoproteins involved in ROS metabolism and observed that E5/E6/E7 diminished catalase activity but augmented significantly the levels of GSH and PRX1.
Conclusions This study demonstrates that cells with E5/E6/E7 together cooperate to augment the malignant transformation of HaCaT cells.

IGCS19-0385

118 CDK12 REGULATES GENE EXPRESSION OF DNMT1 AND ERBB3 BY ALTERING TRANSCRIPTION OF MIR-152

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Objectives The DNA-damage-response (DDR) pathway is a cellular mechanism which has evolved to protect cellular integrity by detection and repair of DNA lesions. Cyclin-dependent kinase 12 (CDK12) maintains genome stability via regulation of transcription of DDR genes, specifically, BRCA1, RAD51. Importantly, down-regulation of the CDK12 caused induction of the 53BP1 and γH2AX foci and accumulation of cells in the G2-M phase of the cell cycle. Since various microRNA (miRNA) are situated within coding genes, such as DDR, we hypothesize that expression of some of them might be also affected by CDK12 depletion.
Methods A pilot study focused on identification of candidate miRNAs in ovarian cancer cells that might be significantly altered in CDK12 deficient cells. Indeed, downregulation of CDK12 protein level led to aberrant expression of several miRNAs. Among studied miRNAs, the level of miR-152 was significantly elevated. By using

predictive algorithm, several proteins that might be targeted by miR-152 were examined.
Results Upregulated expression of miR-152 leads to decreased expression of DNMT1 (DNA methyl transferase 1), RICTOR and MET proteins, which are often found deregulated in rather wide spectrum of oncogenic diseases. In addition to DNMT1, the protein level of ERBB3 was also affected by downregulation of CDK12 in various ovarian cancer cells, such as PEO1, COV362 and OVCAR5.
Conclusions We speculate CDK12 participates in DDR machinery by two distinct mechanisms, either by orchestrating transcription of DDR genes or by stabilization of DNMT1 protein by blocking expression of miR-152 targeting DNMT1.

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119 TARGETED SEQUENCING OF HISTOLOGICALLY DEFINED SEROUS ENDOMETRIAL CANCER REFLECTS PROGNOSIS AND CORRELATES WITH PREOPERATIVE BIOPSY

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Objectives Evaluation of the impact of discordant endometrial sampling on the prognosis of patients finally diagnosed with uterine papillary serous carcinoma (UPSC) and analysis of UPSC mutational profile.
Methods Retrospective cohort study comparing outcomes of patients with UPSC preoperatively diagnosed with endometrioid endometrial cancer (EEC) or UPSC. Genes commonly implicated in carcinogenesis were analyzed in a subgroup of 40 patients, using next generation sequencing.
Results 61 patients with UPSC on post-surgical, final pathology were included in the study. Prior to surgery, 15 were diagnosed with EEC (discordant) and 46 were correctly diagnosed with UPSC (concordant). After a median follow-up of 41.6 months [5.4–106.7], a preoperative diagnosis of EEC was associated with better 3-year progression-free survival (100% vs. 60.9%, P=0.003) and longer disease free interval (63.5 versus 15 months, P=0.026) compared to patients with an initial diagnosis of UPSC. Patients with a concordant diagnosis of UPSC were 5 times more likely to progress or die compared to those with a discordant EEC diagnosis (P=0.02, P=0.03, respectively), and their tumors were associated with higher rates of *TP53* (88.9% vs. 61.5%, P=0.04), and a lower rate of *PTEN* (14.8% vs. 38.5%, P=0.09)and *ARID1A* (3.7% vs. 23.1%, P=0.05) mutations.
Conclusions A pre-surgical diagnosis of EEC is associated with improved prognosis in patients with UPSC. Some histologically defined UPSC tumors contain endometrioid-like molecular characteristics that may confer a survival advantage.

IGCS19-0687

120 FACTORS ASSOCIATED WITH EXTENDED SURVIVAL FOR PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER (PROC) TREATED WITH MODIFIED VACCINIA ONCOLYTIC VIROTHERAPY (VOV)

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Objectives VIRO-15 phase IB trial (NCT02759588) enrolled 11 patients with PROC, extensive tumor burden, and median 5 prior lines of therapy. We aimed to retrospectively determine factors that predict clinical benefit from VOV monotherapy in PROC.
Methods Patients received a modified VOV (GL-ONC1, Genelux Corp.) intra-peritoneally on two consecutive days. Four patients had apparent clinical benefit with >5 mos progression-free survival (PFS) following virotherapy (A). Seven (B) patients had <5 mo PFS. Comparative analyses included: measures of immune-competence with neutralizing antibody (NA) titers, virus-encoded glucuronidase activity (GA), tumor response by RECIST 1.1, Prognostic Nutritional Index (PNI), circulating tumor cells (CTCs), number of prior platinum and total therapies. Mann-Whitney test, *t*-test, *z*-test were used to evaluate differences between the groups.
Results Following GL-ONC1, the PFS was 10.9±5.1 and 2.4 ±1.1 mos for A vs B ($p< 0.05$). Mean OS for A was 21.7 ±8.2 mos vs 3.6±1.5 mos for B ($p<0.05$). Three A pts are alive, and one with stable disease died at 8-mos from pulmonary embolism. Factors that predicted clinical benefit were: i) PNI [mean 49.0±5.7 vs 42.1±4.3 ($p<0.05$)], ii) Week-5 CA125 values < Week-2 [4/4 vs 0/7 ($p<0.01$)], iii) absence of CTC [3/4 vs 1/7 pts ($p<0.05$)].
Conclusions Factors associated with clinical benefit post GL-ONC1 monotherapy in PROC include higher PNI, absence of CTCs, and Week-5 CA125 less than Week-2 levels. In the absence of these factors, cytotoxic therapy should be considered by Week-6 following GL-ONC1. Three patients are currently alive at 22.8–28.2 mos, following additional therapies.

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121 ADENOMYOSIS AND ENDOMETRIAL CANCER – IS THERE A RELATIONSHIP OR ONLY A PARTNERSHIP?

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Objectives Adenomyosis (AM) is very often diagnosed in histology slides of endometrioid endometrial adenocarcinoma (EEAC). The combination of EEAC and AM has not been investigated sufficiently. The aim of this study is to evaluate the combination of AM and EEAC in morphological and morphometrical terms and to reflect a possible role of AM in the pathogenesis of EEAC.