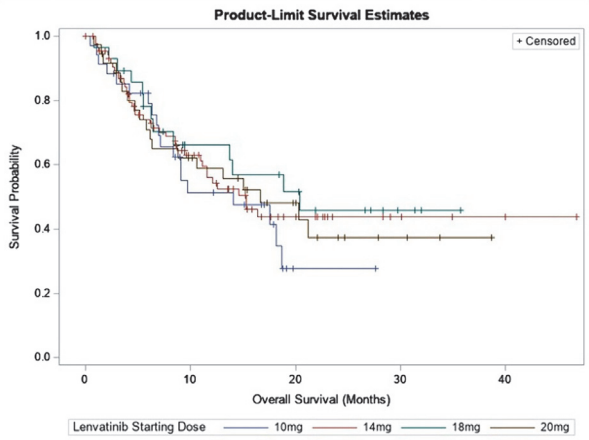

Abstract PR023/#503 Figure 2

9.7% carcinosarcoma, 10.1% mixed, and 2.8% clear cell. 82.9% were MMRp and 4.6% were MMRd. Median dose intensity of lenvatinib was 14 mg. Lenvatinib starting dose was 20 mg in 17.1%, 18 mg in 12.9%, 14 mg in 41%, 10 mg in 15.7%. Rates of any grade >=3 AE related to lenvatinib were 20 mg (13.5%), 18 mg (17.9%), 14 mg (7.9%), 10 mg (17.6%) (p=0.31). Pembrolizumab dosing was 200 mg Q3W in 85.6% and 400 mg Q6W in 6.5%. ORR (p=0.38), PFS (p=0.97) & OS (p=0.31) were similar in White vs. Black patients. ORR in relation to Lenvatinib starting dose 20 mg, 18 mg, 14 mg, 10 mg was 27%, 35.7%, 39.3%, 44.1% (p=0.08). In relation to Lenvatinib starting dose, 12-month PFS rates were 40%, 35%, 35%, 47% respectively (p=0.92), 12-month OS were 59%, 66%, 56%, 51% respectively (p=0.79), and median duration of therapy was 5.1, 4.1, 4.8, 4.6 months respectively (p=0.52).

Conclusion/Implications In a real-world analysis, the predominant starting dose is 14 mg lenvatinib and 200 mg pembrolizumab. Grade >=3 AE's, 12-month PFS/OS, ORR & duration of therapy related to lenvatinib starting dose were not statistically different.

PR024/#394 MOLECULAR PROFILING OF P53 MUTANT ENDOMETRIAL CANCER REVEALS DISTINCT SUBGROUPS WITH OPPORTUNITIES FOR PERSONALIZED THERAPEUTIC APPROACHES

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Introduction Endometrial cancer (EC) can be classified into four molecular subgroups: POLE mutant, MSI/dMMR, non-specific profiles and P53 mutant (P53mut). P53mut EC comprise ~20% of cases and have the worst prognosis. There is an urgent medical need to better understand P53mut EC in order to propose effective new therapeutic strategies.

Methods We conducted a retrospective analysis of P53abn EC patients from PORTEC3 (NCT00411138) with available DNA for a large-scale panel sequencing (Discovery Cohort). Results were confirmed on an independent cohort of EC patients (Gustave Roussy, France and National University Cancer Institute, Singapore) identified by their molecular profile using FoundationOneCDX or FoundationOne Liquid CDX panel (Validation Cohort). Molecular findings were correlated with clinicopathologic features from medical record review.

Results 39 P53abn cases were included in the discovery cohort. Molecular profiling was able to distinguish 4 mutually exclusive subgroups: CCNE1 amplified (15%), ERBB2 amplified (21%), PTEN alteration (21%) and a non-specific group. In the Validation Cohort, 71 P53mut EC patients were included. Median age was 66 years, 40% were serous, 30% endometrioid and 20% carcinosarcoma. 38% presented with primary metastatic diseases. We detected the same four molecular subgroups defined by CCNE1amp (13%), ERBB2amp (16%), and PTEN mutation or loss (34%). Only two patients (3%) harbored co-alterations. We did not observe any overall survival difference between these subgroups.

Conclusion/Implications Among P53mut EC, we detected 3 nearly mutually-exclusive molecular subgroups: CCNE1 amplified, ERBB2 amplified and PTEN loss, accounting together for 60% of cases. Whether these subgroups might benefit from personalized therapeutic strategies is currently being explored.

PR025/#182 PROTEOGENOMICS DELINEATE PATHOGENESIS, MOLECULAR CHARACTERISTICS, AND PREDICTORS OF PROGESTIN RESPONSE IN EARLY-ONSET ENDOMETRIOID ENDOMETRIAL CANCER

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Introduction Endometrial carcinoma (EC) remains a public health concern with a growing incidence particularly in younger women. Women with early-onset endometrioid EC (EEEC) who wish to maintain fertility are a worldwide concern, and biomarkers for predicting which patients will respond to progestin-based fertility-sparing therapy are a major unmet clinical need.

Methods To comprehensively characterize the proteogenomic characteristics of the early-onset endometroid endometrial carcinoma (EEEC), we conducted a multi-omics study (genomics, and proteomics) with FFPE tissues from paired tumor and normal tissues of 222 endometrioid ECs (including 81 EEECs younger than 40 who mainly received fertility-sparing treatment) and 14 atypical endometrial hyperplasia (AEH) patients from Tongji and Fudan Hospital (TJFD cohort) in China.

Results EEEC was featured by exclusive germline muataions,a higher BMI and downstream dysregualted lipid metabolism

signaling. Our integrated multi-omics analysis unexpectedly revealed an exposome-related mutational signature to be associated with EEEC leading to EEEC specific CTNNB1 and SIGLEC10 hotspot mutations and downstream protein pathway disturbance. Interestingly, in EEECs SIGLEC10^{Q144K} mutation resulted in aberrant Siglec-10 protein expression and promoted progestin resistance by interacting with ERα. We identified and validated four (EEF1E1, ILVBL, SRPK1 and NUDT5) biomarkers of progestin resistance.

Conclusion/Implications Our study provides a unique high-quality proteogenomic resource of EEECs, and explicates the distinct clinical and molecular characteristics of EEECs, encompass-ing obesity, genetic susceptibility, and environmental exposure, that are concomitant with pathogenesis and progestin resistance. Furthermore, we identified biomarkers for progestin response in EEEC fertility-sparing treatment. These attributes can be utilized to promote primary prevention and early detection of EEECs.

PR026/#185 PROTEOGENOMICS DECIPHER DISTINCT METASTASIS PATTERNS AND BIOMARKERS OF ENDOMETRIAL CARCINOMA

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Introduction Endometrial carcinoma is a common gynecologic malignancy, and lymph node metastasis greatly affects patient outcomes. Proteogenomics analysis has emerged as a powerful tool for identifying molecular mechanisms involved in cancer progression and metastasis, offering potential for biomarkers discovery and personalized treatment strategies.

Methods In this study, we utilized WES, proteomics, and multiplex immunohistochemistry to investigate the metastasis patterns of different molecular subtypes in a cohort of 96 EC patients with lymph-node metastasis and 126 without metastasis. Our aim was to elucidate the molecular characteristics that distinguish between these two groups and identify potential biomarkers for metastasis.

Results Proteogenomics analysis identified two distinct metastasis patterns of EC associated with TME. One pattern is characterized by an immune-cold phenotype, which is predominantly observed in patients with the MSI subtype. These patients often exhibit JAK1 mutations, defects in immunoproteasome components and HLA complexes, leading to deficiencies in antigen presentation pathways, resulting in immune evasion. The other is characterized by an immune-hot phenotype, mainly distributed in the CNL and few MSI subtype, with significant infiltration of macrophages and upregulation of integrin pathways, promoting tumor cells to undergo mesenchymal transition. Additionally, we explored and validated three consensus biomarkers shared across diffrerent molecular subtypes for predicting lymph-node metastasis.

Conclusion/Implications Our research provides an unprecedented large-scale multi-omics resource of lymphatic metastasis EC, offering novel insights and new biomarkers for effectively stratifying high-risk patients for lymphatic metastasis. We have deciphered two distinct metastasis patterns in EC, which can be exploited for the development of personalized screening and targeting strategies.

PR027/#815 CLINICAL IMPACT OF ULTRASTAGING OF SENTINEL LYMPH NODE MAPPING WITH INDOCYANINE GREEN INJECTION IN PATIENTS WITH ENDOMETRIAL CANCER

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Introduction This retrospective study aimed to confirm the clinical impact of ultrastaging of sentinel lymph node (SLN) mapping with Indocyanine green (ICG) injection in patients with endometrial cancer (EC).

Methods This retrospective study obtained data from the electronic medical records of Severance Hospital. The subjects included patients with EC who have undergone surgical staging with SLN mapping using ICG injection between June 2014 to December 2017 at Severance Hospital. The SLN paraffin blocks were sliced into two or three layers at an interval of 200 μm between the layers by 3 μm thickness. The immunohistochemistry was performed with anti-cytokeratin antibodies AE1/AE3.

Results A total of 138 patients included (no metastasis (NM), n=124, 89.9%; macro-metastasis (MAC), n=2, 1.4%; micro-metastasis (MM), n=11, 8.0%; isolated tumor cells (ITC), n=1, 0.7%). A total of 1006 paraffin blocks were examined (NM, n=984, 97.8%; MAC, n=2, 0.2%; MM, n=13, 1.3%; ITC, n=7, 0.7%). The 5-year disease-free survival significantly differed according to the results of ultrastaging (NM, 94.9%; MAC and MM, 69.2%; p<0.001). The 5-year overall survival was no significant difference in the status of ultrastaging (NM, 97.4%; MAC and MM, 100%; p=0.579). Analyzing the Cox proportional hazards model, the prognostic factor of recurrence was ultrastaging (Hazard Ratio 5.70, [95% Confidence Interval 1.50–21.68], p=0.011). The ultrastaging had no prognostic impact on the overall survival.

Conclusion/Implications The ultrastaging detected more MAC, MM, and ITC of SLN and was a prognostic factor of recurrence in patients with EC. Further study is needed for the clinical impact of ultrastaging for adjuvant therapy of EC.

PR028/#496 THE EFFICACY OF METFORMIN IN MEGESTROL ACETATE-BASED FERTILITY-SPARING TREATMENT FOR PATIENTS WITH ENDOMETRIAL ATYPICAL HYPERPLASIA AND ENDOMETRIAL CANCER: LONG-TERM OUTCOMES OF A RANDOMISED CONTROLLED TRIAL

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Introduction To assess the long-term efficacy of metformin in megestrol acetate(MA)-based fertility-sparing treatment for patients with endometrial atypical hyperplasia (EAH) and endometrioid endometrial cancer (EEC).

Methods Patients with EAH or EEC were firstly stratified, then randomised to receive MA (160 mg orally, daily) or MA