surgical perspective, to identify which tumors will most benefit from an extensive surgery and in which it could be avoided safely.

Methodology A cohort of 689 patients with EC treated at Hospital Vall d’Hebron, Barcelona, from 1992–2022 were retrospectively recruited. Clinical, surgical and pathological data were reviewed, and molecular profiling was performed in surgical specimen or preoperative biopsy. Tumors were classified according recommendations for molecular classification reported in ESGO-ESTRO-ESP 2020 Guidelines on EC.

Results The distribution of the cohort was as follows: 47 patients were POLEmut EC (6.8%), 104 patients p53abn EC (15.1%), 242 patients MSI EC (35.1%) and 296 patients NSMP (43%). Patients with POLEmut EC were significantly younger (57 y) and p53abn EC were elderly (67 y) than the rest of the cohorts (64 y, p=0.026). Patients with p53abn EC showed a higher proportion of non-endometrioid histologies (table 1).

Conclusion p53abn EC represents a subset of patients diagnosed with high rates of lymph-node involvement and peritoneal spread, and shows the worst oncological results in terms of survival.
nuclear translocation of AR and ER were seen in several models after long-term exposure, also without affecting proliferation.

Conclusion Data indicates that targeting AR and ER pathways in EC is model specific, suggesting context-dependent signaling. Lack of measured effect on proliferation combined with altered HR expression in some models might point to clonal selection in response to HR activation.

### 2022-RA-1499-ESGO

**DIFFERENTIAL RESPONSE OF IN-VITRO MISMATCH REPAIR-DEFICIENT HYPERMETHYLATED ENDOMETRIOD ENDOMETRIAL CANCER MODELS TO DNA-HYPOMETHYLATING AGENTS**

1. Louis El Khoury, 2Wan Hsin Lin, 1James Smadbeck, 1Dorsay Sadeghian, 1John Cheville, 1Faye Harris, 1Lindsey Kinsella, 1Marina Walthr Antonio, 1Giuseppe Cucinella, 1Gabriella Sivardi, 1Alexa McCune, 1Giammoula Karagouga, 1Aaron Mansfield, 1Andrea Mariani, 1George Vasmatis, 2Panos Anastasiadis, 1John Weroha, 1Alyssa Larish, 1Mayo Clinic, Rochester, MN; 1Mayo Clinic, Jacksonville, FL.

Introduction/Background We sought to compare in-vitro mismatch-repair deficient endometrial cancer (EC) methylation and responses to DNA-hypomethylating agents using spheroid-based microcancer 3D tumor cell viability assay. Methodology Study tumor was prospectively collected from a patient with stage 1B, grade 2 endometrioid EC. Characterization entailed whole exome, RNA, and MatePair analysis. Somatic mutations, structural variants and transcriptomic profiling were used to identify potential driver pathways for inhibition. Epigenomic profiling was completed with Assay for Transposase-Accessible Chromatin and DNA-methylation with Reduced Representation Bisulfate Sequencing. A comparative hyper-duplicated, p53-mutated EC underwent identical testing. 3D microcancers of these tumors were subjected to DNA-methyltransferase (DNMT) inhibition. Cell viability was determined by CellTiter-Glow Luminescent Assay. Data transformation and dose-response curves were generated by GraphPad Prism using four-parameter logistic regression. Inhibitory effect (IE) was defined as percent reduction ATP from baseline at maximum plasma concentration (Cmax).

Results Genomic sequencing revealed evidence of microsatellite instability with POLE variant of unknown significance. Global and promoter hypermethylation was observed in sample with fewer copy number variation. When contrasted with comparison tumor, we observed significant (p < 0.01), albeit modest, global (Δβ = 0.51) and promoter (Δβ = 0.52) hypermethylation. Methylation of both MLH1 and PMS2 was observed. While both gene bodies were hypermethylated (Δβ = 0.50 and Δβ = 0.15 respectively), only MLH1 was statistically different. Despite the lack of methylation of promoters for both genes, we noticed a gene expression fold reduction of 2.58 (MLH1) and 1.81 (PMS2). Inhibition of viability in both study and comparison was minimal by decitabine, shown by IE of 0 and 17.939, respectively. Conversely, IE of study tumor by azacitidine was more pronounced at 72.662, compared with 40.951 (figure 1).

Conclusion In MMR-D EC with MLH-1 hypermethylation, in-vitro tumor response to DNMT inhibition is superior for DNA/RNA incorporating azacitidine when compared to DNA-only incorporating decitabine.

### 2022-RA-1504-ESGO

**TAMOXIFEN-MEGESTROL ACETATE COMBINATION HORMONAL THERAPY IS AN EFFECTIVE FERTILITY-SPARING TREATMENT IN EARLY-STAGE ENDOMETRIAL CANCER PATIENTS WHO HAVE FAILED PROGESTIN ONLY HORMONAL THERAPY**

Hyunji Lim, Seung Jun Lee, Seoyoon Lee, Maria Lee, Hee Seung Kim, Hyun Hoon Chung, Jae-Weon Kim, Yong-Sang Song, Noh Hyun Park, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea, Republic of Korea.

Introduction/Background Tamoxifen is a selective estrogen receptor modulator, which inhibits the binding of estradiol to estrogen receptors in endometrial cancer. It can also increase progesterone receptors, making tumors more responsive to progestin therapy. Hence, we investigated the effectiveness of tamoxifen-progestin combination (T-P) therapy as a fertility-sparing treatment option in early-stage endometrial cancer patients who have previously failed progestin only (P-only) therapy.

Methodology We identified 129 patients with 2008 International Federation of Gynecology and Obstetrics stage IA-IB endometrioid endometrial cancer who received one or more hormonal treatment (HT) for preserving fertility between 2003 and 2021. P-only therapy included megestrol aceta (80–400 mg/day), medroxyprogesterone acetate (500 mg/day), and/or levonorgestrel-releasing intrauterine device. T-P therapy consisted of tamoxifen 20 mg/day for 3 weeks followed by megestrol acetate 160–400 mg/day for 3 weeks. We collected patients’ baseline characteristics, HT regimens, cycles, doses, response to HT, and referral for hysterectomy. Patients who failed to follow-up at least 6 months before completion of HT and patients with grade 3 disease were excluded.