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.

### Abstracts

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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.

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

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**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 with DNA-methylation with Reduced Representation Bisulfate Sequencing. A comparative hyper-duplicated, p53-mutated UC underwent identical testing. 3D microcancers of these tumors were subjected to DNA-hypomethylating agents incorporating azacitidine and decitabine. 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 change 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 compared to DNA-only incorporating decitabine.