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 ENDOMETRIOID ENDOMETRIAL CANCER MODELS TO DNA-HYPOMETHYLATING AGENTS

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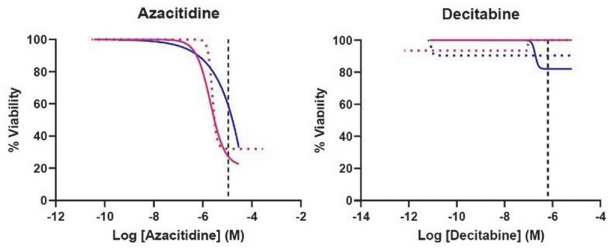
Introduction/Background We sought to compare in-vitro mismatch-repair deficient endometrial cancer (EC) methylation and responses to DNA-hypomethylating agents using spheroid-based microcancer 3D tumor cell viability assay.

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 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 ($\Delta\beta = 0.51$) and promoter ($\Delta\beta = 0.52$) hypermethylation. Methylation of both *MLH1* and *PMS2* was observed. While both gene bodies were hypermethylated ($\Delta\beta = 0.50$ and $\Delta\beta = 0.15$ 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).



Abstract 2022-RA-1499-ESGO Figure 1 Normalized drug responses of study tumor (pink) and comparison tumor (blue) to azacitidine and decitabine. Dose-response curves of treatment were titrated for each agent across maximum inhibitory plasma concentration (black dotted line). Pink and blue dotted lines represent results of previous testing

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

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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 acetate (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.