Oral Abstract 3: Uncovering critical steps of T cell activation in immune checkpoint inhibitor therapy (ICI) in high microsatellite instability (MSI-H) endometrial cancer (EC)

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Topic
Endometrial

Objectives
The efficacy of ICI in EC has largely been attributed to its ability to block the immunosuppressive PD-1/PD-L1 interaction between T cells and tumor cells, allowing neoantigens produced by MSI-H tumors to continually promote a T-cell–mediated immune response. However, 25–40% of MSI-H EC patients fail to achieve a measurable response to initial exposure to ICI, suggesting innate mechanisms of resistance. This study evaluated established biomarkers of a T-cell–inflamed tumor microenvironment (TME) alongside alternative immune pathways to identify determinants of response in MSI-H EC treated with ICI.

Methods
Patients with EC treated with pembrolizumab or dostarlimab were identified from the Caris Life Sciences database with paired whole exome and transcriptome sequencing (WES/WTS). MSI status was determined by immunohistochemistry and next-generation sequencing. Survival was defined from ICI initiation to death or last contact via insurance claims. Patients were stratified as long vs short survivors (LS/SS) using median post-ICI survival. Associations between survival and expression of pre-annotated T- and NK-cell–related genes were assessed using Kaplan–Meier analyses and multivariable Cox models adjusting for clinicopathologic factors.

Results
Of 6,354 patients, 25% were MSI-H and 71% were MSS. Within the MSI-H cohort, immune deconvolution showed higher inferred M1 macrophages in LS vs SS (p=0.003) but no differences in $CD8^+$ T cells, regulatory T cells, B cells, or NK cells. In multivariable analyses, several T- and NK-cell–related genes were associated with improved survival, including NLRC5 (mOS 49.5 vs 31.7 months; HR 0.68, CI 0.54–0.85, p< 0.0001), CRTAM (HR 0.70, CI 0.56-0.87, p=0.001), CTSW (HR 0.70, CI 0.57-0.88, p=0.002), and IL12RB1 (HR 0.72, CI 0.58-0.90, p=0.003). The IFN gamma Tumor Inflammation Signature (TIS) was also associated with survival (HR 0.68, CI 0.54–0.84, p=0.003), along with composite z-scores for newly derived T-cell, NK-cell, and combined T/NK gene signatures based on the most predictive genes.

Conclusions
Improved survival following ICI in MSI-H EC is associated with upregulation of genes involved in antigen presentation and cytotoxic immune activation, suggesting that these pathways are crucial for ICI efficacy and that their absence may underlie resistance in a subset of MSI-H EC.

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