Poster 22: Influence of JAK1 pathogenic variant zygosity on tumor immune microenvironment and survival in endometrial cancer

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Topic
Endometrial

Objectives
JAK1 mutations are common in endometrial cancer and classically linked to immune evasion and immune checkpoint inhibitor (ICI) resistance. Recent data suggest tumors harboring heterozygous (JAK1-HET) pathogenic variants (PV) may be associated with improved survival compared with JAK1 homozygous (JAK1-HOM) and wild-type (JAK1-WT) tumors. Here, we investigate the impact of JAK1 zygosity on tumor immune composition and survival in advanced or recurrent endometrial cancer.

Methods
We used the Tempus Lens Platform (Tempus AI, Inc., Chicago, IL) to query de-identified patients with endometrial cancer who have Tempus xT (DNA; 648 genes) and xR (RNA; whole transcriptome) next-generation sequencing. Eligible patients had either MSI high (MSI-H) or POLE mutated (POLE). Tumors were categorized into JAK1-HOM, JAK1-HET, or JAK1-WT based on JAK1 variant allele frequency (VAF) relative to median VAF. Immune cell infiltration was estimated from RNA using quanTIseq. Gene set enrichment analysis was conducted on MHC-I and immune checkpoint signatures. Patient characteristics were compared using Chi-squared tests or Kruskal-Wallis tests. Real-world overall survival (OS) was defined as the time from date of diagnosis to either death or loss to follow up. Median OS (mOS) was estimated using Kaplan Meier curves.

Results
Among 937 tumors, 616 were JAK1-WT, 78 JAK1-HET, and 243 JAK1-HOM. 51% (n=309) of patients had stage IV disease and 20% (n=185) of tumors were from patients who received ICIs. JAK1 PVs were associated with reduced M1 ($p=0.03$) and M2 macrophages ($p< 0.001$), with no difference in CD8+ T cells ($p=0.60$) or NK cells ($p=0.11$). MHC-I gene expression was lower in JAK1-HOM ($p< 0.001$), while immune checkpoint gene signature was higher ($p=0.045$). Median OS was 35.8 (27.3-43.2) months for JAK1-WT, 43.1 (7.3-58.3) for JAK1-HET, and 31.4 (20.5-41.0) for JAK1-HOM ($p=0.619$). Among ICI-treated patients, those with JAK1-HOM tumors had improved OS compared with JAK1-WT tumors (41.0 vs 35.0 months).

Conclusions
The impact of JAK1 PV zygosity on ICI response remains uncertain. JAK1-HOM tumors exhibit reduced MHC-I and increased overall checkpoint gene expression. Despite this, patients with JAK1-HOM tumors may derive greater OS benefit from ICI than those with JAK1-WT tumors, warranting further study.

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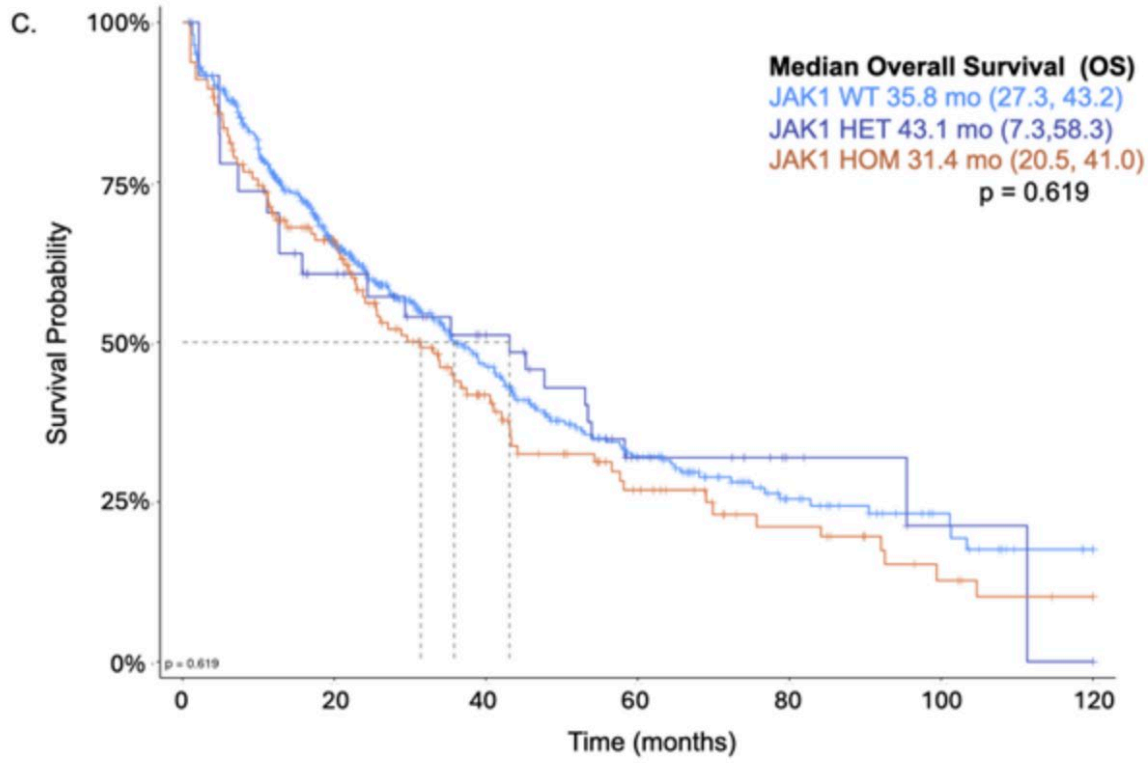
C.
100%
75%
50%
25%
0%
Survival Probability
p = 0.619
0
20
40
60
80
100
120
Time (months)
Median Overall Survival (OS)
JAK1 WT 35.8 mo (27.3, 43.2)
JAK1 HET 43.1 mo (7.3,58.3)
JAK1 HOM 31.4 mo (20.5, 41.0)
p = 0.619