Oral Abstract 25: ESR1 Alterations in Gynecologic Malignancies: Prevalence, Genomic Landscape, and Therapeutic Implications

Presenting Author: Eliya Shachar, MD, University of California Los Angeles

Topic
Translational Research

Objectives
Activating ESR1 alterations are key mediators of endocrine resistance in breast cancer; however, their prevalence, biological context, and clinical relevance in gynecologic malignancies remain poorly defined. We hypothesized that ESR1 alterations in gynecologic cancers reflect endocrine selection pressure and may identify tumors with reduced sensitivity to aromatase inhibitors but potential susceptibility to selective ER-targeted degradation (SERD) strategies. To address this, we evaluated the prevalence, acquisition status (de novo vs acquired), genomic landscape, and therapeutic implications of ESR1 alterations across gynecologic cancers.

Methods
We conducted a retrospective analysis of 705 patients with gynecologic malignancies who underwent genomic testing. The prevalence of ESR1 alterations, clinicopathologic characteristics, prior endocrine therapy exposure, and co-mutation patterns were evaluated across ovarian and uterine cancer cohorts.

Results
ESR1 alterations were identified in 30/705 patients (4.3%), with higher prevalence in uterine cancers (7.2%) compared with ovarian cancers (2.8%). Most alterations were de novo (80.0%) and predominantly missense mutations (76.7%), followed by amplifications (20.0%). Co-mutations were frequent, most commonly in TP53 (60.0%), as well as PTEN, ARID1A, and CTNNB1 (36.7% each), with additional recurrent alterations in PIK3CA, ERBB2, MAP3K1, and CDK12 (20.0% each). Ovarian cancers were predominantly advanced stage (92.3% stage III–IV), whereas uterine cancers showed a broader stage distribution, including 41.2% stage I disease. High-grade tumors predominated overall (63.3%), with ovarian cancers almost exclusively grade 3, while uterine cancers demonstrated more heterogeneous grading. Thirteen patients received 26 endocrine therapy regimens, most commonly aromatase inhibitors (n=10) and SERDs (n=4), with frequent use of combination strategies including CDK4/6, mTOR, and AKT inhibitors.

Conclusions
ESR1 alterations occur at low but clinically meaningful frequency in gynecologic malignancies, with enrichment in uterine cancer and distinct co-mutation patterns. These findings suggest a potential role for ESR1 as a biomarker to guide endocrine therapy selection, including identifying patients less likely to benefit from aromatase inhibitors and potential candidates for SERD-based strategies.

Uploaded File(s)
Abstract Table or Graph
INEXBPJK-2394942-1-ANY.pdf