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FOXL2 mutation is prevalent in metastatic adult granulosa cell tumors and is associated with improved survival

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Objective

- To describe the molecular profile of adult granulosa cell tumors (AGCT) of the ovary in order to improve prognostication and elucidate molecular therapeutic targets

Background

- AGCT represent less than 5% of all ovarian tumors
- Nearly 1/3 of patients with AGCT develop recurrent disease, and targeted therapies are limited
- Existing data suggest that FOXL2 mutations are common in AGCT and may be pivotal in the development of AGCT
- Further molecular profiling of AGCT may improve prognostication and identify novel therapeutic targets

Methods

AGCT samples were analyzed using next-generation sequencing (NGS), immunohistochemistry (IHC) and whole transcriptome sequencing (NovaSeq) (Caris Life Sciences, Phoenix, AZ). PD-L1 expression was tested by SP-142 (Ventana; positive cut-off ≥ 1%). Microsatellite instability (MSI) was tested by fragment analysis, IHC and NGS. Tumor mutational burden (TMB) was measured by counting all somatic mutations per tumor (TMB-high cut-off ≥ 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine). Gene Set Enrichment Analysis (GSEA) was used to determine enrichment of cancer hallmark pathways (Broad Institute). Survival analyses were performed using the Kaplan-Meier estimate.

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Table 1: Patient and Tumor Characteristics

Characteristic	FOXL2 Wild-Type	FOXL2 Mutations	P-value
Total, n (%)	31 (9.7)	280 (87.8)	
Median Age, years	47	56	0.003
Disease Status			0.045
Metastatic, n (%)	21 (67.7)	234 (83.6)	
Primary disease or local recurrence, n (%)	10 (32.3)	46 (16.4)	

Figure 1: Overall Survival by FOXL2 Status

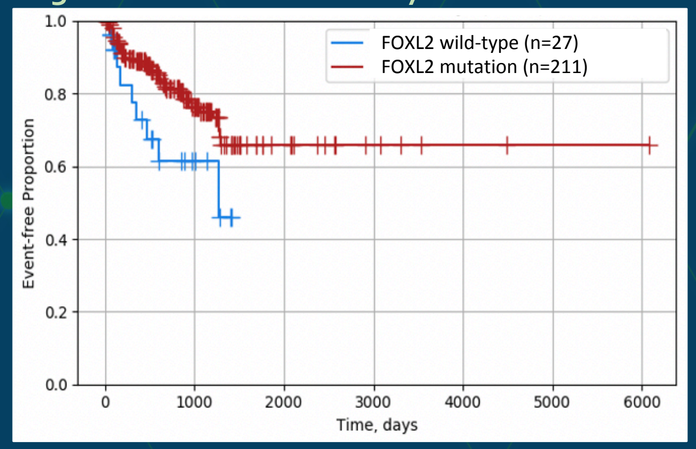
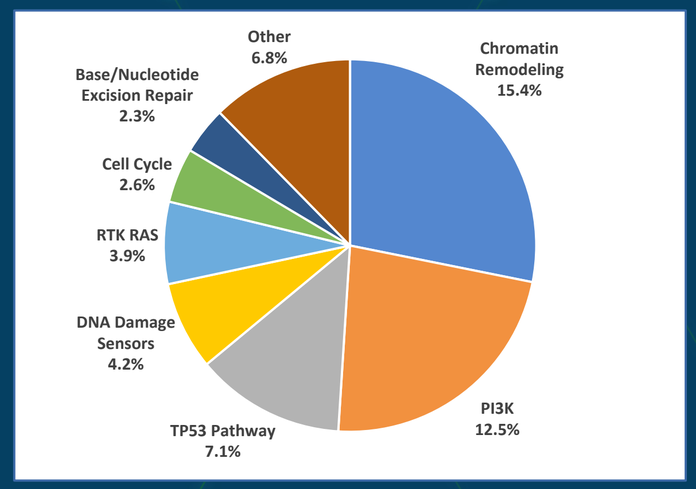


Figure 2: Pathway Alterations in AGCT (All Cases)



Results

- Tumor samples from 319 patients with AGCT were analyzed
- A majority of tumors carried FOXL2 mutations (87.8%), of which 90% demonstrated a *C134W* missense mutation
- Patients with tumors with FOXL2 mutations were significantly older (56 versus 47 years, p=0.003), more likely to have metastatic disease (p=0.045), and had improved overall survival (HR 2.07, CI 1.01-4.25, p=0.043) compared to tumors with wild-type FOXL2
- Tumors with FOXL2 mutations were more likely to have alterations in chromatin remodeling compared to wild-type FOXL2 tumors (16.1% versus 9.7%, p<0.05)
- Other frequent mutations for all tumors included KMT2D (14%) and PI3KCA (8%), but these were not associated with differences in survival compared to wild-type tumors
- Copy number alterations in the genes GPHN, HOOK3, SPEN, CAMTA1 and BCL2L11 were associated with survival differences in patients treated with bevacizumab

Conclusions

- Mutation of FOXL2 is common in AGCT and is associated with improved overall survival
- Copy number alterations in specific genes correlate with differences in survival associated with bevacizumab use

Future Directions:

- Evaluation of survival analysis for additional therapeutic regimens
- Molecular profiling of further ovarian tumor samples for analysis of FOX L2 outside of AGCT