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Molecular and clinical correlates of high PSMA/*FOLH1* mRNA expression in primary and metastatic prostate cancer (PC).

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Background: The *FOLH1* gene encodes prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein that is expressed in PC cells. PSMA is a target for diagnostic imaging and treatment in PC. We utilized a database of molecularly profiled PC tumors to evaluate correlates of high *FOLH1* mRNA expression. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on PC specimens (n=7,558) through Caris Life Sciences. *FOLH1*-High/Low expression was defined as above/below median RNA transcripts per million (TPM). Androgen receptor (AR), neuroendocrine (NEPC), MAPK, and T-cell inflamed RNA signature scores were calculated. Tumor cell PD-L1+ expression (≥2+, ≥5%; SP142) was assessed by IHC. Overall survival (OS) and time on treatment (TOT) were calculated from time of diagnosis or therapy start. **Results:** Specimens were derived from the prostate gland (n=4495, 59.5%), lymph nodes (n=858, 11.4%), bone (n=568, 7.5%), liver (n=359, 4.7%), urinary tract (n=340, 4.5%), lung (n=116, 1.5%), and other metastatic sites (n=822, 10.9%). Relative to the prostate (390.9 TPM), *FOLH1* mRNA expression varied by metastatic site, with highest expression in lymph nodes (518.2 TPM, $p<0.001$) and lowest expression in lung (209.7 TPM, $p<0.001$) and liver metastases (143.1 TPM, $p<0.001$). Higher *FOLH1* expression significantly correlated with presence of AR-V7 variants (18% vs 15%) and *ASXL1* (6% vs 3.9%) alterations, and fewer alterations in *FOX1A* (7.9% vs 10.6%), *APC* (4% vs 10.3%), *PIK3CA*(3.1% vs 6.4%), *CTNNB1* (3.1% vs 4.8%), and *PIK3R1* (0.7% vs 2%). High *FOLH1* expression positively associated with AR signaling score, MAPK activation, and T-cell inflammation, and negatively correlated with NEPC signaling (all $p<0.001$). Tumors with high *FOLH1* expression were more frequently PD-L1+ (3.9% vs 2.2%, $p<0.01$). Among primary tumors, OS was similar between *FOLH1* high and low groups; however, among metastatic tumors, OS was improved in patients (pts) with high *FOLH1* expression compared to low expression (96.3 vs 87.9 months, HR 0.82 95% CI 0.73-0.92). There was no difference in TOT among pts receiving ARSIs, taxanes, or PARPi. Among 149 pts that received 177Lu-PSMA-617, there was a trend towards improved TOT in *FOLH1*-high (n=78) versus -low (n=71) tumors (HR 0.76, 95%CI 0.55-1.05). **Conclusions:** This is the largest combined genomic, transcriptomic and survival outcomes analysis of PSMA (*FOLH1*) expression in PC. In PC, greater *FOLH1* mRNA expression was associated with higher AR signaling scores and AR-V7 expression, and fewer mutations in the Wnt and PI3K pathways. *FOLH1*-high pts showed greater T cell inflammation and PD-L1 expression, and lower NEPC signaling. High *FOLH1* expression was associated with greater OS among patients with metastatic tumors, with a trend towards improved outcomes to 177Lu-PSMA-617. Such pts may benefit from distinct therapeutic strategies. Research Sponsor: None.