Title

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

Journal

Journal of Clinical Oncology, 42(16_suppl)

ISSN

0732-183X

Authors

McKay, Rana R

Nazari, Shayan

Elliott, Andrew

et al.

Publication Date

2024-06-01

DOI

10.1200/jco.2024.42.16_suppl.5051

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

Rana R. McKay, Shayan Nazari, Andrew Elliott, Brent S. Rose, Pedro C. Barata, Deepak Kilari, Rohan Garje, Neeraj Agarwal, Chadi Nabhan, Himisha Beltran, Emmanuel S. Antonarakis, Aditya Bagrodia; University of California, San Diego Health, La Jolla, CA; Caris Life Sciences, Phoenix, AZ; University of California, San Diego, San Diego, CA; University Hospitals Seidman Cancer Center, Cleveland, OH; The Medical College of Wisconsin, Department of Medicine, Division of Hematology and Oncology, Milwaukee, WI; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Huntsman Cancer Institute, Salt Lake City, UT; Caris Life Sciences and the University of South Carolina, Deerfield, IL; DFCI/PCC Fellowship Program - Attendings, Boston, MA; University of Minnesota Masonic Cancer Center, Minneapolis, MN

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.