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Ibrahim Azar

Nishant Gandhi

Misako Nagasaka

Jun Gong

Bassel Nazha

See next page for additional authors

Authors

Ibrahim Azar, Nishant Gandhi, Misako Nagasaka, Jun Gong, Bassel Nazha, Khalil Choucair, Moh'd M. Khushman, Heloisa P. Soares, Wafik S. El-Deiry, Philip A. Philip, Emil Lou, Alex P. Farrell, Jeffrey Swensen, Matthew J. Oberley, Jim Abraham, Chadi Nabhan, Sanjay Goel, Wolfgang M. Korn, and Anthony F. Shields

Molecular characterization and clinical outcomes of pancreatic neuroendocrine tumors (pNENs) harboring PAK4-NAMPT alterations.

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Background: The mTOR inhibitor, Everolimus (EVE), is FDA-approved for the treatment of advanced PNENs on the basis of delay of progression. The RADIANT-3 trial showed an increase in PFS from 4.6 to 11 months compared to placebo with an ORR of only 5%. Prior studies suggest that targeting the aberrant expression of mTOR regulators p21 activated kinase 4 (PAK4) and nicotinamide adenine dinucleotide biosynthesis enzyme nicotinamide phosphoribosyltransferase (NAMPT) in PNENs sensitizes these tumors to EVE. To further qualify these observations, we queried a large real-world dataset of PNENs, characterizing the molecular and immune landscapes, as well as the clinical outcomes associated with aberrant PAK4 and NAMPT expression. **Methods:** 294 cases of PNENs were analyzed using Next Generation Sequencing (NextSeq) and Whole Exome and Whole Transcriptome Sequencing (NovaSeq) at Caris Life Sciences (Phoenix, AZ). For our analyses, we stratified our study cohort into four groups based on the median expression of PAK4 and NAMPT: PAK4-low/NAMPT-low, PAK4-low/NAMPT-high, PAK4-high/NAMPT-low and PAK4-high/NAMPT-high. Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U, and p-values were adjusted for multiple comparisons ($q < 0.05$). **Results:** High prevalence of mutations in *PTEN (10.71% vs 1.18%; $p < 0.05$, $q > 0.05$)*, a tumor suppressor of the mTOR pathway and high expression of genes activated in response to mTOR activation such as *SLC2A1* (3.07-fold), *PFKP* (3.32-fold), *SCD* (2.70-fold), *MVK* (2.92-fold) and *G6PD* (2.58-fold) were observed in PAK4-high/NAMPT-high compared to the PAK4-low/NAMPT-low tumors (all $q < 0.05$). A congruent enrichment of PI3K/AKT/mTOR and glycolysis pathways by single-sample gene set enrichment analysis was observed in these tumors (all $q < 0.05$). When querying the immune landscape, we observed enrichment in inflammatory response, IL6/JAK/STAT3, IL2/STAT5 signaling pathways and immune checkpoint genes such as *PDCD1* (5.14-fold), *CD274* (2.84-fold), *PDCD1LG2* (2.44-fold), *CD80* (3.00-fold), *CD86* (2.82-fold), *IDO1* (1.92-fold), *LAG3* (3.09-fold), *HAVCR2* (2.66-fold) and *CTLA4* (4.49-fold) in the PAK4-high/NAMPT-high tumors (all $q < 0.05$). Immune cell infiltration estimates revealed an increase in Neutrophils, NK cells and Tregs in the PAK4-high/NAMPT-high tumors ($p < 0.05$, $q > 0.05$). **Conclusions:** Our study demonstrates that PAK4-high/NAMPT-high PNENs are associated with distinct molecular and immune profiles. While the dual blockade of PAK4 and NAMPT has been reported to enhance the efficacy of EVE in PNENs, whether such a blockade would enhance the efficacy of immunotherapeutics warrants further investigation. Research Sponsor: None.