Comparative molecular analyses of pancreatic cancer (PC): KRAS wild type vs. KRAS mutant tumors and versus distant metastases


Lambert-Comprehensive Cancer Center, Georgetown University, Washington, DC; Caris Life Sciences, Phoenix, AZ; Fox Chase Cancer Center, Philadelphia, PA; Vaneone Cancer Institute, Carolinas Healthcare System; Charlotte, NC; Department of Medicine and Oncology and Innovation Center for Biomedical Informatics, Georgetown University, Washington, D.C.; Karmanos Cancer Institute, Wayne State University, Detroit, MI

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Background: Targeted therapies have a minimal role in PC partly because of the molecular characterization is not well understood. Little is known about the molecular characteristics of subset of PC that does not carry KRAS mutations. Better knowledge would enhance our ability to develop targeted therapies.

Methods: PC tumors submitted to Caris Life Sciences for IHC (protein expression), ISH (gene amplification), and NGS sequencing between 2009 and 2015 were studied. Chi-square tests determined differences.

Results: A total of 2426 PC tumors were examined. KRAS mutations (85%) were the most frequent genetic alteration. Other commonly mutated genes were TP53 (63%), SMAD4 (13%), BRC2A (12%),ATM/APC/NUMA1 (9% each), BRCA1 (4%) and MET/PIK3CA (3% each). BRAF mutations were seen in 6% of the RAS-WT tumors. When compared to RAS MT, KRAS WT tumors had a greater frequency of BRCA1 (9% vs. 3%, p < 0.05), TNNT1(3%) vs. 0.2%, p < 0.01), and PTEN and PIK3CA amplification (2.1% vs. 0.16, p < 0.01) mutations, whereasSMAD4 and TP53 mutations were higher in KRAS MT (15% vs. 5%, p < 0.02, 68% vs. 28%, p < 0.01, respectively). KRAS MT had higher expression and amplification of cmET (66% vs. 49%, p < 0.01, 2.5% vs. 0%, p < 0.04), and higher expression of EGF (90% vs. 82%, p < 0.04), whereas, KRAS WT tumors had higher HER2 expression and amplification (2% vs. 0.4%, 0.7%, both p-values < 0.01). Comparing 10 (n = 1099) with Met (n = 1327) PC, 10 tumors had a higher frequency of “low” ERCC1 (83% vs. 63%, p = 0.01) and “low” RRM1 (87% vs. 66%, p < 0.01), and higher PD1 TILs (50% vs. 33%; p = 0.03) than liver Mets, whereas, the frequency of “low” ERCC1 (81% vs. 63%, p < 0.01) and “low” RRM1 (87% vs. 66%, p < 0.01) amplification (2% vs. 0.4%, 6% vs. 0.7%; both p-values < 0.01) was higher in PC MT than in liver Mets. In addition to a disease lacking targeted therapy approaches, approximately half of all PC are metastatic at diagnosis, typically to the liver or peritoneal cavity, and patients are usually treated with systemic chemotherapies.

Conclusion: Genomic differences between KRAS WT vs. MT suggest different carcinogenic pathway and tumor biology. Primary tumors may carry genetic alterations that are distinct from distant metastases. Mutations in druggable genes (e.g., HER-2, PIK3CA, BRCA2) may provide therapeutic opportunities.

References