AB098. P072. Investigation of BRCAness in pancreatic cancer using patient-derived organoid models

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Background: Efforts to characterize the mutational landscape in pancreatic cancer have revealed almost ubiquitous activating mutation of KRAS, high incidence of inactivation of TP53, SMAD4, CDKN2A and KDM6A but a very low prevalence of currently actionable targets. However, patients with high genomic instability suggesting defective DNA maintenance (up to 20%) show high response rate to platinum agents with or without PARP inhibition. While no more than 5% of patients harbor germline BRCA1/2 inactivation, molecular alterations in other genes related to homologous recombination are also found in these pancreatic tumors. These observations support the concept of BRCAness in pancreatic cancer, where tumors showing traits of defective homologous recombination (HR) even in the absence of BRCA1/2 deficiency are associated with exquisite sensitivity to DNA-damaging agents. This study seeks to identify new molecular determinants of BRCAness in Pancreatic cancer and what assay constitutes the best predicator of a favorable response to therapeutic targeting HR defects.

Methods: Given the heterogeneous mechanisms that can drive BRCAness, we have performed a comprehensive analysis of a large repository of pancreatic cancer patient-derived organoids including molecular characterization by next-generation sequencing (exome and transcriptome) allowing quantification of genomic scars and mutational signatures concomitantly to an evaluation of HR proficiency by IRIF assay and drug sensitivity profiling including platinum-based agents and PARPi.

Results: Multidimensional characterization of 75 pancreatic cancer led to the identification of 9 tumors (12%) so far that showed clear evidence of BRCAness, featuring high HR deficiency score (elevated amount of genomic scars), sub-micromolar sensitivity to cisplatin and PARPi, low induction of rad51 foci following irradiation and a highly operative BRCA mutational signature. Interestingly, in the absence of alteration in BRCA1 and BRCA2 some of these specimens show enrichment in alterations of HR component genes (RAD51, PALB2) and in RecQ helicase family (BLM, WRM) or ATM.

Conclusions: This study identifies evidence of BRCAness in pancreatic cancer tumors without any deficiency in BRCA1 and BRCA2 and therefore broadens the scope of patients who may benefit from platinum and/or PARP therapy.

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