Next-Generation Sequencing (NGS) in Pancreatic Neuroendocrine Tumors (panNETs): Defining Differentiation and Grade Genetically

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Background: Advances in tumor sequencing technology have improved our understanding of the genetic basis of NETs. Specifically, whole exome sequencing of well differentiated (WD) panNETs demonstrated an increased number of mutations in chromatin remodeling genes; in poorly differentiated (PD) neuroendocrine carcinomas, alterations along the TP53/RB signaling pathways have been observed. We sought to validate these observations in clinical practice.

Methods: This prospective study (NCT01775072) used the MSK-IMPACT assay to do NGS on panNETs in a routine practice setting. MSK-IMPACT is an assay providing full exon coverage of 410 cancer related genes, detecting base substitutions, small indels, copy number and select gene rearrangements.

Results: Results are available in 56 patients (mean age 55, 45% female); 21 patients (38%) with low grade tumors, 23 patients (41%) with intermediate grade tumors, and 12 patients (21%) with high grade tumors; 5 patients (9%) with PD tumors and 51 patients (91%) with WD tumors. RB1 alterations were identified in 3 tumors (5%); all of these tumors were PD and high grade. TP53 alterations were identified in 5 tumors (9%); 3/5 tumors (60%) were PD and high grade and 2/5 tumors (40%) were WD and intermediate grade, but exhibited aggressive clinical behavior. Alterations in chromatin remodeling genes were only observed in WD tumors of low/intermediate grade; MEN1 alterations in 31 tumors (55%), DAXX alterations in 19 tumors (34%), ATRX alterations in 12 tumors (21%), and SETD2 alterations in 9 tumors (16%).

Conclusion: In line with prior work in panNETs, using an institutional NGS platform, we demonstrated tumor grade/differentiation genetically. Changes in chromatin remodeling genes were exclusive to WD, low/intermediate grade tumors. To contrast, alterations in RB1/TP53 were seen either in PD, high grade tumors, or in aggressively behaving WD, intermediate grade tumors. We will further categorize these genetic alterations and present updated results at the meeting.

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