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Is Next-Generation Sequencing (NGS) Ready for Routine Clinical Practice in Advanced Well Differentiated Pancreatic Neuroendocrine Tumors (WD panNETs): Results of a Prospective Study Utilizing MSK-IMPACT (Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets)

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Background: Whole exome sequencing in WD panNETs demonstrated an increased number of mutations in genes implicated in chromatin modeling (MEN1, DAXX, and ATRX), and in the PI3K/AKT/mTOR pathway. NGS allows us to bring this technology to the clinic but its relevance in clinical practice has been questioned. In this prospective, IRB-approved study (NCT01775072), we used the MSK-IMPACT assay to perform NGS on WD panNETs in a routine practice setting. MSK-IMPACT, performed in a CLIA-compliant laboratory, is a multiplexed assay (Illumina HiSeq) providing full exon coverage of 410 cancer related genes, detecting base substitutions, small indels, copy number and select gene rearrangements.

Methods: After written consent, tumor and germline DNA were analyzed. Genomic alterations were catalogued. Actionable alterations were classified according to 5 levels (Figure 1).

Results: MSK-IMPACT results are available in 29 patients with WD panNETs. Actionable alterations were identified in 13/29 patients (44.8%). No level 1 or level 2A alterations were identified. Two level 2B alterations were identified, both in

BRAF V600E. Four level 3 alterations were identified, 1 in TSC1 and 3 in TSC2. Seven level 4 alterations were identified, 3 in PTEN, 1 in CDKN1B, 1 in CDKN2C, and 2 in ARID1A. 19/29 (65.5%) patients had alterations in MEN1, 8/29 (27.6%) patients had alterations in DAXX, and 9/29 patients (31.0%) had alterations in ATRX. Other notable findings included 2/29 patients (6.9%) with TP53 alterations, and 5/29 (17.2%) patients with SETD2 alterations.

Conclusion: The mutational landscape in our study was in line with prior work in whole exome sequencing. In almost half of the patient cohort, potentially actionable genomic alterations were identified through NGS but have not yet been shown to be therapeutically relevant or prognostic. An exploratory analysis to identify responses to different therapy types (chemotherapy, targeted agents) is ongoing and will be reported at the meeting.

Figure 1: Genomic Alteration Tier Classification	
Level 1	FDA-approved biomarker
Level 2a	FDA-approved biomarker in another indication, and NCCN-compendium listed for this indication
Level 2b	FDA-approved biomarker in another indication, but not FDA or NCCN-compendium listed for this indication
Level 3	Not FDA-approved or NCCN-compendium listed biomarker, but clinical evidence potentially links this biomarker to response
Level 4	Not FDA-approved or NCCN-compendium listed biomarker, but preclinical evidence potentially links this biomarker to response