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Identification of SETD2 Genetic Alterations in Patients with Advanced Well Differentiated Pancreatic Neuroendocrine Tumors (WD panNETs)

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Background: SETD2 is a histone methyltransferase specific for lysine-36 of histone H3, and has a role in chromatin remodeling. SETD2 also has a tumor suppressor role. SETD2 is frequently altered in clear cell renal cell carcinoma (ccRCC); in ccRCC, SETD2 alterations have been linked to poorer cancer specific and overall survival. A role for SETD2 in WD panNETs has not been described; based on ccRCC data, SETD2 alterations may contribute to tumorigenesis and disease aggressiveness.

Methods: A next-generation sequencing platform developed at Memorial Sloan Kettering Cancer Center, MSK-IMPACT (Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets), was utilized. This platform screens for 410 cancer related genes, including SETD2. MSK-IMPACT results are available in 29 patients with advanced WD panNETs.

Results: 5/29 (17.2%) patients demonstrated SETD2 alterations. All 5 patients had metastatic disease to the liver. No tumors were low grade; 4/5 (80%) tumors were intermediate grade and 1/5 (20%) tumors were high grade. All 5 patients harboring tumors with SETD2 alterations received capecitabine/temozolomide (cape/tem) chemotherapy; looking at best therapy response with cape/tem, 4/5 (80%) patients had disease shrinkage and 1/5 (20%) patients had stable disease. One patient exhibited a dramatic response to cape/tem and underwent surgical resection of the primary pancreatic

lesion; after surgery, this patient has minimal liver disease remaining, with no evidence of disease progression more than one year after surgery and stopping cape/tem.

Conclusion: SETD2 alterations have not been previously reported in WD panNETs but have been observed in ccRCC, where they are thought to play a role in tumorigenesis. Interestingly, all WD panNETs with SETD2 alterations were intermediate to high grade, and responded to cytotoxic therapy with cape/tem. Further investigation is warranted to determine the role of SETD2 in panNETs, and the clinical significance of these observations. Evaluation using panNET tissue microarrays is ongoing.