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Outcomes after Cessation of Therapy with Alkylating Agents (AA) For Pancreatic Neuroendocrine Tumors (PanNETs)

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BACKGROUND: Treatment-related toxicity precludes the use of all therapies available for panNETs. AA are an effective therapy in panNETs but can cause irreversible bone marrow suppression. For this reason, our institutional approach is to treat patients with AA for a defined time period of up to 12 months prior to a treatment holiday; anecdotally, we observed continued disease shrinkage or stability after drug cessation. We aimed to identify and characterize these exceptional responders.

METHODS: We retrospectively evaluated patients with well differentiated panNETs treated at MSKCC with AA from 2007 to 2019, and identified those who were placed on a treatment holiday after response to therapy. Patients with continued disease response by radiographic report (tumor shrinkage or stable disease) for greater than 9 months while on a treatment holiday were considered exceptional responders (ER).

RESULTS: 124 patients were evaluable, with 104 patients (84%) receiving temozolomide and 18 (15%) receiving dacarbazine. 40 (32%), 57 (46%), and 22 (18%) patients had low, intermediate and high-grade tumors, respectively. Fifty-eight patients (47%) had either stable disease or disease response to AA and entered a treatment holiday; 39/58 patients (67%) were ER and 16/58 patients (28%) had progression in <9 months. No significant differences in tumor grade (P = 0.85) were seen between ER and those who had disease growth in <9 months. Next generation sequencing results were available in 17 tumors of patients classified as ER; 14/17 (82%) with alterations in chromatin

remodeling genes (MEN1/DAXX/ATRX). Upon disease progression, 11 ER were reintroduced to alkylating agents; 9/11 (82%) had progressive disease or death after reintroduction of drug, and 2/11 (18%) responded and went on a second treatment break.

CONCLUSION: We observed durable responses to AA after cessation of therapy. Many of the ER tumors harbored alterations in chromatin remodeling genes. Reintroduction of AA upon disease progression was generally ineffective.