

# B-17

## Establishment of a Patient-derived Xenograft Model of Pancreatic Grade 3 Well-Differentiated Neuroendocrine Tumor

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**BACKGROUND:** Recently, a new pathologic category of pancreatic neuroendocrine tumors (PNETs), grade 3 well-differentiated-PNET (G3 WD-PNET), was recognized by the WHO with an intermediate prognosis compared to G2 WD-PNET and G3 poorly differentiated neuroendocrine carcinoma. The molecular and clinical features of G3 WD-PNET are ill-defined, and no standard treatment exists. We developed a patient-derived xenograft (PDX) model of G3 WD-PNET as a platform to study its biology and to inform prospective trials.

**METHODS:** Surgically resected liver metastasis tissue from a patient with a G3 WD-PNET was implanted s.c. into NSG mice. Pathologic examination of the original patient tumor revealed a WD-PNET with 33 mitotic figures/10 hpf, Ki67 index 47%, and loss of ATRX, indicating a G3 WD-PNET. PDX tumors were passed into the next generation when the tumor volume reached 1,000-2,000 mm<sup>3</sup>. The morphologic and molecular features of the PDX tumors were compared to the original tumor. Mice bearing PDX tumors were treated with control vehicle or everolimus (5 mg/kg/day p.o.) for 28 days.

**RESULTS:** Tumors grew successfully in all mice (100% take rate). Chromogranin A was diffusely positive, and the mitotic figures and Ki67 index were comparable with those of the original patient tumor. The patient and PDX tumor showed similar phospho-kinase activity, including phosphorylation of mTOR and p53. These findings were consistent with targeted sequencing results of the patient tumor showing mutations in p53 and TSC2, a negative regulator of mTOR.

Everolimus significantly inhibited G3 WD-PNET PDX growth compared to control vehicle (median volume change -48% versus 150%, Wilcoxon P = 0.005), showing the importance of the mTOR pathway for tumor growth.

**CONCLUSION:** We successfully established a G3 WD-PNET PDX model. This model will facilitate studies of the underlying biology of G3 WD-PNET and help inform prospective clinical trials, which are desperately needed for this new disease.