

# The 2nd Gen mTOR Inhibitor INK128 Overcomes Resistance to Everolimus (1st Gen) in Pancreatic Neuroendocrine Tumors

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**Background:** Dysfunction of the mTOR pathway is a critical event in pancreatic neuroendocrine tumors (pNETs). The 1st Gen mTOR inhibitor (rapalog), everolimus, is approved for the treatment of pNETs, but therapeutic resistance frequently emerges. Using a novel in vivo model of pNETs, we hypothesized that the 2nd Gen mTOR inhibitor (ATP-competitive inhibitor), INK128, can effectively overcome resistance to everolimus.

**Methods:** We developed a patient-derived xenograft pNET model that exhibits key features of the disease, such as a NE phenotype and mTOR pathway activation. Nude mice bearing pNET xenografts were treated with everolimus (10 mg/kd/d) p.o. until the development of resistance. Secondary or acquired resistance to everolimus was defined as a 100% increase in tumor volume. Resistant tumors were treated with INK128 (1 mg/kg/d) p.o., and tumor volume was measured by caliper twice weekly.

**Results:** Most (82 %, 28/34) tumors exhibited no change or a decrease in size after everolimus treatment. This data is very similar to what was reported in humans receiving everolimus in the RADIANT-3 Trial. During the study period, 12 tumors developed resistance to everolimus and were subsequently treated with INK128. Strikingly, treatment of everolimus-resistant tumors with INK128 effectively halted tumor growth or caused tumor shrinkage most of the time (75%, 8 of 12 cases).

**Conclusion:** As in patients, our pNET model shows that the mTOR pathway is a critical driver of pNET growth and that everolimus effectively inhibits tumor growth initially. However, as in patients, pNETs developed resistance overtime to everolimus in our model. Importantly, INK128 was able to overcome resistance to everolimus in our pNET model. Our findings provide the preclinical rationale to use 2nd Gen mTOR inhibitors, such as INK128, to overcome resistance to everolimus in patients with advanced pNETs.