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mTOR Pathway Inhibition Sensitizes Insulinoma Cells to Streptozotocin Induced Apoptosis

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Background: Pancreatic neuroendocrine tumors (pNETs) are generally chemoresistants probably due to low proliferation rate and defects in apoptotic pathway. Targeted therapies are new encouraging options for pNETs however; clinical trials show limited objective response. Combination of chemotherapy and targeted therapy could be a new solution in therapeutic care. Streptozotocin (STZ) is the 1st line therapy for unresectable pNETs.

Methods: Based on the literature, we hypothesized that mTOR pathway over-activation could lead to resistance to STZ.
To evaluate this, we combined mTOR pathway inhibitors to STZ in *in vitro* and *in vivo* models. 4 mTOR pathway inhibitors (Everolimus, MK2206, BKM120 and BEZ235) were tested. Cell viability, proliferation and apoptosis were assessed in INS-1E and MIN6 cells (insulinoma cell lines). Development of tumor

nodules was analyzed in an intra-splenic xenograft model. We also analyzed effects on these combinations on glycaemia and normal β cell mass to evaluate side effects.

Results: We show that all 4 combinations have synergistic effect *in vitro*. These combinations lead to heterogeneous mTOR pathway inhibition and increased apoptosis. *In vivo*, combinations lead to decreased tumor dissemination with variable efficacy depending on the inhibitor used. Hyperglycaemia and toxicity observed with BKM120 were avoided by decreasing doses.

Conclusions: These results suggest that combination of mTOR pathway inhibitors and STZ should be assessed in clinical trial.

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