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Potentiating mTOR's Antineoplastic Effects with Rovalpituzumab Tesirate in Neuroendocrine Tumors

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BACKGROUND: Neuroendocrine tumors (NETs) are relatively rare tumors which can arise throughout the body. Treatment options for progressive metastatic neuroendocrine tumors are limited. Everolimus, an m-TOR inhibitor has recently been approved as front line treatment for metastatic gastroenteropancreatic and bronchial NETs. Despite improvement in progression free survival, most patients eventually progress on everolimus. Secondly, everolimus is a cytostatic drug and is not ideal for a patient in visceral crisis needing rapid cytoreduction. Rovalpituzumab, a DLL-3 antibody drug conjugate, is a targeted agent which has shown significant efficacy in small cell lung cancer. We explore activity and efficacy of single agent rovalpituzumab and in combination with everolimus in GEPNETs.

METHODS: In-vitro assessment of efficacy of everolimus and rovalpituzumab in pre-clinical NET models. Our study models includes two pancreatic NET cell lines (BON, QGP-1) and one bronchial carcinoid cell line (NCI H727). Commercially available Abcam, (Cat # ab103102) DLL-3 antibody was used for Immunohistochemistry. Abbvie-Stemcentrx sponsored the experimental drug and controls. Efficacy was assessed with help of automated cell viability analyzer, apoptosis assay (Cleaved PARP and p21 expression) and proliferation assay. Chou-Talalay Method will be used to evaluate for synergy between two experimental agents.

RESULTS: All three NET cell lines were found to express DLL-3. Antineoplastic activity of the combination of rovalpituzumab and everolimus showed heightened efficacy as compared to equivalent single agent dose.

CONCLUSION: Our data is first ever to show preclinical efficacy of single agent DLL-3 ADC (rovalpituzumab) and combination with mTOR inhibitor (everolimus) in GI and lung NET cell lines. Our next goal is to validate our results in in-vivo models. Our pre-clinical data will help in developing an early phase clinical trial for novel therapeutic combination targeting NOTCH pathway ligand (DLL-3 ADC) and m-TOR inhibitor (everolimus).