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The Synergistic Effect of Pasireotide (SOM230) and a Raf-1 Activating Agent in Carcinoids

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Introduction: Somatostatin analogs are mainstay for carcinoid treatment and management. The new somatostatin analog Pasireotide (SOM230) may be more effective given its relatively elevated receptor affinity and broader binding spectrum. Data suggest ERK1/2 phosphorylation may potentiate the anti-tumor effects of somatostatin analogs in carcinoids. We've shown that ERK1/2 phosphorylation suppresses carcinoid biomarker expression. Therefore, Raf-1/MEK/ERK1/2 pathway activating drugs may synergize with somatostatin analogs like SOM230. Here, we investigate the effects of SOM230 combined with Teriflunomide (TFN), a Raf-1 activator, in vitro.

Methods: Human GI carcinoids (BON) were incubated in TFN, SOM230 or both, for 96 hours. Cell growth was measured using methylthiazolyldiphenyl-tetrazolium bromide (MTT) colorimetric assay. Western analysis showed expression levels of achaete-scute complex-like1 (ASCL1) and Chromogranin A (CgA), known carcinoid malignancy markers, along with phosphorylated and total ERK1/2, and other apoptotic and cell survival markers.

Results: Combination treatment with SOM230 and TFN reduced cell growth beyond their sum individual effects. Combination indices confirmed synergy. TFN alone dose dependently reduced ASCL1 and CgA by approximately 20% and 50% with 35μM and 50μM TFN

respectively, while SOM230 alone had no affect. Notably, addition of SOM230 following these TFN doses inhibited ASCL1 and CgA levels well beyond their added individual effects- 0.5μM SOM230 following 50μM TFN reduced ASCL1 and CgA levels over 75%. Combination treatment increased phospho-ERK1/2, cleaved poly(ADP)-ribose polymerase and cleaved caspase-3 levels, and reduced total caspase-3, X-linked inhibitor of apoptosis, survivin and Mcl-1 levels.

Conclusions: Combined SOM230 and TFN treatment of BON cells synergistically inhibits cell proliferation and biomarker expression through induction of apoptosis. Since treatment efficacy can be achieved at lower doses of either drug, combination therapy may presumably palliate carcinoid syndrome symptomatology at toxicity levels that are safer and tolerable. Because each drug has already been evaluated in clinical trials, animal models and combinatorial drug trials are warranted.