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MK-2206, a Novel AKT Inhibitor, Suppresses Medullary Thyroid Cancer Proliferation

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Background: Development of targeted therapies for medullary thyroid cancer (MTC) has focused on inhibition of the RET proto-oncogene with minimal success. Akt is a downstream target of RET via the key mediator phosphoinositide-3-kinase. Targeting Akt in MTC may thus be more effective for anti-tumor treatments. MK-2206 is an orally administered allosteric Akt inhibitor that exhibited minimal toxicity in phase 1 trials. We therefore explored the anti-tumor effects of this novel compound in MTC.

Methods: Human MTC-TT cells were treated with MK-2206 (0-20 μ M) for 2, 4, and 6 days. Assays for cell viability were performed at each time point with MTT. Western blot analysis was performed on protein lysates from TT cells treated with MK-2206 (0-10 μ M) for 4 days to assess mechanism of action, mechanism of growth inhibition, and production of neuroendocrine tumor markers.

Results: MK-2206 suppressed MTC cell proliferation in a dose-dependent manner ($p \leq 0.02$). Levels of Akt phosphorylated at serine residue 473 declined with increasing doses of MK-2206, indicating successful Akt inhibition. The apoptotic proteins cleaved PARP and cleaved caspase 3 increased in a dose-dependent manner with MK-2206, while survivin, an apoptosis inhibitor, was markedly reduced. Importantly, the anti-tumor effects of MK-2206 were independent of RET, as the levels of RET protein were not blocked.

Conclusion: The Akt inhibitor MK-2206 significantly suppresses MTC proliferation independent of RET modulation. Given the high oral bioavailability and low toxicity profile, Phase II studies with this drug alone or in combination with RET inhibitors are warranted.