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Rational Design of a Combination Therapy for MTC and Evaluation of an Imaging Biomarker for Prediction of Treatment Response

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BACKGROUND: Medullary thyroid carcinoma (MTC) originates from the thyroid gland neuroendocrine C-cells. Treatment options for progressive, metastatic MTC patients consist of the FDA-approved tyrosine kinase inhibitors (TKIs), Vandetanib and Cabozantinib. Another TKI, Nintedanib, is currently undergoing Phase II clinical trials. TKI resistance is common and improving current treatments is needed. Here we investigate Nintedanib and the HDAC inhibitor, Romidepsin, as monotherapies in a preclinical MTC mouse model. We evaluate subsequently Nintedanib/Romidepsin as a combination therapy for MTC. Furthermore we assess a new magnetic resonance imaging (MRI) technique, Amide Proton Transfer (APT), as an imaging biomarker for the prediction of therapeutic response.

METHODS: We used the NSE/p25-gfp bi-transgenic MTC mouse model. Mice were dosed daily intraperitoneally for 3 weeks with either Nintedanib (100 mg/kg/day) or Romidepsin (0.75 mg/kg/day) or [Nintedanib (35 mg/kg/day) + Romidepsin (0.37 mg/kg/day)] or vehicle. Tumor progression was monitored weekly using T2W-imaging on a 7T system. APT was performed on a single 1-mm-slice delineating the tumor maximum diameter. Proliferation and microvessel density were determined by immunostaining fixed tumors with Ki67 and CD31 antibodies, respectively. Frozen tumors were analyzed for oncogenic signaling pathways by immunoblotting.

RESULTS: Nintedanib blocked MTC growth by 50% by an apparent anti-angiogenic effect. CD31 signal dropped indeed by 5-folds while Ki67 signal remain unchanged. Romidepsin caused a 1.5-fold Ki67 signal reduction, had no effect on microvessel density or tumor growth. The Nintedanib/Romidepsin combination reduced tumor growth by 50%, proliferation and microvessel density by ~2.7-folds. Mechanistically RET, VEGFR2, AKT and mTor signaling were inhibited by Nintedanib and Nintedanib/Romidepsin combination. The APT signal correlated with Ki67 but not CD31 signal. Consistently changes in APT signal were detected in combination therapy-treated animals, 1 week earlier as with conventional MRI.

CONCLUSION: The Nintedanib/Romidepsin combination may be a valid strategy for MTC. APT can be used to predict tumor response to this therapeutic combination.