

**Evaluation of Nintedanib and Romidepsin as
Single-Agent Therapies or as a Combinatorial
Treatment for Medullary Thyroid Carcinoma:
A Preclinical Study**

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Background: Medullary thyroid carcinoma is a neuroendocrine cancer originating from calcitonin-producing parafollicular cells in the thyroid gland. The best treatment currently available is surgical removal of the thyroid, but recurrence is common. Two tyrosine kinase inhibitors (TKI), Vandetanib and Cabozantinib, have been FDA-approved for the treatment of metastatic MTC patients, but their efficacy is limited and development of resistance to TKI is commonly observed. Thus additional therapies are needed. Here we evaluate the anticancer effect of the TKI, Nintedanib, and of the histone deacetylase (HDAC) inhibitor, Romidepsin, administered individually or in combination in a mouse model of MTC.

Methods: We used the NSE/p25-gfp bi-transgenic mouse line, which develops MTC upon overexpression of the cyclin-dependent kinase 5 activator, p25, in the thyroid parafollicular cells. For monotherapies, mice were dosed with either Nintedanib (100 mg/kg/day) or Romidepsin (0.75 mg/kg/day) or vehicle. For combination therapies, mice were treated with either Nintedanib (35 mg/kg/day) + Romidepsin (0.37 mg/kg/day) or with vehicle. Drugs were administered intraperitoneally or by oral gavage for a 3-week period. Tumor progression was monitored using a T2 weighted magnetic resonance imaging on a 7 Tesla system. Tumor tissues were analyzed for oncogenic signaling pathways by immunoblotting and by immunohistochemistry.

Results: Nintedanib administered alone, or in combination with Romidepsin can stop tumor growth. The density of the vascular marker, CD31, was reduced following Nintedanib treatment while the proliferation marker, PCNA, remained high in Nintedanib-treated tumors. Co-administrating Romidepsin and Nintedanib increases the number of necrotic foci within the tumor tissue suggesting higher levels of cell death induced by using this drug combination.

Conclusion: Combinatorial treatment with a TKI and an HDAC inhibitor is a valid strategy to stop MTC progression. More studies are necessary to determine the drugs mode of action and their anticancer effect in MTC patients.