Molecular alterations in RET, including rearrangements (fusions) and activating point mutations, have been identified in a significant portion of papillary thyroid cancer (PTC), up to 2% of non-small cell lung cancers (NSCLC) and at lower frequencies in other malignancies including colorectal cancer (CRC). Point mutations in RET are typically detected in multiple endocrine neoplasia (MEN), as well as familial medullary thyroid carcinoma. Although multiple-kinase inhibitors with RET activity have shown evidence of clinical activity, there remains a need for better tolerated, more efficacious RET inhibitors for the treatment of patients with relevant molecular alterations. Molecular alterations in BRAF are commonly identified in 10% to 15% of metastatic colorectal cancers (mCRC), and 1% to 2% of NSCLC. Although notable clinical activity has been achieved with single-agent vemurafenib and dabrafenib in melanoma harboring the BRAF V600E mutation, their clinical efficacy in non-melanoma solid tumor types, including mCRC, has not been satisfactory.

RXDX-105 is a VEGFR-sparing, potent inhibitor of RET and BRAF alterations. In cell-based assays, RXDX-105 demonstrated significant dose-dependent inhibition of RET and mutated RET proteins. In cell-based assays, RXDX-105 demonstrated significant dose-dependent inhibition of RET and mutated RET proteins. In cell-based assays, RXDX-105 demonstrated significant dose-dependent inhibition of RET and mutated RET proteins. In cell-based assays, RXDX-105 demonstrated significant dose-dependent inhibition of RET and mutated RET proteins.

RESULTS

RXDX-105 is a VEGFR-sparing, potent inhibitor of RET and BRAF

RXDX-105 inhibits proliferation of RET driven cell lines in vitro

RXDX-105 inhibits RET signaling and induces apoptosis in RET driven cell lines

RXDX-105 induces regression of RET fusion driven PDX models in vivo

RXDX-105 inhibits BRAF alterations and downstream signaling in vitro without EGFR feedback activation

CONCLUSIONS

RXDX-105 is a VEGFR-sparing, potent inhibitor of RET and has demonstrated significant antitumor activity in preclinical models harboring RET fusions. RXDX-105 also demonstrated significant antitumor activity in preclinical models harboring BRAF alterations. RXDX-105 is currently being developed as an oral therapy for patients with solid tumors that harbor activating RET alterations (NCT 01877811).