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BLU-667 is a potent and highly selective RET inhibitor being developed for RET-driven cancers

Introduction:  CCDC6-RET/PTC1 (papillary thyroid cancer gene 1) was one of the first gene fusions identified from a malignant epithelial tumor.  Over the past 5 years, additional cancer types have been found to have oncogenic RET fusions, most notably non-small cell lung adenocarcinoma (NSCLC) and colorectal carcinoma (CRC).  Activating RET mutations are also known to drive multiple endocrine neoplasia and are the most prevalent type of alteration found in medullary thyroid cancer (MTC).  Multi-kinase inhibitors (mKIs) with in vitro activity against RET, such as cabozantinib and vandetanib, are frequently used to treat RET-altered tumors, yet toxicities limit their use and likely their ability to fully inhibit RET kinase activation.  BLU-667 is a next-generation kinase inhibitor specifically tailored to target the activated forms of RET while sparing other kinases such as VEGFR-2.  Given that secondary mutations are a common resistance mechanism for approved kinase inhibitors, we prospectively identified RET resistance mutations that may abrogate mKI activity and designed BLU-667 to also remain potent against these emergent mutations.

Results:  BLU-667 potently inhibited both wild-type and activating RET mutants (IC50 = 0.4 nM) and demonstrated 88-fold selectivity over VEGFR-2 in enzymatic assays.  In several RET-driven cancer cell lines from diverse lineages, including MZ-CRC-1 (MTC), TT (MTC), TPC-1 (PTC), and LC2/ad (NSCLC), BLU-667 inhibited RET autophosphorylation and cell proliferation in the low nanomolar range (4 – 15 nM).  Oral administration of BLU-667 to mice was well tolerated at all doses and exhibited dose-dependent inhibition of oncogenic RET kinase activity in all animal models tested, including a RET(C634W) mutant MTC xenograft, a KIF5B-RET NSCLC PDX, a CCDC6-RET CRC PDX, as well as a CCDC6-RET (V804M) CRC PDX model with a gatekeeper mutation conferring resistance to the mKI ponatinib.  Notably, BLU-667, but not cabozantinib, inhibited tumor growth without biomarker evidence of VEGFR-2 inhibition.  This provides strong evidence that selective inhibition of RET alone is sufficient for anti-tumor activity in vivo.

Conclusion:  BLU-667 is an investigational agent that potently and selectively inhibits oncogenic RET mutants and fusions in a wide variety of cancer models that have genetically activated RET kinase.  BLU-667 administration led to sustained kinase inhibition without evidence of VEGFR-2 inhibition.  By sparing off-target kinases with known toxicity profiles, BLU-667 is predicted to robustly inhibit RET at clinically achievable doses.  Moreover, with activity against predicted mKI resistance mutations, BLU-667 may prevent or delay the emergence of resistant clones with these secondary mutations.  As such, BLU-667 holds the promise to provide patients with RET-driven malignancies an opportunity for more durable and effective treatment.  BLU-667 is currently in a first-in-human phase 1 trial for patients with RET-driven solid tumors with activating RET alterations (NCT03037385).