

Abstract for Presentation by Blueprint Medicines Corporation on Sunday, October 29, 2017 at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics

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 ($IC_{50} = 0.4$ 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).