BLU-667 is a Potent and Highly Selective RET Inhibitor Being Developed for RET-Driven Cancers

Rami Rahal, Michelle Maynard, Wei Hu, Jason D. Brubaker, Qiongfang Cao, Joseph L. Kim, Michael P. Sheets, Douglas P. Wilson, Kevin J. Wilson, Lucian DiPietro, Paul Fleming, Timothy P. LaBranche, Beni Wolf, Timothy Guzi, Christoph Lengauer, Erica K. Evans.

Blue Medicines Corporation, Cambridge, MA

Poster B151

BLU-667 is a highly potent RET inhibitor that exhibits 100X selectivity for RET over 96% of kinases tested.

BLU-667 is Designed to Transform Treatment of RET-Altered Cancers

- Crafted to target oncogenic RET fusions and activating mutations
- Highly active against activating and resistance mutations at the gatekeeper (V604E) residue
- Kinase selectivity allowing full in vivo RET Inhibition at well tolerated doses

BLU-667 is a sub-nanomolar RET inhibitor with GEO > 100X fully over VEGFR2

BLU-667 Potency Inhibits RET Activity and is Active on GSK3B (C634W) Mutations

- BLU-667 potently inhibits RET kinase activity in vitro with >96% selectivity for RET over 96% of kinases tested.
- BLU-667 robustly suppresses oncogenic KIF5B-RET signaling in vivo

BLU-667 Robustly Suppresses Oncogenic KIF5B-RET Signaling and Tumor Growth Without Functionally Impacting VEGFR-2

- BLU-667 potently inhibits both RET and VEGFR2 activity in cell lines harboring oncogenic KIF5B-RET activity without functional impact of VEGFR2.
- BLU-667 is well-tolerated in all models at all doses tested.

BLU-667 Inhibits RET Signaling and Cell Proliferation of Thyroid Cancer Cells with Activating RET Alterations

- BLU-667 potently inhibits the proliferation of MTC and PTC cells harboring activating RET alterations.
- Overexpression of RET in a cell line harboring a RET fusion was associated with potent inhibition of RET signaling by BLU-667.

Conclusions

- BLU-667 potently and selectively inhibits oncogenic RET fusions and activating mutations in preclinical models.
- Broad, robust, anti-tumor activity against multiple RET-driven solid tumor types.
- Highly active against V604E gatekeeper substitutions that are mKIs resistant.
- Spares VEGFR2 at doses that completely inhibit RET.
- DUSP6 and SFRY4 have been identified as robust PD biomarkers of RET activity.
- BLU-667 has entered Phase 1 clinical testing in patients with RET-altered NSCLC, thyroid cancer and other solid tumors.

BLU-667 has the potential to be a transformative medicine for patients with RET-driven malignancies.