LNG-451 (BLU-451) is a potent, CNS-penetrant, wild-type EGFR sparing inhibitor of EGFR exon 20 insertion mutations

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Background

Epithelial growth factor receptor (EGFR) ex20 insertions (ex20ins) are some of the most common EGFR mutations in patients with lung cancer, and are most frequently found in tumors with T790M mutations. 1Lengo Therapeutics, Cambridge, MA, USA; 2Jubilant Biosys Limited, Bengaluru, Karnataka, India.

Methods

• BLU-451 cellular activity was tested by cell viability assays in both tumor and Ba/F3 engineered cell lines expressing EGFR mutations as well as cell lines dependent on WT EGFR.

• BLU-451 (10 and 50 mg/kg) treatment of HuPrime® xenograft tumor models harboring the EGFR ex20ins-driven cell line-derived xenograft (CDX) tumor model, were potent in vivo with >90% suppression of the phosphorylation of EGFR on tyrosine residue 1068 as a surrogate marker of EGFR activation (vehicle treated tumor tissue) (Figure 4).

• Single-dose PK/PD line curve analysis of BLU-451 (50 mg/kg) performed in a Ba/F3 EGFR ex20ins/WT/EGFRex20insAVV xenograft tumor model using phosphorylation of EGFR on tyrosine residue 1068 as a surrogate marker for EGFR activation (vehicle treated tumor tissue) (Figure 4).

Results

• In ligand binding assays (Figure 1), BLU-451 (10nM) inhibited 1.7% of kinase tested by IC50 >500 nM (IC50 >1000 nM), with the exception of RET1, where BLU-451 was less potent compared to other ATP binding Site B inhibitors (e.g., isomerib).

• In radioactive assays run in the presence of 10 µM ATP, BLU-451 (1 µM) inhibited 2.2% of kinases by IC50 >500 nM accounting for half of the cases.

• EGFR ex20ins were more potent during the ligand active state in which manner renders the first three generations of EGFR inhibitors generally ineffective.

• While there are approved therapies that demonstrate clinical benefit and act on some commonly mutated EGFR exons (e.g., T790M), none have demonstrated meaningful clinical benefit in patients with uncommon EGFR exons, and are not potently targeted by many inhibitors of EGFR ex20ins.

• These inhibitors included mobocertinib led to 17.5% body weight loss (Vehicle; 8 h; 24 h) in Ba/F3 engineered cell lines expressing the EGFR ex20ins (H773-V774insNPH) resulted in marked suppression of tumor growth, but also marked suppression of WT EGFR in skin and large intestine tissues (Figure 5).

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Conclusions


• BLU-451 is a potent inhibitor of EGFR ex20ins as well as other uncommon EGFR exons (Figure 6).

• BLU-451 is selective for EGFR ex20ins relative to the human kinome and WT EGFR, sparing in both cellular proliferation and phosphorylation of EGFR in xenograft tumor models (Figure 6).

• BLU-451 is a potent inhibitor of EGFR ex20ins in the Ba/F3 xenograft tumor model, potently inhibiting EGFR phosphorylation in tumor tissue but also marked suppression of WT EGFR and be CNS penetrant.

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• BLU-451 is a potent and selective kinase inhibitor of EGFR ex20ins at the concentrations tested (Figure 2).


Acknowledgements

A single-dose PK/PD study of BLU-451 and mobocertinib was performed in a Ba/F3 EGFR (V790M/D770AVVS) xenograft tumor model using phosphorylation of EGFR on tyrosine residue 1068 as a surrogate marker for EGFR activation. Vehicle-treated tumor tissue was used as a control for each xenograft tumor model. Mobocertinib potently inhibited EGFR ex20ins in tumor tissue but also suppressed WT EGFR in skin and large intestine tissues (Figure 5A). PK/PD analysis showed similar exposure for BLU-451 and mobocertinib in tumor, large intestine, and skin tissue 3 h post dosing.

Both inhibitors suppressed EGFR phosphorylation in tumor, but only BLU-451 did not potently suppress EGFR phosphorylation in the large intestine and skin tissue samples (Figure 5B).