LNG-451 (BLU-451), a potent inhibitor of EGFR exon 20 insertion mutations with high CNS exposure

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Background

Epithelial growth factor receptor (EGFR) activated ERBB20 insertions (ex20ins) are oncogenic driver mutations that constitutively upregulate EGFR kinase activity, and are the third most common type of activating EGFR mutation. While these mutations are generally shared by many inhibitors of common activation mutations such as L858R and exon 19 mutations1, EGFR ex20ins are in-frame insertions of 1 to 7 amino acids in the c-helix or following the c-helix2 with the most prevalent insertions V790_D791insA, D790_T791insD, and H773_V774insN,8,9 accounting for half of the cases1,2.

Since brain metastases are common in non-small cell lung cancer (NSCLC) with 30% of patients developing them during the course of their disease, brain penetrant EGFR-directed therapies are necessary for better treatment outcomes.10

While there are approved therapies such as mobocertinib and amivantamab and anti-EGFR ADCs for EGFR mutations as well as cell lines dependent on WT EGFR signaling11-13, the translational aspect平 of these therapies remains to be fully demonstrated.

Methods

BLU-451 activity was tested in tumor cell lines and Ba/F3 engineered cells expressing EGFR mutations as well as cell lines dependent on WT EGFR.

- BLU-451 50 mg/kg QD10 mg/kg QD
- Mobocertinib (BCR-963) 10 mg/kg QD
- Osimertinib (AZD9291) 10 mg/kg QD

Figure 3A-B shows BLU-451 PK in BalbC mice at dosages of 2 mg/kg, 10 mg/kg (AUC ~4,590 ng-h/mL), and 50 mg/kg.

- BLU-451 treatment resulted in suppression of EGFR phosphorylation in Ba/F3 EGFR ex20ins 19G970insA57 tumor model (Figure 3C).

- Following BLU-451 pharmacokinetic half-life is expected as EGFR tumor regressions were only observed for 27 hours.

In a murine intracranial tumor model, BLU-451 treatment resulted in brain tumor regression and suppression of metastatic dissemination (Figure 3B). Ex vivo analysis showed that BLU-451 reduced luminescence in the brain and spinal cords consistent with activity in the CNS compartment (Figure 5C).

Conclusions

- BLU-451 is a WT EGFR sparing, selective, CNS-penetrant investigational EGFR ex20ins covalent inhibitor.
- BLU-451 is not a substrate for Pgp (MDR1) or BCRP and is orally bioavailable in mouse.
- BLU-451, shown an extended pharmacodynamic half-life for inhibition of EGFR phosphorylation in tumors, as expected given its covalent mechanism of action.
- In a murine intracranial tumor model, BLU-451 treatment resulted in measurable tumor regression.
- These in vivo and ex vivo PK and pharmacodynamic results strongly support a first-in-human phase 1/2 clinical trial of BLU-451 in patients with advanced or metastatic solid tumors harboring EGFR ex20ins mutations (NCT05241873).

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References


Disclosures

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