BLU-945, a four-generation, potent and highly selective epidermal growth factor receptor tyrosine kinase inhibitor with intracranial activity, demonstrates robust in vivo anti-tumor activity in models of osimertinib-resistant non-small cell lung cancer

Sun Min Lim1*, Chae-Won Park2*, Zhong Zhang2, Rich Wousma3, Tom Dineen4, Faith Slavson5, John Hersh6, Meredith Eo1, Doug Wilson7, John Campbell2, Caitlin Ut1, Faris Albayali3, Nicolas Lamantagne3, Marion Dorsch8, Klaus Hoeflich9, Byung Chul Cho10, Stephanie Schalm11

1Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; 2Blueprint Medicines Corporation, Cambridge, Massachusetts, USA

Background

- Lung cancer is the leading cause of cancer death globally.
- The sensitizing/activating EGFR exon 19 deletion (ex19del) and L858R mutations are the genomic drivers in ~15% of patients with lung adenocarcinoma, the most common form of non-small cell lung cancer (NSCLC).
- First- (1G) and third-generation (3G) EGFR inhibitors such as gefitinib and osimertinib, respectively, have improved treatment outcomes for patients with EGFR-mutant NSCLC, but resistance inevitably emerges, leading to disease progression and often with central nervous system (CNS) metastasis.3,4 Tumors harboring activating or wild-type (WT) EGFR are frequently reported with 1G inhibitors.5-7
- The T790M and C797S mutations are the most common on-target resistance mechanisms in 1G inhibitors and 3G inhibitors, respectively.8-10
- There are no approved therapies for patients with disease progression following treatment with a first or third-generation EGFR inhibitor or following sequential treatment with first-line 1G and second-line 3G inhibitors.5-10
- BLU-945 and BLU-701 are fourth-generation (4G) investigational EGFR inhibitors designed for use as monotherapy or combination therapy (together or with other agents) to potently suppress activating and on-target resistance EGFR mutants, and spare WT EGFR, with potential to treat or prevent CNS metastases (Conti C et al. AACR 2021. Abstract 1206).

Here we provide further preclinical data to support the clinical development of BLU-945 in patients with EGFR-mutant NSCLC.

Methods

- Cellular activity was evaluated by a phosphorylation-specific EGFR AlphaLisa assay in WT cell lines and in cell lines expressing EGFR mutants.
- In vivo anti-tumor activity and pathway inhibition of BLU-945 was assessed in an engineered triple mutant, osimertinib-resistant cell line-derived xenograft (CDX) and an osimertinib-resistant patient-derived xenograft (PDOX) model.
- In vivo CNS activity was assessed in an intracranial implantation model of luciferase-expressing YU-1097 patient-derived cells harboring EGFR ex19del/T790M/C797S mutations, tumor burden of intracranial lesions was measured by bioluminescence imaging.
- Figure 1: BLU-945 and BLU-701 are optimized for single agent and combination therapy.

Conclusions

- BLU-945 is a potential best-in-class, selective, potent, four-generation EGFR TKI with activity against the EGFR ex19del/T790M/C797S triple mutant.
- BLU-945 demonstrated potent, robust EGFR pathway inhibition and anti-tumor activity in triple mutant osimertinib-resistant Ba/F3 CDX and PDOX models.
- In the same triple-mutant PDOX model, combination of BLU-945 with either gefitinib or osimertinib showed enhanced anti-tumor activity when compared with single-agent treatment.
- Clinical development of BLU-945 monotherapy is expected to begin with an international phase I dose-escalation trial in patients with EGFR-driven CNS lesions in the first half of 2023, and future clinical development of BLU-945 in combination with other agents across multiple treatment settings is planned.

References


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