Antitumor activity of BLU-945 and BLU-701 as single agents and in combination in EGFR L858R-driven models of NSCLC

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Abstract

Background

• Lung cancer is the leading cause of cancer death worldwide.1 EGFR mutations are the most common targeted actionable drivers of non-small cell lung cancer (NSCLC), occurring in ~17% and up to 40% of Asian patients, respectively.2,3
• Exon 19 deletions (ex19del) and L858R are the most common EGFR mutations4
• Treatment resistance can emerge following treatment with 1st-generation (1G) and/or 2nd-generation (2G) EGFR tyrosine kinase inhibitors (TKIs) in the USA5 and China6

Methods

• In vivo antitumor activities of BLU-945 and BLU-701 as single-agents were evaluated in two EGFR/L858R-driven, treatment-naive, patient-derived xenograft (PDX) subcutaneous tumor models (LUN-439 and LUN-487)
• In vivo antitumor activities of BLU-945 and BLU-701, as single agents and in combination, were evaluated in the Ba/F3 cell line-derived xenograft (CDX) subcutaneous tumor model engineered to overexpress EGFR L858R/C797S

Results

• Oral administration of single-agent BLU-945 100 mg/kg twice a day (BID) and BLU-701 30 mg/kg QD once a day (QD) resulted in significant tumor regression in the EGFR/L858R-driven treatment-naive LUN-439 (Figure 2A) and LUN-487 (Figure 2B and 2D) PDX tumor models
• Response to treatment with single-agent BLU-945 100 mg/kg BID and BLU-701 30 mg/kg QD was sustained even after treatment cessation in these models (Figure 2D)
• The osimertinib-resistant EGFR L858R/C797S Ba/F3 CDX tumor model is a fast-growing aggressive model driven by mutant EGFR, which has primary resistance to osimertinib; tumor escape due to resistance mechanisms is responsive to high target coverage achieved with BLU-701 and BLU-945 was expected (Figure 3)
• BLU-945 150 mg/kg BID and BLU-701 30 mg/kg QD as single agents and in combination resulted in tumor regression and prolonged responses; BLU-945 100 mg/kg BID + BLU-701 30 mg/kg QD combination treatment resulted in further potent antitumor regression when compared to treatment with the single agents (Figure 3)
• The addition of BLU-945 likely extends the duration of response and provides coverage of the T790M mutation: the emergence of this mutation was documented in all progressing tumors in the BLU-701 monotherapy cohort (Figure 3)

Conclusions

• BLU-945 and BLU-701 are investigational, reversible, selective, and orally available TKIs designed to target common activating and osimertinib-resistant mutations in EGFR-mutated NSCLC
• Single-agent BLU-945 and BLU-701 prolonged tumor regression compared to vehicle in both an EGFR/L858R-driven, treatment-naive PDX model as well as an aggressive osimertinib-resistant, EGFR/L858R/C797S-driven (Ba/F3) CDX model
• This suggests that BLU-945 and BLU-701 may have potential benefit in patients with NSCLC harboring the EGFR L858R mutation, including patients with treatment-naive or previously treated with a 3G TKI
• While single-agent BLU-945 and BLU-701 individually led to significant tumor regression in the EGFR L858R/C797S-driven Ba/F3 CDX model, regression was prolonged even further by combination treatment, possibly due to the broader resistance coverage, which includes the common L858R activating mutation and the frequent on-target C797S resistance mutation

Figure 1: BLU-945 and BLU-701 are optimized for single agent and combination therapy

Figure 2: Administration of single agent BLU-945 100 mg/kg BID and BLU-701 30 mg/kg QD showed prolonged tumor regression in EGFR/L858R-driven treatment-naive PDX models (cont.)

Figure 3: BLU-945 150 mg/kg BID + BLU-701 30 mg/kg QD exhibited marked antitumor activity in the osimertinib-resistant EGFR/L858R/C797S Ba/F3 CDX model

References


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Disclosures

• All authors have conflicts of interest with Blueprint Medicines Corporation. The authors had full editorial control of the manuscript and provided their final approval of all content.

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