BLU-701 tumour suppression and intracranial antitumour activity as a single agent and in combination with BLU-945 in models of non-small cell lung cancer driven by EGFR mutations

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Background

- EGFR mutations are the most common targetable alterations in non-small cell lung cancer (NSCLC), occurring in ~17% of Caucasian and up to 50% of Asian patients1, with over 19 different (ex19del) and L858R being the most common.
- 30–50% of patients with NSCLC have brain metastases2,3.
- Resistance inevitably emerges after treatment with 1st-generation (1G) and/or 2nd-generation (2G) EGFR tyrosine kinase inhibitors (TKI) or EGFR T790M and C797S are the most common on-target mutations to 1G and 2G EGFR TKIs, respectively4,5.
- There are no approved therapies for patients who have progressed while receiving a 2G EGFR TKI, either as frontline therapy or second-line treatment6,7.
- BLU-701 and BLU-945 are investigational, reversible, selective, and oral TKIs designed for use as a single agent or in combination therapy to target and antagonise EGFR mutations while sparing normal EGFR while sparing normal EGFR pathways8,9.
- BLU-701 selectively targets EGFR ex19del and L858R activating mutations and the C797S resistance mutation with nanomolar potency; it shows in vivo tumour shrinkage in xenograft-resistant models10,11 and high central nervous system penetration (CNS)12,13.
- BLU-945 targets mutant EGFR exons harbouring activating and resistance (T790M and C797S) mutations with nanomolar potency and shows in vivo tumour shrinkage in a xenograft-resistant model14.

Methods

- In vivo subcutaneous antitumour activity of BLU-701 as a single agent and/or in combination with BLU-945 was evaluated in an ex19del-driven patient-derived xenograft (PDX) model (LUPF104), derived from a treatment-naive patient, the EGFR ex19del/C797S-expressing BLU-945 cell line-driven xenograft (C797S model), and an ex19del/C797S-driven BRCA cell line-driven xenograft (C797S model) and an ex19del/C797S-driven BRCA cell line-driven xenograft (C797S model) and an ex19del/C797S-driven xenograft (C797S model).
- In vivo inhibition of brain metastases was evaluated in a Rats in vivo expressing EGFR ex19del PDX luciferase model through either (i) direct intracranial implantation or (ii) intracranial inoculation followed by dissemination to the brain.

Results

Figure 2: BLU-701 has sustained antitumour activity at wide-type-sparing doses in the EGFR ex19del-driven LUNA414 PDX model derived from a treatment-naive patient

A. Tumour regression up to day 28 (last day of treatment

- Daily oral administration of BLU-701 (5 mg/kg QD) or the combination of BLU-701 and osimertinib (100 mg/kg BID) resulted in a >50% dose-dependent tumour regression, greater than either gefitinib (6.25 mg/kg QD) or cetuximab 25 mg/kg QD (Figure 3A).
- Response with BLU-701 30 mg/kg QD was sustained even after treatment discontinuation (Figure 3B).
- Combination with osimertinib 100 mg/kg BID resulted in complete tumour regression (Figure 3B).
- 2 mice mice treated with BLU-701 had tumour regrowth, which regressed following retreatment (one only) or 6 out of 8 mice treated with cetuximab.

Figure 3: BLU-701 exhibits dose-dependent intracranial antitumour activity in the EGFR ex19del/PDX luciferase model

A. Intracranial tumour inoculation (inoculation whole brain)

- One administration of BLU-701 30 mg/kg QD + BLU-945 100 mg/kg BID resulted in enhanced subcutaneous tumour regression compared with single agents, in the xenograft-resistant ex19del/C797S-driven BRCA xenograft model, representative of 2G15.
- The xenograft-resistant ex19del/C797S-driven BRCA xenograft model, representative of (4G) treatment, was chosen to demonstrate the benefit of BLU-945 in combination with BLU-701 30 mg/kg QD + BLU-945 100 mg/kg BID resulted in enhanced subcutaneous tumour regression compared with single agents (Figure 4B).

Figure 4: Subcutaneous antitumour activity is enhanced with BLU-701 + BLU-945 combination treatment at wide-type-sparing doses in the xenograft-resistant and PDX tumour models

A. BLU-701 + BLU-945 combination treatment at day 15

- BLU-701 + BLU-945 combination treatment led to a significant increase in survival compared with BLU-701 and BLU-945 monotherapies (P<0.0001).

Figure 5: Concentrations of BLU-701 30 mg/kg and BLU-945 100 mg/kg are below wide-type EGFR IC50 when administered as single agents and in combination

A. BLU-701 + BLU-945 combination treatment at day 15

- BLU-701 + BLU-945 combination treatment led to a significant increase in survival compared with BLU-701 and BLU-945 monotherapies (P<0.0001).

Conclusions

- BLU-701 (NCT05153408) and BLU-945 (NCT04887280) are reversible, selective, and orally available TKIs that target common activating and resistance mutations in EGFR.
- Administration of BLU-701 30 mg/kg led to sustained tumour regression not observed with concurrent 25 mg/kg QD osimertinib 100 mg/kg BID in PDX model derived from a treatment naive patient, suggesting promising frontline efficacy.
- BLU-945 is brain penetrant and administration of single-agent BLU-945 10–30 mg/kg QD showed intracranial activity.
- Treatment with BLU-701 + BLU-945 in combination, at doses that spare wide-type EGFR, resulted in intracranial tumour regression compared with single agents in xenograft-resistant CDX and PDX models driven by mutant EGFR.
- These data support the clinical development of BLU-701 as monotherapy or combination therapy with BLU-945 in ex19del/R701G NSCLC across multiple lines of treatment.

References


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