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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Background

- Lung cancer is the leading cause of cancer death worldwide.[1] *EGFR* mutations are the most common targetable genomic drivers of non-small cell lung cancer (NSCLC), occurring in ~17% and up to 50% of Caucasian and Asian patients, respectively[2,3]
- Exon 19 deletions (ex19del) and L858R are the most common *EGFR* mutations[4]
- Treatment resistance can emerge following treatment with 1st-generation (1G) and/or 3rd-generation (3G) EGFR tyrosine kinase inhibitors (TKIs)[4–6]; T790M and C797S are the most common on-target resistance mutations to 1G and 3G EGFR TKIs, respectively[4,6]
- L858R accounts for 39% of all *EGFR* mutations in NSCLC,[7] including 32% of patients in the USA[8], and 46% of patients in China[9]
- NSCLC patients with *EGFR* L858R mutations have poorer outcomes than those with *EGFR* ex19del, suggesting a significant clinical unmet need in this population[10–12]; the median progression-free survival of previously untreated patients on osimertinib with *EGFR* L858R is 14.4 months *vs* 21.4 months in those with the *EGFR* ex19del[11]
- BLU-945 and BLU-701 are investigational, reversible, selective, and orally available TKIs that suppress activating and on-target resistance EGFR mutants while sparing the wildtype (WT) kinase; they are optimized for single-agent and combination therapies (**Figure 1**) across multiple lines of treatment, including against heterogenous tumors, and are being studied with the potential to treat or prevent central nervous system metastases[13–16]
- BLU-945 selectively targets EGFR mutants harboring the L858R activating mutation, and the T790M and C797S on-target resistance mutations with nanomolar potency and has shown *in vivo* tumor shrinkage in treatment-naïve and osimertinib-resistant models[15,16]
- BLU-701 selectively targets EGFR mutants harboring the ex19del and L858R activating mutations and the C797S resistance mutation with nanomolar potency and has shown *in vivo* tumor shrinkage in treatment-naïve and in osimertinib-resistant models as well[14]
- Preclinically, BLU-945 and BLU-701 in combination exhibited enhanced and prolonged antitumor activity compared with single agents at doses that spare WT EGFR in ex19del-driven osimertinib-resistant tumor models[17]
- Clinical evaluation of BLU-945 in the Phase 1/2 SYMPHONY study (NCT04862780; Shum et al. AACR 2022; New Orleans [Poster CT184]) and of BLU-701 in the HARMONY study (NCT05153408) in patients with *EGFR*-mutated NSCLC are in progress[18]
- This study aimed to evaluate the antitumor activity of BLU-945 and BLU-701, as single agents and in combination, in preclinical NSCLC tumor models driven by *EGFR* L858R in the absence of the T790M mutation

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

		1G	3G	Next generation		Potential combinations		
Line	EGFR mutational coverage[a]	Gefitinib	Osimertinib	BLU-701	BLU-945	BLU-701 + osimertinib	BLU-945 + osimertinib	BLU-701 + BLU-945
1L	L858R (LR)							
1L	ex19del							
2L	LR or ex19del / T790M							
2L	LR / C797S							
2L	ex19del / C797S							
3L	LR or ex19del / T790M / C797S							

IC_{50} ≤10 nM IC_{50} >50 nM

[a]Based on biochemical IC_{50}:
1G, 1st-generation; 3G, 3rd-generation; IC_{50}, half-maximal inhibitory concentration.

Methods

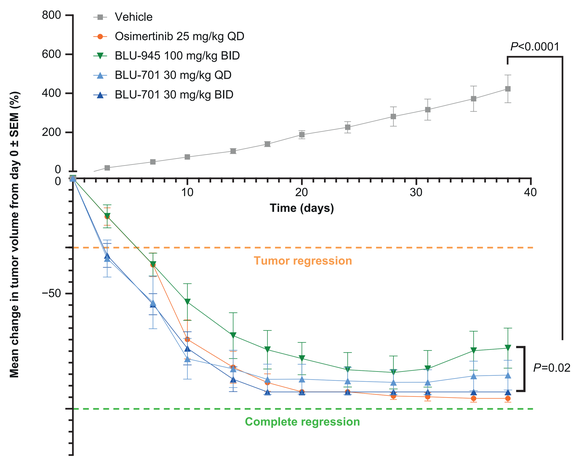
- *In vivo* antitumor activities of BLU-945 and BLU-701 as single-agents were evaluated in two *EGFR* L858R-driven, treatment-naïve, patient-derived xenograft (PDX) subcutaneous tumor models (LUN-439 and LUN-487)
- *In vivo* antitumor activities of BLU-945 and BLU-701, as single agents and in combination,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

Results

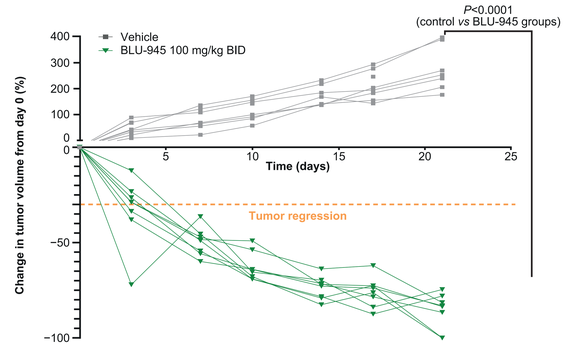
- Oral administration of single-agent BLU-945 100 mg/kg twice a day (BID) and BLU-701 30 mg/kg once a day (QD) resulted in significant tumor regression in the *EGFR* L858R-driven treatment-naïve LUN-439 (**Figure 2A**) and LUN-487 (**Figures 2B** and **2C**) PDX tumor models
- Response to treatment with 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 in response to high target coverage achieved with BLU-701 and BLU-945 was expected (**Figure 3**)
- BLU-945 100 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 prolonged tumor 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**)

Figure 2: Administration of single agent BLU-945 100 mg/kg BID and BLU-701 30 mg/kg QD or BID showed prolonged tumor regression in *EGFR* L858R-driven treatment-naïve PDX models

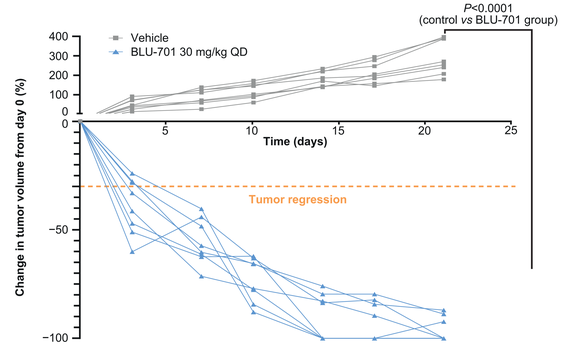
A. Tumor regression with BLU-945, BLU-701, and osimertinib in the LUN-439 PDX model



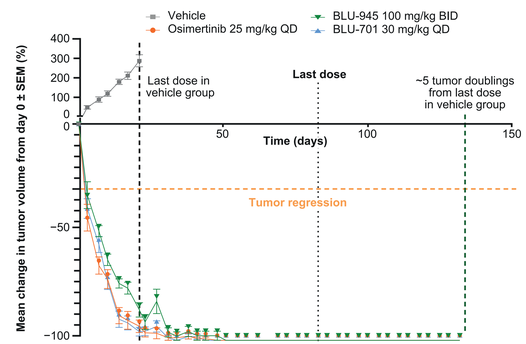
B. Tumor regression with BLU-945 in LUN-487 PDX model, shown for individual mice



C. Tumor regression with BLU-701 in the LUN-487 PDX model, shown for individual mice

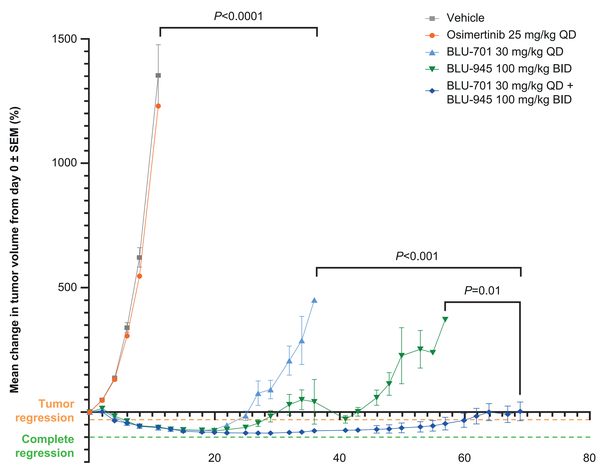


D. Tumor regression with BLU-945, BLU-701, and osimertinib in the LUN-487 PDX model



P values per 2-way repeated measures ANOVA. ANOVA, analysis of variance; BID, twice a day; PDX, patient-derived xenograft; QD, once a day; SEM, standard error of the mean.

Figure 3: BLU-945 100 mg/kg BID + BLU-701 30 mg/kg QD exhibited marked antitumor activity in the osimertinib-resistant *EGFR* L858R/C797S Ba/F3 CDX tumor model[a]



[a]Animals were treated QD (osimertinib 25 mg/kg) or BLU-701 (30 mg/kg), or BID (BLU-945 100 mg/kg) throughout the study, or until death.
P values per 2-way repeated measures ANOVA. CDX, cell line-derived xenograft.

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-naïve PDX model as well as in 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 who are treatment naïve or previously treated with a 3G TKI
- While both 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 mutational coverage which includes the common L858R activating mutation and the frequent on-target C797S resistance mutation
- Phase 1/2 studies of BLU-945 (SYMPHONY; NCT04862780; Shum et al. AACR 2022; New Orleans [Poster CT184]) and BLU-701 (HARMONY; NCT05153408) in patients with *EGFR*-mutated NSCLC are in progress[18]

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