BLU-701 tumour suppression and intracranial 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 patients,[1,2] with exon 19 deletions (ex19del) and L858R being the most common[3]
- 30%–50% of patients with NSCLC have brain metastases[4,5]
- Resistance inevitably emerges after treatment with 1st-generation (1G) and/or 3rd-generation (3G) EGFR tyrosine kinase inhibitors (TKIs); *EGFR* T790M and C797S are the most common on-target mutations to 1G and 3G EGFR TKIs, respectively[3,6,7]
- There are no approved therapies for patients who have progressed while receiving a 3G EGFR TKI, either as first-line treatment or second-line treatment following a first-line 1G TKI[3,7]
- BLU-701 and BLU-945 are investigational, reversible, selective, and oral TKIs optimized for use as single-agent or combination therapy to suppress activating and on-target resistance *EGFR* mutants while sparing WT EGFR (**Figure 1A**), and have the potential to treat or prevent central nervous system metastases[8-10]
- BLU-701 selectively targets EGFR ex19del and L858R activating mutations and the C797S resistance mutation with nanomolar potency. It showed in vivo tumour shrinkage in osimertinib-resistant models (**Figure 1B**) and high central nervous system penetration ($Kp_{u,u}$=0.98 from IV infusion)[8]
- BLU-945 selectively targets EGFR mutants harbouring activating and resistance (T790M and C797S) mutations with nanomolar potency and shows in vivo tumour shrinkage in an osimertinib-resistant model (**Figure 1C**)[9,10]
- This study aimed to evaluate the antitumour activity (subcutaneous and intracranial) of BLU-701 as a single-agent in treatment naïve preclinical models and in combination with BLU-945 in resistant models of *EGFR* mutant NSCLC

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

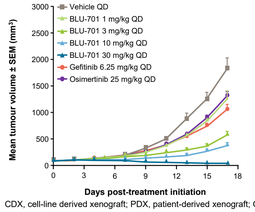
A.

		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 or ex19del / C797S							
3L	LR or ex19del / T790M / C797S							

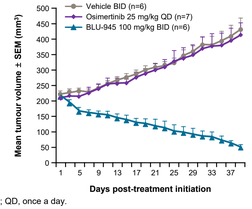
IC_{50} ≤10 nM; 10 nM < IC_{50} ≤50 nM; IC_{50} >50 nM

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

B. BLU-701 in *EGFR* ex19del/C797S-driven BaF3 CDX[8]



C. BLU-945 in *EGFR* ex19del/T790M/C797S-driven YU-1097 PDX[9]



CDX, cell-line derived xenograft; PDX, patient-derived xenograft; QD, once a day.

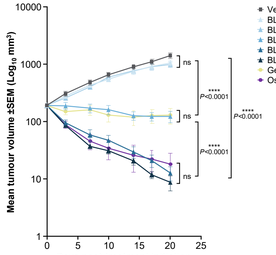
Methods

- In vivo subcutaneous antitumour activity of BLU-701 as single agent and/or in combination with BLU-945 was evaluated in an *EGFR* ex19del-driven patient-derived xenograft (PDX) model (LUN441; derived from a treatment-naïve patient), the *EGFR* ex19del/C797S-driven Ba/F3 cell line-derived xenograft (CDX) model, and an *EGFR* ex19del/T790M/C797S-driven PDX model (LUPF104)
- In vivo inhibition of brain metastases was evaluated in a luciferase-expressing *EGFR* ex19del PC9-luc CDX model through either (1) direct intracranial implantation or (2) intracarotid inoculation followed by dissemination to the brain

Results

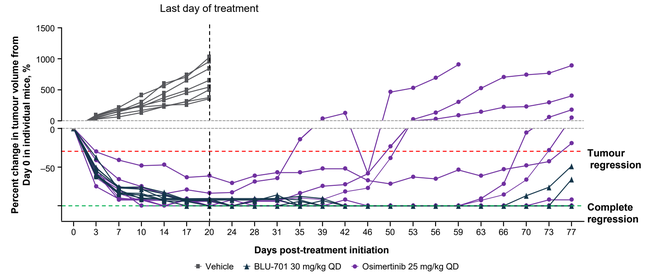
Figure 2: BLU-701 has sustained antitumour activity at wildtype-sparing doses in the *EGFR* ex19del-driven LUN441 PDX model derived from a treatment-naïve patient

A. Tumour regression up to Day 20 (last day of treatment)



- Daily oral administration of BLU-701 30 mg/kg QD for 20 days resulted in dose-dependent tumour regression, greater than either gefitinib 6.25 mg/kg QD or osimertinib 25 mg/kg QD (**Figure 2A**)
- Response with BLU-701 30 mg/kg QD was sustained even after treatment cessation, which was not observed with osimertinib 25 mg/kg QD (**Figure 2B**), indicating significant protection benefit from tumour regrowth
  - 2 out of 8 mice treated with BLU-701 had tumour regrowth, which regressed following retreatment (not shown), vs 6 out of 8 mice treated with osimertinib

B. Tumour regression[a] in individual mice up to Day 77

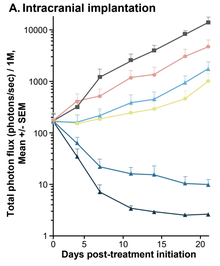


[a]Statistically significant difference (P<0.0001) in tumour regrowth between the 2 treatment groups (unpaired t-test).
ns, not statistically significant; QD, once a day; SEM, standard error of mean.

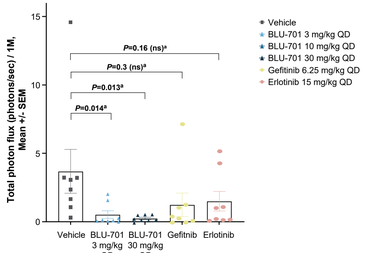
- LUN441 was derived from a treatment-naïve patient. The sustained antitumour activity of BLU-701 in this PDX model suggests promising clinical efficacy as first-line treatment

Figure 3: BLU-701 exhibits dose-dependent intracranial antitumour activity in the *EGFR* ex19del PC9-luc CDX model

A. Intracranial implantation



B. Intracarotid inoculation: isolated whole brains[a]

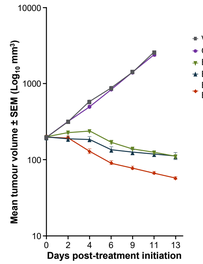


[a]Isolated brains minus average background. Statistical analyses using 1-way ANOVA multiple comparison tests.
ANOVA, analysis of variance; ns, not statistically significant; QD, once a day; SEM, standard error of mean.

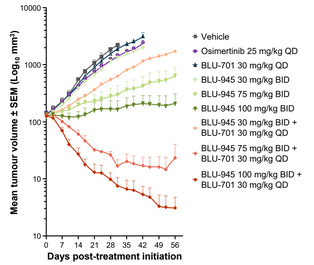
- Oral once-daily administration of BLU-701 10–30 mg/kg resulted in intracranial antitumour responses not observed with either erlotinib 15 mg/kg QD or gefitinib 6.25 mg/kg QD (**Figures 3A** and **3B**)
- Intracranial implantation (**Figure 3A**) of cancer cells can compromise the blood-brain-barrier (BBB), which remains intact when cells are inoculated in the carotid artery and migrate to the brain
- Consistent with comparable exposures to BLU-701 in the brain and plasma ($Kp_{u,u}$ = 0.98),[8] reduced luciferase activity was observed in the intracarotid brain metastasis model (**Figure 3B**), which suggests that BLU-701 is able to penetrate the intact BBB in vivo and inhibit metastasis growth in the brain

Figure 4: Subcutaneous antitumour activity is enhanced with BLU-701 + BLU-945 combination treatment (at wildtype-sparing doses) in osimertinib-resistant CDX and PDX tumour models

A. *EGFR* ex19del/C797S Ba/F3 CDX[a]



B. *EGFR* ex19del/T790M/C797S LUPF104 PDX



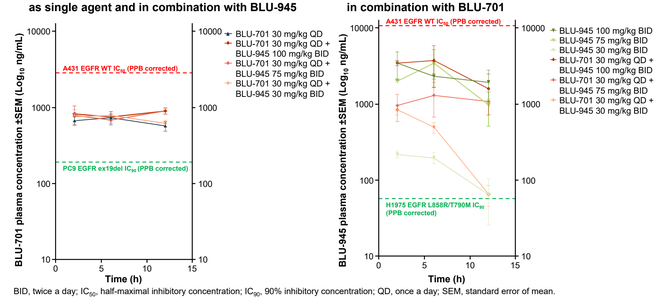
[a]Statistically significant difference (2-way repeated measures ANOVA) with vehicle or osimertinib vs all other treatment groups (P<0.0001) and with BLU-701 + BLU-945 combination therapy vs all other treatment groups (P<0.0001).
ANOVA, analysis of variance; BID, twice a day; QD, once a day; SEM, standard error of mean.

- Oral 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 osimertinib-resistant *EGFR* ex19del/C797S Ba/F3 CDX tumour model, representative of 2nd-line treatment (**Figure 4A**)
- The osimertinib-resistant, *EGFR* ex19del/T790M/C797S-driven LUPF104 PDX tumour model, representative of ≥3rd-line treatment, was chosen to demonstrate the benefit of BLU-945 in combination with BLU-701; oral administration of BLU-701 + BLU-945 resulted in enhanced subcutaneous tumour regression compared with single agents (**Figure 4B**)

Figure 5: Concentrations of BLU-701 30 mg/kg and BLU-945 100 mg/kg are below wildtype EGFR IC_{50} when administered as single agents and in combination

A. End of study area under the curve (AUC) for BLU-701 as single agent and in combination with BLU-945

B. End of study AUC for BLU-945 as single agent and in combination with BLU-701



BID, twice a day; IC_{50}, half-maximal inhibitory concentration; IC_{90}, 90% inhibitory concentration; QD, once a day; SEM, standard error of mean.

- Plasma concentration of BLU-701 (**Figure 5A**) and BLU-945 (**Figure 5B**), from the study with *EGFR* ex19del/T790M/C797S LUPF104 PDX (**Figure 4B**), showed that the exposure to each molecule was below the IC_{50} of wildtype EGFR (using A431 cells), suggesting that the treatment is WT-sparing

Conclusions

- BLU-701 (NCT05153408) and BLU-945 (NCT04862780) 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 osimertinib 25 mg/kg QD in an *EGFR* ex19del-driven PDX model derived from a treatment naïve patient, suggesting promising first-line efficacy
- BLU-701 is brain penetrant and administration of single-agent BLU-701 10–30 mg/kg QD showed intracranial antitumour activity
- Treatment with BLU-701 + BLU-945 in combination, at doses that spare wildtype EGFR, resulted in enhanced tumour regression (compared with single agents) in osimertinib-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 *EGFR*-mutated NSCLC across multiple lines of treatment

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