BLU-945 or BLU-701 as single agents versus their combination with osimertinib in *EGFR* L858R-driven tumor models

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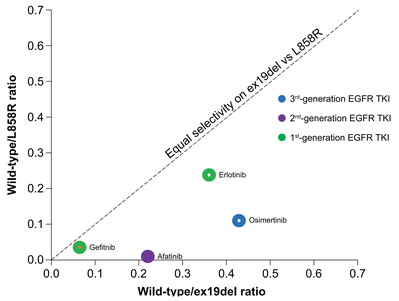
Background

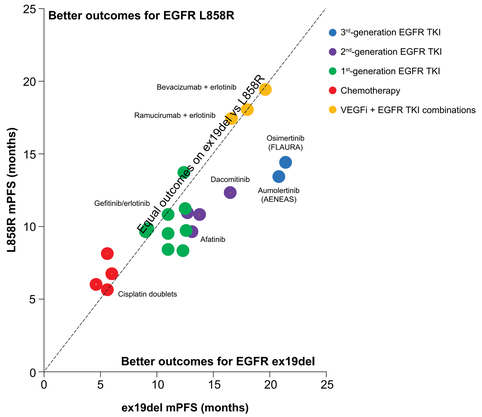
- Osimertinib is the standard of care in front-line patients with advanced epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC), with median progression-free survival (PFS) of 14.4 months in patients with *EGFR* L858R mutations and 21.4 months in those with *EGFR* exon 19 deletions (ex19del).[1] A corresponding increased overall survival (OS) benefit has also been seen in patients with *EGFR* ex19del compared to those with *EGFR* L858R mutations[2]
- Across three generations of EGFR tyrosine kinase inhibitors (TKIs), a selectivity bias for EGFR ex19del over L858R has been shown in EGFR mutant cellular models (**Figure 1**), demonstrating that EGFR L858R is not as potently inhibited as EGFR ex19del at the same dose of a given TKI
- While patients with *EGFR* L858R mutations have similar outcomes to patients with *EGFR* ex19del on platinum-based chemotherapy, or when vascular endothelial growth factor receptor (VEGFR) inhibitors are added in combination to EGFR TKIs, EGFR TKI monotherapy shows preferential patient outcomes toward EGFR ex19del (**Figure 2**)[1,3,4]
- Other mechanisms for treatment failure have been documented as well, including patients that progress on osimertinib commonly (up to 12.5%) have the *EGFR* C797X mutation.[5–7] Additionally, despite central nervous system (CNS) activity, patients treated with osimertinib can have isolated CNS progression[8]
- BLU-945 is a next-generation, reversible, investigational, oral EGFR TKI that selectively targets EGFR L858R with or without the EGFR C797X mutation, while being highly selective against EGFR wild-type (WT).[9,10] Additionally, BLU-945 targets the EGFR T790M and C797X resistance mutations regardless of the activating mutation[9–12]
- BLU-701 is an investigational, highly brain-penetrant, reversible EGFR TKI that potently and selectively inhibits EGFR ex19del and EGFR L858R, as well as EGFR C797X mutations.[9,10] BLU-525 is a next-generation clinical candidate with the same target profile as BLU-701
- The combination of BLU-945 and osimertinib has the potential to provide superior inhibition of EGFR L858R mutation in front-line patients, while covering EGFR C797X and T790M+C797X mutations, which are potential mechanisms of resistance. BLU-701 and osimertinib in combination has the potential to provide superior CNS activity while covering EGFR C797X mutations. BLU-945 and BLU-701 in combination has the potential to provide greater primary and on-target resistance with CNS activity
- Preclinical studies were conducted to evaluate the activity of BLU-945 or BLU-701 in combination with osimertinib in delaying tumor regrowth or prolonging survival in NSCLC tumor models driven by the *EGFR* L858R mutation

Figure 1: Selectivity for EGFR ex19del and L858R mutations in preclinical models



EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Figure 2: Median PFS is longer in EGFR ex19del than in EGFR L858R mutation when using EGFR TKIs



EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; mPFS, median progression-free survival; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Methods

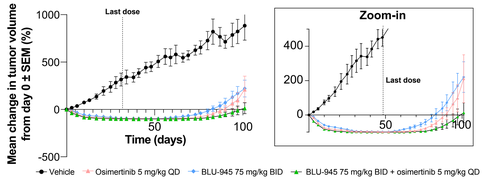
- The cellular selectivity was assessed by comparing the inhibition of phosphorylated EGFR in cell models expressing WT, EGFR ex19del, or L858R mutants
- The *in vivo* antitumor activity of BLU-945 75 mg/kg twice a day (BID) and BLU-701 30 mg/kg once a day (QD), as single agents or in combination with osimertinib 5 mg/kg QD were evaluated in NSCLC *EGFR* L858R-driven patient-derived treatment-naïve xenograft (PDX) tumor models LUN-439 and LUN-210
  - The 5 mg/kg QD osimertinib dose was selected based on data showing that the sum of the Area Under Curve of its equipotent metabolites (27 and 28) was 85% of the parent when dosed at 14 mg/kg QD. The lower dose was selected to better reflect the human total exposure (sum of the AUC of the metabolites with osimertinib was 98.4% of the parent)
- The doses for compounds used in this study are as follows: BLU-945 (sub-maximal dose: 75 mg/kg BID; maximal dose:100 mg/kg BID), BLU-701 (sub-maximal dose: 30 mg/kg QD) and osimertinib (sub-maximal dose:5 mg/kg QD; maximal dose: 25 mg/kg QD by exposure, or 14 mg/kg by allometric scaling). A sub-maximum dose is a clinically effective concentration of compound that is less than the maximal dose of the compound. This was done to enable a limited study duration
- Kinome selectivity, potency, and CNS penetration were evaluated for BLU-525, a structurally different, investigational, reversible, selective, orally available TKI designed to have a similar clinical profile to BLU-701

Results

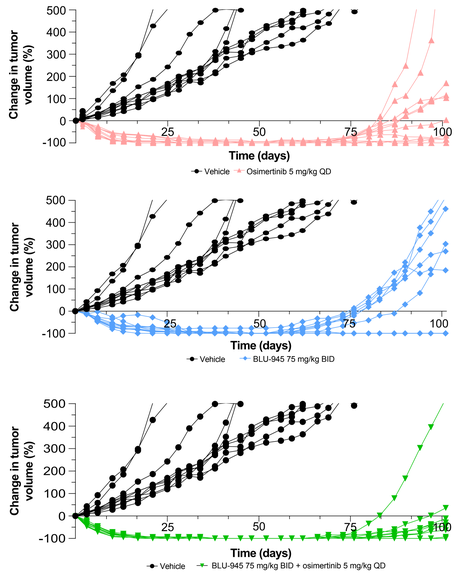
- BLU-945 in combination with osimertinib administered at sub-maximum doses resulted in prolonged tumor growth inhibition compared to single agents in the *EGFR* L858R-driven LUN-439 PDX model, and increased animal survival (**Figure 3**)
- BLU-701 in combination with osimertinib administered at sub-maximum doses resulted in tumor regression when compared to single agents in the *EGFR* L858R-driven LUN-210 PDX model (**Figure 4**)
- Evaluation of BLU-525 demonstrated high selectivity and brain penetrative activity (**Table 1**; **Figure 5**)

Figure 3: Administration of BLU-945 in combination with osimertinib resulted in tumor regression in *EGFR* L858R-driven treatment-naïve LUN-439 PDX model (A, B), and increased animal survival (C)

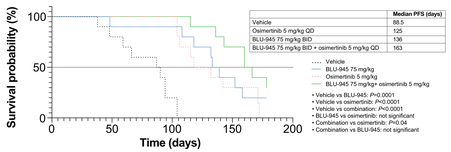
A. Proof of concept experiment combining BLU-945 with osimertinib shows longer durability of response compared to single agents



B. Tumor regression with BLU-945 and osimertinib in the LUN-439 PDX model, shown for individual mice



C. Oral administration of BLU-945 in combination with osimertinib prolonged survival of animals with EGFR L858R-driven treatment-naïve PDX tumor models

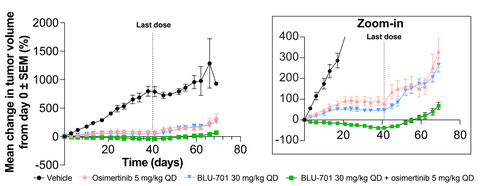


	Median PFS (days)
Vehicle	88.5
Osimertinib 5 mg/kg QD	125
BLU-945 75 mg/kg BID	136
BLU-945 75 mg/kg BID + osimertinib 5 mg/kg QD	163

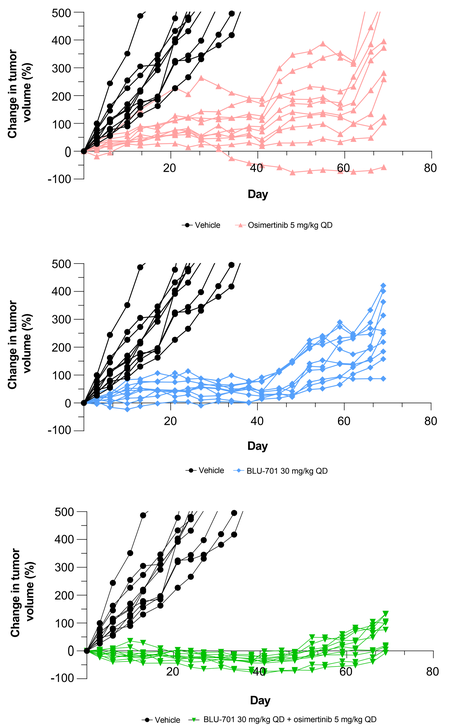
Treatment was stopped at day 50, and PFS was monitored until day 104.Maximum doses for BLU-945 (100 mg/kg BID) and osimertinib (25 mg/kg QD) were tolerated in models (data not shown). Tumor growth inhibition in the combination arm is comparable to BLU-945 and osimertinib when dosed as single agents at higher doses (data not shown).
BID, twice a day; PDX, patient-derived xenograft; PFS, progression free survival; SEM, standard error of the mean; QD, once a day.

Figure 4: Oral administration of BLU-701 in combination with osimertinib showed tumor regression in *EGFR* L858R-driven treatment-naïve LUN-210 PDX model

A. Proof of concept combining BLU-701 with osimertinib at sub-maximal doses showed tumor regression compared to single agents



B. Tumor regression with BLU-701 and osimertinib in the LUN-210 PDX model, shown for individual mice



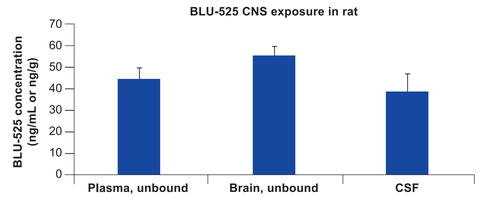
Treatment was stopped at day 41, and PFS was monitored until day 69. Tumor growth inhibition in the combination arm is comparable to osimertinib when dosed as a single agent or in combination at higher dose (data not shown).
EGFR, epidermal growth factor receptor; PDX, patient-derived xenograft; PFS, progression free survival; SEM, standard error of the mean; QD, once a day.

Table 1: EGFR autophosphorylation and CNS penetration of BLU-701 and BLU-525

		BLU-701	BLU-525	Osimertinib
Kinome selectivity	S(10) at 3 μM[a]	0.060	0.015	0.012 AZ7550: 0.060; AZ5104: 0.094
Potency (IC_{50}, nM) [WT-selectivity]	Enzyme L858R Ex19del	2.6 [21x] 0.5 [109x]	1.6 [10x] 0.9 [19x]	1.2 [1x] 1.1 [1x]
	Cell pEGFR PC9 Ex19del	1.3 [83x]	1.2 [96x]	1.8 [63x]
	Cell pEGFR Ba/F3 L858R	3.3 [33x]	4.2 [27x]	10.3 [11x]
	Cell pEGFR Ba/F3 L858R/C797S	3.3 [33x]	8.5 [14x]	>10000
	Cell pEGFR Ba/F3 Ex19del/C797S	1.8 [60x]	9.5 [12x]	>10000
Brain penetration	Rat brain K_{puu}	0.98	1.1	0.3

[a]DiscoverX's KINOMEscan selectivity profiling at 3 μM. S(10) = (number of non-mutant kinases with %Ctrl < 10)/(number of non-mutant kinases tested).
CNS, central nervous system; EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; IC_{50}, half maximal inhibitory concentration; K_{puu}, unbound partition coefficient; pEGFR, phosphorylated EGFR; WT, wild-type.

Figure 5: BLU-525 CNS exposure in rat models following IV infusion for 24 hours



CNS, central nervous system; CFS, cerebrospinal fluid; IV, intravenous.

Conclusions

- The *in vivo* antitumor activities of BLU-945 and BLU-701 as single agents suggest both BLU-945 and BLU-701 have clinical potential in patients with *EGFR* L858R-driven NSCLC
- The *in vivo* antitumor activity of BLU-945 or BLU-701 in combination with osimertinib vs osimertinib monotherapy in prolonging tumor growth inhibition and survival in these models may have clinical application in improving outcomes of patients with *EGFR* L858R-driven NSCLC in 1L settings
- Due to the ongoing challenge of CNS metastases in NSCLC, BLU-701 and a next-generation clinical candidate, BLU-525, were developed. BLU-525 is a structurally different, investigational, reversible, selective, orally available TKI designed to have a similar profile to BLU-701

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Disclosures

LE Tavera-Mendoza and J Campbell are former employees and/or equity holders of Blueprint Medicines Corporation. A Dhande, T Dineen, M Iliou, T Rouskin-Faust, E Rozsahegyi, and C Conti are current employees and/or equity holders of Blueprint Medicines Corporation.

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