BLU-945, a highly potent and selective 4th-generation EGFR TKI for the treatment of EGFR+/T790M/C797S resistant NSCLC

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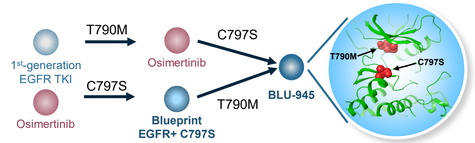
Background

- Osimertinib, a 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has favorably impacted the treatment of patients with *EGFR*-driven non-small cell lung cancer (NSCLC) and extended overall survival compared with older EGFR TKIs, including the 1st-generation agent gefitinib[1]
- The C797S mutation is the most frequent on-target resistance mechanism to osimertinib and there are no targeted therapies approved for patients with disease progression[2]
- We are developing targeted agents to treat C797S-driven resistance with the goal of improving patient outcomes and prolonging clinical benefit
  - BLU-945 (**Figure 1**) is a 4th-generation EGFR TKI designed to target the EGFR+(L858R or ex19del)/T790M/C797S triple mutant following treatment with a 1st-line 1st-generation EGFR TKI and 2nd-line osimertinib[3,4]
  - A second 4th-generation EGFR TKI aims to target the EGFR+/C797S double mutant following treatment with 1st-line osimertinib[3]
- Here we describe preclinical data for BLU-945 supporting initiation of clinical development in *EGFR*-driven NSCLC

Figure 1: Rationale for the development of BLU-945 targeting EGFR+/T790M/C797S



Methods

- BLU-945 activity on EGFR mutants and EGFR wild-type (WT) was tested in biochemical assays and cellular phosphorylation-specific EGFR AlphaLisa assays
- The *in vivo* antitumor activity of BLU-945 was evaluated in an NCI-H1975 cell line-derived tumor xenograft (CDX) model, as well as in osimertinib-resistant CDX-derived and patient-derived xenograft (PDX) models of NSCLC

Results

BLU-945 is a highly potent and selective EGFR+ T790M/C797S inhibitor

- Highly potent inhibitor of EGFR+/T790M/C797S and EGFR+/T790M resistant mutants
- Excellent EGFR WT and overall kinome selectivity
- BLU-945 only inhibits 1% of the kinome >90% at a concentration of 3 μM
- Selectivity profile enables combinations to cover wide spectrum of resistant mechanisms

Table 1: BLU-945 is a subnanomolar EGFR+/T790M/C797S and EGFR+/T790M inhibitor with >900-fold selectivity over EGFR WT

	Enzyme activities IC_{50} (nM) at 1 mM ATP with enzyme-inhibitor pre-incubation						
Compound	L858R	L858R/ T790M	L858R/ T790M/C797S	ex19del (746–750)	ex19del/ T790M	ex19del/ T790M/C797S	EGFR WT
BLU-945	7.1	0.4	0.5	71.4	0.8	0.8	736.3
Erlotinib	0.3	3132.7	5654.7	0.2	1394.7	1906.6	9.8
Gefitinib	0.1	1667.2	3921.8	0.1	632.7	1219.7	3.5
Osimertinib	0.9	0.6	5461.6	0.8	0.6	649.9	1.6

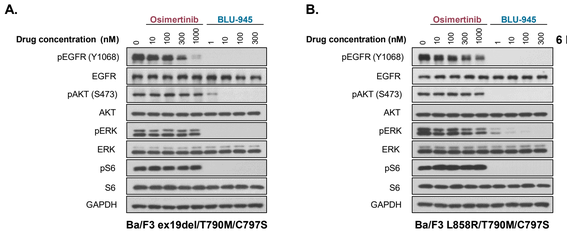
ATP, adenosine triphosphate; IC_{50}, half maximal inhibitory concentration.

BLU-945 inhibits EGFR+/T790M/C797S driven pathway activation

Table 2: BLU-945 potently inhibits EGFR+/T790M/C797S and EGFR+/T790M autophosphorylation

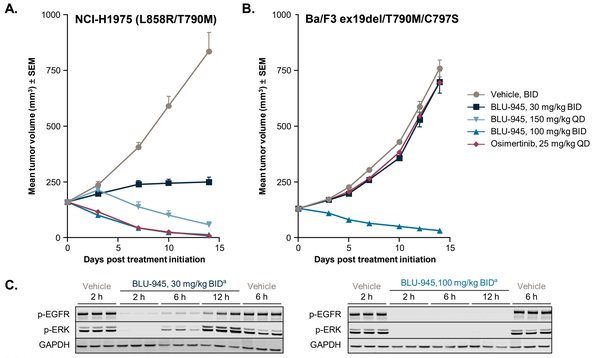
	Cellular pEGFR inhibition IC_{50} (nM)					
	Cell lines			Engineered Ba/F3 cell lines		
Compound	NCI-H1975 (L858R/T790M)	PC-9 (ex19del)	A431 (EGFR WT)	L858R	L858R/ T790M/C797S	ex19del/ T790M/C797S
BLU-945	1.2	129.5	544.4	21.5	2.9	4.4
Erlotinib	>10,000	3.9	140.6	5.9	6655.5	4524.8
Gefitinib	4679.8	1.8	16.5	4.6	6707.7	4864.7
Osimertinib	4.7	2.1	115.9	11.0	7754.6	>10,000

Figure 2: BLU-945, but not osimertinib, inhibits the EGFR pathway in (A) ex19del/T790M/C797S and (B) L858R/T790M/C797S driven Ba/F3 cell lines



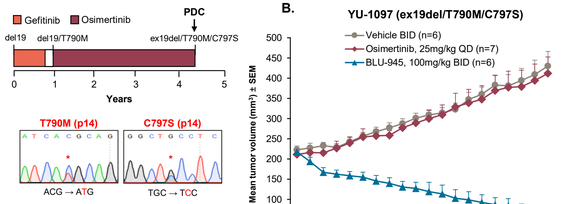
BLU-945 has antitumor activity on EGFR+/T790M and EGFR+/T790M/C797S driven cancers

Figure 3: Oral administration of BLU-945 showed significant tumor regression in (A) NCI-H1975 NSCLC CDX (L858R/T790M) tumor model similar to covalent drug osimertinib and (B) an osimertinib resistant Ba/F3 CDX (ex19del/T790M/C797S) model; (C) PD analysis for 3A



BID, twice daily; PD, pharmacodynamic; QD, once daily; SEM, standard error of the mean. [a]Dosed for 3 days.

Figure 4: In an (A) osimertinib-resistant EFGR ex19del/T790M/C797S patient-derived cell line xenograft (PDCX) model, (B) oral administration of BLU-945 led to significant tumor regression

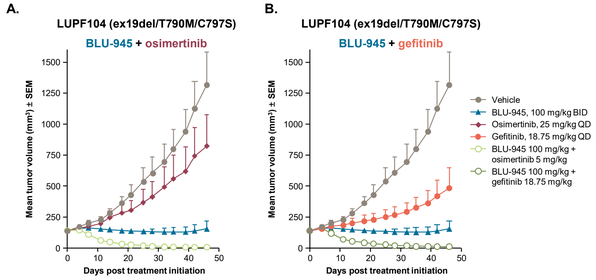


- PDCX model developed from patient who progressed on gefitinib and osimertinib
- RNA sequencing (RNA-seq) analysis of PDX model suggests *EGFR* amplification and allelic heterogeneity
- Oral administration of BLU-945 (100 mg/kg BID) was sufficient for tumor regression in this PDCX model
- BLU-945 was well tolerated in the PDCX animal model

BLU-945 combination with 1st-and 3rd-generation EGFR TKIs resulted in further improved tumor regression compared with BLU-945 alone

Figure 5: BLU-945 showed significant tumor regression in combination with osimertinib (A) or (B) gefitinib, in a NSCLC PDX (ex19del/T790M/C797S) model with EGFR amplification and allelic heterogeneity

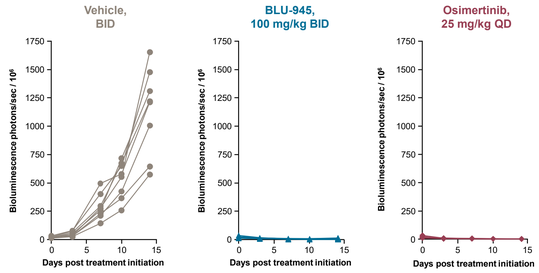
- PDX (ex19del/T790M/C797S) model developed from patient with NSCLC (poorly-moderately differentiated adenocarcinoma) who progressed through >5 lines of therapy, including chemotherapy, icotinib, erlotinib, and osimertinib
  - RNA-seq analysis of PDX model suggested EGFR amplification and allelic heterogeneity



- Single agent BLU-945 was sufficient for tumor stasis in this model
- Co-dosing BLU-945 with either osimertinib or gefitinib led to significant tumor regression
- Single agent and combination doses were well tolerated in the animal model
- Data suggest that BLU-945 can be combined with other EGFR TKIs to address allelic EGFR heterogeneity

BLU-945 demonstrates intracranial activity when administered orally

Figure 6: Oral administration of BLU-945 100 mg/kg resulted in intracranial activity in a NCI-H1975 L858R/T790M-luc intracranial model



Conclusions

- BLU-945 is a potentially best-in-class oral, selective, potent, 4th-generation EGFR TKI with activity against the EGFR+(L858R or ex19del)/T790M/C797S triple mutants
- In preclinical models, BLU-945 demonstrated potent, robust EGFR pathway inhibition and antitumor activity at well-tolerated doses in the NCI-H1975 CDX model and osimertinib-resistant CDX and PDX models of NSCLC
- Combination of BLU-945 with either 1st-generation (gefitinib) or 3rd-generation (osimertinib) EGFR TKI showed enhanced antitumor activity compared with single agent treatment in an EGFR+/T790M/C797S-driven PDX model, suggesting potential for monotherapy and/or combination therapy in the clinical setting
- BLU-945 demonstrated robust antitumor activity in an NCI-H1975 L858R/T790M-luc intracranial model
- Clinical development of BLU-945 monotherapy is expected to begin with an international phase 1 dose-escalation trial in patients with *EGFR*-driven NSCLC in the first half of 2021, and future clinical development of BLU-945 in combination with other TKIs across multiple treatment settings is planned

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Disclosures

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