BLU-451 Is a CNS-Penetrant, Wild-Type–Sparing EGFR Inhibitor With Broad Coverage of Uncommon EGFR Mutations Across Structure-Based Subsets

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Introduction

- Uncommon epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC), including atypical mutations and exon 20 insertions (ex20ins), have limited treatment options and are generally associated with poorer clinical outcomes compared with common (classical; exon 19 deletion [ex19del] and L858R) EGFR mutations[1]
- Afatinib, the only approved EGFR tyrosine kinase inhibitor (TKI) for patients with atypical EGFR mutations, is potent against atypical EGFR mutations but is frequently associated with severe wild-type (WT) EGFR-related toxicity. This leads to high rates of dose reduction and discontinuation, limiting its clinical utility. Additionally, afatinib, like other early-generation TKIs, has limited central nervous system (CNS) penetration[1–5]
- Chemotherapy remains the first-line standard of care for ex20ins EGFR. Post chemotherapy, amivantamab and mobocertinib are conditionally approved for patients with relapsed ex20ins EGFR-mutant NSCLC but have limitations in efficacy, tolerability, and CNS activity[2,6,7]
- While it is the standard of care for common mutations, osimertinib is not approved for the treatment of uncommon mutations. Osimertinib lacks consistent coverage across the broad range of atypical EGFR mutations, resulting in mixed clinical efficacy[8–10]
- BLU-451 is an investigational, oral, CNS-penetrant, EGFR WT-sparing, potent, and selective EGFR inhibitor of atypical and ex20ins EGFR mutations. It is currently being evaluated in the ongoing phase 1/2 CONCERTO study (NCT05241873).[11,12] Initial escalation data showed that BLU-451 has clinical activity against both atypical and ex20ins mutations and is well tolerated, with no grade >3 WT EGFR-associated toxicity reported to date (N=59)[12]
- While uncommon mutations represent a smaller subset than classical mutations,[13] the overall incidence of atypical and ex20ins mutations is poorly understood. Here, we report the prevalence of atypical and ex20ins EGFR mutations from a single-center, real-world data set (MD Anderson Cancer Center [MDACC])
- We present further preclinical evidence demonstrating that BLU-451 has strong potency and selectivity against a broad spectrum of atypical and ex20ins EGFR mutations, across structure-based subsets[1]

Methods

Real-world analyses

- The MDACC Moon Shot™ Genomic Marker-Guided Therapy Initiative (GEMINI) database was searched for patients with NSCLC whose tumors harbored EGFR kinase domain mutations of the classical (common) and uncommon type (atypical mutations and ex20ins).[1] The data cut-off was Jan 2023

Cellular proliferation and EGFR phosphorylation assays

- Cellular proliferation half maximal inhibitory concentrations (IC_{50}) were determined by CellTiter-Glo® Luminescent Cell Viability Assay in engineered Ba/F3 cell lines expressing atypical and ex20ins mutations belonging to the classical-like (CL), P-loop and αC-helix compressing (PACC), and exon 20 loop insertions (ex20ins-L) structure-based subsets, as well as WT EGFR. The IC_{50} ratio between mutants and WT EGFR was then calculated
- Cellular phosphorylated EGFR IC_{50} was determined by a phosphorylation-specific EGFR AlphaLISA® assay in engineered Ba/F3 cell lines expressing atypical and ex20ins EGFR mutations

In vivo antitumor activity

- *In vivo* antitumor activity was evaluated after once-daily (QD) oral (PO) administration in a Ba/F3 cell line–derived subcutaneous tumor model expressing the EGFR G719S-mutant protein in NOD.Cg-*Prkdc*^{scid}/J female mice
- *In vivo* growth inhibition of brain metastases was evaluated in BALB/c nude female mice injected with luciferase-expressing PC9 cells (human cell line with an EGFR ex19del) in the carotid artery. Animals received BLU-451 at 1, 2.5, or 25 mg/kg PO QD starting 17 days after cell injection and head bioluminescence was imaged over time. Bioluminescence in isolated whole brain was measured at the end of the study

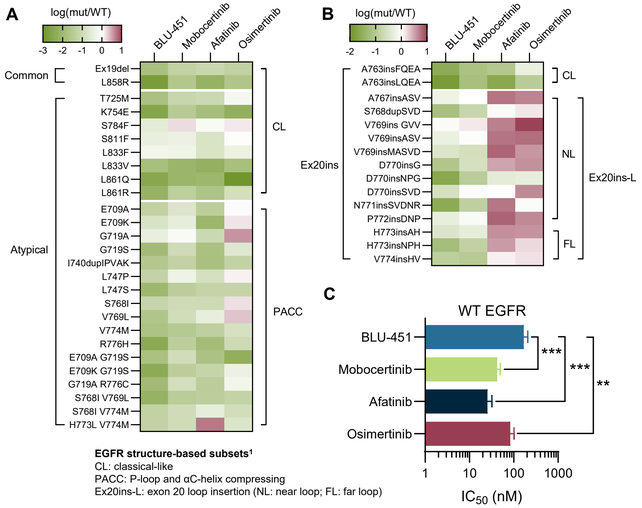
Results

Table 1. Frequency of classical and uncommon (atypical and ex20ins) EGFR mutations in patients with NSCLC

Category	Mutation(s)	N (%)
Classical	Ex19del	383 (26)
	L858R	295 (20)
Classical + T790M	Ex19del/T790M	51 (4)
	L858R/T790M	42 (3)
T790M	T790M	12 (1)
	PACC/T790M	12 (1)
Ex20ins	Ex20ins	144 (10)
Atypical	Classical-like only	28 (2)
	Classical + Classical-like	20 (1)
	PACC only	153 (11)
	Classical + PACC	14 (1)
	PACC + PACC	40 (3)
Others[a]		253 (17)
Total		**1447**

[a]Includes amplifications and other EGFR alterations inside and outside of exon 18-21 kinase domain.
EGFR, epidermal growth factor receptor; ex19del; exon 19 deletion; ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer; PACC, P-loop and αC-helix compressing.

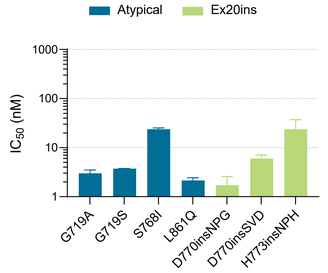
Figure 1. BLU-451 was potent and selective against EGFR atypical (A) and ex20ins (B) mutations across CL, PACC, and ex20ins-L subsets,[1] and WT-sparing (C) in Ba/F3 cellular proliferation assays



EGFR structure-based subsets[1]
CL: classical-like
PACC: P-loop and αC-helix compressing
Ex20ins-L: exon 20 loop insertion (NL: near loop; FL: far loop)

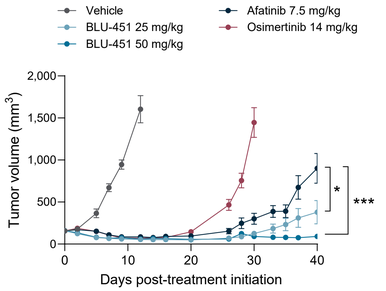
Data represent means +/- standard deviations. ***P<0.001; **P<0.01.
CL, classical-like; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; ex20ins-L, exon 20 loop insertion; FL, far loop; IC_{50}, half maximal inhibitory concentration; mut, mutation; NL, near loop; PACC, P-loop and αC-helix compressing; WT, wild type.

Figure 2. BLU-451 potency against frequent atypical and ex20ins mutations was confirmed by cellular EGFR phosphorylation assays



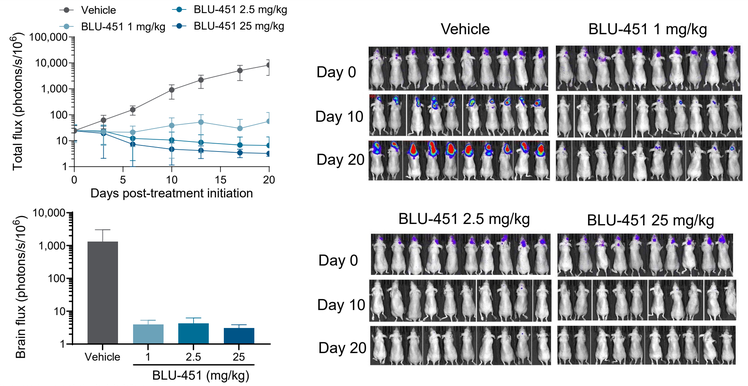
Data represent means +/- standard deviations.
EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; IC_{50}, half maximal inhibitory concentration.

Figure 3. BLU-451 prolonged tumor regression in a G719S EGFR Ba/F3 subcutaneous tumor model compared with afatinib or osimertinib



Data represent means +/- standard error of the mean. ***P<0.001; *P<0.05.
EGFR, epidermal growth factor receptor.

Figure 4. BLU-451 reduced brain luciferase activity in an intra-carotid PC9-Luc cancer cell injection model of brain metastasis suggesting that BLU-451 can penetrate the intact blood-brain barrier *in vivo* and inhibit metastatic growth in the brain



Data represent means +/- standard deviations.
Luc, luciferase.

Conclusions

- Real-world data from a single institution demonstrated that atypical EGFR mutations represent a sizable EGFR NSCLC subpopulation, of similar or greater magnitude to that of ex20ins EGFR mutations
- BLU-451 has clinically relevant potency across a broad range of atypical EGFR mutations, comparable to the only approved agent, afatinib
- BLU-451 has higher WT EGFR selectivity than afatinib and mobocertinib. These preclinical data are further supported clinically by the observed low rates of WT EGFR–related toxicity in phase 1 escalation to date[12]
- Preclinical data continue to show that BLU-451 can inhibit metastatic tumor growth in the brain, consistent with previous preclinical[11] and early clinical[12] data, highlighting BLU-451 CNS penetration
- Together, these data make BLU-451 a compelling next-generation EGFR TKI candidate that combines clinically relevant potency against uncommon EGFR mutations with differentiated CNS penetration and WT EGFR selectivity. The phase 1/2 CONCERTO study is open globally and currently enrolling

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