Emerging phase 1 data of BLU-451 in advanced NSCLC with EGFR exon 20 insertions

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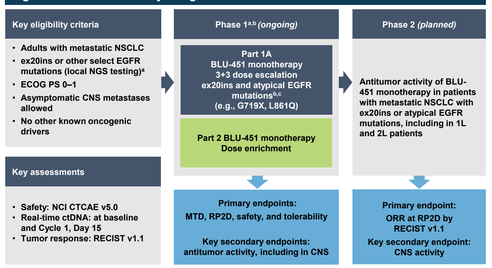
Introduction

- Uncommon epidermal growth factor receptor (EGFR) mutations encompass EGFR exon 20 insertions (ex20ins) and atypical EGFR mutations and collectively represent approximately 20% of all EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC) cases worldwide.[1,2] Clinical outcomes are poor for uncommon EGFRm NSCLC and current treatment options for this subpopulation of NSCLC are limited[3]
- Approximately 20%–30% of patients with EGFRm ex20ins NSCLC have central nervous system (CNS) metastases at the time of initial presentation[2,4,5] and an additional proportion of patients will develop CNS disease at progression.[6] As in other types of EGFRm NSCLC, CNS metastases are a challenge to treat and are associated with poor outcomes
- Current available treatments for EGFRm ex20ins NSCLC have limited CNS activity, and are associated with a high frequency of adverse events (AE), including edema and severe gastrointestinal AEs[7,8]
- Atypical EGFRm NSCLC represents 8%–10% of all EGFRm NSCLC cases and the only approved therapy is associated with challenging toxicity and limited CNS activity[3]
- BLU-451 is an investigational, potent and selective, EGFR WT-sparing, CNS-penetrant covalent inhibitor of uncommon EGFR mutations.[9] Initial data from phase 1 dose escalation of BLU-451 monotherapy in patients with uncommon EGFR mutations are reported here

Methods

- CONCERTO (NCT05241873) is an ongoing, global, first-in-human phase 1/2 dose-escalation study of BLU-451 in patients with EGFRm metastatic NSCLC (**Figure 1**)
- Phase 1 will determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of BLU-451 as monotherapy. Part 1A will utilize a 3+3 design to evaluate BLU-451 administered orally, in 21-day cycles, once daily (QD), twice daily (BID), and with/without food
  - To be dose-limiting toxicity (DLT) evaluable, patients must experience a DLT within the 28-day DLT-evaluable window or have received ≥75% of all planned doses within the DLT period and not experienced a DLT
  - Intrapatient dose escalation was permitted
- For phase 1, key eligibility in addition to those described in **Figure 1** included progression on or after intolerance to the most recent systemic therapy. Prior platinum-based chemotherapy was required for patients with ex20ins and ≥1 EGFR tyrosine kinase inhibitor was required for patients with atypical mutations. Prior ex20ins-targeted therapy was allowed but not required for patients with ex20ins mutations
- Phase 1, Part 2 monotherapy enrichment was allowed at any dose level deemed safe in Part 1A, enrolling up to 6 additional patients per dose level, for more robust characterization of safety, pharmacokinetics (PK), pharmacodynamics, and preliminary clinical activity

Figure 1: CONCERTO study design



Study information is available at: https://clinicaltrials.gov/ct2/show/NCT05241873.
[a]Using the FoundationOne Liquid CDx (F1LCDx) NGS platform for ctDNA profiling; [b]Patients with other EGFR ex20ins-positive metastatic cancers, with the exception of primary CNS tumors, could enroll in phase 1, Part 1A and Part 2 only. [c]Prior platinum-based chemotherapy and ≥1 EGFR TKI were required for patients with ex20ins and atypical mutations, respectively. Prior immune checkpoint inhibitors are allowed but not required.
1L, first line; 2L, second line; CNS, central nervous system; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; ORR, objective response rate; RP2D, recommended phase 2 dose; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor.

Results

Disposition and Patients

- As of data cut-off (April 21, 2023), 59 patients were treated with BLU-451 monotherapy in phase 1 (Part 1A + Part 2) at total daily doses of 100 mg to 600 mg fasted (N=54) and 100 mg to 200 mg with food (N=5) (**Table 1**)
- Of patients with ex20ins (n=48), 54% had 3 or more prior systemic therapies, and 75% received prior ex20ins-targeted agents
- Of patients with atypical mutations (n=9), 67% had 3 or more prior systemic therapies

Table 1: Demographics and baseline characteristics

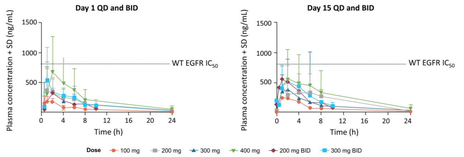
	Ex20insa (N=48)	Atypicala (N=9)
Age, years, median (min, max)	57.8 (39, 79)	58.6 (35, 77)
Age group, years, n (%)		
<65	34 (71)	5 (56)
≥65	14 (29)	4 (44)
Sex, n (%)		
Female	33 (69)	6 (67)
ECOG PS, n (%)		
0	7 (15)	1 (11)
1	41 (85)	8 (89)
CNS disease at baseline, n (%)	28 (58)	6 (67)
EGFR mutation status (local), n (%)		
Ex20insb	48 (100)	–
Atypicalc	–	9 (100)
Prior lines of therapy, median (min, max)	3 (1, 10)	3 (1, 5)
Prior ex20ins-targeted agents, n (%)	36 (75)	1 (11)
Amivantamab	23 (48)	1 (11)
Mobocertinib	18 (38)	0
Amivantamab and mobocertinib	11 (23)	0
Other ex20ins EGFR inhibitors	11 (23)	0
Zipalertinib (CLN-081)	3 (6)	0
Sunvozertinib (DZD-9008)	2 (4)	0
Poziotinib	8 (17)	0

[a]Two patients were not included in this table: 1 with ex20ins and 1 with L861Q EGFR mutations.
[b]Mutations included A763_Y764insX, V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, H773_V774insX, V774_C775insX, and others.
[c]Mutations included G719X, L861Q, and others.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Pharmacokinetics

- In early escalation, dose-dependent increases in plasma exposure to BLU-451 were observed from 100 to 400 mg QD and from 200 mg to 300 mg BID (**Figure 2**)
- BLU-451 200 mg BID achieved similar exposure to 400 mg QD at steady state (Day 15), based on estimated plasma $AUC_{0–24}$ values
- Mean plasma elimination half-life ranged from 12 to 25 hours
- Protocol was amended to initiate dose escalation with food to explore the effect of food on PK as a part of RP2D optimization

Figure 2: Mean BLU-451 plasma concentrations versus time after QD dosing of BLU-451 100–400 mg



BID, twice daily; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentration; QD, once daily; SD, standard deviation; WT, wild-type.

BLU-451 activity in EGFRm ex20ins NSCLC

ctDNA profiling

- During dose escalation, evidence of on-target activity via circulating tumor DNA (ctDNA) was observed, with reduction and clearance of ctDNA at Day 15 in patients with ex20ins mutations (**Figure 3a**)

Antitumor activity

- Early evidence of tumor reduction was observed in efficacy-evaluable patients (**Figure 3b**). Confirmed partial responses (PR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) were seen
- Early evidence of meaningful CNS antitumor activity was seen (**Figure 3b, patient cases 1 and 2**)
- Escalation remains ongoing at the time of data analysis

Figure 3A: ctDNA

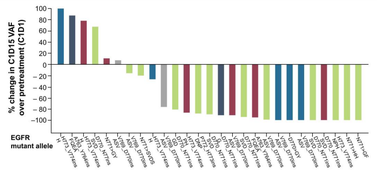
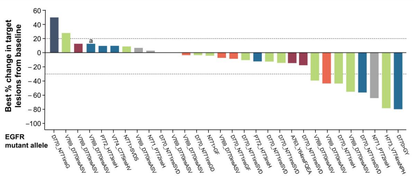


Figure 3B: Best percent change of target lesions



BID, twice daily; C, cycle; CNS, central nervous system; ctDNA, circulating tumor DNA; D, day; EGFR, epidermal growth factor receptor; QD, once daily; VAF, variant allele frequency.
[a]Mutation status is based on central testing.

BLU-451 activity in atypical EGFRm NSCLC

ctDNA profiling

- In the atypical EGFRm NSCLC patient subset, comparable evidence of on-target activity via ctDNA reductions was observed, with dose-dependent reduction and clearance of ctDNA at Day 15 in patients with atypical mutations (**Figure 4a**)

Antitumor activity

- Early evidence of dose-dependent tumor reduction was observed in efficacy-evaluable patients (**Figure 4b**)
- Escalation remains ongoing at the time of data analysis

Figure 4A: ctDNA

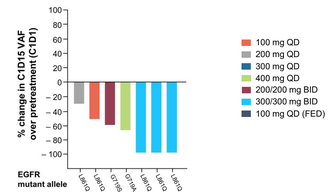
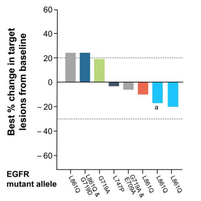


Figure 4B: Best percent change of target lesions



BID, twice daily; C, cycle; CNS, central nervous system; ctDNA, circulating tumor DNA; D, day; EGFR, epidermal growth factor receptor; QD, once daily; VAF, variant allele frequency.
[a]Mutation status is based on central testing.

Safety

- At data cut-off, 41 (69.5%) patients experienced treatment related adverse events (TRAE); most were Grade 1–2 (**Table 2**)
- The most common TRAEs (≥15%) included rash (22%) and dermatitis acneiform (15%)
- No Grade ≥3 EGFR WT–associated toxicity such as rash, diarrhea, or paronychia were observed
- No DLTs were observed; no patients discontinued due to a TRAE

Table 2: Treatment-related adverse events reported in ≥10% of patients in the overall safety population (N=59)

Preferred term, n (%)	Treatment-related adverse events			
	All grade	Grade 1	Grade 2	Grade ≥3
Any adverse event	41 (69.5)	26 (44.1)	12 (20.3)	3 (5.1)
Rash	13 (22.0)	11 (18.6)	2 (3.4)	0
Dermatitis acneiform	9 (15.3)	9 (15.3)	0	0
Fatigue	8 (13.6)	7 (11.9)	1 (1.7)	0
Diarrhea	7 (11.9)	7 (11.9)	0	0
Dry skin	6 (10.2)	6 (10.2)	0	0
Pruritus	6 (10.2)	6 (10.2)	0	0

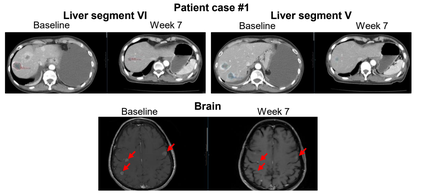
Patient vignettes

Patient case #1

A 59-year-old, White, never-smoker female with NSCLC metastatic to the liver and brain. She presented with EGFR ex20ins (D770>GY) and non-EGFR alterations (*BRIP* N1006FS*1, *DNMT3A* R326H, *TP53* M246V) by local NGS-testing. The patient previously received systemic therapy in the metastatic setting that included carboplatin and pemetrexed, followed by dacomitinib

Course of treatment with BLU-451

- The patient was enrolled in the CONCERTO phase 1 portion of the study and initiated BLU-451 monotherapy at 300 mg QD. Through intrapatient dose escalation, her dose was adjusted to 200 mg BID after 40 days of treatment
- PR per RECIST v1.1 was seen on the first scan at Week 7, which was confirmed at Week 13, with 71% reduction in the target lesions from baseline. CNS activity was seen, with 2 brain target lesions being stable at Week 7 but showing PR at Week 13
- The patient continues to tolerate treatment well with no dose interruptions/reductions, and remains on therapy



Patient case #2

A 59-year-old, White, never-smoker female had NSCLC metastatic to the brain. She presented with EGFR ex20ins (D770_N771insSVD) and non-EGFR alterations (*CDKN2B* loss, *CDKN2A* loss, *MTAP* loss) by local NGS-testing. The patient previously received systemic therapy in the metastatic setting that included carboplatin, pemetrexed, and pembrolizumab, followed by amivantamab

Course of treatment with BLU-451

- The patient was enrolled in CONCERTO and initiated BLU-451 monotherapy at 400 mg QD
- Stable disease per RECIST v1.1 was seen on the first, second, and third scans (Weeks 7, 13, and 19)
- The patient had multiple non-target lesions in the brain, which were stable on the Week 7 scan, but showed complete response on Week 13 and was confirmed on Week 19 imaging
- The patient continues to tolerate treatment well with no dose interruptions/reductions, and remains on therapy

Conclusions

- BLU-451 is a potential best-in-class, potent and selective, EGFR WT-sparing, CNS-penetrant inhibitor of uncommon EGFR mutations
- The initial data from phase 1 BLU-451 monotherapy dose escalation show that BLU-451 was generally well tolerated, with no DLTs observed at all doses to date. Observed TRAEs commonly associated with EGFR WT inhibition were low grade, with the majority being Grade 1
- Early efficacy, including ctDNA clearance, confirmed systemic responses, and compelling CNS activity was observed in heavily pretreated patients with ex20ins EGFRm NSCLC
- Robust ctDNA clearance and early tumor reduction were also observed in atypical EGFRm NSCLC. These data support further BLU-451 clinical development across all uncommon EGFRm NSCLC
- Phase 1 monotherapy dose escalation is ongoing in patients with ex20ins and atypical EGFRm NSCLC, with MTD and/or RP2D yet to be determined

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https://meetings.asco.org/abstracts-presentations/218866

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