Emerging evidence of activity of BLU-945 in patients with advanced *EGFR*-mutant NSCLC utilizing circulating tumor DNA in the phase 1/2 SYMPHONY study

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Background

- Epidermal growth factor receptor mutations (*EGFRm*), the most frequent oncogenic drivers of non-small cell lung cancer (NSCLC), are found in ~17% of Caucasian and up to 50% of Asian patients,[1,2] with the most common mutations being exon 19 deletion (ex19del) and L858R[3]
- Use of tyrosine kinase inhibitors (TKIs) such as osimertinib has prolonged survival, but resistance eventually develops via multiple on- and off-target mutations, often simultaneously found in distinct clones within an individual patient.[4,5] The most frequent resistance mutations to emerge are *EGFR* T790M (after first [1G]- and second [2G]-generation TKIs) and *EGFR* C797S (after third [3G]-generation TKIs)[4]; there are currently no approved targeted therapies after progression on 3G TKIs, including those that target both C797S and T790M[5]
- Circulating tumor DNA (ctDNA), is being increasingly adopted as a method to monitor response to treatment and emergence of resistance in clinical practice. Clearance of ctDNA after 6–8 weeks of treatment is predictive of TKI benefit while increases in ctDNA or appearance of new mutations has been associated with progression[6–8]
- An additional advancement to the treatment paradigm of *EGFRm* NSCLC is preventing emergence of multiple resistance mutations in the treatment naïve setting,[9,10] and several combination studies are currently underway to address this heterogeneity[11–13]
- BLU-945 is an investigational, oral next-generation *EGFR* TKI designed to target *EGFR* T790M-carrying clones (regardless of driver mutation), including those with C797S.[14] In addition, it inhibits L858R regardless of the presence of T790M and C797S mutations at clinically relevant exposures (**Figure 1**)
- The high selectivity of BLU-945 allows mutational targeting without inhibition of wild type (WT) EGFR, which may enable combination with other TKIs that can address multiple mechanisms of resistance without added toxicity. BLU-945 has demonstrated *in vivo* antitumor monotherapy activity in treatment-naïve *EGFRm* xenograft and osimertinib-resistant *EGFRm* models with C797S, with and without T790M[15,16]
- In osimertinib resistant tumor models, BLU-945 has demonstrated enhanced antitumor activity in combination with complementary EGFR TKIs such as osimertinib[17] and the next-generation EGFR TKI BLU-701[16]
- Here we present emerging safety and efficacy data, including real-time ctDNA assessment, from the first five cohorts of the ongoing monotherapy dose escalation of SYMPHONY, a phase 1/2 study of BLU-945 in *EGFRm* NSCLC

Figure 1: Combination of EGFR inhibitors provides broadest coverage of common EGFR resistance mutations

	1G	3G	Next generation		Potential combinations	
EGFR mutational coverage[a]	Gefitinib	Osimertinib	BLU-701	BLU-945	BLU-945 + osimertinib	BLU-701 + BLU-945
L858R (LR)	■	■	■	■	■	■
ex19del	■	■	■	■	■	■
EGFRm / T790M	■	■	■	■	■	■
LR / C797S	■	■	■	■	■	■
ex19del / C797S	■	■	■	■	■	■
EGFRm / T790M / C797S	■	■	■	■	■	■

■ IC_{90} ≤10 nM ■ IC_{90} >50 nM

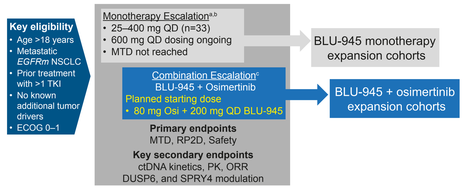
[a]Based on biochemical IC_{90}.
1G, 1st-generation; 3G, 3rd-generation; EGFRm, primary EGFR mutation, either L858R or ex19del; IC_{90}, half-maximal inhibitory concentration.

Methods

Study design

- SYMPHONY (NCT04862780) is an ongoing phase 1/2, open-label first-in-human study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anticancer activity of BLU-945 as monotherapy and in combination with osimertinib in patients with metastatic *EGFRm* NSCLC in the US and Japan (**Figure 2**)
- The phase 1 dose escalation part of the study employs a Bayesian Optimal Interval (BOIN) design with up to 12 patients evaluable for dose-limiting toxicities (DLTs) for any given dose level and dose escalation will be considered complete when 12 patients are evaluable for DLT at one dose level. BLU-945 is given orally in continuous 4-week cycles. The DLT evaluation period is the first 28 days (Cycle 1 of each cohort in the Phase 1 dose escalation). Patients who experience a DLT or who receive at least 75% of the prescribed BLU-945 dose (i.e., ≥21 days) and complete the 28-day DLT evaluation period will be evaluable for DLT assessment. Intrapatient dose escalation is permitted. Patients may continue study treatment post-progression if ongoing clinical benefit is observed (as assessed by the investigator, and approved by the Sponsor)

Figure 2: SYMPHONY study design



ctDNA, circulating tumor DNA; DUSP6, dual specificity phosphatase 6; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRm, mutant epidermal growth factor receptor gene; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; QD, once daily; RP2D, recommended phase 2 dose; SPRY4, sprouty RTK signaling antagonist 4; TKI, tyrosine kinase inhibitors.
[a]Based on Bayesian Optimal Interval escalation design (BOIN); [b]BID dosing will also be evaluated; [c]Part 1B and Phase 2 have not been initiated and are dependent on Part 1A results.

- BLU-945 and osimertinib combination treatment escalation will be initiated at 50% of the recommended phase 2 dose (RP2D) or 50% of the highest safe dose in the ongoing phase 1 BLU-945 monotherapy part of the study

Key assessments (phase 1)

- The maximum tolerated dose (MTD) will be determined based on the safety profile during the first 28-day treatment cycle
- The RP2D will be determined based on DLT, PK, PD, and preliminary safety and antitumor activity data
- ctDNA will be assessed in real-time using the FoundationOne Liquid CDx assay at cycle (C) 1 day (D) 1, C1D15, and end of treatment/progression
- Response to treatment is Investigator-assessed per Response Evaluation Criteria in Solid Tumors version 1.1 every 28 days for the first 2 scans, every 8 weeks through the first year, and then every 12 weeks thereafter

Results

Patients

- As of the data cut-off (March 9, 2022), 33 patients have been treated with BLU-945 at 25–400 mg once daily (QD) in the first 5 cohorts
- Baseline characteristics for these patients are shown in **Table 1**
- Most patients were non-smokers and the majority (n=26 [79%]) had received ≥3 lines of prior systemic therapy

Table 1: Baseline characteristics

Characteristic	All patients (N=33)
Median age (range), years	61 (39–78)
Female, n (%)	23 (70)
Race, n (%)	
White	14 (42)
Asian	18 (55)
Other/unknown	1 (3)
Smoking history, n (%)	
Current/former	10 (30)
Never	22 (67)
Unknown	1 (3)
ECOG PS, n (%)[a]	
0	8 (24)
1	23 (70)
2	2 (6)
History of intracranial disease, n (%)	21 (64)
Prior therapy, median (range)	4 (1–9)
Prior osimertinib, n (%)	32 (97)
1–2 prior lines, n (%)	7 (21)
≥3 prior lines, n (%)	26 (79)
EGFR mutation status at C1D1 by central ctDNA NGS assessment[b], n (%)	
EGFRm/T790M/C797S	11 (33)
EGFRm/T790M	1 (3)
EGFRm/C797S	1 (3)
EGFRm primary only	6 (18)
T790M only	1 (3)
No EGFR mutations detected	9 (27)
Not available[c]	4 (12)

C, cycle; ctDNA NGS, circulating tumor DNA next-generation sequencing; D, day; EGFRm, primary *EGFR* activating mutation, exon 19 deletion or L858R.
[a]Original study protocol permitted ECOG PS of 0–2, but was later amended to ECOG PS of 0–1.
[b]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with follow-up central ctDNA assessment at C1D1.
[c]Results for all patients were not available at the time of the data cut.

Safety

- Safety data are summarized in **Table 2**
- No Grade 4 or 5 adverse events (AEs) have been reported
- One DLT, grade 3 transaminitis, occurred in the 400 mg QD cohort, which improved with dose interruption, and the patient remains on therapy
- AEs typically associated with EGFR wildtype inhibition were minimal (rash 3%, grade 1; dry skin 3%, grade 1; diarrhea 9%, grade 1; no paronychia reported)
- No interstitial lung disease reported, no QTC prolongation reported
- Overall, there were eight (24%) serious AEs, out of which only two (6%) were deemed to be related to the study drug: one grade 3 vomiting and one grade 3 transaminitis
- No treatment discontinuations due to AEs have been reported
- Dose escalation continues and the MTD has yet to be determined

Table 2: Most common AEs by preferred term in ≥10% of patients

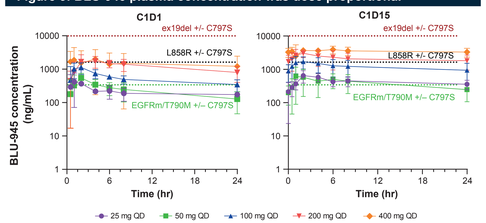
AEs, regardless of causality, n (%)	All AEs N=33		Treatment-related AEs N=33	
	Any grade	Grade 3	Any grade	Grade 3
Nausea	10 (30)	2 (6)	7 (21)	1 (3)
Headache	6 (18)	2 (6)	1 (3)	0
Fatigue	6 (18)	0	5 (15)	0
Cough	5 (15)	0	1 (3)	0
Dyspnea	5 (15)	1 (3)	0	0
Vomiting	5 (15)	1 (3)	3 (9)	1 (3)
Hyponatremia	4 (12)	0	0	0
Dry Mouth	4 (12)	0	3 (9)	0
Anemia	4 (12)	1 (3)	0	0

AEs, adverse events.

Pharmacokinetics

- BLU-945 exposure was dose-proportional at both C1D1 and C1D15 (**Figure 3**)
- The average effective half-life was 24.1 hours (calculated from the extent of accumulation)
- Exposure at 400 mg exceeds EGFRm/T790M +/− C797S IC_{90} in all patients and exceeds L858R +/− C797S IC_{90} in most patients

Figure 3: BLU-945 plasma concentration was dose proportional

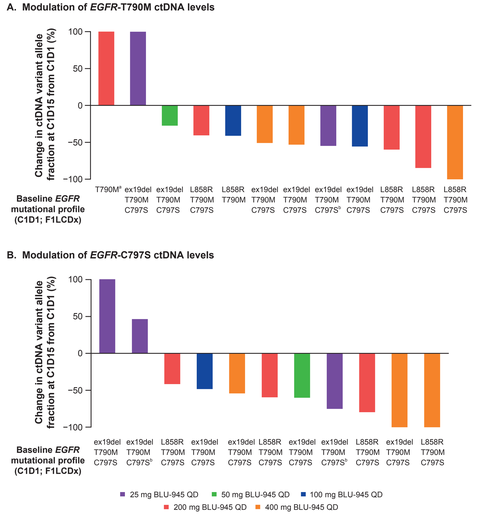


Dashed lines represent IC_{90} for indicated EGFR mutants.

Antitumor activity

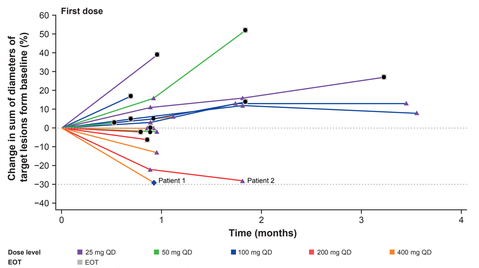
- BLU-945 treatment demonstrated activity on *EGFR* T790M and C797S variant allele fractions as assessed by ctDNA after 14 days of therapy in every dose-cohort tested
- 83% (10/12) of *EGFR* T790M (**Figure 4A**) and 81% (9/11) of *EGFR* C797S (**Figure 4B**) variant alleles were reduced with BLU-945 treatment
- In the 400-mg cohort, all detectable T790M and C797S alleles showed reduction, including three that fell below the limit of detection (clearance)
- Increasing BLU-945 doses were associated with increasing antitumor activity (**Figure 5**), with tumor shrinkage noted at doses of 200 mg QD and above, including an unconfirmed partial response at C2D1 in a patient with documented ex19del/T790M/C797S treated at 400 mg QD
- Two patients started at 100 mg QD experienced stabilization of tumor growth when escalated to 200 mg at C3D1

Figure 4: Reduced *EGFR* T790M and C797S ctDNA variant allele fractions with BLU-945 treatment



[a]Patient had on-treatment measurement at C2D1, rather than C1D15. [b]Patient had two different DNA mutations in C797S.
Note: reductions in individual variant allele fractions as shown; therefore, patients with multiple mutations may be represented on both plots. All T790M and C797S allele fractions with available baseline and C1D15 data are shown. Increases of greater than 100% were truncated at 100%.

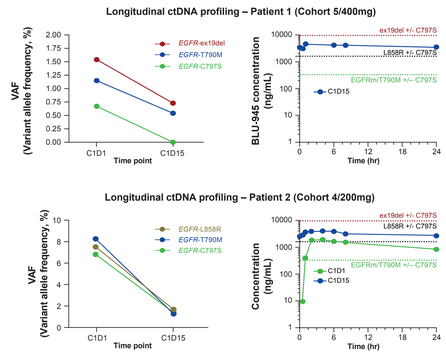
Figure 5: Dose-dependent tumor shrinkage with BLU-945 treatment[a,b]



[a]Patients with measurable target lesions at baseline with post-baseline scans; [b]Data cut off, March 9, 2022.
CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

Patient vignettes

- Patient 1 is a 69-year-old Caucasian woman who never smoked, diagnosed with stage IV NSCLC, harboring ex19del, T790M and C797S mutations by ctDNA assessment
- The patient was previously treated with platinum-based chemotherapy, erlotinib, and osimertinib, with best response of stable disease (SD) to all prior therapies
- The patient had two target lesions in the liver with multiple non-target lesions in the brain, bone, liver, and retroperitoneal and mediastinal lymph nodes
- Started treatment at 400 mg QD. Patient had reduction in all three detectable *EGFR* mutations at C1D15, with clearance of C797S and then an unconfirmed partial response with −30% tumor shrinkage at C2D1. The patient continues on therapy and tolerates treatment well
- Patient 2 is a 70-year-old Asian woman who never smoked, diagnosed with *EGFR* L858R positive stage IVB NSCLC, harboring L858R, T790M, and C797S mutations
- Patient was previously treated with osimertinib and savolitinib with partial responses and had progressive disease to platinum-based chemotherapy with bevacizumab
- Two target lesions in the right lung, with multiple non-target lesions in the lung and left femoral head
- Started treatment at 200 mg QD. Patient had reduction in all three detectable *EGFR* mutations at C1D15 with −21% and −28% tumor shrinkage at C2D1 and C3D1, respectively. Patient continues on therapy



Dashed lines represent IC_{90} for indicated EGFR mutants.

Conclusions

- BLU-945, a highly potent and selective oral EGFR inhibitor, was generally well tolerated at clinically active doses in heavily pre-treated patients with *EGFRm* NSCLC, with few AEs characteristic of wildtype EGFR toxicity observed at doses up to 400 mg QD
- Despite presence of *EGFR* mutations conferring resistance to osimertinib, treatment with BLU-945 resulted in rapid dose-dependent reduction in ctDNA, consistent with preclinical data
- Increasing BLU-945 doses were associated with increasing antitumor activity, with tumor shrinkage noted at doses of 200 mg QD and above, including an unconfirmed partial response at 400 mg QD
- The clonal evolution and resulting mutational complexity of *EGFR*-driven NSCLC tumor cells demonstrates the need for precision medicine combinations to improve clinical outcomes
- Initial safety and clinical activity results from the phase 1 SYMPHONY trial support expanded clinical development of BLU-945 in combination with osimertinib and other complementary agents. Dose escalation continues to determine the MTD and RP2D of BLU-945 as a monotherapy and in combination with osimertinib

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