A phase 1/2 study of BLU-945 in patients with common activating *EGFR*-mutant non-small cell lung cancer (NSCLC) (SYMPHONY trial-in-progress)

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Background

- The most frequent oncogenic drivers of non-small cell lung cancer (NSCLC) are epidermal growth factor receptor mutations (*EGFRm*), with the most common mutations being exon 19 deletion (ex19del) and L858R[1–3]
- Although EGFR-targeted therapies such as tyrosine kinase inhibitors (TKIs) have improved outcomes in patients with *EGFRm* NSCLC, on- and off-target resistance mutations to these drugs is inevitable[4]
- The most frequent mutations, *EGFR* T790M and *EGFR* C797S, can occur simultaneously within an individual patient and develop after treatment with first- and second-generation TKIs and third-generation TKIs, respectively[4,5]
- There are unmet medical needs for patients with *EGFRm* NSCLC and resistance mutations, highlighted by the current lack of approved therapies after progression on available therapies[5]
- BLU-945 is an investigational oral next-generation EGFR TKI designed to selectively target the L858R activating mutation, and the C797S and T790M on-target resistance EGFR mutations with nanomolar potency while sparing wildtype EGFR[6] (**Figure 1**)
- Preclinically, it has shown activity as monotherapy in treatment-naïve *EGFRm* xenograft and osimertinib-resistant, *EGFRm* patient-derived xenograft (PDX) models[7,8]
- Importantly, as BLU-945 has high selectivity for EGFR mutations while sparing wildtype, this could be advantageous for combination treatment with complementary therapies, such as osimertinib and the next-generation EGFR TKI BLU-701. Such combinations may provide the benefit of treating multiple mutations without increased toxicity. BLU-945 in combination with other agents has previously shown enhanced activity in *EGFRm* PDX models[7,8]

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	■	■	■	■	■	■

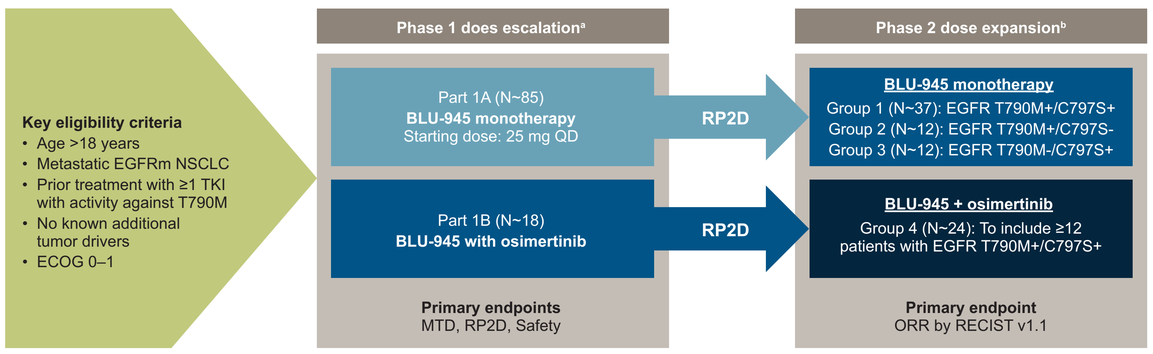
■ IC_{50} ≤10 nM ■ IC_{50} >50 nM

[a]Based on biochemical IC_{50}. 1G, first-generation; 3G, third-generation; IC_{50}, half-maximal inhibitory concentration.
EGFRm: primary EGFR mutation, either L858R or ex19del.

Study objectives and design

- The SYMPHONY trial (BLU-945; NCT04862780) is an international, open-label, first-in-human, phase 1/2 study designed to evaluate safety, tolerability, and antitumor activity of BLU-945 as monotherapy and in combination with osimertinib in patients with *EGFRm* NSCLC (**Figure 2**)

Figure 2: Study design



[a]Based on Bayesian Optimal Interval escalation design (BOIN). [b]Initiation of phase 2 will be dependent on results of phase 1.
ECOG, 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; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

- Phase 1 dose escalation will be conducted using 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. 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
- Intra-patient dose escalation will be permitted for patients enrolled at previously tested dose levels that have been evaluated for safety
- 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. Osimertinib will be given at the standard dose of 80 mg once daily (QD)
- In phase 1 part B, the dose level increase should be <100% of BLU-945 in the cohort(s) subsequent to cohort 1 and the next dose of BLU-945 will be selected such that the projected area under the plasma concentration time curve (AUC) of BLU-945 in combination with osimertinib will not be more than the AUC of BLU-945 as monotherapy at the maximum tolerated dose (MTD) or the highest dose deemed safe in part 1A in the combination dose-escalation
- The MTD will be determined based on the DLT rate and the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate (30%)
- The RP2D will not exceed the MTD and will be determined based on pharmacokinetics (PK), pharmacodynamics (PD), cumulative toxicity, and antitumor activity. If a MTD is not identified then PK, PD, and safety data, along with pertinent nonclinical data suggestive of a dose-effect relationship, will be used to define a RP2D
- In phase 2, patients will be enrolled based on specific *EGFRm* profiles at the RP2D determined in phase 1:
  - Groups 1–3 will be treated with BLU-945 monotherapy at the RP2D and schedule selected in phase 1 part A: *EGFR* T790M+/C797S+, *EGFR* T790M+/C797S-, *EGFR* T790M-/C797S+
  - Group 4 will be treated with BLU-945 combined with osimertinib at the RP2D and schedule selected in phase 1 part B: to include at least 12 patients with *EGFR* T790M+/C797S+
- Patients with disease progression may continue study treatment if ongoing clinical benefit is observed (as assessed by the investigator, and approved by the Sponsor)

Summary of key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Pathologically confirmed metastatic *EGFRm* NSCLC • Prior treatment with ≥1 EGFR-targeted TKI against T790M • Tumor mutation profile determined locally using tissue or plasma specimen via a sponsor-approved methodology (preferably NGS) • Pretreatment tumor sample (archival sample or pretreatment biopsy) submitted for central analysis • Part 1A: willing to undergo on-treatment biopsy at doses expected to result in efficacious exposure levels if safe and medically feasible • ECOG performance status 0–1	• Additional known tumor drivers[a] • NSCLC with mixed cell histology or with histologic transformation • Any immunotherapy or other antibody therapy within 28 days prior to first dose • Any other systemic anticancer therapy within 14 days or 5 half-lives (whichever is shortest) prior to first dose • Radiation within 14 days before first dose if including a vital organ, or 7 days if not including a vital organ • CNS metastases or spinal cord compression associated with progressive neurological symptoms. Patients with asymptomatic brain metastases who are on stable doses of corticosteroids are allowed

[a]Including, but not limited to *EGFR* exon 20 insertion, or pathologic abnormalities of *KRAS, BRAF, V600E, NTRK1/2/3, HER2, ALK, ROS1, MET,* or *RET*.
CNS, central nervous system; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *EGFRm*, epithelial growth factor receptor mutant; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Key study endpoints

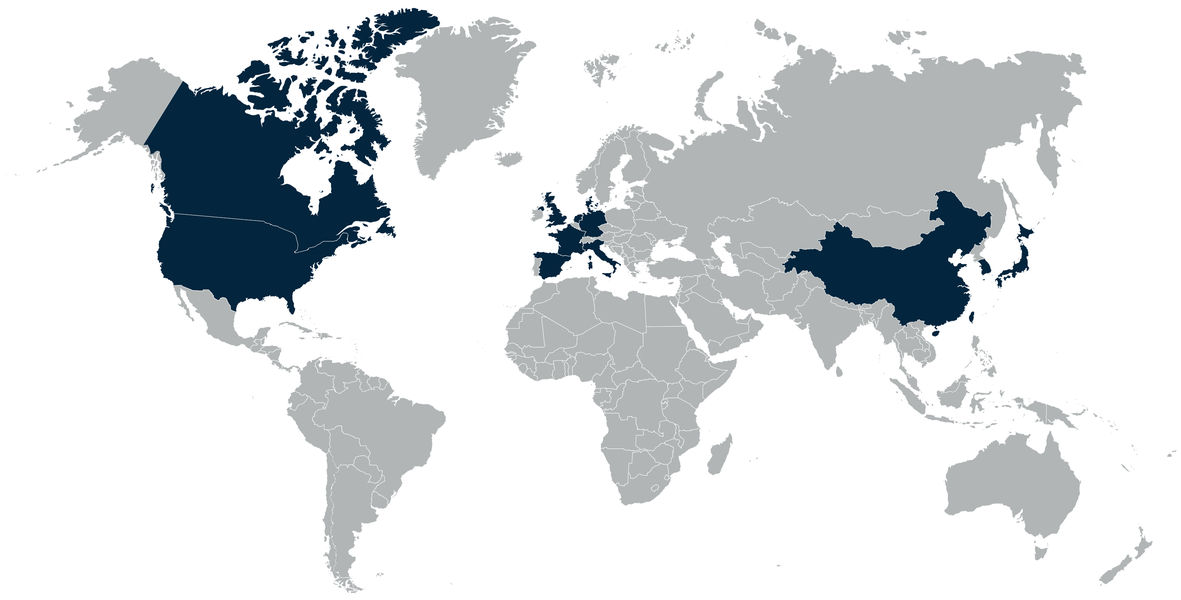
Phase 1	Phase 2
• **Primary endpoints** – Maximum tolerated dose – Recommended phase 2 dose – Safety and tolerability • **Secondary endpoints** – Overall Response Rate (RECIST 1.1) – Duration of response – Pharmacokinetics – Modulation of *DUSP6* and *SPRY4* expression levels	• **Primary endpoint** – Overall Response Rate (RECIST 1.1) • **Secondary endpoints** – Duration of response – Disease control rate – Clinical benefit rate – Progression-free survival – Overall survival – Safety and tolerability – Cardiovascular parameters, including QTcF – Pharmacokinetics – CNS anticancer activity • Overall response rate (RECIST 1.1) • Duration of response • Progression rate

[a]ctDNA will be assessed in real-time using the FoundationOne Liquid CDx assay.
CNS, central nervous system; ctDNA, circulating tumor DNA; DUSP6, Dual specificity phosphatase 6; *EGFR*, epithelial growth factor receptor; QTcF; QT interval corrected using Fridericia's formula; RECIST 1.1,
Response Evaluation Criteria in Solid Tumors version 1.1; SPRY4, sprouty RTK signaling antagonist 4.

Enrollment and status

- The phase 1 dose-escalation portion of the study is ongoing
- The study is planned for approximately 30 centers in North America, Europe, and Asia

Anticipated study locations



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