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)

Elaine Shum,1 Yasir Elamin,2 Zofia Piotrowska,2 David R Spigel,1 Karen L Reckamp,1 Julia Rotow,4 Daniel SW Tan,1 Sun Min Lim,2 Tae Min Kim,2 Chia-Chi Lin,1 Terufumi Kato,4 Jagan Parepally,1 Faris Albayes,3 Melinda Louise-Gao,3 Teisa Weing,2 Alena Zalutskaya,3 Koichi Soto,1

1National Cancer Center, New York University Langone Health, New York, NY, USA; 2MD Anderson Cancer Center, University of Texas, Houston, TX, USA; 3Massachusetts General Hospital, Boston, MA, USA; 4Sarah Cannon Research Institute, Nashville, TN, USA.

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 (ex/19del) and L858R.
- Although EGFR-targeted therapies such as tyrosine kinase inhibitors (TKIs) have been derived outcomes in patients with EGFRm NSCLC, on- and off-target resistance mutations to these drugs is inevitable.
- The most frequent mutations, EGFR T790M and EGFR C797S, can occur simultaneously within an individual patient (TKI resistance) and between different TKIs (cross-resistance), respectively.
- 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.
- 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.

Study objectives and design

- The SYMPHONY trial (BLU-945; NCT04862780) is an international, open-label, first-in-human, phase 1/2 study of BLU-945 in patients with common activating EGFRm NSCLC.

Summary of key inclusion and exclusion criteria

Key inclusion 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-sponsored 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

Key exclusion criteria

- Additional known tumor drivers
- 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 antitumor therapy within 14 days or 5 half-lives (whichever is shorter) 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

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

Figure 2: Study design