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A phase 1/2 study of BLU-945, a highly potent and selective inhibitor of epidermal growth factor receptor (*EGFR*) resistance mutations, in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC)

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I will discuss the following investigational use in my presentation: BLU-945 in patients with *EGFR*-mutant NSCLC resistant to standard of care EGFR TKIs (SYMPHONY trial)

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Introduction

- Lung cancer is the leading cause of cancer mortality worldwide.[1] Activating mutations in the epidermal growth factor receptor (*EGFR*) gene, predominantly exon 19 deletion (ex19del) and L858R mutations, are oncogenic drivers in the most common subtype of non-small cell lung cancer (NSCLC), adenocarcinoma[2]
- First- (1G), second- (2G), and third- (3G) generation EGFR tyrosine kinase inhibitors (TKIs) have achieved high response rates, but resistance typically develops within the first two years of treatment.[3-5] Toxicities due to wild-type (WT) EGFR inhibition are also associated with 1G and 2G EGFR TKIs[3-5]
- Although 3G TKIs such as osimertinib have shown high potency for the additional *EGFR* T790M mutation that results from resistance to 1G and 2G TKIs in approximately 60% of cases, a further, common on-target resistance mutation, C797S, inevitably develops following treatment with osimertinib[3,5]
- There is unmet medical need for patients with *EGFRm* NSCLC and resistance mutations T790M and C797S, which highlights the importance of developing EGFR TKIs that can inhibit these mutations and demonstrate high selectivity

1. GLOBOCAN World Fact Sheet. November 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf. Accessed March 26, 2021; 2. Hsu W-H et al. *Ann Oncol*. 2018;29(suppl. 1):i3–i9;
3. Leonetti A et al. *Br J Cancer*. 2019;121(9):725–737; 4. Piper-Vallillo AJ et al. *J Clin Oncol*. 2020;38(25):2926–2936; 5. Park S et al. *Cancer Res Treat*. 2020;52:1288–1290; 6. Yu et al. *Clin Cancer Res*. 2013;19(8):2240-7.

BLU-945 and the SYMPHONY study

- BLU-945, a novel, oral EGFR TKI, was developed to selectively suppress acquired T790M- and C797S-mediated resistance mutations that occur after prior treatment with EGFR TKIs
- Preclinical data demonstrated nanomolar potency of BLU-945 towards *EGFRm*/T790M and *EGFRm*/T790M/C797S mutants, with >900-fold selectivity over WT EGFR, as well as robust antitumor activity[1]
- BLU-945 showed promising intracranial activity in a NSCLC PDC (YU-1097)-luc (EGFR ex19del/T790M/C797S) model[2]
- SYMPHONY (NCT04862780) is an ongoing, global, first-in-human, phase 1/2 study of BLU-945 designed to evaluate the safety and efficacy of this novel, oral EGFR TKI in patients with *EGFR*-mutant NSCLC who have previously received at least 1 prior EGFR-targeted TKI

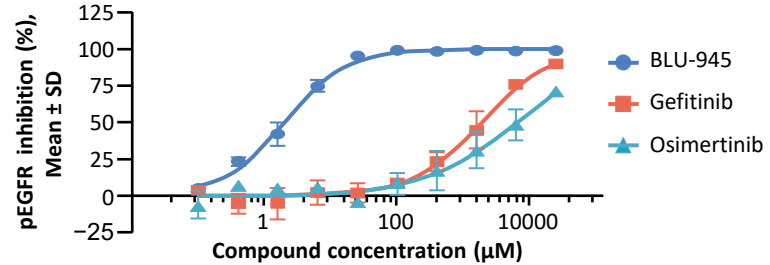
	1G	3G	4G
EGFR mutational coverage[a]	**Gefitinib**	**Osimertinib**	**BLU-945**
L858R (LR)			
ex19del			
LR or ex19del / T790M			
LR or ex19del/ C797S			
LR or ex19del / T790M / C797S			

$IC_{50} \leq 10$ nM

10 nM < $IC_{50} \leq 50$ nM

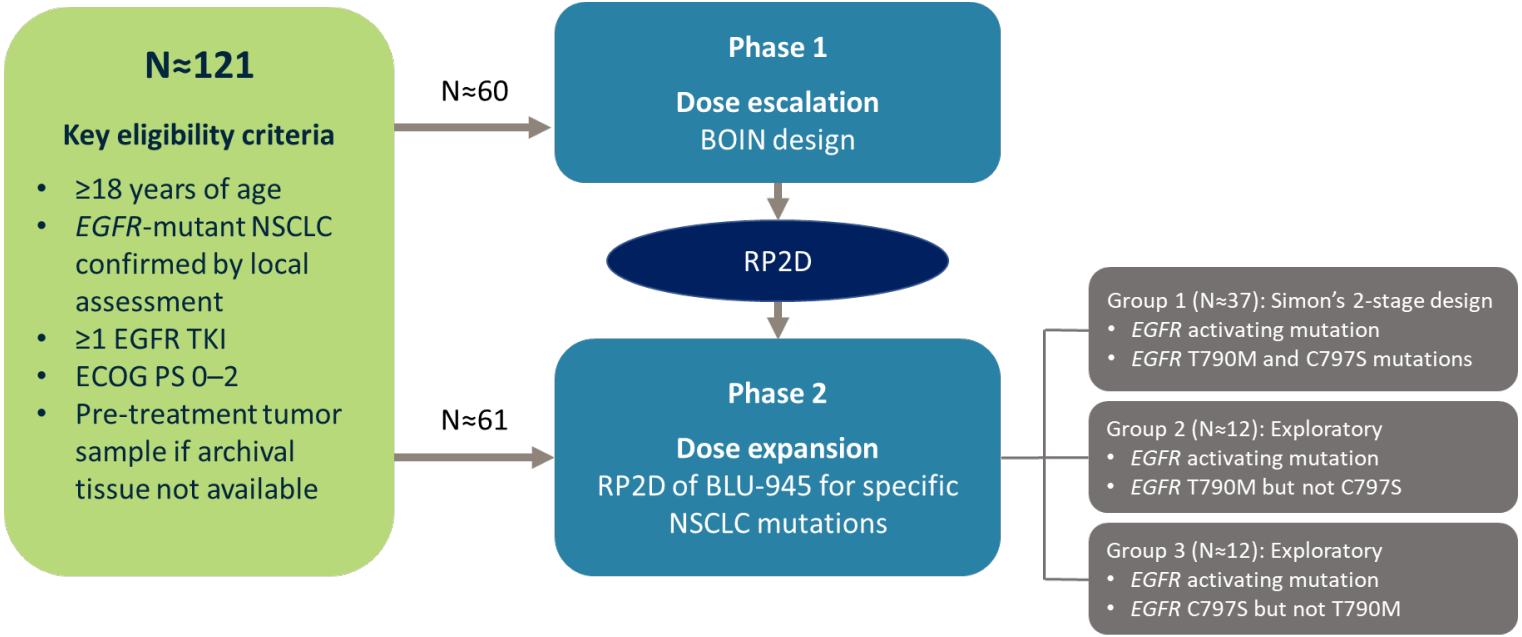
$IC_{50} > 50$ nM

BLU-945 is highly potent in EGFR L858R/T790M/C797S (Ba/F3) cells[2]



1. Schalm S et al. ESMO 2020. Abstract 1296P; 2. Lim SM et al. AACR 2021. Abstract 1467. [a]Based on biochemical IC_{50}. 1G, first generation; 3G, third generation; 4G, fourth generation; IC_{50}, half-maximal inhibitory concentration; PDC, patient-derived cells.

SYMPHONY Study design

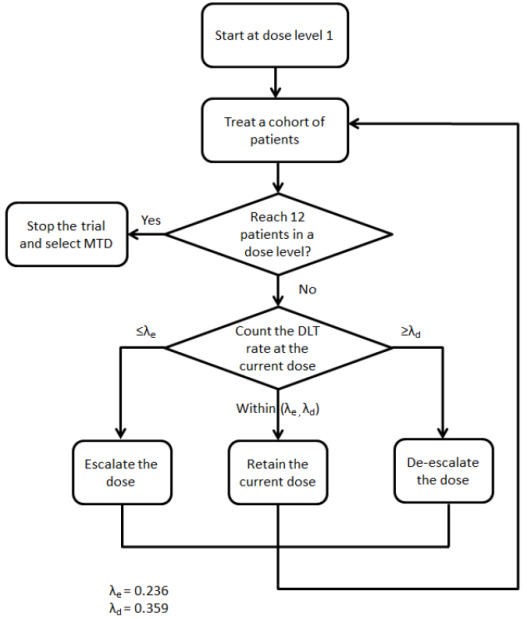


BOIN, Bayesian optimal interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; RP2D, recommended phase 2 dose.

SYMPHONY Study design (continued)

- Primary objectives
  - Phase 1: MTD, RP2D and safety of BLU-945
  - Phase 2: ORR of BLU-945 in patients with the eligible *EGFR* resistance mutations, T790M and/or C797S
- Phase 1 dose escalation (N≈60) will be conducted using BOIN design to determine the MTD and RP2D
- Phase 2 dose expansion (N≈61), will enroll patients with *EGFR*-mutated NSCLC in 3 groups, who will receive the RP2D
  - Primary group 1: patients with *EGFR* T790M and C797S (n≈37)
  - Exploratory group 2: patients with *EGFR* T790M but not C797S (n≈12)
  - Exploratory group 3: patients with *EGFR* C797S but not T790M (n≈12)
- Patients may be treated until disease progression or unacceptable toxicity

Phase 1 dose escalation BOIN design



DLT, dose limiting toxicity; λ_e, dose escalation boundary; λ_d, dose de-escalation boundary; MTD, maximum tolerated dose; ORR, overall response rate.

SYMPHONY Key inclusion criteria

- ≥18 years of age
- Pathologically confirmed, definitively diagnosed, metastatic NSCLC harboring an activating EGFR mutation per local assessment via a Sponsor-approved testing methodology[a]
- Previously received ≥1 prior EGFR-targeted TKI[b]
- Eastern Cooperative Oncology Group performance status is 0–2
- Pretreatment tumor sample (archival or pretreatment biopsy) submitted for central analysis. Patients with no sample will be considered on a case-by-case basis
- Phase 2 Expansion Groups: patient has ≥1 measurable target lesion evaluable by RECIST v1.1

[a]Expansion Groups: Patients must have NSCLC harboring *EGFR* T790M and C797S mutation (Group 1); *EGFR* T790M but not C797S (Group 2); or *EGFR* C797S but not T790M (Group 3). [b]For patients enrolled into expansion Group 2, prior treatment must include an approved EGFR-targeted TKI with activity against the T790M mutation. NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1;

SYMPHONY Key exclusion criteria

- Any additional known primary driver alterations, including but not limited to pathologic aberrations of *EGFR* exon 20 (insertions), *KRAS*, *BRAF V600E*, *NTRK1/2/3*, *HER2*, *ALK*, *ROS1*, *MET*, or *RET*
- NSCLC with mixed squamous cell histology as well as tumors with histologic transformation (NSCLC to small cell lung cancer and with epithelial to mesenchymal transition)
- Received the following anticancer therapy prior to first dose of the study drug:
  - EGFR-targeted TKI within 7 days
  - Immunotherapy/antibody therapy within 28 days
  - Any other systemic therapy within 14 days or 5 half-lives, whichever is shortest
  - Radiotherapy to a large field or including a vital organ within 14 days
- Central nervous system metastases or spinal cord compression associated with neurological symptoms or requiring increasing doses of corticosteroids
- Laboratory abnormalities prior to first dose of study drug[a]

[a]Including absolute neutrophil count <1.0×10⁹/L; platelet count <75×10⁹/L; hemoglobin ≤8.0 g/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3× the upper limit of normal (ULN) if no hepatic metastases are present, >5× ULN if hepatic metastases are present; total bilirubin >1.5× ULN, >3× ULN in presence of Gilbert's disease; estimated or measured creatinine clearance <40 mL/min; international normalized ratio (INR) >2.3 or prothrombin time (PT) >6 seconds above control or a patient-specific INR or PT abnormality that the treating investigator considers clinically relevant and/or increases the risk for hemorrhage.

SYMPHONY Study key endpoints

Primary endpoints	Secondary endpoints
• **Phase 1** - Determination of MTD - Determination of RP2D - Safety and tolerability • **Phase 2** - Overall response rate per RECIST v1.1 - Group 1 will utilize the Simon's 2-stage design to test the null hypothesis of ORR ≤20% against a 1-sided alternative of ≥40%	• **Phase 1** - Overall response rate per RECIST v1.1 • **Phase 1 & 2** - Duration of response - PK and PD parameters • **Phase 2** - Disease control rate[a] per RECIST v1.1 - Clinical benefit rate[b] per RECIST v1.1 - Progression free survival - Overall survival - Time to intracranial progression and intracranial response rate - Safety and tolerability

[a]Proportion of patients with a best response of complete or partial response or stable disease; [b]Proportion of patients with a best response of complete or partial response or stable disease of duration ≥16 weeks from first dose.
PD, pharmacodynamic; PK, pharmacokinetic.

SYMPHONY study sites

- Recruitment has started, and approximately 30 sites will be open for enrollment across North America, Europe, and Asia
- Please see https://clinicaltrials.gov/ct2/show/NCT04862780 for more information and up-to-date study sites