A phase 1/2 study of the highly selective EGFR inhibitor, BLU-701, in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC)

TPS9142

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Background

- Epidermal growth factor receptor mutations (*EFGRm*), specifically exon 19 deletions and L858R substitutions, are the most common targetable driver mutations in non-small cell lung cancer (NSCLC)[1–3]
- Although third-generation tyrosine kinase inhibitors (TKIs), such as osimertinib, are effective frontline therapy and have improved the outcomes in patients with *EGFR*m NSCLC, treatment resistance ultimately occurs, including the emergence of the on-target *EGFR* C797X mutation for which there are no approved TKIs[3–5]
- Central nervous system (CNS) metastases are present in approximately 25–30% of patients with *EGFR*m metastatic NSCLC at diagnosis. Additionally, 15–20% of patients with *EGFR*m metastatic NSCLC are at risk of CNS progression during treatment with an EGFR TKI[6]
- BLU-701 is an investigational, reversible, brain-penetrant, wildtype-sparing oral TKI with nanomolar potency on common activating (exon 19 deletion and L858R) and C797X resistance mutations (**Figure 1**), with at least 30-fold selectivity for these mutants over wildtype (WT) EGFR in cellular assays[7]
- Preclinically, BLU-701 has shown promising antitumor activity in treatment-naïve and osimertinib-resistant tumor models, as well as antitumor CNS activity[7,8]
- Additionally, combining BLU-701 with other targeted or standard of care therapies, may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with *EGFR*m NSCLC (**Figure 1**)

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

		1G	3G	Next generation		Potential combinations	
Line	EGFR mutational coverage[a]	Gefitinib	Osimertinib	BLU-701	BLU-945	BLU-701 + osimertinib	BLU-701 + BLU-945
1L	L858R (LR)						
1L	ex19del						
2L	LR or ex19del/T790M						
2L	LR/C797S						
2L	ex19del/C797S						
3L	LR or ex19del/T790M/C797S						

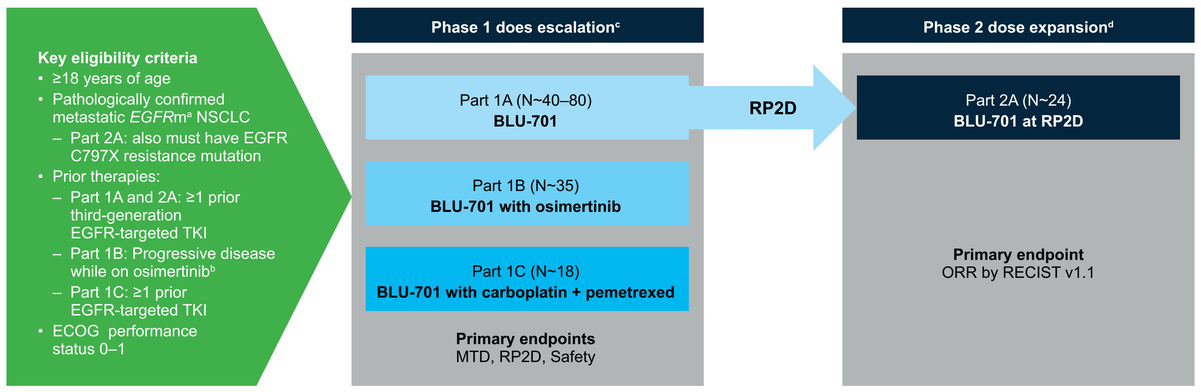
■ IC_{50} ≤10 nM ■ IC_{50} >50 nM

[a]Based on biochemical IC_{50}. 1G, first-generation; 3G, third-generation; IC_{50}, half-maximal inhibitory concentration.

Study objectives and design

- The HARMONY trial (NCT05153408) is an ongoing, global phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BLU-701 as a monotherapy or in combination with osimertinib or platinum-based chemotherapy in patients with *EGFR*m NSCLC
- The phase 1 dose escalation part of this study is conducted using a Bayesian optimal interval (BOIN) design to determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and safety of BLU-701 in monotherapy (Part 1A), BLU-701 + osimertinib (Part 1B), and BLU-701 + carboplatin and pemetrexed combinations (Part 1C) (**Figure 2**)
- Phase 2 dose expansion will initiate upon completion of Part 1A, and will investigate the safety and efficacy of BLU-701 monotherapy at the RP2D (**Figure 2**)

Figure 2: Study design



[a]*EGFR*m encompasses ex19del and L858R substitutions. [b]Patients who have discontinued osimertinib may be eligible, if no more than 6 weeks have elapsed between the discontinuation of prior osimertinib and resumption of osimertinib on study. [c]Based on Bayesian Optimal Interval escalation design (BOIN). [d]Phase 2 will be initiated upon determination of RP2D in Part 1A (dose level and schedule). BOIN, Bayesian Optimal Interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

- In Part 1A, BLU-701 will initially be administered once-daily (QD) over 28-day cycles with the option to evaluate twice-daily (BID) dosing if supported by emerging PK and safety data
- In Part 1B, BLU-701 will be administered in combination with osimertinib 80 mg QD or 40 mg QD depending on the dose-escalation cohort
- In Part 1C, BLU-701 will be administered daily in combination with standard intravenous doses of carboplatin area under the concentration time curve 5–6 mg/ml/min and pemetrexed (500 mg/m^2) every 3 weeks over 21-day cycles for 4–6 cycles. Pemetrexed maintenance can be used for up to 2 years
- The starting dose of BLU-701 in Part 1B and Part 1C will be 50% of RP2D or a dose equivalent to ~50% of the highest BLU-701 monotherapy dose deemed safe for further escalation in Part 1A
- The MTD will be determined based on the dose-limiting toxicity (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 PK, 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. A minimum of 15 patients must be treated at the potential RP2D to confirm it is the RP2D
- DLT-evaluable patients are those who experience a DLT, or who receive ≥75% of the intended dose of BLU-701, and for Part 1B, osimertinib, and complete follow-up safety evaluations through the first treatment cycle (i.e., 28 days for Parts 1A and 1B, and 21 days for Part 1C)
- Intra-patient dose escalation is permitted
- Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met

Summary of key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• ≥18 years of age • Pathologically confirmed metastatic NSCLC • EGFR mutation profile determined locally using either tumor tissue (preferably from a progressing lesion) and/or ctDNA in plasma: – All Parts: Tumor must harbor an activating *EGFR* mutation (ex19del or L858R) – Part 2A only: Tumor must additionally harbor an *EGFR* C797X resistance mutation • Part 1A: willing to undergo on-treatment biopsy at doses expected to result in efficacious exposure levels if safe and medically feasible • Prior therapies: – Part 1A and 2A: At least one prior third-generation EGFR-targeted TKI, such as osimertinib – Part 1B: Patients must have experienced progressive disease while on osimertinib[a] – Part 1C: At least one prior EGFR-targeted TKI • Part 2A: at least one measurable target lesion per RECIST 1.1 • ECOG performance status 0–1	• Disease that is suitable for local therapy administered with curative intent • Tumors that harbor *EGFR* T790M mutation or any additional known driver alterations[b] • Have NSCLC with mixed cell histology or a tumor with known histologic transformation • Received the following therapy prior to first dose of study drug: – Any third-generation EGFR TKI <7 days[c] – Part 2A: Previous therapy with first- or second-generation EGFR TKIs – Part 1C: Prior platinum-based chemotherapy for advanced or metastatic disease – Immunotherapy or other antibody therapy <21 days – Radiotherapy to a large field or including a vital organ <14 days, or <7 days if vital organ not included • CNS metastases or spinal cord compression associated with progressive neurological symptoms or requires increasing doses of corticosteroids[d] • Asymptomatic CNS and leptomeningeal disease is allowed, and when measurable, should be captured as target lesions • Inadequate end organ function based on safety laboratory assessments

[a]Patients who have discontinued osimertinib may be eligible, if no more than 6 weeks have elapsed between the discontinuation of prior osimertinib and resumption of osimertinib on study. [b]Other additional driver alterations include but are not limited to, *EGFR* exon 20 insertions or pathologic abnormalities of *KRAS*, *BRAF V600E*, *NTRK1/2/3*, *HER2*, *ALK*, *ROS1*, *MET*, or *RET*. [c]Patients in Part 1B do not require a wash-out period for osimertinib. [d]If a patient requires corticosteroids for management of CNS disease, the dose must have been stable for the 2 weeks preceding treatment. CNS, central nervous system; ctDNA, circulating tumor DNA; ex19del, exon 19 deletion.

Key study endpoints

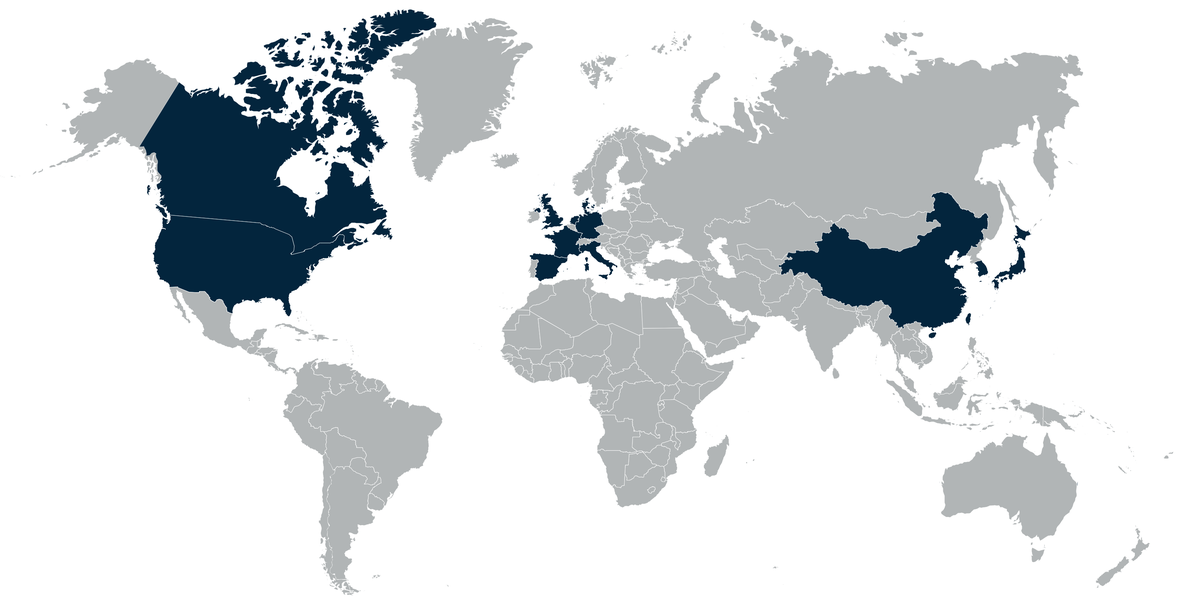
Phase 1	Phase 2
• **Primary endpoints** – Maximum tolerated dose (MTD)[a] – Recommended phase 2 dose (RP2D)[b] – Safety and tolerability • **Secondary endpoints** – Overall response rate (RECIST 1.1) – Duration of response – Pharmacokinetics (PK) and pharmacodynamics (PD)	• **Primary endpoint** – Overall response rate (RECIST 1.1) • **Secondary endpoints** – Safety and tolerability – Duration of response – Disease control rate – Clinical benefit rate – Progression-free survival – Overall survival – CNS overall response rate, duration of response, and progression rate by RECIST 1.1 – Cardiovascular parameters, including QTcF

[a]Based on dose limiting toxicities. [b]Based on dose limiting toxicities, pharmacokinetics, pharmacodynamics, and preliminary safety and antitumor activity. QTcF, QT interval corrected using Fridericia's formula.

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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Acknowledgements

Medical writing support was provided by Kyle Wiid, MSc, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Disclosures

A Spira has a leadership role with NEXT Oncology Virginia; stock or other ownership interests in Eli Lilly; received honoraria from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol-Myers Squibb, and Bayer; consulting or advisory roles for Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Takeda, Janssen Research and Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Array BioPharma, AstraZeneca/MedImmune, Merck, Bristol-Myers Squibb, and Blueprint Medicines Corporation; and research funding from LAM Therapeutics, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, NewLink Genetics, Incyte, AbbVie, Ignyta, Trovagene, Takeda, MacroGenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol-Myers Squibb, Loxo, Arch Therapeutics, Gritstone, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen Oncology, Mirati Therapeutics, Rubius, Synthekine, Mersana, and Blueprint Medicines Corporation.
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Poster available for download at:

Presented at **ASCO Annual Meeting, June 3–7, 2022**. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute.