A phase 1/2 study of BLU-451, a central nervous system (CNS) penetrant, small molecule inhibitor of EGFR, in incurable advanced cancers with EGFR exon 20 insertion (ex20ins) mutations

TPS9155

Alexander Spira,[1] Helena Yu,[2] Lova Sun,[3] Danny Nguyen,[4] Paul Pearson,[5] Jennifer Shim-Lopez,[5] Diana Hausman,[5] Xiuning Le[6]

[1]Next Oncology Virginia and Virginia Cancer Specialists, Fairfax, VA, USA, and US Oncology Research, The Woodlands, TX, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Division of Hematology Oncology, University of Pennsylvania, Philadelphia, PA, USA; [4]City of Hope, Huntington Beach, CA, USA; [5]Lengo Therapeutics, San Diego, CA, USA; [6]University of Texas MD Anderson Cancer

[a]A wholly owned subsidiary of Blueprint Medicines Corporation, Cambridge, MA, USA.

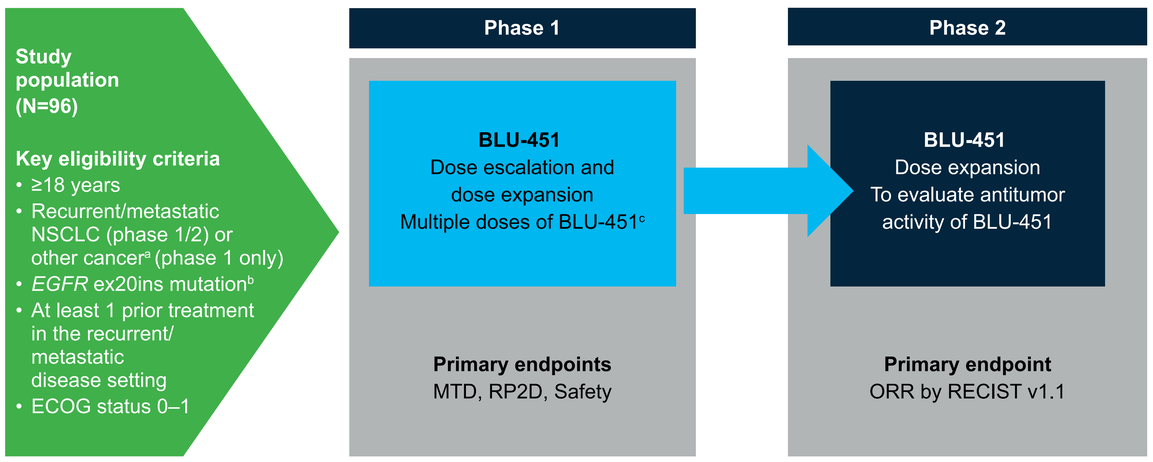
Background

- Oncogenic *EGFR* ex20ins mutations are the third most common type of activating *EGFR* activating mutation in non-small cell lung cancer (NSCLC), and are not potently targeted by many inhibitors of common activating mutations such as L858R and exon 19 mutations[1–3]
- Like other types of *EGFR*-mutated NSCLC, CNS metastases are a challenge to treat. Approximately 25% of patients with *EGFR* ex20ins NSCLC have brain metastases at the time of initial presentation, and progression can be associated with development of CNS metastases[4,5]
- The presence of CNS metastases (brain and leptomeninges) complicates disease management, can cause significant morbidity, and has been associated with poorer outcomes for patients with *EGFR* ex20ins NSCLC[6]
- The standard of care (SOC) for patients with NSCLC with activating *EGFR* mutations is treatment with a tyrosine kinase inhibitor (TKI) or platinum-based chemotherapy[7,8]
- The US Food and Drug Administration has recently approved two agents, amivantamab and mobocertinib, for patients who progress after a platinum-based chemotherapy, but neither have established CNS activity[9,10]
- BLU-451 is a CNS penetrant, wild type-sparing, covalent small molecule inhibitor of EGFR ex20ins as well as of atypical (G719C, G719S, L861Q) and common EGFR mutants
- Preclinical data have shown BLU-451 to have potent antitumor activity, including in an intracranial xenograft model,[11] which has led to its clinical development in *EGFR*-mutant NSCLC

Study Objectives and design

- BLU-451-1101 (NCT05241873) is a phase 1/2, global, open-label study designed to evaluate single-agent BLU-451 in patients with NSCLC harboring *EGFR* ex20ins that has progressed following prior treatment for incurable recurrent or metastatic disease
- Phase 1 consists of two parts: a 3+3 dose escalation and a dose expansion
  - Part 1 (dose-escalation): two to six patients enrolled per dose to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of single dose BLU-451. Additional cohorts may be added to evaluate intermediate dose levels or a twice daily (BID) dosing schedule
  - Part 2 (dose expansion): additional patients enrolled to further evaluate safety and pharmacokinetics (PK) at a given dose level or in specific sub-populations
- Phase 2 will evaluate the antitumor activity of BLU-451 administered at the RP2D in patients with or without brain metastases in three cohorts (n=18 each):
  - Cohort 2A: patients with prior platinum-based chemotherapy and EGFR ex20ins-targeted agent
  - Cohort 2B: patients with prior platinum but no EGFR ex20ins-targeted agent
  - Cohort 2C: patients with active asymptomatic brain metastases with prior platinum with or without EGFR ex20ins-targeted agent

Figure 1: BLU-451 study design



[a]Any other cancer except primary CNS tumor. [b]For phase 1 only, patients with *EGFR* exon 18 G719X or exon 21 L861Q mutations that have failed standard of care therapy are eligible with sponsor approval. Other *EGFR* mutations (e.g., L858R or exon 19 deletion) may be eligible if T790M mutation is not present and ≥1 EGFR TKI was tried and failed, and if approved by the Sponsor Medical Monitor. [c]Once daily then twice daily dosing if supported by emerging PK and safety data.
CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

- PK will be assessed by evaluating plasma levels of BLU-451 in Cycle 1 and periodically in subsequent cycles
- Biomarker assessments may include circulating tumor DNA (ctDNA) or tumor biopsy to identify the presence of *EGFR* mutations including *EGFR* ex20ins
- All patients will receive BLU-451 as a single agent administered once daily, or twice daily on a 21-day treatment cycle

Summary of key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Males and females ≥18 years of age • ECOG performance status 0–1 • Histologically or cytologically confirmed metastatic NSCLC (phase 1 and phase 2) or other cancer except for primary CNS tumors (phase 1 only) • Documented *EGFR* ex20ins mutation based on NGS testing of tumor or liquid biopsy[a] • Prior treatment in the recurrent/metastatic disease setting: – Phase 1 patients with NSCLC: platinum-based chemotherapy,[b] at least one prior EGFR ex20ins targeted therapy (amivantamab or mobocertinib),[c] prior ICI[c] – Phase 1 other cancers: any approved standard therapy – Phase 2: platinum-based chemotherapy,[b] prior ICI.[c] In addition; • Cohort 2A - one prior EGFR ex20ins targeted therapy including amivantamab or mobocertinib required • Cohort 2B - no prior EGFR ex20ins targeted therapy • Cohort 2C - prior treatment with up to 1 line of EGFR ex20ins targeted therapy[c] • Brain metastases not associated with progressive neurological symptoms and not requiring increasing doses of corticosteroids[c,d] • Disease progression on or after or intolerance to most recent systemic therapy • Evaluable disease (phase 1 only) or measurable disease (phase 1 and phase 2) per RECIST v1.1	• Tumor harboring known alternate driver alteration (*ROS, BRAF V600E, ALK, RET, HER2, MET, KRAS, NTRK1/2/3,* or *EGFR C797X*[e]) • Prior EGFR TKI ≤ 5 days; immunotherapy or bi-specific antibody ≤ 28 days, other systemic anticancer treatment ≤ 14 days prior to the first dose of study drug BLU-451 • Symptomatic brain metastases, any lesion in an anatomic location thought to require immediate treatment, any lesion > 2 cm in size unless specifically approved by the Sponsor Medical Monitor, radiation treatment for brain metastases < 28 days prior to first dose of study drug, or brain metastases that require increasing doses of corticosteroids • Leptomeningeal disease • Intracranial hemorrhage within 28 days prior to the first dose

[a]Performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or equivalent. [b]Other chemotherapy if platinum-based is contraindicated. [c]Allowed but not required. [d]In cohort 2C, patients are required to have ≥1 measurable brain lesion per RECIST 1.1. [e]Including but not limited to these mutations.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NGS, next-generation sequencing, ICI, immune checkpoint inhibitors; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Key study endpoints

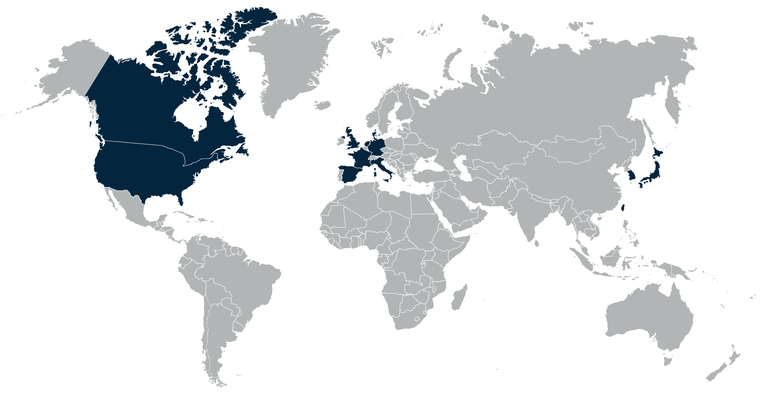
Phase 1	Phase 2
• **Primary endpoints** – Maximum tolerated dose – Recommended phase 2 dose on DLTs[a] – Safety and tolerability • **Secondary endpoints** – Antitumor activity using RECIST v1.1 • Objective response rate • Duration of response • Disease control rate • Clinical benefit rate • Progression-free survival • Overall survival – CNS antitumor activity using RECIST v1.1[b] • CNS objective response rate • CNS duration of response • CNS progression-free survival – Pharmacokinetics	• **Primary endpoint** – Objective response rate at RP2D using RECIST v1.1 • **Secondary endpoints** – Additional measures of anti-tumor activity • Duration of response • Disease control rate • Clinical benefit rate • Progression-free survival • Overall survival – CNS antitumor activity using RECIST v1.1[a] • CNS objective response rate • CNS duration of response • CNS progression-free survival – Pharmacokinetics – Safety and tolerability

[a]The DLT evaluation window is 28 days (within the first 28 days of taking BLU-451) even if the cycles are 21 day. [b]In patients with measurable baseline brain metastases.
CNS, central nervous system, DLTs, dose-limiting toxicities; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Enrollment and status

- The phase 1 dose-escalation portion of the study is ongoing
- The study is planned for approximately 40 centers in North America, Asia, and European Union for phase 2 only

Anticipated study locations



References

1. Riess JW et al. *J Thorac Oncol*. 2018;13:1560-1568.
2. Udager AM et al. *Cancer Res*. 2015;75(13):2600–2606.
3. Mondal G et al. *Acta Neuropathol*. 2020;139(6):1071–1088.
4. Yang G et al. *Lung Cancer*. 2020;145:186–194.
5. Leal JL et al. *Clin Lung Cancer*. 2021;22(6):e859-e869.
6. Rangachari D et al. *Lung Cancer*. 2015;88(1):108–111.
7. Ettinger DS et al. *J Natl Compr Canc Netw*. 2021;19(3):254–266.
8. Choudhury NJ et al. *Clin Cancer Res*. 2021;27(10):2920–2927.
9. RYBREVANT (amivantamab-vmjw) Injection, for Intravenous Use. 2021. Janssen Pharmaceutical Companies.
10. Riely GJ et al. *Cancer Discovery*. 2021;11(7):1688–1699.
11. Pearson P et al. Presented at AACR 2022. Poster # 3261.

Acknowledgements

Medical writing support was provided by Mselenge Mdegela, MPhil. 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

This research was funded by Blueprint Medicines Corporation. Blueprint Medicines reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content. A Spira had 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. H Yu. had was a consultant with Blueprint Medicines Corporation, Black Diamond, Daiichi, Janssen, AstraZeneca, C4 therapeutics, Cullinan; institutional research funding to from Pfizer, AstraZeneca, Novartis, Daiichi, Cullinan, Janssen, and ERASCA. L Sun had nothing to declare. D Nguyen had an immediate family member with stock and/or other ownership interests in Intuitive Surgical and Teledoc, and has other relationships with Takeda. P Pearson, J Shim-Lopez, and D Hausman are former employees of Lengo Therapeutics, a wholly-owned subsidiary of Blueprint Medicines Corporation, and are consultants to Blueprint Medicines Corporation. X Le has received consulting/advisory fees from EMD Serono (Merck KGaA), AstraZeneca, Spectrum Pharmaceutics, Novartis, Eli Lilly, Boehringer Ingelheim, Hengrui Therapeutics, Janssen, and AbbVie; and research funding from Eli Lilly, EMD Serono, Regeneron, and Boehringer Ingelheim.

Poster available for download at:

Presented at ASCO Annual Meeting, June 3–7, 2022