

# 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

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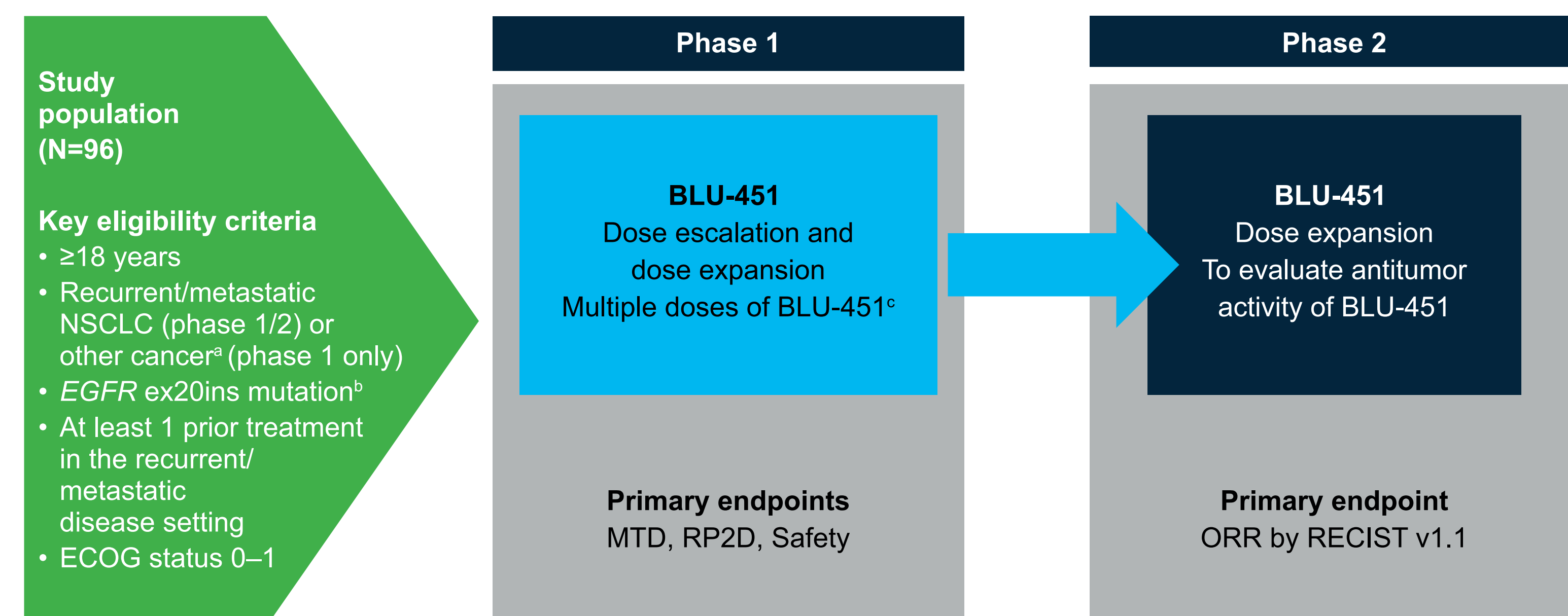
## Background

- 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<sup>1-3</sup>
- 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<sup>4,5</sup>
- 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<sup>6</sup>
- 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<sup>7,8</sup>
- 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<sup>9,10</sup>
- 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,<sup>11</sup> 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



<sup>a</sup>Any other cancer except primary CNS tumor. <sup>b</sup>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. <sup>c</sup>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
<ul style="list-style-type: none"> <li>Males and females ≥18 years of age</li> <li>ECOG performance status 0–1</li> <li>Histologically or cytologically confirmed metastatic NSCLC (phase 1 and phase 2) or other cancer except for primary CNS tumors (phase 1 only)</li> <li>Documented <i>EGFR</i> ex20ins mutation based on NGS testing of tumor or liquid biopsy<sup>a</sup></li> <li>Prior treatment in the recurrent/metastatic disease setting:               <ul style="list-style-type: none"> <li>Phase 1 patients with NSCLC: platinum-based chemotherapy,<sup>b</sup> at least one prior <i>EGFR</i> ex20ins targeted therapy (amivantamab or mobocertinib),<sup>c</sup> prior ICI<sup>c</sup></li> <li>Phase 1 other cancers: any approved standard therapy</li> <li>Phase 2: platinum-based chemotherapy,<sup>b</sup> prior ICI.<sup>c</sup> In addition;                   <ul style="list-style-type: none"> <li>Cohort 2A - one prior <i>EGFR</i> ex20ins targeted therapy including amivantamab or mobocertinib required</li> <li>Cohort 2B - no prior <i>EGFR</i> ex20ins targeted therapy</li> <li>Cohort 2C - prior treatment with up to 1 line of <i>EGFR</i> ex20ins targeted therapy<sup>c</sup></li> </ul> </li> </ul> </li> <li>Brain metastases not associated with progressive neurological symptoms and not requiring increasing doses of corticosteroids<sup>c,d</sup></li> <li>Disease progression on or after or intolerance to most recent systemic therapy</li> <li>Evaluable disease (phase 1 only) or measurable disease (phase 1 and phase 2) per RECIST v1.1</li> </ul>	<ul style="list-style-type: none"> <li>Tumor harboring known alternate driver alteration (<i>ROS</i>, <i>BRAF</i> V600E, <i>ALK</i>, <i>RET</i>, <i>HER2</i>, <i>MET</i>, <i>KRAS</i>, <i>NTRK1/2/3</i>, or <i>EGFR</i> C797X<sup>e</sup>)</li> <li>Prior <i>EGFR</i> 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</li> <li>Symptomatic brain metastases, any lesion in an anatomic location thought to require immediate treatment, any lesion &gt; 2 cm in size unless specifically approved by the Sponsor Medical Monitor, radiation treatment for brain metastases &lt; 28 days prior to first dose of study drug, or brain metastases that require increasing doses of corticosteroids</li> <li>Leptomeningeal disease</li> <li>Intracranial hemorrhage within 28 days prior to the first dose</li> </ul>

<sup>a</sup>Performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or equivalent. <sup>b</sup>Other chemotherapy if platinum-based is contraindicated. <sup>c</sup>Allowed but not required. <sup>d</sup>In cohort 2C, patients are required to have ≥1 measurable brain lesion per RECIST 1.1. <sup>e</sup>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

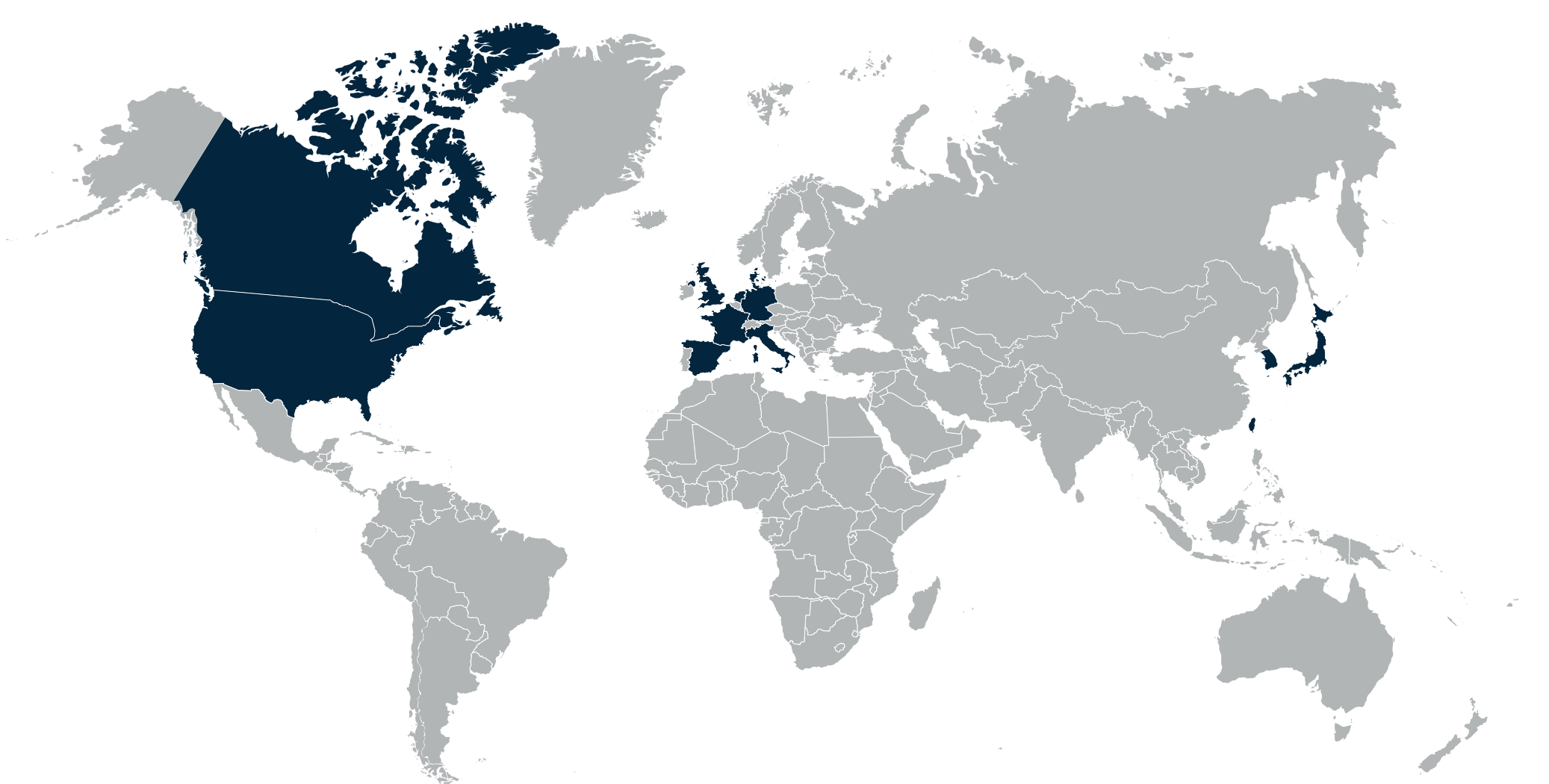
Phase 1	Phase 2
<ul style="list-style-type: none"> <li><b>Primary endpoints</b> <ul style="list-style-type: none"> <li>Maximum tolerated dose</li> <li>Recommended phase 2 dose on DLTs<sup>a</sup></li> <li>Safety and tolerability</li> </ul> </li> <li><b>Secondary endpoints</b> <ul style="list-style-type: none"> <li>Antitumor activity using RECIST v1.1               <ul style="list-style-type: none"> <li>Objective response rate</li> <li>Duration of response</li> <li>Disease control rate</li> <li>Clinical benefit rate</li> <li>Progression-free survival</li> <li>Overall survival</li> </ul> </li> <li>CNS antitumor activity using RECIST v1.1<sup>b</sup> <ul style="list-style-type: none"> <li>CNS objective response rate</li> <li>CNS duration of response</li> <li>CNS progression-free survival</li> </ul> </li> <li>Pharmacokinetics</li> </ul> </li></ul>	<ul style="list-style-type: none"> <li><b>Primary endpoint</b> <ul style="list-style-type: none"> <li>Objective response rate at RP2D using RECIST v1.1</li> </ul> </li> <li><b>Secondary endpoints</b> <ul style="list-style-type: none"> <li>Additional measures of anti-tumor activity               <ul style="list-style-type: none"> <li>Duration of response</li> <li>Disease control rate</li> <li>Clinical benefit rate</li> <li>Progression-free survival</li> <li>Overall survival</li> </ul> </li> <li>CNS antitumor activity using RECIST v1.1<sup>a</sup> <ul style="list-style-type: none"> <li>CNS objective response rate</li> <li>CNS duration of response</li> <li>CNS progression-free survival</li> </ul> </li> <li>Pharmacokinetics</li> <li>Safety and tolerability</li> </ul> </li></ul>

<sup>a</sup>The DLT evaluation window is 28 days (within the first 28 days of taking BLU-451) even if the cycles are 21 day. <sup>b</sup>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



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