**Background**

- Cyclins are regulatory proteins that, when paired with cyclin-dependent kinases (CDKs), are essential for the regulation of cell growth and proliferation.
- The formation of the cyclin CDK4/6 complex increases the expression of cyclin E and E2F, which bind and activate CDKs, leading to cell cycle progression.
- A broad range of aggressive cancers overexpress and/or harbor CCNE1 gene amplifications encoding Cyclin E1.
- The use of CDK inhibitors such as palbociclib or ribociclib is an effective treatment in patients with hormone receptor-positive (HR+), human epithelial growth factor receptor 2-negative (HER2-) breast cancer; however, resistance to treatment eventually occurs.

**Key exclusion criteria**

- In Phase 1 Part 1A, BLU-222 monotherapy will be administered as a twice-daily or once-daily (QD) dosing regimen.
- Patients with previous CDK2, PKMYT1, or WEE1 inhibitor therapy (10 patients permitted in each group).
- Patients with any immunotherapy/antibody therapy <28 days prior to the first dose of BLU-222.
- Any patient with a history of prolonged QT syndrome.
- Defined as progression during or <4 weeks of first-line platinum-based chemotherapy.
- Patients with prior PKMYT1 or WEE1 inhibitors.
- Patients with PIK3CA mutations are not eligible.
- Patients with platinum-resistant/refractory OC; BC, BOIN, CCNE1 amplification with second line progression; advanced endometrial cancer; advanced GC or EC.

**Study objectives and design**

- **V-ELA (NCT03271218)** is an international, open-label, first-in-Human phase 1/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BLU-222 in adult patients with solid tumor malignancies, with planned dose escalation in adult patients with CCNE1-amplified or HER2-positive breast cancer with disease progression on previous CDK4/6i therapy.

**Key inclusion criteria**

- **Phase 1:**
  - Pathologically confirmed non-small cell advanced solid tumor.
  - Within 180 days of disease progression from prior systemic therapy.
  - Any systemic or intramuscular fulvestrant or intravenous or intramuscular chemotherapy within 14 days prior to the first dose of BLU-222.
  - Any prior CDK1 or CDK5 inhibitor.
  - One or two prior systemic regimens.
  - Measurable, non-visceral, non-osteolytic, non-leptomeningeal, non-lymphangitic, non-lung, non-cerebral, non-lymphoid tumors.
  - Requires that a tumor tissue sample is available for CCNE1 IHC and/or CCNE1 gene amplification with prior ADR/other agents.

- **Phase 2:**
  - Patients must complete phase 1 (continuous treatment allowed).
  - Patients must complete phase 1 without dose reduction.
  - Patients must remain on the same approved regimens.

**Key exclusion criteria**

- **Phase 1:**
  - Pathologically confirmed non-recombinant advanced solid tumor.
  - Any prior systemic or intramuscular fulvestrant or intravenous or intramuscular chemotherapy within 14 days prior to the first dose of BLU-222.
  - Any prior CDK1 or CDK5 inhibitor.
  - One or two prior systemic regimens.
  - Measurable, non-visceral, non-osteolytic, non-leptomeningeal, non-lymphangitic, non-lung, non-cerebral, non-lymphoid tumors.
  - Requires that a tumor tissue sample is available for CCNE1 IHC and/or CCNE1 gene amplification with prior ADR/other agents.

- **Phase 2:**
  - Patients must complete phase 1 (continuous treatment allowed).
  - Patients must complete phase 1 without dose reduction.
  - Patients must remain on the same approved regimens.

**Summary of key inclusion and exclusion criteria**

- **Key inclusion criteria:**
  - Patients must be aged ≥18 years.
  - Histologically confirmed, non-small cell advanced solid tumor.
  - Within 180 days of disease progression from prior systemic therapy.
  - Any systemic or intramuscular fulvestrant or intravenous or intramuscular chemotherapy within 14 days prior to the first dose of BLU-222.
  - Any prior CDK1 or CDK5 inhibitor.
  - One or two prior systemic regimens.
  - Measurable, non-visceral, non-osteolytic, non-leptomeningeal, non-lymphangitic, non-lung, non-cerebral, non-lymphoid tumors.

- **Key exclusion criteria:**
  - Patients with prior PKMYT1 or WEE1 inhibitors.
  - Patients with PIK3CA mutations are not eligible.
  - Patients with platinum-resistant/refractory OC; BC, BOIN, CCNE1 amplification with second line progression; advanced endometrial cancer; advanced GC or EC.

**Primary endpoints**

- In Phase 1 dose escalation, Part 1B does not exist.
- In Part 1C, the first cohort will receive BLU-222 at 80% of the median dose RP2D (or if the RP2D is not yet determined, at ≤75% of the highest median dose dose range safe for further escalation) in combination with carboplatin at a stable dose and fixed schedule.
- In Part 1D, the first cohort will receive BLU-222 at ≤75% of the median dose RP2D (or if the RP2D is not yet determined, at ≤75% of the highest median dose dose range safe for further escalation) in combination with ribociclib at approved doses (450 mg or 500 mg). Not solely visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.
- Visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis.

**Secondary endpoints**

- Time to progression
- Progression-free survival
- Overall survival
- Safety and tolerability
- Pharmacokinetics
- Serum lactate dehydrogenase (LDH) levels
- Pharmacodynamic assessment of CDK2 and CDK5 activities
- Safety and tolerability

**Key end points**

**Phase 1**

- **Primary endpoints:**
  - Maximum tolerated dose (MTD) and maximum observed toxicity (MOT).
  - Safety and tolerability.

- **Secondary endpoints:**
  - Pharmacokinetics
  - Serum lactate dehydrogenase (LDH) levels
  - Pharmacodynamic assessment of CDK2 and CDK5 activities
  - Safety and tolerability

**Phase 2**

- **Primary endpoints:**
  - Overall response rate (ORR; RECIST v1.1).
  - Progression-free survival
  - Overall survival
  - C0-A response

- **Secondary endpoints:**
  - PFS
  - OS
  - DCR
  - Safety and tolerability

**Conclusions**

- In Phase 1 dose escalation portion of the study is ongoing.
- The study is planned for approximately 50 sites in North America, Europe, and Asia/Pacific region.

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**References**


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