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A first-in-human phase 1/2 study of BLU-222, a potent, selective CDK2 inhibitor in patients with *CCNE1*-amplified or CDK4/6 inhibitor-resistant advanced solid tumors

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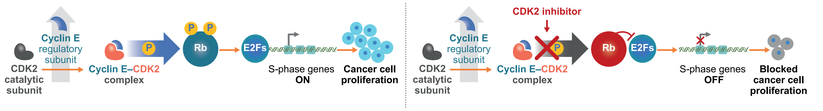
Background

- Cyclins are regulatory proteins that, when partnered with cyclin dependent kinases (CDKs), are essential for the regulation of cell growth and proliferation[1]
- The formation of the cyclin D-CDK4/6 complex increases the expression of cyclin E1 and E2. Cyclin E1 and E2 bind to and activate CDK2; this results in a cyclin E-CDK2 complex that assists with downstream expression of DNA synthesis machinery[1,2]
- A broad range of aggressive cancers overexpress and/or harbor *CCNE* gene amplifications encoding Cyclin E[3]
- The use of CDK4/6 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[4,5]
- Aberrant cyclin E-CDK2 activity has been identified as a potential resistance mechanism to CDK4/6 inhibitors and represents a viable therapeutic target (**Figure 1**)[5]
- BLU-222 is an oral, investigational, potent, and selective CDK2 inhibitor
- Preclinically, BLU-222 has shown potent CDK2 inhibition and antitumor activity, and in combination with carboplatin/paclitaxel led to significant tumor regression

Figure 1: Cyclin E-CDK2 is a viable therapeutic target in *CCNE1*-amplified solid tumors



Study objectives and design

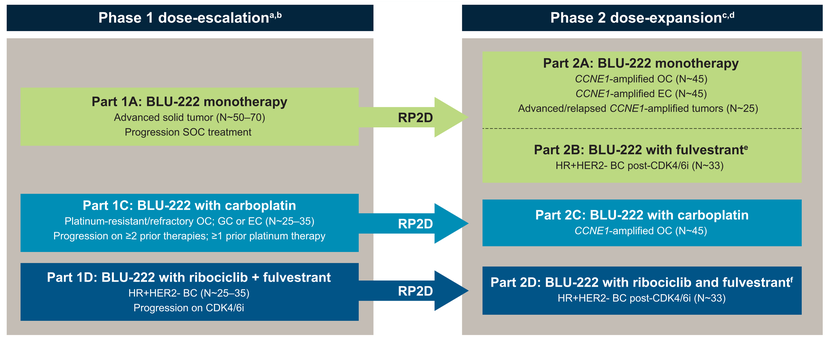
- VELA (NCT05252416) is an international, open-label, first-in-human phase 1/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BLU-222 in adult patients with advanced solid tumors, with planned dose expansion in adult patients with *CCNE1*-amplified tumors or HR+HER2- breast cancer with disease progression on CDK4/6 inhibitors (**Figure 2**)

Summary of key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• ≥18 years of age • ECOG performance status 0–2 • **Phase 1:** – ***Part 1A:*** Pathologically confirmed non-resectable advanced solid tumor with progression following SOC – ***Part 1C:*** Platinum-resistant/refractory ovarian cancer; gastric cancer or endometrial cancer with progression on ≥2 prior therapies (including ≥1 prior platinum therapy) – ***Part 1D:*** HR+HER2- breast cancer that has progressed following treatment with a CDK4/6i and able to receive intramuscular fulvestrant • **Phase 2:** – ≥1 measurable target lesion per RECIST v1.1 per investigator – ***Part 2A:*** Platinum-resistant[a] or platinum-refractory[b] advanced ovarian cancer with *CCNE1* amplification; advanced endometrial cancer with *CCNE1* amplification with second line progression; advanced solid tumor with *CCNE1* amplification with progression after SOC and other therapies[c] – ***Part 2B*** and ***2D:*** CDK4/6i-resistant HR+HER2- breast cancer; CDK4/6i as part of most recent therapy; patients with PIK3CA mutations are eligible for enrollment but will be capped at 30% of the entire population (Part 2B) or group (Part 2D); in Part 2D, patients must be able to receive intramuscular fulvestrant – ***Part 2C:*** Platinum-resistant[a] or platinum-refractory[b] advanced ovarian cancer with *CCNE1* amplification	• Disease that is suitable for local therapy administered with curative intent • Visceral crisis[d], lymphangitic spread, or leptomeningeal carcinomatosis • Received the following anticancer therapy: – Previous CDK2, PKMYT1, or WEE1 inhibitor (10 patients permitted in Part 1A with prior PKMYT1 or WEE1 inhibitors) – Any immunotherapy/antibody therapy <28 days prior to the first dose of study drug – Any other systemic anticancer therapy <14 days or 5 half-lives prior to the first dose of study drug, whichever is the shortest[e] – 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[f] • Known intracranial hemorrhage and/or bleeding diatheses • Clinically active ongoing ILD of any etiology[f] • Unresolved toxicities from prior therapy greater than CTCAE Grade 1 or that have not resolved to baseline at the time of starting the study • Cardiovascular disease[g] with/without a mean resting QTcF>450 msec, a history of prolonged QT syndrome or Torsades de pointes, or a familial history of prolonged QT syndrome • Inadequate end organ function based on safety laboratory assessments • Received neutrophil or platelet growth factor support, blood transfusions, or erythroid stimulating agent <14 days of the first dose of study drug (phase 1)

[a]Defined as relapse <6 months after first-line platinum-based chemotherapy. [b]Defined as progression during or <4 weeks of first-line platinum-based chemotherapy. [c]Prior treatment is appropriate for the tumor type and patients within this group are not eligible for any of the other groups. [d]Not solely visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease. [e]≥7 days in all circumstances. [f]Includes drug-induced ILD, and radiation pneumonitis <28 days prior to initiation of study treatment. [g]Includes congestive heart failure Grade III or IV according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmia that may cause QT prolongation.
CCNE1, cyclin E1; CDK, cyclin-dependent kinase; CDK4/6i, CDK4/6 inhibitors; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HER2-, human epithelial growth factor receptor-2; HR+, hormone receptor-positive; ILD, interstitial lung disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PKMYT1, protein kinase membrane associated tyrosine/threonine 1; QTcF, QT interval corrected for heart rate using Fridericia's formula; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.

Figure 2: Study design



[a]Based on BOIN escalation design. [b]In Phase 1 dose escalation, Part 1B does not exist. [c]Phase 2 will be initiated upon determination of RP2D. [d]Phase 2 groups will be treated with BLU-222 at the RP2D for BLU-222 monotherapy in Part 2A and Part 2B, RP2D for BLU-222 and carboplatin in Part 2C, and RP2D for BLU-222 and ribociclib in Part 2D. In the combination therapy arms (Parts 2B, 2C, 2D), the dose of BLU-222 will not exceed that of the monotherapy BLU-222 RP2D. [e]For Part 2B, fulvestrant will be administered in accordance with local prescribing information and institutional standards. [f]For Part 2D, ribociclib and fulvestrant will be administered in accordance with local prescribing information and institutional standards, at the dose level determined for the specific dose-escalation cohort.
BC, breast cancer; BOIN, Bayesian Optimal Interval; CCNE1, cyclin E1; CDK, cyclin-dependent kinase; CDK4/6i, CDK4/6 inhibitors; EC, endometrial cancer; GC, gastric cancer; HER2-, human epithelial growth factor receptor-2 negative; HR+, hormone receptor-positive; OC, ovarian cancer; RP2D, recommended phase 2 dose; SOC, standard of care.

- The phase 1 dose-escalation part of this study is being conducted using a Bayesian optimal interval design to determine the maximum tolerated dose, recommended phase 2 dose (RP2D), and safety of BLU-222 monotherapy and in combination with either carboplatin or ribociclib and fulvestrant
  - In Phase 1 Part 1A, BLU-222 monotherapy will be administered as a twice-daily or once-daily (QD) dosing regimen
  - In Part 1C, the initial cohort will receive BLU-222 at no higher than 50% of the monotherapy RP2D (or, if the RP2D is not yet determined, at ~25% of the highest monotherapy dose deemed safe for further escalation), in combination with carboplatin at a starting dose of area under the curve 4 mg/mL·min intravenous once on Day 1 of each 28-day cycle
  - In Part 1D, the initial cohort will receive BLU-222 at ~25% of the monotherapy RP2D (or, if the RP2D is not yet determined, at ~25% of the highest monotherapy dose deemed safe for further escalation) in combination with ribociclib at approved doses (400 mg or 600 mg if tolerable, orally QD) and fulvestrant at the approved dose (500 mg)
- Phase 2 dose expansion will initiate upon determination of the RP2D and will further assess the activity, safety and efficacy of BLU-222 monotherapy or in combination at the RP2D in specific patient populations
- Intrapatient dose escalation may be permitted after a patient has completed ≥8 weeks of treatment with no Grade >2 adverse events during the previous treatment cycle
- Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met

Key study endpoints

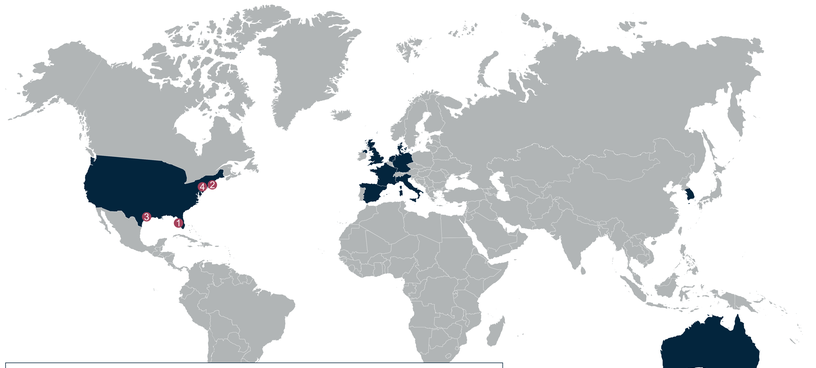
Phase 1	Phase 2
• **Primary endpoints** – Maximum tolerated dose[a] – Recommended phase 2 dose[b] – Safety and tolerability	• **Primary endpoints** – Overall response rate (RECIST v1.1) – Safety and tolerability
• **Secondary endpoints** – Overall response rate (RECIST v1.1) – Duration of response – Disease control rate – Clinical benefit rate – Pharmacokinetics and pharmacodynamics – CA-125 response (GCIG criteria)	• **Secondary endpoints** – Duration of response – Disease control rate – Clinical benefit rate – Progression-free survival – Overall survival – CA-125 response (GCIG criteria)

[a]Based on dose-limiting toxicities. [b]Based on dose-limiting toxicities, pharmacokinetics, pharmacodynamics, and preliminary safety data.
CGIG, The Gynecological Cancer Intergroup; 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 (**Figure 3**)
- The study is planned for approximately 50 sites in North America, Europe, and the Asia/Pacific region

Figure 3: Study locations



Sites currently recruiting

1. Florida Cancer Specialists, Sarasota, FL, USA, 34232.
2. Massachusetts General Hospital, Boston, MA, USA, 02114.
3. MD Anderson Cancer Center, Houston, TX, USA, 77030.
4. Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA, 10032.

Anticipated study regions

For up-to-date information on currently active recruitment sites please visit:
https://clinicaltrials.gov/ct2/show/NCT05252416

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Disclosures

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