BLU-222, an oral, potent and selective CDK2 inhibitor, in patients with advanced solid tumors: phase 1 monotherapy dose escalation

Poster 293

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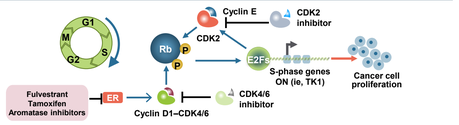
Introduction

- Cyclin-dependent kinase (CDK) 4/6 inhibitors (CDK4/6i) have transformed the treatment of hormone receptor–positive (HR+)/human epidermal growth factor receptor-2–negative (HER2−) breast cancer; however, resistance inevitably develops
- Aberrant activation of CDK2/cyclin E complex and the resultant induction of DNA synthesis and cell cycle progression is a key resistance mechanism by which tumors evade CDK4/6 blockade (**Figure 1**)[1–3]
- A broad range of aggressive cancers overexpress cyclin E and/or harbor cyclin E1 (*CCNE1*) gene amplifications, which is one important mechanism that can activate CDK2 and confer sensitivity to inhibition or loss of CDK2[4,5]
- CDK2 inhibition represents a promising, novel therapeutic approach to treat or prevent CDK4/6i resistance in HR+/HER2− breast cancer, particularly in combination with CDK4/6i and/or endocrine therapy, and to treat *CCNE1*-aberrant cancers alone or in combination with standard of care treatment[1,6]
- BLU-222 is an investigational, oral, potent, and selective CDK2 inhibitor in early clinical development with best-in-class potential
- Here, we present the first clinical data from the dose-escalation part of the ongoing VELA study assessing BLU-222 monotherapy in heavily pretreated patients with advanced solid tumors

Figure 1: CDK2-cyclin E plays a central role in cell cycle progression and resistance to CDK4/6 inhibitors, and in *CCNE1*-abberant cancers

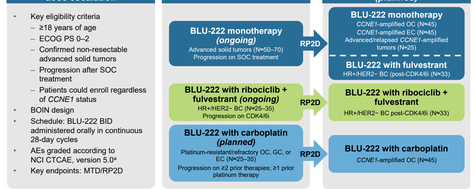


CCNE, cyclin E; CDK, cyclin-dependent kinase; ER, estrogen receptor; P, phosphorylation; Rb, retinoblastoma protein; TK1, thymidine kinase 1.

Methods

- VELA (NCT05252416) is an international, open-label, first-in-human, phase 1/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of BLU-222 in adult patients with advanced solid tumors (**Figure 2**)

Figure 2: Study design



[a]DLT was defined as any TEAE of Grade ≥3 occurring within Cycle 1 (28 days) for patients in the dose-escalation phase 1 that is not clearly caused by underlying disease or intercurrent illness. Patients who experienced a DLT or received ≥75% of the prescribed BLU-222 dose (21 days) and completed the 28-day DLT evaluation period were evaluable for DLT assessment. MTD may be identified based on the safety and tolerability observed during the first 28-day treatment cycle.

AE, adverse event; BC, breast cancer; BID, twice daily; BOIN, Bayesian Optimal Interval; CCNE1, cyclin E1; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DLT, dose-limiting toxicity; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; HR+, hormone receptor positive; HER2−, human epidermal growth factor receptor 2 negative; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; MTD, maximum tolerated dose; OC, ovarian cancer; RP2D, recommended phase 2 dose; SOC, standard of care.

Key assessments (phase 1)

- Recommended phase 2 dose (RP2D) of BLU-222 as monotherapy and in combination with ribociclib and fulvestrant or carboplatin
- Plasma BLU-222 concentrations and biomarker assessments, including circulating tumor DNA and serum thymidine kinase 1 (TK1) activity (proliferation marker and downstream target of pRb-E2F pathway)[7]
- Tumor tissue to assess treatment-induced modulation of key CCNE/CDK2 pathway biomarkers including pRb, the immediate downstream target of CDK2[8]
- Disease response assessment (per Response Evaluation Criteria in Solid Tumors version 1.1)

Results

- As of April 25, 2023, 27 patients were enrolled in 6 escalating-dose cohorts (50–800 mg) of BLU-222 monotherapy administered twice daily (BID) and included in the safety population
- Baseline characteristics are shown in **Table 1**
- Patients were heavily pretreated, with most patients (77.8%) having received ≥4 lines of prior therapy

Table 1: Demographics and baseline characteristics

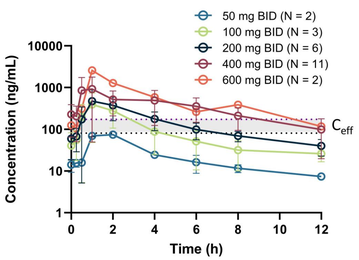
	Safety population (N=27)
Age, years, median (min, max)	64.0 (29, 85)
Age group, years, n (%)	
<65	14 (51.9)
≥65	13 (48.1)
Sex, n (%)	
Female	23 (85.2)
ECOG PS, n (%)	
0	12 (44.4)
1	14 (51.9)
2	1 (3.7)
Tumor type, n (%)	
Breast	13 (48.1)
Endometrial	4 (14.8)
Ovarian	3 (11.1)
Other[a]	7 (25.9)
Number of regimens of prior anticancer therapy, median (min, max)	5 (1, 10)

[a]Other cancers included prostate (n=3) and pancreatic, hepatocellular carcinoma, uterine, and chondroblastic osteosarcoma in 1 patient each.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Pharmacokinetics

- BLU-222 plasma concentrations increased proportionally up to 600 mg BID (**Figure 3**)
- The average effective half-life was 12 hours (calculated from the extent of accumulation)
- Effective concentrations (C_{eff}) range represents effective BLU-222 monotherapy concentrations that lead to tumor stasis in preclinical OVCAR-3, MKN-1, and T47D models, and corresponds to 25%, 25%, and 60% inhibition of pRb S807/811 in these models, respectively

Figure 3: Plasma concentration-time profiles after multiple oral administrations of BLU-222 given BID



Safety of BLU-222 monotherapy

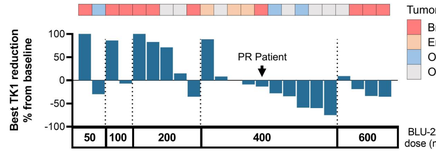
- BLU-222 monotherapy has been generally well tolerated to date; maximum tolerated dose has not been identified; dose escalation is ongoing. The most frequent reported treatment-related adverse events (AE) are shown in **Table 3**
- No patients discontinued study treatment due to AEs
- Two patients experience dose-limiting toxicities (DLT); both improved after dose reduction:
  - Grade 3 nausea in 1 patient at 800 mg BID
  - Grade 3 blurred vision/photophobia in 1 patient at 600 mg BID
- No cardiac AEs or QTc prolongation observed
- Treatment-related hematologic AEs were generally mild and primarily seen in patients with a history of, and/or baseline cytopenias:
  - 1 patient at 800 mg BID had Grade 3 thrombocytopenia and Grade 2 anemia; both improved after dose reduction for nausea
  - 1 patient at 50 mg BID had Grade 2 anemia and Grade 2 neutropenia that stabilized without dose reduction
  - 5 other patients had Grade 1–2 anemia; all remained stable without dose reduction
- Transient visual AEs were reported in 5 (18.5%) patients (some experienced >1): vision blurred (11.1% [3/27]), photophobia (7.4% [2/27]), and change in color perception (7.4% [2/27]); all were transient and reversible
  - Symptoms were mild except in 1 patient with Grade 3 blurred vision and photophobia (DLT)
  - All events were intermittent (intervals were seconds to hours), occurred shortly after dosing, and then fully resolved (either spontaneously or after dose interruption/reduction)
  - Comprehensive ophthalmologic examination, including optical coherence tomography was unremarkable in all patients, with no treatment-emergent abnormal findings

Table 3: Treatment-related adverse events (TRAE)

Preferred term, n (%)	Safety population (N=27)	
	Any grade	Grade ≥3
Any TRAEs	17 (63.0)	5 (18.5)
TRAEs reported in ≥10%		
Diarrhea	11 (40.7)	2 (7.4)
Nausea	8 (29.6)	1 (3.7)
Fatigue	7 (25.9)	0
Anemia	6 (22.2)	0
Vision blurred	3 (11.1)	1 (3.7)
Vomiting	3 (11.1)	0

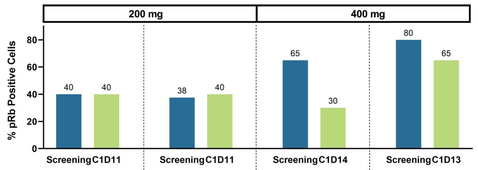
Pharmacodynamics

Figure 4: Dose-dependent serum TK1 responses in patients treated with escalating doses of BLU-222 monotherapy by dose cohort



BID, twice daily.
Patients who were off treatment at the time of sampling (n=3) or who were missing a baseline sample (n=1) were excluded.
[a]Other tumor types include prostate, pancreatic, hepatocellular carcinoma, and osteosarcoma.

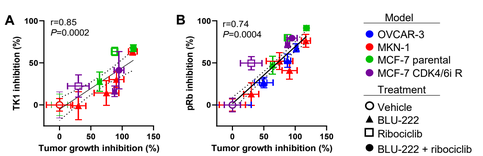
Figure 5: Percentage of pRb-positive cells in tumor biopsies from patients at baseline and on BLU-222 treatment



	Patient 1	Patient 2	Patient 3	Patient 4
Time post dose	6 h	3 h	3 h	12 h*
% pRb change	0%	+14%	-54%	-19%
Tumor type	Breast	Breast	Prostate	Breast

C, cycle; D, day; PR, partial response.

Figure 6: Preclinical tumor growth inhibition correlates with pathway modulation measured by (A) TK1 inhibition and (B) pRb inhibition



CDK4/6i R, cyclin-dependent kinase 4/6 inhibitor resistant; pRb, phosphorylated retinoblastoma; TK1, thymidine kinase 1.

- In patients treated with BLU-222 monotherapy, reductions in TK1 activity were observed at higher study dose levels (**Figure 4**)
- Reduction in pRb was seen in 2 patients treated with BLU-222 at 400 mg BID (**Figure 5**)
- The on-treatment tumor biopsy for Patient 4* (with a PR described in patient vignette) very likely underestimates the extent of pRb inhibition, as the biopsy occurred late (12 hours after the most recent BLU-222 dose), and pRb has been shown to recover with time
- Preclinical tumor growth inhibition correlates with TK1 (**Figure 6A**) and pRb S807/811 inhibition (**Figure 6B**) in *CCNE1*-amplified (OVCAR-3 and MKN-1) and breast cancer (MCF-7) xenograft models treated with BLU-222, ribociclib, or the combination[9]

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Preliminary efficacy of BLU-222 monotherapy

Patient vignette (Patient 4 in Figure 5): partial response (PR)

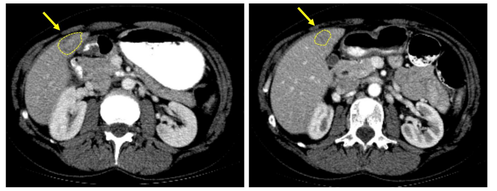
57-year-old female with metastatic HR+/HER2− breast cancer (liver and bone) treated with 5 prior lines of therapy, including 2 prior CDK4/6i:

- Doxorubicin + cyclophosphamide + paclitaxel, tamoxifen, **palbociclib** + fulvestrant, **abemaciclib** + anastrozole, capecitabine

Course of treatment with BLU-222

- Initiated BLU-222 at 800 mg BID × 4 days; dose reduced to 400 mg BID on Cycle 1, Day 8
- Grade 3 nausea (DLT) improved after dose reduction
- 43% decrease in liver lesion after 2 cycles (PR); PR confirmed after 4 cycles (**Figure 7**)

Figure 7: Partial response to BLU-222 monotherapy in target liver lesion in a patient with HR+/HER2− metastatic breast cancer



Baseline Week 8

Conclusions

- Escalating monotherapy doses of BLU-222, a potent and selective CDK2 inhibitor, were generally well tolerated in an unselected population of heavily pretreated patients with advanced cancer
- Antitumor activity of BLU-222 monotherapy in a heavily pretreated patient with HR+/HER2− metastatic breast cancer demonstrates potential for BLU-222 to improve outcomes for patients with cancers vulnerable to CDK2 inhibition
- Increasing doses of BLU-222 monotherapy were associated with reductions in TK1 activity and pRb, providing preliminary evidence of cell cycle pathway modulation
- Monotherapy dose escalation is ongoing to determine the RP2D, with an eye toward BLU-222 combinations; enrollment has begun in the BLU-222 + ribociclib + fulvestrant HR+/HER2− breast cancer dose escalation cohort
- BLU-222 monotherapy safety and emerging evidence of pathway modulation and clinical activity in breast cancer illustrates therapeutic promise and potential for combination therapy of BLU-222 in *CCNE1*-aberrant cancers and HR+/HER2− metastatic breast cancer

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