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

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Background: CDK inhibitors are in development for cancers depending on cell cycle pathway modulation and clinical activity in breast cancer. Here, we report on the phase 1 monotherapy (M) safety and tolerability of BLU-222 at dose levels up to and including 600 mg twice daily (BID) in patients with advanced solid tumors. We also present data supporting the clinical activity of BLU-222 in combination with fulvestrant with or without ribociclib.

Methods: This was a single-arm, open-label, dose escalation study in patients with advanced solid tumors (N = 35). Eligible patients were aged 18 years or older with metastatic breast cancer at risk of disease progression, with or without visceral metastasis. The dose-escalation strategy was based on a broken line design. After an initial cohort of 6 patients treated at 100 mg BID, additional patients were treated in 3 patient cohorts (cohorts 2–4) at escalating dose levels (200 mg, 400 mg, and 600 mg BID). Key eligibility criteria included a performance status of 0–1, an ECOG PS of 0, a known or concurrent primary malignancy that had been treated, and no prior treatment with CDK4/6 inhibitors.

Safety and tolerability data were analyzed descriptively. Efficacy endpoints were collected for patients who received ≥1 dose of BLU-222. The primary safety endpoints were dose-limiting toxicities (DLTs) and other significant toxicities for 28 days following the last dose of BLU-222. The incidence of relevant pharmacokinetics was assessed in a subset of patients.

Results: As of April 26, 2023, 37 patients were enrolled and included in the safety analysis. The median age was 58 years, and 84% were women. Nineteen patients (51%) had breast cancer, 13 (35.1%) had chondroblastic osteosarcoma, 3 (8%) had endometrial cancer, 2 (5.4%) had ovarian cancer, and 2 (5.4%) had other cancers. The most common prior therapies were endocrine therapy, immunotherapy, and chemotherapy. The most frequent AEs were fatigue, diarrhea, hair color change, and constipation. The most frequent Grade 3 or 4 AEs were diarrhea (26.7%) and fatigue (18.1%). AEs grade 1 or 2 were reported in 86% of patients, and Grade 1 or 2 fatigue was reported in 40% of patients. AEs leading to discontinuation were reported in 3 patients. No treatment-related deaths occurred.

Conclusions: BLU-222 was well tolerated at doses of 400 mg and 600 mg BID. Of note, 1 patient with endometrial cancer experienced a complete response with a 10% target volume reduction in a pelvic lymph node. Tumors with 

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