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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Phase 1 Study of BXCL701, a Dipeptidyl Peptidase Inhibitor, in Relapsed/Refractory Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

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Background and Significance: BXCL701 is an oral small molecule inhibitor of dipeptidyl peptidases (DPP)-primarily DPP8/9-that has been extensively studied in humans with metastatic castration-resistant prostate cancer (both small cell neuroendocrine and adenocarcinoma), non-small cell lung cancer, melanoma, non-Hodgkin's lymphoma, and GI malignancies. Inhibition of DPP8/9 triggers the inflammasome to alert and prime immune cells, leading to induction of IL-18 and IL-1ß, bridging innate and adaptive immunity. Preclinical studies have demonstrated that BXCL701 may have direct induction of apoptosis in AML cells through activation of CARD8 and subsequent activation of inflammatory cytokines and Gasdermin D. Mouse model studies demonstrated a reduction in AML blasts and AML tumor size when treated with BXCL701. We hypothesize that BXCL701 can be safe and effective in patients with relapsed/refractory AML or patients with relapsed/refractory MDS with blasts ≥ 10%.

Study Design and Methods: This is a Phase 1 single center investigator-initiated trial of BXCL701 in patients with relapsed/refractory AML or relapsed/refractory MDS with blasts ≥10% (ClinicalTrials.gov Identifier: NCT05703542). In the lead-in stage, we will use a 3 + 3 design with 4 dose levels of BXCL701 (0.2 mg, 0.4 mg, 0.6 mg and 0.8 mg). Doses of BXCL701 will be given on Days 1-3, Days 8-10, Days 15-17, and Days 22-24 on a 28-day cycle. The primary objective is to evaluate the safety of BXCL701 in the AML or MDS with ≥ 10% blasts. Secondary objectives include determining the maximum tolerated dose or recommended phase 2 dose, pharmacokinetics, and to estimate response, duration of response and overall survival. Exploratory endpoints include: pharmacodynamic profiling, T-cell response, inhibitory effect on DPP8/9, and evaluation of potential biomarkers such as Copy Number Variants and mRNA levels of DPP8, DPP9, FAP, Caspase-1, Pro-caspase-1, NLRP1, and CARD8.

Major eligibility criteria include: ≥18 years of age, relapsed or refractory AML or relapsed or refractory MDS with ≥10%.refractory to at least 4 cycles of hypomethylating agent, ECOG performance status ≤2, adequate renal function (CrCl ≥30 mL/min), adequate liver function (total bilirubin ≤1.5 x ULN, ALT and AST ≤3 x ULN), WBC <25,000/µL on Day 1 Cycle 1 (hydroxyurea permitted), no symptomatic CNS disease, no active viral or bacterial infections, and >100 days from allogeneic bone marrow transplant with no active graft versus host disease. Patients on gliptin therapy are not permitted on the study due to drug interaction; patients are also excluded if they have a history of orthostatic hypotension or uncontrolled hypertension. There will be a second phase of the study that will evaluate BXCL701 in combination with a hypomethylating agent (decitabine or azacytidine) and venetoclax. Dose selection of BXCL701 in the combination stage will be based on the data from the single agent study.

Conclusion: The trial is currently open and continuing to enroll.

Disclosures Winer: *Abbvie:* Consultancy; *Curis Inc:* Consultancy. **Garcia:** *Genentech:* Consultancy, Research Funding; *Bristol Myers Squibb:* Consultancy; *Prelude:* Research Funding; *Pfizer:* Research Funding; *AstraZeneca:* Research Funding; *Astellas:* Consultancy; *AbbVie:* Consultancy, Research Funding; *New Wave:* Research Funding; *Servier:* Consultancy; *Gilead:* Consultancy. **Stone:** *Amgen:* Consultancy; *Takeda:* Other: DSMB; *BerGenBio:* Consultancy; *AvenCell:* Consultancy; *Lava Therapeutics:* Consultancy; *Ligand Pharma:* Consultancy; *Rigel:* Consultancy; *Kura One:* Consultancy; *Jazz:* Consultancy; *Cellular-*

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