(PF494) A FIRST-IN-HUMAN STUDY OF THE ORAL CLK INHIBITOR BH-30236 IN ADULTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA OR HIGHER-RISK MYELODYSPLASTIC SYNDROME: MONOTHERAPY AND VENETOCLAX COMBINATION

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Relapsed/refractory (R/R) acute myeloid leukemia (AML) and higher-risk myelodysplastic syndromes (HR-MDS) have limited options after intensive chemotherapy or hypomethylating agent/venetoclax-based (HMA/VEN) standard of care (SOC). Aberrant alternative splicing (AS) promotes leukemic survival and therapy resistance. CDC-like kinases (CLKs) regulate AS by modulating serine/arginine rich splicing factor phosphorylation leading to DNA repair and apoptosis pathway modulation. BH-30236 is an orally bioavailable, macrocyclic CLK inhibitor which shows activity in preclinical models including robust synergy with VEN. This is the initial clinical report of the first-in-human dose escalation study of BH-30236 in adults with R/R AML and HR-MDS as monotherapy or in combination with VEN.

Aims

(1) Evaluate safety/tolerability and identify recommended dose(s) for expansion of BH-30236; (2) Characterize single agent and combination pharmacokinetics (PK); (3) Assess preliminary anti-leukemic activity.

Methods

BH-30236-01 (NCT06501196) is an open-label phase 1/1b BOIN dose escalation/expansion study in adults with R/R AML or HR-MDS as monotherapy or in combination with VEN (≤ 5 prior lines; prior VEN allowed). BH-30236 is dosed orally once daily (QD) in continuous 28-day cycles. Combination cohorts add oral VEN (target dose 400mg QD, 15-28 days/cycle). Responses are assessed per 2022 ELN (AML) and 2023 IWG (MDS) criteria.

Results

As of 23 Jan 2026, 28 patients (23 AML; 5 HR-MDS) received BH-30236 at 5–120mg as monotherapy. Median age was 71 years (23-85); median 2 prior lines of therapy; 86% (24/28) had prior VEN; median duration of treatment 1.4 months (0.2-7.6). PK exposure increased with dose with no accumulation observed. BH-30236 was generally well tolerated up to 90mg as a continuous daily dose. One DLT of grade 3 diarrhea occurred at 120mg. Treatment-related AEs (TRAEs) occurred in 15/28 (53.6%) patients; mostly ≤ Grade 2, most commonly (≥10%) diarrhea, nausea and vomiting. Grade ≥3 TRAEs occurring in ≥10% included diarrhea. Two cases of possible differentiation syndrome were observed, both managed with corticosteroids and no dose interruption. Of 17 monotherapy patients with post-baseline marrow assessments, 5 (29%) had ≥50% blast count reduction during treatment, including one HR-MDS patient treated at 60mg with sustained blast count reduction with duration of treatment 7.6 months. 11 patients (9 AML; 2 HR-MDS) received BH-30236 at 20-60mg in combination with VEN. Median age was 61 years (range 27-80); median 3 prior lines of therapy; 91% (10/11) had prior VEN; median duration of treatment 1.9 months (0.4-2.9). No apparent drug interaction was observed between BH-30236 and VEN. TRAEs were consistent with a VEN-based regimen, occurring in 6/11 (54.5%) patients, most commonly (≥10%) decreased appetite, fatigue, neutrophil count decreased, platelet count decreased and white blood cell count decreased. Among 9 evaluable patients at 20-30mg, 5 (55%) had ≥50% blast count reduction during treatment including one AML patient refractory to all prior therapy including VEN achieving MRD-negative complete response (CR) and coming off study to undergo transplant.

Summary/Conclusion

BH-30236 is the first CLK inhibitor to demonstrate tolerability with once daily dosing and in combination with VEN. Preliminary anti-leukemic activity includes a CR observed early in VEN combination dose escalation, which is ongoing in the US and aiming to further validate the preclinical synergy seen with VEN.