(PF507) RESULTS FROM THE PHASE 1 MONOTHERAPY DOSE ESCALATION OF APL-4098, AN ORAL GCN2 INHIBITOR, IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML) AND MYELODYSPLASTIC SYNDROMES (MDS)/AML PATIENTS

Topic: 04. Acute myeloid leukemia - Clinical

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Background

There remains an unmet medical need for new effective therapies to manage R/R AML and MDS/AML. General control nondepressible 2 (GCN2) is an evolutionarily conserved kinase and a pivotal regulator of the integrated stress response (ISR). Activation of GCN2 in response to amino acid deprivation results in the attenuation of global protein synthesis and an orchestrated transcriptional rescue response. GCN2 activation is a mechanism by which tumor cells, including leukemic cells, can survive under nutrient stress. GCN2 inhibitors may thus represent a novel class of therapeutic agents with anti-leukemic activity. APL-4098 is a potent small molecule inhibitor of GCN2. APL-4098 inhibits AML leukemic cell viability *ex vivo* and reduces AML tumor burden in non-clinical *in vivo* models where APL-4098 depletes AML patient-derived (PDX) leukemic stem cells (LSCs) and acts synergistically with the BCL-2 inhibitor venetoclax.

Aims

The purpose of this Phase 1 study (NCT06372717) was to establish the Recommended Phase 2 Dose (RP2D) for APL-4098. Additional objectives included assessment of preliminary efficacy and pharmacodynamics (PD) of APL-4098.

Methods

The study included APL-4098 dose escalation as monotherapy. Dose escalation was performed initially using an Accelerated Titration Design (ATD) and then the Bayesian Optimal Interval (BOIN) design. The study enrolled patients with R/R AML and MDS/AML with no available therapies known to provide clinical benefit. APL-4098 was administered orally once daily in 28-day cycles until disease progression, unacceptable toxicity, or patient withdrawal from the study.

Results

28 patients have been treated with APL-4098 monotherapy across 5 dose levels ranging from 20 to 150 mg. The median age was 73 years (range: 37-84). 26 (93%) patients had R/R AML of which 21 (81%) had adverse genetics; 2 patients had MDS/AML. The median prior lines of therapy was 2 (range: 1-6). The median duration of treatment was 41 days (range: 9-165). APL-4098 was well tolerated up to 100 mg. Dose limiting toxicities (DLTs) of diarrhoea, nausea and a reversible increase in alanine aminotransferase levels (not associated with bilirubin increase) were observed in the 150 mg dose level in 2 patients. Treatment-emergent adverse events (TEAEs) have been predominantly grades 1 and 2. Most frequently observed TEAEs suspected to be related to APL-4098 include nausea (57% any grade; 21% grade 3) and diarrhoea (46% any grade; 14% grade 3). A reduction in AML blasts was observed in 8 of 19 evaluable patients. 7 of these had high risk cytogenetics including 2 with *TP53* mutations. 3 patients (including 2 with adverse cytogenetics) achieved >50% reduction in bone marrow blast count. The PK profile of APL-4098 showed linear and dose-proportional characteristics. An exposure-dependent induction in mRNA expression of CHAC-1, a pro-apoptotic stress response gene, was observed indicative of APL-4098 therapeutic activity.

Summary/Conclusion

APL-4098 is a potent, selective GCN2 inhibitor that has demonstrated excellent non-clinical potency and efficacy properties. Dose escalation of APL-4098 monotherapy in R/R AML and MDS/AML patients is now complete, confirming a favourable tolerability and safety profile. APL-4098 has shown predictable, dose-proportionate PK supporting once daily oral dosing and has demonstrated exposure-driven PD activity. APL-4098 is currently being evaluated in combination studies with azacitidine and venetoclax / azacitidine in R/R AML and newly diagnosed AML patients.