(PS1611) SAFETY, TOLERABILITY, AND PRELIMINARY ACTIVITY OF ROGOCEKIB IN PATIENTS WITH RELAPSED/REFRACTORY MYELOID MALIGNANCIES: RESULTS FROM A PHASE 1/2 STUDY (CTX-712-CL-02)

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Mutations in RNA splicing factor (SF) genes are common in myeloid neoplasms, are linked to poor outcomes, and currently have no approved targeted therapies. The CDC2-like kinase (CLK) family phosphorylates SR proteins that regulate splicing, making CLK inhibition a rational therapeutic strategy in myeloid malignancies with SF-mutations (SFm). Rogocekib is a first-in-class, oral, selective small-molecule CLK inhibitor. An ongoing phase 1/2 study is evaluating its safety and efficacy in relapsed or refractory (R/R) acute myeloid leukemia (AML) and higher-risk myelodysplastic syndromes (HR-MDS).

Aims

To assess safety, determine the maximum tolerated dose of rogocekib given once weekly (QW) or twice weekly (BIW), evaluate pharmacokinetic/pharmacodynamic (PD) and preliminary antileukemic activity.

Methods

CTX-712-CL-02 (NCT05732103) is an open-label, multicenter phase 1/2 study enrolling adults with R/R AML, HR-MDS, or MDS/MPN (including CMML). Rogocekib is given at escalating QW doses (20-140 mg), followed by BIW (60–100 mg). Safety assessments include treatment-emergent adverse events (TEAEs), and dose-limiting toxicities (DLTs). PD activity is assessed via exon-skipping biomarkers. AML and MDS responses are assessed per ELN 2017 and IWG 2006 criteria.

Results

To date, 41 patients (pts) have been enrolled (78% ≥65 years), including AML (53.7%), HR-MDS (39.0%), and MDS/MPN (7.3%). Pts were heavily pretreated (29.3% with ≥4 prior lines). The most common TEAEs included diarrhea (65.9%), nausea (58.5%), fatigue (39.0%), and constipation (34.1%). At QW dosing (n=25), TEAEs included nausea (48.0%), diarrhea (32.0%), ALT/AST increases (16.0%), platelet count decrease/headache (16.0%), leukopenia/fatigue (12.0%). At BIW dosing (n=16), TEAEs included nausea (62.5%), diarrhea (43.8%), constipation/vomiting (25.0% each), decreased appetite, dysgeusia, anemia, dizziness (18.8% each), worsening thrombocytopenia/neutropenia, dyspnea, hypotension, and hypokalemia (12.5% each). Grade ≥3 drug-related TEAEs occurred in 53.7%, and Grade ≥3 drug-related cytopenia in ≤15% of pts. DLTs occurred in 2 pts at 140 mg QW (pericardial/pleural effusions with dyspnea and hypotension), 1 at 80 mg BIW (esophagitis hemorrhagic), and 1 at 100 mg BIW (ALT/AST elevations). So far, the MTD for QW dosing has been determined to be 100 mg QW with BIW investigation ongoing.

Rogocekib plasma concentrations increased dose-dependently. PD analysis showed target engagement via intra-patient, baseline-normalized fold changes in THAP9-AS1 and S6K splicing ratios consistent with CLK inhibition.

Among 30 evaluable pts, 4 responses were observed in both SFm and WT pts (11.8%): 3 complete remissions with incomplete count recovery (CRi; AML) and 1 marrow CR (mCR; MDS). Stable disease (SD) was observed in 16.7% of AML and 56.3% of MDS pts. SFm were identified in 18 pts (47.4%): SRSF2 (26.3%), SF3B1 (13.2%), U2AF1/ZRSR2 (5.3%). Among SFm pts with evaluable responses (n=10), 1 CRi, 1 mCR, and 8 SD were observed. Responses were observed in both AML and MDS, including cases with co-occurring adverse-risk mutations (TP53, ASXL1, RUNX1).

Updated results will be presented at the EHA Congress.

Summary/Conclusion

Rogocekib demonstrated a manageable and tolerable safety profile and preliminary antileukemic activity in a heavily pretreated, high-risk population, with encouraging signals in AML (3 CRi, 16.7%). These findings support continued dose optimization and further clinical development in R/R AML and HR-MDS.