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POSTER ABSTRACTS

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

Preliminary Safety and Efficacy of Emavusertib (CA-4948) in Acute Myeloid Leukemia Patients with *FLT3* Mutation

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Background

Acute myeloid leukemia (AML) is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses. Internal tandem duplication (ITD) of FLT3 is considered an acquired late-event mutation and is associated with a poor prognosis in AML. Emavusertib is a potent oral inhibitor of IRAK4 and FLT3, conferring potential efficacy advantages compared to other IRAK4 and FLT3 inhibitors. IRAK4 is upregulated during anti-FLT3- or other cytotoxic therapies, which could drive a resistance pathway of early relapse and progression (Melgar 2019; Li 2019). Presence of spliceosome mutations U2AF1 or SF3B1 results in excessive IRAK4-L and further enhance toll-like receptor pathway activation (Smith 2019).

Methods

The safety, clinical activity, and potential biomarkers of emavusertib in relapsed/refractory (R/R) AML and higher-risk myelodysplastic syndrome are being investigated in the ongoing open-label, Phase 1/2a TakeAim Leukemia trial (NCT04278768). Here we present preliminary safety and efficacy data in the subset of enrolled AML patients who carried FLT3 mutation (FLT3m) at baseline and were treated with emavusertib monotherapy. Patients' mutational profiles were documented based on local testing results.

Results

As of 12 June 2023, 10 R/R AML patients with FLT3m have been treated at initial doses of 200, 300, or 400 mg BID. There was 1 patient with FLT3-TKD and 9 patients with FLT3-ITD, of which 2 carry both FLT3-ITD and U2AF1 mutations, and 1 with both FLT3-TKD and SF3B1 mutations. The median number of prior anti-cancer therapies was 3 (range 1-6) and 7 out of 10 patients had prior exposure to gilteritinib. Two patients with prior gilteritinib exposure also received midostaurin therapy. Treatment-emergent adverse events (TEAEs) Grade $\geq$ 3 were reported in 7/10 (70%) patients, and the majority of Grade $\geq$ 3 TEAEs were reversible and manageable. No dose-limiting toxicity was reported in these 10 patients. Five of 9 response evaluable patients demonstrated more than 90% bone marrow blast reduction compared to baseline. Enrollment is being expanded in this trial at the Recommended Phase 2 Dose (RP2D) of 300 mg BID for patients with $\leq$ 2 prior lines of therapy. Preliminary data for the 3 response evaluable patients in this population (for whom baseline and post-treatment marrow assessments were available) include blast count reductions of 99%, 100%, and 100% and include 2 CRs and 1 morphologic leukemia-free state (MLFS), with on-treatment duration of 213 days, 225 days, and 134 days, respectively. FLT3-ITD became undetectable in both patients achieving CR.

Conclusion

Emavusertib has a favorable safety profile in heavily pretreated AML patients with FLT3m and demonstrated anti-cancer activity in patients with FLT3m, including patients who have progressed on prior FLT3 inhibitor. No dose-limiting myelosuppression was reported. In addition, mutational profiles are suggestive of disease-modifying activity of emavusertib. Enrollment in this trial is continuing at a dose of 300mg BID (phase 2 expansion cohort) for patients with $\leq$ 2 prior lines of therapy.

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