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Blood 142 (2023) 5964

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

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

Treatment with GT1708F, an Oral Smoothened Inhibitor, in Patients with Myeloid Malignancies: A Phase I Study

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Introduction: Activation of the Hedgehog signaling pathway has been correlated with the development and disease progression of myeloid leukemia. This Phase I clinical trial aimed to evaluate the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), safety and tolerability of GT1708F in patients with myeloid malignancies.
Methods: This Phase I study enrolled patients with myeloid malignancies who were refractory, resistant or intolerant to previous treatments at three centers in China. Eligible patients were enrolled at each dose cohort to evaluate DLTs during the first continuous 28-day dosing period. The dose levels were determined employing the escalation with overdose control (EWOC) method, guided by an adaptive Bayesian logical analysis model (ABLRM). The decision to escalate the dosage to the subsequent cohort was informed by the recommendations of the safety monitoring committee after each round. Pharmacokinetic blood samples were collected in the first cycle of the treatment.
Results: As of May 25, 2023, 18 patients have been enrolled in 7 dose cohorts: 15 with acute myeloid leukemia (AML) and 3 with myelodysplastic syndromes (MDS). Patients received GT1708F once daily orally at 20 mg QD (n=1), 40 mg QD (n=1), 80 mg QD (n=4), 120 mg QD (n=3), 180 mg QD (n=3), 240 mg QD (n=3), 320 mg QD (n=3). No DLT was reported across these dose cohorts and the MTD was not reached. 17(93.3%) patients experienced at least one treatment-emergent adverse event (TEAE). 13 (72.2%) patients experienced at least one treatment related AE (TRAE). 11(61%) patients experienced at least one TEAE of Grade 3 or higher in severity, 4 (22.2%) of whom had TRAE(s) including lung infection, anemia, pharyngitis, and creatine kinase increased. Eight patients experienced 13 serious adverse events (SAE), two of which were assessed by the investigator as possibly related to GT1708F, both being lung infections. 15 patients completed at least one efficacy evaluation. No patient achieved complete or partial remission while 5 AML patients achieved stable disease with one patient lasting for 6 cycles and 2 patients lasting for 3 cycles. GT1708F is rapidly absorbed in the body with a peak time of 0.5-1hr after a single oral dose. As the dose increased from 20mg QD to 320 QD, the maximum concentration of the drug in the body increased linearly, showing quasi-linear pharmacokinetic characteristics.
Conclusions: Our study indicated good safety and tolerability of GT1708F in patients with myeloid malignancies. In addition, a potential efficacy signal of GT1708F for these patients was observed, providing a rationale for further exploration in combination with other therapeutic modalities.

Disclosures Tong: *Kintor Pharmaceutical Ltd:* Current Employment, Current equity holder in publicly-traded company. **Ni:** *Kintor Pharmaceutical Ltd:* Current Employment. **Dong:** *Kintor Pharmaceutical Ltd:* Current Employment. **He:** *Kintor Pharmaceutical Ltd:* Current Employment.

https://doi.org/10.1182/blood-2023-180494

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