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POSTER ABSTRACTS

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

Covalent-103: A Phase 1, Open-Label, Dose-Escalation, and Dose-Expansion Study of Bmf-500, an Oral Covalent FLT3 Inhibitor, in Adults with Acute Leukemia (AL)

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Background: FLT3 mutations occur in 25-35% of patients with AML and are associated with poor prognosis. FLT3 mutations are most frequently the result of an internal tandem duplication (ITD) of amino acids in the juxtamembrane region of FLT3 or point mutations in the tyrosine kinase domain (TKD). FLT3-ITD mutations are associated with increased incidence of relapse, shorter duration of remission, and decreased disease-free and overall survival.
BMF-500 is a novel orally bioavailable, highly potent and selective covalent inhibitor of FLT3 including wildtype (WT), ITD, TKD, as well as a variety of additional resistance-conferring mutations such as the gatekeeper F691. BMF-500 has demonstrated high affinity for FLT3, lack of cKIT inhibition, and sustained cell-killing capacity despite drug washout (Law et al., ASH 2022 Abstract 2756). BMF-500 has shown sustained tumor regression and improved survival in both subcutaneous and disseminated xenograft models of mutant FLT3-driven AML.
Study Design: COVALENT-103 (NCT05918692) is an open-label, non-randomized, multicenter, first-in-human Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of twice daily oral BMF-500 in patients with relapsed or refractory (R/R) AL, including AML, ALL, or MPAL, with or without FLT3 mutations.
The trial has 2 arms that will undergo dose escalation in parallel: Arm A (without) and Arm B (with) concomitant use of a moderate or strong CYP3A4 inhibitor. Utilizing an accelerated titration design (ATD), doses of BMF-500 will be escalated in single-subject cohorts until 1 subject experiences either a Grade 2 or higher related-adverse event or dose-limiting toxicity (DLT). At that point, the cohort will switch to a classical "3 +3" design. Patients with WT FLT3 AL may be enrolled, up to a limit of 33% per arm. Treatment will continue in 28-day cycles until progression or intolerability. Expansion cohorts will enroll additional patients to obtain further safety and efficacy data.
Patients must be refractory, relapsed or must have progressed on or following discontinuation of the most recent anti-cancer therapy or be ineligible for any approved standard of care therapies, including HSCT. Participants with FLT3-mutant AML must have received treatment with a FLT3 inhibitor approved for treatment of relapsed or refractory FLT3-mutant AML.
Key inclusion criteria include ECOG PS $\leq$ 2, adequate organ function, and documented FLT3 mutation status. Key exclusion criteria include known CNS disease involvement, clinically significant cardiovascular disease, and WBC count >50,000/μL (uncontrollable with cytoreductive therapy).
Objectives: The primary objective of the study is to evaluate safety and tolerability and to determine the optimal biological dose (OBD)/ recommended Phase 2 dose (RP2D) of BMF-500 oral monotherapy based on evaluation of available PK/ PD, safety and efficacy data. Secondary objectives include characterization of the pharmacodynamics and pharmacokinetics of BMF-500, and assessment of its antitumor activity per modified Cheson (2003) criteria or the NCCN Clinical Practice Guidelines (ALL Version 1.2022) as determined by the investigator. Endpoints include best overall response rate (ORR), complete remission (CRc), duration of response (DOR), relapse-free survival (RFS) and overall survival (OS).
The study was initiated in July 2023 and will enroll ~110 participants at approximately 30 sites.

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