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

2024 ASCO® ANNUAL MEETING

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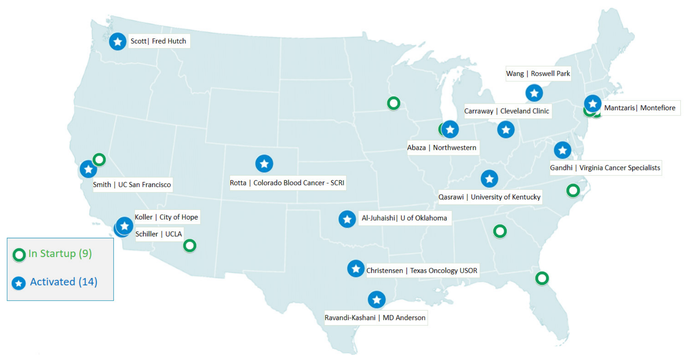
FLT3 MUTATION IN ACUTE LEUKEMIA

- FLT3 mutations occur in 25%-35% of patients with AML, and in ~ 5% of ALL patients and are associated with poor prognosis[1, 2]
- FLT3 abnormalities are most commonly internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations

BMF-500 BACKGROUND

- BMF-500 is an orally bioavailable, selective, covalent, small-molecule inhibitor of FLT3, including wild-type (WT), and ITD and TKD mutants, and retains potency against FLT3 inhibitor resistance mutations such as the F691 gatekeeper and D835 mutations
- BMF-500 has demonstrated high affinity for FLT3, lack of cKIT inhibition, and sustained cell-killing capacity that persists even after prolonged drug washout[3]
- BMF-500 has shown sustained tumor regression and improved survival in both subcutaneous and disseminated xenograft models of mutant FLT3-driven AML[3]
- BMF-500 is currently supplied as 25 and 100 mg strength tablets for oral administration

COVALENT-103 STUDY OVERVIEW

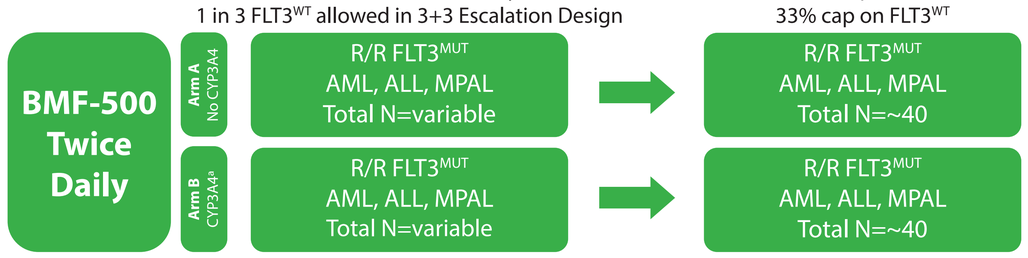


- COVALENT-103 (NCT05918692) is an open-label, nonrandomized, first-in-human, Phase I study evaluating the safety, tolerability, and activity of escalating doses of twice daily oral BMF-500 in patients with R/R AL, including AML, ALL, or MPAL, with or without FLT3 mutations
- As of Apr 2024, the study is open for enrollment at 14 sites in the United States; additional sites to open soon
- Enrollment commenced in Sep 2023 and patients have been dosed at Dose Levels 1, 2, and 3; escalation continues at the time of this reporting

OBJECTIVES & ENDPOINTS

	Objectives	Endpoints
Primary	• Evaluate safety and tolerability of BMF-500 • Determine OBD and RP2D of BMF-500	• Incidence of TEAEs and SAEs • OBD/RP2D determination based on evaluation of available PK/ PD, safety and tolerability, and efficacy data
Secondary	• Determine single and multiple dose PK of BMF-500 • Assess effect of food on the PK exposure of BMF-500 • Evaluate efficacy of BMF-500 • Assess additional evidence of antitumor activity per investigator assessment as per corresponding response criteria	• C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$ of BMF-500 after a single dose, and C_{max}, t_{max}, C_{min}, t_{min}, AUC_{last}, steady-state AUC_t, $t_{1/2}$, AR after multiple dosing • CRc (CR, CRh, CRp, CRi), ORR: CR, CRh, CRp, CRi, MLFS, or PR as measured by PI using ELN 2017 • DOR , RFS, OS
Exploratory	• Assess MRD • Characterize PD effects over the course of treatment with BMF-500	• Rate of MRD-negativity in patients with AL who achieve CR or CRi • Changes in molecular profiling as well FLT3 signaling by plasma inhibitory assay

STUDY DESIGN



[a]Necessary azole antifungals that are moderate or strong CYP3A4 inhibitors (excluding other moderate or strong CYP3A4 inhibitors).

Fig. 1 Study Schema

Dose Escalation Scheme

DOSE LEVELS FOR ESCALATION PHASE

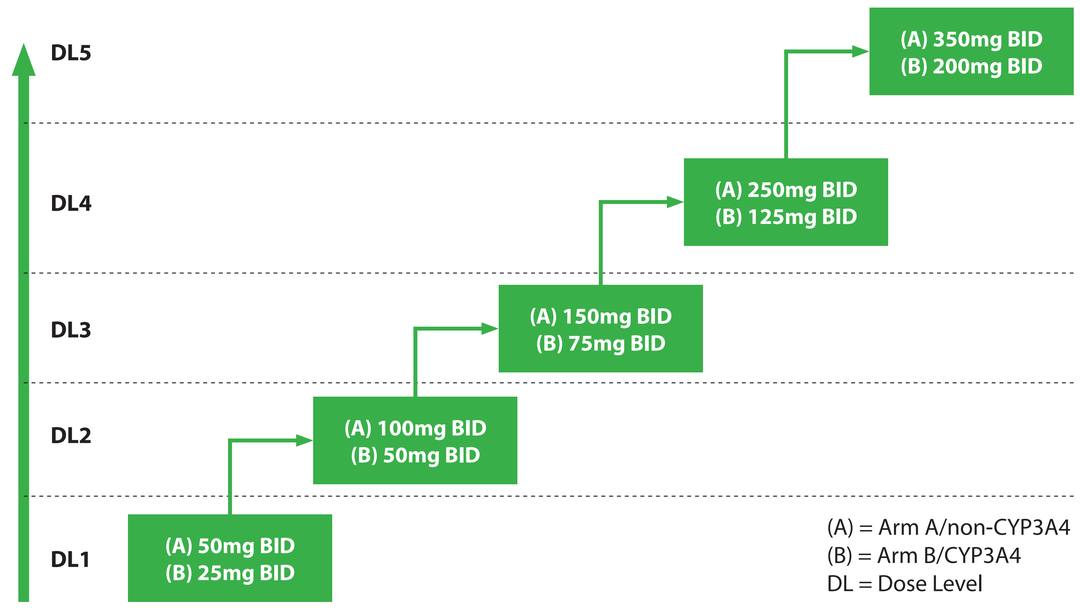


Fig. 2 Accelerated titration design followed by modified 3+3

- BMF-500 doses are escalated in single-subject cohorts independently for each Arm until 1 subject experiences either any ≥ Grade 2 TRAE which does not meet DLT criteria, or a DLT in the first 28-day cycle
- At that point, the dose level for the specific Arm follows the classical "3 + 3" dose escalation design

STUDY FLOWCHART

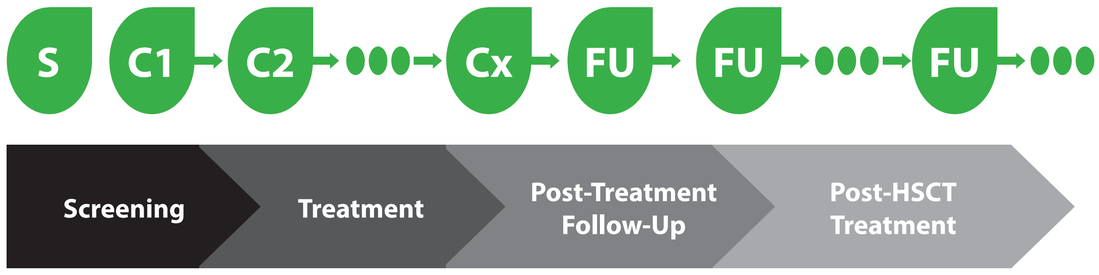


Fig. 3 Study Flowchart

Screening	• Up to 28 days from consent
Treatment	• BMF-500 administered BID in 28-day cycles
Post-Treatment Follow-Up	• Efficacy follow-up assessments for patients who discontinued in absence of progression • Long-term survival follow-up for patients post-progression or after initiation of subsequent anti-cancer therapy
Post-HSCT Follow-Up	• BMF-500 treatment post-HSCT may be permitted as part of ongoing study participation

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- Adults (≥18 years of age) with ECOG performance status of 0-2 and estimated life expectancy of >3 months
- R/R FLT3-mutant AML, ALL, MPAL, and R/R FLT3-WT AML, ALL, MPAL (≤33% per Arm)
- Histologically or pathologically confirmed diagnosis of AML, ALL, or MPAL and documentation of FLT3 status
- Must be R/R or must have progressed on or following discontinuation of the most recent anti-cancer therapy and/ or ineligible for any approved standard of care therapies, including HSCT
- Patients with FLT3-mutant AML must have received treatment with an approved FLT3 inhibitor and must have relapsed, progressed and/or discontinued the inhibitor
- Adequate washout from prior therapies (e.g., ≥60 days from TBI; ≥60 days from stem cell infusion; ≥14 days from biologics or steroids, immunotherapy, and chemotherapy)
- Adequate liver function: Bilirubin ≤1.5 x ULN; ALT/AST ≤2.0 x ULN
- Adequate renal function: eCrCl ≥60 mL/min using the Cockcroft-Gault equation

Exclusion Criteria

- Diagnosis of acute promyelocytic leukemia, chronic myeloid leukemia in blast crisis
- WBC count >50,000/µL (uncontrollable with cytoreductive therapy)
- Clinically active CNS leukemia; previously controlled CNS leukemia is acceptable
- Known positive test for HIV, Hep C, Hep B surface antigen
- Active uncontrolled acute or chronic systemic fungal, bacterial, or viral infection
- Clinically significant cardiovascular disease; LVEF <45%
- Mean QTcF or QTcB of >470 millisecond
- Acute or chronic GVHD except disease limited to skin with adequate control using topical steroids
- GI disease that may affect oral absorption
- Concurrent malignancy in the previous 2 years

REFERENCES

- Bystrom R, Levis MJ. An Update on FLT3 in Acute Myeloid Leukemia: Pathophysiology and Therapeutic Landscape. Curr Oncol Rep. 2023 Apr;25(4):369-378. doi: 10.1007/s11912-023-01389-2. Epub 2023 Feb 18. PMID: 36808557.
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