FT-2102, an IDH1m Inhibitor, in Combination with Azacitidine in Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS): Results from a Phase 1 Study

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**Background**

- Isothermal methyltransferase 1 mutations (IDH1m) produce 2-HG that blocks differentiation of normal hematopoietic precursors, leading to epigenetic alterations, yielding hypermethylated DNA and histones.
- AZA, a hypomethylating agent (HMA), is a standard of care for MDS and AML, patients with IDH1m AML.

**Study Design**

- IDH1m AML/MDS (NCT02719574): FT-2102 administration is 75 mg/m² AZA (n = 8)
- Dose Escalation (n = 15)
- FT-2102 administered 150 mg BID + AZA (n = 8)
- Treatment-naive AML/MDS (n = 26)
- AZA, a hypomethylating agent (HMA), is a standard of care for MDS

**Key Study Objectives**

- Determine IDH1m RP2D
- Evaluate safety
- Evaluate PK in FT/IDH (2HG)-relationship
- Evaluate epigenetic and leukemia activity as a function of dose
- Evaluate AEs

**Pharmacodynamics**

- **Correlation Between FT-2102 and 2-HG Plasma Levels**
  - The MPD relationship of individual subjects' plasma FT-2102 and 2-HG concentration scores treatment effect and independent of time on treatment is presented.
  - FT-2102 concentrations < 1,000 ng/mL correspond to early time point assessment (C1D0 - C1D15) responses.
  - No correlation of exposure to 2-HG reduction is observed until FT-2102 concentrations cross the C50 predicted in vivo model to result in 2-HG reduction in plasma 2HG.
  - Maximum, most consistent exposure was observed at the median Ceff predicted by linear regression fit.

**Pharmacokinetics**

- **Mean Plasma 2-HG Concentration (ng/mL)**
  - Normal for healthy volunteers
  - Increases with dose escalation
  - Crossed the C50 – 1000 ng/mL
  - Sustained over the treatment duration

**Study Conclusions**

- FT-2102 is well tolerated in combination with azacitidine
- TEAEs ≥ 10%, All Grades Regardless of Causality
  - Hematologic:
    - Neutropenia
    - Anemia
    - Thrombocytopenia
  - Non-hematologic:
    - Cough
    - Fatigue
    - Infection
    - Fatigue
    - Gastrointestinal

**Clinical Activity**

- **Response starts CR/CRh/Crim**
  - 36 (44%) patients; all resolved with treatment
  - Among the patients with 2-HG > 800 ng/mL, 82% had complete response durations > 12 mo.

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