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POSTER ABSTRACTS

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

Preliminary Results from a Phase 1 Dose Escalation Study of FHD-286, a Novel BRG1/BRM (SMARCA4/SMARCA2) Inhibitor, Administered As an Oral Monotherapy in Patients with Advanced Hematologic Malignancies

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The BRG/Brahma-associated factors (BAF) family of chromatin remodeling complexes (also referred to as the mSWI/SNF complex) regulates the chromatin landscape of the genome. Through its adenosine triphosphate (ATP)-dependent chromatin remodeling activity, BAF complexes regulate the accessibility of gene-control elements, allowing for the binding of transcription factors. Thus, BAF is a major regulator of lineage- and disease-specific transcriptional programs. FHD-286 is a first-in-class, orally administered compound that potently and selectively inhibits the ATPase components of the BAF complexes, SMARCA4 and SMARCA2 (also called BRG1 and BRM, respectively). In preclinical models, acute myeloid leukemia (AML) cell lines were highly sensitive to BAF inhibition.

FHD-286-C-002 (NCT04891757) is a multicenter, open-label, Phase 1 dose escalation study designed to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose and/or the recommended phase 2 dose(s), as well as to evaluate the preliminary clinical activity of FHD-286, in patients with advanced hematologic malignancies.

Patients with relapsed or refractory (R/R) AML or myelodysplastic syndrome (MDS) failing all available standard therapies were eligible to receive FHD-286 doses ranging from 2.5 mg once daily (QD) to 10 mg QD on a continuous dosing regimen. Patients had regularly scheduled assessments to evaluate safety, pharmacokinetics (PK), pharmacodynamics, preliminary clinical activity, and exploratory biomarkers.

As of 02 Aug 2022, 40 patients with a median age of 65.5 years (range 25 to 84) with R/R AML (36 patients) or MDS (4 patients) had received at least 1 dose of FHD-286. 67.5% of patients had received ≥3 prior lines of therapy for AML/MDS/other antecedent hematologic disorder, with 22.5% having received ≥5 prior lines. 32.5% of patients had prior hematopoietic stem cell transplant. 65% of patients had adverse risk genetics by 2017 ELN recommendations.

85% of patients experienced a treatment-related adverse event (TRAE) of any grade; the most common (≥20% of patients) were dry mouth (27.5%), increased blood bilirubin (22.5%), and alanine aminotransferase (ALT) increased and rash (20% each). 50% of patients experienced a Grade ≥3 TRAE, the most common of which was increased blood bilirubin (12.5%); stomatitis, ALT increased, differentiation syndrome (DS), and hypocalcemia occurred in 7.5% (each).

2 DLTs were reported: Grade 3 hyperbilirubinemia in 1 patient receiving 5 mg QD and Grade 3 muscular weakness in 1 patient receiving 10 mg QD.

Treatment-related DS of any grade was investigator-reported in 4 patients (10%). An independent adjudication committee determined that the rate of suspected DS was 15% (6 patients).

16 patients (15 AML; 1 MDS) had a best overall response of stable disease. Markers of myeloid differentiation with neutrophil recovery and reductions in bone marrow and/or peripheral blasts have been observed in a subset of patients in the study who had a broad range of cytogenetic backgrounds, including patients with enhancer-driven leukemias such as MECOM and KMT2A.

Preliminary PK analysis indicates that FHD-286 appears to have a long half-life, at a minimum of >24 hours, and that plasma concentrations of FHD-286 increase with increasing dose.
Exploratory flow cytometry assessment of markers of differentiation, hematopoietic stem cell identity, and apoptosis suggested dose-dependent target engagement. Additionally, exploratory sequencing analysis on bone marrow blasts revealed comprehensive impacts on AML-specific expression pathways and stemness genes in response to FHD-286. An exposure-response analysis using the percentage of peripheral blasts showed a trend toward lower blast count with higher FHD-286 area-under-the-curve.
Enrollment into the single-agent dose escalation phase of the study is complete. Based on nonclinical, translational, and single-agent clinical data, FHD-286 in combination with decitabine or low-dose cytarabine is being evaluated in the combination dose escalation phase of the study.

Disclosures DiNardo: *Schrödinger:* Consultancy; *ImmuniOnc:* Honoraria; *Fogham:* Honoraria; *Notable Labs:* Honoraria; *Novartis:* Honoraria; *Astellas:* Honoraria; *Takeda:* Honoraria; *AbbVie/Genentech:* Honoraria; *BMS:* Honoraria; *Servier:* Honoraria. **Savona:** *Taiho:* Membership on an entity's Board of Directors or advisory committees; *CTI BioPharma Corp.:* Membership on an entity's Board of Directors or advisory committees; *Forma Therapeutics Inc.:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Geron Corporation:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm Therapeutics Inc.:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *AbbVie Inc.:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees; *Incyte Corporation:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *ALX Oncology:* Research Funding; *Boehringer Ingelheim:* Patents & Royalties; *TG Therapeutics, Inc.:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda Pharmaceutical Company:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Sierra Oncology, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Ryvu Therapeutics:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Kishtagari:** *Geron Corporation:* Honoraria; *Servier Pharmaceuticals:* Consultancy; *CTI BioPharma Corp., a Sobi company:* Consultancy, Honoraria, Speakers Bureau. **Fathi:** *AbbVie:* Consultancy, Research Funding; *Agios:* Consultancy; *Amgen:* Consultancy; *Astellas:* Consultancy; *Autolus:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Celgene:* Consultancy, Research Funding; *Enclear:* Consultancy; *Forma:* Consultancy; *Rigel:* Consultancy; *Mablytics:* Consultancy; *Kite:* Consultancy; *Ipsen:* Consultancy; *Daiichi Sankyo:* Consultancy; *Novartis:* Consultancy; *Orum:* Consultancy; *Menarini:* Consultancy; *PureTech:* Consultancy; *Genentech:* Consultancy; *Immunogen:* Consultancy; *Remix:* Consultancy; *Pfizer:* Consultancy; *Servier:* Consultancy, Research Funding; *Takeda:* Consultancy; *Gilead:* Consultancy. **Bhalla:** *Foghorn Therapeutics Inc.:* Research Funding. **Agresta:** *Foghorn Therapeutics Inc.:* Current Employment. **Reilly:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Almon:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Hentemann:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Hickman:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Corrigan:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Macaraeg:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Piel:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Horrigan:** *Foghorn Therapeutics Inc.:* Current Employment, Current equity holder in publicly-traded company. **Nabhan:** *Foghorn Therapeutics Inc.:* Current equity holder in publicly-traded company, Ended employment in the past 24 months. **Martin:** *Certara Integrated Drug Development:* Current Employment; *Foghorn Therapeutics Inc.:* Consultancy. **Stein:** *Agios:* Consultancy; *Janssen:* Consultancy; *PinotBio:* Consultancy; *Novartis:* Consultancy; *Bristol Myers Squib:* Consultancy, Research Funding; *Eisai:* Research Funding; *Jazz:* Consultancy; *Menarini:* Consultancy; *Genesis:* Consultancy; *Genentech:* Consultancy; *Abbvie:* Consultancy; *Neoleukin:* Consultancy; *Gilead:* Consultancy; *Syndax:* Consultancy; *OnCusp:* Consultancy; *CTI Biopharma:* Consultancy; *Foghorn:* Consultancy; *Servier:* Consultancy; *Calithera:* Consultancy; *Daiichi:* Consultancy; *Aptose:* Consultancy; *Syros:* Consultancy; *Astellas:* Consultancy; *Ono Pharma:* Consultancy; *Blueprint:* Consultancy.

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